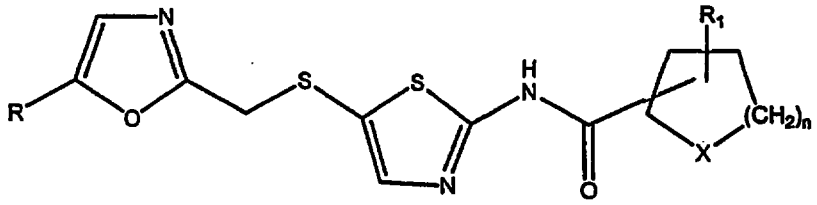
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N-[5-[[[5-ALKYL-2-OXAZOLYL]METHYL]THIO]-2-THIAZOLYL] CARBOXAMIDE INHIBITORS OF CYCLIN DEPENDENT KINASES

The present invention is directed to compounds of formula I



(I)

and enantiomers, diastereomers, solvates, and pharmaceutically acceptable salts thereof wherein

R is alkyl;

R^1 is hydrogen or alkyl;

X is NR^2 or $CHNR^2R^3$;

159159

R^2 and R^3 are each independently hydrogen, alkyl, substituted alkyl, cycloalkyl or substituted cycloalkyl; and

n is 0, 1, 2 or 3.

The compounds of formula I are particularly useful as potent, protein kinase inhibitors and are useful in the treatment of proliferative diseases, for example, cancer, inflammation and arthritis. They may also be useful in the treatment of Alzheimer's disease, chemotherapy-induced alopecia, and cardiovascular disease.

The present invention provides for compounds of formula I, pharmaceutical compositions employing such compounds, and for methods of using such compounds.

Listed below are definitions of various terms used to describe the compounds of the instant invention. These definitions apply to the terms as they are used throughout the specification (unless they are otherwise limited in specific instances) either individually or as part of a larger group.

The term "alkyl" or "alk" refers to a monovalent alkane (hydrocarbon) derived radical containing from 1 to 12, preferably 1 to 6, and more preferably 1 to 4, carbon atoms unless otherwise defined. An alkyl group is an optionally substituted straight, branched or cyclic saturated hydrocarbon group. When substituted, alkyl groups can be substituted with

up to four substituent groups, R^4 as defined, at any available point of attachment. When the alkyl group is said to be substituted with an alkyl group, this is used interchangeably with "branched alkyl group". Exemplary unsubstituted such groups include methyl, ethyl, propyl, isopropyl, n-butyl, t-butyl, isobutyl, pentyl, hexyl, isohexyl, heptyl, 4,4-dimethylpentyl, octyl, 2,2,4-trimethylpentyl, nonyl, decyl, undecyl, dodecyl, and the like. Exemplary substituents may include, but are not limited to, one or more of the following groups: halo (such as F, Cl, Br or I), haloalkyl (such as CCl_3 or CF_3), alkoxy, alkylthio, hydroxy, carboxy, alkylcarbonyl, alkyloxycarbonyl, alkylcarbonyloxy, amino, carbamoyl, urea, amidinyl, or thiol.

Cycloalkyl is a specie of alkyl containing from 3 to 15 carbon atoms, without alternating or resonating double bonds between carbon atoms. It may contain from 1 to 4 rings. Exemplary unsubstituted such groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, etc. Exemplary substituents include one or more of the following groups: halogen, alkyl, alkoxy, alkyl hydroxy, amino, nitro, cyano, thiol and/or alkylthio.

The terms "alkoxy" or "alkylthio", as used herein, denote an alkyl group as described above bonded through an oxygen linkage (-O-) or a sulfur linkage (-S-), respectively.

The term "alkyloxycarbonyl", as used herein, denotes an alkoxy group bonded through a carbonyl group. An alkoxycarbonyl radical is represented by the formula: $-C(O)OR^5$, where the R^5 group is a straight or branched C_{1-6} alkyl group.

The term "alkylcarbonyl" refers to an alkyl group bonded through a carbonyl group.

The term "alkylcarbonyloxy", as used herein, denotes an alkylcarbonyl group which is bonded through an oxygen linkage.

As used herein, the phrase "compounds of the invention" means, collectively, compounds falling within formula I and pharmaceutically-acceptable salts, and solvates including hydrates thereof. Methods of salt formation, solvation, and hydrate formation are well known in the art. The invention also encompasses mixtures of stereoisomers of compounds of the invention. Stereoisomers include, but are not limited to, enantiomers, diastereomers, and racemates where the compound has one or more chiral centers. All stereoisomers of the compounds of the instant invention are contemplated, either in admixture or in pure or substantially pure form. The definition of the compounds according to the invention embraces all possible stereoisomers and their mixtures. It very particularly embraces the racemic forms and the isolated optical isomers having the specified activity. The racemic forms can be resolved by physical methods, such as, for example, fractional crystallization, separation or crystallization of diastereomeric derivatives or separation by chiral column chromatography. The individual optical isomers

can be obtained from the racemates by conventional methods, such as, for example, salt formation with an optically active acid followed by crystallization. All configurational isomers of compounds of the present invention are contemplated, either in admixture or in pure or substantially pure form. The definition of compounds of the present invention very particularly embraces both *cis* (Z) and *trans* (E) alkene isomers, as well as *cis* and *trans* isomers of cycloalkyl or heterocycloalkyl rings.

In addition, salts of compounds of formula I that are pharmaceutically unsuitable but useful in other respects, for example, for the isolation or purification of compounds of formula I, are also encompassed by the invention.

The compounds of the invention are defined herein by their chemical structures and/or chemical names. Where a compound is referred to by both a chemical structure and a chemical name, and the chemical structure and chemical name conflict, the chemical structure is determinative of the compound's identity.

The phrase "pharmaceutically-acceptable salt(s)," as used herein includes, but is not limited to, salts of acidic or basic groups that may be present in the compounds of the invention. Examples of such pharmaceutically acceptable salts include, but are not limited to, hydrochloride, hydrobromide, dihydrochloride, sulfate, trifluoroacetate, tartrate, fumarate, succinate, maleate, citrate, methanesulfonate, bromate and iodate salts and mixtures thereof. Also included are salts formed with other organic and inorganic acids such as hydroxymethane sulfonic acid, acetic acid, benzenesulfonic acid, toluenesulfonic acid and various others, *e.g.*, nitrates, phosphates, borates, benzoates, ascorbates, salicylates, and the like. In addition, pharmaceutically acceptable salts of compounds of formula I can be formed with alkali metals, such as sodium, potassium and lithium; alkaline earth metals, such as calcium and magnesium; organic bases, such as dicyclohexylamine, tributylamine, and pyridines, and the like; and amino acids, such as arginine, lysine, and the like.

Salts of compounds of the invention encompass solvates, racemates, and all stereoisomeric forms thereof, including enantiomers and diastereomers (for example, D-tartrate and L-tartrate salts).

As used herein, the term "solvate" means a compound of the invention or a salt thereof, that further includes a stoichiometric or non-stoichiometric amount of one or more solvent molecules bound by non-covalent intermolecular forces. Preferred solvents are volatile, non-toxic, and/or acceptable for administration to humans in trace amounts. When the solvent is water the solvate is termed a "hydrate".

Compounds of formula I can be prepared by adapting the methods set forth in WO 99/65884 and WO 99/24416, both of which are incorporated herein by reference. Alternatively, the generic method shown in Scheme A below, that illustrates synthesis of

the broad genus of compounds of formula XIV, can be used to synthesize compounds of formula I. The starting compounds are commercially available or may be prepared by methods known to one of ordinary skill in the art. The following terms apply in Scheme A:

R^7, R^8, and R^{10} are independently hydrogen or alkyl;

R is alkyl, aryl, or heteroaryl;

R^9 is hydrogen, alkyl, aryl, or heteroaryl;

R^1 and R^{11} are independently hydrogen, alkyl, aryl, heteroaryl, halogen, hydroxy, or alkoxy;

R^{12} is hydrogen, alkyl, cycloalkyl, aryl, heteroaryl, $CONR^{13}R^{14}$, COR^{15}, or $COOR^{16}$;

R^{13}, R^{14}, R^{15} and R^{16} are independently hydrogen, alkyl, or aryl;

r is an integer ranging from 0 to 5;

s is an integer ranging from 0 to 5;

L is a suitable leaving group, such as halogen or sulfonate ($R^6SO_2O^-$, $CF_3SO_2O^-$, *etc.*, wherein R^6 is alkyl, cycloalkyl, or aryl);

M is hydrogen, Li, Na, K, Cs, or a quaternary ammonium ion, *e.g.*, $(R^6)_4N$ or quaternary ammonium ions comprising cyclic alkenetetramines, such as hexamethylenetetramine;

Q is hydroxy, halogen or acyloxy (R^6COO^-, R^6OCOO^-, *etc.*);

Y is O, S, NH, N-alkyl, N-aryl or N-acyl;

Z is hydrogen, alkyl, aryl, O-alkyl, O-aryl, S-alkyl, S-aryl, NH_2, N-alkyl, N-aryl or N-acyl; and

P is a nitrogen-protecting group (Boc, Cbz, R_3Si, *etc.*). When a functional group is termed "protected," this means that the group is in modified form to preclude undesired side reactions at the protected site. Suitable protecting groups for the compounds involved in the present processes will be recognized from the specification taking into account the level of skill in the art, and with reference to standard textbooks such as Greene, T.W., *Protective Groups in Organic Synthesis*, 3rd edition (1999), incorporated herein by reference.

The processes generally involve reaction of α-halo ketones II (commercially available or readily synthesized by well-known methods) with an azide to give α-azido ketones III. Reduction of III with a reducing reagent gives α-amino ketones IV.

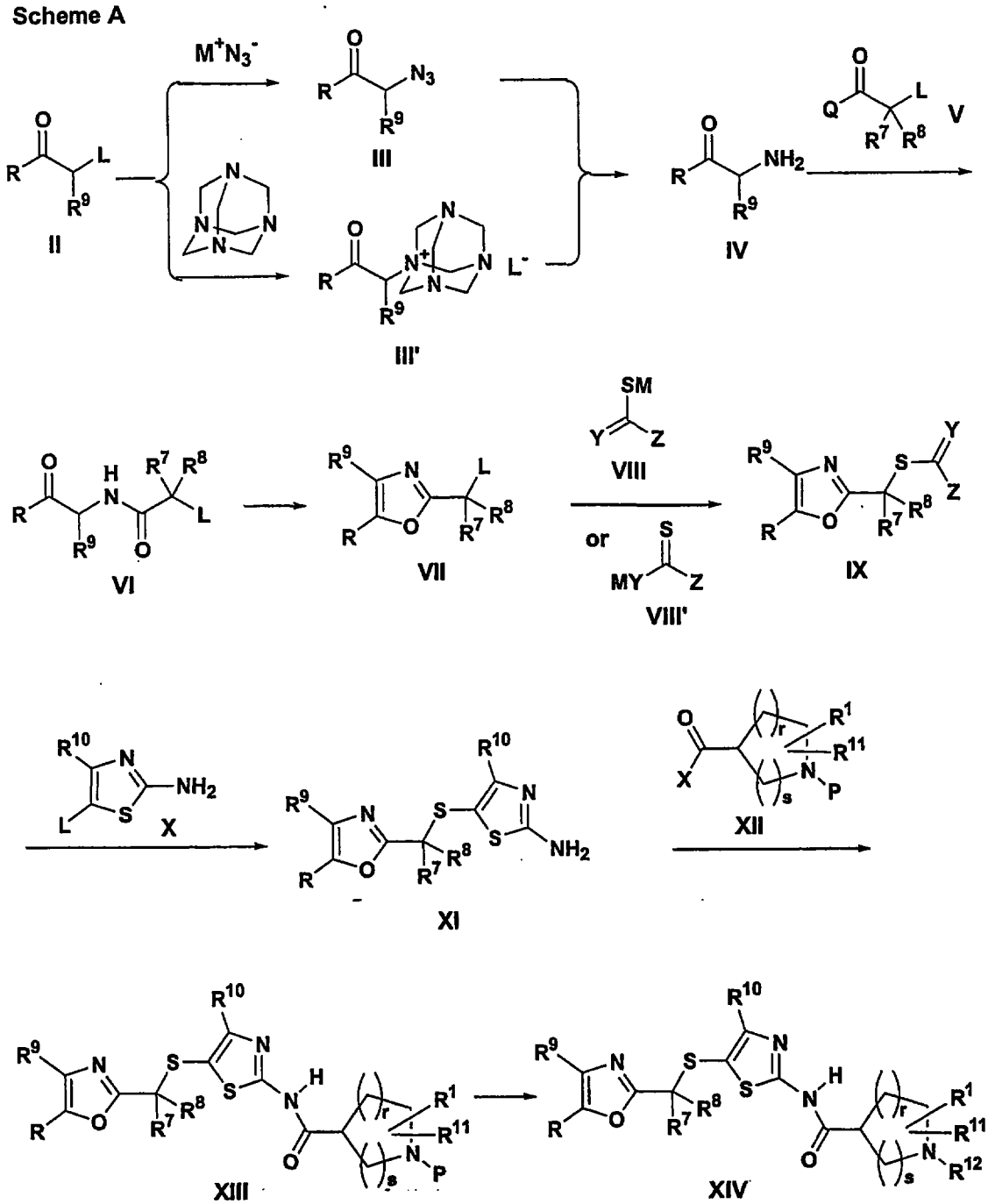
Alternatively and more advantageously, the α-amino ketones IV are prepared by reaction of α-halo ketones II with a cyclic alkylenetetramine such as hexamethylenetetramine and the like, followed by hydrolysis of the resulting, new quaternary ammonium salt III'. This reaction provides excellent yields of the desired intermediate compound IV, above 90%.

Thereafter, reacting the α-amino ketones IV with an α-halo acyl halide V in the presence of a base or, alternatively, coupling the α-amino ketones IV with an α-halo acid,

produces the corresponding amides VI. Then, ring closure of VI with a dehydrating reagent affords 2-oxazolylalkyl halides VII. When a conventional dehydrating reagent, such as trihalophosphorus oxide like $POCl_3$ is used, product isolation is difficult due to the formation of large amounts of hydrochloric and phosphoric acids. Thus, the process of the present invention preferably utilizes the Burgess' reagent which produces excellent yields and permits easy, safe product isolation from water.

Subsequent treatment of 2-oxazolylalkyl halides VII with sulfur-containing reagent VIII or VIII' affords new key intermediate compounds, 2-oxazolylalkyl sulfides IX. Coupling of IX with 5-halo-2-aminothiazole X gives 5-(2-oxazolylalkylthio)-2-aminothiazoles XI. Coupling of XI with an azacycloalkanoic acid derivative XII affords thiazolyl amides XIII, which may be deprotected (in the case where P is a protecting group, *e.g.*, Boc) to give 5-(2-oxazolylalkylthio)-2-azacycloalkanoylaminothiazoles XIV.

Scheme A



As set forth in Scheme A, the processes for the preparation of 5-(2-oxazolylalkylthio)-2-azacycloalkanoylaminothiazoles and analogs involve the following transformations:

Step (a) involves reacting an α-substituted ketone II such as, for example, an α-halo ketone, with an azide in a suitable solvent or solvent mixtures to give an α-azido ketone III; or, more desirably, (a') reacting an α-substituted ketone II like the α-halo ketone with a cyclic alkylenetetramine such as, for example, hexamethylenetetramine in a suitable solvent or solvent mixtures to give a new quaternary ammonium salt III'.

The α-halo ketone includes α-halo aliphatic and α-halo aromatic ketones. The preferred α-halo ketones are α-halo pinacolones with α-bromo pinacolone most preferred. A sulfonate, for example, RSO_2O- (where R is alkyl, aryl or heteroaryl), CF_3SO_2O- and the like, may be substituted for the halogen in the α-position. The azides include both metal azides and quaternary ammonium azides. The metal azides are preferred with sodium azide most preferred. Suitable solvent(s) include solvents such as hydrocarbons, ethers, amides, for example, dimethylformamide, ketones, *etc.*, or mixtures thereof, with ketones such as acetone preferred for both reactions (a) and (a').

Step (b) comprises reacting the α-azido ketone III obtained in step (a) with a reducing reagent in a suitable solvent or solvent mixtures to give an α-amino ketone IV, or, more desirably, (b') reacting the quaternary ammonium salt III' obtained in step (a') with an acid in a suitable solvent or solvent mixtures to give an α-amino ketone IV.

The reducing reagent in reaction (b) includes hydrogen in the presence of a transition metal catalyst such as palladium, trialkyl or triarylphosphines like triphenylphosphine. Hydrogen in the presence of a transition metal catalyst is preferred with hydrogen and palladium over activated carbon most preferred. Suitable solvent(s) in reaction (b) include solvents such as hydrocarbons, ethers, alcohols and the like, or mixtures thereof, with alcohol such as methanol preferred. Alternatively, the reduction reaction can be carried out in the presence of an acidic medium such as, for example, hydrochloric acid in ethanol to give α-amino ketone acid salt which can be isolated as the acid salt or free amine forms.

The acid in reaction (b') includes, but is not limited to, protic acids such as HCl, HBr, HI, H_2SO_4, H_3PO_4, *etc.*, with HCl preferred. Suitable solvent(s) in reaction (b') include solvents such as hydrocarbons, ethers, alcohols and the like, or mixtures thereof, with alcohol such as ethanol preferred. The α-amino ketone product may be isolated as the salt or free base forms.

Step (c) involves reacting (acylating) the α-amino ketone IV or its acid salt obtained in step (b) or (b') with an α-substituted acyl derivative V such as, for example, an α-halo

acyl halide, in the presence of a base and in a suitable solvent or solvent mixtures to give an amide VI.

The α-halo acyl halide V includes α-alkyl or aryl substituted or unsubstituted α-halo acyl halide with the latter preferred. The most preferred α-halo acyl halide is α-chloroacetyl chloride. The base used in the reaction includes, but is not limited to, aromatic and aliphatic organic amines with the latter preferred. The most preferred base is triethylamine. Suitable solvent(s) include aprotic solvents such as hydrocarbons, halogenated hydrocarbons, ethers, esters and the like, or mixtures thereof, with halogenated hydrocarbons such as dichloromethane preferred. Alternatively, the reaction can be carried out using an α-substituted acid instead of the α-substituted acyl derivative and then employing a coupling reagent such as a water-soluble diimide like carbodiimide, haloformate, thionyl halide, *etc.* In either reaction, a sulfonate, for example, RSO_2O- (where R is an alkyl, aryl or heteroaryl), CF_3SO_2O- and the like, may be substituted for the halogen in the α-position of the α-halo acyl halide or the α-halo acid reactants which are illustrated.

Step (d) concerns reacting the amide VI obtained in step (c) with a dehydrating reagent in a suitable solvent or solvent mixtures to give the cyclized 2-oxazolylalkyl derivative VII such as, for example, the 2-oxazolylalkyl halide.

Advantageously, the reaction is carried out using (methoxycarbonylsulfamoyl)-triethylammonium hydroxide (Burgess' reagent) as the dehydrating reagent. Suitable solvent(s) include hydrocarbons, halogenated hydrocarbons, ethers and the like, or mixtures thereof. Most preferred is the use of the Burgess' reagent in tetrahydrofuran. Suitable dehydrating reagents also include, but are not limited to, other bases, acids, acid anhydrides and the like, such as, *e.g.*, concentrated sulfuric acid, polyphosphoric acid, *etc.* Although less conveniently, the dehydrating reagent, for instance, can be trihalophosphorus oxide such as tribromophosphorus oxide or trichlorophosphorus oxide, alone or with a solvent like toluene.

Step (e) is directed to reacting the 2-oxazolylalkyl derivative VII obtained in step (d) with a sulfur-containing reagent VIII or VIII' in a suitable solvent or solvent mixtures to give 2-oxazolylalkyl sulfide IX, a new key intermediate compound.

The sulfur-containing reagent includes N-substituted or unsubstituted thioureas, thio acids or salts such as thioacetic acid or its salt, xanthic acids or salts such as ethylxanthic acid potassium salt. Unsubstituted thiourea is preferred. Suitable solvent(s) include hydrocarbons, halogenated hydrocarbons, ethers, esters, amides, alcohols and the like, or mixtures thereof, with alcohol such as methanol or ethanol preferred.

Step (f) concerns reacting the 2-oxazolylalkyl sulfide IX obtained in step (e) with a 5-halo-2-aminothiazole X in the presence of a base and in a suitable solvent or solvent mixtures to give 5-(2-oxazolylalkylthio)-2-aminothiazole XI.

The 5-halo-2-aminothiazole includes 4-N-substituted or unsubstituted 5-halo-2-aminothiazoles with 5-bromo-2-aminothiazole preferred. A suitable base includes, but is not limited to, metal hydroxide, metal alkoxides, metal carbonates and aqueous amines such as ammonium hydroxide. Sodium hydroxide is preferred. Suitable solvent(s) include solvents such as hydrocarbons, halogenated hydrocarbons, ethers, esters, amides, alcohols and the like, or mixtures thereof, with halogenated hydrocarbons such as dichloromethane preferred.

Step (g) involves reacting the 5-(2-oxazolylalkylthio)-2-aminothiazole XI obtained in step (f) with an azacycloalkanoic acid derivative XII in the presence of a coupling reagent in a suitable solvent or solvent mixtures to give thiazolyl amide XIII.

The azacycloalkanoic acid derivative includes N-protected derivatives, for example, N-protected isonipecotic acid or N-protected nipecotic acid. The preferred nitrogen-protecting groups are Boc, Cbz, silicon derivatives and the like with Boc being the most preferred. The coupling reagent includes, but is not limited to, water-soluble carbodiimides, haloformates and the like, with carbodiimides such as alkylcarbodiimides being preferred. Suitable solvent(s) include solvents such as hydrocarbons, halogenated hydrocarbons, ethers, esters, amides, *etc.*, or mixtures thereof, with halogenated hydrocarbons such as dichloromethane preferred.

Step (h) is directed to reacting the thiazolyl amide XIII obtained in step (g) with a deprotecting reagent in a suitable solvent or solvent mixtures to give a desired 5-(2-oxazolylalkylthio)-2-azacycloalkanoylaminothiazole XIV (where R^{11} is hydrogen).

The choice of the deprotecting reagent is based on the nature of the protecting group (P). For the Boc protecting group, the preferred deprotecting reagent is an acid such as hydrochloric acid or trifluoroacetic acid and suitable solvent(s) for such deprotecting reaction include solvents such as hydrocarbons, halogenated hydrocarbons, ethers, esters, amides and the like, or mixtures thereof, with halogenated hydrocarbons such as dichloromethane preferred.

A more detailed synthesis of compounds of formula I is shown in Schemes 1-5 below. The starting compounds are commercially available or may be prepared by methods known to one of ordinary skill in the art. In Schemes 1-5 below, the following terms apply:

L is a suitable leaving group, such as halogen or sulfonate (*e.g.*, Br, Cl, I, $R^6SO_2O^-$, $CF_3SO_2O^-$, wherein R^6 is alkyl, cycloalkyl, heteroaryl, or aryl);

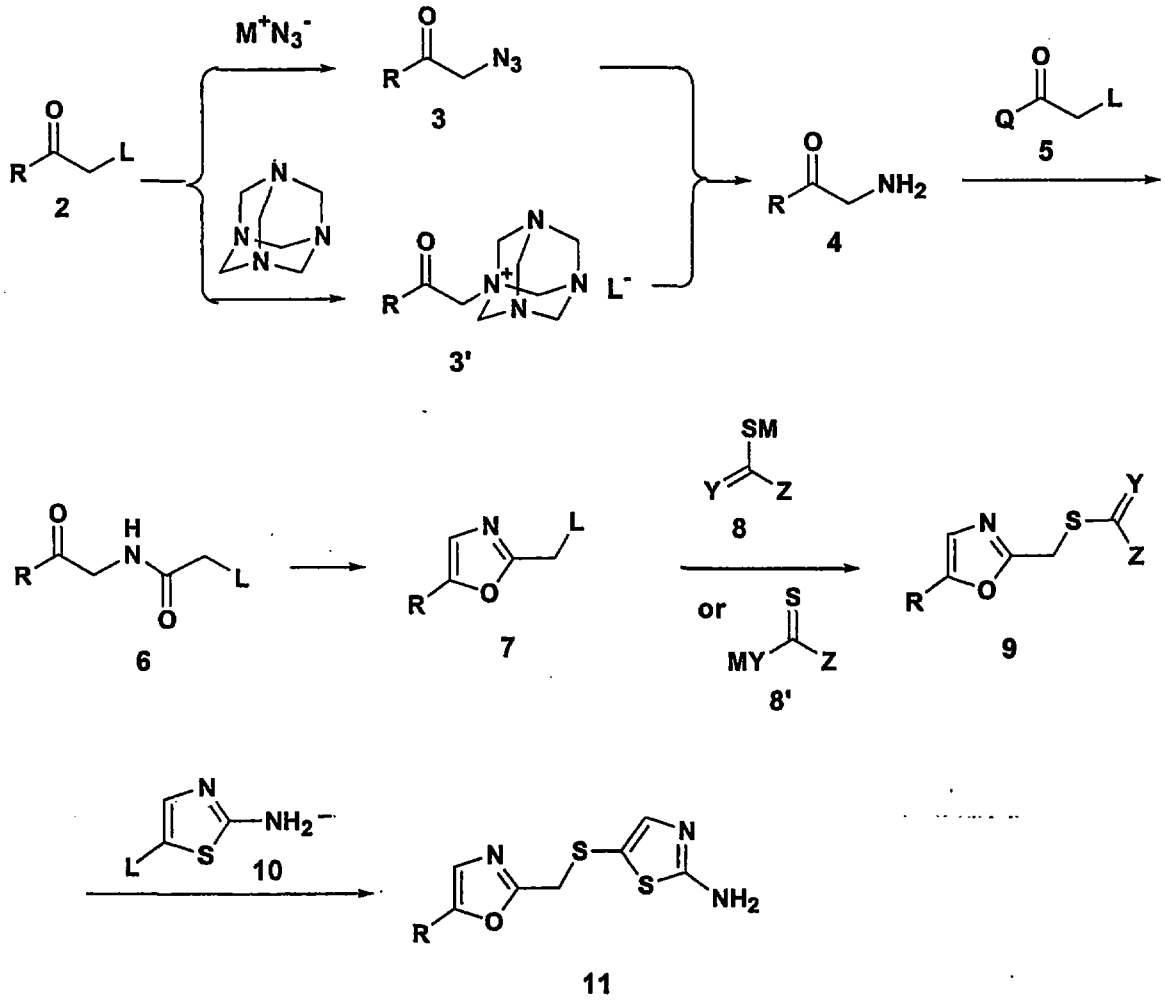
M is hydrogen, Li, Na, K, Cs, or a quaternary ammonium ion, *e.g.*, $(R^6)_4N$ or quaternary ammonium ions comprising cyclic alkenetetramines, such as hexamethylenetetramine;

Q is hydroxy, halogen or acyloxy (R^6COO^-, R^6OCOO^-, *etc.*);

Y is O, S, NH, N-alkyl, N-aryl or N-acyl; and

Z is hydrogen, alkyl, aryl, O-alkyl, O-aryl, S-alkyl, S-aryl, NH_2, N-alkyl, N-aryl or N-acyl. Scheme 1 sets forth a synthesis of compounds of formula **11**.

Scheme 1: Synthesis of Compounds of Formula **11**



First, step (a) involves reacting a suitable α-substituted ketone **2**, such as an α-halo ketone, with an azide in a suitable solvent or solvent mixtures to give an α-azido ketone **3**; or, more desirably, (a') reacting ketone **2** with a cyclic alkylenetetramine, such as

hexamethylenetetramine in a suitable solvent or solvent mixtures to give quaternary ammonium salt **3'**.

Suitable α-halo ketones **2** include α-halo aliphatic and α-halo aromatic ketones. The preferred α-halo ketones are α-halo pinacolones with α-bromo pinacolone most preferred. A sulfonate, for example, $R^6SO_2O^-$ (where, as defined above, R^6 is alkyl, cycloalkyl, heteroaryl, or aryl), $CF_3SO_2O^-$ and the like, can be substituted for the halogen (as group L) in the α-position. The azides include both metal azides and quaternary ammonium azides. The metal azides are preferred, with sodium azide most preferred. Suitable solvent(s) include hydrocarbons, ethers, amides, such as dimethylformamide, ketones, *etc.*, or mixtures thereof, with ketones such as acetone preferred for both reactions (a) and (a').

Step (b) involves reacting the α-azido ketone **3** obtained in step (a) with a reducing reagent in a suitable solvent or solvent mixtures to give an α-amino ketone **4**, or, more desirably, (b') reacting the quaternary ammonium salt **3'** obtained in step (a') with an acid in a suitable solvent or solvent mixtures to give an α-amino ketone **4**.

The reducing reagent in reaction (b) includes hydrogen in the presence of a transition metal catalyst such as palladium, trialkyl- or triarylphosphines, such as triphenylphosphine. Hydrogen in the presence of a transition-metal catalyst is preferred with hydrogen and palladium over activated carbon most preferred. Suitable solvent(s) in reaction (b) include hydrocarbons, ethers, alcohols and the like, or mixtures thereof, with alcohols, such as methanol preferred. Alternatively, the reduction reaction can be carried out in the presence of an acidic medium such as, hydrochloric acid in ethanol to give an α-amino ketone acid salt which can be isolated as the acid salt or free amine forms.

Suitable acids for use in reaction (b') include, but are not limited to, HCl, HBr, HI, H_2SO_4, H_3PO_4, *etc.*, with HCl preferred. Suitable solvent(s) in reaction (b') include hydrocarbons, ethers, alcohols and the like, or mixtures thereof, with alcohols, such as ethanol preferred. The α-amino ketone product can be isolated as the salt or free-base forms.

Step (c) comprises reacting (acylating) the α-amino ketone **4** or its acid salt obtained in step (b) or (b') with an α-substituted acyl derivative **5**, such as an α-halo acyl halide (i.e., Q and L = halo), in the presence of a base and in a suitable solvent or solvent mixtures to give an amide **6**.

The α-halo acyl halide **5** includes alkyl or aryl-α-halo acyl halides (substituted or unsubstituted), with the latter preferred. The most preferred α-halo acyl halide is α-chloroacetyl chloride. The base used in the reaction includes, but is not limited to, aromatic and aliphatic organic amines, with the latter preferred. The most preferred base is triethylamine. Suitable solvent(s) include aprotic solvents such as hydrocarbons,

halogenated hydrocarbons, ethers, esters and the like, or mixtures thereof, with halogenated hydrocarbons such as dichloromethane preferred. Alternatively, the reaction can be carried out using an α-substituted acid (Q = OH) instead of the α-substituted acyl derivative and then employing a coupling reagent, such as a water-soluble diimide (*e.g.*, carbodiimide), a haloformate, a thionyl halide, *etc.* In either reaction, a sulfonate, for example, $R^6SO_2O^-$ (where R^6 is an alkyl, cycloallkyl, aryl or heteroaryl), $CF_3SO_2O^-$ can be substituted for the halogen in the α-position (*i.e.*, at group L) of compounds **5**.

Step (d) involves reacting the amide **6** obtained in step (c) with a dehydrating reagent in a suitable solvent or solvent mixtures to give the cyclized 2-oxazolylalkyl derivative **7**, for example, the 2-oxazolylalkyl halide (*i.e.*, L is halo).

Advantageously, the reaction is carried out using (methoxycarbonylsulfamoyl)-triethylammonium hydroxide (Burgess' reagent) as the dehydrating reagent. Suitable solvent(s) include hydrocarbons, halogenated hydrocarbons, ethers and the like, or mixtures thereof. Most preferred is the use of the Burgess' reagent in tetrahydrofuran. Suitable dehydrating reagents also include, but are not limited to, other bases, acids, acid anhydrides and the like, such as concentrated sulfuric acid, polyphosphoric acid, *etc.* Less conveniently, the dehydrating can be a trihalophosphorus oxide, such as tribromophosphorus oxide or trichlorophosphorus oxide, alone or with a solvent like toluene.

Step (e) comprises reacting the 2-oxazolylalkyl derivative **7** obtained in step (d) with a sulfur-containing reagent **8** or **8'** in a suitable solvent or solvent mixtures to give 2-oxazolylalkyl sulfide **9**.

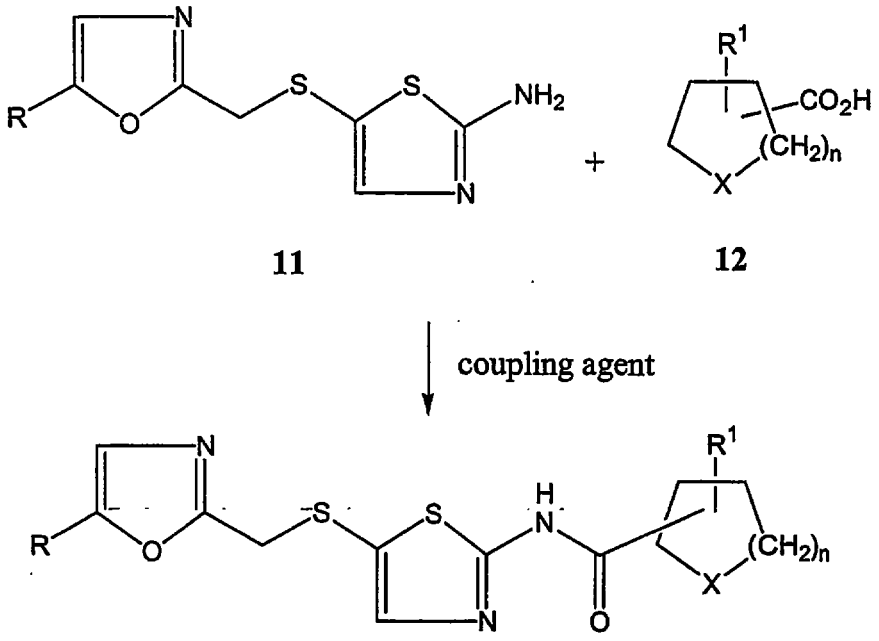
The sulfur-containing reagent includes N-substituted or unsubstituted thioureas, thio acids or salts such as thioacetic acid or its salt, xanthic acids or salts such as ethylxanthic acid potassium salt. Unsubstituted thiourea is preferred. Suitable solvent(s) include hydrocarbons, halogenated hydrocarbons, ethers, esters, amides, alcohols and the like, or mixtures thereof, with alcohols such as methanol or ethanol preferred.

Step (f) illustrates reacting the 2-oxazolylalkyl sulfide **9** obtained in step (e) with a 2-aminothiazole **10** (preferably L is halo) in the presence of a base and in a suitable solvent or solvent mixtures to give 5-(2-oxazolylalkylthio)-2-aminothiazole **11**.

The 2-aminothiazole **10** includes 4-*N*-substituted or unsubstituted 5-halo-2-aminothiazoles with 5-bromo-2-aminothiazole preferred. A suitable base includes, but is not limited to, metal hydroxides, metal alkoxides, metal carbonates and aqueous amines, such as ammonium hydroxide. Sodium hydroxide is preferred. Suitable solvent(s) include hydrocarbons, halogenated hydrocarbons, ethers, esters, amides, alcohols and the like, or mixtures thereof, with halogenated hydrocarbons such as dichloromethane preferred.

Scheme 2 sets forth a general synthesis of compounds of formula I via reaction of amine **11** with a carboxylic acid of formula **12** in the presence of a coupling agent. Suitable coupling reagents include, but are not limited to, water-soluble carbodiimides, haloformates and the like, with carbodiimides such as alkylcarbodiimides being preferred, for example, the combination of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and a base.

Scheme 2

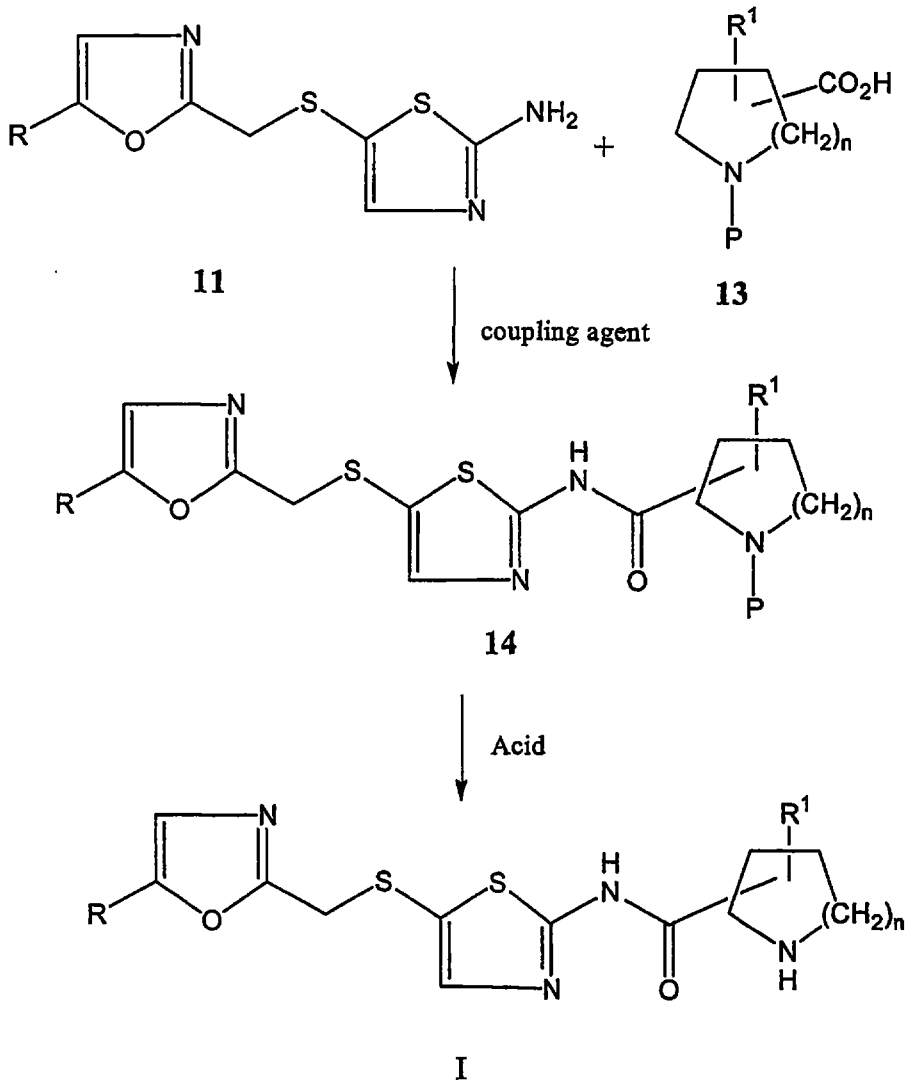


11 **12**

(I)

Scheme 3 below illustrates the synthesis of compounds of formula I, wherein X is NR^2 and R^2 is H. First, an amine of formula **11** is reacted with a N-protected carboxylic acid of formula **13** in the presence of a coupling agent to form an N-protected compound of formula **14**. Then compound **14** is deprotected to give compounds of formula I. Suitable coupling reagents include, but are not limited to, water-soluble carbodiimides, haloformates and the like, with carbodiimides such as alkylcarbodiimides being preferred, for example, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and a base.

Scheme 3

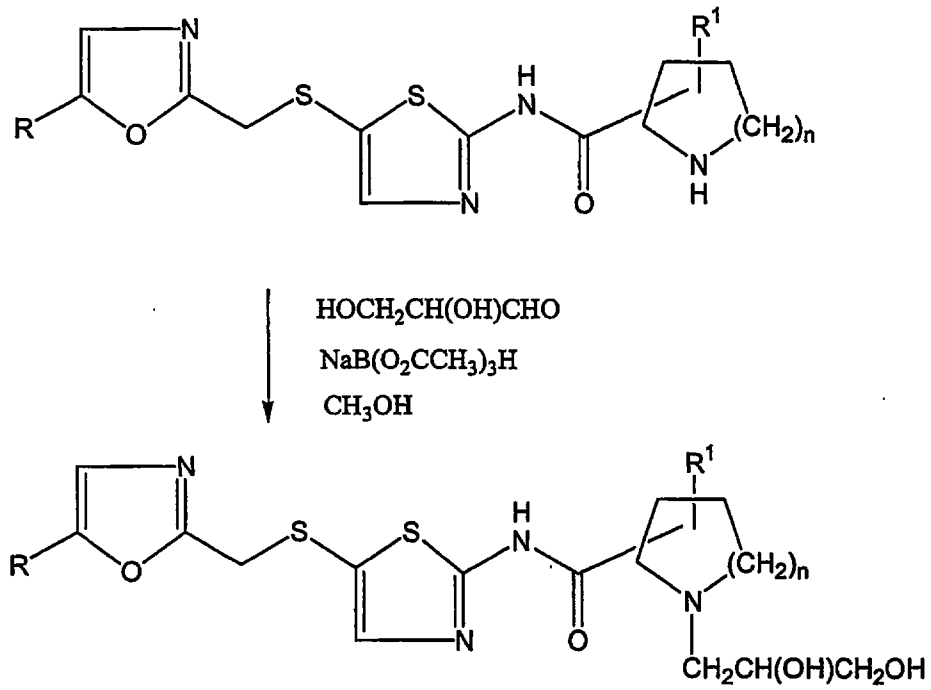


In the Scheme above, P is a nitrogen-protecting group (for example, Boc, Cbz, R_3Si, *etc.*). When a functional group is termed "protected," this means that the group is in modified form to preclude undesired side reactions at the protected site. Suitable protecting groups for the compounds involved in the present processes will be recognized from the specification taking into account the level of skill in the art, and with reference to standard textbooks such as Greene, T.W., *Protective Groups in Organic Synthesis*, 3rd edition (1999), incorporated herein by reference. The preferred nitrogen-protecting groups are Boc, Cbz, silicon derivatives, with Boc being the most preferred. Suitable solvent(s) include hydrocarbons, halogenated hydrocarbons, ethers, esters, amides, *etc.*, or mixtures thereof, with halogenated hydrocarbons such as dichloromethane preferred. The choice of the

deprotecting reagent is based on the nature of the protecting group (P). For the Boc protecting group, the preferred deprotecting reagent is an acid such as hydrochloric acid or trifluoroacetic acid and suitable solvent(s) for such deprotecting reaction include solvents such as hydrocarbons, halogenated hydrocarbons, ethers, esters, amides and the like, or mixtures thereof, with halogenated hydrocarbons such as dichloromethane preferred.

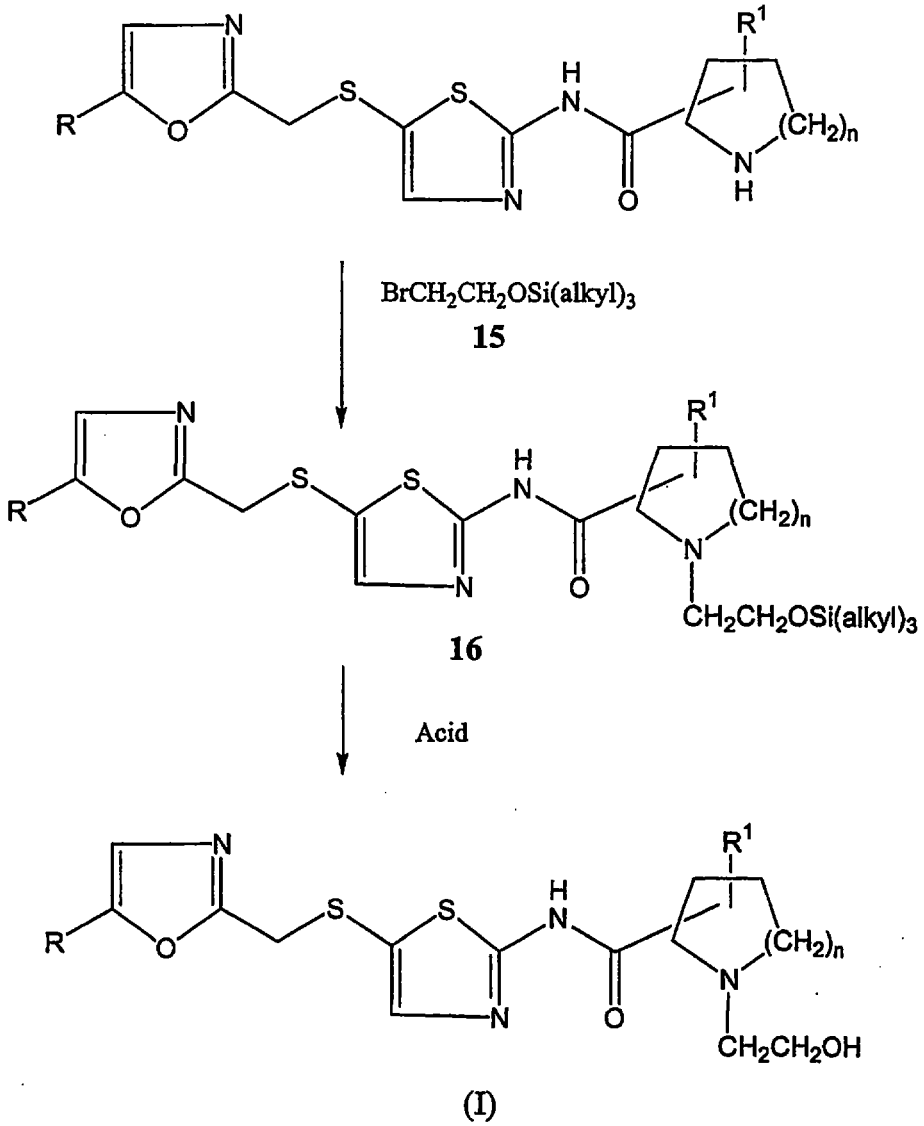
Scheme 4 below illustrates the synthesis of compounds of formula I, wherein X is NR^2 and R^2 is 2,3-dihydroxypropyl, by reacting a compound of formula I wherein X is NR^2 and R^2 is hydrogen with glyceraldehyde in the presence of a reducing agent such as sodium triacetoxyborohydride and an alcohol such as methanol.

Scheme 4



Scheme 5 below illustrates the synthesis of compounds of formula I, wherein X is NR^2 and R^2 is 2-hydroxyethyl, by reacting a compound of formula I wherein X is NR^2 and R^2 is hydrogen with a 2-(bromoethoxy)trialkylsilane of formula **15** to give intermediate **16**, and deprotecting intermediate **16** with an acid such as hydrogen fluoride.

Scheme 5



Preferred compounds of formula I are those wherein:

R is alkyl;

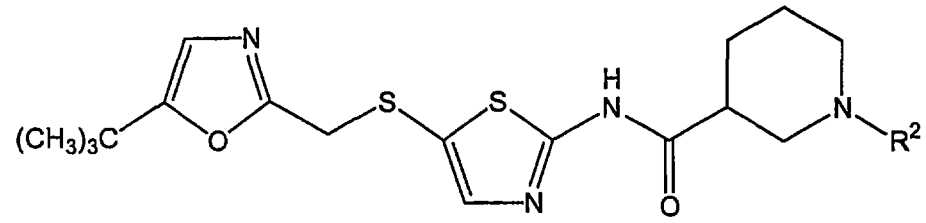
R^1 is hydrogen;

X is NR^2 or $CHNR^2R^3$; and

R^2 and R^3 are independently hydrogen, alkyl, substituted alkyl or cycloalkyl; and

n is 2.

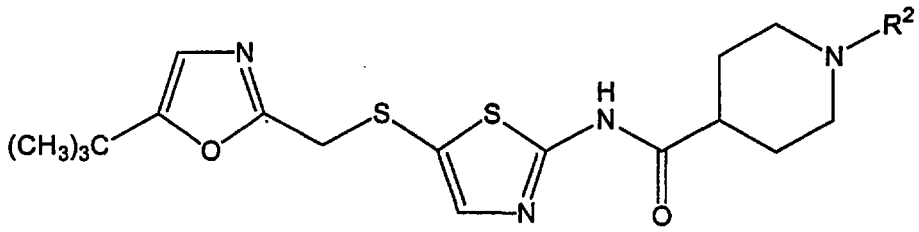
A first group of more preferred compounds of the present invention are those of formula Ia:



(Ia)

and enantiomers, diastereomers, solvates, and pharmaceutically acceptable salts thereof wherein R^2 is hydrogen, alkyl, substituted alkyl, or cycloalkyl.

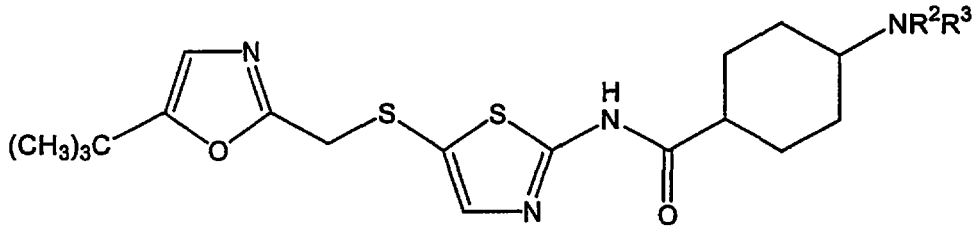
A second group of more preferred compounds of this invention are those of formula Ib:



(Ib)

and enantiomers, diastereomers, solvates, and pharmaceutically acceptable salts thereof wherein R^2 is hydrogen, alkyl, substituted alkyl, or cycloalkyl.

A third group of more preferred compounds of the present invention are those of formula Ic:



(Ic)

and enantiomers, diastereomers, solvates, and pharmaceutically acceptable salts thereof wherein R^2 and R^3 are each independently hydrogen, alkyl, substituted alkyl, or cycloalkyl.

In another embodiment, compounds of formula I include, but are not limited, to those listed in Table 1 below and enantiomers, diastereomers, solvates, and pharmaceutically acceptable salts thereof.

Table 1: Compounds of the Invention

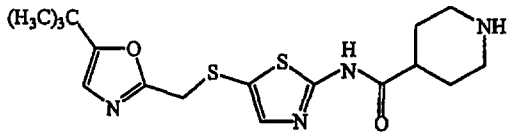
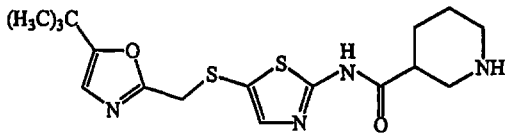
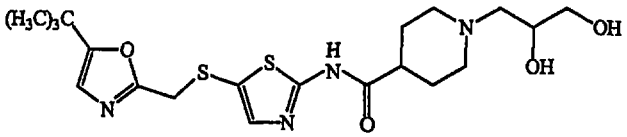
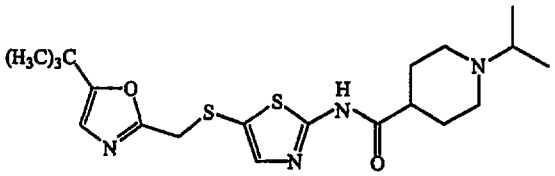
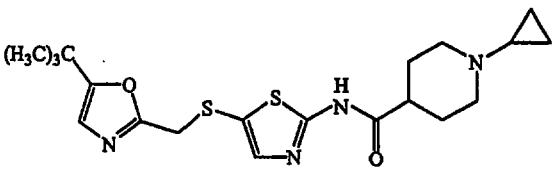
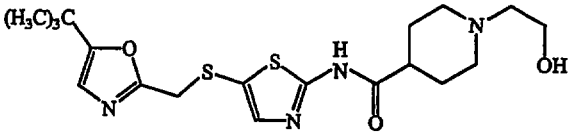
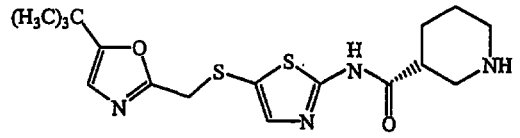
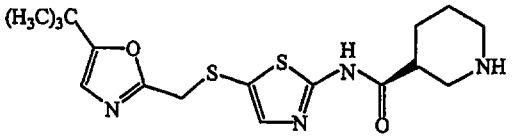
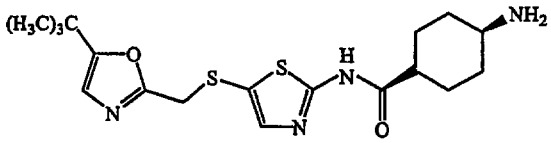
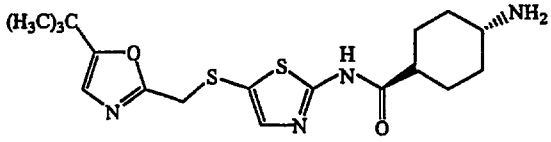
Name	Structure
N-[5-[[[5-(1,1-dimethylethyl)-2-oxazolyl]methyl]thio]-2-thiazolyl]-4-piperidinecarboxamide	
(±)-*N*-[5-[[[5-(1,1-dimethylethyl)-2-oxazolyl]methyl]thio]-2-thiazolyl]-3-piperidinecarboxamide	
(±)-1-(2,3-dihydroxypropyl)-*N*-[5-[[[5-(1,1-dimethylethyl)-2-oxazolyl]methyl]thio]-2-thiazolyl]-4-piperidinecarboxamide	
N-[5-[[[5-(1,1-dimethylethyl)-2-oxazolyl]methyl]thio]-2-thiazolyl]-1-(1-methylethyl)-4-piperidinecarboxamide	
1-cyclopropyl-*N*-[5-[[[5-(1,1-dimethylethyl)-2-oxazolyl]methyl]thio]-2-thiazolyl]-4-piperidinecarboxamide	
N-[5-[[[5-(1,1-dimethylethyl)-2-oxazolyl]methyl]thio]-2-thiazolyl]-1-(2-hydroxyethyl)-4-piperidinecarboxamide	

Table 1: (Cont.)

Name	Structure
(R)-*N*-[5-[[[5-(1,1-dimethylethyl)-2-oxazolyl]methyl]thio]-2-thiazolyl]-3-piperidinecarboxamide	
(S)-*N*-[5-[[[5-(1,1-dimethylethyl)-2-oxazolyl]methyl]thio]-2-thiazolyl]-3-piperidinecarboxamide	
cis-4-amino-*N*-[5-[[[5-(1,1-dimethylethyl)-2-oxazolyl]methyl]thio]-2-thiazolyl]cyclohexylcarboxamide	
trans-4-amino-*N*-[5-[[[5-(1,1-dimethylethyl)-2-oxazolyl]methyl]thio]-2-thiazolyl]cyclohexylcarboxamide	

Preferred salts of the above compounds are the hydrochloride, the hydrobromide, the dihydrochloride, the sulfate, the trifluoroacetate, the tartrate, the fumarate, the succinate, the maleate, the citrate, the methanesulfonate, the bromate, and the iodate salts or mixtures thereof.

The present invention also includes methods based upon the pharmacological properties of the compounds of the invention. The compounds according to the invention have pharmacological properties; in particular, the compounds of formula I are inhibitors of protein kinases such as the cyclin dependent kinases (cdks), for example, cdc2 (cdk1), cdk2, cdk3, cdk4, cdk5, cdk6, cdk7 and cdk8. Thus, the invention encompasses the use of compounds of the invention in the treatment, prevention, and/or management of cancer, inflammation or inflammatory disease, arthritis, Alzheimer's disease and cardiovascular disease. The invention also encompasses, in a more specific embodiment, the use of compounds of the invention to treat, prevent, and/or manage proliferative diseases or symptoms thereof. The invention also encompasses use of compounds of the invention in the treatment or prevention of topical and systemic fungal infections.

More specifically, the compounds of formula I are useful in the treatment of a variety of cancers, including (but not limited to) the following:

-carcinoma, including that of the bladder, breast, colon, kidney, liver, lung, ovary, pancreas, stomach, cervix, thyroid, prostate, and skin;

-hematopoietic tumors of lymphoid lineage, including acute lymphocytic leukemia, B-cell lymphoma, and Burkett's lymphoma;

-hematopoietic tumors of myeloid lineage, including acute and chronic myelogenous leukemias and promyelocytic leukemia;

-tumors of mesenchymal origin, including fibrosarcoma and rhabdomyosarcoma; and

-other tumors, including melanoma, seminoma, teratocarcinoma, osteosarcoma, neuroblastoma and glioma.

Without being limited by any theory, due to the key role of cdks in the regulation of cellular proliferation in general, inhibitors could act as reversible cytostatic agents which may be useful in the treatment of any disease process which features abnormal cellular proliferation, e.g., neuro-fibromatosis, atherosclerosis, pulmonary fibrosis, arthritis, psoriasis, glomerulonephritis, restenosis following angioplasty or vascular surgery, hypertrophic scar formation, inflammatory bowel disease, transplantation rejection, angiogenesis, and endotoxic shock.

The invention also encompasses use of compounds of the invention in the treatment of Alzheimer's disease, as suggested by the recent finding that cdk5 is involved in the phosphorylation of tau protein (*J. Biochem*, 117, 741-749 (1995)).

The invention also encompasses use of compounds of the invention as inhibitors of other protein kinases, e.g., protein kinase C, her2, raf1, MEK1, MAP kinase, EGF receptor, PDGF receptor, IGF receptor, PI3 kinase, wee1 kinase, Src, Abl, VEGF, and lck, and thus be effective in the treatment of diseases associated with other protein kinases.

The invention also encompasses use of compounds of the invention to induce or inhibit apoptosis, a physiological cell death process critical for normal development and homeostasis. Alterations of apoptotic pathways contribute to the pathogenesis of a variety of human diseases. Compounds of formula I, as modulators of apoptosis, will be useful in the treatment of a variety of human diseases with abberations in apoptosis including cancer (particularly, but not limited to, follicular lymphomas, carcinomas with p53 mutations, hormone dependent tumors of the breast, prostate and ovary, and precancerous lesions such as familial adenomatous polyposis), viral infections (including, but not limited to, herpesvirus, poxvirus, Epstein-Barr virus, Sindbis virus and adenovirus), autoimmune diseases (including, but not limited to, systemic lupus, erythematosus, immune mediated

glomerulonephritis, rheumatoid arthritis, psoriasis, inflammatory bowel diseases, and autoimmune diabetes mellitus), neurodegenerative disorders (including, but not limited to, Alzheimer's disease, AIDS-related dementia, Parkinson's disease, amyotrophic lateral sclerosis, retinitis pigmentosa, spinal muscular atrophy and cerebellar degeneration), AIDS, myelodysplastic syndromes, aplastic anemia, ischemic injury associated myocardial infarctions, stroke and reperfusion injury, arrhythmia, atherosclerosis, toxin-induced or alcohol induced liver diseases, hematological diseases (including, but not limited to, chronic anemia and aplastic anemia), degenerative diseases of the musculoskeletal system (including, but not limited to, osteoporosis and arthritis), aspirin-sensitive rhinosinusitis, cystic fibrosis, multiple sclerosis, kidney diseases, and cancer pain.

In another embodiment, the invention encompasses a method of inhibiting cdk in a cell. In particular, the invention encompasses treatment or prevention of diseases associated with cdk modulation by administering one or more compounds of the invention to a mammal in need thereof.

The invention encompasses treatment of mammals, particularly humans.

In addition, compounds of the invention can be used for treating chemotherapy-induced alopecia, chemotherapy-induced thrombocytopenia, chemotherapy-induced leukopenia or mucocitis. In the treatment of chemotherapy-induced alopecia, the compounds of the invention are preferably topically applied in the form of a medicament such as a gel, solution, dispersion or paste.

The compounds of this invention may be used in combination (before, during, after, including cycling administration) with known anti-cancer treatments such as radiation therapy or with cytostatic and cytotoxic agents including, but not limited to, microtuble-stabilizing agents, microtuble-disruptor agents, alkylating agents, anti-metabolites, epidophyllotoxin, an antineoplastic enzyme, a topoisomerase inhibitor, procarbazine, mitoxantrone, platinum coordination complexes, biological response modifiers, growth inhibitors, hormonal/anti-hormonal therapeutic agents, haematopoietic growth factors, and the like.

Classes of anti-cancer agents which may be used in combination with the formula I compounds of this invention include, but are not limited to, the anthracycline family of drugs, the vinca drugs, the mitomycins, the bleomycins, the cytotoxic nucleosides, the taxanes, the epothilones, discodermolide, the pteridine family of drugs, diynenes, aromatase inhibitors, and the podophyllotoxins. Particular members of those classes include, for example, paclitaxel, docetaxel, 7-O-methylthiomethylpaclitaxel (disclosed in U.S. 5,646,176), 3'-*tert*-butyl-3'-*N*-*tert*-butyloxycarbonyl-4-deacetyl-3'-dephenyl-3'-*N*-debenzoyl-4-O-methoxycarbonyl-paclitaxel (disclosed in USSN 60/179,965) filed on

February 3, 2000 which is incorporated herein by reference thereto), C-4 methyl carbonate paclitaxel (disclosed in WO 94/14787), epothilone A, epothilone B, epothilone C, epothilone D, desoxyepothilone A, desoxyepothilone B, [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*, 16S*]]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4-aza-17-oxabicyclo[14.1.0]heptadecane-5,9-dione (disclosed in WO 99/02514), [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-3-[2-[2-(aminomethyl)-4-thiazolyl]-1-methylethenyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione (disclosed in USSN 09/506,481 filed on February 17, 2000 which is incorporated herein by reference thereto), doxorubicin, carminomycin, daunorubicin, aminopterin, methotrexate, methopterin, dichloro-methotrexate, mitomycin C, porfiromycin, 5-fluorouracil, 6-mercaptopurine, gemcitabine, cytosine arabinoside, podophyllotoxin or podophyllotoxin derivatives such as etoposide, etoposide phosphate or teniposide, melphalan, vinblastine, vincristine, leurosidine, vindesine, leurosine, and the like. Other useful anti-cancer agents which may be used in combination with the compounds of the present invention include, but are not limited to, estramustine, cisplatin, carboplatin, cyclophosphamide, bleomycin, tamoxifen, ifosamide, melphalan, hexamethyl melamine, thiotepa, cytarabin, idatrexate, trimetrexate, dacarbazine, L-asparaginase, camptothecin, CPT-11, topotecan, ara-C, bicalutamide, flutamide, leuprolide, pyridobenzoindole derivatives, interferons, interleukins, and the like. In addition, the compounds of this invention may be used in combination with inhibitors of farnesyl protein transferase such as those described in U.S. 6,011,029; anti-angiogenic agents such as angiostatin and endostatin; kinase inhibitors such as her2 specific antibodies; and modulators of p53 transactivation.

If formulated as a fixed dose, such combination products employ the compounds of this invention within the dosage range described below and the other pharmaceutically active agent within its approved dosage range. Compounds of formula I may be used sequentially, in any order, with known anti-cancer or cytotoxic agents when a combination formulation is inappropriate.

The present invention also provides pharmaceutical compositions which comprise a compound of this invention and a pharmaceutically acceptable carrier. It should be noted that, in the context of the pharmaceutical compositions of the present invention, the compounds of the invention, or compounds of formula I, refer to the free base, enantiomers, diastereomers, solvates, as well as pharmaceutically acceptable salts. Examples of such pharmaceutically acceptable salts include, but are not limited to, hydrochloride, dihydrochloride, sulfate, trifluoroacetate, mixture of trifluoroacetate and hydrochloride, tartrate, fumarate, succinate, maleate, citrate, methanesulfonate, bromate and iodate salts.

Also included are salts formed with other organic and inorganic acids such as hydroxymethane sulfonic acid, acetic acid, benzenesulfonic acid, toluenesulfonic acid and various others, e.g., nitrates, phosphates, borates, benzoates, ascorbates, salicylates, and the like. These salts include racemic forms as well as enantiomers and diastereomers (such as, for example, D-tartrate and L-tartrate salts). In addition, pharmaceutically acceptable salts of compounds of formula I may be formed with alkali metals such as sodium, potassium and lithium; alkaline earth metals such as calcium and magnesium; organic bases such as dicyclohexylamine, tributylamine, and pyridines, and the like; and amino acids such as arginine, lysine and the like.

The pharmaceutical compositions of the present invention may further comprise one or more pharmaceutically acceptable additional carriers, excipients, or diluents including, but not limited to, ingredient(s) such as alum, stabilizers, antimicrobial agents, buffers, coloring agents, flavoring agents, and the like. The compounds and compositions of this invention may be administered orally or parenterally including the intravenous, intramuscular, intraperitoneal, subcutaneous, rectal and topical routes of administration.

For oral use, the compounds and compositions of this invention may be administered, for example, in the form of tablets or capsules, or as solutions or suspensions. In the case of tablets for oral use, carriers which are commonly used include lactose and corn starch, and lubricating agents such as magnesium stearate are commonly added. For oral administration in capsule form, useful carriers include lactose and corn starch. When aqueous suspensions are used for oral administration, emulsifying and/or suspending agents are commonly added. In addition, sweetening and/or flavoring agents may be added to the oral compositions. For intramuscular, intraperitoneal, subcutaneous and intravenous use, sterile solutions of the active ingredient(s) are usually employed, and the pH of the solutions should be suitably adjusted and buffered. For intravenous use, the total concentration of the solute(s) should be controlled in order to render the preparation isotonic.

Daily dosages for human administration of the compounds of this invention will normally be determined by the prescribing physician with the dosages generally varying according to the age, weight, route of administration, and response of the individual patient, as well as the severity of the patient's symptoms. A formula I compound of this invention is preferably administered to humans in an amount from about 0.001 mg/kg of body weight to about 100 mg/kg of body weight per day, more preferably from about 0.01 mg/kg of body weight to about 50 mg/kg of body weight per day, and most preferably from about 0.1 mg/kg of body weight to about 20 mg/kg of body weight per day.

cdc2/cyclin B1 Kinase Assay

cdc2/cyclin B1 kinase activity was determined by monitoring the incorporation of ^{32}P into histone HI. The reaction consisted of 50 ng baculovirus expressed GST-cdc2, 75 ng baculovirus expressed GST-cyclin B1, 1 μg histone HI (Boehringer Mannheim), 0.2 μCi of ^{32}P γ-ATP and 25 μM ATP in kinase buffer (50 mM Tris, pH 8.0, 10 mM $MgCl_2$, 1 mM EGTA, 0.5 mM DTT). The reaction was incubated at 30 °C for 30 minutes and then stopped by the addition of cold trichloroacetic acid (TCA) to a final concentration of 15 % and incubated on ice for 20 minutes. The reaction was harvested onto GF/C unifilter plates (Packard) using a Packard Filtermate Universal harvester, and the filters were counted on a Packard TopCount 96-well liquid scintillation counter (Marshak, D.R., Vanderberg, M.T., Bae, Y.S., Yu, I.J., *J. of Cellular Biochemistry*, 45, 391-400 (1991), incorporated by reference herein).

cdk2/cyclin E Kinase Assay

cdk2/cyclin E kinase activity was determined by monitoring the incorporation of ^{32}P into the retinoblastoma protein. The reaction consisted of 2.5 ng baculovirus expressed GST-cdk2/cyclin E, 500 ng bacterially produced GST-retinoblastoma protein (aa 776-928), 0.2 μCi ^{32}P γ-ATP and 25 μM ATP in kinase buffer (50 mM Hepes, pH 8.0, 10 mM $MgCl_2$, 5 mM EGTA, 2 mM DTT). The reaction was incubated at 30 °C for 30 minutes and then stopped by the addition of cold trichloroacetic acid (TCA) to a final concentration of 15 % and incubated on ice for 20 minutes. The reaction was harvested onto GF/C unifilter plates (Packard) using a Packard Filtermate Universal harvester, and the filters were counted on a Packard TopCount 96-well liquid scintillation counter.

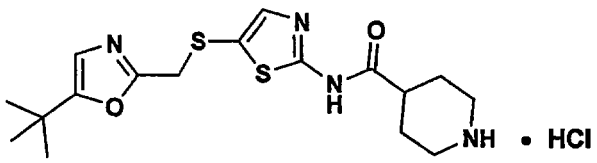
cdk 4/cyclin D1 Kinase Activity

cdk4/cyclin D1 kinase activity was determined by monitoring the incorporation of ^{32}P in to the retinoblastoma protein. The reaction consisted of 165 ng baculovirus expressed as GST-cdk4, 282 ng bacterially expressed as S-tag cyclin D1, 500 ng bacterially produced GST-retinoblastoma protein (aa 776-928), 0.2 μCi ^{32}P γ-ATP and 25 μM ATP in kinase buffer (50 mM Hepes, pH 8.0, 10 mM $MgCl_2$, 5 mM EGTA, 2 mM DTT). The reaction was incubated at 30 °C for 1 hour and then stopped by the addition of cold trichloroacetic acid (TCA) to a final concentration of 15 % and incubated on ice for 20 minutes. The reaction was harvested onto GF/C unifilter plates (Packard) using a Packard Filtermate Universal harvester, and the filters were counted on a Packard TopCount 96-well liquid scintillation counter (Coleman, K.G., Wautlet, B.S., Morissey, D, Mulheron, J.G., Sedman, S., Brinkley, P., Price, S., Webster, K.R. (1997) Identification of CDK4 Sequences involved

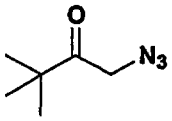
in cyclin D, and p16 binding. *J. Biol. Chem.* 272,30:18869-18874, incorporated by reference herein).

In order to facilitate a further understanding of the invention, the following examples are presented primarily for the purpose of illustrating specific compounds of the invention. The scope of the invention should not be deemed limited by the examples, but encompasses the entire subject matter defined in the claims.

EXAMPLE 1: Preparation of 5-[5-(t-Butyl)-2-oxazolylmethylthio]-2-(azacycloalkanoyl)amino-thiazole hydrochloride

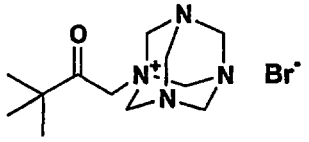


A. Preparation of α-Azido-pinacolone



α-Bromo-pinacolone (199.07 g, 1.1115 mol, 1 eq) was combined in 1.785 L of acetone with sodium azide (93.9 g, 1.4444 mol, 1.3 eq). The reaction was stirred at room temperature for 27.5 hours. The resulting slurry was filtered and washed with acetone (3 × 150 mL). The filtrate was concentrated *in vacuo* to provide 154.3 g (98.4%) of the title compound. HPLC 83.85% at 2.57 minutes (Phenomenex Inc., Torrance, CA, 5 μm C18 column 4.6 × 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm).

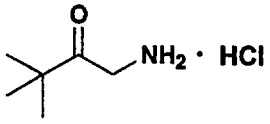
B. Preparation of α-Hexamethylenetetramino-pinacolone Bromide



α-Bromo-pinacolone (179 g, 1 mol, 1 eq) was combined in 2 L of acetone with hexamethylenetetramine (154.21 g, 1.1 mol, 1.1 eq) and the reaction stirred under N_2 at room temperature for 26 hours. The resulting slurry was filtered, the filter cake was washed

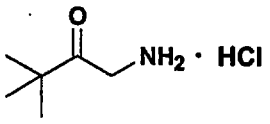
with ether (3 × 50 mL) and dried *in vacuo* at 50°C overnight to provide 330 g (100%) of the title compound containing 7% hexamethylenetetramine. HPLC R.T.=0.17 min (Phenomenex Inc., 5 µm C18 column 4.6 × 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm).

C. Preparation of α-Amino-pinacolone Hydrochloride



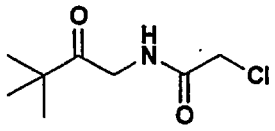
α-Azido-pinacolone (128.5 g, 0.911 mol) was combined in 4.2 L of methanol with 77.1 mL of concentrated HCl and 15.42 g of 10% Pd/C. The reaction mixture was stirred under hydrogen for 1.5 hours. The catalyst was removed by filtration. The solvent was distilled to give a wet solid. The residual water was azeotropically removed with isopropanol (2 × 500 mL). Tert-butyl methyl ether (300 mL) was added and the resulting slurry was stirred, filtered, washed with t-butyl methyl ether (3 × 100 mL) and dried to give 131.0 g (95.5%) of the title compound.

D. Preparation of α-Amino-pinacolone Hydrochloride



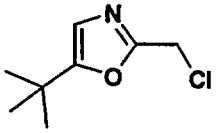
α-Hexamethylenetetramino-pinacolone bromide (400 g, 1.254 mol, 1 eq) was combined in 2 L of ethanol with 12 N aqueous HCl (439 mL, 5.26 mol, 4.2 eq). The reaction was stirred at 75°C for 1 hour and then allowed to cool to room temperature, the resulting slurry filtered, the filtrate concentrated *in vacuo* and isopropyl alcohol was added. The solution was filtered again. Addition of 1.2 L of ether caused the desired material to precipitate from solution. The material was filtered, washed with ether (2 × 300 mL), and dried *in vacuo* at 50°C overnight to provide 184.1 g (97%) of the title compound.

E. Preparation of α-N-(2-Chloroacetylamino)-pinacolone



The title compound of part D (130.96 g, 0.8637 mol, 1 eq) was dissolved in 3.025 L of CH_2Cl_2 under N_2 at -5°C. Triethylamine (301 mL, 2.16 mol, 2.5 eq) was added, followed by chloroacetyl chloride (75.7 mL, 0.450 mol, 1.1 eq) in 175 mL of CH_2Cl_2. The resulting slurry was stirred at -5 to -10°C for 2 hours. Water (1.575 L) was added, followed by 175 mL of concentrated HCl. The organic phase was washed a second time with 1.75 L of 10% aqueous HCl, and then with 500 mL of water. The organic phase was dried over Na_2SO_4 and concentrated *in vacuo* to provide 155.26 g (93.8%) of the title compound. HPLC R.T.=2.27 min (Phenomenex Inc., 5 μm C18 column 4.6 × 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm).

F. Preparation of 5-(t-Butyl)-2-Oxazolylmethyl Chloride

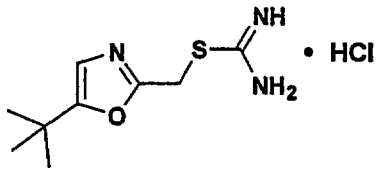


The title compound of part E (180.13 g, 0.9398 mol, 1 eq) was combined with phosphorus oxychloride (262 mL, 2.8109 mol, 3 eq) under N_2. The reaction was heated at 105°C for 1 hour, the mixture was cooled to room temperature, and quenched with 1.3 kg of ice. The aqueous phase was extracted with ethyl acetate (1 L, then 2 × 500 mL). The organic extracts were washed with saturated aqueous $NaHCO_3$ (4 × 1 L) which was back-extracted several times with ethyl acetate. The organic phases were combined, washed with saturated aqueous $NaHCO_3$ (500 mL) followed by saturated aqueous NaCl (300 mL), dried over $MgSO_4$, and concentrated *in vacuo* to give a brown oil. The crude material was distilled under high vacuum at 100°C to provide 155.92 g (96%) of the title compound. HPLC R.T.=3.62 min (Phenomenex Inc., 5 μm C18 column 4.6 × 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm).

Alternatively, the title compound of part E (10.0 g, 52.17 mmol, 1 eq.) in 50 mL of tetrahydrofuran (THF) was combined with (methoxycarbonylsulfamyl)-triethylammonium hydroxide (Burgess' reagent, 105.70 mmol, 2.03 eq., generated in situ from 9.2 mL of

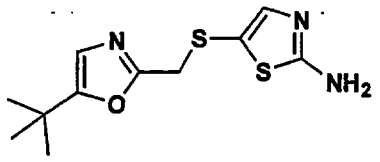
chlorosulfonyl isocyanate, 4.4 mL of methanol and 14.8 mL of triethylamine in 100 mL THF). The reaction was heated to 45°C for 1.5 hours. After cooling to room temperature, the reaction was quenched with water (50 mL). The organic layer was separated and washed with saturated $NaHCO_3$ (2 × 50 mL) and water (50 mL), dried over $MgSO_4$ and passed through a small silica gel plug. The solvent was removed to give an oil which was taken up in a mixture of 15 mL heptane and 90 mL of t-butyl methyl ether, and then washed with 0.2 N HCl (2 × 25 mL), saturated brine (25 mL) and dried ($MgSO_4$). Filtration and removal of solvent gave 10.9 g of the title compound.

G. Preparation of 5-(t-Butyl)-2-oxazolylmethyl Thiouronium Hydrochloride



The title compound of part F (1.77 g, 10.2 mmol, 1.02 eq) was combined with thiourea (0.76 g, 9.98 mmol, 1 eq) under N_2 in 10 mL of absolute ethanol. The reaction was heated at reflux for 1.5 hours. The mixture was cooled to room temperature and concentrated *in vacuo*. Trituration of the resulting crude material with t-butyl methyl ether provided 2.32 g (93%) of the title compound. HPLC R.T.=2.05 min (Phenomenex Inc., 5 µm C18 column 4.6 × 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm); ^{1}H NMR (d_6-DMSO): δ 9.48 (s, 3H), 6.85 (s, 1H), 4.73 (s, 2H), 1.24 (s, 9H).

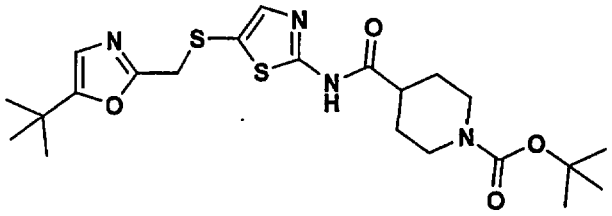
H. Preparation of 5-[5-(t-Butyl)-2-oxazolylmethylthio]-2-aminothiazole



The title compound of part G (1.25 g, 5 mmol, 1 eq) was added to a mixture of NaOH (3.0 g, 75 mmol, 15 eq), water (10 mL), toluene (10 mL) and tetrabutylammonium sulfate (50 mg, 0.086 mmol, 0.017 eq). 5-Bromo-2-aminothiazole hydrobromide (1.70 g, 5 mmol, 1 eq) was added and the reaction was stirred at room temperature for 14.5 hours. The

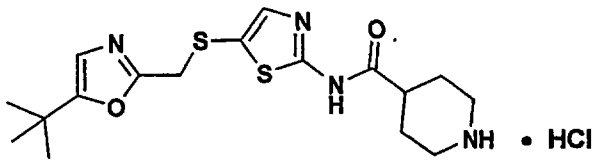
mixture was diluted with water and extracted twice with ethyl acetate, the organic extracts washed with water (4 × 10 mL), dried over $MgSO_4$ and concentrated *in vacuo* to provide 1.1 g (82%) of the title compound. HPLC 86.3% at 2.75 min (Phenomenex Inc., 5 μm C18 column 4.6 × 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm); ^1H NMR ($CDCl_3$): δ 6.97 (s, 1H), 6.59 (s, 1H), 5.40 (br s, 2H), 3.89 (s, 2H), 1.27 (s, 9H).

I. Preparation of 5-[5-(t-Butyl)-2-oxazolylmethylthio]-2-[(N-t-butoxycarbonyl)-azacycloalkanoyl]aminothiazole



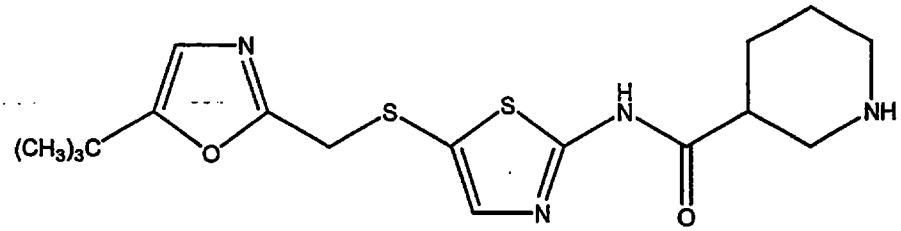
The title compound of part H (9.6 g, 35.6 mmol) was dissolved in N,N-dimethylformamide (36 mL) and CH_2Cl_2 (100 mL), to which was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (13.8 g, 72 mmol, 2 eq), N-t-butoxycarbonyl-azacycloalkanoic acid (12.6 g, 55 mmol, 1.5 eq), and 4-(dimethylamino)pyridine (2 g, 16 mmol, 0.45 eq). The clear reaction mixture became cloudy as it was stirred at room temperature for 3.5 hours. Water (300 mL) and ethyl acetate (200 mL) were added and the resulting precipitate was removed by filtration. The filtrate was extracted with ethyl acetate, the organic extracts dried over $MgSO_4$ and concentrated *in vacuo* to provide a yellow solid which was combined with the precipitate obtained by filtration. The solid was boiled in a mixture of ethanol, acetone and water for 20 minutes, filtered, washed with an ethanol/water mixture and dried to give 16.6 g (97%) of the title compound.

J. Preparation of 5-[5-(t-Butyl)-2-oxazolylmethylthio]-2-(azacycloalkanoyl)amino-thiazole hydrochloride

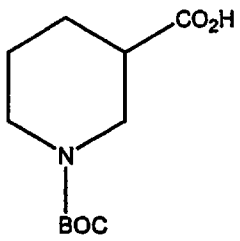


The title compound of part I (16.6 g) was dissolved in 150 mL of CH_2Cl_2, trifluoroacetic acid (30 mL) was added dropwise, and the mixture was stirred at room temperature for 2 hours. The reaction was concentrated *in vacuo*, diluted with water (300 mL), cooled in ice, made basic with sodium hydroxide, and the resulting solid filtered and recrystallized from ethanol, water and methanol to provide 11.2 g (83%) of the title compound as a yellow solid. The white solid hydrochloride could be obtained by addition of 18 mL of 1N aqueous HCl to 7 g of this material in methanol. MS: 381 $[M+H]^+$; HPLC: 100% at 3.12 min (YMC S5 ODS column 4.6 × 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm).

Example 2: Preparation of (±)-N-[5-[[[5-(1,1-Dimethylethyl)-2-oxazolyl]-methyl]thio]-2-thiazolyl]-3-piperidinecarboxamide



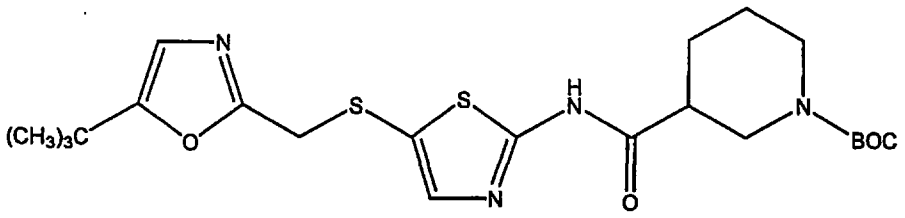
A. (±)-N-*t*-butoxycarbonyl-nipecotic acid



Nipecotic acid (1.3 g, 10 mmol, 1 eq) was combined with 10 mL of dioxane, 2 mL of acetonitrile, 10 mL of water, and 10 mL of 1N aqueous NaOH (1 eq). Di-*t*-butyl

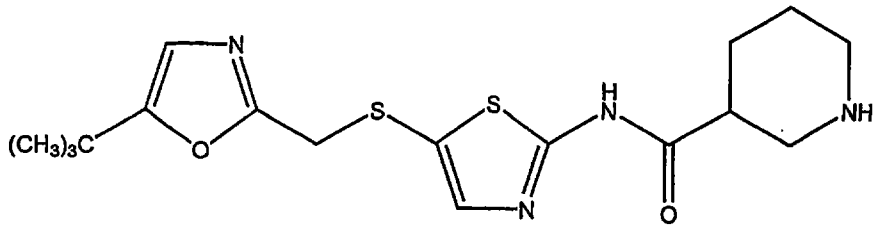
dicarbonate (3.3 g, 15 mmol, 1.5 eq) was added and the reaction mixture was stirred at rt overnight. The reaction mixture was concentrated *in vacuo* to remove organic solvent and 10 % aqueous citric acid was added The mixture was extracted with ethyl acetate (3 × 100 mL). The organic extracts were dried over Na_2SO_4, filtered through silica gel, and concentrated *in vacuo*. The crude material was recrystallized from ethyl acetate and hexanes to provide 2.2 g (96 %) of (±)-N-*t*-butoxycarbonyl-nipecotic acid as a white solid.

B. (±)-N-[5-[[[5-(1,1-Dimethylethyl)-2-oxazolyl]methyl]thio]-2-thiazolyl]-(N-*t*-butoxycarbonyl)-3-piperidinecarboxamide



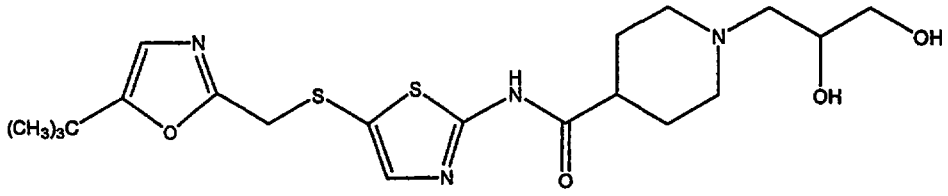
1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (383 mg, 2 mmol, 2 eq) was added to a mixture of 2-amino-5-[[[5-(1,1-dimethylethyl)-2-oxazolyl]methyl]thio]thiazole (270 mg, 1 mmol, 1 eq), N-*t*-butoxycarbonyl-nipecotic acid (344 mg, 1.5 mmol, 1.5 eq), 4-(dimethylamino)pyridine (61 mg, 0.5 mmol, 0.5 eq), N,N-dimethylformamide (1 mL) and CH_2Cl_2 (6 mL). The reaction mixture was stirred at rt for 1.3 h. Triethylamine (0.28 mL, 2 mmol, 2 eq) was added, and the reaction mixture was stirred for 1h. Additional N-*t*-butoxycarbonyl-nipecotic acid (340 mg), triethylamine (0.28 mL) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (380 mg) were added. After 1 h, no further change was observed. Additional 4-(dimethylamino)pyridine, N,N-dimethylformamide, triethylamine and starting acid were added and the reaction was stirred overnight at rt. The resulting black solution was diluted with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The organic extracts were dried, concentrated *in vacuo*, and purified by flash chromatography on silica gel eluting with a gradient of 50-100% ethyl acetate in hexanes to provide 397 mg (83 %) of (±)-N-[5-[[[5-(1,1-dimethylethyl)-2-oxazolyl]methyl]thio]-2-thiazolyl]-(N-*t*-butoxycarbonyl)-3-piperidinecarboxamide as a yellow glassy solid.

C. (±)-N-[5-[[[5-(1,1-Dimethylethyl)-2-oxazolyl]methyl]thio]-2-thiazolyl]-3-piperidinecarboxamide



(±)-N-[5-[[[5-(1,1-Dimethylethyl)-2-oxazolyl]methyl]thio]-2-thiazolyl]-(N-*t*-butoxycarbonyl)-3-piperidinecarboxamide (355 mg, 0.74 mmol, 1 eq) was dissolved in 3 mL of CH_2Cl_2. Trifluoroacetic acid (3 mL) was added, and the mixture was stirred at rt for 20 min. The reaction mixture was concentrated *in vacuo* and neutralized with saturated aqueous $NaHCO_3$. The resulting mixture was extracted with ethyl acetate. The organic extracts were dried over Na_2SO_4, concentrated *in vacuo*, and recrystallized from ethyl acetate to provide 142 mg (50 %) of (±)-N-[5-[[[5-(1,1-dimethylethyl)-2-oxazolyl]methyl]thio]-2-thiazolyl]-3-piperidinecarboxamide as a white solid. MS: 381 $[M+H]^+$; HPLC: 100 % at 3.15 min (YMC S5 ODS column 4.6 × 50 mm, 10-90 % aqueous methanol over 4 minutes containing 0.2 % phosphoric acid, 4 mL/min, monitoring at 220 nm).

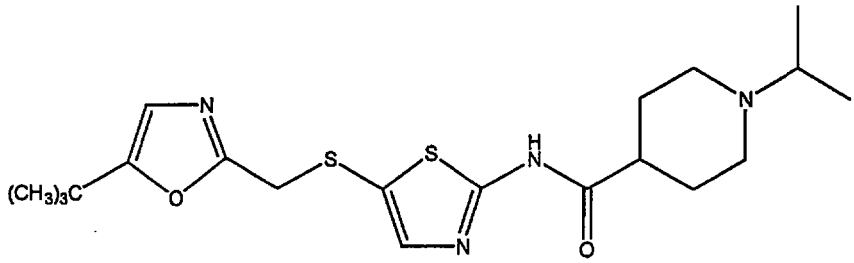
Example 3: Preparation of (±)-1-(2,3-Dihydroxypropyl)-N-[5-[[[5-(1,1-dimethylethyl)-2-oxazolyl]methyl]thio]-2-thiazolyl]-4-piperidinecarboxamide



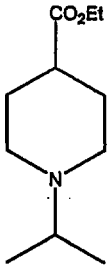
N-[5-[[[5-(1,1-Dimethylethyl)-2-oxazolyl]methyl]thio]-2-thiazolyl]-4-piperidinecarboxamide (66 mg, 0.17 mmol, 1 eq) was combined with glyceraldehyde (69 mg, 0.77 mmol, 4.5 eq), sodium triacetoxyborohydride (163 mg, 0.77 mmol, 4.5 eq) and 1,2-dichloroethane (4 mL). The resulting suspension was stirred at rt for 4 h. Methanol (1 mL) was added and the reaction mixture was stirred at rt overnight, concentrated *in vacuo* and purified by preparative HPLC to provide 69 mg (59 %) of (±)-1-(2,3-dihydroxypropyl)-N-[5-[[[5-(1,1-dimethylethyl)-2-oxazolyl]methyl]thio]-2-thiazolyl]-4-

piperidinecarboxamide as a white solid. MS: 455 $[M+H]^+$; HPLC: 100 % at 3.06 min (YMC S5 ODS column 4.6 × 50 mm, 10-90 % aqueous methanol over 4 minutes containing 0.2 % phosphoric acid, 4 mL/min, monitoring at 220 nm).

Example 4: Preparation of N-[5-[[[5-(1,1-Dimethylethyl)-2-oxazolyl]methyl]thio]-2-thiazolyl]-1-(1-methylethyl)-4-piperidinecarboxamide

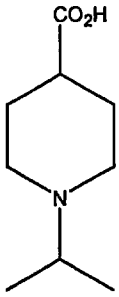


A. Ethyl-1-(1-methylethyl)-4-piperidine carboxylate



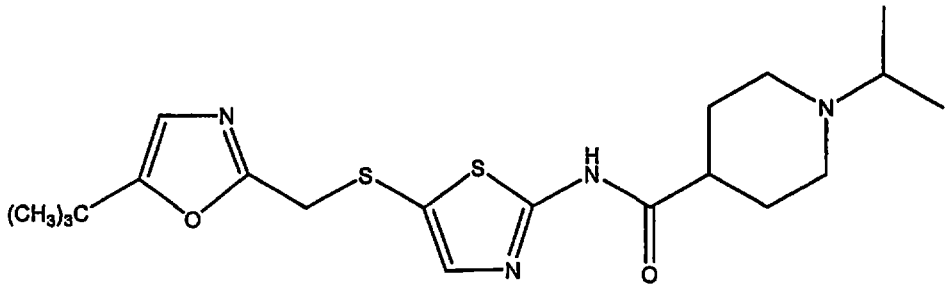
Ethyl isonipecotate (3.2 g, 20 mmol, 1 eq) was combined with acetone (5.8 g, 100 mmol, 5 eq), sodium triacetoxyborohydride (10.5 g, 50 mmol, 2.5 eq) and 1,2-dichloroethane (200 mL). The reaction mixture was stirred at rt for 72 h. Saturated aqueous $NaHCO_3$ was added, and the mixture was extracted with CH_2Cl_2. The organic extracts were dried, filtered through a silica gel pad, and concentrated *in vacuo* to provide 3.72 g (93 %) of ethyl 1-(1-methylethyl)-4-piperidine carboxylate as a colorless liquid.

B. 1-(1-Methylethyl)-4-piperidine carboxylic acid



Ethyl 1-(1-methylethyl)-4-piperidine carboxylate (3.6 g, 18 mmol, 1 eq) was combined with barium hydroxide octahydrate (10.4 g, 33 mmol, 1.8 eq) in a mixture of 70 mL of water with 44 mL of ethanol. The mixture was heated at 60°C for 1.3 h. The reaction mixture was concentrated *in vacuo* and diluted with 70 mL of water. Ammonium carbonate (6.9 g, 87 mmol, 4.8 eq) was added portionwise and the reaction mixture was stirred at rt overnight. The mixture was filtered through diatomaceous earth, concentrated, and lyophilized to provide 3.1 g (100 %) of 1-(1-methylethyl)-4-piperidine carboxylic acid as a white solid.

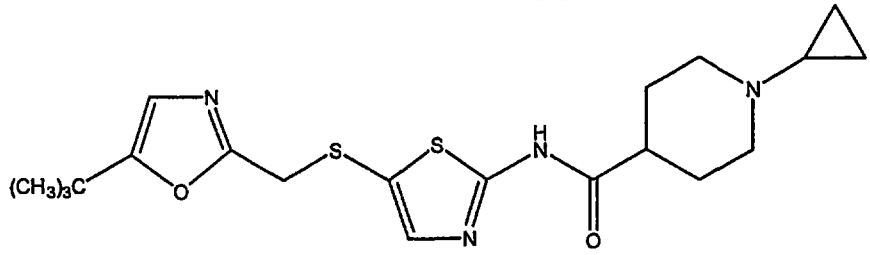
C. N-[5-[[[5-(1,1-Dimethylethyl)-2-oxazolyl]methyl]thio]-2-thiazolyl]-1-(1-methylethyl)-4-piperidinecarboxamide



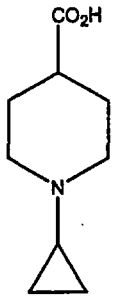
1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.0 g, 5.2 mmol, 2 eq) was added to a mixture of 2-amino-5-[[[5-(1,1-dimethylethyl)-2-oxazolyl]methyl]thio]thiazole (0.7 g, 2.6 mmol, 1 eq), 1-(1-methylethyl)-4-piperidine carboxylic acid (0.78 g, 3.9 mmol, 1.5 eq), 4-(dimethylamino)pyridine (0.16 g, 1.3 mmol, 0.5 eq), N,N-dimethylformamide (2.6 mL) and CH_2Cl_2 (7.8 mL). The reaction mixture was stirred at rt for 1 h, diluted with 30 mL of water and extracted with ethyl acetate (2 × 70 mL). The organic extracts were dried over Na_2SO_4, concentrated *in vacuo*, and purified by flash chromatography on silica gel eluting with a gradient of 5-10 % triethylamine in ethyl acetate. The material was recrystallized from ethanol and water to provide 0.93 g (85

%) of N-[5-[[[5-(1,1-dimethylethyl)-2-oxazolyl]methyl]thio]-2-thiazolyl]-1-(1-methylethyl)-4-piperidinecarboxamide as a yellowish solid. MS: 423 $[M+H]^+$; HPLC: 100 % at 3.15 min (YMC S5 ODS column 4.6 × 50 mm, 10-90 % aqueous methanol over 4 minutes containing 0.2 % phosphoric acid, 4 mL/min, monitoring at 220 nm).

Example 5: Preparation of 1-Cyclopropyl-N-[5-[[[5-(1,1-dimethylethyl)-2-oxazolyl]methyl]thio]-2-thiazolyl]-4-piperidinecarboxamide



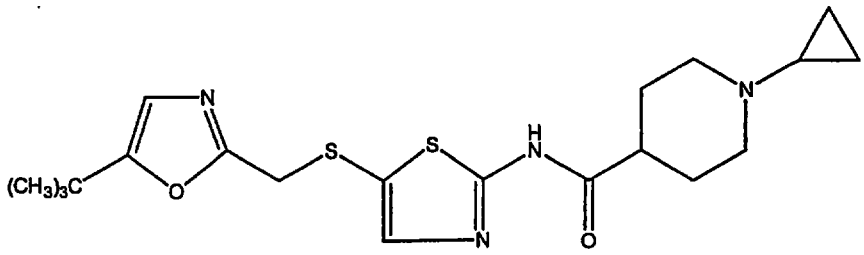
A. 1-Cyclopropyl-4-piperidine carboxylic acid



Ethyl isonipecotate (1.57 g, 10 mmol, 1 eq) was combined with ((1-ethoxycyclopropyl)oxy)trimethyl silane (8.7 g, 50 mmol, 5 eq) in 100 mL of methanol. Acetic acid (5.7 mL, 100 mmol, 10 eq) and molecular sieves were added. After 30 min at rt, sodium triacetoxyborohydride (2.5 g, 40 mmol, 4 eq) was added and the reaction mixture was heated at 65°C overnight. The reaction mixture was cooled and Na_2CO_3 (20 g) was added. The mixture was stirred at rt for 2 h and filtered through diatomaceous earth. The diatomaceous earth was washed with methanol. The filtrates were combined, concentrated *in vacuo*, diluted with water, and extracted with ethyl acetate. The organic extracts were dried, filtered through a silica gel pad, and concentrated *in vacuo* to provide 2.4 g of colorless liquid. This material was combined with barium hydroxide octahydrate (5.7 g, 18 mmol, 1.8 eq) in a mixture of 38 mL of water with 24 mL of ethanol. The mixture was heated at 60°C for 1 h. The reaction mixture was concentrated *in vacuo* and diluted with 38 mL of water. Ammonium carbonate (3.8 g) was added portionwise and the reaction was stirred at rt for 2 h. The mixture was filtered through diatomaceous earth, washing with

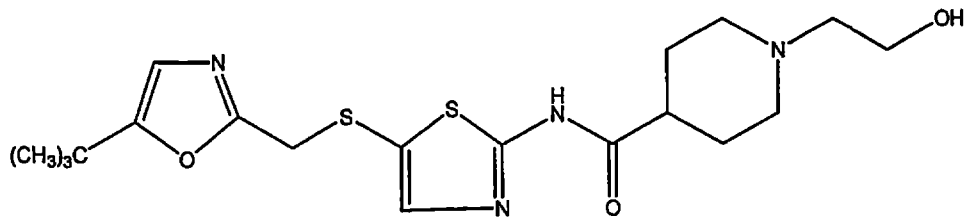
water. The filtrate was washed with ethyl acetate. Concentration of the aqueous phase provided 1.56 g (92 %) of 1-cyclopropyl-4-piperidine carboxylic acid as a hygroscopic white solid.

B. 1-Cyclopropyl-N-[5-[[[5-(1,1-dimethylethyl)-2-oxazolyl]-methyl]thio]-2-thiazolyl]-4-piperidinecarboxamide

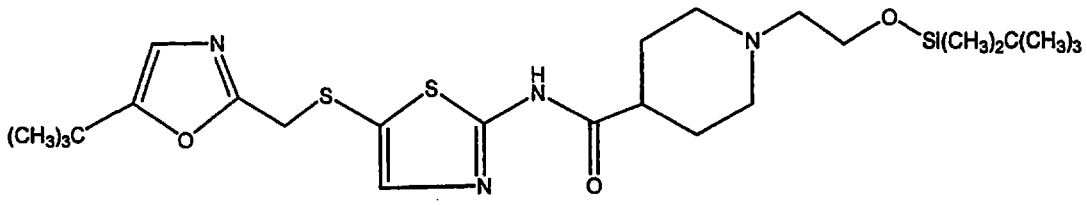


1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.0 g, 5.2 mmol, 2 eq) was added to a mixture of 2-amino-5-[[[5-(1,1-dimethylethyl)-2-oxazolyl]methyl]thio]thiazole (0.7 g, 2.6 mmol, 1 eq), 1-cyclopropyl-4-piperidine carboxylic acid (0.77 g, 3.9 mmol, 1.5 eq), 4-(dimethylamino)pyridine (0.16 g, 1.3 mmol, 0.5 eq), N,N-dimethylformamide (2.6 mL) and CH_2Cl_2 (7.8 mL). The reaction mixture was stirred at rt for 1 h, diluted with water (30 mL), and extracted with ethyl acetate (2 × 70 mL). The combined organic extracts were dried over anhydrous sodium sulfate, concentrated *in vacuo*, and purified by flash chromatography on silica gel eluting with a gradient of 0-10 % triethylamine in ethyl acetate. The material was crystallized from ethyl acetate and hexanes to provide 0.7 g (65 %) of 1-cyclopropyl-N-[5-[[[5-(1,1-dimethylethyl)-2-oxazolyl]methyl]thio]-2-thiazolyl]-4-piperidinecarboxamide as white crystals. MS: 421 $[M+H]^+$; HPLC: 100 % at 3.13 min (YMC S5 ODS column 4.6 × 50 mm, 10-90 % aqueous methanol over 4 minutes containing 0.2 % phosphoric acid, 4 mL/min, monitoring at 220 nm).

Example 6: Preparation of N-[5-[[[5-(1,1-Dimethylethyl)-2-oxazolyl]methyl]thio]-2-thiazolyl]-1-(2-hydroxyethyl)-4-piperidinecarboxamide

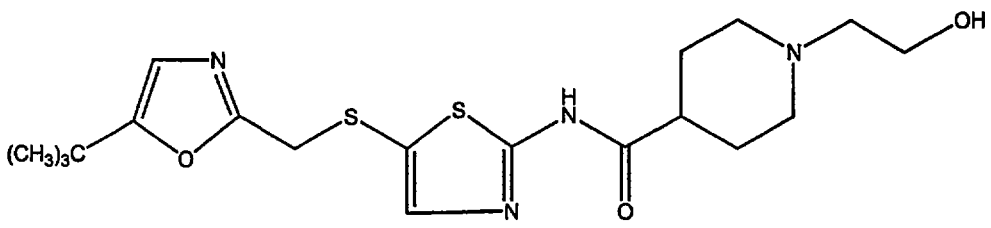


A. N-[5-[[[5-(1,1-Dimethylethyl)-2-oxazolyl]methyl]thio]-2-thiazolyl]-1-(2-dimethyl-*t*-butylsilyloxyethyl)-4-piperidinecarboxamide



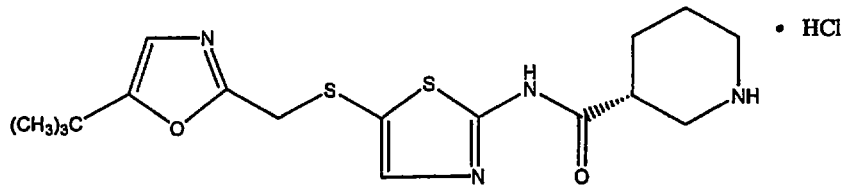
N-[5-[[[5-(1,1-dimethylethyl)-2-oxazolyl]methyl]thio]-2-thiazolyl]-4-piperidinecarboxamide (1.4 g, 3.68 mmol, 1 eq) was dissolved in 30 mL of N,N-dimethylformamide and 100 mL of tetrahydrofuran. 2-(Bromoethoxy)-*t*-butyldimethylsilane (0.79 mL, 3.68 mmol, 1 eq), and $NaHCO_3$ were added and the reaction mixture was stirred at 50°C for 23 h. Additional 2-(bromoethoxy)-*t*-butyldimethylsilane (0.9 mL) was added, and the reaction mixture was stirred at 50°C for 22 h, cooled, concentrated *in vacuo* and diluted with water (25 mL). The resultant aqueous mixture was extracted with ethyl acetate (50 mL). The organic extract was dried over Na_2SO_4, concentrated *in vacuo*, and purified by flash chromatography on silica gel eluting with a gradient of 0-5 % triethylamine in ethyl acetate to provide 1.7g (84 %) of N-[5-[[[5-(1,1-dimethylethyl)-2-oxazolyl]methyl]thio]-2-thiazolyl]-1-(2-dimethyl-*t*-butylsilyloxyethyl)-4-piperidinecarboxamide as a yellow solid. MS: 539 $[M+H]^+$; HPLC: 98 % at 4.01 min (YMC S5 ODS column 4.6 × 50 mm, 10-90 % aqueous methanol over 4 minutes containing 0.2 % phosphoric acid, 4 mL/min, monitoring at 220 nm).

B. N-[5-[[[5-(1,1-Dimethylethyl)-2-oxazolyl]methyl]thio]-2-thiazolyl]-1-(2-hydroxyethyl)-4-piperidinecarboxamide

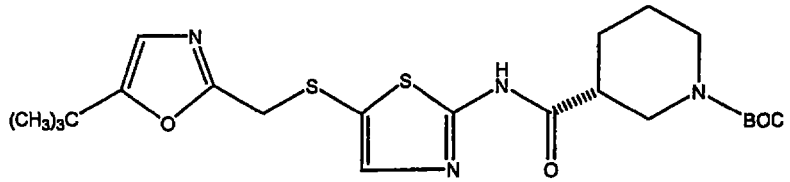


N-[5-[[[5-(1,1-Dimethylethyl)-2-oxazolyl]methyl]thio]-2-thiazolyl]-1-(2-dimethyl-*t*-butylsilyloxyethyl)-4-piperidinecarboxamide (1.45 g, 2.7 mmol, 1 eq) was dissolved in 100 mL of acetonitrile and combined with aqueous HF (48 % aqueous, 2.5 mL). The reaction mixture was stirred for 4 h at rt. An additional 2.5 mL of aqueous HF was added, and the reaction mixture was stirred overnight. Ethyl acetate (100 mL) and saturated aqueous $NaHCO_3$ (50 mL) were added. Additional solid $NaHCO_3$ was added to make the mixture basic. The mixture was extracted with ethyl acetate (2 × 50 mL). The organic extracts were dried over Na_2SO_4, filtered through a pad of silica gel, and concentrated *in vacuo*. The resulting white solid was crystallized from ethanol and water to provide 1.6 g (59 %) of N-[5-[[[5-(1,1-dimethylethyl)-2-oxazolyl]methyl]thio]-2-thiazolyl]-1-(2-hydroxyethyl)-4-piperidinecarboxamide as a white solid. MS: 425 $[M+H]^+$; HPLC: 100 % at 3.05 min (YMC S5 ODS column 4.6 × 50 mm, 10-90 % aqueous methanol over 4 minutes containing 0.2 % phosphoric acid, 4 mL/min, monitoring at 220 nm).

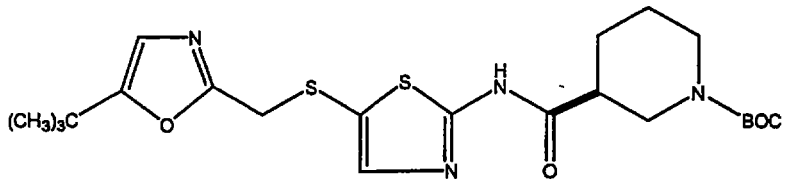
Example 7: Preparation of (R)-N-[5-[[[5-(1,1-Dimethylethyl)-2-oxazolyl]methyl]thio]-2-thiazolyl]-3-piperidine-carboxamide hydrochloride



A. (R)- and (S)-N-[5-[[[5-(1,1-Dimethylethyl)-2-oxazolyl]methyl]thio]-2-thiazolyl-(N-*t*-butoxycarbonyl)-3-piperidinecarboxamide



(R)

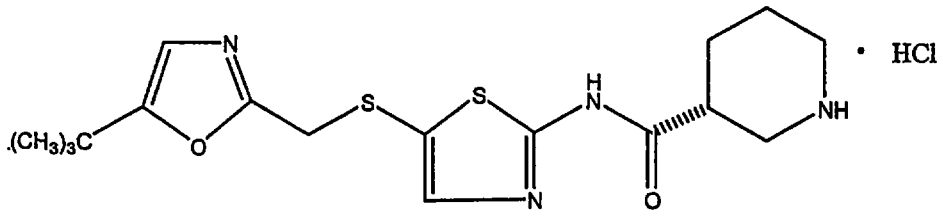


(S)

1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (3.8 g, 20 mmol, 2 eq) was added to a mixture of 2-amino-5-[[[5-(1,1-dimethylethyl)-2-oxazolyl]methyl]thio]thiazole (2.7 g, 10 mmol, 1 eq), N-*t*-butoxycarbonyl-nipecotic acid (3.4 g, 1.5 mmol, 1.5 eq), N,N-dimethylformamide (10 mL) and CH_2Cl_2 (30 mL). The reaction mixture was stirred at rt for 4 h. The resulting black solution was concentrated *in vacuo*, diluted with water (90 mL) and extracted with ethyl acetate (100 mL, then 2 × 75 mL). The organic extracts were dried over Na_2CO_3, concentrated *in vacuo*, and purified by flash chromatography on silica gel eluting with a gradient of 50-100 % ethyl acetate in hexanes to provide 3.8 g (79 %) of a yellow solid. The enantiomers were separated by chiral HPLC (Chiral Pak AD 5 × 50 cm 20 μ: eluent 10 % (0.1 % triethylamine in isopropanol) in hexanes; 45 mL/min, detection at 254 nm, loading 300 mg in 5 mL of

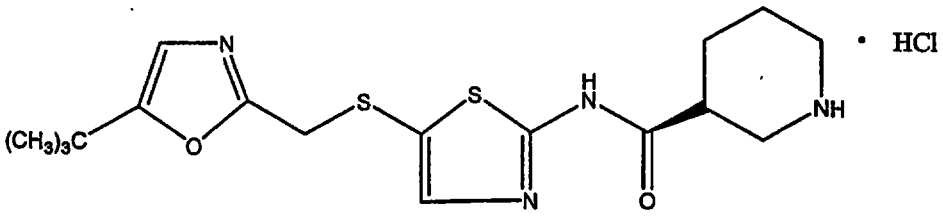
isopropanol) to give each of the two optically pure isomers: 1.65 g of the R isomer and 1.65 g of the S isomer.

B. (R)-N-[5-[[[5-(1,1-Dimethylethyl)-2-oxazolyl]methyl]thio]-2-thiazolyl]-3-piperidinecarboxamide hydrochloride



The (R) isomer of Part A (1.65 g, 3.43 mmol, 1 eq) was dissolved in 10 mL of CH_2Cl_2. Trifluoroacetic acid (6 mL) was added, and the mixture was stirred at rt for several hours. The reaction mixture was concentrated *in vacuo* and neutralized with saturated aqueous $NaHCO_3$. The resulting mixture was stirred with ethyl acetate for 1 h. The organic extracts were dried over Na_2SO_4 and concentrated *in vacuo* to provide a yellowish solid. The solid was dissolved in methanol and 1 eq of 1N aqueous HCl was added. The resulting solution was lyophilized to provide 1 g (77 %) of (R)-N-[5-[[[5-(1,1-dimethylethyl)-2-oxazolyl]methyl]thio]-2-thiazolyl]-3-piperidinecarboxamide hydrochloride as a yellow solid: MS: 381 $[M+H]^+$; HPLC: 100 % at 3.14 min (YMC S5 ODS column 4.6 × 50 mm, 10-90 % aqueous methanol over 4 minutes containing 0.2 % phosphoric acid, 4 mL/min, monitoring at 220 nm).

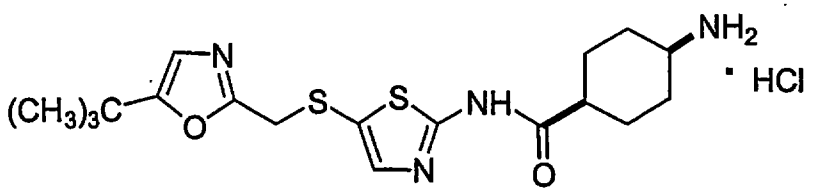
Example 8: Preparation of (S)-N-[5-[[[5-(1,1-Dimethylethyl)-2-oxazolyl]-methyl]thio]-2-thiazolyl]-3-piperidine carboxamide hydrochloride

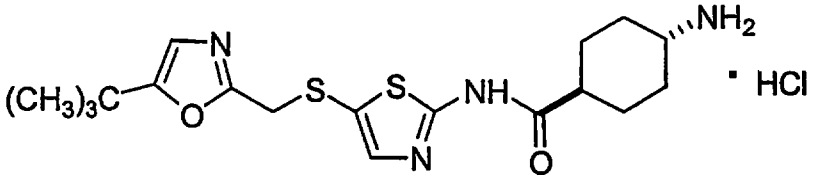


The (S) isomer of Example 7, Part A (1.65 g, 3.43 mmol, 1 eq) was dissolved in 10 mL of CH_2Cl_2. Trifluoroacetic acid (6 mL) was added, and the mixture was stirred at rt for several hours. The reaction was concentrated *in vacuo* and neutralized with saturated aqueous $NaHCO_3$. The resulting mixture was stirred with ethyl acetate for 1 h. The organic extracts were dried over Na_2SO_4 and concentrated *in vacuo* to provide a yellowish solid.

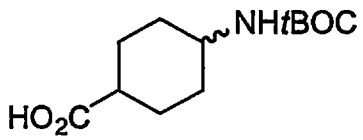
The solid was dissolved in methanol and 1 eq of 1N aqueous HCl was added. The resulting solution was lyophilized to provide 0.918 g (70 %) of (S)-N-[5-[[[5-(1,1-dimethylethyl)-2-oxazolyl]methyl]thio]-2-thiazolyl]-3-piperidinecarboxamide hydrochloride as a yellow solid. MS: 381 $[M+H]^+$; HPLC: 100 % at 3.15 min (YMC S5 ODS column 4.6 × 50 mm, 10-90 % aqueous methanol over 4 minutes containing 0.2 % phosphoric acid, 4 mL/min, monitoring at 220 nm).

Example 9: Preparation of *cis*-4-Amino-N-[5-[[[5-(1,1-dimethylethyl)-2-oxazolyl]-methyl]thio]-2-thiazolyl]cyclohexylcarboxamide hydrochloride and *trans*-4-Amino-N-[5-[[[5-(1,1-dimethylethyl)-2-oxazolyl]methyl]thio]-2-thiazolyl]-cyclohexylcarboxamide hydrochloride



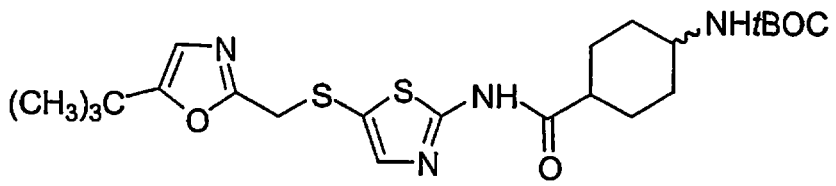


A. 4-(*t*-Butoxycarbonylamino)cyclohexane carboxylic acid



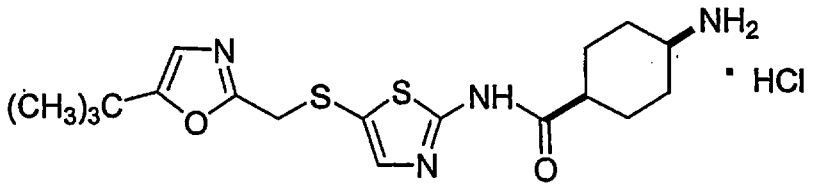
To a solution of 2.86 g (20 mmol) of 4-aminocyclohexane carboxylic acid in 40 mL of 0.5M aqueous NaOH solution, 20 mL of dioxane and 4 mL of acetonitrile was added a total of 6.5 g (30 mmol) of *t*Boc anhydride at room temperature. After 20 h, 100 mL of ethyl acetate and 100 mL of 10 % aqueous citric acid solution were introduced. The aqueous layer which formed was separated and extracted with three-50 mL portions of ethyl acetate. The organic phases were combined, dried (sodium sulfate) and concentrated *in vacuo* to give 6.0 g (125 %) of crude 4-(*t*-butoxycarbonylamino)cyclohexane carboxylic acid as a colorless oil which solidified upon standing.

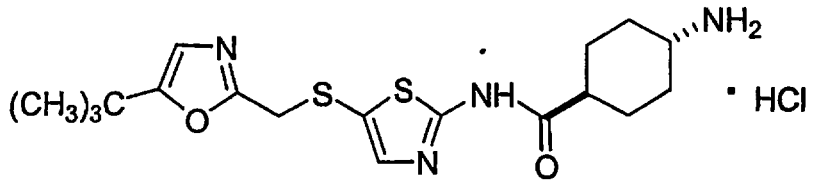
B. 4-(*t*-Butoxycarbonylamino)-N-[5-[[[5-(1,1-dimethylethyl)-2-oxazolyl]-methyl]thio]-2-thiazolyl]cyclohexylcarboxamide



To a solution of 5 g of crude 4-(*t*-butoxycarbonylamino)cyclohexane carboxylic acid and 3.50 g (13 mmol) of 2-amino-5-[[[5-(1,1-dimethylethyl)-2-oxazolyl]methyl]thio]thiazole in 13 mL of N,N-dimethylformamide and 36 mL of methylene chloride was added 5.0 g (26 mmol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride at room temperature. The reaction mixture was stirred overnight and diluted with 100 mL of water. The aqueous layer was separated and extracted with two-150 mL portions of ethyl acetate. The combined organic phases were dried (sodium sulfate) then filtered through a pad of silica gel. The filtrate was concentrated *in vacuo* to afford an orange solid. The crude material was recrystallized (95 % ethanol) to give 4-(*t*-butoxycarbonylamino)-N-[5-[[[5-(1,1-dimethylethyl)-2-oxazolyl]methyl]thio]-2-thiazolyl]cyclohexylcarboxamide as a yellow solid. The mother liquors were also concentrated *in vacuo* to give additional 4-(*t*-butoxycarbonylamino)-N-[5-[[[5-(1,1-dimethylethyl)-2-oxazolyl]methyl]thio]-2-thiazolyl]cyclohexylcarboxamide as a brown solid.

C. *cis*-4-Amino-N-[5-[[[5-(1,1-dimethylethyl)-2-oxazolyl]methyl]thio]-2-thiazolyl]cyclohexylcarboxamide hydrochloride and trans-4-Amino-N-[5-[[[5-(1,1-dimethylethyl)-2-oxazolyl]methyl]thio]-2-thiazolyl]-cyclohexylcarboxamide hydrochloride

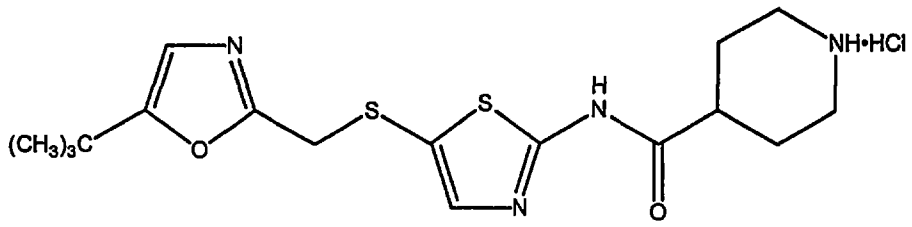




To a suspension of 4-(*t*-butoxycarbonylamino)-N-[5-[[[5-(1,1-dimethylethyl)-2-oxazolyl]methyl]thio]-2-thiazolyl]cyclohexylcarboxamide (from Part B mother liquors) suspended in 15 mL of methylene chloride was added 5 mL of trifluoroacetic acid at room temperature. The reaction mixture was stirred for 2 h then concentrated *in vacuo* to remove volatiles. The residue was diluted with water, basified with aqueous NaOH solution then the resulting aqueous solution was extracted with ethyl acetate. The combined organic extracts were dried (sodium sulfate) to give a crude cis/trans product. The crude material was purified by flash chromatography (Merck silica, 25x3 cm, 1:9 isopropylamine/ethyl acetate then 1:2:7 methanol/isopropylamine/ethyl acetate) to afford 0.74 g of the cis isomer as a yellow solid and 0.50 g of the trans isomer as a brown solid. The cis isomer was dissolved in methanol then 0.34 mL of 5N aqueous HCl was added. The solution was concentrated *in vacuo*, washed with ether, diluted with water and lyophilized to afford 0.80 g of cis-4-amino-N-[5-[[[5-(1,1-dimethylethyl)-2-oxazolyl]methyl]thio]-2-thiazolyl]cyclohexylcarboxamide hydrochloride as a yellow solid. MS: 395 $[M+H]^+$; HPLC-HI 98 % at 3.17 min (YMC S5 ODS column 4.6 × 50 mm, 10-90 % aqueous methanol over 4 minutes containing 0.2 % phosphoric acid, 4 mL/min, monitoring at 220 nm). The trans isomer was dissolved in methanol then 0.24 mL of 5N aqueous HCl was added. The solution was concentrated *in vacuo*, washed with ether, diluted with water and lyophilized to afford 0.54 g of trans-4-amino-N-[5-[[[5-(1,1-dimethylethyl)-2-oxazolyl]methyl]thio]-2-thiazolyl]cyclohexylcarboxamide hydrochloride as an orange solid. MS: 395 $[M+H]^+$; HPLC-HI 96 % at 3.22 min (YMC S5 ODS column 4.6 × 50 mm, 10-90

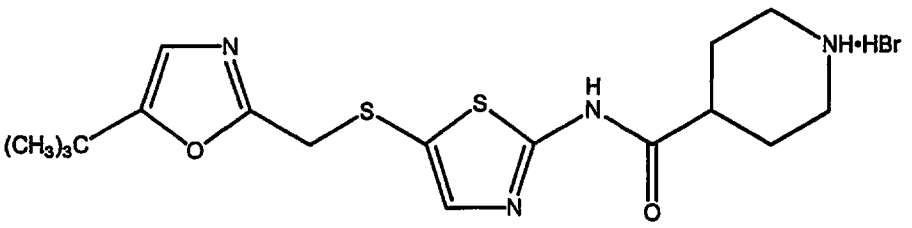
% aqueous methanol over 4 minutes containing 0.2 % phosphoric acid, 4 mL/min, monitoring at 220 nm).

Example 10: N-[5-[[[5-(1,1-Dimethylethyl)-2-oxazolyl]methyl]thio]-2-thiazolyl]-4-piperidinecarboxamide, monohydrochloride



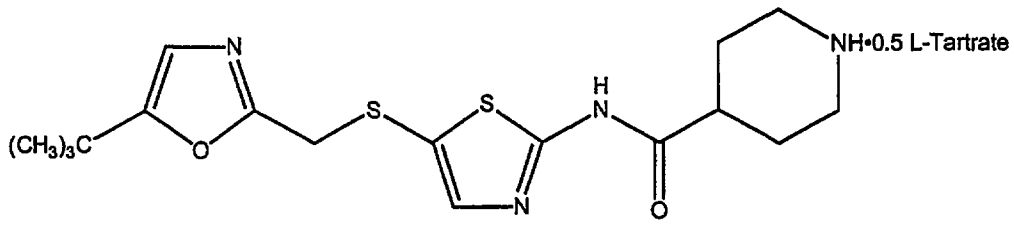
To a solution of 40 mL of absolute EtOH cooled in an ice-bath was added acetyl chloride (0.28 mL, 3.9 mmol) dropwise. The reaction mixture was allowed to warm to room temperature over 30 min then N-[5-[[[5-(1,1-dimethylethyl)-2-oxazolyl]methyl]-thio]-2-thiazolyl]-4-piperidinecarboxamide (1.50 g, 3.94 mmol, 1 eq) was introduced in one portion with stirring to give a thick slurry. Water (~4 mL) was added until homogeneous then concentrated in vacuo to give a crude pale yellow solid. The crude material was recrystallized (aq EtOH) to afford the title compound (70%) as a white solid, mp 256-258°. Analysis calc'd for C17H24N4O2S2•HCl: C, 48.96; H, 6.04; N, 13.43; S, 15.38; Cl, 8.50. Found: C, 48.69; H, 5.99; N, 13.24; S, 15.27; Cl, 8.31.

Example 11: N-[5-[[[5-(1,1-Dimethylethyl)-2-oxazolyl]methyl]thio]-2-thiazolyl]-4-piperidinecarboxamide, monohydrobromide



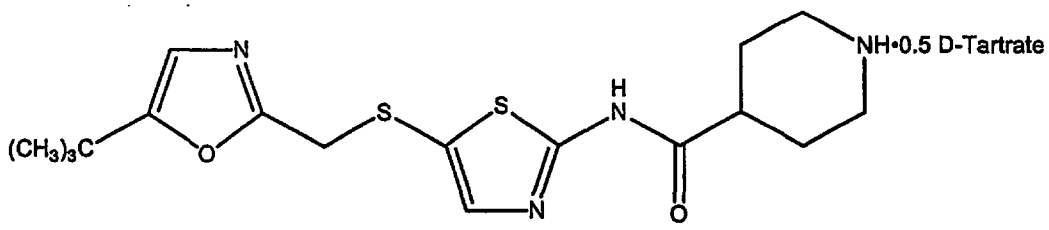
To a solution of 1M HBr in EtOH (0.5 mL) was added N-[5-[[[5-(1,1-dimethylethyl)-2-oxazolyl]methyl]thio]-2-thiazolyl]-4-piperidinecarboxamide (190 mg, 0.5 mmol, 1 eq) then cooled to -40°C overnight. The solid precipitate that formed was collected on a Buchner funnel, washed with absolute EtOH then dried under vacuum at 100°C to afford the title compound (72%) as a fine white powder, mp 235-237° C. Analysis calc'd for C17H24N4O2S2•HBr: C, 44.24; H, 5.46; N, 12.14; S, 13.89; Br, 17.31. Found: C, 44.16; H, 5.40; N, 12.12; S, 13.91; Br, 17.70.

Example 12: N-[5-[[[5-(1,1-Dimethylethyl)-2-oxazolyl]methyl]thio]-2-thiazolyl]-4-piperidinecarboxamide, 0.5-L-tartaric acid salt



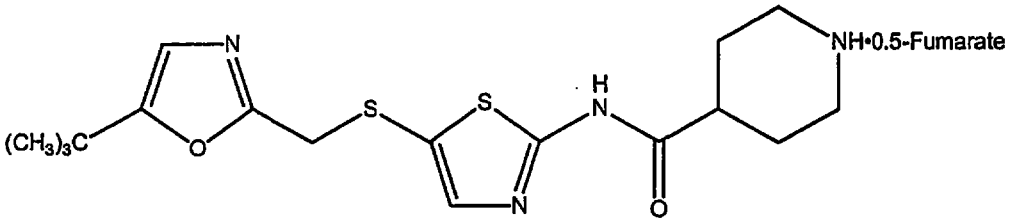
To a warm solution of N-[5-[[[5-(1,1-dimethylethyl)-2-oxazolyl]methyl]thio]-2-thiazolyl]-4-piperidinecarboxamide (1.75 g, 4.6 mmol) in absolute EtOH (70 mL) was added a solution of L-tartaric acid (345 mg, 2.3 mmol, 0.5 eq) in absolute EtOH (5 mL). A precipitate started to form after several minutes. The mixture was allowed to stand for 4 hr at room temperature then the solid precipitate was collected on a Buchner funnel, washed with absolute EtOH and dried under vacuum at 85°C for 24 hr to afford the title compound (94%) as pale yellow crystals, mp 234-236°C. Analysis calc'd for C17H24N4O2S2•0.5-L-Tartaric acid: C, 50.09; H, 5.97; N, 12.29; S, 14.07. Found: C, 49.85; H, 5.90; N, 12.12; S, 13.75.

Example 13: N-[5-[[[5-(1,1-Dimethylethyl)-2-oxazolyl]methyl]thio]-2-thiazolyl]-4-piperidinecarboxamide, 0.5-D-tartaric acid salt



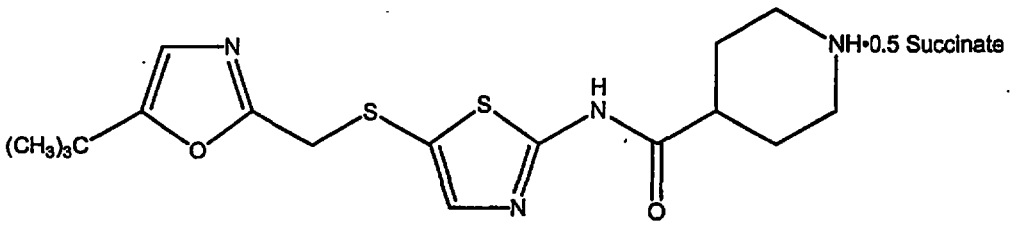
To a warm solution of N-[5-[[[5-(1,1-dimethylethyl)-2-oxazolyl]methyl]thio]-2-thiazolyl]-4-piperidinecarboxamide (1.00 g, 2.63 mmol) in absolute EtOH (40 mL) was added a solution of D-tartaric acid (198 mg, 1.32 mmol, 0.5 eq) in absolute EtOH (4 mL). A precipitate started to form after several minutes. The mixture was allowed to stand for 18 hr at room temperature then the solid precipitate was collected on a Buchner funnel, washed with absolute EtOH and dried under vacuum at 65°C for 6 hr to afford the title compound (73%) as a white solid, mp 232-233°C. Analysis calc'd for C17H24N4O2S2•0.5-D-Tartaric acid: C, 50.09; H, 5.97; N, 12.29; S, 14.07. Found: C, 49.75; H, 5.81; N, 12.04; S, 13.37.

Example 14: N-[5-[[[5-(1,1-Dimethylethyl)-2-oxazolyl]methyl]thio]-2-thiazolyl]-4-piperidinecarboxamide, 0.5-fumaric acid salt



To a warm solution of N-[5-[[[5-(1,1-dimethylethyl)-2-oxazolyl]methyl]thio]-2-thiazolyl]-4-piperidinecarboxamide (1.75 g, 4.6 mmol) in absolute EtOH (100 mL) was added a solution of fumaric acid (276 mg, 2.3 mmol, 0.5 eq) in absolute EtOH (5 mL). A precipitate started to form after 10 minutes. The mixture was allowed to stand for 2 hr at room temperature then at 5°C for 16 hr. The solid precipitate which formed was collected on a Buchner funnel, washed with absolute EtOH and dried under vacuum at 65°C for 24 hr to afford the title compound (84%) as a white solid, mp 206-207° C. Analysis calc'd for C17H24N4O2S2•0.5-Fumaric acid: C, 52.04; H, 5.98; N, 12.77; S, 14.62. Found: C, 51.74; H, 5.76; N, 12.57; S, 14.19. Recrystallization (95% aq EtOH) afforded the title compound containing 1 mol EtOH (83%) as large colorless crystals, mp 212-214° C. Analysis calc'd for C17H24N4O2S2•0.5-Fumaric acid•EtOH: C, 52.05; H, 6.66; N, 11.56; S, 13.23. Found: C, 52.03; H, 6.06; N, 11.50; S, 12.99.

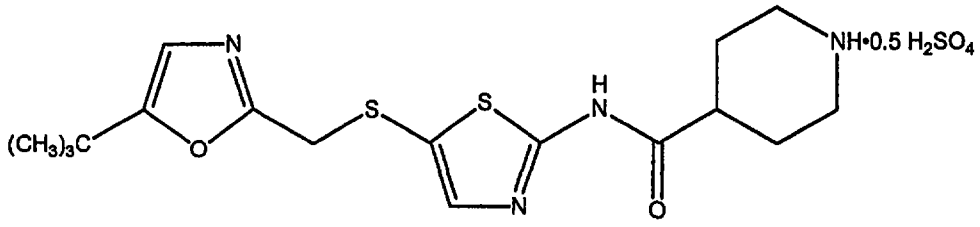
Example 15: N-[5-[[[5-(1,1-Dimethylethyl)-2-oxazolyl]methyl]thio]-2-thiazolyl]-4-piperidinecarboxamide, 0.5-succinic acid salt



To a warm solution of N-[5-[[[5-(1,1-dimethylethyl)-2-oxazolyl]methyl]thio]-2-thiazolyl]-4-piperidinecarboxamide (50 mg, 0.13 mmol) in absolute EtOH (2 mL) was added a solution of succinic acid (7.7 mg, 0.065 mmol, 0.5 eq) in absolute EtOH (0.25 mL). A precipitate started to form after 10 minutes. The mixture was allowed to stand for 1 hr at room temperature then the precipitate was collected on a Buchner funnel, washed with absolute EtOH and dried under vacuum at 100° C for 24 hr to afford the title compound (70%) as a white solid, mp 190-192° C. Analysis calc'd for C17H24N4O2S2•0.5-Succinic

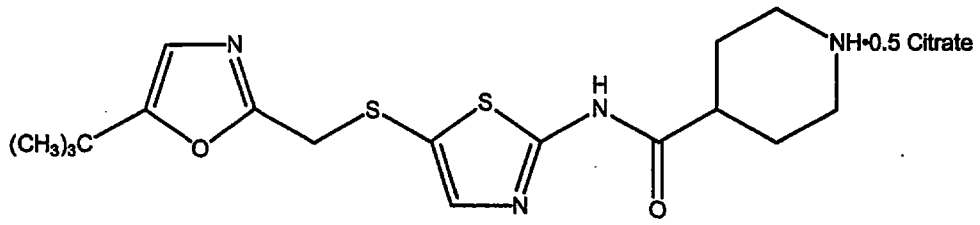
acid•0.46H2O: C, 50.96; H, 6.28; N, 12.51; S, 14.32. Found: C, 50.96; H, 6.20; N, 12.49; S, 14.23.

Example 16: N-[5-[[[5-(1,1-Dimethylethyl)-2-oxazolyl]methyl]thio]-2-thiazolyl]-4-piperidinecarboxamide, 0.5-sulfuric acid salt



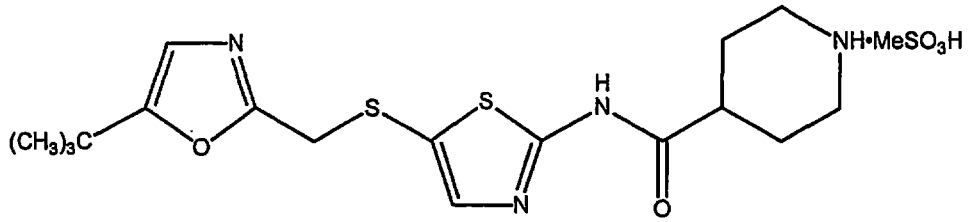
To a warm solution of N-[5-[[[5-(1,1-dimethylethyl)-2-oxazolyl]methyl]thio]-2-thiazolyl]-4-piperidinecarboxamide (50 mg, 0.13 mmol) in absolute EtOH (2 mL) was added a 1M aq solution of sulfuric acid (0.065 mL, 0.065 mmol, 0.5 eq). A precipitate formed almost immediately. The mixture was cooled to 5° C. for 2 hr then the precipitate was collected on a Buchner funnel, washed with absolute EtOH and dried under vacuum at 100° C for 24 hr to afford the title compound (79%) as a white solid, mp 256-258° C. Analysis calc'd for C17H24N4O2S2•0.5H2SO4•0.68H2O: C, 46.22; H, 6.01; N, 12.68; S, 18.14. Found: C, 46.21; H, 5.95; N, 12.71; S, 18.23.

Example 17: N-[5-[[[5-(1,1-Dimethylethyl)-2-oxazolyl]methyl]thio]-2-thiazolyl]-4-piperidinecarboxamide, 0.5-citric acid salt



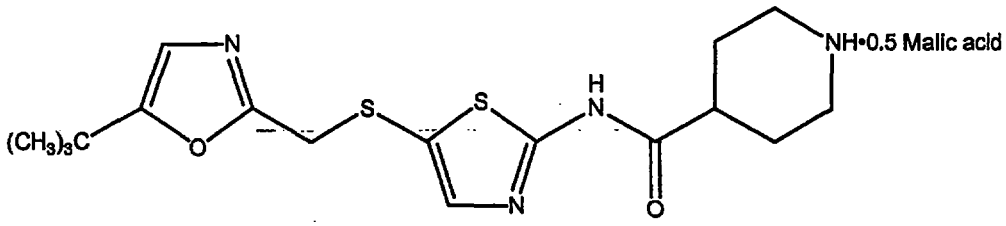
To a warm solution of N-[5-[[[5-(1,1-dimethylethyl)-2-oxazolyl]methyl]thio]-2-thiazolyl]-4-piperidinecarboxamide (50 mg, 0.13 mmol) in absolute EtOH (2 mL) was added a solution of citric acid (8.3 mg, 0.043 mmol, 0.33 eq). The solution was cooled to 5° C for 18 hr then the precipitate which formed was collected on a Buchner funnel, washed with absolute EtOH and dried under vacuum at 100° C for 24 hr to afford the title compound (68%) as a white solid, mp 214-216° C. Analysis calc'd for C17H24N4O2S2•0.5-Citric acid•0.10H2O: C, 50.21; H, 5.94; N, 11.71; S, 13.40. Found: C, 50.21; H, 6.01; N, 11.83; S, 13.44.

Example 18: N-[5-[[[5-(1,1-Dimethylethyl)-2-oxazolyl]methyl]thio]-2-thiazolyl]-4-piperidinecarboxamide, methanesulfonic acid salt



To a slurry of N-[5-[[[5-(1,1-dimethylethyl)-2-oxazolyl]methyl]thio]-2-thiazolyl]-4-piperidinecarboxamide (100 mg, 0.26 mmol) in isopropyl alcohol (0.75 mL) was added methanesulfonic acid (0.017 mL, 0.26 mmol, 1 eq). The slurry was heated to 70° C to give a clear solution then methyl t-butyl ether (1.5 mL) was added. Within 15 minutes a precipitate formed. The resulting mixture was stirred at 55° C for 2 hr then at room temperature for 14 hr. The precipitate which formed was collected by filtration then dried under vacuum at 50° C for 14 hr to afford the title compound (85%) as a colorless powder, mp 105° C. Analysis calc'd for C17H24N4O2S2•MSA•H2O: C, 43.70; H, 6.11; N, 11.32; S, 19.44. Found: C, 43.53; H, 6.14; N, 11.15; S, 19.15.

Example 19: N-[5-[[[5-(1,1-Dimethylethyl)-2-oxazolyl]methyl]thio]-2-thiazolyl]-4-piperidinecarboxamide, 0.5-D,L-malic acid salt

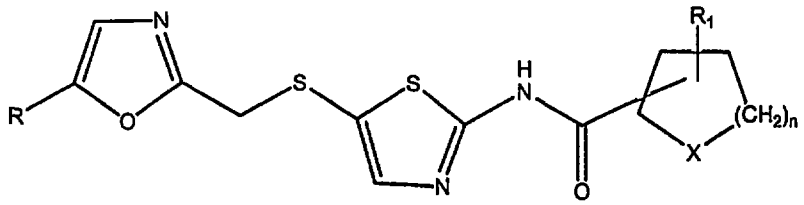


To a solution of N-[5-[[[5-(1,1-dimethylethyl)-2-oxazolyl]methyl]thio]-2-thiazolyl]-4-piperidinecarboxamide (100 mg, 0.26 mmol) in isopropyl alcohol (0.80 mL) was added slowly at 70° C a solution of D,L-malic acid (35 mg, 0.13 mmol, 0.5 eq) in isopropyl alcohol (0.3 mL). A precipitate formed immediately. The resulting mixture was stirred at 55° C for 2 hr then at room temperature for 14 hr. The precipitate was collected by filtration then dried under vacuum at 50° C for 14 hr to afford the title compound (75%) as a colorless powder, mp 216° C. Analysis calc'd for C17H24N4O2S2•0.5-C4H6O5•H2O: C, 50.98; H, 6.08; N, 12.51; S, 14.32. Found: C, 50.55; H, 6.17; N, 12.29; S, 14.05.

Claims

What is claimed is:

1. A compound of formula I



(I)

and enantiomers, diastereomers, solvates, and pharmaceutically acceptable salts thereof, wherein:

R is alkyl;

R^1 is hydrogen or alkyl;

X is NR^2 or $CHNR^2R^3$;

R^2 and R^3 are each independently hydrogen, alkyl, substituted alkyl, cycloalkyl or substituted cycloalkyl; and

n is 0, 1, 2 or 3.

2. The compound according to claim 1 wherein:

R is alkyl;

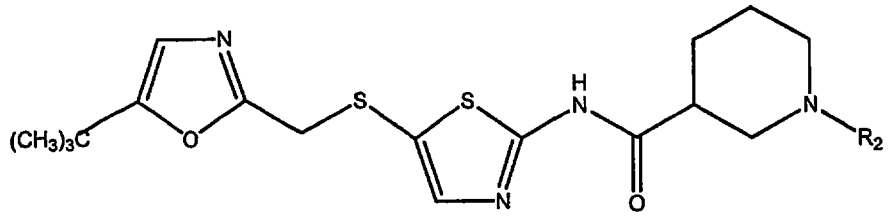
R^1 is hydrogen;

X is NR^2 or $CHNR^2R^3$;

R^2 and R^3 are each independently hydrogen, alkyl, substituted alkyl or cycloalkyl; and

n is 2.

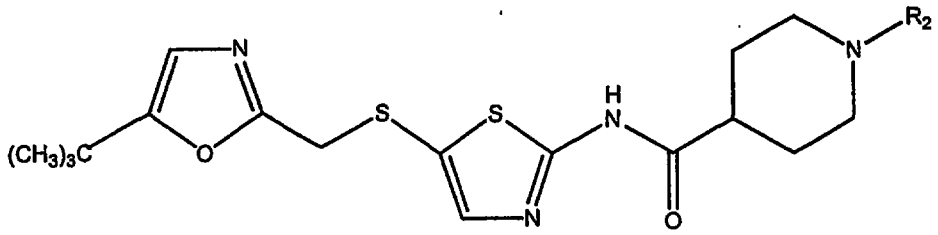
3. The compound according to claim 1 of formula Ia



(Ia)

and enantiomers, diastereomers, solvates, and pharmaceutically acceptable salts thereof wherein R^2 is hydrogen, alkyl, substituted alkyl or cycloalkyl.

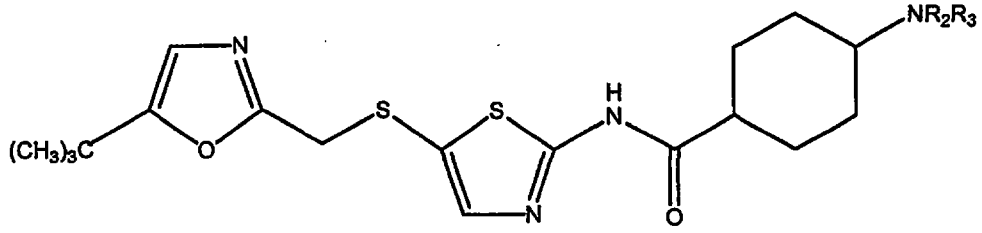
4. The compound according to claim 1 of formula Ib



(Ib)

and enantiomers, diastereomers, solvates, and pharmaceutically acceptable salts thereof wherein R^2 is hydrogen, alkyl, substituted alkyl or cycloalkyl.

5. The compound according to claim 1 of formula Ic



(Ic)

and enantiomers, diasteromers, solvates, and pharmaceutically acceptable salts thereof wherein

R^2 and R^3 are each independently hydrogen, alkyl, substituted alkyl or cycloalkyl.

6. The compound according to claim 1 selected from the group consisting of:

N-[5-[[[5-(1,1-dimethylethyl)-2-oxazolyl]methyl]thio]-2-thiazolyl]-4-piperidinecarboxamide;

(±)-*N*-[5-[[[5-(1,1-dimethylethyl)-2-oxazolyl]methyl]thio]-2-thiazolyl]-3-piperidinecarboxamide;

(±)-1-(2,3-dihydroxypropyl)-*N*-[5-[[[5-(1,1-dimethylethyl)-2-oxazolyl]methyl]thio]-2-thiazolyl]-4-piperidinecarboxamide;

N-[5-[[[5-(1,1-dimethylethyl)-2-oxazolyl]methyl]thio]-2-thiazolyl]-1-(1-methylethyl)-4-piperidinecarboxamide;

1-cyclopropyl-*N*-[5-[[[5-(1,1-dimethylethyl)-2-oxazolyl]methyl]thio]-2-thiazolyl]-4-piperidinecarboxamide;

N-[5-[[[5-(1,1-dimethylethyl)-2-oxazolyl]methyl]thio]-2-thiazolyl]-1-(2-hydroxyethyl)-4-piperidinecarboxamide;

(R)-*N*-[5-[[[5-(1,1-dimethylethyl)-2-oxazolyl]methyl]thio]-2-thiazolyl]-3-piperidinecarboxamide;

(S)-*N*-[5-[[[5-(1,1-dimethylethyl)-2-oxazolyl]methyl]thio]-2-thiazolyl]-3-piperidinecarboxamide;

cis-4-amino-*N*-[5-[[[5-(1,1-dimethylethyl)-2-oxazolyl]methyl]thio]-2-thiazolyl]cyclohexylcarboxamide; and

trans-4-amino-*N*-[5-[[[5-(1,1-dimethylethyl)-2-oxazolyl]methyl]thio]-2-thiazolyl]cyclohexylcarboxamide; and enantiomers, diastereomers, solvates, and pharmaceutically acceptable salts thereof.

7. *N*-[5-[[[5-(1,1-dimethylethyl)-2-oxazolyl]methyl]thio]-2-thiazolyl]-4-piperidinecarboxamide and enantiomers, diastereomers, solvates, and pharmaceutically acceptable salts thereof.

8. (±)-*N*-[5-[[[5-(1,1-dimethylethyl)-2-oxazolyl]methyl]thio]-2-thiazolyl]-3-piperidinecarboxamide and enantiomers, diastereomers, solvates, and pharmaceutically acceptable salts thereof.

9. (R)-*N*-[5-[[[5-(1,1-dimethylethyl)-2-oxazolyl]methyl]thio]-2-thiazolyl]-3-piperidinecarboxamide and pharmaceutically acceptable salts thereof.

10. (S)-*N*-[5-[[[5-(1,1-dimethylethyl)-2-oxazolyl]methyl]thio]-2-thiazolyl]-3-piperidinecarboxamide and pharmaceutically acceptable salts thereof.

11. *cis*-4-amino-*N*-[5-[[[5-(1,1-dimethylethyl)-2-oxazolyl]methyl]thio]-2-thiazolyl]cyclohexylcarboxamide and enantiomers, diastereomers, solvates, and pharmaceutically acceptable salts thereof.

12. *trans*-4-amino-*N*-[5-[[[5-(1,1-dimethylethyl)-2-oxazolyl]methyl]thio]-2-thiazolyl]cyclohexylcarboxamide and enantiomers, diastereomers, solvates, and pharmaceutically acceptable salts thereof.

13. A pharmaceutical composition comprising a compound of claim 1 and a pharmaceutically acceptable carrier.

14. A pharmaceutical composition comprising a compound of claim 1 in combination with a pharmaceutically acceptable carrier and an anti-cancer agent formulated as a fixed dose.

15. A pharmaceutical composition comprising a compound of claim 1 in combination with a pharmaceutically acceptable carrier and a modulator of p53 transactivation formulated as a fixed dose.

16. A method for modulating apoptosis comprising administering to a mammalian specie in need thereof an effective apoptosis modulating amount of a compound of claim 1.

17. A method for inhibiting protein kinases comprising administering to a mammalian specie in need thereof an effective protein kinase inhibiting amount of a compound of claim 1.

18. A method for inhibiting cyclin dependent kinases comprising administering to a mammalian specie in need thereof an effective cyclin dependent kinase inhibiting amount of a compound of claim 1.

19. A method for inhibiting cdc2 (cdk1) comprising administering to a mammalian specie in need thereof an effective cdc2 inhibiting amount of a compound of claim 1.

20. A method for inhibiting cdk2 comprising administering to a mammalian specie in need thereof an effective cdk2 inhibiting amount of a compound of claim 1.

21. A method for inhibiting cdk3 comprising administering to a mammalian specie in need thereof an effective cdk3 inhibiting amount of a compound of claim 1.

22. A method for inhibiting cdk4 comprising administering to a mammalian specie in need thereof an effective cdk4 inhibiting amount of a compound of claim 1.

23. A method for inhibiting cdk5 comprising administering to a mammalian specie in need thereof an effective cdk5 inhibiting amount of a compound of claim 1.

24. A method for inhibiting cdk6 comprising administering to a mammalian specie in need thereof an effective cdk6 inhibiting amount of a compound of claim 1.

25. A method for inhibiting cdk7 comprising administering to a mammalian specie in need thereof an effective cdk7 inhibiting amount of a compound of claim 1.

26. A method for inhibiting cdk8 comprising administering to a mammalian specie in need thereof an effective cdk8 inhibiting amount of a compound of claim 1.

27. A method for treating proliferative diseases comprising administering to a mammalian specie in need thereof a therapeutically effective amount of a composition of claim 13.

28. A method for treating cancer comprising administering to a mammalian specie in need thereof a therapeutically effective amount of a composition of claim 13.

29. A method for treating inflammation, inflammatory bowel disease or transplantation rejection comprising administering to a mammalian specie in need thereof a therapeutically effective amount of a composition of claim 13.

30. A method for treating arthritis comprising administering to a mammalian specie in need thereof a therapeutically effective amount of a composition of claim 13.

31. A method for treating proliferative diseases comprising administering to a mammalian specie in need thereof a therapeutically effective amount of a composition of claim 14.

32. A method for treating cancer comprising administering to a mammalian specie in need thereof a therapeutically effective amount of a composition of claim 14.

33. A method for treating proliferative diseases comprising administering to a mammalian specie in need thereof a therapeutically effective amount of a composition of claim 15.

34. A method for treating cancer comprising administering to a mammalian specie in need thereof a therapeutically effective amount of a composition of claim 15.

35. A method for the treatment of a cyclin dependent kinase-associated disorder comprising administering to a subject in need thereof an amount effective therefor of at least one compound of claim 1.

36. A method for treating chemotherapy-induced alopecia, chemotherapy-induced thrombocytopenia, chemotherapy-induced leukopenia or mucocitis comprising administering to a mammalian specie in need thereof a therapeutically effective amount of a compound of claim 1.

37. The compound of claim 1 wherein said pharmaceutically acceptable salt is selected from the group consisting of hydrochloride, dihydrochloride, sulfate, trifluoroacetate, mixture of trifluoroacetate and hydrochloride, tartrate, fumarate, succinate, maleate, citrate, methanesulfonate, bromate and iodate salts.

38. The compound of claim 2 wherein said pharmaceutically acceptable salt is selected from the group consisting of hydrochloride, dihydrochloride, sulfate, trifluoroacetate, mixture of trifluoroacetate and hydrochloride, tartrate, fumarate, succinate, maleate, citrate, methanesulfonate, bromate and iodate salts.

39. The compound of claim 3 wherein said pharmaceutically acceptable salt is selected from the group consisting of hydrochloride, dihydrochloride, sulfate,

trifluoroacetate, mixture of trifluoroacetate and hydrochloride, tartrate, fumarate, succinate, maleate, citrate, methanesulfonate, bromate and iodate salts.

40. The compound of claim 4 wherein said pharmaceutically acceptable salt is selected from the group consisting of hydrochloride, dihydrochloride, sulfate, trifluoroacetate, mixture of trifluoroacetate and hydrochloride, tartrate, fumarate, succinate, maleate, citrate, methanesulfonate, bromate and iodate salts.

41. The compound of claim 5 wherein said pharmaceutically acceptable salt is selected from the group consisting of hydrochloride, dihydrochloride, sulfate, trifluoroacetate, mixture of trifluoroacetate and hydrochloride, tartrate, fumarate, succinate, maleate, citrate, methanesulfonate, bromate and iodate salts.

42. The compound of claim 6 wherein said pharmaceutically acceptable salt is selected from the group consisting of hydrochloride, dihydrochloride, sulfate, trifluoroacetate, mixture of trifluoroacetate and hydrochloride, tartrate, fumarate, succinate, maleate, citrate, methanesulfonate, bromate and iodate salts.

43. The compound of claim 7 wherein said pharmaceutically acceptable salt is selected from the group consisting of hydrochloride, dihydrochloride, sulfate, trifluoroacetate, mixture of trifluoroacetate and hydrochloride, tartrate, fumarate, succinate, maleate, citrate, methanesulfonate, bromate and iodate salts.

44. The compound of claim 8 wherein said pharmaceutically acceptable salt is selected from the group consisting of hydrochloride, dihydrochloride, sulfate, trifluoroacetate, mixture of trifluoroacetate and hydrochloride, tartrate, fumarate, succinate, maleate, citrate, methanesulfonate, bromate and iodate salts.

45. The compound of claim 9 wherein said pharmaceutically acceptable salt is selected from the group consisting of hydrochloride, dihydrochloride, sulfate, trifluoroacetate, mixture of trifluoroacetate and hydrochloride, tartrate, fumarate, succinate, maleate, citrate, methanesulfonate, bromate and iodate salts.

46. The compound of claim 10 wherein said pharmaceutically acceptable salt is selected from the group consisting of hydrochloride, dihydrochloride, sulfate,

trifluoroacetate, mixture of trifluoroacetate and hydrochloride, tartrate, fumarate, succinate, maleate, citrate, methanesulfonate, bromate and iodate salts.

47. The compound of claim 11 wherein said pharmaceutically acceptable salt is selected from the group consisting of hydrochloride, dihydrochloride, sulfate, trifluoroacetate, mixture of trifluoroacetate and hydrochloride, tartrate, fumarate, succinate, maleate, citrate, methanesulfonate, bromate and iodate salts.

48. The compound of claim 12 wherein said pharmaceutically acceptable salt is selected from the group consisting of hydrochloride, dihydrochloride, sulfate, trifluoroacetate, mixture of trifluoroacetate and hydrochloride, tartrate, fumarate, succinate, maleate, citrate, methanesulfonate, bromate and iodate salts.

49. The pharmaceutical composition of claim 13 wherein said pharmaceutically acceptable salt is selected from the group consisting of hydrochloride, dihydrochloride, sulfate, trifluoroacetate, mixture of trifluoroacetate and hydrochloride, tartrate, fumarate, succinate, maleate, citrate, methanesulfonate, bromate and iodate salts.

50. The pharmaceutical composition of claim 14 wherein said pharmaceutically acceptable salt is selected from the group consisting of hydrochloride, dihydrochloride, sulfate, trifluoroacetate, mixture of trifluoroacetate and hydrochloride, tartrate, fumarate, succinate, maleate, citrate, methanesulfonate, bromate and iodate salts.

51. The pharmaceutical composition of claim 15 wherein said pharmaceutically acceptable salt is selected from the group consisting of hydrochloride, dihydrochloride, sulfate, trifluoroacetate, mixture of trifluoroacetate and hydrochloride, tartrate, fumarate, succinate, maleate, citrate, methanesulfonate, bromate and iodate salts.

52. The method of claim 17 wherein said pharmaceutically acceptable salt of said compound is selected from the group consisting of hydrochloride, dihydrochloride, sulfate, trifluoroacetate, mixture of trifluoroacetate and hydrochloride, tartrate, fumarate, succinate, maleate, citrate, methanesulfonate, bromate and iodate salts.

53. The method of claim 18 wherein said pharmaceutically acceptable salt of said compound is selected from the group consisting of hydrochloride, dihydrochloride,

sulfate, trifluoroacetate, mixture of trifluoroacetate and hydrochloride, tartrate, fumarate, succinate, maleate, citrate, methanesulfonate, bromate and iodate salts.

54. The method of claim 20 wherein said pharmaceutically acceptable salt of said compound is selected from the group consisting of hydrochloride, dihydrochloride, sulfate, trifluoroacetate, mixture of trifluoroacetate and hydrochloride, tartrate, fumarate, succinate, maleate, citrate, methanesulfonate, bromate and iodate salts.

55. The method of claim 27 wherein said pharmaceutically acceptable salt of said compound is selected from the group consisting of hydrochloride, dihydrochloride, sulfate, trifluoroacetate, mixture of trifluoroacetate and hydrochloride, tartrate, fumarate, succinate, maleate, citrate, methanesulfonate, bromate and iodate salts.

56. The method of claim 28 wherein said pharmaceutically acceptable salt of said compound is selected from the group consisting of hydrochloride, dihydrochloride, sulfate, trifluoroacetate, mixture of trifluoroacetate and hydrochloride, tartrate, fumarate, succinate, maleate, citrate, methanesulfonate, bromate and iodate salts.

57. The method of claim 31 wherein said pharmaceutically acceptable salt of said compound is selected from the group consisting of hydrochloride, dihydrochloride, sulfate, trifluoroacetate, mixture of trifluoroacetate and hydrochloride, tartrate, fumarate, succinate, maleate, citrate, methanesulfonate, bromate and iodate salts.

58. The method of claim 32 wherein said pharmaceutically acceptable salt of said compound is selected from the group consisting of hydrochloride, dihydrochloride, sulfate, trifluoroacetate, mixture of trifluoroacetate and hydrochloride, tartrate, fumarate, succinate, maleate, citrate, methanesulfonate, bromate and iodate salts.

59. The method of claim 36 wherein said pharmaceutically acceptable salt of said compound is selected from the group consisting of hydrochloride, dihydrochloride, sulfate, trifluoroacetate, mixture of trifluoroacetate and hydrochloride, tartrate, fumarate, succinate, maleate, citrate, methanesulfonate, bromate and iodate salts.