QUINAZOLINYLMETHYLENETHIAZOLINONES AS CDK1 INHIBITORS

The field of this invention relates to quinazoline thiazolinone derivatives which demonstrate CDK1 antiproliferative activity and are useful as anti-cancer agents.

Cyclin-dependent kinases (CDKs) are serine-threonine protein kinases that play critical roles in regulating the transitions between different phases of the cell-cycle, such as the progression from a quiescent stage in G_1 (the gap between mitosis and the onset of DNA replication for a new round of cell division) to S (the period of active DNA synthesis), or the progression from G_2 to M phase, in which active mitosis and cell-division occurs. (See, e.g., the articles compiled in *Science*, **274**:1643-1677 (1996); and *Ann. Rev. Cell Dev. Biol.*, **13**:261-291 (1997)). CDK complexes are formed through association of a regulatory cyclin subunit (e.g., cyclin A, B1, B2, D1, D2, D3 and E) and a catalytic kinase subunit (e.g., CDK1, CDK2, CDK4, CDK5 and CDK6). As the name implies, the CDKs display an absolute dependence on the cyclin subunit in order to phosphorylate their target substrates, and different kinase/cyclin pairs function to regulate progression through specific phases of the cell-cycle.

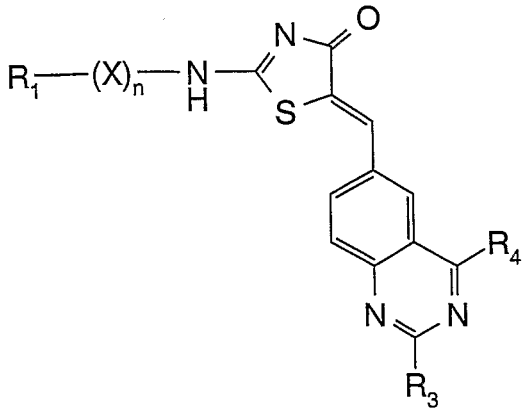
As seen above, these protein kinases are a class of proteins (enzymes) that regulate a variety of cellular functions. This is accomplished by the phosphorylation of specific amino acids on protein substrates resulting in conformational alteration of the substrate protein. The conformational change modulates the activity of the substrate or its ability to interact with other binding partners. The enzyme activity of the protein kinase refers to the rate at which the kinase adds phosphate groups to a substrate. It can be measured, for example, by determining the amount of a substrate that is

converted to a product as a function of time. Phosphorylation of a substrate occurs at the active-site of a protein kinase.

In view of the above properties, these kinases play an important part in the propagation of growth factor signal transduction that leads to cellular proliferation, differentiation and migration. Fibroblast growth factor (FGF) and vascular endothelial growth factor (VEGF) have been recognized as important mediators of tumor promoted angiogenesis. VEGF activates endothelial cells by signaling through two high affinity receptors, one of which is the kinase insert domain-containing receptor (KDR). (See, Hennequin L. F. et. al., *J. Med. Chem.* **45(6):**1300 (2002)). FGF activates endothelial cells by signaling through the FGF receptor (FGFR). Solid tumors depend upon the formation of new blood vessels (angiogenesis) to grow. Accordingly, inhibitors of the receptors FGFR and KDR that interfere with the growth signal transduction, and thus slow down or prevent angiogenesis, are useful agents in the prevention and treatment of solid tumors. (See, Klohs W.E. et. al., *Current Opinion in Biotechnology,* **10:**544 (1999).

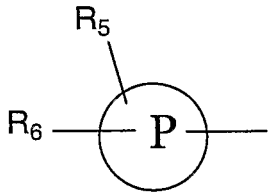
Because CDKs, such as CDK1, serve as general activators of cell division, inhibitors of CDK1 can be used as antiproliferative agents. These inhibitors can be used for developing therapeutic intervention in suppressing deregulated cell cycle progression.

In accordance with this invention, it has been discovered that the compound of the formula I

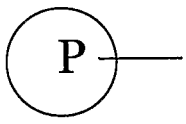


I

wherein

R_1 is hydrogen, lower alkyl or  ;

X is selected from lower alkylene, cyclolower alkylene containing from 3 to 6 carbon atoms and hydroxy lower alkylene;

 is selected from

an aryl ring,

a cycloalkyl ring containing from 3 to 6 carbon atoms,

a 4 to 6 membered heterocycloalkyl ring containing from 3 to 5 carbon atoms and from 1 to 2 hetero atoms selected from the group consisting of oxygen, nitrogen and sulfur, and

a 5 or 6 membered heteroaromatic ring containing from 1 to 2 hetero atoms selected from the group consisting of oxygen, sulfur and nitrogen;

R_5 and R_6 are independently selected from the group consisting of hydrogen, hydroxy, hydroxy-lower alkyl, lower alkyl, halogen, perfluro-lower alkyl and lower alkoxy;

R_3 is selected from hydrogen, -NH-R_7 and -NH-C(O)-R_8;

R_4 is selected from hydrogen, lower alkyl and $-O(CH_2CH_2O)_y-R_{10}$;

R_7 is hydrogen or lower alkyl;

R_8 and R_{10} are lower alkyl;

n is an integer from 0 to 1; and

y is an integer of from 0 to 3;

with the proviso that when n is 0 and R_1 is hydrogen or lower alkyl then R_3/R_4 cannot both be hydrogen; or

N-oxides of compounds where R_1 contains a nitrogen in the heteroaromatic ring, sulfones where R_1 contains a sulfur in the heterocycloalkyl ring or heteroaromatic ring; or

pharmaceutically acceptable salts thereof,

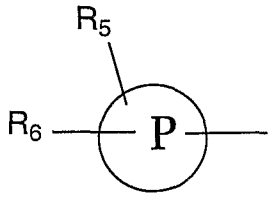
inhibit the activity of CDKs, particularly, CDK1. These inventive agents and pharmaceutical compositions containing such agents are useful in treating various diseases or disorder states associated with uncontrolled or unwanted cellular proliferation, such as cancer, autoimmune diseases, viral diseases, fungal diseases, neurodegenerative disorders and cardiovascular diseases.

Inhibiting and/or modulating the activity of CDKs, particularly CDK1, makes these compounds of formula I and compositions containing these compounds useful in treating diseases medicated by kinase activity, particularly as anti-tumor agents in treating cancers, particularly solid tumors and more particularly lung cancer, breast cancer, colon cancer and prostate cancer.

As pointed out herein, the compounds of formula I are potential anti-proliferation agents and are useful for mediating and/or inhibiting the activity of CDKs, particularly CDK1, thus providing anti-tumor agents for treatment of cancer or other diseases associated with uncontrolled or abnormal cell proliferation.

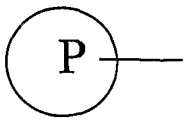
In one preferred embodiment of the present invention there are provided the compounds of formula I

wherein

R_1 is hydrogen, or 

;

X is selected from lower alkylene, cyclolower alkylene containing from 3 to 6 carbon atoms and hydroxy lower alkylene;



is selected from an aryl ring, cyclolower alkyl ring containing from 3 to 6 carbon atoms, a 4 to 6 membered heterocycloalkyl ring containing from 3 to 5 carbon atoms and from 1 to 2 hetero atoms selected from the group consisting of oxygen, nitrogen and sulfur, and a 5 or 6 membered heteroaromatic ring containing from 1 to 2 hetero atoms selected from the group consisting of oxygen, sulfur and nitrogen;

R_5 and R_6 are independently selected from the group consisting of hydrogen, hydroxy, hydroxy-lower alkyl, lower alkyl, halogen, perfluro-lower alkyl and lower alkoxy;

R_3 is selected from hydrogen, $-NHR_7$, and $-NH-C(O)-R_8$;

R_4 is selected from hydrogen, lower alkyl, and $-O(CH_2CH_2O)_y-R_{10}$;

$R_7$is hydrogen or lower alkyl;

R_8 and R_{10} are lower alkyl;

n is an integer from 0 to 1; and

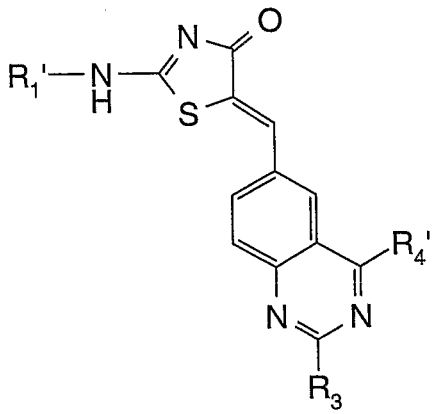
y is an integer of from 0 to 3;

with the proviso that when n is 0, one of R_1, R_3 and R_4 is other then hydrogen; or

N-oxides of compounds where R_1 contains a nitrogen in the heteroaromatic ring, sulfones where R_1 contains a sulfur in the heterocycloalkyl ring or heteroaromatic ring, or

pharmaceutically acceptable salts thereof.

Among the preferred compounds of formula I are compounds where n is 0. These compounds include the compounds of the formula:



I-A

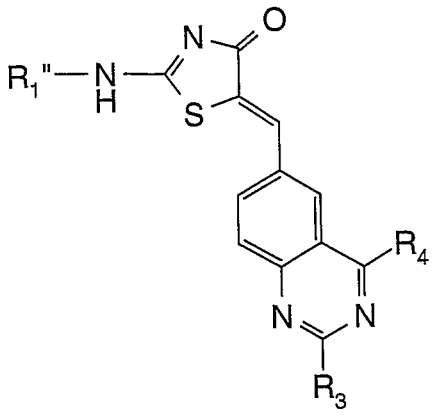
wherein R_1' is hydrogen or a lower alkyl;

R_4' is lower alkyl or $-O(CH_2CH_2O)_y-R_{10}$; and

R_3, R_{10} and y are as above; or

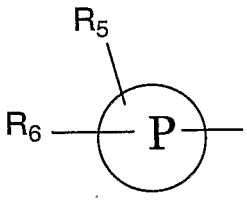
pharmaceutically acceptable salts thereof.

The compounds of formula I where n is 0 also includes the compounds of the formula:



I-B

wherein



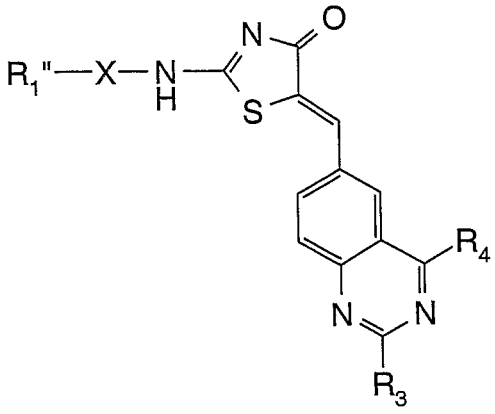
R_1" is ;

R_3, R_4, R_5, R_6 and  are as above; or

N-oxides of compounds where R_1" contains a nitrogen in the heteroaromatic ring, sulfones where R_1" contains a sulfur in the hetero ring or heteroaromatic ring; or

pharmaceutically acceptable salts thereof.

When n in the compound of formula I is 1, this compound has the formula:



I-C

wherein

R_1", X, R_3, R_4 and  are as above; or

N-oxides of compounds where R_1" contains a nitrogen in the heteroaromatic ring, sulfones where R_1" contains a sulfur in the hetero ring or heteroaromatic ring; or

pharmaceutically acceptable salts thereof.

In compounds I, I-B and I-C, where R_1 and R_1" are substituents containing an aryl moiety, the preferred aryl moiety is phenyl. As used herein the halogen includes all four halogens such as chlorine, fluorine, bromine and iodine.

As used in the specification, the term "lower alkyl", alone or in combination, means a monovalent straight or branched-chain saturated hydrocarbon alkyl group containing from 1 to 6 carbon atoms, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, n-hexyl and the like.

The term "cycloalkyl" means a cyclo-lower alkyl substituent which designates a monovalent, unsubstituted, 3- to 6-membered saturated hydrocarbon ring. Among the

preferred cycloalkyl substituents are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like.

The term "lower alkoxy" means a straight-chain or branched-chain -O-lower alkyl group formed from lower alkyl as defined above, such as methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, tert-butoxy and the like.

The term "aryl" means a monovalent mono- or bicyclic unsubstituted aromatic hydrocarbon ring, such as phenyl or naphthyl, with phenyl being preferred.

The term "heterocycloalkyl" refers to a 4 to 6 membered monocyclic saturated ring containing 3 to 4 carbon atoms and 1 or 2 hetero atoms selected from the group consisting of oxygen, nitrogen and sulfur. Among the preferred heterocyclic alkyl groups are included mopholinyl, tetrahydro, thiopyranyl or tetrahydro pyranyl and the like.

The term "heteroaromatic ring" refers to a monovalent 5 or 6 membered monocyclic heteroaromatic ring containing from 4 to 5 carbon atoms and from 1 to 2 hetero atoms selected from the group consisting of oxygen, nitrogen and sulfur. Among the preferred heteroaromatic groups are included thiopenyl, thioazole, pyridinyl, furanyl, and the like.

The term "lower alkylene" designates a divalent, saturated straight or branched chain hydrocarbon substituent containing from 1 to 6 carbon atoms.

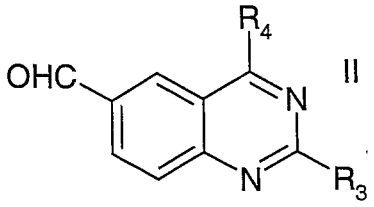
The term "hydroxy-lower alkylene" designates a lower alkylene substituent as defined above substituted, preferably monosubstituted, with a hydroxy group. Similarly, where an "amido-lower alkylene" is used, this designates a lower alkylene substituent as set forth hereinbefore substituted with an amido substituent.

The term "cyclo lower alkylene" or "cycloalkylene" designates a divalent, unsubstituted 3 to 6 membered saturated hydrocarbon ring. Among the preferred cycloalkylene substituents are divalent cyclopropyl and cyclobutyl.

The term "perfluoro-lower alkyl" means any lower alkyl group as defined above, wherein all the hydrogens of the lower alkyl group are substituted or replaced by fluorine. Among the preferred perfluoro-lower alkyl groups are trifluoromethyl, pentafluoroethyl, heptafluoropropyl, etc with trifluoromethyl being especially preferred.

The term "pharmaceutically acceptable salts" refers to conventional acid-addition salts or base-addition salts that retain the biological effectiveness and properties of the compounds of formulas I, I-A, I-B and I-C are formed from suitable non-toxic organic or inorganic acids, or organic or inorganic bases. Sample acid-addition salts include those derived from inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, sulfamic acid, phosphoric acid and nitric acid, and those derived from organic acids such as p-toluenesulfonic acid, salicylic acid, methanesulfonic acid, oxalic acid, succinic acid, citric acid, maleic acid, lactic acid, fumaric acid, and the like. Sample base-addition salts include those derived from ammonium, potassium, sodium and, quaternary ammonium hydroxides, such as for example, tetramethylammonium hydroxide. The chemical modification of a pharmaceutical compound (i.e., drug) into a salt is a technique well known to pharmaceutical chemists to obtain improved physical and chemical stability, hygroscopicity, flowability and solubility of compounds. *See, e.g.*, H. Ansel et al., *Pharmaceutical Dosage Forms and Drug Delivery Systems* (6th Ed. 1995) at pp. 196 and 1456-1457.

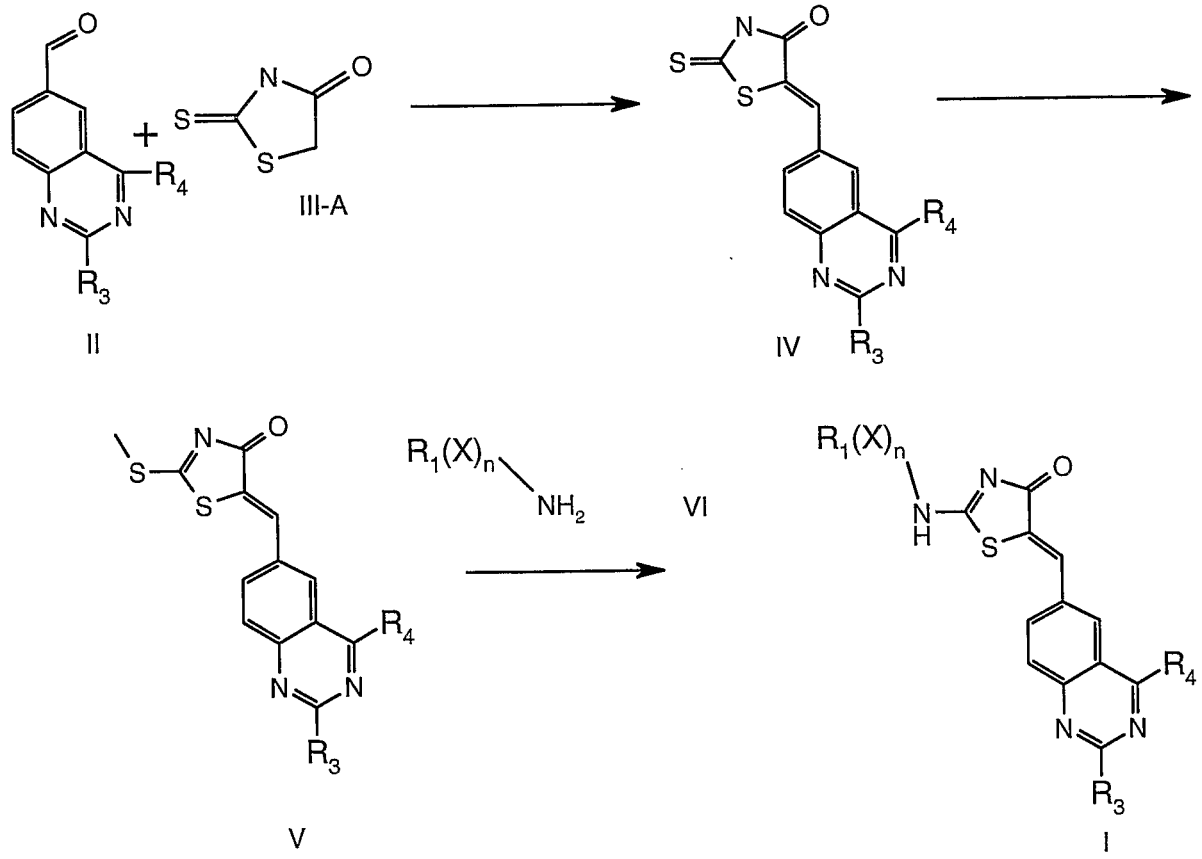
In accordance with this invention, the compounds of formula I can be prepared from a compound of the formula:



II

wherein R_3 and R_4 are as above.

The compound of formula II is converted to the compound of formula I via the following reaction scheme 1, wherein X, R_1, R_3, R_4 and n are as defined above.



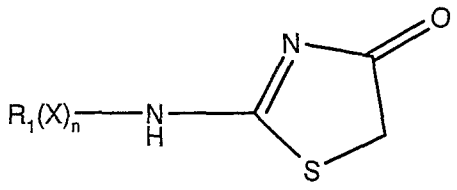
scheme 1

In accordance with this invention, the compound of formula II is reacted with the compound of formula III-A [rhodanine (2-thio-4-thiazolin-4-one)] via a Knoevenegel reaction to produce the compound of formula IV. Any of the conditions conventional in carrying out Knoevenegel reaction can be utilized in carrying out this condensation. Generally this reaction is carried out at reflux temperature in the presence of alkali metal acetate and acetic acid.

In the next step of this synthesis, the resulting substituted thiazolidine of formula IV is treated with a methylating agent to methylate the thio group on the compound of formula IV to produce the compound of formula V. The preferred methylating agent is iodomethane. This reaction is carried out in an organic amine base such as diisopropylethylamine (DIEA). In carrying out this reaction temperature and pressure are not critical and this reaction can be carried out at room temperature and atmospheric pressure. In fact in carrying out this reaction, any of the conditions conventional in methylating a thio group can be used.

In the next step of this synthesis, the compound of formula V is reacted with the compound of formula VI to produce the compound of formula I. The compound of formula VI is an amine and any means conventionally used in amine substitution of the methylthio group can be used in carrying out this reaction. In accordance with one embodiment this substitution is carried out by reacting the compound of formula VI with the compound of formula V in the presence of a conventional solvent such as acetonitrile. Generally this reaction is carried out in the presence of an amine base such as diisopropylethylamine.

On the other hand, the compound of formula I can be prepared by reacting the compound of formula II with a compound of the formula:



VII

wherein R_1 is as above.

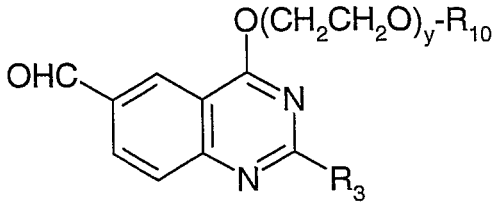
The reaction of the compound of formula VII with the compound of formula II to produce the compound of formula I, is carried out in an organic solvent such as benzene or toluene at high temperature of from 100ºC to 200ºC in a closed system. In this manner, this reaction is carried out under high temperatures and pressure. The compound of formula VII can be directly formed by direct replacement thorough reacting the compound of the formula

$$R_1(X)_n—NH_2 \qquad VI$$

wherein R_1, X and n are as above,

with a compound of the formula III-A. The replacement reaction is generally carried out in the presence of an activator and an amine base. Among the preferred activators is mercuric chloride. This reaction is carried out in an inert organic solvent. Any conventional inert organic solvent such as acetonitrile, methylene chloride, etc. can be utilized. In carrying out this reaction, an amine base, such as diisoproprylethylamine, is used. In carrying out this reaction, temperature and pressure are not critical and this reaction can be carried out at room temperature and atmospheric pressure. In carrying out this reaction, any conventional method of replacing a mercapto group with an amine can be utilized.

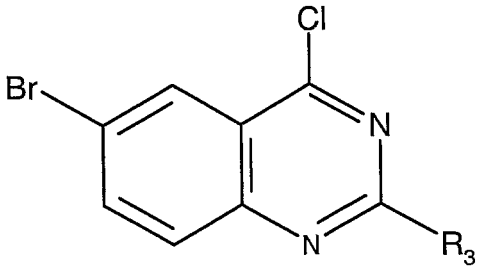
In accordance with an embodiment of this in the compound of formula II, when R_4 is $-O(CH_2CH_2O)_y-R_{10}$, and R_{10} and y are as above has the formula:



II-A

wherein R_3, R_{10} and y are as above.

The compound of formula II-A can be prepared from a compound of the formula



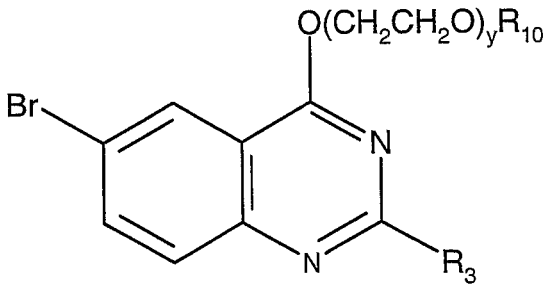
X

by reacting with a compound of the formula,

$$NaO(CH_2CH_2O)_y\text{-}R_{10} \qquad XI$$

wherein R_{10} and y are as above,

to produce

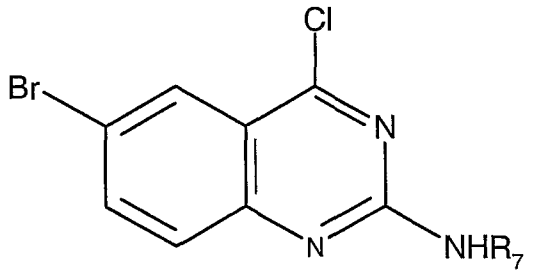


XII

wherein R_{10}, R_3 and y are as above

The reaction of the compound of formula X with the compound of formula XI to produce a compound XII is carried out by conventional mean of reacting a chloride with an alkali metal alkoxide to produce an ether. Any conventional mean of reacting a chloride with an alkali metal alkoxide can be used to form the compound of formula XII. In the next step of this reaction to produce the compound of formula II-A using formylation reaction to convert the bromo group to the CHO substituent on the phenyl ring. This reaction is carried out by reacting the compound of formula XI with carbon monoxide under pressure in the presence of diphenyl propyl phosphine (dpp) and a base utilizing palladium acetate as catalyst at temperature of from 60 to 100ºC. Pressures generally from 70 to 80 psi are utilized in carrying out this reaction. Any conventional method of formylation reaction to convert a halide group on a phenyl ring by means of reaction with carbon monoxide can be utilized to carry out this conversion.

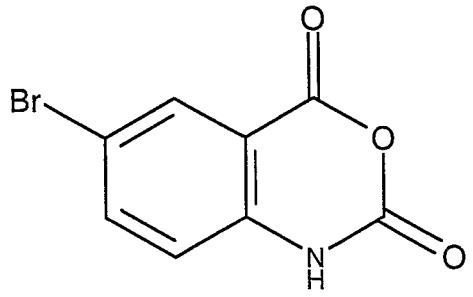
Where R_3 is the compound of formula X is $-NHR_7$, this compound has the formula:



X-A

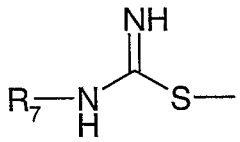
wherein R_7 is as above.

The compound of formula X-A can be prepared from a compound of the formula:



XV

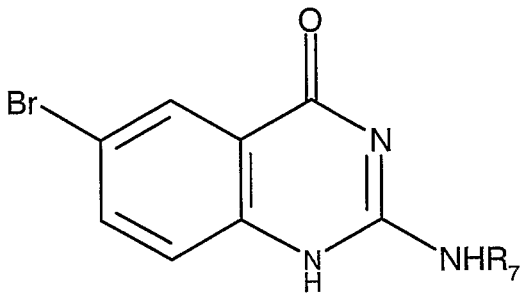
by reacting the compound of formula XV (the synthesis of the compound of formula is described in example 12 b) with a compound of formula:



XVI

wherein R_7 is as above,

to produce the compound of formula:



XVII

wherein R_7 is as above

which can be converted to the compound of formula X-A.

The compound of formula XV converted to the compound of formula XVII by reacting the compound of formula XV with the compound of formula XVI. This reaction is carried out by adding the compound of formula XVI to the compound of formula XV in

the presence of an inert solvent. Any conventional inert solvent such as acetonitrile and water can be utilized as the reaction medium. The reaction can be carried out by

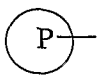
heating the resulting mixture to reflux. The compound of formula XVII can be converted to the compound of formula X-A by treating with a conventional chlorinating agent such as phosphorous oxychloride. This reaction is carried out by heating to reflux generally under a nitrogen atmosphere.

The compound of formula XVI is either commercially available or can be prepared from their corresponding thiourea, R_7-NH-C(=S)-NH_2, with alkylating reagent, such as iodomethane.

In the compounds of formula I, I-B and I-C, preferred are those class of compounds where R_3 and R_4 are both hydrogen and those class of compounds where R_3 is -NHR_7 and R_4 is hydrogen or -$O(CH_2CH_2O)_y$-R_{10}.

In compound I and I-B where n is 1 the substituents for R_1 and R_1' are aryl rings the preferred ring is a phenyl which can be unsubstituted or substituted with this substituents defined as R_5 and R_6.

One embodiment of the compound of formula I-A are those compounds where R_1' is hydrogen. Among these class of compounds are those compounds where R_4' is -$O(CH_2CH_2O)_y$-R_{10}.

Another embodiment of this invention are the compounds of formula I-B where n is 0 and  is phenyl or a heteroaromatic ring containing from 1 to 2 heteroatoms. The preferred heteroaromatic rings are those rings containing two hetero atoms one being nitrogen and the other being sulfur, and thiazole being most preferred. Another

preferred heteroaromatic ring is that having one hetero atom, preferably sulfur, with thiophene being especially preferred.

In accordance with another embodiment of the compound of formula I-B where n is 1 are those compounds where X is a lower alkylene substituent. This embodiment includes a class of compounds where R_1 contains a phenyl ring which can be phenyl or substituted phenyl. Another class of compounds are those compounds where n is 1 are those compounds where X is a lower alkylene substituent and R_1' is a heteroaromatic ring. The preferred heteroaromatic rings are those which contain two hetero atoms, one being nitrogen and the other being sulfur, and thiazole being most preferred. Another preferred heteroaromatic ring are those containing one heteroatom, preferably sulfur, with thiophene being especially preferred. In this preferred class of compounds R_4 is preferably $-O(CH_2CH_2O)_y-R_{10}$.

Another embodiment of the compound of formula I-B where n is 1 are those compounds where X is a hydroxy-lower alkylene substituent. In this class of compounds is included those compounds where R_1 is a heteroaromatic ring. The preferred heteroaromatic rings are those which contain two hetero atoms one being nitrogen and the other being sulfur, with thiazole being most preferred. Another preferred heteroaromatic ring is that having one heteroatom, preferably sulfur, with thiophene being especially preferred. In this preferred class of compounds, R_4 is preferably $-O(CH_2CH_2O)_y-R_{10}$. Another preferred class of compounds where n is I and X' is a hydroxy-lower alkylene substituent are those compounds where R_1 is a phenyl ring which can be phenyl or substituted phenyl. In this preferred class of compounds, R_4 is preferably $-O(CH_2CH_2O)_y-R_{10}$.

Pharmaceutical compositions according to the invention may, alternatively or in addition to a compound of Formula I, comprise as an active ingredient pharmaceutically acceptable prodrugs, pharmaceutically active metabolites, and pharmaceutically acceptable salts of such compounds and metabolites. Such compounds, prodrugs,

multimers, salts, and metabolites are sometimes referred to herein collectively as "active agents" or "agents."

In the case of agents that are solids, it is understood by those skilled in the art that the inventive compounds and salts may exist in different crystal or polymorphic forms, all of which are intended to be within the scope of the present invention and specified formulas.

Therapeutically effective amounts of the active agents of the invention may be used to treat diseases mediated by modulation or regulation of the protein kinases CDK1. An "effective amount" is intended to mean that amount of an agent that significantly inhibits proliferation and/or prevents de-differentiation of a eukaryotic cell, e.g., a mammalian, insect, plant or fungal cell, and is effective for the indicated utility, e.g., specific therapeutic treatment.

The amount of a given agent that will correspond to such an amount will vary depending upon factors such as the particular compound, disease condition and its severity, the identity (e.g., weight) of the subject or host in need of treatment, but can nevertheless be routinely determined in a manner known in the art according to the particular circumstances surrounding the case, including, e.g., the specific agent being administered, the route of administration, the condition being treated, and the subject or host being treated. "Treating" is intended to mean at least the mitigation of a disease condition in a subject such as mammal (e.g., human), that is affected, at least in part, by the activity of CDK1 protein kinase includes: preventing the disease condition from occurring in a mammal, particularly when the mammal is found to be predisposed to having the disease condition but has not yet been diagnosed as having it; modulating and/or inhibiting the disease condition; and/or alleviating the disease condition.

The present invention is further directed to methods of modulating or inhibiting protein kinase CDK1 activity, for example in mammalian tissue, by administering the

inventive agent. The activity of agents as anti-proliferatives is easily measured by known methods, for example by using whole cell cultures in an MTT assay. The activity of the inventive agents as modulators of CDK1 protein kinase activity may be measured by any of the methods available to those skilled in the art, including in vivo and/or in vitro assays. Examples of suitable assays for activity measurements include those described in International Publication No. WO 99/21845; Parast et al., Biochemistry, 37, 16788-16801 (1998); Connell-Crowley and Harpes, Cell Cycle: Materials and Methods, (Michele Pagano, ed. Springer, Berlin, Germany)(1995); International Publication No. WO 97/34876; and International Publication No. WO 96/14843. These properties may be assessed, for example, by using one or more of the biological testing procedures set out in the examples below.

The active agents of the invention may be formulated into pharmaceutical compositions as described below. Pharmaceutical compositions of this invention comprise an effective modulating, regulating, or inhibiting amount of a compound of Formula I and an inert, pharmaceutically acceptable carrier or diluent. In one embodiment of the pharmaceutical compositions, efficacious levels of the inventive agents are provided so as to provide therapeutic benefits involving anti-proliferative ability. By "efficacious levels" is meant levels in which proliferation is inhibited, or controlled. These compositions are prepared in unit-dosage form appropriate for the mode of administration, e.g., parenteral or oral administration.

An inventive agent can be administered in conventional dosage form prepared by combining a therapeutically effective amount of an agent (e.g., a compound of Formula I) as an active ingredient with appropriate pharmaceutical carriers or diluents according to conventional procedures. These procedures may involve mixing, granulating and compressing or dissolving the ingredients as appropriate to the desired preparation.

The pharmaceutical carrier employed may be either a solid or liquid. Exemplary of solid carriers are lactose, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, stearic acid and the like. Exemplary of liquid carriers are syrup, peanut oil, olive oil, water and the like. Similarly, the carrier or diluent may include time-delay or time-release material known in the art, such as glyceryl monostearate or glyceryl distearate alone or with a wax, ethylcellulose, hydroxypropylmethylcellulose, methyl methacrylate and the like.

A variety of pharmaceutical forms can be employed. Thus, if a solid carrier is used, the preparation can be tableted, placed in a hard gelatin capsule in powder or pellet form or in the form of a troche or lozenge. The amount of solid carrier may vary. If a liquid carrier is used, the preparation will be in the form of syrup, emulsion, soft gelatin capsule, sterile injectable solution or suspension in an ampoule or vial or non-aqueous liquid suspension.

To obtain a stable water-soluble dose form, a pharmaceutically acceptable salt of an inventive agent can be dissolved in an aqueous solution of an organic or inorganic acid. If a soluble salt form is not available, the agent may be dissolved in a suitable cosolvent or combinations of cosolvents.

It will be appreciated that the actual dosages of the agents used in the compositions of this invention will vary according to the particular complex being used, the particular composition formulated, the mode of administration and the particular site, host and disease being treated. Optimal dosages for a given set of conditions can be ascertained by those skilled in the art using conventional dosage determination tests in view of the experimental data for an agent.

The compositions of the invention may be manufactured in manners generally known for preparing pharmaceutical compositions, e.g., using conventional techniques such as mixing, dissolving, granulating, dragee-making, levigating, emulsifying,

encapsulating, entrapping or lyophilizing. Pharmaceutical compositions may be formulated in a conventional manner using one or more physiologically acceptable carriers, which may be selected from excipients and auxiliaries that facilitate processing of the active compounds into preparations which can be used pharmaceutically.

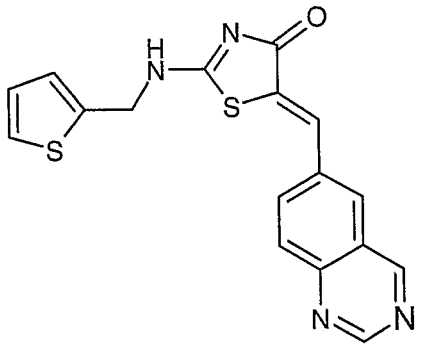
For oral administration, the compounds can be formulated readily by combining the compounds with pharmaceutically acceptable carriers known in the art. Such carriers enable the compounds of the invention to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a patient to be treated. Pharmaceutical preparations for oral use can be obtained using a solid excipient in admixture with the active ingredient (agent), optionally grinding the resulting mixture, and processing the mixture of granules after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores.

The present invention is now further illustrated by the following examples which are not meant to limit its scope. If not explicitly otherwise stated temperatures are indicated in Celsius degrees (°C).

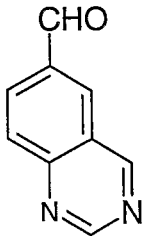
Examples

Example 1

5-[1-Quinazolin-6-yl-meth-(Z)-ylidene]-2-[(thiophen-2-ylmethyl)-amino]-thiazol-4-one

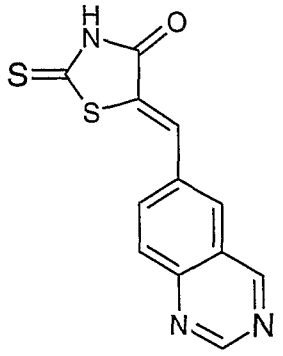


Preparation of 6-quinazolinecarboxaldehyde



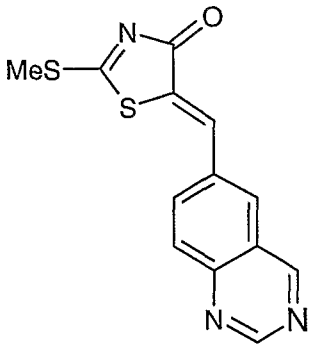
The mixture of 6-methyl-quinazoline (5.0 g, 34.7 mmol) and selenium dioxide (7.7 g, 69.4 mmol) was heated at 160°C for 12 hours. After cooling to room temperature, methanol was added with stirring. After removal of solid by filtration, the filtrate was concentrated. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 0%-30% ethyl acetate in hexane in 30 min) afforded 6-quinazolinecarboxaldehyde (2.4 g, 43.7%) as a white solid: LC-MS m/e 159 (MH^+).

Preparation of 5-quinazolin-6-ylmethylene-2-thioxo-thiazolidin-4-one



The suspension of 6-quinazolinecarboxaldehyde (example 1a, 1.5 g, 9.5 mmol), rhodanine (1.26 g, 9.5 mmol) and sodium acetate (3.11 g, 38 mmol) in acetic acid (10 mL) was stirred at 130°C for 12 h. After cooling to room temperature, water (40 mL) was added. The solid was collected by filtration, washed with water and dried to obtain 5-quinazolin-6-ylmethylene-2-thioxo-thiazolidin-4-one (2.6 g, 100%) as a solid. LC-MS m/e 274 (MH^+).

Preparation of 2-methylsulfanyl-5-quinazolin-6-ylmethylene-thiazol-4-one



The suspension of 5-quinazolin-6-ylmethylene-2-thioxo-thiazolidin-4-one (example 1b, 2.6 g, 9.52 mmol), iodomethane (1.2 mL, 19.0 mmol) and diisopropylethylamine (DIEA) (2.4 mL, 14.3 mmol) in anhydrous ethanol (100 mL) was stirred at room temperature for 12 h. After adding water (200 mL), the solid was collected by filtration, washed with water and dried to obtain 2-methylsulfanyl-5-

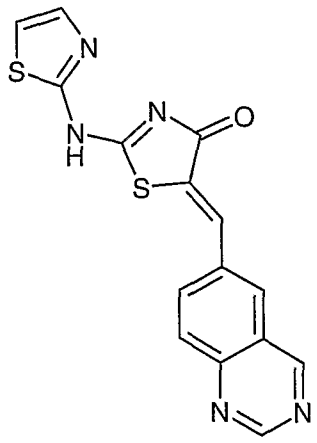
quinazolin-6-ylmethylene-thiazol-4-one (2.5 g, 92%) as a black solid. LC-MS m/e 288 (MH^+).

Preparation of 5-[1-quinazolin-6-yl-meth-(Z)-ylidene]-2-[(thiophen-2-ylmethyl)-amino]-thiazol-4-one

The suspension of 2-methylsulfanyl-5-quinazolin-6-ylmethylene-thiazol-4-one (example 1c, 58 mg, 0.2 mmol), thiophene methyl amine (45.3 mg, 0.4 mmol) and diisopropylethylamine (DIEA) (70 uL, 0.4 mmol) in acetonitrile (1 mL) was heated to 145°C by microwave for 20 min. After cooling to room temperature, the solid was collected by filtration, washed with a small amount of acetonitrile and dried. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 0%-5% methanol in methylene chloride in 30 min) afforded 5-[1-quinazolin-6-yl-meth-(Z)-ylidene]-2-[(thiophen-2-ylmethyl)-amino]-thiazol-4-one as a light yellow solid: LC-MS m/e 353 (MH^+).

Example 2

5-[1-Quinazolin-6-yl-meth-(Z)-ylidene]-2-(thiazol-2-ylamino)-thiazol-4-one

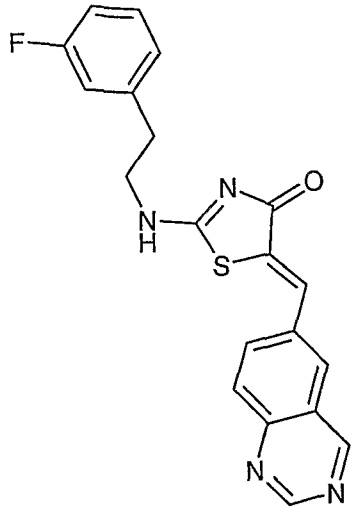


Similar procedure as described in example 1d was used, starting from 2-methylsulfanyl-5-quinazolin-6-ylmethylene-thiazol-4-one, thiazol-2-ylamine and DIEA to

give 5-[1-quinazolin-6-yl-meth-(Z)-ylidene]-2-(thiazol-2-ylamino)-thiazol-4-one: LC-MS m/e observed. LC-MS m/e 340 (MH^+).

Example 3

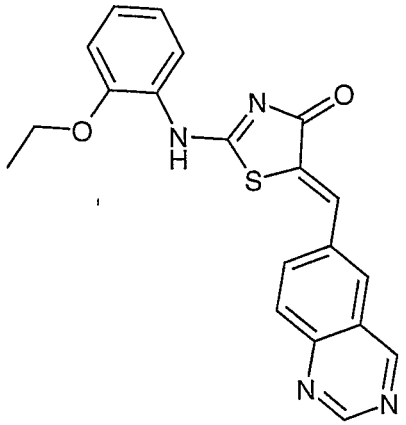
2-[2-(3-Fluoro-phenyl)-ethylamino]-5-[1-quinazolin-6-yl-meth-(Z)-ylidene]-thiazol-4-one



Similar procedure as described in example 1d was used, starting from 2-methylsulfanyl-5-quinazolin-6-ylmethylene-thiazol-4-one, 2-(3-fluoro-phenyl)-ethylamine and DIEA to give 2-[2-(3-fluoro-phenyl)-ethylamino]-5-[1-quinazolin-6-yl-meth-(Z)-ylidene]-thiazol-4-one: LC-MS m/e observed. LC-MS m/e 379 (MH^+).

Example 4

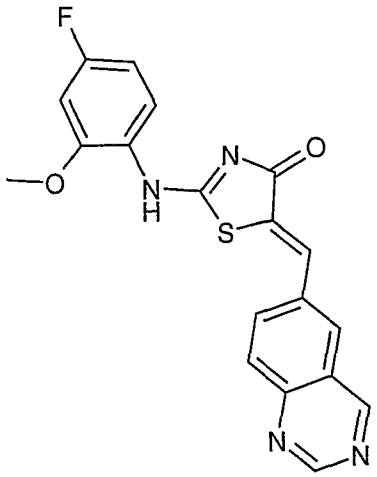
2-(2-Ethoxy-phenylamino)-5-[1-quinazolin-6-yl-meth-(Z)-ylidene]-thiazol-4-one



Similar procedure as described in example 1d was used, starting from 2-methylsulfanyl-5-quinazolin-6-ylmethylene-thiazol-4-one, 2-ethoxyaniline and DIEA to give 2-(2-ethoxy-phenylamino)-5-[1-quinazolin-6-yl-meth-(Z)-ylidene]-thiazol-4-one: LC-MS m/e observed. LC-MS m/e 377 (MH^+).

Example 5

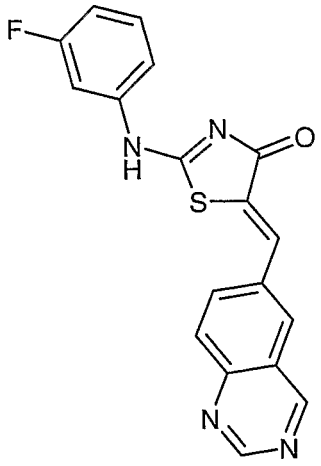
2-(4-Fluoro-2-methoxy-phenylamino)-5-[1-quinazolin-6-yl-meth-(Z)-ylidene]-thiazol-4-one



Similar procedure as described in example 1d was used, starting from 2-methylsulfanyl-5-quinazolin-6-ylmethylene-thiazol-4-one, 4-fluoro-2-methoxy-aniline and DIEA to give 2-(4-fluoro-2-methoxy-phenylamino)-5-[1-quinazolin-6-yl-meth-(Z)-ylidene]-thiazol-4-one: LC-MS m/e observed. LC-MS m/e 381 (MH^+).

Example 6

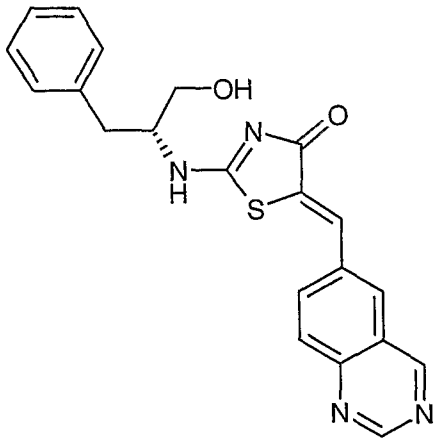
2-(3-Fluoro-phenylamino)-5-[1-quinazolin-6-yl-meth-(Z)-ylidene]-thiazol-4-one



Similar procedure as described in example 1d was used, starting from 2-methylsulfanyl-5-quinazolin-6-ylmethylene-thiazol-4-one, 3-fluoroaniline and DIEA to give 2-(3-fluoro-phenylamino)-5-[1-quinazolin-6-yl-meth-(Z)-ylidene]-thiazol-4-one: LC-MS m/e observed. LC-MS m/e 351 (MH^+).

Example 7

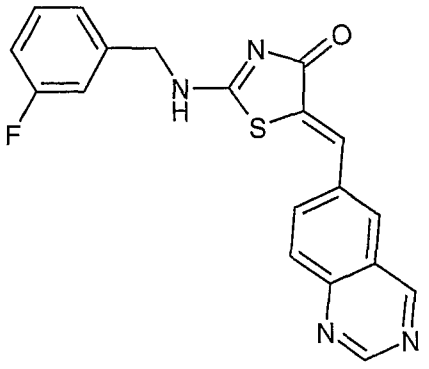
2-((R)-1-Hydroxymethyl-2-phenyl-ethylamino)-5-[1-quinazolin-6-yl-meth-(Z)-ylidene]-thiazol-4-one



Similar procedure as described in example 1d was used, starting from 2-methylsulfanyl-5-quinazolin-6-ylmethylene-thiazol-4-one, 2-((R)-1-hydroxymethyl-2-phenyl-ethylamine and DIEA to give 2-((R)-1-hydroxymethyl-2-phenyl-ethylamino)-5-[1-quinazolin-6-yl-meth-(Z)-ylidene]-thiazol-4-one: LC-MS m/e observed. LC-MS m/e 391 (MH^+).

Example 8

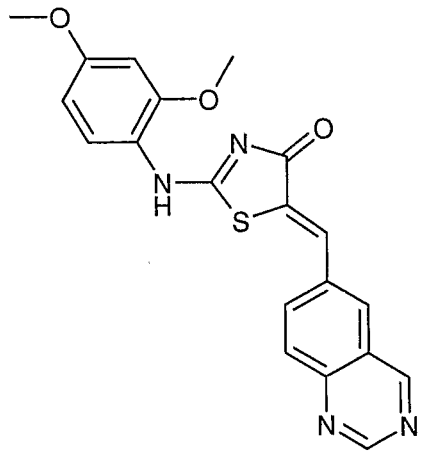
2-(3-Fluoro-benzylamino)-5-[1-quinazolin-6-yl-meth-(Z)-ylidene]-thiazol-4-one



Similar procedure as described in example 1d was used, starting from 2-methylsulfanyl-5-quinazolin-6-ylmethylene-thiazol-4-one, 3-fluoro-benzylamine and DIEA to give 2-(3-fluoro-benzylamino)-5-[1-quinazolin-6-yl-meth-(Z)-ylidene]-thiazol-4-one: LC-MS m/e observed. LC-MS m/e 379 (MH^+).

Example 9

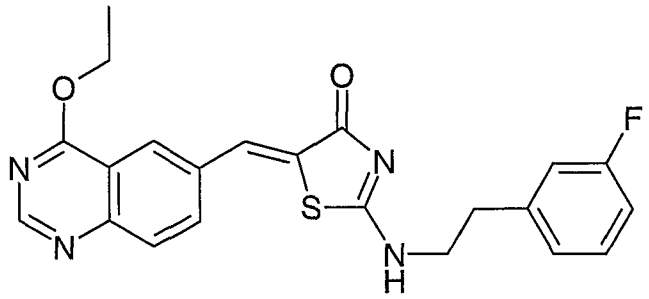
2-(2,4-Dimethoxy-phenylamino)-5-[1-quinazolin-6-yl-meth-(Z)-ylidene]-thiazol-4-one



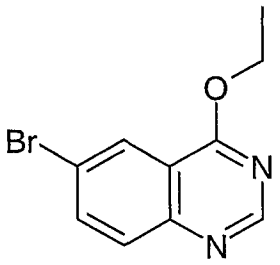
Similar procedure as described in example 1d was used, starting from 2-methylsulfanyl-5-quinazolin-6-ylmethylene-thiazol-4-one, 2,4-dimethoxy-phenylamine and DIEA to give 2-(2,4-dimethoxy-phenylamino)-5-[1-quinazolin-6-yl-meth-(Z)-ylidene]-thiazol-4-one: LC-MS m/e observed. LC-MS m/e 393 (MH^+).

Example 10

5-[1-(4-Ethoxy-quinazolin-6-yl)-meth-(Z)-ylidene]-2-[2-(3-fluoro-phenyl)-ethylamino]-thiazol-4-one

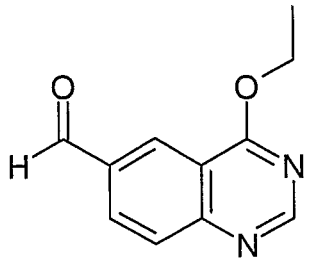


Preparation of 6-bromo-4-ethoxy-quinazoline



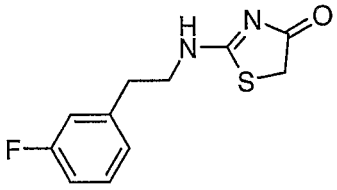
The suspension of 6-bromo-4-chloro-quinazoline (4.87g, 20 mmol), sodium ethoxide (95%, 14.32 g, 200 mmol) in anhydrous ethyl alcohol (150 ml) was stirred at room temperature for 4 hr. After the reaction, solvent was evaporated. Then, ice water was added, followed by addition of 3 N HCL aq to adjust the pH to 9, and precipitate formed. The solid was collected and washed with H_2O three times, then dried. Flash chromatography (Merck silica gel 60, 230-400 mesh, 10%-50% ethyl acetate in hexane for 30 min) afforded 6-Bromo-4-ethoxy-quinazoline (2.13 g, 55%) as a light yellow solid. LC-MS m/e 254 (MH^+).

Preparation of 4-ethoxy-quinazoline-6-carbaldehyde



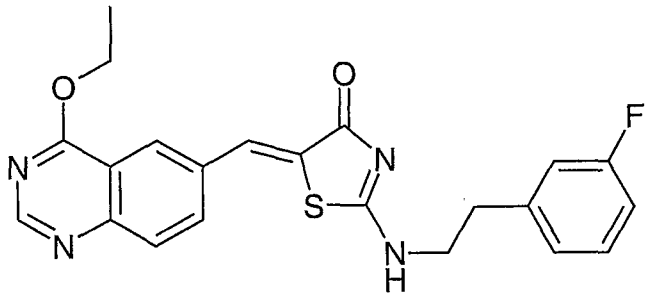
The mixture of 6-bromo-4-ethoxy-quinazoline (example 10a, 506 mg, 2 mmol,), diphenylpropyl phosphine (45.6 mg, 0.2 mmol), palladium acetate (44.8 mg, 0.2 mmol) and triethyl amine (505 mg, 5 mmol) in anhydrous N,N-dimethylformamide (DMF) (25 ml) was charged with carbon monoxide at 75 psi. After the above reaction mixture was stirred at room temperature for 15 min, the carbon monoxide was released, and trihexylsilane (1140 mg, 4 mmol) was added. The resulted reaction mixture was charged with carbon monoxide at 75 psi, and heated at 80°C for 18 hr. After cooling the reaction to room temperature, dichlormethane was added. The resulted solution was extracted with water for 3 times. Organic layer was collected and concentrated to give a yellow solid. Flash chromatography (Merck silica gel 60, 230-400 mesh, 10%-40% ethyl acetate in hexane for 40 min) gave 4-ethoxy-quinazoline-6-carbaldehyde (256 mg, 66%) as a light yellow solid. LC-MS m/e 203 (MH^+).

Preparation of 2-[(3-fluorophenyl)-ethylamino]-thiazol-4-one.



To a solution of (3-fluorophenyl)-ethylamine (3.06 g, 22 mmol) and rhodanine (2.66 g, 20 mmol) in acetonitrile (70 mL) was added DIEA (7.66 mL, 44 mmol) at room temperature. Then, this solution was cooled to 0°C and mercuric chloride (5.97 g, 22 mmol) was added in two portions. After addition, the suspension was allowed to warm to room temperature and stirred for 3 days. The resulting black solids were filtered through a plug of celite and washed with dichloromethane (500 mL) and methanol (250 mL). The combined solvents were removed under the vacuum and the crude residue was dissolved in ethyl acetate (25 mL) at hot condition and stored in the refrigerator overnight. Then, the solids were collected by filtration and washed with ethyl acetate. After drying in air, 3.65 g (76.6% yield) of 2-[(3-fluorophenyl)-ethylamino]-thiazol-4-one was isolated as a white amorphous solid: HRES(+) m/e calcd for $C_{11}H_{11}FN_2OS$ $(M+H)^+$ 239.0649, found 239.0647.

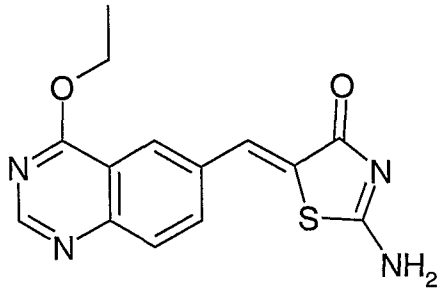
Preparation of 5-[1-(4-ethoxy-quinazolin-6-yl)-meth-(Z)-ylidene]-2-[2-(3-fluoro-phenyl)-ethylamino]-thiazol-4-one



The mixture of 4-ethoxy-quinazoline-6-carbaldehyde (example 10b, 20 mg, 0.1 mmol,), 2-[2-(3-Fluoro-phenyl)-ethylamino]-thiazol-4-one (example 10c, 24 mg, 0.1 mmol) and piperidine (10 ul, 0.1 mmol) in anhydrous ethyl alcohol (1 ml) was microwaved at 160°C for 25 min. After cooling the reaction to room temperature, the solid was collected by filtration, then washed with MeOH and dried to afford 5-[1-(4-ethoxy-quinazolin-6-yl)-meth-(Z)-ylidene]-2-[2-(3-fluoro-phenyl)-ethylamino]-thiazol-4-one (12 mg, 30%) as light yellow solid. LC-MS m/e 423 (MH^+).

Example 11

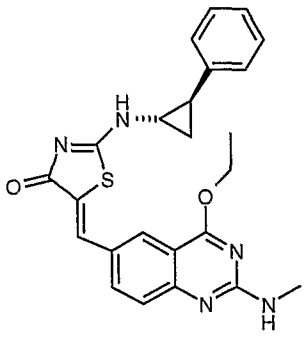
2-Amino-5-[1-(4-ethoxy-quinazolin-6-yl)-meth-(Z)-ylidene]-thiazol-4-one



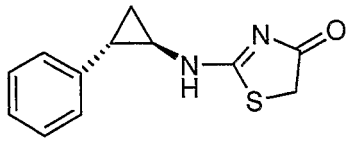
The suspension of 4-ethoxy-quinazoline-6-carbaldehyde (example 10b) (1 equiv.), pseudothiohydantoin (1 equiv.), and sodium acetate (4 equiv.) in acetic acid was stirred under reflux for 12 h. After cooling to room temperature, water was added. The solid was collected by filtration, washed with water and dried to 2-amino-5-[1-(4-ethoxy-quinazolin-6-yl)-meth-(Z)-ylidene]-thiazol-4-one. LC-MS m/e 301 (MH^+) as a slight yellow solid. LC-MS m/e 256 (MH^+).

Example 12

5-[1-(4-Ethoxy-2-methylamino-quinazolin-6-yl)-meth-(Z)-ylidene]-2-((1R,2S)-2-phenyl-cyclopropylamino)-thiazol-4-one

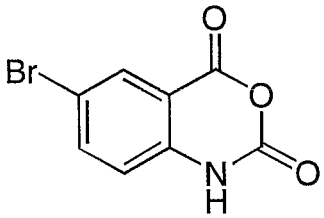


Preparation of 2-((1R,2S)-2-phenyl-cyclopropylamino)-thiazol-4-one



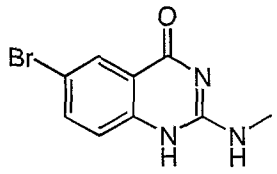
Similar procedure as described in example 10c was used, starting with (1R,2S)-2-phenyl-cyclopropylamine, rhodanine, mercuric chloride and DIEA to give 2-((1R,2S)-2-phenyl-cyclopropylamino)-thiazol-4-one. LC-MS m/e 232 (MH^+).

Preparation of 6-bromo-1H-benzo[d][1,3]oxazine-2,4-dione



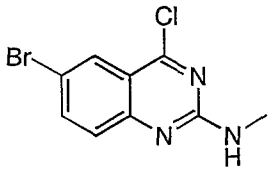
To a suspension of 2-amino-5-bromo-benzoic acid (270 g, 1.25 mol) in acetonitrile (1250 mL) was added a solution of triphosgene (123.8 g, 416.7 mmol) in dichloromethane (DCM) (500 mL) and pyridine (197.5 g, 2.5 mol) simultaneously at 55 °C. The resultant mixture was stirred for another 3 hours then cooled to room temperature. The precipitate was collected by filtration, washed with acetonitrile and dried to afford 6-bromo-1H-benzo[d][1,3]oxazine-2,4-dione as a pale powder (280 g, 93%). ^1H NMR (DMSO-d_6): δ 11.83 (s, 1H), 7.98 (s, 1H), 7.89-7.87 (d, 1H,), 7.09-7.07 (d, 1H).

Preparation of 6-bromo-2-methylamino-1H-quinazolin-4-one



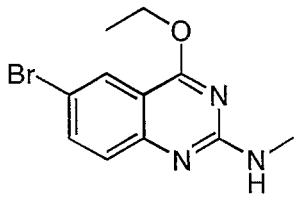
To a combined solution of acetonitrile (360 mL) and water (90 mL) was added 6-bromo-1H-benzo[d][1,3]oxazine-2,4-dione (24.2 g, 0.1 mol), 1,2-dimethyl-isothiourea hydriodic (23.2 g, 0.1 mol) followed by anhydrous sodium carbonate (11.7 g, 0.11 mol) and the mixture was heated to reflux for 3 hours. After cooling down, the precipitate was collected by filtration, washed with water to afford 6-bromo-2-methylamino-1H-quinazolin-4-one (16.5 g, 65 mmol, 65%) as a light yellow powder. ^{1}H NMR (DMSO-d_6): δ 11.20 (b, 1H), 7.91-7.90 (d, 1H), 7.64-7.63 (d, 1H), 7.20-7.18 (d, 1H), 6.30 (b, 1H), 2.82-2.81 (d, 3H).

Preparation of (6-bromo-4-chloro-quinazolin-2-yl)-methyl-amine



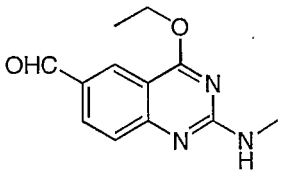
To a solution of phosphorus oxychloride (50 mL) was added powdered 6-bromo-2-methylamino-1H-quinazolin-4-one (10.0 g, 39.4 mmol) followed by dimethyl-phenyl-amine (8 mL) and the mixture was heated to reflux under N_2 atmosphere for half an hour. After cooling down, the mixture was poured onto ice and basified with aqueous NaOH solution (2 M). The precipitate was collected by filtration and purified by column to afford (6-bromo-4-chloro-quinazolin-2-yl)-methyl-amine (5 g, 18.3 mmol, 46.6 %) as a yellow solid. ^{1}H NMR (DMSO-d_6): δ 8.03 (s, 1H), 7.86-7.84 (m, 2H), 7.47-7.45 (d, 1H), 2.86-2.84 (d, 3H).

Preparation of (6-bromo-4-ethoxy-quinazolin-2-yl)-methyl-amine



To a solution of sodium ethoxide (8.11 g, 119.3 mmol) in absolute alcohol (150 mL) was added powder (6-bromo-4-chloro-quinazolin-2-yl)-methyl-amine (13 g, 47.7 mmol) in one portion and the mixture was stirred for 3 hours at room temperature under N_2 atmosphere. The excess of alcohol was removed in *vacuo* and the residue was purified by column to afford (6-bromo-4-ethoxy-quinazolin-2-yl)-methyl-amine (4 g, 14.2 mmol, 29.8%) as a light yellow solid. ^{1}H NMR (DMSO-d_6): δ 7.90-7.89 (d, 1H), 7.70-7.67 (dd, 1H), 7.33-7.31 (m, 1H), 7.21-7.20 (dd, 1H), 4.45-4.44 (q, 2H), 2.83-2.82 (d, 3H), 1.40-1.37 (t, 3H).

Preparation of 4-ethoxy-2-methylamino-quinazoline-6-carbaldehyde



To a combined solution of acetonitrile (40 mL) and DMSO (40 mL) was added tetrakis(triphenylphosphine)palladium(0) (1.65 g, 1.43 mmol), anhydrous sodium formate (5.82 g, 85.6 mmol) followed by powder (6-bromo-4-ethoxy-quinazolin-2-yl)-methyl-amine (4 g, 14.3 mmol) and the resultant mixture was heated to 85 °C, 50 psi under CO atmosphere. After being stirred for 48 hours, the cooled mixture was poured to water and extracted with DCM (3 x 200 mL). The combined organic phase was washed with brine, dried over Na_2SO_4, evaporated to give a brown solid which was

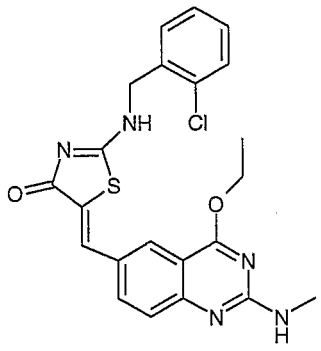
purified by column to afford 4-ethoxy-2-methylamino-quinazoline-6-carbaldehyde (1 g, 4.3 mmol, 30%) as a pale solid. ^{1}H NMR (DMSO-d_6): δ 9.95 (s, 1H), 8.38 (s, 1H), 8.00-7.97 (d, 1H), 7.59-7.56 (m, 1H), 7.46-7.44 (d, 1H), 4.53-4.48 (q, 2H), 2.89-2.87 (d, 3H), 1.44-1.40 (t, 3H).

Preparation of 5-[1-(4-ethoxy-2-methylamino-quinazolin-6-yl)-meth-(Z)-ylidene]-2-((1R,2S)-2-phenyl-cyclopropylamino)-thiazol-4-one

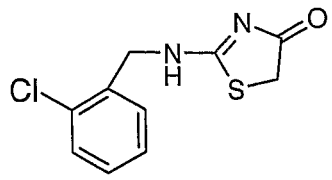
To a suspension of 2-(trans)-phenylcyclopylamino-thiazol-4-one (example 12a, 38.0 mg, 0.16 mmole), and 4-ethoxy-2-methylamino-quinazoline-6-carbaldehyde (example 12f, 45.5 mg, 0.20 mmole) in 2 mL of toluene in a microwave tube were added benzoic acid (2.0 mg, 0.016 mmole) and piperidine (1.5 mg, 0.02 mmole). The reaction mixture was heated to 150 °C with microwave for 1 h. The reaction mixture was then cooled to r.t. and diluted with toluene. The solid was collected by filtration and the solid was washed with toluene, CH_2Cl_2 and ether to give 5-[1-(4-ethoxy-2-methylamino-quinazolin-6-yl)-meth-(Z)-ylidene]-2-((1R,2S)-2-phenyl-cyclopropylamino)-thiazol-4-one as a brown solid: 52 mg (72.9%), MS: m/e 446 (MH^+).

Example 13

2-(2-Chloro-benzylamino)-5-(4-ethoxy-2-methylamino-quinazolin-6-ylmethylene)-thiazol-4-one



Preparation of 2-(2-chloro-benzylamino)-thiazol-4-one



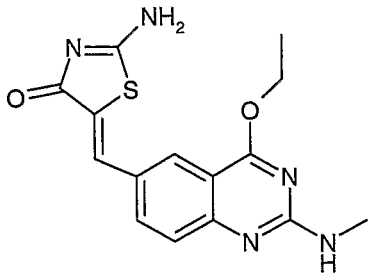
Similar procedure as described in example 10c was used, starting with 2-chloro-benzylamine, rhodanine, mercuric chloride and DIEA to give 2-(2-chloro-benzylamino)-thiazol-4-one. LC-MS m/e 241 (MH^+).

Preparation of 2-(2-chloro-benzylamino)-5-(4-ethoxy-2-methylamino-quinazolin-6-ylmethylene)-thiazol-4-one

To a suspension of 2-(2-chloro-benzylamino)-thiazol-4-one (example 13a, 38.5. mg, 0.16 mmole), and 4-ethoxy-2-methylamino-quinazoline-6-carbaldehyde (example 12f, 45.5 mg, 0.20 mmole) in 2 mL of toluene in a microwave tube were added benzoic acid (2.0 mg, 0.016 mmole) and piperidine (1.5 mg, 0.02 mmole). The reaction mixture was heated to 150 °C with microwave for 45 min. The reaction mixture was then cooled to r.t. and the solid was filtered off, washed with toluene, MeOH and ether to give 2-(2-chloro-benzylamino)-5-(4-ethoxy-2-methylamino-quinazolin-6-ylmethylene)-thiazol-4-one as a brown solid: 43.2 mg (59.5%), MS: m/e 454 (MH^+).

Example 14

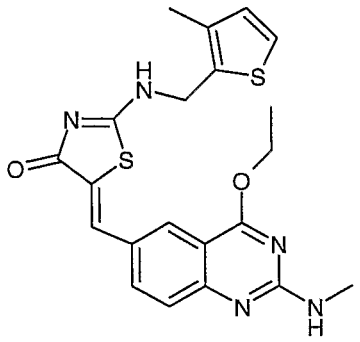
2-Amino-5-(4-ethoxy-2-methylamino-quinazolin-6-ylmethylene)-thiazol-4-one



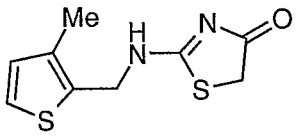
To a suspension of pseudothiohydontoin (40.6 mg, 0.35 mmole), 4-ethoxy-2-methylamino-quinazoline-6-carbaldehyde (example 12f, 81.0 mg, 0.35 mmole) and NaOAc (82.0 mg, 1.0 mmole) in 2.5 mL of xylene was added acetic acid (78.6 mg, 1.3 mmole). The reaction mixture was heated under refluxing overnight. The reaction mixture was then cooled to r.t. and the solid was filtered off, washed with MeCN to give the crude product which was triturated with 2-amino-5-(4-ethoxy-2-methylamino-quinazolin-6-ylmethylene)-thiazol-4-one as a brown solid: 4.5 mg (3.9%), MS: m/e 330 (MH^+).

Example 15

5-(4-Ethoxy-2-methylamino-quinazolin-6-ylmethylene)-2-[(3-methyl-thiophen-2-ylmethyl)-amino]-thiazol-4-one



Preparation of 2-[(3-methyl-thiophen-2-ylmethyl)-amino]-thiazol-4-one.



To a solution of 3-methyl-thiophen-2-ylmethylamine (700 mg, 5.5 mmol) and rhodanine (732 mg, 5.5 mmol) in acetonitrile (30 mL) was added diisopropylethylamine (DIEA) (1.91 mL, 11 mmol) at room temperature. Then, this solution was cooled to 0°C and mercuric chloride (1.52 g, 5.6 mmol) was added in one portion. After addition, the suspension was allowed to warm to room temperature and stirred for 3 days. The resulting black solids were filtered through a plug of celite and washed with acetonitrile (200 mL) and ethyl acetate (250 mL). The filtrates were removed under the vacuum and the crude residue was dissolved in dichloromethane (150 mL) and washed with water and brine solution. After drying over magnesium sulfate, the filtrate was removed under the vacuum and the residue was dissolved in dichloromethane (10 mL) and diluted with

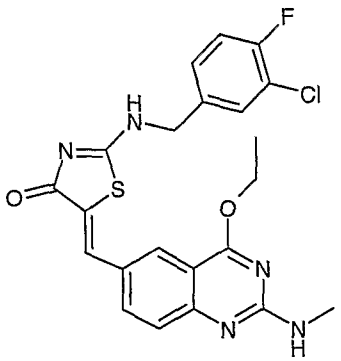
hexanes (10 mL). After overnight storage in the refrigerator, the solids were collected by filtration and washed with dichloromethane. After drying in air, 390 mg (31.5% yield) of 2-[(3-methyl-thiophen-2-ylmethyl)-amino]-thiazol-4-one was isolated as a light yellow amorphous solid: EI-HRMS m/e calcd for $C_9H_{10}N_2OS_2$ (M^+) 226.0235, found 226.0232.

Preparation of 5-(4-ethoxy-2-methylamino-quinazolin-6-ylmethylene)-2-[(3-methyl-thiophen-2-ylmethyl)-amino]-thiazol-4-one

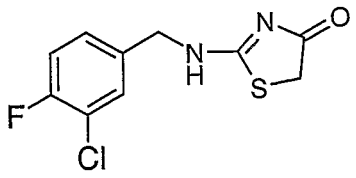
To a suspension of 2-[(3-methyl-thiophen-2-ylmethyl)-amino]-thiazol-4-one (36.2. mg, 0.16 mmole), and 4-ethoxy-2-methylamino-quinazoline-6-carbaldehyde (example 12f, 45.5 mg, 0.20 mmole) in 2 mL of toluene in a microwave tube were added benzoic acid (2.0 mg, 0.016 mmole) and piperidine (1.5 mg, 0.02 mmole). The reaction mixture was heated to 150 °C with microwave for 45 min. The reaction mixture was then cooled to r.t. and the solid was filtered off, washed with toluene, MeOH and ether to give 5-(4-ethoxy-2-methylamino-quinazolin-6-ylmethylene)-2-[(3-methyl-thiophen-2-ylmethyl)-amino]-thiazol-4-one as a brown solid: 56.5 mg (80.4%), MS: m/e 440 (MH^+).

Example 16

2-(3-Chloro-4-fluoro-benzylamino)-5-(4-ethoxy-2-methylamino-quinazolin-6-ylmethylene)-thiazol-4-one



Preparation of 2-(3-chloro-4-fluoro-benzylamino)-thiazol-4-one



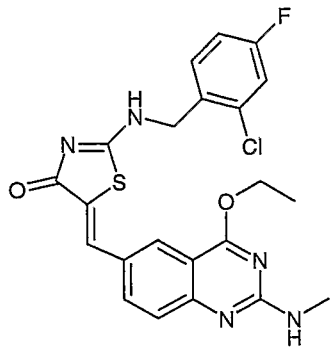
Similar procedure as described in example 15a was used, starting with 3-chloro-4-fluoro-benzylamine, rhodanine, mercuric chloride and DIEA to give 2-(3-chloro-4-fluoro-benzylamino)-thiazol-4-one. LC-MS m/e 259 (MH^+).

Preparation of 2-(3-chloro-4-fluoro-benzylamino)-5-(4-ethoxy-2-methylamino-quinazolin-6-ylmethylene)-thiazol-4-one

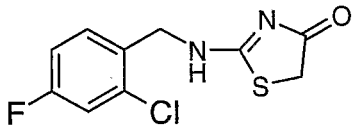
To a suspension of 2-(3-chloro-4-fluoro-benzylamino-thiazol-4-one (example 16a, 41.4. mg, 0.16 mmole), and 4-ethoxy-2-methylamino-quinazoline-6-carbaldehyde (example 12f, 45.5 mg, 0.20 mmole) in 2 mL of toluene in a microwave tube were added benzoic acid (2.0 mg, 0.016 mmole) and piperidine (1.5 mg, 0.02 mmole). The reaction mixture was heated to 150 °C with microwave for 30 min. The reaction mixture was then cooled to r.t. and the solid was filtered off, washed with toluene to give the crude product 58.8 mg (77.9 %) which was re-dissolved in 0.5 mL hot DMF and diluted with water at r.t. The precipitates were collected and washed with water, acetone and ether, dried over $NaSO_4$ and concentrated to give 2-(3-chloro-4-fluoro-benzylamino)-5-(4-ethoxy-2-methylamino-quinazolin-6-ylmethylene)-thiazol-4-one as a light yellow solid: 43.6 mg (57.7%), MS: m/e 472 (MH^+).

Example 17

2-(2-Chloro-4-fluoro-benzylamino)-5-(4-ethoxy-2-methylamino-quinazolin-6-ylmethylene)-thiazol-4-one



Preparation of 2-(2-chloro-4-fluoro-benzylamino)-thiazol-4-one



Similar procedure as described in example 15a was used, starting with 2-chloro-4-fluoro-benzylamine, rhodanine, mercuric chloride and DIEA to give 2-(2-chloro-4-fluoro-benzylamino)-thiazol-4-one. LC-MS m/e 259 (MH^+).

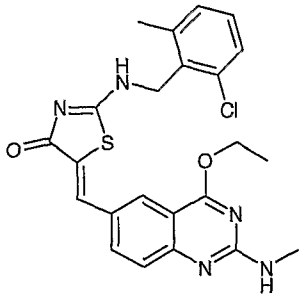
Preparation of 2-(2-chloro-4-fluoro-benzylamino)-5-(4-ethoxy-2-methylamino-quinazolin-6-ylmethylene)-thiazol-4-one

To a suspension of 2-(2-chloro-4-fluoro-benzylamino)-thiazol-4-one (example 17a, 41.4. mg, 0.16 mmole), and 4-ethoxy-2-methylamino-quinazoline-6-carbaldehyde (example 12f, 45.5 mg, 0.20 mmole) in 2 mL of toluene in a microwave tube were added benzoic acid (2.0 mg, 0.016 mmole) and piperidine (1.5 mg, 0.02 mmole). The reaction mixture was heated to 150 °C with microwave for 30 min. The reaction mixture was then

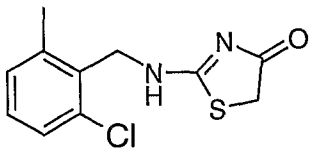
cooled to r.t. and the solid was filtered off, washed with toluene, MeOH and ether to give 2-(2-chloro-4-fluoro-benzylamino)-5-(4-ethoxy-2-methylamino-quinazolin-6-ylmethylene)-thiazol-4-one as a light brown solid: 46.6 mg (61.7%), MS: m/e 472 (MH^+).

Example 18

2-(2-Chloro-6-methyl-benzylamino)-5-(4-ethoxy-2-methylamino-quinazolin-6-ylmethylene)-thiazol-4-one



Preparation of 2-(2-chloro-6-methyl-benzylamino)-thiazol-4-one



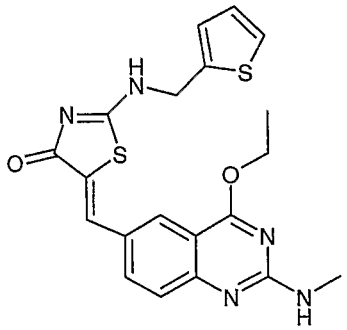
Similar procedure as described in example 15a was used, starting with 2-chloro-6-methyl-benzylamine, rhodanine, mercuric chloride and DIEA to give 2-(2-chloro-6-methyl-benzylamino)-thiazol-4-one. LC-MS m/e 259 (MH^+).

Preparation of 2-(2-chloro-6-methyl-benzylamino)-5-(4-ethoxy-2-methylamino-quinazolin-6-ylmethylene)-thiazol-4-one

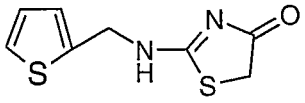
To a suspension of 2-(2-chloro-6-methyl-benzylamino)-thiazol-4-one (example 18a, 40.8. mg, 0.16 mmole), and 4-ethoxy-2-methylamino-quinazoline-6-carbaldehyde (example 12f, 45.5 mg, 0.20 mmole) in 2 mL of toluene in a microwave tube were added benzoic acid (2.0 mg, 0.016 mmole) and piperidine (1.5 mg, 0.02 mmole). The reaction mixture was heated to 150 °C with microwave for 30 min. The reaction mixture was then cooled to r.t. and the solid was filtered off, washed with toluene, MeOH and ether to give 2-(2-chloro-6-methyl-benzylamino)-5-(4-ethoxy-2-methylamino-quinazolin-6-ylmethylene)-thiazol-4-one as a light brown solid: 45.9 mg (61.3%), MS: m/e 468 (MH^+).

Example 19

5-(4-Ethoxy-2-methylamino-quinazolin-6-ylmethylene)-2-[(thiophen-2-ylmethyl)-amino]-thiazol-4-one



Preparation of 2-(thiophen-2-ylmethyl)-amino)-thiazol-4-one



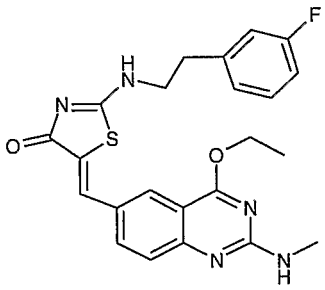
Similar procedure as described in example 15a was used, starting with thiophen-2-ylmethyl-amine, rhodanine, mercuric chloride and DIEA to give 2-(thiophen-2-ylmethyl-amino)-thiazol-4-one. LC-MS m/e 259 (MH^+).

Preparation of 5-(4-ethoxy-2-methylamino-quinazolin-6-ylmethylene)-2-[(thiophen-2-ylmethyl)-amino]-thiazol-4-one

To a suspension of 2-[(thiophen-2-ylmethyl)-amino]-thiazol-4-one (34.0. mg, 0.16 mmole), and 4-ethoxy-2-methylamino-quinazoline-6-carbaldehyde (example 12f, 45.5 mg, 0.20 mmole) in 2 mL of toluene in a microwave tube were added benzoic acid (2.0 mg, 0.016 mmole) and piperidine (1.5 mg, 0.02 mmole). The reaction mixture was heated to 150 °C with microwave for 30 min. The reaction mixture was then cooled to r.t. and the solid was filtered off, washed with toluene, MeOH and ether to give 5-(4-ethoxy-2-methylamino-quinazolin-6-ylmethylene)-2-[(thiophen-2-ylmethyl)-amino]-thiazol-4-one as a brown solid: 48.6 mg (69.1%), MS: m/e 426 (MH^+).

Example 20

5-(4-Ethoxy-2-methylamino-quinazolin-6-ylmethylene)-2-[2-(3-fluoro-phenyl)-ethylamino]-thiazol-4-one



To a suspension of 2-[2-(3-fluoro-phenyl)-ethylamino]-thiazol-4-one (example 10c, 38.1. mg, 0.16 mmole), and 4-ethoxy-2-methylamino-quinazoline-6-carbaldehyde (example 12f, 45.5 mg, 0.20 mmole) in 2 mL of toluene in a microwave tube were added benzoic acid (2.0 mg, 0.016 mmole) and piperidine (1.5 mg, 0.02 mmole). The reaction mixture was heated to 150 °C with microwave for 30 min. The reaction mixture was then cooled to r.t. and the solid was filtered off, washed with toluene, MeOH and ether to give

5-(4-ethoxy-2-methylamino-quinazolin-6-ylmethylene)-2-[2-(3-fluoro-phenyl)-ethylamino]-thiazol-4-one as a light brown solid: 52.3 mg (72.4%), MS: m/e 452 (MH^+).

Example 21

The pharmacological properties of the compounds of this invention may be confirmed by a number of pharmacological assays. The exemplified pharmacological assays which follow have been carried out with the compounds according to the invention and their salts. The compounds of the invention exhibited CDK1/Cyclin B activity with Ki values of less than 5.0 µM. This demonstrates that all of these compounds were active to inhibit CDK1/Cyclin B.

To determine inhibition of CDK1 activity, either FlashPlate™ (NEN™-Life Science Products) assay or HTRF assay was performed. Both types of kinase assays were carried out using recombinant human CDK1/Cyclin B complex. GST-cyclinB (GST-cycB) and CDK1 cDNA clones in baculovirus vectors were provided by Dr. W. Harper at the Baylor College of Medicine, Houston, TX. Proteins were co-expressed in High Five™ insect cells and the complex was purified on glutathione Sepharose resin (Pharmacia, Piscataway, NJ) as previously described (Harper, J. W. et al. Cell 1993, 75, 805-816). A 6x-Histidine tagged truncated form of retinoblastoma (Rb) protein (amino acid 386-928) was used as the substrate for the CDK1/Cyclin B assay (the expression plasmid was provided by Dr. Veronica Sullivan, Department of Molecular Virology, Roche Research Centre, Welwyn Garden City, United Kingdom). The Rb protein is a natural substrate for phosphorylation by CDK1 (see Herwig and Strauss Eur. J. Biochem. Vol. 246 (1997) pp. 581-601 and the references cited therein). The expression of the 62Kd protein was under the control of an IPTG inducible promoter in an M15 E. coli strain. Cells were lysed by sonication and purification was carried out by binding lysates at pH 8.0 to a Ni-chelated agarose column pretreated with 1 mM imidazole. The resin was then washed several times with incrementally decreasing pH buffers to pH 6.0, and eluted with 500 mM imidazole. Eluted protein was dialyzed against 20 mM HEPES pH 7.5, 30% glycerol, 200 mM NaCl, and 1 mM DTT. Purified

Rb fusion protein stocks were quantitated for protein concentration, aliquoted, and stored at -70°C.

For the FlashPlate kinase assay, 96-well FlashPlates were coated with Rb protein at 10 µg/ml, using 100 µl per well. Plates were incubated at 4°C overnight or at room temperature for 3 hours on a shaker. To control for nonspecific phosphorylation, one row of wells was coated with 100 µl/well coating buffer (20 mM HEPES, 0.2 M NaCl). Plates were then washed twice with wash buffer (0.01% Tween 20 in phosphate-buffered saline). Compounds to be tested ("test compounds") were added to the wells at 5x final concentration. Reactions were initiated by immediate addition of 40 µl reaction mix (25 mM HEPES, 20 mM $MgCl_2$, 0.002% Tween 20, 2mM DTT, 1 µM ATP, 4 nM 33P-ATP) and a sufficient amount of enzyme to give counts that were at least 10-fold above background. Plates were incubated at room temperature on a shaker for 30 minutes. Plates were washed four times with the wash buffer, sealed, and counted on the TopCount scintillation counter (Packard Instrument Co., Downers Grove, IL]. The percent inhibition of Rb phosphorylation, which is a measure of the inhibition of CDK activity, was determined according to the following formula:

$$100 \times \left(1 - \frac{\text{test compound - nonspecific}}{\text{total – nonspecific}}\right)$$

where "test compound" refers to the average counts per minute of the test duplicates, "nonspecific" refers to the average counts per minute when no CDK1/Cyclin B , etc., was added, and "total" refers to the average counts per minute when no compound was added. The IC_{50} value is the concentration of test compound that reduces by 50% the protein-kinase induced incorporation of the radiolabel under the test conditions described. The value of the inhibitor constant Ki is calculated by the following: Ki = IC50/(1 + [S]/Km), where [S] is the ATP concentration and Km is Michaelis constant.

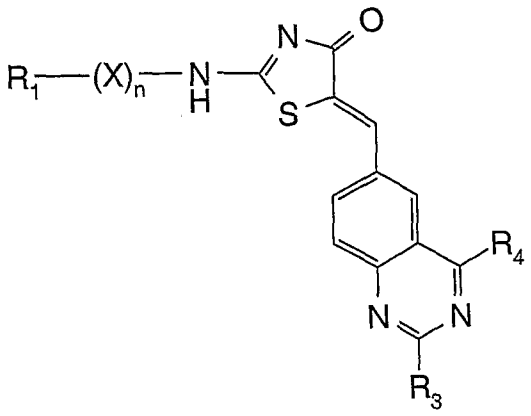
The Homogeneous Time Resolved Fluorescence (HTRF) kinase assay was carried out in 96-well polypropylene plates (BD Biosciences, Bedford, MA). Test compounds were first dissolved in DMSO, and then diluted in kinase assay buffer 1 (25 mM HEPES, pH7.0, 8 mM $MgCl_2$, 1.5 mM DTT, and 162 μM ATP) with DMSO concentration at 15%. The CDK1/Cyclin B enzyme was diluted in kinase assay buffer 2 (25 mM HEPES, pH 7.0, 8 mM $MgCl_2$, 0.003% Tween 20, 0.045 % BSA, 1.5 mM DTT, and 0.338 μM Rb protein). To initiate the kinase reaction, 20 μL of compound solution was mixed with 40 μL of CDK1/Cyclin B solution in assay plates with final concentration of CDK1/Cyclin B and Rb at 0.1 μg/mL and 0.113 μM, respectively, and incubated at 37ºC for 30 min. 15 μL of anti-phospho-Rb (Ser 780) antibody (Cell Signaling Technology, Beverly, MA,) was added with a 1:7692 dilution of the antibody. Incubation was continued at 37ºC for 25 min, after which LANCE Eu-W1024 labeled anti-rabbit IgG (1 nM, PerkinElmer, Wellesley, MA) and anti-His antibody conjugated to SureLight-Allophucocyanin (20 nM, PerkinElmer, Wellesley, MA) were added to the wells. Incubation was continued at 37ºC for another 40 min. At the completion of the incubation, 35 μL of reaction mixture was transferred to fresh 384-well black polystyrene plates (Corning Incorporated, Corning, NY) and read on a fluorescent plate reader at excitation wavelength of 340 nm and emission wavelength of 665/615 nm.

Ki values showing CDK1/Cyclin B activity that applied to compounds of the subject matter of this invention ranges from about 0.001 μM to about 5.000 μM. Specific data for some examples are as follows:

Example	Ki (μM)
1	1.224
3	0.881
5	1.838
7	1.110

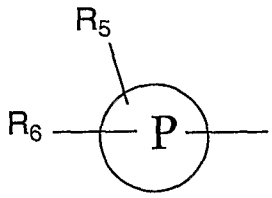
Claims

1. A compound having the formula:

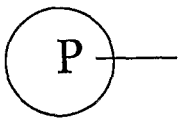


I

wherein

R_1 is hydrogen, lower alkyl or  ;

X is selected from lower alkylene, cyclolower alkylene containing from 3 to 6 carbon atoms and hydroxy lower alkylene;

 is selected from

an aryl ring,

a cycloalkyl ring containing from 3 to 6 carbon atoms,

a 4 to 6 membered heterocycloalkyl ring containing from 3 to 5 carbon atoms and from 1 to 2 hetero atoms selected from the group consisting of oxygen, nitrogen and sulfur, and

a 5 or 6 membered heteroaromatic ring containing from 1 to 2 hetero atoms selected from the group consisting of oxygen, sulfur and nitrogen;

R_5 and R_6 are independently selected from the group consisting of hydrogen, hydroxy, hydroxy-lower alkyl, lower alkyl, halogen, perfluro-lower alkyl and lower alkoxy;

R_3 is selected from hydrogen, -NH-R_7 and -NH-C(O)-R_8;

R_4 is selected from hydrogen, lower alkyl and -O$(CH_2CH_2O)_y$-R_{10};

R_7 is hydrogen or lower alkyl;

R_8 and R_{10} are lower alkyl;

n is an integer from 0 to 1; and

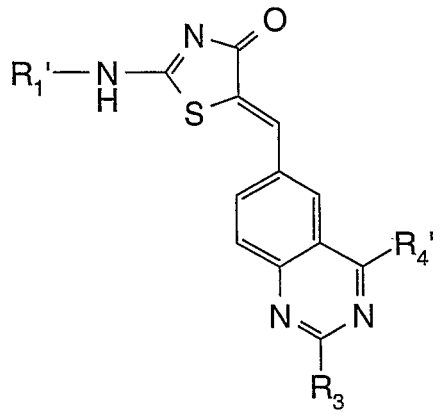
y is an integer of from 0 to 3;

with the proviso that when n is 0 and R_1 is hydrogen or lower alkyl then R_3/R_4 cannot both be hydrogen; or

N-oxides of compounds where R_1 contains a nitrogen in the heteroaromatic ring, sulfones where R_1 contains a sulfur in the heterocycloalkyl ring or heteroaromatic ring; or

pharmaceutically acceptable salts thereof.

2. The compound of claim 1, wherein said compound has the formula I-A



I-A

wherein

R_1' is hydrogen or a lower alkyl;

R_4' is lower alkyl or $-O(CH_2CH_2O)_y-R_{10}$; and

R_3, R_{10} and y are as defined in claim 1; or

pharmaceutically acceptable salts thereof.

3. The compound of claim 2, wherein R_1' is hydrogen.

4. The compound of claim 3, where said compound is

2-amino-5-[1-(4-ethoxy-quinazolin-6-yl)-methylidene]-thiazol-4-one.

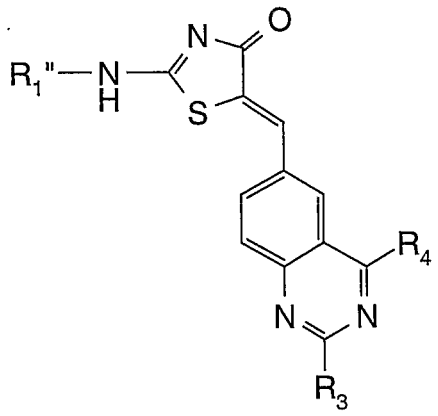
5. The compound of claim 2, wherein

R_3 is $-NHR_7$ and R_7 is as defined in claim 1.

6. The compound of claim 5, wherein said compound is

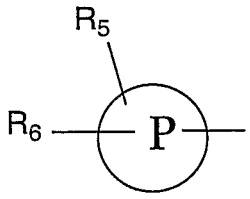
2-amino-5-(4-ethoxy-2-methylamino-quinazolin-6-ylmethylene)-thiazol-4-one.

7. The compound of claim 1, wherein said compound has the formula I-B



I-B

wherein



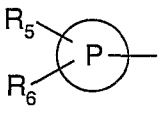
R_1" is ; and

R_3, R_4, R_5, R_6 and  are as defined in claim 1; or

N-oxides of compounds where R_1" contains a nitrogen in the heteroaromatic ring, sulfones where R_1" contains a sulfur in

the hetero ring or heteroaromatic ring, or pharmaceutically acceptable salts thereof.

8. The compound of claim 7, wherein

R_1" is  and  is phenyl; and

R_5 and R_6 are as defined in claim 1.

9. The compound of claim 8, wherein said compound is

2-(2,4-dimethoxy-phenylamino)-5-[1-quinazolin-6-yl-methylidene]-thiazol-4-one.

10. The compound of claim 8, wherein said compound is

2-(2-ethoxy-phenylamino)-5-[1-quinazolin-6-yl-methylidene]-thiazol-4-one.

11. The compound of claim 8, wherein said compound is

2-(4-fluoro-2-methoxy-phenylamino)-5-[1-quinazolin-6-yl-methylidene]-thiazol-4-one.

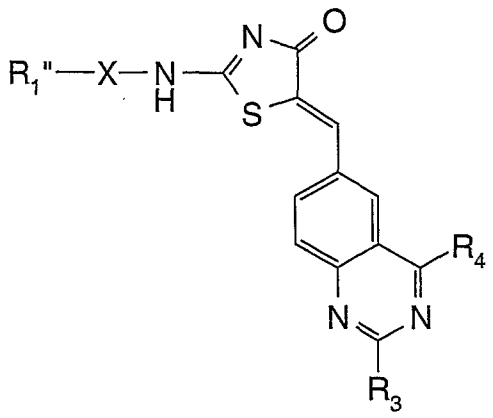
12. The compound of claim 7, wherein  is a heteroaromatic ring containing from 1 to 2 heteroatoms.

13. The compound of claim 12, wherein said heteroaromatic ring contains two heteroatoms, one being sulfur and the other being nitrogen.

14. The compound of claim 13, wherein said compound is

5-[1-quinazolin-6-yl-methylidene]-2-(thiazol-2-ylamino)-thiazol-4-one.

15. A compound of claim 1, wherein said compound has the formula:



I-C

wherein

R_1" is as R_1 in claim 1; and

X, R_3, R_4 and  are as in claim 1; or

N-oxides of compounds where R_1 " contains a nitrogen in the heteroaromatic ring, sulfones where R_1" contains a sulfur in the hetero ring or heteroaromatic ring; or

pharmaceutically acceptable salts thereof.

16. The compound of claim 15, wherein X is lower alkylene.

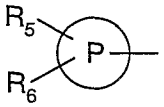
17. The compound of claim 16, wherein

R_3 is hydrogen, and

R_4 is hydrogen or $-O(CH_2CH_2O)_y-R_{10}$, and

R_{10} and y are as defined in claim 1.

18. The compound of claim 17, wherein

R_1" is  and  is phenyl; and

R_5 and R_6 are as defined in claim 1.

19. The compound of claim 18, wherein said compound is

2-[2-(3-fluoro-phenyl)-ethylamino]-5-[1-quinazolin-6-yl-methylidene]-thiazol-4-one.

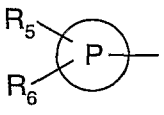
20. The compound of claim 18, wherein said compound is

2-(3-fluoro-benzylamino)-5-[1-quinazolin-6-yl-methylidene]-thiazol-4-one.

21. The compound of claim 18, wherein said compound is

5-[1-(4-ethoxy-quinazolin-6-yl)-methylidene]-2-[2-(3-fluoro-phenyl)-ethylamino]-thiazol-4-one.

22. The compound of claim 16, wherein

R_1'' is  and  is phenyl;

R_3 is $-NHR_7$,

R_4 is hydrogen or $-O(CH_2CH_2O)_y-R_{10}$, and

R_5, R_6, R_7, R_{10} and y are as defined in claim 1.

23. The compound of claim 22, wherein said compound is

2-(2-chloro-benzylamino)-5-(4-ethoxy-2-methylamino-quinazolin-6-ylmethylene)-thiazol-4-one.

24. The compound of claim 22, wherein said compound is

2-(3-chloro-4-fluoro-benzylamino)-5-(4-ethoxy-2-methylamino-quinazolin-6-ylmethylene)-thiazol-4-one.

25. The compound of claim 22, wherein said compound is

2-(2-chloro-4-fluoro-benzylamino)-5-(4-ethoxy-2-methylamino-quinazolin-6-ylmethylene)-thiazol-4-one.

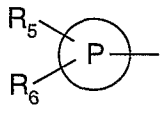
26. The compound of claim 22, wherein said compound is

2-(2-chloro-6-methyl-benzylamino)-5-(4-ethoxy-2-methylamino-quinazolin-6-ylmethylene)-thiazol-4-one.

27. The compound of claim 22, wherein said compound is

5-(4-ethoxy-2-methylamino-quinazolin-6-ylmethylene)-2-[2-(3-fluoro-phenyl)-ethylamino]-thiazol-4-one.

28. The compound of claim 16, wherein

R_1" is  and  is a heteroaromatic ring containing from 1 to 2 heteroatoms, and

R_5 and R_6 have the meanings given in claim 1.

29. The compound of claim 28, wherein said heteroaromatic ring contains two hetero atoms, one being sulfur and the other being nitrogen.

30. The compound of claim 29, wherein said heteroaromatic ring is a thiazole ring.

31. The compound of claim 28, wherein said heteroaromatic ring contains one heteroatom which is a sulfur atom.

32. The compound of claim 31, wherein R_3 and R_4 are hydrogen.

33. The compound of claim 32, wherein said compound is

5-[1-quinazolin-6-yl-methylidene]-2-[(thiophen-2-ylmethyl)-amino]-thiazol-4-one.

34. The compound of claim 31, wherein

R_3 is $-NHR_7$, and

R_4 and R_7 are as defined in claim 1.

35. The compound of claim 34, wherein said compound is

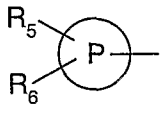
5-(4-ethoxy-2-methylamino-quinazolin-6-ylmethylene)-2-[(3-methyl-thiophen-2-ylmethyl)-amino]-thiazol-4-one.

36. The compound of claim 34, wherein said compounds is

5-(4-ethoxy-2-methylamino-quinazolin-6-ylmethylene)-2-[(thiophen-2-ylmethyl)-amino]-thiazol-4-one.

37. The compound of claim 15, wherein X is cycloalkylene.

38. The compound of claim 37, wherein

R_1" is  and  is phenyl; and

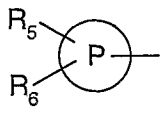
R_5 and R_6 are as defined in claim 1.

39. The compound of claim 38, wherein said compound is

5-[1-(4-ethoxy-2-methylamino-quinazolin-6-yl)-meth-(Z)-ylidene]-2-2-phenyl-cyclopropylamino)-thiazol-4-one.

40. The compound of claim 15, wherein X is hydroxy-lower alkylene.

41. The compound of claim 40, wherein

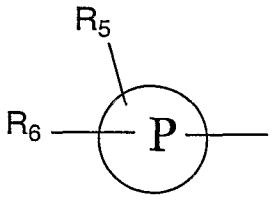
R_1" is  and  is a phenyl ring; and

R_5 and R_6 are as defined in claim 1.

42. The compound of claim 41, wherein said compound is

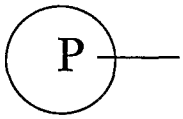
2-(1-hydroxymethyl-2-phenyl-ethylamino)-5-[1-quinazolin-6-yl-methylidene]-thiazol-4-one.

43. The compounds of formula I according to claim 1, wherein



R_1 is hydrogen, or ;

X is selected from lower alkylene, cyclolower alkylene containing from 3 to 6 carbon atoms and hydroxy lower alkylene;



is selected from an aryl ring, cyclolower alkyl ring containing from 3 to 6 carbon atoms, a 4 to 6 membered heterocycloalkyl ring containing from 3 to 5 carbon atoms and from 1 to 2 hetero atoms selected from the group consisting of oxygen, nitrogen and sulfur, and a 5 or 6 membered heteroaromatic ring containing from 1 to 2 hetero atoms selected from the group consisting of oxygen, sulfur and nitrogen;

R_5 and R_6 are independently selected from the group consisting of hydrogen, hydroxy, hydroxy-lower alkyl, lower alkyl, halogen, perfluro-lower alkyl and lower alkoxy;

R_3 is selected from hydrogen, $-NHR_7$, and $-NH-C(O)-R_8$;

R_4 is selected from hydrogen, lower alkyl, and $-O(CH_2CH_2O)_y-R_{10}$;

$R_7$is hydrogen or lower alkyl;

R_8 and R_{10} are lower alkyl;

n is an integer from 0 to 1; and

y is an integer of from 0 to 3;

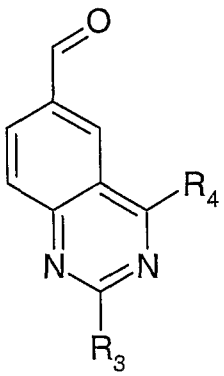
with the proviso that when n is 0, one of R_1, R_3 and R_4 is other then hydrogen; or

N-oxides of compounds where R_1 contains a nitrogen in the heteroaromatic ring, sulfones where R_1 contains a sulfur in the heterocycloalkyl ring or heteroaromatic ring, or

pharmaceutically acceptable salts thereof.

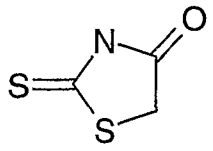
44. A process for the manufacture of the compounds of formula I according to claim 1, wherein

a) a compound of formula II



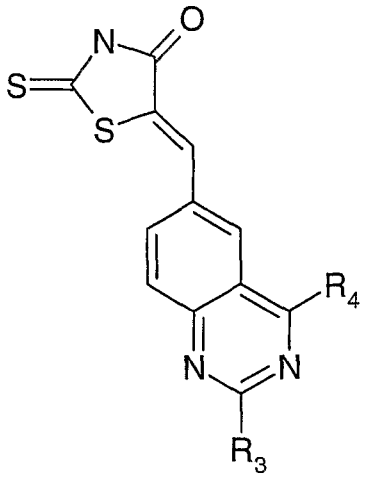
II,

is reacted in the presence of a compound of formula III-A



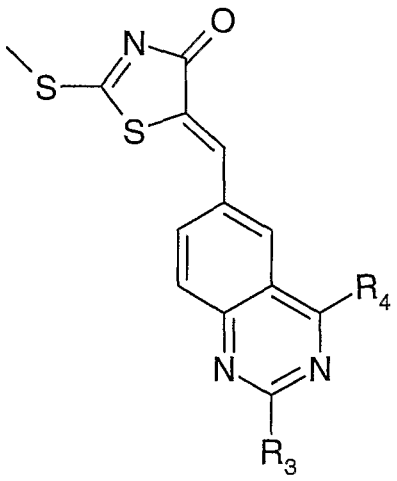
III-A,

to give a compound of formula IV



IV, and

b) said compound of formula IV is reacted in the presence of a methylating agent, such as iodomethane, to give a compound of formula V



V, and

c) said compound of formula V is reacted in the presence of a primary amine of the formula VI

R_1-$(X)_n$-NH_2 VI,

to give a compound of formula I according to claim 1,

d) said compound of formula I according to claim 1 is isolated from the reaction mixture and, if desired, turned into a pharmaceutically acceptable salt.

45. The compounds of formula I according to claim 1 for the treatment of cancer, in particular solid tumors, more particularly lung cancer, breast cancer, colon cancer and prostate cancer.

46. A pharmaceutical composition comprising at least one compound of formula I according to claim 1 together with pharmaceutically acceptable adjuvants.

47. The pharmaceutical composition of claim 46 for the treatment of cancer, in particular solid tumors, more particularly lung cancer, breast cancer, colon cancer and prostate cancer.

48. The use of a compound of formula I according to claim 1 in the manufacture of medicaments for the treatment of cancer, in particular solid tumors, more particularly lung cancer, breast cancer, colon cancer and prostate cancer.

49. A compound of formula I according to claim 1, prepared by a process according to claim 44.

50. The novel compounds, processes, compositions and uses substantially as described herein before.