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(54) Title: SUBSTITUTED AMINOTHIAZOLES AS INHIBITORS OF CANCERS, INCLUDING HEPATOCELLULAR CARCINOMA, AND AS INHIBITORS OF HEPATITIS VIRUS REPLICATION

(57) Abstract: Pharmaceutical compositions of the invention are presented which comprise substiuted aminothiazoles derivatives. The substiuted aminothiazoles derivatives have a disease-modifying action in the treatment of diseases associated with unregulated cell growth. Such diseases include cancers such as hepatocellular carcinoma, and viral infections from a hepatitis virus.

Substituted Aminothiazoles as Inhibitors of Cancers, Including Hepatocellular Carcinoma, and as Inhibitors of Hepatitis Virus Replication

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application No. 61542907 filed October 4th, 2011, which is herein incorporated by reference in its entirety.

FIELD OF INVENTION

[0002] The present invention describes compounds and methods useful for the treatment of cancer, including primary liver cancer, hepatocellular carcinoma, hepatoblastoma, and cholangiocarcinoma, and the treatment of viral hepatitis infection, including but not limited to hepatitis A virus infection, hepatitis B virus infection, hepatitis C virus infection, hepatitis D virus infection, and hepatitis E virus infection, as well as other viral species that infect the liver.

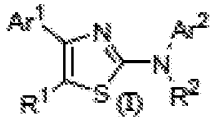
BACKGROUND OF THE INVENTION

[0003] Primary liver cancer is currently the fifth most common cause of cancer deaths among men, and ninth among women in the US, with the numbers increasing yearly. The most recent data indicate that in 2008 there were an estimated 21,370 new cases of liver and bile duct cancer of which the majority are hepatocellular carcinomas (HCCs), with 18,410 deaths (Institute, N.C., SEER Cancer Statistics Review, 1975-2005, Ries LAG, et al., Editors. 2008.). Worldwide, it is the fourth most common cancer, with approximately 663,00 fatal cases reported in 2008; based on current trends and baseline models, the incidence is expected to rise to 756,000 in 2015, and 955,000 in 2030 (Mathers, C.D. and D. Loncar, Projections of global mortality and burden of disease from 2002 to 2030. PLoS Med, 2006. 3, 11, p. e442.). Although it is comparatively uncommon in the US, its incidence has been rising over the last 20 years partially as a result of burgeoning numbers of cases of chronic hepatitis C (Caldwell, S. and S.H. Park, The epidemiology of hepatocellular cancer: from the perspectives of public health problem to tumor biology. J Gastroenterol, 2009. 44 Suppl 19: p. 96-101. El-Serag, H.B., et al., The continuing increase in the incidence of hepatocellular carcinoma in the United States: an update. Ann Intern Med, 2003. 139(10): p. 817-23) one of the principal causes along with hepatitis B and aflatoxin exposure.

[0004] There is a long felt need for new drugs that are both disease-modifying and effective in treating patients with primary liver cancer,including but not limited to hepatocellular carcinoma, hepatoblastoma, and cholangiocarcinoma. There is also a clear and present need for new therapeutic agents that are both disease modifying and effective in treating patients that are infected with a hepatitis virus. The present invention addresses the need for new drugs that are both disease-modifying and effective in treating patients suffering from primary liver cancer and hepatocellular carcinoma. Because the present invention targets the cell types that have been demonstrated to support viral infection in the liver,the present invention addresses also the need for new antiviral drugs that are both disease-modifying and effective in treating patients that are infected with hepatitis A virus, hepatitis B virus, hepatitis C virus, hepatitis D virus, and hepatitis E virus., as well as other viral species that infect the liver.

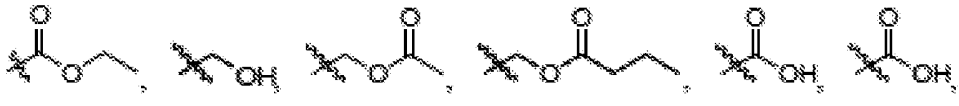
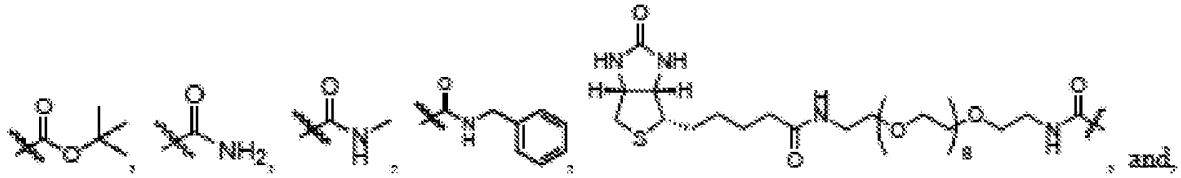
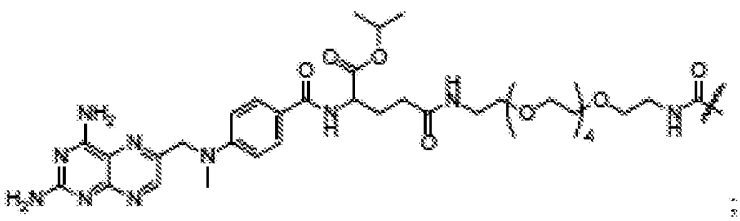
BRIEF SUMMARY OF THE INVENTION

[0005] The present invention is directed toward novel substituted aminothiazoles, compounds of formula (I),

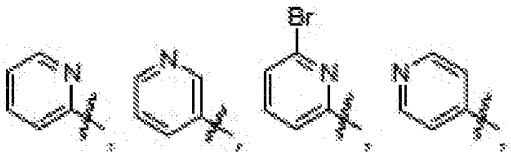
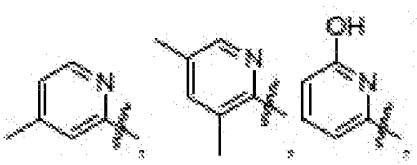
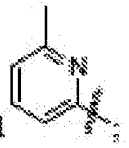


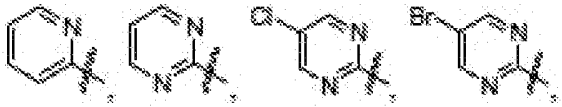
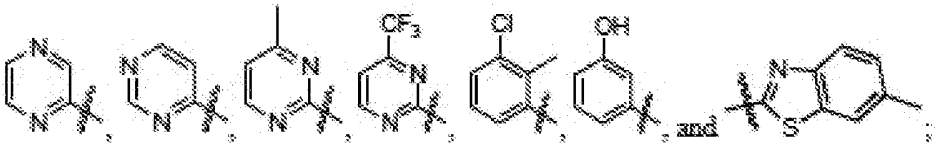
(I)

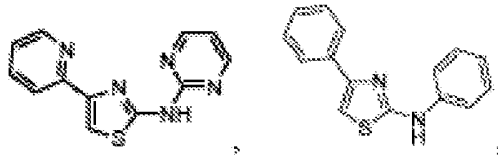
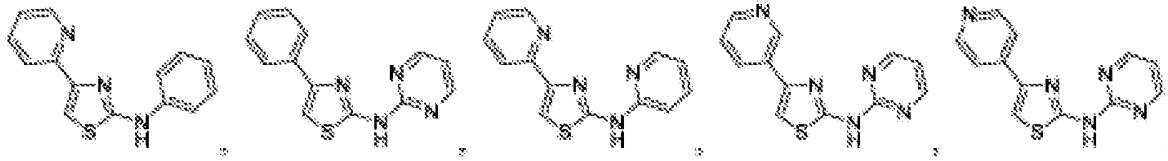
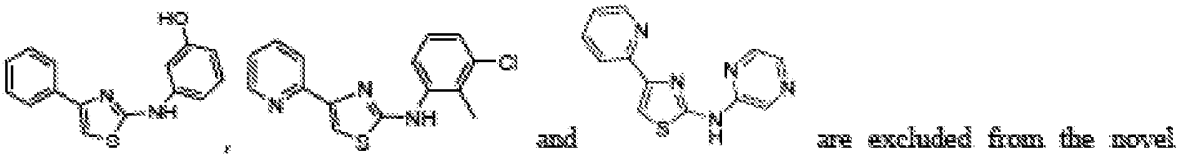
Including hydrates, solvates, pharmaceutically acceptable salts, prodrugs and complexes thereof, wherein:

R^1 is selected from a group consisting of hydrogen, C_1-C_9 linear alkyl, isopropyl, cyclohexyl, bromine, cyano,  ,  , and  ;

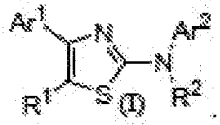
R^2 is selected from a group consisting of hydrogen, methyl, isopropyl, tert-butyl, benzyl, and  ;

Ar^1 is selected fromm group consisting of phenyl,  ,  , and  ;

Ar^2 is selected fromm group consisting of phenyl,  ,  , and ;

[0006] Compounds of the structures  ,  ,  , and are excluded from the novel compounds of formula (I).

[0007] The present invention is also directed toward novel methods of use of compounds of the structure



(I)

[0008] The present invention further relates to compositions comprising:
an effective amount of one or more compounds according to the present invention and an excipient.

[0009] The present invention also relates to a method for treating or preventing diseases that involve unregulated cell growth, including, for example, primary liver cancer,hepatocellular carcinoma, hepatoblastoma, cholangiocarcinoma breast cancer, ovarian cancer, lung cancer, leukemia, and metastatic disease, said method comprising administering to a subject an effective amount of a compound or composition according to the present invention.

[0010] The present invention yet further relates to a method for treating or preventing diseases that involve unregulated cell growth, including, for example, primary liver cancer,hepatocellular carcinoma, hepatoblastoma, and cholangiocarcinoma, breast cancer, ovarian cancer, lung cancer, leukemia, and metastatic disease, wherein said method comprises administering to a subject a composition comprising an effective amount of one or more compounds according to the present invention and an excipient.

[0011] The present invention also relates to a method for treating or preventing disease or conditions associated with primary liver cancer,hepatocellular carcinoma, hepatoblastoma, and cholangiocarcinoma, breast cancer, ovarian cancer, lung cancer, leukemia, and metastatic disease, and diseases that involve unregulated cell growth. Said methods comprise administering to a subject an effective amount of a compound or composition according to the present invention.

[0012] The present invention yet further relates to a method for treating or preventing disease or conditions associated with primary liver cancer,hepatocellular carcinoma, hepatoblastoma, and cholangiocarcinoma, breast cancer, ovarian cancer, lung cancer, leukemia, and metastatic disease, and diseases that involve unregulated cell growth, wherein said method comprises administering to a subject a composition comprising an effective amount of one or more compounds according to the present invention and an excipient.

[0013] The present invention also relates to a method for treating or preventing disease or conditions associated with unregulated cell growth. Said methods comprise administering to a subject an effective amount of a compound or composition according to the present invention.

[0014] The present invention yet further relates to a method for treating or preventing disease or conditions associated with unregulated cell growth, wherein said method comprises administering to a subject a composition comprising an effective amount of one or more compounds according to the present invention and an excipient.

[0015] The present invention also relates to a method for treating or preventing diseases that involve infection with a hepatitis virus, including, for example, hepatitis A virus, hepatitis B virus, hepatitis C virus, hepatitis D virus, and hepatitis E virus, as well as other viral species that infect the liver, said method comprising administering to a subject an effective amount of a compound or composition according to the present invention.

[0016] The present invention yet further relates to a method for treating or preventing diseases that involve infection with a hepatitis virus, including, for example, hepatitis A virus, hepatitis B virus, hepatitis C virus, hepatitis D virus, and hepatitis E virus, as well as other viral species that infect the liver, wherein said method comprises administering to a subject a composition comprising an effective amount of one or more compounds according to the present invention and an excipient.

[0017] The present invention also relates to a method for treating or preventing disease or conditions associated with hepatitis A virus, hepatitis B virus, hepatitis C virus, hepatitis D virus, and hepatitis E virus, and diseases that involve infection with a hepatits virus as well as other viral species that infect the liver. Said methods comprise administering to a subject an effective amount of a compound or composition according to the present invention.

[0018] The present invention yet further relates to a method for treating or preventing disease or conditions associated with hepatitis A virus, hepatitis B virus, hepatitis C virus, hepatitis D virus, and Hepatitis E virus, and diseases that involve infection with a hepatits virus as well as other viral species that infect the liver, wherein said method comprises administering to a subject a composition comprising an effective amount of one or more compounds according to the present invention and an excipient.

[0019] The present invention also relates to a method for treating or preventing disease or conditions associated with infection with a hepatits virus, as well as other viral species that infect the liver. Said methods comprise administering to a subject an effective amount of a compound or composition according to the present invention.

[0020] The present invention yet further relates to a method for treating or preventing disease or conditions associated with infection with a hepatits virus, as well as other viral species that infect the liver, wherein said method comprises administering to a subject a composition comprising an effective amount of one or more compounds according to the present invention and an excipient.

[0021] The present invention further relates to a process for preparing the compounds of the present invention.

[0022] These and other objects, features, and advantages will become apparent to those of ordinary skill in the art from a reading of the following detailed description and the appended claims. All percentages, ratios and proportions herein are by weight, unless otherwise specified. All temperatures are in degrees Celsius (° C) unless otherwise specified. All documents cited are in relevant part, incorporated herein by reference; the citation of any document is not to be construed as an admission that it is prior art with respect to the present invention.

DETAILED DESCRIPTION OF THE INVENTION

[0023] The substituted aminothiazoles of the present invention are capable of treating and preventing diseases associated with unregulated cell growth, for example primary liver cancer hepatocellular carcinoma, hepatoblastoma, and cholangiocarcinoma, breast cancer, ovarian cancer, lung cancer, leukemia, and metastatic disease. The substituted aminothiazoles of the present invention are also capable of treating and preventing diseases associated with infection with a hepatits virus, for example hepatitis A virus, hepatitis B virus, hepatitis C virus, hepatitis D virus, and hepatitis E virus, as well as other viruses that infect the liver. It has been discovered that compounds of the disclosure cause cell cycle arrest and apoptosis in hepatocellular carcinoma (HCC)-derived cells as well as hepatoblastoma, breast cancer cells, and ovarian carcinoma cells. In addition, it has been determined that the effect on sensitive cells, for example HCC-derived cells as well as hepatoblastoma, breast cancer cells, and ovarian carcinoma cells, is non-reversible, and that the compounds of the disclosure act through inhibition of mitotic anti-apoptotic signaling by the regulatory kinases AKT, mTORC1 and mTORC2. Further, the substituted aminothiazoles of the disclosure destroy cells that support infection with a hepatits virus, for example hepatitis A virus, hepatitis B virus, hepatitis C virus, hepatitis D virus, and Hepatitis E virus, such as (cell type to support Hepatitis infection), and can serve as antiviral agents for the treatment and prevention of diseases associated with infection with a hepatits virus, for example hepatitis A virus, hepatitis B

virus, hepatitis C virus, hepatitis D virus, and Hepatitis E virus, as well as other viral species that infect the liver.

[0024] Without wishing to be limited by theory, it is believed that the substituted aminothiazoles of the disclosure can ameliorate, abate, otherwise cause to be controlled, diseases associated unregulated cell growth. In addition, and also without wishing to be limited by theory, it is believed that the substituted aminothiazoles of the disclosure can ameliorate, abate, otherwise cause to be controlled, diseases associated with infection of the liver with a virus.

[0025] Throughout the description, where compositions are described as having, including, or comprising specific components, or where processes are described as having, including, or comprising specific process steps, it is contemplated that compositions of the present teachings also consist essentially of, or consist of, the recited components, and that the processes of the present teachings also consist essentially of, or consist of, the recited processing steps.

[0026] In the application, where an element or component is said to be included in and/or selected from a list of recited elements or components, it should be understood that the element or component can be any one of the recited elements or components and can be selected from a group consisting of two or more of the recited elements or components.

[0027] The use of the singular herein includes the plural (and vice versa) unless specifically stated otherwise. In addition, where the use of the term "about" is before a quantitative value, the present teachings also include the specific quantitative value itself, unless specifically stated otherwise.

[0028] It should be understood that the order of steps or order for performing certain actions is immaterial so long as the present teachings remain operable. Moreover, two or more steps or actions can be conducted simultaneously

[0029] As used herein, the term "halogen" shall mean chlorine, bromine, fluorine and iodine.

[0030] As used herein, unless otherwise noted, "alkyl" and/or "aliphatic" whether used alone or as part of a substituent group refers to straight and branched carbon chains having 1 to 20 carbon atoms or any number within this range, for example 1 to 6 carbon atoms or 1 to 4 carbon atoms. Designated numbers of carbon atoms (e.g. C_{1-4}) shall refer independently to the number of carbon atoms in an alkyl moiety or to the alkyl portion of a larger alkyl-containing substituent. Non-limiting

examples of alkyl groups include methyl, ethyl, n-propyl, *iso*-propyl, n-butyl, *sec*-butyl, *iso*-butyl, *tert*-butyl, and the like. Alkyl groups can be optionally substituted. Non-limiting examples of substituted alkyl groups include hydroxymethyl, chloromethyl, trifluoromethyl, aminomethyl, 1-chloroethyl, 2-hydroxyethyl, 1,2-difluoroethyl, 3-carboxypropyl, and the like. In substituent groups with multiple alkyl groups such as $(C_{1-6}alkyl)_2amino$, the alkyl groups may be the same or different.

[0031] As used herein, the terms "alkenyl" and "alkynyl" groups, whether used alone or as part of a substituent group, refer to straight and branched carbon chains having 2 or more carbon atoms, preferably 2 to 20, wherein an alkenyl chain has at least one double bond in the chain and an alkynyl chain has at least one triple bond in the chain. Alkenyl and alkynyl groups can be optionally substituted. Nonlimiting examples of alkenyl groups include ethenyl, 3-propenyl, 1-propenyl (*also* 2-methylethenyl), isopropenyl (*also* 2-methylethen-2-yl), buten-4-yl, and the like. Nonlimiting examples of substituted alkenyl groups include 2-chloroethenyl (*also* 2-chlorovinyl), 4-hydroxybuten-1-yl, 7-hydroxy-7-methyloct-4-en-2-yl, 7-hydroxy-7-methyloct-3,5-dien-2-yl, and the like. Nonlimiting examples of alkynyl groups include ethynyl, prop-3-ynyl (*also* propargyl), propyn-1-yl, and 2-methyl-hex-4-yn-1-yl. Nonlimiting examples of substituted alkynyl groups include, 5-hydroxy-5-methylhex-3-ynyl, 6-hydroxy-6-methylhept-3-yn-2-yl, 5-hydroxy-5-ethylhept-3-ynyl, and the like.

[0032] As used herein, "cycloalkyl," whether used alone or as part of another group, refers to a non-aromatic carbon-containing ring including cyclized alkyl, alkenyl, and alkynyl groups, e.g., having from 3 to 14 ring carbon atoms, preferably from 3 to 7 or 3 to 6 ring carbon atoms, or even 3 to 4 ring carbon atoms, and optionally containing one or more (e.g., 1, 2, or 3) double or triple bond. Cycloalkyl groups can be monocyclic (e.g., cyclohexyl) or polycyclic (e.g., containing fused, bridged, and/or spiro ring systems), wherein the carbon atoms are located inside or outside of the ring system. Any suitable ring position of the cycloalkyl group can be covalently linked to the defined chemical structure. Cycloalkyl rings can be optionally substituted. Nonlimiting examples of cycloalkyl groups include: cyclopropyl, 2-methyl-cyclopropyl, cyclopropenyl, cyclobutyl, 2,3-dihydroxycyclobutyl, cyclobutenyl, cyclopentyl, cyclopentenyl, cyclopentadienyl, cyclohexyl, cyclohexenyl, cycloheptyl, cyclooctanyl, decalinyl, 2,5-dimethylcyclopentyl, 3,5-dichlorocyclohexyl, 4-hydroxycyclohexyl, 3,3,5-trimethylcyclohex-1-yl, octahydropentalenyl, octahydro-1*H*-indenyl, 3a,4,5,6,7,7a-hexahydro-3*H*-inden-4-yl, decahydroazulenyl; bicyclo[6.2.0]decanyl, decahydronaphthalenyl, and dodecahydro-1*H*-fluorenyl. The term "cycloalkyl" also includes carbocyclic rings which are bicyclic hydrocarbon

rings, non-limiting examples of which include, bicyclo-[2.1.1]hexanyl, bicyclo[2.2.1]heptanyl, bicyclo[3.1.1]heptanyl, 1,3-dimethyl[2.2.1]heptan-2-yl, bicyclo[2.2.2]octanyl, and bicyclo[3.3.3]undecanyl.

[0033] "Haloalkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms, substituted with 1 or more halogen. Haloalkyl groups include perhaloalkyl groups, wherein all hydrogens of an alkyl group have been replaced with halogens (e.g., $-CF_3$, $-CF_2CF_3$). Haloalkyl groups can optionally be substituted with one or more substituents in addition to halogen. Examples of haloalkyl groups include, but are not limited to, fluoromethyl, dichloroethyl, trifluoromethyl, trichloromethyl, pentafluoroethyl, and pentachloroethyl groups.

[0034] The term "alkoxy" refers to the group –O-alkyl, wherein the alkyl group is as defined above. Alkoxy groups optionally may be substituted. The term C_3-C_6 cyclic alkoxy refers to a ring containing 3 to 6 carbon atoms and at least one oxygen atom (e.g., tetrahydrofuran, tetrahydro-2H-pyran). C_3-C_6 cyclic alkoxy groups optionally may be substituted.

[0035] The term "aryl," wherein used alone or as part of another group, is defined herein as a an unsaturated, aromatic monocyclic ring of 6 carbon members or to an unsaturated, aromatic polycyclic ring of from 10 to 14 carbon members. Aryl rings can be, for example, phenyl or naphthyl ring each optionally substituted with one or more moieties capable of replacing one or more hydrogen atoms. Non-limiting examples of aryl groups include: phenyl, naphthylen-1-yl, naphthylen-2-yl, 4-fluorophenyl, 2-hydroxyphenyl, 3-methylphenyl, 2-amino-4-fluorophenyl, 2-(*N*,*N*-diethylamino)phenyl, 2-cyanophenyl, 2,6-di-*tert*-butylphenyl, 3-methoxyphenyl, 8-hydroxynaphthylen-2-yl 4,5-dimethoxynaphthylen-1-yl, and 6-cyano-naphthylen-1-yl. Aryl groups also include, for example, phenyl or naphthyl rings fused with one or more saturated or partially saturated carbon rings (e.g., bicyclo[4.2.0]octa-1,3,5-trienyl, indanyl), which can be substituted at one or more carbon atoms of the aromatic and/or saturated or partially saturated rings.

[0036] The term "arylalkyl" or "aralkyl" refers to the group –alkyl-aryl, where the alkyl and aryl groups are as defined herein. Aralkyl groups of the present invention are optionally substituted. Examples of arylalkyl groups include, for example, benzyl, 1-phenylethyl, 2-phenylethyl, 3-phenylpropyl, 2-phenylpropyl, fluorenylmethyl and the like.

[0037] The terms "heterocyclic" and/or "heterocycle" and/or "heterocylyl," whether used alone or as part of another group, are defined herein as one or more ring having from 3 to 20 atoms wherein at least one atom in at least one ring is a heteroatom selected from nitrogen (N), oxygen (O), or sulfur (S), and wherein further the ring that includes the heteroatom is non-aromatic. In heterocycle groups that include 2 or more fused rings, the non-heteroatom bearing ring may be aryl (e.g., indolinyl, tetrahydroquinolinyl, chromanyl). Exemplary heterocycle groups have from 3 to 14 ring atoms of which from 1 to 5 are heteroatoms independently selected from nitrogen (N), oxygen (O), or sulfur (S). One or more N or S atoms in a heterocycle group can be oxidized. Heterocycle groups can be optionally substituted.

[0038] Non-limiting examples of heterocyclic units having a single ring include: diazirinyl, aziridinyl, urazolyl, azetidinyl, pyrazolidinyl, imidazolidinyl, oxazolidinyl, isoxazolinyl, isoxazolyl, thiazolidinyl, isothiazolyl, isothiazolinyl oxathiazolidinonyl, oxazolidinonyl, hydantoinyl, tetrahydrofuranyl, pyrrolidinyl, morpholinyl, piperazinyl, piperidinyl, dihydropyranyl, tetrahydropyranyl, piperidin-2-onyl (valerolactam), 2,3,4,5-tetrahydro-1*H*-azepinyl, 2,3-dihydro-1*H*-indole, and 1,2,3,4-tetrahydro-quinoline. Non-limiting examples of heterocyclic units having 2 or more rings include: hexahydro-1*H*-pyrrolizinyl, 3a,4,5,6,7,7a-hexahydro-1*H*-benzo[d]imidazolyl, 3a,4,5,6,7,7a-hexahydro-1*H*-indolyl, 1,2,3,4-tetrahydroquinolinyl, chromanyl, isochromanyl, indolinyl, isoindolinyl, and decahydro-1*H*-cycloocta[b]pyrrolyl.

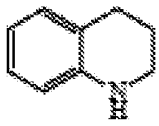
[0039] The term "heteroaryl," whether used alone or as part of another group, is defined herein as one or more rings having from 5 to 20 atoms wherein at least one atom in at least one ring is a heteroatom chosen from nitrogen (N), oxygen (O), or sulfur (S), and wherein further at least one of the rings that includes a heteroatom is aromatic. In heteroaryl groups that include 2 or more fused rings, the non-heteroatom bearing ring may be a carbocycle (e.g., 6,7-Dihydro-5*H*-cyclopentapyrimidine) or aryl (e.g., benzofuranyl, benzothiophenyl, indolyl). Exemplary heteroaryl groups have from 5 to 14 ring atoms and contain from 1 to 5 ring heteroatoms independently selected from nitrogen (N), oxygen (O), or sulfur (S). One or more N or S atoms in a heteroaryl group can be oxidized. Heteroaryl groups can be substituted. Non-limiting examples of heteroaryl rings containing a single ring include: 1,2,3,4-tetrazolyl, [1,2,3]triazolyl, [1,2,4]triazolyl, triazinyl, thiazolyl, 1*H*-imidazolyl, oxazolyl, furanyl, thiopheneyl, pyrimidinyl, 2-phenylpyrimidinyl, pyridinyl, 3-methylpyridinyl, and 4-dimethylaminopyridinyl. Non-limiting examples of heteroaryl rings containing 2 or more fused rings include: benzofuranyl, benzothiophenyl, benzoxazolyl,

benzthiazolyl, benztriazolyl, cinnolinyl, naphthyridinyl, phenanthridinyl, 7*H*-purinyl, 9*H*-purinyl, 6-amino-9*H*-purinyl, 5*H*-pyrrolo[3,2-*d*]pyrimidinyl, 7*H*-pyrrolo[2,3-*d*]pyrimidinyl, pyrido[2,3-*d*]pyrimidinyl, 2-phenylbenzo[d]thiazolyl, 1*H*-indolyl, 4,5,6,7-tetrahydro-1-*H*-indolyl, quinoxalinyl, 5-methylquinoxalinyl, quinazolinyl, quinolinyl, 8-hydroxy-quinolinyl, and isoquinolinyl.

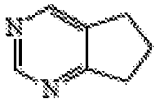
[0040] One non-limiting example of a heteroaryl group as described above is C_1-C_5 heteroaryl, which has 1 to 5 carbon ring atoms and at least one additional ring atom that is a heteroatom (preferably 1 to 4 additional ring atoms that are heteroatoms) independently selected from nitrogen (N), oxygen (O), or sulfur (S). Examples of C_1-C_5 heteroaryl include, but are not limited to, triazinyl, thiazol-2-yl, thiazol-4-yl, imidazol-1-yl, 1*H*-imidazol-2-yl, 1*H*-imidazol-4-yl, isoxazolin-5-yl, furan-2-yl, furan-3-yl, thiophen-2-yl, thiophen-4-yl, pyrimidin-2-yl, pyrimidin-4-yl, pyrimidin-5-yl, pyridin-2-yl, pyridin-3-yl, and pyridin-4-yl.

[0041] Unless otherwise noted, when two substituents are taken together to form a ring having a specified number of ring atoms (e.g., R^3 and R^3 taken together with the nitrogen (N) to which they are attached to form a ring having from 3 to 7 ring members), the ring can have carbon atoms and optionally one or more (e.g., 1 to 3) additional heteroatoms independently selected from nitrogen (N), oxygen (O), or sulfur (S). The ring can be saturated or partially saturated and can be optionally substituted.

[0042] For the purposed of the present invention fused ring units, as well as spirocyclic rings, bicyclic rings and the like, which comprise a single heteroatom will be considered to belong to the cyclic family corresponding to the heteroatom containing ring. For example, 1,2,3,4-tetrahydroquinoline having the formula:

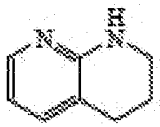


is, for the purposes of the present invention, considered a heterocyclic unit. 6,7-Dihydro-5*H*-cyclopentapyrimidine having the formula:



is, for the purposes of the present invention, considered a heteroaryl unit. When a fused ring unit contains heteroatoms in both a saturated and an aryl ring, the aryl ring will predominate and

determine the type of category to which the ring is assigned. For example, 1,2,3,4-tetrahydro-[1,8]naphthyridine having the formula:



is, for the purposes of the present invention, considered a heteroaryl unit.

[0043] Whenever a term or either of their prefix roots appear in a name of a substituent the name is to be interpreted as including those limitations provided herein. For example, whenever the term "alkyl" or "aryl" or either of their prefix roots appear in a name of a substituent (*e.g.*, arylalkyl, alkylamino) the name is to be interpreted as including those limitations given above for "alkyl" and "aryl."

[0044] The term "substituted" is used throughout the specification. The term "substituted" is defined herein as a moiety, whether acyclic or cyclic, which has one or more hydrogen atoms replaced by a substituent or several (e.g., 1 to 10) substituents as defined herein below. The substituents are capable of replacing one or two hydrogen atoms of a single moiety at a time. In addition, these substituents can replace two hydrogen atoms on two adjacent carbons to form said substituent, new moiety or unit. For example, a substituted unit that requires a single hydrogen atom replacement includes halogen, hydroxyl, and the like. A two hydrogen atom replacement includes carbonyl, oximino, and the like. A two hydrogen atom replacement from adjacent carbon atoms includes epoxy, and the like. The term "substituted" is used throughout the present specification to indicate that a moiety can have one or more of the hydrogen atoms replaced by a substituent. When a moiety is described as "substituted" any number of the hydrogen atoms may be replaced. For example, difluoromethyl is a substituted C_1 alkyl; trifluoromethyl is a substituted C_1 alkyl; 4-hydroxyphenyl is a substituted aromatic ring; (N,N-dimethyl-5-amino)octanyl is a substituted C_8 alkyl; 3-guanidinopropyl is a substituted C_3 alkyl; and 2-carboxypyridinyl is a substituted heteroaryl.

[0045] The variable groups defined herein, *e.g.*, alkyl, alkenyl, alkynyl, cycloalkyl, alkoxy, aryloxy, aryl, heterocycle and heteroaryl groups defined herein, whether used alone or as part of another group, can be optionally substituted. Optionally substituted groups will be so indicated.

[0046] The following are non-limiting examples of substituents which can substitute for hydrogen atoms on a moiety: halogen (chlorine (Cl), bromine (Br), fluorine (F) and iodine(I)), –CN, –NO_2, oxo (=O), –OR^3, –SR^3, –$N(R^3)_2$, –$NR^3C(O)R^3$, –SO_2R^3, –SO_2OR^3, –$SO_2N(R^3)_2$, –$C(O)R^3$, –

$C(O)OR^5$, $-C(O)N(R^5)_2$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, aryl, heterocycle, or heteroaryl, wherein each of the alkyl, haloalkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, aryl, heterocycle, and heteroaryl groups is optionally substituted with 1-10 (e.g., 1-6 or 1-4) groups selected independently from halogen, $-CN$, $-NO_2$, oxo, and R^5; wherein R^3, at each occurrence, independently is hydrogen, $-OR^4$, $-SR^4$, $-C(O)R^4$, $-C(O)OR^4$, $-C(O)N(R^4)_2$, $-SO_2R^4$, $-S(O)_2OR^4$, $-N(R^4)_2$, $-NR^4C(O)R^4$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl (*e.g.*, C_{3-6} cycloalkyl), aryl, heterocycle, or heteroaryl, or two R^3 units taken together with the atom(s) to which they are bound form an optionally substituted carbocycle or heterocycle wherein said carbocycle or heterocycle has 3 to 7 ring atoms; wherein R^4, at each occurrence, independently is hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl (*e.g.*, C_{3-6} cycloalkyl), aryl, heterocycle, or heteroaryl, or two R^4 units taken together with the atom(s) to which they are bound form an optionally substituted carbocycle or heterocycle wherein said carbocycle or heterocycle preferably has 3 to 7 ring atoms.

[0047] In some embodiments, the substituents are selected from

i) $-OR^5$; for example, $-OH$, $-OCH_3$, $-OCH_2CH_3$, $-OCH_2CH_2CH_3$;

ii) $-C(O)R^5$; for example, $-COCH_3$, $-COCH_2CH_3$, $-COCH_2CH_2CH_3$;

iii) $-C(O)OR^5$; for example, $-CO_2CH_3$, $-CO_2CH_2CH_3$, $-CO_2CH_2CH_2CH_3$;

iv) $-C(O)N(R^5)_2$; for example, $-CONH_2$, $-CONHCH_3$, $-CON(CH_3)_2$;

v) $-N(R^5)_2$; for example, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-NH(CH_2CH_3)$;

vi) halogen: $-F$, $-Cl$, $-Br$, and $-I$;

vii) $-CH_mX_g$; wherein X is halogen, m is from 0 to 2, e+g =3; for example, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CCl_3$, or $-CBr_3$;

viii) $-SO_2R^5$; for example, $-SO_2H$; $-SO_2CH_3$; $-SO_2C_6H_5$;

ix) C_1-C_6 linear, branched, or cyclic alkyl;

x) Cyano

xi) Nitro;

xii) $N(R^5)C(O)R^5$;

xiii) Oxo (=O);

xiv) Heterocycle; and

xv) Heteroaryl.

wherein each R^5 is independently hydrogen, optionally substituted C_1-C_6 linear or branched alkyl (e.g., optionally substituted C_1-C_4 linear or branched alkyl), or optionally substituted C_3-C_6 cycloalkyl (e.g optionally substituted C_3-C_4 cycloalkyl); or two R^5 units can be taken together to form a ring comprising 3-7 ring atoms. In certain aspects, each R^5 is independently hydrogen, C_1-C_6 linear or branched alkyl optionally substituted with halogen or C_3-C_6 cycloalkyl or C_3-C_6 cycloalkyl.

[0048] At various places in the present specification, substituents of compounds are disclosed in groups or in ranges. It is specifically intended that the description include each and every individual subcombination of the members of such groups and ranges. For example, the term "C_{1-6} alkyl" is specifically intended to individually disclose C_1, C_2, C_3, C_4, C_5, C_6, C_1-C_6, C_1-C_5, C_1-C_4, C_1-C_3, C_1-C_2, C_2-C_6, C_2-C_5, C_2-C_4, C_2-C_3, C_3-C_6, C_3-C_5, C_3-C_4, C_4-C_6, C_4-C_5, and C_5-C_6, alkyl.

[0049] For the purposes of the present invention the terms "compound," "analog," and "composition of matter" stand equally well for the substituted aminothiazoles described herein, including all enantiomeric forms, diastereomeric forms, salts, and the like, and the terms "compound," "analog," and "composition of matter" are used interchangeably throughout the present specification.

[0050] Compounds described herein can contain an asymmetric atom (also referred as a chiral center), and some of the compounds can contain one or more asymmetric atoms or centers, which can thus give rise to optical isomers (enantiomers) and diastereomers. The present teachings and compounds disclosed herein include such enantiomers and diastereomers, as well as the racemic and resolved, enantiomerically pure R and S stereoisomers, as well as other mixtures of the R and S stereoisomers and pharmaceutically acceptable salts thereof. Optical isomers can be obtained in pure form by standard procedures known to those skilled in the art, which include, but are not limited to, diastereomeric salt formation, kinetic resolution, and asymmetric synthesis. The present teachings also encompass cis and trans isomers of compounds containing alkenyl moieties (e.g., alkenes and imines). It is also understood that the present teachings encompass all possible regioisomers, and mixtures thereof, which can be obtained in pure form by standard separation procedures known to those skilled in the art, and include, but are not limited to, column chromatography, thin-layer chromatography, and high-performance liquid chromatography.

[0051] Pharmaceutically acceptable salts of compounds of the present teachings, which can have an acidic moiety, can be formed using organic and inorganic bases. Both mono and polyanionic

salts are contemplated, depending on the number of acidic hydrogens available for deprotonation. Suitable salts formed with bases include metal salts, such as alkali metal or alkaline earth metal salts, for example sodium, potassium, or magnesium salts; ammonia salts and organic amine salts, such as those formed with morpholine, thiomorpholine, piperidine, pyrrolidine, a mono-, di- or tri-lower alkylamine (e.g., ethyl-tert-butyl-, diethyl-, diisopropyl-, triethyl-, tributyl- or dimethylpropylamine), or a mono-, di-, or trihydroxy lower alkylamine (e.g., mono-, di- or triethanolamine). Specific non-limiting examples of inorganic bases include $NaHCO_3$, Na_2CO_3, $KHCO_3$, K_2CO_3, Cs_2CO_3, LiOH, NaOH, KOH, NaH_2PO_4, Na_2HPO_4, and Na_3PO_4. Internal salts also can be formed. Similarly, when a compound disclosed herein contains a basic moiety, salts can be formed using organic and inorganic acids. For example, salts can be formed from the following acids: acetic, propionic, lactic, benzenesulfonic, benzoic, camphorsulfonic, citric, tartaric, succinic, dichloroacetic, ethenesulfonic, formic, fumaric, gluconic, glutamic, hippuric, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, malonic, mandelic, methanesulfonic, mucic, napthalenesulfonic, nitric, oxalic, pamoic, pantothenic, phosphoric, phthalic, propionic, succinic, sulfuric, tartaric, toluenesulfonic, and camphorsulfonic as well as other known pharmaceutically acceptable acids.

[0052] When any variable occurs more than one time in any constituent or in any formula, its definition in each occurrence is independent of its definition at every other occurrence (e.g., in $N(R^4)_3$, each R^4 may be the same or different than the other). Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

[0053] The terms "treat" and "treating" and "treatment" as used herein, refer to partially or completely alleviating, inhibiting, ameliorating and/or relieving a condition from which a patient is suspected to suffer.

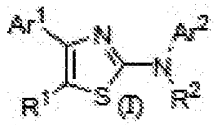
[0054] As used herein, "therapeutically effective" and "effective dose" refer to a substance or an amount that elicits a desirable biological activity or effect.

[0055] Except when noted, the terms "subject" or "patient" are used interchangeably and refer to mammals such as human patients and non-human primates, as well as experimental animals such as rabbits, rats, and mice, and other animals. Accordingly, the term "subject" or "patient" as used herein means any mammalian patient or subject to which the compounds of the invention can be administered. In an exemplary embodiment of the present invention, to identify subject patients for treatment according to the methods of the invention, accepted screening methods are employed to

determine risk factors associated with a targeted or suspected disease or condition or to determine the status of an existing disease or condition in a subject. These screening methods include, for example, conventional work-ups to determine risk factors that may be associated with the targeted or suspected disease or condition. These and other routine methods allow the clinician to select patients in need of therapy using the methods and compounds of the present invention.

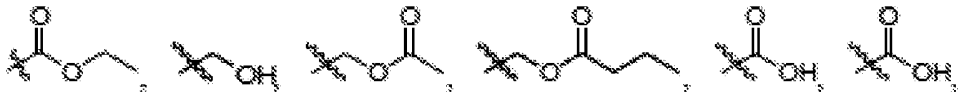
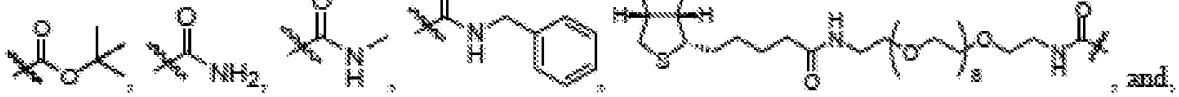
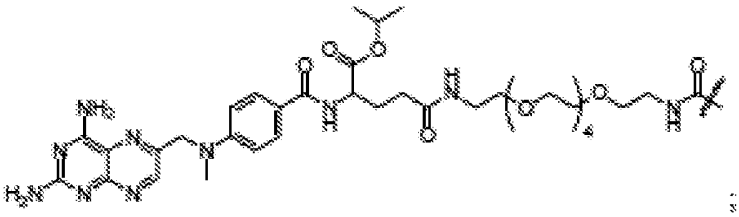
The substituted aminothiazoles

[0056] The compounds of the present invention are substituted aminothiazoles, and include all enantiomeric and diastereomeric forms and pharmaceutically accepted salts thereof having the formula:

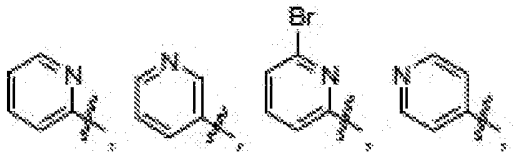
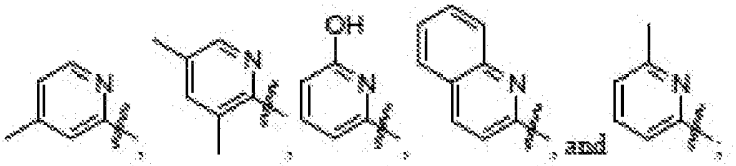


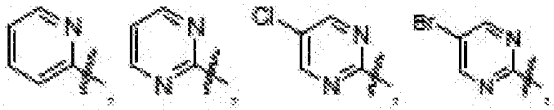
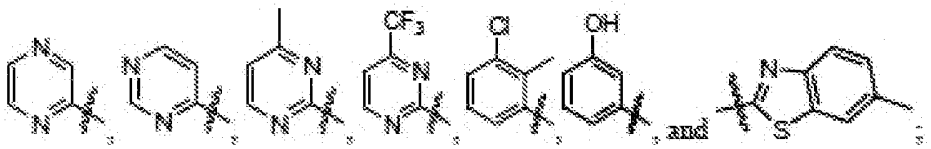
(I)

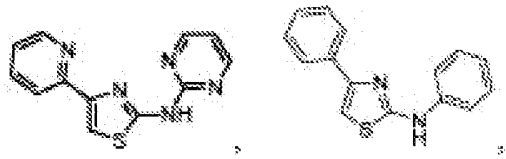
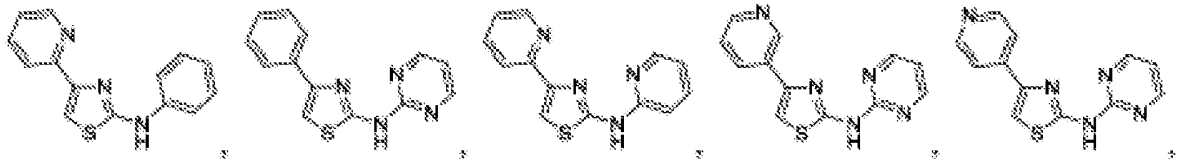
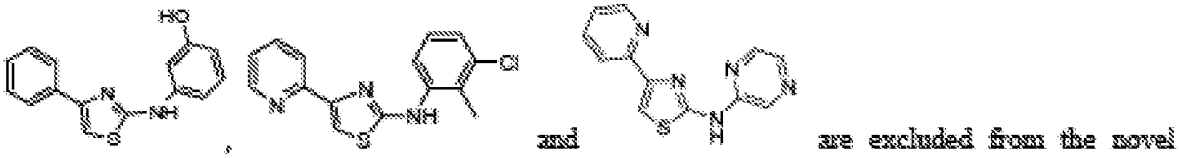
Including hydrates, solvates, pharmaceutically acceptable salts, prodrugs and complexes thereof, wherein:

R^1 is selected from a group consisting of hydrogen, C_1-C_9 linear alkyl, isopropyl, cyclohexyl, bromine, cyano,  ,  , and,  ;

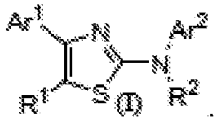
R^2 is selected from a group consisting of hydrogen, methyl, isopropyl, tert-butyl, benzyl, and  ;

Ar^1 is selected from a group consisting of phenyl,  ,  , and ;

Ar^2 is selected from a group consisting of phenyl,  ,  , and ;

[0057] Compounds of the structures  ,  ,  , and are excluded from the novel compounds of formula (I).

[0058] The present invention is also directed toward novel methods of use of compounds of the structure



(I).

[0059] In some embodiments, R^1 is hydrogen.

[0060] In some embodiments, R^1 is C_1-C_9 linear alkyl

[0061] In some embodiments, R^1 is methyl.

[0062] In some embodiments, R^1 is ethyl.

[0063] In some embodiments, R^1 is pentyl.

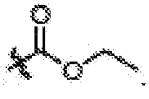
[0064] In some embodiments, R^1 is nonyl.

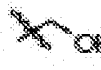
[0065] In some embodiments, R^1 is isopropyl.

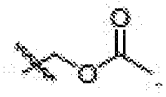
[0066] In some embodiments, R^1 is cyclohexyl.

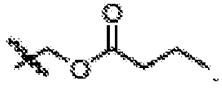
[0067] In some embodiments, R^1 is bromine.

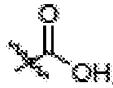
[0068] In some embodiments, R^1 is cyano.

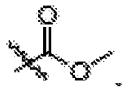
[0069] In some embodiments, R^1 is  .

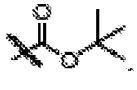
[0070] In some embodiments, R^1 is  .

[0071] In some embodiments, R^1 is  .

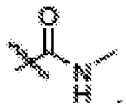
[0072] In some embodiments, R^1 is  .

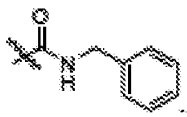
[0073] In some embodiments, R^1 is  .

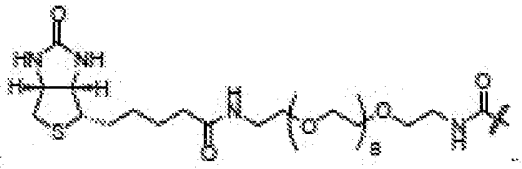
[0074] In some embodiments, R^1 is  .

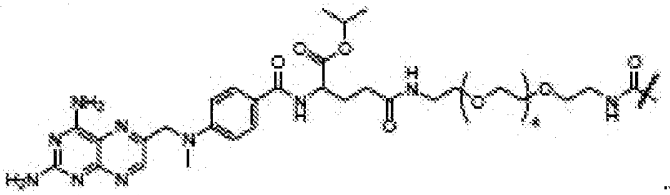
[0075] In some embodiments, R^1 is  .

[0076] In some embodiments, R^1 is  .

[0077] In some embodiments, R^1 is  .

[0078] In some embodiments, R^1 is  .

[0079] In some embodiments, R^1 is  .

[0080] In some embodiments, R^1 is  .

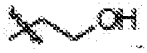
[0081] In some embodiments, R^2 is hydrogen.

[0082] In some embodiments, R^2 is methyl.

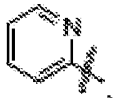
[0083] In some embodiments, R^2 is isopropyl.

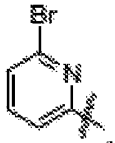
[0084] In some embodiments, R^2 is tert-butyl.

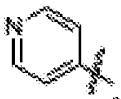
[0085] In some embodiments, R^2 is benzyl.

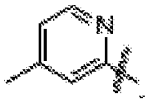
[0086] In some embodiments, R^2 is  .

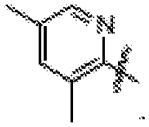
[0087] In some embodiments, Ar^1 is phenyl.

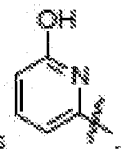
[0088] In some embodiments, Ar^1 is  .

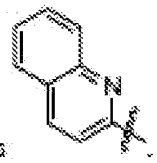
[0089] In some embodiments, Ar^1 is  .

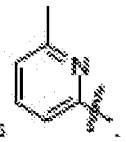
[0090] In some embodiments, Ar^1 is  .

[0091] In some embodiments, Ar^1 is  .

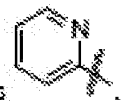
[0092] In some embodiments, Ar^1 is  .

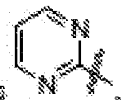
[0093] In some embodiments, Ar^1 is  .

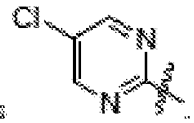
[0094] In some embodiments, Ar^1 is  .

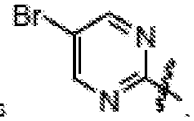
[0095] In some embodiments, Ar^1 is  .

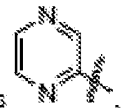
[0096] In some embodiments, Ar^2 is phenyl.

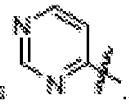
[0097] In some embodiments, Ar^2 is  .

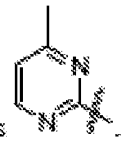
[0098] In some embodiments, Ar^2 is  .

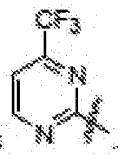
[0099] In some embodiments, Ar^2 is  .

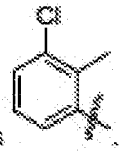
[0100] In some embodiments, Ar^2 is  .

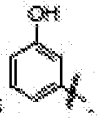
[0101] In some embodiments, Ar^2 is  .

[0102] In some embodiments, Ar^2 is  .

[0103] In some embodiments, Ar^2 is  .

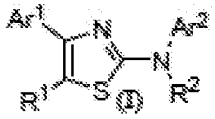
[0104] In some embodiments, Ar^2 is  .

[0105] In some embodiments, Ar^2 is  .

[0106] In some embodiments, Ar^2 is  .

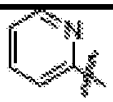
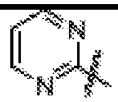
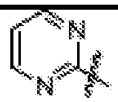
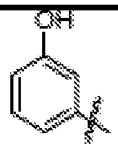
[0107] In some embodiments, Ar^2 is  .

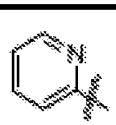
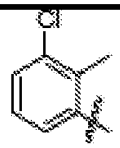
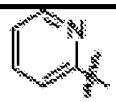
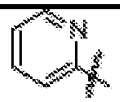
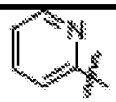
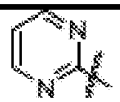
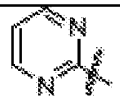
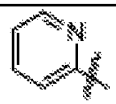
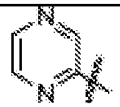
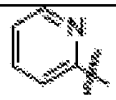
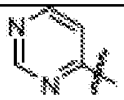
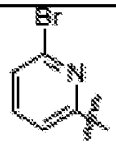
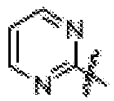
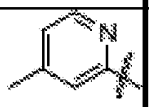
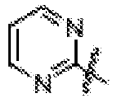
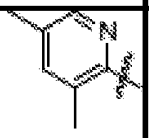
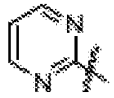
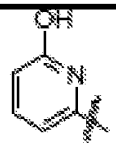
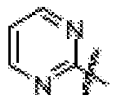
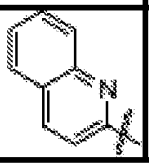
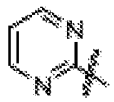
[0108] Exemplary embodiments include compounds having the formula (I) or a pharmaceutically acceptable salt form thereof:

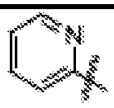
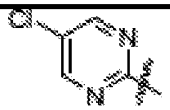
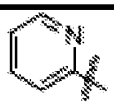
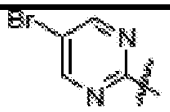
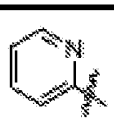
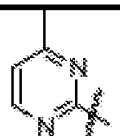
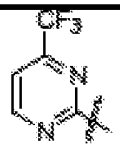
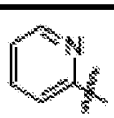
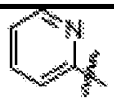
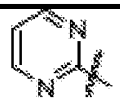
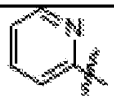
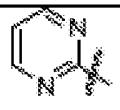
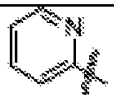
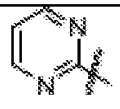
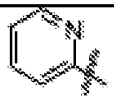
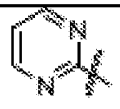
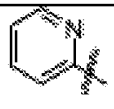
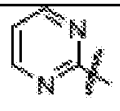
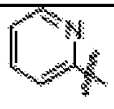
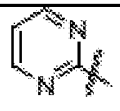
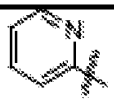
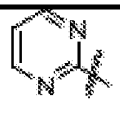


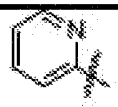
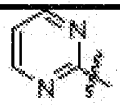
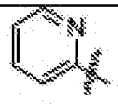
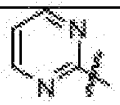
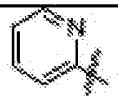
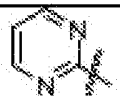
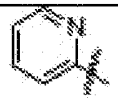
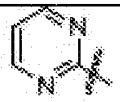
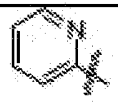
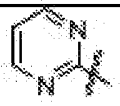
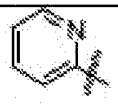
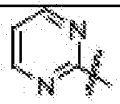
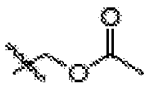
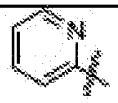
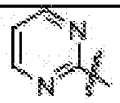
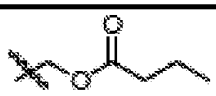
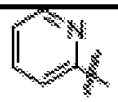
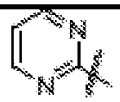
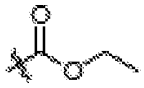
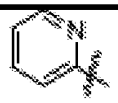
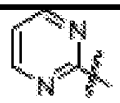
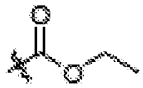
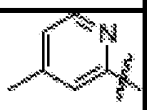
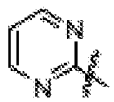
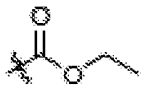
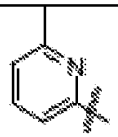
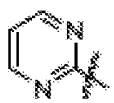
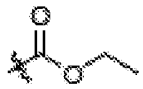
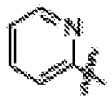
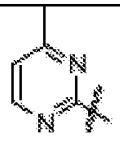
wherein non-limiting examples of R^1, R^2, Ar^1 and Ar^2 are defined herein below in Table 1.

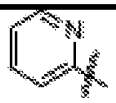
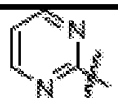
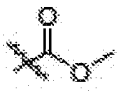
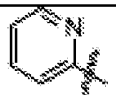
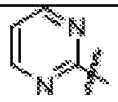
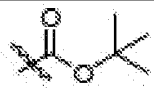
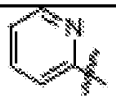
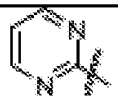
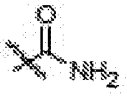
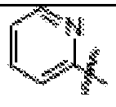
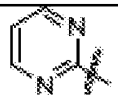
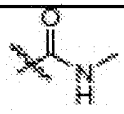
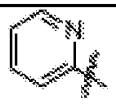
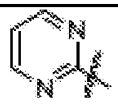
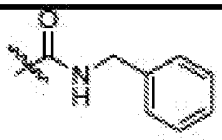
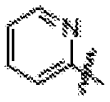
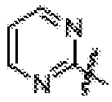
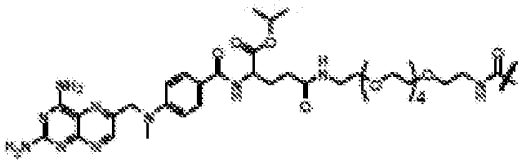
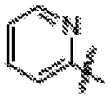
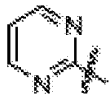
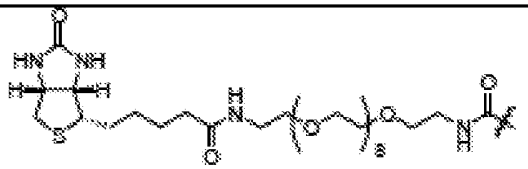
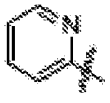
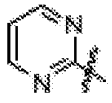
Table 1: Exemplary embodiments of compounds of the formula (I):

Entry	R^1	R^2	Ar^1	Ar^2
1	H	H		
2	H	H	Phenyl	Phenyl
3	H	H	Phenyl	
4	H	H	Phenyl	

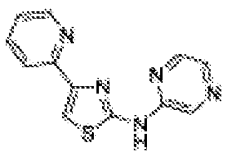
5	H	H		
6	H	H		
7	H	H		
8	H	H		
9	H	H		
10	H	H		
11	H	H		
12	H	H		
13	H	H		
14	H	H		
15	H	H		

16	H	H		
17	H	H		
18	H	H		
19	H	H		
20	H	H		
21	CH_3	H		
22	CH_2CH_3	H		
23	$CH(CH_3)_2$	H		
24	$CH_2(CH_2)_3CH_3$	H		
25	Cyclohexyl	H		
26	Nonyl	H		
27	Cyano	H		

28	H	Isopropyl		
29	H	Methyl		
30	H	Benzyl		
31	H			
32	Br	H		
33		H		
34		H		
35		H		
36		H		
37		H		
38		H		
39		H		

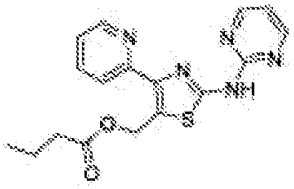
40	CO_2H	H		
41		H		
42				
43		H		
44		H		
45		H		
46		H		
47		H		

[0109] For the purposes of demonstrating the manner in which the compounds of the present invention are named and referred to herein, the compound having the formula:



has the chemical name N-(pyrazin-2-yl)-4-(pyridin-2-yl)thiazol-2-amine.

[0110] For the purposes of demonstrating the manner in which the compounds of the present invention are named and referred to herein, the compound having the formula:



has the chemical name (4-(pyridin-2-yl)-2-(pyrimidin-2-ylamino)thiazol-5-yl)methyl butyrate.

[0111] For the purposes of the present invention, a compound depicted by the racemic formula, will stand equally well for either of the two enantiomers or mixtures thereof, or in the case where a second chiral center is present, all diastereomers.

[0112] In all of the embodiments provided herein, examples of suitable optional substituents are not intended to limit the scope of the claimed invention. The compounds of the invention may contain any of the substituents, or combinations of substituents, provided herein.

PROCESS

[0113] The present invention further relates to a process for preparing the compounds of the present invention. Compounds of the present teachings can be prepared in accordance with the procedures outlined herein, from commercially available starting materials, compounds known in the literature, or readily prepared intermediates, by employing standard synthetic methods and procedures known to those skilled in the art of organic chemistry. Standard synthetic methods and procedures for the preparation of organic molecules and functional group transformations and manipulations can be readily obtained from the relevant scientific literature or from standard textbooks in the field. It will be appreciated that where typical or preferred process conditions (i.e., reaction temperatures, times, mole ratios of reactants, solvents, pressures, etc.) are given, other process conditions can also be used unless otherwise stated. Optimum reaction conditions can vary with the particular reactants or solvent used, but such conditions can be determined by one skilled in the art by routine optimization procedures. Those skilled in the art of organic synthesis will recognize that the nature and order of the synthetic steps presented can be varied for the purpose of optimizing the formation of the compounds described herein.

[0114] The processes described herein can be monitored according to any suitable method known in the art. For example, product formation can be monitored by spectroscopic means, such as nuclear magnetic resonance spectroscopy (e.g., ^{1}H or ^{13}C), infrared spectroscopy, spectrophotometry (e.g., UV-visible), mass spectrometry, or by chromatography such as high pressure liquid chromatography (HPLC), gas chromatography (GC), gel-permeation chromatography (GPC), or thin layer chromatography (TLC).

[0115] Preparation of the compounds can involve protection and deprotection of various chemical groups. The need for protection and deprotection and the selection of appropriate protecting groups can be readily determined by one skilled in the art. The chemistry of protecting groups can be found, for example, in Greene et al., *Protective Groups in Organic Synthesis*, 2d. Ed. (Wiley & Sons, 1991), the entire disclosure of which is incorporated by reference herein for all purposes.

[0116] The reactions or the processes described herein can be carried out in suitable solvents which can be readily selected by one skilled in the art of organic synthesis. Suitable solvents typically are substantially nonreactive with the reactants, intermediates, and/or products at the temperatures at which the reactions are carried out, i.e., temperatures that can range from the solvent's freezing temperature to the solvent's boiling temperature. A given reaction can be carried out in one solvent or a mixture of more than one solvent. Depending on the particular reaction step, suitable solvents for a particular reaction step can be selected.

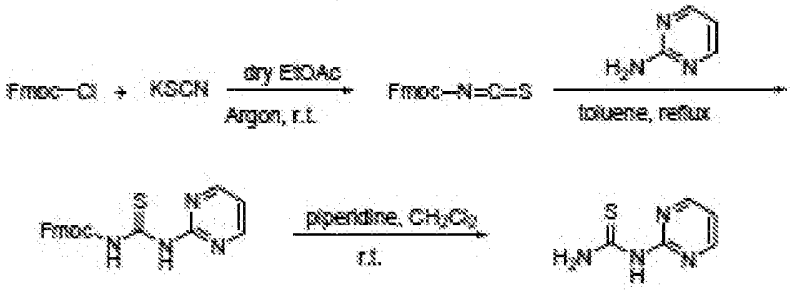
[0117] The Examples provided below provide representative methods for preparing exemplary compounds of the present invention. The skilled practitioner will know how to substitute the appropriate reagents, starting materials and purification methods known to those skilled in the art, in order to prepare the compounds of the present invention.

[0118] ^{1}H NMR spectra were recorded on a 300 MHz ENOVA VARIAN spectrometer. Chemical shifts values are given in ppm and refered as the internal standard to TMS (tetramethylsilane). The peak patterns are indicated as follows: s, singlet; d, doublet; t, triplet; q, quadruplet; m, multiplet and dd, doublet of doublets. The coupling constants (*J*) are reported in Hertz (Hz). Mass Spectra were obtained on a 1200 Aligent LC-MS spectrometer (ES-API, Positive). Silica gel column chromatography was performed over silica gel 100-200 mesh using the solvent systems described herein herein.

[0119] The examples provide methods for preparing representative compounds of formula (I). The skilled practitioner will know how to substitute the appropriate reagents, starting materials

and purification methods known to those skilled in the art, in order to prepare additional compounds of the present invention.

[0120]Example 1: Synthesis of of 1-(pyrimidin-3-yl)thiourea:

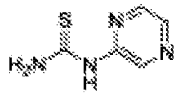


[0121] To a suspension of potassium thiocyanate (3.31 g, 34.0 mmol) in anhydrous ethyl acetate (30 mL) at 0 °C under the argon atmosphere, was added dropwise a solution of fluorenylmethyloxy-carbonyl chloride (8.00 g, 30.9 mmol) in anhydrous ethyl acetate (30 mL). After addition, the reaction mixture was stirred at room temperature for 24 hours. Then, it was concentrated and purified through silica gel column chromatography (dichloromethane:hexanes = 40:60) to afford 5.00 g of pure product O-((9H-fluoren-9-yl)methyl) carbonisothiocyanatidate as colorless oil.

[0122] A reaction mixture of O-((9H-fluoren-9-yl)methyl) carbonisothiocyanatidate (5.00 g, 17.8 mmol) and pyrimidin-2-amine (1.61 g, 16.9 mmol) in toluene (80 mL) was refluxed for 4 hours. Then, it was filtered and washed with toluene to give 6.00 g of product 1-Fmoc-3-(pyrimidin-2-yl)thiourea as white solid, which was directly used in the next step without further purification.

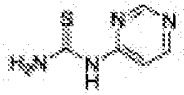
[0123] To a stirred suspension of 1-Fmoc-3-(pyrimidin-2-yl)thiourea (6.00 g, 15.9 mmol) in dichloromethane (120 mL), was added piperidine (24 mL). The reaction mixture was stirred at room temperature for 20 hours, and then filtered and washed with dichloromethane. The crude product was slurried in water (50 mL) for 10 minutes, filtered, washed with water and dried under the vacuum to afforded 2.35 g of pure product 1-(pyrimidin-2-yl)thiourea as white solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.57 (s, 1H, NH), 10.20 (s, 1H, NH), 9.13 (s, 1H, NH), 8.63 (d, J = 4.8 Hz, 2H, CH_{py}), 7.14 (t, J = 5.1 Hz, 1H, CH_{py}).

[0124] Example 2: Synthesis of 1-(pyrazin-2-yl)thiourea.



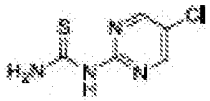
[0125] 1-(pyrazin-2-yl)thiourea was synthesized from pyrazin-2-ylamine in the same manner as Example 1 to provide the product as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.83 (s, 1H, NH), 9.94 (s, 1H, NH), 9.08 (s, 1H, NH), 8.52 (s, 1H, CH_{ar}), 8.23 (s, 2H, CH_{ar}).

[0126] Example 3: Synthesis of 1-(pyrimidin-4-yl)thiourea.



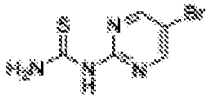
[0127] 1-(pyrimidin-4-yl)thiourea was synthesized from pyrimidin-4-ylamine in the same manner as Example 1 to provide the product as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.83 (s, 1H, NH), 10.28 (s, 1H, NH), 9.29 (s, 1H, NH), 8.78 (d, J = 0.6 Hz, 1H, CH_{ar}), 8.54 (d, J = 6.0 Hz, 1H, CH_{ar}), 7.14 (dd, J = 5.7, 1.2 Hz, 1H, CH_{ar}).

[0128] Example 4: Synthesis of 1-(5-chloropyrimidin-2-yl)thiourea.



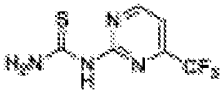
[0129] 1-(5-chloropyrimidin-2-yl)thiourea was synthesized from 5-chloro-pyrimidin-2-ylamine in the same manner as Example 1 to provide the product as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.88 (s, 1H, NH), 9.90 (s, 1H, NH), 9.20 (s, 1H, NH), 8.72 (s, 2H, CH_{ar}).

[0130] Example 5: Synthesis of 1-(5-bromopyrimidin-2-yl)thiourea.



[0131] 1-(5-bromopyrimidin-2-yl)thiourea was synthesized from 5-bromo-pyrimidin-2-ylamine in the same manner as Example 1 to provide the product as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.85 (s, 1H, NH), 9.89 (s, 1H, NH), 9.21 (s, 1H, NH), 8.77 (s, 2H, CH_{ar}).

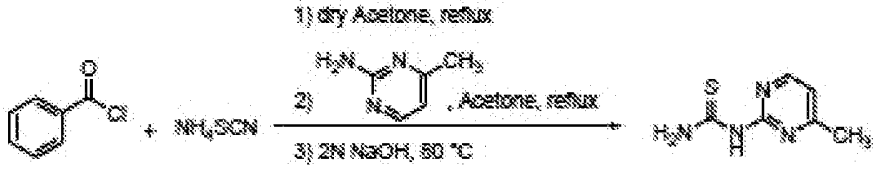
[0132] Example 6: Synthesis of 1-(4-(trifluoromethyl)pyrimidin-2-yl)thiourea.



[0133] 1-(4-(trifluoromethyl)pyrimidin-2-yl)thiourea was synthesized from 4-trifluoromethyl-pyrimidin-2-ylamine in the same manner as Example 1 to provide the

product. ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.85 (s, 1H, NH), 9.33 (s, 1H, NH), 8.97 (d, J = 5.1 Hz, 1H, CH_{ar}), 7.61 (d, J = 4.8 Hz, 1H, CH_{ar}).

[0134] Example 7: Synthesis of 1-(4-methylpyrimidin-2-yl)thiourea.

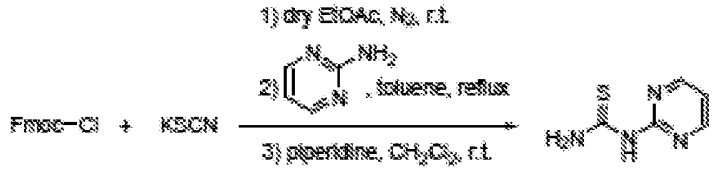


[0135] Benzoyl chloride (1.74 mL, 15 mmol) was added dropwise to a solution of ammonium thiocyanate (1.90 g, 25 mmol) in dry acetone (20 mL) at room temperature. It was heated to reflux for 15 minutes, and then treated with 4-methylpyrimidin-2-amine (1.09 g, 10 mmol). Refluxing was continued for 30 minutes. After cooling down, the reaction mixture was poured onto ice and stirred for 30 minutes. The precipitate was collected by filtration, washed with water, and then hydrolyzed in 2N sodium hydroxide (30 mL) at 80 °C for 30 minutes. It was cooled to room temperature and poured into ice-cold 6 M HCl (20 mL). The pH was adjusted to 8~9 with powder sodium carbonate. The crude product was collected by filtration and washed with water. It was further slurried in dichloromethane and filtered to give 340 mg of compound 1-(4-methylpyrimidin-2-yl)thiourea as white solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.39 (s, 1H, NH), 10.27 (s, 1H, NH), 9.09 (s, 1H, NH), 8.46 (d, J = 5.1 Hz, 1H, CH_{ar}), 7.03 (d, J = 5.1 Hz, 1H, CH_{ar}), 2.40 (s, 3H, $ArCH_3$).

[0136] Example 7: Synthesis of 1-(6-methylbenzo[d]thiazol-2-yl)thiourea.

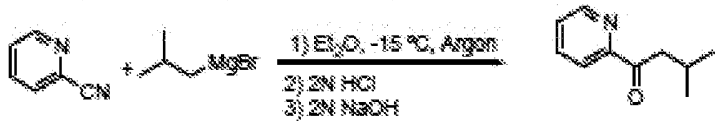
[0137] Synthesis of 1-(6-methylbenzo[d]thiazol-2-yl)thiourea was synthesized from 6-methyl-benzothiazol-2-ylamine in the same manner as Example 7 to provide the product white solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.73 (s, 1H, NH), 9.06 (s, 2H, NH_2), 7.69 (s, 1H, CH_{ar}), 7.56 (d, J = 7.8 Hz, 1H, CH_{ar}), 7.20 (d, J = 7.5 Hz, 1H, CH_{ar}), 2.37 (s, 3H, $ArCH_3$).

[0138] Example 8: Synthesis of 1-(pyrimidin-2-yl)thiourea.



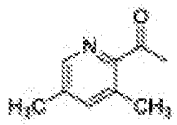
[0139] To a suspension of potassium thiocyanate (4.28 g, 44.0 mmol) in anhydrous ethyl acetate (EtOAc, 50 mL) at 0 °C under the argon atmosphere, was added dropwise a solution of fluorenylmethyloxy-carbonyl chloride (Fmoc-Cl, 10.35 g, 40.0 mmol) in anhydrous ethyl acetate (50 mL). After addition, the reaction mixture was stirred at room temperature for 24 hours. The reaction mixture was diluted with hexanes (100 mL), then filtered through a silica gel pad and washed with a mixture of dichloromethane and hexanes (25:75, 200 mL). The filtrate was concentrated to give the crude O-((9H-fluoren-9-yl)methyl) carbonisothiocyanatidate as light-yellow oil, which was dissolved in toluene (100 mL), followed by addition of pyrimidin-2-amine (3.62 g, 38.0 mmol). It was refluxed for 4 hours, filtered and washed with toluene (100 mL) to afford 1-Fmoc-3-(pyrimidin-2-yl)thiourea, which was suspended in dichloromethane (100 mL) and treated with piperidine (24 mL). After stirred at room temperature for 12 hours, the mixture was filtered and washed with dichloromethane (100 mL) then water (100 mL). The solid was dried under the vacuum to afforded 4.45 g of pure product 1-(pyrimidin-2-yl)thiourea as light-brown solid.

[0140] Example 8: Synthesis of 1-(pyridin-2-yl)propan-1-one.



[0141] To a stirred solution of 2-cyanopyridine (1.04 g, 10 mmol) in anhydrous diethyl ether (20 mL) at < -15 °C under argon atmosphere, was added slowly isobutylmagnesium bromide (2M in diethyl ether, 6.0 mL, 12 mmol). After addition, the reaction mixture was stirred at this temperature for 1 hour, and then allowed to warm up to room temperature over 3 hours. It was quenched with 2N HCl (6 mL) at 0 °C and stirred for another 15 minutes. The pH was adjusted to 8~9 with 2N NaOH. The mixture was diluted with water (15 mL) and extracted with ethyl acetate (30 mL x 3). The combined organic layer was dried over Na_2SO_4, concentrated and purified through silica gel column chromatography (ethyl acetate:hexanes = 4:96 to 16:84) to afford 1.40 g product 1-(pyridin-2-yl)propan-1-one as colorless oil. ^1H NMR (300 MHz, $CDCl_3$): δ 8.68 (dt, J = 4.2, 0.9 Hz, 1H, CH_{ar}), 8.04 (d, J = 8.1 Hz, 1H, CH_{ar}), 7.83 (dt, J = 7.5, 1.8 Hz, 1H, CH_{ar}), 7.48-7.43 (m, 1H, CH_{ar}), 3.11 (d, J = 6.6 Hz, 2H, CH_2CO), 2.34-2.30 (m, 1H, CH), 1.00 (d, J = 6.6 Hz, 6H, $C(CH_3)_2$). MS: MH^+ = 164.

[0142] Example 9: Synthesis of 1-(3,5-dimethylpyridin-2-yl)ethanone.

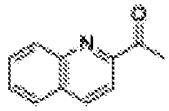


[0143] 1-(3,5-dimethylpyridin-2-yl)ethanone was synthesized from 3,5-dimethyl-pyridine-2-carbonitrile and methylmagnesium bromide in the same manner as Example 8 to provide the product as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.33 (d, J = 0.9 Hz, 1H, CH_{ar}), 7.37 (d, J = 1.5 Hz, 1H, CH_{ar}), 2.69 (s, 3H, CH_3), 2.56 (s, 3H, CH_3), 2.36 (s, 3H, CH_3CO). MS: MH^+ = 150.

[0144] Example 10: Synthesis of 1-(6-methoxypyridin-2-yl)ethanone.

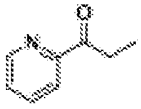
[0145] 1-(6-methoxypyridin-2-yl)ethanone was synthesized from 6-Methoxy-pyridine-2-carbonitrile and methylmagnesium bromide in the same manner as Example 8 to provide the product as a solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.72-7.62 (m, 2H, CH_{ar}), 6.93 (dd, J = 8.1, 0.9 Hz, 1H, CH_{ar}), 4.00 (s, 3H, CH_3OAr), 2.69 (s, 3H, CH_3CO). MS: MH^+ = 152.

[0146] Example 11: Synthesis of 1-(quinolin-2-yl)ethanone.



[0147] 1-(quinolin-2-yl)ethanone was synthesized from Quinoline-2-carbonitrile and methylmagnesium bromide in the same manner as Example 8 to provide the product as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.27 (d, J = 8.4 Hz, 1H, CH_{ar}), 8.20 (d, J = 8.7 Hz, 1H, CH_{ar}), 8.13 (d, J = 8.7 Hz, 1H, CH_{ar}), 7.87 (d, J = 8.4 Hz, 1H, CH_{ar}), 7.82-7.76 (m, 1H, CH_{ar}), 7.68-7.62 (m, 1H, CH_{ar}), 2.88 (s, 3H, CH_3CO). MS: MH^+ = 172.

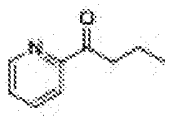
[0148] Example 12: Synthesis of 1-(pyridin-2-yl)propan-1-one.



[0149] 1-(pyridin-2-yl)propan-1-one was synthesized from pyridine-2-carbonitrile and ethylmagnesium bromide in the same manner as Example 8 to provide the product as a Light-

yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.68 (dt, *J* = 4.8, 0.9 Hz, 1H, CH_{ar}), 8.05 (dt, *J* = 8.1, 1.2 Hz, 1H, CH_{ar}), 7.83 (dt, *J* = 7.5, 1.8 Hz, 1H, CH_{ar}), 7.49-7.44 (m, 1H, CH_{ar}), 3.25 (q, *J* = 7.5 Hz, 2H, CH_2CO), 1.22 (t, *J* = 7.5 Hz, 3H, CH_3). MS: MH^+ = 136.

[0150] Example 13: Synthesis of 1-(pyridin-2-yl)butan-1-one.

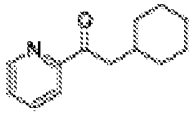


[0151] 1-(pyridin-2-yl)butan-1-one was synthesized from Pyridine-2-carbonitrile and propylmagnesium bromide in the same manner as Example 8 to provide the product as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.68 (dq, *J* = 5.1, 0.9 Hz, 1H, CH_{ar}), 8.04 (dt, *J* = 8.1, 1.2 Hz, 1H, CH_{ar}), 7.83 (dt, *J* = 7.5, 1.8 Hz, 1H, CH_{ar}), 7.48-7.44 (m, 1H, CH_{ar}), 3.20 (t, *J* = 7.5 Hz, 2H, CH_2CO), 1.81-1.74 (m, 2H, CH_2), 1.02 (t, *J* = 7.5 Hz, 3H, CH_3). MS: MH^+ = 150.

[0152] Example 14: Synthesis of 1-(pyridin-2-yl)heptan-1-one.

[0153] 1-(pyridin-2-yl)heptan-1-one was synthesized from pyridine-2-carbonitrile and hexyl magnesium bromide in the same manner as Example 8 to provide the product as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.68 (dq, *J* = 4.8, 0.9 Hz, 1H, CH_{ar}), 8.04 (dt, *J* = 8.1, 0.9 Hz, 1H, CH_{ar}), 7.83 (dt, *J* = 7.5, 1.8 Hz, 1H, CH_{ar}), 7.48-7.44 (m, 1H, CH_{ar}), 3.21 (t, *J* = 7.5 Hz, 2H, CH_2CO), 1.76-1.68 (m, 2H, CH_2), 1.42-1.26 (m, 6H, 3 x CH_2), 0.89 (t, *J* = 7.2 Hz, 3H, CH_3). MS: MH^+ = 192.

[0154] Example 15: Synthesis of 2-cyclohexyl-1-(pyridin-2-yl)ethanone.



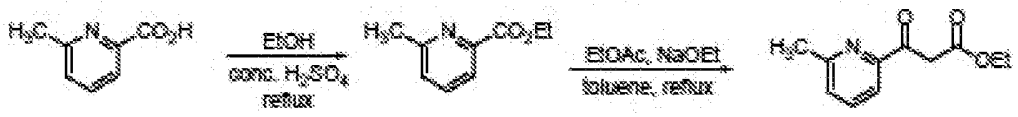
[0155] 2-Cyclohexyl-1-(pyridin-2-yl)ethanone was synthesized from pyridine-2-carbonitrile and cyclohexylmethyl magnesium bromide in the same manner as example 8 to provide the product as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.68 (dt, *J* = 3.9, 0.6 Hz, 1H, CH_{ar}), 8.03 (d, *J* = 8.1 Hz, 1H, CH_{ar}), 7.83 (dt, *J* = 7.8, 1.8 Hz, 1H, CH_{ar}), 7.48-7.43 (m, 1H, CH_{ar}),

3.10 (d, J = 7.2 Hz, 2H, CH_2CO), 2.04-2.00 (m, 1H, CH), 1.78-1.02 (m, 10H, 5 x CH_2). MS: MH^+ = 204.

[0156] Example 16: Synthesis of 1-(pyridin-2-yl)undecan-1-one.

[0157] 1-(pyridin-2-yl)undecan-1-one was synthesized from pyridine-2-carbonitrile and undecanyl magnesium bromide in the same manner as example 8 to provide the product as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$): δ 8.68 (dq, J = 4.8, 0.9 Hz, 1H, CH_{ar}), 8.04 (dt, J = 8.1, 1.2 Hz, 1H, CH_{ar}), 7.83 (dt, J = 7.5, 1.8 Hz, 1H, CH_{ar}), 7.48-7.43 (m, 1H, CH_{ar}), 3.21 (t, J = 7.5 Hz, 2H, CH_2CO), 1.75-1.68 (m, 2H, CH_2), 1.35-1.23 (m, 14H, 7 x CH_2), 0.88 (t, J = 6.9 Hz, 3H, CH_3). MS: MH^+ = 248.

[0158] Example 17: Synthesis of ethyl 3-(6-methylpyridin-2-yl)-3-oxopropanoate.

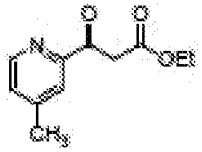


[0159] A reaction mixture of 6-methylpicolinic acid (1.0 g, 7.3 mmol) and conc. sulfuric acid (~98%, 0.6 mL) in ethanol (40 mL) was refluxed for 24 hours. The extra ethanol was evaporated, followed by addition of water (20 mL) at 0 °C. The pH was adjusted to 9 with sodium bicarbonate powder. Then the mixture was extracted with ethyl acetate (30 mL x 3), and the combined organic layer was dried over anhydrous sodium sulfate and concentrated to afford 1.20 g of ethyl 6-methylpicolinate as a colorless oil. MS: MH^+ = 166.

[0160] A solution of anhydrous ethyl acetate (1mL, 9.9 mmol) in toluene (10 mL), was treated with sodium ethoxide (449 mg, 6.6 mg) at room temperature. The mixture was stirred under argon atmosphere for 1 hour, and then, ethyl 6-methylpicolinate (499 mg, 3.3 mmol) was added. The reaction mixture was heated to reflux for 20 hours. After cooling to room temperature, it was acidified (pH = 6) with acetic acid, followed by addition of water (20 mL) and extracted with ethyl acetate (20 mL x 3). The combined organic layer was dried over anhydrous sodium sulfate, concentrated and purified through silica gel column chromatography (ethyl acetate:hexanes = 10:90 to 20:80) to afford 440 mg of compound ethyl 3-(6-methylpyridin-2-yl)-3-oxopropanoate as light-yellow oil. ^1H NMR (300 MHz, $CDCl_3$): δ 7.87 (d, J = 7.8 Hz, 1H, CH_{ar}), 7.72 (t, J = 7.8 Hz, 1H,

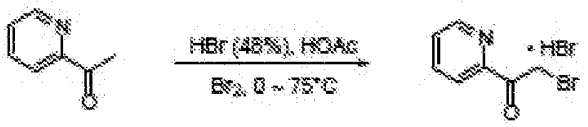
CH_{ar}), 7.33 (d, J = 7.5 Hz, 1H, CH_{ar}), 4.23-4.16 (m, 4H, 2 x CH_2), 2.59 (s, 3H, $ArCH_3$), 1.24 (t, J = 7.2 Hz, 3H, CH_3). MS: MH^+ = 208.

[0161] Example 18: Synthesis of ethyl 3-(4-methylpyridin-2-yl)-3-oxopropanoate.



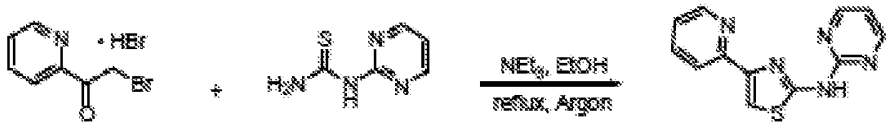
[0162] Ethyl 3-(4-methylpyridin-2-yl)-3-oxopropanoate was synthesized from 4-methyl-pyridine-2-carboxylic acid in the same manner as Example 17 to provide the product as a light yellow oil. ^1H NMR (300 MHz, $CDCl_3$): δ 8.52 (d, J = 5.1 Hz, 1H, CH_{ar}), 7.90 (d, J = 0.6 Hz, 1H, CH_{ar}), 7.30 (dd, J = 5.1, 0.9 Hz, 1H, CH_{ar}), 4.23-4.16 (m, 4H, 2 x CH_2), 2.43 (s, 3H, $ArCH_3$), 1.24 (t, J = 7.2 Hz, 3H, CH_3). MS: MH^+ = 208.

[0163] Example 19: Synthesis of 2-bromo-1-(pyridin-2-yl)ethanone hydrobromide.



[0164] To a solution of 2-acetylpyridine (2.42 g, 20 mmol) in a mixture of 48% hydrobromic acid (2.26 mL, 20 mmol) and acetic acid (22 mL) at 0 °C, was added dropwise bromine (1.13 mL, 22 mmol). The reaction mixture was stirred at room temperature for 1 hour, and then 75 °C for 3hours. After cooling to room temperature, it was diluted with tetrahydrofuran (25 mL) and stirred overnight. The product was collected by filtration, washed with tetrahydrofuran and dried under vacuum. 5.38 g of 2-bromo-1-(pyridin-2-yl)ethanone hydrobromide was afforded as white solid.

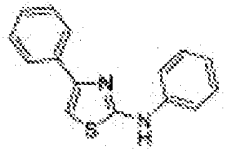
[0165] Example 20: Synthesis of 4-(pyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine.



[0166] A reaction mixture of 2-bromo-1-(pyridin-2-yl) ethanone hydrobromide (1.69 g, 6 mmol), 1-(pyrimidin-2-yl)thiourea (0.93 g, 6 mmol), and triethylamine (2.1 mL, 15 mmol) in ethanol (30 mL) was refluxed for 1 hour under argon atmosphere. After cooling to room temperature, the reaction mixture was quenched with water (100 mL) and stirred for another 2 hours. The crude product was collected by filtration and was further purified by recrystallization in methanol. 1.14 g of compound 4-(pyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine was afforded as white solid. ^1H NMR

(500 MHz, DMSO-d_6): δ 11.88 (s, 1H, NH), 8.67 (d, J = 5.0 Hz, 2H, CH_{ar}), 8.61-8.59 (m, 1H, CH_{ar}), 7.99 (d, J = 8.0 Hz, 1H, CH_{ar}), 7.89 (dt, J = 7.5, 1.5 Hz, 1H, CH_{ar}), 7.75 (s, 1H, CH_{ar}), 7.33-7.31 (m, 1H, CH_{ar}), 7.06 (t, J = 5.0 Hz, 1H, CH_{ar}). MS: MH^+ = 256. 4-(pyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine could be further converted to the HCl salt using the following procedure: A suspension of 4-(pyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine (102 mg, 0.4 mmol) in methanol (10 mL) was treated 4 M HCl solution (in 1,4-dioxane, 1mL). Then, it was heated to reflux and the reaction mixture became a clear solution. The solvent was removed by evaporation and the given residue was further purified by recrystallization in ethyl acetate to afford 130 mg of HCl salt. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.71-8.67 (m, 3H, CH_{ar}), 8.33-8.24 (m, 3H, CH_{ar}), 7.71-7.67 (m, 1H, CH_{ar}), 7.09 (t, J = 5.1 Hz, 1H, CH_{ar}). MS: MH^+ = 256.

[0167] Example 21: Synthesis of N,4-diphenylthiazol-2-amine.



[0168] N,4-diphenylthiazol-2-amine was synthesized from 2-bromo-1-phenyl-ethanone and phenyl-thiourea in the same manner as Example 20 to provide the product as a light-yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.88-7.84 (m, 2H, CH_{ar}), 7.55 (s, 1H, NH), 7.43-7.28 (m, 7H, CH_{ar}), 7.10-7.05 (m, 1H, CH_{ar}), 6.83 (d, J = 1.8 Hz, 1H, CH_{ar}). MS: MH^+ = 253.

[0169] Example 22: Synthesis of N-phenyl-4-(pyridin-2-yl)thiazol-2-amine.

[0170] N-phenyl-4-(pyridin-2-yl)thiazol-2-amine was synthesized from 2-bromo-1-pyridin-2-yl-ethanone and phenyl-thiourea in the same manner as Example 20 to provide the product as a light-yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.62-8.60 (m, 1H, CH_{ar}), 8.00 (dt, J = 8.1, 1.2 Hz, 1H, CH_{ar}), 7.75 (dt, J = 8.1, 2.1 Hz, 1H, CH_{ar}), 7.44-7.34 (m, 6H, 5 x CH_{ar} and NH overlapped), 7.23-7.18 (m, 1H, CH_{ar}), 7.11-7.06 (m, 1H, CH_{ar}). MS: MH^+ = 254.

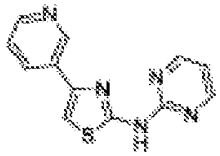
[0171] Example 23: Synthesis of 4-phenyl-N-(pyrimidin-2-yl)thiazol-2-amine.

[0172] 4-Phenyl-N-(pyrimidin-2-yl)thiazol-2-amine was synthesized from 2-bromo-1-phenyl-ethanone and pyrimidin-2-yl-thiourea in the same manner as Example 20 to provide the product as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.80 (s, 1H, NH), 8.63 (d, J = 5.1 Hz, 2H, CH_{ar}), 7.92-7.89 (m, 2H, CH_{ar}), 7.52 (s, 1H, CH_{ar}), 7.43-7.38 (m, 2H, CH_{ar}), 7.31-7.29 (m, 1H, CH_{ar}), 7.03 (t, J = 5.1 Hz, 1H, CH_{ar}). MS: MH^+ = 255.

[0173] Example 24: Synthesis of N,4-di(pyridin-2-yl)thiazol-2-amine.

[0174] N,4-di(pyridin-2-yl)thiazol-2-amine was synthesized from 2-bromo-1-pyridin-2-yl-ethanone and pyridin-2-yl-thiourea in the same manner as Example 20 to provide the product as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.45 (s, 1H, NH), 8.60 (d, J = 4.5 Hz, 1H, CH_{ar}), 8.32 (dd, J = 5.5, 2.0 Hz, 1H, CH_{ar}), 7.97 (d, J = 8.0 Hz, 1H, CH_{ar}), 7.88 (dt, J = 8.0, 2.0 Hz, 1H, CH_{ar}), 7.74-7.71 (m, 1H, CH_{ar}), 7.65 (s, 1H, CH_{ar}), 7.33-7.30 (m, 1H, CH_{ar}), 7.11 (d, J = 8.5 Hz, 1H, CH_{ar}), 6.96-6.93 (m, 1H, CH_{ar}). MS: MH^+ = 255.

[0175] Example 25: Synthesis of 4-(pyridin-3-yl)-N-(pyrimidin-2-yl)thiazol-2-amine.



[0176] 4-(pyridin-3-yl)-N-(pyrimidin-2-yl)thiazol-2-amine was synthesized from 2-bromo-1-pyridin-3-yl-ethanone and pyrimidin-2-yl-thiourea in the same manner as Example 20 to provide the product as a gray solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.93 (s, 1H, NH), 9.14-9.13 (m, 1H, CH_{ar}), 8.65 (d, J = 4.8 Hz, 2H, CH_{ar}), 8.51 (dd, J = 5.1, 1.8 Hz, 1H, CH_{ar}), 8.25-8.21 (m, 1H, CH_{ar}), 7.70 (s, 1H, CH_{ar}), 7.46-7.42 (m, 1H, CH_{ar}), 7.04 (t, J = 4.8 Hz, 1H, CH_{ar}). MS: MH^+ = 256.

[0177] Example 26: Synthesis of 4-(pyridin-4-yl)-N-(pyrimidin-2-yl)thiazol-2-amine.

[0178] 4-(pyridin-4-yl)-N-(pyrimidin-2-yl)thiazol-2-amine was synthesized from 2-bromo-1-pyridin-4-yl-ethanone and pyrimidin-2-yl-thiourea in the same manner as Example 20 to provide the product as a gray solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.93 (s, 1H, NH), 8.65 (d, J = 4.8 Hz, 2H, CH_{ar}), 8.59 (dd, J = 4.8, 1.5 Hz, 2H, CH_{ar}), 7.89 (s, 1H, CH_{ar}), 7.85-7.83 (m, 2H, CH_{ar}), 7.05 (t, J = 4.8 Hz, 1H, CH_{ar}). MS: MH^+ = 256.

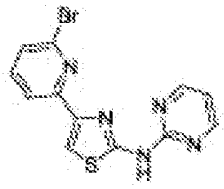
[0179] Example 27: Synthesis of N-(pyrazin-2-yl)-4-(pyridin-3-yl)thiazol-2-amine.

[0180] N-(pyrazin-2-yl)-4-(pyridin-2-yl)thiazol-2-amine was synthesized from 2-bromo-1-pyridin-2-yl-ethanone and pyrimidin-2-yl-thiourea in the same manner as Example 20 to provide the product as a brown solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.87 (s, 1H, NH), 8.60-8.57 (m, 1H, CH_{ar}), 8.51 (d, J = 1.5 Hz, 1H, CH_{ar}), 8.32 (dd, J = 3.0, 1.5 Hz, 1H, CH_{ar}), 8.13 (d, J = 2.4 Hz, 1H, CH_{ar}), 7.96 (dt, J = 7.8, 1.2 Hz, 1H, CH_{ar}), 7.87 (dt, J = 7.8, 1.8 Hz, 1H, CH_{ar}), 7.73 (s, 1H, CH_{ar}), 7.33-7.29 (m, 1H, CH_{ar}). MS: MH^+ = 256.

[0181] Example 28: Synthesis of 4-(pyridin-2-yl)-N-(pyrimidin-4-yl)thiazol-2-amine.

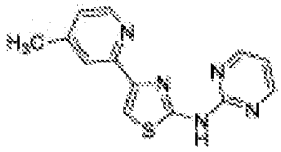
[0182] 4-(pyridin-2-yl)-N-(pyrimidin-4-yl)thiazol-2-amine was synthesized from 2-bromo-1-pyridin-2-yl-ethanone and pyrimidin-4-yl-thiourea in the same manner as Example 20 to provide the product as a brown solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.91 (s, 1H, NH), 8.84 (d, J = 0.9 Hz, 1H, CH_{ar}), 8.60-8.57 (m, 1H, CH_{ar}), 8.46 (d, J = 6.0 Hz, 1H, CH_{ar}), 7.95 (dt, J = 7.8, 1.2 Hz, 1H, CH_{ar}), 7.87 (dt, J = 8.1, 2.1 Hz, 1H, CH_{ar}), 7.80 (s, 1H, CH_{ar}), 7.34-7.29 (m, 1H, CH_{ar}), 7.10 (dd, J = 5.7, 1.2 Hz, 1H, CH_{ar}). MS: MH^+ = 256.

[0183] Example 29: Synthesis of 4-(6-bromopyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine.



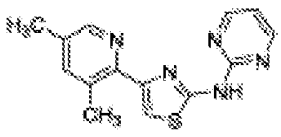
[0184] 4-(6-bromopyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine was synthesized from 2-bromo-1-(6-bromo-pyridin-2-yl)-ethanone and pyrimidin-2-yl-thiourea in the same manner as Example 20 to provide the product as a gray solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.92 (s, 1H, NH), 8.65 (d, J = 4.5 Hz, 2H, CH_{ar}), 7.95 (dd, J = 7.8, 0.9 Hz, 1H, CH_{ar}), 7.82 (t, J = 8.1 Hz, 1H, CH_{ar}), 7.75 (d, J = 0.6 Hz, 1H, CH_{ar}), 7.54 (dd, J = 8.1, 0.9 Hz, 1H, CH_{ar}), 7.05 (t, J = 4.8 Hz, 1H, CH_{ar}). MS: MH^+ = 334.

[0185] Example 30: Synthesis of 4-(4-methylpyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine.



[0186] 4-(4-methylpyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine was synthesized from 2-bromo-1-(4-methyl-pyridin-2-yl)-ethanone and pyrimidin-2-yl-thiourea in the same manner as Example 20 to provide the product as a dark gray solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.81 (s, 1H, NH), 8.64 (d, J = 4.8 Hz, 2H, CH_{ar}), 8.42 (dd, J = 4.2, 0.6 Hz, 1H, CH_{ar}), 7.82 (t, J = 0.9 Hz, 1H, CH_{ar}), 7.70 (s, 1H, CH_{ar}), 7.14-7.12 (m, 1H, CH_{ar}), 7.04 (t, J = 4.8 Hz, 1H, CH_{ar}), 2.36 (s, 3H, $ArCH_3$). MS: MH^+ = 270.

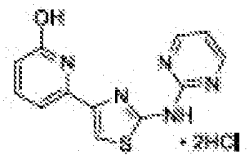
[0187] Example 31: Synthesis of 4-(3,5-dimethylpyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine.



[0188] 4-(3,5-dimethylpyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine was synthesized from 2-bromo-1-(3,5-dimethyl-pyridin-2-yl)-ethanone and pyrimidin-2-yl-thiourea in the same

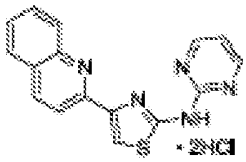
manner as Example 20 to provide the product as a light-gray solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.70 (s, 1H, NH), 8.64 (d, J = 4.8 Hz, 2H, CH_{ar}), 8.24 (s, 1H, CH_{ar}), 7.46 (s, 1H, CH_{ar}), 7.41 (s, 1H, CH_{ar}), 7.02 (t, J = 4.8 Hz, 1H, CH_{ar}), 2.52 (s, 3H, $ArCH_3$), 2.27 (s, 3H, $ArCH_3$). MS: MH^+ = 284.

[0189] Example 32: Synthesis of 6-(2-(pyrimidin-2-ylamino)thiazol-4-yl)pyridin-2-ol dihydrochloride.



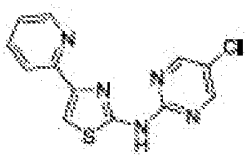
[0190] 6-(2-(pyrimidin-2-ylamino)thiazol-4-yl)pyridin-2-ol dihydrochloride was synthesized from 2-bromo-1-(6-hydroxy-pyridine-2-yl)-ethanone dihydrochloride and pyrimidin-2-yl-thiourea in the same manner as Example 20 to provide the product as a gray solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.93 (s, 1H, NH), 8.64 (d, J = 4.5 Hz, 2H, CH_{ar}), 7.92 (s, 1H, CH_{ar}), 7.53 (t, J = 8.1 Hz, 1H, CH_{ar}), 7.05 (t, J = 4.8 Hz, 1H, CH_{ar}), 6.89 (d, J = 6.9 Hz, 1H, CH_{ar}), 6.33 (d, J = 9.3 Hz, 1H, CH_{ar}). MS: MH^+ = 272.

[0191] Example 33: Synthesis of N-(pyrimidin-2-yl)-4-(quinolin-2-yl)thiazol-2-amine dihydrochloride.



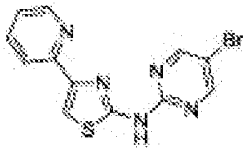
[0192] N-(pyrimidin-2-yl)-4-(quinolin-2-yl)thiazol-2-amine dihydrochloride was synthesized from 2-bromo-1-quinolin-2-yl-ethanone dihydrochloride and pyrimidin-2-yl-thiourea in the same manner as Example 20 to provide the product as a gray solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.84 (d, J = 9.0 Hz, 1H, CH_{ar}), 8.70 (d, J = 5.1 Hz, 1H, CH_{ar}), 8.56 (s, 1H, CH_{ar}), 8.38 (dd, J = 8.7, 3.3 Hz, 1H, CH_{ar}), 8.16 (d, J = 7.8 Hz, 1H, CH_{ar}), 7.96 (t, J = 7.5 Hz, 1H, CH_{ar}), 7.75 (t, J = 7.8 Hz, 1H, CH_{ar}), 7.10 (t, J = 4.8 Hz, 1H, CH_{ar}). MS: MH^+ = 306.

[0193] Example 34: Synthesis of N-(5-chloropyrimidin-2-yl)-4-(pyridin-3-yl)thiazol-2-amine.



[0194] N-(5-chloropyrimidin-2-yl)-4-(pyridin-2-yl)thiazol-2-amine was synthesized from 2-bromo-1-pyridin-2-yl-ethanone and (5-chloro-pyrimidin-2-yl)-thiourea in the same manner as Example 20 to provide the product as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.11 (s, 1H, NH), 8.74 (s, 2H, CH_{ar}), 8.58 (d, J = 5.1 Hz, 1H, CH_{ar}), 7.97 (d, J = 8.1 Hz, 1H, CH_{ar}), 7.87 (m, 1H, CH_{ar}), 7.76 (s, 1H, CH_{ar}), 7.31 (m, 1H, CH_{ar}). MS: MH^+ = 290.

[0195] Example 35: Synthesis of N-(5-bromopyrimidin-2-yl)-4-(pyridin-2-yl)thiazol-2-amine.

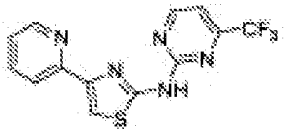


[0196] N-(5-bromopyrimidin-2-yl)-4-(pyridin-2-yl)thiazol-2-amine was synthesized from 2-bromo-1-pyridin-2-yl-ethanone and (5-bromo-pyrimidin-2-yl)-thiourea in the same manner as Example 20 to provide the product as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.10 (s, 1H, NH), 8.79 (s, 2H, CH_{ar}), 8.58-8.57 (m, 1H, CH_{ar}), 7.96 (d, J = 7.8 Hz, 1H, CH_{ar}), 7.86 (dt, J = 8.1, 1.8 Hz, 1H, CH_{ar}), 7.77 (s, 1H, CH_{ar}), 7.33-7.28 (m, 1H, CH_{ar}). MS: MH^+ = 334.

[0197] Example 36: Synthesis of N-(4-methylpyrimidin-2-yl)-4-(pyridin-2-yl)thiazol-2-amine.

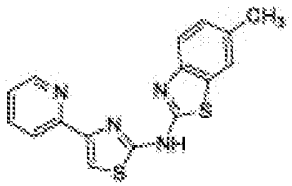
[0198] N-(4-methylpyrimidin-2-yl)-4-(pyridin-2-yl)thiazol-2-amine was synthesized from 2-bromo-1-pyridin-2-yl-ethanone and (4-methyl-pyrimidin-2-yl)-thiourea in the same manner as Example 20 to provide the product as a gray solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.74 (s, 1H, NH), 8.57 (d, J = 4.2 Hz, 1H, CH_{ar}), 8.48 (d, J = 4.8 Hz, 1H, CH_{ar}), 7.96 (d, J = 7.8 Hz, 1H, CH_{ar}), 7.86 (dt, J = 7.5, 1.8 Hz, 1H, CH_{ar}), 7.71 (s, 1H, CH_{ar}), 7.31-7.27 (m, 1H, CH_{ar}), 6.92 (d, J = 4.8 Hz, 1H, CH_{ar}), 2.44 (s, 3H, $ArCH_3$). MS: MH^+ = 270.

[0199] Example 37: Synthesis of 4-(pyridin-2-yl)-N-(4-(trifluoromethyl)pyrimidin-2-yl)thiazol-2-amine.



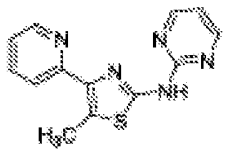
[0200] 4-(pyridin-2-yl)-N-(4-(trifluoromethyl)pyrimidin-2-yl)thiazol-2-amine was synthesized from 2-bromo-1-pyridin-2-yl-ethanone and (4-trifluoromethyl-pyrimidin-2-yl)-thiourea in the same manner as Example 20 to provide the product as a gray solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.42 (s, 1H, NH), 8.98 (d, J = 4.5 Hz, 1H, CH_{ar}), 8.58 (d, J = 3.6 Hz, 1H, CH_{ar}), 7.97 (d, J = 8.1 Hz, 1H, CH_{ar}), 7.89-7.83 (m, 2H, CH_{ar}), 7.48 (d, J = 4.5 Hz, 1H, CH_{ar}), 7.31 (t, J = 5.7 Hz, 1H, CH_{ar}). MS: MH^+ = 324.

[0201] Example 38: Synthesis of 6-methyl-N-(4-(pyridin-2-yl)thiazol-2-yl)benzo[d]thiazol-2-amine.



[0202] 6-methyl-N-(4-(pyridin-2-yl)thiazol-2-yl)benzo[d]thiazol-2-amine was synthesized from 2-bromo-1-pyridin-2-yl-ethanone and (6-methyl-benzothiazol-2-yl)-thiourea in the same manner as Example 20 to provide the product as a light-brown solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.62 (s, 1H, CH_{ar}), 8.13 (d, J = 6.6 Hz, 1H, CH_{ar}), 7.82 (t, J = 7.5 Hz, 1H, CH_{ar}), 7.64-7.59 (m, 1H, CH_{ar}), 7.52-7.48 (m, 2H, CH_{ar}), 7.23-7.18 (m, 2H, CH_{ar}), 2.44 (s, 3H, $ArCH_3$). MS: MH^+ = 325.

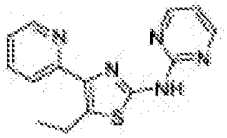
[0203] Example 39: Synthesis of 5-methyl-4-(pyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine.



[0204] 5-methyl-4-(pyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine was synthesized from 2-bromo-1-pyridin-2-yl-propan-1-one and pyrimidin-2-yl-thiourea in the same manner as Example 20 to provide the product as a gray solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.63 (s, 1H, NH), 8.61 (d,

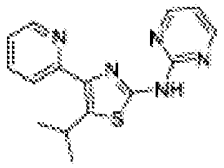
J = 4.5 Hz, 3H, CH_3), 7.97 (d, J = 8.4 Hz, 1H, CH_{ar}), 7.84 (t, J = 7.5 Hz, 1H, CH_{ar}), 7.28-7.24 (m, 1H, CH_{ar}), 7.01 (t, J = 4.8 Hz, 1H, CH_{ar}), 2.72 (s, 3H, $ArCH_3$). MS: MH^+ = 270.

[0205] Example 40: Synthesis of 5-ethyl-4-(pyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine.



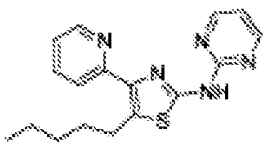
[0206] 5-Ethyl-4-(pyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine was synthesized from 2-bromo-1-pyridin-2-yl-butan-1-one and pyrimidin-2-yl-thiourea in the same manner as Example 20 to provide the product as a gray solid. ^1H NMR (300 MHz, DMSO-d_6): δ 11.61 (s, 1H, NH), 8.62-8.59 (m, 3H, CH_{ar}), 7.97 (d, J = 7.8 Hz, 1H, CH_{ar}), 7.84 (dt, J = 7.8, 1.8 Hz, 1H, CH_{ar}), 7.28-7.24 (m, 1H, CH_{ar}), 7.01 (t, J = 4.8 Hz, 1H, CH_{ar}), 2.49-2.48 (m, 2H, $ArCH_2$, overlapped with the peaks of DMSO), 1.26 (t, J = 7.5 Hz, 3H, CH_3). MS: MH^+ = 284.

[0207] Example 41: Synthesis of 5-isopropyl-4-(pyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine.



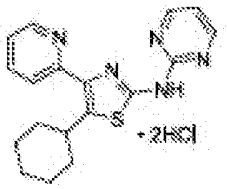
[0208] 5-isopropyl-4-(pyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine was synthesized from 2-bromo-3-methyl-1-pyridin-2-yl-butan-1-one and pyrimidin-2-yl-thiourea in the same manner as Example 20 to provide the product as a light-gray solid. ^1H NMR (300 MHz, $CDCl_3$): δ 9.95 (s, 1H, NH), 8.67-8.66 (m, 3H, CH_{ar}), 7.88 (d, J = 7.8 Hz, 1H, CH_{ar}), 7.73 (t, J = 8.1 Hz, 1H, CH_{ar}), 7.17 (m, 1H, CH_{ar}), 6.89 (t, J = 5.1 Hz, 1H, CH_{ar}), 4.35-4.30 (m, 1H, CH), 1.40 (d, J = 6.6 Hz, 6H, $C(CH_3)_2$). MS: MH^+ = 298.

[0209] Example 42: Synthesis of 5-pentyl-4-(pyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine.



[0210] 5-Pentyl-4-(pyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine was synthesized from 2-bromo-1-pyridin-2-yl-heptan-1-one and pyrimidin-2-yl-thiourea in the same manner as Example 20 to provide the product as a gray solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.07 (s, 1H, NH), 8.66 (m, 3H, CH_{ar}), 7.88 (d, J = 7.5 Hz, 1H, CH_{ar}), 7.73 (t, J = 7.2 Hz, 1H, CH_{ar}), 7.16 (m, 1H, CH_{ar}), 6.89 (m, 1H, CH_{ar}), 3.29 (t, J = 7.5 Hz, 2H, $ArCH_2$), 0.89 (m, 3H, CH_3). MS: MH^+ = 326.

[0211] Example 43: Synthesis of 5-cyclohexyl-4-(pyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine dihydrochloride.



[0212] 5-Cyclohexyl-4-(pyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine dihydrochloride was synthesized from 2-bromo-2-cyclohexyl-1-pyridin-2-yl-ethanone dihydrochloride and pyrimidin-2-yl-thiourea in the same manner as Example 20 to provide the product as a light-yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.74 (d, J = 4.5 Hz, 1H, CH_{ar}), 8.65 (d, J = 4.8 Hz, 1H, CH_{ar}), 8.24 (t, J = 8.1 Hz, 1H, CH_{ar}), 8.04 (d, J = 8.7 Hz, 1H, CH_{ar}), 7.63 (t, J = 6.3 Hz, 1H, CH_{ar}), 7.05 (t, J = 4.8 Hz, 1H, CH_{ar}), 3.58(m, 1H, CH), 2.02-1.29 (m, 10H, 5 x CH_2). MS: MH^+ = 338.

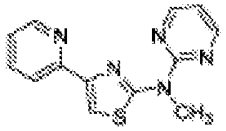
[0213] Example 44: Synthesis of 5-nonyl-4-(pyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine.

[0214] 5-Nonyl-4-(pyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine was synthesized from 2-bromo-1-pyridin-2-yl-undecan-1-one and pyrimidin-2-yl-thiourea in the same manner as Example 20 to provide the product as a silver-gray solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.70 (s, 1H, NH), 8.64 (d, J = 5.1 Hz, 3H, CH_{ar}), 7.88 (d, J = 8.1 Hz, 1H, CH_{ar}), 7.72 (dt, J = 7.8, 1.8 Hz, 1H, CH_{ar}), 7.19-7.14 (m, 1H, CH_{ar}), 6.89 (t, J = 5.1 Hz, 1H, CH_{ar}), 3.29 (t, J = 8.1 Hz, 2H, $ArCH_2$), 1.77-1.69 (m, 2H, CH_2), 1.40-1.25 (m, 12H, 6 x CH_2), 0.87 (t, J = 6.9 Hz, 3H, CH_3). MS: MH^+ = 382.

[0215] Example 45: Synthesis of N-isopropyl-4-(pyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine.

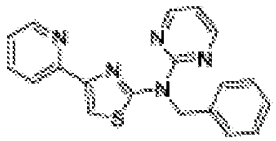
[0216] To a stirred suspension of 4-(pyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine (51 mg, 0.2 mmol) in dimethylformamide (4 mL), was added sodium hydride (60%, 12 mg, 0.3 mmol), 2 minutes later, 2-iodopropane (20 μL, 0.2 mmol) was added. The stirring was continued for 24 hours. The reaction was quenched with sat. ammonium chloride (10 mL) and extracted with ethyl acetate (15 mL x 3). The combined organic layer was dried over anhydrous sodium sulfate, concentrated, and purified through silica gel column chromatography (ethyl acetate:hexanes = 30:70) to afford 54 mg of compound N-isopropyl-4-(pyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine as white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.59 (s, 3H, CH_{ar}), 8.15 (d, J = 7.2 Hz, 1H, CH_{ar}), 7.77 (s, 2H, CH_{ar}), 7.19 (s, 1H, CH_{ar}), 6.85 (s, 1H, CH_{ar}), 5.85 (m, 1H, NCH), 1.69 (d, J = 6.0 Hz, 6H, $C(CH_3)_2$). MS: MH^+ = 298.

[0217] Example 46: Synthesis of N-methyl-4-(pyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine.



[0218] N-methyl-4-(pyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine was synthesized from 4-(pyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine and iodomethane in the same manner as Example 45 to provide the product as a white solid in 50% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.64-8.60 (m, 3H, CH_{ar}), 8.18-8.15 (m, 1H, CH_{ar}), 7.77 (dt, J = 7.8, 1.8 Hz, 1H, CH_{ar}), 7.72 (s, 1H, CH_{ar}), 7.22-7.17 (m, 1H, CH_{ar}), 6.90 (t, J = 4.8 Hz, 1H, CH_{ar}), 4.07 (s, 3H, NCH_3). MS: MH^+ = 270.

[0219] Example 47: Synthesis of N-benzyl-4-(pyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine.



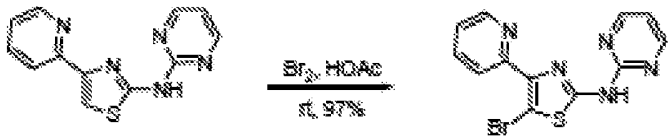
[0220] N-benzyl-4-(pyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine was synthesized from 4-(pyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine and benzyl bromide in the same manner as

Example 45 to provide the product as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.62-8.60 (m, 3H, CH_{ar}), 8.08 (d, J = 7.8 Hz, 1H, CH_{ar}), 7.75-7.70 (m, 2H, CH_{ar}), 7.51 (d, J = 7.2 Hz, 2H, CH_{ar}), 7.29-7.15 (m, 4H, CH_{ar}, overlapped with the peaks of $CHCl_3$), 6.88 (t, J = 4.8 Hz, 1H, CH_{ar}), 5.98 (s, 2H, NCH_2Ar). MS: MH^+ = 346.

[0221] Example 48: Synthesis of 2-((4-(pyridin-2-yl)thiazol-2-yl)(pyrimidin-2-yl)amino)ethanol.

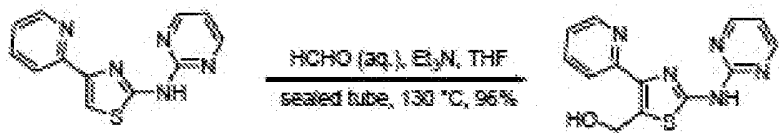
[0222] 2-((4-(pyridin-2-yl)thiazol-2-yl)(pyrimidin-2-yl)amino)ethanol was synthesized from 4-(pyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine and 2-bromoethanol in the same manner as Example 45 to provide the product as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.63-8.60 (m, 3H, CH_{ar}), 8.02 (d, J = 7.8 Hz, 1H, CH_{ar}), 7.79-7.73 (m, 2H, CH_{ar}), 7.23-7.18 (m, 1H, CH_{ar}), 6.93 (t, J = 4.8 Hz, 1H, CH_{ar}), 4.94 (t, J = 5.1 Hz, 2H, NCH_2), 4.71 (t, J = 4.5 Hz, 1H, OH), 4.20-4.15 (m, 2H, OCH_2). MS: MH^+ = 300.

[0223] Example 49: Synthesis of 5-bromo-4-(pyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine.



[0224] To a suspension of 4-(pyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine (102 mg, 0.4 mmol) in acetic acid (2 mL), was added bromine at room temperature. Stirring was continued for 2 hours, and then ethyl acetate (20 mL) was added. The crude product was collected by filtration and re-crystallized in ethyl acetate to afford 130 mg of 5-bromo-4-(pyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine as yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.73-8.67 (m, 3H, CH_{ar}), 8.10 (d, J = 3.3 Hz, 2H, CH_{ar}), 7.57-7.53 (m, 1H, CH_{ar}), 7.11 (t, J = 5.1 Hz, 1H, CH_{ar}). MS: MH^+ = 334.

[0225] Example 50: Synthesis of (4-(pyridin-2-yl)-2-(pyrimidin-2-ylamino)thiazol-5-yl)methanol.

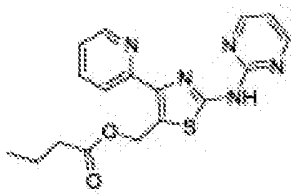


[0226] A suspension of 4-(pyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine (51 mg, 0.2 mmol) in tetrahydrofuran (4 mL) in a sealed tube, was treated with aq. formaldehyde (36.5%, 2 mL), then triethylamine (0.6 mL). It was heated to 130 °C for 12 hours, then cooled down and concentrated. The residue was quenched with water (20 mL), stirred and filtered to give the product, which was washed with water and ethyl acetate in sequence and then dried under vacuum. 55 mg of pure compound (4-(pyridin-2-yl)-2-(pyrimidin-2-ylamino)thiazol-5-yl)methanol was obtained as white solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.63 (s, 1H, NH), 8.63-8.59 (m, 3H, CH_{ar}), 8.00 (d, J = 7.8 Hz, 1H, CH_{ar}), 7.87 (t, J = 7.2 Hz, 1H, CH_{ar}), 7.30-7.26 (m, 1H, CH_{ar}), 7.02 (t, J = 4.8 Hz, 1H, CH_{ar}), 5.81 (t, J = 5.7 Hz, 1H, OH), 5.03 (d, J = 5.7 Hz, 2H, OCH_2Ar). MS: MH^+ = 286.

[0227] Example 51: Synthesis of (4-(pyridin-2-yl)-2-(pyrimidin-2-ylamino)thiazol-5-yl)methyl acetate.

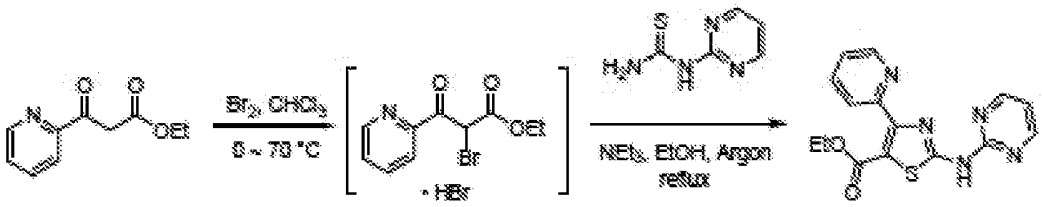
[0228] A suspension of (4-(pyridin-2-yl)-2-(pyrimidin-2-ylamino)thiazol-5-yl)methanol (29 mg, 0.1 mmol) in 1,2-dichloroethane (DCE, 5 mL) was treated with pyridine (81 μL, 1 mmol), followed by the addition of acetic anhydride (38 μL, 0.4 mmol) at room temperature. Then it was heated to reflux for 5 hours. After cooling down, the reaction was quenched with water (50 mL), the pH was adjusted to 10 by using powder sodium carbonate and extracted with dichloromethane (30 mL x 4). The combined organic layer was dried over sodium sulfate, and then concentrated. The resulting residue was suspended in ethyl acetate, filtered and further washed with ethyl acetate. 28 mg of (4-(pyridin-2-yl)-2-(pyrimidin-2-ylamino)thiazol-5-yl)methyl acetate as white solid. MS: MH+ = 281

[0229] Example 52: Synthesis of (4-(pyridin-2-yl)-2-(pyrimidin-2-ylamino)thiazol-5-yl)methyl butyrate.



[0230] (4-(pyridin-2-yl)-2-(pyrimidin-2-ylamino)thiazol-5-yl)methyl butyrate was synthesized from (4-(pyridin-2-yl)-2-(pyrimidin-2-ylamino)thiazol-5-yl)methanol and butyric acid anhydride in the same manner as Example 49 to provide the product as a off-white solid in 57% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.84 (s, 1H, NH), 8.68-8.64 (m, 3H, CH_{ar}), 7.98 (d, J = 7.8 Hz, 1H, CH_{ar}), 7.75 (dt, J = 7.8, 2.1 Hz, 1H, CH_{ar}), 7.20 (dt, J = 6.3, 1.2 Hz, 1H, CH_{ar}), 6.93 (t, J = 4.8 Hz, 1H, CH_{ar}), 5.85 (s, 2H, $ArCH_2O$), 2.38 (t, J = 7.5 Hz, 2H, CH_2CO), 1.74-1.67 (m, 2H, CH_2), 0.97 (t, J = 7.5, 3H, CH_3). MS: MNa^+ = 378.

[0231] Example 53: Synthesis of ethyl 4-(pyridin-2-yl)-2-(pyrimidin-2-ylamino)thiazole-5-carboxylate.

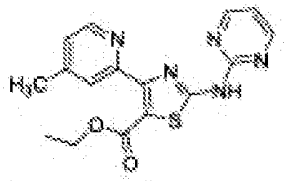


[0232] To a stirred solution of ethyl 3-oxo-3-(pyridin-2-yl)propanoate (1.16 g, 6 mmol) in $CHCl_3$ (20 mL) at 0 °C, was added dropwise bromine (339 μL, 6.6 mmol). The reaction mixture was firstly stirred at 40 °C for 1hr, and then 70 °C for another hour. The solvent was evaporated to give the crude ethyl 2-bromo-3-oxo-3-(pyridin-2-yl)propanoate hydrobromide.

[0233] A reaction mixture of crude ethyl 2-bromo-3-oxo-3-(pyridin-2-yl)propanoate hydrobromide, 1-(pyrimidin-2-yl)thiourea (617 mg, 4 mmol), and triethylamine (1.94 mL, 14 mmol) in ethanol (20 mL) was refluxed for 1 hour under argon atmosphere. After cooling to room temperature, the reaction mixture was quenched with water (200 mL) and stirred for 30 minutes. Then it was filtered and the collected solid was slurried in ethyl acetate/hexanes (1:1, 20 mL). After filtration and drying under vacuum, 910 mg of ethyl 4-(pyridin-2-yl)-2-(pyrimidin-2-ylamino)thiazole-5-carboxylate afforded as brown-reddish solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.34 (s, 1H, NH), 8.73 (d, J = 4.5 Hz, 2H, CH_{ar}), 8.60 (d, J = 3.9 Hz, 1H, CH_{ar}), 7.86 (dt, J = 7.8, 1.8

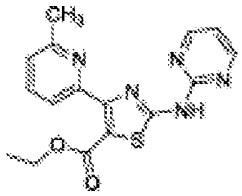
Hz, 1H, CH_{ar}), 7.65 (d, J = 7.5 Hz, 1H, CH_{ar}), 7.43-7.38 (m, 1H, CH_{ar}), 7.14 (t, J = 5.1 Hz, 1H, CH_{ar}), 4.12 (q, J = 7.2 Hz, 2H, OCH_2), 1.12 (t, J = 7.2 Hz, 3H, CH_3). MS: MH^+ = 328.

[0234] Example 54: Synthesis of ethyl 4-(4-methylpyridin-2-yl)-2-(pyrimidin-2-ylamino)thiazole-5-carboxylate.



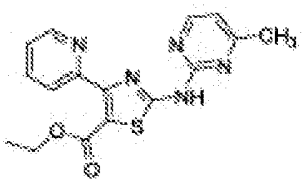
[0235] Ethyl 4-(4-methylpyridin-2-yl)-2-(pyrimidin-2-ylamino)thiazole-5-carboxylate was synthesized from pyrimidin-2-yl-thiourea and 3-(4-methyl-pyridin-2-yl)-3-oxo-propionic acid ethyl ester in the same manner as Example 53 to provide the product as a gray solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.72 (d, J = 5.1 Hz, 2H, CH_{ar}), 8.59 (d, J = 4.8 Hz, 1H, CH_{ar}), 7.62 (s, 1H, CH_{ar}), 7.15 (d, J = 4.2 Hz, 1H, CH_{ar}), 6.98 (t, J = 4.8 Hz, 1H, CH_{ar}), 4.28 (q, J = 7.2 Hz, 2H, OCH_2), 2.43 (s, 3H, $ArCH_3$), 1.29 (t, J = 7.2 Hz, 3H, CH_3). MS: MH^+ = 342.

[0236] Example 55: Synthesis of ethyl 4-(6-methylpyridin-2-yl)-2-(pyrimidin-2-ylamino)thiazole-5-carboxylate.



[0237] Ethyl 4-(6-methylpyridin-2-yl)-2-(pyrimidin-2-ylamino)thiazole-5-carboxylate was synthesized from pyrimidin-2-yl-thiourea and 3-(6-methyl-pyridin-2-yl)-3-oxo-propionic acid ethyl ester in the same manner as Example 53 to provide the product as a brown-reddish solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.95 (s, 1H, NH), 8.71 (d, J = 4.2 Hz, 2H, CH_{ar}), 7.66 (t, J = 7.5 Hz, 1H, CH_{ar}), 7.56 (d, J = 7.8 Hz, 1H, CH_{ar}), 7.20 (d, J = 7.5 Hz, 1H, CH_{ar}), 6.98 (m, 1H, CH_{ar}), 4.26 (q, J = 7.2 Hz, 2H, OCH_2), 2.66 (s, 3H, $ArCH_3$), 1.28 (t, J = 7.2 Hz, 3H, CH_3). MS: MH^+ = 342.

[0238] Example 56: Synthesis of ethyl 2-((4-methylpyrimidin-2-yl)amino)-4-(pyridin-2-yl)thiazole-5-carboxylate

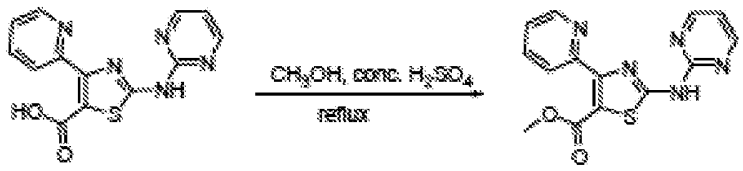


[0239] Ethyl 2-((4-methylpyrimidin-2-yl)amino)-4-(pyridin-2-yl)thiazole-5-carboxylate was synthesized from (4-methyl-pyrimidin-2-yl)-thiourea and 3-oxo-3-pyridin-2-yl-propionic acid ethyl ester in the same manner as Example 53 to provide the product as a brown-reddish solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.43 (s, 1H, NH), 8.74 (d, J = 4.5 Hz, 1H, CH_{ar}), 8.51 (d, J = 5.4 Hz, 1H, CH_{ar}), 7.82-7.73 (m, 2H, CH_{ar}), 7.32 (t, J = 5.7 Hz, 1H, CH_{ar}), 6.84 (d, J = 5.4 Hz, 1H, CH_{ar}), 4.27 (q, J = 7.2 Hz, 2H, OCH_2), 2.56 (s, 3H, $ArCH_3$), 1.28 (t, J = 7.5 Hz, 3H, CH_3). MS: MH^+ = 342.

[0240] Example 57: Synthesis of 4-(pyridin-2-yl)-2-(pyrimidin-2-ylamino)thiazole-5-carboxylic acid

[0241] To a solution of ethyl 4-(pyridin-2-yl)-2-(pyrimidin-2-ylamino)thiazole-5-carboxylate (435 mg, 1.33 mmol) in tetrahydrofuran /CH_3OH/H_2O (5:5:1, 16.5 mL) was added lithium hydroxide monohydrate (391 mg, 9.31 mmol). The reaction mixture was refluxed for 6 hours. After cooling down, the solvent was evaporated and water (20 mL) was added to dissolve the residue. The pH was adjusted to 6 with aq. 6 M HCl and the mixture was stood at 4 °C for 16 hours. The precipitate was filtered, washed with water and dried under vacuum to give 385 mg of 4-(pyridin-2-yl)-2-(pyrimidin-2-ylamino)thiazole-5-carboxylic acid as light-brown solid. MS: MNa^+ = 322.

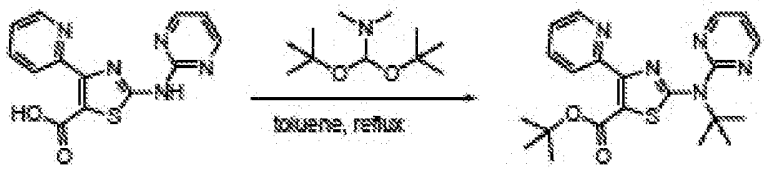
[0242] Example 58: Synthesis of methyl 4-(pyridin-2-yl)-2-(pyrimidin-2-ylamino)thiazole-5-carboxylate



[0243] A suspension of 4-(pyridin-2-yl)-2-(pyrimidin-2-ylamino)thiazole-5-carboxylic acid (60 mg, 0.2 mmol) in methanol (10 mL) was treated with conc. sulfuric acid (~98%, 2 drops). The

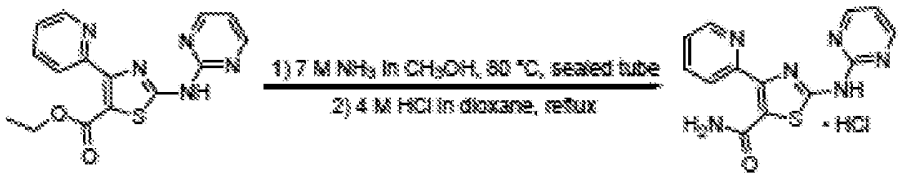
reaction mixture was refluxed for 4 days. After cooling down, the solvent was evaporated and water (20 mL) was added. The pH was adjusted to 8 by sat. sodium bicarbonate and the mixture was extracted with dichloromethane (20 mL x 4). The combined organic layer was dried over anhydrous sodium sulfate and then evaporated to afford 26 mg of methyl 4-(pyridin-2-yl)-2-(pyrimidin-2-ylamino)thiazole-5-carboxylate as white solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.37 (s, 1H, NH), 8.72 (d, J = 4.2 Hz, 2H, CH_{ar}), 8.60 (d, J = 3.3 Hz, 1H, CH_{ar}), 7.86 (t, J = 7.5 Hz, 1H, CH_{ar}), 7.66 (d, J = 7.5 Hz, 1H, CH_{ar}), 7.41 (t, J = 5.7 Hz, 1H, CH_{ar}), 7.14 (t, J = 4.8 Hz, 1H, CH_{ar}), 3.67 (s, 3H, OCH_3). MS: MH^+ = 314.

[0244] Example 59: Synthesis of tert-butyl 2-(tert-butyl(pyrimidin-2-yl)amino)-4-(pyridin-2-yl)thiazole-5-carboxylate.



[0245] A mixture of 4-(pyridin-2-yl)-2-(pyrimidin-2-ylamino)thiazole-5-carboxylic acid (30 mg, 0.1 mmol) and 1,1-di-tert-butoxy-N,N-dimethylmethanamine (120 μL, 0.5 mmol) in toluene (2 mL) was heated to reflux for 24 hours. After cooling down, it was quenched with water (20 mL) and extracted with dichloromethane (10 mL x 3). The combined organic layer was dried over sodium sulfate, concentrated, and then purified by preparative TLC (ethyl acetate : hexanes = 30 : 70) to afforded 12 mg of tert-butyl 2-(tert-butyl(pyrimidin-2-yl)amino)-4-(pyridin-2-yl)thiazole-5-carboxylate as white solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.61 (d, J = 4.8 Hz, 3H, CH_{ar}), 7.87 (dt, J = 7.8, 1.5 Hz, 1H, CH_{ar}), 7.67 (d, J = 7.8 Hz, 1H, CH_{ar}), 7.43-7.38 (m, 1H, CH_{ar}), 7.09 (t, J = 4.8 Hz, 1H, CH_{ar}), 1.55 (s, 9H, $C(CH_3)_3$), 1.31 (s, 9H, $C(CH_3)_3$). MS: MH^+ = 412.

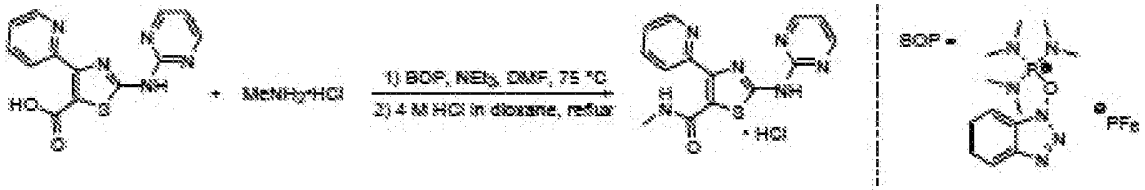
[0246] Example 60: Synthesis of 4-(pyridin-2-yl)-2-(pyrimidin-2-ylamino)thiazole-5-carboxamide.



[0247] In a sealed tube, a suspension of ethyl 4-(pyridin-2-yl)-2-(pyrimidin-2-ylamino)thiazole-5-carboxylate (16 mg, 0.05 mg) in 7M NH_3 solution in methanol (5 mL) was heated

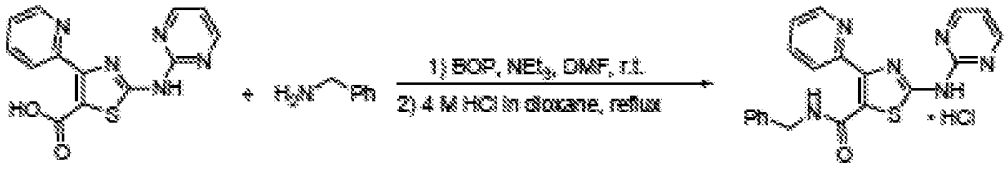
to 80 °C for 7 days. The solvent was evaporated and the residue was washed with ethyl acetate to to give the pure amide. It was suspended in methanol, treated with 4 M HCl in dioxane (0.4 mL) and heated to reflux. The solvent was removed by evaporation and the crude product was washed with ethyl acetate to give 17 mg of 4-(pyridin-2-yl)-2-(pyrimidin-2-ylamino)thiazole-5-carboxamide as light-yellow solid. ^{1}H NMR (300 MHz, CD_3OD): δ 8.93-8.89 (m, 2H, CH_{ar}), 8.71-8.63 (m, 3H, CH_{ar}), 8.04 (t, J = 6.6 Hz, 1H, CH_{ar}), 7.14 (t, J = 5.1 Hz, 1H, CH_{ar}). MS: MH^+ = 299.

[0248] Example 61: Synthesis of N-methyl-4-(pyridin-2-yl)-2-(pyrimidin-2-ylamino)thiazole-5-carboxamide.



[0249] A reaction mixture of 4-(pyridin-2-yl)-2-(pyrimidin-2-ylamino)thiazole-5-carboxylic acid (60 mg, 0.2 mmol), methylamine hydrochloride (27 mg, 0.4 mmol), benzotriazole-1-yl-oxy-tris-(dimethylamino)-phosphonium hexafluorophosphate (BOP, 221 mg, 0.5 mmol), triethylamine (83 μL, 0.6 mmol) in dimethylformamide (2 mL) in a sealed tube was heated to 75 °C for 24 hours. Then it was quenched with water (20 mL), filtered and washed with water. The solid was suspended in methanol (2 mL) and treated with 4 M HCl in dioxane (0.6 mL). It was heated to reflux, and then evaporated to remove solvent. The resulting solid was washed with ethyl acetate and dried under vacuum to give 64 mg of the N-methyl-4-(pyridin-2-yl)-2-(pyrimidin-2-ylamino)thiazole-5-carboxamide hydrochloride as light-yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.85 (m, 1H, CH_{ar}), 8.72 (d, J = 4.8 Hz, 2H, CH_{ar}), 8.93-8.29 (m, 2H, CH_{ar}), 7.72 (m, 1H, CH_{ar}), 7.13 (m, 1H, CH_{ar}), 2.85 (s, 3H, NCH_3). MS: MH^+ = 313.

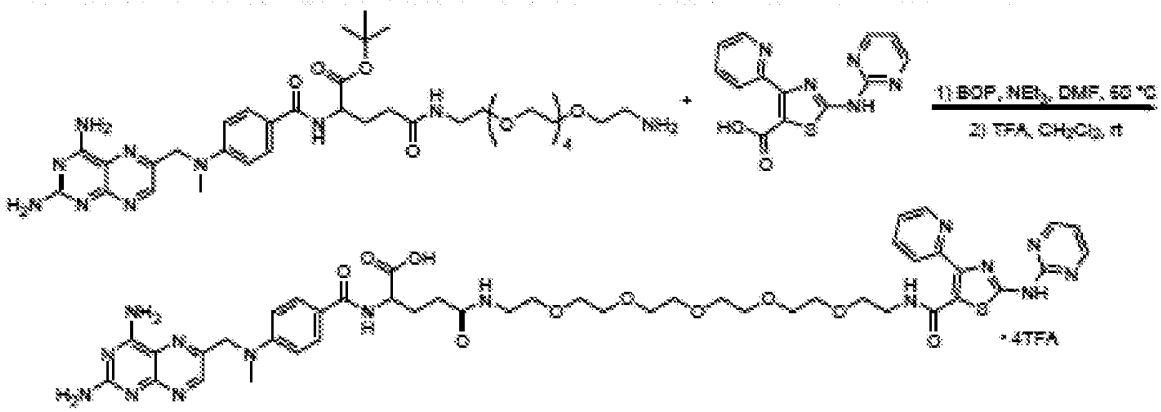
[0250] Example 62: Synthesis of N-benzyl-4-(pyridin-2-yl)-2-(pyrimidin-2-ylamino)thiazole-5-carboxamide.



[0251] A reaction mixture of 4-(pyridin-2-yl)-2-(pyrimidin-2-ylamino)thiazole-5-carboxylic acid (60 mg, 0.2 mmol), benzylamine (43 mg, 0.4 mmol), benzotriazole-1-yl-oxy-tris-

(dimethylamino)-phosphonium hexafluorophosphate (BOP, 195 mg, 0.44 mmol), triethylamine (83 μL, 0.6 mmol) in dimethylformamide (10 mL) was stirred for 4 days. Then it was quenched with water (50 mL), filtered and washed with water. The solid was suspended in methanol/dichloromethane (4:6) and then filtered. The filtrate was concentrated to give 24 mg of the amide as off-white solid in 31% yield. 8 mg of the above amide was suspended in methanol (1 mL) and treated with 4 M HCl in dioxane (0.3 mL). It was heated to reflux, and then evaporated to remove solvent. The resulting solid was washed with ethyl acetate and dried under vacuum to give 9 mg N-benzyl-4-(pyridin-2-yl)-2-(pyrimidin-2-ylamino)thiazole-5-carboxamide hydrochloride as an off-white solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.29 (br, 1H, NH), 12.09 (br, 1H, NH), 8.71 (d, J = 4.5 Hz, 2H, CH_{ar}), 8.40 (s, 1H, CH_{ar}), 8.32 (d, J = 8.4 Hz, 1H, CH_{ar}), 8.09 (t, J = 7.5 Hz, 1H, CH_{ar}), 7.51 (m, 1H, CH_{ar}), 7.37-7.28 (m, 5H, CH_{ar}), 7.11 (m, 1H, CH_{ar}), 4.52 (d, J = 4.5 Hz, 2H, $ArCH_2N$). MS: MH^+ = 389.

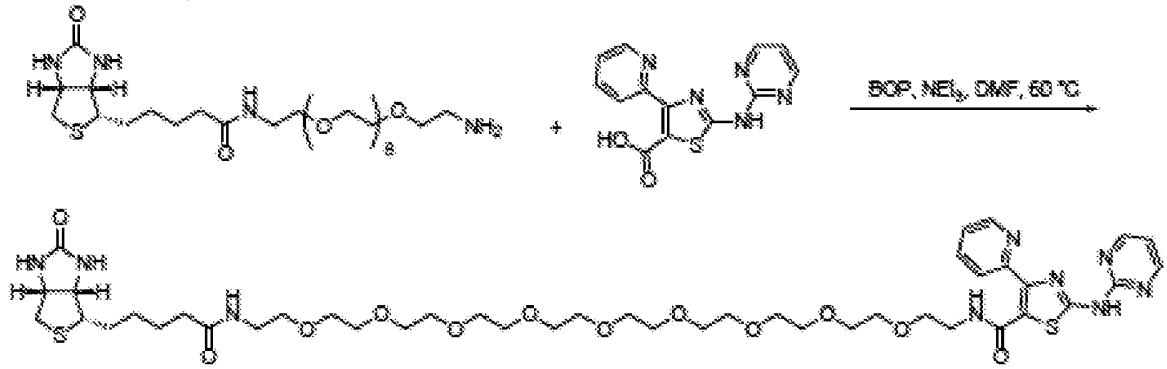
[0252] Example 63: Synthesis of the MTX derivative, 24-(4-(((2,4-diaminopteridin-6-yl)methyl)(methyl)amino)benzamido)-1,21-dioxo-1-(4-(pyridin-2-yl)-2-(pyrimidin-2-ylamino) thiazol-5-yl)-5,8,11,14,17-penta oxa-2,20-diazapentacosan-25-oic acid tri-trifluoroacetate



[0253] In a sealed tube, a reaction mixture of 4-(pyridin-2-yl)-2-(pyrimidin-2-ylamino)thiazole-5-carboxylic acid (66 mg, 0.22 mmol), tert-butyl 1-amino-22-(4-(((2,4-diaminopteridin-6-yl)methyl) (methyl)amino)benzamido)-19-oxo-3,6,9,12,15-pentaoxa-18-azatricosan-23-oate (MTX(CO_2Bu^t)-(PEG)$_5$-NH_2, 170 mg, 0.22 mmol), benzotriazole-1-yl-oxy-tris-(dimethylamino)-phosphonium hexafluorophosphate (BOP, 146 mg, 0.33 mmol), triethylamine (55 μL, 0.4 mmol) in dimethylformamide (2 mL) was heated to 60 °C for 48 hours. After cooling to room

temperature, it was quenched with water (30 mL), filtered and washed with water. The solid was dried, and then suspended in a mixture of dichloromethane and methanol (6:4, 30 mL). It was filtered and the filtrate was concentrated to give the pure *tert*-butyl ester, which was treated with dichloromethane (10 mL), followed by addition of trifluoroacetic acid (2 mL). The mixture was stirred at room temperature for 24 hours and evaporated to give 268 mg of 24-(4-(((2,4-diaminopteridin-6-yl)methyl)(methyl)amino)benzamido)-1,21-dioxo-1-(4-(pyridin-2-yl)-2-(pyrimidin-2-ylamino)thiazol-5-yl)-5,8,11,14,17-penta oxa-2,20-diazapentacosan-25-oic acid tri-trifluoroacetate as brown-reddish solid. ^{1}H NMR (300 MHz, CD_3OD): δ 8.78 (d, *J* = 4.5 Hz, 1H, CH_{ar}), 8.62-8.57 (m, 4H, CH_{ar}), 8.37 (t, *J* = 7.8 Hz, 1H, CH_{ar}), 7.79 (t, *J* = 6.3 Hz, 1H, CH_{ar}), 7.71 (d, *J* = 9.0 Hz, 2H, CH_{ar}), 7.06 (t, *J* = 4.8 Hz, 1H, CH_{ar}), 6.78 (d, *J* = 8.7 Hz, 2H, CH_{ar}), 4.85 (s, 2H, $ArCH_2N$), 4.55-4.50 (m, 1H, CH), 3.70-3.42 (m, 24H), 3.21 (s, 3H, NCH_3), 2.38-2.07 (m, 4H). MS: MNa^+ = 1020.

[0254] Example 64: Synthesis of the Biotin derivative, N-(31-oxo-35-((3aS,4S,6aR)-2-oxohexahydro-1H-thieno[3,4-d]imidazol-4-yl)-3,6,9,12,15,18,21,24,27-nonaoxa-30-azapentatriacontyl)-4-(pyridin-2-yl)-2-(pyrimidin-2-ylamino)thiazole-5-carboxamide



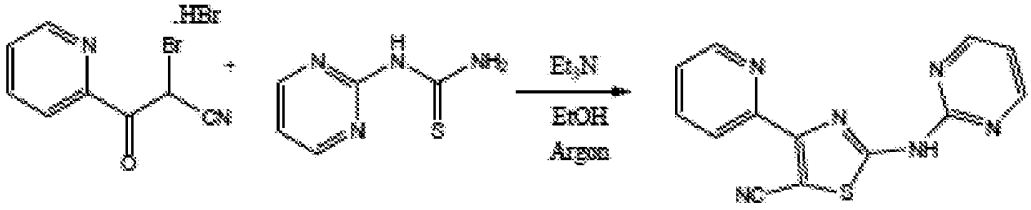
[0255] In a sealed tube, a reaction mixture of 4-(pyridin-2-yl)-2-(pyrimidin-2-ylamino)thiazole-5-carboxylic acid (30 mg, 0.1 mmol), N-(29-amino-3,6,9,12,15,18,21,24,27-nonaoxanonacosyl)-5-((3aS,4S,6aR)-2-oxohexa hydro-1H-thieno[3,4-d]imidazol-4-yl)pentanamide (Biotin-$(PEG)_{10}$-NH_2, 68 mg, 0.1 mmol), benzotriazole-1-yl-oxy-tris-(dimethylamino)-phosphonium hexafluorophosphate (BOP, 66 mg, 0.15 mmol), triethylamine (28 μL, 0.2 mmol) in dimethylformamide (2 mL) was heated to 60 °C for 48 hours. After cooling to room temperature, it was quenched with water (20 mL) and extracted with dichloromethane (20 mL x 4). The combined organic layer was dried over sodium sulfate, concentrated, and then purified by preparative TLC (2 M

NH_3 in methanol : dichloromethane = 5 : 95) to afford 49 mg of N-(31-oxo-35-((3aS,4S,6aR)-2-oxohexahydro-1H-thieno[3,4-d]imidazol-4-yl)-3,6,9,12,15,18,21,24,27-nonaoxa-30-azapentatriacontyl)-4-(pyridin-2-yl)-2-(pyri midin-2-ylamino)thiazole-5-carboxamide as white solid. ^{1}H NMR (300 MHz, CD_3OD): δ 8.70 (m, 1H, CH_{ar}), 8.61 (d, J = 4.8 Hz, 2H, CH_{ar}), 8.43 (d, J = 8.1 Hz, 1H, CH_{ar}), 7.96 (t, J = 7.8 Hz, 1H, CH_{ar}), 7.88 (s, 1H, NH), 7.44 (t, J = 5.7 Hz, 1H, CH_{ar}), 7.00 (t, J = 4.8 Hz, 1H, CH_{ar}), 4.48-4.44 (m, 1H, CH), 4.29-4.25 (m, 1H, CH), 3.74-3.49 (m, 40H), 3.18-3.12 (m, 1H, CH), 2.88 (dd, J = 12.9, 5.4 Hz, 1H,CH), 2.68 (d, J = 12.9 Hz, 1H, CH), 2.20-2.14 (m, 2H), 1.71-1.53 (m, 4H), 1.44-1.37 (m, 2H). MS: MNa^+ = 986.

[0256] Example 65: Synthesis of 2-Bromo-3-oxo-3-pyridin-2-yl-propionitrile hydrobromide

[0257] Bromine (4 ml, 0.8 mmol, 1 eq) was added dropwise to a solution of 3-oxo-3-pyridin-2-yl-propionitrile (117 mg, 0.8 mmol, 1 eq) in$CHCl_3$ (5 ml) at 0-5 °C. Then the reaction mixture was heated to 40 °C for 1hour and 70 °C for another hour. The reaction mixture was evaporated to remove the solvents and the crude product was used directly for next step.

[0258] Example 66: Synthesis of 4-Pyridin-2-yl-2-(pyrimidin-2-ylamino)-thiazole-5-carbonitrile:



[0259] 2-Bromo-3-oxo-3-pyridin-2-yl-propionitrile hydrobromide (46 mg, 0.3 mmol), 1-(pyrimidin-2-yl)thiourea (0.6 mmol) and triethylamine (0.83 ml, 6 mmol, 15 eq) were mixed together in ethanol (5 ml) under argon and refluxed for 1 hour. After cooling to room temperature, the reaction was quenched with water (10 ml) and then extracted with a 3 to 1 mixture of methanol and methylene chloride (1:3) (5 ml x3). The combined organic phase was evaporated. The title compound was obtained by column chromatography. MS: MH+ = 281.

FORMULATIONS

[0260] The present invention also relates to compositions or formulations which comprise the substituted aminothiazoles according to the present invention. In general, the compositions of the present invention comprise an effective amount of one or more substituted aminothiazoles and salts thereof according to the present invention which are effective for providing treatment or preventing diseases that involve unregulated cell growth; and one or more excipients. The compositions of the present invention also comprise an effective amount of one or more substituted aminothiazoles and salts thereof according to the present invention which are effective for treating or preventing diseases that involve infection with a hepatitis virus; and one or more excipients.

[0261] For the purposes of the present invention the term "excipient" and "carrier" are used interchangeably throughout the description of the present invention and said terms are defined herein as, "ingredients which are used in the practice of formulating a safe and effective pharmaceutical composition."

[0262] The formulator will understand that excipients are used primarily to serve in delivering a safe, stable, and functional pharmaceutical, serving not only as part of the overall vehicle for delivery but also as a means for achieving effective absorption by the recipient of the active ingredient. An excipient may fill a role as simple and direct as being an inert filler, or an excipient as used herein may be part of a pH stabilizing system or coating to insure delivery of the ingredients safely to the stomach. The formulator can also take advantage of the fact the compounds of the present invention have improved cellular potency, pharmacokinetic properties, as well as improved oral bioavailability.

[0263] The present teachings also provide pharmaceutical compositions that include at least one compound described herein and one or more pharmaceutically acceptable carriers, excipients, or diluents. Examples of such carriers are well known to those skilled in the art and can be prepared in accordance with acceptable pharmaceutical procedures, such as, for example, those described in *Remington's Pharmaceutical Sciences*, 17th edition, ed. Alfonoso R. Gennaro, Mack Publishing Company, Easton, PA (1985), the entire disclosure of which is incorporated by reference herein for all purposes. As used herein, "pharmaceutically acceptable" refers to a substance that is acceptable for use in pharmaceutical applications from a toxicological perspective and does not adversely interact

with the active ingredient. Accordingly, pharmaceutically acceptable carriers are those that are compatible with the other ingredients in the formulation and are biologically acceptable. Supplementary active ingredients can also be incorporated into the pharmaceutical compositions.

[0264] Compounds of the present teachings can be administered orally or parenterally, neat or in combination with conventional pharmaceutical carriers. Applicable solid carriers can include one or more substances which can also act as flavoring agents, lubricants, solubilizers, suspending agents, fillers, glidants, compression aids, binders or tablet-disintegrating agents, or encapsulating materials. The compounds can be formulated in conventional manner, for example, in a manner similar to that used for known anti-cancer agents. The compounds can also be formulated in conventional manner, for example, in a manner similar to that used for known anti-viral agents. Oral formulations containing a compound disclosed herein can comprise any conventionally used oral form, including tablets, capsules, buccal forms, troches, lozenges and oral liquids, suspensions or solutions. In powders, the carrier can be a finely divided solid, which is an admixture with a finely divided compound. In tablets, a compound disclosed herein can be mixed with a carrier having the necessary compression properties in suitable proportions and compacted in the shape and size desired. The powders and tablets can contain up to 99 % of the compound.

[0265] Capsules can contain mixtures of one or more compound(s) disclosed herein with inert filler(s) and/or diluent(s) such as pharmaceutically acceptable starches (e.g., corn, potato or tapioca starch), sugars, artificial sweetening agents, powdered celluloses (e.g., crystalline and microcrystalline celluloses), flours, gelatins, gums, and the like.

[0266] Useful tablet formulations can be made by conventional compression, wet granulation or dry granulation methods and utilize pharmaceutically acceptable diluents, binding agents, lubricants, disintegrants, surface modifying agents (including surfactants), suspending or stabilizing agents, including, but not limited to, magnesium stearate, stearic acid, sodium lauryl sulfate, talc, sugars, lactose, dextrin, starch, gelatin, cellulose, methyl cellulose, microcrystalline cellulose, sodium carboxymethyl cellulose,

carboxymethylcellulose calcium, polyvinylpyrrolidine, alginic acid, acacia gum, xanthan gum, sodium citrate, complex silicates, calcium carbonate, glycine, sucrose, sorbitol, dicalcium phosphate, calcium sulfate, lactose, kaolin, mannitol, sodium chloride, low melting waxes, and ion exchange resins. Surface modifying agents include nonionic and anionic surface modifying agents. Representative examples of surface modifying agents include, but are not limited to, poloxamer 188, benzalkonium chloride, calcium stearate, cetostearl alcohol, cetomacrogol emulsifying wax, sorbitan esters, colloidal silicon dioxide, phosphates, sodium dodecylsulfate, magnesium aluminum silicate, and triethanolamine. Oral formulations herein can utilize standard delay or time-release formulations to alter the absorption of the compound(s). The oral formulation can also consist of administering a compound disclosed herein in water or fruit juice, containing appropriate solubilizers or emulsifiers as needed.

[0267] Liquid carriers can be used in preparing solutions, suspensions, emulsions, syrups, elixirs, and for inhaled delivery. A compound of the present teachings can be dissolved or suspended in a pharmaceutically acceptable liquid carrier such as water, an organic solvent, or a mixture of both, or a pharmaceutically acceptable oils or fats. The liquid carrier can contain other suitable pharmaceutical additives such as solubilizers, emulsifiers, buffers, preservatives, sweeteners, flavoring agents, suspending agents, thickening agents, colors, viscosity regulators, stabilizers, and osmo-regulators. Examples of liquid carriers for oral and parenteral administration include, but are not limited to, water (particularly containing additives as described herein, e.g., cellulose derivatives such as a sodium carboxymethyl cellulose solution), alcohols (including monohydric alcohols and polyhydric alcohols, e.g., glycols) and their derivatives, and oils (e.g., fractionated coconut oil and arachis oil). For parenteral administration, the carrier can be an oily ester such as ethyl oleate and isopropyl myristate. Sterile liquid carriers are used in sterile liquid form compositions for parenteral administration. The liquid carrier for pressurized compositions can be halogenated hydrocarbon or other pharmaceutically acceptable propellants.

[0268] Liquid pharmaceutical compositions, which are sterile solutions or suspensions, can be utilized by, for example, intramuscular, intraperitoneal or subcutaneous injection. Sterile solutions can also be administered intravenously. Compositions for oral administration can be in either liquid or solid form.

[0269] Preferably the pharmaceutical composition is in unit dosage form, for example, as tablets, capsules, powders, solutions, suspensions, emulsions, granules, or suppositories. In such form, the pharmaceutical composition can be sub-divided in unit dose(s) containing appropriate quantities of the compound. The unit dosage forms can be packaged compositions, for example, packeted powders, vials, ampoules, prefilled syringes or sachets containing liquids. Alternatively, the unit dosage form can be a capsule or tablet itself, or it can be the appropriate number of any such compositions in package form. Such unit dosage form can contain from about 1 mg/kg of compound to about 500 mg/kg of compound, and can be given in a single dose or in two or more doses. Such doses can be administered in any manner useful in directing the compound(s) to the recipient's bloodstream, including orally, via implants, parenterally (including intravenous, intraperitoneal and subcutaneous injections), rectally, vaginally, and transdermally.

[0270] When administered for the treatment or inhibition of a particular disease state or disorder, it is understood that an effective dosage can vary depending upon the particular compound utilized, the mode of administration, and severity of the condition being treated, as well as the various physical factors related to the individual being treated. In therapeutic applications, a compound of the present teachings can be provided to a patient already suffering from a disease in an amount sufficient to cure or at least partially ameliorate the symptoms of the disease and its complications. The dosage to be used in the treatment of a specific individual typically must be subjectively determined by the attending physician. The variables involved include the specific condition and its state as well as the size, age and response pattern of the patient.

[0271] In some cases it may be desirable to administer a compound directly to the airways of the patient, using devices such as, but not limited to, metered dose inhalers,

breath-operated inhalers, multidose dry-powder inhalers, pumps, squeeze-actuated nebulized spray dispensers, aerosol dispensers, and aerosol nebulizers. For administration by intranasal or intrabronchial inhalation, the compounds of the present teachings can be formulated into a liquid composition, a solid composition, or an aerosol composition. The liquid composition can include, by way of illustration, one or more compounds of the present teachings dissolved, partially dissolved, or suspended in one or more pharmaceutically acceptable solvents and can be administered by, for example, a pump or a squeeze-actuated nebulized spray dispenser. The solvents can be, for example, isotonic saline or bacteriostatic water. The solid composition can be, by way of illustration, a powder preparation including one or more compounds of the present teachings intermixed with lactose or other inert powders that are acceptable for intrabronchial use, and can be administered by, for example, an aerosol dispenser or a device that breaks or punctures a capsule encasing the solid composition and delivers the solid composition for inhalation. The aerosol composition can include, by way of illustration, one or more compounds of the present teachings, propellants, surfactants, and co-solvents, and can be administered by, for example, a metered device. The propellants can be a chlorofluorocarbon (CFC), a hydrofluoroalkane (HFA), or other propellants that are physiologically and environmentally acceptable.

[0272] Compounds described herein can be administered parenterally or intraperitoneally. Solutions or suspensions of these compounds or a pharmaceutically acceptable salts, hydrates, or esters thereof can be prepared in water suitably mixed with a surfactant such as hydroxyl-propylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof in oils. Under ordinary conditions of storage and use, these preparations typically contain a preservative to inhibit the growth of microorganisms.

[0273] The pharmaceutical forms suitable for injection can include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In some embodiments, the form can sterile and its viscosity permits it to flow through a syringe. The form preferably is stable under the

conditions of manufacture and storage and can be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g., glycerol, propylene glycol and liquid polyethylene glycol), suitable mixtures thereof, and vegetable oils.

[0274] Compounds described herein can be administered transdermally, i.e., administered across the surface of the body and the inner linings of bodily passages including epithelial and mucosal tissues. Such administration can be carried out using the compounds of the present teachings including pharmaceutically acceptable salts, hydrates, or esters thereof, in lotions, creams, foams, patches, suspensions, solutions, and suppositories (rectal and vaginal).

[0275] Transdermal administration can be accomplished through the use of a transdermal patch containing a compound, such as a compound disclosed herein, and a carrier that can be inert to the compound, can be non-toxic to the skin, and can allow delivery of the compound for systemic absorption into the blood stream via the skin. The carrier can take any number of forms such as creams and ointments, pastes, gels, and occlusive devices. The creams and ointments can be viscous liquid or semisolid emulsions of either the oil-in-water or water-in-oil type. Pastes comprised of absorptive powders dispersed in petroleum or hydrophilic petroleum containing the compound can also be suitable. A variety of occlusive devices can be used to release the compound into the blood stream, such as a semi-permeable membrane covering a reservoir containing the compound with or without a carrier, or a matrix containing the compound. Other occlusive devices are known in the literature.

[0276] Compounds described herein can be administered rectally or vaginally in the form of a conventional suppository. Suppository formulations can be made from traditional materials, including cocoa butter, with or without the addition of waxes to alter the suppository's melting point, and glycerin. Water-soluble suppository bases, such as polyethylene glycols of various molecular weights, can also be used.

[0277] Lipid formulations or nanocapsules can be used to introduce compounds of the present teachings into host cells either *in vitro* or *in vivo*. Lipid formulations and nanocapsules can be prepared by methods known in the art.

[0278] To increase the effectiveness of compounds of the present teachings, it can be desirable to combine a compound with other agents effective in the treatment of the target disease. For example, other active compounds (i.e., other active ingredients or agents) effective in treating the target disease can be administered with compounds of the present teachings. The other agents can be administered at the same time or at different times than the compounds disclosed herein.

[0279] Compounds of the present teachings can be useful for the treatment or inhibition of a pathological condition or disorder in a mammal, for example, a human subject. The present teachings accordingly provide methods of treating or inhibiting a pathological condition or disorder by providing to a mammal a compound of the present teachings including its pharmaceutically acceptable salt) or a pharmaceutical composition that includes one or more compounds of the present teachings in combination or association with pharmaceutically acceptable carriers. Compounds of the present teachings can be administered alone or in combination with other therapeutically effective compounds or therapies for the treatment or inhibition of the pathological condition or disorder.

[0280] Non-limiting examples of compositions according to the present invention include from about 0.001 mg to about 1000 mg of one or more according to the present invention and one or more excipients; from about 0.01 mg to about 100 mg of one or more substituted aminothiazoles according to the present invention and one or more excipients; and from about 0.1 mg to about 10 mg of one or more substituted aminothiazoles according to the present invention; and one or more excipients.

PROCEDURES

[0281] The following procedures can be utilized in evaluating and selecting compounds as effective for providing treatment or preventing diseases that involve unregulated cell growth. The following procedures can also be utilized in evaluating and

selecting compounds as effective for treating or preventing diseases that involve infection with a hepatitis virus.

Cell cultures and conditions

[0282] Huh-7 cells and derived from hepatocellular carcinoma cells, and were donated by Dr. Xuanyong Lu, (Drexel University College of Medicine, Doylestown, PA). THLE-2 were purchased from American Type Culture Collection (Manassas, VA). PH5CH were donated by Dr. Masayuki Noguchi (University of Tsukuba, Ibaraki, Japan). THLE-2 and PH5CH have been immortalized through stable transfection of the SV40 large T antigen in normal hepatocytes, and are thus cell lines that are representative of normal hepatocytes rather than HCC cells. THLE2 have been confirmed to not form tumors in athymic mice. All cell lines were cultured and maintained in 5% CO_2 at 37°C. Huh-7 were maintained in the culture media DMEM/F12 (Dulbecco's Modified Eagle Medium) with 10% Fetal bovine serum (FBS), 100 μg/mL penicillin, 100units/mL streptomycin, and 50μg/mL normocin. THLE-2 and PH5CH were maintained in in the culture media Brochial Epithelial Growth Media (BEGM) with 10% FBS, 100 μg/mL penicillin, 100 units/mL streptomycin, with the following additives form the prepackaged kit: Bovine pituitary extract (BPE), insulin, hydrocortisone, retinoic acid, transferrin, triiodothyronine, supplemented with 5 ng/ml human epidermal growth factor and 70 ng/ml phosphoethanolamine (Lonza Walkersville Inc., Walkersville, MD).

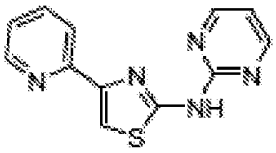
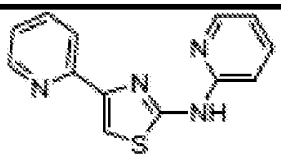
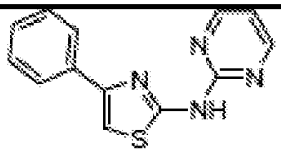
Testing of substituted aminothiazole analogues.

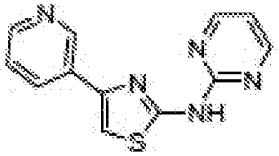
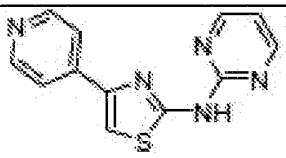
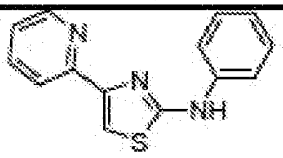
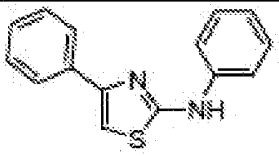
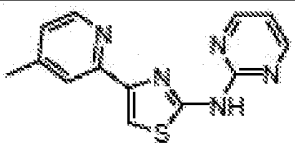
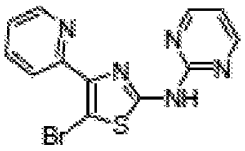
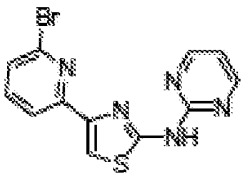
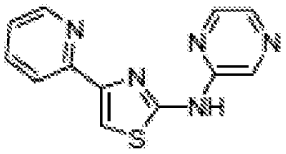
[0283] Huh7 cells were plated on 96-well plates at $2.0x10^4$ cells per well to permit grow in the presence of compounds of the disclosure. Compounds of the disclosure were prediluted and transferred to cell plates by automated liquid handling. Cells were incubated with compounds of the disclosure for 72 hours, after which culture growth and viability were assessed by addition of 50 μg/mL 3-(4,5-Dimethyl-2-thiazolyl)-2,5-diphenyl-2H-tetrazolium bromide (MTT) incubation for 4 hours at 37 °C. Solubilization buffer (0.01M HCl, 10% SDS) was added followed by incubation at 37 °C overnight. Absorbance was measured at

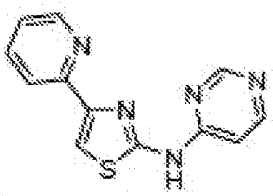
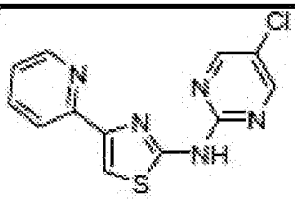
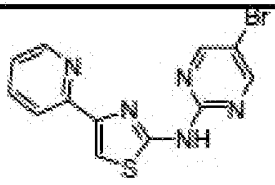
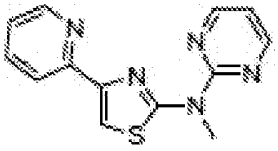
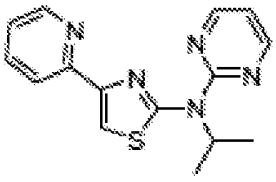
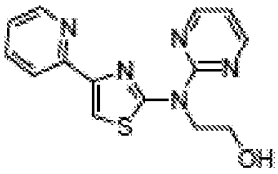
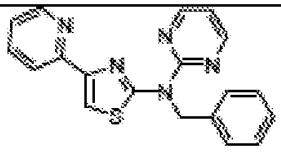
570 nm (reference 630 nm). Compound of the disclosure were tested in in Huh7, THLE-2 and PH5CH, over eight-point dilutions in half-log steps, testing 50.0, 16.6, 5.0, 1.66, 0.5, 0.166, 0.05, and 0.016 μM in 0.5% DMSO, with each concentration in duplicate wells. The mean value of the reduction of viability signal in the MTT assay over the duplicate wells was used to determine the concentration that is cytotoxic to 50% of the cells (CC_{50}), as compared to DMSO-only control wells (n=8), using curve-fitting analysis with XLfit (IDBS, Surrey, UK). Each compound was tested from 2 to 7 times in separate assay trials.

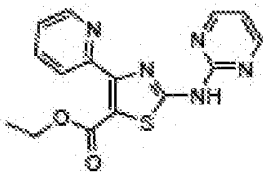
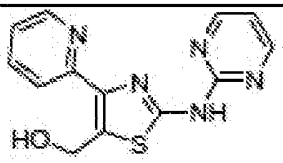
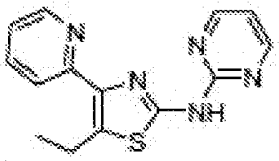
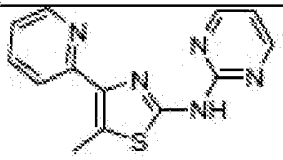
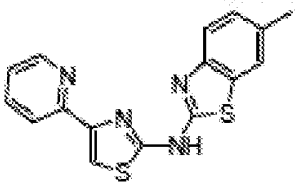
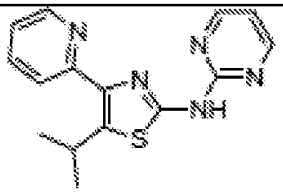
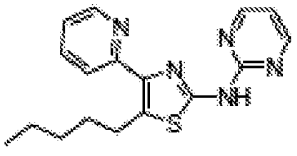
[0284] Selectivity of toxicity in HCC-derived cells over normal liver-derived cells is important for the purposes of developing a therapy that specifically targets the cancer with low toxicity for the whole tumor. The Selective Index (SI) is the ratio of CC_{50} in normal cells (THLE2 or PH5CH) over the CC_{50} in the liver cancer derived cells; thus, the higher the number, the lower the potential toxicity at an efficacious dose.

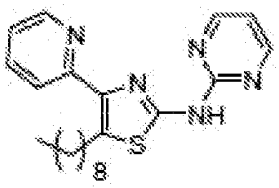
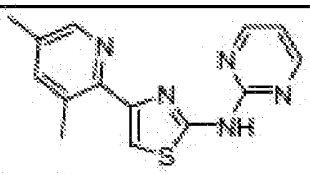
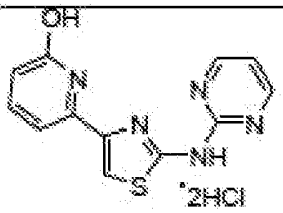
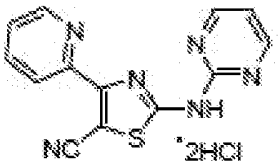
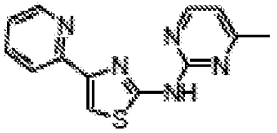
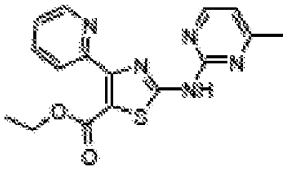
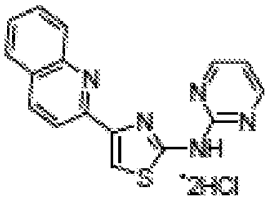
Table 2: Exemplary cell viability screening results for compounds of the disclosure with Huh-7 cells, THLE2 cells and PH5CH cells.

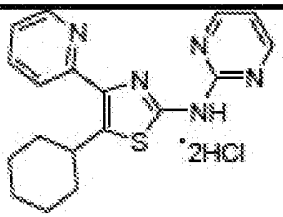
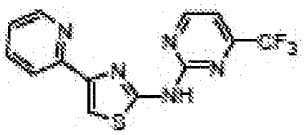
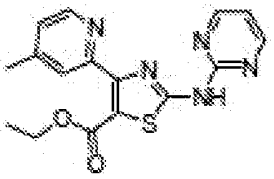
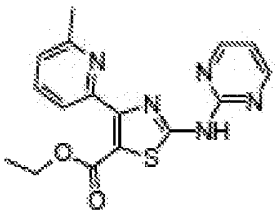
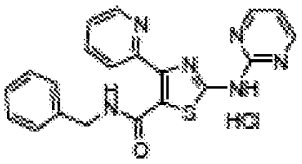
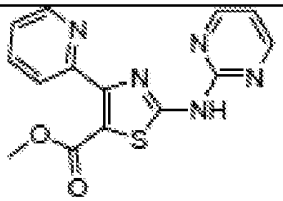
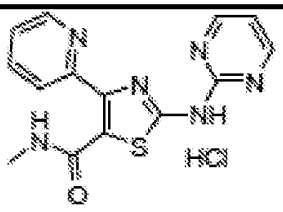
Entry	Structure	Huh7 CC_{50} (uM)	THLE2 CC_{50} (uM)	THLE2/ Huh7 SI	PH5CH CC_{50} (uM)	PH5CH/ Huh7 SI
1		1.387	39.982	28.833	50.000	36.058
2		11.300	2.905	0.257		
3		6.433	9.156	1.423		

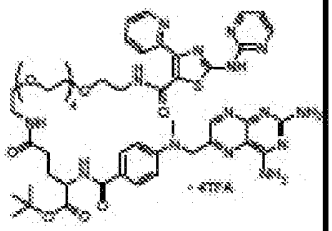
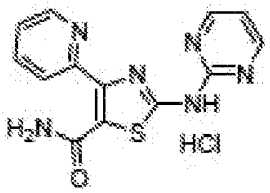
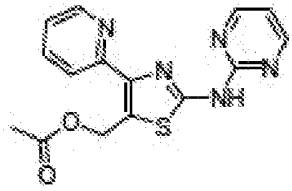
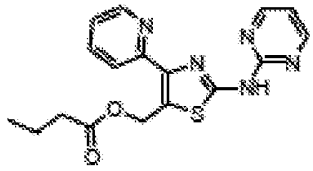
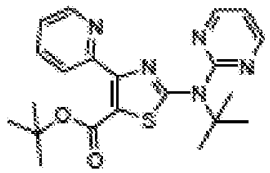
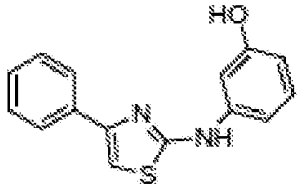
4		6.302	8.660	1.374		
5		14.227	48.471	3.407		
6		6.526	17.783	2.725		
7		10.287	21.083	2.050		
8		0.563	14.018	24.905	33.973	60.358
9		2.532	29.911	11.816		
10		7.816	9.747	1.247		
11		5.000	0.539	0.108		

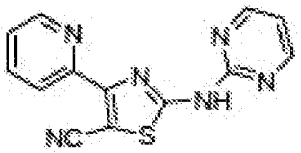
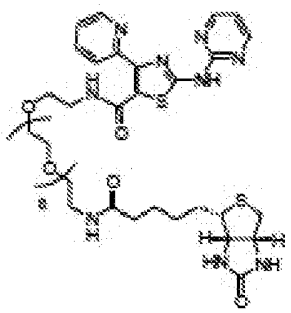
12		3.053	4.471	1.464		
13		35.016	50.000	1.428		
14		31.762	40.966	1.290		
15		5.317	49.120	9.238	49.728	9.353
16		25.705	50.000	1.945	50.000	1.945
17		48.942	50.000	1.022	50.000	1.022
18		50.000	49.755	0.995	46.860	0.937

19		0.362	38.709	106.972	44.017	121.642
20		11.329	31.137	2.748	46.868	4.137
21		15.436	24.733	1.602	44.128	2.859
22		5.925	42.852	7.232	41.985	7.086
23		4.917	3.959	0.805	3.970	0.807
24		11.277	50.000	4.434	50.000	4.434
25		25.877	50.000	1.932	50.000	1.932

26		12.779	2.273	0.178	50.000	3.913
27		2.737	2.234	0.816	47.616	17.397
28		46.188	50.000	1.083	50.000	1.083
29		0.016	50.00	3125	50.00	3125
30		50.000	50.000	1.000	50.000	1.000
31		0.016	50.000	3125	50.000	3125
32		50.000	8.022	0.160	50.000	1.000

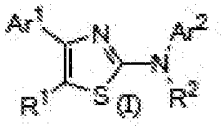
33		50.000	3.537	0.071	50.000	1.000
34		26.621	37.792	1.420	50.000	1.878
35		4.717	37.206	7.888	39.233	8.317
36		50.000	50.000	1.000	50.000	1.000
37		17.742	50.000	2.818	31.485	1.775
38		1.246	29.395	23.591	38.599	30.978
39		12.990	10.292	0.792	2.889	0.222

40		34.843	50.000	1.435	50.000	1.435
41		50.000	26.614	0.532	50.000	1.000
42		39.251	50.000	1.274	50.000	1.274
43		11.003	50.000	4.544	50.000	4.544
44		20.478	50.000	2.442	50.000	2.442
45		8.000	50.000	6.250		

46		3.500	Not tested			
47		0.016	50.000	3125.00	50.000	3125.00
48						

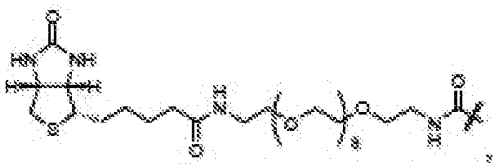
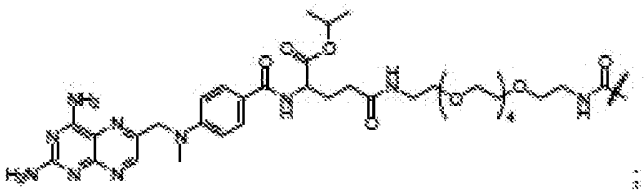
WHAT IS CLAIMED IS:

1. A compound having formula (I):

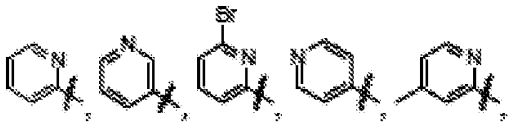
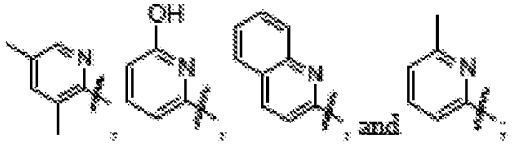


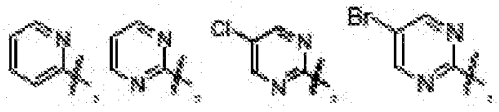
(I)

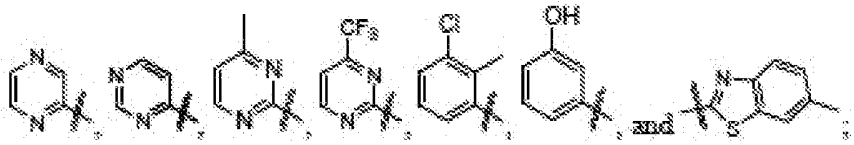
Including hydrates, solvates, pharmaceutically acceptable salts, prodrugs and complexes thereof, wherein:

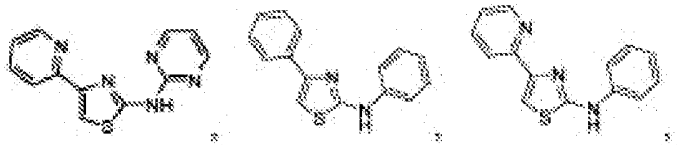
R^1 is selected from a group consisting of hydrogen, C_1-C_9 linear alkyl, isopropyl, cyclohexyl, bromine, cyano,  ,  ,  , and  ;

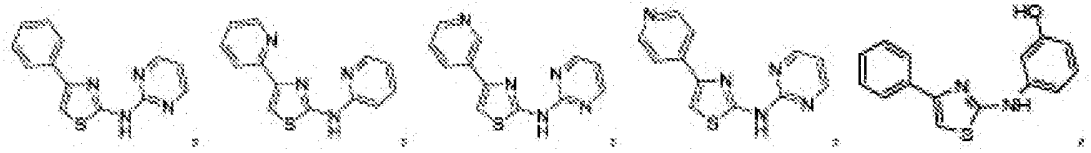
R^2 is selected from a group consisting of hydrogen, methyl, isopropyl, tert-butyl, benzyl, and  ;

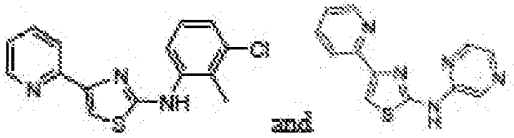
Ar^1 is selected from a group consisting of phenyl,  ,  , and ;

Ar^2 is selected from a group consisting of phenyl, 

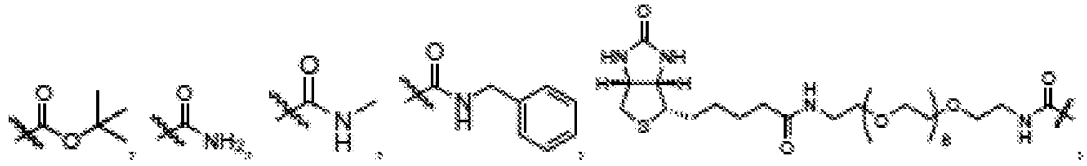


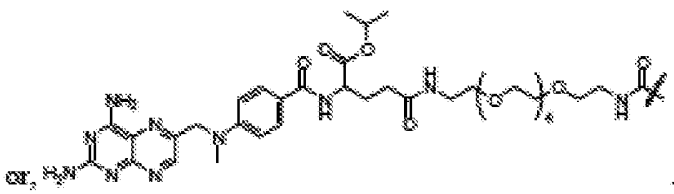
Compounds of the structures 



 and are excluded from the novel compounds of formula (I).

2. The compound according to claim 1 wherein R^1 is hydrogen, C_1-C_9 linear alkyl, isopropyl, cyclohexyl, bromine, cyano, 





3. The compound according to claim 1 or 2, wherein R^2 is hydrogen, methyl, isopropyl, tert-butyl, benzyl, or  .

4. The compound according to any one of claims 1-3, wherein Ar^1 is phenyl,  ,  ,  ,  ,  ,  ,  ,  , or  .

5. The compound according to any one of claims 1-4, wherein Ar^2 is phenyl,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , or  .

6. The compound according to claim 1, which is:

4-(pyridin-2-yl)-N-(pyrimidin-4-yl)thiazol-2-amine;

4-(6-bromopyridin-2-yl)-N-(pyrimidin-2-yl]thiazol-2-amine;

4-(4-methylpyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine;

4-(3,5-dimethylpyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine;

6-(2-(pyrimidin-2-ylamino)thiazol-4-yl)pyridin-2-ol;

N-(pyrimidin-2-yl)-4-(quinolin-2-yl)thiazol-2-amine;

N-(5-chloropyrimidin-2-yl)-4-(pyridin-2-yl)thiazol-2-amine;

N-(5-bromopyrimidin-2-yl)-4-(pyridin-2-yl)thiazol-2-amine;

N-(4-methylpyrimidin-2-yl)-4-(pyridin-2-yl)thiazol-2-amine;

4-(pyridin-2-yl)-N-(4-(trifluoromethyl)pyrimidin-2-yl)thiazol-2-amine;

6-methyl-N-(4-(pyridin-2-yl)thiazol-2-yl)benzo[d]thiazol-2-amine;

5-methyl-4-(pyridin-2-yl)-N-(pyrimidin-2-yl]thiazol-2-amine;

5-ethyl-4-(pyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine;

5-isopropyl-4-(pyridin-2-yl)-N-(pyrimidin-2-yl]thiazol-2-amine;

5-pentyl-4-(pyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine;

5-cyclohexyl-4-(pyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine;

5-nonyl-4-(pyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine;

N-isopropyl-4-(pyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine;
N-methyl-4-(pyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine;
N-benzyl-4-(pyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine;
2-((4-(pyridin-2-yl)thiazol-2-yl)(pyrimidin-2-yl)amino)ethanol;
5-bromo-4-(pyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine;
(4-(pyridin-2-yl)-2-(pyrimidin-2-ylamino)thiazol-5-yl)methanol;
(4-(pyridin-2-yl)-2-(pyrimidin-2-ylamino)thiazol-5-yl)methyl acetate;
(4-(pyridin-2-yl)-2-(pyrimidin-2-ylamino)thiazol-5-yl)methyl butyrate;
Ethyl 4-(pyridin-2-yl)-2-(pyrimidin-2-ylamino)thiazole-5-carboxylate;
Ethyl 4-(4-methylpyridin-2-yl)-2-(pyrimidin-2-ylamino)thiazole-5-carboxylate ;
ethyl 4-(6-methylpyridin-2-yl)-2-(pyrimidin-2-ylamino)thiazole-5-carboxylate ;
ethyl 2-((4-methylpyrimidin-2-yl)amino)-4-(pyridin-2-yl)thiazole-5-carboxylate ;
4-(pyridin-2-yl)-2-(pyrimidin-2-ylamino)thiazole-5-carboxylic acid;
methyl 4-(pyridin-2-yl)-2-(pyrimidin-2-ylamino)thiazole-5-carboxylate;
tert-butyl 2-(tert-butyl(pyrimidin-2-yl)amino)-4-(pyridin-2-yl)thiazole-5-carboxylate;
4-(pyridin-2-yl)-2-(pyrimidin-2-ylamino)thiazole-5-carboxamide;
N-methyl-4-(pyridin-2-yl)-2-(pyrimidin-2-ylamino)thiazole-5-carboxamide;
N-benzyl-4-(pyridin-2-yl)-2-(pyrimidin-2-ylamino)thiazole-5-carboxamide;
24-(4-(((2,4-diaminopteridin-6-yl)methyl)(methyl)amino) benzamido)-1,21-dioxo-1-(4-(pyridin-2-yl)-2-(pyrimidin-2-ylamino)thiazol-5-yl)-5,8,11,14,17-penta oxa-2,20-diazapentacosan-25-oic acid;
N-(31-oxo-35-((3aS,4S,6aR)-2-oxohexahydro-1H-thieno[3, 4-d]imidazol-4-yl)-3, 6, 9, 12, 15, 18, 21, 24, 27-nonaoxa-30-azapentatriacontyl)-4-(pyridin-2-yl)-2-(pyrimidin-2-ylamino) thiazole-5-carboxamide;
4-Pyridin-2-yl-2-(pyrimidin-2-ylamino)-thiazole-5-carbonitrile;
and pharmaceutically acceptable forms thereof.

7. A composition comprising an effective amount of at least one compound according to claim 1.

8. A composition according to claim 7, further comprising at least one excipient.

9. A composition according to claim 8, wherein the at least one compound is at least one member selected from the group consisting of:

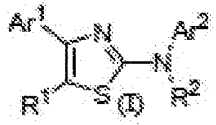
4-(pyridin-2-yl)-N-(pyrimidin-4-yl)thiazol-2-amine;
4-(6-bromopyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine;
4-(4-methylpyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine;
4-(3,5-dimethylpyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine;
6-(2-(pyrimidin-2-ylamino)thiazol-4-yl)pyridin-2-ol;
N-(pyrimidin-2-yl)-4-(quinolin-2-yl)thiazol-2-amine;
N-(5-chloropyrimidin-2-yl)-4-(pyridin-2-yl)thiazol-2-amine;
N-(5-bromopyrimidin-2-yl)-4-(pyridin-2-yl)thiazol-2-amine;
N-(4-methylpyrimidin-2-yl)-4-(pyridin-2-yl)thiazol-2-amine;
4-(pyridin-2-yl)-N-(4-(trifluoromethyl)pyrimidin-2-yl)thiazol-2-amine;
6-methyl-N-(4-(pyridin-2-yl)thiazol-2-yl)benzo[d]thiazol-2-amine;
5-methyl-4-(pyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine;
5-ethyl-4-(pyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine;
5-isopropyl-4-(pyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine;
5-pentyl-4-(pyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine;
5-cyclohexyl-4-(pyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine;
5-nonyl-4-(pyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine;
N-isopropyl-4-(pyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine;
N-methyl-4-(pyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine;
N-benzyl-4-(pyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine;
2-((4-(pyridin-2-yl)thiazol-2-yl)(pyrimidin-2-yl)amino)ethanol;
5-bromo-4-(pyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine;
(4-(pyridin-2-yl)-2-(pyrimidin-2-ylamino)thiazol-5-yl)methanol;
(4-(pyridin-2-yl)-2-(pyrimidin-2-ylamino)thiazol-5-yl)methyl acetate;
(4-(pyridin-2-yl)-2-(pyrimidin-2-ylamino)thiazol-5-yl)methyl butyrate;
Ethyl 4-(pyridin-2-yl)-2-(pyrimidin-2-ylamino)thiazole-5-carboxylate;
Ethyl 4-(4-methylpyridin-2-yl)-2-(pyrimidin-2-ylamino)thiazole-5-carboxylate ;
Ethyl 4-(6-methylpyridin-2-yl)-2-(pyrimidin-2-ylamino)thiazole-5-carboxylate ;
Ethyl 2-((4-methylpyrimidin-2-yl)amino)-4-(pyridin-2-yl)thiazole-5-carboxylate ;
4-(pyridin-2-yl)-2-(pyrimidin-2-ylamino)thiazole-5-carboxylic acid;
Methyl 4-(pyridin-2-yl)-2-(pyrimidin-2-ylamino)thiazole-5-carboxylate;

tert-butyl 2-(tert-butyl(pyrimidin-2-yl)amino)-4-(pyridin-2-yl)thiazole-5-carboxylate;
4-(pyridin-2-yl)-2-(pyrimidin-2-ylamino)thiazole-5-carboxamide;
N-methyl-4-(pyridin-2-yl)-2-(pyrimidin-2-ylamino)thiazole-5-carboxamide;
N-benzyl-4-(pyridin-2-yl)-2-(pyrimidin-2-ylamino)thiazole-5-carboxamide;
24-(4-(((2,4-diaminopteridin-6-yl)methyl)(methyl)amino) benzamido)-1,21-dioxo-1-(4-(pyridin-2-yl)-2-(pyrimidin-2-ylamino)thiazol-5-yl)-5,8,11,14,17-pentaoxa-2,20-diazapentacosan-25-oic acid;
N-(31-oxo-35-((3aS,4S,6aR)-2-oxohexahydro-1H-thieno[3, 4-d]imidazol-4-yl)-3, 6, 9, 12, 15, 18, 21, 24, 27-nonaoxa-30-azapentatriacontyl)-4-(pyridin-2-yl)-2-(pyrimidin-2-ylamino) thiazole-5-carboxamide;
4-Pyridin-2-yl-2-(pyrimidin-2-ylamino)-thiazole-5-carbonitrile
and pharmaceutically acceptable forms thereof.

10. A composition according to claim 8, wherein the at least one compound is at least one member selected from the group consisting of:
4-(pyridin-2-yl)-N-(pyrimidin-4-yl)thiazol-2-amine;
4-(6-bromopyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine;
4-(4-methylpyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine;
4-(3,5-dimethylpyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine;
6-(2-(pyrimidin-2-ylamino)thiazol-4-yl)pyridin-2-ol;
N-(pyrimidin-2-yl)-4-(quinolin-2-yl)thiazol-2-amine;
N-(5-chloropyrimidin-2-yl)-4-(pyridin-2-yl)thiazol-2-amine;
N-(5-bromopyrimidin-2-yl)-4-(pyridin-2-yl)thiazol-2-amine;
N-(4-methylpyrimidin-2-yl)-4-(pyridin-2-yl)thiazol-2-amine:
4-(pyridin-2-yl)-N-(4-(trifluoromethyl)pyrimidin-2-yl)thiazol-2-amine;
6-methyl-N-(4-(pyridin-2-yl)thiazol-2-yl)benzo[d]thiazol-2-amine;
5-methyl-4-(pyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine;
5-ethyl-4-(pyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine;
5-isopropyl-4-(pyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine;
5-pentyl-4-(pyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine;
5-cyclohexyl-4-(pyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine;
5-nonyl-4-(pyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine;

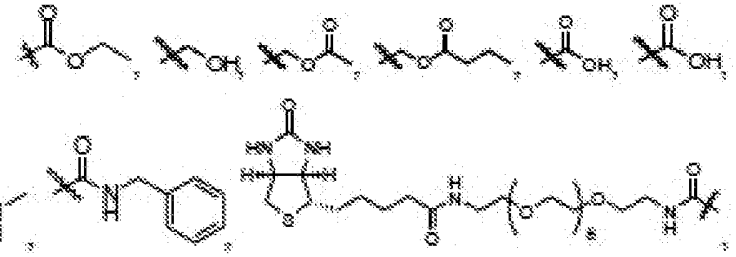
N-isopropyl-4-(pyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine;
N-methyl-4-(pyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine;
N-benzyl-4-(pyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine;
2-((4-(pyridin-2-yl)thiazol-2-yl)(pyrimidin-2-yl)amino)ethanol;
5-bromo-4-(pyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine;
(4-(pyridin-2-yl)-2-(pyrimidin-2-ylamino)thiazol-5-yl)methanol;
(4-(pyridin-2-yl)-2-(pyrimidin-2-ylamino)thiazol-5-yl)methyl acetate;
(4-(pyridin-2-yl)-2-(pyrimidin-2-ylamino)thiazol-5-yl)methyl butyrate;
Ethyl 4-(pyridin-2-yl)-2-(pyrimidin-2-ylamino)thiazole-5-carboxylate;
Ethyl 4-(4-methylpyridin-2-yl)-2-(pyrimidin-2-ylamino)thiazole-5-carboxylate ;
Ethyl 4-(6-methylpyridin-2-yl)-2-(pyrimidin-2-ylamino)thiazole-5-carboxylate ;
Ethyl 2-((4-methylpyrimidin-2-yl)amino)-4-(pyridin-2-yl)thiazole-5-carboxylate ;
4-(pyridin-2-yl)-2-(pyrimidin-2-ylamino)thiazole-5-carboxylic acid;
Methyl 4-(pyridin-2-yl)-2-(pyrimidin-2-ylamino)thiazole-5-carboxylate;
tert-butyl 2-(tert-butyl(pyrimidin-2-yl)amino)-4-(pyridin-2-yl)thiazole-5-carboxylate;
4-(pyridin-3-yl)-2-(pyrimidin-2-ylamino)thiazole-5-carboxamide;
N-methyl-4-(pyridin-2-yl)-2-(pyrimidin-2-ylamino)thiazole-5-carboxamide;
N-benzyl-4-(pyridin-2-yl)-2-(pyrimidin-2-ylamino)thiazole-5-carboxamide;
24-(4-(((2,4-diaminopteridin-6-yl)methyl)(methyl)amino) benzamido)-1,21-dioxo-1-(4-(pyridin-2-yl)-2-(pyrimidin-2-ylamino)thiazol-5-yl)-5,8,11,14,17-pentaoxa-2,20-diazapentacosan-25-oic acid;
N-(31-oxo-35-((3aS,4S,6aR)-2-oxohexahydro-1H-thieno[3, 4-d]imidazol-4-yl)-3, 6, 9, 12, 15, 18, 21, 24, 27-nonaoxa-30-azapentatriacontyl)-4-(pyridin-2-yl)-2-(pyrimidin-2-ylamino) thiazole-5-carboxamide;
4-Pyridin-2-yl-2-(pyrimidin-2-ylamino)-thiazole-5-carbonitrile
and pharmaceutically acceptable forms thereof.

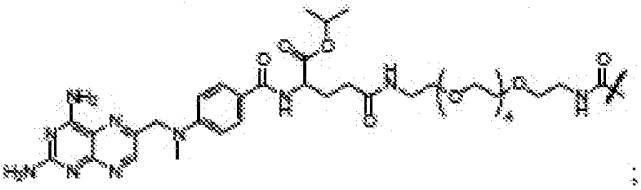
11. A method for treating a disease associated with unregulated cell growth, said method comprising administering to a subject an effective amount of at least one compound of the formula (I),



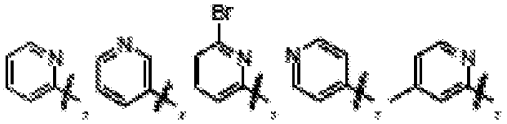
(I)

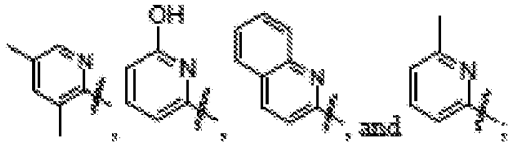
including hydrates, solvates, pharmaceutically acceptable salts, prodrugs and complexes thereof, to treat the disease wherein:

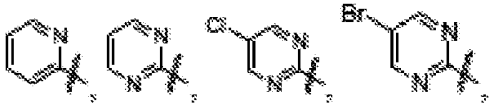
R^1 is selected from a group consisting of hydrogen, C_1-C_9 linear alkyl, isopropyl, cyclohexyl, bromine, cyano, 

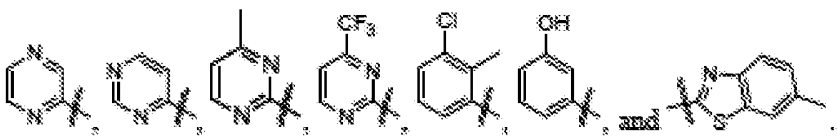
and,  ;

R^2 is selected from a group consisting of hydrogen, methyl, isopropyl, tert-butyl, benzyl, and  ;

Ar^1 is selected fromna group consisting of phenyl, 

 , and ;

Ar^2 is selected fromna group consisting of phenyl, 

 , and .

12. The method of claim 11, wherein the at least one compound is at least one member selected from the group consisting of

4-(pyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine;

N,4-diphenylthiazol-2-amine;

N-phenyl-4-(pyridin-2-yl)thiazol-2-amine;

4-phenyl-N-(pyrimidin-2-yl)thiazol-2-amine;

N,4-di(pyridin-2-yl)thiazol-2-amine;

4-(pyridin-3-yl)-N-(pyrimidin-2-yl)thiazol-2-amine;

4-(pyridin-4-yl)-N-(pyrimidin-2-yl)thiazol-2-amine;

N-(pyrazin-2-yl)-4-(pyridin-2-yl)thiazol-2-amine;

4-(pyridin-2-yl)-N-(pyrimidin-4-yl)thiazol-2-amine;

4-(6-bromopyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine;

4-(4-methylpyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine;

4-(3,5-dimethylpyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine;

6-(2-(pyrimidin-2-ylamino)thiazol-4-yl)pyridin-2-ol;

N-(pyrimidin-2-yl)-4-(quinolin-2-yl)thiazol-2-amine;

N-(5-chloropyrimidin-2-yl)-4-(pyridin-2-yl)thiazol-2-amine;

N-(5-bromopyrimidin-2-yl)-4-(pyridin-2-yl)thiazol-2-amine;

N-(4-methylpyrimidin-2-yl)-4-(pyridin-2-yl)thiazol-2-amine;

4-(pyridin-2-yl)-N-(4-(trifluoromethyl)pyrimidin-2-yl)thiazol-2-amine;

6-methyl-N-(4-(pyridin-2-yl)thiazol-2-yl)benzo[d]thiazol-2-amine;

5-methyl-4-(pyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine;

5-ethyl-4-(pyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine;

5-isopropyl-4-(pyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine;

5-pentyl-4-(pyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine;

5-cyclohexyl-4-(pyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine;

5-nonyl-4-(pyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine;

N-isopropyl-4-(pyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine;

N-methyl-4-(pyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine;

N-benzyl-4-(pyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine;

2-((4-(pyridin-2-yl)thiazol-2-yl)(pyrimidin-2-yl)amino)ethanol;

5-bromo-4-(pyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine;

(4-(pyridin-2-yl)-2-(pyrimidin-2-ylamino)thiazol-5-yl)methanol;

(4-(pyridin-2-yl)-2-(pyrimidin-2-ylamino)thiazol-5-yl)methyl acetate;

(4-(pyridin-2-yl)-2-(pyrimidin-2-ylamino)thiazol-5-yl)methyl butyrate;

Ethyl 4-(pyridin-2-yl)-2-(pyrimidin-2-ylamino)thiazole-5-carboxylate;

Ethyl 4-(4-methylpyridin-2-yl)-2-(pyrimidin-2-ylamino)thiazole-5-carboxylate ;

Ethyl 4-(6-methylpyridin-2-yl)-2-(pyrimidin-2-ylamino)thiazole-5-carboxylate ;

Ethyl 2-((4-methylpyrimidin-2-yl)amino)-4-(pyridin-2-yl)thiazole-5-carboxylate ;

4-(pyridin-2-yl)-2-(pyrimidin-2-ylamino)thiazole-5-carboxylic acid;

Methyl 4-(pyridin-2-yl)-2-(pyrimidin-2-ylamino)thiazole-5-carboxylate;

tert-butyl 2-(tert-butyl(pyrimidin-2-yl)amino)-4-(pyridin-2-yl)thiazole-5-carboxylate;

4-(pyridin-2-yl)-2-(pyrimidin-2-ylamino)thiazole-5-carboxamide;

N-methyl-4-(pyridin-2-yl)-2-(pyrimidin-2-ylamino)thiazole-5-carboxamide;

N-benzyl-4-(pyridin-2-yl)-2-(pyrimidin-2-ylamino)thiazole-5-carboxamide;

24-(4-(((2,4-diaminopteridin-6-yl)methyl)(methyl)amino) benzamido)-1,21-dioxo-1-(4-(pyridin-2-yl)-2-(pyrimidin-2-ylamino)thiazol-5-yl)-5,8,11,14,17-pentaoxa-2,20-diazapentacosan-25-oic acid;

N-(31-oxo-35-((3aS,4S,6aR)-2-oxohexahydro-1H-thieno[3, 4-d]imidazol-4-yl)-3, 6, 9, 12, 15, 18, 21, 24, 27-nonaoxa-30-azapentatriacontyl)-4-(pyridin-2-yl)-2-(pyrimidin-2-ylamino) thiazole-5-carboxamide;

4-Pyridin-2-yl-2-(pyrimidin-2-ylamino)-thiazole-5-carbonitrile;

3-(4-Phenyl-thiazol-2-ylamino)-phenol;

(3-Chloro-2-methyl-phenyl)-(4-pyridin-2-yl-thiazol-2-yl)-amine;

and pharmaceutically acceptable forms thereof.

13. The method of claim 11, wherein the at least one compound is administered in a composition further comprising at least one excipient.

14. The method of claim 13, wherein the at least one compound is at least one member selected from the group consisting of

4-(pyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine;

N,4-diphenylthiazol-2-amine;

N-phenyl-4-(pyridin-2-yl)thiazol-2-amine;

4-phenyl-N-(pyrimidin-2-yl)thiazol-2-amine;
N,4-di(pyridin-2-yl)thiazol-2-amine;
4-(pyridin-3-yl)-N-(pyrimidin-2-yl)thiazol-2-amine;
4-(pyridin-4-yl)-N-(pyrimidin-2-yl)thiazol-2-amine;
N-(pyrazin-2-yl)-4-(pyridin-2-yl)thiazol-2-amine;
4-(pyridin-2-yl)-N-(pyrimidin-4-yl)thiazol-2-amine;
4-(6-bromopyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine;
4-(4-methylpyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine;
4-(3,5-dimethylpyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine;
6-(2-(pyrimidin-2-ylamino)thiazol-4-yl)pyridin-2-ol;
N-(pyrimidin-2-yl)-4-(quinolin-2-yl)thiazol-2-amine;
N-(5-chloropyrimidin-2-yl)-4-(pyridin-2-yl)thiazol-2-amine;
N-(5-bromopyrimidin-2-yl)-4-(pyridin-2-yl)thiazol-2-amine;
N-(4-methylpyrimidin-2-yl)-4-(pyridin-2-yl)thiazol-2-amine;
4-(pyridin-2-yl)-N-(4-(trifluoromethyl)pyrimidin-2-yl)thiazol-2-amine;
6-methyl-N-(4-(pyridin-2-yl)thiazol-2-yl)benzo[d]thiazol-2-amine;
5-methyl-4-(pyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine;
5-ethyl-4-(pyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine;
5-isopropyl-4-(pyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine;
5-pentyl-4-(pyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine;
5-cyclohexyl-4-(pyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine;
5-nonyl-4-(pyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine;
N-isopropyl-4-(pyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine;
N-methyl-4-(pyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine;
N-benzyl-4-(pyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine;
2-((4-(pyridin-2-yl)thiazol-2-yl)(pyrimidin-2-yl)amino)ethanol;
5-bromo-4-(pyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine;
(4-(pyridin-2-yl)-2-(pyrimidin-2-ylamino)thiazol-5-yl)methanol;
(4-(pyridin-2-yl)-2-(pyrimidin-2-ylamino)thiazol-5-yl)methyl acetate;
(4-(pyridin-2-yl)-2-(pyrimidin-2-ylamino)thiazol-5-yl)methyl butyrate;
Ethyl 4-(pyridin-2-yl)-2-(pyrimidin-2-ylamino)thiazole-5-carboxylate;

Ethyl 4-(4-methylpyridin-2-yl)-2-(pyrimidin-2-ylamino)thiazole-5-carboxylate ;
Ethyl 4-(6-methylpyridin-2-yl)-2-(pyrimidin-2-ylamino)thiazole-5-carboxylate ;
Ethyl 2-((4-methylpyrimidin-2-yl)amino)-4-(pyridin-2-yl)thiazole-5-carboxylate ;
4-(pyridin-2-yl)-2-(pyrimidin-2-ylamino)thiazole-5-carboxylic acid;
Methyl 4-(pyridin-2-yl)-2-(pyrimidin-2-ylamino)thiazole-5-carboxylate;
tert-butyl 2-(tert-butyl(pyrimidin-2-yl)amino)-4-(pyridin-2-yl)thiazole-5-carboxylate;
4-(pyridin-2-yl)-2-(pyrimidin-2-ylamino)thiazole-5-carboxamide;
N-methyl-4-(pyridin-2-yl)-2-(pyrimidin-2-ylamino)thiazole-5-carboxamide;
N-benzyl-4-(pyridin-2-yl)-2-(pyrimidin-2-ylamino)thiazole-5-carboxamide;
24-(4-(((2,4-diaminopteridin-6-yl)methyl)(methyl)amino) benzamido)-1,21-dioxo-1-(4-(pyridin-2-yl)-2-(pyrimidin-2-ylamino)thiazol-5-yl)-5,8,11,14,17-pentaoxa-2,20-diazapentacosan-25-oic acid;
N-(31-oxo-35-((3aS,4S,6aR)-2-oxohexahydro-1H-thieno[3, 4-d]imidazol-4-yl)-3, 6, 9, 12, 15, 18, 21, 24, 27-nonaoxa-30-azapentatriacontyl)-4-(pyridin-2-yl)-2-(pyrimidin-2-ylamino) thiazole-5-carboxamide;
4-Pyridin-2-yl-2-(pyrimidin-2-ylamino)-thiazole-5-carbonitrile;
3-(4-Phenyl-thiazol-2-ylamino)-phenol;
(3-Chloro-2-methyl-phenyl)-(4-pyridin-2-yl-thiazol-2-yl)-amine;
and pharmaceutically acceptable forms thereof.

15. The method of claim 11, wherein the disease associated with unregulated cell growth is cancer.

16. The method of claim 11, wherein the disease associated with unregulated cell growth is hepatocellular carcinoma.

17. The method of claim 11, wherein the disease associated with unregulated cell growth is primary liver cancer.

18. The method of claim 11, wherein the disease associated with unregulated cell growth is hepatoblastoma.

19. The method of claim 11, wherein the disease associated with unregulated cell growth is breast cancer.

20. The method of claim 11, wherein the disease associated with unregulated cell growth is ovarian cancer.

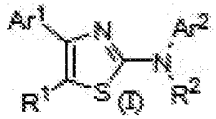
21. The method of claim 11, wherein the disease associated with unregulated cell growth is lung cancer.

22. The method of claim 11, wherein the disease associated with unregulated cell growth is leukemia.

23. The method of claim 11, wherein the disease associated with unregulated cell growth is cholangiocarcinoma.

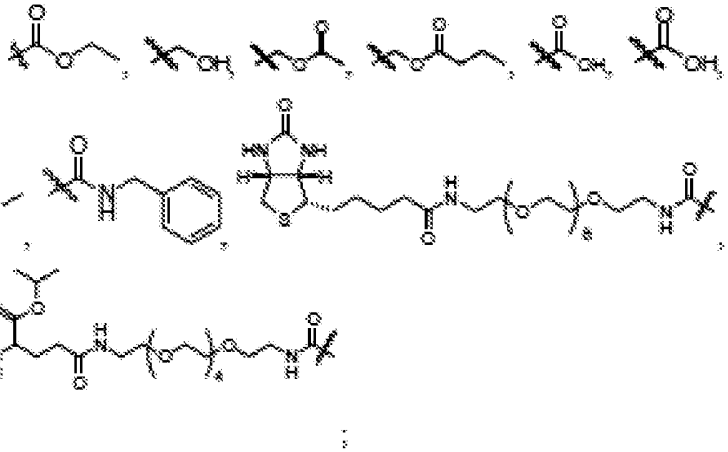
24. The method of claim 11, wherein the disease associated with unregulated cell growth is metastatic disease.

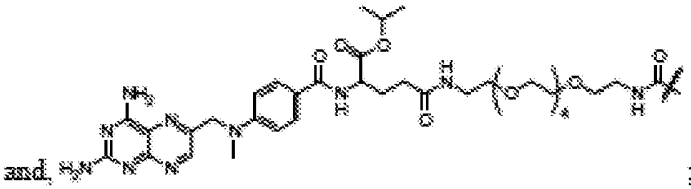
25. A method for treating a disease associated with infection of the liver with a virus, said method comprising administering to a subject an effective amount of at least one compound of the formula (I),



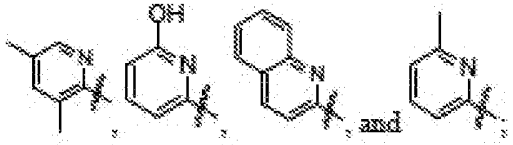
(I)

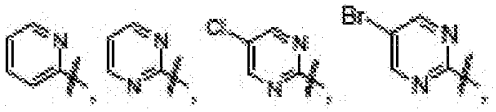
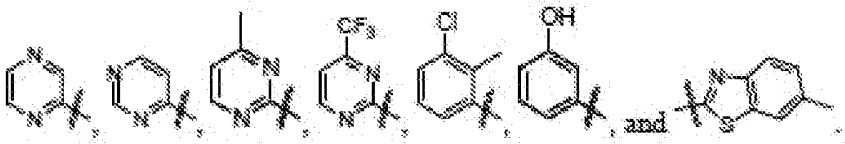
including hydrates, solvates, pharmaceutically acceptable salts, prodrugs and complexes thereof, to treat the disease wherein:

R^1 is selected from a group consisting of hydrogen, C_1-C_9 linear alkyl, isopropyl, cyclohexyl, bromine, cyano, 

and,  ;

R^2 is selected from a group consisting of hydrogen, methyl, isopropyl, tert-butyl, benzyl, and  ;

Ar^1 is selected fromа group consisting of phenyl,  ,  , and ;

Ar^2 is selected fromа group consisting of phenyl,  ,  , and .

26. The method of claim 25, wherein the at least one compound is at least one member selected from the group consisting of

4-(pyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine;

N,4-diphenylthiazol-2-amine;

N-phenyl-4-(pyridin-2-yl)thiazol-2-amine;

4-phenyl-N-(pyrimidin-2-yl)thiazol-2-amine;

N,4-di(pyridin-2-yl)thiazol-2-amine;

4-(pyridin-3-yl)-N-(pyrimidin-2-yl)thiazol-2-amine;

4-(pyridin-4-yl)-N-(pyrimidin-2-yl)thiazol-2-amine;

N-(pyrazin-2-yl)-4-(pyridin-2-yl)thiazol-2-amine;

4-(pyridin-2-yl)-N-(pyrimidin-4-yl)thiazol-2-amine;

4-(6-bromopyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine;

4-(4-methylpyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine;

4-(3,5-dimethylpyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine;

6-(2-(pyrimidin-2-ylamino)thiazol-4-yl)pyridin-2-ol;

N-(pyrimidin-2-yl)-4-(quinolin-2-yl)thiazol-2-amine;

N-(5-chloropyrimidin-2-yl)-4-(pyridin-2-yl)thiazol-2-amine;

N-(5-bromopyrimidin-2-yl)-4-(pyridin-2-yl)thiazol-2-amine;
N-(4-methylpyrimidin-2-yl)-4-(pyridin-2-yl)thiazol-2-amine:
4-(pyridin-2-yl)-N-(4-(trifluoromethyl)pyrimidin-2-yl)thiazol-2-amine;
6-methyl-N-(4-(pyridin-2-yl)thiazol-2-yl)benzo[d]thiazol-2-amine;
5-methyl-4-(pyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine;
5-ethyl-4-(pyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine;
5-isopropyl-4-(pyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine;
5-pentyl-4-(pyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine;
5-cyclohexyl-4-(pyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine;
5-nonyl-4-(pyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine;
N-isopropyl-4-(pyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine;
N-methyl-4-(pyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine;
N-benzyl-4-(pyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine;
2-((4-(pyridin-2-yl)thiazol-2-yl)(pyrimidin-2-yl)amino)ethanol;
5-bromo-4-(pyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine;
(4-(pyridin-2-yl)-2-(pyrimidin-2-ylamino)thiazol-5-yl)methanol;
(4-(pyridin-2-yl)-2-(pyrimidin-2-ylamino)thiazol-5-yl)methyl acetate;
(4-(pyridin-2-yl)-2-(pyrimidin-2-ylamino)thiazol-5-yl)methyl butyrate;
Ethyl 4-(pyridin-2-yl)-2-(pyrimidin-2-ylamino)thiazole-5-carboxylate;
Ethyl 4-(4-methylpyridin-2-yl)-2-(pyrimidin-2-ylamino)thiazole-5-carboxylate ;
Ethyl 4-(6-methylpyridin-2-yl)-2-(pyrimidin-2-ylamino)thiazole-5-carboxylate ;
Ethyl 2-((4-methylpyrimidin-2-yl)amino)-4-(pyridin-2-yl)thiazole-5-carboxylate ;
4-(pyridin-2-yl)-2-(pyrimidin-2-ylamino)thiazole-5-carboxylic acid;
Methyl 4-(pyridin-2-yl)-2-(pyrimidin-2-ylamino)thiazole-5-carboxylate;
tert-butyl 2-(tert-butyl(pyrimidin-2-yl)amino)-4-(pyridin-2-yl)thiazole-5-carboxylate;
4-(pyridin-2-yl)-2-(pyrimidin-2-ylamino)thiazole-5-carboxamide;
N-methyl-4-(pyridin-2-yl)-2-(pyrimidin-2-ylamino)thiazole-5-carboxamide;
N-benzyl-4-(pyridin-2-yl)-2-(pyrimidin-2-ylamino)thiazole-5-carboxamide;
24-(4-(((2,4-diaminopteridin-6-yl)methyl)(methyl)amino) benzamido)-1,21-dioxo-1-(4-(pyridin-2-yl)-2-(pyrimidin-2-ylamino)thiazol-5-yl)-5,8,11,14,17-pentaoxa-2,20-diazapentacosan-25-oic acid;

N-(31-oxo-35-((3aS,4S,6aR)-2-oxohexahydro-1H-thieno[3, 4-d]imidazol-4-yl)-3, 6, 9, 12, 15, 18, 21, 24, 27-nonaoxa-30-azapentatriacontyl)-4-(pyridin-2-yl)-2-(pyrimidin-2-ylamino) thiazole-5-carboxamide;

4-Pyridin-2-yl-2-(pyrimidin-2-ylamino)-thiazole-5-carbonitrile;

3-(4-Phenyl-thiazol-2-ylamino)-phenol;

(3-Chloro-2-methyl-phenyl)-(4-pyridin-2-yl-thiazol-2-yl)-amine;

and pharmaceutically acceptable forms thereof.

27. The method of claim 25, wherein the at least one compound is administered in a composition further comprising at least one excipient.

28. The method of claim 27, wherein the at least one compound is at least one member selected from the group consisting of

4-(pyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine;

N,4-diphenylthiazol-2-amine;

N-phenyl-4-(pyridin-2-yl)thiazol-2-amine;

4-phenyl-N-(pyrimidin-2-yl)thiazol-2-amine;

N,4-di(pyridin-2-yl)thiazol-2-amine;

4-(pyridin-3-yl)-N-(pyrimidin-2-yl)thiazol-2-amine;

4-(pyridin-4-yl)-N-(pyrimidin-2-yl)thiazol-2-amine;

N-(pyrazin-2-yl)-4-(pyridin-2-yl)thiazol-2-amine;

4-(pyridin-2-yl)-N-(pyrimidin-4-yl)thiazol-2-amine;

4-(6-bromopyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine;

4-(4-methylpyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine;

4-(3,5-dimethylpyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine;

6-(2-(pyrimidin-2-ylamino)thiazol-4-yl)pyridin-2-ol;

N-(pyrimidin-2-yl)-4-(quinolin-2-yl)thiazol-2-amine;

N-(5-chloropyrimidin-2-yl)-4-(pyridin-2-yl)thiazol-2-amine;

N-(5-bromopyrimidin-2-yl)-4-(pyridin-2-yl)thiazol-2-amine;

N-(4-methylpyrimidin-2-yl)-4-(pyridin-2-yl)thiazol-2-amine;

4-(pyridin-2-yl)-N-(4-(trifluoromethyl)pyrimidin-2-yl)thiazol-2-amine;

6-methyl-N-(4-(pyridin-2-yl)thiazol-2-yl)benzo[d]thiazol-2-amine;

5-methyl-4-(pyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine;

5-ethyl-4-(pyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine;
5-isopropyl-4-(pyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine;
5-pentyl-4-(pyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine;
5-cyclohexyl-4-(pyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine;
5-nonyl-4-(pyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine;
N-isopropyl-4-(pyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine;
N-methyl-4-(pyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine;
N-benzyl-4-(pyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine;
2-((4-(pyridin-2-yl)thiazol-2-yl)(pyrimidin-2-yl)amino)ethanol;
5-bromo-4-(pyridin-2-yl)-N-(pyrimidin-2-yl)thiazol-2-amine;
(4-(pyridin-2-yl)-2-(pyrimidin-2-ylamino)thiazol-5-yl)methanol;
(4-(pyridin-2-yl)-2-(pyrimidin-2-ylamino)thiazol-5-yl)methyl acetate;
(4-(pyridin-2-yl)-2-(pyrimidin-2-ylamino)thiazol-5-yl)methyl butyrate;
Ethyl 4-(pyridin-2-yl)-2-(pyrimidin-2-ylamino)thiazole-5-carboxylate;
Ethyl 4-(4-methylpyridin-2-yl)-2-(pyrimidin-2-ylamino)thiazole-5-carboxylate ;
Ethyl 4-(6-methylpyridin-2-yl)-2-(pyrimidin-2-ylamino)thiazole-5-carboxylate ;
Ethyl 2-((4-methylpyrimidin-2-yl)amino)-4-(pyridin-2-yl)thiazole-5-carboxylate ;
4-(pyridin-2-yl)-2-(pyrimidin-2-ylamino)thiazole-5-carboxylic acid;
Methyl 4-(pyridin-2-yl)-2-(pyrimidin-2-ylamino)thiazole-5-carboxylate;
tert-butyl 2-(tert-butyl(pyrimidin-2-yl)amino)-4-(pyridin-2-yl)thiazole-5-carboxylate;
4-(pyridin-2-yl)-2-(pyrimidin-2-ylamino)thiazole-5-carboxamide;
N-methyl-4-(pyridin-2-yl)-2-(pyrimidin-2-ylamino)thiazole-5-carboxamide;
N-benzyl-4-(pyridin-2-yl)-2-(pyrimidin-2-ylamino)thiazole-5-carboxamide;
24-(4-(((2,4-diaminopteridin-6-yl)methyl)(methyl)amino) benzamido)-1,21-dioxo-1-(4-(pyridin-2-yl)-2-(pyrimidin-2-ylamino)thiazol-5-yl)-5,8,11,14,17-pentaoxa-2,20-diazapentacosan-25-oic acid;
N-(31-oxo-35-((3aS,4S,6aR)-2-oxohexahydro-1H-thieno[3, 4-d]imidazol-4-yl)-3, 6, 9, 12, 15, 18, 21, 24, 27-nonaoxa-30-azapentatriacontyl)-4-(pyridin-2-yl)-2-(pyrimidin-2-ylamino) thiazole-5-carboxamide;
4-Pyridin-2-yl-2-(pyrimidin-2-ylamino)-thiazole-5-carbonitrile;
3-(4-Phenyl-thiazol-2-ylamino)-phenol;

(3-Chloro-2-methyl-phenyl)-(4-pyridin-2-yl-thiazol-2-yl)-amine;

and pharmaceutically acceptable forms thereof.

29. The method of claim 25, wherein the virus is a hepatitis virus.

30. The method of claim 25, wherein the hepatitis virus is the hepatitis A virus.

31. The method of claim 25, wherein the hepatitis virus is the hepatitis B virus.

32. The method of claim 25, wherein the hepatitis virus is the hepatitis C virus.

33. The method of claim 25, wherein the hepatitis virus is the hepatitis D virus.

34. The method of claim 25, wherein the hepatitis virus is the hepatitis E virus.

35. The method of claim 25, wherein the virus is any virus infecting the liver.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 12/58674

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 31/425, A61K 31/426; C07D 417/00, C07D 417/02 (2013.01)
USPC - 514/365, 514/366, 514/370,
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
USPC - 514/365, 514/366, 514/370,

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 514/365, 514/366, 514/370 (see search terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
*** Databases: WEST; Patbase; Google *** Search Terms Used: Institute for Hepatitis and Virus Research, Cuconati, Xu, Block, aminothiazole, thiazol-2-amine, thiazol-2-yl-amine

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2005/0227989 A1 (Wang et al.) 13 October 2005 (13.10.2005), especially para [0013]-[0014], [0016], [0021], [0068]	1-3 and 6-10
X	US 2007/0213301 A1 (Zhang et al.) 13 September 2007 (13.09.2007), especially para [0012], [0014], [0017]-[0018], [0068]-[0071]	1-3 and 7-8
A	US 2007/0203147 A1 (Coburn et al.) 30 August 2007 (30.08.2007), entire document	1-3 and 6-10

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 January 2013 (23.01.2013)	15 FEB 2013
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 12/58674

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 4-5
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
*** Please see extra sheet ***

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
Claims 1-3 and 6-10

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 12/58674

Box III Observations where unity of invention is lacking

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I: Claims 1-3 and 6-10 relate to a composition comprising a substituted aminothiazoles derivative of formula I.

Group II: Claims 11-24 relate to a method of treating a disease associated with unregulated cell growth, such as cancer, by administering to a subject an effective amount of at least one compound of formula I.

Group III: Claims 25-35 relate to a method of treating a disease associated with infection of the liver with a virus, such as hepatitis, by administering to a subject an effective amount of at least one compound of formula I.

The inventions listed as Groups I-III do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Group I does not include the intentive concept of administering to a subject an effective amount of at least one compound of formula I to treat a disease, such as cancer or hepatitis, as required by Groups II and III.

Group II relates to the specific treatment of diseases associated with unregulated cell growth, such as cancer.

Group III relates to the specific treatment of diseases associated with infection of the liver with a virus, such as hepatitis.

Groups I, II and III share the technical features of being related to a composition comprising a substituted aminothiazoles derivative of formula I. However, the shared technical features fail to make a contribution over the prior art US 2005/0227989 A1 to Wang et al. (hereinafter 'Wang'), which discloses a substiuted aminothiazole derivative of formula I [see claim 1 for formula I] (para [0013]: disclosing a 1,3-thiazole core; para [0014]: disclosing the C-2 'Y' group of Wang as as -NH-, and the C-4 'X' group of Wang as a bond; para [0014]: defining 'A' and 'B' in Wang as independent 5- or 6- membered heteroaryl groups); wherein R1 is hydrogen (para [0016]: defining the R1 -equivalent R2 group in Wang as hydrogen); R2 is hydrogen (para [0014]: disclosing the C-2 'Y' group of Wang as as -NH-); and Ar1 and Ar2 are any of the substituted or unsubstituted heteroaryl groups claimed herein (para [0014]: defining 'A' and 'B' in Wang as independent 5- or 6- membered heteroaryl groups, with para [0032]-[0033] and [0035]: defining 'heteroaryl'). As substituted aminothiazole derivatives of formula I were known, as evidenced by the disclosure of Wang, this cannot be considered a special technical feature that would otherwise unify the groups.

Groups II and III also share the technical features of being related to a method of treating a disease, such as cancer or hepatitis, by administering to a subject an effective amount of at least one compound of formula I. However, the shared technical features fail to make a contribution over the prior art US 2005/0227989 A1 to Wang et al. (hereinafter 'Wang'), which discloses a method of treating various diseases, including cancer, by administering to a subject an effective amount of a substituted aminothiazole derivative of formula I (para [0020], with para [0013]). As methods of treating a disease, such as cancer, by administering to a subject an effective amount of at least one compound of formula I was known, as evidenced by the disclosure of Wang, this cannot be considered a special technical feature that would otherwise unify the groups.

Groups I-III therefore lack unity under PCT Rule 13.1 because they do not share a same or corresponding special technical feature.

(19)中华人民共和国国家知识产权局

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代理人 孟锐
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C07D 417/00(2006.01)
C07D 417/02(2006.01)

权利要求书13页 说明书50页

(54)发明名称

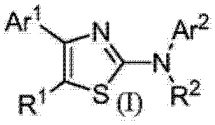
作为包括肝细胞癌在内的癌症的抑制剂和作为肝炎病毒复制抑制剂的取代的氨基噻唑

(57)摘要

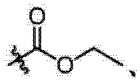
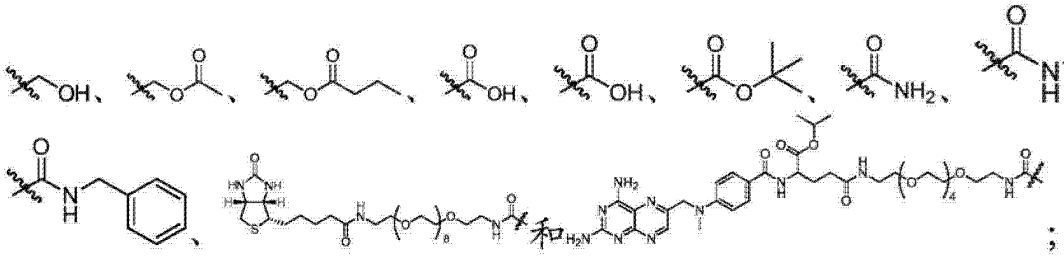
本发明提供了包含取代的氨基噻唑衍生物的药物组合物。所述取代的氨基噻唑衍生物在与细胞生长失调相关的疾病治疗中具有疾病改良作用。此类疾病包括诸如肝细胞癌的癌症和肝炎病毒的病毒感染。

CN 103957908 A

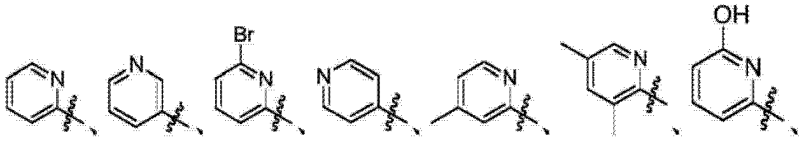
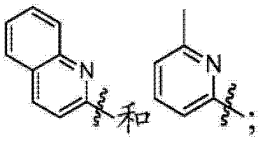
1. 一种化合物，其具有式（I）：

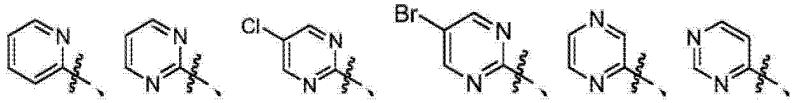
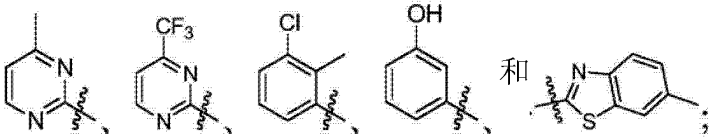


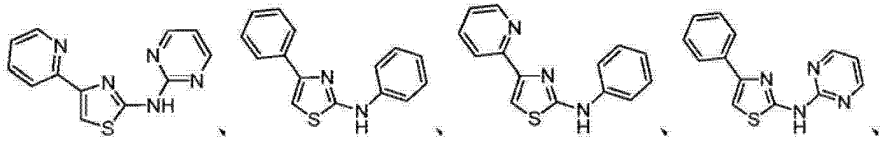
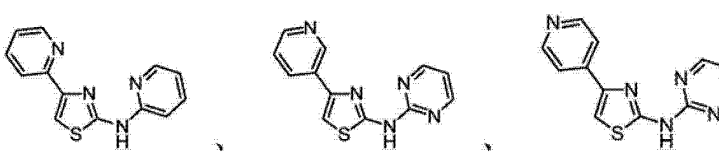
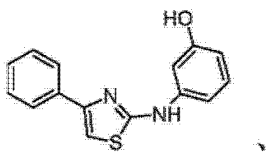
包括其水合物、溶剂合物、药学上可接受的盐、前药和复合物，其中：

R^1 选自氢、C_1-C_9 直链烷基、异丙基、环己基、溴、氰基、  、  ；

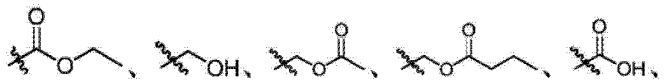
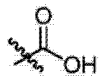
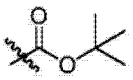
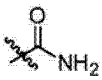
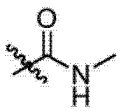
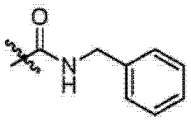
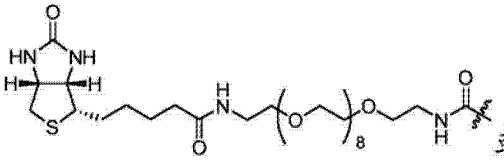
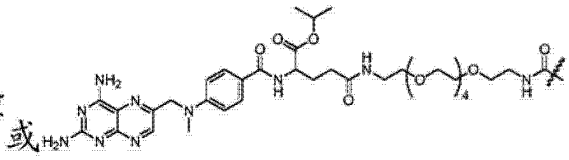
R^2 选自氢、甲基、异丙基、叔丁基、苄基和  ；

Ar^1 选自苯基、  、  ；

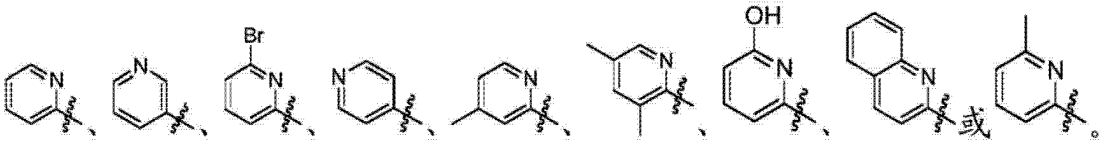
Ar^2 选自苯基、  、  ；

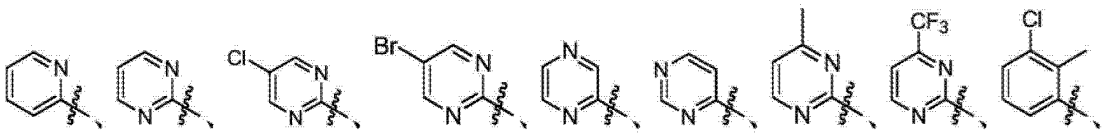
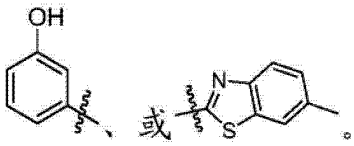
以下结构  、  、、、  的化合物被从所述式（I）的新颖化合物中排除。

2. 根据权利要求 1 所述的化合物，其中 R^1 是氢、C_1-C_9 直链烷基、异

丙 基、环 己 基、溴、氰 基、  、  、  、  、  、  、  或  。

3. 根据权利要求 1 或 2 所述的化合物，其中 R^2 是氢、甲基、异丙基、叔丁基、苄基或  。

4. 根据权利要求 1-3 中任一项所述的化合物，其中 Ar^1 是苯基、  或。

5. 根据权利要求 1-4 中任一项所述的化合物，其中 Ar^2 是苯基、  、  或。

6. 根据权利要求 1 所述的化合物，其是：

4-(吡啶 -2- 基)-N-(嘧啶 -4- 基) 噻唑 -2- 胺；

4-(6- 溴吡啶 -2- 基)-N-(嘧啶 -2- 基) 噻唑 -2- 胺；

4-(4- 甲基吡啶 -2- 基)-N-(嘧啶 -2- 基) 噻唑 -2- 胺；

4-(3,5- 二甲基吡啶 -2- 基)-N-(嘧啶 -2- 基) 噻唑 -2- 胺；

6-(2-(嘧啶 -2- 基氨基) 噻唑 -4- 基) 吡啶 -2- 醇；

N-(嘧啶 -2- 基)-4-(喹啉 -2- 基) 噻唑 -2- 胺；

N-(5- 氯嘧啶 -2- 基)-4-(吡啶 -2- 基) 噻唑 -2- 胺；

N-(5- 溴嘧啶 -2- 基)-4-(吡啶 -2- 基) 噻唑 -2- 胺；

N-(4- 甲基嘧啶 -2- 基)-4-(吡啶 -2- 基) 噻唑 -2- 胺；

4-(吡啶 -2- 基)-N-(4-(三氟甲基) 嘧啶 -2- 基) 噻唑 -2- 胺；

6- 甲基 -N-(4-(吡啶 -2- 基) 噻唑 -2- 基) 苯并 [d] 噻唑 -2- 胺；

5- 甲基 -4-(吡啶 -2- 基)-N-(嘧啶 -2- 基) 噻唑 -2- 胺；

5- 乙基 -4-(吡啶 -2- 基)-N-(嘧啶 -2- 基) 噻唑 -2- 胺；

5- 异丙基 -4-(吡啶 -2- 基)-N-(嘧啶 -2- 基) 噻唑 -2- 胺；

5- 戊基 -4-(吡啶 -2- 基)-N-(嘧啶 -2- 基) 噻唑 -2- 胺；

5- 环己基 -4-(吡啶 -2- 基)-N-(嘧啶 -2- 基) 噻唑 -2- 胺；

5- 壬基 -4-(吡啶 -2- 基)-N-(嘧啶 -2- 基) 噻唑 -2- 胺 ;

N- 异丙基 -4-(吡啶 -2- 基)-N-(嘧啶 -2- 基) 噻唑 -2- 胺 ;

N- 甲基 -4-(吡啶 -2- 基)-N-(嘧啶 -2- 基) 噻唑 -2- 胺 ;

N- 苄基 -4-(吡啶 -2- 基)-N-(嘧啶 -2- 基) 噻唑 -2- 胺 ;

2-((4-(吡啶 -2- 基) 噻唑 -2- 基)(嘧啶 -2- 基) 氨基) 乙醇 ;

5- 溴 -4-(吡啶 -2- 基)-N-(嘧啶 -2- 基) 噻唑 -2- 胺 ;

(4-(吡啶 -2- 基)-2-(嘧啶 -2- 基氨基) 噻唑 -5- 基) 甲醇 ;

(4-(吡啶 -2- 基)-2-(嘧啶 -2- 基氨基) 噻唑 -5- 基) 甲基乙酸酯 ;

(4-(吡啶 -2- 基)-2-(嘧啶 -2- 基氨基) 噻唑 -5- 基) 甲基丁酸酯 ;

4-(吡啶 -2- 基)-2-(嘧啶 -2- 基氨基) 噻唑 -5- 甲酸乙酯 ;

4-(4- 甲基吡啶 -2- 基)-2-(嘧啶 -2- 基氨基) 噻唑 -5- 甲酸乙酯 ;

4-(6- 甲基吡啶 -2- 基)-2-(嘧啶 -2- 基氨基) 噻唑 -5- 甲酸乙酯 ;

2-((4- 甲基嘧啶 -2- 基) 氨基)-4-(吡啶 -2- 基) 噻唑 -5- 甲酸乙酯 ;

4-(吡啶 -2- 基)-2-(嘧啶 -2- 基氨基) 噻唑 -5- 羧酸 ;

4-(吡啶 -2- 基)-2-(嘧啶 -2- 基氨基) 噻唑 -5- 甲酸甲酯 ;

2-(叔 - 丁基 (嘧啶 -2- 基) 氨基)-4-(吡啶 -2- 基) 噻唑 -5- 甲酸叔丁酯 ;

4-(吡啶 -2- 基)-2-(嘧啶 -2- 基氨基) 噻唑 -5- 甲酰胺 ;

N- 甲基 -4-(吡啶 -2- 基)-2-(嘧啶 -2- 基氨基) 噻唑 -5- 甲酰胺 ;

N- 苄基 -4-(吡啶 -2- 基)-2-(嘧啶 -2- 基氨基) 噻唑 -5- 甲酰胺 ;

24-(4-(((2,4- 二氨基蝶啶 -6- 基) 甲基)(甲基) 氨基) 苯甲酰氨基)-1,21- 二氧代 -1-(4-(吡啶 -2- 基)-2-(嘧啶 -2- 基氨基) 噻唑 -5- 基)-5,8,11,14,17- 五氧杂 -2,20- 二氮杂二十五烷 -25- 酸 ;

N-(31- 氧代 -35-((3aS,4S,6aR)-2- 氧代六氢 -1H- 噻吩并 [3,4-d] 咪唑 -4- 基)-3,6,9,12,15,18,21,24,27- 九氧杂 -30- 氮杂正三十五烷基)-4-(吡啶 -2- 基)-2-(嘧啶 -2- 基氨基) 噻唑 -5- 甲酰胺 ;

4- 吡啶 -2- 基 -2-(嘧啶 -2- 基氨基)- 噻唑 -5- 腈 ;

及其药学上可接受的形式。

7. 一种组合物,其包含有效量的至少一种根据权利要求 1 所述的化合物。

8. 根据权利要求 7 所述的组合物,其还包含至少一种赋形剂。

9. 根据权利要求 8 所述的组合物,其中所述至少一种化合物为至少一个选自以下的成员 :

4-(吡啶 -2- 基)-N-(嘧啶 -4- 基) 噻唑 -2- 胺 ;

4-(6- 溴吡啶 -2- 基)-N-(嘧啶 -2- 基) 噻唑 -2- 胺 ;

4-(4- 甲基吡啶 -2- 基)-N-(嘧啶 -2- 基) 噻唑 -2- 胺 ;

4-(3,5- 二甲基吡啶 -2- 基)-N-(嘧啶 -2- 基) 噻唑 -2- 胺 ;

6-(2-(嘧啶 -2- 基氨基) 噻唑 -4- 基) 吡啶 -2- 醇 ;

N-(嘧啶 -2- 基)-4-(喹啉 -2- 基) 噻唑 -2- 胺 ;

N-(5- 氯嘧啶 -2- 基)-4-(吡啶 -2- 基) 噻唑 -2- 胺 ;

N-(5- 溴嘧啶 -2- 基)-4-(吡啶 -2- 基) 噻唑 -2- 胺 ;

N-(4- 甲基嘧啶 -2- 基)-4-(吡啶 -2- 基) 噻唑 -2- 胺 ;

4-(吡啶 -2- 基)-N-(4-(三氟甲基) 嘧啶 -2- 基) 噻唑 -2- 胺 ;

6- 甲基 -N-(4-(吡啶 -2- 基) 噻唑 -2- 基) 苯并 [d] 噻唑 -2- 胺 ;

5- 甲基 -4-(吡啶 -2- 基)-N-(嘧啶 -2- 基) 噻唑 -2- 胺 ;

5- 乙基 -4-(吡啶 -2- 基)-N-(嘧啶 -2- 基) 噻唑 -2- 胺 ;

5- 异丙基 -4-(吡啶 -2- 基)-N-(嘧啶 -2- 基) 噻唑 -2- 胺 ;

5- 戊基 -4-(吡啶 -2- 基)-N-(嘧啶 -2- 基) 噻唑 -2- 胺 ;

5- 环己基 -4-(吡啶 -2- 基)-N-(嘧啶 -2- 基) 噻唑 -2- 胺 ;

5- 壬基 -4-(吡啶 -2- 基)-N-(嘧啶 -2- 基) 噻唑 -2- 胺 ;

N- 异丙基 -4-(吡啶 -2- 基)-N-(嘧啶 -2- 基) 噻唑 -2- 胺 ;

N- 甲基 -4-(吡啶 -2- 基)-N-(嘧啶 -2- 基) 噻唑 -2- 胺 ;

N- 苄基 -4-(吡啶 -2- 基)-N-(嘧啶 -2- 基) 噻唑 -2- 胺 ;

2-((4-(吡啶 -2- 基) 噻唑 -2- 基)(嘧啶 -2- 基) 氨基) 乙醇 ;

5- 溴 -4-(吡啶 -2- 基)-N-(嘧啶 -2- 基) 噻唑 -2- 胺 ;

(4-(吡啶 -2- 基)-2-(嘧啶 -2- 基氨基) 噻唑 -5- 基) 甲醇 ;

(4-(吡啶 -2- 基)-2-(嘧啶 -2- 基氨基) 噻唑 -5- 基) 甲基乙酸酯 ;

(4-(吡啶 -2- 基)-2-(嘧啶 -2- 基氨基) 噻唑 -5- 基) 甲基丁酸酯 ;

4-(吡啶 -2- 基)-2-(嘧啶 -2- 基氨基) 噻唑 -5- 甲酸乙酯 ;

4-(4- 甲基吡啶 -2- 基)-2-(嘧啶 -2- 基氨基) 噻唑 -5- 甲酸乙酯 ;

4-(6- 甲基吡啶 -2- 基)-2-(嘧啶 -2- 基氨基) 噻唑 -5- 甲酸乙酯 ;

2-((4- 甲基嘧啶 -2- 基) 氨基)-4-(吡啶 -2- 基) 噻唑 -5- 甲酸乙酯 ;

4-(吡啶 -2- 基)-2-(嘧啶 -2- 基氨基) 噻唑 -5- 羧酸 ;

4-(吡啶 -2- 基)-2-(嘧啶 -2- 基氨基) 噻唑 -5- 甲酸甲酯 ;

2-(叔 - 丁基 (嘧啶 -2- 基) 氨基)-4-(吡啶 -2- 基) 噻唑 -5- 甲酸叔丁酯 ;

4-(吡啶 -2- 基)-2-(嘧啶 -2- 基氨基) 噻唑 -5- 甲酰胺 ;

N- 甲基 -4-(吡啶 -2- 基)-2-(嘧啶 -2- 基氨基) 噻唑 -5- 甲酰胺 ;

N- 苄基 -4-(吡啶 -2- 基)-2-(嘧啶 -2- 基氨基) 噻唑 -5- 甲酰胺 ;

24-(4-(((2,4- 二氨基蝶啶 -6- 基) 甲基)(甲基) 氨基) 苯甲酰氨基)-1,21- 二氧代 -1-(4-(吡啶 -2- 基)-2-(嘧啶 -2- 基氨基) 噻唑 -5- 基)-5,8,11,14,17- 五氧杂 -2,20- 二氮杂二十五烷 -25- 酸 ;

N-(31- 氧代 -35-((3aS,4S,6aR)-2- 氧代六氢 -1H- 噻吩并 [3,4-d] 咪唑 -4- 基)-3,6,9,12,15,18,21,24,27- 九氧杂 -30- 氮杂正三十五烷基)-4-(吡啶 -2- 基)-2-(嘧啶 -2- 基氨基) 噻唑 -5- 甲酰胺 ;

4- 吡啶 -2- 基 -2-(嘧啶 -2- 基氨基)- 噻唑 -5- 腈

及其药学上可接受的形式。

10. 根据权利要求 8 所述的组合物,其中所述至少一种化合物为至少一个选自以下的成员 :

4-(吡啶 -2- 基)-N-(嘧啶 -4- 基) 噻唑 -2- 胺 ;

4-(6- 溴吡啶 -2- 基)-N-(嘧啶 -2- 基) 噻唑 -2- 胺 ;

4-(4- 甲基吡啶 -2- 基)-N-(嘧啶 -2- 基) 噻唑 -2- 胺 ;

4-(3,5- 二甲基吡啶 -2- 基)-N-(嘧啶 -2- 基) 噻唑 -2- 胺 ;

6-(2-(嘧啶 -2- 基氨基) 噻唑 -4- 基) 吡啶 -2- 醇 ;

N-(嘧啶 -2- 基)-4-(喹啉 -2- 基) 噻唑 -2- 胺 ;

N-(5- 氯嘧啶 -2- 基)-4-(吡啶 -2- 基) 噻唑 -2- 胺 ;

N-(5- 溴嘧啶 -2- 基)-4-(吡啶 -2- 基) 噻唑 -2- 胺 ;

N-(4- 甲基嘧啶 -2- 基)-4-(吡啶 -2- 基) 噻唑 -2- 胺 ;

4-(吡啶 -2- 基)-N-(4-(三氟甲基) 嘧啶 -2- 基) 噻唑 -2- 胺 ;

6- 甲基 -N-(4-(吡啶 -2- 基) 噻唑 -2- 基) 苯并 [d] 噻唑 -2- 胺 ;

5- 甲基 -4-(吡啶 -2- 基)-N-(嘧啶 -2- 基) 噻唑 -2- 胺 ;

5- 乙基 -4-(吡啶 -2- 基)-N-(嘧啶 -2- 基) 噻唑 -2- 胺 ;

5- 异丙基 -4-(吡啶 -2- 基)-N-(嘧啶 -2- 基) 噻唑 -2- 胺 ;

5- 戊基 -4-(吡啶 -2- 基)-N-(嘧啶 -2- 基) 噻唑 -2- 胺 ;

5- 环己基 -4-(吡啶 -2- 基)-N-(嘧啶 -2- 基) 噻唑 -2- 胺 ;

5- 壬基 -4-(吡啶 -2- 基)-N-(嘧啶 -2- 基) 噻唑 -2- 胺 ;

N- 异丙基 -4-(吡啶 -2- 基)-N-(嘧啶 -2- 基) 噻唑 -2- 胺 ;

N- 甲基 -4-(吡啶 -2- 基)-N-(嘧啶 -2- 基) 噻唑 -2- 胺 ;

N- 苄基 -4-(吡啶 -2- 基)-N-(嘧啶 -2- 基) 噻唑 -2- 胺 ;

2-((4-(吡啶 -2- 基) 噻唑 -2- 基)(嘧啶 -2- 基) 氨基) 乙醇 ;

5- 溴 -4-(吡啶 -2- 基)-N-(嘧啶 -2- 基) 噻唑 -2- 胺 ;

(4-(吡啶 -2- 基)-2-(嘧啶 -2- 基氨基) 噻唑 -5- 基) 甲醇 ;

(4-(吡啶 -2- 基)-2-(嘧啶 -2- 基氨基) 噻唑 -5- 基) 甲基乙酸酯 ;

(4-(吡啶 -2- 基)-2-(嘧啶 -2- 基氨基) 噻唑 -5- 基) 甲基丁酸酯 ;

4-(吡啶 -2- 基)-2-(嘧啶 -2- 基氨基) 噻唑 -5- 甲酸乙酯 ;

4-(4- 甲基吡啶 -2- 基)-2-(嘧啶 -2- 基氨基) 噻唑 -5- 甲酸乙酯 ;

4-(6- 甲基吡啶 -2- 基)-2-(嘧啶 -2- 基氨基) 噻唑 -5- 甲酸乙酯 ;

2-((4- 甲基嘧啶 -2- 基) 氨基)-4-(吡啶 -2- 基) 噻唑 -5- 甲酸乙酯 ;

4-(吡啶 -2- 基)-2-(嘧啶 -2- 基氨基) 噻唑 -5- 羧酸 ;

4-(吡啶 -2- 基)-2-(嘧啶 -2- 基氨基) 噻唑 -5- 甲酸甲酯 ;

2-(叔 - 丁基 (嘧啶 -2- 基) 氨基)-4-(吡啶 -2- 基) 噻唑 -5- 甲酸叔丁酯 ;

4-(吡啶 -2- 基)-2-(嘧啶 -2- 基氨基) 噻唑 -5- 甲酰胺 ;

N- 甲基 -4-(吡啶 -2- 基)-2-(嘧啶 -2- 基氨基) 噻唑 -5- 甲酰胺 ;

N- 苄基 -4-(吡啶 -2- 基)-2-(嘧啶 -2- 基氨基) 噻唑 -5- 甲酰胺 ;

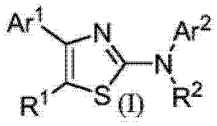
24-(4-(((2,4- 二氨基蝶啶 -6- 基) 甲基)(甲基) 氨基) 苯甲酰氨基)-1,21- 二氧代 -1-(4-(吡啶 -2- 基)-2-(嘧啶 -2- 基氨基) 噻唑 -5- 基)-5,8,11,14,17- 五氧杂 -2,20- 二氮杂二十五烷 -25- 酸 ;

N-(31- 氧代 -35-((3aS,4S,6aR)-2- 氧代六氢 -1H- 噻吩并 [3,4-d] 咪唑 -4- 基)-3,6,9,12,15,18,21,24,27- 九氧杂 -30- 氮杂正三十五烷基)-4-(吡啶 -2- 基)-2-(嘧啶 -2- 基氨基) 噻唑 -5- 甲酰胺 ;

4- 吡啶 -2- 基 -2-(嘧啶 -2- 基氨基)- 噻唑 -5- 腈

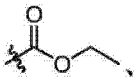
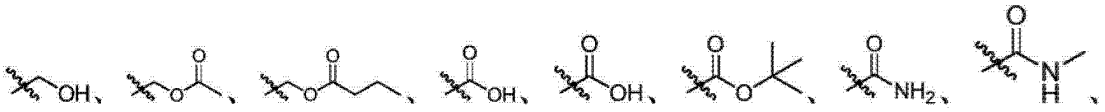
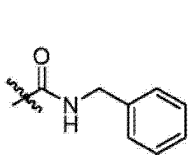
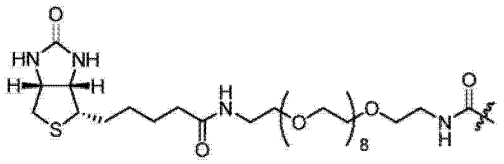
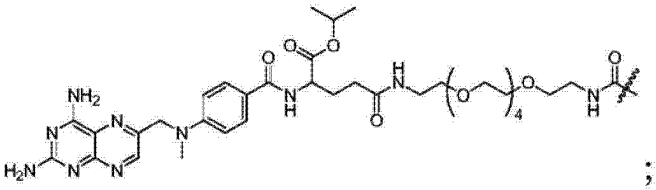
及其药学上可接受的形式。

11. 一种治疗与细胞生长失调相关的疾病的方法，所述方法包括向受试者施用有效量的至少一种所述式 (I) 化合物以治疗所述疾病，

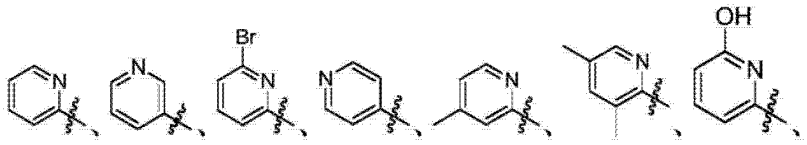
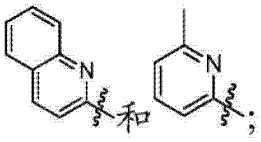


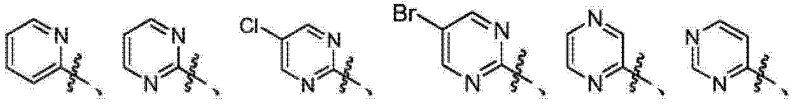
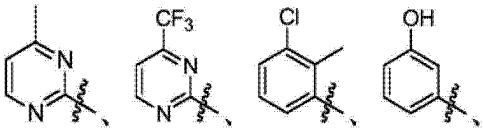
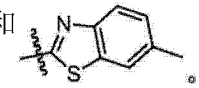
(I)

包括其水合物、溶剂合物、药学上可接受的盐、前药和复合物以治疗所述疾病，其中：

R^1 选自氢、C_1-C_9 直链烷基、异丙基、环己基、溴、氰基、  、  、  、  和  ；

R^2 选自氢、甲基、异丙基、叔丁基、苄基和  ；

Ar^1 选自苯基、  、  和；

Ar^2 选自苯基、  、  和  。

12. 根据权利要求 11 所述的方法，其中所述至少一种化合物为至少一个选自以下的成员

4-(吡啶 -2- 基)-N-(嘧啶 -2- 基) 噻唑 -2- 胺；

N,4- 二苯基噻唑 -2- 胺；

N- 苯基 -4-(吡啶 -2- 基) 噻唑 -2- 胺 ;
4- 苯基 -N-(嘧啶 -2- 基) 噻唑 -2- 胺 ;
N,4- 二 (吡啶 -2- 基) 噻唑 -2- 胺 ;
4-(吡啶 -3- 基)-N-(嘧啶 -2- 基) 噻唑 -2- 胺 ;
4-(吡啶 -4- 基)-N-(嘧啶 -2- 基) 噻唑 -2- 胺 ;
N-(吡嗪 -2- 基)-4-(吡啶 -2- 基) 噻唑 -2- 胺 ;
4-(吡啶 -2- 基)-N-(嘧啶 -4- 基) 噻唑 -2- 胺 ;
4-(6- 溴吡啶 -2- 基)-N-(嘧啶 -2- 基) 噻唑 -2- 胺 ;
4-(4- 甲基吡啶 -2- 基)-N-(嘧啶 -2- 基) 噻唑 -2- 胺 ;
4-(3,5- 二甲基吡啶 -2- 基)-N-(嘧啶 -2- 基) 噻唑 -2- 胺 ;
6-(2-(嘧啶 -2- 基氨基) 噻唑 -4- 基) 吡啶 -2- 醇 ;
N-(嘧啶 -2- 基)-4-(喹啉 -2- 基) 噻唑 -2- 胺 ;
N-(5- 氯嘧啶 -2- 基)-4-(吡啶 -2- 基) 噻唑 -2- 胺 ;
N-(5- 溴嘧啶 -2- 基)-4-(吡啶 -2- 基) 噻唑 -2- 胺 ;
N-(4- 甲基嘧啶 -2- 基)-4-(吡啶 -2- 基) 噻唑 -2- 胺 ;
4-(吡啶 -2- 基)-N-(4-(三氟甲基) 嘧啶 -2- 基) 噻唑 -2- 胺 ;
6- 甲基 -N-(4-(吡啶 -2- 基) 噻唑 -2- 基) 苯并 [d] 噻唑 -2- 胺 ;
5- 甲基 -4-(吡啶 -2- 基)-N-(嘧啶 -2- 基) 噻唑 -2- 胺 ;
5- 乙基 -4-(吡啶 -2- 基)-N-(嘧啶 -2- 基) 噻唑 -2- 胺 ;
5- 异丙基 -4-(吡啶 -2- 基)-N-(嘧啶 -2- 基) 噻唑 -2- 胺 ;
5- 戊基 -4-(吡啶 -2- 基)-N-(嘧啶 -2- 基) 噻唑 -2- 胺 ;
5- 环己基 -4-(吡啶 -2- 基)-N-(嘧啶 -2- 基) 噻唑 -2- 胺 ;
5- 壬基 -4-(吡啶 -2- 基)-N-(嘧啶 -2- 基) 噻唑 -2- 胺 ;
N- 异丙基 -4-(吡啶 -2- 基)-N-(嘧啶 -2- 基) 噻唑 -2- 胺 ;
N- 甲基 -4-(吡啶 -2- 基)-N-(嘧啶 -2- 基) 噻唑 -2- 胺 ;
N- 苄基 -4-(吡啶 -2- 基)-N-(嘧啶 -2- 基) 噻唑 -2- 胺 ;
2-((4-(吡啶 -2- 基) 噻唑 -2- 基)(嘧啶 -2- 基) 氨基) 乙醇 ;
5- 溴 -4-(吡啶 -2- 基)-N-(嘧啶 -2- 基) 噻唑 -2- 胺 ;
(4-(吡啶 -2- 基)-2-(嘧啶 -2- 基氨基) 噻唑 -5- 基) 甲醇 ;
(4-(吡啶 -2- 基)-2-(嘧啶 -2- 基氨基) 噻唑 -5- 基) 甲基乙酸酯 ;
(4-(吡啶 -2- 基)-2-(嘧啶 -2- 基氨基) 噻唑 -5- 基) 甲基丁酸酯 ;
4-(吡啶 -2- 基)-2-(嘧啶 -2- 基氨基) 噻唑 -5- 甲酸乙酯 ;
4-(4- 甲基吡啶 -2- 基)-2-(嘧啶 -2- 基氨基) 噻唑 -5- 甲酸乙酯 ;
4-(6- 甲基吡啶 -2- 基)-2-(嘧啶 -2- 基氨基) 噻唑 -5- 甲酸乙酯 ;
2-((4- 甲基嘧啶 -2- 基) 氨基)-4-(吡啶 -2- 基) 噻唑 -5- 甲酸乙酯 ;
4-(吡啶 -2- 基)-2-(嘧啶 -2- 基氨基) 噻唑 -5- 羧酸 ;
4-(吡啶 -2- 基)-2-(嘧啶 -2- 基氨基) 噻唑 -5- 甲酸甲酯 ;
2-(叔 - 丁基 (嘧啶 -2- 基) 氨基)-4-(吡啶 -2- 基) 噻唑 -5- 甲酸叔丁酯 ;
4-(吡啶 -2- 基)-2-(嘧啶 -2- 基氨基) 噻唑 -5- 甲酰胺 ;

N- 甲基 -4-(吡啶 -2- 基)-2-(嘧啶 -2- 基氨基) 噻唑 -5- 甲酰胺 ;

N- 苄基 -4-(吡啶 -2- 基)-2-(嘧啶 -2- 基氨基) 噻唑 -5- 甲酰胺 ;

24-(4-(((2,4- 二氨基蝶啶 -6- 基) 甲基)(甲基) 氨基) 苯甲酰氨基)-1,21- 二氧代 -1-(4-(吡啶 -2- 基)-2-(嘧啶 -2- 基氨基) 噻唑 -5- 基)-5,8,11,14,17- 五氧杂 -2,20- 二氮杂二十五烷 -25- 酸 ;

N-(31- 氧 代 -35-((3aS,4S,6aR)-2- 氧 代 六 氢 -1H- 噻 吩 并 [3,4-d] 咪唑 -4- 基)-3,6,9,12,15,18,21,24,27- 九 氧 杂 -30- 氮 杂 正 三 十 五 烷 基)-4-(吡啶 -2- 基)-2-(嘧啶 -2- 基氨基) 噻唑 -5- 甲酰胺 ;

4- 吡啶 -2- 基 -2-(嘧啶 -2- 基氨基)- 噻唑 -5- 腈 ;

3-(4- 苯基 - 噻唑 -2- 基氨基)- 苯酚 ;

(3- 氯 -2- 甲基 - 苯基)-(4- 吡啶 -2- 基 - 噻唑 -2- 基)- 胺 ;

及其药学上可接受的形式。

13. 根据权利要求 11 所述的方法,其中所述至少一种化合物以还包含至少一种赋形剂的组合物的形式施用。

14. 根据权利要求 13 所述的方法,其中所述至少一种化合物为至少一个选自以下的成员

4-(吡啶 -2- 基)-N-(嘧啶 -2- 基) 噻唑 -2- 胺 ;

N,4- 二苯基噻唑 -2- 胺 ;

N- 苯基 -4-(吡啶 -2- 基) 噻唑 -2- 胺 ;

4- 苯基 -N-(嘧啶 -2- 基) 噻唑 -2- 胺 ;

N,4- 二 (吡啶 -2- 基) 噻唑 -2- 胺 ;

4-(吡啶 -3- 基)-N-(嘧啶 -2- 基) 噻唑 -2- 胺 ;

4-(吡啶 -4- 基)-N-(嘧啶 -2- 基) 噻唑 -2- 胺 ;

N-(吡嗪 -2- 基)-4-(吡啶 -2- 基) 噻唑 -2- 胺 ;

4-(吡啶 -2- 基)-N-(嘧啶 -4- 基) 噻唑 -2- 胺 ;

4-(6- 溴吡啶 -2- 基)-N-(嘧啶 -2- 基) 噻唑 -2- 胺 ;

4-(4- 甲基吡啶 -2- 基)-N-(嘧啶 -2- 基) 噻唑 -2- 胺 ;

4-(3,5- 二甲基吡啶 -2- 基)-N-(嘧啶 -2- 基) 噻唑 -2- 胺 ;

6-(2-(嘧啶 -2- 基氨基) 噻唑 -4- 基) 吡啶 -2- 醇 ;

N-(嘧啶 -2- 基)-4-(喹啉 -2- 基) 噻唑 -2- 胺 ;

N-(5- 氯嘧啶 -2- 基)-4-(吡啶 -2- 基) 噻唑 -2- 胺 ;

N-(5- 溴嘧啶 -2- 基)-4-(吡啶 -2- 基) 噻唑 -2- 胺 ;

N-(4- 甲基嘧啶 -2- 基)-4-(吡啶 -2- 基) 噻唑 -2- 胺 ;

4-(吡啶 -2- 基)-N-(4-(三氟甲基) 嘧啶 -2- 基) 噻唑 -2- 胺 ;

6- 甲基 -N-(4-(吡啶 -2- 基) 噻唑 -2- 基) 苯并 [d] 噻唑 -2- 胺 ;

5- 甲基 -4-(吡啶 -2- 基)-N-(嘧啶 -2- 基) 噻唑 -2- 胺 ;

5- 乙基 -4-(吡啶 -2- 基)-N-(嘧啶 -2- 基) 噻唑 -2- 胺 ;

5- 异丙基 -4-(吡啶 -2- 基)-N-(嘧啶 -2- 基) 噻唑 -2- 胺 ;

5- 戊基 -4-(吡啶 -2- 基)-N-(嘧啶 -2- 基) 噻唑 -2- 胺 ;

5- 环己基 -4-(吡啶 -2- 基)-N-(嘧啶 -2- 基) 噻唑 -2- 胺 ;

5- 壬基 -4-(吡啶 -2- 基)-N-(嘧啶 -2- 基) 噻唑 -2- 胺 ;

N- 异丙基 -4-(吡啶 -2- 基)-N-(嘧啶 -2- 基) 噻唑 -2- 胺 ;

N- 甲基 -4-(吡啶 -2- 基)-N-(嘧啶 -2- 基) 噻唑 -2- 胺 ;

N- 苄基 -4-(吡啶 -2- 基)-N-(嘧啶 -2- 基) 噻唑 -2- 胺 ;

2-((4-(吡啶 -2- 基) 噻唑 -2- 基)(嘧啶 -2- 基) 氨基) 乙醇 ;

5- 溴 -4-(吡啶 -2- 基)-N-(嘧啶 -2- 基) 噻唑 -2- 胺 ;

(4-(吡啶 -2- 基)-2-(嘧啶 -2- 基氨基) 噻唑 -5- 基) 甲醇 ;

(4-(吡啶 -2- 基)-2-(嘧啶 -2- 基氨基) 噻唑 -5- 基) 甲基乙酸酯 ;

(4-(吡啶 -2- 基)-2-(嘧啶 -2- 基氨基) 噻唑 -5- 基) 甲基丁酸酯 ;

4-(吡啶 -2- 基)-2-(嘧啶 -2- 基氨基) 噻唑 -5- 甲酸乙酯 ;

4-(4- 甲基吡啶 -2- 基)-2-(嘧啶 -2- 基氨基) 噻唑 -5- 甲酸乙酯 ;

4-(6- 甲基吡啶 -2- 基)-2-(嘧啶 -2- 基氨基) 噻唑 -5- 甲酸乙酯 ;

2-((4- 甲基嘧啶 -2- 基) 氨基)-4-(吡啶 -2- 基) 噻唑 -5- 甲酸乙酯 ;

4-(吡啶 -2- 基)-2-(嘧啶 -2- 基氨基) 噻唑 -5- 羧酸 ;

4-(吡啶 -2- 基)-2-(嘧啶 -2- 基氨基) 噻唑 -5- 甲酸甲酯 ;

2-(叔 - 丁基 (嘧啶 -2- 基) 氨基)-4-(吡啶 -2- 基) 噻唑 -5- 甲酸叔丁酯 ;

4-(吡啶 -2- 基)-2-(嘧啶 -2- 基氨基) 噻唑 -5- 甲酰胺 ;

N- 甲基 -4-(吡啶 -2- 基)-2-(嘧啶 -2- 基氨基) 噻唑 -5- 甲酰胺 ;

N- 苄基 -4-(吡啶 -2- 基)-2-(嘧啶 -2- 基氨基) 噻唑 -5- 甲酰胺 ;

24-(4-(((2,4- 二氨基蝶啶 -6- 基) 甲基)(甲基) 氨基) 苯甲酰氨基)-1,21- 二氧代 -1-(4-(吡啶 -2- 基)-2-(嘧啶 -2- 基氨基) 噻唑 -5- 基)-5,8,11,14,17- 五氧杂 -2,20- 二氮杂二十五烷 -25- 酸 ;

N-(31- 氧代 -35-((3aS,4S,6aR)-2- 氧代六氢 -1H- 噻吩并 [3,4-d] 咪唑 -4- 基)-3,6,9,12,15,18,21,24,27- 九氧杂 -30- 氮杂正三十五烷基)-4-(吡啶 -2- 基)-2-(嘧啶 -2- 基氨基) 噻唑 -5- 甲酰胺 ;

4- 吡啶 -2- 基 -2-(嘧啶 -2- 基氨基)- 噻唑 -5- 腈 ;

3-(4- 苯基 - 噻唑 -2- 基氨基)- 苯酚 ;

(3- 氯 -2- 甲基 - 苯基)-(4- 吡啶 -2- 基 - 噻唑 -2- 基)- 胺 ;

及其药学上可接受的形式。

15. 根据权利要求 11 所述的方法,其中所述与细胞生长失调相关的疾病是癌症。

16. 根据权利要求 11 所述的方法,其中所述与细胞生长失调相关的疾病是肝细胞癌。

17. 根据权利要求 11 所述的方法,其中所述与细胞生长失调相关的疾病是原发性肝癌。

18. 根据权利要求 11 所述的方法,其中所述与细胞生长失调相关的疾病是肝母细胞瘤。

19. 根据权利要求 11 所述的方法,其中所述与细胞生长失调相关的疾病是乳腺癌。

20. 根据权利要求 11 所述的方法,其中所述与细胞生长失调相关的疾病是卵巢癌。

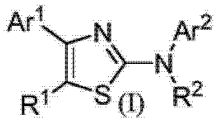
21. 根据权利要求 11 所述的方法,其中所述与细胞生长失调相关的疾病是肺癌。

22. 根据权利要求 11 所述的方法，其中所述与细胞生长失调相关的疾病是白血病。

23. 根据权利要求 11 所述的方法，其中所述与细胞生长失调相关的疾病是胆管癌。

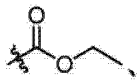
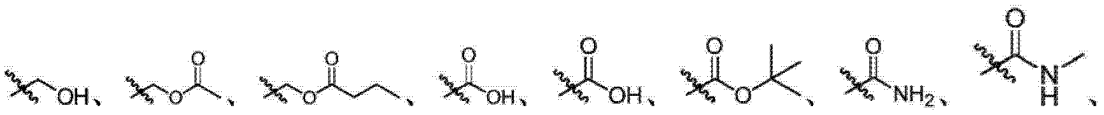
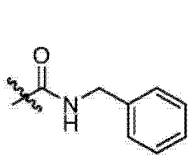
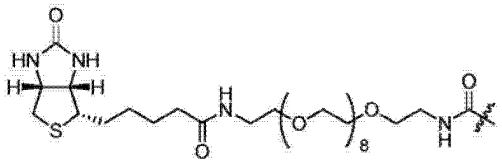
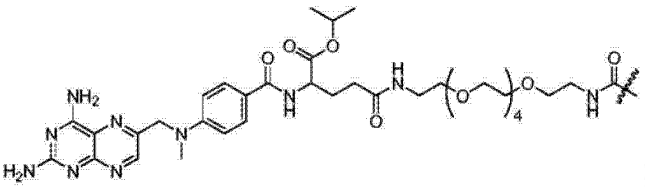
24. 根据权利要求 11 所述的方法，其中所述与细胞生长失调相关的疾病是转移性疾病。

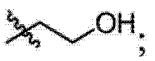
25. 一种治疗与病毒感染肝脏有关的疾病的方法，所述方法包括向受试者施用有效量的至少一种所述式 (I) 化合物，

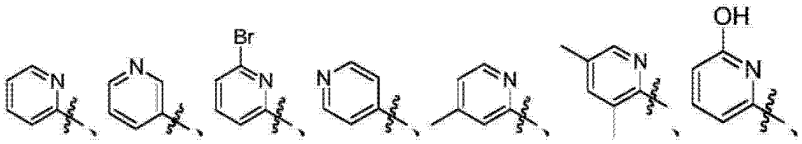
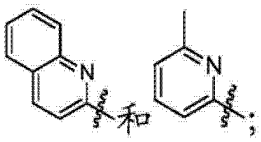


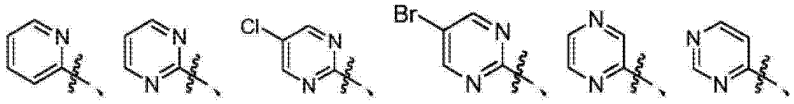
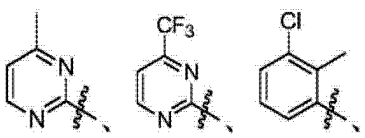
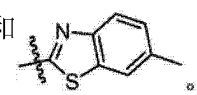
(I)

包括其水合物、溶剂合物、药学上可接受的盐、前药和复合物以治疗所述疾病，其中：

R^1 选自氢、C_1-C_9 直链烷基、异丙基、环己基、溴、氰基、  、  、  、  和  ；

R^2 选自氢、甲基、异丙基、叔丁基、苄基和  ；

Ar^1 选自苯基、  、  和；

Ar^2 选自苯基、  、  和  。

26. 根据权利要求 25 所述的方法，其中所述至少一种化合物为至少一个选自以下的成员

4-(吡啶-2-基)-N-(嘧啶-2-基)噻唑-2-胺;

N,4-二苯基噻唑-2-胺;

N-苯基-4-(吡啶-2-基)噻唑-2-胺;

4-苯基-N-(嘧啶-2-基)噻唑-2-胺;

N,4-二(吡啶-2-基)噻唑-2-胺;

4-(吡啶-3-基)-N-(嘧啶-2-基)噻唑-2-胺;

4-(吡啶-4-基)-N-(嘧啶-2-基)噻唑-2-胺;

N-(吡嗪-2-基)-4-(吡啶-2-基)噻唑-2-胺;

4-(吡啶-2-基)-N-(嘧啶-4-基)噻唑-2-胺;

4-(6-溴吡啶-2-基)-N-(嘧啶-2-基)噻唑-2-胺;

4-(4-甲基吡啶-2-基)-N-(嘧啶-2-基)噻唑-2-胺;

4-(3,5-二甲基吡啶-2-基)-N-(嘧啶-2-基)噻唑-2-胺;

6-(2-(嘧啶-2-基氨基)噻唑-4-基)吡啶-2-醇;

N-(嘧啶-2-基)-4-(喹啉-2-基)噻唑-2-胺;

N-(5-氯嘧啶-2-基)-4-(吡啶-2-基)噻唑-2-胺;

N-(5-溴嘧啶-2-基)-4-(吡啶-2-基)噻唑-2-胺;

N-(4-甲基嘧啶-2-基)-4-(吡啶-2-基)噻唑-2-胺;

4-(吡啶-2-基)-N-(4-(三氟甲基)嘧啶-2-基)噻唑-2-胺;

6-甲基-N-(4-(吡啶-2-基)噻唑-2-基)苯并[d]噻唑-2-胺;

5-甲基-4-(吡啶-2-基)-N-(嘧啶-2-基)噻唑-2-胺;

5-乙基-4-(吡啶-2-基)-N-(嘧啶-2-基)噻唑-2-胺;

5-异丙基-4-(吡啶-2-基)-N-(嘧啶-2-基)噻唑-2-胺;

5-戊基-4-(吡啶-2-基)-N-(嘧啶-2-基)噻唑-2-胺;

5-环己基-4-(吡啶-2-基)-N-(嘧啶-2-基)噻唑-2-胺;

5-壬基-4-(吡啶-2-基)-N-(嘧啶-2-基)噻唑-2-胺;

N-异丙基-4-(吡啶-2-基)-N-(嘧啶-2-基)噻唑-2-胺;

N-甲基-4-(吡啶-2-基)-N-(嘧啶-2-基)噻唑-2-胺;

N-苄基-4-(吡啶-2-基)-N-(嘧啶-2-基)噻唑-2-胺;

2-((4-(吡啶-2-基)噻唑-2-基)(嘧啶-2-基)氨基)乙醇;

5-溴-4-(吡啶-2-基)-N-(嘧啶-2-基)噻唑-2-胺;

(4-(吡啶-2-基)-2-(嘧啶-2-基氨基)噻唑-5-基)甲醇;

(4-(吡啶-2-基)-2-(嘧啶-2-基氨基)噻唑-5-基)甲基乙酸酯;

(4-(吡啶-2-基)-2-(嘧啶-2-基氨基)噻唑-5-基)甲基丁酸酯;

4-(吡啶-2-基)-2-(嘧啶-2-基氨基)噻唑-5-甲酸乙酯;

4-(4-甲基吡啶-2-基)-2-(嘧啶-2-基氨基)噻唑-5-甲酸乙酯;

4-(6-甲基吡啶-2-基)-2-(嘧啶-2-基氨基)噻唑-5-甲酸乙酯;

2-((4-甲基嘧啶-2-基)氨基)-4-(吡啶-2-基)噻唑-5-甲酸乙酯;

4-(吡啶-2-基)-2-(嘧啶-2-基氨基)噻唑-5-羧酸;

4-(吡啶-2-基)-2-(嘧啶-2-基氨基)噻唑-5-甲酸甲酯;

2-(叔-丁基(嘧啶-2-基)氨基)-4-(吡啶-2-基)噻唑-5-甲酸叔丁酯;

4-(吡啶-2-基)-2-(嘧啶-2-基氨基)噻唑-5-甲酰胺;

N-甲基-4-(吡啶-2-基)-2-(嘧啶-2-基氨基)噻唑-5-甲酰胺;

N-苄基-4-(吡啶-2-基)-2-(嘧啶-2-基氨基)噻唑-5-甲酰胺;

24-(4-(((2,4-二氨基蝶啶-6-基)甲基)(甲基)氨基)苯甲酰氨基)-1,21-二氧代-1-(4-(吡啶-2-基)-2-(嘧啶-2-基氨基)噻唑-5-基)-5,8,11,14,17-五氧杂-2,20-二氮杂二十五烷-25-酸;

N-(31-氧代-35-((3aS,4S,6aR)-2-氧代六氢-1H-噻吩并[3,4-d]咪唑-4-基)-3,6,9,12,15,18,21,24,27-九氧杂-30-氮杂正三十五烷基)-4-(吡啶-2-基)-2-(嘧啶-2-基氨基)噻唑-5-甲酰胺;

4-吡啶-2-基-2-(嘧啶-2-基氨基)-噻唑-5-腈;

3-(4-苯基-噻唑-2-基氨基)-苯酚;

(3-氯-2-甲基-苯基)-(4-吡啶-2-基-噻唑-2-基)-胺;

及其药学上可接受的形式。

27. 根据权利要求25所述的方法,其中所述至少一种化合物以还包含至少一种赋形剂的组合物的形式施用。

28. 根据权利要求27所述的方法,其中所述至少一种化合物为至少一个选自以下的成员

4-(吡啶-2-基)-N-(嘧啶-2-基)噻唑-2-胺;

N,4-二苯基噻唑-2-胺;

N-苯基-4-(吡啶-2-基)噻唑-2-胺;

4-苯基-N-(嘧啶-2-基)噻唑-2-胺;

N,4-二(吡啶-2-基)噻唑-2-胺;

4-(吡啶-3-基)-N-(嘧啶-2-基)噻唑-2-胺;

4-(吡啶-4-基)-N-(嘧啶-2-基)噻唑-2-胺;

N-(吡嗪-2-基)-4-(吡啶-2-基)噻唑-2-胺;

4-(吡啶-2-基)-N-(嘧啶-4-基)噻唑-2-胺;

4-(6-溴吡啶-2-基)-N-(嘧啶-2-基)噻唑-2-胺;

4-(4-甲基吡啶-2-基)-N-(嘧啶-2-基)噻唑-2-胺;

4-(3,5-二甲基吡啶-2-基)-N-(嘧啶-2-基)噻唑-2-胺;

6-(2-(嘧啶-2-基氨基)噻唑-4-基)吡啶-2-醇;

N-(嘧啶-2-基)-4-(喹啉-2-基)噻唑-2-胺;

N-(5-氯嘧啶-2-基)-4-(吡啶-2-基)噻唑-2-胺;

N-(5-溴嘧啶-2-基)-4-(吡啶-2-基)噻唑-2-胺;

N-(4-甲基嘧啶-2-基)-4-(吡啶-2-基)噻唑-2-胺;

4-(吡啶-2-基)-N-(4-(三氟甲基)嘧啶-2-基)噻唑-2-胺;

6-甲基-N-(4-(吡啶-2-基)噻唑-2-基)苯并[d]噻唑-2-胺;

5-甲基-4-(吡啶-2-基)-N-(嘧啶-2-基)噻唑-2-胺;

5-乙基-4-(吡啶-2-基)-N-(嘧啶-2-基)噻唑-2-胺;

5- 异丙基 -4-(吡啶 -2- 基)-N-(嘧啶 -2- 基) 噻唑 -2- 胺 ;

5- 戊基 -4-(吡啶 -2- 基)-N-(嘧啶 -2- 基) 噻唑 -2- 胺 ;

5- 环己基 -4-(吡啶 -2- 基)-N-(嘧啶 -2- 基) 噻唑 -2- 胺 ;

5- 壬基 -4-(吡啶 -2- 基)-N-(嘧啶 -2- 基) 噻唑 -2- 胺 ;

N- 异丙基 -4-(吡啶 -2- 基)-N-(嘧啶 -2- 基) 噻唑 -2- 胺 ;

N- 甲基 -4-(吡啶 -2- 基)-N-(嘧啶 -2- 基) 噻唑 -2- 胺 ;

N- 苄基 -4-(吡啶 -2- 基)-N-(嘧啶 -2- 基) 噻唑 -2- 胺 ;

2-((4-(吡啶 -2- 基) 噻唑 -2- 基)(嘧啶 -2- 基) 氨基) 乙醇 ;

5- 溴 -4-(吡啶 -2- 基)-N-(嘧啶 -2- 基) 噻唑 -2- 胺 ;

(4-(吡啶 -2- 基)-2-(嘧啶 -2- 基氨基) 噻唑 -5- 基) 甲醇 ;

(4-(吡啶 -2- 基)-2-(嘧啶 -2- 基氨基) 噻唑 -5- 基) 甲基乙酸酯 ;

(4-(吡啶 -2- 基)-2-(嘧啶 -2- 基氨基) 噻唑 -5- 基) 甲基丁酸酯 ;

4-(吡啶 -2- 基)-2-(嘧啶 -2- 基氨基) 噻唑 -5- 甲酸乙酯 ;

4-(4- 甲基吡啶 -2- 基)-2-(嘧啶 -2- 基氨基) 噻唑 -5- 甲酸乙酯 ;

4-(6- 甲基吡啶 -2- 基)-2-(嘧啶 -2- 基氨基) 噻唑 -5- 甲酸乙酯 ;

2-((4- 甲基嘧啶 -2- 基) 氨基)-4-(吡啶 -2- 基) 噻唑 -5- 甲酸乙酯 ;

4-(吡啶 -2- 基)-2-(嘧啶 -2- 基氨基) 噻唑 -5- 羧酸 ;

4-(吡啶 -2- 基)-2-(嘧啶 -2- 基氨基) 噻唑 -5- 甲酸甲酯 ;

2-(叔 - 丁基 (嘧啶 -2- 基) 氨基)-4-(吡啶 -2- 基) 噻唑 -5- 甲酸叔丁酯 ;

4-(吡啶 -2- 基)-2-(嘧啶 -2- 基氨基) 噻唑 -5- 甲酰胺 ;

N- 甲基 -4-(吡啶 -2- 基)-2-(嘧啶 -2- 基氨基) 噻唑 -5- 甲酰胺 ;

N- 苄基 -4-(吡啶 -2- 基)-2-(嘧啶 -2- 基氨基) 噻唑 -5- 甲酰胺 ;

24-(4-(((2,4- 二氨基蝶啶 -6- 基) 甲基)(甲基) 氨基) 苯甲酰氨基)-1,21- 二氧代 -1-(4-(吡啶 -2- 基)-2-(嘧啶 -2- 基氨基) 噻唑 -5- 基)-5,8,11,14,17- 五氧杂 -2,20- 二氮杂二十五烷 -25- 酸 ;

N-(31- 氧代 -35-((3aS,4S,6aR)-2- 氧代六氢 -1H- 噻吩并 [3,4-d] 咪唑 -4- 基)-3,6,9,12,15,18,21,24,27- 九氧杂 -30- 氮杂正三十五烷基)-4-(吡啶 -2- 基)-2-(嘧啶 -2- 基氨基) 噻唑 -5- 甲酰胺 ;

4- 吡啶 -2- 基 -2-(嘧啶 -2- 基氨基)- 噻唑 -5- 腈 ;

3-(4- 苯基 - 噻唑 -2- 基氨基)- 苯酚 ;

(3- 氯 -2- 甲基 - 苯基)-(4- 吡啶 -2- 基 - 噻唑 -2- 基)- 胺 ;

及其药学上可接受的形式。

29. 根据权利要求 25 所述的方法,其中所述病毒是肝炎病毒。

30. 根据权利要求 25 所述的方法,其中所述肝炎病毒是甲型肝炎病毒。

31. 根据权利要求 25 所述的方法,其中所述肝炎病毒是乙型肝炎病毒。

32. 根据权利要求 25 所述的方法,其中所述肝炎病毒是丙型肝炎病毒。

33. 根据权利要求 25 所述的方法,其中所述肝炎病毒是丁型肝炎病毒。

34. 根据权利要求 25 所述的方法,其中所述肝炎病毒是戊型肝炎病毒。

35. 根据权利要求 25 所述的方法,其中所述病毒是感染肝脏的任何病毒。

作为包括肝细胞癌在内的癌症的抑制剂和作为肝炎病毒复制抑制剂的取代的氨基噻唑

[0001] 相关申请的交叉引用

[0002] 本申请要求于 2011 年 10 月 4 日提交的美国临时专利申请 No.61542907 的权益，该临时申请通过引用整体并入本文。

发明领域

[0003] 本发明描述了用于治疗癌症（包括原发性肝癌、肝细胞癌和胆管癌）和用于治疗病毒性肝炎感染（包括但不限于甲型肝炎病毒感染、乙型肝炎病毒感染、丙型肝炎病毒感染、丁型肝炎病毒感染和戊型肝炎病毒感染）以及其它感染肝脏的病毒物种的化合物和方法。

[0004] 发明背景

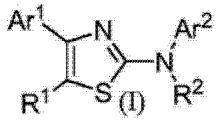
[0005] 目前在美国，原发性肝癌是男性中因癌症死亡的第五位最常见病因，而在女性中则是第九位最常见病因，并且患病人数逐年增加。最近的数据表明，在 2008 年估计有 21,370 例肝癌和胆管癌的新发病例，其中大多数是肝细胞癌 (HCC)，有 18,410 例死亡 (Institute,N.C.,SEER Cancer Statistics Review,1975-2005,Ries LAG, 等 , 编辑 , 2008)。在世界范围内，该病是第四位最常见的癌症，在 2008 年报告了大约 663,00 例致死病例；基于目前的趋势和基准模型，预期发病率在 2015 年将上升至 756,000 例，并在 2030 年上升至 955,000 例 (Mathers,C.D. 和 D.Loncar,Projections of global mortality and burden of disease from2002to2030.PLoS Med,2006.3,11,p.e442.)。尽管肝癌在美国相对少见，但该病的发病率已经在过去的 20 年间一直在升高，部分由于慢性丙型肝炎（一个主要原因）(Caldwell,S. 和 S.H.Park,The epidemiology of hepatocellular cancer:from the perspectives of public health problem to tumor biology.J Gastroenterol,2009.44 增刊 19: 第 96-101 页。El-Serag,H.B., 等 ,The continuing increase in the incidence of hepatocellular carcinoma in the United States:an update.ANN Intern Med,2003.139(10):第 817-23 页）以及乙型肝炎和黄曲霉毒素暴露的病例增多。

[0006] 长期以来需要调节疾病和有效治疗患有原发性肝癌（包括但不限于肝细胞癌、肝母细胞瘤和胆管癌）的患者的新药。当前明确需要调节疾病和有效治疗肝炎病毒感染患者的新治疗剂。本发明满足了对调节疾病和有效治疗患有原发性肝癌和肝细胞癌的患者的新药的需要。因为本发明靶向已证明支持肝脏中病毒感染的细胞类型，本发明还满足了对新颖抗病毒药物的需要，所述药物可调节疾病和有效治疗感染甲型肝炎病毒、乙型肝炎病毒、丙型肝炎病毒、丁型肝炎病毒和戊型肝炎病毒以及其它感染肝脏的病毒物种的患者。

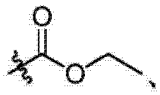
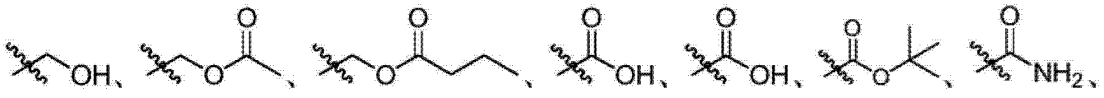
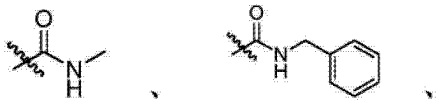
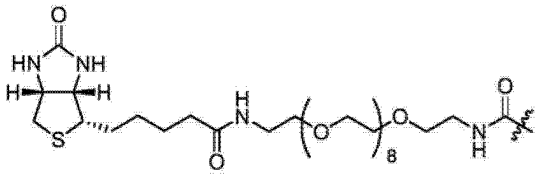
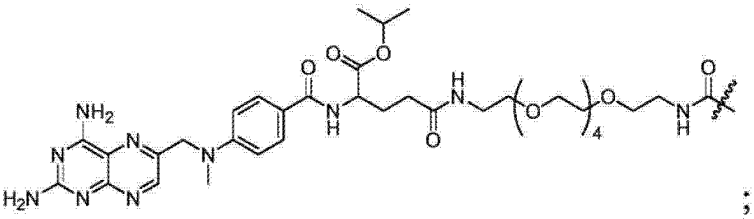
[0007] 发明概述

[0008] 本发明涉及新颖的取代的氨基噻唑，即式 (I) 的化合物，

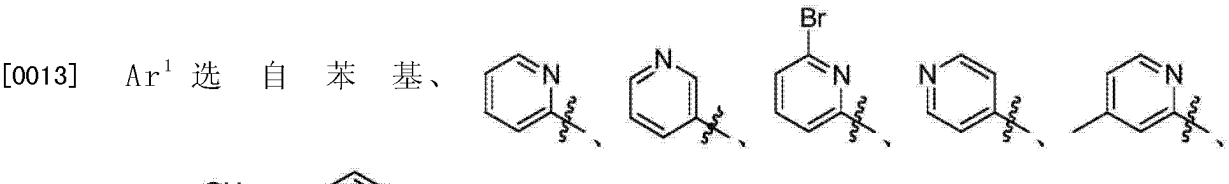
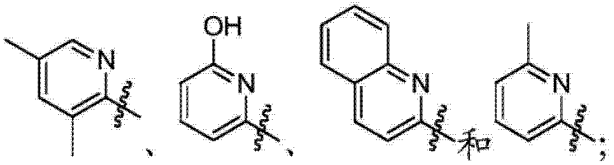
[0009]

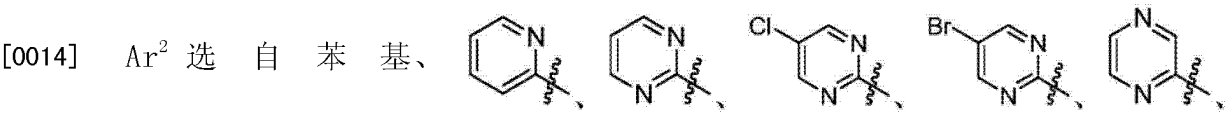
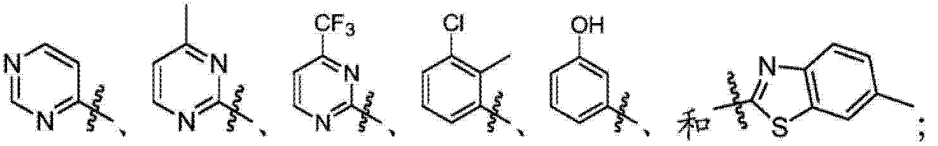


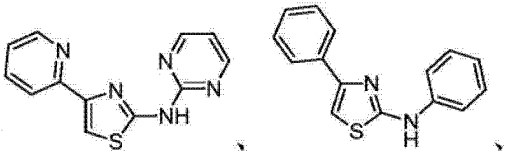
[0010] 包括其水合物、溶剂合物、药学上可接受的盐、前药和复合物，其中：

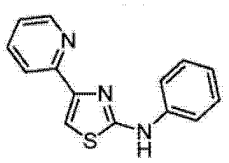
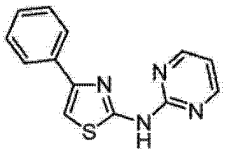
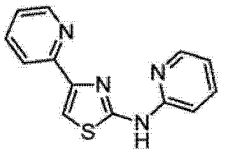
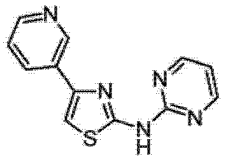
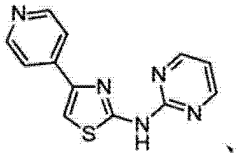
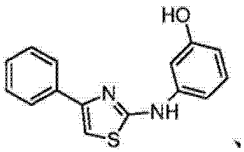
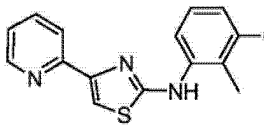
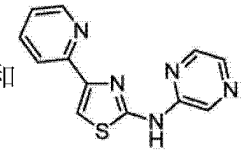
[0011] R^1 选自氢、C_1-C_9 直链烷基、异丙基、环己基、溴、氰基、  、  、  、  和  ；

[0012] R^2 选自氢、甲基、异丙基、叔丁基、苄基和  ；

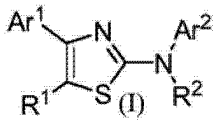
[0013] Ar^1 选自苯基、  、  和；

[0014] Ar^2 选自苯基、  、  ；

[0015] 式(I)的新颖化合物中不包括结构  、

 、  、  、  、  、  、  和  的化合物。

[0016] 本发明还涉及使用结构

[0017]  的化合物的新颖方法。

[0018] 本发明还涉及包含以下的组合物：

[0019] 有效量的一种或多种根据本发明的化合物和赋形剂。

[0020] 本发明还涉及治疗或预防涉及细胞生长失调的疾病的方法，所述疾病包括例如原发性肝癌、肝细胞癌、肝母细胞瘤、胆管癌乳腺癌、卵巢癌、肺癌、白血病及转移性疾病，所述方法包括向受试者施用有效量的根据本发明的化合物或组合物。

[0021] 本发明还涉及治疗或预防涉及细胞生长失调的疾病的方法，所述疾病包括例如原发性肝癌、肝细胞癌、肝母细胞瘤和胆管癌、乳腺癌、卵巢癌、肺癌、白血病及转移性疾病，其中所述方法包括向受试者施用包含有效量的一种或多种根据本发明的化合物和赋形剂的组合物。

[0022] 本发明还涉及治疗或预防与原发性肝癌、肝细胞癌、肝母细胞瘤和胆管癌、乳腺癌、卵巢癌、肺癌、白血病及转移性疾病有关的疾病或疾患及涉及细胞生长失调的疾病的方法。所述方法包括向受试者施用有效量的根据本发明的化合物或组合物。

[0023] 本发明还涉及治疗或预防与原发性肝癌、肝细胞癌、肝母细胞瘤和胆管癌、乳腺癌、卵巢癌、肺癌、白血病及转移性疾病有关的疾病或疾患及涉及细胞生长失调的疾病的方法，其中所述方法包括向受试者施用包含有效量的一种或多种根据本发明的化合物和赋形剂的组合物。

[0024] 本发明还涉及治疗或预防与细胞生长失调有关的疾病或疾患的方法。所述方法包括向受试者施用有效量的根据本发明的化合物或组合物。

[0025] 本发明还涉及治疗或预防与细胞生长失调相关的疾病或疾患的方法，其中所述方法包括向受试者施用包含有效量的一种或多种根据本发明的化合物和赋形剂的组合物。

[0026] 本发明还涉及治疗或预防涉及肝炎病毒（包括例如甲型肝炎病毒、乙型肝炎病毒、丙型肝炎病毒、丁型肝炎病毒和戊型肝炎病毒）以及其它感染肝脏的病毒物种感染的疾病的方法，所述方法包括向受试者施用有效量的根据本发明的化合物或组合物。

[0027] 本发明还涉及治疗或预防涉及肝炎病毒（包括例如甲型肝炎病毒、乙型肝炎病毒、丙型肝炎病毒、丁型肝炎病毒和戊型肝炎病毒）以及其它感染肝脏的病毒物种感染的疾病的方法，其中所述方法包括向受试者施用包含有效量的一种或多种根据本发明的化合物和赋形剂的组合物。

[0028] 本发明还涉及治疗或预防与甲型肝炎病毒、乙型肝炎病毒、丙型肝炎病毒、丁型肝

炎病毒和戊型肝炎病毒有关的疾病或疾患，和涉及肝炎病毒及其它感染肝脏的病毒物种感染的疾病的方法。所述方法包括向受试者施用有效量的根据本发明的化合物或组合物。

[0029] 本发明还涉及治疗或预防与甲型肝炎病毒、乙型肝炎病毒、丙型肝炎病毒、丁型肝炎病毒和戊型肝炎病毒有关的疾病或疾患，和涉及肝炎病毒以及其它感染肝脏的病毒物种感染的疾病的方法，其中所述方法包括向受试者施用包含有效量的一种或多种根据本发明的化合物和赋形剂的组合物。

[0030] 本发明还涉及治疗或预防与肝炎病毒以及其它感染肝脏病毒物种感染有关的疾病或疾患的方法。所述方法包括向受试者施用有效量的根据本发明的化合物或组合物。

[0031] 本发明还涉及治疗或预防与肝炎病毒以及其它感染肝脏的病毒物种感染有关的疾病或病症的方法，其中所述方法包括向受试者施用包含有效量的一种或多种根据本发明的化合物和赋形剂的组合物。

[0032] 本发明还涉及制备本发明化合物的方法。

[0033] 对本领域的普通技术人员来说，通过阅读以下详述和随附权利要求，这些和其它目的、特征及优点将变得显而易见。除非另有说明，否则所有的百分比、比率及比例在本文中均按重量计。除非另有说明，否则所有温度单位均为摄氏度（℃）。所有引用的文件都位于相关的部分，通过引用并入本文；不得将任何文件的引用理解为承认其是关于本发明的现有技术。

[0034] 发明详述

[0035] 本发明取代的氨基噻唑能够治疗和预防与细胞生长失调相关的疾病，例如原发性肝癌肝细胞癌、肝母细胞瘤和胆管癌、乳腺癌、卵巢癌、肺癌、白血病及转移性疾病。本发明取代的氨基噻唑还能够治疗和预防与肝炎病毒（例如甲型肝炎病毒、乙型肝炎病毒、丙型肝炎病毒、丁型肝炎病毒和戊型肝炎病毒）以及其它感染肝脏病毒感染相关的疾病。已发现，本公开的化合物引起肝细胞癌 (HCC) 来源的细胞以及肝母细胞瘤细胞、乳腺癌细胞和卵巢癌细胞的细胞周期停滞和凋亡。此外，已确定对例如 HCC 来源的细胞以及肝母细胞瘤细胞、乳腺癌细胞和卵巢癌细胞的敏感细胞的作用是不可逆的，并且本公开的化合物通过经由调节性激酶 AKT、mTORC1 和 mTORC2 对有丝分裂的抗凋亡信号传导的抑制起作用。此外，本公开的取代的氨基噻唑破坏支持肝炎病毒（例如甲型肝炎病毒、乙型肝炎病毒、丙型肝炎病毒、丁型肝炎病毒和戊型肝炎病毒）感染的细胞，诸如（支持肝炎感染的细胞类型），并可作为抗病毒剂以用于治疗和预防与肝炎病毒（例如甲型肝炎病毒、乙型肝炎病毒、丙型肝炎病毒、丁型肝炎病毒和戊型肝炎病毒）以及其它感染肝脏病毒物种感染相关的疾病。

[0036] 不希望受到理论束缚，据信本公的开取代的氨基噻唑可改善、减轻或以其它方式使得所述与细胞生长失调相关的疾病受到控制。此外，还不希望受到理论束缚，据信本公的开取代的氨基噻唑可改善、减轻、或以其它方式使得所述与病毒感染肝脏相关的疾病受到控制。

[0037] 在说明书通篇中，当组合物被描述为具有、包含特定组分时，或者当方法被描述为具有、包括特定方法步骤时，可预见本教导的组合物还主要由或者由所引用的组分组成，并且本教导的方法也主要由或者由引用的处理步骤组成。

[0038] 在应用中，当认为元素或组分被包括于和 / 或选自引用的元素或组分的列表中时，应当理解所述元素或组分可以是任何一种引用的元素或组分，并可选自两种或多种引

用的元素或组分。

[0039] 除非另有明确指示，否则用在本文中的单数包括复数（反之亦然）。此外，当本文在数值前使用“约”时，除非另有明确指示，否则本教导还包括特定数值本身。

[0040] 应当理解，只要本教导仍可操作，则步骤的顺序或进行某些操作的顺序是不重要的。另外，两个或多个步骤或操作可同时进行。

[0041] 如本文所用，术语“卤素”应意指氯、溴、氟和碘。

[0042] 如本文所用，除非另外指出，否则“烷基”和/或“脂族”无论单独使用还是作为取代基的一部分使用均指具有 1 至 20 个碳原子或在该范围内任何数目的碳原子（例如 1 至 6 个碳原子或 1 至 4 个碳原子）的直链和支链碳链。碳原子的指定数目（如 C_{1-6}）应独立指烷基或较大的含烷基取代基的烷基部分中的碳原子数目。烷基的非限制实例包括甲基、乙基、正丙基、异丙基、正丁基、仲丁基、异丁基、叔丁基等。烷基可被任选地取代。取代的烷基的非限制实例包括羟甲基、氯甲基、三氟甲基、氨基甲基、1- 氯乙基、2- 羟乙基、1,2- 二氟乙基、3- 羧丙基等。在具有多个烷基的取代基诸如 $(C_{1-6}$ 烷基$)_2$ 氨基中，烷基可以相同或不同。

[0043] 如本文所用，术语“烯基”和“炔基”无论单独使用还是作为取代基的一部分使用，均是指具有 2 个或多个（优选 2 至 20 个）碳原子的直链碳链和支链碳链，其中烯基链在链中具有至少一个双键且炔基链在链中具有至少一个三键。烯基和炔基可被任选地取代。烯基的非限制性实例包括乙烯基、3- 丙烯基、1- 丙烯基（也为 2- 甲基乙烯基）、异丙烯基（也为 2- 甲基乙烯 -2- 基）、丁烯 -4- 基等。取代的烯基的非限制实例包 2- 氯乙烯基 (2-chloroethenyl)（也为 2- 氯乙烯基 (2-chlorovinyl)）、4- 羟基丁烯 -1- 基、7- 羟基 -7- 甲基辛 -4- 烯 -2- 基、7- 羟基 -7- 甲基辛 -3,5- 二烯 -2- 基等。炔基的非限制性实例包括乙炔基、丙 -2- 炔基（也为炔丙基）、丙炔 -1- 基和 2- 甲基 - 己 -4- 炔 -1- 基。取代的炔基的非限制实例包括 5- 羟基 -5- 甲基己 -3- 炔基、6- 羟基 -6- 甲基庚 -3- 炔 -2- 基、5- 羟基 -5- 乙基庚 -3- 炔基等。

[0044] 如本文所用，“环烷基”无论单独使用或作为另一基团的一部分使用均是指包括环化烷基、烯基和炔基的含有非芳族碳的环，所述环如具有 3 至 14 个环碳原子，优选 3 至 7 个或 3 至 6 个环碳原子，或甚至 3 至 4 个环碳原子，并且任选地含有一个或多个（如，1、2 或 3 个）双键或三键。环烷基可为单环（如，环己基）或多环（如，含有稠环、桥环和/或螺环的系统），其中所述碳原子位于所述环系统的内部或外部。环烷基的任何适合的环位置可与定义的化学结构共价连接。环烷基环可被任选地取代。环烷基的非限制性实例包括：环丙基、2- 甲基 - 环丙基、环丙烯基、环丁基、2,3- 二羟基环丁基、环丁烯基、环戊基、环戊烯基、环戊二烯基、环己基、环己烯基、环庚基、环辛烷基、十氢化萘基、2,5- 二甲基环戊基、3,5- 二氯环己基、4- 羟基环己基、3,3,5- 三甲基环己 -1- 基、八氢并环戊二烯基 (octahydropentalenyl)、八氢 -1H- 茚基、3a,4,5,6,7,7a- 六氢 -3H- 茚 -4- 基、十氢甘菊环基；双环 [6.2.0] 癸烷基、十氢萘基和十二氢 -1H- 芴基。术语“环烷基”还包括为双环烃环的碳环，所述碳环的非限制性实例包括双环 -[2.1.1] 己烷基、双环 [2.2.1] 庚烷基、双环 [3.1.1] 庚烷基、1,3- 二甲基 [2.2.1] 庚烷 -2- 基、双环 [2.2.2] 辛烷基和双环 [3.3.3] 十一烷基。

[0045] “卤代烷基”意在包括被 1 个或多个卤基取代的具有指定数目碳原子的直链和支链饱和脂族烃基。卤代烷基包括全卤代烷基，其中烷基的所有氢已被卤素所替代

（如，$-CF_3$、$-CF_2CF_3$）。卤代烷基可被除了卤素之外的一个或多个取代基任选地取代。卤代烷基的实例包括但不限于氟甲基、二氯乙基、三氟甲基、三氯甲基、五氟乙基和五氯乙基。

[0046] 术语“烷氧基”是指 -O- 烷基，其中所述烷基如上所定义。烷氧基可被任选地取代。术语 C_3-C_6 环烷氧基是指含有 3 至 6 个碳原子和至少一个氧原子的环（如，四氢呋喃、四氢 -2H- 吡喃）。C_3-C_6 环烷氧基可被任选地取代。

[0047] 术语“芳基”，其中单独使用或作为另一基团的一部分使用，在本文被定义为 6 个碳成员的不饱和、芳族单环或者 10 至 14 个碳成员的不饱和、芳族多环。芳基环可为例如各自被一个或多个部分任选取代的苯基环或萘基环，所述部分能够替代一个或多个氢原子。芳基的非限制性实例包括：苯基、亚萘 -1- 基、亚萘 -2- 基、4- 氟苯基、2- 羟基苯基、3- 甲基苯基、2- 氨基 -4- 氟苯基、2-(N,N- 二乙基氨基）苯基、2- 氰基苯基、2,6- 二 - 叔 - 丁基苯基、3- 甲氧基苯基、8- 羟基亚萘 -2- 基 4,5- 二甲氧基亚萘 -1- 基和 6- 氰基 - 亚萘 -1- 基。芳基还包括例如与一个或多个饱和或部分饱和碳环稠合的苯基环或萘基环（如，双环 [4.2.0] 八 -1,3,5- 三烯、茚满基 (indanyl)），其可在芳族环和 / 或饱环和或部分饱和环的一个或多个碳原子处被取代。

[0048] 术语“芳基烷基”或“芳烷基”是指 - 烷基 - 芳基，其中所述烷基和芳基如本文所定义。本发明的芳烷基被任选地取代。芳基烷基的实例包括例如苄基、1- 苯基乙基、2- 苯基乙基、3- 苯基丙基、2- 苯基丙基、萘基甲基等。

[0049] 术语“杂环的”和 / 或“杂环”和 / 或“杂环基”无论单独使用或作为另一基团的一部分使用，均在本文中被定义为具有 3 至 20 个原子的一个或多个环，其中至少一个环中的至少一个原子选自氮 (N)、氧 (O) 或硫 (S) 的杂原子，并且其中还包括杂原子的环是非芳族的。在包括 2 个或多个稠环的杂环基中，带有非杂原子的环可为芳基（如，二氢吲哚基、四氢喹啉基、色满基）。示例性杂环基具有 3 至 14 个环原子，其中 1 至 5 个环原子为独立选自氮 (N)、氧 (O) 或硫 (S) 的杂原子。杂环基中的一个或多个 N 或 S 原子可被氧化。杂环基可被任选地取代。

[0050] 具有单环的杂环单元的非限制性实例包括：二吖丙啶基、氮丙啶基、尿唑基、氮杂环丁基、吡唑烷基、咪唑烷基、噁唑烷基、异噁唑啉基、异噁唑基、噻唑烷基、异噻唑基、异噻唑啉基、噁噻唑烷酮基、噁唑烷酮基、乙内酰脲基、四氢呋喃基、吡咯烷基、吗啉基、哌嗪基、哌啶基、二氢吡喃基、四氢吡喃基、哌啶 -2- 酮基（戊内酰胺）、2,3,4,5- 四氢 -1H- 氮杂基、2,3- 二氢 -1H- 吲哚和 1,2,3,4- 四氢 - 喹啉。具有 2 个或多个环的杂环单元的非限制性实例包括：六氢 -1H- 吡咯里嗪基 (pyrrolizinyl)、3a,4,5,6,7,7a- 六氢 -1H- 苯并 [d] 咪唑基、3a,4,5,6,7,7a- 六氢 -1H- 吲哚基、1,2,3,4- 四氢喹啉基、色满基、异色满基、二氢吲哚基、异二氢吲哚基和十氢 -1H- 环辛 [b] 吡咯基。

[0051] 术语“杂芳基”无论单独使用或作为另一基团的一部分使用，在本文中被定义为具有 5 至 20 个原子的一个或多个环，其中至少一个环中的至少一个原子为选自氮 (N)、氧 (O) 或硫 (S) 的杂原子，并且其中至少一个包含杂原子的环还为芳族的。在包含 2 个或多个稠环的杂芳基中，带有非杂原子的环可为碳环（如，6,7- 二氢 -5H- 环戊二烯并嘧啶）或芳基（例如苯并呋喃基、苯并噻吩基、吲哚基）。示例性杂芳基具有 5 至 14 个环原子，并含有 1 至 5 个独立选自氮 (N)、氧 (O) 或硫 (S) 的杂环原子。杂芳基中的一个或多个 N 或 S 原子可被氧化。杂芳基可被取代。含有单环的杂芳基环的非限制性实例包括：1,2,3,4- 四唑基、

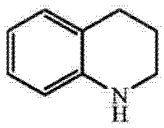
[1,2,3] 三唑基、[1,2,4] 三唑基、三嗪基、噻唑基、1H- 咪唑基、噁唑基、呋喃基、噻吩基、嘧啶基、2- 苯基嘧啶基、吡啶基、3- 甲基吡啶基和 4- 二甲基氨基吡啶基。含有 2 个或多个稠环的杂芳基环的非限制性实例包括 :苯并呋喃基、苯并噻吩基、苯并噁唑基、苯并噻唑基、苯并三唑基、吲哚基、萘啶基、菲啶基、7H- 嘌呤基、9H- 嘌呤基、6- 氨基 -9H- 嘌呤基、5H- 吡咯并 [3,2-d] 嘧啶基、7H- 吡咯并 [2,3-d] 嘧啶基、吡啶并 [2,3-d] 嘧啶基、2- 苯基苯并 [d] 噻唑基、1H- 吲哚基、4,5,6,7- 四氢 -1-H- 吲哚基、喹喔啉基、5- 甲基喹喔啉基、喹唑啉基、喹啉基、8- 羟基 - 喹啉基和异喹啉基。

[0052] 如上所述的杂芳基的一个非限制实例是 C_1-C_5 杂芳基,其具有 1 至 5 个碳环原子和至少一个为杂原子的另外的环原子 (优选 1 至 4 个为杂原子的另外的环原子),所述杂原子独立选自氮 (N)、氧 (O) 或硫 (S)。C_1-C_5 杂芳基的实例包括但不限于三嗪基、噻唑 -2- 基、噻唑 -4- 基、咪唑 -1- 基、1H- 咪唑 -2- 基、1H- 咪唑 -4- 基、异噁唑啉 -5- 基、呋喃 -2- 基、呋喃 -3- 基、噻吩 -2- 基、噻吩 -4- 基、嘧啶 -2- 基、嘧啶 -4- 基、嘧啶 -5- 基、吡啶 -2- 基、吡啶 -3- 基和吡啶 -4- 基。

[0053] 除非另外指出,否则当两个取代基合起来一起形成具有指定数目环原子的环 (如,R^2 和 R^3 与它们连接的氮 (N) 合起来一起形成具有 3 至 7 个环成员的环) 时,所述环可具有碳原子和任选地具有一个或多个 (如,1 至 3 个) 独立选自氮 (N)、氧 (O) 或硫 (S) 的另外的杂原子。所述环可为饱和或部分饱和的,并可被任选地取代。

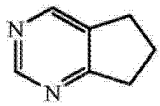
[0054] 为了本发明的目的,包含单个杂原子的稠环单元以及螺环、双环等将被认为属于对应于含杂原子的环的环族 (cyclic family)。例如,为了本发明的目的,具有下式 :

[0055]



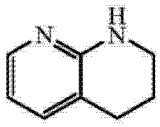
[0056] 的 1,2,3,4- 四氢喹啉被认为是杂环单元。为了本发明的目的,具有下式 :

[0057]



[0058] 的 6,7- 二氢 -5H- 环戊二烯并嘧啶被认为是杂芳基单元。当稠环单元在饱和环和芳基环中都含有杂原子时,芳基环将占大多数,并且决定所述环被分配到何种类别的类型中。例如,为了本发明的目的,具有下式 :

[0059]



[0060] 的 1,2,3,4- 四氢 -[1,8] 萘啶被认为是杂芳基单元。

[0061] 无论是术语还是其前缀词根出现在取代基的名称中时,所述名称都应被理解为包括本文提供的那些限制。例如,无论是术语“烷基”或“芳基”还是其前缀词根出现在取代基的名称中时 (如,芳基烷基、烷基氨基),所述名称都应被理解为包括以上对“烷基”和“芳基”给出的那些限制。

[0062] 术语“取代的”用于说明书全文中。术语“取代的”在本文中被定义为具有一个或多个被一个或若干（如，1 至 10）个如本文以下所定义的取代基替代的氢原子的非环状或环状部分。取代基每次能够取代单个部分的一个或两个氢原子。此外，这些取代基可取代在两个相邻碳上的两个氢原子以形成所述取代基、新的部分或单元。例如，需要单个氢原子取代的取代单元包括卤素、羟基等。两个氢原子取代包括羰基、肟基等。来自相邻碳原子的两个氢原子取代包括环氧基等。术语“取代的”在本说明书全文使用以表明部分可具有被取代基取代的一个或多个氢原子。当部分被描述为“取代的”时，任何数目的氢原子可被取代。例如，二氟甲基是取代的 C_1 烷基；三氟甲基是取代的 C_1 烷基；4- 羟基苯基是取代的芳族环；(N,N- 二甲基 -5- 氨基）辛烷基是取代的 C_8 烷基；3- 胍基丙基是取代的 C_3 烷基；和 2- 羧基吡啶基是取代的杂芳基。

[0063] 本文定义的可变的基团，如本文定义的烷基、烯基、炔基、环烷基、烷氧基、芳氧基、芳基、杂环基和杂芳基，无论单独使用或作为另一基团的一部分使用均可被任选地取代。任选取代的基团将如此表示。

[0064] 以下是可取代部分上的氢原子的取代基的非限制性实例：卤素（氯 (Cl)、溴 (Br)、氟 (F) 和碘 (I)）、- CN、- NO_2、氧代（= O）、- OR^3、- SR^3、- $N(R^3)_2$、- $NR^3C(O)R^3$、- SO_2R^3、- SO_2OR^3、- $SO_2N(R^3)_2$、- $C(O)R^3$、- $C(O)OR^3$、- $C(O)N(R^3)_2$、C_{1-6} 烷基、C_{1-6} 卤代烷基、C_{1-6} 烷氧基、C_{2-8} 烯基、C_{2-8} 炔基、C_{3-14} 环烷基、芳基、杂环或杂芳基，其中烷基、卤代烷基、烯基、炔基、烷氧基、环烷基、芳基、杂环基和杂芳基中的每一个被 1-10（如，1-6 或 1-4）个独立选自卤素、- CN、- NO_2、氧代和 R^3 的基团任选地取代；其中 R^3 在每次出现时独立为氢、- OR^4、- SR^4、- $C(O)R^4$、- $C(O)OR^4$、- $C(O)N(R^4)_2$、- SO_2R^4、-$S(O)_2OR^4$、- $N(R^4)_2$、- $NR^4C(O)R^4$、C_{1-6} 烷基、C_{1-6} 卤代烷基、C_{2-8} 烯基、C_{2-8} 炔基、环烷基（如，C_{3-6} 环烷基）、芳基、杂环或杂芳基，或两个 R^x 单元与它们结合的原子合起来一起形成任选取代的碳环或杂环，其中所述碳环或杂环优选具有 3 至 7 个环原子；其中 R^4 在每次出现时独立为氢、C_{1-6} 烷基、C_{1-6} 卤代烷基、C_{2-8} 烯基、C_{2-8} 炔基、环烷基（如，C_{3-6} 环烷基）、芳基、杂环或杂芳基，或者两个 R^4 单元与它们结合的原子合起来一起形成任选取代的碳环或杂环，其中所述碳环或杂环优选具有 3 至 7 个环原子。

[0065] 在一些实施方案中，取代基选自以下：

[0066] i) - OR^5；例如 - OH、- OCH_3、- OCH_2CH_3、- $OCH_2CH_2CH_3$；

[0067] ii) - $C(O)R^5$；例如 - $COCH_3$、- $COCH_2CH_3$、- $COCH_2CH_2CH_3$；

[0068] iii) - $C(O)OR^5$；例如 - CO_2CH_3、- $CO_2CH_2CH_3$、- $CO_2CH_2CH_2CH_3$；

[0069] iv) - $C(O)N(R^5)_2$；例如 - $CONH_2$、- $CONHCH_3$、- $CON(CH_3)_2$；

[0070] v) - $N(R^5)_2$；例如 - NH_2、- $NHCH_3$、- $N(CH_3)_2$、- $NH(CH_2CH_3)$；

[0071] vi) 卤素：- F、- Cl、- Br 和 - I；

[0072] vii) - CH_eX_g；其中 X 是卤素，m 为 0 至 2，e+g = 3；例如 - CH_2F、- CHF_2、- CF_3、- CCl_3 或 - CBr_3；

[0073] viii) - SO_2R^5；例如 - SO_2H；- SO_2CH_3；- $SO_2C_6H_5$；

[0074] ix) C_1-C_6 直链烷基、支链烷基或环烷基；

[0075] x) 氰基

[0076] xi) 硝基；

[0077] xii) $N(R^5)C(O)R^5$；

[0078] xiii) 氧代（＝O）；

[0079] xiv) 杂环；和

[0080] xv) 杂芳基。

[0081] 其中每个 R^5 独立为氢、任选取代的 C_1-C_6 直链或支链烷基（如，任选取代的 C_1-C_4 直链或支链烷基），或任选取代的 C_3-C_6 环烷基（如任选取代的 C_3-C_4 环烷基）；或两个 R^5 单元可合起来一起形成包含 3-7 个环原子的环。在某些方面，每个 R^5 独立为氢、被卤素或 C_3-C_6 环烷基任选地取代的 C_1-C_6 直链或支链烷基或者 C_3-C_6 环烷基。

[0082] 在本说明书的各处，化合物的取代基以组或范围的形式公开。本描述明确地意在包括此类组成员和范围成员的各个和每个单独的子组合。例如，术语“C_{1-6} 烷基”明确意在单独公开 C_1 烷基、C_2 烷基、C_3 烷基、C_4 烷基、C_5 烷基、C_6 烷基、C_1-C_6 烷基、C_1-C_5 烷基、C_1-C_4 烷基、C_1-C_3 烷基、C_1-C_2 烷基、C_2-C_6 烷基、C_2-C_5 烷基、C_2-C_4 烷基、C_2-C_3 烷基、C_3-C_6 烷基、C_3-C_5 烷基、C_3-C_4 烷基、C_4-C_6 烷基、C_4-C_5 烷基和 C_5-C_6 烷基。

[0083] 为了本发明的目的，术语“化合物”、“类似物”和“物质组合物”同样很好地代表本文描述的取代的氨基噻唑，包括所有对映体形式、非对映体形式、盐等，并且术语“化合物”、“类似物”和“物质组合物”在本说明书全文中可互换使用。

[0084] 本文描述的化合物可含有不对称原子（也称为手性中心），并且一些化合物可含有一个或多个不对称原子或中心，因此其可产生光学异构体（对映体）和非对映体。本文公开的本教导和化合物包括此类对映体和非对映体，以及其外消旋和拆分的对映体纯的 R 和 S 立体异构体，以及 R 和 S 立体异构体的其它混合物及药学上可接受的盐。光学异构体可通过本领域技术人员已知的标准程序以纯的形式获得，所述标准程序包括但不限于非对映体盐的形成、动力学拆分和不对称合成。本教导还涵盖含有烯基部分（如，烯和亚胺）的化合物的顺式和反式异构体。还应当理解，本教导涵盖所有可能的区域异构体及其混合物，其可通过本领域技术人员已知的标准分离程序以纯的形式获得，并包括但不限于柱色谱、薄层色谱和高效液相色谱。

[0085] 可具有酸部分的本教导化合物的药学上可接的盐可使用有机碱和无机碱形成。根据去质子化可用的酸性氢的数目，涵盖了单阴离子盐和多阴离子盐。用碱形成的适合的盐包括诸如碱金属盐或碱土金属盐的金属盐，例如钠盐、钾盐或镁盐；氨盐和有机胺盐，诸如那些用吗啉、硫代吗啉、哌啶、吡咯烷、单 -、二 - 或三 - 低级烷基胺（如，乙基 - 叔 - 丁胺、二乙胺、二异丙胺、三乙胺、三丁胺或二甲基丙胺）或单 -、二 -、三羟基低级烷基胺（如，单 -、二 - 或三乙醇胺）形成的盐。无机碱的特定非限制性实例包括 $NaHCO_3$、Na_2CO_3、$KHCO_3$、K_2CO_3、Cs_2CO_3、LiOH、NaOH、KOH、NaH_2PO_4、Na_2HPO_4 和 Na_3PO_4。还可形成内盐。类似地，当本文公开的化合物含有碱性部分时，可使用有机酸和无机酸形成盐。例如，可由以下酸形成盐：乙酸、丙酸、乳酸、苯磺酸、苯甲酸、樟脑磺酸、柠檬酸、酒石酸、琥珀酸、二氯乙酸、乙烯磺酸、甲酸、富马酸、葡萄糖酸、谷氨酸、马尿酸、氢溴酸、盐酸、羟乙磺酸、乳酸、马来酸、苹果酸、丙二酸、扁桃酸、甲磺酸、黏酸、萘磺酸、硝酸、草酸、双羟萘酸、泛酸、磷酸、苯二甲酸、丙酸、琥珀酸、硫酸、酒石酸、甲苯磺酸和樟脑磺酸以及其它已知的药学上可接受的酸。

[0086] 当任何变量在任何组成或在任何式中出现不止一次时，其每次出现时的定义均与其它每次出现时的定义无关（如，在 $N(R^4)_2$ 中，每个 R^4 可相同或与其它出现时不同）。仅当

此类组合产生稳定化合物时，才可允许取代基和 / 或变量的组合。

[0087] 如本文所用的术语“治疗”是指部分或完全减轻、抑制、改善和 / 或缓解患者疑似患有的疾患。

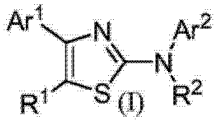
[0088] 如本文所用，“治疗有效的”和“有效剂量”是指引发所需生物活性或作用的物质或量。

[0089] 除非有所指明，术语“受试者”或“患者”可互换使用，并是指哺乳动物（诸如人患者和非人灵长类以及诸如兔、大鼠和小鼠的实验动物）和其它动物。因此，如本文所用的术语“受试者”或“患者”意指可向其施用本发明化合物的任何哺乳动物患者或受试者。在本发明的示例性实施方案中，为了鉴定根据本发明方法治疗的主题患者，采用可接受的筛选方法确定与目标或疑似患有的疾病或疾患有关的风险因素，或确定受试者中存在的疾病或疾患的状态。这些筛选方法包括例如常规处理以确定可与目标或疑似患有的疾病或疾患有关的风险因素。这些和其它常规方法使得临床医生能够选择需要使用本发明的方法和化合物进行治疗的患者。

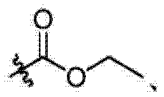
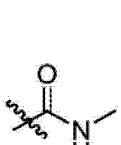
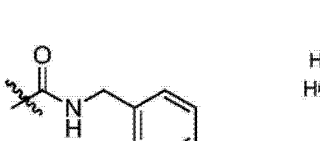
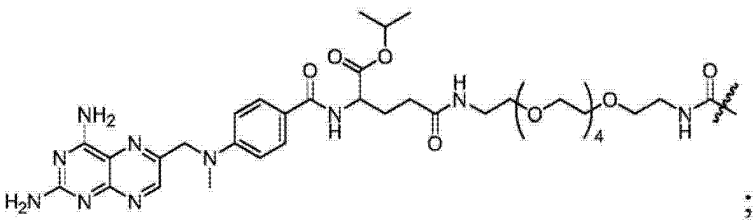
[0090] 取代的氨基噻唑

[0091] 本发明的化合物是取代的氨基噻唑，并包括所有对映体和非对映体形式及其药学上可接受的盐，其具下式：

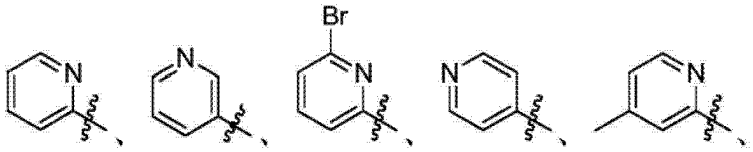
[0092]

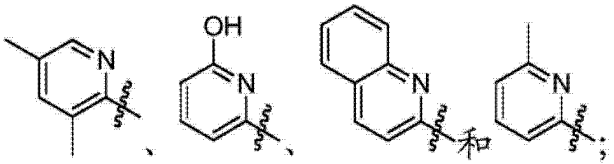


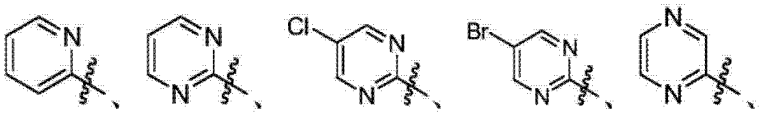
[0093] 包括其水合物、溶剂合物、药学上可接受的盐、前药和复合物，其中：

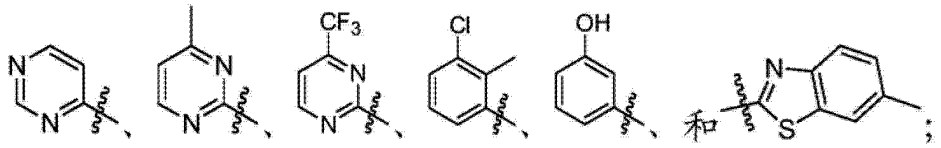
[0094] R^1 选自氢、C_1-C_9 直链烷基、异丙基、环己基、溴、氰基、  、  、  、  和  ；

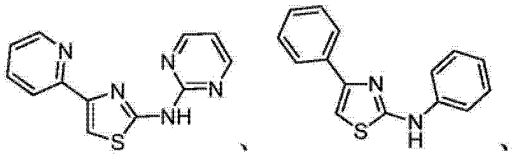
[0095] R^2 选自氢、甲基、异丙基、叔丁基、苄基和  ；

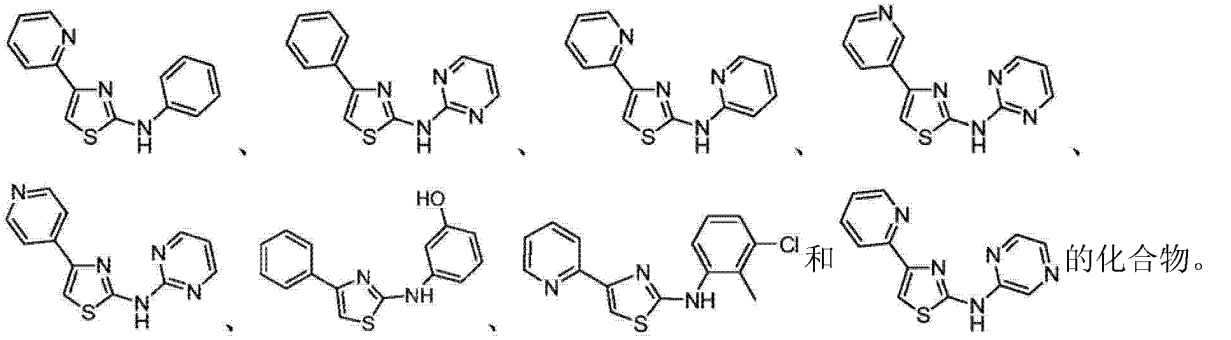
[0096] Ar^1 选自苯基、 



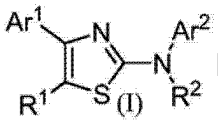
[0097] Ar^2 选自苯基、 



[0098] 式(I)的新颖化合物不包括结构 



[0099] 本发明还涉及使用以下结构

[0100]  的化合物的新颖方法。

[0101] 在一些实施方案中，R^1 是氢。

[0102] 在一些实施方案中，R^1 是 C_1-C_9 直链烷基

[0103] 在一些实施方案中，R^1 是甲基。

[0104] 在一些实施方案中，R^1 是乙基。

[0105] 在一些实施方案中，R^1 是戊基。

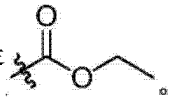
[0106] 在一些实施方案中，R^1 是壬基。

[0107] 在一些实施方案中，R^1 是异丙基。

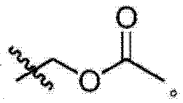
[0108] 在一些实施方案中，R^1 是环己基。

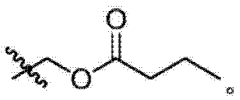
[0109] 在一些实施方案中，R^1 是溴。

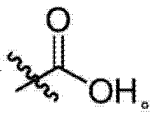
[0110] 在一些实施方案中，R^1 是氰基。

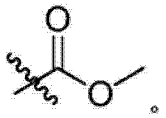
[0111] 在一些实施方案中，R^1 是  。

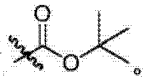
[0112] 在一些实施方案中，R^1 是  。

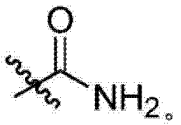
[0113] 在一些实施方案中，R^1 是  。

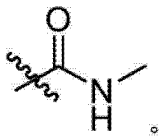
[0114] 在一些实施方案中，R^1 是  。

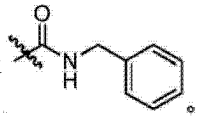
[0115] 在一些实施方案中，R^1 是  。

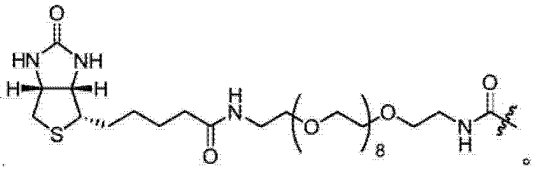
[0116] 在一些实施方案中，R^1 是  。

[0117] 在一些实施方案中，R^1 是  。

[0118] 在一些实施方案中，R^1 是  。

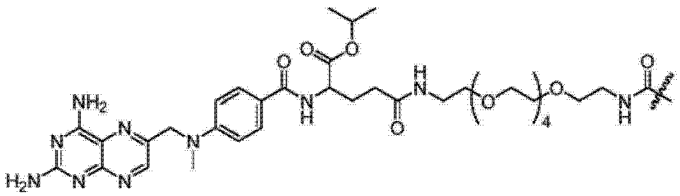
[0119] 在一些实施方案中，R^1 是  。

[0120] 在一些实施方案中，R^1 是  。

[0121] 在一些实施方案中，R^1 是  。

[0122] 在一些实施方案中，R^1 是

[0123]



[0124] 在一些实施方案中，R^2 是氢。

[0125] 在一些实施方案中，R^2 是甲基。

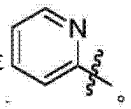
[0126] 在一些实施方案中，R^2 是异丙基。

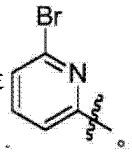
[0127] 在一些实施方案中，R^2 是叔丁基

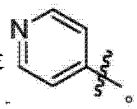
[0128] 在一些实施方案中，R^2 是苄基。

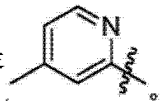
[0129] 在一些实施方案中，R^2 是  。

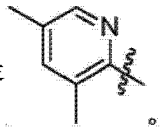
[0130] 在一些实施方案中，Ar^1 是苯基。

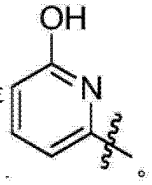
[0131] 在一些实施方案中，Ar^1 是 

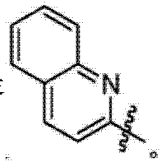
[0132] 在一些实施方案中，Ar^1 是 

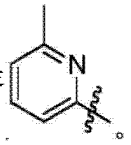
[0133] 在一些实施方案中，Ar^1 是 

[0134] 在一些实施方案中，Ar^1 是 

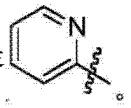
[0135] 在一些实施方案中，Ar^1 是 

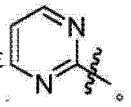
[0136] 在一些实施方案中，Ar^1 是 

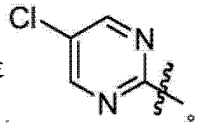
[0137] 在一些实施方案中，Ar^1 是 

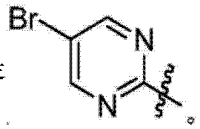
[0138] 在一些实施方案中，Ar^1 是 

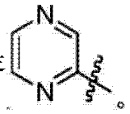
[0139] 在一些实施方案中，Ar^2 是苯基。

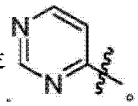
[0140] 在一些实施方案中，Ar^2 是 

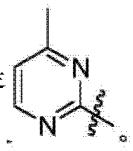
[0141] 在一些实施方案中，Ar^2 是 

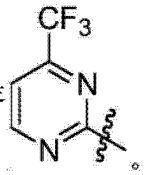
[0142] 在一些实施方案中，Ar^2 是 

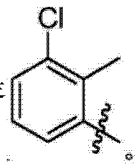
[0143] 在一些实施方案中，Ar^2 是  。

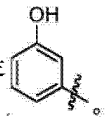
[0144] 在一些实施方案中，Ar^2 是  。

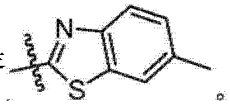
[0145] 在一些实施方案中，Ar^2 是  。

[0146] 在一些实施方案中，Ar^2 是  。

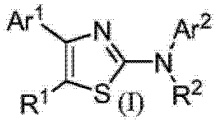
[0147] 在一些实施方案中，Ar^2 是  。

[0148] 在一些实施方案中，Ar^2 是  。

[0149] 在一些实施方案中，Ar^2 是  。

[0150] 在一些实施方案中，Ar^2 是  。

[0151] 示例性实施方案包括具有式 (I) 的化合物或其药学上可接受的盐：

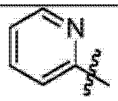
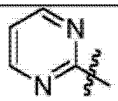
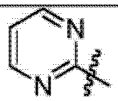
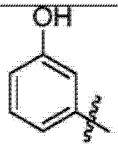
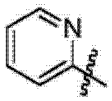
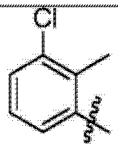
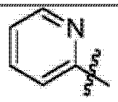
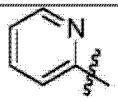
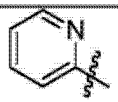
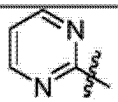
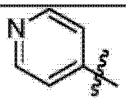
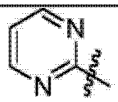
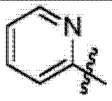
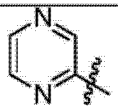
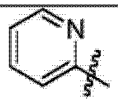
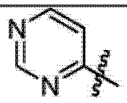
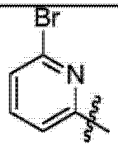
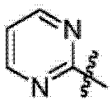
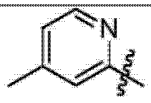
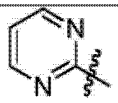
[0152] 

(I)

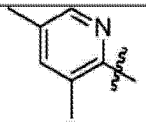
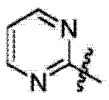
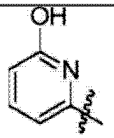
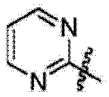
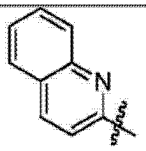
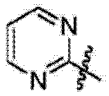
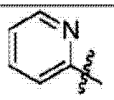
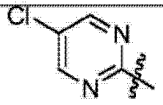
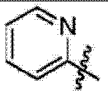
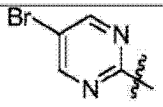
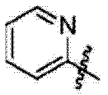
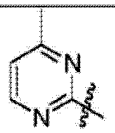
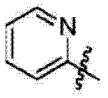
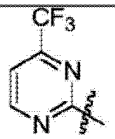
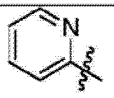
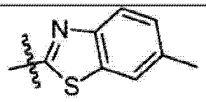
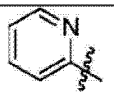
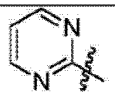
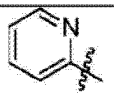
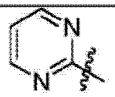
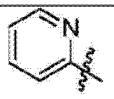
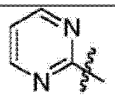
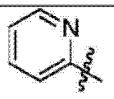
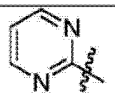
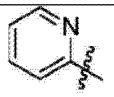
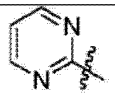
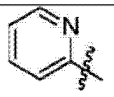
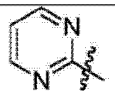
[0153] 其中 R^1、R^2、Ar^1 和 Ar^2 的非限制性实例如本文中的下表 1 所定义。

[0154] 表 1：式 (I) 化合物的示例性实施方案：

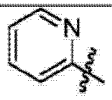
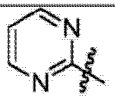
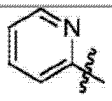
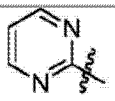
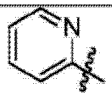
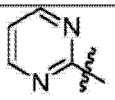
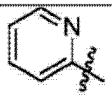
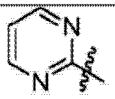
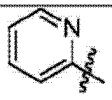
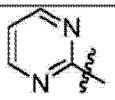
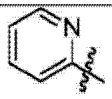
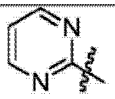
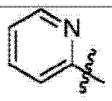
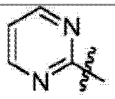
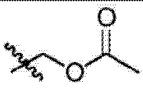
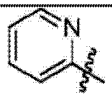
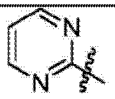
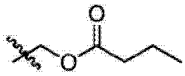
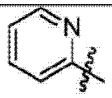
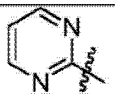
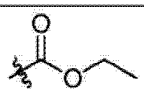
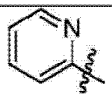
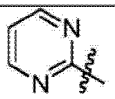
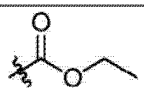
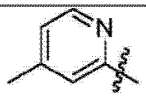
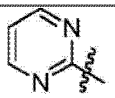
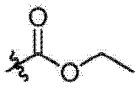
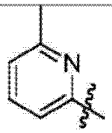
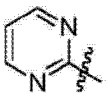
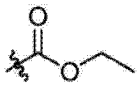
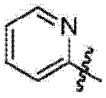
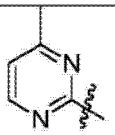
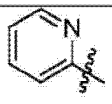
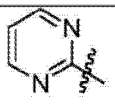
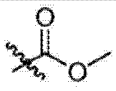
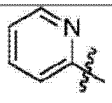
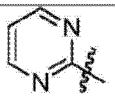
[0155]

条目	R^1	R^2	Ar^1	Ar^2
1	H	H		
2	H	H	苯基	苯基
3	H	H	苯基	
4	H	H	苯基	
5	H	H		
6	H	H		
7	H	H		
8	H	H		
9	H	H		
10	H	H		
11	H	H		
12	H	H		

[0156]

13	H	H		
14	H	H		
15	H	H		
16	H	H		
17	H	H		
18	H	H		
19	H	H		
20	H	H		
21	CH_3	H		
22	CH_2CH_3	H		
23	$CH(CH_3)_2$	H		
24	$CH_2(CH_3)_3CH_3$	H		
25	环己基	H		
26	壬基	H		

[0157]

27	氰基	H		
28	H	异丙基		
29	H	甲基		
30	H	苄基		
31	H			
32	Br	H		
33		H		
34		H		
35		H		
36		H		
37		H		
38		H		
39		H		
40	CO_2H	H		
41		H		

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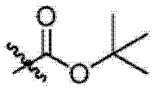
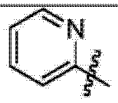
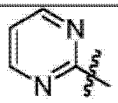
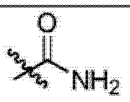
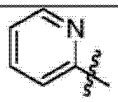
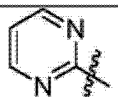
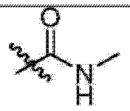
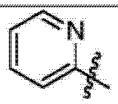
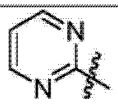
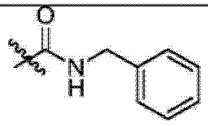
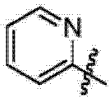
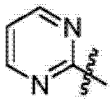
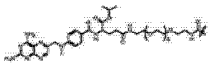
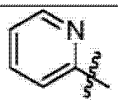
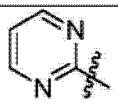
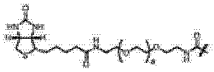
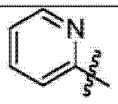
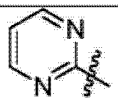
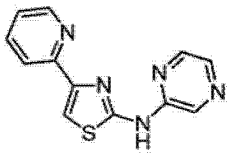
42				
43		H		
44		H		
45		H		
46		H		
47		H		

[0159] 为了表明本文中命名和指代本发明化合物的方式，具有下式：

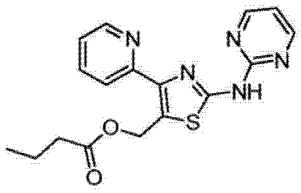
[0160]



[0161] 的化合物具有 N-（吡嗪 -2- 基）-4-（吡啶 -2- 基）噻唑 -2- 胺的化学名。

[0162] 为了表明本文中命名和指代本发明化合物的方式，具有下式：

[0163]



[0164] 的化合物具有（4-（吡啶 -2- 基）-2-（嘧啶 -2- 基氨基）噻唑 -5- 基）甲基丁酸酯的化学名。

[0165] 为了本发明的目的，通过外消旋式描述的化合物将同样很好地代表两种对映体中的任一种或其混合物，或者在第二手性中心存在的情况下代表所有非对映体。

[0166] 在本文提供的所有实施方案中，适合的任选取代基的实例并非意在限制要求保护的发明的范围。本发明的化合物可含有任何一种本文提供的取代基或所述取代基的组合。

[0167] 方法

[0168] 本发明还涉及制备本发明化合物的方法。本教导的化合物可根据本文概述的程序通过采用有机化学领域技术人员已知的标准合成方法和程序，由可商购获得的原料、文献中已知的化合物或容易制备的中间体来制备。用于制备有机分子的标准合成方法与程序、和官能团转化及操作可容易地从相关的科学文献或从本领域的标准教科书获得。应当

理解，当给定典型或优选的工艺条件（即，反应温度、时间、反应物的摩尔比、溶剂、压力等）时，除非另有说明，否则还可使用其它的工艺条件。最佳反应条件可根据使用的具体反应物或溶剂而变化，但是此类条件可由本领域的技术人员通过常规优化程序来确定。有机合成领域的技术人员将认识到提供的合成步骤的性质和顺序可以为了优化本文描述的化合物的形成而改变。

[0169] 本文描述的方法可根据本领域已知的任何适合的方法监测。例如，产物形成可通过光谱的方式（诸如核磁共振光谱法（如，^{1}H 或 ^{13}C）、红外光谱法、分光光度法（如，UV- 可见的）、质谱法）或通过色谱（诸如高压液相色谱 (HPLC)、气相色谱 (GC)、胶凝渗透色谱 (GPC) 或薄层色谱 (TLC)）监测。

[0170] 化合物的制备可涉及各种化学基团的保护和去保护。保护和去保护的需要及适当的保护基团的选择可容易地由本领域的技术人员确定。保护基团的组成和化学性质可在例如 Greene 等，Protective Groups in Organic Synthesis, 第 2 版 (Wiley & Sons, 1991) 中找到，其全部公开内容为了所有目的通过引用并入本文。

[0171] 本文描述的反应或方法可在适合的溶剂中进行，所述溶剂可容易地由有机合成领域的技术人员选择。适合的溶剂通常基本上不与反应物、中间体和 / 或产物在反应进行的温度（即温度范围可从溶剂凝固温度到沸腾温度）下反应。给定的反应可以在一种溶剂或多于一种溶剂的混合物中进行。根据具体反应步骤，可选择适用于具体反应步骤的溶剂。

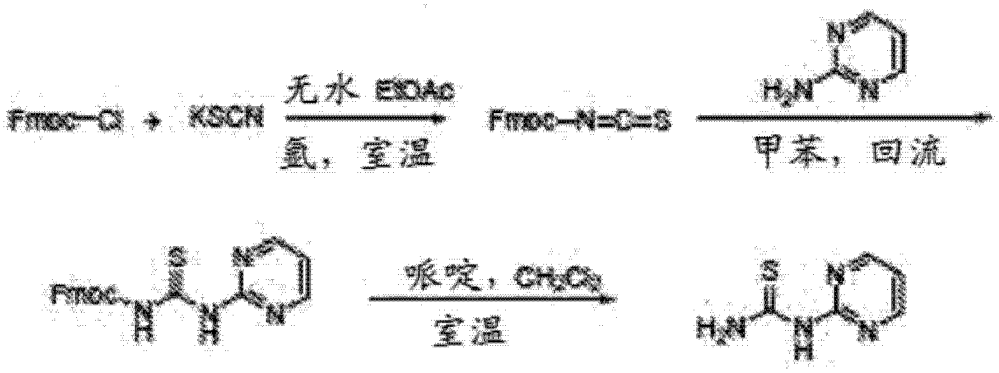
[0172] 以下提供的实施例提供制备本发明示例性化合物的代表性方法。有经验的从业者将知道如何取代适当的试剂、原料及本领域技术人员已知的纯化方法，以制备本发明的化合物。

[0173] 在 300MHz INOVA VARIAN 的光谱仪上记录 ^{1}H NMR 光谱。按 ppm 给出化学位移值，并将 TMS（四甲基硅烷）称为内标。峰模式表示如下 :s，单峰 ;d，双重峰 ;t，三重峰 ;q，四重峰 ;m，多重峰和 dd，双双峰。按赫兹 (Hz) 报告耦合常数 (J)。在 1200Aligent LC-MS 光谱仪上 (ES-API，Positive) 获得质谱。使用本文描述的溶剂系统，经过 100-200 目的硅胶柱进行硅胶柱色谱。

[0174] 实施例提供制备式 (I) 的代表性化合物的方法。有经验的从业者将知道如何取代适当的试剂、原料和本领域技术人员已知的纯化方法，以制备本发明的另外的化合物。

[0175] 实施例 1 :1-（嘧啶 -2- 基）硫脲的合成 :

[0176]



[0177] 在 0℃和氩气氛下，向硫氰酸钾 (3.31g，34.0mmol) 在无水乙酸乙酯 (30mL) 中的悬浮液滴加芴基甲基氧基 - 碳酰氯 (8.00g，30.9mmol) 在无水乙酸乙酯 (30mL) 中的溶液。添

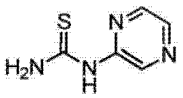
加后，将反应混合物在室温下搅拌 24 小时。然后将其浓缩并通过凝胶柱色谱纯化（二氯甲烷：己烷＝ 40 :60)，得到 5.00g 呈无色油状物的纯产物 O-((9H- 芴 -9- 基）甲基）羰酰异硫氰酸酯 (O-((9H-fluoren-9-yl)methyl)carbonisothiocyana tidate)。

[0178] 将 O-((9H- 芴 -9- 基）甲基）羰酰异硫氰酸酯 (5.00g，17.8mmol) 和嘧啶 -2- 胺 (1.61g，16.9mmol) 在甲苯 (80mL) 中的反应混合物回流 4 小时。然后，将其过滤并用甲苯洗涤，获得 6.00g 呈白色固体的产物 1-Fmoc-3-（嘧啶 -2- 基）硫脲，直接用于下一步而不经过进一步纯化。

[0179] 向 1-Fmoc-3-（嘧啶 -2- 基）硫脲 (6.00g，15.9mmol) 在二氯甲烷 (120mL) 中的搅拌悬浮液添加哌啶 (24mL)。在室温下搅拌反应混合物 20 小时，然后过滤并用二氯甲烷洗涤。将粗产物在水 (50mL) 中浆化 10 分钟、过滤、用水洗涤和真空干燥，得到 2.35g 呈白色固体的纯产物 1-（嘧啶 -2- 基）硫脲。^{1}H NMR(300MHz, DMSO-d_6)：δ 10.57(s, 1H, NH)，10.20(s, 1H, NH)，9.13(s, 1H, NH)，8.63(d, J ＝ 4.8Hz, 2H, CH_{ar})，7.14(t, J ＝ 5.1Hz, 1H, CH_{ar})。

[0180] 实施例 2 :1-（吡嗪 -2- 基）硫脲的合成。

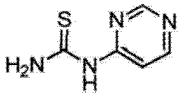
[0181]



[0182] 按照与实施例 1 相同的方式从吡嗪 -2- 基胺合成 1-（吡嗪 -2- 基）硫脲，得到呈白色固体的产物。^{1}H NMR(300MHz, DMSO-d_6)：δ 10.83(s, 1H, NH)，9.94(s, 1H, NH)，9.08(s, 1H, NH)，8.52(s, 1H, CH_{ar})，8.23(s, 2H, CH_{ar})。

[0183] 实施例 3 :1-（嘧啶 -4- 基）硫脲的合成。

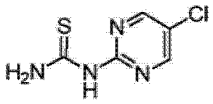
[0184]



[0185] 按照与实施例 1 相同的方式由嘧啶 -4- 基胺合成 1-（嘧啶 -4- 基）硫脲，得到呈白色固体的产物。^{1}H NMR(300MHz, DMSO-d_6)：δ 10.83(s, 1H, NH)，10.28(s, 1H, NH)，9.29(s, 1H, NH)，8.78(d, J ＝ 0.6Hz, 1H, CH_{ar})，8.54(d, J ＝ 6.0Hz, 1H, CH_{ar})，7.14(dd, J ＝ 5.7, 1.2Hz, 1H, CH_{ar})。

[0186] 实施例 4 :1-(5- 氯嘧啶 -2- 基）硫脲的合成。

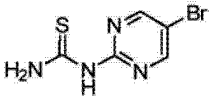
[0187]



[0188] 按照与实施例 1 相同的方式由 5- 氯 - 嘧啶 -2- 基胺合成 1-(5- 氯嘧啶 -2- 基）硫脲，得到呈白色固体的产物。^{1}H NMR(300MHz, DMSO-d_6)：δ 10.88(s, 1H, NH)，9.90(s, 1H, NH)，9.20(s, 1H, NH)，8.72(s, 2H, CH_{ar})。

[0189] 实施例 5 :1-(5- 溴嘧啶 -2- 基）硫脲的合成。

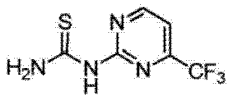
[0190]



[0191] 按照与实施例 1 相同的方式由 5- 溴 - 嘧啶 -2- 基胺按合成 1-(5- 溴嘧啶 -2- 基) 硫脲，得到呈白色固体的产物。^{1}H NMR(300MHz, DMSO-d_6) : δ 10.85(s, 1H, NH), 9.89(s, 1H, NH), 9.21(s, 1H, NH), 8.77(s, 2H, CH_{ar})。

[0192] 实施例 6 :1-(4-(三氟甲基) 嘧啶 -2- 基) 硫脲的合成。

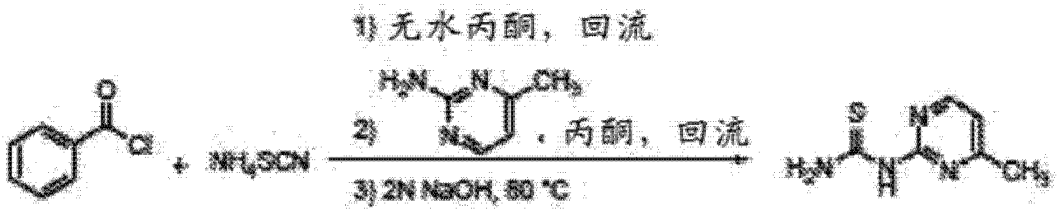
[0193]



[0194] 按照与实施例 1 相同的方式由 4- 三氟甲基 - 嘧啶 -2- 基胺合成 1-(4-(三氟甲基) 嘧啶 -2- 基) 硫脲，得到产物。^{1}H NMR(300MHz, DMSO-d_6) : δ 9.85(s, 1H, NH), 9.33(s, 1H, NH), 8.97(d, J = 5.1Hz, 1H, CH_{ar}), 7.61(d, J = 4.8Hz, 1H, CH_{ar})。

[0195] 实施例 7 :1-(4- 甲基嘧啶 -2- 基) 硫脲的合成。

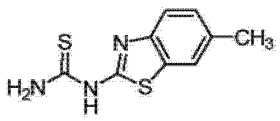
[0196]



[0197] 将苯甲酰氯 (1.74mL, 15mmol) 在室温下滴加至硫氰酸铵 (1.90g, 25mmol) 在无水丙酮 (20mL) 中的溶液。将其加热至回流 15 分钟，然后用 4- 甲基嘧啶 -2- 胺 (1.09g, 10mmol) 处理。继续回流 30 分钟。冷却后，将反应混合物倾倒在冰上，并搅拌 30 分钟。将沉淀通过过滤收集，用水洗涤，然后在 2N 氢氧化钠 (30mL) 中在 80℃下水解 30 分钟。将其冷却至室温，并倾倒在冰冷的 6M HCl(20mL) 内。用粉末碳酸钠将 pH 调节至 8 ～ 9。通过过滤收集粗产物，并用水洗涤。将其在二氯甲烷中进一步浆化并过滤，获得 340mg 呈白色固体的化合物 1-(4- 甲基嘧啶 -2- 基) 硫脲。^{1}H NMR(300MHz, DMSO-d_6) : δ 10.39(s, 1H, NH), 10.27(s, 1H, NH), 9.09(s, 1H, NH), 8.46(d, J = 5.1Hz, 1H, CH_{ar}), 7.03(d, J = 5.1Hz, 1H, CH_{ar}), 2.40(s, 3H, $ArCH_3$)。

[0198] 实施例 7 :1-(6- 甲基苯并 [d] 噻唑 -2- 基) 硫脲的合成。

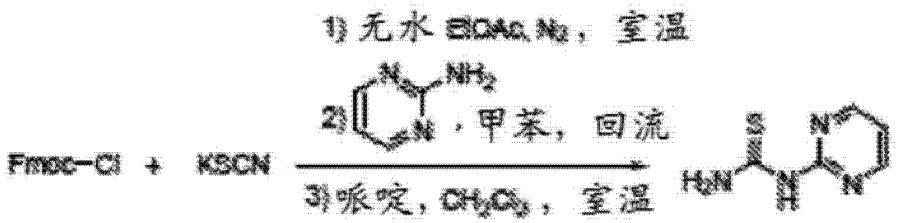
[0199]



[0200] 按照与实施例 7 相同的方式由 6- 甲基 - 苯并噻唑 -2- 基胺合成 1-(6- 甲基苯并 [d] 噻唑 -2- 基) 硫脲，得到呈白色固体的产物。^{1}H NMR(300MHz, DMSO-d_6) : δ 11.73(s, 1H, NH), 9.06(s, 2H, NH_2), 7.69(s, 1H, CH_{ar}), 7.56(d, J = 7.8Hz, 1H, CH_{ar}), 7.20(d, J = 7.5Hz, 1H, CH_{ar}), 2.37(s, 3H, $ArCH_3$)。

[0201] 实施例 8 :1-(嘧啶 -2- 基) 硫脲的合成。

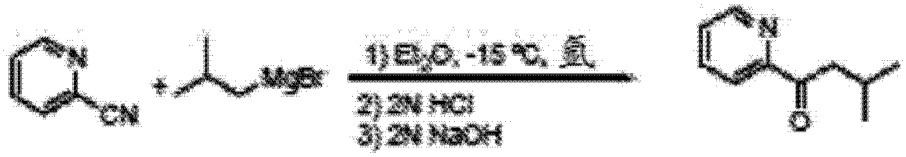
[0202]



[0203] 向硫氰酸钾 (4.28g,44.0mmol) 在无水乙酸乙酯 (EtOAc,50mL) 中的悬浮液在 0℃下在氩气氛下滴加芴基甲基氧基 - 碳酰氯 (Fmoc-Cl,10.35g,40.0mmol) 在无水乙酸乙酯 (50mL) 中的溶液。添加后,将反应混合物在室温下搅拌 24 小时。用己烷 (100mL) 稀释反应混合物,然后通过硅胶垫过滤并用二氯甲烷和己烷 (25 :75,200mL) 的混合物洗涤。将滤液浓缩,获得呈浅黄色油状物的粗 O-((9H- 芴 -9- 基) 甲基) 羰酰异硫氰酸酯,将其溶解于甲苯 (100mL) 中,随后添加嘧啶 -2- 胺 (3.62g,38.0mmol)。将其回流 4 小时,过滤并用甲苯 (100mL) 洗涤,得到 1-Fmoc-3-(嘧啶 -2- 基) 硫脲,将其悬浮于二氯甲烷 (100mL) 中并用哌啶 (24mL) 处理。在室温下搅拌 12 小时后,过滤混合物,并先用二氯甲烷 (100mL) 然后用水 (100mL) 洗涤。真空干燥固体,得到 4.45g 呈浅棕色固体的纯产物 1-(嘧啶 -2- 基) 硫脲。

[0204] 实施例 8 :1-(吡啶 -2- 基) 丙 -1- 酮的合成。

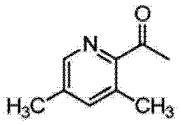
[0205]



[0206] 向 2- 氰基吡啶 (1.04g,10mmol) 在无水二乙醚 (20mL) 中的搅拌溶液在 <-15℃下在氩气氛下缓慢添加异丁基溴化镁 (于二乙醚中的 2M,6.0mL,12mmol)。添加后,将反应混合物在该温度下搅拌 1 小时,然后使其升温至室温,持续 3 小时。将其用 2N HCl(6mL) 在 0℃下淬灭,并再搅拌 15 分钟。将 pH 用 2N NaOH 调节至 8 ～ 9。将混合物用水 (15mL) 稀释,并用乙酸乙酯 (30mL×3) 萃取。将合并的有机层经 Na_2SO_4 干燥、浓缩并通过凝胶柱色谱 (乙酸乙酯 :己烷 = 4 :96 至 16 :84) 纯化,得到 1.40g 呈无色油状物的产物 1-(吡啶 -2- 基) 丙 -1- 酮。^{1}HNMR(300MHz, $CDCl_3$) : δ 8.68(dt, J = 4.2, 0.9Hz, 1H, CH_{ar}), 8.04(d, J = 8.1Hz, 1H, CH_{ar}), 7.83(dt, J = 7.5, 1.8Hz, 1H, CH_{ar}), 7.48-7.43(m, 1H, CH_{ar}), 3.11(d, J = 6.6Hz, 2H, CH_2CO), 2.34-2.30(m, 1H, CH), 1.00(d, J = 6.6Hz, 6H, $C(CH_3)_2$)。MS:MH^+ = 164。

[0207] 实施例 9 :1-(3,5- 二甲基吡啶 -2- 基) 乙酮的合成。

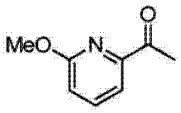
[0208]



[0209] 按照与实施例 8 相同的方式由 3,5- 二甲基 - 吡啶 -2- 腈和甲基溴化镁合成 1-(3,5- 二甲基吡啶 -2- 基) 乙酮,得到呈无色油状物的产物。^{1}HNMR(300MHz, $CDCl_3$) : δ 8.33(d, J = 0.9Hz, 1H, CH_{ar}), 7.37(d, J = 1.5Hz, 1H, CH_{ar}), 2.69(s, 3H, CH_3), 2.56(s, 3H, CH_3), 2.36(s, 3H, CH_3CO)。MS:MH^+ = 150。

[0210] 实施例 10 :1-(6- 甲氧基吡啶 -2- 基) 乙酮的合成。

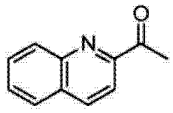
[0211]



[0212] 按照与实施例 8 相同的方式由 6- 甲氧基 - 吡啶 -2- 腈和甲基溴化镁合成 1-(6- 甲氧基吡啶 -2- 基) 乙酮，得到呈白色固体的产物。^{1}H NMR(300MHz, $CDCl_3$) : δ 7.72-7.62(m, 2H, CH_{ar}), 6.93(dd, J = 8.1, 0.9Hz, 1H, CH_{ar}), 4.00(s, 3H, CH_3OAr), 2.69(s, 3H, CH_3CO)。MS:MH^+ = 152。

[0213] 实施例 11 :1-(喹啉 -2- 基) 乙酮的合成。

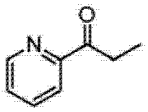
[0214]



[0215] 按照与实施例 8 相同的方式由喹啉 -2- 腈和甲基溴化镁合成 1-(喹啉 -2- 基) 乙酮，得到呈白色固体的产物。^{1}H NMR(300MHz, $CDCl_3$) : δ 8.27(d, J = 8.4Hz, 1H, CH_{ar}), 8.20(d, J = 8.7Hz, 1H, CH_{ar}), 8.13(d, J = 8.7Hz, 1H, CH_{ar}), 7.87(d, J = 8.4Hz, 1H, CH_{ar}), 7.82-7.76(m, 1H, CH_{ar}), 7.68-7.62(m, 1H, CH_{ar}), 2.88(s, 3H, CH_3CO)。MS:MH^+ = 172。

[0216] 实施例 12 :1-(吡啶 -2- 基) 丙 -1- 酮的合成。

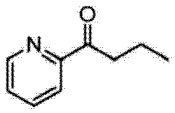
[0217]



[0218] 按照与实施例 8 相同的方式由吡啶 -2- 腈和乙基溴化镁合成 1-(吡啶 -2- 基) 丙 -1- 酮，得到呈浅黄色油状物的产物。^{1}H NMR(300MHz, $CDCl_3$) : δ 8.68(dt, J = 4.8, 0.9Hz, 1H, CH_{ar}), 8.05(dt, J = 8.1, 1.2Hz, 1H, CH_{ar}), 7.83(dt, J = 7.5, 1.8Hz, 1H, CH_{ar}), 7.49-7.44(m, 1H, CH_{ar}), 3.25(q, J = 7.5Hz, 2H, CH_2CO), 1.22(t, J = 7.5Hz, 3H, CH_3)。MS:MH^+ = 136。

[0219] 实施例 13 :1-(吡啶 -2- 基) 丁 -1- 酮的合成。

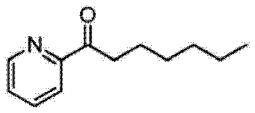
[0220]



[0221] 按照与实施例 8 相同的方式由吡啶 -2- 腈和丙基溴化镁合成 1-(吡啶 -2- 基) 丁 -1- 酮，得到呈无色油状物的产物。^{1}H NMR(300MHz, $CDCl_3$) : δ 8.68(dq, J = 5.1, 0.9Hz, 1H, CH_{ar}), 8.04(dt, J = 8.1, 1.2Hz, 1H, CH_{ar}), 7.83(dt, J = 7.5, 1.8Hz, 1H, CH_{ar}), 7.48-7.44(m, 1H, CH_{ar}), 3.20(t, J = 7.5Hz, 2H, CH_2CO), 1.81-1.74(m, 2H, CH_2), 1.02(t, J = 7.5Hz, 3H, CH_3)。MS:MH^+ = 150。

[0222] 实施例 14 :1-(吡啶 -2- 基) 庚 -1- 酮的合成。

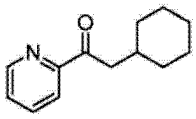
[0223]



[0224] 按照与实施例 8 相同的方式由吡啶 -2- 腈和己基溴化镁合成 1-(吡啶 -2- 基) 庚 -1- 酮，得到呈无色油状物的产物。^{1}H NMR(300MHz, $CDCl_3$) : δ 8.68(dq, J = 4.8, 0.9Hz, 1H, CH_{ar}), 8.04(dt, J = 8.1, 0.9Hz, 1H, CH_{ar}), 7.83(dt, J = 7.5, 1.8Hz, 1H, CH_{ar}), 7.48-7.44(m, 1H, CH_{ar}), 3.21(t, J = 7.5Hz, 2H, CH_2CO), 1.76-1.68(m, 2H, CH_2), 1.42-1.26(m, 6H, 3×CH_2), 0.89(t, J = 7.2Hz, 3H, CH_3)。MS:MH^+ = 192。

[0225] 实施例 15 :2- 环己基 -1-(吡啶 -2- 基) 乙酮的合成。

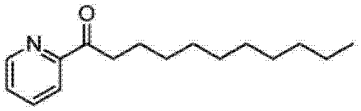
[0226]



[0227] 按照与实施例 8 相同的方式由吡啶 -2- 腈和环己基甲基溴化镁合成 2- 环己基 -1-(吡啶 -2- 基) 乙酮，得到呈无色油状物的产物。^{1}H NMR(300MHz, $CDCl_3$) : δ 8.68(dt, J = 3.9, 0.6Hz, 1H, CH_{ar}), 8.03(d, J = 8.1Hz, 1H, CH_{ar}), 7.83(dt, J = 7.8, 1.8Hz, 1H, CH_{ar}), 7.48-7.43(m, 1H, CH_{ar}), 3.10(d, J = 7.2Hz, 2H, CH_2CO), 2.04-2.00(m, 1H, CH), 1.78-1.02(m, 10H, 5×CH_2)。MS:MH^+ = 204。

[0228] 实施例 16 :1-(吡啶 -2- 基) 十一烷 -1- 酮的合成。

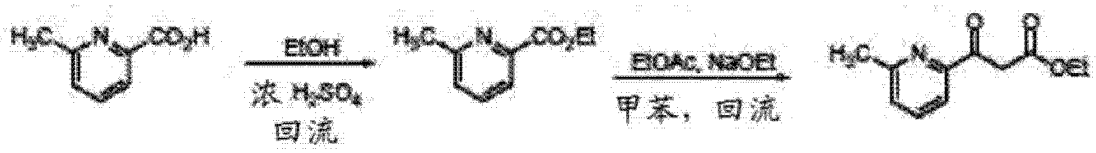
[0229]



[0230] 按照与实施例 8 相同的方式由吡啶 -2- 腈和十一烷基溴化镁合成 1-(吡啶 -2- 基) 十一烷 -1- 酮，得到呈无色油状物的产物。^{1}H NMR(300MHz, $CDCl_3$) : δ 8.68(dq, J = 4.8, 0.9Hz, 1H, CH_{ar}), 8.04(dt, J = 8.1, 1.2Hz, 1H, CH_{ar}), 7.83(dt, J = 7.5, 1.8Hz, 1H, CH_{ar}), 7.48-7.43(m, 1H, CH_{ar}), 3.21(t, J = 7.5Hz, 2H, CH_2CO), 1.75-1.68(m, 2H, CH_2), 1.35-1.23(m, 14H, 7×CH_2), 0.88(t, J = 6.9Hz, 3H, CH_3)。MS:MH^+ = 248。

[0231] 实施例 17 :3-(6- 甲基吡啶 -2- 基)-3- 氧代丙酸乙酯的合成。

[0232]



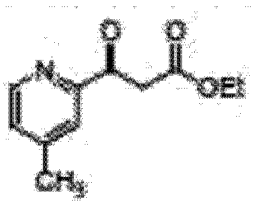
[0233] 将 6- 甲基吡啶甲酸 (1.0g, 7.3mmol) 和浓硫酸 (～ 98%, 0.6mL) 在乙醇 (40mL) 中的反应混合物回流 24 小时。蒸发额外的乙醇，随后在 0℃下添加水 (20mL)。将 pH 用碳酸氢钠粉末调节至 9。然后用乙酸乙酯 (30mL×3) 萃取混合物，并将合并的有机层经无水硫酸钠干燥并浓缩，得到 1.20g 呈无色油状物的 6- 甲基吡啶甲酸乙酯。MS:MH^+ = 166。

[0234] 将无水乙酸乙酯 (1mL, 9.9mmol) 在甲苯 (10mL) 中的溶液用乙醇钠 (449mg, 6.6mg) 在室温下处理。将混合物在氩气氛下搅拌 1 小时，然后添加 6- 甲基吡啶甲酸乙酯 (499mg,

3.3mmol)。将反应混合物加热至回流 20 小时。冷却至室温后,将其用乙酸酸化 (pH = 6),随后添加水 (20mL) 并用乙酸乙酯 (20mL×3) 萃取。将合并的有机层经无水硫酸钠干燥、浓缩并通过凝胶柱色谱 (乙酸乙酯 :己烷= 10 :90 至 20 :80) 纯化,得到 440mg 呈浅黄色油状物的化合物 3-(6- 甲基吡啶 -2- 基)-3- 氧代丙酸乙酯。^{1}H NMR(300MHz, $CDCl_3$) : δ 7.87(d, J = 7.8Hz, 1H, CH_{ar}), 7.72(t, J = 7.8Hz, 1H, CH_{ar}), 7.33(d, J = 7.5Hz, 1H, CH_{ar}), 4.23-4.16(m, 4H, 2×CH_2), 2.59(s, 3H, $ArCH_3$), 1.24(t, J = 7.2Hz, 3H, CH_3)。MS:MH^+ = 208。

[0235] 实施例 18 :3-(4- 甲基吡啶 -2- 基)-3- 氧代丙酸乙酯的合成。

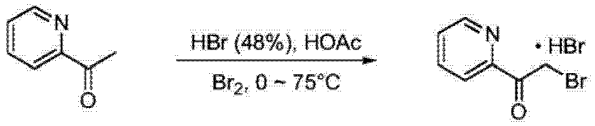
[0236]



[0237] 按照与实施例 17 相同的方式由 4- 甲基 - 吡啶 -2- 羧酸合成 3-(4- 甲基吡啶 -2- 基)-3- 氧代丙酸乙酯,得到呈浅黄色油状物的产物。^{1}H NMR(300MHz, $CDCl_3$) : δ 8.52(d, J = 5.1Hz, 1H, CH_{ar}), 7.90(d, J = 0.6Hz, 1H, CH_{ar}), 7.30(dd, J = 5.1, 0.9Hz, 1H, CH_{ar}), 4.23-4.16(m, 4H, 2×CH_2), 2.43(s, 3H, $ArCH_3$), 1.24(t, J = 7.2Hz, 3H, CH_3)。MS:MH^+ = 208。

[0238] 实施例 19 :2- 溴 -1-(吡啶 -2- 基) 乙酮氢溴酸盐的合成。

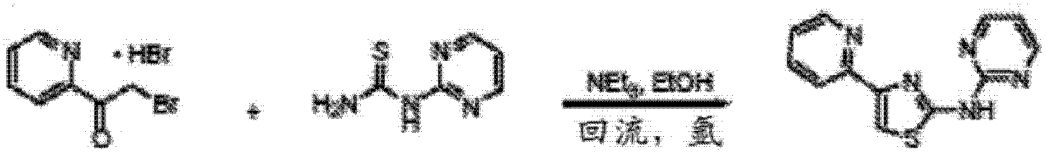
[0239]



[0240] 向 2- 乙酰基吡啶 (2.42g,20mmol) 在 48% 氢溴酸 (2.26mL,20mmol) 和乙酸 (22mL) 的混合物中的溶液在 0℃下滴加溴 (1.13mL,22mmol)。将反应混合物在室温下搅拌 1 小时,然后在 75℃下搅拌 3 小时。冷却至室温后,将其用四氢呋喃 (25mL) 稀释,并搅拌过夜。通过过滤收集产物,用四氢呋喃洗涤并真空干燥。得到 5.38g 呈白色固体的 2- 溴 -1-(吡啶 -2- 基) 乙酮氢溴酸盐。

[0241] 实施例 20 :4-(吡啶 -2- 基)-N-(嘧啶 -2- 基) 噻唑 -2- 胺的合成。

[0242]

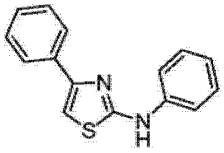


[0243] 将 2- 溴 -1-(吡啶 -2- 基) 乙酮氢溴酸盐 (1.69g,6mmol)、1-(嘧啶 -2- 基) 硫脲 (0.93g,6mmol) 和三乙胺 (2.1mL,15mmol) 在乙醇 (30mL) 中的反应混合物在氩气氛下回流 1 小时。冷却至室温后,将反应混合物用水 (100mL) 淬灭,并再搅拌 2 小时。通过过滤收集粗产物,并通过在甲醇中重结晶进一步纯化。得到 1.14g 呈白色固体的化合物 4-(吡啶 -2- 基)-N-(嘧啶 -2- 基) 噻唑 -2- 胺。^{1}H NMR(500MHz, DMSO-d_6) : δ 11.88(s, 1H, NH), 8.67(d, J = 5.0Hz, 2H, CH_{ar}), 8.61-8.59(m, 1H, CH_{ar}), 7.99(d, J = 8.0Hz, 1H, CH_{ar}), 7.89(dt, J

= 7.5, 1.5Hz, 1H, CH_{ar}), 7.75(s, 1H, CH_{ar}), 7.33-7.31(m, 1H, CH_{ar}), 7.06(t, J = 5.0Hz, 1H, CH_{ar})。MS:MH^+ = 256。可使用以下程序将 4-(吡啶 -2- 基)-N-(嘧啶 -2- 基) 噻唑 -2- 胺进一步转化为 HCl 盐 :将 4-(吡啶 -2- 基)-N-(嘧啶 -2- 基) 噻唑 -2- 胺 (102mg, 0.4mmol) 在甲醇 (10mL) 中的悬浮液用 4M HCl 溶液 (在 1,4- 二噁烷中,1mL) 处理。然后,将其加热至回流,并且反应混合物变为澄清溶液。通过蒸发除去溶剂,并通过在乙酸乙酯中重结晶进一步纯化,得到 130mg HCl 盐。^1H NMR(300MHz, DMSO-d_6): δ 8.71-8.67(m, 3H, CH_{ar}), 8.33-8.24(m, 3H, CH_{ar}), 7.71-7.67(m, 1H, CH_{ar}), 7.09(t, J = 5.1Hz, 1H, CH_{ar})。MS:MH^+ = 256。

[0244] 实施例 21 :N,4- 二苯基噻唑 -2- 胺的合成。

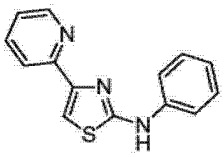
[0245]



[0246] 按照与实施例 20 相同的方式由 2- 溴 -1- 苯基 - 乙酮和苯基 - 硫脲合成 N,4- 二苯基噻唑 -2- 胺,得到呈浅黄色固体的产物。^1H NMR(300MHz, $CDCl_3$): δ 7.88-7.84(m, 2H, CH_{ar}), 7.55(s, 1H, NH), 7.43-7.28(m, 7H, CH_{ar}), 7.10-7.05(m, 1H, CH_{ar}), 6.83(d, J = 1.8Hz, 1H, CH_{ar})。MS:MH^+ = 253。

[0247] 实施例 22 :N- 苯基 -4-(吡啶 -2- 基) 噻唑 -2- 胺的合成。

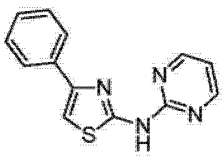
[0248]



[0249] 按照与实施例 20 相同的方式由 2- 溴 -1- 吡啶 -2- 基 - 乙酮和苯基 - 硫脲合成 N- 苯基 -4-(吡啶 -2- 基) 噻唑 -2- 胺,得到呈浅黄色固体的产物。^1H NMR(300MHz, $CDCl_3$): δ 8.62-8.60(m, 1H, CH_{ar}), 8.00(dt, J = 8.1, 1.2Hz, 1H, CH_{ar}), 7.75(dt, J = 8.1, 2.1Hz, 1H, CH_{ar}), 7.44-7.34(m、6H、5×CH_{ar} 和 NH 重叠), 7.23-7.18(m, 1H, CH_{ar}), 7.11-7.06(m, 1H, CH_{ar})。MS:MH^+ = 254。

[0250] 实施例 23 :4- 苯基 -N-(嘧啶 -2- 基) 噻唑 -2- 胺的合成。

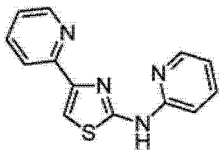
[0251]



[0252] 按照与实施例 20 相同的方式由 2- 溴 -1- 苯基 - 乙酮和嘧啶 -2- 基 - 硫脲合成 4- 苯基 -N-(嘧啶 -2- 基) 噻唑 -2- 胺,得到呈白色固体的产物。^1HNMR(300MHz, DMSO-d_6): δ 11.80(s, 1H, NH), 8.63(d, J = 5.1Hz, 2H, CH_{ar}), 7.92-7.89(m, 2H, CH_{ar}), 7.52(s, 1H, CH_{ar}), 7.43-7.38(m, 2H, CH_{ar}), 7.31-7.29(m, 1H, CH_{ar}), 7.03(t, J = 5.1Hz, 1H, CH_{ar})。MS:MH^+ = 255。

[0253] 实施例 24 :N,4- 二 (吡啶 -2- 基) 噻唑 -2- 胺的合成。

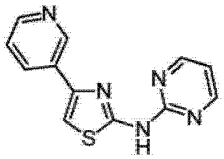
[0254]



[0255] 按照与实施例 20 相同的方式由 2- 溴 -1- 吡啶 -2- 基 - 乙酮和吡啶 -2- 基 - 硫脲合成 N,4- 二 (吡啶 -2- 基) 噻唑 -2- 胺，得到呈白色固体的产物。^{1}H NMR(500MHz, DMSO-d_6) : δ 11.45(s, 1H, NH), 8.60(d, J = 4.5Hz, 1H, CH_{ar}), 8.32(dd, J = 5.5, 2.0Hz, 1H, CH_{ar}), 7.97(d, J = 8.0Hz, 1H, CH_{ar}), 7.88(dt, J = 8.0, 2.0Hz, 1H, CH_{ar}), 7.74-7.71(m, 1H, CH_{ar}), 7.65(s, 1H, CH_{ar}), 7.33-7.30(m, 1H, CH_{ar}), 7.11(d, J = 8.5Hz, 1H, CH_{ar}), 6.96-6.93(m, 1H, CH_{ar})。MS:MH^+ = 255。

[0256] 实施例 25 :4-(吡啶 -3- 基)-N-(嘧啶 -2- 基) 噻唑 -2- 胺的合成。

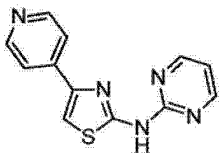
[0257]



[0258] 按照与实施例 20 相同的方式由 2- 溴 -1- 吡啶 -3- 基 - 乙酮和嘧啶 -2- 基 - 硫脲合成 4-(吡啶 -3- 基)-N-(嘧啶 -2- 基) 噻唑 -2- 胺，得到呈灰色固体的产物。^{1}H NMR(300MHz, DMSO-d_6) : δ 11.93(s, 1H, NH), 9.14-9.13(m, 1H, CH_{ar}), 8.65(d, J = 4.8Hz, 2H, CH_{ar}), 8.51(dd, J = 5.1, 1.8Hz, 1H, CH_{ar}), 8.25-8.21(m, 1H, CH_{ar}), 7.70(s, 1H, CH_{ar}), 7.46-7.42(m, 1H, CH_{ar}), 7.04(t, J = 4.8Hz, 1H, CH_{ar})。MS:MH^+ = 256。

[0259] 实施例 26 :4-(吡啶 -4- 基)-N-(嘧啶 -2- 基) 噻唑 -2- 胺的合成。

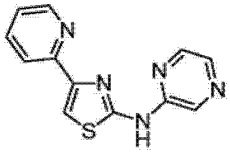
[0260]



[0261] 按照与实施例 20 相同的方式由 2- 溴 -1- 吡啶 -4- 基 - 乙酮和嘧啶 -2- 基 - 硫脲合成 4-(吡啶 -4- 基)-N-(嘧啶 -2- 基) 噻唑 -2- 胺，得到呈灰色固体的产物。^{1}H NMR(300MHz, DMSO-d_6) : δ 11.93(s, 1H, NH), 8.65(d, J = 4.8Hz, 2H, CH_{ar}), 8.59(dd, J = 4.8, 1.5Hz, 2H, CH_{ar}), 7.89(s, 1H, CH_{ar}), 7.85-7.83(m, 2H, CH_{ar}), 7.05(t, J = 4.8Hz, 1H, CH_{ar})。MS:MH^+ = 256。

[0262] 实施例 27 :N-(吡嗪 -2- 基)-4-(吡啶 -2- 基) 噻唑 -2- 胺的合成。

[0263]

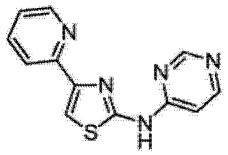


[0264] 按照与实施例 20 相同的方式由 2- 溴 -1- 吡啶 -2- 基 - 乙酮和嘧啶 -2- 基 - 硫脲合成 N-(吡嗪 -2- 基)-4-(吡啶 -2- 基) 噻唑 -2- 胺，得到呈棕色固体的产物。^{1}H NMR(300MHz, DMSO-d_6) : δ 11.87(s, 1H, NH), 8.60-8.57(m, 1H, CH_{ar}), 8.51(d, J =

1.5Hz, 1H, CH_{ar}), 8.32(dd, J = 3.0, 1.5Hz, 1H, CH_{ar}), 8.13(d, J = 2.4Hz, 1H, CH_{ar}), 7.96(dt, J = 7.8, 1.2Hz, 1H, CH_{ar}), 7.87(dt, J = 7.8, 1.8Hz, 1H, CH_{ar}), 7.73(s, 1H, CH_{ar}), 7.33-7.29(m, 1H, CH_{ar})。MS:MH^+ = 256。

[0265] 实施例 28 :4-(吡啶 -2- 基)-N-(嘧啶 -4- 基) 噻唑 -2- 胺的合成。

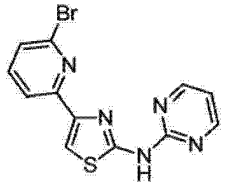
[0266]



[0267] 按照与实施例 20 相同的方式由 2- 溴 -1- 吡啶 -2- 基 - 乙酮和嘧啶 -4- 基 - 硫脲合成 4-(吡啶 -2- 基)-N-(嘧啶 -4- 基) 噻唑 -2- 胺,得到呈棕色固体的产物。^1H NMR(300MHz, DMSO-d_6) : δ 11.91(s, 1H, NH), 8.84(d, J = 0.9Hz, 1H, CH_{ar}), 8.60-8.57(m, 1H, CH_{ar}), 8.46(d, J = 6.0Hz, 1H, CH_{ar}), 7.95(dt, J = 7.8, 1.2Hz, 1H, CH_{ar}), 7.87(dt, J = 8.1, 2.1Hz, 1H, CH_{ar}), 7.80(s, 1H, CH_{ar}), 7.34-7.29(m, 1H, CH_{ar}), 7.10(dd, J = 5.7, 1.2Hz, 1H, CH_{ar})。MS:MH^+ = 256。

[0268] 实施例 29 :4-(6- 溴吡啶 -2- 基)-N-(嘧啶 -2- 基) 噻唑 -2- 胺的合成。

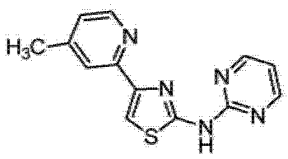
[0269]



[0270] 按照与实施例 20 相同的方式由 2- 溴 -1-(6- 溴 - 吡啶 -2- 基)- 乙酮和嘧啶 -2- 基 - 硫脲合成 4-(6- 溴吡啶 -2- 基)-N-(嘧啶 -2- 基) 噻唑 -2- 胺,得到呈灰色固体的产物。^1H NMR(300MHz, DMSO-d_6) : δ 11.92(s, 1H, NH), 8.65(d, J = 4.5Hz, 2H, CH_{ar}), 7.95(dd, J = 7.8, 0.9Hz, 1H, CH_{ar}), 7.82(t, J = 8.1Hz, 1H, CH_{ar}), 7.75(d, J = 0.6Hz, 1H, CH_{ar}), 7.54(dd, J = 8.1, 0.9Hz, 1H, CH_{ar}), 7.05(t, J = 4.8Hz, 1H, CH_{ar})。MS:MH^+ = 334。

[0271] 实施例 30 :4-(4- 甲基吡啶 -2- 基)-N-(嘧啶 -2- 基) 噻唑 -2- 胺的合成。

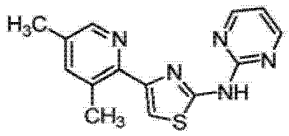
[0272]



[0273] 按照与实施例 20 相同的方式由 2- 溴 -1-(4- 甲基 - 吡啶 -2- 基)- 乙酮和嘧啶 -2- 基 - 硫脲合成 4-(4- 甲基吡啶 -2- 基)-N-(嘧啶 -2- 基) 噻唑 -2- 胺,得到呈深灰色固体的产物。^1H NMR(300MHz, DMSO-d_6) : δ 11.81(s, 1H, NH), 8.64(d, J = 4.8Hz, 2H, CH_{ar}), 8.42(dd, J = 4.2, 0.6Hz, 1H, CH_{ar}), 7.82(t, J = 0.9Hz, 1H, CH_{ar}), 7.70(s, 1H, CH_{ar}), 7.14-7.12(m, 1H, CH_{ar}), 7.04(t, J = 4.8Hz, 1H, CH_{ar}), 2.36(s, 3H, $ArCH_3$)。MS:MH^+ = 270。

[0274] 实施例 31 :4-(3,5- 二甲基吡啶 -2- 基)-N-(嘧啶 -2- 基) 噻唑 -2- 胺的合成。

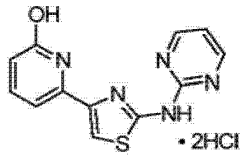
[0275]



[0276] 按照与实施例 20 相同的方式由 2- 溴 -1-(3,5- 二甲基 - 吡啶 -2- 基)- 乙酮和嘧啶 -2- 基 - 硫脲合成 4-(3,5- 二甲基吡啶 -2- 基)-N-(嘧啶 -2- 基) 噻唑 -2- 胺,得到呈浅灰色固体的产物。^{1}H NMR(300MHz,DMSO-d_6):δ 11.70(s,1H,NH),8.64(d,J = 4.8Hz,2H,CH_{ar}),8.24(s,1H,CH_{ar}),7.46(s,1H,CH_{ar}),7.41(s,1H,CH_{ar}),7.02(t,J = 4.8Hz,1H,CH_{ar}),2.52(s,3H,$ArCH_3$),2.27(s,3H,$ArCH_3$)。MS:MH^+ = 284。

[0277] 实施例 32 :6-(2-(嘧啶 -2- 基氨基) 噻唑 -4- 基) 吡啶 -2- 醇二盐酸盐的合成。

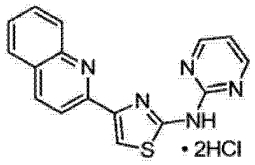
[0278]



[0279] 按照与实施例 20 相同的方式由 2- 溴 -1-(6- 羟基 - 吡啶 -2- 基)- 乙酮二盐酸盐和嘧啶 -2- 基 - 硫脲合成 6-(2-(嘧啶 -2- 基氨基) 噻唑 -4- 基) 吡啶 -2- 醇二盐酸盐,得到呈灰色固体的产物。^{1}H NMR(300MHz,DMSO-d_6):δ 11.93(s,1H,NH),8.64(d,J = 4.5Hz,2H,CH_{ar}),7.92(s,1H,CH_{ar}),7.53(t,J = 8.1Hz,1H,CH_{ar}),7.05(t,J = 4.8Hz,1H,CH_{ar}),6.89(d,J = 6.9Hz,1H,CH_{ar}),6.33(d,J = 9.3Hz,1H,CH_{ar})。MS:MH^+ = 272。

[0280] 实施例 33 :N-(嘧啶 -2- 基)-4-(喹啉 -2- 基) 噻唑 -2- 胺二盐酸盐的合成。

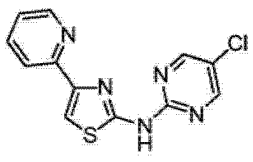
[0281]



[0282] 按照与实施例 20 相同的方式由 2- 溴 -1- 喹啉 -2- 基 - 乙酮二盐酸盐和嘧啶 -2- 基 - 硫脲合成 N-(嘧啶 -2- 基)-4-(喹啉 -2- 基) 噻唑 -2- 胺二盐酸盐,得到呈灰色固体的产物。^{1}H NMR(300MHz,DMSO-d_6):δ 8.84(d,J = 9.0Hz,1H,CH_{ar}),8.70(d,J = 5.1Hz,1H,CH_{ar}),8.56(s,1H,CH_{ar}),8.38(dd,J = 8.7,3.3Hz,1H,CH_{ar}),8.16(d,J = 7.8Hz,1H,CH_{ar}),7.96(t,J = 7.5Hz,1H,CH_{ar}),7.75(t,J = 7.8Hz,1H,CH_{ar}),7.10(t,J = 4.8Hz,1H,CH_{ar})。MS:MH^+ = 306。

[0283] 实施例 34 :N-(5- 氯嘧啶 -2- 基)-4-(吡啶 -2- 基) 噻唑 -2- 胺的合成。

[0284]

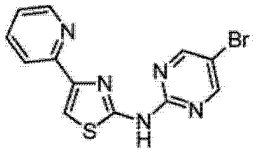


[0285] 按照与实施例 20 相同的方式由 2- 溴 -1- 吡啶 -2- 基 - 乙酮和 (5- 氯 - 嘧啶 -2- 基)- 硫脲合成 N-(5- 氯嘧啶 -2- 基)-4-(吡啶 -2- 基) 噻唑 -2- 胺,得到呈白色

固体的产物。^{1}H NMR(300MHz,DMSO-d_6):δ 12.11(s,1H,NH),8.74(s,2H,CH_{ar}),8.58(d,J = 5.1Hz,1H,CH_{ar}),7.97(d,J = 8.1Hz,1H,CH_{ar}),7.87(m,1H,CH_{ar}),7.76(s,1H,CH_{ar}),7.31(m,1H,CH_{ar})。MS:MH^+ = 290。

[0286] 实施例 35 :N-(5- 溴嘧啶 -2- 基)-4-(吡啶 -2- 基) 噻唑 -2- 胺的合成。

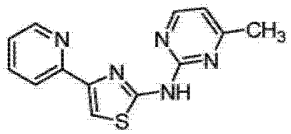
[0287]



[0288] 按照与实施例 20 相同的方式由 2- 溴 -1- 吡啶 -2- 基 - 乙酮和 (5- 溴 - 嘧啶 -2- 基)- 硫脲合成 N-(5- 溴嘧啶 -2- 基)-4-(吡啶 -2- 基) 噻唑 -2- 胺,得到呈白色固体的产物。^{1}H NMR(300MHz,DMSO-d_6):δ 12.10(s,1H,NH),8.79(s,2H,CH_{ar}),8.58-8.57(m,1H,CH_{ar}),7.96(d,J = 7.8Hz,1H,CH_{ar}),7.86(dt,J = 8.1,1.8Hz,1H,CH_{ar}),7.77(s,1H,CH_{ar}),7.33-7.28(m,1H,CH_{ar})。MS:MH^+ = 334。

[0289] 实施例 36 :N-(4- 甲基嘧啶 -2- 基)-4-(吡啶 -2- 基) 噻唑 -2- 胺的合成。

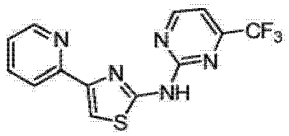
[0290]



[0291] 按照与实施例 20 相同的方式由 2- 溴 -1- 吡啶 -2- 基 - 乙酮和 (4- 甲基 - 嘧啶 -2- 基)- 硫脲合成 N-(4- 甲基嘧啶 -2- 基)-4-(吡啶 -2- 基) 噻唑 -2- 胺,得到呈灰色固体的产物。^{1}H NMR(300MHz,DMSO-d_6):δ 11.74(s,1H,NH),8.57(d,J = 4.2Hz,1H,CH_{ar}),8.48(d,J = 4.8Hz,1H,CH_{ar}),7.96(d,J = 7.8Hz,1H,CH_{ar}),7.86(dt,J = 7.5,1.8Hz,1H,CH_{ar}),7.71(s,1H,CH_{ar}),7.31-7.27(m,1H,CH_{ar}),6.92(d,J = 4.8Hz,1H,CH_{ar}),2.44(s,3H,$ArCH_3$)。MS:MH^+ = 270。

[0292] 实施例 37 :4-(吡啶 -2- 基)-N-(4-(三氟甲基) 嘧啶 -2- 基) 噻唑 -2- 胺的合成。

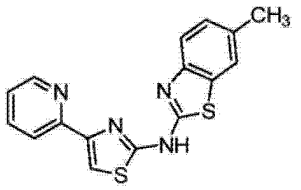
[0293]



[0294] 按照与实施例 20 相同的方式由 2- 溴 -1- 吡啶 -2- 基 - 乙酮和 (4- 三氟甲基 - 嘧啶 -2- 基)- 硫脲合成 4-(吡啶 -2- 基)-N-(4-(三氟甲基) 嘧啶 -2- 基) 噻唑 -2- 胺,得到呈灰色固体的产物。^{1}H NMR(300MHz,DMSO-d_6):δ 12.42(s,1H,NH),8.98(d,J = 4.5Hz,1H,CH_{ar}),8.58(d,J = 3.6Hz,1H,CH_{ar}),7.97(d,J = 8.1Hz,1H,CH_{ar}),7.89-7.83(m,2H,CH_{ar}),7.48(d,J = 4.5Hz,1H,CH_{ar}),7.31(t,J = 5.7Hz,1H,CH_{ar})。MS:MH^+ = 324。

[0295] 实施例 38 :6- 甲基 -N-(4-(吡啶 -2- 基) 噻唑 -2- 基) 苯并 [d] 噻唑 -2- 胺的合成。

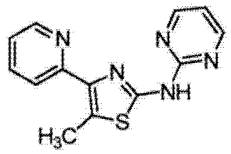
[0296]



[0297] 按照与实施例 20 相同的方式由 2- 溴 -1- 吡啶 -2- 基 - 乙酮和 (6- 甲基 - 苯并噻唑 -2- 基)- 硫脲合成 6- 甲基 -N-(4-(吡啶 -2- 基) 噻唑 -2- 基) 苯并 [d] 噻唑 -2- 胺，得到呈浅棕色固体的产物。^{1}H NMR(300MHz, $CDCl_3$) : δ 8.62(s, 1H, CH_{ar}), 8.13(d, J = 6.6Hz, 1H, CH_{ar}), 7.82(t, J = 7.5Hz, 1H, CH_{ar}), 7.64-7.59(m, 1H, CH_{ar}), 7.52-7.48(m, 2H, CH_{ar}), 7.23-7.18(m, 2H, CH_{ar}), 2.44(s, 3H, $ArCH_3$)。MS:MH^+ = 325。

[0298] 实施例 39 :5- 甲基 -4-(吡啶 -2- 基)-N-(嘧啶 -2- 基) 噻唑 -2- 胺的合成。

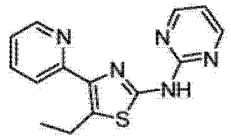
[0299]



[0300] 按照与实施例 20 相同的方式由 2- 溴 -1- 吡啶 -2- 基 - 丙 -1- 酮和嘧啶 -2- 基 - 硫脲合成 5- 甲基 -4-(吡啶 -2- 基)-N-(嘧啶 -2- 基) 噻唑 -2- 胺，得到呈灰色固体的产物。^{1}H NMR(300MHz, DMSO-d_6) : δ 11.63(s, 1H, NH), 8.61(d, J = 4.5Hz, 3H, CH_{ar}), 7.97(d, J = 8.4Hz, 1H, CH_{ar}), 7.84(t, J = 7.5Hz, 1H, CH_{ar}), 7.28-7.24(m, 1H, CH_{ar}), 7.01(t, J = 4.8Hz, 1H, CH_{ar}), 2.72(s, 3H, $ArCH_3$)。MS:MH^+ = 270。

[0301] 实施例 40 :5- 乙基 -4-(吡啶 -2- 基)-N-(嘧啶 -2- 基) 噻唑 -2- 胺的合成。

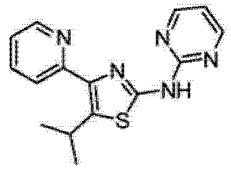
[0302]



[0303] 按照与实施例 20 相同的方式由 2- 溴 -1- 吡啶 -2- 基 - 丁 -1- 酮和嘧啶 -2- 基 - 硫脲合成 5- 乙基 -4-(吡啶 -2- 基)-N-(嘧啶 -2- 基) 噻唑 -2- 胺，得到呈灰色固体的产物。^{1}H NMR(300MHz, DMSO-d_6) : δ 11.61(s, 1H, NH), 8.62-8.59(m, 3H, CH_{ar}), 7.97(d, J = 7.8Hz, 1H, CH_{ar}), 7.84(dt, J = 7.8, 1.8Hz, 1H, CH_{ar}), 7.28-7.24(m, 1H, CH_{ar}), 7.01(t, J = 4.8Hz, 1H, CH_{ar}), 2.49-2.48(m、2H、$ArCH_2$ 与的 DMSO 峰重叠), 1.26(t, J = 7.5Hz, 3H, CH_3)。MS:MH^+ = 284。

[0304] 实施例 41 :5- 异丙基 -4-(吡啶 -2- 基)-N-(嘧啶 -2- 基) 噻唑 -2- 胺的合成。

[0305]

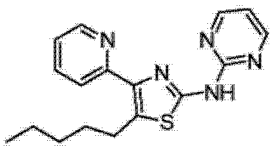


[0306] 按照与实施例 20 相同的方式由 2- 溴 -3- 甲基 -1- 吡啶 -2- 基 - 丁 -1- 酮和嘧啶 -2- 基 - 硫脲合成 5- 异丙基 -4-(吡啶 -2- 基)-N-(嘧啶 -2- 基) 噻唑 -2- 胺，得到呈

浅灰色固体的产物。^{1}H NMR(300MHz, $CDCl_3$):δ 9.95(s, 1H, NH), 8.67-8.66(m, 3H, CH_{ar}), 7.88(d, J = 7.8Hz, 1H, CH_{ar}), 7.73(t, J = 8.1Hz, 1H, CH_{ar}), 7.17(m, 1H, CH_{ar}), 6.89(t, J = 5.1Hz, 1H, CH_{ar}), 4.35-4.30(m, 1H, CH), 1.40(d, J = 6.6Hz, 6H, $C(CH_3)_2$)。MS:MH^+ = 298。

[0307] 实施例 42 :5- 戊基 -4-(吡啶 -2- 基)-N-(嘧啶 -2- 基) 噻唑 -2- 胺的合成。

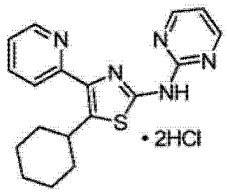
[0308]



[0309] 按照与实施例 20 相同的方式由 2- 溴 -1- 吡啶 -2- 基 - 庚 -1- 酮和嘧啶 -2- 基 - 硫脲合成 5- 戊基 -4-(吡啶 -2- 基)-N-(嘧啶 -2- 基) 噻唑 -2- 胺,得到呈灰色固体的产物。^{1}H NMR(300MHz, $CDCl_3$):δ 10.07(s, 1H, NH), 8.66(m, 3H, CH_{ar}), 7.88(d, J = 7.5Hz, 1H, CH_{ar}), 7.73(t, J = 7.2Hz, 1H, CH_{ar}), 7.16(m, 1H, CH_{ar}), 6.89(m, 1H, CH_{ar}), 3.29(t, J = 7.5Hz, 2H, $ArCH_2$), 0.89(m, 3H, CH_3)。MS:MH^+ = 326。

[0310] 实施例 43 :5- 环己基 -4-(吡啶 -2- 基)-N-(嘧啶 -2- 基) 噻唑 -2- 胺二盐酸盐的合成。

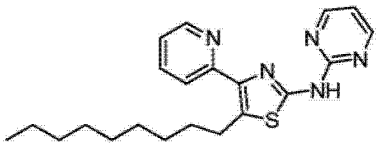
[0311]



[0312] 按照与实施例 20 相同的方式由 2- 溴 -2- 环己基 -1- 吡啶 -2- 基 - 乙酮二盐酸盐和嘧啶 -2- 基 - 硫脲合成 5- 环己基 -4-(吡啶 -2- 基)-N-(嘧啶 -2- 基) 噻唑 -2- 胺二盐酸盐,得到呈浅黄色固体的产物。^{1}H NMR(300MHz, DMSO-d_6):δ 8.74(d, J = 4.5Hz, 1H, CH_{ar}), 8.65(d, J = 4.8Hz, 1H, CH_{ar}), 8.24(t, J = 8.1Hz, 1H, CH_{ar}), 8.04(d, J = 8.7Hz, 1H, CH_{ar}), 7.63(t, J = 6.3Hz, 1H, CH_{ar}), 7.05(t, J = 4.8Hz, 1H, CH_{ar}), 3.58(m, 1H, CH), 2.02-1.29(m, 10H, 5×CH_2)。MS:MH^+ = 338。

[0313] 实施例 44 :5- 壬基 -4-(吡啶 -2- 基)-N-(嘧啶 -2- 基) 噻唑 -2- 胺的合成。

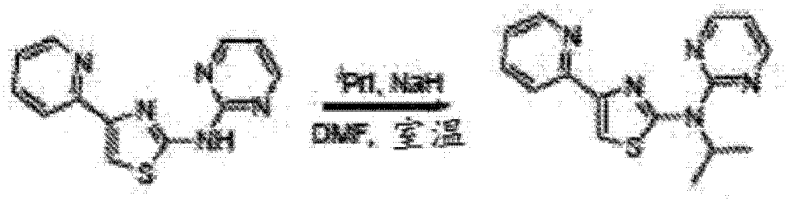
[0314]



[0315] 按照与实施例 20 相同的方式由 2- 溴 -1- 吡啶 -2- 基 - 十一烷 -1- 酮和嘧啶 -2- 基 - 硫脲合成 5- 壬基 -4-(吡啶 -2- 基)-N-(嘧啶 -2- 基) 噻唑 -2- 胺,得到呈银灰色固体的产物。^{1}H NMR(300MHz, $CDCl_3$):δ 9.70(s, 1H, NH), 8.64(d, J = 5.1Hz, 3H, CH_{ar}), 7.88(d, J = 8.1Hz, 1H, CH_{ar}), 7.72(dt, J = 7.8, 1.8Hz, 1H, CH_{ar}), 7.19-7.14(m, 1H, CH_{ar}), 6.89(t, J = 5.1Hz, 1H, CH_{ar}), 3.29(t, J = 8.1Hz, 2H, $ArCH_2$), 1.77-1.69(m, 2H, CH_2), 1.40-1.25(m, 12H, 6×CH_2), 0.87(t, J = 6.9Hz, 3H, CH_3)。MS:MH^+ = 382。

[0316] 实施例 45 :N- 异丙基 -4-(吡啶 -2- 基)-N-(嘧啶 -2- 基) 噻唑 -2- 胺的合成。

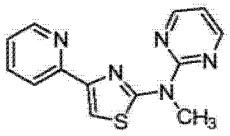
[0317]



[0318] 向 4-(吡啶 -2- 基)-N-(嘧啶 -2- 基) 噻唑 -2- 胺 (51mg,0.2mmol) 在二甲基甲酰胺 (4mL) 中的搅拌悬浮液添加氢化钠 (60％,12mg,0.3mmol),2 分钟后添加 2- 碘丙烷 (20μL,0.2mmol)。继续搅拌 24 小时。用饱和氯化铵 (10mL) 淬灭反应,并用乙酸乙酯 (15mL×3) 萃取。将合并的有机层经无水硫酸钠干燥、浓缩,并通过凝胶柱色谱 (乙酸乙酯 : 己烷 = 30 :70) 纯化,以得到 54mg 呈白色固体的化合物 N- 异丙基 -4-(吡啶 -2- 基)-N-(嘧啶 -2- 基) 噻唑 -2- 胺。^{1}H NMR(300MHz, $CDCl_3$) : δ 8.59(s, 3H, CH_{ar}), 8.15(d, J = 7.2Hz, 1H, CH_{ar}), 7.77(s, 2H, CH_{ar}), 7.19(s, 1H, CH_{ar}), 6.85(s, 1H, CH_{ar}), 5.85(m, 1H, NCH), 1.69(d, J = 6.0Hz, 6H, $C(CH_3)_2$)。MS:MH^+ = 298。

[0319] 实施例 46 :N- 甲基 -4-(吡啶 -2- 基)-N-(嘧啶 -2- 基) 噻唑 -2- 胺的合成。

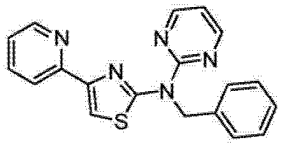
[0320]



[0321] 按照与实施例 45 相同的方式由 4-(吡啶 -2- 基)-N-(嘧啶 -2- 基) 噻唑 -2- 胺和碘甲烷合成 N- 甲基 -4-(吡啶 -2- 基)-N-(嘧啶 -2- 基) 噻唑 -2- 胺,以 50％产率得到呈白色固体的产物。^{1}H NMR(300MHz, $CDCl_3$) : δ 8.64-8.60(m, 3H, CH_{ar}), 8.18-8.15(m, 1H, CH_{ar}), 7.77(dt, J = 7.8, 1.8Hz, 1H, CH_{ar}), 7.72(s, 1H, CH_{ar}), 7.22-7.17(m, 1H, CH_{ar}), 6.90(t, J = 4.8Hz, 1H, CH_{ar}), 4.07(s, 3H, NCH_3)。MS:MH^+ = 270。

[0322] 实施例 47 :N- 苄基 -4-(吡啶 -2- 基)-N-(嘧啶 -2- 基) 噻唑 -2- 胺的合成。

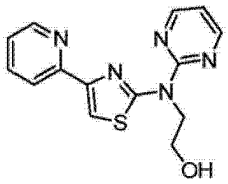
[0323]



[0324] 按照与实施例 45 相同的方式由 4-(吡啶 -2- 基)-N-(嘧啶 -2- 基) 噻唑 -2- 胺和苄基溴化物合成 N- 苄基 -4-(吡啶 -2- 基)-N-(嘧啶 -2- 基) 噻唑 -2- 胺,得到呈白色固体的产物。^{1}H NMR(300MHz, $CDCl_3$) : δ 8.62-8.60(m, 3H, CH_{ar}), 8.08(d, J = 7.8Hz, 1H, CH_{ar}), 7.75-7.70(m, 2H, CH_{ar}), 7.51(d, J = 7.2Hz, 2H, CH_{ar}), 7.29-7.15(m、4H、CH_{ar} 与 $CHCl_3$ 的峰重叠), 6.88(t, J = 4.8Hz, 1H, CH_{ar}), 5.98(s, 2H, NCH_2Ar)。MS:MH^+ = 346。

[0325] 实施例 48 :2-((4-(吡啶 -2- 基) 噻唑 -2- 基)(嘧啶 -2- 基) 氨基) 乙醇的合成。

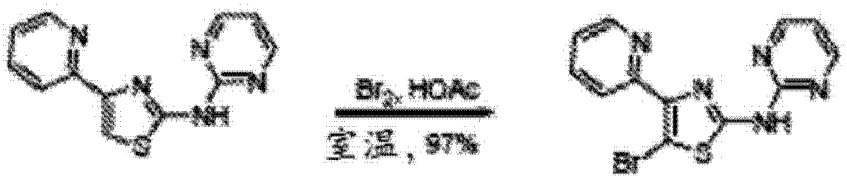
[0326]



[0327] 按照与实施例 45 相同的方式由 4-(吡啶 -2- 基)-N-(嘧啶 -2- 基) 噻唑 -2- 胺和 2- 溴乙醇合成 2-((4-(吡啶 -2- 基) 噻唑 -2- 基)(嘧啶 -2- 基) 氨基) 乙醇,得到呈白色固体的产物。^{1}H NMR(300MHz, $CDCl_3$) : δ 8.63-8.60(m, 3H, CH_{ar}), 8.02(d, J = 7.8Hz, 1H, CH_{ar}), 7.79-7.73(m, 2H, CH_{ar}), 7.23-7.18(m, 1H, CH_{ar}), 6.93(t, J = 4.8Hz, 1H, CH_{ar}), 4.94(t, J = 5.1Hz, 2H, NCH_2), 4.71(t, J = 4.5Hz, 1H, OH), 4.20-4.15(m, 2H, CH_2)。MS:MH^+ = 300。

[0328] 实施例 49 :5- 溴 -4-(吡啶 -2- 基)-N-(嘧啶 -2- 基) 噻唑 -2- 胺的合成。

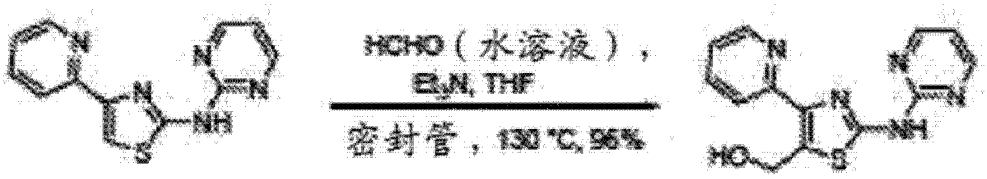
[0329]



[0330] 向 4-(吡啶 -2- 基)-N-(嘧啶 -2- 基) 噻唑 -2- 胺 (102mg, 0.4mmol) 在乙酸 (2mL) 中的悬浮液在室温下添加溴。继续搅拌 2 小时,然后添加乙酸乙酯 (20mL)。通过过滤收集粗产物,并将其在乙酸乙酯中重结晶,得到 130mg 呈黄色固体的 5- 溴 -4-(吡啶 -2- 基)-N-(嘧啶 -2- 基) 噻唑 -2- 胺。^{1}H NMR(300MHz, DMSO-d_6) : δ 8.73-8.67(m, 3H, CH_{ar}), 8.10(d, J = 3.3Hz, 2H, CH_{ar}), 7.57-7.53(m, 1H, CH_{ar}), 7.11(t, J = 5.1Hz, 1H, CH_{ar})。MS:MH^+ = 334。

[0331] 实施例 50 :(4-(吡啶 -2- 基)-2-(嘧啶 -2- 基氨基) 噻唑 -5- 基) 甲醇的合成。

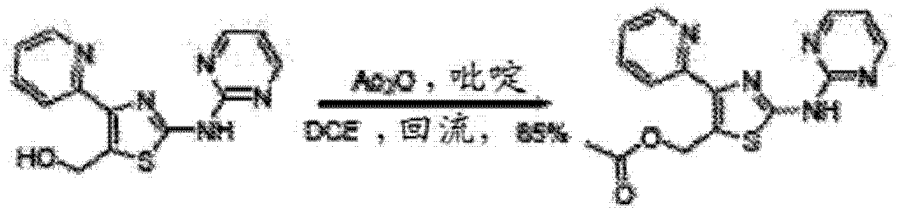
[0332]



[0333] 将 4-(吡啶 -2- 基)-N-(嘧啶 -2- 基) 噻唑 -2- 胺 (51mg, 0.2mmol) 在四氢呋喃 (4mL) 中的悬浮液在密封管中用甲醛水溶液 (36.5%, 2mL) 处理,然后用三乙胺 (0.6mL) 处理。将其加热至 130℃,持续 12 小时,然后冷却并浓缩。将残余物用水 (20mL) 淬灭、搅拌并过滤,获得产物,将其用水和乙酸乙酯依次洗涤,然后真空干燥。获得 55mg 呈白色固体的纯化合物 (4-(吡啶 -2- 基)-2-(嘧啶 -2- 基氨基) 噻唑 -5- 基) 甲醇。^{1}H NMR(300MHz, DMSO-d_6) : δ 11.63(s, 1H, NH), 8.63-8.59(m, 3H, CH_{ar}), 8.00(d, J = 7.8Hz, 1H, CH_{ar}), 7.87(t, J = 7.2Hz, 1H, CH_{ar}), 7.30-7.26(m, 1H, CH_{ar}), 7.02(t, J = 4.8Hz, 1H, CH_{ar}), 5.81(t, J = 5.7Hz, 1H, OH), 5.03(d, J = 5.7Hz, 2H, OCH_2Ar)。MS:MH^+ = 286。

[0334] 实施例 51 :(4-(吡啶 -2- 基)-2-(嘧啶 -2- 基氨基) 噻唑 -5- 基) 甲基乙酸酯的合成。

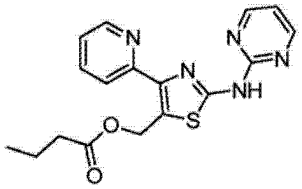
[0335]



[0336] 将(4-(吡啶-2-基)-2-(嘧啶-2-基氨基)噻唑-5-基)甲醇(29mg,0.1mmol)在1,2-二氯乙烷(DCE,5mL)中的悬浮液用吡啶(81μL,1mmol)处理,随后在室温下添加醋酸酐(38μL,0.4mmol)。然后将其加热至回流5小时。冷却后,将反应用水(50mL)淬灭,通过使用粉末状碳酸钠将pH调节至10,并用二氯甲烷(30mL×4)萃取。将合并的有机层经硫酸钠干燥,然后浓缩。将所得残余物悬浮在乙酸乙酯中,过滤并进一步用乙酸乙酯洗涤。28mg呈白色固体的(4-(吡啶-2-基)-2-(嘧啶-2-基氨基)噻唑-5-基)甲基乙酸酯。MS:MH+ = 281

[0337] 实施例52:(4-(吡啶-2-基)-2-(嘧啶-2-基氨基)噻唑-5-基)甲基丁酸酯的合成。

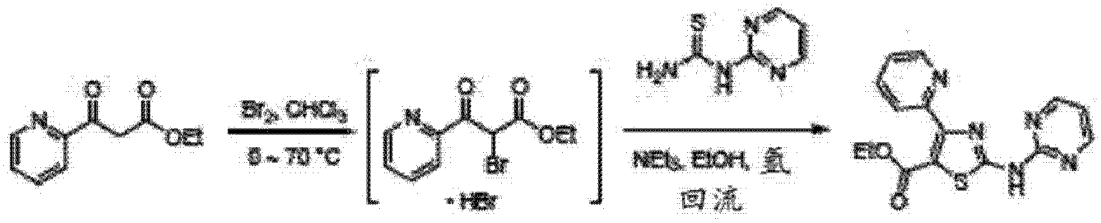
[0338]



[0339] 按照与实施例49相同的方式由(4-(吡啶-2-基)-2-(嘧啶-2-基氨基)噻唑-5-基)甲醇和丁酸酐合成(4-(吡啶-2-基)-2-(嘧啶-2-基氨基)噻唑-5-基)甲基丁酸酯,以57%产率得到呈灰白色固体的产物。^{1}H NMR(300MHz,$CDCl_3$):δ9.84(s,1H,NH),8.68-8.64(m,3H,CH_{ar}),7.98(d,J = 7.8Hz,1H,CH_{ar}),7.75(dt,J = 7.8,2.1Hz,1H,CH_{ar}),7.20(dt,J = 6.3,1.2Hz,1H,CH_{ar}),6.93(t,J = 4.8Hz,1H,CH_{ar}),5.85(s,2H,$ArCH_2O$),2.38(t,J = 7.5Hz,2H,CH_2CO),1.74-1.67(m,2H,CH_2),0.97(t,J = 7.5,3H,CH_3)。MS:MNa^+ = 378。

[0340] 实施例53:4-(吡啶-2-基)-2-(嘧啶-2-基氨基)噻唑-5-甲酸乙酯的合成。

[0341]



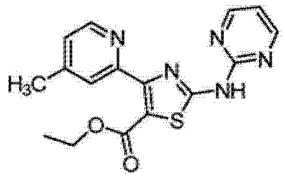
[0342] 向3-氧代-3-(吡啶-2-基)丙酸乙酯(1.16g,6mmol)在$CHCl_3$(20mL)中的搅拌溶液在0℃下滴加溴(339μL,6.6mmol)。首先,将反应混合物在40℃下搅拌1hr,然后在70℃下再搅拌一小时。蒸发溶剂,得到粗2-溴-3-氧代-3-(吡啶-2-基)丙酸乙酯氢溴酸盐。

[0343] 将粗2-溴-3-氧代-3-(吡啶-2-基)丙酸乙酯氢溴酸盐、1-(嘧啶-2-基)硫脲(617mg,4mmol)和三乙胺(1.94mL,14mmol)在乙醇(20mL)中的反应混合物在氩气氛下回流

1 小时。冷却至室温后，将反应混合物用水 (200mL) 淬灭并搅拌 30 分钟。然后将其过滤并将收集的固体在乙酸乙酯 / 己烷 (1:1，20mL) 中浆化。过滤和真空干燥后，得到 910mg 呈棕红色固体的 4-(吡啶 -2- 基)-2-(嘧啶 -2- 基氨基) 噻唑 -5- 甲酸乙酯。^{1}HNMR(300MHz, DMSO-d_6) : δ 12.34(s, 1H, NH), 8.73(d, J = 4.5Hz, 2H, CH_{ar}), 8.60(d, J = 3.9Hz, 1H, CH_{ar}), 7.86(dt, J = 7.8, 1.8Hz, 1H, CH_{ar}), 7.65(d, J = 7.5Hz, 1H, CH_{ar}), 7.43-7.38(m, 1H, CH_{ar}), 7.14(t, J = 5.1Hz, 1H, CH_{ar}), 4.12(q, J = 7.2Hz, 2H, OCH_2), 1.12(t, J = 7.2Hz, 3H, CH_3)。MS:MH^+ = 328。

[0344] 实施例 54 :4-(4- 甲基吡啶 -2- 基)-2-(嘧啶 -2- 基氨基) 噻唑 -5- 甲酸乙酯的合成。

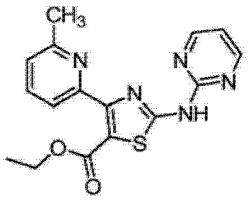
[0345]



[0346] 按照与实施例 53 相同的方式从嘧啶 -2- 基 - 硫脲和 3-(4- 甲基 - 吡啶 -2- 基)-3- 氧代 - 丙酸乙酯合成 4-(4- 甲基吡啶 -2- 基)-2-(嘧啶 -2- 基氨基) 噻唑 -5- 甲酸乙酯，得到呈灰色固体的产物。^{1}H NMR(300MHz, $CDCl_3$) : δ 8.72(d, J = 5.1Hz, 2H, CH_{ar}), 8.59(d, J = 4.8Hz, 1H, CH_{ar}), 7.62(s, 1H, CH_{ar}), 7.15(d, J = 4.2Hz, 1H, CH_{ar}), 6.98(t, J = 4.8Hz, 1H, CH_{ar}), 4.28(q, J = 7.2Hz, 2H, OCH_2), 2.43(s, 3H, $ArCH_3$), 1.29(t, J = 7.2Hz, 3H, CH_3)。MS:MH^+ = 342。

[0347] 实施例 55 :4-(6- 甲基吡啶 -2- 基)-2-(嘧啶 -2- 基氨基) 噻唑 -5- 甲酸乙酯的合成。

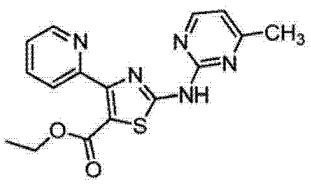
[0348]



[0349] 按照与实施例 53 相同的方式由嘧啶 -2- 基 - 硫脲和 3-(6- 甲基 - 吡啶 -2- 基)-3- 氧代 - 丙酸乙酯合成 4-(6- 甲基吡啶 -2- 基)-2-(嘧啶 -2- 基氨基) 噻唑 -5- 甲酸乙酯，得到呈棕红色固体的产物。^{1}H NMR(300MHz, $CDCl_3$) : δ 9.95(s, 1H, NH), 8.71(d, J = 4.2Hz, 2H, CH_{ar}), 7.66(t, J = 7.5Hz, 1H, CH_{ar}), 7.56(d, J = 7.8Hz, 1H, CH_{ar}), 7.20(d, J = 7.5Hz, 1H, CH_{ar}), 6.98(m, 1H, CH_{ar}), 4.26(q, J = 7.2Hz, 2H, OCH_2), 2.66(s, 3H, $ArCH_3$), 1.28(t, J = 7.2Hz, 3H, CH_3)。MS:MH^+ = 342。

[0350] 实施例 56 :2-((4- 甲基嘧啶 -2- 基) 氨基)-4-(吡啶 -2- 基) 噻唑 -5- 甲酸乙酯的合成

[0351]



[0352] 按与实施例 53 相同的方式由 (4- 甲基 - 嘧啶 -2- 基)- 硫脲和 3- 氧代 -3- 吡啶 -2- 基 - 丙酸乙酯合成 2-((4- 甲基嘧啶 -2- 基) 氨基)-4-(吡啶 -2- 基) 噻唑 -5- 甲酸乙酯，得到呈棕红色固体的产物。^{1}H NMR(300MHz, $CDCl_3$) : δ 9.43(s, 1H, NH), 8.74(d, J = 4.5Hz, 1H, CH_{ar}), 8.51(d, J = 5.4Hz, 1H, CH_{ar}), 7.82-7.73(m, 2H, CH_{ar}), 7.32(t, J = 5.7Hz, 1H, CH_{ar}), 6.84(d, J = 5.4Hz, 1H, CH_{ar}), 4.27(q, J = 7.2Hz, 2H, OCH_2), 2.56(s, 3H, $ArCH_3$), 1.28(t, J = 7.5Hz, 3H, CH_3)。MS:MH^+ = 342。

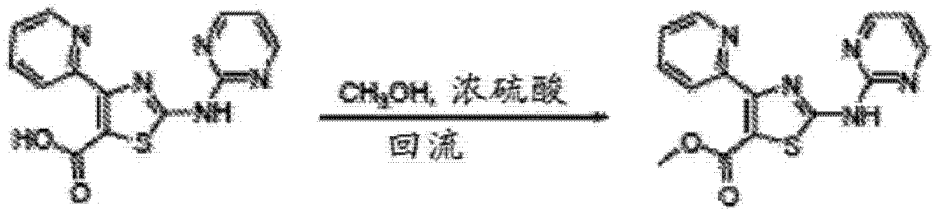
[0353] 实施例 57 :4-(吡啶 -2- 基)-2-(嘧啶 -2- 基氨基) 噻唑 -5- 羧酸的合成。

[0354]

[0355] 向 4-(吡啶 -2- 基)-2-(嘧啶 -2- 基氨基) 噻唑 -5- 甲酸乙酯 (435mg, 1.33mmol) 在四氢呋喃 /CH_3OH/H_2O(5:5:1, 16.5mL) 中的溶液添加一水氢氧化锂 (391mg, 9.31mmol)。将反应混合物回流 6 小时。冷却后，蒸发溶剂，并添加水 (20mL) 以溶解残余物。将 pH 用 6M HCl 水溶液调节至 6，并将混合物在 4℃下保持 16 小时。将沉淀过滤，用水洗涤并真空干燥，获得 385mg 呈浅棕色固体的 4-(吡啶 -2- 基)-2-(嘧啶 -2- 基氨基) 噻唑 -5- 羧酸。MS:MNa^+ = 322。

[0356] 实施例 58 :4-(吡啶 -2- 基)-2-(嘧啶 -2- 基氨基) 噻唑 -5- 甲酸甲酯的合成。

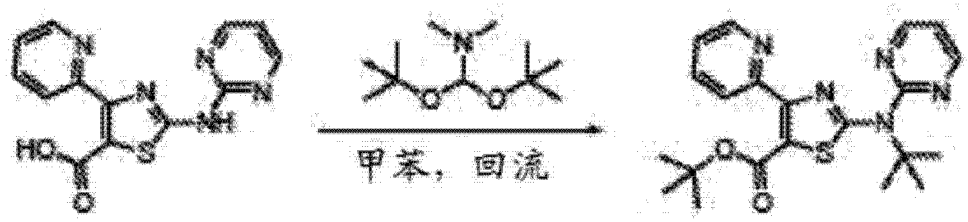
[0357]



[0358] 将 4-(吡啶 -2- 基)-2-(嘧啶 -2- 基氨基) 噻唑 -5- 羧酸 (60mg, 0.2mmol) 在甲醇 (10mL) 中的悬浮液用浓硫酸 (～ 98%, 2 滴) 处理。将反应混合物回流 4 天。冷却后，蒸发溶剂并添加水 (20mL)。将 pH 通过饱和碳酸氢钠调节至 8，并用二氯甲烷 (20mL×4) 萃取混合物。将合并的有机层经无水硫酸钠干燥，然后蒸发，得到 26mg 呈白色固体的 4-(吡啶 -2- 基)-2-(嘧啶 -2- 基氨基) 噻唑 -5- 甲酸甲酯。^{1}H NMR(300MHz, DMSO-d_6) : δ 12.37(s, 1H, NH), 8.72(d, J = 4.2Hz, 2H, CH_{ar}), 8.60(d, J = 3.3Hz, 1H, CH_{ar}), 7.86(t, J = 7.5Hz, 1H, CH_{ar}), 7.66(d, J = 7.5Hz, 1H, CH_{ar}), 7.41(t, J = 5.7Hz, 1H, CH_{ar}), 7.14(t, J = 4.8Hz, 1H, CH_{ar}), 3.67(s, 3H, OCH_3)。MS:MH^+ = 314。

[0359] 实施例 59 :2-(叔 - 丁基 (嘧啶 -2- 基) 氨基)-4-(吡啶 -2- 基) 噻唑 -5- 甲酸叔丁酯的合成。

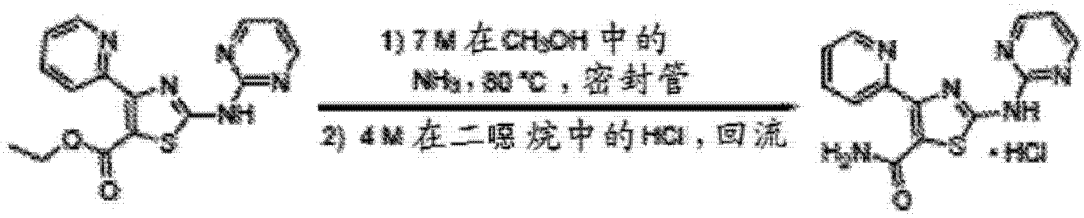
[0360]



[0361] 将 4-(吡啶 -2- 基)-2-(嘧啶 -2- 基氨基) 噻唑 -5- 羧酸 (30mg,0.1mmol) 和 1,1- 二 - 叔 - 丁氧基 -N,N- 二甲基甲胺 (120μL,0.5mmol) 在甲苯 (2mL) 中的混合物加热至回流 24 小时。冷却后，将其用水 (20mL) 淬灭，并用二氯甲烷 (10mL×3) 萃取。将合并的有机层经硫酸钠干燥、浓缩，然后通过制备 TLC(乙酸乙酯 : 己烷 = 30 :70) 纯化，得到 12mg 呈白色固体状的 2-(叔 - 丁基 (嘧啶 -2- 基) 氨基)-4-(吡啶 -2- 基) 噻唑 -5- 甲酸叔丁酯。^{1}H NMR(300MHz, DMSO-d_6) : δ 8.61(d, J = 4.8Hz, 3H, CH_{ar}), 7.87(dt, J = 7.8, 1.5Hz, 1H, CH_{ar}), 7.67(d, J = 7.8Hz, 1H, CH_{ar}), 7.43-7.38(m, 1H, CH_{ar}), 7.09(t, J = 4.8Hz, 1H, CH_{ar}), 1.55(s, 9H, $C(CH_3)_3$), 1.31(s, 9H, $C(CH_3)_3$)。MS:MH^+ = 412。

[0362] 实施例 60 :4-(吡啶 -2- 基)-2-(嘧啶 -2- 基氨基) 噻唑 -5- 甲酰胺的合成。

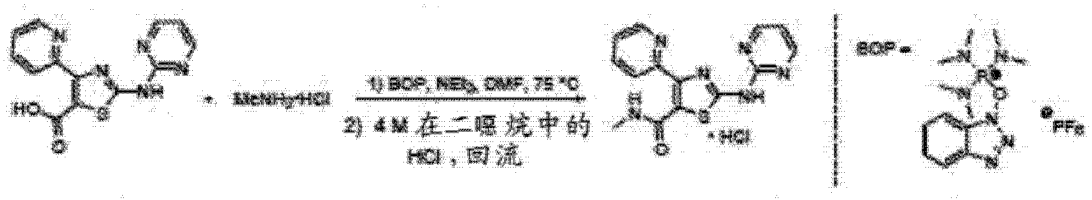
[0363]



[0364] 在密封管中，将 4-(吡啶 -2- 基)-2-(嘧啶 -2- 基氨基) 噻唑 -5- 甲酸乙酯 (16mg, 0.05mg) 在 7M NH_3 的甲醇溶液 (5mL) 中的悬浮液加热至 80℃，持续 7 天。蒸发溶剂，并将残余物用乙酸乙酯洗涤，获得纯酰胺。将其悬浮在甲醇中，用 4M 在二噁烷 (0.4mL) 中的 HCl 处理并加热至回流。通过蒸发除去溶剂，并用乙酸乙酯洗涤粗产物，获得 17mg 呈浅黄色固体的 4-(吡啶 -2- 基)-2-(嘧啶 -2- 基氨基) 噻唑 -5- 甲酰胺。^{1}HNMR(300MHz, CD_3OD) : δ 8.93-8.89(m, 2H, CH_{ar}), 8.71-8.63(m, 3H, CH_{ar}), 8.04(t, J = 6.6Hz, 1H, CH_{ar}), 7.14(t, J = 5.1Hz, 1H, CH_{ar})。MS:MH^+ = 299。

[0365] 实施例 61 :N- 甲基 -4-(吡啶 -2- 基)-2-(嘧啶 -2- 基氨基) 噻唑 -5- 甲酰胺的合成。

[0366]

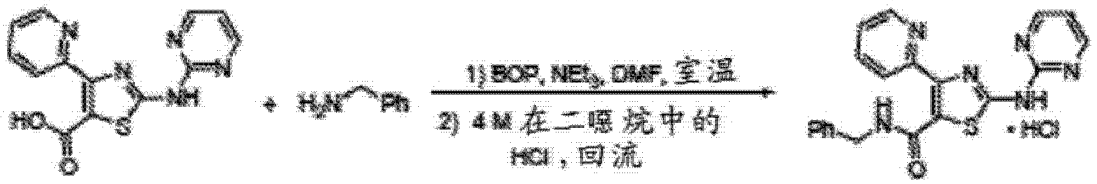


[0367] 将 4-(吡啶 -2- 基)-2-(嘧啶 -2- 基氨基) 噻唑 -5- 羧酸 (60mg,0.2mmol)、甲胺盐酸盐 (27mg,0.4mmol)、苯并三唑 -1- 基 - 氧基 - 三 -(二甲基氨基)- 磷鎓六氟磷酸盐 (BOP, 221mg,0.5mmol)、三乙胺 (83μL,0.6mmol) 在二甲基甲酰胺 (2mL) 中的反应混合物在密封管中加热至 75℃，持续 24 小时。然后将其用水 (20mL) 淬灭、过滤并用水洗涤。将固体悬浮于甲醇 (2mL) 中，并用 4M 在二噁烷中的 HCl(0.6mL) 处理。将其加热至回流，然后蒸发除去

溶剂。将所得固体用乙酸乙酯洗涤，并真空干燥，获得64mg呈浅黄色固体的N-甲基-4-(吡啶-2-基)-2-(嘧啶-2-基氨基)噻唑-5-甲酰胺盐酸盐。^{1}H NMR(300MHz,DMSO-d_6)：δ8.85(m,1H,CH_{ar}),8.72(d,J＝4.8Hz,2H,CH_{ar}),8.93-8.29(m,2H,CH_{ar}),7.72(m,1H,CH_{ar}),7.13(m,1H,CH_{ar}),2.85(s,3H,NCH_3)。MS:MH^+＝313。

[0368] 实施例62:N-苄基-4-(吡啶-2-基)-2-(嘧啶-2-基氨基)噻唑-5-甲酰胺的合成。

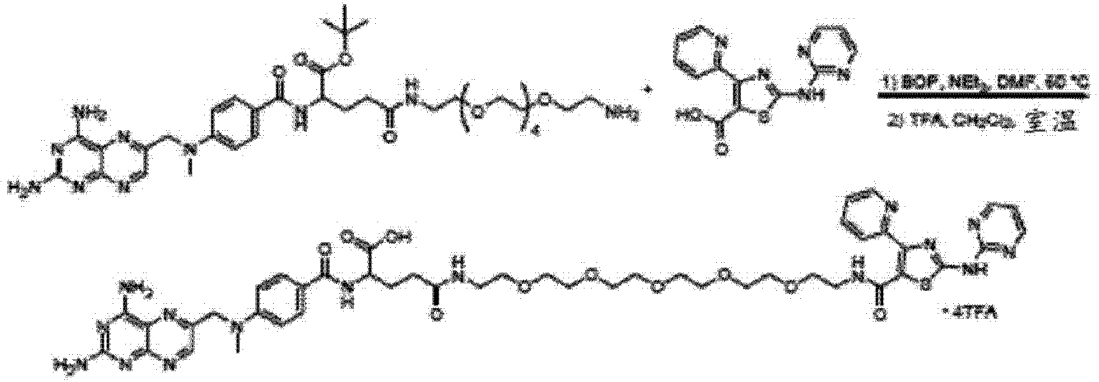
[0369]



[0370] 将4-(吡啶-2-基)-2-(嘧啶-2-基氨基)噻唑-5-羧酸(60mg,0.2mmol)、苄胺(43mg,0.4mmol)、苯并三唑-1-基-氧基-三-(二甲基氨基)-磷鎓六氟磷酸盐(BOP,195mg,0.44mmol)、三乙胺(83μL,0.6mmol)在二甲基甲酰胺(10mL)中的反应混合物搅拌4天。然后将其用水(50mL)淬灭、过滤并用水洗涤。将固体悬浮于甲醇/二氯甲烷(4:6)中，然后过滤。将滤液浓缩，以31％产率获得24mg呈灰白色固体的酰胺。将8mg以上的酰胺悬浮于甲醇(1mL)中，并用4M在二噁烷(0.3mL)中的HCl处理。将其加热至回流，然后蒸发除去溶剂。将所得固体用乙酸乙酯洗涤，并真空干燥，获得9mg呈灰白色固体的N-苄基-4-(吡啶-2-基)-2-(嘧啶-2-基氨基)噻唑-5-甲酰胺盐酸盐。^{1}HNMR(300MHz,DMSO-d_6)：δ12.29(br,1H,NH),12.09(br,1H,NH),8.71(d,J＝4.5Hz,2H,CH_{ar}),8.40(s,1H,CH_{ar}),8.32(d,J＝8.4Hz,1H,CH_{ar}),8.09(t,J＝7.5Hz,1H,CH_{ar}),7.51(m,1H,CH_{ar}),7.37-7.28(m,5H,CH_{ar}),7.11(m,1H,CH_{ar}),4.52(d,J＝4.5Hz,2H,$ArCH_2N$)。MS:MH^+＝389。

[0371] 实施例63:MTX衍生物,24-(4-(((2,4-二氨基蝶啶-6-基)甲基)(甲基)氨基)苯甲酰氨基)-1,21-二氧代-1-(4-(吡啶-2-基)-2-(嘧啶-2-基氨基)噻唑-5-基)-5,8,11,14,17-五氧杂-2,20-二氮杂二十五烷-25-酸三-三氟乙酸酯,的合成

[0372]

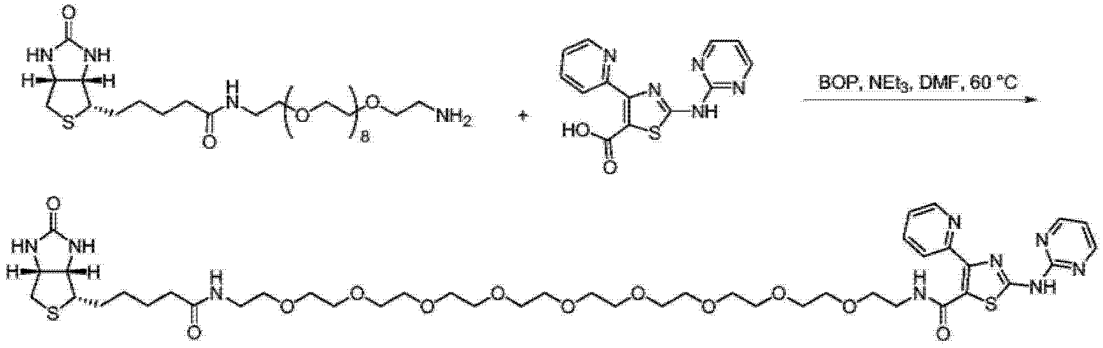


[0373] 在密封管中，将4-(吡啶-2-基)-2-(嘧啶-2-基氨基)噻唑-5-羧酸(66mg,0.22mmol)、1-氨基-22-(4-(((2,4-二氨基蝶啶-6-基)甲基)(甲基)氨基)苯甲酰氨基)-19-氧代-3,6,9,12,15-五氧杂-18-氮杂二十三烷-23-酸叔丁酯(MTX(CO_2Bu^t)-$(PEG)_6$-NH_2,170mg,0.22mmol)、苯并三唑-1-基-氧基-三-(二甲基氨

基)-磷鎓六氟磷酸盐(BOP,146mg,0.33mmol)、三乙胺(55μL,0.4mmol)在二甲基甲酰胺(2mL)中的反应混合物加热至60℃,持续48小时。冷却至室温后,将其用水(30mL)淬灭、过滤并用水洗涤。将固体干燥,然后悬浮于二氯甲烷和甲醇的混合物(6:4,30mL)中。将其过滤,并将滤液浓缩,获得纯的叔-丁酯,将其用二氯甲烷(10mL)处理,随后添加三氟乙酸(2mL)。将混合物在室温下搅拌24小时并蒸发,获得268mg呈棕红色固体的24-(4-(((2,4-二氨基蝶啶-6-基)甲基)(甲基)氨基)苯甲酰氨基)-1,21-二氧代-1-(4-(吡啶-2-基)-2-(嘧啶-2-基氨基)噻唑-5-基)-5,8,11,14,17-五氧杂-2,20-二氮杂二十五烷-25-酸-三氟乙酸酯。^{1}H NMR(300MHz,CD_3OD):δ8.78(d,J = 4.5Hz,1H,CH_{ar}),8.62-8.57(m,4H,CH_{ar}),8.37(t,J = 7.8Hz,1H,CH_{ar}),7.79(t,J = 6.3Hz,1H,CH_{ar}),7.71(d,J = 9.0Hz,2H,CH_{ar}),7.06(t,J = 4.8Hz,1H,CH_{ar}),6.78(d,J = 8.7Hz,2H,CH_{ar}),4.85(s,2H,$ArCH_2N$),4.55-4.50(m,1H,CH),3.70-3.42(m,24H),3.21(s,3H,NCH_3),2.38-2.07(m,4H)。MS:MNa^+ = 1020。

[0374] 实施例64:生物素衍生物,N-(31-氧代-35-((3aS,4S,6aR)-2-氧代六氢-1H-噻吩并[3,4-d]咪唑-4-基)-3,6,9,12,15,18,21,24,27-九氧杂-30-氮杂正五十烷基)-4-(吡啶-2-基)-2-(嘧啶-2-基氨基)噻唑-5-甲酰胺,的合成

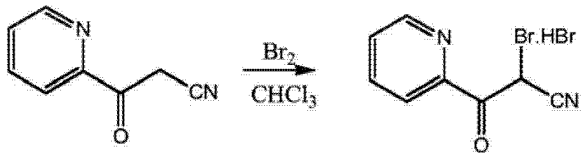
[0375]



[0376] 在密封管中,将4-(吡啶-2-基)-2-(嘧啶-2-基氨基)噻唑-5-羧酸(30mg,0.1mmol)、N-(29-氨基-3,6,9,12,15,18,21,24,27-九氧杂二十九基)-5-((3aS,4S,6aR)-2-氧代六氢-1H-噻吩并[3,4-d]咪唑-4-基)戊酰胺(生物素-$(PEG)_{10}$-NH_2,68mg,0.1mmol)、苯并三唑-1-基-氧基-三-(二甲基氨基)-磷鎓六氟磷酸盐(BOP,66mg,0.15mmol)、三乙胺(28μL,0.2mmol)在二甲基甲酰胺(2mL)中的反应混合物加热至60℃,持续48小时。冷却至室温后,将其用水(20mL)淬灭,并用二氯甲烷(20mL×4)萃取。将合并的有机层经硫酸钠干燥、浓缩,然后通过制备TLC(在甲醇:二氯甲烷= 5:95中的2M NH_3)纯化,得到49mg呈白色固体的N-(31-氧代-35-((3aS,4S,6aR)-2-氧代六氢-1H-噻吩并[3,4-d]咪唑-4-基)-3,6,9,12,15,18,21,24,27-九氧杂-30-氮杂正五十烷基)-4-(吡啶-2-基)-2-(嘧啶-2-基氨基)噻唑-5-甲酰胺。^{1}H NMR(300MHz,CD_3OD):δ8.70(m,1H,CH_{ar}),8.61(d,J = 4.8Hz,2H,CH_{ar}),8.43(d,J = 8.1Hz,1H,CH_{ar}),7.96(t,J = 7.8Hz,1H,CH_{ar}),7.88(s,1H,NH),7.44(t,J = 5.7Hz,1H,CH_{ar}),7.00(t,J = 4.8Hz,1H,CH_{ar}),4.48-4.44(m,1H,CH),4.29-4.25(m,1H,CH),3.74-3.49(m,40H),3.18-3.12(m,1H,CH),2.88(dd,J = 12.9,5.4Hz,1H,CH),2.68(d,J = 12.9Hz,1H,CH),2.20-2.14(m,2H),1.71-1.53(m,4H),1.44-1.37(m,2H)。MS:MNa^+ = 986。

[0377] 实施例 65 :2- 溴 -3- 氧代 -3- 吡啶 -2- 基 - 丙腈氢溴酸盐的合成

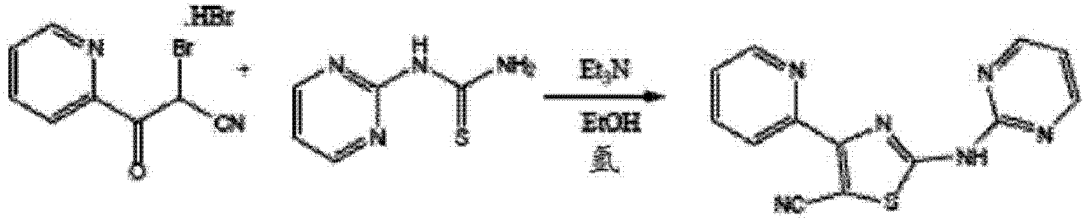
[0378]



[0379] 将溴 (4ml,0.8mmol,1 当量) 在 0-5℃下滴加至 3- 氧代 -3- 吡啶 -2- 基 - 丙腈 (117mg,0.8mmol,1 当量) 在 $CHCl_3$(5ml) 中的溶液。然后将反应混合物加热至 40℃持续 1 小时,并在 70℃下再加热一小时。蒸发反应混合物以除去溶剂,并将粗产物直接用于下一步骤。

[0380] 实施例 66 :4- 吡啶 -2- 基 -2-(嘧啶 -2- 基氨基)- 噻唑 -5- 腈的合成 :

[0381]



[0382] 将 2- 溴 -3- 氧代 -3- 吡啶 -2- 基 - 丙腈氢溴酸盐 (46mg,0.3mmol)、1-(嘧啶 -2- 基) 硫脲 (0.6mmol) 和三乙胺 (0.83ml,6mmol,15 当量) 在乙醇 (5ml) 中在氩气氛下混合在一起,并回流 1 小时。在其冷却至室温后,将反应用水 (10ml) 淬灭,然后将 3 份反应物用 1 份甲醇和二氯甲烷 (1 :3)(5ml x3) 的混合物萃取。将合并的有机相蒸发。通过柱色谱获得标题化合物。MS:MH+ = 281。

[0383] 制剂

[0384] 本发明还涉及包含根据本发明取代的氨基噻唑的组合物或制剂。通常,本发明的组合物包含有效量的根据本发明的一种或多种取代的氨基噻唑及其盐,所述取代的氨基噻唑及其盐用于有效提供涉及细胞生长失调的疾病的治疗或预防 ;及一种或多种赋形剂。本发明的组合物还包含有效量的根据本发明的一种或多种取代的氨基噻唑及其盐,所述取代的氨基噻唑及其盐用于有效治疗或预防涉及肝炎病毒感染的疾病 ;及一种或多种赋形剂。

[0385] 为了本发明的目的,术语“赋形剂”和“载体”可在本发明的描述全文中互换使用,并且所述术语在本文中被定义为“用于安全且有效的药物组合物配制实践中的成分”。

[0386] 配制人员将理解赋形剂主要用于起到递送安全、稳定和有功能的药物的作用,不仅用作为总体递送媒介物的一部分,而且还作为通过活性成分的接受 (recipient) 实现有效吸收的方式。赋形剂可起到简单且直接的作用即作为惰性填料,或者如本文所用的赋形剂可为 pH 稳定系统或包衣的一部分以确保安全递送成分至胃部。配制人员还可利用以下事实 :本发明的化合物具有改进的细胞效能、药代动力学特性以及改进的口服生物利用率。

[0387] 本教导还提供包含至少一种本文描述的化合物和一种或多种药学上可接受的载体、赋形剂或稀释剂的药物组合物。此类载体的实例为本领域的技术人员所熟知,并可根据可接受的药物程序来制备,诸如,例如在 Remington's Pharmaceutical Sciences, 第 17 版 ,Alfonoso R.Gennaro 编辑 ,Mack Publishing Company,Easton,PA(1985) 中描述的那些载体,其全部的公开内容为了所有目的通过引用并入。如本文所用,“药学上可接受的”是

指一种从毒物学角度来看可用于药学应用，且不与活性成分进行不利相互作用的物质。因此，药学上可接受的载体是与制剂中其它组分相容并为生物学上可接受的那些物质。补充性活性成分还可被掺入至药物组合物内。

[0388] 本教导的化合物还可单独或与常见药物载体联合口服或胃肠外施用。适用的固体载体可包括还可作为调味剂、润滑剂、增溶剂、悬浮剂、填充剂、助流剂、助压剂(compression aids)、粘合剂或片剂崩解剂或包囊材料的一种或多种物质。可以常规方式例如以与已知的抗癌剂所用方式类似的方式配制所述化合物。还可以常规方式例如以与已知的抗病毒剂所用方式类似的方式配制所述化合物。含有本文公开的化合物的口服制剂可包括任何常用的口服形式，包括片剂、胶囊、颊形式、含片、锭剂和口服液体、悬浮液或溶液。在粉剂中，载体可为细粒固体，所述细粒固体是具有细粒化合物的混合物。在片剂中，可将本文公开的化合物与具有必要的压制性质的载体按适合的比例混合并且压制成所需形状和尺寸。粉剂和片剂可含有多达99％的化合物。

[0389] 胶囊可含有本文公开的一种或多种化合物与一种或多种惰性填料和/或稀释剂(诸如药学上可接受的淀粉(如，玉米，马铃薯或木薯淀粉)、糖、人工甜味剂、粉状纤维素(如，结晶和微晶纤维素)、面粉、明胶、树胶等)的混合物。

[0390] 有用的片剂可通过常规压缩、湿法制粒或干法制粒方法来制备，并使用药学上可接受的稀释剂、结合剂、润滑剂、崩解剂、表面改性剂(包括表面活性剂)、助悬剂或稳定剂，包括但不限于：硬脂酸镁、硬脂酸、十二烷基硫酸钠、滑石粉、糖、乳糖、糊精、淀粉、明胶、纤维素、甲基纤维素、微晶纤维素、羧甲基纤维素钠、羧甲基纤维素钙、聚乙烯吡咯烷、海藻酸、阿拉伯胶、黄原胶、柠檬酸钠、复合硅酸盐、碳酸钙、甘氨酸、蔗糖、山梨(糖)醇、磷酸二钙、硫酸钙、乳糖、高岭土、甘露醇、氯化钠、低熔点蜡和离子交换树脂。表面改性剂包括非离子和阴离子表面改性剂。表面改性剂的代表性实例包括但不限于泊洛沙姆188、苯扎氯铵、硬脂酸钙、鲸蜡硬脂醇(cetostearl alcohol)、聚西托醇乳化蜡(cetomacrogol emulsifying wax)、脱水山梨醇酯、胶态二氧化硅、磷酸盐、十二烷基硫酸钠、硅酸镁铝和三乙醇胺。本文的口服制剂可使用标准延迟或延时释放制剂以改变所述化合物的吸收。所述口服制剂还可由以水或果汁的形式施用的本文公开的化合物组成，其视需要含有适当的增溶剂或乳化剂。

[0391] 液体载体可用于制备溶液剂、混悬剂、乳剂、糖浆剂、酏剂，并用于吸入递送。本教导的化合物还可溶解或悬浮于药学上可接受的液体载体(诸如水、有机溶剂或这两者的混合物)中，或者药学上可接受的油或脂肪中。液体载体可含有其它适合的药物添加剂，诸如增溶剂、乳化剂、缓冲剂、防腐剂、甜味剂、调味剂、悬浮剂、增稠剂、着色剂、粘性调节剂、稳定剂、渗透压调节剂。用于口服和胃肠外施用的液体载体的实例包括但不限于水(特别含有如上所述的添加剂(如纤维素衍生物)，诸如羧甲基纤维素钠溶液)、醇(包括一元醇和多元醇，如二醇)及其衍生物，和油(如，分馏的椰子油和花生油)。对于胃肠外施用，载体可为油脂，诸如油酸乙酯和肉豆蔻酸异丙酯。在用于胃肠外施用的无菌液体形式组合物中，使用无菌液体载体。用于加压组合物的液体载体可为卤化烃或其它药学上可接受的推进剂。

[0392] 可通过例如肌内、腹膜内或皮下注射使用为无菌溶液或悬浮液的液体药物组合物。无菌溶液还可静脉内施用。用于口服施用的组合物可为液体或固体形式。

[0393] 优选地，所述药物组合物为单位剂型，例如为片剂、胶囊、粉剂、溶液剂、混悬剂、乳剂、颗粒剂或栓剂。在此类形式中，所述药物组合物可被以含有适量化合物的单位剂量的形式细分。单位剂型可为包装的组合物，例如含有液体的包装的粉剂、小瓶(vial)、安瓿剂、预装注射器或囊剂。可选地，单位剂型可为胶囊或片剂本身，或其可为适当数量的包装形式的任何此类组合物。此类单位剂型可含有约 1mg/kg 化合物至约 500mg/kg 化合物，并可被以单个剂量或两个剂量或多个剂量的形式给予。此类剂量可以任何用于将化合物定位至接受者的血流方式施用，所述方式包括口服、经由植入物、胃肠外（包括静脉内、腹膜内和皮下注射）、经直肠、经阴道和经皮施用。

[0394] 当施用以治疗或抑制具体疾病状态或病症时，应该理解有效剂量可根据使用的具体化合物、施用模式和治疗的疾患的严重程度以及与治疗的个体相关的各种身体因素而改变。在治疗应用中，本教导的化合物可被以足以治愈或至少部分缓解疾病症状及其并发症的量提供给已经患有疾病的患者。在特定个体的治疗中使用的剂量通常必须由主治医生主观确定。涉及的变量包括特定疾患及其状态，以及患者的体型、年龄和应答模式 (response pattern)。

[0395] 在一些情况下，可能需要直接向患者的气道施用化合物，使用装置诸如但不限于定量吸入器、呼吸操纵的吸入器、多剂量干粉吸入器、泵、挤压启动雾化型喷雾分配器 (squeeze-actuated nebulized spray dispensers)、气溶胶分配器和气溶胶雾化器。对于鼻内或支气管内吸入施用，本教导的化合物可被配制为液体组合物、固体组合物或气溶胶组合物。举例来说，液体组合物可包含一种或多种溶解、部分溶解或悬浮于药学上可接受的溶剂中的一种或多种本教导的化合物，并且可通过例如泵或挤压启动雾化型喷雾分配器来施用。所述溶剂可为例如等渗盐水或抑菌水。举例来说，固体组合物可为包含与乳糖或对支气管内用途是可接受的其它惰性粉末混合的一种或多种本教导化合物的粉末制剂，并可通过例如气雾剂分配器或者破坏或刺穿围绕所述固体组合物的胶囊并递送所述固体组合物以吸入的装置施用。举例来说，气溶胶组合物可包含一种或多种本教导的化合物、推进剂、表面活性剂和共溶剂，并可通过例如剂量加入装置来施用。所述推进剂可为氯氟烃 (CFC)、氢氟烷烃 (HFA) 或生理学上和环境可接受的其它推进剂。

[0396] 本文描述的化合物可胃肠外或腹膜内施用。这些化合物或其药学上可接受的盐、水合物或酯的溶液或悬浮液可在适当混合有表面活性剂（诸如羟丙基纤维素）的水中制备。分散液还可在甘油、液体聚乙二醇和其在油中的混合物中制备。在普通的贮藏和使用条件下，这些制剂通常含有防腐剂以抑制微生物生长。

[0397] 适于注射的药物形式可包括无菌水溶液或分散液和用于临时制备无菌注射液或分散液的无菌粉末。在一些实施方案中，所述形式可为无菌的，并且其粘度使其能流过注射器。所述形式优选地在生产和贮藏条件下是稳定的，并可保存在防止微生物（诸如细菌和真菌）污染的条件下。所述载体可为溶剂或分散介质，例如水、乙醇、多元醇（如，甘油、丙二醇和液体聚乙二醇）、其适合的混合物及植物油。

[0398] 本文描述的化合物可经皮施用，即经过身体表面和身体通路的衬里（包括上皮和粘膜组织）施用。可使用本教导的化合物（包括其药学上可接受的盐、水合物或酯）进行此类施用，施用形式为洗剂、乳膏剂、泡沫剂、贴剂、混悬剂、溶液剂和栓剂（直肠和阴道）。

[0399] 经皮施用可通过使用含有化合物（诸如本文公开的化合物）的经皮贴剂来完成，

并且对化合物呈惰性的载体可对皮肤无毒，并可使得化合物经由皮肤递送能够全身性吸收进入血管。所述载体可采用多种形式，诸如乳膏剂和软膏剂、贴剂、凝胶剂和闭塞性装置。所述乳膏剂和软膏剂可为水包油型或油包水型的粘性液体或者半固体乳液。由分散于石油或亲水性石油中的含有所述化合物的吸收性粉末组成的贴剂也可为适合的。多种闭塞性装置可用于释放所述化合物至血流内，诸如覆盖含有所述化合物（有或没有载体）的储器的半透膜，或者含有所述化合物的基质。其它闭合性装置是文献中已知的。

[0400] 本文公开的化合物可经直肠或经阴道以常规栓剂的形式施用。栓剂制剂可由包括可可脂（添加或不添加蜡以改变栓剂熔点）和甘油的传统材料制备。还可使用水溶性栓剂基质，诸如各种分子量的聚二乙醇。

[0401] 脂质制剂或纳米胶囊可用于将本教导的化合物体外或体内引入至宿主细胞内。脂质制剂和纳米胶囊可通过本领域已知的方法制备。

[0402] 为了增加本教导化合物的有效性，可能需要将化合物与其它有效治疗目标疾病的试剂合并。例如，其它有效治疗目标疾病的活性化合物（即，其它活性成分或试剂）可与本教导的化合物一起施用。其它试剂可与本文公开的化合物同时或在不同时间点施用。

[0403] 本教导的化合物可用于治疗或抑制哺乳动物（例如人受试者）的病理状态或病症。本教导因此提供通过向哺乳动物提供本教导的化合物（包括其药学上可接受的盐）或药物组合物来治疗或抑制病理状态或病症的方法，所述药物组合物包含与药学上可接受的载体联合或结合的一种或多种本教导的化合物。本教导的化合物可单独施用或与其它治疗有效的化合物或疗法联合施用，以用于治疗或抑制病理状态或病症。

[0404] 根据本发明的组合物的非限制性实例包括约 0.001mg 至约 1000mg 一种或多种根据本发明和一种或多种赋形剂；约 0.01mg 至约 100mg 一种或多种根据本发明的取代的氨基噻唑和一种或多种赋形剂；及约 0.1mg 至约 10mg 一种或多种根据本发明的取代氨基噻唑；和一种或多种赋形剂。

[0405] 程序

[0406] 以下程序可用于评估和选择化合物以有效用于提供治疗或预防涉及细胞生长失调的疾病。以下程序可用于评估和选择化合物以有效用于治疗或预防涉及肝炎病毒感染的疾病。

[0407] 细胞培养物和条件

[0408] Huh-7 细胞和肝细胞癌来源的细胞由 Dr. Xuanyong Lu(Drexel University College of Medicine, Doylestown, PA) 捐献。THLE-2 购自美国典型培养物保藏中心 (American Type Culture Collection)(Manassas, VA)。PH5CH 由 Dr. Masayuki Noguchi(University of Tsukuba, Ibaraki, Japan) 捐献。THLE-2 和 PH5CH 已被通过在正常肝细胞中稳定转染 SV40 大 T 抗原而永生化，并因此为代表正常肝细胞而非 HCC 细胞的细胞系。THLE2 已被证实在无胸腺小鼠中不形成肿瘤。在 37℃下在 5% CO_2 中培养并维持所有细胞系。将 Huh-7 维持在带有 10％胎牛血清 (FBS)、100μg/mL 青霉素、100 单位 /mL 链霉素和 50μg/mL 的培养基 DMEM/F12（贝科氏改进的依格尔氏培养基 (Dulbecco's Modified Eagle Medium)）中。将 THLE-2 和 PH5CH 维持在具有 10％ FBS、100μg/mL 青霉素、100 单位 /mL 链霉素的支气管上皮细胞培养基 (Brochial Epithelial Growth Media)(BEGM) 这一培养基中，与以下添加物形成预包装的试剂盒：补充 5ng/ml 人表皮生长因子和 70ng/ml 磷酸

乙醇胺 (Lonza Walkersville Inc.,Walkersville,MD) 的牛脑垂体提取物 (BPE)、胰岛素、氢化可的松、视黄酸、转铁蛋白、三碘甲状腺原氨酸。

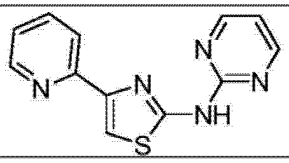
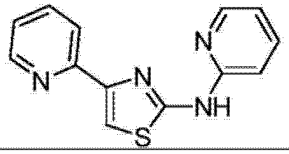
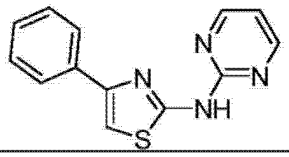
[0409] 取代的氨基噻唑类似物的测试。

[0410] 将 Huh7 细胞以 $2.0x10^4$ 个细胞 / 孔接种在 96 孔板上，使得其在本公开的化合物的存在下能够生长。将本公开的化合物预稀释，并通过自动液体处理转移至细胞板。将细胞与本公开的化合物一起孵育 72 小时，此后通过在 37℃下添加 50μg/mL3-(4,5- 二甲基 -2- 噻唑基)-2,5- 二苯基 -2H- 四氮唑溴盐 (MTT) 孵育 4 小时来评估培养物生长和活力。添加增溶性缓冲液 (0.01M HCl,10% SDS)，随后在 37℃下孵育过夜。在 570nm 处测量吸光度 (参考 630nm)。将本公开的化合物在 Huh7、THLE-2 和 PH5CH 中经半对数步骤 (half-log steps) 中的 8 个稀释点测试，测试点为在 0.5% DMSO 中的 50.0、16.6、5.0、1.66、0.5、0.166、0.05 和 0.016μM，每个浓度均在复孔 (duplicate wells) 中。在 MTT 测定中，与仅有 DMSO 的对照孔 (n = 8) 相比，使用 XLfit(IDBS,Surrey,UK) 的曲线拟合分析，使用超过复孔的活性信号降低的平均值确定对 50% 细胞产生毒性的浓度 (CC_{50})。将每种化合物在单独的测定试验中测试 2 至 7 次。

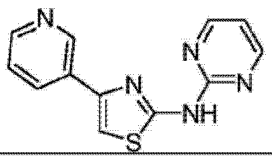
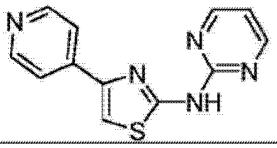
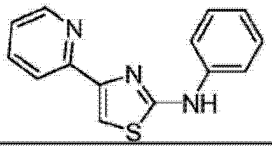
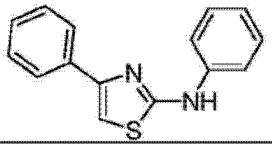
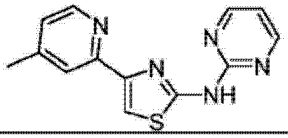
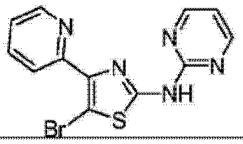
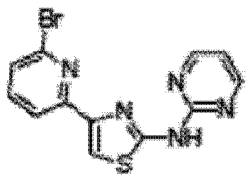
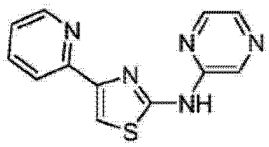
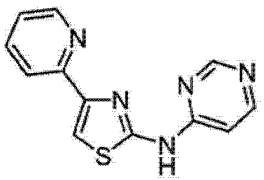
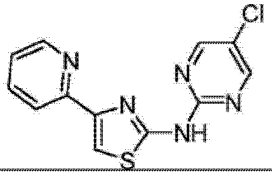
[0411] HCC 来源的细胞超过正常肝脏来源的细胞对毒性选择性对于开发特异性靶向癌症并对整个肿瘤具有低毒性的治疗来说是重要的。选择性指数 (SI) 是正常细胞 (THLE2 或 PH5CH) 中的 CC_{50} 超过肝癌来源细胞的 CC_{50} 的比例，因此该数越高，则在有效剂量下的潜在的毒性越低。

[0412] 表 2 :用 Huh-7 细胞、THLE2 细胞和 PH5CH 细胞对本公开化合物的示例性细胞活性筛选的结果。

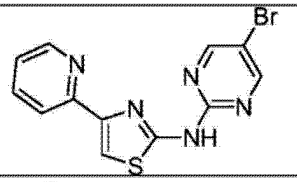
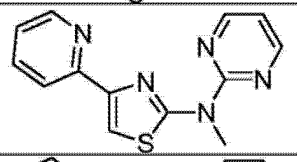
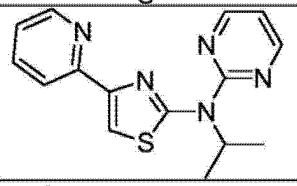
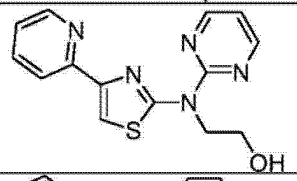
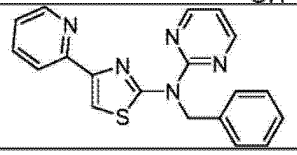
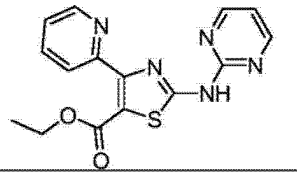
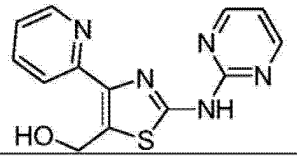
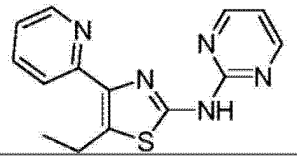
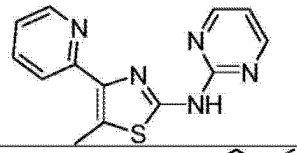
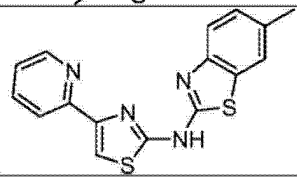
[0413]

条目	结构	Huh7 CC_{50} (uM)	THLE2 CC_{50} (uM)	THLE2/Huh7 SI	PH5CH CC_{50} (uM)	PH5CH/Huh7 SI
1		1.387	39.982	28.833	50.000	36.058
2		11.300	2.905	0.257		
3		6.433	9.156	1.423		

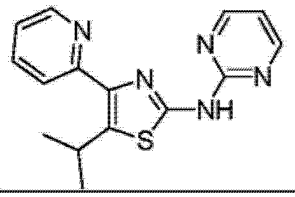
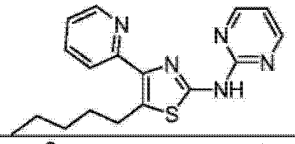
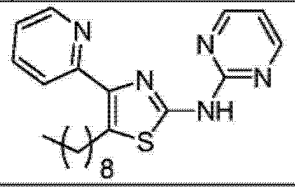
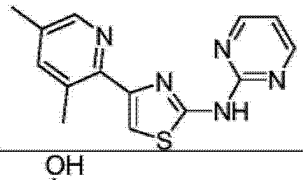
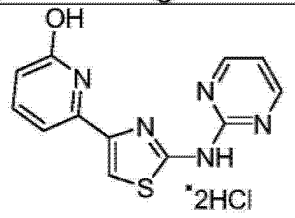
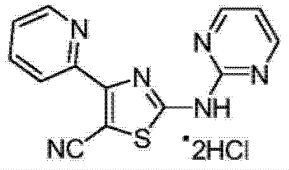
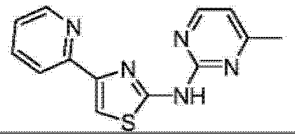
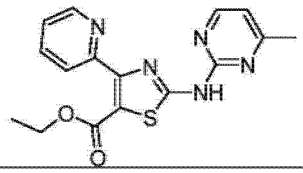
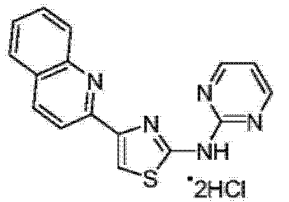
[0414]

4		6.302	8.660	1.374		
5		14.227	48.471	3.407		
6		6.526	17.783	2.725		
7		10.287	21.083	2.050		
8		0.563	14.018	24.905	33.973	60.358
9		2.532	29.911	11.816		
10		7.816	9.747	1.247		
11		5.000	0.539	0.108		
12		3.053	4.471	1.464		
13		35.016	50.000	1.428		

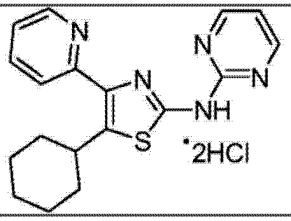
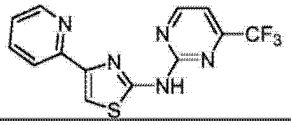
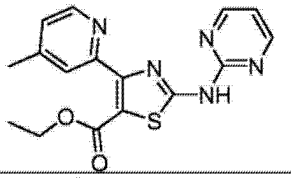
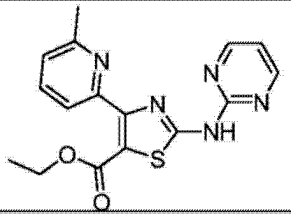
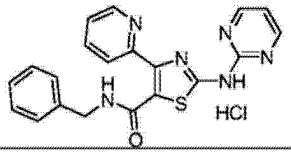
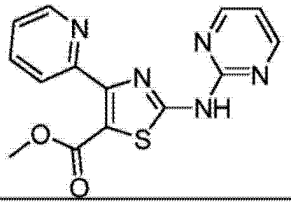
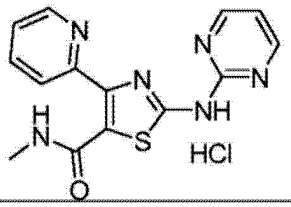
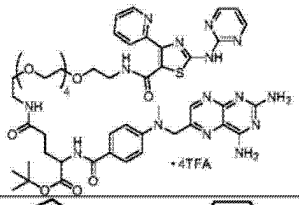
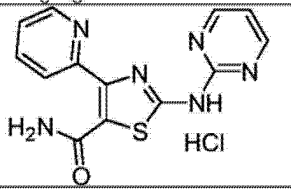
[0415]

14		31.762	40.966	1.290		
15		5.317	49.120	9.238	49.728	9.353
16		25.705	50.000	1.945	50.000	1.945
17		48.942	50.000	1.022	50.000	1.022
18		50.000	49.755	0.995	46.860	0.937
19		0.362	38.709	106.972	44.017	121.642
20		11.329	31.137	2.748	46.868	4.137
21		15.436	24.733	1.602	44.128	2.859
22		5.925	42.852	7.232	41.985	7.086
23		4.917	3.959	0.805	3.970	0.807

[0416]

24		11.277	50.000	4.434	50.000	4.434
25		25.877	50.000	1.932	50.000	1.932
26		12.779	2.273	0.178	50.000	3.913
27		2.737	2.234	0.816	47.616	17.397
28		46.188	50.000	1.083	50.000	1.083
29		0.016	50.00	3125	50.00	3125
30		50.000	50.000	1.000	50.000	1.000
31		0.016	50.000	3125	50.000	3125
32		50.000	8.022	0.160	50.000	1.000

[0417]

33		50.000	3.537	0.071	50.000	1.000
34		26.621	37.792	1.420	50.000	1.878
35		4.717	37.206	7.888	39.233	8.317
36		50.000	50.000	1.000	50.000	1.000
37		17.742	50.000	2.818	31.485	1.775
38		1.246	29.395	23.591	38.599	30.978
39		12.990	10.292	0.792	2.889	0.222
40		34.843	50.000	1.435	50.000	1.435
41		50.000	26.614	0.532	50.000	1.000

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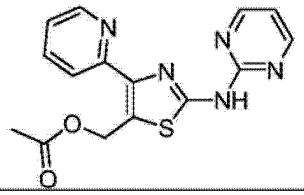
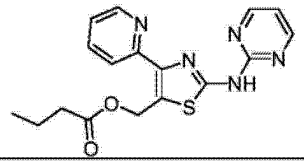
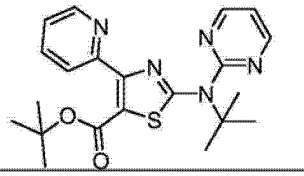
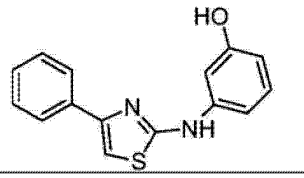
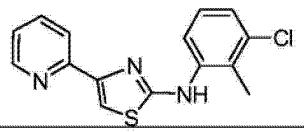
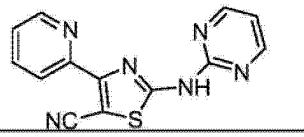
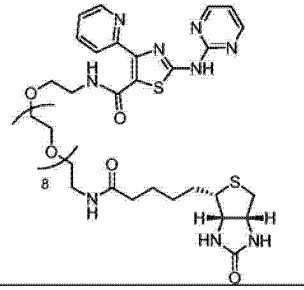
42		39.251	50.000	1.274	50.000	1.274
43		11.003	50.000	4.544	50.000	4.544
44		20.478	50.000	2.442	50.000	2.442
45		8.000	50.000	6.250		
46		3.500	未测试			
47		0.016	50.000	3125.00	50.000	3125.00
48						

Abstract

Pharmaceutical compositions of the invention are presented which comprise substiuted aminothiazoles derivatives. The substiuted aminothiazoles derivatives have a disease-modifying action in the treatment of diseases associated with unregulated cell growth. Such diseases include cancers such as hepatocellular carcinoma, and viral infections from a hepatitis virus.