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(54) Title: PYRIMIDINE COMPOUNDS AND METHODS USING THE SAME

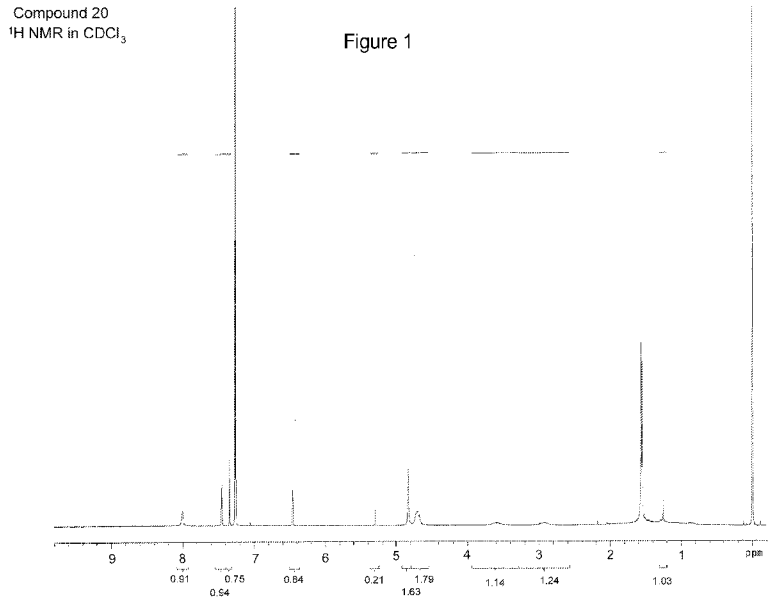

Figure 1

(57) Abstract: The present invention relates to 2-amino-4-arylpyrimidine and 2-amino-4-aryltriazine compounds as inhibitors of heat shock protein 90 family of chaperone proteins. The invention also features pharmaceutical compositions and kits that include the compounds and compositions of the invention. The invention further relates to the medical use of these compounds and compositions for the treatment of a disorder in a subject. For example, the disorder is a neurodegenerative disease.

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PYRIMIDINE COMPOUNDS AND METHODS USING THE SAME

Statement as to Federally Funded Research

This invention was made with government support under Grant No. STTR 1R41G042205-01 awarded by the National Institutes of Health. The government has certain rights in the invention.

Field of the Invention

In general, the present invention relates to pyrimidine-based small molecule inhibitors of heat shock protein 90 (Hsp90) and pharmaceutical compositions thereof. The invention further relates to methods of treatment of a subject having a neurodegenerative disease.

Background of the Invention

Hsp90 proteins are implicated in stabilizing protein conformations, maintaining the function of many cell-signaling proteins, and ATPase activity. Hsp90 activity is also required for the proper folding, stabilization, activation, and localization of oncoproteins involved in tumor progression. The *N*-terminus ATP binding domain is responsible for the ATPase activity of this protein: this adenine nucleotide binding pocket is highly conserved among all Hsp90 proteins from bacteria to mammals but is not present in other chaperones.

Hsp90 protein has emerged as an important target in cancer treatment, as many Hsp90 client proteins themselves were identified as targets for cancer therapies. The exemplary Hsp90 client proteins that are associated with cancer include HER2 (breast cancer), Raf-1/mutant BRAF (melanoma), Mutant EGFR (non-small cell lung cancer, glioblastoma), c-Kit (GIST), c-Met (gastric, lung, glioblastoma), HIF-1α (renal cancer), Zap70 (chronic lymphocytic leukemia), Bcr-Abl (chronic myelogenous leukemia), mBcr-Abl (chronic myelogenous leukemia), Flt-3 (acute myeloid leukemia), IGF-1R/Akt (myeloma), NMP-ALK (lymphoma), and Akt (small cell lung cancer). Overexpression of mutated Hsp90 client or amplification of its clients, such as HER2, leads to the increased dependency of tumor cells on Hsp90 chaperone function. Accordingly, Hsp90 provides a compelling target for treating different classes of tumors.

Increased levels of Hsp90 have also been implicated in neurodegenerative disorders, including Alzheimer's, Parkinson's, and Huntington's disease, and tauopathies. Tauopathies are neurodegenerative diseases characterized by tau protein abnormalities, which then result in the accumulation of hyperphosphorylated and aggregated tau protein. It has been proposed that hyperphosphorylated tau in Alzheimer's disease is a pathogenic process caused by aberrant activation of kinases, particularly cdk5 and GSK β3. Studies have shown that Hsp90 stabilizes p35, an activator of cdk5, leading to increased tau phosphorylation. It has also been shown that Hsp90 inhibition activates heat shock factor 1 (HSF1), which in turn increases the expression of Hsp70. Increased expression of Hsp70 promotes tau solubility and binding to microtubules, inhibits Aβ peptide aggregation, and enhances Aβ peptide degradation.

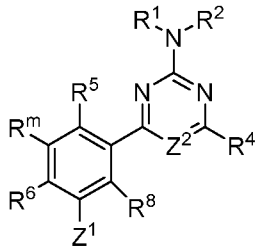
Hsp90 has also emerged as a target for treating viral, fungal, and bacterial infections. For example, an Hsp90 inhibitor (geldanamycin) has been shown to delay the growth of influenza virus in cell culture.

Other viruses that rely on Hsp90 dependent processes include those belonging to the families: Herpesviridae (e.g., herpes simplex virus-1, herpes simplex virus-2, herpes herpesvirus-5, Kaposi's sarcoma-associated herpesvirus, varicella zoster virus, or Epstein-Barr virus), Polyomaviridae (e.g., SV40), Poxviridae (e.g., vaccinia virus), Reoviridae (e.g., rotavirus), Birnaviridae (e.g., infectious bursal disease virus), picornaviridae (e.g., poliovirus, rhinovirus, or coxsackievirus), flaviviridae (e.g., hepatitis C virus or dengue virus), arenaviridae (e.g., lymphocytic choriomeningitis virus), Hepeviridae (e.g., Hepatitis E virus), Rhabdoviridae (e.g., vesicular stomatitis virus), Paramoxyviridae (e.g., human parainfluenza virus 2, human parainfluenza virus 3, SV5, SV41, measles virus, or Sendai virus), Bunyaviridae (e.g., La Crosse virus), Orthomoxyviridae (e.g., influenza A virus), Filoviridae (e.g., Ebola virus), Retroviridae (e.g., HTLV1 or HIV1), and Hepadnaviridae (e.g., hepatitis B virus). Hsp90 inhibitors have also been used *in vivo* for the treatment of fungal infectious diseases, e.g., treatment of *Candida albicans*, *Aspergillus fumigates*, or *Pneumocystis jiroveci*. Moreover, Hsp90 inhibitors are also useful in the treatment of bacterial infections, e.g., mycobacteria, anthrax, or bacterial pneumonia.

In view of the above, inhibitors of Hsp90 represent beneficial therapeutics for the treatment of disorders, e.g., cancer, neurodegenerative diseases, and infectious diseases.

Summary of the Invention

In one aspect, the invention features a compound according to formula (I):



(I), or a pharmaceutically acceptable salt thereof,

where

Z^1 is $-OR^7$, $-N(R^{10})R^7$, $-SR^7$, or $-C(R^{10})(R^{11})R^7$;

Z^2 is $-N=$ or $-C(R^3)=$;

each R^1 and R^2 is, independently, H or optionally substituted C_{1-3} alkyl (e.g., C_{1-3} acyl);

R^3 is H, halogen, cyano, optionally substituted C_{1-6} alkyl, optionally substituted C_{1-3} alkoxy, or optionally substituted amino, and R^4 is halogen, cyano, optionally substituted C_{1-6} alkyl, optionally substituted C_{1-3} alkoxy, optionally substituted amino, optionally substituted C_{1-6} thioalkoxy, or optionally substituted C_{6-10} aryl, or R^3 and R^4, together with the atoms to which each is attached, join to form an optionally substituted five- or six-membered ring optionally comprising from one to three heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur, where the nitrogen is optionally substituted with R^9;

each R^5 and R^6 is, independently, H, optionally substituted C_{1-3} alkyl, optionally substituted C_{1-3} alkoxy, halogen, or CN;

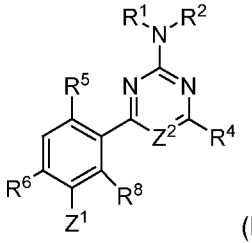
R^7 is optionally substituted C_{1-3} alkyl, optionally substituted C_{1-3} alkcycloalkyl, optionally substituted C_{1-3} alkheterocyclyl, or optionally substituted C_{1-3} alkaryl, and R^8 is H; or R^7 and R^8, together with the atoms to which each is attached, join to form an optionally substituted five- , six-, or seven-membered ring optionally comprising one or two heteroatoms selected from nitrogen, oxygen, and sulfur;

R^9 is H, optionally substituted C_{1-3} alkyl, optionally substituted C_{3-8} cycloalkyl, optionally substituted C_{6-10} aryl, optionally substituted C_{2-9} heteroaryl, optionally substituted C_{2-9} heterocyclyl, optionally substituted C_{1-3} alkcycloalkyl, optionally substituted C_{1-3} alkheterocyclyl, or optionally substituted C_{1-3} alkaryl;

R^{10} is H, optionally substituted C_{1-3} alkyl, optionally substituted C_{3-8} cycloalkyl, optionally substituted C_{6-10} aryl, optionally substituted C_{2-9} heteroaryl, optionally substituted C_{2-9} heterocyclyl, optionally substituted C_{1-3} alkcycloalkyl, optionally substituted C_{1-3} alkheterocyclyl, or optionally substituted C_{1-3} alkaryl, and R^{11} is H, optionally substituted C_{1-3} alkyl, or R^{10} and R^{11} combine to form =O or =S; and

R^m is H, halogen, cyano, optionally substituted C_{1-4} alkyl (e.g., C_{1-4} acyl), or optionally substituted C_{1-3} alkoxy.

In particular embodiments of formula (I), R^m is H (e.g., the compound of formula (I) has the following structure:



(I), or a pharmaceutically acceptable salt thereof).

In certain embodiments of formula (I), when Z^2 is CR^3,each of R^1 and R^2 is H, R^3 is H, R^4 is methyl or halogen (e.g., chloro), and each of R^5 and R^6 is halogen (e.g., chloro),

Z^1 is not methoxy.

In certain embodiments of formula (I), when Z^2 is CR^3, R^3 is H, R^4 is methyl or halogen (e.g., chloro), each of R^5 and R^6 is halogen (e.g., chloro),

Z^2 is not unsubstituted C_{1-3} alkoxy.

In particular embodiments of formula (I), when Z^2 is N, R^3 is H, R^4 is optionally substituted C_{1-6} thioalkoxy, and each of R^5 and R^6 is halogen (e.g., chloro),

Z^1 is not cyanomethoxy or aminomethoxy.

In other embodiments of formula (I), when Z^2 is N, R^3 is H, each of R^5 and R^6 is halogen (e.g., chloro), R^4 is substituted C_{1-6} thioalkoxy,

Z^1 is not cyanomethoxy or aminomethoxy.

In some embodiments of formula (I), when Z^2 is N, R^3 is H, R^4 is optionally substituted C_{1-6} thioalkoxy,

Z^1 is not cyanomethoxy or aminomethoxy.

In certain embodiments of formula (I), when Z^2 is N, R^3 is H, R^4 is substituted C_{1-6} thioalkoxy,

Z^1 is not cyanomethoxy or aminomethoxy.

In further embodiments of formula (I), when Z^2 is N, R^3 is H, R^4 is substituted C_{1-6} thioalkoxy,

Z^1 is not substituted C_1 alkoxy.

In particular embodiments of formula (I), when Z^2 is N, R^3 is H, R^4 is substituted C_{1-6} thioalkoxy,

Z^1 is $-OR^7$, $-N(R^7)R^{10}$, $-SR^7$, or $-C(R^7)(R^{10})R^{11}$, in which R^7 is methyl, dialkylaminoethyl, optionally substituted C_{1-3} alkcycloalkyl, optionally substituted C_{1-3} alkheterocyclyl, or optionally substituted C_{1-3} alkaryl, or R^7 and R^8, together with the atoms to which each is attached, join to form an optionally substituted five- or six-membered ring optionally comprising one or two heteroatoms selected from nitrogen, oxygen, and sulfur.

In other embodiments of formula (I), when Z^2 is CR^3, each of R^5 and R^6 is chloro, R^3 is H, and R^4 is halogen (e.g., chloro),

Z^1 is not 2-amino-2oxoethoxy, 2-(N,N-diethylamino)ethoxy, methoxy, or benzyloxy.

In yet other embodiments of formula (I), when Z^2 is CR^3, R^3 is H, and R^4 is halogen (e.g., chloro),

Z^1 is not 2-amino-2oxoethoxy, 2-(N,N-diethylamino)ethoxy, methoxy, or benzyloxy.

In still other embodiments of formula (I), when Z^2 is CR^3, each of R^5 and R^6 is chloro, R^3 is H, and R^4 is halogen (e.g., chloro),

Z^1 is $-OR^7$, $-N(R^7)R^{10}$, $-SR^7$, or $-C(R^7)(R^{10})R^{11}$, in which R^7 is dimethylaminoethyl, optionally substituted C_{1-3} alkcycloalkyl, or optionally substituted C_{1-3} alkheterocyclyl, or R^7 and R^8, together with the atoms to which each is attached, join to form an optionally substituted five- or six-membered ring optionally comprising one or two heteroatoms selected from nitrogen, oxygen, and sulfur.

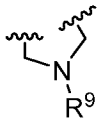
In further embodiments of formula (I), when Z^2 is CR^3, each of R^5 and R^6 is chloro, R^3 is H, and R^4 is halogen (e.g., chloro),

Z^1 is $-OR^7$, $-N(R^7)R^{10}$, $-SR^7$, or $-C(R^7)(R^{10})R^{11}$, in which R^7 is optionally substituted C_{1-3} alkcycloalkyl, or optionally substituted C_{1-3} alkheterocyclyl, or R^7 and R^8, together with the atoms to which each is attached, join to form an optionally substituted five- or six-membered ring optionally comprising one or two heteroatoms selected from nitrogen, oxygen, and sulfur.

In particular embodiments of formula (I), when Z^2 is CR^3, R^3 is H, and R^4 is halogen (e.g., chloro),

Z^1 is $-OR^7$, $-N(R^7)R^{10}$, $-SR^7$, or $-C(R^7)(R^{10})R^{11}$, in which R^7 is optionally substituted C_{1-3} alkcycloalkyl, or optionally substituted C_{1-3} alkheterocyclyl, or R^7 and R^8, together with the atoms to which each is attached, join to form an optionally substituted five- or six-membered ring optionally comprising one or two heteroatoms selected from nitrogen, oxygen, and sulfur.

In some embodiments of formula (I), when R^5 is chloro, R^6 is bromo, Z^1 is $-OR^7$, Z^2 is CR^3, and R^3 and R^4 combine to form a group according to formula (IIa):



(IIa),

R^7 is not methyl, ethyl, n-propyl, 2-(N-pyrazolyl)ethyl, 2-(N-imidazolyl)ethyl, 3-hydroxypropyl, cyanomethyl, 2-chloroethyl, 2-hydroxyethyl, 2-oxo-propyl, 2-(N,N-dimethylamino)ethyl, difluoromethyl, or 2-(*t*-butylamino)ethyl.

In certain embodiments of formula (I), when R^5 is chloro, R^6 is bromo, Z^1 is $-OR^7$, Z^2 is CR^3, and R^3 and R^4 combine to form a group according to formula (IIa),

R^7 is not substituted alkyl, unsubstituted alkyl, or unsubstituted C_2 alkheteroaryl.

In some embodiments of formula (I), when R^5 is chloro, R^6 is bromo, Z^1 is $-OR^7$, Z^2 is CR^3, and R^3 and R^4 combine to form a group according to formula (IIa),

R^7 is not alkyl or unsubstituted C_2 alkheteroaryl.

In particular embodiments of formula (I), when R^5 is chloro, R^6 is bromo, Z^1 is $-OR^7$, Z^2 is CR^3, and R^3 and R^4 combine to form a group according to formula (IIa),

R^7 is not substituted alkyl, unsubstituted alkyl, or unsubstituted C_2 alkheterocyclyl.

In other embodiments of formula (I), when R^5 is chloro, R^6 is bromo, Z^1 is $-OR^7$, Z^2 is CR^3, and R^3 and R^4 combine to form a group according to formula (IIa),

R^7 is not alkyl or C_2 alkheterocyclyl.

In still other embodiments of formula (I), when R^5 is chloro, R^6 is bromo, Z^1 is $-OR^7$, Z^2 is CR^3, and R^3 and R^4 combine to form a group according to formula (IIa),

R^7 and R^8, together with the atoms to which each is attached, join to form an optionally substituted five- or six-membered ring optionally comprising one or two heteroatoms selected from nitrogen, oxygen, and sulfur.

In yet other embodiments of formula (I), when R^5 is chloro, R^6 is bromo, Z^2 is CR^3, and R^3 and R^4 combine to form a group according to formula (IIa),

Z is $-OR^7$, and R^7 and R^8 combine to form $-CH_2-CH_2-$.

In some embodiments of formula (I), when each R^5 and R^6 is bromo, Z^1 is $-OR^7$, Z^2 is CR^3, and R^3 and R^4 combine to form a group according to formula (IIa),

R^7 is not methyl.

In particular embodiments of formula (I), when each R^5 and R^6 is chloro, Z^1 is $-OR^7$, Z^2 is CR^3, and R^3 and R^4 combine to form a group according to formula (IIa),

R^7 is not methyl, 2-(N-imidazolyl)ethyl, methoxymethyl, 2-(N-pyrazolyl)ethyl, 2-(3-methylpyrazol-1-yl)ethyl, 2-pyridyl-methyl, 1,3-dimethyl-1H-1,2,4-triazol-5-yl-methyl, 2-pyrimidinylmethyl, imidazol-2-yl-methyl, 5-methyl-isoxazol-3-yl-methyl, 4-methyl-imidazol-5-yl-methyl, or 3-methyl-1,2,4-oxadiazol-5-yl-

methyl.

In other embodiments of formula (I), when each R^5 and R^6 is chloro, Z^1 is $-OR^7$, Z^2 is CR^3, and R^3 and R^4 combine to form a group according to formula (IIa),

R^7 is not unsubstituted alkyl, substituted alkyl, unsubstituted alkheteroaryl, or substituted alkheteroaryl.

In other embodiments of formula (I), when each R^5 and R^6 is chloro, Z^1 is $-OR^7$, Z^2 is CR^3, and R^3 and R^4 combine to form a group according to formula (IIa),

R^7 is not unsubstituted alkyl, substituted alkyl, unsubstituted alkheterocyclyl, or substituted alkheterocyclyl.

In certain embodiments of formula (I), when each R^5 and R^6 is chloro, Z^1 is $-OR^7$, R^7 and R^8 combine to form $-CH_2-CH_2-$, Z^2 is CR^3, and R^3 and R^4 combine to form a group according to formula (IIa),

R^9 is not ethoxycarbonyl, cyclobutylaminocarbonyl, or cyclobutadienylaminocarbonyl.

In other embodiments of formula (I), when each R^5 and R^6 is chloro, Z^1 is $-OR^7$, R^7 and R^8 combine to form $-CH_2-CH_2-$, Z^2 is CR^3, and R^3 and R^4 combine to form a group according to formula (IIa),

R^9 is H or -C(O)-N(H)-(linear C_{1-3} alkyl).

In particular embodiments of formula (I), when each R^5 and R^6 is halo, Z^2 is CR^3, and R^3 and R^4 combine to form a group according to formula (IIa),

Z is $-OR^7$, R^7 is not methyl or 2-chloroethyl, and R^9 is H or -C(O)-N(H)-(linear C_{1-3} alkyl).

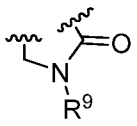
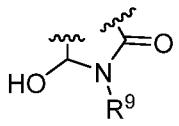
In some embodiments of formula (I), when R^5 is methoxy, R^6 is methyl, Z^1 is $-OR^7$, Z^2 is CR^3, and R^3 and R^4 combine to form a group according to formula (IIa),

R^7 is not methyl.

In certain embodiments of formula (I), when R^5 is chloro, R^6 is ethyl, Z^1 is $-OR^7$, Z^2 is CR^3, and R^3 and R^4 combine to form a group according to formula (IIa),

R^7 is not methyl.

In some embodiments of formula (I), when each R^5 and R^6 is chloro, Z^1 is $-OR^7$, Z^2 is CR^3, and R^3 and R^4 combine to form a group according to formula (IIb) or (IIc),


(IIb) or

(IIc),

R^7 is not methyl or 2-(N,N-diethylamino)ethyl.

In other embodiments of formula (I), when each R^5 and R^6 is chloro, Z^1 is $-OR^7$, Z^2 is CR^3, and R^3 and R^4 combine to form a group according to formula (IIb) or (IIc),

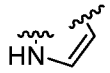
R^7 and R^8, together with the atoms to which each is attached, join to form an optionally

substituted five- or six-membered ring optionally comprising one or two heteroatoms selected from nitrogen, oxygen, and sulfur.

In certain embodiments of formula (I), when each R^5 and R^6 is chloro, Z^2 is CR^3, and R^3 and R^4 combine to form a group according to formula (IIb) or (IIc),

Z^1 is $–OR^7$, and R^7 and R^8 combine to form $-CH_2-CH_2-$.

In some embodiments of formula (I), when R^7 is methyl, R^5 is chloro, Z^1 is $–OR^7$, Z^2 is CR^3, and R^3 and R^4 combine to form a group according to formula (IIIa),


(IIIa),

R^6 is not bromo.

In particular embodiments of formula (I), when each R^5 and R^6 is chloro, Z^1 is $–OR^7$, Z^2 is CR^3, and R^3 and R^4 combine to form a group according to formula (IIIa),

R^7 is not isopropyl, 3,3,3-trifluoropropyl, or 2-(N,N-dimethylamino)ethyl.

In certain embodiments of formula (I), when each R^5 and R^6 is chloro, Z^1 is $–OR^7$, Z^2 is CR^3, and R^3 and R^4 combine to form a group according to formula (IIIa),

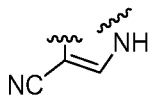
R^8 is not H.

In some embodiments of formula (I), when Z^2 is CR^3, and R^3 and R^4 combine to form a group according to formula (IIIa),

each R^5 and R^6 is chloro, and

R^7 is methyl and R^8 is H, or R^7 and R^8, together with the atoms to which each is attached, join to form an optionally substituted five- or six-membered ring optionally comprising one or two heteroatoms selected from nitrogen, oxygen, and sulfur.

In other embodiments of formula (I), when R^5 is chloro, R^6 is methoxy, Z^1 is $–OR^7$, Z^2 is CR^3, and R^3 and R^4 combine to form a group according to formula (IIIb):

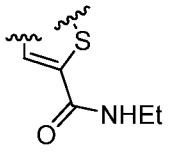

(IIIb),

neither R^1 nor R^2 is 2-(N,N-diethylamino)ethyl.

In certain embodiments of formula (I), when R^5 is chloro, R^6 is methoxy, Z^1 is $–OR^7$, Z^2 is CR^3, and R^3 and R^4 combine to form a group according to formula (IIIb),

each R^1 and R^2 is H.

In some embodiments of formula (I), when each R^5 and R^6 is chloro, Z^1 is $–OR^7$, Z^2 is CR^3, and R^3 and R^4 combine to form a group according to formula (IVa):



(IVa),

R^7 is not 3-(N-morpholinyl)propyl, benzyl, 1-ethyl-pyrrolydin-3-yl, 1-methyl-piperidin-4-yl, 2-(1-methyl-pyrrolidin-2-yl)ethyl, or 3-(N,N-diethylamino)propyl.

In particular embodiments of formula (I), when each R^5 and R^6 is chloro, Z^1 is $-OR^7$, Z^2 is CR^3, and R^3 and R^4 combine to form a group according to formula (IVa),

R^7 is not substituted alkyl, heterocyclyl, alkheterocyclyl, or alkaryl.

In some embodiments of formula (I), when each R^5 and R^6 is chloro, Z^1 is $-OR^7$, Z^2 is CR^3, and R^3 and R^4 combine to form a group according to formula (IVb):

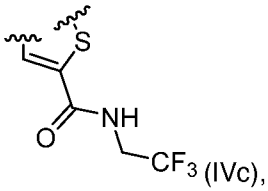
c(IVb),

R^7 is not 2-methoxyethyl or benzyl.

In certain embodiments of formula (I), when each R^5 and R^6 is chloro, Z^1 is $-OR^7$, Z^2 is CR^3, and R^3 and R^4 combine to form a group according to formula (IVb),

R^7 is not substituted alkyl or alkaryl.

In some embodiments of formula (I), when each R^5 and R^6 is chloro, Z^1 is $-OR^7$, Z^2 is CR^3, and R^3 and R^4 combine to form a group according to formula (IVc):



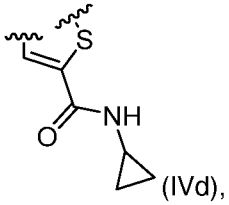
(IVc),

R^7 is not 2-(N,N-diethylamino)ethyl or 3-(N,N-dimethylamino)propyl.

In other embodiments of formula (I), when each R^5 and R^6 is chloro, Z^1 is $-OR^7$, Z^2 is CR^3, and R^3 and R^4 combine to form a group according to formula (IVc),

R^7 is not substituted alkyl.

In particular embodiments of formula (I), when each R^5 and R^6 is chloro, Z^1 is $-OR^7$, Z^2 is CR^3, and R^3 and R^4 combine to form a group according to formula (IVd):



(IVd),

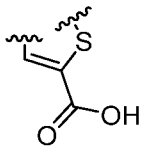
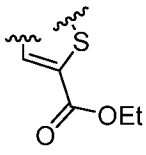
R^7 is not 2-(pyrrolidin-1-yl)ethyl or 2-hydroxyethyl.

In certain embodiments of formula (I), when each R^5 and R^6 is chloro, Z^1 is $-OR^7$, Z^2 is CR^3, and R^3 and

R^4 combine to form a group according to formula (IVd),

R^7 is not substituted alkyl or alkheterocyclyl.

In some embodiments of formula (I), when each R^5 and R^6 is chloro, Z^1 is $-OR^7$, Z^2 is CR^3, and R^3 and R^4 combine to form a group according to formula (IVe) or (IVf):

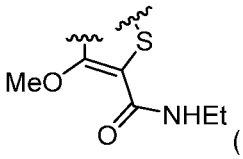
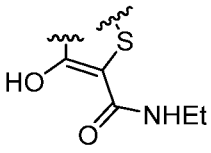
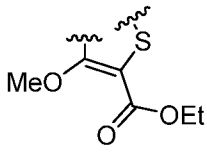
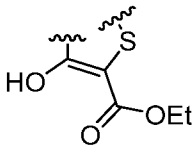
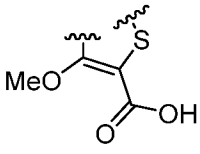

(IVe) or

(IVf),

R^7 is not benzyl.

In other embodiments of formula (I), when each R^5 and R^6 is chloro, Z^1 is $-OR^7$, Z^2 is CR^3, and R^3 and R^4 combine to form a group according to formula (IVe) or (IVf),

R^7 is not alkaryl.

In certain embodiments of formula (I), when R^5 is chloro, R^6 is bromo, Z^1 is $-OR^7$, Z^2 is CR^3, and R^3 and R^4 combine to form a group according to formula (IVg), (IVh), (IVi), (IVj), or (IVk):


(IVg),

(IVh),

(IVi),

(IVj), or

(IVk),

R^7 is not methyl.

In certain embodiments of formula (I), when R^5 is chloro, R^6 is bromo, Z^1 is $-OR^7$, Z^2 is CR^3, and R^3 and R^4 combine to form a group according to formula (IVg), (IVh), (IVi), (IVj), or (IVk),

R^7 is not alkyl.

In some embodiments of formula (I), when R^5 is chloro, R^6 is bromo, Z^1 is $-OR^7$, Z^2 is CR^3, and R^3 and R^4 combine to form a group according to formula (IVg), (IVh), (IVi), (IVj), or (IVk),

R^7 and R^8, together with the atoms to which each is attached, join to form an optionally substituted five- or six-membered ring optionally comprising one or two heteroatoms selected from nitrogen, oxygen, and sulfur.

In particular embodiments of formula (I), when R^5 is chloro, R^6 is bromo, Z^1 is $-OR^7$, and Z^2 is CR^3,

R^3 and R^4 do not combine to form a group according to formula (IVg), (IVh), (IVi), (IVj), or (IVk).

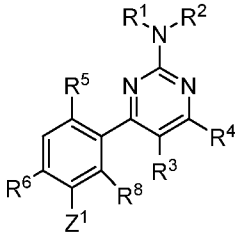
In particular embodiments of formula (I), when R^6 is methyl,

each R^1 and R^2 is H.

In certain embodiments of formula (I), when R^3 is H, and each R^5 and R^6 is chloro,

R^7 is not methyl.

In particular embodiments, the compound is according to formula (Ia):



(Ia), or a pharmaceutically acceptable salt thereof,

where

Z^1 is $-OR^7$, $-N(R^{10})R^7$, $-SR^7$, or $-C(R^{10})(R^{11})R^7$;

each R^1 and R^2 is, independently, H or optionally substituted C_{1-3} alkyl;

R^3 is H, halogen, optionally substituted C_{1-3} alkyl, or optionally substituted C_{1-3} alkoxy, and R^4 is halogen, optionally substituted C_{1-3} alkyl, optionally substituted C_{1-3} alkoxy, optionally substituted amino, optionally substituted C_{1-6} thioalkyl, or optionally substituted C_{6-10} aryl, or R^3 and R^4, together with the atoms to which each is attached, join to form an optionally substituted five-, six-, or seven- membered ring optionally comprising from one to three heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur, where the nitrogen is optionally substituted with R^9;

each R^5 and R^6 is, independently, H, optionally substituted C_{1-3} alkyl, optionally substituted C_{1-3} alkoxy, halogen, or CN;

R^7 is optionally substituted C_{1-3} alkyl, optionally substituted C_{1-3} alkcycloalkyl, optionally substituted C_{1-3} alkheterocyclyl, or optionally substituted C_{1-3} alkaryl, and R^8 is H; or R^7 and R^8, together with the atoms to which each is attached, join to form an optionally substituted five-, six-, or seven-membered ring optionally comprising one or two heteroatoms selected from nitrogen, oxygen, and sulfur;

R^9 is H, optionally substituted C_{1-3} alkyl, optionally substituted C_{3-8} cycloalkyl, optionally substituted C_{6-10} aryl, optionally substituted C_{2-9} heteroaryl, optionally substituted C_{2-9} heterocyclyl, optionally substituted C_{1-3} alkcycloalkyl, optionally substituted C_{1-3} alkheterocyclyl, or optionally substituted C_{1-3} alkaryl;

R^{10} is H, optionally substituted C_{1-3} alkyl (e.g., optionally substituted C_{1-3} acyl), optionally substituted C_{3-8} cycloalkyl, optionally substituted C_{6-10} aryl, optionally substituted C_{2-9} heteroaryl, optionally substituted C_{2-9} heterocyclyl, optionally substituted C_{1-3} alkcycloalkyl, optionally substituted C_{1-3} alkheterocyclyl, or optionally substituted C_{1-3} alkaryl, and R^{11} is H, optionally substituted C_{1-3} alkyl, or R^{10} and R^{11} combine to form =O or =S.

In other embodiments, when each of R^1 and R^2 is H, R^3 is H, R^4 is methyl or chloro, and each of R^5 and R^6 is chloro,

Z^1 is not methoxy.

In yet other embodiments, when R^3 is H, and R^4 is halogen (e.g., chloro),

Z^1 is not 2-amino-2oxoethoxy, 2-(N,N-diethylamino)ethoxy, methoxy, or benzyloxy.

In still other embodiments, when each of R^5 and R^6 is chloro, R^3 is H, and R^4 is halogen (e.g., chloro),

Z^1 is $-OR^7$, $-N(R^7)R^{10}$, $-SR^7$, or $-C(R^7)(R^{10})R^{11}$, in which R^7 is dimethylaminoethyl, optionally substituted C_{1-3} alkcycloalkyl, or optionally substituted C_{1-3} alkheterocyclyl, or R^7 and R^8, together with the atoms to which each is attached, join to form an optionally substituted five- or six-membered ring optionally comprising one or two heteroatoms selected from nitrogen, oxygen, and sulfur.

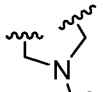
In further embodiments, when each of R^5 and R^6 is chloro, R^3 is H, and R^4 is halogen (e.g., chloro),

Z^1 is $-OR^7$, $-N(R^7)R^{10}$, $-SR^7$, or $-C(R^7)(R^{10})R^{11}$, in which R^7 is optionally substituted C_{1-3} alkcycloalkyl, or optionally substituted C_{1-3} alkheterocyclyl, or R^7 and R^8, together with the atoms to which each is attached, join to form an optionally substituted five- or six-membered ring optionally comprising one or two heteroatoms selected from nitrogen, oxygen, and sulfur.

In particular embodiments, when R^3 is H, and R^4 is halogen (e.g., chloro),

Z^1 is $-OR^7$, $-N(R^7)R^{10}$, $-SR^7$, or $-C(R^7)(R^{10})R^{11}$, in which R^7 is optionally substituted C_{1-3} alkcycloalkyl, or optionally substituted C_{1-3} alkheterocyclyl, or R^7 and R^8, together with the atoms to which each is attached, join to form an optionally substituted five- or six-membered ring optionally comprising one or two heteroatoms selected from nitrogen, oxygen, and sulfur.

In some embodiments, when R^5 is chloro, R^6 is bromo, Z^1 is $-OR^7$, and R^3 and R^4 combine to form a group according to formula (IIa):



(IIa),

R^7 is not methyl, ethyl, n-propyl, 2-(N-pyrazolyl)ethyl, 2-(N-imidazolyl)ethyl, 3-hydroxypropyl, cyanomethyl, 2-chloroethyl, 2-hydroxyethyl, 2-oxo-propyl, 2-(N,N-dimethylamino)ethyl, difluoromethyl, or 2-(*t*-butylamino)ethyl.

In certain embodiments, when R^5 is chloro, R^6 is bromo, Z^1 is $-OR^7$, and R^3 and R^4 combine to form a group according to formula (IIa),

R^7 is not substituted alkyl, unsubstituted alkyl, or unsubstituted C_2 alkheteroaryl.

In some embodiments, when R^5 is chloro, R^6 is bromo, Z^1 is $-OR^7$, and R^3 and R^4 combine to form a group according to formula (IIa),

R^7 is not alkyl or unsubstituted C_2 alkheteroaryl.

In particular embodiments, when R^5 is chloro, R^6 is bromo, Z^1 is $-OR^7$, and R^3 and R^4 combine to form a group according to formula (IIa),

R^7 is not substituted alkyl, unsubstituted alkyl, or unsubstituted C_2 alkheterocyclyl.

In other embodiments, when R^5 is chloro, R^6 is bromo, Z^1 is $-OR^7$, and R^3 and R^4 combine to form a group according to formula (IIa),

R^7 is not alkyl or C_2 alkheterocyclyl.

In still other embodiments, when R^5 is chloro, R^6 is bromo, Z^1 is $-OR^7$, and R^3 and R^4 combine to form a group according to formula (IIa),

R^7 and R^8, together with the atoms to which each is attached, join to form an optionally substituted five- or six-membered ring optionally comprising one or two heteroatoms selected from nitrogen, oxygen, and sulfur.

In yet other embodiments, when R^5 is chloro, R^6 is bromo, and R^3 and R^4 combine to form a group according to formula (IIa),

Z is $-OR^7$, and R^7 and R^8 combine to form $-CH_2-CH_2-$.

In some embodiments, when each R^5 and R^6 is bromo, Z^1 is $-OR^7$, and R^3 and R^4 combine to form a group according to formula (IIa),

R^7 is not methyl.

In particular embodiments, when each R^5 and R^6 is chloro, Z^1 is $-OR^7$, and R^3 and R^4 combine to form a group according to formula (IIa),

R^7 is not methyl, 2-(N-imidazolyl)ethyl, methoxymethyl, 2-(N-pyrazolyl)ethyl, 2-(3-methylpyrazol-1-yl)ethyl, 2-pyridyl-methyl, 1,3-dimethyl-1H-1,2,4-triazol-5-yl-methyl, 2-pyrimidinylmethyl, imidazol-2-yl-methyl, 5-methyl-isoxazol-3-yl-methyl, 4-methyl-imidazol-5-yl-methyl, or 3-methyl-1,2,4-oxadiazol-5-yl-methyl.

In other embodiments, when each R^5 and R^6 is chloro, Z^1 is $-OR^7$, and R^3 and R^4 combine to form a group according to formula (IIa),

R^7 is not unsubstituted alkyl, substituted alkyl, unsubstituted alkheteroaryl, or substituted alkheteroaryl.

In other embodiments, when each R^5 and R^6 is chloro, Z^1 is $-OR^7$, and R^3 and R^4 combine to form a group according to formula (IIa),

R^7 is not unsubstituted alkyl, substituted alkyl, unsubstituted alkheterocyclyl, or substituted alkheterocyclyl.

In certain embodiments, when each R^5 and R^6 is chloro, Z^1 is $-OR^7$, R^7 and R^8 combine to form $-CH_2-CH_2-$, and R^3 and R^4 combine to form a group according to formula (IIa),

R^9 is not ethoxycarbonyl, cyclobutylaminocarbonyl, or cyclobutadienylaminocarbonyl.

In other embodiments, when each R^5 and R^6 is chloro, Z^1 is $-OR^7$, R^7 and R^8 combine to form $-CH_2-CH_2-$, and R^3 and R^4 combine to form a group according to formula (IIa),

R^9 is H or -C(O)-N(H)-(linear C_{1-3} alkyl).

In particular embodiments, when each R^5 and R^6 is halo, and R^3 and R^4 combine to form a group according to formula (IIa),

Z is –OR^7, R^7 is not methyl or 2-chloroethyl, and R^9 is H or -C(O)-N(H)-(linear C_{1-3} alkyl).

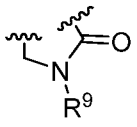
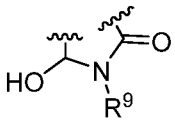
In some embodiments, when R^5 is methoxy, R^6 is methyl, Z^1 is –OR^7, and R^3 and R^4 combine to form a group according to formula (IIa),

R^7 is not methyl.

In certain embodiments, when R^5 is chloro, R^6 is ethyl, Z^1 is –OR^7, and R^3 and R^4 combine to form a group according to formula (IIa),

R^7 is not methyl.

In some embodiments, when each R^5 and R^6 is chloro, Z^1 is –OR^7, and R^3 and R^4 combine to form a group according to formula (IIb) or (IIc),


(IIb) or

(IIc),

R^7 is not methyl or 2-(N,N-diethylamino)ethyl.

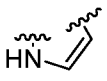
In other embodiments, when each R^5 and R^6 is chloro, Z^1 is –OR^7, and R^3 and R^4 combine to form a group according to formula (IIb) or (IIc),

R^7 and R^8, together with the atoms to which each is attached, join to form an optionally substituted five- or six-membered ring optionally comprising one or two heteroatoms selected from nitrogen, oxygen, and sulfur.

In certain embodiments, when each R^5 and R^6 is chloro, and R^3 and R^4 combine to form a group according to formula (IIb) or (IIc),

Z^1 is –OR^7, and R^7 and R^8 combine to form -CH_2-CH_2-.

In some embodiments, when R^7 is methyl, R^5 is chloro, Z^1 is –OR^7, and R^3 and R^4 combine to form a group according to formula (IIIa),


(IIIa),

R^6 is not bromo.

In particular embodiments, when each R^5 and R^6 is chloro, Z^1 is –OR^7, and R^3 and R^4 combine to form a group according to formula (IIIa),

R^7 is not isopropyl, 3,3,3-trifluoropropyl, or 2-(N,N-dimethylamino)ethyl.

In certain embodiments, when each R^5 and R^6 is chloro, Z^1 is –OR^7, and R^3 and R^4 combine to form a group according to formula (IIIa),

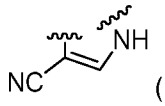
R^8 is not H.

In some embodiments, when R^3 and R^4 combine to form a group according to formula (IIIa),

each R^5 and R^6 is chloro, and

R^7 is methyl and R^8 is H, or R^7 and R^8, together with the atoms to which each is attached, join to form an optionally substituted five- or six-membered ring optionally comprising one or two heteroatoms selected from nitrogen, oxygen, and sulfur.

In other embodiments, when R^5 is chloro, R^6 is methoxy, Z^1 is $-OR^7$, and R^3 and R^4 combine to form a group according to formula (IIIb):



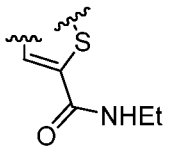
(IIIb),

neither R^1 nor R^2 is 2-(N,N-diethylamino)ethyl.

In certain embodiments, when R^5 is chloro, R^6 is methoxy, Z^1 is $-OR^7$, and R^3 and R^4 combine to form a group according to formula (IIIb),

each R^1 and R^2 is H.

In some embodiments, when each R^5 and R^6 is chloro, Z^1 is $-OR^7$, and R^3 and R^4 combine to form a group according to formula (IVa):



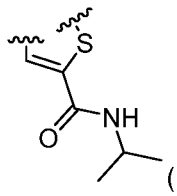
(IVa),

R^7 is not 3-(N-morpholinyl)propyl, benzyl, 1-ethyl-pyrrolydin-3-yl, 1-methyl-piperidin-4-yl, 2-(1-methyl-pyrrolidin-2-yl)ethyl, or 3-(N,N-diethylamino)propyl.

In particular embodiments, when each R^5 and R^6 is chloro, Z^1 is $-OR^7$, and R^3 and R^4 combine to form a group according to formula (IVa),

R^7 is not substituted alkyl, heterocyclyl, alkheterocyclyl, or alkaryl.

In some embodiments, when each R^5 and R^6 is chloro, Z^1 is $-OR^7$, and R^3 and R^4 combine to form a group according to formula (IVb):



(IVb),

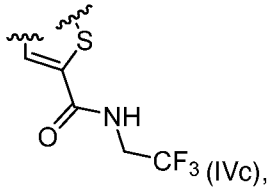
R^7 is not 2-methoxyethyl or benzyl.

In certain embodiments, when each R^5 and R^6 is chloro, Z^1 is $-OR^7$, and R^3 and R^4 combine to form a group according to formula (IVb),

R^7 is not substituted alkyl or alkaryl.

In some embodiments, when each R^5 and R^6 is chloro, Z^1 is $-OR^7$, and R^3 and R^4 combine to form a

group according to formula (IVc):



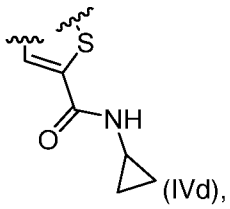
(IVc),

R^7 is not 2-(N,N-diethylamino)ethyl or 3-(N,N-dimethylamino)propyl.

In other embodiments, when each R^5 and R^6 is chloro, Z^1 is $-OR^7$, and R^3 and R^4 combine to form a group according to formula (IVc),

R^7 is not substituted alkyl.

In particular embodiments, when each R^5 and R^6 is chloro, Z^1 is $-OR^7$, and R^3 and R^4 combine to form a group according to formula (IVd):



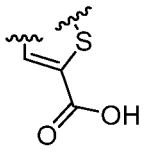
(IVd),

R^7 is not 2-(pyrrolidin-1-yl)ethyl or 2-hydroxyethyl.

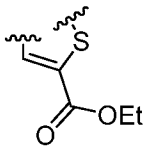
In certain embodiments, when each R^5 and R^6 is chloro, Z^1 is $-OR^7$, and R^3 and R^4 combine to form a group according to formula (IVd),

R^7 is not substituted alkyl or alkheterocyclyl.

In some embodiments, when each R^5 and R^6 is chloro, Z^1 is $-OR^7$, and R^3 and R^4 combine to form a group according to formula (IVe) or (IVf):



(IVe) or



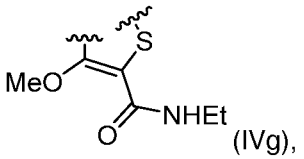
(IVf),

R^7 is not benzyl.

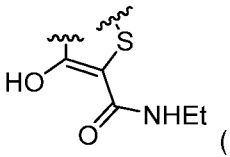
In other embodiments, when each R^5 and R^6 is chloro, Z^1 is $-OR^7$, and R^3 and R^4 combine to form a group according to formula (IVe) or (IVf),

R^7 is not alkaryl.

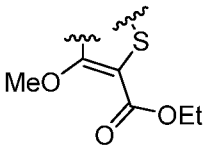
In certain embodiments, when R^5 is chloro, R^6 is bromo, Z^1 is $-OR^7$, and R^3 and R^4 combine to form a group according to formula (IVg), (IVh), (IVi), (IVj), or (IVk):



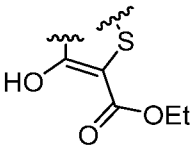
(IVg),



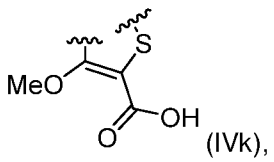
(IVh),



(IVi),



(IVj), or



(IVk),

R^7 is not methyl.

In certain embodiments, when R^5 is chloro, R^6 is bromo, Z^1 is $-OR^7$, and R^3 and R^4 combine to form a group according to formula (IVg), (IVh), (IVi), (IVj), or (IVk),

R^7 is not alkyl.

In some embodiments, when R^5 is chloro, R^6 is bromo, Z^1 is $-OR^7$, and R^3 and R^4 combine to form a group according to formula (IVg), (IVh), (IVi), (IVj), or (IVk),

R^7 and R^8, together with the atoms to which each is attached, join to form an optionally substituted five- or six-membered ring optionally comprising one or two heteroatoms selected from nitrogen, oxygen, and sulfur.

In particular embodiments, when R^5 is chloro, R^6 is bromo, and Z^1 is $-OR^7$,

R^3 and R^4 do not combine to form a group according to formula (IVg), (IVh), (IVi), (IVj), or (IVk).

In particular embodiments, when R^6 is methyl,

each R^1 and R^2 is H.

In certain embodiments, when R^3 is H, and each R^5 and R^6 is chloro,

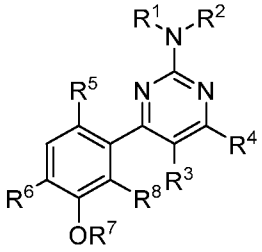
R^7 is not methyl.

In certain embodiments, when R^3 and R^4, together with the atoms to which each is attached, join to form a substituted five-membered ring comprising one nitrogen, the five-membered ring is not substituted with oxo. In particular embodiments, when R^3 and R^4, together with the atoms to which each is attached, join to form a substituted five-membered ring comprising one sulfur, the five-membered ring is not substituted with hydroxy or C_{1-3} alkoxy. In further embodiments, when R^3 and R^4, together with the atoms to which each is attached, join to form an optionally substituted five-membered ring comprising one sulfur, R^7 and R^8, together with the atoms to which each is attached, join to form an optionally substituted five- or six-membered ring optionally comprising one or two heteroatoms selected from nitrogen, oxygen, and sulfur.

In particular embodiments, R^7 and R^8, together with the atoms to which each is attached, join to form an optionally substituted five- or six-membered ring optionally comprising one or two heteroatoms selected from nitrogen, oxygen, and sulfur. In other embodiments, R^7 and R^8, together with the atoms to which each is attached, join to form an optionally substituted five- or six-membered saturated ring optionally comprising one or two heteroatoms selected from nitrogen, oxygen, and sulfur. In yet other embodiments, R^7 and R^8, together with the atoms to which each is attached, join to form an optionally substituted five- of six-membered ring optionally comprising one or two heteroatoms selected from nitrogen and oxygen. In certain embodiments, R^7 and R^8, together with the atoms to which each is

attached, join to form an optionally substituted five-membered ring.

In some embodiments, a compound is according to formula (Ib):



(Ib), or a pharmaceutically acceptable salt thereof,

where

each of R^1 and R^2 is, independently, H or optionally substituted C_{1-3} alkyl;

R^3 is H, halogen, optionally substituted C_{1-3} alkyl, or optionally substituted C_{1-3} alkoxy, and R^4 is halogen, optionally substituted C_{1-3} alkyl, optionally substituted C_{1-3} alkoxy, optionally substituted amino, optionally substituted C_{1-6} thioalkoxy, or optionally substituted C_{6-10} aryl, or R^3 and R^4, together with the atoms to which each is attached, join to form an optionally substituted five- or six-membered ring optionally comprising one nitrogen, one sulfur, or one oxygen, where the nitrogen is optionally substituted with R^9;

each of R^5 and R^6 is, independently, optionally substituted C_{1-3} alkyl (e.g., optionally substituted C_{1-3} acyl), optionally substituted C_{1-3} alkoxy, halogen, or CN;

R^7 is optionally substituted C_{1-3} alkyl, optionally substituted C_{1-3} alkcycloalkyl, optionally substituted C_{1-3} alkheterocyclyl, or optionally substituted C_{1-3} alkaryl, and R^8 is H; or R^7 and R^8, together with the atoms to which each is attached, join to form an optionally substituted five- or six-membered ring; and

R^9 is H, optionally substituted C_{1-3} alkyl, optionally substituted C_{3-8} cycloalkyl, optionally substituted C_{6-10} aryl, optionally substituted C_{2-9} heteroaryl, optionally substituted C_{2-9} heterocyclyl, optionally substituted C_{1-3} alkcycloalkyl, optionally substituted C_{1-3} alkheterocyclyl, or optionally substituted C_{1-3} alkaryl.

In other embodiments, when each of R^1 and R^2 is H, R^3 is H, R^4 is methyl or chloro, and each of R^5 and R^6 is chloro,

R^7 is not methyl.

In yet other embodiments, when R^3 is H, and R^4 is halogen (e.g., chloro),

R^7 is not 2-amino-2oxoethyl, 2-(N,N-diethylamino)ethyl, methyl, or benzyl.

In still other embodiments, when each of R^5 and R^6 is chloro, R^3 is H, and R^4 is halogen (e.g., chloro),

R^7 is dimethylaminoethyl, optionally substituted C_{1-3} alkcycloalkyl, or optionally substituted C_{1-3} alkheterocyclyl, or R^7 and R^8, together with the atoms to which each is attached, join to form an optionally substituted five- or six-membered ring optionally comprising one or two heteroatoms selected from nitrogen, oxygen, and sulfur.

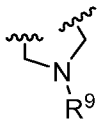
In further embodiments, when each of R^5 and R^6 is chloro, R^3 is H, and R^4 is halogen (e.g., chloro),

R^7 is optionally substituted C_{1-3} alkcycloalkyl, or optionally substituted C_{1-3} alkheterocyclyl, or R^7 and R^8, together with the atoms to which each is attached, join to form an optionally substituted five- or six-membered ring optionally comprising one or two heteroatoms selected from nitrogen, oxygen, and sulfur.

In particular embodiments, when R^3 is H, and R^4 is halogen (e.g., chloro),

R^7 is optionally substituted C_{1-3} alkcycloalkyl, or optionally substituted C_{1-3} alkheterocyclyl, or R^7 and R^8, together with the atoms to which each is attached, join to form an optionally substituted five- or six-membered ring optionally comprising one or two heteroatoms selected from nitrogen, oxygen, and sulfur.

In some embodiments, when R^5 is chloro, R^6 is bromo, and R^3 and R^4 combine to form a group according to formula (IIa):



(IIa),

R^7 is not methyl, ethyl, n-propyl, 2-(N-pyrazolyl)ethyl, 2-(N-imidazolyl)ethyl, 3-hydroxypropyl, cyanomethyl, 2-chloroethyl, 2-hydroxyethyl, 2-oxo-propyl, 2-(N,N-dimethylamino)-ethyl, difluoromethyl, or 2-(*t*-butylamino)ethyl.

In certain embodiments, when R^5 is chloro, R^6 is bromo, and R^3 and R^4 combine to form a group according to formula (IIa),

R^7 is not substituted alkyl, unsubstituted alkyl, or unsubstituted C_2 alkheteroaryl.

In other embodiments, when R^5 is chloro, R^6 is bromo, and R^3 and R^4 combine to form a group according to formula (IIa),

R^7 is not alkyl or C_2 alkheteroaryl.

In particular embodiments, when R^5 is chloro, R^6 is bromo, and R^3 and R^4 combine to form a group according to formula (IIa),

R^7 is not substituted alkyl, unsubstituted alkyl, or unsubstituted C_2 alkheterocyclyl.

In some embodiments, when R^5 is chloro, R^6 is bromo, and R^3 and R^4 combine to form a group according to formula (IIa),

R^7 is not alkyl or C_2 alkheterocyclyl.

In still other embodiments, when R^5 is chloro, R^6 is bromo, and R^3 and R^4 combine to form a group according to formula (IIa),

R^7 and R^8, together with the atoms to which each is attached, join to form an optionally substituted five- or six-membered ring comprising one oxygen atom and optionally comprising one more heteroatom selected from nitrogen, oxygen, and sulfur.

In yet other embodiments, when R^5 is chloro, R^6 is bromo, and R^3 and R^4 combine to form a group according to formula (IIa),

R^7 and R^8 combine to form $-CH_2-CH_2-$.

In some embodiments, when each R^5 and R^6 is bromo, and R^3 and R^4 combine to form a group according to formula (IIa),

R^7 is not methyl.

In particular embodiments, when each R^5 and R^6 is chloro, and R^3 and R^4 combine to form a group according to formula (IIa),

R^7 is not methyl, 2-(N-imidazolyl)ethyl, methoxymethyl, 2-(N-pyrazolyl)ethyl, 2-(3-methylpyrazol-1-yl)ethyl, 2-pyridyl-methyl, 1,3-dimethyl-1H-1,2,4-triazol-5-yl-methyl, 2-pyrimidinylmethyl, imidazol-2-yl-methyl, 5-methyl-isoxazol-3-yl-methyl, 4-methyl-imidazol-5-yl-methyl, or 3-methyl-1,2,4-oxadiazol-5-yl-methyl.

In other embodiments, when each R^5 and R^6 is chloro, and R^3 and R^4 combine to form a group according to formula (IIa),

R^7 is not unsubstituted alkyl, substituted alkyl, unsubstituted alkheteroaryl, or substituted alkheteroaryl.

In other embodiments, when each R^5 and R^6 is chloro, and R^3 and R^4 combine to form a group according to formula (IIa),

R^7 is not unsubstituted alkyl, substituted alkyl, unsubstituted alkheterocyclyl, or substituted alkheterocyclyl.

In certain embodiments, when each R^5 and R^6 is chloro, R^7 and R^8 combine to form $-CH_2-CH_2-$, and R^3 and R^4 combine to form a group according to formula (IIa),

R^9 is not ethoxycarbonyl, cyclobutylaminocarbonyl, or cyclobutadienylaminocarbonyl.

In other embodiments, when each R^5 and R^6 is chloro, R^7 and R^8 combine to form $-CH_2-CH_2-$, and R^3 and R^4 combine to form a group according to formula (IIa),

R^9 is H or -C(O)-N(H)-(linear C_{1-3} alkyl).

In particular embodiments, when each R^5 and R^6 is halo, and R^3 and R^4 combine to form a group according to formula (IIa),

and R^9 is H or -C(O)-N(H)-(linear C_{1-3} alkyl).

In some embodiments, when R^5 is methoxy, R^6 is methyl, and R^3 and R^4 combine to form a group according to formula (IIa),

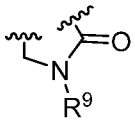
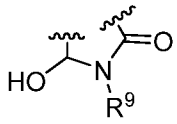
R^7 is not methyl.

In certain embodiments, when R^5 is chloro, R^6 is ethyl, and R^3 and R^4 combine to form a group according

to formula (IIa),

R^7 is not methyl.

In some embodiments, when each R^5 and R^6 is chloro, and R^3 and R^4 combine to form a group according to formula (IIb) or (IIc),


(IIb) or

(IIc),

R^7 is not methyl or 2-(N,N-diethylamino)ethyl.

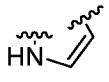
In other embodiments, when each R^5 and R^6 is chloro and R^3 and R^4 combine to form a group according to formula (IIb) or (IIc),

R^7 and R^8, together with the atoms to which each is attached, join to form an optionally substituted five- or six-membered ring comprising one oxygen atom and optionally comprising one more heteroatom selected from nitrogen, oxygen, and sulfur.

In certain embodiments, when each R^5 and R^6 is chloro and R^3 and R^4 combine to form a group according to formula (IIb) or (IIc),

R^7 and R^8 combine to form $-CH_2-CH_2-$.

In some embodiments, when R^7 is methyl, R^5 is chloro, and R^3 and R^4 combine to form a group according to formula (IIIa),


(IIIa),

R^6 is not bromo.

In particular embodiments, when each R^5 and R^6 is chloro, and R^3 and R^4 combine to form a group according to formula (IIIa),

R^7 is not isopropyl, 3,3,3-trifluoropropyl, or 2-(N,N-dimethylamino)ethyl.

In particular embodiments, when each R^5 and R^6 is chloro, and R^3 and R^4 combine to form a group according to formula (IIIa),

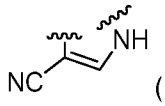
R^8 is not H.

In some embodiments, when R^3 and R^4 combine to form a group according to formula (IIIa),

each R^5 and R^6 is chloro,

R^7 is methyl, and R^8 is H, or R^7 and R^8, together with the atoms to which each is attached, join to form an optionally substituted five- or six-membered ring comprising one oxygen atom and optionally comprising one more heteroatom selected from nitrogen, oxygen, and sulfur.

In other embodiments, when R^5 is chloro, R^6 is methoxy, and R^3 and R^4 combine to form a group according to formula (IIIb):

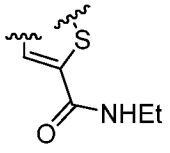

(IIIb),

neither R^1 nor R^2 is 2-(N,N-diethylamino)ethyl.

In certain embodiments, when R^5 is chloro, R^6 is methoxy, and R^3 and R^4 combine to form a group according to formula (IIIb),

each R^1 and R^2 is H.

In some embodiments, when each R^5 and R^6 is chloro, and R^3 and R^4 combine to form a group according to formula (IVa):

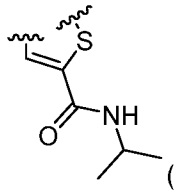

(IVa),

R^7 is not 3-(N-morpholinyl)propyl, benzyl, 1-ethyl-pyrrolydin-3-yl, 1-methyl-piperidin-4-yl, 2-(1-methyl-pyrrolidin-2-yl)ethyl, or 3-(N,N-diethylamino)propyl.

In particular embodiments, when each R^5 and R^6 is chloro, and R^3 and R^4 combine to form a group according to formula (IVa),

R^7 is not substituted alkyl, heterocyclyl, alkheterocyclyl, or alkaryl.

In some embodiments, when each R^5 and R^6 is chloro, and R^3 and R^4 combine to form a group according to formula (IVb):

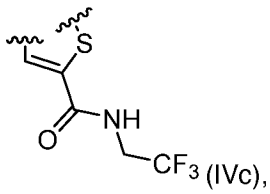

(IVb),

R^7 is not 2-methoxyethyl or benzyl.

In certain embodiments, when each R^5 and R^6 is chloro, and R^3 and R^4 combine to form a group according to formula (IVb),

R^7 is not substituted alkyl or alkaryl.

In some embodiments, when each R^5 and R^6 is chloro, and R^3 and R^4 combine to form a group according to formula (IVc):

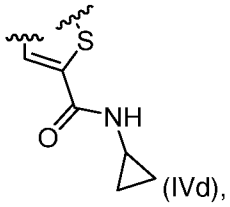

(IVc),

R^7 is not 2-(N,N-diethylamino)ethyl or 3-(N,N-dimethylamino)propyl.

In other embodiments, when each R^5 and R^6 is chloro, and R^3 and R^4 combine to form a group according to formula (IVc),

R^7 is not substituted alkyl.

In particular embodiments, when each R^5 and R^6 is chloro, and R^3 and R^4 combine to form a group according to formula (IVd):

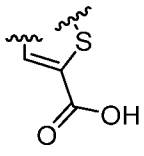
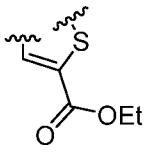

(IVd),

R^7 is not 2-(pyrrolidin-1-yl)ethyl or 2-hydroxyethyl.

In certain embodiments, when each R^5 and R^6 is chloro, and R^3 and R^4 combine to form a group according to formula (IVd),

R^7 is not substituted alkyl or alkheterocyclyl.

In some embodiments, when each R^5 and R^6 is chloro, and R^3 and R^4 combine to form a group according to formula (IVe) or (IVf):

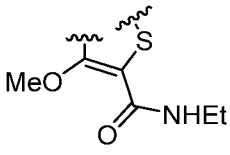
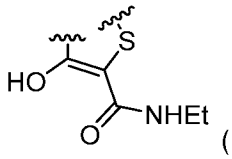
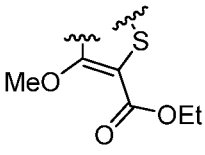
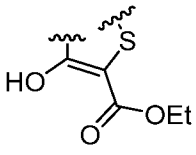
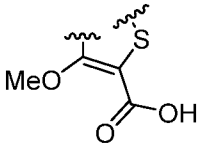

(IVe) or 
(IVf),

R^7 is not benzyl.

In other embodiments, when each R^5 and R^6 is chloro, and R^3 and R^4 combine to form a group according to formula (IVe) or (IVf),

R^7 is not substituted alkyl or alkaryl.

In certain embodiments, when R^5 is chloro, R^6 is bromo, and R^3 and R^4 combine to form a group according to formula (IVg), (IVh), (IVi), (IVj), or (IVk):


(IVg), 
(IVh), 
(IVi), 
(IVj), or 
(IVk),

R^7 is not methyl.

In some embodiments, when R^5 is chloro, R^6 is bromo, and R^3 and R^4 combine to form a group according to formula (IVg), (IVh), (IVi), (IVj), or (IVk),

R^7 and R^8 together with the atoms to which each is attached, join to form an optionally substituted five- or six-membered ring optionally comprising one or two heteroatoms selected from nitrogen, oxygen, and sulfur.

In particular embodiments, when R^5 is chloro, R^6 is bromo,

R^3 and R^4 do not combine to form a group according to formula (IVg), (IVh), (IVi), (IVj), or (IVk).

In particular embodiments, when R^6 is methoxy,

each R^1 and R^2 is H.

In certain embodiments, when R^3 is H, and each R^5 and R^6 is chloro,

R^7 is not methyl.

In some embodiments of formula (I), (Ia), or (Ib), R^3 is H, halogen, optionally substituted C_{1-3} alkyl (e.g., optionally substituted C_{1-3} acyl), or optionally substituted C_{1-3} alkoxy, and R^4 is halogen, optionally substituted C_{1-3} alkyl (e.g., optionally substituted C_{1-3} acyl), optionally substituted C_{1-3} alkoxy, optionally substituted amino, optionally substituted C_{1-6} thioalkyl, or optionally substituted C_{6-10} aryl, or R^3 and R^4, together with the atoms to which each is attached, join to form an optionally substituted five- or six-membered ring optionally comprising one nitrogen, one oxygen, or one sulfur, where the nitrogen is optionally substituted with R^9.

In further embodiments of formula (I), (Ia), or (Ib), R^7 is optionally substituted C_{1-3} alkyl, optionally substituted C_{1-3} alkcycloalkyl, optionally substituted C_{1-3} alkheterocyclyl, or optionally substituted C_{1-3} alkaryl, and R^8 is H; or R^7 and R^8, together with the atoms to which each is attached, join to form an optionally substituted five- or six- membered ring optionally comprising one or two heteroatoms selected from nitrogen, oxygen, and sulfur.

In particular embodiments, when R^3 and R^4 combine to form a group according formula (IIb) or (IIc), the carbonyl group of formula (IIb) or (IIc) is proximal to C^6. In other embodiments, when R^3 and R^4 combine to form a group according to formula (IIb) or (IIc), the carbonyl group of formula (IIb) or (IIc) is proximal to C^5 or C^6.

In certain embodiments, when R^3 and R^4 combine to form a group according to formula (IIIa), the N atom of the group according to formula (IIIa) is proximal to C^5. In particular embodiments, when R^3 and R^4 combine to form a group according to formula (IIIa), the N atom of the group according to formula (IIIb) is proximal to C^5 or C^6.

In some embodiments, when R^3 and R^4 combine to form a group according to formula (IIIb), the N atom of the group according to formula (IIIb) is proximal to C^6. In other embodiments, when R^3 and R^4 combine to form a group according to formula (IIIb), the N atom of the group according to formula (IIIb) is proximal to C^5 or C^6.

In particular embodiments, when R^3 and R^4 combine to form a group according to any one of formulae (IVa)-(IVk), the S atom of the group according to any one of formulae (IVa)-(IVk) is proximal to C^6. In particular embodiments, when R^3 and R^4 combine to form a group according to any one of formulae (IVa)-(IVk), the S atom of the group according to any one of formulae (IVa)-(IVk) is proximal to C^5 or C^6.

In some embodiments, when R^3 and R^4, together with the atoms to which each is attached, join to form an optionally substituted five-membered ring comprising one sulfur, R^7 and R^8, together with the atoms to which each is attached, join to form an optionally substituted five- or six-membered ring. In certain embodiments, when R^3 and R^4, together with the atoms to which each is attached, join to form an optionally substituted five-membered ring comprising one sulfur, R^7 and R^8, together with the atoms to which each is attached, join to form an optionally substituted five-membered ring. In particular embodiments, when R^3 and R^4, together with the atoms to which each is attached, join to form an optionally substituted five-membered ring comprising one sulfur, R^7 and R^8 combine to form a $–CH_2CH_2–$ group.

In other embodiments, R^7 and R^8, together with the atoms to which each is attached, join to form a five- or six-membered ring.

In particular embodiments, R^7 is optionally substituted C_{1-3} alkyl. In other embodiments, R^7 is unsubstituted C_{1-3} alkyl, C_{1-3} alkylamino-C_{1-3}-alkyl (e.g., C_{1-3} haloalkylamino-C_{1-3}-alkyl (e.g., C_{1-3} fluoroalkylamino-C_{1-3}-alkyl)), di-(C_{1-3} alkyl)amino-C_{1-3}-alkyl (e.g., $R^{Y1}N(R^{Y2})$-(C_{1-3} alkyl)-, where each of R^{Y1} and R^{Y2} is, independently, unsubstituted C_{1-3} alkyl or C_{1-3} haloalkylamino-C_{1-3}-alkyl, (e.g., C_{1-3} fluoroalkylamino-C_{1-3}-alkyl), or C_{1-3} haloalkyl (e.g., C_{1-3} fluoroalkyl). In particular embodiments, R^7 is unsubstituted C_{1-3} alkyl, C_{1-3} alkylamino-C_{1-3}-alkyl (e.g., C_{1-3} haloalkylamino-C_{1-3}-alkyl, e.g., C_{1-3} fluoroalkylamino-C_{1-3}-alkyl), or di-(C_{1-3} alkyl)amino-C_{1-3}-alkyl (e.g., $R^{Y1}N(R^{Y2})$-(C_{1-3} alkyl)-, where each of R^{Y1} and R^{Y2} is, independently, unsubstituted C_{1-3} alkyl, or C_{1-3} haloalkylamino-C_{1-3}-alkyl, e.g., C_{1-3} fluoroalkylamino-C_{1-3}-alkyl).

In still other embodiments, R^7 is optionally substituted C_{1-3} alkyl (e.g., R^7 is methyl), or R^7 is $-(CH_2)_k-N(R^{24})R^{25}$, where k is 2 or 3 (e.g., k is 2), and where each of R^{24} and R^{25} is, independently, H or optionally substituted C_{1-3} alkyl (e.g., each of R^{24} and R^{25} is, independently, optionally substituted C_{1-3} alkyl, e.g., each of R^{24} and R^{25} is, independently, C_{1-3} haloalkyl (e.g., C_{1-3} fluoroalkyl); alternatively each of R^{24} and R^{25} is, independently, unsubstituted C_{1-3} alkyl, e.g., methyl).

In other embodiments, when R^3 and R^4, together with the atoms to which each is attached, join to form an optionally substituted five-membered ring comprising one nitrogen, an optional substituent on the ring is not oxo. In certain embodiments, when R^3 and R^4, together with the atoms to which each is attached, join to form an optionally substituted five-membered ring comprising one sulfur, an optional substitutent on the ring is not hydroxyl or C_{1-3} alkoxy.

In yet other embodiments, each R^1 and R^2 is H. In particular embodiments, each R^3 and R^4 is, independently, optionally substituted C_{1-3} alkyl or optionally substituted C_{1-3} alkoxy; or R^3 and R^4, together

with the atoms to which each is attached, join to form an optionally substituted five- or six-membered ring optionally comprising one nitrogen, one sulfur, or one oxygen, where the nitrogen is optionally substituted with R^9. In some embodiments, R^3 and R^4, together with the atoms to which each is attached, join to form an optionally substituted five-membered ring. In certain embodiments, R^3 and R^4 combine to form $-CH_2CH_2CH_2-$. In particular embodiments, R^3 and R^4, together with the atoms to which each is attached, join to form an optionally substituted five-membered ring comprising one nitrogen. In some embodiments, R^3 and R^4 combine to form $-N(R^9)-CH=CH-$ (e.g., R^9 is H or optionally substituted C_{1-3} alkyl, e.g., C_{1-3} haloalkyl (e.g., C_{1-3} fluoroalkyl); alternatively R^9 is H). In certain embodiments, the N atom is proximal to C^5 of Formula (I). In particular embodiments, R^3 and R^4, together with the atoms to which each is attached, join to form an optionally substituted five-membered ring comprising one sulfur. In yet other embodiments, R^3 and R^4 combine to form $-C(R^{13A})=C(R^{13B})-S-$, where R^{13A} is H, and R^{13B} is H or optionally substituted C_{1-3} alkyl. In particular embodiments, the S atom is proximal to C^6 of the compound of the invention. In some embodiments, R^{13} is optionally substituted C_{1-3} alkyl, e.g., R^{13B} is $-C(O)-R^{13C}$, where R^{13C} is optionally substituted C_{1-3} alkoxy or optionally substituted amino. In other embodiments, R^4 is C_{1-3} alkyl. In specific embodiments, R^4 is methyl, ethyl, or isopropyl. In certain embodiments, R^4 is C_{1-3} alkoxy (e.g., R^4 is methoxy). In other embodiments, R^4 is optionally substituted C_{1-6} thioalkoxy (e.g., R^4 is 4-amino-4-oxobutyl). In yet other embodiments, R^4 is optionally substituted amino (e.g., R^4 is methylamino). In still other embodiments, R^4 is halogen (e.g., R^4 is chloro). In particular embodiments, R^3 is hydrogen or C_{1-3} alkyl (e.g., R^3 is hydrogen, methyl, or ethyl). In further embodiments, R^3 and R^4 combine to form $-C(R^{13A})=C(R^{13B})-S-$ group, where R^{13A} is H, and R^{13B} is H or $-C(O)-R^{13C}$, where R^{13C} is optionally substituted C_{1-3} alkyl, optionally substituted C_{1-3} alkoxy, optionally substituted amino, or optionally substituted C_{2-9} heterocyclyl.

In some embodiments, R^3 and R^4 combine to form $-X^1-X^2-X^3-$, where

X^1 is $-S-$, $-O-$, $-(CR^{14}R^{15})-$, $-C(R^{16})=$, $-N(R^9)-$, $-N=$, H, or optionally substituted C_{1-3} alkyl;

X^2 is absent,$-(CR^{17}R^{18})_n-$, $-S-$, $-O-$, $-N=$, $-N(R^9)-$, $-C(R^{19})=$, $=N-$, $=C(R^{20})-$, or $=C(R^{21})-C(R^{22})=$;

X^3 is $-(CR^{14}R^{15})-$, $-S-$, $-O-$, $-N(R^9)-$, $=N-$, $=C(R^{23})-$, halogen, optionally substituted C_{1-3} alkyl, optionally substituted C_{1-6} thioalkoxy, optionally substituted C_{1-3} alkoxy, or optionally substituted C_{6-10} aryl;

each R^{14} and R^{15} is, independently, H or optionally substituted C_{1-3} alkyl, or R^{14} and R^{15} combine to form =O or =S;

each R^{17} and R^{18} is, independently, H or optionally substituted C_{1-3} alkyl, or R^{17} and R^{18} combine to form =O or =S;

each R^{16}, R^{19}, R^{20}, R^{21}, R^{22}, and R^{23} is, independently, H, or optionally substituted C_{1-3} alkyl; and

n is 1 or 2.

In some embodiments, when X^2 is not absent,

the chain of atoms $-X^1-X^2-X^3-$ includes no more than one heteroatom, the heteroatom being selected from nitrogen, oxygen, and sulfur.

In particular embodiments, X^1 is $-(CR^{14}R^{15})-$, $-C(R^{16})=$, $-N(R^9)-$, -N=, or optionally substituted C_{1-3} alkyl.

In certain embodiments, X^1 is $-(CR^{14}R^{15})-$. In particular embodiments, each R^{14} and R^{15} is H. In other embodiments, X^1 is $-C(R^{16})=$. In yet other embodiments, R^{16} is H. In still other embodiments, X^1 is $-N(R^9)-$. In some embodiments, R^9 is H or optionally substituted C_{1-3} alkyl. In certain embodiments, R^9 is hydrogen, methyl, or ethyl. In particular embodiments, X^1 is $-N=$. In other embodiments, X^1 is optionally substituted C_{1-3} alkyl. In yet other embodiments, X^2 is absent, $-(CH_2)_n-$, $-N(R^9)-$, $-C(H)=$, $=C(R^{20})-$, or $=C(H)-C(H)=$. In still other embodiments, X^2 is $-C(H)=$. In further embodiments, X^2 is $-N(R^9)-$. In some embodiments, R^9 is H. In certain embodiments, R^9 is optionally substituted C_{1-3} alkyl (e.g., R^9 is $-C(O)-N(H)-Et$). In particular embodiments, X^2 is $=C(R^{20})-$. In other embodiments, R^{20} is optionally substituted C_{1-3} alkyl. In yet other embodiments, X^2 is absent. In still other embodiments, X^3 is $-CH_2-$, $-S-$, $=C(H)-$, $-N(R^9)-$, halogen, optionally substituted C_{1-3} alkyl, optionally substituted C_{1-3} alkoxy, optionally substituted C_{1-6} thioalkoxy, optionally substituted C_{6-10} aryl. In certain embodiments, X^3 is $-CH_2-$. In particular embodiments, X^3 is $-S-$. In some embodiments, X^3 is $=C(H)-$. In other embodiments, X^3 is $-N(R^9)$-. In yet other embodiments, X^3 is halogen, optionally substituted C_{1-3} alkyl, optionally substituted C_{1-3} alkoxy, optionally substituted C_{1-6} thioalkoxy, or optionally substituted C_{6-10} aryl.

In certain embodiments, Z^1 and R^8 combine to form $-Z^3-Y^1-Y^2-$, where

Z^3 is $-O-$, $-N(R^{10})-$, $-N=$, $-S-$, or $-(CR^{11}R^{12})-$;

Y^1 is $-O-$, $-N(R^{10})-$, $-S-$, $-(CR^{26}R^{27})_m-$, $-C(R^{20})=$, $=C(R^{20})-$, $=C(R^{21})-C(R^{22})=$, optionally substituted C_{1-3} alkyl, optionally substituted C_{1-3} alkheterocyclyl, optionally substituted C_{1-3} alkcycloalkyl, or optionally substituted C_{1-3} alkaryl; and

Y^2 is $-O-$, $-S-$, $-N(R^{10})-$, $-(CR^{26}R^{27})-$, $=C(R^{20})-$, $=N-$, or H; where

each R^{20}, R^{21}, and R^{22} is, independently, H or optionally substituted C_{1-3} alkyl; and

each R^{26} and R^{27} is, independently, H or optionally substituted C_{1-3} alkyl, or R^{26} and R^{27} combine to form =O or =S;

m is 1 or 2; and

where, when Y^2 is H,

the chain of atoms $-Z^3-Y^1-Y^2-$ comprises no more than two heteroatoms, the heteroatom selected from nitrogen, oxygen, and sulfur.

In yet other embodiments, R^7 and R^8 form a group $-Y^1-Y^2-$, where:

Y^1 is $-(CR^{26}R^{27})_m-$, $-C(R^{20})=$, optionally substituted C_{1-3} alkyl, optionally substituted C_{1-3} alkheterocyclyl, optionally substituted C_{1-3} alkcycloalkyl, or optionally substituted C_{1-3} alkaryl; and

Y^2 is $-(CR^{26}R^{27})-$, $=C(R^{20})-$, or H; where

each R^{26} and R^{27} is, independently, H or optionally substituted C_{1-3} alkyl; and

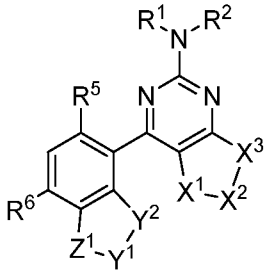
m is 1 or 2.

In particular embodiments, Z^3 is oxygen. In some embodiments, Y^1 is $-(CR^{26}R^{27})_m-$, $-C(R^{20})=$, optionally substituted C_{1-3} alkyl, optionally substituted C_{1-3} alkheterocyclyl, optionally substituted C_{1-3} alkcycloalkyl, or optionally substituted C_{1-3} alkaryl. In further embodiments, Y^1 is $-(CR^{26}R^{27})_m-$ or optionally substituted C_{1-3} alkyl. In other embodiments, Y^1 is $-(CR^{26}R^{27})_m-$. In other embodiments, Y^1 is optionally substituted C_{1-3} alkyl (e.g., Y^1 is methyl). In yet other embodiments, Y^1 is $-(CH_2)_k-N(R^{24})R^{25}$, where k is 2 or 3, and where each R^{24} and R^{25} is, independently, H or optionally substituted C_{1-3} alkyl. In still other

embodiments, k is 2. In further embodiments, each R^{24} and R^{25} is, independently, optionally substituted C_{1-3} alkyl (e.g., each R^{24} and R^{25} is methyl). In certain embodiments, Y^2 is $–(CR^{26}R^{27})–$ or H. In other embodiments, Y^2 is $–(CR^{26}R^{27})–$.

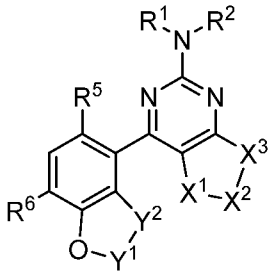
In some embodiments of any aspect, each R^1 and R^2 is H

In certain embodiments of formula (I) or (Ia), a compound of the invention has a structure according to formula (Va):



(Va), or a pharmaceutically acceptable salt thereof, where all substituents are as defined herein.

In particular embodiments of formula (I), (Ia), or (Ib), a compound of the invention has a structure according to formula (Vb):



(Vb), or a pharmaceutically acceptable salt thereof,

where

X^1 is –S–, –O–, $–(CR^{14}R^{15})–$, $–C(R^{16})=$, $–N(R^9)–$, –N=, –H, or optionally substituted C_{1-3} alkyl;

X^2 is absent,$–(CR^{17}R^{18})_n–$, –S–, –O–, –N=, $–N(R^9)–$, $–C(R^{19})=$, =N–, $=C(R^{20})–$, or $=C(R^{21})–C(R^{22})=$;

X^3 is $–(CR^{14}R^{15})–$, –S–, –O–, $–N(R^9)–$, =N–, $=C(R^{23})–$, halogen, optionally substituted C_{1-3} alkyl, optionally substituted C_{1-6} thioalkoxy, optionally substituted C_{1-3} alkoxy, or optionally substituted C_{6-10} aryl;

Y^1 is $–(CR^{26}R^{27})_m–$, $–C(R^{20})=$, $=C(R^{20})–$, $=C(R^{21})–C(R^{22})=$, optionally substituted C_{1-3} alkyl, optionally substituted C_{1-3} alkheterocyclyl, optionally substituted C_{1-3} alkcycloalkyl, or optionally substituted C_{1-3} alkaryl;

Y^2 is –O–, –S–, $–N(R^{10})–$, $–(CR^{26}R^{27})–$, $=C(R^{20})–$, =N–, or H;

each R^1 and R^2 is, independently, H or optionally substituted C_{1-3} alkyl;

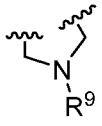
each R^5 and R^6 is, independently, optionally substituted C_{1-3} alkyl, optionally substituted C_{1-3} alkoxy, halogen, or CN;

each R^{14}, R^{15}, R^{16}, R^{17}, R^{17}, R^{18}, R^{20}, R^{19}, R^{20}, R^{21}, R^{22}, R^{23}, R^{26}, and R^{27} is, independently, H or optionally substituted C_{1-3} alkyl;

n is 1 or 2; and

m is 1 or 2.

In some embodiments, when R^5 is chloro, R^6 is bromo, and $–X^1–X^2–X^3–$ forms a group according to formula (IIa):



(IIa),

Y^1 is not methyl, ethyl, n-propyl, 2-(N-pyrazolyl)ethyl, 2-(N-imidazolyl)ethyl, 3-hydroxypropyl, cyanomethyl, 2-chloroethyl, 2-hydroxyethyl, 2-oxo-propyl, 2-(N,N-dimethylamino)-ethyl, difluoromethyl, or 2-(*t*-butylamino)ethyl.

In certain embodiments, when R^5 is chloro, R^6 is bromo, and $–X^1–X^2–X^3–$ forms a group according to formula (IIa),

Y^1 is not optionally substituted $C_{1\text{-}3}$ alkyl or optionally substituted C_2 alkheteroaryl.

In particular embodiments, when R^5 is chloro, R^6 is bromo, and $–X^1–X^2–X^3–$ forms a group according to formula (IIa),

Y^1 is not optionally substituted $C_{1\text{-}3}$ alkyl or optionally substituted C_2 alkheterocyclyl.

In still other embodiments, when R^5 is chloro, R^6 is bromo, and $–X^1–X^2–X^3–$ forms a group according to formula (IIa),

Y^2 is not H.

In yet other embodiments, when R^5 is chloro, R^6 is bromo, and $–X^1–X^2–X^3–$ forms a group according to formula (IIa),

each Y^1 and Y^2 is $–CH_2–$.

In some embodiments, when each R^5 and R^6 is bromo, and $–X^1–X^2–X^3–$ forms a group according to formula (IIa),

Y^1 is not methyl.

In particular embodiments, when each R^5 and R^6 is chloro, and $–X^1–X^2–X^3–$ forms a group according to formula (IIa),

Y^1 is not methyl, 2-(N-imidazolyl)ethyl, methoxymethyl, 2-(N-pyrazolyl)ethyl, 2-(3-methylpyrazol-1-yl)ethyl, 2-pyridyl-methyl, 1,3-dimethyl-1H-1,2,4-triazol-5-yl-methyl, 2-pyrimidinylmethyl, imidazol-2-yl-methyl, 5-methyl-isoxazol-3-yl-methyl, 4-methyl-imidazol-5-yl-methyl, or 3-methyl-1,2,4-oxadiazol-5-yl-methyl.

In other embodiments, when each R^5 and R^6 is chloro, and $–X^1–X^2–X^3–$ forms a group according to formula (IIa),

Y^1 is not unsubstituted alkyl, substituted alkyl, unsubstituted alkheteroaryl, or substituted alkheteroaryl.

In some embodiments, when each R^5 and R^6 is chloro, and $–X^1–X^2–X^3–$ forms a group according to formula (IIa),

Y^1 is not unsubstituted alkyl, substituted alkyl, unsubstituted alkheterocyclyl, or substituted alkheterocyclyl.

In certain embodiments, when each R^5 and R^6 is chloro, each Y^1 and Y^2 is $-CH_2-$, and $–X^1–X^2–X^3–$ forms a group according to formula (IIa),

R^9 is not ethoxycarbonyl, cyclobutylaminocarbonyl, or cyclobutadienylaminocarbonyl.

In other embodiments, when each R^5 and R^6 is chloro, R^7 and R^8 combine to form $-CH_2-CH_2-$, and $–X^1–X^2–X^3–$ forms a group according to formula (IIa),

R^9 is H or -C(O)-N(H)-(linear C_{1-3} alkyl).

In particular embodiments, when each R^5 and R^6 is halo, and $–X^1–X^2–X^3–$ forms a group according to formula (IIa),

and R^9 is H or -C(O)-N(H)-(linear C_{1-3} alkyl).

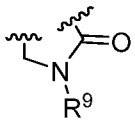
In some embodiments, when R^5 is methoxy, R^6 is methyl, and $–X^1–X^2–X^3–$ forms a group according to formula (IIa),

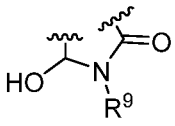
Y^1 is not methyl.

In certain embodiments, when R^5 is chloro, R^6 is ethyl, and $–X^1–X^2–X^3–$ forms a group according to formula (IIa),

Y^1 is not methyl.

In some embodiments, when each R^5 and R^6 is chloro, and $–X^1–X^2–X^3–$ forms a group according to formula (IIb) or (IIc),



(IIb) or


(IIc),

Y^1 is not methyl or 2-(N,N-diethylamino)ethyl.

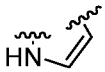
In other embodiments, when each R^5 and R^6 is chloro and $–X^1–X^2–X^3–$ forms a group according to formula (IIb) or (IIc),

Y^2 is not H.

In certain embodiments, when each R^5 and R^6 is chloro and $–X^1–X^2–X^3–$ forms a group according to formula (IIb) or (IIc),

each Y^1 and Y^2 is $-CH_2-$.

In some embodiments, when R^7 is methyl, R^5 is chloro, and $–X^1–X^2–X^3–$ forms a group according to formula (IIIa),


(IIIa),

R^6 is not bromo.

In particular embodiments, when each R^5 and R^6 is chloro, and $–X^1–X^2–X^3–$ forms a group according to formula (IIIa),

R^7 is not isopropyl, 3,3,3-trifluoropropyl, or 2-(N,N-dimethylamino)ethyl.

In some embodiments, when $–X^1–X^2–X^3–$ forms a group according to formula (IIIa),

each R^5 and R^6 is chloro, and

Y^1 is methyl and Y^2 is H, or

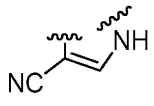
Y^1 is $–(CR^{26}R^{27})_m–$, $–C(R^{20})=$, $=C(R^{20})–$, or $=C(R^{21})–C(R^{22})=$, and Y^2 is –O–, –S–, $–N(R^{10})–$, $–(CR^{26}R^{27})–$, $=C(R^{20})–$, or =N–.

In some embodiments, when $–X^1–X^2–X^3–$ forms a group according to formula (IIIa),

each R^5 and R^6 is chloro, and

Y^2 is not H.

In other embodiments, when R^5 is chloro, R^6 is methoxy, and $–X^1–X^2–X^3–$ forms a group according to formula (IIIb):

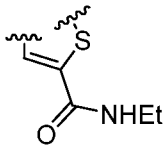

(IIIb),

neither R^1 nor R^2 is 2-(N,N-diethylamino)ethyl.

In certain embodiments, when R^5 is chloro, R^6 is methoxy, and $–X^1–X^2–X^3–$ forms a group according to formula (IIIb),

each R^1 and R^2 is H.

In some embodiments, when each R^5 and R^6 is chloro, and $–X^1–X^2–X^3–$ forms a group according to formula (IVa):


(IVa),

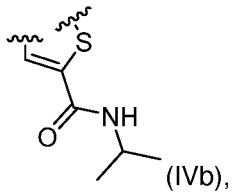
Y^1 is not 3-(N-morpholinyl)propyl, benzyl, 1-ethyl-pyrrolydin-3-yl, 1-methyl-piperidin-4-yl, 2-(1-methyl-pyrrolidin-2-yl)ethyl, or 3-(N,N-diethylamino)propyl.

In particular embodiments, when each R^5 and R^6 is chloro, and $–X^1–X^2–X^3–$ forms a group according to formula (IVa),

Y^1 is not heterocyclyl, alkheterocyclyl, or alkaryl.

In some embodiments, when each R^5 and R^6 is chloro, and $–X^1–X^2–X^3–$ forms a group according to

formula (IVb):



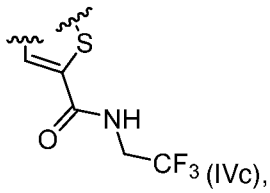
(IVb),

Y^1 is not 2-methoxyethyl or benzyl.

In certain embodiments, when each R^5 and R^6 is chloro, and $–X^1–X^2–X^3–$ forms a group according to formula (IVb),

Y^1 is not substituted alkyl or alkaryl.

In some embodiments, when each R^5 and R^6 is chloro, and $–X^1–X^2–X^3–$ forms a group according to formula (IVc):



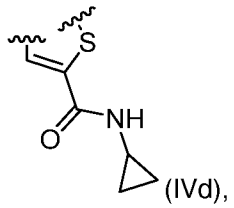
(IVc),

Y^1 is not 2-(N,N-diethylamino)ethyl or 3-(N,N-dimethylamino)propyl.

In other embodiments, when each R^5 and R^6 is chloro, and $–X^1–X^2–X^3–$ forms a group according to formula (IVc),

Y^1 is not substituted alkyl.

In particular embodiments, when each R^5 and R^6 is chloro, and $–X^1–X^2–X^3–$ forms a group according to formula (IVd):



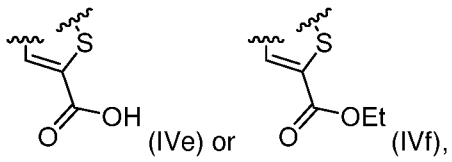
(IVd),

Y^1 is not 2-(pyrrolidin-1-yl)ethyl or 2-hydroxyethyl.

In certain embodiments, when each R^5 and R^6 is chloro, and R^3 and R^4 combine to form a group according to formula (IVd),

Y^1 is not substituted alkyl or alkheterocyclyl.

In some embodiments, when each R^5 and R^6 is chloro, and $–X^1–X^2–X^3–$ forms a group according to formula (IVe) or (IVf):



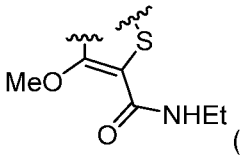
(IVe) or (IVf),

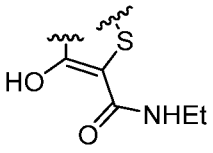
Y^1 is not benzyl.

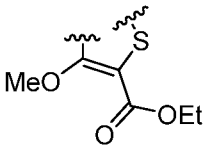
In other embodiments, when each R^5 and R^6 is chloro, and $–X^1–X^2–X^3–$ forms a group according to formula (IVe) or (IVf),

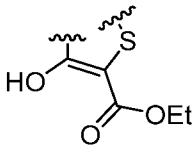
Y^1 is not alkaryl or substituted alkyl.

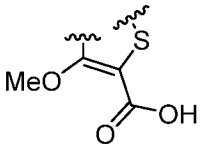
In certain embodiments, when R^5 is chloro, R^6 is bromo, and $–X^1–X^2–X^3–$ forms a group according to formula (IVg), (IVh), (IVi), (IVj), or (IVk):



(IVg),


(IVh),


(IVi),


(IVj), or


(IVk),

Y^1 is not methyl.

In some embodiments, when R^5 is chloro, R^6 is bromo, $–X^1–X^2–X^3–$ forms a group according to formula (IVg), (IVh), (IVi), (IVj), or (IVk),

Y^2 is not H.

In particular embodiments, when R^5 is chloro, R^6 is bromo,

R^3 and R^4 do not combine to form a group according to formula (IVg), (IVh), (IVi), (IVj), or (IVk).

In particular embodiments, when R^6 is methoxy,

each R^1 and R^2 is H.

In certain embodiments, when X^1 is H, and each R^5 and R^6 is chloro,

Y^1 is not methyl.

In some embodiments, R^{10} is H, optionally substituted C_{1-3} alkyl, optionally substituted C_{3-8} cycloalkyl, optionally substituted C_{1-3} alkcycloalkyl, optionally substituted C_{1-3} alkheterocyclyl, or optionally substituted C_{1-3} alkaryl. In other embodiments, R^{10} is H, optionally substituted C_{1-3} alkyl, optionally substituted C_{1-3} alkcycloalkyl, optionally substituted C_{1-3} alkheterocyclyl, or optionally substituted C_{1-3} alkaryl.

In particular embodiments, when X^1 is $–(CR^{14}R^{15})–$, X^2 is $–N(R^9)–$, X^3 is $–(CR^{14}R^{15})–$, and each of R^{14} and R^{15} is H, R^9 is H or –C(O)–N(H)–Et, and each of Y^1 and Y^2 is $–CH_2–$. In other embodiments, when X^1 is $–(CR^{14}R^{15})–$, X^2 is $–N(R^9)–$, and X^3 is $–(CR^{14}R^{15})–$, R^9 is H or –C(O)–N(H)–Et, and each of Y^1 and Y^2 is $–CH_2–$. In some embodiments, when X^1 is $–N(R^9)–$, X^2 is $–C(R^{19})=$, X^3 is $=C(R^{23})–$, and each of R^{17}, R^{19}, and R^{23} is H, Y^1 is $–(CR^{26}R^{27})_m–$, and Y^2 is $–(CR^{26}R^{27})–$. In other embodiments, when X^1 is $–N(R^9)–$, X^2

is -C(R^{19})=, X^3 is =C(R^{23})–, and each of R^9, R^{19}, and R^{23} is H, each of Y^1 and Y^2 is –CH_2–. In some embodiments, when X^1 is –N(R^9)–, X^2 is –C(R^{19})=, X^3 is =C(R^{23})–, and each of R^{19} and R^{23} is H, Y^1 is –($CR^{26}R^{27}$)$_m$–, and Y^2 is –($CR^{26}R^{27}$)–. In certain embodiments, when X^1 is –N(R^9)–, X^2 is –C(R^{19})=, X^3 is =C(R^{23})–, Y^2 is H, and each of R^5 and R^6 is –Cl, Y^1 is Me. In particular embodiments, when X^1 is –C(R^{16})=, X^2 is =C(R^{20})–, and X^3 is –S–, R^{16} is H. In some embodiments, when X^1 is –C(R^{16})=, X^2 is =C(R^{20})–, and X^3 is –S–, Y^1 is –($CR^{26}R^{27}$)$_m$–, and Y^2 is –($CR^{26}R^{27}$)–. In certain embodiments, when X^1 is –C(R^{16})=, X^2 is =C(R^{20})–, and X^3 is –S–, each of Y^1 and Y^2 is –CH_2–. In some embodiments, when X^1 is –C(R^{16})=, X^2 is =C(R^{20})–, and X^3 is –S–, each of R^5 and R^6 is –Cl. In certain embodiments, when X^1 is H, and each of R^5 and R^6 is Cl, Y^1 is –($CR^{26}R^{27}$)$_m$–, and Y^2 is –($CR^{26}R^{27}$)–. In particular embodiments, when X^1 is H, and each of R^5 and R^6 is hal, Y^1 is –($CR^{26}R^{27}$)$_m$–, and Y^2 is –($CR^{26}R^{27}$)– (e.g., each of Y^1 and Y^2 is –CH_2–). In particular embodiments, when X^1 is H, Y^1 is –($CR^{26}R^{27}$)$_m$–, and Y^2 is –($CR^{26}R^{27}$)– (e.g., each of Y^1 and Y^2 is –CH_2–).

In particular embodiments, X^1 is –($CR^{14}R^{15}$)–, –C(R^{16})=, –N(R^9)–, or optionally substituted C_{1-3} alkyl (e.g.,–CH_2–, –C(H)=, –N=, optionally substituted C_{1-3} alkyl, or–N(R^9)– (e.g., R^{17} is H or optionally substituted C_{1-3} alkyl (e.g.,R^9 is H, –Me, or –Et).

In some embodiments, X^2 is absent, –(CH_2)$_n$–, –N(R^9)–, –C(H)=, =C(R^{20})–, or =C(H)–C(H)=. In certain embodiments, X^2 is absent, –C(H)=, –N(R^9)– (e.g., R^9 is H or optionally substituted C_{1-3} alkyl (e.g., R^9 is C_{1-3} haloalkyl, e.g., C_{1-3} fluoroalkyl), or R^9 is -C(O)–N(H)–Et), or =C(R^{20})–, where R^{20} is, e.g., optionally substituted C_{1-3} alkyl.

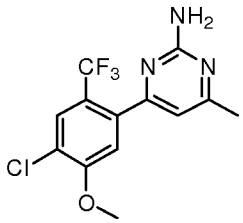
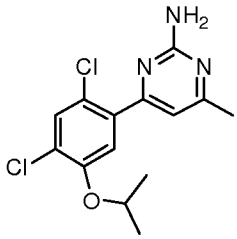
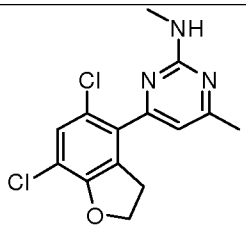
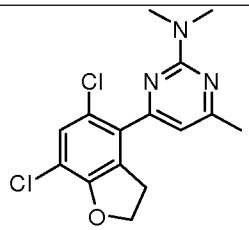
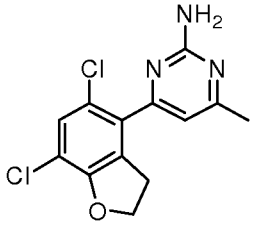
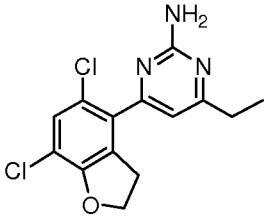
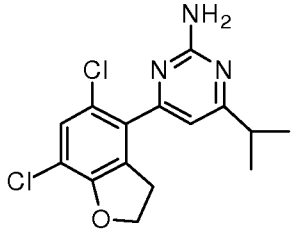
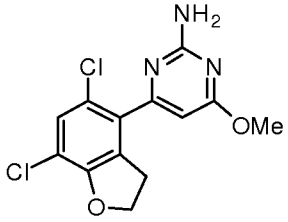
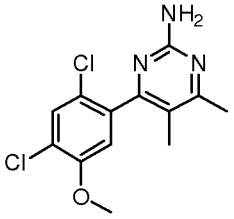
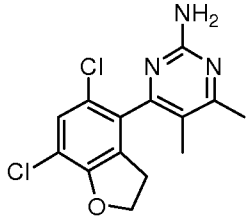
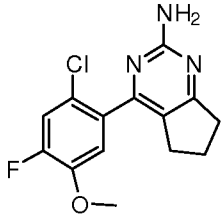
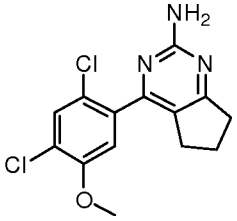
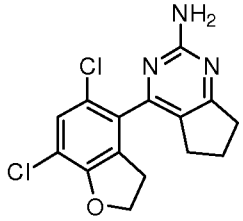
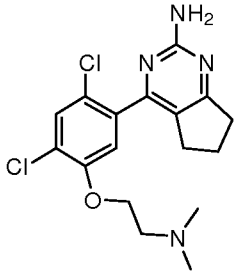
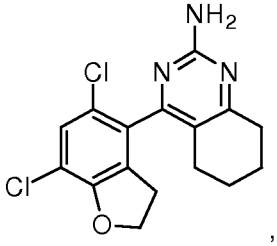
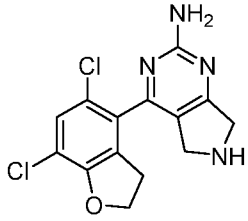
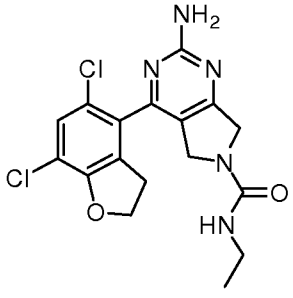
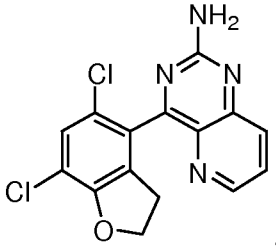
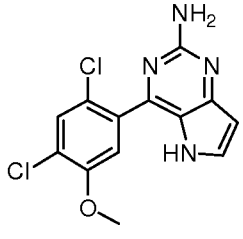
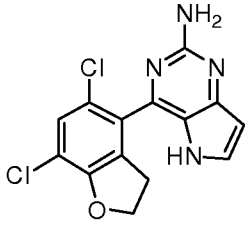
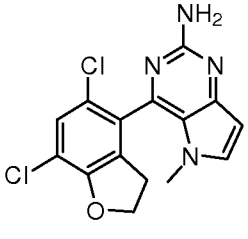
In certain embodiments, X^3 is –CH_2–, –S–, =C(H)–, or optionally substituted C_{1-3} alkyl.

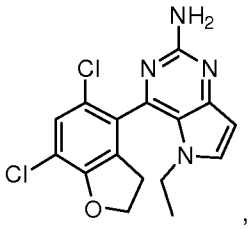
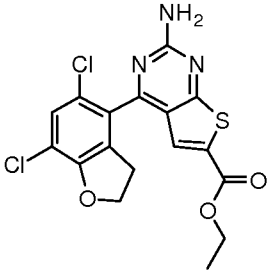
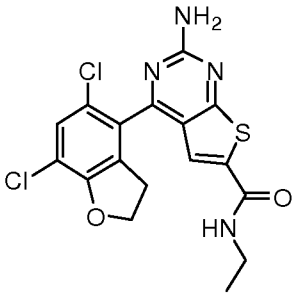
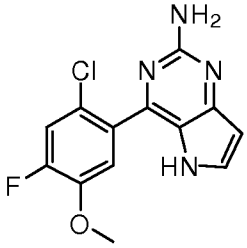
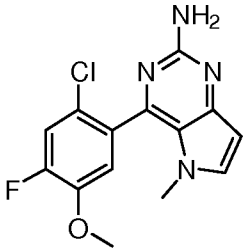
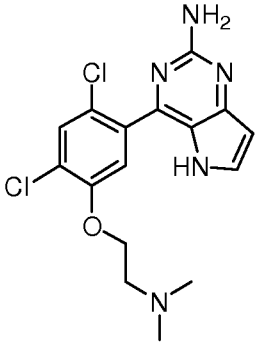
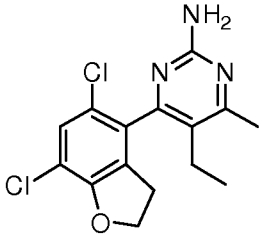
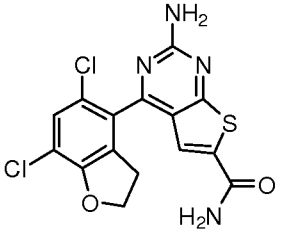
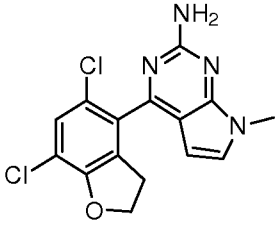
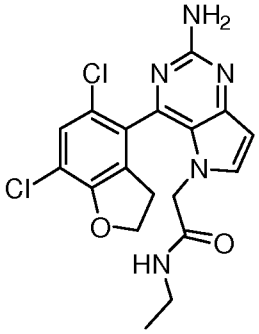
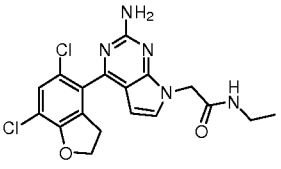
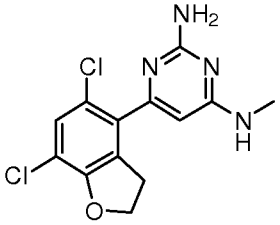
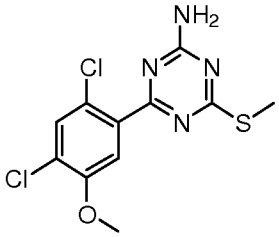
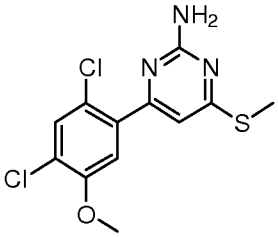
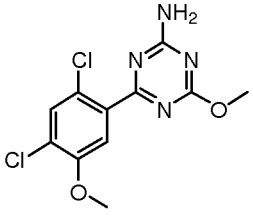
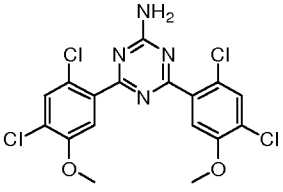
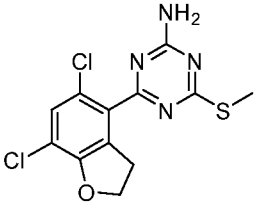
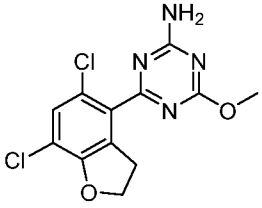
In some embodiments, each of R^5 and R^6 is, independently, halo, or optionally substituted C_{1-3} alkyl, e.g., each of R^5 and R^6 is halo (e.g., each of R^5 and R^6 is –Cl).

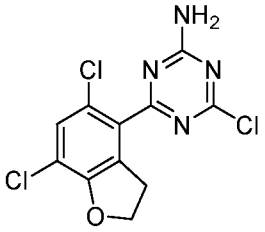
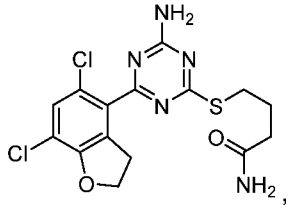
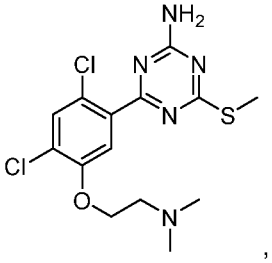
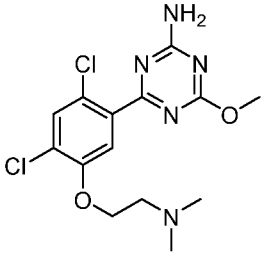
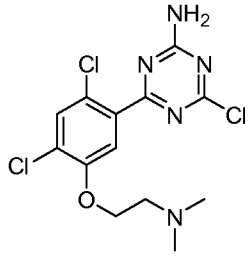
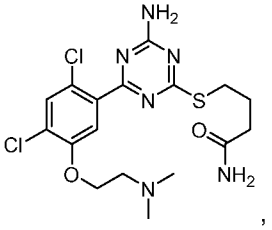
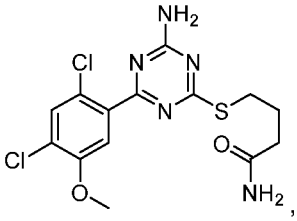
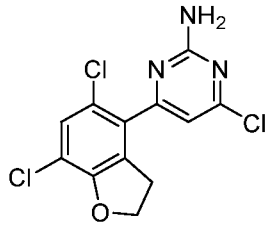
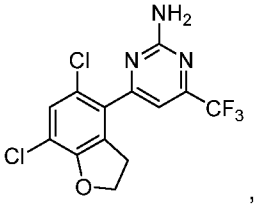
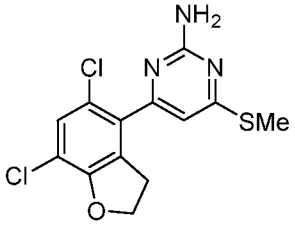
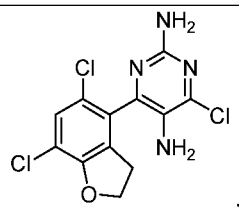
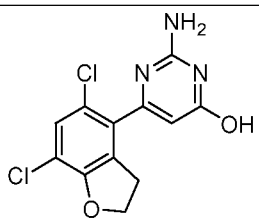
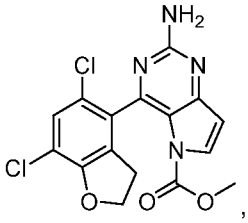
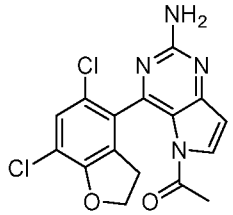
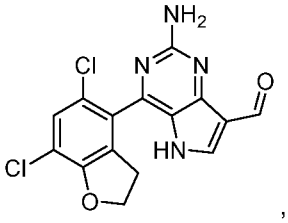
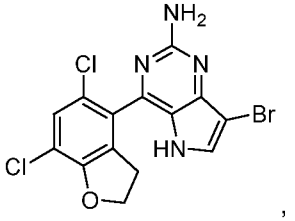
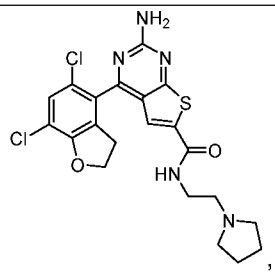
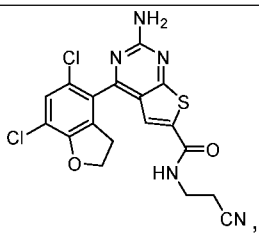
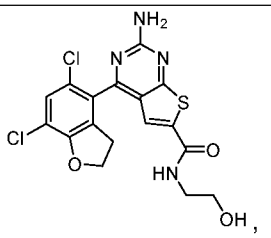
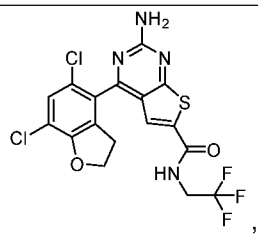
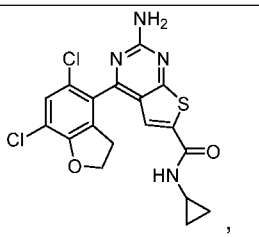
In some embodiments, R^{26} is H. In other embodiments, R^{27} is H. In certain embodiments, n is 1. In other embodiments, m is 1. In particular embodiments, Y^1 is optionally substituted C_{1-3} alkyl. In other embodiments, Y^1 is unsubstituted C_{1-3} alkyl, C_{1-3} alkylamino-C_{1-3}-alkyl (e.g., C_{1-3} haloalkylamino-C_{1-3}-alkyl, e.g., C_{1-3} fluoroalkylamino-C_{1-3}-alkyl), di-(C_{1-3} alkyl)amino-C_{1-3}-alkyl (e.g., $R^{Y1}N(R^{Y2})$-(C_{1-3} alkyl)-, where each of R^{Y1} and R^{Y2} is, independently, unsubstituted C_{1-3} alkyl, or C_{1-3} haloalkylamino-C_{1-3}-alkyl, e.g., C_{1-3} fluoroalkylamino-C_{1-3}-alkyl), or C_{1-3} haloalkyl (e.g., C_{1-3} fluoroalkyl). In particular embodiments, Y^1 is unsubstituted C_{1-3} alkyl, C_{1-3} alkylamino-C_{1-3}-alkyl (e.g., C_{1-3} haloalkylamino-C_{1-3}-alkyl, e.g., C_{1-3} fluoroalkylamino-C_{1-3}-alkyl), or di-(C_{1-3} alkyl)amino-C_{1-3}-alkyl (e.g., $R^{Y1}N(R^{Y2})$-(C_{1-3} alkyl)-, where each of R^{Y1} and R^{Y2} is, independently, unsubstituted C_{1-3} alkyl, or C_{1-3} haloalkylamino-C_{1-3}-alkyl, e.g., C_{1-3} fluoroalkylamino-C_{1-3}-alkyl).

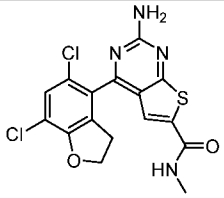
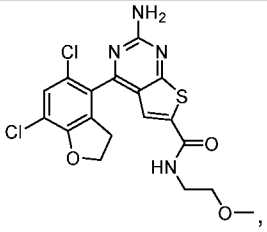
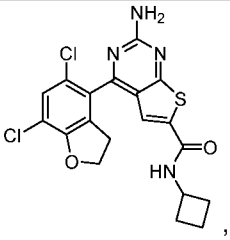
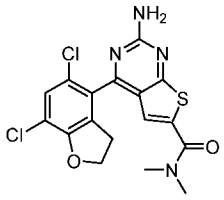
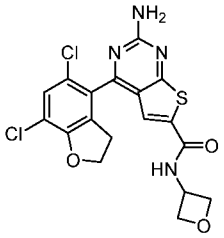
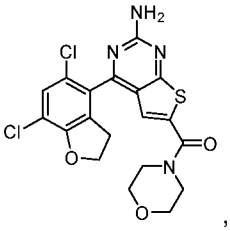
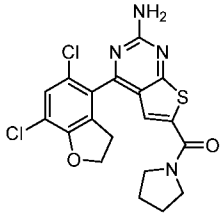
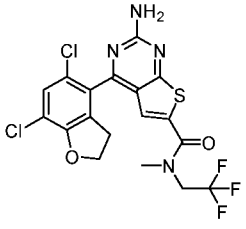
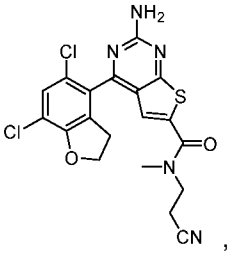
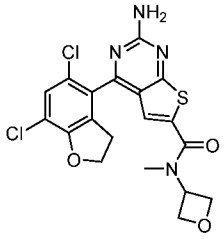
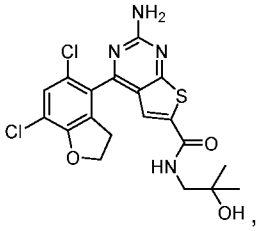
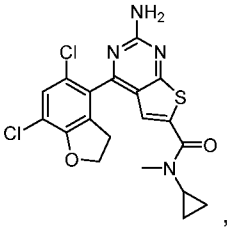
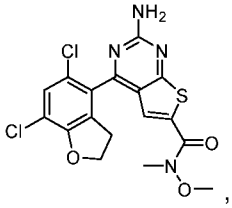
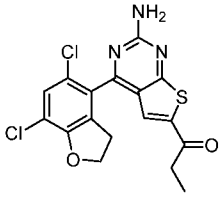
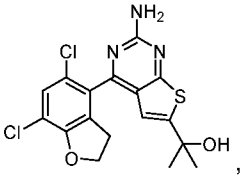
In certain embodiments, a compound of the invention has the formula as shown in Table 1:

Table 1.

1		**2**		**3**	
4		**5**		**6**	
7		**8**		**9**	
10		**11**		**12**	
13		**14**		**15**	
16		**17**		**18**	
19		**20**		**21**	

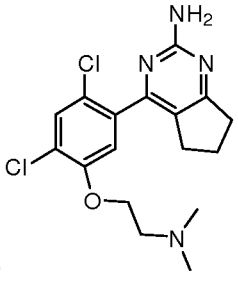
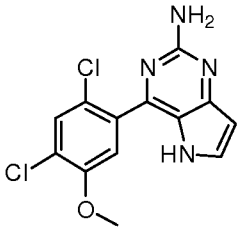
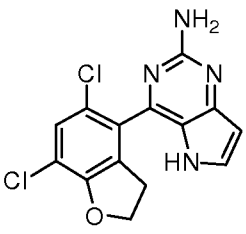
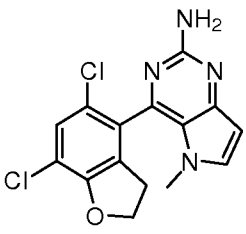
22	 ,	**23**	 ,	**24**	 ,
25	 ,	**26**	 ,	**27**	 ,
28	 ,	**29**	 ,	**30**	 ,
31	 ,	**32**	 ,	**33**	 ,
34	 ,	**35**	 ,	**36**	 ,
37	 ,	**40**	 ,	**41**	 ,

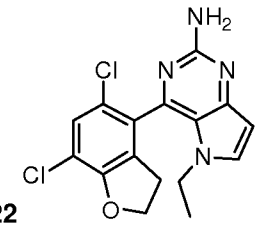
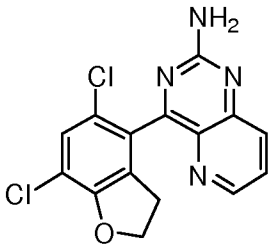
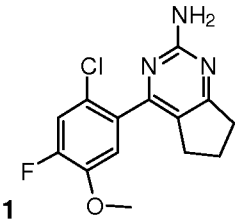
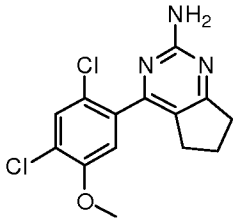
42		43		44	
45		46		47	
48		49		50	
51		52		53	
54		55		56	
57		58		59	
60		61		62	

63		**64**		**65**	
66		**67**		**68**	
69		**70**		**71**	
72		**73**		**74**	
75		**76**		**77**	

or a pharmaceutically acceptable salt thereof.

In particular embodiments, a compound of the invention has the formula:

14  , **19**  , **20**  , **21**  ,


22, 
18, 
11, 
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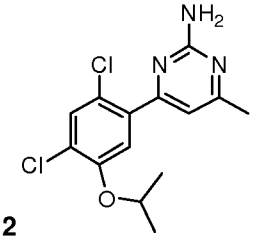
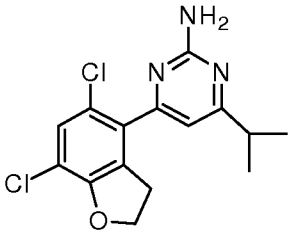
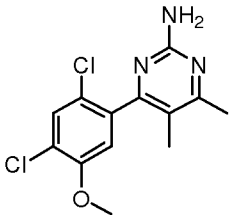
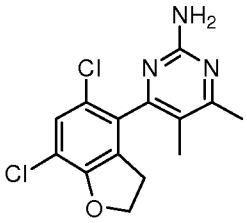

2, 
7, 
9, 
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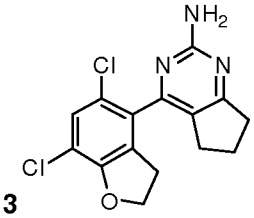
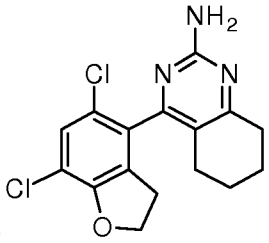
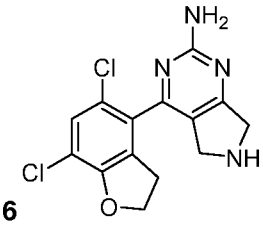
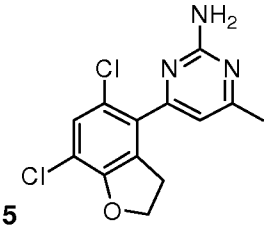

13, 
15, 
16, 
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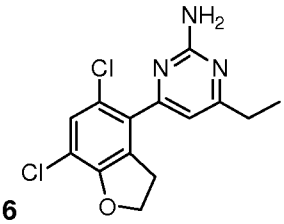
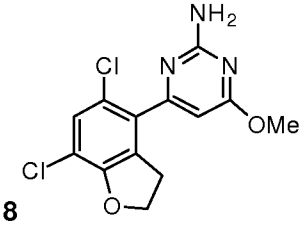
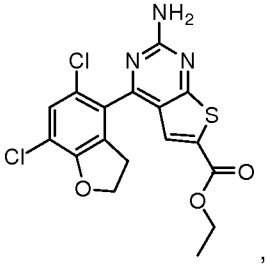

6, 
8, 
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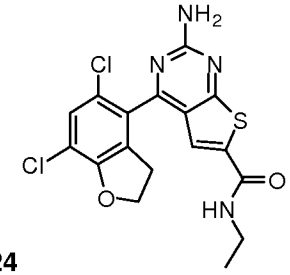
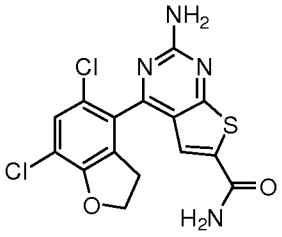
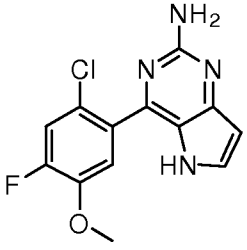

24, 
29, 
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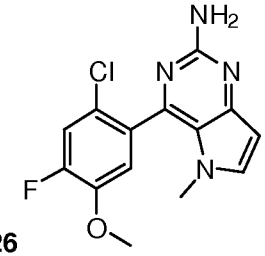
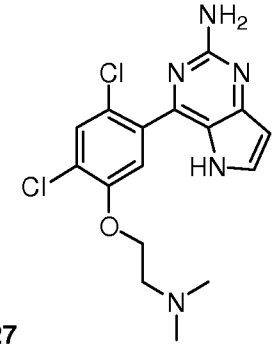
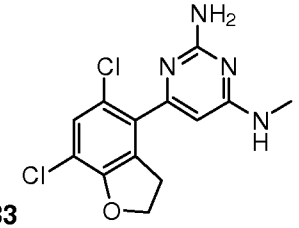

26, 
27, 
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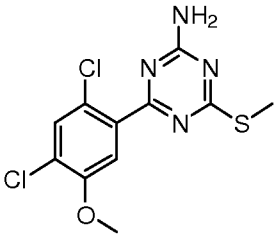
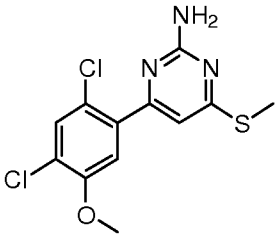
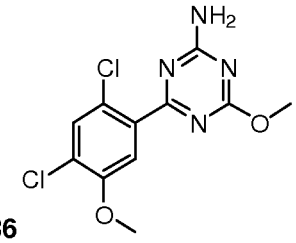

34, 
35, 
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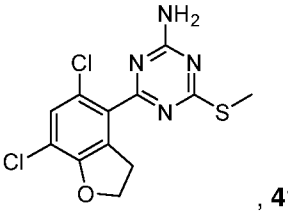
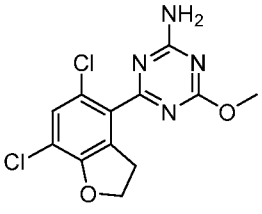
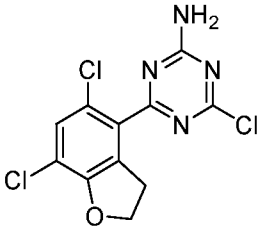

40, 
41, 
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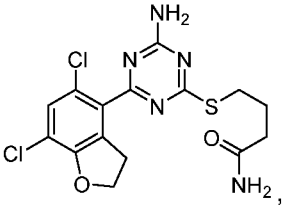
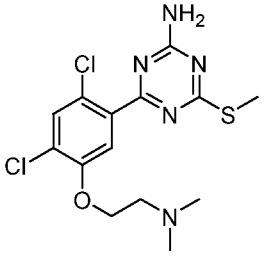
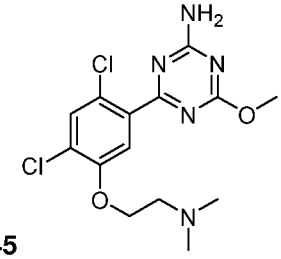

43, 
44, 
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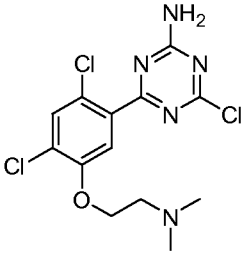
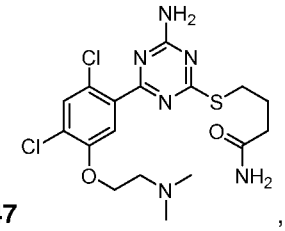
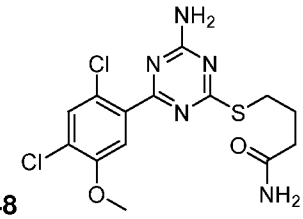
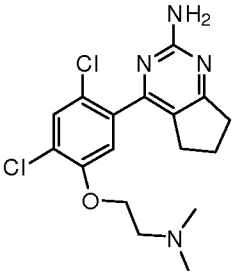
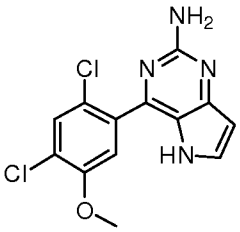
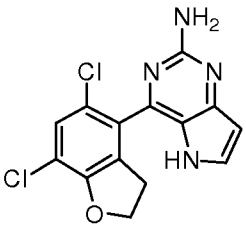
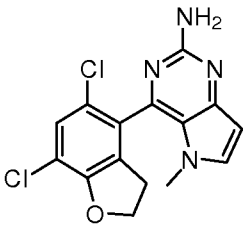

46, 
47, or 
48, or a pharmaceutically acceptable salt thereof.

In some embodiments, a compound of the invention has the formula:


14, 
19, 
20, 
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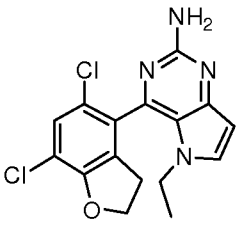
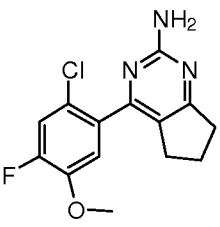
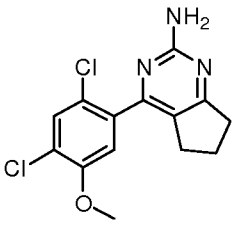

22, 
11, 
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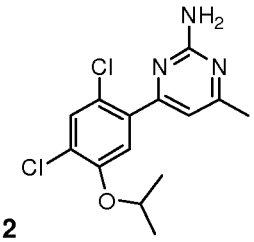
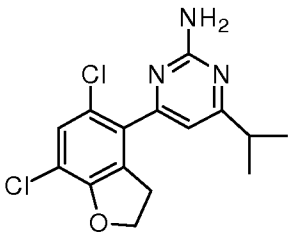
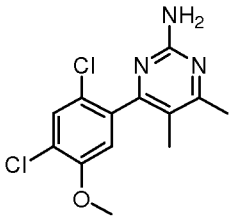
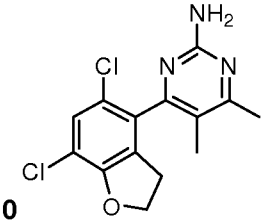

2, 
7, 
9, 
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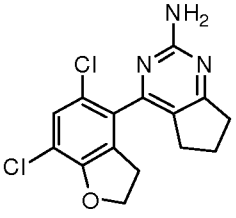
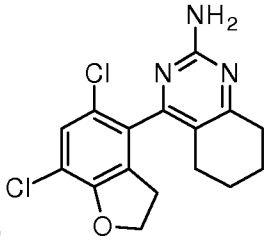
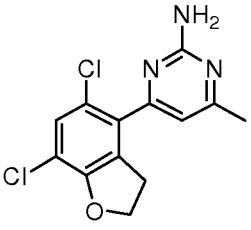
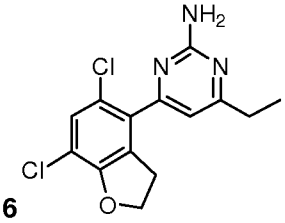

13, 
15, 
5, 
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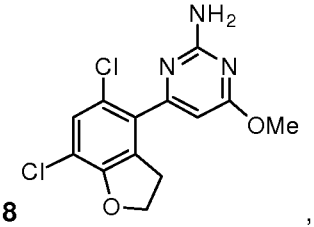
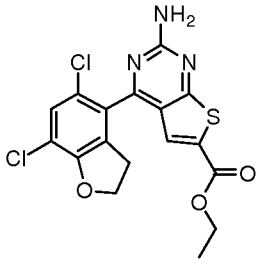
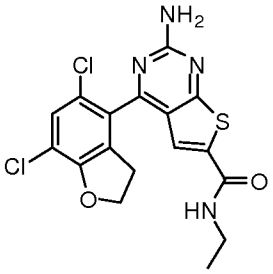

8, 
23, 
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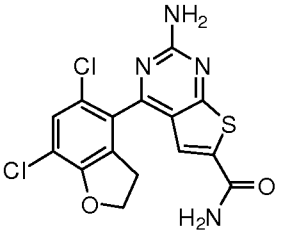
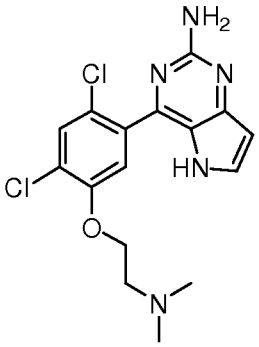
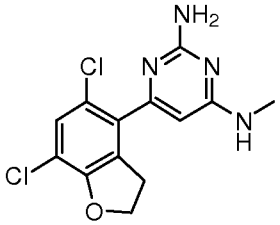

29, 
27, 
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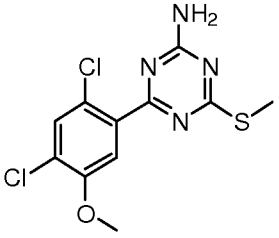
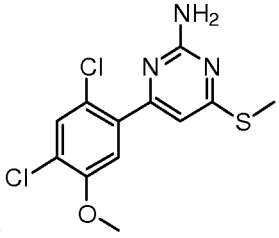
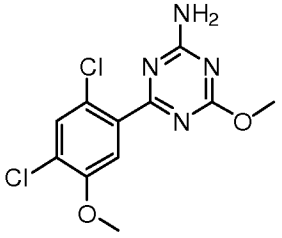

34, 
35, or 
36,

or a pharmaceutically acceptable salt thereof.

In further embodiments, the compound is not compound **38** or compound **39**.

In certain embodiments of any formula described herein, each of R^1 and R^2 is H, R^5 is Cl, and R^6 is F or Cl.

In other embodiments of formula (I), (Ia), or (Ib), R^3 is H, halogen, optionally substituted C_{1-3} alkyl, or optionally substituted C_{1-3} alkoxy, and R^4 is halogen, optionally substituted C_{1-3} alkyl, optionally substituted C_{1-3} alkoxy, optionally substituted amino, or optionally substituted C_{1-6} thioalkoxy, or R^3 and

R^4, together with the atoms to which each is attached, join to form an optionally substituted five- or six-membered ring optionally comprising one nitrogen, one oxygen, or one sulfur, where the nitrogen is optionally substituted with R^9.

In yet other embodiments of formula (I), (Ia), or (Ib), R^3 is H, optionally substituted C_1 alkyl, or optionally substituted C_{1-3} alkoxy, and R^4 is halogen, optionally substituted C_{1-3} alkyl, optionally substituted C_{1-3} alkoxy, optionally substituted amino, or optionally substituted C_{1-6} thioalkoxy, or R^3 and R^4, together with the atoms to which each is attached, join to form an optionally substituted five- or six-membered ring optionally comprising one nitrogen, one oxygen, or one sulfur, where the nitrogen is optionally substituted with R^9.

In still other embodiments of formula (I), (Ia), or (Ib), R^3 is H, optionally substituted C_1 alkyl, or optionally substituted C_{1-3} alkoxy, and R^4 is halogen, optionally substituted C_{1-3} alkyl, optionally substituted C_{1-3} alkoxy, optionally substituted amino, or optionally substituted C_{1-6} thioalkoxy, or R^3 and R^4 join to form one of the following groups:

$–N(R^9)–CH=CH–$, $–CH_2CH_2CH_2–$, $–CH_2CH_2CH_2CH_2–$, and $–C(R^{13A})=C(R^{13B})–S–$,

where N is proximal to position 5, and R^9 is H or C_{1-3} alkyl.

In certain embodimentsof formula (I), Z^2 is N, and R^4 is halogen, optionally substituted C_{1-3} alkyl, optionally substituted C_{1-3} alkoxy, optionally substituted amino, or optionally substituted C_{1-6} thioalkoxy.

In particular embodiments of formula (I), Z^2 is N, and R^4 is optionally substituted C_{1-3} alkoxy or optionally substituted C_{1-6} thioalkoxy.

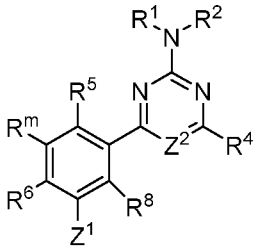
In other embodiments, X^1 is $–N(R^9)–$, $–(CR^{14}R^{15})–$, $–C(R^{16})=$, H, or optionally substituted C_1 alkyl. In yet other embodiments, X^2 is absent,$–(CR^{17}R^{18})_n–$, $–C(R^{19})=$, or $=C(R^{20})–$. In still other embodiments, X^3 is $–(CR^{14}R^{15})–$, –S–, $=C(R^{23})–$, halogen, optionally substituted C_{1-3} alkyl, optionally substituted C_{1-6} thioalkoxy, or optionally substituted C_{1-3} alkoxy. In certain embodiments, R^9 is H or C_{1-3} alkyl.

In some embodiments, the compound of the invention has a molecular weight of less than about 500 g/mol (e.g., less than about 450 g/mol, or less than about 400 g/mol). In other embodiments, the compound of the invention exhibits apical to basal (A→B) permeability in MDR1-MDCK assay of greater than about 1×10^{-7} cm/sec (e.g., greater than about 5×10^{-7} cm/sec, greater than about 1×10^{-6} cm/sec, or greater than about 3×10^{-6} cm/sec). In particular embodiments, the compound of the invention exhibits the (B→A)/(A→B) ratio of less than about 30 (e.g., less than about 10, less than about 5, or less than about 3).

In another aspect, the invention features a pharmaceutical composition comprising a compound of the invention, or a pharmaceutically acceptable salt thereof, and one or more of pharmaceutically acceptable carriers or excipients. In certain embodiments, the composition is formulated for administration orally, intradermally, intramuscularly, parenterally, intravenously, intra-arterially, intracranially, subcutaneously, intraorbitally, intraventricularly, intraspinally, intraperitoneally, or intranasally. Preferably, the composition

is formulated for oral administration.

In yet another aspect, the invention features a method of treating a disorder in a mammal (e.g., a human) caused by the action of heat shock protein 90 (Hsp90). The method involves administering to the mammal an effective amount of a compound according to formula (I):



(I), or a pharmaceutically acceptable salt thereof,

where

Z^1 is -OR^7, -$N(R^{10})R^7$, -SR^7, or –$C(R^{10})(R^{11})R^7$;

Z^2 is –N= or –$C(R^3)$=;

each R^1 and R^2 is, independently, H or optionally substituted C_{1-3} alkyl;

R^3 is H, halogen, cyano, optionally substituted C_{1-6} alkyl, optionally substituted C_{1-3} alkoxy, or optionally substituted amino, and R^4 is halogen, cyano, optionally substituted C_{1-6} alkyl, optionally substituted C_{1-3} alkoxy, optionally substituted amino, optionally substituted C_{1-6} thioalkoxy, or optionally substituted C_{6-10} aryl, or R^3 and R^4, together with the atoms to which each is attached, join to form an optionally substituted five- or six-membered ring optionally comprising one nitrogen, one oxygen, or one sulfur, where the nitrogen is optionally substituted with R^9;

each R^5 and R^6 is, independently, optionally substituted C_{1-3} alkyl, optionally substituted C_{1-3} alkoxy, halogen, or CN;

R^7 is optionally substituted C_{1-3} alkyl, optionally substituted C_{1-3} alkcycloalkyl, optionally substituted C_{1-3} alkheterocyclyl, or optionally substituted C_{1-3} alkaryl, and R^8 is H; or R^7 and R^8, together with the atoms to which each is attached, join to form an optionally substituted five- or six-membered ring optionally comprising one or two heteroatoms selected from nitrogen, oxygen, and sulfur;

R^9 is H, optionally substituted C_{1-3} alkyl, optionally substituted C_{3-8} cycloalkyl, optionally substituted C_{6-10} aryl, optionally substituted C_{2-9} heteroaryl, optionally substituted C_{2-9} heterocyclyl, optionally substituted C_{1-3} alkcycloalkyl, optionally substituted C_{1-3} alkheterocyclyl, or optionally substituted C_{1-3} alkaryl;

R^{10} is H, optionally substituted C_{1-3} alkyl, optionally substituted C_{3-8} cycloalkyl, optionally substituted C_{6-10} aryl, optionally substituted C_{2-9} heteroaryl, optionally substituted C_{2-9} heterocyclyl, optionally substituted C_{1-3} alkcycloalkyl, optionally substituted C_{1-3} alkheterocyclyl, or optionally substituted C_{1-3} alkaryl, and R^{11} is H, optionally substituted C_{1-3} alkyl, or R^{10} and R^{11} combine to form =O or =S and

R^m is H, halogen, optionally substituted C_{1-4} alkyl, or optionally substituted C_{1-3} alkoxy;.

In certain embodiments of formula (I), when Z^2 is CR^3,each of R^1 and R^2 is H, R^3 is H, R^4 is methyl or halogen (e.g., chloro), and each of R^5 and R^6 is halogen (e.g., chloro),

Z^1 is not methoxy.

In certain embodiments of formula (I), when Z^2 is CR^3, R^3 is H, R^4 is methyl or halogen (e.g., chloro), each of R^5 and R^6 is halogen (e.g., chloro),

Z^2 is not unsubstituted C_{1-3} alkoxy.

In particular embodiments of formula (I), when Z^2 is N, R^3 is H, R^4 is optionally substituted C_{1-6} thioalkoxy, and each of R^5 and R^6 is halogen (e.g., chloro),

Z^1 is not cyanomethoxy or aminomethoxy.

In other embodiments of formula (I), when Z^2 is N, R^3 is H, each of R^5 and R^6 is halogen (e.g., chloro), R^4 is substituted C_{1-6} thioalkoxy,

Z^1 is not cyanomethoxy or aminomethoxy.

In some embodiments of formula (I), when Z^2 is N, R^3 is H, R^4 is optionally substituted C_{1-6} thioalkoxy,

Z^1 is not cyanomethoxy or aminomethoxy.

In certain embodiments of formula (I), when Z^2 is N, R^3 is H, R^4 is substituted C_{1-6} thioalkoxy,

Z^1 is not cyanomethoxy or aminomethoxy.

In further embodiments of formula (I), when Z^2 is N, R^3 is H, R^4 is substituted C_{1-6} thioalkoxy,

Z^1 is not substituted C_1 alkoxy.

In particular embodiments of formula (I), when Z^2 is N, R^3 is H, R^4 is substituted C_{1-6} thioalkoxy,

Z^1 is $-OR^7$, $-N(R^7)R^{10}$, $-SR^7$, or $-C(R^7)(R^{10})R^{11}$, in which R^7 is methyl, dialkylaminoethyl, optionally substituted C_{1-3} alkcycloalkyl, optionally substituted C_{1-3} alkheterocyclyl, or optionally substituted C_{1-3} alkaryl, or R^7 and R^8, together with the atoms to which each is attached, join to form an optionally substituted five- or six-membered ring optionally comprising one or two heteroatoms selected from nitrogen, oxygen, and sulfur.

In other embodiments of formula (I), when Z^2 is CR^3, each of R^5 and R^6 is chloro, R^3 is H, and R^4 is halogen (e.g., chloro),

Z^1 is not 2-amino-2oxoethoxy, 2-(N,N-diethylamino)ethoxy, methoxy, or benzyloxy.

In yet other embodiments of formula (I), when Z^2 is CR^3, R^3 is H, and R^4 is halogen (e.g., chloro),

Z^1 is not 2-amino-2oxoethoxy, 2-(N,N-diethylamino)ethoxy, methoxy, or benzyloxy.

In still other embodiments of formula (I), when Z^2 is CR^3, each of R^5 and R^6 is chloro, R^3 is H, and R^4 is halogen (e.g., chloro),

Z^1 is $-OR^7$, $-N(R^7)R^{10}$, $-SR^7$, or $-C(R^7)(R^{10})R^{11}$, in which R^7 is dimethylaminoethyl, optionally substituted C_{1-3} alkcycloalkyl, or optionally substituted C_{1-3} alkheterocyclyl, or R^7 and R^8, together with the atoms to which each is attached, join to form an optionally substituted five- or six-membered ring optionally comprising one or two heteroatoms selected from nitrogen, oxygen, and sulfur.

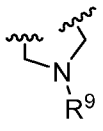
In further embodiments of formula (I), when Z^2 is CR^3, each of R^5 and R^6 is chloro, R^3 is H, and R^4 is halogen (e.g., chloro),

Z^1 is $-OR^7$, $-N(R^7)R^{10}$, $-SR^7$, or $-C(R^7)(R^{10})R^{11}$, in which R^7 is optionally substituted C_{1-3} alkcycloalkyl, or optionally substituted C_{1-3} alkheterocyclyl, or R^7 and R^8, together with the atoms to which each is attached, join to form an optionally substituted five- or six-membered ring optionally comprising one or two heteroatoms selected from nitrogen, oxygen, and sulfur.

In particular embodiments of formula (I), when Z^2 is CR^3, R^3 is H, and R^4 is halogen (e.g., chloro),

Z^1 is $-OR^7$, $-N(R^7)R^{10}$, $-SR^7$, or $-C(R^7)(R^{10})R^{11}$, in which R^7 is optionally substituted C_{1-3} alkcycloalkyl, or optionally substituted C_{1-3} alkheterocyclyl, or R^7 and R^8, together with the atoms to which each is attached, join to form an optionally substituted five- or six-membered ring optionally comprising one or two heteroatoms selected from nitrogen, oxygen, and sulfur.

In some embodiments of formula (I), when R^5 is chloro, R^6 is bromo, Z^1 is $-OR^7$, Z^2 is CR^3, and R^3 and R^4 combine to form a group according to formula (IIa):



(IIa),

R^7 is not methyl, ethyl, n-propyl, 2-(N-pyrazolyl)ethyl, 2-(N-imidazolyl)ethyl, 3-hydroxypropyl, cyanomethyl, 2-chloroethyl, 2-hydroxyethyl, 2-oxo-propyl, 2-(N,N-dimethylamino)ethyl, difluoromethyl, or 2-(*t*-butylamino)ethyl.

In certain embodiments of formula (I), when R^5 is chloro, R^6 is bromo, Z^1 is $-OR^7$, Z^2 is CR^3, and R^3 and R^4 combine to form a group according to formula (IIa),

R^7 is not substituted alkyl, unsubstituted alkyl, or unsubstituted C_2 alkheteroaryl.

In some embodiments of formula (I), when R^5 is chloro, R^6 is bromo, Z^1 is $-OR^7$, Z^2 is CR^3, and R^3 and R^4 combine to form a group according to formula (IIa),

R^7 is not alkyl or unsubstituted C_2 alkheteroaryl.

In particular embodiments of formula (I), when R^5 is chloro, R^6 is bromo, Z^1 is $-OR^7$, Z^2 is CR^3, and R^3 and R^4 combine to form a group according to formula (IIa),

R^7 is not substituted alkyl, unsubstituted alkyl, or unsubstituted C_2 alkheterocyclyl.

In other embodiments of formula (I), when R^5 is chloro, R^6 is bromo, Z^1 is $-OR^7$, Z^2 is CR^3, and R^3 and R^4 combine to form a group according to formula (IIa),

R^7 is not alkyl or C_2 alkheterocyclyl.

In still other embodiments of formula (I), when R^5 is chloro, R^6 is bromo, Z^1 is $-OR^7$, Z^2 is CR^3, and R^3 and R^4 combine to form a group according to formula (IIa),

R^7 and R^8, together with the atoms to which each is attached, join to form an optionally substituted five- or six-membered ring optionally comprising one or two heteroatoms selected from

nitrogen, oxygen, and sulfur.

In yet other embodiments of formula (I), when R^5 is chloro, R^6 is bromo, Z^2 is CR^3, and R^3 and R^4 combine to form a group according to formula (IIa),

Z is $–OR^7$, and R^7 and R^8 combine to form $-CH_2-CH_2-$.

In some embodiments of formula (I), when each R^5 and R^6 is bromo, Z^1 is $–OR^7$, Z^2 is CR^3, and R^3 and R^4 combine to form a group according to formula (IIa),

R^7 is not methyl.

In particular embodiments of formula (I), when each R^5 and R^6 is chloro, Z^1 is $–OR^7$, Z^2 is CR^3, and R^3 and R^4 combine to form a group according to formula (IIa),

R^7 is not methyl, 2-(N-imidazolyl)ethyl, methoxymethyl, 2-(N-pyrazolyl)ethyl, 2-(3-methylpyrazol-1-yl)ethyl, 2-pyridyl-methyl, 1,3-dimethyl-1H-1,2,4-triazol-5-yl-methyl, 2-pyrimidinylmethyl, imidazol-2-yl-methyl, 5-methyl-isoxazol-3-yl-methyl, 4-methyl-imidazol-5-yl-methyl, or 3-methyl-1,2,4-oxadiazol-5-yl-methyl.

In other embodiments of formula (I), when each R^5 and R^6 is chloro, Z^1 is $–OR^7$, Z^2 is CR^3, and R^3 and R^4 combine to form a group according to formula (IIa),

R^7 is not unsubstituted alkyl, substituted alkyl, unsubstituted alkheteroaryl, or substituted alkheteroaryl.

In other embodiments of formula (I), when each R^5 and R^6 is chloro, Z^1 is $–OR^7$, Z^2 is CR^3, and R^3 and R^4 combine to form a group according to formula (IIa),

R^7 is not unsubstituted alkyl, substituted alkyl, unsubstituted alkheterocyclyl, or substituted alkheterocyclyl.

In certain embodiments of formula (I), when each R^5 and R^6 is chloro, Z^1 is $–OR^7$, R^7 and R^8 combine to form $-CH_2-CH_2-$, Z^2 is CR^3, and R^3 and R^4 combine to form a group according to formula (IIa),

R^9 is not ethoxycarbonyl, cyclobutylaminocarbonyl, or cyclobutadienylaminocarbonyl.

In other embodiments of formula (I), when each R^5 and R^6 is chloro, Z^1 is $–OR^7$, R^7 and R^8 combine to form $-CH_2-CH_2-$, Z^2 is CR^3, and R^3 and R^4 combine to form a group according to formula (IIa),

R^9 is H or -C(O)-N(H)-(linear C_{1-3} alkyl).

In particular embodiments of formula (I), when each R^5 and R^6 is halo, Z^2 is CR^3, and R^3 and R^4 combine to form a group according to formula (IIa),

Z is $–OR^7$, R^7 is not methyl or 2-chloroethyl, and R^9 is H or -C(O)-N(H)-(linear C_{1-3} alkyl).

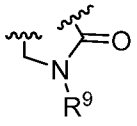
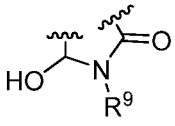
In some embodiments of formula (I), when R^5 is methoxy, R^6 is methyl, Z^1 is $–OR^7$, Z^2 is CR^3, and R^3 and R^4 combine to form a group according to formula (IIa),

R^7 is not methyl.

In certain embodiments of formula (I), when R^5 is chloro, R^6 is ethyl, Z^1 is $-OR^7$, Z^2 is CR^3, and R^3 and R^4 combine to form a group according to formula (IIa),

R^7 is not methyl.

In some embodiments of formula (I), when each R^5 and R^6 is chloro, Z^1 is $-OR^7$, Z^2 is CR^3, and R^3 and R^4 combine to form a group according to formula (IIb) or (IIc),


(IIb) or

(IIc),

R^7 is not methyl or 2-(N,N-diethylamino)ethyl.

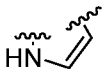
In other embodiments of formula (I), when each R^5 and R^6 is chloro, Z^1 is $-OR^7$, Z^2 is CR^3, and R^3 and R^4 combine to form a group according to formula (IIb) or (IIc),

R^7 and R^8, together with the atoms to which each is attached, join to form an optionally substituted five- or six-membered ring optionally comprising one or two heteroatoms selected from nitrogen, oxygen, and sulfur.

In certain embodiments of formula (I), when each R^5 and R^6 is chloro, Z^2 is CR^3, and R^3 and R^4 combine to form a group according to formula (IIb) or (IIc),

Z^1 is $-OR^7$, and R^7 and R^8 combine to form $-CH_2-CH_2-$.

In some embodiments of formula (I), when R^7 is methyl, R^5 is chloro, Z^1 is $-OR^7$, Z^2 is CR^3, and R^3 and R^4 combine to form a group according to formula (IIIa),


(IIIa),

R^6 is not bromo.

In particular embodiments of formula (I), when each R^5 and R^6 is chloro, Z^1 is $-OR^7$, Z^2 is CR^3, and R^3 and R^4 combine to form a group according to formula (IIIa),

R^7 is not isopropyl, 3,3,3-trifluoropropyl, or 2-(N,N-dimethylamino)ethyl.

In certain embodiments of formula (I), when each R^5 and R^6 is chloro, Z^1 is $-OR^7$, Z^2 is CR^3, and R^3 and R^4 combine to form a group according to formula (IIIa),

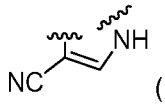
R^8 is not H.

In some embodiments of formula (I), when Z^2 is CR^3, and R^3 and R^4 combine to form a group according to formula (IIIa),

each R^5 and R^6 is chloro, and

R^7 is methyl and R^8 is H, or R^7 and R^8, together with the atoms to which each is attached, join to form an optionally substituted five- or six-membered ring optionally comprising one or two heteroatoms selected from nitrogen, oxygen, and sulfur.

In other embodiments of formula (I), when R^5 is chloro, R^6 is methoxy, Z^1 is $-OR^7$, Z^2 is CR^3, and R^3 and R^4 combine to form a group according to formula (IIIb):



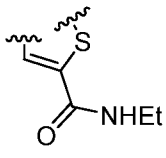
(IIIb),

neither R^1 nor R^2 is 2-(N,N-diethylamino)ethyl.

In certain embodiments of formula (I), when R^5 is chloro, R^6 is methoxy, Z^1 is $-OR^7$, Z^2 is CR^3, and R^3 and R^4 combine to form a group according to formula (IIIb),

each R^1 and R^2 is H.

In some embodiments of formula (I), when each R^5 and R^6 is chloro, Z^1 is $-OR^7$, Z^2 is CR^3, and R^3 and R^4 combine to form a group according to formula (IVa):



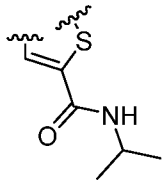
(IVa),

R^7 is not 3-(N-morpholinyl)propyl, benzyl, 1-ethyl-pyrrolydin-3-yl, 1-methyl-piperidin-4-yl, 2-(1-methyl-pyrrolidin-2-yl)ethyl, or 3-(N,N-diethylamino)propyl.

In particular embodiments of formula (I), when each R^5 and R^6 is chloro, Z^1 is $-OR^7$, Z^2 is CR^3, and R^3 and R^4 combine to form a group according to formula (IVa),

R^7 is not substituted alkyl, heterocyclyl, alkheterocyclyl, or alkaryl.

In some embodiments of formula (I), when each R^5 and R^6 is chloro, Z^1 is $-OR^7$, Z^2 is CR^3, and R^3 and R^4 combine to form a group according to formula (IVb):



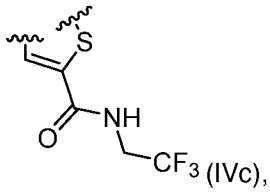
(IVb),

R^7 is not 2-methoxyethyl or benzyl.

In certain embodiments of formula (I), when each R^5 and R^6 is chloro, Z^1 is $-OR^7$, Z^2 is CR^3, and R^3 and R^4 combine to form a group according to formula (IVb),

R^7 is not substituted alkyl or alkaryl.

In some embodiments of formula (I), when each R^5 and R^6 is chloro, Z^1 is $-OR^7$, Z^2 is CR^3, and R^3 and R^4 combine to form a group according to formula (IVc):

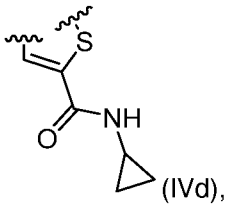

(IVc),

R^7 is not 2-(N,N-diethylamino)ethyl or 3-(N,N-dimethylamino)propyl.

In other embodiments of formula (I), when each R^5 and R^6 is chloro, Z^1 is $-OR^7$, Z^2 is CR^3, and R^3 and R^4 combine to form a group according to formula (IVc),

R^7 is not substituted alkyl.

In particular embodiments of formula (I), when each R^5 and R^6 is chloro, Z^1 is $-OR^7$, Z^2 is CR^3, and R^3 and R^4 combine to form a group according to formula (IVd):

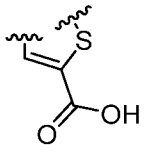
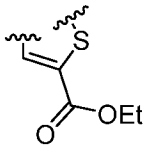

(IVd),

R^7 is not 2-(pyrrolidin-1-yl)ethyl or 2-hydroxyethyl.

In certain embodiments of formula (I), when each R^5 and R^6 is chloro, Z^1 is $-OR^7$, Z^2 is CR^3, and R^3 and R^4 combine to form a group according to formula (IVd),

R^7 is not substituted alkyl or alkheterocyclyl.

In some embodiments of formula (I), when each R^5 and R^6 is chloro, Z^1 is $-OR^7$, Z^2 is CR^3, and R^3 and R^4 combine to form a group according to formula (IVe) or (IVf):

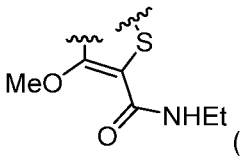
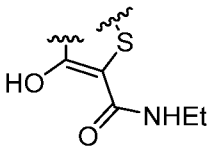
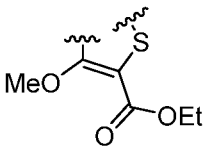
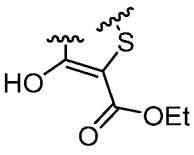

(IVe) or 
(IVf),

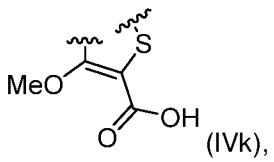
R^7 is not benzyl.

In other embodiments of formula (I), when each R^5 and R^6 is chloro, Z^1 is $-OR^7$, Z^2 is CR^3, and R^3 and R^4 combine to form a group according to formula (IVe) or (IVf),

R^7 is not alkaryl.

In certain embodiments of formula (I), when R^5 is chloro, R^6 is bromo, Z^1 is $-OR^7$, Z^2 is CR^3, and R^3 and R^4 combine to form a group according to formula (IVg), (IVh), (IVi), (IVj), or (IVk):


(IVg), 
(IVh), 
(IVi), 
(IVj), or



(IVk),

R^7 is not methyl.

In certain embodiments of formula (I), when R^5 is chloro, R^6 is bromo, Z^1 is $-OR^7$, Z^2 is CR^3, and R^3 and R^4 combine to form a group according to formula (IVg), (IVh), (IVi), (IVj), or (IVk),

R^7 is not alkyl.

In some embodiments of formula (I), when R^5 is chloro, R^6 is bromo, Z^1 is $-OR^7$, Z^2 is CR^3, and R^3 and R^4 combine to form a group according to formula (IVg), (IVh), (IVi), (IVj), or (IVk),

R^7 and R^8, together with the atoms to which each is attached, join to form an optionally substituted five- or six-membered ring optionally comprising one or two heteroatoms selected from nitrogen, oxygen, and sulfur.

In particular embodiments of formula (I), when R^5 is chloro, R^6 is bromo, Z^1 is $-OR^7$, and Z^2 is CR^3,

R^3 and R^4 do not combine to form a group according to formula (IVg), (IVh), (IVi), (IVj), or (IVk).

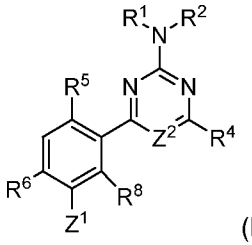
In particular embodiments of formula (I), when R^6 is methyl,

each R^1 and R^2 is H.

In certain embodiments of formula (I), when R^3 is H, and each R^5 and R^6 is chloro,

R^7 is not methyl.

In particular embodiments of formula (I), R^m is H (e.g., the compound of formula (I) has the following structure:



(I), or a pharmaceutically acceptable salt thereof.

In certain embodiments of formula (I),

In some embodiments of the methods of the invention, the substituents are defined as described herein. In particular embodiments of the methods of the invention, the method involves administering to the mammal an effective amount of a compound according to formula (I). In certain embodiments of the methods of the invention, the method involves administering to the mammal an effective amount of a compound according to formula (Ib). In other embodiments, the method involves administering to the mammal an effective amount of a compound according to formula (Va). In certain embodiments, the

method involves administering to the mammal an effective amount of a compound according to formula (Vb). In particular embodiments, the compound may be selected from Table 2, (e.g., any one of compounds **2**, **5-16**, **18-27**, **29**, **33-36**, **40-48**, and **58-77**, or a or a pharmaceutically acceptable salt thereof). In further embodiments, the method involves administering to the mammal an effective amount of compound **38** or **39** or a pharmaceutically acceptable salt thereof.

In certain embodiments of the methods of the invention, the method involves treating a mammal having a neurodegenerative disorder by administering to the mammal the compound of formula (I) (e.g., formula (Ia), (Ib), (Va), or (Vb)).

In some embodiments, the disorder is a neurodegenerative disorder (e.g., a tauopathy). The neurodegenerative disorder may be Alzheimer's disease, Huntington's disease, progressive supranuclear palsy, Parkinson's syndrome, Pick's disease, corticobasal degeneration, chronic traumatic encephalopathy, traumatic brain injury, or frontotemporal dementia. Preferably, the neurodegenerative disorder is Alzheimer's disease. In other embodiments, the disorder is a proliferative disorder (e.g., a cancer, e.g., acute myeloid leukemia, gastrointestinal stromal tumor, gastric cancer, glioblastoma, lung cancer, lymphoma, melanoma, myeloma, non-small cell lung cancer, renal cancer, small cell lung cancer, blast-phase chronic myelogenous leukemia, leukemia, lymphoproliferative disorder, metastatic melanoma, relapsed multiple myeloma, refractory multiple myeloma, myeloproliferative disorders, pancreatic cancer, small intestine cancer, or solid tumor).

In particular embodiments, the disorder is an inflammatory or autoimmune disease (e.g., rheumatoid arthritis, systemic lupus erythermatosus, or asthma). In certain embodiments, the disorder is a cardiovascular disease (e.g., atherosclerosis or cardiomyoapthy). In other embodiments, the disorder is an allergy.

In yet another aspect, the invention features a method of treating an infectious disease in a mammal by administering an effective amount of the compound of the invention (e.g., compounds of the aspects described above), or a pharmaceutically acceptable salt thereof to the mammal.

In some embodiments, the infectious disease is a viral infection. In certain embodiments, the viral infection is a virus of Herpesviridae family (e.g., herpes simplex virus-1, herpes simplex virus-2, herpes herpesvirus-5, Kaposi's sarcoma-associated herpesvirus, varicella zoster virus, or Epstein-Barr virus), Polyomaviridae family (e.g., SV40), Poxviridae family (e.g., vaccinia virus), Reoviridae family (e.g., rotavirus), Birnaviridae family (e.g., infectious bursal disease virus), Picornaviridae family (e.g., poliovirus, rhinovirus, or coxsackievirus), Flaviviridae family (e.g., hepatitis C virus or dengue virus), Arenaviridae family (e.g., lymphocytic choriomeningitis virus), Hepeviridae family (e.g., Hepatitis E virus), Rhabdoviridae family (e.g., vesicular stomatitis virus), Paramoxyviridae family (e.g., human parainfluenza virus 2, human parainfluenza virus 3, SV5, SV41, measles virus, or Sendai virus), Bunyaviridae family (e.g., La Crosse virus), Orthomoxyviridae family (e.g., influenza A virus), Filoviridae family (e.g., Ebola virus), Retroviridae family (e.g., HTLV1 or HIV1), or Hepadnaviridae family (e.g., hepatitis B virus).

In particular embodiments, the infectious disease is a fungal infection (e.g., *Candida albicans*, *Aspergillus fumigates*, or *Pneumocystis jiroveci*).

In other embodiments, the infectious disease is a bacterial infection (e.g., mycobacteria, anthrax, or bacterial pneumonia).

In some embodiments of any aspect of the methods of the invention, the compound is administered orally, sublingually, buccally, transdermally, intradermally, intramuscularly, parenterally, intravenously, intra-arterially, intracranially, subcutaneously, intraorbitally, intraventricularly, intraspinally, intraperitoneally, intranasally, by inhalation, and topically. Preferably, the compound is administered orally.

In certain embodiments of any aspect of the methods of the invention, the mammal is human.

In a further aspect, the invention features a method of inhibiting Hsp90 by contacting a cell with the compound of the invention, or a pharmaceutically acceptable salt thereof. In some embodiments, the method is carried out *in vitro*. In other embodiments, the method is carried out *in vivo*.

In another aspect, the invention features a kit containing:

(i) the pharmaceutical composition of the invention; and

(ii) instructions for use of the pharmaceutical compositions of (i) to treat a disorder in a mammal (e.g., a human) caused by the action of Hsp90.

In yet another aspect, the invention features the compounds of the invention for use in treating a disorder caused by the action of heat shock protein 90 (Hsp90). In some embodiments of this aspect, the disorder is any one of the disorders described in the aspect featuring methods of the invention. In a related aspect, the invention features the compounds of the invention for use in treating an infectious disease. In certain embodiments of this aspect, the infectious disease is any one of the infectious diseases described in the aspect featuring methods of the invention.

In still another aspect, the invention features uses of a compound of the invention in treating a disorder caused by the action of heat shock protein 90 (Hsp90). In some embodiments of this aspect, the disorder can be any one of the disorders described in the aspect featuring methods of the invention. In a related aspect, the invention features uses of a compound of the invention in treating an infectious disease. In certain embodiments of this aspect, the infectious disease is any one of the infectious diseases described in the aspect featuring methods of the invention.

In a further aspect, the invention features uses of a compound of the invention in the manufacture of a medicament for treating a disorder caused by the action of heat shock protein 90 (Hsp90). In some embodiments of this aspect, the disorder can be any one of the disorders described in the aspect featuring methods of the invention. In a related aspect, the invention features uses of a compound of the invention in the manufacture of a medicament for treating an infectious disease. In certain embodiments

of this aspect, the infectious disease is any one of the infectious diseases described in the aspect featuring methods of the invention.

Definitions

Chemical Substituents

The term "about," as used herein, represents a value that is ±10% of the recited value.

The term "acyl" or "alkanoyl," as used interchangeably herein, represent an alkyl group, as defined herein, or hydrogen attached to the parent molecular group through a carbonyl group, as defined herein, and is exemplified by formyl, acetyl, propionyl, butanoyl, and the like. Exemplary unsubstituted acyl groups include from 2 to 7 carbons. Acyl can be unsubstituted or substituted in the same as defined for alkyl.

The term "alkaryl," as defined herein, represents a chemical substituent of formula –(alkylene)-(aryl), where each group is as defined herein and may be substituted or unsubstituted according to each respective definition.

The term "alkheterocyclyl," as defined herein, represents a chemical substituent of formula –(alkylene)-(heterocyclyl), where each group is as defined herein and may be substituted or unsubstituted according to each respective definition.

The term "alkoxy," as used herein, represents a chemical substituent of formula –OR, where R is a C_{1-6} alkyl group, unless otherwise specified (e.g., R is C_{1-3} alkyl). Alkoxy may be unsubstituted or substituted with one, two, or three substituents independently selected from the group consisting of: (1) alkoxy of one to six carbons; (2) hydroxyl; (3) amino; (4) alkylamino of one to six carbons; (5) dialkylamino, where each of alkyl groups is, independently, one to six carbons; (6) cycloalkyl of three to eight carbons; (7) oxo; (8) hal; (9) alkylsulfonyl of one to six carbon atoms; (10) thioalkoxy of one to six carbon atoms; (11) aryl; (12) $-CO_2R^A$, where R^A is selected from the group consisting of (a) hydrogen, (b) alkyl, (c) cycloalkyl, (d) alkcycloalkyl, and (e) alkaryl, where the alkylene group is of one to six carbon atoms; or (13) $-C(O)NR^BR^C$, where each of R^B and R^C is, independently, selected from the group consisting of (a) hydrogen, (b) alkyl, (c) cycloalkyl, (d) alkcycloalkyl, and (e) alkaryl, where the alkylene group is of one to six carbon atoms; with the proviso that no more than one substituent (2)-(5) may be attached to a single carbon atom of the alkyl group, and none of the substituents (2)-(5) may be attached to the carbon connected to the oxygen atom of the alkoxy group. No more than one oxo substituent may be attached to a single carbon of the alkoxy group, and no more than two oxo substituents may be found in any of the alkoxy group as defined herein.

The term "alkoxyalkyl," as used herein, represents an alkyl group that is substituted with an alkoxy group. Exemplary unsubstituted alkoxyalkyl groups include from 2 to 9 carbons. In some embodiments, the alkyl and the alkoxy each can be further substituted with 1, 2, 3, 4, or 5 substituent groups as defined herein for each respective group.

The terms “alkyl,” as used herein, are inclusive of both straight chain and branched chain saturated groups of from 1 to 6 carbons, unless otherwise specified (e.g., from 1 to 3 carbons). Alkyl groups are exemplified by methyl, ethyl, n- and iso-propyl, and may be optionally substituted with one, two, three, or, in the case of alkyl groups of two carbons or more, four substituents, unless otherwise specified, independently selected from the group consisting of: (1) alkoxy of one to six carbons; (2) hydroxyl; (3) amino; (4) alkylamino of one to six carbons; (5) dialkylamino, where each of alkyl groups is, independently, one to six carbons; (6) cycloalkyl of three to eight carbons; (7) oxo; (8) hal; (9) alkylsulfonyl of one to six carbon atoms; (10) thioalkoxy of one to six carbon atoms; (11) aryl; (12) -CO_2R^A, where R^A is selected from the group consisting of (a) hydrogen, (b) alkyl, (c) cycloalkyl, (d) alkcycloalkyl, and (e) alkaryl, where the alkylene group is of one to six carbon atoms; (13) -$C(O)NR^BR^C$, where each of R^B and R^C is, independently, selected from the group consisting of (a) hydrogen, (b) alkyl, (c) cycloalkyl, (d) alkcycloalkyl, and (e) alkaryl, where the alkylene group is of one to six carbon atoms, or R^B and R^C combine to form C_{2-9} heterocyclyl; and (14) cyano; with the proviso that no more than one substituent (2)-(5) may be attached to a single carbon atom of the alkyl group. No more than one oxo substituent may be attached to a single carbon of the alkyl group, and no more than two oxo substituents may be found in any of the alkyl group as defined herein.

The term “alkylene” and the prefix “alk-,” as used herein, represent a saturated divalent C_{1-10} hydrocarbon group derived from a straight or branched chain saturated hydrocarbon by the removal of two hydrogen atoms, and is exemplified by methylene, ethylene, propylene, isopropylene, and the like. The term “C_{x-y} alkylene” and the prefix “C_{x-y} alk-” represent alkylene groups having between x and y carbons. Exemplary values for x are 1, 2, 3, 4, 5, and 6, and exemplary values for y are 2, 3, 4, 5, 6, 7, 8, 9, or 10. In some embodiments, the alkylene can be further substituted with 1, 2, 3, or 4 substituent groups as defined herein for the alkyl group.

The term “alkylsulfonyl,” as used herein, represents an alkyl group attached to the parent molecular group through an -$S(O)_2$- group. Exemplary unsubstituted alkylsulfonyl groups are of from 1 to 6 carbons. In some embodiments, the alkyl group can be further substituted with 1, 2, 3, or 4 substituent groups as defined herein.

The term “amino,” as used herein, represents a chemical substituent of formula –NH_2. Amino group may be singly substituted with, e.g., an alkyl, alkanoyl, aryl, aryloyl, cycloalkyl, heterocyclyl, or alkheterocyclyl group (e.g., “alkylamino” having formula –NH–(optionally substituted C_{1-6} alkyl), e.g., –NH–(unsubstituted C_{1-6} alkyl)), or doubly substituted with, e.g., alkyl, alkanoyl, aryl, aryloyl, cycloalkyl, heterocyclyl, or alkheterocyclyl group (e.g., “dialkylamino” having formula –NR’R”, where each of R’ and R” is, independently, optionally substituted C_{1-6} alkyl, e.g., –NR’R”, where each of R’ and R” is, independently, unsubstituted C_{1-6} alkyl). Optionally substituted C_{1-6} alkyl group may be a C_{1-6} haloalkyl, e.g., a C_{1-6} fluoroalkyl.

The term “aminoalkyl,” as used herein, represents an alkyl group that is substituted with an amino group. Each of the alkyl and amino groups may be, independently, substituted or unsubstituted as defined herein for each respective group.

The term “aryl,” as used herein, represents a mono-, bicyclic, or multicyclic carbocyclic ring system having between three and twelve carbons and having one or two aromatic rings. Non-limiting examples of aryl groups include phenyl, naphthyl, 1,2-dihydronaphthyl, 1,2,3,4-tetrahydronaphthyl, fluorenyl, indanyl, indenyl, and the like. An aryl group may be optionally substituted with one, two, three, four, or five substituents independently selected from the group consisting of: (1) alkyl of one to six carbons; (2) alkoxy of one to six carbons; (3) hydroxyl; (4) amino; (5) alkylamino of one to six carbons; (6) dialkylamino, where each of alkyl groups is, independently, one to six carbons; (7) cycloalkyl of three to eight carbons; (8) oxo; (9) hal; (10) alkylsulfonyl of one to six carbon atoms; (11) thioalkoxy of one to six carbon atoms; (12) aryl; (13) alkaryl, where alkylene group is one to six carbon atoms; (14) $-CO_2R^A$, where R^A is selected from the group consisting of (a) alkyl, (b) cycloalkyl, (c) alkcycloalkyl, (d) alkaryl, and (e) hydrogen, where the alkylene group is of one to six carbon atoms; and (15) $-C(O)NR^BR^C$, where each of R^B and R^C is, independently, selected from the group consisting of (a) alkyl, (b) cycloalkyl, (c) alkcycloalkyl, (d) alkaryl, and (e) hydrogen, where the alkylene group is of one to six carbon atoms.

The term “aryloyl,” as used herein, represents an aryl group attached to the oarent molecular group through an alkyl group.

The term “carbonyl,” as used herein, represents a C(O) group, which can also be represented as C=O, and results from the combination of a tetravalent carbon atom and an oxo substituent.

The term “cyano,” as used herein represents –CN group.

The term “cyanoalkyl,” as used herein represents an alkyl group that is substituted with cyano. Exemplary unsubstituted cyanoalkyl groups include from 2 to 9 carbons. In some embodiments, the alkyl group can be further substituted with 1, 2, 3, 4, or 5 substituent groups as defined herein for each respective group.

The term “cycloalkyl,” as used herein represents a monovalent saturated or unsaturated non-aromatic cyclic hydrocarbon group of from three to eight carbons, unless otherwise specified, and is exemplified by cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, bicyclo[2.2.1.]heptyl, and the like. Cycloalkyl groups may be optionally substituted with, for example, one, two, three, or four substituents, independently, selected from the group consisting of: (1) alkyl of one to six carbons; (2) alkoxy of one to six carbons; (3) hydroxyl; (4) amino; (5) alkylamino of one to six carbons; (6) dialkylamino, where each of alkyl groups is, independently, one to six carbons; (7) cycloalkyl of three to eight carbons; (8) oxo; (9) halo; (10) alkylsulfonyl of one to six carbon atoms; (11) thioalkoxy of one to six carbon atoms; (12) aryl; (13) alkaryl, where alkylene group is one to six carbon atoms; (14) $-CO_2R^A$, where R^A is selected from the group consisting of (a) alkyl, (b) cycloalkyl, (c) alkcycloalkyl, (d) alkaryl, and (e) hydrogen, where the alkylene group is of one to six carbon atoms; or (15) $-C(O)NR^BR^C$, where each of R^B and R^C is, independently, selected from the group consisting of (a) alkyl, (b) cycloalkyl, (c) alkcycloalkyl, (d) alkaryl, and (e) hydrogen, where the alkylene group is of one to six carbon atoms, or R^B and R^C combine to form C_{2-9} heterocyclyl.

The term "five-membered ring," as used herein, represent a saturated or unsaturated aromatic or non-aromatic group having five atoms in a cyclic array, where, unless otherwise specified, four atoms are carbons and the remaining atom is selected from the group consisting of carbon, nitrogen, sulfur, and oxygen. A five-membered ring may be fused to another cyclic group selected from heterocyclyl, heteroaryl, cycloalkyl, and aryl. A five-membered ring may be unsubstituted or substituted with, for example, one, two, three, or four substituents, independently selected from the group consisting of: (1) alkoxy of one to six carbons; (2) hydroxyl; (3) amino; (4) alkylamino of one to six carbons; (5) dialkylamino, where each of alkyl groups is, independently, one to six carbons; (6) cycloalkyl of three to eight carbons; (7) oxo; (8) alkylsulfonyl of one to six carbon atoms; (9) thioalkoxy of one to six carbon atoms; (10) aryl; (11) alkaryl, where alkylene group is one to six carbon atoms; (12) optionally substituted alkyl of one to six carbons (e.g., unsubstituted alkyl, alkoxyalkyl, hydroxyalkyl, haloalkyl, or cyanoalkyl); (13) $-CO_2R^A$, where R^A is selected from the group consisting of (a) alkyl, (b) cycloalkyl, (c) alkcycloalkyl, (d) alkaryl, and (e) hydrogen, where the alkylene group is of one to six carbon atoms; (14) $-C(O)NR^BR^C$, where each of R^B and R^C is, independently, selected from the group consisting of (a) optionally substituted alkyl (e.g., unsubstituted alkyl, alkoxyalkyl, hydroxyalkyl, haloalkyl, or cyanoalkyl), (b) cycloalkyl, (c) alkcycloalkyl, (d) alkaryl, (e) heterocyclyl, (f) alkheterocyclyl, (g) alkoxy, and (h) hydrogen, where the alkylene group is of one to six carbon atoms, or R^B and R^C combine to form C_{2-9} heterocyclyl; and (15) cyano.

The term "fluoroalkyl," as used herein, represents an alkyl group, as defined herein, where one or more hydrogen radicals (e.g., 1, 2, 3, 4, or 5, or more hydrogen radicals) bound to the alkyl group have been replaced by a fluorine radical. In some embodiments, fluoroalkyl group may be perfluoroalkyl. Prefix "fluoro" indicates that the group in question is substituted by one or more (e.g., 1, 2, 3, 4, or 5, or more) fluorine radicals.

The term "haloalkyl," as used herein, represents an alkyl group, as defined herein, substituted by a halogen group (i.e., F, Cl, Br, or I). A C_{1-6} haloalkyl may be substituted with one two, three, or in the case of alkyl groups of two carbons or more, four or five halogens. Haloalkyl groups include perfluoroalkyls. In certain embodiments, haloalkyl is fluoroalkyl. In some embodiments, the C_{1-6} haloalkyl group may be further substituted with 1, 2, 3, or 4 substituent groups as described herein for alkyl groups.

The terms "halogen," "hal," or "halo," as used interchangeably herein, represent a group selected from fluorine (-F), chlorine (-Cl), bromine (-Br), and iodine (-I). Prefix "halo" indicates that the group in question is substituted by a halogen group (i.e., F, Cl, Br, or I).

The term "heterocyclyl," as used herein represents a 5-, 6- or 7-membered ring, unless otherwise specified, containing one, two, three, or four heteroatoms independently selected from the group consisting of nitrogen, oxygen, and sulfur. The 5-membered ring has zero to two double bonds, and the 6- and 7-membered rings have zero to three double bonds. The term "heterocyclyl" also represents a heterocyclic compound having a bridged multicyclic structure in which one or more carbons and/or heteroatoms bridges two non-adjacent members of a monocyclic ring, e.g., a quinuclidinyl group. The

term “heterocyclyl” also includes bicyclic, tricyclic, and tetracyclic groups in which any of the above heterocyclic rings is fused to one, two, or three carbocyclic rings, e.g., an aryl ring, a cyclohexane ring, a cyclohexene ring, a cyclopentane ring, a cyclopentene ring, or another monocyclic heterocyclic ring, e.g., indolyl, quinolyl, isoquinolyl, tetrahydroquinolyl, benzofuryl, benzothienyl and the like. Examples of fused heterocyclyls include tropanes and 1,2,3,5,8,8a-hexahydroindolizine. Heterocyclics include pyrrolyl, pyrrolinyl, pyrrolidinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, imidazolyl, imidazolinyl, imidazolidinyl, pyridyl, piperidinyl, homopiperidinyl, pyrazinyl, piperazinyl, pyrimidinyl, pyridazinyl, oxazolyl, oxazolidinyl, isoxazolyl, isoxazolidiniyl, morpholinyl, thiomorpholinyl, thiazolyl, thiazolidinyl, isothiazolyl, isothiazolidinyl, indolyl, quinolinyl, isoquinolinyl, benzimidazolyl, benzothiazolyl, benzoxazolyl, furyl, thienyl, thiazolidinyl, isothiazolyl, isoindazoyl, triazolyl, tetrazolyl, oxadiazolyl, uricyl, thiadiazolyl, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothienyl, dihydrothienyl, dihydroindolyl, tetrahydroquinolyl, tetrahydroisoquinolyl, pyranyl, dihydropyranyl, dithiazolyl, benzofuranyl, benzothienyl and the like. The heterocyclyl group may be optionally substituted with one, two, three, four, or five substituents independently selected from the group consisting of: (1) alkyl of one to six carbons; (2) alkoxy of one to six carbons; (3) hydroxyl; (4) amino; (5) alkylamino of one to six carbons; (6) dialkylamino, where each of alkyl groups is, independently, one to six carbons; (7) cycloalkyl of three to eight carbons; (8) oxo; (9) hal; (10) alkylsulfonyl of one to six carbon atoms; (11) thioalkoxy of one to six carbon atoms; (12) aryl; (13) alkaryl; (14) $-CO_2R^A$, where R^A is selected from the group consisting of (a) alkyl, (b) cycloalkyl, (c) alkcycloalkyl, (d) alkaryl, and (e) hydrogen, where the alkylene group is of one to six carbon atoms; or (15) $-C(O)NR^BR^C$, where each of R^B and R^C is, independently, selected from the group consisting of (a) alkyl, (b) cycloalkyl, (c) alkcycloalkyl, (d) alkaryl, and (e) hydrogen, where the alkylene group is of one to six carbon atoms, or R^B and R^C combine to form C_{2-9} heterocyclyl.

The term “heteroaryl,” as used herein, represents that subset of heterocyclyls, as defined herein, which are aromatic: i.e., they contain $4n+2$ pi electrons within the mono- or multicyclic ring system. In some embodiments, the heteroaryl is substituted with, e.g., 1, 2, 3, or 4 substituent groups independently selected from the group consisting of: (1) alkyl of one to six carbons; (2) alkoxy of one to six carbons; (3) hydroxyl; (4) amino; (5) alkylamino of one to six carbons; (6) dialkylamino, where each of alkyl groups is, independently, one to six carbons; (7) cycloalkyl of three to eight carbons; (8) oxo; (9) hal; (10) alkylsulfonyl of one to six carbon atoms; (11) thioalkoxy of one to six carbon atoms; (12) aryl; (13) alkaryl; (14) $-CO_2R^A$, where R^A is selected from the group consisting of (a) alkyl, (b) cycloalkyl, (c) alkcycloalkyl, (d) alkaryl, and (e) hydrogen, where the alkylene group is of one to six carbon atoms; or (15) $-C(O)NR^BR^C$, where each of R^B and R^C is, independently, selected from the group consisting of (a) alkyl, (b) cycloalkyl, (c) alkcycloalkyl, (d) alkaryl, and (e) hydrogen, where the alkylene group is of one to six carbon atoms.

The term “hydroxy,” as used herein, represents an -OH group.

The term “hydroxyalkyl,” as used herein, represents an alkyl group, as defined herein, substituted by one or two hydroxy groups, with the proviso that no more than one hydroxy group may be attached to a single carbon atom of the alkyl group and is exemplified by hydroxymethyl, dihydroxypropyl, and the like.

The term "*N*-protected amino," as used herein, refers to an amino group, as defined herein, to which is attached an *N*-protecting group, as defined herein.

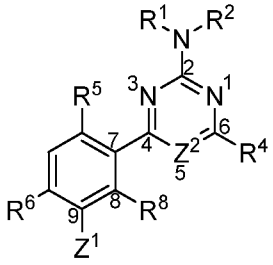
The term "*N*-protecting group," as used herein, represents those groups intended to protect an amino group against undesirable reactions during synthetic procedures. Commonly used *N*-protecting groups are disclosed in Greene, *Protective Groups in Organic Synthesis*, 3rd Edition (John Wiley & Sons, New York, 1999), which is incorporated herein by reference. N-protecting groups include acyl, aroyl, or carbamyl groups, e.g., formyl, acetyl, propionyl, pivaloyl, t-butylacetyl, 2-chloroacetyl, 2-bromoacetyl, trifluoroacetyl, trichloroacetyl, phthalyl, o-nitrophenoxyacetyl, α-chlorobutyryl, benzoyl, 4-chlorobenzoyl, 4-bromobenzoyl, 4-nitrobenzoyl, and chiral auxiliaries, e.g., protected or unprotected D, L or D, L-amino acids, e.g., alanine, leucine, phenylalanine, and the like; sulfonyl groups, e.g., benzenesulfonyl, p-toluenesulfonyl, and the like; carbamate forming groups, e.g., benzyloxycarbonyl, p-chlorobenzyloxycarbonyl, p-methoxybenzyloxycarbonyl, p-nitrobenzyloxycarbonyl, 2-nitrobenzyloxycarbonyl, p-bromobenzyloxycarbonyl, 3,4-dimethoxybenzyloxycarbonyl, 3,5-dimethoxybenzyl oxycarbonyl, 2,4-dimethoxybenzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 2-nitro-4,5-dimethoxybenzyloxycarbonyl, 3,4,5-trimethoxybenzyloxycarbonyl, 1-(p-biphenylyl)-1-methylethoxycarbonyl, α,α-dimethyl-3,5-dimethoxybenzyloxycarbonyl, benzhydryloxy carbonyl, t-butyloxycarbonyl, diisopropylmethoxycarbonyl, isopropyloxycarbonyl, ethoxycarbonyl, methoxycarbonyl, allyloxycarbonyl, 2,2,2,-trichloroethoxycarbonyl, phenoxycarbonyl, 4-nitrophenoxy carbonyl, fluorenyl-9-methoxycarbonyl, cyclopentyloxycarbonyl, adamantyloxycarbonyl, cyclohexyloxycarbonyl, phenylthiocarbonyl, and the like, arylalkyl groups, e.g., benzyl, triphenylmethyl, benzyloxymethyl, and the like and silyl groups, e.g., trimethylsilyl, and the like. Preferred N-protecting groups are formyl, acetyl, benzoyl, pivaloyl, t-butylacetyl, alanyl, phenylsulfonyl, benzyl, t-butyloxycarbonyl (Boc), and benzyloxycarbonyl (Cbz).

The term "six-membered ring," as used herein, represent a saturated or unsaturated aromatic or non-aromatic group having six atoms in a cyclic array, where, unless otherwise specified, five atoms are carbons and the remaining atom is selected from the group consisting of carbon, nitrogen, sulfur, and oxygen. A six-membered ring may be fused to another cyclic group selected from heterocyclyl, heteroaryl, cycloalkyl, and aryl. A six-membered ring may be unsubstituted or substituted with, for example, one, two, three, or four substituents, independently selected from the group consisting of: (1) alkyl of one to six carbons; (2) alkoxy of one to six carbons; (3) hydroxyl; (4) amino; (5) alkylamino of one to six carbons; (6) dialkylamino, where each of alkyl groups is, independently, one to six carbons; (7) cycloalkyl of six to eight carbons; (8) oxo; (9) alkylsulfonyl of one to six carbon atoms; (10) thioalkoxy of one to six carbon atoms; (11) aryl; (12) alkaryl, where alkylene group is one to six carbon atoms; (13) -CO_2R^A, where R^A is selected from the group consisting of (a) alkyl, (b) cycloalkyl, (c) alkcycloalkyl, (d) alkaryl, and (e) hydrogen, where the alkylene group is of one to six carbon atoms; (14) -$C(O)NR^BR^C$, where each of R^B and R^C is, independently, selected from the group consisting of (a) alkyl, (b) cycloalkyl, (c) alkcycloalkyl, (d) alkaryl, and (e) hydrogen, where the alkylene group is of one to six carbon atoms, or R^B and R^C combine to form C_{2-9} heterocyclyl; and (15) cyano.

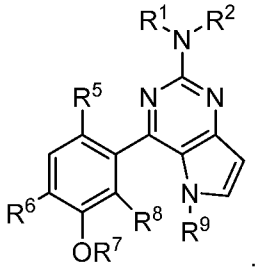
The term "thioalkoxy," as used herein, represents a chemical substituent of formula –SR, where R is an alkyl group. In some embodiments, the alkyl group can be further substituted with 1, 2, 3, or 4 substituent groups as described herein for alkyl groups.

The term "thiol," as used herein, represents a chemical substituent of formula –SH.

When referring to numbered position within the compounds of the invention, the following numbering system is employed:



. For example, the statement "R^3 and R^4 combine to form –N(R^9)–CH=CH–" indicates that the nitrogen atom of –N(R^9)–CH=CH– may be proximal to either C^5 carbon or C^6 carbon. The statement "R^3 and R^4 combine to form –N(R^9)–CH=CH–" in combination with "the nitrogen atom of –N(R^9)–CH=CH– is proximal to C^5" indicates the following compound:



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Asymmetric or chiral centers may exist in any of the compounds of the present invention. The present invention contemplates the various stereoisomers and mixtures thereof. Individual stereoisomers of compounds of the present invention are prepared synthetically from commercially available starting materials that contain asymmetric or chiral centers or by preparation of mixtures of enantiomeric compounds followed by resolution well known to those of ordinary skill in the art. These methods of resolution are exemplified by (1) attachment of a racemic mixture of enantiomers, designated (+/-), to a chiral auxiliary, separation of the resulting diastereomers by recrystallization or chromatography and liberation of the optically pure product from the auxiliary or (2) direct separation of the mixture of optical enantiomers on chiral chromatographic columns or by chiral HPLC methods. Methods of chiral separations have been described previously (G.B. Cox (ed.) in *Preparative Enantioselective Chromatography*, 2005, Blackwell Publishing). Alternatively, chiral compounds can be prepared by an asymmetric synthesis that favors the preparation of one enantiomer over the other. Alternatively a chiral pool synthesis (starting with an enantiomerically pure building block) can be used where the chiral group or center is retained in the intermediate or final product. Enantiomers are designated herein by the symbols "*R*," or "*S*," depending on the configuration of substituents around the chiral atom. Alternatively, enantiomers are designated as (+) or (-) depending on whether a solution of the enantiomer rotates the plane of polarized light clockwise or counterclockwise, respectively.

Geometric isomers may also exist in the compounds of the present invention. The present invention contemplates the various geometric isomers and mixtures thereof resulting from the arrangement of substituents around a carbon-carbon double bond and designates such isomers as of the Z or E configuration, where the term "Z" represents substituents on the same side of the carbon-carbon double bond and the term "E" represents substituents on opposite sides of the carbon-carbon double bond. It is also recognized that for structures in which tautomeric forms are possible, the description of one tautomeric form is equivalent to the description of both, unless otherwise specified.

Each position in the compounds of the invention may include elements in their natural isotopic abundance. Alternatively, one or more positions in the compound of the invention may include an element enriched in a naturally occurring or a synthetic isotope. For example, one or more positions of the compound of the invention including hydrogen may be enriched with, e.g., deuterium or tritium. In some embodiments, one or more positions of the compound of the invention including carbon may be enriched with, e.g., ^{14}C or ^{13}C. In other embodiments, one or more positions of the compound of the invention including nitrogen may be enriched with, e.g., ^{15}N. In certain embodiments, one or more positions of the compound of the invention including oxygen may be enriched with, e.g., ^{18}O, ^{17}O, or ^{15}O. In particular embodiments, one or more positions of the compound of the invention including fluorine may be enriched with, e.g., ^{18}F. In other embodiments, one or more positions of the compound of the invention including carbon may be enriched with, e.g., ^{32}S, ^{33}S, ^{34}S, ^{35}S, or ^{36}S. In yet other embodiments, one or more positions of the compound of the invention including chlorine may be enriched with, e.g., ^{35}Cl, ^{36}Cl, or ^{37}Cl.

Some abbreviations used herein:

BINAP – 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl;
t-Bu – *tert*-butyl or 1,1-dimethylethyl;
cat – catecholato;
dppb – bis(diphenylphosphino)butane;
dppf – bis(diphenylphosphino)ferrocene;
Et – ethyl;
Me – methyl;
OAc – acetate;
OMs – mesylate or methanesulfunoate;
ONf – nonaflate or nonafluoro-n-butylsulfonate;
OTf – triflate or trifluoromethanesulfonate;
pin –pinacolato;
i-Pr – isopropyl or 1-methylethyl; and
n-Pr – *n*-propyl;
SIMes – 1,3-bis(2,4,6-trimethylphenyl)imidazolin-2-ylidene;
SIPr – 1,3,-bis(2,6-diisopropylphenyl)imidazolin-2-ylidene; and
THF – tetrahydrofuran.

Other Terms

The term "about" is used herein to mean a value that is ±10% of the recited value.

The terms "effective amount" or "amount effective to" or "therapeutically effective amount" mean an amount of a compound of the invention sufficient to produce a desired result, for example, one or more of a decrease in Hsp90 activity (e.g., inhibition of Hsp90), an increase in expression of Hsp70, a decrease in aggregation of Aβ peptide (e.g., inhibition of aggregation of Aβ peptide), an increase in degradation of Aβ peptide, and a decrease in phosphorylation of tau protein, and/or a decrease in, or amelioration of symptoms of, a neurodegenerative disease (e.g., Alzheimer's disease) in a subject upon administration of a composition containing the compound of the invention. The increases and decreases related to administration an effective amount of a compound are relative to levels or symptoms, as applicable, in a subject that has not been administered a compound of the invention or relative to the subject prior to administration of a compound of the invention.

The term "element," as used herein, refers to a substance consisting of a single type of atoms, that is, each nucleus of each atom of a single element contains the same number of protons.

The term "neurodegeneration," as used herein, refers to the progressive loss of structure or function of neurons, including death of neurons. The term "neurodegenerative disease" refers to diseases in which neurodegeneration is, at least in part, a cause, symptom, or phenotype.

The terms "patient" and "subject," as used interchangeably herein, refer to any animal (e.g., a mammal, e.g., a human). A subject to be treated according to the methods described herein may be one who has been diagnosed with a neurodegenerative disease, e.g., tauopathy (e.g., Alzheimer's disease), or a proliferative disease as having such a condition or one at risk of developing the condition. Diagnosis may be performed by any method or technique known in the art. One skilled in the art will understand that a subject to be treated according to the present invention may have been subjected to standard tests or may have been identified, without examination, as one at high risk due to the presence of one or more risk factors, e.g., increased total level of tau protein or an increased level of phosphorylated tau protein in a sample (e.g., cerebrospinal fluid) from the subject in comparison to the levels in a sample from a healthy subject.

The term "pharmaceutical composition," as used herein, represents a composition containing a compound described herein, formulated with a pharmaceutically acceptable excipient, and manufactured or sold with the approval of a governmental regulatory agency as part of a therapeutic regimen for the treatment of disease in a mammal. Pharmaceutical compositions can be formulated, for example, for oral administration in unit dosage form (e.g., a tablet, capsule, caplet, gelcap, or syrup); for topical administration (e.g., as a cream, gel, lotion, or ointment); for intravenous administration (e.g., as a sterile solution free of particulate emboli and in a solvent system suitable for intravenous use); or in any other formulation described herein.

The term "pharmaceutically acceptable excipient" or "pharmaceutically acceptable carrier," as used interchangeably herein, refers to any ingredient other than the compounds described herein (e.g., a vehicle capable of suspending or dissolving the active compound) and having the properties of being nontoxic and non-inflammatory in a patient. Excipients may include, for example: antiadherents, antioxidants, binders, coatings, compression aids, disintegrants, dyes (colors), emollients, emulsifiers, fillers (diluents), film formers or coatings, flavors, fragrances, glidants (flow enhancers), lubricants, preservatives, printing inks, sorbents, suspensing or dispersing agents, sweeteners, or waters of hydration. Exemplary excipients include, but are not limited to: butylated hydroxytoluene (BHT), calcium carbonate, calcium phosphate (dibasic), calcium stearate, croscarmellose, crosslinked polyvinyl pyrrolidone, citric acid, crospovidone, cysteine, ethylcellulose, gelatin, hydroxypropyl cellulose, hydroxypropyl methylcellulose, lactose, magnesium stearate, maltitol, mannitol, methionine, methylcellulose, methyl paraben, microcrystalline cellulose, polyethylene glycol, polyvinyl pyrrolidone, povidone, pregelatinized starch, propyl paraben, retinyl palmitate, shellac, silicon dioxide, sodium carboxymethyl cellulose, sodium citrate, sodium starch glycolate, sorbitol, starch (corn), stearic acid, stearic acid, sucrose, talc, titanium dioxide, vitamin A, vitamin E, vitamin C, and xylitol.

The term "pharmaceutically acceptable prodrugs" as used herein, represents those prodrugs of the compounds of the present invention which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and animals with undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio, and effective for their intended use.

The term "pharmaceutically acceptable salt," as use herein, represents those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and animals without undue toxicity, irritation, allergic response and the like and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, pharmaceutically acceptable salts are described in: Berge et al., *J. Pharmaceutical Sciences* 66:1-19, 1977 and in *Pharmaceutical Salts: Properties, Selection, and Use*, (Eds. P.H. Stahl and C.G. Wermuth), Wiley-VCH, 2008. The salts can be prepared in situ during the final isolation and purification of the compounds described herein or separately by reacting the free base group with a suitable organic acid. Representative acid addition salts include acetate, adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptonate, glycerophosphate, hemisulfate, heptonate, hexanoate, hydrobromide, hydrochloride, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, toluenesulfonate, undecanoate, valerate salts, and the like. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like, as well as nontoxic ammonium, quaternary ammonium, and amine cations, including, but not limited to ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, ethylamine, and the like.

The term "pharmaceutically acceptable solvate" as used herein means a compound as described herein wherein molecules of a suitable solvent are incorporated in the crystal lattice. A suitable solvent is physiologically tolerable at the dosage administered. For example, solvates may be prepared by crystallization, recrystallization, or precipitation from a solution that includes organic solvents, water, or a mixture thereof. Examples of suitable solvents are ethanol, water (for example, mono-, di-, and tri-hydrates), *N*-methylpyrrolidinone (NMP), dimethyl sulfoxide (DMSO), *N,N'*-dimethylformamide (DMF), *N,N'*-dimethylacetamide (DMAC), 1,3-dimethyl-2-imidazolidinone (DMEU), 1,3-dimethyl-3,4,5,6-tetrahydro-2-(1H)-pyrimidinone (DMPU), acetonitrile (ACN), propylene glycol, ethyl acetate, benzyl alcohol, 2-pyrrolidone, benzyl benzoate, and the like. When water is the solvent, the molecule is referred to as a "hydrate."

The abbreviation "PSA" and the term "polar surface area" of a molecule, as used interchangeably herein, are defined as the surface sum over all polar atoms. The units of PSA are $Å^2$ (angstrom squared).

The term "prevent," as used herein, refers to prophylactic treatment or treatment that prevents one or more symptoms or conditions of a disease, disorder, or conditions described herein. Preventive treatment that includes administration of a compound described herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof, can be acute, short-term, or chronic. The doses administered may be varied during the course of preventative treatment.

The term "prodrug," as used herein, represents compounds that are rapidly transformed in vivo to the parent compound of the above formula, for example, by hydrolysis in blood. Prodrugs of the compounds described herein may be conventional esters. Some common esters that have been utilized as prodrugs are phenyl esters, aliphatic (C_1-C_8 or C_8-C_{24}) esters, cholesterol esters, acyloxymethyl esters, carbamates, and amino acid esters. For example, a compound that contains an OH group may be acylated at this position in its prodrug form. A thorough discussion is provided in Higuchi and Stella, *Pro-drugs as Novel Delivery Systems*, Vol. 14 of the A.C.S. Symposium Series, Edward B. Roche, ed., *Bioreversible Carriers in Drug Design*, American Pharmaceutical Association and Pergamon Press, 1987, and Judkins et al., *Synthetic Communications* 26(23):4351-4367, 1996, each of which is incorporated herein by reference. Preferably, prodrugs of the compounds of the present invention are suitable for use in contact with the tissues of humans and animals with undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio, and effective for their intended use.

The term "proliferative disease," as used herein, refers to both cancer and non-cancer disease. The proliferative disease is one characterized by unregulated proliferation of cells of a certain type (e.g., astrocytes). Preferably, the tumor cells associated with a proliferative disease (e.g., cancer) respond to the inhibition of Hsp90 by apoptosis. Proliferative diseases to be treated using compounds of the invention and according to the methods of the invention may include glioma, meningioma, pituitary adenoma, nerve sheath tumor (e.g., schwannoma or neurofibroma). Proliferative diseases within the scope of the present invention may be a cancer, e.g., acute myeloid leukemia, gastrointestinal stromal tumor, gastric cancer, lung cancer, lymphoma, melanoma, myeloma, non-small cell lung cancer, renal cancer, small cell lung cancer, blast-phase chronic myelogenous leukemia, leukemia, lymphoproliferative

disorder, metastatic melanoma, relapsed multiple myeloma, refractory multiple myeloma, myeloproliferative disorders, pancreatic cancer, small intestine cancer, or solid tumor. Preferably, a proliferative disease to be treated using compounds of the invention according to the methods of the invention may include brain tumors (e.g., malignant brain tumors). For example, the brain tumors that may be treated with blood-brain-barrier penetrant compounds of the invention can be glioma or meningioma, in particular, glioma (e.g., glioblastoma), or a malignant version thereof. The cancers that may be treated according to the present invention may also be a cancer that has metastasized to the brain (e.g., lung cancer, breast cancer, melanoma, colon cancer, renal cancer, and thyroid cancer).

As used herein, and as well understood in the art, "treatment" is an approach for obtaining beneficial or desired results, e.g., clinical results. Beneficial or desired results can include, but are not limited to, alleviation or amelioration of one or more symptoms or conditions; diminishment of extent of disease, disorder, or condition; stabilized (i.e., not worsening) state of disease, disorder, or condition; preventing spread of disease, disorder, or condition; delay or slowing the progress of the disease, disorder, or condition; amelioration or palliation of the disease, disorder, or condition; and remission (whether partial or total), whether detectable or undetectable. "Palliating" a disease, disorder, or condition means that the extent and/or undesirable clinical manifestations of the disease, disorder, or condition are lessened and/or time course of the progression is slowed or lengthened, as compared to the extent or time course in the absence of treatment.

Brief Description of Drawings

Figure 1 shows a 500 MHz ^{1}H NMR spectrum of compound **20** in $CDCl_3$.

Figure 2 shows a 500 MHz ^{1}H NMR spectrum of compound **34** in $CDCl_3$.

Figure 3 shows a 500 MHz ^{1}H NMR spectrum of compound **36** in $CDCl_3$.

Figure 4 shows five graphs providing IC_{50} data for compounds **20**, **36**, **37**, and **39** and for a known Hsp90 inhibitor, as measured using a fluorescence polarization assay described in Example 2.

Figure 5A shows a graph comparing relative association/dissociation rates to the concentration of compound **20**.

Figure 5B is a photograph of a gel demonstrating increase of the expression of Hsp70 at higher concentrations of compound **20** in a cell based functional assay. Further, Figure 5B shows that expression of Hsp90 remains unchanged relative to variation in the concentration of compound **20**.

Figure 6A shows a histogram comparing % cell viability in viable cells (VC), cells contacted with compound **20**, and cells contacted with a control compound (JNK inhibitor).

Figure 6B shows a graph comparing pTau231 levels in viable cells (VC), cells contacted with compound **20**, and cells contacted with a control compound (JNK inhibitor).

Figure 6C shows a graph comparing pTau396 levels in viable cells (VC), cells contacted with compound **20**, and cells contacted with a control compound (JNK inhibitor).

Figure 7 shows a graph of the concentration of compound **20** in mouse plasma. The data in this graph excludes the plasma level of compound **20** in animal IRN 12.

Figure 8 shows a graph of the concentration of compound **20** in mouse plasma. The data in this graph includes all mouse plasma data points.

Figure 9 shows a graph of the concentration of compound **20** in mouse brain tissue. The data in this graph excludes the plasma level of compound **20** in animal IRN 12.

Figure 10 shows a graph of the concentration of compound **20** in mouse brain tissue. The data in this graph includes all mouse brain tissue data points.

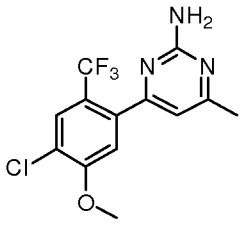
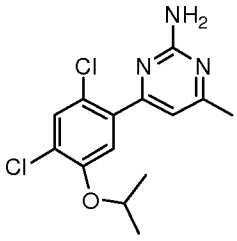
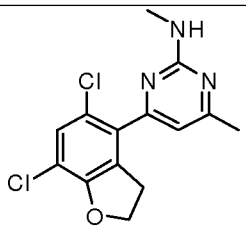
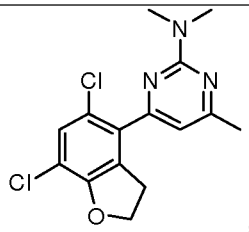
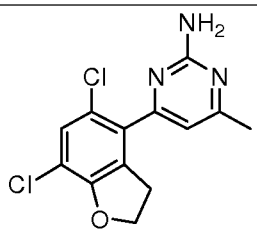
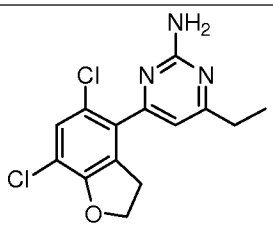
Detailed Description

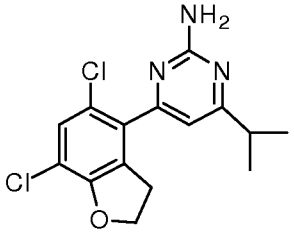
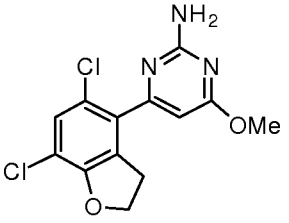
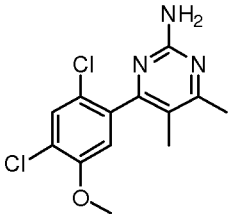
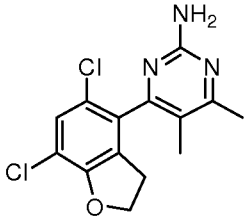
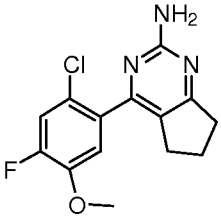
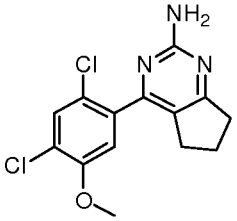
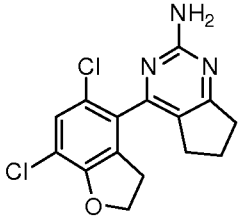
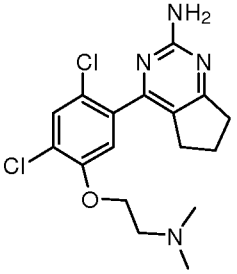
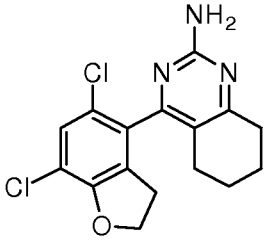
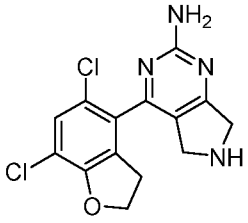
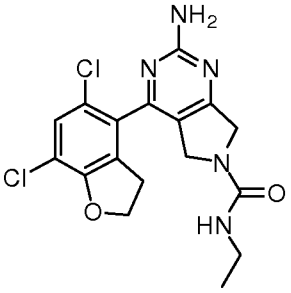
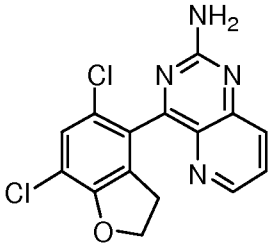
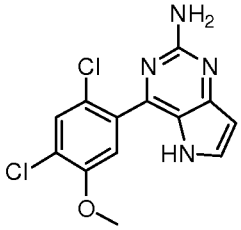
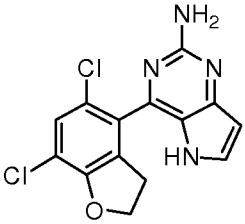
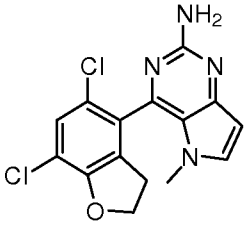
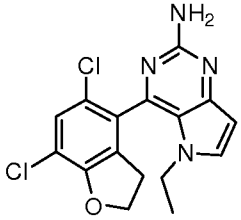
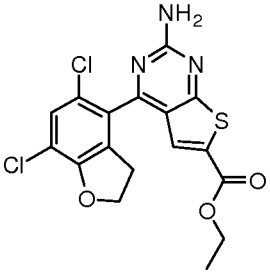
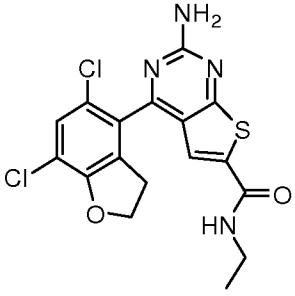
The invention features novel aminopyrimidines and related compounds having Hsp90 inhibitory activity, pharmaceutical compositions containing them, and their medical use (e.g., treatment of a proliferative disease (e.g., cancer) or a neurodegenerative disease (e.g., a tauopathy)). In particular, the compounds of the invention are capable to penetrate blood-brain-barrier. Therefore, medical use of these compounds encompasses diseases and conditions afflicting mammalian (e.g., human) brain.

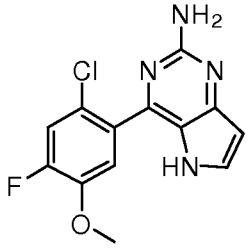
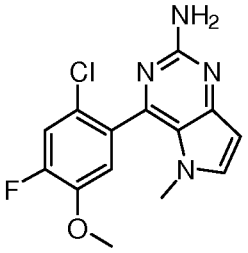
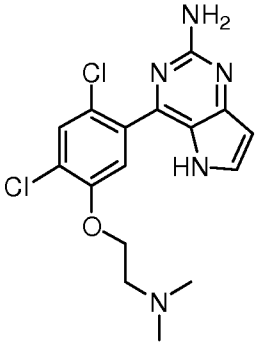
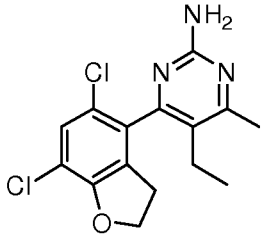
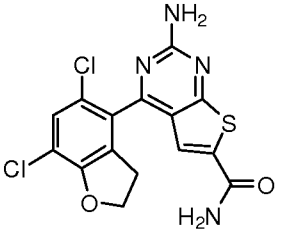
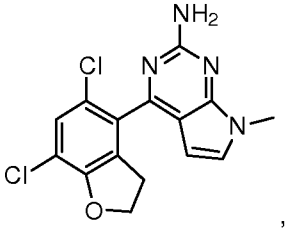
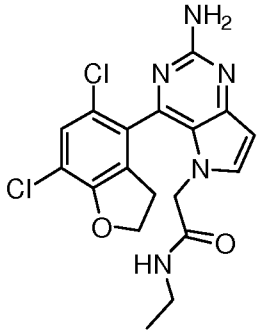
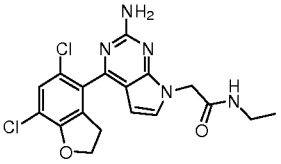
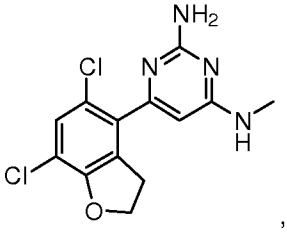
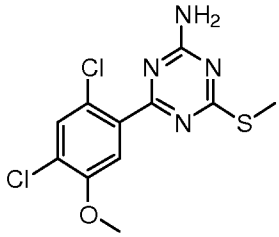
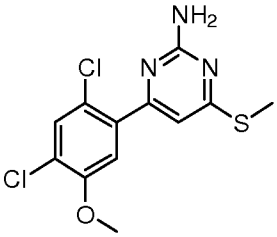
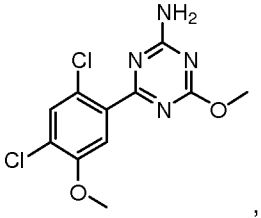
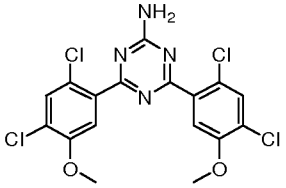
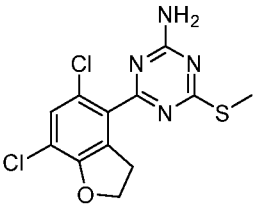
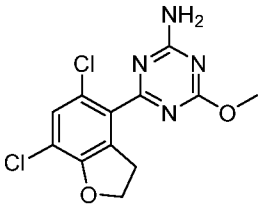
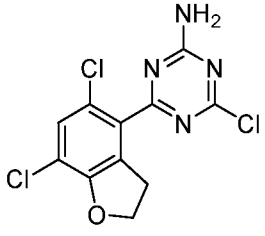
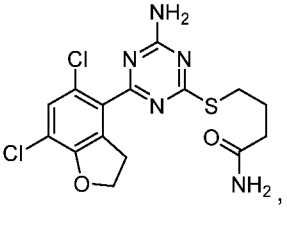
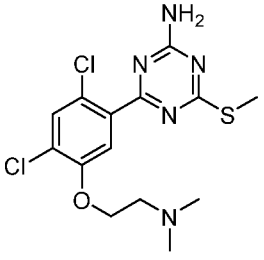
Compounds of the Invention

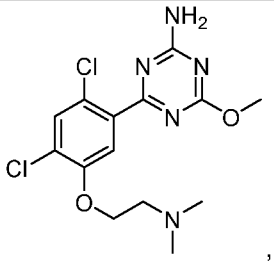
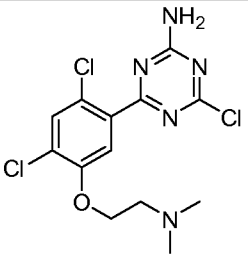
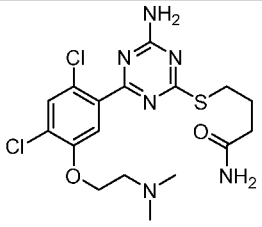
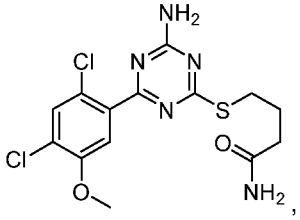
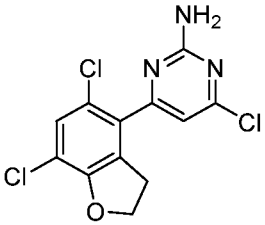
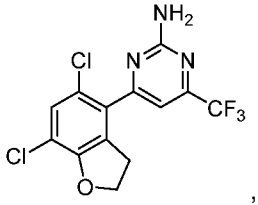
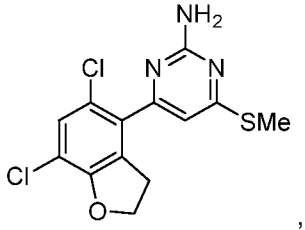
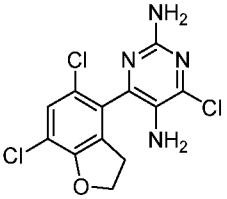
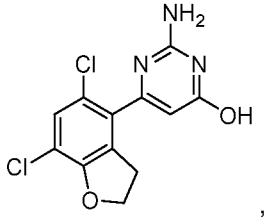
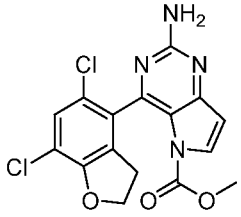
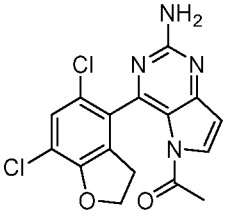
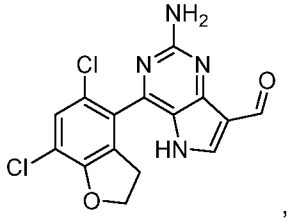
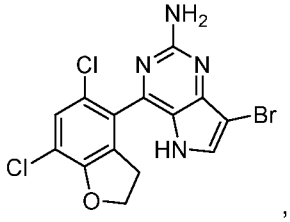
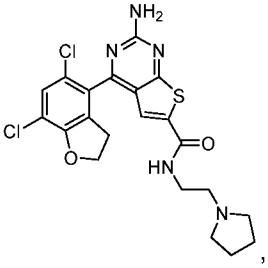
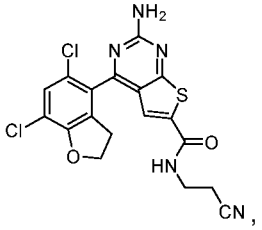
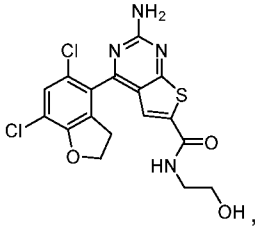
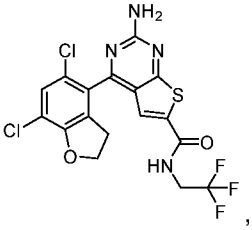
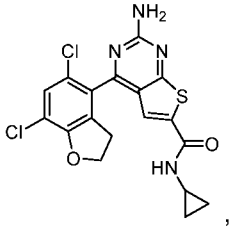
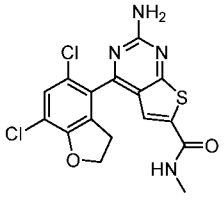
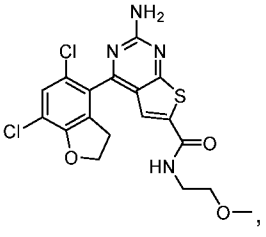
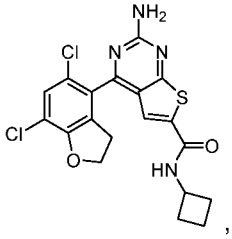
Exemplary compounds of the invention are shown in Table 2.

Table 2.

1 	**2** 	**3** 
4 	**5** 	**6** 

7		8		9	
10		11		12	
13		14		15	
16		17		18	
19		20		21	
22		23		24	

25	 ,	**26**	 ,	**27**	 ,
28	 ,	**29**	 ,	**30**	 ,
31	 ,	**32**	 ,	**33**	 ,
34	 ,	**35**	 ,	**36**	 ,
37	 ,	**40**	 ,	**41**	 ,
42	 ,	**43**	 ,	**44**	 ,

45	 ,	46	 ,	47	 , or
48	 ,	49	 ,	50	 ,
51	 ,	52	 ,	53	 ,
54	 ,	55	 ,	56	 ,
57	 ,	58	 ,	59	 ,
60	 ,	61	 ,	62	 ,
63	 ,	64	 ,	65	 ,

66 ,	**67** ,	**68** ,
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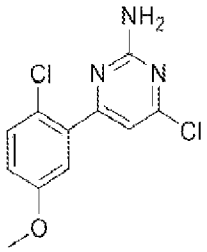
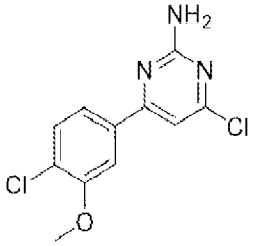
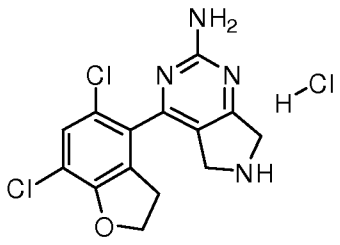
77  ,	**78**  ,	

or a pharmaceutically acceptable salt thereof.

A non-limiting example of a pharmaceutically acceptable salt of a compound of the invention is:



16-HCl .

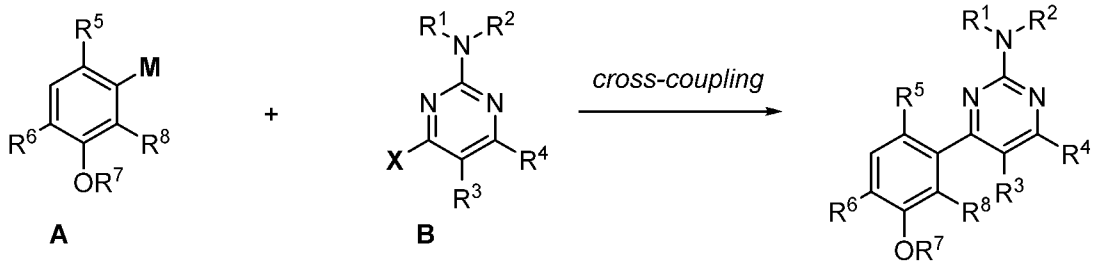
Exemplary methods for synthesizing compounds of the invention are described herein.

Methods of Preparing Compounds of the Invention

The compounds of the invention can be prepared by processes analogous to those established in the art, for example, by the reaction sequence shown in Scheme 1. The numbering system used for the general schemes does not necessarily correspond to that employed elsewhere in the description or in the claims.

As shown in Scheme 1, one strategy to access compounds of the invention (**C**) is to utilize standard cross-coupling reactions (e.g., Suzuki coupling, Hiyama coupling, Stille coupling, Negishi coupling, Tamao-Kumada coupling, or Murahashi coupling), where a nucleophile **A** and an electrophile **B** are coupled in the presence of a metal salt, e.g., a palladium, copper, iron, or nickel salt (e.g., $PdCl_2$, $Pd(OAc)_2$, CuBr, CuI, $(CuOTf)_2$·toluene complex, $Fe(OTf)_3$, $FeCl_3$, $FeBr_3$, $NiCl_2$, or $NiBr_2$). Optionally ligands, e.g., a phosphine (e.g., PPh_3, $P(2\text{-furyl})_3$, $P(t\text{-Bu})_3$, dppf, dppb, or BINAP), an *N*-heterocyclic carbene (e.g., SIMes or SIPr), or di-pyridine (e.g., 2,2'-bipyridyl or 1,10-phenanthroline), may be added to promote the reaction. Alternatively, an organometallic complex, e.g., $Pd(PPh_3)_4$ or $(dppf)PdCl_2$, may be employed directly with or without additional ligands. Additives, e.g., tetrabutylammonium fluoride, LiCl, KOAc, or AgOTf, may be added to minimize dehalogenation or to facilitate the cross-coupling reaction. One of skill in the art would be able to determine an appropriate solvent for the reaction through standard screening. Non-limiting examples of solvents used in cross-coupling reactions are water, ethanol, acetone, tetrahydrofuran, toluene, 1,4-dioxane, and mixtures thereof. For non-limiting examples of conditions and catalysts that can be used to prepare a compound of the invention according to formula **C** using cross-coupling chemistry, see Miyaura et al., "Cross-Coupling Reactions: A Practical Guide" in *Topics in Current Chemistry*, Springer, 2002, and Nicolaou et al., *Angew. Chem. Int. Ed.*, 44:4442-4489, 2005, which are incorporated herein by reference. Alternatively, a compound of formula **A** may be an electrophile and have a leaving group **X** instead of **M**, while compound of formula **B** may be a nucleophile and have a metal or metalloid group **M** instead of **X**.

Scheme 1.



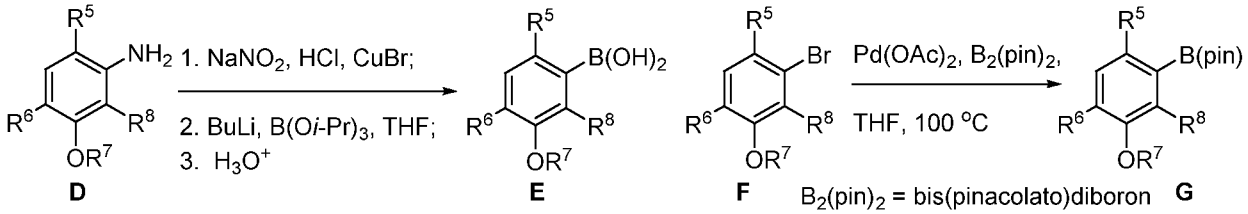
M = $B(OH)_2$, B(pin), B(cat), $SiMe_3$, $SnBu_3$, ZnCl, ZnBr, ZnI, MgCl, MgBr, MgI, Li,
where
cat = catecholato
pin = pinacolato

X = hal, e.g., -F, -Cl, -Br, -I, or pseudohalogen, such as -OMs, -OTf, -ONf, or $-OP(O)(OR)_2$,
where
-OMs = mesylate,
-OTf = triflate,
-ONf = nonaflate.

A compound of formula **A** may be prepared according any method known in the art, e.g., metal-halogen

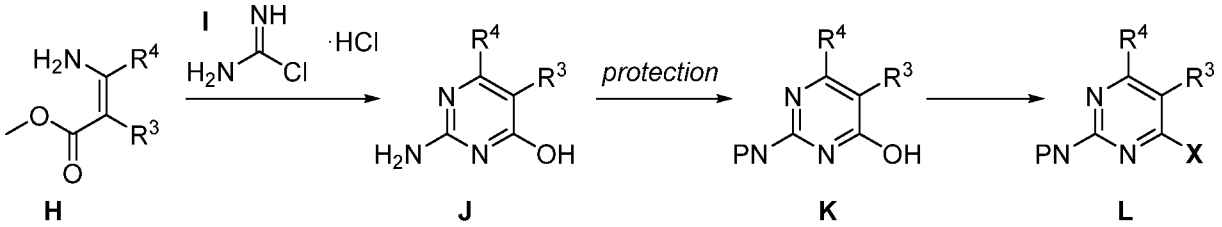
(e.g., lithium-halogen) exchange (with or without a subsequent addition of boron-based, silicon-based, tin-based, zinc-based, or magnesium-based agents), preparation of Grignard reagent, Sandmeyer reaction, or cross-coupling with di-metalloid agent (e.g., Miyaura borylation reaction). Non-limiting examples of preparation of **A** (Sandmeyer reaction and lithium halogen exchange to prepare **E**, and Miyaura borylation reaction to prepare **G**) are shown in Scheme 2.

Scheme 2. Preparation of nucleophile **A**, e.g., **E** or **G**



A compound of formula **B** may be prepared according to any method known in the art, e.g., Biginelli reaction followed by oxidation of the resulting 2-aminodihydropyrimidine derivative. Alternatively, a synthetic approach outlines in Scheme 3 can be used to access a compound of formula **B**.

Scheme 3. Preparation of electrophile **B**, e.g., an *N*-protected **B**, i.e. **L**



As shown in Scheme 3, a compound of formula **H** may undergo condensation with a compound of formula **I** to give a compound of formula **J**. The amino group of 2-aminopyrimidine derivative **J** may then be protected (P = a divalent *N*-protecting group, two monovalent *N*-protecting groups, or one monovalent *N*-protecting group and one hydrogen) to furnish a compound of formula **K**. The hydroxyl group in the compound of formula **K** may then be converted to a halogen in the compound of formula **L** according to any method known in the art, e.g., using dehydrating-halogenating reagents (e.g., $POCl_3$, PCl_5, $SOCl_2$, SO_2Cl_2, and brominating or iodinating variants thereof). Alternatively, the hydroxyl group of the compound of formula **K** may be converted into a pseudohalogen in the compound of formula **L** using reagents, e.g., Tf_2O, $PhNTf_2$, $PhNNf_2$, or $P(O)(OR)_2Cl$, and, optionally, a base (e.g., Et_3N, $(iPr)_2NEt$, or pyridine) and/or catalyst (e.g., 4-dimethylaminopyridine). *N*-protecting group P may be removed from the compound **L** before or after the cross coupling shown in Scheme 1 according to methods known in the art (see, e.g., Greene, *Protective Groups in Organic Synthesis*, 3rd Edition (John Wiley & Sons, New York, 1999)).

In the reactions described above, it may be necessary to protect reactive functional groups (e.g., hydroxy, amino, thio, or carboxy groups) to avoid their unwanted participation in the reactions. The incorporation of such groups, and the methods required to introduce and remove them are known to those skilled in the art (for example, Greene, *supra*). The deprotection step may be the final step in the synthesis such that the removal of protecting groups affords compounds of formula (Ia) as disclosed herein. Starting

materials used in any of the schemes above can be purchased or prepared by methods described in the chemical literature, or by adaptations thereof, using methods known by those skilled in the art. The order in which the steps are performed can vary depending on the groups introduced and the reagents used, but would be apparent to those skilled in the art.

Compounds of any of formula (I), (Ia), (Ib), (Va), or (Vb), or any of the intermediates described in the schemes above, can be further derivatized by using one or more standard synthetic methods known to those skilled in the art. Such methods can involve substitution, oxidation or reduction reactions. These methods can also be used to obtain or modify compounds of formula (I), (Ia), (Ib), (Va), or (Vb), or any preceding intermediates by modifying, introducing or removing appropriate functional groups. Particular substitution approaches include alkylation, arylation, heteroarylation, acylation, thioacylation, halogenation, sulphonylation, nitration, formylation, hydrolysis, and coupling procedures. These procedures can be used to introduce a functional group onto the parent molecule (e.g., the nitration or sulphonylation of aromatic rings) or to couple two molecules together (for example to couple an amine to a carboxylic acid to afford an amide; or to form a carbon-carbon bond between two heterocycles). For example, alcohol or phenol groups can be converted to ether groups by coupling a phenol with an alcohol in a solvent, e.g., tetrahydrofuran in the presence of a phosphine (e.g., triphenylphosphine) and a dehydrating agent (e.g., diethyl-, diisopropyl-, or dimethylazodicarboxylate). Alternatively, ether groups can be prepared by deprotonation of an alcohol, using a suitable base (e.g., sodium hydride) followed by the addition of an alkylating agent (e.g., an alkyl halide or an alkylsulphonate).

In another example, a primary or secondary amine can be alkylated using a reductive alkylation process. For example, the amine can be treated with an aldehyde and a borohydride (e.g., sodium triacetoxyborohydride, or sodium cyanoborohydride) in a solvent (e.g., a halogenated hydrocarbon, for example, dichloromethane, or an alcohol, for example, ethanol) and, where necessary, in the presence of an acid (e.g., acetic acid).

In another example, -OH groups may be generated from the corresponding ester, acid, acid chloride or aldehyde by reduction with a suitable reducing agent, e.g., a complex metal hydride, e.g., lithium aluminium hydride in a solvent (e.g., tetrahydrofuran).

In another example, hydroxy groups (including phenolic OH groups) can be converted into leaving groups, e.g., halogen atoms or sulphonyloxy groups (e.g., alkylsulphonyloxy, e.g., trifluoromethylsulphonyloxy, or arylsuphonyl, e.g., *p*-toluenesulphonyloxy) using conditions known to those skilled in the art. For example, an aliphatic alcohol can be reacted with thionyl chloride in a halogenated hydrocarbon (e.g., dichloromethane) to afford the corresponding alkylchloride. A base (e.g., triethylamine) can also be used in the reaction.

In another example, ester groups can be converted to the corresponding carboxylic acid by acid- or base-catalysed hydrolysis depending on the nature of the ester group. Acid catalysed hydrolysis can be achieved by treatment with an organic or inorganic acid (e.g., trifluoroacetic acid in an aqueous solvent, or a mineral acid, e.g., hydrochloric acid in a solvent, e.g., dioxan). Base catalysed hydrolysis can be

achieved by treatment with an alkali metal hydroxide (e.g., lithium hydroxide in an aqueous alcohol, e.g., methanol).

In another example, aromatic halogen substituents in the compounds may be subjected to halogen-metal exchange by treatment with a base (e.g., a lithium base, e.g., *n*-butyl or *t*-butyl lithium) optionally at a low temperature (e.g., -78°C) in a solvent (e.g., tetrahydrofuran) and the mixture may then quenched with an electrophile to introduce a desired substituent. Thus, for example, a formyl group can be introduced by using dimethylformamide as the electrophile. Aromatic halogen substituents can also be subjected to palladium catalysed reactions to introduce groups, e.g., carboxylic acids, esters, cyano, or amino substituents.

In another example, aromatic halogen substituents in the compounds may participate in a range of metal catalysed reactions to introduce alternative functional groups, e.g., amines, amides, ethers, thiols, aryl groups, or heteroaryl groups.

Particular oxidation approaches include dehydrogenations and aromatisation, and the addition of oxygen to certain functional groups. For example, aldehyde groups can be prepared by oxidation of the corresponding alcohol using conditions well known to those skilled in the art. For example, an alcohol can be treated with an oxidising agent (e.g., the Dess-Martin reagent) in a solvent (e.g., a halogenated hydrocarbon, for example dichloromethane). Alternative oxidising conditions can be used, e.g., treatment with oxalyl chloride and an activating amount of dimethylsulphoxide and subsequent quenching by the addition of an amine (e.g., triethylamine). Such a reaction can be carried out in an appropriate solvent (e.g., a halogenated hydrocarbon, for example dichloromethane) and under appropriate conditions (e.g., cooling below room temperature, e.g., to -78°C followed by warming to room temperature). In another example, sulphur atoms can be oxidised to the corresponding sulphoxide or sulphone using an oxidising agent (e.g., a peroxy acid, e.g., 3-chloroperoxybenzoic acid) in an inert solvent (e.g., a halogenated hydrocarbon, e.g., dichloromethane) at around ambient temperature.

Particular reduction approaches include the removal of oxygen atoms from particular functional groups, saturation (or partial saturation) of unsaturated compounds including aromatic rings. For example, primary alcohols can be generated from the corresponding ester or aldehyde by reduction, using a metal hydride (e.g., lithium aluminium hydride or sodium borohydride in a solvent, e.g., methanol). Alternatively, -OH groups can be generated from the corresponding carboxylic acid by reduction, using a metal hydride (e.g., lithium aluminium hydride in a solvent, e.g., tetrahydrofuran). In another example, a nitro group may be reduced to an amine by catalytic hydrogenation in the presence of a metal catalyst (e.g., palladium on a solid support, e.g., carbon) in a solvent (e.g., an ether, e.g., tetrahydrofuran, or an alcohol, e.g., methanol), or by chemical reduction using a metal (e.g., tin or iron) in the presence of an acid (e.g., hydrochloric acid). In a further example an amine can be obtained by reduction of a nitrile, e.g., by catalytic hydrogenation in the presence of a metal catalyst (e.g., palladium on a solid support, e.g., carbon), or Raney nickel in a solvent (e.g., tetrahydrofuran) and under suitable conditions (e.g., cooling to below room temperature, e.g., to -78°C, or heating, e.g., to reflux).

Pharmaceutical Compositions

The compounds used in the methods described herein are preferably formulated into pharmaceutical compositions for administration to human subjects in a biologically compatible form suitable for administration in vivo. Pharmaceutical compositions typically include a compound as described herein and a pharmaceutically acceptable excipient.

The compounds described herein can also be used in the form of the free base, in the form of salts, zwitterions, solvates, or as prodrugs, or pharmaceutical compositions thereof. All forms are within the scope of the invention. The compounds, salts, zwitterions, solvates, prodrugs, or pharmaceutical compositions thereof, may be administered to a patient in a variety of forms depending on the selected route of administration, as will be understood by those skilled in the art. The compounds used in the methods described herein may be administered, for example, by oral, parenteral, buccal, sublingual, nasal, rectal, patch, pump, or transdermal administration, and the pharmaceutical compositions formulated accordingly. Parenteral administration includes intravenous, intraperitoneal, subcutaneous, intramuscular, transepithelial, nasal, intrapulmonary, intrathecal, rectal, and topical modes of administration. Parenteral administration may be by continuous infusion over a selected period of time.

For human use, a compound of the invention can be administered alone or in admixture with a pharmaceutical carrier selected with regard to the intended route of administration and standard pharmaceutical practice. Pharmaceutical compositions for use in accordance with the present invention thus can be formulated in a conventional manner using one or more physiologically acceptable carriers comprising excipients and auxiliaries that facilitate processing of compounds of Formula (I), (Ia), (Ib), (Va), or (Vb) into preparations which can be used pharmaceutically.

This invention also includes pharmaceutical compositions which can contain one or more pharmaceutically acceptable carriers. In making the pharmaceutical compositions of the invention, the active ingredient is typically mixed with an excipient, diluted by an excipient or enclosed within such a carrier in the form of, for example, a capsule, sachet, paper, or other container. When the excipient serves as a diluent, it can be a solid, semisolid, or liquid material (e.g., normal saline), which acts as a vehicle, carrier or medium for the active ingredient. Thus, the compositions can be in the form of tablets, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, and soft and hard gelatin capsules. As is known in the art, the type of diluent can vary depending upon the intended route of administration. The resulting compositions can include additional agents, e.g., preservatives.

The excipient or carrier is selected on the basis of the mode and route of administration. Suitable pharmaceutical carriers, as well as pharmaceutical necessities for use in pharmaceutical formulations, are described in *Remington: The Science and Practice of Pharmacy*, 21st Ed., Gennaro, Ed., Lippencott Williams & Wilkins (2005), a well-known reference text in this field, and in the USP/NF (United States Pharmacopeia and the National Formulary). Examples of suitable excipients are lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, water, syrup, and methyl cellulose. The formulations can additionally include: lubricating agents, e.g., talc, magnesium stearate,

and mineral oil; wetting agents; emulsifying and suspending agents; preserving agents, e.g., methyl- and propylhydroxy-benzoates; sweetening agents; and flavoring agents. Other exemplary excipients are described in *Handbook of Pharmaceutical Excipients*, 6th Edition, Rowe et al., Eds., Pharmaceutical Press (2009).

These pharmaceutical compositions can be manufactured in a conventional manner, e.g., by conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping, or lyophilizing processes. Methods well known in the art for making formulations are found, for example, in *Remington: The Science and Practice of Pharmacy*, 21st Ed., Gennaro, Ed., Lippencott Williams & Wilkins (2005), and Encyclopedia of Pharmaceutical Technology, eds. J. Swarbrick and J. C. Boylan, 1988-1999, Marcel Dekker, New York. Proper formulation is dependent upon the route of administration chosen. The formulation and preparation of such compositions is well-known to those skilled in the art of pharmaceutical formulation. In preparing a formulation, the active compound can be milled to provide the appropriate particle size prior to combining with the other ingredients. If the active compound is substantially insoluble, it can be milled to a particle size of less than 200 mesh. If the active compound is substantially water soluble, the particle size can be adjusted by milling to provide a substantially uniform distribution in the formulation, e.g., about 40 mesh.

Dosages

The dosage of the compound used in the methods described herein, or pharmaceutically acceptable salts or prodrugs thereof, or pharmaceutical compositions thereof, can vary depending on many factors, e.g., the pharmacodynamic properties of the compound; the mode of administration; the age, health, and weight of the recipient; the nature and extent of the symptoms; the frequency of the treatment, and the type of concurrent treatment, if any; and the clearance rate of the compound in the animal to be treated. One of skill in the art can determine the appropriate dosage based on the above factors. The compounds used in the methods described herein may be administered initially in a suitable dosage that may be adjusted as required, depending on the clinical response. In general, a suitable daily dose of a compound of the invention will be that amount of the compound that is the lowest dose effective to produce a therapeutic effect. Such an effective dose will generally depend upon the factors described above.

A compound of the invention may be administered to the patient in a single dose or in multiple doses. When multiple doses are administered, the doses may be separated from one another by, for example, 1-24 hours, 1-7 days, 1-4 weeks, or 1-12 months. The compound may be administered according to a schedule or the compound may be administered without a predetermined schedule. An active compound may be administered, for example, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 times per day, every 2nd, 3rd, 4th, 5th, or 6th day, 1, 2, 3, 4, 5, 6, or 7 times per week, 1, 2, 3, 4, 5, or 6 times per month, or 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 times per year. It is to be understood that, for any particular subject, specific dosage regimes should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions.

While the attending physician ultimately will decide the appropriate amount and dosage regimen, an effective amount of a compound of the invention may be, for example, a total daily dosage of, e.g., between 0.05 mg and 3000 mg of any of the compounds described herein. Alternatively, the dosage amount can be calculated using the body weight of the patient. Such dose ranges may include, for example, between 10-1000 mg (e.g., 50-800 mg). In some embodiments, 50, 100, 150, 200, 250, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950, or 1000 mg of the compound is administered.

In the methods of the invention, the time period during which multiple doses of a compound of the invention are administered to a patient can vary. For example, in some embodiments doses of the compounds of the invention are administered to a patient over a time period that is 1-7 days; 1-12 weeks; or 1-3 months. In other embodiments, the compounds are administered to the patient over a time period that is, for example, 4-11 months or 1-30 years. In other embodiments, the compounds are administered to a patient at the onset of symptoms. In any of these embodiments, the amount of compound that is administered may vary during the time period of administration. When a compound is administered daily, administration may occur, for example, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 times per day.

Formulations

A compound identified as capable of treating any of the conditions described herein, using any of the methods described herein, may be administered to patients or animals with a pharmaceutically-acceptable diluent, carrier, or excipient, in unit dosage form. The chemical compounds for use in such therapies may be produced and isolated by any standard technique known to those in the field of medicinal chemistry. Conventional pharmaceutical practice may be employed to provide suitable formulations or compositions to administer the identified compound to patients suffering from a disease in which necrosis occurs. Administration may begin before the patient is symptomatic.

Exemplary routes of administration of the compounds (e.g., the compounds having Formula (I), (Ia), (Ib), (Va) or (Vb)), or pharmaceutical compositions thereof, used in the present invention include oral, sublingual, buccal, transdermal, intradermal, intramuscular, parenteral, intravenous, intra-arterial, intracranial, subcutaneous, intraorbital, intraventricular, intraspinal, intraperitoneal, intranasal, inhalation, and topical administration. The compounds desirably are administered with a pharmaceutically acceptable carrier. Pharmaceutical formulations of the compounds described herein formulated for treatment of the disorders described herein are also part of the present invention.

Formulations for Oral Administration

The pharmaceutical compositions contemplated by the invention include those formulated for oral administration ("oral dosage forms"). Oral dosage forms can be, for example, in the form of tablets, capsules, a liquid solution or suspension, a powder, or liquid or solid crystals, which contain the active ingredient(s) in a mixture with non-toxic pharmaceutically acceptable excipients. These excipients may be, for example, inert diluents or fillers (e.g., sucrose, sorbitol, sugar, mannitol, microcrystalline cellulose, starches including potato starch, calcium carbonate, sodium chloride, lactose, calcium phosphate, calcium sulfate, or sodium phosphate); granulating and disintegrating agents (e.g., cellulose derivatives

including microcrystalline cellulose, starches including potato starch, croscarmellose sodium, alginates, or alginic acid); binding agents (e.g., sucrose, glucose, sorbitol, acacia, alginic acid, sodium alginate, gelatin, starch, pregelatinized starch, microcrystalline cellulose, magnesium aluminum silicate, carboxymethylcellulose sodium, methylcellulose, hydroxypropyl methylcellulose, ethylcellulose, polyvinylpyrrolidone, or polyethylene glycol); and lubricating agents, glidants, and antiadhesives (e.g., magnesium stearate, zinc stearate, stearic acid, silicas, hydrogenated vegetable oils, or talc). Other pharmaceutically acceptable excipients can be colorants, flavoring agents, plasticizers, humectants, buffering agents, and the like.

Formulations for oral administration may also be presented as chewable tablets, as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent (e.g., potato starch, lactose, microcrystalline cellulose, calcium carbonate, calcium phosphate or kaolin), or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example, peanut oil, liquid paraffin, or olive oil. Powders, granulates, and pellets may be prepared using the ingredients mentioned above under tablets and capsules in a conventional manner using, e.g., a mixer, a fluid bed apparatus or a spray drying equipment.

Controlled release compositions for oral use may be constructed to release the active drug by controlling the dissolution and/or the diffusion of the active drug substance. Any of a number of strategies can be pursued in order to obtain controlled release and the targeted plasma concentration versus time profile. In one example, controlled release is obtained by appropriate selection of various formulation parameters and ingredients, including, e.g., various types of controlled release compositions and coatings. Examples include single or multiple unit tablet or capsule compositions, oil solutions, suspensions, emulsions, microcapsules, microspheres, nanoparticles, patches, and liposomes. In certain embodiments, compositions include biodegradable, pH, and/or temperature-sensitive polymer coatings.

Dissolution or diffusion controlled release can be achieved by appropriate coating of a tablet, capsule, pellet, or granulate formulation of compounds, or by incorporating the compound into an appropriate matrix. A controlled release coating may include one or more of the coating substances mentioned above and/or, e.g., shellac, beeswax, glycowax, castor wax, carnauba wax, stearyl alcohol, glyceryl monostearate, glyceryl distearate, glycerol palmitostearate, ethylcellulose, acrylic resins, dl-polylactic acid, cellulose acetate butyrate, polyvinyl chloride, polyvinyl acetate, vinyl pyrrolidone, polyethylene, polymethacrylate, methylmethacrylate, 2-hydroxymethacrylate, methacrylate hydrogels, 1,3 butylene glycol, ethylene glycol methacrylate, and/or polyethylene glycols. In a controlled release matrix formulation, the matrix material may also include, e.g., hydrated methylcellulose, carnauba wax and stearyl alcohol, carbopol 934, silicone, glyceryl tristearate, methyl acrylate-methyl methacrylate, polyvinyl chloride, polyethylene, and/or halogenated fluorocarbon.

The liquid forms in which the compounds and compositions of the present invention can be incorporated for administration orally include aqueous solutions, suitably flavored syrups, aqueous or oil suspensions, and flavored emulsions with edible oils, e.g., cottonseed oil, sesame oil, coconut oil, or peanut oil, as well as elixirs and similar pharmaceutical vehicles.

Formulations for Buccal Administration

Dosages for buccal or sublingual administration typically are 0.1 to 500 mg per single dose as required. In practice, the physician determines the actual dosing regimen which is most suitable for an individual patient, and the dosage varies with the age, weight, and response of the particular patient. The above dosages are exemplary of the average case, but individual instances exist wherein higher or lower dosages are merited, and such are within the scope of this invention.

For buccal administration, the compositions may take the form of tablets, lozenges, etc. formulated in a conventional manner. Liquid drug formulations suitable for use with nebulizers and liquid spray devices and electrohydrodynamic (EHD) aerosol devices will typically include a compound of the invention with a pharmaceutically acceptable carrier. Preferably, the pharmaceutically acceptable carrier is a liquid, e.g., alcohol, water, polyethylene glycol, or a perfluorocarbon. Optionally, another material may be added to alter the aerosol properties of the solution or suspension of compounds of the invention. Desirably, this material is liquid, e.g., an alcohol, glycol, polyglycol, or a fatty acid. Other methods of formulating liquid drug solutions or suspension suitable for use in aerosol devices are known to those of skill in the art (see, e.g., Biesalski, U.S. Pat. No. 5,112,598 and Biesalski, U.S. Pat. No. 5,556,611, each of which is herein incorporated by reference).

Formulations for Nasal or Inhalation Administration

The compounds may also be formulated for nasal administration. Compositions for nasal administration also may conveniently be formulated as aerosols, drops, gels, and powders. The formulations may be provided in a single or multidose form. In the case of a dropper or pipette, dosing may be achieved by the patient administering an appropriate, predetermined volume of the solution or suspension. In the case of a spray, this may be achieved, for example, by means of a metering atomizing spray pump.

The compounds may further be formulated for aerosol administration, particularly to the respiratory tract by inhalation and including intranasal administration. The compound will generally have a small particle size for example on the order of five (5) microns or less. Such a particle size may be obtained by means known in the art, for example by micronization. The active ingredient is provided in a pressurized pack with a suitable propellant, e.g., a chlorofluorocarbon (CFC), for example, dichlorodifluoromethane, trichlorofluoromethane, or dichlorotetrafluoroethane, or carbon dioxide, or other suitable gas. The aerosol may conveniently also contain a surfactant, e.g., lecithin. The dose of drug may be controlled by a metered valve. Alternatively, the active ingredients may be provided in a form of a dry powder, e.g., a powder mix of the compound in a suitable powder base, e.g., lactose, starch, and starch derivatives, e.g., hydroxypropylmethyl cellulose, and polyvinylpyrrolidine (PVP). The powder carrier will form a gel in the nasal cavity. The powder composition may be presented in unit dose form for example in capsules or cartridges of e.g., gelatin or blister packs from which the powder may be administered by means of an inhaler.

Aerosol formulations typically include a solution or fine suspension of the active substance in a physiologically acceptable aqueous or non-aqueous solvent and are usually presented in single or

multidose quantities in sterile form in a sealed container, which can take the form of a cartridge or refill for use with an atomizing device. Alternatively, the sealed container may be a unitary dispensing device, e.g., a single dose nasal inhaler or an aerosol dispenser fitted with a metering valve which is intended for disposal after use. Where the dosage form comprises an aerosol dispenser, it will contain a propellant, which can be a compressed gas, e.g., compressed air or an organic propellant, e.g., fluorochlorohydrocarbon. The aerosol dosage forms can also take the form of a pump-atomizer.

Formulations for Parenteral Administration

The compounds described herein for use in the methods of the invention can be administered in a pharmaceutically acceptable parenteral (e.g., intravenous or intramuscular) formulation as described herein. The pharmaceutical formulation may also be administered parenterally (intravenous, intramuscular, subcutaneous or the like) in dosage forms or formulations containing conventional, non-toxic pharmaceutically acceptable carriers and adjuvants. In particular, formulations suitable for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. For example, to prepare such a composition, the compounds of the invention may be dissolved or suspended in a parenterally acceptable liquid vehicle. Among acceptable vehicles and solvents that may be employed are water, water adjusted to a suitable pH by addition of an appropriate amount of hydrochloric acid, sodium hydroxide or a suitable buffer, 1,3-butanediol, Ringer's solution and isotonic sodium chloride solution. The aqueous formulation may also contain one or more preservatives, for example, methyl, ethyl or n-propyl p-hydroxybenzoate. Additional information regarding parenteral formulations can be found, for example, in the United States Pharmacopeia-National Formulary (USP-NF), herein incorporated by reference.

The parenteral formulation can be any of the five general types of preparations identified by the USP-NF as suitable for parenteral administration:

(1) "Drug Injection:" a liquid preparation that is a drug substance (e.g., a compound of Formula (I), (Ia), (Ib), (Va) or (Vb)), or a solution thereof;

(2) "Drug for Injection:" the drug substance (e.g., a compound of Formula (I), (Ia), (Ib), (Va) or (Vb)) as a dry solid that will be combined with the appropriate sterile vehicle for parenteral administration as a drug injection;

(3) "Drug Injectable Emulsion:" a liquid preparation of the drug substance (e.g., a compound of Formula (I), (Ia), (Ib), (Va) or (Vb)) that is dissolved or dispersed in a suitable emulsion medium;

(4) "Drug Injectable Suspension:" a liquid preparation of the drug substance (e.g., a compound of Formula (I), (Ia), (Ib), (Va) or (Vb)) suspended in a suitable liquid medium; and

(5) "Drug for Injectable Suspension:" the drug substance (e.g., a compound of Formula (I), (Ia), (Ib), (Va) or (Vb)) as a dry solid that will be combined with the appropriate sterile vehicle for parenteral administration as a drug injectable suspension.

Exemplary formulations for parenteral administration include solutions of the compound prepared in water suitably mixed with a surfactant, e.g., hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, DMSO and mixtures thereof with or without alcohol, and in oils. Under ordinary conditions of storage and use, these preparations may contain a preservative to prevent the growth of microorganisms. Conventional procedures and ingredients for the selection and preparation of suitable formulations are described, for example, in *Remington: The Science and Practice of Pharmacy*, 21st Ed., Gennaro, Ed., Lippencott Williams & Wilkins (2005)and in The United States Pharmacopeia: The National Formulary (USP 36 NF31), published in 2013.

Formulations for parenteral administration may, for example, contain excipients, sterile water, or saline, polyalkylene glycols, e.g., polyethylene glycol, oils of vegetable origin, or hydrogenated napthalenes. Biocompatible, biodegradable lactide polymer, lactide/glycolide copolymer, or polyoxyethylene-polyoxypropylene copolymers may be used to control the release of the compounds. Other potentially useful parenteral delivery systems for compounds include ethylene-vinyl acetate copolymer particles, osmotic pumps, implantable infusion systems, and liposomes. Formulations for inhalation may contain excipients, for example, lactose, or may be aqueous solutions containing, for example, polyoxyethylene-9-lauryl ether, glycocholate and deoxycholate, or may be oily solutions for administration in the form of nasal drops, or as a gel.

The parenteral formulation can be formulated for prompt release or for sustained/extended release of the compound. Exemplary formulations for parenteral release of the compound include: aqueous solutions, powders for reconstitution, cosolvent solutions, oil/water emulsions, suspensions, oil-based solutions, liposomes, microspheres, and polymeric gels.

Methods of Treatment

The compounds and compositions described herein can be used in the treatment of conditions and disorders in which Hsp90 has been implicated, e.g., cell proliferative disorders, e.g., cancers, neurodegenerative diseases, e.g., tauopathies (e.g., Alzheimer's disease), and infectious diseases.

Cell Proliferative Disorders

Hsp90 has emerged as a key therapeutic target for cancer therapy due to the involvement of this multichaperone complex in various pathogenic cellular processes. Hsp90 client proteins include those implicated in: acute myeloid leukemia (Flt-3), breast cancer (HER2), chronic lymphoid leukemia (Zap70), chronic myeloid leukemia (Bcr-Abl or mBcr-Abl), gastrointestinal stromal tumor (c-Kit), gastric cancer (c-Met), glioblastoma (mutant EGFR or c-Met), lung cancer (c-Met), lymphoma (NMP-ALK), melanoma (Raf-1/mutant BRAF), myeloma (IGF-1R/Akt), non-small cell lung cancer (mutant EGFR), renal cancer, (HIF-1α), and small cell lung cancer (Akt). The compounds of the invention are particularly useful in the treatment of brain tumors due to their blood-brain-barrier penetrant properties. Brain tumors that may be treated using compounds of the invention include glioma or meningioma, in particular, glioma (e.g., glioblastoma) or neuroblastoma. The brain tumors (e.g., brain cancers) that may be treated using compounds of the invention according to the methods of the invention may include primary tumors (those tumors that originated in the brain) and metastatic tumors (those tumors that originated in tissues other

than brain tissues and spread to the brain). Still other cell proliferative disorders that may be treated by the inhibition of Hsp90 include: blast-phase chronic myelogenous leukemia, leukemia, lymphoproliferative disorder, metastatic melanoma, multiple myeloma (e.g., relapsed or refractory multiple myeloma), myeloproliferative disorders, pancreatic cancer, small intestine cancer, and solid tumor. Moreover, cancer cells have been shown to be more sensitive to Hsp90 inhibition than non-pathogenic cells. Accordingly, the compounds described herein may be useful treatments for cell proliferative disorders.

Neurodegenerative Diseases

Increased levels of Hsp90 have been implicated in neurodegenerative disorders. For example, aberrant Hsp90 activity has been shown in tauopathies, which are conditions characterized by accumulation of abnormal Tauproteins (e.g., hyperphosphorylated and aggregated Tau). Accordingly, compounds and compositions described herein can be useful for the treatment of neurodegenerative diseases and tauopathies that include Alzheimer's disease (AD), argyrophilic grain disease, amyotrophic lateral sclerosis, corticobasal degeneration, dementia pugislistica, Down's syndrome, familial British dementia, frontal lobe degeneration (dementia lacking distinctive histopathological features), chronic traumatic encephalopathy, traumatic brain injury, frontotemporal dementia (FTD; e.g., fronto-temporal dementia with parkinsonism linked to chromosome 17 (FTDP-17)), hippocampal tauopathy in cerebral aging, myotonic dystrophy of type I , Niemann–Pick disease of type C, Parkinson's disease (e.g., parkinsonism-dementia complex of Guam, Parkinsonism with dementia of Guadeloupe, or postencephalitic parkinsonism), Pick's disease (PiD), and progressive supranuclear palsy. Accordingly, the compounds described herein may be useful in treating a neurodegenerative disorder, e.g., tauopathy (e.g., Alzheimer's disease).

Infectious Diseases

Hsp90 has emerged as a therapeutic target for treating infectious diseases, e.g., viral infections, fungal infections, and bacterial infections. Many pathogens (e.g., viruses, fungi, and bacteria) rely on Hsp90-dependent processes (see, e.g., Geller et al., *Biochim. Biophys. Acta – Mol. Cell Res.*, 1823:698-706, 2012; the disclosure of which is incorporate herein in its entirety). Thus, inhibition of Hsp90 provides a therapeutic benefit to a patient afflicted with an infection that relies on the activity of Hsp90. For example, an Hsp90 inhibitor (geldanamycin) was shown to delay the growth of influenza virus in cell culture. Other viruses that rely on Hsp90 dependent processes include those belonging to the families: Herpesviridae (e.g., herpes simplex virus-1, herpes simplex virus-2, herpes herpesvirus-5, Kaposi's sarcoma-associated herpesvirus, varicella zoster virus, or Epstein-Barr virus), Polyomaviridae (e.g., SV40), Poxviridae (e.g., vaccinia virus), Reoviridae (e.g., rotavirus), Birnaviridae (e.g., infectious bursal disease virus), Picornaviridae (e.g., poliovirus, rhinovirus, or coxsackievirus), Flaviviridae (e.g., hepatitis C virus or dengue virus), Arenaviridae (e.g., lymphocytic choriomeningitis virus), Hepeviridae (e.g., Hepatitis E virus), Rhabdoviridae (e.g., vesicular stomatitis virus), Paramoxyviridae (e.g., human parainfluenza virus 2, human parainfluenza virus 3, SV5, SV41, measles virus, or Sendai virus), Bunyaviridae (e.g., La Crosse virus), Orthomoxyviridae (e.g., influenza A virus), Filoviridae (e.g., Ebola virus), Retroviridae (e.g., HTLV1 or HIV1), and Hepadnaviridae (e.g., hepatitis B virus). Hsp90 inhibitors have also been used *in vivo* for the treatment of fungal infectious diseases, e.g., treatment of *Candida albicans*, *Aspergillus*

fumigates, or *Pneumocystis jiroveci*. Moreover, Hsp90 inhibitors are also useful in the treatment of bacterial infections, e.g., mycobacteria, anthrax, or bacterial pneumonia. A discussion of the diseases that may be treated with Hsp90 inhibitors is provided in the U.S. Patent Application Publication 2011/0201587, the disclosure of which is incorporated herein by reference in its entirety. Therefore, the compounds of the invention may be used according to the method of the invention to treat infectious diseases, e.g., viral infections, fungal infections, or bacterial infections.

Inflammatory and Autoimmune Diseases, Allergy

Hsp90 has been shown to play a role in antigen presentation, activation of lymphocytes, macrophages, maturation of dendritic cells, and in the enhanceosome mediated induction of inflammation. Hsp90 inhibition is associated with blockage of components of inflammation, e.g., reduction of cytokine and NO production, as well as blockage of NFκB nuclear translocation. Further, considerable body of work indicates that chaperones, such as Hsp90, may be capable of inducing the production of proinflammatory cytokines by the monocyte-macrophage system and the activation and maturation of dendritic cells via the TLR2-and 4-signal transduction pathways. Thus, Hsp90 apparently can function as a potent activator of the innate immune system. Indeed, elevated levels of Hsp90 were detected in the serum of systemic lupus erythematosus patients. Autoantibodies and cells reactive to Hsp have been detected in patients with rheumatoid arthritis. Antiinflammatory effect of inhibiting Hsp90 was also observed to reduce airway inflammation in murine model of asthma. The compounds of the invention may be applicable to the treatment of inflammatory or autoimmune diseases in a patient. Moreover, anti-inflammatory effect of Hsp90 inhibition can have therapeutic application in the treatment of allergies. Thus, the compounds of the invention may be used in the treatment of allergy.

Cardiovascular Diseases

Hsp90 has recently been implicated in etiology of cardiovascular disorders, such as atherosclerosis and cardiomyopathy. Thus, the compounds of the present invention may be applicable to the treatment of cardiovascular diseases (e.g., atherosclerosis or cardiomyopathy).

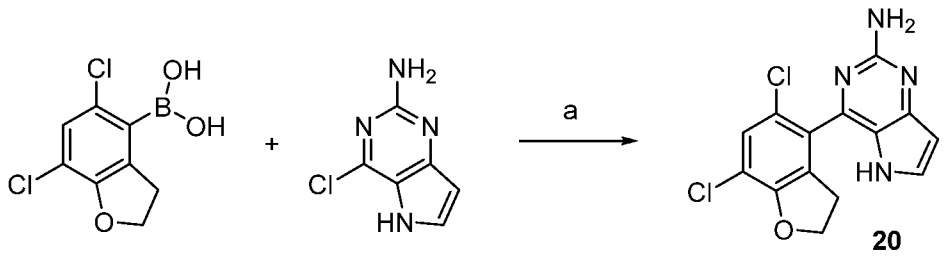
Kits of the Invention

The present invention also provides kits containing (i) a pharmaceutical composition of the invention, and (ii) instructions for use of the pharmaceutical composition to treat a disorder in a mammal caused by the action of Hsp90, e.g., a neurodegenerative disorder, a proliferative disorder, or an infectious disease, as described herein. Kits of the invention may include instructions explaining how a practitioner (e.g., a physician, a nurse, a care-giver, or a patient) may administer the composition contained therein. The pharmaceutical composition within the kit of the invention may be provided in a container (e.g., a bottle, an ampule, a tube, or a blister pack). Furthermore, the kits may also include additional components, e.g., instructions or administration schedules for a patient suffering from a neurodegenerative disease or a proliferative disease, and optionally, a device(s) for administering the pharmaceutical composition (e.g., a syringe).

The following examples are meant to illustrate the invention. They are not meant to limit the invention in any way.

Examples

Example 1. Synthesis of the Compounds of the Invention

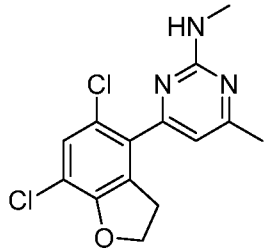


20

Scheme 1. Reagents and conditions: (a) $Pd(PPh_3)_4$, Na_2CO_3, dioxane/H_2O (9/5), 90 ºC, 72%.

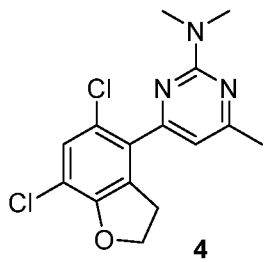
4-(5,7-Dichloro-2,3-dihydrobenzofuran-4-yl)-5*H*-pyrrolo[3,2-*d*]pyrimidin-2-amine (20). A mixture of 5,7-dichloro-2,3-dihydro-1-benzofuran-4-yl boronic acid (233 mg, 1.0 mmol), 4-chloro-5*H*-pyrrolo[3,2-d]pyrimidin-2-amine (219 mg, 1.3 mmol), sodium carbonate (318 mg, 3.0 mmol), palladium tetrakis(triphenylphosphine), and dioxane/water (9/5, 14 ml) was stirred at 90 ºC under argon for 20 h, then cooled down to room temperature, quenched with brine (25 ml), and extracted with ethyl acetate (30 ml x 2). The combined organic layers were dried over sodium sulfate and concentrated. The residue was purified by chromatography on silica gel using cyclohexane/ethyl acetate (100/0 to 30/70, 15 min) to give a product as a white solid (230 mg, 72%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.01 (s, 1H), 7.45 (t, J = 3 Hz, 1H), 7.34 (s, 1H), 6.46 (m, 1H), 4.83 (s, 2H), 4.71 (m, 2H), 3.60 (m, 1H), 2.94 (m, 1H); LCMS $[M + H]^+$: 321.0 (calcd for $[C_{14}H_{10}Cl_2N_4O + H]^+$: 321.0).

The following compounds of the invention have been prepared according to the procedure described herein.



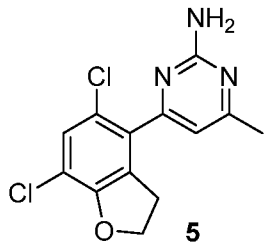
3

4-(5,7-Dichloro-2,3-dihydrobenzofuran-4-yl)-*N*,6-dimethylpyrimidin-2-amine(3). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.25 (s, 1H), 6.57 (s, 1H), 5.07 (d, J = 10 Hz, 1H), 4.68 (t, J = 9 Hz, 2H), 3.29 (t, J = 9 Hz, 2H), 3.02 (d, J = 10 Hz, 3H), 2.40 (s, 3H).



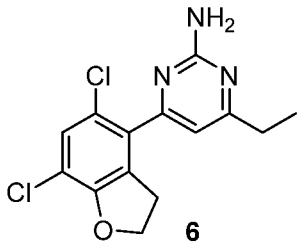
4

4-(5,7-Dichloro-2,3-dihydrobenzofuran-4-yl)-*N*,*N*,6-trimethylpyrimidin-2-amine(4). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.25 (s, 1H), 6.51 (s, 1H), 4.67 (t, *J* = 9 Hz, 2H), 3.30 (t, *J* = 9 Hz, 2H), 3.20 (s, 6H), 2.40 (s, 3H).



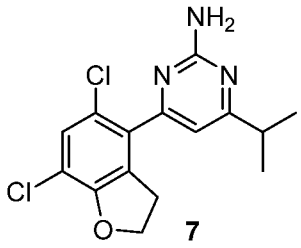
5

4-(5,7-Dichloro-2,3-dihydrobenzofuran-4-yl)-6-methylpyrimidin-2-amine(5). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.27 (s, 1H), 6.64 (s, 1H), 5.04 (s, 2H), 4.68 (t, *J* = 9 Hz, 2H), 3.25 (t, *J* = 9 Hz, 2H), 2.42 (s, 3H).



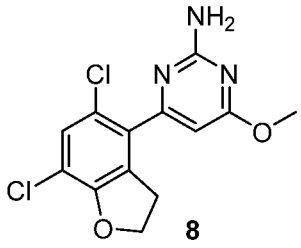
6

4-(5,7-dichloro-2,3-dihydrobenzofuran-4-yl)-6-ethylpyrimidin-2-amine (6). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.27 (s, 1H), 6.65 (s, 1H), 5.05 (s, 2H), 4.68 (t, *J* = 9 Hz, 2H), 3.26 (t, *J* = 8.5 Hz, 2H), 2.68 (q, *J* = 8 Hz, 2H), 1.29 (t, *J* = 7.5 Hz, 3H); LCMS $[M + H]^+$: 310.1 (calcd for $[C14H13Cl2N3O + H]^+$: 310.04).



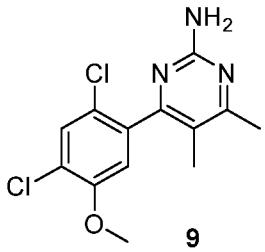
7

4-(5,7-dichloro-2,3-dihydrobenzofuran-4-yl)-6-isopropylpyrimidin-2-amine (7). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.28 (s, 1H), 6.66 (s, 1H), 5.04 (s, 2H), 4.69 (t, *J* = 9 Hz, 2H), 3.27 (t, *J* = 9 Hz, 2H), 2.87 (m, 1H), 1.28 (d, *J* = 7 Hz, 6H); LCMS $[M + H]^+$: 324.02 (calcd for $[C15H15Cl2N3O + H]^+$: 324.06).



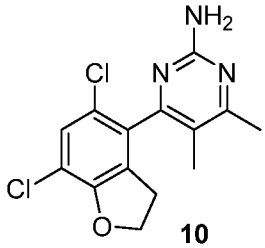
8

4-(5,7-dichloro-2,3-dihydrobenzofuran-4-yl)-6-methoxypyrimidin-2-amine (8). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.28 (s, 1H), 6.19 (s, 1H), 4.98 (s, 2H), 4.68 (t, *J* = 8.5 Hz, 2H), 3.94 (s, 3H), 3.25 (t, *J* = 9 Hz, 2H); LCMS $[M + H]^+$: 311.87 (calcd for $[C13H11Cl2N3O2 + H]^+$: 312.02).



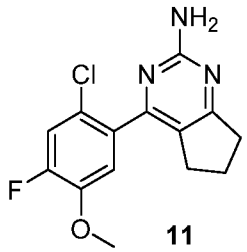
9

4-(2,4-Dichloro-5-methoxyphenyl)-5,6-dimethylpyrimidin-2-amine(9). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.47 (s, 1H), 6.83 (s, 1H), 4.88 (s, 2H), 3.90 (s, 3H), 2.42 (s, 3H), 1.95 (s, 3H).



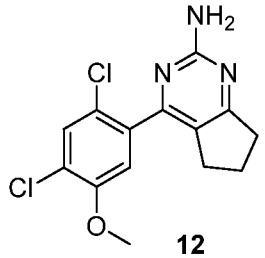
10

4-(5,7-Dichloro-2,3-dihydrobenzofuran-4-yl)-5,6-dimethylpyrimidin-2-amine(10). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.25 (s, 1H), 4.89 (s, 2H), 4.69 (t, *J* = 9 Hz, 2H), 3.25 (m, 1H), 2.88 (m, 1H), 2.42 (s, 3H), 1.93 (s, 3H).



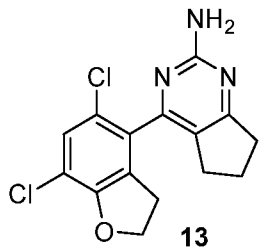
11

4-(2-chloro-4-fluoro-5-methoxyphenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine (11). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.20 (d, *J* = 10.5 Hz, 1H), 6.94(d, *J* = 9 Hz, 1H), 4.99 (s, 2H), 3.90 (s, 3H), 2.91 (t, *J* = 8 Hz, 2H), 2.72 (t, *J* = 7.5 Hz, 2H), 2.08 (m, 2H); LCMS $[M + H]^+$: 294.2 (calcd for $[C14H13ClFN3O + H]^+$: 294.07).



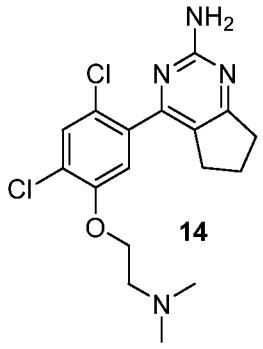
12

4-(2,4-Dichloro-5-methoxyphenyl)-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-2-amine(12). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.47 (s, 1H), 6.90 (s, 1H), 4.98 (s, 2H), 3.91 (s, 3H), 2.92 (t, *J* = 7.5 Hz, 2H), 2.72 (t, *J* = 7.5 Hz, 2H), 2.08 (m, 2H).



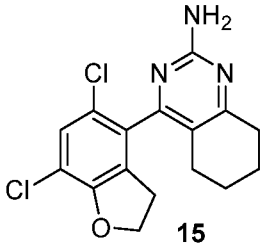
13

4-(5,7-Dichloro-2,3-dihydrobenzofuran-4-yl)-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-2-amine(13). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.25 (s, 1H), 4.69 (m, 2H), 3.38 (m, 1H), 2.99-2.81 (m, 4H), 2.49 (m, 1H), 2.17-2.00 (m, 2H).



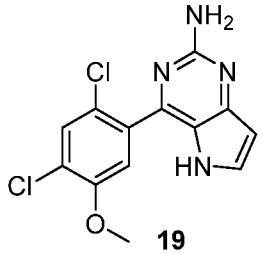
14

4-(2,4-dichloro-5-(2-(dimethylamino)ethoxy)phenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine (14). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.46 (s, 1H), 6.90 (s, 1H), 4.97 (s, 2H), 4.13 (t, *J* = 6 Hz, 2H), 2.91 (t, *J* = 8 Hz, 2H), 2.80 (t, *J* = 6 Hz, 2H),2.71 (t, *J* = 7.5 Hz, 2H), 2.36 (s, 6H), 2.08 (m, 2H); LCMS [M + H]$^+$: 367.1 (calcd for [C17H20Cl2N4O + H]$^+$: 367.10).



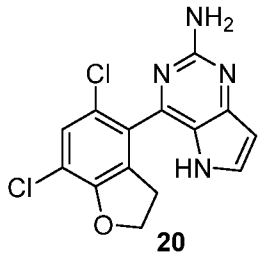
15

4-(5,7-dichloro-2,3-dihydrobenzofuran-4-yl)-5,6,7,8-tetrahydroquinazolin-2-amine (15). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.28 (s, 1H), 4.88 (s, 2H), 4.69 (t, *J* = 9 Hz, 2H), 3.21 (m, 1H), 2.89 (m, 1H), 2.78 (m, 2H), 2.44 (m, 1H), 2.15 (m, 1H), 1.86 (m, 2H), 1.72 (m, 2H); LCMS [M + H]$^+$: 336.1 (calcd for [C16H15Cl2N3O + H]$^+$: 336.06).



19

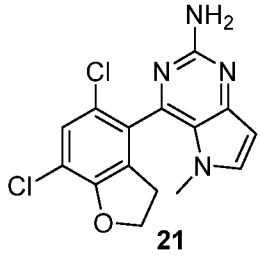
4-(2,4-Dichloro-5-methoxyphenyl)-5*H*-pyrrolo[3,2-*d*]pyrimidin-2-amine (19). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.15 (s, 1H), 7.54 (s, 1H), 7.46 (m, 1H), 7.15 (s, 1H), 6.45 (m, 1H), 4.86 (s, 2H), 3.94 (s, 3H).



20

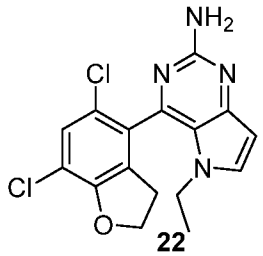
4-(5,7-Dichloro-2,3-dihydrobenzofuran-4-yl)-5*H*-pyrrolo[3,2-*d*]pyrimidin-2-amine (20). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.01 (s, 1H), 7.45 (t, *J* = 3 Hz, 1H), 7.34 (s, 1H), 6.46 (m, 1H), 4.83 (s, 2H), 4.71 (m, 2H),

3.60 (m, 1H), 2.94 (m, 1H); LCMS $[M + H]^+$: 321.0 (calcd for $[C_{14}H_{10}Cl_2N_4O + H]^+$: 321.0). The ^1H NMR spectrum is shown in Figure 1.



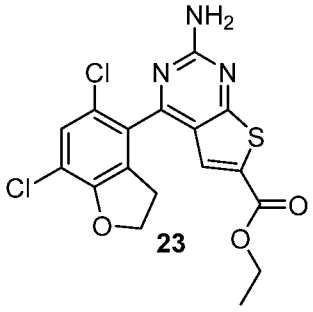
21

4-(5,7-dichloro-2,3-dihydrobenzofuran-4-yl)-5-methyl-5H-pyrrolo[3,2-d]pyrimidin-2-amine (21). ^1H NMR (500 MHz, $CDCl_3$): δ 7.32 (s, 1H), 7.22 (d, *J* = 3 Hz, 1H), 6.36(d, *J* = 3 Hz, 1H), 4.81 (s, 2H), 4.72 (m, 2H), 3.40 (s, 3H), 3.34 (m, 1H), 2.91 (m, 1H); LCMS $[M + H]^+$: 335.0 (calcd for [C15H12Cl2N4O + H]$^+$: 335.04).



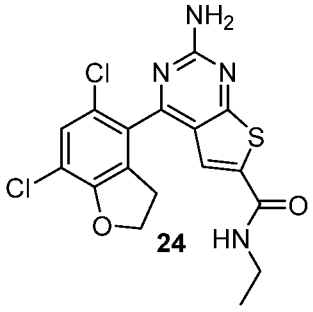
22

4-(5,7-dichloro-2,3-dihydrobenzofuran-4-yl)-5-ethyl-5H-pyrrolo[3,2-d]pyrimidin-2-amine (22). ^1H NMR (500 MHz, $CDCl_3$): δ 7.33 (m, 2H), 6.40 (d, *J* = 2.5 Hz, 1H), 4.80 (s, 2H), 4.70 (m, 2H), 3.72 (d, *J* = 7 Hz, 2H), 3.33 (m, 1H), 2.91 (m, 1H), 1.14 (t, *J* = 7.5 Hz, 3H); LCMS $[M + H]^+$: 349.1 (calcd for [C16H14Cl2N4O + H]$^+$: 349.05).



23

Ethyl-2-amino-4-(5,7-dichloro-2,3-dihydrobenzofuran-4-yl)thieno[2,3-d]pyrimidine-6-carboxylate (23). ^1H NMR (500 MHz, $CDCl_3$): δ 7.54 (s, 1H), 7.35 (s, 1H), 5.32 (s, 2H), 4.70 (m, 2H), 4.37 (m, 2H), 3.35 (m, 1H), 2.92 (m, 1H), 1.38 (t, *J* = 7 Hz, 3H); LCMS $[M + H]^+$: 410.0 (calcd for [C17H13Cl2N3O3S + H]$^+$: 410.01).

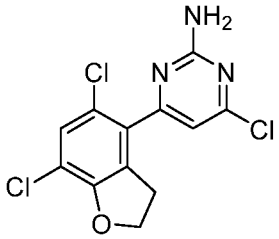


24

2-amino-4-(5,7-dichloro-2,3-dihydrobenzofuran-4-yl)-N-ethylthieno[2,3-d]pyrimidine-6-carboxamide (24). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34 (s, 1H), 7.21 (s, 1H), 5.91 (s, 1H), 5.28 (s, 2H), 4.70 (m, 2H), 4.48 (m, 2H), 3.36 (m, 1H), 2.91 (m, 1H), 1.26 (t, *J* = 3.5 Hz, 3H); LCMS $[M + H]^+$: 409.0 (calcd for $[C17H14Cl2N4O2S + H]^+$: 409.02).

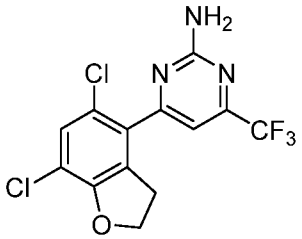
Compounds **34** and **36** were prepared according to methods known in the art, e.g., those described herein. The ^{1}H NMR spectra ($CDCl_3$) for compounds **34** and **36** are provided in Figures 2 and 3, respectively.

Compounds **40-48** can be prepared according to methods known in the art, e.g., those described herein.



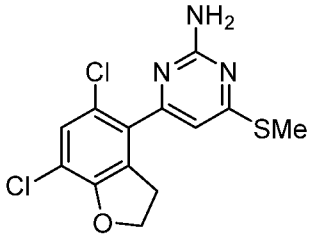
49

4-chloro-6-(5,7-dichloro-2,3-dihydrobenzofuran-4-yl)pyrimidin-2-amine (49). ^{1}H NMR (400 MHz, DMSO-d6): δ = 7.48 (s, 1 H), 7.30 (s, 2 H), 6.78 (s, 1 H), 4.64 (t, J = 8.8 Hz, 2 H), 3.20 (t, J = 8.8 Hz, 2 H). LCMS: *m/z* calcd for $C_{12}H_8Cl_3N_3O$ $[M+H]^+$: 316.0; found: 316.0.



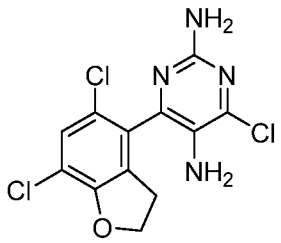
50

4-trifluoromethyl-6-(5,7-dichloro-2,3-dihydrobenzofuran-4-yl)pyrimidin-2-amine (50). ^{1}H NMR (400 MHz, DMSO-d6): δ 7.520 (br s, 2H, NH_2), 7.093 (s, 1H), 4.655 (t, 2H, J = 8.8 Hz), 3.547 (s, 1H), 3.221 (t, 2H, J = 8.8 Hz). LCMS: *m/z* calcd for $C_{13}H_8Cl_2F_3N_3O$ $[M+H]^+$: 350.1; found: 350.0.



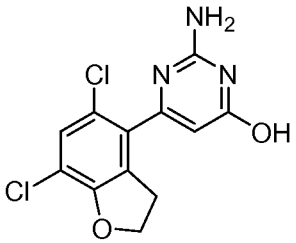
51

4-thiomethyl-6-(5,7-dichloro-2,3-dihydrobenzofuran-4-yl)pyrimidin-2-amine (51). ^{1}H NMR (400 MHz, DMSO-d6): δ 7.438 (s, 1H), 6.815 (br s, 2H, NH_2), 6.549 (s, 1H), 4.633 (t, 2H, J = 8.8 Hz), 3.178 (t, 2H, J = 8.8 Hz), 2.453 (s, 3H). LCMS: *m/z* calcd for $C_{13}H_{11}Cl_2N_3OS$ $[M+H]^+$: 328.2; found: 328.1.



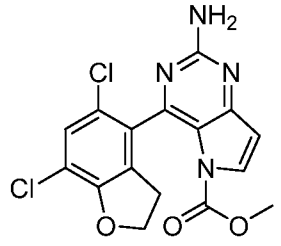
52

4-chloro-6-(5,7-dichloro-2,3-dihydrobenzofuran-4-yl)pyrimidine-2,5-diamine (52). ^{1}H NMR (400 MHz, DMSO-d6): δ = 7.46 (s, 1 H), 6.25 (s, 2 H), 4.67 (t, J = 8.8 Hz, 2 H), 4.30 (s, 2 H), 3.15-3.07 m, 2 H). HPLC/MS: *m/z* calcd for $C_{12}H_9Cl_3N_4O$ $[M+H]^+$: 331.0; found: 331.1.



53

2-amino-6-(5,7-dichloro-2,3-dihydrobenzofuran-4-yl)pyrimidin-4-ol (53). To a flask containing dioxane:1 N NaOH aq. (50:50; 1 mL:1 mL) were added 4-chloro-6-(5,7-dichloro-2,3-dihydrobenzofuran-4-yl)pyrimidin-2-amine (49) (20 mg, 0.063 mmol), and DABCO (8 mg, 0.069 mmol), at rt. The reaction was subsequently heated at 80 °C. The reaction was cooled down, acidified by addition of 1 N HCl aq. (2 mL), taken up in ethyl acetate (5 mL) and washed with brine (3 × 5 mL). The organic layer was dried over Na_2SO_4, filtered, and volatiles were evaporated. The residue was purified by silica gel chromatography using a gradient of DCM:MeOH (100:0 to 90:10). The product was obtained in 77 % yield as a white solid. ^{1}H NMR (400 MHz, DMSO-d6): δ = 7.39 (s, 1 H), 5.57 (s, 1 H), 4.62 (t, J = 8.8 Hz, 2 H), 3.20 (t, J = 8.8 Hz, 2 H). HPLC/MS: *m/z* calcd for $C_{12}H_9Cl_2N_3O_2$ $[M+H]^+$: 298.0; found: 298.1.

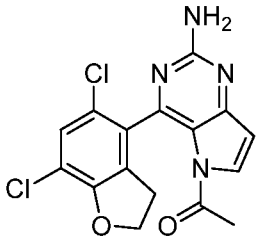


54

Methyl 2-amino-4-(5,7-dichloro-2,3-dihydrobenzofuran-4-yl)-5H-pyrrolo[3,2-d]pyrimidine-5-carboxylate (54). To a flask containing 4-(5,7-dichloro-2,3-dihydrobenzofuran-4-yl)-5H-pyrrolo[3,2-d]pyrimidin-2-amine (20) (20 mg, 0.062 mmol) in DCM (1 mL) were added dry K_2CO_3 (30 mg, 0.22 mmol),

and methyl chloroformate (0.014 mL, 0.186 mmol), at 0 °C. The reaction was allowed to stir for 8 h at rt. Afterwards, the reaction was quenched by addition of 1 N NaOH aq. (1 mL) and stirred at rt for 1 h. The reaction was taken up in DCM (10 mL) and washed with sat. $NaHCO_3$ aq. (10 mL). The organic layer was dried over Na_2SO_4, filtered, and volatiles were evaporated. The residue was purified by silica gel chromatography using a gradient of DCM:MeOH (100:0 to 90:10). The product was obtained in 66 % yield as a yellow solid.

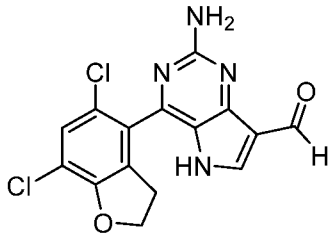
^{1}H NMR (400 MHz, CDCl3): δ = 7.61 (s, 1 H), 7.23 (s, 1 H), 6.51 (s, 1 H), 4.63 (br s, 2 H), 3.77 (s, 3 H), 3.65 (br s, 1 H), 2.85 (br s, 1 H). HPLC/MS: *m/z* calcd for $C_{16}H_{12}Cl_2N_4O_3$ $[M+H]^+$: 379.0; found: 379.1.



55

1-(2-amino-4-(5,7-dichloro-2,3-dihydrobenzofuran-4-yl)-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethan-1-one (55). To a flask containing 4-(5,7-dichloro-2,3-dihydrobenzofuran-4-yl)-5H-pyrrolo[3,2-d]pyrimidin-2-amine (20 mg, 0.062 mmol) in DCM (1 mL) were added dry K_2CO_3 (30 mg, 0.22 mmol), and acetyl chloride (0.006 mL, 0.074 mmol), at 0 °C. The reaction was allowed to stir for 8 h at rt. Afterwards, the reaction was quenched by addition of 1 N NaOH aq. (1 mL) and stirred at rt for 1 h. The reaction was taken up in DCM (10 mL) and washed with sat. $NaHCO_3$ aq. (10 mL). The organic layer was dried over Na_2SO_4, filtered, and volatiles were evaporated. The residue was purified by silica gel chromatography using a gradient of DCM:MeOH (100:0 to 90:10). The product was obtained in 81 % yield as a yellow solid.

^{1}H NMR (400 MHz, CDCl3): δ = 7.57 (s, 1 H), 7.23 (s, 1 H), 6.55 (s, 1 H), 4.63 (br s, 2 H), 3.45 (br s, 1 H), 3.35 (s, 3 H), 2.85 (br s, 1 H). HPLC/MS: *m/z* calcd for $C_{16}H_{12}Cl_2N_4O_2$ $[M+H]^+$: 363.0; found: 363.1.

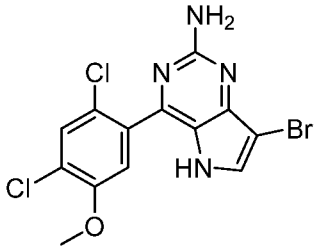


56

2-amino-4-(5,7-dichloro-2,3-dihydrobenzofuran-4-yl)-5H-pyrrolo[3,2-d]pyrimidine-7-carbaldehyde (56). To a flask containing dry THF (2 mL), were added dry DMF (0.1 mL) and $POCl_3$ (0.015 mL, 0.16 mmol), at 0 °C. Reaction was stirred at 0 °C for 30 min, under argon, upon which 4-(5,7-dichloro-2,3-dihydrobenzofuran-4-yl)-5H-pyrrolo[3,2-d]pyrimidin-2-amine (20 mg, 0.062 mmol) in THF (1 mL) was added dropwise. The reaction was allowed to stir for 8 h warming to rt. To the reaction was then added 1 N NaOH aq. (2 mL) and heated to 80 °C for 1 h. The reaction was cooled to rt and taken up in EtOAc (20 mL) and washed with sat. $NaHCO_3$ aq. (20 mL). The organic layer was dried over Na_2SO_4, filtered, and

volatiles were evaporated. The residue was purified by silica gel chromatography using a gradient of DCM:MeOH (100:0 to 90:10). The product was obtained in 58 % yield as a white solid.

^{1}H NMR (400 MHz, CDCl3): δ = 10.05 (s, 1 H), 7.96 (s, 1 H), 7.24 (s, 1 H), 4.63 (br s, 2 H), 3.31 (br s, 1 H), 2.85 (br s, 1 H). HPLC/MS: *m/z* calcd for $C_{15}H_{10}Cl_2N_4O_2$ $[M+H]^+$: 349.0; found: 349.1.

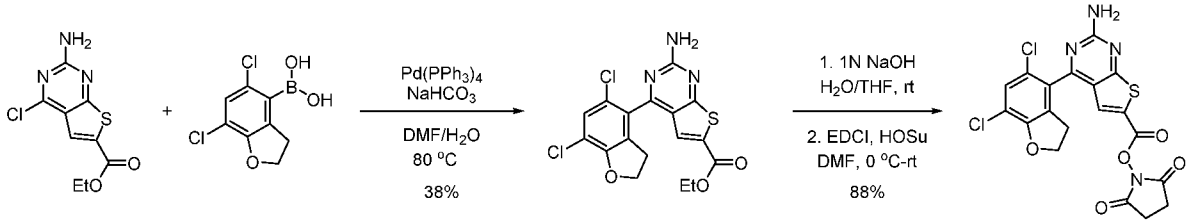


57

7-bromo-4-(2,4-dichloro-5-methoxyphenyl)-5H-pyrrolo[3,2-d]pyrimidin-2-amine (57). To a flask containing 4-(2,4-dichloro-5-methoxyphenyl)-5H-pyrrolo[3,2-d]pyrimidin-2-amine (20 mg, 0.065 mmol) in AcOH:tBuOH (50:50, 0.5 mL:0.5 mL) were added LiBr (18 mg, 0.22 mmol), and Br_2 (0.011 mL, 0.22 mmol), at 0 °C. The reaction was allowed to stir for 8 h at rt. Afterwards, the reaction was taken up in EtOAc (20 mL) and washed with sat. $NaHCO_3$ aq. (3 × 20 mL), and $Na_2S_2O_3$ (10 % wt. aq., 20 mL). The organic layer was dried over Na_2SO_4, filtered, and volatiles were evaporated. The residue was purified by silica gel chromatography using a gradient of DCM:MeOH (100:0 to 90:10). The product was obtained in 56 % yield as a yellow solid.

^{1}H NMR (400 MHz, DMSO-d6): δ = 7.75 (s, 1 H), 7.72 (s, 1 H), 7.26 (s, 1 H), 6.24 (s, 2 H), 3.86 (s, 3 H). HPLC/MS: *m/z* calcd for $C_{13}H_9BrCl_2N_4O$ $[M+H]^+$: 386.9; found: 387.0.

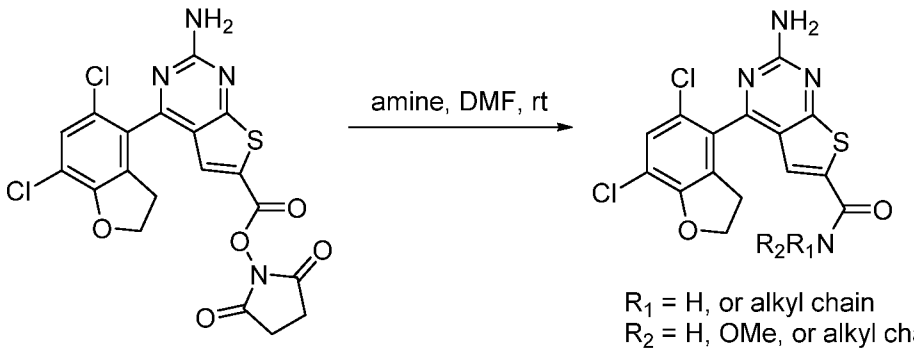
General procedure for synthesis of 2-amino-4-(5,7-dichloro-2,3-dihydrobenzofuran-4-yl)thieno[2,3-d]pyrimidine-6-carboxamides:



Step 1: Synthesis of precursor 2,5-dioxopyrrolidin-1-yl 2-amino-4-(5,7-dichloro-2,3-dihydrobenzofuran-4-yl)thieno[2,3-d]pyrimidine-6-carboxylate. To a flask containing degassed DMF:H_2O (50:50; 2 mL:2 mL) were added ethyl 2-amino-4-chlorothieno[2,3-d]pyrimidine-6-carboxylate (100 mg, 0.39 mmol), (5,7-dichloro-2,3-dihydrobenzofuran-4-yl)boronic acid (91 mg, 0.39 mmol), $NaHCO_3$ (82 mg, 0.98 mmol), and $Pd(PPh_3)_4$ (22 mg, 0.02 mmol), at rt. The reaction was subsequently heated at 80 °C for 8 h under argon. The reaction was cooled down, taken up in ethyl acetate (20 mL) and washed with brine (3 × 20 mL). The organic layer was dried over Na_2SO_4, filtered, and volatiles were evaporated. The residue was purified by silica gel chromatography using a gradient of DCM:MeOH (100:0 to 90:10). The product ethyl 2-amino-4-(5,7-dichloro-2,3-dihydrobenzofuran-4-yl)thieno[2,3-d]pyrimidine-6-carboxylate was obtained in 38 % yield as a yellow solid.

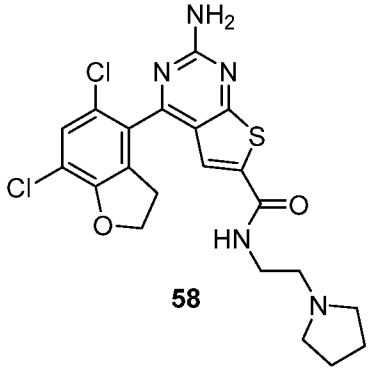
Ethyl 2-amino-4-(5,7-dichloro-2,3-dihydrobenzofuran-4-yl)thieno[2,3-d]pyrimidine-6-carboxylate (60 mg, 0.15 mmol) was dissolved in THF (1 mL) and to the flask was added 1 N NaOH aq. (1 mL). The reaction was stirred for 8 h at rt. Subsequently, the solution was cooled to 0 °C and acidified by addition of 1 N HCl aq. (2 mL), resulting in formation of white precipitate, which was filtered and dried, affording 2-amino-4-(5,7-dichloro-2,3-dihydrobenzofuran-4-yl)thieno[2,3-d]pyrimidine-6-carboxylic acid in quantitative yield, without further purification. The filtrand (57 mg, 0.15 mmol) was dissolved in dry DMF (1 mL), cooled to 0 °C, and to the reaction vessel were added N-hydroxysuccinimide (23 mg, 0.2 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide HCl (38 mg, 0.2 mmol). The reaction was left to stir warming to rt over 8h. The solution was taken up into DCM (20 mL) and washed with sat. NH_4Cl aq. (3 × 20 mL). The organic layer was dried over Na_2SO_4, filtered, and volatiles were evaporated. The residue was purified by silica gel chromatography using a gradient of DCM:MeOH (100:0 to 90:10). The product 2,5-dioxopyrrolidin-1-yl 2-amino-4-(5,7-dichloro-2,3-dihydrobenzofuran-4-yl)thieno[2,3-d]pyrimidine-6-carboxylate was obtained as a white solid in 88% yield.

Step 2: General procedure for formation of amides:



R_1 = H, or alkyl chain
R_2 = H, OMe, or alkyl chain

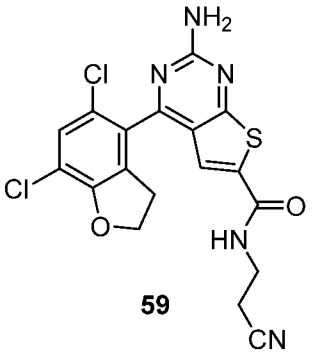
To a flask containing the 2,5-dioxopyrrolidin-1-yl 2-amino-4-(5,7-dichloro-2,3-dihydrobenzofuran-4-yl)thieno[2,3-d]pyrimidine-6-carboxylate (10 mg, 0.02 mmol) was added dry DMF (0.5 mL), followed by addition of an amine (3 eq., 0.06 mmol), (e.g. ammonia, primary amine, or secondary amine). The reaction was allowed to stir at rt for 12 h, upon which it was taken up in DCM (5 mL) and washed with sat. NH_4Cl aq. (3 × 5 mL). The organic layer was dried over Na_2SO_4, filtered, and volatiles were evaporated. The residue was purified by silica gel chromatography using a gradient of DCM:MeOH (100:0 to 90:10). The resulting amides were obtained in good to excellent yields.



58

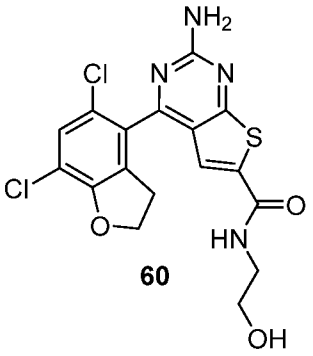
2-amino-4-(5,7-dichloro-2,3-dihydrobenzofuran-4-yl)-N-(2-(pyrrolidin-1-yl)ethyl)thieno[2,3-d]pyrimidine-6-carboxamide (58). ^{1}H NMR (400 MHz, DMSO-d6): δ = 8.79 (s, 1 H), 7.61 (s, 1H), 7.58

(s, 1 H), 7.28 (s, 2 H), 4.67 (t, J = 8.8 Hz, 2 H), 3.44-3.11 (m, 6 H), 2.90-2.75 (m, 4 H), 1.77-1.73 (m, 4 H). HPLC/MS: *m/z* calcd for $C_{21}H_{21}Cl_2N_5O_2S$ $[M+H]^+$: 478.1; found: 478.1



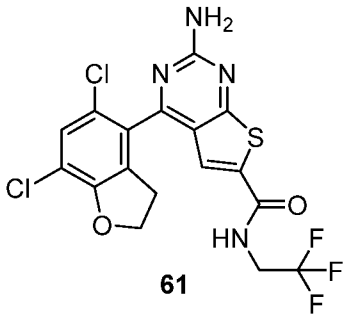
59

2-amino-N-(2-cyanoethyl)-4-(5,7-dichloro-2,3-dihydrobenzofuran-4-yl)thieno[2,3-d]pyrimidine-6-carboxamide (59). ^{1}H NMR (400 MHz, DMSO-d6): δ = 8.94 (t, J = 5.6 Hz, 1 H), 7.63 (s, 1H), 7.60 (s, 1 H), 7.34 (s, 2 H), 4.69 (t, J = 8.8 Hz, 2 H), 3.46-3.41 (m, 2 H), 3.23-3.15 (m, 1 H), 3.03-2.97 (m, 1 H), 2.76 (t, J = 6.4 Hz, 2 H). HPLC/MS: *m/z* calcd for $C_{18}H_{13}Cl_2N_5O_2S$ $[M+H]^+$: 434.0; found: 434.1.



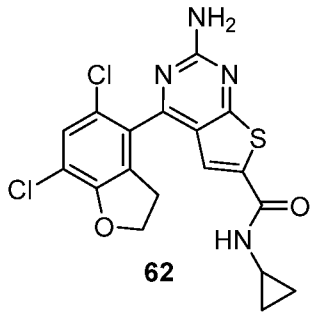
60

2-amino-4-(5,7-dichloro-2,3-dihydrobenzofuran-4-yl)-N-(2-hydroxyethyl)thieno[2,3-d]pyrimidine-6-carboxamide (60). ^{1}H NMR (400 MHz, DMSO-d6): δ = 8.57 (t, J = 5.6 Hz, 1 H), 7.59 (s, 2 H), 7.26 (s, 2 H), 4.73 (t, J = 5.6 Hz, 1 H), 4.67 (t, J = 8.8 Hz, 2 H), 3.46-3.41 (m, 2 H), 3.26-3.12 (m, 3 H), 3.03-2.94 (m, 1 H). HPLC/MS: *m/z* calcd for $C_{17}H_{14}Cl_2N_4O_3S$ $[M+H]^+$: 425.0; found: 425.1.



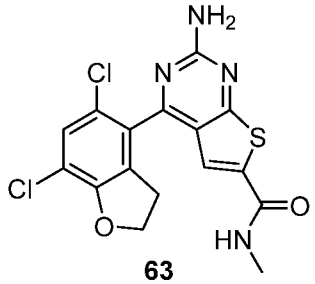
61

2-amino-4-(5,7-dichloro-2,3-dihydrobenzofuran-4-yl)-N-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidine-6-carboxamide (61). ^{1}H NMR (400 MHz, DMSO-d6): δ = 9.18 (t, J = 6.0 Hz, 1 H), 7.72 (s, 1 H), 7.63 (s, 1 H), 7.38 (s, 2 H), 4.69 (t, J = 8.8 Hz, 2 H), 4.12-4.03 (m, 2 H), 3.26-3.18 (m, 1 H), 3.03-2.94 (m, 1 H). HPLC/MS: *m/z* calcd for $C_{17}H_{11}Cl_2F_3N_4O_2S$ $[M+H]^+$: 463.0; found: 463.1.



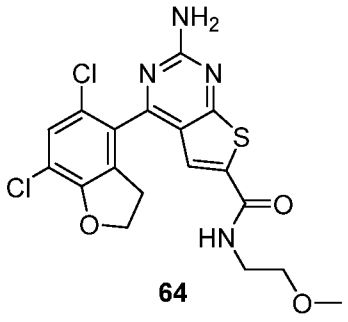
62

2-amino-N-cyclopropyl-4-(5,7-dichloro-2,3-dihydrobenzofuran-4-yl)thieno[2,3-d]pyrimidine-6-carboxamide (62). ^{1}H NMR (400 MHz, DMSO-d6): δ = 8.54 (s, 1 H), 7.61 (s, 1 H), 7.53 (s, 1 H), 7.29 (s, 2 H), 4.68 (t, J = 8.8 Hz, 2 H), 3.26-3.18 (m, 1 H), 3.03-2.94 (m, 1 H), 2.81-2.71 (m, 1 H), 0.75-0.61 (m, 2 H), 0.55-0.40 (m, 2H). HPLC/MS: *m/z* calcd for $C_{18}H_{14}Cl_2N_4O_2S$ $[M+H]^+$: 421.0; found: 421.1.



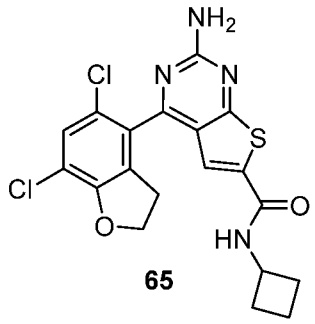
63

2-amino-4-(5,7-dichloro-2,3-dihydrobenzofuran-4-yl)-N-methylthieno[2,3-d]pyrimidine-6-carboxamide (63). ^{1}H NMR (400 MHz, DMSO-d6): δ = 8.62-8.59 (m, 1 H), 7.61 (s, 2 H), 7.27 (s, 2 H), 4.64 (t, J = 8.8 Hz, 2 H), 3.24 (s, 3 H), 3.23-3.18 (m, 1 H), 3.03-2.91 (m, 1 H). HPLC/MS: *m/z* calcd for $C_{16}H_{12}Cl_2N_4O_2S$ $[M+H]^+$: 395.0; found: 395.1.



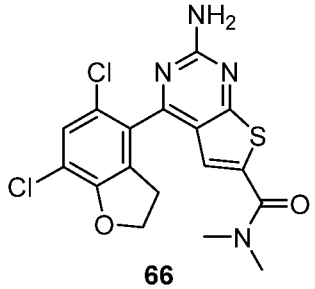
64

2-amino-4-(5,7-dichloro-2,3-dihydrobenzofuran-4-yl)-N-(2-methoxyethyl)thieno[2,3-d]pyrimidine-6-carboxamide (64). ^{1}H NMR (400 MHz, DMSO-d6): δ = 8.51-8.41 (m, 1 H), 7.59 (s, 1 H), 7.50 (s, 1 H), 7.26 (s, 2 H), 4.67 (t, J = 8.8 Hz, 2 H), 3.23-3.10 (m, 4 H), 3.03-2.91 (m, 2 H), 2.72-2.67 (m, 3 H). HPLC/MS: *m/z* calcd for $C_{18}H_{16}Cl_2N_4O_3S$ $[M+H]^+$: 439.0; found: 439.1.



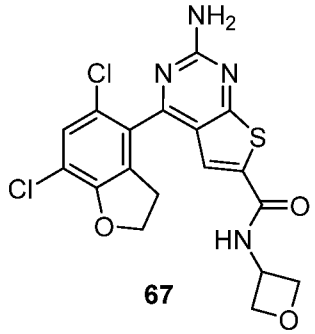
65

2-amino-N-cyclobutyl-4-(5,7-dichloro-2,3-dihydrobenzofuran-4-yl)thieno[2,3-d]pyrimidine-6-carboxamide (65). ^{1}H NMR (400 MHz, DMSO-d6): δ = 8.68 (d, J = 6.8 Hz, 1 H), 7.61 (s, 1 H), 7.56 (s, 1 H), 7.26 (s, 2 H), 4.67 (t, J = 8.8 Hz, 2 H), 4.33-4.26 (m, 1 H), 3.23-3.18 (m, 1 H), 3.03-2.91 (m, 1 H), 2.16-1.92 (m, 2 H), 1.70-1.60 (m, 1H), 1.33-1.20 (m, 2 H), 0.90-0.78 (m, 1 H). HPLC/MS: *m/z* calcd for $C_{19}H_{16}Cl_2N_4O_2S$ $[M+H]^+$: 435.0; found: 435.1.



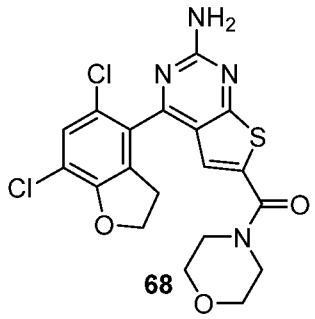
66

2-amino-4-(5,7-dichloro-2,3-dihydrobenzofuran-4-yl)-N,N-dimethylthieno[2,3-d]pyrimidine-6-carboxamide (66). ^{1}H NMR (400 MHz, DMSO-d6): δ = 7.54 (s, 1 H), 7.23 (s, 2 H), 7.15 (s, 1 H), 4.66 (t, J = 8.8 Hz, 2 H), 3.31 (s, 3 H), 3.23-2.90 (m, 5 H). HPLC/MS: *m/z* calcd for $C_{17}H_{14}Cl_2N_4O_2S$ $[M+H]^+$: 409.0; found: 409.1.



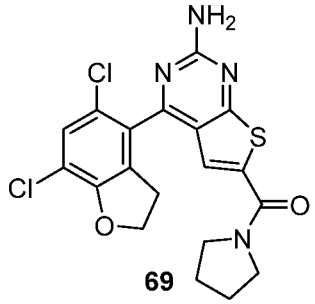
67

2-amino-4-(5,7-dichloro-2,3-dihydrobenzofuran-4-yl)-N-(oxetan-3-yl)thieno[2,3-d]pyrimidine-6-carboxamide (67). ^{1}H NMR (400 MHz, DMSO-d6): δ = 9.17 (d, J = 6.8 Hz, 1 H), 7.64 (s, 1 H), 7.62 (s, 1 H), 7.31 (s, 2 H), 4.97-4.90 (m, 1 H), 4.75-4.65 (m, 4 H), 4.55-4.45 (m, 2 H), 3.20-3.11 (m, 1 H), 3.02-2.92 (m, 1 H). HPLC/MS: *m/z* calcd for $C_{18}H_{14}Cl_2N_4O_3S$ $[M+H]^+$: 437.0; found: 437.1.



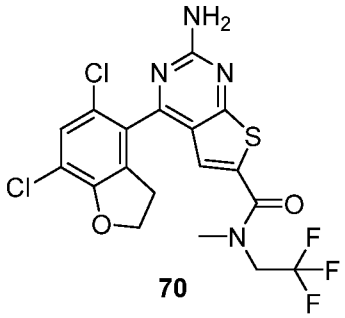
68

(2-amino-4-(5,7-dichloro-2,3-dihydrobenzofuran-4-yl)thieno[2,3-d]pyrimidin-6-yl)(morpholino)methanone (68). ^{1}H NMR (400 MHz, DMSO-d6): δ = 7.54 (s, 1 H), 7.23 (s, 2 H), 7.12 (s, 1 H), 4.66 (t, J = 8.8 Hz, 2 H), 3.59 (br s, 8 H), 3.26-3.21 (m, 1 H), 3.02-2.92 (m, 1 H). HPLC/MS: *m/z* calcd for $C_{19}H_{16}Cl_2N_4O_3S$ $[M+H]^+$: 451.0; found: 451.1.



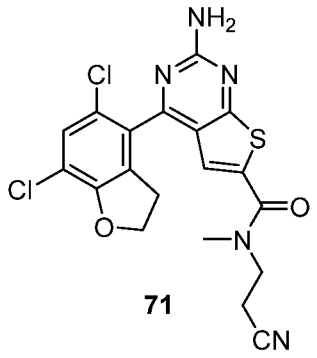
69

(2-amino-4-(5,7-dichloro-2,3-dihydrobenzofuran-4-yl)thieno[2,3-d]pyrimidin-6-yl)(pyrrolidin-1-yl)methanone (69). ^{1}H NMR (400 MHz, DMSO-d6): δ = 7.54 (s, 1 H), 7.23 (s, 2 H), 7.21 (s, 1 H), 4.66 (t, J = 8.8 Hz, 2 H), 3.68-3.64 (m, 2 H), 3.44 (br s, 2 H), 3.26-3.16 (m, 1 H), 3.02-2.92 (m, 1 H), 1.91-1.76 (m, 4 H). HPLC/MS: *m/z* calcd for $C_{19}H_{16}Cl_2N_4O_2S$ $[M+H]^+$: 435.0; found: 435.1.



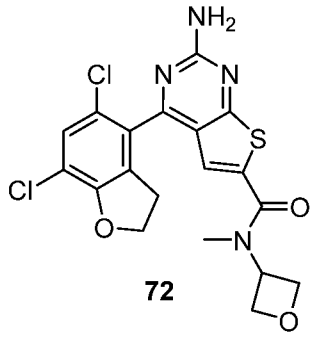
70

2-amino-4-(5,7-dichloro-2,3-dihydrobenzofuran-4-yl)-N-methyl-N-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidine-6-carboxamide (70). ^{1}H NMR (400 MHz, DMSO-d6): δ = 7.54 (s, 1 H), 7.33 (s, 3 H), 4.66 (t, J = 8.8 Hz, 2 H), 4.41-4.28 (m, 2 H), 3.27 (s, 3 H), 3.26-3.16 (m, 1 H), 3.02-2.92 (m, 1 H). HPLC/MS: *m/z* calcd for $C_{18}H_{13}Cl_2F_3N_4O_2S$ $[M+H]^+$: 477.0; found: 477.1.



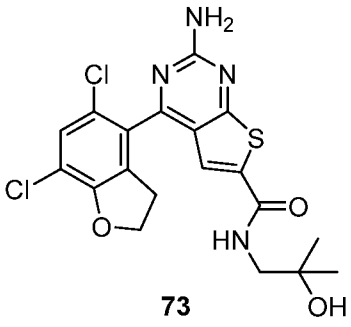
71

2-amino-N-(2-cyanoethyl)-4-(5,7-dichloro-2,3-dihydrobenzofuran-4-yl)-N-methylthieno[2,3-d]pyrimidine-6-carboxamide (71). ^{1}H NMR (400 MHz, DMSO-d6): δ = 7.54 (s, 1 H), 7.28 (s, 2 H), 7.20 (s, 1 H), 4.66 (t, J = 8.8 Hz, 2 H), 3.69 (br s, 2 H), 3.26-3.16 (m, 4 H), 3.02-2.92 (m, 1 H), 2.82-2.70 (m, 2 H). HPLC/MS: *m/z* calcd for $C_{19}H_{15}Cl_2N_5O_2S$ $[M+H]^+$: 448.0; found: 448.1.



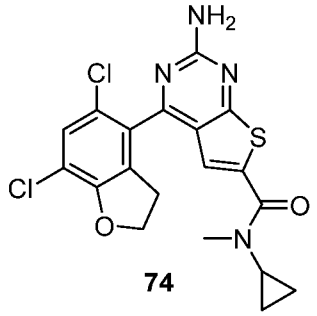
72

2-amino-4-(5,7-dichloro-2,3-dihydrobenzofuran-4-yl)-N-methyl-N-(oxetan-3-yl)thieno[2,3-d]pyrimidine-6-carboxamide (72). ^{1}H NMR (400 MHz, DMSO-d6): δ = 7.55 (s, 1 H), 7.26 (s, 2 H), 7.16 (s, 1 H), 5.21-5.16 (m, 1 H), 4.69-4.60 (m, 6 H), 3.26-3.14 (m, 4 H), 3.02-2.92 (m, 1 H). HPLC/MS: *m/z* calcd for $C_{19}H_{16}Cl_2N_4O_3S$ $[M+H]^+$: 451.0; found: 451.1.



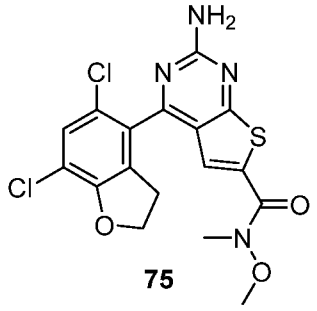
73

2-amino-4-(5,7-dichloro-2,3-dihydrobenzofuran-4-yl)-N-(2-hydroxy-2-methylpropyl)thieno[2,3-d]pyrimidine-6-carboxamide (73). ^{1}H NMR (400 MHz, DMSO-d6): δ = 8.44 (s, 1 H), 7.69 (s, 1 H), 7.59 (s, 1 H), 7.23 (s, 2 H), 4.67 (t, J = 8.8 Hz, 2 H), 4.45 (s, 1 H), 3.21-3.12 (m, 3 H), 3.02-2.92 (m, 1 H), 1.04 (s, 6 H). HPLC/MS: *m/z* calcd for $C_{19}H_{18}Cl_2N_4O_3S$ $[M+H]^+$: 453.0; found: 453.1.



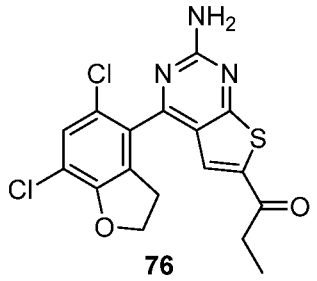
74

2-amino-N-cyclopropyl-4-(5,7-dichloro-2,3-dihydrobenzofuran-4-yl)-N-methylthieno[2,3-d]pyrimidine-6-carboxamide (74). ^{1}H NMR (400 MHz, DMSO-d6): δ = 7.55 (s, 1 H), 7.36 (s, 1 H), 7.28 (s, 2 H), 4.70-4.62 (m, 2 H), 3.13-3.06 (m, 1 H), 3.00-2.91 (m, 4 H), 0.80-0.72 (m, 2 H), 0.68-0.63 (m, 2 H). HPLC/MS: *m/z* calcd for $C_{19}H_{16}Cl_2N_4O_2S$ $[M+H]^+$: 435.0; found: 435.1.



75

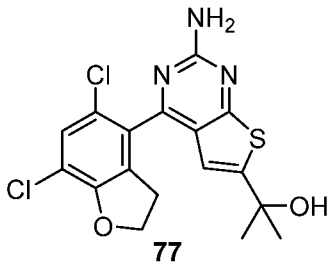
2-amino-4-(5,7-dichloro-2,3-dihydrobenzofuran-4-yl)-N-methoxy-N-methylthieno[2,3-d]pyrimidine-6-carboxamide (75). ^{1}H NMR (400 MHz, DMSO-d6): δ = 7.57 (s, 1 H), 7.47 (s, 1 H), 7.37 (s, 2 H), 4.70-4.62 (m, 2 H), 3.74 (s, 3 H), 3.27-3.19 (m, 4 H), 3.00-2.91 (m, 1 H). HPLC/MS: *m/z* calcd for $C_{17}H_{14}Cl_2N_4O_3S$ $[M+H]^+$: 425.0; found: 425.1.



76

1-(2-amino-4-(5,7-dichloro-2,3-dihydrobenzofuran-4-yl)thieno[2,3-d]pyrimidin-6-yl)propan-1-one (76). To a flask containing 2-amino-4-(5,7-dichloro-2,3-dihydrobenzofuran-4-yl)-N-methoxy-N-methylthieno[2,3-d]pyrimidine-6-carboxamide (20 mg, 0.048 mmol) in dry THF (1 mL), was added EtMgBr (2.0 M in THF; 0.029 mL, 0.057 mmol), at 0 °C. The reaction was stirred for 8 h, upon which it was quenched by addition of sat. NH_4Cl aq (1 mL). The aqueous layer was extracted with EtOAc (3 × 2 mL), dried over Na_2SO_4, filtered, and volatiles were evaporated. The residue was purified by silica gel chromatography using a gradient of DCM:MeOH (100:0 to 90:10). The product was obtained in 91 % yield as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41 (s, 1 H), 7.34 (s, 1 H), 5.84 (br s, 2 H), 4.74-4.64 (m, 2 H), 3.87-3.76 (m, 1 H), 3.30-3.10 (m, 3 H), 1.50-1.41 (m, 3 H). HPLC/MS: *m/z* calcd for $C_{17}H_{13}Cl_2N_3O_2S$ $[M+H]^+$: 394.0; found: 394.1.



77

2-(2-amino-4-(5,7-dichloro-2,3-dihydrobenzofuran-4-yl)thieno[2,3-d]pyrimidin-6-yl)propan-2-ol (77). To a flask containing ethyl 2-amino-4-(5,7-dichloro-2,3-dihydrobenzofuran-4-yl)thieno[2,3-d]pyrimidine-6-carboxylate (20 mg, 0.048 mmol) in dry THF (1 mL), was added MeMgBr (2.0 M in THF; 0.072 mL, 0.144 mmol), at 0 °C. The reaction was stirred for 8 h, upon which it was quenched by addition of sat. NH_4Cl aq (1 mL). The aqueous layer was extracted with EtOAc (3 × 2 mL), dried over Na_2SO_4, filtered, and volatiles were evaporated. The residue was purified by silica gel chromatography using a gradient of DCM:MeOH (100:0 to 90:10). The product was obtained in 78 % yield as a white solid.

^{1}H NMR (400 MHz, DMSO-d6): δ = 7.53 (s, 1 H), 6.85 (s, 2 H), 6.54 (s, 1 H), 5.95 (s, 1 H), 4.64 (t, *J* = 8.8 Hz, 2 H), 3.20-3.12 (m, 1 H), 3.00-2.90 (m, 1 H), 1.46 (s, 3 H), 1.44 (s, 3H). HPLC/MS: *m/z* calcd for $C_{17}H_{15}Cl_2N_3O_2S$ $[M+H]^+$: 396.0; found: 396.1.

Example 2. In Vitro Assays of the Compounds of the Invention

Hsp90 biochemical assay (fluorescence polarization)

Hsp90 inhibitory activity of the compounds of the invention was assessed using a fluorescence polarization (FP) assay using FITC-labeled geldanamycin and truncated alpha-Hsp90 protein. Measurement of binding activity was performed on BMG CLARIOstar® reader (BMG Labtech, Ortenberg, Germany). This assay is homogeneous and is performed in 384-well plates performing consistently with known standards. The assay was validated with known Hsp90 inhibitors, e.g., PU-H71 (IC_{50} = 60 nM), which is in agreement with the reported IC_{50} (Luo et al., *supra*). The results of this assay for compounds **20**, **36**, **37**, and **39** and for the known Hsp90 inhibitor are shown in Figure 4.

Hsp90 biochemical assay (AlphaLISA)

Hsp90 inhibitory activity of the compounds of the invention was assessed using a robust and reproducible assay based on the AlphaLISA format was developed (PerkinElmer, Inc., Waltham, MA; the format of the assay is described in, e.g., *ELISA to AlphaLISA Conversion Guide*, PerkinElmer, Inc., published in August, 2012). This assay employs biotinylated geldanamycin, His-tagged-Hsp90, and Ni^{+2} coated beads. This assay is homogenous and miniaturized to 384-well plates. Measurement of binding activity was performed on an Envision reader. The assay was validated with known Hsp90 inhibitors, including PU-H71 (IC_{50} = 60 nM) which is in agreement with the reported IC_{50} (Luo et al., *supra*). This assay is the primary assay for evaluating compounds of the invention. In this assay, compound **20** showed Hsp90 inhibitory activity (IC_{50} of 0.74 ± 0.1 μM; see Figure 5A).

Hsp90 cell based functional assays

Cells were treated with compounds of the invention for 24 h and then lysed in a buffer containing NP-40, orthovanadate, and protease inhibitors. Western blots were performed with antibodies specific to Hsp70, Hsp90, or actin (as control). Tau phosphorylation was assayed using, e.g., a method of Liu et al., *Biochemistry*, 49:4921-4929, 2010, with SHSY5Y-hTau441V337M/R406W cell line (Loeffler et al., *J. Mol. Neurosci.*, 47:192-203, 2012). This cell line represents stable transfected cell line that has been shown to have hyper-phosphorylated tau by over-express the longest human tau isoform, hTAU441 with two mutations: V337M and R406W. The functional assay described herein provides an in vitro model of tauopathy and can be used to evaluate the effect of Hsp90 inhibitors on phosphorylated tau protein (p-Tau). In these assays, compound **20** showed increase in the expression of Hsp70 (see Figure 5B), significant decreases in the levels of pTau231 at 0.1 and 0.5 μM (see Figure 6B), and significant decreases in the levels of pTau396 at 0.05, 0.1, and 0.5 μM (see Figure 6C).

Cytotoxicity assays

SH-SY5Y-hTAU441 cell viability was determined using the MTT assay. As shown in Figure 6A, compound **20** did not affect cell viability of SH-SY5Y-hTAU441 cells. SH-SY5Y cell viability may also be measured after 24 and 48 h with the CellTiter-Glo® assay that measures ATP-levels. In addition, cytotoxicity may be assessed using the Celigo® with live cell microscopic imaging and a GE InCell Analyzer 2000 to measure multiple outcomes including apoptosis markers, membrane permeability, and mitochondrial activity.

Mouse liver microsomal stability

Metabolic stability of the compounds of the invention was assessed by monitoring their degradation in mouse liver microsomes. Compound **20** demonstrated good microsomal stability ($T_{1/2}$ = 26 min).

Solubility

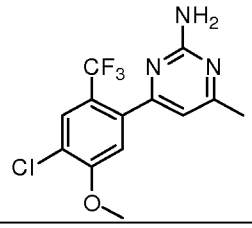
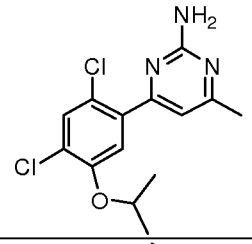
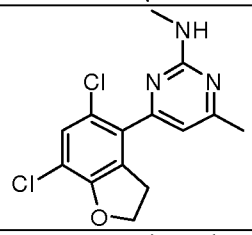
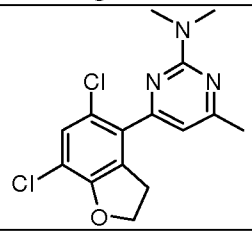
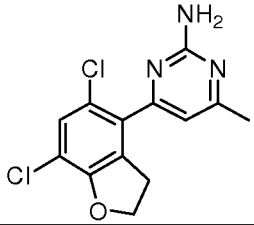
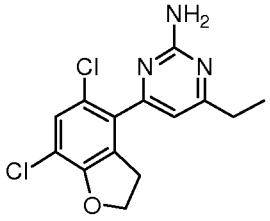
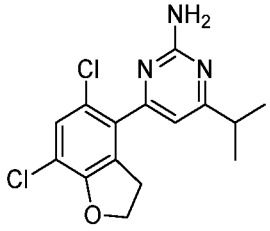
Compound solubility was determined in pH 7.4 buffer. Aqueous solubility of greater than or equal to about 0.5 μM (e.g., greater than or equal to about 1 μM, greater than or equal to about 2 μM, greater than or equal to about 5 μM, greater than or equal to about 10 μM, greater than or equal to about 20 μM, or greater than or equal to about 30 μM) may indicate a compound having acceptable solubility for medical use, e.g., for treatment of a neurodegenerative disorder. At pH of 7.4, compound **20** exhibits an aqueous solubility of 30 μM.

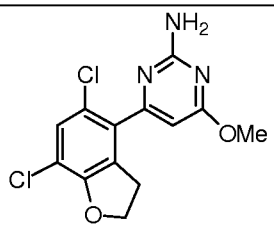
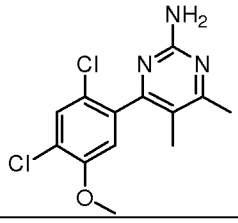
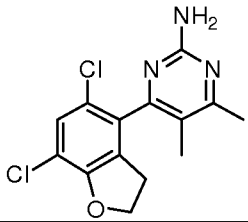
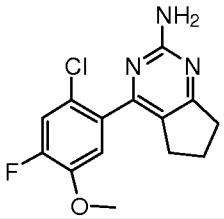
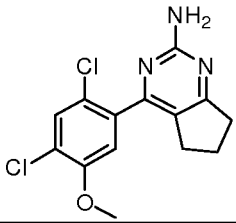
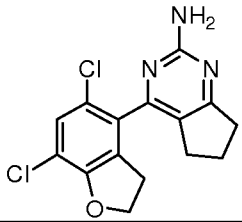
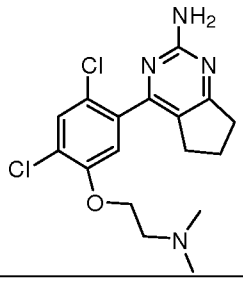
Cell permeability

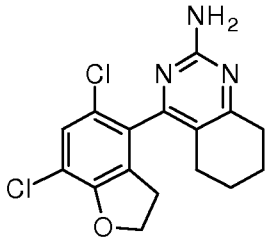
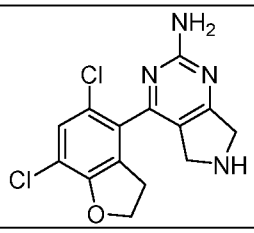
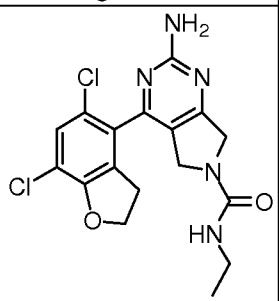
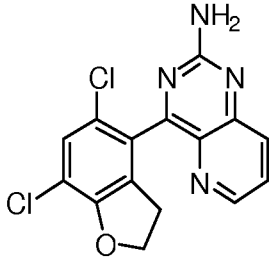
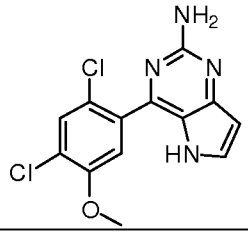
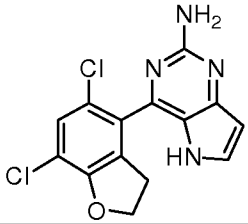
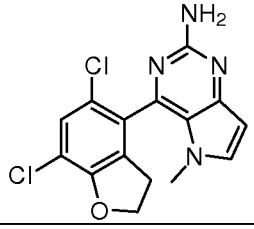
Compounds may be assessed in MDR1-MDCK permeability assay or Caco-2 permeability assay to determine their permeability. Apical (A) to basal (B) permeability >3 $X10^{-6}$ cm/sec and B→A/A→B asymmetry < 3 for a compound are considered acceptable predictors of brain penetration, and compounds having such properties are unlikely to be P-glycoprotein (P-gp) substrates. Compound **20** has shown excellent permeability in MDR1-MDCK assay (A-B = 28 x 10^{-6} cm/s) with low asymmetry (B→A/A→B asymmetry = 0.9).

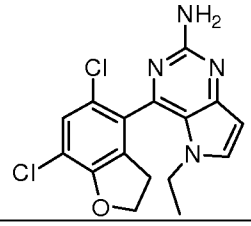
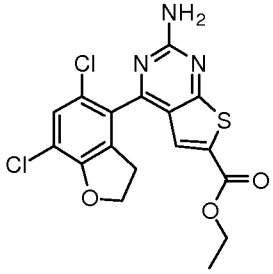
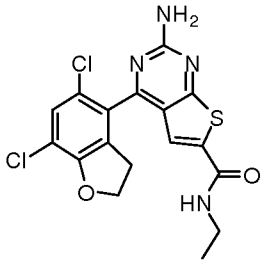
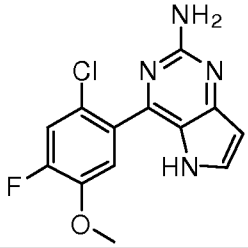
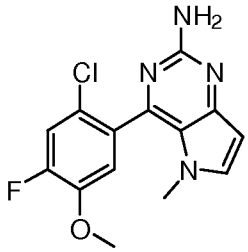
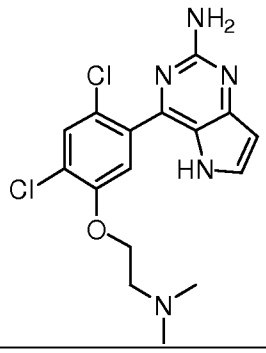
Results of the above-described assays for certain compounds of the invention are summarized in Table 3.

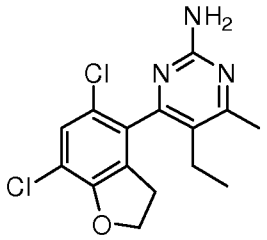
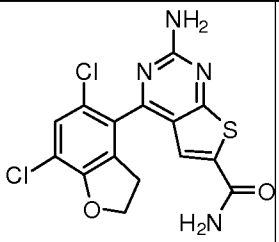
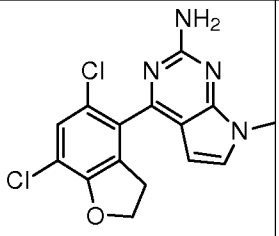
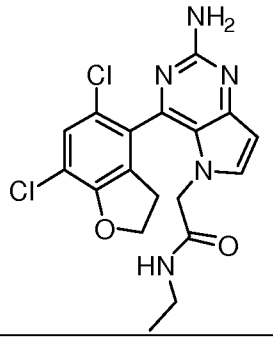
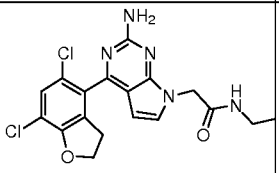
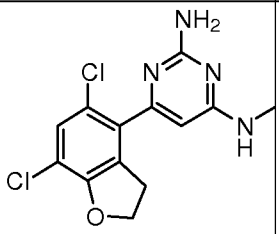
Table 3.

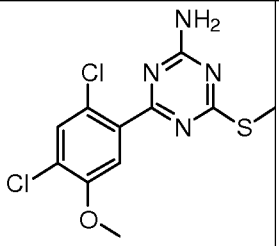
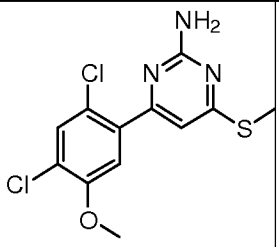
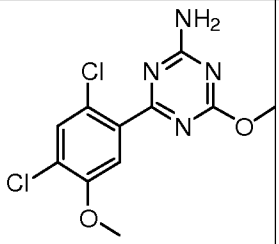
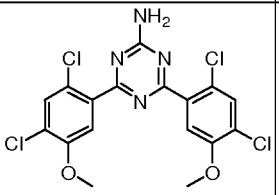
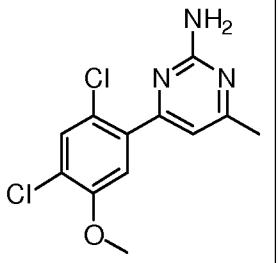
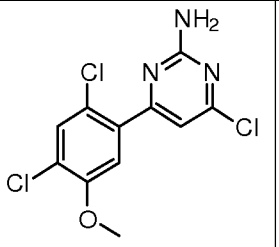
Compound	MW	cLogP	PSA	Hsp90 inhibitory activity	Hsp 70 agonist activity
1 	317	4	60	-	
2 	311	4.3	60	++	
3 	309	3.9	46	-	
4 	323	4.7	37	-	
5 	295	3.6	60	+++	>2 fold at 0.4-1.0 μM
6 	310	4.1	60	+++	≥10 μM
7 	324	4.5	60	+++(1)	-

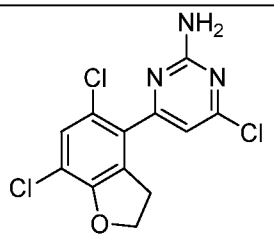
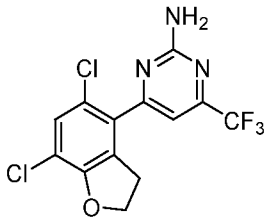
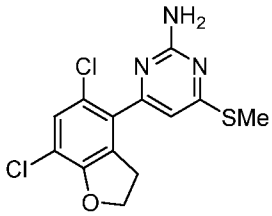
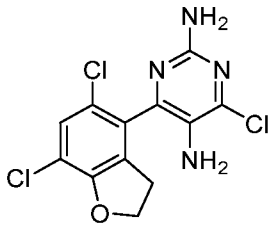
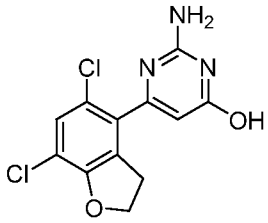
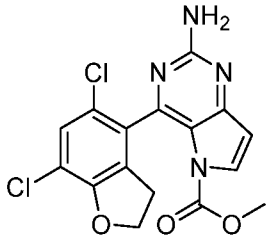
Compound	MW	cLogP	PSA	Hsp90 inhibitory activity	Hsp 70 agonist activity
8 	312	3.5	69	+++(2)	-
9 	298	3.5	60	+++(3)	1.5-fold at 1 μM
10 	310	3.9	60	+++(4)	>2-fold at 0.4 μM
11 	293	3.7	60	+	
12 	310	3.9	60	+++(5)	>2-fold at ≥ 10 μM
13 	322	4.2	60	+++(6)	-
14 	367	4.1	63	+++	2-fold at 10 μM

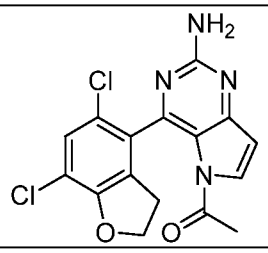
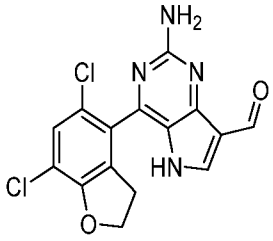
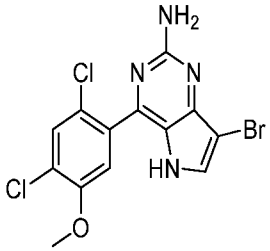
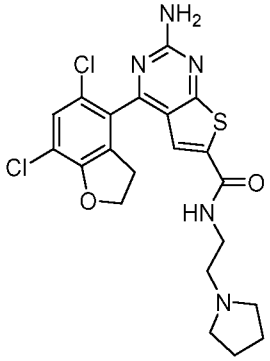
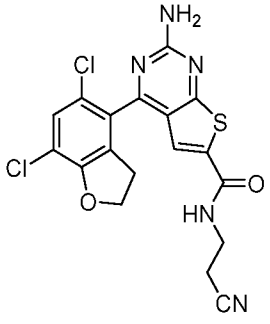
Compound	MW	cLogP	PSA	Hsp90 inhibitory activity	Hsp 70 agonist activity
15 	336	4.5	60	+	
16 	323				
17 	394			-	
18 	333				
19 	309	3.8	72	+++	>2-fold at 0.4-1 µM
20 	321	4.1	72	+++	-
21 	335	3.1	63	++	-

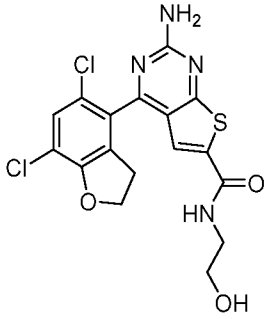
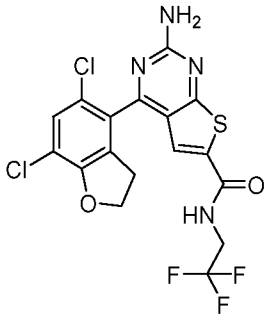
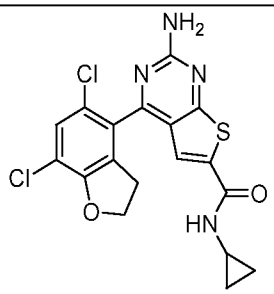
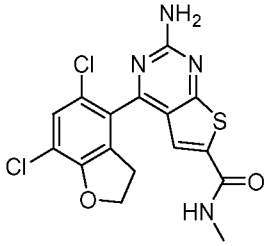
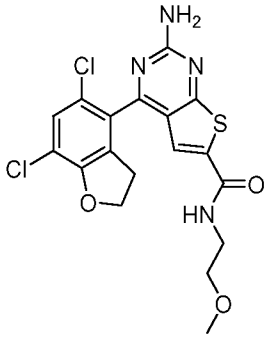
Compound	MW	cLogP	PSA	Hsp90 inhibitory activity	Hsp 70 agonist activity
22 	349	3.4	63	+	-
23 	410	4.8	86	+(7)	3.3 μM
24 	409	4.1	89	+++	0.4 μM
25 	292.70	2.5	72	+(8)	1.5 fold, or no observable effect
26 	306.73	2.7	63	++(9)	2 fold at 3.3 μM, or no observable effect
27 	366.25	2.9	75	++	10 μM

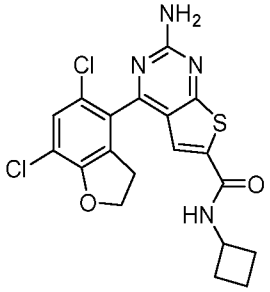
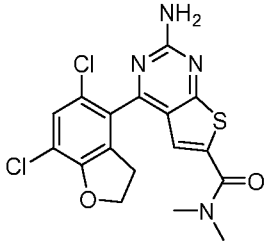
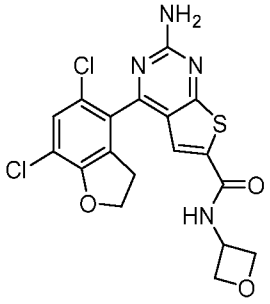
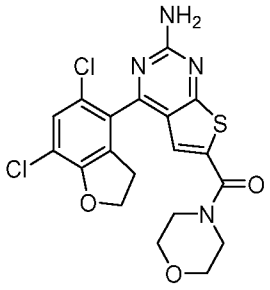
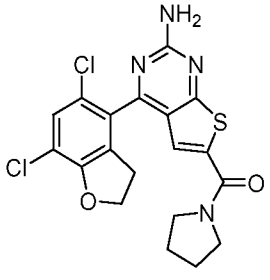
Compound	MW	cLogP	PSA	Hsp90 inhibitory activity	Hsp 70 agonist activity
28 	324.21	4.5	60	-	
29 	381.23	3.6	103	+++	0.4 μM
30 	335.19	3.4	63	-	
31 	406.27	2.3	92	-	
32 	406.27	2.6	92	-	
33 	311.17	3.1	72	+	

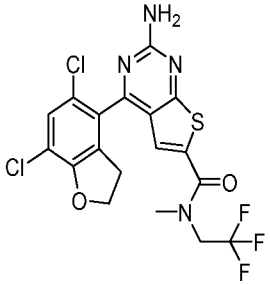
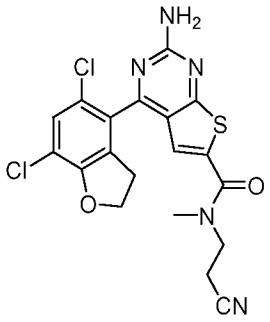
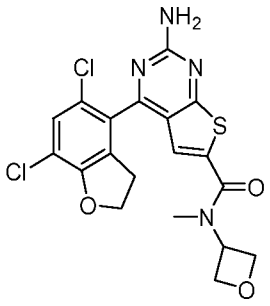
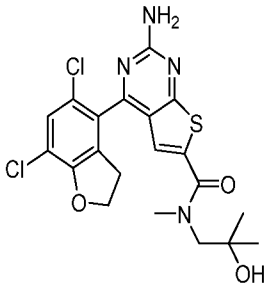
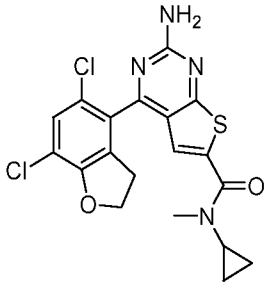
Compound	MW	cLogP	PSA	Hsp90 inhibitory activity	Hsp 70 agonist activity
34 	317.19	4.5	72	+++	3.3 μM; 10 μM
35 	316.20	4.0	60	+++	3.3 μM; 10 μM
36 	301.13	3.9	82	+++	>10 μM
37 	446.11	7.0	82	-	
38 	284.14	3.6	60	++	
39 	304.56	3.8	60	+++	0.4 μM

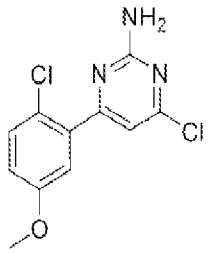
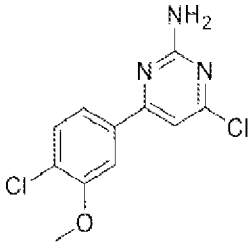
Compound	MW	cLogP	PSA	Hsp90 inhibitory activity	Hsp 70 agonist activity
49 	316.6	3.8	60	+++	
50 	350.1	4.0	60	++	
51 	328.2	4.0	60	+++	
52 	331.6	3.0	86	+++	
53 	298.1	3.2	80	-	
54 	379.2	3.4	90	-	

Compound	MW	cLogP	PSA	Hsp90 inhibitory activity	Hsp 70 agonist activity
55 	363.2	2.8	80	-	
56 	348.0	2.6	89	-	
57 	388.1	3.7	72	-	
58 	478.4	4.1	9.2	+++	
59 	434.3	3.8	113	+++	

Compound	MW	cLogP	PSA	Hsp90 inhibitory activity	Hsp 70 agonist activity
60 	425.3	3.3	109	+++	
61 	463.3	4.8	89	+++	
62 	421.3	4.1	89	+++	
63 	395.3	3.8	89	+++	
64 	439.3	3.6	98	+++	

Compound	MW	cLogP	PSA	Hsp90 inhibitory activity	Hsp 70 agonist activity
65 	435.3	4.5	89	+++	
66 	409.3	4.0	80	+++	
67 	437.3	3.4	98	+++	
68 	451.3	3.6	89	++	
69 	435.3	4.3	80	++	

Compound	MW	cLogP	PSA	Hsp90 inhibitory activity	Hsp 70 agonist activity
70 	477.3	5.0	89	+	
71 	448.3	4.1	104	+++	
72 	451.3	3.6	89	++	
73 	453.3	3.8	109	+++	
74 	435.3	4.3	80	++	

Compound	MW	cLogP	PSA	Hsp90 inhibitory activity	Hsp 70 agonist activity
75	425.3		89	+++	
76	394.3	4.6	77	+++	
77	396.3	4.6	80	++	
78 	269.01			++	
79 	269.01			+++	

In Table 3, "Hsp90 inhibitory activity" provides an assessment of exemplary compounds for their ability to inhibit Hsp90. In particular, "-" indicates that the compound has IC_{50} of greater than about 10 μM, "+" indicates that the compound has IC_{50} in the range of about 4 μM to about 10 μM; "++" indicates that the compound has IC_{50} in the range of about 1 μM to about 4 μM; "+++" indicates that the compound has IC_{50} of less than about 1 μM. "Hsp 70 agonist activity" indicates EC_{50} (μM) of the exemplary compound at which Hsp70 is increased two-fold unless otherwise noted; "-" designates lack of observable effect at concentrations exceeding 10 μM. (1) Data according to AlphaLISA assay, FP assay result: >10 μM. (2) Data according to AlphaLISA assay, FP assay result: 5.5 and 6.2 μM. (3) Data according to AlphaLISA assay, FP assay result: 1 and 1.4 μM. (4) Data according to AlphaLISA assay, FP assay result: 2.3 and 2.4 μM. (5) Data according to AlphaLISA assay, FP assay result: 1.7 μM. (6) Data according to

AlphaLISA assay, FP assay result: 1.8 μM. (7) Data according to AlphaLISA assay, FP assay result: 11.1 μM. (8) Data according to AlphaLISA assay, FP assay result: 12.1 and 19.3 μM. (9) Data according to AlphaLISA assay, FP assay result: 8.5 and 11.2 μM.

Example 3. Pharmacokinetic Properties of the Compounds of the Invention

The pre-clinical study included 85 mice, distributed over 6 groups; a summary of treatment groups is given in Table 4.

Table 4.

Group	n	Sacrificed at	Sample reference
A	5	Pre-dose	A_0
B	3	15 minutes	B_0.25
C	3	30 minutes	C_0.5
D	3	1 hour	D_1
E	3	2 hours	E_2
F	3	8 hours	F_8

Plasma and brain samples were taken pre-dose and at post dose time points of pre-dose, 15 and 30 minutes, 1, 2, and 8 hours. The pre-dose group was represented by 5 animals, whereas the post-dose groups were represented by 3 animals.

Bioanalysis methods

Bioanalysis of mouse plasma samples for compound **20** was conducted by protein precipitation and LC-MS/MS with compound **22** as the internal standard. The method was based on a 'generic assay' and some method development was conducted to tailor that assay to the particular compound and internal standard. The eventual non-GLP assay was first tested by analyzing a bioanalytical run with spiked mouse plasma samples. The qualification run passed by the run acceptance criteria (see below). Bioanalysis was then conducted of plasma sample extracts and of brain sample homogenate extracts, using a calibration and quality control samples spiked in mouse plasma. The assay is described below.

*Assay of mouse plasma levels of compound **20***

Sample treatment

Compound **20** and compound **22** were extracted from the mouse plasma matrix by protein precipitation. To 20.0 μL of sample was added 10.0 μL of internal standard working solution (1000 ng/mL in MeOH) and 200 μL of MeCN. The mixture was vortexed (~5 sec) and centrifuged (14000 rpm, 5 min). The supernatant was then recovered and evaporated to dryness. The residue was redissolved in 100 μL of redissolving solution (80:20 v:v of mobile phases A:B). For analysis, 20.0 μL was injected in to the LC-MS/MS system.

Chromatography

All chromatography was done with a type 1100 liquid chromatograph (Agilent), equipped with an auto-injector. The analytical column was an Xbridge C18 3.5µm 2.1 x 50 mm (Waters), employed at 50 °C. The mobile phase was a gradient, composed of solvent A :1 g/L ammonium acetate in Milli-Q water, and solvent B: MeCN. The gradient was as shown in Table 5.

Table 5.

Step	Total time (min)	Flow rate (µL/min)	A (%)	B (%)
0	0.00	700	80	20
1	0.20	700	80	20
2	1.00	700	0	100
3	2.00	700	0	100
4	2.10	700	80	20
5	5.00	700	80	20

Mass spectrometry

All experiments were done on an API 3000 triple quadrupole instrument (AB Sciex), operated in positive turbo-ionspray mode ('TIS+'). The instrument parameters had been optimized during method development. The MS/MS transitions employed were as shown in Table 6.

Table 6.

Compound	Q1, [M+H]+ (35Cl2) (Da)	Q3 [M+H-HCl]+ (35Cl2) (Da)
Compound **20**	321.1	285.0
Compound **22**	349.2	318.9

Description of bioanalytical experiment and acceptance criteria

The calibration range for compound **20** was set up to cover concentrations between 0.988 and 20000 ng/mL. Two sets of calibration samples were used, one set placed before and the other placed after the study samples. In addition, QC samples at 5 levels (two samples at each level) were included in the run, as performance indicators and for run acceptance.

Acceptance criteria for calibration and QC samples were applied, as follows:

- The absolute %RE (|%RE|) relative to the nominal concentration for individual calibration and QC samples should be within 20 % (or 25 % at LLOQ);
- A calibration level was considered valid when at least one of the calibration samples at that concentration level was accepted by the above |%RE| criterion;
- A QC level was considered valid when at least one of the QC samples at that concentration level was accepted by the above |%RE| criterion.

The lowest and highest accepted calibration concentration levels were adopted as the lower and upper limit of quantification, LLOQ and HLOQ, respectively.

Bioanalytical results

For compound **20**, the highest calibration level (STD L, 20000 ng/mL) did not pass acceptance criteria as both calibration samples displayed too high a bias (see Table 7). All other calibration levels of compound

20, STD A through STD K, were accepted with single samples at STD C and STD G displaying too high bias. As a consequence, the lowest level (STD A, 0.988 ng/mL) was adopted as the LLOQ and the next higher level (STD K, 8000 ng/mL) was adopted as the HLOQ. One of the QC LLOQ and one of the QC Med sample results had too high a bias. The overall method performance in the bioanalytical run was accepted for compound **20**.

Calibration and QC concentration levels employed are shown in Table 7:

Table 7.

Sample indicator	**Compound 20 concentration (ng/mL)**
STD A	0.988
STD B	2.37
STD C	5.93
STD D	14.8
STD E	35.6
STD F	88.9
STD G	222
STD H	533
STD I	1333
STD J	3333
STD K	8000
STD L	20000
QCLLQ	2.37
QCLow	14.8
QCMed	88.9
QCHigh	1333
QCOC	8000

The bioanalysis results for plasma and brain samples are presented in Tables 8 and 9.

Table 8.

Group	IRN	Concentration compound 20 (ng/mL)
A_0	2	0.00 [a]
A_0	4	2.16
A_0	6	0.00 [a]
A_0	8	0.00 [a]
A_0	10	0.00 [a]
B_0.25	12	2.66
B_0.25	14	17,900 [b]
B_0.25	16	12,000 [b]
C_0.5	18	11,500 [b]
C_0.5	20	10,500 [b]
C_0.5	22	11,100 [b]
D_1	24	6,890
D_1	26	7,130
D_1	28	7,470
E_2	30	4,150
E_2	32	4,180
E_2	34	4,440
F_8	36	99.3
F_8	38	22.5
F_8	40	21.9

(a) "0.00" represents 'below limit of quantification' (LLOQ; the LLOQ was 0.988 ng/mL).

(b) Value is out of range (0.988 – 8000 ng/mL); two calibrators at 20000 ng/mL were rejected but showed an average response of 14000 ng/mL.

Table 9.

Group	IRN	Homogenate concentration (ng/mL)	Brain weight (g)	Brain concentration of compound 20 (ng/g)
A_0	2	0.00 [a]	0.453	0.00 [a]
A_0	4	0.00 [a]	0.483	0.00 [a]
A_0	6	0.00 [a]	0.451	0.00 [a]
A_0	8	0.00 [a]	0.487	0.00 [a]
A_0	10	0.00 [a]	0.472	0.00 [a]
B_0.25	12	0.00 [a]	0.463	0.00 [a]
B_0.25	14	2300	0.445	20674
B_0.25	16	1250	0.460	10870
C_0.5	18	1400	0.482	11618
C_0.5	20	844	0.458	7371
C_0.5	22	1200	0.458	10480
D_1	24	888	0.474	7494
D_1	26	859	0.459	7486
D_1	28	789	0.461	6846
E_2	30	410	0.455	3604
E_2	32	385	0.461	3341
E_2	34	294	0.467	2518
F_8	36	7.53	0.478	63.0
F_8	38	1.83	0.489	15.0
F_8	40	1.53	0.476	12.9

(a) "0.00" represents "below limit of quantification" (LLOQ; the LLOQ was 0.988 ng/mL).

In the plasma samples, the following observations were made:

- There was one minor response in a pre-dose sample (one A_0 sample; found at 2.16 ng/mL). This response may have come from a minor contamination or from assay interference. Although selectivity of LC-MS/MS methods is generally high, selectivity for compound **20** in plasma was not tested. Conclusions can only be drawn after more elaborate method qualification or even method validation. At less than 3 times LLOQ, this pre-dose response is considered negligible here.
- Results for most measurements in time point B_0.25 and all measurements in time point C_0.5 are above the upper limit of quantification (ULOQ, at 8000 ng/mL). For obtaining more reliable results, these samples would have to be diluted prior to analysis. It is noted that a highest calibrator at 20000 ng/mL was included in the run but failed on bias. The mean back-calculated concentration of 20000 ng/mL was 14000 ng/mL., indicating a bias of -30 % at that level. The above ULOQ results were included in this Example as indicative values, in support of PK evaluation. However, the results from B_0.25 and C_0.5 time points should be treated with caution.
- Results from the first subject in the time point B_0.25 (IRN 12) are unlikely to be near the observed 2.66 ng/mL, as that does not match with the relatively high concentrations observed in the other two subjects at this first post-dose time point(IRN 14 and 16). Provisionally, PK evaluation for this time point was conducted for both cases: (1) mean of 3 and (2) mean of two with exclusion of this BLOQ result.

In the brain (homogenate) samples one result appear different from expectation:

- results from the first subject in the time point B_0.25 (IRN 12) are unlikely to be below LLOQ, as that does not match with the relatively high concentrations observed in the other two subjects at

this first post-dose time point (IRN 14 and 16). Please note that this parallels the findings for plasma from this subject (IRN 12). Provisionally, PK evaluation for this time point was conducted for both cases: (1) mean of 3 and (2) mean of two with exclusion of this BLOQ result.

Pharmacokinetic evaluation

Evaluation of pharmacokinetic parameters was conducted by calculation from the mean concentration (n=5 pre-dose, n=3 post-dose) at each time point. The pharmacokinetic results are summarized below.

Mouse Plasma

Results for pharmacokinetic evaluation are given in Tables 10-12 and Figures 7 and 8. No corrections were made for results above the ULOQ or for the inclusion of the result for animal IRN12 in group B_0.25.

Table 10.

Group	Time Point (h)	Mean Group Concentration (ng/mL)
A_0	0.00	0.432
B_0.25	0.25	9968 [a]
C_0.5	0.50	11033
D_1	1.00	7163
E_2	2.00	4257
F_8	8.00	47.9

(a) Excluding IRN 12 result: 14950 ng/mL

Tables 11 and 12 provide plasma pharmacokinetic profile of compound **20**.

Table 11. [(a)]

Parameter	Value	Unit
C_{max}	11033	ng/mL
T_{max}	0.50	hours (h)
$K_{elimination}$	0.725	per hour (h^{-1})
Half life ($t_{1/2}$)	0.96	hours (h)
AUC(0-8h)	27044	ng/mL . h
AUC(0-inf)	27055	ng/mL . h

(a) excluding IRN12 result.

Table 12. [(a)]{

Parameter	Value	Unit
C_{max}	14950	ng/mL
T_{max}	0.25	hours (h)
$K_{elimination}$	0.730	per hour (h^{-1})
Half life ($t_{1/2}$)	0.95	hours (h)
AUC(0-8h)	28290	ng/mL . h
AUC(0-inf)	28301	ng/mL . h

(a) including IRN12 result.

Mouse Brain Tissue

Results for brain tissue pharmacokinetic evaluation are given in Figures 9 and 10 and Tables 13-15. No corrections were made for the inclusion of the odd result for animal IRN 12 in group B_0.25.

Table 13.

Group	Time Point (h)	Mean Group Concentration	
		Homogenate (ng/mL)	Tissue (ng/g)
A_0	0.00	0.00	0.00
B_0.25	0.25	1183	10515 [a]
C_0.5	0.50	1148	9823
D_1	1.00	845	7275
E_2	2.00	363	3154
F_8	8.00	3.63	30.0

(a) excluding IRN 12 result: 15772 ng/g.

Tables 14 and 15 provide brain tissue pharmacokinetic profile of compound **20**.

Table 14. [(a)]

Parameter	Value	Unit
C_{max}	10515	ng/mL
T_{max}	0.25	hours (h)
$K_{elimination}$	0.769	per hour (h^{-1})
Half life ($t_{1/2}$)	0.90	hours (h)
AUC(0-8h)	22898	ng/mL . h
AUC(0-inf)	22908	ng/mL . h

(a) excluding IRN 12 result.

Table 15. [(a)]

Parameter	Value	Unit
C_{max}	15772	ng/mL
T_{max}	0.25	hours (h)
$K_{elimination}$	0.789	per hour (h^{-1})
Half life ($t_{1/2}$)	0.88	hours (h)
AUC(0-8h)	24212	ng/mL . h
AUC(0-inf)	22908	ng/mL . h

(a) including IRN 12 result.

Example 4. Effect of the Compounds of the Invention on the Total Level of Tau and Level of p-Tau in Cerebrospinal Fluid (CSF) and Brain in the Tau Transgenic Mouse Model (hTAU441)

To assess the effect of the compounds of the invention on p-tau accumulation, age-matched (e.g., 5 month old) transgenic mice humanized for the tau gene (hTAU mice) may be treated with low- or high-dose of a compound of the invention or vehicle by intraperitoneal administration for 7 days (N = 6 per arm). Dose of the compound of the invention may be calculated based on the PK results. hTAU transgenic mice (C57BL/6 background) over-express TAU441 bearing the missense mutations V337M and R406W under the control of the brain specific murine Thy-1 promoter. This human mutated tau isoform is expressed in high levels and the tau pathology and is visible at an early age starting at four months. Severity of the brain pathology correlates with increasing age and behavioral deficits, whereas no motor deficits occur. All animals may be sacrificed and quantified for soluble and insoluble tau and p-tau brain (hippocampus and cortex) using MSD multiarray p-tau ($ThR^{21}1$) immunosorbent assay (Meso Scale Discovery, Rockville, MD) to establish total tau and p-tau levels in CSF and Hsp70 levels in brain extracts. Specifically, the animals may be anaesthetized with ketamine/xylazin mix (note: isoflurane is known to influence p-tau levels), kept warm and in a horizontal position, prior to and during the collection of CSF followed by blood. The volume of CSF collected in hTAU441 is only 2-6 µL/mouse compared to some strains (2-15 µL/mouse). p-Tau ($ThR^{21}1$) and total tau levels may be assessed using phospho-

PHF-Tau pThR^{21}1 (MSD duplex kit, Meso Scale Discovery, Rockville, MD).

Administration of a compound of the invention may lead to a decrease in p-tau levels in mice treated with a compound of the invention relative to p-tau levels in mice administered a vehicle.

Example 5. Effect of the Compounds of the Invention on Memory and Learning in the hTAU441 Transgenic Mouse Model

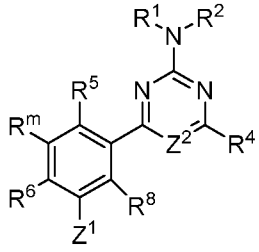
Five month old transgenic hTAU mice described in Example 3 may be administered intraperitoneally a low- or high-dose of a compound of the invention groups or a vehicle daily for 12 weeks (N = 15 per arm). A corresponding untreated group of mice will be analyzed as baseline. Behavioral testing, e.g., Probe Trial, Nose Poke Curiosity and Activity Test, and the Morris Water Maze task may be performed. Upon completion of the study, CSF may be collected and brain tissue may be harvested from these animals. Total tau levels and p-tau levels may be assessed in the CSF and brain. Additionally, immunohistochemical determination of tau pathology may be conducted. Tau depositions may be determined using the monoclonal antibodies AT180 (Thermo Scientific Pierce Antibodies, Rockford, IL) and HT7 (Thermo Scientific Pierce Antibodies, Rockford, IL). Sodium selenate, a PP2A phosphatase activator that dephosphorylates tau and reverses memory deficits, is effective in the TMHT tau model (Corcoran et al., *J. Clin. Neuroscience*, 17:1025-1033, 2010).

If chronic treatment with a compound of the invention is associated with a general improvement in memory function as measured by the Morris Maze, reduced levels of p-tau in the brain may be observed.

Other Embodiments

The invention is also described by the following numbered embodiments:

1. A compound according to formula (I):



(I), or a pharmaceutically acceptable salt thereof,

where

Z^1 is -OR^7, -$N(R^{10})R^7$, -SR^7, or –$C(R^{10})(R^{11})R^7$;

Z^2 is –N= or –$C(R^3)$=;

each R^1 and R^2 is, independently, H or optionally substituted C_{1-3} alkyl;

R^3 is H, halogen, cyano, optionally substituted C_{1-6} alkyl, optionally substituted C_{1-3} alkoxy, or optionally substituted amino, and R^4 is halogen, cyano, optionally substituted C_{1-6} alkyl, optionally substituted C_{1-3} alkoxy, optionally substituted amino, optionally substituted C_{1-6} thioalkoxy, or optionally substituted C_{6-10} aryl, or R^3 and R^4, together with the atoms to which each is attached, join to form an optionally substituted five- or six-membered ring optionally including one nitrogen, one oxygen, or one sulfur, where the nitrogen is optionally substituted with R^9;

each R^5 and R^6 is, independently, H, optionally substituted C_{1-3} alkyl, optionally substituted C_{1-3} alkoxy, halogen, or CN;

R^7 is optionally substituted C_{1-3} alkyl, optionally substituted C_{1-3} alkcycloalkyl, optionally substituted C_{1-3} alkheterocyclyl, or optionally substituted C_{1-3} alkaryl, and R^8 is H; or R^7 and R^8, together with the atoms to which each is attached, join to form an optionally substituted five- or six-membered ring optionally including one or two heteroatoms selected from nitrogen, oxygen, and sulfur;

R^9 is H, optionally substituted C_{1-3} alkyl, optionally substituted C_{3-8} cycloalkyl, optionally substituted C_{6-10} aryl, optionally substituted C_{2-9} heteroaryl, optionally substituted C_{2-9} heterocyclyl, optionally substituted C_{1-3} alkcycloalkyl, optionally substituted C_{1-3} alkheterocyclyl, or optionally substituted C_{1-3} alkaryl;

R^{10} is H, optionally substituted C_{1-3} alkyl, optionally substituted C_{3-8} cycloalkyl, optionally substituted C_{6-10} aryl, optionally substituted C_{2-9} heteroaryl, optionally substituted C_{2-9} heterocyclyl, optionally substituted C_{1-3} alkcycloalkyl, optionally substituted C_{1-3} alkheterocyclyl, or optionally substituted C_{1-3} alkaryl, and R^{11} is H, optionally substituted C_{1-3} alkyl, or R^{10} and R^{11} combine to form =O or =S;

R^m is H, halogen, optionally substituted C_{1-4} alkyl, or optionally substituted C_{1-3} alkoxy;

where,

when Z^2 is CR^3, each of R^1 and R^2 is H, R^3 is H, R^4 is methyl or chloro, and each of R^5 and R^6 is chloro,

Z^1 is not methoxy;

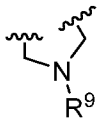
when Z^2 is N, each of R^5 and R^6 is chloro, R^3 is H, R^4 is substituted C_{1-6} thioalkoxy,

Z^1 is not cyanomethoxy or aminomethoxy;

when Z^2 is CR^3, each of R^5 and R^6 is chloro, R^3 is H, and R^4 is halogen,

Z^1 is not 2-amino-2-oxoethoxy, 2-(N,N-diethylamino)ethoxy, methoxy, or benzyloxy;

when R^5 is chloro, R^6 is bromo, Z^1 is $-OR^7$, and R^3 and R^4 combine to form a group according to formula (IIa):



(IIa),

R^7 is not methyl, ethyl, n-propyl, 2-(N-pyrazolyl)ethyl, 2-(N-imidazolyl)ethyl, 3-hydroxypropyl, cyanomethyl, 2-chloroethyl, 2-hydroxyethyl, 2-oxo-propyl, 2-(N,N-dimethylamino)ethyl, difluoromethyl, or 2-(*t*-butylamino)ethyl;

when each R^5 and R^6 is bromo, Z^1 is $-OR^7$, and R^3 and R^4 combine to form a group according to formula (IIa),

R^7 is not methyl;

when each R^5 and R^6 is chloro, Z^1 is $-OR^7$, and R^3 and R^4 combine to form a group according to formula (IIa),

R^7 is not methyl, 2-(N-imidazolyl)ethyl, methoxymethyl, 2-(N-pyrazolyl)ethyl, 2-(3-methylpyrazol-1-yl)ethyl, 2-pyridyl-methyl, 1,3-dimethyl-1H-1,2,4-triazol-5-yl-methyl, 2-pyrimidinylmethyl, imidazol-2-yl-methyl, 5-methyl-isoxazol-3-yl-methyl, 4-methyl-imidazol-5-yl-methyl, or 3-methyl-1,2,4-oxadiazol-5-yl-methyl;

when each R^5 and R^6 is chloro, Z^1 is $-OR^7$, R^7 and R^8 combine to form $-CH_2-CH_2-$, and R^3 and R^4

combine to form a group according to formula (IIa),

R^9 is not ethoxycarbonyl, cyclobutylaminocarbonyl, or cyclobutadienylaminocarbonyl

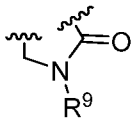
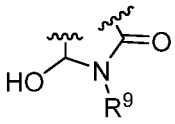
when R^5 is methoxy, R^6 is methyl, Z^1 is $-OR^7$, and R^3 and R^4 combine to form a group according to formula (IIa),

R^7 is not methyl;

when R^5 is chloro, R^6 is ethyl, Z^1 is $-OR^7$, and R^3 and R^4 combine to form a group according to formula (IIa),

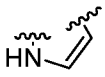
R^7 is not methyl;

when each R^5 and R^6 is chloro, Z^1 is $-OR^7$, and R^3 and R^4 combine to form a group according to formula (IIb) or (IIc),


(IIb) or

(IIc),

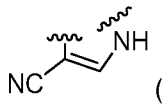
R^7 is not methyl or 2-(N,N-diethylamino)ethyl;

when R^7 is methyl, R^5 is chloro, Z^1 is $-OR^7$, and R^3 and R^4 combine to form a group according to formula (IIIa),


(IIIa),

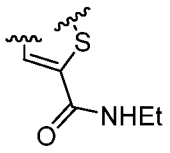
R^6 is not bromo;

when R^5 is chloro, R^6 is methoxy, Z^1 is $-OR^7$, and R^3 and R^4 combine to form a group according to formula (IIIb):


(IIIb),

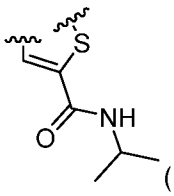
neither R^1 nor R^2 is 2-(N,N-diethylamino)ethyl;

when each R^5 and R^6 is chloro, Z^1 is $-OR^7$, and R^3 and R^4 combine to form a group according to formula (IVa):


(IVa),

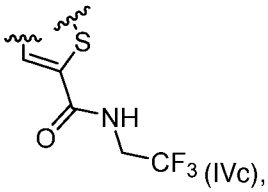
R^7 is not 3-(N-morpholinyl)propyl, benzyl, 1-ethyl-pyrrolydin-3-yl, 1-methyl-piperidin-4-yl, 2-(1-methyl-pyrrolidin-2-yl)ethyl, or 3-(N,N-diethylamino)propyl;

when each R^5 and R^6 is chloro, Z^1 is $-OR^7$, and R^3 and R^4 combine to form a group according to formula (IVb):


(IVb),

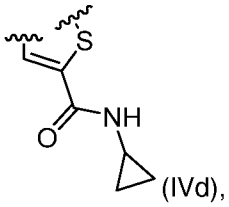
R^7 is not 2-methoxyethyl or benzyl;

when each R^5 and R^6 is chloro, Z^1 is $-OR^7$, and R^3 and R^4 combine to form a group according to formula (IVc):


(IVc),

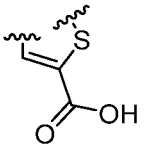
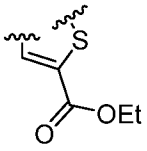
R^7 is not 2-(N,N-diethylamino)ethyl or 3-(N,N-dimethylamino)propyl;

when each R^5 and R^6 is chloro, Z^1 is $-OR^7$, and R^3 and R^4 combine to form a group according to formula (IVd):


(IVd),

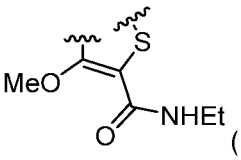
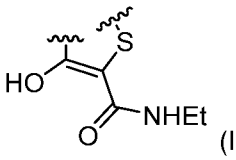
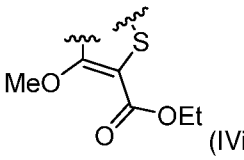
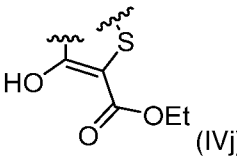
R^7 is not 2-(pyrrolidin-1-yl)ethyl or 2-hydroxyethyl;

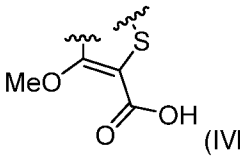
when each R^5 and R^6 is chloro, Z^1 is $-OR^7$, and R^3 and R^4 combine to form a group according to formula (IVe) or (IVf):


(IVe) or 
(IVf),

R^7 is not benzyl;

when R^5 is chloro, R^6 is bromo, Z^1 is $-OR^7$, and R^3 and R^4 combine to form a group according to formula (IVg), (IVh), (IVi), (IVj), or (IVk):


(IVg), 
(IVh), 
(IVi), 
(IVj), or


(IVk),

R^7 is not methyl;

when R^6 is methyl,

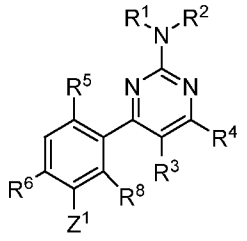
each R^1 and R^2 is H; and

when R^3 is H, Z^1 is $-OR^7$, and each R^5 and R^6 is chloro,

R^7 is not methyl.

2. The compound of embodiment 1, where R^m is H.

3. A compound according to formula (Ia):



(Ia), or a pharmaceutically acceptable salt thereof,

where

each R^1 and R^2 is, independently, H or optionally substituted C_{1-3} alkyl;

R^3 is H, halogen, cyano, optionally substituted C_{1-6} alkyl, optionally substituted C_{1-3} alkoxy, or optionally substituted amino, and R^4 is halogen, cyano, optionally substituted C_{1-6} alkyl, optionally substituted C_{1-3} alkoxy, optionally substituted amino, optionally substituted C_{1-6} thioalkyl, or optionally substituted C_{6-10} aryl, or R^3 and R^4, together with the atoms to which each is attached, join to form an optionally substituted five- or six-membered ring optionally including one nitrogen, one oxygen, or one sulfur, where the nitrogen is optionally substituted with R^9;

each R^5 and R^6 is, independently, H, optionally substituted C_{1-3} alkyl, optionally substituted C_{1-3} alkoxy, halogen, or CN;

R^7 is optionally substituted C_{1-3} alkyl, optionally substituted C_{1-3} alkcycloalkyl, optionally substituted C_{1-3} alkheterocyclyl, or optionally substituted C_{1-3} alkaryl, and R^8 is H; or R^7 and R^8, together with the atoms to which each is attached, join to form an optionally substituted five- or six-membered ring optionally including one or two heteroatoms selected from nitrogen, oxygen, and sulfur;

R^9 is H, optionally substituted C_{1-3} alkyl, optionally substituted C_{3-8} cycloalkyl, optionally substituted C_{6-10} aryl, optionally substituted C_{2-9} heteroaryl, optionally substituted C_{2-9} heterocyclyl, optionally substituted C_{1-3} alkcycloalkyl, optionally substituted C_{1-3} alkheterocyclyl, or optionally substituted C_{1-3} alkaryl;

Z^1 is $-OR^7$, $-N(R^{10})R^7$, $-SR^7$, or $-C(R^{10})(R^{11})R^7$; and

R^{10} is H, optionally substituted C_{1-3} alkyl, optionally substituted C_{3-8} cycloalkyl, optionally substituted C_{6-10} aryl, optionally substituted C_{2-9} heteroaryl, optionally substituted C_{2-9} heterocyclyl, optionally substituted C_{1-3} alkcycloalkyl, optionally substituted C_{1-3} alkheterocyclyl, or optionally substituted C_{1-3} alkaryl, and R^{11} is H, optionally substituted C_{1-3} alkyl, or R^{10} and R^{11} combine to form =O or =S;

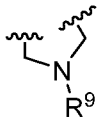
where,

when each of R^1 and R^2 is H, R^3 is H, R^4 is methyl or chloro, and each of R^5 and R^6 is chloro, Z^1 is not methoxy;

when each of R^5 and R^6 is chloro, R^3 is H, and R^4 is halogen,

Z^1 is not 2-amino-2-oxoethoxy, 2-(N,N-diethylamino)ethoxy, methoxy, or benzyloxy;

when R^5 is chloro, R^6 is bromo, Z^1 is $-OR^7$, and R^3 and R^4 combine to form a group according to formula (IIa):



(IIa),

R^7 is not methyl, ethyl, n-propyl, 2-(N-pyrazolyl)ethyl, 2-(N-imidazolyl)ethyl, 3-hydroxypropyl, cyanomethyl, 2-chloroethyl, 2-hydroxyethyl, 2-oxo-propyl, 2-(N,N-dimethylamino)ethyl,

difluoromethyl, or 2-(*t*-butylamino)ethyl;

when each R^5 and R^6 is bromo, Z^1 is $-OR^7$, and R^3 and R^4 combine to form a group according to formula (IIa),

R^7 is not methyl;

when each R^5 and R^6 is chloro, Z^1 is $-OR^7$, and R^3 and R^4 combine to form a group according to formula (IIa),

R^7 is not methyl, 2-(N-imidazolyl)ethyl, methoxymethyl, 2-(N-pyrazolyl)ethyl, 2-(3-methylpyrazol-1-yl)ethyl, 2-pyridyl-methyl, 1,3-dimethyl-1H-1,2,4-triazol-5-yl-methyl, 2-pyrimidinylmethyl, imidazol-2-yl-methyl, 5-methyl-isoxazol-3-yl-methyl, 4-methyl-imidazol-5-yl-methyl, or 3-methyl-1,2,4-oxadiazol-5-yl-methyl;

when each R^5 and R^6 is chloro, Z^1 is $-OR^7$, R^7 and R^8 combine to form $-CH_2-CH_2-$, and R^3 and R^4 combine to form a group according to formula (IIa),

R^9 is not ethoxycarbonyl, cyclobutylaminocarbonyl, or cyclobutadienylaminocarbonyl

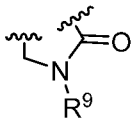
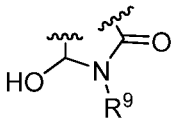
when R^5 is methoxy, R^6 is methyl, Z^1 is $-OR^7$, and R^3 and R^4 combine to form a group according to formula (IIa),

R^7 is not methyl;

when R^5 is chloro, R^6 is ethyl, Z^1 is $-OR^7$, and R^3 and R^4 combine to form a group according to formula (IIa),

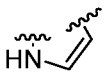
R^7 is not methyl;

when each R^5 and R^6 is chloro, Z^1 is $-OR^7$, and R^3 and R^4 combine to form a group according to formula (IIb) or (IIc),


(IIb) or

(IIc),

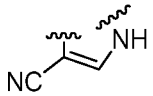
R^7 is not methyl or 2-(N,N-diethylamino)ethyl;

when R^7 is methyl, R^5 is chloro, Z^1 is $-OR^7$, and R^3 and R^4 combine to form a group according to formula (IIIa),


(IIIa),

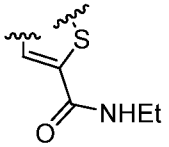
R^6 is not bromo;

when R^5 is chloro, R^6 is methoxy, Z^1 is $-OR^7$, and R^3 and R^4 combine to form a group according to formula (IIIb):


(IIIb),

neither R^1 nor R^2 is 2-(N,N-diethylamino)ethyl;

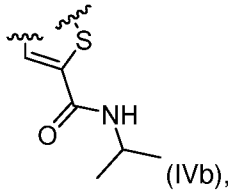
when each R^5 and R^6 is chloro, Z^1 is $-OR^7$, and R^3 and R^4 combine to form a group according to formula (IVa):


(IVa),

R^7 is not 3-(N-morpholinyl)propyl, benzyl, 1-ethyl-pyrrolydin-3-yl, 1-methyl-piperidin-4-yl, 2-(1-

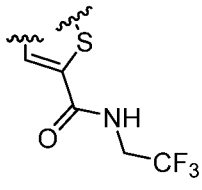
methyl-pyrrolidin-2-yl)ethyl, or 3-(N,N-diethylamino)propyl;

when each R^5 and R^6 is chloro, Z^1 is $-OR^7$, and R^3 and R^4 combine to form a group according to formula (IVb):


(IVb),

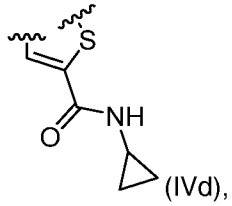
R^7 is not 2-methoxyethyl or benzyl;

when each R^5 and R^6 is chloro, Z^1 is $-OR^7$, and R^3 and R^4 combine to form a group according to formula (IVc):


(IVc),

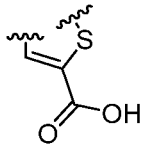
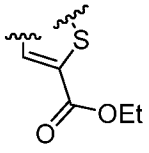
R^7 is not 2-(N,N-diethylamino)ethyl or 3-(N,N-dimethylamino)propyl;

when each R^5 and R^6 is chloro, Z^1 is $-OR^7$, and R^3 and R^4 combine to form a group according to formula (IVd):


(IVd),

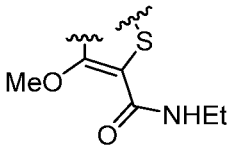
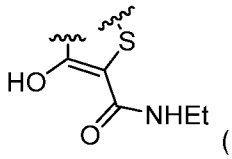
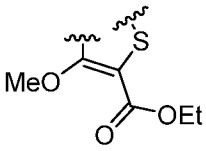
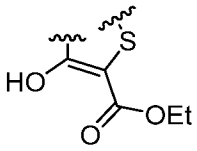
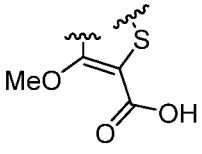
R^7 is not 2-(pyrrolidin-1-yl)ethyl or 2-hydroxyethyl;

when each R^5 and R^6 is chloro, Z^1 is $-OR^7$, and R^3 and R^4 combine to form a group according to formula (IVe) or (IVf):


(IVe) or

(IVf),

R^7 is not benzyl;

when R^5 is chloro, R^6 is bromo, Z^1 is $-OR^7$, and R^3 and R^4 combine to form a group according to formula (IVg), (IVh), (IVi), (IVj), or (IVk):


(IVg),

(IVh),

(IVi),

(IVj), or

(IVk),

R^7 is not methyl;

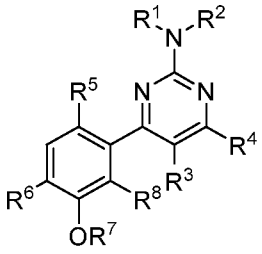
when R^6 is methyl,

each R^1 and R^2 is H; and

when R^3 is H, Z^1 is -OR^7, and each R^5 and R^6 is chloro,

R^7 is not methyl.

4. A compound according to formula (Ib):



(Ib), or a pharmaceutically acceptable salt thereof,

where

each of R^1 and R^2 is, independently, H or optionally substituted C_{1-3} alkyl;

R^3 is H, halogen, cyano, optionally substituted C_{1-6} alkyl, optionally substituted C_{1-3} alkoxy, or optionally substituted amino, and R^4 is halogen, cyano, optionally substituted C_{1-6} alkyl, optionally substituted C_{1-3} alkoxy, optionally substituted amino, optionally substituted C_{1-6} thioalkoxy, or optionally substituted C_{6-10} aryl, or R^3 and R^4, together with the atoms to which each is attached, join to form an optionally substituted five- or six-membered ring optionally including one nitrogen, one sulfur, or one oxygen, where the nitrogen is optionally substituted with R^9;

each of R^5 and R^6 is, independently, H, optionally substituted C_{1-3} alkyl, optionally substituted C_{1-3} alkoxy, halogen, or CN;

R^7 is optionally substituted C_{1-3} alkyl, optionally substituted C_{1-3} alkcycloalkyl, optionally substituted C_{1-3} alkheterocyclyl, or optionally substituted C_{1-3} alkaryl, and R^8 is H; or R^7 and R^8, together with the atoms to which each is attached, join to form an optionally substituted five- or six-membered ring; and

R^9 is H, optionally substituted C_{1-3} alkyl, optionally substituted C_{3-8} cycloalkyl, optionally substituted C_{6-10} aryl, optionally substituted C_{2-9} heteroaryl, optionally substituted C_{2-9} heterocyclyl, optionally substituted C_{1-3} alkcycloalkyl, optionally substituted C_{1-3} alkheterocyclyl, or optionally substituted C_{1-3} alkaryl;

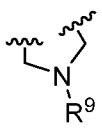
where,

when each of R^1 and R^2 is H, R^3 is H, R^4 is methyl or chloro, and each of R^5 and R^6 is chloro, R^7 is not methyl;

when each of R^5 and R^6 is chloro, R^3 is H, and R^4 is halogen,

R^7 is not 2-amino-2-oxoethyl, 2-(N,N-diethylamino)ethyl, methyl, or benzyl;

when R^5 is chloro, R^6 is bromo, and R^3 and R^4 combine to form a group according to formula (IIa):



(IIa),

R^7 is not methyl, ethyl, n-propyl, 2-(N-pyrazolyl)ethyl, 2-(N-imidazolyl)ethyl, 3-hydroxypropyl, cyanomethyl, 2-chloroethyl, 2-hydroxyethyl, 2-oxo-propyl, 2-(N,N-dimethylamino)-ethyl, difluoromethyl, or 2-(*t*-butylamino)ethyl;

when each R^5 and R^6 is bromo, and R^3 and R^4 combine to form a group according to formula (IIa),

R^7 is not methyl;

when each R^5 and R^6 is chloro, R^8 is H, and R^3 and R^4 combine to form a group according to formula (IIa),

R^7 is not methyl, 2-(N-imidazolyl)ethyl, methoxymethyl, 2-(N-pyrazolyl)ethyl, 2-(3-methylpyrazol-1-yl)ethyl, 2-pyridyl-methyl, 1,3-dimethyl-1H-1,2,4-triazol-5-yl-methyl, 2-pyrimidinylmethyl, imidazol-2-yl-methyl, 5-methyl-isoxazol-3-yl-methyl, 4-methyl-imidazol-5-yl-methyl, or 3-methyl-1,2,4-oxadiazol-5-yl-methyl;

when each R^5 and R^6 is chloro, R^7 and R^8 combine to form $-CH_2-CH_2-$, and R^3 and R^4 combine to form a group according to formula (IIa),

R^9 is not ethoxycarbonyl, cyclobutylaminocarbonyl, or cyclobutadienylaminocarbonyl;

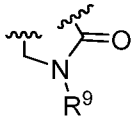
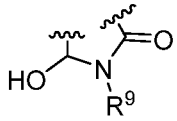
when R^5 is methoxy, R^6 is methyl, and R^3 and R^4 combine to form a group according to formula (IIa),

R^7 is not methyl;

when R^5 is chloro, R^6 is ethyl, and R^3 and R^4 combine to form a group according to formula (IIa),

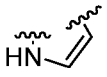
R^7 is not methyl;

when each R^5 and R^6 is chloro, and R^3 and R^4 combine to form a group according to formula (IIb) or (IIc),


(IIb) or

(IIc),

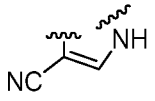
R^7 is not methyl or 2-(N,N-diethylamino)ethyl;

when R^7 is methyl, R^5 is chloro, and R^3 and R^4 combine to form a group according to formula (IIIa),


(IIIa),

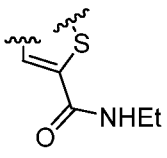
R^6 is not bromo;

when R^5 is chloro, R^6 is methoxy, and R^3 and R^4 combine to form a group according to formula (IIIb):


(IIIb),

neither R^1 nor R^2 is 2-(N,N-diethylamino)ethyl;

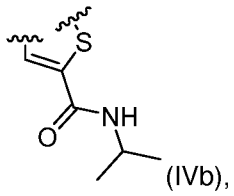
when each R^5 and R^6 is chloro, and R^3 and R^4 combine to form a group according to formula (IVa):


(IVa),

R^7 is not 3-(N-morpholinyl)propyl, benzyl, 1-ethyl-pyrrolydin-3-yl, 1-methyl-piperidin-4-yl, 2-(1-methyl-pyrrolidin-2-yl)ethyl, or 3-(N,N-diethylamino)propyl;

when each R^5 and R^6 is chloro, and R^3 and R^4 combine to form a group according to formula

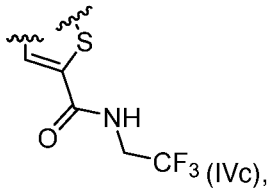
(IVb):



(IVb),

R^7 is not 2-methoxyethyl or benzyl;

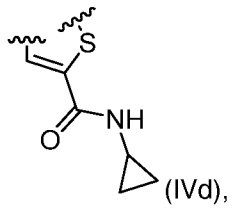
when each R^5 and R^6 is chloro, and R^3 and R^4 combine to form a group according to formula (IVc):



(IVc),

R^7 is not 2-(N,N-diethylamino)ethyl or 3-(N,N-dimethylamino)propyl;

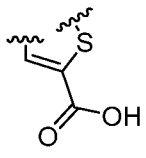
when each R^5 and R^6 is chloro, and R^3 and R^4 combine to form a group according to formula (IVd):



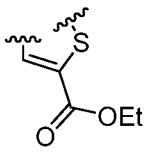
(IVd),

R^7 is not 2-(pyrrolidin-1-yl)ethyl or 2-hydroxyethyl;

when each R^5 and R^6 is chloro, and R^3 and R^4 combine to form a group according to formula (IVe) or (IVf):



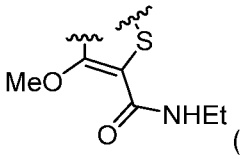
(IVe) or



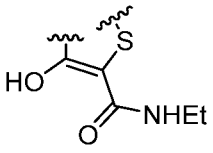
(IVf),

R^7 is not benzyl;

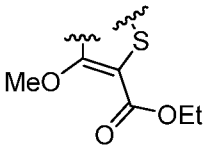
when R^5 is chloro, R^6 is bromo, and R^3 and R^4 combine to form a group according to formula (IVg), (IVh), (IVi), (IVj), or (IVk):



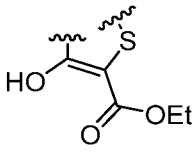
(IVg),



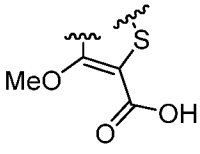
(IVh),



(IVi),



(IVj), or



(IVk),

R^7 is not methyl;

when R^6 is methyl,

each R^1 and R^2 is H; and

when R^3 is H, and each R^5 and R^6 is chloro,

R^7 is not methyl.

5. The compound of any one of embodiments 1 to 4, where R^3 is H, halogen, optionally substituted C_{1-3} alkyl, or optionally substituted C_{1-3} alkoxy, and R^4 is halogen, optionally substituted C_{1-3} alkyl, optionally substituted C_{1-3} alkoxy, optionally substituted amino, optionally substituted C_{1-6} thioalkyl, or optionally substituted C_{6-10} aryl, or R^3 and R^4, together with the atoms to which each is attached, join to form an optionally substituted five- or six-membered ring optionally including one nitrogen, one oxygen, or one sulfur, where the nitrogen is optionally substituted with R^9.

6. The compound of any one of embodiments 1 to 5, where R^3 and R^4, together with the atoms to which each is attached, join to form an optionally substituted five-membered ring.

7. The compound of any one of embodiments 1 to 5, where R^3 and R^4 combine to form $–CH_2CH_2CH_2–$ group.

8. The compound of any one of embodiments 1 to 5, where R^3 and R^4, together with the atoms to which each is attached, join to form an optionally substituted five-membered ring including one nitrogen.

9. The compound of embodiment 8, where R^3 and R^4 combine to form $–N(R^9)–CH=CH–$ group.

10. The compound of embodiment 9, where R^9 is H.

11. The compounds of any one of embodiments 1 to 5, where R^3 and R^4, together with the atoms to which each is attached, join to form an optionally substituted five-membered ring including one sulfur.

12. The compound of any one of embodiments 1 to 5, where R^3 and R^4 combine to form $–C(R^{13A})=C(R^{13B})–S–$ group, where R^{13A} is H, and R^{13B} is H or optionally substituted C_{1-3} alkyl.

13. The compound of embodiment 12, where R^{13B} is optionally substituted C_{1-3} alkyl.

14. The compound of embodiment 13, where R^{13B} is $–C(O)–R^{13C}$, where R^{13C} is optionally substituted C_{1-3} alkoxy or optionally substituted amino.

15. The compound of any one of embodiments 1 to 5, where R^3 and R^4 combine to form $–C(R^{13A})=C(R^{13B})–S–$ group, where R^{13A} is H, and R^{13B} is H or $–C(O)–R^{13C}$, where R^{13C} is optionally substituted C_{1-3} alkyl, optionally substituted C_{1-3} alkoxy, optionally substituted amino, or optionally substituted C_{2-9} heterocyclyl.

16. The compound of any one of embodiments 1 to 5, where R^4 is C_{1-3} alkyl.

17. The compound of embodiment 16, where R^4 is methyl, ethyl, or isopropyl.

18. The compound of any one of embodiments 1 to 5, where R^4 is C_{1-3} alkoxy.

19. The compound of embodiment 18, where R^4 is methoxy.

20. The compound of any one of embodiments 1 to 5, where R^4 is optionally substituted C_{1-6} thioalkoxy.

21. The compound of embodiment 20, where R^4 is 4-amino-4-oxobutyl.

22. The compound of any one of embodiments 1 to 5, where R^4 is optionally substituted amino.

23. The compound of embodiment 22, where R^4 is methylamino.

24. The compound of any one of embodiments 1 to 5, where R^4 is halogen.

25. The compound of embodiment 24, where R^4 is chloro.

26. The compound of any one of embodiments 1-5 and 15-25, where R^3 is hydrogen or C_{1-3} alkyl.

27. The compound of embodiment 26, where R^3 is hydrogen, methyl, or ethyl.

28. The compound of any one of embodiments 1 to 5, where R^3 and R^4 combine to form $–X^1–X^2–X^3–$, where

X^1 is –S–, –O–, $–(CR^{14}R^{15})–$, $–C(R^{16})=$, $–N(R^9)–$, –N=, H, or optionally substituted C_{1-3} alkyl;

X^2 is absent,$–(CR^{17}R^{18})_n–$, –S–, –O–, –N=, $–N(R^9)–$, $–C(R^{19})=$, =N–, $=C(R^{20})–$, or $=C(R^{21})–C(R^{22})=$;

X^3 is $–(CR^{14}R^{15})–$, –S–, –O–, $–N(R^9)–$, =N–, $=C(R^{23})–$, halogen, optionally substituted C_{1-3} alkyl, optionally substituted C_{1-6} thioalkoxy, optionally substituted C_{1-3} alkoxy, or optionally substituted C_{6-10} aryl;

each R^{14} and R^{15} is, independently, H or optionally substituted C_{1-3} alkyl, or R^{14} and R^{15} combine to form =O or =S;

each R^{17} and R^{18} is, independently, H or optionally substituted C_{1-3} alkyl, or R^{17} and R^{18} combine to form =O or =S;

each R^{16}, R^{19}, R^{20}, R^{21}, R^{22}, and R^{23} is, independently, H, or optionally substituted C_{1-3} alkyl; and

n is 1 or 2; and

where, when X^2 is not absent,

the chain of atoms $–X^1–X^2–X^3–$ includes no more than one heteroatom, the heteroatom being selected from the group consisting of nitrogen, oxygen, and sulfur.

29. The compound of embodiment 28, where X^1 is $–(CR^{14}R^{15})–$, $–C(R^{16})=$, $–N(R^9)–$, -N=, or optionally substituted C_{1-3} alkyl.

30. The compound of embodiment 29, where X^1 is $–(CR^{14}R^{15})–$.

31. The compound of embodiment 30, where each R^{14} and R^{15} is H.

32. The compound of embodiment 29, where X^1 is $–C(R^{16})=$.

33. The compound of embodiment 32, where R^{16} is H.

34. The compound of embodiment 29, where X^1 is $–N(R^9)–$.

35. The compound of embodiment 34, where R^9 is H or optionally substituted C_{1-3} alkyl.

36. The compound of embodiment 35, where R^9 is hydrogen, methyl, or ethyl.

37. The compound of embodiment 29, where X^1 is –N=.

38. The compound of embodiment 29, where X^1 is optionally substituted C_{1-3} alkyl.

39. The compound of any one of embodiments 28 to 37, where X^2 is absent, $–(CH_2)_n–$, $–N(R^9)–$, –C(H)=, $=C(R^{20})–$, or =C(H)–C(H)=.

40. The compound of embodiment 39, where X^2 is –C(H)=.

41. The compound of embodiment 39, where X^2 is $–N(R^9)–$.

42. The compound of embodiment 41, where R^9 is H.

43. The compound of embodiment 41, where R^9 is optionally substituted C_{1-3} alkyl.

44. The compound of embodiment 43, where R^9 is –C(O)–N(H)–Et.

45. The compound of embodiment 39, where X^2 is $=C(R^{20})–$.

46. The compound of embodiment 45, where R^{20} is optionally substituted C_{1-3} alkyl.

47. The compound of embodiment 39, where X^2 is absent.

48. The compound of any one of embodiments 28-37 and 39-47, where X^3 is $–CH_2–$, –S–, =C(H)–, $–N(R^9)–$, halogen, optionally substituted C_{1-3} alkyl, optionally substituted C_{1-3} alkoxy, optionally substituted C_{1-6} thioalkoxy, optionally substituted C_{6-10} aryl.

49. The compound of embodiment 48, where X^3 is $–CH_2–$.

50. The compound of embodiment 48, where X^3 is –S–.

51. The compound of embodiment 48, where X^3 is =C(H)–.

52. The compound of embodiment 48, where X^3 is –N(R^9)-.

53. The compound of embodiment 48, where X^3 is halogen, optionally substituted C_{1-3} alkyl, optionally substituted C_{1-3} alkoxy, optionally substituted C_{1-6} thioalkoxy, or optionally substituted C_{6-10} aryl.

54. The compound of any one of embodiments 1 to 53, where each R^5 and R^6 is, independently, halo or optionally substituted C_{1-3} alkyl.

55. The compound of embodiment 54, where each R^5 and R^6 is halo.

56. The compound of embodiment 55, where each R^5 and R^6 is chloro.

57. The compound of any one of embodiments 1 to 56, where R^7 and R^8, together with the atoms to which each is attached, join to form an optionally substituted five- or six-membered ring optionally including one or two heteroatoms selected from nitrogen, oxygen, and sulfur.

58. The compound of any one of embodiments 1 to 56, where R^7 and R^8, together with the atoms to which each is attached, join to form an optionally substituted five- or six-membered saturated ring optionally including one or two heteroatoms selected from nitrogen, oxygen, and sulfur.

59. The compound of any one of embodiments 1 to 56, where R^7 and R^8, together with the atoms to which each is attached, join to form an optionally substituted five- of six-membered ring optionally including one or two heteroatoms selected from nitrogen and oxygen.

60. The compound of any one of embodiments 1 to 56, where R^7 and R^8, together with the atoms to which each is attached, join to form an optionally substituted five-membered ring.

61. The compound of any one of embodiments 1 to 56, where the R^7 and R^8, together with the atoms to which each is attached, join to form an optionally substituted saturated five-membered ring.

62. The compound of any one of embodiments 1 to 56, where the R^7 and R^8 combine to form a –CH_2CH_2– group.

63. The compound of any one of embodiments 1 to 56, where R^7 is optionally substituted C_{1-3} alkyl.

64. The compound of embodiment 63, where R^7 is methyl.

65. The compound of embodiment 63, where R^7 is –$(CH_2)_k$–N(R^{24})R^{25}, where k is 2 or 3, and where each R^{24} and R^{25} is, independently, H or optionally substituted C_{1-3} alkyl.

66. The compound of embodiment 65, where k is 2.

67. The compound of embodiment 65 or 66, where each R^{24} and R^{25} is, independently, optionally substituted C_{1-3} alkyl.

68. The compound of any one of embodiments 65 to 67, where each R^{24} and R^{25} is methyl.

69. The compound of any one of embodiments 1 to 56, where R^7 and R^8 form a group $–Y^1–Y^2–$, where:

Y^1 is $–(CR^{26}R^{27})_m–$ or optionally substituted C_{1-3} alkyl, optionally substituted C_{1-3} alkheterocyclyl, optionally substituted C_{1-3} alkcycloalkyl, or optionally substituted C_{1-3} alkaryl; and

Y^2 is $–(CR^{26}R^{27})–$ or H; where

each R^{26} and R^{27} is, independently, H or optionally substituted C_{1-3} alkyl; and

m is 1 or 2.

70. The compound of any one of embodiments 1 to 5, where Z^1 and R^8 combine to form $–Z^3–Y^1–Y^2–$, where

Z^3 is –O–, $–N(R^{10})–$, –N=, –S–, or $–(CR^{14}R^{15})–$;

Y^1 is –O–, $–N(R^{10})–$, –S–, $–(CR^{26}R^{27})_m–$, $–C(R^{20})=$, $=C(R^{20})–$, $=C(R^{21})–C(R^{22})=$, optionally substituted C_{1-3} alkyl, optionally substituted C_{1-3} alkheterocyclyl, optionally substituted C_{1-3} alkcycloalkyl, or optionally substituted C_{1-3} alkaryl; and

Y^2 is –O–, –S–, $–N(R^{10})–$, $–(CR^{26}R^{27})–$, $=C(R^{20})–$, =N–, or H;

where

each R^{20}, R^{21}, and R^{22} is, independently, H or optionally substituted C_{1-3} alkyl; and

each R^{26} and R^{27} is, independently, H or optionally substituted C_{1-3} alkyl, or R^{26} and R^{27} combine to form =O or =S;

m is 1 or 2; and

where, when Y^2 is H,

the chain of atoms $–Z^3–Y^1–Y^2–$ includes no more than two heteroatoms, the heteroatom selected from nitrogen, oxygen, and sulfur.

71. The compound of embodiment 70, where Z^3 is –O–.

72. The compound of embodiment 69 or 71, where Y^1 is $–(CR^{26}R^{27})_m–$ or optionally substituted C_{1-3} alkyl, optionally substituted C_{1-3} alkheterocyclyl, optionally substituted C_{1-3} alkcycloalkyl, or optionally substituted C_{1-3} alkaryl.

73. The compound of any one of embodiments 69 to 72, where Y^1 is $–(CR^{26}R^{27})_m–$ or optionally substituted C_{1-3} alkyl.

74. The compound of any one of embodiments 69 to 73, where Y^2 is $–(CR^{26}R^{27})–$ or H.

75. The compound of any one of embodiments 69 to 74, where Y^2 is $-(CR^{26}R^{27})-$.

76. The compound of any one of embodiments 69 to 75, where R^{26} is H.

77. The compound of any one of embodiments 69 to 76, where R^{27} is H.

78. The compound of any one of embodiments 69 to 77, where m is 1.

79. The compound of any one of embodiments 69 to 78, where Y^1 is optionally substituted C_{1-3} alkyl.

80. The compound of embodiment 79, where Y^1 is methyl.

81. The compound of embodiment 80, where Y^1 is $-(CH_2)_k-N(R^{24})R^{25}$, where k is 2 or 3, and where each R^{24} and R^{25} is, independently, H or optionally substituted C_{1-3} alkyl.

82. The compound of embodiment 81, where k is 2.

83. The compound of embodiment 81 or 82, where each R^{24} and R^{25} is, independently, optionally substituted C_{1-3} alkyl.

84. The compound of any one of embodiments 81 to 83, where each R^{24} and R^{25} is methyl.

85. The compound of any one of embodiments 1 to 84, where each R^1 and R^2 is H.

86. A compound:

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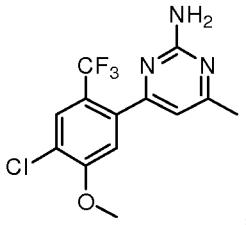

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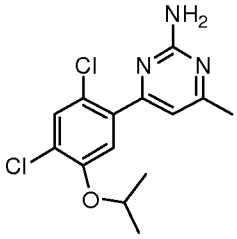

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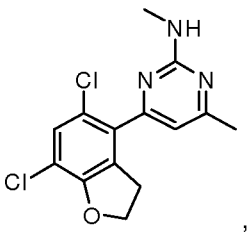

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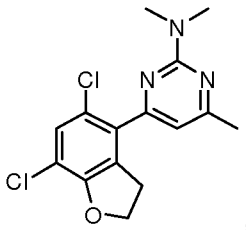

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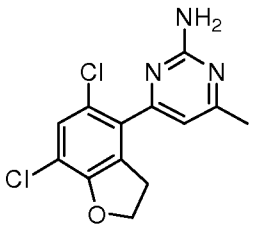

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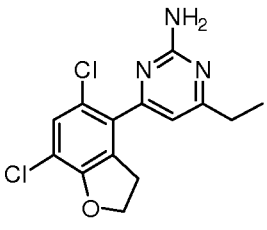

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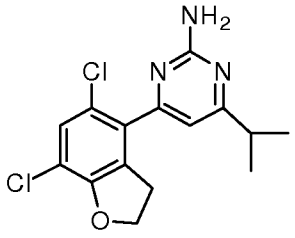

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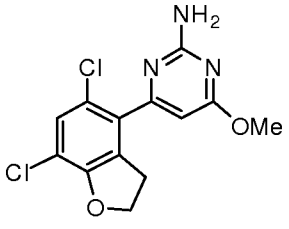

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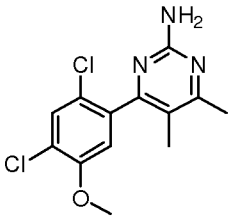

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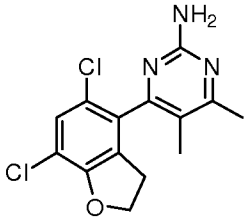
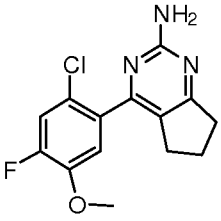
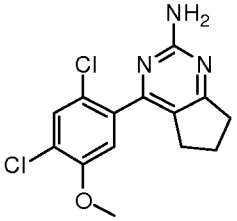
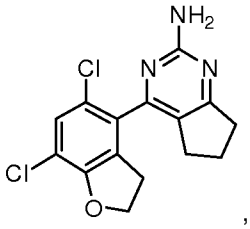
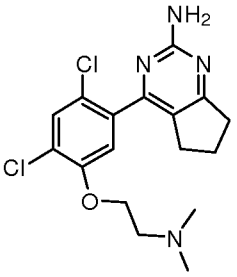
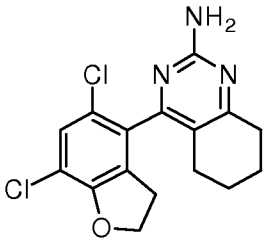
10  ,

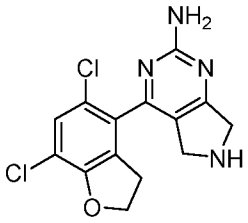
11  ,

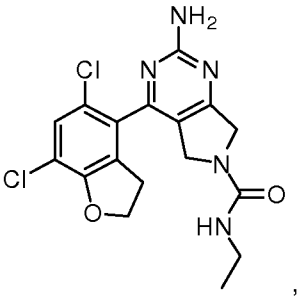
12  ,

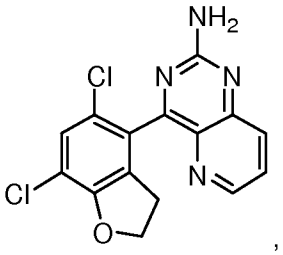
13  ,

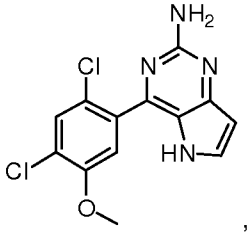
14  ,

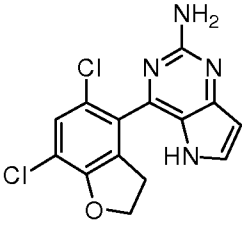
15  ,

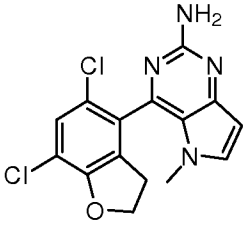
16  ,

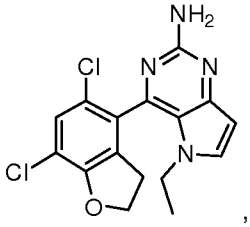
17  ,

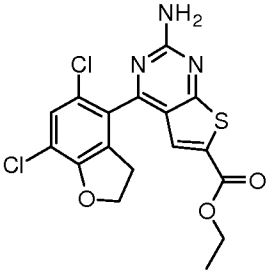
18  ,

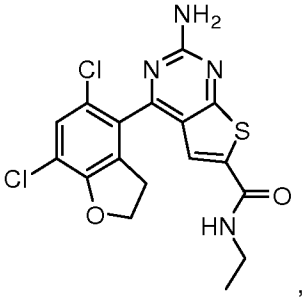
19  ,

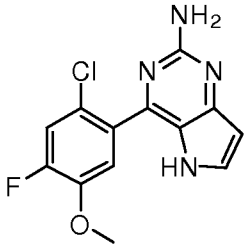
20  ,

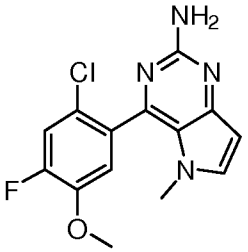
21  ,

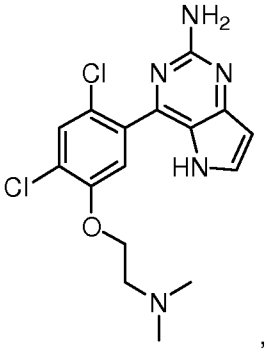
22  ,

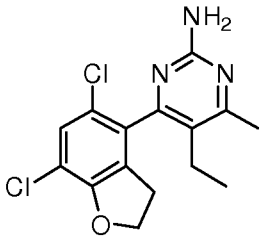
23  ,

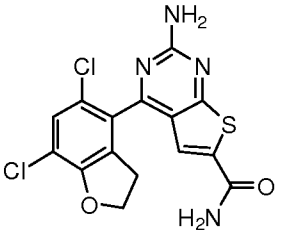
24  ,

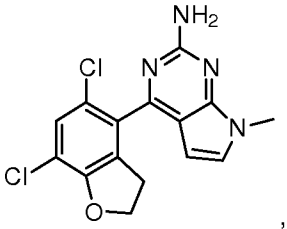
25  ,

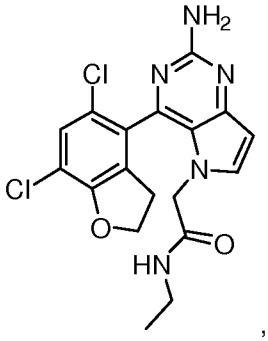
26  ,

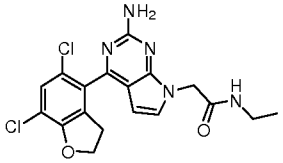
27  ,

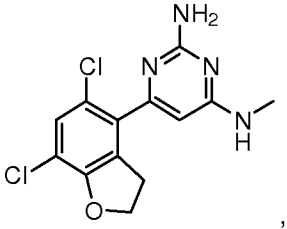
28  ,

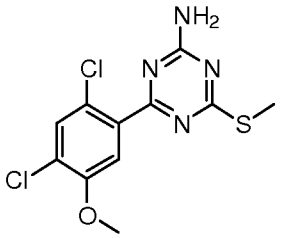
29  ,

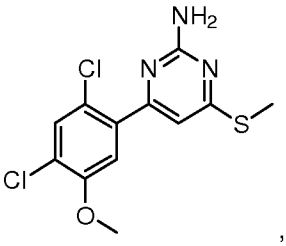
30  ,

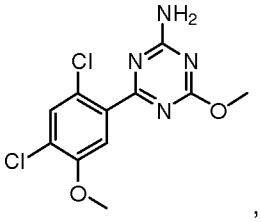
31  ,

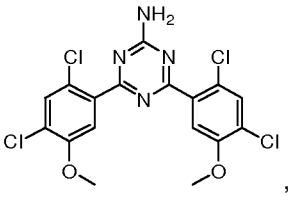
32  ,

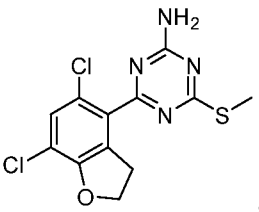
33  ,

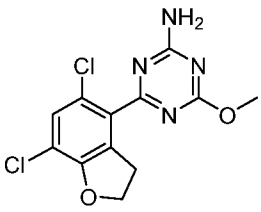
34  ,

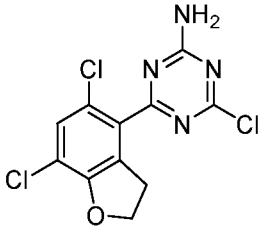
35  ,

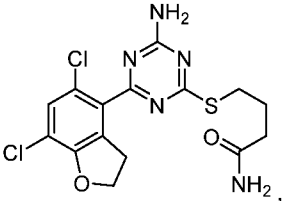
36  ,

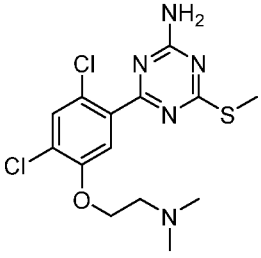
37  ,

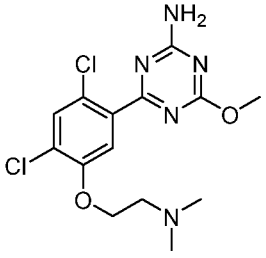
40  ,

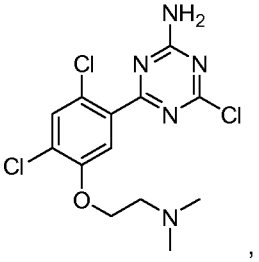
41  ,

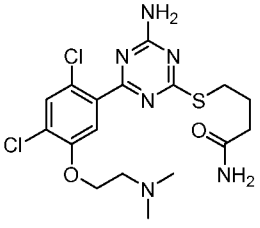
42  ,

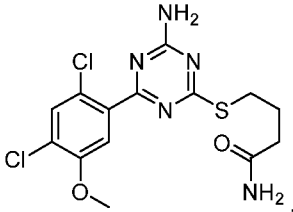
43  ,

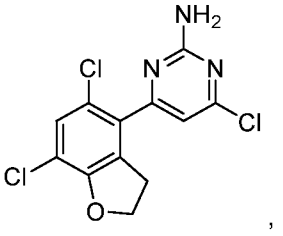
44  ,

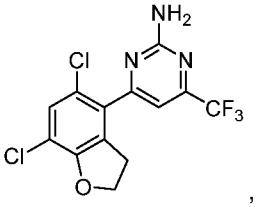
45  ,

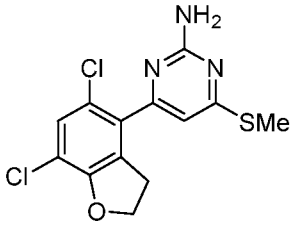
46  ,

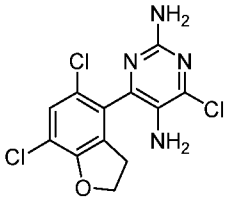
47  ,

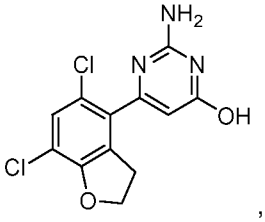
48  ,

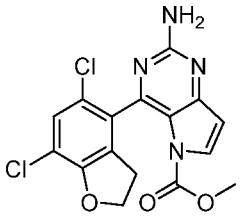
49  ,

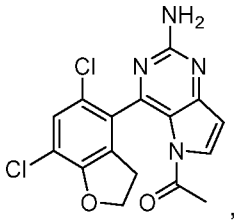
50  ,

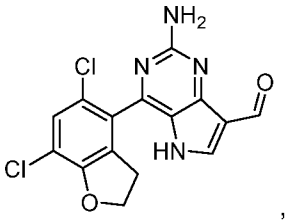
51  ,

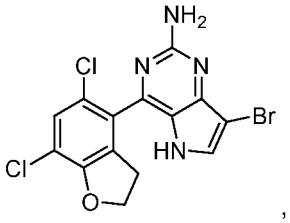
52  ,

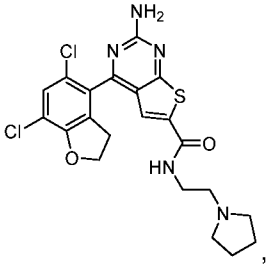
53  ,

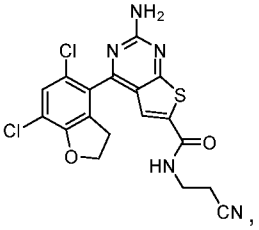
54  ,

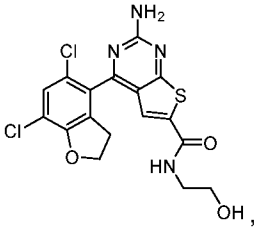
55  ,

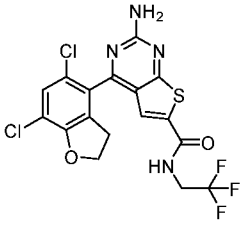
56  ,

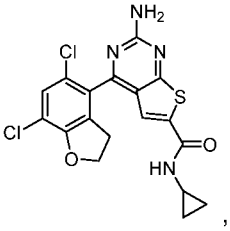
57  ,

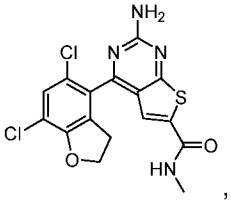
58  ,

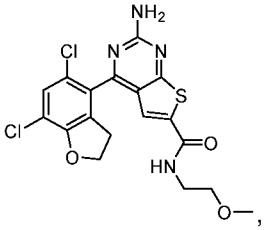
59  ,

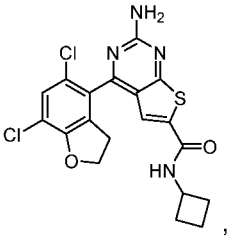
60  ,

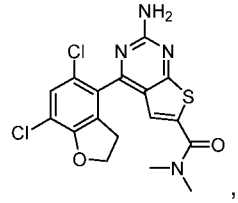
61  ,

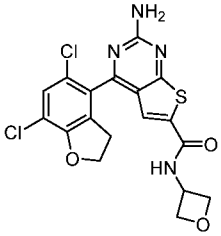
62  ,

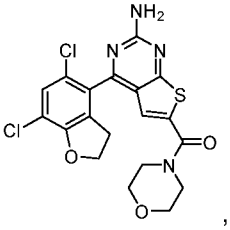
63  ,

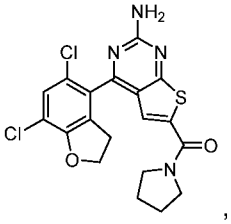
64  ,

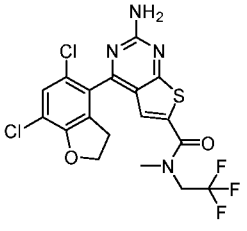
65  ,

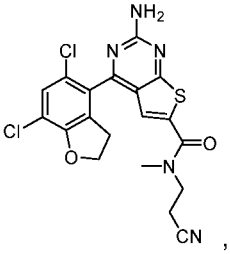
66  ,

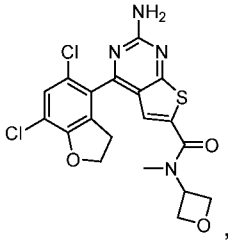
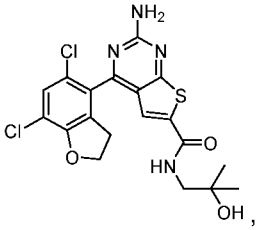
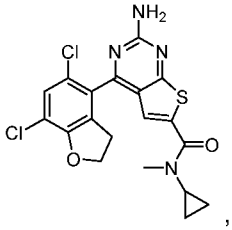
67  ,

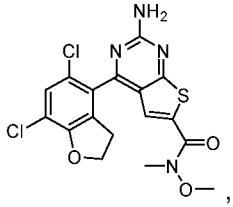
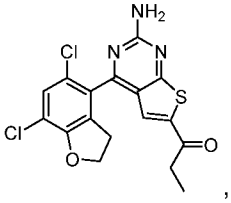
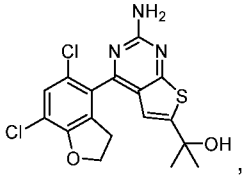
68  ,

69  ,

70  ,

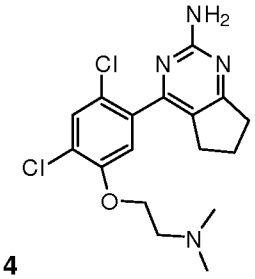
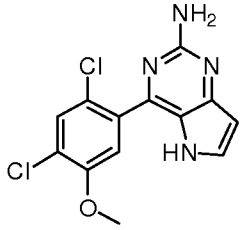
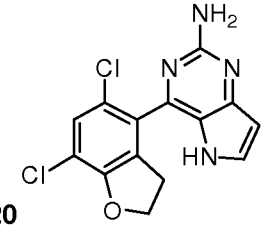
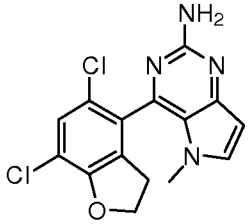
71  ,

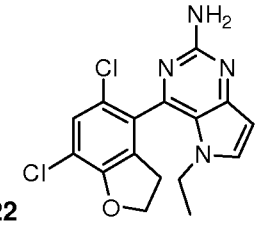
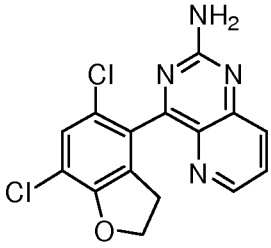
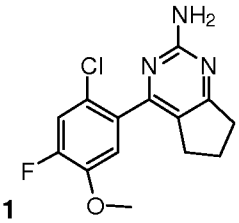
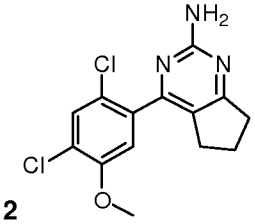
72  , **73**  , **74**  ,

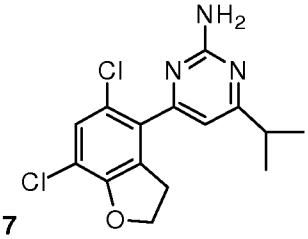
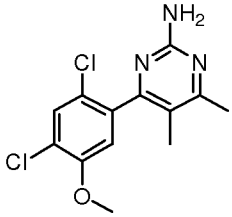
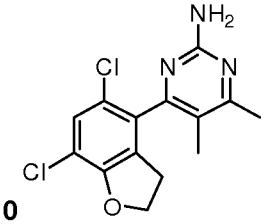
75  , **76**  , or **77**  ,

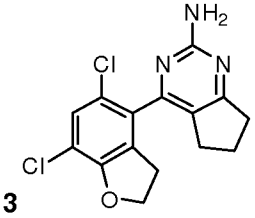
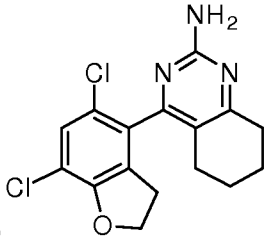
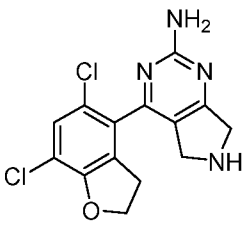
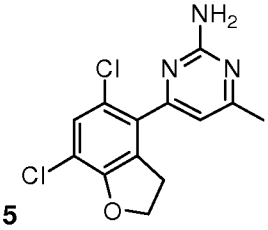
or a pharmaceutically acceptable salt thereof.

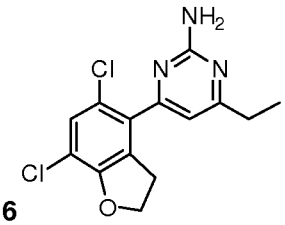
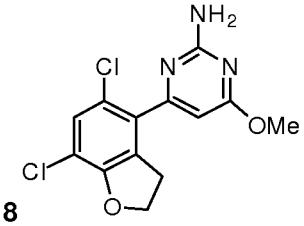
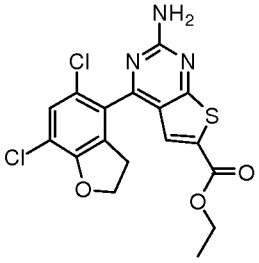
87. The compound of embodiment 84 having the formula:

 **14** ,  **19** ,  **20** ,  **21** ,

 **22** ,  **18** ,  **11** ,  **12** ,

 **7** ,  **9** ,  **10** ,

 **13** ,  **15** ,  **16** ,  **5** ,


6, 
8, 
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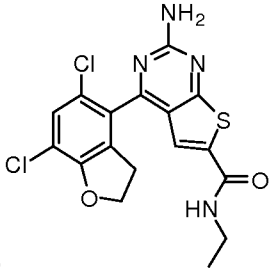
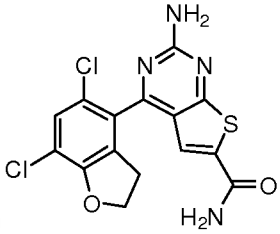
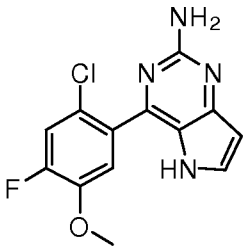

24, 
30, 
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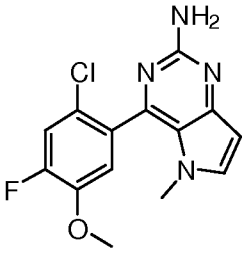
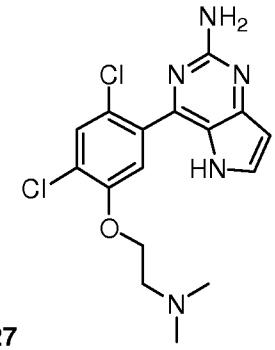
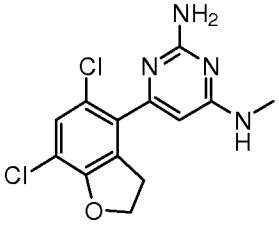

26, 
27, 
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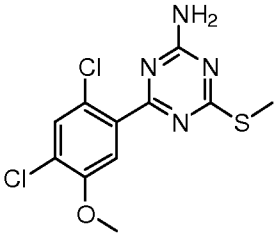
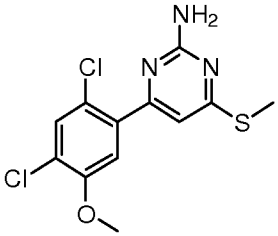
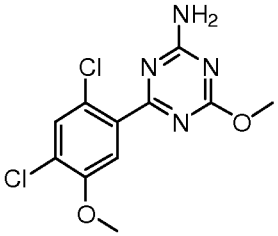

34, 
35, 
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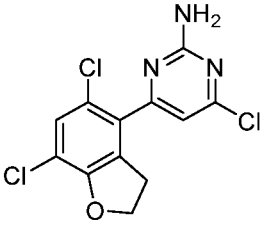
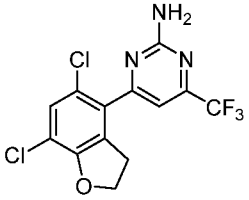
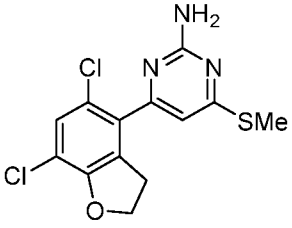

49, 
50, 
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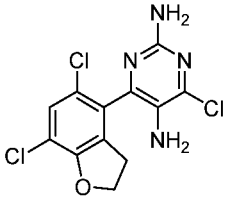
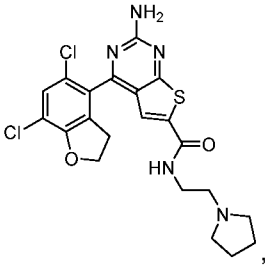
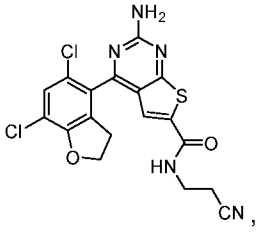

52, 
58, 
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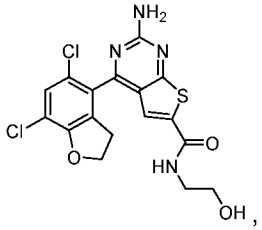
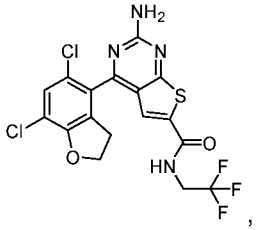
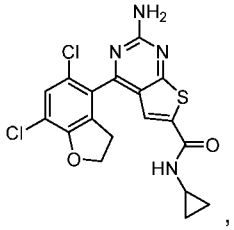
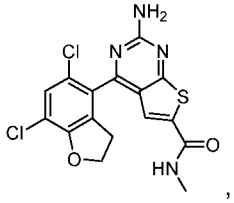
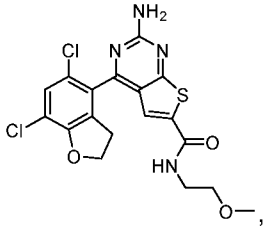
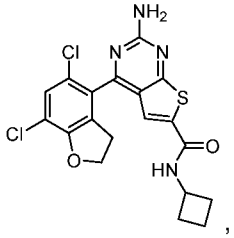
60  ,

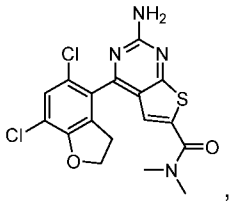
61  ,

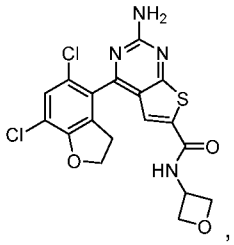
62  ,

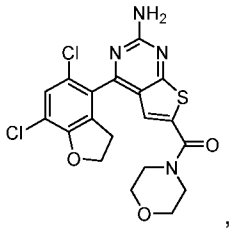
63  ,

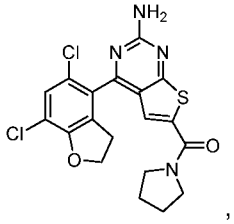
64  ,

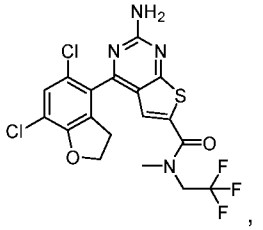
65  ,

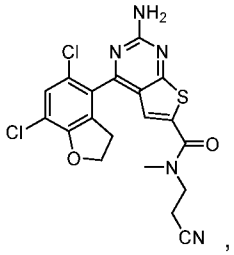
66  ,

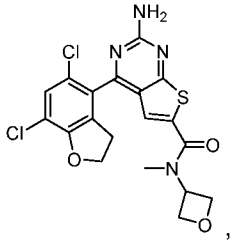
67  ,

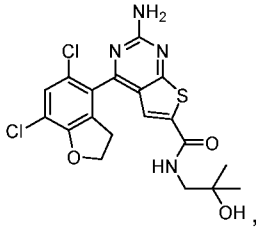
68  ,

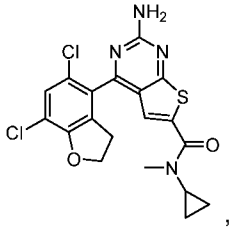
69  ,

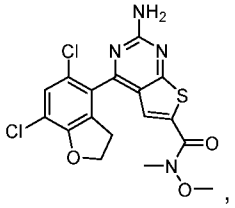
70  ,

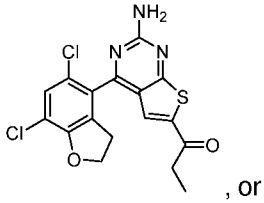
71  ,

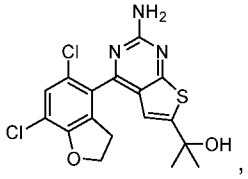
72  ,

73  ,

74  ,

75  ,

76  , or

77  ,

or a pharmaceutically acceptable salt thereof.

88. A pharmaceutical composition including the compound of any one of embodiments 1 to 87, or a pharmaceutically acceptable salt thereof, and one or more of pharmaceutically acceptable carriers or excipients.

89. The pharmaceutical composition of embodiment 88, where the composition is formulated for administration orally, sublingually, buccally, transdermally, intradermally, intramuscularly, parenterally, intravenously, intra-arterially, intracranially, subcutaneously, intraorbitally, intraventricularly, intraspinally,

intraperitoneally, intranasally, by inhalation, and topically.

90. The pharmaceutical composition of embodiment 89, where the composition is formulated for oral administration.

91. A method of treating a disorder in a mammal caused by the action of heat shock protein 90 (Hsp90), the method including administering an effective amount of the compound of any one of embodiments 1 to 87 or a pharmaceutically acceptable salt thereof or the pharmaceutical composition of embodiment 88 to the mammal.

92. The method of embodiment 91, where the disorder is a neurodegenerative disorder.

93. The method of embodiment 92, where the neurodegenerative disorder is a tauopathy.

94. The method of embodiment 92 or 93, where the neurodegenerative disorder is Alzheimer's disease, Huntington's disease, progressive supranuclear palsy, Parkinson's disease, Pick's disease, corticobasal degeneration, chronic traumatic encephalopathy, traumatic brain injury, or frontotemporal dementia.

95. The method of embodiment 94, where the neurodegenerative disorder is Alzheimer's disease.

96. The method of embodiment 91, where the disorder is a proliferative disorder.

97. The method of embodiment 96, where the proliferative disorder is a cancer.

98. The method of embodiment 97, where the cancer is acute myeloid leukemia, gastrointestinal stromal tumor, gastric cancer, glioma, neuroblastoma, glioblastoma, lung cancer, lymphoma, melanoma, myeloma, non-small cell lung cancer, renal cancer, small cell lung cancer, blast-phase chronic myelogenous leukemia, leukemia, lymphoproliferative disorder, metastatic melanoma, relapsed multiple myeloma, refractory multiple myeloma, myeloproliferative disorders, pancreatic cancer, small intestine cancer, or solid tumor.

99. A method of treating an infectious disease in a mammal, the method including administering an effective amount of the compound of any one of embodiments 1 to 87 or a pharmaceutically acceptable salt or the pharmaceutical composition of embodiment 88 thereof to the mammal.

100. The method of embodiment 99, where the infectious disease is a viral infection.

101. The method of embodiment 100, where the viral infection is an infection by a virus of a family selected from the group consisting of Herpesviridae, Polyomaviridae, Poxviridae, Reoviridae, Birnaviridae, Picornaviridae, Flaviviridae, Arenaviridae, Hepeviridae, Rhabdoviridae, Paramoxyviridae, Bunyaviridae, Orthomoxyviridae, Filoviridae, Retroviridae, and Hepadnaviridae.

102. The method of embodiment 101, where the virus of a family Herpesviridae is herpes simplex virus-1, herpes simplex virus-2, herpes herpesvirus-5, Kaposi's sarcoma-associated herpesvirus, varicella zoster virus, or Epstein-Barr virus.

103. The method of embodiment 101, where the virus of Polyomaviridae family is SV40.

104. The method of embodiment 101, where the virus of Poxviridae family is vaccinia virus.

105. The method of embodiment 101, where the virus of Reoviridae family is rotavirus.

106. The method of embodiment 101, where the virus of Birnaviridae family is infectious bursal disease virus.

107. The method of embodiment 101, where the virus of Picornaviridae family is poliovirus, rhinovirus, or coxsackievirus.

108. The method of embodiment 101, where the virus of Flaviviridae family is hepatitis C virus or dengue virus.

109. The method of embodiment 101, where the virus of Arenaviridae family is lymphocytic choriomeningitis virus.

110. The method of embodiment 101, where the virus of Hepeviridae family is Hepatitis E virus.

111. The method of embodiment 101, where the virus of Rhabdoviridae family is vesicular stomatitis virus.

112. The method of embodiment 101, where the virus of Paramoxyviridae family is human parainfluenza virus 2, human parainfluenza virus 3, SV5, SV41, measles virus, or Sendai virus.

113. The method of embodiment 101, where the virus of Bunyaviridae family is La Crosse virus.

114. The method of embodiment 101, where the virus of Orthomoxyviridae family is influenza A virus.

115. The method of embodiment 101, where the virus of Filoviridae family is Ebola virus.

116. The method of embodiment 101, where the virus of Retroviridae family is HTLV1 or HIV1.

117. The method of embodiment 101, where the virus of Hepadnaviridae family is hepatitis B virus.

118. The method of embodiment 99, where the infectious disease is a fungal infection.

119. The method of embodiment 118, where the fungal infection is a *Candida albicans* infection, an *Aspergillus fumigates* infection, or *Pneumocystis jiroveci* infection.

120. The method of embodiment 99, where the infectious disease is a bacterial infection.

121. The method of embodiment 120, where the bacterial infection is a mycobacteria infection or anthrax infection.

122. The method of embodiment 120, where the bacterial infection is a bacterial pneumonia.

123. The method of embodiment 91, where the disorder an inflammatory or autoimmune disease.

124. The method of embodiment 123, where the inflammatory or autoimmune disease is rheumatoid arthritis, systemic lupus erythermatosus, or asthma.

125. The method of embodiment 91, where the disorder is a cardiovascular disease.

126. The method of embodiment 125, where the cardiovascular disease is atherosclerosis or cardiomyopathy.

127. The method of embodiment 91, where the disorder is an allergy.

128. The method of any one of embodiments 91 to 127, where the compound is administered orally, sublingually, buccally, transdermally, intradermally, intramuscularly, parenterally, intravenously, intra-arterially, intracranially, subcutaneously, intraorbitally, intraventricularly, intraspinally, intraperitoneally, intranasally, by inhalation, and topically.

129. The method of embodiment 128, where the compound is administered orally.

130. The method of any one of embodiments 91 to 129, where the mammal is human.

131. The method of any one of embodiments 91 to 130, where the compound is administered orally, sublingually, buccally, transdermally, intradermally, intramuscularly, parenterally, intravenously, intra-arterially, intracranially, subcutaneously, intraorbitally, intraventricularly, intraspinally, intraperitoneally, intranasally, by inhalation, and topically.

132. The method of embodiment 131, where the compound is administered orally.

133. The method of any one of embodiments 91 to 132, where the mammal is human.

134. A compound for use in treating a disorder in a mammal caused by the action of heat shock protein 90 (Hsp90), where the compound is the compound of any one of embodiments 1 to 87 or a

pharmaceutically acceptable salt thereof.

135. The compound of embodiment 134, where the disorder is a neurodegenerative disorder.

136. The compound of embodiment 135, where the neurodegenerative disorder is a tauopathy.

137. The compound of embodiment 134 or 135, where the neurodegenerative disorder is Alzheimer's disease, Huntington's disease, progressive supranuclear palsy, Parkinson's disease, Pick's disease, corticobasal degeneration, chronic traumatic encephalopathy, traumatic brain injury, or frontotemporal dementia.

138. The compound of embodiment 137, where the neurodegenerative disorder is Alzheimer's disease.

139. The compound of embodiment 134, where the disorder is a proliferative disorder.

140. The compound of embodiment 139, where the proliferative disorder is a cancer.

141. The compound of embodiment 140, where the cancer is acute myeloid leukemia, gastrointestinal stromal tumor, gastric cancer, glioblastoma, lung cancer, lymphoma, melanoma, myeloma, non-small cell lung cancer, renal cancer, small cell lung cancer, blast-phase chronic myelogenous leukemia, leukemia, lymphoproliferative disorder, metastatic melanoma, relapsed multiple myeloma, refractory multiple myeloma, myeloproliferative disorders, pancreatic cancer, small intestine cancer, or solid tumor.

142. The compound of embodiment 134, where the disorder is an infectious disease.

143. The compound of embodiment 142, where the infectious disease is a viral infection.

144. The compound of embodiment 143, where the viral infection is an infection by a virus of a family selected from the group consisting of Herpesviridae, Polyomaviridae, Poxviridae, Reoviridae, Birnaviridae, Picornaviridae, Flaviviridae, Arenaviridae, Hepeviridae, Rhabdoviridae, Paramoxyviridae, Bunyaviridae, Orthomoxyviridae, Filoviridae, Retroviridae, and Hepadnaviridae.

145. The compound of embodiment 144, where the virus of a family Herpesviridae is herpes simplex virus-1, herpes simplex virus-2, herpes herpesvirus-5, Kaposi's sarcoma-associated herpesvirus, varicella zoster virus, or Epstein-Barr virus.

146. The compound of embodiment 144, where the virus of Polyomaviridae family is SV40.

147. The compound of embodiment 144, where the virus of Poxviridae family is vaccinia virus.

148. The compound of embodiment 144, where the virus of Reoviridae family is rotavirus.

149. The compound of embodiment 144, where the virus of Birnaviridae family is infectious bursal disease virus.

150. The compound of embodiment 144, where the virus of Picornaviridae family is poliovirus, rhinovirus, or coxsackievirus.

141. The compound of embodiment 144, where the virus of Flaviviridae family is hepatitis C virus or dengue virus.

152. The compound of embodiment 144, where the virus of Arenaviridae family is lymphocytic choriomeningitis virus.

153. The compound of embodiment 144, where the virus of Hepeviridae family is Hepatitis E virus.

154. The compound of embodiment 144, where the virus of Rhabdoviridae family is vesicular stomatitis virus.

155. The compound of embodiment 144, where the virus of Paramoxyviridae family is human parainfluenza virus 2, human parainfluenza virus 3, SV5, SV41, measles virus, or Sendai virus.

156. The compound of embodiment 144, where the virus of Bunyaviridae family is La Crosse virus.

157. The compound of embodiment 144, where the virus of Orthomoxyviridae family is influenza A virus.

158. The compound of embodiment 144, where the virus of Filoviridae family is Ebola virus.

159. The compound of embodiment 144, where the virus of Retroviridae family is HTLV1 or HIV1.

160. The compound of embodiment 144, where the virus of Hepadnaviridae family is hepatitis B virus.

161. The compound of embodiment 134, where the infectious disease is a fungal infection.

162. The compound of embodiment 161, where the fungal infection is a *Candida albicans* infection, an *Aspergillus fumigates* infection, or *Pneumocystis jiroveci* infection.

163. The compound of embodiment 134, where the infectious disease is a bacterial infection.

165. The compound of embodiment 163, where the bacterial infection is a mycobacteria infection or anthrax infection.

166. The compound of embodiment 163, where the bacterial infection is a bacterial pneumonia.

167. The compound of embodiment 134, where the disorder an inflammatory or autoimmune disease.

168. The compound of embodiment 167, where the inflammatory or autoimmune disease is rheumatoid arthritis, systemic lupus erythermatosus, or asthma.

169. The compound of embodiment 134, where the disorder is a cardiovascular disease.

170. The compound of embodiment 169, where the cardiovascular disease is atherosclerosis or cardiomyopathy.

171. The compound of embodiment 170, where the disorder is an allergy.

172. Use of a compound in the manufacture of a medicament for treating a disorder in a mammal caused by the action of heat shock protein 90 (Hsp90), where the compound is the compound of any one of embodiments 1 to 87 or a pharmaceutically acceptable salt thereof.

173. Use of a compound for treating a disorder in a mammal caused by the action of heat shock protein 90 (Hsp90), where the compound is the compound of any one of embodiments 1 to 87 or a pharmaceutically acceptable salt thereof.

174. The use of embodiment 172 or 173, where the disorder is a neurodegenerative disorder.

175. The use of embodiment 174, where the neurodegenerative disorder is a tauopathy.

176. The use of embodiment 174 or 175, where the neurodegenerative disorder is Alzheimer's disease, Huntington's disease, progressive supranuclear palsy, Parkinson's disease, Pick's disease, corticobasal degeneration, chronic traumatic encephalopathy, traumatic brain injury, or frontotemporal dementia.

177. The use of embodiment 176, where the neurodegenerative disorder is Alzheimer's disease.

178. The use of embodiment 172 or 173, where the disorder is a proliferative disorder.

179. The use of embodiment 178, where the proliferative disorder is a cancer.

180. The use of embodiment 179, where the cancer is acute myeloid leukemia, gastrointestinal stromal tumor, gastric cancer, glioblastoma, lung cancer, lymphoma, melanoma, myeloma, non-small cell lung cancer, renal cancer, small cell lung cancer, blast-phase chronic myelogenous leukemia, leukemia, lymphoproliferative disorder, metastatic melanoma, relapsed multiple myeloma, refractory multiple myeloma, myeloproliferative disorders, pancreatic cancer, small intestine cancer, or solid tumor.

181. Use of a compound for treating, or in the manufacture of a meadicament for treating, an infectious disease, where the compound is the compound of any one of embodiments 1 to 87.

182. The use of embodiment 181, where the infectious disease is a viral infection.

183. The use of embodiment 182, where the viral infection is an infection by a virus of a family selected from the group consisting of Herpesviridae, Polyomaviridae, Poxviridae, Reoviridae, Birnaviridae, Picornaviridae, Flaviviridae, Arenaviridae, Hepeviridae, Rhabdoviridae, Paramoxyviridae, Bunyaviridae, Orthomoxyviridae, Filoviridae, Retroviridae, and Hepadnaviridae.

184. The use of embodiment 183, where the virus of a family Herpesviridae is herpes simplex virus-1, herpes simplex virus-2, herpes herpesvirus-5, Kaposi's sarcoma-associated herpesvirus, varicella zoster virus, or Epstein-Barr virus.

185. The use of embodiment 183, where the virus of Polyomaviridae family is SV40.

186. The use of embodiment 183, where the virus of Poxviridae family is vaccinia virus.

187. The use of embodiment 183, where the virus of Reoviridae family is rotavirus.

188. The use of embodiment 183, where the virus of Birnaviridae family is infectious bursal disease virus.

189. The use of embodiment 183, where the virus of Picornaviridae family is poliovirus, rhinovirus, or coxsackievirus.

190. The use of embodiment 183, where the virus of Flaviviridae family is hepatitis C virus or dengue virus.

191. The use of embodiment 183, where the virus of Arenaviridae family is lymphocytic choriomeningitis virus.

192. The use of embodiment 183, where the virus of Hepeviridae family is Hepatitis E virus.

193. The use of embodiment 183, where the virus of Rhabdoviridae family is vesicular stomatitis virus.

194. The use of embodiment 183, where the virus of Paramoxyviridae family is human parainfluenza virus 2, human parainfluenza virus 3, SV5, SV41, measles virus, or Sendai virus.

195. The use of embodiment 183, where the virus of Bunyaviridae family is La Crosse virus.

196. The use of embodiment 183, where the virus of Orthomoxyviridae family is influenza A virus.

197. The use of embodiment 183, where the virus of Filoviridae family is Ebola virus.

198. The use of embodiment 183, where the virus of Retroviridae family is HTLV1 or HIV1.

199. The use of embodiment 183, where the virus of Hepadnaviridae family is hepatitis B virus.

200. The use of embodiment 172 or 173, where the infectious disease is a fungal infection.

201. The use of embodiment 200, where the fungal infection is a *Candida albicans* infection, an *Aspergillus fumigates* infection, or *Pneumocystis jiroveci* infection.

202. The use of embodiment 172 or 173, where the infectious disease is a bacterial infection.

203. The use of embodiment 202, where the bacterial infection is a mycobacteria infection or anthrax infection.

204. The use of embodiment 203, where the bacterial infection is a bacterial pneumonia.

205. The use of embodiment 172 or 173, where the disorder an inflammatory or autoimmune disease.

206. The use of embodiment 205, where the inflammatory or autoimmune disease is rheumatoid arthritis, systemic lupus erythermatosus, or asthma.

207. The use of embodiment 172 or 173, where the disorder is a cardiovascular disease.

208. The use of embodiment 207, where the cardiovascular disease is atherosclerosis cardiomyopathy.

209. The use of embodiment 172 or 173, where the disorder is an allergy.

210. The compound of any one of embodiments 134 to 171 or the use of any one of embodiments 172 to 209, where the compound is formulated for administration by a route selected from the group consistin of oral, sublingual, buccal, transdermal, intradermal, intramuscular, parenteral, intravenous, intra-arterial, intracranial, subcutaneous, intraorbital, intraventricular, intraspinal, intraperitoneal, intranasal, by inhalation, and topical.

211. The compound or the use of embodiment 128, where the compound is formulated for oral administration.

212. A method of inhibiting Hsp90, the method including contacting a cell with the compound of any one of embodiments 1 to 87 or a pharmaceutically acceptable salt thereof.

213. The method of embodiment 212, where the cell is in vitro.

214. A compound for use in inhibiting Hsp90, where the compound is the compound of any one of

embodiments 1 to 87 or a pharmaceutically acceptable salt thereof.

215. Use of a compound for inhibiting Hsp90, where the compound is the compound of any one of embodiments 1 to 87 or a pharmaceutically acceptable salt thereof.

216. A kit including:

(i) the pharmaceutical composition of any one of embodiments 88 to 90; and

(ii) instructions for use of the pharmaceutical compositions of (i) to treat a disorder in a mammal caused by the action of Hsp90.

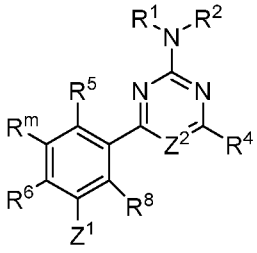
All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each independent publication or patent application was specifically and individually indicated to be incorporated by reference.

While the invention has been described in connection with specific embodiments thereof, it will be understood that it is capable of further modifications and this application is intended to cover any variations, uses, or adaptations of the invention following, in general, the principles of the invention and including such departures from the present disclosure that come within known or customary practice within the art to which the invention pertains and may be applied to the essential features hereinbefore set forth, and follows in the scope of the claims.

Other embodiments are in the claims.

Claims

1. A compound according to formula (I):



(I), or a pharmaceutically acceptable salt thereof,

wherein

Z^1 is $-OR^7$, $-N(R^{10})R^7$, $-SR^7$, or $-C(R^{10})(R^{11})R^7$;

Z^2 is $-C(R^3)=$ or $-N=$;

each R^1 and R^2 is, independently, H, optionally substituted C_{1-3} acyl, or optionally substituted C_{1-3} alkyl;

R^3 and R^4, together with the atoms to which each is attached, join to form an optionally substituted five- or six-membered ring optionally comprising one to three heteroatoms selected from the group consisting of sulfur, oxygen, and nitrogen, wherein said nitrogen is optionally substituted with R^9, or R^3 is H, halogen, cyano, optionally substituted C_{1-6} alkyl, optionally substituted C_{1-3} alkoxy, or optionally substituted amino, and R^4 is halogen, cyano, optionally substituted C_{1-6} alkyl, optionally substituted C_{1-3} alkoxy, optionally substituted amino, optionally substituted C_{1-6} thioalkoxy, or optionally substituted C_{6-10} aryl;

R^5 is halogen, H, optionally substituted C_{1-3} alkyl, optionally substituted C_{1-3} alkoxy, or CN;

R^6 is halogen, H, optionally substituted C_{1-3} alkyl, optionally substituted C_{1-3} alkoxy, or CN;

R^7 and R^8, together with the atoms to which each is attached, join to form an optionally substituted five-, six-, or seven- membered ring optionally comprising one or two heteroatoms selected from nitrogen, oxygen, and sulfur; or R^7 is optionally substituted C_{1-3} alkyl, optionally substituted C_{1-3} alkcycloalkyl, optionally substituted C_{1-3} alkheterocyclyl, or optionally substituted C_{1-3} alkaryl, and R^8 is H;

R^9 is H, optionally substituted C_{1-3} alkyl, optionally substituted C_{3-8} cycloalkyl, optionally substituted C_{6-10} aryl, optionally substituted C_{2-9} heteroaryl, optionally substituted C_{2-9} heterocyclyl, optionally substituted C_{1-3} alkcycloalkyl, optionally substituted C_{1-3} alkheterocyclyl, or optionally substituted C_{1-3} alkaryl;

R^{10} is H, optionally substituted C_{1-3} alkyl, optionally substituted C_{3-8} cycloalkyl, optionally substituted C_{6-10} aryl, optionally substituted C_{2-9} heteroaryl, optionally substituted C_{2-9} heterocyclyl, optionally substituted C_{1-3} alkcycloalkyl, optionally substituted C_{1-3} alkheterocyclyl, or optionally substituted C_{1-3} alkaryl, and R^{11} is H, optionally substituted C_{1-3} alkyl, or R^{10} and R^{11} combine to form =O or =S; and

R^m is H, halogen, cyano, optionally substituted C_{1-4} acyl, optionally substituted C_{1-4} alkyl, or optionally substituted C_{1-3} alkoxy;

wherein,

when Z^2 is CR^3, each of R^1 and R^2 is H, R^3 is H, R^4 is methyl or chloro, and each of R^5 and R^6 is chloro,

Z^1 is not methoxy;

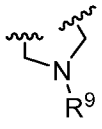
when Z^2 is N, each of R^5 and R^6 is chloro, R^3 is H, R^4 is substituted C_{1-6} thioalkoxy,

Z^1 is not cyanomethoxy or aminomethoxy;

when Z^2 is CR^3, each of R^5 and R^6 is chloro, R^3 is H, and R^4 is halogen,

Z^1 is not 2-amino-2-oxoethoxy, 2-(N,N-diethylamino)ethoxy, methoxy, or benzyloxy;

when R^5 is chloro, R^6 is bromo, Z^1 is $-OR^7$, and R^3 and R^4 combine to form a group according to formula (IIa):


(IIa),

R^7 is not methyl, ethyl, n-propyl, 2-(N-pyrazolyl)ethyl, 2-(N-imidazolyl)ethyl, 3-hydroxypropyl, cyanomethyl, 2-chloroethyl, 2-hydroxyethyl, 2-oxo-propyl, 2-(N,N-dimethylamino)ethyl, difluoromethyl, or 2-(*t*-butylamino)ethyl;

when each R^5 and R^6 is bromo, Z^1 is $-OR^7$, and R^3 and R^4 combine to form a group according to formula (IIa),

R^7 is not methyl;

when each R^5 and R^6 is chloro, Z^1 is $-OR^7$, and R^3 and R^4 combine to form a group according to formula (IIa),

R^7 is not methyl, 2-(N-imidazolyl)ethyl, methoxymethyl, 2-(N-pyrazolyl)ethyl, 2-(3-methylpyrazol-1-yl)ethyl, 2-pyridyl-methyl, 1,3-dimethyl-1H-1,2,4-triazol-5-yl-methyl, 2-pyrimidinylmethyl, imidazol-2-yl-methyl, 5-methyl-isoxazol-3-yl-methyl, 4-methyl-imidazol-5-yl-methyl, or 3-methyl-1,2,4-oxadiazol-5-yl-methyl;

when each R^5 and R^6 is chloro, Z^1 is $-OR^7$, R^7 and R^8 combine to form $-CH_2-CH_2-$, and R^3 and R^4 combine to form a group according to formula (IIa),

R^9 is not ethoxycarbonyl, cyclobutylaminocarbonyl, or cyclobutadienylaminocarbonyl

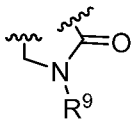
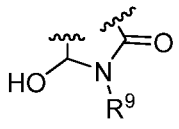
when R^5 is methoxy, R^6 is methyl, Z^1 is $-OR^7$, and R^3 and R^4 combine to form a group according to formula (IIa),

R^7 is not methyl;

when R^5 is chloro, R^6 is ethyl, Z^1 is $-OR^7$, and R^3 and R^4 combine to form a group according to formula (IIa),

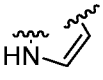
R^7 is not methyl;

when each R^5 and R^6 is chloro, Z^1 is $-OR^7$, and R^3 and R^4 combine to form a group according to formula (IIb) or (IIc),


(IIb) or 
(IIc),

R^7 is not methyl or 2-(N,N-diethylamino)ethyl;

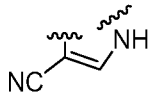
when R^7 is methyl, R^5 is chloro, Z^1 is $-OR^7$, and R^3 and R^4 combine to form a group according to formula (IIIa),


(IIIa),

R^6 is not bromo;

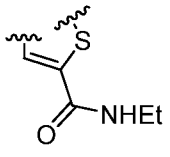
when R^5 is chloro, R^6 is methoxy, Z^1 is $-OR^7$, and R^3 and R^4 combine to form a group according to

formula (IIIb):


(IIIb),

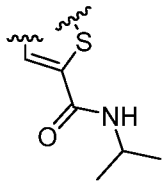
neither R^1 nor R^2 is 2-(N,N-diethylamino)ethyl;

when each R^5 and R^6 is chloro, Z^1 is -OR^7, and R^3 and R^4 combine to form a group according to formula (IVa):


(IVa),

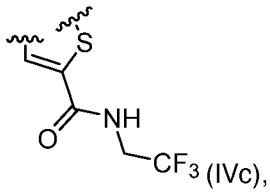
R^7 is not 3-(N-morpholinyl)propyl, benzyl, 1-ethyl-pyrrolydin-3-yl, 1-methyl-piperidin-4-yl, 2-(1-methyl-pyrrolidin-2-yl)ethyl, or 3-(N,N-diethylamino)propyl;

when each R^5 and R^6 is chloro, Z^1 is -OR^7, and R^3 and R^4 combine to form a group according to formula (IVb):


(IVb),

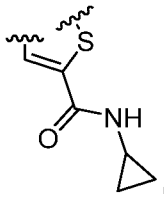
R^7 is not 2-methoxyethyl or benzyl;

when each R^5 and R^6 is chloro, Z^1 is -OR^7, and R^3 and R^4 combine to form a group according to formula (IVc):


(IVc),

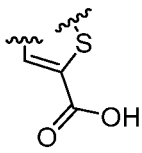
R^7 is not 2-(N,N-diethylamino)ethyl or 3-(N,N-dimethylamino)propyl;

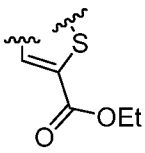
when each R^5 and R^6 is chloro, Z^1 is -OR^7, and R^3 and R^4 combine to form a group according to formula (IVd):


(IVd),

R^7 is not 2-(pyrrolidin-1-yl)ethyl or 2-hydroxyethyl;

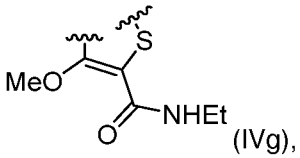
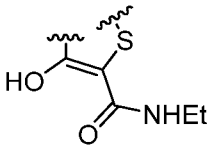
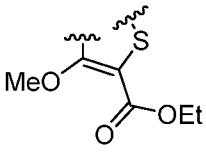
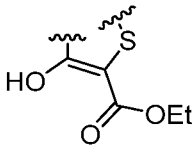
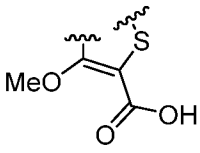
when each R^5 and R^6 is chloro, Z^1 is -OR^7, and R^3 and R^4 combine to form a group according to formula (IVe) or (IVf):


(IVe) or


(IVf),

R^7 is not benzyl;

when R^5 is chloro, R^6 is bromo, Z^1 is -OR^7, and R^3 and R^4 combine to form a group according to formula (IVg), (IVh), (IVi), (IVj), or (IVk):


(IVg),

(IVh),

(IVi),

(IVj), or

(IVk),

R^7 is not methyl;

when R^6 is methyl,

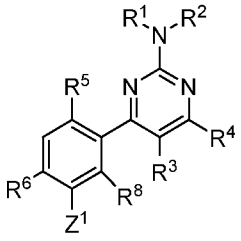
each R^1 and R^2 is H; and

when R^3 is H, Z^1 is -OR^7, and each R^5 and R^6 is chloro,

R^7 is not methyl.

2. The compound of claim 1, wherein R^m is H.

3. A compound according to formula (Ia):


(Ia), or a pharmaceutically acceptable salt thereof,

wherein

each R^1 and R^2 is, independently, H or optionally substituted C_{1-3} alkyl;

R^3 and R^4, together with the atoms to which each is attached, join to form an optionally substituted five- or six-membered ring optionally comprising from one to three heteroatoms selected from the group consisting of sulfur, oxygen, and nitrogen, wherein said nitrogen is optionally substituted with R^9, or R^3 is H, halogen, cyano, optionally substituted C_{1-6} alkyl, optionally substituted C_{1-3} alkoxy, or optionally substituted amino, and R^4 is halogen, cyano, optionally substituted C_{1-6} alkyl, optionally substituted C_{1-3} alkoxy, optionally substituted amino, optionally substituted C_{1-6} thioalkyl, or optionally substituted C_{6-10} aryl;

R^5 is halogen, H, optionally substituted C_{1-3} alkyl, optionally substituted C_{1-3} alkoxy, or CN;

R^6 is halogen, H, optionally substituted C_{1-3} alkyl, optionally substituted C_{1-3} alkoxy, or CN;

R^7 and R^8, together with the atoms to which each is attached, join to form an optionally substituted five-, six-, or seven- membered ring optionally comprising one or two heteroatoms selected from nitrogen, oxygen, and sulfur; or R^7 is optionally substituted C_{1-3} alkyl, optionally substituted C_{1-3} alkcycloalkyl, optionally substituted C_{1-3} alkheterocyclyl, or optionally substituted C_{1-3} alkaryl, and R^8 is H;

R^9 is H, optionally substituted C_{1-3} alkyl, optionally substituted C_{3-8} cycloalkyl, optionally substituted C_{6-10} aryl, optionally substituted C_{2-9} heteroaryl, optionally substituted C_{2-9} heterocyclyl, optionally substituted C_{1-3} alkcycloalkyl, optionally substituted C_{1-3} alkheterocyclyl, or optionally

substituted C_{1-3} alkaryl;

Z^1 is $-OR^7$, $-N(R^{10})R^7$, $-SR^7$, or $-C(R^{10})(R^{11})R^7$; and

R^{10} is H, optionally substituted C_{1-3} acyl, optionally substituted C_{1-3} alkyl, optionally substituted C_{3-8} cycloalkyl, optionally substituted C_{6-10} aryl, optionally substituted C_{2-9} heteroaryl, optionally substituted C_{2-9} heterocyclyl, optionally substituted C_{1-3} alkcycloalkyl, optionally substituted C_{1-3} alkheterocyclyl, or optionally substituted C_{1-3} alkaryl, and R^{11} is H, optionally substituted C_{1-3} alkyl, or R^{10} and R^{11} combine to form =O or =S;

wherein,

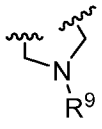
when each of R^1 and R^2 is H, R^3 is H, R^4 is methyl or chloro, and each of R^5 and R^6 is chloro,

Z^1 is not methoxy;

when each of R^5 and R^6 is chloro, R^3 is H, and R^4 is halogen,

Z^1 is not 2-amino-2-oxoethoxy, 2-(N,N-diethylamino)ethoxy, methoxy, or benzyloxy;

when R^5 is chloro, R^6 is bromo, Z^1 is $-OR^7$, and R^3 and R^4 combine to form a group according to formula (IIa):



(IIa),

R^7 is not methyl, ethyl, n-propyl, 2-(N-pyrazolyl)ethyl, 2-(N-imidazolyl)ethyl, 3-hydroxypropyl, cyanomethyl, 2-chloroethyl, 2-hydroxyethyl, 2-oxo-propyl, 2-(N,N-dimethylamino)ethyl, difluoromethyl, or 2-(*t*-butylamino)ethyl;

when each R^5 and R^6 is bromo, Z^1 is $-OR^7$, and R^3 and R^4 combine to form a group according to formula (IIa),

R^7 is not methyl;

when each R^5 and R^6 is chloro, Z^1 is $-OR^7$, and R^3 and R^4 combine to form a group according to formula (IIa),

R^7 is not methyl, 2-(N-imidazolyl)ethyl, methoxymethyl, 2-(N-pyrazolyl)ethyl, 2-(3-methylpyrazol-1-yl)ethyl, 2-pyridyl-methyl, 1,3-dimethyl-1H-1,2,4-triazol-5-yl-methyl, 2-pyrimidinylmethyl, imidazol-2-yl-methyl, 5-methyl-isoxazol-3-yl-methyl, 4-methyl-imidazol-5-yl-methyl, or 3-methyl-1,2,4-oxadiazol-5-yl-methyl;

when each R^5 and R^6 is chloro, Z^1 is $-OR^7$, R^7 and R^8 combine to form $-CH_2-CH_2-$, and R^3 and R^4 combine to form a group according to formula (IIa),

R^9 is not ethoxycarbonyl, cyclobutylaminocarbonyl, or cyclobutadienylaminocarbonyl

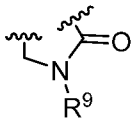
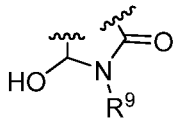
when R^5 is methoxy, R^6 is methyl, Z^1 is $-OR^7$, and R^3 and R^4 combine to form a group according to formula (IIa),

R^7 is not methyl;

when R^5 is chloro, R^6 is ethyl, Z^1 is $-OR^7$, and R^3 and R^4 combine to form a group according to formula (IIa),

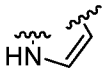
R^7 is not methyl;

when each R^5 and R^6 is chloro, Z^1 is $-OR^7$, and R^3 and R^4 combine to form a group according to formula (IIb) or (IIc),


(IIb) or 
(IIc),

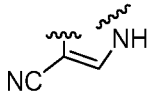
R^7 is not methyl or 2-(N,N-diethylamino)ethyl;

when R^7 is methyl, R^5 is chloro, Z^1 is -OR^7, and R^3 and R^4 combine to form a group according to formula (IIIa),


(IIIa),

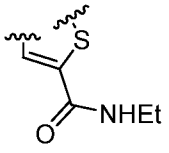
R^6 is not bromo;

when R^5 is chloro, R^6 is methoxy, Z^1 is -OR^7, and R^3 and R^4 combine to form a group according to formula (IIIb):


(IIIb),

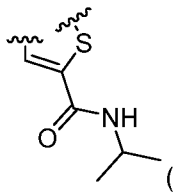
neither R^1 nor R^2 is 2-(N,N-diethylamino)ethyl;

when each R^5 and R^6 is chloro, Z^1 is -OR^7, and R^3 and R^4 combine to form a group according to formula (IVa):


(IVa),

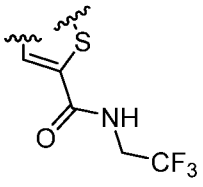
R^7 is not 3-(N-morpholinyl)propyl, benzyl, 1-ethyl-pyrrolydin-3-yl, 1-methyl-piperidin-4-yl, 2-(1-methyl-pyrrolidin-2-yl)ethyl, or 3-(N,N-diethylamino)propyl;

when each R^5 and R^6 is chloro, Z^1 is -OR^7, and R^3 and R^4 combine to form a group according to formula (IVb):


(IVb),

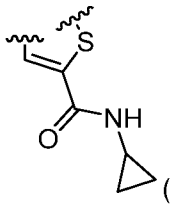
R^7 is not 2-methoxyethyl or benzyl;

when each R^5 and R^6 is chloro, Z^1 is -OR^7, and R^3 and R^4 combine to form a group according to formula (IVc):


(IVc),

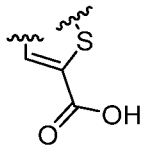
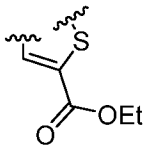
R^7 is not 2-(N,N-diethylamino)ethyl or 3-(N,N-dimethylamino)propyl;

when each R^5 and R^6 is chloro, Z^1 is -OR^7, and R^3 and R^4 combine to form a group according to formula (IVd):


(IVd),

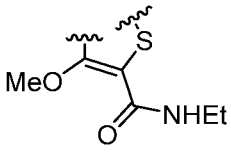
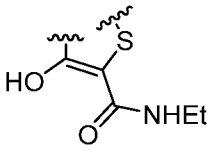
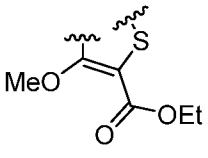
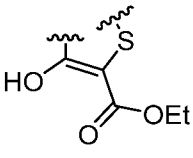
R^7 is not 2-(pyrrolidin-1-yl)ethyl or 2-hydroxyethyl;

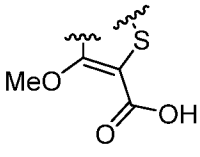
when each R^5 and R^6 is chloro, Z^1 is -OR^7, and R^3 and R^4 combine to form a group according to formula (IVe) or (IVf):


(IVe) or 
(IVf),

R^7 is not benzyl;

when R^5 is chloro, R^6 is bromo, Z^1 is -OR^7, and R^3 and R^4 combine to form a group according to formula (IVg), (IVh), (IVi), (IVj), or (IVk):


(IVg), 
(IVh), 
(IVi), 
(IVj), or


(IVk),

R^7 is not methyl;

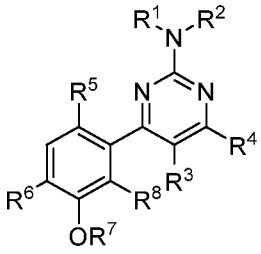
when R^6 is methyl,

each R^1 and R^2 is H; and

when R^3 is H, Z^1 is -OR^7, and each R^5 and R^6 is chloro,

R^7 is not methyl.

4. A compound according to formula (Ib):


(Ib), or a pharmaceutically acceptable salt thereof,

wherein

each of R^1 and R^2 is, independently, H or optionally substituted C_{1-3} alkyl;

R^3 and R^4, together with the atoms to which each is attached, join to form an optionally substituted five- or six-membered ring optionally comprising one nitrogen, one sulfur, or one oxygen, wherein the nitrogen is optionally substituted with R^9, or R^3 is H, halogen, cyano, optionally substituted C_{1-6} alkyl, optionally substituted C_{1-3} alkoxy, or optionally substituted amino, and R^4 is halogen, cyano, optionally substituted C_{1-6} alkyl, optionally substituted C_{1-3} alkoxy, optionally substituted amino, optionally

substituted C_{1-6} thioalkoxy, or optionally substituted C_{6-10} aryl;

R^5 is halogen, H, optionally substituted C_{1-3} alkyl, optionally substituted C_{1-3} alkoxy, or CN;

R^6 is halogen, H, optionally substituted C_{1-3} alkyl, optionally substituted C_{1-3} alkoxy, or CN;

R^7 is optionally substituted C_{1-3} alkyl, optionally substituted C_{1-3} alkcycloalkyl, optionally substituted C_{1-3} alkheterocyclyl, or optionally substituted C_{1-3} alkaryl, and R^8 is H; or R^7 and R^8, together with the atoms to which each is attached, join to form an optionally substituted five-, six-, or seven-membered ring; and

R^9 is H, optionally substituted C_{1-3} alkyl, optionally substituted C_{3-8} cycloalkyl, optionally substituted C_{6-10} aryl, optionally substituted C_{2-9} heteroaryl, optionally substituted C_{2-9} heterocyclyl, optionally substituted C_{1-3} alkcycloalkyl, optionally substituted C_{1-3} alkheterocyclyl, or optionally substituted C_{1-3} alkaryl;

wherein,

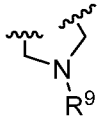
when each of R^1 and R^2 is H, R^3 is H, R^4 is methyl or chloro, and each of R^5 and R^6 is chloro,

R^7 is not methyl;

when each of R^5 and R^6 is chloro, R^3 is H, and R^4 is halogen,

R^7 is not 2-amino-2-oxoethyl, 2-(N,N-diethylamino)ethyl, methyl, or benzyl;

when R^5 is chloro, R^6 is bromo, and R^3 and R^4 combine to form a group according to formula (IIa):



(IIa),

R^7 is not methyl, ethyl, n-propyl, 2-(N-pyrazolyl)ethyl, 2-(N-imidazolyl)ethyl, 3-hydroxypropyl, cyanomethyl, 2-chloroethyl, 2-hydroxyethyl, 2-oxo-propyl, 2-(N,N-dimethylamino)-ethyl, difluoromethyl, or 2-(*t*-butylamino)ethyl;

when each R^5 and R^6 is bromo, and R^3 and R^4 combine to form a group according to formula (IIa),

R^7 is not methyl;

when each R^5 and R^6 is chloro, R^8 is H, and R^3 and R^4 combine to form a group according to formula (IIa),

R^7 is not methyl, 2-(N-imidazolyl)ethyl, methoxymethyl, 2-(N-pyrazolyl)ethyl, 2-(3-methylpyrazol-1-yl)ethyl, 2-pyridyl-methyl, 1,3-dimethyl-1H-1,2,4-triazol-5-yl-methyl, 2-pyrimidinylmethyl, imidazol-2-yl-methyl, 5-methyl-isoxazol-3-yl-methyl, 4-methyl-imidazol-5-yl-methyl, or 3-methyl-1,2,4-oxadiazol-5-yl-methyl;

when each R^5 and R^6 is chloro, R^7 and R^8 combine to form $-CH_2-CH_2-$, and R^3 and R^4 combine to form a group according to formula (IIa),

R^9 is not ethoxycarbonyl, cyclobutylaminocarbonyl, or cyclobutadienylaminocarbonyl;

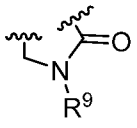
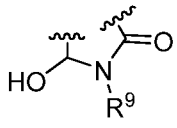
when R^5 is methoxy, R^6 is methyl, and R^3 and R^4 combine to form a group according to formula (IIa),

R^7 is not methyl;

when R^5 is chloro, R^6 is ethyl, and R^3 and R^4 combine to form a group according to formula (IIa),

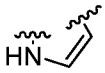
R^7 is not methyl;

when each R^5 and R^6 is chloro, and R^3 and R^4 combine to form a group according to formula (IIb) or (IIc),


(IIb) or 
(IIc),

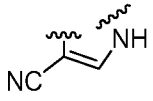
R^7 is not methyl or 2-(N,N-diethylamino)ethyl;

when R^7 is methyl, R^5 is chloro, and R^3 and R^4 combine to form a group according to formula (IIIa),


(IIIa),

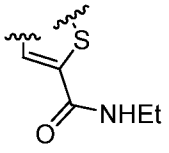
R^6 is not bromo;

when R^5 is chloro, R^6 is methoxy, and R^3 and R^4 combine to form a group according to formula (IIIb):


(IIIb),

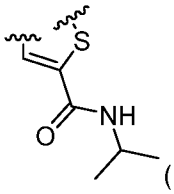
neither R^1 nor R^2 is 2-(N,N-diethylamino)ethyl;

when each R^5 and R^6 is chloro, and R^3 and R^4 combine to form a group according to formula (IVa):


(IVa),

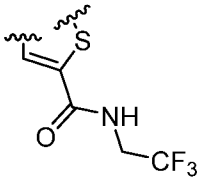
R^7 is not 3-(N-morpholinyl)propyl, benzyl, 1-ethyl-pyrrolydin-3-yl, 1-methyl-piperidin-4-yl, 2-(1-methyl-pyrrolidin-2-yl)ethyl, or 3-(N,N-diethylamino)propyl;

when each R^5 and R^6 is chloro, and R^3 and R^4 combine to form a group according to formula (IVb):


(IVb),

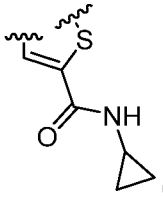
R^7 is not 2-methoxyethyl or benzyl;

when each R^5 and R^6 is chloro, and R^3 and R^4 combine to form a group according to formula (IVc):


(IVc),

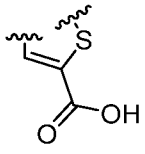
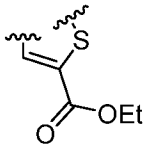
R^7 is not 2-(N,N-diethylamino)ethyl or 3-(N,N-dimethylamino)propyl;

when each R^5 and R^6 is chloro, and R^3 and R^4 combine to form a group according to formula (IVd):


(IVd),

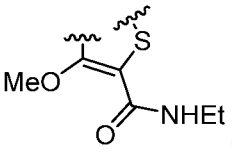
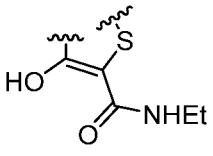
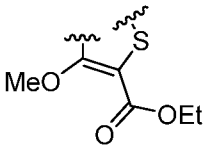
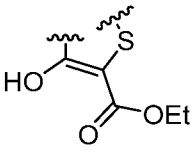
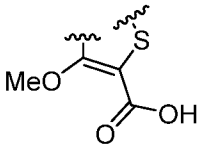
R^7 is not 2-(pyrrolidin-1-yl)ethyl or 2-hydroxyethyl;

when each R^5 and R^6 is chloro, and R^3 and R^4 combine to form a group according to formula (IVe) or (IVf):


(IVe) or 
(IVf),

R^7 is not benzyl;

when R^5 is chloro, R^6 is bromo, and R^3 and R^4 combine to form a group according to formula (IVg), (IVh), (IVi), (IVj), or (IVk):


(IVg), 
(IVh), 
(IVi), 
(IVj), or 
(IVk),

R^7 is not methyl;

when R^6 is methyl,

each R^1 and R^2 is H; and

when R^3 is H, and each R^5 and R^6 is chloro,

R^7 is not methyl.

5. The compound of any one of claims 1 to 4, wherein R^3 and R^4, together with the atoms to which each is attached, join to form an optionally substituted five- or six-membered ring optionally comprising one nitrogen, one oxygen, or one sulfur, wherein said nitrogen is optionally substituted with R^9, or R^3 is H, halogen, optionally substituted C_{1-3} acyl, optionally substituted C_{1-3} alkyl, or optionally substituted C_{1-3} alkoxy, and R^4 is halogen, optionally substituted C_{1-3} acyl, optionally substituted C_{1-3} alkyl, optionally substituted C_{1-3} alkoxy, optionally substituted amino, optionally substituted C_{1-6} thioalkyl, or optionally substituted C_{6-10} aryl.

6. The compounds of any one of claims 1 to 5, wherein R^3 and R^4, together with the atoms to which each is attached, join to form an optionally substituted five-membered ring comprising one sulfur.

7. The compound of any one of claims 1 to 5, wherein R^3 and R^4 combine to form $–C(R^{13A})=C(R^{13B})–S–$ group, wherein R^{13A} is H, and R^{13B} is optionally substituted C_{1-3} alkyl or H.

8. The compound of claim 11, wherein R^{13B} is optionally substituted C_{1-3} alkyl.

9. The compound of claim 12, wherein R^{13B} is $–C(O)–R^{13C}$, wherein R^{13C} is optionally substituted amino or optionally substituted C_{1-3} alkoxy.

10. The compound of any one of claims 1 to 5, wherein R^3 and R^4 combine to form $–C(R^{13A})=C(R^{13B})–S–$ group, wherein R^{13A} is H, and R^{13B} is $–C(O)–R^{13C}$,H, or C_{1-6} aminoalkyl, wherein R^{13C} is optionally substituted C_{1-3} alkyl, optionally substituted C_{1-3} alkoxy, optionally substituted amino, or optionally substituted C_{2-9} heterocyclyl.

11. The compound of any one of claims 1 to 5, wherein R^3 and R^4, together with the atoms to which each is attached, join to form an optionally substituted five-membered ring.

12. The compound of any one of claims 1 to 5, wherein R^3 and R^4 combine to form $–CH_2CH_2CH_2–$ group.

13. The compound of any one of claims 1 to 5, wherein R^3 and R^4, together with the atoms to which each is attached, join to form an optionally substituted five-membered ring comprising one nitrogen.

14. The compound of claim 13, wherein R^3 and R^4 combine to form $–N(R^9)–CH=CH–$ group.

15. The compound of any one of claims 1 to 5, wherein R^3 and R^4 combine to form $–X^1–X^2–X^3–$, wherein

X^1 is –S–, –O–, $–(CR^{14}R^{15})–$, $–C(R^{16})=$, $–N(R^9)–$, –N=, H, or optionally substituted C_{1-3} alkyl;

X^2 is absent,$–(CR^{17}R^{18})_n–$, –S–, –O–, –N=, $–N(R^9)–$, $–C(R^{19})=$, =N–, $=C(R^{20})–$, or $=C(R^{21})–C(R^{22})=$;

X^3 is $–(CR^{14}R^{15})–$, –S–, –O–, $–N(R^9)–$, =N–, $=C(R^{23})–$, halogen, optionally substituted C_{1-3} alkyl, optionally substituted C_{1-6} thioalkoxy, optionally substituted C_{1-3} alkoxy, or optionally substituted C_{6-10} aryl;

each R^{14} and R^{15} is, independently, H or optionally substituted C_{1-3} alkyl, or R^{14} and R^{15} combine to form =O or =S;

each R^{17} and R^{18} is, independently, H or optionally substituted C_{1-3} alkyl, or R^{17} and R^{18} combine to form =O or =S;

each R^{16}, R^{19}, R^{20}, R^{21}, R^{22}, and R^{23} is, independently, H, or optionally substituted C_{1-3} alkyl; and

n is 1 or 2.

16. The compound of any one of claims 1 to 15, wherein R^7 and R^8 form a group $–Y^1–Y^2–$, wherein:

Y^1 is $–(CR^{26}R^{27})_m–$ or optionally substituted C_{1-3} alkyl, optionally substituted C_{1-3} alkheterocyclyl, optionally substituted C_{1-3} alkcycloalkyl, or optionally substituted C_{1-3} alkaryl; and

Y^2 is $–(CR^{26}R^{27})–$ or H; wherein

each R^{26} and R^{27} is, independently, H or optionally substituted C_{1-3} alkyl;

m is 1, 2, or ; and

when Y^1 is optionally substituted C_{1-3} alkyl, optionally substituted C_{1-3} alkheterocyclyl, optionally substituted C_{1-3} alkcycloalkyl, or optionally substituted C_{1-3} alkaryl,

Y^2 is H, and Y^1 is not directly bonded to Y^2.

17. The compound of any one of claims 1 to 5, wherein Z^1 and R^8 combine to form $–Z^3–Y^1–Y^2–$, wherein

Z^3 is –O–, $–N(R^{10})–$, –N=, –S–, or $–(CR^{14}R^{15})–$;

Y^1 is –O–, $–N(R^{10})–$, –S–, $–(CR^{26}R^{27})_m–$, $–C(R^{20})=$, $=C(R^{20})–$, $=C(R^{21})–C(R^{22})=$, optionally substituted C_{1-3} alkyl, optionally substituted C_{1-3} alkheterocyclyl, optionally substituted C_{1-3} alkcycloalkyl, or optionally substituted C_{1-3} alkaryl; and

Y^2 is –O–, –S–, $–N(R^{10})–$, $–(CR^{26}R^{27})–$, $=C(R^{20})–$, =N–, or H;

wherein

each R^{20}, R^{21}, and R^{22} is, independently, H or optionally substituted C_{1-3} alkyl; and

each R^{26} and R^{27} is, independently, H or optionally substituted C_{1-3} alkyl, or R^{26} and R^{27} combine to form =O or =S;

m is 1 or 2; and

wherein, when Y^2 is H,

the chain of atoms $–Z^3–Y^1–Y^2–$ comprises no more than two heteroatoms, each said heteroatom independently selected from nitrogen, oxygen, and sulfur.

18. A compound:

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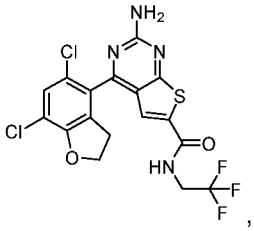

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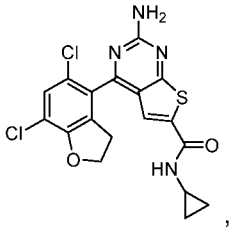

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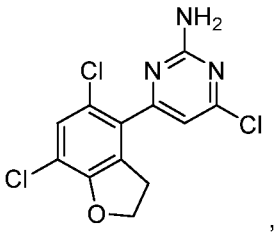

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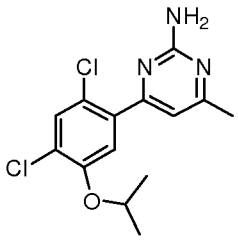

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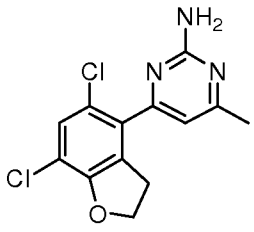

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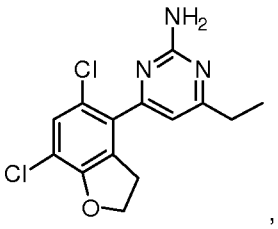

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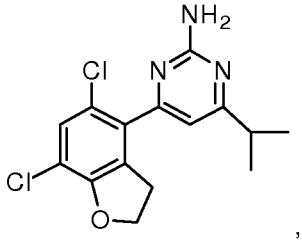

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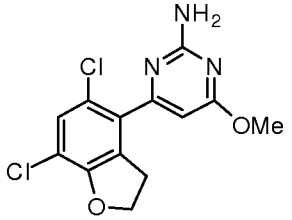

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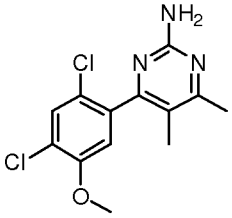

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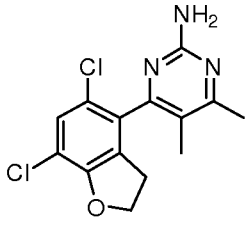

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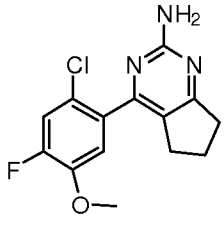

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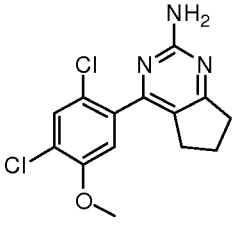
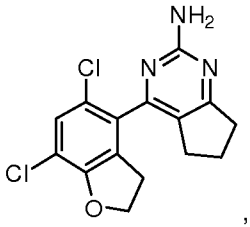
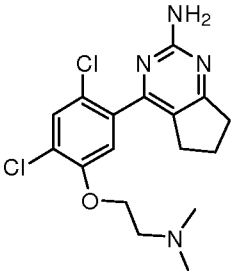
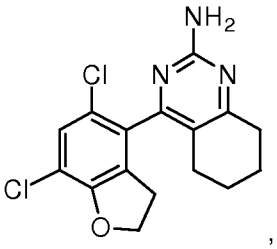
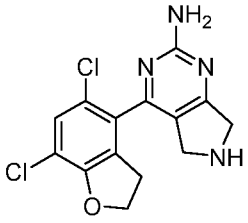
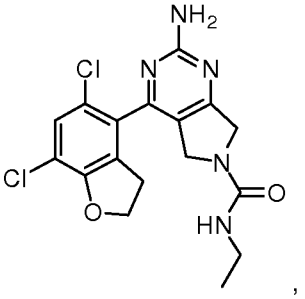


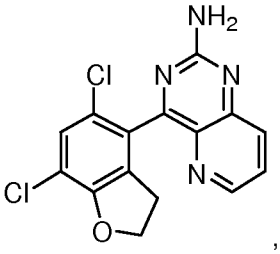
13  ,

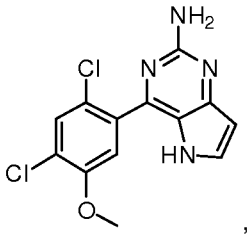
14  ,

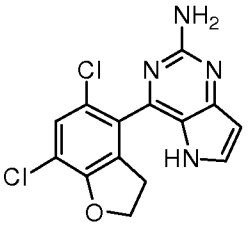
15  ,

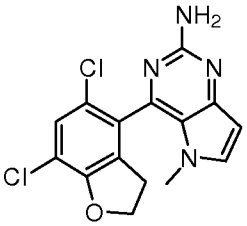
16  ,

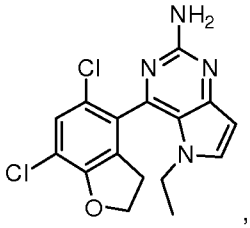
17  ,

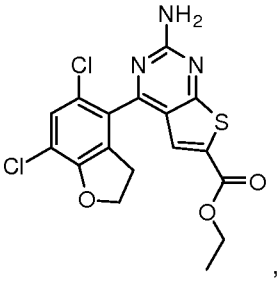
18  ,

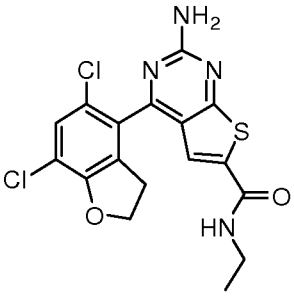
19  ,

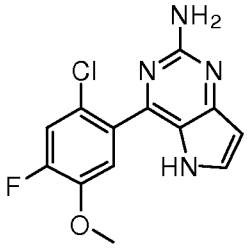
20  ,

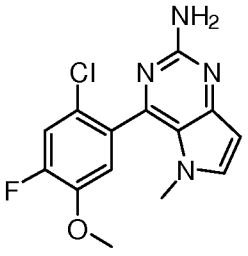
21  ,

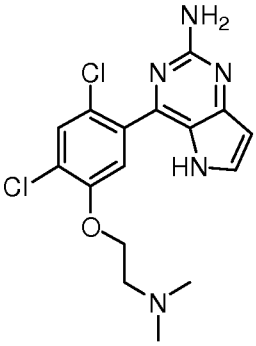
22  ,

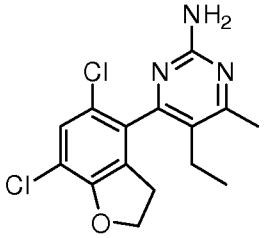
23  ,

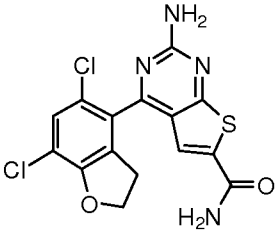
24  ,

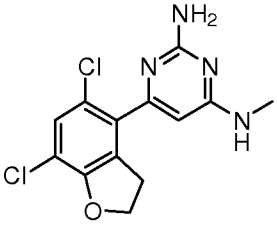
25  ,

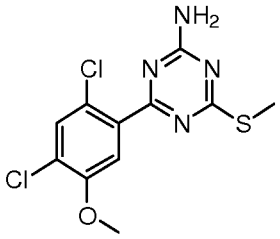
26  ,

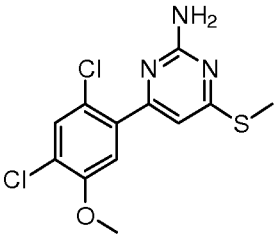
27  ,

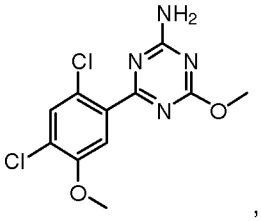
28  ,

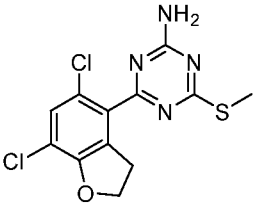
29  ,

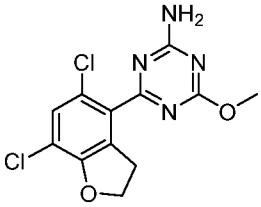
33  ,

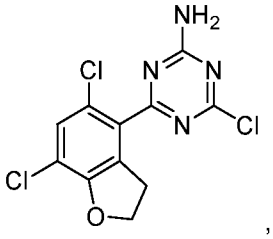
34  ,

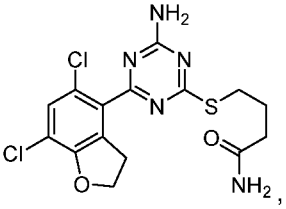
35  ,

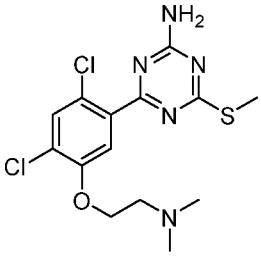
36  ,

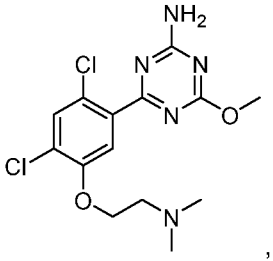
40  ,

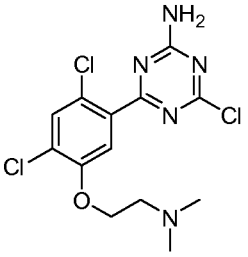
41  ,

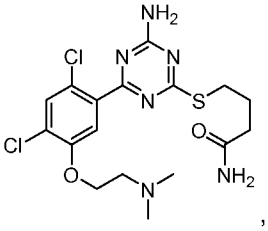
42  ,

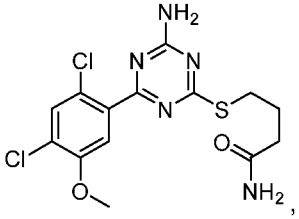
43  ,

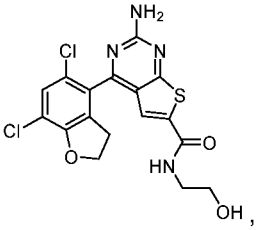
44  ,

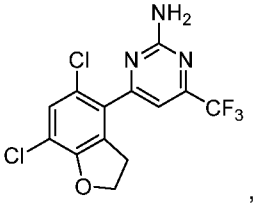
45  ,

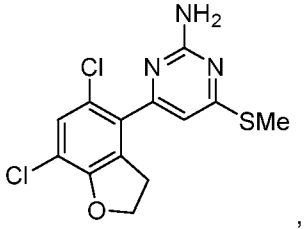
46  ,

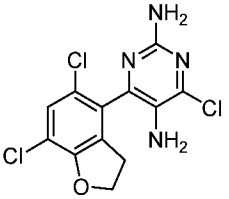
47  ,

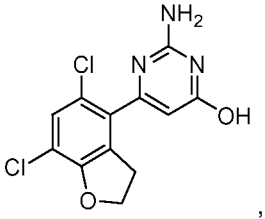
48  ,

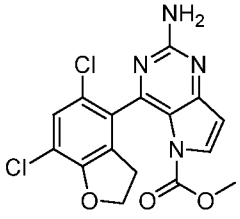
60  ,

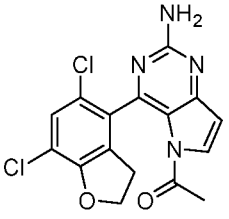
50  ,

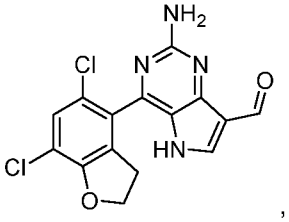
51  ,

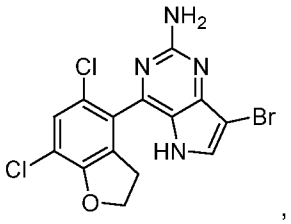
52  ,

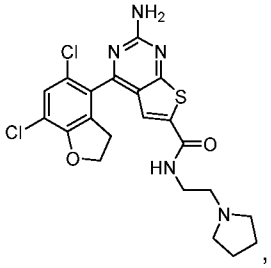
53  ,

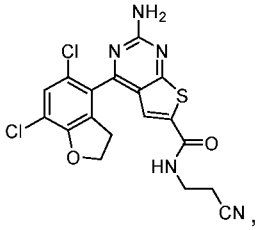
54  ,

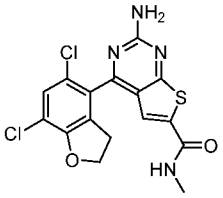
55  ,

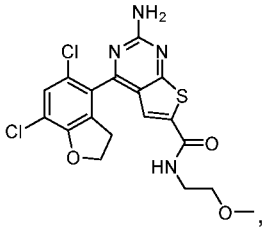
56  ,

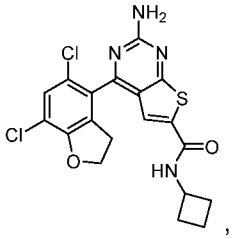
57  ,

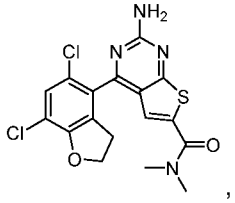
58  ,

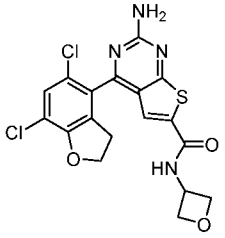
59  ,

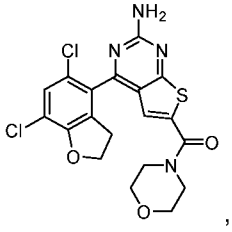
63  ,

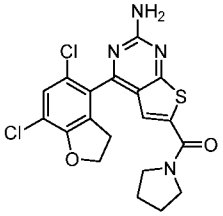
64  ,

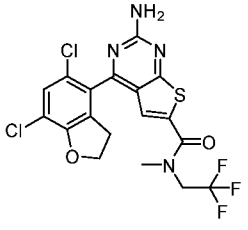
65  ,

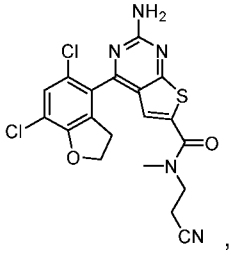
66  ,

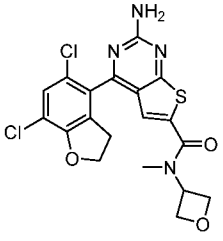
67  ,

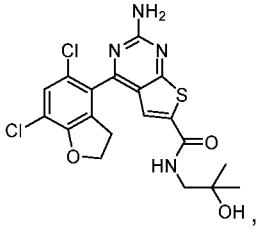
68  ,

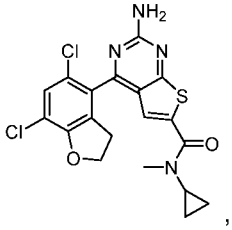
69  ,

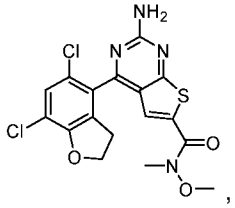
70  ,

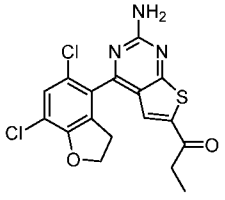
71  ,

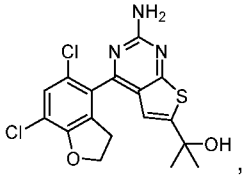
72  ,

73  ,

74  ,

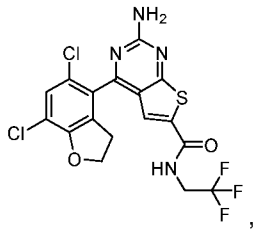
75  ,

76  , or

77  ,

or a pharmaceutically acceptable salt thereof.

19. The compound of claim 18 having the formula: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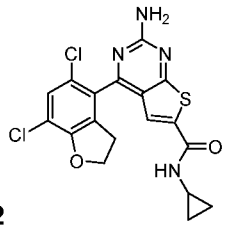
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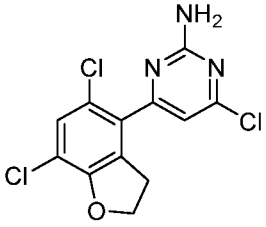
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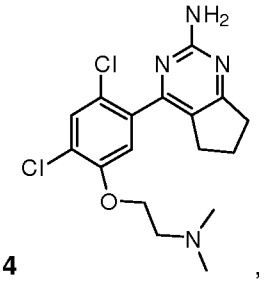
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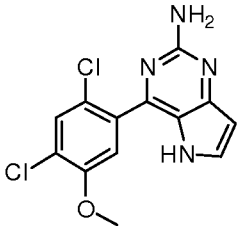
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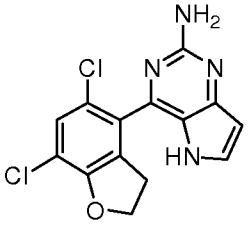
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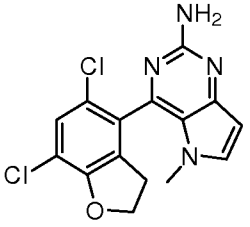
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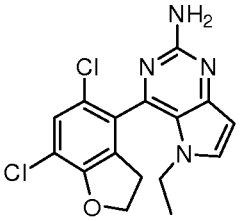
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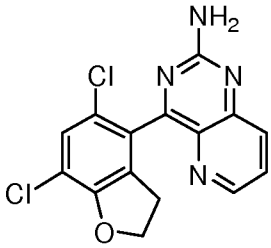
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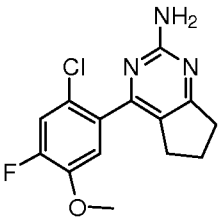
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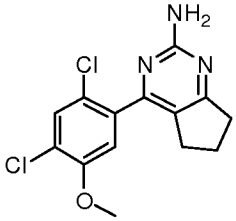
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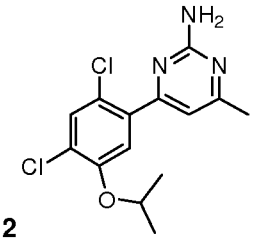
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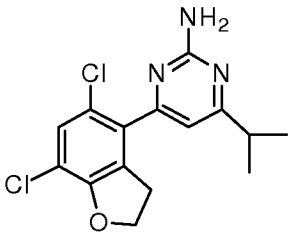
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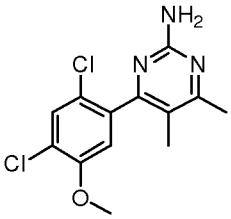
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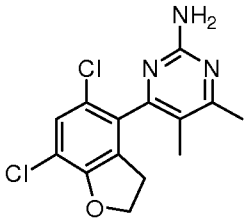
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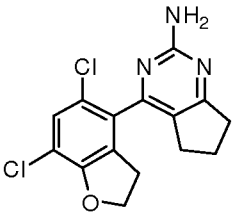
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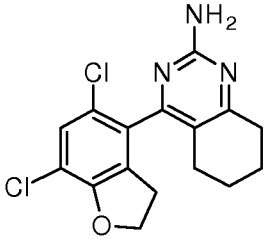
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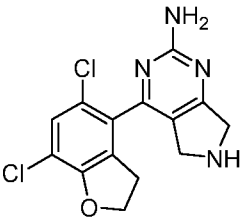
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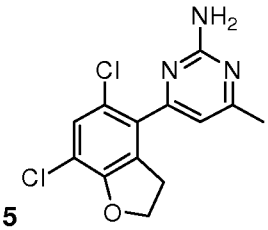
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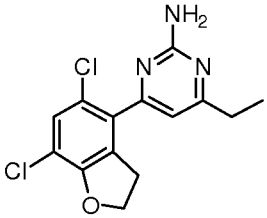
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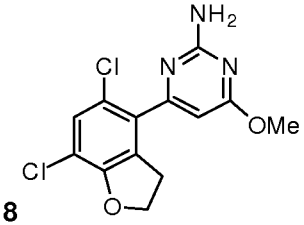
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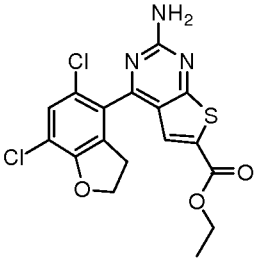
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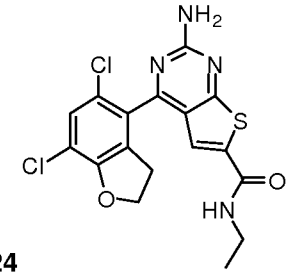
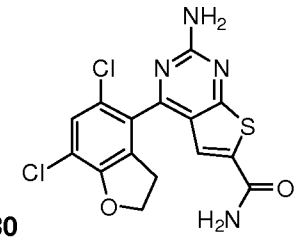
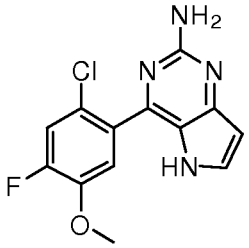


24 , 

30 , 

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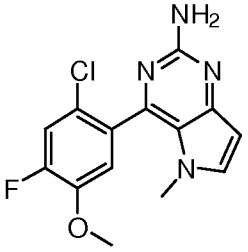
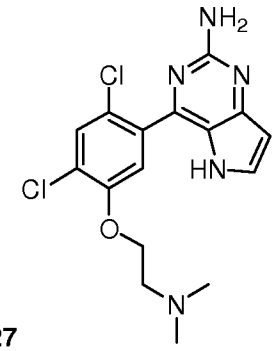
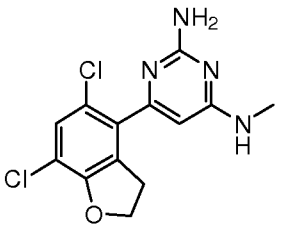


26 , 

27 , 

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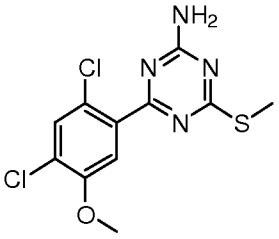
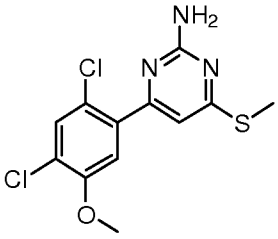
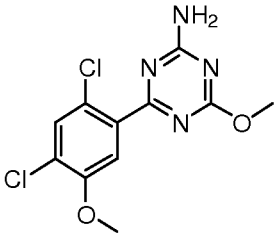


34 , 

35 , 

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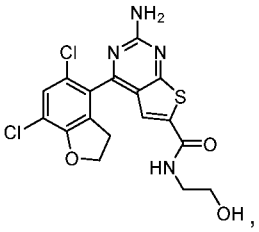
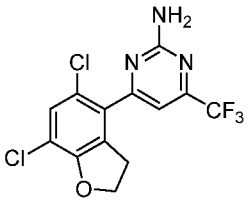
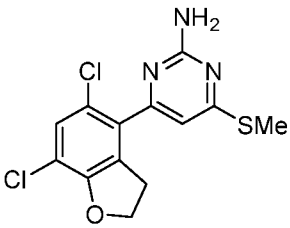
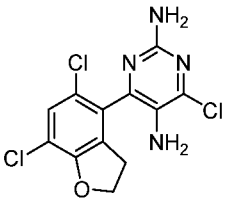
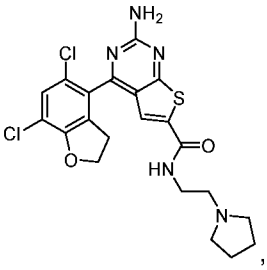
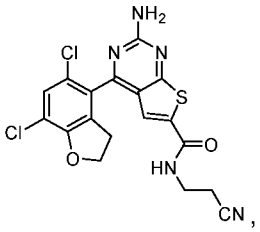
60 

50 

, 51 

52 

58 

, 59 

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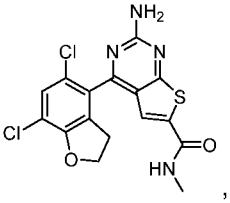
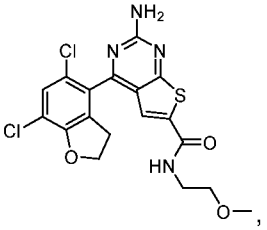
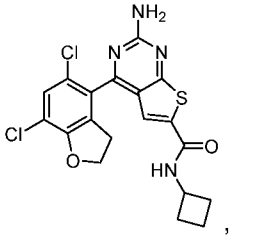
63 

, 64 

, 65 

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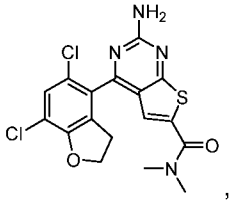
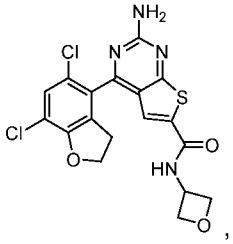
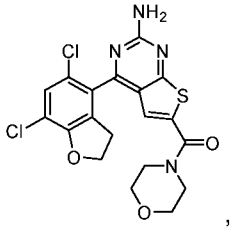
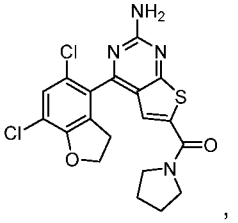
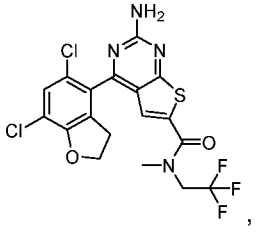
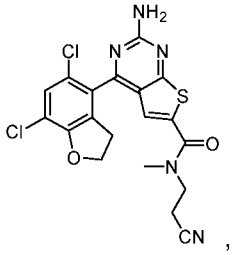
66  ,

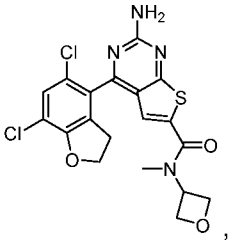
67  ,

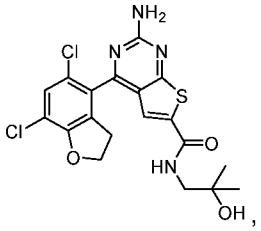
68  ,

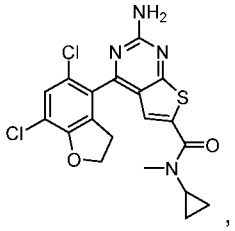
69  ,

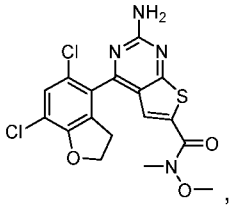
70  ,

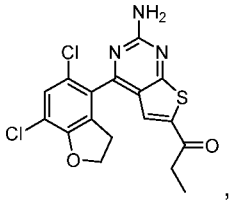
71  ,

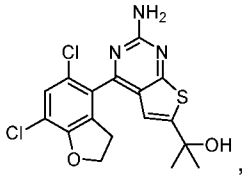
72  ,

73  ,

74  ,

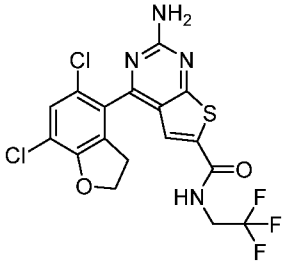
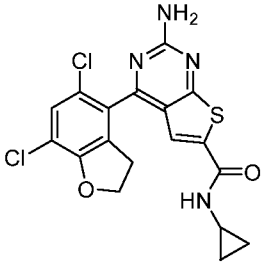
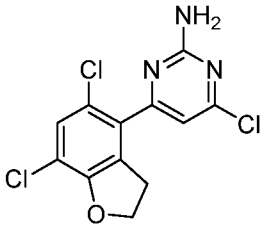
75  ,

76  , or

77  ,

or a pharmaceutically acceptable salt thereof.

20. The compound of claim 19, wherein said compound is:

61  , **62**  , or **49**  , or a pharmaceutically acceptabl salt thereof.

21. A pharmaceutical composition comprising the compound of any one of claims 1 to 20, or a pharmaceutically acceptable salt thereof, and one or more of pharmaceutically acceptable carriers or excipients.

22. The pharmaceutical composition of claim 21, wherein said composition is formulated for administration orally, sublingually, buccally, transdermally, intradermally, intramuscularly, parenterally, intravenously, intra-arterially, intracranially, subcutaneously, intraorbitally, intraventricularly, intraspinally, intraperitoneally, intranasally, by inhalation, and topically.

23. The pharmaceutical composition of claim 22, wherein said composition is formulated for oral administration.

24. A method of treating a disorder in a mammal caused by the action of heat shock protein 90 (Hsp90), said method comprising administering an effective amount of the compound of any one of claims 1 to 20 or a pharmaceutically acceptable salt thereof or the pharmaceutical composition of claim 21 to said mammal.

25. The method of claim 25, wherein said disorder is a neurodegenerative disorder.

26. The method of claim 25, wherein said neurodegenerative disorder is a tauopathy.

27. The method of claim 24 or 25, wherein said neurodegenerative disorder is Alzheimer's disease, Huntington's disease, progressive supranuclear palsy, Parkinson's disease, Pick's disease, corticobasal degeneration, chronic traumatic encephalopathy, traumatic brain injury, or frontotemporal dementia.

28. The method of claim 27, wherein said neurodegenerative disorder is Alzheimer's disease.

29. The method of claim 24, wherein said disorder is a proliferative disorder.

30. The method of claim 29, wherein said proliferative disorder is a cancer.

31. A method of treating an infectious disease in a mammal, said method comprising administering an effective amount of the compound of any one of claims 1 to 20 or a pharmaceutically acceptable salt or the pharmaceutical composition of claim 21 thereof to said mammal.

32. The method of claim 31, wherein said infectious disease is a viral infection.

33. The method of claim 32, wherein said viral infection is an infection by a virus of a family selected from the group consisting of Herpesviridae, Polyomaviridae, Poxviridae, Reoviridae, Birnaviridae, Picornaviridae, Flaviviridae, Arenaviridae, Hepeviridae, Rhabdoviridae, Paramoxyviridae, Bunyaviridae, Orthomoxyviridae, Filoviridae, Retroviridae, and Hepadnaviridae.

34. The method of claim 31, wherein said infectious disease is a fungal infection.

35. The method of claim 31, wherein said infectious disease is a bacterial infection.

36. The method of claim 24, wherein said disorder an inflammatory or autoimmune disease.

37. The method of claim 36, wherein said inflammatory or autoimmune disease is rheumatoid arthritis, systemic lupus erythermatosus, or asthma.

38. The method of claim 24, wherein said disorder is a cardiovascular disease.

39. The method of claim 38, wherein said cardiovascular disease is atherosclerosis.

40. The method of claim 24, wherein said disorder is an allergy.

41. The method of any one of claims 24 to 40, wherein said compound is administered orally, sublingually, buccally, transdermally, intradermally, intramuscularly, parenterally, intravenously, intra-arterially, intracranially, subcutaneously, intraorbitally, intraventricularly, intraspinally, intraperitoneally, intranasally, by inhalation, and topically.

42. The method of claim 41, wherein said compound is administered orally.

43. The method of any one of claims 24 to 42, wherein said mammal is human.

44. A method of inhibiting Hsp90, said method comprising contacting a cell with the compound of any one of claims 1 to 20 or a pharmaceutically acceptable salt thereof.

45. The method of claim 44, wherein said cell is in vitro.

46. A kit comprising:

(i) the pharmaceutical composition of any one of claims 21 to 23; and

(ii) instructions for use of the pharmaceutical compositions of (i) to treat a disorder in a mammal caused by the action of Hsp90.

Figure 1

Compound 20
^{1}H NMR in $CDCl_3$

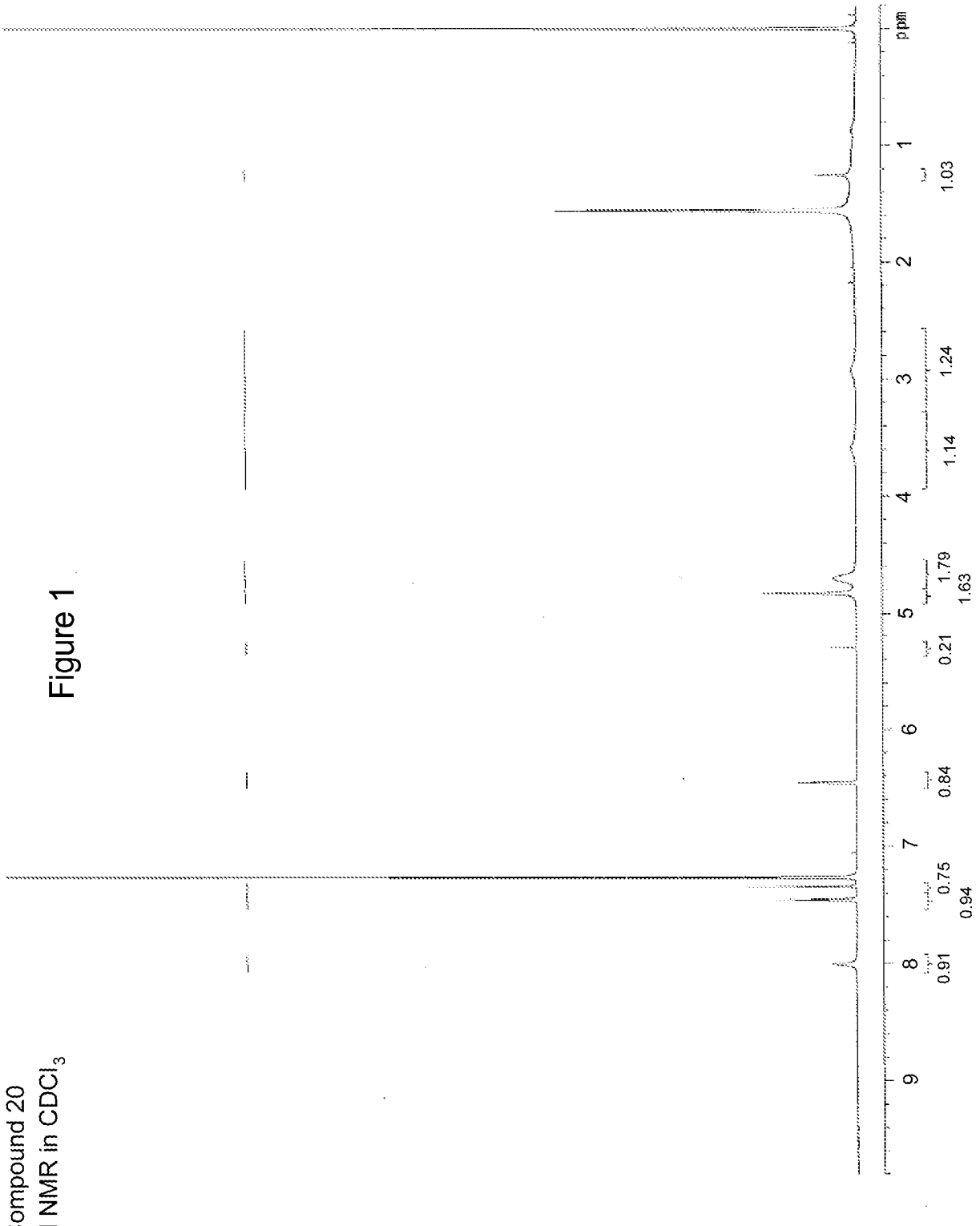


Figure 2

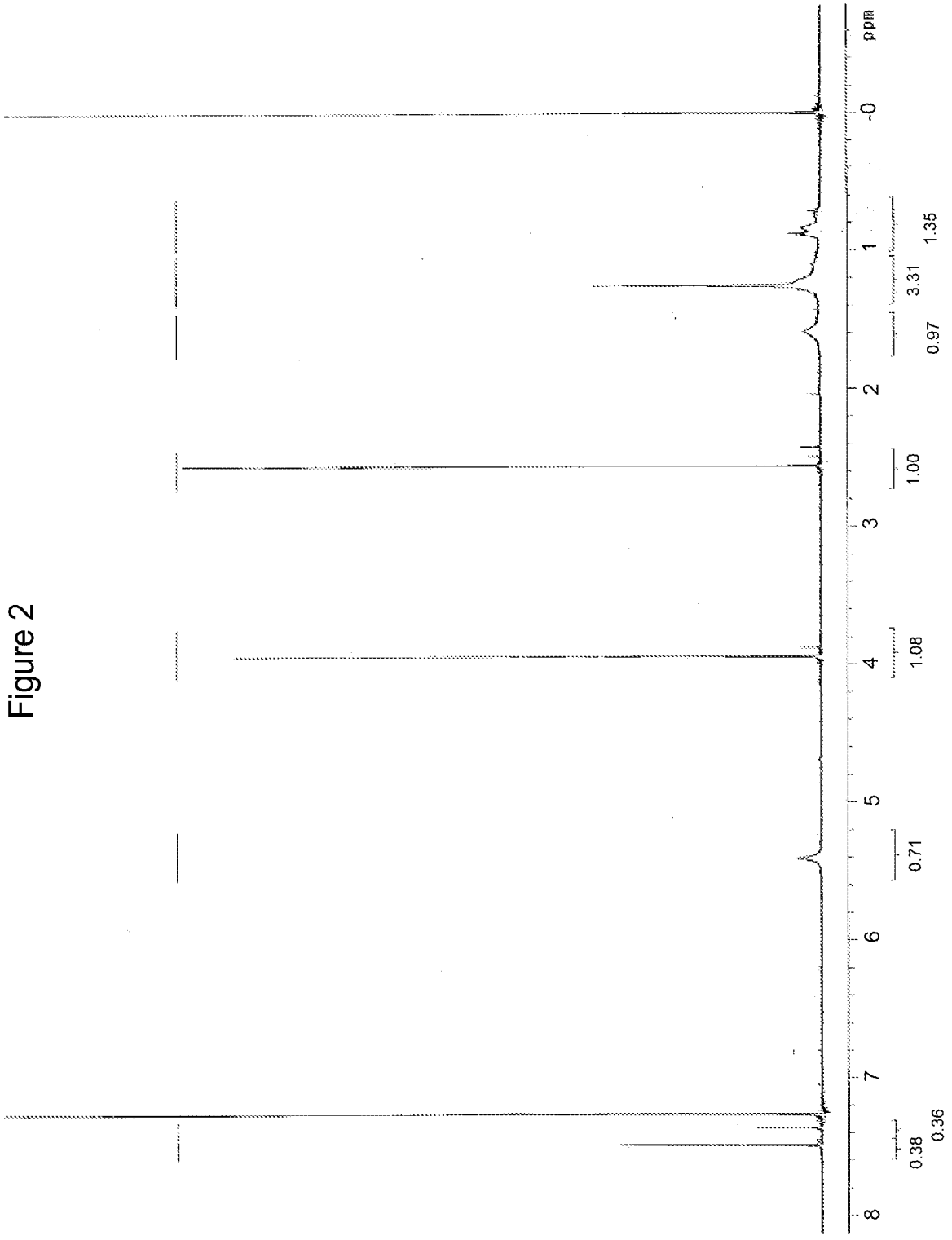


Figure 3

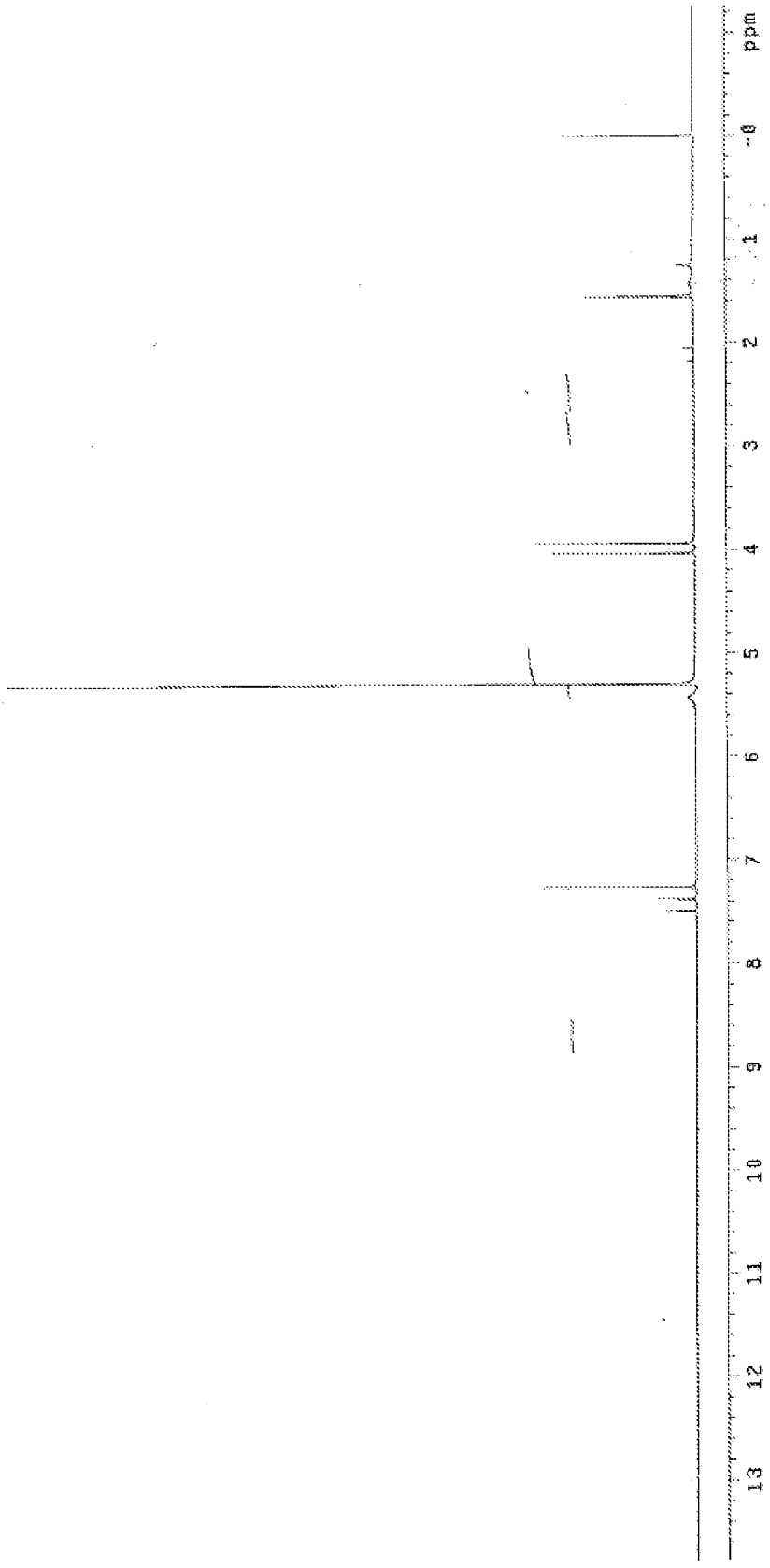


Figure 4

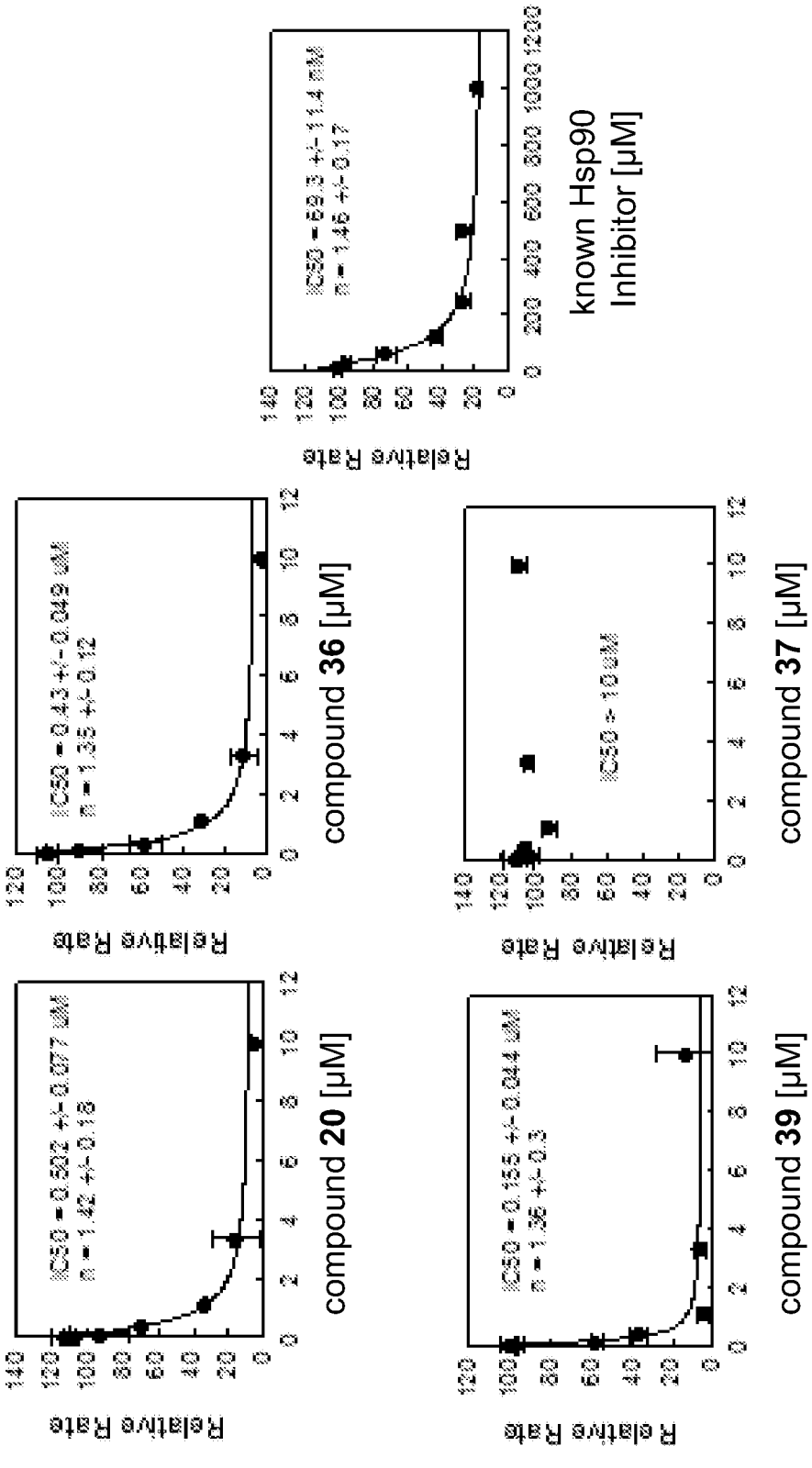

Relative Rate
IC50 = 0.502 +/- 0.077 uM
n = 1.42 +/- 0.18
compound 20 [µM]
IC50 = 0.43 +/- 0.049 uM
n = 1.35 +/- 0.12
compound 36 [µM]
IC50 = 0.135 +/- 0.044 uM
n = 1.36 +/- 0.3
compound 39 [µM]
IC50 = ~10 uM
compound 37 [µM]
IC50 = 69.3 +/- 11.4 nM
n = 1.46 +/- 0.17
known Hsp90
Inhibitor [µM]

Figure 5

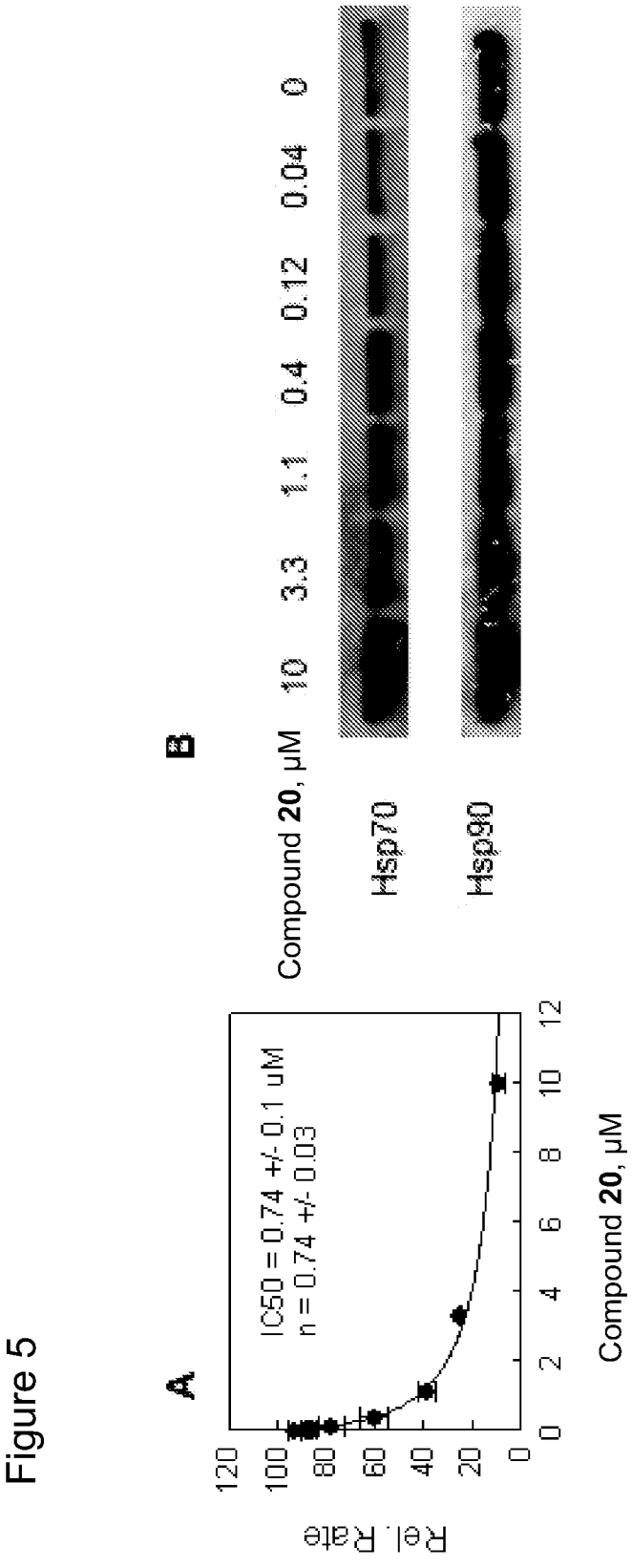

A
IC50 = 0.74 +/- 0.1 uM
n = 0.74 +/- 0.03
Rel. Rate
Compound 20, µM
B
Compound 20, µM
10
3.3
1.1
0.4
0.12
0.04
0
Hsp70
Hsp90

Figure 6

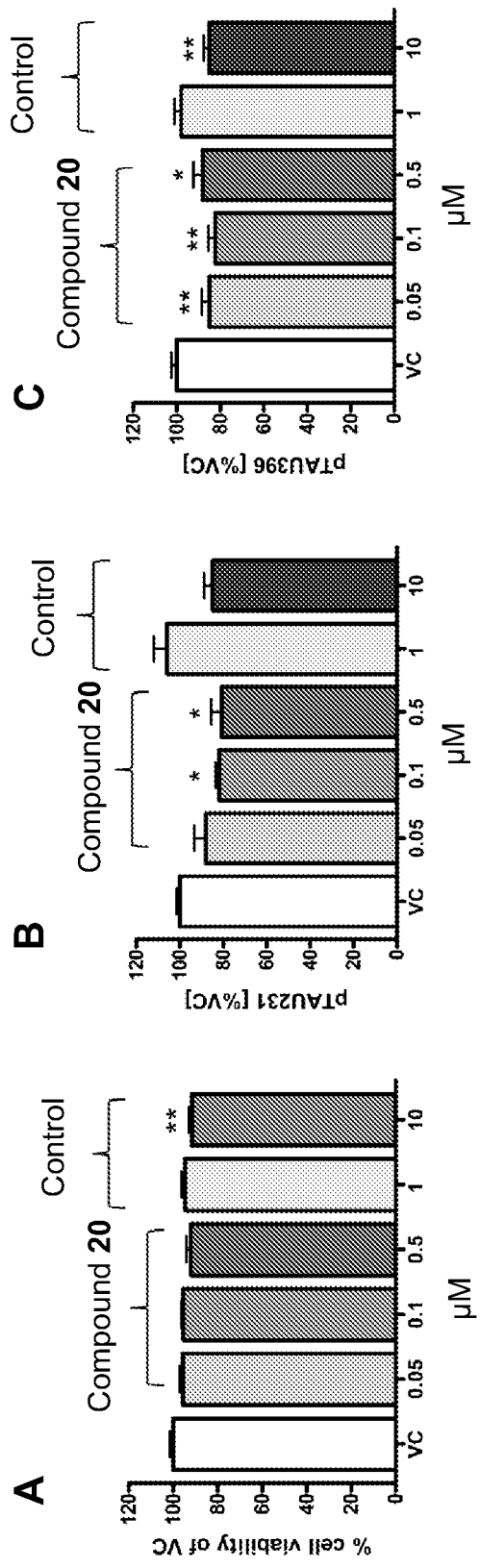

A
% cell viability of VC
Compound 20
Control
VC
0.05
0.1
0.5
1
10
μM
B
pTAU231 [%VC]
C
pTAU396 [%VC]

Figure 7

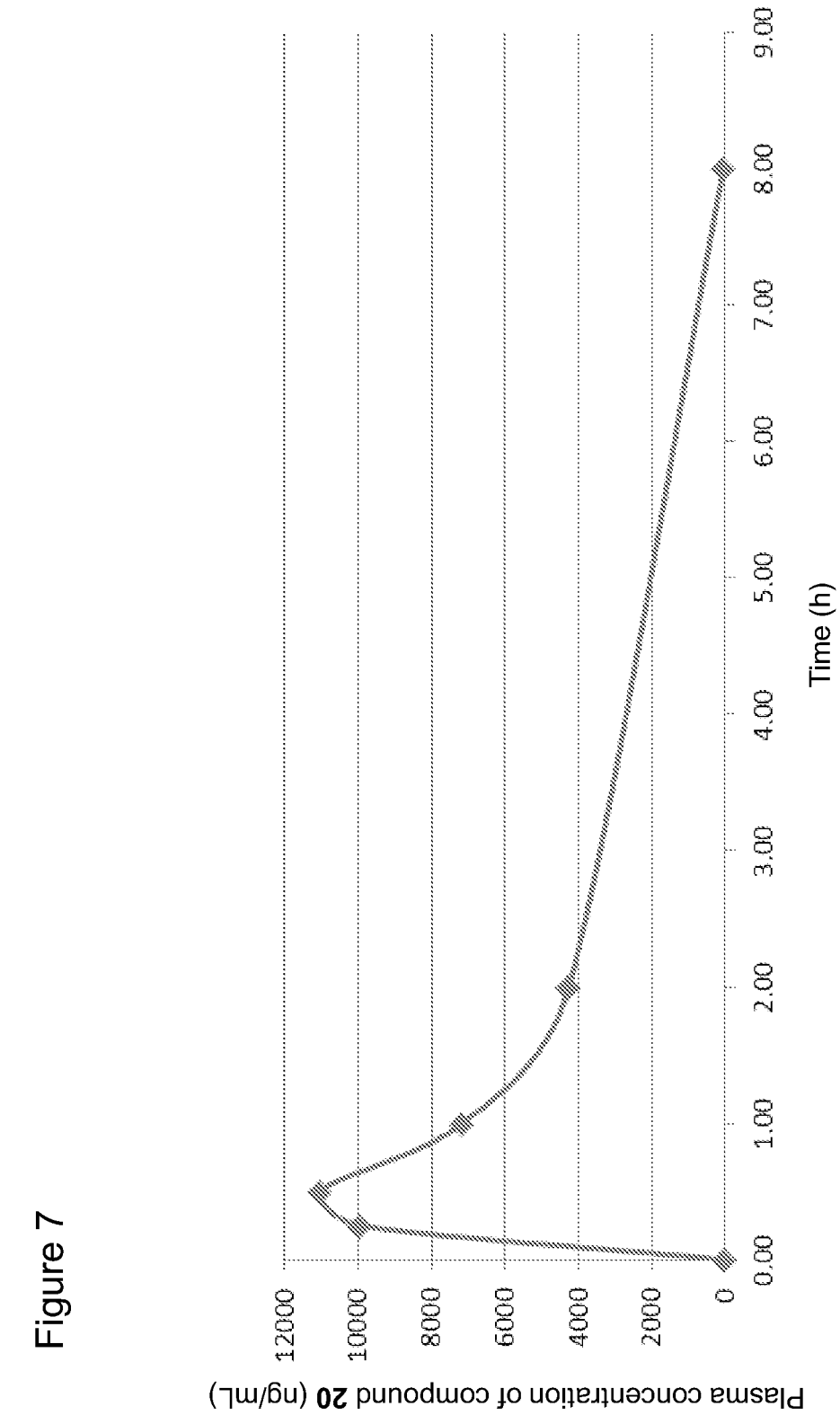

Plasma concentration of compound 20 (ng/mL)
12000
10000
8000
6000
4000
2000
0
0.00
1.00
2.00
3.00
4.00
5.00
6.00
7.00
8.00
9.00
Time (h)

Figure 8

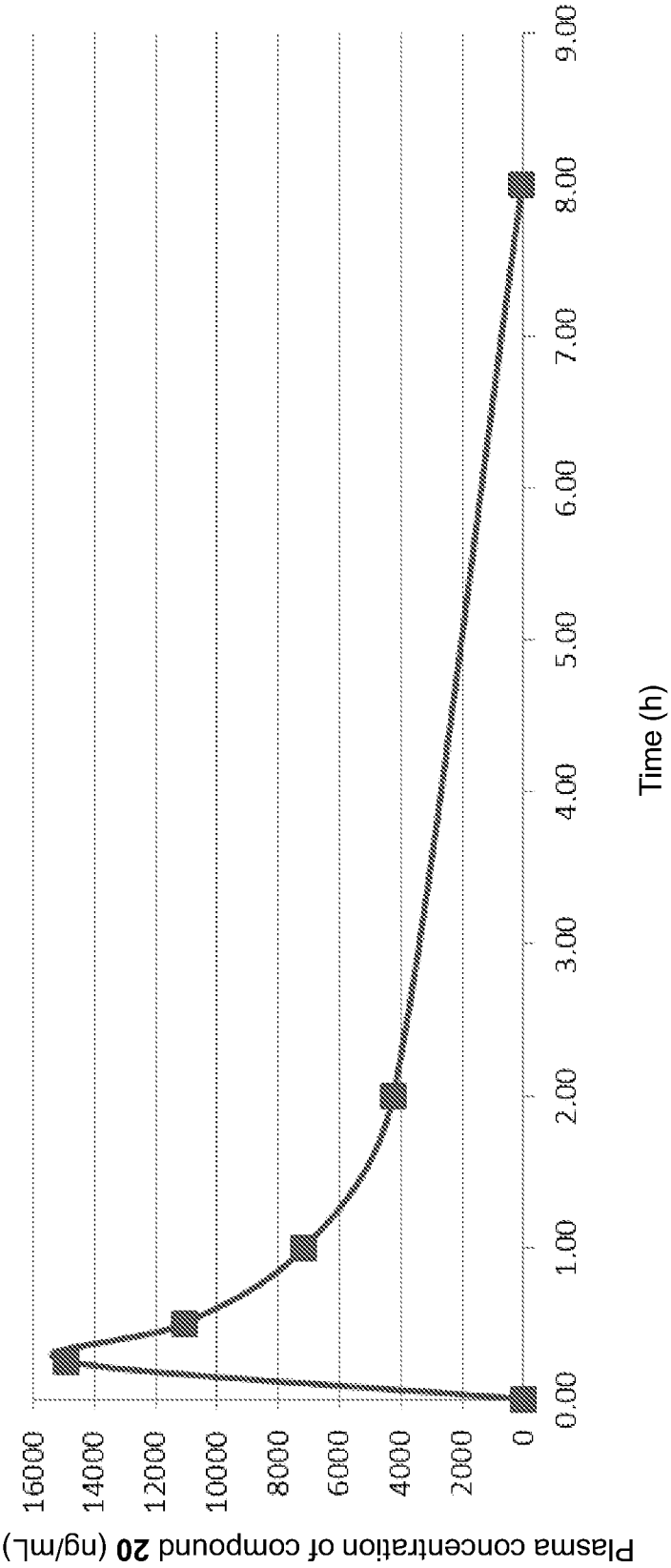

Plasma concentration of compound 20 (ng/mL)
16000
14000
12000
10000
8000
6000
4000
2000
0
0.00
1.00
2.00
3.00
4.00
5.00
6.00
7.00
8.00
9.00
Time (h)

Figure 9

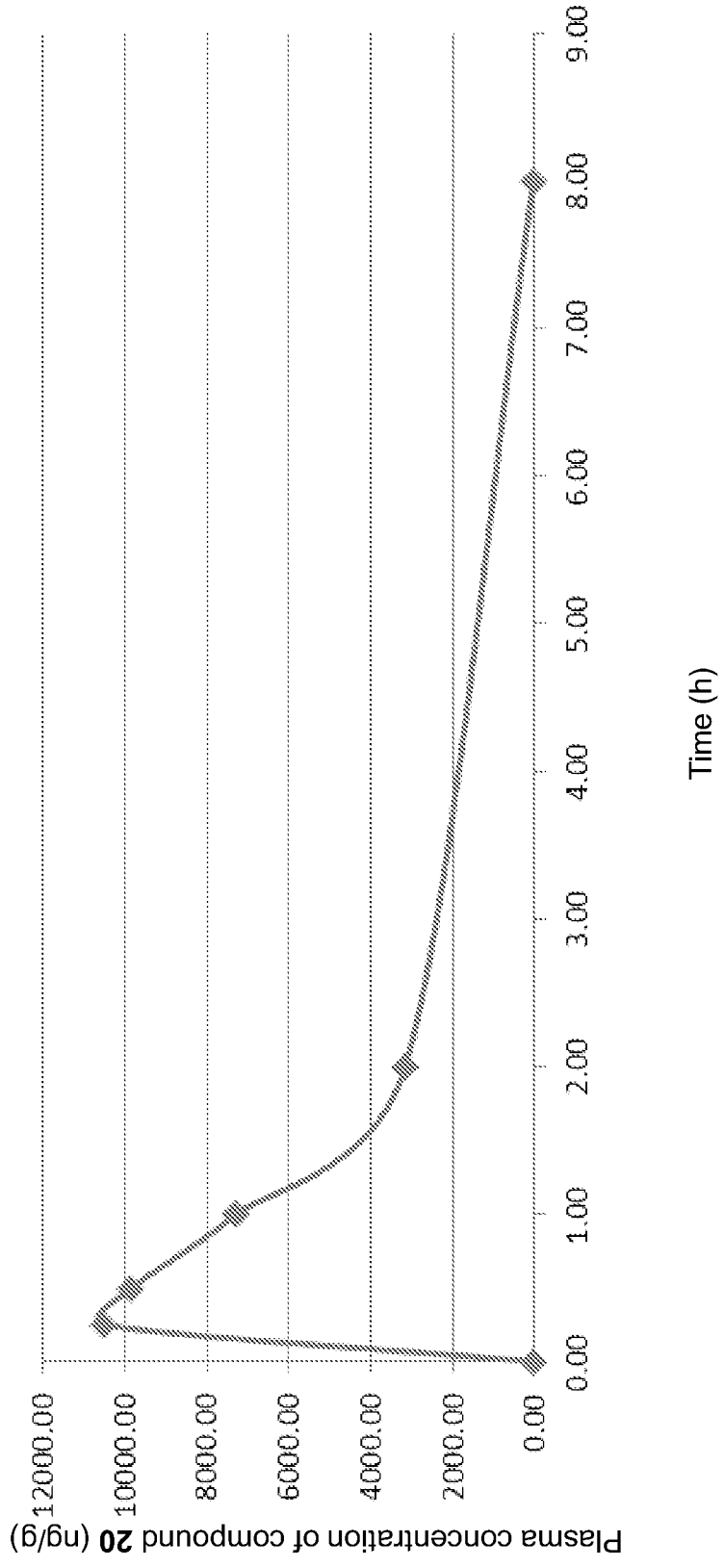
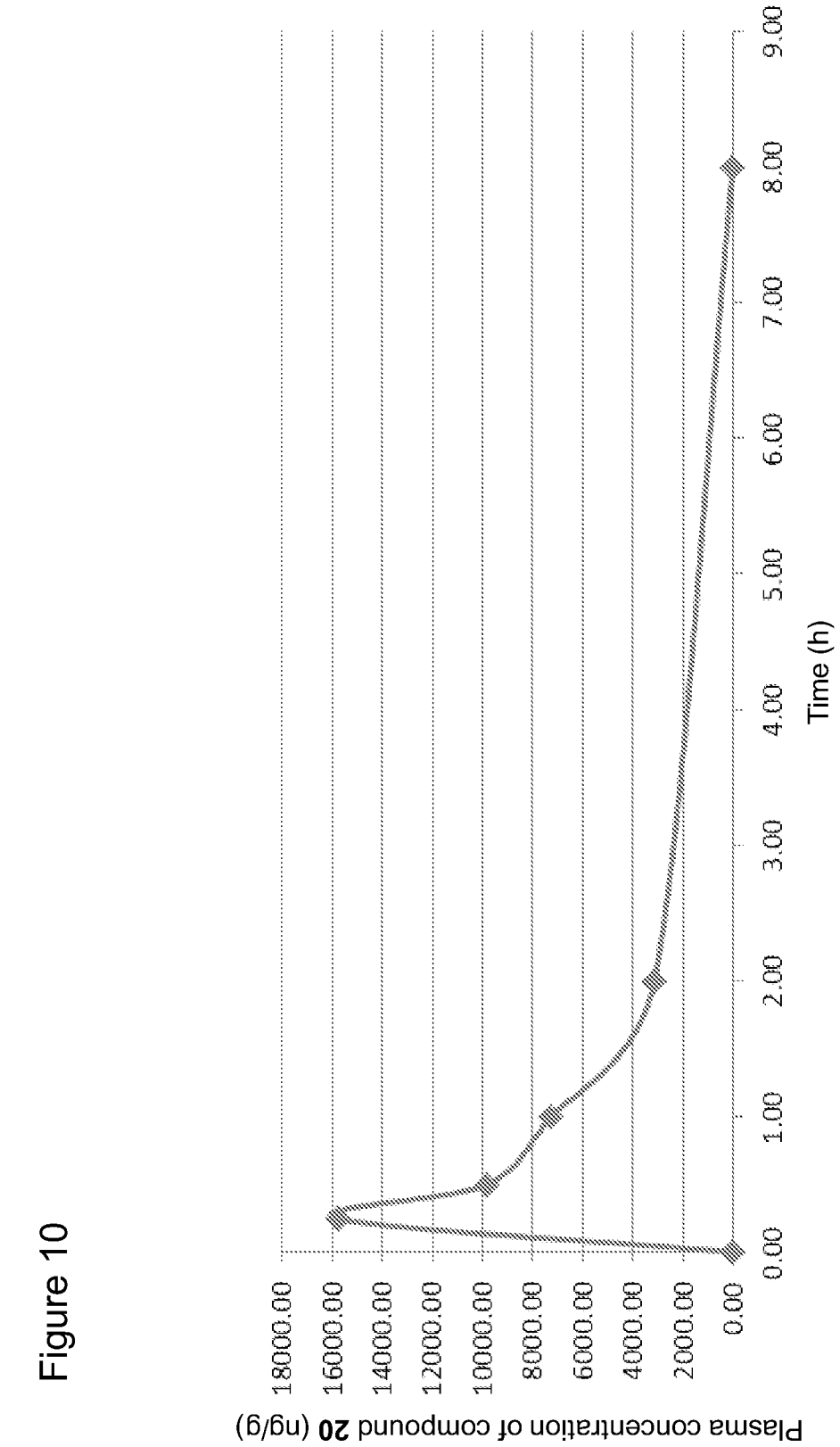

Plasma concentration of compound 20 (ng/g)
12000.00
10000.00
8000.00
6000.00
4000.00
2000.00
0.00
0.00
1.00
2.00
3.00
4.00
5.00
6.00
7.00
8.00
9.00
Time (h)

Figure 10


Plasma concentration of compound 20 (ng/g)
18000.00
16000.00
14000.00
12000.00
10000.00
8000.00
6000.00
4000.00
2000.00
0.00
0.00
1.00
2.00
3.00
4.00
5.00
6.00
7.00
8.00
9.00
Time (h)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2015/035735

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.: 6-17, 21-46
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:

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.:

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/US2015/035735

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 31/505 (2015.01)
CPC - A61K 31/505 (2015.05)
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)
IPC(8) - A61K 31/505, 31/517, 31/519; C07D 487/04 (2015.01)
CPC - A61K 31/505, 31/517, 31/519; C07D 487/04 (2015.05)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 514/210.210, 234.200, 258.100, 264.110, 265.100; 544/279; CPC - A61K 31/505, 31/517, 31/519; C07D 487/04 (2015.05) (keyword delimited)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Orbit, Google Patents, Google, STN, SureChem
Search terms used: pyrimidine, hsp90, neurodegenerative

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2008/059368 A2 (PFIZER PRODUCTS INC) 22 May 2008 (22.05.2008) entire document	1-5, 18, 19
A	US 2010/0093696 A1 (BENNETT et al) 15 April 2010 (15.04.2010) entire document	1-5, 18-20
A	US 8,642,594 B2 (VERNALIS R&D LIMITED) 04 February 2014 (04.02.2014) entire document	1-5, 18-20
A	WO 2013/177535 A2 (BERG PHARMA LLC) 28 November 2013 (28.11.2013) entire document	1-5, 18-20

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* 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
11 August 2015	14 SEP 2015
Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Blaine Copenheaver PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

(19)中华人民共和国国家知识产权局

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(43)申请公布日 2017.05.17

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(22)申请日 2015.06.15

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62/012152 2014.06.13 US

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2017.02.10

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WO2015/192119 EN 2015.12.17

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(74)专利代理机构 中国专利代理(香港)有限公司 72001
代理人 张萍 周李军

(51)Int.Cl.
A61K 31/505(2006.01)

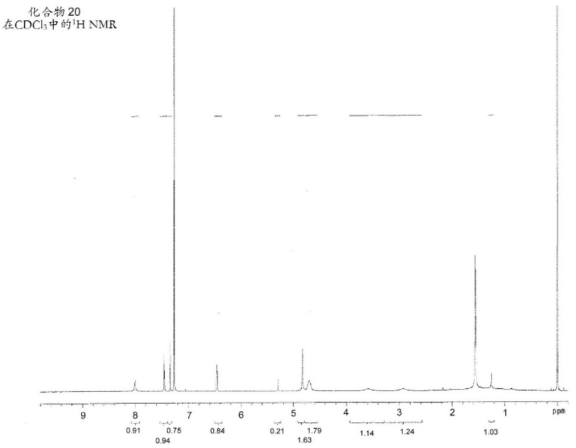
权利要求书18页 说明书130页 附图9页

(54)发明名称

嘧啶化合物及其使用方法

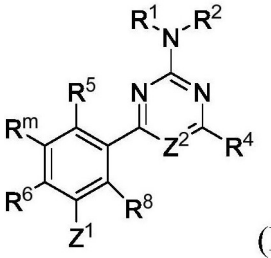
(57)摘要

本发明涉及作为伴侣蛋白的热休克蛋白90家族的抑制剂的2-氨基-4-芳基嘧啶和2-氨基-4-芳基三嗪化合物。本发明的特征还在于包括本发明的化合物和组合物的药物组合物和试剂盒。本发明进一步涉及这些化合物和组合物在治疗受试者的障碍中的医学用途。例如,该障碍是神经退行性疾病。



CN 106687114 A

1.一种根据式(I)的化合物：



或其药学上可接受的盐，

(I)，

其中

Z^1是-OR^7、-$N(R^{10})R^7$、-SR^7、或-$C(R^{10})(R^{11})R^7$；

Z^2是-$C(R^3)$=或-N=；

每个R^1和R^2独立地是H、任选取代的C_{1-3}酰基、或任选取代的C_{1-3}烷基；

R^3和R^4与各自附接的原子一起连接以形成任选取代的五元或六元环，该五元或六元环任选地包括一至三个选自由硫、氧、和氮组成的组的杂原子，其中所述氮任选地被R^9取代，或者R^3是H、卤素、氰基、任选取代的C_{1-6}烷基、任选取代的C_{1-3}烷氧基、或任选取代的氨，并且R^4是卤素、氰基、任选取代的C_{1-6}烷基、任选取代的C_{1-3}烷氧基、任选取代的氨、任选取代的C_{1-6}硫代烷氧基、或任选取代的C_{6-10}芳基；

R^5是卤素、H、任选取代的C_{1-3}烷基、任选取代的C_{1-3}烷氧基、或CN；

R^6是卤素、H、任选取代的C_{1-3}烷基、任选取代的C_{1-3}烷氧基、或CN；

R^7和R^8与各自附接的原子一起连接以形成任选取代的五元、六元或七元环，该五元、六元或七元环任选地包括一个或两个选自氮、氧和硫的杂原子；或者R^7是任选取代的C_{1-3}烷基、任选取代的C_{1-3}烷环烷基、任选取代的C_{1-3}烷杂环基、或任选取代的C_{1-3}烷芳基，并且R^8是H；

R^9是H、任选取代的C_{1-3}烷基、任选取代的C_{3-8}环烷基、任选取代的C_{6-10}芳基、任选取代的C_{2-9}杂芳基、任选取代的C_{2-9}杂环基、任选取代的C_{1-3}烷环烷基、任选取代的C_{1-3}烷杂环基、或任选取代的C_{1-3}烷芳基；

R^{10}是H、任选取代的C_{1-3}烷基、任选取代的C_{3-8}环烷基、任选取代的C_{6-10}芳基、任选取代的C_{2-9}杂芳基、任选取代的C_{2-9}杂环基、任选取代的C_{1-3}烷环烷基、任选取代的C_{1-3}烷杂环基、或任选取代的C_{1-3}烷芳基，并且R^{11}是H、任选取代的C_{1-3}烷基，或者R^{10}和R^{11}结合以形成=O或=S；并且

R^m是H、卤素、氰基、任选取代的C_{1-4}酰基、任选取代的C_{1-4}烷基、或任选取代的C_{1-3}烷氧基；

其中，

当Z^2是CR^3，每个R^1和R^2是H，R^3是H，R^4是甲基或氯，并且每个R^5和R^6是氯时，

Z^1不是甲氧基；

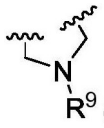
当Z^2是N，每个R^5和R^6是氯，R^3是H，R^4是经取代的C_{1-6}硫代烷氧基时，

Z^1不是氰基甲氧基或氨基甲氧基；

当Z^2是CR^3，每个R^5和R^6是氯，R^3是H，并且R^4是卤素时，

Z^1不是2-氨基-2-氧代乙氧基、2-(N,N-二乙氨基)乙氧基、甲氧基、或苄氧基；

当R^5是氯，R^6是溴，Z^1是-OR^7，并且R^3和R^4结合以形成根据式(IIa)的基团时：



(IIa),

R^7不是甲基、乙基、正丙基、2-(N-吡唑基)乙基、2-(N-咪唑基)乙基、3-羟丙基、氰甲基、2-氯乙基、2-羟乙基、2-氧代丙基、2-(N,N-二甲氨基)乙基、二氟甲基或2-(叔丁氨基)乙基；

当每个R^5和R^6是溴，Z^1是-OR^7，并且R^3和R^4结合以形成根据式(IIa)的基团时，

R^7不是甲基；

当每个R^5和R^6是氯，Z^1是-OR^7，并且R^3和R^4结合以形成根据式(IIa)的基团时，

R^7不是甲基、2-(N-咪唑基)乙基、甲氧基甲基、2-(N-吡唑基)乙基、2-(3-甲基吡唑-1-基)乙基、2-吡啶基-甲基、1,3-二甲基-1H-1,2,4-三唑-5-基-甲基、2-嘧啶基甲基、咪唑-2-基-甲基、5-甲基-异噁唑-3-基-甲基、4-甲基-咪唑-5-基-甲基、或3-甲基-1,2,4-噁二唑-5-基-甲基；

当每个R^5和R^6是氯，Z^1是-OR^7，R^7和R^8结合以形成-CH_2-CH_2-，并且R^3和R^4结合以形成根据式(IIa)的基团时，

R^9不是乙氧基羰基、环丁基氨基羰基、或环丁二烯基氨基羰基；

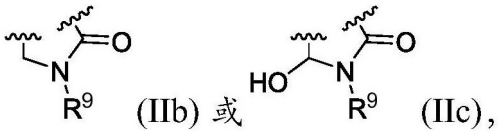
当R^5是甲氧基，R^6是甲基，Z^1是-OR^7，并且R^3和R^4结合以形成根据式(IIa)的基团时，

R^7不是甲基；

当R^5是氯，R^6是乙基，Z^1是-OR^7，并且R^3和R^4结合以形成根据式(IIa)的基团时，

R^7不是甲基；

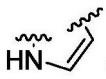
当每个R^5和R^6是氯，Z^1是-OR^7，并且R^3和R^4结合以形成根据式(IIb)或(IIc)的基团时，



(IIb)或 (IIc),

R^7不是甲基或2-(N,N-二乙基氨基)乙基；

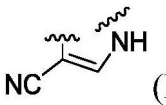
当R^7是甲基，R^5是氯，Z^1是-OR^7，并且R^3和R^4结合以形成根据式(IIIa)的基团时，



(IIIa),

R^6不是溴；

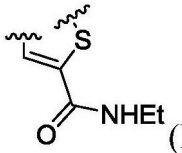
当R^5是氯，R^6是甲氧基，Z^1是-OR^7，并且R^3和R^4结合以形成根据式(IIIb)的基团时：



(IIIb),

R^1和R^2都不是2-(N,N-二乙基氨基)乙基；

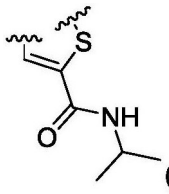
当每个R^5和R^6是氯，Z^1是-OR^7，并且R^3和R^4结合以形成根据式(IVa)的基团时：



(IVa),

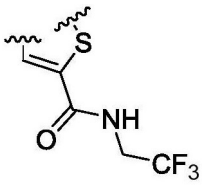
R^7不是3-(N-吗啉基)丙基、苄基、1-乙基-吡咯烷-3-基、1-甲基-哌啶-4-基、2-(1-甲基-吡咯烷-2-基)乙基、或3-(N,N-二乙基氨基)丙基；

当每个R^5和R^6是氯，Z^1是-OR^7，并且R^3和R^4结合以形成根据式(IVb)的基团时：


(IVb)，

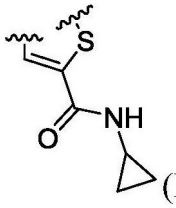
R^7不是2-甲氧基乙基或苄基；

当每个R^5和R^6是氯，Z^1是-OR^7，并且R^3和R^4结合以形成根据式(IVc)的基团时：


(IVc)，

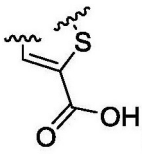
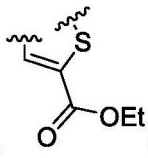
R^7不是2-(N,N-二乙基氨基)乙基或3-(N,N-二甲基氨基)丙基；

当每个R^5和R^6是氯，Z^1是-OR^7，并且R^3和R^4结合以形成根据式(IVd)的基团时：


(IVd)，

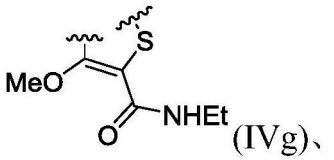
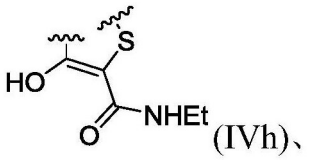
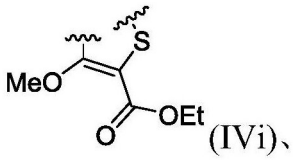
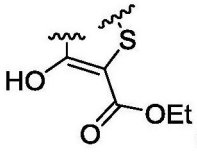
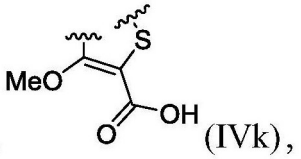
R^7不是2-(吡咯烷-1-基)乙基或2-羟基乙基；

当每个R^5和R^6是氯，Z^1是-OR^7，并且R^3和R^4结合以形成根据式(IVe)或(IVf)的基团时：


(IVe) 或

(IVf)，

R^7不是苄基；

当R^5是氯，R^6是溴，Z^1是-OR^7，并且R^3和R^4结合以形成根据式(IVg)、(IVh)、(IVi)、(IVj)、或(IVk)的基团时：


(IVg)、

(IVh)、

(IVi)、

(IVj)、或

(IVk)，

R^7不是甲基；

当R^6是甲基时，

每个R^1和R^2是H；并且

当R^3是H，Z^1是-OR^7，并且每个R^5和R^6是氯时，

R^7不是甲基。

2.如权利要求1所述的化合物，其中R^m是H。

3.一种根据式(Ia)的化合物：

或其药学上可接受的盐，

(Ia)，

其中

每个R^1和R^2独立地是H或任选取代的C_{1-3}烷基；

R^3和R^4与各自附接的原子一起连接以形成任选取代的五元或六元环，该五元或六元环任选地包括一至三个选自由硫、氧和氮组成的组的杂原子，其中所述氮任选地被R^9取代，或者R^3是H、卤素、氰基、任选取代的C_{1-6}烷基、任选取代的C_{1-3}烷氧基、或任选取代的氨基，并且R^4是卤素、氰基、任选取代的C_{1-6}烷基、任选取代的C_{1-3}烷氧基、任选取代的氨基、任选取代的C_{1-6}硫代烷基、或任选取代的C_{6-10}芳基；

R^5是卤素、H、任选取代的C_{1-3}烷基、任选取代的C_{1-3}烷氧基、或CN；

R^6是卤素、H、任选取代的C_{1-3}烷基、任选取代的C_{1-3}烷氧基、或CN；

R^7和R^8与各自附接的原子一起连接以形成任选取代的五元、六元或七元环，该五元、六元或七元环任选地包括一个或两个选自氮、氧和硫的杂原子；或者R^7是任选取代的C_{1-3}烷基、任选取代的C_{1-3}烷环烷基、任选取代的C_{1-3}烷杂环基、或任选取代的C_{1-3}烷芳基，并且R^8是H；

R^9是H、任选取代的C_{1-3}烷基、任选取代的C_{3-8}环烷基、任选取代的C_{6-10}芳基、任选取代的C_{2-9}杂芳基、任选取代的C_{2-9}杂环基、任选取代的C_{1-3}烷环烷基、任选取代的C_{1-3}烷杂环基、或任选取代的C_{1-3}烷芳基；

Z^1是$-OR^7$、$-N(R^{10})R^7$、$-SR^7$、或$-C(R^{10})(R^{11})R^7$；并且

R^{10}是H、任选取代的C_{1-3}酰基、任选取代的C_{1-3}烷基、任选取代的C_{3-8}环烷基、任选取代的C_{6-10}芳基、任选取代的C_{2-9}杂芳基、任选取代的C_{2-9}杂环基、任选取代的C_{1-3}烷环烷基、任选取代的C_{1-3}烷杂环基、或任选取代的C_{1-3}烷芳基，并且R^{11}是H、任选取代的C_{1-3}烷基，或者R^{10}和R^{11}结合以形成=O或=S；

其中，

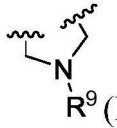
当每个R^1和R^2是H，R^3是H，R^4是甲基或氯，并且每个R^5和R^6是氯时，

Z^1不是甲氧基；

当每个R^5和R^6是氯，R^3是H，和R^4是卤素时，

Z^1不是2-氨基-2-氧代乙氧基、2-(N,N-二乙氨基)乙氧基、甲氧基、或苄氧基；

当R^5是氯，R^6是溴，Z^1是$-OR^7$，并且R^3和R^4结合以形成根据式(IIa)的基团时：



(IIa)，

R^7不是甲基、乙基、正丙基、2-(N-吡唑基)乙基、2-(N-咪唑基)乙基、3-羟丙基、氰甲基、

2-氯乙基、2-羟乙基、2-氧代丙基、2-(N,N-二甲氨基)乙基、二氟甲基或2-(叔丁氨基)乙基；

当每个R^5和R^6是溴，Z^1是$-OR^7$，并且R^3和R^4结合以形成根据式(IIa)的基团时，

R^7不是甲基；

当每个R^5和R^6是氯，Z^1是$-OR^7$，并且R^3和R^4结合以形成根据式(IIa)的基团时，

R^7不是甲基、2-(N-咪唑基)乙基、甲氧基甲基、2-(N-吡唑基)乙基、2-(3-甲基吡唑-1-基)乙基、2-吡啶基-甲基、1,3-二甲基-1H-1,2,4-三唑-5-基-甲基、2-嘧啶基甲基、咪唑-2-基-甲基、5-甲基-异噁唑-3-基-甲基、4-甲基-咪唑-5-基-甲基、或3-甲基-1,2,4-噁二唑-5-基-甲基；

当每个R^5和R^6是氯，Z^1是$-OR^7$，R^7和R^8结合以形成$-CH_2-CH_2-$，并且R^3和R^4结合以形成根据式(IIa)的基团时，

R^9不是乙氧基羰基、环丁基氨基羰基、或环丁二烯基氨基羰基；

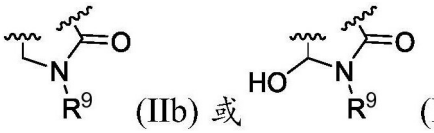
当R^5是甲氧基，R^6是甲基，Z^1是$-OR^7$，并且R^3和R^4结合以形成根据式(IIa)的基团时，

R^7不是甲基；

当R^5是氯，R^6是乙基，Z^1是$-OR^7$，并且R^3和R^4结合以形成根据式(IIa)的基团时，

R^7不是甲基；

当每个R^5和R^6是氯，Z^1是$-OR^7$，并且R^3和R^4结合以形成根据式(IIb)或(IIc)的基团时，



(IIb) 或 (IIc)，

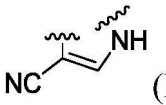
R^7不是甲基或2-(N,N-二乙基氨基)乙基；

当R^7是甲基，R^5是氯，Z^1是$-OR^7$，并且R^3和R^4结合以形成根据式(IIIa)的基团时，

(IIIa)，

R^6不是溴；

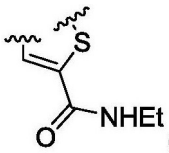
当R^5是氯，R^6是甲氧基，Z^1是$-OR^7$，并且R^3和R^4结合以形成根据式(IIIb)的基团时：



(IIIb)，

R^1和R^2都不是2-(N,N-二乙基氨基)乙基；

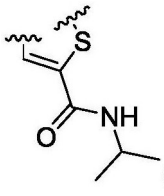
当每个R^5和R^6是氯，Z^1是$-OR^7$，并且R^3和R^4结合以形成根据式(IVa)的基团时：



(IVa)，

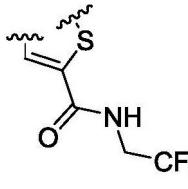
R^7不是3-(N-吗啉基)丙基、苄基、1-乙基-吡咯烷-3-基、1-甲基-哌啶-4-基、2-(1-甲基-吡咯烷-2-基)乙基、或3-(N,N-二乙基氨基)丙基；

当每个R^5和R^6是氯，Z^1是$-OR^7$，并且R^3和R^4结合以形成根据式(IVb)的基团时：


(IVb),

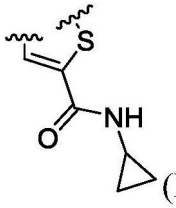
R^7不是2-甲氧基乙基或苄基；

当每个R^5和R^6是氯，Z^1是-OR^7，并且R^3和R^4结合以形成根据式(IVc)的基团时：


(IVc),

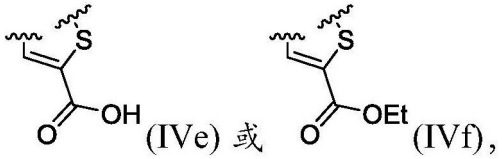
R^7不是2-(N,N-二乙基氨基)乙基或3-(N,N-二甲基氨基)丙基；

当每个R^5和R^6是氯，Z^1是-OR^7，并且R^3和R^4结合以形成根据式(IVd)的基团时：


(IVd),

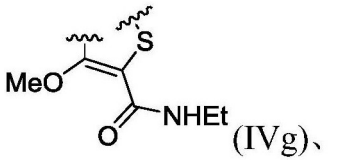
R^7不是2-(吡咯烷-1-基)乙基或2-羟基乙基；

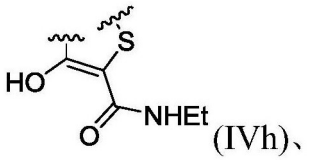
当每个R^5和R^6是氯，Z^1是-OR^7，并且R^3和R^4结合以形成根据式(IVe)或(IVf)的基团时：

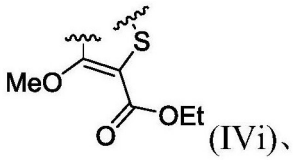

(IVe) 或 (IVf),

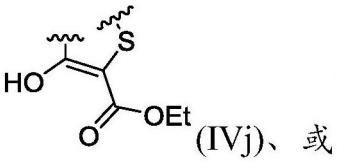
R^7不是苄基；

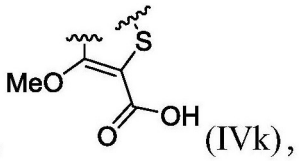
当R^5是氯，R^6是溴，Z^1是-OR^7，并且R^3和R^4结合以形成根据式(IVg)、(IVh)、(IVi)、(IVj)、或(IVk)的基团时：


(IVg)、


(IVh)、


(IVi)、


(IVj)、或


(IVk),

R^7不是甲基；

当R^6是甲基时，

每个R^1和R^2是H；并且

当R^3是H，Z^1是-OR^7，并且每个R^5和R^6是氯时，

R^7不是甲基。

4.一种根据式(Ib)的化合物：

或其药学上可接受的盐，

(Ib)，

其中

每个R^1和R^2独立地是H或任选取代的C_{1-3}烷基；

R^3和R^4与各自附接的原子一起连接以形成任选取代的五元或六元环，该五元或六元环任选地包括一个氮、一个硫、或一个氧，其中该氮任选地被R^9取代，或者R^3是H、卤素、氰基、任选取代的C_{1-6}烷基、任选取代的C_{1-3}烷氧基、或任选取代的氨，并且R^4是卤素、氰基、任选取代的C_{1-6}烷基、任选取代的C_{1-3}烷氧基、任选取代的氨、任选取代的C_{1-6}硫代烷氧基、或任选取代的C_{6-10}芳基；

R^5是卤素、H、任选取代的C_{1-3}烷基、任选取代的C_{1-3}烷氧基、或CN；

R^6是卤素、H、任选取代的C_{1-3}烷基、任选取代的C_{1-3}烷氧基、或CN；

R^7是任选取代的C_{1-3}烷基、任选取代的C_{1-3}烷环烷基、任选取代的C_{1-3}烷杂环基、或任选取代的C_{1-3}烷芳基，并且R^8是H；或者R^7和R^8与各自附接的原子一起连接以形成任选取代的五元、六元、或七元环；并且

R^9是H、任选取代的C_{1-3}烷基、任选取代的C_{3-8}环烷基、任选取代的C_{6-10}芳基、任选取代的C_{2-9}杂芳基、任选取代的C_{2-9}杂环基、任选取代的C_{1-3}烷环烷基、任选取代的C_{1-3}烷杂环基、或任选取代的C_{1-3}烷芳基；

其中，

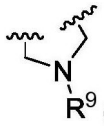
当每个R^1和R^2是H，R^3是H，R^4是甲基或氯，并且每个R^5和R^6是氯时，

R^7不是甲基；

当每个R^5和R^6是氯，R^3是H，和R^4是卤素时，

R^7不是2-氨基-2-氧代乙基、2-(N,N-二乙基氨基)乙基、甲基、或苄基；

当R^5是氯时，R^6是溴，并且R^3和R^4结合以形成根据式(IIa)的基团时：



(IIa)，

R^7不是甲基、乙基、正丙基、2-(N-吡唑基)乙基、2-(N-咪唑基)乙基、3-羟丙基、氰甲基、2-氯乙基、2-羟乙基、2-氧代丙基、2-(N,N-二甲氨基)乙基、二氟甲基或2-(叔丁氨基)乙基；

当每个R^5和R^6是溴，并且R^3和R^4结合以形成根据式(IIa)的基团时，

R^7不是甲基；

当每个R^5和R^6是氯，R^8是H，并且R^3和R^4结合以形成根据式(IIa)的基团时，

R^7不是甲基、2-(N-咪唑基)乙基、甲氧基甲基、2-(N-吡唑基)乙基、2-(3-甲基吡唑-1-基)乙基、2-吡啶基-甲基、1,3-二甲基-1H-1,2,4-三唑-5-基-甲基、2-嘧啶基甲基、咪唑-2-基-甲基、5-甲基-异噁唑-3-基-甲基、4-甲基-咪唑-5-基-甲基、或3-甲基-1,2,4-噁二唑-5-基-甲基；

当每个R^5和R^6是氯，R^7和R^8结合以形成-CH_2-CH_2-，并且R^3和R^4结合以形成根据式(IIa)的基团时，

R^9不是乙氧基羰基、环丁基氨基羰基、或环丁二烯基氨基羰基；

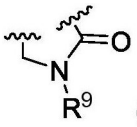
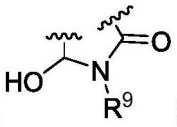
当R^5是甲氧基，R^6是甲基，并且R^3和R^4结合以形成根据式(IIa)的基团时，

R^7不是甲基；

当R^5是氯，R^6是乙基，并且R^3和R^4结合以形成根据式(IIa)的基团时，

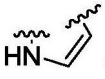
R^7不是甲基；

当每个R^5和R^6是氯，并且R^3和R^4结合以形成根据式(IIb)或(IIc)的基团时，


(IIb) 或

(IIc)，

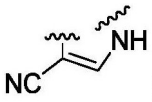
R^7不是甲基或2-(N,N-二乙基氨基)乙基；

当R^7是甲基，R^5是氯，并且R^3和R^4结合以形成根据式(IIIa)的基团时，


(IIIa)，

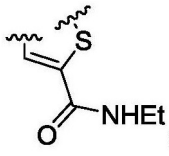
R^6不是溴；

当R^5是氯，R^6是甲氧基，并且R^3和R^4结合以形成根据式(IIIb)的基团时：


(IIIb)，

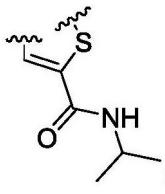
R^1和R^2都不是2-(N,N-二乙基氨基)乙基；

当每个R^5和R^6是氯，并且R^3和R^4结合以形成根据式(IVa)的基团时：


(IVa)，

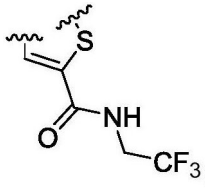
R^7不是3-(N-吗啉基)丙基、苄基、1-乙基-吡咯烷-3-基、1-甲基-哌啶-4-基、2-(1-甲基-吡咯烷-2-基)乙基、或3-(N,N-二乙基氨基)丙基；

当每个R^5和R^6是氯，并且R^3和R^4结合以形成根据式(IVb)的基团时：


(IVb)，

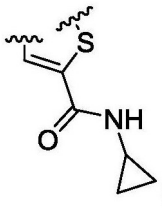
R^7不是2-甲氧基乙基或苄基；

当每个R^5和R^6是氯，并且R^3和R^4结合以形成根据式(IVc)的基团时：


(IVc)，

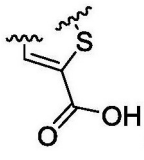
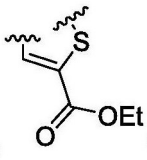
R^7不是2-(N,N-二乙基氨基)乙基或3-(N,N-二甲基氨基)丙基；

当每个R^5和R^6是氯，并且R^3和R^4结合以形成根据式(IVd)的基团时：


(IVd),

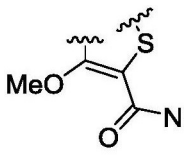
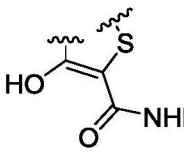
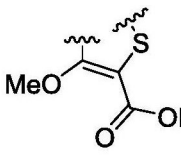
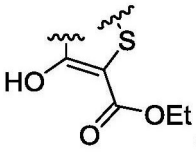
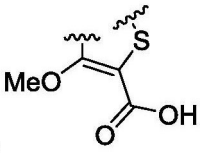
R^7不是2-(吡咯烷-1-基)乙基或2-羟基乙基；

当每个R^5和R^6是氯，并且R^3和R^4结合以形成根据式(Ive)或(IVf)的基团时：


(IVe) 或

(IVf),

R^7不是苄基；

当R^5是氯，R^6是溴，并且R^3和R^4结合以形成根据式(IVg)、(IVh)、(IVi)、(IVj)、或(IVk)的基团时：


(IVg)、

(IVh)、

(IVi)、

(IVj)、或

(IVk),

R^7不是甲基；

当R^6是甲基时，

每个R^1和R^2是H；并且

当R^3是H，并且每个R^5和R^6是氯时，

R^7不是甲基。

5.如权利要求1至4中任一项所述的化合物，其中R^3和R^4与各自附接的原子一起连接以形成任选取代的五元或六元环，该五元或六元环任选地包括一个氮、一个氧或一个硫，其中所述氮任选地被R^9取代，或者R^3是H、卤素、任选取代的C_{1-3}酰基、任选取代的C_{1-3}烷基、或任选取代的C_{1-3}烷氧基，并且R^4是卤素、任选取代的C_{1-3}酰基、任选取代的C_{1-3}烷基、任选取代的C_{1-3}烷氧基、任选取代的氨基、任选取代的C_{1-6}硫代烷基、或任选取代的C_{6-10}芳基。

6.如权利要求1至5中任一项所述的化合物，其中R^3和R^4与各自附接的原子一起连接以形成包括一个硫的任选取代的五元环。

7.如权利要求1至5中任一项的化合物，其中R^3和R^4结合以形成-C(R^{13A})=C(R^{13B})-S-基团，其中R^{13A}是H，并且R^{13B}是任选取代的C_{1-3}烷基或H。

8.如权利要求11所述的化合物，其中R^{13B}是任选取代的C_{1-3}烷基。

9.如权利要求12所述的化合物，其中R^{13B}是-C(O)-R^{13C}，其中R^{13C}是任选取代的氨基或任

选取代的C_{1-3}烷氧基。

10.如权利要求1至5中任一项所述的化合物，其中R^3和R^4结合以形成-C(R^{13A})=C(R^{13B})-S-基团，其中R^{13A}是H，并且R^{13B}是-C(O)-R^{13C}、H、或C_{1-6}氨烷基，其中R^{13C}是任选取代的C_{1-3}烷基、任选取代的C_{1-3}烷氧基、任选取代的氨基、或任选取代的C_{2-9}杂环基。

11.如权利要求1至5中任一项所述的化合物，其中R^3和R^4与各自附接的原子一起连接以形成任选取代的五元环。

12.如权利要求1至5中任一项所述的化合物，其中R^3和R^4结合以形成-$CH_2CH_2CH_2$-基团。

13.如权利要求1至5中任一项所述的化合物，其中R^3和R^4与各自附接的原子一起连接以形成包括一个氮的任选取代的五元环。

14.如权利要求13所述的化合物，其中R^3和R^4结合以形成-N(R^9)-CH=CH-基团。

15.如权利要求1至5中任一项所述的化合物，其中R^3和R^4结合以形成-X^1-X^2-X^3-，其中

X^1是-S-、-O-、-($CR^{14}R^{15}$)-、-C(R^{16})=、-N(R^9)-、-N=、H、或任选取代的C_{1-3}烷基；

X^2是不存在的、-($CR^{17}R^{18}$)$_n$-、-S-、-O-、-N=、-N(R^9)-、-C(R^{19})=、=N-、=C(R^{20})-、或=C(R^{21})-C(R^{22})=；

X^3是-($CR^{14}R^{15}$)-、-S-、-O-、-N(R^9)-、=N-、=C(R^{23})-、卤素、任选取代的C_{1-3}烷基、任选取代的C_{1-6}硫代烷氧基、任选取代的C_{1-3}烷氧基、或任选取代的C_{6-10}芳基；

每个R^{14}和R^{15}独立地是H或任选取代的C_{1-3}烷基、或者R^{14}和R^{15}结合以形成=O或=S；

每个R^{17}和R^{18}独立地是H或任选取代的C_{1-3}烷基、或者R^{17}和R^{18}结合以形成=O或=S；

每个R^{16}、R^{19}、R^{20}、R^{21}、R^{22}、和R^{23}独立地是H、或任选取代的C_{1-3}烷基；并且

n是1或2。

16.如权利要求1至15中任一项所述的化合物，其中R^7和R^8形成基团-Y^1-Y^2-，其中：

Y^1是-($CR^{26}R^{27}$)$_m$-或任选取代的C_{1-3}烷基、任选取代的C_{1-3}烷杂环基、任选取代的C_{1-3}烷环烷基、或任选取代的C_{1-3}烷芳基；并且

Y^2是-($CR^{26}R^{27}$)-或H；其中

每个R^{26}和R^{27}独立地是H或任选取代的C_{1-3}烷基；

m是1、2、或；并且

当Y^1是任选取代的C_{1-3}烷基、任选取代的C_{1-3}烷杂环基、任选取代的C_{1-3}烷环烷基、或任选取代的C_{1-3}烷芳基时，

Y^2是H，并且Y^1不直接键合到Y^2。

17.如权利要求1至5中任一项所述的化合物，其中Z^1和R^8结合以形成-Z^3-Y^1-Y^2-，其中

Z^3是-O-、-N(R^{10})-、-N=、-S-、或-($CR^{14}R^{15}$)-；

Y^1是-O-、-N(R^{10})-、-S-、-($CR^{26}R^{27}$)$_m$-、-C(R^{20})=、=C(R^{20})-、=C(R^{21})-C(R^{22})=、任选取代的C_{1-3}烷基、任选取代的C_{1-3}烷杂环基、任选取代的C_{1-3}烷环烷基、或任选取代的C_{1-3}烷芳基；并且

Y^2是-O-、-S-、-N(R^{10})-、-($CR^{26}R^{27}$)-、=C(R^{20})-、=N-、或H；

其中

每个R^{20}、R^{21}、和R^{22}独立地是H或任选取代的C_{1-3}烷基；并且

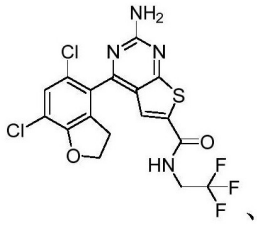
每个R^{26}和R^{27}独立地是H或任选取代的C_{1-3}烷基、或者R^{26}和R^{27}结合以形成=O或=S；

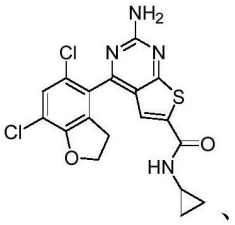
m是1或2；并且

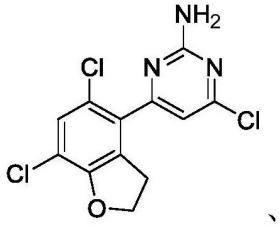
其中，当Y^2是H时，

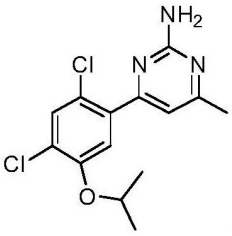
原子链-Z^3-Y^1-Y^2-包括不超过两个杂原子，每一个所述杂原子独立地选自氮、氧、和硫。

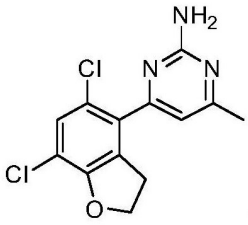
18.一种化合物：

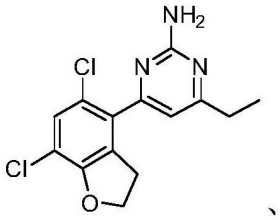
61  、

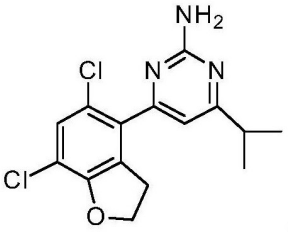
62  、

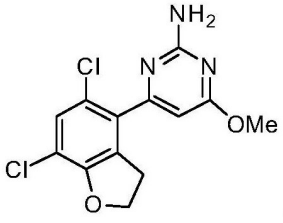
49  、

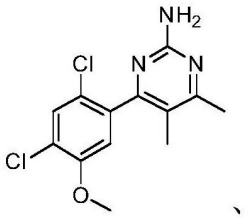
2  、

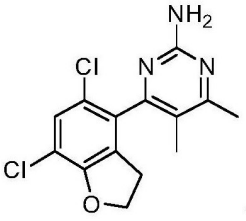
5  、

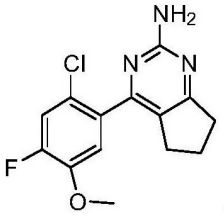
6  、

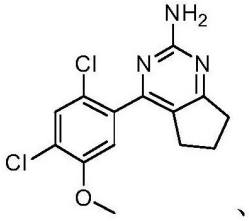
7  、

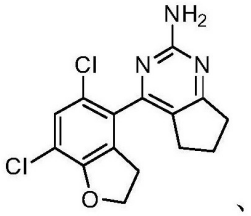
8  、

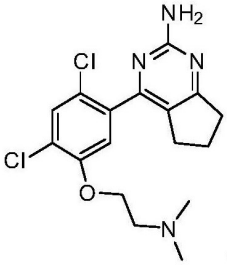
9  、

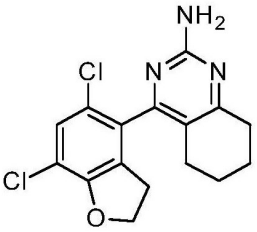
10  、

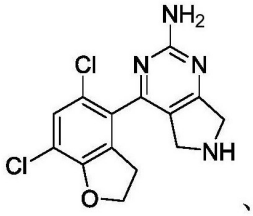
11  、

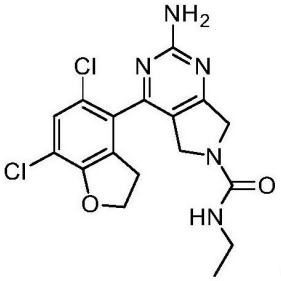
12  、

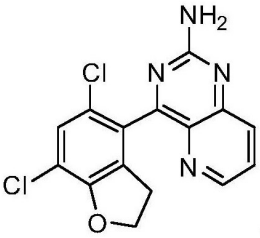
13 

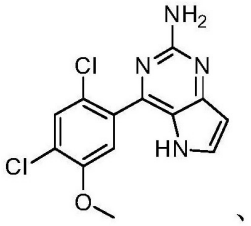
14 

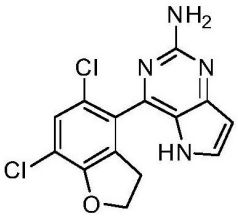
15 

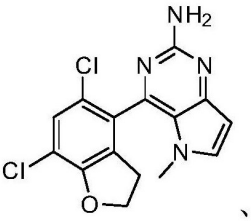
16 

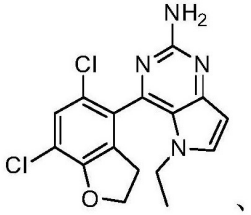
17 

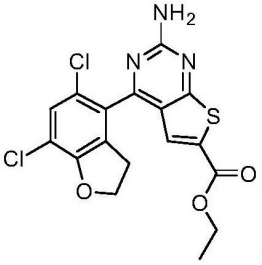
18 

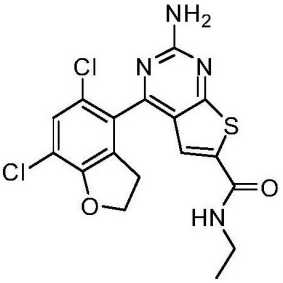
19 

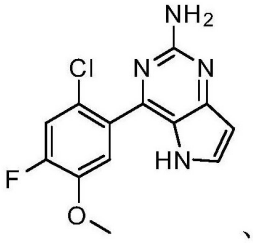
20 

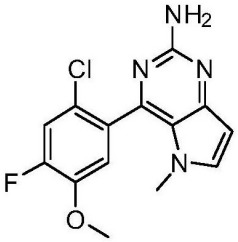
21 

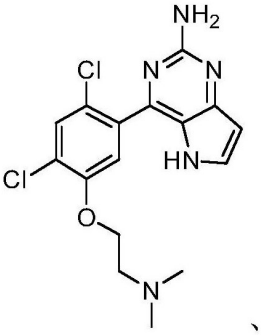
22 

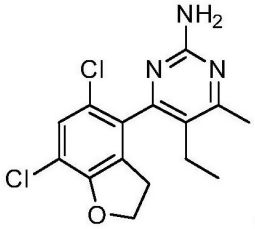
23 

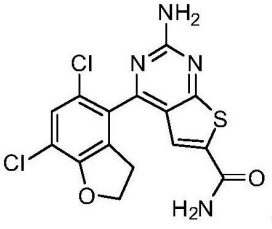
24 

25 

26 

27 

28 

29 

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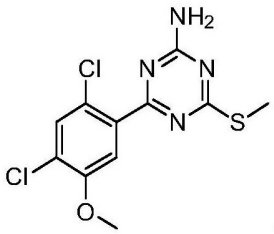
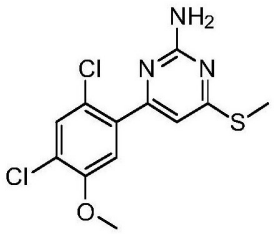
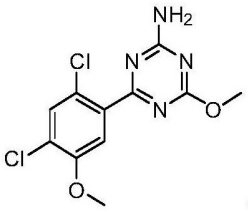
34 

35 

36 

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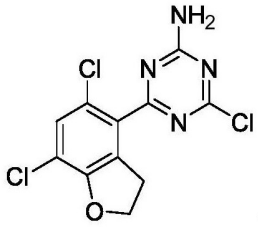
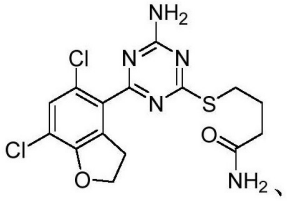
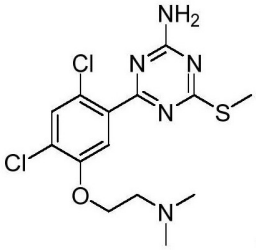
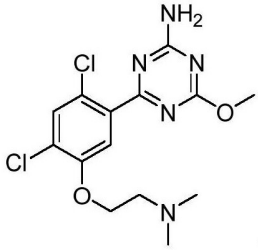
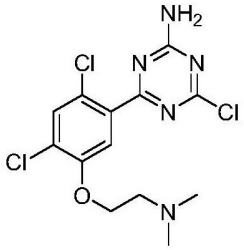
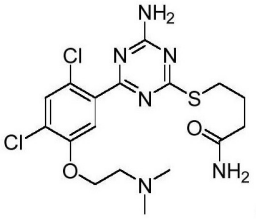
42 

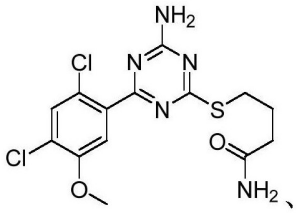
43 

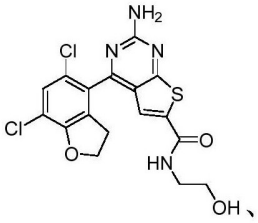
44 

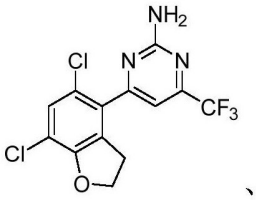
45 

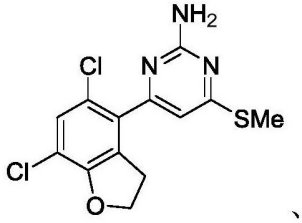
46 

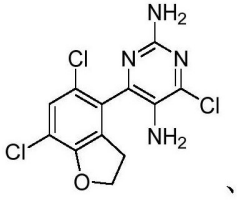
47 

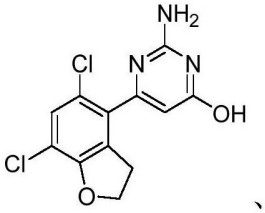
48 

60 

50 

51 

52 

53 

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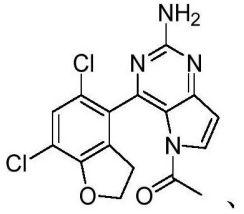
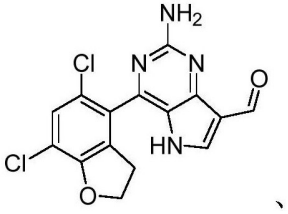
55 

56 

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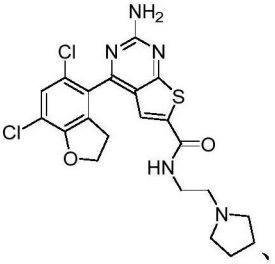
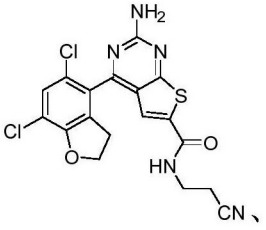
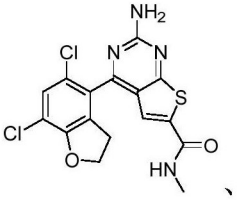
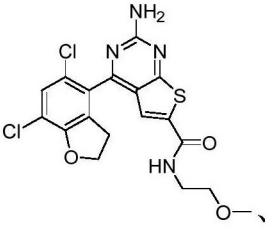
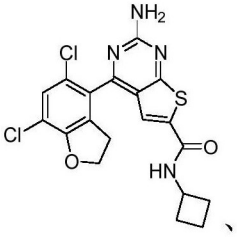
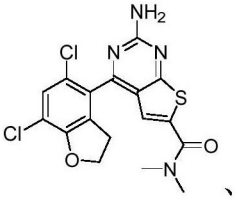
58  、

59  、

63  、

64  、

65  、

66  、

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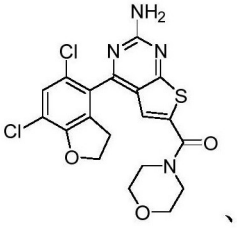
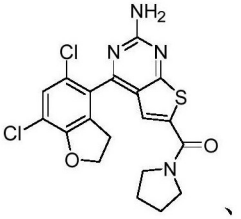
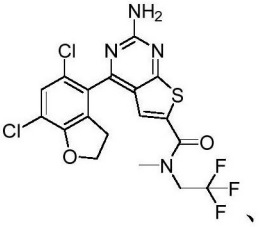
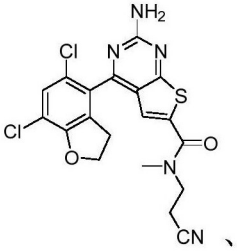
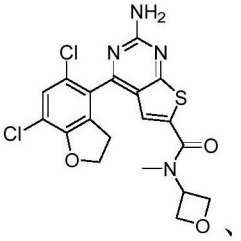
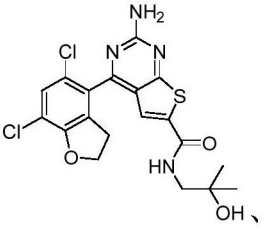
68  、

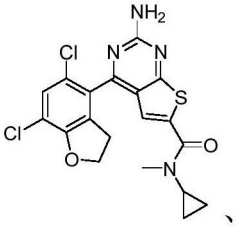
69  、

70  、

71  、

72  、

73  、

74  、

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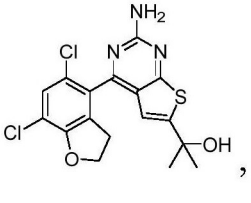
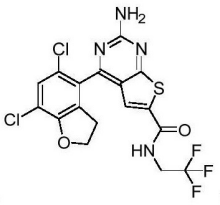
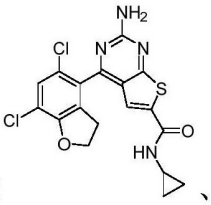
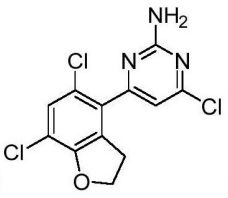
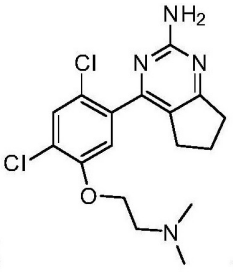
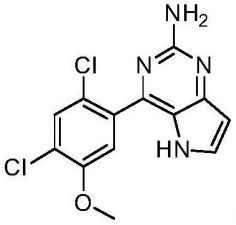
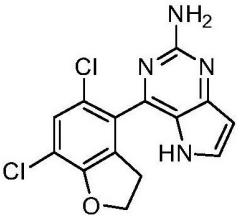
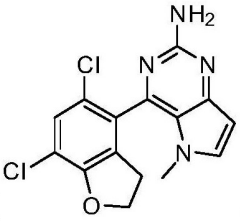
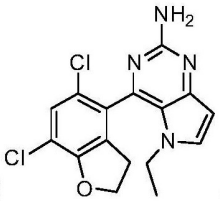
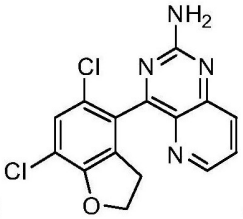
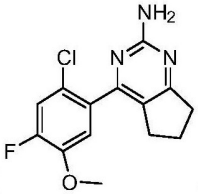
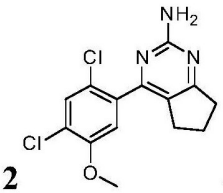
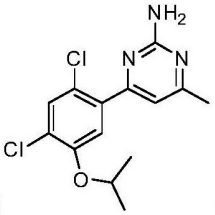
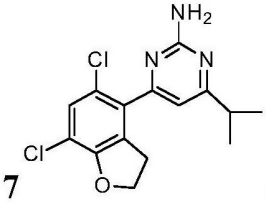
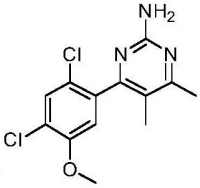
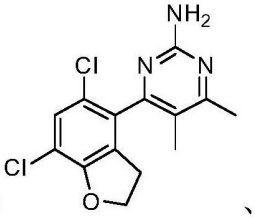
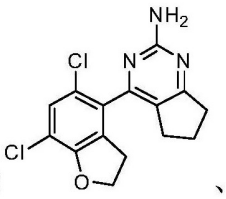
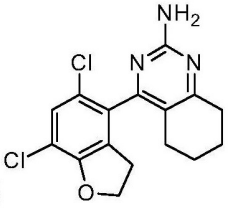
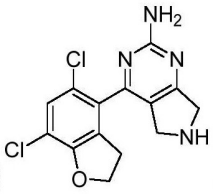
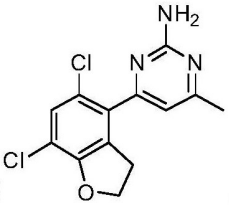
77  ，

或其药学上可接受的盐。

19.如权利要求18所述的化合物，具有式：


61、 
62、 
49、 
14、 
19、 
20、 
21、 
22、 
18、 
11、 
12、 
2、 
7、 
9、 
10、 
13、 
15、 
16、 
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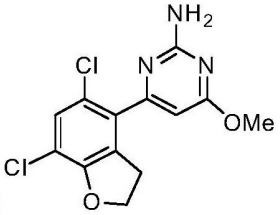
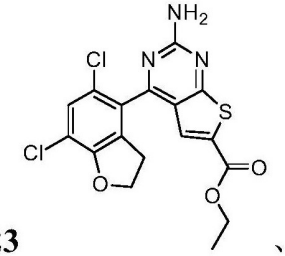
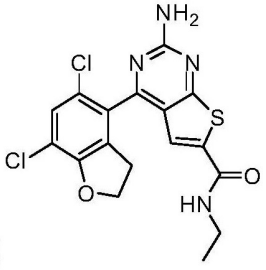
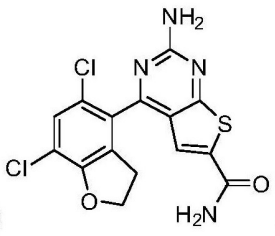
6、 
8、 
23、 
24、 
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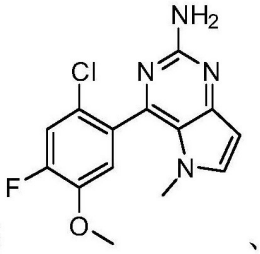
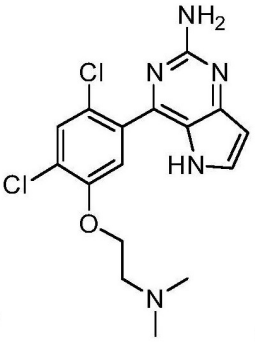
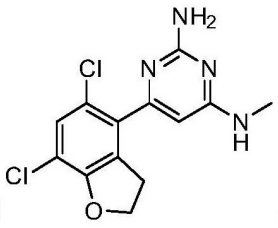
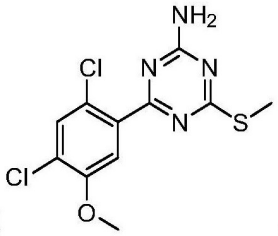
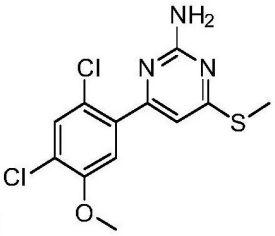
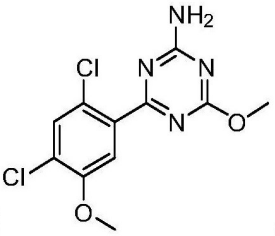
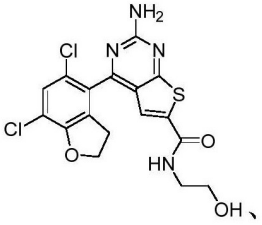
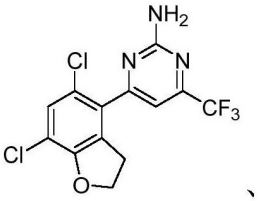
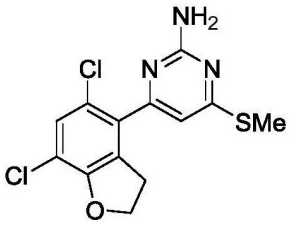
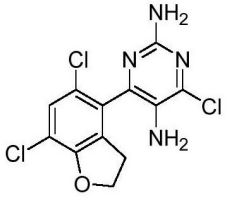
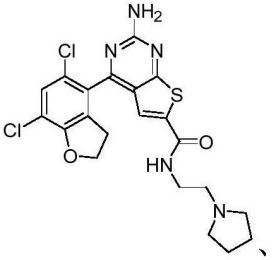
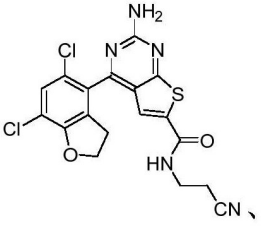
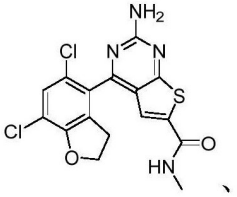
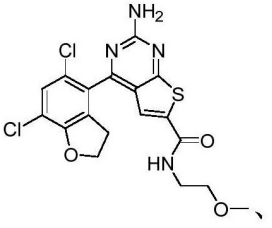
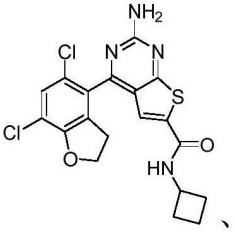
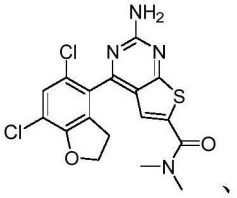
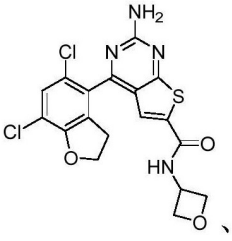
26  、27  、33  、

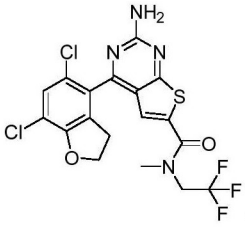
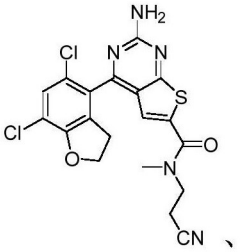
34  、35  、36  、

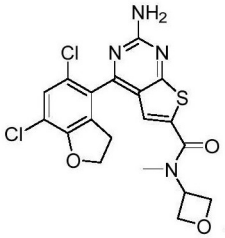
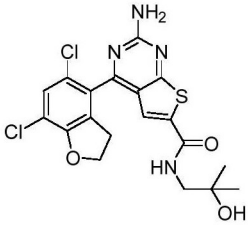
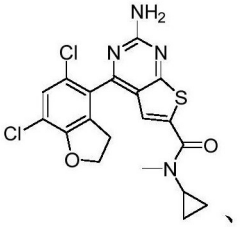
60  、50  、51 

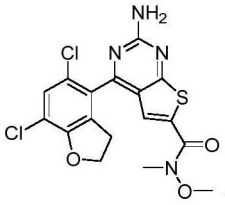
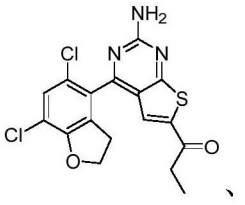
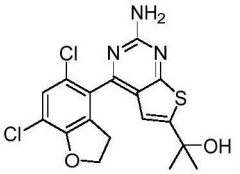
52  、58  、59  、

63  、64  、65  、

66  、67  、68 、

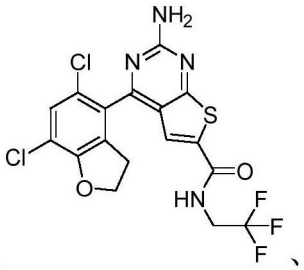
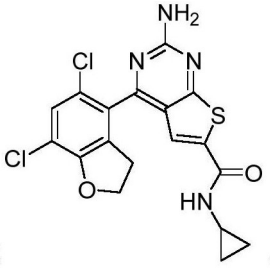
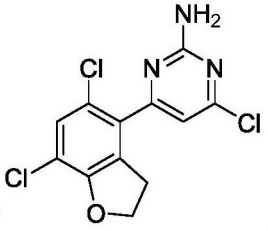
69 、 **70**  、 **71**  、

72  、 **73**  、 **74**  、

75  、 **76**  、或 **77**  ，

或其药学上可接受的盐。

20.如权利要求19所述的化合物，其中所述化合物是：

61  、 **62**  、或 **49**  ，或其药学上可接受的盐。

21.一种药物组合物，包括如权利要求1至20中任一项所述的化合物或其药学上可接受的盐，以及一种或多种药学上可接受的载体或赋形剂。

22.如权利要求21所述的药物组合物，其中所述组合物被配制为用于经口、舌下、颊部、经皮、皮内、肌内、胃肠外、静脉内、动脉内、颅内、皮下、眶内、心室内、脊柱内、腹膜内、鼻内、通过吸入、以及局部给予。

23.如权利要求22所述的药物组合物，其中所述组合物被配制为用于口服给予。

24.一种治疗哺乳动物中由热休克蛋白90(Hsp90)的作用引起的障碍的方法，所述方法包括给予所述哺乳动物有效量的如权利要求1至20中任一项所述的化合物或其药学上可接受的盐或如权利要求21所述的药物组合物。

25.如权利要求25所述的方法，其中所述障碍是神经退行性障碍。

26.如权利要求25所述的方法，其中所述神经退行性障碍是tau蛋白病变。

27.如权利要求24或25所述的方法，其中所述神经退行性障碍是阿尔茨海默氏病、亨廷顿舞蹈病、进行性核上性麻痹、帕金森病、皮克氏病、皮质基底节变性、慢性创伤性脑病、创伤性脑损伤、或额颞痴呆。

28.如权利要求27所述的方法，其中所述神经退行性障碍是阿尔茨海默氏病。

29.如权利要求24所述的方法，其中所述障碍是增殖性疾病。

30.如权利要求29所述的方法，其中所述增殖性疾病是癌症。

31.一种治疗哺乳动物的传染病的方法，所述方法包括给予所述哺乳动物有效量的如权利要求1至20中任一项所述的化合物或其药学上可接受的盐或如权利要求21所述的药物组合物。

32.如权利要求31所述的方法，其中所述传染病是病毒感染。

33.如实施例32所述的方法，其中所述病毒感染是由选自下组的科的病毒引起的感染，该组由以下各项组成：疱疹病毒科、多瘤病毒科、痘病毒科、呼肠弧病毒科、双RNA病毒科、小核糖核酸病毒科、黄病毒科、沙粒病毒科、戊型肝炎病毒科、弹状病毒科、副黏液病毒科、布尼亚病毒科、正粘病毒科、丝状病毒科、逆转录病毒科、和嗜肝病毒科。

34.如权利要求31所述的方法，其中所述传染病是真菌感染。

35.如权利要求31所述的方法，其中所述传染病是细菌感染。

36.如权利要求24所述的方法，其中所述障碍是炎性或自身免疫疾病。

37.如权利要求36所述的方法，其中所述炎性或自身免疫疾病是类风湿性关节炎、系统性红斑狼疮、或哮喘。

38.如权利要求24所述的方法，其中所述障碍是心血管疾病。

39.如权利要求38所述的方法，其中所述心血管疾病是动脉粥样硬化。

40.如权利要求24所述的方法，其中所述障碍是过敏。

41.如权利要求24至40中任一项所述的方法，其中所述化合物经口、舌下、颊部、经皮、皮内、肌内、胃肠外、静脉内、动脉内、颅内、皮下、眶内、心室内、脊柱内、腹膜内、鼻内、通过吸入、以及局部进行给予。

42.如权利要求41所述的方法，其中所述化合物是口服给予的。

43.如权利要求24至42中任一项所述的方法，其中所述哺乳动物是人类。

44.一种抑制Hsp90的方法，所述方法包括使细胞与如权利要求1至20中任一项所述的化合物或其药学上可接受的盐相接触。

45.如权利要求44所述的方法，其中所述细胞是在体外。

46.一种试剂盒，包括：

(i)如权利要求21至23中任一项所述的药物组合物；以及

(ii)使用(i)的药物组合物治疗哺乳动物中由Hsp90的作用引起的障碍的说明书。

嘧啶化合物及其使用方法

[0001] 关于联邦资助研究的声明

[0002] 本发明是由国立卫生研究院授予的在授权号STTR 1R41GO42205-01下的政府支持所完成的。政府在本发明中享有一定的权利。

发明领域

[0003] 一般而言，本发明涉及热休克蛋白90(Hsp90)的基于嘧啶的小分子抑制剂及其药物组合物。本发明还涉及治疗患有神经退行性疾病的受试者的方法。

[0004] 发明背景

[0005] Hsp90蛋白与稳定蛋白质构象、保持许多细胞信号蛋白的功能和ATP酶活性有关。Hsp90活性还是参与肿瘤进展的癌蛋白的正确折叠、稳定化、活化和定位所必需的。N-末端ATP结合结构域负责该蛋白质的ATP酶活性：这种腺嘌呤核苷酸结合口袋在从细菌到哺乳动物的所有Hsp90蛋白中高度保守，但不存在于其他分子伴侣中。

[0006] Hsp90蛋白已经作为癌症治疗中的重要靶标出现，因为许多Hsp90客户蛋白本身被鉴定为癌症治疗的靶标。与癌症相关的示例性Hsp90客户蛋白包括HER2(乳腺癌)、Raf-1/突变体BRAF(黑色素瘤)、突变型EGFR(非小细胞肺癌、成胶质细胞瘤)、c-Kit(GIST)、c-Met(胃癌、肺癌、成胶质细胞瘤)、HIF-1α(肾癌)、Zap70(慢性淋巴细胞白血病)、Bcr-Abl(慢性骨髓性白血病)、mBcr-Abl(慢性骨髓性白血病)、Flt-3(急性髓细胞性白血病)、IGF-1R/Akt(骨髓瘤)、NMP-ALK(淋巴瘤)和Akt(小细胞肺癌)。突变的Hsp90客户的超表达或其客户(例如HER2)的扩增导致肿瘤细胞对Hsp90分子伴侣功能的依赖性增加。因此，Hsp90提供了用于治疗不同类别的肿瘤的强制性靶标。

[0007] Hsp90的水平升高也涉及神经退行性障碍，包括阿尔茨海默氏病、帕金森氏病和亨廷顿舞蹈病、和tau蛋白病变。tau蛋白病变是以tau蛋白异常为特征的神经退行性疾病，其然后导致过度磷酸化和聚集的tau蛋白的积累。已经提出阿尔茨海默病中的过度磷酸化的tau是由激酶，特别是cdk5和GSKβ3的异常激活引起的致病过程。研究已经表明Hsp90使p35这一cdk5的活化剂稳定化，从而导致了增加的tau磷酸化。还已经表明，Hsp90抑制激活了热休克因子1(HSF1)，这反过来又增加了Hsp70的表达。Hsp70的增加表达促进了tau溶解度和结合到微管上，抑制了Aβ肽聚集，并且增强了Aβ肽降解。

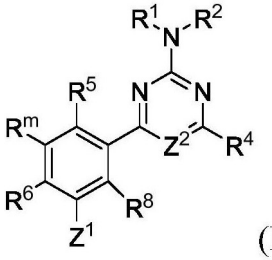
[0008] Hsp90也已经成为用于治疗病毒、真菌和细菌感染的靶标。例如，Hsp90抑制剂(格尔德霉素)已显示延缓细胞培养物中流感病毒的生长。依赖于Hsp90依赖性过程的其他病毒包括属于以下科的那些病毒：疱疹病毒科(例如，单纯疱疹病毒-1、单纯疱疹病毒-2、疱疹病毒-5、卡波西氏肉瘤相关的疱疹病毒、水痘带状疱疹病毒或埃-巴二氏病毒)、多瘤病毒科(例如，SV40)、痘病毒科(例如，痘苗病毒)、呼肠弧病毒科(例如，轮状病毒)、双RNA病毒科(例如，感染性囊病病毒)、小核糖核酸病毒科(例如，脊髓灰质炎病毒、鼻病毒或柯萨奇病毒)、黄病毒科(例如，丙型肝炎病毒或登革热病毒)、沙粒病毒科(例如，淋巴细胞性脉络丛脑膜炎病毒)、戊型肝炎病毒科(例如，戊型肝炎病毒)、弹状病毒科(例如，水泡性口炎病毒)、副伤寒病毒科(例如，人副流感病毒2、人副流感病毒3、SV5、SV41、麻疹病毒或仙台病

毒)、布尼亚病毒科(例如,拉克罗斯病毒)、正甲型病毒科(例如,甲型流感病毒)、丝状病毒科(例如,埃博拉病毒)、逆转录病毒科(例如,HTLV1或HIV1)、和嗜肝DNA病毒(例如,乙型肝炎病毒)。Hsp90抑制剂也已经用于治疗在体内的真菌感染性疾病,例如,白色念珠菌、烟曲霉或肺囊虫的治疗。此外,Hsp90抑制剂还可用于治疗细菌感染,例如,分枝杆菌病、炭疽或细菌性肺炎。

[0009] 鉴于上述,Hsp90的抑制剂代表用于治疗疾病,例如,癌症、神经退行性疾病、和感染性疾病的有益治疗剂。

[0010] 发明概述

[0011] 一方面,本发明的特征在于一种根据式(I)的化合物:

[0012]  或其药学上可接受的盐,

(I),

[0013] 其中

[0014] Z^1是-OR^7、-$N(R^{10})R^7$、-SR^7、或-$C(R^{10})(R^{11})R^7$;

[0015] Z^2是-N=或-$C(R^3)$=;

[0016] 每个R^1和R^2独立地是H或任选取代的C_{1-3}烷基(例如,C_{1-3}酰基);

[0017] R^3是H、卤素、氰基、任选取代的C_{1-6}烷基、任选取代的C_{1-3}烷氧基、或任选取代的氨基,并且R^4是卤素、氰基、任选取代的C_{1-6}烷基、任选取代的C_{1-3}烷氧基、任选取代的氨基、任选取代的C_{1-6}硫代烷氧基、或任选取代的C_{6-10}芳基,或者R^3和R^4与各自附接的原子一起连接以形成任选取代的五或六元环,该五或六元环任选地包括1至3个选自下组的杂原子,该组由以下各项组成:氮、氧和硫,其中该氮任选地被R^9取代;

[0018] 每个R^5和R^6独立地是H、任选取代的C_{1-3}烷基、任选取代的C_{1-3}烷氧基、卤素或CN;

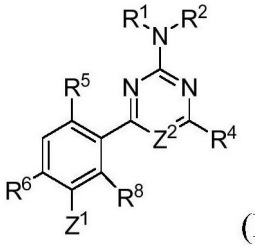
[0019] R^7是任选取代的C_{1-3}烷基、任选取代的C_{1-3}烷环烷基、任选取代的C_{1-3}烷杂环基、或任选取代的C_{1-3}烷芳基,并且R^8是H;或者R^7和R^8与各自附接的原子一起连接以形成任选取代的五元、六元或七元环,该五元、六元或七元环任选地包括一个或两个选自氮、氧和硫的杂原子;

[0020] R^9是H、任选取代的C_{1-3}烷基、任选取代的C_{3-8}环烷基、任选取代的C_{6-10}芳基、任选取代的C_{2-9}杂芳基、任选取代的C_{2-9}杂环基、任选取代的C_{1-3}烷环烷基、任选取代的C_{1-3}烷杂环基、或任选取代的C_{1-3}烷芳基;

[0021] R^{10}是H、任选取代的C_{1-3}烷基、任选取代的C_{3-8}环烷基、任选取代的C_{6-10}芳基、任选取代的C_{2-9}杂芳基、任选取代的C_{2-9}杂环基、任选取代的C_{1-3}烷环烷基、任选取代的C_{1-3}烷杂环基、或任选取代的C_{1-3}烷芳基,并且R^{11}是H、任选取代的C_{1-3}烷基,或者R^{10}和R^{11}结合以形成=O或=S;并且

[0022] R^m是H、卤素、氰基、任选取代的C_{1-4}烷基(例如,C_{1-4}酰基)、或任选取代的C_{1-3}烷氧基。

[0023] 在式(I)的特定实施例中,R^m是H(例如,式(I)的化合物具有以下结构:

[0024]  或其药学上可接受的盐)。

(I),

[0025] 在式(I)的某些实施例中,当Z^2是CR^3,每个R^1和R^2是H,R^3是H,R^4是甲基或卤素(例如,氯),并且每个R^5和R^6是卤素(例如,氯)时,

[0026] Z^1不是甲氧基。

[0027] 在式(I)的某些实施例中,当Z^2是CR^3,R^3是H,R^4是甲基或卤素(例如,氯),每个R^5和R^6是卤素(例如,氯)时,

[0028] Z^2不是未经取代的C_{1-3}烷氧基。

[0029] 在式(I)的特定实施例中,当Z^2是N,R^3是H,R^4是任选取代的C_{1-6}硫代烷氧基,并且每个R^5和R^6是卤素(例如,氯)时,

[0030] Z^1不是氰基甲氧基或氨基甲氧基。

[0031] 在式(I)的其他实施例中,当Z^2是N,R^3是H,每个R^5和R^6是卤素(例如,氯),R^4是经取代的C_{1-6}硫代烷氧基时,

[0032] Z^1不是氰基甲氧基或氨基甲氧基。

[0033] 在式(I)的一些实施例中,当Z^2是N,R^3是H,R^4是任选取代的C_{1-6}硫代烷氧基时,

[0034] Z^1不是氰基甲氧基或氨基甲氧基。

[0035] 在式(I)的某些实施例中,当Z^2是N,R^3是H,R^4是经取代的C_{1-6}硫代烷氧基时,

[0036] Z^1不是氰基甲氧基或氨基甲氧基。

[0037] 在式(I)的进一步的实施例中,当Z^2是N,R^3是H,R^4是经取代的C_{1-6}硫代烷氧基时,

[0038] Z^1不是经取代的C_1烷氧基。

[0039] 在式(I)的具体实施例中,当Z^2是N,R^3是H,R^4是经取代的C_{1-6}硫代烷氧基时,

[0040] Z^1是$-OR^7$、$-N(R^7)R^{10}$、$-SR^7$、或$-C(R^7)(R^{10})R^{11}$,其中R^7是甲基、二烷氨基乙基、任选取代的C_{1-3}烷环烷基、任选取代的C_{1-3}烷杂环基、或任选取代的C_{1-3}烷芳基,或者R^7和R^8与各自附接的原子一起连接以形成任选取代的五元或六元环,该五元或六元环任选地包括一个或两个选自氮、氧和硫的杂原子。

[0041] 在式(I)的其他实施例中,当Z^2是CR^3,每个R^5和R^6是氯,R^3是H,并且R^4是卤素(例如,氯)时,

[0042] Z^1不是2-氨基-2氧代乙氧基、2-(N,N-二乙氨基)乙氧基、甲氧基、或苄氧基。

[0043] 在式(I)的仍然其他实施例中,当Z^2是CR^3,R^3是H,并且R^4是卤素(例如,氯)时,

[0044] Z^1不是2-氨基-2氧代乙氧基、2-(N,N-二乙氨基)乙氧基、甲氧基、或苄氧基。

[0045] 在式(I)的仍然其他实施例中,当Z^2是CR^3时,每个R^5和R^6是氯,R^3是H,并且R^4是卤素(例如,氯)时,

[0046] Z^1是$-OR^7$、$-N(R^7)R^{10}$、$-SR^7$、或$-C(R^7)(R^{10})R^{11}$,其中R^7是二甲氨乙基、任选取代的C_{1-3}烷环烷基、或任选取代的C_{1-3}烷杂环基,或R^7和R^8与各自附接的原子一起连接以形成任选取代的五元或六元环,该五元或六元环任选地包括一个或两个选自氮、氧和硫的杂原子。

[0047] 在式(I)的进一步的实施例中,当Z^2是CR^3,每个R^5和R^6是氯,R^3是H,并且R^4是卤素

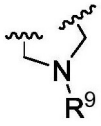
(例如,氯)时,

[0048] Z^1是-OR^7、-$N(R^7)R^{10}$、-SR^7、或-$C(R^7)(R^{10})R^{11}$,其中R^7是任选取代的C_{1-3}烷环烷基、或任选取代的C_{1-3}烷杂环基,或者R^7和R^8与各自附接的原子一起连接以形成任选取代的五元或六元环,该五元或六元环任选地包括一个或两个选自氮、氧和硫的杂原子。

[0049] 在式(I)的具体实施例中,当Z^2是CR^3,R^3是H,并且R^4是卤素(例如,氯)时,

[0050] Z^1是-OR^7、-$N(R^7)R^{10}$、-SR^7、或-$C(R^7)(R^{10})R^{11}$,其中R^7是任选取代的C_{1-3}烷环烷基、或任选取代的C_{1-3}烷杂环基,或者R^7和R^8与各自附接的原子一起连接以形成任选取代的五元或六元环,该五元或六元环任选地包括一个或两个选自氮、氧和硫的杂原子。

[0051] 在式(I)的一些实施例中,当R^5是氯,R^6是溴,Z^1是-OR^7,Z^2是CR^3,并且R^3和R^4结合以形成根据式(IIa)的基团时:

[0052] 

(IIa),

[0053] R^7不是甲基、乙基、正丙基、2-(N-吡唑基)乙基、2-(N-咪唑基)乙基、3-羟丙基、氰甲基、2-氯乙基、2-羟乙基、2-氧代丙基、2-(N,N-二甲氨基)乙基、二氟甲基或2-(叔丁氨基)乙基。

[0054] 在式(I)的某些实施例中,当R^5是氯,R^6是溴,Z^1是-OR^7,Z^2是CR^3,并且R^3和R^4结合以形成根据式(IIa)的基团时,

[0055] R^7不是经取代的烷基、未经取代的烷基或未经取代的C_2烷杂芳基。

[0056] 在式(I)的一些实施例中,当R^5是氯,R^6是溴,Z^1是-OR^7,Z^2是CR^3,且R^3和R^4结合以形成根据式(IIa)的基团时,

[0057] R^7不是烷基或未经取代的C_2烷杂芳基。

[0058] 在式(I)的具体实施例中,当R^5是氯,R^6是溴,Z^1是-OR^7,Z^2是CR^3,并且R^3和R^4结合以形成根据式(IIa)的基团时,

[0059] R^7不是经取代的烷基、未经取代的烷基、或未经取代的C_2烷杂环基。

[0060] 在式(I)的其他实施例中,当R^5是氯,R^6是溴,Z^1是-OR^7,Z^2是CR^3,并且R^3和R^4结合以形成根据式(IIa)的基团时,

[0061] R^7不是烷基或C_2烷杂环基。

[0062] 在式(I)的仍然其他实施例中,当R^5是氯,R^6是溴,Z^1是-OR^7,Z^2是CR^3,并且R^3和R^4结合以形成根据式(IIa)的基团时,

[0063] R^7和R^8与各自附接的原子一起连接以形成任选取代的五元或六元环,该五元或六元环任选地包括一个或两个选自氮、氧和硫的杂原子。

[0064] 在式(I)的仍然其他实施例中,当R^5是氯,R^6是溴,Z^2是CR^3,并且R^3和R^4结合以形成根据式(IIa)的基团时,

[0065] Z是-OR^7,并且R^7和R^8结合以形成-CH_2-CH_2-。

[0066] 在式(I)的一些实施例中,当每个R^5和R^6是溴,Z^1是-OR^7,Z^2是CR^3,并且R^3和R^4结合以形成根据式(IIa)的基团时,

[0067] R^7不是甲基。

[0068] 在式(I)的具体实施例中,当每个R^5和R^6是氯,Z^1是-OR^7,Z^2是CR^3,并且R^3和R^4结合以

形成根据式(IIa)的基团时，

[0069] R^7不是甲基、2-(N-咪唑基)乙基、甲氧基甲基、2-(N-吡唑基)乙基、2-(3-甲基吡唑-1-基)乙基、2-吡啶基-甲基、1,3-二甲基-1H-1,2,4-三唑-5-基-甲基、2-嘧啶基甲基、咪唑-2-基-甲基、5-甲基-异噁唑-3-基-甲基、4-甲基-咪唑-5-基-甲基、或3-甲基-1,2,4-噁二唑-5-基-甲基。

[0070] 在式(I)的其他实施例中，当每个R^5和R^6是氯，Z^1是-OR^7，Z^2是CR^3，并且R^3和R^4结合以形成根据式(IIa)的基团时，

[0071] R^7不是未经取代的烷基、经取代的烷基、未经取代的烷杂芳基、或经取代的烷杂芳基。

[0072] 在式(I)的其他实施例中，当每个R^5和R^6是氯，Z^1是-OR^7，Z^2是CR^3，并且R^3和R^4结合以形成根据式(IIa)的基团时，

[0073] R^7不是未经取代的烷基、经取代的烷基、未经取代的烷杂环基、或经取代的烷杂环基。

[0074] 在式(I)的某些实施例中，当每个R^5和R^6是氯，Z^1是-OR^7，R^7和R^8结合以形成-CH_2-CH_2-，Z^2是CR^3，并且R^3和R^4结合以形成根据式(IIa)的基团时，

[0075] R^9不是乙氧基羰基、环丁基氨基羰基、或环丁二烯基氨基羰基。

[0076] 在式(I)的其他实施例中，当每个R^5和R^6是氯，Z^1是-OR^7，R^7和R^8结合以形成-CH_2-CH_2-，Z^2是CR^3，并且R^3和R^4结合以形成根据式(IIa)的基团时，

[0077] R^9是H或-C(O)-N(H)-(直链C_{1-3}烷基)。

[0078] 在式(I)的具体实施例中，当每个R^5和R^6是卤素，Z^2是CR^3，并且R^3和R^4结合以形成根据式(IIa)的基团时，

[0079] Z是-OR^7，R^7不是甲基或2-氯乙基，并且R^9是H或-C(O)-N(H)-(直链C_{1-3}烷基)。

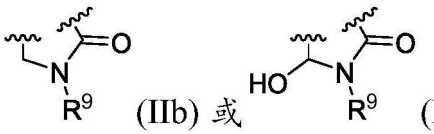
[0080] 在式(I)的一些实施例中，当R^5是甲氧基，R^6是甲基，Z^1是-OR^7，Z^2是CR^3，并且R^3和R^4结合以形成根据式(IIa)的基团时，

[0081] R^7不是甲基。

[0082] 在式(I)的某些实施例中，当R^5是氯，R^6是乙基，Z^1是-OR^7，Z^2是CR^3，且R^3和R^4结合以形成根据式(IIa)的基团时，

[0083] R^7不是甲基。

[0084] 在式(I)的一些实施例中，当每个R^5和R^6是氯，Z^1是-OR^7，Z^2是CR^3，并且R^3和R^4结合以形成根据式(IIb)或(IIc)的基团时，

[0085] 
(IIb)或
(IIc)，

[0086] R^7不是甲基或2-(N,N-二乙基氨基)乙基。

[0087] 在式(I)的其他实施例中，当每个R^5和R^6是氯，Z^1是-OR^7，Z^2是CR^3，并且R^3和R^4结合以形成根据式(IIb)或(IIc)的基团时，

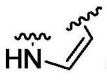
[0088] R^7和R^8与各自附接的原子一起连接以形成任选取代的五元或六元环，该五元或六元环任选地包括一个或两个选自氮、氧和硫的杂原子。

[0089] 在式(I)的某些实施例中，当每个R^5和R^6是氯，Z^2是CR^3，并且R^3和R^4结合以形成根据

式(IIb)或(IIc)的基团时，

[0090] Z^1是-OR^7，并且R^7和R^8结合以形成-CH_2-CH_2-。

[0091] 在式(I)的一些实施例中，当R^7是甲基，R^5是氯，Z^1是-OR^7，Z^2是CR^3，并且R^3和R^4结合以形成根据式(IIIa)的基团时，

[0092]  (IIIa)，

[0093] R^6不是溴。

[0094] 在式(I)的具体实施例中，当每个R^5和R^6是氯，Z^1是-OR^7，Z^2是CR^3，并且R^3和R^4结合以形成根据式(IIIa)的基团时，

[0095] R^7不是异丙基、3,3,3-三氟丙基、或2-(N,N-二甲氨基)乙基。

[0096] 在式(I)的一些实施例中，当每个R^5和R^6是氯，Z^1是-OR^7，Z^2是CR^3，并且R^3和R^4结合以形成根据式(IIIa)的基团时，

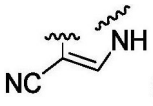
[0097] R^8不是H。

[0098] 在式(I)的一些实施例中，当Z^2是CR^3且R^3和R^4结合以形成根据式(IIIa)的基团时，

[0099] 每个R^5和R^6是氯，并且

[0100] R^7是甲基并且R^8是H，或者R^7和R^8与各自附接的原子一起连接以形成任选取代的五元或六元环，该五元或六元环任选地包括一个或两个选自氮、氧和硫的杂原子。

[0101] 在式(I)的其他实施例中，当R^5是氯，R^6是甲氧基，Z^1是-OR^7，Z^2是CR^3，并且R^3和R^4结合以形成根据式(IIIb)的基团时：

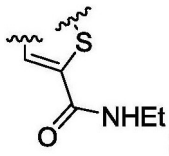
[0102]  (IIIb)，

[0103] R^1和R^2都不是2-(N,N-二乙基氨基)乙基。

[0104] 在式(I)的某些实施例中，当R^5是氯，R^6是甲氧基，Z^1是-OR^7，Z^2是CR^3，并且R^3和R^4结合以形成根据式(IIIb)的基团时，

[0105] 每个R^1和R^2是H。

[0106] 在式(I)的一些实施例中，当每个R^5和R^6是氯，Z^1是-OR^7，Z^2是CR^3，并且R^3和R^4结合以形成根据式(IVa)的基团时：

[0107]  (IVa)，

[0108] R^7不是3-(N-吗啉基)丙基、苄基、1-乙基-吡咯烷-3-基、1-甲基-哌啶-4-基、2-(1-甲基-吡咯烷-2-基)乙基、或3-(N,N-二乙基氨基)丙基。

[0109] 在式(I)的具体实施例中，当每个R^5和R^6是氯，Z^1是-OR^7，Z^2是CR^3，并且R^3和R^4结合以形成根据式(IVa)的基团时，

[0110] R^7不是经取代的烷基、杂环基、烷杂环基、或烷芳基。

[0111] 在式(I)的一些实施例中，当每个R^5和R^6是氯，Z^1是-OR^7，Z^2是CR^3，并且R^3和R^4结合以形成根据式(IVb)的基团时：

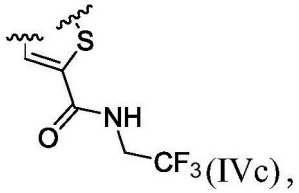
[0112] c(IVb)，

[0113] R^7不是2-甲氧基乙基或苄基。

[0114] 在式(I)的某些实施例中，当每个R^5和R^6是氯，Z^1是-OR^7，Z^2是CR^3，并且R^3和R^4结合以形成根据式(IVb)的基团时，

[0115] R^7不是经取代的烷基或烷芳基。

[0116] 在式(I)的一些实施例中，当每个R^5和R^6是氯，Z^1是-OR^7，Z^2是CR^3，并且R^3和R^4结合以形成根据式(IVc)的基团时：

[0117] 

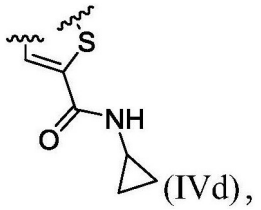
(IVc)，

[0118] R^7不是2-(N,N-二乙基氨基)乙基或3-(N,N-二甲基氨基)丙基。

[0119] 在式(I)的其他实施例中，当每个R^5和R^6是氯，Z^1是-OR^7，Z^2是CR^3，并且R^3和R^4结合以形成根据式(IVc)的基团时，

[0120] R^7不是经取代的烷基。

[0121] 在式(I)的具体实施例中，当每个R^5和R^6是氯，Z^1是-OR^7，Z^2是CR^3，并且R^3和R^4结合以形成根据式(IVd)的基团时：

[0122] 

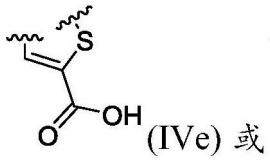
(IVd)，

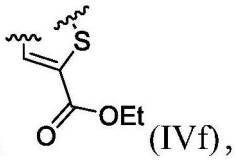
[0123] R^7不是2-(吡咯烷-1-基)乙基或2-羟基乙基。

[0124] 在式(I)的某些实施例中，当每个R^5和R^6是氯，Z^1是-OR^7，Z^2是CR^3，并且R^3和R^4结合以形成根据式(IVd)的基团时，

[0125] R^7不是经取代的烷基或烷杂环基。

[0126] 在式(I)的一些实施例中，当每个R^5和R^6是氯，Z^1是-OR^7，Z^2是CR^3，并且R^3和R^4结合以形成根据式(IVe)或(IVf)的基团时：

[0127] 

(IVe)或 

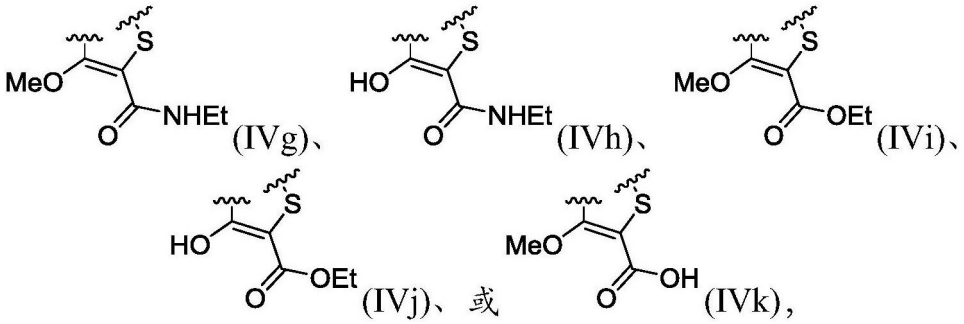
(IVf)，

[0128] R^7不是苄基。

[0129] 在式(I)的其他实施例中，当每个R^5和R^6是氯，Z^1是-OR^7，Z^2是CR^3，并且R^3和R^4结合以形成根据式(IVe)或(IVf)的基团时：

[0130] R^7不是烷芳基。

[0131] 在式(I)的某些实施例中，当R^5是氯，R^6是溴，Z^1是-OR^7，Z^2是CR^3，并且R^3和R^4结合以形成根据式(IVg)、(IVh)、(IVi)、(IVj)、或(IVk)的基团时：

[0132] 

[0133] R^7不是甲基。

[0134] 在式(I)的某些实施例中，当R^5是氯，R^6是溴，Z^1是-OR^7，Z^2是CR^3，并且R^3和R^4结合以形成根据式(IVg)、(IVh)、(IVi)、(IVj)、或(IVk)的基团时，

[0135] R^7不是烷基。

[0136] 在式(I)的一些实施例中，当R^5是氯，R^6是溴，Z^1是-OR^7，Z^2是CR^3，并且R^3和R^4结合以形成根据式(IVg)、(IVh)、(IVi)、(IVj)、或(IVk)的基团时，

[0137] R^7和R^8与各自附接的原子一起连接以形成任选取代的五元或六元环，该五元或六元环任选地包括一个或两个选自氮、氧和硫的杂原子。

[0138] 在式(I)的具体实施例中，当R^5是氯，R^6是溴，Z^1是-OR^7，并且Z^2是CR^3时，

[0139] R^3和R^4不结合以形成根据式(IVg)、(IVh)、(IVi)、(IVj)、或(IVk)的基团。

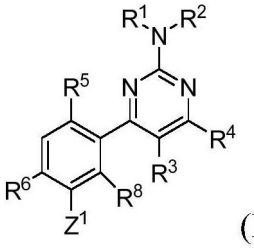
[0140] 在式(I)的具体实施例中，当R^6是甲基时，

[0141] 每个R^1和R^2是H。

[0142] 在式(I)的某些实施例中，当R^3是H，且每个R^5和R^6是氯时，

[0143] R^7不是甲基。

[0144] 在具体实施例中，该化合物根据式(Ia)：

[0145]  或其药学上可接受的盐，

(Ia)，

[0146] 其中

[0147] Z^1是-OR^7、-$N(R^{10})R^7$、-SR^7、或-$C(R^{10})(R^{11})R^7$；

[0148] 每个R^1和R^2独立地是H或任选取代的C_{1-3}烷基；

[0149] R^3是H、卤素、任选取代的C_{1-3}烷基、或任选取代的C_{1-3}烷氧基，并且R^4是卤素、任选取代的C_{1-3}烷基、任选取代的C_{1-3}烷氧基、任选取代的氨基、任选取代的C_{1-6}硫烷基、或任选取代的C_{6-10}芳基，或者R^3和R^4与各自附接的原子一起连接以形成任选取代的五元、六元、或七元环，该五元、六元、或七元环任选地包括1至3个选自氮、氧和硫的杂原子，其中氮任选地被R^9取代；

[0150] 每个R^5和R^6独立地是H、任选取代的C_{1-3}烷基、任选取代的C_{1-3}烷氧基、卤素或CN；

[0151] R^7是任选取代的C_{1-3}烷基、任选取代的C_{1-3}烷环烷基、任选取代的C_{1-3}烷杂环基、或任选取代的C_{1-3}烷芳基，并且R^8是H；或者R^7和R^8与各自附接的原子一起连接以形成任选取代

的五元、六元或七元环，该五元、六元或七元环任选地包括一个或两个选自氮、氧和硫的杂原子；

[0152] R^9是H、任选取代的C_{1-3}烷基、任选取代的C_{3-8}环烷基、任选取代的C_{6-10}芳基、任选取代的C_{2-9}杂芳基、任选取代的C_{2-9}杂环基、任选取代的C_{1-3}烷环烷基、任选取代的C_{1-3}烷杂环基、或任选取代的C_{1-3}烷芳基；

[0153] R^{10}是H、任选取代的C_{1-3}烷基(例如，任选取代的C_{1-3}酰基)、任选取代的C_{3-8}环烷基、任选取代的C_{6-10}芳基、任选取代的C_{2-9}杂芳基、任选取代的C_{2-9}杂环基、任选取代的C_{1-3}烷环烷基、任选取代的C_{1-3}烷杂环基、或任选取代的C_{1-3}烷芳基，并且R^{11}是H、任选取代的C_{1-3}烷基，或者R^{10}和R^{11}结合以形成=O或=S。

[0154] 在其他实施例中，当每个R^1和R^2是H，R^3是H，R^4是甲基或氯，并且每个R^5和R^6是氯时，

[0155] Z^1不是甲氧基。

[0156] 在仍然其他实施例中，当R^3是H，并且R^4是卤素(例如，氯)时，

[0157] Z^1不是2-氨基-2氧代乙氧基、2-(N,N-二乙氨基)乙氧基、甲氧基、或苄氧基。

[0158] 在仍然其他实施例中，当每个R^5和R^6是氯，R^3是H，并且R^4是卤素(例如，氯)时，

[0159] Z^1是$-OR^7$、$-N(R^7)R^{10}$、$-SR^7$、或$-C(R^7)(R^{10})R^{11}$，其中R^7是二甲氨乙基、任选取代的C_{1-3}烷环烷基、或任选取代的C_{1-3}烷杂环基，或者R^7和R^8与各自附接的原子一起连接以形成任选取代的五元或六元环，该五元或六元环任选地包括一个或两个选自氮、氧和硫的杂原子。

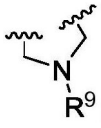
[0160] 在进一步的实施例中，当每个R^5和R^6是氯，R^3是H，并且R^4是卤素(例如，氯)时，

[0161] Z^1是$-OR^7$、$-N(R^7)R^{10}$、$-SR^7$、或$-C(R^7)(R^{10})R^{11}$，其中R^7是任选取代的C_{1-3}烷环烷基、或任选取代的C_{1-3}烷杂环基，或者R^7和R^8与各自附接的原子一起连接以形成任选取代的五元或六元环，该五元或六元环任选地包括一个或两个选自氮、氧和硫的杂原子。

[0162] 在具体实施例中，当R^3是H，并且R^4是卤素(例如，氯)时，

[0163] Z^1是$-OR^7$、$-N(R^7)R^{10}$、$-SR^7$、或$-C(R^7)(R^{10})R^{11}$，其中R^7是任选取代的C_{1-3}烷环烷基、或任选取代的C_{1-3}烷杂环基，或者R^7和R^8与各自附接的原子一起连接以形成任选取代的五元或六元环，该五元或六元环任选地包括一个或两个选自氮、氧和硫的杂原子。

[0164] 在一些实施例中，当R^5是氯，R^6是溴，Z^1是$-OR^7$，并且R^3和R^4结合以形成根据式(IIa)的基团时：

[0165] 

(IIa)，

[0166] R^7不是甲基、乙基、正丙基、2-(N-吡唑基)乙基、2-(N-咪唑基)乙基、3-羟丙基、氰甲基、2-氯乙基、2-羟乙基、2-氧代丙基、2-(N,N-二甲氨基)乙基、二氟甲基或2-(叔丁氨基)乙基。

[0167] 在某些实施例中，当R^5是氯，R^6是溴，Z^1是$-OR^7$，并且R^3和R^4结合以形成根据式(IIa)的基团，

[0168] R^7不是经取代的烷基、未经取代的烷基、或未经取代的C_2烷杂芳基。

[0169] 在一些实施例中，当R^5是氯，R^6是溴，Z^1是$-OR^7$，并且R^3和R^4结合以形成根据式(IIa)的基团时，

[0170] R^7不是烷基或未经取代的C_2烷杂芳基。

[0171] 在具体实施例中，当R^5是氯，R^6是溴，Z^1是$-OR^7$，并且R^3和R^4结合以形成根据式(IIa)的基团时，

[0172] R^7不是经取代的烷基、未经取代的烷基、或未经取代的C_2烷杂环基。

[0173] 在其他实施例中，当R^5是氯，R^6是溴，Z^1是$-OR^7$，并且R^3和R^4结合以形成根据式(IIa)的基团时，

[0174] R^7不是烷基或C_2烷杂环基。

[0175] 在仍然其他实施例中，当R^5是氯，R^6是溴，Z^1是$-OR^7$，并且R^3和R^4结合以形成根据式(IIa)的基团时，

[0176] R^7和R^8与各自附接的原子一起连接以形成任选取代的五元或六元环，该五元或六元环任选地包括一个或两个选自氮、氧和硫的杂原子。

[0177] 在仍然其他实施例中，当R^5是氯，R^6是溴，并且R^3和R^4结合以形成根据式(IIa)的基团时，

[0178] Z是$-OR^7$，并且R^7和R^8结合以形成$-CH_2-CH_2-$。

[0179] 在一些实施例中，当每个R^5和R^6是溴，Z^1是$-OR^7$，并且R^3和R^4结合以形成根据式(IIa)的基团时，

[0180] R^7不是甲基。

[0181] 在具体实施例中，当每个R^5和R^6是氯，Z^1是$-OR^7$，并且R^3和R^4结合以形成根据式(IIa)的基团时，

[0182] R^7不是甲基、2-(N-咪唑基)乙基、甲氧基甲基、2-(N-吡唑基)乙基、2-(3-甲基吡唑-1-基)乙基、2-吡啶基-甲基、1,3-二甲基-1H-1,2,4-三唑-5-基-甲基、2-嘧啶基甲基、咪唑-2-基-甲基、5-甲基-异噁唑-3-基-甲基、4-甲基-咪唑-5-基-甲基、或3-甲基-1,2,4-噁二唑-5-基-甲基。

[0183] 在其他实施例中，当每个R^5和R^6是氯，Z^1是$-OR^7$，并且R^3和R^4结合以形成根据式(IIa)的基团时，

[0184] R^7不是未经取代的烷基、经取代的烷基、未经取代的烷杂芳基、或经取代的烷杂芳基。

[0185] 在其他实施例中，当每个R^5和R^6是氯，Z^1是$-OR^7$，并且R^3和R^4结合以形成根据式(IIa)的基团时，

[0186] R^7不是未经取代的烷基、经取代的烷基、未经取代的烷杂环基、或经取代的烷杂环基。

[0187] 在某些实施例中，当每个R^5和R^6是氯，Z^1是$-OR^7$，R^7和R^8结合以形成$-CH_2-CH_2-$，并且R^3和R^4结合以形成根据式(IIa)的基团时，

[0188] R^9不是乙氧基羰基、环丁基氨基羰基、或环丁二烯基氨基羰基。

[0189] 在其他实施例中，当每个R^5和R^6是氯，Z^1是$-OR^7$，R^7和R^8结合以形成$-CH_2-CH_2-$，并且R^3和R^4结合以形成根据式(IIa)的基团时，

[0190] R^9是H或$-C(O)-N(H)-$(直链C_{1-3}烷基)。

[0191] 在具体实施例中，当每个R^5和R^6是卤素，并且R^3和R^4结合以形成根据式(IIa)的基团时，

[0192] Z是$-OR^7$，R^7不是甲基或2-氯乙基，并且R^9是H或$-C(O)-N(H)-$(直链C_{1-3}烷基)。

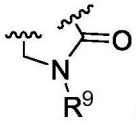
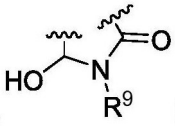
[0193] 在一些实施例中，当R^5是甲氧基，R^6是甲基，Z^1是-OR^7，并且R^3和R^4结合以形成根据式(IIa)的基团时，

[0194] R^7不是甲基。

[0195] 在某些实施例中，当R^5是氯，R^6是乙基，Z^1是-OR^7，并且R^3和R^4结合以形成根据式(IIa)的基团时，

[0196] R^7不是甲基。

[0197] 在一些实施例中，当每个R^5和R^6是氯，Z^1是-OR^7，并且R^3和R^4结合以形成根据式(IIb)或(IIc)的基团时，

[0198]  (IIb) 或  (IIc)，

[0199] R^7不是甲基或2-(N,N-二乙基氨基)乙基。

[0200] 在其他实施例中，当每个R^5和R^6是氯，Z^1是-OR^7，并且R^3和R^4结合以形成根据式(IIb)或(IIc)的基团时，

[0201] R^7和R^8与各自附接的原子一起连接以形成任选取代的五元或六元环，该五元或六元环任选地包括一个或两个选自氮、氧和硫的杂原子。

[0202] 在某些实施例中，当每个R^5和R^6是氯，并且R^3和R^4结合以形成根据式(IIb)或(IIc)的基团时，

[0203] Z^1是-OR^7，并且R^7和R^8结合以形成-CH_2-CH_2-。

[0204] 在一些实施例中，当R^7是甲基，R^5是氯，Z^1是-OR^7，并且R^3和R^4结合以形成根据式(IIIa)的基团时，

[0205] (IIIa)，

[0206] R^6不是溴。

[0207] 在具体实施例中，当每个R^5和R^6是氯，Z^1是-OR^7，并且R^3和R^4结合以形成根据式(IIIa)的基团时，

[0208] R^7不是异丙基、3,3,3-三氟丙基、或2-(N,N-二甲氨基)乙基。

[0209] 在某些实施例中，当每个R^5和R^6是氯，Z^1是-OR^7，并且R^3和R^4结合以形成根据式(IIIa)的基团时，

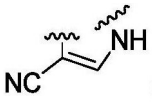
[0210] R^8不是H。

[0211] 在一些实施例中，当R^3和R^4结合以形成根据式(IIIa)的基团时，

[0212] 每个R^5和R^6是氯，并且

[0213] R^7是甲基并且R^8是H，或者R^7和R^8与各自附接的原子一起连接以形成任选取代的五元或六元环，该五元或六元环任选地包括一个或两个选自氮、氧和硫的杂原子。

[0214] 在其他实施例中，当R^5是氯，R^6是甲氧基，Z^1是-OR^7，并且R^3和R^4结合以形成根据式(IIIb)的基团时：

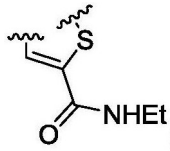
[0215]  (IIIb)，

[0216] R^1和R^2都不是2-(N,N-二乙基氨基)乙基。

[0217] 在某些实施例中，当R^5是氯，R^6是甲氧基，Z^1是-OR^7，并且R^3和R^4结合以形成根据式(IIIb)的基团时，

[0218] 每个R^1和R^2是H。

[0219] 在一些实施例中，当每个R^5和R^6是氯，Z^1是-OR^7，并且R^3和R^4结合以形成根据式(IVa)的基团时，

[0220] 

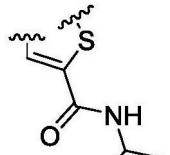
(IVa)，

[0221] R^7不是3-(N-吗啉基)丙基、苄基、1-乙基-吡咯烷-3-基、1-甲基-哌啶-4-基、2-(1-甲基-吡咯烷-2-基)乙基、或3-(N,N-二乙基氨基)丙基。

[0222] 在具体实施例中，当每个R^5和R^6是氯，Z^1是-OR^7，并且R^3和R^4结合以形成根据式(IVa)的基团时，

[0223] R^7不是经取代的烷基、杂环基、烷杂环基、或烷芳基。

[0224] 在一些实施例中，当每个R^5和R^6是氯，Z^1是-OR^7，并且R^3和R^4结合以形成根据式(IVb)的基团时：

[0225] 

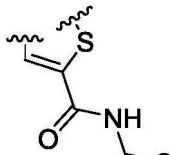
(IVb)，

[0226] R^7不是2-甲氧基乙基或苄基。

[0227] 在某些实施例中，当每个R^5和R^6是氯，Z^1是-OR^7，并且R^3和R^4结合以形成根据式(IVb)的基团时，

[0228] R^7不是经取代的烷基或烷芳基。

[0229] 在一些实施例中，当每个R^5和R^6是氯，Z^1是-OR^7，并且R^3和R^4结合以形成根据式(IVc)的基团时，

[0230] 

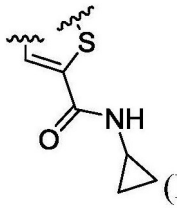
(IVc)，

[0231] R^7不是2-(N,N-二乙基氨基)乙基或3-(N,N-二甲基氨基)丙基。

[0232] 在其他实施例中，当每个R^5和R^6是氯，Z^1是-OR^7，并且R^3和R^4结合以形成根据式(IVc)的基团时，

[0233] R^7不是经取代的烷基。

[0234] 在具体实施例中，当每个R^5和R^6是氯，Z^1是-OR^7，并且R^3和R^4结合以形成根据式(IVd)的基团时：

[0235] 

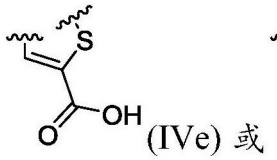
(IVd),

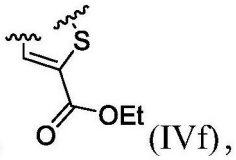
[0236] R^7不是2-(吡咯烷-1-基)乙基或2-羟基乙基。

[0237] 在某些实施例中，当每个R^5和R^6是氯，Z^1是-OR^7，并且R^3和R^4结合以形成根据式(IVd)的基团时，

[0238] R^7不是经取代的烷基或烷杂环基。

[0239] 在一些实施例中，当每个R^5和R^6是氯，Z^1是-OR^7，并且R^3和R^4结合以形成根据式(IVe)或(IVf)的基团时：

[0240] 

(IVe)或 

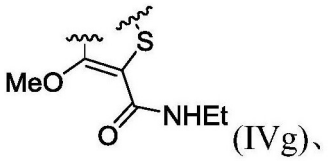
(IVf),

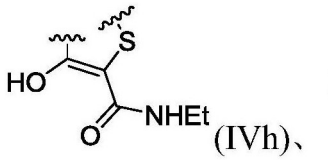
[0241] R^7不是苄基。

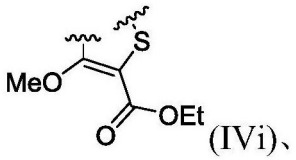
[0242] 在其他实施例中，当每个R^5和R^6是氯，Z^1是-OR^7，并且R^3和R^4结合以形成根据式(IVe)或(IVf)的基团时，

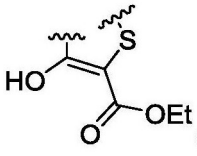
[0243] R^7不是烷芳基。

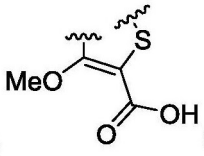
[0244] 在某些实施例中，当R^5是氯，R^6是溴，Z^1是-OR^7，并且R^3和R^4结合以形成根据式(IVg)、(IVh)、(IVi)、(IVj)、或(IVk)的基团时：

[0245] 

(IVg)、 

(IVh)、 

(IVi)、 

(IVj)、或 

(IVk),

[0246] R^7不是甲基。

[0247] 在某些实施例中，当R^5是氯，R^6是溴，Z^1是-OR^7，并且R^3和R^4结合以形成根据式(IVg)、(IVh)、(IVi)、(IVj)、或(IVk)的基团时，

[0248] R^7不是烷基。

[0249] 在一些实施例中，当R^5是氯，R^6是溴，Z^1是-OR^7，并且R^3和R^4结合以形成根据式(IVg)、(IVh)、(IVi)、(IVj)、或(IVk)的基团时，

[0250] R^7和R^8与各自附接的原子一起连接以形成任选取代的五元或六元环，该五元或六元环任选地包括一个或两个选自氮、氧和硫的杂原子。

[0251] 在具体实施例中，当R^5是氯，R^6是溴，并且Z^1是-OR^7时，

[0252] R^3和R^4不结合以形成根据式(IVg)、(IVh)、(IVi)、(IVj)、或(IVk)的基团。

[0253] 在具体实施例中，当R^6是甲基时，

[0254] 每个R^1和R^2是H。

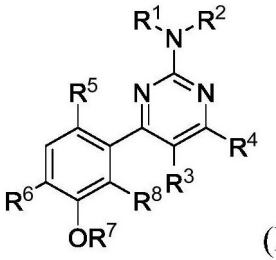
[0255] 在某些实施例中，当R^3是H，并且每个R^5和R^6是氯时，

[0256] R^7不是甲基。

[0257] 在某些实施例中，当R_3和R^4与各自附接的原子一起连接以形成包含一个氮的取代的五元环时，该五元环不被氧取代。在具体实施例中，当R^3和R^4与各自附接的原子一起连接以形成包含一个硫的取代的五元环时，该五元环不被羟基或C_{1-3}烷氧基取代。在进一步的实施例中，当R^3和R^4与各自附接的原子一起连接以形成任选取代的包含一个硫的五元环时，R^7和R^8与各自附接的原子一起连接以形成任选取代的五元或六元环，该五元或六元环任选地包括一个或两个选自氮、氧和硫的杂原子。

[0258] 在具体实施例中，R^7和R^8与各自附接的原子一起连接以形成任选取代的五元或六元环，该五元或六元环任选地包括一个或两个选自氮、氧和硫的杂原子。在其他实施例中，R^7和R^8与各自附接的原子一起连接以形成任选取代的五元或六元饱和环，该五元或六元饱和环任选地包括一个或两个选自氮、氧和硫的杂原子。在仍然其他实施例中，R^7和R^8与各自附接的原子一起连接以形成任选取代的五元或六元环，该五元或六元环任选地包括一个或两个选自氮和氧的杂原子。在某些实施例中，R^7和R^8与各自附接的原子一起连接以形成任选取代的五元环。

[0259] 在一些实施例中，化合物是根据式(Ib)：

[0260]  或其药学上可接受的盐，

(Ib)，

[0261] 其中

[0262] 每个R^1和R^2独立地是H或任选取代的C_{1-3}烷基；

[0263] R^3是H、卤素、任选取代的C_{1-3}烷基、或任选取代的C_{1-3}烷氧基，并且R^4是卤素、任选取代的C_{1-3}烷基、任选取代的C_{1-3}烷氧基、任选取代的氨基、任选取代的C_{1-6}硫代烷氧基、或任选取代的C_{6-10}芳基，或者R^3和R^4与各自附接的原子一起连接以形成任选取代的五元或六元环，该五元或六元环任选包括一个氮、一个硫、或一个氧，其中该氮任选地被R^9取代；

[0264] 每个R^5和R^6独立地是任选取代的C_{1-3}烷基(例如，任选取代的C_{1-3}酰基)、任选取代的C_{1-3}烷氧基、卤素、或CN；

[0265] R^7是任选取代的C_{1-3}烷基、任选取代的C_{1-3}烷环烷基、任选取代的C_{1-3}烷杂环基、或任选取代的C_{1-3}烷芳基，并且R^8是H；或者R^7和R^8与各自附接的原子一起连接以形成任选取代的五元或六元环；并且

[0266] R^9是H、任选取代的C_{1-3}烷基、任选取代的C_{3-8}环烷基、任选取代的C_{6-10}芳基、任选取代的C_{2-9}杂芳基、任选取代的C_{2-9}杂环基、任选取代的C_{1-3}烷环烷基、任选取代的C_{1-3}烷杂环基、或任选取代的C_{1-3}烷芳基。

[0267] 在其他实施例中，当每个R^1和R^2是H，R^3是H，R^4是甲基或氯，并且每个R^5和R^6是氯时，

[0268] R^7不是甲基。

[0269] 在仍然其他实施例中，当R^3是H，并且R^4是卤素(例如，氯)时，

[0270] R^7不是2-氨基-2氧代乙基、2-(N,N-二乙基氨基)乙基、甲基、或苄基。

[0271] 在仍然其他实施例中，当每个R^5和R^6是氯，R^3是H，并且R^4是卤素(例如，氯)时，

[0272] R^7是二甲氨乙基、任选取代的C_{1-3}烷环烷基、或任选取代的C_{1-3}烷杂环基，或者R^7和R^8与各自附接的原子一起连接以形成任选取代的五元或六元环，该五元或六元环任选地包括一个或两个选自氮、氧和硫的杂原子。

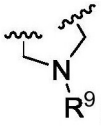
[0273] 在进一步的实施例中，当每个R^5和R^6是氯，R^3是H，并且R^4是卤素(例如，氯)时，

[0274] R^7是任选取代的C_{1-3}烷环烷基、或任选取代的C_{1-3}烷杂环基，或者R^7和R^8与各自附接的原子一起连接以形成任选取代的五元或六元环，该五元或六元环任选地包括一个或两个选自氮、氧和硫的杂原子。

[0275] 在具体实施例中，当R^3是H，并且R^4是卤素(例如，氯)时，

[0276] R^7是任选取代的C_{1-3}烷环烷基、或任选取代的C_{1-3}烷杂环基，或者R^7和R^8与各自附接的原子一起连接以形成任选取代的五元或六元环，该五元或六元环任选地包括一个或两个选自氮、氧和硫的杂原子。

[0277] 在一些实施例中，当R^5是氯，R^6是溴，并且R^3和R^4结合以形成根据式(IIa)的基团时：

[0278] 

(IIa)，

[0279] R^7不是甲基、乙基、正丙基、2-(N-吡唑基)乙基、2-(N-咪唑基)乙基、3-羟丙基、氰甲基、2-氯乙基、2-羟乙基、2-氧代丙基、2-(N,N-二甲氨基)乙基、二氟甲基或2-(叔丁氨基)乙基。

[0280] 在某些实施例中，当R^5是氯，R^6是溴，并且R^3和R^4结合以形成根据式(IIa)的基团时，

[0281] R^7不是经取代的烷基、未经取代的烷基、或未经取代的C_2烷杂芳基。

[0282] 在其他实施例中，当R^5是氯，R^6是溴，并且R^3和R^4结合以形成根据式(IIa)的基团时，

[0283] R^7不是烷基或C_2烷杂芳基。

[0284] 在具体实施例中，当R^5是氯，R^6是溴，并且R^3和R^4结合以形成根据式(IIa)的基团时，

[0285] R^7不是经取代的烷基、未经取代的烷基、或未经取代的C_2烷杂环基。

[0286] 在一些实施例中，当R^5是氯，R^6是溴，并且R^3和R^4结合以形成根据式(IIa)的基团时，

[0287] R^7不是烷基或C_2烷杂环基。

[0288] 在仍然其他实施例中，当R^5是氯，R^6是溴，并且R^3和R^4结合以形成根据式(IIa)的基团时，

[0289] R^7和R^8与各自附接的原子一起连接以形成任选取代的五元或六元环，该五元或六元环包含一个氧原子并且任选地包括又一个选自氮、氧和硫的杂原子。

[0290] 在仍然其他实施例中，当R^5是氯，R^6是溴，并且R^3和R^4结合以形成根据式(IIa)的基团时，

[0291] R^7和R^8结合以形成-CH_2-CH_2-。

[0292] 在一些实施例中，当每个R^5和R^6是溴，并且R^3和R^4结合以形成根据式(IIa)的基团时，

[0293] R^7不是甲基。

[0294] 在具体实施例中，当每个R^5和R^6是氯，并且R^3和R^4结合以形成根据式(IIa)的基团时，

[0295] R^7不是甲基、2-(N-咪唑基)乙基、甲氧基甲基、2-(N-吡唑基)乙基、2-(3-甲基吡唑-1-基)乙基、2-吡啶基-甲基、1,3-二甲基-1H-1,2,4-三唑-5-基-甲基、2-嘧啶基甲基、咪唑-2-基-甲基、5-甲基-异噁唑-3-基-甲基、4-甲基-咪唑-5-基-甲基、或3-甲基-1,2,4-噁二唑-5-基-甲基。

[0296] 在其他实施例中，当每个R^5和R^6是氯，并且R^3和R^4结合以形成根据式(IIa)的基团时，

[0297] R^7不是未经取代的烷基、经取代的烷基、未经取代的烷杂芳基、或经取代的烷杂芳基。

[0298] 在其他实施例中，当每个R^5和R^6是氯，并且R^3和R^4结合以形成根据式(IIa)的基团时，

[0299] R^7不是未经取代的烷基、经取代的烷基、未经取代的烷杂环基、或经取代的烷杂环基。

[0300] 在某些实施例中，当每个R^5和R^6是氯，R^7和R^8结合以形成-CH_2-CH_2-，并且R^3和R^4结合以形成根据式(IIa)的基团时，

[0301] R^9不是乙氧基羰基、环丁基氨基羰基、或环丁二烯基氨基羰基。

[0302] 在其他实施例中，当每个R^5和R^6是氯，R^7和R^8结合以形成-CH_2-CH_2-，并且R^3和R^4结合以形成根据式(IIa)的基团时，

[0303] R^9是H或-C(O)-N(H)-(直链C_{1-3}烷基)。

[0304] 在具体实施例中，当每个R^5和R^6是卤素，并且R^3和R^4结合以形成根据式(IIa)的基团时，

[0305] 并且R^9是H或-C(O)-N(H)-(直链C_{1-3}烷基)。

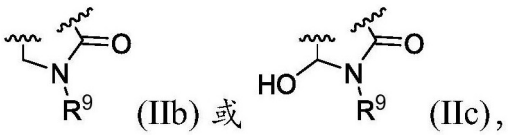
[0306] 在一些实施例中，当R^5是甲氧基，R^6是甲基，并且R^3和R^4结合以形成根据式(IIa)的基团时，

[0307] R^7不是甲基。

[0308] 在某些实施例中，当R^5是氯，R^6是乙基，并且R^3和R^4结合以形成根据式(IIa)的基团时，

[0309] R^7不是甲基。

[0310] 在一些实施例中，当每个R^5和R^6是氯，并且R^3和R^4结合以形成根据式(IIb)或(IIc)的基团时，

[0311]  (IIb)或 (IIc)，

[0312] R^7不是甲基或2-(N,N-二乙基氨基)乙基。

[0313] 在其他实施例中，当每个R^5和R^6是氯并且R^3和R^4结合以形成根据式(IIb)或(IIc)的基团时，

[0314] R^7和R^8与各自附接的原子一起连接以形成任选取代的五元或六元环，该五元或六元环包含一个氧原子并且任选地包括又一个选自氮、氧和硫的杂原子。

[0315] 在某些实施例中，当每个R^5和R^6是氯并且R^3和R^4结合以形成根据式(IIb)或(IIc)的基团时，

[0316] R^7和R^8结合以形成$-CH_2-CH_2-$。

[0317] 在一些实施例中，当R^7是甲基，R^5是氯，并且R^3和R^4结合以形成根据式(IIIa)的基团时，

[0318] (IIIa)，

[0319] R^6不是溴。

[0320] 在具体实施例中，当每个R^5和R^6是氯，并且R^3和R^4结合以形成根据式(IIIa)的基团时，

[0321] R^7不是异丙基、3,3,3-三氟丙基、或2-(N,N-二甲氨基)乙基。

[0322] 在具体实施例中，当每个R^5和R^6是氯，并且R^3和R^4结合以形成根据式(IIIa)的基团时，

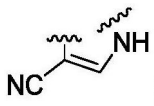
[0323] R^8不是H。

[0324] 在一些实施例中，当R^3和R^4结合以形成根据式(IIIa)的基团时，

[0325] 每个R^5和R^6是氯，

[0326] R^7是甲基，并且R^8是H，或者R^7和R^8与各自附接的原子一起连接以形成任选取代的五元或六元环，该五元或六元环包含一个氧原子并且任选地包括又一个选自氮、氧和硫的杂原子。

[0327] 在其他实施例中，当R^5是氯，R^6是甲氧基，并且R^3和R^4结合以形成根据式(IIIb)的基团时：

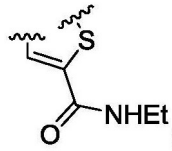
[0328]  (IIIb)，

[0329] R^1和R^2都不是2-(N,N-二乙基氨基)乙基。

[0330] 在某些实施例中，当R^5是氯，R^6是甲氧基，并且R^3和R^4结合以形成根据式(IIIb)的基团时，

[0331] 每个R^1和R^2是H。

[0332] 在一些实施例中，当每个R^5和R^6是氯，并且R^3和R^4结合以形成根据式(IVa)的基团时：

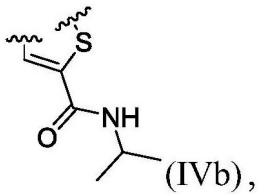
[0333]  (IVa)，

[0334] R^7不是3-(N-吗啉基)丙基、苄基、1-乙基-吡咯烷-3-基、1-甲基-哌啶-4-基、2-(1-甲基-吡咯烷-2-基)乙基、或3-(N,N-二乙基氨基)丙基。

[0335] 在具体实施例中，当每个R^5和R^6是氯，并且R^3和R^4结合以形成根据式(IVa)的基团时，

[0336] R^7不是经取代的烷基、杂环基、烷杂环基、或烷芳基。

[0337] 在一些实施例中，当每个R^5和R^6是氯，并且R^3和R^4结合以形成根据式(IVb)的基团时：

[0338] 

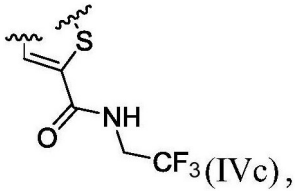
(IVb)，

[0339] R^7不是2-甲氧基乙基或苄基。

[0340] 在某些实施例中，当每个R^5和R^6是氯，并且R^3和R^4结合以形成根据式(IVb)的基团时，

[0341] R^7不是经取代的烷基或烷芳基。

[0342] 在一些实施例中，当每个R^5和R^6是氯，并且R^3和R^4结合以形成根据式(IVc)的基团时：

[0343] 

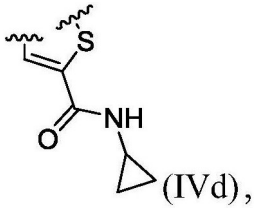
(IVc)，

[0344] R^7不是2-(N,N-二乙基氨基)乙基或3-(N,N-二甲基氨基)丙基。

[0345] 在其他实施例中，当每个R^5和R^6是氯，并且R^3和R^4结合以形成根据式(IVc)的基团时，

[0346] R^7不是经取代的烷基。

[0347] 在具体实施例中，当每个R^5和R^6是氯，并且R^3和R^4结合以形成根据式(IVd)的基团时：

[0348] 

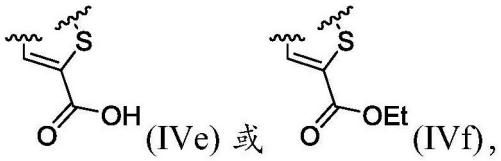
(IVd)，

[0349] R^7不是2-(吡咯烷-1-基)乙基或2-羟基乙基。

[0350] 在某些实施例中，当每个R^5和R^6是氯，并且R^3和R^4结合以形成根据式(IVd)的基团时，

[0351] R^7不是经取代的烷基或烷杂环基。

[0352] 在一些实施例中，当每个R^5和R^6是氯，并且R^3和R^4结合以形成根据式(IVe)或(IVf)的基团时：

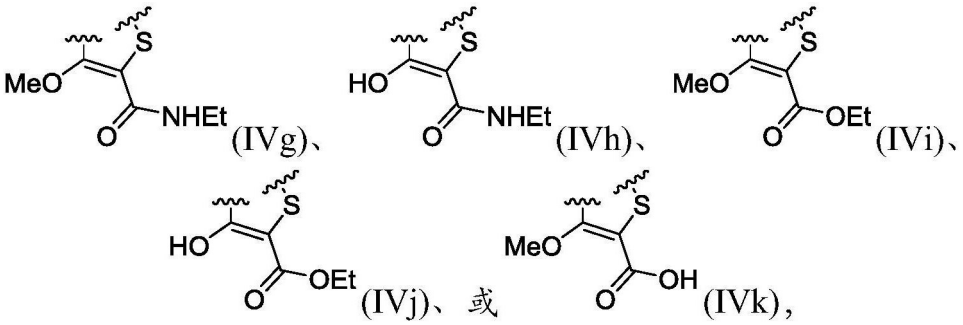
[0353] 

[0354] R^7不是苄基。

[0355] 在其他实施例中，当每个R^5和R^6是氯，并且R^3和R^4结合以形成根据式(IVe)或(IVf)的基团时，

[0356] R^7不是经取代的烷基或烷芳基。

[0357] 在某些实施例中，当R^5是氯时，R^6是溴，并且R^3和R^4结合以形成根据式(IVg)、(IVh)、(IVi)、(IVj)、或(IVk)的基团时：

[0358] 

[0359] R^7不是甲基。

[0360] 在一些实施例中，当R^5是氯时，R^6是溴，并且R^3和R^4结合以形成根据式(IVg)、(IVh)、(IVi)、(IVj)、或(IVk)的基团时，

[0361] R^7和R^8与各自附接的原子一起连接以形成任选取代的五元或六元环，该五元或六元环任选地包括一个或两个选自氮、氧和硫的杂原子。

[0362] 在具体实施例中，当R^5是氯，R^6是溴时，

[0363] R^3和R^4不结合以形成根据式(IVg)、(IVh)、(IVi)、(IVj)、或(IVk)的基团。

[0364] 在具体实施例中，当R^6是甲氧基时，

[0365] 每个R^1和R^2是H。

[0366] 在某些实施例中，当R^3是H，并且每个R^5和R^6是氯时，

[0367] R^7不是甲基。

[0368] 在式(I)、(Ia)、或(Ib)的一些实施例中，R^3是H、卤素、任选取代的C_{1-3}烷基(例如，任选取代的C_{1-3}酰基)、或任选取代的C_{1-3}烷氧基，并且R^4是卤素、任选取代的C_{1-3}烷基(例如，任选取代的C_{1-3}酰基)、任选取代的C_{1-3}烷氧基、任选取代的氨基、任选取代的C_{1-6}硫烷基、或任选取代的C_{6-10}芳基，或者R^3和R^4与各自附接的原子一起连接以形成任选取代的五元或六元环，该五元或六元环任选地包括一个氮、一个氧或一个硫，其中氮任选地被R^9取代。

[0369] 在式(I)、(Ia)、或(Ib)的进一步的实施例中，R^7是任选取代的C_{1-3}烷基、任选取代的C_{1-3}烷环烷基、任选取代的C_{1-3}烷杂环基、或任选取代的C_{1-3}烷芳基，并且R^8是H；或者R^7和R^8与各自附接的原子一起连接以形成任选取代的五元或六元环，该五元或六元环任选地包括一个或两个选自氮、氧和硫的杂原子。

[0370] 在具体实施例中，当R^3和R^4结合以形成根据式(IIb)或(IIc)的基团时，式(IIb)或(IIc)的羰基邻近C^6。在其他实施例中，当R^3和R^4结合以形成根据式(IIb)或(IIc)的基团时，

式(IIb)或(IIc)的羰基邻近C^5或C^6。

[0371] 在某些实施例中,当R^3和R^4结合以形成根据式(IIIa)的基团时,根据式(IIIa)的基团的N原子邻近C^5。在具体实施例中,当R^3和R^4结合以形成根据式(IIIa)的基团时,根据式(IIIb)的基团的N原子邻近C^5或C^6。

[0372] 在一些实施例中,当R^3和R^4结合以形成根据式(IIIb)的基团时,根据式(IIIb)的基团的N原子邻近C^6。在其他实施例中,当R^3和R^4结合以形成根据式(IIIb)的基团时,根据式(IIIb)的基团的N原子邻近C^5或C^6。

[0373] 在具体实施例中,当R^3和R^4结合以形成根据式(IVa)-(IVk)中任一个的基团时,根据式(IVa)-(IVk)中任一个的基团的S原子邻近C^6。在具体实施例中,当R^3和R^4结合以形成根据式(IVa)-(IVk)中任一个的基团时,根据式(IVa)-(IVk)中任一个的基团的S原子邻近C^5或C^6。

[0374] 在一些实施例中,当R^3和R^4与各自附接的原子一起连接以形成任选取代的包含一个硫的五元环时,R^7和R^8与各自附接的原子一起连接以形成任选取代的五元或六元环。在某些实施例中,当R^3和R^4与各自附接的原子一起连接以形成任选取代的包含一个硫的五元环时,R^7和R^8与各自附接的原子一起连接以形成任选取代的五元环。在具体实施例中,当R^3和R^4与各自附接的原子一起连接以形成任选取代的包含一个硫的五元环时,R^7和R^8结合以形成$-CH_2CH_2-$基团。

[0375] 在其他实施例中,R^7和R^8与各自附接的原子一起连接以形成五元或六元环。

[0376] 在具体实施例中,R^7是任选取代的C_{1-3}烷基。在其他实施例中,R^7是未经取代的C_{1-3}烷基、C_{1-3}烷基氨基-C_{1-3}烷基(例如,C_{1-3}卤代烷基氨基-C_{1-3}-烷基(例如,C_{1-3}氟烷基氨基-C_{1-3}-烷基))、二-(C_{1-3}烷基)氨基-C_{1-3}-烷基(例如,$R^{Y1}N(R^{Y2})-(C_{1-3}$-烷基)-),其中每个R^{Y1}和R^{Y2}独立地是未经取代的C_{1-3}烷基或C_{1-3}卤代烷基氨基-C_{1-3}-烷基,(例如,C_{1-3}氟烷基氨基-C_{1-3}-烷基)、或C_{1-3}卤代烷基(例如,C_{1-3}氟烷基)。在具体实施例中,R^7是未经取代的C_{1-3}烷基、C_{1-3}烷基氨基-C_{1-3}-烷基(例如,C_{1-3}卤代烷基氨基-C_{1-3}-烷基,例如C_{1-3}氟烷基氨基-C_{1-3}-烷基),或二-(C_{1-3}烷基)氨基-C_{1-3}-烷基(例如,$R^{Y1}N(R^{Y2})-(C_{1-3}$烷基)-,其中每个R^{Y1}和R^{Y2}独立地是未经取代的C_{1-3}烷基、或C_{1-3}卤代烷基氨基-C_{1-3}-烷基,例如,C_{1-3}氟烷基氨基-C_{1-3}-烷基)。

[0377] 在仍然其他实施例中,R^7是任选取代的C_{1-3}烷基(例如,R^7是甲基),或R^7是$-(CH_2)_k-N(R^{24})R^{25}$,其中k是2或3(例如,k是2),并且其中每个$R^{24}$和$R^{25}$独立地是H或任选取代的$C_{1-3}$烷基(例如,每个$R^{24}$和$R^{25}$独立地是任选取代的$C_{1-3}$烷基,例如,每个$R^{24}$和$R^{25}$独立地是$C_{1-3}$卤代烷基(例如,$C_{1-3}$氟烷基);可替代地,每个$R^{24}$和$R^{25}$独立地是未经取代的$C_{1-3}$烷基,例如,甲基。

[0378] 在其他实施例中,当R^3和R^4与各自附接的原子一起连接以连接形成任选取代的包含一个氮的五元环时,环上的任选取代基不是氧。在某些实施例中,当R^3和R^4与各自附接的原子一起连接以形成任选取代的包含一个硫的五元环时,环上的任选取代基不是羟基或C_{1-3}烷氧基。

[0379] 在仍然其他实施例中,每个R^1和R^2是H。在具体实施例中,每个R^3和R^4独立地是任选取代的C_{1-3}烷基或任选取代的C_{1-3}烷氧基;或者R^3和R^4与各自附接的原子一起连接以形成任选取代的五元或六元环,该五元或六元环任选地包括一个氮、一个硫或一个氧,其中氮任选地被R^9取代。在一些实施例中,R^3和R^4与各自附接的原子一起连接以形成任选取代的五元环。在某些实施例中,R^3和R^4结合以形成$-CH_2CH_2CH_2-$。在具体实施例中,R^3和R^4与各自附接的

原子一起连接以形成任选取代的包含一个氮的五元环。在一些实施例中，R^3和R^4结合以形成-N(R^9)-CH=CH-(例如，R^9是H或任选取代的C_{1-3}烷基，例如，C_{1-3}卤代烷基(例如，C_{1-3}氟烷基)；可替代地，R^9是H)。在某些实施例中，N原子邻近式(I)的C^5。在具体实施例中，R^3和R^4与各自附接的原子一起连接以形成任选取代的包含一个硫的五元环。在仍然其他实施例中，R^3和R^4结合以形成-C(R^{13A})=C(R^{13B})-S-，其中R^{13A}是H，并且R^{13B}是H或任选取代的C_{1-3}烷基。在具体实施例中，S原子邻近本发明化合物的C^6。在一些实施例中，R^{13}是任选取代的C_{1-3}烷基，例如，R^{13B}是-C(O)-R^{13C}，其中R^{13C}是任选取代的C^{1-3}烷氧基或任选取代的氨基。在其他实施例中，R^4是C_{1-3}烷基。在具体实施例中，R^4是甲基、乙基或异丙基。在某些实施例中，R^4是C_{1-3}烷氧基(例如，R^4是甲氧基)。在其他实施例中，R^4是任选取代的C_{1-6}硫代烷氧基(例如，R^4是4-氨基-4-氧代丁基)。在仍然其他实施例中，R^4是任选取代的氨基(例如，R^4是甲氨基)。在仍然其他实施例中，R^4是卤素(例如，R^4是氯)。在具体实施例中，R^3是氢或C_{1-3}烷基(例如，R^3是氢、甲基或乙基)。在进一步的实施例中，R^3和R^4结合以形成-C(R^{13A})=C(R^{13B})-S-基团，其中R^{13A}是H，并且R^{13B}是H或-C(O)-R^{13C}，其中R^{13C}是任选取代的C_{1-3}烷基、任选取代的C_{1-3}烷氧基、任选取代的氨基、或任选取代的C_{2-9}杂环基。

[0380] 在一些实施例中，R^3和R^4结合以形成-X^1-X^2-X^3-，其中

[0381] X^1是-S-、-O-、-($CR^{14}R^{15}$)-、-C(R^{16})=、-N(R^9)-、-N=、H、或任选取代的C_{1-3}烷基；

[0382] X^2是不存在的、-($CR^{17}R^{18}$)$_n$-、-S-、-O-、-N=、-N(R^9)-、-C(R^{19})=、=N-、=C(R^{20})-、或=C(R^{21})-C(R^{22})=；

[0383] X^3是-($CR^{14}R^{15}$)-、-S-、-O-、-N(R^9)-、=N-、=C(R^{23})-、卤素、任选取代的C_{1-3}烷基、任选取代的C_{1-6}硫代烷氧基、任选取代的C_{1-3}烷氧基、或任选取代的C_{6-10}芳基；

[0384] 每个R^{14}和R^{15}独立地是H或任选取代的C_{1-3}烷基、或者R^{14}和R^{15}结合以形成=O或=S；

[0385] 每个R^{17}和R^{18}独立地是H或任选取代的C_{1-3}烷基、或者R^{17}和R^{18}结合以形成=O或=S；

[0386] 每个R^{16}、R^{19}、R^{20}、R^{21}、R^{22}、和R^{23}独立地是H、或任选取代的C_{1-3}烷基；并且

[0387] n是1或2。

[0388] 在一些实施例中，当X^2是不存在的时，

[0389] 原子链-X^1-X^2-X^3-包括不超过一个杂原子，该杂原子选自氮、氧和硫。

[0390] 在具体实施例中，X^1是-($CR^{14}R^{15}$)-、-C(R^{16})=、-N(R^9)-、-N=、或任选取代的C_{1-3}烷基。

[0391] 在某些实施例中，X^1是-($CR^{14}R^{15}$)-。在具体实施例中，每个R^{14}和R^{15}是H。在其他实施例中，X^1是-C(R^{16})=。在仍然其他实施例中，R^{16}是H。在仍然其他实施例中，X^1是-N(R^9)-。在一些实施例中，R^9是H或任选取代的C_{1-3}烷基。在某些实施例中，R^9是卤素、甲基、或乙基。在具体实施例中，X^1是-N=。在其他实施例中，X^1是任选取代的C_{1-3}烷基。在仍然其他实施例中，X^2是不存在的、-(CH_2)$_n$-、-N(R^9)-、-C(H)=、=C(R^{20})-、或=C(H)-C(H)=。在仍然其他实施例中，X^2是-C(H)=。在进一步的实施例中，X^2是-N(R^9)-。在一些实施例中，R^9是H。在某些实施例中，R^9是任选取代的C_{1-3}烷基(例如，R^9是-C(O)-N(H)-Et)。在具体实施例中，X^2是=C(R^{20})-。在其他实施例中，R^{20}是任选取代的C_{1-3}烷基。在仍然其他实施例中，X^2是不存在的。在仍然其他实施例中，X^3是-CH_2-、-S-、=C(H)-、-N(R^9)-、卤素、任选取代的C_{1-3}烷基、任选取代的C_{1-3}烷氧基、任选取代的C_{1-6}硫代烷氧基、任选取代的C_{6-10}芳基。在某些实施例中，X^3是-CH_2-。在具体实施例中，X^3是-S-。在一些实施例中，X^3是=C(H)-。在其他实施例中，X^3是-N

(R^9)-。在仍然其他实施例中，X^3是卤素、任选取代的C_{1-3}烷基、任选取代的C_{1-3}烷氧基、任选取代的C_{1-6}硫代烷氧基、或任选取代的C_{6-10}芳基。

[0392] 在某些实施例中，Z^1和R^8结合以形成$-Z^3-Y^1-Y^2-$，其中

[0393] Z^3是-O-、$-N(R^{10})-$、-N=、-S-、或$-(CR^{11}R^{12})-$；

[0394] Y^1是-O-、$-N(R^{10})-$、-S-、$-(CR^{26}R^{27})_m-$、$-C(R^{20})=$、$=C(R^{20})-$、$=C(R^{21})-C(R^{22})=$、任选取代的C_{1-3}烷基、任选取代的C_{1-3}烷杂环基、任选取代的C_{1-3}烷环烷基、或任选取代的C_{1-3}烷芳基；并且

[0395] Y^2是-O-、-S-、$-N(R^{10})-$、$-(CR^{26}R^{27})-$、$=C(R^{20})-$、=N-、或H；其中

[0396] 每个R^{20}、R^{21}、和R^{22}独立地是H或任选取代的C_{1-3}烷基；并且

[0397] 每个R^{26}和R^{27}独立地是H或任选取代的C_{1-3}烷基、或者R^{26}和R^{27}结合以形成=O或=S；

[0398] m是1或2；并且

[0399] 其中，当Y^2是H时，

[0400] 原子链$-Z^3-Y^1-Y^2-$包括不超过两个杂原子，该杂原子选自氮、氧、和硫。

[0401] 在仍然其他实施例中，R^7和R^8形成基团$-Y^1-Y^2-$，其中：

[0402] Y^1是$-(CR^{26}R^{27})_m-$、$-C(R^{20})=$、任选取代的C_{1-3}烷基、任选取代的C_{1-3}烷杂环基、任选取代的C_{1-3}烷环烷基、或任选取代的C_{1-3}烷芳基；并且

[0403] Y^2是$-(CR^{26}R^{27})-$、$=C(R^{20})-$、或H；其中

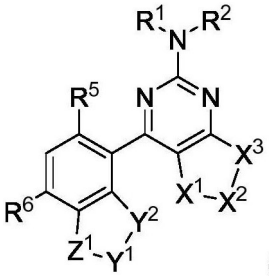
[0404] 每个R^{26}和R^{27}独立地是H或任选取代的C_{1-3}烷基；并且

[0405] m是1或2。

[0406] 在具体实施例中，Z^3是氧。在一些实施例中，Y^1是$-(CR^{26}R^{27})_m-$、$-C(R^{20})=$、任选取代的C_{1-3}烷基、任选取代的C_{1-3}烷杂环基、任选取代的C_{1-3}烷环烷基、或任选取代的C_{1-3}烷芳基。在进一步的实施例中，Y^1是$-(CR^{26}R^{27})_m-$或任选取代的C_{1-3}烷基。在其他实施例中，Y^1是$-(CR^{26}R^{27})_m-$。在其他实施例中，Y^1是任选取代的C_{1-3}烷基(例如，Y^1是甲基)。在仍然其他实施例中，Y^1是$-(CH_2)_k-N(R^{24})R^{25}$，其中k是2或3，并且其中每个$R^{24}$和$R^{25}$独立地是H或任选取代的$C_{1-3}$烷基。在仍然其他实施例中，k是2。在进一步的实施例中，每个R^{24}和R^{25}独立地是任选取代的C_{1-3}烷基(例如，每个R^{24}和R^{25}是甲基)。在某些实施例中，Y^2是$-(CR^{26}R^{27})-$或H。在其他实施例中，Y^2是$-(CR^{26}R^{27})-$。

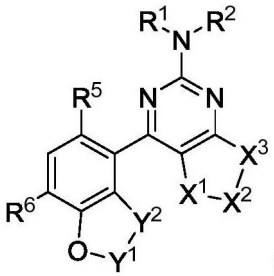
[0407] 在任一方面的一些实施例中，每个R^1和R^2是H。

[0408] 在式(I)或(Ia)的某些实施例中，本发明的化合物具有根据式(Va)的结构：

[0409] 

(Va)，或其药学上可接受的盐，其中全部取代基如此处所定义。

[0410] 在式(I)、(Ia)、或(Ib)的具体实施例中，本发明的化合物具有根据式(Vb)的结构：

[0411]  或或其药学上可接受的盐，

(Vb)，

[0412] 其中

[0413] X^1是-S-、-O-、-($CR^{14}R^{15}$)-、-C(R^{16})=、-N(R^9)-、-N=、-H、或任选取代的C_{1-3}烷基；

[0414] X^2是不存在的、-($CR^{17}R^{18}$)$_n$-、-S-、-O-、-N=、-N(R^9)-、-C(R^{19})=、=N-、=C(R^{20})-、或=C(R^{21})-C(R^{22})=；

[0415] X^3是-($CR^{14}R^{15}$)-、-S-、-O-、-N(R^9)-、=N-、=C(R^{23})-、卤素、任选取代的C_{1-3}烷基、任选取代的C_{1-6}硫代烷氧基、任选取代的C_{1-3}烷氧基、或任选取代的C_{6-10}芳基；

[0416] Y^1是-($CR^{26}R^{27}$)$_m$-、-C(R^{20})=、=C(R^{20})-、=C(R^{21})-C(R^{22})=、任选取代的C_{1-3}烷基、任选取代的C_{1-3}烷杂环基、任选取代的C_{1-3}烷环烷基、或任选取代的C_{1-3}烷芳基；

[0417] Y^2是-O-、-S-、-N(R^{10})-、-($CR^{26}R^{27}$)-、=C(R^{20})-、=N-、或H；

[0418] 每个R^1和R^2独立地是H或任选取代的C_{1-3}烷基；

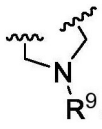
[0419] 每个R^5和R^6独立地是任选取代的C_{1-3}烷基、任选取代的C_{1-3}烷氧基、卤素、或CN；

[0420] 每个R^{14}、R^{15}、R^{16}、R^{17}、R^{17}、R^{18}、R^{20}、R^{19}、R^{20}、R^{21}、R^{22}、R^{23}、R^{26}、和R^{27}独立地是H或任选取代的C_{1-3}烷基；

[0421] n是1或2；并且

[0422] m是1或2。

[0423] 在一些实施例中，当R^5是氯，R^6是溴，并且-X^1-X^2-X^3-形成根据式(IIa)的基团时：

[0424] 

(IIa)，

[0425] Y^1不是甲基、乙基、正丙基、2-(N-吡唑基)乙基、2-(N-咪唑基)乙基、3-羟丙基、氰甲基、2-氯乙基、2-羟乙基、2-氧代丙基、2-(N,N-二甲氨基)乙基、二氟甲基或2-(叔丁氨基)乙基。

[0426] 在某些实施例中，当R^5是氯，R^6是溴，并且-X^1-X^2-X^3-形成根据式(IIa)的基团时，

[0427] Y^1不是任选取代的C_{1-3}烷基或任选取代的C_2烷杂芳基。

[0428] 在具体实施例中，当R^5是氯，R^6是溴，并且-X^1-X^2-X^3-形成根据式(IIa)的基团时，

[0429] Y^1不是任选取代的C_{1-3}烷基或任选取代的C_2烷杂环基。

[0430] 在仍然其他实施例中，当R^5是氯，R^6是溴，并且-X^1-X^2-X^3-形成根据式(IIa)的基团时，

[0431] Y^2不是H。

[0432] 在仍然其他实施例中，当R^5是氯，R^6是溴，并且-X^1-X^2-X^3-形成根据式(IIa)的基团时，

[0433] 每个Y^1和Y^2是-CH_2-。

[0434] 在一些实施例中，当每个R^5和R^6是溴，并且-X^1-X^2-X^3-形成根据式(IIa)的基团时，

[0435] Y^1不是甲基。

[0436] 在具体实施例中，当每个R^5和R^6是氯，并且$-X^1-X^2-X^3-$形成根据式(IIa)的基团时，

[0437] Y^1不是甲基、2-(N-咪唑基)乙基、甲氧基甲基、2-(N-吡唑基)乙基、2-(3-甲基吡唑-1-基)乙基、2-吡啶基-甲基、1,3-二甲基-1H-1,2,4-三唑-5-基-甲基、2-嘧啶基甲基、咪唑-2-基-甲基、5-甲基-异噁唑-3-基-甲基、4-甲基-咪唑-5-基-甲基、或3-甲基-1,2,4-噁二唑-5-基-甲基。

[0438] 在其他实施例中，当每个R^5和R^6是氯，并且$-X^1-X^2-X^3-$形成根据式(IIa)的基团时，

[0439] Y^1不是未经取代的烷基、经取代的烷基、未经取代的烷杂芳基、或经取代的烷杂芳基。

[0440] 在一些实施例中，当每个R^5和R^6是氯，并且$-X^1-X^2-X^3-$形成根据式(IIa)的基团时，

[0441] Y^1不是未经取代的烷基、经取代的烷基、未经取代的烷杂环基、或经取代的烷杂环基。

[0442] 在某些实施例中，当每个R^5和R^6是氯，每个Y^1和Y^2是$-CH_2-$，并且$-X^1-X^2-X^3-$形成根据式(IIa)的基团时，

[0443] R^9不是乙氧基羰基、环丁基氨基羰基、或环丁二烯基氨基羰基。

[0444] 在其他实施例中，当每个R^5和R^6是氯，R^7和R^8结合以形成$-CH_2-CH_2-$，并且$-X^1-X^2-X^3-$形成根据式(IIa)的基团时，

[0445] R^9是H或-C(O)-N(H)-(直链C_{1-3}烷基)。

[0446] 在具体实施例中，当每个R^5和R^6是卤素，并且$-X^1-X^2-X^3-$形成根据式(IIa)的基团时，

[0447] 并且R^9是H或-C(O)-N(H)-(直链C_{1-3}烷基)。

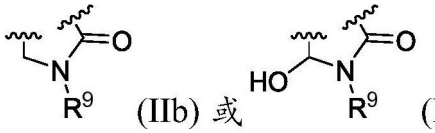
[0448] 在一些实施例中，当R^5是甲氧基，R^6是甲基，并且$-X^1-X^2-X^3-$形成根据式(IIa)的基团时，

[0449] Y^1不是甲基。

[0450] 在某些实施例中，当R^5是氯，R^6是乙基，并且$-X^1-X^2-X^3-$形成根据式(IIa)的基团时，

[0451] Y^1不是甲基。

[0452] 在一些实施例中，当每个R^5和R^6是氯，并且$-X^1-X^2-X^3-$形成根据式(IIb)或(IIc)的基团时，

[0453] 
(IIb)或
(IIc)，

[0454] Y^1不是甲基或2-(N,N-二乙基氨基)乙基。

[0455] 在其他实施例中，当每个R^5和R^6是氯并且$-X^1-X^2-X^3-$形成根据式(IIb)或(IIc)的基团时，

[0456] Y^2不是H。

[0457] 在某些实施例中，当每个R^5和R^6是氯并且$-X^1-X^2-X^3-$形成根据式(IIb)或(IIc)的基团时，

[0458] 每个Y^1和Y^2是$-CH_2-$。

[0459] 在一些实施例中，当R^7是甲，R^5是氯，并且$-X^1-X^2-X^3-$形成根据式(IIIa)的基团时，

[0460] (IIIa),

[0461] R^6不是溴。

[0462] 在具体实施例中，当每个R^5和R^6是氯，并且$-X^1-X^2-X^3-$形成根据式(IIIa)的基团时，

[0463] R^7不是异丙基、3,3,3-三氟丙基、或2-(N,N-二甲氨基)乙基。

[0464] 在一些实施例中，当$-X^1-X^2-X^3-$形成根据式(IIIa)的基团时，

[0465] 每个R^5和R^6是氯，并且

[0466] Y^1是甲基并且Y^2是H，或者

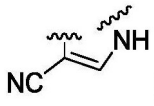
[0467] Y^1是$-(CR^{26}R^{27})_m-$、$-C(R^{20})=$、$=C(R^{20})-$、或$=C(R^{21})-C(R^{22})=$，并且Y^2是-O-、-S-、$-N(R^{10})-$、$-(CR^{26}R^{27})-$、$=C(R^{20})-$、或=N-。

[0468] 在一些实施例中，当$-X^1-X^2-X^3-$形成根据式(IIIa)的基团时，

[0469] 每个R^5和R^6是氯，并且

[0470] Y^2不是H。

[0471] 在其他实施例中，当R^5是氯，R^6是甲氧基，并且$-X^1-X^2-X^3-$形成根据式(IIIb)的基团时，

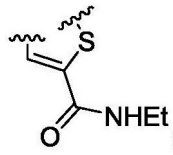
[0472]  (IIIb),

[0473] R^1和R^2都不是2-(N,N-二乙基氨基)乙基。

[0474] 在某些实施例中，当R^5是氯，R^6是甲氧基，并且$-X^1-X^2-X^3-$形成根据式(IIIb)的基团时，

[0475] 每个R^1和R^2是H。

[0476] 在一些实施例中，当每个R^5和R^6是氯，并且$-X^1-X^2-X^3-$形成根据式(IVa)的基团时，

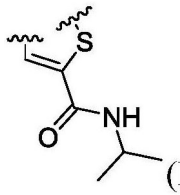
[0477]  (IVa),

[0478] Y^1不是3-(N-吗啉基)丙基、苄基、1-乙基-吡咯烷-3-基、1-甲基-哌啶-4-基、2-(1-甲基-吡咯烷-2-基)乙基、或3-(N,N-二乙基氨基)丙基。

[0479] 在具体实施例中，当每个R^5和R^6是氯，并且$-X^1-X^2-X^3-$形成根据式(IVa)的基团时，

[0480] Y^1不是杂环基、烷杂环基、或烷芳基。

[0481] 在一些实施例中，当每个R^5和R^6是氯，并且$-X^1-X^2-X^3-$形成根据式(IVb)的基团时，

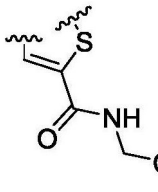
[0482]  (IVb),

[0483] Y^1不是2-甲氧基乙基或苄基。

[0484] 在某些实施例中，当每个R^5和R^6是氯，并且$-X^1-X^2-X^3-$形成根据式(IVb)的基团时，

[0485] Y^1不是经取代的烷基或烷芳基。

[0486] 在一些实施例中，当每个R^5和R^6是氯，并且-X^1-X^2-X^3-形成根据式(IVc)的基团时，

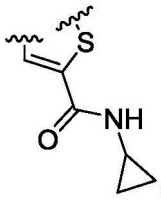
[0487]  (IVc)，

[0488] Y^1不是2-(N,N-二乙基氨基)乙基或3-(N,N-二甲氨基)丙基。

[0489] 在其他实施例中，当每个R^5和R^6是氯，并且-X^1-X^2-X^3-形成根据式(IVc)的基团时，

[0490] Y^1不是经取代的烷基。

[0491] 在具体实施例中，当每个R^5和R^6是氯，并且-X^1-X^2-X^3-形成根据式(IVd)的基团时，

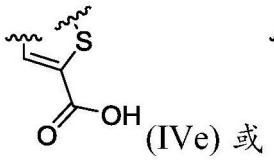
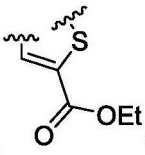
[0492]  (IVd)，

[0493] Y^1不是2-(吡咯烷-1-基)乙基或2-羟乙基。

[0494] 在某些实施例中，当每个R^5和R^6是氯，并且R^3和R^4结合以形成根据式(IVd)的基团时，

[0495] Y^1不是经取代的烷基或烷杂环基。

[0496] 在一些实施例中，当每个R^5和R^6是氯，并且-X^1-X^2-X^3-形成根据式(IVe)或(IVf)的基团时，

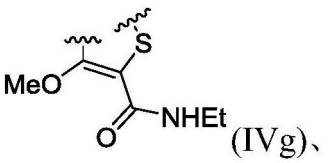
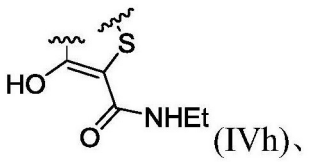
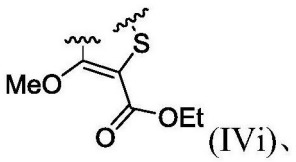
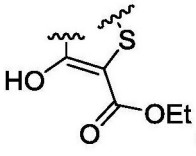
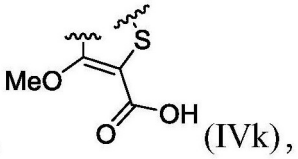
[0497]  (IVe)或  (IVf)，

[0498] Y^1不是苄基。

[0499] 在其他实施例中，当每个R^5和R^6是氯，并且-X^1-X^2-X^3-形成根据式(IVe)或(IVf)的基团时，

[0500] Y^1不是烷芳基或经取代的烷基。

[0501] 在某些实施例中，当R^5是氯，R^6是溴，并且-X^1-X^2-X^3-形成根据式(IVg)、(IVh)、(IVi)、(IVj)、或(IVk)的基团时，

[0502]  (IVg)、  (IVh)、  (IVi)、  (IVj)、或  (IVk)，

[0503] Y^1不是甲基。

[0504] 在一些实施例中，当R^5是氯，R^6是溴，-X^1-X^2-X^3-形成根据式(IVg)、(IVh)、(IVi)、

(IVj)、或(IVk)的基团时，

[0505] Y^2不是H。

[0506] 在具体实施例中，当R^5是氯，R^6是溴时，

[0507] R^3和R^4不结合以形成根据式(IVg)、(IVh)、(IVi)、(IVj)、或(IVk)的基团。

[0508] 在具体实施例中，当R^6是甲氧基时，

[0509] 每个R^1和R^2是H。

[0510] 在某些实施例中，当X^1是H，并且每个R^5和R^6是氯时，

[0511] Y^1不是甲基。

[0512] 在一些实施例中，R^{10}是H、任选取代的C_{1-3}烷基、任选取代的C_{3-8}环烷基、任选取代的C_{1-3}烷环烷基、任选取代的C_{1-3}烷杂环基、或任选取代的C_{1-3}烷芳基。在其他实施例中，R^{10}是H、任选取代的C_{1-3}烷基、任选取代的C_{1-3}烷环烷基、任选取代的C_{1-3}烷杂环基、或任选取代的C_{1-3}烷芳基。

[0513] 在具体实施例中，当X^1是$-(CR^{14}R^{15})-$，X^2是$-N(R^9)-$，X^3是$-(CR^{14}R^{15})-$，并且每个R^{14}和R^{15}是H时，R^9是H或$-C(O)-N(H)-Et$，并且每个Y^1和Y^2是$-CH_2-$。在其他实施例中，当X^1是$-(CR^{14}R^{15})-$，X^2是$-N(R^9)-$，并且X^3是$-(CR^{14}R^{15})-$时，R^9是H或$-C(O)-N(H)-Et$，并且每个Y^1和Y^2是$-CH_2-$。在一些实施例中，当X^1是$-N(R^9)-$，X^2是$-C(R^{19})=$，X^3是$=C(R^{23})-$，并且每个R^{17}、R^{19}、和R^{23}是H时，Y^1是$-(CR^{26}R^{27})_m-$，并且Y^2是$-(CR^{26}R^{27})-$。在其他实施例中，当X^1是$-N(R^9)-$，X^2是$-C(R^{19})=$，X^3是$=C(R^{23})-$，并且每个R^9、R^{19}、和R^{23}是H时，每个Y^1和Y^2是$-CH_2-$。在一些实施例中，当X^1是$-N(R^9)-$，X^2是$-C(R^{19})=$，X^3是$=C(R^{23})-$，并且每个R^{19}和R^{23}是H时，Y^1是$-(CR^{26}R^{27})_m-$，并且Y^2是$-(CR^{26}R^{27})-$。在某些实施例中，当X^1是$-N(R^9)-$，X^2是$-C(R^{19})=$，X^3是$=C(R^{23})-$，Y^2是H，并且每个R^5和R^6是-Cl时，Y^1是Me。在具体实施例中，当X^1是$-C(R^{16})=$，X^2是$=C(R^{20})-$，并且X^3是-S-时，R^{16}是H。在一些实施例中，当X^1是$-C(R^{16})=$，X^2是$=C(R^{20})-$，并且X^3是-S-时，Y^1是$-(CR^{26}R^{27})_m-$，并且Y^2是$-(CR^{26}R^{27})-$。在某些实施例中，当X^1是$-C(R^{16})=$，X^2是$=C(R^{20})-$，并且X^3是-S-时，每个Y^1和Y^2是$-CH_2-$。在一些实施例中，当X^1是$-C(R^{16})=$，X^2是$=C(R^{20})-$，并且X^3是-S-时，每个R^5和R^6是-Cl。在某些实施例中，当X^1是H，并且每个R^5和R^6是Cl时，Y^1是$-(CR^{26}R^{27})_m-$，并且Y^2是$-(CR^{26}R^{27})-$。在具体实施例中，当X^1是H，并且每个R^5和R^6是卤素时，Y^1是$-(CR^{26}R^{27})_m-$，并且Y^2是$-(CR^{26}R^{27})-$(例如，每个Y^1和Y^2是$-CH_2-$)。在具体实施例中，当X^1是H时，Y^1是$-(CR^{26}R^{27})_m-$，并且Y^2是$-(CR^{26}R^{27})-$(例如，每个Y^1和Y^2是$-CH_2-$)。

[0514] 在具体实施例中，X^1是$-(CR^{14}R^{15})-$、$-C(R^{16})=$、$-N(R^9)-$、或任选取代的C_{1-3}烷基(例如，$-CH_2-$、$-C(H)=$、-N=、任选取代的C_{1-3}烷基、或$-N(R^9)-$(例如，R^{17}是H或任选取代的C_{1-3}烷基(例如，R^9是H、-Me、或-Et)。

[0515] 在一些实施例中，X^2是不存在的、$-(CH_2)_n-$、$-N(R^9)-$、$-C(H)=$、$=C(R^{20})-$、或$=C(H)-C(H)=$。在某些实施例中，X^2是不存在的、$-C(H)=$、$-N(R^9)-$(例如，R^9是H或任选取代的C_{1-3}烷基(例如，R^9是C_{1-3}卤代烷基，例如，C_{1-3}氟烷基)，或R^9是$-C(O)-N(H)-Et$)、或$=C(R^{20})-$，其中R^{20}是，例如，任选取代的C_{1-3}烷基。

[0516] 在某些实施例中，X^3是$-CH_2-$、-S-、$=C(H)-$、或任选取代的C_{1-3}烷基。

[0517] 在一些实施例中，每个R^5和R^6独立地是卤素、或任选取代的C_{1-3}烷基，例如，每个R^5和R^6是卤素(例如，每个R^5和R^6是-Cl)。

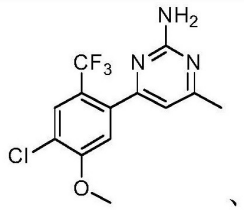
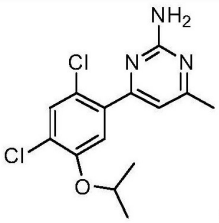
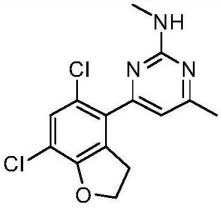
[0518] 在一些实施例中，R^{26}是H。在其他实施例中，R^{27}是H。在某些实施例中，n是1。在其他

实施例中，m是1。在具体实施例中，Y^1是任选取代的C_{1-3}烷基。在其他实施例中，Y^1是未经取代的C_{1-3}烷基、C_{1-3}烷基氨基-C_{1-3}-烷基(例如，C_{1-3}卤代烷基氨基-C_{1-3}-烷基，例如，C_{1-3}氟烷基氨基-C_{1-3}-烷基)、二-(C_{1-3}烷基)氨基-C_{1-3}-烷基(例如，$R^{Y1}N(R^{Y2})$-(C_{1-3}烷基)-，其中每个R^{Y1}和R^{Y2}独立地是未经取代的C_{1-3}烷基、或C_{1-3}卤代烷基氨基-C_{1-3}-烷基，例如，C_{1-3}氟烷基氨基-C_{1-3}-烷基)，或C_{1-3}卤代烷基(例如，C_{1-3}氟烷基)。在具体实施例中，Y^1是未经取代的C_{1-3}烷基、C_{1-3}烷基氨基-C_{1-3}-烷基(例如，C_{1-3}卤代烷基氨基-C_{1-3}-烷基，例如，C_{1-3}氟烷基氨基-C_{1-3}-烷基)、或二-(C_{1-3}烷基)氨基C_{1-3}-烷基(例如，$R^{Y1}N(R^{Y2})$-(C_{1-3}烷基)-，其中每个R^{Y1}和R^{Y2}独立地是未经取代的C_{1-3}烷基、或C_{1-3}卤代烷基氨基-C_{1-3}-烷基，例如，C_{1-3}氟烷基氨基-C_{1-3}-烷基)。

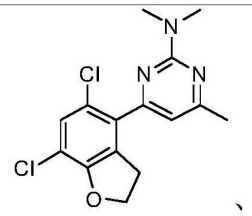
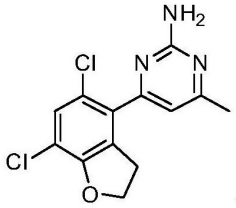
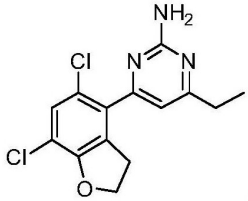
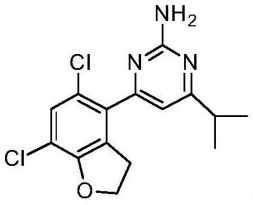
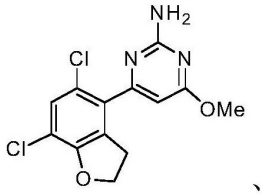
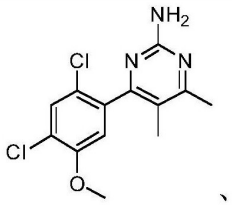
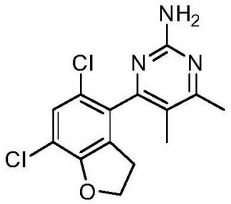
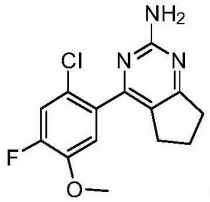
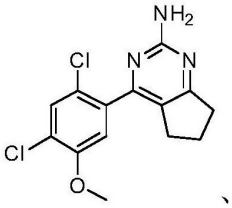
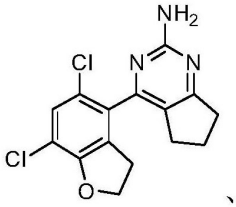
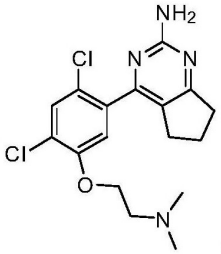
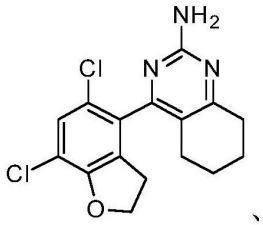
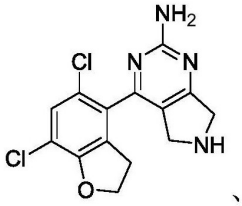
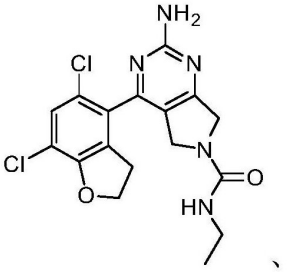
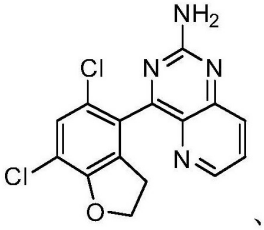
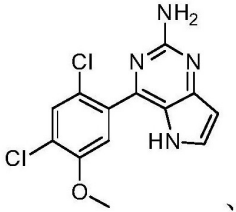
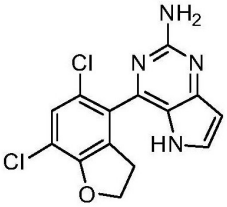
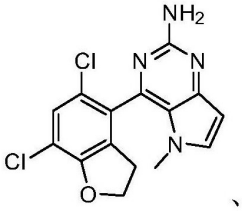
[0519] 在某些实施例中，本发明的化合物具有如表1所示的式：

[0520] 表1.

[0521]

1		2	
3			

[0522]

4		5		6	
7		8		9	
10		11		12	
13		14		15	
16		17		18	
19		20		21	

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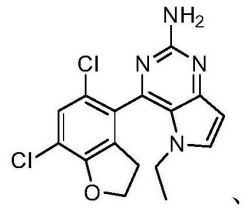
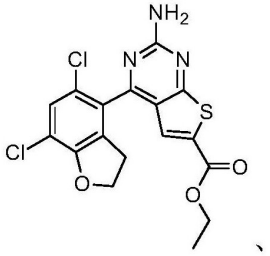
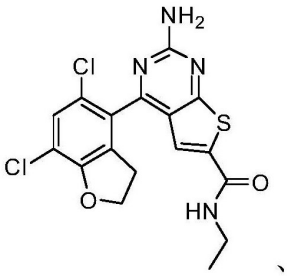
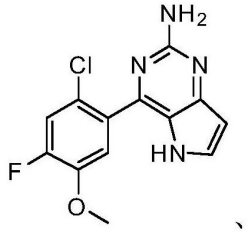
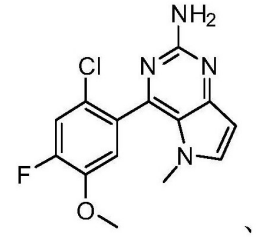
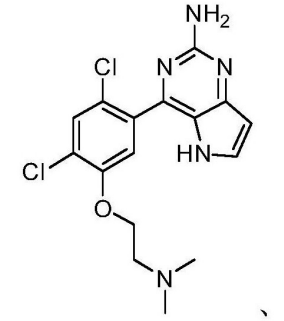
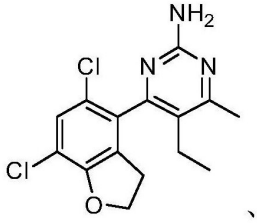
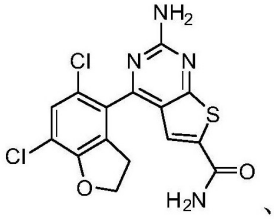
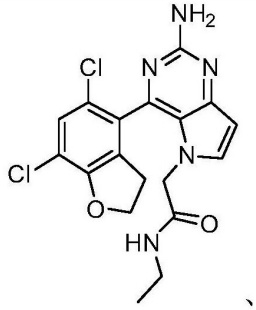
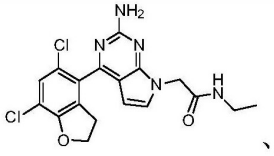
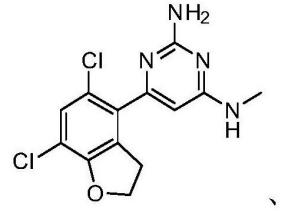
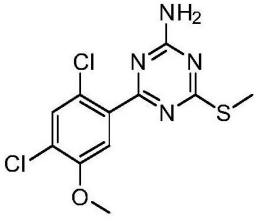
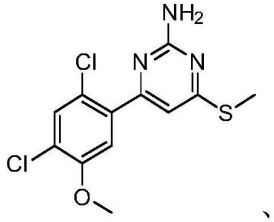
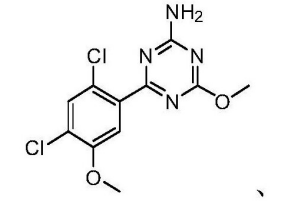
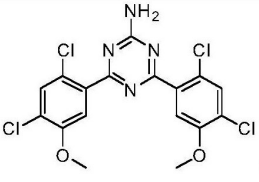
22		**23**		**24**	
25		**26**		**27**	
28		**29**		**30**	
31		**32**		**33**	
34		**35**		**36**	
37		**40**		**41**	

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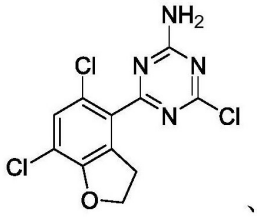
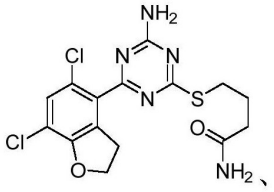
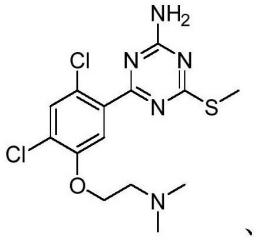
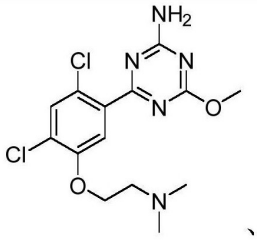
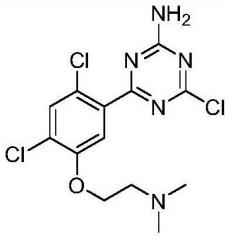
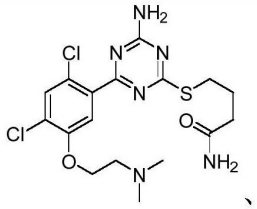
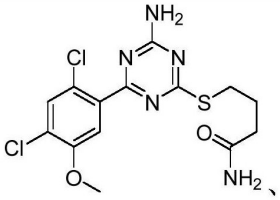
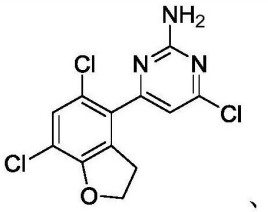
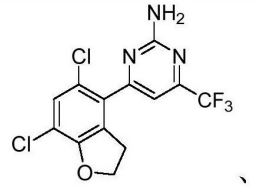
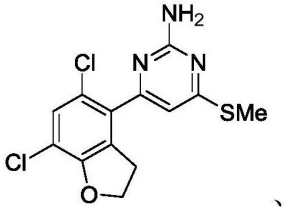
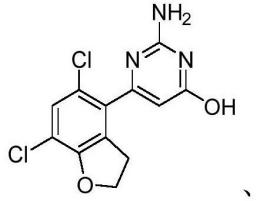
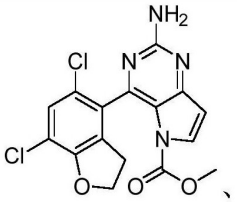
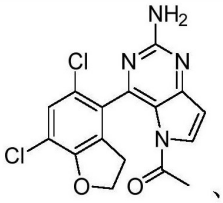
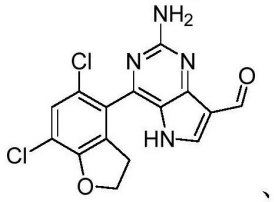
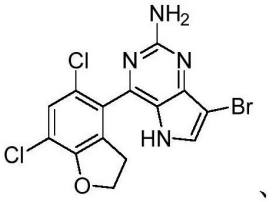
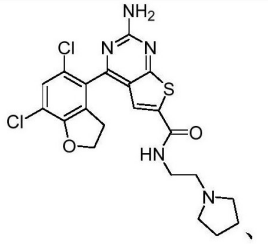
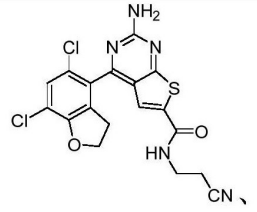
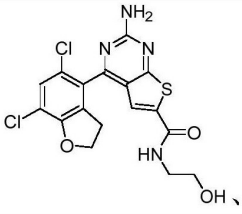
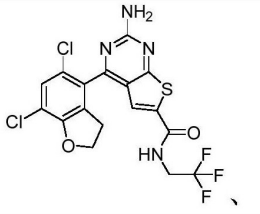
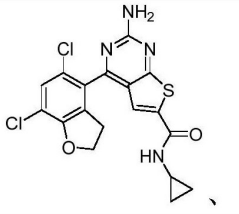
42		43		44	
45		46		47	
48		49		50	
51		52		53	
54		55		56	
57		58		59	
60		61		62	

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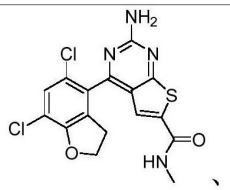
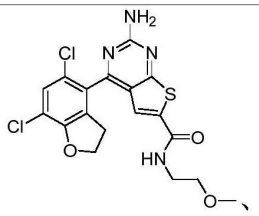
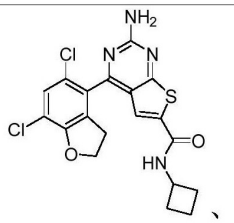
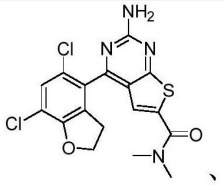
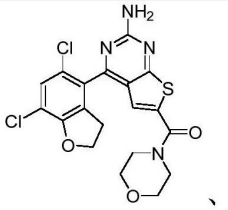
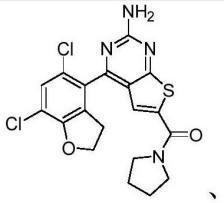
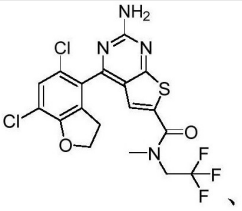
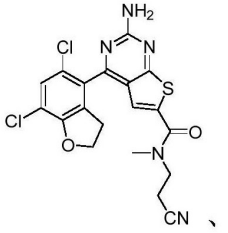
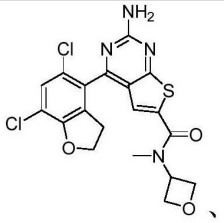
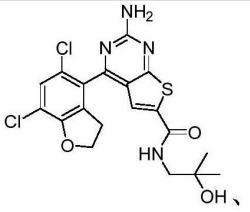
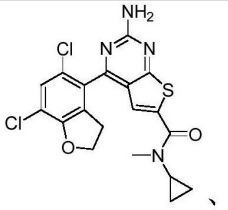
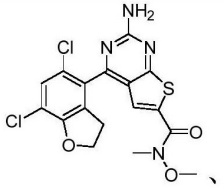
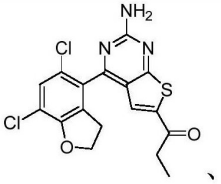
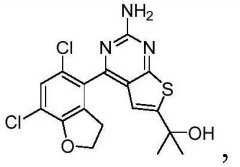
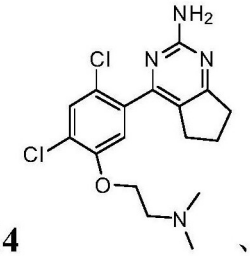
63		**64**		**65**	
66		**67**		**68**	
69		**70**		**71**	
72		**73**		**74**	
75		**76**		**77**	

[0526] 或其药学上可接受的盐。

[0527] 在具体实施例中,本发明的化合物具有式:

[0528]



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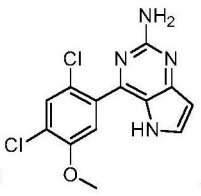

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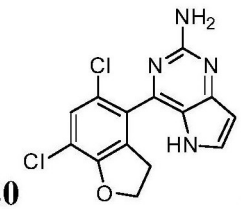

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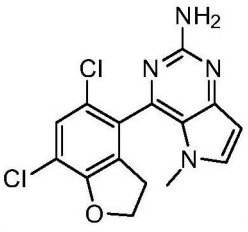

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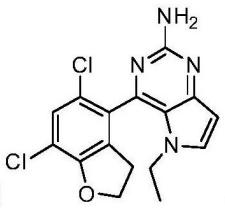
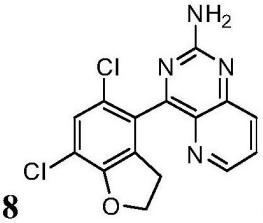
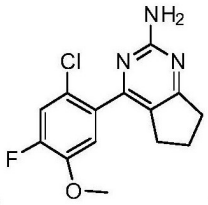
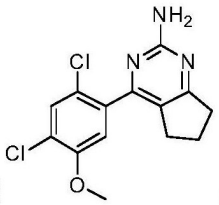
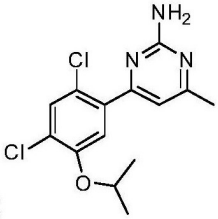

22、 
18、 
11、 
12、 
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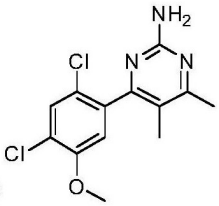
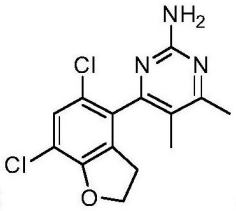
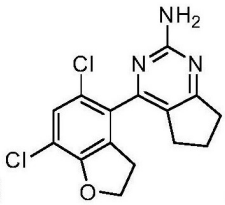
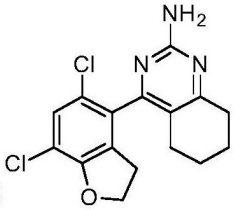
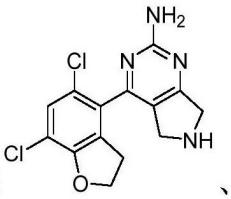
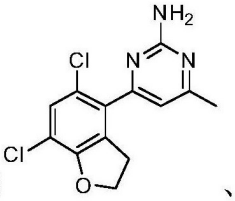
7、 
9、 
10、 
13、 
15、 
16、 
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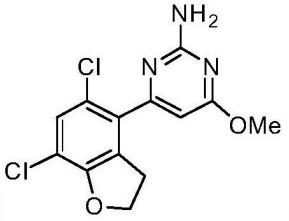
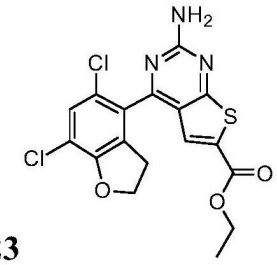
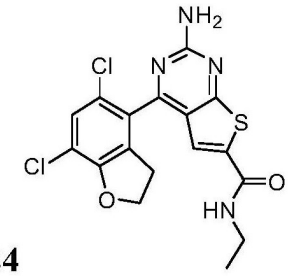
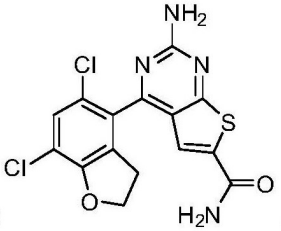
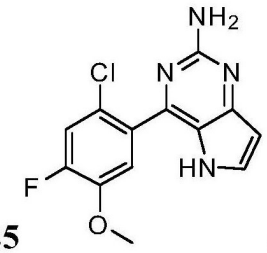
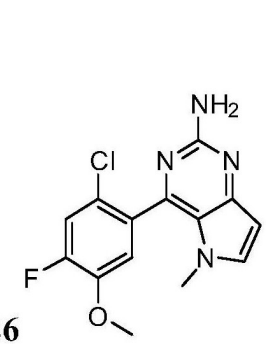
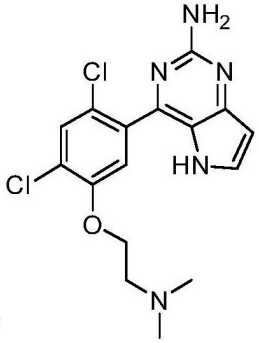
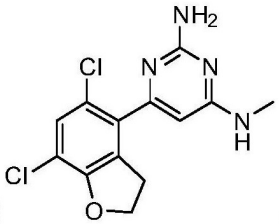
6、 
8、 
23、 
24、 
29、 
25、 
26、 
27、 
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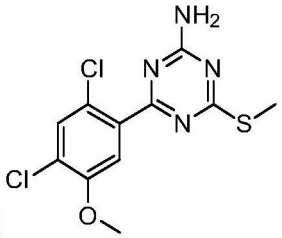
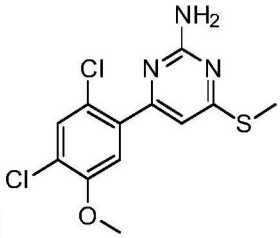
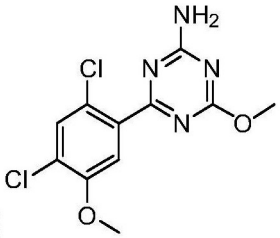

34、 
35、 
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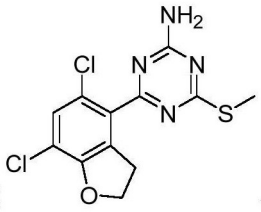
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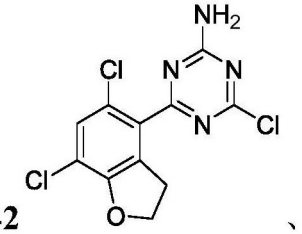
41、 
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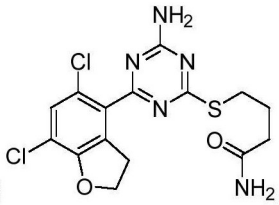
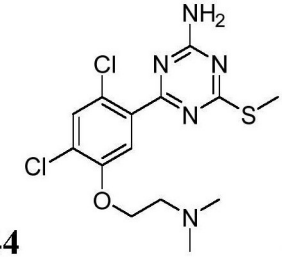
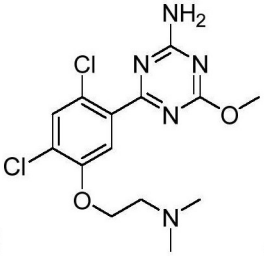

43、 
44、 
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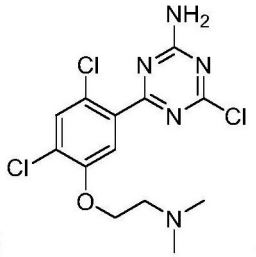
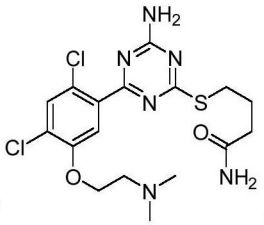
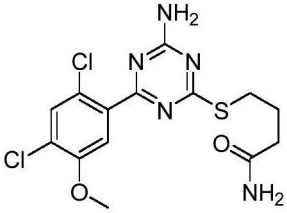
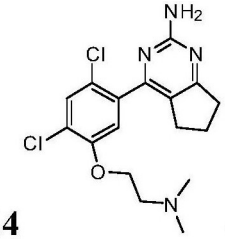
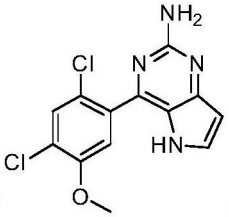
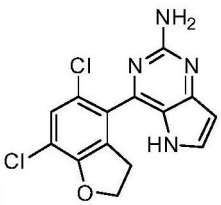
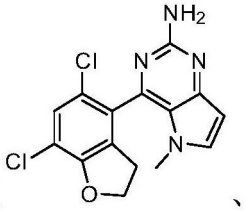

46、 
47、或 
48，或其药学上可接受的盐。

[0529] 在一些实施例中，本发明的化合物具有式：

[0530]


14、 
19、 
20、 
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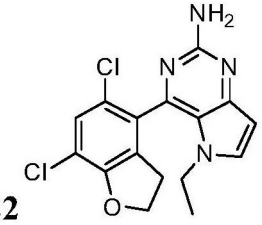
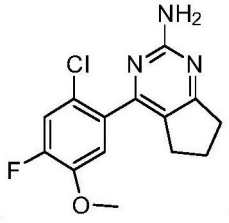
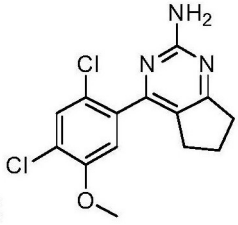

22、 
11、 
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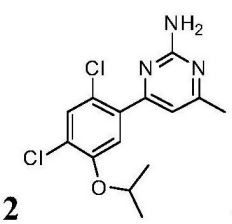
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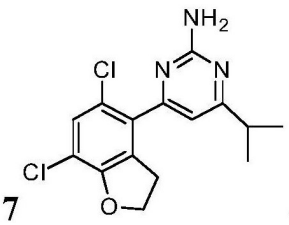
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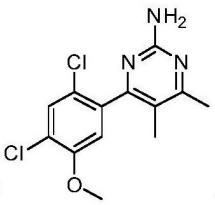
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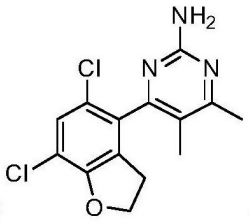
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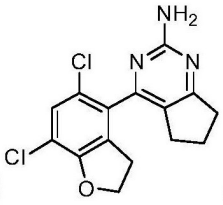
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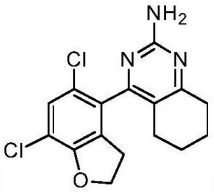
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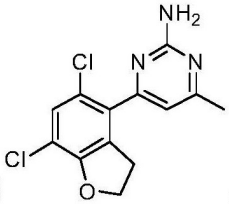
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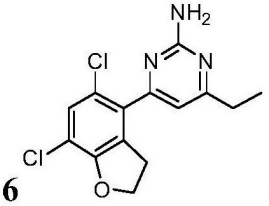
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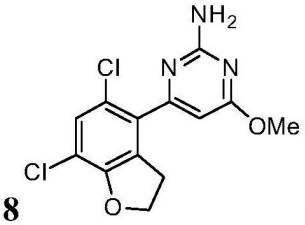
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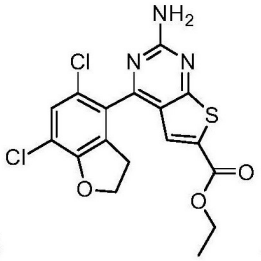
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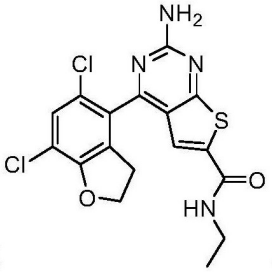
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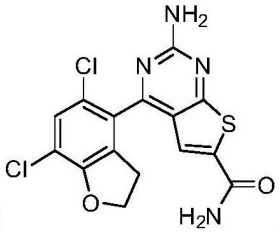
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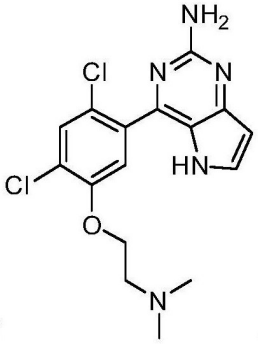
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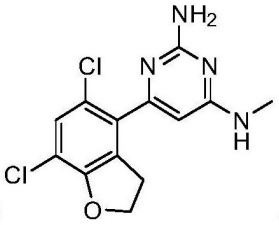
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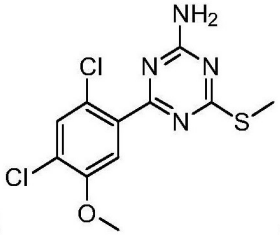
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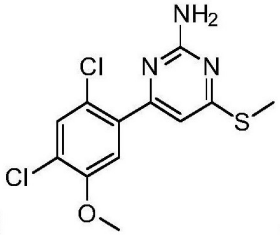
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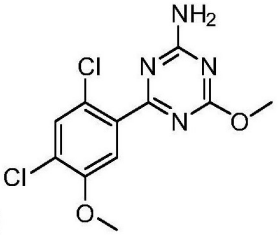

36，

[0532] 或其药学上可接受的盐。

[0533] 在进一步的实施例中，该化合物不是化合物38或化合物39。

[0534] 在此处描述的任何式的某些实施例中，每个R^1和R^2是H，R^5是Cl，并且R^6是F或Cl。

[0535] 在式(I)、(Ia)、或(Ib)的其他实施例中，R^3是H、卤素、任选取代的C_{1-3}烷基、或任选取代的C_{1-3}烷氧基，并且R^4是卤素、任选取代的C_{1-3}烷基、任选取代的C_{1-3}烷氧基、任选取代的氨基、或任选取代的C_{1-6}硫代烷氧基，或者R^3和R^4与各自附接的原子一起连接以形成任选取代的五元或六元环，该五元或六元环任选地包括一个氮、一个氧或一个硫，其中氮任选地被R^9取代。

[0536] 在式(I)、(Ia)、或(Ib)的仍然其他实施例中，R^3是H、任选取代的C_1烷基、或任选取

代的C_{1-3}烷氧基，并且R^4是卤素、任选取代的C_{1-3}烷基、任选取代的C_{1-3}烷氧基、任选取代的氨基、或任选取代的C_{1-6}硫代烷氧基，或者R^3和R^4与各自附接的原子一起连接以形成任选取代的五元或六元环，该五元或六元环任选地包括一个氮、一个氧或一个硫，其中氮任选地被R^9取代。

[0537] 在式(I)、(Ia)、或(Ib)的仍然其他实施例中，R^3是H、任选取代的C_1烷基、或任选取代的C_{1-3}烷氧基，并且R^4是卤素、任选取代的C_{1-3}烷基、任选取代的C_{1-3}烷氧基、任选取代的氨基、或任选取代的C_{1-6}硫代烷氧基，或者R^3和R^4结合以形成以下基团中的一个：

[0538] $-N(R^9)-CH=CH-$、$-CH_2CH_2CH_2-$、$-CH_2CH_2CH_2CH_2-$、和$-C(R^{13A})=C(R^{13B})-S-$，

[0539] 其中N邻近位置5，并且R^9是H或C_{1-3}烷基。

[0540] 在式(I)的某些实施例中，Z^2是N，并且R^4是卤素、任选取代的C_{1-3}烷基、任选取代的C_{1-3}烷氧基、任选取代的氨基、或任选取代的C_{1-6}硫代烷氧基。

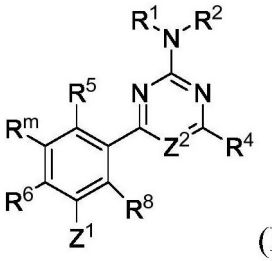
[0541] 在式(I)的具体实施例中，Z^2是N，并且R^4是任选取代的C_{1-3}烷氧基或任选取代的C_{1-6}硫代烷氧基。

[0542] 在其他实施例中，X^1是$-N(R^9)-$、$-(CR^{14}R^{15})-$、$-C(R^{16})=$、H、或任选取代的C_1烷基。在仍然其他实施例中，X^2是不存在的、$-(CR^{17}R^{18})_n-$、$-C(R^{19})=$、或$=C(R^{20})-$。在仍然其他实施例中，X^3是$-(CR^{14}R^{15})-$、$-S-$、$=C(R^{23})-$、卤素、任选取代的C_{1-3}烷基、任选取代的C_{1-6}硫代烷氧基、或任选取代的C_{1-3}烷氧基。在某些实施例中，R^9是H或C_{1-3}烷基。

[0543] 在一些实施例中，本发明的化合物具有小于约500g/mol(例如，小于约450g/mol，或小于约400g/mol)的分子量。在其他实施例中，本发明的化合物在MDR1-MDCK测定中显示出大于约$1x\ 10^{-7}$cm/sec(例如，大于约$5x\ 10^{-7}$cm/sec、大于约$1x\ 10^{-6}$cm/sec、或大于约$3x\ 10^{-6}$cm/sec)的顶端至基底(A→B)的渗透性。在具体实施例中，本发明的化合物显示小于约30(例如，小于约10、小于约5、或小于约3)的(B→A)/(A→B)比。

[0544] 在另一方面，本发明的特征在于一种包括本发明的化合物、或其药学上可接受的盐、和一种或多种药学上可接受的载体或赋形剂的药物组合物。在某些实施例中，该组合物被配制用于口服，皮内、肌内、胃肠外、静脉内、动脉内、颅内、皮下、眶内、心室内、脊柱内、腹膜内或鼻内给予。优选地，该组合物被配制用于口服给予。

[0545] 在仍然另一方面，本发明的特征在于一种治疗由热休克蛋白90(Hsp90)的作用引起的哺乳动物(例如，人)的病症的方法。该方法涉及给予哺乳动物有效量的根据式(I)化合物：

[0546]  或其药学上可接受的盐，

(I)，

[0547] 其中

[0548] Z^1是$-OR^7$、$-N(R^{10})R^7$、$-SR^7$、或$-C(R^{10})(R^{11})R^7$；

[0549] Z^2是$-N=$或$-C(R^3)=$；

[0550] 每个R^1和R^2独立地是H或任选取代的C_{1-3}烷基；

[0551] R^3是H、卤素、氰基、任选取代的C_{1-6}烷基、任选取代的C_{1-3}烷氧基、或任选取代的氨基，并且R^4是卤素、氰基、任选取代的C_{1-6}烷基、任选取代的C1-$_3$烷氧基、任选取代的氨基、任选取代的C_{1-6}硫代烷氧基、或任选取代的C_{6-10}烷基，或者R^3和R^4与各自附接的原子一起连接以形成任选取代的五元或六元环，该五元或六元环任选地包括一个氮、一个氧或一个硫，其中所述氮任选地被R^9取代；

[0552] 每个R^5和R^6独立地是任选取代的C_{1-3}烷基、任选取代的C_{1-3}烷氧基、卤素、或CN；

[0553] R^7是任选取代的C_{1-3}烷基、任选取代的C_{1-3}烷环烷基、任选取代的C_{1-3}烷杂环基、或任选取代的C_{1-3}烷芳基，并且R^8是H；或者R^7和R^8与各自附接的原子一起连接以形成任选取代的五元或六元环，该五元或六元环任选地包括一个或两个选自氮、氧和硫的杂原子；

[0554] R^9是H、任选取代的C_{1-3}烷基、任选取代的C_{3-8}环烷基、任选取代的C_{6-10}芳基、任选取代的C_{2-9}杂芳基、任选取代的C_{2-9}杂环基、任选取代的C_{1-3}烷环烷基、任选取代的C_{1-3}烷杂环基、或任选取代的C_{1-3}烷芳基；

[0555] R^{10}是H、任选取代的C_{1-3}烷基、任选取代的C_{3-8}环烷基、任选取代的C_{6-10}芳基、任选取代的C_{2-9}杂芳基、任选取代的C_{2-9}杂环基、任选取代的C_{1-3}烷环烷基、任选取代的C_{1-3}烷杂环基、或任选取代的C_{1-3}烷芳基，并且R^{11}是H、任选取代的C_{1-3}烷基，或者R^{10}和R^{11}结合以形成＝O或＝S并且

[0556] R^m是H、卤素、任选取代的C_{1-4}烷基、或任选取代的C_{1-3}烷氧基。

[0557] 在式(I)的某些实施例中，当Z^2是CR^3，每个R^1和R^2是H，R^3是H，R^4是甲基或卤素(例如,氯)，并且每个R^5和R^6是卤素(例如氯)时，

[0558] Z^1不是甲氧基。

[0559] 在式(I)的某些实施例中，当Z^2是CR^3，R^3是H，R^4是甲基或卤素(例如，氯)，每个R^5和R^6是卤素(例如，氯)时，

[0560] Z^2不是未经取代的C_{1-3}烷氧基。

[0561] 在式(I)的特定实施例中，当Z^2是N，R^3是H，R^4是任选取代的C_{1-6}硫代烷氧基，并且每个R^5和R^6是卤素(例如，氯)时，

[0562] Z^1不是氰基甲氧基或氨基甲氧基。

[0563] 在式(I)的其他实施例中，当Z^2是N，R^3是H，每个R^5和R^6是卤素(例如，氯)，R^4是经取代的C_{1-6}硫代烷氧基时，

[0564] Z^1不是氰基甲氧基或氨基甲氧基。

[0565] 在式(I)的一些实施例中，当Z^2是N，R^3是H，R^4是任选取代的C_{1-6}硫代烷氧基时，

[0566] Z^1不是氰基甲氧基或氨基甲氧基。

[0567] 在式(I)的某些实施例中，当Z^2是N，R^3是H，R^4是经取代的C_{1-6}硫代烷氧基时，

[0568] Z^1不是氰基甲氧基或氨基甲氧基。

[0569] 在式(I)的进一步的实施例中，当Z^2是N，R^3是H，R^4是经取代的C_{1-6}硫代烷氧基时，

[0570] Z^1不是经取代的C_1烷氧基。

[0571] 在式(I)的具体实施例中，当Z^2是N，R^3是H，R^4是经取代的C_{1-6}硫代烷氧基时，

[0572] Z^1是$-OR^7$、$-N(R^7)R^{10}$、$-SR^7$、或$-C(R^7)(R^{10})R^{11}$，其中R^7是甲基、二烷氨基乙基、任选取代的C_{1-3}烷环烷基、任选取代的C_{1-3}烷杂环基、或任选取代的C_{1-3}烷芳基，或者R^7和R^8与各自附接的原子一起连接以形成任选取代的五元或六元环，该五元或六元环任选地包括一个或两

个选自氮、氧和硫的杂原子。

[0573] 在式(I)的其他实施例中，当Z^2是CR^3，每个R^5和R^6是氯，R^3是H，并且R^4是卤素(例如，氯)时，

[0574] Z^1不是2-氨基-2氧代乙氧基、2-(N,N-二乙氨基)乙氧基、甲氧基、或苄氧基。

[0575] 在式(I)的仍然其他实施例中，当Z^2是CR^3，R^3是H，并且R^4是卤素(例如，氯)时，

[0576] Z^1不是2-氨基-2氧代乙氧基、2-(N,N-二乙氨基)乙氧基、甲氧基、或苄氧基。

[0577] 在式(I)的仍然其他实施例中，当Z^2是CR^3时，每个R^5和R^6是氯，R^3是H，并且R^4是卤素(例如，氯)时，

[0578] Z^1是$-OR^7$、$-N(R^7)R^{10}$、$-SR^7$、或$-C(R^7)(R^{10})R^{11}$，其中R^7是二甲氨乙基、任选取代的C_{1-3}烷环烷基、或任选取代的C_{1-3}烷杂环基，或者R^7和R^8与各自附接的原子一起连接以形成任选取代的五元或六元环，该五元或六元环任选地包括一个或两个选自氮、氧和硫的杂原子。

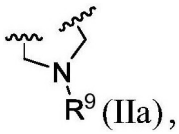
[0579] 在式(I)的进一步的实施例中，当Z^2是CR^3，每个R^5和R^6是氯，R^3是H，并且R^4是卤素(例如，氯)时，

[0580] Z^1是$-OR^7$、$-N(R^7)R^{10}$、$-SR^7$、或$-C(R^7)(R^{10})R^{11}$，其中R^7是任选取代的C_{1-3}烷环烷基、或任选取代的C_{1-3}烷杂环基，或者R^7和R^8与各自附接的原子一起连接以形成任选取代的五元或六元环，该五元或六元环任选地包括一个或两个选自氮、氧和硫的杂原子。

[0581] 在式(I)的具体实施例中，当Z^2是CR^3，R^3是H，并且R^4是卤素(例如，氯)时，

[0582] Z^1是$-OR^7$、$-N(R^7)R^{10}$、$-SR^7$、或$-C(R^7)(R^{10})R^{11}$，其中R^7是任选取代的C_{1-3}烷环烷基、或任选取代的C_{1-3}烷杂环基，或者R^7和R^8与各自附接的原子一起连接以形成任选取代的五元或六元环，该五元或六元环任选地包括一个或两个选自氮、氧和硫的杂原子。

[0583] 在式(I)的一些实施例中，当R^5是氯，R^6是溴，Z^1是$-OR^7$，Z^2是CR^3，并且R^3和R^4结合以形成根据式(IIa)的基团时：

[0584] 

(IIa)，

[0585] R^7不是甲基、乙基、正丙基、2-(N-吡唑基)乙基、2-(N-咪唑基)乙基、3-羟丙基、氰甲基、2-氯乙基、2-羟乙基、2-氧代丙基、2-(N,N-二甲氨基)乙基、二氟甲基或2-(叔丁氨基)乙基。

[0586] 在式(I)的某些实施例中，当R^5是氯，R^6是溴，Z^1是$-OR^7$，Z^2是CR^3，R^3和R^4结合以形成根据式(IIa)的基团时，

[0587] R^7不是经取代的烷基、未经取代的烷基、或未经取代的C_2烷杂芳基。

[0588] 在式(I)的一些实施例中，当R^5是氯，R^6是溴，Z^1是$-OR^7$，Z^2是CR^3，且R^3和R^4结合以形成根据式(IIa)的基团时，

[0589] R^7不是烷基或未经取代的C_2烷杂芳基。

[0590] 在式(I)的具体实施例中，当R^5是氯，R^6是溴，Z^1是$-OR^7$，Z^2是CR^3，R^3和R^4结合以形成根据式(IIa)的基团时，

[0591] R^7不是经取代的烷基、未经取代的烷基、或未经取代的C_2烷杂环基。

[0592] 在式(I)的其他实施例中，当R^5是氯，R^6是溴，Z^1是$-OR^7$，Z^2是CR^3，并且R^3和R^4结合以形成根据式(IIa)的基团时，

[0593] R^7不是烷基或C_2烷杂环基。

[0594] 在式(I)的仍然其他实施例中，当R^5是氯，R^6是溴，Z^1是-OR^7，Z^2是CR^3，并且R^3和R^4结合以形成根据式(IIa)的基团时，

[0595] R^7和R^8与各自附接的原子一起连接以形成任选取代的五元或六元环，该五元或六元环任选地包括一个或两个选自氮、氧和硫的杂原子。

[0596] 在式(I)的仍然其他实施例中，当R^5是氯，R^6是溴，Z^2是CR^3，并且R^3和R^4结合以形成根据式(IIa)的基团时，

[0597] Z是-OR^7，并且R^7和R^8结合以形成-CH_2-CH_2-。

[0598] 在式(I)的一些实施例中，当每个R^5和R^6是溴，Z^1是-OR^7，Z^2是CR^3，并且R^3和R^4结合以形成根据式(IIa)的基团时，

[0599] R^7不是甲基。

[0600] 在式(I)的具体实施例中，当每个R^5和R^6是氯，Z^1是-OR^7，Z^2是CR^3，并且R^3和R^4结合以形成根据式(IIa)的基团时，

[0601] R^7不是甲基、2-(N-咪唑基)乙基、甲氧基甲基、2-(N-吡唑基)乙基、2-(3-甲基吡唑-1-基)乙基、2-吡啶基-甲基、1,3-二甲基-1H-1,2,4-三唑-5-基-甲基、2-嘧啶基甲基、咪唑-2-基-甲基、5-甲基-异噁唑-3-基-甲基、4-甲基-咪唑-5-基-甲基、或3-甲基-1,2,4-噁二唑-5-基-甲基。

[0602] 在式(I)的其他实施例中，当每个R^5和R^6是氯，Z^1是-OR^7，Z^2是CR^3，并且R^3和R^4结合以形成根据式(IIa)的基团时，

[0603] R^7不是未经取代的烷基、经取代的烷基、未经取代的烷杂芳基、或经取代的烷杂芳基。

[0604] 在式(I)的其他实施例中，当每个R^5和R^6是氯，Z^1是-OR^7，Z^2是CR^3，并且R^3和R^4结合以形成根据式(IIa)的基团时，

[0605] R^7不是未经取代的烷基、经取代的烷基、未经取代的烷杂环基、或经取代的烷杂环基。

[0606] 在式(I)的某些实施例中，当每个R^5和R^6是氯，Z^1是-OR^7，R^7和R^8结合以形成-CH_2-CH_2-，Z^2是CR^3，并且R^3和R^4结合以形成根据式(IIa)的基团时，

[0607] R^9不是乙氧基羰基、环丁基氨基羰基、或环丁二烯基氨基羰基。

[0608] 在式(I)的其他实施例中，当每个R^5和R^6是氯，Z^1是-OR^7，R^7和R^8结合以形成-CH_2-CH_2-，Z^2是CR^3，并且R^3和R^4结合以形成根据式(IIa)的基团时，

[0609] R^9是H或-C(O)-N(H)-(直链C_{1-3}烷基)。

[0610] 在式(I)的具体实施例中，当每个R^5和R^6是卤素，Z^2是CR^3，并且R^3和R^4结合以形成根据式(IIa)的基团时，

[0611] Z是-OR^7，R^7不是甲基或2-氯乙基，并且R^9是H或-C(O)-N(H)-(直链C_{1-3}烷基)。

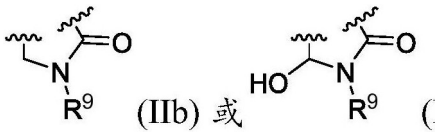
[0612] 在式(I)的一些实施例中，当R^5是甲氧基，R^6是甲基，Z^1是-OR^7，Z^2是CR^3，并且R^3和R^4结合以形成根据式(IIa)的基团时，

[0613] R^7不是甲基。

[0614] 在式(I)的某些实施例中，当R^5是氯，R^6是乙基，Z^1是-OR^7，Z^2是CR^3，且R^3和R^4结合以形成根据式(IIa)的基团时，

[0615] R^7不是甲基。

[0616] 在式(I)的一些实施例中，当每个R^5和R^6是氯，Z^1是-OR^7，Z^2是CR^3，并且R^3和R^4结合以形成根据式(IIb)或(IIc)的基团时，

[0617]  (IIb) 或 (IIc)，

[0618] R^7不是甲基或2-(N,N-二乙基氨基)乙基。

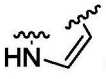
[0619] 在式(I)的其他实施例中，当每个R^5和R^6是氯，Z^1是-OR^7，Z^2是CR^3，并且R^3和R^4结合以形成根据式(IIb)或(IIc)的基团时，

[0620] R^7和R^8与各自附接的原子一起连接以形成任选取代的五元或六元环，该五元或六元环任选地包括一个或两个选自氮、氧和硫的杂原子。

[0621] 在式(I)的某些实施例中，当每个R^5和R^6是氯，Z^2是CR^3，并且R^3和R^4结合以形成根据式(IIb)或(IIc)的基团时，

[0622] Z^1是-OR^7，并且R^7和R^8结合以形成-CH_2-CH_2-。

[0623] 在式(I)的一些实施例中，当R^7是甲基，R^5是氯，Z^1是-OR^7，Z^2是CR^3，R^3和R^4结合以形成根据式(IIIa)的基团时，

[0624]  (IIIa)，

[0625] R^6不是溴。

[0626] 在式(I)的具体实施例中，当每个R^5和R^6是氯，Z^1是-OR^7，Z^2是CR^3，并且R^3和R^4结合以形成根据式(IIIa)的基团时，

[0627] R^7不是异丙基、3,3,3-三氟丙基、或2-(N,N-二甲氨基)乙基。

[0628] 在式(I)的一些实施例中，当每个R^5和R^6是氯，Z^1是-OR^7，Z^2是CR^3，并且R^3和R^4结合以形成根据式(IIIa)的基团时，

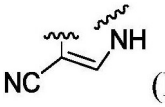
[0629] R^8不是H。

[0630] 在式(I)的一些实施例中，当Z^2是CR^3且R^3和R^4结合以形成根据式(IIIa)的基团时，

[0631] 每个R^5和R^6是氯，并且

[0632] R^7是甲基并且R^8是H，或者R^7和R^8与各自附接的原子一起连接以形成任选取代的五元或六元环，该五元或六元环任选地包括一个或两个选自氮、氧和硫的杂原子。

[0633] 在式(I)的其他实施例中，当R^5是氯，R^6是甲氧基，Z^1是-OR^7，Z^2是CR^3，并且R^3和R^4结合以形成根据式(IIIb)的基团时：

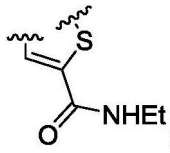
[0634]  (IIIb)，

[0635] R^1和R^2都不是2-(N,N-二乙基氨基)乙基。

[0636] 在式(I)的某些实施例中，当R^5是氯，R^6是甲氧基，Z^1是-OR^7，Z^2是CR^3，并且R^3和R^4结合以形成根据式(IIIb)的基团时：

[0637] 每个R^1和R^2是H。

[0638] 在式(I)的一些实施例中，当每个R^5和R^6是氯，Z^1是-OR^7，Z^2是CR^3，并且R^3和R^4结合以形成根据式(IVa)的基团时，

[0639] 

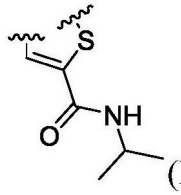
(IVa),

[0640] R^7不是3-(N-吗啉基)丙基、苄基、1-乙基-吡咯烷-3-基、1-甲基-哌啶-4-基、2-(1-甲基-吡咯烷-2-基)乙基、或3-(N,N-二乙基氨基)丙基。

[0641] 在式(I)的具体实施例中,当每个R^5和R^6是氯,Z^1是-OR^7,Z^2是CR^3,并且R^3和R^4结合以形成根据式(IVa)的基团时,

[0642] R^7不是经取代的烷基、杂环基、烷杂环基、或烷芳基。

[0643] 在式(I)的一些实施例中,当每个R^5和R^6是氯,Z^1是-OR^7,Z^2是CR^3,并且R^3和R^4结合以形成根据式(IVb)的基团时:

[0644] 

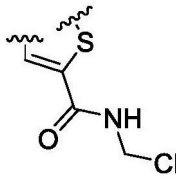
(IVb),

[0645] R^7不是2-甲氧基乙基或苄基。

[0646] 在式(I)的某些实施例中,当每个R^5和R^6是氯,Z^1是-OR^7,Z^2是CR^3,并且R^3和R^4结合以形成根据式(IVb)的基团时:

[0647] R^7不是经取代的烷基或烷芳基。

[0648] 在式(I)的一些实施例中,当每个R^5和R^6是氯,Z^1是-OR^7,Z^2是CR^3,并且R^3和R^4结合以形成根据式(IVc)的基团时:

[0649] 

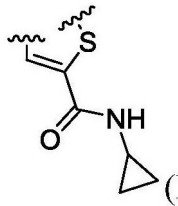
(IVc),

[0650] R^7不是2-(N,N-二乙基氨基)乙基或3-(N,N-二甲基氨基)丙基。

[0651] 在式(I)的其他实施例中,当每个R^5和R^6是氯,Z^1是-OR^7,Z^2是CR^3,并且R^3和R^4结合以形成根据式(IVc)的基团时:

[0652] R^7不是经取代的烷基。

[0653] 在式(I)的具体实施例中,当每个R^5和R^6是氯,Z^1是-OR^7,Z^2是CR^3,并且R^3和R^4结合以形成根据式(IVd)的基团时:

[0654] 

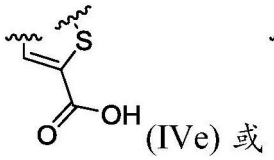
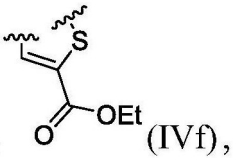
(IVd),

[0655] R^7不是2-(吡咯烷-1-基)乙基或2-羟基乙基。

[0656] 在式(I)的某些实施例中,当每个R^5和R^6是氯,Z^1是-OR^7,Z^2是CR^3,并且R^3和R^4结合以形成根据式(IVd)的基团时:

[0657] R^7不是经取代的烷基或烷杂环基。

[0658] 在式(I)的一些实施例中，当每个R^5和R^6是氯，Z^1是-OR^7，Z^2是CR^3，并且R^3和R^4结合以形成根据式(IVe)或(IVf)的基团时：

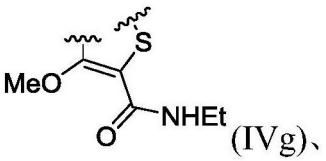
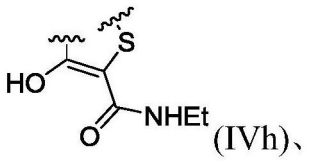
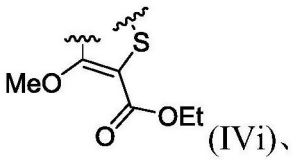
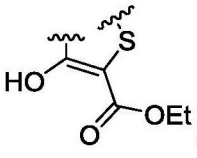
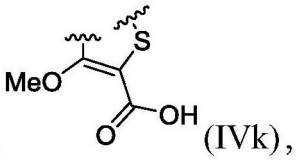
[0659] 
(IVe) 或 
(IVf)，

[0660] R^7不是苄基。

[0661] 在式(I)的其他实施例中，当每个R^5和R^6是氯，Z^1是-OR^7，Z^2是CR^3，并且R^3和R^4结合以形成根据式(IVe)或(IVf)的基团时：

[0662] R^7不是烷芳基。

[0663] 在式(I)的某些实施例中，当R^5是氯，R^6是溴，Z^1是-OR^7，Z^2是CR^3，R^3和R^4结合以形成根据式(IVg)、(IVh)、(IVi)、(IVj)、或(IVk)的基团时：

[0664] 
(IVg)、 
(IVh)、 
(IVi)、 
(IVj)、或 
(IVk)，

[0665] R^7不是甲基。

[0666] 在式(I)的某些实施例中，当R^5是氯，R^6是溴，Z^1是-OR^7，Z^2是CR^3，R^3和R^4结合以形成根据式(IVg)、(IVh)、(IVi)、(IVj)、或(IVk)的基团时，

[0667] R^7不是烷基。

[0668] 在式(I)的一些实施例中，当R^5是氯，R^6是溴，Z^1是-OR^7，Z^2是CR^3，R^3和R^4结合以形成根据式(IVg)、(IVh)、(IVi)、(IVj)、或(IVk)的基团时，

[0669] R^7和R^8与各自附接的原子一起连接以形成任选取代的五元或六元环，该五元或六元环任选地包括一个或两个选自氮、氧和硫的杂原子。

[0670] 在式(I)的具体实施例中，当R^5是氯，R^6是溴，Z^1是-OR^7，并且Z^2是CR^3时，

[0671] R^3和R^4不结合以形成根据式(IVg)、(IVh)、(IVi)、(IVj)、或(IVk)的基团。

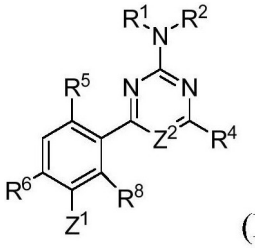
[0672] 在式(I)的具体实施例中，当R^6是甲基时，

[0673] 每个R^1和R^2是H。

[0674] 在式(I)的某些实施例中，当R^3是H，且每个R^5和R^6是氯时，

[0675] R^7不是甲基。

[0676] 在式(I)的特定实施例中，R^m是H(例如，式(I)的化合物具有以下结构：

[0677]  或其药学上可接受的盐。

(I),

[0678] 在式(I)的某些实施例中，

[0679] 在本发明的方法的一些实施例中，取代基如本文所述定义。在本发明的方法的具体实施例中，该方法包括给予哺乳动物有效量的根据式(I)的化合物。在本发明的方法的某些实施例中，该方法包括给予哺乳动物有效量的根据式(Ib)的化合物。在其他实施例中，该方法涉及给予哺乳动物有效量的根据式(Va)化合物。在某些实施例中，该方法涉及给予哺乳动物有效量的根据式(Vb)化合物。在具体实施例中，该化合物可以选自表2，(例如，化合物2、5-16、18-27、29、33-36、40-48、和58-77中的任一种，或其药学上可接受的盐)。在进一步的实施例中，该方法包括给予哺乳动物有效量的化合物38或39或其药学上可接受的盐。

[0680] 在本发明的方法的某些实施例中，该方法包括通过给予哺乳动物具有式(I)(例如，式(Ia)、(Ib)、(Va)、或(Vb))的化合物来治疗患有神经退行性障碍的哺乳动物。

[0681] 在一些实施例中，该障碍是神经退行性障碍(例如，tau蛋白病变)。神经退行性障碍可以是阿尔茨海默氏病、亨廷顿舞蹈病、进行性核上性麻痹、帕金森综合征、皮克氏病、皮质基底节变性、慢性创伤性脑病、创伤性脑损伤、或额颞痴呆。优选地，神经退行性障碍是阿尔茨海默病。在其他实施例中，该障碍是增殖性疾病(例如癌症，例如急性髓细胞性白血病、胃肠道间质瘤、胃癌、成胶质细胞瘤、肺癌、淋巴瘤、黑色素瘤、骨髓瘤、非小细胞肺癌、肾癌、小细胞肺癌、胚细胞阶段慢性骨髓性白血病、白血病、淋巴增生性障碍、转移性黑色素瘤、复发性多发性骨髓瘤、难治性多发性骨髓瘤、骨髓增生性障碍、胰腺癌、小肠癌、或实体瘤)。

[0682] 在具体实施例中，该障碍是炎性或自身免疫性疾病(例如，类风湿性关节炎、系统性红斑狼疮、或哮喘)。在某些实施例中，该障碍是心血管疾病(例如动脉粥样硬化或心肌病)。在其他实施例中，该障碍是过敏。

[0683] 在仍然另一方面，本发明的特征在于一种通过向哺乳动物给予有效量的本发明的化合物(例如，上述方面的化合物)或其药学上可接受的盐来治疗哺乳动物的传染病的方法。

[0684] 在一些实施例中，该传染病是病毒感染。在某些实施方案中，病毒感染是疱疹病毒科(例如，单纯疱疹病毒-1、单纯疱疹病毒-2、疱疹病毒-5、卡波西氏肉瘤相关的疱疹病毒、水痘带状疱疹病毒或埃-巴二氏病毒)、多瘤病毒科(例如，SV40)、痘病毒科(例如痘苗病毒)、呼肠弧病毒科(例如轮状病毒)、双RNA病毒科(例如感染性囊病病毒)、小核糖核酸病毒科(例如脊髓灰质炎病毒、鼻病毒或柯萨奇病毒)、黄病毒科(例如，丙型肝炎病毒或登革热病毒)、沙粒病毒科(例如，淋巴细胞性脉络丛脑膜炎病毒)、戊型肝炎病毒科(例如，戊型肝炎病毒)、弹状病毒科(例如，水泡性口炎病毒)、副伤寒病毒科(例如，人副流感病毒2、人副流感病毒3、SV5、SV41、麻疹病毒或仙台病毒)、布尼亚病毒科(例如，拉克罗斯病毒)、正甲型病毒科(例如，甲型流感病毒)、丝状病毒科(例如，埃博拉病毒)、逆转录病毒科(例如，HTLV1或HIV1)、或嗜肝DNA病毒科(例如，乙型肝炎病毒)的病毒。

[0685] 在具体实施例中，传染病是真菌感染(例如，白色念珠菌、烟曲霉或肺囊虫)。

[0686] 在其他实施例中，传染病是细菌感染(例如，分枝杆菌、炭疽或细菌性肺炎)。

[0687] 在本发明的方法的任何方面的一些实施例中，化合物经口、舌下、颊部、经皮、皮内、肌内、胃肠外、静脉内、动脉内、颅内、皮下、眶内、心室内、脊柱内、腹膜内、鼻内、通过吸入、以及局部进行给予。优选地，该化合物是口服给予的。

[0688] 在本发明的方法的任一方面的某些实施例中，该哺乳动物是人类。

[0689] 在进一步的方面中，本发明的特征在于一种通过使细胞与本发明的化合物或其药学上可接受的盐接触来抑制Hsp90的方法。在一些实施例中，该方法在体外进行。在其他实施例中，该方法在体内进行。

[0690] 在另一方面，本发明的特征在于一种试剂盒，包含：

[0691] (i)本发明的药物组合物；以及

[0692] (ii)使用(i)的药物组合物以治疗由Hsp90的作用引起的哺乳动物(例如，人类)障碍的说明书。

[0693] 在仍然另一方面，本发明的特征在于本发明的化合物用于在治疗由热休克蛋白90(Hsp90)的作用引起的障碍中使用。在这个方面的一些实施例中，该障碍是本发明的方法的特征方面中描述的任何一种障碍。在相关方面，本发明的特征在于本发明的化合物在用于治疗传染病中使用。在这个方面的某些实施例中，传染病是本发明的方法的特征方面中描述的任何一种传染病。

[0694] 在仍然另一方面，本发明的特征在于本发明的化合物在治疗由热休克蛋白90(Hsp90)的作用引起的障碍中的用途。在这个方面的一些实施例中，该障碍可以是本发明的方法的特征方面中描述的任何一种障碍。在相关方面，本发明的特征在于本发明的化合物在治疗传染病中的用途。在这个方面的某些实施例中，传染病是本发明的方法的特征方面中描述的任何一种传染病。

[0695] 在进一步的方面中，本发明的特征在于本发明的化合物在生产用于治疗由热休克蛋白90(Hsp90)的作用引起的障碍的药物中的用途。在这个方面的一些实施例中，该障碍可以是本发明的方法的特征方面中描述的任何一种障碍。在相关方面，本发明的特征在于本发明的化合物在生产用于治疗传染病的药物中的用途。在这个方面的某些实施例中，传染病是本发明的方法的特征方面中描述的任何一种传染病。

[0696] 定义

[0697] 化学取代基

[0698] 如在此所用，术语“约”表示为所列举值的±10％的一个值。

[0699] 本文可互换使用的术语“酰基”或“烷酰基”表示如本文所定义的烷基或通过如本文定义的羰基与母体分子基团连接的氢，且例示为甲酰基、乙酰基、丙酰基、丁酰基等。示例性的未经取代的酰基包括2至7个碳。酰基可以是未经取代的或者经取代的，与对烷基所定义的相同。

[0700] 本文定义的术语“烷芳基”表示式-(亚烷基)-(芳基)的化学取代基，其中每个基团如本文所定义，并且可以根据各自的定义是经取代的或未经取代的。

[0701] 如本文所定义的术语“烷杂环基”表示式-(亚烷基)-(杂环基)的化学取代基，其中每个基团如本文所定义，并且可根据各自的定义是经取代的或未经取代的。

[0702] 除非另有说明(例如，R是C_{1-3}烷基)，本文所用的术语“烷氧基”表示式-OR的化学取

代基，其中R是C_{1-6}烷基。烷氧基可以是未经取代的或被一个、两个、或三个独立地选自下组的取代基取代的，该组由以下各项组成：(1)1至6个碳的烷氧基；(2)羟基；(3)氨基；(4)1至6个碳的烷基氨基；(5)二烷基氨基，其中每个烷基基团独立地是1至6个碳；(6)3至8个碳的环烷基；(7)氧代；(8)卤素；(9)1至6个碳原子的烷基磺酰基；(10)1至6个碳原子的硫代烷氧基；(11)芳基；(12)$-CO_2R^A$，其中R^A选自下组，该组由以下各项组成：(a)氢、(b)烷基、(c)环烷基、(d)烷环烷基、和(e)烷芳基，其中亚烷基是1至6个碳原子的；或(13)$-C(O)NR^BR^C$，其中每个R^B和R^C独立地选自下组，该组由以下各项组成：(a)氢、(b)烷基、(c)环烷基、(d)烷环烷基、和(e)烷芳基，其中亚烷基是1至6个碳原子的；条件是不超过一个取代基(2)-(5)可以连接到烷基的单个碳原子上，并且取代基(2)-(5)都不能连接到与烷氧基的氧原子相连的碳上。不超过一个氧代取代基可以连接到烷氧基的单个碳上，并且在本文定义的任何烷氧基中可以发现不超过两个氧代取代基。

[0703] 本文所用的术语“烷氧基烷基”表示被烷氧基取代的烷基。示例性的未经取代的烷氧基烷基包括2至9个碳。在一些实施例中，烷基和烷氧基各自可以进一步被如本文对于每个相应基团所定义的1、2、3、4或5个取代基进一步取代。

[0704] 除非另有说明(例如，1至3个碳)，本文所用的术语“烷基”包括1至6个碳的直链和支链饱和基团。烷基的实例为甲基、乙基、正丙基和异丙基，并且可以任选地被一个、两个、三个，或者在两个碳或更多的烷基的情况下被四个取代基取代，该取代基独立地选自下组，该组由以下各项组成：(1)1至6个碳的烷氧基；(2)羟基；(3)氨基；(4)1至6个碳的烷基氨基；(5)二烷基氨基，其中每个烷基基团独立地是1至6个碳；(6)3至8个碳的环烷基；(7)氧代；(8)卤素；(9)1至6个碳原子的烷基磺酰基；(10)1至6个碳原子的硫代烷氧基；(11)芳基；(12)$-CO_2R^A$，其中R^A选自下组，该组由以下各项组成：(a)氢、(b)烷基、(c)环烷基、(d)烷环烷基、和(e)烷芳基，其中亚烷基是1至6个碳原子的；(13)$-C(O)NR^BR^C$，其中每个R^B和R^C独立地选自下组，该组由以下各项组成：(a)氢、(b)烷基、(c)环烷基、(d)烷环烷基、和(e)烷芳基，其中亚烷基是1至6个碳原子的，或者R^B和R^C结合以形成C_{2-9}杂环基；以及(14)氰基；条件是不超过一个取代基(2)-(5)可以连接到烷基的单个碳原子上。不超过一个氧代取代基可以连接到烷基的单个碳上，并且在本文定义的任何烷基中可以发现不超过两个氧代取代基。

[0705] 本文所用的术语“亚烷基”和前缀“烷-”表示通过除去两个氢原子的由直链或支链饱和烃衍生的饱和二价C_{1-10}烃基，并且例示为亚甲基、亚乙基、丙烯、异丙烯等。术语“C_{x-y}亚烷基”和前缀“C_{x-y}烷-”表示具有具有x和y个之间的碳的亚烷基。x的示例性值是1、2、3、4、5、和6，并且y的示例性值是2、3、4、5、6、7、8、9、或10。在一些实施例中，亚烷基可以进一步被如在此针对烷基基团所定义的1、2、3、或4个取代基基团取代。

[0706] 本文所用的术语“烷基磺酰基”表示通过$-S(O)_2-$基团连接至母体分子基团的烷基。示例性未经取代的烷基磺酰基具有1至6个碳。在一些实施例中，烷基基团可以进一步被如在此定义的1、2、3、或4个取代基基团取代。

[0707] 本文所用的术语“氨基”表示式$-NH_2$的化学取代基。氨基可以被例如，烷基、烷酰基、芳基、芳酰基、环烷基、杂环基、或杂环烷杂环基(例如，具有式-NH-的“烷基氨基”(任选取代的C_{1-6}烷基)，例如，-NH-(未经取代的C_{1-6}烷基))单取代，或者被例如，烷基、烷酰基、芳基、芳酰基、环烷基、杂环基、或杂环烷杂环基(例如，具有式-NR’R”的“二烷基氨基”，其中每个R’和R”独立地是任选取代的C_{1-6}烷基，例如，-NR’R”，其中每个R’和R”独立地是未经取代

的C_{1-6}烷基)双取代。任选取代的C_{1-6}烷基可以是C_{1-6}卤代烷基,例如,C_{1-6}氟烷基。

[0708] 本文所用的术语“氨基烷基”表示被氨基取代的烷基。每个烷基和氨基可以是独立地经取代的或未经取代的,如本文对于每个相应基团所定义。

[0709] 本文所用的术语“芳基”表示具有三至十二个碳且具有一个或两个芳环的单环、双环或多环碳环系统。芳基的非限制性实例包括苯基、萘基、1,2-二氢萘基、1,2,3,4-四氢萘基、芴基、茚满基、茚基等。芳基可任选地被一个、两个、三个、四个或五个取代基取代,该取代基独立地选自下组,该组由以下各项组成:(1)1至6个碳的烷基;(2)1至6个碳的烷氧基;(3)羟基;(4)氨基;(5)1至6个碳的烷基氨基;(6)二烷基氨基,其中每个烷基基团独立地是1至6个碳;(7)3至8个碳的环烷基;(8)氧代;(9)卤素;(10)1至6个碳原子的烷基磺酰基;(11)1至6个碳原子的硫代烷氧基;(12)芳基;(13)烷芳基,其中亚烷基是1至6个碳原子的;(14)$-CO_2R^A$,其中R^A选自下组,该组由以下各项组成:(a)烷基、(b)环烷基、(c)烷环烷基、(d)烷芳基、和(e)卤素,其中亚烷基是1至6个碳原子的;和(15)$-C(O)NR^BR^C$,其中每个R^B和R^C独立地选自下组,该组由以下各项组成:(a)烷基、(b)环烷基、(c)烷环烷基、(d)烷芳基、和(e)卤素,其中亚烷基是是1至6个碳原子的。

[0710] 本文所用的术语“芳酰基”表示通过烷基与母体分子基团连接的芳基。

[0711] 本文所用的术语“羰基”表示C(O)基团,其也可以表示为C=O,并且由四价碳原子和氧代取代基的组合产生。

[0712] 本文所用的术语“氰基”表示-CN基团。

[0713] 本文所用的术语“氰烷基”表示被氰基取代的烷基。示例性未经取代的氰烷基包括2至9个碳。在一些实施例中,该烷基可以进一步被各个相应基团的1、2、3、4、或5个如本文所定义的取代基进一步取代。

[0714] 除非另有说明,否则本文所用的术语“环烷基”表示3至8个碳的一价饱和或不饱和非芳族环状烃基,且例示为环丙基、环丁基、环戊基、环己基、环庚基、双环[2.2.1.]庚基等。环烷基可以任选地被例如,一个、两个、三个、或四个取代基取代,所述取代基独立地选自:(1)1至6个碳的烷基;(2)1至6个碳的烷氧基;(3)羟基;(4)氨基;(5)1至6个碳的烷基氨基;(6)二烷基氨基,其中每个烷基基团独立地是1至6个碳;(7)3至8个碳的环烷基;(8)氧代;(9)卤素;(10)1至6个碳原子的烷基磺酰基;(11)1至6个碳原子的硫代烷氧基;(12)芳基;(13)烷芳基,其中亚烷基是1至6个碳原子的;(14)$-CO_2R^A$,其中R^A选自下组,该组由以下各项组成:(a)烷基、(b)环烷基、(c)烷环烷基、(d)烷芳基、和(e)卤素,其中亚烷基是1至6个碳原子的;或(15)$-C(O)NR^BR^C$,其中每个R^B和R^C独立地选自下组,该组由以下各项组成:(a)烷基、(b)环烷基、(c)烷环烷基、(d)烷芳基、和(e)卤素,其中亚烷基是1至6个碳原子的,或者R^B和R^C结合以形成C_{2-9}杂环基。

[0715] 本文所用的术语“五元环”表示在环状阵列中具有五个原子的饱和或不饱和的芳族或非芳族基团,其中除非另有说明,四个原子是碳,剩余的原子选自由碳、氮、硫和氧组成的组。五元环可以与选自杂环基、杂芳基、环烷基和芳基的另一个环基团稠合。五元环可以是未经取代的或被例如,一个、两个、三个、或四个独立地选自下组的取代基取代的,该组由以下各项组成:(1)1至6个碳的烷氧基;(2)羟基;(3)氨基;(4)1至6个碳的烷基氨基;(5)二烷基氨基,其中每个烷基基团独立地是1至6个碳;(6)3至8个碳的环烷基;(7)氧代;(8)1至6个碳原子的烷基磺酰基;(9)1至6个碳原子的硫代烷氧基;(10)芳基;(11)烷芳基,其中亚烷

基是1至6个碳原子的；(12)任选取代的1至6个碳的烷基(例如，未经取代的烷基、烷氧基烷基、羟基烷基、卤代烷基或氰烷基)；(13)-CO_2R^A，其中R^A选自下组，该组由以下各项组成：(a)烷基、(b)环烷基、(c)烷环烷基、(d)烷芳基、和(e)卤素，其中亚烷基是1至6个碳原子的；(14)-C(O)NR^BR^C，其中每个R^B和R^C独立地选自下组，该组由以下各项组成：(a)任选取代的烷基(例如，未经取代的烷基、烷氧基烷基、羟烷基、卤代烷基、或氰烷基)、(b)环烷基、(c)烷环烷基、(d)烷芳基、(e)杂环基、(f)烷杂环基、(g)烷氧基、和(h)卤素，其中亚烷基是1至6个碳原子的，或者R^B和R^C结合以形成C_{2-9}杂环基；和(15)氰基。

[0716] 本文所用的术语“氟代烷基”表示如本文所定义的烷基，其中与烷基结合的一个或多个氢基团(例如，1、2、3、4、或5个或更多个氢基团)被氟基团取代。在一些实施例中，氟烷基可以是全氟烷基。前缀“氟”表示所述基团被一个或多个(例如，1、2、3、4或5个或更多个)氟基团取代。

[0717] 如在此所用，术语“卤代烷基”表示被一个卤素基团(即，F、Cl、Br、或I)取代的如在此所定义的一个烷基基团。C_{1-6}卤代烷基可以被一个、两个、三个，或者在两个或更多个碳的烷基的情况下，被四、或五个卤素取代。卤代烷基基团包括全氟烷基。在某些实施例中，卤代烷基是氟烷基。在一些实施例中，C_{1-6}卤代烷基可以进一步被1、2、3或4个如本文对烷基所述的取代基取代。

[0718] 本文中可互换使用的术语“卤素(halogen)”、“卤(hal)”或“卤代(halo)”表示选自氟(-F)、氯(-Cl)、溴(-Br)和碘(-I)的基团。前缀“卤素”表示所述基团被卤素基团(即F、Cl、Br或I)取代。

[0719] 除非另有说明，本文所用的术语“杂环基”表示含有一个、两个、三个或四个独立地选自氮、氧和硫的杂原子的5-、6-或7-元环。5元环具有0至2个双键，并且6元环和7元环具有0至3个双键。术语“杂环基”还表示具有一个桥联的多环结构的一种杂环化合物，其中一个或多个碳和/或杂原子桥联一个单环的两个非相邻成员，例如一个奎宁环基基团。术语“杂环基”还包括双环、三环和四环基团，其中任何上述杂环与一个、两个、或三个碳环稠合，例如芳环、环己烷环、环己烯环、环戊烷环、环戊烯环或另一单环杂环，例如吲哚基、喹啉基、异喹啉基、四氢喹啉基、苯并呋喃基、苯并噻吩基等。稠合杂环基的实例包括萘萘烷和1,2,3,5,8,8a-六氢吲嗪。杂环包括吡咯基、吡咯啉基、吡咯烷基、吡唑基、吡唑啉基、吡唑烷基、咪唑基、咪唑啉基、咪唑烷基、吡啶基、哌啶基、高哌啶基、吡嗪基、哌嗪基、嘧啶基、哒嗪基、噁唑基、噁唑烷基、异噁唑基、异噁唑烷基、吗啉基、硫代吗啉基、噻唑基、噻唑烷基、异噻唑基、异噻唑烷基、吲哚基、喹啉基、异喹啉基、苯并咪唑基、苯并噻唑基、苯并噁唑基、呋喃基、噻吩基、噻唑烷基、异噻唑基、异吲唑基(isoindazoyl)、三唑基、四唑基、噁二唑基、嘌呤基(uricyl)、噻二唑基、四氢呋喃基、二氢呋喃基、四氢噻吩基、二氢噻吩基、二氢吲哚基、四氢喹啉基、四氢异喹啉基、吡喃基、二氢吡喃基、二噻唑基、苯并呋喃基、苯并噻吩基等。杂环基可任选地被一个、两个、三个、四个或五个取代基取代，该取代基独立地选自下组，该组由以下各项组成：(1)1至6个碳的烷基；(2)1至6个碳的烷氧基；(3)羟基；(4)氨基；(5)1至6个碳的烷基氨基；(6)二烷基氨基，其中每个烷基基团独立地是1至6个碳；(7)3至8个碳的环烷基；(8)氧代；(9)卤素；(10)1至6个碳原子的烷基磺酰基；(11)1至6个碳原子的硫代烷氧基；(12)芳基；(13)烷芳基；(14)-CO_2R^A，其中R^A选自下组，该组由以下各项组成：(a)烷基、(b)环烷基、(c)烷环烷基、(d)烷芳基、和(e)卤素，其中亚烷基是1至6个碳原子的；或(15)-C(O)

NR^BR^C，其中每个R^B和R^C独立地选自下组，该组由以下各项组成：(a)烷基、(b)环烷基、(c)烷环烷基、(d)烷芳基、和(e)卤素，其中亚烷基是1至6个碳原子的，或者R^B和R^C结合以形成C_{2-9}杂环基。

[0720] 如在此所用，术语“杂芳基”表示为芳香族的如在此所定义的杂环基的子集：即，它们在单环或多环环系统内含有4n+2个π电子。在一些实施例中，杂芳基被例如1、2、3或4个独立地选自下组的取代基取代，该组由以下各项组成：(1)1至6个碳的烷基；(2)1至6个碳的烷氧基；(3)羟基；(4)氨基；(5)1至6个碳的烷基氨基；(6)二烷基氨基，其中每个烷基基团独立地是1至6个碳；(7)3至8个碳的环烷基；(8)氧代；(9)卤素；(10)1至6个碳原子的烷基磺酰基；(11)1至6个碳原子的硫代烷氧基；(12)芳基；(13)烷芳基；(14)$-CO_2R^A$，其中R^A选自下组，该组由以下各项组成：(a)烷基、(b)环烷基、(c)烷环烷基、(d)烷芳基、和(e)卤素，其中亚烷基是1至6个碳原子的；或(15)$-C(O)NR^BR^C$，其中每个R^B和R^C独立地选自下组，该组由以下各项组成：(a)烷基、(b)环烷基、(c)烷环烷基、(d)烷芳基、和(e)卤素，其中亚烷基是1至6个碳原子的。

[0721] 本文所用的术语“羟基”表示-OH基团。

[0722] 本文所用的术语“羟基烷基”表示被一个或两个羟基取代的如本文定义的烷基，条件是不超过一个羟基可以连接到烷基的单个碳原子上，并且示例为羟甲基、二羟丙基等。

[0723] 本文所用的术语“N-保护的氨基”是指如本文所定义的氨基，其连接有如本文定义的N-保护基团。

[0724] 本文所用的术语“N-保护基团”表示旨在保护氨基在合成过程中防止不期望的反应的那些基团。常用的N-保护基公开于格林(Greene)，《有机合成中的保护基》(Protective Groups in Organic Synthesis)，第3版(约翰·威利父子公司(John Wiley&Sons)，纽约，1999))，其通过引用并入本文。N-保护基包括酰基、芳酰基或氨基甲酰基，例如甲酰基、乙酰基、丙酰基、新戊酰基、叔丁基乙酰基、2-氯乙酰基、2-溴乙酰基、三氟乙酰基、三氯乙酰基、邻苯二甲酰基、邻硝基苯氧基乙酰基、α-氯丁酰基、苯甲酰基、4-氯苯甲酰基、4-溴苯甲酰基、4-硝基苯甲酰基和手性助剂，例如，受保护或未受保护的D,L或D,L-氨基酸，例如丙氨酸、亮氨酸、苯丙氨酸等；磺酰基，例如苯磺酰基、对甲苯磺酰基等；氨基甲酸酯形成基团，例如苄氧羰基、对氯苄氧羰基、对-甲氧基苄氧羰基、对硝基苄氧羰基、2-硝基苄氧羰基、对-溴苄氧羰基、3,4-二甲氧基苄氧羰基、3,5-二甲氧苄氧羰基、2,4-二甲氧苄氧羰基、4--甲氧苄氧羰基、2-硝基-4,5-二甲氧基苄氧羰基、3,4,5-三甲氧基苄氧基羰基、1-(对联苯基)-1-甲基乙氧基羰基、α,α-二甲基-3,5--二甲氧基苄氧羰基、苯甲酰氧基羰基、叔丁氧羰基、二异丙基甲氧羰基、异丙氧羰基、乙氧羰基、甲氧羰基、烯丙氧羰基、2,2,2,-三氯乙氧基羰基、苯氧基羰基、4-硝基苯氧基羰基、芴基-9-甲氧基羰基、环戊氧基羰基、金刚烷氧基羰基、环己氧基羰基、苯硫基羰基等，芳烷基例如苄基、三苯甲基、苄氧基甲基等和甲硅烷基，例如三甲基甲硅烷基等。优选的N-保护基是甲酰基、乙酰基、苯甲酰基、新戊酰基、叔丁基乙酰基、丙氨酰基、苯磺酰基、苄基、叔丁氧羰基(Boc)和苄氧羰基(Cbz)。

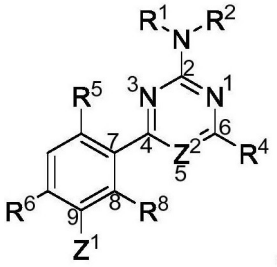
[0725] 本文所用的术语“六元环”表示在环状阵列中具有六个原子的饱和或不饱和的芳族或非芳族基团，其中除非另有说明，五个原子是碳，剩余的原子选自由碳、氮、硫和氧组成的基团。六元环可以与选自杂环基、杂芳基、环烷基和芳基的另一个环基稠合。六元环可以是未经取代的或被例如，一个、两个、三个、或四个独立地选自下组的取代基取代的，该组由

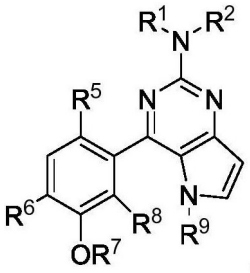
以下各项组成：(1)1至6个碳的烷基；(2)1至6个碳的烷氧基；(3)羟基；(4)氨基；(5)1至6个碳的烷基氨基；(6)二烷基氨基，其中每个烷基基团独立地是1至6个碳；(7)1至8个碳环烷基；(8)氧代；(9)1至6个碳原子的烷基磺酰基；(10)1至6个碳原子的硫代烷氧基；(11)芳基；(12)烷芳基，其中亚烷基是1至6个碳原子的；(13)$-CO_2R^A$，其中R^A选自下组，该组由以下各项组成：(a)烷基、(b)环烷基、(c)烷环烷基、(d)烷芳基、和(e)卤素，其中亚烷基是1至6个碳原子的；(14)$-C(O)NR^BR^C$，其中每个R^B和R^C独立地选自下组，该组由以下各项组成：(a)烷基、(b)环烷基、(c)烷环烷基、(d)烷芳基、和(e)卤素，其中亚烷基是1至6个碳原子的，或者R^B和R^C结合以形成C_{2-9}杂环基；和(15)氰基。

[0726] 本文所用的术语“硫代烷氧基”表示式-SR的化学取代基，其中R是烷基。在一些实施例中，烷基可以进一步被1、2、3、或4个如本文对烷基所述的取代基取代。

[0727] 本文所用的术语“硫醇”表示式-SH的化学取代基。

[0728] 当提及本发明化合物中的编号位置时，使用以下编号系统：

[0729]  例如，表述“R^3和R^4结合以形成$-N(R^9)-CH=CH-$”表示$-N(R^9)-CH=CH-$的氮原子可邻近C^5碳或C^6碳。表述“R^3和R^4结合以形成$-N(R^9)-CH=CH-$”与“$-N(R^9)-CH=CH-$的氮原子邻近C^5”结合表示以下化合物：

[0730] 

[0731] 不对称或手性中心可存在于本发明的任何化合物中。本发明涵盖各种立体异构体及其混合物。本发明化合物的单独立体异构体由含有不对称或手性中心的可商购的起始材料合成制备，或通过制备对映异构体化合物的混合物，然后通过本领域普通技术人员所熟知的分离合成制备。这些分离方法的示例如下：(1)将指定为(+/-)的对映异构体的外消旋混合物连接到手性助剂上，通过重结晶或色谱法分离所得非对映异构体，并从辅助剂中释放光学纯产物，或(2)在手性色谱柱上或通过手性HPLC方法直接分离光学对映异构体的混合物。之前已经描述了手性分离的方法(G.B.科克斯(Cox)(编辑)在《制备型对映选择性色谱》(Preparative Enantioselective Chromatography)，2005，布莱克威尔出版社(Blackwell Publishing))。可替代地，手性化合物可以通过不对称合成制备，其有利于制备一种对映异构体而不是另一种对映异构体。可替代地，可以使用手性池合成(从对映体纯的结构单元开始)，其中手性基团或中心保留在中间体或最终产物中。对映异构体在本文中用符号“R”或“S”表示，这取决于手性原子周围的取代基的构型。可替代地，依赖于对映异构体的溶液是否分别使偏振光平面顺时针或逆时针旋转，将对映异构体指定为(+)或(-)。

[0732] 几何异构体也可存在于本发明的化合物中。本发明涉及由围绕碳-碳双键的取代基排列产生的各种几何异构体及其混合物，并且指定Z或E构型这样的异构体，其中术语“Z”表示在碳-碳双键同一侧上的取代基，术语“E”表示在碳-碳双键的相对侧上的取代基。还认识到，对于其中可能存在互变异构形式的结构，除非另有说明，一种互变异构形式的描述等同于对两者的描述。

[0733] 本发明化合物中的每个位置可以包括其天然同位素丰度的元素。可替代地，本发明化合物中的一个或多个位置可包括富含天然存在或合成的同位素的元素。例如，包括氢的本发明化合物的一个或多个位置可以用例如，氘或氚进行富集。在一些实施例中，包括碳的本发明化合物的一个或多个位置可以用例如^{14}C或^{13}C富集。在其他实施例中，包括氮的本发明的化合物的一个或多个位置上可以用例如^{15}N来富集。在某些实施例中，包括氧的本发明的化合物的一个或多个位置上可以用例如^{18}O、^{17}O、或^{15}O来富集。在具体实施例中，包括氟的本发明的化合物的一个或多个位置上可以用例如^{18}F来富集。在其他实施例中，包括碳的本发明的化合物的一个或多个位置上可以用例如^{32}S、^{33}S、^{34}S、^{35}S、或^{36}S来富集。在仍然其他实施例中，包括氯的本发明的化合物在一个或多个位置上可以用例如^{35}Cl、^{36}Cl、或^{37}Cl来富集。

[0734] 在此使用的一些缩写：

[0735] BINAP-2,2’-二(二苯基膦)-1,1’-联萘；

[0736] t-Bu-叔丁基或1,1-二甲基乙基；

[0737] cat-邻苯二酚；

[0738] dppb-二(二苯基膦)丁烷；

[0739] dppf-二(二苯基膦)二茂铁；

[0740] Et-乙基；

[0741] Me-甲基；

[0742] OAc-乙酸酯；

[0743] OMs-甲磺酸或甲磺酸盐；

[0744] ONf-九氟丁基磺酸盐或九氟正丁基磺酸盐；

[0745] OTf-三氟甲磺酸酯或三氟甲磺酸盐；

[0746] pin-频那醇；

[0747] i-Pr-异丙基或1-甲基乙基；以及

[0748] n-Pr-n-丙基；

[0749] SIMes-1,3-二(2,4,6-三甲苯基)咪唑啉-2-亚基；

[0750] SIPr-1,3,-二(2,6-二异丙基苯基)咪唑啉-2-亚基；以及

[0751] THF-四氢呋喃。

[0752] 其他术语

[0753] 术语“约”在本文中用于表示所述值的±10％的值。

[0754] 术语“有效量”或“对……有效的量”或“治疗有效量”是指足以产生所需结果的本发明化合物的量，例如一种或多种Hsp90活性的降低(例如抑制的Hsp90)、Hsp70的表达增加、Aβ肽的聚集减少(例如，Aβ肽的聚集的抑制)，Aβ肽的降解的增加和tau蛋白的磷酸化的减少，和/或在给予含有本发明化合物的组合物时，受试者的神经退行性疾病(例如，阿尔茨

海默氏病)的症状的减轻或改善。与给予有效量的化合物相关的增加和减少是相对于未给予本发明化合物的受试者的水平或症状(如适用)或相对于给予本发明化合物之前的受试者。

[0755] 本文所用的术语“元素”是指由单一类型的原子组成的物质,即,单个元素的每个原子的每个核包含相同数量的质子。

[0756] 本文所用的术语“神经退行性”是指神经元的结构或功能的进行性丧失,包括神经元的死亡。术语“神经变性疾病”是指其中神经变性至少部分是原因、症状或表型的疾病。

[0757] 如本文可互换使用的术语“患者”和“受试者”是指任何动物(例如,哺乳动物,例如人)。待根据本文所述的方法治疗的受试者可以是已经被诊断患有神经退行性疾病例如tau蛋白病变(例如阿尔茨海默病)或增殖性疾病(如具有这样的病症或处于患上疾病风险中)的人。诊断可以通过本领域已知的任何方法或技术进行。本领域技术人员将理解,根据本发明治疗的受试者可能已经进行标准测试,或者可能由于存在一种或多种风险因素而未经检查而鉴定为高风险的受试者,这些风险因素例如与来自健康受试者的样品中的水平相比,来自受试者的样品(例如脑脊液)中tau蛋白的总水平增加或磷酸化tau蛋白水平增加。

[0758] 本文所用的术语“药物组合物”表示含有本文所述化合物的组合物,其与药学上可接受的赋形剂一起配制,并且在政府管理机构批准下作为治疗哺乳动物疾病的治疗方案的一部分制造或出售。药物组合物可以配制成用于例如口服给予的单位剂型(例如片剂、胶囊、囊片、软胶囊、或糖浆);用于局部给予(例如,作为乳膏、凝胶、洗剂、或软膏);用于静脉内给予(例如,作为无颗粒栓塞的无菌溶液和在适于静脉内使用的溶剂体系中);或本文所述的任何其他制剂。

[0759] 本文可互换使用的术语“药学上可接受的赋形剂”或“药学上可接受的载体”是指除了本文所述的化合物之外的任何成分(例如,能够悬浮或溶解活性化合物的载体),并且其在患者中具有无毒并且非炎性的性质。赋形剂可包括例如:抗粘附剂、抗氧化剂、粘合剂、涂层、压缩助剂、崩解剂、染料(颜料)、润肤剂、乳化剂、填充剂(稀释剂)、成膜剂或涂层、香料、香精、助流剂(流动增强剂)、润滑剂、防腐剂、印刷油墨、吸附剂、悬浮剂或分散剂、甜味剂或水合水。示例性赋形剂包括但不限于:丁基化羟基甲苯(BHT)、碳酸钙、磷酸钙(二碱价)、硬脂酸钙、交联羧甲基纤维素、交联聚乙烯吡咯烷酮、柠檬酸、交联聚维酮、半胱氨酸、乙基纤维素、明胶、羟丙基纤维素、羟丙基甲基纤维素、乳糖、硬脂酸镁、麦芽糖醇、甘露醇、甲硫氨酸、甲基纤维素、对羟基苯甲酸甲酯、微晶纤维素、聚乙二醇、聚乙烯吡咯烷酮、聚乙烯吡咯烷酮、预胶化淀粉、对羟基苯甲酸丙酯、棕榈酸视黄酯、虫胶、二氧化硅、羧甲基纤维素钠、柠檬酸钠、淀粉羟乙酸盐、山梨醇、淀粉(玉米)、硬脂酸、硬脂酸、蔗糖、滑石、二氧化钛、维生素A、维生素E、维生素C和木糖醇。

[0760] 本文所用的术语“药学上可接受的前药”表示本发明化合物的那些前药,其在合理的医学判断范围内,适用于与人和动物的组织接触,具有不当的毒性、刺激、过敏反应等,具有合理的利益/风险比,并且对于它们的预期用途是有效的。

[0761] 如在此所使用的术语“药学上可接受的盐”表示在合理医学判断的范围内,适于与人类和动物的组织接触使用而无不当毒性、刺激、过敏反应等并且与合理的效益/风险比相称的盐。药学上可接受的盐是本领域公知的。例如,药学上可接受的盐描述于:贝格尔(Berge)等人,《药物科学杂志》(J.Pharmaceutical Sciences)66:1-19,1977和《药用盐:属

性、选择、和用途》(Pharmaceutical Salts:Properties,Selection,and Use),(P.H.斯特尔(Stahl)和C.G.韦穆特(Wermuth)编),Wiley-VCH,2008。这些盐可以在如本文中描述的化合物的最终分离和纯化过程中原位制备,或者通过使游离碱基团与适合的有机酸反应而单独地制备。代表性的酸加成盐包括乙酸盐、己二酸盐、藻酸盐、抗坏血酸盐、天冬氨酸盐、苯磺酸盐、苯甲酸盐、硫酸氢盐、硼酸盐、丁酸盐、樟脑酸盐、樟脑磺酸盐、柠檬酸盐、环戊烷、二葡糖酸盐、十二烷基硫酸盐、乙磺酸盐、富马酸盐、葡庚糖酸盐、甘油磷酸盐、半硫酸盐、庚酸酯、己盐、氢溴酸盐、盐酸盐、氢碘酸盐、2-羟基-乙磺酸盐、乳糖酸盐、乳酸盐、月桂酸盐、月桂基硫酸盐、苹果酸盐、马来酸盐、丙二酸盐、甲磺酸盐、2-萘磺酸盐、烟酸盐、硝酸盐、油酸盐、草酸盐、棕榈酸盐、扑酸盐、果胶酸盐、过硫酸盐、3-苯基、磷酸盐、苦味酸盐、新戊酸盐、丙酸盐、硬脂酸盐、琥珀酸盐、硫酸盐、酒石酸盐、硫氰酸盐、甲苯磺酸盐、十一酸盐、戊酸盐等。代表性的碱金属或碱土金属盐包括钠、锂、钾、钙、镁等,以及无毒的铵、季铵和胺阳离子,包括但不限于铵、四甲基铵、四乙基铵、甲胺、二甲胺、三甲胺、三乙胺、乙胺等。

[0762] 本文所用的术语“药学上可接受的溶剂化物”是指如本文所述的化合物,其中合适溶剂的分子并入晶格中。合适的溶剂在给药剂量下是生理上可耐受的。例如,溶剂化物可以通过结晶、重结晶或从包括有机溶剂、水或其混合物的溶液中沉淀来制备。合适溶剂的实例是乙醇、水(例如,一水合物、二水合物和三水合物)、N-甲基吡咯烷酮(NMP)、二甲基亚砜(DMSO)、N,N’-二甲基甲酰胺(DMF)、N,N’-二甲基乙酰胺(DMAC)、1,3-二甲基-2-咪唑啉酮(DMEU)、1,3-二甲基-3,4,5,6-四氢-2-(1H)-嘧啶酮(DMPU)、乙腈(ACN)、丙二醇、乙酸乙酯、苄醇、2-吡咯烷酮、苯甲酸苄酯等。当水是溶剂时,该分子被称为“水合物”。

[0763] 本文可互换使用的分子的缩写“PSA”和术语“极性表面积”定义为在所有极性原子上的表面和。PSA的单位为$Å^2$(埃平方)。

[0764] 本文所用的术语“预防”是指预防本文所述的疾病、病症或病状的一种或多种症状或病状的预防性治疗或治疗。包括给予本文所述的化合物或其药学上可接受的盐或其药物组合物的预防性治疗可以是急性、短期或慢性的。给予的剂量可以在预防性治疗过程中变化。

[0765] 本文所用的术语“前药”表示在体内快速转化为上式的母体化合物的化合物,例如通过在血液中水解。本文所述的化合物的前药可以是常规的酯。已经用作前药的一些常见的酯是苯基酯、脂族(C_1-C_8或C_8-C_{24})酯、胆固醇酯、酰氧基甲基酯、氨基甲酸酯、和氨基酸酯。例如,含有OH基团的化合物可以在其前药形式的该位置上被酰化。详细讨论提供于《A.C.S.研讨会系列》(A.C.S.Symposium Series),爱德华·B·罗氏(Edward B.Roche)编,第14卷,“作为新型递送系统的前药(Pro-drugs as Novel Delivery Systems)”,通口(Higuchi)和斯特拉(Stella),《药物设计的生物可逆性载体》(Bioreversible Carriers in DrugDesign),美国药学协会和培格曼出版社(American Pharmaceutical Association and Pergamon Press),1987,及贾金斯(Judkins)等人,合成通信(Synthetic Communications),26(23):4351-4367,1996,其各自通过引用并入本文。优选地,本发明化合物的前药适用于与人和动物的组织接触,具有不当的毒性、刺激、过敏反应等,与合理的利益/风险比相称,并且对于它们的预期用途是有效的。

[0766] 本文所用的术语“增殖性疾病”是指癌症和非癌症疾病。增殖性疾病是以某种类型的细胞(例如,星形胶质细胞)的不受调节的增殖为特征的疾病。优选地,与增殖性疾病(例

如癌症)相关的肿瘤细胞通过凋亡来响应Hsp90的抑制。使用本发明的化合物并根据本发明的方法治疗的增殖性疾病可包括神经胶质瘤、脑膜瘤、垂体腺瘤、神经鞘瘤(例如,神经鞘瘤或神经纤维瘤)。本发明范围内的增殖性疾病可以是癌症,例如,急性骨髓性白血病、胃肠道间质瘤、胃癌、肺癌、淋巴瘤、黑素瘤、骨髓瘤、非小细胞肺癌、肾癌、小细胞肺癌、胚期慢性骨髓性白血病、白血病、淋巴增生性障碍、转移性黑素瘤、复发性多发性骨髓瘤、难治性多发性骨髓瘤、骨髓增生性障碍、胰腺癌、小肠癌或实体瘤。优选地,根据本发明的方法使用本发明化合物治疗的增殖性疾病可以包括脑肿瘤(例如,恶性脑肿瘤)。例如,可用本发明的血脑屏障渗透剂化合物治疗的脑肿瘤可以是神经胶质瘤或脑膜瘤,特别是神经胶质瘤(例如胶质母细胞瘤)或其恶性形式。根据本发明可以治疗的癌症还可以是已转移到脑的癌症(例如肺癌、乳腺癌、黑素瘤、结肠癌、肾癌和甲状腺癌)。

[0767] 如在此所使用,并且如在本领域中很好地理解,“治疗”是一种用于获得有益的或所希望的结果(例如,临床结果)的途径。有益的或所希望的结果可以包括但不限于一种或多种症状或病状的缓和或改善;疾病、病症或病状的程度的缩减;疾病、病症或病状的稳定状态(即,未恶化);阻止疾病、病症或病状的传播;疾病、病症或病状的进展的延迟或减缓;疾病、病症或病状的改善或减轻;以及缓解(不管是部分缓解还是完全缓解),不管是可检测的还是不可检测的。“减轻”疾病、病症或病状意指与缺乏治疗下的程度或时间进程相比,该疾病、病症或病状的程度和/或不良临床表现减少和/或进展的时间进程被减缓或加长。

[0768] 附图简要说明

[0769] 图1示出了化合物20在$CDCl_3$中的500MHz ^1H NMR光谱。

[0770] 图2示出了化合物34在$CDCl_3$中的500MHz ^1H NMR光谱。

[0771] 图3示出了化合物36在$CDCl_3$中的500MHz ^1H NMR光谱。

[0772] 图4示出了提供化合物20、36、37和39以及已知Hsp90抑制剂的IC_{50}数据的五幅图,如使用实例2中所述的荧光偏振测定法测量的。

[0773] 图5A示出了比较相对结合/解离速率与化合物20的浓度的图。

[0774] 图5B是示出在基于细胞的功能测定中Hsp70在较高浓度的化合物20的表达增加的凝胶照片。此外,图5B示出了相对于化合物20的浓度变化,Hsp90的表达保持不变。

[0775] 图6A示出了比较活细胞(VC)、与化合物20接触的细胞和与对照化合物(JNK抑制剂)接触的细胞的细胞活力%的直方图。

[0776] 图6B示出了比较活细胞(VC)、与化合物20接触的细胞和与对照化合物(JNK抑制剂)接触的细胞的pTau231水平的图。

[0777] 图6C示出了比较活细胞(VC)、与化合物20接触的细胞和与对照化合物(JNK抑制剂)接触的细胞中的pTau396水平的图。

[0778] 图7示出了小鼠血浆中化合物20的浓度的图。该图中的数据排除了动物IRN 12中化合物20的血浆水平。

[0779] 图8示出了小鼠血浆中化合物20的浓度的图。该图中的数据包括所有小鼠等离子体数据点。

[0780] 图9示出了小鼠脑组织中化合物20的浓度的图。该图中的数据排除了动物IRN 12中化合物20的血浆水平。

[0781] 图10示出了小鼠脑组织中化合物20的浓度的图。该图中的数据包括所有小鼠脑组

织数据点。

[0782] 详细描述

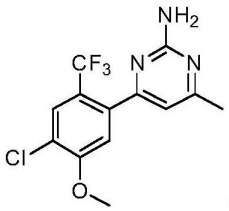
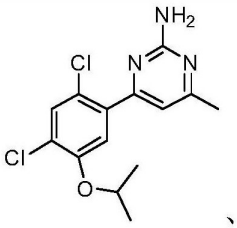
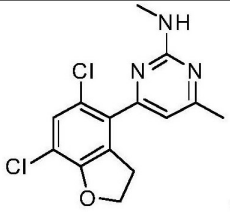
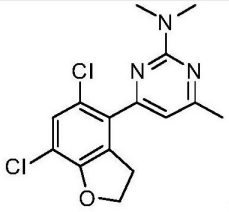
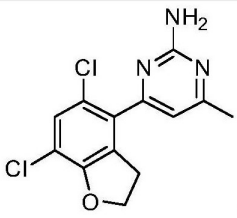
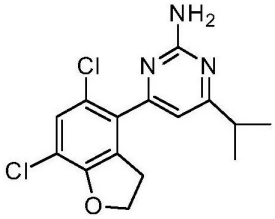
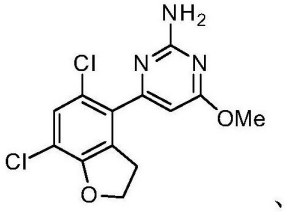
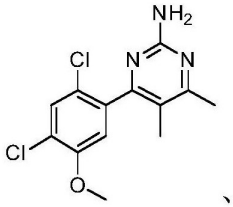
[0783] 本发明的特征在于新型氨基嘧啶和具有Hsp90抑制活性的相关化合物、含有它们的药物组合物及其医学用途(例如,治疗增殖性疾病(例如,癌症)或神经退行性疾病(例如,tau蛋白病变))。具体而言,本发明的化合物能够穿透血脑屏障。因此,这些化合物的医学用途包括折磨哺乳动物(例如,人)大脑的疾病和病症。

[0784] 本发明的化合物

[0785] 表2示出了本发明的示例性化合物。

[0786] 表2.

[0787]

1		2		3	
4		5		6	
7		8		9	

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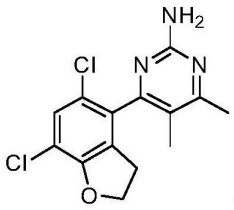
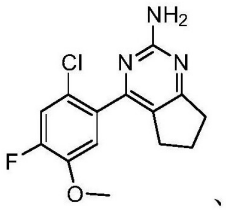
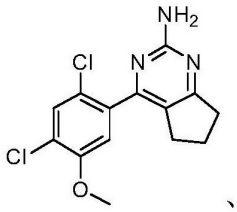
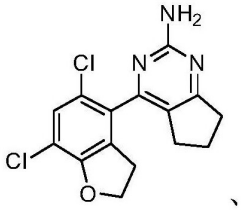
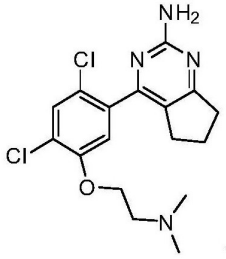
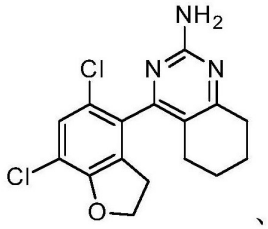
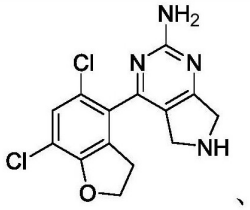
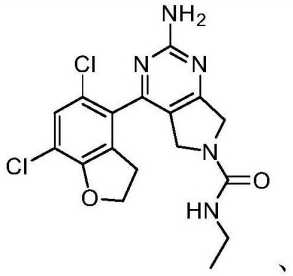
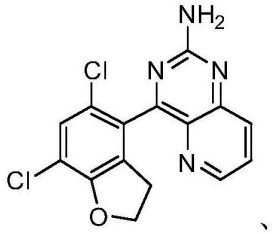
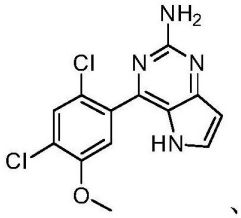
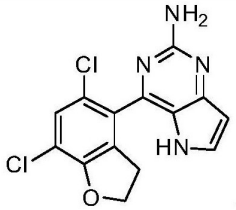
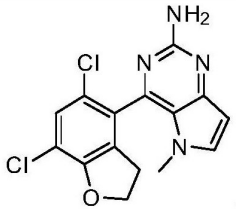
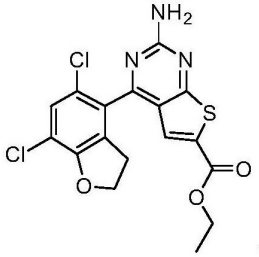
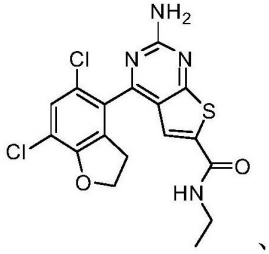
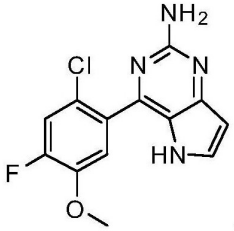
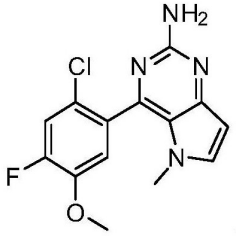
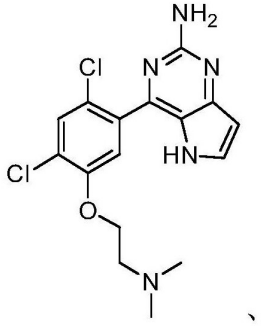
10		11		12	
13		14		15	
16		17		18	
19		20		21	
22		23		24	
25		26		27	

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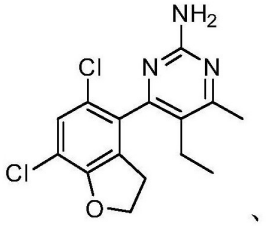
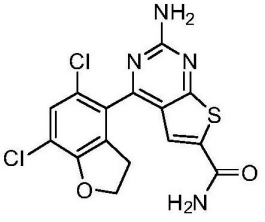
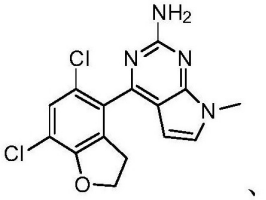
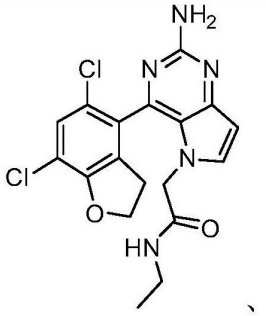
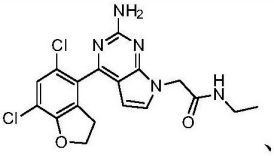
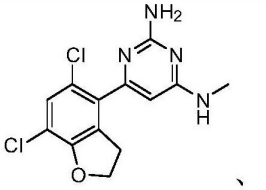
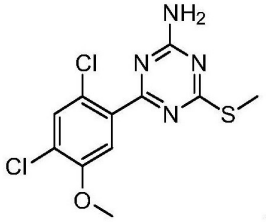
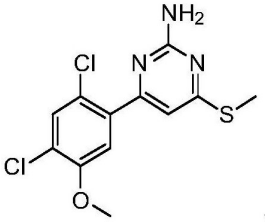
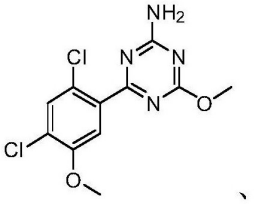
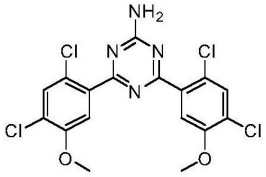
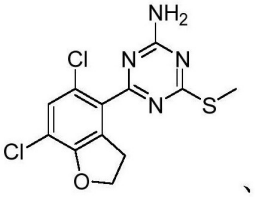
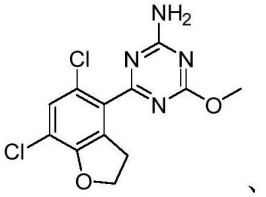
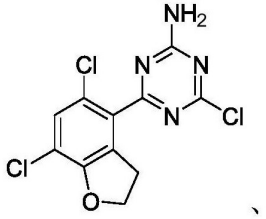
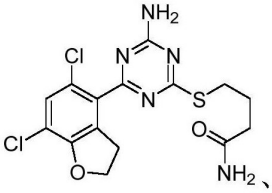
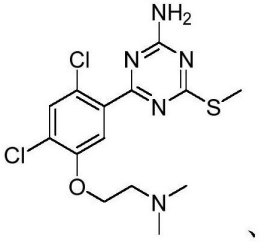
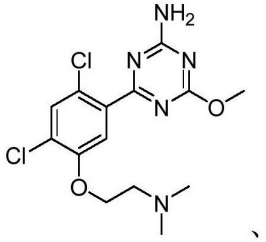
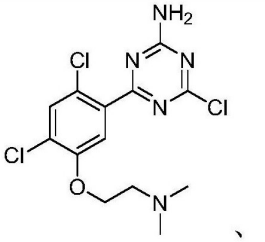
28		29		30	
31		32		33	
34		35		36	
37		40		41	
42		43		44	
45		46		47	或

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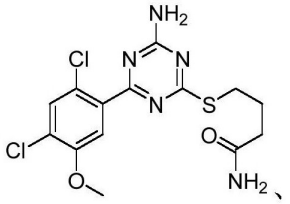
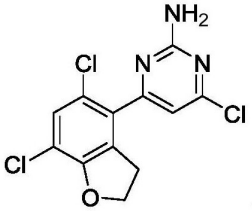
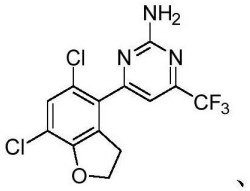
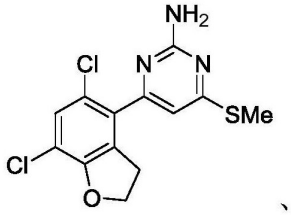
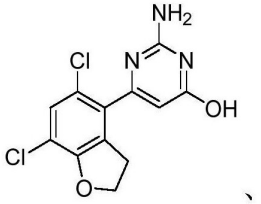
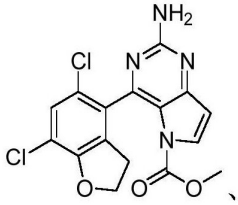
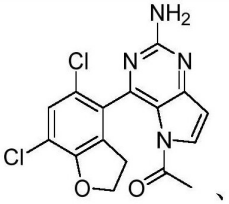
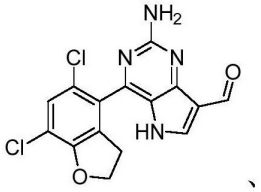
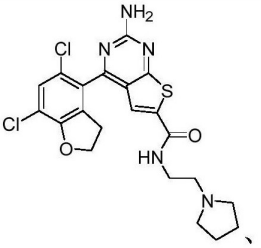
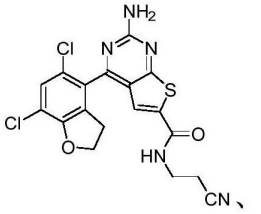
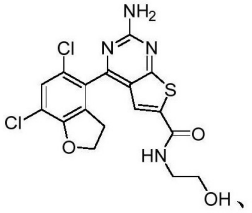
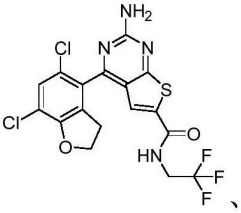
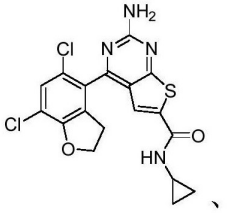
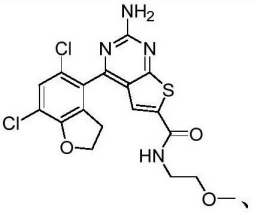
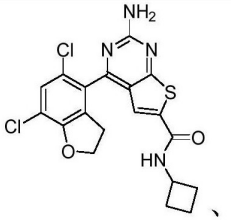
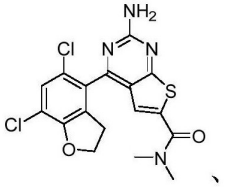
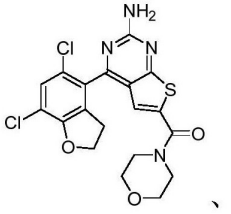
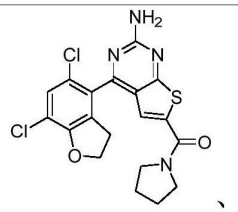
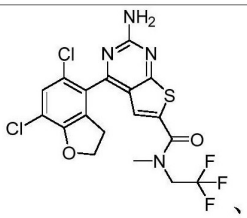
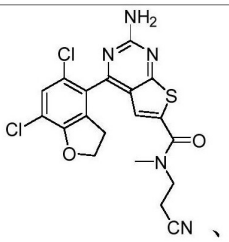
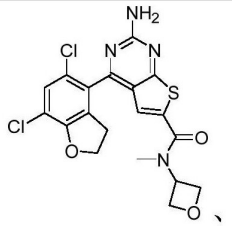
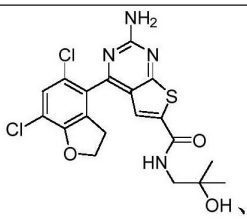
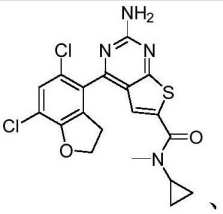
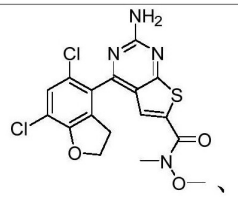
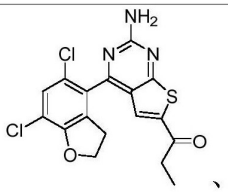
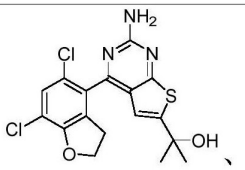
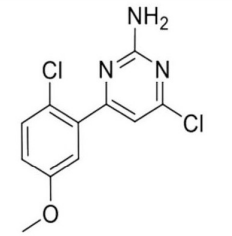
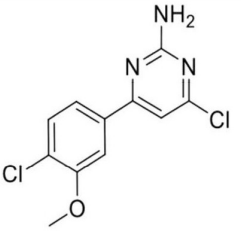
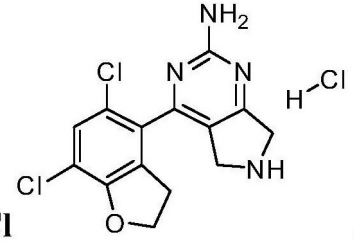
48		49		50	
51		52		53	
54		55		56	
57		58		59	
60		61		62	
63		64		65	
66		67		68	

[0791]

69  、	70  、	71  、
72  、	73  、	74  、
75  、	76  、	77  、
77  ,	78  ,	

[0792] 或其药学上可接受的盐。

[0793] 本发明化合物的药学上可接受的盐的非限制性实例是：

[0794] 
16-HCl 。

[0795] 本文描述了用于合成本发明化合物的示例性方法。

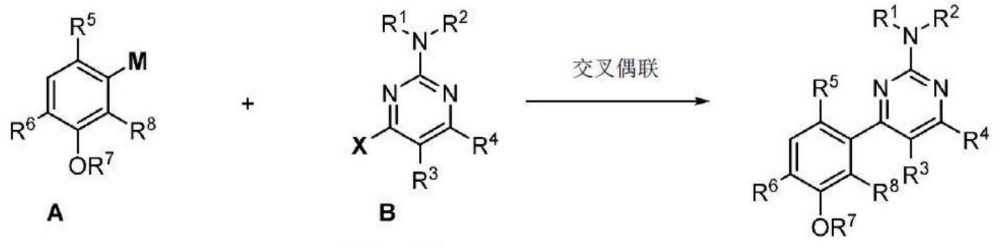
[0796] 制备本发明化合物的方法

[0797] 本发明的化合物可以通过与本领域中所建立的类似的方法来制备，例如通过方案1中所示的反应顺序。用于一般方案的编号系统不一定对应于在说明书或权利要求中其他地方使用的编号系统。

[0798] 如方案1所示，获得本发明化合物(C)的一种策略是利用标准交叉偶联反应(例如铃木偶联(Suzuki coupling)、桧山偶联(Hiyama coupling)、施蒂勒偶联(Stille coupling)、根岸(Negishi)偶联、玉尾-熊田(Tamao-Kumada)偶联、或村桥(Murahashi)偶联)，其中亲核体A和亲电体B在金属盐例如钯、铜、铁、或镍盐(例如$PdCl_2$、$Pd(OAc)_2$、CuBr、CuI、$(CuOTf)_2$甲苯络合物、$Fe(OTf)_3$、$FeCl_3$、$FeBr_3$、$NiCl_2$、或$NiBr_2$)的存在下偶联。任选地，

可以添加配体例如膦(例如,PPh_3、P(2-呋喃基)$_3$、P(t-Bu)$_3$、dppf、dppb、或BINAP)、N-杂环卡宾(例如,SIMes或SIPr)、或二吡啶(例如,2,2'-联吡啶或1,10-菲咯啉)以促进反应。可替代地,可以直接使用结合或不结合额外配体的有机金属络合物,例如Pd$(PPh_3)_4$或(dppf)$PdCl_2$。可以加入添加剂,例如,四丁基氟化铵、LiCl、KOAc、或AgOTf,以使脱卤作用最小化或促进交叉偶联反应。本领域技术人员能够通过标准筛选确定用于反应的适当溶剂。用于交叉偶联反应的溶剂的非限制性实例是水、乙醇、丙酮、四氢呋喃、甲苯,1,4-二噁烷、及其混合物。对于可用于使用交叉偶联化学制备根据式C的本发明化合物的条件和催化剂的非限制性实例,参见宫浦(Miyaura)等人,"交叉耦合反应:实用指南(Cross-Coupling Reactions:A Practical Guide)"于当代化学专题(Topics in Current Chemistry),施普林格出版集团(Springer),2002,和尼科拉乌(Nicolaou)等人,应用化学国际版(Angew.Chem.Int.Ed.),44:4442-4489,2005,其通过引用并入本文。可替代地,式A的化合物可以是亲电体并且具有离去基团X而不是M,而式B的化合物可以是亲核体并且具有金属或准金属基团M而不是X。

[0799] 方案1.

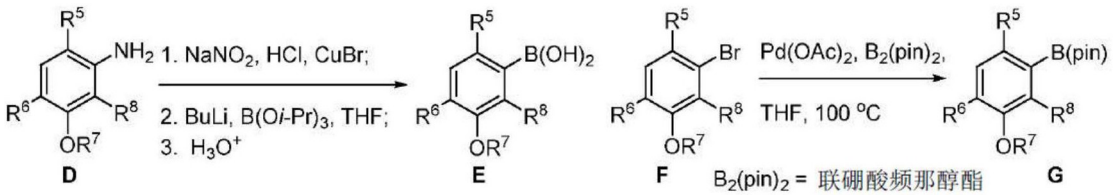


[0800] **M** = $B(OH)_2$, B(pin), B(cat), $SiMe_3$, $SnBu_3$, ZnCl, ZnBr, ZnI, MgCl, MgBr, MgI, Li,
其中
cat = 邻苯二酚
pin = 频那醇

X = 卤素,例如,
-F, -Cl, -Br, -I, 或
假卤素,
例如 -OMs, -OTf,
-ONf, 或 $-OP(O)(OR)_2$,
其中
-OMs = 甲磺酸盐,
-OTf = 三氟甲磺酸酯 ,
-ONf = 九氟丁基磺酸盐。

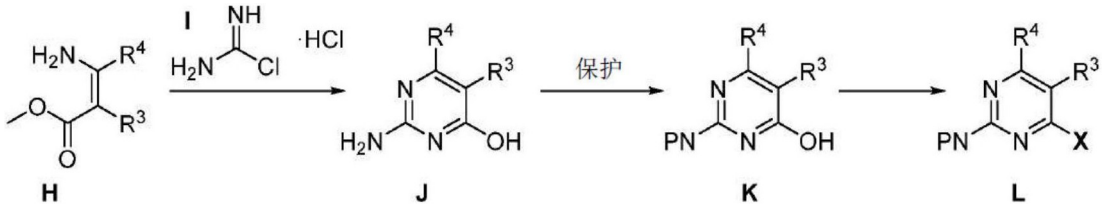
[0801] 式A的化合物可以根据本领域已知的任何方法制备,例如,金属-卤素(例如,锂-卤素)交换(随后添加或不添加硼基、硅基、锡基、锌基、或镁基剂),格里纳德试剂的制备、桑德迈尔反应、或与二非金属试剂交叉偶联(例如,宫浦硼化反应)。制备A(桑德迈尔反应和锂卤素交换来制备E以及宫浦硼化反应来制备G)的非限制性实例示于方案2中。

[0802] 方案2.制备亲核体A,例如E或G的制备

[0803] 

[0804] 式B的化合物可以根据本领域已知的任何方法来制备,例如比吉内利(Biginelli)反应,随后氧化所得的2-氨基二氢嘧啶衍生物。可替代地,方案3中的合成方法概述可用于获得式B的化合物。

[0805] 方案3.亲电体B的制备,例如N-保护的B,即L

[0806] 

[0807] 如方案3所示，式H的化合物可以与式I的化合物缩合，以给出式J的化合物。然后可以保护2-氨基嘧啶衍生物J的氨基(P＝二价N-保护基、两个一价N-保护基、或一个一价N-保护基和一个氢)，得到式K的化合物。然后可以根据本领域已知的任何方法将式K的化合物中的羟基转化为式L的化合物中的卤素，例如，使用脱水-卤化试剂(例如，$POCl_3$、PCl_5、$SOCl_2$、SO_2Cl_2、和其溴化或碘化变体)。可替代地，式K化合物的羟基可以使用试剂，例如Tf_2O、$PhNTf_2$、$PhNNf_2$、或P(O)(OR)$_2$Cl、和任选地，碱基(例如、Et_3N、(iPr)$_2$NEt、或吡啶)和/或催化剂(例如，4-二甲氨基吡啶)来转化成式L化合物的假卤素。N-保护基P可以根据本领域已知的方法在方案1中所示的交叉偶联之前或之后从化合物L中除去(参见，例如，格林(Greene)，有机合成中的保护基(Protective Groups in Organic Synthesis)，第3版(约翰威利父子出版公司，纽约，1999))。

[0808] 在上述反应中、可能需要保护反应性官能团(例如羟基、氨基、硫基或羧基)以避免它们不希望地参与反应。这些基团的引入以及引入和除去它们所需的方法是本领域技术人员已知的(例如，格林，同上)。脱保护步骤可以是合成中的最后步骤，因此除去保护基团可以得到如本文所公开的式(Ia)的化合物。可以通过使用本领域技术人员已知的方法购买或者通过化学文献中描述的方法或通过其改变来制备在上述任何方案中使用的起始原料。进行步骤的顺序可以根据引入的基团和所用的试剂而变化，但是对于本领域技术人员是显而易见的。

[0809] 任何式(I)、(Ia)、(Ib)、(Va)、或(Vb)的化合物或上述方案中描述的任何中间体可以通过使用一种或多种本领域技术人员已知的标准合成方法进一步衍生。这些方法可包括取代、氧化或还原反应。这些方法也可以用于通过修饰、引入或除去适当的官能团来获得或修饰式(I)、(Ia)、(Ib)、(Va)、或(Vb)的化合物或任何前述中间体。具体的取代方法包括烷基化、芳基化、杂芳基化、酰化、硫代酰化、卤化、磺酰化、硝化、甲酰化、水解和偶联过程。这些步骤可用于将官能团引入母体分子(例如，芳环的硝化或磺酰化)或将两个分子偶联在一起(例如，将胺偶联至羧酸以得到酰胺；或在两个杂环之间形成碳-碳键)。例如，醇或酚基团可以通过在溶剂中，例如，四氢呋喃在膦(例如，三苯基膦)和脱水剂(例如，二乙基-、二异丙基-、或二甲基偶氮二羧酸酯)的存在下，将酚与醇偶联而转化成醚基。可替代地，可以通过醇的脱质子化，使用合适的碱(例如，氢化钠)，然后添加烷基化剂(例如，烷基卤或烷基磺酸酯)来制备醚基。

[0810] 在另一个实例中，伯胺或仲胺可以使用还原烷基化方法来烷基化。例如，可以用醛和硼氢化物(例如，三乙酰氧基硼氢化钠、或氰基硼氢化钠)在溶剂(例如，卤代烃，例如二氯甲烷、或醇，例如，乙醇)中，并且当需要时，在酸(例如乙酸)的存在下处理胺。

[0811] 在另一个实例中，-OH基团可以通过用合适的还原剂例如，络合金属氢化物，例如氢化铝锂在溶剂(例如，四氢呋喃)中还原，从相应的酯、酸、酰氯或醛产生。

[0812] 在另一个实例中，可以使用本领域技术人员已知的条件将羟基(包括酚羟基)转化

为离去基团，例如，卤素原子或磺酰氧基(例如，烷基磺酰氧基，例如三氟甲基磺酰氧基或芳基磺酰基，例如，对甲苯磺酰氧基)。例如，脂族醇可以与卤化烃(例如，二氯甲烷)中的亚硫酰氯反应，得到相应的烷基氯化物。在反应中也可以使用碱(例如，三乙胺)。

[0813] 另一个实例是，酯基可以通过酸或碱催化水解转化成相应的羧酸，这取决于酯基的性质。酸催化的水解可以通过用有机或无机酸(例如，在水性溶剂中的三氟乙酸，或无机酸，例如在溶剂如二噁烷中的盐酸)处理来实现。碱的催化水解可以通过用碱金属氢氧化物(例如，氢氧化锂在含水醇(例如甲醇)中)处理来实现。

[0814] 在另一个实例中，化合物中的芳族卤素取代基可以通过用碱(例如，锂碱，例如正丁基锂或叔丁基锂)任选地在低温(例如，-78℃)下在溶剂(例如，四氢呋喃)中处理，进行卤素-金属交换，然后将混合物淬灭，在亲电体下引入所需的取代基。因此，例如，可以通过使用二甲基甲酰胺作为亲电子试剂引入甲酰基。芳族卤素取代基也可以进行钯催化反应以引入基团，例如，羧酸、酯、氰基、或氨基取代基。

[0815] 在另一实例中，该化合物在芳族卤素取代基可参与一系列的金属催化反应以引入替代性的官能团，例如，胺、酰胺、醚、硫醇、芳基、或杂芳基。

[0816] 具体的氧化方法包括脱氢和芳构化、以及向某些官能团添加氧。例如，醛基可以通过使用本领域技术人员熟知的条件氧化相应的醇来制备。例如，醇可以在溶剂(例如，卤代烃，例如二氯甲烷)中用氧化剂(例如，戴斯马丁(Dess-Martin)试剂)处理。可以使用替代的氧化条件，例如，用草酰氯和活化量的二甲基亚砜处理，然后通过添加胺(例如三乙胺)淬灭。此类反应可以在适当的溶剂(例如卤代烃，例如二氯甲烷)中和在适当的条件下(例如，冷却至低于室温，例如至-78℃，随后升温至室温)进行。在另一个实例中，可以在惰性溶剂(例如，卤代烃，例如二氯甲烷)中在周围环境温度下使用氧化剂(例如，过氧酸，例如3-氯过氧苯甲酸)将硫原子氧化成相应的亚砜或砜。

[0817] 具体的还原方法包括从特定官能团除去氧原子，包括芳环的不饱和化合物的饱和(或部分饱和)。例如，伯醇可以通过使用金属氢化物(例如，在溶剂例如，甲醇中的氢化铝锂或硼氢化钠)从相应的酯或醛通过还原产生。可替代地，可以使用金属氢化物(例如，在溶剂例如四氢呋喃中的氢化铝锂)从相应的羧酸中通过还原产生-OH基团。在另一个实例中，硝基可以在金属催化剂(例如，固相支持体例如碳上的钯)的存在下在溶剂(例如，醚，例如四氢呋喃，或醇，例如甲醇)中通过催化氢化，或者通过在酸(例如，盐酸)的存在下使用金属(例如，锡或铁)的化学还原来还原为胺。在一个进一步的实例中，胺可以通过还原腈来获得，例如，通过在金属催化剂(例如，固相支持体例如碳上的钯)、或雷尼镍的存在下在溶剂(例如，四氢呋喃)中和在合适的条件(例如，冷却至低于室温，例如至-78℃，或加热以例如回流)下的催化氢化。

[0818] 药物组合物

[0819] 用于本文所述方法的化合物优选配制成药物组合物，用于以适合于体内给予的生物相容形式给予人类受试者。药物组合物通常包括本文所述的化合物和药学上可接受的赋形剂。

[0820] 本文所述的化合物还可以以游离碱的形式，以盐、两性离子、溶剂化物的形式，或作为前药、或其药物组合物使用。所有形式都在本发明的范围内。如本领域技术人员将理解的，取决于所选择的给药途径，可以以多种形式向患者给予化合物、盐、两性离子、溶剂合

物、前药、或药物组合物。用于本文所述方法中的化合物可以例如通过口服、胃肠外、口腔、舌下、鼻、直肠、贴片、泵、或经皮给予，以及以相应地配制的药物组合物给予。肠胃外给予包括静脉内、腹膜内、皮下、肌内、经上皮、鼻、肺内、鞘内、直肠、和局部模式给予。肠胃外给予可以是通过在选定的时间段内连续输注。

[0821] 对于人类使用，本发明的化合物可以单独给予或者与根据预期的给药途径和标准药学实践选择的药物载体混合给予。因此，可以以常规方式使用一种或多种生理学上可接受的载体配制根据本发明使用的药物组合物，所述生理学可接受的载体包括赋形剂和助剂，该赋形剂和助剂有助于式(I)、(Ia)、(Ib)、(Va)、或(Vb)的化合物转化为可以药学上使用的制剂。

[0822] 本发明还包括可以含有一种或多种药学上可接受的载体的药物组合物。在制备本发明的药物组合物时，通常将活性成分与赋形剂混合，用赋形剂稀释或以例如胶囊、小药囊、纸、或其他容器的形式的此类载体包封。当赋形剂用作稀释剂时，其可以是固体、半固体、或液体材料(例如，生理盐水)，其用作活性成分的媒介、载体或介质。因此，组合物可以是片剂、粉末、锭剂、小药囊、扁囊剂、酏剂、混悬剂、乳剂、溶液剂、糖浆剂、以及软和硬明胶胶囊的形式。如本领域已知的，稀释剂的类型可以根据预期的给药途径而变化。所得组合物可包括另外的试剂，例如，防腐剂。

[0823] 根据给药方式和途径选择赋形剂或载体。用于药物制剂的合适的药物载体以及药物必需品描述于雷明顿:药学科学与实践(Remington:The Science and Practice of Pharmacy)，第21版，真纳罗(Gennaro)编辑，利平科特·威廉斯&威尔金斯出版公司(Lippencott Williams&Wilkins)(2005)，该领域公知的参考文献，以及在USP/NF(美国药典和国家处方集)中。合适的赋形剂的实例是乳糖、葡萄糖、蔗糖、山梨醇、甘露醇、淀粉、阿拉伯胶、磷酸钙、藻酸盐、黄蓍胶、明胶、硅酸钙、微晶纤维素、聚乙烯吡咯烷酮、纤维素、水、糖浆和甲基纤维素。这些制剂可以另外包括:润滑剂，例如滑石、硬脂酸镁和矿物油;润湿剂;乳化剂和悬浮剂;防腐剂，例如苯甲酸甲基酯和丙基羟基苯甲酸酯;甜味剂;以及调味剂。其他示例性赋形剂描述于《药用辅料手册》(Handbook of Pharmaceutical Excipients)，第6版，罗(Rowe)等人编，医药出版社(Pharmaceutical Press)(2009)中。

[0824] 这些药物组合物可以以常规方式生产，例如，通过常规混合、溶解、制粒、制糖衣丸、研磨、乳化、包封、包埋、或冻干的方法。用于制备制剂的本领域公知的方法见于，例如《雷明顿:药学科学与实践》(Remington:The Science and Practice of Pharmacy)，第21版，真纳罗(Gennaro)编辑，利平科特·威廉斯&威尔金斯出版公司(Lippencott Williams&Wilkins)(2005)和《药物技术百科全书》(Encyclopedia of Pharmaceutical Technology)，J.斯沃布里克(Swarbrick)和J.C.博伊兰(Boylan)编，1988-1999，马塞尔·德克尔出版社(Marcel Dekker)，纽约。适当的制剂取决于所选择的给予途径。此类组合物的制剂和制备是药物制剂领域技术人员众所周知的。在制备制剂中，在与其他成分组合之前，可以将活性化合物研磨以便提供适当的粒径。如果活性化合物是基本上不可溶的，可以将它研磨到小于200目的粒径。如果活性化合物是基本上水可溶的，可以通过研磨调整粒径，以便在制剂中提供基本上均匀的分布，例如约40目。

[0825] 剂量

[0826] 用于本文所述方法的化合物、或其药学上可接受的盐或前药、或其药物组合物的

剂量可以根据许多因素而变化，例如化合物的药效学性质，给药方式，接受者的年龄、健康情况、和体重，症状的性质和程度，治疗的频率，和同期治疗的类型(如果有的话)，和待治疗的动物中化合物的清除率。本领域技术人员可以基于上述因素确定合适的剂量。用于本文所述方法的化合物可以最初以合适的剂量给予，该剂量可根据临床反应，根据需要进行调整。通常，合适的本发明的化合物的每日剂量，将是有效产生治疗效果的最低剂量的化合物的量。通常这样一种有效剂量将取决于以上描述的这些因素。

[0827] 本发明的化合物可以以单剂量或多剂量给予患者。当给予多个剂量时，可以分开彼此的剂量，例如1-24小时、1-7天、1-4周、或1-12个月。化合物可以根据时间安排给予，或者化合物可以不用预定的时间安排来给予。可以例如，每天1、2、3、4、5、6、7、8、9、10、11、或12次，每第2、3、4、5、或6天，每周1、2、3、4、5、6、或7次，每月1、2、3、4、5、或6次，或每年1、2、3、4、5、6、7、8、9、10、11、或12次给予活性化合物。应当理解，对于任何具体的受试者，应根据个体需要和给予或监督组合物给予的人的专业判断随时间调整具体的剂量方案。

[0828] 尽管主治医师最终将决定适当的量和剂量方案，但是本发明化合物的有效量可以是，例如，总日剂量为例如0.05mg至3000mg的本文所述的任何化合物。可替代地，可以使用患者的体重来计算剂量。此类剂量范围可以包括，例如，10mg-1000mg(例如50mg-800mg)。在一些实施例中，可以给予50mg、100mg、150mg、200mg、250mg、300mg、350mg、400mg、450mg、500mg、550mg、600mg、650mg、700mg、750mg、800mg、850mg、900mg、950mg、或1000mg化合物。

[0829] 在本发明的方法中，向患者给予多剂量的本发明化合物的时间段可以变化。例如，在一些实施例中，将本发明化合物的剂量在超过1-7天，1-12周，或1-3个月的时间段内给予患者。在其他实施例中，将化合物在超过例如，4-11个月、或1-30年的时间段内给予患者。在其他实施例中，在症状发作时将化合物给予患者。在这些实施例的任一个中，给予的化合物的量可以在给予的时间段内变化。当每天给予化合物时，可以例如每天给予1、2、3、4、5、6、7、8、9、10、11、或12次。

[0830] 制剂

[0831] 使用本文所述的任何方法，被鉴定为能够治疗本文所述的任何症病的化合物可以以单位剂量形式，用药学上可接受的稀释剂、载体或赋形剂给予患者或动物。用于这些疗法的化合物可以通过药物化学领域中已知的任何标准技术产生和分离。可以使用常规的药物实践来提供合适的制剂或组合物，以向患有发生坏死的疾病的患者给予鉴定的化合物。可以在患者有症状之前开始给予。

[0832] 用于本发明的化合物(例如具有式(I)、(Ia)、(Ib)、(Va)或(Vb)的化合物)或其药物组合物的示例性给药途径包括口腔、舌下、颊部、经皮、皮内、肌内、胃肠外、静脉内、动脉内、颅内、皮下、眶内、心室内、脊柱内、腹膜内、鼻内、吸入、和局部给予。理想地是将化合物与药学上可接受的载体一起给予。配制用于治疗本文所述病症的本文所述化合物的药物制剂也是本发明的一部分。

[0833] 用于口服给予的制剂

[0834] 本发明考虑的药物组合物包括被配制用于口服给予的那些(“口服剂型”)。口服剂型可以是，例如，片剂、胶囊、液体溶液或悬浮液、粉末、或液体或固体晶体的形式，其在与无毒的药学上可接受的赋形剂的混合物中含有一种或多种活性成分。这些赋形剂可以是例如惰性稀释剂或填充剂(例如，蔗糖、山梨糖醇、糖、甘露醇、微晶纤维素、淀粉包括马铃薯淀

粉、碳酸钙、氯化钠、乳糖、磷酸钙、硫酸钙、或磷酸钠)；造粒和崩解剂(例如，纤维素衍生物包括微晶纤维素、淀粉包括马铃薯淀粉、交联羧甲基纤维素钠、藻酸盐、或藻酸)；结合剂(例如，蔗糖、葡萄糖、山梨醇、阿拉伯胶、海藻酸、藻酸钠、明胶、淀粉、预胶化淀粉、微晶纤维素、硅酸铝镁、羧甲基纤维素钠、甲基纤维素、羟丙基甲基纤维素、乙基纤维素、聚乙烯吡咯烷酮、或聚乙二醇)；和润滑剂、助流剂和防粘剂(例如，硬脂酸镁、硬脂酸锌、硬脂酸、二氧化硅、氢化植物油、或滑石)。其他药学上可接受的赋形剂可以是着色剂、调味剂、增塑剂、保湿剂、缓冲剂等。

[0835] 用于口服给予的制剂也可以作为咀嚼片、作为硬明胶胶囊呈现，其中活性成分与惰性固体稀释剂(例如，马铃薯淀粉、乳糖、微晶纤维素、碳酸钙、磷酸钙或高岭土)混合，或作为软明胶胶囊呈现，其中活性成分与水或油介质(例如花生油、液体石蜡、或橄榄油)混合。可以使用例如混合器、流化床设备或喷雾干燥设备以常规方式使用在片剂和胶囊中上述成分制备粉剂、颗粒和丸剂。

[0836] 用于口服使用的控释组合物可以被构建为通过控制活性药物物质的溶解和/或扩散来释放活性药物。可以进行多种策略中的任何一种以获得控释和靶向血浆浓度对时间曲线。在一个实例中，通过适当选择各种制剂参数和成分，包括例如各种类型的控释组合物和包衣来获得控释。实例包括单或多单位片剂或胶囊组合物、油溶液、悬浮液、乳剂、微胶囊、微球、纳米颗粒、膏药、以及脂质体。在某些实施例中，组合物包括可生物降解的、pH和/或温度敏感的聚合物涂层。

[0837] 溶解或扩散控制释放可以通过适当包衣化合物的片剂、胶囊、丸剂、或颗粒制剂，或通过将化合物掺入合适的基质中来实现。控释包衣可以包括一种或多种上述包衣物质和/或例如紫胶、蜂蜡、聚糖蜡、蓖麻蜡、巴西棕榈蜡、硬脂醇、单硬脂酸甘油酯、二硬脂酸甘油酯、棕榈酸硬脂酸甘油酯、乙基纤维素、丙烯酸树脂、dl-聚乳酸、乙酸丁酸纤维素、聚氯乙烯、聚乙酸乙烯酯、乙烯基吡咯烷酮、聚乙烯、聚甲基丙烯酸酯、甲基丙烯酸甲酯、2-羟基甲基丙烯酸酯、甲基丙烯酸酯水凝胶、1,3-丁二醇、甲基丙烯酸乙二醇酯、和/或聚乙二醇。在控释基质制剂中，基质材料还可包括例如，水合甲基纤维素、巴西棕榈蜡和硬脂醇、carbopol 934、硅酮、三硬脂酸甘油酯、丙烯酸甲酯-甲基丙烯酸甲酯、聚氯乙烯、聚乙烯和/或卤化碳氟化合物。

[0838] 本发明的化合物和组合物可以掺入其中以用于口服给予的液体形式包括水溶液、适当调味的糖浆、水性或油悬浮液以及用食用油(如棉籽油、芝麻油、椰子油或花生油)调味的乳液，连同酏剂和类似的药物运载体。

[0839] 用于颊部给予的制剂

[0840] 根据需要，用于颊部或舌下给予的剂量通常为每个单剂量0.1mg至500mg。在实践中，医师确定最适合个体患者的实际给药方案，并且剂量随特定患者的年龄、体重和反应而变化。上述剂量是平均情况的示例，但是存在其中需要更高或更低剂量的个别实例，并且这些是在本发明的范围内的。

[0841] 对于颊部给予，组合物可以采取以常规方式配制的片剂、锭剂等形式。适合与喷雾器和液体喷雾装置以及电动流体(EHD)气溶胶装置一起使用的液体药物制剂通常包括具有药学上可接受的载体的本发明的化合物。优选地，药学上可接受的载体是液体，例如醇、水、聚乙二醇、或全氟化碳。任选地，可以加入另一种材料以改变本发明化合物的溶液或悬浮液

的气溶胶性质。理想地，该材料是液体，例如醇、乙二醇、聚乙二醇、或脂肪酸。配制适合用于气雾剂装置的液体药物溶液或悬浮液的其他方法是本领域技术人员已知的(参见，例如比萨尔斯基(Biesalski)，美国专利号5,112,598和比萨尔斯基，美国专利号5,556,611，其中每个均通过引用并入本文)。

[0842] 用于鼻或吸入给予的制剂

[0843] 所述化合物还可以配制用于经鼻给予。用于鼻内给予的组合物也可以方便地配制成气雾剂、滴剂、凝胶剂和粉剂。制剂可以以单剂量或多剂量形式提供。在滴管或移液管的情况下，给予可通过患者给予适当的预定体积的溶液或悬浮液来实现。在喷雾器的情况下，这可例如借助于计量雾化喷雾泵来达成。

[0844] 该化合物还可以配制用于气雾剂给予，特别是通过吸入和包括鼻内给予至呼吸道。该化合物通常具有小的粒度，例如大约五(5)微米或更小。此类粒径可以通过本领域已知的方法获得，例如通过微粉化。活性成分以具有合适的推进剂(例如氯氟烃(CFC)，例如二氯二氟甲烷、三氯氟甲烷、或二氯四氟乙烷，或二氧化碳，或其他合适的气体)的加压包装提供。气溶胶还可以方便地含有表面活性剂，例如，卵磷脂。药物的剂量可以通过量阀控制。可替代地，活性成分可以以干粉形式提供，例如化合物在合适的粉末基质(例如乳糖、淀粉和淀粉衍生物，例如羟丙基甲基纤维素、和聚乙烯吡咯烷酮(PVP))中的粉末混合物。粉末载体将在鼻腔中形成凝胶。粉末组合物可以以单位剂量形式存在，例如，在例如明胶或泡罩包装的胶囊或药筒中，粉末可以从其中通过吸入器给予。

[0845] 气溶胶制剂通常包括活性物质在生理上可接受的水性或非水性溶剂中的溶液或细悬浮液，并且通常以无菌形式、以单剂量或多剂量形式存在于密封容器中，其可以采取筒或再填充的形式以与雾化装置一起使用。可替代地，密封容器可以是整体分配装置，例如单剂量鼻腔吸入器或配有量阀的气雾剂分配器，该量阀用于在使用后处理。当剂型包括气溶胶分配器时，其将包含推进剂，其可以是压缩气体，例如压缩空气或有机推进剂，例如氟氯烃。气雾剂剂型也可以采用泵-雾化器的形式。

[0846] 用于肠胃外给予的制剂

[0847] 本文所述的用于本发明方法的化合物可以，如本文所述，以药学上可接受的肠胃外(例如静脉内或肌肉内)制剂给予。药物制剂还可以以含有常规无毒的药学上可接受的载体和佐剂的剂型或制剂肠胃外(静脉内、肌内、皮下等)给予。具体而言，适于胃肠外给予的制剂包括水性和非水性无菌注射液，它们可以包含抗氧化剂、缓冲剂、抑菌剂和使制剂与预期的受者的血液等渗的溶质；以及水性和非水性无菌悬浮液(其可包括助悬剂和增稠剂)。例如，为了制备此类组合物，本发明的化合物可以溶解或悬浮在胃肠外可接受的液体载体中。可以使用的可接的受载体和溶剂是水，通过加入适量的盐酸、氢氧化钠或合适的缓冲液调节至合适的pH的水，1,3-丁二醇，林格氏溶液和等渗氯化钠溶液。水性制剂还可以含有一种或多种防腐剂，例如，对羟基苯甲酸甲酯、乙酯或正丙酯。关于肠胃外制剂的其他信息可以在例如美国药典-国家处方集(United States Pharmacopeia-National Formulary (USP-NF))中找到，其通过引用并入本文。

[0848] 肠胃外制剂可以是由USP-NF鉴定为适于肠胃外给予的五种一般类型的制剂中的任一种：

[0849] (1)“药物注射”：是药物物质(例如，式(I)、(Ia)、(Ib)、(Va)或(Vb)的化合物)的液

体制剂,或其溶液;

[0850] (2)“注射用药物”:作为干燥固体的药物物质(例如,式(I)、(Ia)、(Ib)、(Va)或(Vb)的化合物),其将与适当的无菌载体结合作为药物注射剂用于肠胃外给予;

[0851] (3)“药物注射乳剂”:溶解或分散在合适的乳剂介质中的药物物质(例如,式(I)、(Ia)、(Ib)、(Va)或(Vb)的化合物)的液体制剂;

[0852] (4)“药物注射悬浮液”:悬浮在合适的液体介质中的药物物质(例如,式(I)、(Ia)、(Ib)、(Va)或(Vb)的化合物)的液体制剂;以及

[0853] (5)“用于可注射悬浮液的药物”:作为干燥固体的药物物质(例如,式(I)、(Ia)、(Ib)、(Va)或(Vb)的化合物),其将与适当的无菌媒介结合作为药物可注射悬浮液用于肠胃外给予。

[0854] 用于肠胃外给予的示例性制剂包括在水中适当地与表面活性剂例如,羟丙基纤维素混合制备的化合物的溶液。胶体溶液也可以在有或没有醇的甘油、液体聚乙二醇、DMSO及其混合物中,以及在油中制备。在普通贮存和使用条件下,此类制剂可以含有防腐剂以防止微生物生长。用于选择和制备合适制剂的常规方法和成分描述于例如雷明顿:药物科学与实践(Remington:The Science and Practice ofPharmacy),第21版,真纳罗(Gennaro)编辑,利平科特·威廉斯&威尔金斯出版公司(Lippencott Williams&Wilkins)(2005)和2013年出版的美国药典:国家处方集(The United States Pharmacopeia:The National Formulary)(USP 36 NF31)中。

[0855] 用于肠胃外给予的制剂可以,例如含有赋形剂、无菌水、或盐水、聚亚烷基二醇(例如聚乙二醇)、植物来源的油或氢化萘。生物相容性的、生物可降解的丙交酯聚合物、丙交酯/乙交酯共聚物、或聚氧乙烯-聚氧丙烯共聚物可用于控制化合物的释放。针对这些化合物而言,其他潜在有用的肠胃外递送系统包括乙烯-乙酸乙烯酯共聚物颗粒、渗透泵、可植入的输注系统、以及脂质体。用于吸入的制剂可以含有赋形剂,例如乳糖,或者可以是含有例如聚氧乙烯-9-月桂醚、甘胆酸盐和脱氧胆酸盐的水溶液,或者可以是用于以滴鼻剂形式、或作为凝胶给予的油性溶液。

[0856] 肠胃外制剂可以制配用于化合物的迅速释放或持续/延长释放。用于肠胃外释放化合物的示例性制剂包括:水溶液、用于重构的粉末、共溶剂溶液、油/水乳液、悬浮液、油基溶液、脂质体、微球、和聚合物凝胶。

[0857] 治疗方法

[0858] 本文所述的化合物和组合物可用于治疗其中涉及Hsp90的病症和疾病,例如,细胞增殖性疾病,例如癌症、神经退行性疾病,例如tau蛋白病变(例如阿尔茨海默氏病)和传染病。

[0859] 细胞增殖性疾病

[0860] 由于这种多伴侣复合物参与各种病原性细胞过程,Hsp90已经作为癌症治疗的关键治疗靶标出现。Hsp90客户蛋白包括涉及下以的那些:急性髓性白血病(Flt-3)、乳腺癌(HER2)、慢性淋巴细胞白血病(Zap70)、慢性髓性白血病(Bcr-Abl或mBcr-Abl)、胃肠道间质肿瘤(c-Kit)、胃癌(c-Met)、成胶质细胞瘤(突变EGFR或c-Met)、肺癌(c-Met)、淋巴瘤(NMP-ALK)、黑素瘤(Raf-1/突变体BRAF)、骨髓瘤(IGF-1R/Akt)、非小细胞肺癌(突变EGFR)、肾癌(HIF-1α)、和小细胞肺癌(Akt)。本发明的化合物由于其血脑屏障渗透性在治疗脑肿瘤上尤

其有用。可以使用本发明的化合物治疗的脑肿瘤包括神经胶质瘤或脑膜瘤，特别是神经胶质瘤(例如，胶质母细胞瘤)或神经母细胞瘤。可以根据本发明的方法使用本发明的化合物治疗的脑肿瘤(例如脑癌)可以包括原发性肿瘤(那些起源于脑的肿瘤)和转移性肿瘤(那些起源于除了脑组织以外的组织并扩散到脑的肿瘤)。可以通过抑制Hsp90治疗的其他细胞增殖性疾病包括：胚胎期慢性髓性白血病、白血病、淋巴增生性障碍、转移性黑素瘤、多发性骨髓瘤(例如复发性或难治性多发性骨髓瘤)、骨髓增殖性疾病、胰腺癌、小肠癌、和实体瘤。此外，癌细胞已显示对Hsp90抑制比非致病细胞更敏感。因此，本文所述的化合物可用于细胞增殖性疾病的治疗。

[0861] 神经退行性疾病

[0862] 增加的Hsp90水平已经涉及神经退行性障碍。例如，在tau蛋白病变中已经显示出异常的Hsp90活性，其是以异常Tau蛋白(例如，高度磷酸化和聚集的Tau)的累积为特征的病症。因此，本文所述的化合物和组合物可用于治疗神经退行性疾病和tau蛋白病变，包括阿尔茨海默病(AD)、嗜银颗粒性痴呆、肌萎缩性侧束硬化症、皮质基底节变性、拳击手脑病综合症(dementia pugislistica)、唐氏综合征、家族性英国型痴呆、额叶退化(缺乏特征性组织病理学特征的痴呆)、慢性创伤性脑病、创伤性脑损伤、额颞叶性痴呆(FTD；与17号染色体(FTDP-17)相关的伴有帕金森综合征的额颞痴呆)、大脑老化中的海马tau蛋白病变、I型肌强直性营养不良、C型尼曼-皮克病、帕金森病(例如，关岛震颤麻痹痴呆综合征、与瓜德罗普岛痴呆相关的帕金森综合征、或脑炎后帕金森综合征)、皮克病(PiD)、和进行性核上性麻痹。因此，本文所述的化合物可用于治疗神经退行性障碍，例如，tau蛋白病变(例如，阿尔茨海默氏病)。

[0863] 传染病

[0864] Hsp90已经作为用于治疗传染病例如病毒感染、真菌感染和细菌感染的治疗靶标出现。许多病原体(例如，病毒、真菌和细菌)依赖于Hsp90依赖性过程(参见，例如盖勒(Geller)等人，生物化学与生物物理学报-分子细胞生物学研究(Biochim.Biophys.Acta-Mol.Cell Res.)，1823:698-706，2012；本公开的全部内容并入本文)。因此，Hsp90的抑制对患有依赖于Hsp90活性的感染的患者提供了治疗益处。例如，Hsp90抑制剂(格尔德霉素)已显示延迟了细胞培养物中流感病毒的生长。依赖于Hsp90依赖性过程的其他病毒包括属于以下家族的那些：疱疹病毒科(例如，单纯疱疹病毒-1、单纯疱疹病毒-2、疱疹病毒-5、卡波西氏肉瘤相关的疱疹病毒、水痘带状疱疹病毒或埃-巴二氏病毒)、多瘤病毒科(例如，SV40)、痘病毒科(例如痘苗病毒)、呼肠弧病毒科(例如轮状病毒)、双RNA病毒科(例如感染性囊病病毒)、小核糖核酸病毒科(例如脊髓灰质炎病毒、鼻病毒或柯萨奇病毒)、黄病毒科(例如，丙型肝炎病毒或登革热病毒)、沙粒病毒科(例如，淋巴细胞性脉络丛脑膜炎病毒)、戊型肝炎病毒科(例如，戊型肝炎病毒)、弹状病毒科(例如，水泡性口炎病毒)、副黏液病毒科(例如，人副流感病毒2、人副流感病毒3、SV5、SV41、麻疹病毒或仙台病毒)、布尼亚病毒科(例如，拉克罗斯病毒)、正粘病毒科(例如，甲型流感病毒)、丝状病毒科(例如，埃博拉病毒)、逆转录病毒科(例如，HTLV1或HIV1)、和嗜肝病毒科(例如，乙型肝炎病毒)。Hsp90抑制剂也已经用于治疗在体内的真菌感染性疾病，例如，白色念珠菌、烟曲霉或肺囊虫的治疗。此外，Hsp90抑制剂还可用于治疗细菌感染，例如，分枝杆菌病、炭疽或细菌性肺炎。可以用Hsp90抑制剂治疗的疾病的讨论在美国专利申请公开2011/0201587中提供，其公开内容通

过引用整体并入本文。因此，本发明的化合物可以根据本发明的方法用于治疗传染病，例如，病毒感染、真菌感染、或细菌感染。

[0865] 炎性和自身免疫疾病、过敏

[0866] 已经显示Hsp90在抗原呈递，淋巴细胞、巨噬细胞的活化，树突细胞的成熟和增强体介导的炎症诱导中起作用。Hsp90抑制与炎症组分的阻断有关，例如，细胞因子和NO产生的减少，以及NFκB核转运的阻断。此外，大量的工作表明，分子伴侣，例如Hsp90，可能能够诱导单核细胞-巨噬细胞系统产生前炎性细胞活素，并通过TLR2-和4-信号转导途径诱导树突细胞的激活和成熟。因此，Hsp90显然可以作为先天免疫系统的有效活化剂起作用。事实上，在系统性红斑狼疮患者的血清中检测到Hsp90水平升高了。已经在类风湿关性节炎患者身体内中检测到了自身抗体和对Hsp具有反应性的细胞。还观察到抑制Hsp90的抗炎作用减少了有哮喘的鼠模型的气道炎症。本发明的化合物可适用于治疗患者的炎性或自身免疫性疾病。此外，Hsp90抑制的抗炎效应可以在治疗过敏中具有治疗应用。因此，本发明的化合物可用于治疗过敏。

[0867] 心血管疾病

[0868] Hsp90最近涉及了心血管疾病，例如动脉粥样硬化和心肌病的病因。因此，本发明的化合物可适用于治疗心血管疾病(例如，动脉粥样硬化或心肌病)。

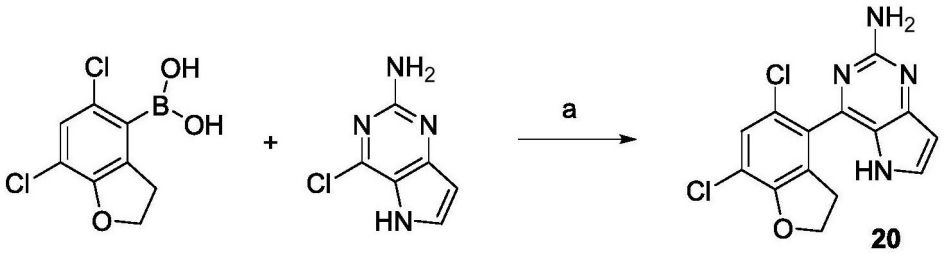
[0869] 本发明的试剂盒

[0870] 本发明还提供试剂盒，其包含(i)本发明的药物组合物，和(ii)如本文所述的使用该药物组合物以治疗由Hsp90的作用引起的哺乳动物疾病(例如，神经退行性障碍、增殖性疾病、或传染病)的说明。本发明的试剂盒可以包括解释实践者(例如，医生、护士、护理人员、或患者)如何给予其中所含的组合物的说明书。本发明的试剂盒内的药物组合物可以在容器(例如，瓶、安瓿、管、或泡罩包装)中提供。此外，试剂盒还可以包括额外的组分，例如，给患有神经退行性疾病或增殖性疾病的患者的说明书或用药方案，以及任选地，用于给予药物组合物的装置(例如注射器)。

[0871] 以下实例意在说明本发明。这些实例不意欲以任何方式限制本发明。

[0872] 实例

[0873] 实例1本发明的化合物的合成

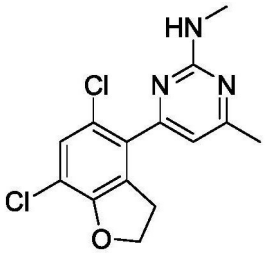
[0874] 

[0875] 方案1.试剂和条件：(a)Pd(PPh3)4、Na2CO3、二噁烷/H2O(9/5)，90℃，72％。

[0876] 4-(5,7-二氯-2,3-苯并二氢呋喃-4-基)-5H-吡咯[3,2-d]嘧啶-2-胺(20)。将5,7-二氯-2,3-二氢-1-苯并呋喃-4-基硼酸(233mg，1.0mmol)，4-氯-5H-吡咯并[3,2-d]嘧啶-2-胺(219mg，1.3mmol)，碳酸钠(318mg，3.0mmol)，钯四(三苯基膦)和二噁烷/水(9/5，14ml)的混合物在90℃下在氩气中搅拌20小时，然后冷却至室温，用盐水(25ml)淬灭，并且用乙酸乙酯(30ml×2)萃取。将合并的有机层用硫酸钠干燥并浓缩。残余物通过硅胶色谱法在硅胶上

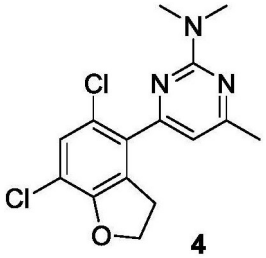
纯化，使用环己烷/乙酸乙酯(100/0至30/70，15分钟)，以给出呈白色固体的产物(230mg，72％)。^{1}H NMR(500MHz，$CDCl_3$)：δ8.01(s，1H)，7.45(t，J＝3Hz，1H)，7.34(s，1H)，6.46(m，1H)，4.83(s，2H)，4.71(m，2H)，3.60(m，1H)，2.94(m，1H)；LCMS[M+H]$^+$：321.0(针对$[C_{14}H_{10}Cl_2N_4O+H]^+$的计算值：321.0)。

[0877] 已根据本文所述的方法制备了本发明的下列化合物。

[0878] 

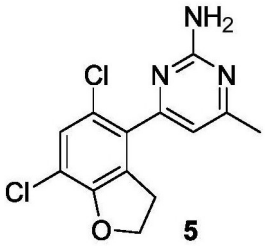
3

[0879] 4-(5，7-二氯-2，3-苯并二氢呋喃-4-基)-N，6-二甲基嘧啶-2-胺(3)。^{1}H NMR(500MHz，$CDCl_3$)：δ7.25(s，1H)，6.57(s，1H)，5.07(d，J＝10Hz，1H)，4.68(t，J＝9Hz，2H)，3.29(t，J＝9Hz，2H)，3.02(d，J＝10Hz，3H)，2.40(s，3H)。

[0880] 

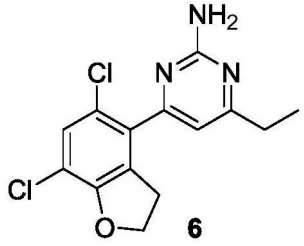
4

[0881] 4-(5，7-二氯-2，3-苯并二氢呋喃-4-基)-N，N，6-三甲基嘧啶-2-胺(4)。^{1}H NMR(500MHz，$CDCl_3$)：δ7.25(s，1H)，6.51(s，1H)，4.67(t，J＝9Hz，2H)，3.30(t，J＝9Hz，2H)，3.20(s，6H)，2.40(s，3H)。

[0882] 

5

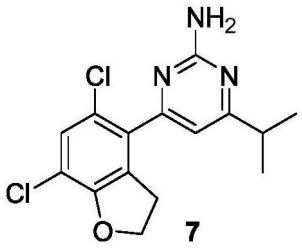
[0883] 4-(5，7-二氯-2，3-苯并二氢呋喃-4-基)-6-甲基嘧啶-2-胺(5)。^{1}H NMR(500MHz，$CDCl_3$)：δ7.27(s，1H)，6.64(s，1H)，5.04(s，2H)，4.68(t，J＝9Hz，2H)，3.25(t，J＝9Hz，2H)，2.42(s，3H)。

[0884] 

6

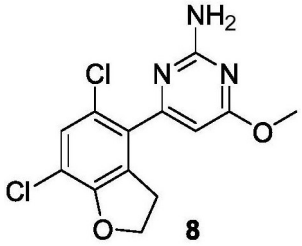
[0885] 4-(5，7-二氯-2，3-苯并二氢呋喃-4-基)-6-乙基嘧啶-2-胺(6)。^{1}H NMR(500MHz，$CDCl_3$)：δ7.27(s，1H)，6.65(s，1H)，5.05(s，2H)，4.68(t，J＝9Hz，2H)，3.26(t，J＝8.5Hz，

2H),2.68(q,J＝8Hz,2H),1.29(t,J＝7.5Hz,3H);LCMS[M+H]$^+$:310.1(针对[C14H13Cl2N3O+H]$^+$的计算值:310.04)。

[0886] 

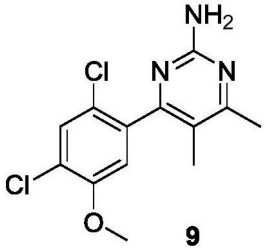
7

[0887] 4-(5,7-二氯-2,3-苯并二氢呋喃-4-基)-6-异丙基嘧啶-2-胺(7)。^{1}H NMR(500MHz,$CDCl_3$):δ7.28(s,1H),6.66(s,1H),5.04(s,2H),4.69(t,J＝9Hz,2H),3.27(t,J＝9Hz,2H),2.87(m,1H),1.28(d,J＝7Hz,6H);LCMS[M+H]$^+$:324.02(针对[C15H15Cl2N3O+H]$^+$的计算值:324.06)。

[0888] 

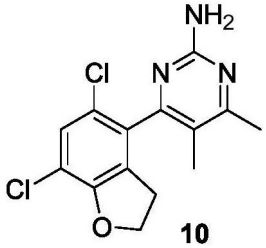
8

[0889] 4-(5,7-二氯-2,3-苯并二氢呋喃-4-基)-6-甲氧基嘧啶-2-胺(8)。^{1}H NMR(500MHz,$CDCl_3$):δ7.28(s,1H),6.19(s,1H),4.98(s,2H),4.68(t,J＝8.5Hz,2H),3.94(s,3H),3.25(t,J＝9Hz,2H);LCMS[M+H]$^+$:311.87(针对[C13H11Cl2N3O2+H]$^+$的计算值:312.02)。

[0890] 

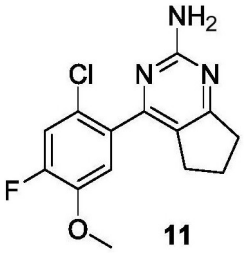
9

[0891] 4-(2,4-二氯-5-甲氧基苯基)-5,6-二甲基嘧啶-2-胺(9)。^{1}H NMR(500MHz,$CDCl_3$):δ7.47(s,1H),6.83(s,1H),4.88(s,2H),3.90(s,3H),2.42(s,3H),1.95(s,3H)。

[0892] 

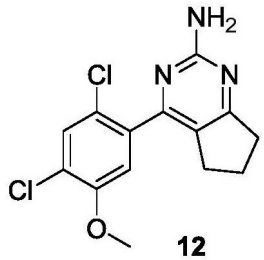
10

[0893] 4-(5,7-二氯-2,3-苯并二氢呋喃-4-基)-5,6-二甲基嘧啶-2-胺(10)。^{1}H NMR(500MHz,$CDCl_3$):δ7.25(s,1H),4.89(s,2H),4.69(t,J＝9Hz,2H),3.25(m,1H),2.88(m,1H),2.42(s,3H),1.93(s,3H)。

[0894] 

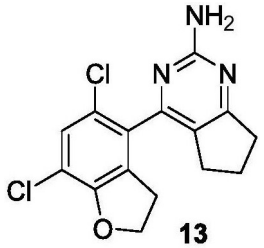
11

[0895] 4-(2-氯-4-氟-5-甲氧基苯基)-6,7-二氢-5H-环戊二烯[d]嘧啶-2-胺(11)。^{1}H NMR(500MHz,$CDCl_3$):δ7.20(d,J=10.5Hz,1H),6.94(d,J=9Hz,1H),4.99(s,2H),3.90(s,3H),2.91(t,J=8Hz,2H),2.72(t,J=7.5Hz,2H),2.08(m,2H);LCMS $[M+H]^+$:294.2(针对$[C_{14}H_{13}ClFN_3O+H]^+$的计算值:294.07)。

[0896] 

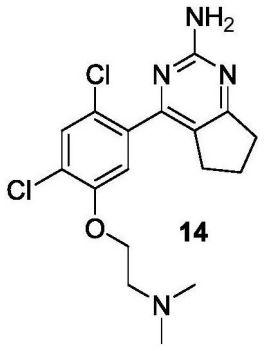
12

[0897] 4-(2,4-二氯-5-甲氧基苯基)-6,7-二氢-5H-环戊二烯[d]嘧啶-2-胺(12)。^{1}H NMR(500MHz,$CDCl_3$):δ7.47(s,1H),6.90(s,1H),4.98(s,2H),3.91(s,3H),2.92(t,J=7.5Hz,2H),2.72(t,J=7.5Hz,2H),2.08(m,2H)。

[0898] 

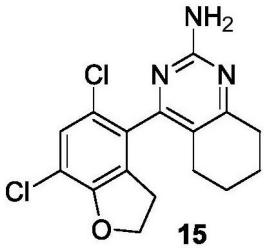
13

[0899] 4-(5,7-二氯-2,3-苯并二氢呋喃-4-基)-6,7-二氢-5H-环戊二烯[d]嘧啶-2-胺(13)。^{1}H NMR(500MHz,$CDCl_3$):δ7.25(s,1H),4.69(m,2H),3.38(m,1H),2.99-2.81(m,4H),2.49(m,1H),2.17-2.00(m,2H)。

[0900] 

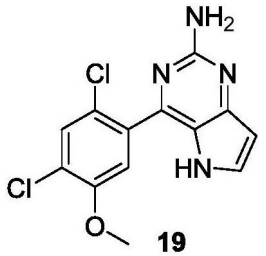
14

[0901] 4-(2,4-二氯-5-(2-(二甲氨基)乙氧基)苯基)-6,7-二氢-5H-环戊二烯[d]嘧啶-2-胺(14)。^{1}H NMR(500MHz,$CDCl_3$):δ7.46(s,1H),6.90(s,1H),4.97(s,2H),4.13(t,J=6Hz,2H),2.91(t,J=8Hz,2H),2.80(t,J=6Hz,2H),2.71(t,J=7.5Hz,2H),2.36(s,6H),2.08(m,2H);LCMS $[M+H]^+$:367.1(针对$[C_{17}H_{20}Cl_2N_4O+H]^+$的计算值:367.10)。

[0902] 

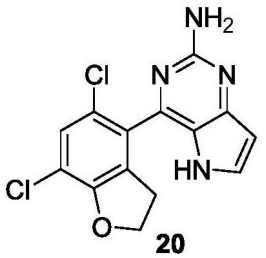
15

[0903] 4-(5,7-二氯-2,3-苯并二氢呋喃-4-基)-5,6,7,8-四氢喹唑啉-2-胺(15)。^{1}H NMR(500MHz,$CDCl_3$):δ7.28(s,1H),4.88(s,2H),4.69(t,J＝9Hz,2H),3.21(m,1H),2.89(m,1H),2.78(m,2H),2.44(m,1H),2.15(m,1H),1.86(m,2H),1.72(m,2H);LCMS $[M+H]^+$:336.1(针对$[C16H15Cl2N3O+H]^+$的计算值:336.06)。

[0904] 

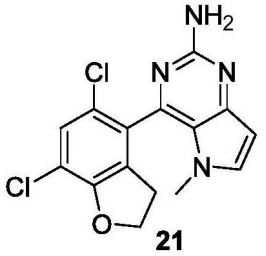
19

[0905] 4-(2,4-二氯-5-甲氧基苯基)-5H-吡咯[3,2-d]嘧啶-2-胺(19)。^{1}H NMR(500MHz,$CDCl_3$):δ8.15(s,1H),7.54(s,1H),7.46(m,1H),7.15(s,1H),6.45(m,1H),4.86(s,2H),3.94(s,3H)。

[0906] 

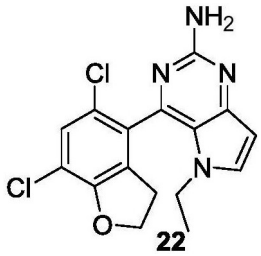
20

[0907] 4-(5,7-二氯-2,3-苯并二氢呋喃-4-基)-5H-吡咯[3,2-d]嘧啶-2-胺(20)。^{1}H NMR(500MHz,$CDCl_3$):δ8.01(s,1H),7.45(t,J＝3Hz,1H),7.34(s,1H),6.46(m,1H),4.83(s,2H),4.71(m,2H),3.60(m,1H),2.94(m,1H);LCMS $[M+H]^+$:321.0(针对$[C_{14}H_{10}Cl_2N_4O+H]^+$的计算值:321.0)。^{1}H NMR光谱示于图1中。

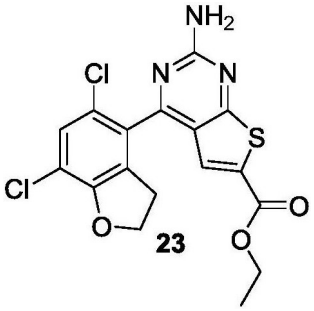
[0908] 

21

[0909] 4-(5,7-二氯-2,3-苯并二氢呋喃-4-基)-5-甲基-5H-吡咯[3,2-d]嘧啶-2-胺(21)。^{1}H NMR(500MHz,$CDCl_3$):δ7.32(s,1H),7.22(d,J＝3Hz,1H),6.36(d,J＝3Hz,1H),4.81(s,2H),4.72(m,2H),3.40(s,3H),3.34(m,1H),2.91(m,1H);LCMS $[M+H]^+$:335.0(针对$[C15H12Cl2N4O+H]^+$的计算值:335.04)。

[0910] 

[0911] 4-(5,7-二氯-2,3-苯并二氢呋喃-4-基)-5-乙基-5H-吡咯[3,2-d]嘧啶-2-胺(22)。^{1}H NMR(500MHz,$CDCl_3$):δ7.33(m,2H),6.40(d,J=2.5Hz,1H),4.80(s,2H),4.70(m,2H),3.72(d,J=7Hz,2H),3.33(m,1H),2.91(m,1H),1.14(t,J=7.5Hz,3H);LCMS[M+H]$^+$:349.1(针对[C16H14Cl2N4O+H]$^+$的计算值:349.05)。

[0912] 

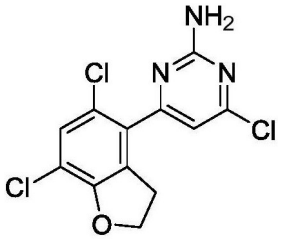
[0913] 乙基-2-氨基-4-(5,7-二氯-2,3-苯并二氢呋喃-4-基)噻吩并[2,3-d]嘧啶-6-羧酸酯(23)。^{1}H NMR(500MHz,$CDCl_3$):δ7.54(s,1H),7.35(s,1H),5.32(s,2H),4.70(m,2H),4.37(m,2H),3.35(m,1H),2.92(m,1H),1.38(t,J=7Hz,3H);LCMS[M+H]$^+$:410.0(针对[C17H13Cl2N3O3S+H]$^+$:4的计算值:410.01)。

[0914]

[0915] 2-氨基-4-(5,7-二氯-2,3-苯并二氢呋喃-4-基)-N-乙基噻吩并[2,3-d]嘧啶-6-甲酰胺(24)。^{1}H NMR(500MHz,$CDCl_3$):δ7.34(s,1H),7.21(s,1H),5.91(s,1H),5.28(s,2H),4.70(m,2H),4.48(m,2H),3.36(m,1H),2.91(m,1H),1.26(t,J=3.5Hz,3H);LCMS[M+H]$^+$:409.0(针对[C17H14Cl2N4O2S+H]$^+$:4的计算值:409.02)。

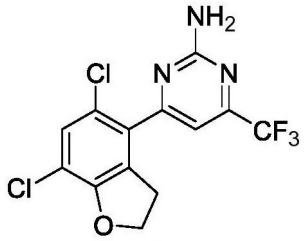
[0916] 化合物34和36根据本领域已知的方法制备,例如本文所述的那些。化合物34和36的^{1}H NMR光谱($CDCl_3$)分别提供于图2和3中。

[0917] 化合物40-48可以根据本领域已知的方法制备,例如本文所述的那些。

[0918] 

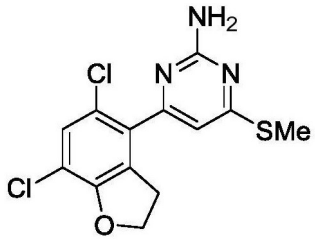
49

[0919] 4-氯-6-(5,7-二氯-2,3-苯并二氢呋喃-4-基)嘧啶-2-胺(49)。^{1}H NMR(400MHz,DMSO-d6):δ=7.48(s,1H),7.30(s,2H),6.78(s,1H),4.64(t,J=8.8Hz,2H),3.20(t,J=8.8Hz,2H)。LCMS:m/z针对$C_{12}H_8Cl_3N_3O$[M+H]$^+$的计算值:316.0;发现值:316.0。

[0920] 

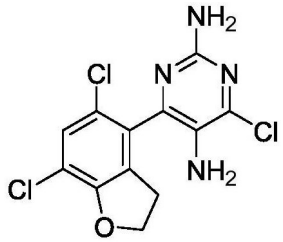
50

[0921] 4-三氟甲基-6-(5,7-二氯-2,3-苯并二氢呋喃-4-基)嘧啶-2-胺(50)。^{1}H NMR(400MHz,DMSO-d6):δ7.520(br s,2H,NH_2),7.093(s,1H),4.655(t,2H,J=8.8Hz),3.547(s,1H),3.221(t,2H,J=8.8Hz)。LCMS:m/z针对$C_{13}H_8Cl_2F_3N_3O$[M+H]$^+$的计算值:350.1;发现值:350.0。

[0922] 

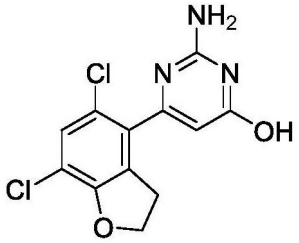
51

[0923] 4-硫代甲基-6-(5,7-二氯-2,3-苯并二氢呋喃-4-基)嘧啶-2-胺(51)。^{1}H NMR(400MHz,DMSO-d6):δ7.438(s,1H),6.815(br s,2H,NH_2),6.549(s,1H),4.633(t,2H,J=8.8Hz),3.178(t,2H,J=8.8Hz),2.453(s,3H)。LCMS:m/z针对$C_{13}H_{11}Cl_2N_3OS$[M+H]$^+$的计算值:328.2;发现值:328.1。

[0924] 

52

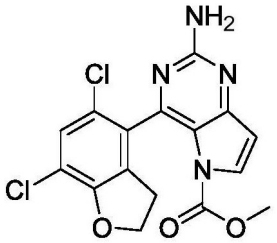
[0925] 4-氯-6-(5,7-二氯-2,3-苯并二氢呋喃-4-基)嘧啶-2,5-二胺(52)。^{1}H NMR(400MHz,DMSO-d6):δ=7.46(s,1H),6.25(s,2H),4.67(t,J=8.8Hz,2H),4.30(s,2H),3.15-3.07m,2H)。HPLC/MS:m/z针对$C_{12}H_9Cl_3N_4O$[M+H]$^+$的计算值:331.0;发现值:331.1。

[0926] 

53

[0927] 2-氨基-6-(5,7-二氯-2,3-苯并二氢呋喃-4-基)嘧啶-4-醇(53)。在室温下,向含有二噁烷:1N NaOH水性(50:50;1mL:1mL)的烧瓶中添加4-氯-6-(5,7-二氯-2,3-二氢苯并呋喃-4-基)嘧啶-2-胺(49)(20mg,0.063mmol)和DABCO(8mg,0.069mmol)。随后将反应在80℃下加热。将反应冷却,通过添加1N HCl水溶液(2mL)酸化,溶于乙酸乙酯(5mL)中,用盐水(3×5mL)洗涤。将有机层用Na_2SO_4干燥,过滤,并将挥发物蒸发。通过硅胶色谱法使用DCM:MeOH(100:0至90:10)的梯度纯化残余物。得到呈白色固体的产物,产率为77%。

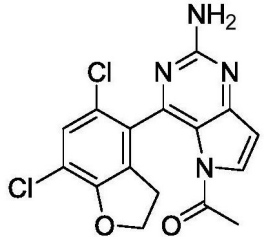
[0928] ^{1}H NMR(400MHz,DMSO-d6):δ=7.39(s,1H),5.57(s,1H),4.62(t,J=8.8Hz,2H),3.20(t,J=8.8Hz,2H)。HPLC/MS:m/z针对$C_{12}H_9Cl_2N_3O_2$[M+H]$^+$的计算值:298.0;发现值:298.1。

[0929] 

54

[0930] 甲基2-氨基-4-(5,7-二氯-2,3-苯并二氢呋喃-4-基)-5H-吡咯[3,2-d]嘧啶-5-羧酸酯(54)。在0℃下,向含有在DCM(1mL)中的4-(5,7-二氯-2,3-二氢苯并呋喃-4-基)-5H-吡咯并[3,2-d]嘧啶-2-胺(20)(20mg,0.062mmol)的烧瓶中添加干燥的K_2CO_3(30mg,0.22mmol)和氯甲酸甲酯(0.014mL,0.186mmol)。将反应在室温下搅拌8小时。然后,通过添加1N NaOH水性(1mL)淬灭反应,并在室温下搅拌1小时。将反应物溶于DCM(10mL)中并用饱和$NaHCO_3$水溶液洗涤(10mL)。将有机层用Na_2SO_4干燥,过滤,并将挥发物蒸发。通过硅胶色谱法使用DCM:MeOH(100:0至90:10)的梯度纯化残余物。得到呈黄色固体的产物,产率为66%。

[0931] ^{1}H NMR(400MHz,CDCl3):δ=7.61(s,1H),7.23(s,1H),6.51(s,1H),4.63(br s,2H),3.77(s,3H),3.65(br s,1H),2.85(br s,1H)。HPLC/MS:m/z针对$C_{16}H_{12}Cl_2N_4O_3$[M+H]$^+$的计算值:379.0;发现值:379.1。

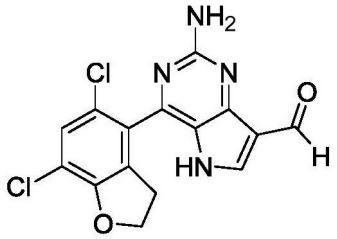
[0932] 

55

[0933] 1-(2-氨基-4-(5,7-二氯-2,3-苯并二氢呋喃-4-基)-5H-吡咯[3,2-d]嘧啶-5-基)

乙-1-酮(55)。在0℃下,向含有在DCM(1mL)中的4-(5,7-二氯-2,3-二氢苯并呋喃-4-基)-5H-吡咯并[3,2-d]嘧啶-2-胺(20mg,0.062mmol)的烧瓶中添加干燥的K_2CO_3(30mg,0.22mmol)和乙酰氯(0.006mL,0.074mmol)。将反应在室温下搅拌8小时。然后,通过添加1N NaOH水性(1mL)淬灭反应,并在室温下搅拌1小时。将反应物溶于DCM(10mL)中并用饱和$NaHCO_3$水溶液洗涤(10mL)。将有机层用Na_2SO_4干燥,过滤,并将挥发物蒸发。通过硅胶色谱法使用DCM:MeOH(100:0至90:10)的梯度纯化残余物。得到呈黄色固体的产物,产率为81%。

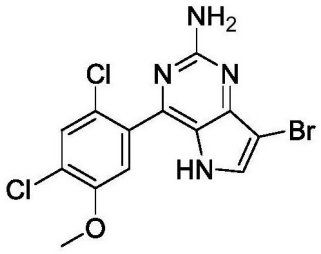
[0934] ^1H NMR(400MHz,CDCl3):δ=7.57(s,1H),7.23(s,1H),6.55(s,1H),4.63(br s,2H),3.45(br s,1H),3.35(s,3H),2.85(br s,1H)。HPLC/MS:m/z针对$C_{16}H_{12}Cl_2N_4O_2[M+H]^+$的计算值:363.0;发现值:363.1。

[0935] 

56

[0936] 2-氨基-4-(5,7-二氯-2,3-苯并二氢呋喃-4-基)-5H-吡咯[3,2-d]嘧啶-7-甲醛(56)。在0℃下,向含有干燥THF(2mL)的烧瓶中加入无水DMF(0.1mL)和$POCl_3$(0.015mL,0.16mmol)。将反应在氩气下在0℃下搅拌30分钟,然后逐滴添加在THF(1mL)中的4-(5,7-二氯-2,3-二氢苯并呋喃-4-基)-5H-吡咯并[3,2-d]嘧啶-2-胺(20mg,0.062mmol)。将反应物搅拌8小时,加热至室温。然后向反应中添加1N NaOH水溶液(2mL),并加热至80℃持续1小时。将反应冷却至室温,并溶于EtOAc(20mL)中,并且用饱和$NaHCO_3$水溶液(20mL)洗涤。将有机层用Na_2SO_4干燥,过滤,并将挥发物蒸发。通过硅胶色谱法使用DCM:MeOH(100:0至90:10)的梯度纯化残余物。得到呈白色固体的产物,产率为58%。

[0937] ^1H NMR(400MHz,CDCl3):δ=10.05(s,1H),7.96(s,1H),7.24(s,1H),4.63(br s,2H),3.31(br s,1H),2.85(br s,1H)。HPLC/MS:m/z针对$C_{15}H_{10}Cl_2N_4O_2[M+H]^+$的计算值:349.0;发现值:349.1。

[0938] 

57

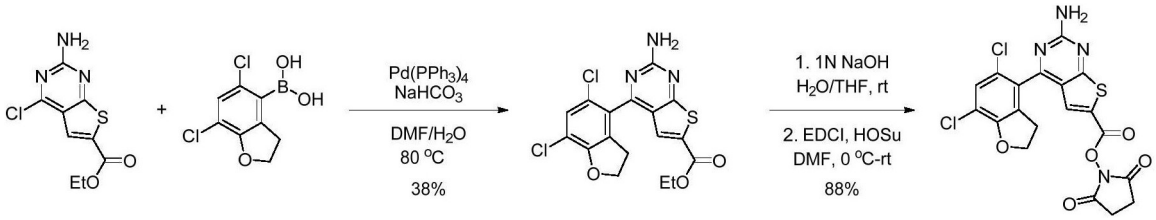
[0939] 7-溴-4-(2,4-二氯-5-甲氧基苯基)-5H-吡咯[3,2-d]嘧啶-2-胺(57)。在0℃下,向含有在AcOH:tBuOH(50:50,0.5mL:0.5mL)中的4-(2,4-二氯-5-甲氧基苯基)-5H-吡咯并[3,2-d]嘧啶-2-胺(20mg,0.065mmol)的烧瓶中添加LiBr(18mg,0.22mmol)和Br_2(0.011mL,0.22mmol)。将反应在室温下搅拌8小时。然后,将反应物溶于EtOAc(20mL)中,并且用饱和$NaHCO_3$水溶液(3×20mL)和$Na_2S_2O_3$(10%wt.水溶液,20mL)洗涤。将有机层用Na_2SO_4干燥,过滤,并将挥发物蒸发。通过硅胶色谱法使用DCM:MeOH(100:0至90:10)的梯度纯化残余物。得

到呈黄色固体的产物，产率为56％。

[0940] ^{1}H NMR(400MHz,DMSO-d6):δ＝7.75(s,1H),7.72(s,1H),7.26(s,1H),6.24(s,2H),3.86(s,3H)。HPLC/MS:m/z针对$C_{13}H_9BrCl_2N_4O$[M+H]$^+$的计算值:386.9;发现值:387.0。

[0941] 2-氨基-4-(5,7-二氯-2,3-苯并二氢呋喃-4-基)噻吩并[2,3-d]嘧啶-6-甲酰胺一般合成方法：

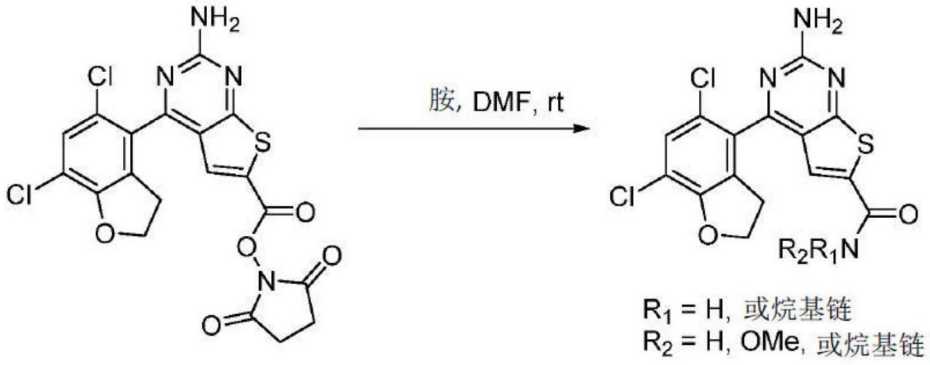
[0942]



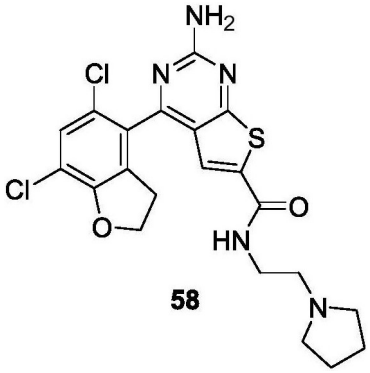
[0943] 步骤1：前体2,5-二氧吡咯烷-1-基2-氨基-4-(5,7-二氯-2,3-苯并二氢呋喃-4-基)噻吩并[2,3-d]嘧啶-6-羧酸酯的合成。在室温下，向含有脱气的DMF:H_2O(50:50;2mL:2mL)的烧瓶中添加2-氨基-4-氯噻吩并[2,3-d]嘧啶-6-甲酸乙酯(100mg,0.39mmol)、(5,7-二氯-2,3-二氢苯并呋喃-4-基)硼酸(91mg,0.39mmol)、$NaHCO_3$(82mg,0.98mmol)、和Pd$(PPh_3)_4$(22mg,0.02mmol)。随后将反应在氩气下在80℃下加热8小时。将反应冷却，溶于乙酸乙酯(20mL)中，并用盐水(3×20mL)洗涤。将有机层用Na_2SO_4干燥，过滤，并将挥发物蒸发。通过硅胶色谱法使用DCM:MeOH(100:0至90:10)的梯度纯化残余物。得到产物2-氨基-4-(5,7-二氯-2,3-二氢苯并呋喃-4-基)噻吩并[2,3-d]嘧啶-6-甲酸乙酯，产率为38％，为黄色固体。

[0944] 将2-氨基-4-(5,7-二氯-2,3-二氢苯并呋喃-4-基)噻吩并[2,3-d]嘧啶-6-甲酸乙酯(60mg,0.15mmol)溶于THF(1mL)中，并且向烧瓶中加入1N NaOH水溶液(1mL)。将反应在室温下搅拌8小时。随后，将溶液冷却至0℃，并通过添加1N HCl水溶液(2mL)酸化，导致形成白色沉淀，将其过滤并干燥，以定量产率得到2-氨基-4-(5,7-二氯-2,3-二氢苯并呋喃-4-基)噻吩并[2,3-d]嘧啶-6-羧酸，未进一步纯化。将滤液(57mg,0.15mmol)溶于干燥的DMF(1mL)中，冷却至0℃，向反应容器中添加N-羟基丁二酰亚胺(23mg,0.2mmol)和1-乙基-3-(3-二甲基氨基丙基)碳二亚胺HCl(38mg,0.2mmol)。将反应物搅拌加热至室温8小时以上。将该溶液溶于DCM(20mL)中并用饱和NH_4Cl水溶液(3×20mL)洗涤。将有机层用Na_2SO_4干燥，过滤，并将挥发物蒸发。通过硅胶色谱法使用DCM:MeOH(100:0至90:10)的梯度纯化残余物。得到产物2,5-二氧代吡咯烷-1-基2-氨基-4-(5,7-二氯-2,3-二氢苯并呋喃-4-基)噻吩并[2,3-d]嘧啶-6-羧酸酯，为白色固体，88％产率。

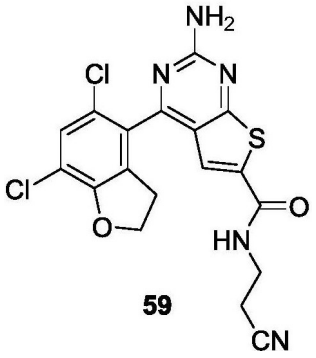
[0945] 步骤2：形成酰胺的一般程序：

[0946] 

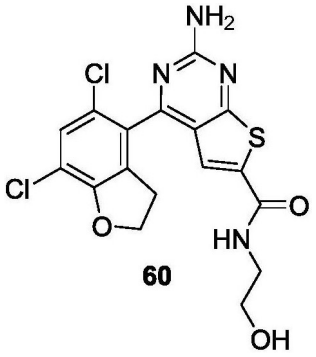
[0947] 向含有2,5-二氧代吡咯烷-1-基2-氨基-4-(5,7-二氯-2,3-二氢苯并呋喃-4-基)噻吩并[2,3-d]嘧啶-6-羧酸酯(10mg,0.02mmol)的烧瓶中添加干燥的DMF(0.5mL),然后添加胺(3当量,0.06mmol)(例如氨、伯胺或仲胺)。将反应在室温下搅拌12小时,然后将其溶于DCM(5mL)中,并用饱和NH_4Cl水溶液(3×5mL)洗涤。将有机层用Na_2SO_4干燥,过滤,并将挥发物蒸发。通过硅胶色谱法使用DCM:MeOH(100:0至90:10)的梯度纯化残余物。以良好至优异的产率获得所得的酰胺。

[0948] 

[0949] 2-氨基-4-(5,7-二氯-2,3-苯并二氢呋喃-4-基)-N-(2-(吡咯烷-1-基)乙基)噻吩并[2,3-d]嘧啶-6-甲酰胺(58)。^1H NMR(400MHz,DMSO-d6):δ=8.79(s,1H),7.61(s,1H),7.58(s,1H),7.28(s,2H),4.67(t,J=8.8Hz,2H),3.44-3.11(m,6H),2.90-2.75(m,4H),1.77-1.73(m,4H)。HPLC/MS:m/z针对$C_{21}H_{21}Cl_2N_5O_2S$[M+H]$^+$的计算值:478.1;发现值:478.1

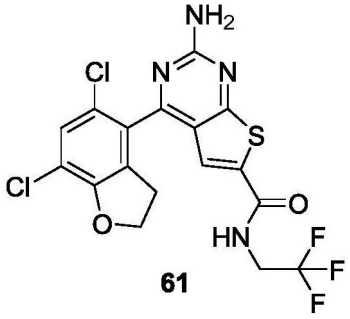
[0950] 

[0951] 2-氨基-N-(2-氰乙基)-4-(5,7-二氯-2,3-苯并二氢呋喃-4-基)噻吩并[2,3-d]嘧啶-6-甲酰胺(59)。^1H NMR(400MHz,DMSO-d6):δ=8.94(t,J=5.6Hz,1H),7.63(s,1H),7.60(s,1H),7.34(s,2H),4.69(t,J=8.8Hz,2H),3.46-3.41(m,2H),3.23-3.15(m,1H),3.03-2.97(m,1H),2.76(t,J=6.4Hz,2H)。HPLC/MS:m/z针对$C_{18}H_{13}Cl_2N_5O_2S$[M+H]$^+$的计算值:434.0;发现值:434.1。

[0952] 

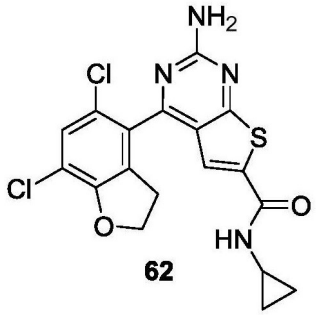
60

[0953] 2-氨基-4-(5,7-二氯-2,3-苯并二氢呋喃-4-基)-N-(2-羟乙基)噻吩并[2,3-d]嘧啶-6-甲酰胺(60)。^{1}H NMR(400MHz,DMSO-d6):δ=8.57(t,J=5.6Hz,1H),7.59(s,2H),7.26(s,2H),4.73(t,J=5.6Hz,1H),4.67(t,J=8.8Hz,2H),3.46-3.41(m,2H),3.26-3.12(m,3H),3.03-2.94(m,1H)。HPLC/MS:m/z针对$C_{17}H_{14}Cl_2N_4O_3S$[M+H]$^+$的计算值:425.0;发现值:425.1。

[0954] 

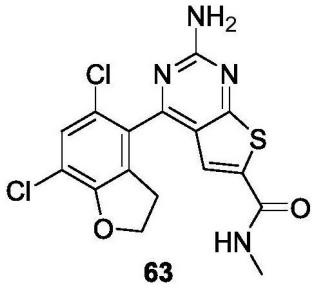
61

[0955] 2-氨基-4-(5,7-二氯-2,3-苯并二氢呋喃-4-基)-N-(2,2,2-三氟乙基)噻吩并[2,3-d]嘧啶-6-甲酰胺(61)。^{1}H NMR(400MHz,DMSO-d6):δ=9.18(t,J=6.0Hz,1H),7.72(s,1H),7.63(s,1H),7.38(s,2H),4.69(t,J=8.8Hz,2H),4.12-4.03(m,2H),3.26-3.18(m,1H),3.03-2.94(m,1H)。HPLC/MS:m/z针对$C_{17}H_{11}Cl_2F_3N_4O_2S$[M+H]$^+$的计算值:463.0;发现值:463.1。

[0956] 

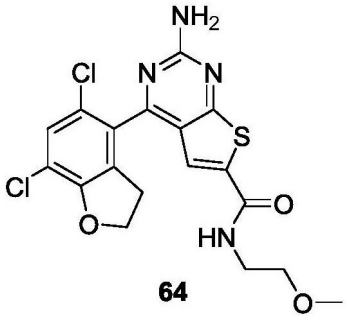
62

[0957] 2-氨基-N-环丙基-4-(5,7-二氯-2,3-苯并二氢呋喃-4-基)噻吩并[2,3-d]嘧啶-6-甲酰胺(62)。^{1}H NMR(400MHz,DMSO-d6):δ=8.54(s,1H),7.61(s,1H),7.53(s,1H),7.29(s,2H),4.68(t,J=8.8Hz,2H),3.26-3.18(m,1H),3.03-2.94(m,1H),2.81-2.71(m,1H),0.75-0.61(m,2H),0.55-0.40(m,2H)。HPLC/MS:m/z针对$C_{18}H_{14}Cl_2N_4O_2S$[M+H]$^+$的计算值:421.0;发现值:421.1。

[0958] 

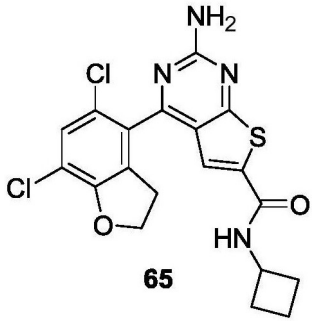
63

[0959] 2-氨基-4-(5,7-二氯-2,3-苯并二氢呋喃-4-基)-N-甲基噻吩并[2,3-d]嘧啶-6-甲酰胺(63)。^{1}H NMR(400MHz,DMSO-d6):δ=8.62-8.59(m,1H),7.61(s,2H),7.27(s,2H),4.64(t,J=8.8Hz,2H),3.24(s,3H),3.23-3.18(m,1H),3.03-2.91(m,1H)。HPLC/MS:m/z针对$C_{16}H_{12}Cl_2N_4O_2S$[M+H]$^+$的计算值:395.0;发现值:395.1。

[0960] 

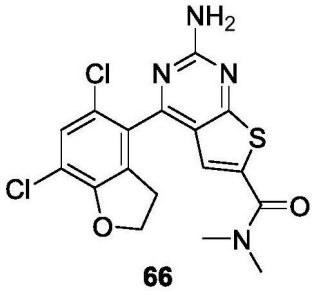
64

[0961] 2-氨基-4-(5,7-二氯-2,3-苯并二氢呋喃-4-基)-N-(2-甲氧基乙基)噻吩并[2,3-d]嘧啶-6-甲酰胺(64)。^{1}H NMR(400MHz,DMSO-d6):δ=8.51-8.41(m,1H),7.59(s,1H),7.50(s,1H),7.26(s,2H),4.67(t,J=8.8Hz,2H),3.23-3.10(m,4H),3.03-2.91(m,2H),2.72-2.67(m,3H)。HPLC/MS:m/z针对$C_{18}H_{16}Cl_2N_4O_3S$[M+H]$^+$的计算值:439.0;发现值:439.1。

[0962] 

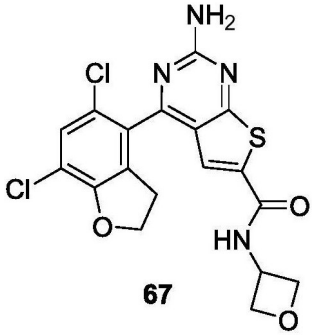
65

[0963] 2-氨基-N-环丁基-4-(5,7-二氯-2,3-苯并二氢呋喃-4-基)噻吩并[2,3-d]嘧啶-6-甲酰胺(65)。^{1}H NMR(400MHz,DMSO-d6):δ=8.68(d,J=6.8Hz,1H),7.61(s,1H),7.56(s,1H),7.26(s,2H),4.67(t,J=8.8Hz,2H),4.33-4.26(m,1H),3.23-3.18(m,1H),3.03-2.91(m,1H),2.16-1.92(m,2H),1.70-1.60(m,1H),1.33-1.20(m,2H),0.90-0.78(m,1H)。HPLC/MS:m/z针对$C_{19}H_{16}Cl_2N_4O_2S$[M+H]$^+$的计算值:435.0;发现值:435.1。

[0964] 

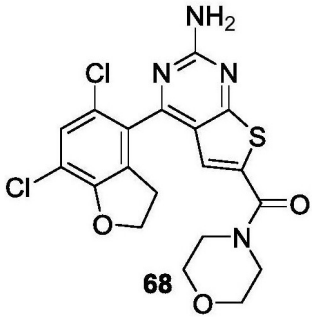
66

[0965] 2-氨基-4-(5,7-二氯-2,3-苯并二氢呋喃-4-基)-N,N-二甲基噻吩并[2,3-d]嘧啶-6-甲酰胺(66)。^{1}H NMR(400MHz,DMSO-d6):δ=7.54(s,1H),7.23(s,2H),7.15(s,1H),4.66(t,J=8.8Hz,2H),3.31(s,3H),3.23-2.90(m,5H)。HPLC/MS:m/z针对$C_{17}H_{14}Cl_2N_4O_2S$[M+H]$^+$的计算值:409.0;发现值:409.1。

[0966] 

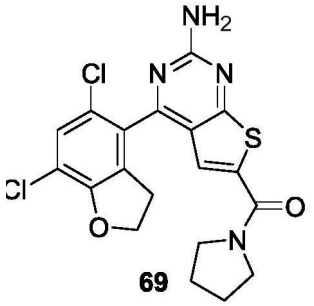
67

[0967] 2-氨基-4-(5,7-二氯-2,3-苯并二氢呋喃-4-基)-N-(氧杂环丁-3-基)噻吩并[2,3-d]嘧啶-6-甲酰胺(67)。^{1}H NMR(400MHz,DMSO-d6):δ=9.17(d,J=6.8Hz,1H),7.64(s,1H),7.62(s,1H),7.31(s,2H),4.97-4.90(m,1H),4.75-4.65(m,4H),4.55-4.45(m,2H),3.20-3.11(m,1H),3.02-2.92(m,1H)。HPLC/MS:m/z针对$C_{18}H_{14}Cl_2N_4O_3S$[M+H]$^+$的计算值:437.0;发现值:437.1。

[0968] 

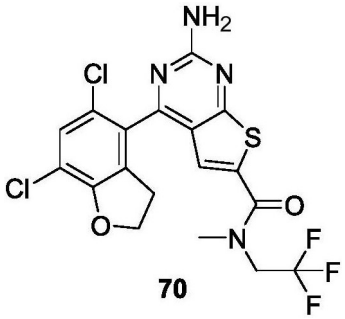
68

[0969] (2-氨基-4-(5,7-二氯-2,3-苯并二氢呋喃-4-基)噻吩并[2,3-d]嘧啶-6-基)(吗啉代)甲酮(68)。^{1}H NMR(400MHz,DMSO-d6):δ=7.54(s,1H),7.23(s,2H),7.12(s,1H),4.66(t,J=8.8Hz,2H),3.59(br s,8H),3.26-3.21(m,1H),3.02-2.92(m,1H)。HPLC/MS:m/z针对$C_{19}H_{16}Cl_2N_4O_3S$[M+H]$^+$的计算值:451.0;发现值:451.1。

[0970] 

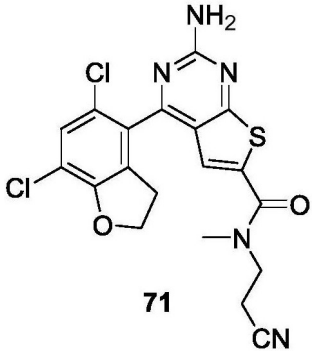
69

[0971] (2-氨基-4-(5,7-二氯-2,3-苯并二氢呋喃-4-基)噻吩并[2,3-d]嘧啶-6-基)(吡咯烷-1-基)甲酮(69)。^{1}H NMR(400MHz,DMSO-d6):δ=7.54(s,1H),7.23(s,2H),7.21(s,1H),4.66(t,J=8.8Hz,2H),3.68-3.64(m,2H),3.44(br s,2H),3.26-3.16(m,1H),3.02-2.92(m,1H),1.91-1.76(m,4H)。HPLC/MS:m/z针对$C_{19}H_{16}Cl_2N_4O_2S$[M+H]$^+$的计算值:435.0;发现值:435.1。

[0972] 

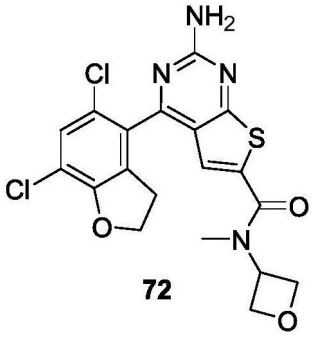
70

[0973] 2-氨基-4-(5,7-二氯-2,3-苯并二氢呋喃-4-基)-N-甲基-N-(2,2,2-三氟乙基)噻吩并[2,3-d]嘧啶-6-甲酰胺(70)。^{1}H NMR(400MHz,DMSO-d6):δ=7.54(s,1H),7.33(s,3H),4.66(t,J=8.8Hz,2H),4.41-4.28(m,2H),3.27(s,3H),3.26-3.16(m,1H),3.02-2.92(m,1H)。HPLC/MS:m/z针对$C_{18}H_{13}Cl_2F_3N_4O_2S$[M+H]$^+$的计算值:477.0;发现值:477.1。

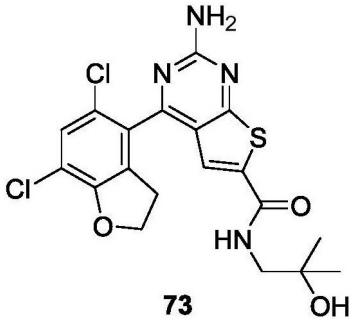
[0974] 

71

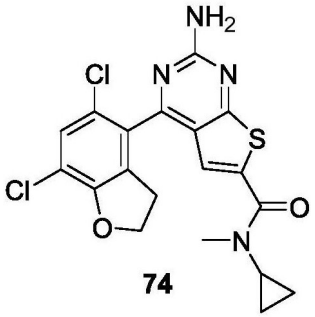
[0975] 2-氨基-N-(2-氰乙基)-4-(5,7-二氯-2,3-苯并二氢呋喃-4-基)-N-甲基噻吩并[2,3-d]嘧啶-6-甲酰胺(71)。^{1}H NMR(400MHz,DMSO-d6):δ=7.54(s,1H),7.28(s,2H),7.20(s,1H),4.66(t,J=8.8Hz,2H),3.69(br s,2H),3.26-3.16(m,4H),3.02-2.92(m,1H),2.82-2.70(m,2H)。HPLC/MS:m/z针对$C_{19}H_{15}Cl_2N_5O_2S$[M+H]$^+$的计算值:448.0;发现值:448.1。

[0976] 

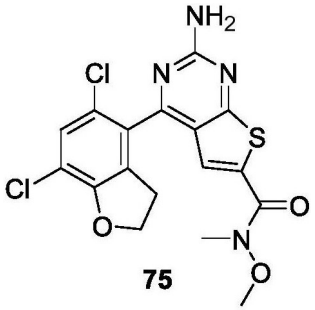
[0977] 2-氨基-4-(5,7-二氯-2,3-苯并二氢呋喃-4-基)-N-甲基-N-(氧杂环丁-3-基)噻吩并[2,3-d]嘧啶-6-甲酰胺(72)。^{1}H NMR(400MHz,DMSO-d6):δ=7.55(s,1H),7.26(s,2H),7.16(s,1H),5.21-5.16(m,1H),4.69-4.60(m,6H),3.26-3.14(m,4H),3.02-2.92(m,1H)。HPLC/MS:m/z针对$C_{19}H_{16}Cl_2N_4O_3S$[M+H]$^+$的计算值:451.0;发现值:451.1。

[0978] 

[0979] 2-氨基-4-(5,7-二氯-2,3-苯并二氢呋喃-4-基)-N-(2-羟基-2-甲基丙基)噻吩并[2,3-d]嘧啶-6-甲酰胺(73)。^{1}H NMR(400MHz,DMSO-d6):δ=8.44(s,1H),7.69(s,1H),7.59(s,1H),7.23(s,2H),4.67(t,J=8.8Hz,2H),4.45(s,1H),3.21-3.12(m,3H),3.02-2.92(m,1H),1.04(s,6H)。HPLC/MS:m/z针对$C_{19}H_{18}Cl_2N_4O_3S$[M+H]$^+$的计算值:453.0;发现值:453.1。

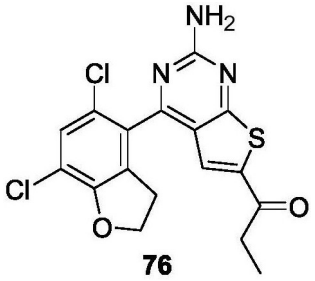
[0980] 

[0981] 2-氨基-N-环丙基-4-(5,7-二氯-2,3-苯并二氢呋喃-4-基)-N-甲基噻吩并[2,3-d]嘧啶-6-甲酰胺(74)。^{1}H NMR(400MHz,DMSO-d6):δ=7.55(s,1H),7.36(s,1H),7.28(s,2H),4.70-4.62(m,2H),3.13-3.06(m,1H),3.00-2.91(m,4H),0.80-0.72(m,2H),0.68-0.63(m,2H)。HPLC/MS:m/z针对$C_{19}H_{16}Cl_2N_4O_2S$[M+H]$^+$的计算值:435.0;发现值:435.1。

[0982] 

75

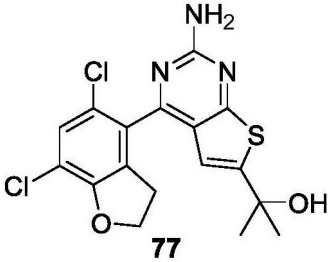
[0983] 2-氨基-4-(5,7-二氯-2,3-苯并二氢呋喃-4-基)-N-甲氧基-N-甲基噻吩并[2,3-d]嘧啶-6-甲酰胺(75)。^{1}H NMR(400MHz,DMSO-d6):δ=7.57(s,1H),7.47(s,1H),7.37(s,2H),4.70-4.62(m,2H),3.74(s,3H),3.27-3.19(m,4H),3.00-2.91(m,1H)。HPLC/MS:m/z针对$C_{17}H_{14}Cl_2N_4O_3S$[M+H]$^+$的计算值:425.0;发现值:425.1。

[0984] 

76

[0985] 1-(2-氨基-4-(5,7-二氯-2,3-苯并二氢呋喃-4-基)噻吩并[2,3-d]嘧啶-6-基)丙-1-酮(76)。在0℃下,向含有在干燥THF(1mL)中的2-氨基-4-(5,7-二氯-2,3-二氢苯并呋喃-4-基)-N-甲氧基-N-甲基噻吩并[2,3-d]嘧啶-6-甲酰胺(20mg,0.048mmol)的烧杯中添加EtMgBr(2.0M在THF中;0.029mL,0.057mmol)。将反应搅拌8小时,然后通过添加饱和NH_4Cl水溶液(1mL)淬灭。水层用EtOAc(3×2mL)萃取,经Na_2SO_4干燥,过滤,并蒸发挥发物。通过硅胶色谱法使用DCM:MeOH(100:0至90:10)的梯度纯化残余物。得到呈白色固体的产物,产率为91%。

[0986] ^{1}H NMR(400MHz,$CDCl_3$):δ=7.41(s,1H),7.34(s,1H),5.84(br s,2H),4.74-4.64(m,2H),3.87-3.76(m,1H),3.30-3.10(m,3H),1.50-1.41(m,3H)。HPLC/MS:m/z针对$C_{17}H_{13}Cl_2N_3O_2S$[M+H]$^+$的计算值:394.0;发现值:394.1。

[0987] 

77

[0988] 2-(2-氨基-4-(5,7-二氯-2,3-苯并二氢呋喃-4-基)噻吩并[2,3-d]嘧啶-6-基)丙-2-醇(77)。在0℃下,向含有在干燥THF(1mL)中的2-氨基-4-(5,7-二氯-2,3-二氢苯并呋喃-4-基)噻吩并[2,3-d]嘧啶-6-甲酸乙酯(20mg,0.048mmol)的烧杯中添加MeMgBr(2.0M在THF中;0.072mL,0.144mmol)。将反应搅拌8小时,然后通过添加饱和NH_4Cl水溶液(1mL)淬灭。水层用EtOAc(3×2mL)萃取,经Na_2SO_4干燥,过滤,并蒸发挥发物。通过硅胶色谱法使用DCM:MeOH(100:0至90:10)的梯度纯化残余物。得到呈白色固体的产物,产率为78%。

[0989] ^{1}H NMR(400MHz,DMSO-d6):δ＝7.53(s,1H),6.85(s,2H),6.54(s,1H),5.95(s,1H),4.64(t,J＝8.8Hz,2H),3.20-3.12(m,1H),3.00-2.90(m,1H),1.46(s,3H),1.44(s,3H)。HPLC/MS:m/z针对$C_{17}H_{15}Cl_2N_3O_2S$[M+H]$^{+}$的计算值:396.0;发现值:396.1。

[0990] 实例2.本发明化合物的体外测定

[0991] Hsp90生化测定(荧光偏振)

[0992] 使用FITC标记的格尔德霉素和截短的α-Hsp90蛋白,使用荧光偏振(FP)测定来评估本发明的化合物的Hsp90抑制活性。在BMG CLARIOstar®读数器(德国奥登伯格(Ortenberg,Germany)BMG Labtech)上进行结合活性的测量。该测定是均相的,并且在384孔板中进行,其与已知标准一致地进行。用已知的Hsp90抑制剂例如,PU-H71(IC_{50}＝60nM)验证该测定,其与报道的IC_{50}一致(罗(Luo)等人,同上)。化合物20、36、37、和39以及已知的Hsp90抑制剂的该测定的结果示于图4中。

[0993] Hsp90生化测定(AlphaLISA)

[0994] 基于(珀金埃尔默公司(PerkinElmer,Inc.),沃尔瑟姆(Waltham,MA))研发的AlphaLISA格式,使用鲁棒性的且可再现的测定来评价本发明化合物的Hsp90抑制活性(测定的形式描述于例如"ELISA到AlphaLISA转化指南",(珀金埃尔默公司(PerkinElmer,Inc.),2012年8月出版)。该测定使用生物素化的格尔德霉素、His标记的Hsp90、和Ni^{+2}包被的珠球。该测定是均相的并经微型化至384孔板。在Envision检测仪上进行结合活性的测量。用已知的Hsp90抑制剂(包括与所报道的IC_{50}(罗等人,同上)一致的PU-H71(IC_{50}＝60nM))验证该测定。该测定法是评价本发明化合物的主要测定法。在该测定中,化合物20显示Hsp90抑制活性(IC_{50}为0.74±0.1μM;参见图5A)。

[0995] 基于Hsp90细胞的功能测定

[0996] 用本发明的化合物处理细胞24小时,然后在含有NP-40、原钒酸盐、和蛋白酶抑制剂的缓冲液中裂解。使用对Hsp70、Hsp90、或肌动蛋白(作为对照)特异性的抗体进行蛋白印记。使用例如刘(Liu)等人,生物化学(Biochemistry),49:4921-4929,2010的方法,用SHSY5Y-hTau441V337M/R406W细胞系(勒夫勒(Loeffler)等人,分子神经科学杂志(J.Mol.Neurosci.),47:192-203,2012)测定了Tau磷酸化。该细胞系代表稳定转染的细胞系,其已经通过过度表达具有两种突变:V337M和R406W的最长的人体tau同种型hTAU441显示具有过度磷酸化的tau。本文所述的功能测定提供tau蛋白病变的体外模型,并且可用于评价Hsp90抑制剂对磷酸化的tau蛋白(p-Tau)的影响。在这些测定中,化合物20显示Hsp70的表达增加(参见图5B),在0.1μM和0.5μM处的的pTau231水平的显着降低(参见图6B),以及在0.05μM、0.1μM、和0.5μM处的pTau396水平的显着降低(参见图6C)。

[0997] 细胞毒性测定

[0998] 使用MTT测定法测定SH-SY5Y-hTAU441细胞活力。如图6A所示,化合物20不影响SH-SY5Y-hTAU441细胞的细胞活力。还可以在24小时和48小时后与测量ATP水平的CellTiter-Glo®测定一起测量SH-SY5Y细胞活力。此外,可以使用具有活细胞显微镜成像的Celigo®和GE InCell分析仪2000来测量多种结果,包括凋亡标记、膜通透性和线粒体活性以测量细胞毒性。

[0999] 小鼠肝微粒体稳定性

[1000] 通过监测它们在小鼠肝微粒体中的降解来评估本发明化合物的代谢稳定性。化合

物20表现出良好的微粒体稳定性($T_{1/2}$＝26min)。

[1001] 溶解度

[1002] 在pH 7.4的缓冲液中测定化合物溶解度。水溶解度大于或等于约0.5μM(例如大于或等于约1μM,大于或等于约2μM,大于或等于约5μM,大于或等于约10μM,大于或等于约20μM,或大于或等于约30μM)可以表示在医学用途(例如用于治疗神经退行性障碍)上具有可接受的溶解度的化合物。在pH为7.4时,化合物20的水溶解度为30μM。

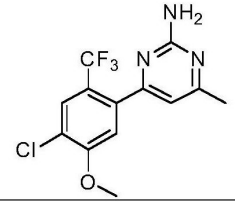
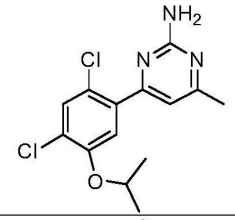
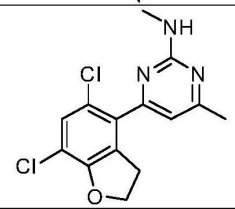
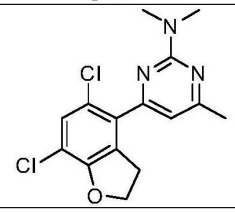
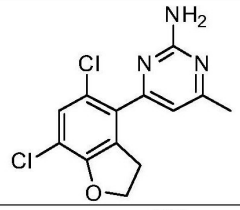
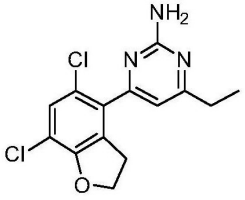
[1003] 细胞通透性

[1004] 可以在MDR1-MDCK渗透性测定或Caco-2渗透性测定中评估化合物以确定其渗透性。化合物的顶端(A)至基部(B)渗透性>3×10^{-6}cm/sec和B→A/A→B不对称性<3被认为是脑渗透的可接受的预测因子,并且具有这种性质的化合物不太可能是P-糖蛋白(P-gp)底物。化合物20在MDR1-MDCK测定中(A-B＝28×10^{-6}cm/s)显示出优异的渗透性并具有低不对称性(B→A/A→B不对称性＝0.9)。

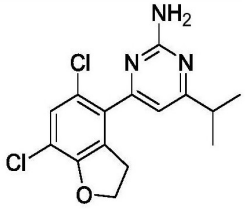
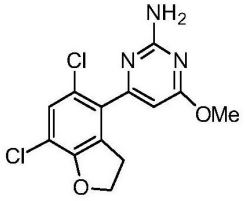
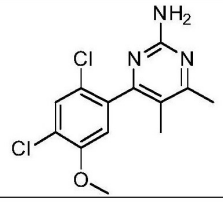
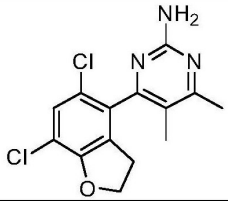
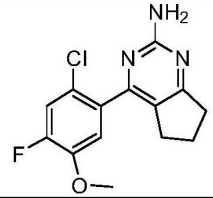
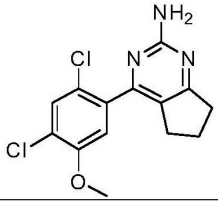
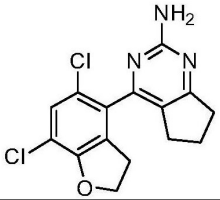
[1005] 本发明的某些化合物的上述测定的结果总结在表3中。

[1006] 表3.

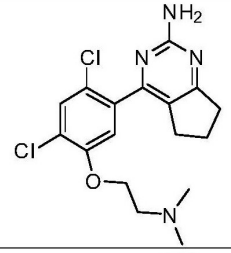
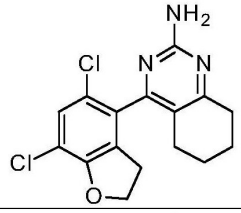
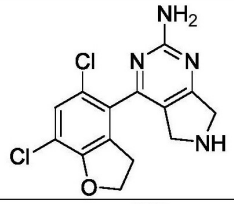
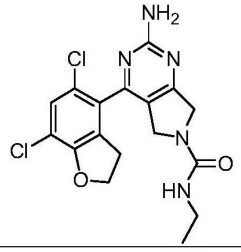
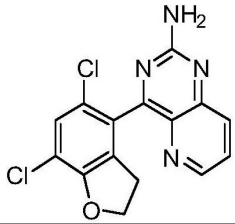
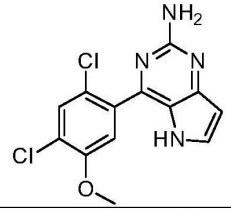
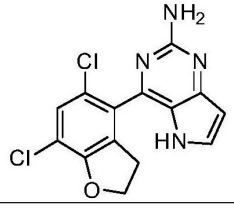
[1007]

化合物	MW	cLogP	PSA	Hsp90 抑制活性	Hsp 70激动剂活性
1 	317	4	60	-	
2 	311	4.3	60	++	
3 	309	3.9	46	-	
4 	323	4.7	37	-	
5 	295	3.6	60	+++	在0.4-1.0 μM处 > 2 倍
6 	310	4.1	60	+++	≥ 10 μM

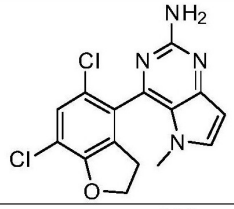
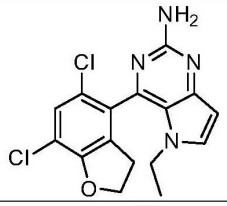
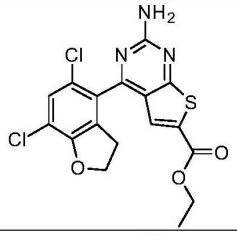
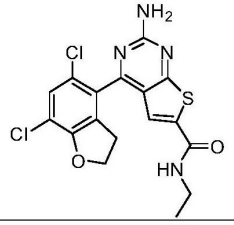
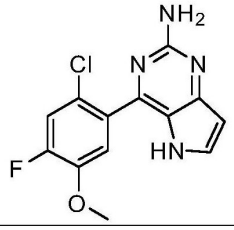
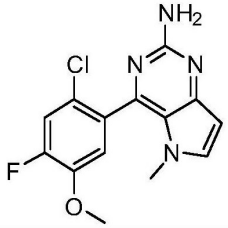
[1008]

化合物	MW	cLogP	PSA	Hsp90 抑制活性	Hsp 70激动剂活性
7 	324	4.5	60	+++(1)	-
8 	312	3.5	69	+++(2)	-
9 	298	3.5	60	+++(3)	在 1 μM 处为 1.5 倍
10 	310	3.9	60	+++(4)	在 0.4 μM 处 > 2 倍
11 	293	3.7	60	+	
12 	310	3.9	60	+++(5)	在 ≥ 10 μM 处 > 2 倍
13 	322	4.2	60	+++(6)	-

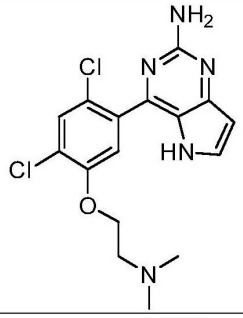
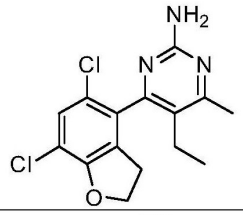
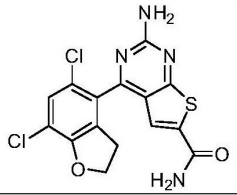
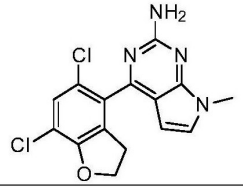
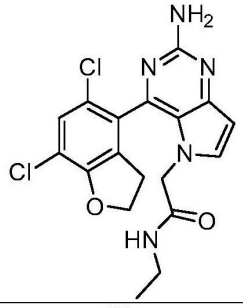
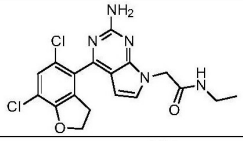
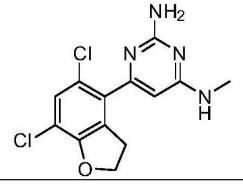
[1009]

化合物	MW	cLogP	PSA	Hsp90 抑制活性	Hsp 70激动剂活性
14 	367	4.1	63	+++	在 10 μM 处 2 倍
15 	336	4.5	60	+	
16 	323				
17 	394			-	
18 	333				
19 	309	3.8	72	+++	在 0.4-1 μM 处 > 2 倍
20 	321	4.1	72	+++	-

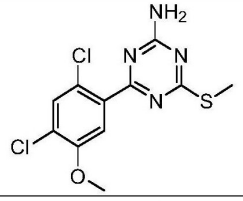
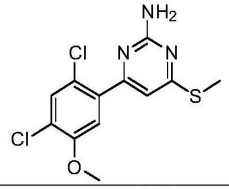
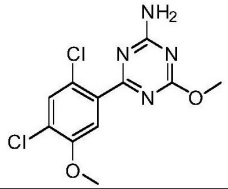
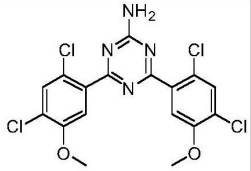
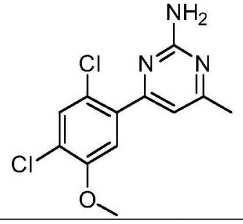
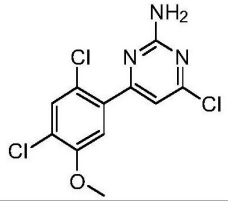
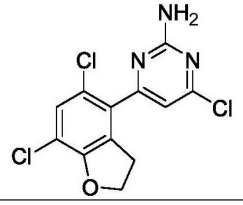
[1010]

化合物	MW	cLogP	PSA	Hsp90 抑制活性	Hsp 70激动剂活性
21 	335	3.1	63	++	-
22 	349	3.4	63	+	-
23 	410	4.8	86	+(7)	3.3 μM
24 	409	4.1	89	+++	0.4 μM
25 	292.70	2.5	72	+(8)	1.5 倍，或没有可观察到的效果
26 	306.73	2.7	63	++(9)	在 3.3 μM 处为 2 倍，或没有可观察到的效果

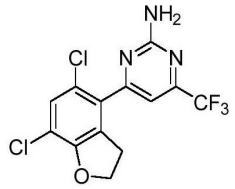
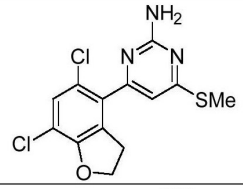
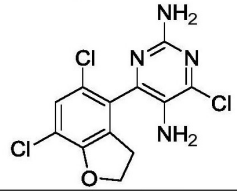
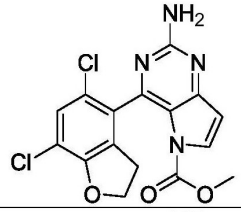
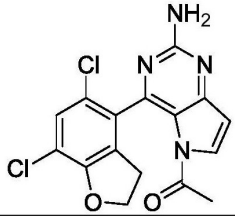
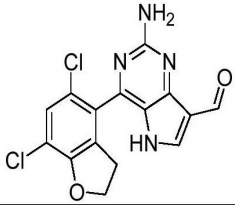
[1011]

化合物	MW	cLogP	PSA	Hsp90 抑制活性	Hsp 70激动剂活性
27 	366.25	2.9	75	++	10 μM
28 	324.21	4.5	60	-	
29 	381.23	3.6	103	+++	0.4 μM
30 	335.19	3.4	63	-	
31 	406.27	2.3	92	-	
32 	406.27	2.6	92	-	
33 	311.17	3.1	72	+	

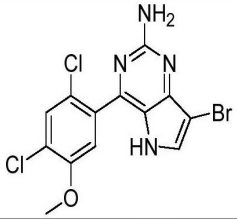
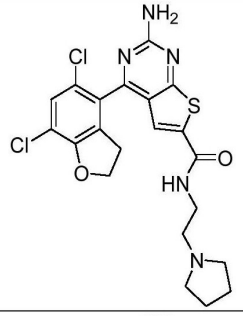
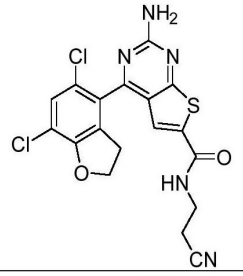
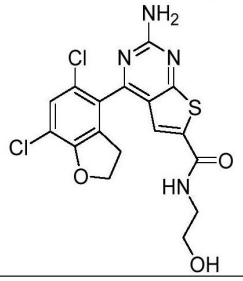
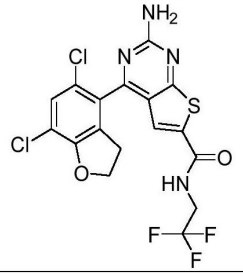
[1012]

化合物	MW	cLogP	PSA	Hsp90 抑制活性	Hsp 70激动剂活性
34 	317.19	4.5	72	+++	3.3 μM; 10 μM
35 	316.20	4.0	60	+++	3.3 μM; 10 μM
36 	301.13	3.9	82	+++	> 10 μM
37 	446.11	7.0	82	-	
38 	284.14	3.6	60	++	
39 	304.56	3.8	60	+++	0.4 μM
49 	316.6	3.8	60	+++	

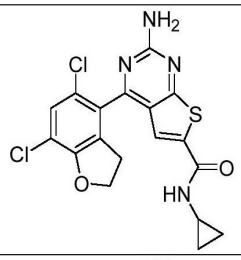
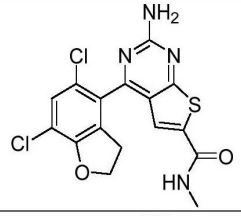
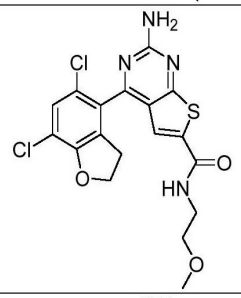
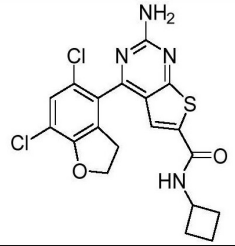
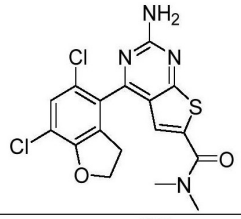
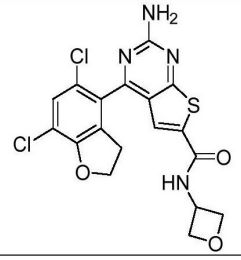
[1013]

化合物	MW	cLogP	PSA	Hsp90 抑制活性	Hsp 70激动剂活性
50 	350.1	4.0	60	++	
51 	328.2	4.0	60	+++	
52 	331.6	3.0	86	+++	
53	298.1	3.2	80	-	
54 	379.2	3.4	90	-	
55 	363.2	2.8	80	-	
56 	348.0	2.6	89	-	

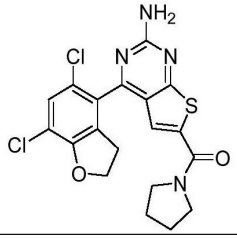
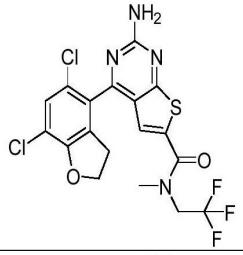
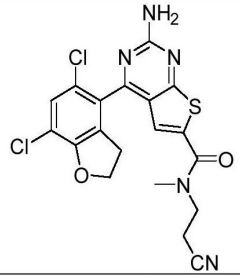
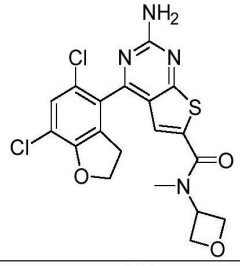
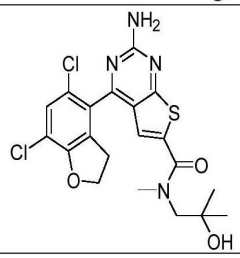
[1014]

化合物	MW	cLogP	PSA	Hsp90 抑制活性	Hsp 70激动剂活性
57 	388.1	3.7	72	-	
58 	478.4	4.1	9.2	+++	
59 	434.3	3.8	113	+++	
60 	425.3	3.3	109	+++	
61 	463.3	4.8	89	+++	

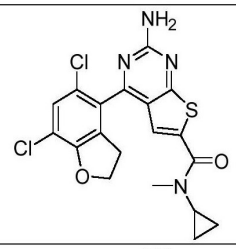
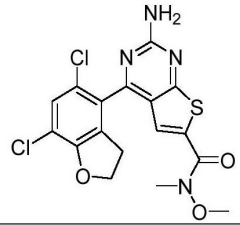
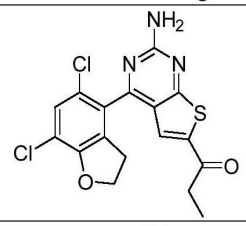
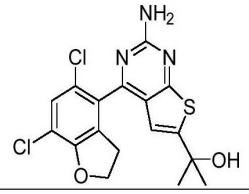
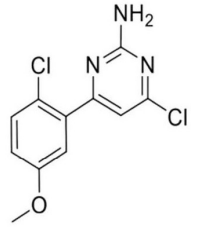
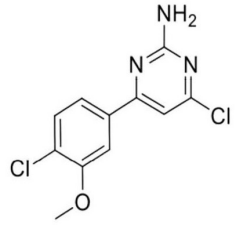
[1015]

化合物	MW	cLogP	PSA	Hsp90 抑制活性	Hsp 70激动剂活性
62 	421.3	4.1	89	+++	
63 	395.3	3.8	89	+++	
64 	439.3	3.6	98	+++	
65 	435.3	4.5	89	+++	
66 	409.3	4.0	80	+++	
67 	437.3	3.4	98	+++	

[1016]

化合物	MW	cLogP	PSA	Hsp90 抑制活性	Hsp 70激动剂活性
68	451.3	3.6	89	++	
69 	435.3	4.3	80	++	
70 	477.3	5.0	89	+	
71 	448.3	4.1	104	+++	
72 	451.3	3.6	89	++	
73 	453.3	3.8	109	+++	

[1017]

化合物	MW	cLogP	PSA	Hsp90抑制活性	Hsp 70激动剂活性
74 	435.3	4.3	80	++	
75 	425.3		89	+++	
76 	394.3	4.6	77	+++	
77 	396.3	4.6	80	++	
78 	269.01			++	
79 	269.01			+++	

[1018] 在表3中，“Hsp90抑制活性”提供了示例性化合物抑制Hsp90的能力的评估。具体地，“-”表示化合物具有大于约10μM的IC_{50}，“+”表示该化合物具有在约4μM至约10μM范围内的IC_{50}；“++”表示该化合物具有在约1μM至约4μM的范围内的IC_{50}；“+++”表示该化合物具有小于约1μM的IC_{50}。“Hsp70激动剂活性”表示Hsp70增加两倍的示例性化合物的EC_{50}(μM)，除非另有说明；“-”表示在超过10μM的浓度下缺乏可观察到的效果。(1)根据AlphaLISA测定的数据，FP测定结果：>10μM。(2)根据AlphaLISA测定的数据，FP测定结果：5.5μM和6.2μM。(3)根据AlphaLISA测定的数据，FP测定结果：1μM和1.4μM。(4)根据AlphaLISA测定的数据，FP测

定结果:2.3μM和2.4μM。(5)根据AlphaLISA测定的数据,FP测定结果:1.7μM。(6)根据AlphaLISA测定的数据,FP测定结果:1.8μM。(7)根据AlphaLISA测定的数据,FP测定结果:11.1μM。(8)根据AlphaLISA测定的数据,FP测定结果:12.1μM和19.3μM。(9)根据AlphaLISA测定的数据,FP测定结果:8.5μM和11.2μM。

[1019] 实例3.本发明化合物的药代动力学性质

[1020] 临床前研究包括分布在6组的85只小鼠;治疗组的概述在表4中给出。

[1021] 表4.

[1022]

组	n	处死在	对照样品
A	5	给药前	A_0
B	3	15分钟	B_0.25
C	3	30分钟	C_0.5
D	3	1小时	D_1
E	3	2小时	E_2
F	3	8小时	F_8

[1023] 在给药前,给药后15分钟和30分钟、1小时、2小时、和8小时的给药后时间点上取血浆和脑样品。给药前组用5只动物代表,而给药后组用3只动物代表。

[1024] 生物分析方法

[1025] 通过蛋白质沉淀和LC-MS/MS进行化合物20的小鼠血浆样品的生物分析,以化合物22作为内标。该方法基于'通用测定法',并且进行了一些方法开发以针对特定化合物和内标物定制该测定法。最终的非GLP测定首先通过用有掺加的小鼠血浆样品来分析生物分析活动来测试。运行验收标准(见下文)通过了定量运行。然后使用在小鼠血浆中掺入的校准和质量控制样品对血浆样品提取物和脑样品匀浆提取物进行生物分析。测定描述如下。

[1026] 化合物20的小鼠血浆水平的测定

[1027] 样品处理

[1028] 通过蛋白质沉淀从小鼠血浆基质中提取化合物20和化合物22。向20.0μL样品中添加10.0μL内标工作溶液(在MeOH中1000ng/mL)和200μL的MeCN。将混合物涡旋(约5秒)并离心(14000rpm,5分钟)。然后回收上清液并蒸发至干燥。将残余物再溶解在100μL的再溶解溶液(80:20v:v的流动相A:B)中。为了分析,将20.0μL注入LC-MS/MS系统。

[1029] 色谱法

[1030] 所有色谱均用装配有自动注射器的1100型液相色谱仪(安捷伦(Agilent))进行。分析柱为Xbridge C183.5μm 2.1×50mm(沃特斯(Waters)),在50℃下使用。流动相是梯度,由溶剂A:在Milli-Q水中的1g/L乙酸铵、和溶剂B:MeCN组成。梯度如表5所示。

[1031] 表5.

[1032]

步骤	总时长（min）	流速（μL/min）	A（%）	B（%）
0	0.00	700	80	20
1	0.20	700	80	20
2	1.00	700	0	100
3	2.00	700	0	100
4	2.10	700	80	20
5	5.00	700	80	20

[1033] 质谱法

[1034] 所有实验都是在API 3000三重四极杆仪器(AB Sciex)上进行，以正涡轮离子喷射模式('TIS+')操作。仪器参数在方法开发过程中进行了优化。所用的MS/MS转换如表6所示。

[1035] 表6.

[1036]

化合物	Q1，[M+H]+(35Cl2)(Da)	Q3 [M+H-HCl]+(35Cl2)(Da)
化合物**20**	321.1	285.0
化合物**22**	349.2	318.9

[1037] 生物分析实验和验收标准的描述

[1038] 设定化合物20的校准范围设置为覆盖0.988ng/mL和20000ng/mL之间的浓度。使用两组校准样品，一组置于研究样品之前，而另一组置于研究样品之后。此外，5个级别的QC样品(每个级别两个样品)被包括在运行中，作为性能指标和运行验收。

[1039] 应用校准和QC样品的验收标准如下：

[1040] • 相对于单独校准和QC样品的标称浓度的绝对%RE(|%RE|)应在20%(或LLOQ的25%)内；

[1041] • 当在该浓度水平的至少一个校准样品被上述|%RE|接受时，认为校准水平是有效的标准；

[1042] • 当该浓度水平的至少一个QC样品被上述|%RE|接受时，认为QC水平是有效的标准。

[1043] 将最低和最高的接受校准浓度水平分别用作定量的下限和上限、LLOQ和HLOQ。

[1044] 生物分析结果

[1045] 对于化合物20，最高校准水平(STD L，20000ng/mL)没有通过验收标准，因为两个校准样品显示出了太高的偏差(参见表7)。单个样品在STD C和STD G中显示出过高偏差，化合物20，STD A至STD K的所有其他校准水平被接受。结果，采用最低水平(STD A，0.988ng/mL)作为LLOQ，并且采用下一较高水平(STD K，8000ng/mL)作为HLOQ。QC LLOQ和QC Med样品结果中的一个具有太高的偏差。化合物20接受生物分析运行中的总体方法性能。

[1046] 使用的校准和QC浓度水平显示在表7中：

[1047] 表7.

[1048]

样品指标	化合物20浓度 (ng/mL)
STD A	0.988
STD B	2.37
STD C	5.93
STD D	14.8
STD E	35.6
STD F	88.9
STD G	222
STD H	533
STD I	1333
STD J	3333
STD K	8000
STD L	20000
QCLLQ	2.37
QC低	14.8
QC中等	88.9
QC高	1333
QCOC	8000

[1049] 血浆和脑样品的生物分析结果示于表8和9中。

[1050] 表8.

[1051]

组	IRN	浓度 化合物20 (ng/mL)
A_0	2	0.00 [a]
A_0	4	2.16

[1052]

A_0	6	0.00 [a]
A_0	8	0.00 [a]
A_0	10	0.00 [a]
B_0.25	12	2.66
B_0.25	14	17,900 [b]
B_0.25	16	12,000 [b]
C_0.5	18	11,500 [b]
C_0.5	20	10,500 [b]
C_0.5	22	11,100 [b]
D_1	24	6,890
D_1	26	7,130
D_1	28	7,470
E_2	30	4,150
E_2	32	4,180
E_2	34	4,440
F_8	36	99.3
F_8	38	22.5
F_8	40	21.9

[1053] (a)“0.00”表示“低于定量限值”(LLOQ;LLOQ为0.988ng/mL)。

[1054] (b)值超出范围(0.988-8000ng/mL);两个在20000ng/mL的校准品被拒绝,但在14000ng/mL显示出平均水平的反应。

[1055] 表9.

[1056]

组	IRN	匀浆浓度 (ng/mL)	脑重量 (g)	化合物20的脑浓度 (ng/g)
A_0	2	0.00 [a]	0.453	0.00 [a]
A_0	4	0.00 [a]	0.483	0.00 [a]
A_0	6	0.00 [a]	0.451	0.00 [a]
A_0	8	0.00 [a]	0.487	0.00 [a]
A_0	10	0.00 [a]	0.472	0.00 [a]
B_0.25	12	0.00 [a]	0.463	0.00 [a]
B_0.25	14	2300	0.445	20674
B_0.25	16	1250	0.460	10870
C_0.5	18	1400	0.482	11618
C_0.5	20	844	0.458	7371
C_0.5	22	1200	0.458	10480
D_1	24	888	0.474	7494
D_1	26	859	0.459	7486
D_1	28	789	0.461	6846
E_2	30	410	0.455	3604
E_2	32	385	0.461	3341
E_2	34	294	0.467	2518
F_8	36	7.53	0.478	63.0
F_8	38	1.83	0.489	15.0

[1057]

F_8	40	1.53	0.476	12.9

(a)“0.00”表示“低于定量限值”(LLOQ;LLOQ为0.988ng/mL)。

[1058] 在血浆样品中,进行了以下观察:

[1059] •在给药前样品(一个A_0样品;发现在于2.16ng/mL)中存在一个次要反应。这种反应可能来自轻微的污染或测验干扰。虽然LC-MS/MS方法的选择性通常较高,但未测试对血浆中化合物20的选择性。结论只能在更复杂的方法鉴定或甚至在方法验证后得出。在小于3倍LLOQ时,这种剂量前反应在这里被认为是可忽略的。

[1060] •在时间点B_0.25的大多数测量的结果和在时间点C_0.5的所有测量的结果高于定量的上限(ULOQ,于8000ng/mL处)。为了获得更可靠的结果,这些样品必须在分析前稀释。应注意,在运行中包括了20000ng/mL的最高校准物,但在偏差上失败。20000ng/mL的平均反向计算浓度为14000ng/mL,这表明在该水平上的偏差为-30%。上述ULOQ结果作为指示值包括在本实例中,以支持PK评价。然而,B_0.25和C_0.5时间点的结果应谨慎对待。

[1061] •在时间点B_0.25(IRN 12)上来自第一受试者的结果不可能接近观察到的2.66ng/mL,因为其与在该第一给药后的时间点(IRN 14和16)上从其他两个受试者中观察到的相对高浓度不匹配。暂时地,对以下两个情况进行这个时间点的PK评价:(1)平均值为3,以及(2)排除该BLOQ结果,平均值为2。

[1062] 在脑(匀浆)样品中,出现了一个与期望不同的结果:

[1063] •在时间点B_0.25(IRN 12)上来自第一受试者的结果不可能低于LLOQ,因为其与在该第一给药后时间点(IRN 14和16)处上从其他两个受试者中观察到的相对高浓度不匹配。请注意,这与来自受试者(IRN 12)的血浆中的发现相似。暂时地,对以下两个情况进行这个时间点的PK评价:(1)平均值为3,以及(2)排除该BLOQ结果,平均值为2。

[1064] 药代动力学评价

[1065] 通过从每个时间点的平均浓度(给药前n=5,给药后n=3)的计算进行药代动力学参数的评价。药代动力学结果总结如下。

[1066] 小鼠血浆

[1067] 药代动力学评价的结果在表10-12和图7和8中给出。对于超过ULOQ的结果或对于将动物IRN12的结果包括在组B_0.25中没有进行校正。

[1068] 表10.

[1069]

组	时间点(h)	平均组浓度(ng/mL)
A_0	0.00	0.432
B_0.25	0.25	9968 [a]
C_0.5	0.50	11033

[1070]

D_1	1.00	7163
E_2	2.00	4257
F_8	8.00	47.9

[1071] (a)不包括IRN 12结果:14950ng/mL

[1072] 表11和12提供了化合物20的血浆药代动力学曲线。

[1073] 表11.[(a)]

参数	值	单位
$C_{最大}$	11033	ng/mL
$T_{最大}$	0.50	小时（h）
$K_{排除}$	0.725	每小时（h^{-1}）
半衰期（$t_{1/2}$）	0.96	小时（h）
AUC(0-8h)	27044	ng/mL.h
AUC(0-inf)	27055	ng/mL.h

[1074]

[1075] (a)不包括IRN12结果。

[1076] 表12.[(a)]{

参数	值	单位
$C_{最大}$	14950	ng/mL
$T_{最大}$	0.25	小时（h）
$K_{排除}$	0.730	每小时（h^{-1}）
半衰期（$t_{1/2}$）	0.95	小时（h）
AUC(0-8h)	28290	ng/mL.h
AUC(0-inf)	28301	ng/mL.h

[1077]

[1078] (a)包括IRN12结果。

[1079] 小鼠脑组织

[1080] 脑组织药代动力学评价的结果在图9和10以及表13-15中给出。对于包含在内的对B_0.25组中动物IRN12的额外结果没有进行校正。

[1081] 表13.

[1082]

组	时间点（h）	平均组浓度	
		匀浆（ng/mL）	组织（ng/g）
A_0	0.00	0.00	0.00
B_0.25	0.25	1183	10515 [a]
C_0.5	0.50	1148	9823
D_1	1.00	845	7275
E_2	2.00	363	3154
F_8	8.00	3.63	30.0

[1083] (a)不包括IRN 12结果:15772ng/g。

[1084] 表14和15提供了化合物20的脑组织药代动力学曲线。

[1085] 表14.[(a)]

[1086]

参数	值	单位

[1087]

$C_{最大}$	10515	ng/mL
$T_{最大}$	0.25	小时（h）
$K_{排除}$	0.769	每小时（h^{-1}）
半衰期（$t_{1/2}$）	0.90	小时（h）
AUC(0-8h)	22898	ng/mL.h
AUC(0-inf)	22908	ng/mL.h

[1088] (a)不包括IRN 12结果。

[1089] 表15.[(a)]

[1090]

参数	值	单位
$C_{最大}$	15772	ng/mL
$T_{最大}$	0.25	小时（h）
$K_{排除}$	0.789	每小时（h^{-1}）
半衰期（$t_{1/2}$）	0.88	小时（h）
AUC(0-8h)	24212	ng/mL.h
AUC(0-inf)	22908	ng/mL.h

[1091] (a)包括IRN 12结果。

[1092] 实例4.本发明化合物对Tau转基因小鼠模型(hTAU441)中的脑脊液(CSF)和脑的Tau总水平和p-Tau水平的影响

[1093] 为了评估本发明化合物对p-tau积累的影响，对tau蛋白基因(hTAU小鼠)人源化的年龄匹配(例如，5个月大)的转基因小鼠可以用低剂量或高剂量的本发明的化合物或载体通过腹膜内给予7天(每只手臂N＝6)来处理。本发明化合物的剂量可以基于PK结果计算。hTAU转基因小鼠(C57BL/6背景)过度表达的TAU441携带在脑特异性鼠Thy-1启动子控制下的错义突变V337M和R406W。这种人突变tau异构体以高水平表达，并且病状早期可见，从4个月开始。脑病症的严重性与增加的年龄和行为缺陷相关，然而没有运动缺陷发生。可以使用MSD多阵列p-tau(ThR^{21}1)免疫吸附测定(细观发现公司(Meso Scale Discovery)，罗克维尔市(Rockville)，马里兰州(MD))处死所有动物并定量可溶性和不溶性tau和p-tau脑(海马和皮质)，以建立脑提取物中CSF和Hsp70水平的总tau和p-tau水平。具体地，可以在收集CSF之前和期间，用氯胺酮/赛拉嗪混合物(注意：异氟烷已知会影响p-tau水平)麻醉动物，使其保持温暖并处于水平位置，然后收集血液。与一些菌株(2-15μL/小鼠)相比，在hTAU441中收集的CSF的体积仅为2-6μL/小鼠。可以使用磷酸-PHF-Tau pThR^{21}1(MSD双重试剂盒，细观发现公司，罗克维尔市，马里兰州)评估p-Tau(ThR^{21}1)和总tau水平。

[1094] 本发明化合物的给药可以导致用本发明化合物治疗的小鼠的p-tau水平相对于给予载体的小鼠中的p-tau水平降低。

[1095] 实例5.本发明的化合物对hTAU441转基因小鼠模型的记忆和学习的影响

[1096] 实施例3中所述的5个月龄的转基因hTAU小鼠可以每天腹膜内给予低剂量或高剂量的本发明组的化合物或载体，持续12周(每臂N＝15)。将相应的未处理组的小鼠作为基线进行分析。可以进行行为测试，例如，探测试验、鼻子刺激兴趣和活动测试，和Morris水迷宫任务。完成研究后，可收集CSF并从这些动物收获脑组织。可以评估在CSF和脑中的总tau水

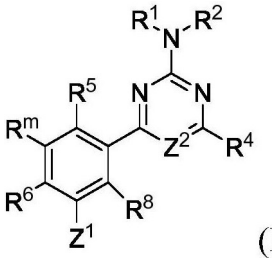
平和p-tau水平。另外，可以进行tau病理学的免疫组织化学测定。可以使用单克隆抗体AT180(赛默飞科技公司(Thermo Scientific)皮尔斯抗体公司(Pierce Antibodies)，罗克福德(Rockford)，伊利诺伊州(IL))和HT7(赛默飞科技公司皮尔斯抗体公司，罗克福德，伊利诺伊州)测定Tau沉积。硒酸钠，一种使tau去磷酸化并逆转记忆缺陷的PP2A磷酸酶激活剂在TMHT tau模型中是有效的(科克伦(Corcoran)等人，《临床神经科学杂志》(J.Clin.Neuroscience)，17:1025-1033，2010)。

[1097] 如果用本发明化合物的慢性治疗与通过Morris迷宫测量的记忆功能的一般改善相关，可观察到脑中p-tau水平的降低。

[1098] 其他实施例

[1099] 本发明还通过以下编号的实施例来描述：

[1100] 1.一种根据式(I)的化合物：

[1101]  或其药学上可接受的盐，

(I)，

[1102] 其中

[1103] Z^1是-OR^7、-$N(R^{10})R^7$、-SR^7、或-$C(R^{10})(R^{11})R^7$；

[1104] Z^2是-N=或-$C(R^3)$=；

[1105] 每个R^1和R^2独立地是H或任选取代的C_{1-3}烷基；

[1106] R^3是H、卤素、氰基、任选取代的C_{1-6}烷基、任选取代的C_{1-3}烷氧基、或任选取代的氨基，并且R^4是卤素、氰基、任选取代的C_{1-6}烷基、任选取代的C_{1-3}烷氧基、任选取代的氨基、任选取代的C_{1-6}硫代烷氧基、或任选取代的C_{6-10}芳基，或者R^3和R^4与各自附接的原子一起连接以形成任选取代的五元或六元环，该五元或六元环任选地包括一个氮、一个氧或一个硫，其中该氮任选地被R^9取代；

[1107] 每个R^5和R^6独立地是H、任选取代的C_{1-3}烷基、任选取代的C_{1-3}烷氧基、卤素、或CN；

[1108] R^7是任选取代的C_{1-3}烷基、任选取代的C_{1-3}烷环烷基、任选取代的C_{1-3}烷杂环基、或任选取代的C_{1-3}烷芳基，并且R^8是H；或者R^7和R^8与各自附接的原子一起连接以形成任选取代的五元或六元环，该五元或六元环任选地包括一个或两个选自氮、氧和硫的杂原子；

[1109] R^9是H、任选取代的C_{1-3}烷基、任选取代的C_{3-8}环烷基、任选取代的C_{6-10}芳基、任选取代的C_{2-9}杂芳基、任选取代的C_{2-9}杂环基、任选取代的C_{1-3}烷环烷基、任选取代的C_{1-3}烷杂环基、或任选取代的C_{1-3}烷芳基；

[1110] R^{10}是H、任选取代的C_{1-3}烷基、任选取代的C_{3-8}环烷基、任选取代的C_{6-10}芳基、任选取代的C_{2-9}杂芳基、任选取代的C_{2-9}杂环基、任选取代的C_{1-3}烷环烷基、任选取代的C_{1-3}烷杂环基、或任选取代的C_{1-3}烷芳基，并且R^{11}是H、任选取代的C_{1-3}烷基，或者R^{10}和R^{11}结合以形成=O或=S；

[1111] R^m是H、卤素、任选取代的C_{1-4}烷基、或任选取代的C_{1-3}烷氧基；

[1112] 其中，

[1113] 当Z^2是CR^3,每个R^1和R^2是H,R^3是H,R^4是甲基或氯,并且每个R^5和R^6是氯时,

[1114] Z^1不是甲氧基;

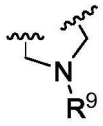
[1115] 当Z^2是N,每个R^5和R^6是氯,R^3是H,R^4是经取代的C_{1-6}硫代烷氧基时,

[1116] Z^1不是氰基甲氧基或氨基甲氧基;

[1117] 当Z^2是CR^3,每个R^5和R^6是氯,R^3是H,并且R^4是卤素时,

[1118] Z^1不是2-氨基-2-氧代乙氧基、2-(N,N-二乙氨基)乙氧基、甲氧基、或苄氧基;

[1119] 当R^5是氯,R^6是溴,Z^1是$-OR^7$,并且R^3和R^4结合以形成根据式(IIa)的基团时:

[1120] 

(IIa),

[1121] R^7不是甲基、乙基、正丙基、2-(N-吡唑基)乙基、2-(N-咪唑基)乙基、3-羟丙基、氰甲基、2-氯乙基、2-羟乙基、2-氧代丙基、2-(N,N-二甲氨基)乙基、二氟甲基或2-(叔丁氨基)乙基;

[1122] 当每个R^5和R^6是溴,Z^1是$-OR^7$,并且R^3和R^4结合以形成根据式(IIa)的基团时,

[1123] R^7不是甲基;

[1124] 当每个R^5和R^6是氯,Z^1是$-OR^7$,并且R^3和R^4结合以形成根据式(IIa)的基团时,

[1125] R^7不是甲基、2-(N-咪唑基)乙基、甲氧基甲基、2-(N-吡唑基)乙基、2-(3-甲基吡唑-1-基)乙基、2-吡啶基-甲基、1,3-二甲基-1H-1,2,4-三唑-5-基-甲基、2-嘧啶基甲基、咪唑-2-基-甲基、5-甲基-异噁唑-3-基-甲基、4-甲基-咪唑-5-基-甲基、或3-甲基-1,2,4-噁二唑-5-基-甲基;

[1126] 当每个R^5和R^6是氯,Z^1是$-OR^7$,R^7和R^8结合以形成$-CH_2-CH_2-$,并且R^3和R^4结合以形成根据式(IIa)的基团时,

[1127] R^9不是乙氧基羰基、环丁基氨基羰基、或环丁二烯基氨基羰基;

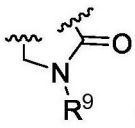
[1128] 当R^5是甲氧基,R^6是甲基,Z^1是$-OR^7$,并且R^3和R^4结合以形成根据式(IIa)的基团时,

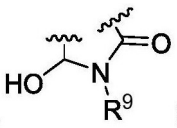
[1129] R^7不是甲基;

[1130] 当R^5是氯,R^6是乙基,Z^1是$-OR^7$,并且R^3和R^4结合以形成根据式(IIa)的基团,

[1131] R^7不是甲基;

[1132] 当每个R^5和R^6是氯,Z^1是$-OR^7$,并且R^3和R^4结合以形成根据式(IIb)或(IIc)的基团时,

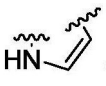
[1133] 

(IIb) 或 

(IIc),

[1134] R^7不是甲基或2-(N,N-二乙基氨基)乙基;

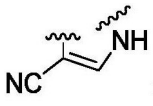
[1135] 当R^7是甲基,R^5是氯,Z^1是$-OR^7$,并且R^3和R^4结合以形成根据式(IIIa)的基团时,

[1136] 

(IIIa),

[1137] R^6不是溴;

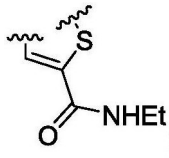
[1138] 当R^5是氯,R^6是甲氧基,Z^1是$-OR^7$,并且R^3和R^4结合以形成根据式(IIIb)的基团时:

[1139] 

(IIIb),

[1140] R^1和R^2都不是2-(N,N-二乙基氨基)乙基；

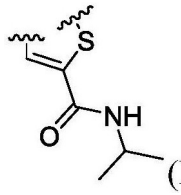
[1141] 当每个R^5和R^6是氯，Z^1是-OR^7，并且R^3和R^4结合以形成根据式(IVa)的基团时：

[1142] 

(IVa),

[1143] R^7不是3-(N-吗啉基)丙基、苄基、1-乙基-吡咯烷-3-基、1-甲基-哌啶-4-基、2-(1-甲基-吡咯烷-2-基)乙基、或3-(N,N-二乙基氨基)丙基；

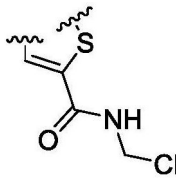
[1144] 当每个R^5和R^6是氯，Z^1是-OR^7，并且R^3和R^4结合以形成根据式(IVb)的基团时：

[1145] 

(IVb),

[1146] R^7不是2-甲氧基乙基或苄基；

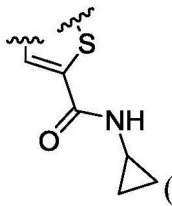
[1147] 当每个R^5和R^6是氯，Z^1是-OR^7，并且R^3和R^4结合以形成根据式(IVc)的基团时：

[1148] 

(IVc),

[1149] R^7不是2-(N,N-二乙基氨基)乙基或3-(N,N-二甲基氨基)丙基；

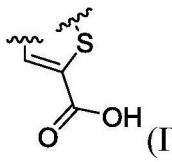
[1150] 当每个R^5和R^6是氯，Z^1是-OR^7，并且R^3和R^4结合以形成根据式(IVd)的基团时：

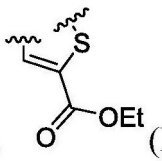
[1151] 

(IVd),

[1152] R^7不是2-(吡咯烷-1-基)乙基或2-羟基乙基；

[1153] 当每个R^5和R^6是氯，Z^1是-OR^7，并且R^3和R^4结合以形成根据式(IVe)或(IVf)的基团时：

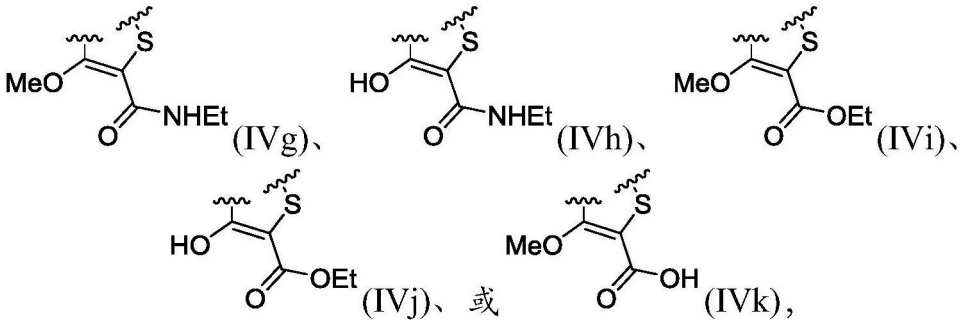
[1154] 

(IVe) 或 

(IVf),

[1155] R^7不是苄基；

[1156] 当R^5是氯，R^6是溴，Z^1是-OR^7，并且R^3和R^4结合以形成根据式(IVg)、(IVh)、(IVi)、(IVj)、或(IVk)的基团时：

[1157] 

[1158] R^7不是甲基；

[1159] 当R^6是甲基时，

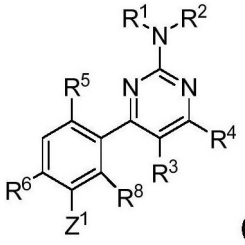
[1160] 每个R^1和R^2是H；并且

[1161] 当R^3是H，Z^1是-OR^7，并且每个R^5和R^6是氯时，

[1162] R^7不是甲基。

[1163] 2.如实施例1所述的化合物，其中R^m是H。

[1164] 3.一种根据式(Ia)的化合物：

[1165] 

(Ia)，或其药学上可接受的盐，

[1166] 其中

[1167] 每个R^1和R^2独立地是H或任选取代的C_{1-3}烷基；

[1168] R^3是H、卤素、氰基、任选取代的C_{1-6}烷基、任选取代的C_{1-3}烷氧基、或任选取代的氨基，并且R^4是卤素、氰基、任选取代的C_{1-6}烷基、任选取代的C_{1-3}烷氧基、任选取代的氨基、任选取代的C_{1-6}硫烷基、或任选取代的C_{6-10}芳基，或者R^3和R^4与各自附接的原子一起连接以形成任选取代的五元或六元环，该五元或六元环任选地包括一个氮、一个氧或一个硫，其中该氮任选地被R^9取代；

[1169] 每个R^5和R^6独立地是H、任选取代的C_{1-3}烷基、任选取代的C_{1-3}烷氧基、卤素、或CN；

[1170] R^7是任选取代的C_{1-3}烷基、任选取代的C_{1-3}烷环烷基、任选取代的C_{1-3}烷杂环基、或任选取代的C_{1-3}烷芳基，并且R^8是H；或者R^7和R^8与各自附接的原子一起连接以形成任选取代的五元或六元环，该五元或六元环任选地包括一个或两个选自氮、氧和硫的杂原子；

[1171] R^9是H、任选取代的C_{1-3}烷基、任选取代的C_{3-8}环烷基、任选取代的C_{6-10}芳基、任选取代的C_{2-9}杂芳基、任选取代的C_{2-9}杂环基、任选取代的C_{1-3}烷环烷基、任选取代的C_{1-3}烷杂环基、或任选取代的C_{1-3}烷芳基；

[1172] Z^1是-OR^7、-$N(R^{10})R^7$、-SR^7、或-$C(R^{10})(R^{11})R^7$；以及

[1173] R^{10}是H、任选取代的C_{1-3}烷基、任选取代的C_{3-8}环烷基、任选取代的C_{6-10}芳基、任选取代的C_{2-9}杂芳基、任选取代的C_{2-9}杂环基、任选取代的C_{1-3}烷环烷基、任选取代的C_{1-3}烷杂环基、或任选取代的C_{1-3}烷芳基，并且R^{11}是H、任选取代的C_{1-3}烷基，或者R^{10}和R^{11}结合以形成=O或=S；

[1174] 其中，

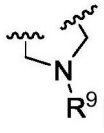
[1175] 当每个R^1和R^2是H,R^3是H,R^4是甲基或氯,并且每个R^5和R^6是氯时,

[1176] Z^1不是甲氧基;

[1177] 当每个R^5和R^6是氯,R^3是H,并且R^4是卤素时,

[1178] Z^1不是2-氨基-2-氧代乙氧基、2-(N,N-二乙氨基)乙氧基、甲氧基、或苄氧基;

[1179] 当R^5是氯,R^6是溴,Z^1是-OR^7,并且R^3和R^4结合以形成根据式(IIa)的基团时:

[1180]  (IIa),

[1181] R^7不是甲基、乙基、正丙基、2-(N-吡唑基)乙基、2-(N-咪唑基)乙基、3-羟丙基、氰甲基、2-氯乙基、2-羟乙基、2-氧代丙基、2-(N,N-二甲氨基)乙基、二氟甲基或2-(叔丁氨基)乙基;

[1182] 当每个R^5和R^6是溴,Z^1是-OR^7,并且R^3和R^4结合以形成根据式(IIa)的基团时,

[1183] R^7不是甲基;

[1184] 当每个R^5和R^6是氯,Z^1是-OR^7,并且R^3和R^4结合以形成根据式(IIa)的基团时,

[1185] R^7不是甲基、2-(N-咪唑基)乙基、甲氧基甲基、2-(N-吡唑基)乙基、2-(3-甲基吡唑-1-基)乙基、2-吡啶基-甲基、1,3-二甲基-1H-1,2,4-三唑-5-基-甲基、2-嘧啶基甲基、咪唑-2-基-甲基、5-甲基-异噁唑-3-基-甲基、4-甲基-咪唑-5-基-甲基、或3-甲基-1,2,4-噁二唑-5-基-甲基;

[1186] 当每个R^5和R^6是氯,Z^1是-OR^7,R^7和R^8结合以形成-CH_2-CH_2-,并且R^3和R^4结合以形成根据式(IIa)的基团时,

[1187] R^9不是乙氧基羰基、环丁基氨基羰基、或环丁二烯基氨基羰基;

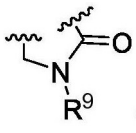
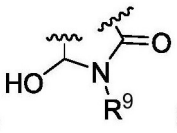
[1188] 当R^5是甲氧基,R^6是甲基,Z^1是-OR^7,并且R^3和R^4结合以形成根据式(IIa)的基团时,

[1189] R^7不是甲基;

[1190] 当R^5是氯,R^6是乙基,Z^1是-OR^7,并且R^3和R^4结合以形成根据式(IIa)的基团,

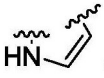
[1191] R^7不是甲基;

[1192] 当每个R^5和R^6是氯,Z^1是-OR^7,并且R^3和R^4结合以形成根据式(IIb)或(IIc)的基团时,

[1193]  (IIb) 或  (IIc),

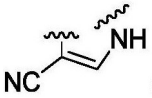
[1194] R^7不是甲基或2-(N,N-二乙基氨基)乙基;

[1195] 当R^7是甲基,R^5是氯,Z^1是-OR^7,并且R^3和R^4结合以形成根据式(IIIa)的基团时,

[1196]  (IIIa),

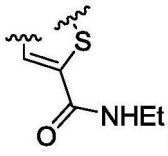
[1197] R^6不是溴;

[1198] 当R^5是氯,R^6是甲氧基,Z^1是-OR^7,并且R^3和R^4结合以形成根据式(IIIb)的基团时:

[1199]  (IIIb),

[1200] R^1和R^2都不是2-(N,N-二乙基氨基)乙基；

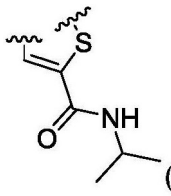
[1201] 当每个R^5和R^6是氯，Z^1是-OR^7，并且R^3和R^4结合以形成根据式(IVa)的基团时：

[1202] 

(IVa)，

[1203] R^7不是3-(N-吗啉基)丙基、苄基、1-乙基-吡咯烷-3-基、1-甲基-哌啶-4-基、2-(1-甲基-吡咯烷-2-基)乙基、或3-(N,N-二乙基氨基)丙基；

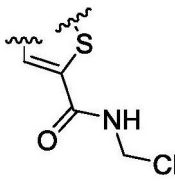
[1204] 当每个R^5和R^6是氯，Z^1是-OR^7，并且R^3和R^4结合以形成根据式(IVb)的基团时：

[1205] 

(IVb)，

[1206] R^7不是2-甲氧基乙基或苄基；

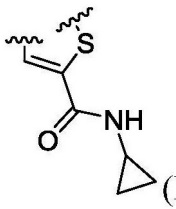
[1207] 当每个R^5和R^6是氯，Z^1是-OR^7，并且R^3和R^4结合以形成根据式(IVc)的基团时：

[1208] 

(IVc)，

[1209] R^7不是2-(N,N-二乙基氨基)乙基或3-(N,N-二甲基氨基)丙基；

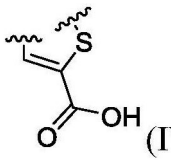
[1210] 当每个R^5和R^6是氯，Z^1是-OR^7，并且R^3和R^4结合以形成根据式(IVd)的基团时：

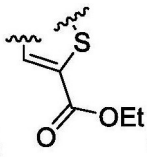
[1211] 

(IVd)，

[1212] R^7不是2-(吡咯烷-1-基)乙基或2-羟基乙基；

[1213] 当每个R^5和R^6是氯，Z^1是-OR^7，并且R^3和R^4结合以形成根据式(IVe)或(IVf)的基团时：

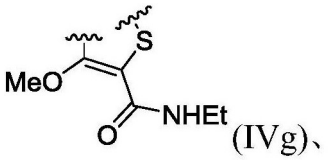
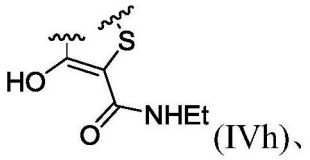
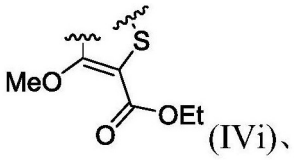
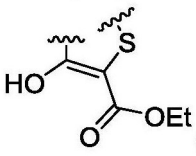
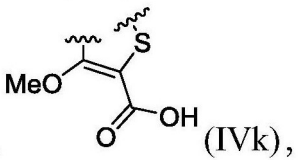
[1214] 

(IVe)或 

(IVf)，

[1215] R^7不是苄基；

[1216] 当R^5是氯，R^6是溴，Z^1是-OR^7，并且R^3和R^4结合以形成根据式(IVg)、(IVh)、(IVi)、(IVj)、或(IVk)的基团时：

[1217]  (IVg)、  (IVh)、  (IVi)、  (IVj)、或  (IVk)，

[1218] R^7不是甲基；

[1219] 当R^6是甲基时，

[1220] 每个R^1和R^2是H；并且

[1221] 当R^3是H，Z^1是-OR^7，并且每个R^5和R^6是氯时，

[1222] R^7不是甲基。

[1223] 4.一种根据式(Ib)的化合物：

[1224] (Ib)，或其药学上可接受的盐，

[1225] 其中

[1226] 每个R^1和R^2独立地是H或任选取代的C_{1-3}烷基；

[1227] R^3是H、卤素、氰基、任选取代的C_{1-6}烷基、任选取代的C_{1-3}烷氧基、或任选取代的氨基，并且R^4是卤素、氰基、任选取代的C_{1-6}烷基、任选取代的C_{1-3}烷氧基、任选取代的氨基、任选取代的C_{1-6}硫代烷氧基、或任选取代的C_{6-10}芳基，或者R^3和R^4与各自附接的原子一起连接以形成任选取代的五元或六元环，该五元或六元环任选地包括一个氮、一个硫或一个氧，其中该氮任选地被R^9取代；

[1228] 每个R^5和R^6独立地是H、任选取代的C_{1-3}烷基、任选取代的C_{1-3}烷氧基、卤素、或CN；

[1229] R^7是任选取代的C_{1-3}烷基、任选取代的C_{1-3}烷环烷基、任选取代的C_{1-3}烷杂环基、或任选取代的C_{1-3}烷芳基，并且R^8是H；或者R^7和R^8与各自附接的原子一起连接以形成任选取代的五元或六元环；并且

[1230] R^9是H、任选取代的C_{1-3}烷基、任选取代的C_{3-8}环烷基、任选取代的C_{6-10}芳基、任选取代的C_{2-9}杂芳基、任选取代的C_{2-9}杂环基、任选取代的C_{1-3}烷环烷基、任选取代的C_{1-3}烷杂环基、或任选取代的C_{1-3}烷芳基；

[1231] 其中，

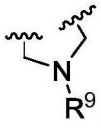
[1232] 当每个R^1和R^2是H，R^3是H，R^4是甲基或氯，并且每个R^5和R^6是氯时，

[1233] R^7不是甲基；

[1234] 当每个R^5和R^6是氯，R^3是H，和R^4是卤素时，

[1235] R^7不是2-氨基-2-氧代乙基、2-(N,N-二乙基氨基)乙基、甲基、或苄基；

[1236] 当R^5是氯时，R^6是溴，并且R^3和R^4结合以形成根据式(IIa)的基团时：

[1237] 

[1238] R^7不是甲基、乙基、正丙基、2-(N-吡唑基)乙基、2-(N-咪唑基)乙基、3-羟丙基、氰甲基、2-氯乙基、2-羟乙基、2-氧代丙基、2-(N,N-二甲氨基)乙基、二氟甲基或2-(叔丁氨基)乙基；

[1239] 当每个R^5和R^6是溴，并且R^3和R^4结合以形成根据式(IIa)的基团时，

[1240] R^7不是甲基；

[1241] 当每个R^5和R^6是氯，R^8是H，并且R^3和R^4结合以形成根据式(IIa)的基团时，

[1242] R^7不是甲基、2-(N-咪唑基)乙基、甲氧基甲基、2-(N-吡唑基)乙基、2-(3-甲基吡唑-1-基)乙基、2-吡啶基-甲基、1,3-二甲基-1H-1,2,4-三唑-5-基-甲基、2-嘧啶基甲基、咪唑-2-基-甲基、5-甲基-异噁唑-3-基-甲基、4-甲基-咪唑-5-基-甲基、或3-甲基-1,2,4-噁二唑-5-基-甲基；

[1243] 当每个R^5和R^6是氯，R^7和R^8结合以形成$-CH_2-CH_2-$，并且R^3和R^4结合以形成根据式(IIa)的基团时，

[1244] R^9不是乙氧基羰基、环丁基氨基羰基、或环丁二烯基氨基羰基；

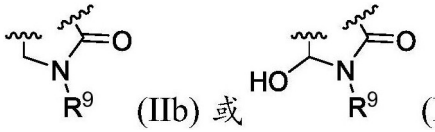
[1245] 当R^5是甲氧基，R^6是甲基，并且R^3和R^4结合以形成根据式(IIa)的基团时，

[1246] R^7不是甲基；

[1247] 当R^5是氯，R^6是乙基，并且R^3和R^4结合以形成根据式(IIa)的基团时，

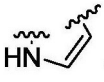
[1248] R^7不是甲基；

[1249] 当每个R^5和R^6是氯，并且R^3和R^4结合以形成根据式(IIb)或(IIc)的基团时，

[1250] 

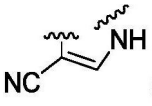
[1251] R^7不是甲基或2-(N,N-二乙基氨基)乙基；

[1252] 当R^7是甲基，R^5是氯，并且R^3和R^4结合以形成根据式(IIIa)的基团时，

[1253] 

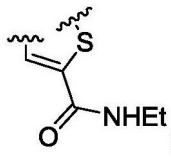
[1254] R^6不是溴；

[1255] 当R^5是氯，R^6是甲氧基，并且R^3和R^4结合以形成根据式(IIIb)的基团时：

[1256] 

[1257] R^1和R^2都不是2-(N,N-二乙基氨基)乙基；

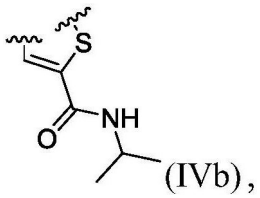
[1258] 当每个R^5和R^6是氯，并且R^3和R^4结合以形成根据式(IVa)的基团时：

[1259] 

[1260] R^7不是3-(N-吗啉基)丙基、苄基、1-乙基-吡咯烷-3-基、1-甲基-哌啶-4-基、2-(1-

甲基-吡咯烷-2-基)乙基、或3-(N,N-二乙基氨基)丙基；

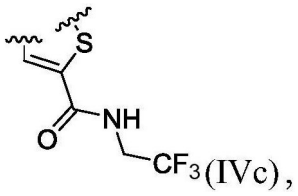
[1261] 当每个R^5和R^6是氯，并且R^3和R^4结合以形成根据式(IVb)的基团时：

[1262] 

(IVb)，

[1263] R^7不是2-甲氧基乙基或苄基；

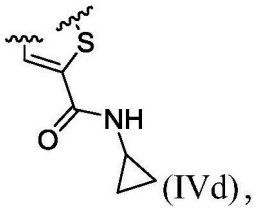
[1264] 当每个R^5和R^6是氯，并且R^3和R^4结合以形成根据式(IVc)的基团时：

[1265] 

(IVc)，

[1266] R^7不是2-(N,N-二乙基氨基)乙基或3-(N,N-二甲基氨基)丙基；

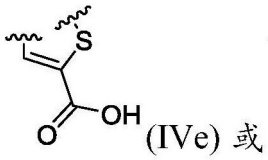
[1267] 当每个R^5和R^6是氯，并且R^3和R^4结合以形成根据式(IVd)的基团时：

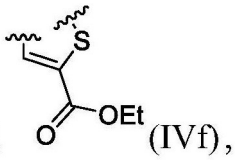
[1268] 

(IVd)，

[1269] R^7不是2-(吡咯烷-1-基)乙基或2-羟基乙基；

[1270] 当每个R^5和R^6是氯，并且R^3和R^4结合以形成根据式(Ive)或(IVf)的基团时：

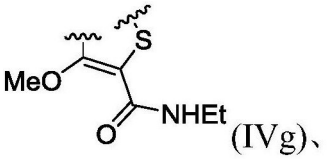
[1271] 

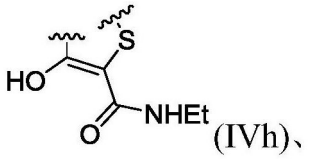
(IVe)或 

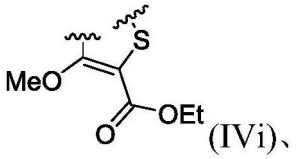
(IVf)，

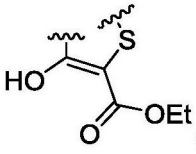
[1272] R^7不是苄基；

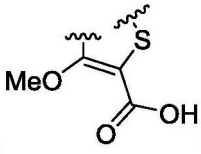
[1273] 当R^5是氯，R^6是溴，并且R^3和R^4结合以形成根据式(IVg)、(IVh)、(IVi)、(IVj)、或(IVk)的基团时：

[1274] 

(IVg)、 

(IVh)、 

(IVi)、 

(IVj)、或 

(IVk)，

[1275] R^7不是甲基；

[1276] 当R^6是甲基时，

[1277] 每个R^1和R^2是H；并且

[1278] 当R^3是H，并且每个R^5和R^6是氯时，

[1279] R^7不是甲基。

[1280] 5.如实施例1至4中任一项所述的化合物，其中R^3是H、卤素、任选取代的C_{1-3}烷基、或任选取代的C_{1-3}烷氧基，R^4是卤素、任选取代的C_{1-3}烷基、任选取代的C_{1-3}烷氧基、任选取代的氨基、任选取代的C_{1-6}硫烷基、或任选取代的C_{6-10}芳基，或者R^3和R^4与各自附接的原子一起连接以形成任选取代的五元或六元环，该五元或六元环任选包括一个氮、一个氧、或一个硫，其中该氮任选地被R^9取代。

[1281] 6.如实施例1至5中任一项所述的化合物，其中R^3和R^4与各自附接的原子一起连接以形成任选取代的五元环。

[1282] 7.如实施例1至5中任一项所述的化合物，其中R^3和R^4结合以形成$-CH_2CH_2CH_2-$基团。

[1283] 8.如实施例1至5中任一项所述的化合物，其中R^3和R^4与各自附接的原子一起连接以形成包括一个氮的任选取代的五元环。

[1284] 9.如实施例8所述的化合物，其中R^3和R^4结合以形成$-N(R^9)-CH=CH-$基团。

[1285] 10.如实施例9所述的化合物，其中R^9是H。

[1286] 11.如实施例1至5中任一项所述的化合物，其中R^3和R^4与各自附接的原子一起连接以形成包括一个硫的任选取代的五元环。

[1287] 12.如实施例1至5中任一项所述的化合物，其中R^3和R^4结合以形成$-C(R^{13A})=C(R^{13B})-S-$基团，其中$R^{13A}$是H，并且$R^{13B}$是H或任选取代的$C_{1-3}$烷基。

[1288] 13.如实施例12所述的化合物，其中R^{13B}是任选取代的C_{1-3}烷基。

[1289] 14.如实施例13所述的化合物，其中R^{13B}是$-C(O)-R^{13C}$，其中R^{13C}是任选取代的C_{1-3}烷氧基或任选取代的氨基。

[1290] 15.如实施例1至5中任一项所述的化合物，其中R^3和R^4结合以形成$-C(R^{13A})=C(R^{13B})-S-$基团，其中$R^{13A}$是H，并且$R^{13B}$是H或$-C(O)-R^{13C}$，其中$R^{13C}$是任选取代的$C_{1-3}$烷基、任选取代的$C_{1-3}$烷氧基、任选取代的氨基、或任选取代的$C_{2-9}$杂环基。

[1291] 16.如实施例1至5中任一项所述的化合物，其中R^4是C_{1-3}烷基。

[1292] 17.如实施例16所述的化合物，其中R^4是甲基、乙基、或异丙基。

[1293] 18.如实施例1至5中任一项所述的化合物，其中R^4是C_{1-3}烷氧基。

[1294] 19.如实施例18所述的化合物，其中R^4是甲氧基。

[1295] 20.如实施例1至5中任一项所述的化合物，其中R^4是任选取代的C_{1-6}硫代烷氧基。

[1296] 21.如实施例20所述的化合物，其中R^4是4-氨基-4-氧代丁基。

[1297] 22.如实施例1至5中任一项所述的化合物，其中R^4是任选取代的氨基。

[1298] 23.如实施例22所述的化合物，其中R^4是甲基氨基。

[1299] 24.如实施例1至5中任一项所述的化合物，其中R^4是卤素。

[1300] 25.如实施例24所述的化合物，其中R^4是氯。

[1301] 26.如实施例1-5以及15-25中任一项所述的化合物，其中R^3是氢或C_{1-3}烷基。

[1302] 27.如实施例26所述的化合物，其中R^3是卤素、甲基、或乙基。

[1303] 28.如实施例1至5中任一项所述的化合物，其中R^3和R^4结合以形成$-X^1-X^2-X^3-$，其中

[1304] X^1是-S-、-O-、$-(CR^{14}R^{15})-$、$-C(R^{16})=$、$-N(R^9)-$、-N=、H、或任选取代的C_{1-3}烷基；

[1305] X^2是不存在的、$-(CR^{17}R^{18})_n-$、-S-、-O-、-N=、$-N(R^9)-$、$-C(R^{19})=$、$=N-$、$=C(R^{20})-$、或$=C(R^{21})-C(R^{22})=$；

[1306] X^3是-(CR^{14}R^{15})-、-S-、-O-、-N(R^9)-、=N-、=C(R^{23})-、卤素、任选取代的C_{1-3}烷基、任选取代的C_{1-6}硫代烷氧基、任选取代的C_{1-3}烷氧基、或任选取代的C_{6-10}芳基；

[1307] 每个R^{14}和R^{15}独立地是H或任选取代的C_{1-3}烷基、或者R^{14}和R^{15}结合以形成=O或=S；

[1308] 每个R^{17}和R^{18}独立地是H或任选取代的C_{1-3}烷基、或者R^{17}和R^{18}结合以形成=O或=S；

[1309] 每个R^{16}、R^{19}、R^{20}、R^{21}、R^{22}、和R^{23}独立地是H、或任选取代的C_{1-3}烷基；并且

[1310] n是1或2；并且

[1311] 其中，当X^2不是不存在的时，

[1312] 原子链-X^1-X^2-X^3-包括不超过一个杂原子，该杂原子选自下组，该组由以下各项组成：氮、氧和硫。

[1313] 29.如实施例28所述的化合物，其中X^1是-(CR^{14}R^{15})-、-C(R^{16})=、-N(R^9)-、-N=、或任选取代的C_{1-3}烷基。

[1314] 30.如实施例29所述的化合物，其中X^1是-(CR^{14}R^{15})-。

[1315] 31.如实施例30所述的化合物，其中每个R^{14}和R^{15}是H。

[1316] 32.如实施例29所述的化合物，其中X^1是-C(R^{16})=。

[1317] 33.如实施例32所述的化合物，其中R^{16}是H。

[1318] 34.如实施例29所述的化合物，其中X^1是-N(R^9)-。

[1319] 35.如实施例34所述的化合物，其中R^{9}是H或任选取代的C_{1-3}烷基。

[1320] 36.如实施例35所述的化合物，其中R^{9}是卤素、甲基、或乙基。

[1321] 37.如实施例29所述的化合物，其中X^1是-N=。

[1322] 38.如实施例29所述的化合物，其中X^1是任选取代的C_{1-3}烷基。

[1323] 39.如实施例28至37中任一项所述的化合物，其中X^2是不存在的、-$(CH_2)_n$-、-N(R^9)-、-C(H)=、=C(R^{20})-、或=C(H)-C(H)=。

[1324] 40.如实施例39所述的化合物，其中X^2是-C(H)=。

[1325] 41.如实施例39所述的化合物，其中X^2是-N(R^9)-。

[1326] 42.如实施例41所述的化合物，其中R^{9}是H。

[1327] 43.如实施例41所述的化合物，其中R^{9}是任选取代的C_{1-3}烷基。

[1328] 44.如实施例43所述的化合物，其中R^{9}是-C(O)-N(H)-Et。

[1329] 45.如实施例39所述的化合物，其中X^2是=C(R^{20})-。

[1330] 46.如实施例45所述的化合物，其中R^{20}是任选取代的C_{1-3}烷基。

[1331] 47.如实施例39所述的化合物，其中X^2是不存在的。

[1332] 48.如实施例28-37以及39-47中任一项所述的化合物，其中X^3是-CH_2-、-S-、=C(H)-、-N(R^9)-、卤素、任选取代的C_{1-3}烷基、任选取代的C_{1-3}烷氧基、任选取代的C_{1-6}硫代烷氧基、任选取代的C_{6-10}芳基。

[1333] 49.如实施例48所述的化合物，其中X^3是-CH_2-。

[1334] 50.如实施例48所述的化合物，其中X^3是-S-。

[1335] 51.如实施例48所述的化合物，其中X^3是=C(H)-。

[1336] 52.如实施例48所述的化合物，其中X^3是-N(R^9)-。

[1337] 53.如实施例48所述的化合物，其中X^3是卤素、任选取代的C_{1-3}烷基、任选取代的C_{1-3}烷氧基、任选取代的C_{1-6}硫代烷氧基、或任选取代的C_{6-10}芳基。

[1338] 54.如实施例1-53中任一项所述的化合物，其中每个R^5和R^6独立地是卤素或任选取代的C_{1-3}烷基。

[1339] 55.如实施例54所述的化合物，其中每个R^5和R^6是卤素。

[1340] 56.如实施例55所述的化合物，其中每个R^5和R^6是氯。

[1341] 57.如实施例1至56中任一项所述的化合物，其中R^7和R^8与各自附接的原子一起连接以形成任选取代的五元或六元环，该五元或六元环任选地包括一个或两个选自氮、氧和硫的杂原子。

[1342] 58.如实施例1至56中任一项所述的化合物，其中R^7和R^8与各自附接的原子一起连接以形成任选取代的五元或六元饱和环，该五元或六元饱和环任选地包括一个或两个选自氮、氧和硫的杂原子。

[1343] 59.如实施例1至56中任一项所述的化合物，其中R^7和R^8与各自附接的原子一起连接以形成任选取代的五元或六元环，该五元或六元环任选地包括一个或两个选自氮和氧的杂原子。

[1344] 60.如实施例1至56中任一项所述的化合物，其中R^7和R^8与各自附接的原子一起连接以形成任选取代的五元环。

[1345] 61.如实施例1至56中任一项所述的化合物，其中R^7和R^8与各自附接的原子一起连接以形成任选取代的饱和五元环。

[1346] 62.如实施例1至56中任一项所述的化合物，其中R^7和R^8结合以形成$-CH_2CH_2-$基团。

[1347] 63.如实施例1至56中任一项所述的化合物，其中R^7是任选取代的C_{1-3}烷基。

[1348] 64.如实施例63所述的化合物，其中R^7是甲基。

[1349] 65.如实施例63所述的化合物，其中R^7是$-(CH_2)_k-N(R^{24})R^{25}$，其中k是2或3，并且每个$R^{24}$和$R^{25}$独立地是H或任选取代的$C_{1-3}$烷基。

[1350] 66.如实施例65所述的化合物，其中k是2。

[1351] 67.如实施例65或66所述的化合物，其中每个R^{24}和R^{25}独立地是任选取代的C_{1-3}烷基。

[1352] 68.如实施例65至67中任一项所述的化合物，其中每个R^{24}和R^{25}是甲基。

[1353] 69.如实施例1至56中任一项所述的化合物，其中R^7和R^8形成基团$-Y^1-Y^2-$，其中：

[1354] Y^1是$-(CR^{26}R^{27})_m-$或任选取代的C_{1-3}烷基、任选取代的C_{1-3}烷杂环基、任选取代的C_{1-3}烷环烷基、或任选取代的C_{1-3}烷芳基；并且

[1355] Y^2是$-(CR^{26}R^{27})-$或H；其中

[1356] 每个R^{26}和R^{27}独立地是H或任选取代的C_{1-3}烷基；并且

[1357] m是1或2。

[1358] 70.如实施例1至5中任一项所述的化合物，其中Z^1和R^8结合以形成

[1359] $-Z^3-Y^1-Y^2-$，其中

[1360] Z^3是-O-、$-N(R^{10})-$、-N=、-S-、或$-(CR^{14}R^{15})-$；

[1361] Y^1是-O-、$-N(R^{10})-$、-S-、$-(CR^{26}R^{27})_m-$、$-C(R^{20})=$、$=C(R^{20})-$、$=C(R^{21})-C(R^{22})=$、任选取代的C_{1-3}烷基、任选取代的C_{1-3}烷杂环基、任选取代的C_{1-3}烷环烷基、或任选取代的C_{1-3}烷芳基；并且

[1362] Y^2是-O-、-S-、$-N(R^{10})-$、$-(CR^{26}R^{27})-$、$=C(R^{20})-$、=N-、或H；

[1363] 其中

[1364] 每个R^{20}、R^{21}、和R^{22}独立地是H或任选取代的C_{1-3}烷基;并且

[1365] 每个R^{26}和R^{27}独立地是H或任选取代的C_{1-3}烷基、或者R^{26}和R^{27}结合以形成=O或=S;

[1366] m是1或2;并且

[1367] 其中,当Y^2是H时,

[1368] 原子链-Z^3-Y^1-Y^2-包括不超过两个杂原子,该杂原子选自氮、氧、和硫。

[1369] 71.如实施例70所述的化合物,其中Z^3是-O-。

[1370] 72.如实施例69或71所述的化合物,其中Y^1是-$(CR^{26}R^{27})_m$-或任选取代的C_{1-3}烷基、任选取代的C_{1-3}烷杂环基、任选取代的C_{1-3}烷环烷基、或任选取代的C_{1-3}烷芳基。

[1371] 73.如实施例69至72中任一项所述的化合物,其中Y^1是-$(CR^{26}R^{27})_m$-或任选取代的C_{1-3}烷基。

[1372] 74.如实施例69至73中任一项所述的化合物,其中Y^2是-$(CR^{26}R^{27})$-或H。

[1373] 75.如实施例69至74中任一项所述的化合物,其中Y^2是-$(CR^{26}R^{27})$-。

[1374] 76.如实施例69至75中任一项所述的化合物,其中R^{26}是H。

[1375] 77.如实施例69至76中任一项所述的化合物,其中R^{27}是H。

[1376] 78.如实施例69至77中任一项所述的化合物,其中m是1。

[1377] 79.如实施例69至78中任一项所述的化合物,其中Y^1是任选取代的C_{1-3}烷基。

[1378] 80.如实施例79所述的化合物,其中Y^1是甲基。

[1379] 81.如实施例80所述的化合物,其中Y^1是-$(CH_2)_k$-$N(R^{24})R^{25}$,其中k是2或3,并且其中每个R^{24}和R^{25}独立地是H或任选取代的C_{1-3}烷基。

[1380] 82.如实施例81所述的化合物,其中k是2。

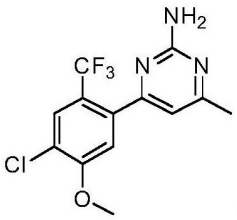
[1381] 83.如实施例81或82所述的化合物,其中每个R^{24}和R^{25}独立地是任选取代的C_{1-3}烷基。

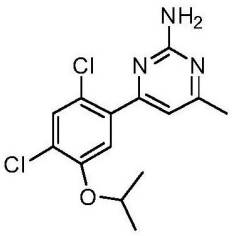
[1382] 84.如实施例81至83中任一项所述的化合物,其中每个R^{24}和R^{25}是甲基。

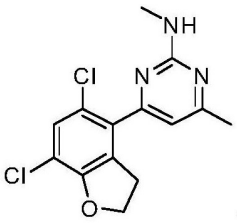
[1383] 85.如实施例1至84中任一项所述的化合物,其中每个R^1和R^2是H。

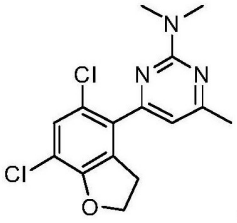
[1384] 86.一种化合物:

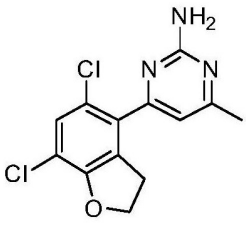
[1385]

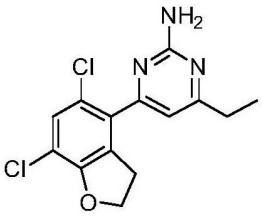
1 

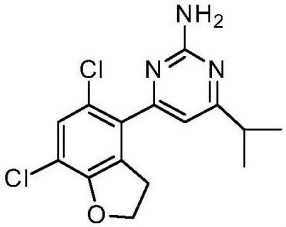
2 

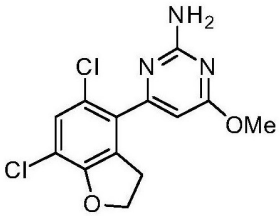
3 

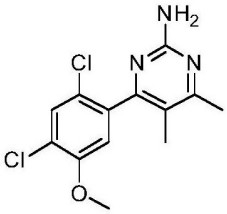
4 

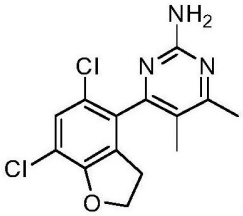
5 

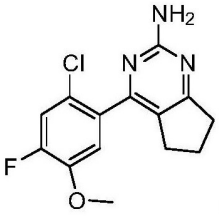
6 

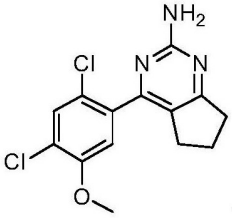
7 

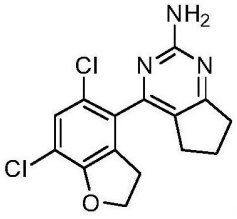
8 

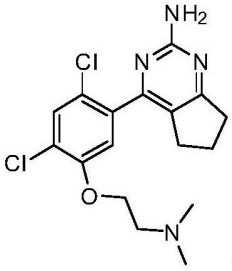
9 

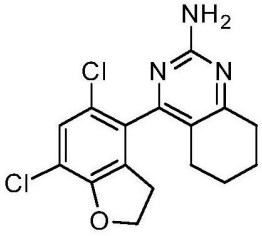
10 

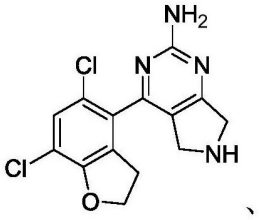
11 

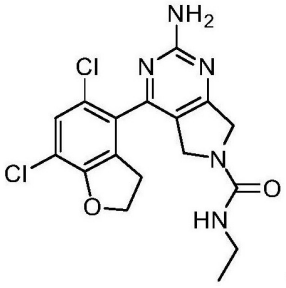
12 

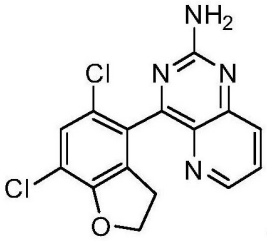
13 

14 

15 

16 

17 

18 

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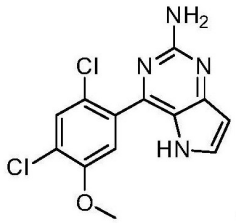
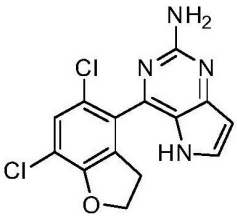
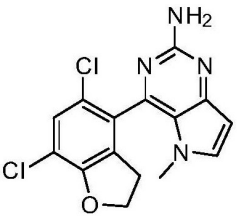
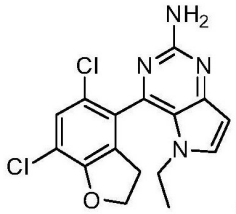
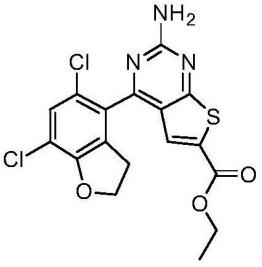
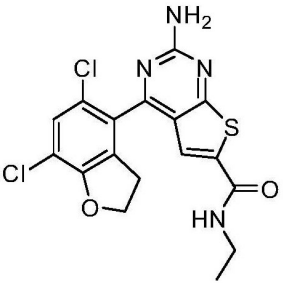
19 

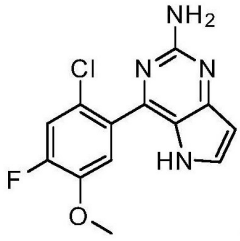
20 

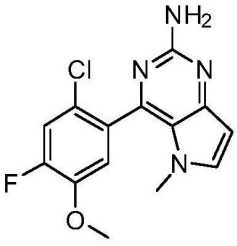
21 

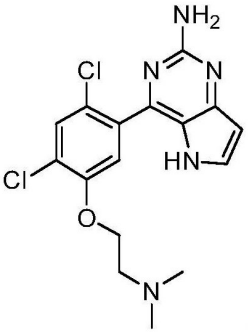
22 

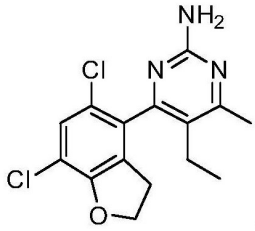
23 

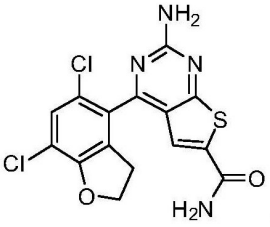
24 

25 

26 

27 

28 

29 

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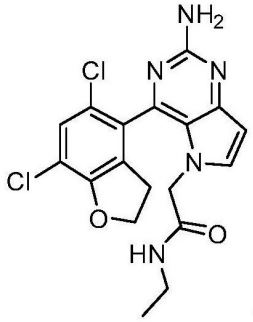
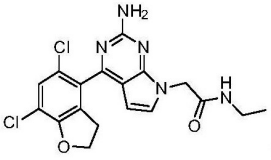
31 

32 

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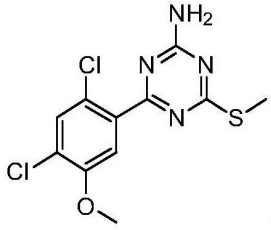
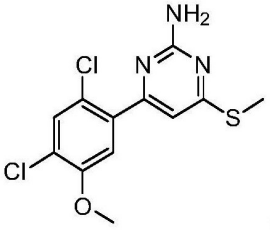
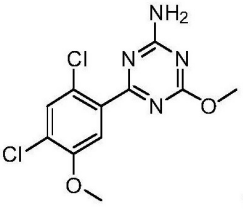
34 

35 

36 

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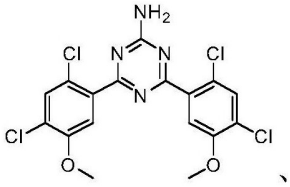
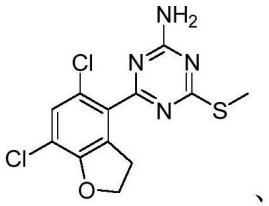
37 

40 

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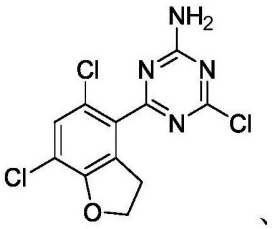
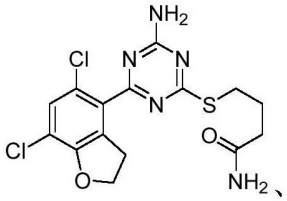
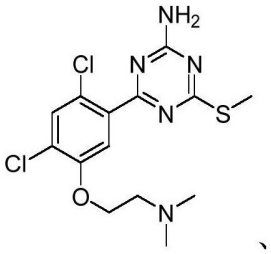
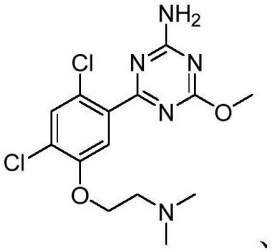
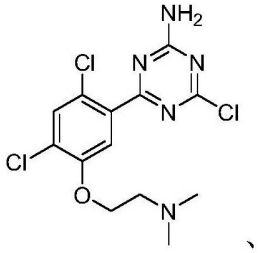
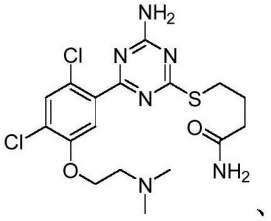
42 

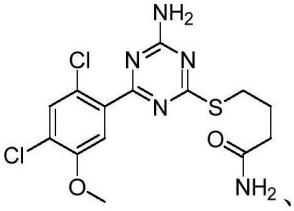
43 

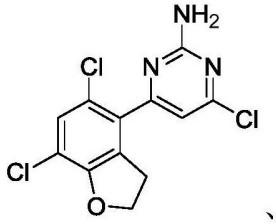
44 

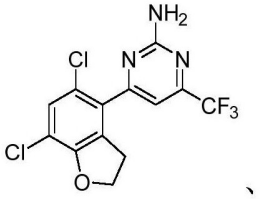
45 

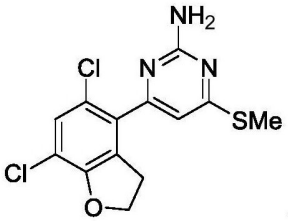
46 

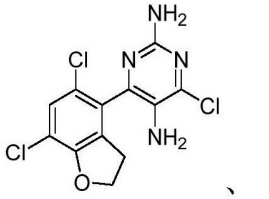
47 

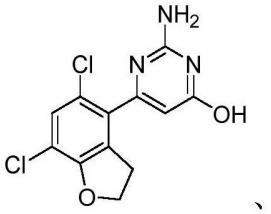
48 

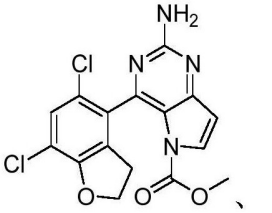
49 

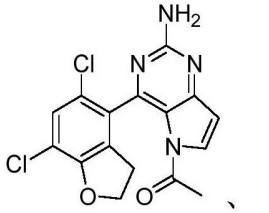
50 

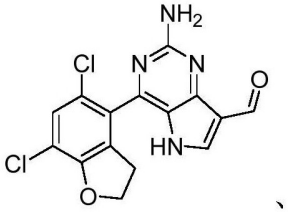
51 

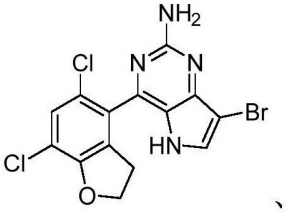
52 

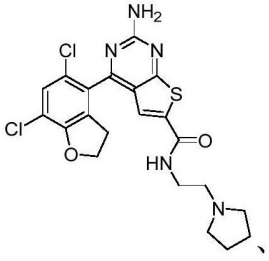
53 

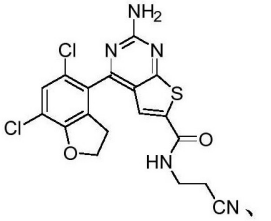
54 

55 

56 

57 

58 

59 

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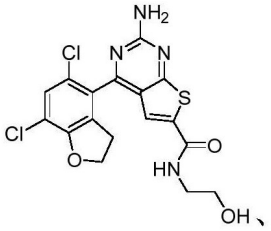
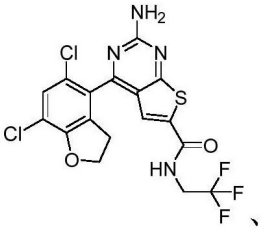
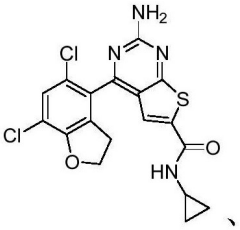
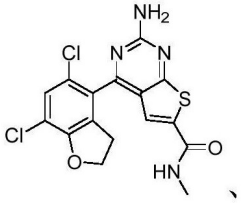
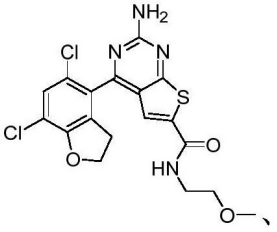
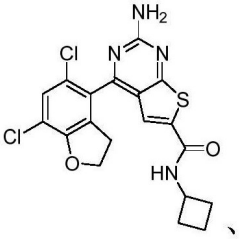
60  、

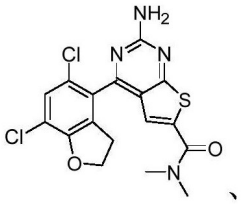
61  、

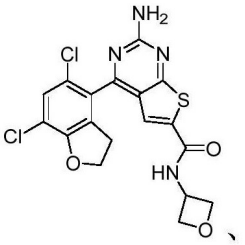
62  、

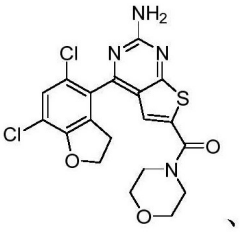
63  、

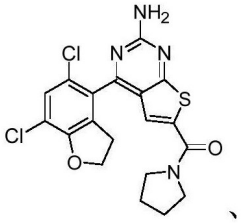
64  、

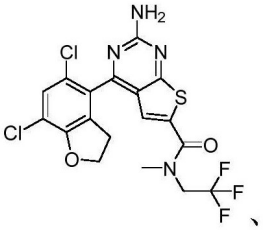
65  、

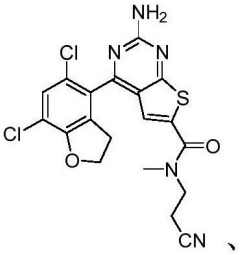
66  、

67  、

68  、

69  、

70  、

71  、

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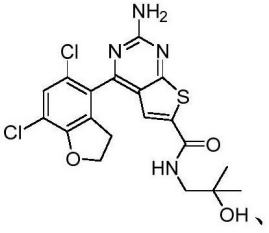
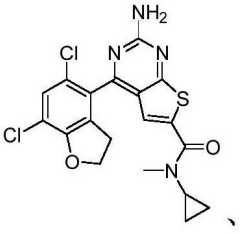
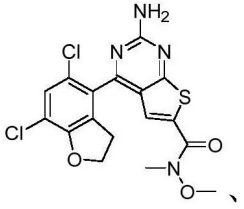
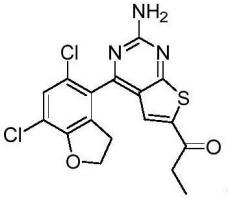
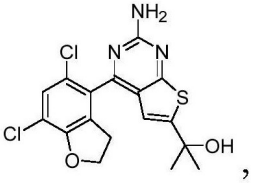
73  、

74  、

75  、

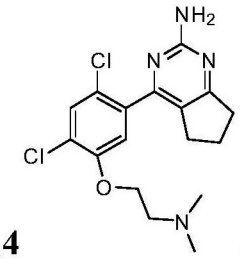
76  、或

77  ，

[1389] 或其药学上可接受的盐。

[1390] 87.如实施例84所述的化合物，具有式：

[1391]



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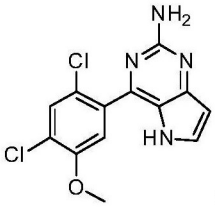

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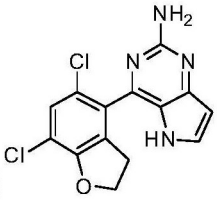

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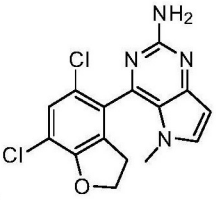

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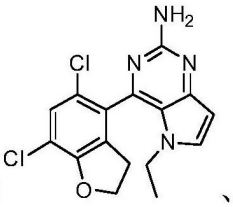
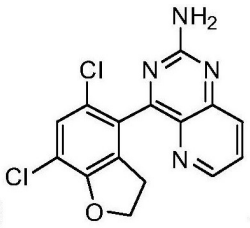
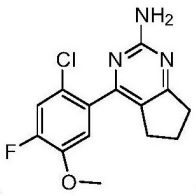
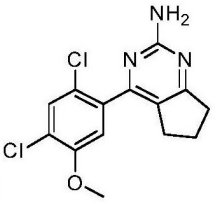
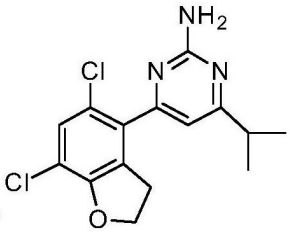
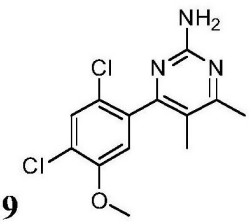
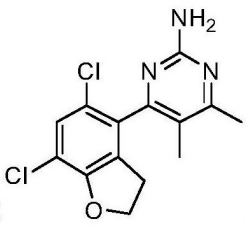
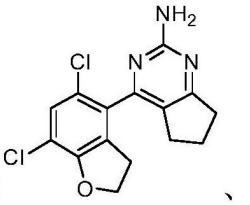
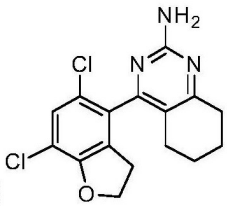
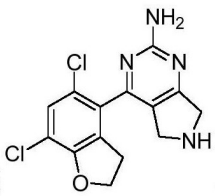
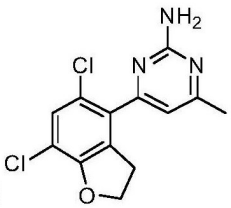
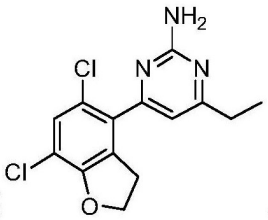
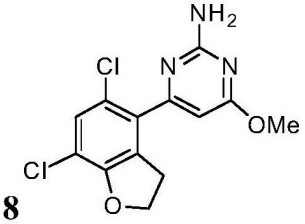

22、 
18、 
11、 
12、 
7、 
9、 
10、 
13、 
15、 
16、 
5、 
6、 
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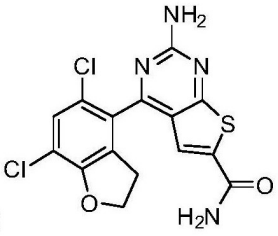
24、 
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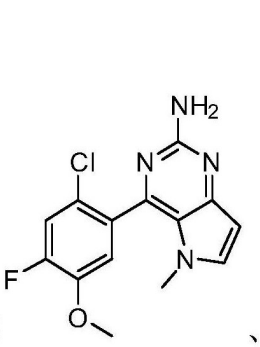
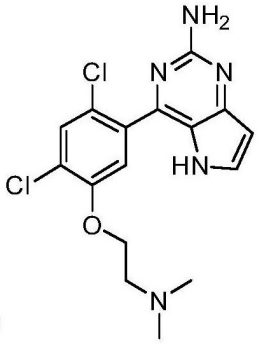
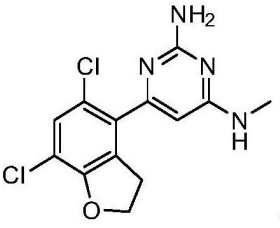
25、 
26、 
27、 
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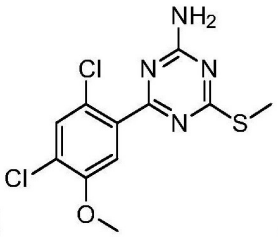
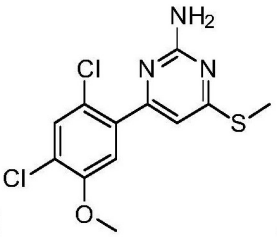
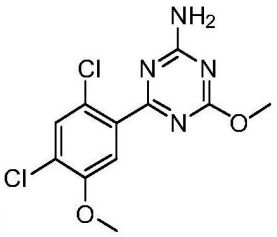
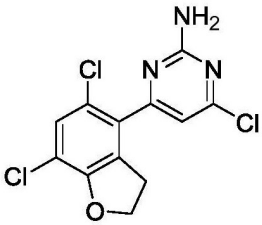
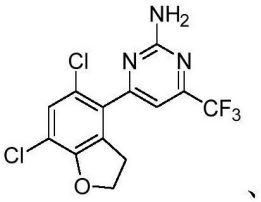
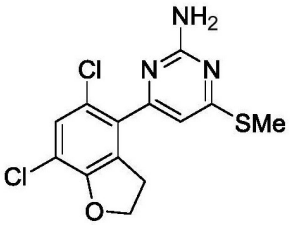
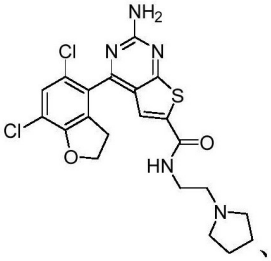
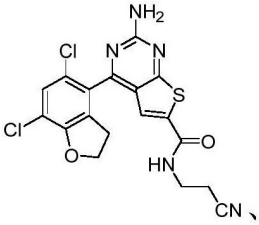
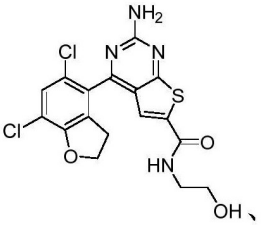
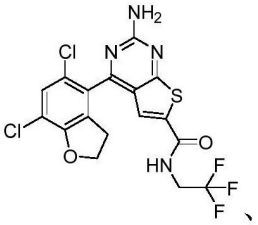
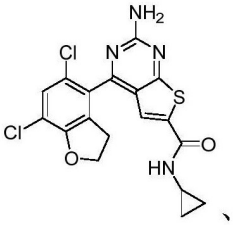
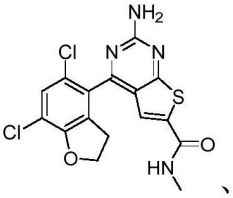
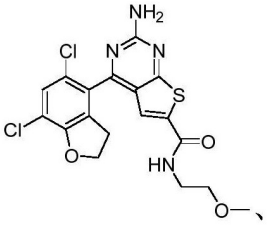
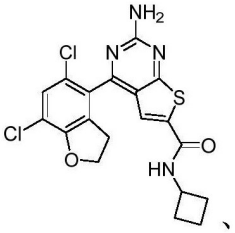
[1393]

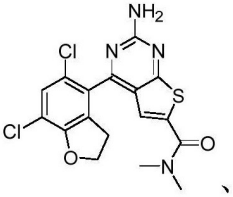
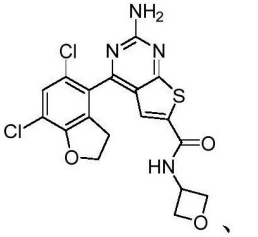
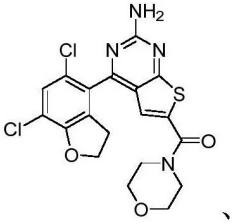
34  、35  、36  、

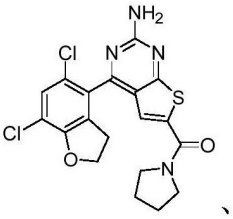
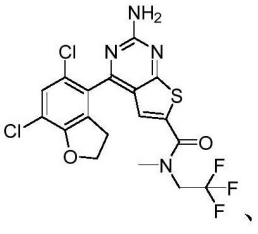
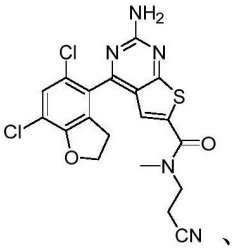
49  、50  、51  、

52 、58  、59  、

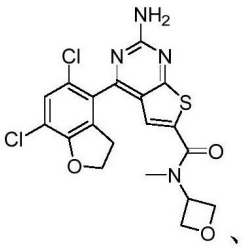
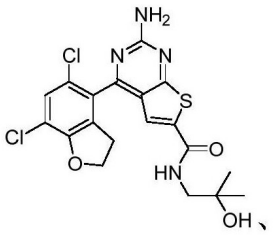
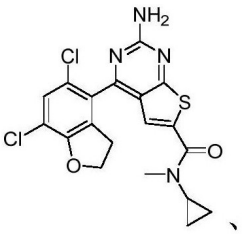
60  、61  、62  、

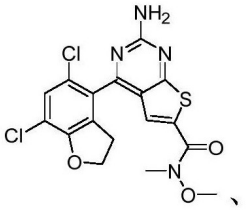
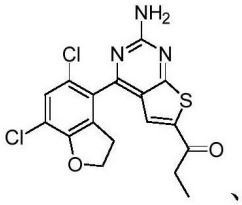
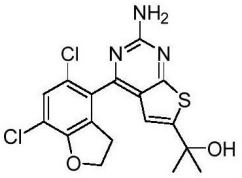
63  、64  、65  、

66  、67  、68  、

69  、70  、71  、

[1394]

72  、 73  、 74  、

75  、 76  、或 77  ，

[1395] 或其药学上可接受的盐。

[1396] 88.一种药物组合物，包括如实施例1至87中任一项所述的化合物或其药学上可接受的盐，以及一种或多种药学上可接受的载体或赋形剂。

[1397] 89.如实施例88所述的药物组合物，其中该组合物被配制为用于经口、舌下、颊部、经皮、皮内、肌内、胃肠外、静脉内、动脉内、颅内、皮下、眶内、心室内、脊柱内、腹膜内、鼻内、通过吸入、以及局部给予。

[1398] 90.如实施例89所述的药物组合物，其中该组合物被配制为用于口服给予。

[1399] 91.一种治疗哺乳动物由热休克蛋白90(Hsp90)的作用引起的障碍的方法，该方法包括给予该哺乳动物有效量的如实施例1至87中任一项所述的化合物或其药学上可接受的盐或如实施例88所述的药物组合物。

[1400] 92.如实施例91所述的方法，其中该障碍是神经退行性障碍。

[1401] 93.如实施例92所述的方法，其中该神经退行性障碍是tau蛋白病变。

[1402] 94.如实施例92或93所述的方法，其中该神经退行性障碍是阿尔茨海默氏病、亨廷顿舞蹈病、进行性核上性麻痹、帕金森病、皮克氏病、皮质基底节变性、慢性创伤性脑病、创伤性脑损伤、或额颞痴呆。

[1403] 95.如实施例94所述的方法，其中该神经退行性障碍是阿尔茨海默氏病。

[1404] 96.如实施例91所述的方法，其中该障碍是增殖性疾病。

[1405] 97.如实施例96所述的方法，其中该增殖性疾病是癌症。

[1406] 98.如实施例97所述的方法，其中该癌症是急性骨髓性白血病、胃肠道间质瘤、胃癌、神经胶质瘤、成神经细胞瘤、成胶质细胞瘤、肺癌、淋巴瘤、黑素瘤、骨髓瘤、非小细胞肺癌、肾癌、小细胞肺癌、胚期慢性骨髓性白血病、白血病、淋巴增生性障碍、转移性黑素瘤、复发性多发性骨髓瘤、难治性多发性骨髓瘤、骨髓增生性障碍、胰腺癌、小肠癌、或实体瘤。

[1407] 99.一种治疗哺乳动物的传染病的方法，该方法包括给予该哺乳动物有效量的如实施例1至87中任一项所述的化合物或其药学上可接受的盐或如实施例88所述的药物组合物。

[1408] 100.如实施例99所述的方法，其中该传染病是病毒感染。

[1409] 101.如实施例100所述的方法，其中该病毒感染是由选自下组的科的病毒引起的感染，该组由以下各项组成：疱疹病毒科、多瘤病毒科、痘病毒科、呼肠弧病毒科、双RNA病毒

科、小核糖核酸病毒科、黄病毒科、沙粒病毒科、戊型肝炎病毒科、弹状病毒科、副黏液病毒科、布尼亚病毒科、正粘病毒科、丝状病毒科、逆转录病毒科、和嗜肝病毒科。

[1410] 102.如实施例101所述的方法，其中疱疹病毒科的病毒是单纯疱疹病毒-1、单纯疱疹病毒-2、疱疹病毒-5、卡波西肉瘤相关的疱疹病毒、水痘带状疱疹病毒、或埃-巴二氏病毒。

[1411] 103.如实施例101所述的方法，其中多瘤病毒科的病毒是SV40。

[1412] 104.如实施例101所述的方法，其中痘病毒科的病毒是痘苗病毒。

[1413] 105.如实施例101所述的方法，其中呼肠孤病毒科的病毒是轮状病毒。

[1414] 106.如实施例101所述的方法，其中双RNA病毒科的病毒是感染性囊病病毒。

[1415] 107.如实施例101所述的方法，其中小核糖核酸病毒科的病毒是脊髓灰质炎病毒、鼻病毒或柯萨奇病毒。

[1416] 108.如实施例101所述的方法，其中黄病毒科的病毒是丙型肝炎病毒或登革热病毒。

[1417] 109.如实施例101所述的方法，其中沙粒病毒科的病毒是淋巴细胞性脉络丛脑膜炎病毒。

[1418] 110.如实施例101所述的方法，其中戊型肝炎病毒科的病毒是戊型肝炎病毒。

[1419] 111.如实施例101所述的方法，其中弹状病毒科的病毒是水泡性口炎病毒。

[1420] 112.如实施例101所述的方法，其中副黏液病毒科的病毒是人副流感病毒2、人副流感病毒3、SV5、SV41、麻疹病毒或仙台病毒。

[1421] 113.如实施例101所述的方法，其中布尼亚病毒科的病毒是拉克罗斯病毒。

[1422] 114.如实施例101所述的方法，其中正粘病毒科的病毒是甲型流感病毒。

[1423] 115.如实施例101所述的方法，其中丝状病毒科的病毒是埃博拉病毒。

[1424] 116.如实施例101所述的方法，其中逆转录病毒科的病毒是HTLV1或HIV1。

[1425] 117.如实施例101所述的方法，其中嗜肝病毒科的病毒是乙型肝炎病毒。

[1426] 118.如实施例99所述的方法，其中该传染病是真菌感染。

[1427] 119.如实施例118所述的方法，其中该真菌感染是白色念珠菌感染、烟曲霉感染或肺囊虫感染。

[1428] 120.如实施例99所述的方法，其中该传染病是细菌感染。

[1429] 121.如实施例120所述的方法，其中该细菌感染是分枝杆菌感染或炭疽感染。

[1430] 122.如实施例120所述的方法，其中该细菌感染是细菌性肺炎。

[1431] 123.如实施例91所述的方法，其中该障碍是炎性或自身免疫疾病。

[1432] 124.如实施例123所述的方法，其中该炎性或自身免疫疾病是类风湿性关节炎、系统性红斑狼疮、或哮喘。

[1433] 125.如实施例91所述的方法，其中该障碍是心血管疾病。

[1434] 126.如实施例125所述的方法，其中该心血管疾病是动脉粥样硬化或心肌病。

[1435] 127.如实施例91所述的方法，其中该障碍是过敏。

[1436] 128.如实施例91至127中任一项所述的方法，其中该化合物经口、舌下、颊部、经皮、皮内、肌内、胃肠外、静脉内、动脉内、颅内、皮下、眶内、心室内、脊柱内、腹膜内、鼻内、通过吸入、以及局部进行给予。

[1437] 129.如实施例128所述的方法，其中该化合物是口服给予的。

[1438] 130.如实施例91至129中任一项所述的方法，其中该哺乳动物是人。

[1439] 131.如实施例91至130中任一项所述的方法，其中该化合物经口、舌下、颊部、经皮、皮内、肌内、胃肠外、静脉内、动脉内、颅内、皮下、眶内、心室内、脊柱内、腹膜内、鼻内、通过吸入、以及局部进行给予。

[1440] 132.如实施例131所述的方法，其中该化合物是口服给予的。

[1441] 133.如实施例91至132中任一项所述的方法，其中该哺乳动物是人。

[1442] 134.一种化合物，用于在治疗哺乳动物中由热休克蛋白90(Hsp90)的作用引起的障碍中使用，其中该化合物是如实施例1至87中任一项所述的化合物或其药学上可接受的盐。

[1443] 135.如实施例134所述的化合物，其中该障碍是神经退行性障碍。

[1444] 136.如实施例135所述的化合物，其中该神经退行性障碍是tau蛋白病变。

[1445] 137.如实施例134或135的化合物，其中该神经退行性障碍是阿尔茨海默病、亨廷顿舞蹈病、进行性核上性麻痹、帕金森病、皮克氏病、皮质基底节变性、慢性创伤性脑病、创伤性脑损伤或额颞痴呆。

[1446] 138.如实施例137所述的化合物，其中该神经退行性障碍是阿尔茨海默氏病。

[1447] 139.如实施例134所述的化合物，其中该障碍是增殖性疾病。

[1448] 140.如实施例139所述的化合物，其中该增殖性疾病是癌症。

[1449] 141.如实施例140所述的化合物，其中该癌症是急性骨髓性白血病、胃肠道间质瘤、胃癌、成胶质细胞瘤、肺癌、淋巴瘤、黑素瘤、骨髓瘤、非小细胞肺癌、肾癌、小细胞肺癌、胚期慢性骨髓性白血病、白血病、淋巴增生性障碍、转移性黑素瘤、复发性多发性骨髓瘤、难治性多发性骨髓瘤、骨髓增生性障碍、胰腺癌、小肠癌、或实体瘤。

[1450] 142.如实施例134所述的化合物，其中该障碍是传染病。

[1451] 143.如实施例142所述的化合物，其中该传染病是病毒感染。

[1452] 144.如实施例143所述的化合物，其中该病毒感染是由选自下组的科的病毒引起的感染，该组由以下各项组成：疱疹病毒科、多瘤病毒科、痘病毒科、呼肠弧病毒科、双RNA病毒科、小核糖核酸病毒科、黄病毒科、沙粒病毒科、戊型肝炎病毒科、弹状病毒科、副黏液病毒科、布尼亚病毒科、正粘病毒科、丝状病毒科、逆转录病毒科、和嗜肝病毒科。

[1453] 145.如实施例144所述的化合物，其中疱疹病毒科的病毒是单纯疱疹病毒-1、单纯疱疹病毒-2、疱疹病毒-5、卡波西肉瘤相关的疱疹病毒、水痘带状疱疹病毒、或埃-巴二氏病毒。

[1454] 146.如实施例144所述的化合物，其中多瘤病毒科的病毒是SV40。

[1455] 147.如实施例144所述的化合物，其中痘病毒科的病毒是痘苗病毒。

[1456] 148.如实施例144所述的化合物，其中呼肠孤病毒科的病毒是轮状病毒。

[1457] 149.如实施例144所述的化合物，其中双RNA病毒科的病毒是感染性囊病病毒。

[1458] 150.如实施例144所述的化合物，其中小核糖核酸病毒科的病毒是脊髓灰质炎病毒、鼻病毒或柯萨奇病毒。

[1459] 141.如实施例144所述的化合物，其中黄病毒科的病毒是丙型肝炎病毒或登革热病毒。

[1460] 152.如实施例144所述的化合物，其中沙粒病毒科的病毒是淋巴细胞性脉络丛脑膜炎病毒。

[1461] 153.如实施例144所述的化合物，其中戊型肝炎病毒科的病毒是戊型肝炎病毒。

[1462] 154.如实施例144所述的化合物，其中弹状病毒科的病毒是水泡性口炎病毒。

[1463] 155.如实施例144所述的化合物，其中副黏液病毒科的病毒是人副流感病毒2、人副流感病毒3、SV5、SV41、麻疹病毒或仙台病毒。

[1464] 156.如实施例144所述的化合物，其中布尼亚病毒科的病毒是拉克罗斯病毒。

[1465] 157.如实施例144所述的化合物，其中正粘病毒科的病毒是甲型流感病毒。

[1466] 158.如实施例144所述的化合物，其中丝状病毒科的病毒是埃博拉病毒。

[1467] 159.如实施例144所述的化合物，其中逆转录病毒科的病毒是HTLV1或HIV1。

[1468] 160.如实施例144所述的化合物，其中嗜肝病毒科的病毒是乙型肝炎病毒。

[1469] 161.如实施例134所述的化合物，其中该传染病是真菌感染。

[1470] 162.如实施例161所述的化合物，其中该真菌感染是白色念珠菌感染、烟曲霉感染或肺囊虫感染。

[1471] 163.如实施例134所述的化合物，其中该传染病是细菌感染。

[1472] 165.如实施例163所述的化合物，其中该细菌感染是分枝杆菌感染或炭疽感染。

[1473] 166.如实施例163所述的化合物，其中该细菌感染是细菌性肺炎。

[1474] 167.如实施例134所述的化合物，其中该病症是炎性或自身免疫疾病。

[1475] 168.如实施例167所述的化合物，其中该炎性或自身免疫疾病是类风湿性关节炎、系统性红斑狼疮、或哮喘。

[1476] 169.如实施例134所述的化合物，其中该障碍是心血管疾病。

[1477] 170.如实施例169所述的化合物，其中该心血管疾病是动脉粥样硬化或心肌病。

[1478] 171.如实施例170所述的化合物，其中该障碍是过敏。

[1479] 172.一种化合物在生产用于治疗哺乳动物中由热休克蛋白90(Hsp90)的作用引起的障碍的药物中的用途，其中该化合物是如实施例1至87中任一项所述的化合物或其药学上可接受的盐。

[1480] 173.一种化合物用于治疗哺乳动物中由热休克蛋白90(Hsp90)的作用引起的障碍的用途，其中该化合物是如实施例1至87中任一项所述的化合物或其药学上可接受的盐。

[1481] 174.如实施例172或173所述的用途，其中该障碍是神经退行性障碍。

[1482] 175.如实施例174所述的用途，其中该神经退行性障碍是tau蛋白病变。

[1483] 176.如实施例174或175所述的用途，其中该神经退行性障碍是阿尔茨海默病、亨廷顿舞蹈病、进行性核上性麻痹、帕金森病、皮克氏病、皮质基底节变性、慢性创伤性脑病、创伤性脑损伤或额颞痴呆。

[1484] 177.如实施例176所述的用途，其中该神经退行性障碍是阿尔茨海默氏病。

[1485] 178.如实施例172或173所述的用途，其中该障碍是增殖性疾病。

[1486] 179.如实施例178所述的用途，其中该增殖性疾病是癌症。

[1487] 180.如实施例179所述的用途，其中该癌症是急性骨髓性白血病、胃肠道间质瘤、胃癌、成胶质细胞瘤、肺癌、淋巴瘤、黑素瘤、骨髓瘤、非小细胞肺癌、肾癌、小细胞肺癌、胚期慢性骨髓性白血病、白血病、淋巴增生性障碍、转移性黑素瘤、复发性多发性骨髓瘤、难治性

多发性骨髓瘤、骨髓增生性障碍、胰腺癌、小肠癌、或实体瘤。

[1488] 181.一种化合物用于治疗传染病、或在生产用于治疗传染病的药物中的用途，其中该化合物是如实施例1至87中任一项所述的化合物。

[1489] 182.如实施例181所述的用途，其中该传染病是病毒感染。

[1490] 183.如实施例182所述的用途，其中该病毒感染是由选自下组的科的病毒引起的感染，该组由以下各项组成：疱疹病毒科、多瘤病毒科、痘病毒科、呼肠弧病毒科、双RNA病毒科、小核糖核酸病毒科、黄病毒科、沙粒病毒科、戊型肝炎病毒科、弹状病毒科、副黏液病毒科、布尼亚病毒科、正粘病毒科、丝状病毒科、逆转录病毒科、和嗜肝病毒科。

[1491] 184.如实施例183所述的用途，其中疱疹病毒科的病毒是单纯疱疹病毒-1、单纯疱疹病毒-2、疱疹病毒-5、卡波西肉瘤相关的疱疹病毒、水痘带状疱疹病毒、或埃-巴二氏病毒。

[1492] 185.如实施例183所述的用途，其中多瘤病毒科的病毒是SV40。

[1493] 186.如实施例183所述的用途，其中痘病毒科的病毒是痘苗病毒。

[1494] 187.如实施例183所述的用途，其中呼肠孤病毒科的病毒是轮状病毒。

[1495] 188.如实施例183所述的用途，其中双RNA病毒科的病毒是感染性囊病病毒。

[1496] 189.如实施例183所述的用途，其中小核糖核酸病毒科的病毒是脊髓灰质炎病毒、鼻病毒或柯萨奇病毒。

[1497] 190.如实施例183所述的用途，其中黄病毒科的病毒是丙型肝炎病毒或登革热病毒。

[1498] 191.如实施例183所述的用途，其中沙粒病毒科的病毒是淋巴细胞性脉络丛脑膜炎病毒。

[1499] 192.如实施例183所述的用途，其中戊型肝炎病毒科的病毒是戊型肝炎病毒。

[1500] 193.如实施例183所述的用途，其中弹状病毒科的病毒是水泡性口炎病毒。

[1501] 194.如实施例183所述的用途，其中副黏液病毒科的病毒是人副流感病毒2、人副流感病毒3、SV5、SV41、麻疹病毒或仙台病毒。

[1502] 195.如实施例183所述的用途，其中布尼亚病毒科的病毒是拉克罗斯病毒。

[1503] 196.如实施例183所述的用途，其中正粘病毒科的病毒是甲型流感病毒。

[1504] 197.如实施例183所述的用途，其中丝状病毒科的病毒是埃博拉病毒。

[1505] 198.如实施例183所述的用途，其中逆转录病毒科的病毒是HTLV1或HIV1。

[1506] 199.如实施例183所述的用途，其中嗜肝病毒科的病毒是乙型肝炎病毒。

[1507] 200.如实施例172或173所述的用途，其中该传染病是真菌感染。

[1508] 201.如实施例200所述的用途，其中该真菌感染是白色念珠菌感染、烟曲霉感染、或肺囊虫感染。

[1509] 202.如实施例172或173所述的用途，其中该传染病是细菌感染。

[1510] 203.如实施例202所述的用途，其中该细菌感染是分枝杆菌感染或炭疽感染。

[1511] 204.如实施例203所述的用途，其中该细菌感染是细菌性肺炎。

[1512] 205.如实施例172或173所述的用途，其中该障碍是炎性或自身免疫疾病。

[1513] 206.如实施例205所述的用途，其中该炎性或自身免疫疾病是类风湿性关节炎、系统性红斑狼疮、或哮喘。

[1514] 207.如实施例172或173所述的用途,其中该障碍是心血管疾病。

[1515] 208.如实施例207所述的用途,其中该心血管疾病是动脉粥样硬化或心肌病。

[1516] 209.如实施例172或173所述的用途,其中该障碍是过敏。

[1517] 210.如实施例134至171中任一项所述的化合物或如实施例172至209中任一项所述的用途,其中该化合物被配制用于通过选自下组的途径给予,该组由以下各项组成:口腔、舌下、颊部、经皮、皮内、肌肉内、肠胃外、静脉内、动脉内、颅内、皮下、眶内、心室内、脊柱内、腹膜内、鼻内、通过吸入、以及局部。

[1518] 211.如实施例128的化合物或用途,其中该化合物被配制用于口服给予。

[1519] 212.一种抑制Hsp90的方法,该方法包括使细胞与如实施例1至87中任一项所述的化合物或其药学上可接受的盐相接触。

[1520] 213.如实施例212所述的方法,其中该细胞是在体外。

[1521] 214.一种化合物,用于在抑制Hsp90中使用,其中该化合物是如实施例1至87中任一项所述的化合物或其药学上可接受的盐。

[1522] 215.一种化合物用于抑制Hsp90的用途,其中该化合物是如实施例1至87中任一项所述的化合物或其药学上可接受的盐。

[1523] 216.一种试剂盒,包括:

[1524] (i)如实施例88至90中任一项的药物组合物;以及

[1525] (ii)使用(i)的药物组合物治疗哺乳动物中由Hsp90的作用引起的障碍的说明书。

[1526] 本说明书中提到的所有出版物、专利和专利申请都通过引用结合在此,如同每一独立的出版物、或专利申请具体且单独地指明通过引用结合在此。

[1527] 虽然本发明已结合其特定实施例予以描述,但是应理解其能够进行进一步修改,并且希望本申请涵盖本发明的通常遵循本发明原则并且涉及与本申请的偏差的任何变化形式、应用或改造,这些偏差在本发明所属技术的已知或常规实践范围内,并且可适用于如上阐明并且在该权利要求范围内出现的基本特征。

[1528] 其他实施例在权利要求中。

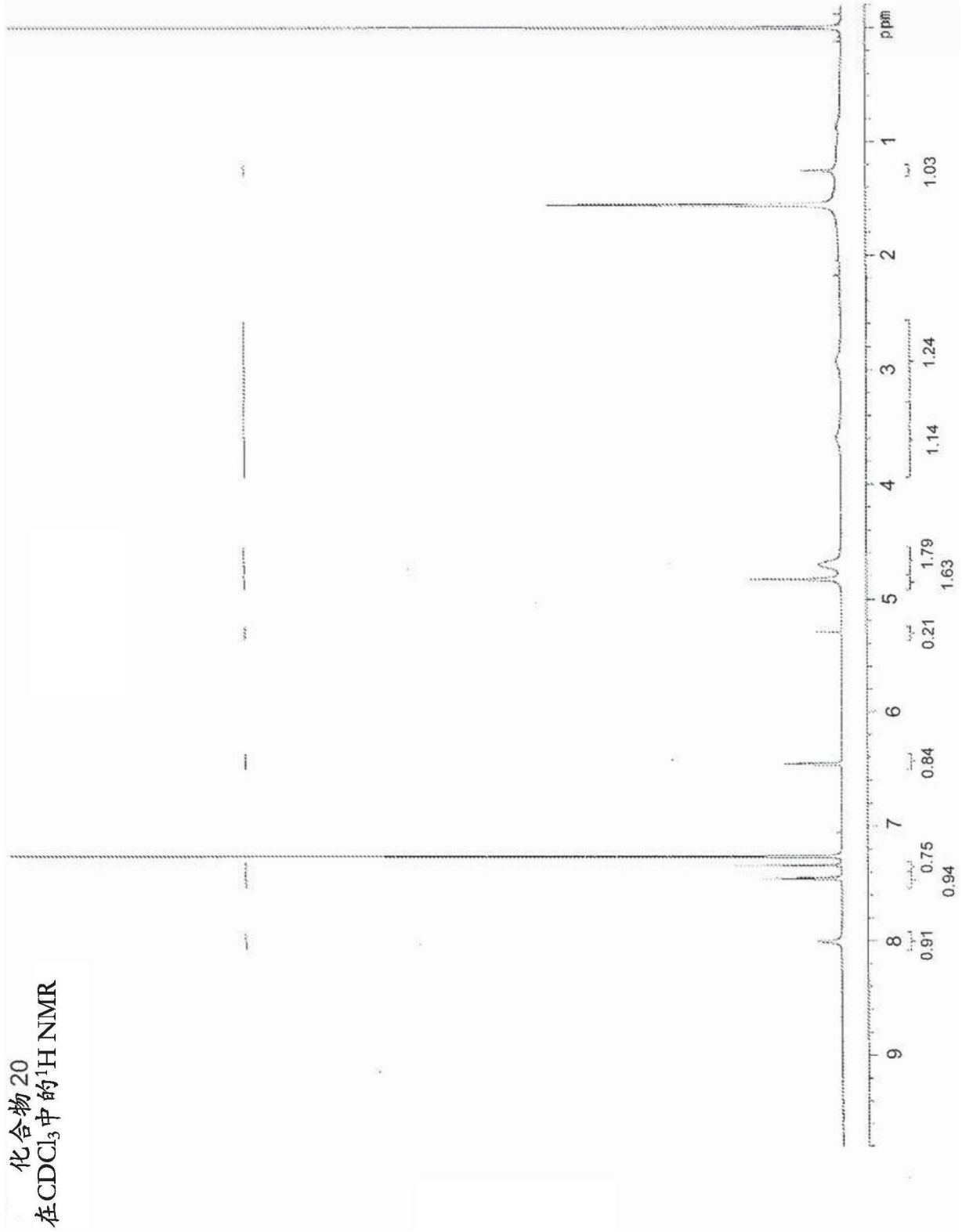

化合物20
在$CDCl_3$中的^1H NMR
ppm
1
2
3
4
5
6
7
8
9
1.03
1.24
1.14
1.79
1.63
0.21
0.84
0.75
0.94
0.91

图1

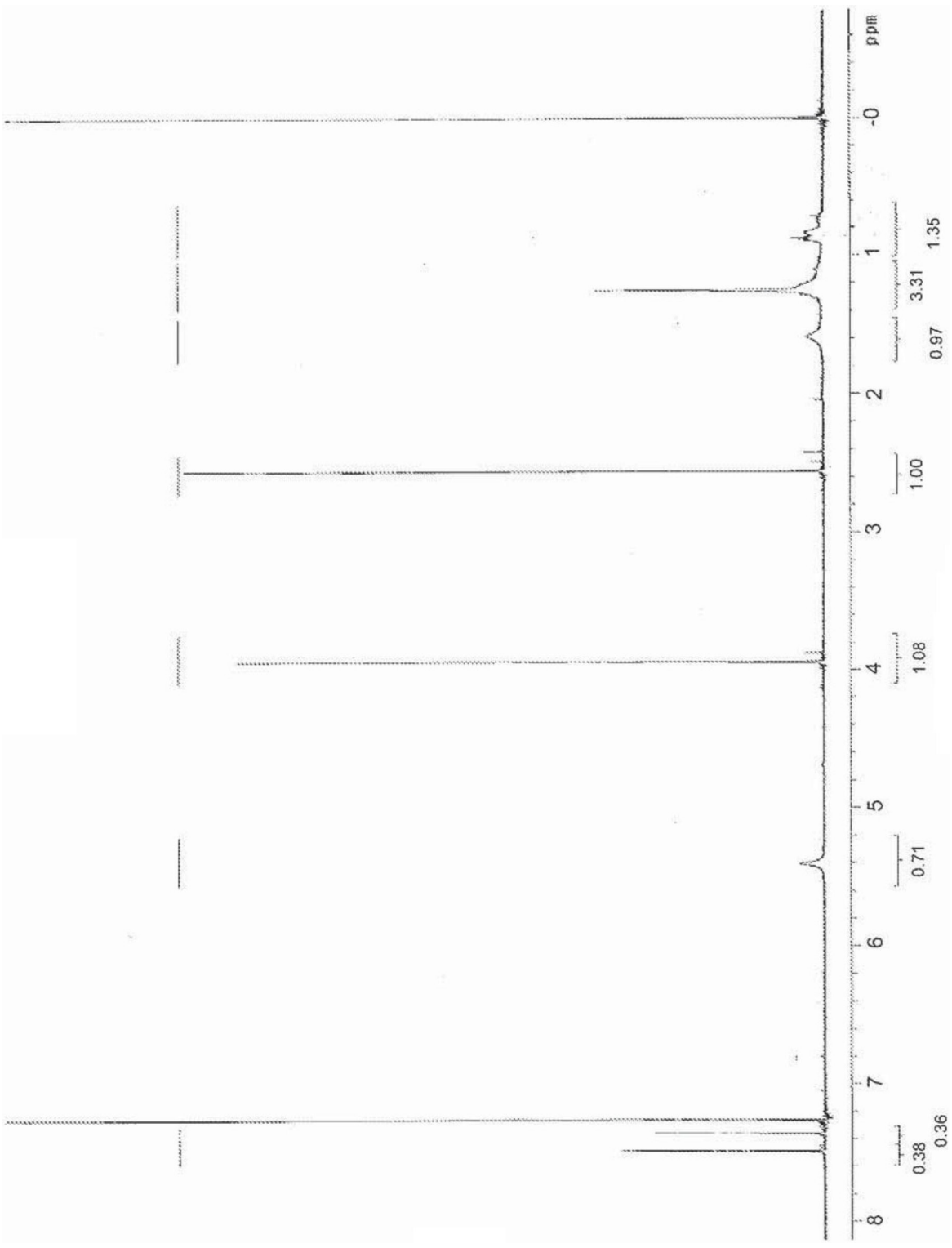


图2

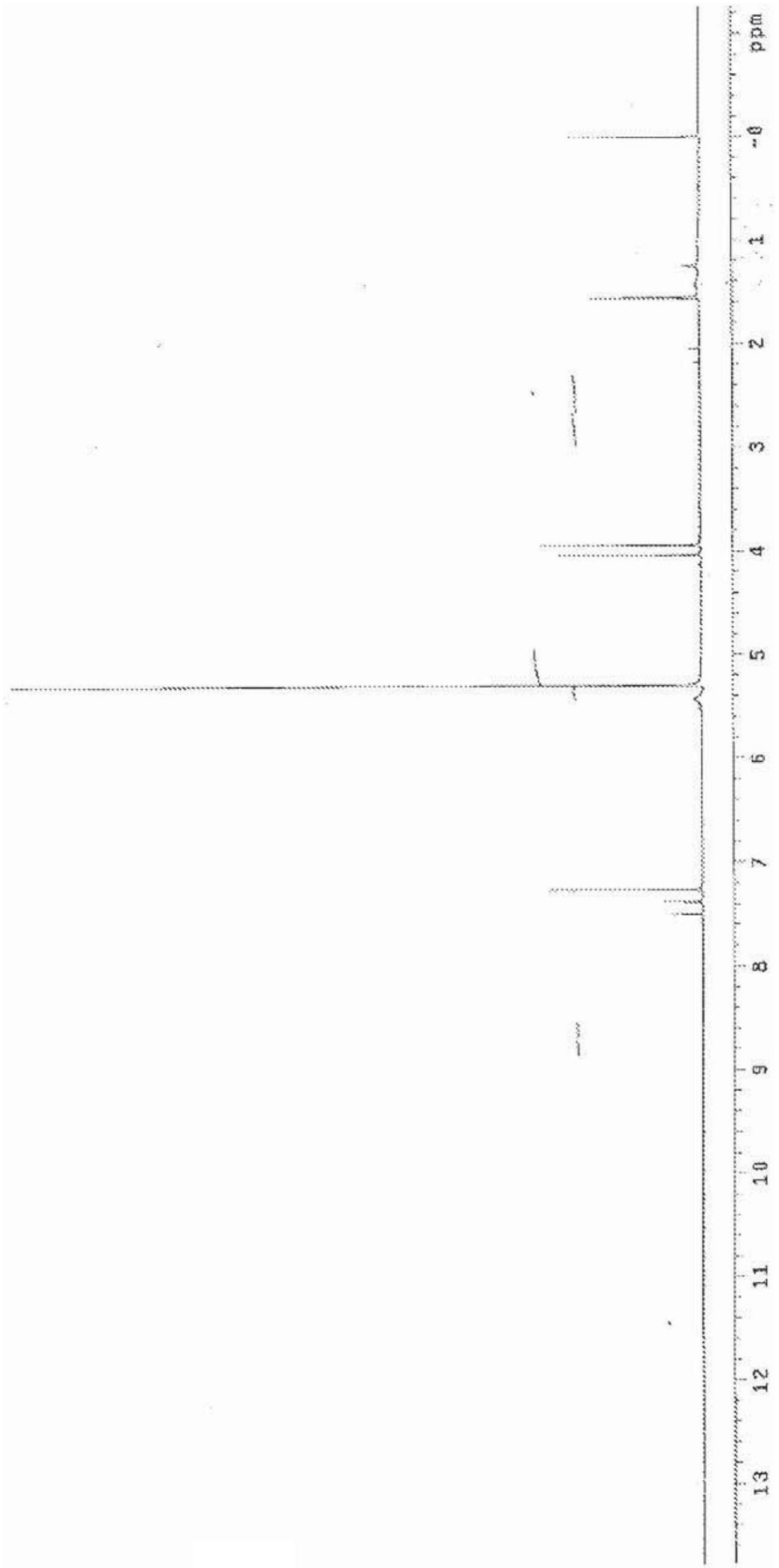


图3

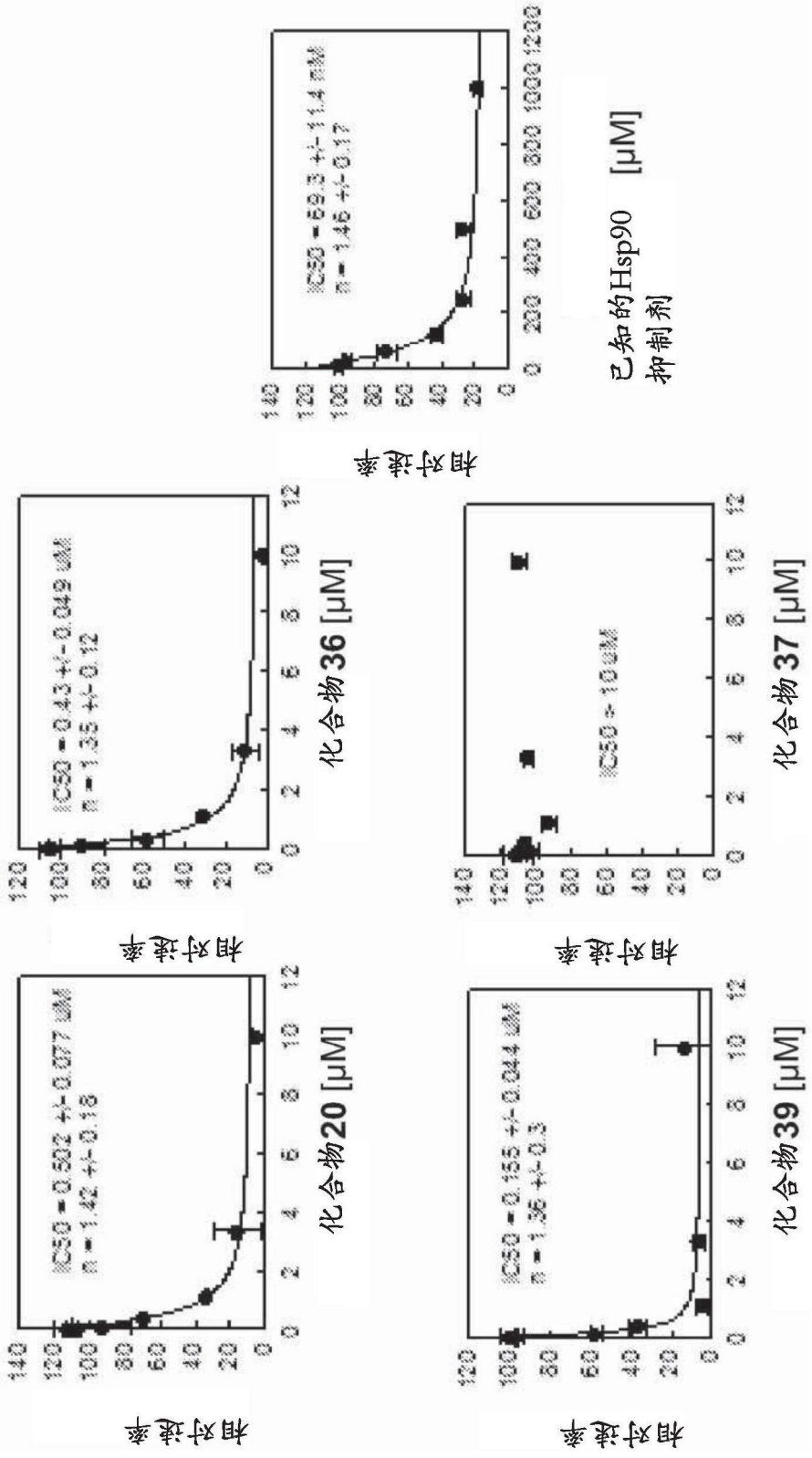


图4

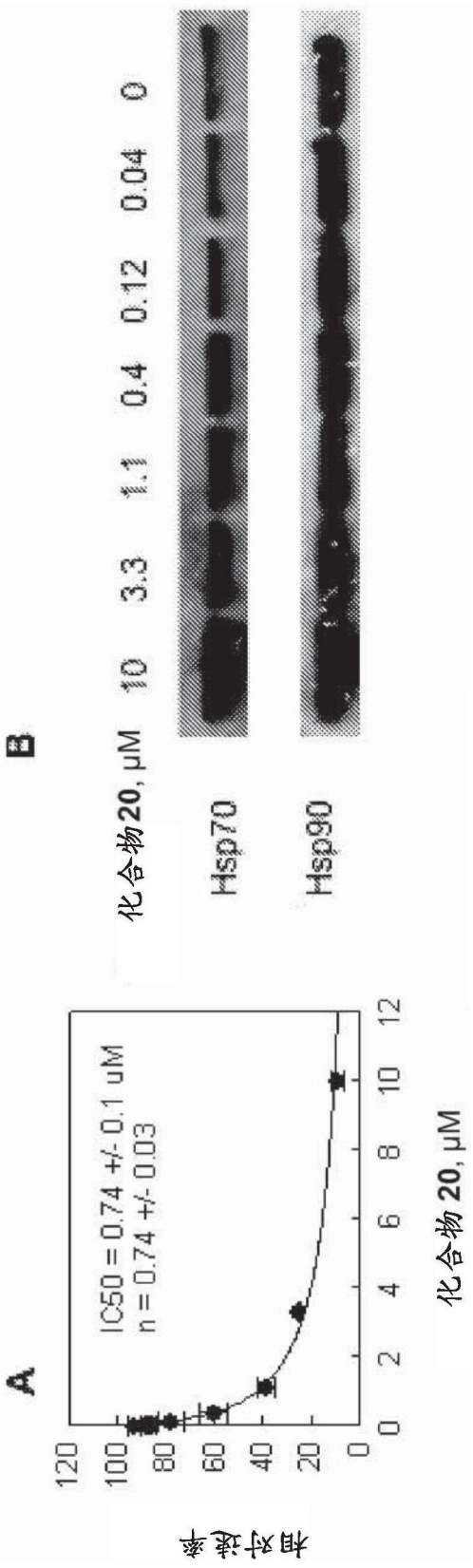

A
IC50 = 0.74 +/- 0.1 uM
n = 0.74 +/- 0.03
相对速率
化合物 20, μM
B
化合物 20, μM 10 3.3 1.1 0.4 0.12 0.04 0
Hsp70
Hsp90

图5

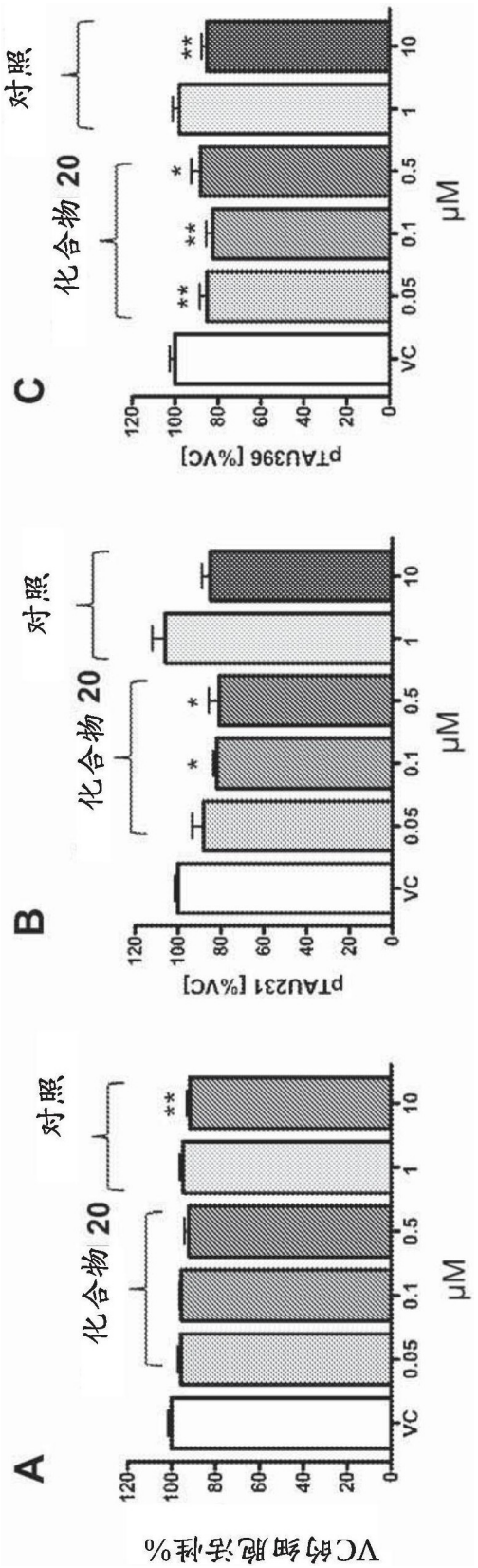

A
对照
化合物 20
VC 0.05 0.1 0.5 1 10 μM
VC的细胞活性%
B
对照
化合物 20
pTAU231 [%VC]
C
对照
化合物 20
pTAU396 [%VC]

图6

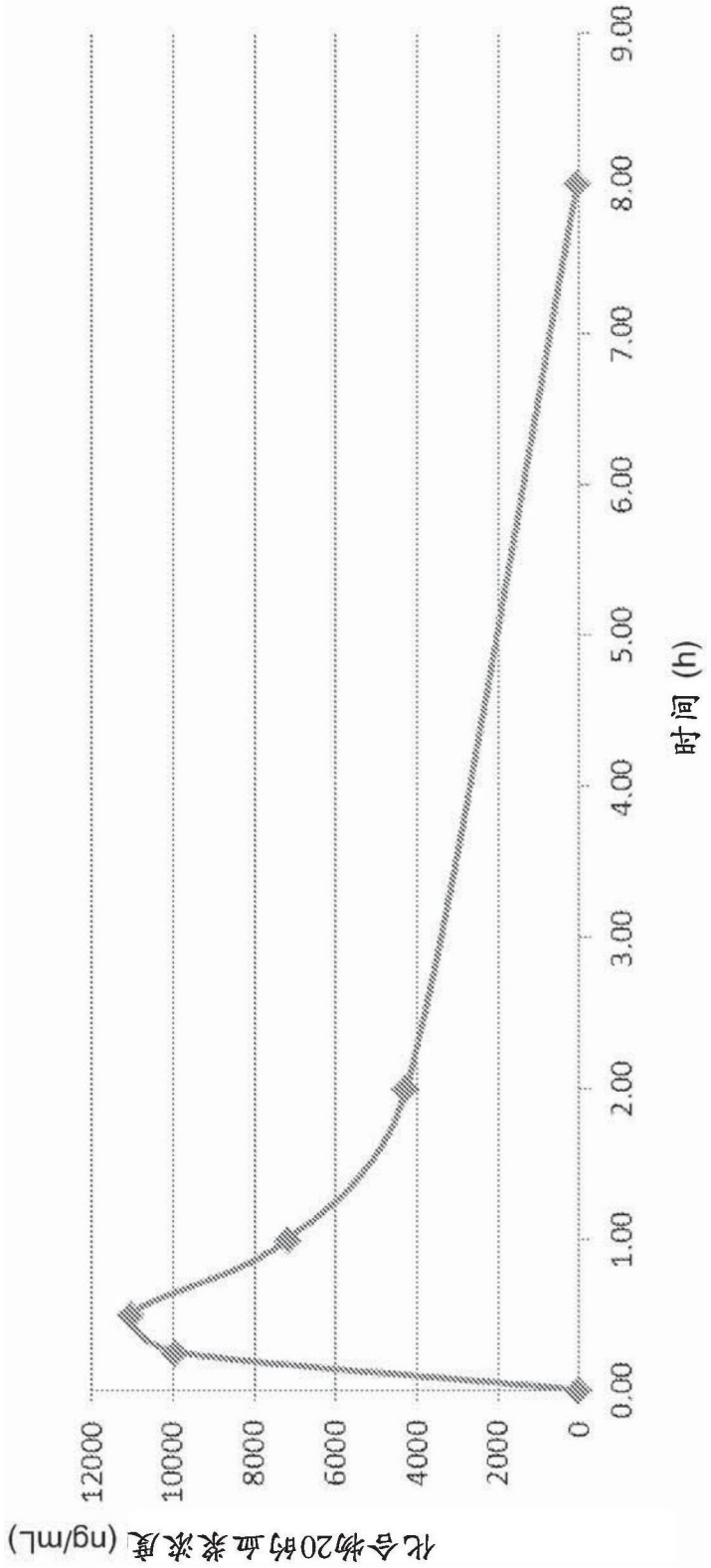

化合物20的血浆浓度 (ng/mL)
12000
10000
8000
6000
4000
2000
0
0.00
1.00
2.00
3.00
4.00
5.00
6.00
7.00
8.00
9.00
时间 (h)

图7

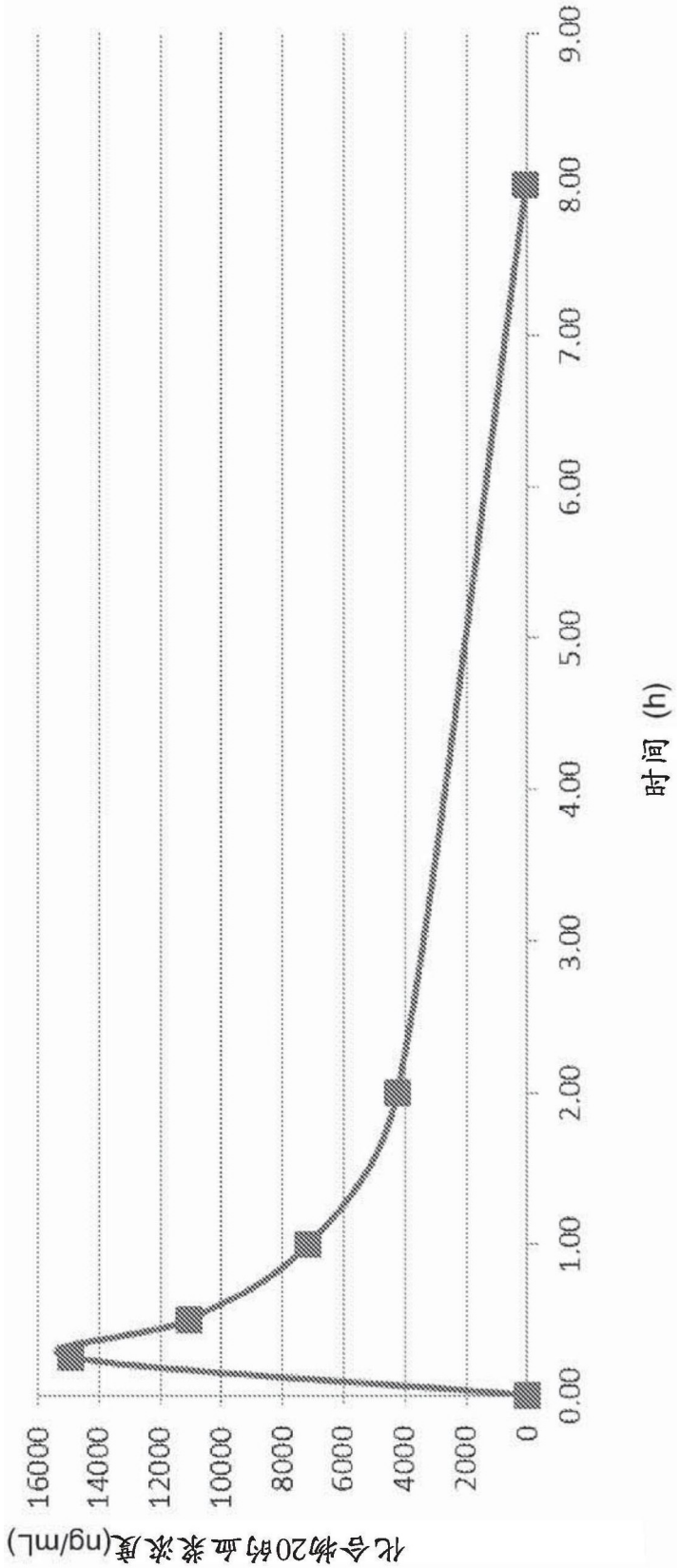

化合物20的血浆浓度(ng/mL)
16000
14000
12000
10000
8000
6000
4000
2000
0
0.00
1.00
2.00
3.00
4.00
5.00
6.00
7.00
8.00
9.00
时间 (h)

图8

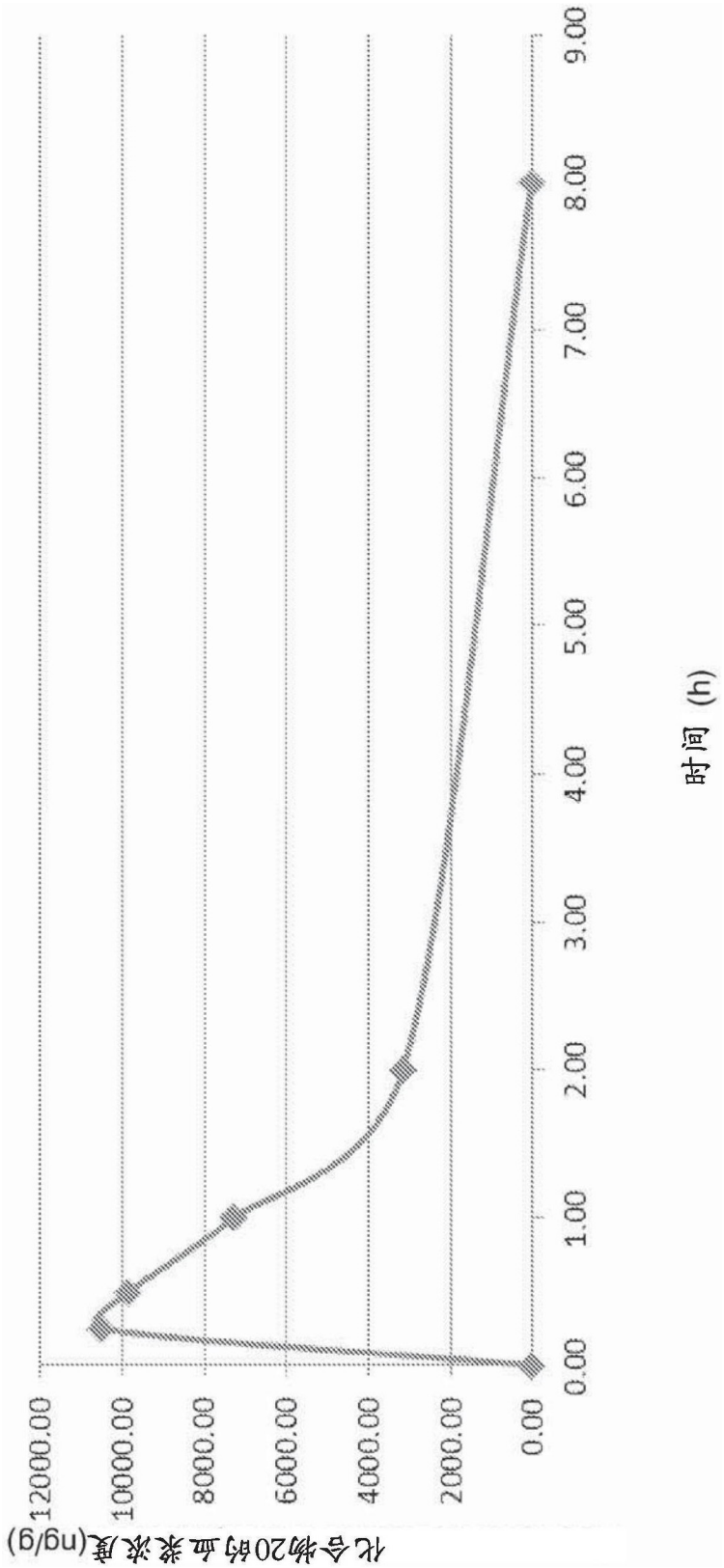

12000.00
10000.00
8000.00
6000.00
4000.00
2000.00
0.00
0.00
1.00
2.00
3.00
4.00
5.00
6.00
7.00
8.00
9.00
时间 (h)
化合物20的血浆浓度(ng/g)

图9

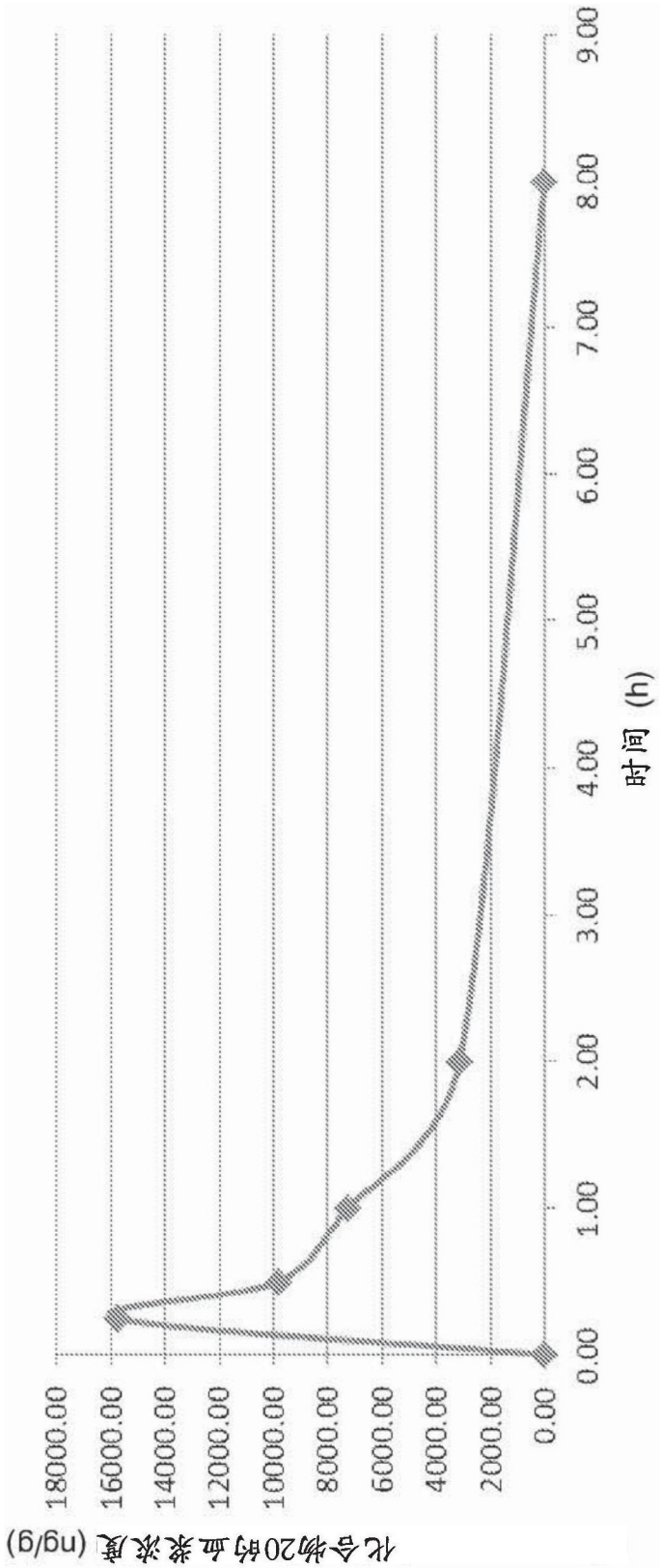

18000.00
16000.00
14000.00
12000.00
10000.00
8000.00
6000.00
4000.00
2000.00
0.00
0.00
1.00
2.00
3.00
4.00
5.00
6.00
7.00
8.00
9.00
时间 (h)
化合物20的血浆浓度 (ng/g)

图10