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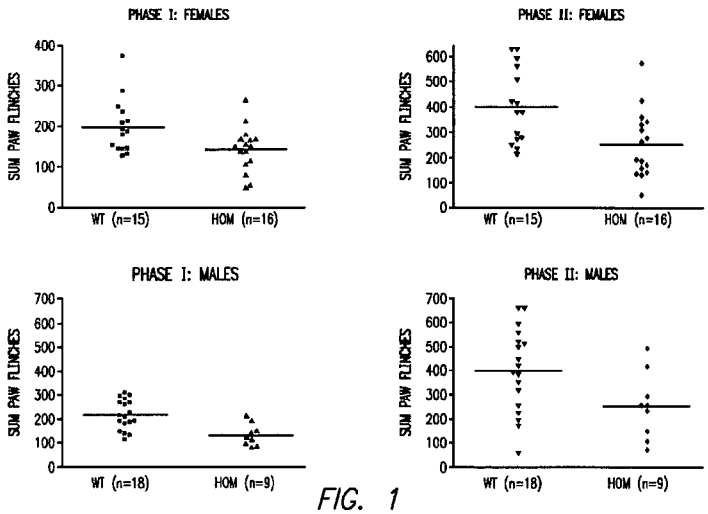

FIG. 1

(57) Abstract: This invention is directed to the treatment of pain by inhibiting adaptor associated kinase 1 (AAK1). Numerous AAK1 inhibitors are disclosed.

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INHIBITION OF ADAPTOR ASSOCIATED KINASE 1 FOR THE TREATMENT OF PAIN

This application claims priority to U.S. provisional patent application no. 61/608,849, filed March 9, 2012, the entirety of which is incorporated herein by reference.

1. FIELD OF THE INVENTION

This invention is directed to methods of treating pain by inhibiting adaptor associated kinase 1 (AAK1).

2. BACKGROUND OF THE INVENTION

Pain can generally be divided into three different types: acute, inflammatory, and neuropathic. Acute pain by its very nature generally is short lasting and intense. Inflammatory pain on the other hand may last for much longer periods of time and its intensity is more graded. Inflammation may occur for many reasons, including tissue damage, autoimmune response, and pathogen invasion. The third class of pain is neuropathic and is presumed to involve nerve damage that results in reorganization of neuronal proteins and circuits to yield a pathologic "sensitized" state that can produce chronic pain lasting for years. This type of pain is particularly difficult to treat with existing therapies.

Pain, particularly neuropathic and intractable pain, is a large unmet medical need. Millions of individuals suffer from severe pain that is not well controlled by current therapeutics. The current drugs used to treat pain include NSAIDS, COX2 inhibitors, opioids, tricyclic antidepressants, and anticonvulsants. Neuropathic pain has been particularly difficult to treat as it does not respond well to opioids until high doses are reached. Gabapentin is currently the favored therapeutic for the treatment of neuropathic pain, although it works in only 60% of patients, where it shows modest efficacy.

Adaptor associated kinase 1 (AAK1) is a member of the Ark1/Prk1 family of serine/threonine kinases. AAK1 mRNA exists in two splice forms termed short and long. The long form predominates and is highly expressed in brain and heart (Henderson and Conner, Mol. Biol. Cell. 2007, 18, 2698-2706). AAK1 is enriched in synaptosomal preparations and is co-localized with endocytic structures in cultured cells. AAK1 modulates clatherin coated endocytosis, a process that is important in synaptic vesicle recycling and receptor-mediated endocytosis. AAK1 associates with the AP2 complex, a hetero-tetramer which links receptor cargo to the clatherin coat. The binding of clatherin to AAK1 stimulates AAK1 kinase activity (Conner et. al., Traffic 2003, 4, 885-890; Jackson et. al., J. Cell. Biol. 2003, 163, 231-236). AAK1 phosphorylates the mu-2 subunit of AP-2, which promotes the binding of mu-2 to tyrosine containing sorting motifs on cargo receptors (Ricotta et. al., J. Cell Bio. 2002, 156, 791-795; Conner and Schmid, J. Cell Bio. 2002, 156, 921-929). Mu2 phosphorylation is

not required for receptor uptake, but phosphorylation enhances the efficiency of internalization (Motely et. al., Mol. Biol. Cell. 2006, 17, 5298-5308).

AAK1 has been identified as an inhibitor of Neuregulin-1/ErbB4 signaling in PC12 cells. Loss of AAK1 expression through RNA interference mediated gene silencing or treatment with the kinase inhibitor K252a (which inhibits AAK1 kinase activity) results in the potentiation of Neuregulin-1 induced neurite outgrowth. These treatments result in increased expression of ErbB4 and accumulation of ErbB4 in or near the plasma membrane (Kuai et. al., Chemistry and Biology 2011, 18, 891-906). NRG1 and ErbB4 are putative schizophrenia susceptibility genes (Buonanno, Brain Res. Bull. 2010, 83, 122-131). SNPs in both genes have been associated with multiple schizophrenia endophenotypes (Greenwood et. al., Am. J. Psychiatry 2011, 168, 930-946). Neuregulin 1 and ErbB4 KO mouse models have shown schizophrenia relevant morphological changes and behavioral phenotypes (Jaaro-Peled et. al., Schizophrenia Bulletin 2010, 36, 301-313; Wen et. al., Proc. Natl. Acad. Sci. USA. 2010, 107, 1211-1216). In addition, a single nucleotide polymorphism in an intron of the AAK1 gene has been associated with the age of onset of Parkinson's disease (Latourelle et. al., BMC Med. Genet. 2009, 10, 98).

3. SUMMARY OF THE INVENTION

This invention is based upon Applicants' seminal discovery that inhibition of AAK1 can mitigate pain, and upon the subsequent discovery of multiple classes of AAK1 inhibitors.

The invention itself encompasses a method of treating or managing pain, which comprises inhibiting AAK1 activity in a patient in need thereof. A particular pain is neuropathic pain, such as fibromyalgia or peripheral neuropathy (e.g., diabetic neuropathy).

4. BRIEF DESCRIPTION OF THE FIGURES

Aspects of the invention are illustrated in Figure 1, which shows results obtained from a formalin pain model using AAK1 homozygous (-/-) knockout mice and their wild-type (+/+) littermates. The AAK1 homozygous (-/-) knockout mice show a clear reduction in both acute and tonic pain response as compared to their wild-type (+/+) littermates.

5. DETAILED DESCRIPTION OF THE INVENTION

This invention is based on Applicants' discovery that AAK1 knockout mice exhibit a high resistance to pain. That discovery prompted research that ultimately led to the discovery of a wide range of AAK1 inhibitors that may be used in the treatment and management of pain. In short, this invention provides an entirely new mechanism by which pain may be treated or managed, as well as compounds useful therein.

5.1. DEFINITIONS

Unless otherwise indicated, the phrases "compounds of the invention," "compounds of the present disclosure," and the like refer to the compounds disclosed herein.

Unless otherwise indicated, the term "hydrocarbyl" means an aliphatic or alicyclic moiety having an all-carbon backbone and consisting of carbon and hydrogen atoms. Examples of hydrocarbyl groups include those having 1-20, 1-12, 1-6, and 1-4 carbon atoms (referred to as C_{1-20} hydrocarbyl, C_{1-12} hydrocarbyl, C_{1-6} hydrocarbyl, and C_{1-4} hydrocarbyl, respectively). Particular examples include alkyl, alkenyl, alkynyl, aryl, benzyl, cycloalkyl, cycloalkenyl, cycloalkylalkyl, cycloalkenylalkyl, napthyl, phenyl, and phenylethyl.

Examples of alkyl moeites include straight-chain and branched moieties having 1-20, 1-12, 1-6, 1-4 and 1-3 carbon atoms (referred to as C_{1-20} alkyl, C_{1-12} alkyl, C_{1-6} alkyl, C_{1-4} alkyl and C_{1-3} alkyl, respectively). Particular examples include methyl, ethyl, propyl, isopropyl, n-butyl, t-butyl, isobutyl, pentyl, hexyl, isohexyl, heptyl, 4,4-dimethylpentyl, octyl, 2,2,4-trimethylpentyl, nonyl, decyl, undecyl and dodecyl.

Examples of alkenyl moieties include straight-chain and branched C_{2-20}, C_{2-12} and C_{2-6} alkenyl. Particular examples include vinyl, allyl, 1-butenyl, 2-butenyl, isobutylenyl, 1-pentenyl, 2-pentenyl, 3-methyl-1-butenyl, 2-methyl-2-butenyl, 2,3-dimethyl-2-butenyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 1-heptenyl, 2-heptenyl, 3-heptenyl, 1-octenyl, 2-octenyl, 3-octenyl, 1-nonenyl, 2-nonenyl, 3-nonenyl, 1-decenyl, 2-decenyl and 3-decenyl.

Examples of alkynyl moeites include include straight-chain and branched C_{2-20}, C_{2-12} and C_{2-6} alkynyl. Particular examples include ethynyl and 2-propynyl (propargyl).

Examples of aryl moeites include anthracenyl, azulenyl, fluorenyl, indan, indenyl, naphthyl, phenyl and phenanthrenyl.

Examples of cycloalkyl moeites include C_{3-12}, C_{3-7}, C_{4-6} and C_6 cycloalkyl. Particular examples include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and adamantyl.

Unless otherwise indicated, the term "halo" encompass fluoro, chloro, bromo, and iodo.

Unless otherwise indicated, the term "heterocarbyl" refers to a moiety having a backbone made up of one or more carbon atoms and one or more heteroatoms. Particular heteroatoms are nitrogen, oxygen and sulfur. A heterocarbyl moieties can be thought of as a hydrocarbyl moiety wherein at least one carbon atom, CH, CH_2, or CH_3 group is replaced with one or more heteroatoms and the requisite number of hydrogen atoms to satisy valencies. Examples of heterocarbyl include 2-20, 2-12, 2-8, 2-6 and 2-4 membered heterocarbyl moieties, wherein the number range refers to the sum total of carbon, nitrogen, oxygen, and/or sulfur atoms in the moiety. The term "2-12 membered heterocarbyl" thus refers to a heterocarbyl moiety having a total of 2-12 carbon, nitrogen, oxygen, and/or sulfur atoms. Particular heterocarbyl moeites include straight chain and branched heteroalkyl, heteroalkenyl, and heteroalkynyl, as well as heterocycle and heteroaryl.

Examples of heteroalkyl moieties include 2-8-membered, 2-6-membered and 2-4-membered heteroalkyl moieties. Particular examples include alkoxyl, acyl (*e.g.*, formyl, acetyl, benzoyl), alkylamino (*e.g.*, di-(C_{1-3}-alkyl)amino), arylamino, aryloxime, carbamates, carbamides, alkylcarbonyl, arylcarbonyl, aminocarbonyl, alkylaminocarbonyl, alkylsulfanyl, arylsulfanyl, alkylsulfinyl, arylsulfinyl, alkylsulfonyl, arylsulfonyl, alkylsulfonylamino, and arylsulfonylamino.

Unless otherwise indicated, the term "heterocycle" refers to a cyclic (monocyclic or polycyclic) heterocarbyl moiety which may be aromatic, partially aromatic or non-aromatic. Heterocycles include heteroaryls. Examples include 4-10-membered, 4-7-membered, 6-membered, and 5-membered heterocycles. Particular examples include benzo[1,3]dioxolyl, 2,3-dihydro-benzo[1,4]dioxinyl, cinnolinyl, furanyl, hydantoinyl, morpholinyl, oxetanyl, oxiranyl, piperazinyl, piperidinyl, pyrrolidinonyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydropyridinyl, tetrahydropyrimidinyl, tetrahydrothiophenyl, tetrahydrothiopyranyl and valerolactamyl. Because the term "heterocycle" refers to a ring, standing alone it does not encompass moieities such as oxazolidinone and imidazolidinone: such moieties are considered substituted heterocycles, *viz.* heterocycles substituted with oxo.

Examples of heteroaryl moieties include acridinyl, benzimidazolyl, benzofuranyl, benzoisothiazolyl, benzoisoxazolyl, benzoquinazolinyl, benzothiazolyl, benzoxazolyl, furyl, imidazolyl, indolyl, isothiazolyl, isoxazolyl, oxadiazolyl, oxazolyl, phthalazinyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridyl, pyrimidinyl, pyrimidyl, pyrrolyl, quinazolinyl, quinolinyl, tetrazolyl, thiazolyl, and triazinyl.

Unless otherwise indicated, the term "include" has the same meaning as "include, but are not limited to," and the term "includes" has the same meaning as "includes, but is not limited to." Similarly, the term "such as" has the same meaning as the term "such as, but not limited to."

Unless otherwise indicated, the terms "manage," "managing" and "management" encompass preventing the recurrence of the specified disease or disorder in a patient who has already suffered from the disease or disorder, and/or lengthening the time that a patient who has suffered from the disease or disorder remains in remission. The terms encompass modulating the threshold, development and/or duration of the disease or disorder, or changing the way that a patient responds to the disease or disorder.

Unless otherwise indicated, a "therapeutically effective amount" of a compound is an amount sufficient to provide a therapeutic benefit in the treatment or management of a disease or condition, or to delay or minimize one or more symptoms associated with the disease or condition. A "therapeutically effective amount" of a compound means an amount of therapeutic agent, alone or in combination with other therapies, that provides a therapeutic benefit in the treatment or management of the disease or condition. The term "therapeutically effective amount" can encompass an amount that improves overall therapy, reduces or avoids symptoms or causes of a disease or condition, or enhances the therapeutic efficacy of another therapeutic agent.

Unless otherwise indicated, the terms "treat," "treating" and "treatment" contemplate an action that occurs while a patient is suffering from the specified disease or disorder, which reduces the severity of the disease or disorder, or retards or slows the progression of the disease or disorder.

Unless otherwise indicated, one or more adjectives immediately preceding a series of nouns is to be construed as applying to each of the nouns. For example, the phrase "optionally substituted alky, aryl, or heteroaryl" has the same meaning as "optionally substituted alky, optionally substituted aryl, or optionally substituted heteroaryl."

5.2. COMPOUNDS

Compounds that may be used to inhibit AAK1 are disclosed in U.S. provisional patent application nos. 61/608,758 , 61/608,765, and 61/608,737, all filed March 9, 2012, as well as in U.S. patent application nos. 13/777,144, filed February 26, 2013, 13/785,271, filed March 5, 2013, and 13/785,355, also filed March 5, 2013.

Compounds of the invention can have one or more asymmetric centers. Unless otherwise indicated, this invention encompasses all stereoisomers of the compounds, as well as mixtures thereof. Individual stereoisomers of compounds can be prepared synthetically from commercially available starting materials which contain chiral centers or by preparation of mixtures of enantiomeric products followed by separation such as conversion to a mixture of diastereomers followed by separation or recrystallization, chromatographic techniques, or direct separation of enantiomers on chiral chromatographic columns. Starting compounds of particular stereochemistry are either commercially available or can be made and resolved by techniques known in the art.

Certain compounds of the present disclosure may also exist in different stable conformational forms which may be separable. Torsional asymmetry due to restricted rotation about an asymmetric single bond, for example because of steric hindrance or ring strain, may permit separation of different conformers. The present disclosure includes each conformational isomer of these compounds and mixtures thereof.

The present disclosure is intended to include all isotopes of atoms occurring in the present compounds. Isotopes include those atoms having the same atomic number but different mass numbers. By way of general example and without limitation, isotopes of hydrogen include deuterium and tritium. Isotopes of carbon include ^{13}C and ^{14}C. Isotopically-labeled compounds of the invention can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described herein, using an appropriate isotopically-labeled reagent in place of the non-labeled reagent otherwise employed. Such compounds may have a variety of potential uses, for example as standards and reagents in determining biological activity. In the case of stable isotopes, such compounds may have the potential to favorably modify biological, pharmacological, or pharmacokinetic properties.

The compounds of the present disclosure can exist as pharmaceutically acceptable salts. The term "pharmaceutically acceptable salt," as used herein, represents salts or zwitterionic forms of the compounds of the present disclosure which are water or oil-soluble or dispersible, which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of patients without excessive toxicity, irritation, allergic response, or other problem or complication commensurate with a reasonable benefit/risk ratio, and are effective for their intended use. The salts can be prepared during the final isolation and purification of the compounds or separately by reacting a suitable nitrogen atom with a suitable acid. Representative acid addition salts include acetate, adipate, alginate, citrate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate; digluconate, dihydrobromide, diydrochloride, dihydroiodide, glycerophosphate, hemisulfate, heptanoate, hexanoate, formate, fumarate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, mesitylenesulfonate, methanesulfonate, naphthylenesulfonate, nicotinate, 2-naphthalenesulfonate, oxalate, palmoate, pectinate, persulfate, 3-phenylproprionate, picrate, pivalate, propionate, succinate, tartrate, trichloroacetate, trifluoroacetate, phosphate, glutamate, bicarbonate, para-toluenesulfonate, and undecanoate. Examples of acids which can be employed to form pharmaceutically acceptable addition salts include inorganic acids such as hydrochloric, hydrobromic, sulfuric, and phosphoric, and organic acids such as oxalic, maleic, succinic, and citric.

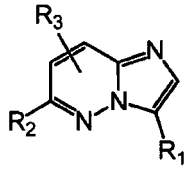
Basic addition salts can be prepared during the final isolation and purification of the compounds by reacting a carboxy group with a suitable base such as the hydroxide, carbonate, or bicarbonate of a metal cation or with ammonia or an organic primary, secondary, or tertiary amine. The cations of pharmaceutically acceptable salts include lithium, sodium, potassium, calcium, magnesium, and aluminum, as well as nontoxic quaternary amine cations such as ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, diethylamine, ethylamine, tributylamine, pyridine, N,N-dimethylaniline, N-methylpiperidine, N-methylmorpholine, dicyclohexylamine, procaine, dibenzylamine, N,N-dibenzylphenethylamine, and N,N'-dibenzylethylenediamine. Other representative organic amines useful for the formation of base addition salts include ethylenediamine, ethanolamine, diethanolamine, piperidine, and piperazine.

Particular compounds inhibit AAK1 with an IC_{50} of less than 0.1, 0.01 or 0.001 μM as measured in the P81 filter plate assay described below in the Examples. Particular compounds inhibit AAK1 with an IC_{50} of less than 0.1, 0.01 or 0.001 μM as measured in the HEK281 cell-based assay described described below in the Examples.

5.2.1. Imidazo[1,2-b]pyridazine-based Inhibitors

One class of compounds that may be used in embodiments of the invention is disclosed in U.S. patent application no. 13/785,271, filed March 5, 2013, entitled "Imidazo[1,2-b]pyridazine-

based Compounds, Compositions Comprising Them, and Methods of Their Use." That application encompasses compounds of the formula:



and pharmaceutically acceptable salts thereof, wherein: R_1 is R_{1A} or optionally substituted C_{1-12} hydrocarbyl or 2-12-membered heterocarbyl, which optional substitution is with one or more R_{1A}; each R_{1A} is independently $-OR_{1C}$, $-N(R_{1C})_2$, $-C(O)R_{1C}$, $-C(O)OR_{1C}$, $-C(O)N(R_{1C})_2$, $-N(R_{1C})C(O)OR_{1C}$, cyano, halo, or optionally substituted C_{1-12} hydrocarbyl or 2-12-membered heterocarbyl, which optional substitution is with one or more R_{1B}; each R_{1B} is independently $-OR_{1C}$, $-N(R_{1C})_2$, $-C(O)R_{1C}$, $-C(O)OR_{1C}$, $-C(O)N(R_{1C})_2$, $-N(R_{1C})C(O)OR_{1C}$, cyano or halo; each R_{1C} is independently hydrogen or optionally substituted C_{1-12} hydrocarbyl or 2-12-membered heterocarbyl, which optional substitution is with one or more of cyano, halo or hydroxyl; R_2 is $-NR_{2A}R_{2B}$, wherein R_{2A} is hydrogen and R_{2B} is optionally substituted C_{1-12} hydrocarbyl or 2-12-membered heterocarbyl, which optional substitution is with one or more R_{2C}; or R_{2A} and R_{2B} are taken together to form a 4-7-membered heterocycle optionally substituted with one or more R_{2C}; each R_{2C} is independently $-OR_{2D}$, $-N(R_{2D})_2$, $-C(O)R_{2D}$, $-C(O)OR_{2D}$, $-C(O)N(R_{2D})_2$, $-N(R_{2D})C(O)OR_{2D}$, cyano, halo, or optionally substituted C_{1-12} hydrocarbyl or 2-12-membered heterocarbyl, which optional substitution is with one or more with one or more R_{2D}; each R_{2D} is independently hydrogen or optionally substituted C_{1-12} hydrocarbyl or 2-12-membered heterocarbyl, which optional substitution is with one or more of cyano, halo or hydroxyl; and R_3 is hydrogen or C_{1-6} alkyl optionally substituted with one or more of cyano, halo or hydroxyl.

In particular compounds, R_1 is R_{1A}. In particular compounds, R_1 is optionally substituted C_{1-12} hydrocarbyl. In particular compounds, R_1 is optionally substituted phenyl. In particular compounds, R_1 is optionally substituted 2-12-membered heterocarbyl (*e.g.*, 2-8 membered heterocarbyl, 2-6 membered heterocarbyl, 2-6 membered heterocarbyl). In particular compounds, R_1 is optionally substituted pyridinyl, thiophen, or imidazol.

In particular compounds, R_{1A} is halo. In some, R_{1A} is $-OR_{1C}$, $-N(R_{1C})_2$, $-C(O)R_{1C}$, $-C(O)OR_{1C}$, or $-C(O)N(R_{1C})_2$. In some, R_{1A} is $-OR_{1C}$. In some, R_{1B} is $-N(R_{1C})_2$, $-OR_{1C}$, halo.

In particular compounds, R_{2A} and R_{2B} are taken together to form a 4-7-membered heterocycle optionally substituted with one or more R_{2C}.

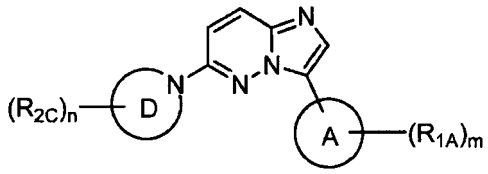
In particular compounds, R_{1C} is hydrogen. In some, R_{1C} is C_{1-12} hydrocarbyl (*e.g.*, C_{1-6} hydrocarbyl, C_{1-4} hydrocarbyl such as methyl, ethyl, propyl).

In particular compounds, R_{2C} is $-C(O)OR_{2D}$, $-C(O)N(R_{2D})_2$, or $-N(R_{2D})C(O)OR_{2D}$.

In particular compounds, R_{2D} is hydrogen. In some, R_{2D} is C_{1-12} hydrocarbyl (*e.g.*, C_{1-6} hydrocarbyl, C_{1-4} hydrocarbyl such as methyl, ethyl, propyl).

In particular compounds, R_3 is hydrogen.

One embodiement of the invention encompasses compounds of the formula:



and pharmaceutically acceptable salt thereof, wherein: A is cyclic C_{1-12} hydrocarbyl or 4-7-membered heterocycle; D is 4-7-membered heterocycle; each R_{1A} is independently $-OR_{1C}$, $-N(R_{1C})_2$, $-C(O)R_{1C}$, $-C(O)OR_{1C}$, $-C(O)N(R_{1C})_2$, $-N(R_{1C})C(O)OR_{1C}$, cyano, halo, or optionally substituted C_{1-12} hydrocarbyl or 2-12-membered heterocarbyl, which optional substitution is with one or more R_{1B}; each R_{1B} is independently $-OR_{1C}$, $-N(R_{1C})_2$, $-C(O)R_{1C}$, $-C(O)OR_{1C}$, $-C(O)N(R_{1C})_2$, $-N(R_{1C})C(O)OR_{1C}$, cyano or halo; each R_{1C} is independently hydrogen or optionally substituted C_{1-12} hydrocarbyl or 2-12-membered heterocarbyl, which optional substitution is with one or more of cyano, halo or hydroxyl; each R_{2C} is independently $-OR_{2D}$, $-N(R_{2D})_2$, $-C(O)R_{2D}$, $-C(O)OR_{2D}$, $-C(O)N(R_{2D})_2$, $-N(R_{2D})C(O)OR_{2D}$, cyano, halo, or optionally substituted C_{1-12} hydrocarbyl or 2-12-membered heterocarbyl, which optional substitution is with one or more with one or more R_{2D}; each R_{2D} is independently hydrogen or optionally substituted C_{1-12} hydrocarbyl or 2-12-membered heterocarbyl, which optional substitution is with one or more of cyano, halo or hydroxyl; n is 1-3; and m is 0-3.

In particular compounds, R_{2C} is not hydroxyl or optionally substituted phenyl or pyridinyl.

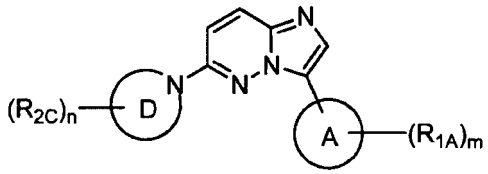
In particular compounds, when D is diazapine and A is pyridinyl, R_{2C} is not -C(O)O-tert-butyl.

In particular compounds, when D is piperazin, A is phenyl and R_{1A} is chloro, R_{2C} is not -C(O)O-tert-butyl.

In particular compounds, when D is piperidinyl, A is pyridinyl and R_{1A} is chloro, R_{2C} is not –NHC(O)O-tert-butyl.

In particular compounds, when D is piperidinyl, A is pyridinyl and R_{1A} is $-NHCH_2CH_2CH(CH_3)_2$, R_{2C} is not NH_2.

One embodiment of the invention encompasses compounds of the formula:



and pharmaceutically acceptable salt thereof, wherein: A is cyclic C_{1-12} hydrocarbyl or 4-7-membered heterocycle; D is 4-7-membered heterocycle; each R_{1A} is independently $-OR_{1C}$, $-N(R_{1C})_2$, $-C(O)R_{1C}$, $-C(O)OR_{1C}$, $-C(O)N(R_{1C})_2$, $-N(R_{1C})C(O)OR_{1C}$, cyano, halo, or optionally substituted C_{1-12} hydrocarbyl or 2-12-membered heterocarbyl, which optional substitution is with one or more R_{1B}; each R_{1B} is independently $-OR_{1C}$, $-N(R_{1C})_2$, $-C(O)R_{1C}$, $-C(O)OR_{1C}$, $-C(O)N(R_{1C})_2$, $-N(R_{1C})C(O)OR_{1C}$, cyano or halo; each R_{1C} is independently hydrogen or optionally substituted C_{1-12} hydrocarbyl or 2-12-membered heterocarbyl, which optional substitution is with one or more of cyano, halo or hydroxyl; each R_{2C} is

independently $-OR_{2D}$, $-N(R_{2D})_2$, $-C(O)R_{2D}$, $-C(O)OR_{2D}$, $-C(O)N(R_{2D})_2$, $-N(R_{2D})C(O)OR_{2D}$, cyano, halo, or optionally substituted C_{1-12} hydrocarbyl or 2-12-membered heterocarbyl, which optional substitution is with one or more with one or more R_{2D}; each R_{2D} is independently hydrogen or optionally substituted C_{1-12} hydrocarbyl or 2-12-membered heterocarbyl, which optional substitution is with one or more of cyano, halo or hydroxyl; n is 1-3; and m is 0-3.

In particular compounds encompassed by this embodiment: 1) R_{2C} is not hydroxyl or optionally substituted phenyl or pyridinyl; 2) when D is diazapine and A is pyridinyl, R_{2C} is not –C(O)O-tert-butyl; 3) when D is piperazin, A is phenyl and R_{1A} is chloro, R_{2C} is not -C(O)O-tert-butyl; 4) when D is piperidinyl, A is pyridinyl and R_{1A} is chloro, R_{2C} is not -NHC(O)O-tert-butyl; and 5) when D is piperidinyl, A is pyridinyl and R_{1A} is $-NHCH_2CH_2CH(CH_3)_2$, R_{2C} is not NH_2.

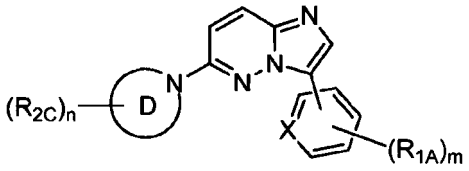
In particular compounds, D is piperazin or pyrrolidin.

In particular compounds, n is 1.

In particular compounds, m is 1.

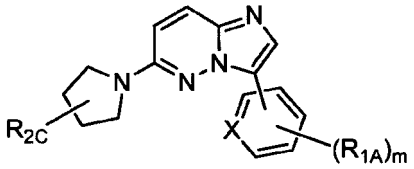
In particular compounds, A is pyridinyl, thiophen, or imidazol.

Particular compounds of the invention are of the formula:



wherein X is CH or N.

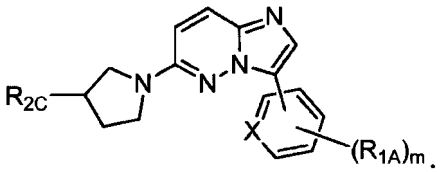
One embodiment of the invention encompasses compounds of the formula:



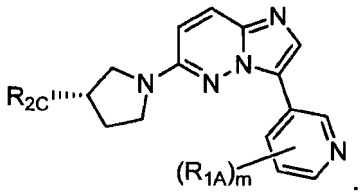
and pharmaceutically acceptable salt thereof, wherein: X is CH or N; each R_{1A} is independently $-OR_{1C}$, $-N(R_{1C})_2$, $-C(O)R_{1C}$, $-C(O)OR_{1C}$, $-C(O)N(R_{1C})_2$, $-N(R_{1C})C(O)OR_{1C}$, cyano, halo, or optionally substituted C_{1-12} hydrocarbyl or 2-12-membered heterocarbyl, which optional substitution is with one or more R_{1B}; each R_{1B} is independently $-OR_{1C}$, $-N(R_{1C})_2$, $-C(O)R_{1C}$, $-C(O)OR_{1C}$, $-C(O)N(R_{1C})_2$, $-N(R_{1C})C(O)OR_{1C}$, cyano or halo; each R_{1C} is independently hydrogen or optionally substituted C_{1-12} hydrocarbyl or 2-12-membered heterocarbyl, which optional substitution is with one or more of cyano, halo or hydroxyl; each R_{2C} is independently $-OR_{2D}$, $-N(R_{2D})_2$, $-C(O)R_{2D}$, $-C(O)OR_{2D}$, $-C(O)N(R_{2D})_2$, $-N(R_{2D})C(O)OR_{2D}$, cyano, halo, or optionally substituted C_{1-12} hydrocarbyl or 2-12-membered heterocarbyl, which optional substitution is with one or more with one or more R_{2D}; each R_{2D} is independently hydrogen or optionally substituted C_{1-12} hydrocarbyl or 2-12-membered heterocarbyl, which optional substitution is with one or more of cyano, halo or hydroxyl; and m is 0-3.

In some compounds of this embodiment, R_{2C} is not optionally substituted phenyl or pyridinyl.

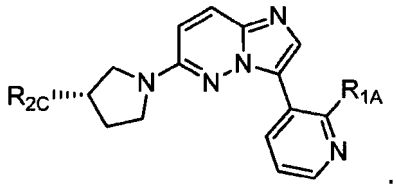
Particular compounds of the invention are of the formula:



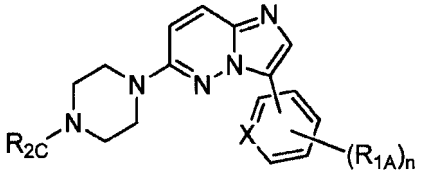
Particular compounds of the invention are of the formula:



Particular compounds of the invention are of the formula:



One embodiment of the invention encompasses compounds of the formula:

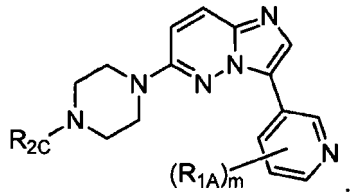


and pharmaceutically acceptable salts thereof, wherein: X is CH or N; each R_{1A} is independently $-OR_{1C}$, $-N(R_{1C})_2$, $-C(O)R_{1C}$, $-C(O)OR_{1C}$, $-C(O)N(R_{1C})_2$, $-N(R_{1C})C(O)OR_{1C}$, cyano, halo, or optionally substituted C_{1-12} hydrocarbyl or 2-12-membered heterocarbyl, which optional substitution is with one or more R_{1B}; each R_{1B} is independently $-OR_{1C}$, $-N(R_{1C})_2$, $-C(O)R_{1C}$, $-C(O)OR_{1C}$, $-C(O)N(R_{1C})_2$, $-N(R_{1C})C(O)OR_{1C}$, cyano or halo; each R_{1C} is independently hydrogen or optionally substituted C_{1-12} hydrocarbyl or 2-12-membered heterocarbyl, which optional substitution is with one or more of cyano, halo or hydroxyl; each R_{2C} is independently $-OR_{2D}$, $-N(R_{2D})_2$, $-C(O)R_{2D}$, $-C(O)OR_{2D}$, $-C(O)N(R_{2D})_2$, $-N(R_{2D})C(O)OR_{2D}$, cyano, halo, or optionally substituted C_{1-12} hydrocarbyl or 2-12-membered heterocarbyl, which optional substitution is with one or more with one or more R_{2D}; each R_{2D} is independently hydrogen or optionally substituted C_{1-12} hydrocarbyl or 2-12-membered heterocarbyl, which optional substitution is with one or more of cyano, halo or hydroxyl; and m is 0-3.

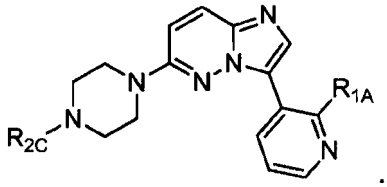
In some compounds of this embodiment, when X is CH, m is 1 and R_{1A} is chloro, R_{2C} is not t-butyl.

In some compounds of this embodiment, R_{2C} is not optionally substituted phenyl or pyridinyl.

Particular compounds of the invention are of the formula:



Particular compounds of the invention are of the formula:



In particular compounds, R_{1A} is $-OR_{1C}$.

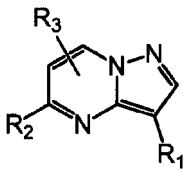
In particular compounds, R_{1C} is optionally substituted C_{1-12} hydrocarbyl (*e.g.*, C_{1-6} hydrocarbyl, C_{1-4} hydrocarbyl).

In particular compounds, R_{2C} is $-C(O)OR_{2D}$, $-C(O)N(R_{2D})_2$, or $-N(R_{2D})C(O)OR_{2D}$.

In particular compounds, each R_{2D} is independently hydrogen or C_{1-12} hydrocarbyl (*e.g.*, C_{1-6} hydrocarbyl, C_{1-4} hydrocarbyl).

5.2.2. Pyrazolo[1,5-a]pyrimidine-based Inhibitors

Another class of compounds that may be used in embodiments of the invention is disclosed in U.S. patent application no. 13/785,355, filed March 5, 2013, entitled "Pyrazolo[1,5-a]pyrimidine-based Compounds, Compositions Comprising Them, and Methods of Their Use." That application encompasses compounds of the formula:



and pharmaceutically acceptable salts thereof, wherein: R_1 is R_{1A} or optionally substituted C_{1-12} hydrocarbyl or 2-12-membered heterocarbyl, which optional substitution is with one or more R_{1A}; each R_{1A} is independently $-OR_{1C}$, $-N(R_{1C})_2$, $-C(O)R_{1C}$, $-C(O)OR_{1C}$, $-C(O)N(R_{1C})_2$, $-N(R_{1C})C(O)OR_{1C}$, cyano, halo, or optionally substituted C_{1-12} hydrocarbyl or 2-12-membered heterocarbyl, which optional substitution is with one or more R_{1B}; each R_{1B} is independently $-OR_{1C}$, $-N(R_{1C})_2$, $-C(O)R_{1C}$, $-C(O)OR_{1C}$, $-C(O)N(R_{1C})_2$, $-N(R_{1C})C(O)OR_{1C}$, cyano or halo; each R_{1C} is independently hydrogen or optionally substituted C_{1-12} hydrocarbyl or 2-12-membered heterocarbyl, which optional substitution is with one or more of cyano, halo or hydroxyl; R_2 is $-NR_{2A}R_{2B}$, wherein R_{2A} is hydrogen and R_{2B} is optionally substituted C_{1-12} hydrocarbyl or 2-12-membered heterocarbyl, which optional substitution is with one or more R_{2C}; or R_{2A} and R_{2B} are taken together to form a 4-7-membered heterocycle optionally substituted with one or more R_{2C}; each R_{2C} is independently $-OR_{2D}$, $-N(R_{2D})_2$, $-C(O)R_{2D}$, $-C(O)OR_{2D}$, -

$C(O)N(R_{2D})_2$, $-N(R_{2D})C(O)OR_{2D}$, cyano, halo, or optionally substituted C_{1-12} hydrocarbyl or 2-12-membered heterocarbyl, which optional substitution is with one or more with one or more R_{2D}; each R_{2D} is independently hydrogen or optionally substituted C_{1-12} hydrocarbyl or 2-12-membered heterocarbyl, which optional substitution is with one or more of cyano, halo or hydroxyl; and R_3 is hydrogen or C_{1-6} alkyl optionally substituted with one or more of cyano, halo or hydroxyl.

In particular compounds, R_1 is R_{1A}. In some, R_1 is optionally substituted C_{1-12} hydrocarbyl. In some, R_1 is optionally substituted phenyl. In some, R_1 is optionally substituted 2-12-membered heterocarbyl (*e.g.*, 2-8 membered heterocarbyl, 2-6 membered heterocarbyl, 2-6 membered heterocarbyl). In some, R_1 is optionally substituted pyridinyl, thiophen, or imidazol.

In particular compounds, R_{1A} is halo. In some, R_{1A} is $-OR_{1C}$, $-N(R_{1C})_2$, $-C(O)R_{1C}$, $-C(O)OR_{1C}$, or $-C(O)N(R_{1C})_2$. In some, R_{1A} is $-OR_{1C}$.

In particular compounds, R_{1B} is $-N(R_{1C})_2$, $-OR_{1C}$, halo.

In particular compounds, R_{2A} and R_{2B} are taken together to form a 4-7-membered heterocycle optionally substituted with one or more R_{2C}.

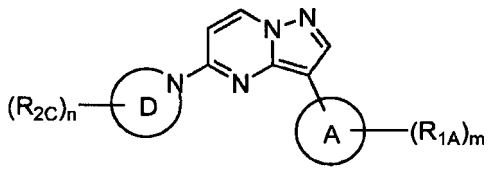
In particular compounds, R_{1C} is hydrogen. In some, R_{1C} is C_{1-12} hydrocarbyl (*e.g.*, C_{1-6} hydrocarbyl, C_{1-4} hydrocarbyl such as methyl, ethyl, propyl). In some, R_{2C} is $-C(O)OR_{2D}$, $-C(O)N(R_{2D})_2$, or $-N(R_{2D})C(O)OR_{2D}$.

In particular compounds, R_{2D} is hydrogen.

In particular compounds, R_{2D} is C_{1-12} hydrocarbyl (*e.g.*, C_{1-6} hydrocarbyl, C_{1-4} hydrocarbyl such as methyl, ethyl, propyl).

In particular compounds, R_3 is hydrogen.

One embodiment of the invention encompasses compounds of the formula:



and pharmaceutically acceptable salt thereof, wherein: A is cyclic C_{1-12} hydrocarbyl or 4-7-membered heterocycle; D is 4-7-membered heterocycle; each R_{1A} is independently $-OR_{1C}$, $-N(R_{1C})_2$, $-C(O)R_{1C}$, $-C(O)OR_{1C}$, $-C(O)N(R_{1C})_2$, $-N(R_{1C})C(O)OR_{1C}$, cyano, halo, or optionally substituted C_{1-12} hydrocarbyl or 2-12-membered heterocarbyl, which optional substitution is with one or more R_{1B}; each R_{1B} is independently $-OR_{1C}$, $-N(R_{1C})_2$, $-C(O)R_{1C}$, $-C(O)OR_{1C}$, $-C(O)N(R_{1C})_2$, $-N(R_{1C})C(O)OR_{1C}$, cyano or halo; each R_{1C} is independently hydrogen or optionally substituted C_{1-12} hydrocarbyl or 2-12-membered heterocarbyl, which optional substitution is with one or more of cyano, halo or hydroxyl; each R_{2C} is independently $-OR_{2D}$, $-N(R_{2D})_2$, $-C(O)R_{2D}$, $-C(O)OR_{2D}$, $-C(O)N(R_{2D})_2$, $-N(R_{2D})C(O)OR_{2D}$, cyano, halo, or optionally substituted C_{1-12} hydrocarbyl or 2-12-membered heterocarbyl, which optional substitution is with one or more with one or more R_{2D}; each R_{2D} is independently hydrogen or optionally

substituted C_{1-12} hydrocarbyl or 2-12-membered heterocarbyl, which optional substitution is with one or more of cyano, halo or hydroxyl; n is 1-3; and m is 0-3.

In particular compounds, D is not piperidinyl.

In particular compounds, R_{2C} is not $-N(R_{2D})_2$.

In particular compounds, A is not phenyl.

In particular compounds, m is 1.

In particular compounds, R_{2D} is not ethyl.

In particular compounds, when D is piperidinyl, A is phenyl, and R_{2C} is $-N(R_{2D})_2$, R_{2D} is not ethyl.

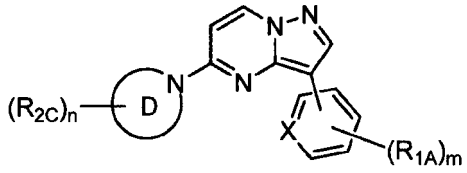
In particular compounds, D is piperazin or pyrrolidin.

In particular compounds, n is 1.

In particular compounds, m is 1.

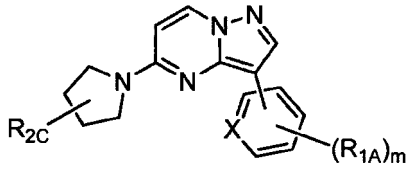
In particular compounds, A is pyridinyl, thiophen, or imidazol.

Particular compounds are of the formula:



wherein X is CH or N.

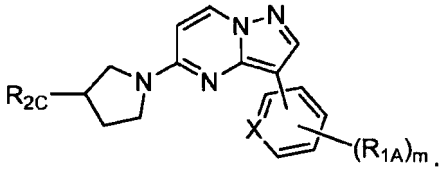
Another embodiment of the invention encompasses compounds of the formula:



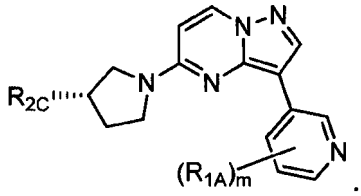
and pharmaceutically acceptable salt thereof, wherein: X is CH or N; each R_{1A} is independently $-OR_{1C}$, $-N(R_{1C})_2$, $-C(O)R_{1C}$, $-C(O)OR_{1C}$, $-C(O)N(R_{1C})_2$, $-N(R_{1C})C(O)OR_{1C}$, cyano, halo, or optionally substituted C_{1-12} hydrocarbyl or 2-12-membered heterocarbyl, which optional substitution is with one or more R_{1B}; each R_{1B} is independently $-OR_{1C}$, $-N(R_{1C})_2$, $-C(O)R_{1C}$, $-C(O)OR_{1C}$, $-C(O)N(R_{1C})_2$, $-N(R_{1C})C(O)OR_{1C}$, cyano or halo; each R_{1C} is independently hydrogen or optionally substituted C_{1-12} hydrocarbyl or 2-12-membered heterocarbyl, which optional substitution is with one or more of cyano, halo or hydroxyl; each R_{2C} is independently $-OR_{2D}$, $-N(R_{2D})_2$, $-C(O)R_{2D}$, $-C(O)OR_{2D}$, $-C(O)N(R_{2D})_2$, $-N(R_{2D})C(O)OR_{2D}$, cyano, halo, or optionally substituted C_{1-12} hydrocarbyl or 2-12-membered heterocarbyl, which optional substitution is with one or more with one or more R_{2D}; each R_{2D} is independently hydrogen or optionally substituted C_{1-12} hydrocarbyl or 2-12-membered heterocarbyl, which optional substitution is with one or more of cyano, halo or hydroxyl; and m is 0-3.

In particular compounds, R_{2C} is not optionally substituted phenyl or pyridinyl.

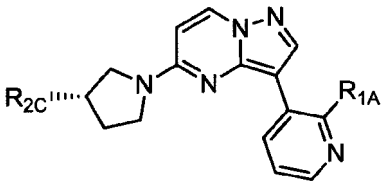
Particular compounds are of the formula:



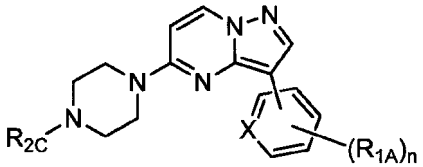
Particular compounds are of the formula:



Particular compounds are of the formula:

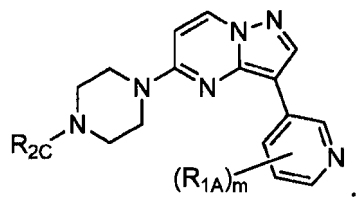


Another embodiment of the invention encompasses compounds of the formula:

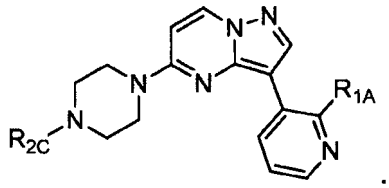


and pharmaceutically acceptable salt thereof, wherein: X is CH or N; each R_{1A} is independently -OR_{1C}, -$N(R_{1C})_2$, -$C(O)R_{1C}$, -$C(O)OR_{1C}$, -$C(O)N(R_{1C})_2$, -$N(R_{1C})C(O)OR_{1C}$, cyano, halo, or optionally substituted C_{1-12} hydrocarbyl or 2-12-membered heterocarbyl, which optional substitution is with one or more R_{1B}; each R_{1B} is independently -OR_{1C}, -$N(R_{1C})_2$, -$C(O)R_{1C}$, -$C(O)OR_{1C}$, -$C(O)N(R_{1C})_2$, -$N(R_{1C})C(O)OR_{1C}$, cyano or halo; each R_{1C} is independently hydrogen or optionally substituted C_{1-12} hydrocarbyl or 2-12-membered heterocarbyl, which optional substitution is with one or more of cyano, halo or hydroxyl; each R_{2C} is independently -OR_{2D}, -$N(R_{2D})_2$, -$C(O)R_{2D}$, -$C(O)OR_{2D}$, -$C(O)N(R_{2D})_2$, -$N(R_{2D})C(O)OR_{2D}$, cyano, halo, or optionally substituted C_{1-12} hydrocarbyl or 2-12-membered heterocarbyl, which optional substitution is with one or more with one or more R_{2D}; each R_{2D} is independently hydrogen or optionally substituted C_{1-12} hydrocarbyl or 2-12-membered heterocarbyl, which optional substitution is with one or more of cyano, halo or hydroxyl; and m is 0-3.

Particular compounds are of the formula:



Particular compounds are of the formula:



In particular compounds, R_{1A} is $-OR_{1C}$,

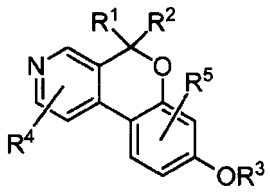
In particular compounds, R_{1C} is optionally substituted C_{1-12} hydrocarbyl (*e.g.*, C_{1-6} hydrocarbyl, C_{1-4} hydrocarbyl).

In particular compounds, R_{2C} is $-C(O)OR_{2D}$, $-C(O)N(R_{2D})_2$, or $-N(R_{2D})C(O)OR_{2D}$.

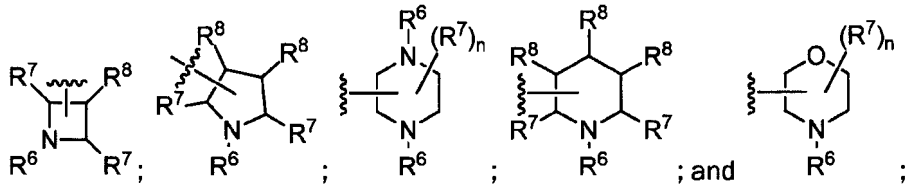
In particular compounds, R_{2D} is independently hydrogen or C_{1-12} hydrocarbyl (*e.g.*, C_{1-6} hydrocarbyl, C_{1-4} hydrocarbyl).

5.2.3. **Aryl ether-based Inhibitors**

Another class of compounds that may be used in embodiments of the invention is disclosed in U.S. patent application no. 13/777,144, filed February 26, 2013, entitled "Aryl Ether-Base Kinase Inhibitors." That application encompasses compounds of the formula:



and pharmaceutically acceptable salts thereof, wherein: R^1 and R^2 are independently selected from hydrogen, C_3-C_6cycloalkyl, and C_1-C_3alkyl wherein the C_1-C_3alkyl is optionally substituted with one, two, or three groups independently selected from C_1-C_3alkoxy, C_1-C_3alkylamino, amino, cyano, C_1-C_3dialkylamino, halo, and hydroxy; or R^1 and R^2 together are oxo; R^3 is C_1-C_3alkyl-Y or C_2-C_8alkyl, wherein the C_2-C_8alkyl is optionally substituted with one, two, or three groups independently selected from C_1-C_3alkoxy, C_1-C_3alkylamino, C_1-C_3alkoxyC_2-C_3alkylamino, amino, aryl, halo, C_1-C_3haloalkylamino, C_1-C_3haloalkylcarbonylamino, hydroxy, $-NR^xR^y$, and C_3-C_8cycloalkyl, wherein the cycloalkyl is further optionally substituted with one, two, or three groups independently selected from C_1-C_3alkoxy, C_1-C_3alkyl, C_1-C_3alkylamino, C_1-C_3alkoxyC_2-C_3alkylamino, amino, aryl, arylC_1-C_3alkyl, halo, C_1-C_3haloalkyl, C_1-C_3haloalkylamino and hydroxy; R^4 is selected from hydrogen, C_1-C_3alkoxy, C_1-C_3alkoxycarbonylamino, C_1-C_3alkyl, C_1-C_3alkylamino, C_1-C_3alkylcarbonylamino, amino, arylamino, arylcarbonylamino, C_3-C_6cycloalkylamino, C_3-C_6cycloalkylcarbonylamino, C_3-C_6cycloalkyloxy, halo, C_1-C_3haloalkoxy, C_2-C_3haloalkylamino, C_2-C_3haloalkylcarbonylamino, and hydroxy; R^5 is selected from hydrogen, C_1-C_3alkyl, cyano, C_3cycloalkyl, and halo; R^x and R^y, together with the nitrogen atom to which they are attached, form a three- to six-membered ring; and Y is selected from



wherein R^6 is selected from hydrogen, C_1-C_6alkyl, C_3-C_6cycloalkyl, and C_1-C_6alkylcarbonyl; n is 0, 1, 2, or 3; each R^7 is independently selected from hydrogen, C_1-C_6alkyl, aryl, arylC_1-C_3alkyl, C_3-C_6cycloalkyl, halo, and C_1-C_3haloalkyl; and each R^8 is independently selected from hydrogen, C_1-C_3alkoxy and hydroxy.

In particular compunds, R^1 and R^2 are each hydrogen. In some, one of R^1 and R^2 is hydrogen and the other is C_1-C_3alkyl. In some, one of R^1 and R^2 is hydrogen and the other is C_3-C_6cycloalkyl. In some, R^1 and R^2 together are oxo.

In particular compunds, R^3 is C_2-C_8alkyl, optionally substituted with an amino group. In some, R^3 is C_2-C_8alkyl, optionally substituted with an amino group and an aryl group, wherein the aryl is phenyl.

In particular compunds, R^4 is hydrogen. In some, R^4 is amino. In some, R^4 is C_1-C_3alkylcarbonylamino.

In particular compounds, R^5 is hydrogen. In some, R^5 is halo.

5.3. METHODS OF USE

This invention is based on the seminal discovery that inhibition of adaptor associated kinase 1 (AAK1)—both as a result of genetic mutation and by the administration of an AAK1 inhibitor—can alleviate pain.

Thus, one embodiment of the invention encompasses a method of treating or managing pain, which comprises inhibiting AAK1 in patient in need thereof. Particular types of pain include chronic pain, acute pain, and neuropathic pain. Particular types of neuropathic pain include fibromyalgia and peripheral neuropathy (e.g., diabetic neuropathy). In a particular embodiement, the inhibition is achieved by administering to a patient a therapeutically effective amount of an AAK1 inhibitor.

5.4. EXAMPLES

Certain aspects of the invention can be understood from the following examples.

5.4.1. AAK1 Knockout Mice

Mice homozygous (-/-) for the disruption of the AAK1 gene were prepared by two methods; gene trapping and homologous recombination.

Gene trapping is a method of random insertional mutagenesis that uses a fragment of DNA coding for a reporter or selectable marker gene as a mutagen. Gene trap vectors have been designed to integrate into introns or genes in a manner that allows the cellular splicing machinery to

splice vector encoded exons to cellular mRNAs. Commonly, gene trap vectors contain selectable marker sequences that are preceded by strong splice acceptor sequences and are not preceded by a promoter. Thus, when such vectors integrate into a gene, the cellular splicing machinery splices exons from the trapped gene onto the 5' end of the selectable marker sequence. Typically, such selectable marker genes can only be expressed if the vector encoding the gene has integrated into an intron. The resulting gene trap events are subsequently identified by selecting for cells that can survive selective culture.

Embryonic stem cells (Lex-1 cells from derived murine strain A129), were mutated by a process involving the insertion of at least a portion of a genetically engineered vector sequence into the gene of interest, the mutated embryonic stem cells were microinjected into blastocysts which were subsequently introduced into pseudopregnant female hosts and carried to term using established methods. *See, e.g.*, "Mouse Mutagenesis", 1998, Zambrowicz et al., eds., Lexicon Press, The Woodlands, TX. The resulting chimeric animals were subsequently bred to produce offspring capable of germline transmission of an allele containing the engineered mutation in the gene of interest.

AAK1-gene disrupted mice were also made by homologous recombination. In this case, the second coding exon of the murine AAK1 gene (see GenBank Accession Number NM_177762) was removed by methods known in the art. *See, e.g.*, U.S. Patent Nos. 5,487,992, 5,627,059, and 5,789,215.

Mice homozygous (-/-) for the disruption of the AAK1 gene were studied in conjunction with mice heterozygous (+/-) for the disruption of the AAK1 gene, and wild-type (+/+) litter mates. During this analysis, the mice were subject to a medical work-up using an integrated suite of medical diagnostic procedures designed to assess the function of the major organ systems in a mammalian subject. Homozygous (-/-) "knockout" mice were studied in conjunction with their heterozygous (+/-) and wild-type (+/+) litter mates. Disruption of the AAK1 gene was confirmed by Southern analysis. Expression of the murine homolog of AAK1 was detected by RT-PCR in murine brain; spinal cord; eye; thymus; spleen; lung; kidney; liver; skeletal muscle; bone; stomach, small intestine and colon; heart; adipose; asthmatic lung; LPS liver; blood; banded heart; aortic tree; prostate; and mammary gland (5 week virgin, mature virgin, 12 DPC, 3 day post-partum (lactating), 3 day post-weaning (early involution), and 7 day post-weaning (late involution)).

AAK1 homozygous (-/-) and their wild-type (+/+) littermates were tested using the formalin paw test in order to assess their acute and tonic nociceptive responses. For these tests, Automatic Nociception Analyzers (purchased from the Ozaki lab at University of California, San Diego) were used. A metal band was placed around the left hind paw of each mouse 30 minutes prior to testing. After the 30-minute acclimation period, 20 µl of 5% formalin is subcutaneously injected in the dorsal surface of the left hind paw. Mice were individually housed in cylindrical chambers for 45 minutes. A computer recorded flinches per minute, total flinches for phase I (acute phase = first 8 minutes), and

total flinches for phase II (tonic phase = time between minutes 20 - 40) through an electromagnetic field. See Yaksh TL, Ozaki G, McCumber D, Rathbun M, Svensson C, Malkmus S, Yaksh MC. *An automated flinch detecting system for use in the formalin nociceptive bioassay.* J Appl Physiol., 2001; 90:2386-402.

As shown in Figure 1, phase 1 and phase 2 data were obtained using homozygous (-/-) mice females (n = 16), wild-type females (n = 15), homozygous (-/-) mice males (n = 9), and wild-type males (n = 18). In all groups and in both phases, the AAK1 homozygous (-/-) mice exhibited significantly less recorded paw flinching than their wild-type (+/+) littermates.

5.4.2. **Caliper Assay**

The assays were performed in U-bottom 384-well plates. The final assay volume was 30 µl prepared from 15 µl additions of enzyme and substrates (fluoresceinated peptide (5-FAM)-Aha-KEEQSQITSQVTGQIGWR-NH2 and ATP) and test compounds in assay buffer (10 mM Tris-HCL pH 7.4, 10 mM $MgCl_2$, 0.01% Tween-20 and 1.0 mM DTT). The reactions were initiated by the combination of bacterially expressed, GST-Xa-hAAK1 with substrates and test compounds. The reactions were incubated at room temperature for 3 hours and terminated by adding 60 µl of 35 mM EDTA buffer to each sample. The reactions were analyzed on the Caliper LabChip 3000 (Caliper, Hopkinton, MA) by electrophoretic separation of the fluorescent substrate and phosphorylated product. Inhibition data were calculated by comparison to EDTA quenched control reactions for 100% inhibition and vehicle-only reactions for 0% inhibition. The final concentration of reagents in the assays are ATP, 22 µM; (5-FAM)-Aha-KEEQSQITSQVTGQIGWR-NH2, 1.5 µM; GST-Xa-hAAK1, 3.5 nM; and DMSO, 1.6%. Dose response curves were generated to determine the concentration required inhibiting 50% of kinase activity (IC_{50}). Compounds were dissolved at 10 mM in dimethylsulfoxide (DMSO) and evaluated at eleven concentrations. IC_{50} values were derived by non-linear regression analysis.

5.4.3. **P81 Filter Plate Assay**

Compounds were serially diluted into a Labcyte LDV plate (Labcyte, cat# LP-0200) using a Mutiprobe (PerkinElmer) and Biomek FX (Beckman Coulter) so that the highest compound concentration was at 96 µM. Compounds were then pinged (75 nL per well) into a Greiner 384-well reaction plate (Greiner, # 781076) using an ECHO 550 Liquid Handler (Labcyte). A total of 12µl reaction buffer (IMAP buffer containing Tween and DTT, from Molecular Devices) was then added to each well of columns 1 and 13 for the negative controls and 12µl of 2X AAK1 (0.2 nM full-length human protein, NCBI accession no. NP_055726.2) was added to the remaining wells. Enzyme was then pre-incubated with compound for 10 minutes at RT. Reactions were initiated upon Minitrak (PerkinElmer) addition of 12µl substrate mix containing 2X Mu2 (0.2 µM, full length human protein), 2x cold ATP (2 µM), and 1.3 µCi of hot ^{33}P-ATP. Reactions proceeded for one hour at RT. Meanwhile, Millipore 384-well P81 filter plates (Millipore, catalog # MZPHN0W10) were placed on a plate washer (Zoom ZW, from Titertek) and pre-wet with 50µl 1% phosphoric acid. Kinase reactions were then

stopped upon addition of 24µl of 2% phosphoric acid to each well and the Minitrak was then used to transfer 40µl from each well into the pre-wet Millipore 384-well P81 filter plates. Reaction mixtures were incubated for 10 minutes at RT in the P81 plates, followed by washing five times with 100µl/well of 1% phosphoric acid using the Zoom filter washer. The bottom of each filter plate was sealed followed by addition of 20µl Microscint 40 to each well, sealing the top of the plates with Flashplate cover, and then waiting one hour until reading on the TopCount (PerkinElmer).

5.4.4. **HEK281 Cell-Based Assay**

HEK293F cells were cultured in media containing DMEM (Gibco, cat. #11965), 10% FBS (SAFC Biosciences, cat. #12103C), 1X GPS (glutamine, penicillin and streptomycin). On day one, cells were plated on a 10cm dish so that they are ~80% confluent at time of transfection. Roughly 12 million cells were in a 10cm dish at time of transfection. On day two, each dish was transfected with 48 ug DNA and 144 ul Lipofectamine 2000 (Invitrogen, cat.# 11668-019). The DNA was comprised of a mixture (per 10cm dish) containing 3 ug AAK1/HA/pIRES (full length human, NCBI accession no. NP_055726.2), 45 µg Flag/AP2MI/pcDNA (full length human), and 1.5 ml OPTI-MEM. The Lipofectamine 2000 is made up of a mixture (per 10cm dish) containing 144 µl Lipofectamine 2000 and 1.5 ml OPTI-MEM. Each mixture was transferred to individual 15ml tubes and incubated at RT for 5 minutes, and then the two mixes were combined and incubated at RT for 20 minutes. Growth media was then aspirated from each 10cm plate and replaced with 10ml of DMEM+10% FBS (no GPS). Finally, 3 ml DNA/Lipofectamine mix was added to each 10cm dish and mix gently followed by incubate of plate overnight at 37°C and 5% CO_2.

On day three, compounds were diluted in 100% DMSO at 1000X final concentration, followed by 3-fold serial dilutions for a total of 5 concentrations tested. Four compounds were tested per 10cm dish. One ul of each compound dilution was then pipetted into a deep-well, 96-well plate, followed by addition of 500 µl DMEM + 0.5% FBS into each well for a 2X final concentration of each compound. Cells were resuspended in a 10cm dish by simple pipetting (HEK293 cells come off the plate that easy at this point) and then transferred to a 50 ml conical tube and pelleted by centrifugation at 1000rpm for 5 min. Cell pellets were then resuspended in 2.75 ml DMEM + 0.5% FBS per 10cm dish and 100 µl of cell suspension transferred into each well of 96-well TC plate. Finally, 100 µl of 2X compound diluted in DMEM + 0.5% FBS was then added into wells containing cell suspension for a 1X final concentration. Plates were then incubated at 37°C and 5% CO_2 for 3 hours followed by transferring of cell suspensions from each well into 12-tube PCR strips. The PCR strips were spun in a tip rack at 1000rpm for 5 minutes to pellet cells and media was then removed by pipetting without disturbing the cell pellet.

To prepare for Western Blot analysis, cell pellets were resuspend in 40ul 1X LDS-PAGE sample buffer (Invitrogen, cat.# NP0008) + 2X Halt phophatase and protease inhibitor cocktail (Thermo Scientific, cat.#1861284), followed by sonicating each with microtip sonicator set at 5 for 8-10 seconds. Five ul of 10X NuPage Sample Reducing Agent (with 50 mM DTT) was to each sample

followed by heat denaturing at 70C for 10 min on PCR machine. A total of 10µl per sample was loaded into each lane of a 4-20% Tris-Glycine Criterion 26-well gel (Biorad, cat.# 345-0034) for the phospho-mu2 blot and 10µl per lane in a 4-12% Bis-Tris (+MES buffer) NuPAGE 26-well gel (Invitrogen, cat.# WG1403BX10) for the mu2 blot. For controls, 2ng of phospho-mu2 or 20ng mu2/Flag proteins were loaded in the last well of each gel. After SDS-PAGE, samples on each gel were transferred to PVDF membrane using an iBlot and membranes were blocked for one hour in TBST + 5% milk, followed by wash 3X for 5-10 min with TBST. Criterion gels were probed with rabbit anti-phospho-mu2 (1:5000; a rabbit polyclonal antibody produced by New England Peptide and affinity purified at Lexicon) in TBST + 5% BSA, whereas, NuPAGE gels were probed with mouse anti-Flag (1:500; Sigma, cat.# F1804) in TBST + 5% milk, and these primary antibodies were incubated overnight at 4°C on a rocker.

On day four, Western blots were washed 3X for 5-10 minutes with TBST, probe with anti-rabbit-HRP (1:2000; BioRad, cat.# 170-6515) or anti-mouse-HRP (1:2000; Biorad, cat.# 170-6516) in TBST + 5% milk for 1 hour at RT, washed 3X for 10 minutes with TBST, and developed with ECL reagent (GE Healthcare, cat.# RPN2132) on a Versadoc. Finally, the camera was set up to take a picture every 30 seconds for 10 minutes and the best image saved for each blot with no saturated signal (when the signal is saturated, the bands will be highlighted red). A volume analysis on each band was performed to obtain density values. Percent inhibition was calculated for each sample by first normalizing to total Mu2 expression levels and then comparing to 0% and 100% controls. IC_{50} values were then calculated using Excel fitting software.

5.4.5. **Imidazo[1,2-b]pyridazine-based Inhibitor In Vitro Data**

In vitro data obtained for various compounds of the invention are provided below in Table 1, wherein "MW" means molecular weight, "P81 Assay" refers to the P81 filter plate assay described above, "CBA" refers to the HEK281 cell-based assay described above, "--" means that results for the given assay were not obtained, "*" means less than or equal to 1.0 µM, "**" means a value of less than or equal to 0.1 µM, and "***" means less than or equal to 0.01 µM.

Table 1

Compound	MW	CBA IC_{50}	P81 IC_{50}
(2S)-ethyl 2-(((3-(4-(pyrrolidin-2-yl)phenyl)imidazo[1,2-b]pyridazin-6-yl)amino)methyl)pyrrolidine-1-carboxylate	434.5	**	-
(2S)-methyl 2-(((3-(4-(pyrrolidin-2-yl)phenyl)imidazo[1,2-b]pyridazin-6-yl)amino)methyl)pyrrolidine-1-carboxylate	420.5	**	-
(2S)-tetrahydrofuran-3-yl 2-(((3-(pyridin-4-yl)imidazo[1,2-b]pyridazin-6-yl)amino)methyl)pyrrolidine-1-carboxylate	408.5	-	***
(2S)-tetrahydrofuran-3-yl 2-(((3-bromoimidazo[1,2-b]pyridazin-6-yl)amino)methyl)pyrrolidine-1-carboxylate	410.3	-	***

(4-(3-(2-methoxyphenyl)imidazo[1,2-b]pyridazin-6-yl)piperazin-1-yl)(pyrrolidin-1-yl)methanone	406.5	**	***
(4-(3-(2-methoxyphenyl)imidazo[1,2-b]pyridazin-6-yl)piperazin-1-yl)(piperidin-1-yl)methanone	420.5	**	***
(4-(3-(2-methoxypyridin-3-yl)imidazo[1,2-b]pyridazin-6-yl)piperazin-1-yl)(pyrrolidin-1-yl)methanone	407.5	**	***
(4-(3-(2-methoxypyridin-3-yl)imidazo[1,2-b]pyridazin-6-yl)piperazin-1-yl)(piperidin-1-yl)methanone	421.5	**	***
(4-(3-(3-methoxypyridin-4-yl)imidazo[1,2-b]pyridazin-6-yl)piperazin-1-yl)(pyrrolidin-1-yl)methanone	407.5	**	***
(4-(3-(pyridin-2-yl)imidazo[1,2-b]pyridazin-6-yl)piperazin-1-yl)(pyrrolidin-1-yl)methanone	377.4	**	***
(4-(3-phenylimidazo[1,2-b]pyridazin-6-yl)piperazin-1-yl)(piperidin-1-yl)methanone	390.5	**	***
(4-(3-phenylimidazo[1,2-b]pyridazin-6-yl)piperazin-1-yl)(pyrrolidin-1-yl)methanone	376.5	*	***
(4-(6-((2-(cyclopentyloxy)ethyl)amino)imidazo[1,2-b]pyridazin-3-yl)phenyl)methanol	352.4	–	***
(4-(6-(butylthio)imidazo[1,2-b]pyridazin-3-yl)phenyl)methanamine	312.4	*	–
(4-aminopiperidin-1-yl)(4-(6-(butylamino)imidazo[1,2-b]pyridazin-3-yl)phenyl)methanone	392.5	*	–
(R)-isopropyl methyl(2-((3-(4-(pyrrolidin-2-yl)phenyl)imidazo[1,2-b]pyridazin-6-yl)amino)ethyl)carbamate	422.5	**	–
(R)-N-butyl-3-(4-(pyrrolidin-2-yl)phenyl)imidazo[1,2-b]pyridazin-6-amine	335.4	*	–
(S)-1-(2-(((3-(2,4-dimethylthiazol-5-yl)imidazo[1,2-b]pyridazin-6-yl)amino)methyl)pyrrolidin-1-yl)-3-methylbutan-1-one	412.6	***	***
(S)-1-(2-(((3-(2-chlorophenyl)imidazo[1,2-b]pyridazin-6-yl)amino)methyl)pyrrolidin-1-yl)-3-methylbutan-1-one	411.9	–	–
(S)-1-(2-(((3-(2-fluoropyridin-4-yl)imidazo[1,2-b]pyridazin-6-yl)amino)methyl)pyrrolidin-1-yl)-3-methylbutan-1-one	396.5	–	***
(S)-1-(2-(((3-(2-methoxyphenyl)imidazo[1,2-b]pyridazin-6-yl)amino)methyl)pyrrolidin-1-yl)-3-methylbutan-1-one	407.5	***	–
(S)-1-(2-(((3-(2-methoxyphenyl)imidazo[1,2-b]pyridazin-6-yl)amino)methyl)pyrrolidin-1-yl)ethanone	365.4	**	–
(S)-1-(2-(((3-(3-chlorophenyl)imidazo[1,2-b]pyridazin-6-yl)amino)methyl)pyrrolidin-1-yl)-3-methylbutan-1-one	411.9	***	***
(S)-1-(2-(((3-(3-fluorophenyl)imidazo[1,2-b]pyridazin-6-yl)amino)methyl)pyrrolidin-1-yl)-3-methylbutan-1-one	395.5	***	***
(S)-1-(2-(((3-(3-methoxyphenyl)imidazo[1,2-b]pyridazin-6-yl)amino)methyl)pyrrolidin-1-yl)-3-methylbutan-1-one	407.5	**	***

(S)-1-(2-(((3-(3-methoxypyridin-4-yl)imidazo[1,2-b]pyridazin-6-yl)amino)methyl)pyrrolidin-1-yl)ethanone	366.4	**	-
(S)-1-(2-(((3-(3-methoxypyridin-4-yl)imidazo[1,2-b]pyridazin-6-yl)amino)methyl)pyrrolidin-1-yl)-3-methylbutan-1-one	408.5	***	-
(S)-1-(2-(((3-(4-(aminomethyl)phenyl)imidazo[1,2-b]pyridazin-6-yl)amino)methyl)pyrrolidin-1-yl)-3-methylbutan-1-one	406.5	***	-
(S)-1-(2-(((3-(4-(aminomethyl)phenyl)imidazo[1,2-b]pyridazin-6-yl)amino)methyl)pyrrolidin-1-yl)-2,2-dimethylpropan-1-one	406.5	**	***
(S)-1-(2-(((3-(4-(aminomethyl)phenyl)imidazo[1,2-b]pyridazin-6-yl)amino)methyl)pyrrolidin-1-yl)butan-1-one	392.5	***	***
(S)-1-(2-(((3-(4-(aminomethyl)phenyl)imidazo[1,2-b]pyridazin-6-yl)amino)methyl)pyrrolidin-1-yl)-3,3-dimethylbutan-1-one	420.6	**	***
(S)-1-(2-(((3-(4-fluorophenyl)imidazo[1,2-b]pyridazin-6-yl)amino)methyl)pyrrolidin-1-yl)-3-methylbutan-1-one	395.5	**	***
(S)-1-(2-(((3-(4-methoxyphenyl)imidazo[1,2-b]pyridazin-6-yl)amino)methyl)pyrrolidin-1-yl)-3-methylbutan-1-one	407.5	*	***
(S)-1-(2-(((3-(cyclopent-1-en-1-yl)imidazo[1,2-b]pyridazin-6-yl)amino)methyl)pyrrolidin-1-yl)-3-methylbutan-1-one	367.5	-	***
(S)-1-(2-(((3-(pyridin-4-yl)imidazo[1,2-b]pyridazin-6-yl)amino)methyl)pyrrolidin-1-yl)butan-1-one	364.4	-	***
(S)-1-(2-(((3-bromoimidazo[1,2-b]pyridazin-6-yl)amino)methyl)pyrrolidin-1-yl)-3-methylbutan-1-one	380.3	**	-
(S)-1-(3,3-dimethylbutyl)-5-(((3-(2-methoxyphenyl)imidazo[1,2-b]pyridazin-6-yl)amino)methyl)pyrrolidin-2-one	421.5	*	***
(S)-1-(3,3-dimethylbutyl)-5-(((3-(2-methoxypyridin-3-yl)imidazo[1,2-b]pyridazin-6-yl)amino)methyl)pyrrolidin-2-one	422.5	***	***
(S)-1-(3,3-dimethylbutyl)-5-(((3-(pyridin-4-yl)imidazo[1,2-b]pyridazin-6-yl)amino)methyl)pyrrolidin-2-one	392.5	-	***
(S)-1-(3,3-dimethylbutyl)-5-(((3-phenylimidazo[1,2-b]pyridazin-6-yl)amino)methyl)pyrrolidin-2-one	391.5	*	***
(S)-1-methylcyclopentyl 2-(((3-bromoimidazo[1,2-b]pyridazin-6-yl)amino)methyl)pyrrolidine-1-carboxylate	422.3	*	***
(S)-2-(((3-bromoimidazo[1,2-b]pyridazin-6-yl)amino)methyl)-N-(tert-butyl)pyrrolidine-1-carboxamide	395.3	**	***
(S)-2,2,2-trifluoroethyl (1-(3-(2-methoxypyridin-3-yl)imidazo[1,2-b]pyridazin-6-yl)pyrrolidin-3-yl)(methyl)carbamate	450.4	**	***
(S)-2-amino-N-(4-(6-(butylamino)imidazo[1,2-b]pyridazin-3-yl)benzyl)-4-methylpentanamide	408.5	**	-

(S)-2-cyclopropyl-N-(1-(3-(2-hydroxypyridin-3-yl)imidazo[1,2-b]pyridazin-6-yl)pyrrolidin-3-yl)-N-methylacetamide	392.5	-	***
(S)-2-methoxyethyl (1-(3-(2-methoxypyridin-3-yl)imidazo[1,2-b]pyridazin-6-yl)pyrrolidin-3-yl)(methyl)carbamate	426.5	-	**
(S)-3-(4-(aminomethyl)phenyl)-N-((tetrahydrofuran-2-yl)methyl)imidazo[1,2-b]pyridazin-6-amine	323.4	**	-
(S)-3-(6-(((1-(3-methylbutanoyl)pyrrolidin-2-yl)methyl)amino)imidazo[1,2-b]pyridazin-3-yl)benzonitrile	402.5	**	***
(S)-3,3,3-trifluoro-1-(2-(((3-phenylimidazo[1,2-b]pyridazin-6-yl)amino)methyl)pyrrolidin-1-yl)propan-1-one	403.4	***	***
(S)-3,3,3-trifluoro-N-(1-(3-(2-hydroxypyridin-3-yl)imidazo[1,2-b]pyridazin-6-yl)pyrrolidin-3-yl)-N-methylpropanamide	420.4	-	***
(S)-3,3-dimethyl-1-(2-(((3-(pyridin-4-yl)imidazo[1,2-b]pyridazin-6-yl)amino)methyl)pyrrolidin-1-yl)butan-1-one	392.5	**	***
(S)-3-methyl-1-(2-(((3-(2-methylpyridin-4-yl)imidazo[1,2-b]pyridazin-6-yl)amino)methyl)pyrrolidin-1-yl)butan-1-one	392.5	**	***
(S)-3-methyl-1-(2-(((3-(m-tolyl)imidazo[1,2-b]pyridazin-6-yl)amino)methyl)pyrrolidin-1-yl)butan-1-one	391.5	*	***
(S)-3-methyl-1-(2-(((3-(pyridin-4-yl)imidazo[1,2-b]pyridazin-6-yl)amino)methyl)pyrrolidin-1-yl)butan-1-one	378.5	**	-
(S)-3-methyl-1-(2-(((3-phenylimidazo[1,2-b]pyridazin-6-yl)amino)methyl)pyrrolidin-1-yl)butan-1-one	377.5	**	***
(S)-4-(6-(((1-(3-methylbutanoyl)pyrrolidin-2-yl)methyl)amino)imidazo[1,2-b]pyridazin-3-yl)benzonitrile	402.5	***	***
(S)-5-(((3-(4-(aminomethyl)phenyl)imidazo[1,2-b]pyridazin-6-yl)amino)methyl)-1-isopentylpyrrolidin-2-one	406.5	**	***
(S)-5-(((3-(4-(aminomethyl)phenyl)imidazo[1,2-b]pyridazin-6-yl)amino)methyl)-1-(3,3-dimethylbutyl)pyrrolidin-2-one	420.6	**	***
(S)-5-(((3-bromoimidazo[1,2-b]pyridazin-6-yl)amino)methyl)-1-(3,3-dimethylbutyl)pyrrolidin-2-one	394.3	**	***
(S)-cyclobutyl 2-(((3-(2-methoxyphenyl)imidazo[1,2-b]pyridazin-6-yl)amino)methyl)pyrrolidine-1-carboxylate	421.5	**	***
(S)-cyclobutyl 2-(((3-(pyridin-4-yl)imidazo[1,2-b]pyridazin-6-yl)amino)methyl)pyrrolidine-1-carboxylate	392.5	***	***
(S)-cyclobutyl 2-(((3-bromoimidazo[1,2-b]pyridazin-6-yl)amino)methyl)pyrrolidine-1-carboxylate	394.3	**	***
(S)-cyclopentyl 2-(((3-(4-(aminomethyl)phenyl)imidazo[1,2-b]pyridazin-6-yl)amino)methyl)pyrrolidine-1-carboxylate	434.5	***	***
(S)-cyclopentyl 2-(((3-(pyridin-4-yl)imidazo[1,2-b]pyridazin-6-yl)amino)methyl)pyrrolidine-1-carboxylate	406.5	***	***

(S)-cyclopentyl 2-(((3-bromoimidazo[1,2-b]pyridazin-6-yl)amino)methyl)pyrrolidine-1-carboxylate	408.3	***	***
(S)-cyclopentyl 2-(((3-cyanoimidazo[1,2-b]pyridazin-6-yl)amino)methyl)pyrrolidine-1-carboxylate	354.4	-	***
(S)-cyclopentyl 2-(((3-phenylimidazo[1,2-b]pyridazin-6-yl)amino)methyl)pyrrolidine-1-carboxylate	405.5	**	***
(S)-cyclopropylmethyl 2-(((3-(pyridin-4-yl)imidazo[1,2-b]pyridazin-6-yl)amino)methyl)pyrrolidine-1-carboxylate	392.5	-	***
(S)-cyclopropylmethyl 2-(((3-bromoimidazo[1,2-b]pyridazin-6-yl)amino)methyl)pyrrolidine-1-carboxylate	394.3	-	***
(S)-ethyl (1-(3-(2-methoxypyridin-3-yl)imidazo[1,2-b]pyridazin-6-yl)pyrrolidin-3-yl)(methyl)carbamate	396.4	**	***
(S)-ethyl 2-(((3-(2-methoxyphenyl)imidazo[1,2-b]pyridazin-6-yl)amino)methyl)pyrrolidine-1-carboxylate	395.5	**	-
(S)-ethyl 2-(((3-(3-methoxypyridin-4-yl)imidazo[1,2-b]pyridazin-6-yl)amino)methyl)pyrrolidine-1-carboxylate	396.4	**	-
(S)-ethyl 2-(((3-(4-(aminomethyl)phenyl)imidazo[1,2-b]pyridazin-6-yl)amino)methyl)pyrrolidine-1-carboxylate	394.5	***	-
(S)-ethyl 2-(((3-(pyridin-4-yl)imidazo[1,2-b]pyridazin-6-yl)amino)methyl)pyrrolidine-1-carboxylate	366.4	**	-
(S)-ethyl 2-(((3-bromoimidazo[1,2-b]pyridazin-6-yl)amino)methyl)pyrrolidine-1-carboxylate	368.2	**	-
(S)-isopropyl (1-(3-(2-(difluoromethoxy)pyridin-3-yl)imidazo[1,2-b]pyridazin-6-yl)pyrrolidin-3-yl)(methyl)carbamate	446.5	-	***
(S)-isopropyl (1-(3-(2-methoxy-6-methylpyridin-3-yl)imidazo[1,2-b]pyridazin-6-yl)pyrrolidin-3-yl)(methyl)carbamate	424.5	***	***
(S)-isopropyl (1-(3-(2-methoxypyridin-3-yl)imidazo[1,2-b]pyridazin-6-yl)pyrrolidin-3-yl)(methyl)carbamate	410.5	***	***
(S)-isopropyl (1-(3-(3,6-dimethoxypyridazin-4-yl)imidazo[1,2-b]pyridazin-6-yl)pyrrolidin-3-yl)(methyl)carbamate	441.5	**	***
(S)-isopropyl (1-(3-bromoimidazo[1,2-b]pyridazin-6-yl)pyrrolidin-3-yl)(methyl)carbamate	382.3	-	***
(S)-isopropyl 2-(((3-(2-methoxyphenyl)imidazo[1,2-b]pyridazin-6-yl)amino)methyl)pyrrolidine-1-carboxylate	409.5	***	-
(S)-isopropyl 2-(((3-(3-methoxypyridin-4-yl)imidazo[1,2-b]pyridazin-6-yl)amino)methyl)pyrrolidine-1-carboxylate	410.5	***	-
(S)-isopropyl 2-(((3-(4-(aminomethyl)phenyl)imidazo[1,2-b]pyridazin-6-yl)amino)methyl)pyrrolidine-1-carboxylate	408.5	***	-
(S)-isopropyl 2-(((3-(prop-1-en-2-yl)imidazo[1,2-b]pyridazin-6-yl)amino)methyl)pyrrolidine-1-carboxylate	343.4	**	-

(S)-isopropyl 2-(((3-bromoimidazo[1,2-b]pyridazin-6-yl)amino)methyl)pyrrolidine-1-carboxylate	382.3	*	–
(S)-isopropyl 2-(((3-chloroimidazo[1,2-b]pyridazin-6-yl)amino)methyl)pyrrolidine-1-carboxylate	337.8	**	–
(S)-isopropyl 2-(((3-cyanoimidazo[1,2-b]pyridazin-6-yl)amino)methyl)pyrrolidine-1-carboxylate	328.4	*	***
(S)-isopropyl 2-(((3-cyclopropylimidazo[1,2-b]pyridazin-6-yl)amino)methyl)pyrrolidine-1-carboxylate	343.4	*	–
(S)-isopropyl 2-(((3-vinylimidazo[1,2-b]pyridazin-6-yl)amino)methyl)pyrrolidine-1-carboxylate	329.4	***	–
(S)-isopropyl methyl(1-(3-(pyridin-3-yl)imidazo[1,2-b]pyridazin-6-yl)pyrrolidin-3-yl)carbamate	380.4	**	***
(S)-isopropyl methyl(1-(3-(pyridin-4-yl)imidazo[1,2-b]pyridazin-6-yl)pyrrolidin-3-yl)carbamate	380.4	–	**
(S)-isopropyl methyl(2-((3-(4-(pyrrolidin-2-yl)phenyl)imidazo[1,2-b]pyridazin-6-yl)amino)ethyl)carbamate	422.5	**	–
(S)-methyl 2-(((3-(2-methoxyphenyl)imidazo[1,2-b]pyridazin-6-yl)amino)methyl)pyrrolidine-1-carboxylate	381.4	**	–
(S)-methyl 2-(((3-(3-methoxypyridin-4-yl)imidazo[1,2-b]pyridazin-6-yl)amino)methyl)pyrrolidine-1-carboxylate	382.4	**	–
(S)-methyl 2-(((3-(4-(aminomethyl)phenyl)imidazo[1,2-b]pyridazin-6-yl)amino)methyl)pyrrolidine-1-carboxylate	380.4	**	–
(S)-methyl 2-(((3-bromoimidazo[1,2-b]pyridazin-6-yl)amino)methyl)pyrrolidine-1-carboxylate	354.2	*	–
(S)-N-(1-(3-(2-hydroxypyridin-3-yl)imidazo[1,2-b]pyridazin-6-yl)pyrrolidin-3-yl)-N-methylcyclopentanecarboxamide	406.5	–	**
(S)-N-(1-(3-(2-hydroxypyridin-3-yl)imidazo[1,2-b]pyridazin-6-yl)pyrrolidin-3-yl)-2-methoxy-N-methylacetamide	382.4	–	*
(S)-N-(1-(3-(2-hydroxypyridin-3-yl)imidazo[1,2-b]pyridazin-6-yl)pyrrolidin-3-yl)-N,3-dimethylbutanamide	394.5	–	**
(S)-N-(1-(3-(2-hydroxypyridin-3-yl)imidazo[1,2-b]pyridazin-6-yl)pyrrolidin-3-yl)-N,3,3-trimethylbutanamide	408.5	*	**
(S)-N-(1-(3-(2-hydroxypyridin-3-yl)imidazo[1,2-b]pyridazin-6-yl)pyrrolidin-3-yl)-N-methylbutyramide	380.4	–	**
(S)-N-(1-(3-(2-methoxyphenyl)imidazo[1,2-b]pyridazin-6-yl)pyrrolidin-3-yl)-N-methylpyrrolidine-1-carboxamide	420.5	**	***
(S)-N-(1-(3-(2-methoxypyridin-3-yl)imidazo[1,2-b]pyridazin-6-yl)pyrrolidin-3-yl)-N-methylpyrrolidine-1-carboxamide	421.5	**	***
(S)-N-(1-(3-(2-methoxypyridin-3-yl)imidazo[1,2-b]pyridazin-6-yl)pyrrolidin-3-yl)-N-methylbutyramide	394.5	–	**
(S)-N-(1-(3-bromoimidazo[1,2-b]pyridazin-6-yl)pyrrolidin-3-yl)-N-methylbutyramide	366.3	–	*

(S)-N-(1-(3-bromoimidazo[1,2-b]pyridazin-6-yl)pyrrolidin-3-yl)-N-methylpyrrolidine-1-carboxamide	393.3	-	**
(S)-N-(tert-butyl)-2-(((3-(2-methoxyphenyl)imidazo[1,2-b]pyridazin-6-yl)amino)methyl)pyrrolidine-1-carboxamide	422.5	**	***
(S)-N-(tert-butyl)-2-(((3-(pyridin-4-yl)imidazo[1,2-b]pyridazin-6-yl)amino)methyl)pyrrolidine-1-carboxamide	393.5	**	***
(S)-N-(tert-butyl)-2-(((3-phenylimidazo[1,2-b]pyridazin-6-yl)amino)methyl)pyrrolidine-1-carboxamide	392.5	**	***
(S)-N-butyl-3-(4-(pyrrolidin-2-yl)phenyl)imidazo[1,2-b]pyridazin-6-amine	335.4	**	-
(S)-N-cyclopentyl-2-(((3-(2-methoxyphenyl)imidazo[1,2-b]pyridazin-6-yl)amino)methyl)pyrrolidine-1-carboxamide	434.5	*	***
(S)-neopentyl 2-(((3-(4-(aminomethyl)phenyl)imidazo[1,2-b]pyridazin-6-yl)amino)methyl)pyrrolidine-1-carboxylate	436.5	***	***
(S)-neopentyl 2-(((3-(pyridin-4-yl)imidazo[1,2-b]pyridazin-6-yl)amino)methyl)pyrrolidine-1-carboxylate	408.5	**	***
(S)-neopentyl 2-(((3-bromoimidazo[1,2-b]pyridazin-6-yl)amino)methyl)pyrrolidine-1-carboxylate	410.3	**	-
(S)-N-methyl-N-(1-(3-(pyridin-2-yl)imidazo[1,2-b]pyridazin-6-yl)pyrrolidin-3-yl)pyrrolidine-1-carboxamide	391.5	-	**
(S)-N-methyl-N-(1-(3-(pyridin-3-yl)imidazo[1,2-b]pyridazin-6-yl)pyrrolidin-3-yl)butyramide	364.4	-	*
(S)-N-methyl-N-(1-(3-(pyridin-4-yl)imidazo[1,2-b]pyridazin-6-yl)pyrrolidin-3-yl)pyrrolidine-1-carboxamide	391.5	-	**
(S)-N-methyl-N-(1-(3-(pyridin-4-yl)imidazo[1,2-b]pyridazin-6-yl)pyrrolidin-3-yl)butyramide	364.4	-	**
(S)-N-neopentyl-2-(((3-phenylimidazo[1,2-b]pyridazin-6-yl)amino)methyl)pyrrolidine-1-carboxamide	406.5	**	***
(S)-propyl 2-(((3-bromoimidazo[1,2-b]pyridazin-6-yl)amino)methyl)pyrrolidine-1-carboxylate	382.3	-	***
(S)-tert-butyl (1-(3-(2-methoxyphenyl)imidazo[1,2-b]pyridazin-6-yl)pyrrolidin-3-yl)(methyl)carbamate	423.5	**	***
(S)-tert-butyl (1-(3-(2-methoxypyridin-3-yl)imidazo[1,2-b]pyridazin-6-yl)pyrrolidin-3-yl)(methyl)carbamate	424.5	**	***
(S)-tert-butyl (1-(3-bromoimidazo[1,2-b]pyridazin-6-yl)pyrrolidin-3-yl)(methyl)carbamate	396.3	*	***
(S)-tert-butyl 2-(((3-(2-methoxyphenyl)imidazo[1,2-b]pyridazin-6-yl)amino)methyl)pyrrolidine-1-carboxylate	423.5	***	-
(S)-tert-butyl 2-(((3-(3-methoxypyridin-4-yl)imidazo[1,2-b]pyridazin-6-yl)amino)methyl)piperidine-1-carboxylate	438.5	**	-
(S)-tert-butyl 2-(((3-(4-(aminomethyl)phenyl)imidazo[1,2-b]pyridazin-6-yl)amino)methyl)pyrrolidine-1-carboxylate	422.5	***	***
(S)-tert-butyl 2-(((3-(4-(aminomethyl)phenyl)imidazo[1,2-b]pyridazin-6-yl)amino)methyl)piperidine-1-carboxylate	436.5	***	-

(S)-tert-butyl 2-(((3-(4-carbamoylphenyl)imidazo[1,2-b]pyridazin-6-yl)amino)methyl)pyrrolidine-1-carboxylate	436.5	***	***
(S)-tert-butyl 2-(((3-(difluoromethyl)imidazo[1,2-b]pyridazin-6-yl)amino)methyl)pyrrolidine-1-carboxylate	367.4	*	***
(S)-tert-butyl 2-(((3-(methylcarbamoyl)imidazo[1,2-b]pyridazin-6-yl)amino)methyl)pyrrolidine-1-carboxylate	374.4	**	***
(S)-tert-butyl 2-(((3-(pyridin-4-yl)imidazo[1,2-b]pyridazin-6-yl)amino)methyl)piperidine-1-carboxylate	408.5	**	-
(S)-tert-butyl 2-(((3-(trifluoromethyl)imidazo[1,2-b]pyridazin-6-yl)amino)methyl)pyrrolidine-1-carboxylate	385.4	**	-
(S)-tert-butyl 2-(((3-bromoimidazo[1,2-b]pyridazin-6-yl)amino)methyl)pyrrolidine-1-carboxylate	396.3	**	-
(S)-tert-butyl 2-(((3-bromoimidazo[1,2-b]pyridazin-6-yl)amino)methyl)azetidine-1-carboxylate	382.3	**	***
(S)-tert-butyl 2-(((3-chloroimidazo[1,2-b]pyridazin-6-yl)amino)methyl)pyrrolidine-1-carboxylate	351.8	**	-
(S)-tert-butyl 2-(((3-ethylimidazo[1,2-b]pyridazin-6-yl)amino)methyl)pyrrolidine-1-carboxylate	345.4	**	-
(S)-tert-butyl 2-(((3-iodoimidazo[1,2-b]pyridazin-6-yl)amino)methyl)pyrrolidine-1-carboxylate	443.3	***	-
(S)-tert-butyl 2-(((3-methylimidazo[1,2-b]pyridazin-6-yl)amino)methyl)pyrrolidine-1-carboxylate	331.4	**	***
(S)-tert-butyl 2-(((3-phenylimidazo[1,2-b]pyridazin-6-yl)amino)methyl)pyrrolidine-1-carboxylate	393.5	***	***
(S)-tert-butyl 2-(2-((3-(4-(aminomethyl)phenyl)imidazo[1,2-b]pyridazin-6-yl)amino)ethyl)pyrrolidine-1-carboxylate	436.5	**	-
(S)-tert-butyl 3-(((3-(3-methoxypyridin-4-yl)imidazo[1,2-b]pyridazin-6-yl)amino)methyl)pyrrolidine-1-carboxylate	424.5	*	-
(S)-tert-butyl 3-(((3-(4-(aminomethyl)phenyl)imidazo[1,2-b]pyridazin-6-yl)amino)methyl)pyrrolidine-1-carboxylate	422.5	**	-
(S)-tert-butyl 3-(((3-bromoimidazo[1,2-b]pyridazin-6-yl)amino)methyl)pyrrolidine-1-carboxylate	396.3	*	-
(S)-tert-butyl methyl(1-(3-(pyridin-3-yl)imidazo[1,2-b]pyridazin-6-yl)pyrrolidin-3-yl)carbamate	394.5	-	***
(S)-tert-butyl methyl(1-(3-(pyridin-4-yl)imidazo[1,2-b]pyridazin-6-yl)pyrrolidin-3-yl)carbamate	394.5	*	***
(S)-vinyl 2-(((3-(2-methoxyphenyl)imidazo[1,2-b]pyridazin-6-yl)amino)methyl)pyrrolidine-1-carboxylate	393.4	**	***
1-(2-((3-(4-(aminomethyl)phenyl)imidazo[1,2-b]pyridazin-6-yl)amino)ethyl)-3-(tert-butyl)imidazolidin-2-one	407.5	**	-
1-(3-(3-(3-methoxypyridin-4-yl)imidazo[1,2-b]pyridazin-6-yl)phenyl)-4-methylpentan-1-one	400.5	**	-
1-(3-(3-(4-(aminomethyl)phenyl)imidazo[1,2-b]pyridazin-6-yl)phenyl)ethanone	342.4	**	-

1-(3-(3-(4-(aminomethyl)phenyl)imidazo[1,2-b]pyridazin-6-yl)phenyl)-4-methylpentan-1-one	398.5	**	–
1-(4-(3-(3-methoxypyridin-4-yl)imidazo[1,2-b]pyridazin-6-yl)piperazin-1-yl)-3,3-dimethylbutan-1-one	408.5	**	–
1-(5-(6-((2-(methyl(phenyl)amino)ethyl)amino)imidazo[1,2-b]pyridazin-3-yl)thiophen-2-yl)ethanone	391.5	**	–
1-(5-(6-((3-(methylamino)propyl)amino)imidazo[1,2-b]pyridazin-3-yl)thiophen-2-yl)ethanone	329.4	*	–
1-(5-(6-((3-methoxypropyl)amino)imidazo[1,2-b]pyridazin-3-yl)thiophen-2-yl)ethanone	330.4	*	–
1-(5-(6-(butyl(methyl)amino)imidazo[1,2-b]pyridazin-3-yl)thiophen-2-yl)ethanone	328.4	**	–
1-(5-(6-(isobutylamino)imidazo[1,2-b]pyridazin-3-yl)thiophen-2-yl)ethanone	314.4	*	–
1-(5-(6-(propylamino)imidazo[1,2-b]pyridazin-3-yl)thiophen-2-yl)ethanone	300.4	*	–
1-(tert-butyl)-3-(2-((3-(3-methoxypyridin-4-yl)imidazo[1,2-b]pyridazin-6-yl)amino)ethyl)imidazolidin-2-one	409.5	**	–
2,2-dimethyl-1-(4-(3-phenylimidazo[1,2-b]pyridazin-6-yl)piperazin-1-yl)propan-1-one	363.5	–	**
2-fluoroethyl isopropyl(2-((3-(3-methoxypyridin-4-yl)imidazo[1,2-b]pyridazin-6-yl)amino)ethyl)carbamate	416.4	*	–
3-(2,4-dimethylthiazol-5-yl)-N-(2-isobutoxyethyl)imidazo[1,2-b]pyridazin-6-amine	345.5	*	–
3-(2-aminopyridin-4-yl)-N-(3-(tert-butoxy)propyl)imidazo[1,2-b]pyridazin-6-amine	340.4	*	–
3-(2-aminopyridin-4-yl)-N-butylimidazo[1,2-b]pyridazin-6-amine	282.3	*	–
3-(2-methoxypyridin-3-yl)-N-((tetrahydrofuran-3-yl)methyl)imidazo[1,2-b]pyridazin-6-amine	325.4	*	–
3-(3-(4-(aminomethyl)phenyl)imidazo[1,2-b]pyridazin-6-yl)-N-isobutylbenzamide	399.5	**	–
3-(3-methoxypyridin-4-yl)-N-(4,4,4-trifluorobutyl)imidazo[1,2-b]pyridazin-6-amine	351.3	***	–
3-(4-(((2-methoxyethyl)amino)methyl)phenyl)-N-pentylimidazo[1,2-b]pyridazin-6-amine	367.5	*	–
3-(4-((2-(dimethylamino)ethoxy)methyl)phenyl)-N-(3,3-dimethylbutyl)imidazo[1,2-b]pyridazin-6-amine	395.5	**	–
3-(4-((2-aminoethoxy)methyl)phenyl)-N-(3,3-dimethylbutyl)imidazo[1,2-b]pyridazin-6-amine	367.5	**	–
3-(4-(1H-tetrazol-5-yl)phenyl)-N-butylimidazo[1,2-b]pyridazin-6-amine	334.4	*	–

3-(4-(2-aminoethoxy)phenyl)-N-butylimidazo[1,2-b]pyridazin-6-amine	325.4	**	-
3-(4-(3-aminopropoxy)phenyl)-N-(3,3-dimethylbutyl)imidazo[1,2-b]pyridazin-6-amine	367.5	**	-
3-(4-(3-aminopropoxy)phenyl)-N-(3-phenylpropyl)imidazo[1,2-b]pyridazin-6-amine	401.5	**	-
3-(4-(aminomethyl)-3-fluorophenyl)-N-butylimidazo[1,2-b]pyridazin-6-amine	313.4	*	-
3-(4-(aminomethyl)phenyl)-N-((1-(2,2,2-trifluoroethyl)pyrrolidin-2-yl)methyl)imidazo[1,2-b]pyridazin-6-amine	404.4	**	***
3-(4-(aminomethyl)phenyl)-N-((tetrahydrofuran-3-yl)methyl)imidazo[1,2-b]pyridazin-6-amine	323.4	*	-
3-(4-(aminomethyl)phenyl)-N-(1-oxaspiro[4.4]nonan-3-yl)imidazo[1,2-b]pyridazin-6-amine	363.5	**	-
3-(4-(aminomethyl)phenyl)-N-(2-(cyclopentyloxy)ethyl)imidazo[1,2-b]pyridazin-6-amine	351.4	**	-
3-(4-(aminomethyl)phenyl)-N-(2-(neopentyloxy)ethyl)imidazo[1,2-b]pyridazin-6-amine	353.5	**	-
3-(4-(aminomethyl)phenyl)-N-(2-(tert-butoxy)ethyl)imidazo[1,2-b]pyridazin-6-amine	339.4	**	-
3-(4-(aminomethyl)phenyl)-N-(2-(trifluoromethoxy)phenethyl)imidazo[1,2-b]pyridazin-6-amine	427.4	***	-
3-(4-(aminomethyl)phenyl)-N-(2-cyclohexylethyl)imidazo[1,2-b]pyridazin-6-amine	349.5	**	-
3-(4-(aminomethyl)phenyl)-N-(2-cyclopropylethyl)imidazo[1,2-b]pyridazin-6-amine	307.4	*	-
3-(4-(aminomethyl)phenyl)-N-(2-ethoxyphenethyl)imidazo[1,2-b]pyridazin-6-amine	387.5	**	-
3-(4-(aminomethyl)phenyl)-N-(2-fluorophenethyl)imidazo[1,2-b]pyridazin-6-amine	361.4	**	-
3-(4-(aminomethyl)phenyl)-N-(2-isobutoxyethyl)imidazo[1,2-b]pyridazin-6-amine	339.4	**	-
3-(4-(aminomethyl)phenyl)-N-(2-isopropoxyethyl)imidazo[1,2-b]pyridazin-6-amine	325.4	**	-
3-(4-(aminomethyl)phenyl)-N-(2-methoxyphenethyl)imidazo[1,2-b]pyridazin-6-amine	373.5	***	-
3-(4-(aminomethyl)phenyl)-N-(2-methylbutyl)imidazo[1,2-b]pyridazin-6-amine	309.4	*	-
3-(4-(aminomethyl)phenyl)-N-(2-phenoxyethyl)imidazo[1,2-b]pyridazin-6-amine	359.4	*	-
3-(4-(aminomethyl)phenyl)-N-(3-(2-fluorophenyl)propyl)imidazo[1,2-b]pyridazin-6-amine	375.4	**	-

3-(4-(aminomethyl)phenyl)-N-(3-(3-fluorophenyl)propyl)imidazo[1,2-b]pyridazin-6-amine	375.4	**	–
3-(4-(aminomethyl)phenyl)-N-(3-(4-fluorophenyl)propyl)imidazo[1,2-b]pyridazin-6-amine	375.4	**	–
3-(4-(aminomethyl)phenyl)-N-(3-(cyclopentyloxy)propyl)imidazo[1,2-b]pyridazin-6-amine	365.5	**	–
3-(4-(aminomethyl)phenyl)-N-(3-(tert-butoxy)propyl)imidazo[1,2-b]pyridazin-6-amine	353.5	**	–
3-(4-(aminomethyl)phenyl)-N-(3-(trifluoromethyl)phenethyl)imidazo[1,2-b]pyridazin-6-amine	411.4	**	–
3-(4-(aminomethyl)phenyl)-N-(3,3-dimethylbutyl)imidazo[1,2-b]pyridazin-6-amine	323.4	**	–
3-(4-(aminomethyl)phenyl)-N-(3-fluorophenethyl)imidazo[1,2-b]pyridazin-6-amine	361.4	**	–
3-(4-(aminomethyl)phenyl)-N-(3-fluoropropyl)imidazo[1,2-b]pyridazin-6-amine	299.3	*	–
3-(4-(aminomethyl)phenyl)-N-(3-methoxyphenethyl)imidazo[1,2-b]pyridazin-6-amine	373.5	**	–
3-(4-(aminomethyl)phenyl)-N-(3-phenylpropyl)imidazo[1,2-b]pyridazin-6-amine	357.5	**	–
3-(4-(aminomethyl)phenyl)-N-(4-fluorobutyl)imidazo[1,2-b]pyridazin-6-amine	313.4	**	–
3-(4-(aminomethyl)phenyl)-N-(4-fluorophenethyl)imidazo[1,2-b]pyridazin-6-amine	361.4	*	–
3-(4-(aminomethyl)phenyl)-N-(4-methoxyphenethyl)imidazo[1,2-b]pyridazin-6-amine	373.5	**	–
3-(4-(aminomethyl)phenyl)-N-(4-phenylbutyl)imidazo[1,2-b]pyridazin-6-amine	371.5	**	–
3-(4-(aminomethyl)phenyl)-N-(5-fluoropentyl)imidazo[1,2-b]pyridazin-6-amine	327.4	*	–
3-(4-(aminomethyl)phenyl)-N-(cyclobutylmethyl)imidazo[1,2-b]pyridazin-6-amine	307.4	*	–
3-(4-(aminomethyl)phenyl)-N-(cyclohexylmethyl)imidazo[1,2-b]pyridazin-6-amine	335.4	*	–
3-(4-(aminomethyl)phenyl)-N-(cyclopentylmethyl)imidazo[1,2-b]pyridazin-6-amine	321.4	*	–
3-(4-(aminomethyl)phenyl)-N-(cyclopropylmethyl)imidazo[1,2-b]pyridazin-6-amine	293.4	*	–
3-(4-(aminomethyl)phenyl)-N-butyl-7-methylimidazo[1,2-b]pyridazin-6-amine	309.4	**	–
3-(4-(aminomethyl)phenyl)-N-butylimidazo[1,2-b]pyridazin-6-amine	295.4	*	–

3-(4-(aminomethyl)phenyl)-N-butyl-N-methylimidazo[1,2-b]pyridazin-6-amine	309.4	*	–
3-(4-(aminomethyl)phenyl)-N-cyclohexylimidazo[1,2-b]pyridazin-6-amine	321.4	*	–
3-(4-(aminomethyl)phenyl)-N-isobutylimidazo[1,2-b]pyridazin-6-amine	295.4	*	–
3-(4-(aminomethyl)phenyl)-N-isopentylimidazo[1,2-b]pyridazin-6-amine	309.4	*	–
3-(4-(aminomethyl)phenyl)-N-neopentylimidazo[1,2-b]pyridazin-6-amine	309.4	**	–
3-(4-(aminomethyl)phenyl)-N-pentylimidazo[1,2-b]pyridazin-6-amine	309.4	*	–
3-(4-(aminomethyl)phenyl)-N-phenethylimidazo[1,2-b]pyridazin-6-amine	343.4	*	–
3-(4-(aminomethyl)phenyl)-N-propylimidazo[1,2-b]pyridazin-6-amine	281.4	*	–
3-(6-((2-(cyclopentyloxy)ethyl)amino)imidazo[1,2-b]pyridazin-3-yl)phenol	338.4	*	***
3-(benzo[d][1,3]dioxol-5-yl)-N-(2-(cyclopentyloxy)ethyl)imidazo[1,2-b]pyridazin-6-amine	366.4	*	**
3,3-dimethyl-1-(4-(3-phenylimidazo[1,2-b]pyridazin-6-yl)piperazin-1-yl)butan-1-one	377.5	**	***
4-((3-(4-(aminomethyl)phenyl)imidazo[1,2-b]pyridazin-6-yl)amino)-2-methylbutan-2-ol	325.4	**	–
4-(3-bromoimidazo[1,2-b]pyridazin-6-yl)-N-(tert-butyl)piperazine-1-carboxamide	381.3	**	***
4-(6-((2-(N,3,3-trimethylbutanamido)ethyl)amino)imidazo[1,2-b]pyridazin-3-yl)benzamide	408.5	**	–
4-(6-((2-(tert-butoxy)ethyl)amino)imidazo[1,2-b]pyridazin-3-yl)benzamide	353.4	**	–
4-(6-((2-(tert-butoxy)ethyl)amino)imidazo[1,2-b]pyridazin-3-yl)-N-(2-(diethylamino)ethyl)benzamide	452.6	**	–
4-(6-((2-(tert-butoxy)ethyl)amino)imidazo[1,2-b]pyridazin-3-yl)-N-methylbenzamide	367.4	**	–
4-(6-((2-(trifluoromethoxy)phenethyl)amino)imidazo[1,2-b]pyridazin-3-yl)benzamide	441.4	***	–
4-(6-((2-ethoxyphenethyl)amino)imidazo[1,2-b]pyridazin-3-yl)-N-methylbenzamide	415.5	***	–
4-(6-((2-isobutoxyethyl)amino)imidazo[1,2-b]pyridazin-3-yl)-N-(2-(pyrrolidin-1-yl)ethyl)benzamide	450.6	**	–
4-(6-((2-isopropoxyethyl)amino)imidazo[1,2-b]pyridazin-3-yl)-N-(2-(pyrrolidin-1-yl)ethyl)benzamide	436.5	**	–

4-(6-((2-methoxyphenethyl)amino)imidazo[1,2-b]pyridazin-3-yl)benzamide	387.4	***	-
4-(6-((3-(trifluoromethyl)phenethyl)amino)imidazo[1,2-b]pyridazin-3-yl)benzamide	425.4	**	-
4-(6-((3-methoxyphenethyl)amino)imidazo[1,2-b]pyridazin-3-yl)benzamide	387.4	**	-
4-(6-(butylamino)imidazo[1,2-b]pyridazin-3-yl)-2-fluoro-N-(2-(methylamino)ethyl)benzamide	384.5	**	-
4-(6-(butylamino)imidazo[1,2-b]pyridazin-3-yl)benzamide	309.4	**	-
4-(6-(butylamino)imidazo[1,2-b]pyridazin-3-yl)-N-(2-(diethylamino)ethyl)benzamide	408.5	***	-
4-(6-(butylamino)imidazo[1,2-b]pyridazin-3-yl)-N-(2-(dimethylamino)ethyl)benzamide	380.5	**	-
4-(6-(butylamino)imidazo[1,2-b]pyridazin-3-yl)-N-(2-(methylamino)ethyl)benzamide	366.5	**	-
4-(6-(butylamino)imidazo[1,2-b]pyridazin-3-yl)-N-(2-(pyrrolidin-1-yl)ethyl)benzamide	406.5	**	-
5-(3-(4-(aminomethyl)phenyl)imidazo[1,2-b]pyridazin-6-yl)-N-isobutylnicotinamide	400.5	**	-
5-(6-((2-(cyclopentyloxy)ethyl)amino)imidazo[1,2-b]pyridazin-3-yl)thiophene-2-carbonitrile	353.4	**	***
5-(6-(butylamino)imidazo[1,2-b]pyridazin-3-yl)thiophene-2-carboxamide	315.4	*	-
5-(6-(propylamino)imidazo[1,2-b]pyridazin-3-yl)thiophene-2-carbaldehyde	286.4	*	-
6-(butylamino)-N-(1H-pyrazol-4-yl)imidazo[1,2-b]pyridazine-3-carboxamide	299.3	*	-
6-(butylamino)-N-(4-((2-(dimethylamino)ethyl)carbamoyl)phenyl)imidazo[1,2-b]pyridazine-3-carboxamide	423.5	**	-
cyclopentyl (2-((3-(4-carbamoylphenyl)imidazo[1,2-b]pyridazin-6-yl)amino)ethyl)(isopropyl)carbamate	450.5	**	-
ethyl (2-((3-(3-methoxypyridin-4-yl)imidazo[1,2-b]pyridazin-6-yl)amino)ethyl)(methyl)carbamate	370.4	***	-
ethyl (2-((3-(4-(isopentylcarbamoyl)phenyl)imidazo[1,2-b]pyridazin-6-yl)amino)ethyl)(methyl)carbamate	452.5	**	-
ethyl (2-((3-(4-(tert-butylcarbamoyl)phenyl)imidazo[1,2-b]pyridazin-6-yl)amino)ethyl)(methyl)carbamate	438.5	**	-
ethyl (2-((3-(4-carbamoylphenyl)imidazo[1,2-b]pyridazin-6-yl)amino)ethyl)(methyl)carbamate	382.4	**	-
ethyl (2-((3-(4-carbamoylphenyl)imidazo[1,2-b]pyridazin-6-yl)amino)ethyl)(isopropyl)carbamate	410.5	**	-
ethyl (3-((3-(5-acetylthiophen-2-yl)imidazo[1,2-b]pyridazin-6-yl)amino)propyl)(methyl)carbamate	401.5	*	-

ethyl 4-((3-(4-(aminomethyl)phenyl)imidazo[1,2-b]pyridazin-6-yl)amino)butanoate	353.4	**	-
ethyl 4-((3-(5-acetylthiophen-2-yl)imidazo[1,2-b]pyridazin-6-yl)amino)butanoate	372.4	**	-
ethyl 4-(3-(methylcarbamoyl)imidazo[1,2-b]pyridazin-6-yl)piperazine-1-carboxylate	332.4	-	**
ethyl 4-(3-phenylimidazo[1,2-b]pyridazin-6-yl)piperazine-1-carboxylate	351.4	**	***
ethyl isopropyl(2-((3-(3-methoxypyridin-4-yl)imidazo[1,2-b]pyridazin-6-yl)amino)ethyl)carbamate	398.5	***	-
ethyl methyl(2-((3-(4-(methylcarbamoyl)phenyl)imidazo[1,2-b]pyridazin-6-yl)amino)ethyl)carbamate	396.4	**	-
ethyl methyl(2-((3-(5-(methylcarbamoyl)thiophen-2-yl)imidazo[1,2-b]pyridazin-6-yl)amino)ethyl)carbamate	402.5	**	-
isobutyl (2-((3-(4-carbamoylphenyl)imidazo[1,2-b]pyridazin-6-yl)amino)ethyl)(methyl)carbamate	410.5	**	-
isobutyl isopropyl(2-((3-(3-methoxypyridin-4-yl)imidazo[1,2-b]pyridazin-6-yl)amino)ethyl)carbamate	426.5	**	-
isobutyl methyl(2-((3-(4-(methylcarbamoyl)phenyl)imidazo[1,2-b]pyridazin-6-yl)amino)ethyl)carbamate	424.5	**	-
isopropyl (2-((3-(1H-pyrazol-4-yl)imidazo[1,2-b]pyridazin-6-yl)amino)ethyl)(methyl)carbamate	343.4	**	-
isopropyl (2-((3-(2,4-dimethylthiazol-5-yl)imidazo[1,2-b]pyridazin-6-yl)amino)ethyl)(methyl)carbamate	388.5	**	-
isopropyl (2-((3-(2-aminopyridin-4-yl)imidazo[1,2-b]pyridazin-6-yl)amino)ethyl)(methyl)carbamate	369.4	**	-
isopropyl (2-((3-(2-fluorophenyl)imidazo[1,2-b]pyridazin-6-yl)amino)ethyl)(methyl)carbamate	371.4	**	-
isopropyl (2-((3-(2-methoxyphenyl)imidazo[1,2-b]pyridazin-6-yl)amino)ethyl)(methyl)carbamate	383.4	**	-
isopropyl (2-((3-(3-methoxypyridin-4-yl)imidazo[1,2-b]pyridazin-6-yl)amino)ethyl)(methyl)carbamate	384.4	**	-
isopropyl (2-((3-(3-methoxypyridin-4-yl)imidazo[1,2-b]pyridazin-6-yl)amino)ethyl)carbamate	370.4	**	-
isopropyl (2-((3-(4,5-difluoro-2-methoxyphenyl)imidazo[1,2-b]pyridazin-6-yl)amino)ethyl)(isopropyl)carbamate	447.5	**	-
isopropyl (2-((3-(4-carbamoylphenyl)imidazo[1,2-b]pyridazin-6-yl)amino)ethyl)(isopropyl)carbamate	424.5	**	-
isopropyl (2-((3-(4-carbamoylphenyl)imidazo[1,2-b]pyridazin-6-yl)amino)ethyl)(methyl)carbamate	396.4	***	-

isopropyl (2-((3-(4-fluoro-2-methoxyphenyl)imidazo[1,2-b]pyridazin-6-yl)amino)ethyl)(methyl)carbamate	401.4	**	-
isopropyl (2-((3-(5-fluoro-2-methoxyphenyl)imidazo[1,2-b]pyridazin-6-yl)amino)ethyl)(methyl)carbamate	401.4	***	-
isopropyl (2-((3-(5-fluoro-2-methoxyphenyl)imidazo[1,2-b]pyridazin-6-yl)amino)ethyl)(isopropyl)carbamate	429.5	**	-
isopropyl (3-((3-(4-(aminomethyl)phenyl)imidazo[1,2-b]pyridazin-6-yl)amino)propyl)(methyl)carbamate	396.5	**	-
isopropyl (3-((3-(5-acetylthiophen-2-yl)imidazo[1,2-b]pyridazin-6-yl)amino)propyl)(methyl)carbamate	415.5	**	-
isopropyl 4-(3-(2-(difluoromethoxy)phenyl)imidazo[1,2-b]pyridazin-6-yl)piperazine-1-carboxylate	431.4	**	***
isopropyl 4-(3-(2-(difluoromethoxy)pyridin-3-yl)imidazo[1,2-b]pyridazin-6-yl)piperazine-1-carboxylate	432.4	**	***
isopropyl 4-(3-(2,2-difluorobenzo[d][1,3]dioxol-4-yl)imidazo[1,2-b]pyridazin-6-yl)piperazine-1-carboxylate	445.4	*	***
isopropyl 4-(3-(2,3-dihydrobenzofuran-7-yl)imidazo[1,2-b]pyridazin-6-yl)piperazine-1-carboxylate	407.5	**	-
isopropyl 4-(3-(2,3-dimethoxyphenyl)imidazo[1,2-b]pyridazin-6-yl)piperazine-1-carboxylate	425.5	**	***
isopropyl 4-(3-(2,5-dimethoxyphenyl)imidazo[1,2-b]pyridazin-6-yl)piperazine-1-carboxylate	425.5	**	***
isopropyl 4-(3-(2-ethoxyphenyl)imidazo[1,2-b]pyridazin-6-yl)piperazine-1-carboxylate	409.5	**	***
isopropyl 4-(3-(2-fluoro-3-methoxyphenyl)imidazo[1,2-b]pyridazin-6-yl)piperazine-1-carboxylate	413.4	**	***
isopropyl 4-(3-(2-fluorophenyl)imidazo[1,2-b]pyridazin-6-yl)piperazine-1-carboxylate	383.4	**	***
isopropyl 4-(3-(2-methoxyphenyl)imidazo[1,2-b]pyridazin-6-yl)piperazine-1-carboxylate	395.5	***	***
isopropyl 4-(3-(2-methoxypyridin-3-yl)imidazo[1,2-b]pyridazin-6-yl)piperazine-1-carboxylate	396.4	***	***
isopropyl 4-(3-(2-methoxypyridin-4-yl)imidazo[1,2-b]pyridazin-6-yl)piperazine-1-carboxylate	396.4	**	***
isopropyl 4-(3-(2-oxo-1,2-dihydropyridin-3-yl)imidazo[1,2-b]pyridazin-6-yl)piperazine-1-carboxylate	382.4	**	***
isopropyl 4-(3-(3-chlorophenyl)imidazo[1,2-b]pyridazin-6-yl)piperazine-1-carboxylate	399.9	*	***
isopropyl 4-(3-(3-methoxyphenyl)imidazo[1,2-b]pyridazin-6-yl)piperazine-1-carboxylate	395.5	**	***
isopropyl 4-(3-(3-methoxypyridin-4-yl)imidazo[1,2-b]pyridazin-6-yl)piperazine-1-carboxylate	396.4	***	-
isopropyl 4-(3-(benzo[d][1,3]dioxol-4-yl)imidazo[1,2-b]pyridazin-6-yl)piperazine-1-carboxylate	409.4	**	-

isopropyl 4-(3-(methylcarbamoyl)imidazo[1,2-b]pyridazin-6-yl)piperazine-1-carboxylate	346.4	–	**
isopropyl 4-(3-(pyridin-4-yl)imidazo[1,2-b]pyridazin-6-yl)piperazine-1-carboxylate	366.4	**	–
isopropyl 4-(3-phenylimidazo[1,2-b]pyridazin-6-yl)piperazine-1-carboxylate	365.4	**	–
isopropyl ethyl(2-((3-(3-methoxypyridin-4-yl)imidazo[1,2-b]pyridazin-6-yl)amino)ethyl)carbamate	398.5	**	–
isopropyl ethyl(2-((3-(4-(methylcarbamoyl)phenyl)imidazo[1,2-b]pyridazin-6-yl)amino)ethyl)carbamate	424.5	**	–
isopropyl isopropyl(2-((3-(2-methoxyphenyl)imidazo[1,2-b]pyridazin-6-yl)amino)ethyl)carbamate	411.5	**	–
isopropyl isopropyl(2-((3-(3-methoxypyridin-4-yl)imidazo[1,2-b]pyridazin-6-yl)amino)ethyl)carbamate	412.5	***	–
isopropyl isopropyl(2-((3-(4-(methylcarbamoyl)phenyl)imidazo[1,2-b]pyridazin-6-yl)amino)ethyl)carbamate	438.5	**	–
isopropyl isopropyl(2-((3-(pyridin-4-yl)imidazo[1,2-b]pyridazin-6-yl)amino)ethyl)carbamate	382.5	**	–
isopropyl isopropyl(2-((3-phenylimidazo[1,2-b]pyridazin-6-yl)amino)ethyl)carbamate	381.5	**	–
isopropyl methyl(2-((3-(4-(methylcarbamoyl)phenyl)imidazo[1,2-b]pyridazin-6-yl)amino)ethyl)carbamate	410.5	**	–
isopropyl methyl(2-((3-(4-(pyrrolidin-2-yl)phenyl)imidazo[1,2-b]pyridazin-6-yl)amino)ethyl)carbamate	422.5	***	–
isopropyl methyl(2-((3-(thiazol-4-yl)imidazo[1,2-b]pyridazin-6-yl)amino)ethyl)carbamate	360.4	**	–
methyl isopropyl(2-((3-(3-methoxypyridin-4-yl)imidazo[1,2-b]pyridazin-6-yl)amino)ethyl)carbamate	384.4	***	–
N-((1R,2S)-2-aminocyclohexyl)-4-(6-(butylamino)imidazo[1,2-b]pyridazin-3-yl)benzamide	406.5	**	–
N-(2-((3-(4-cyanophenyl)imidazo[1,2-b]pyridazin-6-yl)amino)ethyl)-N,3,3-trimethylbutanamide	390.5	**	–
N-(2-((3-(4-cyanophenyl)imidazo[1,2-b]pyridazin-6-yl)amino)ethyl)-N-methylpivalamide	376.5	**	–
N-(2-(cyclopentyloxy)ethyl)-3-(1H-pyrazol-3-yl)imidazo[1,2-b]pyridazin-6-amine	312.4	*	**
N-(2-(cyclopentyloxy)ethyl)-3-(2-fluoropyridin-3-yl)imidazo[1,2-b]pyridazin-6-amine	341.4	*	***
N-(2-(cyclopentyloxy)ethyl)-3-(2-methoxypyridin-3-yl)imidazo[1,2-b]pyridazin-6-amine	353.4	**	–

N-(2-(cyclopentyloxy)ethyl)-3-(3-fluoropyridin-4-yl)imidazo[1,2-b]pyridazin-6-amine	341.4	**	–
N-(2-(cyclopentyloxy)ethyl)-3-(3-methoxyphenyl)imidazo[1,2-b]pyridazin-6-amine	352.4	–	**
N-(2-(cyclopentyloxy)ethyl)-3-(3-methoxypyridin-4-yl)imidazo[1,2-b]pyridazin-6-amine	353.4	*	–
N-(2-(cyclopentyloxy)ethyl)-3-(4-(pyrrolidin-2-yl)phenyl)imidazo[1,2-b]pyridazin-6-amine	391.5	**	–
N-(2-(cyclopentyloxy)ethyl)-3-(4-methylthiophen-2-yl)imidazo[1,2-b]pyridazin-6-amine	342.5	–	**
N-(2-(cyclopentyloxy)ethyl)-3-(5-methoxypyridin-3-yl)imidazo[1,2-b]pyridazin-6-amine	353.4	**	***
N-(2-(cyclopentyloxy)ethyl)-3-(5-methylthiophen-2-yl)imidazo[1,2-b]pyridazin-6-amine	342.5	–	**
N-(2-(cyclopentyloxy)ethyl)-3-(pyridin-2-yl)imidazo[1,2-b]pyridazin-6-amine	323.4	**	***
N-(2-(cyclopentyloxy)ethyl)-3-(thiophen-2-yl)imidazo[1,2-b]pyridazin-6-amine	328.4	–	***
N-(2-(cyclopentyloxy)ethyl)-3-(thiophen-3-yl)imidazo[1,2-b]pyridazin-6-amine	328.4	–	**
N-(2-(diethylamino)ethyl)-4-(6-((2-isobutoxyethyl)amino)imidazo[1,2-b]pyridazin-3-yl)benzamide	452.6	**	–
N-(2-(diethylamino)ethyl)-4-(6-((2-isopropoxyethyl)amino)imidazo[1,2-b]pyridazin-3-yl)benzamide	438.6	**	–
N-(2-(methylamino)ethyl)-4-(6-((3-(N-methylpivalamido)propyl)amino)imidazo[1,2-b]pyridazin-3-yl)benzamide	465.6	*	–
N-(2-(tert-butoxy)ethyl)-3-(3-methoxypyridin-4-yl)imidazo[1,2-b]pyridazin-6-amine	341.4	**	–
N-(2-(tert-butoxy)ethyl)-3-(4-(pyrrolidin-2-yl)phenyl)imidazo[1,2-b]pyridazin-6-amine	379.5	**	–
N-(2-aminoethyl)-4-(6-((3-(tert-butoxy)propyl)amino)imidazo[1,2-b]pyridazin-3-yl)benzamide	410.5	*	–
N-(2-aminoethyl)-4-(6-((3,3-dimethylbutyl)amino)imidazo[1,2-b]pyridazin-3-yl)benzamide	380.5	*	–
N-(2-aminoethyl)-4-(6-((3-phenylpropyl)amino)imidazo[1,2-b]pyridazin-3-yl)benzamide	414.5	*	–
N-(2-aminoethyl)-4-(6-(butylamino)imidazo[1,2-b]pyridazin-3-yl)-2-methoxybenzamide	382.5	*	–

N-(2-aminoethyl)-4-(6-(butylamino)imidazo[1,2-b]pyridazin-3-yl)-2-fluorobenzamide	370.4	**	–
N-(2-aminoethyl)-4-(6-(butylamino)imidazo[1,2-b]pyridazin-3-yl)-3-fluorobenzamide	370.4	*	–
N-(2-aminoethyl)-4-(6-(butylamino)imidazo[1,2-b]pyridazin-3-yl)benzamide	352.4	*	–
N-(2-aminopropyl)-4-(6-(butylamino)imidazo[1,2-b]pyridazin-3-yl)benzamide	366.5	*	–
N-(2-ethoxyphenethyl)-3-(3-methoxypyridin-4-yl)imidazo[1,2-b]pyridazin-6-amine	389.5	**	–
N-(2-isobutoxyethyl)-3-(2-methoxyphenyl)imidazo[1,2-b]pyridazin-6-amine	340.4	*	–
N-(2-isobutoxyethyl)-3-(3-methoxypyridin-4-yl)imidazo[1,2-b]pyridazin-6-amine	341.4	**	–
N-(2-isobutoxyethyl)-3-(pyridin-4-yl)imidazo[1,2-b]pyridazin-6-amine	311.4	*	–
N-(2-isopropoxyethyl)-3-(1H-pyrazol-3-yl)imidazo[1,2-b]pyridazin-6-amine	286.3	*	–
N-(2-isopropoxyethyl)-3-(3-methoxypyridin-4-yl)imidazo[1,2-b]pyridazin-6-amine	327.4	***	–
N-(2-isopropoxyethyl)-3-(4-(pyrrolidin-2-yl)phenyl)imidazo[1,2-b]pyridazin-6-amine	365.5	**	–
N-(2-isopropoxyethyl)-3-(isothiazol-5-yl)imidazo[1,2-b]pyridazin-6-amine	303.4	**	–
N-(2-isopropoxyethyl)-3-(thiazol-4-yl)imidazo[1,2-b]pyridazin-6-amine	303.4	*	–
N-(3-((3-(4-(aminomethyl)phenyl)imidazo[1,2-b]pyridazin-6-yl)amino)propyl)-N-methylpivalamide	394.5	*	–
N-(3-(6-((2-(cyclopentyloxy)ethyl)amino)imidazo[1,2-b]pyridazin-3-yl)phenyl)acetamide	379.5	**	**
N-(3-(tert-butoxy)propyl)-3-(3-methoxypyridin-4-yl)imidazo[1,2-b]pyridazin-6-amine	355.4	*	–
N-(3,3-dimethylbutyl)-3-(4-((2-(methylamino)ethoxy)methyl)phenyl)imidazo[1,2-b]pyridazin-6-amine	381.5	**	–
N-(3,3-dimethylbutyl)-3-(4-(pyrrolidin-2-yl)phenyl)imidazo[1,2-b]pyridazin-6-amine	363.5	*	–
N-(3-aminopropyl)-4-(6-(butylamino)imidazo[1,2-b]pyridazin-3-yl)benzamide	366.5	*	–
N-(3-fluoropropyl)-3-(4-(pyrrolidin-2-yl)phenyl)imidazo[1,2-b]pyridazin-6-amine	339.4	**	–
N-(3-phenylpropyl)-3-(4-(pyrrolidin-2-yl)phenyl)imidazo[1,2-b]pyridazin-6-amine	397.5	*	–

N-(4-(2-aminoethoxy)phenyl)-6-(butylamino)imidazo[1,2-b]pyridazine-3-carboxamide	368.4	*	–
N-(4-(aminomethyl)phenyl)-6-(butylamino)imidazo[1,2-b]pyridazine-3-carboxamide	338.4	*	–
N-(cyclopentylmethyl)-3-(3-methoxypyridin-4-yl)imidazo[1,2-b]pyridazin-6-amine	323.4	**	–
N-(tert-butyl)-4-(3-phenylimidazo[1,2-b]pyridazin-6-yl)piperazine-1-carboxamide	378.5	**	***
N,N-dimethyl-3-(6-(4-(pyrrolidine-1-carbonyl)piperazin-1-yl)imidazo[1,2-b]pyridazin-3-yl)benzamide	447.5	**	***
N1-(3-(4-(aminomethyl)phenyl)imidazo[1,2-b]pyridazin-6-yl)-N2-methyl-N2-phenylethane-1,2-diamine	372.5	**	–
N1-(3-(4-(aminomethyl)phenyl)imidazo[1,2-b]pyridazin-6-yl)-N3-methyl-N3-phenylpropane-1,3-diamine	386.5	**	–
N1-(3-(5-(aminomethyl)thiophen-2-yl)imidazo[1,2-b]pyridazin-6-yl)-N3-methyl-N3-phenylpropane-1,3-diamine	392.5	*	–
N1-(4-(6-((3,3-dimethylbutyl)amino)imidazo[1,2-b]pyridazin-3-yl)benzyl)ethane-1,2-diamine	366.5	*	–
N1-(4-(6-(butylamino)imidazo[1,2-b]pyridazin-3-yl)benzyl)ethane-1,2-diamine	338.4	*	–
N1-(4-(6-(butylamino)imidazo[1,2-b]pyridazin-3-yl)benzyl)propane-1,3-diamine	352.5	*	–
N-butyl-3-(1H-pyrazol-3-yl)imidazo[1,2-b]pyridazin-6-amine	256.3	**	–
N-butyl-3-(2,4-dimethylthiazol-5-yl)imidazo[1,2-b]pyridazin-6-amine	301.4	**	–
N-butyl-3-(3-methoxypyridin-4-yl)imidazo[1,2-b]pyridazin-6-amine	297.4	**	–
N-butyl-3-(4-((((tetrahydrofuran-2-yl)methyl)amino)methyl)phenyl)imidazo[1,2-b]pyridazin-6-amine	379.5	*	–
N-butyl-3-(4-(((2-methoxyethyl)amino)methyl)phenyl)imidazo[1,2-b]pyridazin-6-amine	353.5	*	–
N-butyl-3-(4-(((cyclopropylmethyl)amino)methyl)phenyl)imidazo[1,2-b]pyridazin-6-amine	349.5	*	–
N-butyl-3-(4-((isopropylamino)methyl)phenyl)imidazo[1,2-b]pyridazin-6-amine	337.5	*	–
N-butyl-3-(4-((propylamino)methyl)phenyl)imidazo[1,2-b]pyridazin-6-amine	337.5	*	–
N-butyl-3-(4-((tert-butylamino)methyl)-2-fluorophenyl)imidazo[1,2-b]pyridazin-6-amine	369.5	*	–

N-butyl-3-(4-((tert-butylamino)methyl)-3-fluorophenyl)imidazo[1,2-b]pyridazin-6-amine	369.5	**	-
N-butyl-3-(4-(pyrrolidin-2-yl)phenyl)imidazo[1,2-b]pyridazin-6-amine	335.4	*	-
N-butyl-3-(isoindolin-5-yl)imidazo[1,2-b]pyridazin-6-amine	307.4	*	-
N-butyl-3-(isoquinolin-6-yl)imidazo[1,2-b]pyridazin-6-amine	317.4	**	-
N-cyclohexyl-3-(3-methoxypyridin-4-yl)imidazo[1,2-b]pyridazin-6-amine	323.4		***
N-isobutyl-3-(3-(3-methoxypyridin-4-yl)imidazo[1,2-b]pyridazin-6-yl)benzamide	401.5	**	-
N-isobutyl-3-(3-(4-(methylcarbamoyl)phenyl)imidazo[1,2-b]pyridazin-6-yl)benzamide	427.5	**	-
N-isopentyl-3-(3-methoxypyridin-4-yl)imidazo[1,2-b]pyridazin-6-amine	311.4	**	-
N-isopropyl-4-(3-(2-methoxyphenyl)imidazo[1,2-b]pyridazin-6-yl)-N-methylpiperazine-1-carboxamide	408.5	**	***
N-isopropyl-4-(3-(2-methoxyphenyl)imidazo[1,2-b]pyridazin-6-yl)piperazine-1-carboxamide	394.5	*	***
N-isopropyl-4-(3-phenylimidazo[1,2-b]pyridazin-6-yl)piperazine-1-carboxamide	364.4	**	***
N-methyl-4-(6-((2-(trifluoromethoxy)phenethyl)amino)imidazo[1,2-b]pyridazin-3-yl)benzamide	455.4	***	-
N-pentyl-3-(4-(pyrrolidin-2-yl)phenyl)imidazo[1,2-b]pyridazin-6-amine	349.5	*	-
piperidin-1-yl(4-(3-(pyridin-2-yl)imidazo[1,2-b]pyridazin-6-yl)piperazin-1-yl)methanone	391.5	**	***
propyl isopropyl(2-((3-(3-methoxypyridin-4-yl)imidazo[1,2-b]pyridazin-6-yl)amino)ethyl)carbamate	412.5	*	-
S-isopropyl 4-(3-phenylimidazo[1,2-b]pyridazin-6-yl)piperazine-1-carbothioate	381.5	*	***
tert-butyl (1-(3-(2-methoxyphenyl)imidazo[1,2-b]pyridazin-6-yl)pyrrolidin-3-yl)(methyl)carbamate	423.5	*	***
tert-butyl (1-(3-(2-methoxypyridin-3-yl)imidazo[1,2-b]pyridazin-6-yl)pyrrolidin-3-yl)(methyl)carbamate	424.5	**	***
tert-butyl (1-(3-(2-methoxypyridin-3-yl)imidazo[1,2-b]pyridazin-6-yl)azetidin-3-yl)(methyl)carbamate	410.5	-	*
tert-butyl (2-((3-(2-aminopyridin-4-yl)imidazo[1,2-b]pyridazin-6-yl)amino)ethyl)(methyl)carbamate	383.4	***	-
tert-butyl (2-((3-(2-fluorophenyl)imidazo[1,2-b]pyridazin-6-yl)amino)ethyl)(methyl)carbamate	385.4	**	-
tert-butyl (2-((3-(2-fluoropyridin-4-yl)imidazo[1,2-b]pyridazin-6-yl)amino)ethyl)(methyl)carbamate	386.4	**	-

tert-butyl (2-((3-(2-methoxyphenyl)imidazo[1,2-b]pyridazin-6-yl)amino)ethyl)(methyl)carbamate	397.5	**	-
tert-butyl (2-((3-(3-carbamoylphenyl)imidazo[1,2-b]pyridazin-6-yl)amino)ethyl)(methyl)carbamate	410.5	**	-
tert-butyl (2-((3-(3-methoxyphenyl)imidazo[1,2-b]pyridazin-6-yl)amino)ethyl)(methyl)carbamate	397.5	**	-
tert-butyl (2-((3-(3-methoxypyridin-4-yl)imidazo[1,2-b]pyridazin-6-yl)amino)ethyl)(methyl)carbamate	398.5	*	-
tert-butyl (2-((3-(4-(aminomethyl)phenyl)imidazo[1,2-b]pyridazin-6-yl)amino)ethyl)carbamate	382.5	**	-
tert-butyl (2-((3-(4-(cyanomethyl)phenyl)imidazo[1,2-b]pyridazin-6-yl)amino)ethyl)(methyl)carbamate	406.5	**	-
tert-butyl (2-((3-(4-carbamoylphenyl)imidazo[1,2-b]pyridazin-6-yl)amino)ethyl)(methyl)carbamate	410.5	**	***
tert-butyl (2-((3-(4-carbamoylphenyl)imidazo[1,2-b]pyridazin-6-yl)amino)ethyl)(isopropyl)carbamate	438.5	***	-
tert-butyl (2-((3-(4-cyanophenyl)imidazo[1,2-b]pyridazin-6-yl)amino)ethyl)(methyl)carbamate	392.5	**	-
tert-butyl (2-((3-(5-acetylthiophen-2-yl)imidazo[1,2-b]pyridazin-6-yl)amino)ethyl)(methyl)carbamate	415.5	***	-
tert-butyl (3-((3-(4-(aminomethyl)phenyl)imidazo[1,2-b]pyridazin-6-yl)amino)propyl)(methyl)carbamate	410.5	**	-
tert-butyl (3-((3-(5-acetylthiophen-2-yl)imidazo[1,2-b]pyridazin-6-yl)amino)propyl)(methyl)carbamate	429.5	**	-
tert-butyl 2-(2-((3-(4-(aminomethyl)phenyl)imidazo[1,2-b]pyridazin-6-yl)amino)ethyl)pyrrolidine-1-carboxylate	436.5	***	-
tert-butyl 2-(2-((3-(4-carbamoylphenyl)imidazo[1,2-b]pyridazin-6-yl)amino)ethyl)pyrrolidine-1-carboxylate	450.5	**	-
tert-butyl 4-(3-(3-methoxypyridin-4-yl)imidazo[1,2-b]pyridazin-6-yl)piperazine-1-carboxylate	410.5	***	-
tert-butyl 4-(3-chloroimidazo[1,2-b]pyridazin-6-yl)piperazine-1-carboxylate	337.8	**	-
tert-butyl 4-(3-iodoimidazo[1,2-b]pyridazin-6-yl)piperazine-1-carboxylate	429.3	**	***
tert-butyl 4-(3-phenylimidazo[1,2-b]pyridazin-6-yl)piperazine-1-carboxylate	379.5	**	***
tert-butyl isopropyl(2-((3-(3-methoxypyridin-4-yl)imidazo[1,2-b]pyridazin-6-yl)amino)ethyl)carbamate	426.5	**	-
tert-butyl methyl(1-(3-phenylimidazo[1,2-b]pyridazin-6-yl)pyrrolidin-3-yl)carbamate	393.5	**	**
tert-butyl methyl(2-((3-(4-(methylcarbamoyl)phenyl)imidazo[1,2-b]pyridazin-6-yl)amino)ethyl)carbamate	424.5	**	-

tert-butyl methyl(2-((3-(4-(pyrrolidin-2-yl)phenyl)imidazo[1,2-b]pyridazin-6-yl)amino)ethyl)carbamate	436.5	***	–
tert-butyl methyl(2-((3-(pyridin-4-yl)imidazo[1,2-b]pyridazin-6-yl)amino)ethyl)carbamate	368.4	**	–
tert-butyl methyl(2-((3-phenylimidazo[1,2-b]pyridazin-6-yl)amino)ethyl)carbamate	367.4	**	–

5.4.6. **Pyrazolo[1,5-a]pyrimidine-based Inhibitor In Vitro Data**

In vitro data obtained for various compounds of the invention are provided below in Table 1, wherein "MW" means molecular weight, "P81 Assay" refers to the P81 filter plate assay described above, "CBA" refers to the HEK281 cell-based assay described above, "--" means that results for the given assay were not obtained, "*" means less than or equal to 1.0 μM, "**" means a value of less than or equal to 0.1 μM, and "***" means less than or equal to 0.01 μM.

Table 1

Compound	MW	CBA IC_{50} μM	P81 IC_{50} μM
(4-(3-(2-methoxypyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)piperazin-1-yl)(pyrrolidin-1-yl)methanone	407.5	**	***
(S)-1-(2-(((3-(2-methoxyphenyl)pyrazolo[1,5-a]pyrimidin-5-yl)amino)methyl)pyrrolidin-1-yl)butan-1-one	393.5	**	***
(S)-1-(2-(((3-(2-methoxyphenyl)pyrazolo[1,5-a]pyrimidin-5-yl)amino)methyl)pyrrolidin-1-yl)-3,3-dimethylbutan-1-one	421.5	***	***
(S)-1-(3,3-dimethylbutyl)-5-(((3-(2-ethoxyphenyl)pyrazolo[1,5-a]pyrimidin-5-yl)amino)methyl)pyrrolidin-2-one	435.6	**	***
(S)-1-(3,3-dimethylbutyl)-5-(((3-(2-methoxyphenyl)pyrazolo[1,5-a]pyrimidin-5-yl)amino)methyl)pyrrolidin-2-one	421.5	***	***
(S)-1-(3,3-dimethylbutyl)-5-(((3-(2-methoxypyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)amino)methyl)pyrrolidin-2-one	422.5	**	***
(S)-1-(3,3-dimethylbutyl)-5-(((3-(3-methoxypyridin-4-yl)pyrazolo[1,5-a]pyrimidin-5-yl)amino)methyl)pyrrolidin-2-one	422.5	**	***
(S)-1-(3,3-dimethylbutyl)-5-(((3-phenylpyrazolo[1,5-a]pyrimidin-5-yl)amino)methyl)pyrrolidin-2-one	391.5	–	***
(S)-2-(((3-bromopyrazolo[1,5-a]pyrimidin-5-yl)amino)methyl)-N-(tert-butyl)pyrrolidine-1-carboxamide	395.3	***	***
(S)-2-cyclopropyl-N-methyl-N-(1-(3-(pyridin-2-yl)pyrazolo[1,5-a]pyrimidin-5-yl)pyrrolidin-3-yl)acetamide	376.5	–	**

(S)-3,3,3-trifluoro-1-(2-(((3-(2-methoxyphenyl)pyrazolo[1,5-a]pyrimidin-5-yl)amino)methyl)pyrrolidin-1-yl)propan-1-one	433.4	**	***
(S)-3,3,3-trifluoro-1-(2-(((3-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidin-5-yl)amino)methyl)pyrrolidin-1-yl)propan-1-one	404.4	**	***
(S)-3,3,3-trifluoro-N-(1-(3-(2-methoxyphenyl)pyrazolo[1,5-a]pyrimidin-5-yl)pyrrolidin-3-yl)-N-methylpropanamide	433.4	–	**
(S)-3,3,3-trifluoro-N-(1-(3-(2-methoxypyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)pyrrolidin-3-yl)-N-methylpropanamide	434.4	***	***
(S)-3,3,3-trifluoro-N-methyl-N-(1-(3-(pyridin-2-yl)pyrazolo[1,5-a]pyrimidin-5-yl)pyrrolidin-3-yl)propanamide	404.4	***	***
(S)-5-(((3-bromopyrazolo[1,5-a]pyrimidin-5-yl)amino)methyl)-1-(3,3-dimethylbutyl)pyrrolidin-2-one	394.3	**	***
(S)-ethyl 2-(((3-(2-methoxyphenyl)pyrazolo[1,5-a]pyrimidin-5-yl)amino)methyl)pyrrolidine-1-carboxylate	395.5	***	***
(S)-isopropyl (1-(3-(2-methoxyphenyl)pyrazolo[1,5-a]pyrimidin-5-yl)pyrrolidin-3-yl)(methyl)carbamate	409.5	–	**
(S)-isopropyl (1-(3-(2-methoxypyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)pyrrolidin-3-yl)(methyl)carbamate	410.5	–	**
(S)-isopropyl 2-(((3-(2-methoxyphenyl)pyrazolo[1,5-a]pyrimidin-5-yl)amino)methyl)pyrrolidine-1-carboxylate	409.5	***	***
(S)-isopropyl methyl(1-(3-(pyridin-2-yl)pyrazolo[1,5-a]pyrimidin-5-yl)pyrrolidin-3-yl)carbamate	380.4	–	*
(S)-isopropyl methyl(1-(3-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidin-5-yl)pyrrolidin-3-yl)carbamate	380.4	–	**
(S)-methyl 2-(((3-(2-methoxyphenyl)pyrazolo[1,5-a]pyrimidin-5-yl)amino)methyl)pyrrolidine-1-carboxylate	381.4	**	***
(S)-N-(1-(3-(2-methoxyphenyl)pyrazolo[1,5-a]pyrimidin-5-yl)pyrrolidin-3-yl)-N-methylbutyramide	393.5	*	***
(S)-N-(1-(3-(2-methoxypyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)pyrrolidin-3-yl)-N-methylbutyramide	394.5	*	***
(S)-N-(1-(3-bromopyrazolo[1,5-a]pyrimidin-5-yl)pyrrolidin-3-yl)-3,3,3-trifluoro-N-methylpropanamide	406.2	–	**
(S)-N-(1-(3-bromopyrazolo[1,5-a]pyrimidin-5-yl)pyrrolidin-3-yl)-N-methylpyrrolidine-1-carboxamide	393.3	–	**
(S)-N-(tert-butyl)-2-(((3-(2-methoxyphenyl)pyrazolo[1,5-a]pyrimidin-5-yl)amino)methyl)pyrrolidine-1-carboxamide	422.5	**	***
(S)-N-methyl-N-(1-(3-(pyridin-2-yl)pyrazolo[1,5-a]pyrimidin-5-yl)pyrrolidin-3-yl)butyramide	364.4	–	*
(S)-tert-butyl (1-(3-(2-methoxyphenyl)pyrazolo[1,5-a]pyrimidin-5-yl)pyrrolidin-3-yl)(methyl)carbamate	423.5	**	***

(S)-tert-butyl 2-(((3-(2-(methoxymethyl)phenyl)pyrazolo[1,5-a]pyrimidin-5-yl)amino)methyl)pyrrolidine-1-carboxylate	437.5	**	***
(S)-tert-butyl 2-(((3-(2-ethylphenyl)pyrazolo[1,5-a]pyrimidin-5-yl)amino)methyl)pyrrolidine-1-carboxylate	421.5	**	***
(S)-tert-butyl 2-(((3-(2-hydroxyphenyl)pyrazolo[1,5-a]pyrimidin-5-yl)amino)methyl)pyrrolidine-1-carboxylate	409.5	**	***
(S)-tert-butyl 2-(((3-(2-isopropoxyphenyl)pyrazolo[1,5-a]pyrimidin-5-yl)amino)methyl)pyrrolidine-1-carboxylate	451.6	***	***
(S)-tert-butyl 2-(((3-(2-methoxyphenyl)pyrazolo[1,5-a]pyrimidin-5-yl)amino)methyl)pyrrolidine-1-carboxylate	423.5	***	–
(S)-tert-butyl 2-(((3-(3-methoxyphenyl)pyrazolo[1,5-a]pyrimidin-5-yl)amino)methyl)pyrrolidine-1-carboxylate	423.5	***	***
(S)-tert-butyl 2-(((3-(4-(aminomethyl)phenyl)pyrazolo[1,5-a]pyrimidin-5-yl)amino)methyl)pyrrolidine-1-carboxylate	422.5	***	***
(S)-tert-butyl 2-(((3-(4-carbamoylphenyl)pyrazolo[1,5-a]pyrimidin-5-yl)amino)methyl)pyrrolidine-1-carboxylate	436.5	*	***
(S)-tert-butyl 2-(((3-(4-methoxyphenyl)pyrazolo[1,5-a]pyrimidin-5-yl)amino)methyl)pyrrolidine-1-carboxylate	423.5	***	***
(S)-tert-butyl 2-(((3-(4-methoxypyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)amino)methyl)pyrrolidine-1-carboxylate	424.5	***	***
(S)-tert-butyl 2-(((3-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidin-5-yl)amino)methyl)pyrrolidine-1-carboxylate	394.5	***	–
(S)-tert-butyl 2-(((3-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidin-5-yl)amino)methyl)pyrrolidine-1-carboxylate	394.5	***	–
(S)-tert-butyl 2-(((3-(trifluoromethyl)pyrazolo[1,5-a]pyrimidin-5-yl)amino)methyl)pyrrolidine-1-carboxylate	385.4	**	***
(S)-tert-butyl 2-(((3-iodopyrazolo[1,5-a]pyrimidin-5-yl)amino)methyl)pyrrolidine-1-carboxylate	443.3	**	–
(S)-tert-butyl 2-(((3-phenylpyrazolo[1,5-a]pyrimidin-5-yl)amino)methyl)pyrrolidine-1-carboxylate	393.5	**	***
(S)-tert-butyl methyl(1-(3-(2-methylpyridin-4-yl)pyrazolo[1,5-a]pyrimidin-5-yl)pyrrolidin-3-yl)carbamate	408.5	**	***
(S)-tert-butyl methyl(1-(3-(pyridin-2-yl)pyrazolo[1,5-a]pyrimidin-5-yl)pyrrolidin-3-yl)carbamate	394.5	–	*
1-(4-(3-(2-methoxypyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)piperazin-1-yl)-3-methylbutan-1-one	394.5	**	***
2,2,2-trifluoroethyl 4-(3-(2-methoxypyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)piperazine-1-carboxylate	436.4	***	***
2-fluoroethyl 4-(3-(2-methoxypyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)piperazine-1-carboxylate	400.4	***	***
2-methoxyethyl 4-(3-(2-methoxyphenyl)pyrazolo[1,5-a]pyrimidin-5-yl)piperazine-1-carboxylate	411.5	–	***

2-methoxyethyl 4-(3-(2-methoxypyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)piperazine-1-carboxylate	412.4	**	***
3-(2-methoxypyridin-3-yl)-N-(4,4,4-trifluorobutyl)pyrazolo[1,5-a]pyrimidin-5-amine	351.3	**	***
3-(3-methoxypyridin-4-yl)-N-(2-(trifluoromethoxy)phenethyl)pyrazolo[1,5-a]pyrimidin-5-amine	429.4	***	–
3-(4-(aminomethyl)phenyl)-N-(2-(cyclopentyloxy)ethyl)pyrazolo[1,5-a]pyrimidin-5-amine	351.4	**	–
3-(4-(aminomethyl)phenyl)-N-(2-(neopentyloxy)ethyl)pyrazolo[1,5-a]pyrimidin-5-amine	353.5	**	–
3-(4-(aminomethyl)phenyl)-N-(2-(tert-butoxy)ethyl)pyrazolo[1,5-a]pyrimidin-5-amine	339.4	**	–
3-(4-(aminomethyl)phenyl)-N-(2-(trifluoromethoxy)phenethyl)pyrazolo[1,5-a]pyrimidin-5-amine	427.4	***	–
3-(4-(aminomethyl)phenyl)-N-(2-methoxyethyl)pyrazolo[1,5-a]pyrimidin-5-amine	297.4	**	–
3-(4-(aminomethyl)phenyl)-N-(3-(cyclopentyloxy)propyl)pyrazolo[1,5-a]pyrimidin-5-amine	365.5	**	–
3-(4-(aminomethyl)phenyl)-N-butylpyrazolo[1,5-a]pyrimidin-5-amine	295.4	**	–
3-(4-methoxypyridin-3-yl)-N-(2-(trifluoromethoxy)phenethyl)pyrazolo[1,5-a]pyrimidin-5-amine	429.4	**	–
3-bromo-N-((1-(2,2,2-trifluoroethyl)pyrrolidin-2-yl)methyl)pyrazolo[1,5-a]pyrimidin-5-amine	378.2	**	***
3-bromo-N-(3-(cyclopentyloxy)propyl)pyrazolo[1,5-a]pyrimidin-5-amine	339.2	*	–
4-(5-(butylamino)pyrazolo[1,5-a]pyrimidin-3-yl)-N-(2-(methylamino)ethyl)benzamide	366.5	**	–
5-(4-(isobutylsulfonyl)piperazin-1-yl)-3-(2-methoxypyridin-3-yl)pyrazolo[1,5-a]pyrimidine	430.5		**
cyclopentyl 4-(3-(2-methoxypyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)piperazine-1-carboxylate	422.5	***	***
ethyl 4-(3-(2-ethoxypyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)piperazine-1-carboxylate	396.4	***	***
ethyl 4-(3-(2-methoxypyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)piperazine-1-carboxylate	382.4	**	***
ethyl 5-(4-(isopropoxycarbonyl)piperazin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylate	361.4		**
ethyl methyl(2-((3-(4-(methylcarbamoyl)phenyl)pyrazolo[1,5-a]pyrimidin-5-yl)amino)ethyl)carbamate	396.4	**	–

isobutyl (2-((3-(4-carbamoylphenyl)pyrazolo[1,5-a]pyrimidin-5-yl)amino)ethyl)(methyl)carbamate	410.5	***	–
isobutyl methyl(2-((3-(4-(methylcarbamoyl)phenyl)pyrazolo[1,5-a]pyrimidin-5-yl)amino)ethyl)carbamate	424.5	*	–
isopropyl (1-(3-(2-methoxypyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)azetidin-3-yl)(methyl)carbamate	396.4	–	**
isopropyl (2-((3-(3-methoxypyridin-4-yl)pyrazolo[1,5-a]pyrimidin-5-yl)amino)ethyl)(methyl)carbamate	384.4	***	–
isopropyl (2-((3-(4-(aminomethyl)phenyl)pyrazolo[1,5-a]pyrimidin-5-yl)amino)ethyl)(methyl)carbamate	382.5	**	–
isopropyl (2-((3-(4-carbamoylphenyl)pyrazolo[1,5-a]pyrimidin-5-yl)amino)ethyl)(methyl)carbamate	396.4	***	–
isopropyl (2-((3-(4-methoxypyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)amino)ethyl)(methyl)carbamate	384.4	**	–
isopropyl 4-(3-(1,3,5-trimethyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidin-5-yl)piperazine-1-carboxylate	397.5	–	**
isopropyl 4-(3-(1-isobutyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidin-5-yl)piperazine-1-carboxylate	411.5	–	**
isopropyl 4-(3-(1-methyl-2-oxo-1,2-dihydropyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)piperazine-1-carboxylate	396.4	**	***
isopropyl 4-(3-(2-(methoxymethyl)phenyl)pyrazolo[1,5-a]pyrimidin-5-yl)piperazine-1-carboxylate	409.5	–	*
isopropyl 4-(3-(2-(methylthio)pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)piperazine-1-carboxylate	412.5	–	**
isopropyl 4-(3-(2,6-dimethoxypyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)piperazine-1-carboxylate	426.5	***	***
isopropyl 4-(3-(2-aminopyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)piperazine-1-carboxylate	381.4	–	**
isopropyl 4-(3-(2-chloropyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)piperazine-1-carboxylate	400.9	*	**
isopropyl 4-(3-(2-ethoxypyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)piperazine-1-carboxylate	410.5	**	***
isopropyl 4-(3-(2-fluoropyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)piperazine-1-carboxylate	384.4	**	***
isopropyl 4-(3-(2-hydroxypyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)piperazine-1-carboxylate	382.4	**	***
isopropyl 4-(3-(2-isopropoxypyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)piperazine-1-carboxylate	424.5	**	***
isopropyl 4-(3-(2-methoxy-5-methylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)piperazine-1-carboxylate	410.5	***	***
isopropyl 4-(3-(2-methoxy-6-methylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)piperazine-1-carboxylate	410.5	**	***

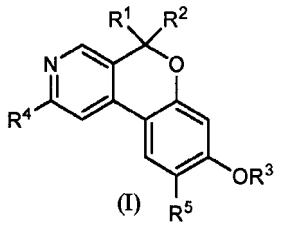
isopropyl 4-(3-(2-methoxyphenyl)pyrazolo[1,5-a]pyrimidin-5-yl)piperazine-1-carboxylate	395.5	–	***
isopropyl 4-(3-(2-methoxypyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)piperazine-1-carboxylate	396.4	–	***
isopropyl 4-(3-(2-methoxypyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-5,6-dihydropyridine-1(2H)-carboxylate	393.4	***	***
isopropyl 4-(3-(2-methoxypyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-3-oxopiperazine-1-carboxylate	410.4	***	***
isopropyl 4-(3-(2-methoxypyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-2,2-dimethylpiperazine-1-carboxylate	424.5	–	**
isopropyl 4-(3-(2-methylpyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)piperazine-1-carboxylate	380.4	–	**
isopropyl 4-(3-(3,6-dimethoxypyridazin-4-yl)pyrazolo[1,5-a]pyrimidin-5-yl)piperazine-1-carboxylate	427.5	***	***
isopropyl 4-(3-(3-ethoxyphenyl)pyrazolo[1,5-a]pyrimidin-5-yl)piperazine-1-carboxylate	409.5	–	***
isopropyl 4-(3-(3-fluoro-2-methoxyphenyl)pyrazolo[1,5-a]pyrimidin-5-yl)piperazine-1-carboxylate	413.4	–	**
isopropyl 4-(3-(3-methoxypyridin-2-yl)pyrazolo[1,5-a]pyrimidin-5-yl)piperazine-1-carboxylate	396.4	–	*
isopropyl 4-(3-(3-methoxypyridin-4-yl)pyrazolo[1,5-a]pyrimidin-5-yl)piperazine-1-carboxylate	396.4	**	***
isopropyl 4-(3-(4-fluoropyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)piperazine-1-carboxylate	384.4	–	**
isopropyl 4-(3-(4-methoxypyridin-2-yl)pyrazolo[1,5-a]pyrimidin-5-yl)piperazine-1-carboxylate	396.4	–	***
isopropyl 4-(3-(4-methoxypyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)piperazine-1-carboxylate	396.4	**	***
isopropyl 4-(3-(5-fluoro-2-methoxyphenyl)pyrazolo[1,5-a]pyrimidin-5-yl)piperazine-1-carboxylate	413.4	***	***
isopropyl 4-(3-(5-fluoro-2-methoxypyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)piperazine-1-carboxylate	414.4	**	***
isopropyl 4-(3-(5-fluoropyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)piperazine-1-carboxylate	384.4	–	***
isopropyl 4-(3-(5-methoxypyridin-2-yl)pyrazolo[1,5-a]pyrimidin-5-yl)piperazine-1-carboxylate	396.4	***	***
isopropyl 4-(3-(5-methoxypyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)piperazine-1-carboxylate	396.4	**	***
isopropyl 4-(3-(6-fluoropyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)piperazine-1-carboxylate	384.4	–	**
isopropyl 4-(3-(6-methoxypyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)piperazine-1-carboxylate	396.4	*	***
isopropyl 4-(3-(ethylcarbamoyl)pyrazolo[1,5-a]pyrimidin-5-yl)piperazine-1-carboxylate	360.4	–	**

isopropyl 4-(3-(isopropylcarbamoyl)pyrazolo[1,5-a]pyrimidin-5-yl)piperazine-1-carboxylate	374.4	–	*
isopropyl 4-(3-(methylcarbamoyl)pyrazolo[1,5-a]pyrimidin-5-yl)piperazine-1-carboxylate	346.4	–	**
isopropyl 4-(3-(pyrazin-2-yl)pyrazolo[1,5-a]pyrimidin-5-yl)piperazine-1-carboxylate	367.4	–	**
isopropyl 4-(3-(pyridin-2-yl)pyrazolo[1,5-a]pyrimidin-5-yl)piperazine-1-carboxylate	366.4	**	***
isopropyl 4-(3-(pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)piperazine-1-carboxylate	366.4	–	***
isopropyl 4-(3-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidin-5-yl)piperazine-1-carboxylate	366.4	**	***
isopropyl 4-(3-(pyrimidin-5-yl)pyrazolo[1,5-a]pyrimidin-5-yl)piperazine-1-carboxylate	367.4	–	**
isopropyl 4-(3-isopropylpyrazolo[1,5-a]pyrimidin-5-yl)piperazine-1-carboxylate	331.4	–	**
isopropyl 4-(pyrazolo[1,5-a]pyrimidin-5-yl)piperazine-1-carboxylate	289.3	–	***
isopropyl methyl(2-((3-(4-((2-(methylamino)ethyl)carbamoyl)phenyl)pyrazolo[1,5-a]pyrimidin-5-yl)amino)ethyl)carbamate	453.5	**	–
isopropyl methyl(2-((3-(4-(methylcarbamoyl)phenyl)pyrazolo[1,5-a]pyrimidin-5-yl)amino)ethyl)carbamate	410.5	***	–
isopropyl methyl(2-((3-(4-(pyrrolidin-2-yl)phenyl)pyrazolo[1,5-a]pyrimidin-5-yl)amino)ethyl)carbamate	422.5	***	–
methyl 4-(3-(2-methoxypyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)piperazine-1-carboxylate	368.4	**	**
N-(2-(cyclopentyloxy)ethyl)-3-(3-methoxypyridin-4-yl)pyrazolo[1,5-a]pyrimidin-5-amine	353.4	**	–
N-(2-(tert-butoxy)ethyl)-3-(3-methoxypyridin-4-yl)pyrazolo[1,5-a]pyrimidin-5-amine	341.4	**	–
N-(2-aminoethyl)-4-(5-((2-methoxyethyl)amino)pyrazolo[1,5-a]pyrimidin-3-yl)benzamide	354.4	*	–
N-(2-aminoethyl)-4-(5-((3,3-dimethylbutyl)amino)pyrazolo[1,5-a]pyrimidin-3-yl)benzamide	380.5	*	–
N-(2-aminoethyl)-4-(5-(butylamino)pyrazolo[1,5-a]pyrimidin-3-yl)benzamide	352.4	**	–
N-(2-methoxyethyl)-3-phenylpyrazolo[1,5-a]pyrimidin-5-amine	268.3	*	–
N-(3-(2-methoxypyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-N-(4,4,4-trifluorobutyl)acetamide	393.4	–	*

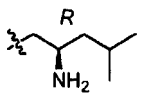
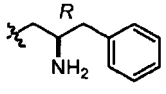
N-(3-(cyclopentyloxy)propyl)-3-(3-methoxypyridin-4-yl)pyrazolo[1,5-a]pyrimidin-5-amine	367.4	**	–
N-(tert-butyl)-4-(3-(2-methoxypyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)piperazine-1-carboxamide	409.5	**	***
N-(tert-butyl)-4-(3-(2-methoxypyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-N-methylpiperazine-1-carboxamide	423.5	**	***
N-isopropyl-4-(3-(2-methoxypyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)piperazine-1-carboxamide	395.5	***	***
N-isopropyl-4-(3-(2-methoxypyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)-N-methylpiperazine-1-carboxamide	409.5	**	***
tert-butyl (1-(3-(2-methoxypyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)azetidin-3-yl)(methyl)carbamate	410.5	–	*
tert-butyl (2-((3-(3-methoxypyridin-4-yl)pyrazolo[1,5-a]pyrimidin-5-yl)amino)ethyl)(methyl)carbamate	398.5	***	–
tert-butyl (2-((3-(4-carbamoylphenyl)pyrazolo[1,5-a]pyrimidin-5-yl)amino)ethyl)(methyl)carbamate	410.5	***	–
tert-butyl (2-(4-(5-((2-methoxyethyl)amino)pyrazolo[1,5-a]pyrimidin-3-yl)benzamido)ethyl)carbamate	454.5	*	–
tert-butyl 4-(3-(2-methoxypyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)piperazine-1-carboxylate	410.5	***	***
tert-butyl 4-(pyrazolo[1,5-a]pyrimidin-5-yl)-5,6-dihydropyridine-1(2H)-carboxylate	300.4	–	**
tert-butyl methyl(2-((3-(4-(methylcarbamoyl)phenyl)pyrazolo[1,5-a]pyrimidin-5-yl)amino)ethyl)carbamate	424.5	***	–

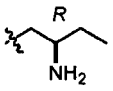
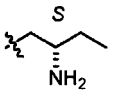
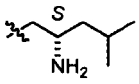
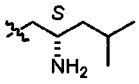
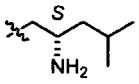
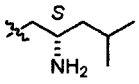
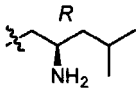
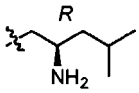
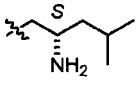
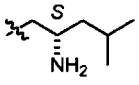
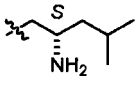
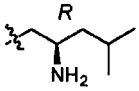
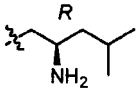
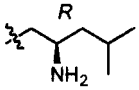
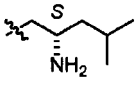
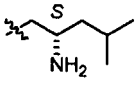
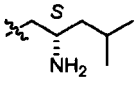
5.4.7. **Aryl ether-based Inhibitor In Vitro Data**

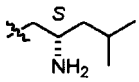
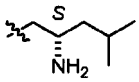
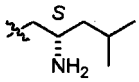
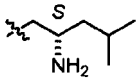
The Caliper and HEK281 assays described above were used to obtain *in vitro* data for various aryl ether-based compounds:



(I)

R1	R2	R4	R5	R3	Caliper IC50 (nM)	CBA IC50
H	H	H	H		c	
H	H	H	H		293	

H	H	H	H		d	
H	H	H	H		c	
H	H	H	H		3.3	8.4
Me	H	H	H		4.9	
Me	H	H	H		c	25
H	Me	H	H		c	b
Me	H	H	H		c	>300
H	Me	H	H		c	
Cyc-Pr	H	H	H		c	c
Cyc-Pr	H	H	H		d	
H	*Cyc*-Pr	H	H		b	18
Cyc-Pr	H	H	H		d	
Cyc-Pr	H	H	H		d	d
H	*Cyc*-Pr	H	H		d	d
Et	H	H	Et		c	18
Et	H	H	H		c	c
H	Et	H	H		12	56

=O		H	H		c	c
H	H	NHAc	H		c	c
H	H	NH_2	H		b	b
H	H	H	Br		0.86	2.5

where: a = <1 nM; b = 1-10 nM; c = 10-100 nM; d = 100-1000 nM.

5.4.8. **Pharmacological Effects**

Studies of AAK1 knockout mice showed that disruption of the AAK1 gene affects pain response as measured using the formalin paw test. See example 5.4.1, above. The same test was used to confirm that the administration of an AAK1 inhibitor can also affect pain response.

Mice were tested for nociception with Automatic Nociception Analyzers (purchased from the Ozaki lab at University of California, San Diego). A metal band was placed around the left hind paw of each mouse with superglue 30 minutes prior to testing. After the 30-minute acclimation period, 20 µl of 5% formalin was subcutaneously injected in the dorsal surface of the left hind paw. Mice were individually housed in cylindrical chambers for 45 minutes. Fresh 5 % formalin solution was prepared by diluting formaldehyde (Formalde-fresh 20%, Fisher Scientific, Fair Lawn, NJ) with distilled water. Investigatory compounds were administered 30 minutes prior to formalin injection.

A computer software recorded flinches per minute, total flinches for Phase I (acute phase = first 8 minutes), and total flinches for Phase II (tonic phase between 20 - 40 minutes) through an electromagnetic field. See Yaksh TL, Ozaki G, McCumber D, Rathbun M, Svensson C, Malkmus S, Yaksh MC. *An automated flinch detecting system for use in the formalin nociceptive bioassay.* J Appl Physiol., 2001; 90:2386-402.

Various compounds of the invention were tested at different doses. Gabapentin and pregabalin were used as positive controls. Results are shown below in Table 2, wherein "*" means an effect equal to or greater than 50 percent of that of gabapentin at 200 mpk, "**" means an effect equal to or greater than 100 percent of that of gabapentin at 200 mpk, "sc" means subcutaneous administration, "ip" means in intraperitoneal administration, and "po" means oral administration.

Table 2

Compound	Dose (mpk)	Effect
Gabapentin	50 sc	*
Gabapentin	200 sc	**
Pregabalin	50 sc	*
(S)-isopropyl (1-(3-(2-methoxypyridin-3-yl)imidazo[1,2-b]pyridazin-6-yl)pyrrolidin-3-yl)(methyl)carbamate	10 po	*
(S)-isopropyl (1-(3-(2-methoxypyridin-3-yl)imidazo[1,2-b]pyridazin-6-yl)pyrrolidin-3-yl)(methyl)carbamate	30 po	**
(S)-isopropyl (1-(3-(2-methoxypyridin-3-yl)imidazo[1,2-b]pyridazin-6-yl)pyrrolidin-3-yl)(methyl)carbamate	60 po	**
(S)-tert-butyl 2-(((3-(4-(aminomethyl)phenyl)imidazo[1,2-b]pyridazin-6-yl)amino)methyl)pyrrolidine-1-carboxylate	60 sc	**
(S)-tert-butyl 2-(((3-bromoimidazo[1,2-b]pyridazin-6-yl)amino)methyl)pyrrolidine-1-carboxylate	30 sc	**
(S)-tert-butyl 2-(((3-bromoimidazo[1,2-b]pyridazin-6-yl)amino)methyl)pyrrolidine-1-carboxylate	60 sc	**
3-(4-(1H-tetrazol-5-yl)phenyl)-N-butylimidazo[1,2-b]pyridazin-6-amine	60 ip	**
3-(4-(aminomethyl)phenyl)-N-(2-(cyclopentyloxy)ethyl)Imidazo[1,2-b]pyridazin-6-amine	60 sc	**
3-(4-(aminomethyl)phenyl)-N-(2-(cyclopentyloxy)ethyl)imidazo[1,2-b]pyridazin-6-amine	100 sc	**
3-(4-(aminomethyl)phenyl)-N-(2-(tert-butoxy)ethyl)imidazo[1,2-b]pyridazin-6-amine	60 sc	**
3-(4-(aminomethyl)phenyl)-N-(3-(tert-butoxy)propyl)imidazo[1,2-b]pyridazin-6-amine	60 sc	**
3-(4-(aminomethyl)phenyl)-N-(3-phenylpropyl)imidazo[1,2-b]pyridazin-6-amine	30 ip	**
isopropyl 4-(3-(2-methoxyphenyl)imidazo[1,2-b]pyridazin-6-yl)piperazine-1-carboxylate	30 sc	**
isopropyl 4-(3-(2-methoxyphenyl)imidazo[1,2-b]pyridazin-6-yl)piperazine-1-carboxylate	60 sc	**
N-(2-aminoethyl)-4-(6-(butylamino)imidazo[1,2-b]pyridazin-3-yl)benzamide	30 ip	**
tert-butyl (2-((3-(4-carbamoylphenyl)imidazo[1,2-b]pyridazin-6-yl)amino)ethyl)(methyl)carbamate	100 po	**
tert-butyl (2-((3-(4-carbamoylphenyl)imidazo[1,2-b]pyridazin-6-yl)amino)ethyl)(methyl)carbamate	60 sc	**
(S)-tert-butyl 2-(((3-(2-methoxyphenyl)pyrazolo[1,5-a]pyrimidin-5-yl)amino)methyl)pyrrolidine-1-carboxylate	10 sc	*
(S)-tert-butyl 2-(((3-(2-methoxyphenyl)pyrazolo[1,5-a]pyrimidin-5-yl)amino)methyl)pyrrolidine-1-carboxylate	60 sc	*

(S)-tert-butyl 2-(((3-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidin-5-yl)amino)methyl)pyrrolidine-1-carboxylate	30 sc	**
isopropyl 4-(3-(2-methoxyphenyl)pyrazolo[1,5-a]pyrimidin-5-yl)piperazine-1-carboxylate	30 sc	**
isopropyl 4-(3-(2-methoxypyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)piperazine-1-carboxylate	10 po	*
isopropyl 4-(3-(2-methoxypyridin-3-yl)pyrazolo[1,5-a]pyrimidin-5-yl)piperazine-1-carboxylate	30 po	**
(*R*)-1-(5*H*-chromeno[3,4-*c*]pyridin-8-yloxy)-4-methylpentan-2-amine	10 sc	45%
(*R*)-1-(5*H*-chromeno[3,4-*c*]pyridin-8-yloxy)-4-methylpentan-2-amine	30 sc	*

These results demonstrate that AAK1 inhibitors can be used to treat pain.

All publications (e.g., patents and patent applications) cited above are incorporated herein by reference in their entireties.

CLAIMS

What is claimed is:

1. A method of treating or managing pain, which comprises inhibiting adaptor associated kinase 1 (AAK1) activity in a patient in need thereof.

2. The method of claim 1, wherein the pain is neuropathic pain.

3. The method of claim 2, wherein the neuropathic pain is fibromyalgia or peripheral neuropathy.

4. The method of claim 3, wherein the peripheral neuropathy is diabetic neuropathy.

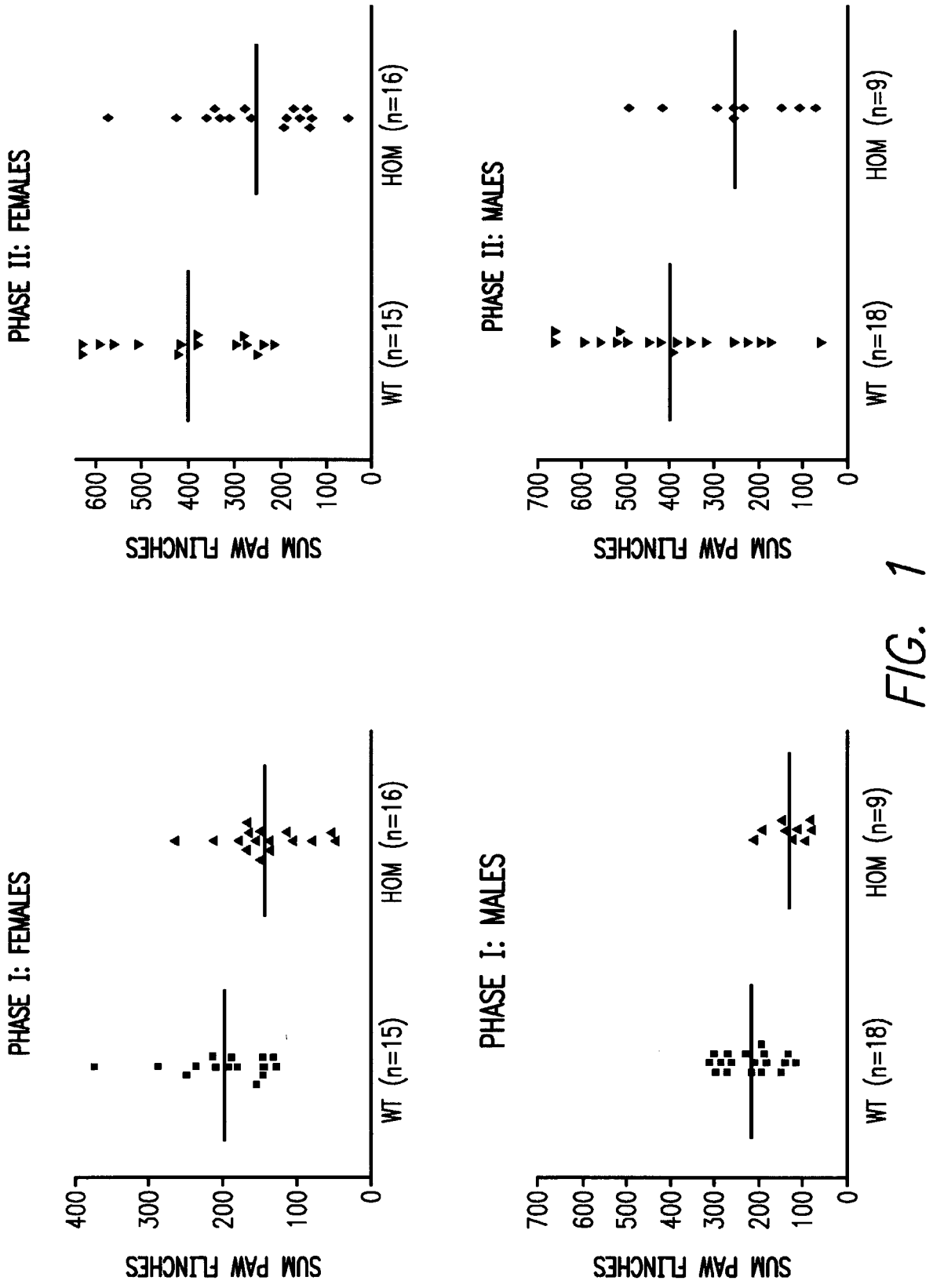

PHASE II: FEMALES
SUM PAW FLINCHES
0
100
200
300
400
500
600
WT (n=15)
HOM (n=16)
PHASE II: MALES
SUM PAW FLINCHES
0
100
200
300
400
500
600
700
WT (n=18)
HOM (n=9)
PHASE I: FEMALES
SUM PAW FLINCHES
0
100
200
300
400
WT (n=15)
HOM (n=16)
PHASE I: MALES
SUM PAW FLINCHES
0
100
200
300
400
500
600
700
WT (n=18)
HOM (n=9)

FIG. 1

(19)中华人民共和国国家知识产权局

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A61P 25/00(2006.01)
A61K 31/35(2006.01)
A61K 31/5025(2006.01)

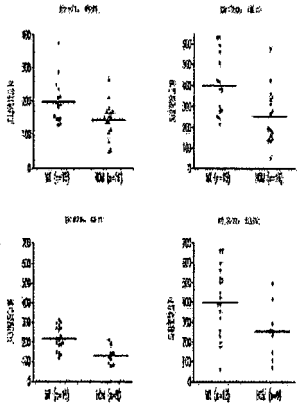
权利要求书1页 说明书59页 附图1页

(54)发明名称

抑制转接物关联激酶1以治疗疼痛

(57)摘要

本发明涉及通过抑制转接物关联激酶1(adaptor associated kinase1)(AAK1)来治疗疼痛。公开了大量AAK1抑制剂。



CN 104220071 A

1. 一种治疗或管理疼痛的方法，所述方法包括在需要的患者中抑制转接物关联激酶1(AAK1)活性。

2. 权利要求1的方法，其中所述疼痛是神经病理性疼痛。

3. 权利要求2的方法，其中所述神经病理性疼痛是纤维肌痛或外周神经病。

4. 权利要求3的方法，其中所述外周神经病是糖尿病性神经病。

抑制转接物关联激酶 1 以治疗疼痛

[0001] 本申请要求 2012 年 3 月 9 日提交的美国临时专利申请号 61/608,849 的优先权，所述临时专利申请的全部内容通过参考并入本文。

技术领域

[0002] 本发明涉及通过抑制转接物关联激酶 1(adaptor associated kinase1)(AAK1) 来治疗疼痛的方法。

背景技术

[0003] 疼痛一般可以分成三种不同类型 :急性、炎性和神经病理性。从最本质上来说，急性疼痛一般持续时间短且强烈。另一方面，炎性疼痛可能持续长得多的时间段，并且其强度分成更多级别。炎症可能因许多原因而发生，包括组织损伤、自体免疫应答和病原体侵入。第三类疼痛是神经病理性的，并推测涉及引起神经元蛋白和回路重新组构的神经损伤，产生病理性“敏化”状态，其可以产生持续数年的长期疼痛。使用现存的疗法，这种疼痛类型特别难以治疗。

[0004] 疼痛、尤其是神经病理性和难治性疼痛，是巨大的、尚未满足的医疗需求。数百万个体苦于不能通过当前疗法充分地控制的严重疼痛。当前用于治疗疼痛的药物包括 NSAID、COX2 抑制剂、鸦片类药物、三环抗抑郁剂和抗惊厥剂。神经病理性疼痛特别难以治疗，因为它不能良好地对鸦片类药物响应，除非达到高的剂量。加巴喷丁目前是用于治疗神经病理性疼痛的偏好的治疗剂，尽管它仅在 60％的患者中起效，它在所述患者中显示出中等效能。

[0005] 转接物关联激酶 1(AAK1) 是丝氨酸 / 苏氨酸激酶的 Ark1/Prk1 家族的成员。AAK1mRNA 以被称为短和长的两种剪接形式存在。长形式占优势并在脑和心脏中高表达 (Henderson 和 Conner，Mol. Biol. Cell. 2007, 18, 2698-2706)。AAK1 富集在突触体制备物中，并且在培养的细胞中与细胞内吞性结构共定位。AAK1 介导网格蛋白 (clatherin) 包被的细胞内吞作用，这是一种在突触小泡循环利用和受体介导的细胞内吞中重要的过程。AAK1 与 AP2 复合体这种将受体运载物连接到网格蛋白包被的异源四聚体结合。网格蛋白与 AAK1 的结合刺激 AAK1 激酶活性 (Conner 等，Traffic 2003, 4, 885-890 ;Jackson 等，J. Cell. Biol. 2003, 163, 231-236)。AAK1 将 AP-2 的 mu-2 亚基磷酸化，其促进 mu-2 与运载物受体上的含酪氨酸分拣基序的结合 (Ricotta 等，J. Cell Bio. 2002, 156, 791-795 ;Conner 和 Schmid，J. Cell Bio. 2002, 156, 921-929)。Mu2 磷酸化对于受体摄入来说不是必需的，但磷酸化提高内化效率 (Motely 等，Mol. Biol. Cell. 2006, 17, 5298-5308)。

[0006] AAK1 已被鉴定为是在 PC12 细胞中的神经调节蛋白 -1/ErbB4 信号传导的抑制剂。通过 RNA 干扰介导的基因沉默或用激酶抑制剂 K252a(其抑制 AAK1 激酶活性) 处理使 AAK1 表达丧失，导致神经调节蛋白 -1 诱导的神经突过度生长的增强。这些处理引起 ErbB4 表达增加和 ErbB4 在细胞质膜中或其附近积累 (Kuai 等，Chemistry and Biology2011, 18, 891-906)。NRG1 和 ErbB4 是推测的精神分裂症易感性基因 (Buonanno, Brain Res. Bull. 2010, 83, 122-131)。已将两个基因中的 SNP 与多个精神分

裂症内表型相关联 (Greenwood 等，Am. J. Psychiatry2011, 168, 930-946)。神经调节蛋白 1 和 ErbB4KO 小鼠模型已显示出精神分裂症相关的形态变化和行为表型 (Jaaro-Peled 等，Schizophrenia Bulletin 2010, 36, 301-313 ;Wen 等，Proc. Natl. Acad. Sci. USA. 2010, 107, 1211-1216)。此外，已将 AAK1 基因的内含子中的单核苷酸多态性与帕金森氏病的发作年龄相关联 (Latourelle 等，BMC Med. Genet. 2009, 10, 98)。

[0007] 发明概述

[0008] 本发明是基于 AAK1 的抑制能够减轻疼痛这一本申请人的创新发现，以及随后多种类型的 AAK1 抑制剂的发现。

[0009] 本发明本身涵盖了治疗或管理疼痛的方法，所述方法包括在需要的患者中抑制 AAK1 活性。具体的疼痛是神经病理性疼痛，例如纤维肌痛或外周神经病（例如糖尿病性神经病）。

附图说明

[0010] 本发明的情况示出在图 1 中，该图示出了使用 AAK1 纯合 (-/-) 敲除小鼠和它们的野生型 (+/+) 同窝仔畜，从福尔马林疼痛模型获得的结果。AAK1 纯合 (-/-) 敲除小鼠与它们的野生型 (+/+) 同窝仔畜相比，显示出急性和强直性疼痛响应两者的明显减轻。

[0011] 发明概述

[0012] 本发明部分是基于 AAK1 敲除小鼠对疼痛表现出高抗性这一本申请人的发现。该发现促使的研究最终导致发现了可用于疼痛的治疗和管理的广范围的 AAK1 抑制剂。简短来说，本发明提供了可以治疗或管理疼痛的全新机制以及可用于其中的化合物。

[0013] 定义

[0014] 除非另有指明，否则短语“本发明的化合物”、“本公开的化合物”等是指本文中公开的化合物。

[0015] 除非另有指明，否则术语“烃基”是指具有全碳骨架并由碳和氢原子构成的脂族或脂环族组成部分。烃基的实例包括具有 1-20、1-12、1-6 和 1-4 个碳原子的烃基（分别被称为 C_{1-20} 烃基、C_{1-12} 烃基、C_{1-6} 烃基和 C_{1-4} 烃基）。具体实例包括烷基、烯基、炔基、芳基、苯甲基、环烷基、环烯基、环烷基烷基、环烯基烷基、萘基、苯基和苯乙基。

[0016] 烷基组成部分的实例包括具有 1-20、1-12、1-6、1-4 和 1-3 个碳原子的直链和支链组成部分（分别被称为 C_{1-20} 烷基、C_{1-12} 烷基、C_{1-6} 烷基、C_{1-4} 烷基和 C_{1-3} 烷基）。具体实例包括甲基、乙基、丙基、异丙基、正丁基、叔丁基、异丁基、戊基、己基、异己基、庚基、4,4- 二甲基戊基、辛基、2,2,4- 三甲基戊基、壬基、癸基、十一烷基和十二烷基。

[0017] 烯基组成部分的实例包括直链和支链 C_{2-20}、C_{2-12} 和 C_{2-6} 烯基。具体实例包括乙烯基、烯丙基、1- 丁烯基、2- 丁烯基、异丁烯基、1- 戊烯基、2- 戊烯基、3- 甲基 -1- 丁烯基、2- 甲基 -2- 丁烯基、2,3- 二甲基 -2- 丁烯基、1- 己烯基、2- 己烯基、3- 己烯基、1- 庚烯基、2- 庚烯基、3- 庚烯基、1- 辛烯基、2- 辛烯基、3- 辛烯基、1- 壬烯基、2- 壬烯基、3- 壬烯基、1- 癸烯基、2- 癸烯基和 3- 癸烯基。

[0018] 炔基组成部分的实例包括直链和支链 C_{2-20}、C_{2-12} 和 C_{2-6} 炔基。具体实例包括乙炔基和 2- 丙炔基（炔丙基）。

[0019] 芳基组成部分的实例包括蒽基、甘菊环基、芴基、茚满、茚基、萘基、苯基和菲基。

[0020] 环烷基组成部分的实例包括 C_{3-12}、C_{3-7}、C_{4-6} 和 C_6 环烷基。具体实例包括环丙基、环丁基、环戊基、环己基和金刚烷基。

[0021] 除非另有指明，否则术语“卤素”涵盖氟、氯、溴和碘。

[0022] 除非另有指明，否则术语“杂烃基”是指具有由一个或多个碳原子和一个或多个杂原子构成的骨架的组成部分。具体的杂原子是氮、氧和硫。杂烃基组成部分可以被认为是其中至少一个碳原子、CH、CH_2 或 CH_3 基团被一个或多个杂原子以及满足价数所必需数目的氢原子替换的烃基组成部分。杂烃基的实例包括 2-20、2-12、2-8、2-6 和 2-4 元杂烃基组成部分，其中所述数目范围是指组成部分中碳、氮、氧和 / 或硫原子的总和。因此，术语“2-12 元杂烃基”是指具有总共 2-12 个碳、氮、氧和 / 或硫原子的杂烃基组成部分。具体的杂烃基组成部分包括直链和支链杂烷基、杂烯基和杂炔基，以及杂环和杂芳基。

[0023] 杂烷基组成部分的实例包括 2-8 元、2-6 元和 2-4 元杂烷基组成部分。具体实例包括烷氧基、酰基（例如甲酰基、乙酰基、苯甲酰基）、烷基氨基（例如二（C_{1-3}- 烷基）氨基）、芳基氨基、芳基肼、氨基甲酸酯、羧酰胺、烷基羰基、芳基羰基、氨基羰基、烷基氨基羰基、烷基硫烷基、芳基硫烷基、烷基亚硫酰基、芳基亚硫酰基、烷基磺酰基、芳基磺酰基、烷基磺酰基氨基和芳基磺酰基氨基。

[0024] 除非另有指明，否则术语“杂环”是指环状（单环或多环）杂烃基组成部分，其可以是芳香族、部分芳香族或非芳香族的。杂环包括杂芳基。实例包括 4-10 元、4-7 元、6 元和 5 元杂环。具体实例包括苯并 [1,3] 间二氧杂环戊烯基、2,3- 二氢 - 苯并 [1,4] 二氧杂芑基、邻二氮杂萘基、呋喃基、海因基、吗啉基、氧杂环丁基、氧杂环丙基、哌嗪基、哌啶基、吡咯烷酮基、吡咯烷基、四氢呋喃基、四氢吡喃基、四氢吡啶基、四氢嘧啶基、四氢噻吩基、四氢噻喃基和戊内酰胺基。由于术语“杂环”是指环，单独情况下它不涵盖组成部分例如噁唑烷酮和咪唑烷酮：这样的组成部分被认为是取代的杂环，即用氧基取代的杂环。

[0025] 杂芳基组成部分的实例包括吖啶基、苯并咪唑基、苯并呋喃基、苯并异噻唑基、苯并异噁唑基、苯并喹唑啉基、苯并噻唑基、苯并噁唑基、呋喃基、咪唑基、吲哚基、异噻唑基、异噁唑基、噁二唑基、噁唑基、酞嗪基、吡嗪基、吡唑基、哒嗪基、吡啶基、嘧啶基、嘧啶基、吡咯基、喹唑啉基、喹啉基、四唑基、噻唑基和三嗪基。

[0026] 除非另有指明，否则术语“包括”具有与“包括但不限于”相同的意义。同样地，术语“例如”具有与术语“例如但不限于”相同的意义。

[0027] 除非另有指明，否则术语“管理”涵盖了在已经患有特定疾病或障碍的患者中防止所述疾病或障碍的复发，和 / 或延长已患有所述疾病或障碍的患者处于缓解期的时间。所述术语涵盖调节所述疾病或障碍的阈值、发展和 / 或持续时间，或改变患者对所述疾病或障碍的响应方式。

[0028] 除非另有指明，否则化合物的“治疗有效量”是足以在疾病或病症的治疗或管理中提供治疗益处，或延迟或最小化与所述疾病或病症相关的一种或多种症状的量。化合物的“治疗有效量”是指单独或与其他疗法组合的治疗剂的在疾病或病症的治疗或管理中提供治疗益处的量。术语“治疗有效量”可以涵盖改进总体疗法、减轻或避免疾病或病症的症状或病因，或增强另一种治疗剂的治疗效能的量。

[0029] 除非另有指明，否则术语“治疗”设想了在患者患有指定疾病或障碍时发生的，降低所述疾病或障碍的严重性或延迟或减缓所述疾病或障碍的进展的行动。

[0030] 除非另有指明，否则紧邻一系列名词之前的一个或多个形容词应该被解释为适用于每个所述名词。例如，短语“任选被取代的烷基、芳基或杂芳基”具有与“任选被取代的烷基、任选被取代的芳基或任选被取代的杂芳基”相同的意义。

[0031] 化合物

[0032] 可用于抑制AAK1的化合物公开在2012年3月9日提交的美国临时专利申请号61/608,758、61/608,765和61/608,737中，以及在2013年2月26日提交的美国专利申请号13/777,144、2013年3月5日提交的13/785,271以及也在2013年3月5日提交的13/785,355中。

[0033] 本发明的化合物可以具有一个或多个不对称中心。除非另有指明，否则本发明涵盖所述化合物的所有立体异构体及其混合物。化合物的单个立体异构体，可以从含有手性中心的可商购的起始原料合成地制备，或通过制备对映异构体产物的混合物，然后进行分离例如转变成非对映异构体的混合物，随后进行分离或重结晶、层析技术，或者在手性层析柱上直接分离对映异构体，来制备。特定立体化学的起始原料可以商购或者可以通过本领域中已知的技术来制造和拆分。

[0034] 本公开的某些化合物也可以以可能可分离的不同的稳定构象形式存在。由于围绕不对称单键的旋转受限、例如由于空间位阻或环应变造成的扭转不对称，可以允许分离不同的构象异构体。本公开包括这些化合物的每种构象异构体及其混合物。

[0035] 本公开打算包含本发明的化合物中出现的原子的所有同位素。同位素包括具有相同原子序数但具有不同质量数的原子。作为一般性实例而不是限制性的，氢的同位素包括氘和氚。碳的同位素包括^{13}C和^{14}C。同位素标记的本发明的化合物一般可以通过本领域技术人员已知的常规技术或通过与本文中所描述的类似的方法，使用适合的同位素标记的试剂代替原本使用的未标记的试剂来制备。这样的化合物可能具有各种潜在用途，例如在测定生物学活性中作为标准品和试剂。在稳定同位素的情况下，这样的化合物可能具有有利地修改生物学、药理学或药物动力学性质的潜力。

[0036] 本公开的化合物可以作为可药用盐存在。当在本文中使用时，术语“可药用盐”表示本发明的化合物的可溶于或可分散于水或油中的盐或两性离子形式，其在合理的医学判断范围内，适合用于与患者的组织相接触而没有过度毒性、刺激性、过敏反应或与合理的利益／风险比相称的其他问题或并发症，并且可有效地用于其目标用途。盐可以在化合物的最终分离和纯化期间制备，或者单独地通过将适合的氮原子与适合的酸进行反应来制备。代表性的酸加成盐包括乙酸盐、己二酸盐、藻酸盐、柠檬酸盐、天冬氨酸盐、苯甲酸盐、苯磺酸盐、硫酸氢盐、丁酸盐、樟脑酸盐、樟脑磺酸盐、二葡萄糖酸盐、二氢溴酸盐、二盐酸盐、二氢碘酸盐、甘油磷酸盐、半硫酸盐、庚酸盐、己酸盐、甲酸盐、延胡索酸盐、盐酸盐、氢溴酸盐、氢碘酸盐、2-羟基乙磺酸盐、乳酸盐、马来酸盐、均三甲苯磺酸盐、甲磺酸盐、萘磺酸盐、烟酸盐、2-萘磺酸盐、草酸盐、棕榈酸盐、果胶酸盐、过硫酸盐、3-苯基丙酸盐、苦味酸盐、新戊酸盐、丙酸盐、琥珀酸盐、酒石酸盐、三氯乙酸盐、磷酸盐、谷氨酸盐、碳酸氢盐、对甲苯磺酸盐和十一烷酸盐。可用于形成可药用加成盐的酸的实例包括无机酸例如盐酸、氢溴酸、硫酸和磷酸以及有机酸例如草酸、马来酸、琥珀酸和柠檬酸。

[0037] 碱加成盐可以在化合物的最终分离和纯化期间，通过将羧基与适合的碱例如金属阳离子的氢氧化物、碳酸盐或碳酸氢盐，或与氨或有机伯胺、仲胺或叔胺进行反应来制

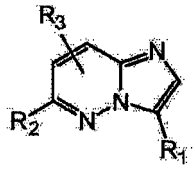
备。可药用盐的阳离子包括锂、钠、钾、钙、镁和铝，以及无毒性的季铵阳离子例如铵、四甲基铵、四乙基铵、甲胺、二甲胺、三甲胺、三乙胺、二乙胺、乙胺、三丁胺、吡啶、N,N- 二甲基苯胺、N- 甲基哌啶、N- 甲基吗啉、二环己胺、普鲁卡因、二苯甲基胺、N,N- 二苯甲基苯乙基胺和 N,N'- 二苯甲基乙二胺。可用于形成碱加成盐的其他代表性的有机胺包括乙二胺、乙醇胺、二乙醇胺、哌啶和哌嗪。

[0038] 当在下面实施例中描述的 P81 过滤板测定法中测量时，特定化合物以低于 0.1、0.01 或 0.001 μM 的 IC_{50} 抑制 AAK1。当在下面实施例中描述的基于 HEK281 细胞的测定法中测量时，特定化合物以低于 0.1、0.01 或 0.001 μM 的 IC_{50} 抑制 AAK1。

[0039] 基于咪唑并 [1,2-b] 哒嗪的抑制剂

[0040] 可用于本发明的实施方式的一类化合物公开在 2013 年 3 月 5 日提交的题为“基于咪唑并 [1,2-b] 哒嗪的化合物、包含它们的组合物及其使用方法”(Imidazo[1,2-b] pyridazine-based Compounds, Compositions Comprising Them, and Methods of Their Use) 的美国专利申请号 13/785,271 中。所述申请涵盖了下式的化合物及其可药用盐：

[0041]



[0042] 其中：R_1 是 R_{1A} 或任选被取代的 C_{1-12} 烷基或 2-12 元杂烷基，所述任选的取代是用一个或多个 R_{1A} 取代；每个 R_{1A} 独立地是 $-OR_{1C}$、$-N(R_{1C})_2$、$-C(O)R_{1C}$、$-C(O)OR_{1C}$、$-C(O)N(R_{1C})_2$、$-N(R_{1C})C(O)OR_{1C}$、氰基、卤素或任选被取代的 C_{1-12} 烷基或 2-12 元杂烷基，所述任选的取代是用一个或多个 R_{1B} 取代；每个 R_{1B} 独立地是 $-OR_{1C}$、$-N(R_{1C})_2$、$-C(O)R_{1C}$、$-C(O)OR_{1C}$、$-C(O)N(R_{1C})_2$、$-N(R_{1C})C(O)OR_{1C}$、氰基或卤素；每个 R_{1C} 独立地是氢或任选被取代的 C_{1-12} 烷基或 2-12 元杂烷基，所述任选的取代是用一个或多个氰基、卤素或羟基取代；R_2 是 $-NR_{2A}R_{2B}$，其中 R_{2A} 是氢并且 R_{2B} 是任选被取代的 C_{1-12} 烷基或 2-12 元杂烷基，所述任选的取代是用一个或多个 R_{2C} 取代；或者 R_{2A} 和 R_{2B} 合在一起形成任选被一个或多个 R_{2C} 取代的 4-7 元杂环；每个 R_{2C} 独立地是 $-OR_{2D}$、$-N(R_{2D})_2$、$-C(O)R_{2D}$、$-C(O)OR_{2D}$、$-C(O)N(R_{2D})_2$、$-N(R_{2D})C(O)OR_{2D}$、氰基、卤素或任选被取代的 C_{1-12} 烷基或 2-12 元杂烷基，所述任选的取代是用一个或多个 R_{2D} 取代；每个 R_{2D} 独立地是氢或任选被取代的 C_{1-12} 烷基或 2-12 元杂烷基，所述任选的取代是用一个或多个氰基、卤素或羟基取代；并且 R_3 是氢或任选被一个或多个氰基、卤素或羟基取代的 C_{1-6} 烷基。

[0043] 在特定化合物中，R_1 是 R_{1A}。在特定化合物中，R_1 是任选被取代的 C_{1-12} 烷基。在特定化合物中，R_1 是任选被取代的苯基。在特定化合物中，R_1 是任选被取代的 2-12 元杂烷基（例如 2-8 元杂烷基、2-6 元杂烷基、2-6 元杂烷基）。在特定化合物中，R_1 是任选被取代的吡啶基、噻吩或咪唑。

[0044] 在特定化合物中，R_{1A} 是卤素。在某些化合物中，R_{1A} 是 $-OR_{1C}$、$-N(R_{1C})_2$、$-C(O)R_{1C}$、$-C(O)OR_{1C}$ 或 $-C(O)N(R_{1C})_2$。在某些化合物中，R_{1A} 是 $-OR_{1C}$。在某些化合物中，R_{1B} 是 $-N(R_{1C})_2$、$-OR_{1C}$、卤素。

[0045] 在特定化合物中，R_{2A} 和 R_{2B} 合在一起形成任选被一个或多个 R_{2C} 取代的 4-7 元杂

环。

[0046] 在特定化合物中，R_{1C} 是氢。在某些化合物中，R_{1C} 是 C_{1-12} 烃基（例如 C_{1-6} 烃基、C_{1-4} 烃基例如甲基、乙基、丙基）。

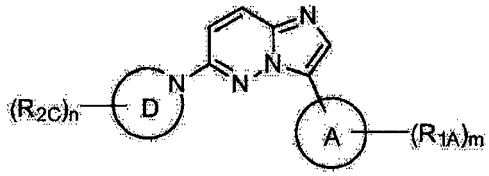
[0047] 在特定化合物中，R_{2C} 是 $-C(O)OR_{2D}$、$-C(O)N(R_{2D})_2$ 或 $-N(R_{2D})C(O)OR_{2D}$。

[0048] 在特定化合物中，R_{2D} 是氢。在某些化合物中，R_{2D} 是 C_{1-12} 烃基（例如 C_{1-6} 烃基、C_{1-4} 烃基例如甲基、乙基、丙基）。

[0049] 在特定化合物中，R_3 是氢。

[0050] 本发明的一种实施方式涵盖了下式的化合物及其可药用盐：

[0051]



[0052] 其中：A 是环 C_{1-12} 烃基或 4-7 元杂环；D 是 4-7 元杂环；每个 R_{1A} 独立地是 $-OR_{1C}$、$-N(R_{1C})_2$、$-C(O)R_{1C}$、$-C(O)OR_{1C}$、$-C(O)N(R_{1C})_2$、$-N(R_{1C})C(O)OR_{1C}$、氰基、卤素或任选被取代的 C_{1-12} 烃基或 2-12 元杂烃基，所述任选的取代是用一个或多个 R_{1B} 取代；每个 R_{1B} 独立地是 $-OR_{1C}$、$-N(R_{1C})_2$、$-C(O)R_{1C}$、$-C(O)OR_{1C}$、$-C(O)N(R_{1C})_2$、$-N(R_{1C})C(O)OR_{1C}$、氰基或卤素；每个 R_{1C} 独立地是氢或任选被取代的 C_{1-12} 烃基或 2-12 元杂烃基，所述任选的取代是用一个或多个氰基、卤素或羟基取代；每个 R_{2C} 独立地是 $-OR_{2D}$、$-N(R_{2D})_2$、$-C(O)R_{2D}$、$-C(O)OR_{2D}$、$-C(O)N(R_{2D})_2$、$-N(R_{2D})C(O)OR_{2D}$、氰基、卤素或任选被取代的 C_{1-12} 烃基或 2-12 元杂烃基，所述任选的取代是用一个或多个 R_{2D} 取代；每个 R_{2D} 独立地是氢或任选被取代的 C_{1-12} 烃基或 2-12 元杂烃基，所述任选的取代是用一个或多个氰基、卤素或羟基取代；n 是 1-3；并且 m 是 0-3。

[0053] 在特定化合物中，R_{2C} 不是羟基或任选被取代的苯基或吡啶基。

[0054] 在特定化合物中，当 D 是二氮杂环庚烷并且 A 是吡啶基时，R_{2C} 不是 -C(O)O- 叔丁基。

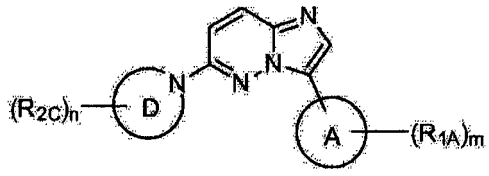
[0055] 在特定化合物中，当 D 是哌嗪、A 是苯基并且 R_{1A} 是氯时，R_{2C} 不是 -C(O)O- 叔丁基。

[0056] 在特定化合物中，当 D 是哌啶基、A 是吡啶基并且 R_{1A} 是氯时，R_{2C} 不是 -NHC(O)O- 叔丁基。

[0057] 在特定化合物中，当 D 是哌啶基、A 是吡啶基并且 R_{1A} 是 $-NHCH_2CH_2CH(CH_3)_2$ 时，R_{2C} 不是 NH_2。

[0058] 本发明的一种实施方式涵盖下式的化合物及其可药用盐：

[0059]



[0060] 其中：A 是环 C_{1-12} 烃基或 4-7 元杂环；D 是 4-7 元杂环；每个 R_{1A} 独立地是 $-OR_{1C}$、$-N(R_{1C})_2$、$-C(O)R_{1C}$、$-C(O)OR_{1C}$、$-C(O)N(R_{1C})_2$、$-N(R_{1C})C(O)OR_{1C}$、氰基、卤素或任选被取代的 C_{1-12} 烃基或 2-12 元杂烃基，所述任选的取代是用一个或多个 R_{1B} 取代；每个 R_{1B} 独立地是 $-OR_{1C}$、-

$N(R_{1C})_2$、$-C(O)R_{1C}$、$-C(O)OR_{1C}$、$-C(O)N(R_{1C})_2$、$-N(R_{1C})C(O)OR_{1C}$、氰基或卤素；每个 R_{1C} 独立地是氢或任选被取代的 C_{1-12} 烃基或 2-12 元杂烃基，所述任选的取代是用一个或多个氰基、卤素或羟基取代；每个 R_{2C} 独立地是 $-OR_{2D}$、$-N(R_{2D})_2$、$-C(O)R_{2D}$、$-C(O)OR_{2D}$、$-C(O)N(R_{2D})_2$、$-N(R_{2D})C(O)OR_{2D}$、氰基、卤素或任选被取代的 C_{1-12} 烃基或 2-12 元杂烃基，所述任选的取代是用一个或多个 R_{2D} 取代；每个 R_{2D} 独立地是氢或任选被取代的 C_{1-12} 烃基或 2-12 元杂烃基，所述任选的取代是用一个或多个氰基、卤素或羟基取代；n 是 1-3；并且 m 是 0-3。

[0061] 在这一实施方式所涵盖的具体化合物中：1) R_{2C} 不是羟基或任选被取代的苯基或吡啶基；2) 当 D 是二氮杂环庚烷并且 A 是吡啶基时，R_{2C} 不是 -C(O)O- 叔丁基；3) 当 D 是哌嗪、A 是苯基并且 R_{1A} 是氯时，R_{2C} 不是 -C(O)O- 叔丁基；4) 当 D 是哌啶基、A 是吡啶基并且 R_{1A} 是氯时，R_{2C} 不是 -NHC(O)O- 叔丁基；并且 5) 当 D 是哌啶基、A 是吡啶基并且 R_{1A} 是 $-NHCH_2CH_2CH(CH_3)_2$ 时，R_{2C} 不是 NH_2。

[0062] 在特定化合物中，D 是哌嗪或吡咯烷。

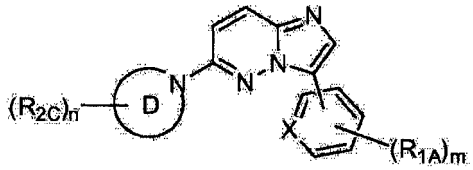
[0063] 在特定化合物中，n 是 1。

[0064] 在特定化合物中，m 是 1。

[0065] 在特定化合物中，A 是吡啶基、噻吩或咪唑。

[0066] 本发明的特定化合物是下式的化合物：

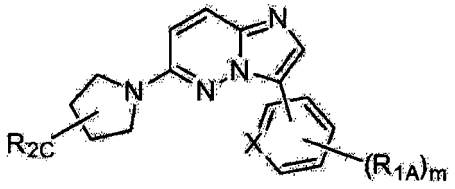
[0067]



[0068] 其中 X 是 CH 或 N。

[0069] 本发明的一种实施方式涵盖下式的化合物及其可药用盐：

[0070]

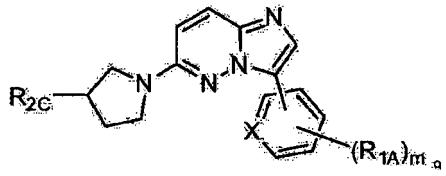


[0071] 其中：X 是 CH 或 N；每个 R_{1A} 独立地是 $-OR_{1C}$、$-N(R_{1C})_2$、$-C(O)R_{1C}$、$-C(O)OR_{1C}$、$-C(O)N(R_{1C})_2$、$-N(R_{1C})C(O)OR_{1C}$、氰基、卤素或任选被取代的 C_{1-12} 烃基或 2-12 元杂烃基，所述任选的取代是用一个或多个 R_{1B} 取代；每个 R_{1B} 独立地是 $-OR_{1C}$、$-N(R_{1C})_2$、$-C(O)R_{1C}$、$-C(O)OR_{1C}$、$-C(O)N(R_{1C})_2$、$-N(R_{1C})C(O)OR_{1C}$、氰基或卤素；每个 R_{1C} 独立地是氢或任选被取代的 C_{1-12} 烃基或 2-12 元杂烃基，所述任选的取代是用一个或多个氰基、卤素或羟基取代；每个 R_{2C} 独立地是 $-OR_{2D}$、$-N(R_{2D})_2$、$-C(O)R_{2D}$、$-C(O)OR_{2D}$、$-C(O)N(R_{2D})_2$、$-N(R_{2D})C(O)OR_{2D}$、氰基、卤素或任选被取代的 C_{1-12} 烃基或 2-12 元杂烃基，所述任选的取代是用一个或多个 R_{2D} 取代；每个 R_{2D} 独立地是氢或任选被取代的 C_{1-12} 烃基或 2-12 元杂烃基，所述任选的取代是用一个或多个氰基、卤素或羟基取代；并且 m 是 0-3。

[0072] 在这一实施方式的某些化合物中，R_{2C} 不是任选被取代的苯基或吡啶基。

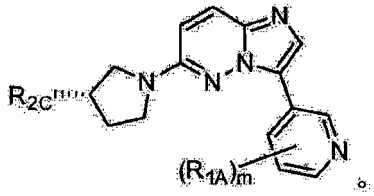
[0073] 本发明的特定化合物是下式的化合物：

[0074]



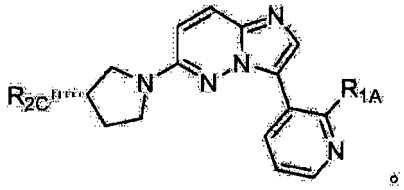
[0075] 本发明的特定化合物是下式的化合物：

[0076]



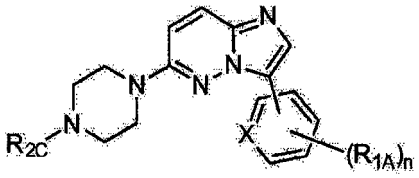
[0077] 本发明的特定化合物是下式的化合物：

[0078]



[0079] 本发明的一种实施方式涵盖下式的化合物及其可药用盐：

[0080]



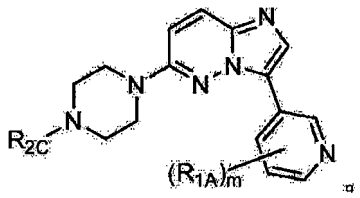
[0081] 其中：X 是 CH 或 N；每个 R_{1A} 独立地是 $-OR_{1C}$、$-N(R_{1C})_2$、$-C(O)R_{1C}$、$-C(O)OR_{1C}$、$-C(O)N(R_{1C})_2$、$-N(R_{1C})C(O)OR_{1C}$、氰基、卤素或任选被取代的 C_{1-12} 烃基或 2-12 元杂烃基，所述任选的取代是用一个或多个 R_{1B} 取代；每个 R_{1B} 独立地是 $-OR_{1C}$、$-N(R_{1C})_2$、$-C(O)R_{1C}$、$-C(O)OR_{1C}$、$-C(O)N(R_{1C})_2$、$-N(R_{1C})C(O)OR_{1C}$、氰基或卤素；每个 R_{1C} 独立地是氢或任选被取代的 C_{1-12} 烃基或 2-12 元杂烃基，所述任选的取代是用一个或多个氰基、卤素或羟基取代；每个 R_{2C} 独立地是 $-OR_{2D}$、$-N(R_{2D})_2$、$-C(O)R_{2D}$、$-C(O)OR_{2D}$、$-C(O)N(R_{2D})_2$、$-N(R_{2D})C(O)OR_{2D}$、氰基、卤素或任选被取代的 C_{1-12} 烃基或 2-12 元杂烃基，所述任选的取代是用一个或多个 R_{2D} 取代；每个 R_{2D} 独立地是氢或任选被取代的 C_{1-12} 烃基或 2-12 元杂烃基，所述任选的取代是用一个或多个氰基、卤素或羟基取代；并且 m 是 0-3。

[0082] 在这一实施方式的某些化合物中，当 X 是 CH、m 是 1 并且 R_{1A} 是氯时，R_{2C} 不是叔丁基。

[0083] 在这一实施方式的某些化合物中，R_{2C} 不是任选被取代的苯基或吡啶基。

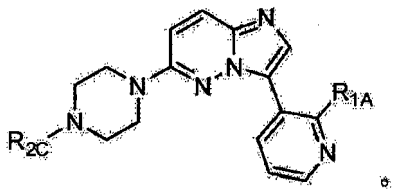
[0084] 本发明的具体的化合物是下式的化合物：

[0085]



[0086] 本发明的具体的化合物是下式的化合物：

[0087]



[0088] 在特定化合物中，R_{1A} 是 $-OR_{1C}$。

[0089] 在特定化合物中，R_{1C} 是任选被取代的 C_{1-12} 烃基（例如 C_{1-6} 烃基、C_{1-4} 烃基）。

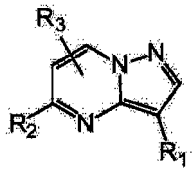
[0090] 在特定化合物中，R_{2C} 是 $-C(O)OR_{2D}$、$-C(O)N(R_{2D})_2$ 或 $-N(R_{2D})C(O)OR_{2D}$。

[0091] 在特定化合物中，每个 R_{2D} 独立地是氢或 C_{1-12} 烃基（例如 C_{1-6} 烃基、C_{1-4} 烃基）。

[0092] 基于吡唑并 [1,5-a] 嘧啶的抑制剂

[0093] 可以在本发明的实施方式中使用的另一类化合物公开在 2013 年 3 月 5 日提交的题为“基于吡唑并 [1,5-a] 嘧啶的化合物、包含它们的组合物以及它们的使用方法”(Pyrazolo[1,5-a]pyrimidine-based Compounds, Compositions Comprising Them, and Methods of Their Use) 的美国专利申请号 13/785,355 中。该申请涵盖了下式的化合物及其可药用盐：

[0094]



[0095] 其中：R_1 是 R_{1A} 或任选被取代的 C_{1-12} 烃基或 2-12 元杂烃基，所述任选的取代是用一个或多个 R_{1A} 取代；每个 R_{1A} 独立地是 $-OR_{1C}$、$-N(R_{1C})_2$、$-C(O)R_{1C}$、$-C(O)OR_{1C}$、$-C(O)N(R_{1C})_2$、$-N(R_{1C})C(O)OR_{1C}$、氰基、卤素或任选被取代的 C_{1-12} 烃基或 2-12 元杂烃基，所述任选的取代是用一个或多个 R_{1B} 取代；每个 R_{1B} 独立地是 $-OR_{1C}$、$-N(R_{1C})_2$、$-C(O)R_{1C}$、$-C(O)OR_{1C}$、$-C(O)N(R_{1C})_2$、$-N(R_{1C})C(O)OR_{1C}$、氰基或卤素；每个 R_{1C} 独立地是氢或任选被取代的 C_{1-12} 烃基或 2-12 元杂烃基，所述任选的取代是用一个或多个氰基、卤素或羟基取代；R_2 是 $-NR_{2A}R_{2B}$，其中 R_{2A} 是氢并且 R_{2B} 是任选被取代的 C_{1-12} 烃基或 2-12 元杂烃基，所述任选的取代是用一个或多个 R_{2C} 取代；或者 R_{2A} 与 R_{2B} 合在一起形成任选被一个或多个 R_{2C} 取代的 4-7 元杂环；每个 R_{2C} 独立地是 $-OR_{2D}$、$-N(R_{2D})_2$、$-C(O)R_{2D}$、$-C(O)OR_{2D}$、$-C(O)N(R_{2D})_2$、$-N(R_{2D})C(O)OR_{2D}$、氰基、卤素或任选被取代的 C_{1-12} 烃基或 2-12 元杂烃基，所述任选的取代是用一个或多个 R_{2D} 取代；每个 R_{2D} 独立地是氢或任选被取代的 C_{1-12} 烃基或 2-12 元杂烃基，所述任选的取代是用一个或多个氰基、卤素或羟基取代；并且 R_3 是氢或任选被一个或多个氰基、卤素或羟基取代的 C_{1-6} 烷基。

[0096] 在特定化合物中，R_1 是 R_{1A}。在某些化合物中，R_1 是任选被取代的 C_{1-12} 烃基。在某些化合物中，R_1 是任选被取代的苯基。在某些化合物中，R_1 是任选被取代的 2-12 元杂烃基（例如 2-8 元杂烃基、2-6 元杂烃基、2-6 元杂烃基）。在某些化合物中，R_1 是任选被取代的吡啶基、噻吩或咪唑。

[0097] 在特定化合物中，R_{1A} 是卤素。在某些化合物中，R_{1A} 是 $-OR_{1C}$、$-N(R_{1C})_2$、$-C(O)R_{1C}$、$-C(O)OR_{1C}$ 或 $-C(O)N(R_{1C})_2$。在某些化合物中，R_{1A} 是 $-OR_{1C}$。

[0098] 在特定化合物中，R_{1B} 是 $-N(R_{1C})_2$、$-OR_{1C}$、卤素。

[0099] 在特定化合物中，R_{2A} 与 R_{2B} 合在一起形成任选被一个或多个 R_{2C} 取代的 4-7 元杂环。

[0100] 在特定化合物中，R_{1C} 是氢。在某些化合物中，R_{1C} 是 C_{1-12} 烃基（例如 C_{1-6} 烃基、C_{1-4} 烃基例如甲基、乙基、丙基）。在某些化合物中，R_{2C} 是 $-C(O)OR_{2D}$、$-C(O)N(R_{2D})_2$ 或 $-N(R_{2D})C(O)OR_{2D}$。

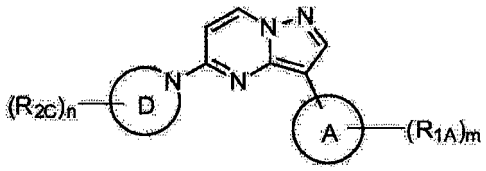
[0101] 在特定化合物中，R_{2D} 是氢。

[0102] 在特定化合物中，R_{2D} 是 C_{1-12} 烃基（例如 C_{1-6} 烃基、C_{1-4} 烃基例如甲基、乙基、丙基）。

[0103] 在特定化合物中，R_3 是氢。

[0104] 本发明的一种实施方式涵盖下式的化合物及其可药用盐：

[0105]



[0106] 其中：A 是环 C_{1-12} 烃基或 4-7 元杂环；D 是 4-7 元杂环；每个 R_{1A} 独立地是 $-OR_{1C}$、$-N(R_{1C})_2$、$-C(O)R_{1C}$、$-C(O)OR_{1C}$、$-C(O)N(R_{1C})_2$、$-N(R_{1C})C(O)OR_{1C}$、氰基、卤素或任选被取代的 C_{1-12} 烃基或 2-12 元杂烃基，所述任选的取代是用一个或多个 R_{1B} 取代；每个 R_{1B} 独立地是 $-OR_{1C}$、$-N(R_{1C})_2$、$-C(O)R_{1C}$、$-C(O)OR_{1C}$、$-C(O)N(R_{1C})_2$、$-N(R_{1C})C(O)OR_{1C}$、氰基或卤素；每个 R_{1C} 独立地是氢或任选被取代的 C_{1-12} 烃基或 2-12 元杂烃基，所述任选的取代是用一个或多个氰基、卤素或羟基取代；每个 R_{2C} 独立地是 $-OR_{2D}$、$-N(R_{2D})_2$、$-C(O)R_{2D}$、$-C(O)OR_{2D}$、$-C(O)N(R_{2D})_2$、$-N(R_{2D})C(O)OR_{2D}$、氰基、卤素或任选被取代的 C_{1-12} 烃基或 2-12 元杂烃基，所述任选的取代是用一个或多个 R_{2D} 取代；每个 R_{2D} 独立地是氢或任选被取代的 C_{1-12} 烃基或 2-12 元杂烃基，所述任选的取代是用一个或多个氰基、卤素或羟基取代；n 是 1-3；并且 m 是 0-3。

[0107] 在特定化合物中，D 不是哌啶基。

[0108] 在特定化合物中，R_{2C} 不是 $-N(R_{2D})_2$。

[0109] 在特定化合物中，A 不是苯基。

[0110] 在特定化合物中，m 是 1。

[0111] 在特定化合物中，R_{2D} 不是乙基。

[0112] 在特定化合物中，当 D 是哌啶基、A 是苯基并且 R_{2C} 是 $-N(R_{2D})_2$ 时，R_{2D} 不是乙基。

[0113] 在特定化合物中，D 是哌嗪或吡咯烷。

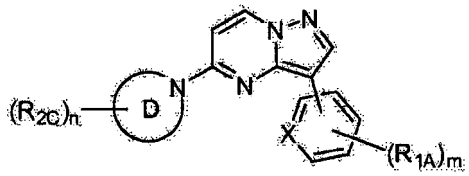
[0114] 在特定化合物中，n 是 1。

[0115] 在特定化合物中，m 是 1。

[0116] 在特定化合物中，A 是吡啶基、噻吩或咪唑。

[0117] 具体的化合物是下式的化合物：

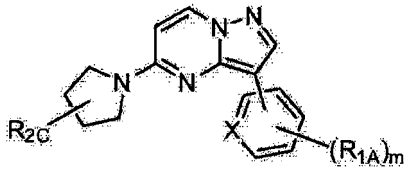
[0118]



[0119] 其中 X 是 CH 或 N。

[0120] 本发明的另一种实施方式涵盖下式的化合物及其可药用盐：

[0121]

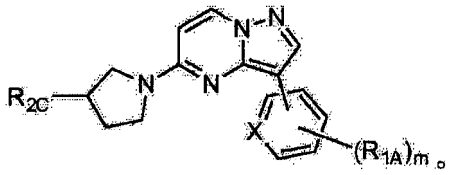


[0122] 其中：X 是 CH 或 N；每个 R_{1A} 独立地是 $-OR_{1C}$、$-N(R_{1C})_2$、$-C(O)R_{1C}$、$-C(O)OR_{1C}$、$-C(O)N(R_{1C})_2$、$-N(R_{1C})C(O)OR_{1C}$、氰基、卤素或任选被取代的 C_{1-12} 烃基或 2-12 元杂烃基，所述任选的取代是用一个或多个 R_{1B} 取代；每个 R_{1B} 独立地是 $-OR_{1C}$、$-N(R_{1C})_2$、$-C(O)R_{1C}$、$-C(O)OR_{1C}$、$-C(O)N(R_{1C})_2$、$-N(R_{1C})C(O)OR_{1C}$、氰基或卤素；每个 R_{1C} 独立地是氢或任选被取代的 C_{1-12} 烃基或 2-12 元杂烃基，所述任选的取代是用一个或多个氰基、卤素或羟基取代；每个 R_{2C} 独立地是 $-OR_{2D}$、$-N(R_{2D})_2$、$-C(O)R_{2D}$、$-C(O)OR_{2D}$、$-C(O)N(R_{2D})_2$、$-N(R_{2D})C(O)OR_{2D}$、氰基、卤素或任选被取代的 C_{1-12} 烃基或 2-12 元杂烃基，所述任选的取代是用一个或多个 R_{2D} 取代；每个 R_{2D} 独立地是氢或任选被取代的 C_{1-12} 烃基或 2-12 元杂烃基，所述任选的取代是用一个或多个氰基、卤素或羟基取代；并且 m 是 0-3。

[0123] 在特定化合物中，R_{2C} 不是任选被取代的苯基或吡啶基。

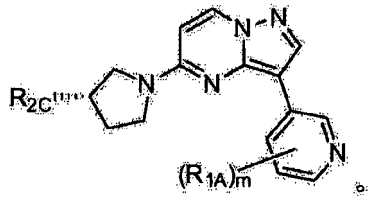
[0124] 具体的化合物是下式的化合物：

[0125]



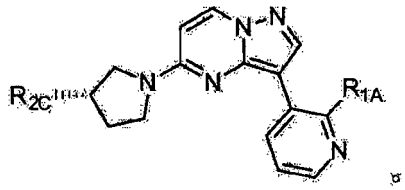
[0126] 具体的化合物是下式的化合物：

[0127]



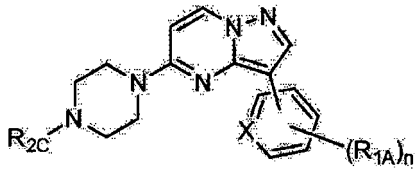
[0128] 具体的化合物是下式的化合物：

[0129]



[0130] 本发明的另一种实施方式涵盖下式的化合物及其可药用盐：

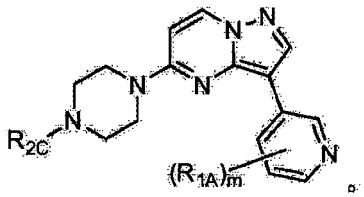
[0131]



[0132] 其中：X 是 CH 或 N；每个 R_{1A} 独立地是 $-OR_{1C}$、$-N(R_{1C})_2$、$-C(O)R_{1C}$、$-C(O)OR_{1C}$、$-C(O)N(R_{1C})_2$、$-N(R_{1C})C(O)OR_{1C}$、氰基、卤素或任选被取代的 C_{1-12} 烃基或 2-12 元杂烃基，所述任选的取代是用一个或多个 R_{1B} 取代；每个 R_{1B} 独立地是 $-OR_{1C}$、$-N(R_{1C})_2$、$-C(O)R_{1C}$、$-C(O)OR_{1C}$、$-C(O)N(R_{1C})_2$、$-N(R_{1C})C(O)OR_{1C}$、氰基或卤素；每个 R_{1C} 独立地是氢或任选被取代的 C_{1-12} 烃基或 2-12 元杂烃基，所述任选的取代是用一个或多个 of 氰基、卤素或羟基取代；每个 R_{2C} 独立地是 $-OR_{2D}$、$-N(R_{2D})_2$、$-C(O)R_{2D}$、$-C(O)OR_{2D}$、$-C(O)N(R_{2D})_2$、$-N(R_{2D})C(O)OR_{2D}$、氰基、卤素或任选被取代的 C_{1-12} 烃基或 2-12 元杂烃基，所述任选的取代是用一个或多个 R_{2D} 取代；每个 R_{2D} 独立地是氢或任选被取代的 C_{1-12} 烃基或 2-12 元杂烃基，所述任选的取代是用一个或多个氰基、卤素或羟基取代；并且 m 是 0-3。

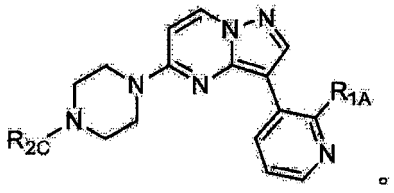
[0133] 具体的化合物是下式的化合物：

[0134]



[0135] 具体的化合物是下式的化合物：

[0136]



[0137] 在特定化合物中，R_{1A} 是 $-OR_{1C}$。

[0138] 在特定化合物中，R_{1C} 是任选被取代的 C_{1-12} 烃基（例如 C_{1-6} 烃基、C_{1-4} 烃基）。

[0139] 在特定化合物中，R_{2C} 是 $-C(O)OR_{2D}$、$-C(O)N(R_{2D})_2$ 或 $-N(R_{2D})C(O)OR_{2D}$。

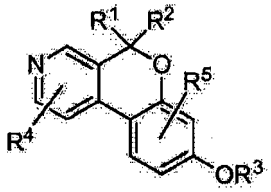
[0140] 在特定化合物中，R_{2D} 独立地是氢或 C_{1-12} 烃基（例如 C_{1-6} 烃基、C_{1-4} 烃基）。

[0141] 基于芳基醚的抑制剂

[0142] 可以在本发明的实施方式中使用的另一类化合物，公开在 2013 年 2 月 26 日提交的题为“基于芳基醚的激酶抑制剂”(Aryl Ether-Base Kinase Inhibitors) 的美国专利申

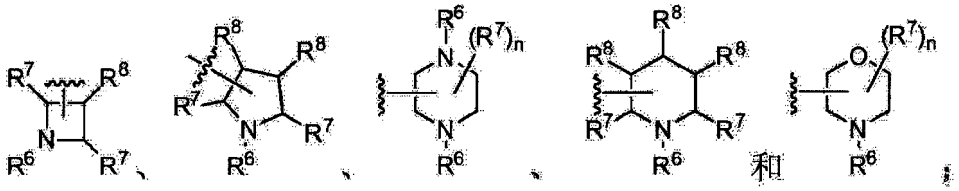
请号 13/777,144 中。该申请涵盖了下式的化合物及其可药用盐：

[0143]



[0144] 其中：R^1 和 R^2 独立地选自氢、C_3-C_6 环烷基和 C_1-C_3 烷基，其中所述 C_1-C_3 烷基任选地被一个、两个或三个基团取代，所述基团独立地选自 C_1-C_3 烷氧基、C_1-C_3 烷基氨基、氨基、氰基、C_1-C_3 二烷基氨基、卤素和羟基；或者 R^1 和 R^2 一起是氧基；R^3 是 C_1-C_3 烷基 -Y 或 C_2-C_8 烷基，其中所述 C_2-C_8 烷基任选地被一个、两个或三个基团取代，所述基团独立地选自 C_1-C_3 烷氧基、C_1-C_3 烷基氨基、C_1-C_3 烷氧基 C_2-C_3 烷基氨基、氨基、芳基、卤素、C_1-C_3 卤素烷基氨基、C_1-C_3 卤素烷基羰基氨基、羟基、$-NR^xR^y$ 和 C_3-C_8 环烷基，其中所述环烷基进一步任选地被一个、两个或三个基团取代，所述基团独立地选自 C_1-C_3 烷氧基、C_1-C_3 烷基、C_1-C_3 烷基氨基、C_1-C_3 烷氧基 C_2-C_3 烷基氨基、氨基、芳基、芳基 C_1-C_3 烷基、卤素、C_1-C_3 卤素烷基、C_1-C_3 卤素烷基氨基和羟基；R^4 选自氢、C_1-C_3 烷氧基、C_1-C_3 烷氧基羰基氨基、C_1-C_3 烷基、C_1-C_3 烷基氨基、C_1-C_3 烷基羰基氨基、氨基、芳基氨基、芳基羰基氨基、C_3-C_6 环烷基氨基、C_3-C_6 环烷基羰基氨基、C_3-C_6 环烷基氧基、卤素、C_1-C_3 卤素烷氧基、C_2-C_3 卤素烷基氨基、C_2-C_3 卤素烷基羰基氨基和羟基；R^5 选自氢、C_1-C_3 烷基、氰基、C_3 环烷基和卤素；R^x 和 R^y 与它们所附连的氮原子一起形成 3 至 6 元环；并且 Y 选自

[0145]



[0146] 其中 R^6 选自氢、C_1-C_6 烷基、C_3-C_6 环烷基和 C_1-C_6 烷基羰基；n 是 0、1、2 或 3；每个 R^7 独立地选自氢、C_1-C_6 烷基、芳基、芳基 C_1-C_3 烷基、C_3-C_6 环烷基、卤素和 C_1-C_3 卤素烷基；并且每个 R^8 独立地选自氢、C_1-C_3 烷氧基和羟基。

[0147] 在特定化合物中，R^1 和 R^2 各为氢。在某些化合物中，R^1 和 R^2 中的一个是氢，另一个是 C_1-C_3 烷基。在某些化合物中，R^1 和 R^2 中的一个是氢，另一个是 C_3-C_6 环烷基。在某些化合物中，R^1 和 R^2 一起是氧基。

[0148] 在特定化合物中，R^3 是任选被氨基取代的 C_2-C_8 烷基。在某些化合物中，R^3 是任选被氨基和芳基取代的 C_2-C_8 烷基，其中所述芳基是苯基。

[0149] 在特定化合物中，R^4 是氢。在某些化合物中，R^4 是氨基。在某些化合物中，R^4 是 C_1-C_3 烷基羰基氨基。

[0150] 在特定化合物中，R^5 是氢。在某些化合物中，R^5 是卤素。

[0151] 使用方法

[0152] 本发明是基于下述创新发现，即作为遗传突变和通过 AAK1 抑制剂给药两者的结果的转接物关联激酶 1(AAK1) 的抑制，能够缓解疼痛。

[0153] 因此，本发明的一种实施方式涵盖治疗或管理疼痛的方法，所述方法包括在需要的患者中抑制 AAK1。疼痛的具体类型包括慢性疼痛、急性疼痛和神经病理性疼痛。神经病理性疼痛的具体类型包括纤维肌痛和外周神经病（例如糖尿病性神经病）。在特定实施方式中，所述抑制通过向患者给药治疗有效量的 AAK1 抑制剂来实现。

具体实施方式

[0154] 从下面的实施例，可以理解本发明的某些方面。

[0155] AAK1 敲除小鼠

[0156] 对 AAK1 基因的破坏纯合 (-/-) 的小鼠通过两种方法来制备：基因捕获和同源重组。

[0157] 基因捕获是一种随机插入突变方法，其使用编码受体或可选择标志物基因的 DNA 片段作为诱变剂。已经设计了以允许细胞剪接机制将载体编码的外显子剪接到细胞 mRNA 中的方式整合到内含子或基因中的基因捕获载体。通常，基因捕获载体含有可选择标志物序列，其前方带有强的剪接受体序列并且没有启动子。因此，当这样的载体整合到基因中时，细胞剪接机制将来自于被捕获的基因的外显子剪接在可选择标志物序列的 5' 末端上。通常，这样的可选择标志物基因只有在编码所述基因的载体已整合到内含子中时才能表达。得到的基因捕获事件随后通过选择能够在选择性培养基中存活的细胞来鉴定。

[0158] 胚胎干细胞（来自于衍生的鼠类株系 A129 的 Lex-1 细胞）通过包括将至少一部分遗传工程改造的载体序列插入到目标基因中的过程来突变，将突变的胚胎干细胞微注射到胚囊中，随后使用已建立的方法将其导入到假孕的雌性宿主中并养育到分娩。参见例如《小鼠诱变》(Mouse Mutagenesis)，1998，Zambrowicz 等主编，Lexicon Press，The Woodlands，TX。随后繁育得到的嵌合动物，以产生能够对在目标基因中含有工程化突变的等位基因进行种系传递的后代。

[0159] AAK1 基因破坏的小鼠也通过同源重组来制造。在这种情况下，通过本领域中已知的方法移除鼠类 AAK1 基因的第二个编码外显子（参见 GenBank 登记号 NM_177762）。参见例如美国专利号 5,487,992、5,627,059 和 5,789,215。

[0160] 将对 AAK1 基因的破坏纯合 (-/-) 的小鼠与对 AAK1 基因的破坏杂合 (+/-) 的小鼠和野生型 (+/+) 同窝仔畜联合进行研究。在这一分析期间，使用被设计用于评估哺乳动物对象中主要器官系统的功能的医学诊断程序的集成套件，对小鼠进行医学病情检查。纯合 (-/-) “敲除”小鼠与它们的杂合 (+/-) 和野生型 (+/+) 同窝仔畜联合进行研究。AAK1 基因的破坏通过 Southern 分析来验证。通过 RT-PCR 来检测 AAK1 的鼠类同源物在鼠大脑、脊髓、眼、胸腺、脾、肺、肾、肝、骨骼肌、骨、胃、小肠和结肠、心、脂肪、哮喘的肺、LPS 肝、血液、捆绑的心脏、主动脉树、前列腺和乳腺（5 周处女鼠、成熟处女鼠、12DPC、分娩后 3 天（泌乳）、哺乳期后 3 天（早期退化）和哺乳期后 7 天（晚期退化））中的表达。

[0161] AAK1 纯合 (-/-) 和它们的野生型 (+/+) 同窝仔畜使用福尔马林爪试验来测试，以便评估它们的急性和强直性伤害感受响应。对于这些试验来说，使用自动化伤害感受分析仪 (Automatic Nociception Analyzers)（购自 University of California，San Diego 的 Ozaki 实验室）。在试验前 30 分钟，将金属带置于每只小鼠的左后爪周围。在 30 分钟的适应期后，将 20μl 5%福尔马林皮下注射到左后爪的背侧表面中。将小鼠分开饲养在圆柱

形仓室中 45 分钟。通过电磁场，用计算机记录每分钟退缩数、阶段 I（急性阶段＝前 8 分钟）的总退缩数和阶段 II（强直阶段＝ 20-40 分钟之间的时间）的总退缩数。参见 Yaksh TL, Ozaki G, McCumber D, Rathbun M, Svensson C, Malkmus S, Yaksh MC.，用于福尔马林伤害感受生物测定法的自动退缩检测系统 (An automated flinch detecting system for use in the formalin nociceptive bioassay)，J Appl Physiol.，2001 ;90:2386-402。

[0162] 如图 1 中所示，使用纯合 (-/-) 雌性小鼠 (n ＝ 16)、野生型雌性 (n ＝ 15)、纯合 (-/-) 雄性小鼠 (n ＝ 9) 和野生型雄性 (n ＝ 18) 获得了阶段 1 和阶段 2 的数据。在所有组中和两个阶段中，AAK1 纯合 (-/-) 小鼠与它们的野生型 (+/+) 同窝仔畜相比表现出明显更少的记录到的爪退缩。

[0163] Caliper 测定法

[0164] 测定法在U型底384孔板中进行。最终测定体积为30μl，其从在测定缓冲液 (10mM Tris-HCL pH 7.4，10mM $MgCl_2$，0.01% Tween-20 和 1.0mM DTT) 中添加 15μl 酶和底物（荧光素化的肽 (5-FAM)-Aha-KEEQSQITSQVTGQIGWR-NH2 和 ATP) 和试验化合物来制备。通过将细菌表达的 GST-Xa-hAAK1 与底物和试验化合物合并来启动反应。将反应在室温温育 3 小时，并通过向每个样品加入 60μl 35mM EDTA 缓冲液来终止反应。反应在 Caliper LabChip 3000 (Caliper, Hopkinton, MA) 上，通过荧光底物和磷酸化产物的电泳分离来分析。通过与作为 100% 抑制的 EDTA 淬灭的对照反应和作为 0% 抑制的仅仅介质的反应进行比较，来计算抑制数据。测定体系中试剂的终浓度是 ATP，22μM ;(5-FAM)-Aha-KEEQSQITSQVTGQIGWR-NH2，1.5μM ;GST-Xa-hAAK1，3.5nM ;以及 DMSO，1.6%。产生剂量响应曲线以确定抑制 50% 的激酶活性所需的浓度 (IC_{50})。将化合物以 10mM 浓度溶解在二甲基亚枫 (DMSO) 中，并在 11 个浓度下进行评估。IC_{50} 值通过非线性回归分析来推衍。

[0165] P81 过滤板测定法

[0166] 使用 Mutiprobe (PerkinElmer) 和 Biomek FX (Beckman Coulter) 将化合物在 Labcyte LDV 板 (Labcyte，目录号 LP-0200) 中连续稀释，使得最高化合物浓度为 96μM。然后使用 ECHO 550 液体操作器 (Labcyte) 将化合物加入 (75nL 每孔）到 Greiner 384 孔反应板 (Greiner，#781076) 中，然后向用于阴性对照的第 1 和 13 列的每个孔加入总共 12μl 反应缓冲液（含有 Tween 和 DTT 的 IMAP 缓冲液，来自于 Molecular Devices)，并向剩余的孔加入 12μl 2X AAK1 (0.2nM 全长人类蛋白，NCBI 登记号 NP_055726.2)。然后将酶与化合物在 RT 预温育 10 分钟。在使用 Minitrak (PerkinElmer) 添加 12μl 含有 2XMu2 (0.2μM，全长人类蛋白）、2x 冷 ATP (2μM) 和 1.3μCi 热 ^{33}P-ATP 的底物混合物后，反应开始。反应在 RT 进行 1 小时。同时，将 Millipore 384 孔 P81 过滤板 (Millipore，目录号 MZPHNOW10) 置于洗板机 (Zoom ZW，来自于 Titertek) 上，并用 50μl 1% 磷酸预先润湿。然后在向每个孔添加 24μl 2% 磷酸后停止激酶反应，然后使用 Minitrak 从每个孔转移 40μl 到预先润湿的 Millipore 384 孔 P81 过滤板中。将反应混合物在 P81 板中在 RT 温育 10 分钟，然后使用 Zoom 过滤板清洗机用 100μl/ 孔的 1% 磷酸清洗 5 次。将每个过滤板的底部密封，然后向每个孔加入 20μlMicroscint 40，用 Flashplate 盖子密封板的顶部，然后等待 1 小时，随后在 TopCount (PerkinElmer) 上读数。

[0167] 基于 HEK281 细胞的测定法

[0168] HEK293F 细胞培养在含有 DMEM (Gibco，目录号 11965)、10 % FBS (SAFC

Biosciences，目录号 12103C)、1X GPS(谷氨酰胺、青霉素和链霉素)的培养基中。在第 1 天，将细胞铺在 10cm 培养皿上，使得它们在转染时～ 80％合生。在转染时，10cm 培养皿中约有 1 千 2 百万个细胞。在第 2 天，将每个培养皿用 48ug DNA 和 144ul Lipofectamine 2000(Invitrogen，目录号 11668-019) 转染。所述 DNA 包含含有 3ug AAK1/HA/pIRES(全长人类，NCBI 登记号 NP_055726.2)、45μg Flag/AP2M1/pcDNA(全长人类)和 1.5ml OPTI-MEM 的混合物(每个 10cm 培养皿)。所述 Lipofectamine 2000 由含有 144μl Lipofectamine 2000 和 1.5ml OPTI-MEM 的混合物构成(每个 10cm 培养皿)。将每种混合物转移到单独的 15ml 管中并在 RT 温育 5 分钟，然后将两种混合物合并，并在 RT 温育 20 分钟。然后从每个 10cm 培养皿吸取出生长培养基，并更换为 10ml DMEM+10％ FBS(无 GPS)。最后，向每个 10cm 培养皿加入 3ml DNA/Lipofectamine 混合物并轻柔混合，然后将培养皿在 37℃和 5％ CO_2 下温育过夜。

[0169] 在第 3 天，将化合物在 100％ DMSO 中稀释至最终 1000X 浓度，然后进行 3 倍连续稀释，获得总共 5 个试验浓度。每个 10cm 培养皿试验 4 种化合物。然后将 1ul 每种化合物稀释液移取到 96 孔深孔板中，然后在每个孔中加入 500μl DMEM+0.5％ FBS，以获得每种化合物的 2X 终浓度。通过简单的吸取 (HEK293 细胞在此时容易从培养皿上下来)将细胞重悬浮在 10cm 培养皿中，然后转移至 50ml 锥形管中，并通过以 1000rpm 离心 5min 沉淀细胞。然后将每个 10cm 培养皿的细胞沉淀物重悬浮在 2.75ml DMEM+0.5％ FBS 中，并将 100μl 细胞悬液转移至 96 孔 TC 板的每个孔中。最后，将 100μl 在 DMEM+0.5％ FBS 中稀释的 2X 化合物加入到含有细胞悬液的孔中，以获得 1X 终浓度。然后将板在 37℃和 5％ CO_2 下温育 3 小时，随后将来自于每个孔的细胞悬液转移至 12 管 PCR 条板中。将 PCR 条板在移液器吸头盒中以 1000rpm 离心 5 分钟以沉淀细胞，然后通过移液除去培养基而不扰动细胞沉淀物。

[0170] 为了准备用于 Western 印迹分析，将细胞沉淀物重悬浮在 40ul 1X LDS-PAGE 样品缓冲液 (Invitrogen，目录号 NP0008)+2X Halt 磷酸酶和蛋白酶抑制剂混合物 (Thermo Scientific，目录号 1861284) 中，然后用设置在 5 的 microtip 超声仪对每个样品超声 8-10 秒。向每个样品加入 5ul 10X NuPage 样品还原试剂(含有 50mM DTT)，然后在 PCR 仪上在 70℃热变性 10min。将每个样品总共 10μl 上样到 4-20％ Tris- 甘氨酸 Criterion 26 孔凝胶 (Biorad，目录号 345-0034) 的每条道中用于 phospho-mu2 印迹，并将每条道 10μl 样品上样到 4-12％ Bis-Tris(+MES 缓冲液)NuPAGE 26 孔凝胶 (Invitrogen，目录号 WG1403BX10) 中用于 mu2 印迹。作为对照，将 2ng phospho-mu2 或 20ng mu2/Flag 蛋白上样到每块凝胶的最后一个孔中。在 SDS-PAGE 后，使用 iBlot 将每块凝胶上的样品转移到 PVDF 膜，并将膜在 TBST+5％奶粉中阻断 1 小时，然后用 TBST 清洗 3 次，每次 5-10min。Criterion 凝胶用 TBST+5％ BSA 中的兔抗 phospho-mu2 抗体 (1:5000；由 New England Peptide 生产的兔多克隆抗体，并在 Lexicon 亲和纯化)探测，而 NuPAGE 凝胶用 TBST+5％奶粉中的小鼠抗 Flag 抗体 (1:500；Sigma，目录号 F1804) 探测，并将这些第一抗体在振荡器上在 4℃温育过夜。

[0171] 在第 4 天，将 Western 印迹用 TBST 清洗三次，每次 5-10 分钟，用 TBST+5％奶粉中的抗兔抗体 -HRP(1:2000；BioRad，目录号 170-6515) 或抗小鼠抗体 -HRP(1:2000；Biorad，目录号 170-6516) 在 RT 下探测 1 小时，用 TBST 清洗 3 次，每次 10 分钟，并在 Versadoc 上用 ECL 试剂 (GE Healthcare，目录号 RPN2132) 显色。最后，将相机设置成每 30 秒获取照片

共 10 分钟，并为每个印迹保存没有饱和信号的最佳图像（当信号饱和时，条带将突显为红色）。对每个条带进行体积分析以获得密度值。通过首先对 Mu2 总表达水平进行归一化，然后与 0％和 100％对照进行比较，来计算每个样品的抑制百分率。然后使用 Excel 拟合软件计算 IC_{50} 值。

[0172] 基于咪唑并 [1,2-b] 哒嗪的抑制剂的体外数据

[0173] 为本发明的各种化合物获得的体外数据提供在下面的表 1 中，其中“MW”是指分子量，“P81 测定法”是指上面描述的 P81 过滤板测定法，“CBA”是指上面描述的基于 HEK281 细胞的测定法，“--”是指未获得给定测定法的结果，“*”是指小于或等于 1.0μM，“**”是指小于或等于 0.1μM 的值，并且“***”是指小于或等于 0.01μM。

[0174] 表 1

[0175]

化合物	MW	CBA IC_{50}	P81 IC_{50}
(2S)-2-(((3-(4-(吡咯烷-2-yl)苯基)咪唑并[1,2-b]哒嗪-6-基)氨基)甲基)吡咯烷-1-甲酸乙基酯	434.5	**	--
(2S)-2-(((3-(4-(吡咯烷-2-基)苯基)咪唑并[1,2-b]哒嗪-6-基)氨基)甲基)吡咯烷-1-甲酸甲基酯	420.5	**	--
(2S)-2-(((3-(吡啶-4-基)咪唑并[1,2-b]哒嗪-6-基)氨基)甲基)吡咯烷-1-甲酸四氢呋喃-3-基酯	408.5	--	***
(2S)-2-(((3-溴咪唑并[1,2-b]哒嗪-6-基)氨基)甲基)吡咯烷-1-甲酸四氢呋喃-3-基酯	410.3	--	***
(4-(3-(2-甲氧基苯基)咪唑并[1,2-b]哒嗪-6-基)哌嗪-1-基)(吡咯烷-1-基)甲酮	406.5	**	***
(4-(3-(2-甲氧基苯基)咪唑并[1,2-b]哒嗪-6-基)哌嗪-1-基)(哌啶-1-基)甲酮	420.5	**	***
(4-(3-(2-甲氧基吡啶-3-基)咪唑并[1,2-b]哒嗪-6-基)哌嗪-1-基)(吡咯烷-1-基)甲酮	407.5	**	***
(4-(3-(2-甲氧基吡啶-3-基)咪唑并[1,2-b]哒嗪-6-基)哌嗪-1-基)(哌啶-1-基)甲酮	421.5	**	***
(4-(3-(3-甲氧基吡啶-4-基)咪唑并[1,2-b]哒嗪-6-基)哌嗪-1-基)(吡咯烷-1-基)甲酮	407.5	**	***
(4-(3-(吡啶-2-基)咪唑并[1,2-b]哒嗪-6-基)哌嗪-1-基)(吡咯烷-1-基)甲酮	377.4	**	***
(4-(3-苯基咪唑并[1,2-b]哒嗪-6-基)哌嗪-1-基)(哌啶-1-基)甲酮	390.5	**	***
(4-(3-苯基咪唑并[1,2-b]哒嗪-6-基)哌嗪-1-基)(吡咯烷-1-基)甲酮	376.5	*	***
(4-(6-((2-(环戊基氧基)乙基)氨基)咪唑并[1,2-b]哒嗪-3-基)苯基)甲醇	352.4	--	***
(4-(6-(丁基硫基)咪唑并[1,2-b]哒嗪-3-基)苯基)甲胺	312.4	*	--

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(4-氨基哌啶-1-基)(4-(6-(丁基氨基)咪唑并[1,2-b]哒嗪-3-基)苯基)甲酮	392.5	*	--
(R)-甲基(2-((3-(4-(吡咯烷-2-基)苯基)咪唑并[1,2-b]哒嗪-6-基)氨基)乙基)氨基甲酸异丙基酯	422.5	**	--
(R)-N-丁基-3-(4-(吡咯烷-2-基)苯基)咪唑并[1,2-b]哒嗪-6-胺	335.4	*	--
(S)-1-(2-(((3-(2,4-二甲基噻唑-5-基)咪唑并[1,2-b]哒嗪-6-基)氨基)甲基)吡咯烷-1-基)-3-甲基丁-1-酮	412.6	***	***
(S)-1-(2-(((3-(2-氯苯基)咪唑并[1,2-b]哒嗪-6-基)氨基)甲基)吡咯烷-1-基)-3-甲基丁-1-酮	411.9	--	--
(S)-1-(2-(((3-(2-氟吡啶-4-基)咪唑并[1,2-b]哒嗪-6-基)氨基)甲基)吡咯烷-1-基)-3-甲基丁-1-酮	396.5	--	***
(S)-1-(2-(((3-(2-甲氧基苯基)咪唑并[1,2-b]哒嗪-6-基)氨基)甲基)吡咯烷-1-基)-3-甲基丁-1-酮	407.5	***	--
(S)-1-(2-(((3-(2-甲氧基苯基)咪唑并[1,2-b]哒嗪-6-基)氨基)甲基)吡咯烷-1-基)乙酮	365.4	**	--
(S)-1-(2-(((3-(3-氯苯基)咪唑并[1,2-b]哒嗪-6-基)氨基)甲基)吡咯烷-1-基)-3-甲基丁-1-酮	411.9	***	***
(S)-1-(2-(((3-(3-氟苯基)咪唑并[1,2-b]哒嗪-6-基)氨基)甲基)吡咯烷-1-基)-3-甲基丁-1-酮	395.5	***	***
(S)-1-(2-(((3-(3-甲氧基苯基)咪唑并[1,2-b]哒嗪-6-基)氨基)甲基)吡咯烷-1-基)-3-甲基丁-1-酮	407.5	**	***
(S)-1-(2-(((3-(3-甲氧基吡啶-4-基)咪唑并[1,2-b]哒嗪-6-基)氨基)甲基)吡咯烷-1-基)乙酮	366.4	**	--
(S)-1-(2-(((3-(3-甲氧基吡啶-4-基)咪唑并[1,2-b]哒嗪-6-基)氨基)甲基)吡咯烷-1-基)-3-甲基丁-1-酮	408.5	***	--
(S)-1-(2-(((3-(4-(氨基甲基)苯基)咪唑并[1,2-b]哒嗪-6-基)氨基)甲基)吡咯烷-1-基)-3-甲基丁-1-酮	406.5	***	--
(S)-1-(2-(((3-(4-(氨基甲基)苯基)咪唑并[1,2-b]哒嗪-6-基)氨基)甲基)吡咯烷-1-基)-2,2-二甲基丙-1-酮	406.5	**	***

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(S)-1-(2-(((3-(4-(氨基甲基)苯基)咪唑并[1,2-b]哒嗪-6-基)氨基)甲基)吡咯烷-1-基)丁-1-酮	392.5	***	***
(S)-1-(2-(((3-(4-(氨基甲基)苯基)咪唑并[1,2-b]哒嗪-6-基)氨基)甲基)吡咯烷-1-基)-3,3-二甲基丁-1-酮	420.6	**	***
(S)-1-(2-(((3-(4-氟苯基)咪唑并[1,2-b]哒嗪-6-基)氨基)甲基)吡咯烷-1-基)-3-甲基丁-1-酮	395.5	**	***
(S)-1-(2-(((3-(4-甲氧基苯基)咪唑并[1,2-b]哒嗪-6-基)氨基)甲基)吡咯烷-1-基)-3-甲基丁-1-酮	407.5	*	***
(S)-1-(2-(((3-(环戊-1-烯-1-基)咪唑并[1,2-b]哒嗪-6-基)氨基)甲基)吡咯烷-1-基)-3-甲基丁-1-酮	367.5	--	***
(S)-1-(2-(((3-(吡啶-4-基)咪唑并[1,2-b]哒嗪-6-基)氨基)甲基)吡咯烷-1-基)丁-1-酮	364.4	--	***
(S)-1-(2-(((3-溴咪唑并[1,2-b]哒嗪-6-基)氨基)甲基)吡咯烷-1-基)-3-甲基丁-1-酮	380.3	**	--
(S)-1-(3,3-二甲基丁基)-5-(((3-(2-甲氧基苯基)咪唑并[1,2-b]哒嗪-6-基)氨基)甲基)吡咯烷-2-酮	421.5	*	***
(S)-1-(3,3-二甲基丁基)-5-(((3-(2-甲氧基吡啶-3-基)咪唑并[1,2-b]哒嗪-6-基)氨基)甲基)吡咯烷-2-酮	422.5	***	***
(S)-1-(3,3-二甲基丁基)-5-(((3-(吡啶-4-基)咪唑并[1,2-b]哒嗪-6-基)氨基)甲基)吡咯烷-2-酮	392.5	--	***
(S)-1-(3,3-二甲基丁基)-5-(((3-苯基咪唑并[1,2-b]哒嗪-6-基)氨基)甲基)吡咯烷-2-酮	391.5	*	***
(S)-1-甲基环戊基 2-(((3-溴咪唑并[1,2-b]哒嗪-6-基)氨基)甲基)吡咯烷-1-甲酸酯	422.3	*	***
(S)-2-(((3-溴咪唑并[1,2-b]哒嗪-6-基)氨基)甲基)-N-(叔丁基)吡咯烷-1-甲酰胺	395.3	**	***
(S)-(1-(3-(2-甲氧基吡啶-3-基)咪唑并[1,2-b]哒嗪-6-基)吡咯烷-3-基)(甲基)氨基甲酸2,2,2-三氟乙基酯	450.4	**	***
(S)-2-氨基-N-(4-(6-(丁基氨基)咪唑并[1,2-b]哒嗪-3-基)苄基)-4-甲基戊酰胺	408.5	**	--

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(S)-2-环丙基-N-(1-(3-(2-羟基吡啶-3-基)咪唑并[1,2-b]哒嗪-6-基)吡咯烷-3-基)-N-甲基乙酰胺	392.5	--	***
(S)-(1-(3-(2-甲氧基吡啶-3-基)咪唑并[1,2-b]哒嗪-6-基)吡咯烷-3-基)(甲基)氨基甲酸2-甲氧基乙基酯	426.5	--	**
(S)-3-(4-(氨基甲基)苯基)-N-((四氢呋喃-2-基)甲基)咪唑并[1,2-b]哒嗪-6-胺	323.4	**	--
(S)-3-(6-(((1-(3-甲基丁酰基)吡咯烷-2-基)甲基)氨基)咪唑并[1,2-b]哒嗪-3-基)苯甲腈	402.5	**	***
(S)-3,3,3-三氟-1-(2-(((3-苯基咪唑并[1,2-b]哒嗪-6-基)氨基)甲基)吡咯烷-1-基)丙-1-酮	403.4	***	***
(S)-3,3,3-三氟-N-(1-(3-(2-羟基吡啶-3-基)咪唑并[1,2-b]哒嗪-6-基)吡咯烷-3-基)-N-甲基丙酰胺	420.4	--	***
(S)-3,3-二甲基-1-(2-(((3-(吡啶-4-基)咪唑并[1,2-b]哒嗪-6-基)氨基)甲基)吡咯烷-1-基)丁-1-酮	392.5	**	***
(S)-3-甲基-1-(2-(((3-(2-甲基吡啶-4-基)咪唑并[1,2-b]哒嗪-6-基)氨基)甲基)吡咯烷-1-基)丁-1-酮	392.5	**	***
(S)-3-甲基-1-(2-(((3-(间甲苯基)咪唑并[1,2-b]哒嗪-6-基)氨基)甲基)吡咯烷-1-基)丁-1-酮	391.5	*	***
(S)-3-甲基-1-(2-(((3-(吡啶-4-基)咪唑并[1,2-b]哒嗪-6-基)氨基)甲基)吡咯烷-1-基)丁-1-酮	378.5	**	--
(S)-3-甲基-1-(2-(((3-苯基咪唑并[1,2-b]哒嗪-6-基)氨基)甲基)吡咯烷-1-基)丁-1-酮	377.5	**	***
(S)-4-(6-(((1-(3-甲基丁酰基)吡咯烷-2-基)甲基)氨基)咪唑并[1,2-b]哒嗪-3-基)苯甲腈	402.5	***	***
(S)-5-(((3-(4-(氨基甲基)苯基)咪唑并[1,2-b]哒嗪-6-基)氨基)甲基)-1-异戊基吡咯烷-2-酮	406.5	**	***
(S)-5-(((3-(4-(氨基甲基)苯基)咪唑并[1,2-b]哒嗪-6-基)氨基)甲基)-1-(3,3-二甲基丁基)吡咯烷-2-酮	420.6	**	***
(S)-5-(((3-溴咪唑并[1,2-b]哒嗪-6-基)氨基)甲基)-1-(3,3-二甲基丁基)吡咯烷-2-酮	394.3	**	***

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(S)-2-(((3-(2-甲氧基苯基)咪唑并[1,2-b]哒嗪-6-基)氨基)甲基)吡咯烷-1-甲酸环丁基酯	421.5	**	***
(S)-2-(((3-(吡啶-4-基)咪唑并[1,2-b]哒嗪-6-基)氨基)甲基)吡咯烷-1-甲酸环丁基酯	392.5	***	***
(S)-2-(((3-溴咪唑并[1,2-b]哒嗪-6-基)氨基)甲基)吡咯烷-1-甲酸环丁基酯	394.3	**	***
(S)-2-(((3-(4-(氨基甲基)苯基)咪唑并[1,2-b]哒嗪-6-基)氨基)甲基)吡咯烷-1-甲酸环戊基酯	434.5	***	***
(S)-2-(((3-(吡啶-4-基)咪唑并[1,2-b]哒嗪-6-基)氨基)甲基)吡咯烷-1-甲酸环戊基酯	406.5	***	***
(S)-2-(((3-溴咪唑并[1,2-b]哒嗪-6-基)氨基)甲基)吡咯烷-1-甲酸环戊基酯	408.3	***	***
(S)-2-(((3-氰基咪唑并[1,2-b]哒嗪-6-基)氨基)甲基)吡咯烷-1-甲酸环戊基酯	354.4	--	***
(S)-2-(((3-苯基咪唑并[1,2-b]哒嗪-6-基)氨基)甲基)吡咯烷-1-甲酸环戊基酯	405.5	**	***
(S)-2-(((3-(吡啶-4-基)咪唑并[1,2-b]哒嗪-6-基)氨基)甲基)吡咯烷-1-甲酸环丙基甲基酯	392.5	--	***
(S)-2-(((3-溴咪唑并[1,2-b]哒嗪-6-基)氨基)甲基)吡咯烷-1-甲酸环丙基甲基酯	394.3	--	***
(S)-(1-(3-(2-甲氧基吡啶-3-基)咪唑并[1,2-b]哒嗪-6-基)吡咯烷-3-基)(甲基)氨基甲酸乙基酯	396.4	**	***
(S)-乙基 2-(((3-(2-甲氧基苯基)咪唑并[1,2-b]哒嗪-6-基)氨基)甲基)吡咯烷-1-甲酸酯	395.5	**	--
(S)-2-(((3-(3-甲氧基吡啶-4-基)咪唑并[1,2-b]哒嗪-6-基)氨基)甲基)吡咯烷-1-甲酸乙基酯	396.4	**	--
(S)-2-(((3-(4-(氨基甲基)苯基)咪唑并[1,2-b]哒嗪-6-基)氨基)甲基)吡咯烷-1-甲酸乙基酯	394.5	***	--
(S)-2-(((3-(吡啶-4-基)咪唑并[1,2-b]哒嗪-6-基)氨基)甲基)吡咯烷-1-甲酸乙基酯	366.4	**	--

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(S)-2-(((3-溴咪唑并[1,2-b]哒嗪-6-基)氨基)甲基)吡咯烷-1-甲酸乙基酯	368.2	**	--
(S)-(1-(3-(2-(二氟甲氧基)吡啶-3-基)咪唑并[1,2-b]哒嗪-6-基)吡咯烷-3-基)(甲基)氨基甲酸异丙基酯	446.5	--	***
(S)-(1-(3-(2-甲氧基-6-甲基吡啶-3-基)咪唑并[1,2-b]哒嗪-6-基)吡咯烷-3-基)(甲基)氨基甲酸异丙基酯	424.5	***	***
(S)-(1-(3-(2-甲氧基吡啶-3-基)咪唑并[1,2-b]哒嗪-6-基)吡咯烷-3-基)(甲基)氨基甲酸异丙基酯	410.5	***	***
(S)-(1-(3-(3,6-二甲氧基哒嗪-4-基)咪唑并[1,2-b]哒嗪-6-基)吡咯烷-3-基)(甲基)氨基甲酸异丙基酯	441.5	**	***
(S)-(1-(3-溴咪唑并[1,2-b]哒嗪-6-基)吡咯烷-3-基)(甲基)氨基甲酸异丙基酯	382.3	--	***
(S)-2-(((3-(2-甲氧基苯基)咪唑并[1,2-b]哒嗪-6-基)氨基)甲基)吡咯烷-1-甲酸异丙基酯	409.5	***	--
(S)-2-(((3-(3-甲氧基吡啶-4-基)咪唑并[1,2-b]哒嗪-6-基)氨基)甲基)吡咯烷-1-甲酸异丙基酯	410.5	***	--
(S)-2-(((3-(4-(氨基甲基)苯基)咪唑并[1,2-b]哒嗪-6-基)氨基)甲基)吡咯烷-1-甲酸异丙基酯	408.5	***	--
(S)-2-(((3-(丙-1-烯-2-基)咪唑并[1,2-b]哒嗪-6-基)氨基)甲基)吡咯烷-1-甲酸异丙基酯	343.4	**	--
(S)-2-(((3-溴咪唑并[1,2-b]哒嗪-6-基)氨基)甲基)吡咯烷-1-甲酸异丙基酯	382.3	*	--
(S)-2-(((3-氯咪唑并[1,2-b]哒嗪-6-基)氨基)甲基)吡咯烷-1-甲酸异丙基酯	337.8	**	--
(S)-2-(((3-氰基咪唑并[1,2-b]哒嗪-6-基)氨基)甲基)吡咯烷-1-甲酸异丙基酯	328.4	*	***
(S)-2-(((3-环丙基咪唑并[1,2-b]哒嗪-6-基)氨基)甲基)吡咯烷-1-甲酸异丙基酯	343.4	*	--
(S)-2-(((3-乙烯基咪唑并[1,2-b]哒嗪-6-基)氨基)甲基)吡咯烷-1-甲酸异丙基酯	329.4	***	--

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(S)-甲基(1-(3-(吡啶-3-基)咪唑并[1,2-b]哒嗪-6-基)吡咯烷-3-基)氨基甲酸异丙基酯	380.4	**	***
(S)-甲基(1-(3-(吡啶-4-基)咪唑并[1,2-b]哒嗪-6-基)吡咯烷-3-基)氨基甲酸异丙基酯	380.4	--	**
(S)-甲基(2-((3-(4-(吡咯烷-2-基)苯基)咪唑并[1,2-b]哒嗪-6-基)氨基)乙基)氨基甲酸异丙基酯	422.5	**	--
(S)-2-(((3-(2-甲氧基苯基)咪唑并[1,2-b]哒嗪-6-基)氨基)甲基)吡咯烷-1-甲酸甲基酯	381.4	**	--
(S)-2-(((3-(3-甲氧基吡啶-4-基)咪唑并[1,2-b]哒嗪-6-基)氨基)甲基)吡咯烷-1-甲酸甲基酯	382.4	**	--
(S)-2-(((3-(4-(氨基甲基)苯基)咪唑并[1,2-b]哒嗪-6-基)氨基)甲基)吡咯烷-1-甲酸甲基酯	380.4	**	--
(S)-2-(((3-溴咪唑并[1,2-b]哒嗪-6-基)氨基)甲基)吡咯烷-1-甲酸甲基酯	354.2	*	--
(S)-N-(1-(3-(2-羟基吡啶-3-基)咪唑并[1,2-b]哒嗪-6-基)吡咯烷-3-基)-N-甲基环戊烷甲酰胺	406.5	--	**
(S)-N-(1-(3-(2-羟基吡啶-3-基)咪唑并[1,2-b]哒嗪-6-基)吡咯烷-3-基)-2-甲氧基-N-甲基乙酰胺	382.4	--	*
(S)-N-(1-(3-(2-羟基吡啶-3-基)咪唑并[1,2-b]哒嗪-6-基)吡咯烷-3-基)-N,3-二甲基丁酰胺	394.5	--	**
(S)-N-(1-(3-(2-羟基吡啶-3-基)咪唑并[1,2-b]哒嗪-6-基)吡咯烷-3-基)-N,3,3-三甲基丁酰胺	408.5	*	**
(S)-N-(1-(3-(2-羟基吡啶-3-基)咪唑并[1,2-b]哒嗪-6-基)吡咯烷-3-基)-N-甲基丁酰胺	380.4	--	**
(S)-N-(1-(3-(2-甲氧基苯基)咪唑并[1,2-b]哒嗪-6-基)吡咯烷-3-基)-N-甲基吡咯烷-1-甲酰胺	420.5	**	***
(S)-N-(1-(3-(2-甲氧基吡啶-3-基)咪唑并[1,2-b]哒嗪-6-基)吡咯烷-3-基)-N-甲基吡咯烷-1-甲酰胺	421.5	**	***
(S)-N-(1-(3-(2-甲氧基吡啶-3-基)咪唑并[1,2-b]哒嗪-6-基)吡咯烷-3-基)-N-甲基丁酰胺	394.5	--	**

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(S)-N-(1-(3-溴咪唑并[1,2-b]哒嗪-6-基)吡咯烷-3-基)-N-甲基丁酰胺	366.3	--	*
(S)-N-(1-(3-溴咪唑并[1,2-b]哒嗪-6-基)吡咯烷-3-基)-N-甲基吡咯烷-1-甲酰胺	393.3	--	**
(S)-N-(叔丁基)-2-(((3-(2-甲氧基苯基)咪唑并[1,2-b]哒嗪-6-基)氨基)甲基)吡咯烷-1-甲酰胺	422.5	**	***
(S)-N-(叔丁基)-2-(((3-(吡啶-4-基)咪唑并[1,2-b]哒嗪-6-基)氨基)甲基)吡咯烷-1-甲酰胺	393.5	**	***
(S)-N-(叔丁基)-2-(((3-苯基咪唑并[1,2-b]哒嗪-6-基)氨基)甲基)吡咯烷-1-甲酰胺	392.5	**	***
(S)-N-丁基-3-(4-(吡咯烷-2-基)苯基)咪唑并[1,2-b]哒嗪-6-胺	335.4	**	--
(S)-N-环戊基-2-(((3-(2-甲氧基苯基)咪唑并[1,2-b]哒嗪-6-基)氨基)甲基)吡咯烷-1-甲酰胺	434.5	*	***
(S)-2-(((3-(4-(氨基甲基)苯基)咪唑并[1,2-b]哒嗪-6-基)氨基)甲基)吡咯烷-1-甲酸新戊基酯	436.5	***	***
(S)-2-(((3-(吡啶-4-基)咪唑并[1,2-b]哒嗪-6-基)氨基)甲基)吡咯烷-1-甲酸新戊基酯	408.5	**	***
(S)-2-(((3-溴咪唑并[1,2-b]哒嗪-6-基)氨基)甲基)吡咯烷-1-甲酸新戊基酯	410.3	**	--
(S)-N-甲基-N-(1-(3-(吡啶-2-基)咪唑并[1,2-b]哒嗪-6-基)吡咯烷-3-基)吡咯烷-1-甲酰胺	391.5	--	**
(S)-N-甲基-N-(1-(3-(吡啶-3-基)咪唑并[1,2-b]哒嗪-6-基)吡咯烷-3-基)丁酰胺	364.4	--	*
(S)-N-甲基-N-(1-(3-(吡啶-4-基)咪唑并[1,2-b]哒嗪-6-基)吡咯烷-3-基)吡咯烷-1-甲酰胺	391.5	--	**
(S)-N-甲基-N-(1-(3-(吡啶-4-基)咪唑并[1,2-b]哒嗪-6-基)吡咯烷-3-基)丁酰胺	364.4	--	**
(S)-N-新戊基-2-(((3-苯基咪唑并[1,2-b]哒嗪-6-基)氨基)甲基)吡咯烷-1-甲酰胺	406.5	**	***

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(S)-2-(((3-溴咪唑并[1,2-b]哒嗪-6-基)氨基)甲基)吡咯烷-1-甲酸丙基酯	382.3	--	***
(S)-(1-(3-(2-甲氧基苯基)咪唑并[1,2-b]哒嗪-6-基)吡咯烷-3-基)(甲基)氨基甲酸叔丁基酯	423.5	**	***
(S)-(1-(3-(2-甲氧基吡啶-3-基)咪唑并[1,2-b]哒嗪-6-基)吡咯烷-3-基)(甲基)氨基甲酸叔丁基酯	424.5	**	***
(S)-(1-(3-溴咪唑并[1,2-b]哒嗪-6-基)吡咯烷-3-基)(甲基)氨基甲酸叔丁基酯	396.3	*	***
(S)-2-(((3-(2-甲氧基苯基)咪唑并[1,2-b]哒嗪-6-基)氨基)甲基)吡咯烷-1-甲酸叔丁基酯	423.5	***	--
(S)-2-(((3-(3-甲氧基吡啶-4-基)咪唑并[1,2-b]哒嗪-6-基)氨基)甲基)哌啶-1-甲酸叔丁基酯	438.5	**	--
(S)-2-(((3-(4-(氨基甲基)苯基)咪唑并[1,2-b]哒嗪-6-基)氨基)甲基)吡咯烷-1-甲酸叔丁基酯	422.5	***	***
(S)-2-(((3-(4-(氨基甲基)苯基)咪唑并[1,2-b]哒嗪-6-基)氨基)甲基)哌啶-1-甲酸叔丁基酯	436.5	***	--
(S)-2-(((3-(4-氨基甲酰基苯基)咪唑并[1,2-b]哒嗪-6-基)氨基)甲基)吡咯烷-1-甲酸叔丁基酯	436.5	***	***
(S)-2-(((3-(二氟甲基)咪唑并[1,2-b]哒嗪-6-基)氨基)甲基)吡咯烷-1-甲酸叔丁基酯	367.4	*	***
(S)-2-(((3-(甲基氨基甲酰基)咪唑并[1,2-b]哒嗪-6-基)氨基)甲基)吡咯烷-1-甲酸叔丁基酯	374.4	**	***
(S)-2-(((3-(吡啶-4-基)咪唑并[1,2-b]哒嗪-6-基)氨基)甲基)哌啶-1-甲酸叔丁基酯	408.5	**	--
(S)-2-(((3-(三氟甲基)咪唑并[1,2-b]哒嗪-6-基)氨基)甲基)吡咯烷-1-甲酸叔丁基酯	385.4	**	--
(S)-2-(((3-溴咪唑并[1,2-b]哒嗪-6-基)氨基)甲基)吡咯烷-1-甲酸叔丁基酯	396.3	**	--
(S)-2-(((3-溴咪唑并[1,2-b]哒嗪-6-基)氨基)甲基)氮杂环丁烷-1-甲酸叔丁基酯	382.3	**	***

[0184]

(S)-2-(((3-氯咪唑并[1,2-b]哒嗪-6-基)氨基)甲基)吡咯烷-1-甲酸叔丁基酯	351.8	**	--
(S)-2-(((3-乙基咪唑并[1,2-b]哒嗪-6-基)氨基)甲基)吡咯烷-1-甲酸叔丁基酯	345.4	**	--
(S)-2-(((3-碘咪唑并[1,2-b]哒嗪-6-基)氨基)甲基)吡咯烷-1-甲酸叔丁基酯	443.3	***	--
(S)-2-(((3-甲基咪唑并[1,2-b]哒嗪-6-基)氨基)甲基)吡咯烷-1-甲酸叔丁基酯	331.4	**	***
(S)-2-(((3-苯基咪唑并[1,2-b]哒嗪-6-基)氨基)甲基)吡咯烷-1-甲酸叔丁基酯	393.5	***	***
(S)-2-(2-((3-(4-(氨基甲基)苯基)咪唑并[1,2-b]哒嗪-6-基)氨基)乙基)吡咯烷-1-甲酸叔丁基酯	436.5	**	--
(S)-3-(((3-(3-甲氧基吡啶-4-基)咪唑并[1,2-b]哒嗪-6-基)氨基)甲基)吡咯烷-1-甲酸叔丁基酯	424.5	*	--
(S)-3-(((3-(4-(氨基甲基)苯基)咪唑并[1,2-b]哒嗪-6-基)氨基)甲基)吡咯烷-1-甲酸叔丁基酯	422.5	**	--
(S)-3-(((3-溴咪唑并[1,2-b]哒嗪-6-基)氨基)甲基)吡咯烷-1-甲酸叔丁基酯	396.3	*	--
(S)-甲基(1-(3-(吡啶-3-基)咪唑并[1,2-b]哒嗪-6-基)吡咯烷-3-基)氨基甲酸叔丁基酯	394.5	--	***
(S)-甲基(1-(3-(吡啶-4-基)咪唑并[1,2-b]哒嗪-6-基)吡咯烷-3-基)氨基甲酸叔丁基酯	394.5	*	***
(S)-2-(((3-(2-甲氧基苯基)咪唑并[1,2-b]哒嗪-6-基)氨基)甲基)吡咯烷-1-甲酸乙烯基酯	393.4	**	***
1-(2-((3-(4-(氨基甲基)苯基)咪唑并[1,2-b]哒嗪-6-基)氨基)乙基)-3-(叔丁基)咪唑烷-2-酮	407.5	**	--
1-(3-(3-(3-甲氧基吡啶-4-基)咪唑并[1,2-b]哒嗪-6-基)苯基)-4-甲基戊-1-酮	400.5	**	--
1-(3-(3-(4-(氨基甲基)苯基)咪唑并[1,2-b]哒嗪-6-基)苯基)乙酮	342.4	**	--

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1-(3-(3-(4-(氨基甲基)苯基)咪唑并[1,2-b]哒嗪-6-基)苯基)-4-甲基戊-1-酮	398.5	**	--
1-(4-(3-(3-甲氧基吡啶-4-基)咪唑并[1,2-b]哒嗪-6-基)哌嗪-1-基)-3,3-二甲基丁-1-酮	408.5	**	--
1-(5-(6-((2-(甲基(苯基)氨基)乙基)氨基)咪唑并[1,2-b]哒嗪-3-基)噻吩-2-基)乙酮	391.5	**	--
1-(5-(6-((3-(甲基氨基)丙基)氨基)咪唑并[1,2-b]哒嗪-3-基)噻吩-2-基)乙酮	329.4	*	--
1-(5-(6-((3-甲氧基丙基)氨基)咪唑并[1,2-b]哒嗪-3-基)噻吩-2-基)乙酮	330.4	*	--
1-(5-(6-(丁基(甲基)氨基)咪唑并[1,2-b]哒嗪-3-基)噻吩-2-基)乙酮	328.4	**	--
1-(5-(6-(异丁基氨基)咪唑并[1,2-b]哒嗪-3-基)噻吩-2-基)乙酮	314.4	*	--
1-(5-(6-(丙基氨基)咪唑并[1,2-b]哒嗪-3-基)噻吩-2-基)乙酮	300.4	*	--
1-(叔丁基)-3-(2-((3-(3-甲氧基吡啶-4-基)咪唑并[1,2-b]哒嗪-6-基)氨基)乙基)咪唑烷-2-酮	409.5	**	--
2,2-二甲基-1-(4-(3-苯基咪唑并[1,2-b]哒嗪-6-基)哌嗪-1-基)丙-1-酮	363.5	--	**
2-氟乙基 异丙基(2-((3-(3-甲氧基吡啶-4-基)咪唑并[1,2-b]哒嗪-6-基)氨基)乙基)氨基甲酸酯	416.4	*	--
3-(2,4-二甲基噻唑-5-基)-N-(2-异丁氧基乙基)咪唑并[1,2-b]哒嗪-6-胺	345.5	*	--
3-(2-氨基吡啶-4-基)-N-(3-(叔丁氧基)丙基)咪唑并[1,2-b]哒嗪-6-胺	340.4	*	--
3-(2-氨基吡啶-4-基)-N-丁基咪唑并[1,2-b]哒嗪-6-胺	282.3	*	--
3-(2-甲氧基吡啶-3-基)-N-((四氢呋喃-3-基)甲基)咪唑并[1,2-b]哒嗪-6-胺	325.4	*	--

[0186]

3-(3-(4-(氨基甲基)苯基)咪唑并[1,2-b]哒嗪-6-基)-N-异丁基苯甲酰胺	399.5	**	--
3-(3-甲氧基吡啶-4-基)-N-(4,4,4-三氟丁基)咪唑并[1,2-b]哒嗪-6-胺	351.3	***	--
3-(4-(((2-甲氧基乙基)氨基)甲基)苯基)-N-戊基咪唑并[1,2-b]哒嗪-6-胺	367.5	*	--
3-(4-((2-(二甲基氨基)乙氧基)甲基)苯基)-N-(3,3-二甲基丁基)咪唑并[1,2-b]哒嗪-6-胺	395.5	**	--
3-(4-((2-氨基乙氧基)甲基)苯基)-N-(3,3-二甲基丁基)咪唑并[1,2-b]哒嗪-6-胺	367.5	**	--
3-(4-(1H-吲唑-5-基)苯基)-N-丁基咪唑并[1,2-b]哒嗪-6-胺	334.4	*	--
3-(4-(2-氨基乙氧基)苯基)-N-丁基咪唑并[1,2-b]哒嗪-6-胺	325.4	**	--
3-(4-(3-氨基丙氧基)苯基)-N-(3,3-二甲基丁基)咪唑并[1,2-b]哒嗪-6-胺	367.5	**	--
3-(4-(3-氨基丙氧基)苯基)-N-(3-苯基丙基)咪唑并[1,2-b]哒嗪-6-胺	401.5	**	--
3-(4-(氨基甲基)-3-氟苯基)-N-丁基咪唑并[1,2-b]哒嗪-6-胺	313.4	*	--
3-(4-(氨基甲基)苯基)-N-((1-(2,2,2-三氟乙基)吡咯烷-2-基)甲基)咪唑并[1,2-b]哒嗪-6-胺	404.4	**	***
3-(4-(氨基甲基)苯基)-N-((四氢呋喃-3-基)甲基)咪唑并[1,2-b]哒嗪-6-胺	323.4	*	--
3-(4-(氨基甲基)苯基)-N-(1-氧杂螺[4.4]壬-3-基)咪唑并[1,2-b]哒嗪-6-胺	363.5	**	--
3-(4-(氨基甲基)苯基)-N-(2-(环戊基氧基)乙基)咪唑并[1,2-b]哒嗪-6-胺	351.4	**	--
3-(4-(氨基甲基)苯基)-N-(2-(新戊基氧基)乙基)咪唑并[1,2-b]哒嗪-6-胺	353.5	**	--

[0187]

3-(4-(氨基甲基)苯基)-N-(2-(叔丁氧基)乙基)咪唑并[1,2-b]哒嗪-6-胺	339.4	**	--
3-(4-(氨基甲基)苯基)-N-(2-(三氟甲氧基)苯乙基)咪唑并[1,2-b]哒嗪-6-胺	427.4	***	--
3-(4-(氨基甲基)苯基)-N-(2-环己基乙基)咪唑并[1,2-b]哒嗪-6-胺	349.5	**	--
3-(4-(氨基甲基)苯基)-N-(2-环丙基乙基)咪唑并[1,2-b]哒嗪-6-胺	307.4	*	--
3-(4-(氨基甲基)苯基)-N-(2-乙氧基苯乙基)咪唑并[1,2-b]哒嗪-6-胺	387.5	**	--
3-(4-(氨基甲基)苯基)-N-(2-氟苯乙基)咪唑并[1,2-b]哒嗪-6-胺	361.4	**	--
3-(4-(氨基甲基)苯基)-N-(2-异丁氧基乙基)咪唑并[1,2-b]哒嗪-6-胺	339.4	**	--
3-(4-(氨基甲基)苯基)-N-(2-异丙氧基乙基)咪唑并[1,2-b]哒嗪-6-胺	325.4	**	--
3-(4-(氨基甲基)苯基)-N-(2-甲氧基苯乙基)咪唑并[1,2-b]哒嗪-6-胺	373.5	***	--
3-(4-(氨基甲基)苯基)-N-(2-甲基丁基)咪唑并[1,2-b]哒嗪-6-胺	309.4	*	--
3-(4-(氨基甲基)苯基)-N-(2-苯氧基乙基)咪唑并[1,2-b]哒嗪-6-胺	359.4	*	--
3-(4-(氨基甲基)苯基)-N-(3-(2-氟苯基)丙基)咪唑并[1,2-b]哒嗪-6-胺	375.4	**	--
3-(4-(氨基甲基)苯基)-N-(3-(3-氟苯基)丙基)咪唑并[1,2-b]哒嗪-6-胺	375.4	**	--
3-(4-(氨基甲基)苯基)-N-(3-(4-氟苯基)丙基)咪唑并[1,2-b]哒嗪-6-胺	375.4	**	--
3-(4-(氨基甲基)苯基)-N-(3-(环戊基氧基)丙基)咪唑并[1,2-b]哒嗪-6-胺	365.5	**	--

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3-(4-(氨基甲基)苯基)-N-(3-(叔丁氧基)丙基)咪唑并[1,2-b]哒嗪-6-胺	353.5	**	--
3-(4-(氨基甲基)苯基)-N-(3-(三氟甲基)苯乙基)咪唑并[1,2-b]哒嗪-6-胺	411.4	**	--
3-(4-(氨基甲基)苯基)-N-(3,3-二甲基丁基)咪唑并[1,2-b]哒嗪-6-胺	323.4	**	--
3-(4-(氨基甲基)苯基)-N-(3-氟苯乙基)咪唑并[1,2-b]哒嗪-6-胺	361.4	**	--
3-(4-(氨基甲基)苯基)-N-(3-氟丙基)咪唑并[1,2-b]哒嗪-6-胺	299.3	*	--
3-(4-(氨基甲基)苯基)-N-(3-甲氧基苯乙基)咪唑并[1,2-b]哒嗪-6-胺	373.5	**	--
3-(4-(氨基甲基)苯基)-N-(3-苯基丙基)咪唑并[1,2-b]哒嗪-6-胺	357.5	**	--
3-(4-(氨基甲基)苯基)-N-(4-氟丁基)咪唑并[1,2-b]哒嗪-6-胺	313.4	**	--
3-(4-(氨基甲基)苯基)-N-(4-氟苯乙基)咪唑并[1,2-b]哒嗪-6-胺	361.4	*	--
3-(4-(氨基甲基)苯基)-N-(4-甲氧基苯乙基)咪唑并[1,2-b]哒嗪-6-胺	373.5	**	--
3-(4-(氨基甲基)苯基)-N-(4-苯基丁基)咪唑并[1,2-b]哒嗪-6-胺	371.5	**	--
3-(4-(氨基甲基)苯基)-N-(5-氟戊基)咪唑并[1,2-b]哒嗪-6-胺	327.4	*	--
3-(4-(氨基甲基)苯基)-N-(环丁基甲基)咪唑并[1,2-b]哒嗪-6-胺	307.4	*	--
3-(4-(氨基甲基)苯基)-N-(环己基甲基)咪唑并[1,2-b]哒嗪-6-胺	335.4	*	--
3-(4-(氨基甲基)苯基)-N-(环戊基甲基)咪唑并[1,2-b]哒嗪-6-胺	321.4	*	--

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3-(4-(氨基甲基)苯基)-N-(环丙基甲基)咪唑并[1,2-b]哒嗪-6-胺	293.4	*	--
3-(4-(氨基甲基)苯基)-N-丁基-7-甲基咪唑并[1,2-b]哒嗪-6-胺	309.4	**	--
3-(4-(氨基甲基)苯基)-N-丁基咪唑并[1,2-b]哒嗪-6-胺	295.4	*	--
3-(4-(氨基甲基)苯基)-N-丁基-N-甲基咪唑并[1,2-b]哒嗪-6-胺	309.4	*	--
3-(4-(氨基甲基)苯基)-N-环己基咪唑并[1,2-b]哒嗪-6-胺	321.4	*	--
3-(4-(氨基甲基)苯基)-N-异丁基咪唑并[1,2-b]哒嗪-6-胺	295.4	*	--
3-(4-(氨基甲基)苯基)-N-异戊基咪唑并[1,2-b]哒嗪-6-胺	309.4	*	--
3-(4-(氨基甲基)苯基)-N-新戊基咪唑并[1,2-b]哒嗪-6-胺	309.4	**	--
3-(4-(氨基甲基)苯基)-N-戊基咪唑并[1,2-b]哒嗪-6-胺	309.4	*	--
3-(4-(氨基甲基)苯基)-N-苯乙基咪唑并[1,2-b]哒嗪-6-胺	343.4	*	--
3-(4-(氨基甲基)苯基)-N-丙基咪唑并[1,2-b]哒嗪-6-胺	281.4	*	--
3-(6-((2-(环戊基氧基)乙基)氨基)咪唑并[1,2-b]哒嗪-3-基)苯酚	338.4	*	***
3-(苯并[d][1,3]间二氧杂环戊烯-5-基)-N-(2-(环戊基氧基)乙基)咪唑并[1,2-b]哒嗪-6-胺	366.4	*	**
3,3-二甲基-1-(4-(3-苯基咪唑并[1,2-b]哒嗪-6-基)哌嗪-1-基)丁-1-酮	377.5	**	***
4-((3-(4-(氨基甲基)苯基)咪唑并[1,2-b]哒嗪-6-基)氨基)-2-甲基丁-2-醇	325.4	**	--

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4-(3-溴咪唑并[1,2-b]哒嗪-6-基)-N-(叔丁基)哌嗪-1-甲酰胺	381.3	**	***
4-(6-((2-(N,3,3-三甲基丁酰胺基)乙基)氨基)咪唑并[1,2-b]哒嗪-3-基)苯甲酰胺	408.5	**	--
4-(6-((2-(叔丁氧基)乙基)氨基)咪唑并[1,2-b]哒嗪-3-基)苯甲酰胺	353.4	**	--
4-(6-((2-(叔丁氧基)乙基)氨基)咪唑并[1,2-b]哒嗪-3-基)-N-(2-(二乙基氨基)乙基)苯甲酰胺	452.6	**	--
4-(6-((2-(叔丁氧基)乙基)氨基)咪唑并[1,2-b]哒嗪-3-基)-N-甲基苯甲酰胺	367.4	**	--
4-(6-((2-(三氟甲氧基)苯乙基)氨基)咪唑并[1,2-b]哒嗪-3-基)苯甲酰胺	441.4	***	--
4-(6-((2-乙氧基苯乙基)氨基)咪唑并[1,2-b]哒嗪-3-基)-N-甲基苯甲酰胺	415.5	***	--
4-(6-((2-异丁氧基乙基)氨基)咪唑并[1,2-b]哒嗪-3-基)-N-(2-(吡咯烷-1-基)乙基)苯甲酰胺	450.6	**	--
4-(6-((2-异丙氧基乙基)氨基)咪唑并[1,2-b]哒嗪-3-基)-N-(2-(吡咯烷-1-基)乙基)苯甲酰胺	436.5	**	--
4-(6-((2-甲氧基苯乙基)氨基)咪唑并[1,2-b]哒嗪-3-基)苯甲酰胺	387.4	***	--
4-(6-((3-(三氟甲基)苯乙基)氨基)咪唑并[1,2-b]哒嗪-3-基)苯甲酰胺	425.4	**	--
4-(6-((3-甲氧基苯乙基)氨基)咪唑并[1,2-b]哒嗪-3-基)苯甲酰胺	387.4	**	--
4-(6-(丁基氨基)咪唑并[1,2-b]哒嗪-3-基)-2-氟-N-(2-(甲基氨基)乙基)苯甲酰胺	384.5	**	--
4-(6-(丁基氨基)咪唑并[1,2-b]哒嗪-3-基)苯甲酰胺	309.4	**	--
4-(6-(丁基氨基)咪唑并[1,2-b]哒嗪-3-基)-N-(2-(二乙基氨基)乙基)苯甲酰胺	408.5	***	--

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4-(6-(丁基氨基)咪唑并[1,2-b]哒嗪-3-基)-N-(2-(二甲基氨基)乙基)苯甲酰胺	380.5	**	--
4-(6-(丁基氨基)咪唑并[1,2-b]哒嗪-3-基)-N-(2-(甲基氨基)乙基)苯甲酰胺	366.5	**	--
4-(6-(丁基氨基)咪唑并[1,2-b]哒嗪-3-基)-N-(2-(吡咯烷-1-基)乙基)苯甲酰胺	406.5	**	--
5-(3-(4-(氨基甲基)苯基)咪唑并[1,2-b]哒嗪-6-基)-N-异丁基烟酰胺	400.5	**	--
5-(6-((2-(环戊基氧基)乙基)氨基)咪唑并[1,2-b]哒嗪-3-基)噻吩-2-甲腈	353.4	**	***
5-(6-(丁基氨基)咪唑并[1,2-b]哒嗪-3-基)噻吩-2-甲酰胺	315.4	*	--
5-(6-(丙基氨基)咪唑并[1,2-b]哒嗪-3-基)噻吩-2-甲醛	286.4	*	--
6-(丁基氨基)-N-(1H-吡唑-4-基)咪唑并[1,2-b]哒嗪-3-甲酰胺	299.3	*	--
6-(丁基氨基)-N-(4-((2-(二甲基氨基)乙基)氨基甲酰基)苯基)咪唑并[1,2-b]哒嗪-3-甲酰胺	423.5	**	--
(2-((3-(4-氨基甲酰基苯基)咪唑并[1,2-b]哒嗪-6-基)氨基)乙基)(异丙基)氨基甲酸环戊基酯	450.5	**	--
(2-((3-(3-甲氧基吡啶-4-基)咪唑并[1,2-b]哒嗪-6-基)氨基)乙基)(甲基)氨基甲酸乙基酯	370.4	***	--
(2-((3-(4-(异戊基氨基甲酰基)苯基)咪唑并[1,2-b]哒嗪-6-基)氨基)乙基)(甲基)氨基甲酸乙基酯	452.5	**	--
(2-((3-(4-(叔丁基氨基甲酰基)苯基)咪唑并[1,2-b]哒嗪-6-基)氨基)乙基)(甲基)氨基甲酸乙基酯	438.5	**	--
(2-((3-(4-氨基甲酰基苯基)咪唑并[1,2-b]哒嗪-6-基)氨基)乙基)(甲基)氨基甲酸乙基酯	382.4	**	--
(2-((3-(4-氨基甲酰基苯基)咪唑并[1,2-b]哒嗪-6-基)氨基)乙基)(异丙基)氨基甲酸乙基酯	410.5	**	--

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(3-((3-(5-乙酰基噻吩-2-基)咪唑并[1,2-b]哒嗪-6-基)氨基)丙基)(甲基)氨基甲酸乙基酯	401.5	*	--
4-((3-(4-(氨基甲基)苯基)咪唑并[1,2-b]哒嗪-6-基)氨基)丁酸乙基酯	353.4	**	--
4-((3-(5-乙酰基噻吩-2-基)咪唑并[1,2-b]哒嗪-6-基)氨基)丁酸乙基酯	372.4	**	--
4-(3-(甲基氨基甲酰基)咪唑并[1,2-b]哒嗪-6-基)哌嗪-1-甲酸乙基酯	332.4	--	**
4-(3-苯基咪唑并[1,2-b]哒嗪-6-基)哌嗪-1-甲酸乙基酯	351.4	**	***
异丙基(2-((3-(3-甲氧基吡啶-4-基)咪唑并[1,2-b]哒嗪-6-基)氨基)乙基)氨基甲酸乙基酯	398.5	***	--
甲基(2-((3-(4-(甲基氨基甲酰基)苯基)咪唑并[1,2-b]哒嗪-6-基)氨基)乙基)氨基甲酸乙基酯	396.4	**	--
甲基(2-((3-(5-(甲基氨基甲酰基)噻吩-2-基)咪唑并[1,2-b]哒嗪-6-基)氨基)乙基)氨基甲酸乙基酯	402.5	**	--
(2-((3-(4-氨基甲酰基苯基)咪唑并[1,2-b]哒嗪-6-基)氨基)乙基)(甲基)氨基甲酸异丁基酯	410.5	**	--
异丙基(2-((3-(3-甲氧基吡啶-4-基)咪唑并[1,2-b]哒嗪-6-基)氨基)乙基)氨基甲酸异丁基酯	426.5	**	--
甲基(2-((3-(4-(甲基氨基甲酰基)苯基)咪唑并[1,2-b]哒嗪-6-基)氨基)乙基)氨基甲酸异丁基酯	424.5	**	--
(2-((3-(1H-吡唑-4-基)咪唑并[1,2-b]哒嗪-6-基)氨基)乙基)(甲基)氨基甲酸异丙基酯	343.4	**	--
(2-((3-(2,4-二甲基噻唑-5-基)咪唑并[1,2-b]哒嗪-6-基)氨基)乙基)(甲基)氨基甲酸异丙基酯	388.5	**	--
(2-((3-(2-氨基吡啶-4-基)咪唑并[1,2-b]哒嗪-6-基)氨基)乙基)(甲基)氨基甲酸异丙基酯	369.4	**	--
(2-((3-(2-氟苯基)咪唑并[1,2-b]哒嗪-6-基)氨基)乙基)(甲基)氨基甲酸异丙基酯	371.4	**	--

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(2-((3-(2-甲氧基苯基)咪唑并[1,2-b]哒嗪-6-基)氨基)乙基)(甲基)氨基甲酸异丙基酯	383.4	**	--
(2-((3-(3-甲氧基吡啶-4-基)咪唑并[1,2-b]哒嗪-6-基)氨基)乙基)(甲基)氨基甲酸异丙基酯	384.4	**	--
(2-((3-(3-甲氧基吡啶-4-基)咪唑并[1,2-b]哒嗪-6-基)氨基)乙基)氨基甲酸异丙基酯	370.4	**	--
(2-((3-(4,5-二氟-2-甲氧基苯基)咪唑并[1,2-b]哒嗪-6-基)氨基)乙基)(异丙基)氨基甲酸异丙基酯	447.5	**	--
(2-((3-(4-氨基甲酰基苯基)咪唑并[1,2-b]哒嗪-6-基)氨基)乙基)(异丙基)氨基甲酸异丙基酯	424.5	**	--
(2-((3-(4-氨基甲酰基苯基)咪唑并[1,2-b]哒嗪-6-基)氨基)乙基)(甲基)氨基甲酸异丙基酯	396.4	***	--
(2-((3-(4-氟-2-甲氧基苯基)咪唑并[1,2-b]哒嗪-6-基)氨基)乙基)(甲基)氨基甲酸异丙基酯	401.4	**	--
(2-((3-(5-氟-2-甲氧基苯基)咪唑并[1,2-b]哒嗪-6-基)氨基)乙基)(甲基)氨基甲酸异丙基酯	401.4	***	--
(2-((3-(5-氟-2-甲氧基苯基)咪唑并[1,2-b]哒嗪-6-基)氨基)乙基)(异丙基)氨基甲酸异丙基酯	429.5	**	--
(3-((3-(4-(氨基甲基)苯基)咪唑并[1,2-b]哒嗪-6-基)氨基)丙基)(甲基)氨基甲酸异丙基酯	396.5	**	--
(3-((3-(5-乙酰基噻吩-2-基)咪唑并[1,2-b]哒嗪-6-基)氨基)丙基)(甲基)氨基甲酸异丙基酯	415.5	**	--
4-(3-(2-(二氟甲氧基)苯基)咪唑并[1,2-b]哒嗪-6-基)哌嗪-1-甲酸异丙基酯	431.4	**	***
4-(3-(2-(二氟甲氧基)吡啶-3-基)咪唑并[1,2-b]哒嗪-6-基)哌嗪-1-甲酸异丙基酯	432.4	**	***
4-(3-(2,2-二氟苯并[d][1,3]间二氧杂环戊烯-4-基)咪唑并[1,2-b]哒嗪-6-基)哌嗪-1-甲酸异丙基酯	445.4	*	***
4-(3-(2,3-二氢苯并呋喃-7-基)咪唑并[1,2-b]哒嗪-6-基)哌嗪-1-甲酸异丙基酯	407.5	**	--

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4-(3-(2,3-二甲氧基苯基)咪唑并[1,2-b]哒嗪-6-基)哌嗪-1-甲酸异丙基酯	425.5	**	***
4-(3-(2,5-二甲氧基苯基)咪唑并[1,2-b]哒嗪-6-基)哌嗪-1-甲酸异丙基酯	425.5	**	***
4-(3-(2-乙氧基苯基)咪唑并[1,2-b]哒嗪-6-基)哌嗪-1-甲酸异丙基酯	409.5	**	***
4-(3-(2-氟-3-甲氧基苯基)咪唑并[1,2-b]哒嗪-6-基)哌嗪-1-甲酸异丙基酯	413.4	**	***
4-(3-(2-氟苯基)咪唑并[1,2-b]哒嗪-6-基)哌嗪-1-甲酸异丙基酯	383.4	**	***
4-(3-(2-甲氧基苯基)咪唑并[1,2-b]哒嗪-6-基)哌嗪-1-甲酸异丙基酯	395.5	***	***
4-(3-(2-甲氧基吡啶-3-基)咪唑并[1,2-b]哒嗪-6-基)哌嗪-1-甲酸异丙基酯	396.4	***	***
4-(3-(2-甲氧基吡啶-4-基)咪唑并[1,2-b]哒嗪-6-基)哌嗪-1-甲酸异丙基酯	396.4	**	***
4-(3-(2-氧基-1,2-二氢吡啶-3-基)咪唑并[1,2-b]哒嗪-6-基)哌嗪-1-甲酸异丙基酯	382.4	**	***
4-(3-(3-氯苯基)咪唑并[1,2-b]哒嗪-6-基)哌嗪-1-甲酸异丙基酯	399.9	*	***
4-(3-(3-甲氧基苯基)咪唑并[1,2-b]哒嗪-6-基)哌嗪-1-甲酸异丙基酯	395.5	**	***
4-(3-(3-甲氧基吡啶-4-基)咪唑并[1,2-b]哒嗪-6-基)哌嗪-1-甲酸异丙基酯	396.4	***	--
4-(3-(苯并[d][1,3]间二氧杂环戊烯-4-基)咪唑并[1,2-b]哒嗪-6-基)哌嗪-1-甲酸异丙基酯	409.4	**	--
4-(3-(甲基氨基甲酰基)咪唑并[1,2-b]哒嗪-6-基)哌嗪-1-甲酸异丙基酯	346.4	--	**
4-(3-(吡啶-4-基)咪唑并[1,2-b]哒嗪-6-基)哌嗪-1-甲酸异丙基酯	366.4	**	--

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4-(3-苯基咪唑并[1,2-b]哒嗪-6-基)哌嗪-1-甲酸异丙基酯	365.4	**	--
乙基(2-((3-(3-甲氧基吡啶-4-基)咪唑并[1,2-b]哒嗪-6-基)氨基)乙基)氨基甲酸异丙基酯	398.5	**	--
乙基(2-((3-(4-(甲基氨基甲酰基)苯基)咪唑并[1,2-b]哒嗪-6-基)氨基)乙基)氨基甲酸异丙基酯	424.5	**	--
异丙基(2-((3-(2-甲氧基苯基)咪唑并[1,2-b]哒嗪-6-基)氨基)乙基)氨基甲酸异丙基酯	411.5	**	--
异丙基(2-((3-(3-甲氧基吡啶-4-基)咪唑并[1,2-b]哒嗪-6-基)氨基)乙基)氨基甲酸异丙基酯	412.5	***	--
异丙基(2-((3-(4-(甲基氨基甲酰基)苯基)咪唑并[1,2-b]哒嗪-6-基)氨基)乙基)氨基甲酸异丙基酯	438.5	**	--
异丙基(2-((3-(吡啶-4-基)咪唑并[1,2-b]哒嗪-6-基)氨基)乙基)氨基甲酸异丙基酯	382.5	**	--
异丙基(2-((3-苯基咪唑并[1,2-b]哒嗪-6-基)氨基)乙基)氨基甲酸异丙基酯	381.5	**	--
甲基(2-((3-(4-(甲基氨基甲酰基)苯基)咪唑并[1,2-b]哒嗪-6-基)氨基)乙基)氨基甲酸异丙基酯	410.5	**	--
甲基(2-((3-(4-(吡咯烷-2-基)苯基)咪唑并[1,2-b]哒嗪-6-基)氨基)乙基)氨基甲酸异丙基酯	422.5	***	--
甲基(2-((3-(噻唑-4-基)咪唑并[1,2-b]哒嗪-6-基)氨基)乙基)氨基甲酸异丙基酯	360.4	**	--
异丙基(2-((3-(3-甲氧基吡啶-4-基)咪唑并[1,2-b]哒嗪-6-基)氨基)乙基)氨基甲酸甲基酯	384.4	***	--
N-((1R,2S)-2-氨基环己基)-4-(6-(丁基氨基)咪唑并[1,2-b]哒嗪-3-基)苯甲酰胺	406.5	**	--
N-(2-((3-(4-氰基苯基)咪唑并[1,2-b]哒嗪-6-基)氨基)乙基)-N,3,3-三甲基丁酰胺	390.5	**	--
N-(2-((3-(4-氰基苯基)咪唑并[1,2-b]哒嗪-6-基)氨基)乙基)-N-甲基新戊酰胺	376.5	**	--

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N-(2-(环戊基氧基)乙基)-3-(1H-吡唑-3-基)咪唑并[1,2-b]哒嗪-6-胺	312.4	*	**
N-(2-(环戊基氧基)乙基)-3-(2-氟吡啶-3-基)咪唑并[1,2-b]哒嗪-6-胺	341.4	*	***
N-(2-(环戊基氧基)乙基)-3-(2-甲氧基吡啶-3-基)咪唑并[1,2-b]哒嗪-6-胺	353.4	**	--
N-(2-(环戊基氧基)乙基)-3-(3-氟吡啶-4-基)咪唑并[1,2-b]哒嗪-6-胺	341.4	**	--
N-(2-(环戊基氧基)乙基)-3-(3-甲氧基苯基)咪唑并[1,2-b]哒嗪-6-胺	352.4	--	**
N-(2-(环戊基氧基)乙基)-3-(3-甲氧基吡啶-4-基)咪唑并[1,2-b]哒嗪-6-胺	353.4	*	--
N-(2-(环戊基氧基)乙基)-3-(4-(吡咯烷-2-基)苯基)咪唑并[1,2-b]哒嗪-6-胺	391.5	**	--
N-(2-(环戊基氧基)乙基)-3-(4-甲基噻吩-2-基)咪唑并[1,2-b]哒嗪-6-胺	342.5	--	**
N-(2-(环戊基氧基)乙基)-3-(5-甲氧基吡啶-3-基)咪唑并[1,2-b]哒嗪-6-胺	353.4	**	***
N-(2-(环戊基氧基)乙基)-3-(5-甲基噻吩-2-基)咪唑并[1,2-b]哒嗪-6-胺	342.5	--	**
N-(2-(环戊基氧基)乙基)-3-(吡啶-2-基)咪唑并[1,2-b]哒嗪-6-胺	323.4	**	***
N-(2-(环戊基氧基)乙基)-3-(噻吩-2-基)咪唑并[1,2-b]哒嗪-6-胺	328.4	--	***
N-(2-(环戊基氧基)乙基)-3-(噻吩-3-基)咪唑并[1,2-b]哒嗪-6-胺	328.4	--	**
N-(2-(二乙基氨基)乙基)-4-(6-((2-异丁氧基乙基)氨基)咪唑并[1,2-b]哒嗪-3-基)苯甲酰胺	452.6	**	--
N-(2-(二乙基氨基)乙基)-4-(6-((2-异丙氧基乙基)氨基)咪唑并[1,2-b]哒嗪-3-基)苯甲酰胺	438.6	**	--

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N-(2-(甲基氨基)乙基)-4-(6-((3-(N-甲基新戊酰胺基)丙基)氨基)咪唑并[1,2-b]哒嗪-3-基)苯甲酰胺	465.6	*	--
N-(2-(叔丁氧基)乙基)-3-(3-甲氧基吡啶-4-基)咪唑并[1,2-b]哒嗪-6-胺	341.4	**	--
N-(2-(叔丁氧基)乙基)-3-(4-(吡咯烷-2-基)苯基)咪唑并[1,2-b]哒嗪-6-胺	379.5	**	--
N-(2-氨基乙基)-4-(6-((3-(叔丁氧基)丙基)氨基)咪唑并[1,2-b]哒嗪-3-基)苯甲酰胺	410.5	*	--
N-(2-氨基乙基)-4-(6-((3,3-二甲基丁基)氨基)咪唑并[1,2-b]哒嗪-3-基)苯甲酰胺	380.5	*	--
N-(2-氨基乙基)-4-(6-((3-苯基丙基)氨基)咪唑并[1,2-b]哒嗪-3-基)苯甲酰胺	414.5	*	--
N-(2-氨基乙基)-4-(6-(丁基氨基)咪唑并[1,2-b]哒嗪-3-基)-2-甲氧基苯甲酰胺	382.5	*	--
N-(2-氨基乙基)-4-(6-(丁基氨基)咪唑并[1,2-b]哒嗪-3-基)-2-氟苯甲酰胺	370.4	**	--
N-(2-氨基乙基)-4-(6-(丁基氨基)咪唑并[1,2-b]哒嗪-3-基)-3-氟苯甲酰胺	370.4	*	--
N-(2-氨基乙基)-4-(6-(丁基氨基)咪唑并[1,2-b]哒嗪-3-基)苯甲酰胺	352.4	*	--
N-(2-氨基丙基)-4-(6-(丁基氨基)咪唑并[1,2-b]哒嗪-3-基)苯甲酰胺	366.5	*	--
N-(2-乙氧基苯乙基)-3-(3-甲氧基吡啶-4-基)咪唑并[1,2-b]哒嗪-6-胺	389.5	**	--
N-(2-异丁氧基乙基)-3-(2-甲氧基苯基)咪唑并[1,2-b]哒嗪-6-胺	340.4	*	--
N-(2-异丁氧基乙基)-3-(3-甲氧基吡啶-4-基)咪唑并[1,2-b]哒嗪-6-胺	341.4	**	--
N-(2-异丁氧基乙基)-3-(吡啶-4-基)咪唑并[1,2-b]哒嗪-6-胺	311.4	*	--

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N-(2-异丙氧基乙基)-3-(1H-吡唑-3-基)咪唑并[1,2-b]哒嗪-6-胺	286.3	*	--
N-(2-异丙氧基乙基)-3-(3-甲氧基吡啶-4-基)咪唑并[1,2-b]哒嗪-6-胺	327.4	***	--
N-(2-异丙氧基乙基)-3-(4-(吡咯烷-2-基)苯基)咪唑并[1,2-b]哒嗪-6-胺	365.5	**	--
N-(2-异丙氧基乙基)-3-(异噻唑-5-基)咪唑并[1,2-b]哒嗪-6-胺	303.4	**	--
N-(2-异丙氧基乙基)-3-(噻唑-4-基)咪唑并[1,2-b]哒嗪-6-胺	303.4	*	--
N-(3-((3-(4-(氨基甲基)苯基)咪唑并[1,2-b]哒嗪-6-基)氨基)丙基)-N-甲基新戊酰胺	394.5	*	--
N-(3-(6-((2-(环戊基氧基)乙基)氨基)咪唑并[1,2-b]哒嗪-3-基)苯基)乙酰胺	379.5	**	**
N-(3-(叔丁氧基)丙基)-3-(3-甲氧基吡啶-4-基)咪唑并[1,2-b]哒嗪-6-胺	355.4	*	--
N-(3,3-二甲基丁基)-3-(4-((2-(甲基氨基)乙氧基)甲基)苯基)咪唑并[1,2-b]哒嗪-6-胺	381.5	**	--
N-(3,3-二甲基丁基)-3-(4-(吡咯烷-2-基)苯基)咪唑并[1,2-b]哒嗪-6-胺	363.5	*	--
N-(3-氨基丙基)-4-(6-(丁基氨基)咪唑并[1,2-b]哒嗪-3-基)苯甲酰胺	366.5	*	--
N-(3-氟丙基)-3-(4-(吡咯烷-2-基)苯基)咪唑并[1,2-b]哒嗪-6-胺	339.4	**	--
N-(3-苯基丙基)-3-(4-(吡咯烷-2-基)苯基)咪唑并[1,2-b]哒嗪-6-胺	397.5	*	--
N-(4-(2-氨基乙氧基)苯基)-6-(丁基氨基)咪唑并[1,2-b]哒嗪-3-甲酰胺	368.4	*	--
N-(4-(氨基甲基)苯基)-6-(丁基氨基)咪唑并[1,2-b]哒嗪-3-甲酰胺	338.4	*	--

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N-(环戊基甲基)-3-(3-甲氧基吡啶-4-基)咪唑并[1,2-b]哒嗪-6-胺	323.4	**	--
N-(叔丁基)-4-(3-苯基咪唑并[1,2-b]哒嗪-6-基)哌嗪-1-甲酰胺	378.5	**	***
N,N-二甲基-3-(6-(4-(吡咯烷-1-羰基)哌嗪-1-基)咪唑并[1,2-b]哒嗪-3-基)苯甲酰胺	447.5	**	***
N1-(3-(4-(氨基甲基)苯基)咪唑并[1,2-b]哒嗪-6-基)-N2-甲基-N2-苯基乙烷-1,2-二胺	372.5	**	--
N1-(3-(4-(氨基甲基)苯基)咪唑并[1,2-b]哒嗪-6-基)-N3-甲基-N3-苯基丙烷-1,3-二胺	386.5	**	--
N1-(3-(5-(氨基甲基)噻吩-2-基)咪唑并[1,2-b]哒嗪-6-基)-N3-甲基-N3-苯基丙烷-1,3-二胺	392.5	*	--
N1-(4-(6-((3,3-二甲基丁基)氨基)咪唑并[1,2-b]哒嗪-3-基)苄甲基)乙烷-1,2-二胺	366.5	*	--
N1-(4-(6-(丁基氨基)咪唑并[1,2-b]哒嗪-3-基)苄甲基)乙烷-1,2-二胺	338.4	*	--
N1-(4-(6-(丁基氨基)咪唑并[1,2-b]哒嗪-3-基)苄甲基)丙烷-1,3-二胺	352.5	*	--
N-丁基-3-(1H-吡唑-3-基)咪唑并[1,2-b]哒嗪-6-胺	256.3	**	--
N-丁基-3-(2,4-二甲基噻唑-5-基)咪唑并[1,2-b]哒嗪-6-胺	301.4	**	--
N-丁基-3-(3-甲氧基吡啶-4-基)咪唑并[1,2-b]哒嗪-6-胺	297.4	**	--
N-丁基-3-(4-((((四氢呋喃-2-基)甲基)氨基)甲基)苯基)咪唑并[1,2-b]哒嗪-6-胺	379.5	*	--
N-丁基-3-(4-(((2-甲氧基乙基)氨基)甲基)苯基)咪唑并[1,2-b]哒嗪-6-胺	353.5	*	--
N-丁基-3-(4-(((环丙基甲基)氨基)甲基)苯基)咪唑并[1,2-b]哒嗪-6-胺	349.5	*	--

[0200]

N-丁基-3-(4-((异丙基氨基)甲基)苯基)咪唑并[1,2-b]哒嗪-6-胺	337.5	*	--
N-丁基-3-(4-((丙基氨基)甲基)苯基)咪唑并[1,2-b]哒嗪-6-胺	337.5	*	--
N-丁基-3-(4-((叔丁基氨基)甲基)-2-氟苯基)咪唑并[1,2-b]哒嗪-6-胺	369.5	*	--
N-丁基-3-(4-((叔丁基氨基)甲基)-3-氟苯基)咪唑并[1,2-b]哒嗪-6-胺	369.5	**	--
N-丁基-3-(4-(吡咯烷-2-基)苯基)咪唑并[1,2-b]哒嗪-6-胺	335.4	*	--
N-丁基-3-(异吲哚啉-5-基)咪唑并[1,2-b]哒嗪-6-胺	307.4	*	--
N-丁基-3-(异喹啉-6-基)咪唑并[1,2-b]哒嗪-6-胺	317.4	**	--
N-环己基-3-(3-甲氧基吡啶-4-基)咪唑并[1,2-b]哒嗪-6-胺	323.4		***
N-异丁基-3-(3-(3-甲氧基吡啶-4-基)咪唑并[1,2-b]哒嗪-6-基)苯甲酰胺	401.5	**	--
N-异丁基-3-(3-(4-(甲基氨基甲酰基)苯基)咪唑并[1,2-b]哒嗪-6-基)苯甲酰胺	427.5	**	--
N-异戊基-3-(3-甲氧基吡啶-4-基)咪唑并[1,2-b]哒嗪-6-胺	311.4	**	--
N-异丙基-4-(3-(2-甲氧基苯基)咪唑并[1,2-b]哒嗪-6-基)-N-甲基哌嗪-1-甲酰胺	408.5	**	***
N-异丙基-4-(3-(2-甲氧基苯基)咪唑并[1,2-b]哒嗪-6-基)哌嗪-1-甲酰胺	394.5	*	***
N-异丙基-4-(3-苯基咪唑并[1,2-b]哒嗪-6-基)哌嗪-1-甲酰胺	364.4	**	***
N-甲基-4-(6-((2-(三氟甲氧基)苯乙基)氨基)咪唑并[1,2-b]哒嗪-3-基)苯甲酰胺	455.4	***	--
N-戊基-3-(4-(吡咯烷-2-基)苯基)咪唑并[1,2-b]哒嗪-6-胺	349.5	*	--

[0201]

哌啶-1-基(4-(3-(吡啶-2-基)咪唑并[1,2-b]哒嗪-6-基)哌嗪-1-基)甲酮	391.5	**	***
丙基 异丙基(2-((3-(3-甲氧基吡啶-4-基)咪唑并[1,2-b]哒嗪-6-基)氨基)乙基)氨基甲酸酯	412.5	*	--
S-4-(3-苯基咪唑并[1,2-b]哒嗪-6-基)哌嗪-1-硫代甲酸异丙基酯	381.5	*	***
(1-(3-(2-甲氧基苯基)咪唑并[1,2-b]哒嗪-6-基)吡咯烷-3-基)(甲基)氨基甲酸叔丁基酯	423.5	*	***
(1-(3-(2-甲氧基吡啶-3-基)咪唑并[1,2-b]哒嗪-6-基)吡咯烷-3-基)(甲基)氨基甲酸叔丁基酯	424.5	**	***
(1-(3-(2-甲氧基吡啶-3-基)咪唑并[1,2-b]哒嗪-6-基)氮杂环丁烷-3-基)(甲基)氨基甲酸叔丁基酯	410.5	--	*
(2-((3-(2-氨基吡啶-4-基)咪唑并[1,2-b]哒嗪-6-基)氨基)乙基)(甲基)氨基甲酸叔丁基酯	383.4	***	--
(2-((3-(2-氟苯基)咪唑并[1,2-b]哒嗪-6-基)氨基)乙基)(甲基)氨基甲酸叔丁基酯	385.4	**	--
(2-((3-(2-氟吡啶-4-基)咪唑并[1,2-b]哒嗪-6-基)氨基)乙基)(甲基)氨基甲酸叔丁基酯	386.4	**	--
(2-((3-(2-甲氧基苯基)咪唑并[1,2-b]哒嗪-6-基)氨基)乙基)(甲基)氨基甲酸叔丁基酯	397.5	**	--
(2-((3-(3-氨基甲酰基苯基)咪唑并[1,2-b]哒嗪-6-基)氨基)乙基)(甲基)氨基甲酸叔丁基酯	410.5	**	--
(2-((3-(3-甲氧基苯基)咪唑并[1,2-b]哒嗪-6-基)氨基)乙基)(甲基)氨基甲酸叔丁基酯	397.5	**	--
(2-((3-(3-甲氧基吡啶-4-基)咪唑并[1,2-b]哒嗪-6-基)氨基)乙基)(甲基)氨基甲酸叔丁基酯	398.5	*	--
(2-((3-(4-(氨基甲基)苯基)咪唑并[1,2-b]哒嗪-6-基)氨基)乙基)氨基甲酸叔丁基酯	382.5	**	--
(2-((3-(4-(氰基甲基)苯基)咪唑并[1,2-b]哒嗪-6-基)氨基)乙基)(甲基)氨基甲酸叔丁基酯	406.5	**	--

[0202]

(2-((3-(4-氨基甲酰基苯基)咪唑并[1,2-b]哒嗪-6-基)氨基)乙基)(甲基)氨基甲酸叔丁基酯	410.5	**	***
(2-((3-(4-氨基甲酰基苯基)咪唑并[1,2-b]哒嗪-6-基)氨基)乙基)(异丙基)氨基甲酸叔丁基酯	438.5	***	--
(2-((3-(4-氰基苯基)咪唑并[1,2-b]哒嗪-6-基)氨基)乙基)(甲基)氨基甲酸叔丁基酯	392.5	**	--
(2-((3-(5-乙酰基噻吩-2-基)咪唑并[1,2-b]哒嗪-6-基)氨基)乙基)(甲基)氨基甲酸叔丁基酯	415.5	***	--
(3-((3-(4-(氨基甲基)苯基)咪唑并[1,2-b]哒嗪-6-基)氨基)丙基)(甲基)氨基甲酸叔丁基酯	410.5	**	--
(3-((3-(5-乙酰基噻吩-2-基)咪唑并[1,2-b]哒嗪-6-基)氨基)丙基)(甲基)氨基甲酸叔丁基酯	429.5	**	--
2-(2-((3-(4-(氨基甲基)苯基)咪唑并[1,2-b]哒嗪-6-基)氨基)乙基)吡咯烷-1-甲酸叔丁基酯	436.5	***	--
2-(2-((3-(4-氨基甲酰基苯基)咪唑并[1,2-b]哒嗪-6-基)氨基)乙基)吡咯烷-1-甲酸叔丁基酯	450.5	**	--
4-(3-(3-甲氧基吡啶-4-基)咪唑并[1,2-b]哒嗪-6-基)哌嗪-1-甲酸叔丁基酯	410.5	***	--
4-(3-氯咪唑并[1,2-b]哒嗪-6-基)哌嗪-1-甲酸叔丁基酯	337.8	**	--
4-(3-碘咪唑并[1,2-b]哒嗪-6-基)哌嗪-1-甲酸叔丁基酯	429.3	**	***
4-(3-苯基咪唑并[1,2-b]哒嗪-6-基)哌嗪-1-甲酸叔丁基酯	379.5	**	***
异丙基(2-((3-(3-甲氧基吡啶-4-基)咪唑并[1,2-b]哒嗪-6-基)氨基)乙基)氨基甲酸叔丁基酯	426.5	**	--
甲基(1-(3-苯基咪唑并[1,2-b]哒嗪-6-基)吡咯烷-3-基)氨基甲酸叔丁基酯	393.5	**	**
甲基(2-((3-(4-(甲基氨基甲酰基)苯基)咪唑并[1,2-b]哒嗪-6-基)氨基)乙基)氨基甲酸叔丁基酯	424.5	**	--

[0203]

甲基(2-((3-(4-(吡咯烷-2-基)苯基)咪唑并[1,2-b]哒嗪-6-基)氨基)乙基)氨基甲酸叔丁基酯	436.5	***	--
甲基(2-((3-(吡啶-4-基)咪唑并[1,2-b]哒嗪-6-基)氨基)乙基)氨基甲酸叔丁基酯	368.4	**	--
甲基(2-((3-苯基咪唑并[1,2-b]哒嗪-6-基)氨基)乙基)氨基甲酸叔丁基酯	367.4	**	--

[0204] 基于吡唑并 [1,5-a] 嘧啶的抑制剂的体外数据

[0205] 为本发明的各种化合物获得的体外数据提供在下面的表 1 中，其中“MW”是指分子量，“P81 测定法”是指上面描述的 P81 过滤板测定法，“CBA”是指上面描述的基于 HEK281 细胞的测定法，“--”是指未获得给定测定法的结果，“*”是指小于或等于 1.0μM，“**”是指小于或等于 0.1μM 的值，并且“***”是指小于或等于 0.01μM。

[0206] 表 1

[0207]

化合物	MW	CBA IC_{50} μM	P81 IC_{50} μM
(4-(3-(2-甲氧基吡啶-3-基)吡唑并[1,5-a]嘧啶-5-基)哌嗪-1-基)(吡咯烷-1-基)甲酮	407.5	**	***
(S)-1-(2-(((3-(2-甲氧基苯基)吡唑并[1,5-a]嘧啶-5-基)氨基)甲基)吡咯烷-1-基)丁-1-酮	393.5	**	***
(S)-1-(2-(((3-(2-甲氧基苯基)吡唑并[1,5-a]嘧啶-5-基)氨基)甲基)吡咯烷-1-基)-3,3-二甲基丁-1-酮	421.5	***	***
(S)-1-(3,3-二甲基丁基)-5-(((3-(2-乙氧基苯基)吡唑并[1,5-a]嘧啶-5-基)氨基)甲基)吡咯烷-2-酮	435.6	**	***
(S)-1-(3,3-二甲基丁基)-5-(((3-(2-甲氧基苯基)吡唑并[1,5-a]嘧啶-5-基)氨基)甲基)吡咯烷-2-酮	421.5	***	***
(S)-1-(3,3-二甲基丁基)-5-(((3-(2-甲氧基吡啶-3-基)吡唑并[1,5-a]嘧啶-5-基)氨基)甲基)吡咯烷-2-酮	422.5	**	***

[0208]

(S)-1-(3,3-二甲基丁基)-5-(((3-(3-甲氧基吡啶-4-基)吡唑并[1,5-a]嘧啶-5-基)氨基)甲基)吡咯烷-2-酮	422.5	**	***
(S)-1-(3,3-二甲基丁基)-5-(((3-苯基吡唑并[1,5-a]嘧啶-5-基)氨基)甲基)吡咯烷-2-酮	391.5	--	***
(S)-2-(((3-溴吡唑并[1,5-a]嘧啶-5-基)氨基)甲基)-N-(叔丁基)吡咯烷-1-甲酰胺	395.3	***	***
(S)-2-环丙基-N-甲基-N-(1-(3-(吡啶-2-基)吡唑并[1,5-a]嘧啶-5-基)吡咯烷-3-基)乙酰胺	376.5	--	**
(S)-3,3,3-三氟-1-(2-(((3-(2-甲氧基苯基)吡唑并[1,5-a]嘧啶-5-基)氨基)甲基)吡咯烷-1-基)丙-1-酮	433.4	**	***
(S)-3,3,3-三氟-1-(2-(((3-(吡啶-4-基)吡唑并[1,5-a]嘧啶-5-基)氨基)甲基)吡咯烷-1-基)丙-1-酮	404.4	**	***
(S)-3,3,3-三氟-N-(1-(3-(2-甲氧基苯基)吡唑并[1,5-a]嘧啶-5-基)吡咯烷-3-基)-N-甲基丙酰胺	433.4	--	**
(S)-3,3,3-三氟-N-(1-(3-(2-甲氧基吡啶-3-基)吡唑并[1,5-a]嘧啶-5-基)吡咯烷-3-基)-N-甲基丙酰胺	434.4	***	***
(S)-3,3,3-三氟-N-甲基-N-(1-(3-(吡啶-2-基)吡唑并[1,5-a]嘧啶-5-基)吡咯烷-3-基)丙酰胺	404.4	***	***
(S)-5-(((3-溴吡唑并[1,5-a]嘧啶-5-基)氨基)甲基)-1-(3,3-二甲基丁基)吡咯烷-2-酮	394.3	**	***
(S)-2-(((3-(2-甲氧基苯基)吡唑并[1,5-a]嘧啶-5-基)氨基)甲基)吡咯烷-1-甲酸乙基酯	395.5	***	***
(S)-(1-(3-(2-甲氧基苯基)吡唑并[1,5-a]嘧啶-5-基)吡咯烷-3-基)(甲基)氨基甲酸异丙基酯	409.5	--	**
(S)-(1-(3-(2-甲氧基吡啶-3-基)吡唑并[1,5-a]嘧啶-5-基)吡咯烷-3-基)(甲基)氨基甲酸异丙基酯	410.5	--	**
(S)-2-(((3-(2-甲氧基苯基)吡唑并[1,5-a]嘧啶-5-基)氨基)甲基)吡咯烷-1-甲酸异丙基酯	409.5	***	***
(S)-甲基(1-(3-(吡啶-2-基)吡唑并[1,5-a]嘧啶-5-基)吡咯烷-3-基)氨基甲酸异丙基酯	380.4	--	*
(S)-甲基(1-(3-(吡啶-4-基)吡唑并[1,5-a]嘧啶-5-基)吡咯烷-3-基)氨基甲酸异丙基酯	380.4	--	**

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(S)-2-(((3-(2-甲氧基苯基)吡唑并[1,5-a]嘧啶-5-基)氨基)甲基)吡咯烷-1-甲酸甲基酯	381.4	**	***
(S)-N-(1-(3-(2-甲氧基苯基)吡唑并[1,5-a]嘧啶-5-基)吡咯烷-3-基)-N-甲基丁酰胺	393.5	*	***
(S)-N-(1-(3-(2-甲氧基吡啶-3-基)吡唑并[1,5-a]嘧啶-5-基)吡咯烷-3-基)-N-甲基丁酰胺	394.5	*	***
(S)-N-(1-(3-溴吡唑并[1,5-a]嘧啶-5-基)吡咯烷-3-基)-3,3,3-三氟-N-甲基丙酰胺	406.2	--	**
(S)-N-(1-(3-溴吡唑并[1,5-a]嘧啶-5-基)吡咯烷-3-基)-N-甲基吡咯烷-1-甲酰胺	393.3	--	**
(S)-N-(叔丁基)-2-(((3-(2-甲氧基苯基)吡唑并[1,5-a]嘧啶-5-基)氨基)甲基)吡咯烷-1-甲酰胺	422.5	**	***
(S)-N-甲基-N-(1-(3-(吡啶-2-基)吡唑并[1,5-a]嘧啶-5-基)吡咯烷-3-基)丁酰胺	364.4	--	*
(S)-(1-(3-(2-甲氧基苯基)吡唑并[1,5-a]嘧啶-5-基)吡咯烷-3-基)(甲基)氨基甲酸叔丁基酯	423.5	**	***
(S)-2-(((3-(2-(甲氧基甲基)苯基)吡唑并[1,5-a]嘧啶-5-基)氨基)甲基)吡咯烷-1-甲酸叔丁基酯	437.5	**	***
(S)-2-(((3-(2-乙基苯基)吡唑并[1,5-a]嘧啶-5-基)氨基)甲基)吡咯烷-1-甲酸叔丁基酯	421.5	**	***
(S)-2-(((3-(2-羟基苯基)吡唑并[1,5-a]嘧啶-5-基)氨基)甲基)吡咯烷-1-甲酸叔丁基酯	409.5	**	***
(S)-2-(((3-(2-异丙氧基苯基)吡唑并[1,5-a]嘧啶-5-基)氨基)甲基)吡咯烷-1-甲酸叔丁基酯	451.6	***	***
(S)-2-(((3-(2-甲氧基苯基)吡唑并[1,5-a]嘧啶-5-基)氨基)甲基)吡咯烷-1-甲酸叔丁基酯	423.5	***	--
(S)-2-(((3-(3-甲氧基苯基)吡唑并[1,5-a]嘧啶-5-基)氨基)甲基)吡咯烷-1-甲酸叔丁基酯	423.5	***	***
(S)-2-(((3-(4-(氨基甲基)苯基)吡唑并[1,5-a]嘧啶-5-基)氨基)甲基)吡咯烷-1-甲酸叔丁基酯	422.5	***	***
(S)-2-(((3-(4-氨基甲酰基苯基)吡唑并[1,5-a]嘧啶-5-基)氨基)甲基)吡咯烷-1-甲酸叔丁基酯	436.5	*	***
(S)-2-(((3-(4-甲氧基苯基)吡唑并[1,5-a]嘧啶-5-基)氨基)甲基)吡咯烷-1-甲酸叔丁基酯	423.5	***	***

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(S)-2-(((3-(4-甲氧基吡啶-3-基)吡唑并[1,5-a]嘧啶-5-基)氨基)甲基)吡咯烷-1-甲酸叔丁基酯	424.5	***	***
(S)-2-(((3-(吡啶-4-基)吡唑并[1,5-a]嘧啶-5-基)氨基)甲基)吡咯烷-1-甲酸叔丁基酯	394.5	***	--
(S)-2-(((3-(吡啶-4-基)吡唑并[1,5-a]嘧啶-5-基)氨基)甲基)吡咯烷-1-甲酸叔丁基酯	394.5	***	--
(S)-2-(((3-(三氟甲基)吡唑并[1,5-a]嘧啶-5-基)氨基)甲基)吡咯烷-1-甲酸叔丁基酯	385.4	**	***
(S)-2-(((3-碘吡唑并[1,5-a]嘧啶-5-基)氨基)甲基)吡咯烷-1-甲酸叔丁基酯	443.3	**	--
(S)-2-(((3-苯基吡唑并[1,5-a]嘧啶-5-基)氨基)甲基)吡咯烷-1-甲酸叔丁基酯	393.5	**	***
(S)-甲基(1-(3-(2-甲基吡啶-4-基)吡唑并[1,5-a]嘧啶-5-基)吡咯烷-3-基)氨基甲酸叔丁基酯	408.5	**	***
(S)-甲基(1-(3-(吡啶-2-基)吡唑并[1,5-a]嘧啶-5-基)吡咯烷-3-基)氨基甲酸叔丁基酯	394.5	--	*
1-(4-(3-(2-甲氧基吡啶-3-基)吡唑并[1,5-a]嘧啶-5-基)哌嗪-1-基)-3-甲基丁-1-酮	394.5	**	***
4-(3-(2-甲氧基吡啶-3-基)吡唑并[1,5-a]嘧啶-5-基)哌嗪-1-甲酸 2,2,2-三氟乙基酯	436.4	***	***
4-(3-(2-甲氧基吡啶-3-基)吡唑并[1,5-a]嘧啶-5-基)哌嗪-1-甲酸 2-氟乙基酯	400.4	***	***
4-(3-(2-甲氧基苯基)吡唑并[1,5-a]嘧啶-5-基)哌嗪-1-甲酸 2-甲氧基乙基酯	411.5	--	***
4-(3-(2-甲氧基吡啶-3-基)吡唑并[1,5-a]嘧啶-5-基)哌嗪-1-甲酸 2-甲氧基乙基酯	412.4	**	***
3-(2-甲氧基吡啶-3-基)-N-(4,4,4-三氟丁基)吡唑并[1,5-a]嘧啶-5-胺	351.3	**	***
3-(3-甲氧基吡啶-4-基)-N-(2-(三氟甲氧基)苯乙基)吡唑并[1,5-a]嘧啶-5-胺	429.4	***	---
3-(4-(氨基甲基)苯基)-N-(2-(环戊基氧基)乙基)吡唑并[1,5-a]嘧啶-5-胺	351.4	**	--
3-(4-(氨基甲基)苯基)-N-(2-(新戊基氧基)乙基)吡唑并[1,5-a]嘧啶-5-胺	353.5	**	--
3-(4-(氨基甲基)苯基)-N-(2-(叔丁氧基)乙基)吡唑并[1,5-a]嘧啶-5-胺	339.4	**	--

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3-(4-(氨基甲基)苯基)-N-(2-(三氟甲氧基)苯乙基)吡唑并[1,5-a]嘧啶-5-胺	427.4	***	--
3-(4-(氨基甲基)苯基)-N-(2-甲氧基乙基)吡唑并[1,5-a]嘧啶-5-胺	297.4	**	--
3-(4-(氨基甲基)苯基)-N-(3-(环戊基氧基)丙基)吡唑并[1,5-a]嘧啶-5-胺	365.5	**	--
3-(4-(氨基甲基)苯基)-N-丁基吡唑并[1,5-a]嘧啶-5-胺	295.4	**	--
3-(4-甲氧基吡啶-3-基)-N-(2-(三氟甲氧基)苯乙基)吡唑并[1,5-a]嘧啶-5-胺	429.4	**	--
3-溴-N-((1-(2,2,2-三氟乙基)吡咯烷-2-基)甲基)吡唑并[1,5-a]嘧啶-5-胺	378.2	**	***
3-溴-N-(3-(环戊基氧基)丙基)吡唑并[1,5-a]嘧啶-5-胺	339.2	*	--
4-(5-(丁基氨基)吡唑并[1,5-a]嘧啶-3-基)-N-(2-(甲基氨基)乙基)苯甲酰胺	366.5	**	--
5-(4-(异丁基磺酰基)哌嗪-1-基)-3-(2-甲氧基吡啶-3-基)吡唑并[1,5-a]嘧啶	430.5		**
4-(3-(2-甲氧基吡啶-3-基)吡唑并[1,5-a]嘧啶-5-基)哌嗪-1-甲酸环戊基酯	422.5	***	***
4-(3-(2-乙氧基吡啶-3-基)吡唑并[1,5-a]嘧啶-5-基)哌嗪-1-甲酸乙基酯	396.4	***	***
4-(3-(2-甲氧基吡啶-3-基)吡唑并[1,5-a]嘧啶-5-基)哌嗪-1-甲酸乙基酯	382.4	**	***
5-(4-(异丙氧基羰基)哌嗪-1-基)吡唑并[1,5-a]嘧啶-3-甲酸乙基酯	361.4		**
甲基(2-((3-(4-(甲基氨基甲酰基)苯基)吡唑并[1,5-a]嘧啶-5-基)氨基)乙基)氨基甲酸乙基酯	396.4	**	--
(2-((3-(4-氨基甲酰基苯基)吡唑并[1,5-a]嘧啶-5-基)氨基)乙基)(甲基)氨基甲酸异丁基酯	410.5	***	--
甲基(2-((3-(4-(甲基氨基甲酰基)苯基)吡唑并[1,5-a]嘧啶-5-基)氨基)乙基)氨基甲酸异丁基酯	424.5	*	--
(1-(3-(2-甲氧基吡啶-3-基)吡唑并[1,5-a]嘧啶-5-基)氮杂环丁烷-3-基)(甲基)氨基甲酸异丙基酯	396.4	--	**
(2-((3-(3-甲氧基吡啶-4-基)吡唑并[1,5-a]嘧啶-5-基)氨基)乙基)(甲基)氨基甲酸异丙基酯	384.4	***	--

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(2-((3-(4-(氨基甲基)苯基)吡唑并[1,5-a]嘧啶-5-基)氨基)乙基)(甲基)氨基甲酸异丙基酯	382.5	**	--
(2-((3-(4-氨基甲酰基苯基)吡唑并[1,5-a]嘧啶-5-基)氨基)乙基)(甲基)氨基甲酸异丙基酯	396.4	***	--
(2-((3-(4-甲氧基吡啶-3-基)吡唑并[1,5-a]嘧啶-5-基)氨基)乙基)(甲基)氨基甲酸异丙基酯	384.4	**	--
4-(3-(1,3,5-三甲基-1H-吡唑-4-基)吡唑并[1,5-a]嘧啶-5-基)哌嗪-1-甲酸异丙基酯	397.5	--	**
4-(3-(1-异丁基-1H-吡唑-4-基)吡唑并[1,5-a]嘧啶-5-基)哌嗪-1-甲酸异丙基酯	411.5	--	**
4-(3-(1-甲基-2-氧基-1,2-二氢吡啶-3-基)吡唑并[1,5-a]嘧啶-5-基)哌嗪-1-甲酸异丙基酯	396.4	**	***
4-(3-(2-(甲氧基甲基)苯基)吡唑并[1,5-a]嘧啶-5-基)哌嗪-1-甲酸异丙基酯	409.5	--	*
4-(3-(2-(甲基硫基)吡啶-3-基)吡唑并[1,5-a]嘧啶-5-基)哌嗪-1-甲酸异丙基酯	412.5	--	**
4-(3-(2,6-二甲氧基吡啶-3-基)吡唑并[1,5-a]嘧啶-5-基)哌嗪-1-甲酸异丙基酯	426.5	***	***
4-(3-(2-氨基吡啶-3-基)吡唑并[1,5-a]嘧啶-5-基)哌嗪-1-甲酸异丙基酯	381.4	--	**
4-(3-(2-氯吡啶-3-基)吡唑并[1,5-a]嘧啶-5-基)哌嗪-1-甲酸异丙基酯	400.9	*	**
4-(3-(2-乙氧基吡啶-3-基)吡唑并[1,5-a]嘧啶-5-基)哌嗪-1-甲酸异丙基酯	410.5	**	***
4-(3-(2-氟吡啶-3-基)吡唑并[1,5-a]嘧啶-5-基)哌嗪-1-甲酸异丙基酯	384.4	**	***
4-(3-(2-羟基吡啶-3-基)吡唑并[1,5-a]嘧啶-5-基)哌嗪-1-甲酸异丙基酯	382.4	**	***
4-(3-(2-异丙氧基吡啶-3-基)吡唑并[1,5-a]嘧啶-5-基)哌嗪-1-甲酸异丙基酯	424.5	**	***
4-(3-(2-甲氧基-5-甲基吡啶-3-基)吡唑并[1,5-a]嘧啶-5-基)哌嗪-1-甲酸异丙基酯	410.5	***	***
4-(3-(2-甲氧基-6-甲基吡啶-3-基)吡唑并[1,5-a]嘧啶-5-基)哌嗪-1-甲酸异丙基酯	410.5	**	***
4-(3-(2-甲氧基苯基)吡唑并[1,5-a]嘧啶-5-基)哌嗪-1-甲酸异丙基酯	395.5	--	***
4-(3-(2-甲氧基吡啶-3-基)吡唑并[1,5-a]嘧啶-5-基)哌嗪-1-甲酸异丙基酯	396.4	--	***

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4-(3-(2-甲氧基吡啶-3-基)吡唑并[1,5-a]嘧啶-5-基)-5,6-二氢吡啶-1(2H)-甲酸异丙基酯	393.4	***	***
4-(3-(2-甲氧基吡啶-3-基)吡唑并[1,5-a]嘧啶-5-基)-3-氧基哌嗪-1-甲酸异丙基酯	410.4	***	***
4-(3-(2-甲氧基吡啶-3-基)吡唑并[1,5-a]嘧啶-5-基)-2,2-二甲基哌嗪-1-甲酸异丙基酯	424.5	--	**
4-(3-(2-甲基吡啶-3-基)吡唑并[1,5-a]嘧啶-5-基)哌嗪-1-甲酸异丙基酯	380.4	--	**
4-(3-(3,6-二甲氧基哒嗪-4-基)吡唑并[1,5-a]嘧啶-5-基)哌嗪-1-甲酸异丙基酯	427.5	***	***
4-(3-(3-乙氧基苯基)吡唑并[1,5-a]嘧啶-5-基)哌嗪-1-甲酸异丙基酯	409.5	--	***
4-(3-(3-氟-2-甲氧基苯基)吡唑并[1,5-a]嘧啶-5-基)哌嗪-1-甲酸异丙基酯	413.4	--	**
4-(3-(3-甲氧基吡啶-2-基)吡唑并[1,5-a]嘧啶-5-基)哌嗪-1-甲酸异丙基酯	396.4	--	*
4-(3-(3-甲氧基吡啶-4-基)吡唑并[1,5-a]嘧啶-5-基)哌嗪-1-甲酸异丙基酯	396.4	**	***
4-(3-(4-氟吡啶-3-基)吡唑并[1,5-a]嘧啶-5-基)哌嗪-1-甲酸异丙基酯	384.4	--	**
4-(3-(4-甲氧基吡啶-2-基)吡唑并[1,5-a]嘧啶-5-基)哌嗪-1-甲酸异丙基酯	396.4	--	***
4-(3-(4-甲氧基吡啶-3-基)吡唑并[1,5-a]嘧啶-5-基)哌嗪-1-甲酸异丙基酯	396.4	**	***
4-(3-(5-氟-2-甲氧基苯基)吡唑并[1,5-a]嘧啶-5-基)哌嗪-1-甲酸异丙基酯	413.4	***	***
4-(3-(5-氟-2-甲氧基吡啶-3-基)吡唑并[1,5-a]嘧啶-5-基)哌嗪-1-甲酸异丙基酯	414.4	**	***
4-(3-(5-氟吡啶-3-基)吡唑并[1,5-a]嘧啶-5-基)哌嗪-1-甲酸异丙基酯	384.4	--	***
4-(3-(5-甲氧基吡啶-2-基)吡唑并[1,5-a]嘧啶-5-基)哌嗪-1-甲酸异丙基酯	396.4	***	***
4-(3-(5-甲氧基吡啶-3-基)吡唑并[1,5-a]嘧啶-5-基)哌嗪-1-甲酸异丙基酯	396.4	**	***
4-(3-(6-氟吡啶-3-基)吡唑并[1,5-a]嘧啶-5-基)哌嗪-1-甲酸异丙基酯	384.4	--	**
4-(3-(6-甲氧基吡啶-3-基)吡唑并[1,5-a]嘧啶-5-基)哌嗪-1-甲酸异丙基酯	396.4	*	***

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4-(3-(乙基氨基甲酰基)吡唑并[1,5-a]嘧啶-5-基)哌嗪-1-甲酸异丙基酯	360.4	--	**
4-(3-(异丙基氨基甲酰基)吡唑并[1,5-a]嘧啶-5-基)哌嗪-1-甲酸异丙基酯	374.4	--	*
4-(3-(甲基氨基甲酰基)吡唑并[1,5-a]嘧啶-5-基)哌嗪-1-甲酸异丙基酯	346.4	--	**
4-(3-(吡嗪-2-基)吡唑并[1,5-a]嘧啶-5-基)哌嗪-1-甲酸异丙基酯	367.4	--	**
4-(3-(吡啶-2-基)吡唑并[1,5-a]嘧啶-5-基)哌嗪-1-甲酸异丙基酯	366.4	**	***
4-(3-(吡啶-3-基)吡唑并[1,5-a]嘧啶-5-基)哌嗪-1-甲酸异丙基酯	366.4	--	***
4-(3-(吡啶-4-基)吡唑并[1,5-a]嘧啶-5-基)哌嗪-1-甲酸异丙基酯	366.4	**	***
4-(3-(嘧啶-5-基)吡唑并[1,5-a]嘧啶-5-基)哌嗪-1-甲酸异丙基酯	367.4	--	**
4-(3-异丙基吡唑并[1,5-a]嘧啶-5-基)哌嗪-1-甲酸异丙基酯	331.4	--	**
4-(吡唑并[1,5-a]嘧啶-5-基)哌嗪-1-甲酸异丙基酯	289.3	--	***
甲基(2-((3-(4-((2-(甲基氨基)乙基)氨基甲酰基)苯基)吡唑并[1,5-a]嘧啶-5-基)氨基)乙基)氨基甲酸异丙基酯	453.5	**	--
甲基(2-((3-(4-(甲基氨基甲酰基)苯基)吡唑并[1,5-a]嘧啶-5-基)氨基)乙基)氨基甲酸异丙基酯	410.5	***	--
甲基(2-((3-(4-(吡咯烷-2-基)苯基)吡唑并[1,5-a]嘧啶-5-基)氨基)乙基)氨基甲酸异丙基酯	422.5	***	--
4-(3-(2-甲氧基吡啶-3-基)吡唑并[1,5-a]嘧啶-5-基)哌嗪-1-甲酸甲基酯	368.4	**	**
N-(2-(环戊基氧基)乙基)-3-(3-甲氧基吡啶-4-基)吡唑并[1,5-a]嘧啶-5-胺	353.4	**	--
N-(2-(叔丁氧基)乙基)-3-(3-甲氧基吡啶-4-基)吡唑并[1,5-a]嘧啶-5-胺	341.4	**	--
N-(2-氨基乙基)-4-(5-((2-甲氧基乙基)氨基)吡唑并[1,5-a]嘧啶-3-基)苯甲酰胺	354.4	*	--

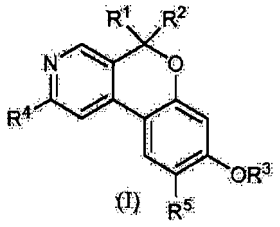
[0215]

N-(2-氨基乙基)-4-(5-((3,3-二甲基丁基)氨基)吡唑并[1,5-a]嘧啶-3-基)苯甲酰胺	380.5	*	--
N-(2-氨基乙基)-4-(5-(丁基氨基)吡唑并[1,5-a]嘧啶-3-基)苯甲酰胺	352.4	**	--
N-(2-甲氧基乙基)-3-苯基吡唑并[1,5-a]嘧啶-5-胺	268.3	*	--
N-(3-(2-甲氧基吡啶-3-基)吡唑并[1,5-a]嘧啶-5-基)-N-(4,4,4-三氟丁基)乙酰胺	393.4	--	*
N-(3-(环戊基氧基)丙基)-3-(3-甲氧基吡啶-4-基)吡唑并[1,5-a]嘧啶-5-胺	367.4	**	--
N-(叔丁基)-4-(3-(2-甲氧基吡啶-3-基)吡唑并[1,5-a]嘧啶-5-基)哌嗪-1-甲酰胺	409.5	**	***
N-(叔丁基)-4-(3-(2-甲氧基吡啶-3-基)吡唑并[1,5-a]嘧啶-5-基)-N-甲基哌嗪-1-甲酰胺	423.5	**	***
N-异丙基-4-(3-(2-甲氧基吡啶-3-基)吡唑并[1,5-a]嘧啶-5-基)哌嗪-1-甲酰胺	395.5	***	***
N-异丙基-4-(3-(2-甲氧基吡啶-3-基)吡唑并[1,5-a]嘧啶-5-基)-N-甲基哌嗪-1-甲酰胺	409.5	**	***
(1-(3-(2-甲氧基吡啶-3-基)吡唑并[1,5-a]嘧啶-5-基)氮杂环丁烷-3-基)(甲基)氨基甲酸叔丁基酯	410.5	--	*
(2-((3-(3-甲氧基吡啶-4-基)吡唑并[1,5-a]嘧啶-5-基)氨基)乙基)(甲基)氨基甲酸叔丁基酯	398.5	***	--
(2-((3-(4-氨基甲酰基苯基)吡唑并[1,5-a]嘧啶-5-基)氨基)乙基)(甲基)氨基甲酸叔丁基酯	410.5	***	--
(2-(4-(5-((2-甲氧基乙基)氨基)吡唑并[1,5-a]嘧啶-3-基)苯甲酰胺基)乙基)氨基甲酸叔丁基酯	454.5	*	--
4-(3-(2-甲氧基吡啶-3-基)吡唑并[1,5-a]嘧啶-5-基)哌嗪-1-甲酸叔丁基酯	410.5	***	***
4-(吡唑并[1,5-a]嘧啶-5-基)-5,6-二氢吡啶-1(2H)-甲酸叔丁基酯	300.4	--	**
甲基(2-((3-(4-(甲基氨基甲酰基)苯基)吡唑并[1,5-a]嘧啶-5-基)氨基)乙基)氨基甲酸叔丁基酯	424.5	***	--

[0216] 基于芳基醚的抑制剂的体外数据

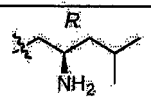
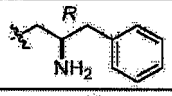
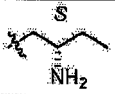
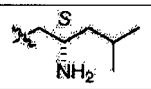
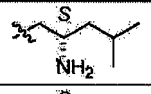
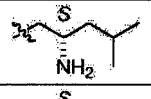
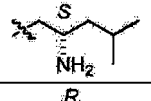
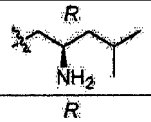
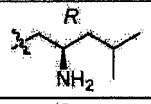
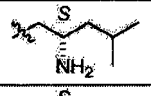
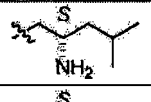
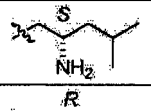
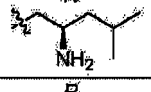
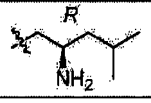
[0217] 使用上面描述的 Caliper 和 HEK281 测定法获得各种基于芳基醚的化合物的体外数据：

[0218]

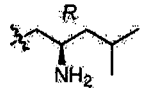
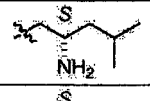
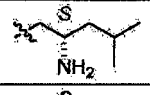
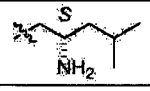
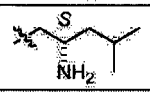
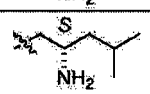
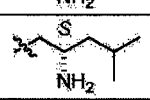
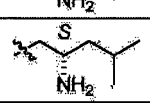


(I)

[0219]

R^1	R^2	R^4	R^5	R^3	Caliper IC_{50} (nM)	CBA IC_{50}
H	H	H	H		c	
H	H	H	H		293	
H	H	H	H		d	
H	H	H	H		c	
H	H	H	H		3.3	8.4
Me	H	H	H		4.9	
Me	H	H	H		c	25
H	Me	H	H		c	b
Me	H	H	H		c	>300
H	Me	H	H		c	
Cyc-Pr	H	H	H		c	c
Cyc-Pr	H	H	H		d	
H	Cyc-Pr	H	H		b	18
Cyc-Pr	H	H	H		d	
Cyc-Pr	H	H	H		d	d

[0220]

H	Cyc-Pr	H	H		d	d
Et	H	H	Et		c	18
Et	H	H	H		c	c
H	Et	H	H		12	56
=O		H	H		c	c
H	H	NHAc	H		c	c
H	H	NH_2	H		b	b
H	H	H	Br		0.86	2.5

[0221] 其中 :a = <1nM ;b = 1-10nM ;c = 10-100nM ;d = 100-1000nM。

[0222] 药理学效果

[0223] AAK1 敲除小鼠的研究显示,正如使用福尔马林爪试验所测量的,AAK1 基因的破坏影响疼痛响应。参见上面的实施例 5.4.1。同样的试验被用于证实 AAK1 抑制剂的给药也能影响疼痛响应。

[0224] 使用自动化伤害感受分析仪 (Automatic Nociception Analyzers)(购自 University of California, San Diego 的 Ozaki 实验室)测试小鼠的伤害感受。在试验前 30 分钟,使用强力胶将金属带置于每只小鼠的左后爪周围。在 30 分钟的适应期后,将 20μl 5%福尔马林皮下注射到左后爪的背侧表面中。将小鼠分开饲养在圆柱形仓室中 45 分钟。通过用蒸馏水稀释甲醛 (Formalde-fresh 20%, Fisher Scientific, Fair Lawn, NJ) 来制备新鲜的 5%福尔马林溶液。在福尔马林注射之前 30 分钟给药调查的化合物。

[0225] 通过电磁场,用计算机记录每分钟退缩数、阶段 I(急性阶段=前 8 分钟)的总退缩数和阶段 II(20-40 分钟之间的强直阶段)的总退缩数。参见 Yaksh TL, Ozaki g, McCumber D, Rathbun M, Svensson C, Malkmus S, Yaksh MC.,用于福尔马林伤害感受生物测定法的自动退缩检测系统 (An automated flinch detecting system for use in the formalin nociceptive bioassay), J Appl Physiol., 2001 ;90:2386-402。

[0226] 在不同剂量下试验了本发明的各种化合物。使用加巴喷丁和普瑞巴林作为阳性对照。结果示出在下面的表 2 中,其中“*”是指等于或大于加巴喷丁在 200mpk 下的效果的 50%的效果,“**”是指等于或大于加巴喷丁在 200mpk 下的效果的 100%的效果,“sc”是指皮下给药,“ip”是指腹膜内给药,“po”是指口服给药。

[0227] 表 2

[0228]

化合物	剂量(mpk)	效果
加巴喷丁	50 sc	*
加巴喷丁	200 sc	**
普瑞巴林	50 sc	*
(S)-(1-(3-(2-甲氧基吡啶-3-基)咪唑并[1,2-b]哒嗪-6-基)吡咯烷-3-基)(甲基)氨基甲酸异丙基酯	10 po	*
(S)-(1-(3-(2-甲氧基吡啶-3-基)咪唑并[1,2-b]哒嗪-6-基)吡咯烷-3-基)(甲基)氨基甲酸异丙基酯	30 po	**
(S)-(1-(3-(2-甲氧基吡啶-3-基)咪唑并[1,2-b]哒嗪-6-基)吡咯烷-3-基)(甲基)氨基甲酸异丙基酯	60 po	**
(S)-2-(((3-(4-(氨基甲基)苯基)咪唑并[1,2-b]哒嗪-6-基)氨基)甲基)吡咯烷-1-甲酸叔丁基酯	60 sc	**
(S)-2-(((3-溴咪唑并[1,2-b]哒嗪-6-基)氨基)甲基)吡咯烷-1-甲酸叔丁基酯	30 sc	**
(S)-2-(((3-溴咪唑并[1,2-b]哒嗪-6-基)氨基)甲基)吡咯烷-1-甲酸叔丁基酯	60 sc	**
3-(4-(1H-四唑-5-基)苯基)-N-丁基咪唑并[1,2-b]哒嗪-6-胺	60 ip	**

[0229]

3-(4-(氨基甲基)苯基)-N-(2-(环戊基氧基)乙基)咪唑并[1,2-b]哒嗪-6-胺	60 sc	**
3-(4-(氨基甲基)苯基)-N-(2-(环戊基氧基)乙基)咪唑并[1,2-b]哒嗪-6-胺	100 sc	**
3-(4-(氨基甲基)苯基)-N-(2-(叔丁氧基)乙基)咪唑并[1,2-b]哒嗪-6-胺	60 sc	**
3-(4-(氨基甲基)苯基)-N-(3-(叔丁氧基)丙基)咪唑并[1,2-b]哒嗪-6-胺	60 sc	**
3-(4-(氨基甲基)苯基)-N-(3-苯基丙基)咪唑并[1,2-b]哒嗪-6-胺	30 ip	**
4-(3-(2-甲氧基苯基)咪唑并[1,2-b]哒嗪-6-基)哌嗪-1-甲酸异丙基酯	30 sc	**
4-(3-(2-甲氧基苯基)咪唑并[1,2-b]哒嗪-6-基)哌嗪-1-甲酸异丙基酯	60 sc	**
N-(2-氨基乙基)-4-(6-(丁基氨基)咪唑并[1,2-b]哒嗪-3-基)苯甲酰胺	30 ip	**
(2-((3-(4-氨基甲酰基苯基)咪唑并[1,2-b]哒嗪-6-基)氨基)乙基)(甲基)氨基甲酸叔丁基酯	100 po	**
(2-((3-(4-氨基甲酰基苯基)咪唑并[1,2-b]哒嗪-6-基)氨基)乙基)(甲基)氨基甲酸叔丁基酯	60 sc	**
(S)-2-(((3-(2-甲氧基苯基)吡唑并[1,5-a]嘧啶-5-基)氨基)甲基)吡咯烷-1-甲酸叔丁基酯	10 sc	*
(S)-2-(((3-(2-甲氧基苯基)吡唑并[1,5-a]嘧啶-5-基)氨基)甲基)吡咯烷-1-甲酸叔丁基酯	60 sc	*
(S)-2-(((3-(吡啶-4-基)吡唑并[1,5-a]嘧啶-5-基)氨基)甲基)吡咯烷-1-甲酸叔丁基酯	30 sc	**
4-(3-(2-甲氧基苯基)吡唑并[1,5-a]嘧啶-5-基)哌嗪-1-甲酸异丙基酯	30 sc	**
4-(3-(2-甲氧基吡啶-3-基)吡唑并[1,5-a]嘧啶-5-基)哌嗪-1-甲酸异丙基酯	10 po	*

[0230]

4-(3-(2-甲氧基吡啶-3-基)吡唑并[1,5-a]嘧啶-5-基)哌嗪-1-甲酸异丙基酯	30 po	**
(*R*)-1-(5*H*-色烯并[3,4-*c*]吡啶-8-基氧基)-4-甲基戊-2-胺	10 sc	45%
(*R*)-1-(5*H*-色烯并[3,4-*c*]吡啶-8-基氧基)-4-甲基戊-2-胺	30 sc	*

[0231] 这些结果证实了 AAK1 抑制剂可用于治疗疼痛。

[0232] 上面引用的所有出版物（例如专利和专利申请）以其全部内容通过参考并入本文。

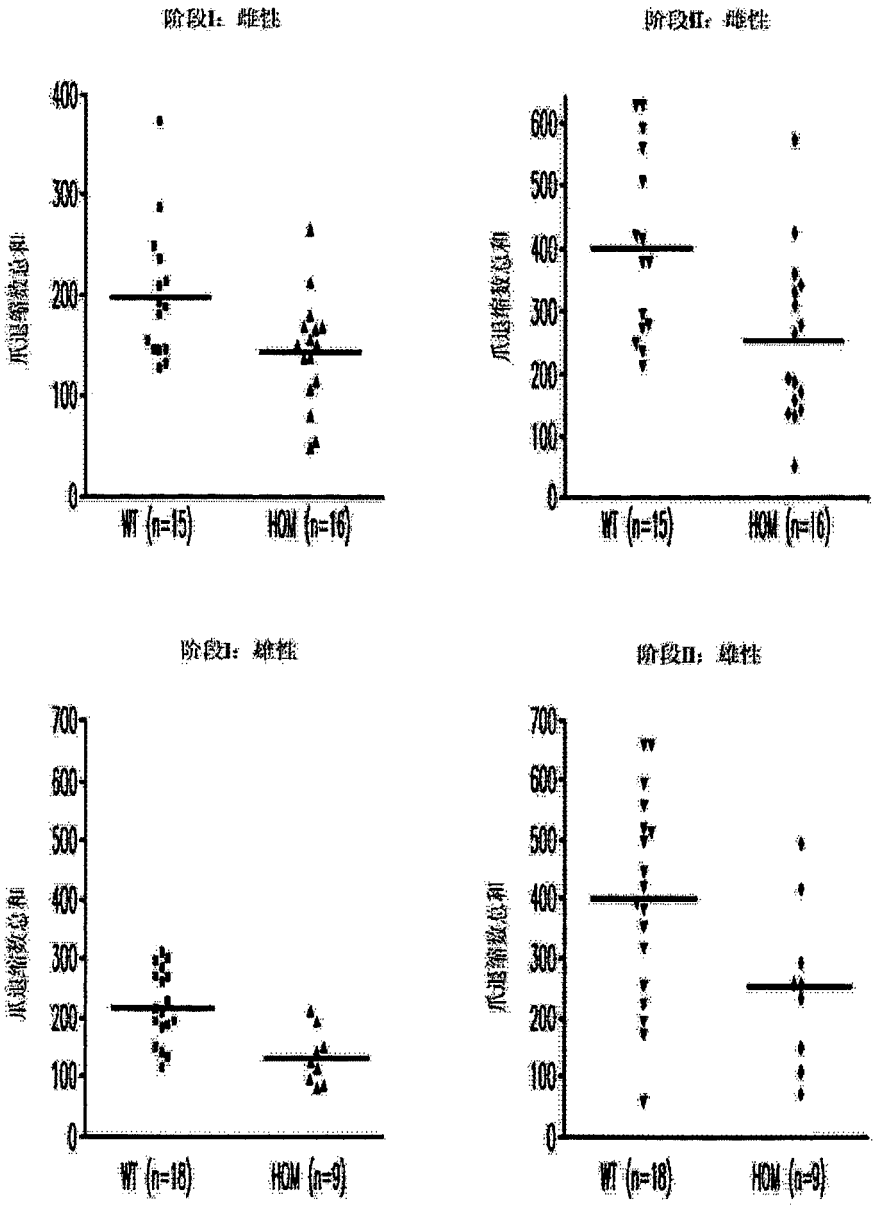

阶段I：雄性
爪退缩数总和
400
300
200
100
0
WT (n=15)
HOM (n=16)
阶段III：雄性
爪退缩数总和
600
500
400
300
200
100
0
WT (n=15)
HOM (n=16)
阶段I：雄性
爪退缩数总和
700
600
500
400
300
200
100
0
WT (n=18)
HOM (n=9)
阶段II：雄性
爪退缩数总和
700
600
500
400
300
200
100
0
WT (n=18)
HOM (n=9)

图 1