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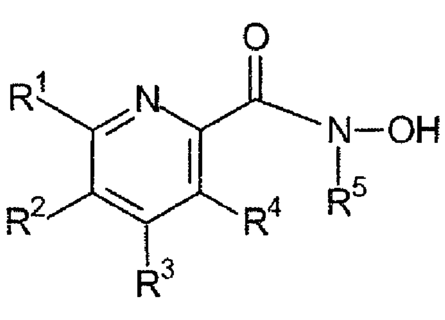
(54) Title: HETEROARYL HYDROXAMIC ACID DERIVATIVES AND THEIR USE IN THE TREATMENT, AMELIORATION OR PREVENTION OF A VIRAL DISEASE



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(57) Abstract: The present invention relates to a compound having the general formula I, optionally in the form of a pharmaceutically acceptable salt, solvate, polymorph, prodrug, tautomer, racemate, enantiomer, or dsasiereomer or mixture thereof, which is useful in treating, ameloriating or preventing a viral disease. Furthermore, specific combination therapies are disclosed.

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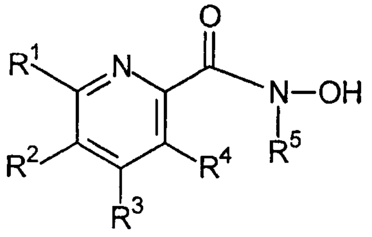
Heteroaryl hydroxamic acid derivatives
and their use in the treatment, amelioration or prevention of a viral disease

Field of the invention

The present invention relates to a compound having the general formula I, optionally in the form of a pharmaceutically acceptable salt, solvate, polymorph, prodrug, tautomer, racemate, enantiomer, or diastereomer or mixture thereof,



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which is useful in treating, ameliorating or preventing a viral disease. Furthermore, specific combination therapies are disclosed.

Background of the invention

In recent years the serious threat posed by influenza virus to worldwide public health has been highlighted by, firstly, the ongoing low level transmission to humans of the highly pathogenic avian H5N1 strain (63% mortality in infected humans, http://www.who.int/csr/disease/avian_influenza/en/) and secondly, the unexpected emergence in 2009 of a novel pandemic strain A/H1N1 that has rapidly spread around the entire world (http://www.who.int/csr/disease/swineflu/en/). Whilst the new strain is highly contagious but currently only generally gives mild illness, the future evolution of this virus is unpredictable.

In a much more serious, but highly plausible scenario, H5N1 could have been more easily transmissible between humans or the new A/H1N1 could have been more virulent and could have carried the single point mutation that confers Tamiflu resistance (Neumann et al., Nature, 2009 (18; 459(7249) 931-939), as many seasonal H1N1 strains have recently done (Dharan et al., The Journal of the American Medical Association, 2009 Mar 11; 301 (10), 1034-1041; Moscona et al., The New England Journal of Medicine, 2009 (Mar 5;360(10) pp 953-956). In this case, the delay in generating and deploying a vaccine (~6 months in the relatively favourable case of A/H1N1 and still not a solved problem for H5N1) could have been catastrophically costly in human lives and societal disruption.

It is widely acknowledged that to bridge the period before a new vaccine becomes available and to treat severe cases, as well as to counter the problem of viral resistance, a wider choice of anti-influenza drugs is required. Development of new anti-influenza drugs has therefore again become a high priority, having been largely abandoned by the major pharmaceutical companies once the anti-neuraminidase drugs became available.

An excellent starting point for the development of antiviral medication is structural data of essential viral proteins. Thus, the crystal structure determination of e.g. the influenza virus surface antigen neuraminidase (Von Itzstein, M. et al., (1993), Nature, 363, pp. 418-423) led directly to the development of neuraminidase inhibitors with anti-viral activity preventing the release of virus from the cells, however, not the virus production. These and their derivatives have subsequently developed into the anti-influenza drugs, zanamivir (Glaxo) and oseltamivir (Roche), which are currently being stockpiled by many countries as a first line of defence against an eventual pandemic. However, these medicaments provide only a reduction in the duration of the clinical disease. Alternatively, other anti-influenza compounds such as amantadine and rimantadine target an ion channel protein, i.e., the M2 protein, in the viral membrane interfering with the uncoating of the virus inside the cell. However, they have not been extensively used due to their side effects and the rapid development of resistant virus mutants (Magden, J. et al., (2005), Appl. Microbiol. Biotechnol., 66, pp. 612-621). In addition, more unspecific viral drugs, such as ribavirin, have been shown to work for treatment of influenza and other virus infections (Eriksson, B. et al., (1977), Antimicrob. Agents Chemother., 11, pp. 946-951). However, ribavirin is only approved in a few countries, probably due to severe side effects (Furuta et al., ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, 2005, p. 981–986). Clearly, new antiviral compounds are needed, preferably directed against different targets.

Influenza virus as well as Thogotovirus belong to the family of Orthomyxoviridae which, as well as the family of the Bunyaviridae, including the Hantavirus, Nairovirus, Orthobunyavirus, and Phlebovirus, are negative stranded RNA viruses. Their genome is segmented and comes in ribonucleoprotein particles that include the RNA dependent RNA polymerase which carries out (i) the initial copying of the single-stranded virion RNA (vRNA) into viral mRNAs and (ii) the vRNA replication. This enzyme, a trimeric complex composed of subunits PA, PB1 and PB2, is central to the life cycle of the virus since it is responsible for the replication and transcription of viral RNA. In previous work the atomic structure of two key domains of the polymerase, the mRNA cap-binding domain in the PB2 subunit (Guilligay et al., Nature Structural & Molecular Biology 2008; May;15(5): 500-506) and the endonuclease-active site in the PA subunit (Dias et al., Nature 2009, 458, 914-918) have been identified and determined. These two sites are critical for the unique cap-snatching mode of transcription that is used by influenza virus to generate viral mRNAs. For the generation of viral mRNA the polymerase makes use of the so called "cap-snatching" mechanism (Plotch, S. J. et al., (1981), Cell, 23, pp. 847-858; Kukkonen, S. K. et al (2005), Arch. Virol., 150, pp. 533-556; Leahy, M. B. et al, (2005), J. Virol., 71, pp. 8347-8351; Noah, D. L. et al., (2005), Adv. Virus Res., 65, pp. 121-145). A 5' cap (also termed an RNA cap, RNA 7-methylguanosine cap or an RNA m7G cap) is a modified guanine nucleotide that has been added to the 5' end of a messenger RNA. The 5' cap consists of a terminal 7-methylguanosine residue which is linked through a 5'-5'-triphosphate bond to the first transcribed nucleotide. The viral polymerase binds to the 5' RNA cap of cellular mRNA molecules and cleaves the RNA cap together with a stretch of 10 to 15 nucleotides. The capped RNA fragments then serve as primers for the synthesis of viral mRNA.

The polymerase complex seems to be an appropriate antiviral drug target since it is essential for synthesis of viral mRNA and viral replication and contains several functional active sites likely to be significantly different from those found in host cell proteins (Magden, J. et al., (2005), Appl. Microbiol. Biotechnol., 66, pp. 612-621). Thus, for example, there have been attempts to interfere with the assembly of polymerase subunits by a 25-amino-acid peptide resembling the PA-binding domain within PB1 (Ghanem, A. et al., (2007), J. Virol., 81, pp. 7801-7804). Furthermore, the endonuclease activity of the polymerase has been targeted and a series of 4-substituted 2,4-dioxobutanoic acid compounds has been identified as selective inhibitors of this activity in influenza viruses (Tomassini, J. et al., (1994), Antimicrob. Agents Chemother., 38, pp. 2827-2837). In addition, flutimide, a substituted 2,6-diketopiperazine, identified in extracts of Delitschia confertaspora, a fungal species, has been shown to inhibit the endonuclease of influenza virus (Tomassini, J. et al., (1996), Antimicrob. Agents Chemother., 40, pp. 1189-1193). Moreover, there have been attempts to interfere with viral transcription by nucleoside analogs, such as 2'-deoxy-2'-fluoroguanosine (Tisdale, M. et al., (1995), Antimicrob. Agents Chemother., 39, pp. 2454-2458).

The suitability of certain N-hydroxamic acid and N-hydroxyimide compounds for inhibiting the influenza virus polymerase has been investigated by Cianci et al. (Cianci C. et al., (1996) Antiviral Chem. & Chemotherapy (1996) 7(6) pp. 353-360). Cianci et al. describe the screening of a proprietary chemical collection in an effort to discover antiviral compounds. One compound, BMY-26270, was identified as an inhibitor of the capped RNA-dependent RNA polymerase of the influenza virus. The inhibitory activity of this compound was attributed to an effect on the endonuclease cleavage function of the influenza polymerase analyzed on entire RNPs and viral lysates, respectively, without knowledge of the location and structure of the viral endonuclease active site. Based on their results, Cianci et al. concluded that a specific phenolic hydroxyl group and a hydroxamic acid moiety are essential components of the polymerase-inhibiting pharmacophore. Cianci et al. further concluded that modification or deletion of either of these elements in the context of the equi-active pyridine homologue leads to the inactivation of the compound.

It is an object of the present invention to identify further compounds which are effective against viral diseases and which have improved pharmacological properties.

Summary of the invention

Accordingly, in a first embodiment, the present invention provides a compound having the general formula I.

It is understood that throughout the present specification the term "a compound having the general formula I" encompasses pharmaceutically acceptable salts, solvates, polymorphs, prodrugs, tautomers, racemates, enantiomers, or diastereomers or mixtures thereof unless mentioned otherwise.

A further embodiment of the present invention relates to a pharmaceutical composition comprising a compound having the general formula I and optionally one or more pharmaceutically acceptable excipient(s) and/or carrier(s).

The compounds having the general formula I are useful for treating, ameliorating or preventing viral diseases.

Detailed description of the invention

Before the present invention is described in detail below, it is to be understood that this invention is not limited to the particular methodology, protocols and reagents described herein as these may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to limit the scope of the present invention which will be limited only by the appended claims. Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of ordinary skill in the art.

Preferably, the terms used herein are defined as described in "A multilingual glossary of biotechnological terms: (IUPAC Recommendations)", Leuenberger, H.G.W, Nagel, B. and Kölbl, H. eds. (1995), Helvetica Chimica Acta, CH-4010 Basel, Switzerland).

Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" and "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps. In the following passages different aspects of the invention are defined in more detail. Each aspect so defined may be combined with any other aspect or aspects unless clearly indicated to the contrary. In particular, any feature indicated as being preferred or advantageous may be combined with any other feature or features indicated as being preferred or advantageous.

Several documents are cited throughout the text of this specification. Each of the documents cited herein (including all patents, patent applications, scientific publications, manufacturer's specifications, instructions, etc.), whether supra or infra, are hereby incorporated by reference in their entirety. Nothing herein is to be construed as an admission that the invention is not entitled to antedate such disclosure by virtue of prior invention.

Definitions

The term "alkyl" refers to a saturated straight or branched carbon chain.

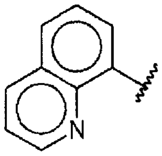
The term "cycloalkyl" represents a cyclic version of "alkyl". The term "cycloalkyl" is also meant to include bicyclic, tricyclic and polycyclic versions thereof. Unless specified otherwise, the cycloalkyl group can have 5 to 12 carbon atoms.

"Hal" represents F, Cl, Br and I.

The term "aryl" preferably refers to an aromatic monocyclic ring containing 6 carbon atoms, an aromatic bicyclic ring system containing 10 carbon atoms or an aromatic tricyclic ring system containing 14 carbon atoms. Examples are phenyl, naphthyl or anthracenyl, preferably phenyl.

The term "5- or 6-membered heterocycle" or "5- or 6-membered heterocyclic" covers any five or six-membered ring wherein at least one of the carbon atoms in the ring has been replaced by 1, 2, 3, or 4 (for the five membered ring) or 1, 2, 3, 4, or 5 (for the six membered ring) of the same or different heteroatoms, whereby the heteroatoms are selected from O, N and S. The term "heterocyclic ring" also covers heteroaryl rings. Examples include pyrrole, pyrrolidine, oxolane, furan, imidazolidine, imidazole, pyrazole, oxazolidine, oxazole, thiazole, piperidine, pyridine, morpholine, piperazine, and dioxolane.

The term "5- to 10-membered mono- or bicyclic heteroring" covers any mono- or bicyclic ring system which contains at least one heteroatom selected from N, O and S. In a preferred embodiment, the 5- to 10-membered mono- or bicyclic heteroring is



The term "heteroaryl" preferably refers to a five or six-membered aromatic ring wherein one or more of the carbon atoms in the ring have been replaced by 1, 2, 3, or 4 (for the five membered ring) or 1, 2, 3, 4, or 5 (for the six membered ring) of the same or different heteroatoms, whereby the heteroatoms are selected from O, N and S. Examples of the heteroaryl group are given above.

The term "heterocyclyl" covers any five or six-membered ring wherein at least one of the carbon atoms in the ring has been replaced by 1, 2, 3, or 4 (for the five membered ring) or 1, 2, 3, 4, or 5 (for the six membered ring) of the same or different heteroatoms, whereby the heteroatoms are selected from O, N and S. The term "heterocyclyl" also covers heteroaryl rings. Examples include pyrrole, pyrrolidine, oxolane, furan, imidazolidine, imidazole, pyrazole, oxazolidine, oxazole, thiazole, piperidine, pyridine, morpholine, piperazine, and dioxolane.

The term "carbocycle" or "carbocyclic" covers any five or six-membered ring which does not include heteroatoms in the ring. The term "carbocyclic ring" also covers aryl rings.

If a compound or moiety is referred to as being "optionally substituted" it can in each instance include 1 or more of the indicated substituents, whereby the substituents can be the same or different.

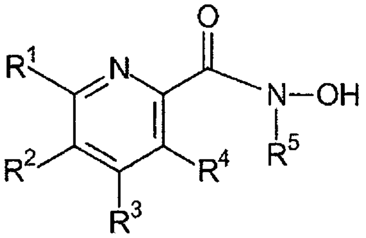
The term "pharmaceutically acceptable salt" refers to a salt of a compound of the present invention. Suitable pharmaceutically acceptable salts include acid addition salts which may, for example, be formed by mixing a solution of compounds of the present invention with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, sulfuric acid, fumaric acid, maleic acid, succinic acid, acetic acid, benzoic acid, citric acid, tartaric acid, carbonic acid or phosphoric acid. Furthermore, where the compound carries an acidic moiety, suitable pharmaceutically acceptable salts thereof may include alkali metal salts (e.g., sodium or potassium salts); alkaline earth metal salts (e.g., calcium or magnesium salts); and salts formed with suitable organic ligands (e.g., ammonium, quaternary ammonium and amine cations formed using counteranions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, alkyl sulfonate and aryl sulfonate). Illustrative examples of pharmaceutically acceptable salts include, but are not limited to, acetate, adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bicarbonate, bisulfate, bitartrate, borate, bromide, butyrate, calcium edetate, camphorate, camphorsulfonate, camsylate, carbonate, chloride, citrate, clavulanate, cyclopentanepropionate, digluconate, dihydrochloride, dodecylsulfate, edetate, edisylate, estolate, esylate, ethanesulfonate, formate, fumarate, gluceptate, glucoheptonate, gluconate, glutamate, glycerophosphate, glycolylarsanilate, hemisulfate, heptanoate, hexanoate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroiodide, 2-hydroxy-ethanesulfonate, hydroxynaphthoate, iodide, isothionate, lactate, lactobionate, laurate, lauryl sulfate, malate, maleate, malonate, mandelate, mesylate, methanesulfonate, methylsulfate, mucate, 2-naphthalenesulfonate, napsylate, nicotinate, nitrate, N-methylglucamine ammonium salt, oleate, oxalate, pamoate (embonate), palmitate, pantothenate, pectinate, persulfate, 3-phenylpropionate, phosphate/diphosphate, picrate, pivalate, polygalacturonate, propionate, salicylate, stearate, sulfate, subacetate, succinate, tannate, tartrate, teoclate, tosylate, triethiodide, undecanoate, valerate, and the like (see, for example, S. M. Berge et al., "Pharmaceutical Salts", J. Pharm. Sci., 66, pp. 1-19 (1977)).

When the compounds of the present invention are provided in crystalline form, the structure can contain solvent molecules. The solvents are typically pharmaceutically acceptable solvents and include, among others, water (hydrates) or organic solvents. Examples of possible solvates include ethanolates and iso-propanolates.

The compounds of the present invention can also be provided in the form of a prodrug, namely a compound which is metabolized *in vivo* to the active metabolite.

Compounds having the general formula I

The present invention provides a compound having the general formula I.



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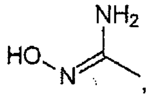
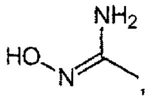
In the appended claims certain provisos are recited. It is understood that any of the compounds which are included in any of the provisos can be excluded, either individually or in combination with other compounds, from one or more of the independent claims having a different category even if it is not currently disclaimed in the independent claim of this category. It is also understood that the disclaimer covers the compounds in the form of their pharmaceutically acceptable salts, solvates, polymorphs, tautomers, racemates, enantiomers, and diastereomers.

The present invention provides a compound having the general formula I in which the following definitions apply.

R^1 is selected from $-H$, $-C_{1-6}$ alkyl, $-(C_{3-7}$ cycloalkyl) and $-CH_2-(C_{3-7}$ cycloalkyl). Preferably R^1 is selected from $-H$, and $-C_{1-6}$ alkyl. Even more preferably R^1 is $-H$.

R^2 is selected from $-H$, , $-C_{1-6}$ alkyl, $-Hal$, $-(C_{3-7}$ cycloalkyl), $-CH_2-(C_{3-7}$ cycloalkyl), $-(CH_2)_m-$(optionally substituted aryl), and $-$(optionally substituted 5- or 6-membered heterocyclic ring which contains at least one heteroatom selected from N, O and S). Preferably R^2 is selected from $-H$, , $-C_{1-6}$ alkyl, $-(CH_2)_m-$(optionally substituted aryl), $-$(optionally substituted 5- or 6-membered heterocyclic ring which contains at least one heteroatom selected from N, O and S). Even more preferably R^2 is selected from $-H$, $-C_{1-6}$ alkyl, $-$phenyl, with R^2 being $-H$ being most preferred. With respect to R^2 the heterocyclic ring is not particularly limited but it is preferably piperidine or pyrrolidine.

The substituent(s) of the optionally substituted aryl and the optionally substituted heterocyclic ring are independently selected from $-C_{1-4}$ alkyl, $-$halogen, $-CN$, $-CHal_3$, $-$aryl,

$-NR^6R^7$, and $-CONR^6R^7$. Preferred examples of the substituent being selected from $-C_{1-4}$ alkyl.

R^3 is selected from –H;
$-C_{1-6}$ alkyl;
$-(CH_2)_n-NR^6R^8$ (with respect to this substituent n is preferably 0 or 1, more preferably 0); and
–(optionally substituted 5- or 6-membered carbo- or heterocyclic ring wherein the heterocyclic ring contains at least one heteroatom selected from N, O and S). The heterocyclic ring can be any carbo- or heterocyclic ring but is preferably phenyl, piperidine, morpholine, or piperazine.

The substituent of the carbo- or heterocyclic ring is selected from –Hal, $-C_{1-4}$ alkyl, $-NR^9R^{10}$, $-(CH_2)_n-OH$, $-C(O)-NR^9R^{10}$, $-SO_2-NR^9R^{10}$, $-NH-C(O)-O-R^{11}$, $-C(O)-O-R^{11}$, and a 5- or 6-membered heterocyclic ring which contains at least one heteroatom selected from N, O and S (with respect to the substituent of the carbo- or heterocyclic ring the heterocyclic ring as a substituent is preferably pyrrolidine, piperidine, or dioxolane).

In a preferred embodiment, **R^3** is selected from –H;
$-C_{1-6}$ alkyl;
$-NR^6-SO_2-(CH_2)_n-$(optionally substituted aryl), wherein the substituent is preferably selected from –Hal, and $-CF_3$;
–(optionally substituted aryl), wherein the substituent is preferably selected from Hal, $-NR^9R^{10}$, and $-C(O)-O-R^{11}$; and
–(optionally substituted 5- or 6-membered heterocyclic ring wherein the heterocyclic ring contains at least one heteroatom selected from N, O and S), wherein the substituent is preferably selected from –Hal, $-NR^9R^{10}$, $-C(O)-O-R^{11}$, and a 5- or 6-membered heterocyclic ring which contains at least one heteroatom selected from N, O and S such as pyrrolidine, piperidine, or dioxolane.

In one embodiment R^1 and R^2 taken together can form a phenyl ring.

In an alternative embodiment R^2 and R^3 taken together can form a phenyl ring.

R^4 is –H.

R^5 is selected from the group consisting of –H or –$(CH_2)_n$–(optionally substituted aryl), preferably **R^5** is selected from the group consisting of –H or –(CH_2)–(optionally substituted phenyl), even more preferably **R^5** is –H. In the definition of R^5 n is 0, 1, 2, or 3, preferably n is 0 or 1, more preferably n is 1. With respect to R^5 the substituent is selected from –Hal and –C_{1-4} alkyl.

In an alternative embodiment, R^4 and R^5 together form a methylene group –CH_2–, ethylene group –CH_2CH_2– or ethyne group –CHCH–, which can be optionally substituted by –C_{1-4} alkyl, –halogen, –$CHal_3$, –R^6R^7, –OR^6, –$CONR^6R^7$, –$SO_2R^6R^7$, aryl or heteroaryl.

R^6 is selected from –H and –C_{1-4} alkyl and is, e.g., –H.

R^7 is selected from –H and –C_{1-4} alkyl.

R^8 is selected from –H, –C_{1-6} alkyl, –$(CH_2)_n$–(optionally substituted aryl), –SO_2–$(CH_2)_n$–(optionally substituted aryl), –SO_2–$(CH_2)_n$–(optionally substituted 5- to 10-membered mono- or bicyclic heteroring which contains at least one heteroatom selected from N, O and S), –$(CH_2)_n$–(optionally substituted 5- or 6-membered heterocyclic ring which contains at least one heteroatom selected from N, O and S) (preferably the heterocyclic ring is piperidine or pyrrolidine), wherein the substituent is selected from –Hal, –CF_3, –C_{1-4} alkyl, and –$(CH_2)_n$–aryl. In a preferred option, R^8 can be –SO_2–$(CH_2)_n$–(optionally substituted aryl), with n being preferably 0 or 1, more preferably being 1.

R^9 is selected from –H, –C_{1-4} alkyl, and –C_{1-4} alkylene–$NR^{11}R^{11}$.

R^{10} is selected from –H, –C_{1-4} alkyl, and –C_{1-4} alkylene–$NR^{11}R^{11}$.

R^{11} is selected from –H, –CF_3, and –C_{1-4} alkyl.

Each **m** is 0 or 1.

Each **n** is independently 0, 1, 2, or 3.

The compounds of the present invention can be administered to a patient in the form of a pharmaceutical composition which can optionally comprise one or more pharmaceutically acceptable excipient(s) and/or carrier(s).

The compounds of the present invention can be administered by various well known routes, including oral, rectal, intragastrical, intracranial and parenteral administration, e.g. intravenous, intramuscular, intranasal, intradermal, subcutaneous, and similar administration routes. Oral, intranasal and parenteral administration are particularly preferred. Depending on the route of administration different pharmaceutical formulations are required and some of those may require that protective coatings are applied to the drug formulation to prevent degradation of a compound of the invention in, for example, the digestive tract.

Thus, preferably, a compound of the invention is formulated as a syrup, an infusion or injection solution, a spray, a tablet, a capsule, a capslet, lozenge, a liposome, a suppository, a plaster, a band-aid, a retard capsule, a powder, or a slow release formulation. Preferably the diluent is water, a buffer, a buffered salt solution or a salt solution and the carrier preferably is selected from the group consisting of cocoa butter and vitebesole.

Particular preferred pharmaceutical forms for the administration of a compound of the invention are forms suitable for injectionable use and include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. In all cases the final solution or dispersion form must be sterile and fluid. Typically, such a solution or dispersion will include a solvent or dispersion medium, containing, for example, water-buffered aqueous solutions, e.g. biocompatible buffers, ethanol, polyol, such as glycerol, propylene glycol, polyethylene glycol, suitable mixtures thereof, surfactants or vegetable oils. A compound of the invention can also be formulated into liposomes, in particular for parenteral administration. Liposomes provide the advantage of increased half life in the circulation, if compared to the free drug and a prolonged more even release of the enclosed drug.

Sterilization of infusion or injection solutions can be accomplished by any number of art recognized techniques including but not limited to addition of preservatives like anti-bacterial or anti-fungal agents, e.g. parabene, chlorobutanol, phenol, sorbic acid or thimersal. Further, isotonic agents, such as sugars or salts, in particular sodium chloride may be incorporated in infusion or injection solutions.

Production of sterile injectable solutions containing one or several of the compounds of the invention is accomplished by incorporating the respective compound in the required amount in the appropriate solvent with various ingredients enumerated above as required followed by sterilization. To obtain a sterile powder the above solutions are vacuum-dried or freeze-dried as necessary. Preferred diluents of the present invention are water, physiological acceptable buffers, physiological acceptable buffer salt solutions or salt solutions. Preferred carriers are cocoa butter and vitebesole. Excipients which can be used with the various pharmaceutical forms of a compound of the invention can be chosen from the following non-limiting list:

a) binders such as lactose, mannitol, crystalline sorbitol, dibasic phosphates, calcium phosphates, sugars, microcrystalline cellulose, carboxymethyl cellulose, hydroxyethyl cellulose, polyvinyl pyrrolidone and the like;
b) lubricants such as magnesium stearate, talc, calcium stearate, zinc stearate, stearic acid, hydrogenated vegetable oil, leucine, glycerids and sodium stearyl fumarates,
c) disintegrants such as starches, croscaramellose, sodium methyl cellulose, agar, bentonite, alginic acid, carboxymethyl cellulose, polyvinyl pyrrolidone and the like.

In one embodiment the formulation is for oral administration and the formulation comprises one or more or all of the following ingredients: pregelatinized starch, talc, povidone K 30, croscarmellose sodium, sodium stearyl fumarate, gelatin, titanium dioxide, sorbitol, monosodium citrate, xanthan gum, titanium dioxide, flavoring, sodium benzoate and saccharin sodium.

If a compound of the invention is administered intranasally in a preferred embodiment, it may be administered in the form of a dry powder inhaler or an aerosol spray from a pressurized container, pump, spray or nebulizer with the use of a suitable propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, a hydrofluoroalkane such as 1,1,1,2-tetrafluoroethane (HFA 134A^{TM}) or 1,1,1,2,3,3,3-heptafluoropropane (HFA 227EA^{TM}), carbon dioxide, or another suitable gas. The pressurized container, pump, spray or nebulizer may contain a solution or suspension of the compound of the invention, e.g., using a mixture of ethanol and the propellant as the solvent, which may additionally contain a lubricant, e.g., sorbitan trioleate.

Other suitable excipients can be found in the Handbook of Pharmaceutical Excipients, published by the American Pharmaceutical Association, which is herein incorporated by reference.

It is to be understood that depending on the severity of the disorder and the particular type which is treatable with one of the compounds of the invention, as well as on the respective patient to be treated, e.g. the general health status of the patient, etc., different doses of the respective compound are required to elicit a therapeutic or prophylactic effect. The determination of the appropriate dose lies within the discretion of the attending physician. It is contemplated that the dosage of a compound of the invention in the therapeutic or prophylactic use of the invention should be in the range of about 0.1 mg to about 1 g of the active ingredient (i.e. compound of the invention) per kg body weight. However, in a preferred use of the present invention a compound of the invention is administered to a subject in need thereof in an amount ranging from 1.0 to 500 mg/kg body weight, preferably ranging from 1 to 200 mg/kg body weight. The duration of therapy with a compound of the invention will vary, depending on the severity of the disease being treated and the condition and idiosyncratic response of each individual patient. In one preferred embodiment of a prophylactic or therapeutic use, between 100 mg to 200 mg of the compound is orally administered to an adult per day, depending on the severity of the disease and/or the degree of exposure to disease carriers.

As is known in the art, the pharmaceutically effective amount of a given composition will also depend on the administration route. In general the required amount will be higher, if the administration is through the gastrointestinal tract, e.g., by suppository, rectal, or by an intragastric probe, and lower if the route of administration is parenteral, e.g., intravenous. Typically, a compound of the invention will be administered in ranges of 50 mg to 1 g/kg body weight, preferably 100 mg to 500 mg/kg body weight, if rectal or intragastric administration is used and in ranges of 10 to 100 mg/kg body weight, if parenteral administration is used.

If a person is known to be at risk of developing a disease treatable with a compound of the invention, prophylactic administration of the biologically active blood serum or the pharmaceutical composition according to the invention may be possible. In these cases the respective compound of the invention is preferably administered in above outlined preferred and particular preferred doses on a daily basis. Preferably, from 0.1 mg to 1 g/kg body weight once a day, preferably 10 to 200 mg/kg body weight. This administration can be continued until the risk of developing the respective viral disorder has lessened. In most instances, however, a compound of the invention will be administered once a disease/disorder has been diagnosed. In these cases it is preferred that a first dose of a compound of the invention is administered one, two, three or four times daily.

The compounds of the present invention are particularly useful for treating, ameliorating, or preventing viral diseases. The type of viral disease is not particularly limited. Examples of possible viral diseases include, but are not limited to, viral diseases which are caused by Poxviridae, Herpesviridae, Adenoviridae, Papillomaviridae, Polyomaviridae, Parvoviridae, Hepadnaviridae, Retroviridae, Reoviridae, Filoviridae, Paramyxoviridae, Rhabdoviridae, Orthomyxoviridae, Bunyaviridae, Arenaviridae, Coronaviridae, Picornaviridae, Hepeviridae, Caliciviridae, Astroviridae, Togaviridae, Flaviviridae, Deltavirus, Bornaviridae, and prions. Preferably viral diseases which are caused by Herpesviridae, Retroviridae, Filoviridae, Paramyxoviridae, Rhabdoviridae, Orthomyxoviridae, Bunyaviridae, Arenaviridae, Coronaviridae, Picornaviridae, Togaviridae, Flaviviridae, more preferably viral diseases which are caused by orthomyxoviridae.

Examples of the various viruses are given in the following table.

Family	**Virus (preferred examples)**
Poxviridae	Smallpox virus Molluscum contagiosum virus
Herpesviridae	Herpes simplex virus Varicella zoster virus Cytomegalovirus Epstein Barr virus Kaposi's sarcoma-associated herpesvirus
Adenoviridae	Human adenovirus A-F
Papillomaviridae	Papillomavirus

Polyomaviridae	BK-virus JC-Virsu
Parvoviridae	B19 virus Adeno associated virus 2/3/5
Hepadnaviridae	Hepatitis B virus
Retroviridae	Human immunodeficiency virus types 1/2 Human T-cell leukemia virus Human foamy virus
Reoviridae	Reovirus 1/2/3 Rotavirus A/B/C Colorado tick fever virus
Filoviridae	Ebola virus Marburg virus
Paramyxoviridae	Parainfluenza virus 1-4 Mumps virus Measles virus Respiratory syncytial virus Hendravirus
Rhabdoviridae	Vesicular stomatitis virus Rabies virus Mokola virus European bat virus Duvenhage virus
Orthomyxoviridae	Influenza virus types A-C
Bunyaviridae	California encephalitis virus La Crosse virus Hantaan virus Puumala virus Sin Nombre virus Seoul virus Crimean- Congo hemorrhagic fever virus Sakhalin virus Rift valley virus Sandfly fever virus Uukuniemi virus
Arenaviridae	Lassa virus Lymphocytic choriomeningitis virus Guanarito virus Junin virus,

	Machupo virus Sabia virus
Coronaviridae	Human coronavirus
Picornaviridae	Human enterovirus types A-D (Poliovirus, Echovirus, Coxsackie virus A/B) Rhinovirus types A/B/C Hepatitis A virus Parechovirus Food and mouth disease virus
Hepeviridae	Hepatitis E virus
Caliciviridae	Norwalk virus Sapporo virus
Astroviridae	Human astrovirus 1
Togaviridae	Ross River virus Chikungunya virus O'nyong-nyong virus Rubella virus
Flaviviridae	Tick-borne encephalitis virus Dengue virus Yellow Fever virus Japanese encephalitis virus Murray Valley virus St. Louis encephalitis virus West Nile virus Hepatitis C virus Hepatitis G virus Hepatitis GB virus
Deltavirus	Hepatitis deltavirus
Bornaviridae	Bornavirus
Prions	

Preferably the compounds of the present invention are employed to treat influenza. Within the present invention, the term "influenza" includes influenza A, B, C, isavirus and thogotovirus and also covers bird flu and swine flu. The subject to be treated is not particularly restricted and can be any vertebrate, such as birds and mammals (including humans).

Without wishing to be bound by theory it is assumed that the compounds of the present invention are capable of inhibiting endonuclease activity, particularly of the influenza virus. More specifically it is assumed that they directly interfere with the N-terminal part of the influenza PA protein, which harbours endonuclease activity. However, delivery of a compound into a cell may represent a problem depending on, e.g., the solubility of the compound or its capabilities to cross the cell membrane. The present invention not only shows that the claimed compounds have *in vitro* polymerase inhibitory activity but also *in vivo* antiviral activity.

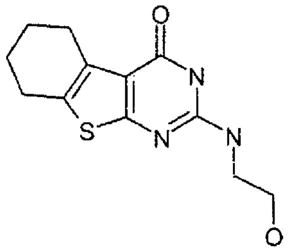
A possible measure of the *in vitro* polymerase inhibitory activity of the compounds having the formula I is the FRET endonuclease activity assay disclosed herein. Preferably the compounds exhibit a % reduction of at least about 50 % at 25 μM in the FRET assay. In this context, the % reduction is the % reduction of the initial reaction velocity (v0) of substrate cleavage of compound-treated samples compared to untreated samples. Preferably the compounds exhibit an IC_{50} of at least about 40 μM, more preferably at least about 20 μM, in the FRET assay. The half maximal inhibitory concentration (IC_{50}) is a measure of the effectiveness of a compound in inhibiting biological or biochemical function and was calculated from the initial reaction velocities (v0) in a given concentration series ranging from maximum 100 μM to at least 2 nM.

A possible measure of the *in vivo* antiviral activity of the compounds having the formula I or II is the CPE assay disclosed herein. Preferably the compounds exhibit a % reduction of at least about 30 % at 50 μM. In this connection, the reduction in the virus-mediated cytopathic effect (CPE) upon treatment with the compounds was calculated as follows: The cell viability of infected-treated and uninfected-treated cells was determined using an ATP-based cell viability assay (Promega). The response in relative luminescent units (RLU) of infected-untreated samples was subtracted from the response (RLU) of the infected-treated samples and then normalized to the viability of the corresponding uninfected sample resulting in % CPE reduction. Preferably the compounds exhibit an IC_{50} of at least about 45 μM, more preferably at least about 10 μM, in the CPE assay. The half maximal inhibitory concentration (IC_{50}) is a measure of the effectiveness of a compound in inhibiting biological or biochemical function and was calculated from the RLU response in a given concentration series ranging from maximum 100 μM to at least 100 nM.

A possible measure of the *in vitro* polymerase inhibitory activity of the compounds having the formula II is the Biacore binding assay disclosed herein. The Biacore system is based on an optical phenomenon known as surface plasmon resonance (SPR). This technique is the basis for measuring adsorption of material onto planar metal surfaces such as gold or silver. SPR is used as a powerful technique to measure biomolecular interactions in real-time in a label free environment. While one of the interactants is immobilized to the sensor surface, the other is free in solution and passed over the surface. Association and dissociation is measured in arbitrary units and displayed in a graph called the sensorgram.

The PB2 cap binding domain (CBD) of an avian H5N1 influenza virus was immobilized on the surface of a CM7 sensor chip (GE Healthcare) by amine coupling according to the manufacturer's protocol. The protein was diluted in a 10 mM phosphate buffer pH 6.5. As running buffer for immobilization a HBS-EP buffer (10mM HEPES, 150mM NaCl, 3mM EDTA, 0,005 % Surfactant p20) was used. Using a protein concentration of 30 µg/ml and a contact time of 12 min an immobilization level of approximately 8000 RU (relative response units) was achieved.

For compound screening a running buffer containing 10 mM TRIS, 3 mM EDTA, 150 mM NaCl, 0.005 % Surfactant p20 (GE Healthcare/Biacore), 1 mM DTT, 0.5 % DMSO was used. 2 mM DMSO stock solutions of each compound were diluted in 1.005X sample buffer without DMSO (1.005X TRIS/EDTA/NaCl/p20/DTT; diluted from a 10X stock) to a final compound concentration of 10 µM and 0.5 % DMSO. m7GTP (Sigma Aldrich) and SAV-7160



were used as references and chip stability controls at a concentration of 4 mM and 10 µM, respectively. Stock solutions of each reference compound were made and aliquots were stored at –20 °C. In this context, the RU is a measure for the binding of the compound to the PB2-CBD and is generally assessed in relation to the binding in RU of SAV-7160.

For buffer bulk effects (matrix) was accounted by reducing the response obtained for the reference flow cell Fc1 from the active flow cell Fc2 resulting in relative response units (RU) reflecting binding of the compounds to the ligand. Organic solvents such as DMSO in the buffer cause high bulk effects which differ in the reference flow cell and the active flow cell due to ligand immobilization. To account for these differences, a calibration curve was established. Eight DMSO concentrations ranging from 0.1 % to 1.5 % in buffer were measured and a linear calibration curve was calculated by plotting Fc2-Fc1 vs. Fc1. The relative response of each sample was then corrected by the solvent factor given by the respective Fc1 signal on the calibration curve and the corresponding Fc2-Fc1 difference. To account for the different size of the compounds, the buffer and solvent corrected response units were normalized to the molecular weight.

Affinity constants (KD values) were determined by measuring the binding affinity of the analyte to the ligand over a concentration range ranging from 200 µM to 1 nM. The KD value is that concentration at which 50% of the binding sites are saturated and was calculated using a linear curve fit model.

In the Biacore assay the binding (RU) of the compounds to the immobilized PB2-CBD is preferably at most 15 RU, more preferably at most 7.5 RU. The affinity constant (KD) is preferably at most 50 µM, more preferably at most 10 µM.

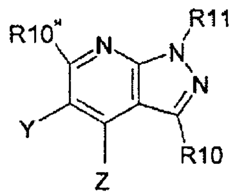
The compounds having the general formula I can be used in combination with one or more other medicaments. The type of the other medicaments is not particularly limited and will depend on the disorder to be treated. Preferably the other medicament will be a further medicament which is useful in treating, ameliorating or preventing a viral disease, more preferably a further medicament which is useful in treating, ameliorating or preventing influenza.

The following combinations of medicaments are envisaged as being particularly suitable:

(i) The combination of endonuclease and cap binding inhibitors (particularly targeting influenza). The endonuclease inhibitors are not particularly limited and can be any endonuclease inhibitor, particularly any viral endonuclease inhibitor. Preferred endonuclease inhibitors are those having the general formula (I).

The cap binding inhibitors are not are not particularly limited either and can be any cap binding inhibitor, particularly any viral cap binding inhibitor. Preferred cap binding inhibitors are those having the general formula (II) and/or the compounds disclosed in WO2011/000566, the complete disclosure of which is incorporated by reference. In particular, all descriptions with respect to the general formula of the compounds according to WO2011/000566, the preferred embodiments of the various substituents as well as the medical utility and advantages of the compounds are incorporated herein by reference.

The compounds of WO2011/000566 have the general formula (XXI):



(XXI)

or a pharmaceutically effective salt, a solvate, a prodrug, a tautomer, a racemate, an enantiomer or a diastereomer thereof;

wherein

one of **Y** and **Z** is $-XR^{12}$ and the other is $R^{10'}$;

$\mathbf{R^{10}}$, $\mathbf{R^{10'}}$ and $\mathbf{R^{10''}}$ are each individually selected from the group consisting of hydrogen, C_1–C_6-alkyl, C_2–C_6-alkenyl, C_2-C_8-alkynyl, $-(CH_2)_nC(O)OH$, $-(CH_2)_nC(O)OR^{16}$, $-(CH_2)_nOH$, $-(CH_2)_nOR^{16}$, $-CF_3$, $-(CH_2)_n$–cycloalkyl, $-(CH_2)_nC(O)NH_2$, $-(CH_2)_nC(O)NHR^{16}$, $-(CH_2)_nC(O)NR^{16}R^{17}$, $-(CH_2)_nS(O)_2NH_2$, $-(CH_2)_nS(O)_2NHR^{16}$, $-(CH_2)_nS(O)_2NR^{16}R^{17}$, $-(CH_2)_nS(O)_2R^{16}$, halogen, $-CN$, $-(CH_2)_n$–aryl, $-(CH_2)_n$–heteroaryl, $-(CH_2)_nNH_2$, $-(CH_2)_nNHR^{16}$, and $-(CH_2)_nNR^{16}R^{17}$; optionally substituted;

$\mathbf{R^{11}}$ is selected from the group consisting of hydrogen, C_1–C_6-alkyl, $-CF_3$, C_2-C_6–alkenyl, C_2–C_8-alkynyl, $-(CH_2)_n$–cycloalkyl, $-(CH_2)_n$–aryl, $-(CH_2)_n$–heterocycloalkyl and $-(CH_2)_n$–heteroaryl; optionally substituted;

X is selected from the group consisting of CH_2, C(O), C(S), CH(OH), CH(OR^{16}), $S(O)_2$, $-S(O)_2-N(H)-$, $-S(O)_2-N(R^{16})-$, $-N(H)-S(O)_2-$, $-N(R^{16})-S(O)_2-$, C(=NH), $C(=N-R^{16})$, $CH(NH_2)$, $CH(NHR^{16})$, $CH(NR^{16}R^{17})$, –C(O)–N(H)–, $-C(O)-N(R^{16})-$, –N(H)–C(O)–, $-N(R^{16})-C(O)-$, N(H), $N(-R^{16})$ and O;

R^{12} is selected from the group consisting of C_1–C_6-alkyl, $-CF_3$, C_2-C_6-alkenyl, C_2-C_8-alkynyl, $-(CH_2)_n$–cycloalkyl, $-(CH_2)_n$–heterocycloalkyl, $-(CH_2)_n$–aryl, $-NR^{16}R^{17}$, and $-(CH_2)_n$–heteroaryl; optionally substituted;

R^{16} and **R^{17}** are independently selected from the group consisting of C_1–C_6-alkyl, C_2–C_6-alkenyl, C_2–C_6-alkynyl, $-(CH_2)_n$–cycloalkyl, $-(CH_2)_n$–aryl, $-CF_3$, $-C(O)R^{18}$ and $-S(O)_2R^{18}$; optionally substituted;

R^{18} is independently selected from the group consisting of C_1–C_6-alkyl, C_2–C_6-alkenyl, C_2–C_6-alkynyl, $-(CH_2)_n$–cycloalkyl and $-CF_3$; optionally substituted; and

n is in each instance selected from 0, 1 and 2.

In the context of WO2011/000566 the term "optionally substituted" in each instance refers to between 1 and 10 substituents, e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 substituents which are in each instance preferably independently selected from the group consisting of halogen, in particular F, Cl, Br or I; $-NO_2$, –CN, –OR', –NR'R", –(CO)OR', –(CO)OR''', –(CO)NR'R", –NR'COR"", –NR'COR', –NR"CONR'R", $-NR''SO_2A$, –COR'''; $-SO_2NR'R''$, –OOCR''', –CR'''R""OH, –R'''OH, =O, and –E;

R' and R" is each independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, –OE, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, and aralkyl or together form a heteroaryl, or heterocycloalkyl; optionally substituted;

R''' and R"" is each independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, alkoxy, aryl, aralkyl, heteroaryl, and –NR'R"; and

E is selected from the group consisting of alkyl, alkenyl, cycloalkyl, alkoxy, alkoxyalkyl, heterocycloalkyl, an alicyclic system, aryl and heteroaryl; optionally substituted.

Widespread resistance to both classes of licensed influenza antivirals (M2 ion channel inhibitors (adamantanes) and neuraminidase inhibitors (Oseltamivir)) occurs in both pandemic and seasonal viruses, rendering these drugs to be of marginal utility in the treatment modality. For M2 ion channel inhibitors, the frequency of viral resistance has been increasing since 2003 and for seasonal influenza A/H3N2, adamantanes are now regarded as ineffective. Virtually all 2009 H1N1 and seasonal H3N2 strains are resistant to the adamantanes (rimantadine and amantadine), and the majority of seasonal H1N1 strains are resistant to oseltamivir, the most widely prescribed neuraminidase inhibitor (NAI). For oseltamivir the WHO reported on significant emergence of influenza A/H1N1 resistance starting in the influenza season 2007/2008; and for the second and third quarters of 2008 in the southern hemisphere. Even more serious numbers were published for the fourth quarter of 2008 (northern hemisphere) where 95% of all tested isolates revealed no Oseltamivir-susceptibility. Considering the fact that now most national governments have been stockpiling Oseltamivir as part of their influenza pandemic preparedness plan, it is obvious that the demand for new, effective drugs is growing significantly. To address the need for more effective therapy, preliminary studies using double or even triple combinations of antiviral drugs with different mechanisms of action have been undertaken. Adamantanes and neuraminidase inhibitors in combination were analysed in vitro and in vivo and found to act highly synergistically. However, it is known that for both types of antivirals resistant viruses emerge rather rapidly and this issue is not tackled by combining these established antiviral drugs.

Influenza virus polymerase inhibitors are novel drugs targeting the transcription activity of the polymerase. Selective inhibitors against the cap-binding and endonuclease active sites of the viral polymerase severely attenuate virus infection by stopping the viral reproductive cycle. These two targets are located within distinct subunits of the polymerase complex and thus represent unique drug targets. Due to the fact that both functions are required for the so-called "cap-snatching" mechanism mandatory for viral transcription, concurrent inhibition of both functions is expected to act highly synergistically. This highly efficient drug combination would result in lower substance concentrations and hence improved dose-response-relationships and better side effect profiles.

Both of these active sites are composed of identical residues in all influenza A strains (e.g., avian and human) and hence this high degree of sequence conservation underpins the perception that these targets are not likely to trigger rapid resistant virus generation. Thus, endonuclease and cap-binding inhibitors individually and in combination are ideal drug candidates to combat both seasonal and pandemic influenza, irrespectively of the virus strain.

The combination of an endonuclease inhibitor and a cap-binding inhibitor or a dual specific polymerase inhibitor targeting both the endonuclease active site and the cap-binding domain would be effective against virus strains resistant against adamantanes and neuraminidase inhibitors and moreover combine the advantage of low susceptibility to resistance generation with activity against a broad range of virus strains.

(ii) The combination of inhibitors of different antiviral targets (particularly targeting influenza) focusing on the combination with (preferably influenza) polymerase inhibitors as dual or multiple combination therapy. Influenza virus polymerase inhibitors are novel drugs targeting the transcription activity of the polymerase. Selective inhibitors against the cap-binding and endonuclease active sites of the viral polymerase severely attenuate virus infection by stopping the viral reproductive cycle. The combination of a polymerase inhibitor specifically addressing a viral intracellular target with an inhibitor of a different antiviral target is expected to act highly synergistically. This is based on the fact that these different types of antiviral drugs exhibit completely different mechanisms of action and pharmacokinetics properties which act advantageously and synergistically on the antiviral efficacy of the combination.

This highly efficient drug combination would result in lower substance concentrations and hence improved dose-response-relationships and better side effect profiles. Moreover, advantages described under (i) for polymerase inhibitors would prevail for combinations of inhibitors of different antiviral targets with polymerase inhibitors.

Typically at least one compound selected from the first group of polymerase inhibitors is combined with at least one compound selected from the second group of polymerase inhibitors.

The first group of polymerase inhibitors which can be used in this type of combination therapy includes, but is not limited to, the compounds having the general formula (I) described below, the compounds having the general formula (II) described above and/or the compounds disclosed in WO2011/000566.

The second group of polymerase inhibitors which can be used in this type of combination therapy includes, but is not limited to, compounds disclosed in WO 2010/110231, WO 2010/110409, WO 2006/030807 and US 5,475,109 as well as flutimide and analogues, favipiravir and analogues, epigallocatechin gallate and analogues, as well as nucleoside analogs such as ribavirine.

(iii) The combination of polymerase inhibitors with neuramidase inhibitors

Influenza virus polymerase inhibitors are novel drugs targeting the transcription activity of the polymerase. Selective inhibitors against the cap-binding and endonuclease active sites of the viral polymerase severely attenuate virus infection by stopping the viral reproductive cycle. The combination of a polymerase inhibitor specifically addressing a viral intracellular target with an inhibitor of a different extracellular antiviral target, especially the (e.g., viral) neuraminidase is expected to act highly synergistically. This is based on the fact that these different types of antiviral drugs exhibit completely different mechanisms of action and pharmacokinetic properties which act advantageously and synergistically on the antiviral efficacy of the combination.

This highly efficient drug combination would result in lower substance concentrations and hence improved dose-response-relationships and better side effect profiles. Moreover, advantages described under (i) for polymerase inhibitors would prevail for combinations of inhibitors of different antiviral targets with polymerase inhibitors.

Typically at least one compound selected from the above mentioned first group of polymerase inhibitors is combined with at least one neuramidase inhibitor.

The neuraminidase inhibitor (particularly influenza neuramidase inhibitor) is not specifically limited. Examples include zanamivir, oseltamivir, peramivir, KDN DANA, FANA, and cyclopentane derivatives.

(iv) The combination of polymerase inhibitors with M2 channel inhibitors

Influenza virus polymerase inhibitors are novel drugs targeting the transcription activity of the polymerase. Selective inhibitors against the cap-binding and endonuclease active sites of the viral polymerase severely attenuate virus infection by stopping the viral reproductive cycle. The combination of a polymerase inhibitor specifically addressing a viral intracellular target with an inhibitor of a different extracellular and cytoplasmic antiviral target, especially the viral M2 ion channel, is expected to act highly synergistically. This is based on the fact that these different types of antiviral drugs exhibit completely different mechanisms of action and pharmacokinetic properties which act advantageously and synergistically on the antiviral efficacy of the combination.

This highly efficient drug combination would result in lower substance concentrations and hence improved dose-response-relationships and better side effect profiles. Moreover, advantages described under (i) for polymerase inhibitors would prevail for combinations of inhibitors of different antiviral targets with polymerase inhibitors.

Typically at least one compound selected from the above mentioned first group of polymerase inhibitors is combined with at least one M2 channel inhibitor.

The M2 channel inhibitor (particularly influenza M2 channel inhibitor) is not specifically limited. Examples include amantadine and rimantadine.

(v) The combination of polymerase inhibitors with alpha glucosidase inhibitors

Influenza virus polymerase inhibitors are novel drugs targeting the transcription activity of the polymerase. Selective inhibitors against the cap-binding and endonuclease active sites of the viral polymerase severely attenuate virus infection by stopping the viral reproductive cycle. The combination of a polymerase inhibitor specifically addressing a viral intracellular target, with an inhibitor of a different extracellular target, especially alpha glucosidase, is expected to act highly synergistically. This is based on the fact that these different types of antiviral drugs exhibit completely different mechanisms of action and pharmacokinetic properties which act advantageously and synergistically on the antiviral efficacy of the combination.

This highly efficient drug combination would result in lower substance concentrations and hence improved dose-response-relationships and better side effect profiles. Moreover, advantages described under (i) for polymerase inhibitors would prevail for combinations of inhibitors of different antiviral targets with polymerase inhibitors.

Typically at least one compound selected from the above mentioned first group of polymerase inhibitors is combined with at least one alpha glucosidase inhibitor.

The alpha glucosidase inhibitor (particularly influenza alpha glucosidase inhibitor) is not specifically limited. Examples include the compounds described in Chang et al., Antiviral Research 2011, 89, 26-34.

(vi) The combination of polymerase inhibitors with ligands of other influenza targets

Influenza virus polymerase inhibitors are novel drugs targeting the transcription activity of the polymerase. Selective inhibitors against the cap-binding and endonuclease active sites of the viral polymerase severely attenuate virus infection by stopping the viral reproductive cycle. The combination of a polymerase inhibitor specifically addressing a viral intracellular target with an inhibitor of different extracellular, cytoplasmic or nucleic antiviral targets is expected to act highly synergistically. This is based on the fact that these different types of antiviral drugs exhibit completely different mechanisms of action and pharmacokinetic properties which act advantageously and synergistically on the antiviral efficacy of the combination.

This highly efficient drug combination would result in lower substance concentrations and hence improved dose-response-relationships and better side effect profiles. Moreover, advantages described under (i) for polymerase inhibitors would prevail for combinations of inhibitors of different antiviral targets with polymerase inhibitors.

Typically at least one compound selected from the above mentioned first group of polymerase inhibitors is combined with at least one ligand of another influenza target.

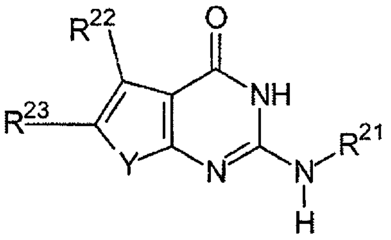
The ligand of another influenza target is not specifically limited. Examples include compounds acting on the sialidase fusion protein, e.g. Fludase (DAS181), siRNAs and phosphorothioate oligonucleotides, signal transduction inhibitors (ErbB tyrosine kinase, Abl kinase family, MAP kinases, PKCa-mediated activation of ERK signaling as well as interferon (inducers).

(vii) The combination of (preferably influenza) polymerase inhibitors with a compound used as an adjuvance to minimize the symptoms of the disease (antibiotics, anti-inflammatory agents like COX inhibitors (e.g., COX-1/COX-2 inhibitors, selective COX-2 inhibitors), lipoxygenase inhibitors, EP ligands (particularly EP4 ligands), bradykinin ligands, and/or cannabinoid ligands (e.g., CB2 agonists). Influenza virus polymerase inhibitors are novel drugs targeting the transcription activity of the polymerase. Selective inhibitors against the cap-binding and endonuclease active sites of the viral polymerase severely attenuate virus infection by stopping the viral reproductive cycle. The combination of a polymerase inhibitor specifically addressing a viral intracellular target with an compound used as an adjuvance to minimize the symptoms of the disease address the causative and symptomatic pathological consequences of viral infection. This combination is expected to act synergistically because these different types of drugs exhibit completely different mechanisms of action and pharmacokinetic properties which act advantageously and synergistically on the antiviral efficacy of the combination.

This highly efficient drug combination would result in lower substance concentrations and hence improved dose-response-relationships and better side effect profiles. Moreover, advantages described under (i) for polymerase inhibitors would prevail for combinations of inhibitors of different antiviral targets with polymerase inhibitors.

Compounds having the general formula II

The compounds having the general formula II are identified in the following.



(II)

It is understood that throughout the present specification the term "a compound having the general formula II" encompasses pharmaceutically acceptable salts, solvates, polymorphs, prodrugs, tautomers, racemates, enantiomers, or diastereomers or mixtures thereof unless mentioned otherwise.

In the present invention the following definitions apply with respect to the compounds having the general formula II.

Y is S.

R^{21} is selected from –H, $–C_{1-6}$alkyl, $–(CH_2)_q$–aryl, $–(CH_2)_q$–heterocyclyl, $–(CH_2)_q$–cycloalkyl, $–(CH_2)_p–OR^{25}$, and $–(CH_2)_p–NR^{25}R^{26}$. Preferably R^{21} is –H, $–C_{1-6}$ alkyl, or $–(CH_2)_p–OR^{25}$, in a more preferred aspect of this embodiment R^{25} is H.

R^{22} is selected from –H, $–C_{1-6}$ alkyl, $–(CH_2)_q$–cycloalkyl, –Hal, $–CF_3$ and –CN. Preferably R^{22} is –H, $–C_{1-6}$ alkyl or Hal (preferably Hal = Cl).

R^{23} is selected from –aryl, –heterocyclyl, –cycloalkyl, $–C(–R^{28})(–R^{29})$–aryl, $–C(–R^{28})(–R^{29})$–heterocyclyl, and $–C(–R^{28})(–R^{29})$–cycloalkyl. In a preferred embodiment, R^{23}

is $-(CH_2)_q-$aryl, or $-(CH_2)_q-$heteroaryl, wherein the aryl group and/or heteroaryl group can be optionally substituted with one or more substituents R^{27}. More preferably R^{23} is –phenyl, –benzyl or –pyridyl, wherein the one or more substituents R^{27} are independently selected from –Hal, $-CF_3$, –CN, $-C_{1-6}$ alkyl, $-C(O)-C_{1-6}$ alkyl, or $-(CH_2)_qNR^{25}R^{26}$, wherein R^{25} and R^{26} are independently selected from H and $-C_{1-6}$ alkyl.

R^{25} is selected from –H, $-C_{1-6}$ alkyl, and $-(CH_2CH_2O)_rH$. Preferably R^{25} is selected from –H and $-C_{1-6}$ alkyl.

R^{26} is selected from –H, and $-C_{1-6}$ alkyl.

R^{27} is independently selected from $-C_{1-6}$ alkyl, $-C(O)-C_{1-6}$ alkyl, –Hal, $-CF_3$, –CN, $-COOR^{25}$, $-OR^{25}$, $-(CH_2)_qNR^{25}R^{26}$, $-C(O)-NR^{25}R^{26}$, and $-NR^{25}-C(O)-C_{1-6}$ alkyl. Preferably R^{27} is independently selected from –Hal, $-CF_3$, –CN, $-C_{1-6}$ alkyl, $-C(O)-C_{1-6}$ alkyl, or $-(CH_2)_qNR^{25}R^{26}$, wherein R^{25} and R^{26} are independently selected from H and $-C_{1-6}$ alkyl.

R^{28} and **R^{29}** are independently selected from –H, $-C_{1-6}$ alkyl, $-(CH_2)_q-$aryl, $-(CH_2)_q-$heterocyclyl, $-(CH_2)_q-$cycloalkyl, –OH, $-O-C_{1-6}$ alkyl, $-O-(CH_2)_q-$aryl, $-O-(CH_2)_q-$heterocyclyl, and $-O-(CH_2)_q-$cycloalkyl. Preferably R^{28} and R^{29} are independently selected from –H and $-C_{1-6}$ alkyl.

In an alternative embodiment **R^{28}** and **R^{29}** are together =O, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, or $-CH_2CH_2CH_2CH_2-$.

p is 1 to 4.

q is 0 to 4, preferably q is 0 or 1.

r is 1 to 3.

In the above definitions, the aryl group, heterocyclyl group and/or cycloalkyl group can be optionally substituted with one or more substituents R^{27}, which can be the same or different.

Without wishing to be bound by theory it is assumed that the compounds having the general formula II are capable of inhibiting binding of host mRNA cap structures to the cap-binding domain (CBD), particularly of the influenza virus. More specifically it is assumed that they directly interfere with the CBD of the influenza PB2 protein. However, delivery of a compound into a cell may represent a problem depending on, e.g., the solubility of the compound or its capabilities to cross the cell membrane. The present invention not only shows that the claimed compounds have *in vitro* polymerase inhibitory activity but also *in vivo* antiviral activity.

Various modifications and variations of the invention will be apparent to those skilled in the art without departing from the scope of the invention. Although the invention has been described in connection with specific preferred embodiments, it should be understood that the invention as claimed should not be unduly limited to such specific embodiments. Indeed, various modifications of the described modes for carrying out the invention which are obvious to those skilled in the relevant fields are intended to be covered by the present invention.

The following examples are merely illustrative of the present invention and should not be construed to limit the scope of the invention as indicated by the appended claims in any way.

EXAMPLES

FRET endonuclease activity assay

The influenza A virus (IAV) PA-Nter fragment (amino acids 1 – 209) harbouring the influenza endonuclease activity was generated and purified as described in Dias et al., Nature 2009; Apr 16;458(7240), 914-918. The protein was dissolved in buffer containing 20mM Tris pH 8.0, 100mM NaCl and 10mM β-mercaptoethanol and aliquots were stored at –20 °C.

A 20 bases dual-labelled RNA oligo with 5′-FAM fluorophore and 3′-BHQ1 quencher was used as a substrate to be cleaved by the endonuclease activity of the PA-Nter. Cleavage of the RNA substrate frees the fluorophore from the quencher resulting in an increase of the fluorescent signal.

All assay components were diluted in assay buffer containing 20mM Tris-HCl pH 8.0, 100mM NaCl, 1mM $MnCl_2$, 10mM $MgCl_2$ and 10mM β-mercaptoethanol. The final concentration of PA-Nter was 0.5µM and 1.6µM RNA substrate. The test compounds were dissolved in DMSO and generally tested at two concentrations or a concentration series resulting in a final plate well DMSO concentration of 0.5 %. In those cases where the compounds were not soluble at that concentration, they were tested at the highest soluble concentration. SAV-6004 was used as a reference in the assay at a concentration of 0.1µM.

5µl of each compound dilution was provided in the wells of white 384-well microtiter plates (PerkinElmer) in eight replicates. After addition of PA-Nter dilution, the plates were sealed and incubated for 30min at room temperature prior to the addition of 1.6µM RNA substrate diluted in assay buffer. Subsequently, the increasing fluorescence signal of cleaved RNA was measured in a microplate reader (Synergy HT, Biotek) at 485nm excitation and 535nm emission wavelength. The kinetic read interval was 35sec at a sensitivity of 35. Fluorescence signal data over a period of 20min were used to calculate the initial velocity (v0) of substrate cleavage. Final readout was the % reduction of v0 of compound-treated samples compared to untreated. The half maximal inhibitory concentration (IC_{50}) is a measure of the effectiveness of a compound in inhibiting biological or biochemical function and was calculated from the initial reaction velocities (v0) ina given concentration series ranging from maximum 100 µM to at least 2 nM.

Cytopathic effect (CPE) assay

The influenza A virus (IAV) was obtained from American Tissue Culture Collection (A/Aichi/2/68 (H3N2); VR-547). Virus stocks were prepared by propagation of virus on Mardin-Darby canine kidney (MDCK; ATCC CCL-34) cells and infectious titres of virus stocks were determined by the 50 % tissue culture infective dose ($TCID_{50}$) analysis as described in Reed, L. J., and H. Muench. 1938, Am. J. Hyg. 27:493-497.

MDCK cells were seeded in 96-well plates at 2×10^4 cells/well using DMEM/Ham's F-12 (1:1) medium containing 10 % foetal bovine serum (FBS), 2 mM L-glutamine and 1 %

antibiotics (all from PAA). Until infection the cells were incubated for 5 hrs at 37 °C, 5.0 % CO_2 to form a ~80 % confluent monolayer on the bottom of the well. Each test compound was dissolved in DMSO and generally tested at 25 µM and 250 µM. In those cases where the compounds were not soluble at that concentration they were tested at the highest soluble concentration. The compounds were diluted in infection medium (DMEM/Ham's F-12 (1:1) containing 5 µg/ml trypsin, and 1 % antibiotics) for a final plate well DMSO concentration of 1 %. The virus stock was diluted in infection medium (DMEM/Ham's F-12 (1:1) containing 5 µg/ml Trypsin, 1 % DMSO, and 1 % antibiotics) to a theoretical multiplicity of infection (MOI) of 0.05.

After removal of the culture medium and one washing step with PBS, virus and compound were added together to the cells. In the wells used for cytotoxicity determination (i.e. in the absence of viral infection), no virus suspension was added. Instead, infection medium was added. Each treatment was conducted in two replicates. After incubation at 37 °C, 5 % CO_2 for 48 hrs, each well was observed microscopically for apparent cytotoxicity, precipitate formation, or other notable abnormalities. Then, cell viability was determined using CellTiter-Glo luminescent cell viability assay (Promega). The supernatant was removed carefully and 65 µl of the reconstituted reagent were added to each well and incubated with gentle shaking for 15 min at room temperature. Then, 60 µl of the solution was transferred to an opaque plate and luminescence (RLU) was measured using Synergy HT plate reader (Biotek).

Relative cell viability values of uninfected-treated versus uninfected-untreated cells were used to evaluate cytotoxicity of the compounds. Substances with a relative viability below 80 % at the tested concentration were regarded as cytotoxic and retested at lower concentrations.

Reduction in the virus-mediated cytopathic effect (CPE) upon treatment with the compounds was calculated as follows: The response (RLU) of infected-untreated samples was subtracted from the response (RLU) of the infected-treated samples and then normalized to the viability of the corresponding uninfected sample resulting in % CPE reduction. The half maximal inhibitory concentration (IC_{50}) is a measure of the effectiveness of a compound in inhibiting biological or biochemical function and was calculated from the RLU response in a given concentration series ranging from maximum 100 µM to at least 100 nM.

Biacore assay

The PB2 cap binding domain (CBD) of an avian H5N1 influenza virus was immobilized on the surface of a CM7 sensor chip (GE Healthcare) by amine coupling according to the manufacturer's protocol. The protein was diluted in a 10 mM phosphate buffer pH 6.5. As running buffer for immobilization a HBS-EP buffer (10mM HEPES, 150mM NaCl, 3mM EDTA, 0,005 % Surfactant p20) was used. Using a protein concentration of 30 µg/ml and a contact time of 12 min an immobilization level of approximately 8000 RU (relative response units) was achieved.

For compound screening a running buffer containing 10 mM TRIS, 3 mM EDTA, 150 mM NaCl, 0.005 % Surfactant p20 (GE Healthcare/Biacore), 1 mM DTT, 0.5 % DMSO was used. 2 mM DMSO stock solutions of each compound were diluted in 1.005X sample buffer without DMSO (1.005X TRIS/EDTA/NaCl/p20/DTT; diluted from a 10X stock) to a final compound concentration of 10 µM and 0.5 % DMSO. m7GTP (Sigma Aldrich) and SAV-7160 were used as references and chip stability controls at a concentration of 4 mM and 10 µM, respectively. Stock solutions of each reference compound were made and aliquots were stored at –20 °C.

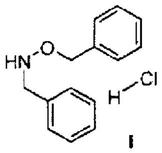
For buffer bulk effects (matrix) was accounted by reducing the response obtained for the reference flow cell Fc1 from the active flow cell Fc2 resulting in relative response units (RU) reflecting binding of the compounds to the ligand. Organic solvents such as DMSO in the buffer cause high bulk effects which differ in the reference flow cell and the active flow cell due to ligand immobilization. To account for these differences, a calibration curve was established. Eight DMSO concentrations ranging from 0.1 % to 1.5 % in buffer were measured and a linear calibration curve was calculated by plotting Fc2-Fc1 vs. Fc1. The relative response of each sample was then corrected by the solvent factor given by the respective Fc1 signal on the calibration curve and the corresponding Fc2-Fc1 difference. To account for the different size of the compounds, the buffer and solvent corrected response units were normalized to the molecular weight.

Affinity constants (KD values) were determined by measuring the binding affinity of the analyte to the ligand over a concentration range ranging from 200 µM to 1 nM. The KD value is that concentration at which 50% of the binding sites are saturated and was calculated using a linear curve fit model.

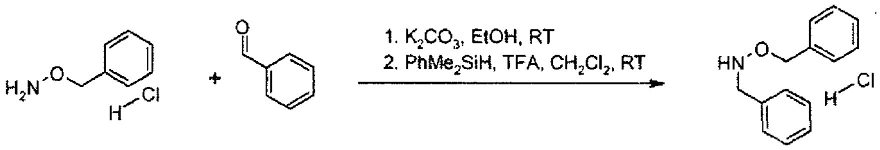
Compounds having the general formula (I)

Key Intermediate I

O, N-Dibenzyl hydroxylamine hydrochloride



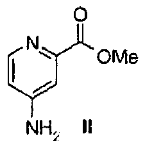
I

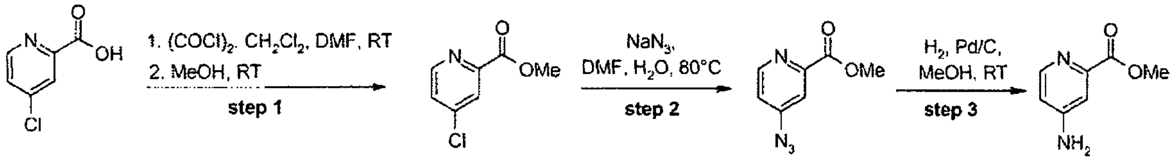


To a suspension of O-benzyl hydroxylamine hydrochloride (1.2 g, 10 mmol, 1 eq) in absolute ethanol (16 mL) was added potassium carbonate (1.5 g, 11 mmol, 1.1 eq) and benzaldehyde (1.0 mL, 10 mmol, 1 eq). The mixture was stirred at room temperature for 5 h and then was poured into water (50 mL). The mixture was extracted with ethyl acetate (3 x 50 mL). The organic layers were dried over magnesium sulfate, filtered and evaporated in vacuo. The residue was dissolved in dichloromethane (21 mL) and cooled down to 0 °C. To this solution were added drop wise under argon dimethylphenylsilane (2.3 mL, 14.3 mmol, 1.4 eq) and trifluoroacetic acid (2.6 mL, 35.6 mmol, 3.5 eq). The reaction mixture was stirred at room temperature for 16 h. The solvents were removed in vacuo and a 2N solution of hydrochloric acid (5 mL) was added into the residue diluted in dichloromethane (5 mL). The precipitate was filtered, washed with diethyl ether and dried in vacuo to afford the expected compound as a white powder (966 mg, 48 % yield).

Key Intermediate II

4-Amino-pyridine-2-carboxylic acid methyl ester


II



Step 1:

Oxalyl chloride (6.7 mL, 76.8 mmol, 1.2 eq) was added to a solution of 4-chloro-pyridine-2-carboxylic acid (10.0 g, 63.4 mmol, 1 eq) in dichloromethane (270 mL). The solution was cooled down to 0 °C and dimethylformamide (1.1 mL) was added drop wise. The mixture was stirred at room temperature for 1.5 h and was evaporated to dryness. The orange residue was diluted in methanol (110 mL) and the mixture was stirred at room temperature for 30 min and evaporated to dryness. A 5% solution of sodium bicarbonate (50 mL) was poured on the residue and the aqueous phase was extracted with ethyl acetate (2 x 40 mL). The organic layers were washed with brine (3 x 20 mL), dried over magnesium sulfate, filtered and evaporated to afford 4-chloro-pyridine-2-carboxylic acid methyl ester as a beige powder (10.0 g, 92 % yield).

Step 2:

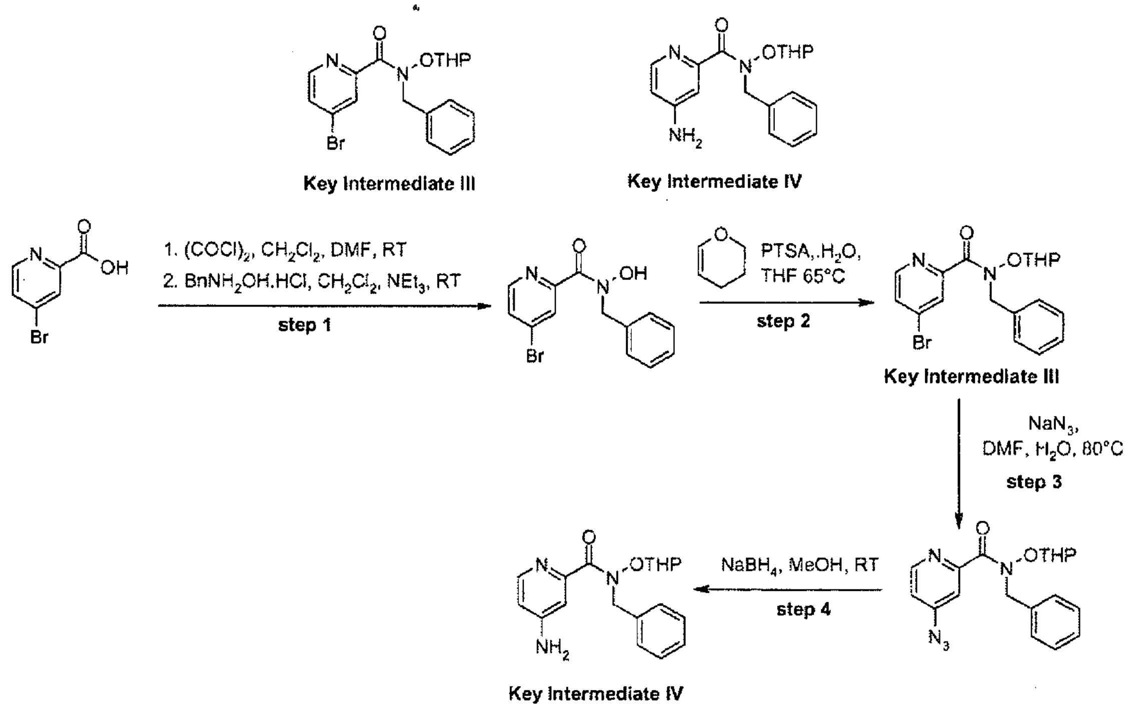
4-Chloro-pyridine-2-carboxylic acid methyl ester (13.7 g, 79.9 mmol, 1 eq) was solubilized in a mixture of dimethylformamide (120 mL) and water (6 mL). Sodium azide was added (6.2 g, 95.9 mmol, 1.2 eq) and the mixture was heated at 80 °C during 24 h. After cooling down, the mixture was diluted with ethyl acetate (40 mL) and washed with water (30 mL) and brine (30 mL). The organic layers were dried over magnesium sulfate, filtered and evaporated in vacuo. At this stage, the reaction was not complete (15% of starting material detected) and the same procedure was run again with new reagents at 80 °C during 24h. After the same treatment, evaporation of the organic layers afforded 4-azido-pyridine-2-carboxylic acid methyl ester as an orange oil which crystallizes (10.2 g, 72 % yield).

Step 3:

4-Azido-pyridine-2-carboxylic acid methyl ester (3.9 g, 22 mmol, 1 eq) was solubilized in methanol (50 mL) and palladium 10% w on carbon (400 mg) was added. The mixture was stirred at room temperature over 4 bars pressure of hydrogen until completion of the reaction. The mixture was then filtered over a short pad of celite, and rinsed with methanol to afford the expected compound as a yellow powder (3.0 g, 90 % yield).

Key Intermediates III and IV

4-Bromo-pyridine-2-carboxylic acid benzyl-(tetrahydro-pyran-2-yloxy)-amide and **4-Amino-pyridine-2-carboxylic acid benzyl-(tetrahydro-pyran-2-yloxy)-amide**



Step 1:

Oxalyl chloride (5.1 mL, 58.6 mmol, 1.3 eq) was added to a solution of 4-bromo-pyridine-2-carboxylic acid (9.1 g, 45.0 mmol, 1 eq) in dichloromethane (250 mL). The solution was cooled down to 0 °C and dimethylformamide (0.6 mL) was added drop wise. The mixture was stirred at room temperature for 1.5 h and was evaporated to dryness. The residue was diluted in dichloromethane (250 mL) and N-benzylhydroxylamine hydrochloride (10.8 g, 67.5 mmol, 1.5 eq) was added. Triethylamine (18.8 mL, 135 mmol, 3 eq) was added drop wise at 0 °C and the mixture was stirred at room temperature for 18 h. The solution was then poured on a saturated solution of sodium bicarbonate (50 mL) and extracted with dichloromethane (3 x 50 mL). The organic layers were dried over magnesium sulfate, filtered and evaporated. The crude residue was purified by flash chromatography using cyclohexane and ethyl acetate (100/0 to 70/30) to afford 4-bromo-pyridine-2-carboxylic acid benzyl-hydroxy-amide as an orange oil (8.0 g, 58 % yield).

Step 2:

Dihydropyrane (9.4 mL, 104 mmol, 4 eq) and paratoluene sulfonic acid (99 mg, 0.52 mmol, 0.02 eq) were added to a solution of 4-bromo-pyridine-2-carboxylic acid benzyl-hydroxy-amide (8.0 g, 26 mmol, 1 eq) in tetrahydrofurane (200 mL). The mixture was heated at 65 °C for 48 h. After cooling, the mixture was poured on a saturated solution of sodium bicarbonate (60 mL) and extracted with etyl acetate (3 x 40 mL). The organic layers were dried over magnesium sulfate, filtered and evaporated. The crude residue was purified by flash chromatography using cyclohexane and ethyl acetate (100/0 to 80/20) to afford **Key Intermediate II** as a pale yellow oil which crystallised (7.8 g, 76 % yield).

Step 3:

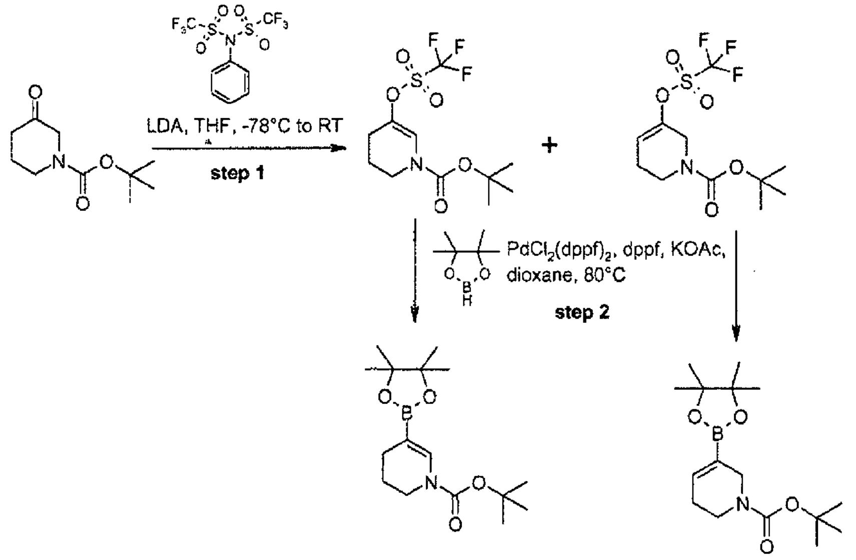
4-Bromo-pyridine-2-carboxylic acid benzyl-(tetrahydro-pyran-2-yloxy)-amide (5.0 g, 12.8 mmol, 1 eq) was solubilized in a mixture of dimethylformamide (41 mL) and water (3 mL). Sodium azide was added (997 mg, 15.3 mmol, 1.2 eq) and the mixture was heated at 80 °C during 24h. After cooling down, the mixture was diluted with ethyl acetate (40 mL) and washed with water (30 mL) and brine (30 mL). The organic layers were dried over magnesium sulfate, filtered and evaporated in vacuo. At this stage, the reaction was not complete and the same procedure was run again with new reagents at 80 °C during 24h. After the same treatment, the crude residue was purified by flash chromatography using cyclohexane and ethyl acetate (100/0 to 60/40) to afford 4-azido-pyridine-2-carboxylic acid benzyl-(tetrahydro-pyran-2-yloxy)-amide (2.8 g, 61 % yield).

Step 4:

To a solution of 4-azido-pyridine-2-carboxylic acid benzyl-(tetrahydro-pyran-2-yloxy)-amide (2.5 g, 7.1 mmol, 1 eq) in methanol (55 mL) was added sodium borohydride (296 mg, 37.8 mmol, 1.1 eq) and the mixture was stirred at room temperature during 1h. Water (20 mL) was then added and the mixture was evaporated to dryness. The residue was diluted with ethyl acetate (20 mL) and the organic layer was washed with water, dried over magnesium sulfate, filtered and evaporated in vacuo. The crude residue was purified by flash chromatography using ethyl acetate and methanol (100/0 to 90/10) to afford **Key Intermediate IV** as a colorless oil (883 mg, 38 % yield).

Key Intermediates V and VI

5-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-3,4-dihydro-2H-pyridine-1-carboxylic acid tert-butyl ester and 5-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-3,6-dihydro-2H-pyridine-1-carboxylic acid tert-butyl ester



Key Intermediate V

Key Intermediate VI

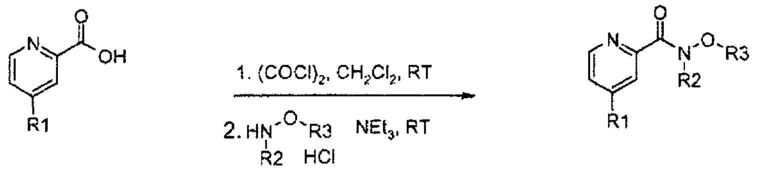
<u>Step 1:</u>

At -78 °C, to a solution of lithium diisopropylamide 1.5 M in cyclohexane (8 mL, 12 mmol, 1.2 eq) in tetrahydrofurane (8 mL) was added drop wise a solution of 3-oxo-piperidine-1-carboxylic acid tert-butyl ester (2.0 g, 10 mmol, 1 eq) in tetrahydrofurane (8 mL). The mixture was stirred at -78 °C for 1 h and a solution of N-phenyl bis trifluoromethanesulfonamide (3.9 g, 11 mmol, 1.1 eq) in tetrahydrofurane (8 mL) was added. The mixture was stirred at -78 °C for 2 h and then was allowed to warm up to room temperature and stirred 18 additional hours at room temperature. The mixture was evaporated to dryness and the residue was taken with diethyl ether (20 mL). The organic layer was washed with water (10 mL), a 2 M solution of sodium hydroxide (3 x 10 mL), water (10 mL) and brine (10 mL). The organic layers were dried over magnesium sulfate, filtered and evaporated in vacuo. The crude residue was purified by flash chromatography using cyclohexane and dichloromethane (100/0 to 0/100) to afford separately 5-trifluoromethanesulfonyloxy-3,4-dihydro-2H-pyridine-1-carboxylic acid tert-butyl ester (980 mg, 29 % yield) and 5-trifluoromethanesulfonyloxy-3,6-dihydro-2H-pyridine-1-carboxylic acid tert-butyl ester (340 mg, 10 % yield).

<u>Step 2:</u>

To a degassed solution of 5-trifluoromethanesulfonyloxy-dihydro-2H-pyridine-1-carboxylic acid tert-butyl ester (340 mg, 1.0 mmol, 1 eq) in dioxane (10 mL) was added bis-(pinacolato)-diboron (287 mg, 1.1 mmol, 1.1 eq), potassium acetate (302 mg, 3.0 mmol, 3 eq), 1,1'-bis(diphenylphosphino)ferrocene (17 mg, 0.03 mmol, 0.03 eq) and dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium) (23 mg, 0.03 mmol, 0.03 eq) were added. The mixture was stirred at 80 °C for 18 h. After cooling down, the mixture was filtered and the filtrate was concentrated and purified by flash chromatography using cyclohexane and ethyl acetate (100/0 to 96/4) to afford the corresponding boronic ester (225 mg, 70 % yield).

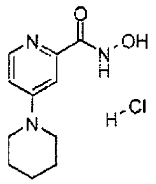
General Procedure A



At 0 °C, to a solution of pyridinyl-2-carboxylic acid hydrochloride (1.0 mmol, 1 eq) in dichloromethane (8 mL) was added one drop of dimethylformamide and oxalyl chloride (1.3 mmol, 1.3 eq). The mixture was stirred at room temperature for 30 min and was evaporated to dryness. The residue was then solubilized in dichloromethane (8 mL) and cooled to 0 °C. Triethylamine (3.1 mmol, 3 eq) and hydroxylamine hydrochloride (2.1 mmol, 2 eq) were added drop wise and the mixture was stirred at room temperature for 20 h. The solvents were then evaporated and the crude residue was purified by flash chromatography using dichloromethane and methanol (100/0 to 80/20) to afford the expected compound.

Example 1:

3,4,5,6-Tetrahydro-2H-[1,4']bipyridinyl-2'-carboxylic acid hydroxyamide chlorhydrate



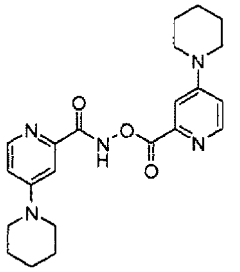
The expected compound was obtained according to **general procedure A** using 3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-2'-carboxylic acid hydrochloride and hydroxylamine hydrochloride. The expected compound was isolated as a white powder (6 % yield).

MS: 222.1

Mp: 200 °C – 202 °C

Example 2:

3,4,5,6-Tetrahydro-2H-[1,4']bipyridinyl-2'-carboxylic acid (3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-2'-carbonyloxy)-amide



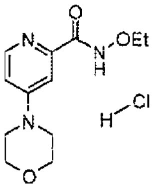
This compound was isolated as a by-product of **example 1** and obtained as a white powder (4 % yield).

MS: 410.2

Mp: 210 °C – 215 °C

Example 3:

4-Morpholin-4-yl-pyridine-2-carboxylic acid ethoxy-amide chlorhydrate



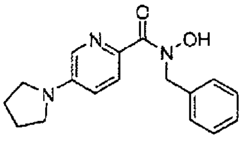
This compound was obtained according to **general procedure A** using 4-morpholin-4-yl-pyridine-2-carboxylic acid hydrochloride and O-ethyl hydroxylamine hydrochloride. The expected compound was isolated as a white powder (42 % yield).

MS: 252.1

Mp: 200 °C – 202 °C

Example 4:

5-Pyrrolidin-1-yl-pyridine-2-carboxylic acid benzyl-hydroxy-amide



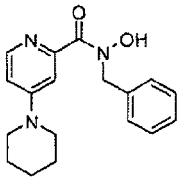
This compound was obtained according to **general procedure A** using 5-pyrrolidin-1-yl-pyridine-2-carboxylic acid and N-benzyl hydroxylamine hydrochloride. The expected compound was isolated as a white powder (32 % yield).

MS: 298.1

Mp: 115 °C – 120 °C

Example 5:

3,4,5,6-Tetrahydro-2H-[1,4']bipyridinyl-2'-carboxylic acid benzyl-hydroxy-amide

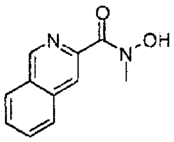


This compound was obtained according to **general procedure A** using 3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-2'-carboxylic acid hydrochloride and N-benzyl hydroxylamine hydrochloride. The expected compound was isolated as a yellow oil (15 % yield).

MS: 312.2

Example 6:

Isoquinoline-3-carboxylic acid hydroxy-methyl-amide



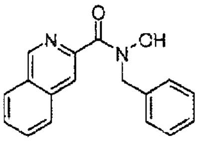
This compound was obtained according to **general procedure A** using isoquinoline-3-carboxylic acid and N-methyl hydroxylamine hydrochloride. The expected compound was isolated as a white powder (43 % yield).

MS: 203.0

Mp: 110 °C – 115 °C

Example 7:

Isoquinoline-3-carboxylic acid benzyl-hydroxy-amide

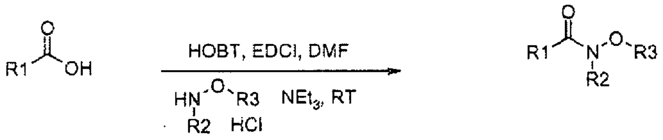


This compound was obtained according to **general procedure A** using isoquinoline-3-carboxylic acid and N-benzyl hydroxylamine hydrochloride. The expected compound was isolated as a white powder (19 % yield).

MS: 279.1

Mp: 120 °C – 125 °C

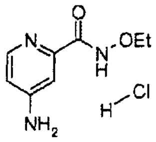
General Procedure B



To a solution of carboxylic acid (3.6 mmol, 1 eq) in dimethylformamide (30 mL) were added HOBT (7.2 mmol, 2 eq), EDCI (7.2 mmol, 2 eq) and then hydroxylamine hydrochloride (7.2 mmol, 2 eq) and triethylamine (10.8 mmol, 3 eq). The mixture was stirred at room temperature for 20 h. Then the mixture was poured on brine solution (20 mL) and extracted with ethyl acetate (3 x 20 mL). The organic layers were dried over magnesium sulfate, filtered and evaporated in vacuo. The crude residue was purified by flash chromatography using dichloromethane and methanol (100/0 to 85/15) to afford the expected compound.

Example 8:

4-Amino-pyridine-2-carboxylic acid ethoxy-amide chlorhydrate



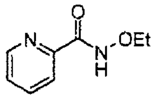
This compound was obtained according to **general procedure B** using 4-amino-pyridine-2-carboxylic acid and O-ethyl hydroxylamine hydrochloride. The expected compound was isolated as a colorless oil (3 % yield).

MS: 182.0

Mp: 114 °C – 120 °C

Example 9:

Pyridine-2-carboxylic acid ethoxy-amide

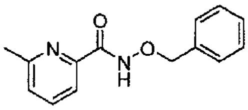


This compound was obtained according to **general procedure B** using pyridine-2-carboxylic acid and O-ethyl hydroxylamine hydrochloride. The expected compound was isolated as a colorless oil (63 % yield).

MS: 167.1

Example 10:

6-Methyl-pyridine-2-carboxylic acid benzyloxy-amide



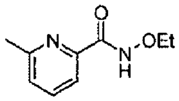
This compound was obtained according to **general procedure B** using 6-methyl-pyridine-2-carboxylic acid and O-benzyl hydroxylamine hydrochloride. The expected compound was isolated as a white powder (71 % yield).

MS: 243.1

Mp: 75 °C – 80 °C

Example 11:

6-Methyl-pyridine-2-carboxylic acid ethoxy-amide

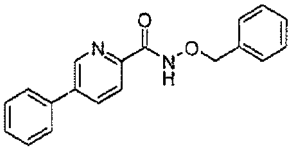


This compound was obtained according **general procedure B** using 6-methyl-pyridine-2-carboxylic acid and O-ethyl hydroxylamine hydrochloride. The expected compound was isolated as a colorless oil (83 % yield).

MS: 181.0

Example 12:

5-Phenyl-pyridine-2-carboxylic acid benzyloxy-amide



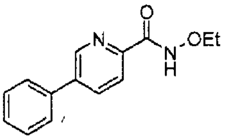
This compound was obtained according to **general procedure B** using 5-phenyl-pyridine-2-carboxylic acid and O-benzyl hydroxylamine hydrochloride. The expected compound was isolated as a white powder (79 % yield).

MS: 305.1

Mp: 155 °C – 160 °C

Example 13:

5-Phenyl-pyridine-2-carboxylic acid ethoxy-amide



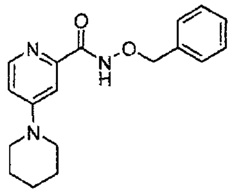
This compound was obtained according to **general procedure B** using 5-phenyl-pyridine-2-carboxylic acid and O-ethyl hydroxylamine hydrochloride. The expected compound was isolated as a white powder (64 % yield).

MS: 243.1

Mp: 100 °C – 105 °C

Example 14:

3,4,5,6-Tetrahydro-2H-[1,4']bipyridinyl-2'-carboxylic acid benzyloxy-amide



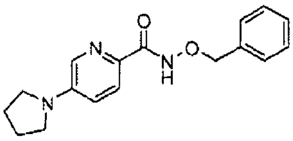
This compound was obtained according to **general procedure B** using 3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-2'-carboxylic acid hydrochloride and O-benzyl hydroxylamine hydrochloride. The expected compound was isolated as a white powder (26 % yield).

MS: 312.2

Mp: 135 °C – 140 °C

Example 15:

5-Pyrrolidin-1-yl-pyridine-2-carboxylic acid benzyloxy-amide



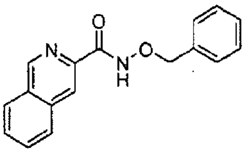
This compound was obtained according to **general procedure B** using 5-pyrrolidin-1-yl-pyridine-2-carboxylic acid and O-benzyl hydroxylamine hydrochloride. The expected compound was isolated as a white powder (54 % yield).

MS: 298.1

Mp: 165 °C – 170 °C

Example 16:

Isoquinoline-3-carboxylic acid benzyloxy-amide



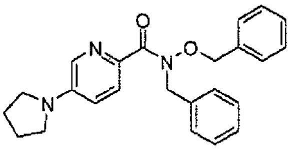
This compound was obtained according to **general procedure B** using isoquinoline-3-carboxylic acid and O-benzyl hydroxylamine hydrochloride. The expected compound was isolated as a white powder (77 % yield).

MS: 279.1

Mp: 85 °C – 90 °C

Example 17:

5-Pyrrolidin-1-yl-pyridine-2-carboxylic acid benzyl-benzyloxy-amide



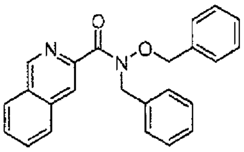
This compound was obtained according to **general procedure B** using 5-pyrrolidin-1-yl-pyridine-2-carboxylic acid and O,N-dibenzyl hydroxylamine hydrochloride (**Key Intermediate I**). The expected compound was isolated as a white powder (12 % yield).

MS: 388.2

Mp: 95 °C – 100 °C

Example 18:

Isoquinoline-3-carboxylic acid benzyl-benzyloxy-amide



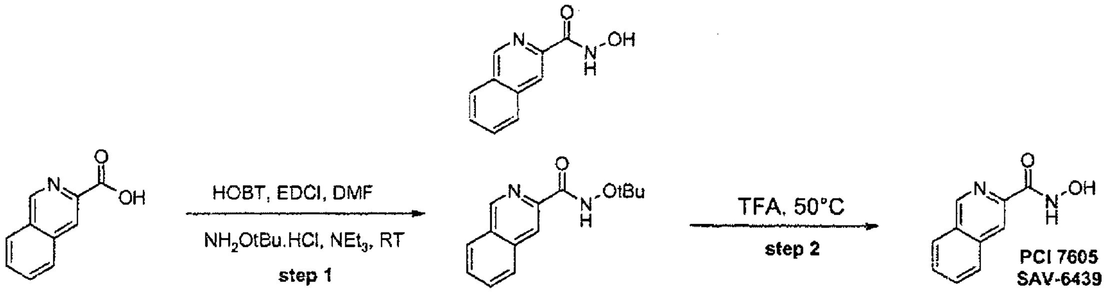
This compound was obtained according to **general procedure B** using isoquinoline-3-carboxylic acid and O, N-dibenzyl hydroxylamine hydrochloride (**Key Intermediate I**). The expected compound was isolated as a white powder (36 % yield).

MS: 369.2

Mp: 70 °C – 75 °C

Example 19:

Isoquinoline-3-carboxylic acid hydroxyamide



Step 1:

Isoquinoline-3-carboxylic acid tert-butoxy-amide was obtained according to **general procedure B** using isoquinoline-3-carboxylic acid and O-tert-butyl hydroxylamine hydrochloride. The expected compound was isolated as a pale yellow powder (46 % yield).

Step 2:

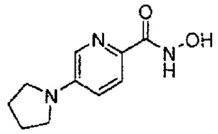
Isoquinoline-3-carboxylic acid tert-butoxy-amide (195 mg, 1 eq) and trifluoroacetic acid (4 mL) were heated at 50 °C during 20 h. The mixture was then evaporated to dryness. The residue was diluted in ethyl acetate (10 mL) and triethylamine (3 mL) was added. The mixture was absorbed on silica gel to be purified by flash chromatography using cyclohexane and ethyl acetate (100/0 to 0/100) to afford the expected compound as a pale pink powder (70 mg, 65 % yield).

MS: 189.0

Mp: 160 °C – 165 °C

Example 20:

5-Pyrrolidin-1-yl-pyridine-2-carboxylic acid hydroxyamide



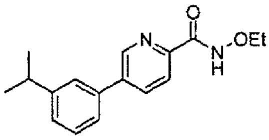
This compound was obtained according to the procedure of **example 19** using 5-pyrrolidin-1-yl-pyridine-2-carboxylic acid. The expected compound was isolated as a white powder.

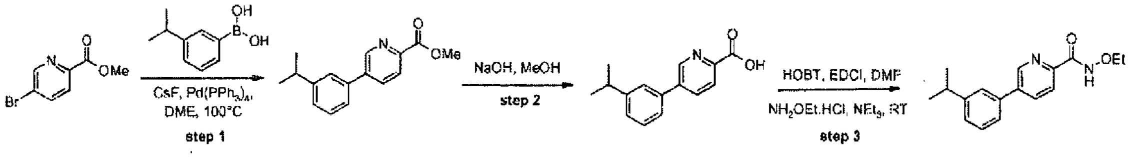
MS: 208.0

Mp: 220 °C – 225 °C

Example 21:

5-(3-Isopropyl-phenyl)-pyridine-2-carboxylic acid ethoxy-amide





Step 1:

To a solution of 5-bromo-pyridine-2-carboxylic acid methyl ester (500 mg, 2.3 mmol, 1 eq) in dimethoxyethane (6 mL) was added 3-isopropylphenylboronic acid (495 mg, 3 mmol, 1.3 eq) and cesium fluoride (1.05 g, 6.9 mmol, 3 eq). The mixture was degassed for 15 min and tetrakis(triphenylphosphine)palladium (133 mg, 0.12 mmol, 0.05 eq) was added. The mixture was heated at 100 °C for 15 min under microwave irradiation. After cooling, the mixture was poured on water (10 mL) and extracted with ethyl acetate (3 x 20 mL). The organic layers were dried over magnesium sulphate, filtered and evaporated to dryness. The crude residue was purified by flash chromatography using cyclohexane and ethyl acetate (100/0 to 0/100) to afford 5-(3-isopropyl-phenyl)-pyridine-2-carboxylic acid methyl ester as a colorless oil (380 mg, 64 % yield).

Step 2:

5-(3-Isopropyl-phenyl)-pyridine-2-carboxylic acid methyl ester (380 mg, 1.5 mmol, 1 eq) diluted in methanol (6 mL) and a 5 N solution of sodium hydroxide (0.5 mL) were heated at 80 °C for 20 h in a sealed tube. After cooling, the mixture was evaporated and the residue was diluted in water (6 mL) and extracted with ethyl acetate (3 x 10 mL). The aqueous layer was then acidified with a 1 N solution of hydrochloric acid and extracted with ethyl acetate (3 x 20 mL). The organic layers were dried over magnesium sulphate, filtered and evaporated to dryness to afford 5-(3-isopropyl-phenyl)-pyridine-2-carboxylic acid as a colorless oil (230 mg, 64 % yield).

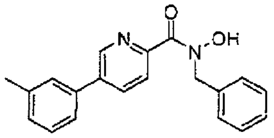
Step 3:

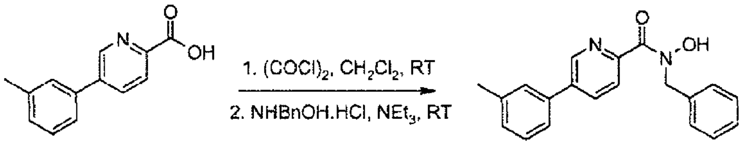
This compound was obtained according to **general procedure B** using 5-(3-isopropyl-phenyl)-pyridine-2-carboxylic acid and O-ethyl hydroxylamine hydrochloride. The expected compound was isolated as a colorless oil (60 % yield).

MS: 285.2

Example 22:

5-m-Tolyl-pyridine-2-carboxylic acid benzyl-hydroxy-amide



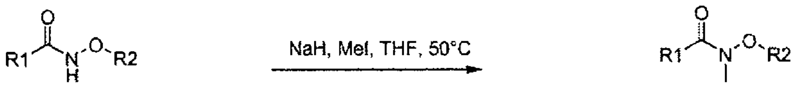


This compound was obtained according to **general procedure A** using 5-m-Tolyl-pyridine-2-carboxylic acid (obtained according the procedure of **example 21, steps 1 and 2**) and N-benzyl hydroxylamine hydrochloride. The expected compound was isolated as a white powder (11 % yield).

MS: 319.1

Mp: 139 °C – 140 °C

General Procedure C

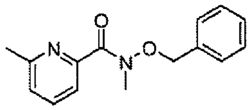


To a solution of carboxylic acid oxy-amide (0.4 mmol, 1 eq) in tetrahydrofurane (5 mL) was added sodium hydride (0.5 mmol, 1.3 eq). The mixture was stirred at room temperature during 15 min and methyl iodide (0.6 mmol, 1.5 eq) was added. The mixture was heated at

50 °C in a sealed tube during 20 h. After cooling, the mixture was poured on water (10 mL) and extracted with ethyl acetate (3 x 20 mL). The organic layers were dried over magnesium sulfate, filtered and evaporated in vacuo. The crude residue was purified by flash chromatography using dichloromethane and methanol (100/0) to (90/10) to afford the expected compound.

Example 23:

6-Methyl-pyridine-2-carboxylic acid benzyloxy-methyl-amide

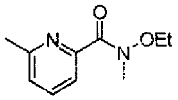


This compound was obtained according to **general procedure C** using 6-methyl-pyridine-2-carboxylic acid benzyloxy-amide (described in **example 10**).The expected compound was isolated as a colorless oil (55 % yield).

MS: 257.1

Example 24:

6-Methyl-pyridine-2-carboxylic acid ethoxy-methyl-amide

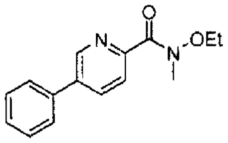


This compound was obtained according to **general procedure C** starting from 6-methyl-pyridine-2-carboxylic acid ethoxy-amide (described in **example 11**). The expected compound was isolated as a colorless oil (51 % yield).

MS: 195.0

Example 25:

5-Phenyl-pyridine-2-carboxylic acid ethoxy-methyl-amide



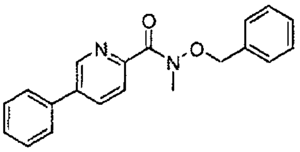
This compound was obtained according to **general procedure C** starting from 5-phenyl-pyridine-2-carboxylic acid ethoxy-amide (described in **example 13**). The expected compound was isolated as a white powder (41 % yield).

MS: 257.1

Mp: 70 °C – 75 °C

Example 26:

5-Phenyl-pyridine-2-carboxylic acid benzyloxy-methyl-amide

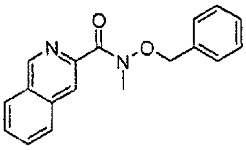


This compound was obtained according to **general procedure C** starting from 5-phenyl-pyridine-2-carboxylic acid benzyloxy-amide (described in **example 12**). The expected compound was isolated as a yellow oil (30 % yield).

MS: 319.1

Example 27:

Isoquinoline-3-carboxylic acid benzyloxy-methyl-amide



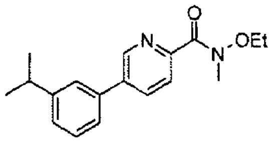
This compound was obtained according to **general procedure C** starting from isoquinoline-3-carboxylic acid benzyloxy-amide (described in **example 16**). The expected compound was isolated as a beige powder (45 % yield).

MS: 293.1

Mp: 70 °C – 75 °C

Example 28:

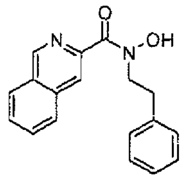
5-(3-Isopropyl-phenyl)-pyridine-2-carboxylic acid ethoxy-methyl-amide

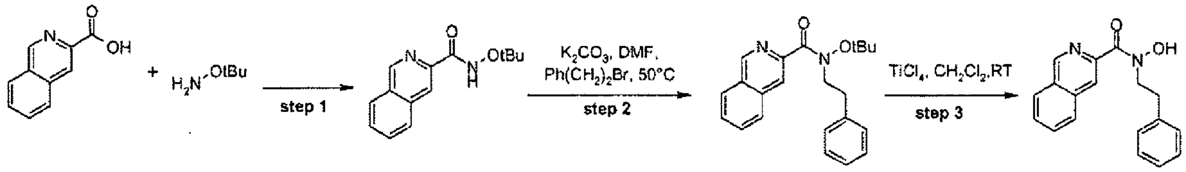


This compound was prepared according to **general procedure C** starting from 5-(3-isopropyl-phenyl)-pyridine-2-carboxylic acid ethoxy-methyl-amide (described in **example 21**). The expected compound was isolated as a colorless oil (50 % yield).
MS: 299.2

Example 29:

Isoquinoline-3-carboxylic acid hydroxy-phenethyl-amide





Step 1:

Isoquinoline-3-carboxylic acid tert-butoxy-amide was prepared according to **general procedure B** using isoquinoline-3-carboxylic acid and tert-butoxy-hydroxylamide hydrochloride. The expected compound was isolated as a white powder (86 % yield).

Step 2:

To a solution of isoquinoline-3-carboxylic acid tert-butoxy-amide (200 mg, 0.8 mmol, 1 eq) in dimethylformamide (7 mL) was added potassium carbonate (454 mg, 3.3 mmol, 4 eq) and (2-bromoethyl)benzene (220 µL, 1.6 mmol, 2 eq). The mixture was stirred at 50 °C for 20 h. After cooling, the mixture was poured on water (10 mL) and extracted with ethyl acetate (3 x 20 mL). The organic layers were dried over magnesium sulfate, filtered and evaporated in vacuo. The crude residue was purified by flash chromatography using cyclohexane and ethyl acetate (100/0 to 80/20) to afford isoquinoline-3-carboxylic acid tert-butoxy-phenethyl-amide as a colorless oil (220 mg, 77 % yield).

Step 3:

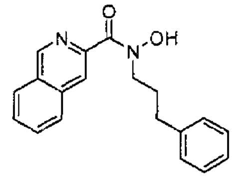
To a solution of isoquinoline-3-carboxylic acid tert-butoxy-phenethyl-amide (220 mg, 0.63 mmol, 1 eq) in dichloromethane (10 mL) was added drop wise at 0 °C a 1M solution of titanium tetrachloride in dichloromethane (1.7 mL, 1.7 mmol, 3 eq). The mixture was stirred at room temperature for 20 h. It was then added to isopropanol (15 mL) and the resulting mixture was stirred at room temperature for 1 h and evaporated to dryness. The residue was diluted with ethyl acetate (15 mL) and washed with a saturated solution of sodium bicarbonate (3 x 20 mL). The organic layer was filtered on celite and the filtrate was evaporated to dryness. The residue was triturated in diethyl ether and filtered to afford the expected compound as a white solid (75 mg, 11 % yield).

MS: 293.2

Mp: 90 °C – 95 °C

Example 30:

Isoquinoline-3-carboxylic acid hydroxy-(3-phenyl-propyl)-amide

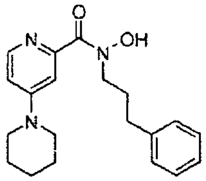


This compound was prepared according to the procedure of **example 29** starting with isoquinoline-3-carboxylic acid. The expected compound was isolated as a colorless oil.

MS: 307.2

Example 31:

3,4,5,6-Tetrahydro-2H-[1,4']bipyridinyl-2'-carboxylic acid hydroxy-(3-phenyl-propyl)-amide



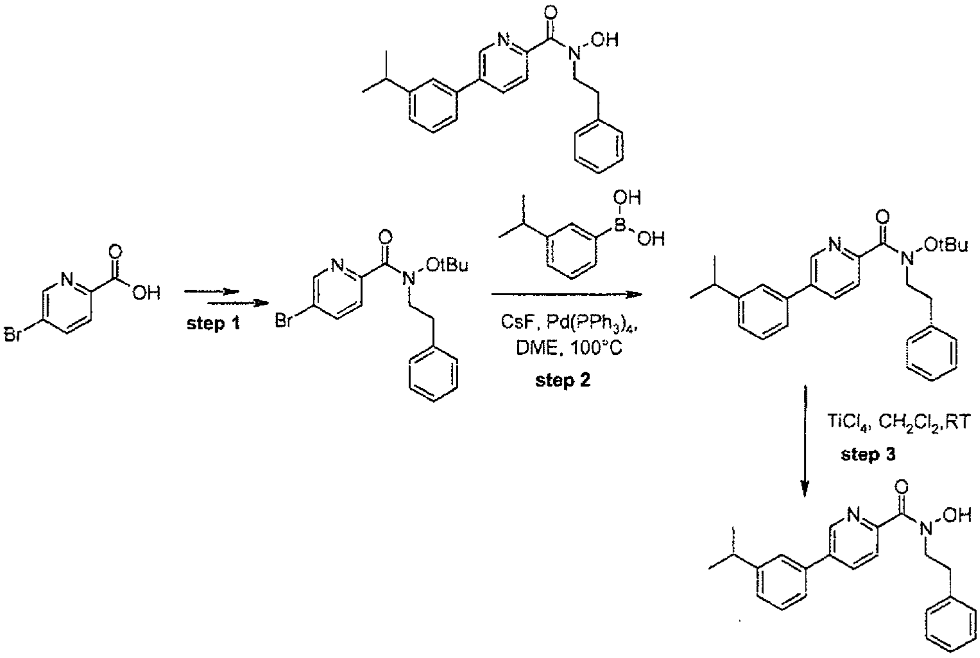
This compound was prepared according to the procedure of **example 29** starting with 3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-2'-carboxylic acid hydrochloride and using **general procedure A** for step 1 instead of **general procedure B**. The expected compound was isolated as a white powder.

MS: 340.2

Mp: 125 °C – 130 °C

Example 32:

5-(3-Isopropyl-phenyl)-pyridine-2-carboxylic acid hydroxy-phenethyl-amide



Step 1:

5-Bromo-pyridine-2-carboxylic acid tert-butoxy-phenethyl-amide was prepared according to **example 29, steps 1 and 2** starting from 5-bromo-pyridine-2-carboxylic acid. The desired compound was obtained as a colorless oil (65 % overall yield).

Step 2:

5-(3-Isopropyl-phenyl)-pyridine-2-carboxylic acid tert-butoxy-phenethyl-amide was prepared according to **example 21, step 1** starting from 5-bromo-pyridine-2-carboxylic acid tert-butoxy-phenethyl-amide and 3-isopropylphenylboronic acid. The expected compound was isolated as a yellow oil (86 % yield).

Step 3:

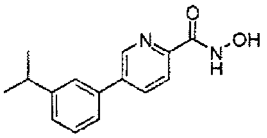
The expected compound was prepared according to **example 29 step 3** starting from 5-(3-isopropyl-phenyl)-pyridine-2-carboxylic acid tert-butoxy-phenethyl-amide. It was isolated as a yellow powder (15 % yield).

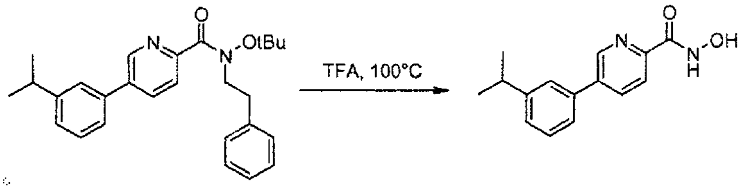
MS: 361.2

Mp: 110 °C – 115 °C

Example 33:

5-(3-Isopropyl-phenyl)-pyridine-2-carboxylic acid hydroxyamide





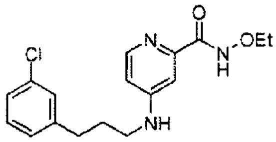
5-(3-Isopropyl-phenyl)-pyridine-2-carboxylic acid tert-butoxy-phenethyl-amide prepared according to step **example 32 steps 1 and 2** (220 mg, 0.53 mmol, 1 eq) was solubilized in trifluoroacetic acid (5 mL) and heated at 100 °C during 10 min under microwave irradiation. The mixture was then evaporated to dryness and the residue was purified by flash chromatography using cyclohexane and ethyl acetate (100/0 to 80/20) to afford the expected compound as a yellow powder (19 mg, 10 % yield).

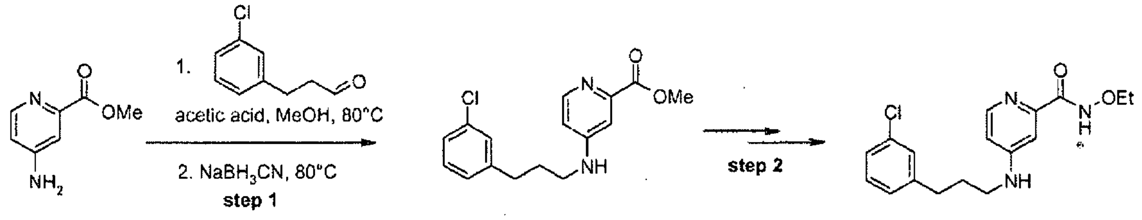
MS: 257.1

Mp: 130 °C-135 °C

Example 34:

4-[3-(3-Chloro-phenyl)-propylamino]-pyridine-2-carboxylic acid ethoxy-amide





Step 1:

In a sealed tube, 4-amino-pyridine-2-carboxylic acid methyl ester (200 mg, 1.3 mmol, 1 eq) and 3-(3-chloro-phenyl)-propionaldehyde (0.4 mL, 2.6 mmol, 2 eq) were solubilized in acetic acid (190 µL, 3.3 mmol, 2.5 eq) and anhydrous methanol (7 mL) in the presence of molecular sieves. The mixture was heated at 80 °C for 20 h. After cooling, sodium cyanoborohydride (123 mg, 1.9 mmol, 1.5 eq) was added and the mixture was heated at 80 °C for 4 h. After cooling, the mixture was poured on a saturated solution of sodium bicarbonate (10 mL) and extracted with ethyl acetate (3 x 20 mL). The organic layers were dried over magnesium sulfate, filtered and evaporated in vacuo. The crude residue was purified by flash chromatography using dichloromethane and methanol (100/0 to 90/10) to afford the expected compound as a colorless oil (144 mg, 36 % yield).

Step 2:

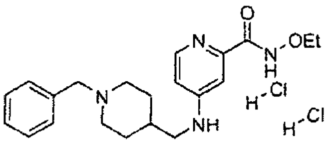
The expected compound was prepared according to **example 21, steps 2 and 3** starting with 4-[3-(3-chloro-phenyl)-propylamino]-pyridine-2-carboxylic acid methyl ester. The expected compound was isolated as a white powder.

MS: 334.2

Mp: 100 °C – 105 °C

Example 35:

4-[(1-Benzyl-piperidin-4-ylmethyl)-amino]-pyridine-2-carboxylic acid ethoxy-amide chlorhydrate



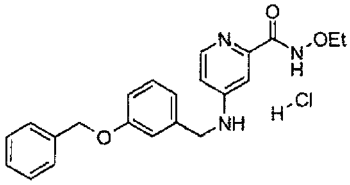
This compound was prepared according to the procedure of **example 34** starting from 4-amino-pyridine-2-carboxylic acid methyl ester and 1-benzyl-piperidine-4-carbaldehyde. The expected compound was isolated as a white powder.

MS: 369.3

Mp: 125 °C – 130 °C

Example 36:

4-(3-Benzyloxy-benzylamino)-pyridine-2-carboxylic acid ethoxy-amide hydrochloride



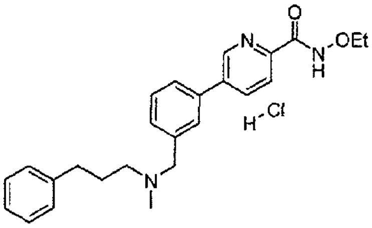
This compound was prepared according to the procedure of **example 34** starting from 4-amino-pyridine-2-carboxylic acid methyl ester and 3-benzyloxy-benzaldehyde. The expected compound was isolated as a pink powder.

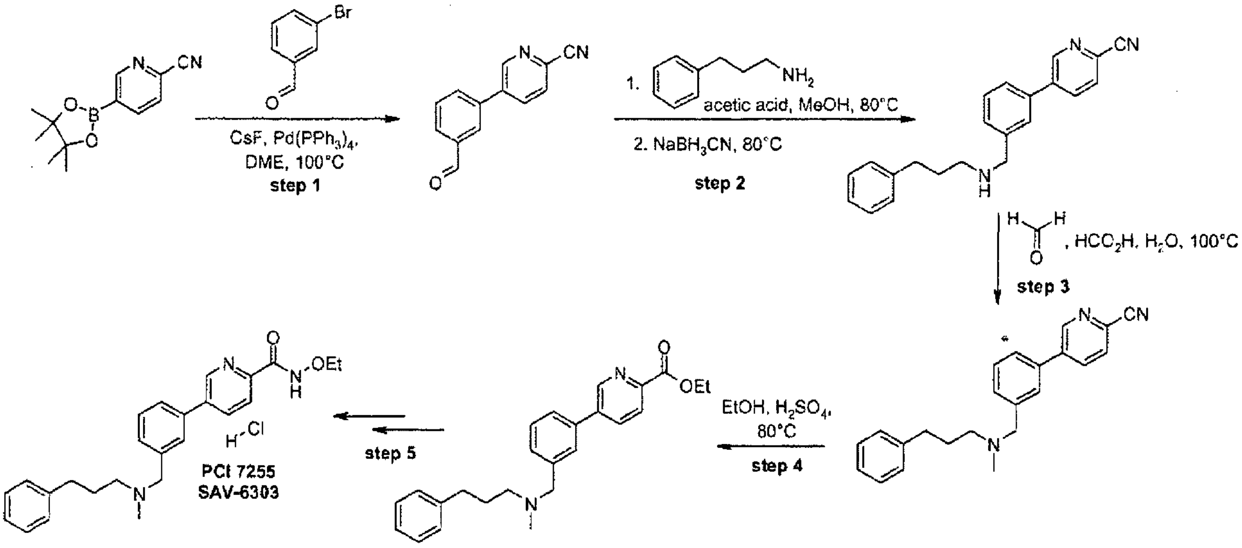
MS: 378.2

Mp: 70 °C – 75 °C

Example 37:

5-(3-{[Methyl-(3-phenyl-propyl)-amino]-methyl}-phenyl)-pyridine-2-carboxylic acid ethoxy-amide chlorhydrate





Step 1:

5-(3-Formyl-phenyl)-pyridine-2-carbonitrile was prepared according to **example 21 step 1** starting from 3-bromo-benzaldehyde and 5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-pyridine-2-carbonitrile. The expected compound was isolated as a white powder (88 % yield).

Step 2:

5-{3-[(3-Phenyl-propylamino)-methyl]-phenyl}-pyridine-2-carbonitrile was prepared according to **example 34, step 1** starting from 5-(3-formyl-phenyl)-pyridine-2-carbonitrile and 3-phenyl-propylamine. The expected compound was isolated as a colorless oil (quant. yield).

Step 3:

5-{3-[(3-Phenyl-propylamino)-methyl]-phenyl}-pyridine-2-carbonitrile (384 mg, 1.1 mmol, 1 eq), formaldehyde 37 % in water (210 µL), formic acid (97 µL, 2.6 mmol, 2.4 eq) were solubilized in water (5 mL) and heated at 100 °C for 20 h. After cooling, the mixture was basified with a 5 N solution of sodium hydroxide, poured on water (10 mL) and extracted with ethyl acetate (3 x 20 mL). The organic layer was dried over magnesium sulfate, filtered and evaporated in vacuo. The crude residue was purified by flash chromatography using cyclohexane and ethyl acetate (100/0 to 80/20) to afford 5-(3-{[methyl-(3-phenyl-propyl)-amino]-methyl}-phenyl)-pyridine-2-carbonitrile as a colorless oil (quant. yield).

Step 4:

In a sealed tube, 5-(3-{[methyl-(3-phenyl-propyl)-amino]-methyl}-phenyl)-pyridine-2-carbonitrile (365 mg, 1.1 mmol, 1 eq), sulfuric acid (5 mL) and ethanol (5 mL) were heated at 80 °C during 48 h. After cooling, the mixture was evaporated to dryness. The residue was taken in ethyl acetate (10 mL) and washed with a saturated solution of sodium bicarbonate (3 x 10 mL). The organic layer was dried over magnesium sulfate, filtered and evaporated in vacuo to afford 5-(3-{[methyl-(3-phenyl-propyl)-amino]-methyl}-phenyl)-pyridine-2-carboxylic acid ethyl ester as a yellow oil (224 mg, quant. yield).

Step 5:

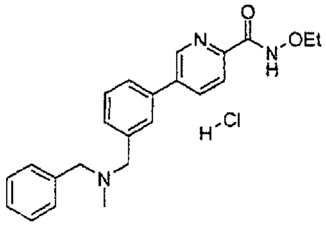
This compound was prepared according to **example 21 steps 2 and 3** starting from 5-(3-{[methyl-(3-phenyl-propyl)-amino]-methyl}-phenyl)-pyridine-2-carboxylic acid ethyl ester. The expected compound was isolated as a white powder.

MS: 404.3

Mp: 50 °C – 55 °C

Example 38:

5-{3-[(Benzyl-methyl-amino)-methyl]-phenyl}-pyridine-2-carboxylic acid ethoxy-amide chlorhydrate



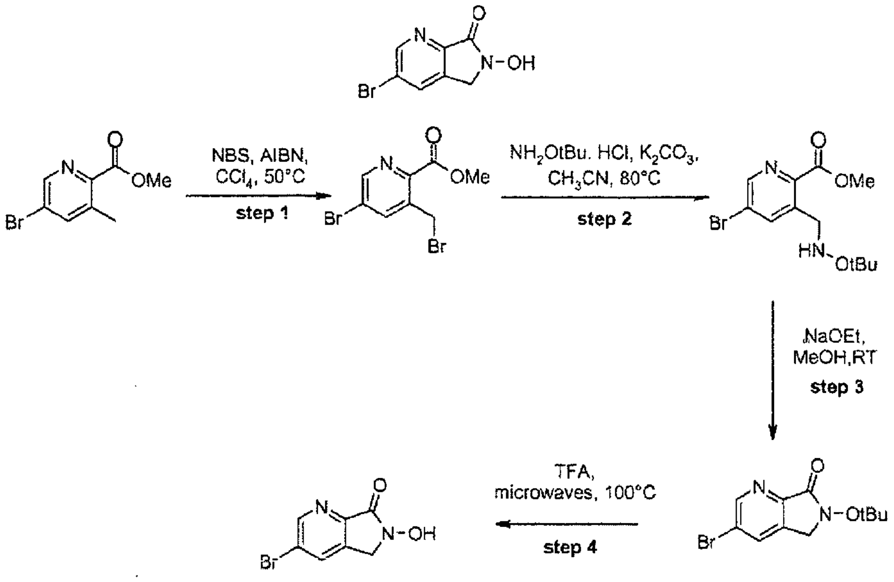
This compound was prepared according to the procedure of **example 37** starting from bromo-benzaldehyde and 5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-pyridine-2-carbonitrile and using benzylamine instead of 3-phenyl-propylamine in step 2. The expected compound was isolated as a white powder.

MS: 376.2

Mp: 85 °C – 90 °C

Example 39:

3-Bromo-6-hydroxy-5,6-dihydro-pyrrolo[3,4-b]pyridin-7-one



Step 1:

To a solution of 5-bromo-3-methyl-pyridine-2-carboxylic acid methyl ester (200 mg, 0.87 mmol, 1 eq) in tetrachloromethane (10 mL) were added N-bromosuccinimide (162 mg, 0.91 mmol, 1.05 eq) and 2,2'-azobis(2-methylpropionitrile) (3 mg, 0.017 mmol, 0.02 eq). The mixture was stirred at 50 °C during 5 h. The solvent was then evaporated and the crude residue was purified by flash chromatography using cyclohexane and ethyl acetate (100/0 to 80/20). 5-Bromo-3-bromomethyl-pyridine-2-carboxylic acid methyl ester was isolated as a white powder as a 6/4 mixture with the starting material (160 mg, 39 % yield). The mixture was used in the next step.

Step 2:

A suspension of 5-bromo-3-bromomethyl-pyridine-2-carboxylic acid methyl ester (160 mg, 0.5 mmol, 1 eq), potassium carbonate (716 mg, 5.2 mmol, 1 eq) and O-tert-butyl-hydroxylamine hydrochloride (325 mg, 2.6 mmol, 5 eq) in acetonirile (8 mL) was heated at 80 °C during 20 h. After cooling, the mixture was filtered and washed with ethyl acetate (10 mL). The filtrate was evaporated and the crude residue was purified by flash chromatography using cyclohexane and ethyl acetate (100/0 to 70/30) to afford 5-bromo-3-(tert-butoxyamino-methyl)-pyridine-2-carboxylic acid methyl ester as a white powder (70 mg, 43 % yield).

Step 3:

To a solution of 5-bromo-3-(tert-butoxyamino-methyl)-pyridine-2-carboxylic acid methyl ester (70 mg, 0.22 mmol, 1 eq) in methanol (2 mL) was added sodium ethoxide (30 mg, 0.44 mmol, 2 eq) freshly prepared. The mixture was stirred at room temperature for 20 h. A few drops of acetic acid and water (5 mL) were added. The precipitate was filtered and washed with water (5 mL), solubilized in methanol (10 mL) and evaporated to dryness to afford 3-bromo-6-tert-butoxy-5,6-dihydro-pyrrolo[3,4-b]pyridin-7-one as a white powder (45 mg, 72 % yield).

Step 4:

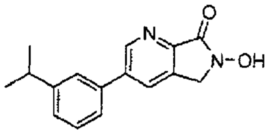
3-Bromo-6-tert-butoxy-5,6-dihydro-pyrrolo[3,4-b]pyridin-7-one (45 mg, 0.16 mmol, 1 eq) was solubilized in trifluoroacetic acid (2 mL) and heated at 100 °C during 5 min under microwave irradiation. The mixture was then evaporated to dryness and the residue was triturated water (5 mL). The precipitate was filtered and dried in vacuo to afford the expected compound as a beige powder (22 mg, 60 % yield).

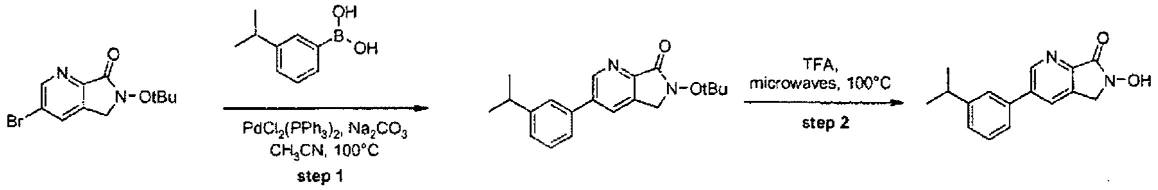
MS: 228.9

Mp: decomposes at 230 °C – 235 °C.

Example 40:

6-Hydroxy-3-(3-isopropyl-phenyl)-5,6-dihydro-pyrrolo[3,4-b]pyridin-7-one





Step 1:

To a solution of 3-bromo-6-tert-butoxy-5,6-dihydro-pyrrolo[3,4-b]pyridin-7-one described in **example 39, steps 1 to 3** (200 mg, 0.7 mmol, 1 eq) in acetonitrile (3 mL) were added 3-isopropylphenylboronic acid (150 mg, 0.9 mmol, 1.3 eq) and a 2 M solution of sodium carbonate (3 mL). The mixture was degassed for 15 min and trans-dichlorobis(triphenylphosphine)palladium (25 mg, 0.035 mmol, 0.05 eq) was added. The mixture was heated at 100 °C for 10 min under microwave irradiation. After cooling, the mixture was poured on water (10 mL) and extracted with ethyl acetate (3 x 20 mL). The organic layers were dried over magnesium sulphate, filtered and evaporated to dryness. The crude residue was purified by flash chromatography using cyclohexane and ethyl acetate (100/0 to 50/50) to afford 6-tert-butoxy-3-(3-isopropyl-phenyl)-5,6-dihydro-pyrrolo[3,4-b]pyridin-7-one as a white powder (150 mg, 66 % yield).

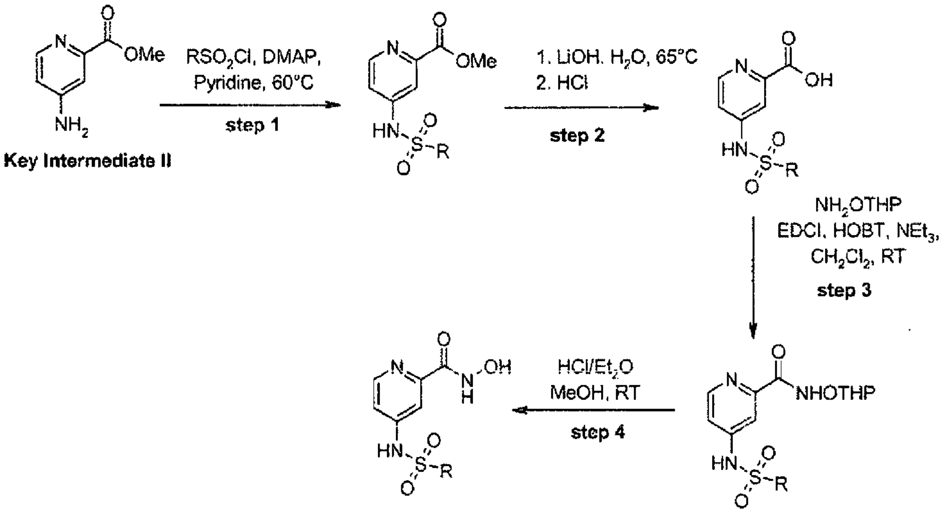
Step 2:

The compound was prepared according to **example 39, step 4**. After trituration, the powder was purified by flash chromatography using dichloromethane and methanol (100/0 to 80/20) to afford the expected compound as a yellow powder (16 % yield).

MS: 269.1

Mp: decomposes at 155 °C – 160 °C.

General procedure D



Step 1:

4-Amino-pyridine-2-carboxylic acid methyl ester (**Key Intermediate II**) (600 mg, 3.9 mmol, 1 eq) was solubilized in pyridine (20 mL). Dimethylaminopyridine (482 mg, 3.9 mmol, 1 eq) and sulfonyl chloride (1.3 eq) were added and the mixture was stirred at 60 °C during 15 h. After cooling down, the solvent was evaporated. Water (10 mL) was added and the aqueous layer was extracted with ethyl acetate (3 x 20 mL). The organic layers were dried over magnesium sulfate, filtered and evaporated in vacuo. The crude residue was purified by flash chromatography to afford the expected compound.

Step 2:

The sulfonylamino-pyridine-2-carboxylic acid methyl ester (1.0 g, 1 eq) was solubilized in a mixture of methanol / water (17 mL / 1.7 mL) and lithium hydroxide was added (2 eq). The mixture was heated at 65 °C during 18 h. After cooling down, a 2 M solution of hydrogen chloride in diethyl ether was added until pH = 1. The mixture was then evaporated to dryness to afford the corresponding acid with quantitative yield.

Step 3:

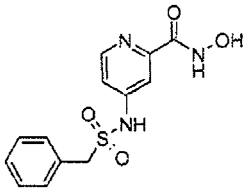
To a solution of sulfonylamino-pyridine-2-carboxylic acid (800 mg, 1 eq) in dichloromethane (13 mL) were added HOBT (2 eq), EDCI (2 eq), triethylamine (3 eq) and O-(tetrahydro-pyran-2-yl)-hydroxylamine (2 eq). The mixture was stirred at room temperature for 18 h. The reaction was quenched with water (10 mL) and the mixture was extracted with dichloromethane (3 X 15 mL). The organic layers were dried over magnesium sulfate, filtered and evaporated in vacuo. The crude residue was purified by flash chromatography to afford sulfonylamino-pyridine-2-carboxylic acid (tetrahydro-pyran-2-yloxy)-amide.

Step 4:

To a solution of sulfonylamino-pyridine-2-carboxylic acid (tetrahydro-pyran-2-yloxy)-amide (1 eq) in methanol (10 mL) was added a 2 M solution on hydrogen chloride in diethyl ether (2 eq). The mixture was stirred at room temperature for 1 h. The precipitate was filtered, rinsed with diethyl ether and dried in vacuo to afford sulfonylamino-pyridine-2-carboxylic acid hydroxyamide hydrochloride salt.

Example 41:

4-Phenylmethanesulfonylamino-pyridine-2-carboxylic acid hydroxyamide



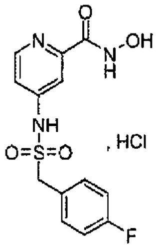
This compound was obtained according to **general procedure D** using phenylmethane-sulfonyl chloride. The expected compound was isolated as a beige powder.

MS: 308.1

Mp: 187 °C – 192 °C

Example 42:

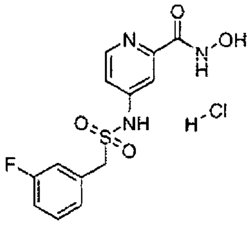
4-(4-Fluoro-phenylmethanesulfonylamino)-pyridine-2-carboxylic acid benzyl-hydroxy-amide



This compound was obtained according to **general procedure D** using (4-fluoro-phenyl)-methanesulfonyl chloride. The expected compound was isolated as a white powder.
MS: 326.1
Mp: 183 °C – 188 °C

Example 43:

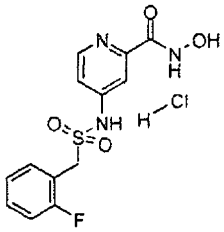
4-(3-Fluoro-phenylmethanesulfonylamino)-pyridine-2-carboxylic acid hydroxyamide hydrochloride



This compound was obtained according to **general procedure D** using (3-fluoro-phenyl)-methanesulfonyl chloride. The expected compound was isolated as a white powder.
MS: 326.1
Mp: 195 °C – 200 °C

Example 44:

4-(2-Fluorophenylmethanesulfonylamino)-pyridine-2-carboxylic acid hydroxyamide hydrochloride



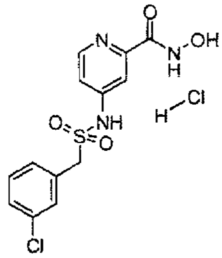
This compound was obtained according to **general procedure D** using 2-fluorophenylmethanesulfonyl chloride. The expected compound was isolated as a white powder.

MS: 326.1

Mp: 209 °C – 216 °C

Example 45:

4-(3-Chlorophenylmethanesulfonylamino)-pyridine-2-carboxylic acid hydroxyamide hydrochloride



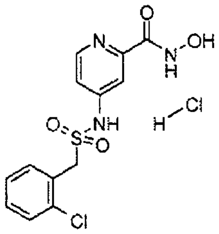
This compound was obtained according to **general procedure D** using 3-chlorophenylmethanesulfonyl chloride. The expected compound was isolated as a white powder.

MS: 342.1

Mp: 198 °C – 204 °C

Example 46:

4-(2-Chloro-phenylmethanesulfonylamino)-pyridine-2-carboxylic acid hydroxyamide hydrochloride



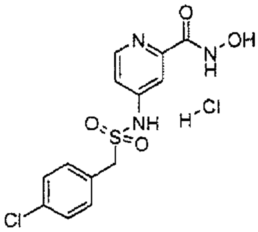
This compound was obtained according to **general procedure D** using 2-chlorophenylmethanesulfonyl chloride. The expected compound was isolated as a white powder.

MS: 342.1

Mp: 215 °C – 220 °C

Example 47:

4-(4-Chloro-phenylmethanesulfonylamino)-pyridine-2-carboxylic acid hydroxyamide hydrochloride



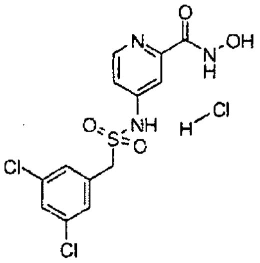
This compound was obtained according to **general procedure D** using 4-chlorophenylmethanesulfonyl chloride. The expected compound was isolated as a beige powder.

MS: 342.1

Mp: 210 °C – 230 °C

Example 48:

4-(3,5-Dichlorophenylmethanesulfonylamino)-pyridine-2-carboxylic acid hydroxyamide hydrochloride



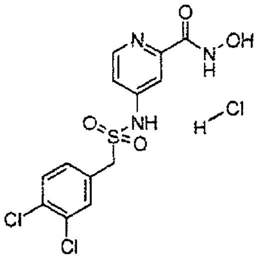
This compound was obtained according to **general procedure D** using 3,5-dichlorophenylmethanesulfonyl chloride. The expected compound was isolated as a white powder.

MS: 376.2

Mp: 203 °C – 205 °C

Example 49:

4-(3,4-Dichloro-phenylmethanesulfonylamino)-pyridine-2-carboxylic acid hydroxyamide hydrochloride



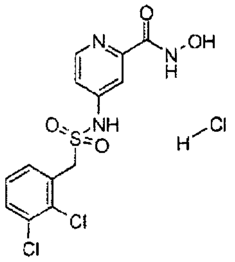
This compound was obtained according to **general procedure D** using 3,4-dichlorophenylmethanesulfonyl chloride. The expected compound was isolated as a white powder.

MS: 376.2

Mp: 228 °C – 238 °C

Example 50:

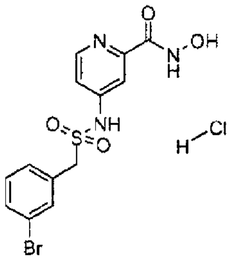
4-(2,3-Dichloro-phenylmethanesulfonylamino)-pyridine-2-carboxylic acid hydroxyamide hydrochloride



This compound was obtained according to **general procedure D** using 2,3-dichlorophenylmethanesulfonyl chloride. The expected compound was isolated as a white powder.
MS: 376.2
Mp: 210 °C – 218 °C

Example 51:

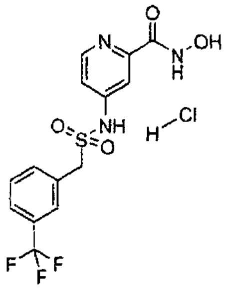
4-(3-Bromophenylmethanesulfonylamino)-pyridine-2-carboxylic acid hydroxyamide hydrochloride



This compound was obtained according to **general procedure D** using 3-bromophenylmethanesulfonyl chloride. The expected compound was isolated as a white powder.
MS: 386.3
Mp: 197 °C – 205 °C

Example 52:

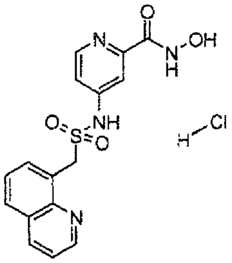
4-(3-Trifluoromethylphenylmethanesulfonylamino)-pyridine-2-carboxylic acid hydroxyamide hydrochloride



This compound was obtained according to **general procedure D** using 3-trifluoromethyl-phenylmethanesulfonyl chloride. The expected compound was isolated as a white powder.
MS: 376.1
Mp: 201 °C – 204 °C

Example 53:

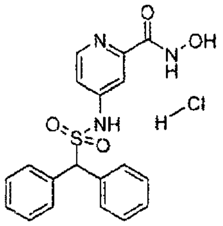
4-(Quinolin-8-ylmethanesulfonylamino)-pyridine-2-carboxylic acid hydroxyamide hydrochloride



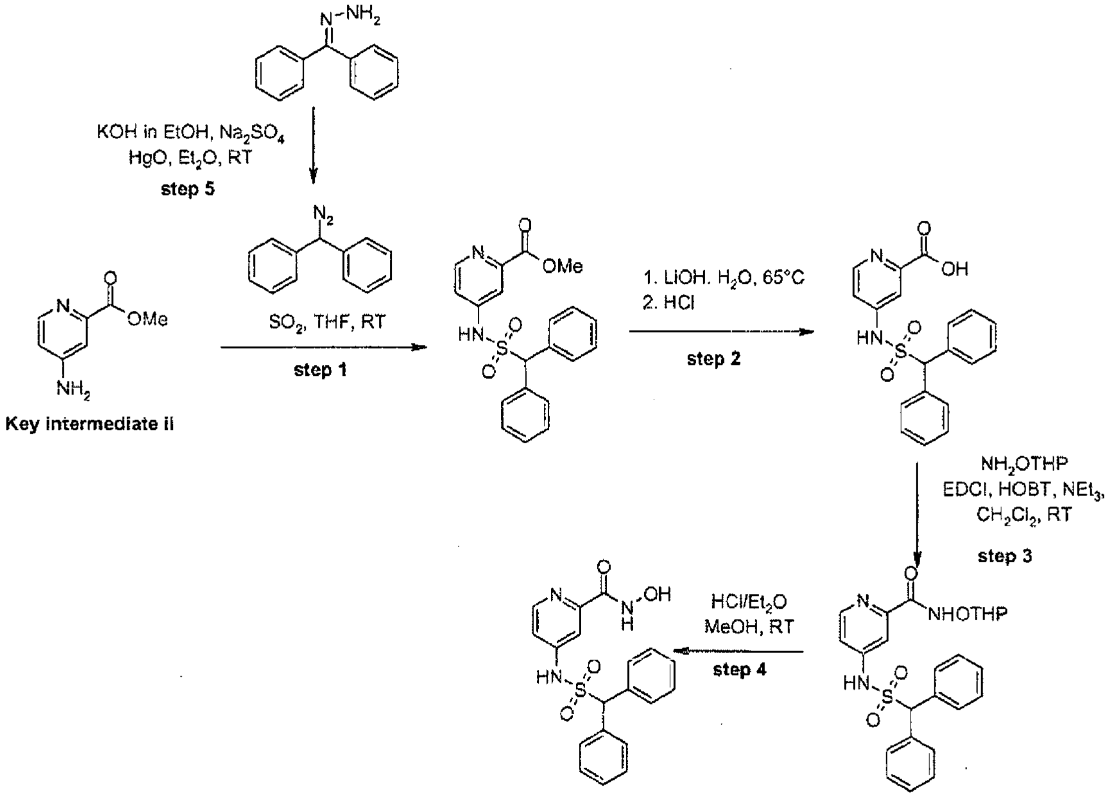
This compound was obtained according to **general procedure D** using quinolin-8-yl-methanesulfonyl chloride. The expected compound was isolated as a white powder.
MS: 359.0
Mp: 220 °C – 228 °C

Example 54:

4-(Diphenylmethanesulfonylamino)-pyridine-2-carboxylic acid hydroxyamide hydrochloride



Because diphenylmethanesulfonyl chloride is not commercially available, this compound was obtained according to a **modified version of general procedure D**.



Step 5:

To a suspension of benzophenone hydrazone (5.0 g, 25.5 mmol, 1 eq) and sodium sulfate (5.4 g, 38.2 mmol, 1.5 eq) in diethyl ether (80 mL) was added a saturated solution of potassium hydroxide in ethanol (2 mL). Mercury oxide (13.8 g, 63.7 mmol, 2.5 eq) was added and the red solution obtained was stirred at room temperature during 1.5h. The solid obtained was filtered and the filtrate was evaporated to dryness. The residue was dissolved with hexane (40 mL) and the solution was placed in the refrigerator overnight. The white crystals obtained were filtered and the filtrate was concentrated to afford diphenyldiazomethane as a partially crystallized purple oil (4.0 g, 80 % yield).

Step 1:

At 0 °C, in a solution of 4-amino-pyridine-2-carboxylic acid methyl ester (**Key Intermediate II**) (1.2 g, 7.8 mmol, 2 eq) and diphenyldiazomethane (758 mg, 3.9 mmol, 1 eq) in tetrahydrofurane (40 mL), was bubbled sulfur dioxide until the red color disappeared. The solution was then stirred from 0 °C to room temperature for 3 days. The mixture was filtered and the filtrate was evaporated. The crude residue was purified by flash chromatography using cyclohexane and ethyl acetate (0/100 to 100/0) to afford 4-(diphenyl-methanesulfonylamino)-pyridine-2-carboxylic acid methyl ester as a pale yellow powder (665 mg, 45 % yield).

Step 2 to Step 4:

These steps were similar to **general procedure D, steps 2 to 4.**

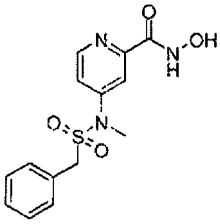
The final expected compound was isolated as a beige powder.

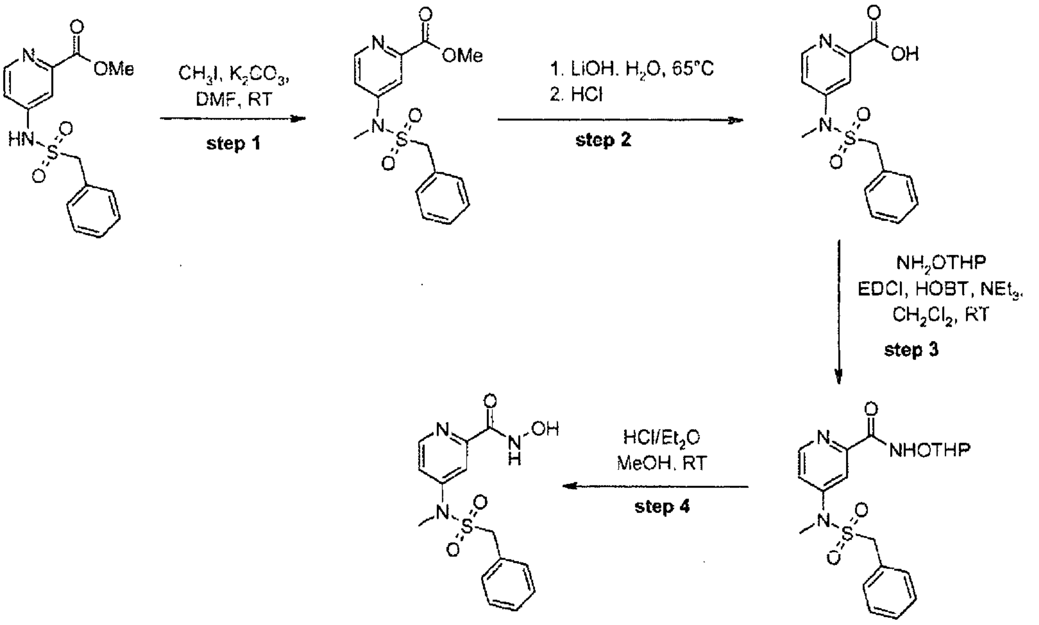
MS: 384.0

Mp: 162 °C – 168 °C

Example 55:

4-(Methyl-phenylmethanesulfonyl-amino)-pyridine-2-carboxylic acid hydroxyamide





Step 1:

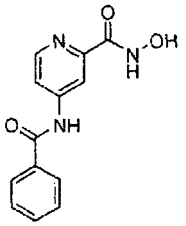
To a solution of 4-phenylmethanesulfonylamino-pyridine-2-carboxylic acid methyl ester prepared according to **general procedure D step 1** (500 mg, 1.6 mmol, 1 eq) in dimethylformamide (10 mL) were added potassium carbonate (676 mg, 4.9 mmol, 3 eq) and methyl iodide (0.2 mL, 3.3 mmol, 2 eq). The mixture was stirred at room temperature for 20 h. The mixture was then poured on water (10 mL) and extracted with ethyl acetate (3 x 15 mL). The organic layers were washed with brine (3 x 15 mL), dried over magnesium sulfate, filtered and evaporated to dryness to afford 4-(methyl-phenylmethanesulfonyl-amino)-pyridine-2-carboxylic acid methyl ester as an orange oil (400 mg, 77 % yield).

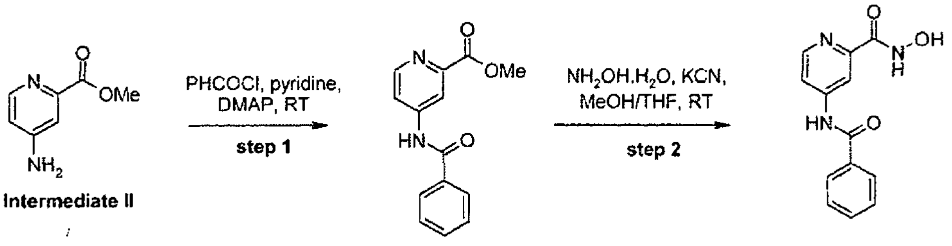
Steps 2 to 4:

These procedures were similar to **general procedure D, steps 2 to 4.**
The expected compound was isolated as a pale orange foam.
MS: 322.1

Example 56:

4-Benzoylaminopyridine-2-carboxylic acid hydroxyamide





Step 1:

4-Amino-pyridine-2-carboxylic acid methyl ester (**Key Intermediate II**) (400 mg, 2.6 mmol, 1 eq) was solubilized in pyridine (10 mL). Dimethylaminopyridine (catalytic amount) and benzoyl chloride (366 µL, 3.15 mmol, 1.2 eq) were added and the mixture was stirred at room temperature during 18 h. The solvent was then evaporated, water (10 mL) was added and the aqueous layer was extracted with ethyl acetate (3 x 20 mL). The organic layers were dried over magnesium sulfate, filtered and evaporated in vacuo. The crude residue was purified by flash chromatography using cyclohexane and ethyl acetate (100/0 to 50/50) to afford 4-benzoylamino-pyridine-2-carboxylic acid methyl ester as a white foam (654 mg, 97 % yield).

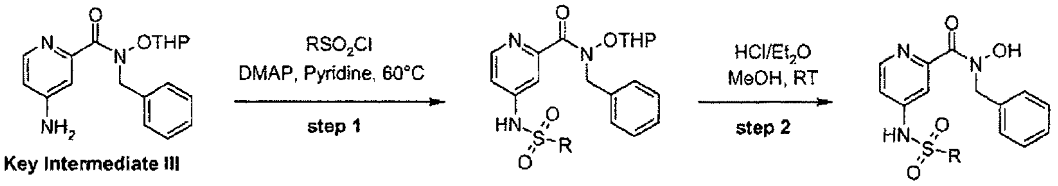
Step 2:

To a solution of 4-benzoylamino-pyridine-2-carboxylic acid methyl ester (100 mg, 0.4 mmol, 1 eq) in a mixture of methanol (2 mL) and tetrahydrofurane (2mL) were added potassium cyanide (catalytic amount) and a 50% aqueous solution of hydroxylamine (1.6 mL). The mixture was stirred at room temperature during 4 days. A saturated solution of citric acid (10 mL) and water (10 mL) were then added and the aqueous layer was extracted with ethyl acetate (3 x 20 mL). The organic layers were dried over magnesium sulfate, filtered and evaporated in vacuo. The crude residue was taken in ethyl acetate (5 mL) and dichloromethane (5 mL) and sonicated. The solid was filtered and dried to afford the expected compound as white powder (78 mg, 78 % yield).

MS: 258.0

Mp: 175 °C – 184 °C

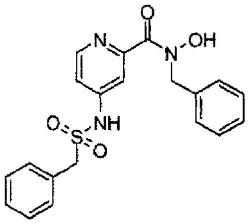
General procedure E



This procedure was similar to **general procedure D, steps 1 and 4.**

Example 57:

4-Phenylmethanesulfonylamino-pyridine-2-carboxylic acid benzyl-hydroxy-amide



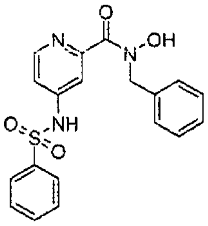
This compound was obtained according to **general procedure E** using phenylmethanesulfonyl chloride. The expected compound was isolated as a white powder.

MS: 398.2

Mp: 190 °C – 195 °C

Example 58:

4-Benzenesulfonylamino-pyridine-2-carboxylic acid benzyl-hydroxy-amide



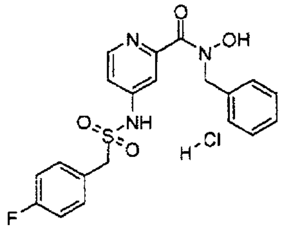
This compound was obtained according to **general procedure E** using benzene sulfonyl chloride. The expected compound was isolated as a pale rose oil.

MS: 384.2

Mp: 175 °C – 180 °C

Example 59:

4-(4-Fluoro-phenylmethanesulfonylamino)-pyridine-2-carboxylic acid benzyl-hydroxy-amide hydrochloride



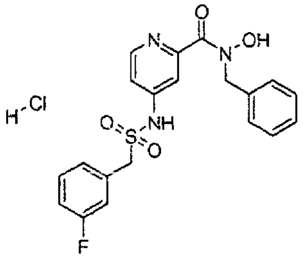
This compound was obtained according to **general procedure E** using 4-fluorophenyl-methanesulfonyl chloride. The expected compound was isolated as a beige powder.

MS: 416.3

Mp: 178 °C – 183 °C

Example 60:

4-(3-Fluoro-phenylmethanesulfonylamino)-pyridine-2-carboxylic acid benzyl-hydroxy-amide hydrochloride



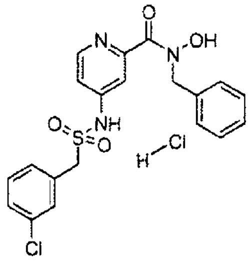
This compound was obtained according to **general procedure E** using 3-fluorophenyl-methanesulfonyl chloride. The expected compound was obtained as a beige powder.

MS: 416.2

Mp: 111 °C – 113 °C

Example 61:

4-(3-Chlorophenylmethanesulfonylamino)-pyridine-2-carboxylic acid benzylhydroxyamide hydrochloride



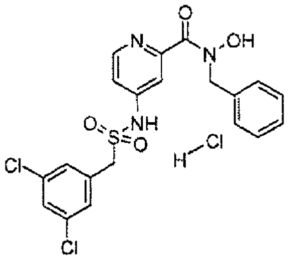
This compound was obtained according to **general procedure E** using 3-chlorophenylmethanesulfonyl chloride. The expected compound was isolated as a white powder.

MS: 432.3

Mp: 115 °C – 125 °C

Example 62:

4-(3,5-Dichlorophenylmethanesulfonylamino)-pyridine-2-carboxylic acid benzylhydroxyamide hydrochloride



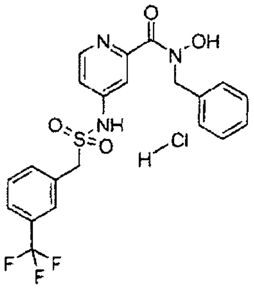
This compound was obtained according to **general procedure E** using 3,5-dichlorophenylmethanesulfonyl chloride. The expected compound was isolated as a white powder.

MS: 466.3

Mp: 189 °C – 194 °C

Example 63:

4-(3-Trifluoromethylphenylmethanesulfonylamino)-pyridine-2-carboxylic acid benzylhydroxyamide hydrochloride

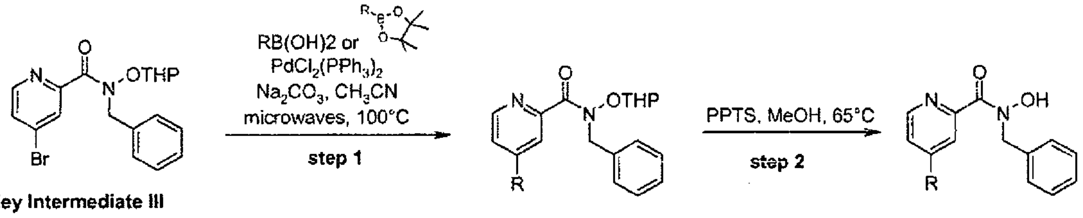


This compound was obtained according to **general procedure E** using 3-trifluoromethyl-phenylmethanesulfonyl chloride. The expected compound was isolated as a beige powder.

MS: 466.2

Mp: 178 °C – 182 °C

General procedure F



Step 1:

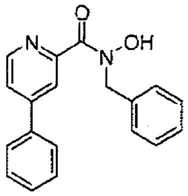
To a degassed solution of 4-bromo-pyridine-2-carboxylic acid benzyl-(tetrahydro-pyran-2-yloxy)-amide **(Key Intermediate III)** (150 mg, 0.4 mmol, 1 eq) in a mixture of acetonitrile (3 mL) and 1 M solution of sodium carbonate (3 mL) were added boronic acid (0.5 mmol, 1.3 eq) and trans-dichlorobis(triphenylphosphine)palladium (II) (13 mg, 0.02 mmol, 0.05 eq). The mixture was heated under microwave irradiation at 100 °C during 10 min. After cooling, the mixture was poured on water (5 mL) and extracted with ethyl acetate (3 x 10 mL). The organic layers were dried over magnesium sulfate, filtered and evaporated in vacuo. The crude residue was purified by flash chromatography to afford the expected compound.

Step 2:

The compound from step 1 (1 eq) was solubilized in methanol (10 mL) and pyridinium *p*-toluenesulfonate (1 eq) was added. The mixture was heated at 65 °C for 5 h and evaporated to dryness. The residue was triturated in water, filtered, rinsed with water and dried to afford the expected compound.

Example 64:

4-Phenyl-pyridine-2-carboxylic acid benzyl-hydroxy-amide



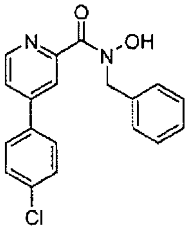
This compound was obtained according to **general procedure F** using phenylboronic acid. The expected compound was isolated as a pale rose powder.

MS: 304.9

Mp: 160 °C – 165 °C

Example 65:

4-(4-chloro-phenyl)-pyridine-2-carboxylic acid benzyl-hydroxy-amide



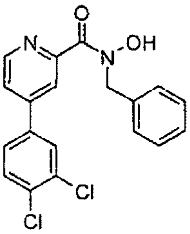
This compound was obtained according to **general procedure F** using 4-chlorophenyl-boronic acid. The expected compound was isolated as a white powder.

MS: 339.2

Mp: 190 °C – 195 °C

Example 66:

4-(3,4-Dichloro-phenyl)-pyridine-2-carboxylic acid benzyl-hydroxy-amide



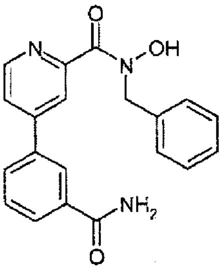
This compound was obtained according to **general procedure F** using 3,4-dichlorophenylboronic acid. The expected compound was isolated as a pale orange powder.

MS: 373.2

Mp: 125 °C – 130 °C

Example 67:

4-(3-Carbamoyl-phenyl)-pyridine-2-carboxylic acid benzyl-hydroxy-amide



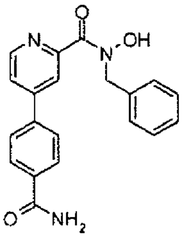
This compound was obtained according to **general procedure F** using 3-carbamoylphenylboronic acid. The expected compound was isolated as a beige powder.

MS: 348.1

Mp: 158 °C – 162 °C

Example 68:

4-(4-Carbamoyl-phenyl)-pyridine-2-carboxylic acid benzyl-hydroxy-amide



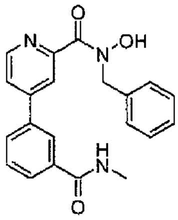
This compound was obtained according to **general procedure F** using 4-carbamoyl-phenylboronic acid. The expected compound was isolated as a pale yellow powder.

MS: 348.2

Mp: 155 °C – 160 °C

Example 69:

4-(3-Methylcarbamoyl-phenyl)-pyridine-2-carboxylic acid benzyl-hydroxy-amide

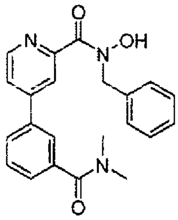


This compound was obtained according to **general procedure F** using 3-methylcarbamoyl-phenylboronic acid. The expected compound was isolated as a pale yellow foam.

MS: 362.2

Example 70:

4-(3-Dimethylcarbamoyl-phenyl)-pyridine-2-carboxylic acid benzyl-hydroxy-amide

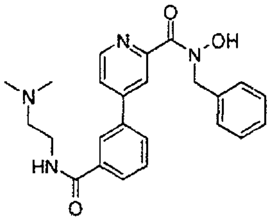


This compound was obtained according to **general procedure F** using 3-dimethyl-carbamoyl-phenylboronic acid. The expected compound was isolated as a yellow foam.

MS: 376.2

Example 71:

4-[3-(2-Dimethylamino-ethylcarbamoyl)-phenyl]-pyridine-2-carboxylic acid benzyl-hydroxy-amide



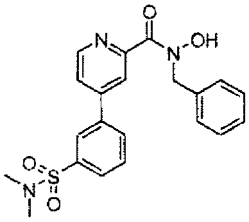
This compound was obtained according to **general procedure F** using 3-(2-(dimethylamino)ethylcarbamoyl)phenylboronic acid. The expected compound was isolated as a white foam.

MS: 419.3

Mp: 65 °C – 70 °C

Example 72:

4-(3-Dimethylsulfamoyl-phenyl)-pyridine-2-carboxylic acid benzyl-hydroxy-amide



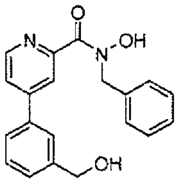
This compound was obtained according to **general procedure F** using 3-dimethylsulfamoyl-phenylboronic acid. The expected compound was isolated as a yellow powder.

MS: 412.2

Mp: 110 °C – 115 °C

Example 73:

4-(3-Hydroxymethyl-phenyl)-pyridine-2-carboxylic acid benzyl-hydroxy-amide



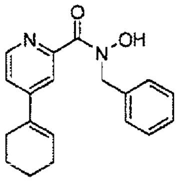
This compound was obtained according to **general procedure F** using 3-hydroxymethyl-phenylboronic acid. The expected compound was isolated as a white powder.

MS: 335.2

Mp: 150 °C – 155 °C

Example 74:

4-Cyclohex-1-enyl-pyridine-2-carboxylic acid benzylhydroxyamide



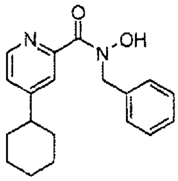
This compound was obtained according to **general procedure F** using cyclohexen-1-ylboronic acid, pinacol ester. The expected compound was isolated as a white powder.

MS: 309.2

Mp: 118 °C – 122 °C

Example 75:

4-Cyclohexylpyridine-2-carboxylic acid benzylhydroxy-amide



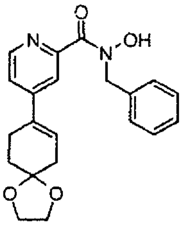
4-Cyclohex-1-enyl-pyridine-2-carboxylic acid benzylhydroxyamide (100 mg, 0.3 mmol, 1 eq) obtained in **example 74** was solubilized in ethanol (10 mL) and palladium 10% w on carbon was added. The mixture was stirred at room temperature over hydrogen atmosphere for 30 min. The mixture was then filtered over a short pad of celite, and rinsed with ethanol and dichloromethane. The crude residue was purified by flash chromatography using cyclohexane and ethyl acetate (100/0 to 70/30) to afford the expected compound as a white powder (72 mg, 72 % yield).

MS: 311.2

Mp: 106 °C – 110 °C

Example 76:

4-(1,4-Dioxa-spiro[4.5]dec-7-en-8-yl)-pyridine-2-carboxylic acid benzyl-hydroxy-amide

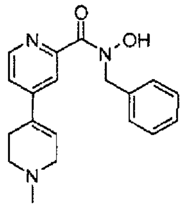


This compound was obtained according to **general procedure F** using 1,4-dioxa-spiro[4,5]dec-7-en-8-boronic acid, pinacol ester. The expected compound was isolated as a yellow foam.

MS: 367.2

Example 77:

1'-Methyl-1',2',3',6'-tetrahydro-[4,4']bipyridinyl-2-carboxylic acid benzyl-hydroxy-amide



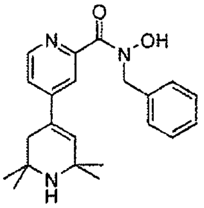
This compound was obtained according to **general procedure F** using 1-methyl-1,2,3,6-tetrahydropyridine-4-boronic acid pinacol ester. The expected compound was isolated as a light yellow powder.

MS: 324.2

Mp: 135 °C – 155 °C

Example 78:

2',2',6',6'-Tetramethyl-1',2',3',6'-tetrahydro-[4,4']bipyridinyl-2-carboxylic acid benzyl-hydroxy-amide

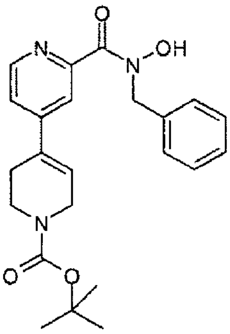


This compound was obtained according to **general procedure F** using 2,2,6,6-tetramethyl-1,2,3,6-tetrahydro-4-pyridineboronic acid pinacol ester. The expected compound was isolated as a yellow crystallized oil.

MS: 366.3

Example 79:

2'-(Benzyl-hydroxy-carbamoyl)-3,6-dihydro-2H-[4,4']bipyridinyl-1-carboxylic acid tert-butyl ester



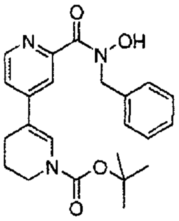
This compound was obtained according to **general procedure F** using N-Boc-1,2,3,6-tetrahydropyridine-4-boronic acid pinacol ester. The expected compound was isolated as a beige powder.

MS: 410.3

Mp: 125 °C

Example 80:

2'-(Benzyl-hydroxy-carbamoyl)-5,6-dihydro-4H-[3,4']bipyridinyl-1-carboxylic acid tert-butyl ester

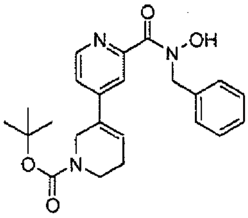


This compound was obtained according to **general procedure F** using 5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-3,4-dihydro-2H-pyridine-1-carboxylic acid tert-butyl ester **(Key Intermediate V)**. The expected compound was isolated as a yellow foam.

MS: 410.3

Example 81:

2'-(Benzylhydroxycarbamoyl)-5,6-dihydro-2H-[3,4']bipyridinyl-1-carboxylic acid tert-butyl ester



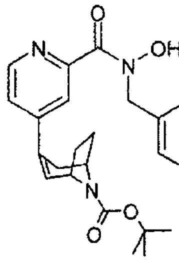
This compound was obtained according to **general procedure F** using 5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-3,6-dihydro-2H-pyridine-1-carboxylic acid tert-butyl ester **(Key Intermediate VI)**.. The expected compound was isolated as a yellow powder.

MS: 410.3

Mp: 128 °C – 134 °C

Example 82:

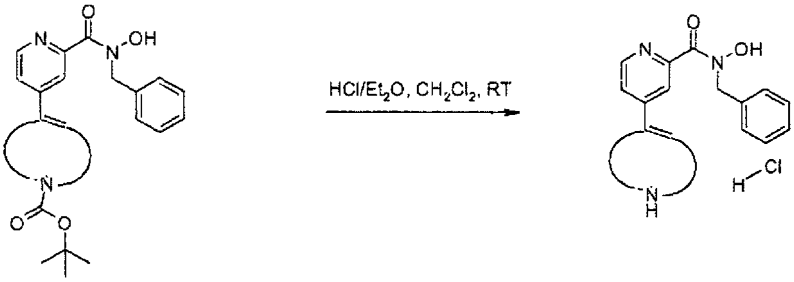
3-[2-(Benzylhydroxycarbamoyl)-pyridin-4-yl]-8-azabicyclo[3.2.1]oct-2-ene-8-carboxylic acid tertbutylester



This compound was obtained according to **general procedure F** using 8-boc-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-8-aza-bicyclo[3.2.1]oct-2-ene. The expected compound was isolated as a yellow oil.

MS: 436.3

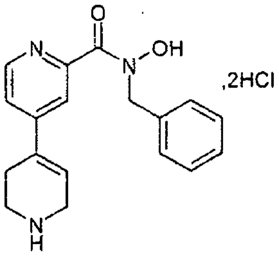
General procedure G



Compound obtained from **general procedure F** (1 eq) was solubilized in dichloromethane (10 mL) and a 2M solution of hydrochloric acid in diethyl ether (16 eq) was added drop wise. The mixture was stirred at room temperature for 2 h. The precipitate was filtered and triturated with dichloromethane and diethyl ether to afford the expected compound (60 % yield).

Example 83:

1',2',3',6'-Tetrahydro-[4,4']bipyridinyl-2-carboxylic acid benzyl-hydroxy-amide dihydrochloride



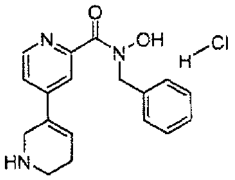
This compound was obtained according to **general procedure G** using 2'-(benzyl-hydroxy-carbamoyl)-3,6-dihydro-2H-[4,4']bipyridinyl-1-carboxylic acid tert-butyl ester described in **example 79**. The expected compound was isolated as a beige powder.

MS: 310.1

Mp: 140 °C – 150 °C

Example 84:

1,2,5,6-Tetrahydro-[3,4']bipyridinyl-2'-carboxylic acid benzylhydroxy-amide hydrochloride

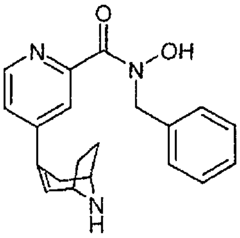


This compound was obtained according to **general procedure G** using 2'-(benzylhydroxy-carbamoyl)-5,6-dihydro-2H-[3,4']bipyridinyl-1-carboxylic acid tert-butyl ester described in **example 81**. The expected compound was isolated as a yellow crystallized oil.

MS: 310.2

Example 85:

4-(8-Azabicyclo[3.2.1]oct-2-en-3-yl)-pyridine-2-carboxylic acid benzylhydroxyamide

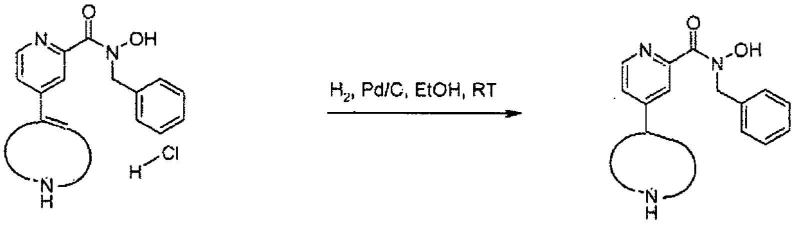


This compound was obtained according to **general procedure G** using 3-[2-(benzylhydroxycarbamoyl)-pyridin-4-yl]-8-azabicyclo[3.2.1]oct-2-ene-8-carboxylic acid tertbutylester described in **example 82**. The expected compound was isolated as a yellow powder.

MS: 336.1

Mp: 95 °C – 100 °C

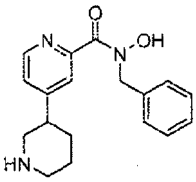
General procedure H



The compound obtained from **general procedure G** (1 eq) was solubilized in ethanol (10 mL) and palladium 10% w on carbon was added. The mixture was stirred at room temperature over hydrogen atmosphere for 30 min. The mixture was then filtered over a short pad of celite and the crude residue was purified by flash chromatography using ethyl acetate and methanol (100/0 to 80/20) to afford the expected compound.

Example 86:

1,2,3,4,5,6-Hexahydro-[3,4']bipyridinyl-2'-carboxylic acid benzylhydroxyamide

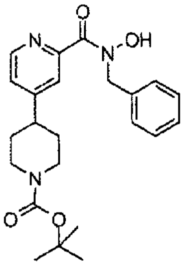


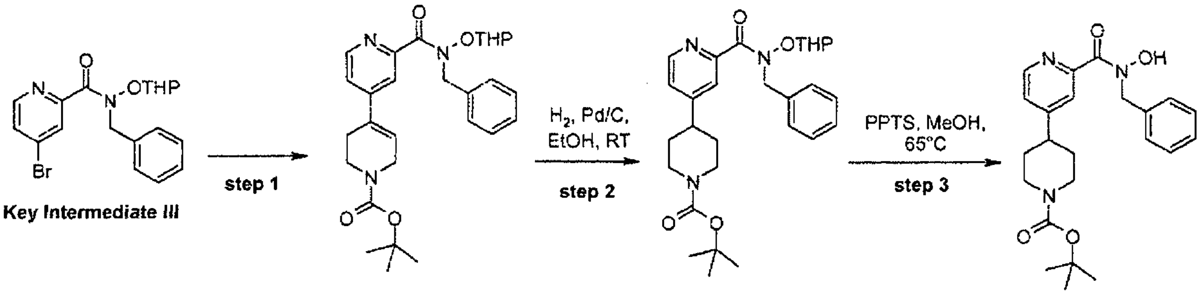
This compound was obtained according to **general procedure H** using 1,2,5,6-tetrahydro-[3,4']bipyridinyl-2'-carboxylic acid benzylhydroxy-amide hydrochloride described in **example 84**. The expected compound was isolated as a yellow crystallized oil.

MS: 312.2

Example 87:

2'-(Benzyl-hydroxy-carbamoyl)-3,4,5,6-tetrahydro-2H-[4,4']bipyridinyl-1-carboxylic acid tert-butyl ester





Step 1:

This compound was obtained according to **general procedure F, step 1** starting from **Key Intermediate III** and N-Boc-1,2,3,6-tetrahydropyridine-4-boronic acid pinacol ester.

Step 2:

The compound from step 1 (485 mg, 1 mmol, 1 eq) was solubilized in ethanol (20 mL) and palladium 10% w on carbon was added. The mixture was stirred at room temperature over hydrogen atmosphere for 1.5 h. The mixture was then filtered over a short pad of celite and the crude residue was purified by flash chromatography using cyclohexane and ethyl acetate (100/0 to 40/60) to afford 2'-[benzyl-(tetrahydro-pyran-2-yloxy)-carbamoyl]-3,4,5,6-tetrahydro-2H-[4,4']bipyridinyl-1-carboxylic acid tert-butyl ester as a colorless oil (320 mg, 66 % yield).

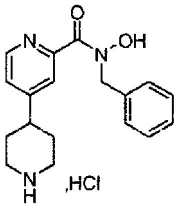
Step 3:

The compound from step 2 (360 mg, 0.6 mmol, 1 eq) was solubilized in methanol (20 mL) and pyridinium *p*-toluenesulfonate (182 mg, 0.6 mmol, 1 eq) was added. The mixture was heated at 65 °C for 18 h and evaporated to dryness. Ethyl acetate (10 mL) was added and the organic layer was washed with a saturated solution of sodium bicarbonate (3 x 10 mL), dried over magnesium sulfate, filtered and evaporated in vacuo. The crude residue was purified by flash chromatography using cyclohexane and ethyl acetate (80/20 to 30/70) to afford the expected compound as an orange oil (230 mg, 77 % yield).

MS: 412.3

Example 88:

1',2',3',4',5',6'-Hexahydro-[4,4']bipyridinyl-2-carboxylic acid benzyl-hydroxy-amide hydrochloride

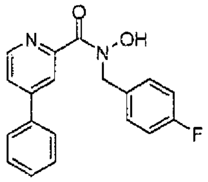


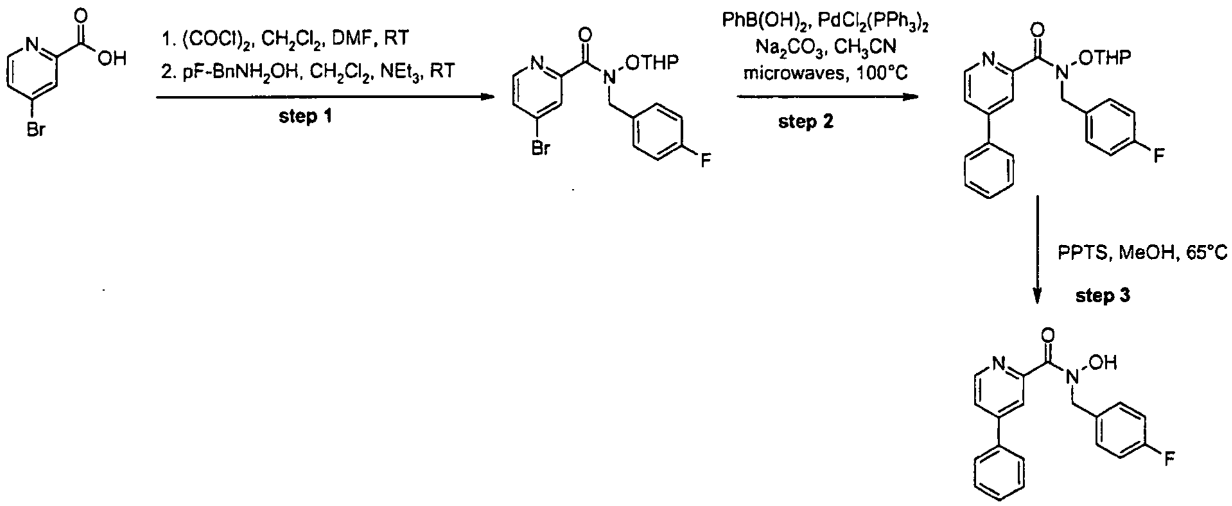
This compound was obtained according to **general procedure G** using 2'-(benzyl-hydroxy-carbamoyl)-3,4,5,6-tetrahydro-2H-[4,4']bipyridinyl-1-carboxylic acid tert-butyl ester described in **example 87**. The expected compound was isolated as a white foam.

MS: 312.1

Example 89:

4-Phenyl-pyridine-2-carboxylic acid(4-fluoro-benzyl)-hydroxy-amide





Step 1:

Oxalyl chloride (0.2 mL, 2.1 mmol, 1.3 eq) was added to a solution of 4-bromo-pyridine-2-carboxylic acid (334 mg, 1.6 mmol, 1 eq) in dichloromethane (15 mL). The solution was cooled down to 0 °C and dimethylformamide (several drops) was added drop wise. The mixture was stirred at room temperature for 30 min and was evaporated to dryness. The residue was diluted in dichloromethane (15 mL) and N-(4-fluoro-benzyl)-O-(tetrahydro-pyran-2-yl)-hydroxylamine (560 mg, 2.5 mmol, 1.5 eq) was added. Triethylamine (0.7 mL, 4.9 mmol, 3 eq) was added drop wise at 0 °C and the mixture was stirred at room temperature for 18 h and absorbed on silica gel to be purified by flash chromatography using cyclohexane and ethyl acetate (100/0 to 70/30) to afford 4-bromo-pyridine-2-carboxylic acid (4-fluoro-benzyl)-(tetrahydro-pyran-2-yloxy)-amide as a colorless oil (230 mg, 34 % yield).

Step 2:

To a degassed solution of 4-bromo-pyridine-2-carboxylic acid (4-fluoro-benzyl)-(tetrahydro-pyran-2-yloxy)-amide (230 mg, 0.6 mmol, 1 eq) in a mixture of acetonitrile (4 mL) and 1 M solution of sodium carbonate (4 mL) were added phenylboronic acid (89 mg, 0.7 mmol, 1.3 eq) and trans-dichlorobis(triphenylphosphine)palladium (20 mg, 0.03 mmol, 0.05 eq). The mixture was heated under microwave irradiation at 100 °C during 10 min. After cooling, the mixture was poured on water (5 mL) and extracted with ethyl acetate (3 x 10 mL). The organic layers were dried over magnesium sulfate, filtered and evaporated in vacuo. The crude residue was purified by flash chromatography using cyclohexane and ethyl acetate (100/0 to 50/50) to afford 4-phenyl-pyridine-2-carboxylic acid (4-fluoro-benzyl)-(tetrahydro-pyran-2-yloxy)-amide as a colorless oil (130 mg, 57 % yield).

Step 3:

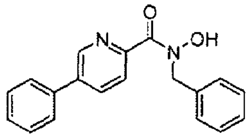
4-Phenyl-pyridine-2-carboxylic acid (4-fluoro-benzyl)-(tetrahydro-pyran-2-yloxy)-amide (130 mg, 0.3 mmol, 1 eq) was solubilized in methanol (5 mL) and pyridinium *p*-toluenesulfonate (97 mg, 0.4 mmol, 1.2 eq) was added. The mixture was heated at 65 °C for 5 h. The precipitate obtained was filtered and washed with a minimum of methanol to afford the expected compound as a white powder (13 mg, 13 % yield).

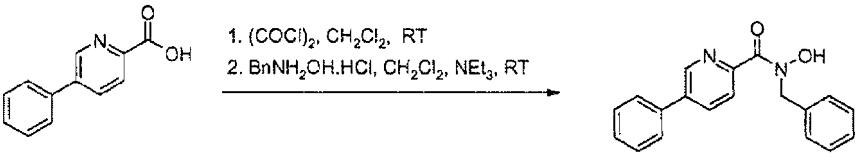
MS: 323.1

Mp: 135 °C – 140 °C

Example 90:

5-Phenyl-pyridine-2-carboxylic acid benzyl-hydroxy-amide





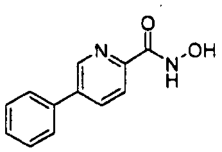
At 0 °C, oxalyl chloride (0.2 mL, 2.3 mmol, 1.5 eq) was added to a solution of 5-phenyl-pyridine-2-carboxylic acid (300 mg, 1.5 mmol, 1 eq) in dichloromethane (10 mL). The mixture was stirred at room temperature for 30 min and was evaporated to dryness. The residue was diluted in dichloromethane (10 mL) and N-benzyl-hydroxylamine hydrochloride (361 mg, 2.3 mmol, 1.5 eq) and triethylamine (0.6 mL, 4.5 mmol, 3 eq) were added. The mixture was stirred at room temperature for 18 h and absorbed on silica gel to be purified by flash chromatography using cyclohexane and ethyl acetate (100/0 to 0/100) to afford the expected compound as a beige powder (60 mg, 13 % yield).

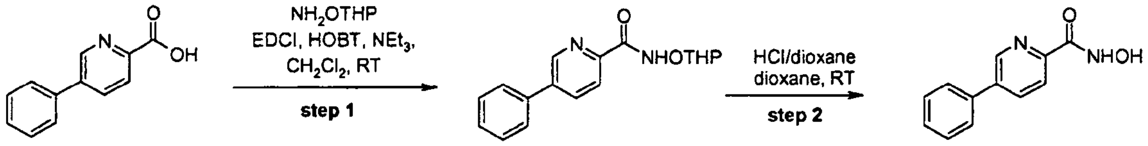
MS: 305.2

Mp: 145 °C – 150 °C

Example 91:

5-Phenyl-pyridine-2-carboxylic acid hydroxyamide





Step 1:

To a solution of 5-phenyl-pyridine-2-carboxylic acid (130 mg, 0.6 mmol, 1 eq) in dichloromethane (6 mL) were added HOBT (176 mg, 1.3 mmol, 2 eq), EDCI (249 mg, 1.3 mmol, 2 eq), triethylamine (0.3 mL, 1.8 mmol, 3 eq) and O-(tetrahydro-pyran-2-yl)-hydroxylamine (153 mg, 1.3 mmol, 2 eq). The mixture was stirred at room temperature for 18 h and absorbed on silica gel to be purified by flash chromatography using cyclohexane and ethyl acetate (100/0 to 50/50) to afford 5-phenyl-pyridine-2-carboxylic acid (tetrahydro-pyran-2-yloxy)-amide as a colorless oil (160 mg, 83 % yield).

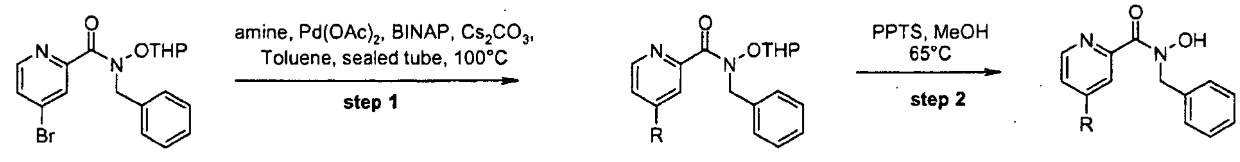
Step 2:

To a solution of 5-phenyl-pyridine-2-carboxylic acid (tetrahydro-pyran-2-yloxy)-amide (160 mg, 0.54 mmol, 1 eq) in dioxane (5 mL) was added a 4 N solution on hydrogen chloride in dioxane (0.5 mL). The mixture was stirred at room temperature for 1 h and evaporated to dryness. The residue was diluted in methanol (5 mL) and ammonia 7 N in methanol (0.5 mL) was added. The mixture was evaporated and the residue was triturated in water to afford the expected compound as a pale rose powder (90 mg, 78 % yield).

MS: 215.1

Mp: 175 °C – 180 °C

General procedure I



Key Intermediate III

Step 1:

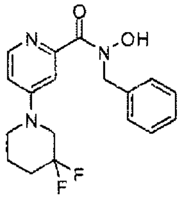
To a degassed solution of 4-bromo-pyridine-2-carboxylic acid benzyl-(tetrahydro-pyran-2-yloxy)-amide (**Key Intermediate III**) (500 mg, 1.3 mmol, 1 eq) in toluene (10 mL) were added cesium carbonate (1.3 g, 3.8 mmol, 3 eq), amine (1.66 mmol, 1.3 eq), BINAP (40 mg, 0.06 mmol, 0.05 eq) and palladium acetate (15 mg, 0.06 mmol, 0.05 eq). The mixture was heated in a sealed tube at 100 °C during 20 h. After cooling, the mixture was poured on water (10 mL) and extracted with ethyl acetate (3 x 10 mL). The organic layers were dried over magnesium sulfate, filtered and evaporated in vacuo. The crude residue was purified by flash chromatography to afford the expected compound.

Step 2:

The compound from step 1 (1 eq) was solubilized in methanol (10 mL) and pyridinium *p*-toluenesulfonate (1 eq) was added. The mixture was heated at 65 °C for 20 h. After cooling, a 7 N solution of ammonia in methanol (10 mL) was added and the mixture was evaporated to dryness. The residue was diluted in dichloromethane (10 mL) and the organic layer was washed with water (3 x 10 mL), dried over magnesium sulfate, filtered and evaporated in vacuo. The crude compound was purified by flash chromatography to afford the expected compound.

Example 92:

3,3-Difluoro-3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-2'-carboxylic acid benzyl-hydroxy-amide



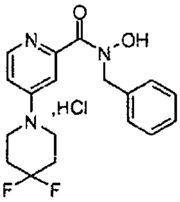
This compound was obtained according to **general procedure I** using 3,3-difluoro-piperidine hydrochloride. The expected compound was isolated as a pale yellow powder.

MS: 348.1

Mp: 140 °C – 145 °C

Example 93:

4,4-Difluoro-3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-2'-carboxylic acid benzyl-hydroxy-amide



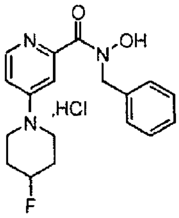
This compound was obtained according to **general procedure I** using 4,4-difluoropiperidine hydrochloride followed by addition of 2 M solution of hydrogen chloride in diethyl ether. After stirring 2 h at room temperature, filtration and trituration with diethyl ether, the expected compound was isolated as a white powder.

MS: 348.2

Mp: 90 °C – 95 °C

Example 94:

4-Fluoro-3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-2'-carboxylic acid benzyl-hydroxy-amide hydrochloride

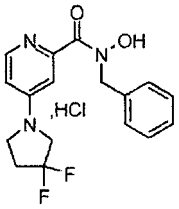


This compound was obtained according to a modified version of **general procedure I** using 4-fluoropiperidine hydrochloride. During step 2, instead of using pyridinium *p*-toluenesulfonate, 2 M solution of hydrogen chloride in diethyl ether (20 eq) was added and the mixture was stirred at room temperature for 2 h. The precipitate was then filtered and triturated with dichloromethane and diethyl ether to afford the expected compound as a light yellow foam.

MS: 330.1

Example 95:

4-(3,3-Difluoro-pyrrolidin-1-yl)-pyridine-2-carboxylic acid benzyl-hydroxy-amide hydrochloride



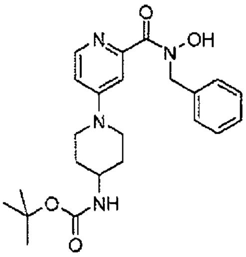
This compound was obtained according to a modified version of **general procedure I** using 3,3-difluoropyrrolidine hydrochloride. During step 2, instead of using pyridinium *p*-toluenesulfonate, 2 M solution of hydrogen chloride in diethyl ether (20 eq) was added and the mixture was stirred at room temperature for 2 h. The precipitate was then filtered and triturated with dichloromethane and diethyl ether to afford the expected compound as a beige powder.

MS: 334.1

Mp: 162 °C – 166 °C

Example 96:

[2'-(Benzyl-hydroxy-carbamoyl)-3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-yl]-carbamic acid tert-butyl ester



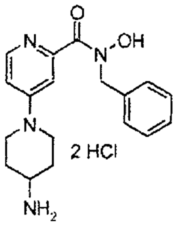
This compound was obtained according to **general procedure I** using 4-N-BOC-aminopiperidine. The expected compound was isolated as a white foam.

MS: 427.3

Mp: 135 °C – 140 °C

Example 97:

4-Amino-3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-2'-carboxylic acid benzyl-hydroxy-amide chlorhydrate



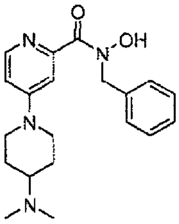
This compound was obtained according to **general procedure G** using [2'-(benzyl-hydroxy-carbamoyl)-3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-yl]-carbamic acid tert-butyl ester described in **example 96**. The expected compound was isolated as a white powder.

MS: 327.2

Mp: decomposes at 160 °C – 165 °C

Example 98:

4-Dimethylamino-3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-2'-carboxylic acid benzyl-hydroxy-amide

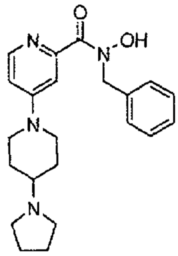


This compound was obtained according to **general procedure I** using dimethyl-piperidin-4-yl-amine. The expected compound was isolated as a yellow oil.

MS: 355.2

Example 99:

4-Pyrrolidin-1-yl-3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-2'-carboxylic acid benzyl-hydroxy-amide



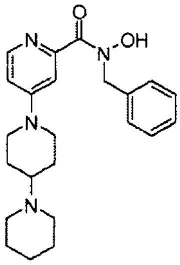
This compound was obtained according to **general procedure I** using 4-(1-pyrrolidinyl)piperidine. The expected compound was isolated as a pale yellow powder.

MS: 381.2

Mp: 135 °C – 140 °C

Example 100:

3,4,5,6,3',4',5',6'-Octahydro-2H,2'H-[1,4';1',4"]terpyridine-2"-carboxylic acid benzyl-hydroxy-amide

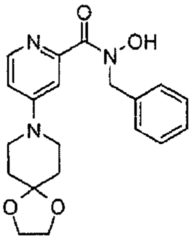


This compound was obtained according to **general procedure I** using 4 N-(4-piperidino)piperidine. The expected compound was isolated as a blue oil.

MS: 395.2

Example 101:

4-(1,4-Dioxa-8-aza-spiro[4.5]dec-8-yl)-pyridine-2-carboxylic acid benzyl-hydroxy-amide



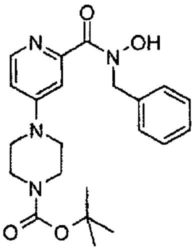
This compound was obtained according to **general procedure I** using 1,4-dioxa-8-azaspiro[4.5]decane. The expected compound was isolated as a yellow powder.

MS: 370.2

Mp: 98 °C – 102 °C

Example 102:

4-[2-(Benzyl-hydroxy-carbamoyl)-pyridin-4-yl]-piperazine-1-carboxylic acid tert-butyl ester

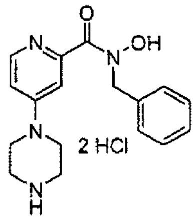


This compound was obtained according to **general procedure I** using N-BOC piperazine. The expected compound was isolated as a yellow foam.

MS: 413.3

Example 103:

4-Piperazin-1-yl-pyridine-2-carboxylic acid benzyl-hydroxy-amide hydrochloride

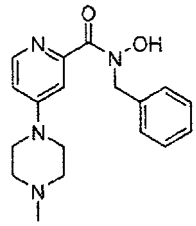


This compound was obtained according to **general procedure G** using 4-[2-(benzyl-hydroxy-carbamoyl)-pyridin-4-yl]-piperazine-1-carboxylic acid tert-butyl ester described in **example 102**. The expected compound was isolated as a yellow foam.

MS: 313.2

Example 104:

4-(4-Methyl-piperazin-1-yl)-pyridine-2-carboxylic acid benzyl-hydroxy-amide

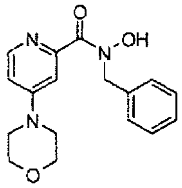


This compound was obtained according to **general procedure I** using N-methyl piperazine. The expected compound was isolated as a yellow oil.

MS: 327.2

Example 105:

4-Morpholin-4-yl-pyridine-2-carboxylic acid benzyl-hydroxy-amide



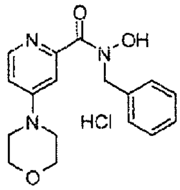
This compound was obtained according to **general procedure I** using morpholine. The expected compound was isolated as a pale yellow powder.

MS: 314.1

Mp: 105 °C – 110 °C

Example 106:

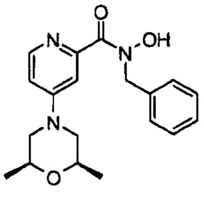
4-Morpholin-4-yl-pyridine-2-carboxylic acid benzyl-hydroxy-amide hydrochloride



4-Morpholin-4-yl-pyridine-2-carboxylic acid benzyl-hydroxy-amide described in **example 105** was solubilized in dichloromethane (10 mL) and 2 M solution of hydrogen chloride in diethyl ether (1.2 eq) was added. The mixture was stirred at room for 3 h and evaporated to dryness to afford the expected compound as a pale yellow powder.

Example 107:

4-((2R,6S)-2,6-Dimethyl-morpholin-4-yl)-pyridine-2-carboxylic acid benzyl-hydroxy-amide



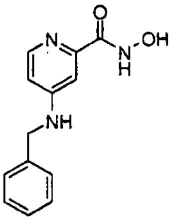
This compound was obtained according to **general procedure I** using (2R,6S)-2,6-dimethyl-morpholine. The expected compound was isolated as an orange powder.

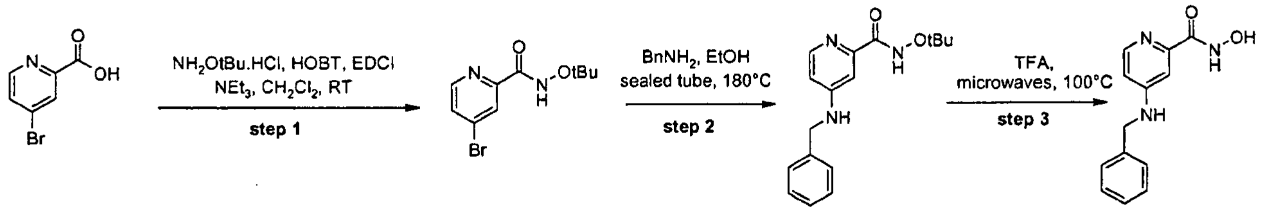
MS: 342.2

Mp: 180 °C – 185 °C

Example 108:

4-Benzylamino-pyridine-2-carboxylic acid hydroxyamide





Step 1:

To a solution of 4-bromo-pyridine-2-carboxylic acid (1.0 g, 4.9 mmol, 1 eq) in dichloromethane (40 mL) were added HOBT (1.3 g, 9.9 mmol, 2 eq), EDCI (1.9 g, 9.9 mmol, 2 eq), triethylamine (2.1 mL, 14.8 mmol, 3 eq) and O-tert-butylhydroxylamine hydrochloride (1.2 g, 9.9 mmol, 2 eq). The mixture was stirred at room temperature for 18 h and poured on water (20 mL). The organic layer was extracted with dichloromethane (3 x 20 mL), dried over magnesium sulfate, filtered and evaporated in vacuo. The crude residue was purified by flash chromatography using cyclohexane and ethyl acetate (100/0 to 50/50) to afford 4-bromo-pyridine-2-carboxylic acid tert-butoxy-amide as a white powder (1.0 g, 74 % yield).

Step 2:

In a sealed tube, 4-bromo-pyridine-2-carboxylic acid tert-butoxy-amide (410 mg, 1.5 mmol, 1 eq) was solubilized in ethanol (10 mL) and benzylamine (161 mg, 3 mmol, 2 eq) was added. The mixture was heated at 180 °C for 20 h. After cooling, the mixture was absorbed on silica gel to be purified by flash chromatography using cyclohexane and ethyl acetate (100/0 to 0/100) to afford 4-benzylamino-pyridine-2-carboxylic acid tert-butoxy-amide as a colorless oil (57 mg, 13 % yield).

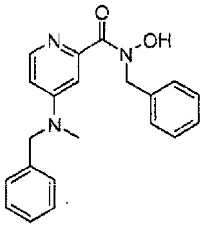
Step 3:

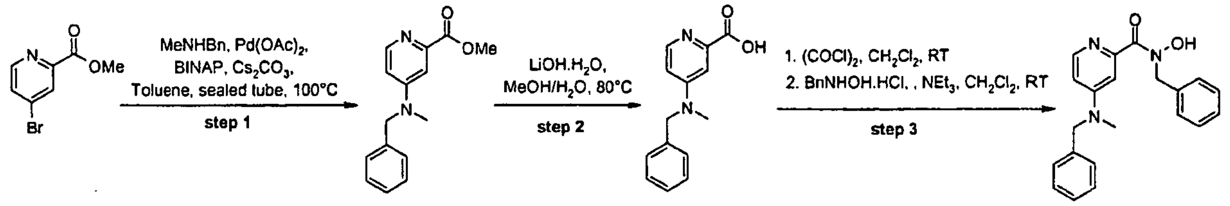
4-Benzylamino-pyridine-2-carboxylic acid tert-butoxy-amide (57 mg, 0.19 mmol, 1 eq) and trifluoroacetic acid (3 mL) were heated under microwave irradiation at 100 °C during 10 min. After cooling, the mixture was evaporated to dryness. The residue was solubilized in dichloromethane (5 mL) and some drops of ammonium hydroxide solution were added. The mixture was absorbed on silica gel to be purified by flash chromatography using dichloromethane and methanol (100/0 to 85/15) to afford the expected compound as a colorless oil (15 mg, 32 % yield).

MS: 244.1

Example 109:

4-(Benzyl-methyl-amino)-pyridine-2-carboxylic acid benzyl-hydroxy-amide





Step 1:

To a degassed solution of 4-bromo-pyridine-2-carboxylic acid methyl ester (650 mg, 3.0 mmol, 1 eq) in toluene (15 mL) were added cesium carbonate (1.9 g, 6.0 mmol, 2 eq), N-methylbenzylamine (0.5 mL, 3.9 mmol, 1.3 eq), BINAP (93 mg, 0.15 mmol, 0.05 eq) and palladium acetate (34 mg, 0.15 mmol, 0.05 eq). The mixture was heated in a sealed tube at 100 °C during 20 h. After cooling, the mixture was poured on water (10 mL) and extracted with ethyl acetate (3 x 10 mL). The organic layers were dried over magnesium sulfate, filtered and evaporated in vacuo. The crude residue was purified by flash chromatography using dichloromethane and methanol (100/0 to 97/3) to afford 4-(benzyl-methyl-amino)-pyridine-2-carboxylic acid methyl ester as a yellow oil (230 mg, 30 % yield).

Step 2:

4-(Benzyl-methyl-amino)-pyridine-2-carboxylic acid methyl ester (230 mg, 0.9 mmol, 1 eq) was solubilized in a mixture methanol / water (6 mL / 1 mL) and lithium hydroxide (75 mg, 1.8 mmol, 2 eq) was added. The mixture was heated at 80 °C during 3 h. After cooling down, a 1 M solution of hydrogen chloride in diethyl ether (1.8 mL, 1.8 mmol, 2 eq) was added. The mixture was then evaporated to dryness to afford 4-(benzyl-methyl-amino)-pyridine-2-carboxylic acid in quantitative yield.

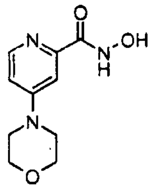
Step 3:

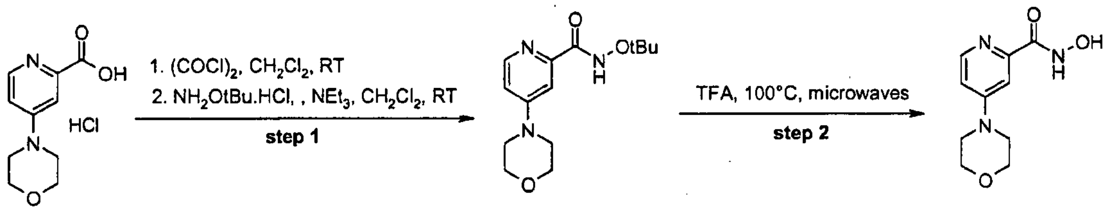
Oxalyl chloride (0.12 mL, 1.3 mmol, 1.5 eq) was added drop wise to a solution of 4-(benzyl-methyl-amino)-pyridine-2-carboxylic acid (0.9 mmol, 1 eq) in dichloromethane (10 mL). The mixture was stirred at room temperature for 15 min and was evaporated to dryness. The residue was diluted in dichloromethane (10 mL) and triethylamine (0.38 mL, 2.7 mmol, 3 eq) and N-benzylhydroxylamine hydrochloride (215 mg, 1.3 mmol, 1.5 eq) were added. After stirring at room temperature for 20 h, the mixture was absorbed on silica gel to be purified using cyclohexane and ethyl acetate (100/0 to 40/60). The expected compound was obtained as a yellow oil (85 mg, 27 % yield).

MS: 348.2

Example 110:

4-Morpholin-4-yl-pyridine-2-carboxylic acid hydroxyamide





Step 1:

Oxalyl chloride (0.11 mL, 1.3 mmol, 1.3 eq) was added drop wise to a solution of 4-morpholin-4-yl-pyridine-2-carboxylic acid hydrochloride (240 mg, 1.0 mmol, 1 eq) in dichloromethane (10 mL). At 0 °C, dimethylformamide (2-3 drops) was added drop wise and the mixture was stirred at room temperature for 15 min and was evaporated to dryness. The residue was diluted in dichloromethane (10 mL) and triethylamine (0.41 mL, 2.9 mmol, 3 eq) and O-tert-butylhydroxylamine hydrochloride (185 mg, 1.5 mmol, 1.5 eq) were added. After stirring at room temperature for 20 h, the mixture was absorbed on silica gel to be purified using cyclohexane and ethyl acetate (100/0 to 0/100). 4-Morpholin-4-yl-pyridine-2-carboxylic acid tert-butoxy-amide was obtained as a white powder (110 mg, 40 % yield).

Step 2:

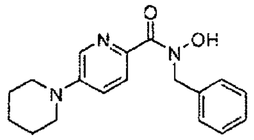
4-Morpholin-4-yl-pyridine-2-carboxylic acid tert-butoxy-amide (110 mg, 0.4 mmol, 1 eq) and trifluoroacetic acid (3 mL) were heated under microwave irradiation at 100 °C during 10 min. After cooling, the mixture was evaporated to dryness. The residue was solubilized in dichloromethane (5 mL) and some drops of ammonium hydroxide solution were added. The mixture was absorbed on silica gel to be purified by flash chromatography using dichloromethane and methanol (100/0 to 90/10) to afford the expected compound as a beige powder (12 mg, 14 % yield).

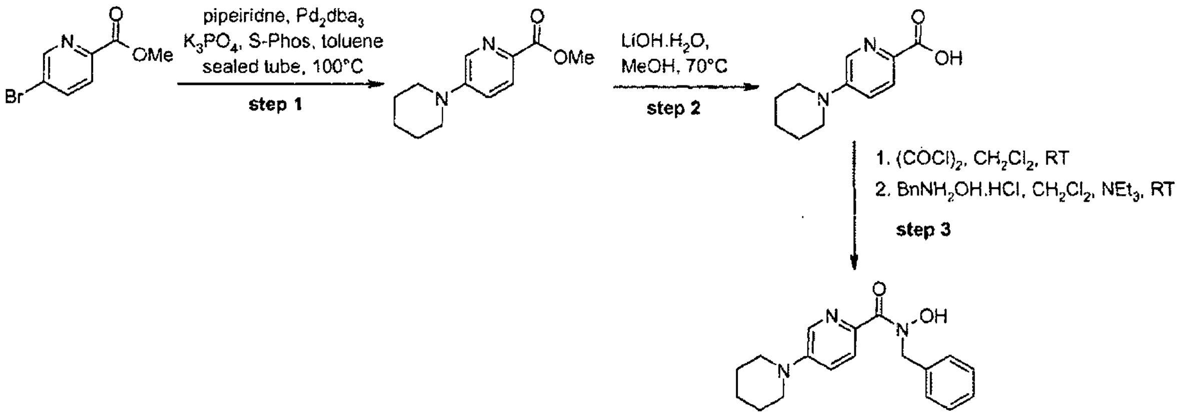
MS: 224.1

Mp: 215 °C – 220 °C (dec.)

Example 111:

3,4,5,6-Tetrahydro-2H-[1,3']bipyridinyl-6'-carboxylic acid benzyl-hydroxy-amide





Step 1:

To a degassed solution of 5-bromo-pyridine-2-carboxylic acid methyl ester (450 mg, 2.1 mmol, 1 eq) in toluene (10 mL) were added piperidine (213 mg, 2.5 mmol, 1.2 eq), potassium phosphate (618 mg, 2.9 mmol, 1.4 eq), 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (171 mg, 0.42 mmol, 0.2 eq) and tris(dibenzylideneacetone)dipalladium (95 mg, 0.10 mmol, 0.05 eq). The mixture was heated in a sealed tube at 100 °C during 48 h. After cooling, the mixture was poured on water (5 mL) and extracted with ethyl acetate (3 x 10 mL). The organic layers were dried over magnesium sulfate, filtered and evaporated in vacuo. The crude residue was purified by flash chromatography using cyclohexane and ethyl acetate (100/0 to 0/100) to afford 3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-6'-carboxylic acid methyl ester as a pale yellow powder (165 mg, 36 % yield).

Step 2:

3,4,5,6-Tetrahydro-2H-[1,3']bipyridinyl-6'-carboxylic acid methyl ester (165 mg, 0.75 mmol, 1 eq) was solubilized in methanol (8 mL) and lithium hydroxide (63 mg, 1.5 mmol, 2 eq) was added. The mixture was heated at 70 °C during 20 h. After cooling, a 3 N solution of hydrogen chloride (0.2 mL) was added. The mixture was then evaporated to dryness to afford 3,4,5,6-tTetrahydro-2H-[1,3']bipyridinyl-6'-carboxylic acid as a yellow oil in quantitative yield.

<u>Step 3:</u>

Oxalyl chloride (0.1 mL, 1.12 mmol, 1.5 eq) was added drop wise to a solution of 3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-6'-carboxylic acid (0.75 mmol, 1 eq) in dichloromethane (6 mL). The mixture was stirred at room temperature for 15 min and was evaporated to dryness. The residue was diluted in dichloromethane (6 mL) and triethylamine (0.31 mL, 2.25 mmol, 3 eq) and N-benzylhydroxylamine hydrochloride (179 mg, 1.12 mmol, 1.5 eq) were added. After stirring at room temperature for 20 h, the mixture was absorbed on silica gel to be purified using cyclohexane and ethyl acetate (100/0 to 30/70). The expected compound was obtained as a pale yellow powder (125 mg, 54 % yield).

MS: 312.2

Mp: 110 °C – 115 °C

Activity data for the compounds having the general formula (I)

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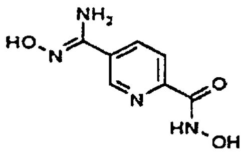
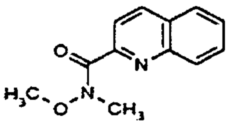
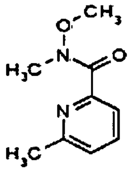
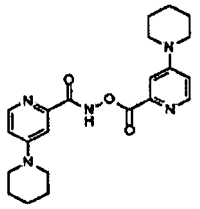
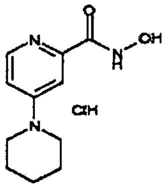
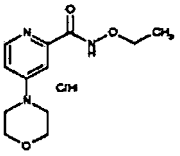
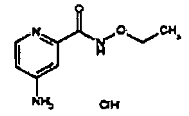
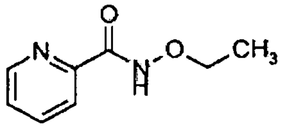
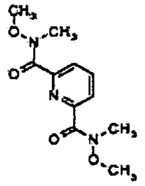
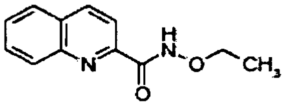
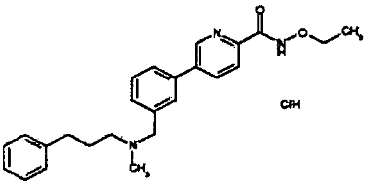
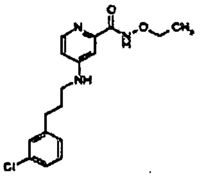
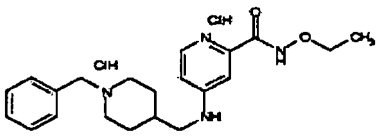
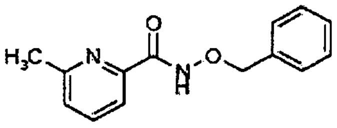
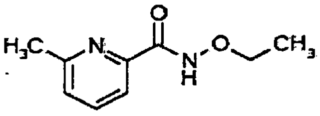
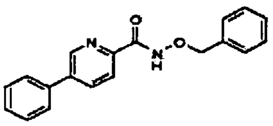
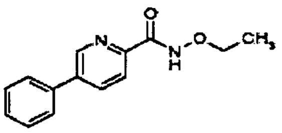
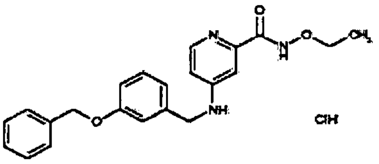
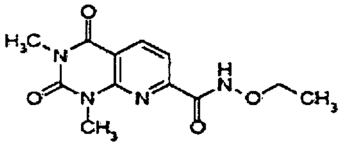
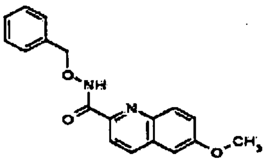
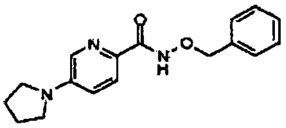
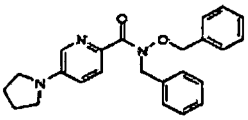
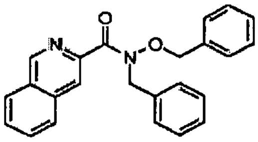
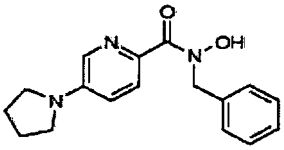
	FRET	IC50 [µM]		20
	CPE H3N2	reduction (%)	50	-4,8
	FRET	IC50 [µM]		
	CPE H3N2	reduction (%)	50	-1,2
	CPE H3N2	reduction (%)	50	-0,9
	CPE H3N2	reduction (%)	50	29
	CPE H3N2	IC50 [µM]		37
	FRET	IC50 [µM]		4,9
	CPE H3N2	reduction (%)	5	-4,1
	FRET	IC50 [µM]		
	CPE H3N2	reduction (%)	50	1,3

Molstructure	activity type	activity endpoint	activity conc	activity result
	CPE H3N2	reduction (%)	50	10,5
	CPE H3N2	reduction (%)	50	12,5
	CPE H3N2	reduction (%)	50	-0,3
	CPE H3N2	reduction (%)	50	-2,2
	CPE H3N2	reduction (%)	20	1,6
	CPE H3N2	reduction (%)	1	-0,3

Molstructure	activity type	activity endpoint	activity conc	activity result
	CPE H3N2	reduction (%)	50	14,8
	CPE H3N2	reduction (%)	50	-2,7
	CPE H3N2	reduction (%)	50	-2,1
	CPE H3N2	reduction (%)	2	-4
	CPE H3N2	reduction (%)	5	-3
	CPE H3N2	reduction (%)	1	1,2
	CPE H3N2	reduction (%)	50	-0,4
	CPE H3N2	reduction (%)	50	-1,9

Molstructure	activity type	activity endpoint	activity conc	activity result
	CPE H3N2	reduction (%)	20	-8,7
	CPE H3N2	reduction (%)	5	-2,7
	CPE H3N2	reduction (%)	5	1,3
	CPE H3N2	reduction (%)	25	1
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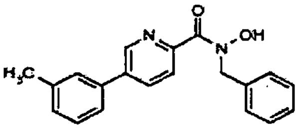
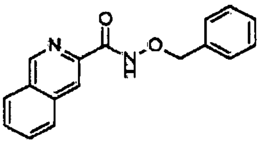
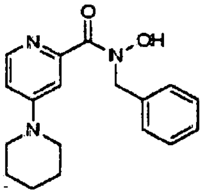
	CPE H3N2	reduction (%)	10	15,5
	CPE H3N2	reduction (%)	5	-1,5
	CPE H3N2	reduction (%)	5	1,1
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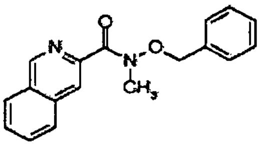
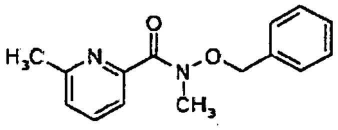
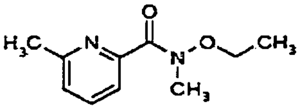
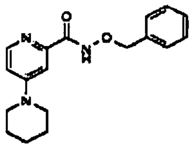
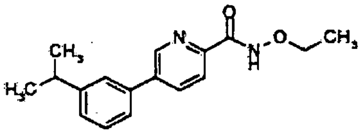
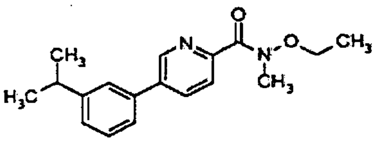
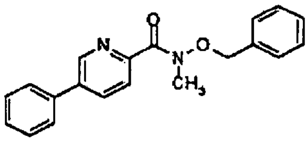
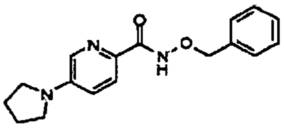
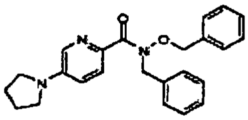
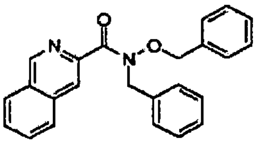
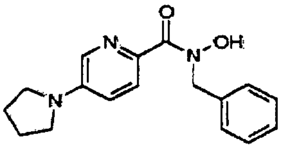
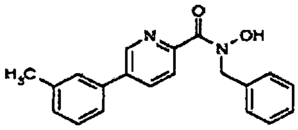
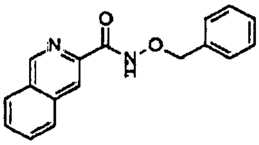
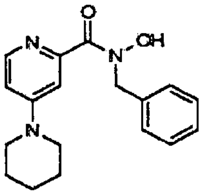
	CPE H3N2	reduction (%)	50	0,6

Molstructure	activity type	activity endpoint	activity conc	activity result
	CPE H3N2	reduction (%)	50	-2,3
	CPE H3N2	reduction (%)	50	-1,9
	CPE H3N2	reduction (%)	5	1
	CPE H3N2	reduction (%)	5	
	CPE H3N2	reduction (%)	5	
	CPE H3N2	reduction (%)	50	-2,6

Molstructure	activity type	activity endpoint	activity conc	activity result
	CPE H3N2	reduction (%)	20	-8,7
	CPE H3N2	reduction (%)	5	-2,7
	CPE H3N2	reduction (%)	5	1,3
	CPE H3N2	reduction (%)	25	1
	FRET	IC50 [µM]		4,3
	CPE H3N2	reduction (%)	10	15,5
	CPE H3N2	reduction (%)	5	-1,5
	CPE H3N2	reduction (%)	5	1,1
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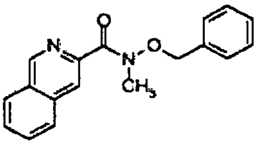
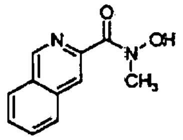
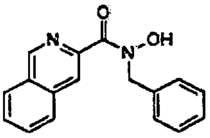
	CPE H3N2	reduction (%)	50	0,6

Molstructure	activity type	activity endpoint	activity conc	activity result
	CPE H3N2	reduction (%)	50	-0,6
	FRET	IC50 [µM]		9,09
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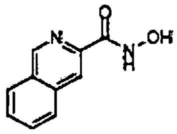	FRET	IC50 [µM]		14,7
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	FRET	IC50 [µM]		16
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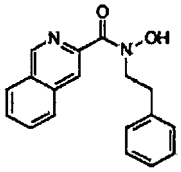
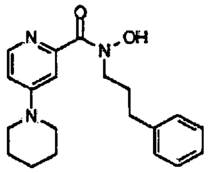
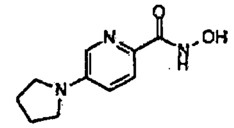
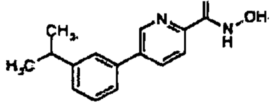
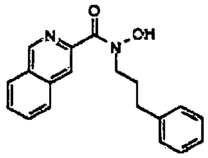
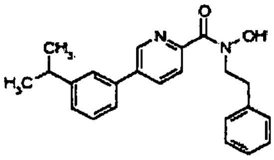
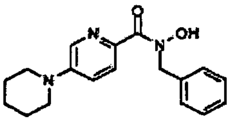
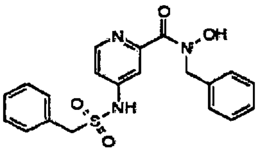
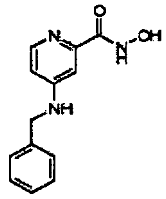
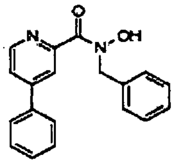
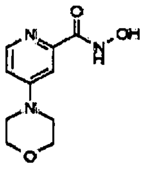
	CPE H3N2	reduction (%)	20	-1,8
	CPE H3N2	reduction (%)	2	7,7
	FRET	IC50 [µM]		6,25
	CPE H3N2	reduction (%)	50	-4,3
	FRET	IC50 [µM]		5,4
	CPE H3N2	reduction (%)	2	-2,1

Molstructure	activity type	activity endpoint	activity conc	activity result
	CPE H3N2	reduction (%)	2	4,4
	CPE H3N2	reduction (%)	2	2,1
	FRET	IC50 [µM]		9,4
	CPE H3N2	reduction (%)	5	-3,4
	FRET	IC50 [µM]		10,1
	FRET	IC50 [µM]		1,7
	CPE H3N2	reduction (%)	50	6,2
	FRET	IC50 [µM]		3,9
	FRET	IC50 [µM]		6,4
	CPE H3N2	reduction (%)	5	-0,5
	FRET	IC50 [µM]		3,1
	CPE H3N2	reduction (%)	10	-9,3
	FRET	IC50 [µM]		5,94
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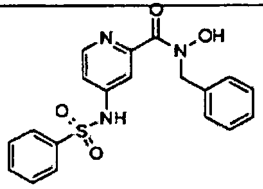
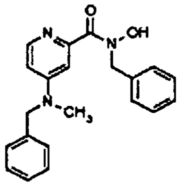
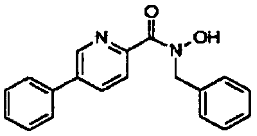
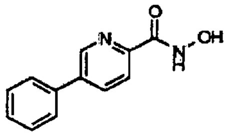
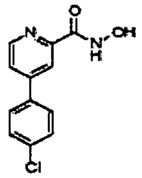
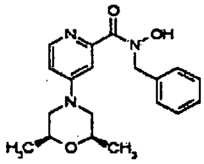
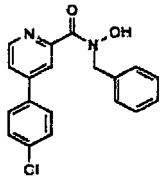
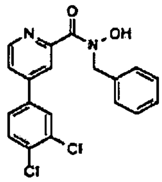
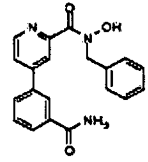
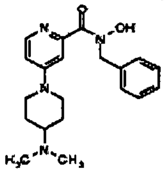
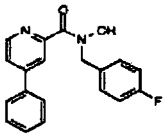
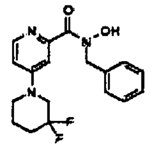
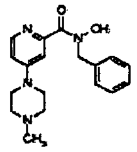
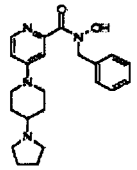
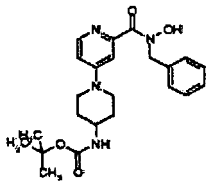
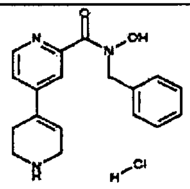
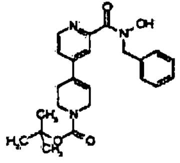
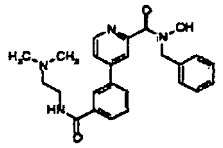
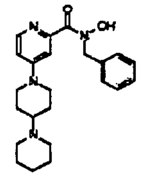
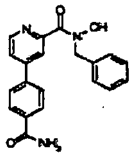
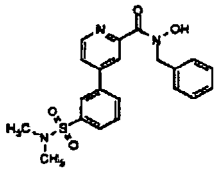
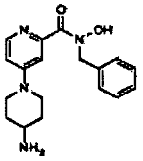
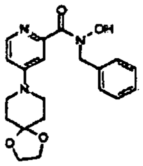
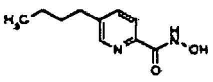
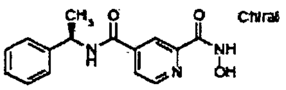
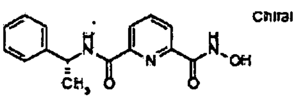
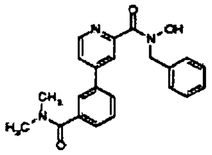
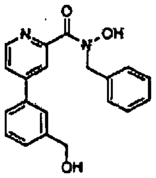
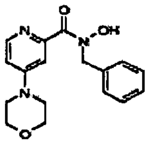
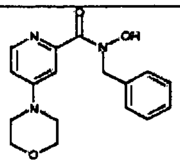
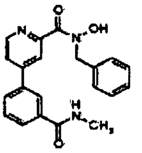
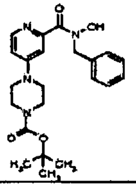
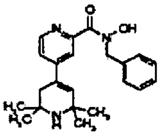
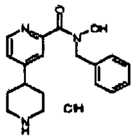
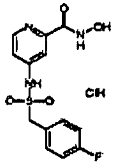
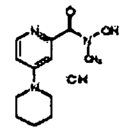
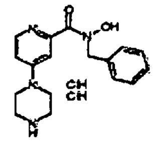
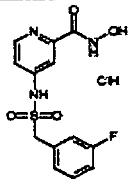
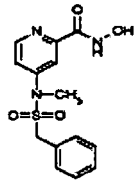
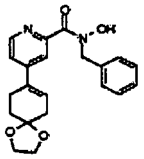
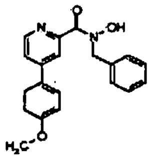
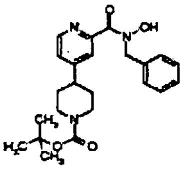
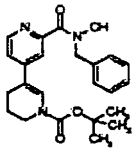
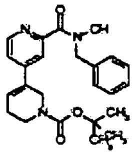
	CPE H3N2	reduction (%)	50	-7,1

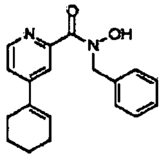
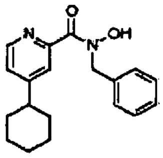
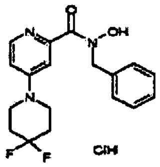
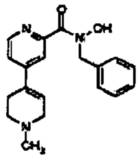
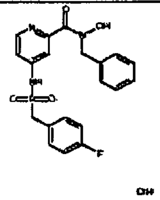
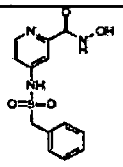
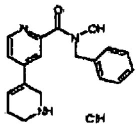
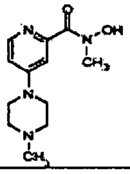
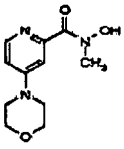
Molstructure	activity type	activity endpoint	activity conc	activity result
	FRET	IC50 [µM]		10
	CPE H3N2	reduction (%)	50	-5,2
	FRET	IC50 [µM]		1,2
	CPE H3N2	reduction (%)	5	3,8
	CPE H3N2	reduction (%)	12	13,4
	FRET	IC50 [µM]		22
	CPE H3N2	reduction (%)	12	21,7
	FRET	IC50 [µM]		2,6
	CPE H3N2	reduction (%)	5	26,6
	FRET	IC50 [µM]		2,9
	CPE H3N2	reduction (%)	50	10,5
	FRET	IC50 [µM]		1,2
	CPE H3N2	reduction (%)	2	-6,7
	FRET	IC50 [µM]		0,91
	CPE H3N2	reduction (%)	5	8,1

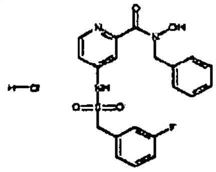
Molstructure	activity type	activity endpoint	activity conc	activity result
	FRET	IC50 [µM]		2
	CPE H3N2	reduction (%)	5	-2,7
	FRET	IC50 [µM]		32
	CPE H3N2	reduction (%)	50	12,3
	FRET	IC50 [µM]		0,6
	CPE H3N2	reduction (%)	1	-3,2
	FRET	IC50 [µM]		1,2
	CPE H3N2	reduction (%)	50	8,9
	FRET	IC50 [µM]		4,6
	CPE H3N2	reduction (%)	50	2,4
	CPE H3N2	reduction (%)	50	10,7
	CPE H3N2	reduction (%)	50	8,3
	FRET	IC50 [µM]		0,33
	CPE H3N2	reduction (%)	50	0,4
	CPE H3N2	reduction (%)	5	1,2

Molstructure	activity type	activity endpoint	activity conc	activity result
	FRET	IC50 [µM]		3,2
	CPE H3N2	reduction (%)	50	8,9
	CPE H3N2	reduction (%)	50	18,8
	FRET	IC50 [µM]		1
	CPE H3N2	reduction (%)	5	-2,5
	FRET	IC50 [µM]		5,8
	CPE H3N2	reduction (%)	5	-1,8
	FRET	IC50 [µM]		38
	CPE H3N2	reduction (%)	50	3,2
	FRET	IC50 [µM]		0,51
	CPE H3N2	reduction (%)	50	9,5
	FRET	IC50 [µM]		15
	FRET	IC50 [µM]		13
	FRET	IC50 [µM]		121

Molstructure	activity type	activity endpoint	activity conc	activity result
	CPE H3N2	reduction (%)	50	5,3
	CPE H3N2	reduction (%)	5	7,7
	FRET	IC50 [µM]		2,6
	CPE H3N2	reduction (%)	50	-3,4
	FRET	IC50 [µM]		2,3
	CPE H3N2	reduction (%)	50	6,3
ClH	FRET	IC50 [µM]		1,9
	CPE H3N2	reduction (%)	5	-7,5
	FRET	IC50 [µM]		3,2
	CPE H3N2	reduction (%)	50	34
	CPE H3N2	reduction (%)	50	2,8
	FRET	IC50 [µM]		2,3
	CPE H3N2	reduction (%)	50	-1,4
	FRET	IC50 [µM]		0,73
	CPE H3N2	reduction (%)	50	-1,4

Molstructure	activity type	activity endpoint	activity conc	activity result
	CPE H3N2	reduction (%)	50	-0,9
	FRET	IC50 [µM]		3,5
	CPE H3N2	reduction (%)	50	-4,5
	FRET	IC50 [µM]		0,67
	CPE H3N2	reduction (%)	50	-2,4
	FRET	IC50 [µM]		32
	CPE H3N2	reduction (%)	5	-1,7
	FRET	IC50 [µM]		2
	CPE H3N2	reduction (%)	50	5,4
	FRET	IC50 [µM]		2,4
	CPE H3N2	reduction (%)	2	-2,5
	CPE H3N2	reduction (%)	20	31,3
	CPE H3N2	reduction (%)	2	3,9
	CPE H3N2	reduction (%)	5	10,2

Molstructure	activity type	activity endpoint	activity conc	activity result
	FRET	IC50 [µM]		3,6
	CPE H3N2	reduction (%)	1	3,4
	FRET	IC50 [µM]		3
	CPE H3N2	reduction (%)	5	-0,5
	FRET	IC50 [µM]		2,9
	CPE H3N2	reduction (%)	50	-3,2
	FRET	IC50 [µM]		7,7
	CPE H3N2	reduction (%)	50	10,6
	FRET	IC50 [µM]		2
	CPE H3N2	reduction (%)	50	-1,1
	FRET	IC50 [µM]		3
	CPE H3N2	reduction (%)	50	5,1
	CPE H3N2	reduction (%)	50	9,5
	CPE H3N2	reduction (%)	50	2,6
	CPE H3N2	reduction (%)	50	5,7

Molstructure	activity type	activity endpoint	activity conc	activity result
	FRET	IC50 [µM]		1,9
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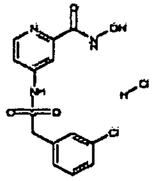
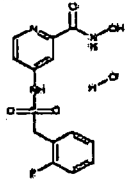
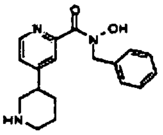
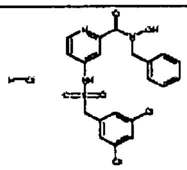
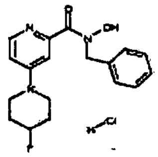
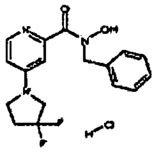
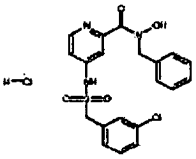
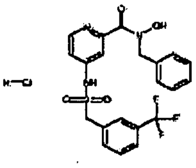
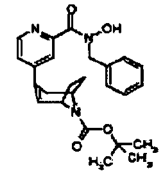
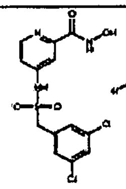
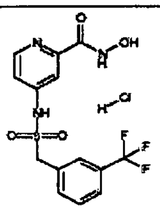
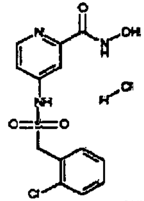
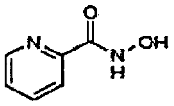
	FRET	IC50 [µM]		0,2
	CPE H3N2	reduction (%)	50	5,9
	FRET	IC50 [µM]		0,78
	CPE H3N2	reduction (%)	50	-0,5
	CPE H3N2	reduction (%)	50	6,1
	FRET	IC50 [µM]		0,4
	CPE H3N2	reduction (%)	20	26,9
	FRET	IC50 [µM]		2,2
	CPE H3N2	reduction (%)	50	34
	FRET	IC50 [µM]		1,8
	CPE H3N2	reduction (%)	20	4,6
	FRET	IC50 [µM]		0,33
	CPE H3N2	reduction (%)	50	9,5
	FRET	IC50 [µM]		2
	CPE H3N2	reduction (%)	50	22,4

Molstructure	activity type	activity endpoint	activity conc	activity result
	CPE H3N2	reduction (%)	2	-5.3
	FRET	IC50 [µM]		0.58
	CPE H3N2	reduction (%)	50	9.3
	FRET	IC50 [µM]		1.8
	CPE H3N2	reduction (%)	50	-5.6
	FRET	IC50 [µM]		0.83
	CPE H3N2	reduction (%)	50	1.5
	FRET	IC50 [µM]		75
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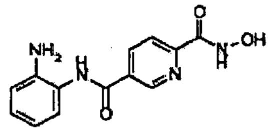
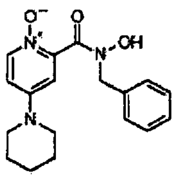
	CPE H3N2	reduction (%)	50	-5.53
	FRET	IC50 [µM]		23
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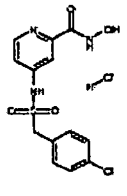
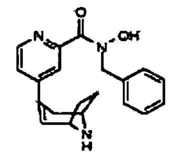
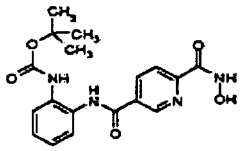
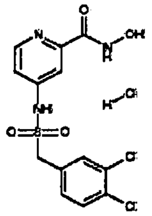
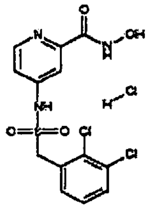
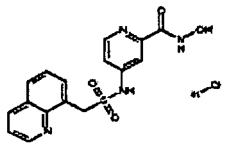
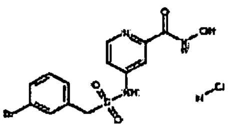
	FRET	IC50 [µM]		1.1
	CPE H3N2	reduction (%)	50	-3.98

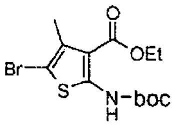
Molstructure	activity type	activity endpoint	activity conc	activity result
	FRET	IC50 [µM]		3,5
	CPE H3N2	reduction (%)	50	5,49
	FRET	IC50 [µM]		
	FRET	IC50 [µM]		3,2
	CPE H3N2	reduction (%)	50	53,43
	FRET	IC50 [µM]		2
	CPE H3N2	IC50 [µM]		
	CPE H3N2	reduction (%)	50	60,07
	CPE H3N2	reduction (%)	50	24,39
	CPE H3N2	IC50 [µM]		78
	FRET	IC50 [µM]		0,28
	CPE H3N2	reduction (%)	50	2,29
	FRET	IC50 [µM]		1,8

Compounds having the general formula (II)

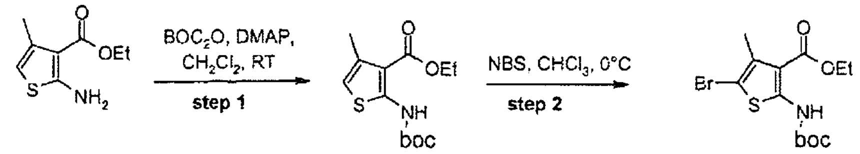
5

Key Intermediate I

5-Bromo-2-tert-butoxycarbonylamino-4-methyl-thiophene-3-carboxylic acid ethyl ester



Key Intermediate I



Step 1:

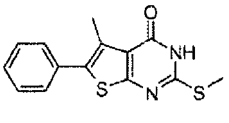
To a solution of 2-amino-4-methyl-thiophene-3-carboxylic acid ethyl ester (25.0 g, 135 mmol, 1 eq) in dichloromethane (80 mL) were added di-tert-butyl dicarbonate (48.0 g, 220 mmol, 1.6 eq) and 4-dimethylaminopyridine (1.6 g, 13.5 mmol, 0.1 eq). The mixture was stirred at room temperature until completion of the reaction. The solvent was then evaporated and the residue was purified by flash chromatography using cyclohexane and ethyl acetate (100/0 to 90/10) to afford 2-tert-butoxycarbonylamino-4-methyl-thiophene-3-carboxylic acid ethyl ester as a white solid (18.8 g, 49% yield).

Step 2:

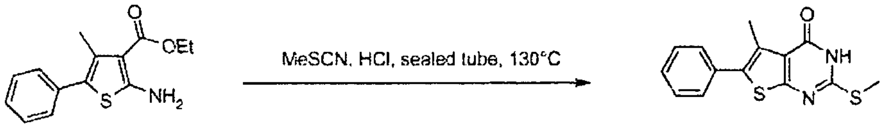
At 0 °C, to a solution of 2-tert-butoxycarbonylamino-4-methyl-thiophene-3-carboxylic acid ethyl ester (10.2 g, 35.9 mmol, 1 eq) in chloroform (40 mL) was added N-bromosuccinimide (6.4 g, 35.9 mmol, 1 eq). The mixture was stirred at 0 °C during 2 h and the solvent was evaporated. The residue was purified by flash chromatography using cyclohexane and ethyl acetate (100/0 to 70/30) to afford the expected compound as a white solid (11.9 g, 91% yield).

Key Intermediate II

5-Methyl-2-methylsulfanyl-6-phenyl-3H-thieno[2,3-d]pyrimidin-4-one



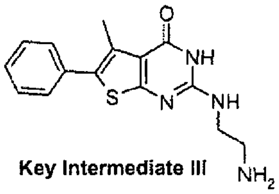
Key Intermediate II



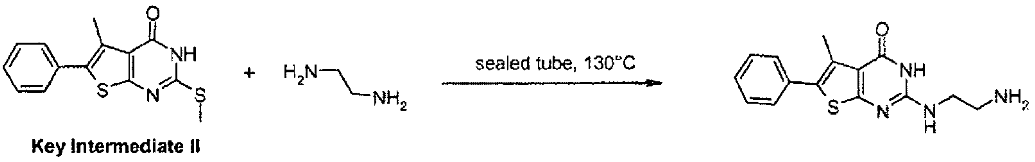
2-Amino-4-methyl-5-phenyl-thiophene-3-carboxylic acid ethyl ester (10.0 g, 38.3 mmol, 1 eq), methyl thiocyanate (2.8 g, 38.3 mmol, 1 eq) and concentrated hydrochloric acid (1.4 mL, 38.3 mmol, 1 eq) were heated in a sealed tube at 130 °C during 18 h. After cooling, the precipitate was filtered, rinsed with ethanol and dried to afford the expected compound as a yellow solid (7.7 g, 70% yield).

Key Intermediate III

2-(2-Amino-ethylamino)-5-methyl-6-phenyl-3H-thieno[2,3-d]pyrimidin-4-one

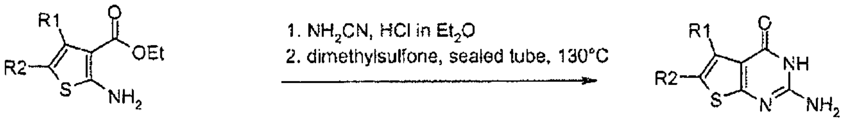


Key Intermediate III



5-Methyl-2-methylsulfanyl-6-phenyl-3H-thieno[2,3-d]pyrimidin-4-one (**Key Intermediate II**) (1.2 g, 4.2 mmol, 1 eq) was solubilized in ethylenediamine (3 mL) and the solution was heated in a sealed tube at 130 °C during 18 h. After cooling down, the yellow suspension was filtered. The precipitate was rinsed with dichloromethane and diethyl ether and dried in vacuo to afford the expected compound as a white powder (550 mg, 44 % yield).

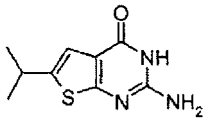
General Procedure A



At 0 °C, cyanamide (1.0 mmol, 1.5 eq) was added to a 2M solution of hydrogen chloride in diethyl ether (1.0 mL, 3 eq). After stirring for 15 min, the suspension was filtered. The resulting white solid was added in a sealed tube to 2-amino-thiophene-3-carboxylic acid ethyl ester (0.7 mmol, 1 eq) and dimethylsulfone (250 mg). The mixture was heated at 130 °C during 2 h. After cooling, the residue was dissolved in methanol and a 7N solution of ammonia in methanol (10 mL) was added. The solvent was then evaporated and the solid obtained was washed with dichloromethane (2 x 10 mL) and water (2 x 10 mL) to afford the expected compound (5% to 90% yield).

Example 1:

2-Amino-6-isopropyl-3H-thieno[2,3-d]pyrimidin-4-one



The expected compound was obtained according to **general procedure A** using commercially available 2-amino-5-isopropyl-thiophene-3-carboxylic acid methyl ester.

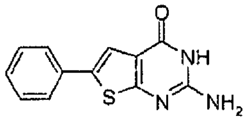
The expected compound was isolated as a beige powder.

MS: 210.0

Mp: 347 °C – 349 °C

Example 2:

2-Amino-6-phenyl-3H-thieno[2,3-d]pyrimidin-4-one



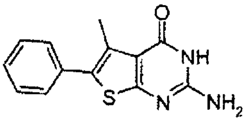
The expected compound was obtained according to **general procedure A** using commercially available 2-amino-5-phenyl-thiophene-3-carboxylic acid methyl ester. The expected compound was isolated as a grey solid.

MS: 244.0

Mp >360 °C

Example 3:

2-Amino-5-methyl-6-phenyl-3H-thieno[2,3-d]pyrimidin-4-one



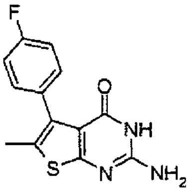
The expected compound was obtained according to **general procedure A** using commercially available 2-amino-4-methyl-5-phenyl-thiophene-3-carboxylic acid ethyl ester. The expected compound was isolated as a beige powder.

MS: 258.1

Mp: 356 °C – 358 °C

Example 4:

2-Amino-5-(4-fluoro-phenyl)-6-methyl-3H-thieno[2,3-d]pyrimidin-4-one



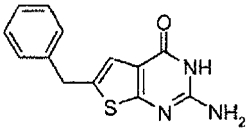
The expected compound was obtained according to **general procedure A** using commercially available 2-amino-4-(4-fluoro-phenyl)-5-methyl-thiophene-3-carboxylic acid methyl ester. The expected compound was isolated as a grey solid.

MS: 276.1

Mp: 360 °C – 362 °C

Example 5:

2-Amino-6-benzyl-3H-thieno[2,3-d]pyrimidin-4-one



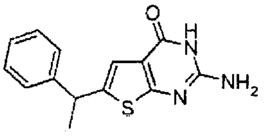
The expected compound was obtained according to **general procedure A** using commercially available 2-amino-5-benzyl-thiophene-3-carboxylic acid ethyl ester. The expected compound was isolated as a green solid.

MS: 258.1

Mp: 294 °C – 296 °C

Example 6:

2-Amino-6-(1-phenyl-ethyl)-3H-thieno[2,3-d]pyrimidin-4-one



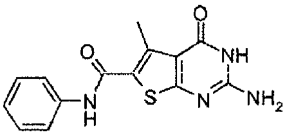
The expected compound was obtained according to **general procedure A** using commercially available 2-amino-5-(1-phenyl-ethyl)-thiophene-3-carboxylic acid methyl ester. The expected compound was isolated as a grey powder.

MS: 272.0

Mp: 260 °C – 270 °C

Example 7:

2-Amino-5-methyl-4-oxo-3,4-dihydro-thieno[2,3-d]pyrimidine-6-carboxylic acid phenylamide

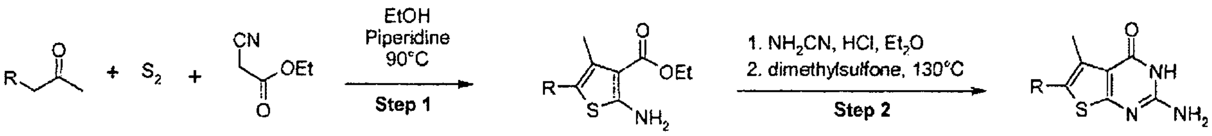


The expected compound was obtained according to **general procedure A** using commercially available 2-amino-4-methyl-5-phenylcarbamoyl-thiophene-3-carboxylic acid ethyl ester. The expected compound was isolated as a yellow powder.

MS: 301.0

Mp: decomposes at 290 °C – 296 °C

General Procedure B



Step 1:

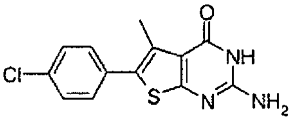
Propan-2-one (28.0 mmol, 1 eq), sulfur (900 mg, 28.0 mmol, 1 eq), ethyl cyanoacetate (3.0 mL, 28.0 mmol, 1 eq) and a catalytic amount of piperidine were put in suspension in ethanol (15 mL) and were heated in a sealed tube at 90 °C during 18 h. The reaction mixture was then evaporated and the crude residue was purified by flash chromatography using cyclohexane and ethyl acetate (100/0 to 0/100) to afford 2-amino-thiophene-3-carboxylic acid ethyl ester (6% to 95% yield).

Step 2:

At 0 °C, cyanamide (1.0 mmol, 1.5 eq) was added to a 2M solution of hydrogen chloride in diethyl ether (1.0 mL, 3 eq). After stirring for 15 min, the suspension was filtered. The resulting white solid was added in a sealed tube to 2-amino-thiophene-3-carboxylic acid ethyl ester obtained in step 1 (0.7 mmol, 1 eq) and dimethylsulfone (250 mg). The mixture was heated at 130 °C during 2 h. After cooling, the residue was dissolved in methanol and a 7N solution of ammonia in methanol (10 mL) was added. The solvent was then evaporated and the solid obtained was washed with dichloromethane (2 x 10 mL) and water (2 x 10 mL) to afford the expected compound (5% to 90% yield).

Example 8:

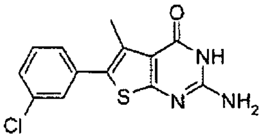
2-Amino-6-(4-chloro-phenyl)-5-methyl-3H-thieno[2,3-d]pyrimidin-4-one



The expected compound was obtained according to **general procedure B** using 1-(4-chloro-phenyl)-propan-2-one. The expected compound was isolated as a grey powder.
MS: 292.0
Mp: decomposes at 351 °C

Example 9:

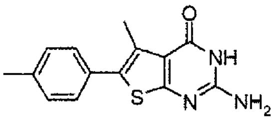
2-Amino-6-(3-chloro-phenyl)-5-methyl-3H-thieno[2,3-d]pyrimidin-4-one



The expected compound was obtained according to **general procedure B** using 1-(3-chloro-phenyl)-propan-2-one. The expected compound was isolated as a white powder.
MS: 292.1
Mp: decomposes at 265 °C

Example 10:

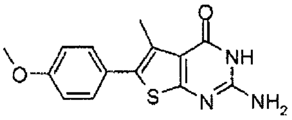
2-Amino-5-methyl-6-p-tolyl-3H-thieno[2,3-d]pyrimidin-4-one



The expected compound was obtained according to **general procedure B** using 1-p-tolyl-propan-2-one. The expected compound was isolated as a white powder.
MS: 272.1
Mp: decomposes at 330 °C

Example 11:

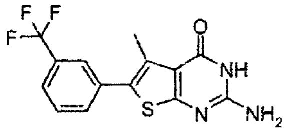
2-Amino-6-(4-methoxy-phenyl)-5-methyl-3H-thieno[2,3-d]pyrimidin-4-one



The expected compound was obtained according to **general procedure B** using 1-(4-methoxy-phenyl)-propan-2-one. The expected compound was isolated as a white powder.
MS: 288.1
Mp: decomposes at 311 °C

Example 12:

2-Amino-5-methyl-6-(3-trifluoromethyl-phenyl)-3H-thieno[2,3-d]pyrimidin-4-one



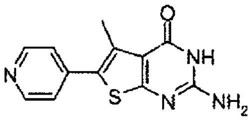
The expected compound was obtained according to **general procedure B** using 1-(3-trifluoromethyl-phenyl)-propan-2-one. The expected compound was isolated as a white powder.

MS: 326.1

Mp: decomposes at 345 °C

Example 13:

2-Amino-5-methyl-6-pyridin-4-yl-3H-thieno[2,3-d]pyrimidin-4-one



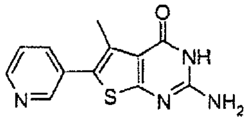
The expected compound was obtained according to **general procedure B** using 1-pyridin-4-yl-propan-2-one. The expected compound was isolated as a yellow powder.

MS: 259.1

Mp: decomposes at 355 °C

Example 14:

2-Amino-5-methyl-6-pyridin-3-yl-3H-thieno[2,3-d]pyrimidin-4-one



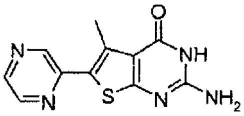
The expected compound was obtained according to **general procedure B** using 1-pyridin-3-yl-propan-2-one. The expected compound was isolated as a yellow powder.

MS: 259.0

Mp: 280 °C – 290 °C

Example 15:

2-Amino-5-methyl-6-pyrazin-2-yl-3H-thieno[2,3-d]pyrimidin-4-one



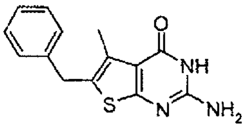
The expected compound was obtained according to **general procedure B** using 1-pyrazin-2-yl-propan-2-one. The expected compound was isolated as an orange powder.

MS: 260.0

Mp: 280 °C – 300 °C

Example 16:

2-Amino-6-benzyl-5-methyl-3H-thieno[2,3-d]pyrimidin-4-one



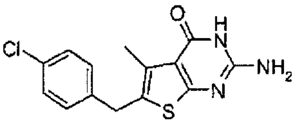
The expected compound was obtained according to **general procedure B** using 4-phenyl-butan-2-one. The expected compound was isolated as a white powder.

MS: 272.1

Mp: 292 °C – 294 °C

Example 17:

2-Amino-6-(4-chloro-benzyl)-5-methyl-3H-thieno[2,3-d]pyrimidin-4-one

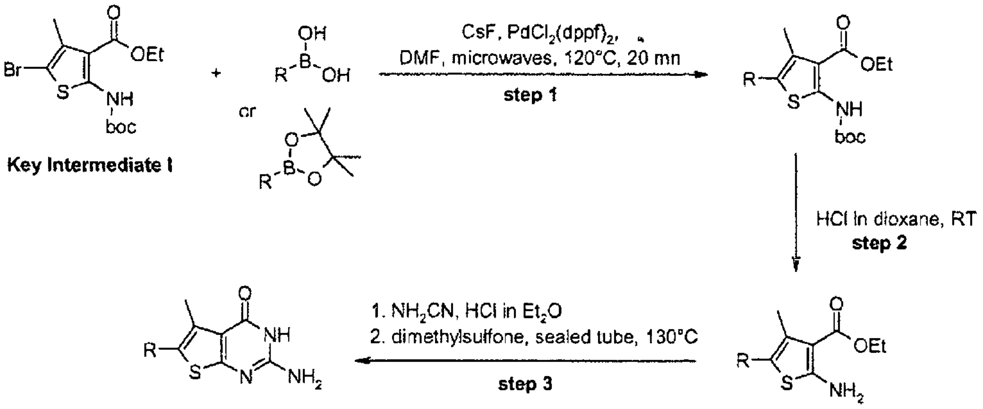


The expected compound was obtained according to **general procedure B** using 4-(4-chloro-phenyl)-butan-2-one. The expected compound was isolated as a white powder.

MS: 306.1

Mp: 300 °C – 320 °C

General Procedure C



Step 1:

To a degassed solution of 5-bromo-2-tert-butoxycarbonylamino-4-methyl-thiophene-3-carboxylic acid ethyl ester (**Key Intermediate I**) (200 mg, 0.6 mmol, 1 eq) and boronic acid or ester (1.8 mmol, 3 eq) in dry dimethylformamide (4 mL) were added cesium fluoride (183 mg, 1.2 mmol, 2.2 eq) and dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium (0.12 mmol, 90 mg, 0.2 eq). The mixture was stirred at 120 °C under microwave radiation during 20 min. After cooling, the mixture was filtered over a short pad of celite and absorbed on silica gel to be purified by flash chromatography (30% to 95% yield).

Step 2:

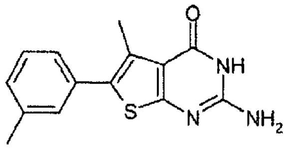
The compound from step 1 (2.4 mmol, 1 eq) was solubilized in a 4N solution of hydrogen chloride in dioxane (10 mL) and the mixture was stirred at room temperature during 18 h. The mixture was then concentrated and the residue was taken in dichloromethane (10 mL) and washed with a saturated solution of sodium bicarbonate (3 x 10 mL). The organic layers were dried over magnesium sulfate, filtered and evaporated in vacuo. The crude residue was purified by flash chromatography to afford the amino ester (35% to quantitative yield).

Step 3:

At 0 °C, cyanamide (1.0 mmol, 1.5 eq) was added to a 2M solution of hydrogen chloride in diethyl ether (1.0 mL, 3 eq). After stirring for 15 min, the suspension was filtered. The resulting white solid was added in a sealed tube to 2-amino-thiophene-3-carboxylic acid ethyl ester (0.7 mmol, 1 eq) and dimethylsulfone (250 mg). The mixture was heated at 130 °C during 2 h. After cooling, the residue was dissolved in methanol and a 7N solution of ammonia in methanol (10 mL) was added. The solvent was then evaporated and the solid obtained was washed with dichloromethane (2 x 10 mL) and water (2 x 10 mL) to afford the expected compound (5% to 90% yield).

Example 18:

2-Amino-5-methyl-6-m-tolyl-3H-thieno [2,3-d]pyrimidin-4-one



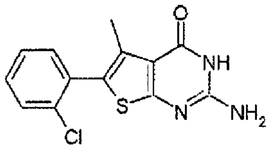
The expected compound was obtained according to **general procedure C** using 3-methylbenzeneboronic acid. The expected compound was isolated as a white powder.

MS: 272.1

Mp: decomposes at 330 °C – 338 °C

Example 19:

2-Amino-6-(2-chloro-phenyl)-5-methyl-3H-thieno[2,3-d]pyrimidin-4-one



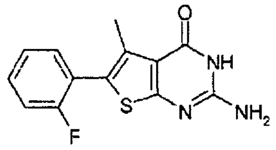
The expected compound was obtained according to **general procedure C** using 2-chlorobenzeneboronic acid. The expected compound was isolated as a pink powder.

MS: 292.1

Mp: 334 °C – 336 °C

Example 20:

2-Amino-6-(2-fluoro-phenyl)-5-methyl-3H-thieno[2,3-d]pyrimidin-4-one



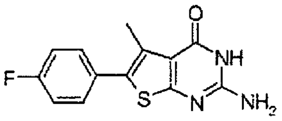
The expected compound was obtained according to **general procedure C** using 2-fluorobenzeneboronic acid. The expected compound was isolated as a beige powder.

MS: 271.1

Mp: 325 °C – 330 °C

Example 21:

2-Amino-6-(4-fluoro-phenyl)-5-methyl-3H-thieno[2,3-d]pyrimidin-4-one



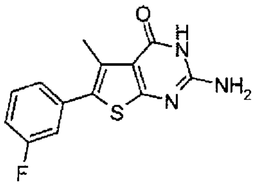
The expected compound was obtained according to **general procedure C** using 4-fluorobenzeneboronic acid. The expected compound was isolated as a grey powder.

MS: 276.0

Mp: 325 °C – 335 °C

Example 22:

2-Amino-6-(3-fluoro-phenyl)-5-methyl-3H-thieno[2,3-d]pyrimidin-4-one



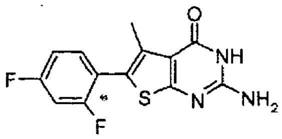
The expected compound was obtained according to **general procedure C** using 3-fluorobenzeneboronic acid. The expected compound was isolated as a purple powder.

MS: 276.0

Mp: 310 °C – 330 °C

Example 23:

2-Amino-6-(2,4-difluoro-phenyl)-5-methyl-3H-thieno[2,3-d]pyrimidin-4-one



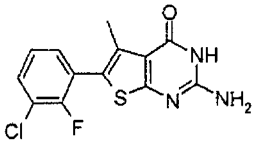
The expected compound was obtained according to **general procedure C** using 2,4-difluorophenylboronic acid. The expected compound was isolated as a purple powder.

MS: 294.1

Mp: 330 °C – 350 °C

Example 24:

2-Amino-6-(3-chloro-2-fluoro-phenyl)-5-methyl-3H-thieno[2,3-d]pyrimidin-4-one



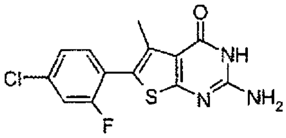
The expected compound was obtained according to **general procedure C** using 3-chloro-2-fluorophenylboronic acid. The expected compound was isolated as a white powder.

MS: 310.1

Mp: 330 °C – 350 °C

Example 25:

2-Amino-6-(4-chloro-2-fluoro-phenyl)-5-methyl-3H-thieno[2,3-d]pyrimidin-4-one



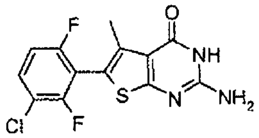
The expected compound was obtained according to **general procedure C** using 4-chloro-2-fluorobenzeneboronic acid. The expected compound was isolated as a white powder.

MS: 310.0

Mp: 320 °C – 340 °C

Example 26:

2-Amino-6-(3-chloro-2,6-difluoro-phenyl)-5-methyl-3H-thieno[2,3-d]pyrimidin-4-one



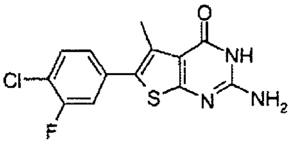
The expected compound was obtained according to **general procedure C** using 3-chloro-2,6-difluorophenylboronic acid. The expected compound was isolated as a white powder.

MS: 328.1

Mp: 330 °C – 350 °C

Example 27:

2-Amino-6-(4-chloro-3-fluoro-phenyl)-5-methyl-3H-thieno[2,3-d]pyrimidin-4-one



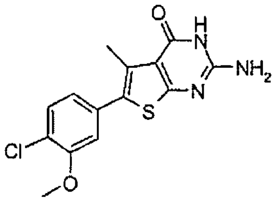
The expected compound was obtained according to **general procedure C** using 4-chloro-3-fluorophenylboronic acid. The expected compound was isolated as a beige powder.

MS: 310.1

Mp: 350 °C – 370 °C

Example 28:

2-Amino-6-(4-chloro-3-methoxy-phenyl)-5-methyl-3H-thieno[2,3-d]pyrimidin-4-one



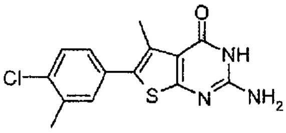
The expected compound was obtained according to **general procedure C** using 4-chloro-3-methoxyphenylboronic acid. The expected compound was isolated as a beige powder.

MS: 322.1

Mp: 312 °C – 322 °C

Example 29:

2-Amino-6-(4-chloro-3-methyl-phenyl)-5-methyl-3H-thieno[2,3-d]pyrimidin-4-one



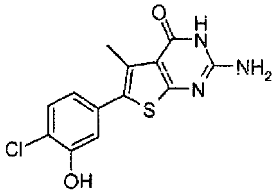
The expected compound was obtained according to **general procedure C** using 4-chloro-3-methylphenylboronic acid. The expected compound was isolated as a white powder.

MS: 306.1

Mp: 330 °C – 350 °C

Example 30:

2-Amino-6-(4-chloro-3-hydroxy-phenyl)-5-methyl-3H-thieno[2,3-d]pyrimidin-4-one



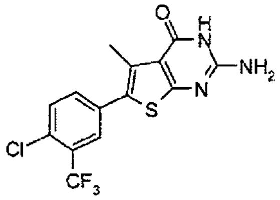
The expected compound was obtained according to **general procedure C** using (4-chloro-3-hydroxyphenyl)boronic acid. The expected compound was isolated as a beige powder.

MS: 308.1

Mp > 350 °C

Example 31:

2-Amino-6-(4-chloro-3-trifluoromethyl-phenyl)-5-methyl-3H-thieno[2,3-d]pyrimidin-4-one



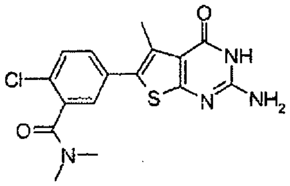
The expected compound was obtained according to **general procedure C** using 4-chloro-3-trifluoromethylphenylboronic acid. The expected compound was isolated as a white powder.

MS: 360.2

Mp > 350 °C

Example 32:

5-(2-Amino-5-methyl-4-oxo-3,4-dihydro-thieno[2,3-d]pyrimidin-6-yl)-2-chloro-N,N-dimethyl-benzamide



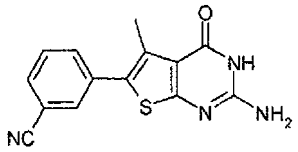
The expected compound was obtained according to **general procedure C** using 4-chloro-3-(dimethylaminocarbonyl)phenylboronic acid. The expected compound was isolated as a white powder.

MS: 363.1

Mp: 300 °C – 320 °C

Example 33:

3-(2-Amino-5-methyl-4-oxo-3,4-dihydro-thieno[2,3-d]pyrimidin-6-yl)-benzonitrile



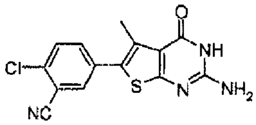
The expected compound was obtained according to **general procedure C** using 3-cyanophenylboronic acid. The expected compound was isolated as a beige powder.

MS: 283.1

Mp > 350 °C

Example 34:

5-(2-Amino-5-methyl-4-oxo-3,4-dihydro-thieno[2,3-d]pyrimidin-6-yl)-2-chloro-benzonitrile



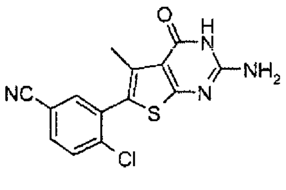
The expected compound was obtained according to **general procedure C** using 4-chloro-3-cyanophenylboronic acid. The expected compound was isolated as a beige powder.

MS: 317.0

Mp > 360 °C

Example 35:

3-(2-Amino-5-methyl-4-oxo-3,4-dihydro-thieno[2,3-d]pyrimidin-6-yl)-4-chloro-benzonitrile



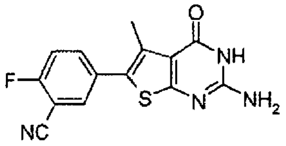
The expected compound was obtained according to **general procedure C** using 2-chloro-5-cyanophenylboronic acid. The expected compound was isolated as a beige powder.

MS: 317.1

Mp > 350 °C

Example 36:

5-(2-Amino-5-methyl-4-oxo-3,4-dihydro-thieno[2,3-d]pyrimidin-6-yl)-2-fluoro-benzonitrile



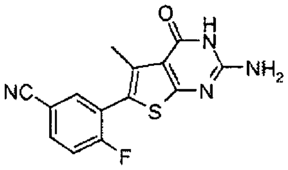
The expected compound was obtained according to **general procedure C** using 3-cyano-4-fluorophenylboronic acid. The expected compound was isolated as a white powder.

MS: 301.1

Mp: 330 °C – 350 °C

Example 37:

3-(2-Amino-5-methyl-4-oxo-3,4-dihydro-thieno[2,3-d]pyrimidin-6-yl)-4-fluoro-benzonitrile



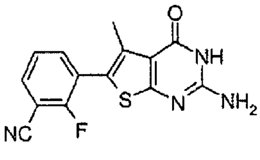
The expected compound was obtained according to **general procedure C** using 5-cyano-2-fluorophenylboronic acid. The expected compound was isolated as a beige powder.

MS: 301.0

Mp: 332 °C – 336 °C

Example 38:

3-(2-Amino-5-methyl-4-oxo-3,4-dihydro-thieno[2,3-d]pyrimidin-6-yl)-2-fluorobenzonitrile



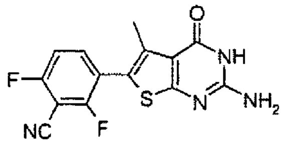
The expected compound was obtained according to **general procedure C** using 3-cyano-2-fluorophenylboronic acid. The expected compound was isolated as a white powder.

MS: 301.0

Mp: 350 °C – 370 °C

Example 39:

3-(2-Amino-5-methyl-4-oxo-3,4-dihydro-thieno[2,3-d]pyrimidin-6-yl)-2,6-difluoro-benzonitrile



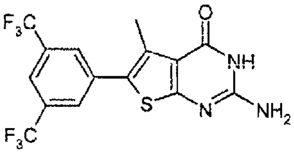
The expected compound was obtained according to **general procedure C** using 2,4-difluoro-3-cyanophenylboronic acid. The expected compound was isolated as a grey powder.

MS: 319.0

Mp: 360 °C – 380 °C

Example 40:

2-Amino-6-(3,5-bis-trifluoromethyl-phenyl)-5-methyl-3H-thieno[2,3-d]pyrimidin-4-one



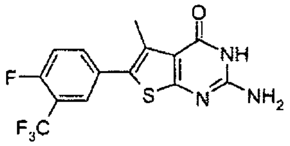
The expected compound was obtained according to **general procedure C** using 3,5-bis(trifluoromethyl)benzeneboronic acid. The expected compound was isolated as a white powder.

MS: 394.1

Mp: 344 °C – 347 °C

Example 41:

2-Amino-6-(4-fluoro-3-trifluoromethyl-phenyl)-5-methyl-3H-thieno[2,3-d]pyrimidin-4-one



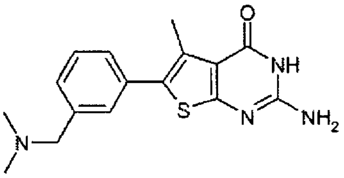
The expected compound was obtained according to **general procedure C** using 4-fluoro-3-trifluoromethylphenylboronic acid. The expected compound was isolated as a white powder.

MS: 343.1

Mp: 310 °C – 330 °C

Example 42:

2-Amino-6-(3-dimethylaminomethyl-phenyl)-5-methyl-3H-thieno[2,3-d]pyrimidin-4-one



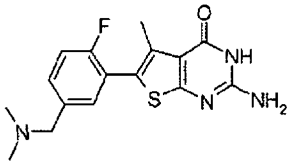
The expected compound was obtained according to **general procedure C** using 3-(N,N-dimethylamino)methylphenylboronic acid, pinacol ester, hydrochloride salt. The expected compound was isolated as a beige powder.

MS: 315.1

Mp: 207 °C – 212 °C

Example 43:

2-Amino-6-(5-dimethylaminomethyl-2-fluoro-phenyl)-5-methyl-3H-thieno[2,3-d]-pyrimidin-4-one



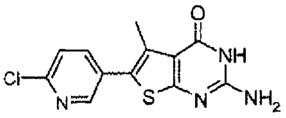
The expected compound was obtained according to **general procedure C** using 2-fluoro-5-(dimethylaminomethyl)phenylboronic acid pinacol ester. The expected compound was isolated as a white powder.

MS: 333.2

Mp: 230 °C – 250 °C

Example 44:

2-Amino-6-(6-chloro-pyridin-3-yl)-5 -methyl-3H-thieno[2,3-d]pyrimidin-4-one



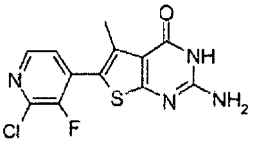
The expected compound was obtained according to **general procedure C** using 2-chloropyridine-5-boronic acid. The expected compound was isolated as a yellow powder.

MS: 293.1

Mp: 230 °C – 250 °C

Example 45:

2-Amino-6-(2-chloro-3-fluoro-pyridin-4-yl)-5-methyl-3H-thieno[2,3-d]pyrimidin-4-one



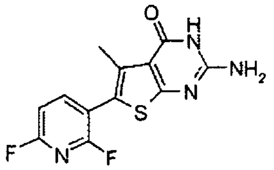
The expected compound was obtained according to **general procedure C** using 2-chloro-3-fluoropyridine-4-boronic acid. The expected compound was isolated as a yellow powder.

MS: 311.1

Mp: 330 °C – 350 °C

Example 46:

2-Amino-6-(2,6-difluoro-pyridin-3-yl)-5-methyl-3H-thieno[2,3-d]pyrimidin-4-one



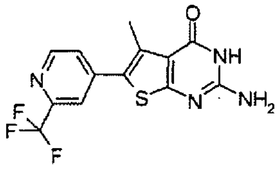
The expected compound was obtained according to **general procedure C** using 2,6-difluoropyridine-3-boronic acid. The expected compound was isolated as a beige powder.

MS: 295.0

Mp: 330 °C – 335 °C

Example 47:

2-Amino-5-methyl-6-(2-trifluoromethyl-pyridin-4-yl)-3H-thieno[2,3-d]pyrimidin-4-one



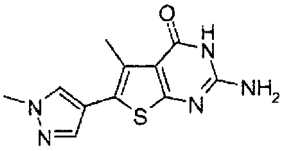
The expected compound was obtained according to **general procedure C** using 2-(trifluoromethyl)pyridine-4-boronic acid. The expected compound was isolated as a yellow powder.

MS: 327.0

Mp: 335 °C – 355 °C

Example 48:

2-Amino-5-methyl-6-(2-methyl-2H-imidazol-4-yl)-3H-thieno[2,3-d]pyrimidin-4-one



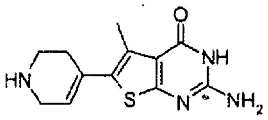
The expected compound was obtained according to **general procedure C** using 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole. The expected compound was isolated as a white powder.

MS: 262.0

Mp: 335 °C – 345 °C

Example 49:

2-Amino-5-methyl-6-(1,2,3,6-tetrahydro-pyridin-4-yl)-3H-thieno[2,3-d]pyrimidin-4-one



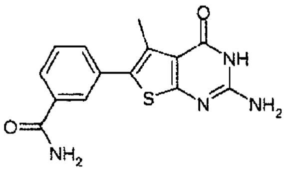
The expected compound was obtained according to **general procedure C** using N-Boc-1,2,3,6-tetrahydropyridine-4-boronic acid pinacol ester. The expected compound was isolated as an orange powder.

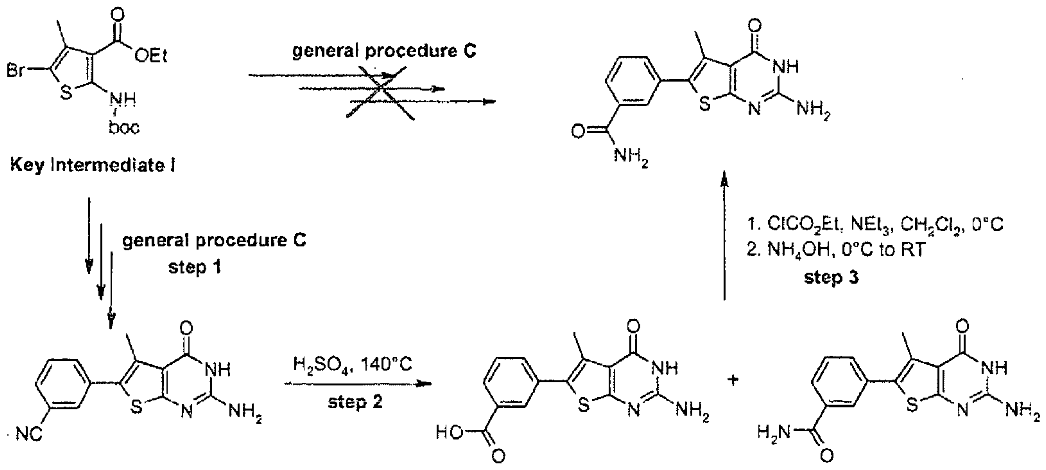
MS: 263.1

Mp: 290 °C – 310 °C

Example 50:

3-(2-Amino-5-methyl-4-oxo-3,4-dihydro-thieno[2,3-d]pyrimidin-6-yl)-benzamide





Step 1:

The procedure to obtain the expected compound began with **general procedure C** using 3-carbamoylphenylboronic acid. After cyclisation, 3-(2-amino-5-methyl-4-oxo-3,4-dihydro-thieno[2,3-d]pyrimidin-6-yl)-benzonitrile was obtained instead of the desired compound.

Step 2:

3-(2-Amino-5-methyl-4-oxo-3,4-dihydro-thieno[2,3-d]pyrimidin-6-yl)-benzonitrile (100 mg, 0.35 mmol, 1 eq) was solubilized in concentrated sulfuric acid (12 mL) and heated at 140 °C during 3 h. After cooling, water (10 mL) was added and the precipitate obtained was filtered to afford a 60/40 mixture of acid and amide compound.

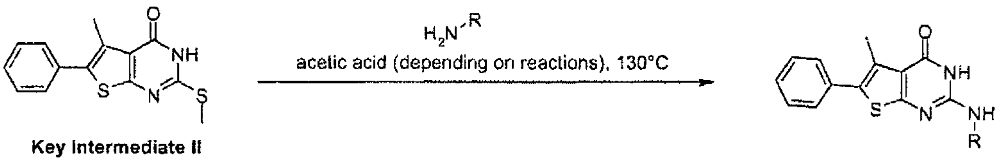
Step 3:

The mixture from step 2 was put in suspension in dichloromethane (6 mL). At 0 °C, triethylamine (42 µL, 0.3 mmol, 1.2 eq) and ethyl chloroformate (26 µL, 0.28 mmol, 1.1 eq) were added. After 1 h at 0 °C, ammonium hydroxide solution (15 mL) was added and the mixture was stirred from 0 °C to room temperature for 3 days. The solvent was evaporated and water (10 mL) was added. The precipitate obtained was filtered and dried in vacuo to afford the expected compound as a beige powder.

MS: 301.1

Mp: decomposes at 295 °C – 300 °C

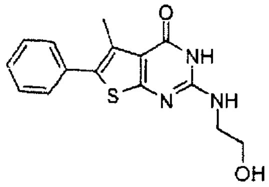
General Procedure D



5-Methyl-2-methylsulfanyl-6-phenyl-3H-thieno[2,3-d]pyrimidin-4-one (**Key Intermediate II**) (1.3 g, 4.4 mmol, 1 eq) was put in suspension in the appropriate amine (3 mL) and depending on reactions, in acetic acid (1 mL). The resulting mixture was heated in a sealed tube at 130 °C during 18 h. After cooling, ethanol (20 mL) was added and the precipitate was filtered, rinsed with methanol, dichloromethane and ether and dried in vacuo to afford the expected compound (10% to 70% yield).

Example 51:

2-(2-Hydroxy-ethylamino)-5-methyl-6-phenyl-3H-thieno[2,3-d]pyrimidin-4-one



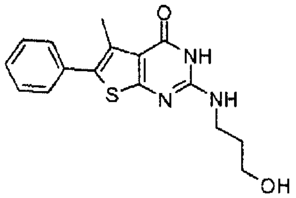
The expected compound was obtained according to **general procedure D** using ethanolamine and acetic acid. The expected compound was isolated as a white powder.

MS: 302.1

Mp: 227 °C – 229 °C

Example 52:

2-(3-Hydroxy-propylamino)-5-methyl-6-phenyl-3H-thieno[2,3-d]pyrimidin-4-one



The expected compound was obtained according to **general procedure D** using 3-amino-propan-1-ol and acetic acid. After cooling , the reaction mixture was evaporated and water was added. The obtained precipitate was filtered and rinsed with diethyl ether and dichloromethane. The expected compound was isolated as a beige powder.

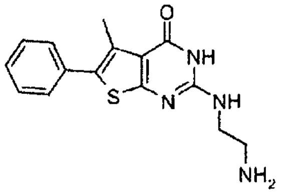
MS: 316.2

Mp: 227 °C – 229 °C

Example 53:

2-(2-Amino-ethylamino)-5-methyl-6-phenyl-3H-thieno[2,3-d]pyrimidin-4-one

Key Intermediate III



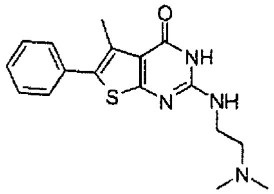
The expected compound was obtained according to **general procedure D** using ethylenediamine. The expected compound was isolated as a white powder.

MS: 301.1

Mp: 192 °C – 194 °C

Example 54:

2-(2-Dimethylamino-ethylamino)-5-methyl-6-phenyl-3H-thieno[2,3-d]pyrimidin-4-one



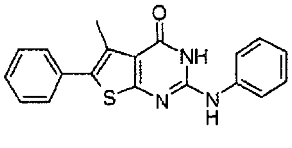
The expected compound was obtained according to **general procedure D** using N,N-dimethyl ethylenediamine and acetic acid. The expected compound was isolated as a beige powder.

MS: 329.2

Mp: 199 °C – 201 °C

Example 55:

5-Methyl-6-phenyl-2-phenylamino-3H-thieno[2,3-d]pyrimidin-4-one



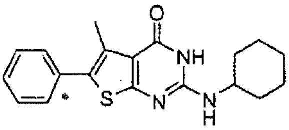
The expected compound was obtained according to **general procedure D** using aniline and acetic acid. The expected compound was isolated as a white powder.

MS: 334.1

Mp: 270 °C – 290 °C

Example 56:

2-Cyclohexylamino-5-methyl-6-phenyl-3H-thieno[2,3-d]pyrimidin-4-one



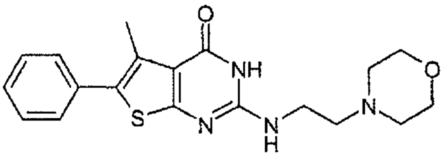
The expected compound was obtained according to **general procedure D** using cyclohexylamine. The expected compound was isolated as a white powder.

MS: 340.2

Mp: 265 °C – 270 °C

Example 57:

5-Methyl-2-(2-morpholin-4-yl-ethylamino)-6-phenyl-3H-thieno[2,3-d]pyrimidin-4-one



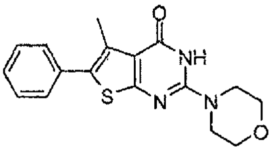
The expected compound was obtained according to **general procedure D** using 4-(2-aminoethyl)morpholine. The expected compound was isolated as a white powder.

MS: 371.1

Mp: 240 °C – 246 °C

Example 58:

5-Methyl-2-morpholin-4-yl-6-phenyl-3H-thieno[2,3-d]pyrimidin-4-one

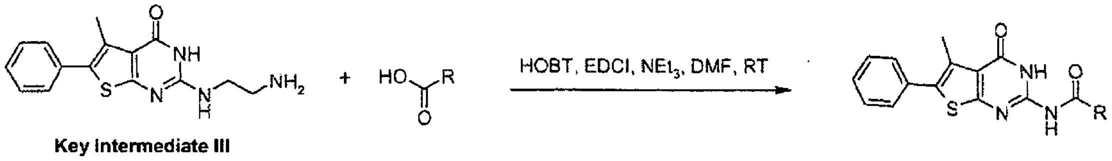


The expected compound was obtained according to **general procedure D** using morpholine. The expected compound was isolated as a white powder.

MS: 328.1

Mp: 300 °C – 320 °C

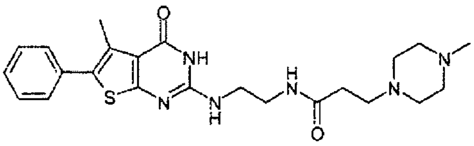
General Procedure E



To a solution of 2-(2-amino-ethylamino)-5-methyl-6-phenyl-3H-thieno[2,3-d]pyrimidin-4-one (**Key Intermediate III**) (200 mg, 0.66 mmol, 1 eq) in dimethylformamide (5 mL) were added HOBT (180 mg, 1.33 mmol, 2 eq), EDCI (255 mg, 1.33 mmol, 2 eq), triethylamine (0.28 mL, 1.98 mmol, 3 eq) and the appropriate carboxylic acid (1.33 mmol, 2 eq). The mixture was stirred at room temperature for 20 h. Then the mixture was poured on water (10 mL) and extracted with dichloromethane (3 x 20mL). The organic layers were dried over magnesium sulfate, filtered and evaporated in vacuo. The crude residue was purified by flash chromatography using dichloromethane and ammonia 7N in methanol (100/0 to 80/20) to afford the expected compound (10 to 40% yield).

Example 59:

N-[2-(5-Methyl-4-oxo-6-phenyl-3,4-dihydro-thieno[2,3-d]pyrimidin-2-ylamino)-ethyl]-3-(4-methyl-piperazin-1-yl)-propionamide



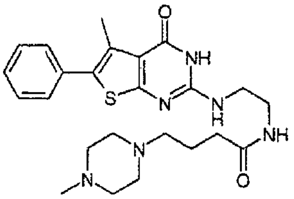
The expected compound was obtained according to **general procedure E** using 3-(4-methyl-piperazin-1-yl)-propionic acid. The expected compound was isolated as a white powder.

MS: 455.1

Mp: 235 °C – 245 °C

Example 60:

N-[2-(5-Methyl-4-oxo-6-phenyl-3,4-dihydro-thieno[2,3-d]pyrimidin-2-ylamino)-ethyl]-4-(4-methyl-piperazin-1-yl)-butyramide



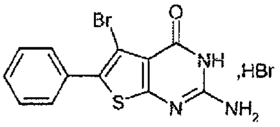
The expected compound was obtained according to **general procedure E** using 4-(4-methylpiperazin-1-yl)butanoic acid hydrochloride. The expected compound was isolated as a white powder.

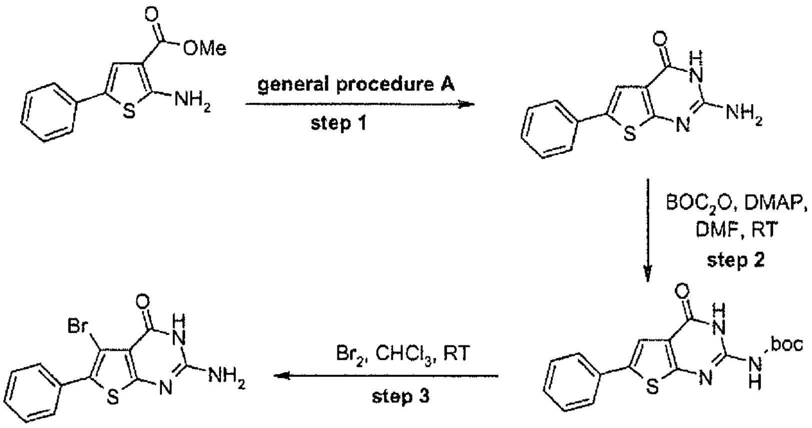
MS: 469.2

Mp: 192 °C – 196 °C

Example 61:

2-Amino-5-bromo-6-phenyl-3H-thieno [2,3-d]pyrimidin-4-one, hydrobromide salt





Step 1:

The expected compound was obtained according to **general procedure A** using 2-amino-5-phenyl-thiophene-3-carboxylic acid methyl ester. The expected compound was isolated as a beige powder (3.5 g, 70% yield).

Step 2:

To a solution of 2-amino-6-phenyl-3H-thieno[2,3-d]pyrimidin-4-one (2.0 g, 8.2 mmol, 1 eq) in dimethylformamide (100 mL) were added di-tert-butyl dicarbonate (3.6 g, 16.4 mmol, 2 eq) and 4-dimethylaminopyridine (200 mg, 1.6 mmol, 0.2 eq). The mixture was stirred at room temperature for 18 h. The solvent was then evaporated and the residue was taken up with dichloromethane (20 mL). The insoluble yellow solid was filtered off and the filtrate was washed with a saturated solution of sodium bicarbonate (2 X 20 mL). The organic layers were dried over magnesium sulfate, filtered and evaporated. The crude residue was purified by flash chromatography using dichloromethane and methanol (100/0 to 80/20) to afford (4-oxo-6-phenyl-3,4-dihydro-thieno[2,3-d]pyrimidin-2-yl)-carbamic acid tert-butyl ester as a light yellow solid (900 mg, 32% yield).

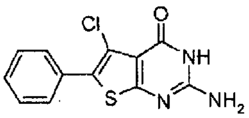
Step 3:

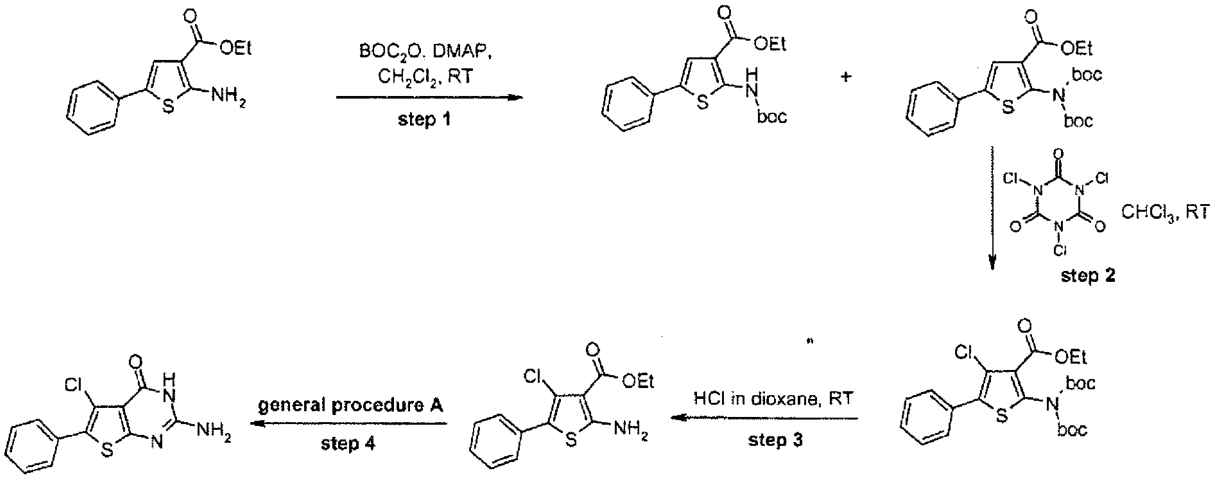
The compound from step 2 (350 mg, 1.0 mmol, 1 eq) was solubilized in chloroform (10 mL) and bromine (52 µL, 1.0 mmol, 1 eq) was added. The mixture was stirred at room temperature for 1 h. More bromine (52 µL, 1.0 mmol, 1 eq) was added and the mixture was stirred for one additional hour at room temperature. The mixture was then evaporated and the residue was washed with dichloromethane (5 mL) and methanol (5 mL) to afford the expected compound as a beige powder (150 mg, 46% yield).

MS: 324.1

Example 62:

2-Amino-5-chloro-6-phenyl-3H-thieno [2,3-d]pyrimidin-4-one





Step 1:

To a solution of 2-amino-5-phenyl-thiophene-3-carboxylic acid ethyl ester (5.0 g, 20.2 mmol, 1 eq) in dichloromethane (40 mL) were added di-tert-butyl dicarbonate (6.6 g, 30.3 mmol, 1.5 eq) and 4-dimethylaminopyridine (247 mg, 2.0 mmol, 0.1 eq). The mixture was stirred at room temperature for 48 h. The mixture was washed with a saturated solution of sodium bicarbonate (3 X 20 mL) and the organic layers were dried over magnesium sulfate, filtered and evaporated. The crude residue was purified by flash chromatography using cyclohexane and ethyl acetate (100/0 to 90/10) to afford separately 2-tert-butoxycarbonylamino-5-phenyl-thiophene-3-carboxylic acid ethyl ester (1.9 g, 27% yield) as a yellow oil and bis(2-tert-butoxycarbonylamino)-5-phenyl-thiophene-3-carboxylic acid ethyl ester (4.1 g, 45% yield) as a light orange powder.

Step 2:

To a solution of the diBoc compound from step 1 (3.1 g, 6.9 mmol, 1 eq) in chloroform (100 mL) was added trichloroisocyanuric acid (640 mg, 2.8 mmol, 0.4 eq). The mixture was stirred at room temperature for 18 h. The precipitate was filtered off and the filtrate was purified by flash chromatography using cyclohexane and ethyl acetate (100/0 to 90/10) to afford the expected compound as a light orange oil (1.1 g, 33% yield).

Step 3:

The compound from step 2 (950 mg, 2.0 mmol, 1 eq) was solubilized in a 4N solution of hydrogen chloride in dioxane (20 mL) and the mixture was stirred at room temperature during 18 h. The mixture was then concentrated and the residue was taken up in dichloromethane (10 mL) and washed with a saturated solution of sodium bicarbonate (3 x

10 mL). The organic layers were dried over magnesium sulfate, filtered and evaporated in vacuo. The crude residue was purified by flash chromatography using cyclohexane and ethyl acetate (100/0 to 85/15) to afford 2-amino-4-chloro-5-phenyl-thiophene-3-carboxylic acid ethyl ester as a light orange oil (300 mg, 54% yield).

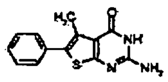
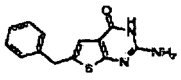
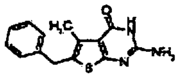
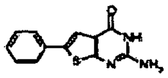
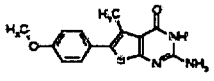
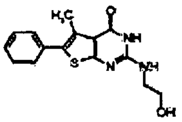
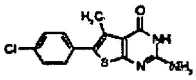
<u>Step 4:</u>

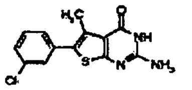
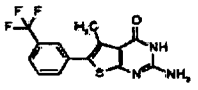
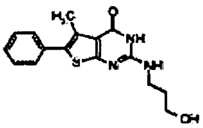
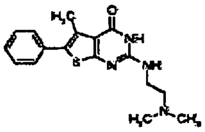
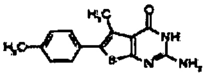
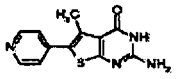
The expected compound was obtained according to **general procedure A** using 2-amino-4-chloro-5-phenyl-thiophene-3-carboxylic acid ethyl ester. The expected compound was isolated as a beige powder (175 mg, 61% yield).

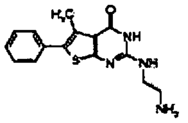
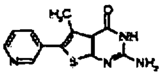
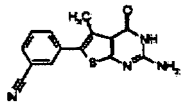
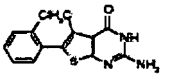
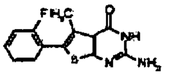
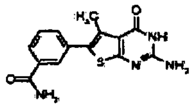
MS: 278.0

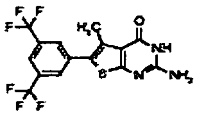
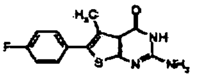
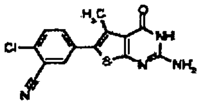
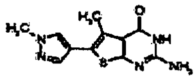
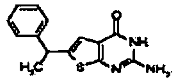
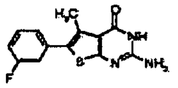
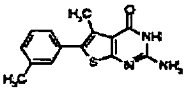
Mp > 350 °C

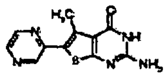
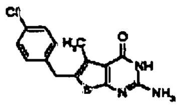
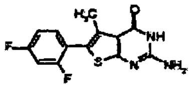
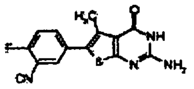
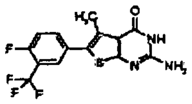
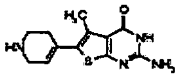
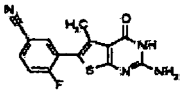
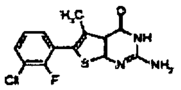
Activity data for the compounds having the general formula (II)

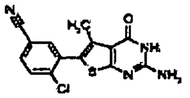
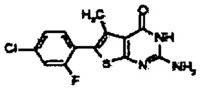
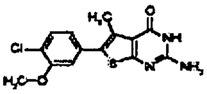
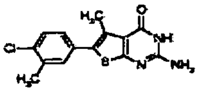
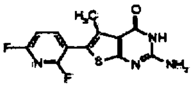
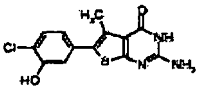
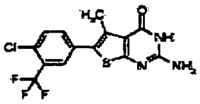
molregno	structure	activity type	activity endpoint	activity conc	activity result
SAV-7475		Biacore	Binding (RU)	10	94,5
		Biacore	KD (µM)		4,6
		CPE H3N2	reduction (%)	5	8,9
		Biacore PA-Nter	Binding (RU)	50	13,16
		CPE H3N2	IC50 (µM)		21
SAV-7517		Biacore	Binding (RU)	10	39,3
		Biacore	KD (µM)		13
		CPE H3N2	reduction (%)	10	-2,64
SAV-7521		Biacore	Binding (RU)	10	64,7
		Biacore	KD (µM)		6
		CPE H3N2	reduction (%)	25	33,6
SAV-7549		Biacore	Binding (RU)	10	65,5
		CPE H3N2	reduction (%)	50	-2,4
		Biacore	KD (µM)		8,8
SAV-7575		Biacore	Binding (RU)	10	35,9
		CPE H3N2	reduction (%)	20	9,02
		Biacore	KD (µM)		4
SAV-7577		Biacore	Binding (RU)	10	81,1
		Biacore	KD (µM)		6,8
		CPE H3N2	reduction (%)	20	2,85
SAV-7579		Biacore	Binding (RU)	10	21,4
		CPE H3N2	reduction (%)	20	11,3
		Biacore	KD (µM)		0,27

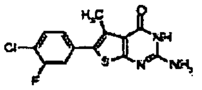
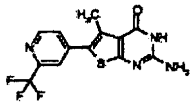
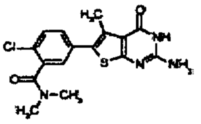
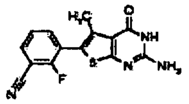
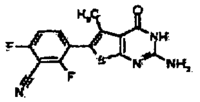
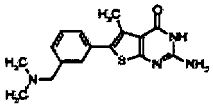
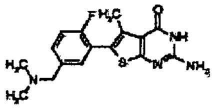
molregno	structure	activity type	activity endpoint	activity conc	activity result
SAV-7580		Biacore	Binding (RU)	10	25,2
		CPE H3N2	reduction (%)	2	89,8
		CPE H3N2	IC50 (µM)		11
		Biacore	KD (µM)		8,9
SAV-7581		Biacore	Binding (RU)	10	20,5
		CPE H3N2	reduction (%)	50	87,8
		Biacore	KD (µM)		1,4
		CPE H3N2	IC50 (µM)		17
SAV-7582		Biacore	Binding (RU)	10	102,9
		Biacore	KD (µM)		4,2
		CPE H3N2	reduction (%)	50	53,1
SAV-7583		Biacore	Binding (RU)	10	77,8
		CPE H3N2	reduction (%)	5	4,8
		Biacore	KD (µM)		68
SAV-7585		CPE H3N2	reduction (%)	2.5	28,9
		Biacore	Binding (RU)	10	29,2
		CPE H3N2	IC50 (µM)		3,5
		Biacore	KD (µM)		2
SAV-7586		CPE H3N2	reduction (%)	15	81,2
		Biacore	Binding (RU)	10	100,2
		Biacore	KD (µM)		12
		CPE H3N2	IC50 (µM)		5,3

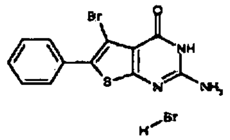
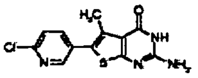
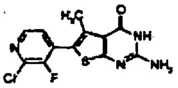
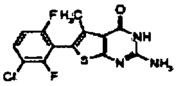
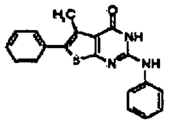
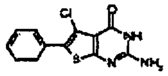
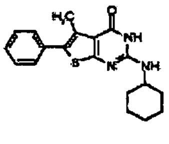
molregno	structure	activity type	activity endpoint	activity conc	activity result
SAV-7588		CPE H3N2	reduction (%)	5	2,2
		Biacore	Binding (RU)	10	110,6
		Biacore	KD (µM)		
SAV-7589		CPE H3N2	reduction (%)	50	63,1
		Biacore	Binding (RU)	10	88
		Biacore	KD (µM)		10
		CPE H3N2	IC50 (µM)		27
SAV-7594		Biacore	KD (µM)		2
		Biacore	Binding (RU)	10	31,9
		CPE H3N2	reduction (%)	5	14,5
		CPE H3N2	IC50 (µM)		14
SAV-7596		Biacore	KD (µM)		11
		Biacore	Binding (RU)	10	29,6
		CPE H3N2	reduction (%)	5	13,6
SAV-7598		Biacore	Binding (RU)	10	21,3
		Biacore	KD (µM)		3,7
		CPE H3N2	reduction (%)	2	11,4
SAV-7599		CPE H3N2	reduction (%)	20	-0,7
		Biacore	Binding (RU)	12.5	65,3
		Biacore	KD (µM)		5,3

molregno	structure	activity type	activity endpoint	activity conc	activity result
SAV-7600		CPE H3N2	reduction (%)	2	5,8
		Biacore	KD (µM)		
		Biacore	Binding (RU)	10	3,8
SAV-7601		CPE H3N2	reduction (%)	50	69,2
		Biacore	KD (µM)		1,1
		Biacore	Binding (RU)	10	44,3
SAV-7602		CPE H3N2	reduction (%)	20	67,9
		Biacore	KD (µM)		1,7
		Biacore	Binding (RU)	10	35,1
SAV-7603		CPE H3N2	reduction (%)	20	1,1
		Biacore	KD (µM)		42
SAV-7604		CPE H3N2	reduction (%)	20	-4,7
		Biacore	KD (µM)		6,4
SAV-7606		Biacore	KD (µM)		8
		CPE H3N2	reduction (%)	5	21,8
SAV-7607		Biacore	KD (µM)		5,4
		CPE H3N2	reduction (%)	2	-0,4

molregno	structure	activity type	activity endpoint	activity conc	activity result
SAV-7608		Biacore	KD (µM)		5,7
		CPE H3N2	reduction (%)	10	3,8
SAV-7609		CPE H3N2 (insoluble)	reduction (%) insoluble		
SAV-7610		Biacore	KD (µM)		3,8
		CPE H3N2	reduction (%)	2	-1,6
		ALPHA screen	EC50 (µM)*		0,62
SAV-7611		Biacore	KD (µM)		1,1
		CPE H3N2	reduction (%)	2	-1
SAV-7613		Biacore	KD (µM)		1,5
		CPE H3N2	reduction (%)	50	2,5
SAV-7614		Biacore	KD (µM)		190
		CPE H3N2	reduction (%)	50	10,6
SAV-7615		Biacore	KD (µM)		3
		CPE H3N2	reduction (%)	20	59,2
		CPE H3N2	IC50 (µM)		12
SAV-7616		Biacore	KD (µM)		3,1
		CPE H3N2	reduction (%)	10	68,7
		CPE H3N2	IC50 (µM)		34

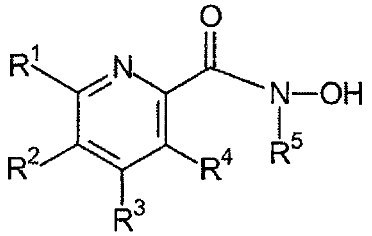
molregno	structure	activity type	activity endpoint	activity conc	activity result
SAV-7617		Biacore	KD (µM)		2
		CPE H3N2	reduction (%)	2	5,1
SAV-7618		Biacore	KD (µM)		0,65
		CPE H3N2	reduction (%)	50	77,4
		CPE H3N2	IC50 (µM)		43
SAV-7619		Biacore	KD (µM)		1,1
		CPE H3N2	reduction (%)	2	3,4
SAV-7620		Biacore	KD (µM)		
		CPE H3N2	reduction (%)	50	57,8
		CPE H3N2	IC50 (µM)		29
SAV-7621		Biacore	KD (µM)		
		CPE H3N2	IC50 (µM)		70
		CPE H3N2	reduction (%)	25	14,3
SAV-7622		Biacore	KD (µM)		2,4
		CPE H3N2	reduction (%)	2	6,2
SAV-7623		Biacore	KD (µM)		
		CPE H3N2	reduction (%)	5	1,9

molregno	structure	activity type	activity endpoint	activity conc	activity result
SAV-7624		Biacore	KD (µM)		0,2
		CPE H3N2	IC50 (µM)		64
SAV-7625		Biacore	KD (µM)		12
		CPE H3N2	reduction (%)	2.5	-4
SAV-7626		Biacore	KD (µM)		6,4
		CPE H3N2	reduction (%)	25	-4,6
SAV-7627		Biacore	KD (µM)		4,2
		CPE H3N2	reduction (%)	50	71,2
		CPE H3N2	IC50 (µM)		10
SAV-7628		Biacore	KD (µM)		7,3
		CPE H3N2	reduction (%)	50	84,3
		CPE H3N2	IC50 (µM)		43
SAV-7629		Biacore	KD (µM)		61
		CPE H3N2	reduction (%)	50	38,3
		CPE H3N2	IC50 (µM)		35
SAV-7630		Biacore	KD (µM)		57
		CPE H3N2	reduction (%)	50	23,2
		CPE H3N2	IC50 (µM)		

molregno	structure	activity type	activity endpoint	activity conc	activity result
SAV-7631		Biacore	KD (µM)		0,86
		CPE H3N2	reduction (%)	5	4
		CPE H3N2	IC50 (µM)		
SAV-7632		Biacore	KD (µM)		0,75
		CPE H3N2	reduction (%)	50	53
		CPE H3N2	IC50 (µM)		
SAV-7633		Biacore	KD (µM)		1,2
		CPE H3N2	reduction (%)	50	63,1
		CPE H3N2	IC50 (µM)		39
SAV-7637		CPE H3N2	reduction (%)	5	1,5
		CPE H3N2	IC50 (µM)		18
		Biacore	KD (µM)		1,1
SAV-7638		CPE H3N2	reduction (%)	5	8,7
		CPE H3N2	IC50 (µM)		
		Biacore	KD (µM)		
SAV-7639		CPE H3N2	reduction (%)	50	59,9
		CPE H3N2	IC50 (µM)		
		Biacore	KD (µM)		1,8
SAV-7640		CPE H3N2	reduction (%)	5	-3,2
		CPE H3N2	IC50 (µM)		
		Biacore	KD (µM)		

CLAIMS

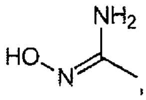
1. A compound having the general formula I, optionally in the form of a pharmaceutically acceptable salt, solvate, polymorph, prodrug, tautomer, racemate, enantiomer, or diastereomer or mixture thereof,



(I)

wherein

R^1 is selected from $-H$, $-C_{1-6}$ alkyl, $-(C_{3-7}$ cycloalkyl) and $-CH_2-(C_{3-7}$ cycloalkyl);

R^2 is selected from $-H$,  , $-C_{1-6}$ alkyl, $-Hal$, $-(C_{3-7}$ cycloalkyl), $-CH_2-(C_{3-7}$ cycloalkyl),
$-(CH_2)_m-$(optionally substituted aryl), $-$(optionally substituted 5- or 6-membered heterocyclic ring which contains at least one heteroatom selected from N, O and S, wherein the substituent is selected from $-C_{1-4}$ alkyl, $-$halogen, $-CN$, $-CHal_3$, $-$aryl, $-NR^6R^7$, and $-CONR^6R^7$;

R^3 is selected from $-H$, $-C_{1-6}$ alkyl,
$-(CH_2)_n-NR^6R^8$,
$-$(optionally substituted 5- or 6-membered carbo- or heterocyclic ring wherein the heterocyclic ring contains at least one heteroatom selected from N, O and S), wherein the substituent is selected from $-Hal$, $-C_{1-4}$ alkyl, $-NR^9R^{10}$, $-(CH_2)_n-OH$, $-C(O)-$

NR^9R^{10}, $-SO_2-NR^9R^{10}$, $-NH-C(O)-O-R^{11}$, $-C(O)-O-R^{11}$, and a 5- or 6-membered heterocyclic ring which contains at least one heteroatom selected from N, O and S;

or wherein R^1 and R^2 together form a phenyl ring or wherein R^2 and R^3 together form a phenyl ring;

R^4 is –H;

R^5 is selected from the group consisting of –H or $-(CH_2)_n-$(optionally substituted aryl), wherein the substituent is selected from –Hal and $-C_{1-4}$ alkyl; or wherein R^4 and R^5 together form a methylene group $-CH_2-$, ethylene group $-CH_2CH_2-$ or ethyne group –CHCH–, which can be optionally substituted by $-C_{1-4}$ alkyl, –halogen, $-CHal_3$, $-R^6R^7$, $-OR^6$, $-CONR^6R^7$, $-SO_2R^6R^7$, aryl or heteroaryl;

R^6 is selected from –H and $-C_{1-4}$ alkyl;

R^7 is selected from –H and $-C_{1-4}$ alkyl;

R^8 is selected from –H, $-C_{1-6}$ alkyl, $-(CH_2)_n-$(optionally substituted aryl), $-SO_2-(CH_2)_n-$(optionally substituted aryl), $-SO_2-(CH_2)_n-$(optionally substituted 5- to 10-membered mono- or bicyclic heteroring which contains at least one heteroatom selected from N, O and S), $-(CH_2)_n-$(optionally substituted 5- or 6-membered heterocyclic ring which contains at least one heteroatom selected from N, O and S), wherein the substituent is selected from –Hal, $-CF_3$, $-C_{1-4}$ alkyl, and $-(CH_2)_n-$aryl;

R^9 is selected from –H, $-C_{1-4}$ alkyl, and $-C_{1-4}$ alkylene–$NR^{11}R^{11}$;

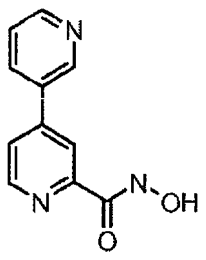
R^{10} is selected from –H, $-C_{1-4}$ alkyl, and $-C_{1-4}$ alkylene–$NR^{11}R^{11}$;

R^{11} is selected from –H, $-CF_3$, and $-C_{1-4}$ alkyl;

each **m** is 0 or 1; and

each **n** is independently 0, 1, 2, or 3;

with the proviso that the compound is not one of the following compounds:



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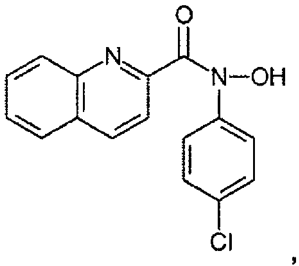

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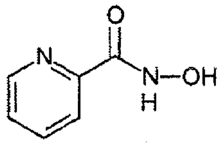

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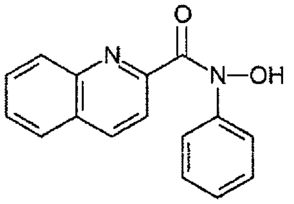

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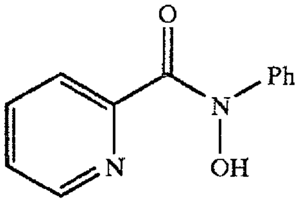

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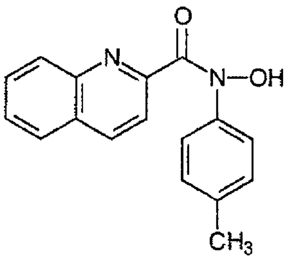

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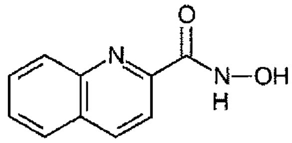

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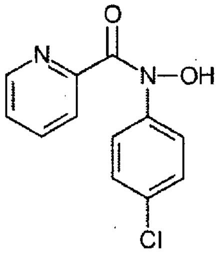

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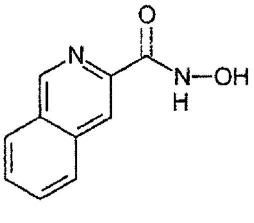
or



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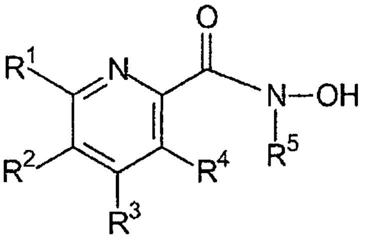
2. A pharmaceutical composition comprising:

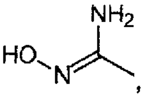
a compound having the general formula I, optionally in the form of a pharmaceutically acceptable salt, solvate, polymorph, prodrug, tautomer, racemate, enantiomer, or diastereomer or mixture thereof,



(I)

wherein

R^1 is selected from –H, –C_{1-6} alkyl, –(C_{3-7} cycloalkyl) and –CH_2–(C_{3-7} cycloalkyl);

R^2 is selected from –H, , –C_{1-6} alkyl, –Hal, –(C_{3-7} cycloalkyl), –CH_2–(C_{3-7} cycloalkyl), –$(CH_2)_m$–(optionally substituted aryl), –(optionally substituted 5- or 6-membered heterocyclic ring which contains at least one heteroatom selected from N, O and S, wherein the substituent is selected from –C_{1-4} alkyl, –halogen, –CN, –$CHal_3$, –aryl, –NR^6R^7, and –$CONR^6R^7$;

R^3 is selected from –H, –C_{1-6} alkyl,
–$(CH_2)_n$–NR^6R^8;
–(optionally substituted 5- or 6-membered carbo- or heterocyclic ring wherein the heterocyclic ring contains at least one heteroatom selected from N, O and S), wherein the substituent is selected from –Hal, –C_{1-4} alkyl, –NR^9R^{10}, –$(CH_2)_n$–OH, –C(O)–NR^9R^{10}, –SO_2–NR^9R^{10}, –NH–C(O)–O–R^{11}, –C(O)–O–R^{11}, and a 5- or 6-membered heterocyclic ring which contains at least one heteroatom selected from N, O and S;

or wherein R^1 and R^2 together form a phenyl ring or wherein R^2 and R^3 together form a phenyl ring;

R^4 is –H;

R^5 is selected from the group consisting of –H or –$(CH_2)_n$–(optionally substituted aryl) wherein the substituent is selected from –Hal and –C_{1-4} alkyl; or wherein R^4 and R^5 together form a methylene group –CH_2–, ethylene group –CH_2CH_2– or ethyne group

–CHCH–, which can be optionally substituted by –C_{1-4} alkyl, –halogen, –$CHal_3$, –R^6R^7, –OR^6, –$CONR^6R^7$, –$SO_2R^6R^7$, aryl or heteroaryl;

R^6 is selected from –H and –C_{1-4} alkyl;

R^7 is selected from –H and –C_{1-4} alkyl;

R^8 is selected from –H, –C_{1-6} alkyl, –$(CH_2)_n$–(optionally substituted aryl), –SO_2–$(CH_2)_n$–(optionally substituted aryl), –SO_2–$(CH_2)_n$–(optionally substituted 5- to 10-membered mono- or bicyclic heteroring which contains at least one heteroatom selected from N, O and S), –$(CH_2)_n$–(optionally substituted 5- or 6-membered heterocyclic ring which contains at least one heteroatom selected from N, O and S), wherein the substituent is selected from –Hal, –CF_3, –C_{1-4} alkyl, and –$(CH_2)_n$–aryl;

R^9 is selected from –H, –C_{1-4} alkyl, and –C_{1-4} alkylene–$NR^{11}R^{11}$;

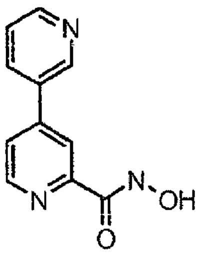
R^{10} is selected from –H, –C_{1-4} alkyl, and –C_{1-4} alkylene–$NR^{11}R^{11}$;

R^{11} is selected from –H, –CF_3, and –C_{1-4} alkyl;

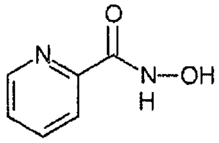
each **m** is 0 or 1; and

each **n** is independently 0, 1, 2, or 3;

with the proviso that the compound is not one of the following compounds:



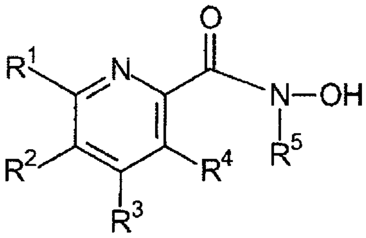
or



;

and optionally one or more pharmaceutically acceptable excipient(s) and/or carrier(s).

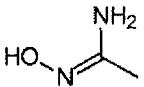
3. A compound having the general formula I, optionally in the form of a pharmaceutically acceptable salt, solvate, polymorph, prodrug, tautomer, racemate, enantiomer, or diastereomer or mixture thereof,



(I)

wherein

R^1 is selected from –H, –C_{1-6} alkyl, –(C_{3-7} cycloalkyl) and –CH_2–(C_{3-7} cycloalkyl);

R^2 is selected from –H, , –C_{1-6} alkyl, –Hal, –(C_{3-7} cycloalkyl) or –CH_2–(C_{3-7} cycloalkyl), –$(CH_2)_m$–(optionally substituted aryl), –(optionally substituted 5- or 6-membered heterocyclic ring which contains at least one heteroatom selected from N, O and S, wherein the substituent is selected from –C_{1-4} alkyl, –halogen, –CN, –$CHal_3$, –aryl, –NR^6R^7, and –$CONR^6R^7$;

R^3 is selected from –H, –C_{1-6} alkyl,
–$(CH_2)_n$–NR^6R^8;
–(optionally substituted 5- or 6-membered carbo- or heterocyclic ring wherein the heterocyclic ring contains at least one heteroatom selected from N, O and S), wherein the substituent is selected from –Hal, –C_{1-4} alkyl, –NR^9R^{10}, –$(CH_2)_n$–OH, –C(O)–NR^9R^{10}, –SO_2–NR^9R^{10}, –NH–C(O)–O–R^{11}, –C(O)–O–R^{11}, and a 5- or 6-membered heterocyclic ring which contains at least one heteroatom selected from N, O and S;

or wherein R^1 and R^2 together form a phenyl ring or wherein R^2 and R^3 together form a phenyl ring;

R^4 is –H;

R^5 is selected from the group consisting of $–H$ or $–(CH_2)_n–$(optionally substituted aryl) wherein the substituent is selected from $–Hal$ and $–C_{1–4}$ alkyl; or wherein R^4 and R^5 together form a methylene group $–CH_2–$, ethylene group $–CH_2CH_2–$ or ethyne group $–CHCH–$, which can be optionally substituted by $–C_{1–4}$ alkyl, –halogen, $–CHal_3$, $–R^6R^7$, $–OR^6$, $–CONR^6R^7$, $–SO_2R^6R^7$, aryl or heteroaryl;

R^6 is selected from $–H$ and $–C_{1–4}$ alkyl;

R^7 is selected from $–H$ and $–C_{1–4}$ alkyl;

R^8 is selected from $–H$, $–C_{1–6}$ alkyl, $–(CH_2)_n–$(optionally substituted aryl), $–SO_2–(CH_2)_n–$(optionally substituted aryl), $–SO_2–(CH_2)_n–$(optionally substituted 5- to 10-membered mono- or bicyclic heteroring which contains at least one heteroatom selected from N, O and S), $–(CH_2)_n–$(optionally substituted 5- or 6-membered heterocyclic ring which contains at least one heteroatom selected from N, O and S), wherein the substituent is selected from $–Hal$, $–CF_3$, $–C_{1–4}$ alkyl, and $–(CH_2)_n–$aryl;

R^9 is selected from $–H$, $–C_{1–4}$ alkyl, and $–C_{1–4}$ alkylene$–NR^{11}R^{11}$;

R^{10} is selected from $–H$, $–C_{1–4}$ alkyl, and $–C_{1–4}$ alkylene$–NR^{11}R^{11}$;

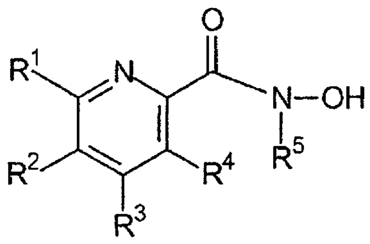
R^{11} is selected from $–H$, $–CF_3$, and $–C_{1–4}$ alkyl;

each **m** is 0 or 1; and

each **n** is independently 0, 1, 2, or 3;

wherein the compound is for use in the treatment, amelioration or prevention of a viral disease.

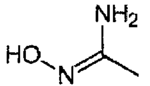
4. A method of treating, ameliorating or preventing a viral disease, the method comprising administering to a patient in need thereof an effective amount of a compound having the general formula I, optionally in the form of a pharmaceutically acceptable salt, solvate, polymorph, prodrug, tautomer, racemate, enantiomer, or diastereomer or mixture thereof,



(I)

wherein

R^1 is selected from –H, –C_{1-6} alkyl, –(C_{3-7} cycloalkyl) and –CH_2–(C_{3-7} cycloalkyl);

R^2 is selected from –H, , –C_{1-6} alkyl, –Hal, –(C_{3-7} cycloalkyl), –CH_2–(C_{3-7} cycloalkyl), –$(CH_2)_m$–(optionally substituted aryl), –(optionally substituted 5- or 6-membered heterocyclic ring which contains at least one heteroatom selected from N, O and S, wherein the substituent is selected from –C_{1-4} alkyl, –halogen, –CN, –$CHal_3$, –aryl, –NR^6R^7, and –$CONR^6R^7$;

R^3 is selected from –H, –C_{1-6} alkyl,
–$(CH_2)_n$–NR^6R^8;
–(optionally substituted 5- or 6-membered carbo- or heterocyclic ring wherein the heterocyclic ring contains at least one heteroatom selected from N, O and S), wherein the substituent is selected from –Hal, –C_{1-4} alkyl, –NR^9R^{10}, –$(CH_2)_n$–OH, –C(O)–NR^9R^{10}, –SO_2–NR^9R^{10}, –NH–C(O)–O–R^{11}, –C(O)–O–R^{11}, and a 5- or 6-membered heterocyclic ring which contains at least one heteroatom selected from N, O and S;

or wherein R^1 and R^2 together form a phenyl ring or wherein R^2 and R^3 together form a phenyl ring;

R^4 is –H;

R^5 is selected from the group consisting of –H or –$(CH_2)_n$–(optionally substituted aryl) wherein the substituent is selected from –Hal and –C_{1-4} alkyl; or wherein R^4 and R^5 together form a methylene group –CH_2–, ethylene group –CH_2CH_2– or ethyne group

–CHCH–, which can be optionally substituted by $-C_{1-4}$ alkyl, –halogen, $-CHal_3$, $-R^6R^7$, $-OR^6$, $-CONR^6R^7$, $-SO_2R^6R^7$, aryl or heteroaryl;

R^6 is selected from –H and $-C_{1-4}$ alkyl;

R^7 is selected from –H and $-C_{1-4}$ alkyl;

R^8 is selected from –H, $-C_{1-6}$ alkyl, $-(CH_2)_n$–(optionally substituted aryl), $-SO_2-(CH_2)_n$–(optionally substituted aryl), $-SO_2-(CH_2)_n$–(optionally substituted 5- to 10-membered mono- or bicyclic heteroring which contains at least one heteroatom selected from N, O and S), $-(CH_2)_n$–(optionally substituted 5- or 6-membered heterocyclic ring which contains at least one heteroatom selected from N, O and S), wherein the substituent is selected from –Hal, $-CF_3$, $-C_{1-4}$ alkyl, and $-(CH_2)_n$–aryl;

R^9 is selected from –H, $-C_{1-4}$ alkyl, and $-C_{1-4}$ alkylene–$NR^{11}R^{11}$;

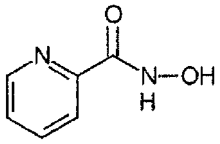
R^{10} is selected from –H, $-C_{1-4}$ alkyl, and $-C_{1-4}$ alkylene–$NR^{11}R^{11}$;

R^{11} is selected from –H, $-CF_3$, and $-C_{1-4}$ alkyl;

each **m** is 0 or 1; and

each **n** is independently 0, 1, 2, or 3.

5. The compound according to claim 3 or the method according to claim 4, wherein the compound is not:



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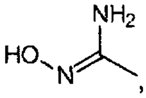
6. The compound according to claim 3 or 5 or the method according to claim 4 or 5, wherein the viral disease is caused by Herpesviridae, Retroviridae, Filoviridae, Paramyxoviridae, Rhabdoviridae, Orthomyxoviridae, Bunyaviridae, Arenaviridae,

Coronaviridae, Picornaviridae, Togaviridae, Flaviviridae; more specifically wherein the viral disease is influenza.

7. The compound according to claim 1, 3, 5 or 6, the pharmaceutical composition according to claim 2 or the method according to claim 4, 5 or 6, wherein **R^1** is selected from –H, and $–C_{1–6}$ alkyl; and wherein **R^1** is preferably –H.

8. The compound, pharmaceutical composition or method according to any of the preceding claims, wherein **R^2** is selected from –H, , $–C_{1–6}$ alkyl, $–(CH_2)_m–$(optionally substituted aryl), –(optionally substituted 5- or 6-membered heterocyclic ring which contains at least one heteroatom selected from N, O and S), wherein the substituent is selected from $–C_{1–4}$ alkyl; and wherein **R^2** is preferably selected from –H, $–C_{1–6}$ alkyl, –phenyl; and wherein **R^2** is more preferably –H.

9. The compound, pharmaceutical composition or method according to any of the preceding claims, wherein **R^3** is selected from
–H;
$–C_{1–6}$ alkyl;
$–NR^6–SO_2–(CH_2)_n–$(optionally substituted aryl), wherein the substituent is selected from –Hal, and $–CF_3$;
–(optionally substituted aryl), wherein the substituent is selected from Hal, $–NR^9R^{10}$, and $–C(O)–O–R^{11}$;
–(optionally substituted 5- or 6-membered heterocyclic ring wherein the heterocyclic ring contains at least one heteroatom selected from N, O and S), wherein the substituent is selected from –Hal, $–NR^9R^{10}$, $–C(O)–O–R^{11}$, and a 5- or 6-membered heterocyclic ring which contains at least one heteroatom selected from N, O and S.

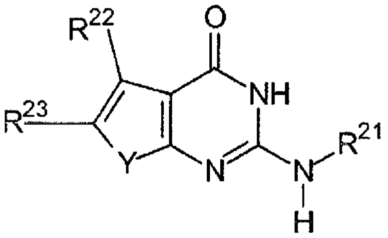
10. The compound, pharmaceutical composition or method according to any of claims 1 to 7, wherein R^2 and R^3 together form a phenyl ring.

11. The compound, pharmaceutical composition or method according to any of the preceding claims, wherein **R^5** is selected from the group consisting of –H or $–(CH_2)–$(optionally substituted phenyl) wherein the substituent is selected from –Hal and $–C_{1–4}$ alkyl; and wherein **R^5** is preferably –H.

12. The compound, pharmaceutical composition or method according to any of the preceding claims, wherein the compound having the general formula I exhibits a % reduction of at least about 30 % at 50 μM in the CPE assay disclosed herein.

13. The compound, pharmaceutical composition or method according to any of the preceding claims, wherein the compound having the general formula I exhibits an IC_{50} of at least about 40 μM in the FRET endonuclease activity assay disclosed herein.

14. A pharmaceutical composition comprising:
    (i) a compound having the general formula II, optionally in the form of a pharmaceutically acceptable salt, solvate, polymorph, prodrug, tautomer, racemate, enantiomer, or diastereomer or mixture thereof,



(II)

wherein

Y is S;

R^{21} is selected from –H, $-C_{1-6}$alkyl, $-(CH_2)_q$–aryl, $-(CH_2)_q$–heterocyclyl, $-(CH_2)_q$–cycloalkyl, $-(CH_2)_p-OR^{25}$, and $-(CH_2)_p-NR^{25}R^{26}$;

R^{22} is selected from –H, $-C_{1-6}$ alkyl, $-(CH_2)_q$–cycloalkyl, –Hal, $-CF_3$ and –CN;

R^{23} is selected from –aryl, –heterocyclyl, –cycloalkyl, $-C(-R^{28})(-R^{29})$–aryl, $-C(-R^{28})(-R^{29})$–heterocyclyl, and $-C(-R^{28})(-R^{29})$–cycloalkyl;

R^{25} is selected from –H, $-C_{1-6}$ alkyl, and $-(CH_2CH_2O)_rH$;

R^{26} is selected from –H, and $-C_{1-6}$ alkyl;

R^{27} is independently selected from $-C_{1-6}$ alkyl, $-C(O)-C_{1-6}$ alkyl, –Hal, $-CF_3$, –CN, $-COOR^{25}$, $-OR^{25}$, $-(CH_2)_qNR^{25}R^{26}$, $-C(O)-NR^{25}R^{26}$, and $-NR^{25}-C(O)-C_{1-6}$ alkyl;

R^{28} and R^{29} are independently selected from –H, $-C_{1-6}$ alkyl, $-(CH_2)_q$–aryl, $-(CH_2)_q$–heterocyclyl, $-(CH_2)_q$–cycloalkyl, –OH, $-O-C_{1-6}$ alkyl, $-O-(CH_2)_q$–aryl, $-O-(CH_2)_q$–heterocyclyl, and $-O-(CH_2)_q$–cycloalkyl;
or R^{28} and R^{29} are together =O, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, or $-CH_2CH_2CH_2CH_2-$;

p is 1 to 4;

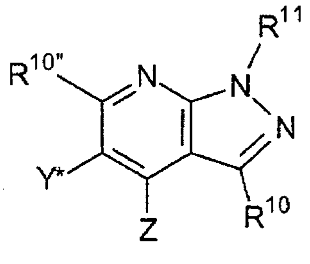
q is 0 to 4; and

r is 1 to 3;

wherein the aryl group, heterocyclyl group and/or cycloalkyl group can be optionally substituted with one or more substituents R^{27};

and/or

a compound having the general formula (XXI):



or a pharmaceutically effective salt, a solvate, a prodrug, a tautomer, a racemate, an enantiomer or a diastereomer thereof;

wherein

one of **Y*** and **Z** is $-XR^{12}$ and the other is $R^{10'}$;

R^{10}, **$R^{10'}$** and **$R^{10''}$** are each individually selected from the group consisting of hydrogen, C_1–C_6-alkyl, C_2–C_6-alkenyl, C_2-C_8-alkynyl, $-(CH_2)_tC(O)OH$, $-(CH_2)_tC(O)OR^{16}$, $-(CH_2)_tOH$, $-(CH_2)_tOR^{16}$, $-CF_3$, $-(CH_2)_t$–cycloalkyl, $-(CH_2)_tC(O)NH_2$, $-(CH_2)_tC(O)NHR^{16}$, $-(CH_2)_tC(O)NR^{16}R^{17}$, $-(CH_2)_tS(O)_2NH_2$, $-(CH_2)_tS(O)_2NHR^{16}$, $-(CH_2)_tS(O)_2NR^{16}R^{17}$, $-(CH_2)_tS(O)_2R^{16}$, halogen, –CN, $-(CH_2)_t$–aryl, $-(CH_2)_t$–heteroaryl, $-(CH_2)_tNH_2$, $-(CH_2)_tNHR^{16}$, and $-(CH_2)_tNR^{16}R^{17}$; optionally substituted;

R^{11} is selected from the group consisting of hydrogen, C_1–C_6-alkyl, $-CF_3$, C_2-C_6–alkenyl, C_2–C_8-alkynyl, $-(CH_2)_t$–cycloalkyl, $-(CH_2)_t$–aryl, $-(CH_2)_t$–heterocycloalkyl and $-(CH_2)_t$–heteroaryl; optionally substituted;

X is selected from the group consisting of CH_2, C(O), C(S), CH(OH), $CH(OR^{16})$, $S(O)_2$, $-S(O)_2-N(H)-$, $-S(O)_2-N(R^{16})-$, $-N(H)-S(O)_2-$, $-N(R^{16})-S(O)_2-$, C(=NH), $C(=N-R^{16})$, $CH(NH_2)$, $CH(NHR^{16})$, $CH(NR^{16}R^{17})$, –C(O)–N(H)–, $-C(O)-N(R^{16})-$, –N(H)–C(O)–, $-N(R^{16})-C(O)-$, N(H), $N(-R^{16})$ and O;

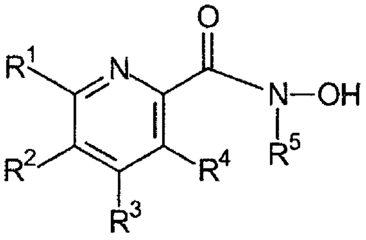
R^{12} is selected from the group consisting of C_1–C_6-alkyl, $-CF_3$, C_2-C_6-alkenyl, C_2-C_8-alkynyl, $-(CH_2)_t$–cycloalkyl, $-(CH_2)_t$–heterocycloalkyl, $-(CH_2)_t$–aryl, $-NR^{16}R^{17}$, and $-(CH_2)_t$–heteroaryl; optionally substituted;

R^{16} and **R^{17}** are independently selected from the group consisting of C_1–C_6-alkyl, C_2–C_6-alkenyl, C_2–C_6-alkynyl, $-(CH_2)_t$–cycloalkyl, $-(CH_2)_t$–aryl, $-CF_3$, $-C(O)R^{18}$ and $-S(O)_2R^{18}$; optionally substituted;

R^{18} is independently selected from the group consisting of C_1–C_6-alkyl, C_2–C_6-alkenyl, C_2–C_6-alkynyl, $-(CH_2)_t$–cycloalkyl and $-CF_3$; optionally substituted; and

t is in each instance selected from 0, 1 and 2;

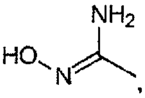
(ii) a compound having the general formula I, optionally in the form of a pharmaceutically acceptable salt, solvate, polymorph, prodrug, tautomer, racemate, enantiomer, or diastereomer or mixture thereof,



(I)

wherein

R^1 is selected from –H, $-C_{1-6}$ alkyl, $-(C_{3-7}$ cycloalkyl) and $-CH_2-(C_{3-7}$ cycloalkyl);

R^2 is selected from –H, , $-C_{1-6}$ alkyl, –Hal, $-(C_{3-7}$ cycloalkyl), $-CH_2-(C_{3-7}$ cycloalkyl), $-(CH_2)_m-$(optionally substituted aryl), –(optionally substituted 5- or 6-membered heterocyclic ring which contains at least one heteroatom selected from N, O and S, wherein the substituent is selected from $-C_{1-4}$ alkyl, –halogen, –CN, $-CHal_3$, –aryl, $-NR^6R^7$, and $-CONR^6R^7$;

R^3 is selected from –H, $-C_{1-6}$ alkyl,
$-(CH_2)_n-NR^6R^8$,
–(optionally substituted 5- or 6-membered carbo- or heterocyclic ring wherein the heterocyclic ring contains at least one heteroatom selected from N, O and S), wherein the substituent is selected from –Hal, $-C_{1-4}$ alkyl, $-NR^9R^{10}$, $-(CH_2)_n-OH$, $-C(O)-NR^9R^{10}$, $-SO_2-NR^9R^{10}$, $-NH-C(O)-O-R^{11}$, $-C(O)-O-R^{11}$, and a 5- or 6-membered heterocyclic ring which contains at least one heteroatom selected from N, O and S;

or wherein R^1 and R^2 together form a phenyl ring or wherein R^2 and R^3 together form a phenyl ring;

R^4 is –H;

R^5 is selected from the group consisting of –H or –$(CH_2)_n$–(optionally substituted aryl), wherein the substituent is selected from –Hal and –C_{1-4} alkyl; or wherein R^4 and R^5 together form a methylene group –CH_2–, ethylene group –CH_2CH_2– or ethyne group –CHCH–, which can be optionally substituted by –C_{1-4} alkyl, –halogen, –$CHal_3$, –R^6R^7, –OR^6, –$CONR^6R^7$, –$SO_2R^6R^7$, aryl or heteroaryl;

R^6 is selected from –H and –C_{1-4} alkyl;

R^7 is selected from –H and –C_{1-4} alkyl;

R^8 is selected from –H, –C_{1-6} alkyl, –$(CH_2)_n$–(optionally substituted aryl), –SO_2–$(CH_2)_n$–(optionally substituted aryl), –SO_2–$(CH_2)_n$–(optionally substituted 5- to 10-membered mono- or bicyclic heteroring which contains at least one heteroatom selected from N, O and S), –$(CH_2)_n$–(optionally substituted 5- to 10-membered mono- or bicyclic heteroring which contains at least one heteroatom selected from N, O and S), wherein the substituent is selected from –Hal, –CF_3, –C_{1-4} alkyl, and –$(CH_2)_n$–aryl;

R^9 is selected from –H, –C_{1-4} alkyl, and –C_{1-4} alkylene–$NR^{11}R^{11}$;

R^{10} is selected from –H, –C_{1-4} alkyl, and –C_{1-4} alkylene–$NR^{11}R^{11}$;

R^{11} is selected from –H, –CF_3, and –C_{1-4} alkyl;

each **m** is 0 or 1; and

each **n** is independently 0, 1, 2, or 3;

and optionally one or more pharmaceutically acceptable excipient(s) and/or carrier(s).

15. A pharmaceutical composition comprising:

(i) a compound having the general formula (I), (II) or (XXI) as defined in claim 14; and

(ii) at least one polymerase inhibitor which is different from the compound having the general formula (I), (II) or (XXI);

and optionally one or more pharmaceutically acceptable excipient(s) and/or carrier(s).

16. A pharmaceutical composition comprising:

(i) a compound having the general formula (I), (II) or (XXI) as defined in claim 14; and
(ii) at least one neuramidase inhibitor;

and optionally one or more pharmaceutically acceptable excipient(s) and/or carrier(s).

17. A pharmaceutical composition comprising:

(i) a compound having the general formula (I), (II) or (XXI) as defined in claim 14; and
(ii) at least one M2 channel inhibitor;

and optionally one or more pharmaceutically acceptable excipient(s) and/or carrier(s).

18. A pharmaceutical composition comprising:

(i) a compound having the general formula (I), (II) or (XXI) as defined in claim 14; and
(ii) at least one alpha glucosidase inhibitor;

and optionally one or more pharmaceutically acceptable excipient(s) and/or carrier(s).

19. A pharmaceutical composition comprising:

(i) a compound having the general formula (I), (II) or (XXI) as defined in claim 14; and
(ii) at least one ligand of another influenza target;

and optionally one or more pharmaceutically acceptable excipient(s) and/or carrier(s).

20. A pharmaceutical composition comprising:

(i) a compound having the general formula (I), (II) or (XXI) as defined in claim 14; and

(ii) at least one medicament selected from antibiotics, anti-inflammatory agents, lipoxygenase inhibitors, EP ligands, bradykinin ligands, and cannabinoid ligands;

and optionally one or more pharmaceutically acceptable excipient(s) and/or carrier(s).

21. The pharmaceutical composition as defined in any of claims 14 to 20 for use in the treatment, amelioration or prevention of a viral disease.

22. A method of treating, ameliorating or preventing a viral disease, the method comprising administering to a patient in need thereof an effective amount of a pharmaceutical composition as defined in any of claims 14 to 20.

23. The pharmaceutical composition according to claim 21 or the method according to claim 22, wherein the viral disease is caused by Herpesviridae, Retroviridae, Filoviridae, Paramyxoviridae, Rhabdoviridae, Orthomyxoviridae, Bunyaviridae, Arenaviridae, Coronaviridae, Picornaviridae, Togaviridae, Flaviviridae; more specifically wherein the viral disease is influenza.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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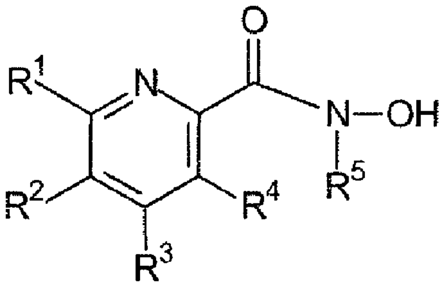
(81) **Designated States** *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) **Designated States** *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

[Continued on next page]

(54) Title: HETEROARYL HYDROXAMIC ACID DERIVATIVES AND THEIR USE IN THE TREATMENT, AMELIORATION OR PREVENTION OF A VIRAL DISEASE



(I)

(57) **Abstract**: The present invention relates to a compound having the general formula I, optionally in the form of a pharmaceutically acceptable salt, solvate, polymorph, prodrug, tautomer, racemate, enantiomer, or dsasiereomer or mixture thereof, which is useful in treating, ameliorating or preventing a viral disease. Furthermore, specific combination therapies are disclosed.

WO 2013/057251 A3

Published:

- *with international search report (Art. 21(3))*
- *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2012/070757

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

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

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

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

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

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

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

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

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

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

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

1-14(completely); 15-23(partially)

Remark on Protest

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

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

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2012/070757

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D213/81 C07D217/26 C07D401/04 C07D401/12 C07D401/14 C07D405/08 C07D413/04 C07D471/04 C07D495/04 A61K31/44 A61P31/16

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2010/100475 A1 (ASTRAZENECA AB [SE]; ASTRAZENECA UK LTD [GB]; BENENATO KERRY ELLEN [US) 10 September 2010 (2010-09-10) claims 10,16 pages 61,64 -----	1,2,7-9, 11-13, 15,20
X	CIANCI C ET AL: "IDENTIFICATION OF N-HYDROXAMIC ACID AND N-HYDROXYIMIDE COMPOUNDS THAT INHIBIT THE INFLUENZA VIRUS POLYMERASE", ANTIVIRAL CHEMISTRY & CHEMOTHERAPY, BLACKWELL SCIENTIFIC PUBL., LONDON, GB, vol. 7, no. 6, 1 January 1996 (1996-01-01), pages 353-360, XP002925548, ISSN: 0956-3202 cited in the application page 356; compounds 3-6 ----- -/--	1-23

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

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 December 2012	22/04/2013

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Gutke, Hans-Jürgen

1

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	MONIKA BARBARIC ET AL: "Synthesis, X-ray Crystal Structure Study, and Cytostatic and Antiviral Evaluation of the Novel Cycloalkyl- N -aryl-hydroxamic Acids", JOURNAL OF MEDICINAL CHEMISTRY, vol. 48, no. 3, 1 February 2005 (2005-02-01), pages 884-887, XP055046169, ISSN: 0022-2623, DOI: 10.1021/jm040878r table 2 -----	1-23
X	LIPCZYNSKA-KOCHANY E ET AL: "Mutagenicity of pyridine- and quinoline-carbohydroxamic acid derivatives", MUTATION RESEARCH/GENETIC TOXICOLOGY, ELSEVIER, vol. 135, no. 3, 1 March 1984 (1984-03-01), pages 139-148, XP025590934, ISSN: 0165-1218, DOI: 10.1016/0165-1218(84)90114-9 [retrieved on 1984-03-01] table 1; compounds I, VIII, XII -----	1,2,7-13
X	AGRAWAL V K ET AL: "Physiochemical properties of hydroxamic acids", JOURNAL OF THE INDIAN CHEMICAL SOCIETY, THE INDIAN CHEMICAL SOCIETY, CALCUTTA; IN, vol. 67, 1 May 1990 (1990-05-01), pages 371-373, XP009165541, ISSN: 0019-4522 table 1; compounds 3,4,8,9 -----	1,2,7-13
X	DATABASE PUBCHEM [Online] NCBI; 21 June 2010 (2010-06-21), XP002689541, Database accession no. CID45588229 the whole document -----	1,7-13
X	DATABASE PUBCHEM [Online] NCBI; 29 February 2008 (2008-02-29), XP002689542, Database accession no. CID 24703650 the whole document -----	1,7-13
A	WO 2011/000566 A2 (SAVIRA PHARMACEUTICALS GMBH [AT]; EUROP MOLECULAR BIOLOGY LAB EMBL [DE) 6 January 2011 (2011-01-06) cited in the application claims 1,31 ----- -/--	1-23

1

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	RASHAD A E ET AL: "Synthesis and screening of some novel fused thiophene and thienopyrimidine derivatives for anti-avian influenza virus (H5N1) activity", EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY, EDITIONS SCIENTIFIQUE ELSEVIER, PARIS, FR, vol. 45, no. 11, 1 November 2010 (2010-11-01), pages 5251-5257, XP027408942, ISSN: 0223-5234 [retrieved on 2010-08-24] figure 1 -----	1-23

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2012/070757

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2010100475 A1	10-09-2010	NONE	
WO 2011000566 A2	06-01-2011	NONE	

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-14(completely); 15-23(partially)

   pyridyl hydroxamic acids of formula I

   \-\-\-

2. claims: 15-23(partially)

   pharmaceutical composition comprising thieno-pyrimidines of formula II and not pyridyl hydroxamic acids of formula I

   \-\-\-

3. claims: 15-23(partially)

   pharmaceutical composition comprising pyrazolo pyridines of formula XXI and neither pyridyl hydroxamic acids of formula I nor thieno-pyrimidines of formula II

   \-\-\-

(19) 中华人民共和国国家知识产权局

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(87) PCT国际申请的公布数据
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C·莫里斯 C·米绍-西蒙
C·苏维塔

(74) 专利代理机构 北京市中咨律师事务所
11247
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C07D 213/81 (2006.01)
C07D 217/26 (2006.01)
C07D 401/04 (2006.01)
C07D 401/12 (2006.01)
C07D 401/14 (2006.01)
C07D 405/08 (2006.01)
C07D 413/04 (2006.01)
C07D 471/04 (2006.01)
C07D 495/04 (2006.01)
A61K 31/44 (2006.01)
A61P 31/16 (2006.01)

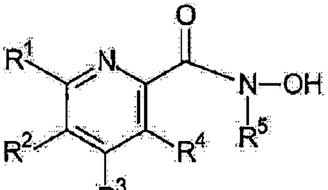
权利要求书9页 说明书121页

(54) 发明名称

杂芳基异羟肟酸衍生物及其在治疗、减轻或预防病毒疾病中的用途

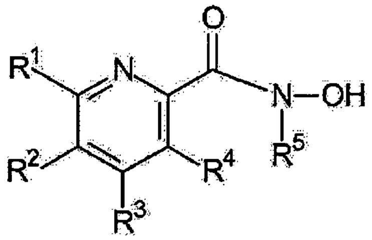
(57) 摘要

本发明涉及具有通式I的化合物、任选地其药学上可接受的盐、溶剂化物、多晶型物、前药、互变异构体、外消旋物、对映异构体、或非对映异构体或混合物的形式，其可用于治疗、减轻或预防病毒疾病。此外，公开了特定的组合疗法。



(I)

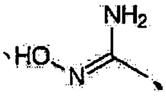
1. 具有通式Ⅰ的化合物、任选地其药学上可接受的盐、溶剂化物、多晶型物、前药、互变异构体、外消旋物、对映异构体、或非对映异构体或混合物的形式，



(I)

其中

R^1 选自 -H、$-C_{1-6}$ 烷基、-(C_{3-7} 环烷基）和 $-CH_2-$(C_{3-7} 环烷基）；

R^2 选自 -H、 $-C_{1-6}$ 烷基、-Hal、-(C_{3-7} 环烷基）、$-CH_2-$(C_{3-7} 环烷基）、$-(CH_2)_m-$（任选取代的芳基）、-（任选取代的 5- 或 6- 元杂环，其含有至少一个选自 N、O 和 S 的杂原子，其中所述取代基选自 $-C_{1-4}$ 烷基、- 卤素、-CN、$-CHal_3$、- 芳基、$-NR^6R^7$ 和 $-CONR^6R^7$；

R^3 选自 -H、$-C_{1-6}$ 烷基、

$-(CH_2)_n-NR^6R^8$，

-（任选取代的 5- 或 6- 元碳环或杂环，其中所述杂环含有至少一个选自 N、O 和 S 的杂原子），其中所述取代基选自 -Hal、$-C_{1-4}$ 烷基、$-NR^9R^{10}$、$-(CH_2)_n-OH$、$-C(O)-NR^9R^{10}$、$-SO_2-NR^9R^{10}$、$-NH-C(O)-O-R^{11}$、$-C(O)-O-R^{11}$ 和含有至少一个选自 N、O 和 S 的杂原子的 5- 或 6- 元杂环；

或其中 R^1 和 R^2 一起形成苯基环或其中 R^2 和 R^3 一起形成苯基环；

R^4 是 -H；

R^5 选自 -H 或 $-(CH_2)_n-$（任选取代的芳基），其中所述取代基选自 -Hal 和 $-C_{1-4}$ 烷基；或其中 R^4 和 R^5 一起形成亚甲基 $-CH_2-$、亚乙基 $-CH_2CH_2-$ 或乙炔基团 -CHCH-，其可任选地被 $-C_{1-4}$ 烷基、- 卤素、$-CHal_3$、$-R^6R^7$、—OR^6、$-CONR^6R^7$、$-SO_2R^6R^7$、芳基或杂芳基取代；

R^6 选自 -H 和 $-C_{1-4}$ 烷基；

R^7 选自 -H 和 $-C_{1-4}$ 烷基；

R^8 选自 -H、$-C_{1-6}$ 烷基、$-(CH_2)_n-$（任选取代的芳基）、$-SO_2-(CH_2)_n-$（任选取代的芳基）、$-SO_2-(CH_2)_n-$（任选取代的 5- 至 10- 元单 - 或双环杂环，其含有至少一个选自 N、O 和 S 的杂原子）、$-(CH_2)_n-$（含有至少 - 个选自 N、O 和 S 的杂原子的任选取代的 5- 或 6- 元杂环），其中所述取代基选自 -Hal、$-CF_3$、$-C_{1-4}$ 烷基和 $-CH_2)_n-$ 芳基；

R^9 选自 -H、$-C_{1-4}$ 烷基和 $-C_{1-4}$ 亚烷基 $-NR^{11}R^{11}$；

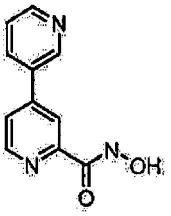
R^{10} 选自 -H、$-C_{1-4}$ 烷基和 $-C_{1-4}$ 亚烷基 $-NR^{11}R^{11}$；

R^{11} 选自 -H、$-CF_3$ 和 $-C_{1-4}$ 烷基；

每个 m 为 0 或 1；且

每个 n 独立地为 0、1、2 或 3；

前提条件是所述化合物不是下列化合物中的一种：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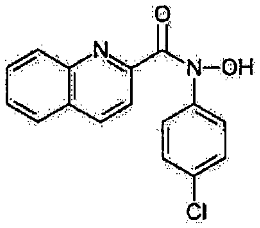
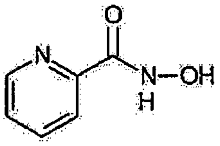
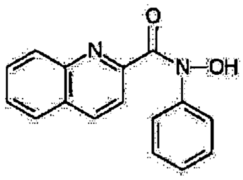
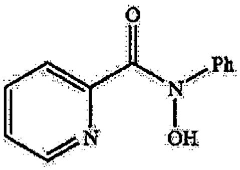

、


、


、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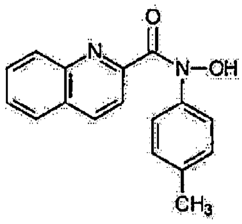
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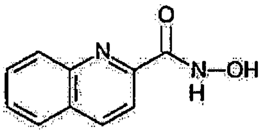
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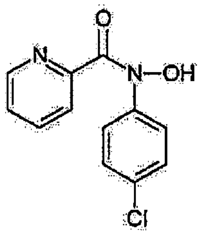
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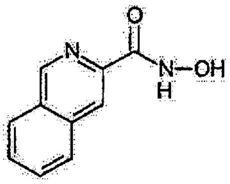
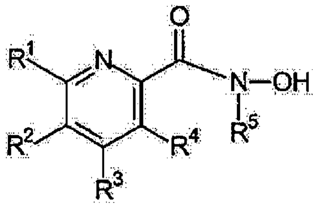
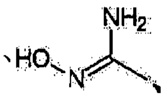
或

。

2. 药物组合物，包含：具有通式 I 的化合物、任选地其药学上可接受的盐、溶剂化物、多晶型物、前药、互变异构体、外消旋物、对映异构体、或非对映异构体或混合物的形式，和任选的一种或多种药学上可接受的赋形剂和/或载体，


(I)

其中

R^1 选自 $-H$、$-C_{1-6}$ 烷基、$-(C_{3-7}$ 环烷基）和 $-CH_2-(C_{3-7}$ 环烷基）；

R^2 选自 $-H$、、$-C_{1-6}$ 烷基、$-Hal$、$-(C_{3-7}$ 环烷基）、$-CH_2-(C_{3-7}$ 环烷基）、$-(CH_2)_m$-（任选取代的芳基）、-（任选取代的 5- 或 6- 元杂环，其含有至少一个选自 N、O 和 S 的杂原子），其中所述取代基选自 $-C_{1-4}$ 烷基、- 卤素、$-CN$、$-CHal_3$、- 芳基、$-NR^6R^7$ 和 $-CONR^6R^7$；

R^3 选自 -H、-C_{1-6} 烷基、

-$(CH_2)_n$—NR^6R^8；

-（任选取代的 5- 或 6- 元碳环或杂环，其中所述杂环含有至少一个选自 N、O 和 S 的杂原子），其中所述取代基选自 -Hal、-C_{1-4} 烷基、-NR^9R^{10}、-$(CH_2)_n$-OH、-C(O)-NR^9R^{10}、 -SO_2-NR^9R^{10}、-NH-C(O)-O-R^{11}、-C(O)-O-R^{11} 和含有至少一个选自 N、O 和 S 的杂原子的 5- 或 6- 元杂环；

或其中 R^1 和 R^2 一起形成苯基环或其中 R^2 和 R^3 一起形成苯基环；

R^4 是 -H；

R^5 选自 -H 或 -$(CH_2)_n$-（任选取代的芳基），其中所述取代基选自 -Hal 和 -C_{1-4} 烷基；或其中 R^4 和 R^5 一起形成亚甲基 -CH_2-、亚乙基 -CH_2CH_2- 或乙炔基团 -CHCH-，其可任选地被 -C_{1-4} 烷基、- 卤素、-$CHal_3$、-R^6R^7、-OR^6、-$CONR^6R^7$、-$SO_2R^6R^7$、芳基或杂芳基取代；

R^6 选自 -H 和 -C_{1-4} 烷基；

R^7 选自 -H 和 -C_{1-4} 烷基；

R^8 选自 -H、-C_1-$_6$ 烷基、-$(CH_2)_n$-（任选取代的芳基）、-SO_2-$(CH_2)_n$-（任选取代的芳基）、-SO_2-$(CH_2)_n$-（任选取代的 5- 至 10- 元单 - 或双环杂环，其含有至少一个选自 N、O 和 S 的杂原子）、-$(CH_2)_n$-（含有至少一个选自 N、O 和 S 的杂原子的任选取代的 5- 或 6- 元杂环），其中所述取代基选自 -Hal、-CF_3、-C_{1-4} 烷基和 -$(CH_2)_n$- 芳基；

R^9 选自 -H、-C_{1-4} 烷基和 -C_{1-4} 亚烷基 -$NR^{11}R^{11}$；

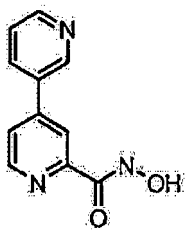
R^{10} 选自 -H、-C_{1-4} 烷基和 -C_{1-4} 亚烷基 -$NR^{11}R^{11}$；

R^{11} 选自 -H、-CF_3 和 -C_{1-4} 烷基；

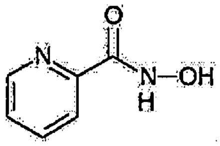
每个 m 为 0 或 1；且

每个 n 独立地为 0、1、2 或 3；

前提条件是所述化合物不是下列化合物中的一种：

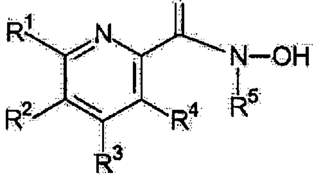


或



。

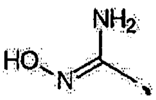
3. 具有通式 I 的化合物、任选地其药学上可接受的盐、溶剂化物、多晶型物、前药、互变异构体、外消旋物、对映异构体、或非对映异构体或混合物的形式，



(I)

其中

R^1 选自 -H、-C_{1-6} 烷基、-（C_{3-7} 环烷基）和 -CH_2-（C_{3-7} 环烷基）；

R^2 选自 -H、 $-C_{1-6}$ 烷基、-Hal、$-(C_{3-7}$ 环烷基）或 $-CH_2-(C_{3-7}$ 环烷基）、$-(CH_2)_m-$（任选取代的芳基）、-（任选取代的 5- 或 6- 元杂环，其含有至少一个选自 N、O 和 S 的杂原子，其中所述取代基选自 $-C_{1-4}$ 烷基、- 卤素、-CN、$-CHal_3$、- 芳基、$-NR^6R^7$ 和 $-CONR^6R^7$；

R^3 选自 -H、$-C_{1-6}$ 烷基、

$-(CH_2)_n-NR^6R^8$；

-（任选取代的 5- 或 6- 元碳环或杂环，其中所述杂环含有至少一个选自 N、O 和 S 的杂原子），其中所述取代基选自 -Hal、$-C_{1-4}$ 烷基、$-NR^9R^{10}$、$-(CH_2)_n-OH$、$-C(O)-NR^9R^{10}$、$-SO_2-NR^9R^{10}$、$-NH-C(O)-O-R^{11}$、$-C(O)-O-R^{11}$ 和含有至少一个选自 N、O 和 S 的杂原子的 5- 或 6- 元杂环；

或其中 R^1 和 R^2 一起形成苯基环或其中 R^2 和 R^3 一起形成苯基环；

R^4 是 -H；

R^5 选自 -H 或 $-(CH_2)_n-$（任选取代的芳基），其中所述取代基选自 -Hal 和 $-C_{1-4}$ 烷基；或其中 R^4 和 R^5 一起形成亚甲基 $-CH_2-$、亚乙基 $-CH_2CH_2-$ 或乙炔基团 -CHCH-，其可任选地被 $-C_{1-4}$ 烷基、- 卤素、$-CHal_3$、$-R^6R^7$、$-OR^6$、$-CONR^6R^7$、$-SO_2R^6R^7$、芳基或杂芳基取代；

R^6 选自 -H 和 $-C_{1-4}$ 烷基；

R^7 选自 -H 和 $-C_{1-4}$ 烷基；

R^8 选自 -H、$-C_{1-6}$ 烷基、$-(CH_2)_n-$（任选取代的芳基）、$-SO_2-(CH_2)_n-$（任选取代的芳基）、$-SO_2-(CH_2)_n-$（任选取代的 5- 至 10- 元单 - 或双环杂环，其含有至少一个选自 N、O 和 S 的杂原子）、$-(CH_2)_n-$（含有至少一个选自 N、O 和 S 的杂原子的任选取代的 5- 或 6- 元杂环），其中所述取代基选自 -Hal、$-CF_3$、$-C_{1-4}$ 烷基和 $-(CH_2)_n-$ 芳基；

R^9 选自 -H、$-C_{1-4}$ 烷基和 $-C_{1-4}$ 亚烷基 $-NR^{11}R^{11}$；

R^{10} 选自 -H、$-C_{1-4}$ 烷基和 $-C_{1-4}$ 亚烷基 $-NR^{11}R^{11}$；

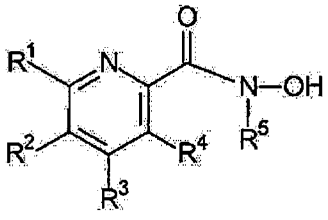
R^{11} 选自 -H、$-CF_3$ 和 $-C_{1-4}$ 烷基；

每个 m 为 0 或 1；且

每个 n 独立地为 0、1、2 或 3；

其中所述化合物用于治疗、减轻或预防病毒疾病。

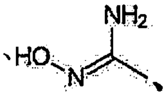
4. 治疗、减轻或预防病毒疾病的方法，所述方法包括向需要其的患者施用有效量的具有通式 I 的化合物、任选地其药学上可接受的盐、溶剂化物、多晶型物、前药、互变异构体、外消旋物、对映异构体、或非对映异构体或混合物的形式，



(I)

其中

R^1 选自 -H、$-C_{1-6}$ 烷基、$-(C_{3-7}$ 环烷基）和 $-CH_2-(C_{3-7}$ 环烷基）；

R^2 选自 -H、

$-C_{1-6}$ 烷基、-Hal、$-(C_{3-7}$ 环烷基)、$-CH_2-(C_{3-7}$ 环烷基)、$-(CH_2)_m-$(任选取代的芳基)、-(任选取代的 5- 或 6- 元杂环，其含有至少一个选自 N、O 和 S 的杂原子，其中所述取代基选自 $-C_{1-4}$ 烷基、- 卤素、-CN、$-CHal_3$、- 芳基、$-NR^6R^7$ 和 $-CONR^6R^7$；

R^3 选自 -H、$-C_{1-6}$ 烷基、

$-(CH_2)_n-NR^6R^8$；

-(任选取代的 5- 或 6- 元碳环或杂环，其中所述杂环含有至少一个选自 N、O 和 S 的杂原子)，其中所述取代基选自 -Hal、$-C_{1-4}$ 烷基、$-NR^9R^{10}$、$-(CH_2)_n-OH$、$-C(O)-NR^9R^{10}$、$-SO_2-NR^9R^{10}$、$-NH-C(O)-O-R^{11}$、$-C(O)-O-R^{11}$ 和含有至少一个选自 N、O 和 S 的杂原子的 5- 或 6- 元杂环；

或其中 R^1 和 R^2 一起形成苯基环或其中 R^2 和 R^3 一起形成苯基环；

R^4 是 -H；

R^5 选自 -H 或 $-(CH_2)_n-$(任选取代的芳基)，其中所述取代基选自 -Hal 和 $-C_{1-4}$ 烷基；或其中 R^4 和 R^5 一起形成亚甲基 $-CH_2-$、亚乙基 $-CH_2CH_2-$ 或乙炔基团 -CHCH-，其可任选地被 $-C_{1-4}$ 烷基、- 卤素、$-CHal_3$、$-R^6R^7$、$-OR^6$、$-CONR^6R^7$、$-SO_2R^6R^7$、芳基或杂芳基取代；

R^6 选自 -H 和 $-C_{1-4}$ 烷基；

R^7 选自 -H 和 $-C_{1-4}$ 烷基；

R^8 选自 -H、$-C_{1-6}$ 烷基、$-(CH_2)_n-$(任选取代的芳基)、$-SO_2-(CH_2)_n-$(任选取代的芳基)、$-SO_2-(CH_2)_n-$(任选取代的 5- 至 10- 元单 - 或双环杂环，其含有至少一个选自 N、O 和 S 的杂原子)、$-(CH_2)_n-$(含无至少一个选自 N、O 和 S 的杂原子的任选取代的 5- 或 6- 元杂环)，其中所述取代基选自 -Hal、$-CF_3$、$-C_{1-4}$ 烷基和 $-(CH_2)_n-$ 芳基；

R^9 选自 -H、$-C_{1-4}$ 烷基和 $-C_{1-4}$ 亚烷基 $-NR^{11}R^{11}$；

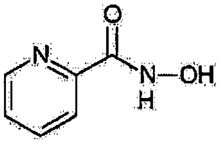
R^{10} 选自 -H、$-C_{1-4}$ 烷基和 $-C_{1-4}$ 亚烷基 $-NR^{11}R^{11}$；

R^{11} 选自 -H、$-CF_3$ 和 $-C_{1-4}$ 烷基；

每个 m 为 0 或 1；且

每个 n 独立地为 0、1、2 或 3。

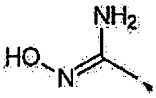
5. 根据权利要求 3 的化合物或根据权利要求 4 的方法，其中所述化合物不是：



。

6. 根据权利要求 3 或 5 的化合物或根据权利要求 4 或 5 的方法，其中所述病毒疾病由疱疹病毒科、逆转录病毒科、纤丝病毒科、副粘液病毒科、弹状病毒科、正粘液病毒科、布尼亚病毒科、砂粒病毒科、冠状病毒科、细小 RNA 病毒科、披膜病毒科、黄病毒科引起；更具体地讲，其中所述病毒疾病是流感。

7. 根据权利要求 1、3、5 或 6 的化合物、根据权利要求 2 的药物组合物或根据权利要求 4、5 或 6 的方法，其中 R^1 选自 -H 和 $-C_{1-6}$ 烷基；且其中 R^1 优选为 -H。

8. 根据前述权利要求中任一项的化合物、药物组合物或方法，其中 R^2 选自 -H、

$-C_{1-6}$ 烷基、$-(CH_2)m-$(任选取代的芳基)、-(含有至少一个选自 N、O 和 S 的杂

原子的任选取代的 5- 或 6- 元杂环），其中所述取代基选自 $-C_{1-4}$ 烷基；且其中 R2 优选选自 -H、$-C_{1-6}$ 烷基、- 苯基；且其中 R^2 更优选地为 -H。

9. 根据前述权利要求中任一项的化合物、药物组合物或方法，其中 R^3 选自

-H；

$-C_{1-6}$ 烷基；

$-NR^6-SO_2-(CH_2)_n-$（任选取代的芳基），其中所述取代基选自 -Hal 和 $-CF_3$；

-（任选取代的芳基），其中所述取代基选自 Hal、$-NR^9R^{10}$ 和 $-C(O)-O-R^{11}$；

-（任选取代的 5- 或 6- 元杂环，其中所述杂环含有至少一个选自 N、O 和 S 的杂原子），其中所述取代基选自 -Hal、$-NR^9R^{10}$、$-C(O)-O-R^{11}$ 和含有至少一个选自 N、O 和 S 的杂原子的 5- 或 6- 元杂环。

10. 根据权利要求 1 至 7 中任一项的化合物、药物组合物或方法，其中 R^2 和 R^3 一起形成苯基环。

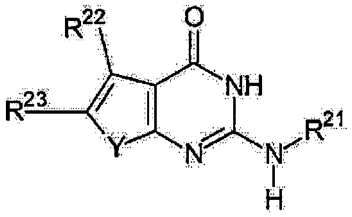
11. 根据前述权利要求中任一项的化合物、药物组合物或方法，其中 R^5 选自 -H 或 $-(CH_2)-$（任选取代的苯基），其中所述取代基选自 -Hal 和 $-C_{1-4}$ 烷基；且其中 R^5 优选为 -H。

12. 根据前述权利要求中任一项的化合物、药物组合物或方法，其中在本文公开的 CPE 测定中，所述具有通式 I 的化合物在 50 μM 时展现出至少约 30% 的减少%。

13. 根据前述权利要求中任一项的化合物、药物组合物或方法，其中在本文公开的 FRET 核酸内切酶活性测定中，所述具有通式 I 的化合物展现出至少约 40 μM 的 IC_{50}。

14. 药物组合物，包含

(i) 具有通式 II 的化合物、任选地其药学上可接受的盐、溶剂化物、多晶型物、前药、互变异构体、外消旋物、对映异构体、或非对映异构体或混合物的形式，



(II)

其中

Y 是 S；

R^{21} 选自 -H、$-C_{1-6}$ 烷基、$-(CH_2)_q-$ 芳基、$-(CH_2)_q-$ 杂环基、$-(CH_2)_q-$ 环烷基、$-(CH_2)_p-OR^{25}$ 和 $-(CH_2)_p-NR^{25}R^{26}$；

R^{22} 选自 -H、$-C_{1-6}$ 烷基、$-(CH_2)_q-$ 环烷基、-Hal、$-CF_3$ 和 -CN；

R^{23} 选自 - 芳基、- 杂环基、- 环烷基、$-C(-R^{28})(-R^{29})-$ 芳基、$-C(-R^{28})(-R^{29})-$ 杂环基、和 $-C(-R^{28})(-R^{29})-$ 环烷基；

R^{25} 选自 -H、$-C_{1-6}$ 烷基和 $-(CH_2CH_2O)_rH$；

R^{26} 选自 -H 和 $-C_{1-6}$ 烷基；

R^{27} 独立地选自 $-C_{1-6}$ 烷基、$-C(O)-C_{1-6}$ 烷基、-Hal、$-CF_3$、-CN、$-COOR^{25}$、$-OR^{25}$、$-(CH_2)_qNR^{25}R^{26}$、$-C(O)-NR^{25}R^{26}$ 和 $-NR^{25}-C(O)-C_{1-6}$ 烷基；

R^{28} 和 R^{29} 独立地选自 -H、$-C_{1-6}$ 烷基、$-(CH_2)_q-$ 芳基、$-(CH_2)_q-$ 杂环基、$-(CH_2)_q-$ 环烷

基、-OH、-O-C_{1-6}烷基、-O-$(CH_2)_q$-芳基、-O-$(CH_2)_q$-杂环基、和-O-$(CH_2)_q$-环烷基；

或R^{28}和R^{29}一起为=O、-CH_2CH_2-、-$CH_2CH_2CH_2$-或—$CH_2CH_2CH_2CH_2$-；

p为1至4；

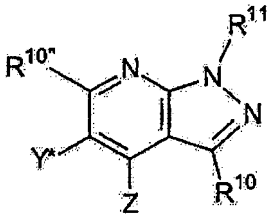
q为0至4；且

r为1至3；

其中所述芳基、杂环基和／或环烷基可任选地被一个或多个取代基R^{27}取代；

和／或

具有通式(XXI)的化合物：



或其药学上可接受的盐、溶剂化物、前药、互变异构体、外消旋物和对映异构体或非对映异构体；

其中

Y*和Z中的一个是-XR^{12}而另一个是$R^{10'}$；

R^{10}、$R^{10'}$和$R^{10''}$各自独立地选自氢、C_1-C_6-烷基、C_2-C_6-烯基、C_2-C_8-炔基、-$(CH_2)_t$C(O)OH、-$(CH_2)_t$C(O)OR^{16}、-$(CH_2)_t$OH、-$(CH_2)_t$OR^{16}、-CF_3、-$(CH_2)_t$-环烷基、、-$(CH_2)_t$C(O)NH_2、-$(CH_2)_t$C(O)NHR^{16}、-$(CH_2)_t$C(O)N$R^{16}R^{17}$、-$(CH_2)_t$S$(O)_2NH_2$、-$(CH_2)_t$S$(O)_2$NHR^{16}、-$(CH_2)_t$S$(O)_2$N$R^{16}R^{17}$、-$(CH_2)_t$S$(O)_2R^{16}$、卤素、-CN、-$(CH_2)_t$-芳基、-$(CH_2)_t$-杂芳基、-$(CH_2)_t NH_2$、-$(CH_2)_t$NHR^{16}、和-$(CH_2)_t$N$R^{16}R^{17}$；任选被取代；

R^{11}选自氢、C_1-C_6-烷基、-CF_3、C_2-C_6-烯基、C_2-C_8-炔基、-$(CH_2)_t$-环烷基、-$(CH_2)_t$-芳基、-$(CH_2)_t$-杂环烷基和-$(CH_2)_t$-杂芳基；任选被取代；

X选自CH_2、C(O)、C(S)、CH(OH)、CH(OR^{16})、S$(O)_2$、-S$(O)_2$-N(H)-、-S$(O)_2$—N(R^{16})-、—N(H)-S$(O)_2$-、—N(R^{16})-S$(O)_2$-、C(=NH)、C(=N-R^{16})、CH(NH_2)、CH(NHR^{16})、CH(N$R^{16}R^{17}$)、-C(O)—N(H)-、-C(O)-N(R^{16})-、—N(H)-C(O)-、—N(R^{16})-C(O)-、N(H)、N(-R^{16})和O；

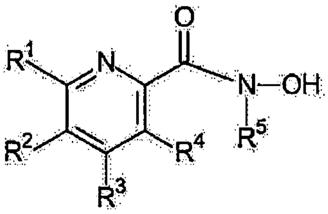
R^{12}选自C_1-C_6-烷基、-CF_3、C_2-C_6-烯基、C_2-C_8-炔基、-$(CH_2)_t$-环烷基、-$(CH_2)_t$-杂环烷基、-$(CH_2)_t$-芳基、—N$R^{16}R^{17}$和-$(CH_2)_t$-杂芳基；任选被取代；

R^{16}和R^{17}独立地选自C_1-C_6-烷基、C_2-C_6-烯基、C_2-C_6-炔基、-$(CH_2)_t$-环烷基、-$(CH_2)_t$-芳基、-CF_3、-C(O)R^{18}和-S$(O)_2R^{18}$；任选被取代；

R^{18}独立地选自C_1-C_6-烷基、C_2-C_6-烯基、C_2-C_6-炔基、-$(CH_2)_t$-环烷基和-CF_3；任选被取代；且

t在每种情况下选自0、1和2；

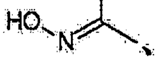
(ii)具有通式I的化合物、任选地其药学上可接受的盐、溶剂化物、多晶型物、前药、互变异构体、外消旋物、对映异构体、或非对映异构体或混合物的形式，



(I)

其中

R^1选自$-H$、$-C_{1-6}$烷基、$-(C_{3-7}$环烷基$)$和$-CH_2-(C_{3-7}$环烷基$)$;

R^2选自$-H$、、$-C_{1-6}$烷基、$-Hal$、$-(C_{3-7}$环烷基$)$、$-CH_2-(C_{3-7}$ 环烷基)、$-(CH_2)_m-$(任选取代的芳基)、-(含有至少一个选自 N、O 和 S 的杂原子的任选取代的 5- 或 6- 元杂环),其中所述取代基选自 $-C_{1-4}$ 烷基、- 卤素、-CN、$-CHal_3$、- 芳基、$-NR^6R^7$ 和 $-CONR^6R^7$;

R^3 选自 -H、$-C_{1-6}$ 烷基、

$-(CH_2)_n-NR^6R^8$、

-(任选取代的 5- 或 6- 元碳环或杂环,其中所述杂环含有至少一个选自 N、O 和 S 的杂原子),其中所述取代基选自 -Hal、$-C_{1-4}$ 烷基、$-NR^9R^{10}$、$-(CH_2)_n-OH$、$-C(O)-NR^9R^{10}$、$-SO_2-NR^9R^{10}$、$-NH-C(O)-O-R^{11}$、$-C(O)-O-R^{11}$ 和含有至少一个选自 N、O 和 S 的杂原子的 5- 或 6- 元杂环;

或其中 R^1 和 R^2 一起形成苯基环或其中 R^2 和 R^3 一起形成苯基环;

R^4 是 -H;

R^5 选自 -H 或 $-(CH_2)_n-$(任选取代的芳基),其中所述取代基选自 -Hal 和 $-C_{1-4}$ 烷基;或其中 R^4 和 R^5 一起形成亚甲基 $-CH_2-$、亚乙基 $-CH_2CH_2-$ 或乙炔基团 -CHCH-,其可任选地被 $-C_{1-4}$ 烷基、- 卤素、$-CHal_3$、$-R^6R^7$、$-OR^6$、$-CONR^6R^7$、$-SO_2R^6R^7$、芳基或杂芳基取代;

R^6 选自 -H 和 $-C_{1-4}$ 烷基;

R^7 选自 -H 和 $-C_{1-4}$ 烷基;

R^8 选自 -H、$-C_{1-6}$ 烷基、$-(CH_2)_n-$(任选取代的芳基)、$-SO_2-(CH_2)_n-$(任选取代的芳基)、$-SO_2-(CH_2)_n-$(任选取代的 5- 至 10- 元单 - 或双环杂环,其含有至少一个选自 N、O 和 S 的杂原子)、$-(CH_2)_n-$(任选取代的 5- 至 10- 元单 - 或双环杂环,其含有至少一个选自 N、O 和 S 的杂原子),其中所述取代基选自 -Hal、$-CF_3$、$-C_{1-4}$ 烷基和 $-(CH_2)_n-$ 芳基;

R^9 选自 -H、$-C_{1-4}$ 烷基和 $-C_{1-4}$ 亚烷基 $-NR^{11}R^{11}$;

R^{10} 选自 -H、$-C_{1-4}$ 烷基和 $-C_{1-4}$ 亚烷基 $-NR^{11}R^{11}$;

R^{11} 选自 -H、$-CF_3$ 和 $-C_{1-4}$ 烷基;

每个 m 为 0 或 1;且

每个 n 独立地为 0、1、2 或 3;

和任选的一种或多种药学上可接受的赋形剂和 / 或载体。

15. 药物组合物,包含

(i) 如权利要求 14 中定义的具有通式 (I)、(II) 或 (XXI) 的化合物;和

(ii) 至少一种聚合酶抑制剂,其与具有通式 (I)、(II) 或 (XXI) 的化合物不同;和任选的一种或多种药学上可接受的赋形剂和 / 或载体。

16. 药物组合物,包含:

(i) 如权利要求 14 中定义的具有通式 (I)、(II) 或 (XXI) 的化合物 ;和

(ii) 至少一种神经酰胺酶抑制剂 ;

和任选的一种或多种药学上可接受的赋形剂和 / 或载体。

17. 药物组合物,包含 :

(i) 如权利要求 14 中定义的具有通式 (I)、(II) 或 (XXI) 的化合物 ;和

(ii) 至少一种 M2 通道抑制剂 ;

和任选的一种或多种药学上可接受的赋形剂和 / 或载体。

18. 药物组合物,包含

(i) 如权利要求 14 中定义的具有通式 (I)、(II) 或 (XXI) 的化合物 ;和

(ii) 至少一种 α 葡糖苷酶抑制剂 ;

和任选的一种或多种药学上可接受的赋形剂和 / 或载体。

19. 药物组合物,包含

(i) 如权利要求 14 中定义的具有通式 (I)、(II) 或 (XXI) 的化合物 ;和

(ii) 另一种流感靶标的至少一种配体 ;

和任选的一种或多种药学上可接受的赋形剂和 / 或载体。

20. 药物组合物,包含

(i) 如权利要求 14 中定义的具有通式 (I)、(II) 或 (XXI) 的化合物 ;和

(ii) 至少一种选自以下的药物 :抗生素、抗炎剂、脂肪氧合酶抑制剂、EP 配体、缓激肽配体和大麻素配体 ;

和任选的一种或多种药学上可接受的赋形剂和 / 或载体。

21. 如权利要求 14 至 20 中任一项定义的药物组合物,其用于治疗、减轻或预防病毒疾病。

22. 治疗、减轻或预防病毒疾病的方法,所述方法包括向需要其的患者施用有效量的如权利要求 14 至 20 中任一项定义的药物组合物。

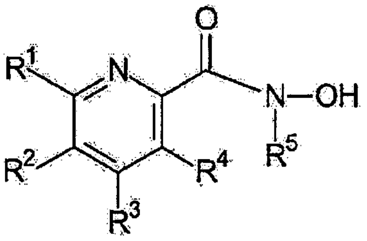
23. 根据权利要求 21 的药物组合物或根据权利要求 22 的方法,其中所述病毒疾病由疱疹病毒科、逆转录病毒科、纤丝病毒科、副粘液病毒科、弹状病毒科、正粘液病毒科、布尼亚病毒科、砂粒病毒科、冠状病毒科、细小 RNA 病毒科、披膜病毒科、黄病毒科引起 ;更具体地讲,其中所述病毒疾病是流感。

杂芳基异羟肟酸衍生物及其在治疗、减轻或预防病毒疾病中的用途

发明领域

[0001]　本发明涉及具有通式 I 的化合物、任选地其药学上可接受的盐、溶剂化物、多晶型物、前药、互变异构体、外消旋物、对映异构体或非对映异构体或混合物的形式，

[0002]



(I)

[0003]　其可用于治疗、减轻或预防病毒疾病。此外，公开了特定的组合疗法。

[0004]　发明背景

[0005]　近年来，由流感病毒引起的对全世界公众健康的严重危险已通过以下突显：首先，持续地向人传递低剂量的高致病性禽 H5N1 菌株（所感染的人的死亡率为 63%，http://www.who.int/csr/disease/avian influenza/en/）以及其次，在 2009 年出乎意料地出现一种新型流行性菌株 A/H1N1，其已快速在全世界扩散（http://www.who.int/csr/disease/swineflu/en/）。尽管新菌株是高度传染性的，但是目前仅仅通常导致轻微病状，但是这种病毒未来的进化是不可预测的。在更严重得多但高度可能的情形下，H5N1 可能更容易在人之间传递，或新 A/H1N1 可能更致命且可能已经携带赋予 Tamiflu 耐药性的单个点突变 (Neumann 等人，Nature，2009(18；459(7249)931-939)，因为很多季节性 H1N1 菌株最近已出现这种情况 (Dharan 等人，The Journal of the American Medical Association，2009 年 3 月 11 日；301(10)，1034-1041；Moscona 等人，The New England Journal of Medicine，2009 年 (3 月 5 日；360(10) 第 953-956 页）。在这种情况下，生产和部署疫苗的延迟（在相对有利的 A/H1N1 例子中为～6 个月，但对于 H5N1 这个问题仍未解决）可能在人生命和社会混乱中的代价极其昂贵。

[0006]　人们普遍认为，为了桥接在新疫苗成为可用之前的时期以及为了治疗严重病例，以及为了对抗病毒耐药性的问题，对抗流感药物需要更广泛的选择。因此，新抗流感药物的开发已再次成为高优先级，而在抗神经氨酸酶药物成为可用时已被主要药物公司基本上放弃。

[0007]　用于开发抗病毒药物的一个极佳起始点是重要病毒蛋白的结构数据。因此，对例如流感病毒表面抗原神经氨酸酶的晶体结构确定 (Von Itzstein，M. 等人，(1993)，Nature，363，第 418-423 页）直接导致开发具有抗病毒活性的神经氨酸酶抑制剂，它们阻止病毒从细胞中释放，但是不阻止病毒产生。随后这些神经氨酸酶抑制剂及其衍生物已被研发成抗流感药物扎那米韦 (Glaxo) 和奥司他韦 (Roche)，它们目前已被很多国家储备为防御可能大流行的第一道防线。但是，这些药物仅仅缩短临床疾病的持续时间。可选地，其它抗

流感化合物如金刚烷胺和金刚烷乙胺靶向病毒膜中的离子通道蛋白即M2蛋白，干扰细胞内病毒的脱壳。但是，它们由于其副作用和耐药性病毒突变体的快速产生而未被广泛应用（Magden, J. 等人，(2005), Appl. Microbiol. Biotechnol., 66，第612-621页）。此外，更不特异的病毒药物如利巴韦林已显示可用于治疗流感和其他病毒感染（Eriksson, B. 等人，(1977), Antimicrob. Agents Chemother., 11，第946-951页）。但是，可能是由于严重的副作用，利巴韦林仅在少数国家中获得批准（Furuta等人，ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, 2005，第981-986页）。显然，需要新抗病毒化合物，优选为针对不同靶标的化合物。

[0008] 流感病毒以及索戈托病毒属(Thogotovirus)属于正粘液病毒科(Orthomyxoviridae)家族，其与布尼亚病毒科(Bunyaviridae)家族（包括汉坦病毒属(Hantavirus)、内罗病毒属(Nairovirus)、正布尼亚病毒属(Orthobunyavirus)和白蛉病毒属(Phlebovirus)）是负链RNA病毒。它们的基因组是分段的，且存在于包括RNA依赖性RNA聚合酶的核糖核蛋白颗粒中，所述RNA依赖性RNA聚合酶(i)将最初的单链病毒体RNA(vRNA)拷贝至病毒mRNA以及(ii)复制vRNA。该酶（一种由亚基PA、PB1和PB2组成的三聚复合体）对于病毒的生存期而言是关键的，因为其负责病毒RNA的复制和转录。在先前工作中，已鉴定和确定聚合酶的两个关键结构域-PB2亚基中的mRNA帽-结合结构域(Guilligay等人，Nature Structural&Molecular Biology 2008；May；15(5)：500-506)和PA亚基中的核酸内切酶-活性位点(Dias等人，Nature 2009, 458, 914-918)的原子结构。这两个位点对于转录的独特帽-攫取（帽-snatching）模式而言是关键的，所述模式被流感病毒用于产生病毒mRNA。对于病毒mRNA的产生，聚合酶利用所谓的“帽-攫取”机理(Plotch, S. J. 等人，(1981), Cell, 23，第847-858页；Kukkonen, S. K. 等人(2005), Arch. Virol., 150，第533-556页；Leahy, M. B. 等人，(2005), J. Virol., 71，第8347-8351页；Noah, D. L. 等人，(2005), Adv. Virus Res., 65，第121-145页）。5′帽（也称为RNA帽、RNA 7-甲基鸟苷帽或RNA m7G帽）是修饰的鸟嘌呤核苷酸，已加入至信使RNA的5′端。5′帽由末端7-甲基鸟苷残基组成，其通过′-5′-三磷酸键连接至第一转录的核苷酸。病毒聚合酶与细胞mRNA分子的5' RNA帽结合且切割RNA帽与10至15个核苷酸的延伸。然后加帽的RNA片段充当合成病毒mRNA的引物。

[0009] 聚合酶复合体看似为适当的抗病毒药物靶标，因为其对于合成病毒mRNA和病毒复制是至关重要的，并且含有数个功能活性位点，其与在宿主细胞蛋白中发现的功能活性位点可能显著不同(Magden, J. 等人，(2005), Appl. Microbiol. Biotechnol., 66，第612-621页）。因此，例如，已尝试通过与PB1内PA-结合结构域类似的25-氨基酸肽干扰聚合酶亚基的装配(Ghanem, A. 等人，(2007), J. Virol., 81，第7801-7804页）。此外，已经靶向聚合酶的核酸内切酶活性并且一系列4-取代的2,4-二氧代丁酸化合物已被鉴定为流感病毒中这种活性的选择性抑制剂(Tomassini, J. 等人，(1994), Antimicrob. Agents Chemother., 38，第2827-2837页）。此外，氟他胺，在真菌物种Delitschia confertaspora的提取物中鉴定到的取代的2,6-二酮哌嗪，已显示抑制流感病毒的核酸内切酶(Tomassini, J. 等人，(1996), Antimicrob. Agents Chemother., 40，第1189-1193页）。此外，已尝试通过核苷类似物如2'-脱氧-2,-氟鸟苷干扰病毒转录(Tisdale, M. 等人，(1995), Antimicrob. Agents Chemother., 39，第2454-2458页）。

[0010] Cianci 等人已研究某些 N- 异羟肟酸和 N- 羟基二酰亚胺化合物用于抑制流感病毒聚合酶的适合性 (Cianci C. 等人,(1996)Antiviral Chem.&Chemotherapy(1996)7(6) 第 353-360 页)。Cianci 等人描述了在发现抗病毒化合物的努力中筛选专利化学集合。一种化合物 BMY-26270 被鉴定为流感病毒的加帽 RNA 依赖性 RNA 聚合酶的抑制剂。该化合物的抑制活性归因于对流感聚合酶的核酸内切酶切割功能的效应,所述流感聚合酶是在不了解病毒核酸内切酶活性位点的位置和结构的情况下,分别对整个 RNP 和病毒裂解产物进行分析的。基于它们的结果,Cianci 等人得出结论,特定的酚式羟基和异羟肟酸部分是聚合酶 - 抑制性药效团的必要元素。Cianci 等人进一步得出结论,在等效活性吡啶同系物的情况下修改或删除任一种这些元素导致化合物的失活。

[0011] 本发明的目的是为了进一步鉴定对抗病毒疾病有效且具有改善的药理学性质的化合物。

[0012] 发明概述

[0013] 因此,在第一实施方案中,本发明提供具有通式 I 的化合物。

[0014] 应理解,除非另有提及,否则在本说明书中术语“具有通式 I 的化合物”包括药学上可接受的盐、溶剂化物、多晶型物、前药、互变异构体、外消旋物、对映异构体、或非对映异构体或其混合物。

[0015] 本发明的另一实施方案涉及包含具有通式 I 的化合物和任选的一种或多种药学上可接受的赋形剂和 / 或载体的药物组合物。

[0016] 具有通式 I 的化合物可用于治疗、减轻或预防病毒疾病。

[0017] 发明详述

[0018] 在下文详细描述本发明之前,应理解本发明并不限于本文所述的具体方法、方案和试剂,因为这些可以变化。还应理解,本文所用的术语仅用于描述具体的实施方案,而不意在限制仅由所附权利要求所限定的本发明的范围。除非另外定义,否则本文所使用的所有技术和科学术语与本领域普通技术人员通常所理解的含义相同。

[0019] 优选地,本文所用的术语如“A multilingual glossary of biotechnological terms:(IUPAC Recommendations)”, Leuenberger, H.G.W, Nagel, B. 和 **Kölbl**, H. 编辑 (1995), Helvetica Chimica Acta、CH-4010Basel, Switzerland) 中所述进行定义。

[0020] 在本说明书及下面权利要求的通篇中,除非上下文另有要求,否则词语“包含”及其变化形式例如“包括”和“含有”应理解为表示包含所述整数或步骤或者整数或步骤的组,但是不排除任何其它的整数或步骤或者整数或步骤的组。在下列段落中,详细定义本发明的不同方面。除非另有相反指示,否则如此定义的每个方面可与任何其他一个或多个方面组合。特别地,被指示为优选或有利的任何特征可与被指示为优选或有利的任何其他一个或多个特征组合。

[0021] 在本说明书文本通篇中引用了一些文件。本文上文或下文中所引用的每个文件(包括所有专利、专利申请、科技文献、制造商说明、说明书等)都通过引用整体并入本文。本文中的任何内容均不应解释为认可本发明不能由于在先发明而早于这些公开内容。

[0022] 定义

[0023] 术语“烷基”是指饱和直链或支链碳链。

[0024] 术语“环烷基”表示“烷基”的环状形式。术语“环烷基”也意指包括其双环、三环

和多环形式。除非另有指明，否则环烷基可具有 5 至 12 个碳原子。

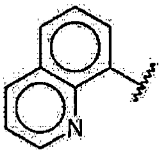
[0025]　“Hal”表示 F、Cl、Br 和 I。

[0026]　术语“芳基”优选地是指含有 6 个碳原子的芳族单环、含有 10 个碳原子的芳族双环系统或含有 14 个碳原子的芳族三环系统。实例为苯基、萘基或蒽基，优选为苯基。

[0027]　术语“5- 或 6- 元杂环”或“5- 或 6- 元杂环”包括任何五或六 - 元环，其中环中的至少一个碳原子已被 1、2、3 或 4 个（对于五元环）或 1、2、3、4 或 5 个（对于六元环）相同或不同杂原子替换，由此杂原子选自 O、N 和 S。术语“杂环”还包括杂芳基环。实例包括吡咯、吡咯烷、四氢呋喃、呋喃、咪唑烷、咪唑、吡唑、噁唑烷、噁唑、噻唑、哌啶、吡啶、吗啉、哌嗪和二氧戊环。

[0028]　术语“5- 至 10- 元单 - 或双环杂环”包括含有至少一个选自 N、O 和 S 的杂原子的任何单 - 或双环系统。在优选的实施方案中，5- 至 10- 元单 - 或双环杂环为

[0029]



[0030]　术语“杂芳基”优选地是指五或六 - 元芳族环，其中环中的一个或多个碳原子已被 1、2、3 或 4 个（对于五元环）或 1、2、3、4 或 5 个（对于六元环）相同或不同杂原子替换，由此杂原子选自 O、N 和 S。上面给出杂芳基的实例。

[0031]　术语“杂环基”包括任何五或六 - 元环，其中环中的至少一个碳原子已被 1、2、3 或 4 个（对于五元环）或 1、2、3、4 或 5 个（对于六元环）相同或不同杂原子替换，由此杂原子选自 O、N 和 S。术语“杂环基”还包括杂芳基环。实例包括吡咯、吡咯烷、四氢呋喃、呋喃、咪唑烷、咪唑、吡唑、噁唑烷、噁唑、噻唑、哌啶、吡啶、吗啉、哌嗪和二氧戊环。

[0032]　术语“碳环”或“碳环的”包括任何五或六 - 元环，其环中不包括杂原子。术语“碳环”还包括芳基环。

[0033]　如果化合物或部分被称为“任选取代的”，那么其可在每种情况下包括 1 或多个所示取代基，由此取代基可以是相同或不同的。

[0034]　术语“药学上可接受的盐”是指本发明化合物的盐。适合的药学上可接受的盐包括可例如通过将本发明化合物的溶液与药学上可接受的酸溶液混合而形成的酸加成盐，所述酸如盐酸、硫酸、富马酸、马来酸、琥珀酸、乙酸、苯甲酸、柠檬酸、酒石酸、碳酸或磷酸。此外，在化合物携带酸性部分时，其适合的药学上可接受的盐可包括碱金属盐（例如钠或钾盐）；碱土金属盐（例如钙或镁盐）；以及与适合的有机配体形成的盐（例如使用抗衡阴离子如卤离子、氢氧根、羧酸根、硫酸根、磷酸根、硝酸根、烷基磺酸根和芳基磺酸根形成的铵、季铵和胺阳离子）。药学上可接受的盐的说明性实例包括但不限于乙酸盐、己二酸盐、藻酸盐、抗坏血酸盐、天冬氨酸盐、苯磺酸盐、苯甲酸盐、碳酸氢盐、硫酸氢盐、二酒石酸盐、硼酸盐、溴化物、丁酸盐、依地酸钙、樟脑酸盐、樟脑磺酸盐、右旋樟脑磺酸盐 (camsylate)、碳酸盐、氯化物、柠檬酸盐、克拉维酸盐、环戊烷丙酸盐、二葡萄糖酸盐、二盐酸盐、十二烷基硫酸盐、依地酸盐、乙二磺酸盐、依托酸盐 (estolate)、乙磺酸盐、乙磺酸盐、甲酸盐、富马酸盐、葡庚糖酸盐 (gluceptate)、葡庚糖酸盐 (glucoheptonate)、葡萄糖酸盐、谷氨酸盐、甘油磷酸盐、对 α - 羟乙酰氨基苯胂酸盐 (glycolylarsanilate)、半硫酸盐、庚酸盐、己酸盐、己

基间苯二酚盐 (hexylresorcinate)、海巴明 (hydrabamine) 盐、氢溴酸盐、盐酸盐、氢碘酸盐、2-羟基-乙磺酸盐、羟基萘甲酸盐、碘化物、羟乙磺酸盐 (isothionate)、乳酸盐、乳糖酸盐、月桂酸盐、月桂基硫酸盐、苹果酸盐、马来酸盐、丙二酸盐、扁桃酸盐、甲磺酸盐、甲烷磺酸盐、甲基硫酸盐、粘酸盐、2-萘磺酸盐、萘磺酸盐、烟酸盐、硝酸盐、N-甲基葡糖胺铵盐、油酸盐、草酸盐、扑酸盐（双羟萘酸盐 / embonate)、棕榈酸盐、泛酸盐、果胶酸盐、过硫酸盐、3-苯基丙酸盐、磷酸盐 / 二磷酸盐、苦味酸盐、新戊酸盐、聚半乳糖醛酸盐、丙酸盐、水杨酸盐、硬脂酸盐、硫酸盐、碱式乙酸盐、琥珀酸盐、单宁酸盐、酒石酸盐、茶氯酸盐 (teoclate)、甲苯磺酸盐、三乙基碘化物 (triethiodide)、十一烷酸盐、戊酸盐等（参见例如，S. M. Berge 等人，" Pharmaceutical Salts"，J. Pharm. Sci.，66，第 1-19 页 (1977))。

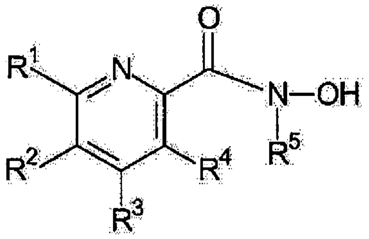
[0035] 当本发明的化合物以结晶形式提供时，结构可含有溶剂分子。溶剂通常为药学上可接受的溶剂并且尤其包括水（水合物）或有机溶剂。可能的溶剂化物的实例包括乙醇合物和异丙醇合物。

[0036] 本发明的化合物也可以前药即在体内代谢为活性代谢物的化合物形式提供。

[0037] 具有通式 I 的化合物

[0038] 本发明提供具有通式 I 的化合物。

[0039]

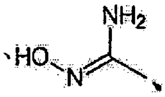
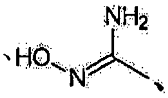


(I)

[0040] 在随附权利要求中引用某些附带条件。应理解，任何附带条件中包括的任何化合物，可单独的或与其他化合物组合，从一个或多个具有不同范畴的独立权利要求中排除，即使其在该范畴的独立权利要求中当前未被具体放弃。还应理解，具体放弃 (disclaimer) 包括其药学上可接受的盐、溶剂化物、多晶型物、互变异构体、外消旋物、对映异构体和非对映异构体的形式的化合物。

[0041] 本发明提供具有通式 I 的化合物，其中下列定义适用。

[0042] R^1 选自 -H、$-C_{1-6}$ 烷基、-(C_{3-7} 环烷基）和 $-CH_2-$(C_{3-7} 环烷基）。优选地，R^1 选自 -H 和 $-C_{1-6}$ 烷基。甚至更优选地，R^1 是 -H。

[0043] R^2 选自 -H、 $-C_{1-6}$ 烷基、-Hal、-(C_{3-7} 环烷基）、$-CH_2-$(C_{3-7} 环烷基）、$-(CH_2)_m-$（任选取代的芳基）和 -（含有至少一个选自 N、O 和 S 的杂原子的任选取代的 5- 或 6- 元杂环）。优选地，R^2 选自 -H、 $-C_{1-6}$ 烷基、$-(CH_2)_m-$（任选取代的芳基）、-（含有至少一个选自 N、O 和 S 的杂原子的任选取代的 5- 或 6- 元杂环）。甚至更优选地，R^2 选自 -H、$-C_{1-6}$ 烷基、- 苯基，其中 R^2 为 -H 是最优选的。关于 R^2，未特别地限定杂环但其优选为哌啶或吡咯烷。

[0044] 任选取代的芳基和任选取代的杂环的一个或多个取代基独立地选自 $-C_{1-4}$ 烷

基、- 卤素、-CN、-CHal$_3$、- 芳基、-NR^{6}R^7 和 -CONR^{6}R^7。取代基的优选实例选自 -C$_{1-4}$ 烷基。

[0045] R^3 选自 -H ;

[0046] -C$_{1-6}$ 烷基 ;

[0047] -(CH$_2$)$_n$-NR^{6}R^8(关于该取代基 n 优选为 0 或 1,更优选为 0);且

[0048] -(任选取代的 5- 或 6- 元碳环或杂环,其中所述杂环含有至少一个选自 N、O 和 S 的杂原子)。杂环可以是任何碳环或杂环但优选为苯基、哌啶、吗啉、或哌嗪。

[0049] 碳环或杂环的取代基选自 -Hal、-C$_{1-4}$ 烷基、-NR^{9}R^{10}、-(CH$_2$)$_n$-OH、-C(O)-NR^{9}R^{10}、-SO$_2$-NR^{9}R^{10}、-NH-C(O)-O-R^{11}、-C(O)-O-R^{11} 和含有至少一个选自 N、O 和 S 的杂原子的 5- 或 6- 元杂环(关于碳环或杂环的取代基,作为取代基的杂环优选为吡咯烷、哌啶或二氧戊环)。

[0050] 在优选的实施方案中,R^3 选自 -H ;

[0051] -C$_{1-6}$ 烷基 ;

[0052] -NR^6-SO$_2$-(CH$_2$)$_n$-(任选取代的芳基),其中所述取代基优选选自 -Hal 和 -CF$_3$;

[0053] -(任选取代的芳基),其中所述取代基优选选自 Hal、-NR^{9}R^{10}、-C(O)-O-R^{11} ;且

[0054] -(任选取代的 5- 或 6- 元杂环,其中所述杂环含有至少一个选自 N、O 和 S 的杂原子),其中所述取代基优选选自 -Hal、-NR^{9}R^{10}、-C(O)-O-R^{11} 和含有至少一个选自 N、O 和 S 的杂原子的 5- 或 6- 元杂环如吡咯烷、哌啶或二氧戊环。

[0055] 在一个实施方案中 R^1 和 R^2 合在一起可形成苯基环。

[0056] 在替代实施方案中 R^2 和 R^3 合在一起可形成苯基环。

[0057] R^4 是 -H。

[0058] R^5 选自 -H 或 -(CH$_2$)$_n$-(任选取代的芳基),优选地,R^5 选自 -H 或 -(CH$_2$)-(任选取代的苯基),甚至更优选地,R^5 是 -H。在 R^5 的定义中 n 为 0、1、2 或 3,优选地,n 为 0 或 1,更优选为 n 为 1。关于 R^5,取代基选自 -Hal 和 -C$_{1-4}$ 烷基。

[0059] 在替代实施方案中,R^4 和 R^5 一起形成亚甲基 -CH$_2$-、亚乙基 -CH$_2$CH$_2$- 或乙炔基团 -CHCH-,其可任选地被 -C$_{1-4}$ 烷基、- 卤素、-CHal$_3$、-R^{6}R^7、-OR^6、-CONR^{6}R^7、-SO$_2$R^{6}R^7、芳基或杂芳基取代。

[0060] R^6 选自 -H 和 -C$_{1-4}$ 烷基且例如为 -H。

[0061] R^7 选自 -H 和 -C$_{1-4}$ 烷基。

[0062] R^8 选自 -H、-C$_{1-6}$ 烷基、-(CH$_2$)$_n$-(任选取代的芳基)、-SO$_2$-(CH$_2$)$_n$-(任选取代的芳基)、-SO$_2$-(CH$_2$)$_n$-(任选取代的 5- 至 10- 元单 - 或双环杂环,其含有至少一个选自 N、O 和 S 的杂原子)、-(CH$_2$)$_n$-(含有至少一个选自 N、O 和 S 的杂原子的任选取代的 5- 或 6- 元杂环)(优选杂环为哌啶或吡咯烷),其中所述取代基选自 -Hal、-CF$_3$、-C$_{1-4}$ 烷基和 -(CH$_2$)$_n$- 芳基。在优选的选项中,R^8 可以是 -SO$_2$-(CH$_2$)$_n$-(任选取代的芳基),其中 n 优选为 0 或 1,更优选为 1。

[0063] R^9 选自 -H、-C$_{1-4}$ 烷基和 -C$_{1-4}$ 亚烷基 -NR^{11}R^{11}。

[0064] R^{10} 选自 -H、-C$_{1-4}$ 烷基和 -C$_{1-4}$ 亚烷基 -NR^{11}R^{11}。

[0065] R^{11} 选自 -H、-CF$_3$ 和 -C$_{1-4}$ 烷基。

[0066] 每个 m 为 0 或 1。

[0067] 每个 n 独立地为 0、1、2 或 3。

[0068] 本发明的化合物可以以药物组合物形式施用至患者,所述药物组合物可任选地包

含一种或多种药学上可接受的赋形剂和 / 或载体。

[0069] 本发明的化合物可通过各种熟知途径施用，包括口服、直肠、胃内、颅内和胃肠外施用，例如静脉内、肌内、鼻内、皮内、皮下和类似施用途径。特别优选口服、鼻内和胃肠外施用。根据施用途径需要不同的药物制剂，并且它们中的一些可需要将保护性包衣施加至药物制剂以预防本发明化合物在例如消化道中的降解。

[0070] 因此，优选地将本发明化合物配制成糖浆、输注或注射溶液、喷雾剂、片剂、胶囊、囊片、锭剂、脂质体、栓剂、硬膏剂、护创膏布(band-aid)、延迟胶囊(retard capsule)、粉末或缓释制剂。优选地，稀释剂是水、缓冲液、缓冲盐溶液、或盐溶液并且载体优选选自可可脂和 vitebesole。

[0071] 特别优选的用于施用本发明化合物的药物形式是适于可注射使用的形式并且包括无菌水溶液或分散液和用于即时制备无菌可注射溶液或分散液的无菌粉末。在所有情况下，最终溶液或分散液形式必须是无菌的且是流体的。典型地，此类溶液或分散液将包括溶剂或分散介质，含有例如水 - 缓冲的水溶液例如生物可相容的缓冲液、乙醇、多元醇如甘油、丙二醇、聚乙二醇、其适合的混合物、表面活性剂或植物油。也可将本发明化合物配制成脂质体，特别是用于胃肠外施用。脂质体提供 (如果与游离药物相比) 循环中增加的半衰期和所包封药物的甚至更延长的释放的优势。

[0072] 输注或注射溶液的灭菌可通过多种领域公认的技术完成，所述技术包括但不限于添加防腐剂如抗菌剂或抗真菌剂例如尼泊金、氯丁醇、苯酚、山梨酸或硫柳汞。此外，可将等渗剂如糖或盐、特别是氯化钠掺入输注或注射溶液中。

[0073] 含有一种或数种本发明化合物的无菌可注射溶液的制备通过将所需量的相应化合物掺入根据需要具有各种上文列举成分的适合溶剂中、随后灭菌来完成。为了获得无菌粉末，必要时将上述溶液真空干燥或冷冻干燥。优选的本发明的稀释剂是水、生理上可接受的缓冲剂、生理上可接受的缓冲盐溶液或盐溶液。优选的载体是可可脂和 vitebesole。可与本发明化合物的各种药物形式一起使用的赋形剂可选自下列非限制列表 :

[0074] a) 粘合剂，如乳糖、甘露醇、结晶山梨糖醇、二碱式磷酸盐、磷酸钙、糖、微晶纤维素、羧基甲基纤维素、羟基乙基纤维素、聚乙烯吡咯烷酮等 ;

[0075] b) 润滑剂，如硬脂酸镁、滑石、硬脂酸钙、硬脂酸锌、硬脂酸、氢化植物油、亮氨酸、甘油酯和硬脂酰富马酸钠，

[0076] c) 崩解剂，如淀粉、交联羧甲基纤维素、甲基纤维素钠、糖、膨润土、藻酸、羧基甲基纤维素、聚乙烯吡咯烷酮等。

[0077] 在一个实施方案中，制剂用于口服施用并且制剂包含一种或多种或所有下列成分 :预胶化淀粉、滑石、聚维酮 K 30、交联羧甲纤维素钠、硬脂酰富马酸钠、明胶、二氧化钛、山梨糖醇、枸橼酸单钠、黄原胶、二氧化钛、调味剂、苯甲酸钠和糖精钠。

[0078] 如果在优选的实施方案中鼻内施用本发明化合物，那么其可借助于使用适合的推进剂以干粉吸入剂或气溶胶喷雾剂形式从加压容器、泵、喷雾器或喷洒器施用，所述推进剂例如二氯二氟甲烷、三氯氟甲烷、二氯四氟乙烷、氢氟烷烃如 1,1,1,2- 四氟乙烷 (HFA 134ATM) 或 1,1,1,2,3,3,3- 七氟丙烷 (HFA 227EATM)、二氧化碳、或另一种适合的气体。加压容器、泵、喷雾器或喷洒器可含有本发明化合物的溶液或悬浮液，例如使用乙醇和推进剂的混合物作为溶剂，其可额外含有润滑剂，例如脱水山梨糖醇三油酸酯。

[0079] 其他适合的赋形剂可在由American Pharmaceutical Association出版的Handbook of Pharmaceutical Excipients中找到，该文献通过引用并入本文。

[0080] 应理解，根据病症的严重程度和可用一种本发明化合物治疗的具体类型、以及各个待治疗患者例如患者的一般健康状态等，需要不同剂量的各个化合物以引发治疗性或预防性效应。对适当剂量的确定在主治医师的判断力范围内。设想本发明的治疗性或预防性使用中本发明化合物的剂量应在约0.1mg至约1g活性成分（即本发明化合物）/ kg体重的范围内。但是，在本发明的优选用途中，向需要其的对象施用范围为1.0至500mg/kg体重、优选范围为1至200mg / kg体重的量的本发明化合物。用本发明化合物治疗的持续时间将根据待治疗疾病的严重程度以及每个单独个体患者的状况和特异体质性响应而不同。在预防性或治疗性用途的一个优选实施方案中，每天向成人口服施用100mg至200mg的化合物，取决于疾病的严重程度和 / 或暴露于疾病媒介物的程度。

[0081] 如本领域已知，药学有效量的给定组合物还将取决于施用途径。一般而言，如果施用经由胃肠道，例如通过栓剂、直肠或通过胃内探头，则所需量较高，而如果施用途径为胃肠外例如静脉内，则所需量较低。典型地，如果采用直肠或胃内施用，则将施用50mg至1g/kg体重、优选100mg至500mg / kg体重范围内的本发明化合物，而如果采用胃肠外施用，则施用范围为10至100mg / kg体重。

[0082] 如果已知人处于患上可用本发明化合物治疗的疾病的危险，那么生物活性血清或根据本发明的药物组合物的预防性施用是可能的。在这些情况下，优选每天以上文概述的优选和特别优选的剂量施用各个本发明化合物。优选地，每天一次0.1mg至1g/kg体重，优选地10至200mg/kg体重。可继续这种施用直至患上各个病毒病症的危险已减少。但是，在大多数情况下，一旦已诊断出疾病 / 病症，就将施用本发明化合物。在这些情况下，优选每天施用第一剂量的本发明化合物一次、两次、三次或四次。

[0083] 本发明的化合物特别可用于治疗、减轻或预防病毒疾病。未特别地限定疾病疾病的类型。可能的病毒疾病的实例包括但不限于由痘病毒科(Poxviridae)、疱疹病毒科(Herpesviridae)、腺病毒科(Adenoviridae)、乳头瘤病毒科(Papillomaviridae)、多瘤病毒科(Polyomaviridae)、细小病毒科(Parvoviridae)、嗜肝病毒科(Hepadnaviridae)、逆转录病毒科(Retroviridae)、呼肠病毒科(Reoviridae)、纤丝病毒科(Filoviridae)、副粘液病毒科(Paramyxoviridae)、弹状病毒科(Rhabdoviridae)、正粘液病毒科、布尼亚病毒科、砂粒病毒科(Arenaviridae)、冠状病毒科(Coronaviridae)、细小RNA病毒科(Picornaviridae)、肝炎病毒科(Hepeviridae)、嵌杯病毒科(Caliciviridae)、星状病毒科(Astroviridae)、披膜病毒科(Togaviridae)、黄病毒科(Flaviviridae)、δ病毒属(Deltavirus)、博尔纳病毒科(Bornaviridae)和阮病毒(prion)引起的病毒疾病。优选由疱疹病毒科、逆转录病毒科、纤丝病毒科、副粘液病毒科、弹状病毒科、正粘液病毒科、布尼亚病毒科、砂粒病毒科、冠状病毒科、细小RNA病毒科、披膜病毒科、黄病毒科引起的病毒疾病，更优选由正粘液病毒科引起的病毒疾病。

[0084] 在下表中给出各种病毒的实例。

[0085]

家族	病毒(优选的实例)
痘病毒科	天花病毒(Smallpox virus) 传染性软疣病毒(MollRNAase ribonucleaseum contagiosum virus)
疱疹病毒科	单纯性疱疹病毒(Herpes simplex virus)

[0086]

	水痘带状疱疹病毒(Varicella zoster virus) 巨细胞病毒(Cytomegalovirus) EB 病毒(Epstein Barr virus) 卡波西肉瘤相关疱疹病毒
腺病毒科	人腺病毒 A-F
乳头瘤病毒科	乳头瘤病毒
多瘤病毒科	BK-病毒 JC-Virsu
细小病毒科	B19 病毒 腺相关病毒 2/3/5
嗜肝病毒科	乙型肝炎病毒
逆转录病毒科	1/2 型人免疫缺陷病毒 人 T 细胞白血病病毒 人泡沫病毒(Human foamy virus)
呼肠病毒科	呼肠弧病毒 1/2/3(Reovirus 1/2/3) 轮状病毒 A/B/C(Rotavirus A/B/C) 科罗拉多蜱传热病毒(Colorado tick fever virus)
纤丝病毒科	埃博拉病毒(Ebola virus) 马尔堡病毒(Marburg virus)
副粘液病毒科	副流感病毒 1-4(Parainfluenza virus 1-4) 腮腺炎病毒(Mumps virus) 麻疹病毒(Measles virus) 呼吸道合胞体病毒(Respiratory syncytial virus) 亨德拉病毒(Hendravirus)
弹状病毒科	水疱性口炎病毒(Vesicular stomatitis virus) 狂犬病病毒(Rabies virus) 莫科拉病毒(Mokola virus) 欧洲蝙蝠病毒(European bat virus)

[0087]

	海格病毒(Duvenhage virus)
正粘液病毒科	A-C 型流感病毒
布尼亚病毒科	加州脑炎病毒 拉克罗斯病毒(La Crosse virus) 汉坦病毒(Hantaan virus) 普马拉病毒(Puumala virus) 辛诺柏病毒(Sin Nombre virus) 汉城型病毒(Seoul virus) 克里米亚-刚果出血热病毒(Crimean- Congo hemorrhagic fever virus) 库页岛病毒(Sakhalin virus) 里夫特山谷热病毒(Rift valley virus) 沙蝇热病毒(Sandfly fever virus) 尤尤库尼米病毒(Uukuniemi virus)
砂粒病毒科 ,	拉沙病毒(Lassa virus) 淋巴细胞性脉络丛脑膜炎病毒(Lymphocytic choriomeningitis virus) 瓜纳里托病毒(Guanarito virus) 胡宁病毒(Junin virus) 马丘波病毒(Machupo virus) 萨比亚病毒(Sabia virus)
冠状病毒科	人冠状病毒
细小 RNA 病毒科	A-D 型人肠道病毒(脊髓灰质炎病毒(Poliovirus)、艾柯病毒(Echovirus)、柯萨奇病毒(Coxsackie virus)A/B) A/B/C 型鼻病毒(Rhinovirus types A/B/C) 甲型肝炎病毒(Hepatitis A virus) 副肠弧病毒(Parechovirus)

[0088]

	口蹄疫病毒(Food and mouth disease virus)
肝炎病毒科	E 型肝炎病毒
嵌杯病毒科	诺沃克病毒(Norwalk virus) 扎幌病毒(Sapporo virus)
星状病毒科	人星状病毒 1
披膜病毒科	罗斯河病毒(Ross River virus) 基孔肯亚病毒(Chikungunya virus) 奥-奈氏病毒(O'nyong-nyong virus) 风疹病毒(Rubella virus)
黄病毒科	蜱传脑炎病毒(Tick-borne encephalitis virus) 登革病毒(Dengue virus) 黄热病毒(Yellow Fever virus) 日本脑炎病毒 Japanese encephalitis virus () 墨累山谷脑炎病毒 (Murray Valley virus) 圣路易斯脑炎病毒(St. Louis encephalitis virus) 西尼罗河病毒(West Nile virus) 丙型肝炎病毒 G 型肝炎病毒 GB 型肝炎病毒
δ 病毒属	δ 型肝炎病毒
博尔纳病毒科	博尔纳病毒(Bornavirus)
阮病毒	

[0089] 优选地，采用本发明化合物治疗流感。在本发明内，术语“流感”包括 A 型、B 型、C 型流感、鲑传贫病毒属（isavirus）和索戈托病毒属并且还包括禽流感和猪流感。未特别限定待治疗的对象并且其可以是任何脊椎动物，如鸟类和哺乳动物（包括人类）。

[0090] 不希望受理论限制，认为本发明的化合物能够抑制核酸内切酶活性，特别是流感病毒的核酸内切酶活性。更具体地讲，认为它们直接干扰流感 PA 蛋白的 N- 末端部分，其呈现核酸内切酶活性。但是，化合物至细胞的递送可代表一个问题，取决于例如化合物的溶解度或其跨过细胞膜的能力。本发明不仅显示所要求保护的化合物具有体外聚合酶抑制活性，而且具有体内抗病毒活性。

[0091] 具有式 I 的化合物的体外聚合酶抑制活性的可能量度为本文公开的 FRET 核酸内切酶活性测定。优选地，在 FRET 测定中化合物在 25μM 时表现出至少约 50％的减少％。

在该上下文中，减少%为经化合物处理的样品的底物切割的初始反应速度（v0）相比于未经处理样品的减少%。优选地，化合物在 FRET 测定中表现出至少约 40 μM、更优选至少约 20 μM 的 IC50。半数最大抑制浓度（IC50）是化合物在抑制生物或生化功能方面效力的量度，并且在范围为最大 100 μM 至至少 2nM 的给定浓度系列中由初始反应速度（v0）计算。

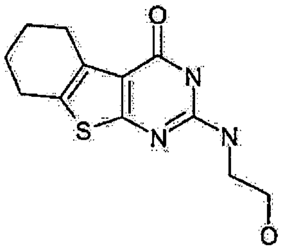
[0092] 具有式 I 或 II 的化合物的体内抗病毒活性的可能量度是本文公开的 CPE 测定。优选地，化合物在 50 μM 时表现出至少约 30%的减少%。在这一点上，在用化合物处理后病毒介导的细胞病变效应（CPE）的减少如下计算：使用基于 ATP 的细胞活力测定（Promega）确定经感染处理的和未经感染处理的细胞的细胞活力。从经感染处理的样品的响应（RLU）扣除未经感染处理样品的以相对荧光单位（RLU）计的响应，然后对相应的未感染样品的活力进行标准化，产生 CPE 减少%。优选地，在 CPE 测定中化合物表现出至少约 45 μM、更优选至少约 10 μM 的 IC50。半数最大抑制浓度（IC50）是化合物在抑制生物或生化功能方面效力的量度并且在范围为最大 100 μM 至至少 100nM 的给定浓度系列中由 RLU 响应计算。

[0093] 具有式 II 的化合物的体外聚合酶抑制活性的可能量度是本文公开的 Biacore 结合测定。Biacore 系统是基于称为表面等离子体共振（SPR）的光学现象。这种技术是用于测量材料在平面金属表面如金或银上的吸收的基础。SPR 被用作一种在无标记环境中实时测量生物分子相互作用的强大技术。将一种反应物固定至传感器表面，但是另一种反应物在溶液中是自由的并且通过表面。以任意单位测量缔合和解离并且在称为传感图的图表中展示。

[0094] 根据制造商方案，将禽 H5N1 流感病毒的 PB2 帽结合结构域（CBD）通过胺偶联固定在 CM7 传感器芯片（GE Healthcare）的表面上。将蛋白质于 10mM 磷酸盐缓冲液（pH 6.5）中稀释。使用 HBS-EP 缓冲液（10mM HEPES、150mM NaCl、3mM EDTA、0.005%表面活性剂 p20）作为用于固定的运行缓冲液。使用 30 μg / ml 的蛋白质浓度和 12min 的接触时间，达到约 8000 RU（相对响应单位）的固定化水平。

[0095] 对于化合物筛选，使用含有 10mM TRIS、3mM EDTA、150mM NaCl、0.005%表面活性剂 p20（GE Healthcare / Biacore）、1mM DTT、0.5%的 DMSO 运行缓冲液。将每种化合物的 2mM DMSO 储备液于 1.005X 不含 DMSO 的样品缓冲液（1.005X TRIS / EDTA / NaCl / p20 / DTT；由 10X 储备液稀释）中稀释，以达到 10 μM 的最终化合物浓度和 0.5% DMSO。m7GTP（Sigma Aldrich）和 SAV-7160 以各自 4 mM 和 10 μM 的浓度

[0096]



[0097] 用作参照和芯片稳定性对照。制备每种参照化合物的储备液并将等份试样在 -20℃贮存。在该上下文中，RU 是化合物与 PB2-CBD 结合的量度并且一般与 SAV-7160 以 RU 计的结合相比较进行评估。

[0098] 对于缓冲液，通过从活性流动池 Fc2 减去针对参照流动池 Fc1 获得的响应、产生化合物与配体的相对响应单位（RU）来解释体效应（基质），所述相对响应单位反映了化合物

与配体的结合。缓冲液中的有机溶剂如 DMSO 导致高体效应，这由于配体固定化而在参照流动池和活性流动池不同。为了解释这些差异，建立校准曲线。测量缓冲液中范围为 0.1%至 1.5%的八个 DMSO 浓度并且通过将 Fc2-Fc1 对 Fc1 作图来计算线性校准曲线。然后通过相应的Fc2-Fc1 差异和由校准曲线上的各个 Fc1 信号给出的溶剂因子来校正每个样品的相对响应。为了解释化合物的不同大小，将经缓冲液和溶剂校正的响应单位对分子量进行标准化。

[0099]　通过在浓度范围为 200μM 至 1nM 内测量分析物与配体的结合亲合力来确定亲合常数（KD 值）。KD 值为 50%的结合位点饱和时的浓度并且使用线性曲线拟合模型来计算。

[0100]　在 Biacore 测定中，化合物与固定化 PB2-CBD 的结合（RU)优选为至多 15 RU，更优选为至多 7.5 RU。亲合常数（KD）优选为至多 50μM，更优选至多 10μM。

[0101]　具有通式 I 的化合物可与一种或多种其他药物组合使用。未特别限定其他药物的类型并且其将取决于待治疗的病症。优选地，其他药物为另一种可用于治疗、减轻或预防病毒疾病的药物，更优选为另一种可用于治疗、减轻或预防流感的药物。

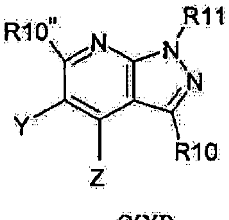
[0102]　将下列药物组合被认为特别适合：

[0103]　（i）核酸内切酶和帽结合抑制剂的组合（特别地靶向流感）。未特别限定核酸内切酶抑制剂，并且其可以是任何核酸内切酶抑制剂，特别地任何病毒核酸内切酶抑制剂。优选的核酸内切酶抑制剂是具有通式（I）的那些。

[0104]　未特别限定帽结合抑制剂，并且其可以是任何帽结合抑制剂，特别地任何病毒帽结合抑制剂。优选的帽结合抑制剂是具有通式（II）的那些和／或在 WO2011／000566 中公开的化合物，其完整公开内容通过引用并入。特别地，关于根据 WO2011/000566 的化合物的通式的描述，各个取代基的优选实施方案以及化合物的医疗用途和优点通过引用并入本文。

[0105]　WO2011／000566 的化合物具有通式（XXI）：

[0106]



(XXI)

[0107]　或其药学上可接受的盐、溶剂化物、前药、互变异构体、外消旋物、对映异构体或非对映异构体；

[0108]　其中

[0109]　Y 和 Z 中的一个是 $-XR^{12}$ 而另一个是 $R^{10'}$；

[0110]　R^{10}、$R^{10'}$ 和 $R^{10''}$ 各自独立地选自氢、C_1-C_6-烷基、C_2-C_6-烯基、C_2-C_8-炔基、$-(CH_2)_nC(O)OH$、$-(CH_2)_nC(O)OR^{16}$、$-(CH_2)_nOH$、$-(CH_2)_nOR^{16}$、$-CF_3$、$-(CH_2)_n$-环烷基、$-(CH_2)_nC(O)NH_2$、$-(CH_2)_nC(O)NHR^{16}$、$-(CH_2)_nC(O)NR^{16}R^{17}$、$-(CH_2)_nS(O)_2NH_2$、$-(CH_2)_nS(O)_2NHR^{16}$、$-(CH_2)_nS(O)_2NR^{16}R^{17}$、$-(CH_2)_nS(O)_2R^{16}$、卤素、$-CN$、$-(CH_2)_n$-芳基、$-(CH_2)_n$-杂芳基、$-(CH_2)_nNH_2$、$-(CH_2)_nNHR^{16}$ 和 $-(CH_2)_nNR^{16}R^{17}$；任选被取代；

[0111]　R^{11} 选自氢、C_1-C_6-烷基、$-CF_3$、C_2-C_6-烯基、C_2-C_8-炔基、$-(CH_2)_n$-环烷基、$-(CH_2)$

$_n$- 芳基、-$(CH_2)_n$- 杂环烷基和 -$(CH_2)_n$- 杂芳基；任选被取代；

[0112] X 选自 CH_2、C(O)、C(S)、CH(OH)、CH(OR^{16})、$S(O)_2$、-$S(O)_2$-N(H)-、-$S(O)_2$—N(R^{16})-、—N(H)-$S(O)_2$-、—N(R^{16})-$S(O)_2$-、C(=NH)、C(=N-R^{16})、CH(NH_2)、CH(NHR^{16})、CH($NR^{16}R^{17}$)、-C(O)—N(H)-、-C(O)—N(R^{16})-、—N(H)-C(O)-、—N(R^{16})-C(O)-、N(H)、N (-R^{16}) 和 O；

[0113] R^{12} 选自 C_1-C_6- 烷基、-CF_3、C_2-C_6- 烯基、C_2-C_8- 炔基、-$(CH_2)_n$- 环烷基、-$(CH_2)_n$- 杂环烷基、-$(CH_2)_n$- 芳基、—$NR^{16}R^{17}$ 和 -$(CH_2)_n$- 杂芳基；任选被取代；

[0114] R^{16} 和 R^{17} 独立地选自 C_1-C_6- 烷基、C_2-C_6- 烯基、C_2-C_6- 炔基、-$(CH_2)_n$- 环烷基、-$(CH_2)_n$- 芳基、-CF_3、-C(O)R^{18} 和 -$S(O)_2R^{18}$；任选被取代；

[0115] R^{18} 独立地选自 C_1-C_6- 烷基、C_2-C_6- 烯基、C_2-C_6- 炔基、-$(CH_2)_n$- 环烷基和 -CF_3；任选被取代；且

[0116] n 在每种情况下选自 0、1 和 2。

[0117] 在 WO2011 / 000566 的上下文中，术语“任选取代的”在每种情况下是指 1 至 10 个取代基、例如 1、2、3、4、5、6、7、8、9 或 10 个取代基，其在每种情况下优选地独立选自卤素、特别是 F、Cl、Br 或 I；-NO_2、-CN、-OR′ 、-NR′ R″ 、-(CO)OR′ 、-(CO)OR′ ″ 、-(CO)NR′ R″ 、-NR′ COR″ ″ 、-NR′ COR′ 、-NR″ CONR′ R″ 、-NR″ SO_2A、-COR′ ″；-SO_2NR′ R″ 、-OOCR′ ″ 、-CR′ ″ R″ ″ OH、-R′ ″ OH、=O 和 -E；

[0118] R′ 和 R″ 各自独立地选自氢、烷基、烯基、炔基、-OE、环烷基、杂环烷基、芳基、杂芳基和芳烷基或一起形成杂芳基或杂环烷基；任选被取代；

[0119] R′ ″ 和 R″ ″ 各自独立地选自烷基、烯基、炔基、环烷基、杂环烷基、烷氧基、芳基、芳烷基、杂芳基和 -NR′ R″ ；且

[0120] E 选自烷基、烯基、环烷基、烷氧基、烷氧基烷基、杂环烷基、脂族系统、芳基和杂芳基；任选被取代。

[0121] 对两类获批的流感抗病毒剂（M2 离子通道抑制剂（金刚烷类）和神经氨酸酶抑制剂（奥司他韦））的广泛耐药性存在于两种流行性和季节性病毒中，使得这些药物在治疗方式中具有边际效用。对于 M2 离子通道抑制剂，病毒耐药性自 2003 以来已增加，并且对于季节性流感 A）H3N2，金刚烷类目前被视为无效的。实质上所有 2009 H1N1 和季节性 H3N2 菌株对金刚烷类（金刚烷乙胺和金刚烷胺）有耐药性，且大多数季节性 H1N1 菌株对奥司他韦（最广泛使用的神经氨酸酶抑制剂 (NAI)）有耐药性。对于奥司他韦，WHO 报道在流感季节 2007/2008 年、以及南半球 2008 的第二和第三季度中开始的流感 A/H1N1 耐药性的大幅出现。2008 的第四季度（北半球）公布了甚至更严重的数量，其中 95％的所有测试分离株揭示没有奥司他韦敏感性。考虑到目前大多数国家政府已储备奥司他韦作为其流感大流行防备计划的部分这一事实，所以明显的是，对新的有效药物的要求明显增加。为了解决对更有效疗法的需要，已开始进行使用具有不同作用机制的抗病毒药物的两种或甚至三种组合的初步研究。体外和体内分析组合的金刚烷类和神经氨酸酶抑制剂，发现其以高度协同的方式起作用。但是，已知对于这两种类型的抗病毒剂而言，耐药性病毒出现相当快速且这个问题未能通过组合这些确定的抗病毒药物得以解决。

[0122] 流感病毒聚合酶抑制剂是靶向聚合酶的转录活性的新型药物。对抗病毒聚合酶的帽 - 结合和核酸内切酶活性位点的选择性抑制剂通过终止病毒繁殖周期严重地减弱病毒感染。这两种靶标位于聚合酶复合体的不同亚基内并由此代表独特的药物靶标。由于所谓

的对于病毒转录而言是强制性的“帽－攫取”机理需要这两种功能这一事实，期望这两种功能的并发抑制以高度协同的方式起作用。这种高效药物组合将导致较低的物质浓度并因此导致改善的剂量－响应关系和更好的副作用特征。

[0123] 这两个活性位点由所有A型流感菌株（例如禽类和人类）中的相同残基组成，并因此这种高度的序列保守性证实这些靶标不可能触发快速耐药性病毒产生的看法。因此，单独的和组合的核酸内切酶和帽－结合抑制剂是对抗季节性和流行性流感（与病毒菌株无关）的理想候选药物。

[0124] 核酸内切酶抑制剂和帽－结合抑制剂的组合或靶向核酸内切酶活性位点和帽－结合结构域两者的双重特异性聚合酶抑制剂，对耐金刚烷类和神经氨酸酶抑制剂的病毒菌株是有效的，而且将耐药性产生的低敏感性的优点与抗多种病毒菌株的活性相组合。

[0125] (ii)不同抗病毒靶标（特别地靶向流感）的抑制剂的组合，其关注与（优选流感）聚合酶抑制剂的组合，作为双重或多重组合疗法。流感病毒聚合酶抑制剂是靶向聚合酶转录活性的新型药物。抗病毒聚合酶的帽－结合和核酸内切酶活性位点的选择性抑制剂通过终止病毒繁殖周期严重地减弱病毒感染。期望特定针对病毒细胞内靶标的聚合酶抑制剂与不同抗病毒靶标的抑制剂的组合以高度协同的方式起作用。这是基于以下事实：这些不同类型的抗病毒药物表现出完全不同的作用机理和药动学性质，其对该组合的抗病毒功效有利地且协同地起作用。

[0126] 这种高效药物组合将导致较低的物质浓度并因此导致改善的剂量－响应关系和更好的副作用特征。此外，对于不同抗病毒靶标的抑制剂与聚合酶抑制剂的组合，在(i)下描述的聚合酶抑制剂的优点占优势。

[0127] 通常，选自第一组的聚合酶抑制剂的至少一种化合物与选自第二组的聚合酶抑制剂的至少一种化合物组合。

[0128] 可用于这种类型的组合疗法的第一组的聚合酶抑制剂包括但不限于下文所述的具有通式(I)的化合物、上文所述的具有通式(II)的化合物和／或WO20 11／000566中公开的化合物。

[0129] 可用于这种类型的组合疗法的第二组的聚合酶抑制剂包括但不限于WO 2010／110231、WO 2010／110409、WO 2006／030807和US 5,475,109中公开的化合物和氟他胺及类似物、法匹拉韦(favipiravir)及类似物、表没食子儿茶素没食子酸酯及类似物、以及核苷类似物如利巴韦林。

[0130] (iii)聚合酶抑制剂与神经酰胺酶抑制剂的组合

[0131] 流感病毒聚合酶抑制剂是靶向聚合酶转录活性的新型药物。对抗病毒聚合酶的帽－结合和核酸内切酶活性位点的选择性抑制剂通过终止病毒繁殖周期严重地减弱病毒感染。期望特定针对病毒细胞内靶标的聚合酶抑制剂与不同的细胞外抗病毒靶标、尤其（例如病毒）神经氨酸酶的组合以高度协同的方式起作用。这是基于以下事实：这些不同类型的抗病毒药物表现出完全不同的作用机理和药动学性质，其对该组合的抗病毒功效有利地且协同地起作用。

[0132] 这种高效药物组将导致较低的物质浓度并因此导致改善的剂量－响应关系和更好的副作用特征。此外，对于不同抗病毒靶标的抑制剂与聚合酶抑制剂的组合，在(i)下描述的聚合酶抑制剂的优点占优势。

[0133] 通常，选自上文提及的第一组的聚合酶抑制剂的至少一种化合物与至少一种神经酰胺酶抑制剂组合。

[0134] 未具体地限定神经氨酸酶抑制剂（特别地流感神经酰胺酶抑制剂）。实例包括扎那米韦、奥司他韦、帕拉米韦（peramivir）、KDN DANA、FANA 和环戊烷衍生物。

[0135] （iv）聚合酶抑制剂与 M2 通道抑制剂的组合

[0136] 流感病毒聚合酶抑制剂是靶向聚合酶的转录活性的新型药物。对抗病毒聚合酶的帽-结合和核酸内切酶活性位点的选择性抑制剂通过终止病毒繁殖周期严重地减弱病毒感染。期望特定针对病毒细胞内靶标的聚合酶抑制剂与不同的细胞外和胞质抗病毒靶标、尤其病毒 M2 离子通道的抑制剂的组合以高度协同的方式起作用。这是基于以下事实：这些不同类型的抗病毒药物表现出完全不同的作用机理和药动学性质，其对该组合的抗病毒功效有利地且协同地起作用。

[0137] 这种高效药物组将导致较低的物质浓度并因此导致改善的剂量-响应关系和更好的副作用特征。此外，对于不同抗病毒靶标的抑制剂与聚合酶抑制剂的组合，在（i）下描述的聚合酶抑制剂的优点占优势。

[0138] 通常，选自上文提及的第一组的聚合酶抑制剂的至少一种化合物与至少一种 M2 通道抑制剂组合。

[0139] 未具体地限定 M2 通道抑制剂（特别地流感 M2 通道抑制剂）。实例包括金刚烷胺和金刚烷乙胺。

[0140] （v）聚合酶抑制剂与 α 葡糖苷酶抑制剂的组合

[0141] 流感病毒聚合酶抑制剂是靶向聚合酶的转录活性的新型药物。对抗病毒聚合酶的帽-结合和核酸内切酶活性位点的选择性抑制剂通过终止病毒繁殖周期严重地减弱病毒感染。期望特定针对病毒细胞内靶标的聚合酶抑制剂与不同的细胞外靶标、尤其 α 葡糖苷酶的抑制剂的组合以高度协同的方式起作用。这是基于以下事实：这些不同类型的抗病毒药物表现出完全不同的作用机理和药动学性质，其对该组合的抗病毒功效有利地且协同地起作用。

[0142] 这种高效药物组将导致较低的物质浓度并因此导致改善的剂量-响应关系和更好的副作用特征。此外，对于不同抗病毒靶标的抑制剂与聚合酶抑制剂的组合，在（i）下描述的聚合酶抑制剂的优点占优势。

[0143] 通常，选自上文提及的第一组的聚合酶抑制剂的至少一种化合物与至少一种 α 葡糖苷酶抑制剂组合。

[0144] 未具体地限定 α 葡糖苷酶抑制剂（特别地流感 α 葡糖苷酶抑制剂）。实例包括描述于 Chang 等人，Antiviral Research 201 1,89,26-34 中的化合物。

[0145] （vi）聚合酶抑制剂与其他流感靶标配体的组合

[0146] 流感病毒聚合酶抑制剂是靶向聚合酶的转录活性的新型药物。对抗病毒聚合酶的帽-结合和核酸内切酶活性位点的选择性抑制剂通过终止病毒繁殖周期严重地减弱病毒感染。期望特定针对病毒细胞内靶标的聚合酶抑制剂与不同的细胞外、胞质或细胞核的抗病毒靶标的抑制剂的组合以高度协同的方式起作用。这是基于以下事实：这些不同类型的抗病毒药物表现出完全不同的作用机理和药动学性质，其对该组合的抗病毒功效有利地且协同地起作用。

[0147] 这种高效药物组将导致较低的物质浓度并因此导致改善的剂量-响应关系和更好的副作用特征。此外，对于不同抗病毒靶标的抑制剂与聚合酶抑制剂的组合，在(i)下描述的聚合酶抑制剂的优点占优势。

[0148] 通常，选自上文提及的第一组的聚合酶抑制剂的至少一种化合物与另一种流感靶标的至少一种配体组合。

[0149] 未具体地限定另一种流感靶标的配体。实例包括对唾液酸酶融合蛋白起作用的化合物，例如Fludase(DAS18 1)、siRNA和硫代硫酸寡核苷酸、信号转导抑制剂(ErbB酪氨酸激酶、Abl激酶家族、MAP激酶、PKCa介导的ERK信号传导激活以及干扰素(诱导剂)。

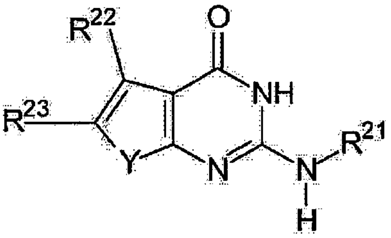
[0150] (vii)(优选流感)聚合酶抑制剂与用作使疾病症状最小化的佐剂(adjuvance)的化合物(抗生素、抗炎剂如COX抑制剂(例如COX-1/COX-2抑制剂、选择性COX-2抑制剂)、脂肪氧合酶抑制剂、EP配体(特别地EP4配体)、缓激肽配体和/或大麻素配体(例如CB2激动剂)的组合。流感病毒聚合酶抑制剂是靶向聚合酶的转录活性的新型药物。对抗病毒聚合酶的帽-结合和核酸内切酶活性位点的选择性抑制剂通过终止病毒繁殖周期严重地减弱病毒感染。期望特定针对病毒细胞内靶标的聚合酶抑制剂与用作使疾病症状最小化的佐剂的化合物的组合解决病毒感染的病因性和症候性病理后果。期望这种组合以协同作用的方式起作用，因为这些不同类型的药物表现出完全不同的作用机理和药动学性质，其对该组合的抗病毒功效有利地且协同地起作用。

[0151] 这种高效药物组将导致较低的物质浓度并因此导致改善的剂量-响应关系和更好的副作用特征。此外，对于不同抗病毒靶标的抑制剂与聚合酶抑制剂的组合，在(i)下描述的聚合酶抑制剂的优点占优势。

[0152] 具有通式II的化合物

[0153] 在下文中鉴定具有通式II的化合物，

[0154]



(II)

[0155] 应理解，除非另有提及，否则在本说明书中术语“具有通式II的化合物”包括药学上可接受的盐、溶剂化物、多晶型物、前药、互变异构体、外消旋物、对映异构体、或非对映异构体或其混合物。

[0156] 在本发明中，关于具有通式II的化合物适用下列定义。

[0157] Y是S。

[0158] R^{21}选自-H、-C_{1-6}烷基、-$(CH_2)_q$-芳基、-$(CH_2)_q$-杂环基、-$(CH_2)_q$-环烷基、-$(CH_2)_p$-OR^{25}和-$(CH_2)_p$-$NR^{25}R^{26}$。优选地，R^{21}是-H、-C_{1-6}烷基、或-$(CH_2)_p$-OR^{25}，在该实施方案的更优选方面R^{25}是H。

[0159] R^{22}选自-H、-C_{1-6}烷基、-$(CH_2)_q$-环烷基、-Hal、-CF_3和-CN。优选地，R^{22}是-H、-C_{1-6}烷基或Hal(优选Hal=Cl)。

[0160] R^{23}选自-芳基、-杂环基、-环烷基、$-C(-R^{28})(-R^{29})$-芳基、$-C(-R^{28})(-R^{29})$-杂环基和$-C(-R^{28})(-R^{29})$-环烷基。在优选的实施方案中，R^{23}是$-(CH_2)_q$-芳基或$-(CH_2)_q$-杂芳基，其中所述芳基和/或杂芳基可任选地被一个或多个取代基R^{27}取代。更优选地，R^23是-苯基、-苄基或-吡啶基，其中所述一个或多个取代基R27独立地选自-Hal、$-CF_3$、-CN、$-C_{1-6}$烷基、$-C(O)-C_{1-6}$烷基或$-(CH_2)_qNR^{25}R^{26}$，其中R^{25}和R^{26}独立地选自H和$-C_{1-6}$烷基。

[0161] R^{25}选自-H、$-C_{1-6}$烷基和$-(CH_2CH_2O)_rH$。优选地，R^{25}选自-H和$-C_{1-6}$烷基。

[0162] R^{26}选自-H和$-C_{1-6}$烷基。

[0163] R^{27}独立地选自$-C_{1-6}$烷基、$-C(O)-C_{1-6}$烷基、-Hal、$-CF_3$、-CN、$-COOR^{25}$、$-OR^{25}$、$-(CH_2)_qNR^{25}R^{26}$、$-C(O)-NR^{25}R^{26}$和$-NR^{25}-C(O)-C_{1-6}$烷基。优选地，R^{27}独立地选自-Hal、$-CF_3$、-CN、$-C_{1-6}$烷基、$-C(O)-C_{1-6}$烷基或$-(CH_2)_qNR^{25}R^{26}$，其中R^{25}和R^{26}独立地选自H和$-C_{1-6}$烷基。

[0164] R^{28}和R^{29}独立地选自-H、$-C_{1-6}$烷基、$-(CH_2)_q$-芳基、$-(CH_2)_q$-杂环基、$-(CH_2)_q$-环烷基、-OH、$-O-C_{1-6}$烷基、$-O-(CH_2)_q$-芳基、$-O-(CH_2)_q$-杂环基和$-O-(CH_2)_q$-环烷基。优选R^{28}和R^{29}独立地选自-H和$-C_{1-6}$烷基。

[0165] 在替代实施方案中，R^{28}和R^{29}一起为=O、$-CH_2CH_2-$、$-CH_2CH_2CH_2-$或$-CH_2CH_2CH_2CH_2-$。

[0166] p为1至4。

[0167] q为0至4，优选地，q为0或1。

[0168] r为1至3。

[0169] 在上述定义中，芳基、杂环基和/或环烷基可任选地一个或多个可以是相同或不同的取代基R^{27}取代。

[0170] 不希望受理论限制，认为具有通式II的化合物能够抑制宿主mRNA帽结构与帽-结合结构域(CBD)、特别是流感病毒的帽-结合结构域的结合。更具体地讲，认为它们直接干扰流感PB2蛋白的CBD。但是，化合物进入细胞的递送可出现问题，取决于例如化合物的溶解度或其跨越细胞膜的能力。本发明不仅显示所要求保护的化合物具有体外聚合酶抑制活性，而且具有体内抗病毒活性。

[0171] 在不偏离本发明的范围下，各种修改和改变将对本领域技术人员而言是显而易见的。尽管已结合特定的优选实施方案描述本发明，但是应理解要求保护的本发明不应不适当地限于此类特定实施方案。事实上，本发明意欲包括对用于实施本发明的描述模式的各种修改，这些修改对相关领域技术人员是明显的。

[0172] 下列实施例仅仅阐述本发明，不应理解为限制本发明的范围，而本发明的范围在任何情况下由随附权利要求所示。

实施例

[0173] FRET核酸内切酶活性测定

[0174] 如Dias等人，Nature 2009；4月16日；458(7240)，914-918中所述，产生并纯化具有流感核酸内切酶活性的流感A病毒(IAV)PA-Nter片段(氨基酸1—209)。将该蛋白溶解于含有20mM Tris pH 8.0，100mM NaCl和10mM β-巯基乙醇的缓冲液中并在-20℃贮存等份试样。

[0175] 用5′-FAM荧光团和3′-BHQ1淬灭剂的双重标记的20碱基RNA寡核苷酸用作通过PA-Nter的核酸内切酶活性切割的底物。对RNA底物的切割使荧光团从淬灭剂释放，

导致荧光信号的增加。

[0176] 将所有测定组分稀释于含有20mM Tris-HCl pH 8.0,100mM NaCl,1mM $MnCl_2$,10mM $MgCl_2$和 10mM β-巯基乙醇的测定缓冲液中。PA-Nter 的最终浓度为 0.5μM 和 1.6μMRNA 底物。将测试化合物溶解于 DMSO 中,通常以两种浓度或浓度系列进行测试,产生 0.5%的最终的板孔 DMSO 浓度。在化合物在该浓度下不可溶的情况下,它们以最高可溶浓度进行测试。浓度为 0.1μM 的 SAV-6004 用作该测定的参照。

[0177] 一式八份在白色 384-孔微量滴定板(PerkinElmer)的孔中提供5μl 每种化合物稀释液。在添加 PA-Nter 稀释液后,将板密封并在添加稀释于测定缓冲液中的 1.6μM RNA 底物之前于室温孵育 30min。随后,在微板读数器(Synergy HT,Biotek)中在 485nm 激发和 535nm 发射波长下测量经切割 RNA 的递增荧光信号。在 35 的灵敏度下动力学读数间隔为 35 秒。使用在 20min 时间内的荧光信号数据来计算底物切割的初始速度(v0)。最终读数为经化合物处理的样品的 v0 相比于未经处理的样品的减少%。半数最大抑制浓度(IC50)是化合物在抑制生物或生化功能方面的效力的量度,并且在范围为最大 100μM 至至少 2nM 的给定浓度系列中由初始反应速度(v0)计算。细胞病变效应(CPE)测定

[0178] 流感 A 病毒(IAV)获自 American Tissue Culture Collection (A / Aichi / 2 / 68(H3N2);VR-547)。通过使病毒在 Mardin-Darby 犬肾(MDCK;ATCC CCL-34)细胞上繁殖来制备病毒储备液,并且病毒储备液的感染滴度通过 Reed,L.J. 和 H.Muench.1938,Am.J.Hyg.27:493-497 中所述的 50%组织培养感染剂量(TCID50)分析来确定。

[0179] 使用含有 10%胎牛血清(FBS)、2mM L-谷氨酰胺和 1%抗生素(所有来自 PAA)的 DMEM / Ham's F-12(1 : 1)培养基将 MDCK 细胞以 2×10^4 个细胞 / 孔接种于 96 孔板中。直到感染,将细胞在 37℃、5.0% CO_2 下孵育 5 小时以在孔底部上形成~ 80%汇合单层。将每种测试化合物溶解于 DMSO 中,通常以 25μM 和 250μM 测试。在化合物在该浓度下不可溶的情况下,它们以最高可溶浓度进行测试。将化合物稀释于感染培养基(含有 5μg / ml 胰蛋白和 1%抗生素的 DMEM / Ham's F-12(1 : 1))中以达到 1%的最终板孔 DMSO 浓度。将病毒储备液稀释于感染培养基(含有 5μg / ml 胰蛋白、1% DMSO 和 1%抗生素的 DMEM / Ham,s F-12(1 : 1))中以达到 0.05 的理论感染复数(MOI)。

[0180] 在去除培养基和利用 PBS 的一个洗涤步骤后,将病毒和化合物一起加入细胞中。在用于细胞毒性确定(即在不存在病毒感染的情况下)的孔中,不加入病毒悬液。相反,加入感染培养基。一式两份进行每个处理。在 37℃、5% CO_2 下孵育 48 小时后,用显微镜观察每个孔的表观细胞毒性、沉淀形成或其他明显的异常。然后,使用 CellTiter-Glo 发光细胞活力测定(Promega)确定细胞活力。将上清液小心去除,将 65μl 复原试剂加入至每孔中,并在轻微振摇下于室温孵育 15min。然后,将 60μl 溶液转移至不透明板并且使用 Synergy HT 板读数器(Biotek)测量发光(RLU)。

[0181] 使用未经感染处理的细胞与经感染处理的细胞的相对细胞活力值来评价化合物的细胞毒性。在测试浓度下相对活力低于 80%的物质被视为细胞毒性的且以较低浓度进行再测试。

[0182] 在用化合物处理后病毒介导的细胞病变效应(CPE)的减少如下计算:从经感染处理的样品的响应(RLU)扣除未经感染处理的样品的响应(RLU),然后对相应的未感染样品的活力进行标准化,产生 CPE 减少%。半数最大抑制浓度(IC50)是化合物在抑制生物或生

化功能方面效力的量度，并且在范围为最大 100μM 至至少 100nM 的给定浓度系列中由 RLU 响应计算。

[0183] Biacore 测定

[0184] 根据制造商方案，将禽 H5N1 流感病毒的 PB2 帽结合结构域（CBD）通过胺偶联固定在 CM7 传感器芯片（GE Healthcare）的表面上。将蛋白质于 10mM 磷酸盐缓冲液（pH 6.5）中稀释。使用 HBS-EP 缓冲液（10mM HEPES、150mM NaCl、3mM EDTA、0.005%表面活性剂 p20）作为用于固定的运行缓冲液。使用 30μg / ml 的蛋白质浓度和 12min 的接触时间，获得约 8000 RU（相对响应单位）的固定化水平。

[0185] 对于化合物筛选，使用含有 10mM TRIS、3 mM EDTA、150mM NaCl、0.005%表面活性剂 p20（GE Healthcare / Biacore）、1mM DTT、0.5% DMSO 的运行缓冲液。将每种化合物的 2mM DMSO 储备液于 1.005X 不含 DMSO 的样品缓冲液（1.005X TRIS / EDTA / NaCl / p20 / DTT；由 10X 储备液稀释）中稀释，以达到 10μM 的最终化合物浓度和 0.5% DMSO。m7GTP（Sigma Aldrich）和 SAV-7160 以各自 4mM 和 10μM 的浓度用作参照和芯片稳定性对照。制备每种参照化合物的储备液并将等份试样在 -20℃贮存。

[0186] 对于缓冲液，通过从活性流动池 Fc2 减去针对参照流动池 Fc1 获得的响应、产生相对响应单位（RU）来解释体效应（基质），所述相对响应单位反映了化合物与配体的结合。缓冲液中的有机溶剂如 DMSO 导致高的体效应，这由于配体固定化而在参照流动池和活性流动池不同。为了解释这些差异，建立校准曲线。测量缓冲液中范围为 0.1%至 1.5%的八个 DMSO 浓度，并通过将 Fc2-Fc1 对 Fc1 作图来计算线性校准曲线。然后通过相应的 Fc2-Fc1 差异和由校准曲线上各个 Fc1 信号给出的溶剂因子来校正每个样品的相对响应。为了解释化合物的不同大小，将经缓冲液和溶剂校正的响应单位对分子量进行标准化。

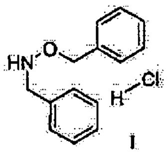
[0187] 通过测量在范围为 200μM 至 1nM 的浓度范围内分析物与配体的结合亲合力，来确定亲合常数（KD 值）。KD 值为 50%的结合位点饱和时的浓度，并使用线性曲线拟合模型来计算。

[0188] 具有通式（I）的化合物

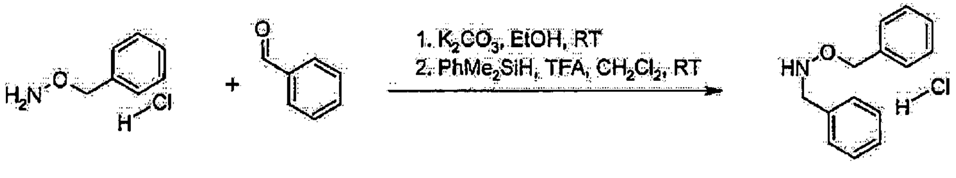
[0189] 关键中间体 I

[0190] O，N- 二苄基羟胺盐酸盐

[0191]



I



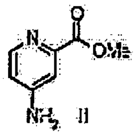
[0192] 向 O- 苄基羟胺盐酸盐（1.2g，10mmol，1 当量）在无水乙醇（16mL）中的悬液加入碳酸钾（1.5g，11mmol，1.1 当量）和苯甲醛（1.0mL，10mmol，1 当量）。将混合物在室温搅拌 5h，然后倒入水（50mL）中。用乙酸乙酯萃取混合物（3 x 50mL）。有机层经硫酸镁干燥，过滤，真空蒸发。将残余物溶解于二氯甲烷（21mL）中，冷却至 0℃。在氩气下向该溶液滴加二

甲基苯基硅烷（2.3mL，14.3mmol，1.4当量）和三氟乙酸（2.6mL，35.6mmol，3.5些量）。将反应混合物在室温搅拌16h。真空除去溶剂，将2N盐酸溶液（5mL加入至于二氯甲烷（5mL）中稀释的残余物。过滤沉淀，用乙醚洗涤，真空干燥，得到期望的化合物，为白色粉末（966mg，48%收率）。

[0193] 关键中间体II

[0194] 4-氨基-吡啶-2-甲酸甲酯

[0195]



II

[0196] 步骤1：

[0197] 将草酰氯（6.7mL，76.8mmol，1.2当量）加入至4-氯-吡定-2-甲酸（10.0g，63.4mmol，1当量）在二氯甲烷（270mL）中的溶液。将溶液冷却至0℃，滴加二甲基甲酰胺（1.1mL）。将混合物在室温搅拌1.5h，蒸发至干。将有机残余物在甲醇（110mL）中稀释，将混合物在室温搅拌30min，蒸发至干。将5%碳酸氢钠溶液（50mL）倒在残余物上，用乙酸乙酯萃取水相（2 x 40mL）。有机层用盐水洗涤（3 x 20mL），经硫酸镁干燥，过滤，蒸发，得到4-氯-吡啶-2-甲酸甲酯，为米色粉末（10.0g，92%收率）。

[0198] 步骤2：

[0199] 将4-氯-吡啶-2-甲酸甲酯（13.7g，79.9mmol，1当量）溶解于二甲基甲酰胺（120mL）和水（6mL）的混合物中。加入叠氮化钠（6.2g，95.9mmol，1.2当量），将混合物在80℃加热24h。冷却后，将混合物用乙酸乙酯（40mL）稀释，用水（30mL）和盐水（30mL）洗涤。有机层经硫酸镁干燥，过滤，真空蒸发。在该阶段，反应未完全（检测到15%的起始材料），在80℃用新试剂再次运行相同程序24h。在相同处理后，蒸发有机层，得到结晶的4-叠氮基-吡啶-2-甲酸甲酯，为橙色油状物（10.2g，72%收率），放置结晶。

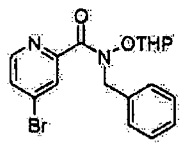
[0200] 步骤3：

[0201] 将4-叠氮基-吡啶-2-甲酸甲酯（3.9g，22mmol，1当量）溶解于甲醇（50mL）中，加入10% w钯/碳（400mg）。将混合物在4巴氢气压力下于室温搅拌直至反应完成。然后将混合物滤过硅藻土短柱，用甲醇漂洗，得到期望的化合物，为黄色粉末（3.0g，90%收率）。

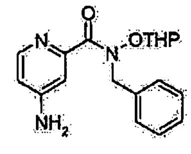
[0202] 关键中间体III和IV

[0203] 4-溴-吡啶-2-甲酸苄基-（四氢-吡喃-2-基氧基）-酰胺和4-氨基-吡啶-2-甲酸苄基-（四氢-吡喃-2-基氧基）-酰胺

[0204]

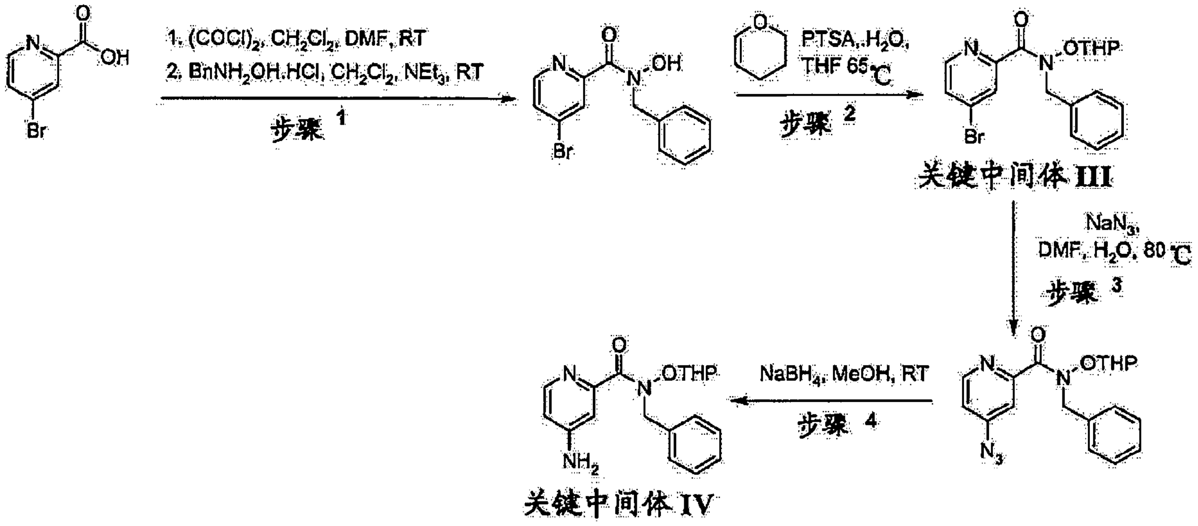


关键中间体 III



关键中间体 IV

[0205]



[0206] 步骤 1：

[0207] 将草酰氯 (5.1mL,58.6mmol,1.3 当量) 加入至 4- 溴 - 吡啶 -2- 甲酸 (9.1g,45.0mmol,1 当量) 在二氯甲烷 (250mL) 中的溶液。将溶液冷却至 0℃，滴加二甲基甲酰胺 (0.6mL)。将混合物在室温搅拌 1.5h，蒸发至干。将残余物稀释于二氯甲烷 (250mL)，加入 N- 苄基羟胺盐酸盐 (10.8g,67.5mmol,1.5 当量)。在 0℃滴加三乙胺 (18.8mL,135mmol,3 当量)，将混合物在室温搅拌 18h。然后将溶液倒入碳酸氢钠饱和溶液 (50mL)，用二氯甲烷萃取 (3 x50mL)。有机层经硫酸镁干燥，过滤，蒸发。将粗残余物通过快速色谱法、使用环己烷和乙酸乙酯 (100 / 0 至 70/30) 纯化，得到 4- 溴 - 吡啶 -2- 甲酸苄基 - 羟基 - 酰胺，为橙色油状物 (8.0g,58％收率)。

[0208] 步骤 2：

[0209] 将二氢吡喃 (9.4mL,104mmol,4 当量) 和对甲苯磺酸 (99mg,0.52mmol,0.02 当量) 加入至 4- 溴 - 吡啶 -2- 甲酸苄基 - 羟基 - 酰胺 (8.0g,26mmol,1 当量) 在四氢呋喃 (200mL) 中的溶液。将混合物在 65℃加热 48h。冷却后，将混合物倒入碳酸氢钠饱和溶液 (60mL)，用乙酸乙酯萃取 (3 x 40mL)。有机层经硫酸镁干燥，过滤，蒸发。将粗残余物通过快速色谱法、使用环己烷和乙酸乙酯 (100 / 0 至 80 / 20) 纯化，得到关键中间体 II，为浅黄色油状物 (7.8g,76％收率)，结晶。

[0210] 步骤 3：

[0211] 将 4- 溴 - 吡啶 -2- 甲酸苄基 -(四氢 - 吡喃 -2- 基氧基)- 酰胺 (5.0g,12.8mmol,1 当量) 溶解于二甲基甲酰胺 (41mL) 和水 (3mL) 的混合物。加入叠氮化钠 (997mg,15.3mmol,1.2 当量)，将混合物在 80℃加热 24h。冷却后，将混合物用乙酸乙酯 (40mL) 稀释，用水 (30mL) 和盐水 (30mL) 洗涤。有机层经硫酸镁干燥，过滤，真空蒸发。在该阶段，反应未完全，在 80℃用新试剂再次运行相同程序 24h。在相同处理后，将粗残余通过快速色谱法、使

用环己烷和乙酸乙酯（100 / 0 至 60 / 40）纯化，得到 4- 叠氮基 - 吡啶 -2- 甲酸苄基 -（四氢 - 吡喃 -2- 基氧基）- 酰胺（2.8g，61％收率）。

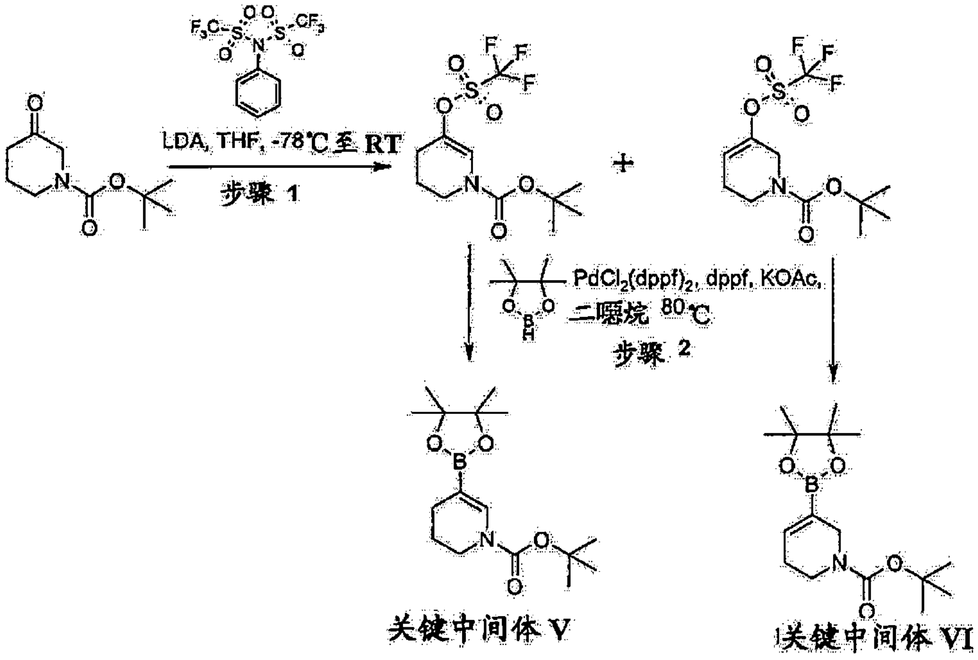
[0212]　步骤 4：

[0213]　向 4- 叠氮基 - 吡啶 -2- 甲酸苄基 -（四氢 - 吡喃 -2- 基氧基）- 酰胺（2.5g，7.1mmol，1 当量）在甲醇（55mL）中的溶液加入硼氢化钠（296mg，37.8mmol，1.1 当量），将混合物在室温搅拌 1h。然后加入水（20mL），将混合物蒸发至干。将残余物用乙酸乙酯稀释（20mL），将有机层用水洗涤，经硫酸镁干燥，过滤，真空蒸发。将粗残余物通过快速色谱法、使用乙酸乙酯和甲醇（100 / 0 至 90 / 10）纯化，得到关键中间体 IV，为无色油状物（883mg，38％收率）。

[0214]　关键中间体 V 和 VI

[0215]　5-（4，4，5，5- 四甲基 -[1，3，2] 二氧硼杂环戊烷 -2- 基）-3，4- 二氢 -2H- 吡啶 -1- 甲酸叔丁酯和 5-（4，4，5，5- 四甲基 -[1，3，2] 二氧硼杂环戊烷 -2- 基）3，6- 二氢 -2H- 吡啶 -1- 甲酸叔丁酯

[0216]



[0217]　步骤 1：

[0218]　在 -78℃，向 1.5M 在环己烷中的二异丙基氨基锂（8mL，12mmol，1.2 当量）在四氢呋喃（8mL）中的溶液滴加 3- 氧代 - 哌啶 -1- 甲酸叔丁酯（2.0g，10mmol，1 当量）在四氢呋喃（8mL）中的溶液。将混合物在 -78℃搅拌 1h，加入 N- 苯基双三氟甲烷磺酰胺（3.9g，11mmol，1.1 当量）在四氢呋喃（8mL）中的溶液。将混合物在 -78℃搅拌 2h，然后升温至室温，再在室温搅拌 18 小时。将混合物蒸发至干，将残余物用乙醚（20mL）溶解。将有机层用水（10mL）、2M 氢氧化钠溶液（3 x 10mL）、水（10mL）和盐水（10mL）洗涤。有机层经硫酸镁干燥，过滤，真空蒸发。将粗残余物通过快速色谱法、使用环己烷和二氯甲烷（100 / 0 至 0 / 100）纯化，分别得到 5- 三氟甲烷磺酰基氧基 -3，4- 二氢 -2H- 吡啶 -1- 甲酸叔丁酯（980mg，29％收率）和 5- 三氟甲烷磺酰基氧基 -3，6- 二氢 2H- 吡啶 -1- 甲酸叔丁酯（340mg，10％收

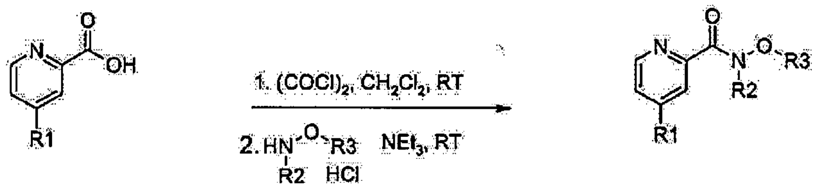
率)。

[0219] 步骤 2:

[0220] 向脱气的 5- 三氟甲烷磺酰基氧基 - 二氢 -2H- 吡啶 -1- 甲酸叔丁酯 (340mg,1.0mmol,1 当量) 在二噁烷 (10mL) 中的溶液加入双 -(频哪醇合)- 二硼 (287mg,1.1mmol,1.1 当量)、乙酸钾 (302mg,3.0mmol,3 当量)、1,1′ - 双 (二苯基膦基) 二茂铁 (17mg,0.03mmol,0.03 当量) 和二氯 [1,1′ - 双 (二苯基膦基) 二茂铁] 钯)(23mg,0.03mmol,0.03 当量)。将混合物在 80℃搅拌 18h。冷却后,过滤混合物,浓缩滤液,通过快速色谱法、使用环己烷和乙酸乙酯 (100 / 0 至 96 / 4) 纯化,得到相应的硼酸酯 (225mg,70% 收率)。

[0221] 一般程序 A

[0222]

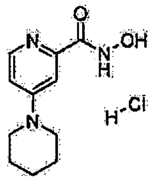


[0223] 在 0℃,向吡啶基 -2- 甲酸盐酸盐 (1.0mmol,1 当量) 在二氯甲烷 (8mL) 中的溶液加入一滴二甲基甲酰胺和草酰氯 (1.3mmol,1.3 当量)。将混合物在室温搅拌 30min,蒸发至干。然后将残余物溶解于二氯甲烷 (8mL) 中,冷却至 0℃。滴加三乙胺 (3.1mmol,3 当量) 和羟胺盐酸盐 (2.1mmol,2 当量),将混合物在室温搅拌 20h。然后蒸发溶剂,将粗残余物通过快速色谱法、使用二氯甲烷和甲醇 (100 / 0 至 80 / 20) 纯化,得到期望的化合物。

[0224] 实施例 1:

[0225] 3,4,5,6- 四氢 -2H-[1,4′] 联吡啶基 -2′ - 甲酸羟基酰胺盐酸盐

[0226]



[0227] 根据一般程序 A、使用 3,4,5,6- 四氢 -2H-[1,4′] 联吡啶基 -2′ - 甲酸盐酸盐和羟胺盐酸盐,获得期望的化合物。分离出期望的化合物,为白色粉末 (6% 收率)。

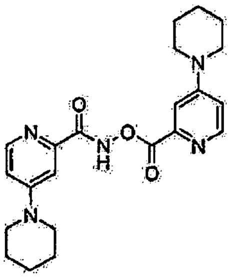
[0228] MS :222.1

[0229] Mp :200℃ -202℃

[0230] 实施例 2:

[0231] 3,4,5,6- 四氢 -2H-[1,4′] 联吡啶基 -2′ - 甲酸 (3,4,5,6- 四氢 -2H-[1,4′] 联吡啶基 -2′ - 羰基氨基)- 酰胺

[0232]



[0233] 该化合物作为实施例 1 的副产物分离，以白色粉末形式获得（4%收率）。

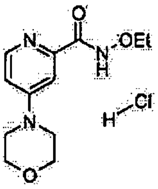
[0234] MS：410.2

[0235] Mp：210℃-215℃

[0236] 实施例 3：

[0237] 4-吗啉-4-基-吡啶-2-甲酸乙氧基-酰胺盐酸盐

[0238]



[0239] 根据一般程序 A、使用 4-吗啉-4-基-吡啶-2-甲酸盐酸盐和 O-乙基羟胺盐酸盐获得该化合物。分离出期望的化合物，为白色粉末（42%收率）。

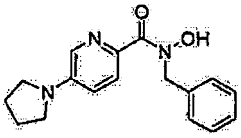
[0240] MS：252.1

[0241] Mp：200℃-202℃

[0242] 实施例 4：

[0243] 5-吡咯烷-1-基-吡啶-2-甲酸苄基-羟基-酰胺

[0244]



[0245] 根据一般程序 A、使用 5-吡咯烷-1-基-吡啶-2-甲酸和 N-苄基羟胺盐酸盐获得该化合物。分离出期望的化合物，为白色粉末（32%收率）。

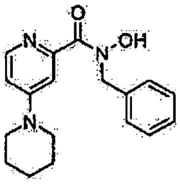
[0246] MS：298.1

[0247] Mp：115℃-120℃

[0248] 实施例 5：

[0249] 3,4,5,6-四氢-2H-[1,4′]联吡啶基-2′-甲酸苄基-羟基-酰胺

[0250]



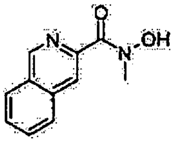
[0251] 根据一般程序 A、使用 3,4,5,6-四氢-2H-[1,4′]联吡啶基-2′-甲酸盐酸盐和 N-苄基羟胺盐酸盐获得该化合物。分离出期望的化合物，为黄色油状物（15%收率）。

[0252] MS：312.2

[0253] 实施例 6：

[0254] 异喹啉 -3- 甲酸羟基 - 甲基 - 酰胺

[0255]



[0256] 根据一般程序 A、使用异喹啉 -3- 甲酸和 N- 甲基羟胺盐酸盐获得该化合物。分离出期望的化合物，为白色粉末（43％收率）。

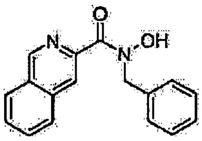
[0257] MS：203.0

[0258] Mp：110℃ -115℃

[0259] 实施例 7：

[0260] 异喹啉 -3- 甲酸苄基 - 羟基 - 酰胺

[0261]



[0262] 根据一般程序 A、使用异喹啉 -3- 甲酸和 N- 苄基羟胺盐酸盐获得该化合物。分离出期望的化合物，为白色粉末（19％收率）。

[0263] MS：279.1

[0264] Mp：120℃ -125℃

[0265] 一般程序 B

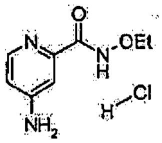
[0266]

[0267] 向羧酸（3.6mmol，1 当量）在二甲基甲酰胺（30mL）中的溶液加入 HOBT（7.2mmol，2 当量）、EDCI（7.2mmol，2 当量），然后加入羟胺盐酸盐（7.2mmol，2 当量）和三乙胺（10.8mmol，3 当量）。将混合物在室温搅拌 20h。然后将混合物倒入盐水溶液（20mL），用乙酸乙酯萃取（3 x 20mL）。有机层经硫酸镁干燥，过滤，真空蒸发。粗残余物通过快速色谱法、使用二氯甲烷和甲醇（100 / 0 至 85 / 15）纯化，得到期望的化合物。

[0268] 实施例 8：

[0269] 4- 氨基 - 吡啶 -2- 甲酸乙氧基 - 酰胺盐酸盐

[0270]



[0271] 根据一般程序 B、使用 4- 氨基 - 吡啶 -2- 甲酸和 O- 乙基羟胺盐酸盐获得该化合物。分离出期望的化合物，为无色油状物（3％收率）。

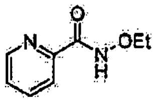
[0272] MS：182.0

[0273] Mp：114℃ -120℃

[0274] 实施例 9：

[0275] 吡啶 12- 甲酸乙氧基 - 酰胺

[0276]



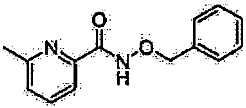
[0277] 根据一般程序 B、使用吡啶 -2- 甲酸和 O- 乙基羟胺盐酸盐获得该化合物。分离出期望的化合物，为无色油状物（63％收率）。

[0278] MS：167.1

[0279] 实施例 10：

[0280] 6- 甲基 - 吡啶 -2- 甲酸苄基氧基 - 酰胺

[0281]



[0282] 根据一般程序 B、使用 6- 甲基 - 吡啶 -2- 甲酸和 O- 苄基羟胺盐酸盐获得该化合物。分离出期望的化合物，为白色粉末（71％收率）。

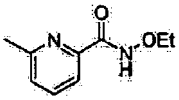
[0283] MS：243.1

[0284] Mp：75℃ -80℃

[0285] 实施例 11：

[0286] 6- 甲基 - 吡啶 -2- 甲酸乙氧基 - 酰胺

[0287]



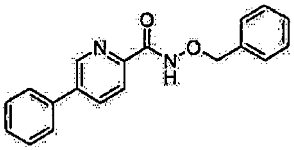
[0288] 根据一般程序 B、使用 6- 甲基 - 吡啶 -2- 甲酸和 O- 乙基羟胺盐酸盐获得该化合物。分离出期望的化合物，为无色油状物（83％收率）。

[0289] MS：181.0

[0290] 实施例 12：

[0291] 5- 苯基 - 吡啶 -2- 甲酸苄基氧基 - 酰胺

[0292]



[0293] 根据一般程序 B、使用 5- 苯基 - 吡啶 -2- 甲酸和 O- 苄基羟胺盐酸盐获得该化合物。分离出期望的化合物，为白色粉末（79％收率）。

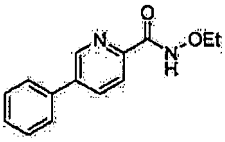
[0294] MS：305.1

[0295] Mp：155℃ -160℃

[0296] 实施例 13：

[0297] 5-苯基-吡啶-2-甲酸乙氧基-酰胺

[0298]



[0299] 根据一般程序B、使用5-苯基-吡啶-2-甲酸和O-乙基羟胺盐酸盐获得该化合物。分离出期望的化合物，为白色粉末（64%收率）。

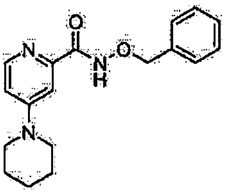
[0300] MS：243.1

[0301] Mp：100℃-105℃

[0302] 实施例14：

[0303] 3,4,5,6-四氢-2H-[1,4′]联吡啶基-2′-甲酸苄基氧基-酰胺

[0304]



[0305] 根据一般程序B、使用3,4,5,6-四氢-2H-[1,4′]联吡啶基-2′-甲酸盐酸盐和O-苄基羟胺盐酸盐获得该化合物。分离出期望的化合物，为白色粉末（26%收率）。

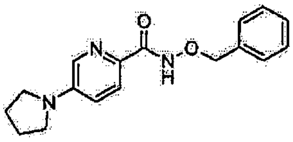
[0306] MS：312.2

[0307] Mp：135℃-140℃

[0308] 实施例15：

[0309] 5-吡咯烷-1-基-吡啶-2-甲酸苄基氧基-酰胺

[0310]



[0311] 根据一般程序B、使用5-吡咯烷-1-基-吡定-2-甲酸和O-苄基羟胺盐酸盐获得该化合物。分离出期望的化合物，为白色粉末（54%收率）。

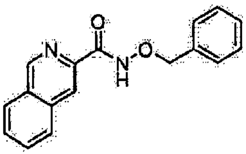
[0312] MS：298.1

[0313] Mp：165℃-170℃

[0314] 实施例16：

[0315] 异喹啉-3-甲酸苄基氧基-酰胺

[0316]



[0317] 根据一般程序B、使用异喹啉-3-甲酸和O-苄基羟胺盐酸盐获得该化合物。分离出期望的化合物，为白色粉末（77%收率）。

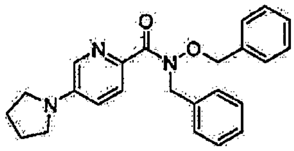
[0318] MS：279.1

[0319] Mp：85℃ -90℃

[0320] 实施例 17：

[0321] 5- 吡咯烷 -1- 基 - 吡啶 -2- 甲酸苄基 - 苄基氧基 - 酰胺

[0322]



[0323] 根据一般程序 B、使用 5- 吡咯烷 -1- 基 - 吡啶 -2- 甲酸和 O，N- 二苄基羟胺盐酸盐（关键中间体 I）获得该化合物。分离出期望的化合物，为白色粉末（12％收率）。

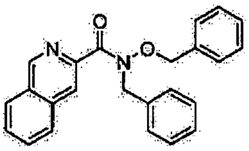
[0324] MS：388.2

[0325] Mp：95℃ -100℃

[0326] 实施例 18：

[0327] 异喹啉 -3- 甲酸苄基 - 苄基氧基 - 酰胺

[0328]



[0329] 根据一般程序 B、使用异喹啉 -3- 甲酸和 O，N- 二苄基羟胺盐酸盐（关键中间体 I）获得该化合物。分离出期望的化合物，为白色粉末（36％收率）。

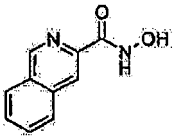
[0330] MS：369.2

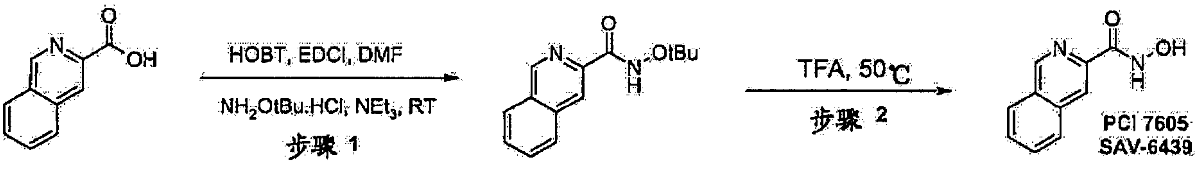
[0331] Mp：70℃ -75℃

[0332] 实施例 19：

[0333] 异喹啉 -3- 甲酸羟基酰胺

[0334]





[0335] 步骤 1：

[0336] 根据一般程序 B、使用异喹啉 -3- 甲酸和 O- 叔丁基羟胺盐酸盐获得异喹啉 -3- 甲酸叔丁氧基 - 酰胺。分离出期望的化合物，为浅黄色粉末（46％收率）。

[0337] 步骤 2：

[0338] 将异喹啉 -3- 甲酸叔丁氧基 - 酰胺（195mg，1 当量）和三氟乙酸（4mL）在 50℃加热 20h。然后将混合物蒸发至干。将残余物稀释于乙酸乙酯（10mL）中，加入三乙胺（3mL）。将混合物吸附在硅胶上，通过快速色谱法、使用环己烷和乙酸乙酯（100 / 0 至 0 / 100）纯

化，得到期望的化合物，为浅粉红色粉末（70mg，65％收率）。

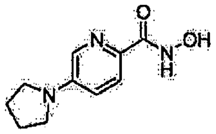
[0339] MS：189.0

[0340] Mp：160℃-165℃

[0341] 实施例 20：

[0342] 5-吡咯烷-1-基-吡定-2-甲酸羟基酰胺

[0343]



[0344] 根据实施例 19 的程序、使用 5-吡咯烷-1-基-吡啶-2-甲酸获得该化合物。分离出期望的化合物，为白色粉末。

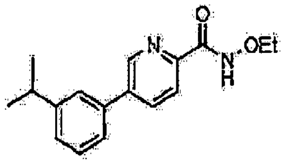
[0345] MS：208.0

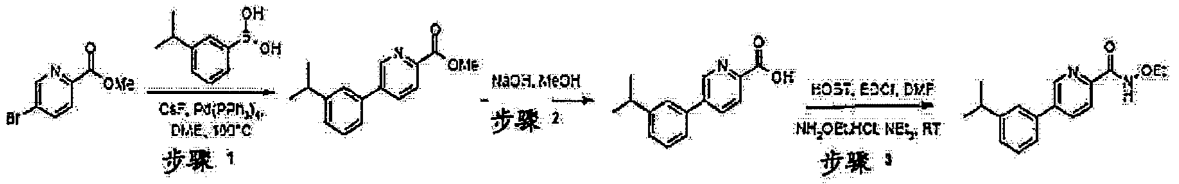
[0346] Mp：220℃-225℃

[0347] 实施例 21：

[0348] 5-(3-异丙基-苯基)-吡啶-2-甲酸乙氧基-酰胺

[0349]





[0350] 步骤 1：

[0351] 向 5-溴-吡定-2-甲酸甲酯（500mg，2.3mmol，1 当量）在二甲氧基乙烷（6mL）中的溶液加入 3-异丙基苯基硼酸（495mg，3mmol，1.3 当量）和氟化铯（1.05g，6.9mmol，3 当量）。将混合物脱气 15min，加入四（三苯基膦）钯（133mg，0.12mmol，0.05 当量）。将混合物在微波辐射下于 100℃加热 15 分钟。冷却后，将混合物倒入水（10mL）中，用乙酸乙酯萃取（3 x 20mL）。将有机层经硫酸镁干燥，过滤，蒸发至干。将粗残余物通过快速色谱法、使用环己烷和乙酸乙酯（100 / 0 至 0 / 100）纯化，得到 5-(3-异丙基-苯基)-吡啶-2-甲酸甲酯，为无色油状物（380mg，64％收率）。

[0352] 步骤 2：

[0353] 将稀释于甲醇（6mL）中的 5-(3-异丙基-苯基)-吡啶-2-甲酸甲酯（380mg，1.5mmol，1 当量）和 5 N 氢氧化钠溶液（0.5mL）于密封管中在 80℃加热 20h。冷却后，蒸发混合物，将残余物稀释于水（6mL）中，用乙酸乙酯萃取（3 x10mL）。然后将 F 层用 1 N 盐酸溶液酸化，用乙酸乙酯萃取（3 x 20mL）。有机层经硫酸镁干燥，过滤，蒸发至干，得到 5-(3-异丙基-苯基)-吡啶-2-甲酸，为无色油状物（230mg，64％收率）。

[0354] 步骤 3：

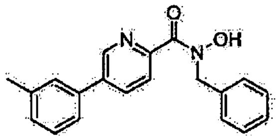
[0355] 根据一般程序B、使用5-(3-异丙基-苯基)-吡啶-2-甲酸和O-乙基羟胺盐酸盐获得该化合物。分离出期望的化合物，为无色油状物（60％收率）。

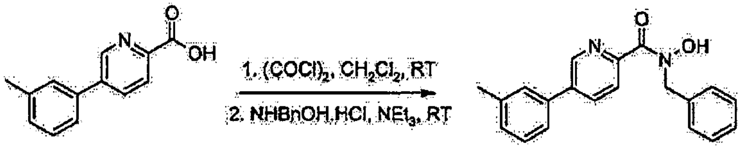
[0356] MS：285.2

[0357] 实施例22：

[0358] 5-间甲苯基-吡啶-2-甲酸苄基-羟基-酰胺

[0359]





[0360] 根据一般程序A、使用5-间甲苯基-吡啶-2-甲酸（根据实施例21步骤1和2的程序获得）和N-苄基羟胺盐酸盐获得该化合物。分离出期望的化合物，为白色粉末（11％收率）。

[0361] MS：319.1

[0362] Mp：139℃-140℃

[0363] 一般程序C

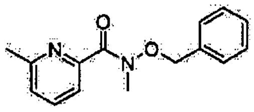
[0364]

[0365] 向羧酸氧基-酰胺（0.4mmol，1当量）在四氢呋喃（5mL）中的溶液加入氢化钠（0.5mmol，1.3当量）。将混合物在室温搅拌15min，加入甲基碘（0.6mmol，1.5当量）。将混合物在密封管中在50℃加热20h。冷却后，将混合物倒入水（10mL）中，用乙酸乙酯萃取（3 x 20mL）。有机层经硫酸镁干燥，过滤，真空蒸发。将粗残余物通过快速色谱法、使用二氯甲烷和甲醇（100/0）至（90/10）纯化，得到期望的化合物。

[0366] 实施例23：

[0367] 6-甲基-吡啶-2-甲酸苄基氧基-甲基-酰胺

[0368]

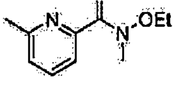


[0369] 根据一般程序C、使用6-甲基-吡啶-2-甲酸苄基氧基-酰胺（于实施例10中所述）获得该化合物。分离出期望的化合物，为无色油状物（55％收率）。MS：257.1

[0370] 实施例24：

[0371] 6-甲基-吡啶-2-甲酸乙氧基-甲基-酰胺

[0372]



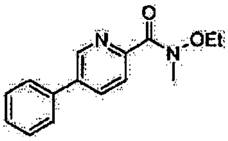
[0373] 根据一般程序 C、由 6- 甲基 - 吡啶 -2- 甲酸乙氧基 - 酰胺（于实施例 11 中所述）开始，获得该化合物。分离出期望的化合物，为无色油状物 (51％收率)。

[0374] MS：195.0

[0375] <u>实施例 25：</u>

[0376] 5- 苯基 - 吡啶 -2- 甲酸乙氧基 - 甲基 - 酰胺

[0377]



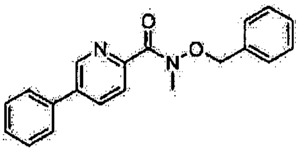
[0378] 根据一般程序 C、由 5- 苯基 - 吡啶 -2- 甲酸乙氧基 - 酰胺（于实施例 13 中所述）开始，获得该化合物。分离出期望的化合物，为白色粉末 (41％收率)。MS：257.1

[0379] Mp：70℃ -75℃

[0380] <u>实施例 26：</u>

[0381] 5- 苯基 - 吡啶 -2- 甲酸苄基氧基 - 甲基 - 酰胺

[0382]



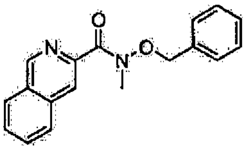
[0383] 根据一般程序 C、由 5- 苯基 - 吡啶 -2- 甲酸苄基氧基 - 酰胺（于实施例 12 中所述）开始，获得该化合物。分离出期望的化合物，为黄色油状物 (30％收率)。

[0384] MS：319.1

[0385] <u>实施例 27：</u>

[0386] 异喹啉 -3- 甲酸苄基氧基 - 甲基 - 酰胺

[0387]



[0388] 根据一般程序 C、由异喹啉 -3- 甲酸苄基氧基 - 酰胺（于实施例 16 中所述）开始，获得该化合物。分离出期望的化合物，为米色粉末 (45％收率)。

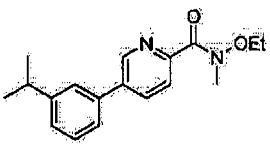
[0389] MS：293.1

[0390] Mp：70℃ -75℃

[0391] <u>实施例 28：</u>

[0392] 5-(3- 异丙基 - 苯基)- 吡啶 -2- 甲酸乙氧基 - 甲基 - 酰胺

[0393]



[0394] 根据一般程序 C、由 5-(3- 异丙基 - 苯基)- 吡啶 -2- 甲酸乙氧基 - 甲基 - 酰胺

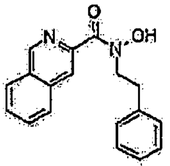
（于实施例 21 中所述）开始，制备该化合物。分离出期望的化合物，为无色油状物（50％收率）。

[0395] MS：299.2

[0396] 实施例 29：

[0397] 异喹啉-3-甲酸羟基-苯乙基-酰胺

[0398]



[0399] 步骤 1：

[0400] 根据一般程序 B、使用异喹啉-3-甲酸和叔丁氧基-羟基酰胺盐酸盐制备异喹啉-3-甲酸叔丁氧基-酰胺。分离出期望的化合物，为白色粉末（86％收率）。

[0401] 步骤 2：

[0402] 向异喹啉-3-甲酸叔丁氧基-酰胺（200mg，0.8mmol，1 当量）在二甲基甲酰胺（7mL）中的溶液加入碳酸钾（454mg，3.3mmol，4 当量）和（2-溴乙基）苯（220 μL，1.6mmol，2 当量）。将混合物在 50℃搅拌 20h。冷却后，将混合物倒入水（10mL）中，用乙酸乙酯萃取（3 x 20mL）。有机层经硫酸镁干燥，过滤，真空蒸发。将粗残余物通过快速色谱法、使用环己烷和乙酸乙酯（100 / 0 至 80 / 20）纯化，得到异喹啉-3-甲酸叔丁氧基-苯乙基-酰胺，为无色油状物（220mg，77％收率）。

[0403] 步骤 3：

[0404] 在 0℃向异喹啉-3-甲酸叔丁氧基-苯乙基-酰胺（220mg，0.63mmol，1 当量）在二氯甲烷（10mL）中的溶液滴加 1M 四氯化钛在二氯甲烷中的溶液（1.7mL，1.7mmol，3 当量）。将混合物在室温搅拌 20h。然后将其加入至异丙醇（15mL），将所得混合物在室温搅拌 1h，蒸发至干。将残余物用乙酸乙酯（15mL）稀释，用碳酸氢钠饱和溶液洗涤（3 x 20mL）。将有机层经硅藻土过滤，将滤液蒸发至干。将残余物在乙醚中磨碎，过滤，得到期望的化合物，为白色固体（75mg，11％收率）。

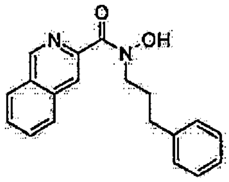
[0405] MS：293.2

[0406] Mp：90℃-95℃

[0407] 实施例 30：

[0408] 异喹啉-3-甲酸羟基-(3-苯基-丙基)-酰胺

[0409]



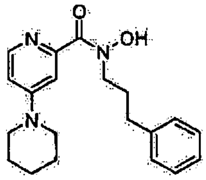
[0410] 根据实施例 29 的程序、由异喹啉 -3- 甲酸开始，制备该化合物。分离出期望的化合物，为无色油状物。

[0411] MS：307.2

[0412] 实施例 31：

[0413] 3,4,5,6- 四氢 -2H-[1,4′]联吡啶基 -2′ - 甲酸羟基 -(3- 苯基 - 丙基)- 酰胺

[0414]



[0415] 根据实施例 29 的程序、由 3,4,5,6- 四氢 -2H-[1,4′]联吡啶基 -2′ - 甲酸盐酸盐开始和使用步骤 1 的一般程序 A 代替一般程序 B，制备该化合物。分离出期望的化合物，为白色粉末。

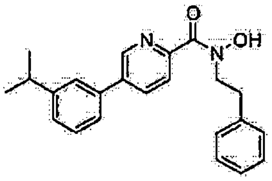
[0416] MS：340.2

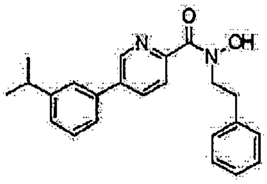
[0417] Mp：125℃ -130℃

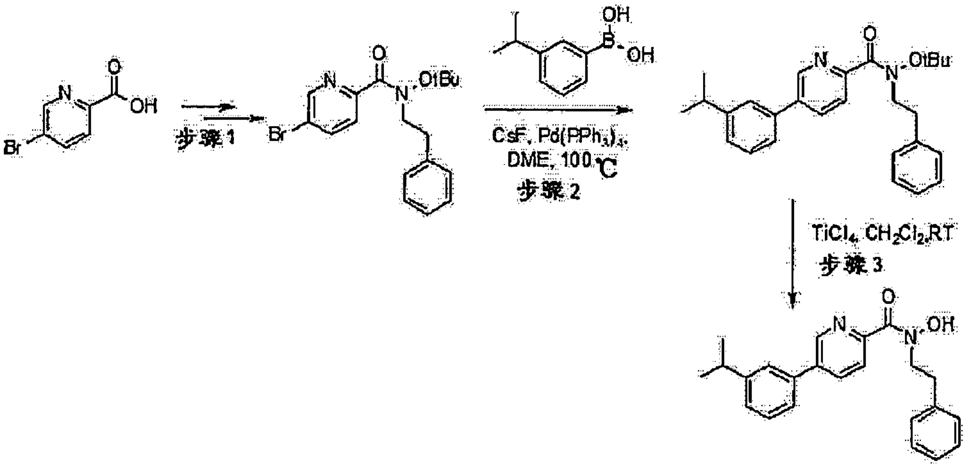
[0418] 实施例 32：

[0419] 5-(3- 异丙基 - 苯基)- 吡啶 -2- 甲酸羟基 - 苯乙基 - 酰胺

[0420]







[0421] 步骤 1：

[0422] 根据实施例 29 步骤 1 和 2、由 5- 溴 - 吡啶 -2- 甲酸开始，制备 5- 溴 - 吡啶 -2- 甲酸叔丁氧基 - 苯乙基 - 酰胺。获得所需化合物，为元色油状物 (65％总收率收率)。

[0423] 步骤 2：

[0424] 根据实施例 21 步骤 1、由 5- 溴 - 吡啶 -2- 甲酸叔丁氧基 - 苯乙基 - 酰胺和 3- 异丙基苯基硼酸开始，制备 5-(3- 异丙基 - 苯基)- 吡啶 -2- 甲酸叔丁氧基 - 苯乙基 - 酰胺。分离出期望的化合物，为黄色油状物 (86％收率)。

[0425] 步骤 3：

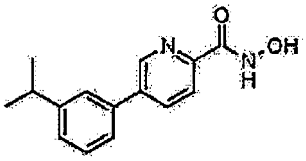
[0426] 根据实施例 29 步骤 3、由 5-(3- 异丙基 - 苯基)- 吡啶 -2- 甲酸叔丁氧基 - 苯乙基 - 酰胺开始，制备期望的化合物。将其分离，为黄色粉末 (15％收率)。MS：361.2

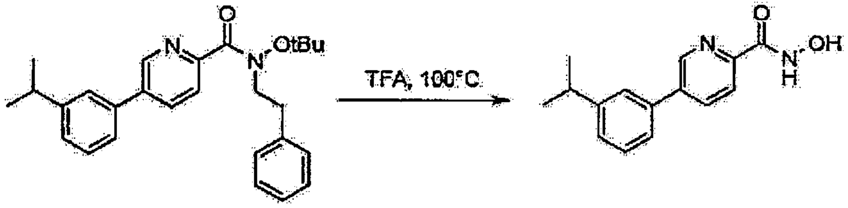
[0427] Mp：110℃ -115℃

[0428] 实施例 33：

[0429] 5-(3- 异丙基 - 苯基)- 吡啶 -2- 甲酸羟基酰胺

[0430]





[0431] 将根据步骤实施例 32 步骤 1 和 2 制备的 5-(3- 异丙基 - 苯基)- 吡啶 -2- 甲酸叔丁氧基 - 苯乙基 - 酰胺 (220mg，0.53mmol，1 当量) 溶解于三氟乙酸 (5mL) 中，在微波辐射下于 100℃加热 10min。然后将混合物蒸发至干，将残余物通过快速色谱法、使用环己烷和乙酸乙酯 (100 / 0 至 80/20) 纯化，得到期望的化合物，为黄色粉末 (19mg，10％收率)。

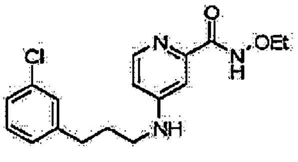
[0432] MS：257.1

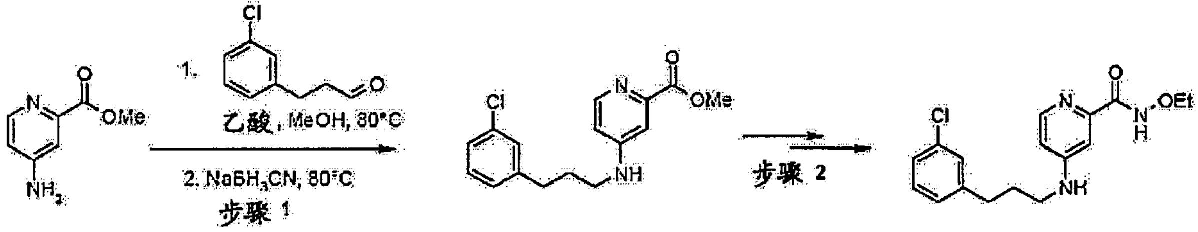
[0433] Mp：130℃ -135℃

[0434] 实施例 34：

[0435] 4-[3-(3- 氯 - 苯基)- 丙基氨基]- 吡啶 -2- 甲酸乙氧基 - 酰胺

[0436]





[0437] 步骤 1：

[0438] 在密闭管中，在分子筛存在下将 4- 氨基 - 吡啶 -2- 甲酸甲酯 (200mg，1.3mmol，1

当量）和3-(3-氯-苯基)-丙醛（0.4mL,2.6mmol,2当量）溶解于乙酸（190μL,3.3mmol,2.5当量）和无水甲醇（7mL）中。将混合物在80℃加热20h。冷却后，加入氰基硼氢化钠（123mg,1.9mmol,1.5当量），将混合物在80℃加热4h。冷却后，将混合物倒入碳酸氢钠饱和溶液（10mL），用乙酸乙酯萃取（3 x 20mL）。有机层经硫酸镁干燥，过滤，真空蒸发。将粗残余物通过快速色谱法、使用二氯甲烷和甲醇（100 / 0至90 / 10）纯化，得到期望的化合物，为无色油状物（144mg,36%收率）。

[0439] 步骤2：

[0440] 根据实施例21步骤2和3、由4-[3-(3-氯-苯基)-丙基氨基]-吡啶-2-甲酸甲酯开始，制备期望的化合物。分离出期望的化合物，为白色粉末。

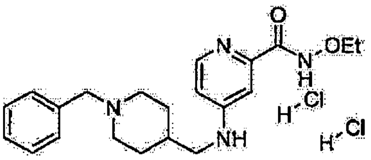
[0441] MS：334.2

[0442] Mp：100℃-105℃

[0443] 实施例35：

[0444] 4-[(1-苄基-哌啶-4-基甲基)-氨基]-吡啶-2-甲酸乙氧基-酰胺盐酸盐

[0445]



[0446] 根据实施例34的程序、由4-氨基-吡啶-2-甲酸甲酯和1-苄基-哌啶-4-甲醛开始，制备该化合物。分离出期望的化合物，为白色粉末。

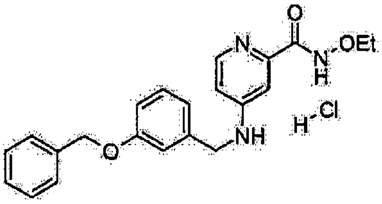
[0447] MS：369.3

[0448] Mp：125℃-130℃

[0449] 实施例36：

[0450] 4-(3-苄基氧基-苄基氨基)-吡啶-2-甲酸乙氧基-酰胺盐酸盐

[0451]



[0452] 根据实施例34的程序、由4-氨基-吡啶-2-甲酸甲酯和3-苄基氧基-苯甲醛开始，制备该化合物。分离出期望的化合物，为粉红色粉末。

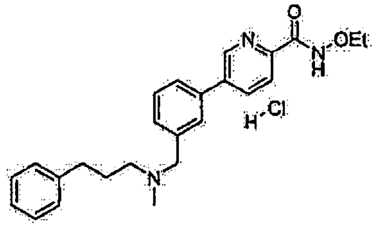
[0453] MS：378.2

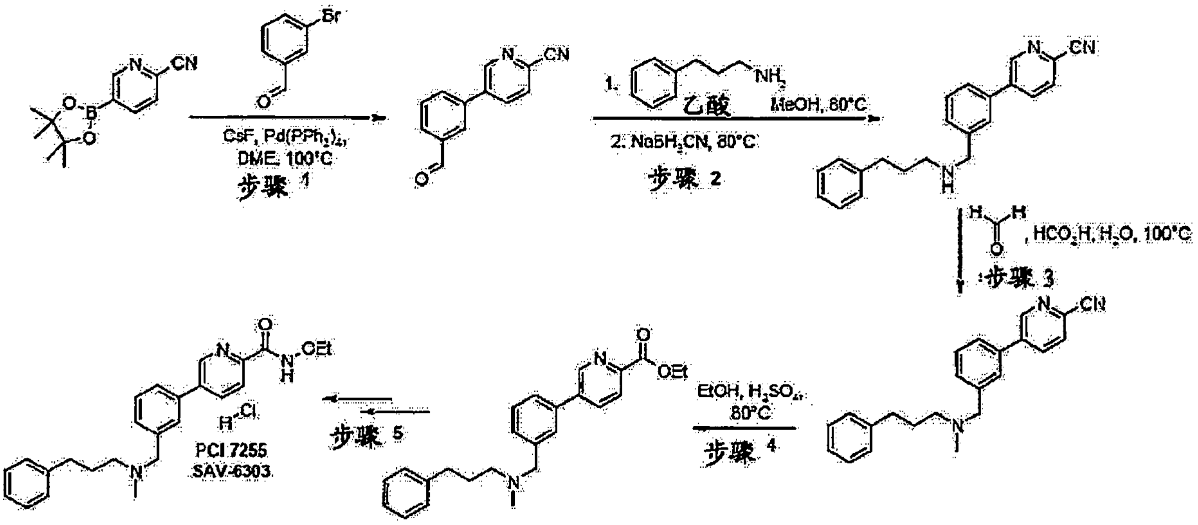
[0454] Mp：70℃-75℃

[0455] 实施例37：

[0456] 5-(3-{[甲基-(3-苯基-丙基)-氨基]-甲基}-苯基)-吡啶-2-甲酸乙氧基-酰胺盐酸盐

[0457]





[0458]　步骤 1：

[0459]　根据实施例 21 步骤 1、由 3- 溴 - 苯甲醛和 5-(4,4,5,5- 四甲基 -[1,3,2] 二氧硼杂环戊烷 -2- 基)- 吡啶 -2- 甲腈开始，制备 5-(3- 甲酰基 - 苯基)- 吡啶 -2- 甲腈。分离出期望的化合物，为白色粉末 (88％收率)。

[0460]　步骤 2：

[0461]　根据实施例 34 步骤 1、由 5-(3- 甲酰基 - 苯基)- 吡啶 -2- 甲腈和 3- 苯基 - 丙胺开始，制备 5-{3-[(3- 苯基 - 丙基氨基)- 甲基]- 苯基 }- 吡啶 -2- 甲腈。分离出期望的化合物，为无色油状物 (定量收率)。

[0462]　步骤 3：

[0463]　将 5-{3-[(3- 苯基 - 丙基氨基)- 甲基]- 苯基 }- 吡啶 -2- 甲腈 (384mg，1.1mmol，1 当量)、37％在水中的甲醛 (210μL)、甲酸 (97μL，2.6mmol，2.4 当量) 溶解于水 (5mL)，在 100℃加热 20h。冷却后，将混合物用 5 N 氢氧化钠溶液碱化，倒入水 (10mL) 中，用乙酸乙酯萃取 (3 x 20mL)。有机层经硫酸镁干燥，过滤，真空蒸发。将粗残余物通过快速色谱法、使用环己烷和乙酸乙酯 (100 / 0 至 80 / 20) 纯化，得到 5-(3-{[甲基 -(3- 苯基 - 丙基)- 氨基]- 甲基 }- 苯基)- 吡啶 -2- 甲腈，为无色油状物 (定量收率)。

[0464]　步骤 4：

[0465]　在密闭管中，将 5-(3-{[甲基 -(3- 苯基 - 丙基)- 氨基]- 甲基 }- 苯基)- 吡啶 -2- 甲腈 (365mg，1.1mmol，1 当量)、硫酸 (5mL) 和乙醇 (5mL) 在 80℃加热 48h。冷却后，将混合物蒸发至干。将残余物溶于乙酸乙酯 (10mL) 中，用碳酸氢钠饱和溶液洗涤 (3 x 10mL)。有机层经硫酸镁干燥，过滤，真空蒸发，得到 5-(3-{[甲基 -(3- 苯基 - 丙基)- 氨基]- 甲基 }- 苯基)- 吡啶 -2- 甲酸乙酯，为黄色油状物 (224mg，定量收率)。

[0466]　步骤 5：

[0467] 根据实施例 21 步骤 2 和 3、由 5-(3-{[甲基 -(3- 苯基 - 丙基)- 氨基]- 甲基 }- 苯基)- 吡啶 -2- 甲酸乙酯开始，制备该化合物。分离出期望的化合物，为白色粉末。

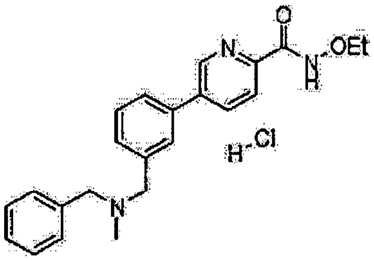
[0468] MS：404.3

[0469] Mp：50℃ -55℃

[0470] 实施例 38：

[0471] 5-{3-[(苄基 - 甲基 - 氨基)- 甲基]- 苯基 }- 吡啶 -2- 甲酸乙氧基 - 酰胺盐酸盐

[0472]



[0473] 根据实施例 37 的程序、由溴 - 苯甲醛和 5-(4,4,5,5- 四甲基 -[1,3,2] 二氧硼杂环戊烷 -2- 基)- 吡啶 -2- 甲腈开始和在步骤 2 中使用苄基胺代替 3- 苯基 - 丙胺，制备该化合物。分离出期望的化合物，为白色粉末。

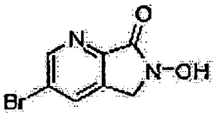
[0474] MS：376.2

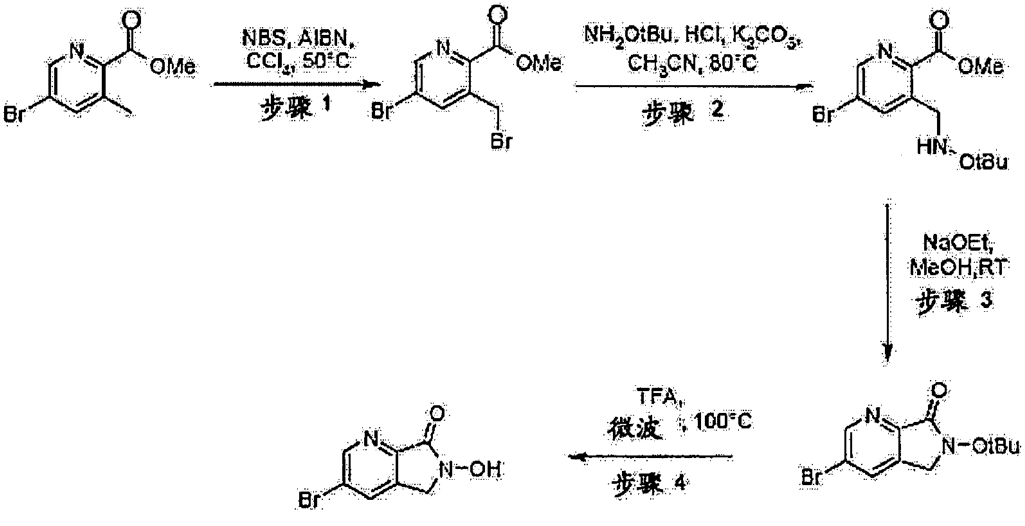
[0475] Mp：85℃ -90℃

[0476] 实施例 39：

[0477] 3- 溴 -6- 羟基 -5,6- 二氢 - 吡咯并 [3,4-b] 吡啶 -7- 酮

[0478]





[0479] 步骤 1：

[0480] 向 5- 溴 -3- 甲基 - 吡啶 -2- 甲酸甲酯 (200mg，0.87mmol，1 当量) 在四氯甲烷 (10mL) 中的溶液加入 N- 溴琥珀酰亚胺 (162mg，0-91mmol，1.05 当量) 和 2,2′ - 偶氮双 (2- 甲基丙腈)(3mg，0.017mmol，0.02 当量)。将混合物在 50℃搅拌 5h。然后蒸发溶剂，

将粗残余物通过快速色谱法、使用环己烷和乙酸乙酯 (100 / 0 至 80 / 20) 纯化。分离 5- 溴 -3- 溴甲基 - 吡啶 -2- 甲酸甲酯，为白色粉末，呈与起始材料的 6 / 4 混合物 (160mg, 39％收率)。混合物用于下一步骤。

[0481] 步骤 2 :

[0482] 将 5- 溴 -3- 溴甲基 - 吡啶 -2- 甲酸甲酯 (160mg,0.5mmol,1 当量)、碳酸钾 (716mg, 5.2mmol,1 当量) 和 O- 叔丁基 - 羟胺盐酸盐 (325mg,2.6mmol,5 当量) 在乙腈 (8mL) 中的悬液在 80℃加热 20h。冷却后，过滤混合物，用乙酸乙酯 (10mL) 洗涤。蒸发滤液，将粗残余物通过快速色谱法、使用环己烷和乙酸乙酯 (100 / 0 至 70 / 30) 纯化，得到 5- 溴 -3-(叔丁氧基氨基 - 甲基)- 吡啶 -2- 甲酸甲酯，为白色粉末 (70mg,43％收率)。

[0483] 步骤 3 :

[0484] 向 5- 溴 -3-(叔丁氧基氨基 - 甲基)- 吡啶 -2- 甲酸甲酯 (70mg,0.22mmol,1 当量) 在甲醇 (2mL) 中的溶液加入新鲜制备的乙醇钠 (30mg,0.44mmol,2 当量)。将混合物在室温搅拌 20h。加入数滴乙酸和水 (5mL)。过滤沉淀，用水 (5mL) 洗涤，溶于甲醇 (10mL) 中，蒸发至干，得到 3- 溴 -6- 叔丁氧基 -5,6- 二氢 - 吡咯并 [3,4-b] 吡定 -7- 酮，为白色粉末 (45mg,72％收率)。

[0485] 步骤 4 :

[0486] 将 3- 溴 -6- 叔丁氧基 -5,6- 二氢 - 吡咯并 [3,4-b] 吡啶 -7- 酮 (45mg,0.16mmol, 1 当量) 溶解于三氟乙酸 (2mL) 中，在微波辐射下于 100℃加热 5min。然后将混合物蒸发至干，将残余物用水 (5mL) 磨碎。过滤沉淀，真空干燥，得到期望的化合物，为米色粉末 (22mg, 60％收率)。

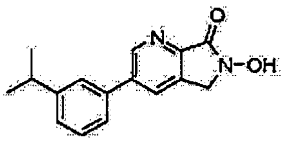
[0487] MS :228.9

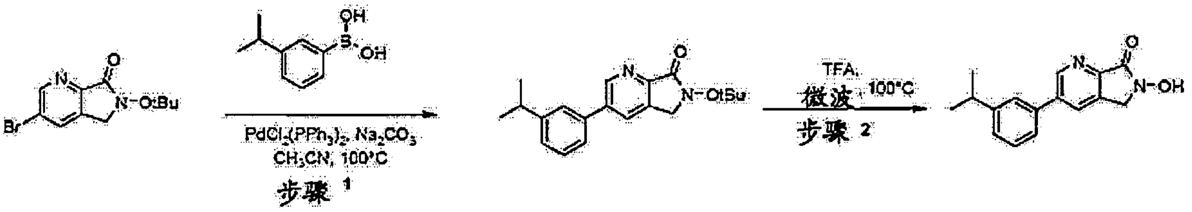
[0488] Mp :在 230℃ -235℃分解

[0489] 实施例 40 :

[0490] 6- 羟基 -3-(3- 异丙基 - 苯基)-5,6- 二氢 - 吡咯并 [3,4-b] 吡啶 -7- 酮

[0491]





[0492] 步骤 1 :

[0493] 向描述于实施例 39 步骤 1 至 3 中的 3- 溴 -6- 叔丁氧基 -5,6- 二氢 - 吡咯并 [3, 4-b] 吡啶 -7- 酮 (200mg,0.7mmol,1 当量) 在乙腈 (3mL) 中的溶液加入 3- 异丙基苯基硼酸 (150mg,0.9mmol,1.3 当量) 和 2M 碳酸钠溶液 (3mL)。将混合物脱气 15min，加入反式 - 二氯双 (三苯基膦) 钯 (25mg,0.035mmol,0.05 当量)。将混合物在微波辐射下于 100℃加热 10min。冷却后，将混合物倒入水 (10mL) 中，用乙酸乙酯萃取 (3 x 20mL)。将有机层经硫酸

镁干燥，过滤，蒸发至干。将粗残余物通过快速色谱法、使用环己烷和乙酸乙酯（100 / 0 至 50 / 50）纯化，得到 6- 叔丁氧基 -3-(3- 异丙基 - 苯基)-5,6- 二氢 - 吡咯并 [3,4-b] 吡啶 -7- 酮，为白色粉末（150mg,66％收率）。

[0494] 步骤 2：

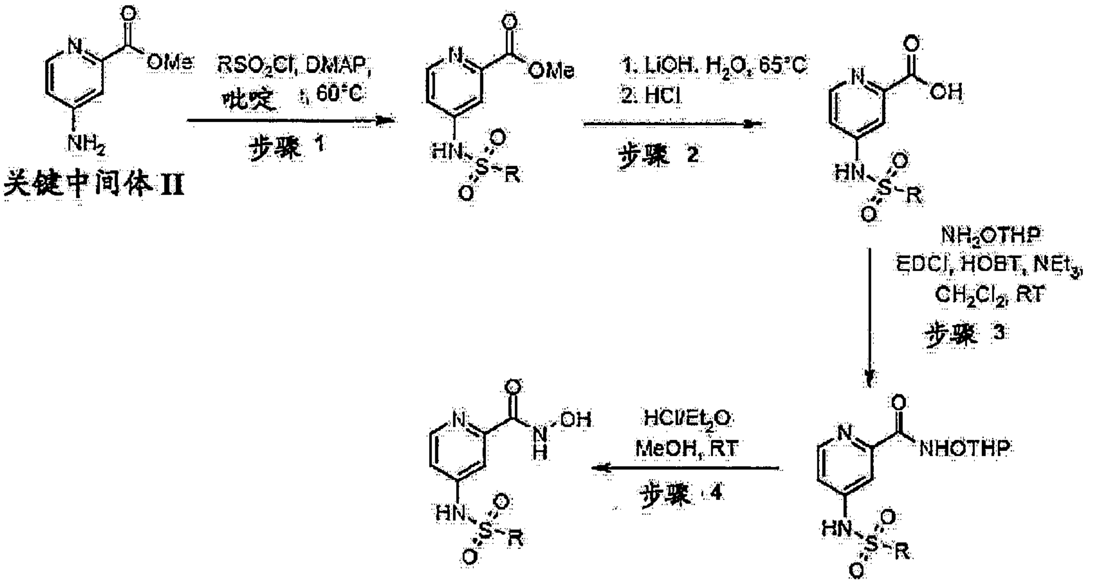
[0495] 根据实施例 39 步骤 4 制备化合物。研磨后，将粉末通过快速色谱法、使用二氯甲烷和甲醇（100 / 0 至 80 / 20）纯化，得到期望的化合物，为黄色粉末（16％收率）。

[0496] MS :269.1

[0497] Mp :在 155℃ -160℃分解

[0498] 一般程序 D

[0499]



[0500] 步骤 1：

[0501] 将 4- 氨基 - 吡啶 -2- 甲酸甲酯（关键中间体 II）(600mg,3.9mmol,1 当量）溶解于吡啶（20mL）中。加入二甲氨基吡啶（482mg,3.9mmol,1 当量）和磺酰氯（1.3 当量），将混合物在 60℃搅拌 15h。冷却后，蒸发溶剂。加入水（10mL），将水层用乙酸乙酯萃取（3 x 20mL）。有机层经硫酸镁干燥，过滤，真空蒸发。粗残余物通过快速色谱法纯化，得到期望的化合物。

[0502] 步骤 2：

[0503] 将磺酰基氨基 - 吡啶 -2- 甲酸甲酯（1.0g,1 当量）溶解于甲醇 / 水（17mL / 1.7mL）的混合物中，加入氢氧化锂（2 当量）。将混合物在 65℃加热 18h。冷却后，加入 2M 氯化氢在乙醚中的溶液，直至 pH=1。然后将混合物蒸发至干，得到具有定量收率的相应的酸。

[0504] 步骤 3：

[0505] 向磺酰基氨基 - 吡啶 -2- 甲酸（800mg,1 当量）在二氯甲烷（13mL）中的溶液加入 HOBT(2 当量）、EDCI(2 当量）、三乙胺（3 当量）和 O-(四氢 - 吡喃 -2- 基）- 羟胺（2 当量）。将混合物在室温搅拌 18h。将反应用水（10mL）淬灭，将混合物用二氯甲烷萃取（3 X 15mL）。有机层经硫酸镁干燥，过滤，真空蒸发。将粗残余物通过快速色谱法纯化，得到磺酰

基氨基 - 吡啶 -2- 甲酸（四氢 - 吡喃 -2- 基氧基）- 酰胺。

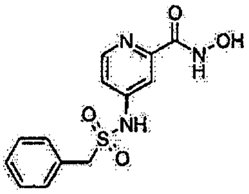
[0506] 步骤 4：

[0507] 向磺酰基氨基 - 吡啶 -2- 甲酸（四氢 - 吡喃 -2- 基氧基）- 酰胺 (1 当量）在甲醇 (10mL) 中的溶液加入 2M 氯化氢在乙醚中的溶液 (2 当量）。将混合物在室温搅拌 1h。过滤沉淀，用乙醚漂洗，真空干燥，得到磺酰基氨基 - 吡啶 -2- 甲酸羟基酰胺盐酸盐。

[0508] 实施例 41：

[0509] 4- 苯基甲烷磺酰基氨基 - 吡啶 -2- 甲酸羟基酰胺

[0510]



[0511] 根据一般程序 D、使用苯基甲烷磺酰氯获得该化合物。分离出期望的化合物，为米色粉末。

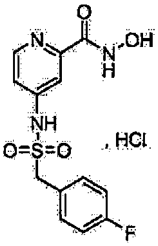
[0512] MS：308.1

[0513] Mp：187℃ -192℃

[0514] 实施例 42：

[0515] 4-(4- 氟 - 苯基甲烷磺酰基氨基）- 吡定 -2- 甲酸苄基 - 羟基 - 酰胺

[0516]



[0517] 根据一般程序 D、使用 (4- 氟 - 苯基）- 甲烷磺酰氯获得该化合物。分离出期望的化合物，为白色粉末。

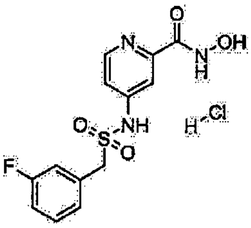
[0518] MS：326.1

[0519] Mp：183℃ -188℃

[0520] 实施例 43：

[0521] 4-(3- 氟 - 苯基甲烷磺酰基氨基）- 吡啶 -2- 甲酸羟基酰胺盐酸盐

[0522]



[0523] 根据一般程序 D、使用 (3- 氟 - 苯基）- 甲烷磺酰氯获得该化合物。分离出期望的化合物，为白色粉末。

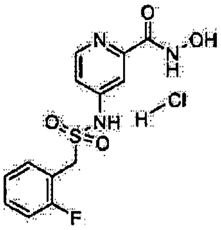
[0524] MS：326.1

[0525] Mp：195℃ -200℃

[0526] 实施例 44：

[0527] 4-(2- 氟苯基甲烷磺酰基氨基)- 吡啶 -2- 甲酸羟基酰胺盐酸盐

[0528]



[0529] 根据一般程序 D、使用 2- 氟苯基 - 甲烷磺酰氯获得该化合物。分离出期望的化合物，为白色粉末。

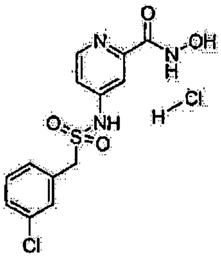
[0530] MS：326.1

[0531] Mp：209℃ -216℃

[0532] 实施例 45：

[0533] 4-(3- 氯苯基甲烷磺酰基氨基)- 吡啶 -2- 甲酸羟基酰胺盐酸盐

[0534]



[0535] 根据一般程序 D、使用 3- 氯苯基 - 甲烷磺酰氯获得该化合物。分离出期望的化合物，为白色粉末。

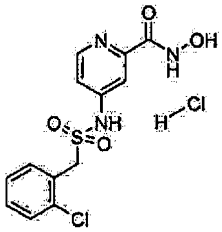
[0536] MS：342.1

[0537] Mp：198℃ -204℃

[0538] 实施例 46：

[0539] 4-(2- 氯 - 苯基甲烷磺酰基氨基)- 吡啶 -2- 甲酸羟基酰胺盐酸盐

[0540]



[0541] 根据一般程序 D、使用 2- 氯苯基 - 甲烷磺酰氯获得该化合物。分离出期望的化合物，为白色粉末。

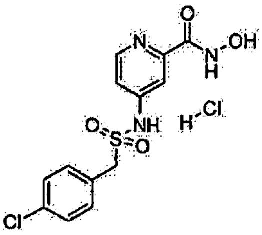
[0542] MS：342.1

[0543] Mp：215℃ -220℃

[0544] 实施例 47：

[0545] 4-(4- 氯 - 苯基甲烷磺酰基氨基)- 吡啶 -2- 甲酸羟基酰胺盐酸盐

[0546]



[0547] 根据一般程序 D、使用 4- 氯苯基 - 甲烷磺酰氯获得该化合物。分离出期望的化合物，为米色粉末。

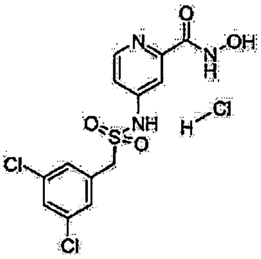
[0548] MS：342.1

[0549] Mp：210℃ -230℃

[0550] 实施例 48：

[0551] 4-(3,5- 二氯苯基甲烷磺酰基氨基)- 吡啶 -2- 甲酸羟基酰胺盐酸盐

[0552]



[0553] 根据一般程序 D、使用 3,5- 二氯苯基 - 甲烷磺酰氯获得该化合物。分离出期望的化合物，为白色粉末。

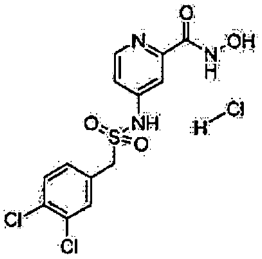
[0554] MS：376.2

[0555] Mp：203℃ -205℃

[0556] 实施例 49：

[0557] 4-(3,4- 二氯 - 苯基甲烷磺酰基氨基)- 吡啶 -2- 甲酸羟基酰胺盐酸盐

[0558]



[0559] 根据一般程序 D、使用 3,4- 二氯苯基 - 甲烷磺酰氯获得该化合物。分离出期望的化合物，为白色粉末。

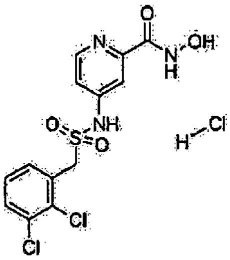
[0560] MS：376.2

[0561] Mp：228℃ -238℃

[0562] 实施例 50：

[0563] 4-(2,3- 二氯 - 苯基甲烷磺酰基氨基)- 吡啶 -2- 甲酸羟基酰胺盐酸盐

[0564]



[0565] 根据一般程序 D、使用 2,3- 二氯苯基 - 甲烷磺酰氯获得该化合物。分离出期望的化合物，为白色粉末。

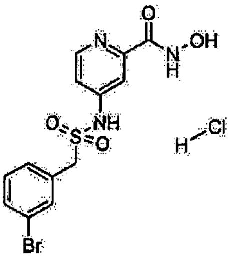
[0566] MS：376.2

[0567] Mp：210℃ -218℃

[0568] 实施例 51：

[0569] 4-(3- 溴苯基甲烷磺酰基氨基) - 吡啶 -2- 甲酸羟基酰胺盐酸盐

[0570]



[0571] 根据一般程序 D、使用 3- 溴苯基 - 甲烷磺酰氯获得该化合物。分离出期望的化合物，为白色粉末。

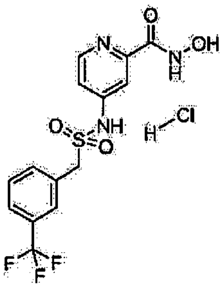
[0572] MS：386.3

[0573] Mp：197℃ -205℃

[0574] 实施例 52：

[0575] 4-(3- 三氟甲基苯基甲烷磺酰基氨基) - 吡啶 -2- 甲酸羟基酰胺盐酸盐

[0576]



[0577] 根据一般程序 D、使用 3- 三氟甲基 - 苯基甲烷磺酰氯获得该化合物。分离出期望的化合物，为白色粉末。

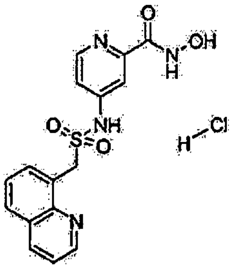
[0578] MS：376.1

[0579] Mp：201℃ -204℃

[0580] 实施例 53：

[0581] 4-(喹啉 -8- 基甲烷磺酰基氨基) - 吡啶 -2- 甲酸羟基酰胺盐酸盐

[0582]



[0583] 根据一般程序D、使用喹啉-8-基-甲烷磺酰氯获得该化合物。分离出期望的化合物，为白色粉末。

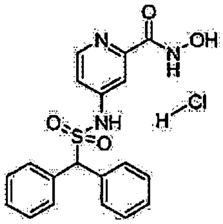
[0584] MS：359.0

[0585] Mp：220℃-228℃

[0586] 实施例54：

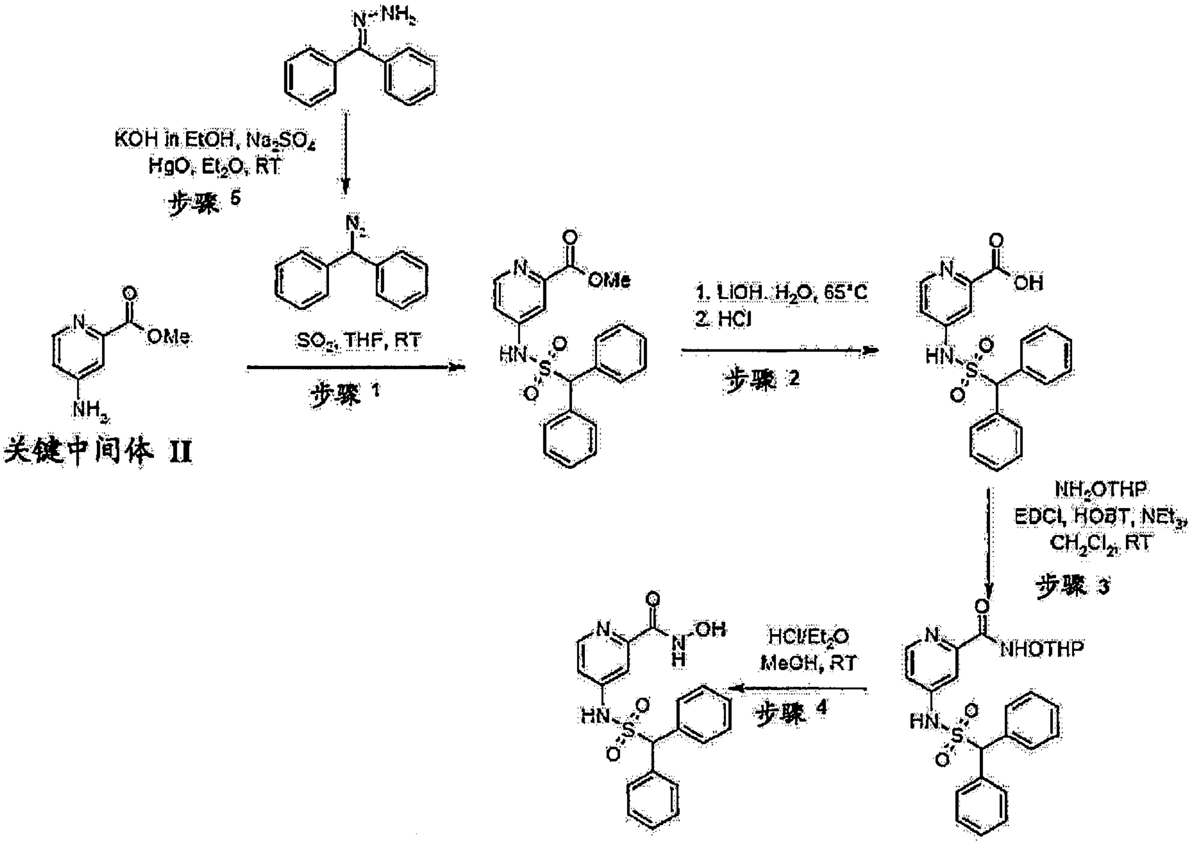
[0587] 4-(二苯基甲烷磺酰基氨基)-吡啶-2-甲酸羟基酰胺盐酸盐

[0588]



[0589] 因为二苯基甲烷磺酰氯不是商购可得，根据一般程序D的改进形式获得该化合物。

[0590]



[0591] 步骤 5：

[0592] 向二苯甲酮腙 (5.0g,25.5mmol,1 当量）和硫酸钠 (5.4g,38.2mmol,1.5 当量）在乙醚 (80mL) 中的悬液加入氢氧化钾在乙醇 (2mL) 中的饱和溶液。加入氧化汞 (13.8g,63.7mmol,2.5 当量)，将所得的红色溶液在室温搅拌 1.5h。过滤所得的固体，将滤液蒸发至干。将残余物用己烷 (40mL) 溶解，将溶液放置在冰箱中过夜。将所得的白色晶体过滤，浓缩滤液，得到二苯基重氮甲烷，为部分结晶的紫色油状物 (4.0g,80％收率）。

[0593] 步骤 1：

[0594] 在 0℃，在 4- 氨基 - 吡啶 -2- 甲酸甲酯（关键中间体 II）(1.2g,7.8mmol,2 当量）和二苯基重氮甲烷 (758mg,3.9mmol,1 当量）在四氢呋喃 (40mL) 中的溶液中鼓入二氧化硫直至红色消失。然后将溶液从 0℃至室温搅拌 3 天。将混合物过滤，蒸发滤液。将粗残余物通过快速色谱法、使用环己烷和乙酸乙酯 (0 / 100 至 100 / 0) 纯化，得到 4-(二苯基 - 甲烷磺酰基氨基)- 吡啶 -2- 甲酸甲酯，为浅黄色粉末 (665mg,45％收率）。

[0595] 步骤 2 至步骤 4：

[0596] 这些步骤与一般程序 D 步骤 2 至 4 类似。

[0597] 分离出期望的最终化合物，为米色粉末。

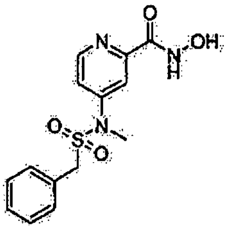
[0598] MS：384.0

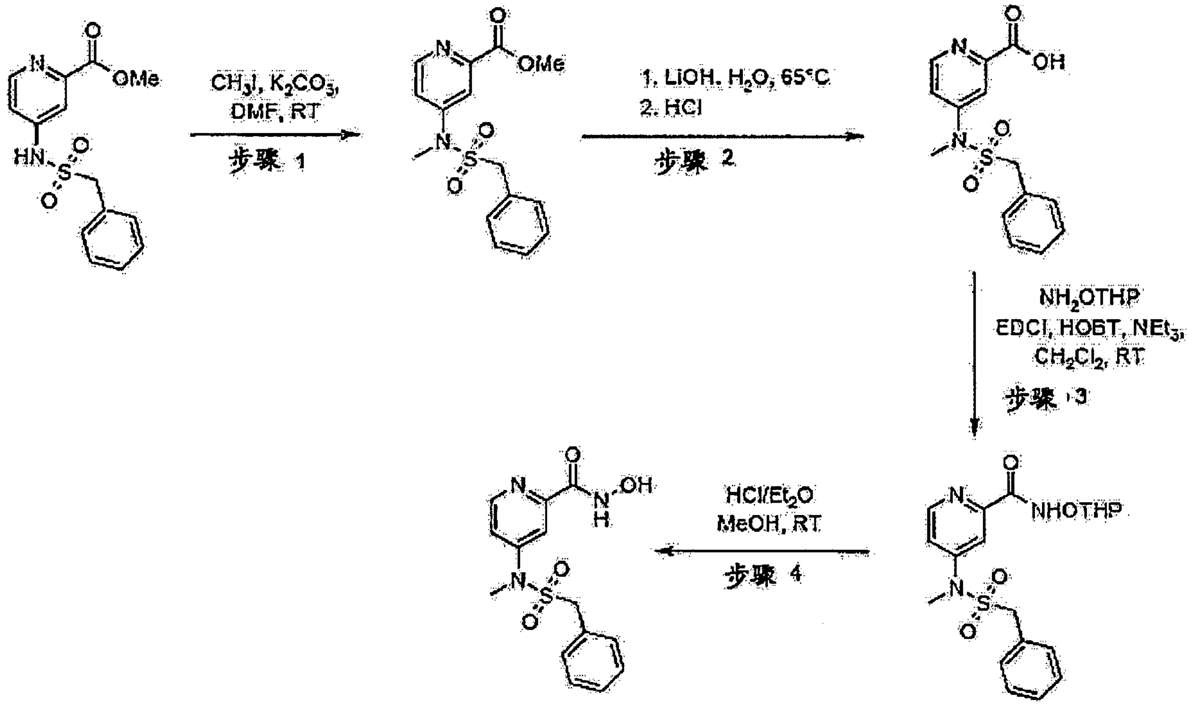
[0599] Mp：162℃ -168℃

[0600] 实施例 55：

[0601] 4-(甲基 - 苯基甲烷磺酰基 - 氨基)- 吡啶 -2- 甲酸羟基酰胺

[0602]





[0603] 步骤 1：

[0604] 向根据一般程序 D 步骤 1 制备的 4- 苯基甲烷磺酰基氨基 - 吡啶 -2- 甲酸甲酯(500mg，1.6mmol，1 当量)在二甲基甲酰胺(10mL)中的溶液加入碳酸钾(676mg，4.9mmol，3 当量)和甲基碘(0.2mL，3.3mmol，2 当量)。将混合物在室温搅拌 20h。然后将混合物倒入水(10mL)，用乙酸乙酯萃取(3 x15mL)。有机层用盐水洗涤(3 x 15mL)，经硫酸镁干燥，过滤，蒸发至干，得到 4-(甲基 - 苯基甲烷磺酰基 - 氨基)- 吡啶 -2- 甲酸甲酯，为橙色油状物(400mg，77％收率)。

[0605] 步骤 2 至 4：

[0606] 这些程序与一般程序 D 步骤 2 至 4 类似。

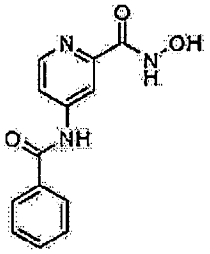
[0607] 分离出期望的化合物，为浅橙色泡沫状物。

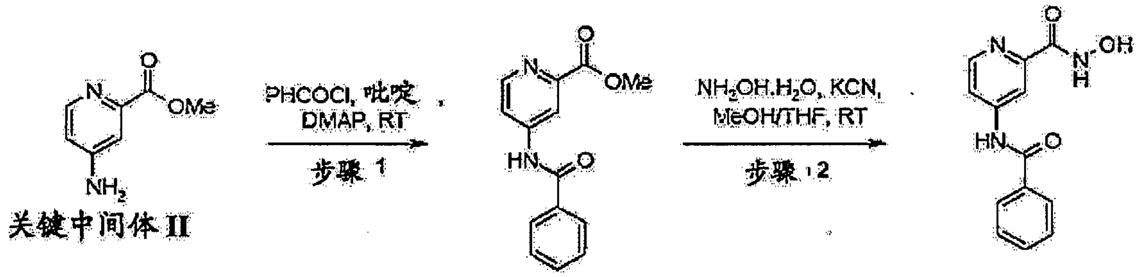
[0608] MS：322.1

[0609] 实施例 56：

[0610] 4- 苯甲酰基氨基吡啶 -2- 甲酸羟基酰胺

[0611]





[0612] 步骤 1：

[0613] 将 4- 氨基 - 吡定 -2- 甲酸甲酯（关键中间体 II）(400mg，2.6mmol，1 当量）溶解于吡啶 (10mL)。加入二甲氨基吡啶（催化量）和苯甲酰氯 (366μL，3.15mmol，1.2 当量)，将混合物在室温搅拌 18h。然后将溶剂蒸发，加入水 (10mL)，将水层用乙酸乙酯萃取 (3 x 20mL)。有机层经硫酸镁干燥，过滤，真空蒸发。将粗残余物通过快速色谱法、使用环己烷和乙酸乙酯 (100 / 0 至 50 / 50) 纯化，得到 4- 苯甲酰基氨基 - 吡啶 12- 甲酸甲酯，为白色泡沫状物 (654mg，97％收率）。

[0614] 步骤 2：

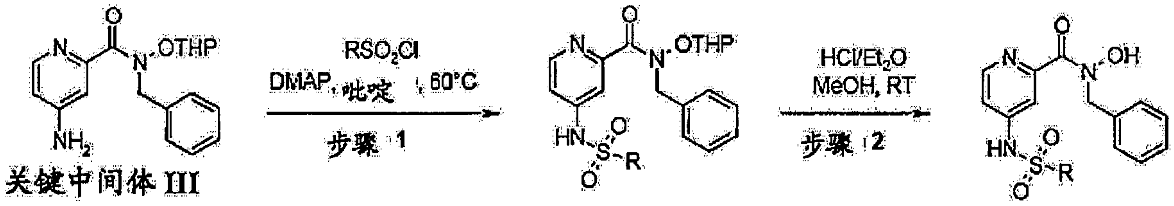
[0615] 向 4- 苯甲酰基氨基 - 吡啶 -2- 甲酸甲酯 (100mg，0.4mmol，1 当量）在甲醇 (2mL) 和四氢呋喃 (2mL) 的混合物中的溶液加入氰化钾（催化量）和 50％羟胺水溶液 (1.6mL)。将混合物在室温搅拌 4 天。然后加入柠檬酸饱和溶液 (10mL) 和水 (1 0mL)，将水层用乙酸乙酯萃取 (3 x 20mL)。有机层经硫酸镁干燥，过滤，真空蒸发。将粗残余物溶于乙酸乙酯 (5mL) 和二氯甲烷 (5mL) 中，超声处理。过滤固体，干燥，得到期望的化合物，为白色粉末 (78mg，78％收率）。

[0616] MS：258.0

[0617] Mp：175℃ -184℃

[0618] 一般程序 E

[0619]

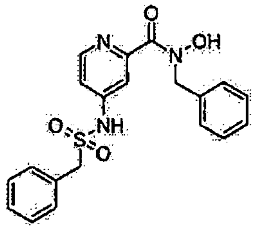


[0620] 该程序与一般程序 D 步骤 1 和 4 类似。

[0621] 实施例 57：

[0622] 4- 苯基甲烷磺酰基氨基 - 吡啶 -2- 甲酸苄基 - 羟基 - 酰胺

[0623]



[0624] 根据一般程序E、使用苯基甲烷－磺酰氯获得该化合物。分离出期望的化合物，为白色粉末。

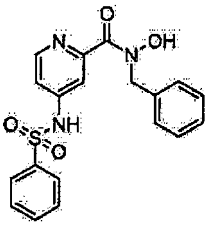
[0625] MS：398.2

[0626] Mp：190℃ -195℃

[0627] 实施例58：

[0628] 4-苯磺酰基氨基－吡啶-2-甲酸苄基－羟基－酰胺

[0629]



[0630] 根据一般程序E、使用苯磺酰氯获得该化合物。分离出期望的化合物，为浅玫色油状物。

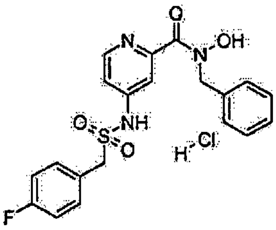
[0631] MS：384.2

[0632] Mp：175℃ -180℃

[0633] 实施例59：

[0634] 4-(4-氟－苯基甲烷磺酰基氨基)－吡啶-2-甲酸苄基－羟基－酰胺盐酸盐

[0635]



[0636] 根据一般程序E、使用4-氟苯基－甲烷磺酰氯获得该化合物。分离出期望的化合物，为米色粉末。

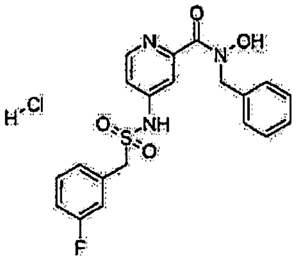
[0637] MS：416.3

[0638] Mp：178℃ -183℃

[0639] 实施例60：

[0640] 4-(3-氟－苯基甲烷磺酰基氨基)－吡定-2-甲酸苄基－羟基－酰胺盐酸盐

[0641]



[0642] 根据一般程序E、使用3-氟苯基-甲烷磺酰氯获得该化合物。获得期望的化合物，为米色粉末。

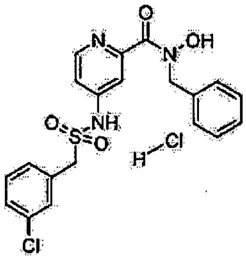
[0643] MS：416.2

[0644] Mp：111℃ -113℃

[0645] 实施例61：

[0646] 4-(3-氯苯基甲烷磺酰基氨基)-吡啶-2-甲酸苄基羟基酰胺盐酸盐

[0647]



[0648] 根据一般程序E、使用3-氯苯基-甲烷磺酰氯获得该化合物。分离出期望的化合物，为白色粉末。

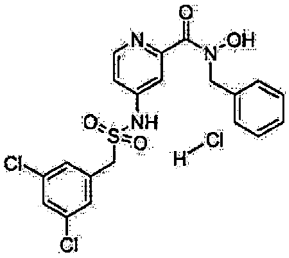
[0649] MS：432.3

[0650] Mp：115℃ -125℃

[0651] 实施例62：

[0652] 4-(3,5-二氯苯基甲烷磺酰基氨基)-吡啶-2-甲酸苄基-羟基酰胺盐酸盐

[0653]



[0654] 根据一般程序E、使用3,5-二氯苯基-甲烷磺酰氯获得该化合物。分离出期望的化合物，为白色粉末。

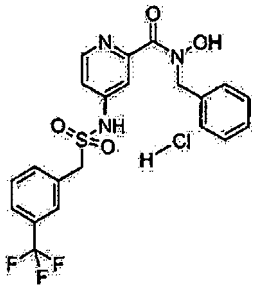
[0655] MS：466.3

[0656] Mp：189℃ -194℃

[0657] 实施例63：

[0658] 4-(3-三氟甲基苯基甲烷磺酰基氨基)-吡啶-2-甲酸苄基羟基酰胺盐酸盐

[0659]



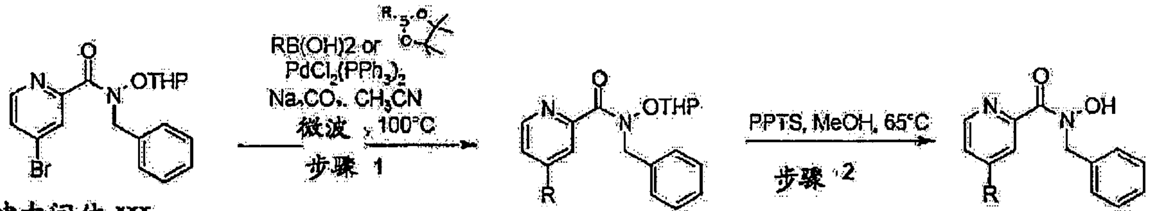
[0660]　根据一般程序 E、使用 3- 三氟甲基 - 苯基甲烷磺酰氯获得该化合物。分离出期望的化合物，为米色粉末。

[0661]　MS：466.2

[0662]　Mp：178℃ -182℃

[0663]　一般程序 F

[0664]



关键中间体 III

[0665]　步骤 1：

[0666]　向脱气的 4- 溴 - 吡啶 -2- 甲酸苄基 -(四氢 - 吡喃 -2- 基氧基)- 酰胺 (关键中间体 III) (150mg，0.4mmol，1 当量) 在乙腈 (3mL) 和 1M 碳酸钠溶液 (3mL) 的混合物中的溶液加入硼酸 (0.5mmol，1.3 当量) 和反式 - 二氯双 (三苯基膦) 钯 (II) (13mg，0.02mmol，0.05 当量)。将混合物在微波辐射下于 100℃加热 10min。冷却后，将混合物倒入水 (5mL) 中，用乙酸乙酯萃取 (3x10mL)。有机层经硫酸镁干燥，过滤，真空蒸发。将粗残余物通过快速色谱法纯化，得到期望的化合物。

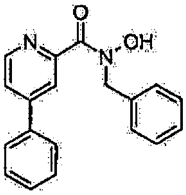
[0667]　步骤 2：

[0668]　将来自步骤 1 的化合物 (1 当量) 溶解于甲醇 (10mL) 中，加入对甲苯磺酸吡啶鎓 (1 当量)。将混合物在 65℃加热 5h，蒸发至干。将残余物在水中磨碎，过滤，用水漂洗，干燥，得到期望的化合物。

[0669]　实施例 64：

[0670]　4- 苯基 - 吡啶 -2- 甲酸苄基 - 羟基 - 酰胺

[0671]



[0672]　根据一般程序 F、使用苯基硼酸获得该化合物。分离出期望的化合物，为浅玫红色粉末。

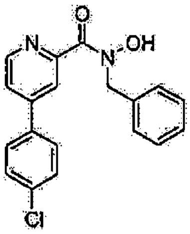
[0673]　MS：304.9

[0674]　Mp：160℃ -165℃

[0675]　实施例 65：

[0676]　4-(4- 氯 - 苯基)- 吡啶 -2- 甲酸苄基 - 羟基 - 酰胺

[0677]



[0678]　根据一般程序 F、使用 4- 氯苯基 - 硼酸获得该化合物。分离出期望的化合物，为白色粉末。

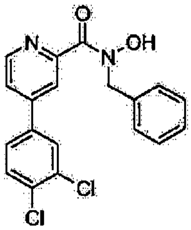
[0679]　MS：339.2

[0680]　Mp：190℃ -195℃

[0681]　实施例 66：

[0682]　4-(3,4- 二氯 - 苯基)- 吡啶 -2- 甲酸苄基 - 羟基 - 酰胺

[0683]



[0684]　根据一般程序 F、使用 3,4- 二氯苯基 - 硼酸获得该化合物。分离出期望的化合物，为浅橙色粉末。

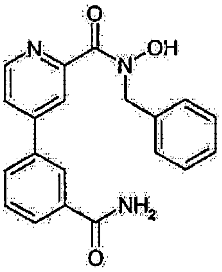
[0685]　MS：373.2

[0686]　Mp：125℃ -130℃

[0687]　实施例 67：

[0688]　4-(3- 氨基甲酰基 - 苯基)- 吡啶 -2- 甲酸苄基 - 羟基 - 酰胺

[0689]



[0690]　根据一般程序 F、使用 3- 氨基甲酰基 - 苯基硼酸获得该化合物。分离出期望的化合物，为米色粉末。

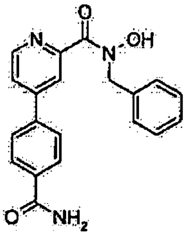
[0691]　MS：348.1

[0692]　Mp：158℃ -162℃

[0693]　实施例 68：

[0694] 4-(4-氨基甲酰基-苯基)-吡啶-2-甲酸苄基-羟基-酰胺

[0695]



[0696] 根据一般程序F、使用4-氨基甲酰基-苯基硼酸获得该化合物。分离出期望的化合物，为浅黄色粉末。

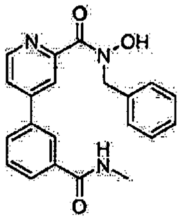
[0697] MS：348.2

[0698] Mp：155℃-160℃

[0699] 实施例69：

[0700] 4-(3-甲基氨基甲酰基-苯基)-吡啶-2-甲酸苄基-羟基-酰胺

[0701]



[0702] 根据一般程序F、使用3-甲基氨基甲酰基-苯基硼酸获得该化合物。分离出期望的化合物，为浅黄色泡沫状物。

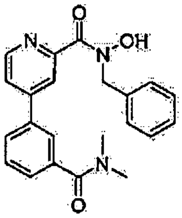
[0703] MS：362.2

[0704] 实施例70：

[0705] 4-(3-二甲基氨基甲酰基-苯基)-吡定-2-甲酸苄基-羟基-酰胺

[0706]

[0707]



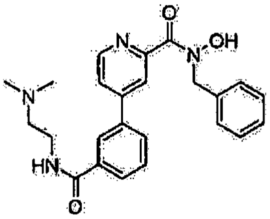
[0708] 根据一般程序F、使用3-二甲基-氨基甲酰基-苯基硼酸获得该化合物。分离出期望的化合物，为黄色泡沫状物。

[0709] MS：376.2

[0710] 实施例71：

[0711] 4-[3-(2-二甲氨基-乙基氨基甲酰基)-苯基]-吡啶-2-甲酸苄基-羟基-酰胺

[0712]



[0713] 根据一般程序F、使用3-(2-(二甲氨基)乙基氨基甲酰)苯基硼酸获得该化合物。分离出期望的化合物，为白色泡沫状物。

[0714] MS：419.3

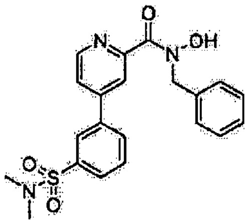
[0715] Mp：65℃-70℃

[0716] 实施例72：

[0717] 4-(3-二甲基氨磺酰基-苯基)-吡啶-2-甲酸苄基-羟基-酰胺

[0718]

[0719]



[0720] 根据一般程序F、使用3-二甲基-氨磺酰基-苯基硼酸获得该化合物。分离出期望的化合物，为黄色粉末。

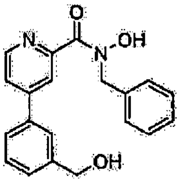
[0721] MS：412.2

[0722] Mp：110℃-115℃

[0723] 实施例73：

[0724] 4-(3-羟基甲基-苯基)-吡啶-2-甲酸苄基-羟基-酰胺

[0725]



[0726] 根据一般程序F、使用3-羟基甲基-苯基硼酸获得该化合物。分离出期望的化合物，为白色粉末。

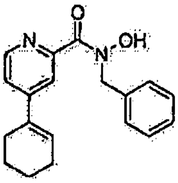
[0727] MS：335.2

[0728] Mp：150℃-155℃

[0729] 实施例74：

[0730] 4-环己-1-烯基-吡啶-2-甲酸苄基羟基酰胺

[0731]



[0732]　根据一般程序F、使用环己烯-1-基硼酸频哪醇酯获得该化合物。分离出期望的化合物，为白色粉末。

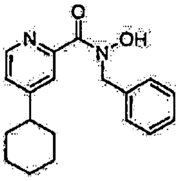
[0733]　MS：309.2

[0734]　Mp：118℃-122℃

[0735]　实施例75：

[0736]　4-环己基吡啶-2-甲酸苄基羟基-酰胺

[0737]



[0738]　将实施例74中获得的4-环己-1-烯基-吡啶-2-甲酸苄基羟基酰胺（100mg，0.3mmol，1当量）溶解于乙醇（10mL）中，加入10％w钯/碳。将混合物在氢气气氛下于室温搅拌30min。然后将混合物滤过硅藻土短柱，用乙醇和二氯甲烷漂洗。将粗残余物通过快速色谱法、使用环己烷和乙酸乙酯（100/0至70/30）纯化，得到期望的化合物，为白色粉末（72mg，72％收率）。

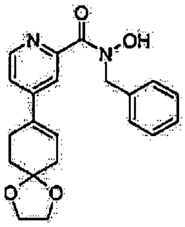
[0739]　MS：311.2

[0740]　Mp：106℃-110℃

[0741]　实施例76：

[0742]　4-(1,4-二氧杂-螺[4.5]癸-7-烯-8-基)-吡啶-2-甲酸苄基-羟基-酰胺

[0743]



[0744]　根据一般程序F、使用1,4-二氧杂-螺[4,5]癸-7-烯-8-硼酸频哪醇酯获得该化合物。分离出期望的化合物，为黄色泡沫状物。

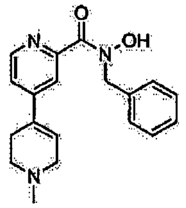
[0745]　MS：367.2

[0746]　实施例77：

[0747]　1′-甲基-1′,2′,3′,6′-四氢-[4,4′]联吡啶基-2-甲酸苄基-羟基-酰胺

[0748]

[0749]



[0750] 根据一般程序F、使用1-甲基-1,2,3,6-四氢吡啶-4-硼酸频哪醇酯获得该化合物。分离出期望的化合物,为浅黄色粉末。

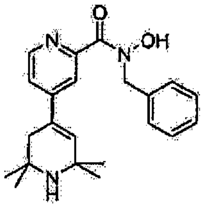
[0751] MS:324.2

[0752] Mp:135℃-155℃

[0753] 实施例78:

[0754] 2′,2′,6′,6′-四甲基-1′,2′,3′,6′-四氢-[4,4′]联吡啶基-2-甲酸苄基-羟基-酰胺

[0755]



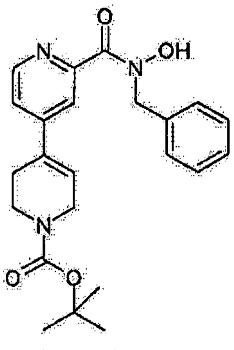
[0756] 根据一般程序F、使用2,2,6,6-四甲基-1,2,3,6-四氢-4-吡啶硼酸频哪醇酯获得该化合物。分离出期望的化合物,为黄色结晶油状物。

[0757] MS:366.3

[0758] 实施例79:

[0759] 2′-(苄基-羟基-氨基甲酰基)-3,6-二氢-2H-[4,4′]联吡啶基-1-甲酸叔丁酯

[0760]



[0761] 根据一般程序F、使用N-Boc-1,2,3,6-四氢吡啶-4-硼酸频哪醇酯获得该化合物。分离出期望的化合物,为米色粉末。

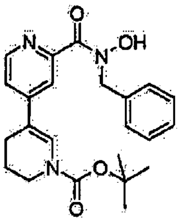
[0762] MS:410.3

[0763] Mp:125℃

[0764] 实施例80:

[0765] 2′-(苄基-羟基-氨基甲酰基)-5,6-二氢-4H-[3,4′]联吡啶基-1-甲酸叔丁酯

[0766]



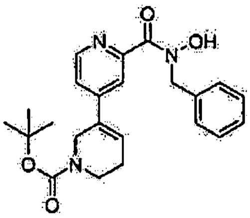
[0767]　根据一般程序F、使用5-(4,4,5,5-四甲基-[1,3,2]二氧硼杂环戊烷-2-基)-3,4-二氢2H-吡定-1-甲酸叔丁酯(关键中间体V)获得该化合物。分离出期望的化合物,为黄色泡沫状物。

[0768]　MS:410.3

[0769]　实施例81:

[0770]　2′-(苄基羟基氨基甲酰基)-5,6-二氢2H-[3,4′]联吡啶基-1-甲酸叔丁酯

[0771]



[0772]　根据一般程序F、使用5-(4,4,5,5-四甲基-[1,3,2]二氧硼杂环戊烷-2-基)-3,6-二氢-2H-吡啶-1-甲酸叔丁酯(关键中间体VI)获得该化合物。分离出期望的化合物,为黄色粉末。

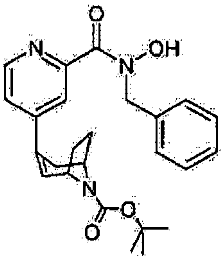
[0773]　MS:410.3

[0774]　Mp:128℃-134℃

[0775]　实施例82:

[0776]　3-[2-(苄基羟基氨基甲酰基)-吡啶-4-基]-8-氮杂双环[3.2.1]辛-2-烯-8-甲酸叔丁酯

[0777]

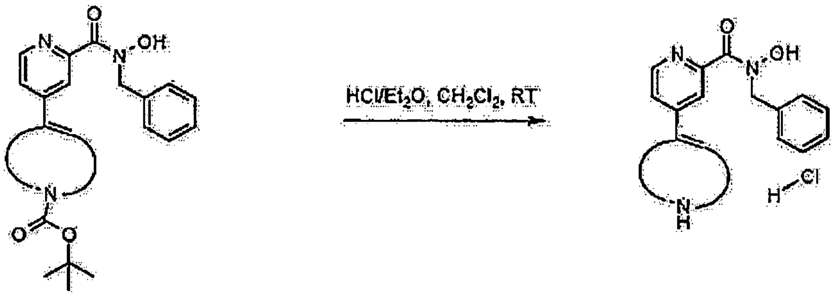


[0778]　根据一般程序F、使用8-boc-3-(4,4,5,5-四甲基-[1,3,2]二氧硼杂环戊烷-2-基)-8-氮杂-双环[3.2.1]辛-2-烯获得该化合物。分离出期望的化合物,为黄色油状物。

[0779]　MS:436.3

[0780]　一般程序G

[0781]

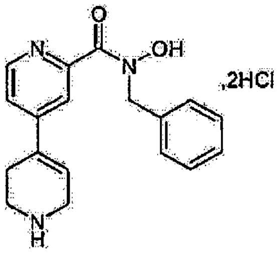


[0782] 将获自一般程序 F 的化合物 (1 当量) 溶解于二氯甲烷 (10mL) 中，滴加 2M 盐酸在乙醚中的溶液 (16 当量)。将混合物在室温搅拌 2h。过滤沉淀，用二氯甲烷和乙醚研磨，得到期望的化合物 (60％收率)。

[0783] 实施例 83：

[0784] 1′,2′,3′,6′-四氢-[4,4′]联吡啶基-2-甲酸苄基-羟基-酰胺二盐酸盐

[0785]



[0786] 根据一般程序 G、使用实施例 79 中描述的 2′-(苄基-羟基-氨基甲酰基)-3,6-二氢-2H-[4,4′]联吡啶基-1-甲酸叔丁酯获得该化合物。分离出期望的化合物，为米色粉末。

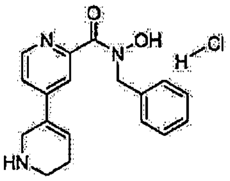
[0787] MS：310.1

[0788] Mp：140℃-150℃

[0789] 实施例 84：

[0790] 1,2,5,6-四氢-[3,4′]联吡啶基-2′-甲酸苄基羟基-酰胺盐酸盐

[0791]



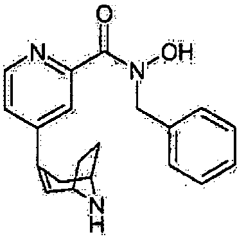
[0792] 根据一般程序 G、使用实施例 81 中描述的 2′-(苄基羟基氨基甲酰基)-5,6-二氢-2H-[3,4′]联吡啶基-1-甲酸叔丁酯获得该化合物。分离出期望的化合物，为黄色结晶油状物。

[0793] MS：310.2

[0794] 实施例 85：

[0795] 4-(8-氮杂双环[3.2.1]辛-2-烯-3-基)-吡啶-2-甲酸苄基羟基酰胺

[0796]



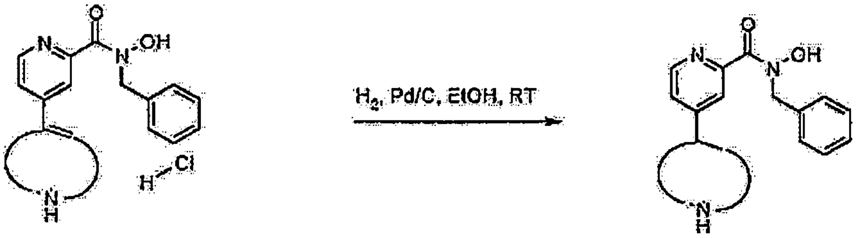
[0797] 根据一般程序G、使用实施例82中描述的3-[2-(苄基羟基氨基甲酰基)-吡啶-4-基]-8-氮杂双环[3.2.1]辛-2-烯-8-甲酸叔丁酯获得该化合物。分离出期望的化合物，为黄色粉末。

[0798] MS：336.1

[0799] Mp：95℃-100℃

[0800] 一般程序H

[0801]

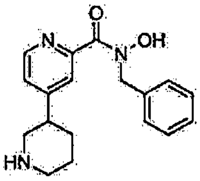


[0802] 将获自一般程序G的化合物（1当量）溶解于乙醇（10mL）中，加入10%w钯/碳。将混合物在氢气气氛下于室温搅拌30min。然后将混合物滤过硅藻土短柱，将粗残余物通过快速色谱法、使用乙酸乙酯和甲醇（100/0至80/20）纯化，得到期望的化合物。

[0803] 实施例86：

[0804] 1,2,3,4,5,6-六氢-[3,4′]联吡啶基-2′-甲酸苄基羟基酰胺

[0805]



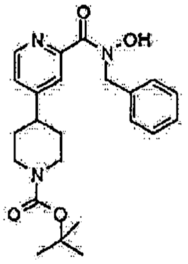
[0806] 根据一般程序H、使用实施例84中描述的1,2,5,6-四氢-[3,4′]联吡啶基-2′-甲酸苄基羟基-酰胺盐酸盐获得该化合物。分离出期望的化合物，为黄色结晶油状物。

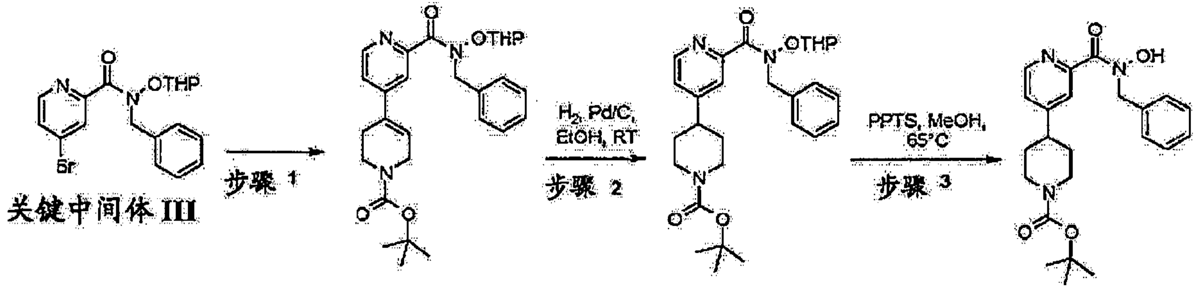
[0807] MS：312.2

[0808] 实施例87：

[0809] 2′-(苄基-羟基-氨基甲酰基)-3,4,5,6-四氢-2H-[4,4′]联吡啶基-1-甲酸叔丁酯

[0810]





[0811] 步骤 1：

[0812] 根据一般程序 F 步骤 1、由关键中间体 III 和 N-Boc-1,2,3,6- 四氢吡啶 -4- 硼酸频哪醇酯开始，获得该化合物

[0813] 步骤 2：

[0814] 将来自步骤 1 的化合物 (485mg，1mmol，1 当量) 溶解于乙醇 (20mL) 中，加入 10％ w 钯 / 碳。将混合物在氢气气氛下于室温搅拌 1.5h。然后将混合物滤过硅藻土短柱，将粗残余物通过快速色谱法、使用环己烷和乙酸乙酯 (100 / 0 至 40 / 60) 纯化，得到 2′ -[苄基 -(四氢 - 吡喃 -2- 基氧基)- 氨基甲酰基]-3,4,5,6- 四氢 -2H-[4,4′] 联吡啶基 -1- 甲酸叔丁酯，为无色油状物 (320mg，66％收率)。

[0815] 步骤 3：

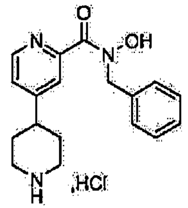
[0816] 将来自步骤 2 的化合物 (360mg，0.6mmol，1 当量) 溶解于甲醇 (20mL) 中，加入对甲苯磺酸吡啶鎓 (182mg，0.6mmol，1 当量)。将混合物在 65℃加热 18h，蒸发至干。加入乙酸乙酯 (10mL)，将有机层用碳酸氢钠饱和溶液洗涤 (3x10mL)，经硫酸镁干燥，过滤，真空蒸发。将粗残余物通过快速色谱法、使用环己烷和乙酸乙酯 (80 / 20 至 30 / 70) 纯化，得到期望的化合物，为橙色油状物 (230mg，77％收率)。

[0817] MS：412.3

[0818] 实施例 88：

[0819] 1′ ,2′ ,3′ ,4′ ,5′ ,6′ - 六氢 -[4,4′] 联吡啶基 -2- 甲酸苄基 - 羟基 - 酰胺盐酸盐

[0820]



[0821] 根据一般程序 G、使用实施例 87 中描述的 2′ -(苄基 - 羟基 - 氨基甲酰基)-3,4,5,6- 四氢 -2H-[4,4′] 联吡啶基 -1- 甲酸叔丁酯获得该化合物。分离出期望的化合物，为

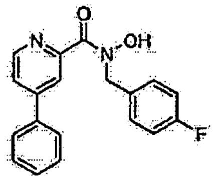
白色泡沫状物。

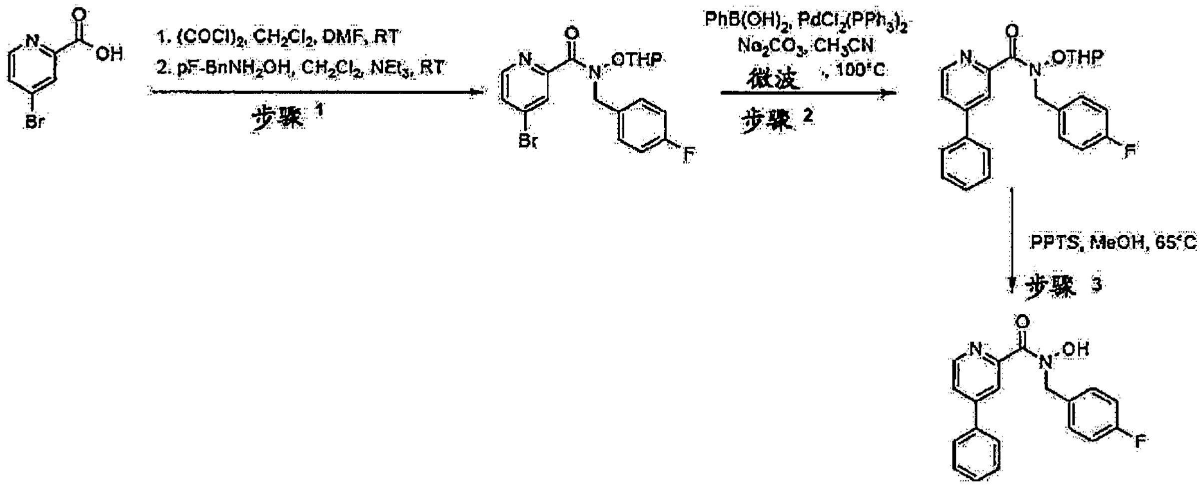
[0822] MS：312.1

[0823] 实施例 89：

[0824] 4- 苯基 - 吡啶 -2- 甲酸 (4- 氟 - 苄基 - 羟基 - 酰胺

[0825]





[0826] 步骤 1：

[0827] 将草酰氯 (0.2mL，2.1mmol，1.3 当量) 加入至 4- 溴 - 吡啶 -2- 甲酸 (334mg，1.6mmol，1 当量) 在二氯甲烷 (15mL) 中的溶液。将溶液冷却至 0℃，滴加二甲基甲酰胺 (数滴)。将混合物在室温搅拌 30min，蒸发至干。将残余物稀释于二氯甲烷 (15mL) 中，加入 N-(4- 氟 - 苄基)-O-(四氢 - 吡喃 -2- 基)- 羟胺 (560mg，2.5mmol，1.5 当量)。在 0℃滴加三乙胺 (0.7mL，4.9mmol，3 当量)，将混合物在室温搅拌 18h，吸附在硅胶上，通过快速色谱法、使用环己烷和乙酸乙酯 (100 / 0 至 70 / 30) 纯化，得到 4- 溴 - 吡啶 -2- 甲酸 (4- 氟 - 苄基)-(四氢 - 吡喃 -2- 基氧基)- 酰胺，为无色油状物 (230mg，34％收率)。

[0828] 步骤 2：

[0829] 向脱气的 4- 溴 - 吡啶 -2- 甲酸 (4- 氟 - 苄基)-(四氢 - 吡喃 -2- 基氧基)- 酰胺 (230mg，0.6mmol，1 当量) 在乙腈 (4mL) 和 1M 碳酸钠溶液 (4mL) 的混合物中的溶液加入苯基硼酸 (89mg，0.7mmol，1.3 当量) 和反式 - 二氯双 (三苯基膦) 钯 (20mg，0.03mmol，0.05 当量)。将混合物在微波辐射下于 100℃加热 10min。冷却后，将混合物倒入水 (5mL) 中，用乙酸乙酯萃取 (3x10mL)。有机层经硫酸镁干燥，过滤，真空蒸发。将粗残余物通过快速色谱法、使用环己烷和乙酸乙酯 (100 / 0 至 50 / 50) 纯化，得到 4- 苯基 - 吡啶 -2- 甲酸 (4- 氟 - 苄基)-(四氢 - 吡喃 -2- 基氧基)- 酰胺，为无色油状物 (130mg，57％收率)。

[0830] 步骤 3：

[0831] 将 4- 苯基 - 吡啶 -2- 甲酸 (4- 氟 - 苄基)-(四氢 - 吡喃 -2- 基氧基)- 酰胺 (130mg， 0.3mmol，1 当量）溶解于甲醇（5mL）中，加入对甲苯磺酸吡啶鎓（97mg，0.4mmol，1.2 当量）。将混合物在 65℃加热 5h。过滤所得的沉淀，用少量甲醇洗涤，得到期望的化合物，为白色粉末（13mg，13％收率）。

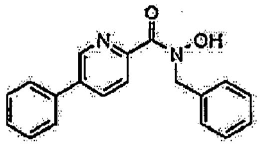
[0832] MS：323.1

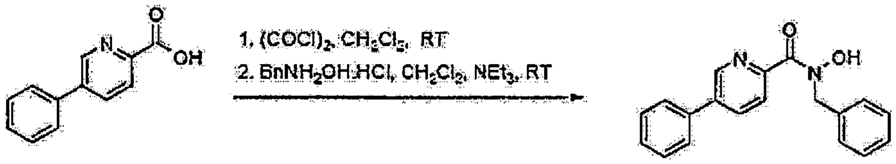
[0833] Mp：135℃ -140℃

[0834] 实施例 90：

[0835] 5- 苯基 - 吡啶 -2- 甲酸苄基 - 羟基 - 酰胺

[0836]





[0837] 在 0℃，将草酰氯（0.2mL，2.3mmol，1.5 当量）加入至 5- 苯基 - 吡啶 -2- 甲酸（300mg，1.5mmol，1 当量）在二氯甲烷（10mL）中的溶液。将混合物在室温搅拌 30min，蒸发至干。将残余物稀释于二氯甲烷（10mL）中，加入 N- 苄基 - 羟胺盐酸盐（361mg，2.3mmol，1.5 当量）和三乙胺（0.6mL，4.5mmol，3 当量）。将混合物在室温搅拌 18h，吸附在硅胶上，通过快速色谱法、使用环己烷和乙酸乙酯（100 / 0 至 0 / 100）纯化，得到期望的化合物，为米色粉末（60mg，13％收率）。

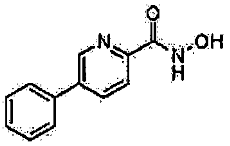
[0838] MS：305.2

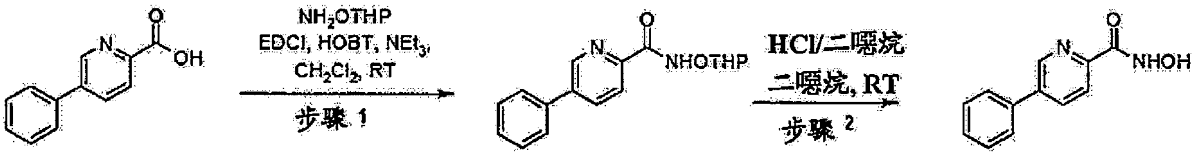
[0839] Mp：145℃ -150℃

[0840] 实施例 91：

[0841] 5- 苯基 - 吡啶 -2- 甲酸羟基酰胺

[0842]





[0843] 步骤 1：

[0844]

[0845] 向 5- 苯基 - 吡啶 -2- 甲酸（130mg，0.6mmol，1 当量）在二氯甲烷（6mL）中的溶液加入 HOBT（176mg，1.3mmol，2 当量）、EDCI（249mg，1.3mmol，2 当量）、三乙胺（0.3mL，1.8mmol，3 当量）和 O-（四氢 - 吡喃 -2- 基）- 羟胺（153mg，1.3mmol，2 当量）。将混合物在室温搅

拌 18h，吸附在硅胶上，通过快速色谱法、使用环己烷和乙酸乙酯（100 / 0 至 50 / 50）纯化，得到 5- 苯基 - 吡啶 -2- 甲酸（四氢 - 吡喃 -2- 基氧基）- 酰胺，为无色油状物（160mg，83％收率）。

[0846]　步骤 2：

[0847]

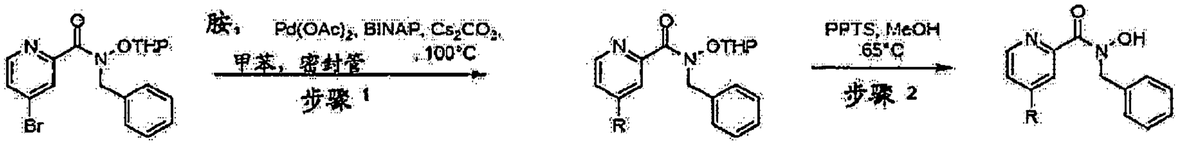
[0848]　向 5- 苯基 - 吡啶 -2- 甲酸（四氢 - 吡喃 -2- 基氧基）- 酰胺（160mg，0.54mmol，1 当量）在二噁烷（5mL）中的溶液加入 4N 氯化氢在二噁烷（0.5mL）中的溶液。将混合物在室温搅拌 1h，蒸发至干。将残余物稀释于甲醇（5mL）中，加入 7N 在甲醇中的氨（0.5mL）。蒸发混合物，将残余物在水中研磨，得到期望的化合物，为浅玫色粉末（90mg，78％收率）。

[0849]　MS：215.1

[0850]　Mp：175℃ -180℃

[0851]　一般程序 I

[0852]



关键中间体 III

[0853]　步骤 1：

[0854]

[0855]　向脱气的 4- 溴 - 吡啶 -2- 甲酸苄基 -（四氢 - 吡喃 -2- 基氧基）- 酰胺（关键中间体 III）（500mg，1.3mmol，1 当量）在甲苯（10mL）中的溶液加入碳酸铯（1.3g，3.8mmol，3 当量）、胺（1.66mmol，1.3 当量）、BINAP（40mg，0.06mmol，0.05 当量）和乙酸钯（15mg，0.06mmol，0.05 当量）。将混合物在密封管中于 100℃加热 20h。冷却后，将混合物倒入水（10mL）中，用乙酸乙酯萃取（3x10mL）。有机层经硫酸镁干燥，过滤，真空蒸发。将粗残余物通过快速色谱法纯化，得到期望的化合物。

[0856]　步骤 2：

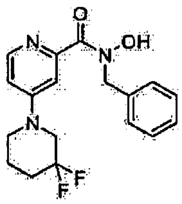
[0857]

[0858]　将来自步骤 1 的化合物（1 当量）溶解于甲醇（10mL）中，加入对甲苯磺酸吡啶鎓（1 当量）。将混合物在 65℃加热 20h。冷却后，加入 7N 氨在甲醇（10mL）中的溶液，将混合物蒸发至干。将残余物稀释于二氯甲烷（10mL）中，将有机层用水洗涤（3x10mL），经硫酸镁干燥，过滤，真空蒸发。将粗化合物通过快速色谱法纯化，得到期望的化合物。

[0859]　实施例 92：

[0860]　3,3- 二氟 -3,4,5,6- 四氢 -2H-[1,4′]联吡啶基 -2′ - 甲酸苄基 - 羟基 - 酰胺

[0861]



[0862] 根据一般程序 I、使用 3,3- 二氟 - 哌啶盐酸盐获得该化合物。分离出期望的化合物，为浅黄色粉末。

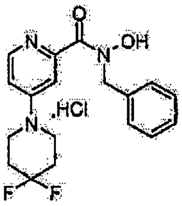
[0863] MS：348.1

[0864] Mp：140℃ -145℃

[0865] 实施例 93：

[0866] 4,4- 二氟 -3,4,5,6- 四氢 -2H-[1,4′] 联吡啶基 -2′ - 甲酸苄基 - 羟基 - 酰胺

[0867]



[0868] 根据一般程序 I、使用 4,4- 二氟哌啶盐酸盐、随后添加 2M 氯化氢在乙醚中的溶液，获得该化合物。在室温搅拌 2h 后，过滤，用乙醚研磨，分离出期望的化合物，为白色粉末。

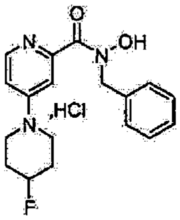
[0869] MS：348.2

[0870] Mp：90℃ -95℃

[0871] 实施例 94：

[0872] 4- 氟 -3,4,5,6- 四氢 -2H-[1,4′] 联吡啶基 -2′ - 甲酸苄基 - 羟基 - 酰胺盐酸盐

[0873]



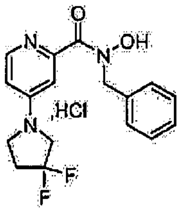
[0874] 根据一般程序 I 的改进形式、使用 4- 氟哌啶盐酸盐获得该化合物。在步骤 2 期间，不使用对甲苯磺酸吡啶鎓，加入 2M 氯化氢在乙醚 (20 当量) 中的溶液，将混合物在室温搅拌 2h。然后过滤沉淀，用二氯甲烷和乙醚研磨，得到期望的化合物，为浅黄色泡沫状物。

[0875] MS：330.1

[0876] 实施例 95：

[0877] 4-(3,3- 二氟 - 吡咯烷 -1- 基)- 吡啶 -2- 甲酸苄基 - 羟基 - 酰胺盐酸盐

[0878]



[0879] 根据一般程序 I 的改进形式、使用 3,3- 二氟吡咯烷盐酸盐获得该化合物。在步骤 2 期间，不使用对甲苯磺酸吡啶鎓，加入 2M 氯化氢在乙醚中的溶液 (20 当量)，将混合物在室温搅拌 2h。然后过滤沉淀，用二氯甲烷和乙醚研磨，得到期望的化合物，为米色粉末。

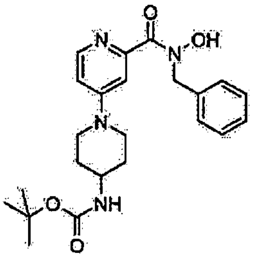
[0880] MS：334.1

[0881] Mp：162℃ -166℃

[0882] 实施例 96：

[0883] [2′-(苄基-羟基-氨基甲酰基)-3,4,5,6-四氢-2H-[1,4′]联吡啶基-4-基]-氨基甲酸叔丁酯

[0884]



[0885] 根据一般程序 I、使用 4-N-BOC-氨基哌啶获得该化合物。分离出期望的化合物，为白色泡沫状物。

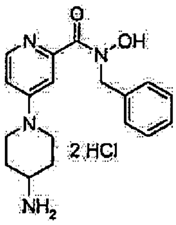
[0886] MS：427.3

[0887] Mp：135℃ -140℃

[0888] 实施例 97：

[0889] 4-氨基-3,4,5,6-四氢-2H-[1,4′]联吡啶基-2′-甲酸苄基-羟基-酰胺盐酸盐

[0890]



[0891] 根据一般程序 G、使用实施例 96 中描述的 [2′-(苄基-羟基-氨基甲酰基)-3,4,5,6-四氢-2H-[1,4′]联吡啶基-4-基]-氨基甲酸叔丁酯获得该化合物。分离出期望的化合物，为白色粉末。

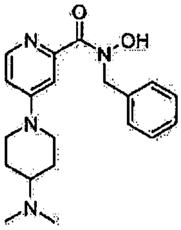
[0892] MS：327.2

[0893] Mp：在 160℃ -165℃分解

[0894] 实施例 98：

[0895] 4-二甲氨基-3,4,5,6-四氢-2H-[1,4′]联吡啶基-2′-甲酸苄基-羟基-酰胺

[0896]



[0897] 根据一般程序 I、使用二甲基-哌啶-4-基-胺获得该化合物。分离出期望的化合

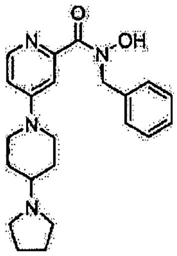
物，为黄色油状物。

[0898] MS：355.2

[0899] 实施例 99：

[0900] 4-吡咯烷-1-基-3,4,5,6-四氢-2H-[1,4′]联吡啶基-2′-甲酸苄基-羟基-酰胺

[0901]



[0902] 根据一般程序 I、使用 4-(1-吡咯烷基)哌啶获得该化合物。分离出期望的化合物，为浅黄色粉末。

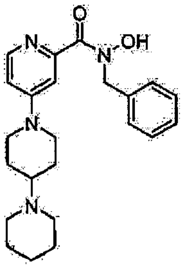
[0903] MS：381.2

[0904] Mp：135℃-140℃

[0905] 实施例 100：

[0906] 3,4,5,6,3′,4′,5′,6′-八氢-2H,2′H-[1,4′;1′,4″]三联吡啶-2″-甲酸苄基-羟基-酰胺

[0907]



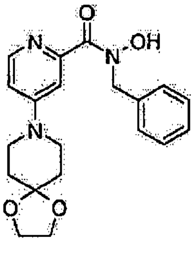
[0908] 根据一般程序 I、使用 4N-(4-哌啶子基)哌啶获得该化合物。分离出期望的化合物，为蓝色油状物。

[0909] MS：395.2

[0910] 实施例 101：

[0911] 4-(1,4-二氧杂-8-氮杂-螺[4.5]癸-8-基)-吡啶-2-甲酸苄基-羟基-酰胺

[0912]



[0913] 根据一般程序 I、使用 1,4-二氧杂-8-氮杂螺[4.5]癸烷获得该化合物。分离出期望的化合物，为黄色粉末。

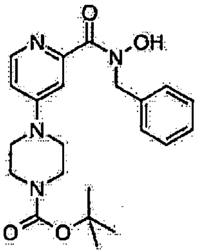
[0914]　MS：370.2

[0915]　Mp：98℃ -102℃

[0916]　实施例 102：

[0917]　4-[2-(苄基-羟基-氨基甲酰基)-吡啶-4-基]-哌嗪-1-甲酸叔丁酯

[0918]



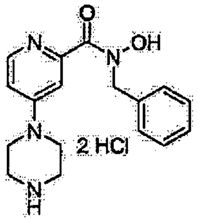
[0919]　根据一般程序 I、使用 N-BOC 哌嗪获得该化合物。分离出期望的化合物，为黄色泡沫状物。

[0920]　MS：413.3

[0921]　实施例 103：

[0922]　4-哌嗪-1-基-吡啶-2-甲酸苄基-羟基-酰胺盐酸盐

[0923]



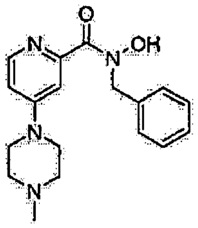
[0924]　根据一般程序 G、使用实施例 102 中描述的 4-[2-(苄基-羟基-氨基甲酰基)-吡啶-4-基]-哌嗪-1-甲酸叔丁酯获得该化合物。分离出期望的化合物，为黄色泡沫状物。

[0925]　MS：313.2

[0926]　实施例 104：

[0927]　4-(4-甲基-哌嗪-1-基)-吡啶-2-甲酸苄基-羟基-酰胺

[0928]



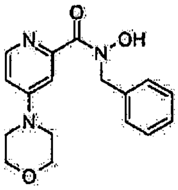
[0929]　根据一般程序 I、使用 N-甲基哌嗪获得该化合物。分离出期望的化合物，为黄色油状物。

[0930]　MS：327.2

[0931]　实施例 105：

[0932]　4-吗啉-4-基-吡啶-2-甲酸苄基-羟基-酰胺

[0933]



[0934]　根据一般程序 I、使用吗啉获得该化合物。分离出期望的化合物，为浅黄色粉末。

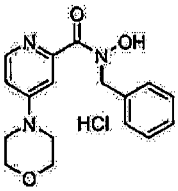
[0935]　MS：314.1

[0936]　Mp：105C-110℃

[0937]　实施例 106：

[0938]　4-吗啉-4-基-吡啶-2-甲酸苄基-羟基-酰胺盐酸盐

[0939]

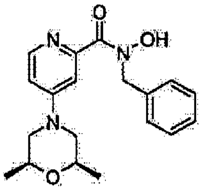


[0940]　将实施例 105 中描述的 4-吗啉-4-基-吡啶-2-甲酸苄基-羟基-酰胺溶解于二氯甲烷（10mL）中，加入 2M 氯化氢在乙醚（1.2 当量）中的溶液。将混合物在室温搅拌 3h，蒸发至干，得到期望的化合物，为浅黄色粉末。

[0941]　实施例 107：

[0942]　4-((2R,6S)-2,6-二甲基-吗啉-4-基)-吡啶-2-甲酸苄基-羟基-酰胺

[0943]



[0944]　根据一般程序 I、使用（2R,6S)-2,6-二甲基-吗啉获得该化合物。分离出期望的化合物，为橙色粉末。

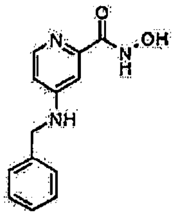
[0945]　MS：342.2

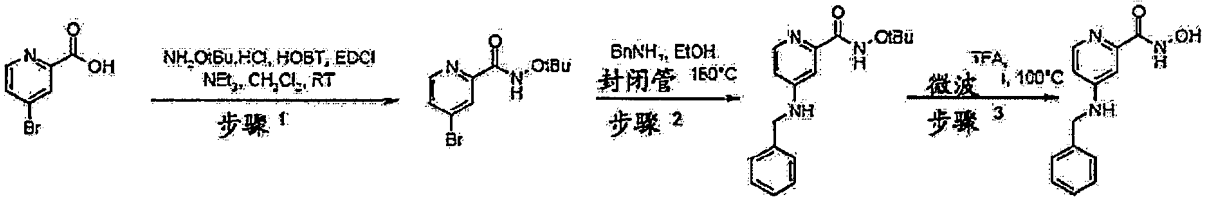
[0946]　Mp：180℃-185℃

[0947]　实施例 108：

[0948]　4-苄基氨基-吡啶-2-甲酸羟基酰胺

[0949]





[0950] 步骤 1：

[0951] 向 4-溴-吡啶-2-甲酸（1.0g，4.9mmol，1 当量）在二氯甲烷（40mL）中的溶液加入 HOBT（1.3g，9.9mmol，2 当量）、EDCI（1.9g，9.9mmol，2 当量）、三乙胺（2.1mL，14.8mmol，3 当量）和 O-叔丁基羟胺盐酸盐（1.2g，9.9mmol，2 当量）。将混合物在室温搅拌 18h，倒入水（20mL）中。将有机层用二氯甲烷萃取（3x20mL），经硫酸镁干燥，过滤，真空蒸发。将粗残余物通过快速色谱法、使用环己烷和乙酸乙酯（100 / 0 至 50 / 50）纯化，得到 4-溴-吡啶-2-甲酸叔丁氧基-酰胺，为白色粉末（1.0g，74%收率）。

[0952] 步骤 2：

[0953] 在密闭管中，将 4-溴-吡啶-2-甲酸叔丁氧基-酰胺（410mg，1.5mmol，1 当量）溶解于乙醇（10mL）中，加入苄基胺（161mg，3mmol，2 当量）。将混合物在 180℃加热 20h。冷却后，将混合物吸附在硅胶上，通过快速色谱法、使用环己烷和乙酸乙酯（100 / 0 至 0 / 100）纯化，得到 4-苄基氨基-吡啶-2-甲酸叔丁氧基-酰胺，为无色油状物（57mg，13%收率）。

[0954] 步骤 3：

[0955]

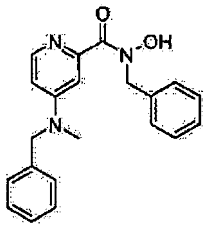
[0956] 将 4-苄基氨基-吡啶-2-甲酸叔丁氧基-酰胺（57mg，0.19mmol，1 当量）和三氟乙酸（3mL）在微波辐射下于 100℃加热 10min。冷却后，将混合物蒸发至干。将残余物溶解于二氯甲烷（5mL）中，加入数滴氢氧化铵溶液。将混合物吸附在硅胶上，通过快速色谱法、使用二氯甲烷和甲醇（100 / 0 至 85 / 15）纯化，得到期望的化合物，为无色油状物（15mg，32%收率）。

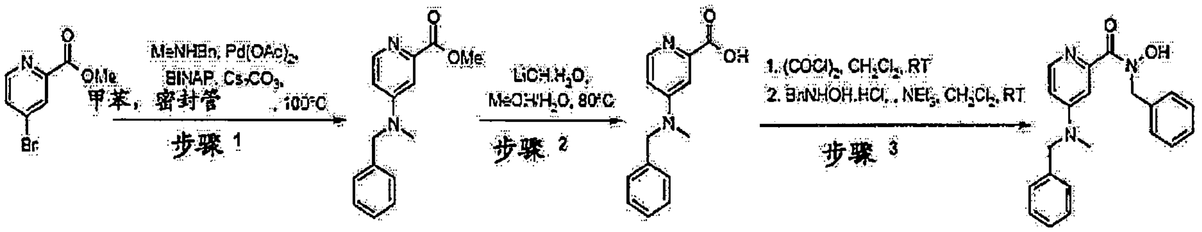
[0957] MS：244.1

[0958] 实施例 109：

[0959] 4-（苄基-甲基-氨基）-吡啶-2-甲酸苄基-羟基-酰胺

[0960]





[0961] 步骤 1 :

[0962] 向脱气的 4- 溴 - 吡啶 -2- 甲酸甲酯 (650mg,3.0mmol,1 当量) 在甲苯 (15mL) 中的溶液加入碳酸铯 (1.9g,6.0mmol,2 当量)、N- 甲基苄基胺 (0.5mL,3.9mmol,1.3 当量)、BINAP(93mg,0.15mmol,0.05 当量) 和乙酸钯 (34mg,0.15mmol,0.05 当量)。将混合物在密封管中于 100℃加热 20h。冷却后,将混合物倒入水 (10mL) 中,用乙酸乙酯萃取 (3x10mL)。有机层经硫酸镁干燥,过滤,真空蒸发。将粗残余物通过快速色谱法、使用二氯甲烷和甲醇 (100 / 0 至 97 / 3) 纯化,得到 4-(苄基 - 甲基 - 氨基)- 吡啶 -2- 甲酸甲酯,为黄色油状物 (230mg,30%收率)。

[0963] 步骤 2 :

[0964] 将 4-(苄基 - 甲基 - 氨基)- 吡啶 -2- 甲酸甲酯 (230mg,0.9mmol,1 当量) 溶解于甲醇 / 水 (6mL / 1mL) 的混合物中,加入氢氧化锂 (75mg,1.8mmol,2 当量)。将混合物在 80℃加热 3h。冷却后,加入 1M 氯化氢在乙醚中的溶液 (1.8mL,1.8mmol,2 当量)。然后将混合物蒸发至干,得到定量收率的 4-(苄基 - 甲基 - 氨基)- 吡啶 -2- 甲酸。

[0965] 步骤 3 :

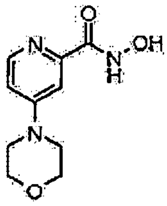
[0966] 将草酰氯 (0.12mL,1.3mmol,1.5 当量) 滴加至 4-(苄基 - 甲基 - 氨基)- 吡定 -2- 甲酸 (0.9mmol,1 当量) 在二氯甲烷 (10mL) 中的溶液。将混合物在室温搅拌 15min,蒸发至干。将残余物稀释于二氯甲烷 (10mL) 中,加入三乙胺 (0.38mL,2.7mmol,3 当量) 和 N- 苄基羟胺盐酸盐 (215mg,1.3mmol,1.5 当量)。在室温搅拌 20h 后,将混合物吸附在硅胶上,使用环己烷和乙酸乙酯 (100 / 0 至 40 / 60) 纯化。获得期望的化合物,为黄色油状物 (85mg,27%收率)。

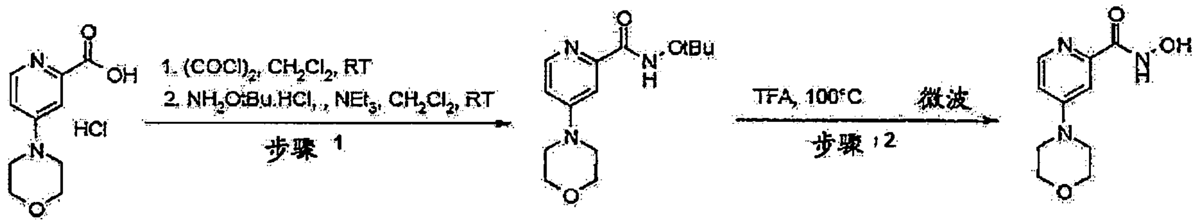
[0967] MS :348.2

[0968] 实施例 110 :

[0969] 4- 吗啉 -4- 基 - 吡啶 -2- 甲酸羟基酰胺

[0970]





[0971] 步骤 1：

[0972] 将草酰氯（0.11mL，1.3mmol，1.3 当量）滴加 4- 吗啉 -4- 基 - 吡定 -2- 甲酸盐酸盐（240mg，1.0mmol，1 当量）在二氯甲烷（10mL）中的溶液 - 在 0℃，滴加二甲基甲酰胺（2-3 滴），将混合物在室温搅拌 15min，蒸发至干。将残余物稀释于二氯甲烷（10mL）和三乙胺（0.41mL，2.9mmol，3 当量）中，加入 O- 叔丁基羟胺盐酸盐（185mg，1.5mmol，1.5 当量）。在室温搅拌 20h 后，将混合物吸附在硅胶上，使用环己烷和乙酸乙酯（100 / 0 至 0 / 100）纯化。获得 4- 吗啉 -4- 基 - 吡啶 -2- 甲酸叔丁氧基 - 酰胺，为白色粉末（110mg，40％收率）。

[0973] 步骤 2：

[0974] 将 4- 吗啉 -4- 基 - 吡啶 -2- 甲酸叔丁氧基 - 酰胺（110mg，0.4mmol，1 当量）和三氟乙酸（3mL）在微波辐射下于 100℃加热 10min。冷却后，将混合物蒸发至干。将残余物溶解于二氯甲烷（5mL）中，加入数滴氢氧化铵溶液。将混合物吸附在硅胶上，通过快速色谱法、使用二氯甲烷和甲醇（100 / 0 至 90 / 10）纯化，得到期望的化合物，为米色粉末（12mg，14％收率）。

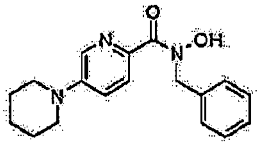
[0975] MS：224.1

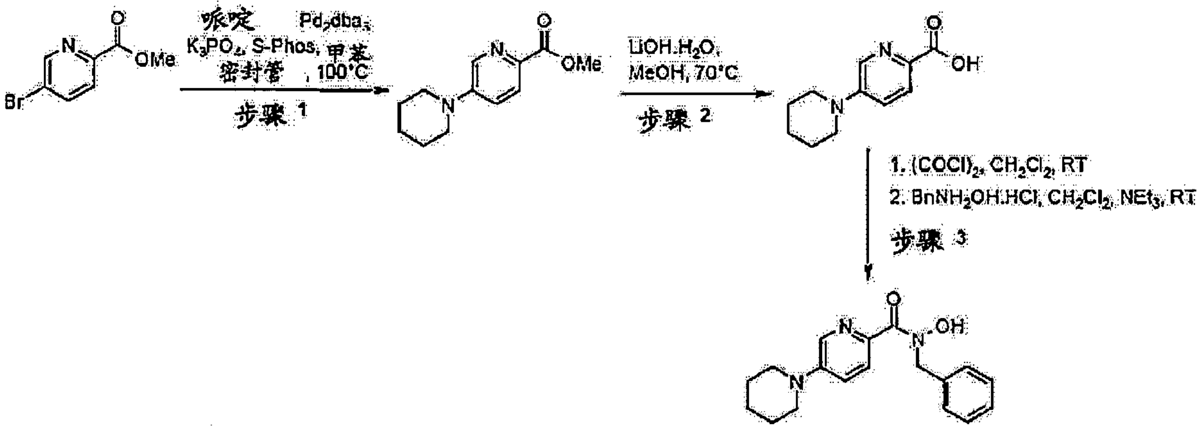
[0976] Mp：215℃ -220℃（度）

[0977] 实施例 111：

[0978] 3,4,5,6- 四氢 -2H-[1,3′] 联吡啶基 -6′ - 甲酸苄基 - 羟基 - 酰胺

[0979]





[0980] 步骤1：

[0981] 向脱气的5-溴-吡啶-2-甲酸甲酯(450mg,2.1mmol,1当量)在甲苯(10mL)中的溶液加入哌啶(213mg,2.5mmol,1.2当量)、磷酸钾(618mg,2.9mmol,1.4当量)、2-二环己基膦基-2′,6′-二甲氧基联苯(171mg,0.42mmol,0.2当量)和三(二苄叉丙酮)二钯(95mg,0.10mmol,0.05当量)。将混合物在密封管中于100℃加热48h。冷却后,将混合物倒入水(5mL),用乙酸乙酯萃取(3x10mL)。有机层经硫酸镁干燥,过滤,真空蒸发。将粗残余物通过快速色谱法、使用环己烷和乙酸乙酯(100/0至0/100)纯化,得到3,4,5,6-四氢-2H-[1,3′]联吡啶基-6′-甲酸甲酯,为浅黄色粉末(165mg,36%收率)。

[0982] 步骤2：

[0983] 将3,4,5,6-四氢-2H-[1,3′]联吡啶基-6′-甲酸甲酯(165mg,0.75mmol,1当量)溶解于甲醇(8mL)中,加入氢氧化锂(63mg,1.5mmol,2当量)。将混合物在70℃加热20h。冷却后,加入3N氯化氢溶液(0.2mL)。然后将混合物蒸发至干,得到定量收率的3,4,5,6-四氢-2H-[1,3′]联吡啶基-6′-甲酸,为黄色油状物。

[0984] 步骤3：

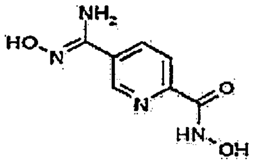
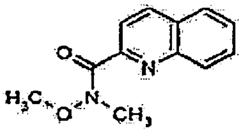
[0985] 将草酰氯(0.1mL,1.12mmol,1.5当量)滴加至3,4,5,6-四氢-2H-[1,3′]联吡啶基-6′-甲酸(0.75mmol,1当量)在二氯甲烷(6mL)中的溶液。将混合物在室温搅拌15min,蒸发至干。将残余物稀释于二氯甲烷(6mL)中,加入三乙胺(0.31mL,2.25mmol,3当量)和N-苄基羟胺盐酸盐(179mg,1.12mmol,1.5当量)。在室温搅拌20h后,将混合物吸附在硅胶上,使用环己烷和乙酸乙酯(100/0至30/70)纯化。获得期望的化合物,为浅黄色粉末(125mg,54%收率)。

[0986] MS：312.2

[0987] Mp：110℃-115℃

[0988] 具有通式(I)的化合物的活性数据

[0989]

分子结构	活性类型	活性终点	活性浓度	活性结果
	FRET	IC50 [μM]		20
	CPE H3N2	减少 (%)	50	-4,8
	FRET	IC50 [μM]		
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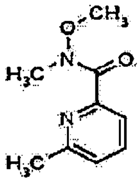
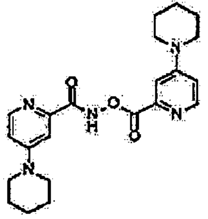
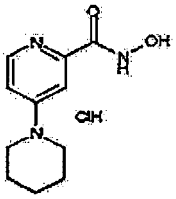
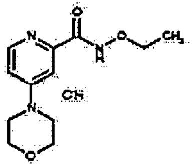
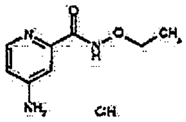
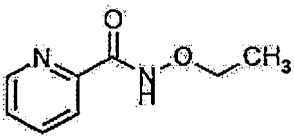
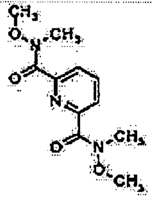
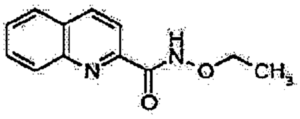
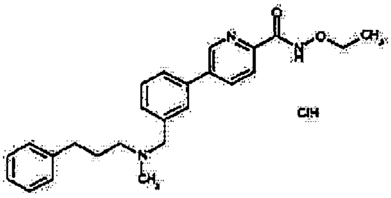
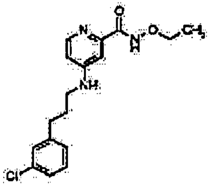
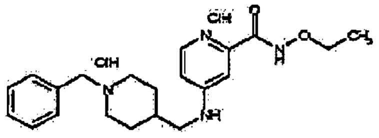
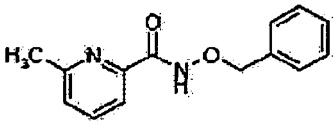
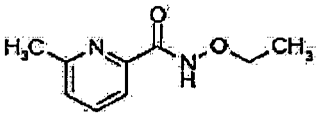
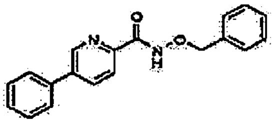
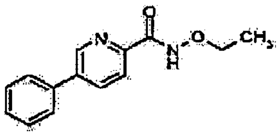
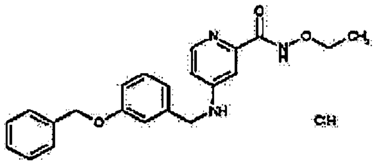
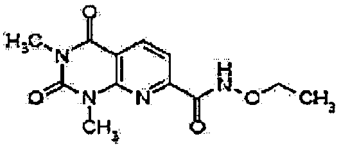
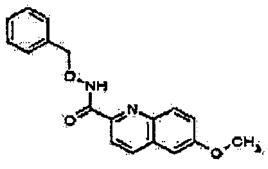
	CPE H3N2	减少 (%)	50	-0,9
	CPE H3N2	减少 (%)	50	29
	CPE H3N2	IC50 [μM]		37
	FRET	IC50 [μM]		4,9
	CPE H3N2	减少 (%)	5	-4,1
	FRET	IC50 [μM]		
	CPE H3N2	减少 (%)	50	1,3

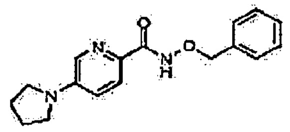
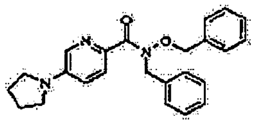
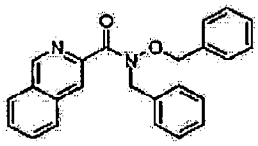
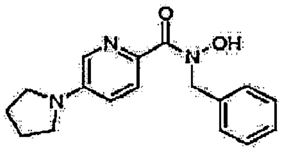
[0990]

分子结构	活性类型	活性终点	活性浓度	活性结果
	CPE H3N2	减少 (%)	50	10,5
	CPE H3N2	减少 (%)	50	12,5
	CPE H3N2	减少 (%)	50	-0,3
	CPE H3N2	减少 (%)	50	-2,2
	CPE H3N2	减少 (%)	20	1,6
	CPE H3N2	减少 (%)	1	-0,3

[0991]

分子结构	活性类型	活性终点	活性浓度	活性结果
	CPE H3N2	减少 (%)	50	14,8
	CPE H3N2	减少 (%)	50	-2,7
	CPE H3N2	减少 (%)	50	-2,1
	CPE H3N2	减少 (%)	2	-4
	CPE H3N2	减少 (%)	5	-3
	CPE H3N2	减少 (%)	1	1,2
	CPE H3N2	减少 (%)	50	-0,4
	CPE H3N2	减少 (%)	50	-1,9

[0992]

分子结构	活性类型	活性终点	活性浓度	活性结果
	CPE H3N2	减少 (%)	20	-8,7
	CPE H3N2	减少 (%)	5	-2,7
	CPE H3N2	减少 (%)	5	1,3
	CPE H3N2	减少 (%)	25	1
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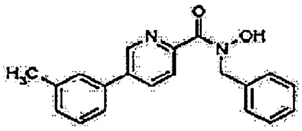
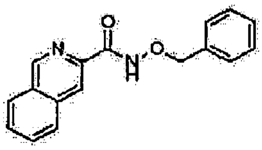
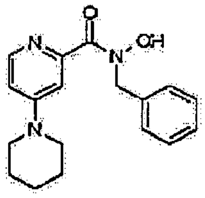
	CPE H3N2	减少 (%)	10	15,5
	CPE H3N2	减少 (%)	5	-1,5
	CPE H3N2	减少 (%)	5	1,1
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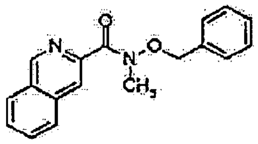
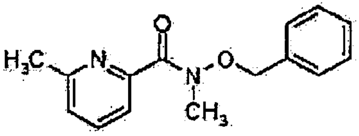
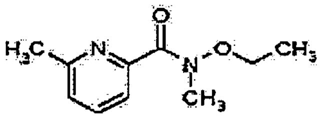
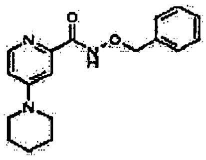
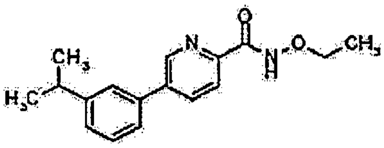
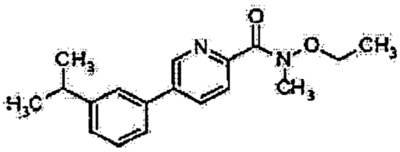
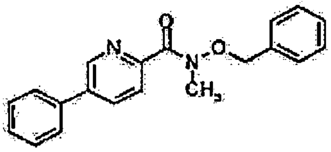
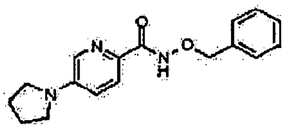
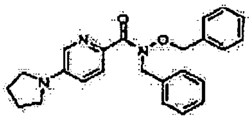
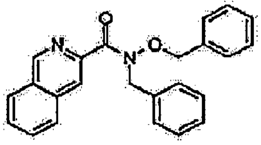
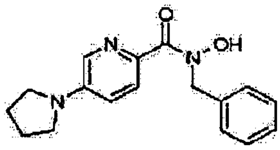
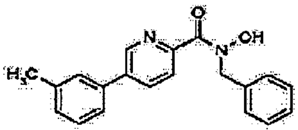
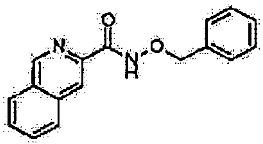
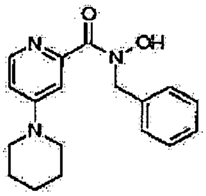
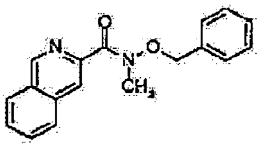
	CPE H3N2	减少 (%)	50	0,6

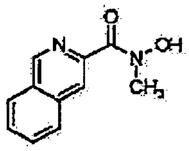
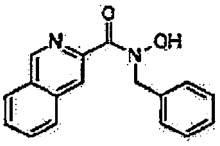
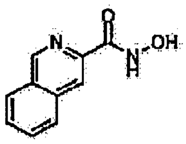
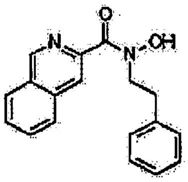
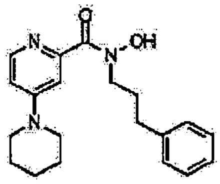
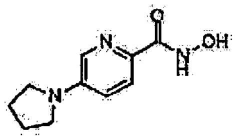
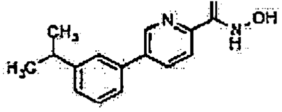
[0993]

分子结构	活性类型	活性终点	活性浓度	活性结果
	CPE H3N2	减少 (%)	50	-2,3
	CPE H3N2	减少 (%)	50	-1,9
	CPE H3N2	减少 (%)	5	1
	CPE H3N2	减少 (%)	5	
	CPE H3N2	减少 (%)	5	
	CPE H3N2	减少 (%)	50	-2,6

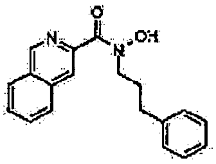
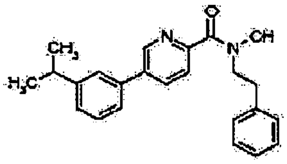
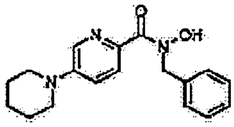
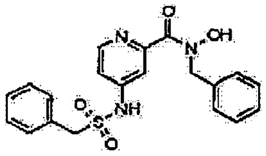
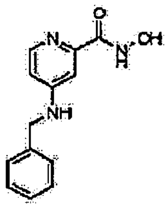
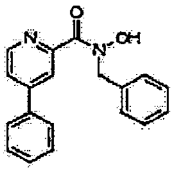
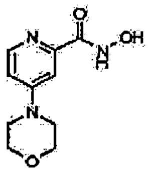
[0994]

分子结构	活性类型	活性终点	活性浓度	活性结果
	CPE H3N2	减少 (%)	20	-8,7
	CPE H3N2	减少 (%)	5	-2,7
	CPE H3N2	减少 (%)	5	1,3
	CPE H3N2	减少 (%)	25	1
	FRET	IC50 [μM]		4,3
	CPE H3N2	减少 (%)	10	15,5
	CPE H3N2	减少 (%)	5	-1,5
	CPE H3N2	减少 (%)	5	1,1
	FRET	IC50 [μM]		1,4
	FRET	IC50 [μM]		1,45
	CPE H3N2	减少 (%)	50	0,6

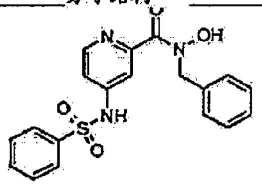
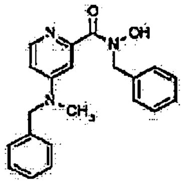
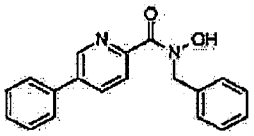
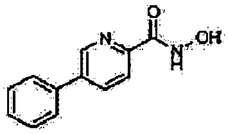
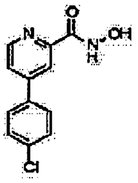
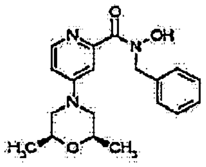
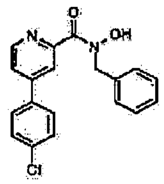
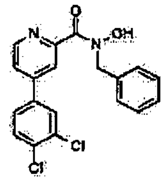
[0995]

分子结构	活性类型	活性终点	活性浓度	活性结果
	CPE H3N2	减少 (%)	50	-0,6
	FRET	IC50 [μM]		9,09
	CPE H3N2	减少 (%)	50	34,2
	FRET	IC50 [μM]		19
	FRET	IC50 [μM]		14,7
	CPE H3N2	减少 (%)	50	94,3
	FRET	IC50 [μM]		16
	CPE H3N2	IC50 [μM]		45
	CPE H3N2	减少 (%)	20	-1,8
	CPE H3N2	减少 (%)	2	7,7
	FRET	IC50 [μM]		6,25
	CPE H3N2	减少 (%)	50	-4,3
	FRET	IC50 [μM]		5.4
	CPE H3N2	减少 (%)	2	-2,1

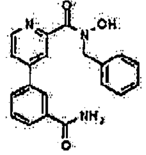
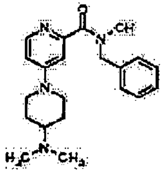
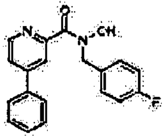
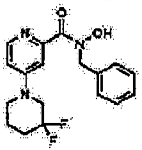
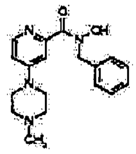
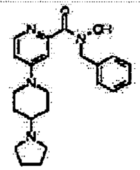
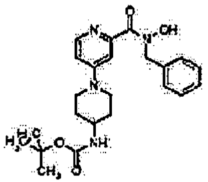
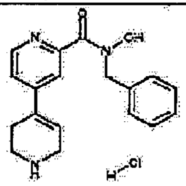
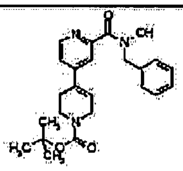
[0996]

分子结构	活性类型	活性终点	活性浓度	活性结果
	CPE H3N2	减少 (%)	2	4,4
	CPE H3N2	减少 (%)	2	2,1
	FRET	IC50 [µM]		9,4
	CPE H3N2	减少 (%)	5	-3,4
	FRET	IC50 [µM]		10,1
	FRET	IC50 [µM]		1,7
	CPE H3N2	减少 (%)	50	6,2
	FRET	IC50 [µM]		3,9
	FRET	IC50 [µM]		6,4
	CPE H3N2	减少 (%)	5	-0,5
	FRET	IC50 [µM]		3,1
	CPE H3N2	减少 (%)	10	-9,3
	FRET	IC50 [µM]		5,94
	FRET	IC50 [µM]		7,1
	CPE H3N2	减少 (%)	50	-7,1

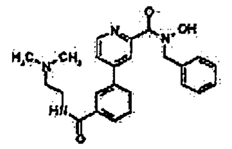
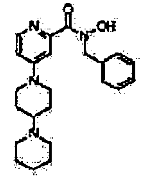
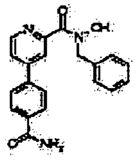
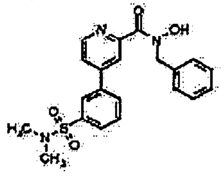
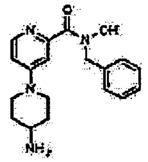
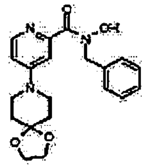
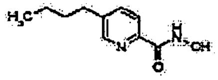
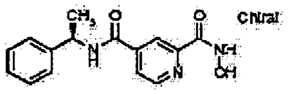
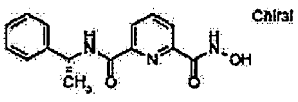
[0997]

分子结构	活性类型	活性终点	活性浓度	活性结果
	FRET	IC50 [μM]		10
	CPE H3N2	减少 (%)	50	-5,2
	FRET	IC50 [μM]		1,2
	CPE H3N2	减少 (%)	5	3,8
	CPE H3N2	减少 (%)	12	13,4
	FRET	IC50 [μM]		22
	CPE H3N2	减少 (%)	12	21,7
	FRET	IC50 [μM]		2,6
	CPE H3N2	减少 (%)	5	26,6
	FRET	IC50 [μM]		2,9
	CPE H3N2	减少 (%)	50	10,5
	FRET	IC50 [μM]		1,2
	CPE H3N2	减少 (%)	2	-6,7
	FRET	IC50 [μM]		0,91
	CPE H3N2	减少 (%)	5	8,1

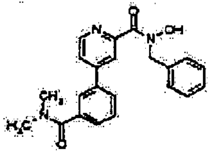
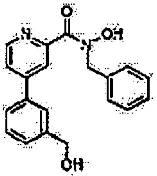
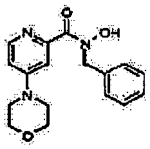
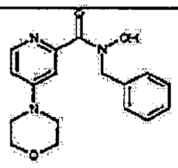
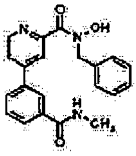
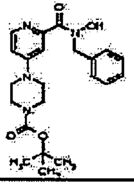
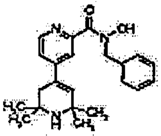
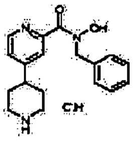
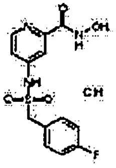
[0998]

分子结构	活性类型	活性终点	活性浓度	活性结果
	FRET	IC50 [µM]		2
	CPE H3N2	减少 (%)	5	-2,7
	FRET	IC50 [µM]		32
	CPE H3N2	减少 (%)	50	12,3
	FRET	IC50 [µM]		0,6
	CPE H3N2	减少 (%)	1	-3,2
	FRET	IC50 [µM]		1,2
	CPE H3N2	减少 (%)	50	8,9
	FRET	IC50 [µM]		4,6
	CPE H3N2	减少 (%)	50	2,4
	CPE H3N2	减少 (%)	50	10,7
	CPE H3N2	减少 (%)	50	8,3
	FRET	IC50 [µM]		0,33
	CPE H3N2	减少 (%)	50	0,4
	CPE H3N2	减少 (%)	5	1,2

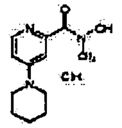
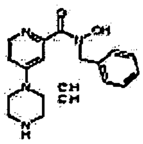
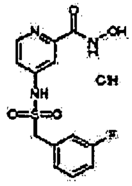
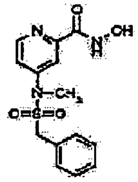
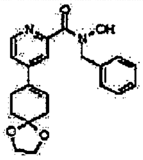
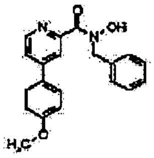
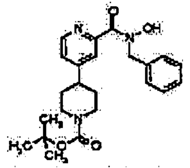
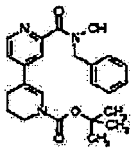
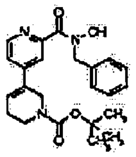
[0999]

分子结构	活性类型	活性终点	活性浓度	活性结果
	FRET	IC50 [μM]		3,2
	CPE H3N2	减少 (%)	50	8.9
	CPE H3N2	减少 (%)	50	18,8
	FRET	IC50 [μM]		1
	CPE H3N2	减少 (%)	5	-2,5
	FRET	IC50 [μM]		5,8
	CPE H3N2	减少 (%)	5	-1.8
	FRET	IC50 [μM]		39
	CPE H3N2	减少 (%)	50	3,2
	FRET	IC50 [μM]		0,51
	CPE H3N2	减少 (%)	50	8,5
	FRET	IC50 [μM]		15
	FRET	IC50 [μM]		13
	FRET	IC50 [μM]		121

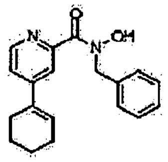
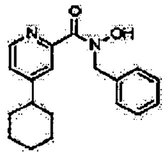
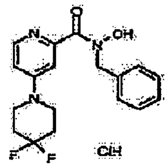
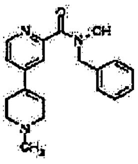
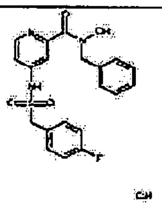
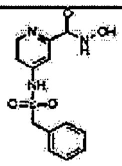
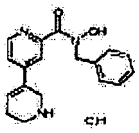
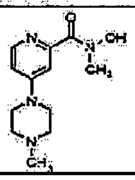
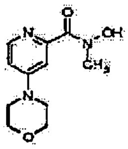
[1000]

分子结构	活性类型	活性终点	活性浓度	活性结果
	CPE H3N2	减少 (%)	50	5,3
	CPE H3N2	减少 (%)	5	7,7
	FRET	IC50 [μM]		2,6
	CPE H3N2	减少 (%)	50	-3,4
	FRET	IC50 [μM]		2,3
 CH	CPE H3N2	减少 (%)	50	6,3
	FRET	IC50 [μM]		1,9
	CPE H3N2	减少 (%)	5	-7,5
	FRET	IC50 [μM]		3,2
	CPE H3N2	减少 (%)	50	34
	CPE H3N2	减少 (%)	50	2,8
	FRET	IC50 [μM]		2,3
	CPE H3N2	减少 (%)	50	-1,4
	FRET	IC50 [μM]		0,73
	CPE H3N2	减少 (%)	50	-1,4

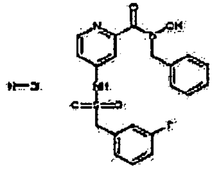
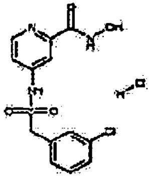
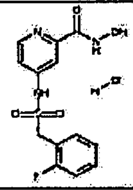
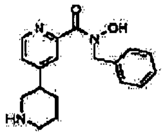
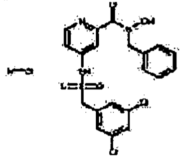
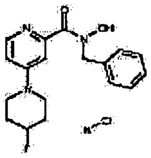
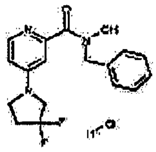
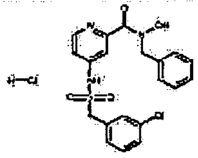
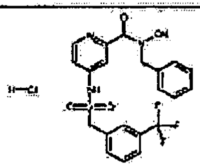
[1001]

分子结构	活性类型	活性终点	活性浓度	活性结果
	CPE H3N2	减少 (%)	50	-0,9
	FRET	IC50 [μM]		3,5
	CPE H3N2	减少 (%)	50	-4,5
	FRET	IC50 [μM]		0,87
	CPE H3N2	减少 (%)	50	-2,4
	FRET	IC50 [μM]		32
	CPE H3N2	减少 (%)	5	-1,7
	FRET	IC50 [μM]		2
	CPE H3N2	减少 (%)	50	5,4
	FRET	IC50 [μM]		2,4
	CPE H3N2	减少 (%)	2	-2,5
	CPE H3N2	减少 (%)	20	31,3
	CPE H3N2	减少 (%)	2	3,9
	CPE H3N2	减少 (%)	5	10,2

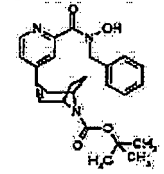
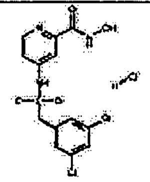
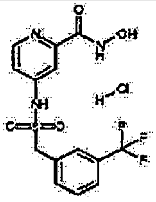
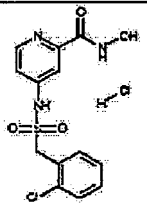
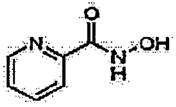
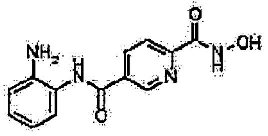
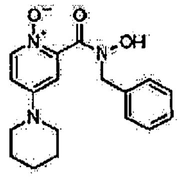
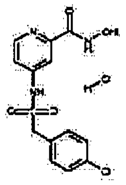
[1002]

分子结构	活性类型	活性终点	活性浓度	活性结果
	FRET	IC50 [μM]		3,6
	CPE H3N2	减少 (%)	1	3,4
	FRET	IC50 [μM]		3
	CPE H3N2	减少 (%)	5	-0,5
	FRET	IC50 [μM]		2,9
	CPE H3N2	减少 (%)	50	-3,2
	FRET	IC50 [μM]		7,7
	CPE H3N2	减少 (%)	50	10,6
	FRET	IC50 [μM]		2
	CPE H3N2	减少 (%)	50	-1,1
	FRET	IC50 [μM]		3
	CPE H3N2	减少 (%)	50	5,1
	CPE H3N2	减少 (%)	50	9,5
	CPE H3N2	减少 (%)	50	2,6
	CPE H3N2	减少 (%)	50	5,7

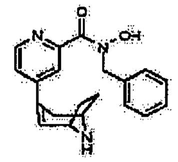
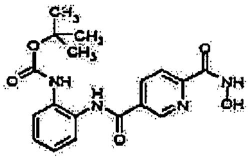
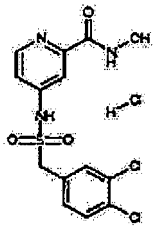
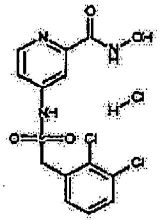
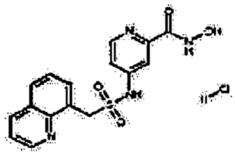
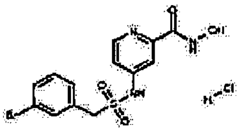
[1003]

分子结构	活性类型	活性终点	活性浓度	活性结果
	FRET	IC50 [μM]		1,9
	CPE H3N2	减少 (%)	50	8,6
	FRET	IC50 [μM]		0,2
	CPE H3N2	减少 (%)	50	5,9
	FRET	IC50 [μM]		0,76
	CPE H3N2	减少 (%)	50	-0,5
	CPE H3N2	减少 (%)	50	6,1
	FRET	IC50 [μM]		0,4
	CPE H3N2	减少 (%)	20	26,9
	FRET	IC50 [μM]		2,2
	CPE H3N2	减少 (%)	50	34
	FRET	IC50 [μM]		1,8
	CPE H3N2	减少 (%)	20	4,6
	FRET	IC50 [μM]		0,33
	CPE H3N2	减少 (%)	50	9,5
	FRET	IC50 [μM]		2
	CPE H3N2	减少 (%)	50	22,4

[1004]

分子结构	活性类型	活性终点	活性浓度	活性结果
	CPE H3N2	减少 (%)	2	-5,3
	FRET	IC50 [μM]		0,59
	CPE H3N2	减少 (%)	50	9,3
	FRET	IC50 [μM]		1,8
	CPE H3N2	减少 (%)	50	-5,6
	FRET	IC50 [μM]		0,83
	CPE H3N2	减少 (%)	50	1,5
	FRET	IC50 [μM]		75
	CPE H3N2	减少 (%)	50	3,15
	CPE H3N2	减少 (%)	50	-5,53
	FRET	IC50 [μM]		23
	CPE H3N2	减少 (%)	5	-1,83
	FRET	IC50 [μM]		1,1
	CPE H3N2	减少 (%)	50	-3,98

[1005]

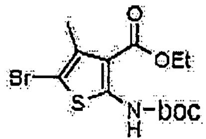
分子结构	活性类型	活性终点	活性浓度	活性结果
	FRET	IC50 [μM]		3,5
	CPE H3N2	减少 (%)	50	5,49
	FRET	IC50 [μM]		
	FRET	IC50 [μM]		3,2
	CPE H3N2	减少 (%)	50	53,43
	FRET	IC50 [μM]		2
	CPE H3N2	IC50 [μM]		
	CPE H3N2	减少 (%)	50	60,07
	CPE H3N2	reduction (%)	50	24,39
	CPE H3N2	IC50 [μM]		78
	FRET	IC50 [μM]		0,28
	CPE H3N2	减少 (%)	50	2,29
	FRET	IC50 [μM]		1.8

[1006] 具有通式(II)的化合物

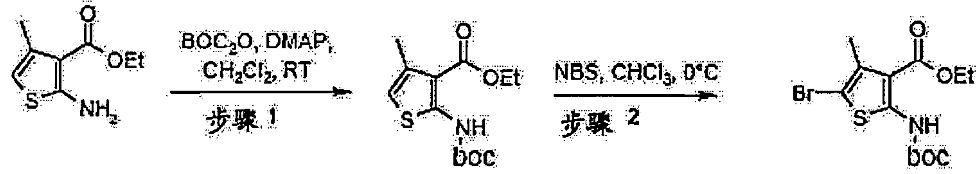
[1007] 关键中间体 I

[1008] 5-溴-2-叔丁氧基羰基氨基-4-甲基-噻吩-3-甲酸乙酯

[1009]



关键中间体 I



[1010] 步骤 1：

[1011] 向 2- 氨基 -4- 甲基 - 噻吩 -3- 甲酸乙酯 (25.0g,135mmol,1 当量) 在二氯甲烷 (80mL) 中的溶液加入二碳酸二叔丁酯 (48.0g,220mmol,1.6 当量) 和 4- 二甲氨基吡啶 (1.6g,13.5mmol,0.1 当量)。将混合物在室温搅拌直至反应完成。然后蒸发溶剂，将残余物通过快速色谱法、使用环己烷和乙酸乙酯 (100 / 0 至 90 / 10) 纯化，得到 2- 叔丁氧基羰基氨基 -4- 甲基 - 噻吩 -3- 甲酸乙酯，为白色固体 (18.8g,49％收率)。

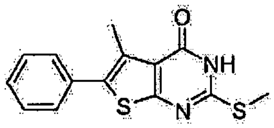
[1012] 步骤 2：

[1013] 在 0℃，向 2- 叔丁氧基羰基氨基 -4- 甲基 - 噻吩 -3- 甲酸乙酯 (10.2g,35.9mmol,1 当量) 在氯仿 (40mL) 中的溶液加入 N- 溴琥珀酰亚胺 (6.4g,35.9mmol,1 当量)。将混合物在 0℃搅拌 2h，蒸发溶剂。将残余物通过快速色谱法、使用环己烷和乙酸乙酯 (100 / 0 至 70 / 30) 纯化，得到期望的化合物，为白色固体 (11.9g,91％收率)。

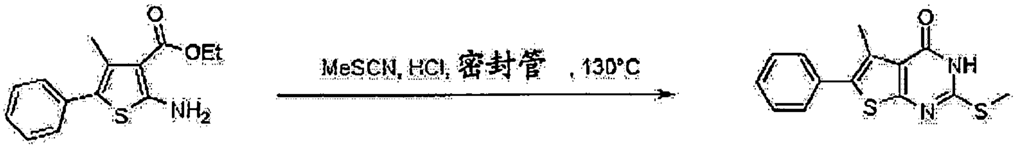
[1014] 关键中间体 II

[1015] 5- 甲基 -2- 甲基硫基 -6- 苯基 -3H- 噻吩并 [2,3-d] 嘧啶 -4- 酮

[1016]



关键中间体 II

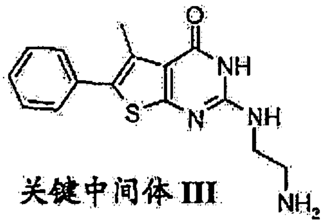


[1017] 将 2- 氨基 -4- 甲基 -5- 苯基 - 噻吩 -3- 甲酸乙酯 (10.0g,38.3mmol,1 当量)、硫氰酸甲酯 (2.8g,38.3mmol,1 当量) 和浓盐酸 (1.4mL,38.3mmol,1 当量) 在密封管中于 130℃加热 18h。冷却后，过滤沉淀，用乙醇漂洗，干燥，得到期望的化合物，为黄色固体 (7.7g,70％收率)。

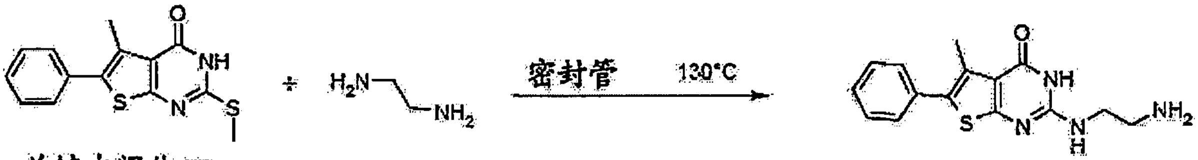
[1018] 关键中间体 III

[1019] 2-(2- 氨基 - 乙基氨基)-5- 甲基 -6- 苯基 -3H- 噻吩并 [2,3-d] 嘧啶 -4- 酮

[1020]



关键中间体 III



关键中间体 II

[1021]　将 5- 甲基 -2- 甲基硫基 -6- 苯基 -3H- 噻吩并 [2,3-d] 嘧啶 -4- 酮 (关键中间体 II)(1.2g,4.2mmol,1 当量) 溶解于乙二胺 (3mL) 中，将溶液在密封管中于 130℃加热 18h。冷却后，过滤黄色悬液。将沉淀用二氯甲烷和乙醚漂洗，真空干燥，得到期望的化合物，为白色粉末 (550mg,44％收率)。

[1022]　一般程序 A

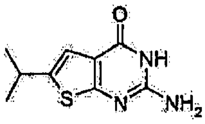
[1023]

[1024]　在 0℃，将氰胺 (1.0mmol,1.5 当量) 加入至 2M 氯化氢在乙醚中的溶液 (1.0mL,3 当量)。搅拌 15min 后，过滤悬液。将所得白色固体在密封管中加至 2- 氨基 - 噻吩 -3- 甲酸乙酯 (0.7mmol,1 当量) 和二甲基砜 (250mg)。将混合物在 130℃加热 2h。冷却后，将残余物溶解于甲醇中，加入 7N 氨在甲醇中的溶液 (10mL)。然后蒸发溶剂，将所得固体用二氯甲烷 (2x10mL) 和水 (2x10mL) 洗涤，得到期望的化合物 (5％至 90％收率)。

[1025]　实施例 1：

[1026]　2- 氨基 -6- 异丙基 -3H- 噻吩并 [2,3-d] 嘧啶 -4- 酮

[1027]



[1028]　根据一般程序 A、使用市售可得的 2- 氨基 -5- 异丙基 - 噻吩 -3- 甲酸甲酯获得期望的化合物。分离出期望的化合物，为米色粉末。

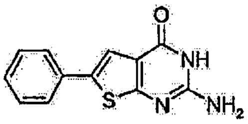
[1029]　MS :210.0

[1030]　Mp :347℃ -349℃

[1031]　实施例 2 :

[1032]　2- 氨基 -6- 苯基 -3H- 噻吩并 [2,3-d] 嘧啶 -4- 酮

[1033]



[1034] 根据一般程序 A、使用市售可得的 2- 氨基 -5- 苯基 - 噻吩 -3- 甲酸甲酯获得期望的化合物。分离出期望的化合物，为灰色固体。

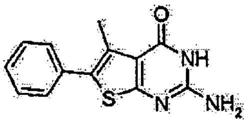
[1035] MS：244.0

[1036] Mp>360℃

[1037] 实施例 3：

[1038] 2- 氨基 -5- 甲基 -6- 苯基 -3H- 噻吩并 [2,3-d] 嘧啶 -4- 酮

[1039]



[1040] 根据一般程序 A、使用市售可得的 2- 氨基 -4- 甲基 -5- 苯基 - 噻吩 -3- 甲酸乙酯获得期望的化合物。分离出期望的化合物，为米色粉末。

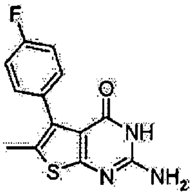
[1041] MS：258.1

[1042] Mp：356℃ -358℃

[1043] 实施例 4：

[1044] 2- 氨基 -5-(4- 氟 - 苯基)-6- 甲基 -3H- 噻吩并 [2,3-d] 嘧啶 -4- 酮

[1045]



[1046] 根据一般程序 A、使用市售可得的 2- 氨基 -4-(4- 氟 - 苯基)-5- 甲基 - 噻吩 -3- 甲酸甲酯获得期望的化合物。分离出期望的化合物，为灰色固体。

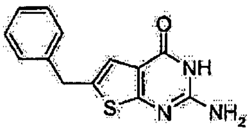
[1047] MS：276.1

[1048] Mp：360℃ -362℃

[1049] 实施例 5：

[1050] 2- 氨基 -6- 苄基 -3H- 噻吩并 [2,3-d] 嘧定 -4- 酮

[1051]



[1052] 根据一般程序 A、使用市售可得的 2- 氨基 -5- 苄基 - 噻吩 -3- 甲酸乙酯获得期望的化合物。分离出期望的化合物，为绿色固体。

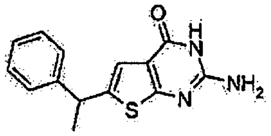
[1053] MS：258.1

[1054] Mp：294℃ -296℃

[1055] 实施例 6：

[1056] 2- 氨基 -6-(1- 苯基 - 乙基)-3H- 噻吩并 [2,3-d] 嘧啶 -4- 酮

[1057]



[1058] 根据一般程序 A、使用市售可得的 2- 氨基 -5-(1- 苯基 - 乙基)- 噻吩 -3- 甲酸甲酯获得期望的化合物。分离出期望的化合物，为灰色粉末。

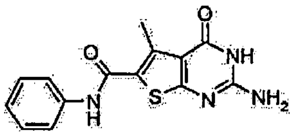
[1059] MS：272.0

[1060] Mp：260℃ -270℃

[1061] <u>实施例 7：</u>

[1062] 2- 氨基 -5- 甲基 -4- 氧代 -3,4- 二氢 - 噻吩并 [2,3-d] 嘧啶 -6- 甲酸苯基酰胺

[1063]



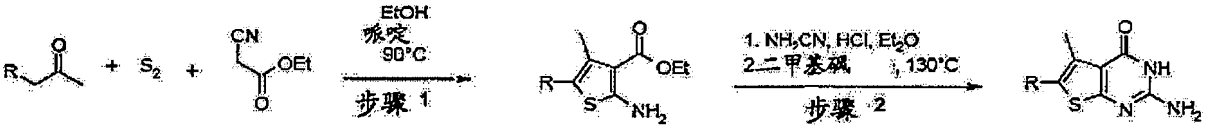
[1064] 根据一般程序 A、使用市售可得的 2- 氨基 -4- 甲基 -5- 苯基氨基甲酰基 - 噻吩 -3- 甲酸乙酯获得期望的化合物。分离出期望的化合物，为黄色粉末。

[1065] MS：301.0

[1066] Mp：在 290℃ -296℃分解

[1067] <u>一般程序 B</u>

[1068]



[1069] <u>步骤 1：</u>

[1070] 将丙 -2- 酮 (28.0mmol，1 当量)、硫 (900mg，28.0mmol，1 当量)、氰基乙酸乙酯 (3.0mL，28.0mmol，1 当量) 和催化量的哌啶放入在乙醇 (15mL) 中的悬液，在密封管中于 90℃加热 18h。然后将反应混合物蒸发，粗残余物通过快速色谱法、使用环己烷和乙酸乙酯 (100 / 0 至 0 / 100) 纯化，得到 2- 氨基 - 噻吩 -3- 甲酸乙酯 (6％至 95％收率)。

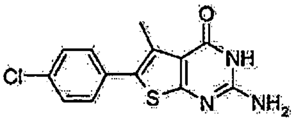
[1071] <u>步骤 2：</u>

[1072] 在 0℃，将氰胺 (L0mmol，1.5 当量) 加入至 2M 氯化氢在乙醚中的溶液 (1.0mL，3 当量)。搅拌 15min 后，过滤悬液。将所得白色固体在密封管中加至步骤 1 中获得的 2- 氨基 - 噻吩 -3- 甲酸乙酯 (0.7mmol，1 当量) 和二甲基砜 (250mg)。将混合物在 130℃加热 2h。冷却后，将残余物溶解于甲醇中，加入 7N 氨在甲醇中的溶液 (10mL)。然后蒸发溶剂，所得固体用二氯甲烷 (2 x 10mL) 和水 (2 x 10mL) 洗涤，得到期望的化合物 (5％至 90％收率)。

[1073] <u>实施例 8：</u>

[1074] 2- 氨基 -6-(4- 氯 - 苯基)-5- 甲基 -3H- 噻吩并 [2,3-d] 嘧啶 -4- 酮

[1075]



[1076] 根据一般程序 B、使用 1-(4- 氯 - 苯基) - 丙 -2- 酮获得期望的化合物。分离出期望的化合物，为灰色粉末。

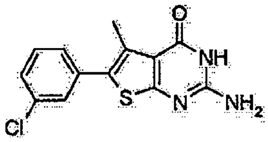
[1077] MS：292.0

[1078] Mp：在 351℃分解

[1079] 实 施例 9：

[1080] 2- 氨基 -6-(3- 氯 - 苯基)-5- 甲基 -3H- 噻吩并 [2,3-d] 嘧啶 -4- 酮

[1081]



[1082] 根据一般程序 B、使用 1-(3- 氯 - 苯基) - 丙 -2- 酮获得期望的化合物。分离出期望的化合物，为白色粉末。

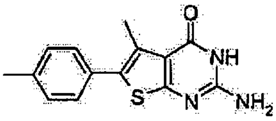
[1083] MS：292.1

[1084] Mp：在 265℃分解

[1085] 实施例 10：

[1086] 2- 氨基 -5- 甲基 -6- 对甲苯基 -3H- 噻吩并 [2,3-d] 嘧啶 -4- 酮

[1087]



[1088] 根据一般程序 B、使用 1- 对甲苯基 - 丙 -2- 酮获得期望的化合物。分离出期望的化合物，为白色粉末。

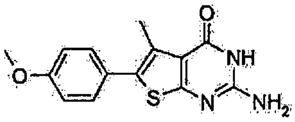
[1089] MS：272.1

[1090] Mp：在 330℃分解

[1091] 实施例 11：

[1092] 2- 氨基 -6-(4- 甲氧基 - 苯基)-5- 甲基 -3H- 噻吩并 [2,3-d] 嘧啶 -4- 酮

[1093]



[1094] 根据一般程序 B、使用 1-(4- 甲氧基 - 苯基)- 丙 -2- 酮获得期望的化合物。分离出期望的化合物，为白色粉末。

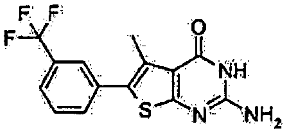
[1095] MS：288.1

[1096] Mp：在 311℃分解

[1097] 实施例 12：

[1098] 2- 氨基 -5- 甲基 -6-(3- 三氟甲基 - 苯基)-3H- 噻吩并 [2,3-d] 嘧啶 -4- 酮

[1099]



[1100]　根据一般程序 B、使用 1-(3- 三氟甲基 - 苯基)- 丙 -2- 酮获得期望的化合物。分离出期望的化合物，为白色粉末。

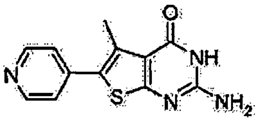
[1101]　MS：326.1

[1102]　Mp：在 345℃分解

[1103]　实施例 13：

[1104]　2- 氨基 -5- 甲基 -6- 吡啶 -4- 基 -3H- 噻吩并 [2,3-d] 嘧啶 -4- 酮

[1105]



[1106]　根据一般程序 B、使用 1- 吡啶 -4- 基 - 丙 -2- 酮获得期望的化合物。分离出期望的化合物，为黄色粉末。

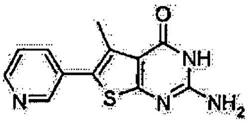
[1107]　MS：259.1

[1108]　Mp：在 355℃分解

[1109]　实施例 14：

[1110]　2- 氨基 -5- 甲基 -6- 吡啶 -3- 基 -3H- 噻吩并 [2,3-d] 嘧啶 -4- 酮

[1111]



[1112]　根据一般程序 B、使用 1- 吡啶 -3- 基 - 丙 -2- 酮获得期望的化合物。分离出期望的化合物，为黄色粉末。

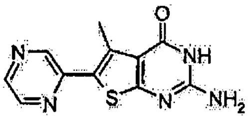
[1113]　MS：259.0

[1114]　Mp：280℃ -290℃

[1115]　实施例 15：

[1116]　2- 氨基 -5- 甲基 -6- 吡嗪 -2- 基 -3H- 噻吩并 [2,3-d] 嘧啶 -4- 酮

[1117]



[1118]　根据一般程序 B、使用 1- 吡嗪 -2- 基 - 丙 -2- 酮获得期望的化合物。分离出期望的化合物，为橙色粉末。

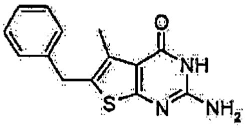
[1119]　MS：260.0

[1120]　Mp：280℃ -300℃

[1121]　实施例 16：

[1122]　2- 氨基 -6- 苄基 -5- 甲基 -3H- 噻吩并 [2,3-d] 嘧啶 -4- 酮

[1123]



[1124] 根据一般程序 B、使用 4- 苯基 - 丁 -2- 酮获得期望的化合物。分离出期望的化合物，为白色粉末。

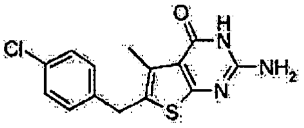
[1125] MS：272.1

[1126] Mp：292℃ -294℃

[1127] <u>实施例 17：</u>

[1128] 2- 氨基 -6-(4- 氯 - 苄基)-5- 甲基 -3H- 噻吩并 [2,3-d] 嘧啶 -4- 酮

[1129]



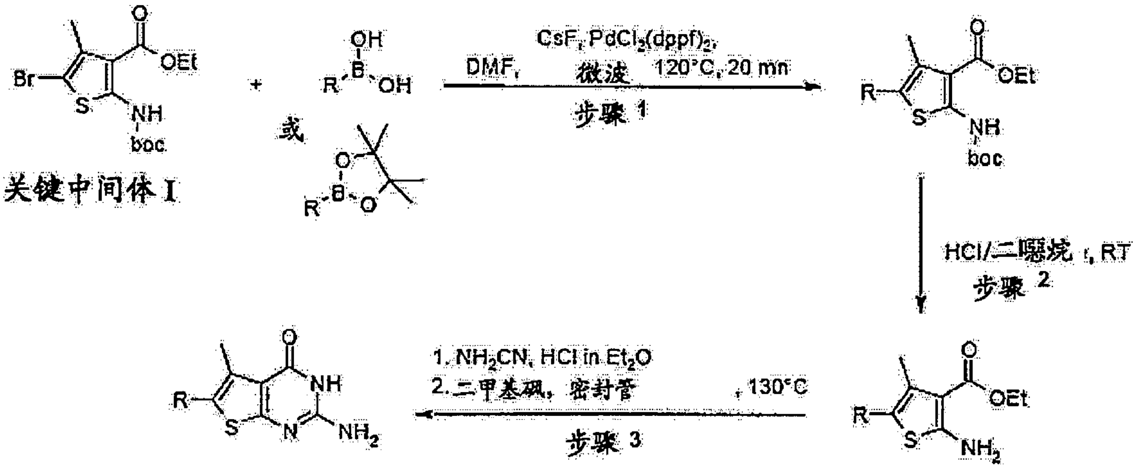
[1130] 根据一般程序 B、使用 4-(4- 氯 - 苯基)- 丁 -2- 酮获得期望的化合物。分离出期望的化合物，为白色粉末。

[1131] MS：306.1

[1132] Mp：300℃ -320℃

[1133] <u>一般程序 C</u>

[1134]



[1135] <u>步骤 1：</u>

[1136] 向脱气的 5- 溴 -2- 叔丁氧基羰基氨基 -4- 甲基 - 噻吩 -3- 甲酸乙酯（关键中间体 I）(200mg，0.6mmol，1 当量）和硼酸或酯 (1.8mmol，3 当量）在干燥二甲基甲酰胺 (4mL) 中的溶液加入氟化铯 (183mg，1.2mmol，2.2 当量）和二氯 [1,1′ - 双（二苯基膦基）二茂铁] 钯 (0.12mmol，90mg，0.2 当量）。将混合物在微波辐射下于 120℃搅拌 20min。冷却后，经硅藻土短柱过滤混合物，吸附在硅胶上，通过快速色谱法纯化 (30％至 95％收率）。

[1137] <u>步骤 2：</u>

[1138] 将来自步骤 1 的化合物 (2.4mmol，1 当量）溶解于 4N 氯化氢在二噁烷中的溶液 (10mL)，将混合物在室温搅拌 18h。然后将混合物浓缩，将残余物溶于二氯甲烷 (10mL) 中，用碳酸氢钠饱和溶液洗涤 (3 x 10mL)。有机层经硫酸镁干燥，过滤，真空蒸发。将粗残余物

通过快速色谱法纯化，得到氨基酯（35％至定量收率）。

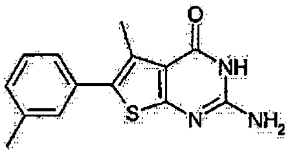
[1139]　步骤 3：

[1140]　在0℃，将氰胺（1.0mmol，1.5当量）加入至2M氯化氢在乙醚中的溶液（1.0mL，3当量）。搅拌15min后，过滤悬液。将所得白色固体加至在密封管中的2-氨基-噻吩-3-甲酸乙酯（0.7mmol，1当量）和二甲基砜（250mg）。将混合物在130℃加热2h。冷却后，将残余物溶解于甲醇中，加入7N氨在甲醇中的溶液（10mL）。然后蒸发溶剂，将所得固体用二氯甲烷（2 x 10mL）和水（2 x 10mL）洗涤，得到期望的化合物（5％至90％收率）。

[1141]　实施例 18：

[1142]　2-氨基-5-甲基-6-间甲苯基-3H-噻吩并[2,3-d]嘧啶-4-酮

[1143]



[1144]　根据一般程序C、使用3-甲基苯硼酸获得期望的化合物。分离出期望的化合物，为白色粉末。

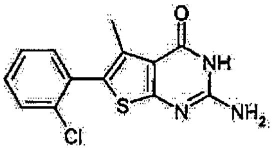
[1145]　MS：272.1

[1146]　Mp：在330℃-338℃分解

[1147]　实施例 19：

[1148]　2-氨基-6-(2-氯-苯基)-5-甲基-3H-噻吩并[2,3-d]嘧啶-4-酮

[1149]



[1150]　根据一般程序C、使用2-氯苯硼酸获得期望的化合物。分离出期望的化合物，为粉红色粉末。

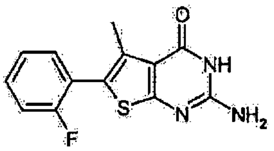
[1151]　MS：292.1

[1152]　Mp：334℃-336℃

[1153]　实施例 20：

[1154]　2-氨基-6-(2-氟-苯基)-5-甲基-3H-噻吩并[2,3-d]嘧啶-4-酮

[1155]



[1156]　根据一般程序C、使用2-氟苯硼酸获得期望的化合物。分离出期望的化合物，为米色粉末。

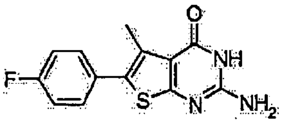
[1157]　MS：271.1

[1158]　Mp：325℃-330℃

[1159]　实施例 21：

[1160] 2-氨基-6-(4-氟-苯基)-5-甲基-3H-噻吩并[2,3-d]嘧啶-4-酮

[1161]



[1162] 根据一般程序C、使用4-氟苯硼酸获得期望的化合物。分离出期望的化合物，为灰色粉末。

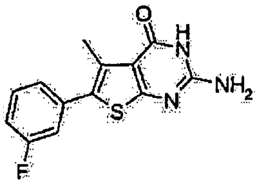
[1163] MS：276.0

[1164] Mp：325℃-335℃

[1165] 实施例22：

[1166] 2-氨基-6-(3-氟-苯基)-5-甲基-3H-噻吩并[2,3-d]嘧啶-4-酮

[1167]



[1168] 根据一般程序C、使用3-氟苯硼酸获得期望的化合物。分离出期望的化合物，为紫色粉末。

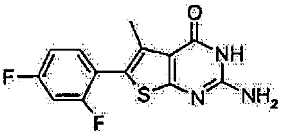
[1169] MS：276.0

[1170] Mp：310℃-330℃

[1171] 实施例23：

[1172] 2-氨基-6-(2,4-二氟-苯基)-5-甲基-3H-噻吩并[2,3-d]嘧啶-4-酮

[1173]



[1174] 根据一般程序C、使用2,4-二氟苯基硼酸获得期望的化合物。分离出期望的化合物，为紫色粉末。

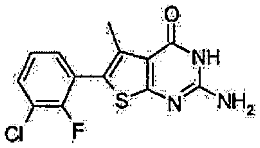
[1175] MS：294.1

[1176] Mp：330℃-350℃

[1177] 实施例24：

[1178] 2-氨基-6-(3-氯-2-氟-苯基)-5-甲基-3H-噻吩并[2,3-d]嘧啶-4-酮

[1179]



[1180] 根据一般程序C、使用3-氯-2-氟苯基硼酸获得期望的化合物。分离出期望的化合物，为白色粉末。

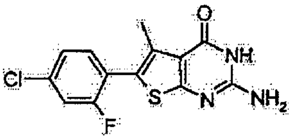
[1181] MS：310.1

[1182] Mp：330℃ -350℃

[1183] 实施例 25：

[1184] 2-氨基-6-(4-氯-2-氟-苯基)-5-甲基-3H-噻吩并[2,3-d]嘧啶-4-酮

[1185]



[1186] 根据一般程序 C、使用 4-氯-2-氟苯硼酸获得期望的化合物。分离出期望的化合物，为白色粉末。

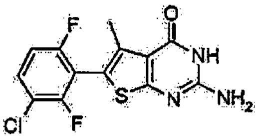
[1187] MS：310.0

[1188] Mp：320℃ -340℃

[1189] 实施例 26：

[1190] 2-氨基-6-(3-氯-2,6-二氟-苯基)-5-甲基-3H-噻吩并[2,3-d]嘧啶-4-酮

[1191]



[1192] 根据一般程序 C、使用 3-氯-2,6-二氟苯基硼酸获得期望的化合物。分离出期望的化合物，为白色粉末。

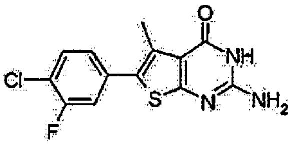
[1193] MS：328.1

[1194] Mp：330℃ -350℃

[1195] 实施例 27：

[1196] 2-氨基-6-(4-氯-3-氟-苯基)-5-甲基-3H-噻吩并[2,3-d]嘧啶-4-酮

[1197]



[1198] 根据一般程序 C、使用 4-氯-3-氟苯基硼酸获得期望的化合物。分离出期望的化合物，为米色粉末。

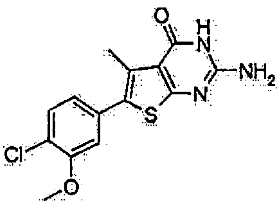
[1199] MS：310.1

[1200] Mp：350℃ -370℃

[1201] 实施例 28：

[1202] 2-氨基-6-(4-氯-3-甲氧基-苯基)-5-甲基-3H-噻吩并[2,3-d]嘧啶-4-酮

[1203]



[1204] 根据一般程序 C、使用 4- 氯 -3- 甲氧基苯基硼酸获得期望的化合物。分离出期望的化合物，为米色粉末。

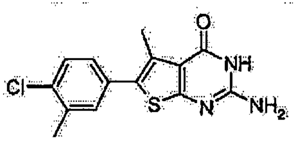
[1205] MS：322.1

[1206] Mp：312℃ -322℃

[1207] 实施例 29：

[1208] 2- 氨基 -6-(4- 氯 -3- 甲基 - 苯基)-5- 甲基 -3H- 噻吩并 [2,3-d] 嘧定 -4- 酮

[1209]



[1210] 根据一般程序 C、使用 4- 氯 -3- 甲基苯基硼酸获得期望的化合物。分离出期望的化合物，为白色粉末。

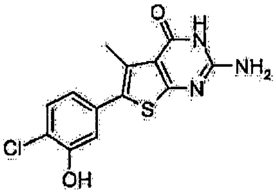
[1211] MS：306.1

[1212] Mp：330℃ -350℃

[1213] 实施例 30：

[1214] 2- 氨基 -6-(4- 氯 -3- 羟基 - 苯基)-5- 甲基 -3H- 噻吩并 [2,3-d] 嘧啶 -4- 酮

[1215]



[1216] 根据一般程序 C、使用 (4- 氯 -3- 羟基苯基) 硼酸获得期望的化合物。分离出期望的化合物，为米色粉末。

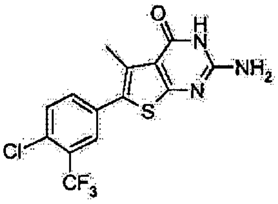
[1217] MS：308.1

[1218] Mp>350℃

[1219] 实施例 31：

[1220] 2- 氨基 -6-(4- 氯 -3- 三氟甲基 - 苯基)-5- 甲基 -3H- 噻吩并 [2,3-d] 嘧啶 -4- 酮

[1221]



[1222] 根据一般程序 C、使用 4- 氯 -3- 三氟甲基苯基硼酸获得期望的化合物。分离出期望的化合物，为白色粉末。

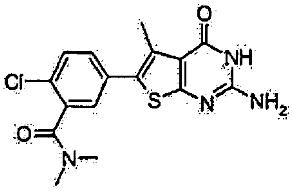
[1223] MS：360.2

[1224] Mp>350℃

[1225] 实施例 32：

[1226] 5-(2- 氨基 -5- 甲基 -4- 氧代 -3,4- 二氢 - 噻吩并 [2,3-d] 嘧啶 -6- 基)-2- 氯 -N, N- 二甲基 - 苯甲酰胺

[1227]



[1228] 根据一般程序 C、使用 4- 氯 -3-(二甲氨基羰基) 苯基硼酸获得期望的化合物。分离出期望的化合物，为白色粉末。

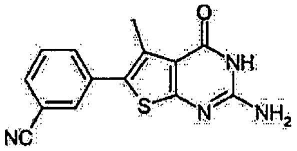
[1229] MS :363.1

[1230] Mp :300℃ -320℃

[1231] 实施例 33 :

[1232] 3-(2- 氨基 -5- 甲基 -4- 氧代 -3,4- 二氢 - 噻吩并 [2,3-d] 嘧定 -6- 基)- 苄腈

[1233]



[1234] 根据一般程序 C、使用 3- 氰基苯基硼酸获得期望的化合物。分离出期望的化合物，为米色粉末。

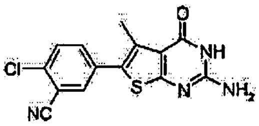
[1235] MS :283.1

[1236] Mp>350℃

[1237] 实施例 34 :

[1238] 5-(2- 氨基 -5- 甲基 -4- 氧代 -3,4- 二 - 氢 - 噻吩并 [2,3-d] 嘧啶 -6- 基)-2- 氯 - 苄腈

[1239]



[1240] 根据一般程序 C、使用 4- 氯 -3- 氰基苯基硼酸获得期望的化合物。分离出期望的化合物，为米色粉末。

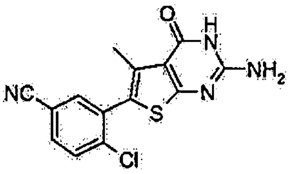
[1241] MS :317.0

[1242] Mp>360℃

[1243] 实施例 35 :

[1244] 3-(2-氨基-5-甲基-4-氧代-3,4-二氢-噻吩并[2,3-d]嘧啶-6-基)-4-氯-苄腈

[1245]



[1246] 根据一般程序 C、使用 2- 氯 -5- 氰基苯基硼酸获得期望的化合物。分离出期望的化合物，为米色粉末。

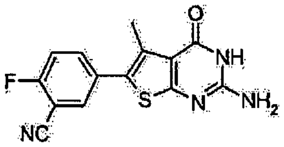
[1247] MS：317-1

[1248] Mp>350℃

[1249] 实施例 36：

[1250] 5-(2-氨基-5-甲基-4-氧代-3，4-二氢-噻吩并[2，3-d]嘧啶-6-基)-2-氟-苄腈

[1251]



[1252] 根据一般程序 C、使用 3- 氰基 -4- 氟苯基硼酸获得期望的化合物。分离出期望的化合物，为白色粉末。

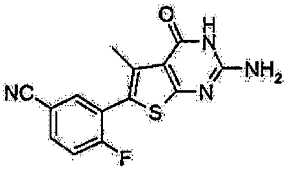
[1253] MS：301.1

[1254] Mp：330℃ -350℃

[1255] 实施例 37：

[1256] 3-(2-氨基-5-甲基..4-氧代-3，4-二氢-噻吩并[2，3-d]嘧啶-6-基)-4-氟-苄腈

[1257]



[1258] 根据一般程序 C、使用 5- 氰基 -2- 氟苯基硼酸获得期望的化合物。分离出期望的化合物，为米色粉末。

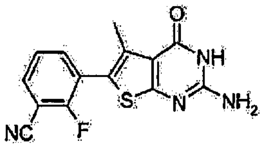
[1259] MS：301.0

[1260] Mp：332℃ -336C

[1261] 实施例 38：

[1262] 3-(2-氨基-5-甲基-4-氧代-3，4-二氢-噻吩并[2，3-d]嘧啶-6-基)-2-氟苄腈

[1263]



[1264] 根据一般程序 C、使用 3- 氰基 -2- 氟苯基硼酸获得期望的化合物。分离出期望的化合物，为白色粉末。

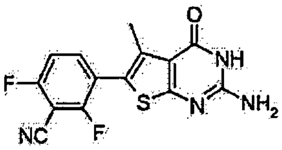
[1265] MS：301.0

[1266] Mp：350℃ -370℃

[1267] 实施例 39：

[1268] 3-(2-氨基-5-甲基-4-氧代-3,4-二氢-噻吩并[2,3-d]嘧啶-6-基)-2,6-二氟-苄腈

[1269]



[1270] 根据一般程序C、使用2,4-二氟-3-氰基苯基硼酸获得期望的化合物。分离出期望的化合物，为灰色粉末。

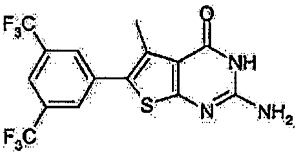
[1271] MS：319.0

[1272] Mp：360℃-380℃

[1273] 实施例40：

[1274] 2-氨基-6-(3,5-双-三氟甲基-苯基)-5-甲基-3H-噻吩并[2,3-d]嘧啶-4-酮

[1275]



[1276] 根据一般程序C、使用3,5-双(三氟甲基)苯硼酸获得期望的化合物。分离出期望的化合物，为白色粉末。

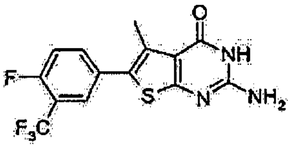
[1277] MS：394.1

[1278] Mp：344℃-347℃

[1279] 实施例41：

[1280] 2-氨基-6-(4-氟-3-三氟甲基-苯基)-5-甲基-3H-噻吩并[2,3-d]嘧啶-4-酮

[1281]



[1282] 根据一般程序C、使用4-氟-3-三氟甲基苯基硼酸获得期望的化合物。分离出期望的化合物，为白色粉末。

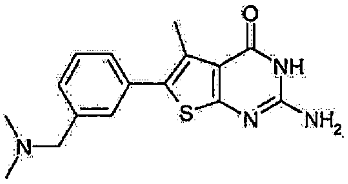
[1283] MS：343.1

[1284] Mp：310℃-330℃

[1285] 实施例42：

[1286] 2-氨基-6-(3-二甲氨基甲基-苯基)-5-甲基-3H-噻吩并[2,3-d]嘧啶-4-酮

[1287]



[1288] 根据一般程序C、使用3-(N，N-二甲氨基)甲基苯基硼酸频哪醇酯盐酸盐获得期

望的化合物。分离出期望的化合物，为米色粉末。

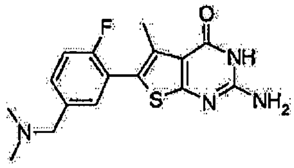
[1289]　MS：315.1

[1290]　Mp：207℃ -212℃

[1291]　实施例 43：

[1292]　2- 氨基 -6-(5- 二甲氨基甲基 -2- 氟 - 苯基)-5- 甲基 -3H- 噻吩并 [2,3-d]- 嘧啶 -4- 酮

[1293]



[1294]　根据一般程序 C、使用 2- 氟 -5-(二甲氨基甲基) 苯基硼酸频哪醇酯获得期望的化合物。分离出期望的化合物，为白色粉末。

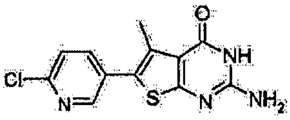
[1295]　MS：333.2

[1296]　Mp：230℃ -250℃

[1297]　实施例 44：

[1298]　2- 氨基 -6-(6- 氯 - 吡啶 -3- 基)-5- 甲基 -3H- 噻吩并 [2,3-d] 嘧啶 -4- 酮

[1299]



[1300]　根据一般程序 C、使用 2- 氯吡啶 -5- 硼酸获得期望的化合物。分离出期望的化合物，为黄色粉末。

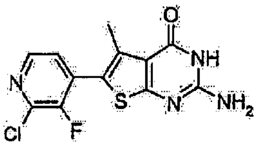
[1301]　MS：293.1

[1302]　Mp：230℃ -250℃

[1303]　实施例 45：

[1304]　2- 氨基一 6-(2- 氯 -3- 氟一吡啶 -4- 基)-5- 甲基 -3H- 噻吩并 [2,3-d]嘧啶 -4- 酮

[1305]



[1306]　根据一般程序 C、使用 2- 氯 -3- 氟吡啶 -4- 硼酸获得期望的化合物。分离出期望的化合物，为黄色粉末。

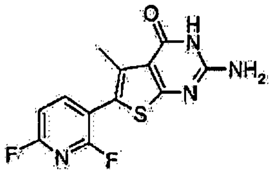
[1307]　MS：311.1

[1308]　Mp：330℃ -350℃

[1309]　实施例 46：

[1310]　2- 氨基 -6-(2,6- 二氟 - 吡啶 -3- 基)-5- 甲基 -3H- 噻吩并 [2,3-d] 嘧啶一 4- 酮

[1311]



[1312] 根据一般程序C、使用2,6-二氟吡啶一3-硼酸获得期望的化合物。分离出期望的化合物,为米色粉末。

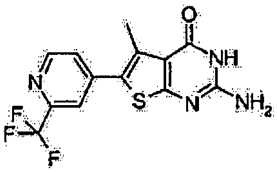
[1313] MS：295.0

[1314] Mp：330℃-335℃

[1315] 实施例47：

[1316] 2-氨基一5一甲基-6-(2-三氟甲基-吡啶-4-基)-3H-噻吩并[2,3-d]嘧啶-4-酮

[1317]



[1318] 根据一般程序C、使用2-(三氟甲基)吡啶-4-硼酸获得期望的化合物。分离出期望的化合物,为黄色粉末。

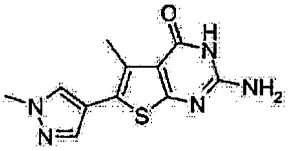
[1319] MS：327.0

[1320] Mp：335℃-355℃

[1321] 实施例48：

[1322] 2-氨基-5-甲基-6-(2-甲基-2H-咪唑-4-基)-3H-噻吩并[2,3-d]嘧啶一4-酮

[1323]



[1324] 根据一般程序C、使用1-甲基-4-(4,4,5,5-四甲基-1,3,2-二氧硼杂环戊烷-2-基)-1H-吡唑获得期望的化合物。分离出期望的化合物,为白色粉末。

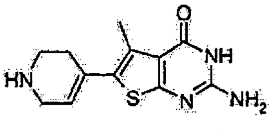
[1325] MS：262.0

[1326] Mp：335℃-345℃

[1327] 实施例49：

[1328] 2-氨基-5-甲基-6-(1,2,3,6-四氢-吡啶-4-基)-3H-噻吩并[2,3-d]嘧啶-4-酮

[1329]



[1330] 根据一般程序C、使用N-Bo c-1,2,3,6-四氢吡啶-4-硼酸频哪醇酯获得期望的化合物。分离出期望的化合物,为橙色粉末。

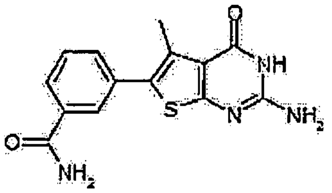
[1331] MS：263.1

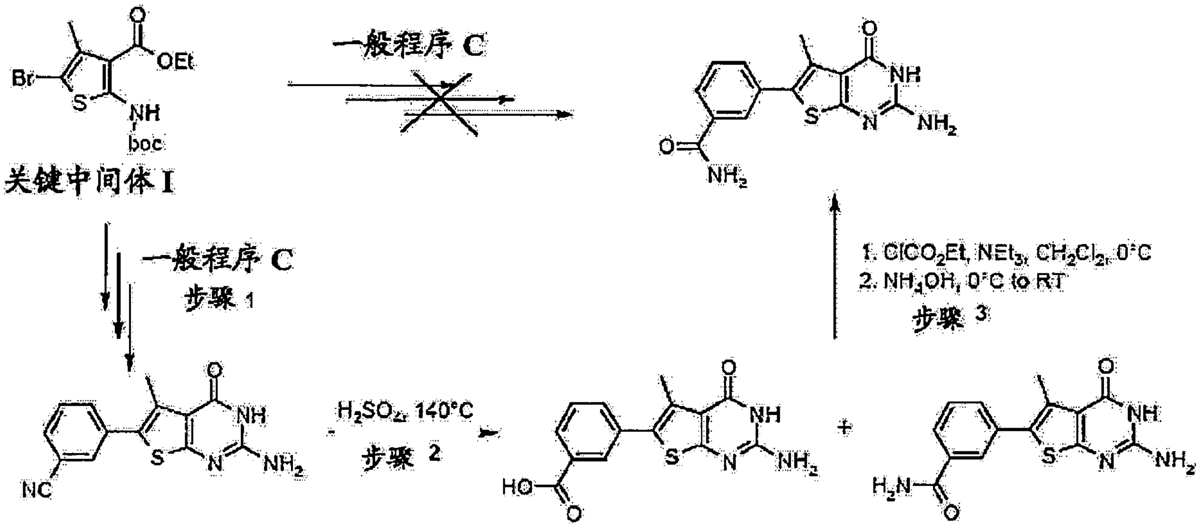
[1332] Mp：290℃-310℃

[1333] 实施例50：

[1334]　3-(2-氨基-5-甲基-4-氧代-3,4-二-氢-噻吩并[2,3-d]嘧啶-6-基)-苯甲酰胺

[1335]





[1336]　步骤 1：

[1337]　以一般程序 C 开始、使用 3-氨基甲酰基苯基硼酸，获得期望的化合物。结晶后，获得 3-(2-氨基-5-甲基-4-氧代-3,4-二氢-噻吩并[2,3-d]嘧啶-6-基)-苄腈，而不是所需化合物。

[1338]　步骤 2：

[1339]　将 3-(2-氨基-5-甲基-4-氧代-3,4-二氢-噻吩并[2,3-d]嘧啶-6-基)-苄腈(100mg,0.35mmol,1 当量)溶解于浓硫酸(12mL)中，在 140℃加热 3h。冷却后，加入水(10mL)，将所得的沉淀过滤，得到酸与酰胺化合物的 60 / 40 混合物。

[1340]　步骤 3：

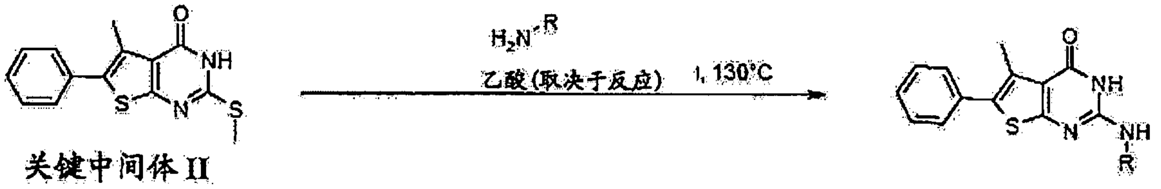
[1341]　将来自步骤 2 的混合物放入在二氯甲烷(6mL)中的悬液。在 0℃，加入三乙胺(42μL,0.3mmol,1.2 当量)和氯甲酸乙酯(26μL,0.28mmol,1.1 当量)。在 0℃ 1h 后，加入氢氧化铵溶液(15mL)，将混合物从 0℃至室温搅拌 3 天。蒸发溶剂，加入水(10mL)。将所得的沉淀过滤，真空干燥，得到期望的化合物，为米色粉末。

[1342]　MS：301.1

[1343]　Mp：在 295℃-300℃分解

[1344]　一般程序 D

[1345]



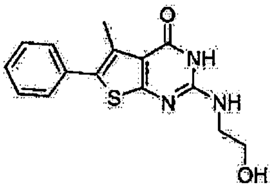
关键中间体 II

[1346] 将 5- 甲基 -2- 甲基硫基 -6- 苯基 -3H- 噻吩并 [2,3-d] 嘧啶 -4- 酮 (关键中间体 II)(1.3g,4.4mmol,1 当量) 放入在适当的胺 (3mL) 中和在乙酸 (1mL)(取决于反应) 中的悬液。将所得混合物在密封管中于 130℃加热 18h。冷却后,加入乙醇 (20mL),过滤沉淀,用甲醇、二氯甲烷和醚漂洗,真空干燥,得到期望的化合物 (10%至 70%收率)。

[1347] 实施例 51 :

[1348] 2-(2- 羟基 - 乙基氨基)-5- 甲基 -6- 苯基 -3H- 噻吩并 [2,3-d] 嘧啶 -4- 酮

[1349]



[1350] 根据一般程序 D、使用乙醇胺和乙酸获得期望的化合物。分离出期望的化合物,为白色粉末。

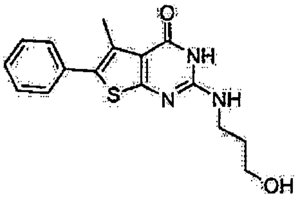
[1351] MS :302.1

[1352] Mp :227℃ -229℃

[1353] 实施例 52 :

[1354] 2-(3- 羟基 - 丙基氨基)-5- 甲基 -6- 苯基 -3H- 噻吩并 [2,3-d] 嘧啶 -4- 酮

[1355]



[1356] 根据一般程序 D、使用 3- 氨基 - 丙 -1- 醇和乙酸获得期望的化合物。冷却后,蒸发反应混合物,加入水。过滤所得的沉淀,用乙醚和二氯甲烷漂洗。分离出期望的化合物,为米色粉末。

[1357] MS :316.2

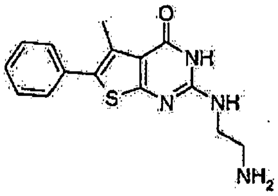
[1358] Mp :227℃ -229℃

[1359] 实施例 53 :

[1360] 2-(2- 氨基 - 乙基氨基)-5- 甲基 -6- 苯基 -3H- 噻吩并 [2,3-d] 嘧定 -4- 酮

[1361] 关键中间体 III

[1362]



[1363]　根据一般程序 D、使用乙二胺获得期望的化合物。分离出期望的化合物，为白色粉末。

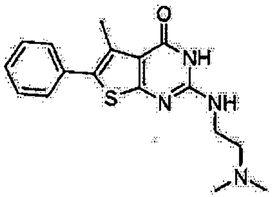
[1364]　MS：301.1

[1365]　Mp：192℃ -194℃

[1366]　实施例 54：

[1367]　2-(2- 二甲氨基 - 乙基氨基)-5- 甲基 -6- 苯基 -3H- 噻吩并 [2,3-d] 嘧啶 -4- 酮

[1368]



[1369]　根据一般程序 D、使用 N,N- 二甲基乙二胺和乙酸获得期望的化合物。分离出期望的化合物，为米色粉末。

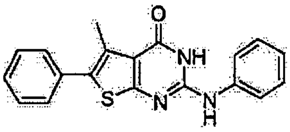
[1370]　MS：329.2

[1371]　Mp：199℃ -201℃

[1372]　实施例 55：

[1373]　5- 甲基 -6- 苯基 -2- 苯基氨基 -3H- 噻吩并 [2,3-d] 嘧啶 -4- 酮

[1374]



[1375]　根据一般程序 D、使用苯胺和乙酸获得期望的化合物。分离出期望的化合物，为白色粉末。

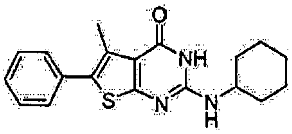
[1376]　MS：334.1

[1377]　Mp：270℃ -290℃

[1378]　实施例 56：

[1379]　2- 环己基氨基 -5- 甲基 -6- 苯基 -3H- 噻吩并 [2,3-d] 嘧啶 -4- 酮

[1380]



[1381]　根据一般程序 D、使用环己胺获得期望的化合物。分离出期望的化合物，为白色粉末。

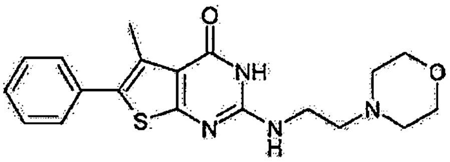
[1382]　MS：340.2

[1383]　Mp：265℃ -270℃

[1384]　实施例 57：

[1385]　5- 甲基 -2-(2- 吗啉 -4- 基 - 乙基氨基)-6- 苯基 -3H- 噻吩并 [2,3-d] 嘧啶 -4- 酮

[1386]



[1387]　根据一般程序 D、使用 4-(2- 氨基乙基) 吗啉获得期望的化合物。分离出期望的化合物，为白色粉末。

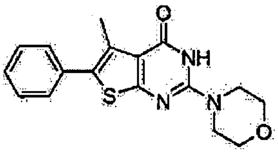
[1388]　MS：371.1

[1389]　Mp：240℃ -246℃

[1390]　实施例 58：

[1391]　5- 甲基 -2- 吗啉 -4- 基 -6- 苯基 -3H- 噻吩并 [2,3-d] 嘧啶 -4- 酮

[1392]



[1393]　根据一般程序 D、使用吗啉获得期望的化合物。分离出期望的化合物，为白色粉末。

[1394]　MS：328.1

[1395]　Mp：300℃ -320℃

[1396]　一般程序 E

[1397]

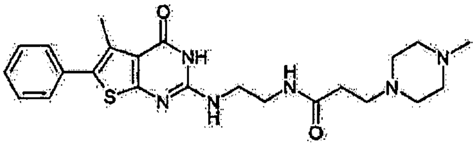
关键中间体 III

[1398]　向 2-(2- 氨基 - 乙基氨基)-5- 甲基 -6- 苯基 -3H- 噻吩并 [2,3-d] 嘧啶 -4- 酮 (关键中间体 III)(200mg，0.66mmol，1 当量) 在二甲基甲酰胺 (5mL) 中的溶液加入 HOBT(180mg，1.33mmol，2 当量)、EDCI(255mg，1.33mmol，2 当量)、三乙胺 (0.28mL，1.98mmol，3 当量) 和适当的羧酸 (1.33mmol，2 当量)。将混合物在室温搅拌 20h。然后将混合物倒入水 (10mL) 中，用二氯甲烷萃取 (3 x 20mL)。有机层经硫酸镁干燥，过滤，真空蒸发。将粗残余物通过快速色谱法、使用二氯甲烷和 7N 在甲醇中的氨 (100 / 0 至 80 / 20) 纯化，得到期望的化合物 (10 至 40％收率)。

[1399]　实施例 59：

[1400]　N-[2-(5- 甲基 -4- 氧代 -6- 苯基 -3，4- 二氢 - 噻吩并 [2,3-d] 嘧啶 -2- 基氨基)- 乙基]-3-(4- 甲基 - 哌嗪 -1- 基)- 丙酰胺

[1401]



[1402] 根据一般程序 E、使用 3-(4- 甲基 - 哌嗪 -1- 基)- 丙酸获得期望的化合物。分离出期望的化合物,为白色粉末。

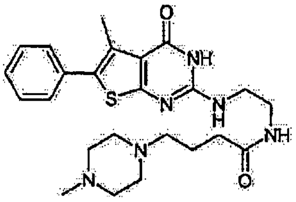
[1403] MS :455.1

[1404] Mp :235℃ -245℃

[1405] 实施例 60 :

[1406] N-[2-(5- 甲基 -4- 氧代 -6- 苯基 -3,4- 二氢 - 噻吩并 [2,3-d] 嘧啶 -2- 基氨基)- 乙基]-4-(4- 甲基 - 哌嗪 -1- 基)- 丁酰胺

[1407]



[1408] 根据一般程序 E、使用 4-(4- 甲基哌嗪 -1- 基) 丁酸盐酸盐获得期望的化合物。分离出期望的化合物,为白色粉末。

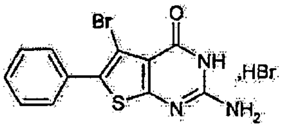
[1409] MS :469.2

[1410] Mp :192℃ -196℃

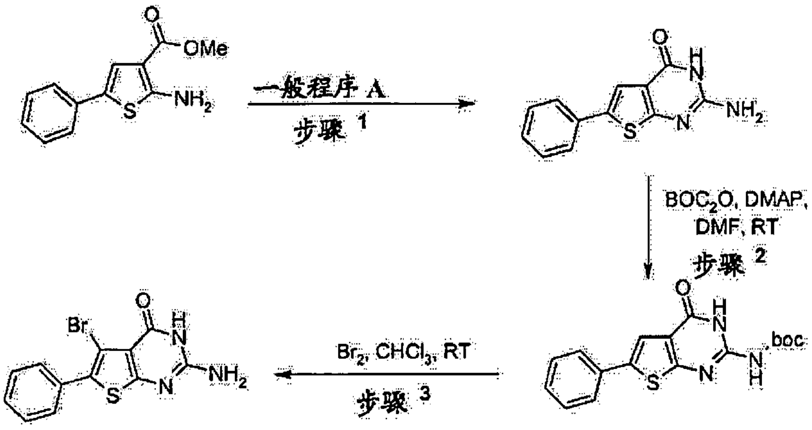
[1411] 实施例 61 :

[1412] 2- 氨基 -5- 溴 -6- 苯基 -3H- 噻吩并 [2,3-d] 嘧啶 -4- 酮氢溴酸盐

[1413]



[1414]



[1415] 步骤 1 :

[1416] 根据一般程序 A、使用 2- 氨基 -5- 苯基 - 噻吩 -3- 甲酸甲酯获得期望的化合物。分离出期望的化合物,为米色粉末 (3.5g,70%收率)。

[1417] 步骤 2：

[1418] 向 2- 氨基 -6- 苯基 -3H- 噻吩并 [2,3-d] 嘧啶 -4- 酮 (2.0g,8.2mmol,1 当量) 在二甲基甲酰胺 (100mL) 中的溶液加入二碳酸二叔丁酯 (3.6g,16.4mmol,2 当量) 和 4- 二甲氨基吡啶 (200mg,1.6mmol,0.2 当量)。将混合物在室温搅拌 18h。然后蒸发溶剂，将残余物溶于二氯甲烷 (20mL)。将不溶的黄色固体滤掉，滤液用碳酸氢钠饱和溶液洗涤 (2 X 20mL)。有机层经硫酸镁干燥，过滤，蒸发。将粗残余物通过快速色谱法、使用二氯甲烷和甲醇纯化 (100 / 0 至 80 / 20)，得到 (4- 氧代 -6- 苯基 -3,4- 二氢 - 噻吩并 [2,3-d] 嘧啶 -2- 基)- 氨基甲酸叔丁酯，为浅黄色固体 (900mg,32％收率)。

[1419] 步骤 3：

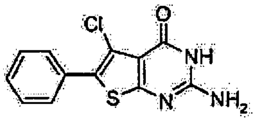
[1420] 将来自步骤 2 的化合物 (350mg,1.0mmol,1 当量) 溶解于氯仿 (10mL) 中，加入溴 (52μL,1.0mmol,1 当量)。将混合物在室温搅拌 1h。加入更多的溴 (52μL,1.0mmol,1 当量)，将混合物在室温再搅拌 1 小时。然后将混合物蒸发，将残余物用二氯甲烷 (5mL) 和甲醇 (5mL) 洗涤，得到期望的化合物，为米色粉末 (150mg,46％收率)。

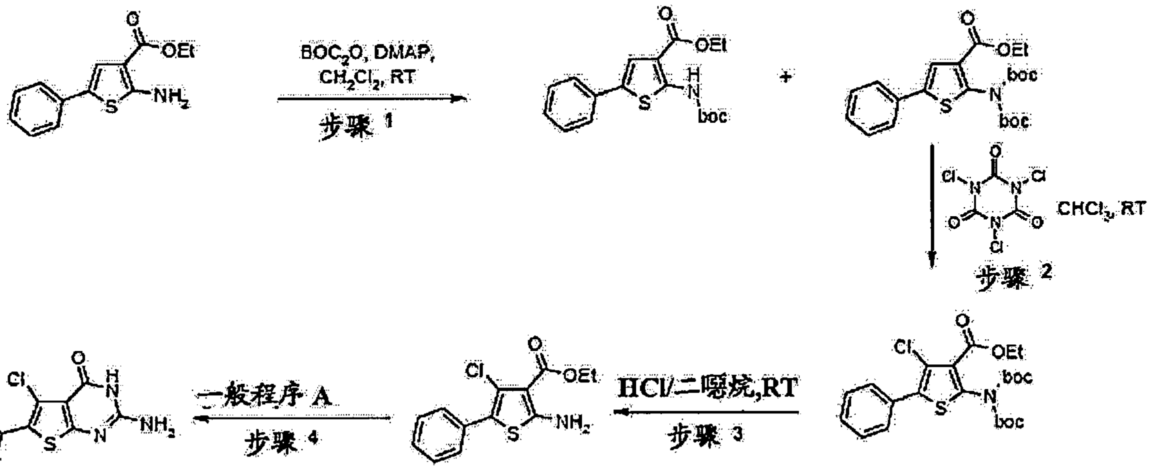
[1421] MS：324.1

[1422] 实施例 62：

[1423] 2- 氨基 -5- 氯 -6- 苯基 -3H- 噻吩并 [2,3-d] 嘧啶 -4- 酮

[1424]





[1425] 步骤 1：

[1426] 向 2- 氨基 -5- 苯基 - 噻吩 -3- 甲酸乙酯 (5.0g,20.2mmol,1 当量) 在二氯甲烷 (40mL) 中的溶液加入二碳酸二叔丁酯 (6.6g,30.3mmol,1.5 当量) 和 4- 二甲氨基吡啶 (247mg,2.0mmol,0.1 当量)。将混合物在室温搅拌 48h。将混合物用碳酸氢钠饱和溶液 (3X20mL) 洗涤，有机层经硫酸镁干燥，过滤，蒸发。将粗残余物通过快速色谱法、使用环己烷和乙酸乙酯 (100 / 0 至 90 / 10) 纯化，分别得到为黄色油状物的 2- 叔丁氧基羰基氨基 -5- 苯基 - 噻吩 -3- 甲酸乙酯 (1.9g,27％收率)，为浅橙色粉末的双 (2- 叔丁氧基羰基氨基)-5- 苯基 - 噻吩 -3- 甲酸乙酯 (4.1g,45％收率)。

[1427] 步骤 2：

[1428] 向来自步骤 1 的 diBoc 化合物 (3.1g,6.9mmol,1 当量) 在氯仿 (100mL) 中的溶液加入三氯异氰脲酸 (trichloroisocyanuric acid)(640mg,2.8mmol,0.4 当量)。将混合物在室温搅拌 18h。过滤沉淀,将滤液通过快速色谱法 / 使用环己烷和乙酸乙酯 (100 / 0 至 90 / 10) 纯化,得到期望的化合物,为浅橙色油状物 (1.1g,33%收率)。

[1429] 步骤 3:

[1430] 将来自步骤 2 的化合物 (950mg,2.0mmol,1 当量) 溶解于 4N 氯化氢在二噁烷中的溶液 (20mL),将混合物在室温搅拌 18h。然后将混合物浓缩,将残余物溶于二氯甲烷 (10mL) 中,用碳酸氢钠饱和溶液洗涤 (3 x 10mL)。有机层经硫酸镁干燥,过滤,真空蒸发。将粗残余物通过快速色谱法、使用环己烷和乙酸乙酯 (100 / 0 至 85 / 15) 纯化,得到 2- 氨基 -4- 氯 -5- 苯基 - 噻吩 -3- 甲酸乙酯,为浅橙色油状物 (300mg,54%收率)。

[1431] 步骤 4:

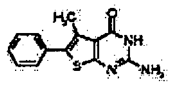
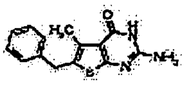
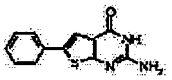
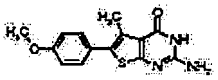
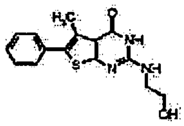
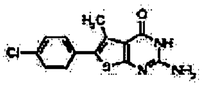
[1432] 根据一般程序 A、使用 2- 氨基 -4- 氯 -5- 苯基 - 噻吩 -3- 甲酸乙酯获得期望的化合物。分离出期望的化合物,为米色粉末 (175mg,61%收率)。

[1433] MS:278.0

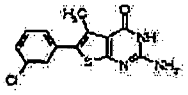
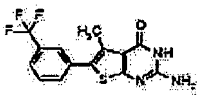
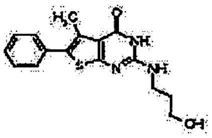
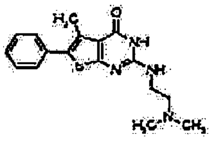
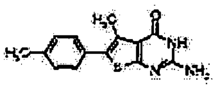
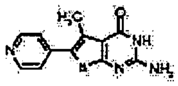
[1434] Mp>350℃

[1435] 具有通式 (II) 的化合物的活性数据

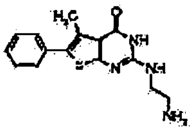
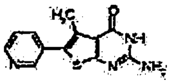
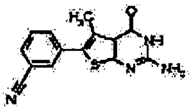
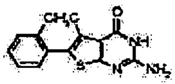
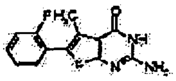
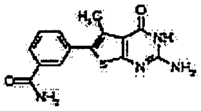
[1436]

molregno	结构	活性类型	活性终点	活性浓度	活性结果
SAV-7475		Biacore	结合 (RU)	10	94,5
		Biacore	KD (μM)		4,6
		CPE H3N2	减少 (%)	5	8,9
		Biacore PA-Nter	结合 (RU)	50	13,16
		CPE H3N2	IC50 (μM)		21
SAV-7517		Biacore	结合 (RU)	10	39,3
		Biacore	KD (μM)		13
		CPE H3N2	减少 (%)	10	-2,64
SAV-7521		Biacore	结合 (RU)	10	64,7
		Biacore	KD (μM)		6
		CPE H3N2	减少 (%)	25	33,6
SAV-7549		Biacore	结合 (RU)	10	65,5
		CPE H3N2	减少 (%)	50	-2,4
		Biacore	KD (μM)		8,8
SAV-7575		Biacore	结合 (RU)	10	35,9
		CPE H3N2	减少 (%)	20	9,02
		Biacore	KD (μM)		4
SAV-7577		Biacore	结合 (RU)	10	81,1
		Biacore	KD (μM)		6,8
		CPE H3N2	减少 (%)	20	2,85
SAV-7579		Biacore	结合 (RU)	10	21,4
		CPE H3N2	减少 (%)	20	11,3
		Biacore	KD (μM)		0,27

[1437]

molregno	结构	活性类型	活性终点	活性浓度	活性结果
SAV-7580		Biacore	结合 (RU)	10	25,2
		CPE H3N2	减少 (%)	2	89,8
		CPE H3N2	IC50 (μM)		11
		Biacore	KD (μM)		8,9
SAV-7581		Biacore	结合 (RU)	10	20,5
		CPE H3N2	减少 (%)	50	87,8
		Biacore	KD (μM)		1,4
		CPE H3N2	IC50 (μM)		17
SAV-7582		Biacore	结合 (RU)	10	102,9
		Biacore	KD (μM)		4,2
		CPE H3N2	减少 (%)	50	53,1
SAV-7583		Biacore	结合 (RU)	10	77,8
		CPE H3N2	减少 (%)	5	4,8
		Biacore	KD (μM)		68
SAV-7585		CPE H3N2	减少 (%)	2,5	28,9
		Biacore	结合 (RU)	10	29,2
		CPE H3N2	IC50 (μM)		3,5
		Biacore	KD (μM)		2
SAV-7586		CPE H3N2	减少 (%)	15	81,2
		Biacore	结合 (RU)	10	100,2
		Biacore	KD (μM)		12
		CPE H3N2	IC50 (μM)		5,3

[1438]

molregno	结构	活性类型	活性终点	活性浓度	活性结果
SAV-7588		CPE H3N2	减少 (%)	5	2,2
		Biacore	结合 (RU)	10	110,6
		Biacore	KD (μM)		
SAV-7589		CPE H3N2	减少 (%)	50	63,1
		Biacore	结合 (RU)	10	88
		Biacore	KD (μM)		10
		CPE H3N2	IC50 (μM)		27
SAV-7594		Biacore	KD (μM)		2
		Biacore	结合 (RU)	10	31,9
		CPE H3N2	减少 (%)	5	14,5
		CPE H3N2	IC50 (μM)		14
SAV-7596		Biacore	KD (μM)		11
		Biacore	Binding (RU)	10	29,6
		CPE H3N2	减少 (%)	5	13,6
SAV-7598		Biacore	结合 (RU)	10	21,3
		Biacore	KD (μM)		3,7
		CPE H3N2	减少 (%)	2	11,4
SAV-7599		CPE H3N2	减少 (%)	20	-0,7
		Biacore	结合 (RU)	12.5	65,3
		Biacore	KD (μM)		5,3

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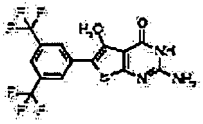
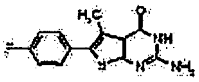
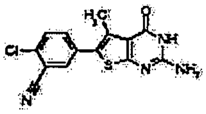
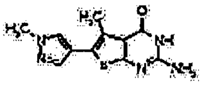
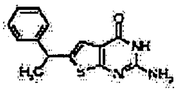
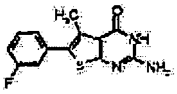
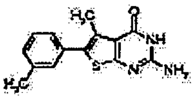
molregno	结构	活性类型	活性终点	活性浓度	活性结果
SAV-7600		CPE H3N2	减少 (%)	2	5,8
		Biacore	KD (µM)		
		Biacore	结合 (RU)	10	3,8
SAV-7601		CPE H3N2	减少 (%)	50	69,2
		Biacore	KD (µM)		1,1
		Biacore	结合 (RU)	10	44,3
SAV-7602		CPE H3N2	减少 (%)	20	67,9
		Biacore	KD (µM)		1,7
		Biacore	结合 (RU)	10	35,1
SAV-7603		CPE H3N2	减少 (%)	20	1,1
		Biacore	KD (µM)		42
SAV-7604		CPE H3N2	减少 (%)	20	-4,7
		Biacore	KD (µM)		6,4
SAV-7606		Biacore	KD (µM)		8
		CPE H3N2	减少 (%)	5	21,8
SAV-7607		Biacore	KD (µM)		5,4
		CPE H3N2	减少 (%)	2	-0,4

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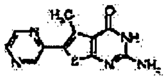
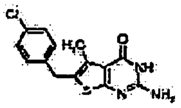
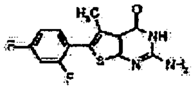
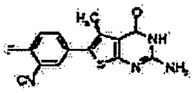
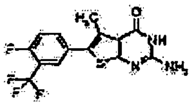
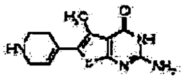
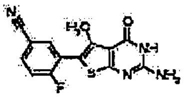
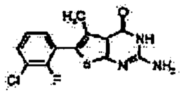
molregno	结构	活性类型	活性终点	活性浓度	活性结果
SAV-7608		Biacore	KD (μM)		5,7
		CPE H3N2	减少 (%)	10	3,8
SAV-7609		CPE H3N2 (不溶性)	减少 (%) 不溶性		
SAV-7610		Biacore	KD (μM)		3,8
		CPE H3N2	减少 (%)	2	-1,6
		ALPHA screen	EC50 (μM)*		0,62
SAV-7611		Biacore	KD (μM)		1,1
		CPE H3N2	减少 (%)	2	-1
SAV-7613		Biacore	KD (μM)		1,5
		CPE H3N2	减少 (%)	50	2,5
SAV-7614		Biacore	KD (μM)		190
		CPE H3N2	减少 (%)	50	10,6
SAV-7615		Biacore	KD (μM)		3
		CPE H3N2	减少 (%)	20	59,2
		CPE H3N2	IC50 (μM)		12
SAV-7616		Biacore	KD (μM)		3,1
		CPE H3N2	减少 (%)	10	68,7
		CPE H3N2	IC50 (μM)		34

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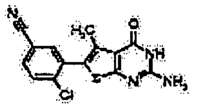
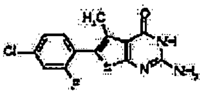
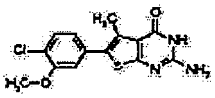
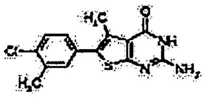
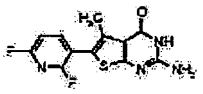
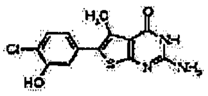
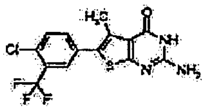
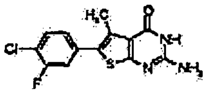
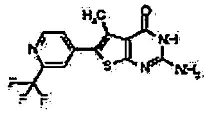
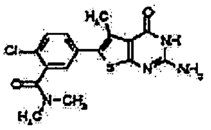
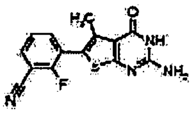
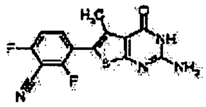
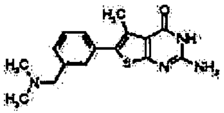
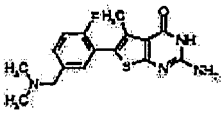
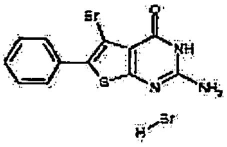
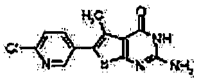
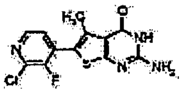
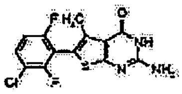
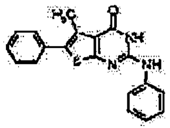
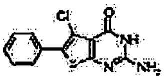
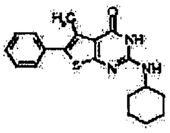
molregno	结构	活性类型	活性终点	活性浓度	活性结果
SAV-7617		Biacore	KD (μM)		2
		CPE H3N2	减少 (%)	2	5,1
SAV-7618		Biacore	KD (μM)		0,65
		CPE H3N2	减少 (%)	50	77,4
		CPE H3N2	IC50 (μM)		43
SAV-7619		Biacore	KD (μM)		1,1
		CPE H3N2	减少 (%)	2	3,4
SAV-7620		Biacore	KD (μM)		
		CPE H3N2	减少 (%)	50	57,8
		CPE H3N2	IC50 (μM)		29
SAV-7621		Biacore	KD (μM)		
		CPE H3N2	IC50 (μM)		70
		CPE H3N2	减少 (%)	25	14,3
SAV-7622		Biacore	KD (μM)		2,4
		CPE H3N2	减少 (%)	2	6,2
SAV-7623		Biacore	KD (μM)		
		CPE H3N2	减少 (%)	5	1,9

[1442]

molregno	结构	活性类型	活性终点	活性浓度	活性结果
SAV-7624		Biacore	KD (μM)		0,2
		CPE H3N2	IC50 (μM)		64
SAV-7625		Biacore	KD (μM)		12
		CPE H3N2	减少 (%)	2.5	-4
SAV-7626		Biacore	KD (μM)		6,4
		CPE H3N2	减少 (%)	25	-4,6
SAV-7627		Biacore	KD (μM)		4,2
		CPE H3N2	减少 (%)	50	71,2
		CPE H3N2	IC50 (μM)		10
SAV-7628		Biacore	KD (μM)		7,3
		CPE H3N2	减少 (%)	50	84,3
		CPE H3N2	IC50 (μM)		43
SAV-7629		Biacore	KD (μM)		61
		CPE H3N2	减少 (%)	50	38,3
		CPE H3N2	IC50 (μM)		35
SAV-7630		Biacore	KD (μM)		57
		CPE H3N2	减少 (%)	50	23,2
		CPE H3N2	IC50 (μM)		

[1443]

molregno	结构	活性类型	活性终点	活性浓度	活性结果
SAV-7631		Biacore	KD (μM)		0,86
		CPE H3N2	减少 (%)	5	4
		CPE H3N2	IC50 (μM)		
SAV-7632		Biacore	KD (μM)		0,75
		CPE H3N2	减少 (%)	50	53
		CPE H3N2	IC50 (μM)		
SAV-7633		Biacore	KD (μM)		1,2
		CPE H3N2	减少 (%)	50	63,1
		CPE H3N2	IC50 (μM)		39
SAV-7637		CPE H3N2	减少 (%)	5	1,5
		CPE H3N2	IC50 (μM)		18
		Biacore	KD (μM)		1,1
SAV-7638		CPE H3N2	减少 (%)	5	8,7
		CPE H3N2	IC50 (μM)		
		Biacore	KD (μM)		
SAV-7639		CPE H3N2	减少 (%)	50	59,9
		CPE H3N2	IC50 (μM)		
		Biacore	KD (μM)		1,8
SAV-7640		CPE H3N2	减少 (%)	5	-3,2
		CPE H3N2	IC50 (μM)		
		Biacore	KD (μM)		

Abstract

The present invention relates to a compound having the general formula I, optionally in the form of a pharmaceutically acceptable salt, solvate, polymorph, prodrug, tautomer, racemate, enantiomer, or dsasiereomer or mixture thereof, which is useful in treating, ameloriating or preventing a viral disease. Furthermore, specific combination therapies are disclosed.