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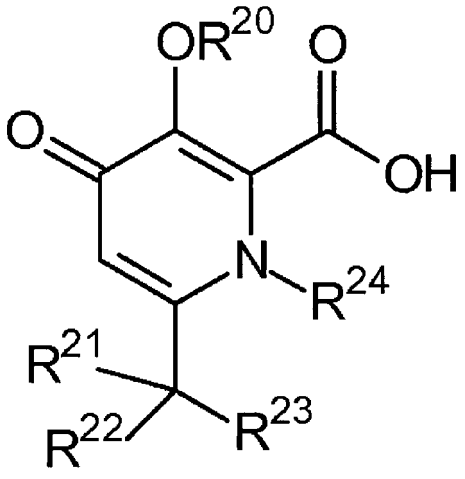
(54) Title: PYRIDONE DERIVATIVES AND THEIR USE IN THE TREATMENT, AMELIORATION OR PREVENTION OF A VIRAL DISEASE



(II)

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

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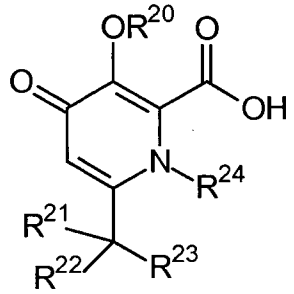
Pyridone derivatives and their use in the treatment, amelioration or prevention of a viral disease

Field of the invention

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



(II)

which is useful in treating, ameloriating 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 infection to worldwide public health has been highlighted by, firstly, the ongoing level transmission to humans of the highly pathogenic avian influenza A virus 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 influenza virus strain A/H1N1 that has rapidly spread around the

entire world (http://www.who.int/csr/disease/swineflu/en/). Whilst the new virus strain is highly contagious but currently generally results in relatively mild illness, the future evolution of this virus is unpredictable. In a much more serious, but highly plausible scenario, H5N1 and related highly pathogenic avian influenza viruses could acquire mutations rendering them more easily transmissible between humans or the new A/H1N1 could become more virulent and only a single point mutation would be enough to confer resistance to oseltamivir (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 accepted that to bridge the period before a new vaccine is 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 high priority, having been largely abandoned by the major pharmaceutical companies once the neuraminidase inhibitors 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 antiviral activity preventing the release of virus from the cells, however, not the virus production itself. 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 a possible pandemic. However, these medicaments only provide a reduction in the duration of the clinical disease. Alternatively, adamantanes, the other class of licenced anti-influenza drugs (e.g.amantadine and rimantadine) target the viral M2 ion channel protein, which is located in the viral membrane interfering with the uncoating of the virus particle 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 and isavirus belong to the family of Orthomyxoviridae which, as well as the family of the Bunyaviridae, including the Hantavirus, Nairovirus, Orthobunyavirus, and Phlebovirus, amongst others, 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 negative-sense viral RNA (vRNA) into viral mRNAs (i.e. transcription) 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 residing within the PA subunit (Dias et al., Nature 2009, 458, 914-918) have been identified and and their molecular architecture has been characterized. These two sites are critical for the unique "cap-snatching" mode used to initiate mRNA transcription that is used by the influenza virus and certain other virus families of this genus to generate viral mRNAs. A 5' cap is a modified guanine nucleotide that has been added to the 5' end of a messenger RNA. The 5' cap (also termed an RNA cap or RNA m7G 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 (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).

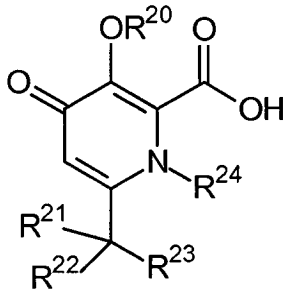
The polymerase complex seems to be an appropriate antiviral drug target since it is essential for synthesis of viral mRNA and viral replication and contains several functional active sites likely to be significantly different from those found in host cell proteins (Magden, J. et al., (2005), Appl. Microbiol. 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).

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 (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, codrugs, cocrystals, 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 (II) and optionally one or more pharmaceutically acceptable excipient(s) and/or carrier(s).

The compounds having the general formula (II) 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 3 to 12 carbon atoms.

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

"3- to 7-membered carbo- or heterocyclic ring" refers to a three-, four-, five-, six- or seven-membered ring wherein none, one or more of the carbon atoms in the ring have been replaced by 1 or 2 (for the three-membered ring), 1, 2 or 3 (for the four-membered ring) 1, 2, 3, or 4 (for the five-membered ring) or 1, 2, 3, 4, or 5 (for the six-membered ring) and 1, 2, 3, 4, 5 or 6 (for the seven-membered ring) of the same or different heteroatoms, whereby the heteroatoms are selected from O, N and S.

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 “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 include pyrrole, pyrrolidine, oxolane, furan, imidazolidine, imidazole, pyrazole, oxazolidine, oxazole, thiazole, piperidine, pyridine, morpholine, piperazine, and dioxolane.

The term "hydrocarbon group which contains from 5 to 20 carbon atoms and optionally 1 to 4 heteroatoms selected from O, N and S and which contains at least one ring" refers to any group having 5 to 20 carbon atoms and optionally 1 to 4 heteroatoms selected from O, N and 2 as long as the group contains at least one ring. The term is also meant to include bicyclic, tricyclic and polycyclic versions thereof. If more than one ring is present, they can be separate from each other or be annelated. The ring(s) can be either carbocyclic or heterocyclic and can be saturated, unsaturated or aromatic. The carbon atoms and heteroatoms can either all be

present in the one or more rings or some of the carbon atoms and/or heteroatoms can be present outside of the ring, e.g., in a linker group (such as $-(CH_2)_p-$ with p = 1 to 6). Examples of these groups include –(optionally substituted C_{3-7} cycloalkyl), –(optionally substituted aryl) wherein the aryl group can be, for example, phenyl, -(optionally substituted biphenyl), adamantyl, -(C_{3-7} cycloalkyl)-aryl as well as the corresponding compounds with a linker.

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 term "codrug" refers to two or more therapeutic compounds bonded via a covalent chemical bond. A detailed definition can be found, e.g., in N. Das et al., European Journal of Pharmaceutical Sciences, 41, 2010, 571–588.

The term "cocrystal" refers to a multiple component crystal in which all components are solid under ambient conditions when in their pure form. These components co-exist as a stoichiometric or non-stoichometric ratio of a target molecule or ion (i.e., compound of the present invention) and one or more neutral molecular cocrystal formers. A detailed discussion can be found, for example, in Ning Shan et al., Drug Discovery Today, 13(9/10), 2008, 440-446 and in D. J. Good et al., Cryst. Growth Des., 9(5), 2009, 2252–2264.

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. Suitable prodrugs are, for instance, esters. Specific examples of suitable groups are given, among others, in US 2007/0072831 in paragraphs [0082] to [0118] under the headings prodrugs and protecting groups. Preferred examples of the prodrug include compounds in which R^{20} is replaced by:

$P(O)(O)OR^{19}$; $C(O)OR^{19}$; $C(O)R^{19}$; or $C–R^{29}$;

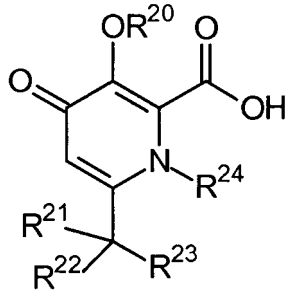
wherein R^{19} is selected from C_{5-10}aryl, C_{1-6}alkyl–C_{5-10}aryl, C_{1-6}alkyl, C_{1-6}alkyl(–O–C_{1-6}alkyl)$_n$ (with n = 1 to 30), C_{1-6}alkyl–C(O)OR, and C_{5-10}aryl–C(O)OR; and

wherein R^{29} is selected from C_{1-6}alkyl(–O–C_{1-6}alkyl)$_n$ (with n = 1 to 30), C_{1-6}alkyl–C(O)OR, and C_{5-10}aryl–C(O)OR.

The group R is H or C_{1-6} alkyl.

Compounds having the general formula (II)

The present invention provides a compound having the general formula (II).



(II)

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

X^{20} is NR^{25}, $N(R^{25})C(O)$, $C(O)NR^{25}$, O, C(O), C(O)O, OC(O); $N(R^{25})SO_2$, $SO_2N(R^{25})$, S, SO, or SO_2; preferably X^{20} is $N(R^{25})$ or $N(R^{25})SO_2$; more preferably X^{20} is $N(R^{25})SO_2$.

R^{20} is –H, a $-C_{1-6}$ alkyl group or a $-C(O)-C_{1-6}$ alkyl group. In a preferred embodiment R^{20} is –H, or –(optionally substituted C_{1-6} alkyl); more preferably –H.

R^{21} is –H, a $-C_{1-6}$ alkyl group, or a $-C_{1-6}$ alkyl group which is substituted by one or more halogen atoms; preferably R^{21} is –H.

R^{22} is –H, a $-C_{1-6}$ alkyl group, or a $-C_{1-6}$ alkyl group which is substituted by one or more halogen atoms; preferably R^{22} is –H.

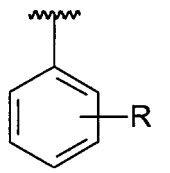
In one embodiment R^{21} and R^{22} can be joined together to form a 3- to 7-membered carbo- or heterocyclic ring.

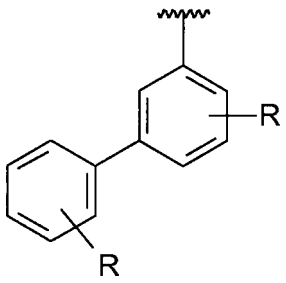
R^{23} is $-R^{26}$, or $-X^{20}-R^{26}$. In one embodiment R^{23} is $-R^{26}$. In an alternative embodiment, R^{23} is $-X^{20}-R^{26}$.

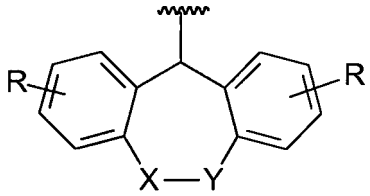
R^{24} is H, or a C_{1-6} alkyl group.

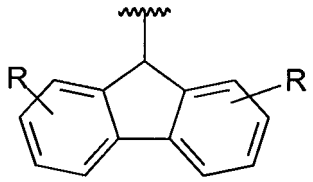
R^{25} is –H, –(optionally substituted C_{1-6} alkyl), –(optionally substituted C_{3-7} cycloalkyl), –(optionally substituted aryl), $-C_{1-4}$ alkyl–(optionally substituted C_{3-7} cycloalkyl), or $-C_{1-4}$ alkyl–(optionally substituted aryl). In a preferred embodiment R^{25} is –H or –(optionally substituted C_{1-6} alkyl).

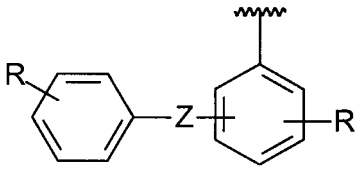
R^{26} is –(optionally substituted hydrocarbon group which contains from 5 to 20 carbon atoms and optionally 1 to 4 heteroatoms selected from O, N and S and which contains at least one ring). Preferably, the at least one ring is aromatic such as an aryl or heteroaryl ring. More preferably, R^{26} is a hydrocarbon group which contains from 5 to 20 carbon atoms and optionally 1 to 4 heteroatoms and which contains at least two rings, wherein the hydrocarbon group can be optionally substituted. Even more preferably, at least one of the at least two rings is aromatic such as an aryl or heteroaryl ring. Preferred examples of R^{26} can be selected from the group consisting of











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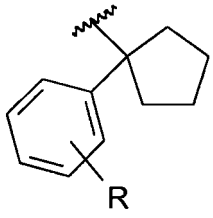


X is absent, CH_2, NH, C(O)NH, S or O. Furthermore,

Y is CH_2.

In an alternative embodiment, X and Y can be joined together to form an annulated, carbo- or heterocylic 3- to 8-membered ring which can be saturated or unsaturated. Specific examples of X-Y include $-CH_2-$, $-CH_2-CH_2-$, -O-, and -NH-.

Z is O or S.

R is independently selected from –H, $-C_{1-6}$ alkyl, $-CF_3$, –halogen, –CN, –OH, and $-O-C_{1-6}$ alkyl.

R^{27} is –H, $-C_{1-6}$ alkyl, or $-(CH_2CH_2O)_rH$; preferably R^{27} is –H, or $-C_{1-6}$ alkyl.

R^{28} is –H, or $-C_{1-6}$ alkyl.

R is independently selected from $-C_{1-6}$ alkyl, $-C(O)-C_{1-6}$ alkyl, –Hal, $-CF_3$, –CN, $-COOR^{27}$, $-OR^{27}$, $-(CH_2)_qNR^{27}R^{28}$, $-C(O)-NR^{27}R^{28}$, and $-NR^{27}-C(O)-C_{1-6}$ alkyl. Preferably R is –Hal, $-CF_3$, or –CN, more preferably –Hal, or $-CF_3$..

q is 0 to 4.

r is 1 to 3.

The optional substituent of the alkyl group, aryl group, hydrocarbon group and/or cycloalkyl group is selected from the group consisting of one or more substituents R, which includes $-C_{1-6}$ alkyl, $-C(O)-C_{1-6}$ alkyl, –Hal, $-CF_3$, –CN, $-COOR^{27}$, $-OR^{27}$, $-(CH_2)_qNR^{27}R^{28}$, $-C(O)-NR^{27}R^{28}$, and $-NR^{27}-C(O)-C_{1-6}$ alkyl. Preferably, the optional substituent of the aryl group, hydrocarbon group and/or cycloalkyl group is -halogen (preferably F), $-OCH_3$ or -CN. Preferably, the optional substituent of the alkyl group is selected from the group consisting of halogen, –CN, $-NR^{28}R^{28}$ (wherein each R^{28} is chosen independently of each other), –OH, and $-O-C_{1-6}$ alkyl. Preferably the substituent of the alkyl group is –halogen, more preferably F.

The present inventors have surprisingly found that the compounds of the present invention which have a bulky moiety R^{23} have improved pharmacological properties compared to corresponding compounds which have a smaller moiety R^{23}. Without wishing to be bound by theory it is assumed that the viral polymerase protein has a pocket for binding and that the bulky moiety R^{23} of the compounds of the present invention fills this pocket to a larger extent. It is further assumed that the larger moiety R^{23} is able to provide more hydrophobic interaction with the pocket than smaller moieties such as methyl.

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 dispersions. 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, croscarmellose, 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 hydrofluoro-alkane 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, from 10 mg to 200 mg of the compound are 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 10 mg to 500 mg/kg body weight, if rectal or intragastric administration is used and in ranges of 1 to 100 mg/kg body weight if parenteral administration is used. For intranasal administration, 1 to 100 mg/kg body weight are envisaged.

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

Family	Virus (preferred examples)
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

Family	Virus (preferred examples)
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. The present invention covers all virus genera belonging to the family of orthomyxoviridae, specifically influenza virus type A, B, and C, isavirus, and thogotovirus. Within the present invention, the term "influenza" includes influenza caused by any influenza virus such as influenza virus type A, B, and C including their various stains and isolates, and also covers influenza A virus strains commonly referred to as bird flu and swine flu. The subject to be treated is not particularly restricted and can be any vvertebrate, 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 that of influenza virus. More specifically it is assumed that they directly interfere with the N-terminal part of the influenza virus PA protein, which harbors endonuclease activity and is essential for influenza virus replication. Influenza virus replication takes place inside the cell within the nucleus. Thus, compounds designed to inhibit PA endonuclease activity need to cross both the cellular and the nuclear membrane, a property which strongly depends on designed-in physico-chemical properties of the compounds. The present invention shows that the claimed compounds have *in vitro* endonuclease inhibitory activity and have antiviral activity *in vitro* in cell-based assays.

A possible measure of the *in vitro* endonuclease inhibitory activity of the compounds having the formula (II) is the FRET (fluorescence-resonance energy transfer)–based 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) measured as fluorescence increase of a dual-labelled RNA substrate cleaved by the influenza virus endonuclease subunit (PA-Nter) upon compound treatment compared to untreated samples. Preferably, the compounds exhibit an IC_{50} of less than about 40 µM, more preferably less than about 20 µM, in this 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.

The compounds having the general formula (II) 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 that has been caused by influenza virus infection and conditions associated with this viral infection such as viral pneumonia or secondary bacterial pneumonia and medicaments to treat symptoms such as chills, fever, sore throat, muscle pains, severe headache, coughing, weakness and fatigue. Furthermore, the compounds having the general formula (I) can be used in combination with anti-inflammatories.

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

(i) The combination with 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 as defined in the US applications with the serial numbers 61/550,045 (filed on October 21, 2011), 61/650,713 (filed on May 23, 2012), 61/650,725 (filed on May 23, 2012) and 61/679,968 (filed on August 6, 2012). The complete disclosure of these applications is incorporated herein by reference. In particular, all descriptions with respect to the general formula of the compounds according to these US applications, the preferred embodiments of the various

substituents as well as the medical utility and advantages of the compounds are incorporated herein by reference.

Further preferred endonuclease inhibitors are the compounds having the general formula (I) as defined in the copending application with attorney's docket number U2797 US, and the compounds having the general formula (V) as defined in the copending application with attorney's docket number U2799 US, which were filed on even date herewith, the complete disclosure of which is incorporated by reference. In particular, all descriptions with respect to the general formula of these compounds, the preferred embodiments of the various substituents as well as the medical utility and advantages of the compounds are incorporated herein by reference. These compounds can be optionally in the form of a pharmaceutically acceptable salt, solvate, polymorph, codrug, cocrystal, prodrug, tautomer, racemate, enantiomer, or diastereomer or mixture thereof.

The cap-binding inhibitors 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) as defined in US application 61/550,057 (filed on October 21, 2011) 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 US 61/550,057 or 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.

Widespread resistance to both classes of licensed influenza antivirals (M2 ion channel inhibitors (adamantanes) and neuraminidase inhibitors (e.g. oseltamivir)) occurs in both pandemic and seasonal emerging influenza strains, 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 adamantanes (rimantadine and amantadine), and for oseltamivir, the most widely prescribed neuraminidase inhibitor (NAI), 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 NAIs 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 were 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 which is essential 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 active sites are highly conserved among all influenza A strains (e.g., avian and human) and even influenza B viruses, and hence this high degree of sequence conservation underpins the perception that these targets are not likely to trigger rapid resistant virus generation. Additionally, close interaction with host proteins render these viral proteins less prone to mutations. 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 virus) focusing on the combination with (preferably influenza virus) polymerase inhibitors as dual or multiple combination therapy. Influenza virus polymerase inhibitors are novel drugs targeting the transcription and replication activity of the polymerase. Selective inhibitors against 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 requiring different 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 above 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 (e.g., cap-binding and endonuclease 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 formula (II).

The second 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) as defined in the US application with the serial number 61/550,045 filed on October 21, 2011, the compounds having the general formula (II) as defined in US application 61/550,057 filed on October 21, 2011, the compounds disclosed in WO 2011/000566, WO 2010/110231, WO 2010/110409, WO 2006/030807 or 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 neuraminidase inhibitors

Influenza virus polymerase inhibitors are novel drugs targeting the transcription and replication activity of the polymerase. 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 requiring different 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 above 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 neuraminidase 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 and replication activity of the polymerase. 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 requiring different 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 above 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 and replication activity of the polymerase. The combination of a polymerase inhibitor specifically addressing a viral intracellular target, with an inhibitor of a different host-cell 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 requiring different 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 above for polymerase inhibitors would prevail for combinations of inhibitors of cellular targets interacting with viral replication 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 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 and replication activity of the polymerase. 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 requiring different 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 above 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 (e.g., ErbB tyrosine kinase, Abl kinase family, MAP kinases, PKCa-mediated activation of ERK signalling) as well as interferon (inducers).

(vii) The combination of (preferably influenza) polymerase inhibitors with a compound used as an adjuvant 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 and replication activity of the polymerase.. The combination of a polymerase inhibitor specifically addressing a viral intracellular target with a 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 requiring different 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 above for polymerase inhibitors would prevail for combinations of inhibitors of different antiviral targets with polymerase inhibitors.

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

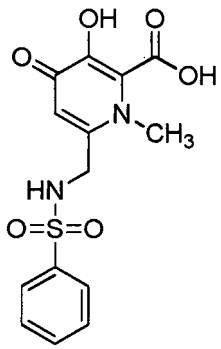
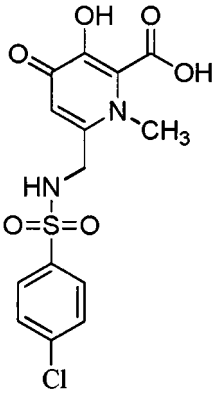
FRET endonuclease activity assay

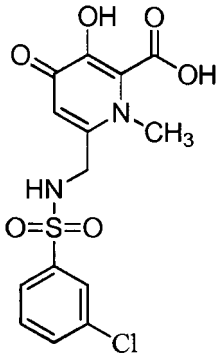
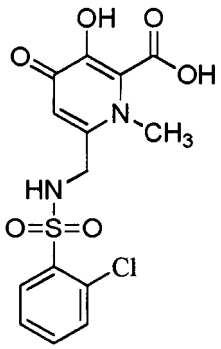
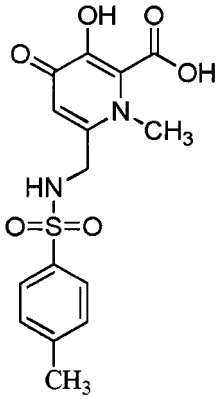
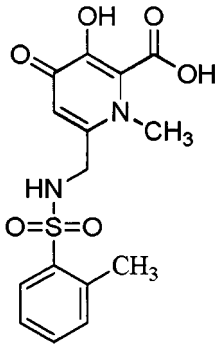
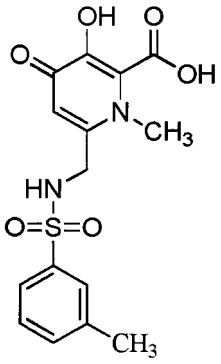
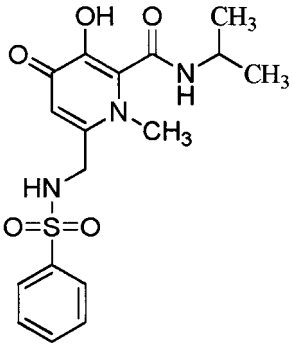
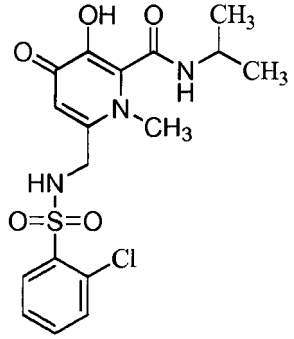
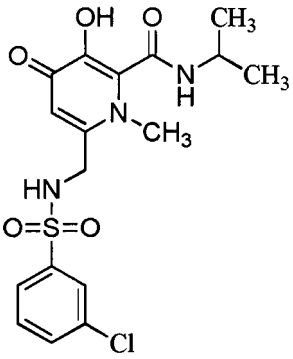
The influenza A virus (IAV) PA-Nter fragment (amino acids 1 – 209) harboring the influenza endonuclease activity was generated and purified as described in Dias et al., Nature 2009; Apr 16; 458(7240), 914-918. The protein was dissolved in buffer containing 20mM Tris pH 8.0, 100mM NaCl and 10mM β-mercaptoethanol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

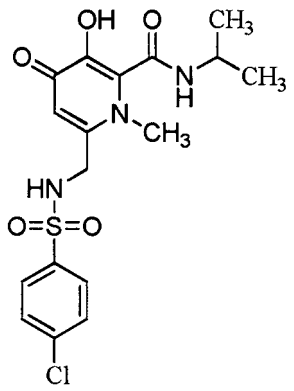
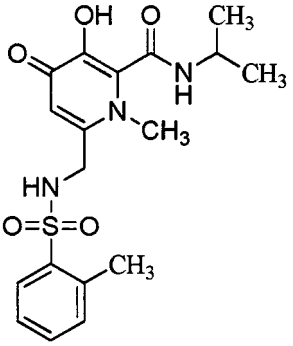
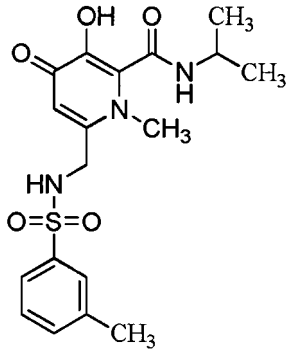
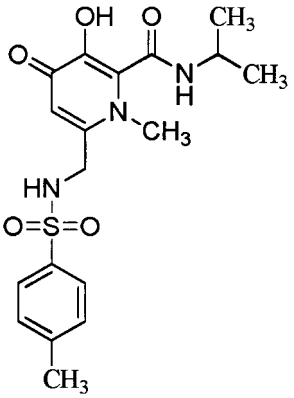
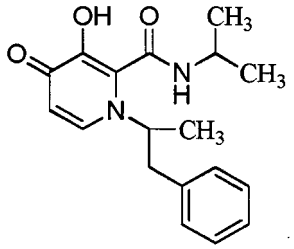
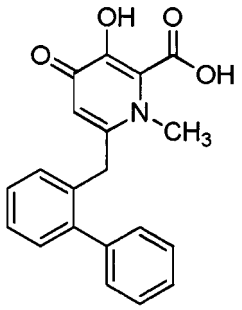
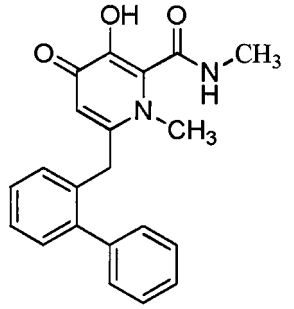
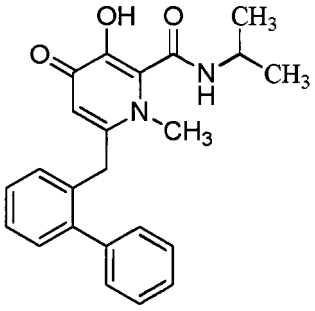
A 20 bases dual-labelled RNA oligo with 5´-FAM fluorophore and 3´-BHQ1 quencher was used as a substrate to be cleaved by the endonuclease activity of the PA-Nter. Cleavage of the RNA substrate frees the fluorophore from the quencher resulting in an increase of the fluorescent signal.

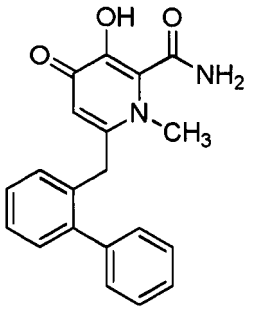
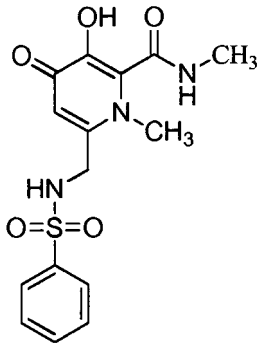
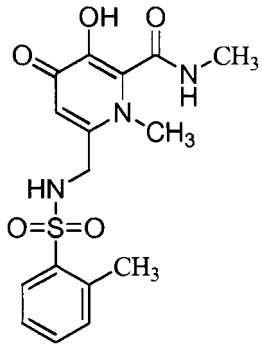
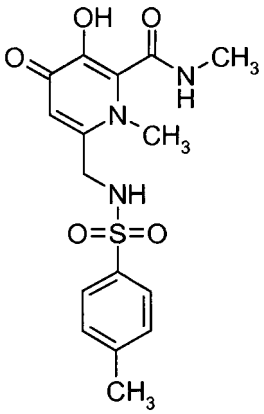
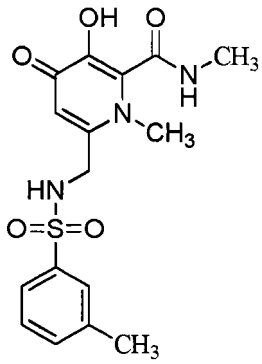
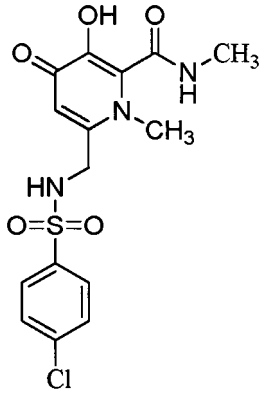
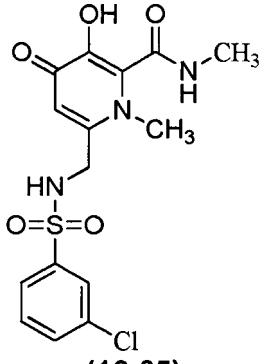
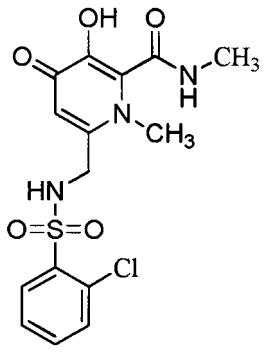
All assay components were diluted in assay buffer containing 20mM Tris-HCl pH 8.0, 100mM NaCl, 1mM $MnCl_2$, 10mM $MgCl_2$ and 10mM β-mercaptoethanol. The final concentration of PA-Nter was 0.5µM and 1.6µM RNA substrate. The test compounds were dissolved in DMSO and generally tested at two concentrations 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.

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) in a given concentration series ranging from maximum 100 µM to at least 2 nM.

Formula no.	FRET	Formula no.	FRET
 (14-01)	IC_{50}=0.56 µM	 (14-07)	IC_{50}=1.14µM

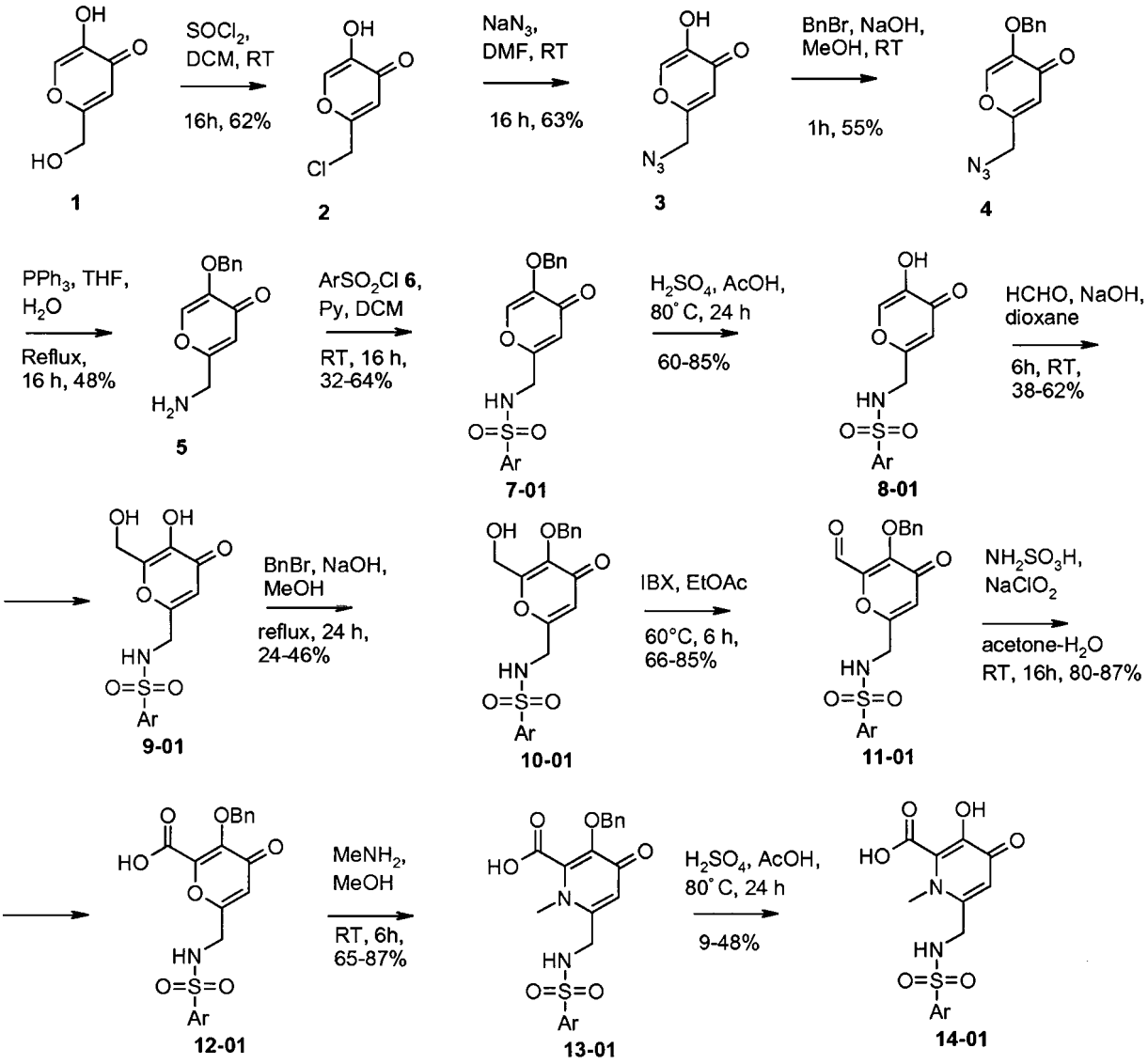
 **(14-05)**	IC_{50}=0.15 µM	 **(14-03)**	IC_{50}=0.11µM
 **(14-06)**	IC_{50}=0.97 µM	 **(14-02)**	IC_{50}=0.28 µM
	IC_{50}=0.53 µM	 **(18-01)**	13% inhibition @ 10 µM
 **(18-03)**	IC_{50}=6.3 µM	 **(18-05)**	13% inhibition @ 10 µM

 **(18-07)**	11% inhibition @ 10 µM	 **(18-02)**	IC_{50}=4.6 µM
 **(18-04)**	36% inhibition @ 10 µM	 **(18-06)**	8% inhibition @ 10 µM
	7% inhibition @ 10 µM		IC_{50}=0.40 µM
	10% inhibition @ 10 µM		13% inhibition @ 10 µM

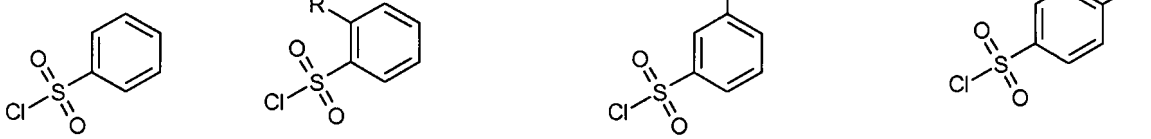
	17% inhibition @ 10 µM	 **(16-01)**	13% inhibition @ 10 µM
 **(16-02)**	IC_{50}=12.2 µM	 **(16-06)**	10% inhibition @ 10 µM
 **(16-04)**	33% inhibition @ 10 µM	 **(16-07)**	7% inhibition @ 10 µM
 **(16-05)**	23% inhibition @ 10 µM	 **(16-03)**	IC_{50}=9.0 µM

Synthetic pathway

Scheme 1:



ArSO$_2$Cl =



14-01

14-02, R = Me
14-03, R = Cl

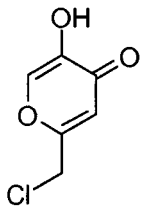
14-04, R = Me
14-05, R = Cl

14-06, R = Me
14-07, R = Cl

5

Experimental:

Preparation of (2):

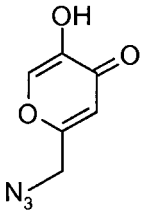


2-Chloromethyl-5-hydroxy-pyran-4-one

To a stirred solution of 5-hydroxy-2-hydroxymethyl-pyran-4-one (**1**) (100.0 g, 703.68 mmol) in dichloromethane (750 mL) was added $SOCl_2$ (102.0 mL) very slowly and the reaction mixture was stirred at room temperature for 16 h. After completion of the reaction, the solvent was evaporated to remove volatile compounds under reduced pressure to get a crude compound. It was then purified by hexane wash to get 2-chloromethyl-5-hydroxy-pyran-4-one (**2**) (70.0 g, 61.96 %) as an off white solid.

LC-MS: 161.2 (M+H).

Preparation of (3):

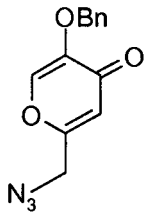


2-Azidomethyl-5-hydroxy-pyran-4-one

To a stirred solution of 2-chloromethyl-5-hydroxy-pyran-4-one (**2**) (105.0 g, 656.2 mmol) in DMF (600 mL) was added NaN_3 (55.45 g, 853.12 mmol) and the reaction mixture was stirred at room temperature for 16 h. After completion of the reaction, the reaction mixture was diluted with water and extracted with ethyl acetate. Then, the combined organic layer was washed with water and brine, and dried over Na_2SO_4 and concentrated under reduced pressure to get 2-azidomethyl-5-hydroxy-pyran-4-one (**3**) (70.0 g, 63.83 %) as a light brown solid.

LC-MS: 168.2 (M+H).

Preparation of (4):

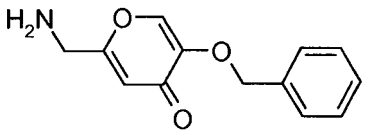


2-Azidomethyl-5-benzyloxy-pyran-4-one

To a stirred solution of 2-azidomethyl-5-hydroxy-pyran-4-one (**3**) (70.0 g, 419.1 mmol) in methanol (500 mL) was added NaOH (20 g, 502.9 mmol, 2M) and benzyl bromide (60.14 mL, 502.9 mmol) and the reaction mixture was stirred at room temperature for 1 h. After completion of the reaction, solvent was evaporated to remove volatile compounds under reduce pressure, then it was diluted with water and extracted with ethyl acetate. Then the combined organic layer was washed with water and brine, dried over Na_2SO_4, concentrated under reduced pressure and purified using normal column chromatography (using 20% ethyl acetate in hexane) to get 2-azidomethyl-5-benzyloxy-pyran-4-one (**4**) (60.0 g, 55.0 %) as a light brown solid.

LC-MS: 258.0 (M+H).

Preparation of (5):



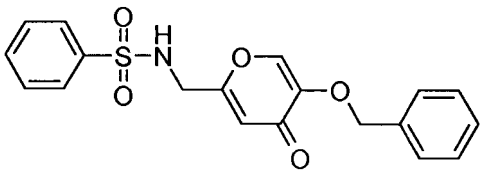
2-Aminomethyl-5-benzyloxy-pyran-4-one

To a stirred solution of 2-azidomethyl-5-benzyloxy-pyran-4-one (**4**) (30.0 g, 116.7 mmol) in tetrahydrofuran (500 mL) were added triphenyl phosphine (61.16 g, 233.46 mmol) and water (5.2 mL) and the mixture was refluxed for 16 h. After completion of the reaction, solvent was

evaporated under reduced pressure, then it was purified by normal column chromatography to get (2-aminomethyl-5-benzyloxy-pyran-4-one (**5**) (13.0 g, 48.16 %) as a brown solid.

LC-MS: 232.2 (M+H).

Preparation of (7-01):

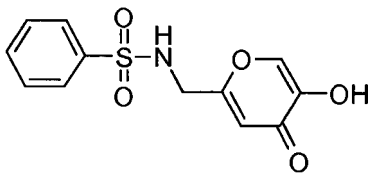


N-(5-Benzyloxy-4-oxo-4H-pyran-2-ylmethyl)-benzenesulfonamide

To a stirred solution of 2-aminomethyl-5-benzyloxy-pyran-4-one (**5**) (4.4 gm, 19.05 mmol) in dichloromethane (100 mL) was added pyridine (6.15 mL, 76.19 mmol) under ice cold conditions, followed by addition of benzene sulfonyl chloride (**6-01**) (6.07 mL, 47.62 mmol) and the reaction mixture was stirred at room temperature for 16 h. After completion of the reaction, it was quenched with water and extracted with ethyl acetate. The combined organic layer was washed with saturated $NaHCO_3$, water and brine, dried over Na_2SO_4 and concentrated under reduced pressure. It was then purified using normal column chromatography to get N-(5-benzyloxy-4-oxo-4H-pyran-2-ylmethyl)-benzene sulfonamide (**7-01**) (2.3 gm, 32.51 %) as an off white solid.

LCMS: 372.0 (M+H).

Preparation of (8-01):

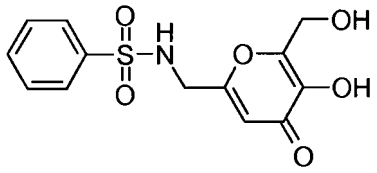


N-(5-Hydroxy-4-oxo-4H-pyran-2-ylmethyl)-benzenesulfonamide

N-(5-Benzyloxy-4-oxo-4H-pyran-2-ylmethyl)-benzene sulfonamide (**7-01**) (2.0 g, 5.39 mmol) was dissolved in acetic acid (25.0 mL) and sulfuric acid (0.058 mL) was added, then the reaction mixture was heated up to 80 °C for 24 h. After completion of the reaction, the mixture was cooled to room temperature and concentrated under vacuum. It was then diluted with water and extracted with ethyl acetate. The combined organic layer was washed with water and brine, dried over Na_2SO_4 and concentrated under reduced pressure. It was then purified by washing with hexane to get N-(5-hydroxy-4-oxo-4H-pyran-2-ylmethyl)-benzene sulfonamide (**8-01**) (1.3 gm, 85.53 %) as a brown solid.

LCMS: 282.0 (M+H).

Preparation of (9-01):

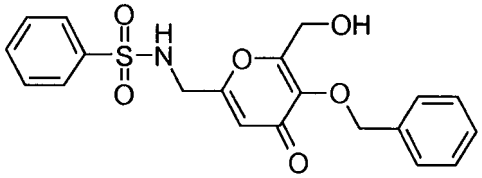


N-(5-Hydroxy-6-hydroxymethyl-4-oxo-4H-pyran-2-ylmethyl)-benzene sulfonamide

To a stirred solution of N-(5-hydroxy-4-oxo-4H-pyran-2-ylmethyl)-benzene sulfonamide (**8-01**) (1.1 g, 3.92 mmol) in dioxane (20 mL) were added 37 % formaldehyde solution (0.47 mL, 4.69 mmol) and aqueous NaOH (1.95 mL, 3.92 mmol, 2M) and the mixture was stirred for 6 h at room temperature. After completion of the reaction, it was concentrated under vacuum to get a crude compound. It was then purified using normal column chromatography to get N-(5-hydroxy-6-hydroxymethyl-4-oxo-4H-pyran-2-ylmethyl)-benzene sulfonamide (**9-01**) (470.0 mg, 38.57 %) as a white solid.

LCMS: 312.2 (M+H).

Preparation of (10-01):

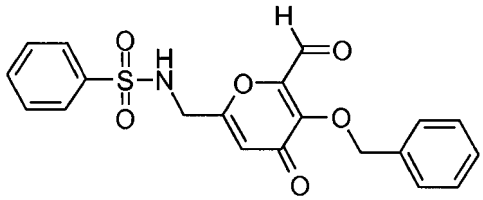


N-(5-Benzyloxy-6-hydroxymethyl-4-oxo-4H-pyran-2-ylmethyl)-benzene sulfonamide

To a stirred solution of N-(5-hydroxy-6-hydroxymethyl-4-oxo-4H-pyran-2-ylmethyl)-benzene sulfonamide (**9-01**) (1.7 g, 5.46 mmol) in methanol (30 mL) aqueous NaOH (218.4 mg, 5.46 mmol, 2M) was added. After heating to reflux, benzyl bromide (0.654 mL, 5.46 mmol) was added and heating was continued for 24 h. After completion of the reaction, the mixture was concentrated to remove methanol, then diluted with water and extracted with dichloromethane. The combined organic layer was washed with saturated $NaHCO_3$ solution, water and brine, dried over Na_2SO_4 and concentrated under reduced pressure. It was then purified using normal column chromatography to get N-(5-benzyloxy-6-hydroxymethyl-4-oxo-4H-pyran-2-ylmethyl)-benzene sulfonamide (**10-01**) (1.02 gm, 46.48 %) as a white solid.

LCMS: (M+H: 402.0).

Preparation of (11-01):

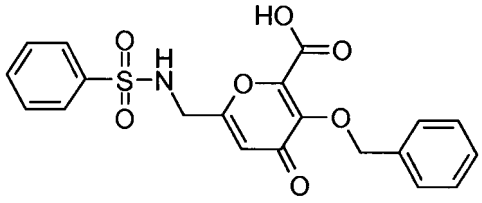


N-(5-Benzyloxy-6-formyl-4-oxo-4H-pyran-2-ylmethyl)-benzene sulfonamide

To a stirred solution of N-(5-benzyloxy-6-hydroxymethyl-4-oxo-4H-pyran-2-ylmethyl)-benzene sulfonamide (**10-01**) (2.8 g, 6.98 mmol) in ethyl acetate (100 mL) IBX (2-iodoxy benzoic acid) (5.86 gm, 20.95 mmol) was added and the reaction mixture was heated up to 60 °C for 6 h. After completion of the reaction, the reaction mixture was filtered and concentrated to get the crude compound. It was then purified using normal column chromatography to get N-(5-benzyloxy-6-formyl-4-oxo-4H-pyran-2-ylmethyl)-benzene sulfonamide (**11-01**) (2.0 g, 71.71 %) as a gummy liquid.

LCMS: (M+H: 400.0).

Preparation of (12-01):

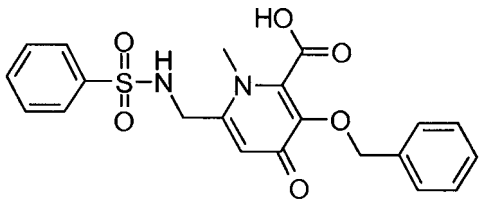


6-(Benzene sulfonyl amino-methyl)-3-benzyloxy-4-oxo-4H-pyran-2-carboxylic acid

To a stirred solution of N-(5-benzyloxy-6-formyl-4-oxo-4H-pyran-2-ylmethyl)-benzene sulfonamide (**11-01**) (700.0 mg, 1.75 mmol) in acetone (10 mL) and water (15 mL) were added sulfamic acid (240.45 mg, 2.45 mmol) and sodium chlorite (166.6 mg, 1.84 mmol) and the reaction mixture was allowed to stir for 16 h at room temperature. After completion of the reaction, the solvent and the volatile substances were removed and extracted with dichloromethane. The combined organic layer was washed with saturated ammonium chloride solution, water and then brine, dried over Na_2SO_4 and concentrated under reduced pressure to get 6-(benzene sulfonyl amino-methyl)-3-benzyloxy-4-oxo-4H-pyran-2-carboxylic acid (**12-01**) (640.0 mg, 87.82 %) as a white solid.

LCMS: 414.2 (M-H).

Preparation of (13-01):



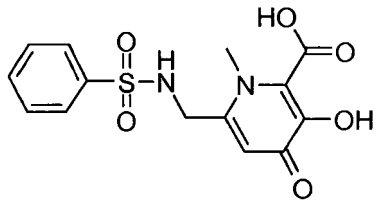
6-(Benzene sulfonyl amino-methyl)-3-benzyloxy-1-methyl-4-oxo-1, 4-dihydro-pyridine-2-carboxylic acid

To a stirred solution of 6-(benzene sulfonyl amino-methyl)-3-benzyloxy-4-oxo-4H-pyran-2-carboxylic acid (**12-01**) (640.0 mg, 1.54 mmol) in MeOH (5.0 mL) was added methylamine (2 M in methanol, 2.0 mL) at room temperature and the mixture was stirred for 6 h at room temperature. After completion of the reaction, the solvent was removed under reduced pressure to get the crude compound. It was then purified using normal column

chromatography to get 6-(benzene sulfonyl amino-methyl)-3-benzyloxy-1-methyl-4-oxo-1,4-dihydro-pyridine-2-carboxylic acid (**13-01**) (430.0 mg, 65.08 %) as a yellow solid.

LCMS: (M+H: 429.0).

Preparation of (14-01):

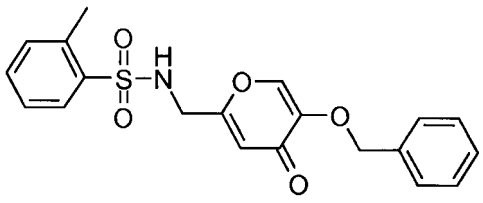


6-(Benzenesulfonyl amino-methyl)-3-hydroxy-1-methyl-4-oxo-1,4-dihydro-pyridine-2-carboxylic acid

To a stirred solution of 6-(benzene sulfonyl amino-methyl)-3-benzyloxy-1-methyl-4-oxo-1,4-dihydro-pyridine-2-carboxylic acid (**13-01**) (430.0 mg, 1.005 mmol) in acetic acid (15 mL) was added sulfuric acid (0.011 mL) and the reaction mixture was heated at 80 °C for 24 h. After completion of the reaction, it was concentrated and the reaction mixture was quenched with ice and solid was precipitated. Resulted solid was filtered and dried to get the crude product. It was then washed with 20 % methanol and ethyl acetate to get 6-(benzene sulfonyl amino-methyl)-3-hydroxy-1-methyl-4-oxo-1,4-dihydro-pyridine-2-carboxylic acid (**14-01**) (160.0 mg, 47.07 %) as an off white solid.

LCMS: 338.8 (M+H).

Preparation of (7-02):

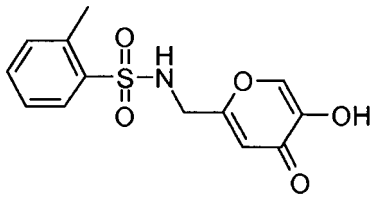


N-(5-Benzyloxy-4-oxo-4H-pyran-2-ylmethyl)-2-methyl-benzenesulfonamide

N-(5-Benzyloxy-4-oxo-4H-pyran-2-ylmethyl)-2-methyl-benzenesulfonamide (**7-02**) (22.0 g, 64.32 %) was synthesized as a light brown solid from 2-aminomethyl-5-benzyloxy-pyran-4-one (**5**) (20.5 g, 88.74 mmol) and 2-methyl-benzenesulfonyl chloride (**6-02**) (20.23 g, 106.49 mmol) following the procedure described for N-(5-benzyloxy-4-oxo-4H-pyran-2-ylmethyl)-benzenesulfonamide (**7-01**).

LC-MS: 386.0 (M+H).

Preparation of (8-02):

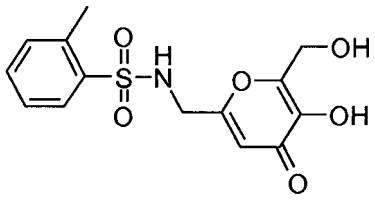


N-(5-Hydroxy-4-oxo-4H-pyran-2-ylmethyl)-2-methyl-benzenesulfonamide

N-(5-Hydroxy-4-oxo-4H-pyran-2-ylmethyl)-2-methyl-benzenesulfonamide (**8-02**) (14.0 g, crude) was synthesized as a light brown solid from N-(5-benzyloxy-4-oxo-4H-pyran-2-ylmethyl)-2-methyl-benzenesulfonamide (**7-02**) (22.0 g, 57.14 mmol) following the procedure described for N-(5-hydroxy-4-oxo-4H-pyran-2-ylmethyl)-benzenesulfonamide (**8-01**).

LC-MS: 296.2 (M+H).

Preparation of (9-02):

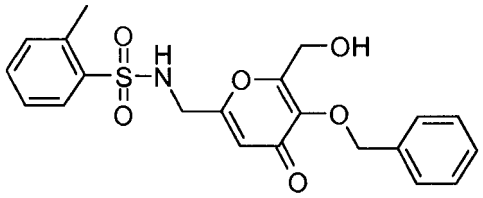


N-(5-Hydroxy-6-hydroxymethyl-4-oxo-4H-pyran-2-ylmethyl)-2-methyl-benzenesulfonamide

N-(5-Hydroxy-6-hydroxymethyl-4-oxo-4H-pyran-2-ylmethyl)-2-methyl-benzenesulfonamide (**9-02**) (9.0 g, 62.78 %) was synthesized as a white solid from N-(5-hydroxy-4-oxo-4H-pyran-2-ylmethyl)-2-methyl-benzenesulfonamide (**8-02**) (13.0 g, 44.06 mmol) following the procedure described for N-(5-hydroxy-6-hydroxymethyl-4-oxo-4H-pyran-2-ylmethyl)-benzenesulfonamide (**9-01**).

LC-MS: 326.2 (M+H).

Preparation of (10-02):

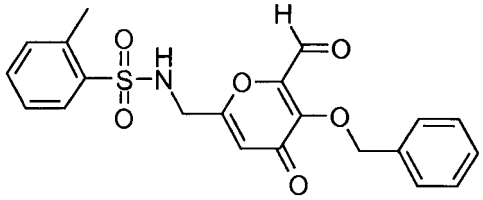


N-(5-Benzyloxy-6-hydroxymethyl-4-oxo-4H-pyran-2-ylmethyl)-2-methyl-benzenesulfonamide

N-(5-Benzyloxy-6-hydroxymethyl-4-oxo-4H-pyran-2-ylmethyl)-2-methyl-benzenesulfonamide (**10-02**) (4.7 g, 40.85 %) was synthesized as a white solid from N-(5-hydroxy-6-hydroxymethyl-4-oxo-4H-pyran-2-ylmethyl)-2-methyl-benzenesulfonamide (**9-02**) (9.0 g, 27.69 mmol) following the procedure described for N-(5-benzyloxy-6-hydroxymethyl-4-oxo-4H-pyran-2-ylmethyl)-benzenesulfonamide (**10-01**).

LC-MS: 416.0 (M+H).

Preparation of (11-02):

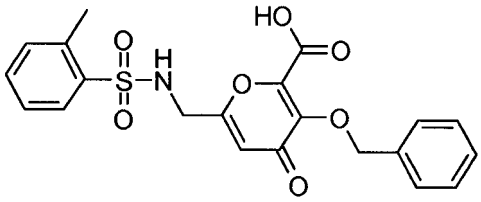


N-(5-Benzyloxy-6-formyl-4-oxo-4H-pyran-2-ylmethyl)-2-methyl-benzenesulfonamide

N-(5-Benzyloxy-6-formyl-4-oxo-4H-pyran-2-ylmethyl)-2-methyl-benzenesulfonamide (**11-02**) (2.8 g, 66.92 %) was synthesized as a white solid from N-(5-benzyloxy-6-hydroxymethyl-4-oxo-4H-pyran-2-ylmethyl)-2-methyl-benzenesulfonamide (**10-02**) (4.2 g, 10.12 mmol) following the procedure described for N-(5-benzyloxy-6-formyl-4-oxo-4H-pyran-2-ylmethyl)-benzenesulfonamide (**11-01**).

LC-MS: 414.0 (M+H).

Preparation of (12-02):

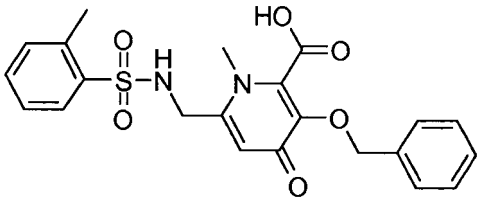


3-Benzyloxy-4-oxo-6-[(toluene-2-sulfonylamino)-methyl]-4H-pyran-2-carboxylic acid

3-Benzyloxy-4-oxo-6-[(toluene-2-sulfonylamino)-methyl]-4H-pyran-2-carboxylic acid (**12-02**) (2.0 g, crude) was synthesized as a white solid from N-(5-benzyloxy-6-formyl-4-oxo-4H-pyran-2-ylmethyl)-2-methyl-benzenesulfonamide (**11-02**) (2.8 g, 6.74 mmol) following the procedure described for 6-(benzenesulfonylamino-methyl)-3-benzyloxy-4-oxo-4H-pyran-2-carboxylic acid (**12-01**).

LC-MS: 430.0 (M+H).

Preparation of (13-02):

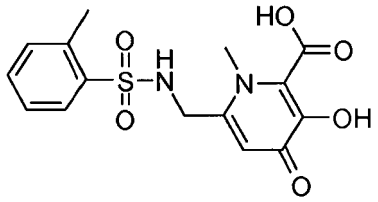


3-Benzyloxy-1-methyl-4-oxo-6-[(toluene-2-sulfonylamino)-methyl]-1,4-dihydro-pyridine-2-carboxylic acid

3-Benzyloxy-1-methyl-4-oxo-6-[(toluene-2-sulfonylamino)-methyl]-1,4-dihydro-pyridine-2-carboxylic acid (**13-02**) (1.8 g, 87.26 %) was synthesized as a yellow solid from 3-benzyloxy-4-oxo-6-[(toluene-2-sulfonylamino)-methyl]-4H-pyran-2-carboxylic acid (**12-02**) (2.0 g, 4.6 mmol) following the procedure described for 6-(benzenesulfonylamino-methyl)-3-benzyloxy-1-methyl-4-oxo-1,4-dihydro-pyridine-2-carboxylic acid (**13-01**).

LC-MS: 443.0 (M+H).

Preparation of (14-02):

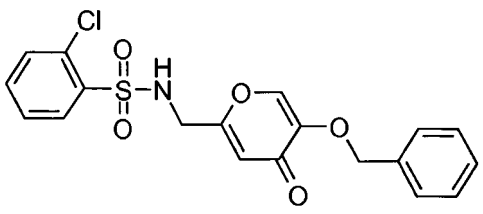


3-Hydroxy-1-methyl-4-oxo-6-[(toluene-2-sulfonylamino)-methyl]-1,4-dihydro-pyridine-2-carboxylic acid

3-Hydroxy-1-methyl-4-oxo-6-[(toluene-2-sulfonylamino)-methyl]-1,4-dihydro-pyridine-2-carboxylic acid (30.0 mg, 9.41 %, purified by Prep-HPLC) was synthesized as an off white solid from 3-benzyloxy-1-methyl-4-oxo-6-[(toluene-2-sulfonylamino)-methyl]-1,4-dihydro-pyridine-2-carboxylic acid (**13-02**) (400.0 mg, 0.905 mmol) following the procedure described for 6-(benzenesulfonylamino-methyl)-3-hydroxy-1-methyl-4-oxo-1,4-dihydro-pyridine-2-carboxylic acid (**14-02**).

LC-MS: 353.0 (M+H).

Preparation of (7-03):

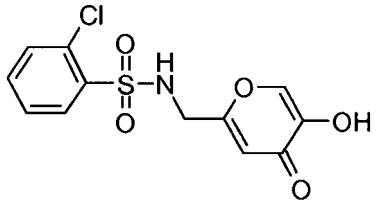


N-(5-Benzyloxy-4-oxo-4H-pyran-2-ylmethyl)-2-chloro-benzenesulfonamide

N-(5-Benzyloxy-4-oxo-4H-pyran-2-ylmethyl)-2-chloro-benzenesulfonamide (**7-03**) (26.0 g, 59.19 %) was synthesized as a light brown solid from 2-aminomethyl-5-benzyloxy-pyran-4-one (**5**) (25.0 g, 108.2 mmol) and 2-chloro-benzenesulfonyl chloride (**6-03**) (27.2 g,129.87 mmol) following the procedure described for N-(5-benzyloxy-4-oxo-4H-pyran-2-ylmethyl)-benzenesulfonamide (**7-01**).

LC-MS: 406.0 (M+H).

Preparation of (8-03):

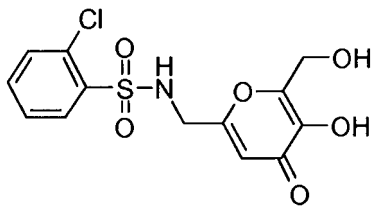


2-Chloro-N-(5-hydroxy-4-oxo-4H-pyran-2-ylmethyl)-benzenesulfonamide

2-Chloro-N-(5-hydroxy-4-oxo-4H-pyran-2-ylmethyl)-benzenesulfonamide (**8-03**) (15.0 g, crude) was synthesized as a light brown solid from N-(5-benzyloxy-4-oxo-4H-pyran-2-ylmethyl)-2-chloro-benzenesulfonamide (**7-03**) (26.0 g, 64.19 mmol) following the procedure described for N-(5-hydroxy-4-oxo-4H-pyran-2-ylmethyl)-benzenesulfonamide (**8-01**).

LC-MS: 314.2 (M-H).

Preparation of (9-03):

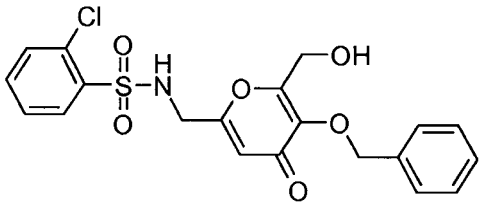


2-Chloro-N-(5-hydroxy-6-hydroxymethyl-4-oxo-4H-pyran-2-ylmethyl)-benzenesulfonamide

2-Chloro-N-(5-hydroxy-6-hydroxymethyl-4-oxo-4H-pyran-2-ylmethyl)-benzenesulfonamide (**9-03**) (8.0 g, 48.59 %) was synthesized as a white solid from 2-chloro-N-(5-hydroxy-4-oxo-4H-pyran-2-ylmethyl)-benzenesulfonamide (**8-03**) (15.0 g, 47.61 mmol) following the procedure described for N-(5-hydroxy-6-hydroxymethyl-4-oxo-4H-pyran-2-ylmethyl)-benzenesulfonamide (**9-01**).

LC-MS: 346.0 (M+H).

Preparation of (10-03):

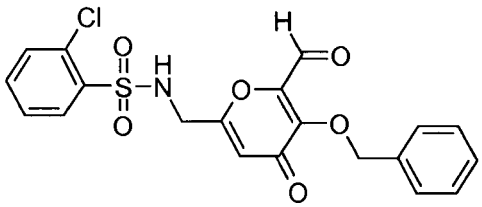


N-(5-Benzyloxy-6-hydroxymethyl-4-oxo-4H-pyran-2-ylmethyl)-2-chloro-benzenesulfonamide

N-(5-Benzyloxy-6-hydroxymethyl-4-oxo-4H-pyran-2-ylmethyl)-2-chloro-benzenesulfonamide (**10-03**) (3.5 g, 35.0 %) was synthesized as a white solid from 2-chloro-N-(5-hydroxy-6-hydroxymethyl-4-oxo-4H-pyran-2-ylmethyl)-benzenesulfonamide (**9-03**) (8.0 g, 23.18 mmol) following the procedure described for N-(5-benzyloxy-6-hydroxymethyl-4-oxo-4H-pyran-2-ylmethyl)-benzenesulfonamide (**10-01**).

LC-MS: 436.0 (M+H).

Preparation of (11-03):

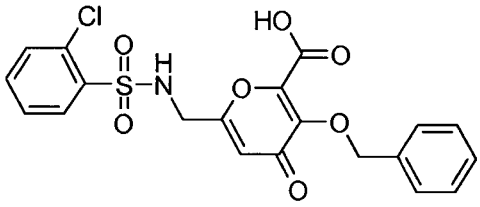


N-(5-Benzyloxy-6-formyl-4-oxo-4H-pyran-2-ylmethyl)-2-chloro-benzenesulfonamide

N-(5-Benzyloxy-6-formyl-4-oxo-4H-pyran-2-ylmethyl)-2-chloro-benzenesulfonamide (**11-03**) (2.8 g, 85.07 %) was synthesized as a brown sticky solid from N-(5-benzyloxy-6-hydroxymethyl-4-oxo-4H-pyran-2-ylmethyl)-2-chloro-benzenesulfonamide (**10-03**) (3.3 g, 7.58 mmol) following the procedure described for N-(5-benzyloxy-6-formyl-4-oxo-4H-pyran-2-ylmethyl)-benzenesulfonamide (**11-01**).

LC-MS: 433.8 (M+H).

Preparation of (12-03):

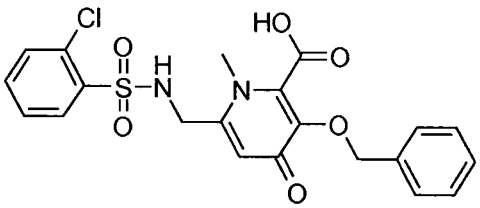


3-Benzyloxy-6-[(2-chloro-benzenesulfonylamino)-methyl]-4-oxo-4H-pyran-2-carboxylic acid

3-Benzyloxy-6-[(2-chloro-benzenesulfonylamino)-methyl]-4-oxo-4H-pyran-2-carboxylic acid (**12-03**) (2 g, crude) was synthesized as a white solid from N-(5-benzyloxy-6-formyl-4-oxo-4H-pyran-2-ylmethyl)-2-chloro-benzenesulfonamide (**11-03**) (2.8 g, 6.46 mmol) following the procedure described for 6-(benzenesulfonylamino-methyl)-3-benzyloxy-4-oxo-4H-pyran-2-carboxylic acid (**12-01**).

LC-MS: 450.0 (M+H).

Preparation of (13-03):

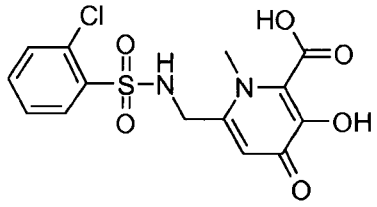


3-Benzyloxy-6-[(2-chloro-benzenesulfonylamino)-methyl]-1-methyl-4-oxo-1,4-dihydro-pyridine-2-carboxylic acid

3-Benzyloxy-6-[(2-chloro-benzenesulfonylamino)-methyl]-1-methyl-4-oxo-1,4-dihydro-pyridine-2-carboxylic acid (**13-03**) (1.7 g, 77.6 %) was synthesized as a white solid from 3-benzyloxy-6-[(2-chloro-benzenesulfonylamino)-methyl]-4-oxo-4H-pyran-2-carboxylic acid (**12-03**) (2.0 g, 4.45 mmol) following the procedure described for 6-(benzenesulfonylamino-methyl)-3-benzyloxy-1-methyl-4-oxo-1,4-dihydro-pyridine-2-carboxylic acid (**13-01**).

LC-MS: 463.0 (M+H).

Preparation of (14-03):

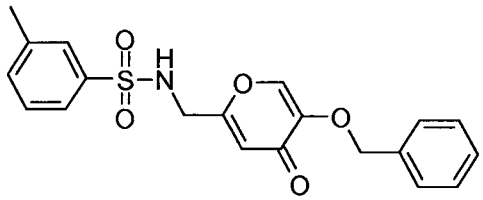


6-[(2-Chloro-benzenesulfonylamino)-methyl]-3-hydroxy-1-methyl-4-oxo-1,4-dihydro-pyridine-2-carboxylic acid

6-[(2-Chloro-benzenesulfonylamino)-methyl]-3-hydroxy-1-methyl-4-oxo-1,4-dihydro-pyridine-2-carboxylic acid (**14-03**) (120.0 mg, 37.18 %, purified by Prep-HPLC) was synthesized as a white solid from 3-benzyloxy-6-[(2-chloro-benzenesulfonylamino)-methyl]-1-methyl-4-oxo-1,4-dihydro-pyridine-2-carboxylic acid (**13-03**) (400.0 mg, 0.866 mmol) following the procedure described for 6-(benzenesulfonylamino-methyl)-3-hydroxy-1-methyl-4-oxo-1,4-dihydro-pyridine-2-carboxylic acid (**14-01**).

LC-MS: 373.4 (M+H).

Preparation of (7-04):

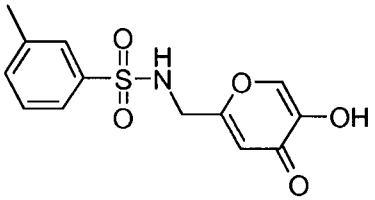


N-(5-Benzyloxy-4-oxo-4H-pyran-2-ylmethyl)-3-methyl-benzenesulfonamide

N-(5-Benzyloxy-4-oxo-4H-pyran-2-ylmethyl)-3-methyl-benzenesulfonamide (**7-04**) (24.0 g, 57.60 %) was synthesized as a light brown solid from 2-aminomethyl-5-benzyloxy-pyran-4-one (**5**) and 3-methyl-benzenesulfonyl chloride (**6-04**) (24.67 g, 129.87 mmol) following the procedure described for N-(5-benzyloxy-4-oxo-4H-pyran-2-ylmethyl)-benzenesulfonamide (**7-01**).

LC-MS: 386.0 (M+H).

Preparation of (8-04):

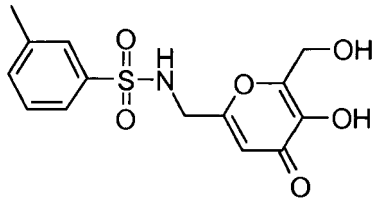


N-(5-Hydroxy-4-oxo-4H-pyran-2-ylmethyl)-3-methyl-benzenesulfonamide

N-(5-Hydroxy-4-oxo-4H-pyran-2-ylmethyl)-3-methyl-benzenesulfonamide (**8-04**) (15 g, crude) was synthesized as a light brown solid from N-(5-benzyloxy-4-oxo-4H-pyran-2-ylmethyl)-3-methyl-benzenesulfonamide (**7-04**) (24.0 g, 62.33 mmol) following the procedure described for N-(5-hydroxy-4-oxo-4H-pyran-2-ylmethyl)-benzenesulfonamide (**8-01**).

LC-MS: 296.2 (M+H).

Preparation of (9-04):

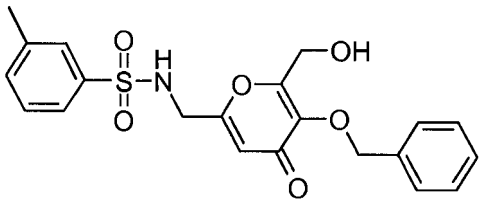


N-(5-Hydroxy-6-hydroxymethyl-4-oxo-4H-pyran-2-ylmethyl)-3-methyl-benzenesulfonamide

N-(5-Hydroxy-6-hydroxymethyl-4-oxo-4H-pyran-2-ylmethyl)-3-methyl-benzenesulfonamide (**9-04**) (7.5 g, 45.34 %) was synthesized as a white solid from N-(5-hydroxy-4-oxo-4H-pyran-2-ylmethyl)-3-methyl-benzenesulfonamide (**8-04**) (15.0 g, 50.84 mmol) following the procedure described for N-(5-hydroxy-6-hydroxymethyl-4-oxo-4H-pyran-2-ylmethyl)-benzenesulfonamide (**9-01**).

LC-MS: 326.2 (M+H).

Preparation of (10-04):

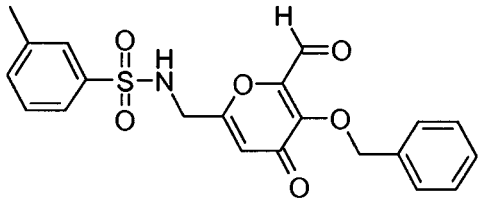


N-(5-Benzyloxy-6-hydroxymethyl-4-oxo-4H-pyran-2-ylmethyl)-3-methyl-benzenesulfonamide

N-(5-Benzyloxy-6-hydroxymethyl-4-oxo-4H-pyran-2-ylmethyl)-3-methyl-benzenesulfonamide (**10-04**) (2.6 g, 27.12 %) was synthesized as a white solid from N-(5-hydroxy-6-hydroxymethyl-4-oxo-4H-pyran-2-ylmethyl)-3-methyl-benzenesulfonamide (**9-04**) (7.5 g, 23.07 mmol) following the procedure described for N-(5-benzyloxy-6-hydroxymethyl-4-oxo-4H-pyran-2-ylmethyl)-benzenesulfonamide (**10-01**).

LC-MS: 415.8 (M+H).

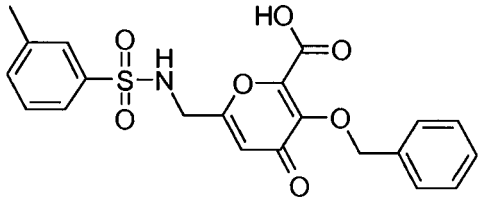
Preparation of (11-04):



N-(5-Benzyloxy-6-formyl-4-oxo-4H-pyran-2-ylmethyl)-3-methyl-benzenesulfonamide

N-(5-Benzyloxy-6-formyl-4-oxo-4H-pyran-2-ylmethyl)-3-methyl-benzenesulfonamide (**11-04**) (1.8 g, 75.28 %) was synthesized as a white solid from N-(5-benzyloxy-6-hydroxymethyl-4-oxo-4H-pyran-2-ylmethyl)-3-methyl-benzenesulfonamide (**10-04**) (2.4 g, 5.78 mmol) following the procedure described for N-(5-benzyloxy-6-formyl-4-oxo-4H-pyran-2-ylmethyl)-benzenesulfonamide (**11-01**).

Preparation of (12-04):

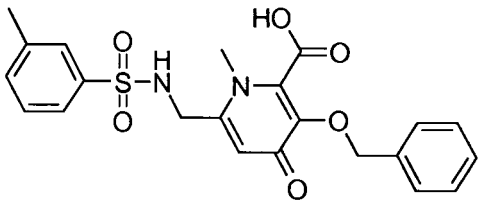


3-Benzyloxy-4-oxo-6-[(toluene-3-sulfonylamino)-methyl]-4H-pyran-2-carboxylic acid

3-Benzyloxy-4-oxo-6-[(toluene-3-sulfonylamino)-methyl]-4H-pyran-2-carboxylic acid (**12-04**) (1.6 g, crude) was synthesized as a white solid from N-(5-benzyloxy-6-formyl-4-oxo-4H-pyran-2-ylmethyl)-3-methyl-benzenesulfonamide (**11-04**) (1.8 g, 4.35 mmol) following the procedure described for 6-(benzenesulfonylamino-methyl)-3-benzyloxy-4-oxo-4H-pyran-2-carboxylic acid (**12-01**).

LC-MS: 429.8 (M+H).

Preparation of (13-04):

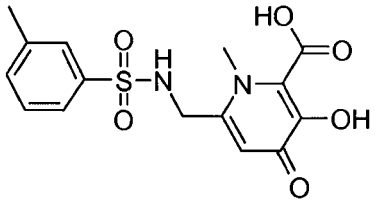


3-Benzyloxy-1-methyl-4-oxo-6-[(toluene-3-sulfonylamino)-methyl]-1,4-dihydro-pyridine-2-carboxylic acid

3-Benzyloxy-1-methyl-4-oxo-6-[(toluene-3-sulfonylamino)-methyl]-1,4-dihydro-pyridine-2-carboxylic acid (**13-04**) (1.3 g, 78.77 %) was synthesized as a white solid from 3-benzyloxy-4-oxo-6-[(toluene-3-sulfonylamino)-methyl]-4H-pyran-2-carboxylic acid (**12-04**) (1.6 g, 3.73 mmol) following the procedure described for 6-(benzenesulfonylamino-methyl)-3-benzyloxy-1-methyl-4-oxo-1,4-dihydro-pyridine-2-carboxylic acid (**13-01**).

LC-MS: 443.2 (M+H).

Preparation of (14-04):

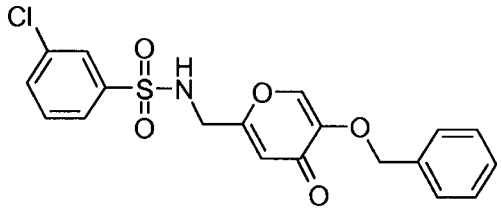


3-Hydroxy-1-methyl-4-oxo-6-[(toluene-3-sulfonylamino)-methyl]-1,4-dihydro-pyridine-2-carboxylic acid

3-Hydroxy-1-methyl-4-oxo-6-[(toluene-3-sulfonylamino)-methyl]-1,4-dihydro-pyridine-2-carboxylic acid (**14-04**) (60.0 mg, 28.41 %, purified by Prep-HPLC) was synthesized as an off white solid from 3-benzyloxy-1-methyl-4-oxo-6-[(toluene-3-sulfonylamino)-methyl]-1,4-dihydro-pyridine-2-carboxylic acid (**13-04**) (260.0 mg, 0.588 mmol) following the procedure described for 6-(benzenesulfonylamino-methyl)-3-hydroxy-1-methyl-4-oxo-1,4-dihydro-pyridine-2-carboxylic acid (**14-01**).

LC-MS: 353.2 (M+H).

Preparation of (7-05):

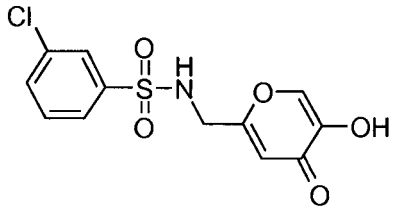


N-(5-Benzyloxy-4-oxo-4H-pyran-2-ylmethyl)-3-chloro-benzenesulfonamide

N-(5-Benzyloxy-4-oxo-4H-pyran-2-ylmethyl)-3-chloro-benzenesulfonamide (**7-05**) (25.0 g, 56.92 %) was synthesized as a brown solid from 2-aminomethyl-5-benzyloxy-pyran-4-one (**5**) (25 g, 108.22 mmol) and 3-chloro-benzenesulfonyl chloride (**6-05**) (22.98 mL, 162.33 mmol) following the procedure described for N-(5-benzyloxy-4-oxo-4H-pyran-2-ylmethyl)-benzenesulfonamide (**7-01**).

LC-MS: 406.0 (M+H).

Preparation of (8-05):

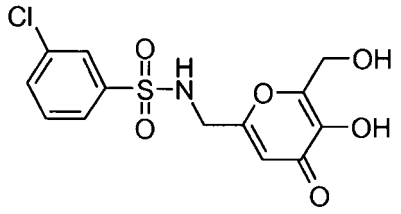


3-Chloro-N-(5-hydroxy-4-oxo-4H-pyran-2-ylmethyl)-benzenesulfonamide

3-Chloro-N-(5-hydroxy-4-oxo-4H-pyran-2-ylmethyl)-benzenesulfonamide (**8-05**) (14.0 g, 71.83 %) was synthesized as a brown solid from N-(5-benzyloxy-4-oxo-4H-pyran-2-ylmethyl)-3-chloro-benzenesulfonamide (**7-05**) (25.0 g, 61.73 mmol) following the procedure described for N-(5-hydroxy-4-oxo-4H-pyran-2-ylmethyl)-benzenesulfonamide (**8-01**).

LC-MS: 316.0 (M+H).

Preparation of (9-05):

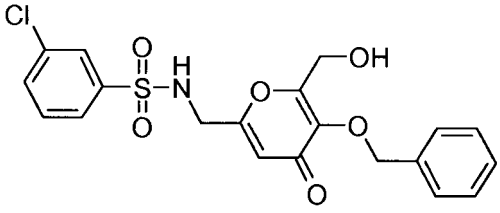


3-Chloro-N-(5-hydroxy-6-hydroxymethyl-4-oxo-4H-pyran-2-ylmethyl)-benzenesulfonamide

3-Chloro-N-(5-hydroxy-6-hydroxymethyl-4-oxo-4H-pyran-2-ylmethyl)-benzenesulfonamide (**9-05**) (7.3 g, 47.50 %) was synthesized as a white solid from 3-chloro-N-(5-hydroxy-4-oxo-4H-pyran-2-ylmethyl)-benzenesulfonamide (**8-05**) (14.0 g, 44.44 mmol) following the procedure described for N-(5-hydroxy-6-hydroxymethyl-4-oxo-4H-pyran-2-ylmethyl)-benzenesulfonamide (**9-01**).

LC-MS: 346.0 (M+H).

Preparation of (10-05):

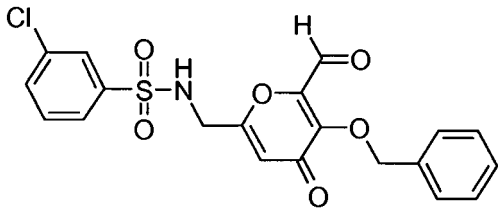


N-(5-Benzyloxy-6-hydroxymethyl-4-oxo-4H-pyran-2-ylmethyl)-3-chloro-benzenesulfonamide

N-(5-Benzyloxy-6-hydroxymethyl-4-oxo-4H-pyran-2-ylmethyl)-3-chloro-benzenesulfonamide (**10-05**) (2.2 g, 24.88 %) was synthesized as a white solid from 3-chloro-N-(5-hydroxy-6-hydroxymethyl-4-oxo-4H-pyran-2-ylmethyl)-benzenesulfonamide (**9-05**) (7.0 g, 20.29 mmol) following the procedure described for N-(5-benzyloxy-6-hydroxymethyl-4-oxo-4H-pyran-2-ylmethyl)-benzenesulfonamide (**10-01**).

LC-MS: 436.2 (M+H).

Preparation of (11-05):

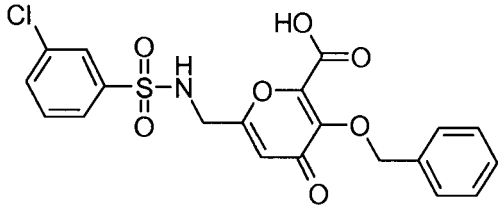


N-(5-Benzyloxy-6-formyl-4-oxo-4H-pyran-2-ylmethyl)-3-chloro-benzenesulfonamide

N-(5-Benzyloxy-6-formyl-4-oxo-4H-pyran-2-ylmethyl)-3-chloro-benzenesulfonamide (**11-05**) (2.3 g, 82.36 %) was synthesized as a white solid from N-(5-benzyloxy-6-hydroxymethyl-4-oxo-4H-pyran-2-ylmethyl)-3-chloro-benzenesulfonamide (**10-05**) (2.8 g, 6.44 mmol) following the procedure described for N-(5-benzyloxy-6-formyl-4-oxo-4H-pyran-2-ylmethyl)-benzenesulfonamide (**11-01**).

LC-MS: 433.6 (M+H).

Preparation of (12-05):

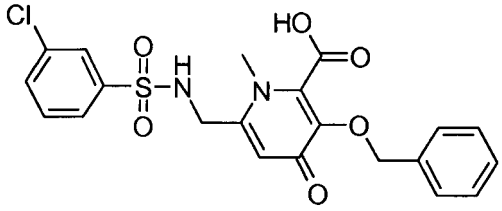


3-Benzyloxy-6-[(3-chloro-benzenesulfonylamino)-methyl]-4-oxo-4H-pyran-2-carboxylic acid

3-Benzyloxy-6-[(3-chloro-benzenesulfonylamino)-methyl]-4-oxo-4H-pyran-2-carboxylic acid (**12-05**) (2.04 g, 89.25 %) was synthesized as a white solid from N-(5-benzyloxy-6-formyl-4-oxo-4H-pyran-2-ylmethyl)-3-chloro-benzenesulfonamide (**11-05**) (2.2 g, 5.08 mmol) following the procedure described for 6-(benzenesulfonylamino-methyl)-3-benzyloxy-4-oxo-4H-pyran-2-carboxylic acid (**12-01**).

LC-MS: 447.8 (M-H).

Preparation of (13-05):

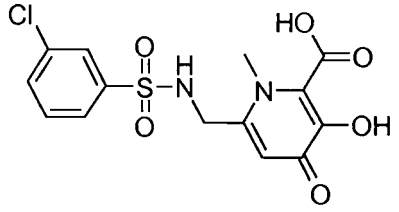


3-Benzyloxy-6-[(3-chloro-benzenesulfonylamino)-methyl]-1-methyl-4-oxo-1,4-dihydro-pyridine-2-carboxylic acid

3-Benzyloxy-6-[(3-chloro-benzenesulfonylamino)-methyl]-1-methyl-4-oxo-1,4-dihydro-pyridine-2-carboxylic acid (**13-05**) (1.62 g, 78.57 %) was synthesized as a yellow solid from 3-benzyloxy-6-[(3-chloro-benzenesulfonylamino)-methyl]-4-oxo-4H-pyran-2-carboxylic acid (**12-05**) (2.0 g, 4.45 mmol) following the procedure described for 6-(benzenesulfonylamino-methyl)-3-benzyloxy-1-methyl-4-oxo-1,4-dihydro-pyridine-2-carboxylic acid (**13-01**).

LC-MS: 462.6 (M+H).

Preparation of (14-05):

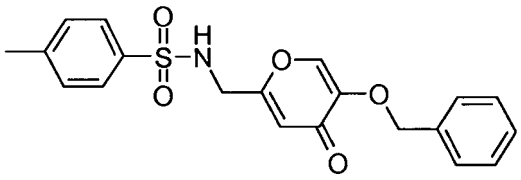


6-[(3-Chloro-benzenesulfonylamino)-methyl]-3-hydroxy-1-methyl-4-oxo-1,4-dihydro-pyridine-2-carboxylic acid

6-[(3-Chloro-benzenesulfonylamino)-methyl]-3-hydroxy-1-methyl-4-oxo-1,4-dihydro-pyridine-2-carboxylic acid (**14-05**) (170.0 mg, 52.67 %) was synthesized as an off white solid from 3-benzyloxy-6-[(3-chloro-benzenesulfonylamino)-methyl]-1-methyl-4-oxo-1,4-dihydro-pyridine-2-carboxylic acid (**13-05**) (400.0 mg, 0.866 mmol) following the procedure described for 6-(benzenesulfonylamino-methyl)-3-hydroxy-1-methyl-4-oxo-1,4-dihydro-pyridine-2-carboxylic acid (**14-01**).

LC-MS: 373.0 (M+H).

Preparation of (7-06):

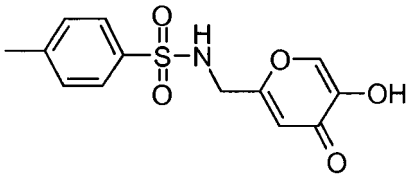


N-(5-Benzyloxy-4-oxo-4H-pyran-2-ylmethyl)-4-methyl-benzenesulfonamide

N-(5-Benzyloxy-4-oxo-4H-pyran-2-ylmethyl)-4-methyl-benzenesulfonamide (**7-06**) (20.0 g, 57.08 %) was synthesized as a light brown solid from 2-aminomethyl-5-benzyloxy-pyran-4-one (**5**) (21.0 g, 90.90 mmol) and 4-methyl-benzenesulfonyl chloride (**6-06**) (20.7 g, 109.09 mmol) following the procedure described for N-(5-benzyloxy-4-oxo-4H-pyran-2-ylmethyl)-benzenesulfonamide (**7-01**).

LC-MS: 386.0 (M+H).

Preparation of (8-06):

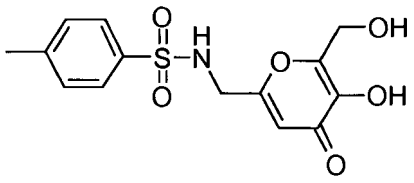


N-(5-Hydroxy-4-oxo-4H-pyran-2-ylmethyl)-4-methyl-benzenesulfonamide

N-(5-Hydroxy-4-oxo-4H-pyran-2-ylmethyl)-4-methyl-benzenesulfonamide (**8-06**) (14.0 g, crude) was synthesized as a light brown solid from N-(5-benzyloxy-4-oxo-4H-pyran-2-ylmethyl)-4-methyl-benzenesulfonamide (**7-06**) (25.0 g, 64.93 mmol) following the procedure described for N-(5-hydroxy-4-oxo-4H-pyran-2-ylmethyl)-benzenesulfonamide (**8-01**).

LC-MS: 294.0 (M-H).

Preparation of (9-06):

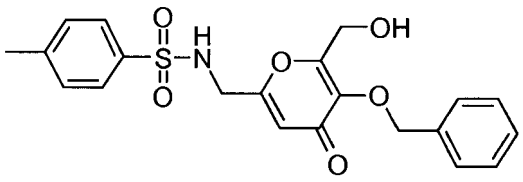


N-(5-Hydroxy-6-hydroxymethyl-4-oxo-4H-pyran-2-ylmethyl)-4-methyl-benzenesulfonamide

N-(5-Hydroxy-6-hydroxymethyl-4-oxo-4H-pyran-2-ylmethyl)-4-methyl-benzenesulfonamide (**9-06**) (7.0 g, 45.34 %) was synthesized as a white solid from N-(5-hydroxy-4-oxo-4H-pyran-2-ylmethyl)-4-methyl-benzenesulfonamide (**8-06**) (14.0 g, 47.45 mmol) following the procedure described for N-(5-hydroxy-6-hydroxymethyl-4-oxo-4H-pyran-2-ylmethyl)-benzenesulfonamide (**9-01**).

LC-MS: 326.2 (M+H).

Preparation of (10-06):

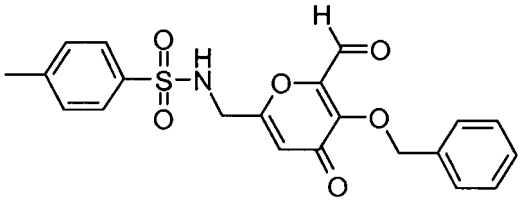


N-(5-Benzyloxy-6-hydroxymethyl-4-oxo-4H-pyran-2-ylmethyl)-4-methyl-benzenesulfonamide

N-(5-Benzyloxy-6-hydroxymethyl-4-oxo-4H-pyran-2-ylmethyl)-3-methyl-benzenesulfonamide (**10-06**) (3.7 g, 41.35 %) was synthesized as a white solid from N-(5-hydroxy-6-hydroxymethyl-4-oxo-4H-pyran-2-ylmethyl)-4-methyl-benzenesulfonamide (**9-06**) (7.0 g, 21.54 mmol) following the procedure described for N-(5-benzyloxy-6-hydroxymethyl-4-oxo-4H-pyran-2-ylmethyl)-benzenesulfonamide (**10-01**).

LC-MS: 416.2 (M+H).

Preparation of (11-06):

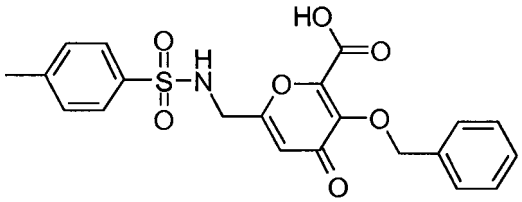


N-(5-Benzyloxy-6-formyl-4-oxo-4H-pyran-2-ylmethyl)-4-methyl-benzenesulfonamide

N-(5-Benzyloxy-6-formyl-4-oxo-4H-pyran-2-ylmethyl)-4-methyl-benzenesulfonamide (**11-06**) (2.2 g, 59.62 %) was synthesized as a yellow sticky solid from N-(5-benzyloxy-6-hydroxymethyl-4-oxo-4H-pyran-2-ylmethyl)-4-methyl-benzenesulfonamide (**10-06**) (3.7 g, 8.92 mmol) following the procedure described for N-(5-benzyloxy-6-formyl-4-oxo-4H-pyran-2-ylmethyl)-benzenesulfonamide (**11-01**).

LC-MS: 414.2 (M+H).

Preparation of (12-06):

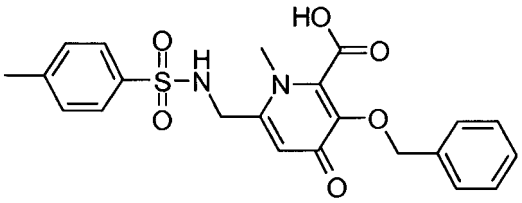


3-Benzyloxy-4-oxo-6-[(toluene-4-sulfonylamino)-methyl]-4H-pyran-2-carboxylic acid

3-Benzyloxy-4-oxo-6-[(toluene-4-sulfonylamino)-methyl]-4H-pyran-2-carboxylic acid (**12-06**) (2.0 g, 80.14 %) was synthesized as a white solid from N-(5-benzyloxy-6-formyl-4-oxo-4H-pyran-2-ylmethyl)-4-methyl-benzenesulfonamide (**11-06**) (2.4 g, 5.81 mmol) following the procedure described for 6-(benzenesulfonylamino-methyl)-3-benzyloxy-4-oxo-4H-pyran-2-carboxylic acid (**12-01**).

LC-MS: 430.0 (M+H).

Preparation of (13-06):

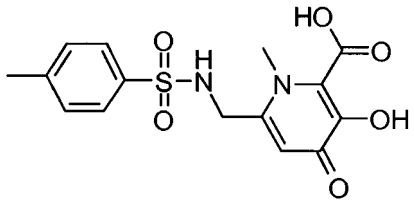


3-Benzyloxy-1-methyl-4-oxo-6-[(toluene-4-sulfonylamino)-methyl]-1,4-dihydro-pyridine-2-carboxylic acid

3-Benzyloxy-1-methyl-4-oxo-6-[(toluene-4-sulfonylamino)-methyl]-1,4-dihydro-pyridine-2-carboxylic acid (**13-06**) (1.6 g, 70.51 %) was synthesized as a white solid from 3-benzyloxy-4-oxo-6-[(toluene-4-sulfonylamino)-methyl]-4H-pyran-2-carboxylic acid (**12-06**) (2.2 g, 5.13 mmol) following the procedure described for 6-(benzenesulfonylamino-methyl)-3-benzyloxy-1-methyl-4-oxo-1,4-dihydro-pyridine-2-carboxylic acid (**13-01**).

LC-MS: 443.0 (M+H).

Preparation of (14-06):

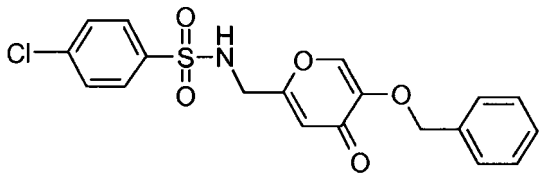


3-Hydroxy-1-methyl-4-oxo-6-[(toluene-4-sulfonylamino)-methyl]-1,4-dihydro-pyridine-2-carboxylic acid

3-Hydroxy-1-methyl-4-oxo-6-[(toluene-4-sulfonylamino)-methyl]-1,4-dihydro-pyridine-2-carboxylic acid (**14-06**) (30.0 mg, 9.41 %, purified by Prep-HPLC) was synthesized as an off white solid from 3-benzyloxy-1-methyl-4-oxo-6-[(toluene-4-sulfonylamino)-methyl]-1,4-dihydro-pyridine-2-carboxylic acid (**13-06**) 400.0 mg, 0.905 mmol) following the procedure described for 6-(benzenesulfonylamino-methyl)-3-hydroxy-1-methyl-4-oxo-1,4-dihydro-pyridine-2-carboxylic acid (**14-01**).

LC-MS: 352.6 (M+H).

Preparation of (7-07):

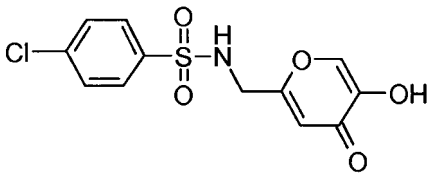


N-(5-Benzyloxy-4-oxo-4H-pyran-2-ylmethyl)-4-chloro-benzenesulfonamide

N-(5-Benzyloxy-4-oxo-4H-pyran-2-ylmethyl)-4-chloro-benzenesulfonamide (**7-07**) (20.0 g, 56.92 %) was synthesized as a brown solid from 2-aminomethyl-5-benzyloxy-pyran-4-one (**5**) (20.0 g, 86.58 mmol) and 4-chloro-benzenesulfonyl chloride (**6-07**) (45.67 g, 216.45 mmol) following the procedure described for N-(5-benzyloxy-4-oxo-4H-pyran-2-ylmethyl)-benzenesulfonamide (**7-01**).

LC-MS: 406.2 (M+H).

Preparation of (8-07):

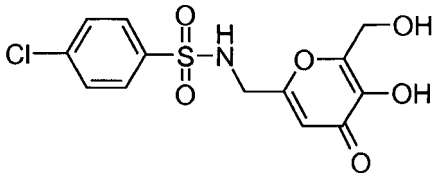


4-Chloro-N-(5-hydroxy-4-oxo-4H-pyran-2-ylmethyl)-benzenesulfonamide

4-Chloro-N-(5-hydroxy-4-oxo-4H-pyran-2-ylmethyl)-benzenesulfonamide (**8-07**) (14.0 g, 89.79 %) was synthesized as a light brown solid from N-(5-benzyloxy-4-oxo-4H-pyran-2-ylmethyl)-4-chloro-benzenesulfonamide (**7-07**) (20.0 g, 49.38 mmol) following the procedure described for N-(5-hydroxy-4-oxo-4H-pyran-2-ylmethyl)-benzenesulfonamide (**8-01**).

LC-MS: 316.0 (M+H).

Preparation of (9-07):

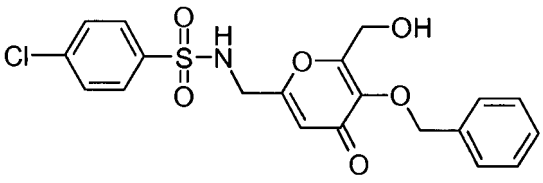


4-Chloro-N-(5-hydroxy-6-hydroxymethyl-4-oxo-4H-pyran-2-ylmethyl)-benzenesulfonamide

4-Chloro-N-(5-hydroxy-6-hydroxymethyl-4-oxo-4H-pyran-2-ylmethyl)-benzenesulfonamide (**9-07**) (7.01 g, 45.62 %) was synthesized as a light yellow solid from 4-chloro-N-(5-hydroxy-4-oxo-4H-pyran-2-ylmethyl)-benzenesulfonamide (**8-07**) (14.0 g, 44.44 mmol) following the procedure described for N-(5-hydroxy-6-hydroxymethyl-4-oxo-4H-pyran-2-ylmethyl)-benzenesulfonamide (**9-01**).

LC-MS: 346.0 (M+H).

Preparation of (10-07):

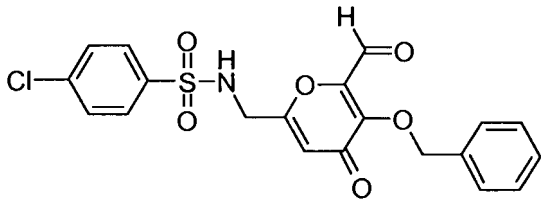


N-(5-Benzyloxy-6-hydroxymethyl-4-oxo-4H-pyran-2-ylmethyl)-4-chloro-benzenesulfonamide

N-(5-Benzyloxy-6-hydroxymethyl-4-oxo-4H-pyran-2-ylmethyl)-4-chloro-benzenesulfonamide (**10-07**) (3.5 g, 46.17 %) was synthesized as a white solid from 4-chloro-N-(5-hydroxy-6-hydroxymethyl-4-oxo-4H-pyran-2-ylmethyl)-benzenesulfonamide (**9-07**) (6.0 g, 17.39 mmol) following the procedure described for N-(5-benzyloxy-6-hydroxymethyl-4-oxo-4H-pyran-2-ylmethyl)-benzenesulfonamide (**10-01**).

LC-MS: 436.2 (M+H).

Preparation of (11-07):

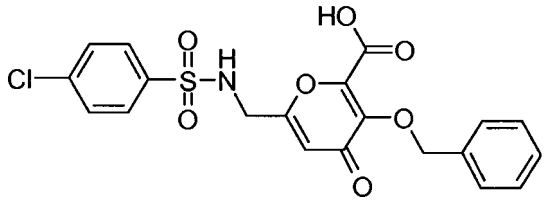


N-(5-Benzyloxy-6-formyl-4-oxo-4H-pyran-2-ylmethyl)-4-chloro-benzenesulfonamide

N-(5-Benzyloxy-6-formyl-4-oxo-4H-pyran-2-ylmethyl)-4-chloro-benzenesulfonamide (**11-07**) (3.4 g, 85.22 %) was synthesized as a white solid from N-(5-benzyloxy-6-hydroxymethyl-4-oxo-4H-pyran-2-ylmethyl)-4-chloro-benzenesulfonamide (**10-07**) (4.0 g, 9.19 mmol) following the procedure described for N-(5-benzyloxy-6-formyl-4-oxo-4H-pyran-2-ylmethyl)-benzenesulfonamide (**11-01**).

LC-MS: 433.8 (M+H).

Preparation of (12-07):

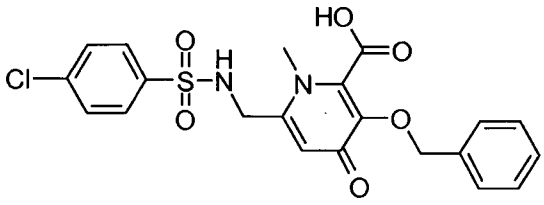


3-Benzyloxy-6-[(4-chloro-benzenesulfonylamino)-methyl]-4-oxo-4H-pyran-2-carboxylic acid

3-Benzyloxy-6-[(4-chloro-benzenesulfonylamino)-methyl]-4-oxo-4H-pyran-2-carboxylic acid (**12-07**) (3.0 g, 84.93 %) was synthesized as a white solid from N-(5-benzyloxy-6-formyl-4-oxo-4H-pyran-2-ylmethyl)-4-chloro-benzenesulfonamide (**11-07**) (3.4 g, 7.85 mmol) following the procedure described for 6-(benzenesulfonylamino-methyl)-3-benzyloxy-4-oxo-4H-pyran-2-carboxylic acid (**12-01**).

LC-MS: 450.2 (M+H).

Preparation of (13-07):

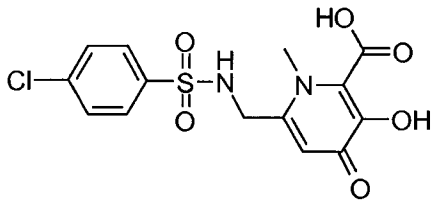


3-Benzyloxy-6-[(4-chloro-benzenesulfonylamino)-methyl]-1-methyl-4-oxo-1,4-dihydro-pyridine-2-carboxylic acid

3-Benzyloxy-6-[(4-chloro-benzenesulfonylamino)-methyl]-1-methyl-4-oxo-1,4-dihydro-pyridine-2-carboxylic acid (**13-07**) (2.3 g, 74.36 %) was synthesized as a yellow solid from 3-benzyloxy-6-[(4-chloro-benzenesulfonylamino)-methyl]-4-oxo-4H-pyran-2-carboxylic acid (**12-07**) (3.0 g, 6.68 mmol) following the procedure described for 6-(benzenesulfonylamino-methyl)-3-benzyloxy-1-methyl-4-oxo-1,4-dihydro-pyridine-2-carboxylic acid (**13-01**).

LC-MS: 462.8 (M+H).

Preparation of (14-07):



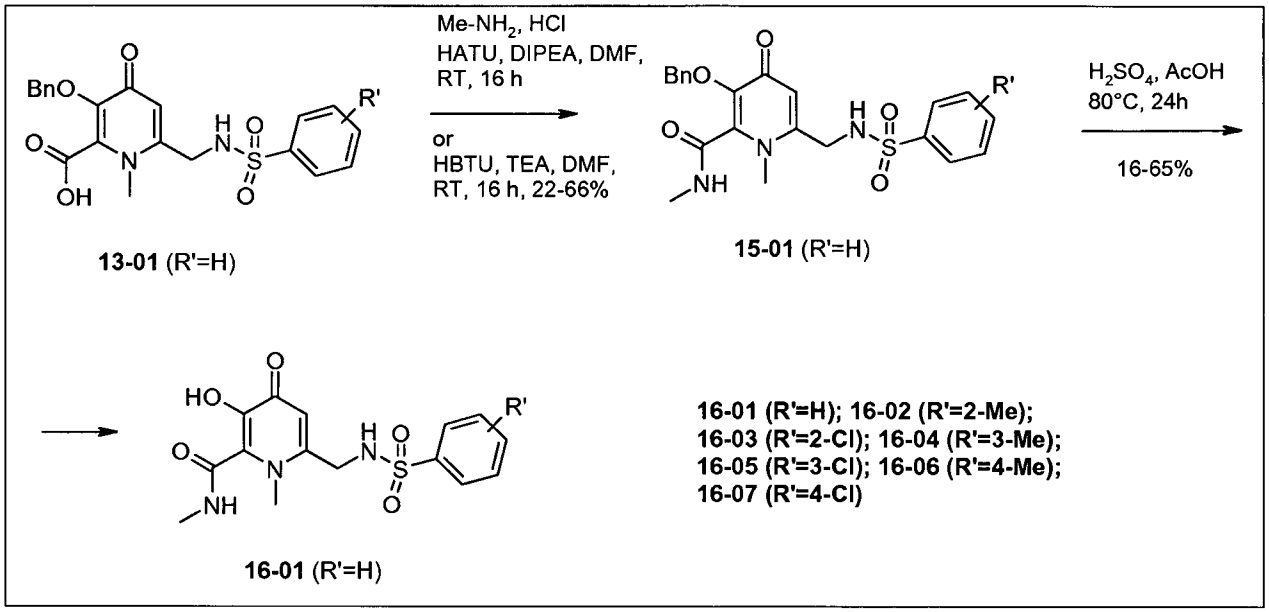
6-[(4-Chloro-benzenesulfonylamino)-methyl]-3-hydroxy-1-methyl-4-oxo-1,4-dihydro-pyridine-2-carboxylic acid

6-[(4-Chloro-benzenesulfonylamino)-methyl]-3-hydroxy-1-methyl-4-oxo-1,4-dihydro-pyridine-2-carboxylic acid (**14-07**) (140.0 mg, 31.55 %) was synthesized as a brown solid from 3-benzyloxy-6-[(4-chloro-benzenesulfonylamino)-methyl]-1-methyl-4-oxo-1,4-dihydro-pyridine-2-carboxylic acid (**13-07**) (550.0 mg, 1.19 mmol) following the procedure described for 6-(benzenesulfonylamino-methyl)-3-hydroxy-1-methyl-4-oxo-1,4-dihydro-pyridine-2-carboxylic acid (**14-01**).

LC-MS: 372.8 (M+H).

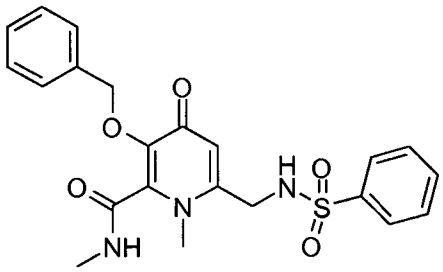
Synthetic route for (16-01) to (16-07):

Scheme 2:



Experimental:

Preparation of (15-01):



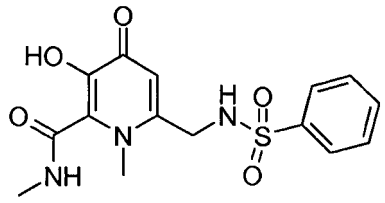
6-(Benzenesulfonylamino-methyl)-3-benzyloxy-1-methyl-4-oxo-1,4-dihydro-pyridine-2-carboxylic acid methyl amide

To a stirred solution of 6-(benzene sulfonyl amino-methyl)-3-benzyloxy-1-methyl-4-oxo-1,4-dihydro-pyridine-2-carboxylic acid (**13-01**) (400.0 mg, 0.935 mmol) in dimethylformamide (10 mL) were added HATU (*O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium hexafluorophosphate) (426.17 mg, 1.12 mmol) and diisopropylethylamine (1.08 mL, 6.54 mmol). The mixture was stirred for 30 min., thenmethylamine hydrochloride salt (189.31 mg, 2.80 mmol) was added and the reaction mixture was stirred at room temperature for 16 h. After completion of the reaction, it was quenched with ice cold water and the reaction mixture was extracted with ethyl acetate. The combined organic layer was washed with water and

brine, dried over Na_2SO_4 and concentrated under reduced pressure. It was then purified using normal column chromatography to get 6-(benzene sulfonyl amino-methyl)-3-benzyloxy-1-methyl-4-oxo-1,4-dihydro-pyridine-2-carboxylic acid methyl amide (**15-01**) (180.0 mg, 43.62 %) as a white solid.

LCMS: 442.0 (M+H).

Preparation of (16-01):

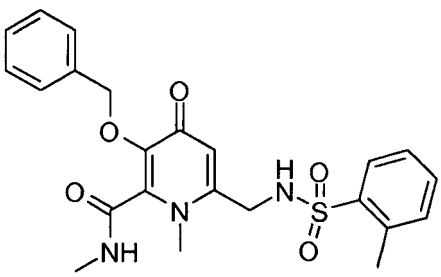


6-(Benzene sulfonyl amino-methyl)-3-hydroxy-1-methyl-4-oxo-1,4-dihydro-pyridine-2-carboxylic acid methyl amide

6-(Benzene sulfonyl amino-methyl)-3-hydroxy-1-methyl-4-oxo-1,4-dihydro-pyridine-2-carboxylic acid methyl amide (**16-01**) (45.0 mg, 33.22 %, purified by Prep-HPLC) was synthesized as an off white solid from 6-(benzene sulfonyl amino-methyl)-3-benzyloxy-1-methyl-4-oxo-1, 4-dihydro-pyridine-2-carboxylic acid methyl amide (**15-01**) (170.0 mg, 0.385 mmol) following the procedure described for 6-(benzene sulfonyl amino-methyl)-3-hydroxy-1-methyl-4-oxo-1,4-dihydro-pyridine-2-carboxylic acid (**14-01**).

LCMS: 351.8 (M+H).

Preparation of (15-02):

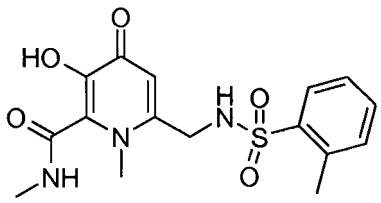


3-Benzyloxy-1-methyl-4-oxo-6-[(toluene-2-sulfonylamino)-methyl]-1,4-dihydro-pyridine-2-carboxylic acid methylamide

To a stirred solution of 3-benzyloxy-1-methyl-4-oxo-6-[(toluene-2-sulfonylamino)-methyl]-1,4-dihydro-pyridine-2-carboxylic acid (**13-02**) (600.0 mg, 1.36 mmol) in dimethylformamide (10 mL) were added HBTU (O-benzotriazole-N,N,N',N'-tetramethyl-uronium-hexafluoro-phosphate) (772.74 mg, 2.04 mmol) and triethylamine Et_3N (0.942 mL, 6.78 mmol). The mixture was stirred for 30 min., then methylamine hydrochloride salt (274.88 mg, 4.07 mmol) was added and the reaction mixture was stirred at room temperature for 16 h. After completion of the reaction, it was quenched with ice cold water and then extracted with ethyl acetate. Then combined organic layer was washed with water and brine, dried over Na_2SO_4 and concentrated under reduced pressure. It was then purified using normal column chromatography to get 3-benzyloxy-1-methyl-4-oxo-6-[(toluene-2-sulfonylamino)-methyl]-1,4-dihydro-pyridine-2-carboxylic acid methylamide (**15-02**) (140.0 mg, 22.64 %) as an off white solid.

LC-MS: 456.0 (M+H).

Preparation of (16-02):

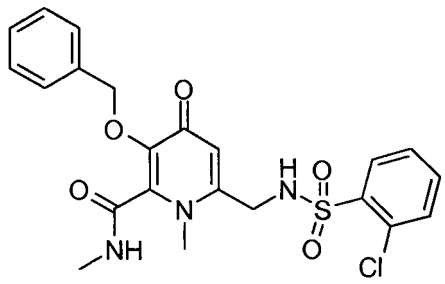


3-Hydroxy-1-methyl-4-oxo-6-[(toluene-2-sulfonylamino)-methyl]-1,4-dihydro-pyridine-2-carboxylic acid methylamide

3-Hydroxy-1-methyl-4-oxo-6-[(toluene-2-sulfonylamino)-methyl]-1,4-dihydro-pyridine-2-carboxylic acid methylamide (**16-02**) (40.0 mg, 35.50 %, purified by Prep-HPLC) was synthesized as an off white solid from 3-benzyloxy-1-methyl-4-oxo-6-[(toluene-2-sulfonylamino)-methyl]-1,4-dihydro-pyridine-2-carboxylic acid methylamide (**15-02**) (140.0 mg, 0.308 mmol) following the procedure described for 6-(benzene sulfonyl amino-methyl)-3-hydroxy-1-methyl-4-oxo-1,4-dihydro-pyridine-2-carboxylic acid (**14-01**).

LC-MS: 365.8 (M+H).

Preparation of (15-03):

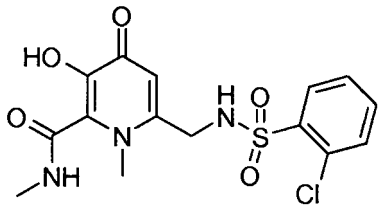


3-Benzyloxy-6-[(2-chloro-benzenesulfonylamino)-methyl]-1-methyl-4-oxo-1,4-dihydro-pyridine-2-carboxylic acid methylamide

3-Benzyloxy-6-[(2-chloro-benzenesulfonylamino)-methyl]-1-methyl-4-oxo-1,4-dihydro-pyridine-2-carboxylic acid methylamide (**15-03**) (210.0 mg, 58.24 %) was synthesized as a brown solid from 3-benzyloxy-6-[(2-chloro-benzenesulfonylamino)-methyl]-1-methyl-4-oxo-1,4-dihydro-pyridine-2-carboxylic acid (**13-03**) (350.0 mg, 0.758 mmol) following the procedure described for 6-(benzenesulfonylamino-methyl)-3-benzyoxy-1-methyl-4-oxo-1,4-dihydro-pyridine-2-carboxylic acid methylamide (**15-01**).

LC-MS: 476.2 (M+H).

Preparation of (16-03):

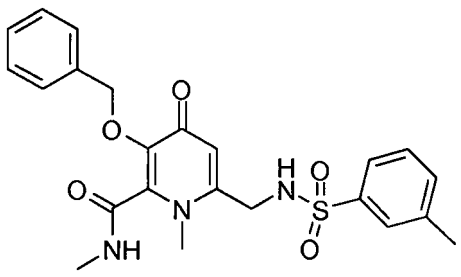


6-[(2-Chloro-benzenesulfonylamino)-methyl]-3-hydroxy-1-methyl-4-oxo-1,4-dihydro-pyridine-2-carboxylic acid methylamide

6-[(2-Chloro-benzenesulfonylamino)-methyl]-3-hydroxy-1-methyl-4-oxo-1,4-dihydro-pyridine-2-carboxylic acid methylamide (**16-03**) (110.0 mg, 52.09 %, purified by Prep-HPLC) was synthesized as a yellow solid from 3-benzyloxy-6-[(2-chloro-benzenesulfonylamino)-methyl]-1-methyl-4-oxo-1,4-dihydro-pyridine-2-carboxylic acid methylamide (**15-03**) (260.0 mg, 0.547 mmol) following the procedure described for 6-(benzene sulfonyl amino-methyl)-3-hydroxy-1-methyl-4-oxo-1,4-dihydro-pyridine-2-carboxylic acid (**14-01**).

LC-MS: 386.2 (M+H).

Preparation of (15-04):



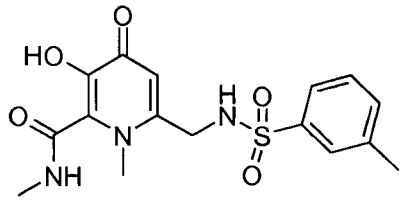
3-Benzyloxy-1-methyl-4-oxo-6-[(toluene-3-sulfonylamino)-methyl]-1,4-dihydro-pyridine-2-carboxylic acid methylamide

3-Benzyloxy-1-methyl-4-oxo-6-[(toluene-3-sulfonylamino)-methyl]-1,4-dihydro-pyridine-2-carboxylic acid methylamide (**15-04**) (250.0 mg, 60.64 %) was synthesized as a white solid from 3-benzyloxy-1-methyl-4-oxo-6-[(toluene-3-sulfonylamino)-methyl]-1,4-dihydro-pyridine-2-carboxylic acid (**13-04**) (400.0 mg, 0.905 mmol) following the procedure described for 6-

(benzenesulfonylamino-methyl)-3-benzyoxy-1-methyl-4-oxo-1,4-dihydro-pyridine-2-carboxylic acid methylamide (**15-01**).

LC-MS: 455.8 (M+H).

Preparation of (16-04):

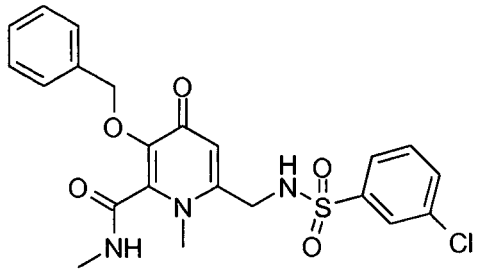


3-Hydroxy-1-methyl-4-oxo-6-[(toluene-3-sulfonylamino)-methyl]-1,4-dihydro-pyridine-2-carboxylic acid methylamide

3-Hydroxy-1-methyl-4-oxo-6-[(toluene-3-sulfonylamino)-methyl]-1,4-dihydro-pyridine-2-carboxylic acid methylamide (**16-04**) (35.0 mg, 16.76 %, purified by Prep-HPLC) was synthesized as an off white solid from 3-benzyloxy-1-methyl-4-oxo-6-[(toluene-2-sulfonylamino)-methyl]-1,4-dihydro-pyridine-2-carboxylic acid methylamide (**14-11**) (260.0 mg, 0.571 mmol) following the procedure described for 6-(benzene sulfonyl amino-methyl)-3-hydroxy-1-methyl-4-oxo-1,4-dihydro-pyridine-2-carboxylic acid (**14-01**).

LC-MS: 366.2 (M+H).

Preparation of (15-05):

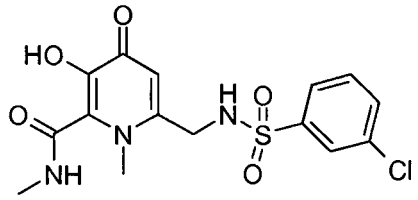


3-Benzyloxy-6-[(3-chloro-benzenesulfonylamino)-methyl]-1-methyl-4-oxo-1,4-dihydro-pyridine-2-carboxylic acid methylamide

3-Benzyloxy-6-[(3-chloro-benzenesulfonylamino)-methyl]-1-methyl-4-oxo-1,4-dihydro-pyridine-2-carboxylic acid methylamide (**15-05**) (410.0 mg, 66.33 %) was synthesized as a white solid from 3-benzyloxy-6-[(3-chloro-benzenesulfonylamino)-methyl]-1-methyl-4-oxo-1,4-dihydro-pyridine-2-carboxylic acid (**13-05**) (600.0 mg, 1.299 mmol) following the procedure described for 6-(benzenesulfonylamino-methyl)-3-benzyoxy-1-methyl-4-oxo-1,4-dihydro-pyridine-2-carboxylic acid methylamide (**15-01**).

LC-MS: 476.0 (M+H).

Preparation of (16-05):

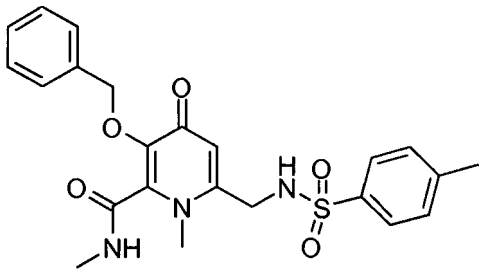


6-[(3-Chloro-benzenesulfonylamino)-methyl]-3-hydroxy-1-methyl-4-oxo-1,4-dihydro-pyridine-2-carboxylic acid methylamide

6-[(3-Chloro-benzenesulfonylamino)-methyl]-3-hydroxy-1-methyl-4-oxo-1,4-dihydro-pyridine-2-carboxylic acid methylamide (**16-05**) (193.0 mg, 59.40 %, purified by Prep-HPLC) was synthesized as an off white solid from 3-benzyloxy-6-[(3-chloro-benzenesulfonylamino)-methyl]-1-methyl-4-oxo-1,4-dihydro-pyridine-2-carboxylic acid methylamide (**15-05**) (400.0 mg, 0.84 mmol) following the procedure described for 6-(benzene sulfonyl amino-methyl)-3-hydroxy-1-methyl-4-oxo-1,4-dihydro-pyridine-2-carboxylic acid (**14-01**).

LC-MS: 385.8 (M+H).

Preparation of (15-06):

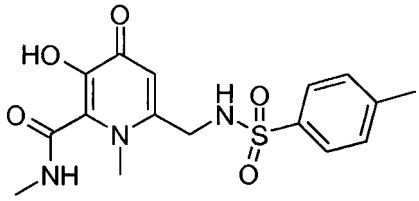


3-Benzyloxy-1-methyl-4-oxo-6-[(toluene-4-sulfonylamino)-methyl]-1,4-dihydro-pyridine-2-carboxylic acid methylamide

3-Benzyloxy-1-methyl-4-oxo-6-[(toluene-4-sulfonylamino)-methyl]-1,4-dihydro-pyridine-2-carboxylic acid methylamide (**15-06**) (280.0 mg, 54.34 %) was synthesized as an off white solid from 3-benzyloxy-1-methyl-4-oxo-6-[(toluene-4-sulfonylamino)-methyl]-1,4-dihydro-pyridine-2-carboxylic acid (**13-06**) (500.0 mg, 1.13 mmol) following the procedure described for 6-(benzenesulfonylamino-methyl)-3-benzyoxy-1-methyl-4-oxo-1,4-dihydro-pyridine-2-carboxylic acid methylamide (**15-01**).

LC-MS: 456.0 (M+H).

Preparation of (16-06):



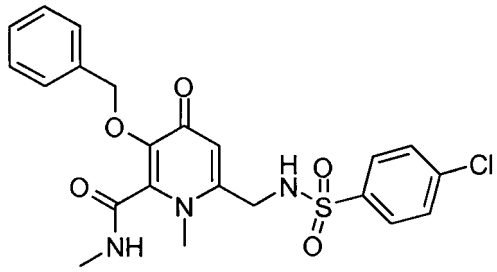
3-Hydroxy-1-methyl-4-oxo-6-[(toluene-4-sulfonylamino)-methyl]-1,4-dihydro-pyridine-2-carboxylic acid methylamide

3-Hydroxy-1-methyl-4-oxo-6-[(toluene-4-sulfonylamino)-methyl]-1,4-dihydro-pyridine-2-carboxylic acid methylamide (**16-06**) (120.0 mg, 59.77 %, purified by Prep-HPLC) was synthesized as an off white solid from 3-benzyloxy-1-methyl-4-oxo-6-[(toluene-4-sulfonylamino)-methyl]-1,4-dihydro-pyridine-2-carboxylic acid methylamide (**15-06**) (250.0 mg,

0.549 mmol) following the procedure described for 6-(benzene sulfonyl amino-methyl)-3-hydroxy-1-methyl-4-oxo-1,4-dihydro-pyridine-2-carboxylic acid (**14-01**).

LC-MS: 366.0 (M+H).

Preparation of (15-07):

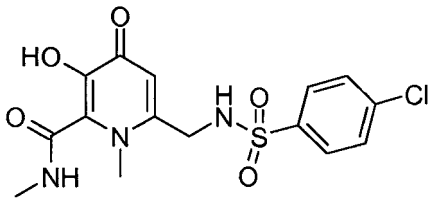


3-Benzyloxy-6-[(4-chloro-benzenesulfonylamino)-methyl]-1-methyl-4-oxo-1,4-dihydro-pyridine-2-carboxylic acid methylamide

3-Benzyloxy-6-[(4-chloro-benzenesulfonylamino)-methyl]-1-methyl-4-oxo-1,4-dihydro-pyridine-2-carboxylic acid methylamide (**15-07**) (340.0 mg, 66.01 %) was synthesized as a light yellow solid from 3-benzyloxy-6-[(4-chloro-benzenesulfonylamino)-methyl]-1-methyl-4-oxo-1,4-dihydro-pyridine-2-carboxylic acid (**13-07**) (500.0 mg, 1.08 mmol) following the procedure described for 6-(benzenesulfonylamino-methyl)-3-benzyoxy-1-methyl-4-oxo-1,4-dihydro-pyridine-2-carboxylic acid methylamide (**15-01**).

LC-MS: 476.2 (M+H).

Preparation of (16-07):

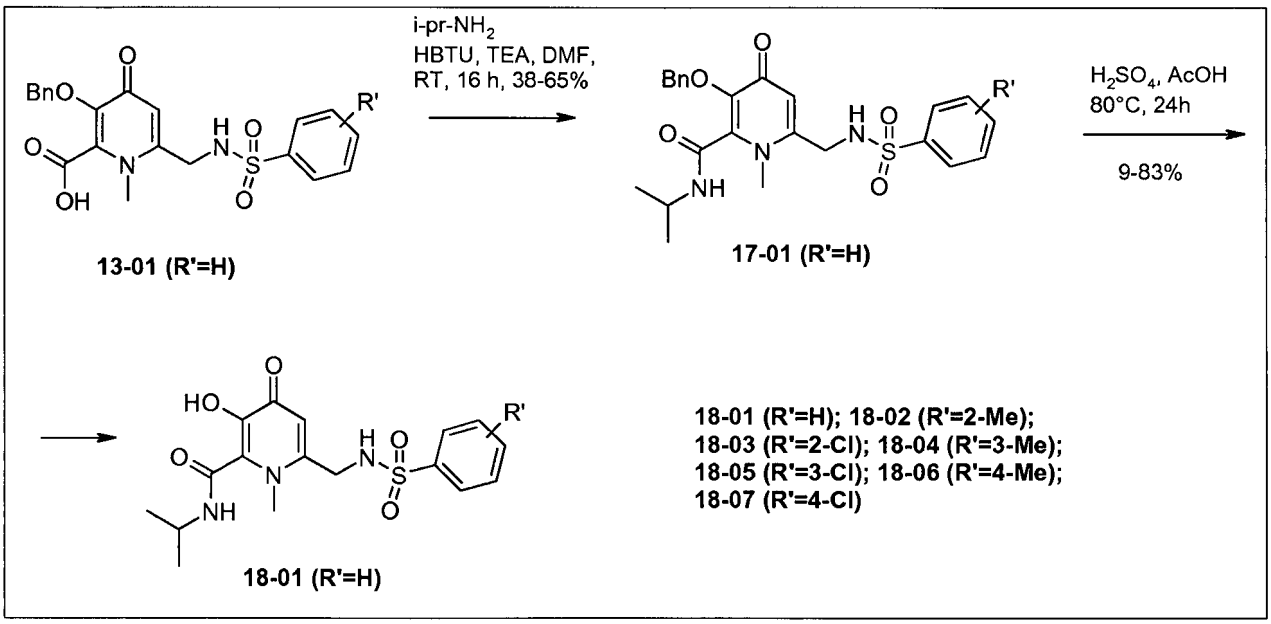


6-[(4-Chloro-benzenesulfonylamino)-methyl]-3-hydroxy-1-methyl-4-oxo-1,4-dihydro-pyridine-2-carboxylic acid methylamide

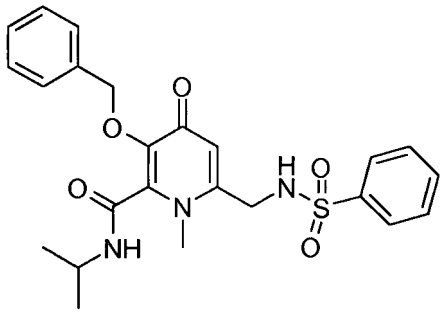
6-[(4-Chloro-benzenesulfonylamino)-methyl]-3-hydroxy-1-methyl-4-oxo-1,4-dihydro-pyridine-2-carboxylic acid methylamide (**16-07**) (375.0 mg, 65.95 %, purified by Prep-HPLC) was synthesized as a light pink solid from 3-benzyloxy-6-[(4-chloro-benzenesulfonylamino)-methyl]-1-methyl-4-oxo-1,4-dihydro-pyridine-2-carboxylic acid methylamide (**15-07**) (700.0 mg, 1.47 mmol) following the procedure described for 6-(benzene sulfonyl amino-methyl)-3-hydroxy-1-methyl-4-oxo-1,4-dihydro-pyridine-2-carboxylic acid (**14-01**).

LC-MS: 386.0 (M+H).

Scheme 3: Synthetic route for (18-01) to (18-07):



Preparation of (17-01):

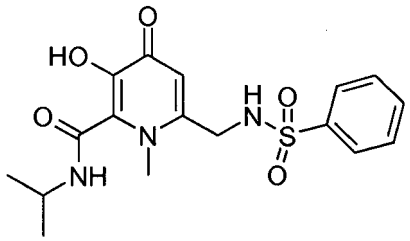


6-(Benzene sulfonyl amino-methyl)-3-benzyloxy-1-methyl-4-oxo-1,4-dihydro-pyridine-2-carboxylic acid isopropyl amide

To a stirred solution of 6-(benzene sulfonyl amino-methyl)-3-benzyloxy-1-methyl-4-oxo-1,4-dihydro-pyridine-2-carboxylic acid (**13-01**) (250.0 mg, 0.584 mmol) in dimethylformamide (15 mL) were added HBTU (O-benzotriazole-N,N,N',N'-tetramethyl-uronium-hexafluoro-phosphate) (332.28 mg, 0.876 mmol) and TEA (triethylamine) (0.406 mL, 2.92 mmol). The mixture was stirred for 30 min., thenisopropyl amine (0.171 mL, 1.75 mmol) was added and the reaction mixture was stirred at room temperature for 16 h. After completion of the reaction, it was quenched with ice cold water and then extracted with ethyl acetate. Then combined organic layer was washed with water and brine, dried over Na_2SO_4 and concentrated under reduced pressure. It was then purified using normal column chromatography to get 6-(benzenesulfonylamino-methyl)-3-benzyloxy-1-methyl-4-oxo-1,4-dihydro-pyridine-2-carboxylic acid isopropyl amide (**17-01**) (180.0 mg, 65.63 %) as a gummy liquid.

LCMS: 470.0 (M+H).

Preparation of (18-01):

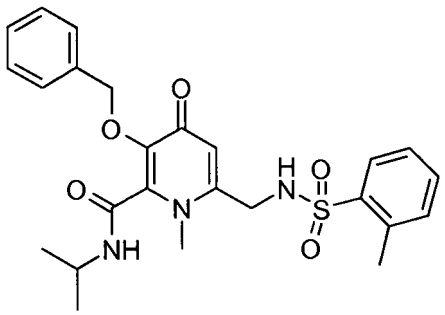


6-(Benzene sulfonyl amino-methyl)-3-hydroxy-1-methyl-4-oxo-1,4-dihydro-pyridine-2-carboxylic acid isopropyl amide

6-(Benzene sulfonyl amino-methyl)-3-hydroxy-1-methyl-4-oxo-1,4-dihydro-pyridine-2-carboxylic acid isopropyl amide (**18-01**) (110.0 mg, 48.56 %, purified by Prep-HPLC) was synthesized as an off white solid from 6-(benzene sulfonyl amino-methyl)-3-benzyloxy-1-methyl-4-oxo-1,4-dihydro-pyridine-2-carboxylic acid isopropyl amide (**17-01**) (280.0 mg, 0.597 mmol) following the procedure described for 6-(benzene sulfonyl amino-methyl)-3-hydroxy-1-methyl-4-oxo-1,4-dihydro-pyridine-2-carboxylic acid (**14-01**).

LCMS: 380.0 (M+H).

Preparation of (17-02):

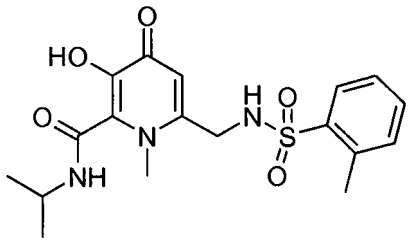


3-Benzyloxy-1-methyl-4-oxo-6-[(toluene-2-sulfonylamino)-methyl]-1,4-dihydro-pyridine-2-carboxylic acid isopropylamide

3-Benzyloxy-1-methyl-4-oxo-6-[(toluene-2-sulfonylamino)-methyl]-1,4-dihydro-pyridine-2-carboxylic acid isopropylamide (**17-02**) (250.0 mg, 45.70 %) was synthesized as a yellow solid from 3-benzyloxy-1-methyl-4-oxo-6-[(toluene-2-sulfonylamino)-methyl]-1,4-dihydro-pyridine-2-carboxylic acid (**13-02**) (500.0 mg, 1.13 mmol) following the procedure described for 6-(benzenesulfonylamino-methyl)-3-benzyloxy-1-methyl-4-oxo-1,4-dihydro-pyridine-2-carboxylic acid isopropylamide (**17-01**).

LC-MS: 484.0 (M+H).

Preparation of (18-02):

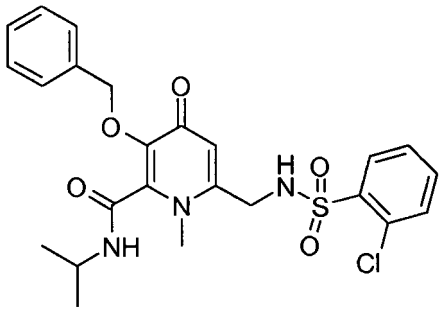


3-Hydroxy-1-methyl-4-oxo-6-[(toluene-2-sulfonylamino)-methyl]-1,4-dihydro-pyridine-2-carboxylic acid isopropylamide

3-Hydroxy-1-methyl-4-oxo-6-[(toluene-2-sulfonylamino)-methyl]-1,4-dihydro-pyridine-2-carboxylic acid isopropylamide (**18-02**) (110.0 mg, 54.01 %, purified by Prep-HPLC) was synthesized as an off white solid from 3-benzyloxy-1-methyl-4-oxo-6-[(toluene-2-sulfonylamino)-methyl]-1,4-dihydro-pyridine-2-carboxylic acid isopropylamide (**17-02**) (250.0 mg, 0.518 mmol) following the procedure described for 6-(benzene sulfonyl amino-methyl)-3-hydroxy-1-methyl-4-oxo-1,4-dihydro-pyridine-2-carboxylic acid (**14-01**).

LC-MS: 394.2 (M+H).

Preparation of (17-03):

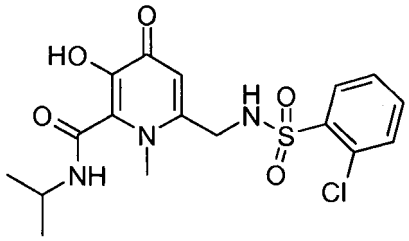


3-Benzyloxy-6-[(2-chloro-benzenesulfonylamino)-methyl]-1-methyl-4-oxo-1,4-dihydro-pyridine-2-carboxylic acid isopropylamide

3-Benzyloxy-6-[(2-chloro-benzenesulfonylamino)-methyl]-1-methyl-4-oxo-1,4-dihydro-pyridine-2-carboxylic acid isopropylamide (**17-03**) (250.0 mg, 45.0 %) was synthesized as a brown solid from 3-benzyloxy-6-[(2-chloro-benzenesulfonylamino)-methyl]-1-methyl-4-oxo-1,4-dihydro-pyridine-2-carboxylic acid (**13-03**) (500.0 mg, 1.08 mmol) following the procedure described for 6-(benzenesulfonylamino-methyl)-3-benzyloxy-1-methyl-4-oxo-1,4-dihydro-pyridine-2-carboxylic acid isopropylamide (**17-01**).

LC-MS: 504.3 (M+H).

Preparation of (18-03):

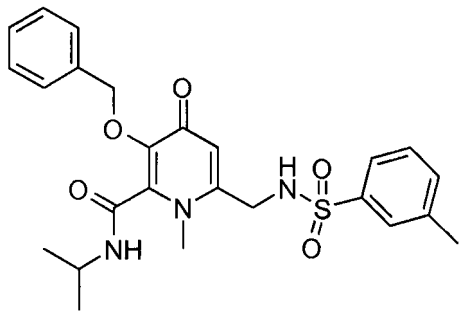


6-[(2-Chloro-benzenesulfonylamino)-methyl]-3-hydroxy-1-methyl-4-oxo-1,4-dihydro-pyridine-2-carboxylic acid isopropylamide

6-[(2-Chloro-benzenesulfonylamino)-methyl]-3-hydroxy-1-methyl-4-oxo-1,4-dihydro-pyridine-2-carboxylic acid isopropylamide (**18-03**) (38.0 mg, 19.24 %, purified by Prep-HPLC) was synthesized as an off white solid from 3-benzyloxy-6-[(2-chloro-benzenesulfonylamino)-methyl]-1-methyl-4-oxo-1,4-dihydro-pyridine-2-carboxylic acid isopropylamide (**17-03**) (240.0 mg, 0.477 mmol) following the procedure described for 6-(benzene sulfonyl amino-methyl)-3-hydroxy-1-methyl-4-oxo-1,4-dihydro-pyridine-2-carboxylic acid (**14-01**).

LC-MS: 414.2 (M+H).

Preparation of (17-04):



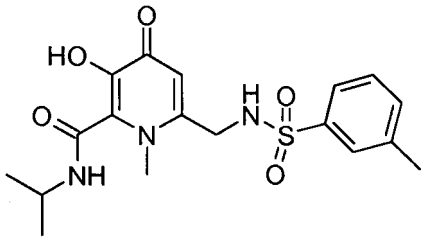
3-Benzyloxy-1-methyl-4-oxo-6-[(toluene-3-sulfonylamino)-methyl]-1,4-dihydro-pyridine-2-carboxylic acid isopropylamide

3-Benzyloxy-1-methyl-4-oxo-6-[(toluene-3-sulfonylamino)-methyl]-1,4-dihydro-pyridine-2-carboxylic acid isopropylamide (**17-04**) (250.0 mg, 45.70%) was synthesized as a white solid from 3-benzyloxy-1-methyl-4-oxo-6-[(toluene-3-sulfonylamino)-methyl]-1,4-dihydro-pyridine-2-

carboxylic acid (**13-04**) (500.0 mg, 1.13 mmol) following the procedure described for 6-(benzenesulfonylamino-methyl)-3-benzyloxy-1-methyl-4-oxo-1,4-dihydro-pyridine-2-carboxylic acid isopropylamide (**17-01**).

LC-MS: 484.2 (M+H).

Preparation of (18-04):

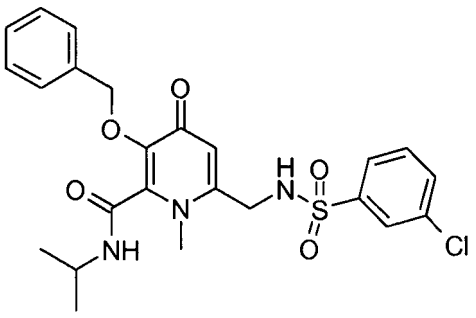


3-Hydroxy-1-methyl-4-oxo-6-[(toluene-3-sulfonylamino)-methyl]-1,4-dihydro-pyridine-2-carboxylic acid isopropylamide

3-Hydroxy-1-methyl-4-oxo-6-[(toluene-3-sulfonylamino)-methyl]-1,4-dihydro-pyridine-2-carboxylic acid isopropylamide (**18-04**) (20.0 mg, 9.82 %, purified by Prep-HPLC) was synthesized as a white solid from 3-benzyloxy-1-methyl-4-oxo-6-[(toluene-3-sulfonylamino)-methyl]-1,4-dihydro-pyridine-2-carboxylic acid isopropylamide (**17-04**) (250.0 mg, 0.518 mmol) following the procedure described for 6-(benzene sulfonyl amino-methyl)-3-hydroxy-1-methyl-4-oxo-1,4-dihydro-pyridine-2-carboxylic acid (**14-01**).

LC-MS: 394.4 (M+H).

Preparation of (17-05):

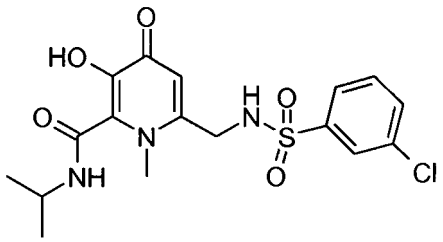


3-Benzyloxy-6-[(3-chloro-benzenesulfonylamino)-methyl]-1-methyl-4-oxo-1,4-dihydro-pyridine-2-carboxylic acid isopropylamide

3-Benzyloxy-6-[(3-chloro-benzenesulfonylamino)-methyl]-1-methyl-4-oxo-1,4-dihydro-pyridine-2-carboxylic acid isopropylamide (**17-05**) (363.0 mg, 55.46 %) was synthesized as a gummy liquid from 3-benzyloxy-6-[(3-chloro-benzenesulfonylamino)-methyl]-1-methyl-4-oxo-1,4-dihydro-pyridine-2-carboxylic acid (**13-05**) (600.0 mg, 1.29 mmol) following the procedure described for 6-(benzenesulfonylamino-methyl)-3-benzyloxy-1-methyl-4-oxo-1,4-dihydro-pyridine-2-carboxylic acid isopropylamide (**17-01**).

LC-MS: 504.2 (M+H).

Preparation of (18-05):

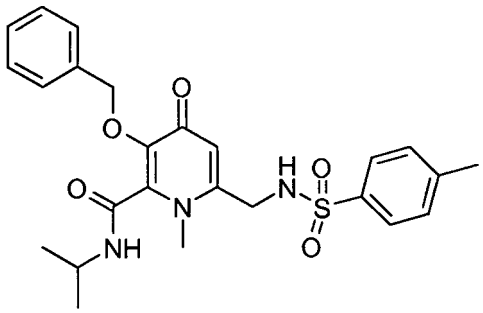


6-[(3-Chloro-benzenesulfonylamino)-methyl]-3-hydroxy-1-methyl-4-oxo-1,4-dihydro-pyridine-2-carboxylic acid isopropylamide

6-[(3-Chloro-benzenesulfonylamino)-methyl]-3-hydroxy-1-methyl-4-oxo-1,4-dihydro-pyridine-2-carboxylic acid isopropylamide (**18-05**) (110.0 mg, 38.2 %, purified by Prep-HPLC) was synthesized as a white solid from 3-benzyloxy-6-[(3-chloro-benzenesulfonylamino)-methyl]-1-methyl-4-oxo-1,4-dihydro-pyridine-2-carboxylic acid isopropylamide (**17-05**) (350.0 mg, 0.69 mmol) following the procedure described for 6-(benzene sulfonyl amino-methyl)-3-hydroxy-1-methyl-4-oxo-1,4-dihydro-pyridine-2-carboxylic acid (**14-01**).

LC-MS: 414.2 (M+H).

Preparation of (17-06):

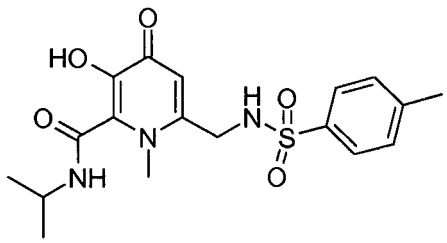


3-Benzyloxy-1-methyl-4-oxo-6-[(toluene-4-sulfonylamino)-methyl]-1,4-dihydro-pyridine-2-carboxylic acid isopropylamide

3-Benzyloxy-1-methyl-4-oxo-6-[(toluene-4-sulfonylamino)-methyl]-1,4-dihydro-pyridine-2-carboxylic acid isopropylamide (**17-06**) (250.0 mg, 38.08 %) was synthesized as a brown solid from 3-benzyloxy-1-methyl-4-oxo-6-[(toluene-4-sulfonylamino)-methyl]-1,4-dihydro-pyridine-2-carboxylic acid (**13-06**) (600.0 mg, 1.36 mmol) following the procedure described for 6-(benzenesulfonylamino-methyl)-3-benzyloxy-1-methyl-4-oxo-1,4-dihydro-pyridine-2-carboxylic acid isopropylamide (**17-01**).

LC-MS: 484.2 (M+H).

Preparation of (18-06):



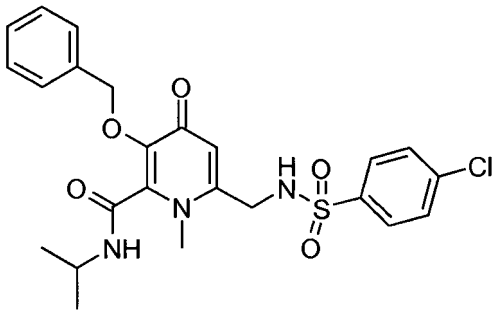
3-Hydroxy-1-methyl-4-oxo-6-[(toluene-4-sulfonylamino)-methyl]-1,4-dihydro-pyridine-2-carboxylic acid isopropylamide

3-Hydroxy-1-methyl-4-oxo-6-[(toluene-4-sulfonylamino)-methyl]-1,4-dihydro-pyridine-2-carboxylic acid isopropylamide (**18-06**) (190.0 mg, 83.3 %, purified by Prep-HPLC) was synthesized as an off white solid from 3-benzyloxy-1-methyl-4-oxo-6-[(toluene-4-

sulfonylamino)-methyl]-1,4-dihydro-pyridine-2-carboxylic acid isopropylamide (**17-06**) (280.0 mg, 0.58 mmol) following the procedure described for 6-(benzene sulfonyl amino-methyl)-3-hydroxy-1-methyl-4-oxo-1,4-dihydro-pyridine-2-carboxylic acid (**14-01**).

LC-MS: 394.0 (M+H).

Preparation of (17-07):

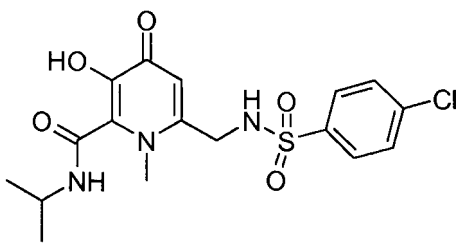


3-Benzyloxy-6-[(4-chloro-benzenesulfonylamino)-methyl]-1-methyl-4-oxo-1,4-dihydro-pyridine-2-carboxylic acid isopropylamide

3-Benzyloxy-6-[(4-chloro-benzenesulfonylamino)-methyl]-1-methyl-4-oxo-1,4-dihydro-pyridine-2-carboxylic acid isopropylamide (**17-07**) (290.0 mg, 53.17 %) was synthesized as a light yellow solid from 3-benzyloxy-6-[(4-chloro-benzenesulfonylamino)-methyl]-1-methyl-4-oxo-1,4-dihydro-pyridine-2-carboxylic acid (**13-07**) (500.0 mg, 1.08 mmol) following the procedure described for 6-(benzenesulfonylamino-methyl)-3-benzyloxy-1-methyl-4-oxo-1,4-dihydro-pyridine-2-carboxylic acid isopropylamide (**17-01**).

LC-MS: 504.0 (M+H).

Preparation of (18-07):



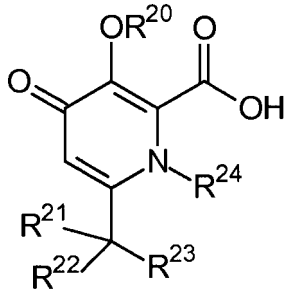
6-[(4-Chloro-benzenesulfonylamino)-methyl]-3-hydroxy-1-methyl-4-oxo-1,4-dihydro-pyridine-2-carboxylic acid isopropylamide

6-[(4-Chloro-benzenesulfonylamino)-methyl]-3-hydroxy-1-methyl-4-oxo-1,4-dihydro-pyridine-2-carboxylic acid isopropylamide (**18-07**) (250.0 mg, 50.64 %, purified by Prep-HPLC) was synthesized as an off white solid from 3-benzyloxy-6-[(4-chloro-benzenesulfonylamino)-methyl]-1-methyl-4-oxo-1,4-dihydro-pyridine-2-carboxylic acid isopropylamide (**17-07**) (600.0 mg, 1.19 mmol) following the procedure described for 6-(benzene sulfonyl amino-methyl)-3-hydroxy-1-methyl-4-oxo-1,4-dihydro-pyridine-2-carboxylic acid (**14-01**).

LC-MS: 414.2 (M+H).

CLAIMS

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



(II)

wherein

X^{20} is NR^{25}, $N(R^{25})C(O)$, $C(O)NR^{25}$, O, C(O), C(O)O, OC(O); $N(R^{25})SO_2$, $SO_2N(R^{25})$, S, SO, or SO_2;

R^{20} is –H, a $–C_{1-6}$ alkyl group or a $–C(O)–C_{1-6}$ alkyl group;

R^{21} is –H, a $–C_{1-6}$ alkyl group, or a $–C_{1-6}$ alkyl group which is substituted by one or more halogen atoms;

R^{22} is –H, a $–C_{1-6}$ alkyl group, or a $–C_{1-6}$ alkyl group which is substituted by one or more halogen atoms;

or wherein **R^{21}** and **R^{22}** can be joined together to form a 3- to 7-membered carbo- or heterocyclic ring;

R^{23} is $–R^{26}$, or $–X^{20}–R^{26}$;

R^{24} is H, or a C_{1-6} alkyl group;

R^{25} is –H, –(optionally substituted C_{1-6} alkyl), –(optionally substituted C_{3-7} cycloalkyl), –(optionally substituted aryl), $-C_{1-4}$ alkyl–(optionally substituted C_{3-7} cycloalkyl), or –C_{1-4} alkyl–(optionally substituted aryl);

R^{26} is –(optionally substituted hydrocarbon group which contains from 5 to 20 carbon atoms and optionally 1 to 4 heteroatoms selected from O, N and S and which contains at least one ring);

R^{27} is –H, $-C_{1-6}$ alkyl, or $-(CH_2CH_2O)_rH$;

R^{28} is –H, or $-C_{1-6}$ alkyl;

R is independently selected from $-C_{1-6}$ alkyl, $-C(O)-C_{1-6}$ alkyl, –Hal, $-CF_3$, –CN, $-COOR^{27}$, $-OR^{27}$, $-(CH_2)_qNR^{27}R^{28}$, $-C(O)-NR^{27}R^{28}$, and $-NR^{27}-C(O)-C_{1-6}$ alkyl;

q is 0 to 4; and

r is 1 to 3;

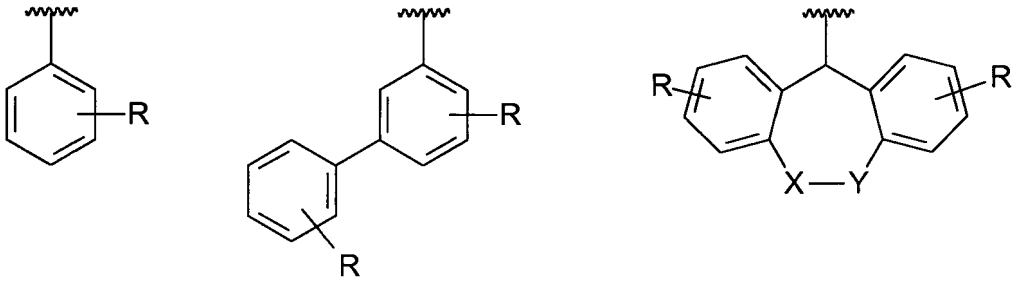
wherein the alkyl group, aryl group, hydrocarbon group and/or cycloalkyl group can be optionally substituted with one or more substituents R.

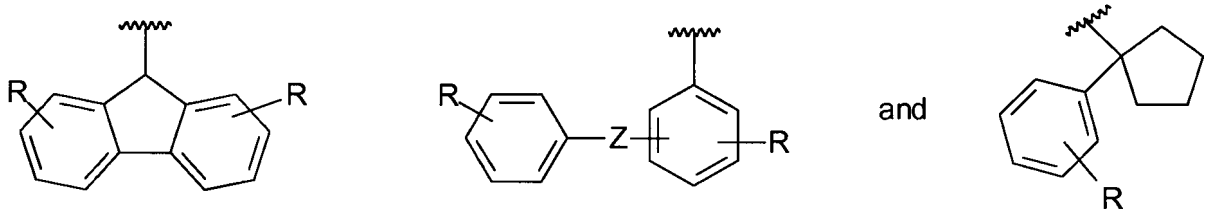
2. The compound according to claim 1, wherein R^{23} is $-R^{26}$.

3. The compound according to claim 1, wherein R^{23} is $-X^{20}-R^{26}$ and X^{20} is $N(R^{25})SO_2$.

4. The compound according to any of claims 1 to 3, wherein R^{21} and R^{22} are –H.

5. The compound according to any of claims 1 to 4, wherein R^{26} is selected from





wherein

X is absent, CH_2, NH, C(O)NH, S or O;

Y is CH_2;

Z is O or S; and

R is independently selected from –H, $-C_{1-6}$ alkyl, $-CF_3$, –halogen, –CN, –OH, and $-O-C_{1-6}$ alkyl.

6. A pharmaceutical composition comprising:
a compound having the general formula (II) as defined in any of claims 1 to 5, optionally in the form of a pharmaceutically acceptable salt, solvate, polymorph, prodrug, codrug, cocrystal, tautomer, racemate, enantiomer, or diastereomer or mixture thereof,
and optionally one or more pharmaceutically acceptable excipient(s) and/or carrier(s).

7. The pharmaceutical composition according to claim 6, which additionally comprises at least one further medicament which is selected from the group consisting of a polymerase inhibitor which is different from the compound having the general formula (II); neuramidase inhibitor; M2 channel inhibitor; alpha glucosidase inhibitor; ligand of another influenza target; antibiotics, anti-inflammatory agents, lipoxygenase inhibitors, EP ligands, bradykinin ligands, and cannabinoid ligands.

8. A compound having the general formula (II) as defined in any of claims 1 to 5, optionally in the form of a pharmaceutically acceptable salt, solvate, polymorph, prodrug, codrug, cocrystal, tautomer, racemate, enantiomer, or diastereomer or mixture thereof,

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

9. 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 (II) as defined in any of claims 1 to 5, optionally in the form of a pharmaceutically acceptable salt, solvate, polymorph, prodrug, codrug, cocrystal, tautomer, racemate, enantiomer, or diastereomer or mixture thereof.

10. The compound according to claim 8 or the method according to claim 9, wherein the viral disease is caused by Herpesviridae, Retroviridae, Filoviridae, Paramyxoviridae, Rhabdoviridae, Orthomyxoviridae, Bunyaviridae, Arenaviridae, Coronaviridae, Picornaviridae, Togaviridae, or Flaviviridae; more specifically wherein the viral disease is influenza.

11. The compound or method according to any of claims 8 to 10, wherein at least one further medicament which is selected from the group consisting of a polymerase inhibitor which is different from the compound having the general formula (II); neuramidase inhibitor; M2 channel inhibitor; alpha glucosidase inhibitor; ligand of another influenza target; antibiotics, anti-inflammatory agents, lipoxygenase inhibitors, EP ligands, bradykinin ligands, and cannabinoid ligands is administered concurrently with, sequentially with or separately from the compound having the general formula (II).

12. The compound, pharmaceutical composition or method according to any of claims 1 to 11, wherein the compound having the general formula (II) exhibits an IC_{50} of less than about 40 µM in the FRET endonuclease activity assay disclosed herein.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2014/050166

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D213/78 A61K31/4412 A61P43/00
ADD.

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 A61K

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2005/074513 A2 (MERCK & CO INC [US]; ANGELETTI P IST RICHERCHE BIO [IT]; JONES PHILIP) 18 August 2005 (2005-08-18) abstract page 11, line 10 - page 13, line 14; claims 1-8,13-18 -----	1-12
X	EP 2 412 708 A1 (SHIONOGI & CO [JP]) 1 February 2012 (2012-02-01) abstract examples 1-247; table 36 ----- -/--	1-12

[X] Further documents are listed in the continuation of Box C.

[X] 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
21 March 2014	01/04/2014

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	Goss, Ilaria

1

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	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 the whole document	1-12
A	LIU Z D ET AL: "SYNTHESIS OF 2-AMIDO-3-HYDROXYPYRIDIN-4(1H)-ONES: NOVEL IRON CHELATORS WITH ENHANCED PFE3+ VALUES", BIOORGANIC & MEDICINAL CHEMISTRY, PERGAMON, GB, vol. 9, no. 3, 1 January 2001 (2001-01-01) , pages 563-573, XP001121004, ISSN: 0968-0896, DOI: 10.1016/S0968-0896(00)00273-X the whole document	1-6

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2014/050166

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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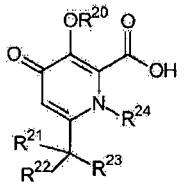
权利要求书3页 说明书55页

(54)发明名称

吡啶酮衍生物及其在治疗、改善或预防病毒疾病中的用途

(57)摘要

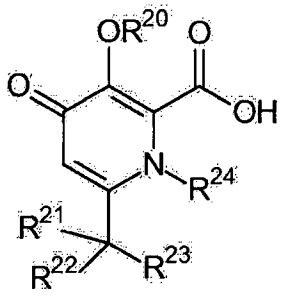
本发明涉及可用于治疗、改善或预防病毒疾病的具有通式(II)的化合物，其任选是药学上可接受的盐、溶剂化物、多晶型物、孪药、共晶、前药、互变异构体、外消旋物、对映体或非对映体或者其混合物形式的。此外，公开了特定的组合疗法。



(II)

CN 104903294 A

1. 具有通式 (II) 的化合物，其任选是药学上可接受的盐、溶剂化物、多晶型物、前药、孪药、共晶、互变异构体、外消旋物、对映体或非对映体或者其混合物形式的，



(II)

其中

X^{20}是 NR^{25}、$N(R^{25})C(O)$、$C(O)NR^{25}$、O、C(O)、C(O)O、OC(O)；$N(R^{25})SO_2$、$SO_2N(R^{25})$、S、SO 或 SO_2；

R^{20}是 -H、$-C_{1-6}$烷基基团或 $-C(O)-C_{1-6}$烷基基团；

R^{21}是 -H、$-C_{1-6}$烷基基团或被一个或多个卤素原子取代的 $-C_{1-6}$烷基基团；

R^{22}是 -H、$-C_{1-6}$烷基基团或被一个或多个卤素原子取代的 $-C_{1-6}$烷基基团；

或其中 R^{21}和 R^{22}可以连接在一起形成 3- 至 7- 元碳环或杂环；

R^{23}是 $-R^{26}$或 $-X^{20}-R^{26}$；

R^{24}是 H、或 C_{1-6}烷基基团；

R^{25}是 -H、-（任选取代的 C_{1-6}烷基）、-（任选取代的 C_{3-7}环烷基）、-（任选取代的芳基）、$-C_{1-4}$烷基 -（任选取代的 C_{3-7}环烷基）或 $-C_{1-4}$烷基 -（任选取代的芳基）；

R^{26}是 -（任选取代的含有 5-20 个碳原子和任选的 1-4 个选自 O、N 和 S 的杂原子并且含有至少一个环的烃基）；

R^{27}是 -H、$-C_{1-6}$烷基或 $-(CH_2CH_2O)_rH$；

R^{28}是 -H 或 $-C_{1-6}$烷基；

R 独立地选自 $-C_{1-6}$烷基、$-C(O)-C_{1-6}$烷基、-Hal、$-CF_3$、-CN、$-COOR^{27}$、$-OR^{27}$、$-(CH_2)_qNR^{27}R^{28}$、$-C(O)-NR^{27}R^{28}$以及 $-NR^{27}-C(O)-C_{1-6}$烷基；

q 是 0 至 4；并且

r 是 1 至 3；

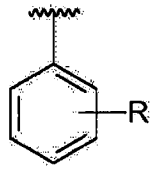
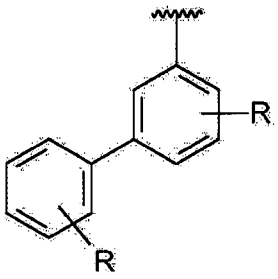
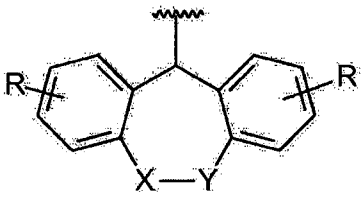
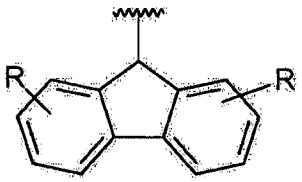
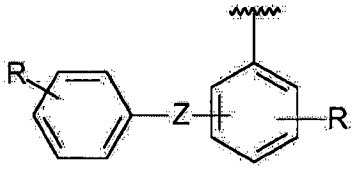
其中所述烷基基团、芳基基团、烃基基团和 / 或环烷基基团可任选地被一个或多个取代基 R 取代。

2. 根据权利要求 1 所述的化合物，其中 R^{23}是 $-R^{26}$。

3. 根据权利要求 1 所述的化合物，其中 R^{23}是 $-X^{20}-R^{26}$并且 X^{20}是 $N(R^{25})SO_2$。

4. 根据权利要求 1-3 任一项所述的化合物，其中 R^{21}和 R^{22}是 -H。

5. 根据权利要求 1-4 任一项所述的化合物，其中 R^{26}选自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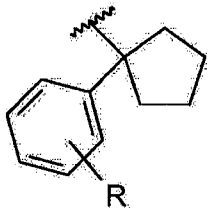


其中

X 为不存在、CH_2、NH、C(O)NH、S 或 O；

Y 是 CH_2；

Z 是 O 或 S；且

R 独立地选自 -H、-C_{1-6}烷基、-CF_3、- 卤素、-CN、-OH 和 -O-C_{1-6}烷基。

6. 药物组合物，其包含：

权利要求 1-5 中任一项定义的具有通式 (II) 的化合物，其任选是药学上可接受的盐、溶剂化物、多晶型物、前药、拿药、共晶、互变异构体、外消旋物、对映体或非对映体或者其混合物形式的，

以及任选的一种或多种药学上可接受的赋形剂和 / 或载体。

7. 根据权利要求 6 所述的药物组合物，其还包含至少一种选自以下的其他药物：与具有通式 (II) 的化合物不同的聚合酶抑制剂；神经氨酸酶抑制剂；M2 通道抑制剂；α 葡糖苷酶抑制剂；另一流感靶点的配体；抗生素；抗炎剂、脂氧合酶抑制剂、EP 配体、缓激肽配体以及大麻素配体。

8. 权利要求 1-5 中任一项定义的具有通式 (II) 的化合物，其任选是药学上可接受的盐、溶剂化物、多晶型物、前药、拿药、共晶、互变异构体、外消旋物、对映体或非对映体或者其混合物形式的，

其中所述化合物用于治疗、改善或预防病毒疾病。

9. 治疗、改善或预防病毒疾病的方法，所述方法包括向有需要的患者施用有效量的权利要求 1-5 中任一项定义的具有通式 (II) 的化合物，所述化合物任选地是药学上可接受的盐、溶剂化物、多晶型物、前药、拿药、共晶、互变异构体、外消旋物、对映体或非对映体或者其混合物形式的。

10. 权利要求 8 的化合物或权利要求 9 的方法，其中所述病毒疾病是由疱疹病毒科、逆转录病毒科、纤丝病毒科、副粘液病毒科、弹状病毒科、正粘病毒科、布尼亚病毒科、沙粒病毒科、冠状病毒科、细小 RNA 病毒科、披膜病毒科或黄病毒科引起的；更特别地，其中所述的病毒疾病是流感。

11. 根据权利要求 8-10 中任何一项的化合物或方法，其中将至少一种其他药物与具有

通式（II）的化合物同时、顺次或分别施用，所述其他药物选自：与具有通式（II）的化合物不同的聚合酶抑制剂；神经氨酸酶抑制剂；M2 通道抑制剂；α 葡糖苷酶抑制剂；另一流感靶点的配体；抗生素；抗炎剂、脂氧合酶抑制剂、EP 配体、缓激肽配体以及大麻素配体。

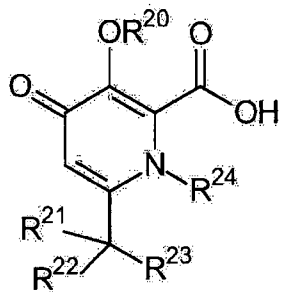
12. 根据权利要求 1-11 中任何一项所述的化合物、药物组合物或方法，其中所述具有通式（II）的化合物在本文所公开的 FRET 内切核酸酶活性测定中表现出低于约 40 μM 的 IC_{50}。

吡啶酮衍生物及其在治疗、改善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 (II) 的化合物，其任选是药学上可接受的盐、溶剂化物、多晶型物、挛药 (codrug)、共晶 (cocrystal)、前药、互变异构体、外消旋物、对映体或非对映体或者其混合物形式的，

[0002]



(II)

[0003] 其可用于治疗、改善或预防病毒疾病。此外，还公开了特定的组合疗法。

[0004] 发明背景

[0005] 最近一些年，流感病毒对全球的公共健康所造成的严重威胁已经凸显在以下方面：首先，高致病性甲型禽流感病毒 H5N1 病毒株向人类的持续水平 (ongoing level) 传播 (在被感染的人中死亡率为 63％，http://www.who.int/csr/disease/avian_influenza/en/)；第二，在 2009 年出乎预料地出现了新的大流行流感病毒株 A/H1N1，其已经迅速扩散到全世界 (http://www.who.int/csr/disease/swineflu/en/)。虽然该新病毒株具有高度接触传染性，但目前通常仅导致轻度疾患，这种病毒将来的演变是不可预期的。在一种严重得多但是高度可能的情形中，H5N1 和相关高致病性禽流感病毒可能获得突变，使得其在人之间更容易地传播或者新的 A/H1N1 可能变得毒力更强，且仅单点突变将足以赋予其对奥司他韦 (oseltamivir) 的抗药性 (Neumann 等人，Nature, 2009(18；459(7249)931-939))；正如许多季节性 H1N1 病毒株最近已经显示的那样 (Dharan 等，The Journal of the American Medical Association, 2009Mar 11；301(10), 1034-1041；Moscona 等人，The New England Journal of Medicine, 2009(Mar 5；360(10)pp 953-956))。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导致灾难性代价。

[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，需要有抗流感药物的更广泛的选择。因此，新抗流感药物的开发已再次成为高优先级，而在神经氨酸酶抑制剂成为可用时这已被主要药物公司大量放弃。

[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本身。这些神经氨酸酶抑制剂及其衍生物随后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作为防御可能大流行的第一道防线而储备。但是，这些药物仅仅缩短临床疾病的持续时间。可选地，另一类批准的抗流感药物——金刚烷类（如金刚烷胺和金刚烷乙胺）靶向位于病毒膜中的病毒 M2 离子通道蛋白，干扰细胞内病毒颗粒的脱壳。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，优选针对不同靶点的化合物。

[0008] 流感病毒以及索戈托病毒属 (Thogotovirus) 和 Isavirus 属于正粘病毒科 (Orthomyxoviridae)，其与布尼亚病毒科 (Bunyaviridae)（尤其包括汉坦病毒属 (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，且进入包括 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) 将最初的单链反义病毒体 RNA (vRNA) 拷贝至病毒 mRNA（即转录）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）对于病毒的生命周期而言是关键的，因为其负责病毒 RNA 的复制和转录。在先前工作中，已鉴定聚合酶的两个关键结构域即 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 亚基中的内切核酸酶 - 活性位点 (Dias 等人，Nature 2009, 458, 914-918) 的原子结构，并且表征了它们的分子结构。这两个位点对于用于启动 mRNA 转录的独特“帽 - 攫取 (cap-snatching)”模式而言是关键的，被流感病毒和这一属的某些其他病毒用于产生病毒 mRNA。5’ 帽是修饰的鸟嘌呤核苷酸，其已被加入至信使 RNA 的 5’ 端。5’ 帽（也称为 RNA 帽或 RNA m7G 帽）由通过 5’-5’- 三磷酸键连接至第一转录的核苷酸的末端 7- 甲基鸟苷残基组成。病毒聚合酶与细胞 mRNA 分子的 5’ RNA 帽结合并将 RNA 帽连同 10-15 个核苷酸的一段序列 (stretch) 一起断裂。加帽的 RNA 片段然后充当用于合成病毒 mRNA 的引物 (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）。

[0009] 聚合酶复合体看似为适当的抗病毒药物靶点，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，已经靶向聚合酶的内切核酸酶活性并且一系列 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，flutimide，一种在真菌物种 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内切

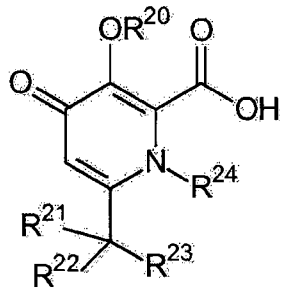
核酸酶 (Tomassini, J. 等人, (1996), Antimicrob. Agents Chemother., 40, 第 1189-1193 页)。此外,已尝试通过核苷类似物如 2'- 脱氧 -2'- 氟鸟苷干扰病毒转录 (Tisdale, M. 等人, (1995), Antimicrob. Agents Chemother., 39, 第 2454-2458 页)。

[0010] 本发明的目的是为了鉴定有效对抗病毒疾病的并且具有改善的药理学性质的化合物。

[0011] 发明概述

[0012] 因此,在第一实施方案中,本发明提供具有通式 (II) 的化合物。

[0013]



[0014] 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"包括其药学上可接受的盐、溶剂化物、多晶型物、前药、挛药、共晶、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] 本发明的其他实施方案涉及包含具有通式 (II) 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 (II) 的化合物可用于治疗、改善或预防病毒疾病。

[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,而不意在限制本发明的范围,本发明的范围将仅由所附权利要求所限定。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体或步骤或者整体或步骤的组,但是不排除任何其它的整体或步骤或者整体或步骤的组。在下列段落中,详细定义本发明的不同方面。除非清楚地相反指出,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、科学出版物、制造商说明、说明书等) 都以其全部内容引入本文作为参考。本文中的任何内容均不应理解为承认由于在先发明从而本发明不早于这类公开内容。

[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”表示环状形式的“烷基”。术语“环烷基”也意指包括其二环、三环和多环形式。除非另有指明，否则环烷基可具有 3 至 12 个碳原子。

[0025] “Hal”或“卤素”表示 F、Cl、Br 和 I。

[0026] “3- 至 7- 元碳环或杂环”是指三、四、五、六或七元环，其中环中的零个、一个或多个碳原子被 1 或 2（对于三元环）、1、2 或 3（对于四元环）、1、2、3 或 4 个（对于五元环）或 1、2、3、4 或 5 个（对于六元环）以及 1、2、3、4、5 或 6 个（对于七元环）相同或不同的杂原子替换，其中杂原子选自 O、N 和 S。

[0027] 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。

[0028] 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，其中杂原子选自 O、N 和 S。杂芳基的实例包括吡咯、吡咯烷、氧杂环戊烷、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。

[0029] 术语“含有 5-20 个碳原子和任选的 1-4 个选自 O、N 和 S 的杂原子并且含有至少一个环的烃基”指具有 5-20 个碳原子和任选的 1-4 个选自 O、N 和 S 的杂原子的任意基团，只要该基团含有至少一个环。该术语还包括其二环、三环和多环形式。如果存在多于一个的环，则它们可以是彼此分开的或捏合的。所述的环可以是碳环或杂环，并且可以是饱和的、不饱和的或芳族的。碳原子和杂原子可以均存在于所述的一个或多个环中，或者碳原子和 / 或杂原子中的一些可以存在于环外，例如，存在于连接体基团（例如 $-(CH_2)_p-$，其中 p = 1-6）中。这些基团的实例包括 -（任选取代的 C_{3-7} 环烷基）、-（任选取代的芳基），其中所述的芳基可以是例如苯基、-（任选取代的联苯基）、金刚烷基、-(C_{3-7} 环烷基）- 芳基，以及具有连接体的相应化合物。

[0030] 如果化合物或基团被称为是“任选取代的”，则它在每种情况下可以包括一个或多个所指示的取代基，其中所述取代基可以相同或不同。

[0031] 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、酒石酸氢盐、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、乙烷磺酸盐、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、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、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)、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、氯茶碱盐 (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))。

[0032] 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。

[0033] 术语"挛药"指通过共价化学键键合的两种或更多种治疗化合物。详细的定义可见于例如N. Das等人, European Journal of Pharmaceutical Sciences, 41, 2010, 571 - 588。

[0034] 术语"共晶"指一种多组分晶体,其中所有组分当是其纯形式时在环境条件下均是固体。这些组分以化学计量比或非化学计量比的靶点分子或离子 (即,本发明的化合物) 和一种或多种中性分子共晶形成物的形式共存。详细讨论可见于例如 Ning Shan 等人, Drug Discovery Today, 13(9/10), 2008, 440-446 和 D. J. Good 等人, Cryst. Growth Des., 9(5), 2009, 2252 - 2264 中。

[0035] 本发明的化合物也可以以前药 (即其在体内代谢成活性代谢物的化合物) 形式提供。适合的前药是例如酯。适合基团的具体实例尤其在 US2007/0072831 的第 [0082] - [0118] 段在标题前药和保护基下给出。前药的优选实例包括其中 R^{20} 被以下基团替换的那些 :

[0036] $P(O)(O)OR^{19}$; $C(O)OR^{19}$; $C(O)R^{19}$ 或 $C-R^{29}$;

[0037] 其中 R^{19} 选自 C_{5-10} 芳基、C_{1-6} 烷基 - C_{5-10} 芳基、C_{1-6} 烷基、C_{1-6} 烷基 (- O - C_{1-6} 烷基)$_n$ (其中 n = 1-30)、C_{1-6} 烷基 - C(O)OR 以及 C_{5-10} 芳基 - C(O)OR ; 以及

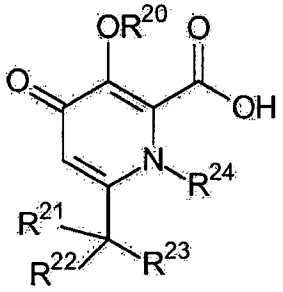
[0038] 其中 R^{29} 选自 C_{1-6} 烷基 (- O - C_{1-6} 烷基)$_n$ (其中 n = 1-30)、C_{1-6} 烷基 - C(O)OR 和 C_{5-10} 芳基 - C(O)OR。

[0039] 基团 R 是 H 或 C_{1-6} 烷基。

[0040] 具有通式 (II) 的化合物

[0041] 本发明提供了具有通式 (II) 的化合物。

[0042]



(II)

[0043] 本发明提供了具有通式(II)的化合物,其中适用以下定义:

[0044] X^{20}是 NR^{25}、$N(R^{25})C(O)$、$C(O)NR^{25}$、O、C(O)、C(O)O、OC(O);$N(R^{25})SO_2$、$SO_2N(R^{25})$、S、SO或SO_2;优选 X^{20}是 $N(R^{25})$ 或 $N(R^{25})SO_2$;更优选 X^{20}是 $N(R^{25})SO_2$。

[0045] R^{20}是 -H、$-C_{1-6}$烷基基团或 $-C(O)-C_{1-6}$烷基基团。在优选的实施方案中,R^{20}是 -H、或 -(任选取代的C_{1-6}烷基;更优选为 -H。

[0046] R^{21}是 -H、$-C_{1-6}$烷基基团、或被一个或多个卤素原子取代的 $-C_{1-6}$烷基基团;优选地,R^{21}是 -H。

[0047] R^{22}是 -H、$-C_{1-6}$烷基基团、或被一个或多个卤素原子取代的 $-C_{1-6}$烷基基团;优选地,R^{22}是 -H。

[0048] 在一个实施方案中,R^{21}和 R^{22}可以连接在一起形成 3- 至 7- 元碳环或杂环。

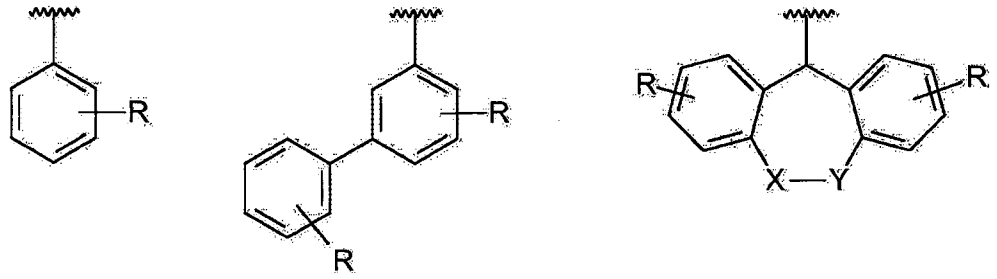
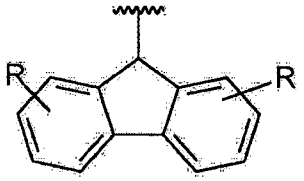
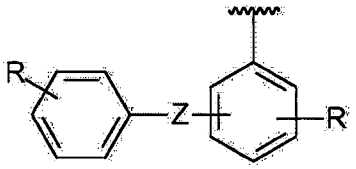
[0049] R^{23}是 $-R^{26}$或 $-X^{20}-R^{26}$。在一个实施方案中 R^{23}是 $-R^{26}$。在备选的实施方案中,R^{23}是 $-X^{20}-R^{26}$。

[0050] R^{24}是 H 或 C_{1-6}烷基基团。

[0051] R^{25}是 -H、-(任选取代的C_{1-6}烷基)、-(任选取代的C_{3-7}环烷基)、-(任选取代的芳基)、$-C_{1-4}$烷基 -(任选取代的C_{3-7}环烷基)或 $-C_{1-4}$烷基 -(任选取代的芳基)。在优选的实施方案中,R^{25}是 -H 或 -(任选取代的C_{1-6}烷基)。

[0052] R^{26}是 -(任选取代的含有 5-20 个碳原子和任选的 1-4 个选自 O、N 和 S 的杂原子的并且含有至少一个环的烃基)。优选地,所述至少一个环是芳香族环,如芳基或杂芳基环。更优选地,R^{26}是含有 5-20 个碳原子和任选的 1-4 个杂原子并且含有至少两个环的烃基,其中该烃基可以是任选被取代的。甚至更优选地,该至少两个环中的至少一个是芳香族环,如芳基或杂芳基环。R^{26}的优选实例可选自:

[0053]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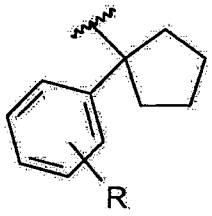


[0054] X 为不存在、CH_2、NH、C(O)NH、S 或 O。而且

[0055] Y 是 CH_2。

[0056] 在备选的实施方案中，X 和 Y 可以连接在一起形成可以是饱和或不饱和的环状碳环或杂环 3 至 8 元环。X-Y 具体的实例包括 $-CH_2-$、$-CH_2-CH_2-$、-O- 和 -NH-。

[0057] Z 是 O 或 S。

[0058] R 独立地选自 -H、$-C_{1-6}$烷基、$-CF_3$、- 卤素、-CN、-OH 以及 $-O-C_{1-6}$烷基。

[0059] R^{27}是 -H、$-C_{1-6}$烷基或 $-(CH_2CH_2O)_rH$；优选地，R^{27}是 -H、或 $-C_{1-6}$烷基。

[0060] R^{28}是 -H、或 $-C_{1-6}$烷基。

[0061] R 独立地选自 $-C_{1-6}$烷基、$-C(O)-C_{1-6}$烷基、-Hal、$-CF_3$、-CN、$-COOR^{27}$、$-OR^{27}$、$-(CH_2)_qNR^{27}R^{28}$、$-C(O)-NR^{27}R^{28}$以及 $-NR^{27}-C(O)-C_{1-6}$烷基。优选地，R 是 -Hal、$-CF_3$或 -CN，更优选是 -Hal 或 $-CF_3$。

[0062] q 是 0 至 4。

[0063] r 是 1 至 3。

[0064] 烷基基团、芳基基团、烃基基团和 / 或环烷基基团的任选取代基选自由一个或多个取代基 R 组成的组，取代基 R 包括 $-C_{1-6}$烷基、$-C(O)-C_{1-6}$烷基、-Hal、$-CF_3$、-CN、$-COOR^{27}$、$-OR^{27}$、$-(CH_2)_qNR^{27}R^{28}$、$-C(O)-NR^{27}R^{28}$和 $-NR^{27}-C(O)-C_{1-6}$烷基。优选地，芳基基团、烃基基团和 / 或环烷基基团的任选取代基是 - 卤素（优选 F）、$-OCH_3$或 -CN。优选地，烷基基团的任选取代基选自卤素、-CN、$-NR^{28}R^{28}$（其中彼此独立地选择每一个 R^{28}）、-OH 和 $-O-C_{1-6}$烷基。优选地，烷基基团的取代基是 - 卤素，更优选为 F。

[0065] 本发明的发明人已经令人惊讶地发现，与具有更小的基团 R^{23}的相应化合物相比，具有大的基团 R^{23}的本发明的化合物具有改善的药理学性质。不希望受理论的束缚，认为病毒聚合酶蛋白质具有用于结合的口袋并且本发明的化合物的大的基团 R^{23}在更大程度上填充该口袋。还认为较大的基团 R^{23}比较小的基团例如甲基能提供与口袋的更疏水的相互作用。

[0066] 本发明的化合物可以以药物组合物的形式施用于患者，所述药物组合物可任选包含一种或多种药学上可接受的赋形剂和 / 或载体。

[0067] 本发明的化合物可以通过各种公知的途径施用，包括口服、直肠、胃内

(intragastrical)、颅内和肠胃外施用，例如静脉内、肌内、鼻内、真皮内、皮下，以及类似的施用途径。特别优选的是口服、鼻内和肠胃外施用。根据施用途径，需要不同的药物制剂，这些施用途径中的一些可能需要给药物制剂施用保护性包衣以防止本发明的化合物在例如消化道内降解。

[0068] 因此，优选地，本发明的化合物被配制成糖浆剂、输液或注射液、喷雾剂、片剂、胶囊、囊片 (capslet)、锭剂、脂质体、栓剂、膏药、绷带 (band-aid)、缓释胶囊 (retard capsule)、散剂或缓慢释放制剂。优选地，稀释剂是水、缓冲剂、缓冲盐溶液或盐溶液，载体优选选自可可脂和 vitebesole。

[0069] 用于施用本发明的化合物的特别优选的药物形式是适合注射使用的形式，包括无菌的水溶液剂或分散体和用于即时制备无菌注射溶液或分散体的无菌粉末。在所有情况中，最终的溶液剂或分散体形式必须是无菌的并且是流体。典型地，这类溶液剂或分散体将包含溶剂或分散介质，其含有例如水 - 缓冲水溶液例如生物相容性的缓冲剂、乙醇、多元醇例如甘油、丙二醇、聚乙二醇、其适合的混合物，表面活性剂或植物油。本发明的化合物也可以被配制成脂质体，特别是用于肠胃外施用的脂质体。脂质体提供在循环中半衰期增加的优点（如果与游离药物相比）以及所包裹的药物的延长的更均匀的释放。

[0070] 输液和注射液的灭菌可以通过任意数量的本领域公认的技术来实现，包括但不限于加入防腐剂如抗细菌剂或抗真菌剂，例如对羟基苯甲酸酯 (parabene)、氯代丁醇、苯酚、山梨酸或 thimersal。此外，还可以在输液和注射液中掺入等渗剂，例如糖或盐，特别是氯化钠。

[0071] 含有一种或多种本发明的化合物的无菌注射液的生产通过以下方法完成：将所需量的各化合物掺入酌情具有上面列出的各种成分的适宜溶剂中，然后灭菌。为了获得无菌粉末，将上述溶液根据需要真空干燥或冷冻干燥。本发明的优选的稀释剂是水、生理学上可接受的缓冲剂、生理学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。可以与本发明的化合物的各种药物形式一起使用的赋形剂可选自下面的非限制性列表：

[0072] a) 粘合剂，例如乳糖、甘露醇、结晶山梨醇、磷酸氢盐、磷酸钙、糖、微晶纤维素、羧甲基纤维素、羟乙基纤维素、聚乙烯吡咯烷酮等；

[0073] b) 润滑剂，例如硬脂酸镁、滑石粉、硬脂酸钙、硬脂酸锌、硬脂酸、氢化植物油、亮氨酸、甘油酯和硬脂酰醇富马酸钠，

[0074] c) 崩解剂，例如淀粉、交联羧甲纤维素、甲基纤维素钠、琼脂、膨润土、海藻酸、羧甲基纤维素、聚乙烯吡咯烷酮等。

[0075] 在一个实施方案中，制剂用于口服施用，并且制剂包含下列成分中的一种或多种或全部：预胶化淀粉、滑石粉、聚乙烯吡咯烷酮 K30、交联羧甲纤维素钠、硬脂酰醇富马酸钠、明胶、二氧化钛、山梨醇、柠檬酸一钠、黄原胶、二氧化钛、矫味剂、苯甲酸钠和糖精钠。

[0076] 如果在一个优选的实施方案中本发明的化合物被鼻内施用，其可以以干粉吸入器或来自使用适合的抛射剂例如二氯二氟甲烷、三氯氟甲烷、二氯四氟乙烷、氢氟烷如 1,1,1,2- 四氟乙烷 (HFA 134A™) 或 1,1,1,2,3,3,3- 七氟丙烷 (HFA 227EA™)、二氧化碳或其它适合的气体的加压容器、泵、喷雾器或雾化器中的气雾喷雾剂的形式被施用。所述的加压容器、泵、喷雾器或雾化器可以含有本发明的化合物的溶液剂或混悬剂（例如使用乙醇

和抛射剂的混合物作为溶剂），其还可以含有润滑剂，例如三油酸山梨坦。

[0077] 其它适合的赋形剂可见于美国药学协会（American Pharmaceutical Association）出版的药物赋形剂手册（Handbook of Pharmaceutical Excipients），通过引用将其合并入本文。

[0078] 应当理解的是，根据可用本发明的化合物之一治疗的病症的严重性和具体类型，以及根据待治疗的各个患者例如患者的总体健康状态等，需要不同剂量的各化合物来产生治疗或预防效果。适宜剂量的确定由主治医师酌情确定。认为在本发明的治疗或预防应用中本发明的化合物的剂量应当在约 0.1mg 至约 1g 活性成分（即，本发明的化合物）/ 千克体重范围内。然而，在一个优选的本发明的应用中，将本发明的化合物以 1.0-500mg/kg 体重、优选 1-200mg/kg 体重的量施用于需要其的个体。用本发明的化合物治疗的持续时间将根据所治疗的疾病的严重性以及每个单个患者的情况和特质反应而变化。在一个优选的预防或治疗应用的实施方案中，每天给成年人口服施用 10mg - 200mg 化合物，这取决于疾病的严重性和 / 或暴露于疾病载体的程度。

[0079] 如本领域中已知的那样，给定组合物的药学有效量还取决于施用途径。一般而言，如果施用是通过胃肠道（例如用栓剂）、直肠或通过胃内探针进行，则所需的量较高，如果施用途径是肠胃外例如静脉内，则所需的量较低。典型地，如果使用直肠或胃内施用，则本发明的化合物将以 50mg-1g/kg 体重、优选 10mg-500mg/kg 体重被施用，如果使用肠胃外施用，则本发明的化合物将以 1-100mg/kg 体重被施用。对于鼻内施用，考虑 1-100mg/kg 体重。

[0080] 如果已知一个人具有发生可用本发明的化合物治疗的疾病的风险，则预防性施用生物学活性血清或本发明的药物组合物可能是可行的。在这些情况下，本发明的各化合物优选每天用上述优选的和特别优选的剂量被施用。优选地，每天一次 0.1mg - 1g/kg 体重，优选 10 - 200mg/kg 体重。该施用可以持续至发生各病毒病症的风险已经减小。然而，在大部分情况下，在已经诊断出疾病 / 病症后施用本发明的化合物。在这些情况中，优选的是每天一次、两次、三次或四次施用首剂量的本发明的化合物。

[0081] 本发明化合物特别可用于治疗、改善或预防病毒疾病。对病毒疾病的类型没有特别限制。可能的病毒疾病的实例包括但不限于由以下病毒引起的病毒疾病：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）、正粘病毒科（Orthomyxoviridae）、布尼亚病毒科（Bunyaviridae）、沙粒病毒科（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（Deltavirus）、博尔纳病毒科（Bornaviridae）和阮病毒（prion）。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、正粘病毒科、布尼亚病毒科、沙粒病毒科、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，更优选由正粘病毒科引起的病毒疾病。

[0082] 各种病毒的实例在下表中给出：

[0083]

科	病毒(优选的实例)
痘病毒科	天花病毒(Smallpox virus) 传染性软疣病毒(Molluscum contagiosum virus)
疱疹病毒科	单纯疱疹病毒(Herpes simplex virus) 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(Kaposi's sarcoma-associated herpesvirus)
腺病毒科	人腺病毒 A-F
乳头瘤病毒科	乳头瘤病毒(Papillomavirus)

[0084]

多瘤病毒科	BK-病毒 JC-Virsu
细小病毒科	B19 病毒 腺伴随病毒 2/3/5(Adeno associated virus 2/3/5)
嗜肝病毒科	乙肝病毒(Hepatitis B virus)
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	呼肠病毒 1/2/3 轮状病毒 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) 杜温黑基病毒(Duvenhage virus)
正粘病毒科	甲-丙型流感病毒(Influenza virus types A-C)
布尼亚病毒	加利福尼亚脑炎病毒(California encephalitis virus) La Crosse 病毒(La Crosse virus) 汉坦病毒(Hantaan virus) 普马拉病毒(Puumala virus) 辛诺瓦病毒(Sin Nombre virus) 汉城病毒(Seoul virus) 克里米亚-刚果出血热病毒(Crimean- Congo hemorrhagic fever virus)

[0085]

	萨哈林岛病毒(Sakhalin virus) 裂谷病毒(Rift valley virus) 白蛉热病毒(Sandfly fever virus) 尤尤库尼米病毒(Uukuniemi virus)
沙粒病毒科	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(Human coronavirus)
细小 RNA 病毒	A-D 型人肠道病毒（脊髓灰质炎病毒(Poliovirus)、埃可病毒(Echovirus)、柯萨奇病毒(Coxsackie virus) A/B) A/B/C 型鼻病毒 甲型肝炎病毒(Hepatitis A virus) 副肠弧病毒(Parechovirus) 口蹄疫病毒(Food and mouth disease virus)
肝炎病毒科	戊型肝炎病毒(Hepatitis E virus)
嵌杯病毒科	诺沃克病毒(Norwalk virus) 札幌病毒(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) 切昆贡亚病毒(Chikungunya virus) 奥尼永尼永病毒(O'nyong-nyong virus) 风疹病毒(Rubella virus)
黄病毒科	蜱传脑炎病毒(Tick-borne encephalitis virus) 登革热病毒(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) 西尼罗病毒(West Nile virus) 丙型肝炎病毒(Hepatitis C virus)

[0086]

	庚型肝炎病毒(Hepatitis G virus) GB 型肝炎病毒(Hepatitis GB virus)
δ病毒	δ型肝炎病毒(Hepatitis deltavirus)
博尔纳病毒科	博尔纳病毒(Bornavirus)
阮病毒	

[0087] 优选地，采用本发明化合物治疗流感。本发明涵盖所有属于正粘病毒科的所有病毒属，尤其是甲型流感病毒、乙型流感病毒、丙型流感病毒、isavirus 和索戈托病毒(thogotovirus)。在本发明中，术语“流感”包括由任何流感病毒引起的流感，所述流感病毒诸如甲型流感病毒、乙型流感病毒、丙型流感病毒，包括其各种病毒株和分离株，以及包括通常称为禽流感和猪流感的甲型流感病毒。未特别限定待治疗的个体并且其可以是任何脊椎动物，如鸟类和哺乳动物（包括人类）。

[0088] 不希望受理论束缚，认为本发明的化合物能抑制内切核酸酶活性、特别是流感病毒的内切核酸酶活性。更具体地，推测它们直接干扰具有内切核酸酶活性并且对病毒复制很重要的流感病毒 PA 蛋白的 N- 末端部分。病毒复制发生在细胞内的细胞核内。因此，设计用于抑制 PA 内切酶活性的化合物需要跨越细胞膜和核膜两者，这一性质很大程度上取决于化合物设计的物理化学性质。本发明显示要求保护的化合物具有体外聚合酶抑制活性，以及在基于细胞的分析中显示其具有体外抗病毒活性。

[0089] 具有式 (II) 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基于 FRET（荧光共振能量转移）的内切核酸酶活性测定。优选地，在 FRET 测定中化合物在 25 μM 时表现出至少约 50％的％减少。在该上下文中，％减少为作为与未经处理样品相比，经化合物处理后流感病毒内切核酸酶亚基 (PA-Nter) 切割的双标记 RNA 底物的荧光升高而测量的初始反应速度 (v0) 的％减少。优选地，化合物在这一测定中表现出低于约 40 μM、更优选低于约 20 μM 的 IC_{50}。半数最大抑制浓度 (IC_{50}) 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。

[0090] 具有通式 (II) 的化合物可与一种或多种其他药物组合使用。不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、改善或预防病毒疾病的药物，更优选为另一种可用于治疗、改善或预防由流感病毒感染引起的流感和与该病毒感染相关的疾患（如病毒性肺炎或继发性细菌性肺炎）的药物，以及治疗诸如寒颤、发烧、喉咙痛、肌肉疼、严重头疼、咳嗽、无力和疲劳的症状的药物。此外，具有通式 (I) 的化合物可与抗炎药联合使用。

[0091] 下面的药物组合被认为是特别适合的：

[0092] (i) 内切核酸酶和帽结合抑制剂（特别是靶向于流感的）的组合。对所述的内切核酸酶抑制剂没有特别限制，可以是任意内切核酸酶抑制剂，特别是任意病毒内切核酸酶抑制剂。优选的内切核酸酶抑制剂是序号为 61/550,045(2011 年 10 月 21 日提交)、61/650,713(2012 年 5 月 23 日提交)、61/650,725(2012 年 5 月 23 日提交）以及 61/679,968(2012 年 8 月 6 日提交）的美国申请中所定义的那些。这些申请通过引用将其全部公开内容合并入本文。特别地，将关于这些美国申请的化合物的通式、各取代基的优选

实施方案以及所述化合物的医学效用和优点的所有描述通过引用合并入本文。

[0093] 另外的优选的内切核酸酶抑制剂是与本申请同一天提交的代理律师案卷编号为U2797US的共同待审的申请中所定义的具有通式(I)结构的化合物，以及代理律师案卷编号为U2799US的共同待审的申请中所定义的具有通式(V)结构的化合物，通过引用将所述申请的全部公开内容合并入本文。特别地，将关于这些化合物的通式、各取代基的优选实施方案以及所述化合物的医学效用和优点的所有描述通过引用合并入本文。这些化合物可以任选地是药学上可接受的盐、溶剂化物、多晶型物、孪药、共晶、前药、互变异构体、外消旋物、对映体或非对映体或者其混合物形式的。

[0094] 对所述的帽结合抑制剂也没有特别限制，可以是任意帽结合抑制剂，特别是任意病毒帽结合抑制剂。优选的帽结合抑制剂是美国申请61/550,057(2011年10月21日提交)中所定义的具有通式(II)的那些和/或WO2011/000566中所公开的化合物，通过引用将其全部公开内容合并入本文。特别地，将关于US 61/550,057或WO2011/000566的化合物的通式、各取代基的优选实施方案以及所述化合物的医学效用和优点的所有描述通过引用合并入本文。

[0095] 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(例如奥司他韦))的广泛耐药性存在于流行性和季节性出现的流感病毒株中，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，病毒耐药性频率自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2009H1N1和季节性H3N2株对金刚烷类(金刚烷乙胺和金刚烷胺)有耐药性，而且对于奥司他韦(被最广泛开具处方的神经氨酸酶抑制剂(NAI))，WHO报道在2007/2008流感季节开始显著出现的流感A/H1N1抗药性；并且在南半球持续了2008年的第二和第三季度。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NAI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，对新的有效药物的需求明显增加。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。

[0096] 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-结合和内切核酸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。这两种靶点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点。由于对于病毒转录而言非常重要的所谓的“帽-攫取”机理需要这两种功能这一事实，预期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性。

[0097] 这两个活性位点在所有甲型流感株(例如禽类和人类)以及甚至乙型流感病毒中是高度保守的，并因此这种高度的序列保守性证实这些靶点不可能触发快速耐药性病毒产生的看法。此外，与宿主蛋白的密切相互作用使得这些病毒蛋白更不倾向于突变。因此，单独的和组合的内切核酸酶和帽-结合抑制剂是对抗季节性和流行性流感(与病毒株无关)的理想候选药物。

[0098] 内切核酸酶抑制剂和帽-结合抑制剂的组合或靶向内切核酸酶活性位点和帽-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株是有效的，而且将耐药性产生的低敏感性的优点与抗广谱病毒株的活性相组合。

[0099] (ii) 不同抗病毒靶点（特别地靶向流感病毒）的抑制剂的组合，其关注与（优选流感病毒）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和复制活性的新型药物。针对病毒聚合酶的选择性抑制剂通过停止病毒繁殖周期而大幅度地减弱了病毒感染。预计特别针对病毒细胞内靶点的聚合酶抑制剂与不同抗病毒靶点的抑制剂的组合高度协同地起作用。这基于以下事实：这些不同类型的抗病毒药物表现出完全不同的作用机理，这些作用机理需要不同的药动学性质，其对该组合的抗病毒功效有利地且协同地起作用。

[0100] 这种高度有效的药物组合会导致更低的物质浓度，并且从而产生改善的剂量-响应关系和更佳的副作用特性。此外，上文针对聚合酶抑制剂所述的优点将存在于不同抗病毒靶点的抑制剂与聚合酶抑制剂的组合中。

[0101] 典型地，将选自第一组聚合酶抑制剂（例如，帽结合和内切核酸酶抑制剂）的至少一种化合物与选自第二组聚合酶抑制剂的至少一种化合物组合。

[0102] 能用于该类型的组合疗法的所述的第一组聚合酶抑制剂包括但不限于具有式(II)的化合物。

[0103] 能用于该类型的组合疗法的所述的第二组聚合酶抑制剂包括但不限于具有2011年10月21日提交的序列号为61/550,045的美国申请中所定义的式(I)的化合物、具有2011年10月21日提交的61/550,057的美国申请中所定义的式(II)的化合物、WO 2011/000566、WO 2010/110231、WO 2010/110409、WO 2006/030807或US 5,475,109中所公开的化合物以及flutimide及其类似物、法匹拉韦(favipiravir)及其类似物、表没食子儿茶素没食子酸酯(epigallocatechin gallate)及其类似物、以及核苷类似物例如利巴韦林(ribavirine)。

[0104] (iii) 聚合酶抑制剂与神经氨酸酶抑制剂的组合

[0105] 流感病毒聚合酶抑制剂是靶向于聚合酶的转录和复制活性的新药。预计特异性地针对病毒细胞内靶点的聚合酶抑制剂与不同的细胞外抗病毒靶点、尤其是（例如病毒）神经氨酸酶的抑制剂的组合高度协同地起作用。这基于以下事实：这些不同类型的抗病毒药物表现出完全不同的作用机理，这些作用机理需要不同的药动学性质，其对该组合的抗病毒功效有利地且协同地起作用。

[0106] 这种高度有效的药物组合会导致更低的物质浓度，并且从而导致改善的剂量-响应关系和更佳的副作用特性。此外，前文针对聚合酶抑制剂所述的优点将存在于不同抗病毒靶点的抑制剂与聚合酶抑制剂的组合中。

[0107] 典型地，将选自上述的第一组聚合酶抑制剂的至少一种化合物与至少一种神经氨酸酶抑制剂组合。

[0108] 对所述的神经氨酸酶抑制剂（特别是流感神经氨酸酶抑制剂）没有特别限制。实例包括扎那米韦、奥塞米韦、帕拉米韦(peramivir)、KDN DANA、FANA和环戊烷衍生物。

[0109] (iv) 聚合酶抑制剂与M2通道抑制剂的组合

[0110] 流感病毒聚合酶抑制剂是靶向于聚合酶的转录和复制活性的新药。预计特异性地

针对病毒细胞内靶点的聚合酶抑制剂与不同的细胞外和细胞质抗病毒靶点、尤其是病毒 M2 离子通道的抑制剂的组合高度协同地起作用。这基于以下事实：这些不同类型的抗病毒药物表现出完全不同的作用机理，这些作用机理需要不同的药动学性质，其对该组合的抗病毒功效有利地且协同地起作用。

[0111] 这种高度有效的药物组合会导致更低的物质浓度，并且从而导致改善的剂量 - 响应关系和更佳的副作用特性。此外，上文针对聚合酶抑制剂所述的优点将存在于不同抗病毒靶点的抑制剂与聚合酶抑制剂的组合中。

[0112] 典型地，将选自上述的第一组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。

[0113] 对 M2 通道抑制剂（特别是流感 M2 通道抑制剂）没有特别限制。实例包括金刚烷胺和金刚乙胺。

[0114] (v) 聚合酶抑制剂与 α 葡糖苷酶抑制剂的组合

[0115] 流感病毒聚合酶抑制剂是靶向于聚合酶的转录和复制活性的新药。预计特异性地针对病毒细胞内靶点的聚合酶抑制剂与不同的宿主细胞靶点、尤其是 α 葡糖苷酶的抑制剂的组合高度协同地起作用。这基于以下事实：这些不同类型的抗病毒药物表现出完全不同的作用机理，这些作用机理需要不同的药动学性质，其对该组合的抗病毒功效有利地且协同地起作用。

[0116] 这种高度有效的药物组合会导致更低的物质浓度，并且从而导致改善的剂量 - 响应关系和更佳的副作用特性。此外，上文针对聚合酶抑制剂所述的优点将存在于与病毒复制相互作用的细胞靶点的抑制剂与聚合酶抑制剂的组合中。

[0117] 典型地，将选自上述的第一组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。

[0118] 对 α 葡糖苷酶抑制剂没有特别限制。实例包括 Chang 等，Antiviral Research 2011, 89, 26-34 中所述的化合物。

[0119] (vi) 聚合酶抑制剂与其它流感靶点的配体的组合

[0120] 流感病毒聚合酶抑制剂是靶向于聚合酶的转录和复制活性的新药。预计特异性地针对病毒细胞内靶点的聚合酶抑制剂与不同的细胞外、细胞质或细胞核抗病毒靶点的抑制剂的组合高度协同地起作用。这基于以下事实：这些不同类型的抗病毒药物表现出完全不同的作用机理，这些作用机理需要不同的药动学性质，其对该组合的抗病毒功效有利地且协同地起作用。

[0121] 这种高度有效的药物组合会导致更低的物质浓度，并且从而导致改善的剂量 - 响应关系和更佳的副作用特性。此外，上文针对聚合酶抑制剂所述的优点将存在于不同抗病毒靶点的抑制剂与聚合酶抑制剂的组合中。

[0122] 典型地，将选自上述的第一组聚合酶抑制剂的至少一种化合物与至少一种另外的流感靶点的配体组合。

[0123] 对另外的流感靶点的配体没有特别限制。实例包括作用于唾液酸酶融合蛋白的化合物（例如 Fludase(DAS181)、siRNA 和硫代磷酸寡核苷酸）、信号转导抑制剂（例如，ErbB 酪氨酸激酶、Abl 激酶家族、MAP 激酶、PKCa- 介导的 ERK 信号活化）以及干扰素（诱导物）。

[0124] (vii)（优选流感）聚合酶抑制剂与用作最小化疾病症状的辅药的化合物（抗生

素、抗炎药如 COX 抑制剂（例如 COX-1/COX-2 抑制剂、选择性 COX-2 抑制剂）、脂氧合酶抑制剂、EP 配体（特别是 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于聚合酶的转录和复制活性的新药。特异性地针对病毒细胞内靶点的聚合酶抑制剂与用作最小化疾病症状的辅药的化合物的组合解决了病毒感染的起因性和症状性病理结果。预计该组合协同地起作用，因为这些不同类型的药物表现出完全不同的作用机理，这些作用机理需要不同的药动学性质，其对该组合的抗病毒功效有利地且协同地起作用。

[0125] 这种高度有效的药物组合会导致更低的物质浓度，并且从而导致改善的剂量 - 响应关系和更佳的副作用特性。此外，上文针对聚合酶抑制剂所述的优点将存在于不同抗病毒靶点的抑制剂与聚合酶抑制剂的组合中。

[0126] 在不偏离本发明的范围的情况下，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显而易见的。

[0127] 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

[0128] FRET 内切核酸酶活性测定

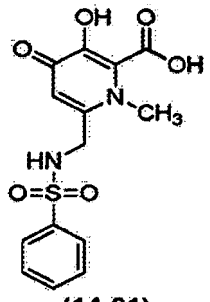
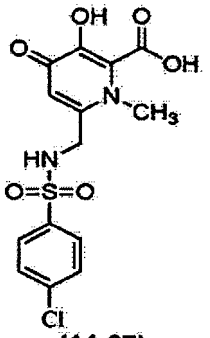
[0129] 如 Dias 等人，Nature 2009 ;4 月 16 ;458(7240),914-918 中所述，产生并纯化具有流感内切核酸酶活性的甲型流感病毒 (IAV)PA-Nter 片段（氨基酸 1-209）。将该蛋白溶解于含有 20mM Tris pH 8.0、100mM NaCl 和 10mM β - 巯基乙醇的缓冲液中并在 -20℃贮存等分试样。

[0130] 具有 5`-FAM 荧光团和 3`-BHQ1 淬灭物的 20 碱基双重标记 RNA 寡核苷酸用作通过 PA-Nter 的内切核酸酶活性切割的底物。对 RNA 底物的切割使荧光团从淬灭物释放，导致荧光信号的增加。

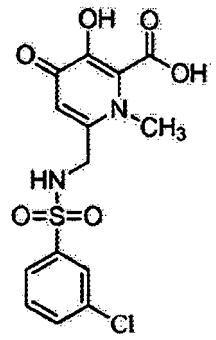
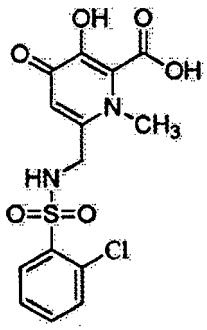
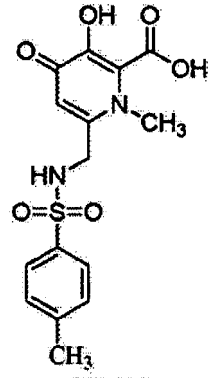
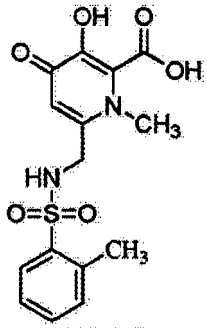
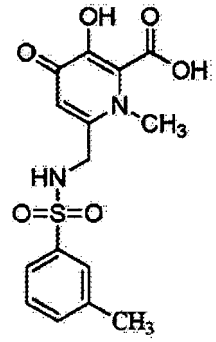
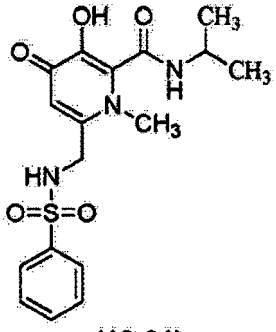
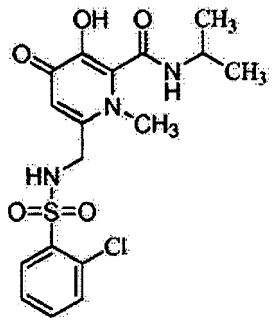
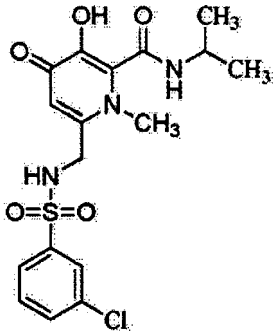
[0131] 将所有测定组分稀释于含有 20mM Tris-HCl pH8.0、100mM NaCl、1mM $MnCl_2$、10mM $MgCl_2$和 10mM β - 巯基乙醇的测定缓冲液中。PA-Nter 的最终浓度为 0.5 μM 和 1.6 μM RNA 底物。将测试化合物溶解于 DMSO 中，通常以两种浓度或浓度系列进行测试，产生 0.5％的最终的板孔 DMSO 浓度。在化合物在该浓度下不可溶的情况中，它们以最高可溶浓度进行测试。

[0132] 一式八份在白色 384- 孔微量滴定板 (PerkinElmer) 的孔中提供 5 μl 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 1.6 μM 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 的增加的荧光信号。在 35 的灵敏度下动态读数间隔为 35 秒。使用历经 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 (IC_{50}) 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 100 μM 至至少 2nM 的给定浓度系列中由初始反应速度 (v0) 计算。

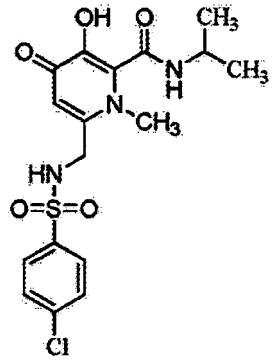
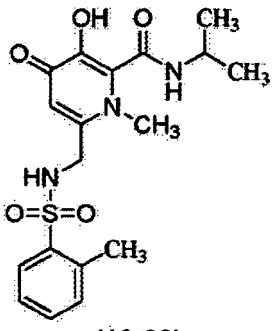
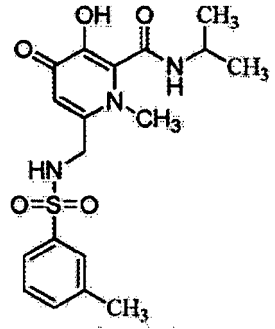
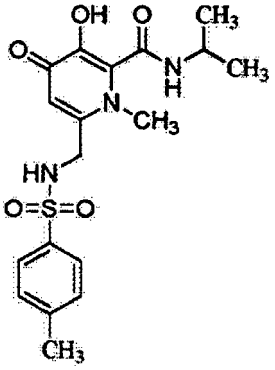
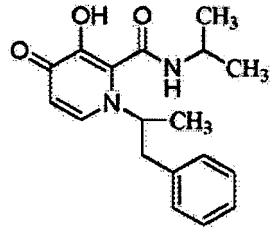
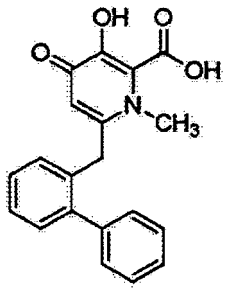
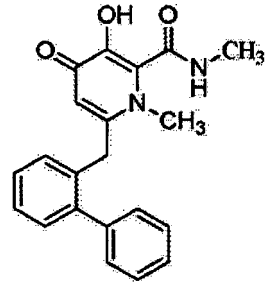
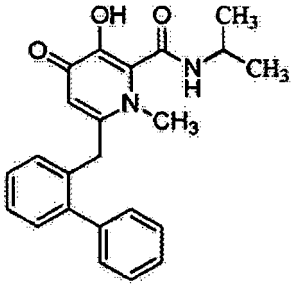
[0133]

式编号	FRET	式编号	FRET
 (14-01)	IC_{50}=0.56 μM	 (14-07)	IC_{50}=1.14μM

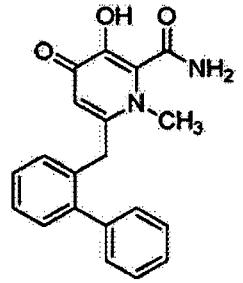
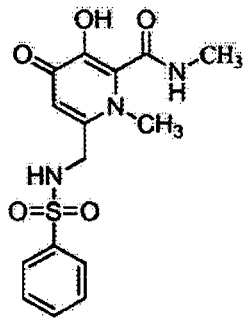
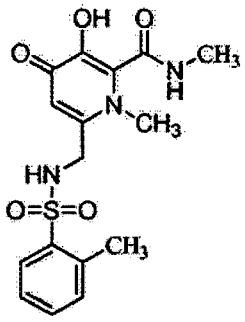
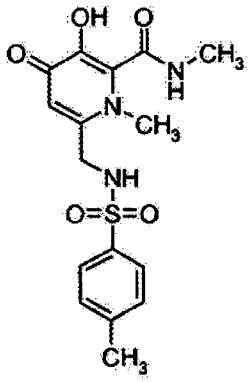
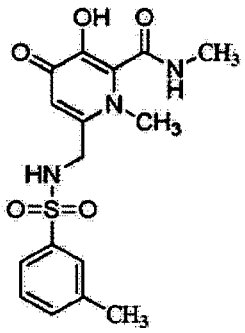
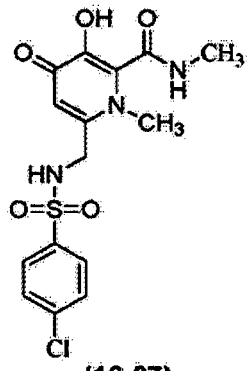
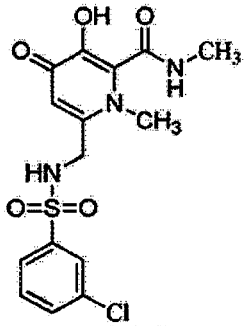
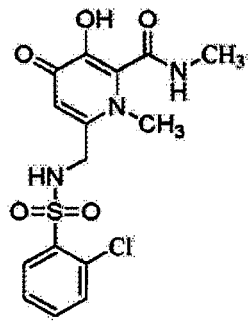
[0134]

 (14-05)	IC_{50}=0.15 μM	 (14-03)	IC_{50}=0.11μM
 (14-06)	IC_{50}=0.97 μM	 (14-02)	IC_{50}=0.28 μM
	IC_{50}=0.53 μM	 (18-01)	13% 抑制 @ 10 μM
 (18-03)	IC_{50}=6.3 μM	 (18-05)	13% 抑制 @ 10 μM

[0135]

 (18-07)	11% 抑制 @ 10 μM	 (18-02)	IC_{50}=4.6 μM
 (18-04)	36% 抑制 @ 10 μM	 (18-06)	8% 抑制 @ 10 μM
	7% 抑制 @ 10 μM		IC_{50}=0.40 μM
	10% 抑制 @ 10 μM		13% 抑制 @ 10 μM

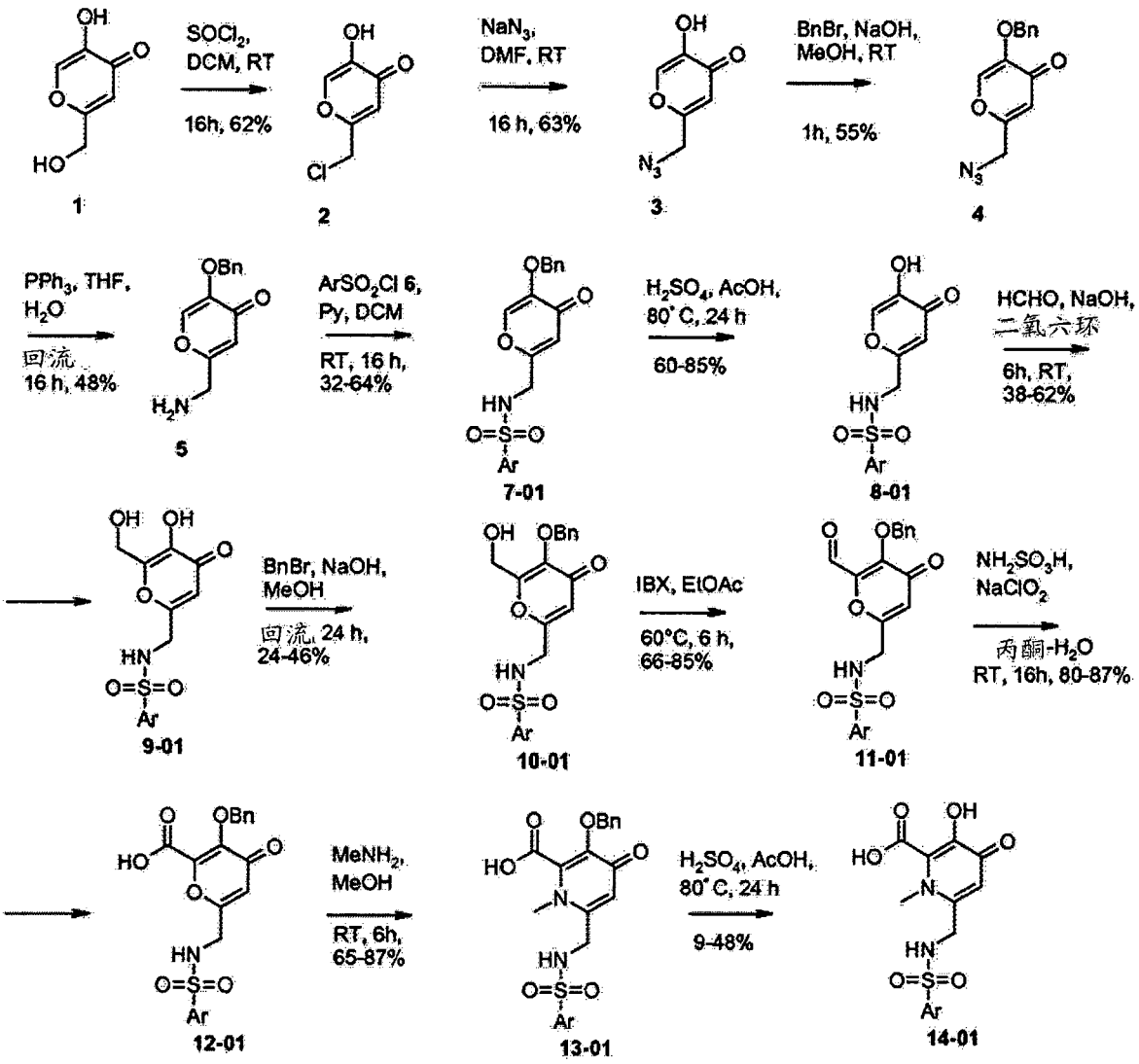
[0136]

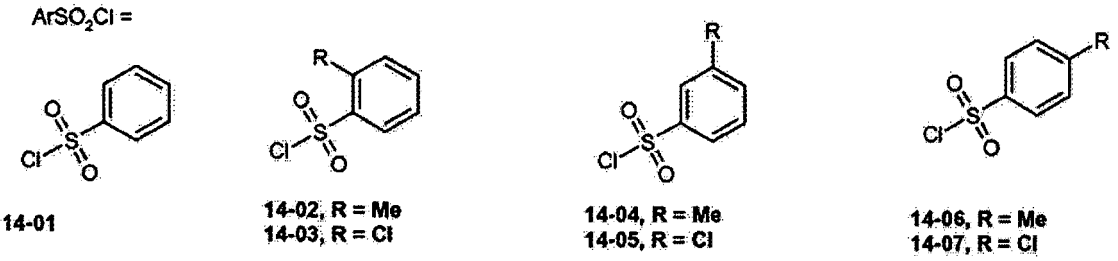
	17% 抑制 @ 10 μM	 (16-01)	13% 抑制 @ 10 μM
 (16-02)	IC_{50}=12.2 μM	 (16-06)	10% 抑制 @ 10 μM
 (16-04)	33% 抑制 @ 10 μM	 (16-07)	7% 抑制 @ 10 μM
 (16-05)	23% 抑制 @ 10 μM	 (16-03)	IC_{50}=9.0 μM

[0137] 合成路径

[0138] 流程 1：

[0139]

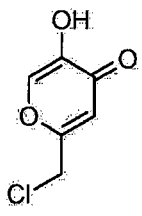




[0140] 实验：

[0141] (2) 的制备

[0142]



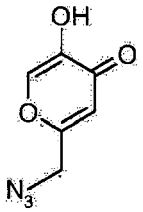
[0143] 2- 氯甲基 -5- 羟基 - 吡喃 -4- 酮

[0144] 向搅拌的 5- 羟基 -2- 羟基甲基 - 吡喃 -4- 酮 (1)(100.0g,703.68mmol) 的二氯甲烷 (750mL) 溶液中非常缓慢地加入 $SOCl_2$(102.0mL),并且在室温下搅拌反应混合物 16h。反应完成后,蒸发溶剂以在减压下移除挥发性化合物,得到粗产物。通过已烷对其进行纯化,得到 2- 氯甲基 -5- 羟基 - 吡喃 -4- 酮 (2)(70.0g,61.96%),为灰白色固体。

[0145] LC-MS:161.2(M+H)。

[0146] (3) 的制备

[0147]



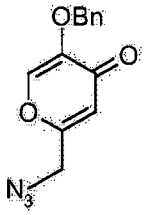
[0148] 2- 叠氮基甲基 -5- 羟基 - 吡喃 -4- 酮

[0149] 向搅拌的 2- 氯甲基 -5- 羟基 - 吡喃 -4- 酮 (2)(105.0g,656.2mmol) 的 DMF(600mL) 溶液中加入 NaN_3(55.45g,853.12mmol),然后室温下搅拌反应混合物 16h。反应完全后,用水稀释反应混合物,并用乙酸乙酯萃取。然后,用水和盐水洗涤合并的有机层,在 Na_2SO_4上干燥,并在减压下浓缩,得到 2- 叠氮基甲基 -5- 羟基 - 吡喃 -4- 酮 (3)(70.0g,63.83%),其为浅棕色固体。

[0150] LC-MS:168.2(M+H)。

[0151] (4) 的制备

[0152]



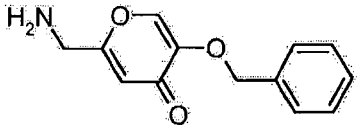
[0153] 2- 叠氮基甲基 -5- 苄氧基 - 吡喃 -4- 酮

[0154] 向搅拌的 2- 叠氮基甲基 -5- 羟基 - 吡喃 -4- 酮 (3)(70.0g,419.1mmol) 的甲醇 (500mL) 溶液中加入 NaOH(20g,502.9mmol,2M) 和苄基溴 (60.14mL,502.9mmol),并在室温下搅拌反应混合物 1h。反应完全后,蒸发溶剂以在减压下移除挥发化合物,然后将其用水稀释并用乙酸乙酯萃取。然后用水和盐水洗涤合并的有机层,在 Na_2SO_4上干燥,减压下浓缩并用正常 (normal) 柱色谱法 (使用 20%的乙酸乙酯的己烷溶液) 纯化,得到 2- 叠氮基甲基 -5- 苄氧基 - 吡喃 -4- 酮 (4)(60.0g,55.0%),其为浅棕色固体。

[0155] LC-MS:258.0(M+H)。

[0156] (5) 的制备

[0157]



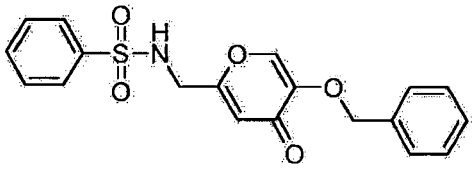
[0158] 2-氨基甲基-5-苄氧基-吡喃-4-酮

[0159] 向搅拌的2-叠氮基甲基-5-苄氧基-吡喃-4-酮(4)(30.0g,116.7mmol)的四氢呋喃(500mL)溶液中加入三苯基膦(61.16g,233.46mmol)和水(5.2mL),并使该混合物回流16h。反应完全后,减压下蒸发溶剂,然后通过正常柱色谱法纯化,得到(2-氨基甲基-5-苄氧基-吡喃-4-酮(5)(13.0g,48.16%),其为棕色固体。

[0160] LC-MS:232.2(M+H)。

[0161] (7-01)的制备:

[0162]



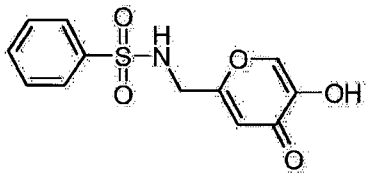
[0163] N-(5-苄氧基-4-氧代-4H-吡喃-2-基甲基)-苯磺酰胺

[0164] 在冰冷条件下,向搅拌的2-氨基甲基-5-苄氧基-吡喃-4-酮(5)(4.4gm,19.05mmol)的二氯甲烷(100mL)溶液中加入吡啶(6.15mL,76.19mmol),然后加入苯磺酰氯(6-01)(6.07mL,47.62mmol),并在室温下搅拌反应混合物16h。反应完全后,用水淬灭反应,并用乙酸乙酯萃取。合并的有机层用饱和$NaHCO_3$溶液、水和盐水洗涤,在Na_2SO_4上干燥,并减压浓缩。然后用正常柱色谱法纯化,得到N-(5-苄氧基-4-氧代-4H-吡喃-2-基甲基)-苯磺酰胺(7-01)(2.3gm,32.51%),其为灰白色固体。

[0165] LCMS:372.0(M+H)

[0166] (8-01)的制备

[0167]



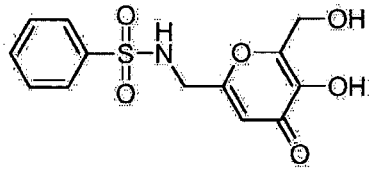
[0168] N-(5-羟基-4-氧代-4H-吡喃-2-基甲基)-苯磺酰胺

[0169] 将N-(5-苄氧基-4-氧代-4H-吡喃-2-基甲基)-苯磺酰胺(7-01)(2.0g,5.39mmol)溶于乙酸(25.0mL)中,并加入硫酸(0.058mL),然后将反应混合物加热至80℃,加热24h。反应完全后,使混合物冷却至室温,并在真空中浓缩。其然后用水洗涤,并用乙酸乙酯萃取。合并有机层用水和盐水洗涤,在Na_2SO_4上干燥,并在减压下浓缩。然后通过用己烷洗涤纯化,得到N-(5-羟基-4-氧代-4H-吡喃-2-基甲基)-苯磺酰胺(8-01)(1.3gm,85.53%),其为棕色固体。

[0170] LCMS:282.0(M+H)。

[0171] (9-01)的制备:

[0172]



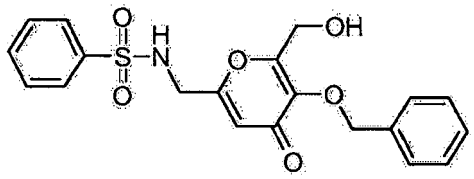
[0173] N-(5-羟基-6-羟基甲基-4-氧代-4H-吡喃-2-基甲基)-苯磺酰胺

[0174] 向搅拌的N-(5-羟基-4-氧代-4H-吡喃-2-基甲基)-苯磺酰胺(8-01)(1.1g,3.92mmol)的二氧六环(20mL)溶液中加入37%甲醛溶液(0.47mL,4.69mmol)和NaOH水溶液(1.95mL,3.92mmol,2M),并在室温下搅拌混合物6h。反应完全后,真空中浓缩,得到粗产物。然后用正常柱色谱法纯化,得到N-(5-羟基-6-羟基甲基-4-氧代-4H-吡喃-2-基甲基)-苯磺酰胺(9-01)(470.0mg,38.57%),其为白色固体。

[0175] LCMS:312.2(M+H)。

[0176] (10-01)的制备:

[0177]



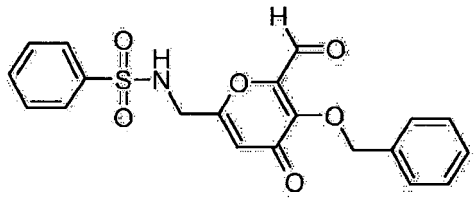
[0178] N-(5-苄氧基-6-羟基甲基-4-氧代-4H-吡喃-2-基甲基)-苯磺酰胺

[0179] 向搅拌的N-(5-羟基-6-羟基甲基-4-氧代-4H-吡喃-2-基甲基)-苯磺酰胺(9-01)(1.7g,5.46mmol)的甲醇(30mL)溶液中加入NaOH水溶液(218.4mg,5.46mmol,2M)。加热至回流后,加入苄基溴(0.654mL,5.46mmol),并继续加热24h。反应完全后,浓缩混合物以移除甲醇,然后用水稀释,并用二氯甲烷萃取。合并的有机层用饱和$NaHCO_3$溶液、水和盐水洗涤,在Na_2SO_4上干燥,并在减压下浓缩。然后应用正常柱色谱法纯化,得到N-(5-苄氧基-6-羟基甲基-4-氧代-4H-吡喃-2-基甲基)-苯磺酰胺(10-01)(1.02gm,46.48%),其为白色固体。

[0180] LCMS:(M+H:402.0)。

[0181] (11-01)的制备:

[0182]



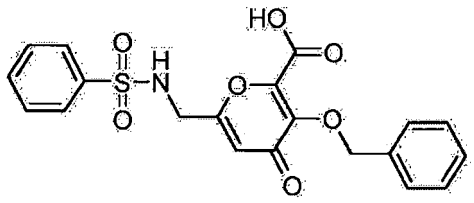
[0183] N-(5-苄氧基-6-甲酰基-4-氧代-4H-吡喃-2-基甲基)-苯磺酰胺

[0184] 向搅拌的N-(5-苄氧基-6-羟基甲基-4-氧代-4H-吡喃-2-基甲基)-苯磺酰胺(10-01)(2.8g,6.98mmol)的乙酸乙酯(100mL)溶液中加入IBX(2-碘酰基苯甲酸)(5.86gm,20.95mmol),并将反应混合物加热至60℃反应6h。反应完全后,过滤反应混合物,并浓缩得到粗产物。然后应用正常柱色谱法纯化,得到N-(5-苄氧基-6-甲酰基-4-氧代-4H-吡喃-2-基甲基)-苯磺酰胺(11-01)(2.0g,71.71%),其为树胶状液体。

[0185] LCMS:(M+H:400.0)。

[0186] (12-1)的制备

[0187]



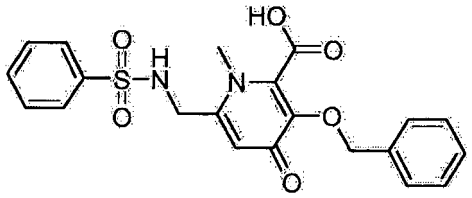
[0188] 6-(苯磺酰氨基-甲基)-3-苄氧基-4-氧代-4H-吡喃-2-甲酸

[0189] 向搅拌的N-(5-苄氧基-6-甲酰基-4-氧代-4H-吡喃-2-基甲基)-苯磺酰胺(11-01)(700.0mg,1.75mmol)的丙酮(10mL)和水(15mL)溶液中加入氨基磺酸(240.45mg,2.45mmol)和亚氯酸钠(166.6mg,1.84mmol),并使反应混合物在室温下搅拌16h。反应完全后,移除溶剂和挥发性物质,并用二氯甲烷萃取。用饱和氯化铵溶液、水及盐水洗涤合并的有机层,在Na_2SO_4上干燥,减压下浓缩,得到6-(苯磺酰氨基-甲基)-3-苄氧基-4-氧代-4H-吡喃-2-甲酸(12-01)(640.0mg,87.82%),其为白色固体。

[0190] LCMS:414.2(M-H)。

[0191] (13-01)的制备:

[0192]



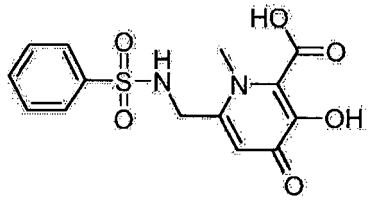
[0193] 6-(苯磺酰氨基-甲基)-3-苄氧基-1-甲基-4-氧代-1,4-二氢-吡啶-2-甲酸

[0194] 室温下向搅拌的6-(苯磺酰氨基-甲基)-3-苄氧基-4-氧代-4H-吡喃-2-甲酸(12-01)(640.0mg,1.54mmol)的MeOH(5.0mL)溶液中加入甲胺(在甲醇中2M,2.0mL),然后室温下搅拌该混合物6h。反应完全后,减压下移除溶剂,得到粗化合物。然后应用正常柱色谱纯化,得到6-(苯磺酰氨基-甲基)-3-苄氧基-1-甲基-4-氧代-1,4-二氢-吡啶-2-甲酸(13-01)(430.0mg,65.08%),其为黄色固体。

[0195] LCMS:(M+H:429.0)。

[0196] (14-01)的制备:

[0197]



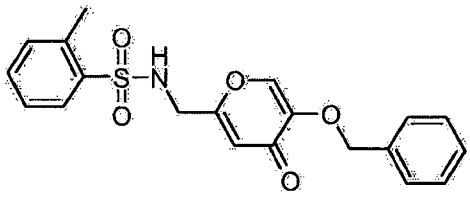
[0198] 6-(苯磺酰氨基-甲基)-3-羟基-1-甲基-4-氧代-1,4-二氢-吡啶-2-甲酸

[0199] 向搅拌的6-(苯磺酰氨基-甲基)-3-苄氧基-1-甲基-4-氧代-1,4-二氢-吡啶-2-甲酸(13-01)(430.0mg,1.005mmol)的乙酸(15mL)溶液中加入硫酸(0.011mL),并在80℃加热反应混合物24h。反应完全后,浓缩反应混合物,并用冰淬灭反应,沉淀固体。过滤和干燥所得到的固体,得到粗产物。然后用20%甲醇和乙酸乙酯洗涤,得到6-(苯磺酰氨基-甲基)-3-羟基-1-甲基-4-氧代-1,4-二氢-吡啶-2-甲酸(14-01)(160.0mg,47.07%),其为灰白色固体。

[0200] LCMS:338.8(M+H)。

[0201] (7-02)的制备：

[0202]



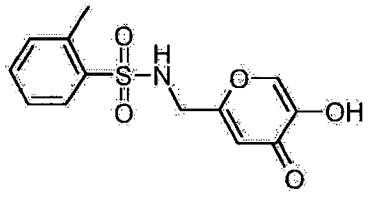
[0203] N-(5-苄氧基-4-氧代-4H-吡喃-2-基甲基)-2-甲基-苯磺酰胺

[0204] 按照为N-(5-苄氧基-4-氧代-4H-吡喃-2-基甲基)-苯磺酰胺(7-01)所描述的方法，从2-氨基甲基-5-苄氧基-吡喃-4-酮(5)(20.5g,88.74mmol)和2-甲基-苯磺酰氯(6-02)(20.23g,106.49mmol)合成N-(5-苄氧基-4-氧代-4H-吡喃-2-基甲基)-2-甲基-苯磺酰胺(7-02)(22.0g,64.32％)，其为浅棕色固体。

[0205] LC-MS:386.0(M+H)。

[0206] (8-02)的制备：

[0207]



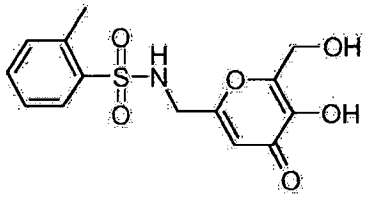
[0208] N-(5-羟基-4-氧代-4H-吡喃-2-基甲基)-2-甲基-苯磺酰胺

[0209] 按照为N-(5-羟基-4-氧代-4H-吡喃-2-基甲基)-苯磺酰胺(8-01)所描述的方法，从N-(5-苄氧基-4-氧代-4H-吡喃-2-基甲基)-2-甲基-苯磺酰胺(7-02)(22.0g,57.14mmol)合成N-(5-羟基-4-氧代-4H-吡喃-2-基甲基)-2-甲基-苯磺酰胺(8-02)(14.0g,粗产物)，其为浅棕色固体。

[0210] LC-MS:296.2(M+H)。

[0211] (9-02)的制备：

[0212]



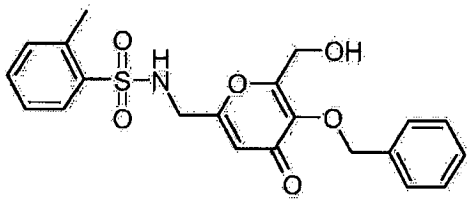
[0213] N-(5-羟基-6-羟基甲基-4-氧代-4H-吡喃-2-基甲基)-2-甲基-苯磺酰胺

[0214] 按照为N-(5-羟基-6-羟基甲基-4-氧代-4H-吡喃-2-基甲基)-苯磺酰胺(9-01)描述的方法，从N-(5-羟基-4-氧代-4H-吡喃-2-基甲基)-2-甲基-苯磺酰胺(8-02)(13.0g,44.06mmol)合成N-(5-羟基-6-羟基甲基-4-氧代-4H-吡喃-2-基甲基)-2-甲基-苯磺酰胺(9-02)(9.0g,62.78％)，其为白色固体。

[0215] LC-MS:326.2(M+H)。

[0216] (10-02)的制备：

[0217]



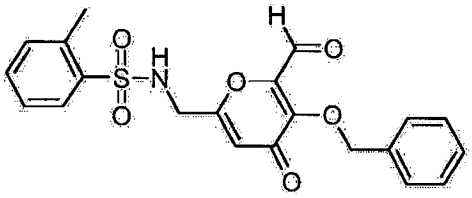
[0218] N-(5- 苄氧基 -6- 羟基甲基 -4- 氧代 -4H- 吡喃 -2- 基甲基)-2- 甲基 - 苯磺酰胺

[0219] 按照为 N-(5- 苄氧基 -6- 羟基甲基 -4- 氧代 -4H- 吡喃 -2- 基甲基)- 苯磺酰胺 (10-01) 描述的方法，从 N-(5- 羟基 -6- 羟基甲基 -4- 氧代 -4H- 吡喃 -2- 基甲基)-2- 甲基 - 苯磺酰胺 (9-02)(9.0g,27.69mmol) 合成 N-(5- 苄氧基 -6- 羟基甲基 -4- 氧代 -4H- 吡喃 -2- 基甲基)-2- 甲基 - 苯磺酰胺 (10-02)(4.7g,40.85％)，其为白色固体。

[0220] LC-MS:416.0(M+H)。

[0221] (11-02) 的制备 ：

[0222]



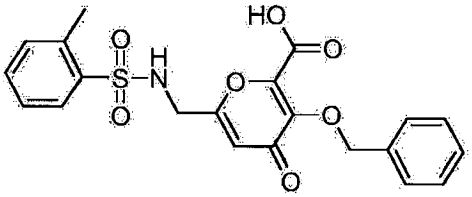
[0223] N-(5- 苄氧基 -6- 甲酰基 -4- 氧代 -4H- 吡喃 -2- 基甲基)-2- 甲基 - 苯磺酰胺

[0224] 按照为 N-(5- 苄氧基 -6- 甲酰基 -4- 氧代 -4H- 吡喃 -2- 基甲基)- 苯磺酰胺 (11-01) 描述的方法，从 N-(5- 苄氧基 -6- 羟基甲基 -4- 氧代 -4H- 吡喃 -2- 基甲基)-2- 甲基 - 苯磺酰胺 (10-02)(4.2g,10.12mmol) 合成 N-(5- 苄氧基 -6- 甲酰基 -4- 氧代 -4H- 吡喃 -2- 基甲基)-2- 甲基 - 苯磺酰胺 (11-02)(2.8g,66.92％)，其为白色固体。

[0225] LC-MS:414.0(M+H)。

[0226] (12-02) 的制备 ：

[0227]



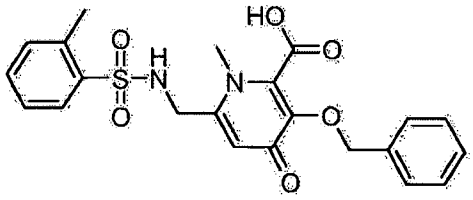
[0228] 3- 苄氧基 -4- 氧代 -6-[(甲苯 -2- 磺酰氨基)- 甲基]-4H- 吡喃 -2- 甲酸

[0229] 按照为 6-(苯磺酰氨基 - 甲基)-3- 苄氧基 -4- 氧代 -4H- 吡喃 -2- 甲酸 (12-01) 所描述的方法，从 N-(5- 苄氧基 -6- 甲酰基 -4- 氧代 -4H- 吡喃 -2- 基甲基)-2- 甲基 - 苯磺酰胺 (11-02)(2.8g,6.74mmol) 合成 3- 苄氧基 -4- 氧代 -6-[(甲苯 -2- 磺酰氨基)- 甲基]-4H- 吡喃 -2- 甲酸 (12-02)(2.0g, 粗产物)，其为白色固体。

[0230] LC-MS:430.0(M+H)。

[0231] (13-02) 的制备 ：

[0232]



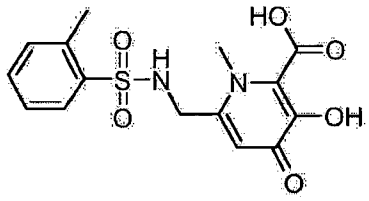
[0233] 3- 苄氧基 -1- 甲基 -4- 氧代 -6-[(甲苯 -2- 磺酰氨基)- 甲基]-1,4- 二氢 - 吡啶 -2- 甲酸

[0234] 按照为 6-(苯磺酰氨基 - 甲基)-3- 苄氧基 -1- 甲基 -4- 氧代 -1,4- 二氢 - 吡啶 -2- 甲酸 (13-01) 所描述的方法，从 3- 苄氧基 -4- 氧代 -6-[(甲苯 -2- 磺酰氨基)- 甲基]-4H- 吡喃 -2- 甲酸 (12-02)(2.0g,4.6mmol) 合成 3- 苄氧基 -1- 甲基 -4- 氧代 -6-[(甲苯 -2- 磺酰氨基)- 甲基]-1,4- 二氢 - 吡啶 -2- 甲酸 (13-02)(1.8g,87.26％)，其为黄色固体。

[0235] LC-MS:443.0(M+H)。

[0236] (14-02) 的制备 ：

[0237]



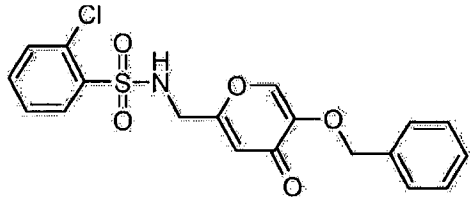
[0238] 3- 羟基 -1- 甲基 -4- 氧代 -6-[(甲苯 -2- 磺酰氨基)- 甲基]-1,4- 二氢 - 吡啶 -2- 甲酸

[0239] 按照为 6-(苯磺酰氨基 - 甲基)-3- 羟基 -1- 甲基 -4- 氧代 -1,4- 二氢 - 吡啶 -2- 甲酸 (14-02) 描述的方法，从 3- 苄氧基 -1- 甲基 -4- 氧代 -6-[(甲苯 -2- 磺酰氨基)- 甲基]-1,4- 二氢 - 吡啶 -2- 甲酸 (13-02)(400.0mg,0.905mmol) 合成 3- 羟基 -1- 甲基 -4- 氧代 -6-[(甲苯 -2- 磺酰氨基)- 甲基]-1,4- 二氢 - 吡啶 -2- 甲酸 (30.0mg,9.41％ , 通过 Prep-HPLC 纯化)，其为灰白色固体。

[0240] LC-MS:353.0(M+H)。

[0241] (7-03) 的制备 ：

[0242]



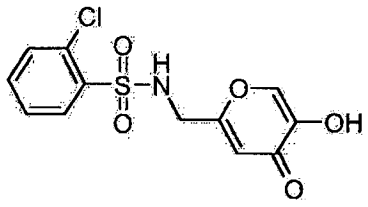
[0243] N-(5- 苄氧基 -4- 氧代 -4H- 吡喃 -2- 基甲基)-2- 氯 - 苯磺酰胺

[0244] 按照为 N-(5- 苄氧基 -4- 氧代 -4H- 吡喃 -2- 基甲基)- 苯磺酰胺 (7-01) 描述的方法，从 2- 氨基甲基 -5- 苄氧基 - 吡喃 -4- 酮 (5)(25.0g,108.2mmol) 和 2- 氯 - 苯磺酰氯 (6-03)(27.2g,129.87mmol) 合成 N-(5- 苄氧基 -4- 氧代 -4H- 吡喃 -2- 基甲基)-2- 氯 - 苯磺酰胺 (7-03)(26.0g,59.19％)，其为浅棕色固体。

[0245] LC-MS:406.0(M+H)。

[0246] (8-03) 的制备：

[0247]



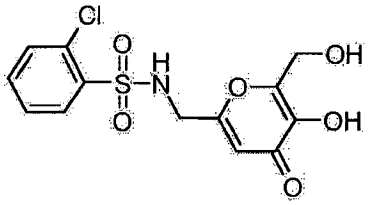
[0248] 2- 氯 -N-(5- 羟基 -4- 氧代 -4H- 吡喃 -2- 基甲基)- 苯磺酰胺

[0249] 按照为 N-(5- 羟基 -4- 氧代 -4H- 吡喃 -2- 基甲基)- 苯磺酰胺 (8-01) 描述的方法，从 N-(5- 苄氧基 -4- 氧代 -4H- 吡喃 -2- 基甲基)-2- 氯 - 苯磺酰胺 (7-03) (26.0g,64.19mmol) 合成 2- 氯 -N-(5- 羟基 -4- 氧代 -4H- 吡喃 -2- 基甲基)- 苯磺酰胺 (8-03)(15.0g, 粗产物)，其为浅棕色固体。

[0250] LC-MS:314.2(M-H)。

[0251] (9-03) 的制备：

[0252]



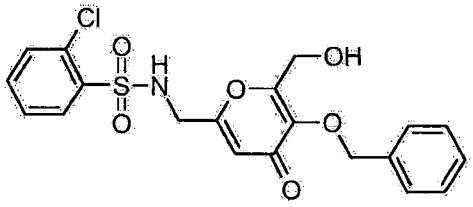
[0253] 2- 氯 -N-(5- 羟基 -6- 羟基甲基 -4- 氧代 -4H- 吡喃 -2- 基甲基)- 苯磺酰胺

[0254] 按照为 N-(5- 羟基 -6- 羟基甲基 -4- 氧代 -4H- 吡喃 -2- 基甲基)- 苯磺酰胺 (9-01) 描述的方法，从 2- 氯 -N-(5- 羟基 -4- 氧代 -4H- 吡喃 -2- 基甲基)- 苯磺酰胺 (8-03) (15.0g,47.61mmol) 合成 2- 氯 -N-(5- 羟基 -6- 羟基甲基 -4- 氧代 -4H- 吡喃 -2- 基甲基)- 苯磺酰胺 (9-03)(8.0g,48.59%)，其为白色固体。

[0255] LC-MS:346.0(M+H)。

[0256] (10-03) 的制备：

[0257]



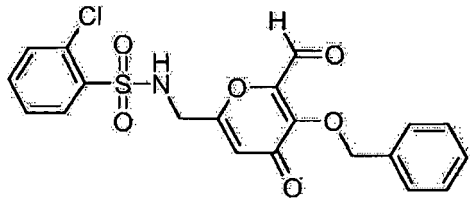
[0258] N-(5- 苄氧基 -6- 羟基甲基 -4- 氧代 -4H- 吡喃 -2- 基甲基)-2- 氯 - 苯磺酰胺

[0259] 按照为 N-(5- 苄氧基 -6- 羟基甲基 -4- 氧代 -4H- 吡喃 -2- 基甲基)- 苯磺酰胺 (10-01) 描述的方法，从 2- 氯 -N-(5- 羟基 -6- 羟基甲基 -4- 氧代 -4H- 吡喃 -2- 基甲基)- 苯磺酰胺 (9-03)(8.0g,23.18mmol) 合成 N-(5- 苄氧基 -6- 羟基甲基 -4- 氧代 -4H- 吡喃 -2- 基甲基)-2- 氯 - 苯磺酰胺 (10-03)(3.5g,35.0%)，其为白色固体。

[0260] LC-MS:436.0(M+H)。

[0261] (11-03) 的制备：

[0262]



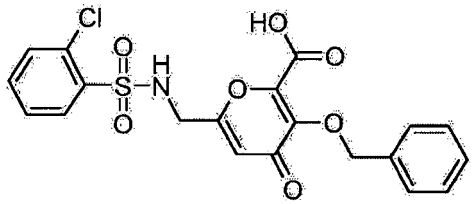
[0263] N-(5-苄氧基-6-甲酰基-4-氧代-4H-吡喃-2-基甲基)-2-氯-苯磺酰胺

[0264] 按照为N-(5-苄氧基-6-甲酰基-4-氧代-4H-吡喃-2-基甲基)-苯磺酰胺(11-01)描述的方法，从N-(5-苄氧基-6-羟基甲基-4-氧代-4H-吡喃-2-基甲基)-2-氯-苯磺酰胺(10-03)(3.3g,7.58mmol)合成N-(5-苄氧基-6-甲酰基-4-氧代-4H-吡喃-2-基甲基)-2-氯-苯磺酰胺(11-03)(2.8g,85.07％)，其为棕色粘性固体。

[0265] LC-MS:433.8(M+H)。

[0266] (12-03)的制备：

[0267]



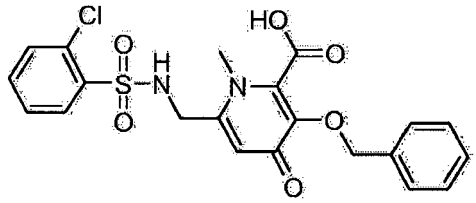
[0268] 3-苄氧基-6-[(2-氯-苯磺酰氨基)-甲基]-4-氧代-4H-吡喃-2-甲酸

[0269] 按照为6-(苯磺酰氨基-甲基)-3-苄氧基-4-氧代-4H-吡喃-2-甲酸(12-01)描述的方法，从N-(5-苄氧基-6-甲酰基-4-氧代-4H-吡喃-2-基甲基)-2-氯-苯磺酰胺(11-03)(2.8g,6.46mmol)合成3-苄氧基-6-[(2-氯-苯磺酰氨基)-甲基]-4-氧代-4H-吡喃-2-甲酸(12-03)(2g,粗产物)，其为白色固体。

[0270] LC-MS:450.0(M+H)。

[0271] (13-03)的制备：

[0272]



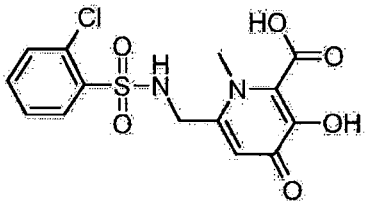
[0273] 3-苄氧基-6-[(2-氯-苯磺酰氨基)-甲基]-1-甲基-4-氧代-1,4-二氢-吡啶-2-甲酸

[0274] 按照为6-(苯磺酰氨基-甲基)-3-苄氧基-1-甲基-4-氧代-1,4-二氢-吡啶-2-甲酸(13-01)描述的方法，从3-苄氧基-6-[(2-氯-苯磺酰氨基)-甲基]-4-氧代-4H-吡喃-2-甲酸(12-03)(2.0g,4.45mmol)合成3-苄氧基-6-[(2-氯-苯磺酰氨基)-甲基]-1-甲基-4-氧代-1,4-二氢-吡啶-2-甲酸(13-03)(1.7g,77.6％)，其为白色固体。

[0275] LC-MS:463.0(M+H)。

[0276] (14-03) 的制备：

[0277]



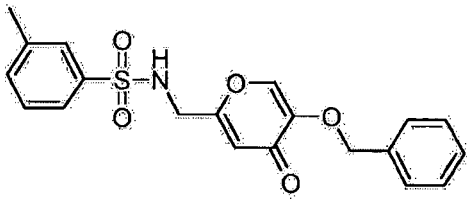
[0278] 6-[(2- 氯 - 苯磺酰氨基)- 甲基]-3- 羟基 -1- 甲基 -4- 氧代 -1,4- 二氢 - 吡啶 -2- 甲酸

[0279] 按照为 6-(苯磺酰氨基 - 甲基)-3- 羟基 -1- 甲基 -4- 氧代 -1,4- 二氢 - 吡啶 -2- 甲酸 (14-01) 描述的方法，从 3- 苄氧基 -6-[(2- 氯 - 苯磺酰氨基)- 甲基]-1- 甲基 -4- 氧代 -1,4- 二氢 - 吡啶 -2- 甲酸 (13-03)(400.0mg,0.866mmol) 合成 6-[(2- 氯 - 苯磺酰氨基)- 甲基]-3- 羟基 -1- 甲基 -4- 氧代 -1,4- 二氢 - 吡啶 -2- 甲酸 (14-03)(120.0mg,37.18%，通过 Prep-HPLC 纯化)，其为白色固体。

[0280] LC-MS:373.4(M+H)。

[0281] (7-04) 的制备：

[0282]



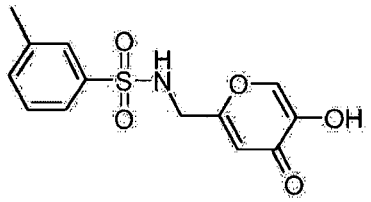
[0283] N-(5- 苄氧基 -4- 氧代 -4H- 吡喃 -2- 基甲基)-3- 甲基 - 苯磺酰胺

[0284] 按照为 N-(5- 苄氧基 -4- 氧代 -4H- 吡喃 -2- 基甲基)- 苯磺酰胺 (7-01) 描述的方法，从 2- 氨基甲基 -5- 苄氧基 - 吡喃 -4- 酮 (5) 和 3- 甲基 - 苯磺酰氯 (6-04)(24.67g,129.87mmol) 合成 N-(5- 苄氧基 -4- 氧代 -4H- 吡喃 -2- 基甲基)-3- 甲基 - 苯磺酰胺 (7-04)(24.0g,57.60%)，其为浅棕色固体。

[0285] LC-MS:386.0(M+H)。

[0286] (8-04) 的制备：

[0287]



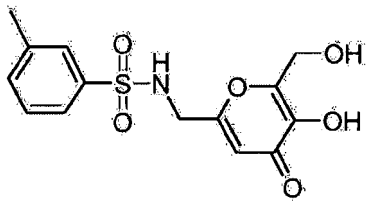
[0288] N-(5- 羟基 -4- 氧代 -4H- 吡喃 -2- 基甲基)-3- 甲基 - 苯磺酰胺

[0289] 按照为 N-(5- 羟基 -4- 氧代 -4H- 吡喃 -2- 基甲基)- 苯磺酰胺 (8-01) 描述的方法，从 N-(5- 苄氧基 -4- 氧代 -4H- 吡喃 -2- 基甲基)-3- 甲基 - 苯磺酰胺 (7-04)(24.0g,62.33mmol) 合成 N-(5- 羟基 -4- 氧代 -4H- 吡喃 -2- 基甲基)-3- 甲基 - 苯磺酰胺 (8-04)(15g, 粗产物)，其为浅棕色固体。

[0290] LC-MS:296.2(M+H)。

[0291] (9-04)的制备：

[0292]



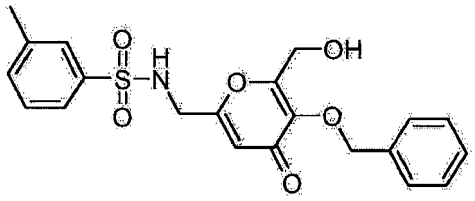
[0293] N-(5-羟基-6-羟基甲基-4-氧代-4H-吡喃-2-基甲基)-3-甲基-苯磺酰胺

[0294] 按照为N-(5-羟基-6-羟基甲基-4-氧代-4H-吡喃-2-基甲基)-苯磺酰胺(9-01)描述的方法，从N-(5-羟基-4-氧代-4H-吡喃-2-基甲基)-3-甲基-苯磺酰胺(8-04)(15.0g,50.84mmol)合成N-(5-羟基-6-羟基甲基-4-氧代-4H-吡喃-2-基甲基)-3-甲基-苯磺酰胺(9-04)(7.5g,45.34％)，其为白色固体。

[0295] LC-MS:326.2(M+H)。

[0296] (10-04)的制备：

[0297]



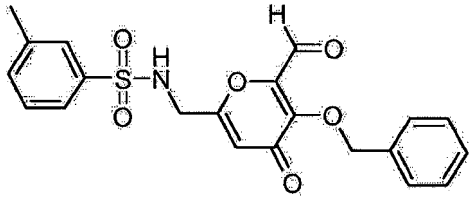
[0298] N-(5-苄氧基-6-羟基甲基-4-氧代-4H-吡喃-2-基甲基)-3-甲基-苯磺酰胺

[0299] 按照为N-(5-苄氧基-6-羟基甲基-4-氧代-4H-吡喃-2-基甲基)-苯磺酰胺(10-01)描述的方法，从N-(5-羟基-6-羟基甲基-4-氧代-4H-吡喃-2-基甲基)-3-甲基-苯磺酰胺(9-04)(7.5g,23.07mmol)合成N-(5-苄氧基-6-羟基甲基-4-氧代-4H-吡喃-2-基甲基)-3-甲基-苯磺酰胺(10-04)(2.6g,27.12％)，其为白色固体。

[0300] LC-MS:415.8(M+H)。

[0301] (11-04)的制备：

[0302]

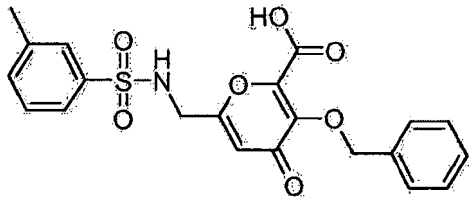


[0303] N-(5-苄氧基-6-甲酰基-4-氧代-4H-吡喃-2-基甲基)-3-甲基-苯磺酰胺

[0304] 按照为N-(5-苄氧基-6-甲酰基-4-氧代-4H-吡喃-2-基甲基)-苯磺酰胺(11-01)描述的方法，从N-(5-苄氧基-6-羟基甲基-4-氧代-4H-吡喃-2-基甲基)-3-甲基-苯磺酰胺(10-04)(2.4g,5.78mmol)合成N-(5-苄氧基-6-甲酰基-4-氧代-4H-吡喃-2-基甲基)-3-甲基-苯磺酰胺(11-04)(1.8g,75.28％)，其为白色固体。

[0305] (12-04)的制备：

[0306]



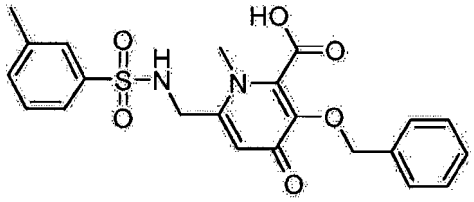
[0307] 3- 苄氧基 -4- 氧代 -6-[(甲苯 -3- 磺酰氨基)- 甲基]-4H- 吡喃 -2- 甲酸

[0308] 按照为 6-(苯磺酰氨基 - 甲基)-3- 苄氧基 -4- 氧代 -4H- 吡喃 -2- 甲酸 (12-01) 描述的方法，从 N-(5- 苄氧基 -6- 甲酰基 -4- 氧代 -4H- 吡喃 -2- 基甲基)-3- 甲基 - 苯磺酰胺 (11-04)(1.8g,4.35mmol) 合成 3- 苄氧基 -4- 氧代 -6-[(甲苯 -3- 磺酰氨基)- 甲基]-4H- 吡喃 -2- 甲酸 (12-04)(1.6g, 粗产物)，其为白色固体。

[0309] LC-MS:429.8(M+H)。

[0310] (13-04) 的制备 ：

[0311]



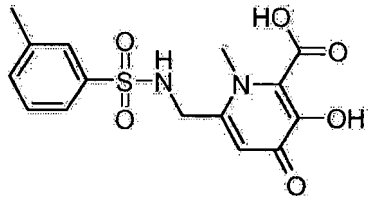
[0312] 3- 苄氧基 -1- 甲基 -4- 氧代 -6-[(甲苯 -3- 磺酰氨基)- 甲基]-1,4- 二氢 - 吡啶 -2- 甲酸

[0313] 按照为 6-(苯磺酰氨基 - 甲基)-3- 苄氧基 -1- 甲基 -4- 氧代 -1,4- 二氢 - 吡啶 -2- 甲酸 (13-01) 描述的方法，从 3- 苄氧基 -4- 氧代 -6-[(甲苯 -3- 磺酰氨基)- 甲基]-4H- 吡喃 -2- 甲酸 (12-04)(1.6g,3.73mmol) 合成 3- 苄氧基 -1- 甲基 -4- 氧代 -6-[(甲苯 -3- 磺酰氨基)- 甲基]-1,4- 二氢 - 吡啶 -2- 甲酸 (13-04)(1.3g,78.77%)，其为白色固体。

[0314] LC-MS:443.2(M+H)。

[0315] (14-04) 的制备 ：

[0316]



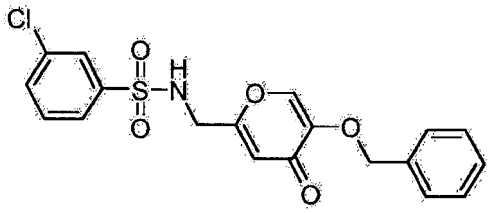
[0317] 3- 羟基 -1- 甲基 -4- 氧代 -6-[(甲苯 -3- 磺酰氨基)- 甲基]-1,4- 二氢 - 吡啶 -2- 甲酸

[0318] 按照为 6-(苯磺酰氨基 - 甲基)-3- 羟基 -1- 甲基 -4- 氧代 -1,4- 二氢 - 吡啶 -2- 甲酸 (14-01) 描述的方法，从 3- 苄氧基 -1- 甲基 -4- 氧代 -6-[(甲苯 -3- 磺酰氨基)- 甲基]-1,4- 二氢 - 吡啶 -2- 甲酸 (13-04)(260.0mg,0.588mmol) 合成 3- 羟基 -1- 甲基 -4- 氧代 -6-[(甲苯 -3- 磺酰氨基)- 甲基]-1,4- 二氢 - 吡啶 -2- 甲酸 (14-04)(60.0mg,28.41% ，通过 Prep-HPLC 纯化)，其为灰白色固体。

[0319] LC-MS:353.2(M+H)。

[0320] (7-05)的制备：

[0321]



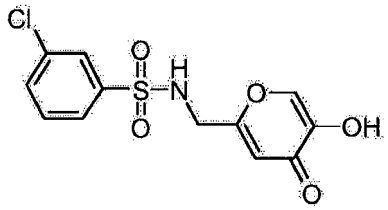
[0322] N-(5-苄氧基-4-氧代-4H-吡喃-2-基甲基)-3-氯-苯磺酰胺

[0323] 按照为N-(5-苄氧基-4-氧代-4H-吡喃-2-基甲基)-苯磺酰胺(7-01)描述的方法，从2-氨基甲基-5-苄氧基-吡喃-4-酮(5)(25g,108.22mmol)和3-氯-苯磺酰氯(6-05)(22.98mL,162.33mmol)合成N-(5-苄氧基-4-氧代-4H-吡喃-2-基甲基)-3-氯-苯磺酰胺(7-05)(25.0g,56.92%)，其为棕色固体。

[0324] LC-MS:406.0(M+H)。

[0325] (8-05)的制备：

[0326]



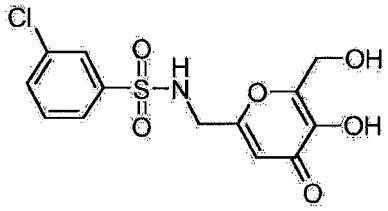
[0327] 3-氯-N-(5-羟基-4-氧代-4H-吡喃-2-基甲基)-苯磺酰胺

[0328] 按照为N-(5-羟基-4-氧代-4H-吡喃-2-基甲基)-苯磺酰胺(8-01)描述的方法，从N-(5-苄氧基-4-氧代-4H-吡喃-2-基甲基)-3-氯-苯磺酰胺(7-05)(25.0g,61.73mmol)合成3-氯-N-(5-羟基-4-氧代-4H-吡喃-2-基甲基)-苯磺酰胺(8-05)(14.0g,71.83%)，其为棕色固体。

[0329] LC-MS:316.0(M+H)。

[0330] (9-05)的制备：

[0331]



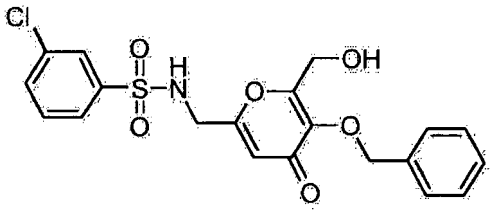
[0332] 3-氯-N-(5-羟基-6-羟基甲基-4-氧代-4H-吡喃-2-基甲基)-苯磺酰胺

[0333] 按照为N-(5-羟基-6-羟基甲基-4-氧代-4H-吡喃-2-基甲基)-苯磺酰胺(9-01)描述的方法，从3-氯-N-(5-羟基-4-氧代-4H-吡喃-2-基甲基)-苯磺酰胺(8-05)(14.0g,44.44mmol)合成3-氯-N-(5-羟基-6-羟基甲基-4-氧代-4H-吡喃-2-基甲基)-苯磺酰胺(9-05)(7.3g,47.50%)，其为白色固体。

[0334] LC-MS:346.0(M+H)。

[0335] (10-05) 的制备：

[0336]



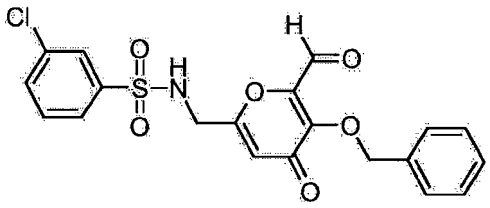
[0337] N-(5- 苄氧基 -6- 羟基甲基 -4- 氧代 -4H- 吡喃 -2- 基甲基)-3- 氯 - 苯磺酰胺

[0338] 按照为 N-(5- 苄氧基 -6- 羟基甲基 -4- 氧代 -4H- 吡喃 -2- 基甲基)- 苯磺酰胺 (10-01) 描述的方法，从 3- 氯 -N-(5- 羟基 -6- 羟基甲基 -4- 氧代 -4H- 吡喃 -2- 基甲基)- 苯磺酰胺 (9-05) (7.0g, 20.29mmol) 合成 N-(5- 苄氧基 -6- 羟基甲基 -4- 氧代 -4H- 吡喃 -2- 基甲基)-3- 氯 - 苯磺酰胺 (10-05) (2.2g, 24.88％)，其为白色固体。

[0339] LC-MS:436.2(M+H)。

[0340] (11-05) 的制备：

[0341]



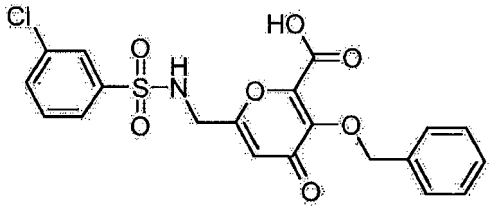
[0342] N-(5- 苄氧基 -6- 甲酰基 -4- 氧代 -4H- 吡喃 -2- 基甲基)-3- 氯 - 苯磺酰胺

[0343] 按照为 N-(5- 苄氧基 -6- 甲酰基 -4- 氧代 -4H- 吡喃 -2- 基甲基)- 苯磺酰胺 (11-01) 描述的方法，从 N-(5- 苄氧基 -6- 羟基甲基 -4- 氧代 -4H- 吡喃 -2- 基甲基)-3- 氯 - 苯磺酰胺 (10-05) (2.8g, 6.44mmol) 合成 N-(5- 苄氧基 -6- 甲酰基 -4- 氧代 -4H- 吡喃 -2- 基甲基)-3- 氯 - 苯磺酰胺 (11-05) (2.3g, 82.36％)，其为白色固体。

[0344] LC-MS:433.6(M+H)。

[0345] (12-05) 的制备：

[0346]



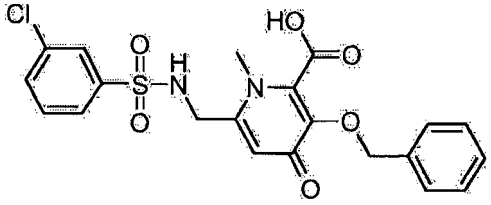
[0347] 3- 苄氧基 -6-[(3- 氯 - 苯磺酰氨基)- 甲基]-4- 氧代 -4H- 吡喃 -2- 甲酸

[0348] 按照为 6-(苯磺酰氨基 - 甲基)-3- 苄氧基 -4- 氧代 -4H- 吡喃 -2- 甲酸 (12-01) 描述的方法，从 N-(5- 苄氧基 -6- 甲酰基 -4- 氧代 -4H- 吡喃 -2- 基甲基)-3- 氯 - 苯磺酰胺 (11-05) (2.2g, 5.08mmol) 合成 3- 苄氧基 -6-[(3- 氯 - 苯磺酰氨基)- 甲基]-4- 氧代 -4H- 吡喃 -2- 甲酸 (12-05) (2.04g, 89.25％)，其为白色固体。

[0349] LC-MS:447.8(M-H)。

[0350] (13-05) 的制备：

[0351]



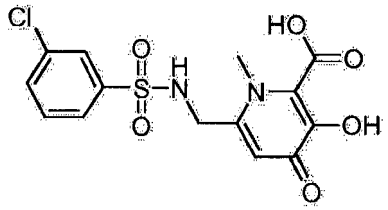
[0352] 3- 苄氧基 -6-[(3- 氯 - 苯磺酰氨基)- 甲基]-1- 甲基 -4- 氧代 -1,4- 二氢 - 吡啶 -2- 甲酸

[0353] 按照为 6-(苯磺酰氨基 - 甲基)-3- 苄氧基 -1- 甲基 -4- 氧代 -1,4- 二氢 - 吡啶 -2- 甲酸 (13-01) 描述的方法，从 3- 苄氧基 -6-[(3- 氯 - 苯磺酰氨基)- 甲基]-4- 氧代 4H- 吡喃 -2- 甲酸 (12-05)(2.0g,4.45mmol) 合成 3- 苄氧基 -6-[(3- 氯 - 苯磺酰氨基)- 甲基]-1- 甲基 -4- 氧代 -1,4- 二氢 - 吡啶 -2- 甲酸 (13-05)(1.62g,78.57％)，其为黄色固体。

[0354] LC-MS:462.6(M+H)。

[0355] (14-05) 的制备 ：

[0356]



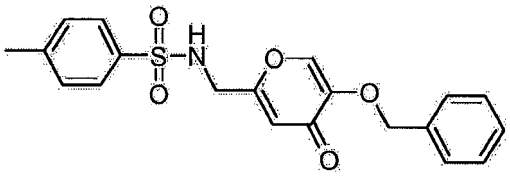
[0357] 6-[(3- 氯 - 苯磺酰氨基)- 甲基]-3- 羟基 -1- 甲基 -4- 氧代 -1,4- 二氢 - 吡啶 -2- 甲酸

[0358] 按照为 6-(苯磺酰氨基 - 甲基)-3- 羟基 -1- 甲基 -4- 氧代 -1,4- 二氢 - 吡啶 -2- 甲酸 (14-01) 描述的方法，从 3- 苄氧基 -6-[(3- 氯 - 苯磺酰氨基)- 甲基]-1- 甲基 -4- 氧代 -1,4- 二氢 - 吡啶 -2- 甲酸 (13-05)(400.0mg,0.866mmol) 合成 6-[(3- 氯 - 苯磺酰氨基)- 甲基]-3- 羟基 -1- 甲基 -4- 氧代 -1,4- 二氢 - 吡啶 -2- 甲酸 (14-05)(170.0mg,52.67％)，其为灰白色固体。

[0359] LC-MS:373.0(M+H)。

[0360] (7-06) 的制备 ：

[0361]



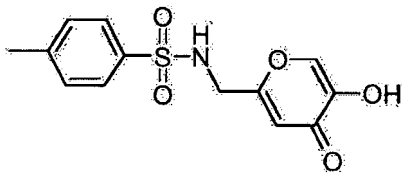
[0362] N-(5- 苄氧基 -4- 氧代 -4H- 吡喃 -2- 基甲基)-4- 甲基 - 苯磺酰胺

[0363] 按照为 N-(5- 苄氧基 -4- 氧代 -4H- 吡喃 -2- 基甲基)- 苯磺酰胺 (7-01) 描述的方法，从 2- 氨基甲基 -5- 苄氧基 - 吡喃 -4- 酮 (5)(21.0g,90.90mmol) 和 4- 甲基 - 苯磺酰氯 (6-06)(20.7g,109.09mmol) 合成 N-(5- 苄氧基 -4- 氧代 -4H- 吡喃 -2- 基甲基)-4- 甲基 - 苯磺酰胺 (7-06)(20.0g,57.08％)，其为浅棕色固体。

[0364] LC-MS:386.0(M+H)。

[0365] (8-06)的制备：

[0366]



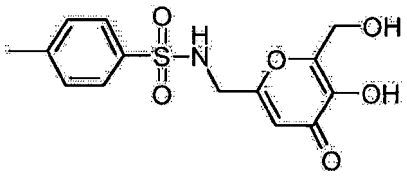
[0367] N-(5-羟基-4-氧代-4H-吡喃-2-基甲基)-4-甲基-苯磺酰胺

[0368] 按照为N-(5-羟基-4-氧代-4H-吡喃-2-基甲基)-苯磺酰胺(8-01)描述的方法，从N-(5-苄氧基-4-氧代-4H-吡喃-2-基甲基)-4-甲基-苯磺酰胺(7-06)(25.0g,64.93mmol)合成N-(5-羟基-4-氧代-4H-吡喃-2-基甲基)-4-甲基-苯磺酰胺(8-06)(14.0g,粗产物)，其为浅棕色固体。

[0369] LC-MS:294.0(M-H)。

[0370] (9-06)的制备：

[0371]



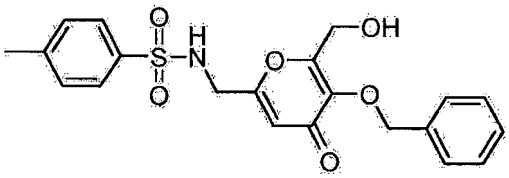
[0372] N-(5-羟基-6-羟基甲基-4-氧代-4H-吡喃-2-基甲基)-4-甲基-苯磺酰胺

[0373] 按照为N-(5-羟基-6-羟基甲基-4-氧代-4H-吡喃-2-基甲基)-苯磺酰胺(9-01)描述的方法，从N-(5-羟基-4-氧代-4H-吡喃-2-基甲基)-4-甲基-苯磺酰胺(8-06)(14.0g,47.45mmol)合成N-(5-羟基-6-羟基甲基-4-氧代-4H-吡喃-2-基甲基)-4-甲基-苯磺酰胺(9-06)(7.0g,45.34%)，其为白色固体。

[0374] LC-MS:326.2(M+H)

[0375] (10-06)的制备：

[0376]



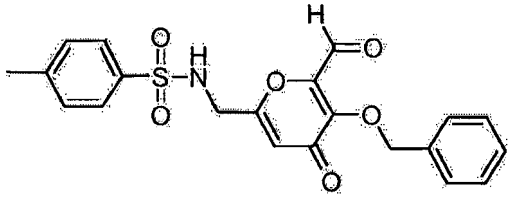
[0377] N-(5-苄氧基-6-羟基甲基-4-氧代-4H-吡喃-2-基甲基)-4-甲基-苯磺酰胺

[0378] 按照为N-(5-苄氧基-6-羟基甲基-4-氧代-4H-吡喃-2-基甲基)-苯磺酰胺(10-01)描述的方法，从N-(5-羟基-6-羟基甲基-4-氧代-4H-吡喃-2-基甲基)-4-甲基-苯磺酰胺(9-06)(7.0g,21.54mmol)合成N-(5-苄氧基-6-羟基甲基-4-氧代-4H-吡喃-2-基甲基)-3-甲基-苯磺酰胺(10-06)(3.7g,41.35%)，其为白色固体。

[0379] LC-MS:416.2(M+H)。

[0380] (11-06)的制备：

[0381]



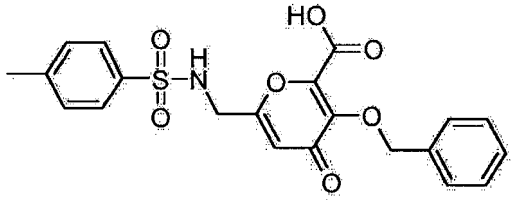
[0382] N-(5- 苄氧基 -6- 甲酰基 -4- 氧代 -4H- 吡喃 -2- 基甲基)-4- 甲基 - 苯磺酰胺

[0383] 按照为 N-(5- 苄氧基 -6- 甲酰基 -4- 氧代 -4H- 吡喃 -2- 基甲基)- 苯磺酰胺 (11-01) 描述的方法，从 N-(5- 苄氧基 -6- 羟基甲基 -4- 氧代 -4H- 吡喃 -2- 基甲基)-4- 甲基 - 苯磺酰胺 (10-06)(3.7g,8.92mmol) 合成 N-(5- 苄氧基 -6- 甲酰基 -4- 氧代 -4H- 吡喃 -2- 基甲基)-4- 甲基 - 苯磺酰胺 (11-06)(2.2g,59.62%)，其为黄色粘性固体。

[0384] LC-MS:414.2(M+H)。

[0385] (12-06) 的制备 ：

[0386]



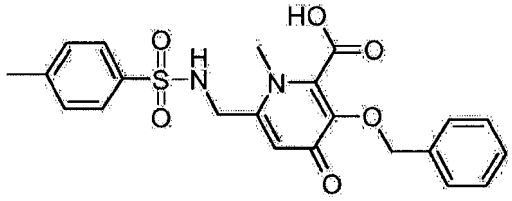
[0387] 3- 苄氧基 -4- 氧代 -6-[(甲苯 -4- 磺酰氨基)- 甲基]-4H- 吡喃 -2- 甲酸

[0388] 按照为 6-(苯磺酰氨基 - 甲基)-3- 苄氧基 -4- 氧代 -4H- 吡喃 -2- 甲酸 (12-01) 描述的方法，从 N-(5- 苄氧基 -6- 甲酰基 -4- 氧代 -4H- 吡喃 -2- 基甲基)-4- 甲基 - 苯磺酰胺 (11-06)(2.4g,5.81mmol) 合成 3- 苄氧基 -4- 氧代 -6-[(甲苯 -4- 磺酰氨基)- 甲基]-4H- 吡喃 -2- 甲酸 (12-06)(2.0g,80.14%)，其为白色固体。

[0389] LC-MS:430.0(M+H)。

[0390] (13-06) 的制备 ：

[0391]



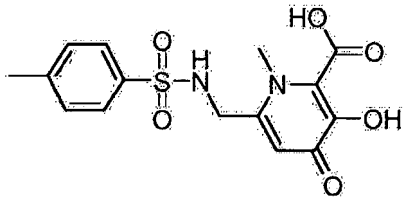
[0392] 3- 苄氧基 -1- 甲基 -4- 氧代 -6-[(甲苯 -4- 磺酰氨基)- 甲基]-1,4- 二氢 - 吡啶 -2- 甲酸

[0393] 按照为 6-(苯磺酰氨基 - 甲基)-3- 苄氧基 -1- 甲基 -4- 氧代 -1,4- 二氢 - 吡啶 -2- 甲酸 (13-01) 描述的方法，从 3- 苄氧基 -4- 氧代 -6-[(甲苯 -4- 磺酰氨基)- 甲基]-4H- 吡喃 -2- 甲酸 (12-06)(2.2g,5.13mmol) 合成 3- 苄氧基 -1- 甲基 -4- 氧代 -6-[(甲苯 -4- 磺酰氨基)- 甲基]-1,4- 二氢 - 吡啶 -2- 甲酸 (13-06)(1.6g,70.51%)，其为白色固体。

[0394] LC-MS:443.0(M+H)。

[0395] (14-06) 的制备 ：

[0396]



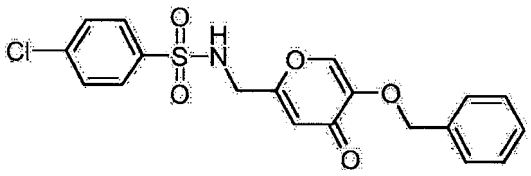
[0397] 3-羟基-1-甲基-4-氧代-6-[(甲苯-4-磺酰氨基)-甲基]-1,4-二氢-吡啶-2-甲酸

[0398] 按照为6-(苯磺酰氨基-甲基)-3-羟基-1-甲基-4-氧代-1,4-二氢-吡啶-2-甲酸(14-01)描述的方法,从3-苄氧基-1-甲基-4-氧代-6-[(甲苯-4-磺酰氨基)-甲基]-1,4-二氢-吡啶-2-甲酸(13-06)400.0mg,0.905mmol)合成3-羟基-1-甲基-4-氧代-6-[(甲苯-4-磺酰氨基)-甲基]-1,4-二氢-吡啶-2-甲酸(14-06)(30.0mg,9.41%,通过Prep-HPLC纯化),其为灰白色固体。

[0399] LC-MS:352.6(M+H)。

[0400] (7-07)的制备:

[0401]



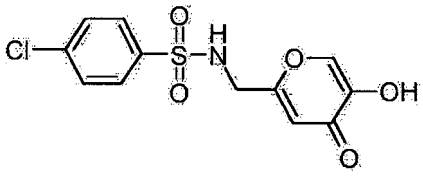
[0402] N-(5-苄氧基-4-氧代-4H-吡喃-2-基甲基)-4-氯-苯磺酰胺

[0403] 按照为N-(5-苄氧基-4-氧代-4H-吡喃-2-基甲基)-苯磺酰胺(7-01)描述的方法,从2-氨基甲基-5-苄氧基-吡喃-4-酮(5)(20.0g,86.58mmol)和4-氯-苯磺酰氯(6-07)(45.67g,216.45mmol)合成N-(5-苄氧基-4-氧代-4H-吡喃-2-基甲基)-4-氯-苯磺酰胺(7-07)(20.0g,56.92%),其为棕色固体。

[0404] LC-MS:406.2(M+H)

[0405] (8-07)的制备:

[0406]



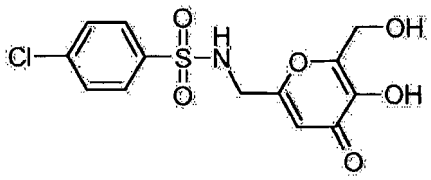
[0407] 4-氯-N-(5-羟基-4-氧代-4H-吡喃-2-基甲基)-苯磺酰胺

[0408] 按照为N-(5-羟基-4-氧代-4H-吡喃-2-基甲基)-苯磺酰胺(8-01)描述的方法,从N-(5-苄氧基-4-氧代-4H-吡喃-2-基甲基)-4-氯-苯磺酰胺(7-07)(20.0g,49.38mmol)合成4-氯-N-(5-羟基-4-氧代-4H-吡喃-2-基甲基)-苯磺酰胺(8-07)(14.0g,89.79%),其为浅棕色固体。

[0409] LC-MS:316.0(M+H)。

[0410] (9-07)的制备:

[0411]



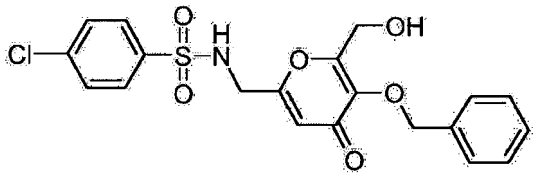
[0412] 4-氯-N-(5-羟基-6-羟基甲基-4-氧代-4H-吡喃-2-基甲基)-苯磺酰胺

[0413] 按照为N-(5-羟基-6-羟基甲基-4-氧代-4H-吡喃-2-基甲基)-苯磺酰胺(9-01)描述的方法,从4-氯-N-(5-羟基-4-氧代-4H-吡喃-2-基甲基)-苯磺酰胺(8-07)(14.0g,44.44mmol)合成4-氯-N-(5-羟基-6-羟基甲基-4-氧代-4H-吡喃-2-基甲基)-苯磺酰胺(9-07)(7.01g,45.62%),其为浅黄色固体。

[0414] LC-MS:346.0(M+H)。

[0415] (10-07)的制备:

[0416]



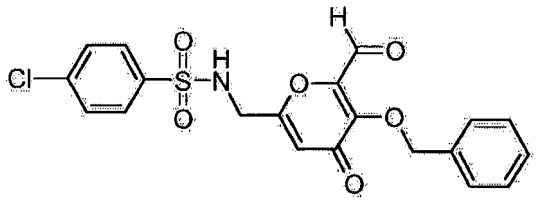
[0417] N-(5-苄氧基-6-羟基甲基-4-氧代-4H-吡喃-2-基甲基)-4-氯-苯磺酰胺

[0418] 按照为N-(5-苄氧基-6-羟基甲基-4-氧代-4H-吡喃-2-基甲基)-苯磺酰胺(10-01)描述的方法,从4-氯-N-(5-羟基-6-羟基甲基-4-氧代-4H-吡喃-2-基甲基)-苯磺酰胺(9-07)(6.0g,17.39mmol)合成N-(5-苄氧基-6-羟基甲基-4-氧代-4H-吡喃-2-基甲基)-4-氯-苯磺酰胺(10-07)(3.5g,46.17%),其为白色固体。

[0419] LC-MS:436.2(M+H)。

[0420] (11-07)的制备:

[0421]



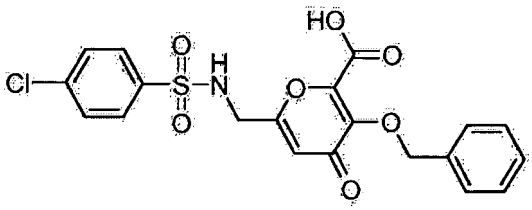
[0422] N-(5-苄氧基-6-甲酰基-4-氧代-4H-吡喃-2-基甲基)-4-氯-苯磺酰胺

[0423] 按照为N-(5-苄氧基-6-甲酰基-4-氧代-4H-吡喃-2-基甲基)-苯磺酰胺(11-01)描述的方法,从N-(5-苄氧基-6-羟基甲基-4-氧代-4H-吡喃-2-基甲基)-4-氯-苯磺酰胺(10-07)(4.0g,9.19mmol)合成N-(5-苄氧基-6-甲酰基-4-氧代-4H-吡喃-2-基甲基)-4-氯-苯磺酰胺(11-07)(3.4g,85.22%),其为白色固体。

[0424] LC-MS:433.8(M+H)。

[0425] (12-07)的制备

[0426]



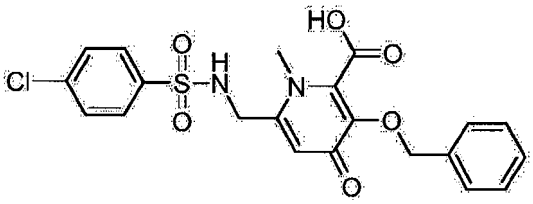
[0427] 3- 苄氧基 -6-[(4- 氯 - 苯磺酰氨基)- 甲基]-4- 氧代 -4H- 吡喃 -2- 甲酸

[0428] 按照为 6-(苯磺酰氨基 - 甲基)-3- 苄氧基 -4- 氧代 -4H- 吡喃 -2- 甲酸 (12-01) 描述的方法，从 N-(5- 苄氧基 -6- 甲酰基 -4- 氧代 -4H- 吡喃 -2- 基甲基)-4- 氯 - 苯磺酰胺 (11-07)(3.4g,7.85mmol) 合成 3- 苄氧基 -6-[(4- 氯 - 苯磺酰氨基)- 甲基]-4- 氧代 -4H- 吡喃 -2- 甲酸 (12-07)(3.0g,84.93％)，其为白色固体。

[0429] LC-MS:450.2(M+H)。

[0430] (13-07) 的制备 ：

[0431]



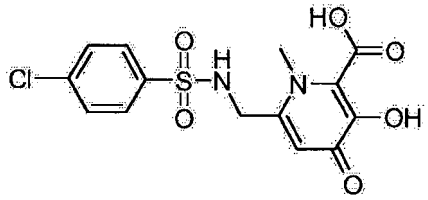
[0432] 3- 苄氧基 -6-[(4- 氯 - 苯磺酰氨基)- 甲基]-1- 甲基 -4- 氧代 -1,4- 二氢 - 吡啶 -2- 甲酸

[0433] 按照为 6-(苯磺酰氨基 - 甲基)-3- 苄氧基 -1- 甲基 -4- 氧代 -1,4- 二氢 - 吡啶 -2- 甲酸 (13-01) 描述的方法，从 3- 苄氧基 -6-[(4- 氯 - 苯磺酰氨基)- 甲基]-4- 氧代 -4H- 吡喃 -2- 甲酸 (12-07)(3.0g,6.68mmol) 合成 3- 苄氧基 -6-[(4- 氯 - 苯磺酰氨基)- 甲基]-1- 甲基 -4- 氧代 -1,4- 二氢 - 吡啶 -2- 甲酸 (13-07)(2.3g,74.36％)，其为黄色固体。

[0434] LC-MS:462.8(M+H)。

[0435] (14-07) 的制备 ：

[0436]



[0437] 6-[(4- 氯 - 苯磺酰氨基)- 甲基]-3- 羟基 -1- 甲基 -4- 氧代 -1,4- 二氢 - 吡啶 -2- 甲酸

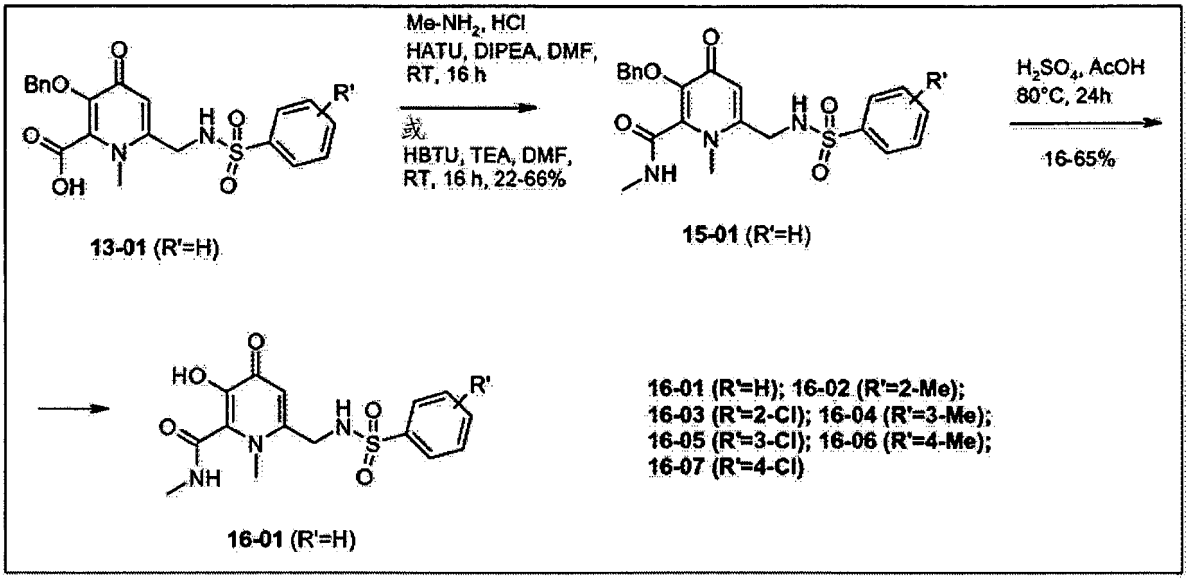
[0438] 按照为 6-(苯磺酰氨基 - 甲基)-3- 羟基 -1- 甲基 -4- 氧代 -1,4- 二氢 - 吡啶 -2- 甲酸 (14-01) 描述的方法，从 3- 苄氧基 -6-[(4- 氯 - 苯磺酰氨基)- 甲基]-1- 甲基 -4- 氧代 -1,4- 二氢 - 吡啶 -2- 甲酸 (13-07)(550.0mg,1.19mmol) 合成 6-[(4- 氯 - 苯磺酰氨基)- 甲基]-3- 羟基 -1- 甲基 -4- 氧代 -1,4- 二氢 - 吡啶 -2- 甲酸 (14-07)(140.0mg,31.55％)，其为棕色固体。

[0439] LC-MS:372.8(M+H)。

[0440] (16-01)至(16-07)的合成路径：

[0441] 流程2：

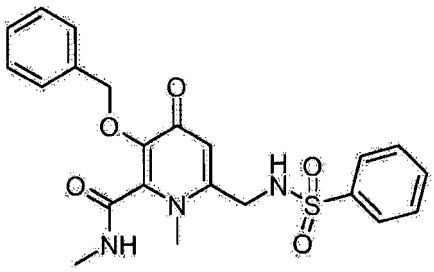
[0442]



[0443] 实验：

[0444] (15-01)的制备：

[0445]



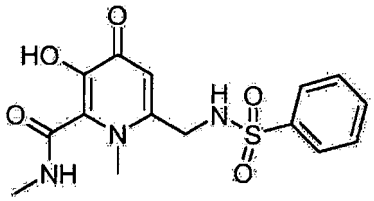
[0446] 6-(苯磺酰氨基-甲基)-3-苄氧基-1-甲基-4-氧代-1,4-二氢-吡啶-2-甲酸甲基酰胺

[0447] 向搅拌的6-(苯磺酰氨基-甲基)-3-苄氧基-1-甲基-4-氧代-1,4-二氢-吡啶-2-甲酸(13-01)(400.0mg,0.935mmol)的二甲基甲酰胺(10mL)溶液中加入HATU(O-(7-氮杂苯并三氮唑-1-基)-N,N,N′,N′-四甲基脲六氟磷酸盐)(426.17mg,1.12mmol)以及二异丙基乙胺(1.08mL,6.54mmol)。搅拌混合物30分钟，然后加入甲胺盐酸盐(189.31mg,2.80mmol)，并在室温下搅拌反应混合物16h。反应完全后，用冰冷水淬灭反应，并用乙酸乙酯萃取反应混合物。合并的有机层用水和盐水洗涤，在Na_2SO_4上干燥，并在减压下浓缩。然后应用正常柱色谱纯化，得到6-(苯磺酰氨基-甲基)-3-苄氧基-1-甲基-4-氧代-1,4-二氢-吡啶-2-甲酸甲基酰胺(15-01)(180.0mg,43.62%)，其为白色固体。

[0448] LCMS:442.0(M+H)。

[0449] (16-01)的制备：

[0450]



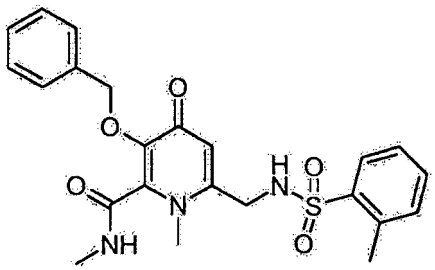
[0451] 6-(苯磺酰氨基-甲基)-3-羟基-1-甲基-4-氧代-1,4-二氢-吡啶-2-甲酸甲基酰胺

[0452] 按照为6-(苯磺酰氨基-甲基)-3-羟基-1-甲基-4-氧代-1,4-二氢-吡啶-2-甲酸(14-01)描述的方法,从6-(苯磺酰氨基-甲基)-3-苄氧基-1-甲基-4-氧代-1,4-二氢-吡啶-2-甲酸甲基酰胺(15-01)(170.0mg,0.385mmol)合成6-(苯磺酰氨基-甲基)-3-羟基-1-甲基-4-氧代-1,4-二氢-吡啶-2-甲酸甲基酰胺(16-01)(45.0mg,33.22%,通过Prep-HPLC纯化),其为灰白色固体。

[0453] LCMS:351.8(M+H)。

[0454] (15-02)的制备:

[0455]

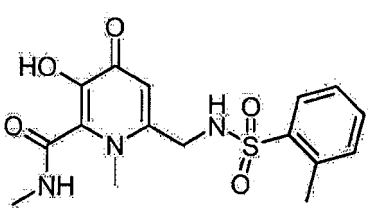


[0456] 3-苄氧基-1-甲基-4-氧代-6-[(甲苯-2-磺酰氨基)-甲基]-1,4-二氢-吡啶-2-甲酸甲基酰胺

[0457] 向搅拌的3-苄氧基-1-甲基-4-氧代-6-[(甲苯-2-磺酰氨基)-甲基]-1,4-二氢-吡啶-2-甲酸(13-02)(600.0mg,1.36mmol)的二甲基甲酰胺(10mL)溶液中加入HBTU(O-苯并三唑-N,N,N',N'-四甲基-脲-六氟-磷酸盐)(772.74mg,2.04mmol)和三乙胺Et_3N(0.942mL,6.78mmol)。搅拌混合物30分钟,然后加入甲胺盐酸盐(274.88mg,4.07mmol),并在室温下搅拌反应混合物16h。反应完全后,用冰冷水淬灭反应,然后用乙酸乙酯萃取。合并的有机层用水和盐水洗涤,在Na_2SO_4上干燥,并在减压下浓缩。然后应用正常柱色谱纯化,得到3-苄氧基-1-甲基-4-氧代-6-[(甲苯-2-磺酰氨基)-甲基]-1,4-二氢-吡啶-2-甲酸甲基酰胺(15-02)(140.0mg,22.64%),其为灰白色固体。LC-MS:456.0(M+H)。

[0458] (16-02)的制备:

[0459]



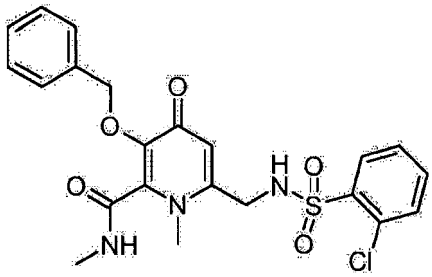
[0460] 3-羟基-1-甲基-4-氧代-6-[(甲苯-2-磺酰氨基)-甲基]-1,4-二氢-吡啶-2-甲酸甲基酰胺

[0461] 按照为6-(苯磺酰氨基-甲基)-3-羟基-1-甲基-4-氧代-1,4-二氢-吡啶-2-甲酸(14-01)描述的方法,从3-苄氧基-1-甲基-4-氧代-6-[(甲苯-2-磺酰氨基)-甲基]-1,4-二氢-吡啶-2-甲酸甲基酰胺(15-02)(140.0mg,0.308mmol)合成3-羟基-1-甲基-4-氧代-6-[(甲苯-2-磺酰氨基)-甲基]-1,4-二氢-吡啶-2-甲酸甲基酰胺(16-02)(40.0mg,35.50%,通过Prep-HPLC纯化),其为灰白色固体。

[0462] LC-MS:365.8(M+H)。

[0463] (15-03)的制备:

[0464]



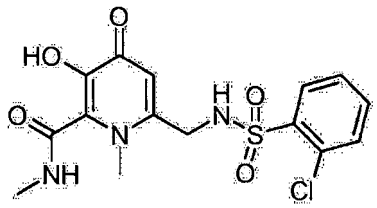
[0465] 3-苄氧基-6-[(2-氯-苯磺酰氨基)-甲基]-1-甲基-4-氧代-1,4-二氢-吡啶-2-甲酸甲基酰胺

[0466] 按照为6-(苯磺酰氨基-甲基)-3-苄氧基-1-甲基-4-氧代-1,4-二氢-吡啶-2-甲酸甲基酰胺(15-01)描述的方法,从3-苄氧基-6-[(2-氯-苯磺酰氨基)-甲基]-1-甲基-4-氧代-1,4-二氢-吡啶-2-甲酸(13-03)(350.0mg,0.758mmol)合成3-苄氧基-6-[(2-氯-苯磺酰氨基)-甲基]-1-甲基-4-氧代-1,4-二氢-吡啶-2-甲酸甲基酰胺(15-03)(210.0mg,58.24%),其为棕色固体。

[0467] LC-MS:476.2(M+H)。

[0468] (16-03)的制备:

[0469]



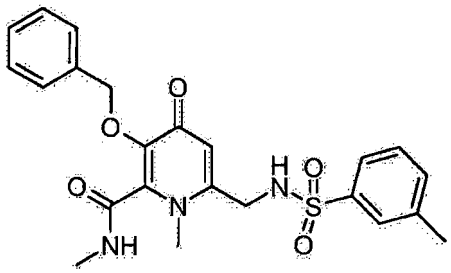
[0470] 6-[(2-氯-苯磺酰氨基)-甲基]-3-羟基-1-甲基-4-氧代-1,4-二氢-吡啶-2-甲酸甲基酰胺

[0471] 按照为6-(苯磺酰氨基-甲基)-3-羟基-1-甲基-4-氧代-1,4-二氢-吡啶-2-甲酸(14-01)描述的方法,从3-苄氧基-6-[(2-氯-苯磺酰氨基)-甲基]-1-甲基-4-氧代-1,4-二氢-吡啶-2-甲酸甲基酰胺(15-03)(260.0mg,0.547mmol)合成6-[(2-氯-苯磺酰氨基)-甲基]-3-羟基-1-甲基-4-氧代-1,4-二氢-吡啶-2-甲酸甲基酰胺(16-03)(110.0mg,52.09%,通过Prep-HPLC纯化),其为黄色固体。

[0472] LC-MS:386.2(M+H)。

[0473] (15-04) 的制备：

[0474]



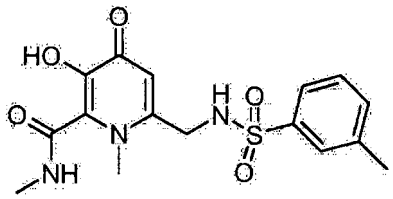
[0475] 3- 苄氧基 -1- 甲基 -4- 氧代 -6-[(甲苯 -3- 磺酰氨基)- 甲基]-1,4- 二氢 - 吡啶 -2- 甲酸甲基酰胺

[0476] 按照为 6-(苯磺酰氨基 - 甲基)-3- 苄氧基 -1- 甲基 -4- 氧代 -1,4- 二氢 - 吡啶 -2- 甲酸甲基酰胺 (15-01) 描述的方法，从 3- 苄氧基 -1- 甲基 -4- 氧代 -6-[(甲苯 -3- 磺酰氨基)- 甲基]-1,4- 二氢 - 吡啶 -2- 甲酸 (13-04)(400.0mg,0.905mmol) 合成 3- 苄氧基 -1- 甲基 -4- 氧代 -6-[(甲苯 -3- 磺酰氨基)- 甲基]-1,4- 二氢 - 吡啶 -2- 甲酸甲基酰胺 (15-04)(250.0mg,60.64%)，其为白色固体。

[0477] LC-MS:455.8(M+H)。

[0478] (16-04) 的制备：

[0479]



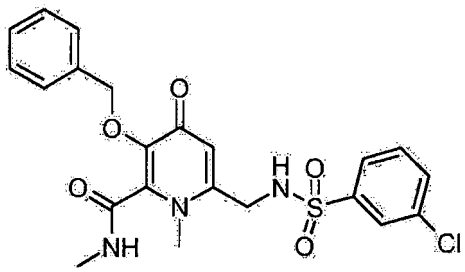
[0480] 3- 羟基 -1- 甲基 -4- 氧代 -6-[(甲苯 -3- 磺酰氨基)- 甲基]-1,4- 二氢 - 吡啶 -2- 甲酸甲基酰胺

[0481] 按照为 6-(苯磺酰氨基 - 甲基)-3- 羟基 -1- 甲基 -4- 氧代 -1,4- 二氢 - 吡啶 -2- 甲酸 (14-01) 描述的方法，从 3- 苄氧基 -1- 甲基 -4- 氧代 -6-[(甲苯 -2- 磺酰氨基)- 甲基]-1,4- 二氢 - 吡啶 -2- 甲酸甲基酰胺 (14-11)(260.0mg,0.571mmol) 合成 3- 羟基 -1- 甲基 -4- 氧代 -6-[(甲苯 -3- 磺酰氨基)- 甲基]-1,4- 二氢 - 吡啶 -2- 甲酸甲基酰胺 (16-04)(35.0mg,16.76%，通过 Prep-HPLC 纯化)，其为灰白色固体。

[0482] LC-MS:366.2(M+H)。

[0483] (15-05) 的制备：

[0484]



[0485] 3- 苄氧基 -6-[(3- 氯 - 苯磺酰氨基)- 甲基]-1- 甲基 -4- 氧代 -1,4- 二氢 - 吡

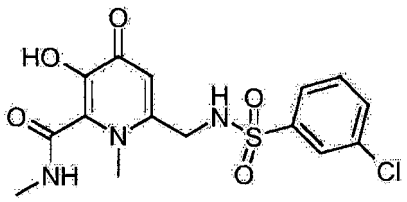
啶 -2- 甲酸甲基酰胺

[0486] 按照为 6-(苯磺酰氨基 - 甲基)-3- 苄氧基 -1- 甲基 -4- 氧代 -1,4- 二氢 - 吡啶 -2- 甲酸甲基酰胺 (15-01) 描述的方法，从 3- 苄氧基 -6-[(3- 氯 - 苯磺酰氨基)- 甲基]-1- 甲基 -4- 氧代 -1,4- 二氢 - 吡啶 -2- 甲酸 (13-05)(600.0mg,1.299mmol) 合成 3- 苄氧基 -6-[(3- 氯 - 苯磺酰氨基)- 甲基]-1- 甲基 -4- 氧代 -1,4- 二氢 - 吡啶 -2- 甲酸甲基酰胺 (15-05)(410.0mg,66.33％)，其为白色固体。

[0487] LC-MS:476.0(M+H)。

[0488] (16-05) 的制备 :

[0489]



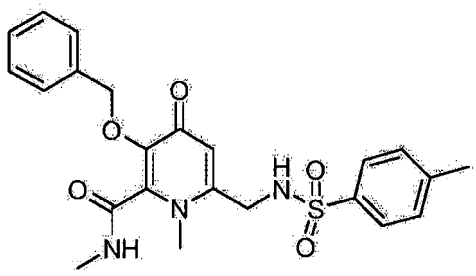
[0490] 6-[(3- 氯 - 苯磺酰氨基)- 甲基]-3- 羟基 -1- 甲基 -4- 氧代 -1,4- 二氢 - 吡啶 -2- 甲酸甲基酰胺

[0491] 按照为 6-(苯磺酰氨基 - 甲基)-3- 羟基 -1- 甲基 -4- 氧代 -1,4- 二氢 - 吡啶 -2- 甲酸 (14-01) 描述的方法，从 3- 苄氧基 -6-[(3- 氯 - 苯磺酰氨基)- 甲基]-1- 甲基 -4- 氧代 -1,4- 二氢 - 吡啶 -2- 甲酸甲基酰胺 (15-05)(400.0mg,0.84mmol) 合成 6-[(3- 氯 - 苯磺酰氨基)- 甲基]-3- 羟基 -1- 甲基 -4- 氧代 -1,4- 二氢 - 吡啶 -2- 甲酸甲基酰胺 (16-05)(193.0mg,59.40％ , 通过 Prep-HPLC 纯化)，其为灰白色固体。

[0492] LC-MS:385.8(M+H)。

[0493] (15-06) 的制备 :

[0494]



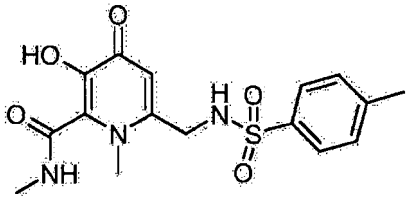
[0495] 3- 苄氧基 -1- 甲基 -4- 氧代 -6-[(甲苯 -4- 磺酰氨基)- 甲基]-1,4- 二氢 - 吡啶 -2- 甲酸甲基酰胺

[0496] 按照为 6-(苯磺酰氨基 - 甲基)-3- 苄氧基 -1- 甲基 -4- 氧代 -1,4- 二氢 - 吡啶 -2- 甲酸甲基酰胺 (15-01) 描述的方法，从 3- 苄氧基 -1- 甲基 -4- 氧代 -6-[(甲苯 -4- 磺酰氨基)- 甲基]-1,4- 二氢 - 吡啶 -2- 甲酸 (13-06)(500.0mg,1.13mmol) 合成 3- 苄氧基 -1- 甲基 -4- 氧代 -6-[(甲苯 -4- 磺酰氨基)- 甲基]-1,4- 二氢 - 吡啶 -2- 甲酸甲基酰胺 (15-06)(280.0mg,54.34％)，其为灰白色固体。

[0497] LC-MS:456.0(M+H)。

[0498] (16-06) 的制备 :

[0499]



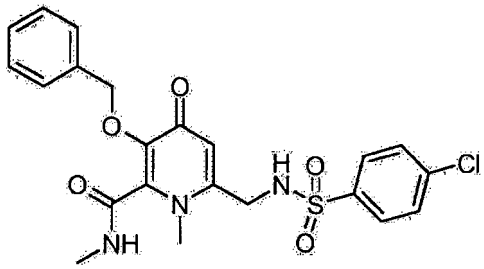
[0500] 3-羟基-1-甲基-4-氧代-6-[(甲苯-4-磺酰氨基)-甲基]-1,4-二氢-吡啶-2-甲酸甲基酰胺

[0501] 按照为6-(苯磺酰氨基-甲基)-3-羟基-1-甲基-4-氧代-1,4-二氢-吡啶-2-甲酸(14-01)描述的方法,从3-苄氧基-1-甲基-4-氧代-6-[(甲苯-4-磺酰氨基)-甲基]-1,4-二氢-吡啶-2-甲酸甲基酰胺(15-06)(250.0mg,0.549mmol)合成3-羟基-1-甲基-4-氧代-6-[(甲苯-4-磺酰氨基)-甲基]-1,4-二氢-吡啶-2-甲酸甲基酰胺(16-06)(120.0mg,59.77%,通过Prep-HPLC纯化),其为灰白色固体。

[0502] LC-MS:366.0(M+H)。

[0503] (15-07)的制备:

[0504]



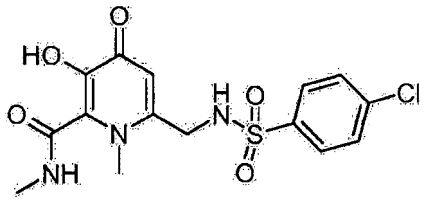
[0505] 3-苄氧基-6-[(4-氯-苯磺酰氨基)-甲基]-1-甲基-4-氧代-1,4-二氢-吡啶-2-甲酸甲基酰胺

[0506] 按照为6-(苯磺酰氨基-甲基)-3-苄氧基-1-甲基-4-氧代-1,4-二氢-吡啶-2-甲酸甲基酰胺(15-01)描述的方法,从3-苄氧基-6-[(4-氯-苯磺酰氨基)-甲基]-1-甲基-4-氧代-1,4-二氢-吡啶-2-甲酸(13-07)(500.0mg,1.08mmol)合成3-苄氧基-6-[(4-氯-苯磺酰氨基)-甲基]-1-甲基-4-氧代-1,4-二氢-吡啶-2-甲酸甲基酰胺(15-07)(340.0mg,66.01%),其为浅黄色固体。

[0507] LC-MS:476.2(M+H)。

[0508] (16-07)的制备:

[0509]



[0510] 6-[(4-氯-苯磺酰氨基)-甲基]-3-羟基-1-甲基-4-氧代-1,4-二氢-吡啶-2-甲酸甲基酰胺

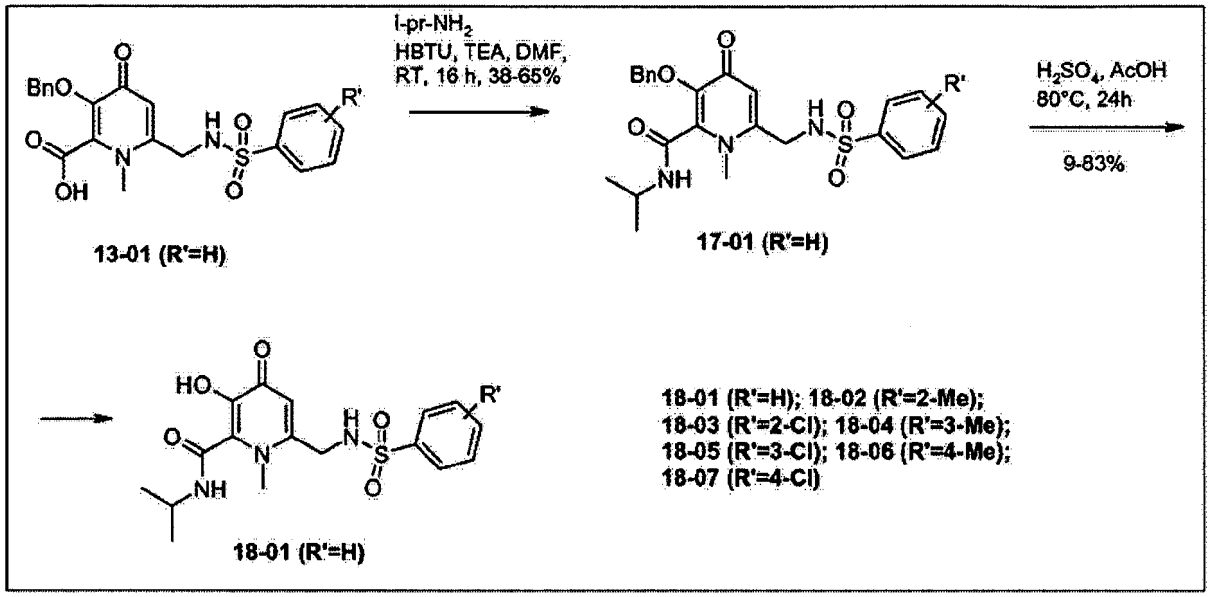
[0511] 按照为6-(苯磺酰氨基-甲基)-3-羟基-1-甲基-4-氧代-1,4-二氢-吡啶-2-甲酸(14-01)描述的方法,从3-苄氧基-6-[(4-氯-苯磺酰氨基)-甲基]-1-甲基-4-氧

代-1,4-二氢-吡啶-2-甲酸甲基酰胺(15-07)(700.0mg,1.47mmol)合成6-[(4-氯-苯磺酰氨基)-甲基]-3-羟基-1-甲基-4-氧代-1,4-二氢-吡啶-2-甲酸甲基酰胺(16-07)(375.0mg,65.95%,通过Prep-HPLC纯化),其为浅粉红色固体。

[0512] LC-MS:386.0(M+H)。

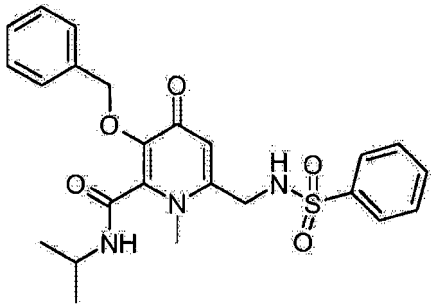
[0513] 流程3:(18-01)至(18-07)的合成路径:

[0514]



[0515] (17-01)的制备:

[0516]



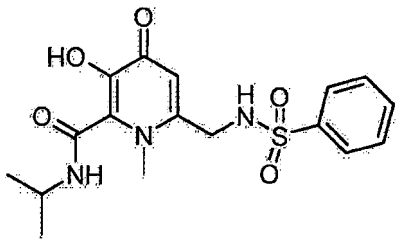
[0517] 6-(苯磺酰氨基-甲基)-3-苄氧基-1-甲基-4-氧代-1,4-二氢-吡啶-2-甲酸异丙基酰胺

[0518] 向将搅拌的6-(苯磺酰氨基-甲基)-3-苄氧基-1-甲基-4-氧代-1,4-二氢-吡啶-2-甲酸(13-01)(250.0mg,0.584mmol)的二甲基甲酰胺(15mL)溶液中加入HBTU(O-苯并三唑-N,N,N',N'-四甲基-脲-六氟-磷酸盐)(332.28mg,0.876mmol)和TEA(三乙胺)(0.406mL,2.92mmol)。搅拌混合物30分钟,然后加入异丙胺(0.171mL,1.75mmol),室温下搅拌反应混合物16h。反应完全后,用冰冷水淬灭反应,然后用乙酸乙酯萃取。合并的有机层用水和盐水洗涤,在Na_2SO_4上干燥,并在减压下浓缩。应用正常柱色谱法纯化,得到6-(苯磺酰氨基-甲基)-3-苄氧基-1-甲基-4-氧代-1,4-二氢-吡啶-2-甲酸异丙基酰胺(17-01)(180.0mg,65.63%),其为树胶状液体。

[0519] LCMS:470.0(M+H)。

[0520] (18-01) 的制备：

[0521]



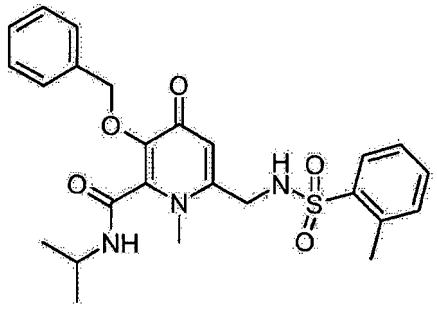
[0522] 6-(苯磺酰氨基-甲基)-3-羟基-1-甲基-4-氧代-1,4-二氢-吡啶-2-甲酸异丙基酰胺

[0523] 按照为6-(苯磺酰氨基-甲基)-3-羟基-1-甲基-4-氧代-1,4-二氢-吡啶-2-甲酸(14-01)描述的方法，从6-(苯磺酰氨基-甲基)-3-苄氧基-1-甲基-4-氧代-1,4-二氢-吡啶-2-甲酸异丙基酰胺(17-01)(280.0mg,0.597mmol)合成6-(苯磺酰氨基-甲基)-3-羟基-1-甲基-4-氧代-1,4-二氢-吡啶-2-甲酸异丙基酰胺(18-01)(110.0mg,48.56%，通过Prep-HPLC纯化)，其为灰白色固体。

[0524] LCMS:380.0(M+H)。

[0525] (17-02) 的制备：

[0526]



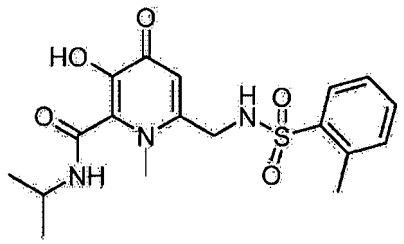
[0527] 3-苄氧基-1-甲基-4-氧代-6-[(甲苯-2-磺酰氨基)-甲基]-1,4-二氢-吡啶-2-甲酸异丙基酰胺

[0528] 按照为6-(苯磺酰氨基-甲基)-3-苄氧基-1-甲基-4-氧代-1,4-二氢-吡啶-2-甲酸异丙基酰胺(17-01)描述的方法，从3-苄氧基-1-甲基-4-氧代-6-[(甲苯-2-磺酰氨基)-甲基]-1,4-二氢-吡啶-2-甲酸(13-02)(500.0mg,1.13mmol)合成3-苄氧基-1-甲基-4-氧代-6-[(甲苯-2-磺酰氨基)-甲基]-1,4-二氢-吡啶-2-甲酸异丙基酰胺(17-02)(250.0mg,45.70%)，其为黄色固体。

[0529] LC-MS:484.0(M+H)。

[0530] (18-02) 的制备：

[0531]



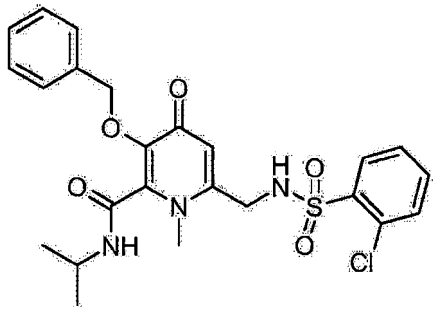
[0532] 3-羟基-1-甲基-4-氧代-6-[(甲苯-2-磺酰氨基)-甲基]-1,4-二氢-吡啶-2-甲酸异丙基酰胺

[0533] 按照为6-(苯磺酰氨基-甲基)-3-羟基-1-甲基-4-氧代-1,4-二氢-吡啶-2-甲酸(14-01)描述的方法,从3-苄氧基-1-甲基-4-氧代-6-[(甲苯-2-磺酰氨基)-甲基]-1,4-二氢-吡啶-2-甲酸异丙基酰胺(17-02)(250.0mg,0.518mmol)合成3-羟基-1-甲基-4-氧代-6-[(甲苯-2-磺酰氨基)-甲基]-1,4-二氢-吡啶-2-甲酸异丙基酰胺(18-02)(110.0mg,54.01%,通过Prep-HPLC纯化),其为灰白色固体。

[0534] LC-MS:394.2(M+H)。

[0535] (17-03)的制备:

[0536]



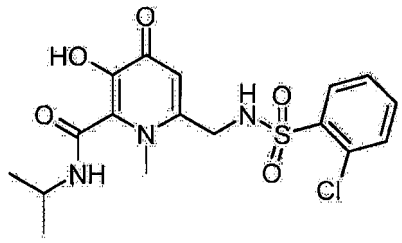
[0537] 3-苄氧基-6-[(2-氯-苯磺酰氨基)-甲基]-1-甲基-4-氧代-1,4-二氢-吡啶-2-甲酸异丙基酰胺

[0538] 按照为6-(苯磺酰氨基-甲基)-3-苄氧基-1-甲基-4-氧代-1,4-二氢-吡啶-2-甲酸异丙基酰胺(17-01)描述的方法,从3-苄氧基-6-[(2-氯-苯磺酰氨基)-甲基]-1-甲基-4-氧代-1,4-二氢-吡啶-2-甲酸(13-03)(500.0mg,1.08mmol)合成3-苄氧基-6-[(2-氯-苯磺酰氨基)-甲基]-1-甲基-4-氧代-1,4-二氢-吡啶-2-甲酸异丙基酰胺(17-03)(250.0mg,45.0%),其为棕色固体。

[0539] LC-MS:504.3(M+H)。

[0540] (18-03)的制备:

[0541]



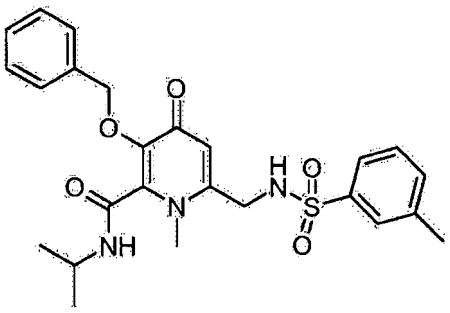
[0542] 6-[(2-氯-苯磺酰氨基)-甲基]-3-羟基-1-甲基-4-氧代-1,4-二氢-吡啶-2-甲酸异丙基酰胺

[0543] 按照为6-(苯磺酰氨基-甲基)-3-羟基-1-甲基-4-氧代-1,4-二氢-吡啶-2-甲酸(14-01)描述的方法,从3-苄氧基-6-[(2-氯-苯磺酰氨基)-甲基]-1-甲基-4-氧代-1,4-二氢-吡啶-2-甲酸异丙基酰胺(17-03)(240.0mg,0.477mmol)合成6-[(2-氯-苯磺酰氨基)-甲基]-3-羟基-1-甲基-4-氧代-1,4-二氢-吡啶-2-甲酸异丙基酰胺(18-03)(38.0mg,19.24%,通过Prep-HPLC纯化),其为灰白色固体。

[0544] LC-MS:414.2(M+H)。

[0545] (17-04)的制备：

[0546]



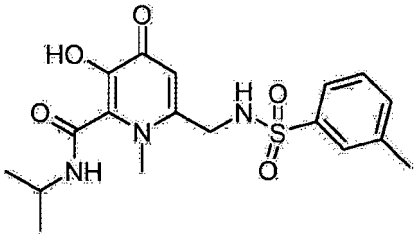
[0547] 3-苄氧基-1-甲基-4-氧代-6-[(甲苯-3-磺酰氨基)-甲基]-1,4-二氢-吡啶-2-甲酸异丙基酰胺

[0548] 按照为6-(苯磺酰氨基-甲基)-3-苄氧基-1-甲基-4-氧代-1,4-二氢-吡啶-2-甲酸异丙基酰胺(17-01)描述的方法，从3-苄氧基-1-甲基-4-氧代-6-[(甲苯-3-磺酰氨基)-甲基]-1,4-二氢-吡啶-2-甲酸(13-04)(500.0mg,1.13mmol)合成3-苄氧基-1-甲基-4-氧代-6-[(甲苯-3-磺酰氨基)-甲基]-1,4-二氢-吡啶-2-甲酸异丙基酰胺(17-04)(250.0mg,45.70%)，其为白色固体。

[0549] LC-MS:484.2(M+H)。

[0550] (18-04)的制备：

[0551]



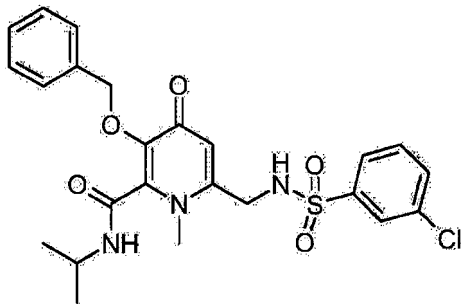
[0552] 3-羟基-1-甲基-4-氧代-6-[(甲苯-3-磺酰氨基)-甲基]-1,4-二氢-吡啶-2-甲酸异丙基酰胺

[0553] 按照为6-(苯磺酰氨基-甲基)-3-羟基-1-甲基-4-氧代-1,4-二氢-吡啶-2-甲酸(14-01)描述的方法，从3-苄氧基-1-甲基-4-氧代-6-[(甲苯-3-磺酰氨基)-甲基]-1,4-二氢-吡啶-2-甲酸异丙基酰胺(17-04)(250.0mg,0.518mmol)合成3-羟基-1-甲基-4-氧代-6-[(甲苯-3-磺酰氨基)-甲基]-1,4-二氢-吡啶-2-甲酸异丙基酰胺(18-04)(20.0mg,9.82%，通过Prep-HPLC纯化)，其为白色固体。

[0554] LC-MS:394.4(M+H)。

[0555] (17-05)的制备：

[0556]



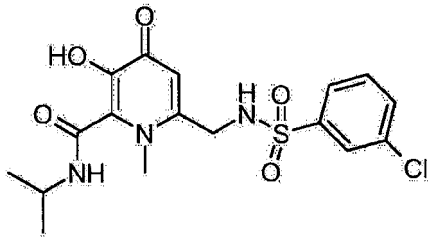
[0557] 3- 苄氧基 -6-[(3- 氯 - 苯磺酰氨基)- 甲基]-1- 甲基 -4- 氧代 -1,4- 二氢 - 吡啶 -2- 甲酸异丙基酰胺

[0558] 按照为 6-(苯磺酰氨基 - 甲基)-3- 苄氧基 -1- 甲基 -4- 氧代 -1,4- 二氢 - 吡啶 -2- 甲酸异丙基酰胺 (17-01) 描述的方法，从 3- 苄氧基 -6-[(3- 氯 - 苯磺酰氨基)- 甲基]-1- 甲基 -4- 氧代 -1,4- 二氢 - 吡啶 -2- 甲酸 (13-05)(600.0mg,1.29mmol) 合成 3- 苄氧基 -6-[(3- 氯 - 苯磺酰氨基)- 甲基]-1- 甲基 -4- 氧代 -1,4- 二氢 - 吡啶 -2- 甲酸异丙基酰胺 (17-05)(363.0mg,55.46％)，其为树胶状液体。

[0559] LC-MS:504.2(M+H)。

[0560] (18-05) 的制备 :

[0561]



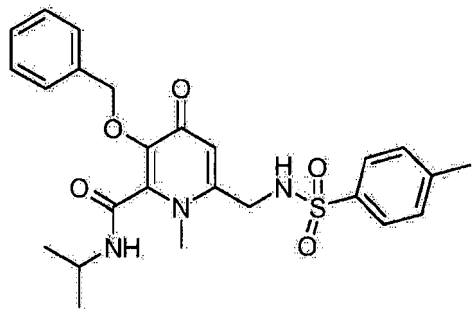
[0562] 6-[(3- 氯 - 苯磺酰氨基)- 甲基]-3- 羟基 -1- 甲基 -4- 氧代 -1,4- 二氢 - 吡啶 -2- 甲酸异丙基酰胺

[0563] 按照为 6-(苯磺酰氨基 - 甲基)-3- 羟基 -1- 甲基 -4- 氧代 -1,4- 二氢 - 吡啶 -2- 甲酸 (14-01) 描述的方法，从 3- 苄氧基 -6-[(3- 氯 - 苯磺酰氨基)- 甲基]-1- 甲基 -4- 氧代 -1,4- 二氢 - 吡啶 -2- 甲酸异丙基酰胺 (17-05)(350.0mg,0.69mmol) 合成 6-[(3- 氯 - 苯磺酰氨基)- 甲基]-3- 羟基 -1- 甲基 -4- 氧代 -1,4- 二氢 - 吡啶 -2- 甲酸异丙基酰胺 (18-05)(110.0mg,38.2％ , 通过 Prep-HPLC 纯化)，其为白色固体。

[0564] LC-MS:414.2(M+H)。

[0565] (17-06) 的制备 :

[0566]



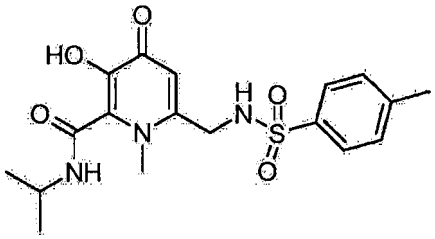
[0567] 3- 苄氧基 -1- 甲基 -4- 氧代 -6-[(甲苯 -4- 磺酰氨基)- 甲基]-1,4- 二氢 - 吡啶 -2- 甲酸异丙基酰胺

[0568] 按照为 6-(苯磺酰氨基 - 甲基)-3- 苄氧基 -1- 甲基 -4- 氧代 -1,4- 二氢 - 吡啶 -2- 甲酸异丙基酰胺 (17-01) 描述的方法，从 3- 苄氧基 -1- 甲基 -4- 氧代 -6-[(甲苯 -4- 磺酰氨基)- 甲基]-1,4- 二氢 - 吡啶 -2- 甲酸 (13-06)(600.0mg,1.36mmol) 合成 3- 苄氧基 -1- 甲基 -4- 氧代 -6-[(甲苯 -4- 磺酰氨基)- 甲基]-1,4- 二氢 - 吡啶 -2- 甲酸异丙基酰胺 (17-06)(250.0mg,38.08％)，其为棕色固体。

[0569] LC-MS:484.2(M+H)。

[0570] (18-06) 的制备 ：

[0571]



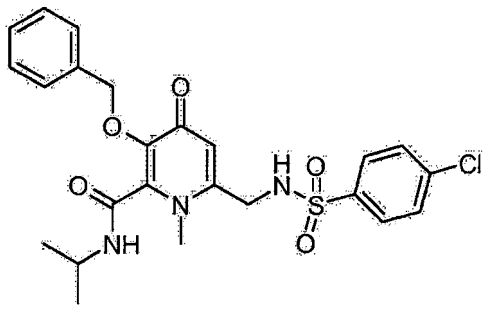
[0572] 3- 羟基 -1- 甲基 -4- 氧代 -6-[(甲苯 -4- 磺酰氨基)- 甲基]-1,4- 二氢 - 吡啶 -2- 甲酸异丙基酰胺

[0573] 按照为 6-(苯磺酰氨基 - 甲基)-3- 羟基 -1- 甲基 -4- 氧代 -1,4- 二氢 - 吡啶 -2- 甲酸 (14-01) 描述的方法，从 3- 苄氧基 -1- 甲基 -4- 氧代 -6-[(甲苯 -4- 磺酰氨基)- 甲基]-1,4- 二氢 - 吡啶 -2- 甲酸异丙基酰胺 (17-06)(280.0mg,0.58mmol) 合成 3- 羟基 -1- 甲基 -4- 氧代 -6-[(甲苯 -4- 磺酰氨基)- 甲基]-1,4- 二氢 - 吡啶 -2- 甲酸异丙基酰胺 (18-06)(190.0mg,83.3％ , 通过 Prep-HPLC 纯化)，其为灰白色固体。

[0574] LC-MS:394.0(M+H)。

[0575] (17-07) 的制备 ：

[0576]



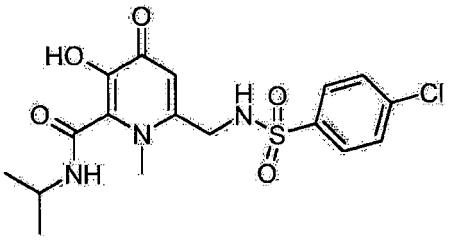
[0577] 3- 苄氧基 -6-[(4- 氯 - 苯磺酰氨基)- 甲基]-1- 甲基 -4- 氧代 -1,4- 二氢 - 吡啶 -2- 甲酸异丙基酰胺

[0578] 按照为 6-(苯磺酰氨基 - 甲基)-3- 苄氧基 -1- 甲基 -4- 氧代 -1,4- 二氢 - 吡啶 -2- 甲酸异丙基酰胺 (17-01) 描述的方法，从 3- 苄氧基 -6-[(4- 氯 - 苯磺酰氨基)- 甲基]-1- 甲基 -4- 氧代 -1,4- 二氢 - 吡啶 -2- 甲酸 (13-07)(500.0mg,1.08mmol) 合成 3- 苄氧基 -6-[(4- 氯 - 苯磺酰氨基)- 甲基]-1- 甲基 -4- 氧代 -1,4- 二氢 - 吡啶 -2- 甲酸异丙基酰胺 (17-07)(290.0mg,53.17％)，其为浅黄色固体。

[0579] LC-MS:504.0(M+H)。

[0580] (18-07)的制备：

[0581]



[0582] 6-[(4-氯-苯磺酰氨基)-甲基]-3-羟基-1-甲基-4-氧代-1,4-二氢-吡啶-2-甲酸异丙基酰胺

[0583] 按照为6-(苯磺酰氨基-甲基)-3-羟基-1-甲基-4-氧代-1,4-二氢-吡啶-2-甲酸(14-01)描述的方法，从3-苄氧基-6-[(4-氯-苯磺酰氨基)-甲基]-1-甲基-4-氧代-1,4-二氢-吡啶-2-甲酸异丙基酰胺(17-07)(600.0mg,1.19mmol)合成6-[(4-氯-苯磺酰氨基)-甲基]-3-羟基-1-甲基-4-氧代-1,4-二氢-吡啶-2-甲酸异丙基酰胺(18-07)(250.0mg,50.64％，通过Prep-HPLC纯化)，其为灰白色固体。

[0584] LC-MS:414.2(M+H)。

Abstract

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