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Westman

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(54) **PYRAZOLO[1,5-A]TRIAZIN-4-AMINE DERIVATIVES USEFUL IN THERAPY**

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A61K 31/53 (2006.01)

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CPC ***C07D 487/04*** (2013.01); ***A61K 31/53*** (2013.01); ***A61P 31/14*** (2018.01)

(58) **Field of Classification Search**
CPC C07D 487/04
See application file for complete search history.

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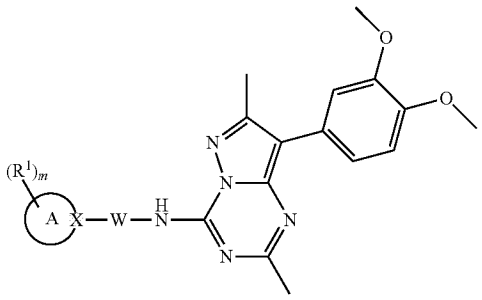
(57) **ABSTRACT**

A compound of formula (I), or a pharmaceutically acceptable salt thereof, useful in therapy, in particular in the treatment of a viral infection.

(I)



17 Claims, No Drawings

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PYRAZOLO[1,5-A]TRIAZIN-4-AMINE DERIVATIVES USEFUL IN THERAPY

This application is a national phase of International Application No. PCT/EP2016/063383 filed Jun. 10, 2016 and published in the English language, which claims priority to European Application No. 15173687.3 filed Jun. 24, 2015.

FIELD OF THE INVENTION

The present invention relates generally to novel compounds having usefulness in therapy, in particular in the treatment of conditions caused by certain viruses, such as diabetes, cancer, neurodegenerative diseases such as Alzheimer's disease and amyotrophic lateral sclerosis.

More particularly the invention relates to pyrazolo[1,5-a] triazin-4-amine derivatives having a usefulness in therapy.

BACKGROUND OF THE INVENTION

Pyrazolo[1,5-a] triazin-4-amine is a scaffold previously used in medicinal chemistry and derivatives thereof are known for their potent utility as corticotropin-releasing factor receptor-1 (CRF1) antagonists which may be potential anxiolytic and antidepressant drugs (for example Gilligan et al (J. Med. Chem. 2009, 52, 3073-3083). Pexacerfont is a pyrazolo[1,5-a]triazin-4-amine drug developed by Bristol-Myers Squibb and acts as a CRF-1 antagonist which have been tested clinically. The scaffold has also been described as present in cyclin-dependent kinase inhibitors (WO2013128029), casein kinase inhibitors and DYRK1A kinase inhibitors (WO2010103486) useful for treatment of various diseases. The scaffold has further been described as present in cannabinoid 1 receptor antagonists (J. Pharm. Exp. Ther. (2010), 335(1), 103-113).

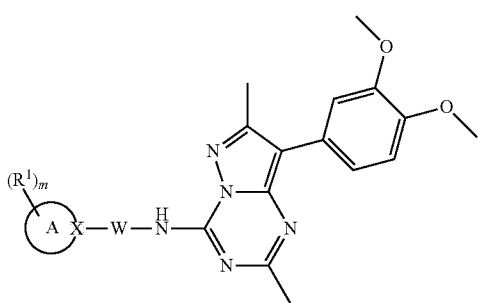
Similar scaffolds have been described as present in phosphatidylinositol 4-kinase (PI4K) inhibitors (McLeod et al (ACS Med. Chem. Lett. 2013, 4(7), 585-589) and van der Schaar et al (Antimicrobial Agents Chemother. 2013, 57(10), 4971-4981) and inhibitors of PI4K have shown to be potent antivirals (Bianco et al, PLoS Pathogens, 2012, 8(3), 1-17; LaMarche et al, Antimicr. Agents and Chemother. 2012, 56(10), 5149-5156; Décor et al, Bioorg Med Chem Lett. 2013, 23, 3841-7).

Pyrazolo[1,5-a] triazin-4-amine have been described as PI4K inhibitors with antiviral potency in Mejdrova et al (J. Med. Chem., 2015, 58 (9), pp 3767-3793).

There still remains a need for new therapeutically active compounds.

SUMMARY OF THE INVENTION

A first aspect is a compound of formula (I)



(I)

or a pharmaceutically acceptable salt thereof, wherein

W is CH_2 or CH_2—CH_2;

X is C or CH;

ring A is 5- or 6-membered carbocyclyl or 5- or 6-membered heterocyclyl;

m is an integer of from 0 to 3;

each R^1 is independently selected from C1-C6 alkyl optionally substituted by one or more halogen, R^2O, halogen, $R^3R^4NC(O)$, $R^5C(O)N(R^6)$, $R^7OC(O)$, $R^8C(O)O$, $R^9S(O)_2$, $R^{10}S(O)_2N(H)$, $R^{11}C(O)$, $R^{12}R^{13}N$, —O and $R^{14}R^{15}NS(O)_2$; and

when m is at least 2, two R^1 attached to adjacent atoms of ring A may form, together with the atoms to which they are attached, a 5- or 6-membered heterocyclic or carbocyclic ring;

each R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13} and R^{14} is independently selected from H and C1-C6 alkyl, wherein any alkyl is optionally substituted by one or more halogen;

R^{15} is selected from H, C1-C6 alkyl, $R^{16}C(O)$, $R^{17}OC(O)$, and $R^{18}R^{19}NC(O)$; and

each R^{16}, R^{17}, R^{18}, and R^{19} is independently selected from H and C1-C6 alkyl, wherein any alkyl is optionally substituted by one or more halogen.

In some embodiments of a compound of formula (I), W is CH_2, X is C, and ring A is phenyl or 5- or 6-membered heteroaryl; e.g. W is CH_2, X is C, and ring A is phenyl; or W is CH_2, X is C, and ring A is 5- or 6-membered heteroaryl; or W is CH_2, X is C, and ring A is 6-membered heteroaryl; or W is CH_2, X is C, and ring A is 5-membered heteroaryl.

A further aspect is a compound of formula (I), or a pharmaceutically acceptable salt thereof, for use as an inhibitor of phosphatidylinositol 4-kinase IIIβ.

A further aspect is a compound of formula (I), or a pharmaceutically acceptable salt thereof, for use in therapy.

A still further aspect is a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, and optionally a pharmaceutically acceptable excipient.

A further aspect is a compound of formula (I), or a pharmaceutically acceptable salt thereof, for use in the treatment of a viral infection. In some embodiments, the viral infection is a non-enveloped single-stranded (+) RNA viral infection.

Still a further aspect is a compound of formula (I), or a pharmaceutically acceptable salt thereof, for use in the treatment of a neurodegenerative disease such as multiple sclerosis, Parkinson's disease, amyotrophic lateral sclerosis, Alzheimer's disease, Huntington's disease, poliomyelitis, encephalitis, meningitis, sepsis, cancer, paralysis, myocarditis, diabetes, common cold, hand-foot-and-mouth disease, herpangina, pleurodynia, diarrhea, mucocutaneous lesions, respiratory illness, conjunctivitis, myositis, and chronic fatigue syndrome.

The use of the compound of formula (I) or the pharmaceutically acceptable salt thereof for the preparation of a pharmaceutical composition for the treatment of a disorder as mentioned herein above also is provided, as well as a method for the treatment of a disorder as mentioned herein above by administration of a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof to a mammal in need thereof.

DETAILED DESCRIPTION OF THE INVENTION

"Pharmaceutically acceptable" means being useful in preparing a pharmaceutical composition that is generally

safe, non-toxic and neither biologically nor otherwise undesirable and includes being useful for veterinary use as well as human pharmaceutical use.

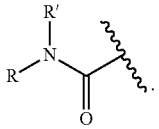
"Treatment" as used herein includes prophylaxis of the named disorder or condition, or amelioration or elimination of the disorder once it has been established.

"An effective amount" refers to an amount of a compound that confers a therapeutic effect on the treated subject. The therapeutic effect may be objective (i.e., measurable by some test or marker) or subjective (i.e., subject gives an indication of or feels an effect).

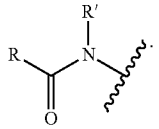
Unless otherwise stated or indicated, the term "C1-6 alkyl" denotes a straight or branched alkyl group having from 1 to 6 carbon atoms. Examples of said C1-6 alkyl include methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, t-butyl and straight- and branched-chain pentyl and hexyl.

Unless otherwise stated or indicated, the term "halogen" (or "halo") refers to fluorine (F), chlorine (Cl), or bromine (Br).

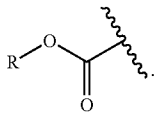
A moiety of the type RR'NC(O) is a moiety of formula



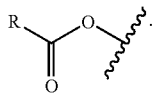
A moiety of the type RC(O)N(R') is a moiety of formula



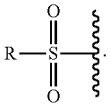
A moiety of the type ROC(O) is a moiety of formula



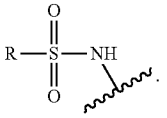
A moiety of the type RC(O)O is a moiety of formula



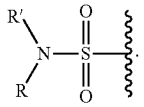
A moiety of the type $RS(O)_2$ is a moiety of formula



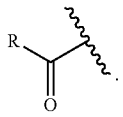
A moiety of the type $RS(O)_2N(H)$ is a moiety of formula



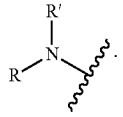
A moiety of the type $RR'NS(O)_2$ is a moiety of formula



A moiety of the type RC(O) is a moiety of formula



A moiety of the type RR'N is a moiety of formula



As used herein, the term "carbocyclyl" or "carbocyclic ring" refers to a saturated or unsaturated (e.g. monounsaturated or diunsaturated), non-aromatic or aromatic cyclic moiety containing only carbon atoms in the ring.

Examples of non-aromatic carbocylyl are pentyl, hexyl or hexenyl, while phenyl is an example of aromatic carbocyclyl.

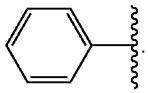
The term "heterocyclyl" (or "heterocyclic ring") refers to a saturated or unsaturated, aromatic or non-aromatic cyclic moiety containing not only carbon atoms, but also at least one other atom in the ring, e.g. selected from nitrogen (N), sulphur (S) and oxygen (O), in particular N and O.

When non-aromatic, the heterocyclyl e.g. may be piperidinyl, or 1,2,3,4-tetrahydropyridinyl. Other examples of non-aromatic heterocyclyl include morpholinyl, pyrrolidinyl, piperazinyl, tetrahydrothienyl, and tetrahydrofuryl.

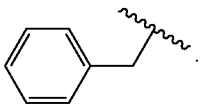
When aromatic, the heterocyclyl also may be referred to as "heteroaryl", which refers to an aromatic ring containing at least one ring heteroatom, such as furyl, isoxazolyl, isothiazolyl, imidazolyl, pyridyl, pyrrolyl, pyrazolyl, pyrimidinyl, pyridazinyl, pyrazinyl, oxadiazolyl, oxazolyl, thienyl, thiadiazolyl, thiazolyl, triazolyl, and tetrazolyl.

The term "aromatic", as used herein, refers to an unsaturated cyclic moiety that has an aromatic character, while the term "non-aromatic", as used herein, refers to a cyclic moiety, that may be saturated or unsaturated, e.g. polyunsaturated, but that does not have an aromatic character.

The term "phenyl" refers to a moiety of formula C_6H_5—, i.e.;



The term "benzyl" refers to a moiety of formula $C_6H_5CH_2$—, i.e.;



A "methylenedioxy biradical" is a biradical of formula —OCH_2O—.

An "ethylenedioxy biradical" is a biradical of formula —OCH_2CH_2O—.

"Treatment" as used herein includes prophylaxis of the named disorder or condition, or amelioration or elimination (i.e. cure) of the disorder once it has been established.

An "effective amount" refers to an amount of a compound that confers a therapeutic effect on the treated subject. The therapeutic effect may be objective (i.e., measurable by some test or marker, e.g. no measurable virus titre in a biological sample from the treated subject) or subjective (i.e., subject gives an indication of or feels an effect).

A "non-enveloped single-stranded (+) RNA viral infection" refers to an infection with a non-enveloped single-stranded (+) RNA virus.

A "non-enveloped virus" is a virus lacking viral envelope.

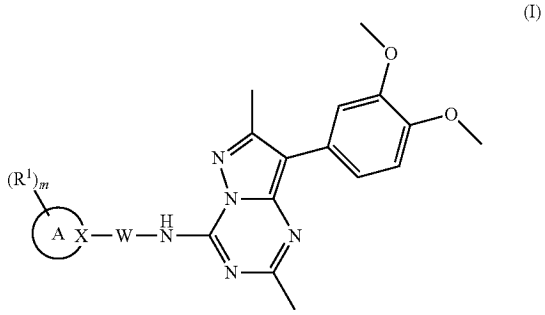
A "single-stranded (+) RNA virus" is a virus having genetic material which is single-stranded RNA and which RNA can be immediately translated to viral protein by the cell infected by the virus.

The term "mammal" refers to a human or any mammalian animal, e.g. a primate, a farm animal, a pet animal, or a laboratory animal. Examples of such animals are monkeys, cows, sheep, goats, horses, pigs, dogs, cats, rabbits, mice, rats etc. Preferably, the mammal is a human. In some embodiments, however, the mammal is an animal, e.g. a farm animal, such as a cow, sheep, goat, horse, or pigs. In some other embodiments, the animal is a pet, e.g. a dog, a cat or a rabbit.

The term "excipient" refers to pharmaceutically acceptable chemicals, such as known to those of ordinary skill in the art of pharmacy to aid the administration of the medicinal agent. It a compound that is useful in preparing a pharmaceutical composition, generally safe, non-toxic and neither biologically nor otherwise undesirable, and includes excipients that are acceptable for veterinary use as well as human pharmaceutical use. Exemplary excipients include binders, surfactants, diluents, disintegrants, antiadherents, and lubricants.

Herein below, any reference to a compound of formula (I) or a compound of the invention, should be construed as referring to a compound for use according to the invention, as defined in the claims.

In a compound of formula (I)



(I)

as defined herein above, W is CH_2 or CH_2CH_2. In some embodiments, W is CH_2. In some other embodiments, W is CH_2CH_2.

In ring A, the moiety X is C or CH. X is CH when attached to the two adjacent atoms in the ring by only single bonds, such as in cyclohexyl or tetrahydrofuryl, and X is C when X is attached by a double bond to an adjacent atom in the ring, such as in phenyl or cyclohexen-1-yl.

The ring A is 5- or 6-membered carbocyclyl or 5- or 6-membered heterocyclyl. In some embodiments, ring A is 5- or 6-membered carbocyclyl or 5- or 6-membered heteroaryl. In some embodiments, ring A is 5- or 6-membered carbocyclyl. In some embodiments, when A is 5- or 6-membered carbocyclyl, it more particularly is 6-membered carbocyclyl, e.g hexyl or phenyl, in particular phenyl.

In some embodiments, e.g. when ring A is phenyl, ring A is substituted by 1-3 moieties R^1, e.g. 1 or 2 moieties R^1, or 1 moiety R^1 (i.e. m is 1-3, m is 1 or 2, or m is 1). In some other embodiments, e.g. when ring A is phenyl, m is 0, 1 or 2, e.g. m is 0 or 1.

In some embodiments, when ring A is phenyl and m is an integer of from 1 to 3, e.g. m is 1 or 2, at least one R^1 is in meta position. In some embodiments, when ring A is phenyl, m is 1, and R^1 is in meta position.

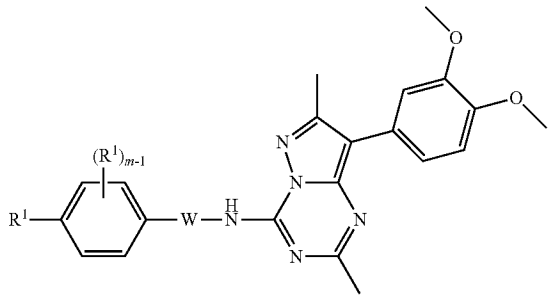
In some particular embodiments, when ring A is phenyl and m is an integer of from 1 to 3, e.g. m is 1 or 2, and least one R^1 is in meta position, said R^1 in meta position is $R^9S(O)_2$, wherein R^9 is as defined herein, e.g. R^9 is C1-C3 alkyl, or R^9 is methyl. In some of these embodiments, m is 1. Furthermore, in some of these embodiments, W is CH_2; e.g. m is 1 and W is CH_2.

Thus, in some particular embodiments of a compound of formula (I), ring A is phenyl substituted in meta position, e.g. with a moiety $R^9S(O)_2$; m is 1, 2 or 3; e.g. m is 1 or 2; or m is 1; and W is CH_2.

In some embodiments, when ring A is phenyl and m is an integer of from 1 to 3, at least one R^1 is in para position.

In some embodiments, the compound of formula (I) may be represented by formula (Ia)

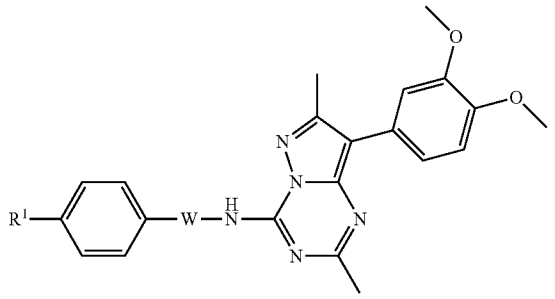
(Ia)



wherein m is 1, 2 or 3, and W and each R^1 are as defined herein.

When m is 1, the compound of formula (Ia) may be represented by formula (Ib)

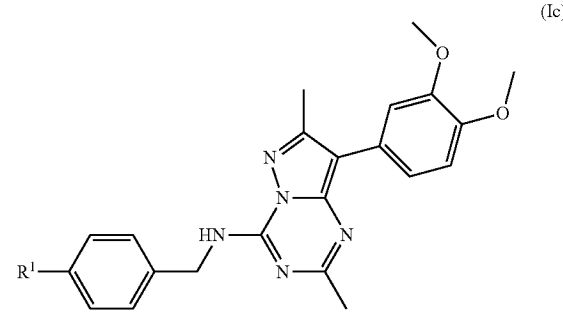
(Ib)



wherein W and R^1 are as defined herein.

In some embodiments of a compound of formula (Ib), W is CH_2 and the compound may be represented by formula (Ic)

(Ic)



wherein R^1 is as defined herein.

In some other embodiments of a compound of formula (I), ring A is 5- or 6-membered heterocyclyl. When ring A is heterocyclyl, said heterocyclyl may contain 1, 2, 3 or 4 heteroatoms, e.g. 1, 2 or 3 heteroatoms, or 1 or 2 heteroatoms, e.g. 1 heteroatom, each heteroatom being independently selected from N, O and S, e.g. from O and S.

In some embodiments, when ring A is 5- or 6-membered heterocyclyl, it more particularly is 5-membered heterocyclyl. In some other embodiments, when ring A is 5- or 6-membered heterocyclyl, it more particularly is 6-membered heterocyclyl. In some embodiments, when ring A is 5- or 6-membered heterocyclyl, said heterocyclyl is aromatic, i.e. ring A is 5- or 6-membered heteroaryl. In some embodiments, ring A is 5-membered heteroaryl. In some other embodiments, ring A is 6-membered heteroaryl.

In some embodiments, ring A is 5-membered heteroaryl containing one or more heteroatoms, e.g. 1-3 heteroatoms; or 1 or 2 heteroatoms, of which at least one is N; e.g. ring A is pyrazolyl, oxazolyl, thiazolyl, thienyl or furyl.

In some embodiments, ring A is 5-membered heteroaryl containing 2 heteroatoms, of which at least one is N, e.g. ring A is pyrazolyl.

In some embodiments, ring A is 5-membered heteroaryl containing one heteroatom selected from O and S, i.e. ring A is thienyl or furyl, e.g. 2-thienyl or 2-furyl.

In some embodiments, ring A is 5-membered heteroaryl, and m is an integer of from 0 to 3, or from 0 to 2, e.g. m is 0 or 1. For example, in some embodiments, ring A is pyrazolyl, e.g. 1H-pyrazol-3-yl; m is 1, 2 or 3, e.g. m is 1 or 2, or m is 1, and at least one R^1 is attached to a ring nitrogen. For example, in some embodiments, ring A, substituted by one R^1, is selected from 1-C_1-C_6 alkyl-1H-pyrazol-3-yl, or 1-C1-C3 alkyl-1H-pyrazol-3-yl, in particular 1-methyl-1H-pyrazolyl-3yl, and is optionally substituted by one or two further R^1, e.g. one further R^1, or is substituted by no further R^1, i.e. m is 1. In some of these embodiments, W is CH_2.

In some embodiments, ring A is 6-membered heteroaryl. When ring A is 6-membered heteroaryl, said heteroaryl e.g. may be selected from pyridinyl, pyrimidinyl, or pyridazinyl, e.g. from pyridyl (also termed pyridinyl), i.e. pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, in particular it may be pyridin-4-yl.

In some embodiments, e.g. of a compound of formula (If) as defined herein below, ring A is pyridin-3-yl or pyridin-4-yl. In some embodiments, ring A is pyridin-3-yl, e.g. ring A is pyridin-3-yl and m is 0, 1 or 2, e.g. m is 0 or 1. In some embodiments, ring A is pyridin-3-yl, m is 1, and R^1 is in para position; e.g. ring A is pyridin-3-yl, m is 1, and R^1 is in para position and is R^2O.

In some other embodiments, ring A is selected from 5- or 6-membered carbocyclyl, in particular 6-membered, carbocyclyl, such as phenyl and hexyl, and from 5- or 6-membered heterocyclyl containing one heteroatom only, e.g. tetrahydrofuryl, thienyl, furyl, and pyridyl.

In some other embodiments, ring A is phenyl or 5- or 6-membered heteroaryl. In some other embodiments, ring A is phenyl or 5-membered heteroaryl. In still other embodiments, ring A is phenyl or 6-membered heteroaryl.

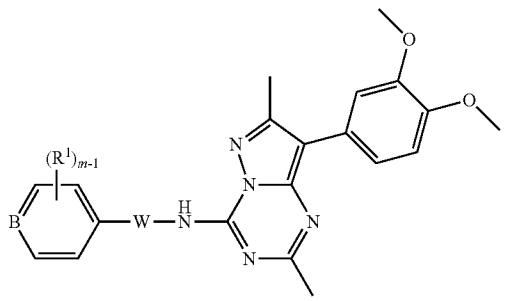
In some embodiments, ring A is phenyl, said phenyl having a substituent R^1 in para position, and optionally being substituted by 1 or 2 further moieties R^1; or ring A is 6-membered heteroaryl having a heteroatom, e.g. nitrogen (N), in para position, said heteroaryl optionally being substituted by 1, 2 or 3 moieties R^1 and said heteroaryl optionally containing one or more further heteroatoms (e.g. N), e.g. 1 or 2 further N; or ring A is 6-membered heteroaryl having $N^+(O^-)$ in para position, said heteroaryl optionally being substituted by 1, 2 or 3 moieties R^1 and said heteroaryl optionally containing one or more further heteroatoms, e.g. 1 or 2 further N.

In some embodiments, ring A is phenyl having a substituent R^1 in para position, said phenyl optionally being substituted by 1 or 2 further moieties R^1; or ring A is 6-membered heteroaryl having a heteroatom, e.g. nitrogen (N), in para position, said heteroaryl optionally being substituted by 1, 2

or 3 moieties R^1 and said heteroaryl optionally containing one or more further heteroatoms (e.g. N), e.g. 1 or 2 further N.

In some embodiments, the compound of formula (I) may be one represented by formula (Id)

(Id)

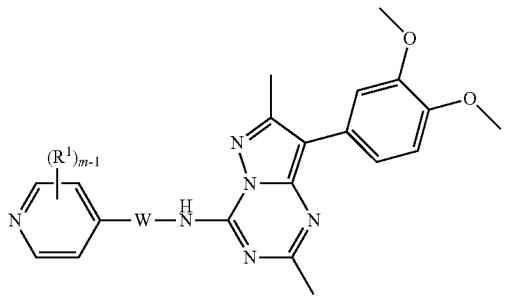


wherein m is 1, 2, or 3, e.g. m is 1 or 2, in particular m is 1; B is N, $N^+(O^-)$ or CR^1, and W and each R^1 are as defined herein; e.g. W is CH_2.

In some embodiments of a compound of formula (Id), B is N or $N^+(O^-)$, in particular B is N.

In some embodiments, B is N, i.e. the compound may be represented by formula (Ie)

(Ie)



wherein m is 1, 2, or 3, e.g. m is 1 or 2, in particular m is 1; and W and each R^1 are as defined herein; e.g. W is CH_2.

In a compound of formula (I), m denotes the number of moieties R^1 attached to ring A, and is an integer of from 0 to 3. In some embodiments, m is an integer of from 1 to 3, e.g. m is 1 or 2. In some other embodiments, m is an integer of from 0 to 2, e.g. m is 0 or 1. In some embodiments, m is 1.

In a compound of formula (I), each R^1 is independently selected from C1-C6 alkyl optionally substituted by one or more halogen, R^2O, halogen, $R^3R^4NC(O)$, $R^5C(O)N(R^6)$, $R^7OC(O)$, $R^8C(O)O$, $R^9S(O)_2$, $R^{10}S(O)_2N(H)$, $R^{11}C(O)$, $R^{12}R^{13}N$, ^-O and $R^{14}R^{15}NS(O)_2$; and when m is at least 2, two R^1 attached to adjacent atoms of ring A may form, together with the atoms to which they are attached, a 5- or 6-membered heterocyclic or carbocyclic ring.

In some embodiments, each R^1 is independently selected from C1-C6 alkyl optionally substituted by one or more halogen, R^2O, halogen, $R^3R^4NC(O)$, $R^5C(O)N(R^6)$, $R^7OC(O)$, $R^8C(O)O$, $R^9S(O)_2$, $R^{10}S(O)_2N(H)$, $R^{11}C(O)$, $R^{12}R^{13}N$, and $R^{14}R^{15}NS(O)_2$; and when m is at least 2, two R^1 attached to adjacent atoms of ring A may form, together with the atoms to which they are attached, a 5- or 6-membered heterocyclic or carbocyclic ring.

In some embodiments, each R^1 is independently selected from C1-C6 alkyl, R^2O, halogen, $R^5C(O)N(R^6)$, $R^9S(O)_2$, $R^{10}S(O)_2N(H)$, ^-O, and $R^{14}R^{15}NS(O)_2$.

When R^1 is C1-C6 alkyl, said alkyl e.g. may be selected from C1-C4 alkyl, e.g. C1-C3 alkyl, such as methyl, ethyl and isopropyl.

In the moieties R^2O, $R^3R^4NC(O)$, $R^5C(O)N(R^6)$, $R^7OC(O)$, $R^8C(O)O$, $R^9S(O)_2$, $R^{10}S(O)_2N(H)$, $R^{11}C(O)$, $R^{12}R^{13}N$, and $R^{14}R^{15}NS(O)_2$; each one R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13} and R^{14} is independently selected from H and C1-C6 alkyl. In some embodiments, each one of R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13} and R^{14} is independently selected from H and C1-C4 alkyl, e.g. from H and C1-C3 alkyl, or from H, methyl and ethyl, in particular from H and methyl.

In some other embodiments, each one of R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13} and R^{14} is independently selected from C1-C6 alkyl, e.g. from C1-C4 alkyl, from C1-C3 alkyl, or from methyl and ethyl, in particular from methyl.

In some embodiments, in the moiety $R^5C(O)N(R^6)$, R^5 is as defined herein above, and R^6 is H.

In the moiety $R^{14}R^{15}NS(O)_2$, R^{14} is as defined herein above, e.g. R^{14} is H or CH_3, or R^{14} is H, and R^{15} is selected from H, C1-C6 alkyl, $R^{16}C(O)$, $R^{17}OC(O)$, and $R^{18}R^{19}NC(O)$. In some embodiments, R^{15} is selected from H and C1-C6 alkyl, e.g. from H and C1-C4 alkyl, or from H and C1-C3 alkyl, such as H and CH_3. In some other embodiments, R^{15} is selected from C1-C6 alkyl, $R^{16}C(O)$, $R^{17}OC(O)$, and $R^{18}R^{19}NC(O)$, e.g. from $R^{16}C(O)$, $R^{17}OC(O)$, and $R^{18}R^{19}NC(O)$.

In any of $R^{16}C(O)$, $R^{17}OC(O)$, and $R^{18}R^{19}NC(O)$, each one of R^{16}, R^{17}, R^{18}, and R^{19} is independently selected from H and C1-C6 alkyl, e.g. from H and C1-C4 alkyl, or from H and C1-C3 alkyl, such as H and CH_3. In some embodiments, each one of R^{16}, R^{17}, R^{18}, and R^{19} is independently selected from C1-C6 alkyl, e.g. from C1-C4 alkyl, or from C1-C3 alkyl, e.g. each is CH_3.

When R^1 is halogen, said halogen e.g. may be selected from F, Cl and Br. In some embodiments, when R^1 is halogen, said halogen is F or Cl, in particular Cl. In some other embodiments, when R^1 is halogen, said halogen is F.

When R^1 is an alkyl moiety or comprises an alkyl moiety, any such alkyl moiety may be substituted by one or more halogen, in particular one or more F.

When any R^1 is ^-O, said ^-O preferably is attached to a nitrogen atom in ring A, i.e. ring A is nitrogen-containing heterocyclyl.

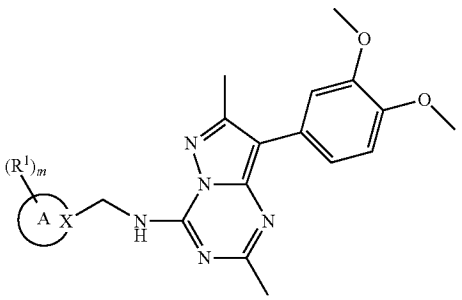
In some embodiments, when m is at least 2, e.g. m is 2, two R^1 attached to adjacent atoms of the ring A form, together with the atoms to which they are attached, a 5- or 6-membered heterocyclic or carbocyclic ring, e.g. a 5- or 6-membered heterocyclic ring, such as a 5- or 6-membered ring containing one or two oxygen atoms. For example, two R^1 attached to adjacent atoms of ring A may form together a methylenedioxy biradical or an ethylenedioxy biradical.

In some embodiments, when two R^1 attached to adjacent atoms of the ring A form, together with the atoms to which they are attached, a 5- or 6-membered heterocyclic or carbocyclic ring, said ring is a 5-membered heterocyclic ring, e.g. 1,3-dioxole or 1,3-dioxolane.

It should be realized that features of the various embodiments described herein may be freely combined within the scope of the present invention, unless mutually incompatible, or unless otherwise specified.

For example, in some embodiments, wherein W is CH_2, the compound is as represented by formula (If)

(If)



wherein

X is C;

ring A is phenyl or 5- or 6-membered heteroaryl;

m is an integer of from 0 to 3; e.g. from 0 to 2; or m is 0 or 1:

and each R^1 is as defined herein above.

In some embodiments of a compound of formula (If), each R^1 is independently selected from C1-C6 alkyl optionally substituted by one or more halogen, R^2O, halogen, $R^5C(O)N(R^6)$, $R^9S(O)_2$, $R^{10}S(O)_2N(H)$, and $R^{14}R^{15}NS(O)_2$; and when m is at least 2, two R^1 attached to adjacent atoms of ring A may form, together with the atoms to which they are attached, a 5- or 6-membered heterocyclic or carbocyclic ring, e.g. a 5- or 6-membered saturated or mono-unsaturated heterocyclic or carbocyclic ring, in particular a ring formed by methylenedioxy biradical or an ethylenedioxy biradical attached to adjacent atoms of ring A;

each R^2, R^5, R^6, R^9, R^{10}, and R^{14} is independently selected from H and C1-C6 alkyl, wherein any alkyl is optionally substituted by one or more halogen;

R^{15} is selected from H, C1-C6 alkyl, $R^{16}C(O)$, $R^{17}OC(O)$, and $R^{18}R^{19}NC(O)$; and

each R^{16}, R^{17}, R^{18}, and R^{19} is independently selected from H and C1-C6 alkyl, wherein any alkyl is optionally substituted by one or more halogen.

In some of these embodiments, each R^1 is independently selected from C1-C6 alkyl optionally substituted by one or more halogen, R^2O, halogen, $R^5C(O)N(R^6)$, $R^9S(O)_2$, $R^{10}S(O)_2N(H)$, and $R^{14}R^{15}NS(O)_2$; and when m is at least 2, two R^1 attached to adjacent atoms of ring A may form, together with the atoms to which they are attached, a 5- or 6-membered heterocyclic or carbocyclic ring, e.g. a 5- or 6-membered saturated or mono-unsaturated heterocyclic or carbocyclic ring, in particular a ring formed by methylenedioxy biradical or an ethylenedioxy biradical attached to adjacent atoms of ring A;

each R^2, R^5, R^6, R^9, R^{10}, and R^{14} is independently selected from H and C1-C6 alkyl, wherein any alkyl is optionally substituted by one or more halogen; and

R^{15} is selected from H and C1-C6 alkyl, and

wherein any alkyl is optionally substituted by one or more halogen.

In the above embodiments, any C1-C6 alkyl preferably is C1-C3 alkyl, e.g. C1-C2 alkyl, in particular CH_3.

Moreover, when any alkyl is substituted by one or more halogen, each such halogen preferably is F. For example, in some embodiments of a compound of formula (If), each R^1 is selected from F, Cl, CF_3, CH_3, $CH_3C(O)NH$, CH_3O, $CH_3S(O)_2$, $NH_2S(O)_2$, OH, $CH_3S(O)_2NH$, and $CH_3NHS(O)_2$, or two R^1, attached to adjacent atoms of ring A, form together a methylenedioxy biradical.

In some of these embodiments, when ring A is phenyl, m is an integer of from 1 to 3, e.g. from 1 to 2, in particular m is 1; and when ring A is heteroaryl, m is an integer of from 0 to 2, e.g. m is 0 or 1.

In some embodiments of a compound of formula (If), ring A is phenyl and m is 1 or 2, or A is 5- or 6-membered heteroaryl and m is 0 or 1.

In some embodiments, ring A is phenyl or 5- or 6-membered heteroaryl and m is 0 or 1. In some of these embodiments, ring A is phenyl. In some other of these embodiments, ring A is 5- or 6-membered heteroaryl. In some of these embodiments, ring A is 6-membered heteroaryl. In some other of these embodiments, ring A is 5-membered heteroaryl.

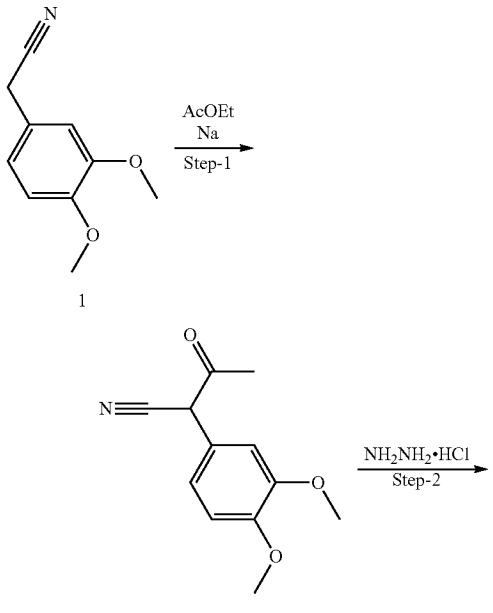
In some embodiments of a compound of formula (I), e.g. a compound of formula (If), ring A is selected from phenyl, pyridyl, thienyl, furyl, pyrazolyl, oxazolyl, pyridmidinyl, and pyridazinyl.

In some embodiments of a compound of formula (I), e.g. a compound of formula (If), ring A is phenyl. In some other of these embodiments, when ring A is 5-membered heteroaryl, it more particularly is selected from thienyl, furyl, pyrazolyl, and oxazolyl.

In some embodiments of a compound of formula (I), e.g. a compound of formula (If), when ring A is 6-membered heteroaryl, it more particularly is selected from 6-membered heteroaryl containing one or more nitrogen atoms in the ring, e.g. 1 or 2 N, e.g. ring A is selected from pyridinyl, pyridmidinyl, and pyridazinyl.

The compounds of the invention may be readily synthesized by the person of ordinary skill e.g. by following the general procedure outlined in Reaction Scheme 1.

Reaction Scheme 1



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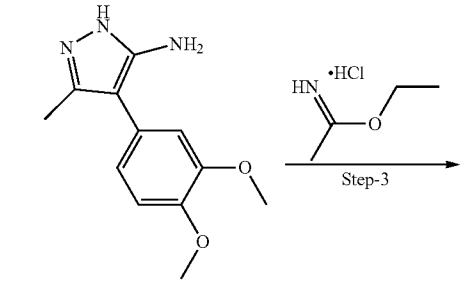

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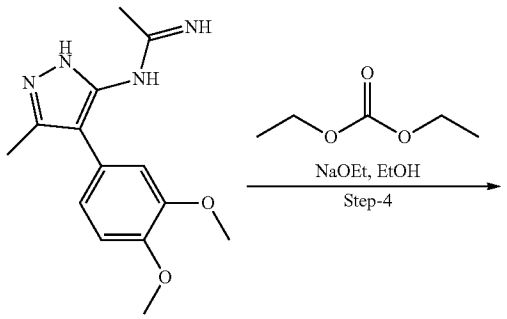

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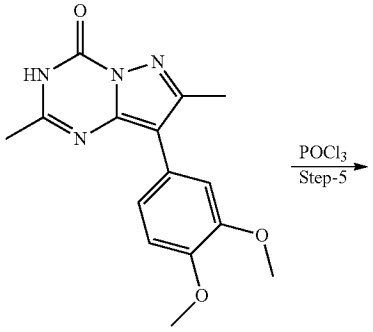

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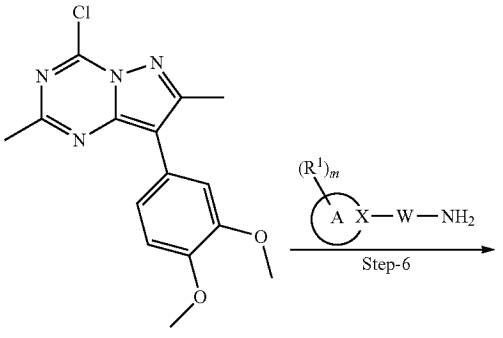

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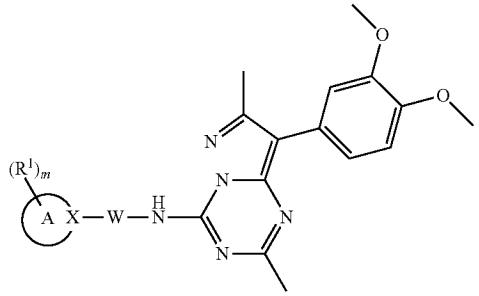


(I)

The compounds may also be synthesized using methods similar to those described in Mejdrova et al (J. Med. Chem., 2015, 58 (9), pp 3767-3793) or Long et al (J. Org. Chem., 2015, 80, 4716-4721).

The compounds of formula (I) also may be transformed into suitable, pharmaceutically acceptable salts. The term pharmaceutically acceptable salt of a compound refers to a salt that is pharmaceutically acceptable, as defined herein, and that possesses the desired pharmacological activity of the parent compound. Pharmaceutically acceptable salts include acid addition salts formed with inorganic acids, e.g. hydrochloric acid, hydrobromic acid, sulphuric acid, nitric acid, phosphoric acid; or formed with organic acids, e.g. acetic acid, benzenesulfonic acid, benzoic acid, camphorsulfonic acid, citric acid, ethanesulfonic acid, fumaric acid, glucoheptonic acid, gluconic acid, glutamic acid, glycolic acid, hydroxynaphtoic acid, 2-hydroxyethanesulfonic acid, lactic acid, maleic acid, malic acid, malonic acid, mandelic acid, methanesulfonic acid, muconic acid, 2-naphthalenesulfonic acid, propionic acid, salicylic acid, succinic acid, tartaric acid, p-toluenesulfonic acid, trimethylacetic acid, etc.

In the preparation of acid addition salts, preferably such acid are used which form suitably therapeutically acceptable salts. Examples of such acids are hydrohalogen acids, sulfuric acid, phosphoric acid, nitric acid, aliphatic, alicyclic, aromatic or heterocyclic carboxylic or sulfonic acids, such as formic acid, acetic acid, propionic acid, succinic acid, glycolic acid, lactic acid, malic acid, tartaric acid, citric acid, ascorbic acid, maleic acid, hydroxymaleic acid, pyruvic acid, p-hydroxybenzoic acid, embonic acid, methanesulfonic acid, ethanesulfonic acid, hydroxyethanesulfonic acid, halogenbenzenesulfonic acid, toluenesulfonic acid or naphthalenesulfonic acid.

Whenever a chiral carbon is present in a chemical structure, it is intended that all stereoisomers associated with that chiral carbon are encompassed by the structure, unless otherwise specified. Using the Cahn-Ingold-Prelog RS notational system, any asymmetric carbon atom may be present in the (R)- or (S)-configuration, and the compound may be present as a mixture of its stereoisomers, e.g. a racemic mixture, or one stereoisomer only.

The present invention includes pharmaceutical compositions comprising at least one compound of formula (I), or an individual isomer, racemic or non-racemic mixture of isomers or a pharmaceutically acceptable salt thereof, together with at least one pharmaceutically acceptable excipient, e.g. a carrier, and optionally other therapeutic and/or prophylactic ingredients.

A pharmaceutical composition according to the invention may be for topical (local) or systemic administration, e.g. for enteral administration, such as rectal or oral administration,

or for parenteral administration to a mammal (especially a human), and comprises a therapeutically effective amount of a compound according to the invention or a pharmaceutically acceptable salt thereof, as active ingredient, in association with a pharmaceutically acceptable excipient, e.g. a pharmaceutically acceptable carrier. The therapeutically effective amount of the active ingredient is as defined herein above and depends e.g. on the species of mammal, the body weight, the age, the individual condition, individual pharmacokinetic data, the disease to be treated and the mode of administration.

For enteral, e.g. oral, administration, the compounds of the invention may be formulated in a wide variety of dosage forms. The pharmaceutical compositions and dosage forms may comprise a compound or compounds of the present invention or pharmaceutically acceptable salt(s) thereof as the active component. The pharmaceutically acceptable carriers may be either solid or liquid. Solid form preparations include powders, tablets, pills, lozenges, capsules, cachets, suppositories, and dispersible granules. A solid carrier may be one or more substances which may also act as diluents, flavouring agents, solubilizers, lubricants, suspending agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material. In powders, the carrier generally is a finely divided solid which is a mixture with the finely divided active component. In tablets, the active component generally is mixed with the carrier having the necessary binding capacity in suitable proportions and compacted in the shape and size desired. Suitable carriers include but are not limited to magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatine, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The formulation of the active compound may comprise an encapsulating material as carrier, providing a capsule in which the active component, with or without carriers, is surrounded by a carrier, which is in association with it.

Other forms suitable for oral administration include liquid form preparations including emulsions, syrups, elixirs, aqueous solutions, aqueous suspensions, or solid form preparations which are intended to be converted shortly before use to liquid form preparations. Emulsions may be prepared in solutions, for example, in aqueous propylene glycol solutions or may contain emulsifying agents, for example, such as lecithin, sorbitan monooleate, or acacia. Aqueous solutions can be prepared by dissolving the active component in water and adding suitable colorants, flavors, stabilizers, and thickening agents. Aqueous suspensions can be prepared by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, and other well-known suspending agents. Solid form preparations include solutions, suspensions, and emulsions, and may contain, in addition to the active component, colorants, flavors, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilising agents, and the like.

Exemplary compositions for rectal administration include suppositories which can contain, for example, a suitable non-irritating excipient, such as cocoa butter, synthetic glyceride esters or polyethylene glycols, which are solid at ordinary temperatures, but liquefy and/or dissolve in the rectal cavity to release the drug.

The compounds of the invention also may be administered parenterally, e.g. by inhalation, injection or infusion, e.g. by intravenous, intraarterial, intraosseous, intramuscular, intracerebral, intracerebroventricular, intrasynovial, intrasternal, intrathecal, intralesional, intracranial, intracutaneous and subcutaneous injection or infusion.

Thus, for parenteral administration, the pharmaceutical compositions of the invention may be in the form of a sterile injectable or infusible preparation, for example, as a sterile aqueous or oleaginous suspension. This suspension may be formulated according to techniques known in the art using suitable dispersing or wetting agents (e.g., Tween 80), and suspending agents. The sterile injectable or infusible preparation may also be a sterile injectable or infusible solution or suspension in a non-toxic parenterally acceptable diluent or solvent. For example, the pharmaceutical composition may be a solution in 1,3-butanediol. Other examples of acceptable vehicles and solvents that may be employed in the compositions of the present invention include, but are not limited to, mannitol, water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed including synthetic mono- or diglycerides. Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant.

Solutions for parenteral use also may contain suitable stabilizing agents, and if necessary, buffer substances. Suitable stabilizing agents include antioxidizing agents, such as sodium bisulfate, sodium sulfite or ascorbic acid, either alone or combined, citric acid and its salts and sodium EDTA. Parenteral solutions may also contain preservatives, such as benzalkonium chloride, methyl- or propyl-paraben, and cholorobutanol.

For inhalation or nasal administration, suitable pharmaceutical formulations are as particles, aerosols, powders, mists or droplets, e.g. with an average size of about 10 μm in diameter or less. For example, compositions for inhalation may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other solubilising or dispersing agents known in the art.

The pharmaceutical compositions of the invention also may be administered topically, to the skin or to a mucous membrane. For topical application, the pharmaceutical composition may be e.g. a lotion, a gel, a paste, a tincture, a transdermal patch, a gel for transmucosal delivery.

The composition may be formulated as a suitable ointment containing the active components suspended or dissolved in a carrier. Carriers for topical administration of the compounds of this invention include, but are not limited to, mineral oil, liquid petroleum, white petroleum, propylene glycol, polyoxyethylene polyoxypropylene compound, emulsifying wax and water.

Alternatively, the pharmaceutical composition may be formulated as a suitable lotion or cream containing the active compound suspended or dissolved in a carrier. Suitable carriers include, but are not limited to, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetaryl alcohol, 2-octyldodecanol, benzyl alcohol and water.

The pharmaceutical compositions of this invention may also be topically applied to the lower intestinal tract by rectal suppository formulation or in a suitable enema formulation.

Suitable pharmaceutical excipients, e.g. carriers, and methods of preparing pharmaceutical dosage forms are

described in Remington's Pharmaceutical Sciences, Mack Publishing Company, a standard reference text in art of drug formulation.

The pharmaceutical compositions may comprise from approximately 1% to approximately 95%, preferably from approximately 20% to approximately 90% of a compound of formula (I), together with at least one pharmaceutically acceptable excipient.

In general, the compounds of the invention will be administered in a therapeutically effective amount by any of the accepted modes of administration for agents that serve similar utilities. Suitable daily dosages typically ranges from 1 to 1000 mg, e.g. 1-500 mg daily, or 1-50 mg daily, depending upon numerous factors such as the severity of the disease to be treated, the age and relative health of the patient, the potency of the compound used, the route and form of administration, and the indication towards which the administration is directed, etc. One of ordinary skill in the art of treating such diseases will be able, without undue experimentation and in reliance upon personal knowledge and the disclosure of this application, to ascertain a therapeutically effective amount of the compounds of the present invention for a given disease. Compounds of the invention may be administered as pharmaceutical formulations including those suitable for enteral or parenteral administration. The preferred manner of administration is generally oral using a convenient daily dosage regimen which can be adjusted according to the degree of affliction.

The compound of the present invention is contemplated as useful for the treatment of diseases caused by RNA viral infection in a mammal, e.g. non-enveloped single-stranded (+) RNA viral infection, in particular diseases caused by picornaviruses, which is either a human or animal, but preferably a human. The picomavirus e.g. may be a Parechovirus (e.g. Ljungan or Parecho), a Cardiovirus (e.g. EMCV or Theiler's virus), Enterovirus (e.g. EV, Coxsackie, Polio, Rhino) or a hepatovirus. For veterinary use, the picornavirus may be e.g. an Aphthovirus or a Teschovirus.

In some embodiments, the viral disease is one linked to or caused by an enterovirus, a coxsackie virus; or a polio virus.

In some embodiments, the viral disease is one linked to or caused by an enterovirus. In some embodiments, the viral disease is one linked to or caused by a coxsackie virus. In some embodiments, the viral disease is one linked to or caused by a polio virus.

Diseases that are considered to be linked to, caused by, or otherwise associated with virus infection, e.g. by picomaviruses, are e.g. neurodegenerative diseases such as multiple sclerosis, Parkinson's disease, amyotrophic lateral sclerosis, Alzheimer's disease, Huntington's disease, poliomyelitis, encephalitis, meningitis, sepsis, cancer, paralysis, myocarditis, diabetes, common cold, hand-foot-and-mouth disease, herpangina, pleurodynia, diarrhea, mucocutaneous lesions, respiratory illness, conjunctivitis, myositis, and chronic fatigue syndrome.

The present invention consequently also includes a compound of formula (I) for use in the treatment of any of the above mentioned conditions, as well as the use of a compound of formula (I) in the manufacturing of a medicament for the treatment of any of the above mentioned conditions and a method of treatment of any of the above mentioned conditions, by administering to an animal or human in need thereof, a compound of formula (I).

The invention is further illustrated by some non-limiting examples.

EXAMPLES

A number of compounds of the inventions (Examples 1-32) were synthesized by following the general procedure illustrated in Reaction Scheme 1, as described herein below:

Step-1

To a solution of 1 (10.0 g, 56.4 mmol) in ethyl acetate (200 mL) was added sodium metal (2.6 g, 112.8 mmol) portion wise at 0-5° C. under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 6 h. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was cooled to 0-5° C., quenched with methanol (50 mL) and the solvent was evaporated under pressure. The resultant solid was dissolved in water (100 mL) and washed with toluene (2×100 mL). The aqueous solution was acidified with acetic acid (pH 4 to 5) and extracted with dichloromethane (3×100 mL). The combined organic layer was washed with water, brine, dried over sodium sulphate, filtered and concentrated under reduced pressure. The crude material was purified by recrystallization using ethyl acetate and hexane to afford 2 (9.5 g, 76.8%) as pale brown solid.

Step-2

To a solution of 2 (9.0 g, 41.05 mmol) in ethanol (90 mL) was added hydrazine monohydrochloride (4.218 g, 61.57 mmol) and acetic acid (2.7 mL, 2.83 g, 47.166 mmol) at room temperature under nitrogen atmosphere. The reaction mixture was heated to 85° C. and stirred for 5-6 h. The reaction was monitored by TLC. After completion of the reaction, the reaction mixture was cooled to room temperature. The reaction mixture was quenched with water (90 mL), concentrated under reduced pressure. The resultant aqueous layer was washed with toluene (3×45 mL) and basified with 10% aq. sodium bicarbonate solution (pH: 8-9). The aqueous layer was extracted with dichloromethane (4×50 mL). The combined organic layer was washed with water, brine, dried over sodium sulphate and concentrated under reduced pressure to afford 3 (7.6 g, 79.36%) as an off-white solid. The product obtained was used without further purification.

Step-3:

To a suspension of 3 (3.0 g, 12.86 mmol) in acetonitrile (75 mL) was added DIPEA until the reaction mixture showed pH in the range of 9-10. To the reaction mixture was added ethyl acetimidate hydrochloride (2.38 g, 19.26 mmol) at room temperature under nitrogen atmosphere. The reaction mixture was again basified with DIPEA (pH 9-10). To the mixture was added acetic acid (0.77 mL, 12.8 mmol) and the mixture was stirred for 16 h at room temperature. The reaction mixture then was diluted with diethyl ether (30 mL), the solid formed was filtered and dried under reduced pressure at 50-55° C. to get 4 (2.5 g, 70.86%) as a colorless solid.

Step-4:

Sodium metal (0.628 g, 27.3 mmol) was dissolved in absolute ethanol (18 mL) at room temperature under nitrogen atmosphere. To the clear solution were added 4 (0.6 g, 2.187 mmol) and diethyl carbonate (2.65 mL, 21.8 mmol) at room temperature and the reaction mixture was heated to reflux for 16 h. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was cooled to room temperature and quenched with water (30 mL). The resultant mass was concentrated under reduced pressure at 50-55° C. The residue was diluted with water, acidified with acetic acid (pH 5-6), extracted with dichloromethane (3×10 mL), the combined organic extract was washed with water,

brine, dried over sodium sulphate, filtered and concentrated under reduced pressure to afford 5 (0.420 g, 63.94%) as colorless solid.

Step-5:

To a suspension of 5 (0.7 g, 2.331 mmol) in dry toluene (15 mL) were added phosphoryl chloride (5.44 mL, 8.948 g, 58.36 mmol) and N,N-diethyl aniline (0.748 mL, 0.7 g, 4.702 mmol) at room temperature under nitrogen atmosphere. The reaction mixture was then heated to 105° C. for 16 h. After 16 h, the reaction mixture was concentrated under reduced pressure at 50-55° C. and co-evaporated with toluene under reduced pressure. The crude material 6 (0.53 g, quantitative) obtained was used as such without further purification.

Step-6:

To a solution of 6 (1.0 eq.) in toluene or acetonitrile or DMF (10-20 V) were added the respective amine (1.3 eq.) and base [DIPEA (5 V)/K_2CO_3/KO^{t}Bu/NaH (2.0 eq.)] sequentially. The reaction mixture was then stirred at room temperature or at 90° C. for 16 h. The progress of the reaction was monitored by TLC. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was diluted with water (20 V), extracted with dichloromethane (3×10 V). The combined organic extract was washed with water, brine, dried over sodium sulphate, filtered and concentrated under reduced pressure. The crude material was purified by flash column chromatography (silica gel, 50% EtOAc in Hexane) to afford the desired compound of formula (I) with >95% HPLC purity.

The chemical names of the compounds of Examples 1-32 are given in Table 1.

TABLE 1

Ex.	Chemical name
1	8-(3,4-dimethoxyphenyl)-N-[(4-fluorophenyl)methyl]-2,7-dimethyl-pyrazolo[1,5-a][1,3,5]triazin-4-amine
2	8-(3,4-dimethoxyphenyl)-2,7-dimethyl-N-[[4-(trifluoromethyl)phenyl]methyl]pyrazolo[1,5-a][1,3,5]triazin-4-amine
3	8-(3,4-dimethoxyphenyl)-2,7-dimethyl-N-(p-tolylmethyl)pyrazolo[1,5-a][1,3,5]triazin-4-amine
4	8-(3,4-dimethoxyphenyl)-N-[(4-isopropylphenyl)methyl]-2,7-dimethyl-pyrazolo[1,5-a][1,3,5]triazin-4-amine
5	8-(3,4-dimethoxyphenyl)-2,7-dimethyl-N-(2-pyridylmethyl)pyrazolo[1,5-a][1,3,5]triazin-4-amine
6	8-(3,4-dimethoxyphenyl)-2,7-dimethyl-N-(4-pyridylmethyl)pyrazolo[1,5-a][1,3,5]triazin-4-amine
7	N-[2-(4-chlorophenyl)ethyl]-8-(3,4-dimethoxyphenyl)-2,7-dimethyl-pyrazolo[1,5-a][1,3,5]triazin-4-amine
8	N-[(4-chlorophenyl)methyl]-8-(3,4-dimethoxyphenyl)-2,7-dimethyl-pyrazolo[1,5-a][1,3,5]triazin-4-amine
9	N-[4-[[[8-(3,4-dimethoxyphenyl)-2,7-dimethyl-pyrazolo[1,5-a][1,3,5]triazin-4-yl]amino]methyl]phenyl]acetamide
10	8-(3,4-dimethoxyphenyl)-N-[(4-methoxyphenyl)methyl]-2,7-dimethyl-pyrazolo[1,5-a][1,3,5]triazin-4-amine
11	8-(3,4-dimethoxyphenyl)-2,7-dimethyl-N-[(3-methylsulfonylphenyl)methyl]pyrazolo[1,5-a][1,3,5]triazin-4-amine
12	8-(3,4-dimethoxyphenyl)-2,7-dimethyl-N-[(1-oxidopyridin-1-ium-4-yl)methyl]pyrazolo[1,5-a][1,3,5]triazin-4-amine
13	8-(3,4-dimethoxyphenyl)-N-[(6-methoxy-3-pyridyl)methyl]-2,7-dimethyl-pyrazolo[1,5-a][1,3,5]triazin-4-amine
14	4-[[[8-(3,4-dimethoxyphenyl)-2,7-dimethyl-pyrazolo[1,5-a][1,3,5]triazin-4-yl]amino]methyl]benzenesulfonamide
15	N-(cyclohexylmethyl)-8-(3,4-dimethoxyphenyl)-2,7-dimethyl-pyrazolo[1,5-a][1,3,5]triazin-4-amine
16	N-(1,3-benzodioxol-5-ylmethyl)-8-(3,4-dimethoxyphenyl)-2,7-dimethyl-pyrazolo[1,5-a][1,3,5]triazin-4-amine
17	4-[[[8-(3,4-dimethoxyphenyl)-2,7-dimethyl-pyrazolo[1,5-a][1,3,5]triazin-4-yl]amino]methyl]phenol
18	8-(3,4-dimethoxyphenyl)-2,7-dimethyl-N-(tetrahydrofuran-2-ylmethyl)pyrazolo[1,5-a][1,3,5]triazin-4-amine
19	N-[4-[[[8-(3,4-dimethoxyphenyl)-2,7-dimethyl-pyrazolo[1,5-a][1,3,5]triazin-4-yl]amino]methyl]phenyl]methanesulfonamide
20	N-benzyl-8-(3,4-dimethoxyphenyl)-2,7-dimethyl-pyrazolo[1,5-a][1,3,5]triazin-4-amine
21	8-(3,4-dimethoxyphenyl)-2,7-dimethyl-N-(2-thienylmethyl)pyrazolo[1,5-a][1,3,5]triazin-4-amine
22	8-(3,4-dimethoxyphenyl)-2,7-dimethyl-N-(3-pyridylmethyl)pyrazolo[1,5-a][1,3,5]triazin-4-amine
23	8-(3,4-dimethoxyphenyl)-2,7-dimethyl-N-[(5-methyl-2-furyl)methyl]pyrazolo[1,5-a][1,3,5]triazin-4-amine
24	methyl N-[4-[[[8-(3,4-dimethoxyphenyl)-2,7-dimethyl-pyrazolo[1,5-a][1,3,5]triazin-4-yl]amino]methyl]phenyl]sulfonylcarbamate
25	N-[4-[[[8-(3,4-dimethoxyphenyl)-2,7-dimethyl-pyrazolo[1,5-a][1,3,5]triazin-4-yl]amino]methyl]phenyl]sulfonylpropanamide
26	N-methyl-4-[[[8-(3,4-dimethoxyphenyl)-2,7-dimethyl-pyrazolo[1,5-a][1,3,5]triazin-4-yl]amino]methyl]benzenesulfonamide
27	8-(3,4-dimethoxyphenyl)-2,7-dimethyl-N-[(1-methyl-1H-pyrazol-3-yl)methyl]pyrazolo[1,5-a][1,3,5]triazin-4-amine
28	8-(3,4-dimethoxyphenyl)-2,7-dimethyl-N-[(1,3-oxazol-5-yl)methyl]pyrazolo[1,5-a][1,3,5]triazin-4-amine

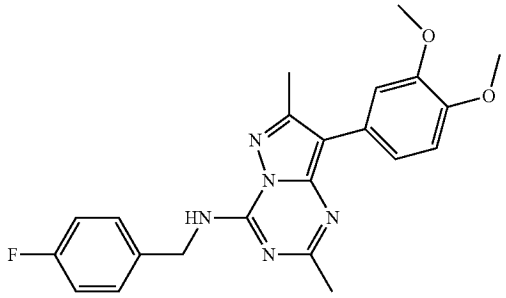
TABLE 1-continued

Ex.	Chemical name
29	8-(3,4-dimethoxyphenyl)-2,7-dimethyl-N-[(piperidin-4-yl)methyl]pyrazolo[1,5-a][1,3,5]triazin-4-amine
30	8-(3,4-dimethoxyphenyl)-2,7-dimethyl-N-[(2-methylpyrimidin-5-yl)methyl]pyrazolo[1,5-a][1,3,5]triazin-4-amine
31	8-(3,4-dimethoxyphenyl)-2,7-dimethyl-N-[(pyridazin-4-yl)methyl]pyrazolo[1,5-a][1,3,5]triazin-4-amine
32	8-(3,4-dimethoxyphenyl)-2,7-dimethyl-N-[(6-methylpyridin-3-yl)methyl]pyrazolo[1,5-a][1,3,5]triazin-4-amine

The structural formulas of the compounds of Examples 1-32 are shown in Table 2.

TABLE 2

Ex. 1



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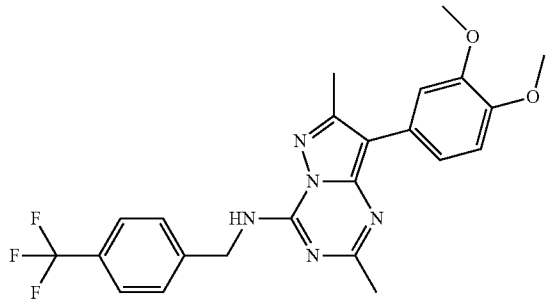

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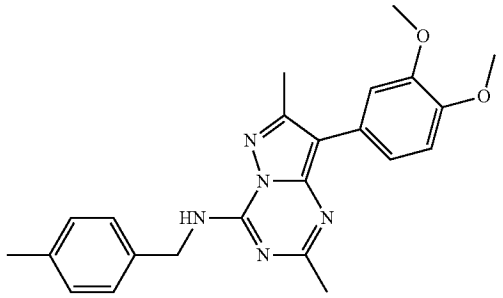

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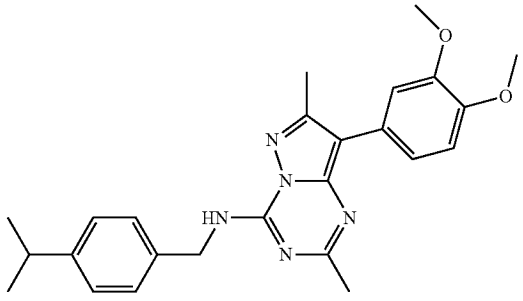

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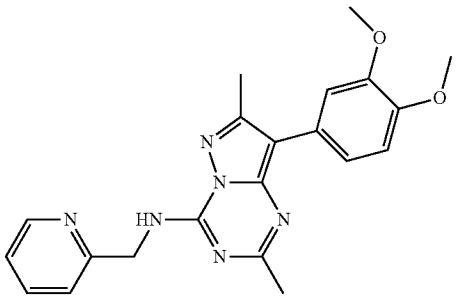
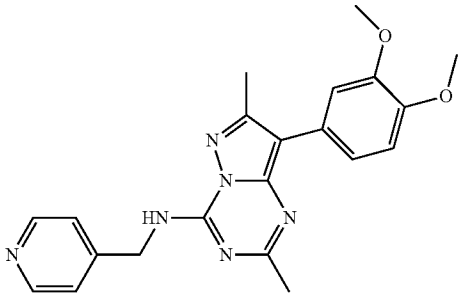
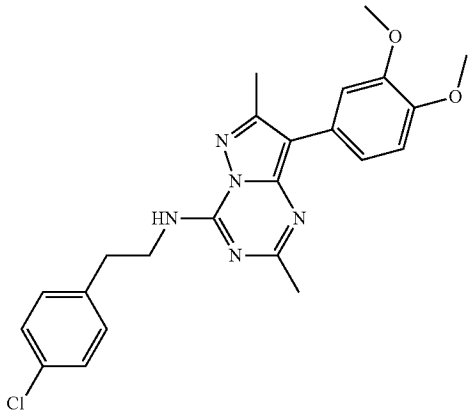
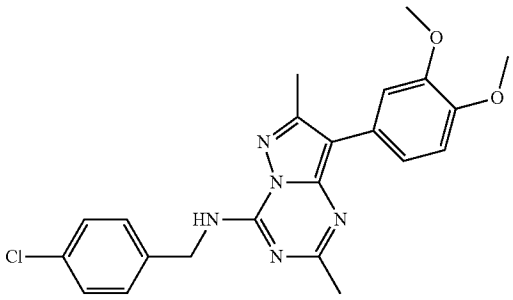
Ex. 5	
Ex. 6	
Ex. 7	
Ex. 8	

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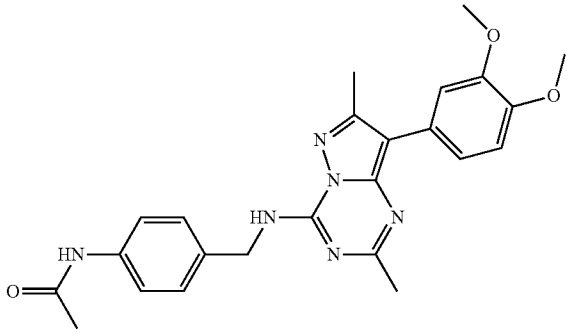

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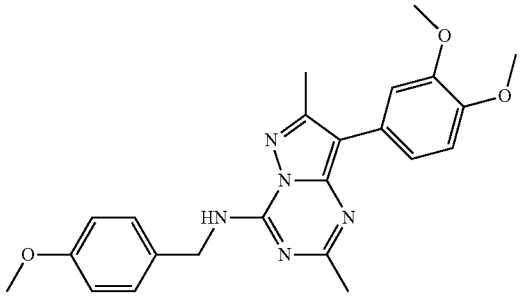

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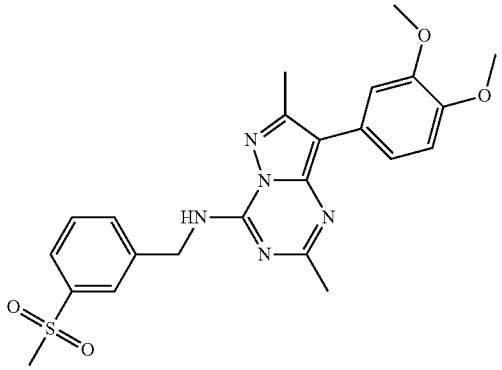

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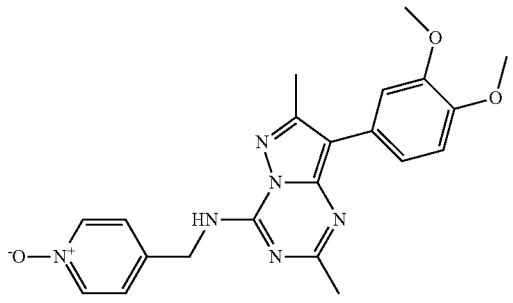

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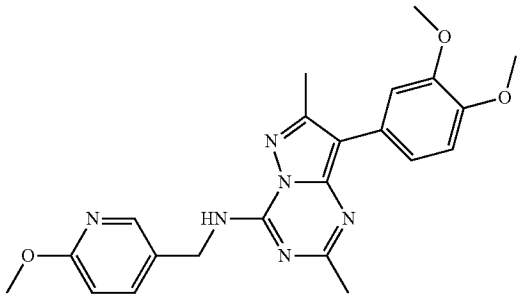

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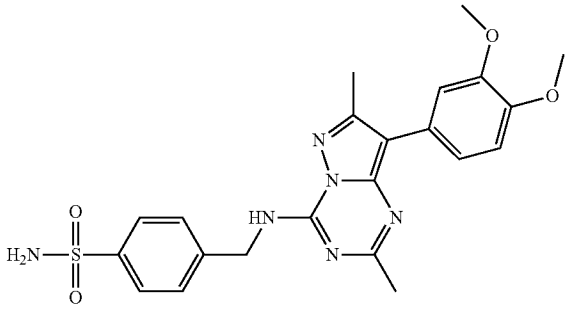
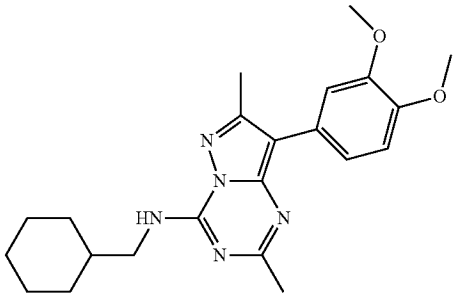
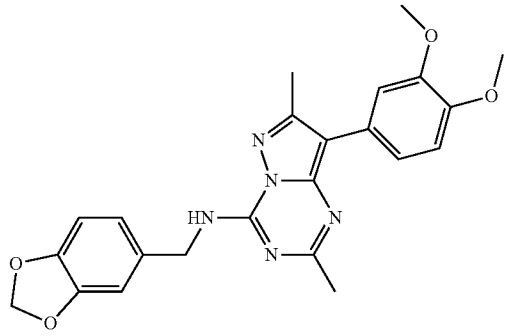
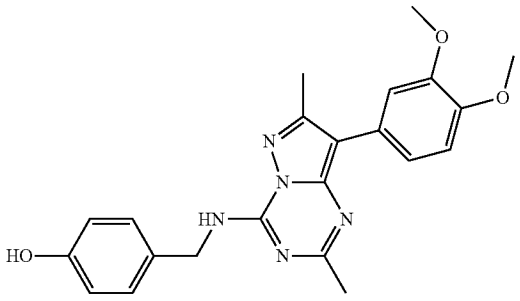
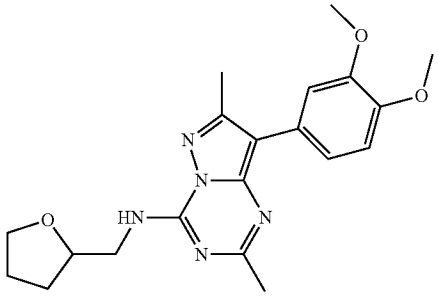
Ex. 14	
Ex. 15	
Ex. 16	
Ex. 17	
Ex. 18	

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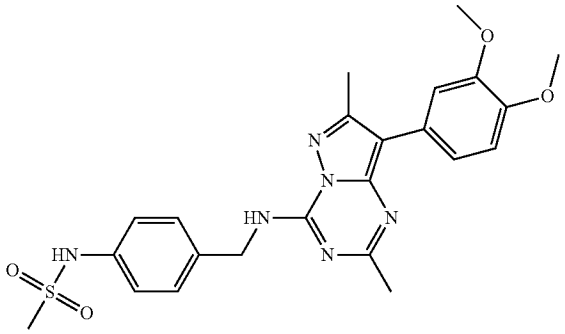
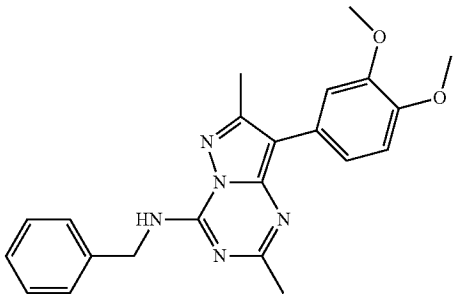
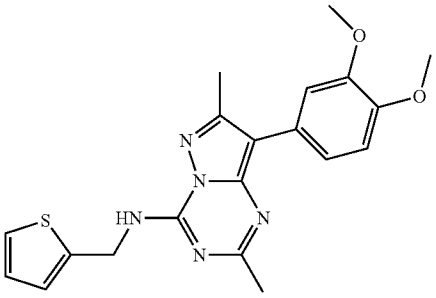
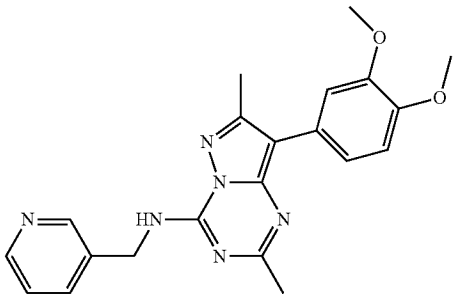
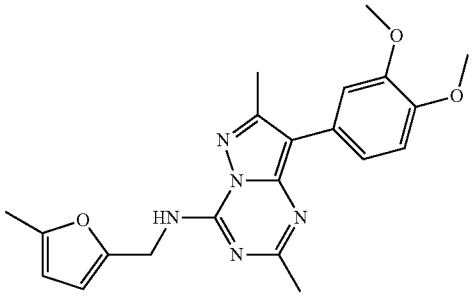
Ex. 19	
Ex. 20	
Ex. 21	
Ex. 22	
Ex. 23	

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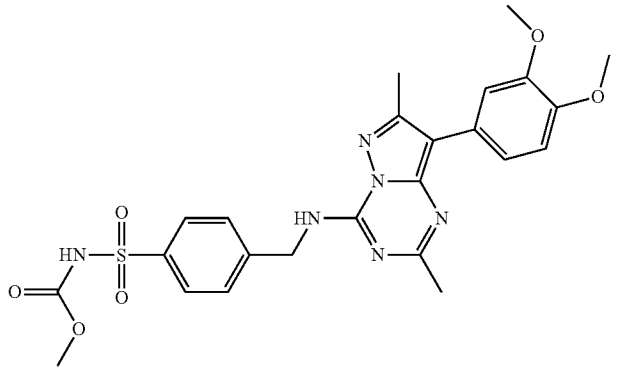

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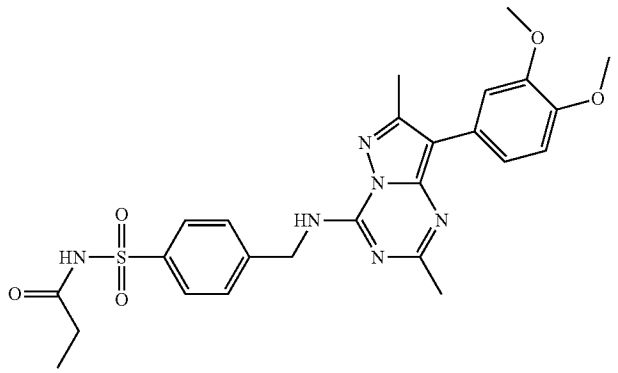

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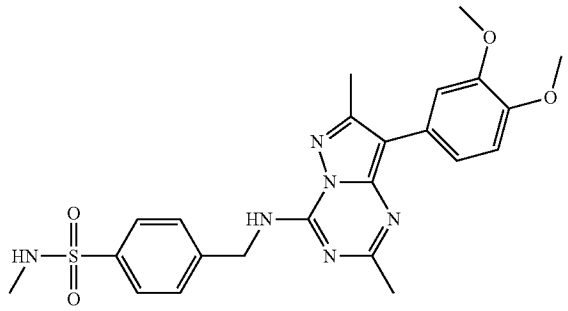

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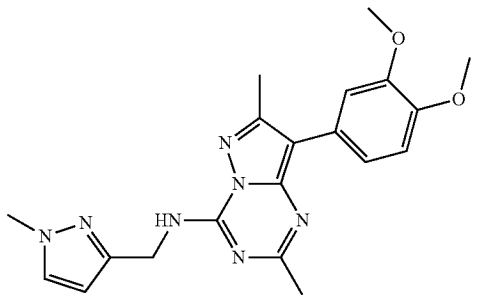

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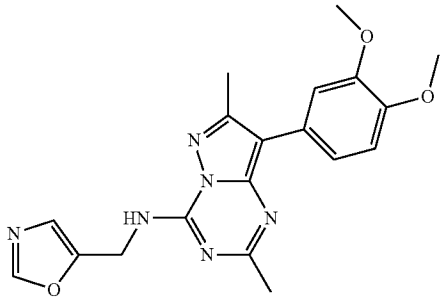
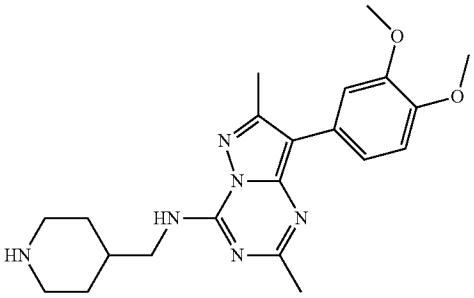
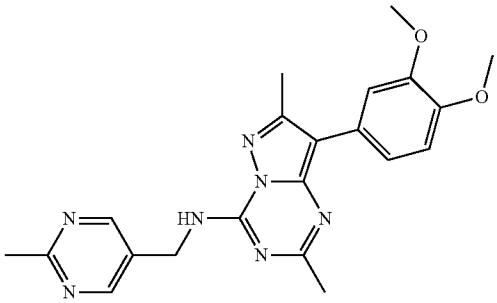
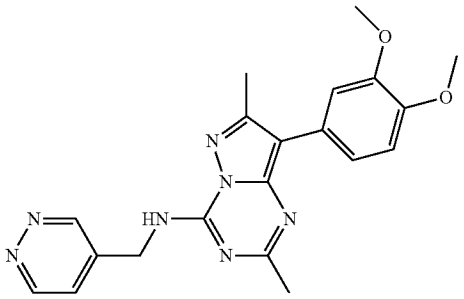
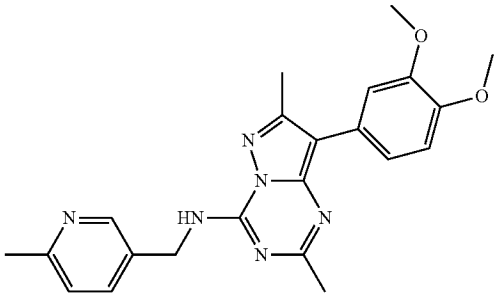
Ex. 28	
Ex. 29	
Ex. 30	
Ex. 31	
Ex. 32	

Analytical data for the compounds of Examples 1-32 are shown in Table 3.

TABLE 3

Ex.	Analytical Data
1	^{1}H-NMR (DMSO, 300 MHz): δ 8.35 (t, 1 H), 7.42 (t, 2 H), 7.12 (t, 2 H), 7.03 (d, 1 H), 6.93 (d, 1 H), 6.66 (s, 1 H), 4.66 (d, 2 H), 3.78 (d, 6 H), 2.44 (s, 3 H), 2.24 (s, 3 H), LCMS: 407.6 [M + H], HPLC purity: 99.98%
2	^{1}H-NMR (MeOD, 300 MHz): δ 7.31 (d, 2 H), 7.23 (d, 1 H), 7.17 (d, 2 H), 7.10 (d, 1 H), 7.05 (d, 1 H), 4.79 (d, 2 H), 3.89 (d, 6 H), 2.50 (s, 3 H), 2.46 (s, 3 H), 2.33 (s, 3 H), LCMS: 404.6 [M + H], HPLC purity: 99.59%
3	^{1}H-NMR (CDCl3, 300 MHz): δ 7.65 (d, 2 H), 7.55 (d, 2 H), 7.18 (d, 1 H), 6.98 (d, 1 H), 6.81 (d, 1 H), 4.95 (d, 2 H), 3.96 (d, 6 H), 2.57 (s, 3 H), 2.55 (s, 3 H), LCMS: 458.6 [M + H], HPLC purity: 99.89%
4	^{1}H-NMR (MeOD, 300 MHz): δ 7.33 (d, 2 H), 7.22 (t, 3 H), 7.09 (d, 1 H), 7.04 (d, 1 4 H), 4.79 (s, 2 H), 3.89 (d, 6 H), 2.89 (m, 1 H), 2.49 (s, 3 H), 2.46 (s, 3 H), 1.25 (s, 3 H), 1.29 (s, 3 H), LCMS: 432.7 [M + H], HPLC purity: 99.87%
5	^{1}H-NMR (MeOD, 300 MHz): δ 8.55 (d, 1 H), 7.83 (t, 1 H), 7.50 (d, 1 H), 7.35 (dd, 1 H), 7.25 (d, 1 H), 7.12 (dd, 1 H), 7.05 (d, 1 H), 4.96 (s, 2 H), 3.89 (d, 6 H), 2.53 (s, 3 H), 2.43 (s, 3 H), LCMS: 391.6 [M + H], HPLC purity: 98.99%
6	^{1}H-NMR (MeOD, 300 MHz): δ 8.78 (d, 2 H), 8.06 (d, 2 H), 7.23 (d, 1 H), 7.13 (d, 1 H), 7.06 (d, 1 H), 5.13 (s, 2 H), 3.89 (d, 6 H), 2.54 (s, 3 H), 2.42 (s, 3 H), LCMS: 391.4 [M + H], HPLC purity: 96.53%
7	^{1}H-NMR (MeOD, 300 MHz): δ 7.28 (s, 4 H), 7.22 (d, 1 H), 7.09 (d, 1 H), 7.04 (d, 1 7 H), 3.89 (d, 6 H), 3.84 (t, 2 H), 3.01 (t, 2 H), 2.49 (s, 3 H), 2.44 (s, 3 H), LCMS: 438.5 [M + H], HPLC purity: 99.45%
8	^{1}H-NMR (DMSO, 300 MHz): δ 7.39 (s, 4 H), 7.30 (d, 1 H), 7.17 (dd, 1 H), 7.04 (d, 1 H), 4.69 (d, 2 H), 3.79 (d, 6 H), 2.49 (s, 3 H), 2.38 (s, 3 H), LCMS: 424.7 [M + H], HPLC purity: 99.94%
9	^{1}H-NMR (MeOD, 300 MHz): δ 7.79 (d, 2 H), 7.63 (d, 2 H), 7.28 (d, 1 H), 7.15 (dd, 1 H), 7.96 (d, 1 H) 3.90 (d, 6 H), 2.57 (s, 3 H), 2.50 (s, 3 H), 2.15 (s, 3 H), LCMS: 433.6 [M + H], HPLC purity: 98.27%
10	^{1}H-NMR (MeOD, 300 MHz): δ 7.35 (d, 2 H), 7.23 (s, 1 H), 7.11 (m, 1 H), 7.05 (d, 1 H), 6.90 (d, 2 H), 4.75 (s, 2 H), 3.89 (d, 6 H), 3.78 (s, 2 H), 2.49 (d, 6 H), LCMS: 420.5 [M + H], HPLC purity: 99.64%
11	^{1}H-NMR (TFA, 300 MHz): δ 11.58, (s, 1 H), 8.25 (s, 1H), 8.03 (d, 1 H), 7.92 (d, 1 H), 7.74 (t, 1 H), 7.14 (d, 1 H), 6.98 (t, 2 H), 5.26 (s, 2 H), 4.01 (s, 3 H), 3.97 (s, 3 H), 3.30 (s, 3 H), 2.77 (s, 3 H), 2.51 (s, 3 H), LCMS: 468.3 [M + H], HPLC purity: 99.86%
12	^{1}H-NMR (DMSO, 300 MHz): δ 9.25, (t, 1 H), 8.15 (d, 2H), 7.38 (d, 1 H), 7.30 (d, 1 H), 7.17 (dd, 1 H), 7.02 (d, 1 H), 4.67 (d, 2 H), 3.78 (d, 6 H), 2.52 (s, 3 H), 2.37 (s, 3 H), LCMS: 407.8 [M + H], HPLC purity: 98.86%
13	^{1}H-NMR (DMSO, 300 MHz): δ 9.19, (t, 1 H), 8.20 (d, 2H), 7.76 (dd, 1 H), 7.29 (d, 1 H), 7.17 (dd, 1 H), 7.02 (d, 1 H), 6.78 (d, 1 H), 4.63 (d, 2 H), 3.92 (s, 3 H), 3.78, (s, 3 H), 2.41 (s, 3 H), LCMS: 421.7 [M + H], HPLC purity: 99.54%
14	^{1}H-NMR (DMSO, 300 MHz): δ 9.29, (t, 1 H), 7.78 (d, 2H), 7.54 (d, 2 H), 7.31 (s, 1 H), 7.29 (d, 2 H), 7.17 (dd, 1 H), 7.03 (d, 1 H), 4.78 (d, 2 H), 3.79 (d, 6 H), 2.53 (s, 3 H), 2.36 (s, 3 H), LCMS: 469.8 [M + H], HPLC purity: 98.53%
15	H-NMR (DMSO, 300 MHz): δ7.22 (s, 1 H), 7.09 (dd, 1 H), 7.03 (d, 1 H), 3.88 (d, 6 H), 3.48 (d, 2 H), 2.49 (s, 3 H), 2.44 (s, 3 H), 1.78 (m, 6 H), 1.28 (m, 4 H), 1.06 (m, 2 H), LCMS: 396.4 [M + H], HPLC purity: 99.77%
16	^{1}H-NMR (DMSO, 300 MHz): δ 9.12, (t, 1 H), 7.30 (d, 1H), 7.17 (dd, 1 H), 7.02 (d, 1 H), 6.97 (d, 1 H), 6.85 (s, 2 H), 5.97 (s, 2 H), 4.60 (d, 2 H), 3.78 (s, 6 H), 2.50 (s, 3 H), 2.39 (s, 3 H), LCMS: 434.0 [M + H], HPLC purity: 99.84%
17	^{1}H-NMR (MeOD, 300 MHz): δ 7.26, (d, 2 H), 7.22 (d, 1H), 7.10 (dd, 1 H), 7.03 (d, 1 H), 6.76 (d, 2 H), 4.71 (s, 2 H), 3.88 (s, 6 H), 2.47 (d, 6 H), LCMS: 406.4 [M + H], HPLC purity: 97.37%
18	^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.30 (d, 1 H), 7.17 (dd, 1 H), 6.96 (d, 1 H), 6.73 (br, 1 H), 4.18 (m, 1 H), 3.92 (m, 1 H), 3.94 (s, 3 H), 3.90 (s, 3 H), 3.86 (m, 1 H), 3.82 (m, 1 H), 3.61 (m, 1 H), 2.54 (d, 6 H), 2.08 (m, 1 H), 1.96 (m, 1 H), 1.68 (m, 1 H), LCMS: 384.1 [M + H], HPLC purity: 97.65%
19	^{1}H-NMR (MeOD, 300 MHz): δ 9.68 (s, 1 H), 9.16 (t, 1 H), 7.35 (d, 1H), 7.30 (d, 1 H), 7.16 (m, 3 H), 7.02 (d, 1 H), 4.66 (d, 2 H), 3.78 (s, 6 H), 2.67 (s, 3 H), 2.50 (s, 3 H), 2.32 (s, 3 H), LCMS: 483.1 [M + H], HPLC purity: 99.45%
20	^{1}H-NMR (DMSO, 300 MHz): δ 9.20 (t, 1 H), 7.37 (d, 2 H), 7.30 (m, 3 H), 7.25 (d, 1 H), 7.17 (d, 1 H), 7.02 (d, 1 H), 4.72 (d, 2 H), 3.78 (s, 6 H), 2.50 (s, 3 H), 2.38 (s, 3 H), LCMS: 390.1 [M + H], HPLC purity: 99.90%
21	^{1}H-NMR (DMSO, 300 MHz): δ 9.27 (t, 1 H), 7.39 (dd, 1 H), 7.30 (d, 1 H), 7.09 (d, 1 H), 7.02 (d, 1 H), 6.97 (d, 1 H), 4.84 (d, 2 H), 3.78 (d, 6 H), 2.50 (s, 3 H), 2.43 (s, 3 H), LCMS: 396.1 [M + H], HPLC purity: 99.96%
22	^{1}H-NMR (DMSO, 300 MHz): δ 9.26 (t, 1 H), 8.62 (d, 1 H), 8.47 (dd, 1 H), 7.80 (m, 1 H), 7.35 (dd, 1 H), 7.29 (d, 1 H), 7.17 (dd, 1 H), 7.02 (d, 1 H), 4.72 (d, 2 H), 3.78 (d, 6 H), 2.50 (s, 3 H), 2.39 (s, 3 H), LCMS: 391.1 [M + H], HPLC purity: 99.97%
23	^{1}H-NMR (DMSO, 300 MHz): δ 9.26 (bs, 1 H), 7.30 (d, 1 H), 7.17 (dd, 1 H), 7.02 (d, 1 H), 6.18 (d, 1 H), 5.99 (d, 1 H), 4.63 (d, 2 H), 3.78 (d, 6 H), 2.50 (s, 3 H), 2.40 (s, 3 H), 2.20 (s, 3 H), LCMS: 394.1 [M + H], HPLC purity: 99.61%
24	^{1}H-NMR (DMSO, 300 MHz): δ 12.01 (s, 1 H), 9.30 (t, 1 H), 7.85 (d, 2 H), 7.59 (d, 2 H), 7.30 (s, 1 H), 7.18 (d, 1 H), 7.03 (d, 1 H), 4.80 (d, 2 H), 3.98 (q, 2 H), 3.79 (d, 6 H), 2.52 (s, 3 H), 2.36 (s, 3 H), 1.10 (t, 3 H), LCMS: 541.0 [M + H], HPLC purity: 97.51%

TABLE 3-continued

Ex.	Analytical Data
25	^{1}H-NMR (DMSO, 300 MHz): δ 12.01 (s, 1 H), 9.29 (t, 1 H), 7.88 (d, 2 H), 7.58 (d, 2 H), 7.30 (s, 1 H), 7.18 (d, 1 H), 7.03 (d, 1 H), 4.80 (d, 2 H), 3.79 (d, 6 H), 2.52 (s, 3 H), 2.34 (s, 3 H), 2.18 (t, 2 H), 0.87 (t, 3 H), LCMS: 525.0 [M + H], HPLC purity: 99.96%
26	^{1}H-NMR (DMSO, 300 MHz): δ 9.30 (t, 1 H), 7.75 (d, 2 H), 7.57 (d, 2 H), 7.42 (dd, 1 H), 7.30 (s, 1 H), 7.18 (d, 1 H), 7.03 (d, 1 H), 4.80 (d, 2 H), 3.79 (d, 6 H), 2.52 (s, 3 H), 2.37 (s, 3 H), 2.33 (t, 2 H), LCMS: 483.2 [M + H], HPLC purity: 97.8%
27	^{1}H-NMR (DMSO, 300 MHz): δ 8.90 (t, 1 H), 7.57 (d, 1 H), 7.30 (d, 1 H), 7.18 (dd, 1 H), 7.02 (d, 1 H), 6.18 (d, 1 H), 4.65 (d, 2 H), 3.79 (d, 9 H), 2.52 (s, 3 H), 2.39 (s, 3 H), LCMS: 394.2 [M + H], HPLC purity: 99.0%
28	^{1}H-NMR (DMSO, 300 MHz): δ 8.16 (s, 1 H), 7.23 (d, 1 H), 7.13 (d, 1 H), 7.09 (dd, 1 H), 7.03 (d, 1 H), 4.91 (d, 2 H), 3.87 (d, 6 H), 2.49 (d, 6 H), LCMS: 381.2 [M + H], HPLC purity: 98.3%
29	^{1}H-NMR (MeOD, 300 MHz): δ 7.12 (d, 1 H), 7.01 (d, 2 H), 3.89 (d, 6 H), 3.74 (d, 2 H), 3.45 (d, 2 H), 3.04 (t, 2 H), 2.63 (s, 3 H), 2.45 (s, 3 H), 2.15 (b, 1 H), 2.05 (d, 2 H), 1.60 (b, 2 H), LCMS: 397.2 [M + H], HPLC purity: 99.9%
30	^{1}H-NMR (MeOH, 300 MHz): δ 8.79 (s, 2 H), 7.22 (d, 1 H), 7.10 (dd, 1 H), 7.03 (d, 1 H), 4.80 (s, 2 H), 3.87 (s, 6 H), 2.67 (s, 3 H), 2.49 (s, 3 H), 2.45 (s, 3 H), LCMS: 406.2 [M + H], HPLC purity: 99.4%
31	^{1}H-NMR (MeOD, 300 MHz): δ 9.28 (d, 1 H), 9.13 (dd, 1 H), 7.75 (d, 1 H), 7.23 (d, 1 H), 7.12 (dd, 1 H), 7.03 (d, 1 H), 4.91 (d, 2 H), 3.88 (s, 6 H), 2.51 (s, 3 H), 2.41 (s, 3 H), LCMS: 392.2 [M + H], HPLC purity: 98.8%
32	^{1}H-NMR (DMSO, 300 MHz): δ 9.22 (t, 1 H), 8.48 (d, 1 H), 7.67 (dd, 1 H), 7.29 (d, 1 H), 7.18 (dd, 1 H), 7.03 (d, 1 H), 4.66 (d, 2 H), 3.78 (s, 6 H), 2.42 (s, 3 H), 2.39 (s, 3 H), LCMS: 405.2 [M + H], HPLC purity: 99.9%

BIOLOGICAL ASSAYS

Phosphatidyl Inositol Kinase Inhibition Assay

Inhibition of PI4 kinases was studied using the ADP-Glo™ Kinase Assay which is a luminescent kinase assay that measures ADP formed from a kinase reaction; ADP is converted into ATP, which is converted into light by Ultra-Glo™ Luciferase. The assay is performed in two steps; first, after the kinase reaction, an equal volume of ADP-Glo™ Reagent is added to terminate the kinase reaction and deplete the remaining ATP. In the second step, the Kinase Detection Reagent is added, which simultaneously converts ADP to ATP and allows the newly synthesized ATP to be measured using a coupled luciferase/luciferin reaction. The luminescent signal produced is proportional to the activity of the kinase.

Inhibition of PI3 kinases was studied using the HTRF (homogeneous time-resolved fluorescence) assay which is a universal method for identifying and characterizing the phosphotransferase activity induced by any ATP/ADP dependent target. The formation of ADP is detected by a specific monoclonal antibody labeled with Eu^{3+} cryptate, and directly correlates with the amount of phosphorylated substrate in kinase assays

Table 4 shows test results, expressed as IC_{50} values (in μM) of some compounds of the invention vs. different kinases.

TABLE 4

Kinase	Example 6 IC_{50} (μM)	Example 14 IC_{50} (μM)
PI4KIIIβ	0.0013	0.0021
PI4KIIIα	3.2	1.3
PI3Kβ	>10	>10
PI3Kα	7.3	>10

In Vitro Assay in Mammalian Cell Culture

The antiviral activity of compounds of the invention has been evaluated based on the ability of the compounds to prevent virus from causing viral cytopathic effects (CPE) in mammalian cell culture. Incubation time, cell line, cell density and virus titer differed from assay to assay but the general procedure was as follows: Cells were cultivated on 96 well flat bottom plates to approximately 90% confluence (20 000-90 000 cells/well) in a suitable media. The titer of the virus was determined by the standard method of tissue culture infective dose ($TCID_{50}$) on cells. Briefly, cells were infected with 50 μl of virus suspension, and diluted 10-fold in media. The plates were incubated in 37° C. with 5% CO_2 for 3-7 days and cells were inspected daily for CPE. After determining CPE, plates were stained with Gram's Crystal Violet solution and optical density was read at 540 nm. The highest virus dilution that resulted in >95% CPE was used in the assays. Substances at a final concentration of 2.5-20 μM and the virus were added to the cells and incubated for 3-7 days depending on the virus and cell line used. As controls, uninfected cells and cells infected with virus (no substance) were included on each plate. The cells were stained with crystal violet after determining the CPE on infected controls and the optical density was read at 540 nm. The inhibition capacity was calculated as a % by comparison with non-infected and infected controls.

Table 5 shows the inhibition capacity of compounds of the invention on different enteroviruses. + indicates IC_{50}<1 □M; ++ indicates IC_{50}<100 nM; +++ indicates IC_{50}<10 nM; EV6: Enterovirus 6; EV30: Enterovirus 30; EV68: Enterovirus 68; EV71: Enterovirus 71; B1: coxsackie B1 virus; B2: coxsackie B2 virus; B3: coxsackie B3 virus; B4: coxsackie B 4 virus; B5: coxsackie B5virus; Polio1: polio virus Sabin 1.

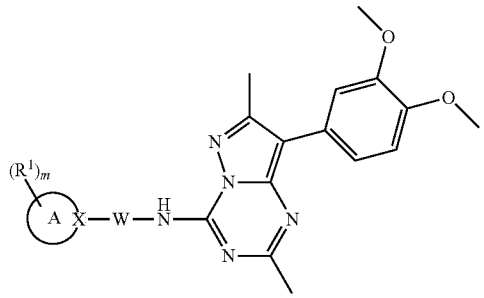
TABLE 5

Ex.	EV6	EV30	EV68	EV71	Bl	B2	B3	B4	B5	Polio 1
1	+	++	nd	+++	++	+++	+	nd	++	+++
2	+	++	+	+	++	++	+	++	++	++
3	+	++	++	++	++	++	++	++	++	++
4	+	+	+	+	+	+	+	+	+	+
5	+	+	+	+	++	++	+	+	+	++
6	+++	++	+++	+++	+++	+++	+++	+++	+++	+++
7	+	+	+	+	+	+	+	+	+	+
8	+	++	++	+	++	++	++	++	+	++
9	++	++	++	++	+	++	++	++	++	+++
10	+	++	++	+	++	++	+	++	++	++
11	++	+++	++	++	+++	+++	+++	+++	+++	+++
12	nd	+	+	+	+	+	+	+	+	+
13	nd	+++	++	++	+++	++	++	++	++	+++
14	nd	+++	+++	+++	++	++	++	++	+++	+++
15	+	+	+	+	+	+	+	+	+	+
16	+	++	++	++	++	++	++	+++	++	++
17	++	++	++	+++	+++	+++	++	++	+++	+++
18	+	+	+	+	+	+	+	+	+	+
19	+	++	++	+++	++	++	++	+++	+	++
20	++	++	++	++	++	++	++	+++	++	++
21	++	++	++	++	+++	+++	++	++	++	++
22	++	++	++	++	++	++	++	++	++	++
23	++	++	++	++	+++	++	++	+++	++	+++
24	–	–	+	+	–	+	–	+	–	+
25	–	–	+	–	–	–	–	–	–	–
26	+	+	–	+	+	++	+	++	+	++
27	+	++	+++	++	+++	+++	++	+++	++	+++
28	++	–	+++	++	++	++	++	++	+	++
29	–	–	–	–	–	–	–	–	–	–
30	+	++	++	++	+	+	+	++	+	++
31	+	–	++	++	+	+	+	+++	+	+
32	++	+++	++	++	++	++	+++	++	++	++

In Table 5 the signs have the following meaning:
+ IC_{50} < 1 μM
++ IC_{50} < 100 nM
+++ IC_{50} < 10 nM
– Not determined or IC_{50} > 1 μM

The invention claimed is:

1. A compound of formula (I)



(I)

or a pharmaceutically acceptable salt thereof, wherein

W is CH_2 or CH_2—CH_2;

X is C;

ring A is phenyl or 5- or 6-membered heteroaryl;

m is an integer of from 0 to 3;

each R^1 is independently selected from C_1-C_6 alkyl optionally substituted by one or more halogen, R^2O, halogen, $R^3R^4NC(O)$, $R^5C(O)N(R^6)$, $R^7OC(O)$, $R^8C(O)O$, $R^9S(O)_2$, $R^{10}S(O)_2N(H)$, $R^{11}C(O)$, $R^{12}R^{13}N$, ^-O and $R^{14}R^{15}NS(O)_2$; and

when m is at least 2, two R^1 attached to adjacent atoms of ring A may form, together with the atoms to which they are attached, a 5- or 6-membered heterocyclic or carbocyclic ring;

each R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13} and R^{14} is independently selected from H and C_1-C_6 alkyl, wherein any alkyl is optionally substituted by one or more halogen;

R^{15} is selected from H, C_1-C_6 alkyl, $R^{16}C(O)$, $R^{17}OC(O)$, and $R^{18}R^{19}NC(O)$; and

each R^{16}, R^{17}, R^{18}, and R^{19} is independently selected from H and C_1-C_6 alkyl, wherein any alkyl is optionally substituted by one or more halogen.

2. The compound of claim **1**, or a pharmaceutically acceptable salt thereof, wherein ring A is 5 or 6-membered heteroaryl.

3. The compound of claim **1**, or a pharmaceutically acceptable salt thereof, wherein ring A is phenyl.

4. The compound of claim **1**, or a pharmaceutically acceptable salt thereof, wherein ring A is 6-membered heteroaryl.

5. The compound of claim **1**, or a pharmaceutically acceptable salt thereof, wherein W is CH_2.

6. The compound of claim **1**, or a pharmaceutically acceptable salt thereof, wherein m is an integer of from 0 to 2.

7. The compound of claim **6**, or a pharmaceutically acceptable salt thereof, wherein m is 1 or 2.

8. The compound of claim **6**, or a pharmaceutically acceptable salt thereof, wherein W is CH_2.

9. A compound according to claim **1**, selected from

8-(3,4-dimethoxyphenyl)-N-[(4-fluorophenyl)methyl]-2,7-dimethyl-pyrazolo[1,5-a][1,3,5]triazin-4-amine,

8-(3,4-dimethoxyphenyl)-2,7-dimethyl-N-[[4-(trifluoromethyl)phenyl]methyl]pyrazolo[1,5-a][1,3,5]triazin-4-amine,

8-(3,4-dimethoxyphenyl)-2,7-dimethyl-N-(p-tolylmethyl)pyrazolo[1,5-a][1,3,5]triazin-4-amine,
8-(3,4-dimethoxyphenyl)-N-[(4-isopropylphenyl)methyl]-2,7-dimethyl-pyrazolo[1,5-a][1,3,5]triazin-4-amine,
8-(3,4-dimethoxyphenyl)-2,7-dimethyl-N-(2-pyridylmethyl)pyrazolo[1,5-a][1,3,5]triazin-4-amine,
8-(3,4-dimethoxyphenyl)-2,7-dimethyl-N-(4-pyridylmethyl)pyrazolo[1,5-a][1,3,5]triazin-4-amine,
N-[2-(4-chlorophenyl)ethyl]-8-(3,4-dimethoxyphenyl)-2,7-dimethyl-pyrazolo[1,5-a][1,3,5]triazin-4-amine,
N-[(4-chlorophenyl)methyl]-8-(3,4-dimethoxyphenyl)-2,7-dimethyl-pyrazolo[1,5-a][1,3,5]triazin-4-amine,
N-[4-[[[8-(3,4-dimethoxyphenyl)-2,7-dimethyl-pyrazolo[1,5-a][1,3,5]triazin-4-yl]amino]methyl]phenyl]acetamide,
8-(3,4-dimethoxyphenyl)-N-[(4-methoxyphenyl)methyl]-2,7-dimethyl-pyrazolo[1,5-a][1,3,5]triazin-4-amine,
8-(3,4-dimethoxyphenyl)-2,7-dimethyl-N-[(3-methylsulfonylphenyl)methyl]pyrazolo[1,5-a][1,3,5]triazin-4-amine,
8-(3,4-dimethoxyphenyl)-2,7-dimethyl-N-[(1-oxidopyridin-1-ium-4-yl)methyl]pyrazolo[1,5-a][1,3,5]triazin-4-amine,
8-(3,4-dimethoxyphenyl)-N-[(6-methoxy-3-pyridyl)methyl]-2,7-dimethyl-pyrazolo[1,5-a][1,3,5]triazin-4-amine,
4-[[[8-(3,4-dimethoxyphenyl)-2,7-dimethyl-pyrazolo[1,5-a][1,3,5]triazin-4-yl]amino]methyl]benzenesulfonamide,
N-(1,3-benzodioxol-5-ylmethyl)-8-(3,4-dimethoxyphenyl)-2,7-dimethyl-pyrazolo[1,5-a][1,3,5]triazin-4-amine,
4-[[[8-(3,4-dimethoxyphenyl)-2,7-dimethyl-pyrazolo[1,5-a][1,3,5]triazin-4-yl]amino]methyl]phenol
N-[4-[[[8-(3,4-dimethoxyphenyl)-2,7-dimethyl-pyrazolo[1,5-a][1,3,5]triazin-4-yl]amino]methyl]phenyl]methanesulfonamide,
N-benzyl-8-(3,4-dimethoxyphenyl)-2,7-dimethyl-pyrazolo[1,5-a][1,3,5]triazin-4-amine,
8-(3,4-dimethoxyphenyl)-2,7-dimethyl-N-(2-thienylmethyl)pyrazolo[1,5-a][1,3,5]triazin-4-amine,
8-(3,4-dimethoxyphenyl)-2,7-dimethyl-N-(3-pyridylmethyl)pyrazolo[1,5-a][1,3,5]triazin-4-amine,
8-(3,4-dimethoxyphenyl)-2,7-dimethyl-N-[(5-methyl-2-furyl)methyl]pyrazolo[1,5-a][1,3,5]triazin-4-amine,
methyl N-[4-[[[8-(3,4-dimethoxyphenyl)-2,7-dimethyl-pyrazolo[1,5-a][1,3,5]triazin-4-yl]amino]methyl]phenyl]sulfonylcarbamate,
N-[4-[[[8-(3,4-dimethoxyphenyl)-2,7-dimethyl-pyrazolo[1,5-a][1,3,5]triazin-4-yl]amino]methyl]phenyl]sulfonylpropanamide,
N-methyl-4-[[[8-(3,4-dimethoxyphenyl)-2,7-dimethyl-pyrazolo[1,5-a][1,3,5]triazin-4-yl]amino]methyl]benzenesulfonamide,
8-(3,4-dimethoxyphenyl)-2,7-dimethyl-N-[(1-methyl-1H-pyrazol-3-yl)methyl]pyrazolo[1,5-a][1,3,5]triazin-4-amine,
8-(3,4-dimethoxyphenyl)-2,7-dimethyl-N-[(1,3-oxazol-5-yl)methyl]pyrazolo[1,5-a][1,3,5]triazin-4-amine,
8-(3,4-dimethoxyphenyl)-2,7-dimethyl-N-[(2-methylpyrimidin-5-yl)methyl]pyrazolo[1,5-a][1,3,5]triazin-4-amine,
8-(3,4-dimethoxyphenyl)-2,7-dimethyl-N-[(pyridazin-4-yl)methyl]pyrazolo[1,5-a][1,3,5]triazin-4-amine, and
8-(3,4-dimethoxyphenyl)-2,7-dimethyl-N-[(6-methylpyridin-3-yl)methyl]pyrazolo[1,5-a][1,3,5]triazin-4-amine,

or a pharmaceutically acceptable salt thereof.

10. A pharmaceutical composition comprising a compound according to claim **1** and optionally a pharmaceutically acceptable excipient.

11. A method of treatment of a viral infection by administering a compound according to claim **1** to a mammal in need thereof.

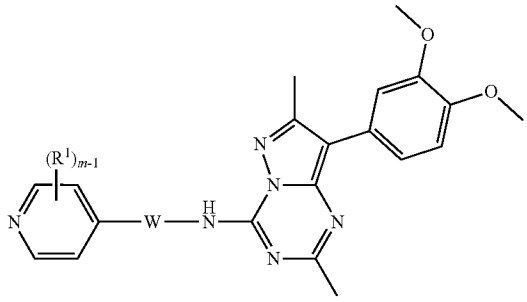
12. The compound of claim **2**, or a pharmaceutically acceptable salt thereof, wherein W is CH_2.

13. The compound of claim **3**, or a pharmaceutically acceptable salt thereof, wherein W is CH_2.

14. The compound of claim **4**, or a pharmaceutically acceptable salt thereof, wherein W is CH_2.

15. The compound of claim **1**, having the formula (Ie)

(Ie)



or a pharmaceutically acceptable salt thereof,

wherein R^1 and W are as defined in claim **1**; and m is 1, 2, or 3.

16. The compound of claim **15**, wherein m is 1 or 2.

17. The compound of claim **15**, wherein W is CH_2.

* * * * *

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15/737,907 **PYRAZOLO[1,5-A]TRIAZIN-4-AMINE DERIVATIVES USEFUL IN THERAPY** **BRNNP0174WOUS** **(/pair/PAIRPrintServlet)**

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Bibliographic Data

Application Number:	15/737,907	Correspondence Address Customer Number:	23908
Filing or 371 (c) Date:	12-19-2017	Status:	Patented Case
Application Type:	Utility	Status Date:	08-21-2019
Examiner Name:	SACKEY, EBENEZER O	Location: (http://www.uspto.gov/ebc/portal/info_location.htm)	ELECTRONIC
Group Art Unit:	1624	Location Date:	-
Confirmation Number:	7015	Earliest Publication No:	US 2018-0298007 A1
Attorney Docket Number:	BRNNP0174WOUS	Earliest Publication Date:	10-18-2018
Class / Subclass:	514/246	Patent Number:	10,407,429
First Named Inventor:	Jacob WESTMAN , Järlåsa, (SE) all Inventors	Issue Date of Patent:	09-10-2019
First Named Applicant:	Curovir AB , Kalmar, (SE) all Applicants	International Registration Number (Hague):	-
Entity Status:	Small	International Registration Publication Date:	-
AIA (First Inventor to File):	Yes		

Title of Invention: PYRAZOLO[1,5-A]TRIAZIN-4-AMINE DERIVATIVES USEFUL IN THERAPY

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Reports (http://www.uspto.gov/main/checkstatus.htm)

Transaction History

Date	Transaction Description
09-10-2019	Recordation of Patent Grant Mailed
08-22-2019	Email Notification
08-21-2019	Issue Notification Mailed
09-10-2019	Patent Issue Date Used in PTA Calculation
08-06-2019	Dispatch to FDC
08-01-2019	Application Is Considered Ready for Issue
07-25-2019	Issue Fee Payment Verified
07-25-2019	Issue Fee Payment Received
04-29-2019	Electronic Review
04-29-2019	Email Notification
04-29-2019	Mail Notice of Allowance
04-25-2019	Notice of Allowance Data Verification Completed
04-24-2019	Examiner's Amendment Communication
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03-02-2019	Case Docketed to Examiner in GAU
01-18-2019	Date Forwarded to Examiner
01-02-2019	Response after Non-Final Action
10-19-2018	Email Notification
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10-18-2018	PG-Pub Issue Notification
10-05-2018	Electronic Review
10-05-2018	Email Notification
10-05-2018	Mail Non-Final Rejection
09-29-2018	Non-Final Rejection
09-27-2018	Information Disclosure Statement considered
08-23-2018	Case Docketed to Examiner in GAU
12-19-2017	Request for Foreign Priority (Priority Papers May Be Included)
12-19-2017	Information Disclosure Statement (IDS) Filed
07-26-2018	Application Is Now Complete
07-26-2018	Application Dispatched from OIPE
07-13-2018	Email Notification
07-13-2018	Email Notification
12-19-2017	371 Completion Date
07-12-2018	Sent to Classification Contractor
07-12-2018	FITF set to YES - revise initial setting
12-19-2017	Patent Term Adjustment - Ready for Examination
07-13-2018	Notice of DO/EO Acceptance Mailed
07-13-2018	Filing Receipt
12-19-2017	PTO/SB/69-Authorize EPO Access to Search Results
12-19-2017	Applicants have given acceptable permission for participating foreign
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Available Documents

Mail Room Date	Document Code	Document Description	Document Category	Page Count
08-21-2019	ISSUE.NTF	Issue Notification	PROSECUTION	1
07-25-2019	IFEE	Issue Fee Payment (PTO-85B)	PROSECUTION	1
07-25-2019	WFEE	Fee Worksheet (SB06)	PROSECUTION	2
07-25-2019	N417	EFS Acknowledgment Receipt	PROSECUTION	2
04-29-2019	NOA	Notice of Allowance and Fees Due (PTOL-85)	PROSECUTION	7
04-29-2019	IIFW	Issue Information including classification, examiner, name, claim, renumbering, etc.	PROSECUTION	3
04-29-2019	SRFW	Search information including classification, databases and other search related notes	PROSECUTION	1
01-02-2019	A...	Amendment/Req. Reconsideration-After Non-Final Reject	PROSECUTION	1
01-02-2019	CLM	Claims	PROSECUTION	6
01-02-2019	REM	Applicant Arguments/Remarks Made in an Amendment	PROSECUTION	2
01-02-2019	N417	EFS Acknowledgment Receipt	PROSECUTION	2
01-02-2019	WFEE	Fee Worksheet (SB06)	PROSECUTION	1
10-18-2018	NTC.PUB	Notice of Publication	PROSECUTION	1
10-05-2018	CTNF	Non-Final Rejection	PROSECUTION	6
10-05-2018	FWCLM	Index of Claims	PROSECUTION	1
10-05-2018	SRFW	Search information including classification, databases and other search related notes	PROSECUTION	1
10-05-2018	BIB	Bibliographic Data Sheet	PROSECUTION	1
10-05-2018	1449	List of References cited by applicant and considered by examiner	PROSECUTION	5
10-05-2018	1449	List of References cited by applicant and considered by examiner	PROSECUTION	5
07-13-2018	APP.FILE.REC	Filing Receipt	PROSECUTION	3
07-13-2018	WFEE	Fee Worksheet (SB06)	PROSECUTION	1
07-13-2018	WCLM	Claims Worksheet (PTO-2022)	PROSECUTION	1
07-13-2018	M903	Notice of DO/EO Acceptance Mailed	PROSECUTION	2
12-19-2017	TRNA	Transmittal of New Application	PROSECUTION	4
12-19-2017	371P	Documents submitted with 371 Applications	PROSECUTION	41
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12-19-2017	371P	Documents submitted with 371 Applications	PROSECUTION	6
12-19-2017	371P	Documents submitted with 371 Applications	PROSECUTION	6
12-19-2017	OATH	Oath or Declaration filed	PROSECUTION	1
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12-19-2017	A.PE	Preliminary Amendment	PROSECUTION	1
12-19-2017	SPEC	Specification	PROSECUTION	1
12-19-2017	CLM	Claims	PROSECUTION	
12-19-2017	REM	Applicant Arguments/Remarks Made in an Amendment	PROSECUTION	

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12-19-2017	FOR	Foreign Reference	PROSECUTION	133	
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12-19-2017	NPL	Non Patent Literature	PROSECUTION	27	
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12-19-2017	NPL	Non Patent Literature	PROSECUTION	11	
12-19-2017	NPL	Non Patent Literature	PROSECUTION	5	
12-19-2017	NPL	Non Patent Literature	PROSECUTION	11	
12-19-2017	NPL	Non Patent Literature	PROSECUTION	17	
12-19-2017	NPL	Non Patent Literature	PROSECUTION	8	
12-19-2017	NPL	Non Patent Literature	PROSECUTION	7	
12-19-2017	NPL	Non Patent Literature	PROSECUTION	6	
12-19-2017	WFEE	Fee Worksheet (SB06)	PROSECUTION	2	
12-19-2017	N417	EFS Acknowledgment Receipt	PROSECUTION	6	
12-19-2017	P.306	IB/306 - Notification of the Recording of a Change	PROSECUTION	1	
12-19-2017	P.N.101.CONV	RO/101 - Request form for new IA - Conventional	PROSECUTION	4	
12-19-2017	FRPR	Certified Copy of Foreign Priority Application	PROSECUTION	38	
12-19-2017	P.SRNT.IN	PCT Search Strategy and results	PROSECUTION	1	
12-19-2017	ABST	Abstract	PROSECUTION	1	
12-19-2017	SPEC	Specification	PROSECUTION	35	
12-19-2017	CLM	Claims	PROSECUTION	5	
12-19-2017	371P	Documents submitted with 371 Applications	PROSECUTION	1	
12-19-2017	371P	Documents submitted with 371 Applications	PROSECUTION	7	

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Patent Term Adjustment

Filing or 371(c) Date:	12-19-2017	Overlapping Days Between {A and B} or {A and C}:	0
Issue Date of Patent:	09-10-2019	Non-Overlapping USPTO Delays:	0
A Delays:	0	PTO Manual Adjustments:	0
B Delays:	0	Applicant Delays:	0
C Delays:	0	Total PTA Adjustments:	0

Patent Term Adjustment History **Explanation Of Calculations**

Number	Date	Contents Description	PTO(Days)	APPL(Days)	Start
62.5	09-10-2019	PTA 36 Months			62.4
62.4	12-19-2017	Commencement Date			0
62	09-10-2019	Patent Issue Date Used in PTA Calculation			0
61	08-07-2019	Export to Final Data Capture			0
60	08-06-2019	Dispatch to FDC			0
59	08-01-2019	Application Is Considered Ready for Issue			0
58	07-25-2019	Issue Fee Payment Verified			0
57	07-25-2019	Issue Fee Payment Received			0
56	06-21-2019	Finished Initial Data Capture			0
55	04-29-2019	Electronic Review			0
54	04-26-2019	Export to Initial Data Capture			0
53	04-29-2019	Email Notification			0
52	04-29-2019	Mail Notice of Allowance			0
51	04-25-2019	Office Action Review			0
50	04-25-2019	Office Action Review			0
49	04-25-2019	Issue Revision Completed			0
48	04-25-2019	Document Verification			0
47	04-25-2019	Notice of Allowance Data Verification Completed			0
46	04-24-2019	Examiner's Amendment Communication			0
45	04-24-2019	Allowability Notice			0
44	03-19-2019	Not Inherited			0
43	03-19-2019	Case Docketed to Examiner in GAU			0
42	03-02-2019	case Inherited			
41	03-02-2019	Case Docketed to Examiner in GAU			

38	01-18-2019	Date Forwarded to Examiner			0
37	01-02-2019	Response after Non-Final Action			0
36	10-19-2018	Email Notification			0
35	10-18-2018	Application ready for PDX access by participating foreign offices			0
34	10-18-2018	PG-Pub Issue Notification			0
33	10-05-2018	Electronic Review			0
32	10-05-2018	Email Notification			0
31	10-05-2018	Mail Non-Final Rejection			0
30	09-29-2018	Non-Final Rejection			0
25	09-27-2018	Information Disclosure Statement considered			0
21	08-23-2018	Case Docketed to Examiner in GAU			0
20	12-19-2017	Request for Foreign Priority (Priority Papers May Be Included)			0
19	12-19-2017	Information Disclosure Statement (IDS) Filed			0
18	07-26-2018	Application Is Now Complete			0
17	07-26-2018	Application Dispatched from OIPE			0
16	07-13-2018	Email Notification			0
15	07-13-2018	Email Notification			0
14	12-19-2017	371 Completion Date			0
13	07-12-2018	Sent to Classification Contractor			0
12	07-12-2018	FITF set to YES - revise initial setting			0
11	12-19-2017	Patent Term Adjustment - Ready for Examination			0
10	07-13-2018	Notice of DO/EO Acceptance Mailed			0
9	07-13-2018	Filing Receipt			0
8	12-19-2017	PTO/SB/69-Authorize EPO Access to Search Results			0
7	12-19-2017	Applicants have given acceptable permission for participating foreign			0
6	07-11-2018	Applicant Has Filed a Verified Statement of Small Entity Status in Compliance with 37 CFR 1.27			0
5	12-19-2017	Request from applicant for the USPTO to retrieve the Priority Document			0
4	12-19-2017	Information Disclosure Statement (IDS) Filed			0
3	12-19-2017	Cleared by OIPE CSR			0
2	12-19-2017	ENTITY STATUS SET TO UNDISCOUNTED (INITIAL DEFAULT SETTING OR STATUS CHANGE)			0
1	12-19-2017	Initial Exam Team nn			

0.5	06-10-2016	International Filing date			0

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Parent Continuity Data

Description	Parent Number	Parent Filing or 371(c) Date	AIA(First Inventor to File)	Parent Status	Patent Number
This application is National Stage Entry of	PCT/EP2016/063383	06-10-2016	-	-	-

Child Continuity Data

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15/737,907 **PYRAZOLO[1,5-A]TRIAZIN-4-AMINE DERIVATIVES USEFUL IN THERAPY** **BRNNP0174WOUS** **(/pair/PAIRPrintServlet)**

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Pre-Grant Publications

Publication Number	Publication Date	Full-Text and Image
2018-0298007 A1	10-18-2018	View

Issued Patents

Patent Number	Issue Date	Full-Text and Image
10,407,429	09-10-2019	View

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75641	Imeli, Kathryn	216-621-1113
37853	Jacobs, Christopher	216-621-1113
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72177	Nesemann, Cory	216-621-1113
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43156	Steffes, Paul	216-621-1113
71209	Steyer, Grant	216-621-1113
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Assignments Data

Patent Assignment Abstract of Title

Total Assignments: 1

Application #:15737907 **Filing Dt:**12/19/2017 **Patent #:**10407429 **Issue Dt:**09/10/2019
PCT #:EP2016063383 **Intl Reg #:** **Publication #:**US20180298007 **Pub Dt:**10/18/2018
Inventor: Jacob WESTMAN
Title:PYRAZOLO[1,5-A]TRIAZIN-4-AMINE DERIVATIVES USEFUL IN THERAPY

Assignment: 1

Reel/Frame:044434 / 0046 **Received:** 12/19/2017 **Recorded:** 12/19/2017 **Mailed:** 12/20/2017 **Pages:** 2
Conveyance:ASSIGNMENT OF ASSIGNORS INTEREST (SEE DOCUMENT FOR DETAILS).
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0-2	International Filing Date	**10 JUN 2016 (10.06.2016)**
0-3	Name of receiving Office and "PCT International Application"	**RO/EP**

0-4	**Form PCT/RO/101 PCT Request**	
0-4-1	Prepared Using	PCT Online Filing Version 3.5.000.244e MT/FOP 20141031/0.20.5.20
0-5	**Petition** The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty	
0-6	**Receiving Office (specified by the applicant)**	European Patent Office (EPO) (RO/EP)
0-7	**Applicant's or agent's file reference**	P11049PC00
I	**Title of Invention**	PYRAZOLO[1,5-A]TRIAZIN-4-AMINE DERIVATIVES USEFUL IN THERAPY
II	**Applicant**	
II-1	This person is	Applicant only
II-2	Applicant for	All designated States
II-4	Name	APODEMUS AB
II-5	Address	Nobels väg 3 171 65 SOLNA Sweden
II-6	State of nationality	SE
II-7	State of residence	SE
III-1	**Applicant and/or inventor**	
III-1-1	This person is	Inventor only
III-1-3	Inventor for	All designated States
III-1-4	Name (LAST, First)	WESTMAN, Jacob
III-1-5	Address	Blomsberg 109 740 21 JÄRLÅSA Sweden

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IV-1	**Agent or common representative; or address for correspondence**	
	The person identified below is hereby/ has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:	Agent
IV-1-1	Name	BRANN AB
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IV-1-3	Telephone No.	+46 8 429 10 00
IV-1-4	Facsimile No.	+46 8 429 10 70
IV-1-5	e-mail	brann@brann.se
IV-1-6	Agent's registration No.	538
V	**DESIGNATIONS**	
V-1	**The filing of this request constitutes under Rule 4.9(a), the designation of all Contracting States bound by the PCT on the international filing date, for the grant of every kind of protection available and, where applicable, for the grant of both regional and national patents.**	
VI-1	**Priority claim of earlier regional application**	
VI-1-1	Filing date	24 June 2015 (24.06.2015)
VI-1-2	Number	15173687.3
VI-1-3	Regional Office	EP
VI-2	**Priority document request**	
	The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) identified above as item(s):	VI-1
VI-3	**Incorporation by reference :**	
	where an element of the international application referred to in Article 11(1)(iii)(d) or (e) or a part of the description, claims or drawings referred to in Rule 20.5(a) is not otherwise contained in this international application but is completely contained in an earlier application whose priority is claimed on the date on which one or more elements referred to in Article 11(1)(iii) were first received by the receiving Office, that element or part is, subject to confirmation under Rule 20.6, incorporated by reference in this international application for the purposes of Rule 20.6.	
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VIII	**Declarations**	Number of declarations	
VIII-1	Declaration as to the identity of the inventor	–	
VIII-2	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent	–	
VIII-3	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application	–	
VIII-4	Declaration of inventorship (only for the purposes of the designation of the United States of America)	–	
VIII-5	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty	–	
IX	**Check list**	Number of sheets	Electronic file(s) attached
IX-1	Request (including declaration sheets)	4	✓
IX-2	Description	35	✓
IX-3	Claims	5	✓
IX-4	Abstract	1	✓
IX-5	Drawings	0	–
IX-7	TOTAL	45	
	Accompanying Items	Paper document(s) attached	Electronic file(s) attached
IX-8	Fee calculation sheet	–	✓
IX-20	**Figure of the drawings which should accompany the abstract**		
IX-21	**Language of filing of the international application**	English	
X-1	**Signature of applicant, agent or common representative**	(PKCS7 Digital Signature)	
X-1-1	Name	BRANN AB	
X-1-2	Name of signatory	Harriet Allee 21115	
X-1-3	Capacity (if such capacity is not obvious from reading the request)	(Representative)	

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10-2	**Drawings:**	
10-2-1	Received	
10-2-2	Not received	
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10-4	**Date of timely receipt of the required corrections under PCT Article 11(2)**	
10-5	**International Searching Authority**	**ISA/EP**
10-6	**Transmittal of search copy delayed until search fee is paid**	

FOR INTERNATIONAL BUREAU USE ONLY

11-1	**Date of receipt of the record copy by the International Bureau**	

VIII-4-1	**Declaration: Inventorship (only for the purposes of the designation of the United States of America)** Declaration of Inventorship (Rules 4.17(iv) and 51bis.1(a)(iv)) for the purposes of the designation of the United States of America:	I hereby declare that I believe I am the original inventor or an original joint inventor of a claimed invention in the application. This declaration is directed to international application No. PCT/EP2016/063383. I hereby declare that the above-identified international application was made or authorized to be made by me. I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.
VIII-4-1-1-1	Name (LAST, First)	WESTMAN, Jacob
VIII-4-1-1-2	Residence: (city and either US state, if applicable, or country)	JÄRLÅSA, Sweden
VIII-4-1-1-3	Mailing Address:	Blomsberg 109, 740 21 JÄRLÅSA
VIII-4-1-1-4	Inventor's Signature: (The signature must be that of the inventor, not that of the agent)	Jacob Westman
VIII-4-1-1-5	Date:	16 September 2016

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

(19) World Intellectual Property Organization
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A61K 31/53 (2006.01)

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10 June 2016 (10.06.2016)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
15173687.3 24 June 2015 (24.06.2015) EP

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(72) Inventor: **WESTMAN, Jacob**; Jonsund Blomsberg 109, 744 97 Järlåsa (SE).

(74) Agent: **BRANN AB**; P.O. Box 3690, 103 59 Stockholm (SE).

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

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Declarations under Rule 4.17:

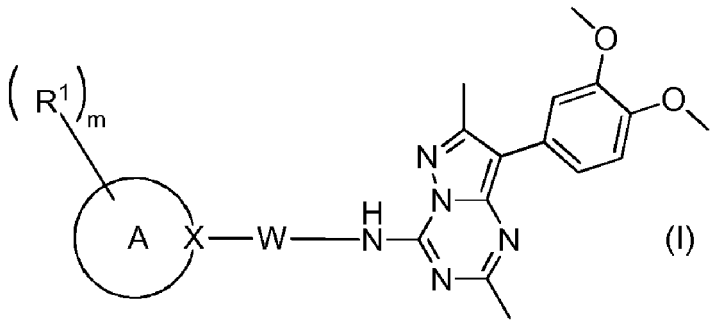
— *of inventorship (Rule 4.17(iv))*

Published:

— *with international search report (Art. 21(3))*

WO 2016/206999 A1

(54) Title: PYRAZOLO[1,5-A]TRIAZIN-4-AMINE DERIVATIVES USEFUL IN THERAPY



(57) Abstract: A compound of formula (I), or a pharmaceutically acceptable salt thereof, useful in therapy, in particular in the treatment of a viral infection.

PYRAZOLO[1,5-A]TRIAZIN-4-AMINE DERIVATIVES USEFUL IN THERAPY

FIELD OF THE INVENTION

The present invention relates generally to novel compounds having usefulness in therapy, in particular in the treatment of conditions caused by certain viruses, such as diabetes, cancer, neurodegenerative diseases such as Alzheimer´s disease and amyotrophic lateral sclerosis.

More particularly the invention relates to pyrazolo[1,5-a]triazin-4-amine derivatives having a usefulness in therapy.

BACKGROUND OF THE INVENTION

Pyrazolo[1,5-a] triazin-4-amine is a scaffold previously used in medicinal chemistry and derivatives thereof are known for their potent utility as corticotropin-releasing factor receptor -1 (CRF1) antagonists which may be potential anxiolytic and antidepressant drugs (for example Gilligan et al (J. Med. Chem. 2009, 52, 3073-3083). Pexacerfont is a pyrazolo[1,5-a] triazin-4-amine drug developed by Bristol-Myers Squibb and acts as a CRF-1 antagonist which have been tested clinically. The scaffold has also been described as present in cyclin-dependent kinase inhibitors (WO2013128029), casein kinase inhibitors and DYRK1A kinase inhibitors (WO2010103486) useful for treatment of various diseases. The scaffold has further been described as present in cannabinoid 1 receptor antagonists (J. Pharm. Exp. Ther. (2010), 335(1), 103-113).

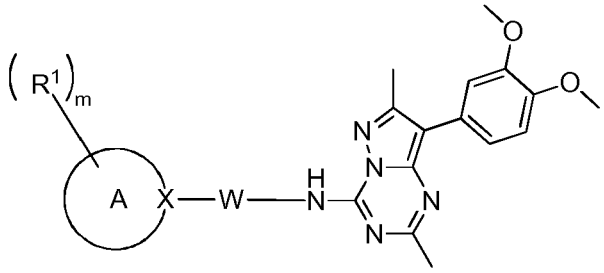
Similar scaffolds have been described as present in phosphatidylinositol 4-kinase (PI4K) inhibitors (McLeod et al (ACS Med. Chem. Lett. 2013, 4(7), 585-589) and van der Schaar et al (Antimicrobial Agents Chemother. 2013, 57(10), 4971-4981) and inhibitors of PI4K have shown to be potent antivirals (Bianco et al, PLoS Pathogens, 2012, 8(3), 1-17; LaMarche et al, Antimicr. Agents and Chemother. 2012, 56(10), 5149-5156; Décor et al, Bioorg Med Chem Lett. 2013, 23, 3841-7).

Pyrazolo[1,5-a] triazin-4-amine have been described as PI4K inhibitors with antiviral potency in Mejdrova et al (J. Med. Chem., 2015, 58 (9), pp 3767–3793).

There still remains a need for new therapeutically active compounds.

SUMMARY OF THE INVENTION

A first aspect is a compound of formula (I)



(I)

or a pharmaceutically acceptable salt thereof, wherein

W is CH_2 or CH_2-CH_2;

X is C or CH;

ring A is 5- or 6-membered carbocyclyl or 5- or 6-membered heterocyclyl;

m is an integer of from 0 to 3;

each R^1 is independently selected from C1-C6 alkyl optionally substituted by one or more halogen, R^2O, halogen, $R^3R^4NC(O)$, $R^5C(O)N(R^6)$, $R^7OC(O)$, $R^8C(O)O$, $R^9S(O)_2$, $R^{10}S(O)_2N(H)$, $R^{11}C(O)$, $R^{12}R^{13}N$, ^-O and $R^{14}R^{15}NS(O)_2$; and

when m is at least 2, two R^1 attached to adjacent atoms of ring A may form, together with the atoms to which they are attached, a 5- or 6-membered heterocyclic or carbocyclic ring;

each R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13} and R^{14} is independently selected from H and C1-C6 alkyl, wherein any alkyl is optionally substituted by one or more halogen;

R^{15} is selected from H, C1-C6 alkyl, $R^{16}C(O)$, $R^{17}OC(O)$, and $R^{18}R^{19}NC(O)$; and

each R^{16}, R^{17}, R^{18}, and R^{19} is independently selected from H and C1-C6 alkyl, wherein any alkyl is optionally substituted by one or more halogen.

In some embodiments of a compound of formula (I), W is CH_2, X is C, and ring A is phenyl or 5- or 6-membered heteroaryl; e.g. W is CH_2, X is C, and ring A is phenyl; or W is CH_2, X is C, and ring A is 5- or 6-membered heteroaryl; or W is CH_2, X is C, and ring A is 6-membered heteroaryl; or W is CH_2, X is C, and ring A is 5-membered heteroaryl.

A further aspect is a compound of formula (I), or a pharmaceutically acceptable salt thereof, for use as an inhibitor of phosphatidylinositol 4-kinase IIIβ.

A further aspect is a compound of formula (I), or a pharmaceutically acceptable salt thereof, for use in therapy.

A still further aspect is a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, and optionally a pharmaceutically acceptable excipient.

A further aspect is a compound of formula (I), or a pharmaceutically acceptable salt thereof, for use in the treatment of a viral infection. In some embodiments, the viral infection is a non-enveloped single-stranded (+) RNA viral infection.

Still a further aspect is a compound of formula (I), or a pharmaceutically acceptable salt thereof, for use in the treatment of a neurodegenerative disease such as multiple sclerosis, Parkinson's disease, amyotrophic lateral sclerosis, Alzheimer's disease, Huntington's disease, poliomyelitis, encephalitis, meningitis, sepsis, cancer, paralysis, myocarditis, diabetes, common cold, hand-foot-and-mouth disease, herpangina, pleurodynia, diarrhea, mucocutaneous lesions, respiratory illness, conjunctivitis, myositis, and chronic fatigue syndrome.

The use of the compound of formula (I) or the pharmaceutically acceptable salt thereof for the preparation of a pharmaceutical composition for the treatment of a disorder as mentioned herein above also is provided, as well as a method for the treatment of a disorder as mentioned herein above by administration of a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof to a mammal in need thereof.

DETAILED DESCRIPTION OF THE INVENTION

"Pharmaceutically acceptable" means being useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable and includes being useful for veterinary use as well as human pharmaceutical use.

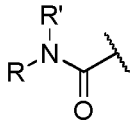
"Treatment" as used herein includes prophylaxis of the named disorder or condition, or amelioration or elimination of the disorder once it has been established.

"An effective amount" refers to an amount of a compound that confers a therapeutic effect on the treated subject. The therapeutic effect may be objective (i.e., measurable by some test or marker) or subjective (i.e., subject gives an indication of or feels an effect).

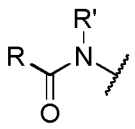
Unless otherwise stated or indicated, the term "C1-6 alkyl" denotes a straight or branched alkyl group having from 1 to 6 carbon atoms. Examples of said C1-6 alkyl include methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, t-butyl and straight- and branched-chain pentyl and hexyl.

Unless otherwise stated or indicated, the term "halogen" (or "halo") refers to fluorine (F), chlorine (Cl), or bromine (Br).

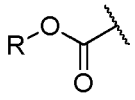
A moiety of the type RR'NC(O) is a moiety of formula



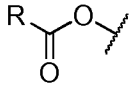
A moiety of the type RC(O)N(R') is a moiety of formula



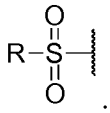
A moiety of the type ROC(O) is a moiety of formula



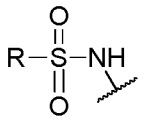
A moiety of the type RC(O)O is a moiety of formula



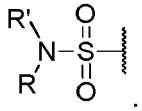
A moiety of the type $RS(O)_2$ is a moiety of formula



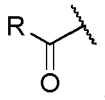
A moiety of the type $RS(O)_2N(H)$ is a moiety of formula



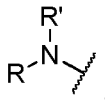
A moiety of the type $RR'NS(O)_2$ is a moiety of formula



A moiety of the type RC(O) is a moiety of formula



A moiety of the type RR'N is a moiety of formula



As used herein, the term "carbocyclyl" or "carbocyclic ring" refers to a saturated or unsaturated (e.g. monounsaturated or diunsaturated), non-aromatic or aromatic cyclic moiety containing only carbon atoms in the ring.

Examples of non-aromatic carbocylyl are pentyl, hexyl or hexenyl, while phenyl is an example of aromatic carbocyclyl.

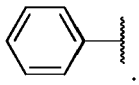
The term "heterocyclyl" (or "heterocyclic ring") refers to a saturated or unsaturated, aromatic or non-aromatic cyclic moiety containing not only carbon atoms, but also at least one other atom in the ring, e.g. selected from nitrogen (N), sulphur (S) and oxygen (O), in particular N and O.

When non-aromatic, the heterocyclyl e.g. may be piperidinyl, or 1,2,3,4-tetrahydropyridinyl. Other examples of non-aromatic heterocyclyl include morpholinyl, pyrrolidinyl, piperazinyl, tetrahydrothienyl, and tetrahydrofuryl.

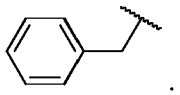
When aromatic, the heterocyclyl also may be referred to as "heteroaryl", which refers refers to an aromatic ring containing at least one ring heteroatom, such as furyl, isoxazolyl, isothiazolyl, imidazolyl, pyridyl, pyrrolyl, pyrazolyl, pyrimidinyl, pyridazinyl, pyrazinyl, oxadiazolyl, oxazolyl, thienyl, thiadiazolyl, thiazolyl, triazolyl, and tetrazolyl.

The term "aromatic", as used herein, refers to an unsaturated cyclic moiety that has an aromatic character, while the term "non-aromatic", as used herein, refers to a cyclic moiety, that may be saturated or unsaturated, e.g. polyunsaturated, but that does not have an aromatic character.

The term "phenyl" refers to a moiety of formula C_6H_5-, i.e.;



The term "benzyl" refers to a moiety of formula $C_6H_5CH_2$-, i.e.;



A "methylenedioxy biradical" is a biradical of formula -OCH_2O-.

An "ethylenedioxy biradical" is a biradical of formula -OCH_2CH_2O-.

"Treatment" as used herein includes prophylaxis of the named disorder or condition, or amelioration or elimination (i.e. cure) of the disorder once it has been established.

An "effective amount" refers to an amount of a compound that confers a therapeutic effect on the treated subject. The therapeutic effect may be objective (i.e., measurable by some test or marker, e.g. no measurable virus titre in a biological sample from the treated subject) or subjective (i.e., subject gives an indication of or feels an effect).

A "non-enveloped single-stranded (+) RNA viral infection" refers to an infection with a non-enveloped single-stranded (+) RNA virus.

A "non-enveloped virus" is a virus lacking viral envelope.

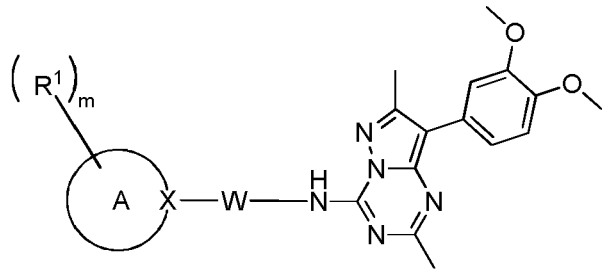
A "single-stranded (+) RNA virus" is a virus having genetic material which is single-stranded RNA and which RNA can be immediately translated to viral protein by the cell infected by the virus.

The term "mammal" refers to a human or any mammalian animal, e.g. a primate, a farm animal, a pet animal, or a laboratory animal. Examples of such animals are monkeys, cows, sheep, goats, horses, pigs, dogs, cats, rabbits, mice, rats etc. Preferably, the mammal is a human. In some embodiments, however, the mammal is an animal, e.g. a farm animal, such as a cow, sheep, goat, horse, or pigs. In some other embodiments, the animal is a pet, e.g. a dog, a cat or a rabbit.

The term "excipient" refers to pharmaceutically acceptable chemicals, such as known to those of ordinary skill in the art of pharmacy to aid the administration of the medicinal agent. It a compound that is useful in preparing a pharmaceutical composition, generally safe, non-toxic and neither biologically nor otherwise undesirable, and includes excipients that are acceptable for veterinary use as well as human pharmaceutical use. Exemplary excipients include binders, surfactants, diluents, disintegrants, antiadherents, and lubricants.

Herein below, any reference to a compound of formula (I) or a compound of the invention, should be construed as referring to a compound for use according to the invention, as defined in the claims.

In a compound of formula (I)



(I)

as defined herein above, W is CH_2 or CH_2CH_2. In some embodiments, W is CH_2. In some other embodiments, W is CH_2CH_2.

In ring A, the moiety X is C or CH. X is CH when attached to the two adjacent atoms in the ring by only single bonds, such as in cyclohexyl or tetrahydrofuryl, and X is C when X is

attached by a double bond to an adjacent atom in the ring, such as in phenyl or cyclohexen-1-yl.

The ring A is 5- or 6-membered carbocyclyl or 5- or 6-membered heterocyclyl. In some embodiments, ring A is 5- or 6-membered carbocyclyl or 5- or 6-membered heteroaryl. In some embodiments, ring A is 5- or 6-membered carbocyclyl. In some embodiments, when A is 5- or 6-membered carbocyclyl, it more particularly is 6-membered carbocyclyl, e.g hexyl or phenyl, in particular phenyl.

In some embodiments, e.g. when ring A is phenyl, ring A is substituted by 1-3 moieties R^1, e.g. 1 or 2 moieties R^1, or 1 moiety R^1 (i.e. m is 1-3, m is 1 or 2, or m is 1). In some other embodiments, e.g. when ring A is phenyl, m is 0, 1 or 2, e.g. m is 0 or 1.

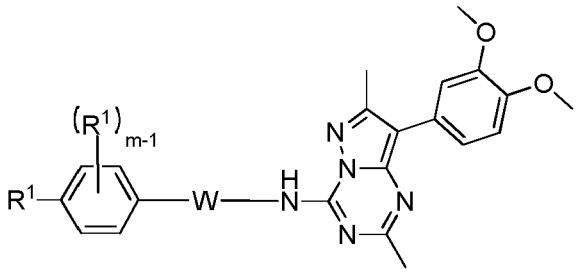
In some embodiments, when ring A is phenyl and m is an integer of from 1 to 3, e.g. m is 1 or 2, at least one R^1 is in meta position. In some embodiments, when ring A is phenyl, m is 1, and R^1 is in meta position.

In some particular embodiments, when ring A is phenyl and m is an integer of from 1 to 3, e.g. m is 1 or 2, and least one R^1 is in meta position, said R^1 in meta position is $R^9S(O)_2$, wherein R^9 is as defined herein, e.g. R^9 is C1-C3 alkyl, or R^9 is methyl. In some of these embodiments, m is 1. Furthermore, in some of these embodiments, W is CH_2; e.g. m is 1 and W is CH_2.

Thus, in some particular embodiments of a compound of formula (I), ring A is phenyl substituted in meta position, e.g. with a moiety $R^9S(O)_2$; m is 1, 2 or 3; e.g. m is 1 or 2; or m is 1; and W is CH_2.

In some embodiments, when ring A is phenyl and m is an integer of from 1 to 3, at least one R^1 is in para position.

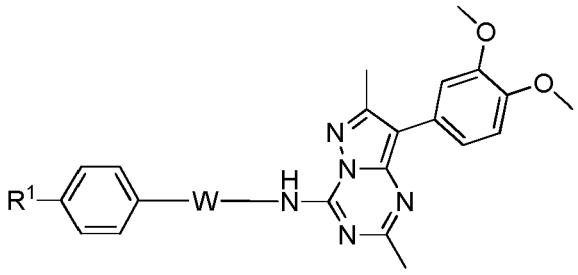
In some embodiments, the compound of formula (I) may be represented by formula (Ia)



(Ia)

wherein m is 1, 2 or 3, and W and each R^1 are as defined herein.

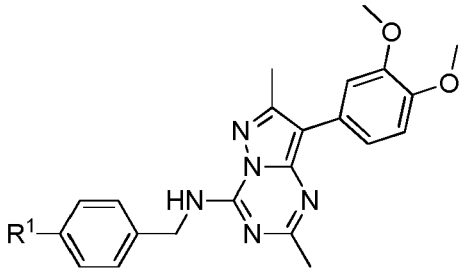
When m is 1, the compound of formula (Ia) may be represented by formula (Ib)



(Ib)

wherein W and R^1 are as defined herein.

In some embodiments of a compound of formula (Ib), W is CH_2 and the compound may be represented by formula (Ic)



(Ic)

wherein R^1 is as defined herein.

In some other embodiments of a compound of formula (I), ring A is 5- or 6-membered heterocyclyl. When ring A is heterocyclyl, said heterocyclyl may contain 1, 2, 3 or 4 heteroatoms, e.g. 1, 2 or 3 heteroatoms, or 1 or 2 heteroatoms, e.g. 1 heteroatom, each heteroatom being independently selected from N, O and S, e.g. from O and S.

In some embodiments, when ring A is 5- or 6-membered heterocyclyl, it more particularly is 5-membered heterocyclyl. In some other embodiments, when ring A is 5- or 6-membered heterocyclyl, it more particularly is 6-membered heterocyclyl. In some embodiments, when ring A is 5- or 6-membered heterocyclyl, said heterocyclyl is aromatic, i.e. ring A is 5- or 6-

membered heteroaryl. In some embodiments, ring A is 5-membered heteroaryl. In some other embodiments, ring A is 6-membered heteroaryl.

In some embodiments, ring A is 5-membered heteroaryl containing one or more heteroatoms, e.g. 1-3 heteroatoms; or 1 or 2 heteroatoms, of which at least one is N; e.g. ring A is pyrazolyl, oxazolyl, thiazolyl, thienyl or furyl.

In some embodiments, ring A is 5-membered heteroaryl containing 2 heteroatoms, of which at least one is N, e.g. ring A is pyrazolyl.

In some embodiments, ring A is 5-membered heteroaryl containing one heteroatom selected from O and S, i.e. ring A is thienyl or furyl, e.g. 2-thienyl or 2-furyl.

In some embodiments, ring A is 5-membered heteroaryl, and m is an integer of from 0 to 3, or from 0 to 2, e.g. m is 0 or 1. For example, in some embodiments, ring A is pyrazolyl, e.g. 1*H*-pyrazol-3-yl; m is 1, 2 or 3, e.g. m is 1 or 2, or m is 1, and at least one R^1 is attached to a ring nitrogen. For example, in some embodiments, ring A, substituted by one R^1, is selected from 1-C_1-C_6 alkyl-1*H*-pyrazol-3-yl, or 1-C1-C3 alkyl-1*H*-pyrazol-3-yl, in particular 1-methyl-1*H*-pyrazolyl-3yl, and is optionally substituted by one or two further R^1, e.g. one further R^1, or is substituted by no further R^1, i.e. m is 1. In some of these embodiments, W is CH_2.

In some embodiments, ring A is 6-membered heteroaryl. When ring A is 6-membered heteroaryl, said heteroaryl e.g. may be selected from pyridinyl, pyrimidinyl, or pyridazinyl, e.g. from pyridyl (also termed pyridinyl), i.e. pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, in particular it may be pyridin-4-yl.

In some embodiments, e.g. of a compound of formula (If) as defined herein below, ring A is pyridin-3-yl or pyridin-4-yl. In some embodiments, ring A is pyridin-3-yl, e.g. ring A is pyridin-3-yl and m is 0, 1 or 2, e.g. m is 0 or 1. In some embodiments, ring A is pyridin-3-yl, m is 1, and R^1 is in para position; e.g. ring A is pyridin-3-yl, m is 1, and R^1 is in para position and is R^2O.

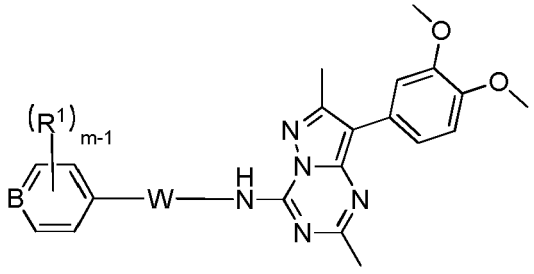
In some other embodiments, ring A is selected from 5- or 6-membered carbocyclyl, in particular 6-membered, carbocyclyl, such as phenyl and hexyl, and from 5- or 6-membered heterocyclyl containing one heteroatom only, e.g. tetrahydrofuryl, thienyl, furyl, and pyridyl.

In some other embodiments, ring A is phenyl or 5- or 6-membered heteroaryl. In some other embodiments, ring A is phenyl or 5-membered heteroaryl. In still other embodiments, ring A is phenyl or 6-membered heteroaryl.

In some embodiments, ring A is phenyl, said phenyl having a substituent R^1 in para position, and optionally being substituted by 1 or 2 further moieties R^1; or ring A is 6-membered heteroaryl having a heteroatom, e.g. nitrogen (N), in para position, said heteroaryl optionally being substituted by 1, 2 or 3 moieties R^1 and said heteroaryl optionally containing one or more further heteroatoms (e.g. N), e.g. 1 or 2 further N; or ring A is 6-membered heteroaryl having $N^+(O^-)$ in para position, said heteroaryl optionally being substituted by 1, 2 or 3 moieties R^1 and said heteroaryl optionally containing one or more further heteroatoms, e.g. 1 or 2 further N.

In some embodiments, ring A is phenyl having a substituent R^1 in para position, said phenyl optionally beng substituted by 1 or 2 further moieties R^1; or ring A is 6-membered heteroaryl having a heteroatom, e.g. nitrogen (N), in para position, said heteroaryl optionally being substituted by 1, 2 or 3 moieties R^1 and said heteroaryl optionally containing one or more further heteroatoms (e.g. N), e.g. 1 or 2 further N.

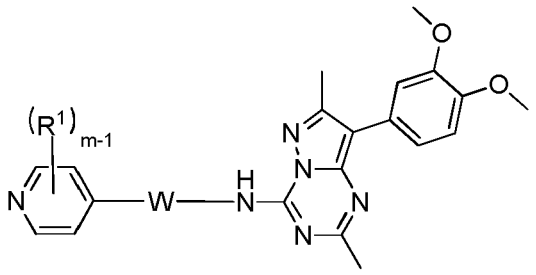
In some embodiments, the compound of formula (I) may be one represented by formula (Id)



(Id)

wherein m is 1, 2, or 3, e.g. m is 1 or 2, in particular m is 1; B is N, $N^+(O^-)$ or CR^1, and W and each R^1 are as defined herein; e.g. W is CH_2.

In some embodiments of a compound of formula (Id), B is N or $N^+(O^-)$, in particular B is N. In some embodiments, B is N, i.e. the compound may be represented by formula (Ie)



(Ie)

wherein m is 1, 2, or 3, e.g. m is 1 or 2, in particular m is 1; and W and each R^1 are as defined herein; e.g. W is CH_2.

In a compound of formula (I), m denotes the number of moieties R^1 attached to ring A, and is an integer of from 0 to 3. In some embodiments, m is an integer of from 1 to 3, e.g. m is 1 or 2. In some other embodiments, m is an integer of from 0 to 2, e.g. m is 0 or 1. In some embodiments, m is 1.

In a compound of formula (I), each R^1 is independently selected from C1-C6 alkyl optionally substituted by one or more halogen, R^2O, halogen, $R^3R^4NC(O)$, $R^5C(O)N(R^6)$, $R^7OC(O)$, $R^8C(O)O$, $R^9S(O)_2$, $R^{10}S(O)_2N(H)$, $R^{11}C(O)$, $R^{12}R^{13}N$, ^-O and $R^{14}R^{15}NS(O)_2$; and when m is at least 2, two R^1 attached to adjacent atoms of ring A may form, together with the atoms to which they are attached, a 5- or 6-membered heterocyclic or carbocyclic ring.

In some embodiments, each R^1 is independently selected from C1-C6 alkyl optionally substituted by one or more halogen, R^2O, halogen, $R^3R^4NC(O)$, $R^5C(O)N(R^6)$, $R^7OC(O)$, $R^8C(O)O$, $R^9S(O)_2$, $R^{10}S(O)_2N(H)$, $R^{11}C(O)$, $R^{12}R^{13}N$, and $R^{14}R^{15}NS(O)_2$; and when m is at least 2, two R^1 attached to adjacent atoms of ring A may form, together with the atoms to which they are attached, a 5- or 6-membered heterocyclic or carbocyclic ring.

In some embodiments, each R^1 is independently selected from C1-C6 alkyl, R^2O, halogen, $R^5C(O)N(R^6)$, $R^9S(O)_2$, $R^{10}S(O)_2N(H)$, ^-O, and $R^{14}R^{15}NS(O)_2$.

When R^1 is C1-C6 alkyl, said alkyl e.g. may be selected from C1-C4 alkyl, e.g. C1-C3 alkyl, such as methyl, ethyl and isopropyl.

In the moieties R^2O, $R^3R^4NC(O)$, $R^5C(O)N(R^6)$, $R^7OC(O)$, $R^8C(O)O$, $R^9S(O)_2$, $R^{10}S(O)_2N(H)$, $R^{11}C(O)$, $R^{12}R^{13}N$, and $R^{14}R^{15}NS(O)_2$; each one R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13} and R^{14} is independently selected from H and C1-C6 alkyl. In some embodiments, each one of R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13} and R^{14} is independently selected from H and C1-C4 alkyl, e.g. from H and C1-C3 alkyl, or from H, methyl and ethyl, in particular from H and methyl.

In some other embodiments, each one of R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13} and R^{14} is independently selected from C1-C6 alkyl, e.g. from C1-C4 alkyl, from C1-C3 alkyl, or from methyl and ethyl, in particular from methyl.

In some embodiments, in the moiety $R^5C(O)N(R^6)$, R^5 is as defined herein above, and R^6 is H.

In the moiety $R^{14}R^{15}NS(O)_2$, R^{14} is as defined herein above, e.g. R^{14} is H or CH_3, or R^{14} is H, and R^{15} is selected from H, C1-C6 alkyl, $R^{16}C(O)$, $R^{17}OC(O)$, and $R^{18}R^{19}NC(O)$. In some embodiments, R^{15} is selected from H and C1-C6 alkyl, e.g. from H and C1-C4 alkyl, or from H and C1-C3 alkyl, such as H and CH_3. In some other embodiments, R^{15} is selected from C1-C6 alkyl, $R^{16}C(O)$, $R^{17}OC(O)$, and $R^{18}R^{19}NC(O)$, e.g. from $R^{16}C(O)$, $R^{17}OC(O)$, and $R^{18}R^{19}NC(O)$.

In any of $R^{16}C(O)$, $R^{17}OC(O)$, and $R^{18}R^{19}NC(O)$, each one of R^{16}, R^{17}, R^{18}, and R^{19} is independently selected from H and C1-C6 alkyl, e.g. from H and C1-C4 alkyl, or from H and C1-C3 alkyl, such as H and CH_3. In some embodiments, each one of R^{16}, R^{17}, R^{18}, and R^{19} is independently selected from C1-C6 alkyl, e.g. from C1-C4 alkyl, or from C1-C3 alkyl, e.g. each is CH_3.

When R^1 is halogen, said halogen e.g. may be selected from F, Cl and Br. In some embodiments, when R^1 is halogen, said halogen is F or Cl, in particular Cl. In some other embodiments, when R^1 is halogen, said halogen is F.

When R^1 is an alkyl moiety or comprises an alkyl moiety, any such alkyl moiety may be substituted by one or more halogen, in particular one or more F.

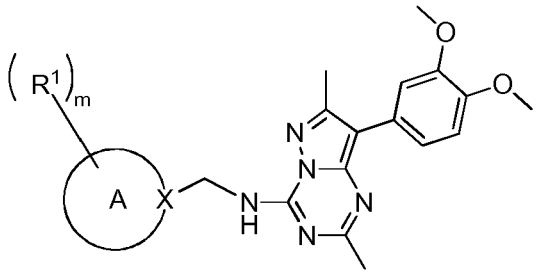
When any R^1 is ^-O, said ^-O preferably is attached to a nitrogen atom in ring A, i.e. ring A is nitrogen-containing heterocyclyl.

In some embodiments, when m is at least 2, e.g. m is 2, two R^1 attached to adjacent atoms of the ring A form, together with the atoms to which they are attached, a 5- or 6-membered heterocyclic or carbocyclic ring, e.g. a 5- or 6-membered heterocyclic ring, such as a 5- or 6-membered ring containing one or two oxygen atoms. For example, two R^1 attached to adjacent atoms of ring A may form together a methylenedioxy biradical or an ethylenedioxy biradical.

In some embodiments, when two R^1 attached to adjacent atoms of the ring A form, together with the atoms to which they are attached, a 5- or 6-membered heterocyclic or carbocyclic ring, said ring is a 5- membered heterocyclic ring, e.g. 1,3-dioxole or 1,3-dioxolane.

It should be realized that features of the various embodiments described herein may be freely combined within the scope of the present invention, unless mutually incompatible, or unless otherwise specified.

For example, in some embodiments, wherein W is CH_2, the compound is as represented by formula (If)



(If)

wherein

X is C;

ring A is phenyl or 5- or 6-membered heteroaryl;

m is an integer of from 0 to 3; e.g. from 0 to 2; or m is 0 or 1:

and each R^1 is as defined herein above.

In some embodiments of a compound of formula (If), each R^1 is independently selected from C1-C6 alkyl optionally substituted by one or more halogen, R^2O, halogen, $R^5C(O)N(R^6)$, $R^9S(O)_2$, $R^{10}S(O)_2N(H)$, and $R^{14}R^{15}NS(O)_2$; and when m is at least 2, two R^1 attached to adjacent atoms of ring A may form, together with the atoms to which they are attached, a 5- or 6-membered heterocyclic or carbocyclic ring, e.g. a 5- or 6-membered saturated or mono-unsaturated heterocyclic or carbocyclic ring, in particular a ring formed by methylenedioxy biradical or an ethylenedioxy biradical attached to adjacent atoms of ring A;

each R^2, R^5, R^6, R^9, R^{10}, and R^{14} is independently selected from H and C1-C6 alkyl, wherein any alkyl is optionally substituted by one or more halogen;

R^{15} is selected from H, C1-C6 alkyl, $R^{16}C(O)$, $R^{17}OC(O)$, and $R^{18}R^{19}NC(O)$; and

each R^{16}, R^{17}, R^{18}, and R^{19} is independently selected from H and C1-C6 alkyl, wherein any alkyl is optionally substituted by one or more halogen.

In some of these embodiments, each R^1 is independently selected from C1-C6 alkyl optionally substituted by one or more halogen, R^2O, halogen, $R^5C(O)N(R^6)$, $R^9S(O)_2$, $R^{10}S(O)_2N(H)$, and $R^{14}R^{15}NS(O)_2$; and when m is at least 2, two R^1 attached to adjacent atoms of ring A may form, together with the atoms to which they are attached, a 5- or 6-membered heterocyclic or carbocyclic ring, e.g. a 5- or 6-membered saturated or mono-unsaturated heterocyclic or carbocyclic ring, in particular a ring formed by methylenedioxy biradical or an ethylenedioxy biradical attached to adjacent atoms of ring A;

each R^2, R^5, R^6, R^9, R^{10}, and R^{14} is independently selected from H and C1-C6 alkyl, wherein any alkyl is optionally substituted by one or more halogen; and

R^{15} is selected from H and C1-C6 alkyl, and

wherein any alkyl is optionally substituted by one or more halogen.

In the above embodiments, any C1-C6 alkyl preferably is C1-C3 alkyl, e.g. C1-C2 alkyl, in particular CH_3.

Moreover, when any alkyl is substituted by one or more halogen, each such halogen preferably is F. For example, in some embodiments of a compound of formula (If), each R^1 is selected from F, Cl, CF_3, CH_3, $CH_3C(O)NH$, CH_3O, $CH_3S(O)_2$, $NH_2S(O)_2$, OH, $CH_3S(O)_2NH$, and $CH_3NHS(O)_2$, or two R^1, attached to adjacent atoms of ring A, form together a methylenedioxy biradical.

In some of these embodiments, when ring A is phenyl, m is an integer of from 1 to 3, e.g. from 1 to 2, in particular m is 1; and when ring A is heteroaryl, m is an integer of from 0 to 2, e.g. m is 0 or 1.

In some embodiments of a compound of formula (If), ring A is phenyl and m is 1 or 2, or A is 5- or 6-membered heteroaryl and m is 0 or 1.

In some embodiments, ring A is phenyl or 5- or 6-membered heteroaryl and m is 0 or 1. In some of these embodiments, ring A is phenyl. In some other of these embodiments, ring A is 5- or 6-membered heteroaryl. In some of these embodiments, ring A is 6-membered heteroaryl. In some other of these embodiments, ring A is 5-membered heteroaryl.

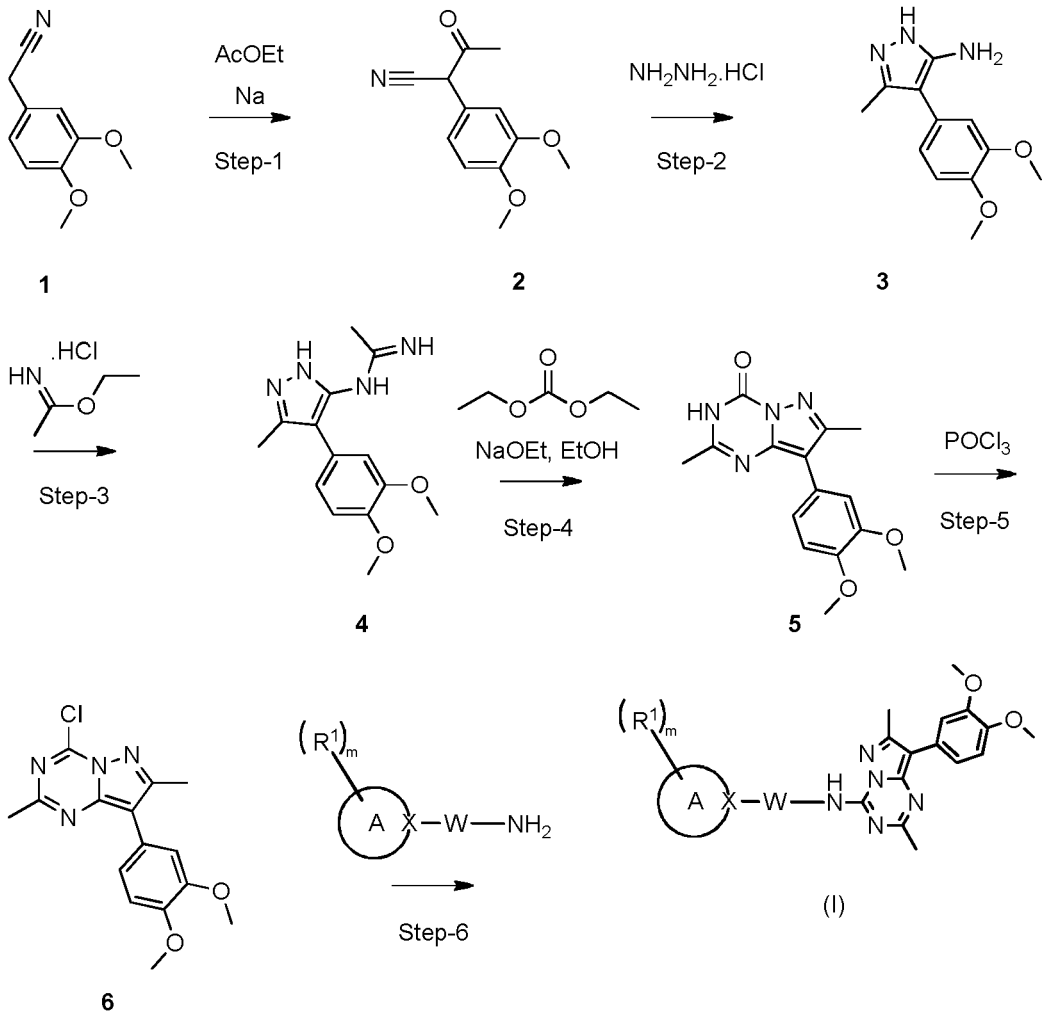
In some embodiments of a compound of formula (I), e.g. a compound of formula (If), ring A is selected from phenyl, pyridyl, thienyl, furyl, pyrazolyl, oxazolyl, pyridmidinyl, and pyridazinyl.

In some embodiments of a compound of formula (I), e.g. a compound of formula (If), ring A is phenyl. In some other of these embodiments, when ring A is 5-membered heteroaryl, it more particularly is selected from thienyl, furyl, pyrazolyl, and oxazolyl.

In some embodiments of a compound of formula (I), e.g. a compound of formula (If), when ring A is 6-membered heteroaryl, it more particularly is selected from 6-membered heteroaryl containing one or more nitrogen atoms in the ring, e.g. 1 or 2 N, e.g. ring A is selected from pyridinyl, pyridmidinyl, and pyridazinyl.

The compounds of the invention may be readily synthesized by the person of ordinary skill e.g. by following the general procedure outlined in Reaction Scheme 1.

Reaction Scheme 1



The compounds may also be synthesized using methods similar to those described in Mejdrova et al (J. Med. Chem., 2015, 58 (9), pp 3767–3793) or Long et al (J. Org. Chem.., 2015, 80, 4716-4721).

The compounds of formula (I) also may be transformed into suitable, pharmaceutically acceptable salts. The term pharmaceutically acceptable salt of a compound refers to a salt that is pharmaceutically acceptable, as defined herein, and that possesses the desired pharmacological activity of the parent compound. Pharmaceutically acceptable salts include acid addition salts formed with inorganic acids, e.g. hydrochloric acid, hydrobromic acid, sulphuric acid, nitric acid, phosphoric acid; or formed with organic acids, e.g. acetic acid,

benzenesulfonic acid, benzoic acid, camphorsulfonic acid, citric acid, ethanesulfonic acid, fumaric acid, glucoheptonic acid, gluconic acid, glutamic acid, glycolic acid, hydroxynaphtoic acid, 2-hydroxyethanesulfonic acid, lactic acid, maleic acid, malic acid, malonic acid, mandelic acid, methanesulfonic acid, muconic acid, 2-naphthalenesulfonic acid, propionic acid, salicylic acid, succinic acid, tartaric acid, p-toluenesulfonic acid, trimethylacetic acid, etc.

In the preparation of acid addition salts, preferably such acid are used which form suitably therapeutically acceptable salts. Examples of such acids are hydrohalogen acids, sulfuric acid, phosphoric acid, nitric acid, aliphatic, alicyclic, aromatic or heterocyclic carboxylic or sulfonic acids, such as formic acid, acetic acid, propionic acid, succinic acid, glycolic acid, lactic acid, malic acid, tartaric acid, citric acid, ascorbic acid, maleic acid, hydroxymaleic acid, pyruvic acid, p-hydroxybenzoic acid, embonic acid, methanesulfonic acid, ethanesulfonic acid, hydroxyethanesulfonic acid, halogenbenzenesulfonic acid, toluenesulfonic acid or naphthalenesulfonic acid.

Whenever a chiral carbon is present in a chemical structure, it is intended that all stereoisomers associated with that chiral carbon are encompassed by the structure, unless otherwise specified. Using the Cahn-Ingold-Prelog RS notational system, any asymmetric carbon atom may be present in the (R)- or (S)-configuration, and the compound may be present as a mixture of its stereoisomers, e.g. a racemic mixture, or one stereoisomer only.

The present invention includes pharmaceutical compositions comprising at least one compound of formula (I), or an individual isomer, racemic or non-racemic mixture of isomers or a pharmaceutically acceptable salt thereof, together with at least one pharmaceutically acceptable excipient, e.g. a carrier, and optionally other therapeutic and/or prophylactic ingredients.

A pharmaceutical composition according to the invention may be for topical (local) or systemic administration, e.g. for enteral administration, such as rectal or oral administration, or for parenteral administration to a mammal (especially a human), and comprises a therapeutically effective amount of a compound according to the invention or a pharmaceutically acceptable salt thereof, as active ingredient, in association with a pharmaceutically acceptable excipient, e.g. a pharmaceutically acceptable carrier. The

therapeutically effective amount of the active ingredient is as defined herein above and depends e.g. on the species of mammal, the body weight, the age, the individual condition, individual pharmacokinetic data, the disease to be treated and the mode of administration.

For enteral, e.g. oral, administration, the compounds of the invention may be formulated in a wide variety of dosage forms. The pharmaceutical compositions and dosage forms may comprise a compound or compounds of the present invention or pharmaceutically acceptable salt(s) thereof as the active component. The pharmaceutically acceptable carriers may be either solid or liquid. Solid form preparations include powders, tablets, pills, lozenges, capsules, cachets, suppositories, and dispersible granules. A solid carrier may be one or more substances which may also act as diluents, flavouring agents, solubilizers, lubricants, suspending agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material. In powders, the carrier generally is a finely divided solid which is a mixture with the finely divided active component. In tablets, the active component generally is mixed with the carrier having the necessary binding capacity in suitable proportions and compacted in the shape and size desired. Suitable carriers include but are not limited to magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatine, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The formulation of the active compound may comprise an encapsulating material as carrier, providing a capsule in which the active component, with or without carriers, is surrounded by a carrier, which is in association with it.

Other forms suitable for oral administration include liquid form preparations including emulsions, syrups, elixirs, aqueous solutions, aqueous suspensions, or solid form preparations which are intended to be converted shortly before use to liquid form preparations. Emulsions may be prepared in solutions, for example, in aqueous propylene glycol solutions or may contain emulsifying agents, for example, such as lecithin, sorbitan monooleate, or acacia. Aqueous solutions can be prepared by dissolving the active component in water and adding suitable colorants, flavors, stabilizers, and thickening agents. Aqueous suspensions can be prepared by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, and other well-known suspending agents. Solid form preparations include solutions, suspensions, and emulsions, and may contain, in addition to the active component, colorants,

flavors, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilising agents, and the like.

Exemplary compositions for rectal administration include suppositories which can contain, for example, a suitable non-irritating excipient, such as cocoa butter, synthetic glyceride esters or polyethylene glycols, which are solid at ordinary temperatures, but liquefy and/or dissolve in the rectal cavity to release the drug.

The compounds of the invention also may be administered parenterally, e.g. by inhalation, injection or infusion, e.g. by intravenous, intraarterial, intraosseous, intramuscular, intracerebral, intracerebroventricular, intrasynovial, intrasternal, intrathecal, intralesional, intracranial, intracutaneous and subcutaneous injection or infusion.

Thus, for parenteral administration, the pharmaceutical compositions of the invention may be in the form of a sterile injectable or infusible preparation, for example, as a sterile aqueous or oleaginous suspension. This suspension may be formulated according to techniques known in the art using suitable dispersing or wetting agents (e.g., Tween 80), and suspending agents. The sterile injectable or infusible preparation may also be a sterile injectable or infusible solution or suspension in a non-toxic parenterally acceptable diluent or solvent. For example, the pharmaceutical composition may be a solution in 1,3-butanediol. Other examples of acceptable vehicles and solvents that may be employed in the compositions of the present invention include, but are not limited to, mannitol, water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed including synthetic mono- or diglycerides. Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant.

Solutions for parenteral use also may contain suitable stabilizing agents, and if necessary, buffer substances. Suitable stabilizing agents include antioxidizing agents, such as sodium bisulfate, sodium sulfite or ascorbic acid, either alone or combined, citric acid and its salts and sodium EDTA. Parenteral solutions may also contain preservatives, such as benzalkonium chloride, methyl- or propyl-paraben, and cholorobutanol.

For inhalation or nasal administration, suitable pharmaceutical formulations are as particles, aerosols, powders, mists or droplets, e.g. with an average size of about 10 μm in diameter or less. For example, compositions for inhalation may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other solubilising or dispersing agents known in the art.

The pharmaceutical compositions of the invention also may be administered topically, to the skin or to a mucous membrane. For topical application, the pharmaceutical composition may be e.g. a lotion, a gel, a paste, a tincture, a transdermal patch, a gel for transmucosal delivery.

The composition may be formulated as a suitable ointment containing the active components suspended or dissolved in a carrier. Carriers for topical administration of the compounds of this invention include, but are not limited to, mineral oil, liquid petroleum, white petroleum, propylene glycol, polyoxyethylene polyoxypropylene compound, emulsifying wax and water.

Alternatively, the pharmaceutical composition may be formulated as a suitable lotion or cream containing the active compound suspended or dissolved in a carrier. Suitable carriers include, but are not limited to, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetaryl alcohol, 2-octyldodecanol, benzyl alcohol and water.

The pharmaceutical compositions of this invention may also be topically applied to the lower intestinal tract by rectal suppository formulation or in a suitable enema formulation.

Suitable pharmaceutical excipients, e.g. carriers, and methods of preparing pharmaceutical dosage forms are described in Remington's Pharmaceutical Sciences, Mack Publishing Company, a standard reference text in art of drug formulation.

The pharmaceutical compositions may comprise from approximately 1 % to approximately 95%, preferably from approximately 20% to approximately 90% of a compound of formula (I), together with at least one pharmaceutically acceptable excipient.

In general, the compounds of the invention will be administered in a therapeutically effective amount by any of the accepted modes of administration for agents that serve similar utilities.

Suitable daily dosages typically ranges from 1 to 1000 mg, e.g. 1-500 mg daily, or 1-50 mg daily, depending upon numerous factors such as the severity of the disease to be treated, the age and relative health of the patient, the potency of the compound used, the route and form of administration, and the indication towards which the administration is directed, etc. One of ordinary skill in the art of treating such diseases will be able, without undue experimentation and in reliance upon personal knowledge and the disclosure of this application, to ascertain a therapeutically effective amount of the compounds of the present invention for a given disease. Compounds of the invention may be administered as pharmaceutical formulations including those suitable for enteral or parenteral administration. The preferred manner of administration is generally oral using a convenient daily dosage regimen which can be adjusted according to the degree of affliction.

The compound of the present invention is contemplated as useful for the treatment of diseases caused by RNA viral infection in a mammal, e.g. non-enveloped single-stranded (+) RNA viral infection, in particular diseases caused by picornaviruses, which is either a human or animal, but preferably a human. The picornavirus e.g. may be a Parechovirus (e.g. Ljungan or Parecho), a Cardiovirus (e.g. EMCV or Theiler's virus), Enterovirus (e.g. EV, Coxsackie, Polio, Rhino) or a hepatovirus. For veterinary use, the picornavirus may be e.g. an Aphthovirus or a Teschovirus.

In some embodiments, the viral disease is one linked to or caused by an enterovirus, a coxsackie virus; or a polio virus.

In some embodiments, the viral disease is one linked to or caused by an enterovirus. In some embodiments, the viral disease is one linked to or caused by a coxsackie virus. In some embodiments, the viral disease is one linked to or caused by a polio virus.

Diseases that are considered to be linked to, caused by, or otherwise associated with virus infection, e.g. by picornaviruses, are e.g. neurodegenerative diseases such as multiple sclerosis, Parkinson's disease, amyotrophic lateral sclerosis, Alzheimer's disease, Huntington's disease, poliomyelitis, encephalitis, meningitis, sepsis, cancer, paralysis, myocarditis, diabetes, common cold, hand-foot-and-mouth disease, herpangina, pleurodynia, diarrhea, mucocutaneous lesions, respiratory illness, conjunctivitis, myositis, and chronic fatigue syndrome.

The present invention consequently also includes a compound of formula (I) for use in the treatment of any of the above mentioned conditions, as well as the use of a compound of formula (I) in the manufacturing of a medicament for the treatment of any of the above mentioned conditions and a method of treatment of any of the above mentioned conditions, by administering to an animal or human in need thereof, a compound of formula (I).

The invention is further illustrated by some non-limiting examples.

EXAMPLES

A number of compounds of the inventions (Examples 1-32) were synthesized by following the general procedure illustrated in Reaction Scheme 1, as described herein below:

Step-1

To a solution of **1** (10.0 g, 56.4 mmol) in ethyl acetate (200 mL) was added sodium metal (2.6 g, 112.8 mmol) portion wise at 0-5 °C under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 6h. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was cooled to 0-5°C, quenched with methanol (50 mL) and the solvent was evaporated under pressure. The resultant solid was dissolved in water (100 mL) and washed with toluene (2 × 100 mL). The aqueous solution was acidified with acetic acid (pH 4 to 5) and extracted with dichloromethane (3 × 100 mL). The combined organic layer was washed with water, brine, dried over sodium sulphate, filtered and concentrated under reduced pressure. The crude material was purified by recrystallization using ethyl acetate and hexane to afford **2** (9.5 g, 76.8%) as pale brown solid.

Step-2

To a solution of **2** (9.0 g, 41.05 mmol) in ethanol (90 mL) was added hydrazine monohydrochloride (4.218 g, 61.57 mmol) and acetic acid (2.7 mL, 2.83 g, 47.166 mmol) at room temperature under nitrogen atmosphere. The reaction mixture was heated to 85 °C and stirred for 5-6 h. The reaction was monitored by TLC. After completion of the reaction, the reaction mixture was cooled to room temperature. The reaction mixture was quenched with water (90 mL), concentrated under reduced pressure. The resultant aqueous layer was washed with toluene (3 × 45 mL) and basified with 10% aq. sodium bicarbonate solution (pH: 8-9). The aqueous layer was extracted with dichloromethane (4 × 50 mL). The combined organic

layer was washed with water, brine, dried over sodium sulphate and concentrated under reduced pressure to afford 3 (7.6 g, 79.36%) as an off-white solid. The product obtained was used without further purification.

Step-3:

To a suspension of **3** (3.0 g, 12.86 mmol) in acetonitrile (75 mL) was added DIPEA until the reaction mixture showed pH in the range of 9-10. To the reaction mixture was added ethyl acetimidate hydrochloride (2.38 g, 19.26 mmol) at room temperature under nitrogen atmosphere. The reaction mixture was again basified with DIPEA (pH 9-10). To the mixture was added acetic acid (0.77 mL, 12.8 mmol) and the mixture was stirred for 16 h at room temperature. The reaction mixture then was diluted with diethyl ether (30 mL), the solid formed was filtered and dried under reduced pressure at 50-55 °C to get **4** (2.5 g, 70.86%) as a colorless solid.

Step-4:

Sodium metal (0.628 g, 27.3 mmol) was dissolved in absolute ethanol (18 mL) at room temperature under nitrogen atmosphere. To the clear solution were added **4** (0.6 g, 2.187 mmol) and diethyl carbonate (2.65 mL, 21.8 mmol) at room temperature and the reaction mixture was heated to reflux for 16 h. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was cooled to room temperature and quenched with water (30 mL). The resultant mass was concentrated under reduced pressure at 50-55 °C. The residue was diluted with water, acidified with acetic acid (pH 5-6), extracted with dichloromethane (3 × 10 mL), the combined organic extract was washed with water, brine, dried over sodium sulphate, filtered and concentrated under reduced pressure to afford **5** (0.420 g, 63.94%) as colorless solid.

Step-5:

To a suspension of **5** (0.7 g, 2.331 mmol) in dry toluene (15 mL) were added phosphoryl chloride (5.44 mL, 8.948 g, 58.36 mmol) and N,N-diethyl aniline (0.748 mL, 0.7 g, 4.702 mmol) at room temperature under nitrogen atmosphere. The reaction mixture was then heated to 105 °C for 16 h. After 16 h, the reaction mixture was concentrated under reduced pressure at 50-55 °C and co-evaporated with toluene under reduced pressure. The crude material **6** (0.53 g, quantitative) obtained was used as such without further purification.

Step-6:

To a solution of **6** (1.0 eq.) in toluene or acetonitrile or DMF (10-20 V) were added the respective amine (1.3 eq.) and base [DIPEA (5 V)/ K_2CO_3 / KO^tBu / NaH (2.0 eq.)] sequentially. The reaction mixture was then stirred at room temperature or at 90 °C for 16 h. The progress of the reaction was monitored by TLC. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was diluted with water (20 V), extracted with dichloromethane (3 × 10 V). The combined organic extract was washed with water, brine, dried over sodium sulphate, filtered and concentrated under reduced pressure. The crude material was purified by flash column chromatography (silica gel, 50% EtOAc in Hexane) to afford the desired compound of formula (I) with >95% HPLC purity.

The chemical names of the compounds of Examples 1-32 are given in **Table 1**.

Table 1

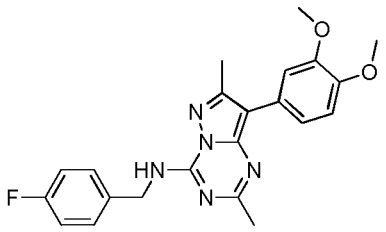
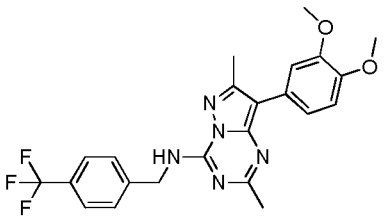
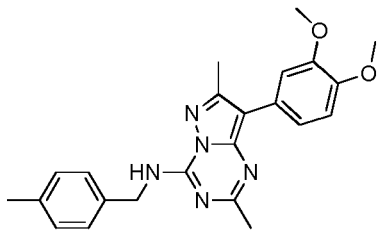
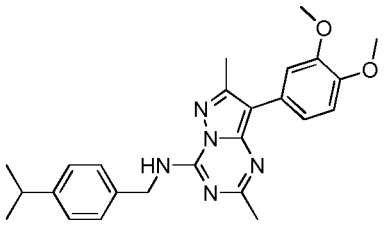
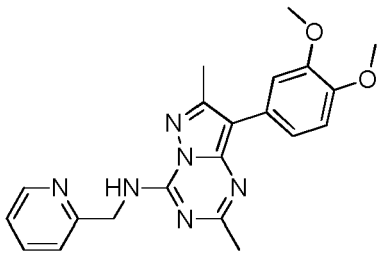
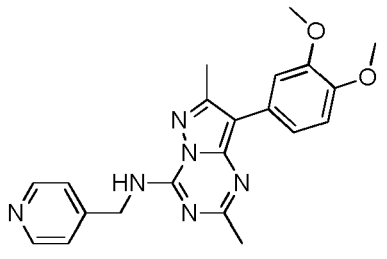
Ex.	Chemical name
1	8-(3,4-dimethoxyphenyl)-N-[(4-fluorophenyl)methyl]-2,7-dimethyl-pyrazolo[1,5-a][1,3,5]triazin-4-amine
2	8-(3,4-dimethoxyphenyl)-2,7-dimethyl-N-[[4-(trifluoromethyl)phenyl]methyl]pyrazolo[1,5-a][1,3,5]triazin-4-amine
3	8-(3,4-dimethoxyphenyl)-2,7-dimethyl-N-(p-tolylmethyl)pyrazolo[1,5-a][1,3,5]triazin-4-amine
4	8-(3,4-dimethoxyphenyl)-N-[(4-isopropylphenyl)methyl]-2,7-dimethyl-pyrazolo[1,5-a][1,3,5]triazin-4-amine
5	8-(3,4-dimethoxyphenyl)-2,7-dimethyl-N-(2-pyridylmethyl)pyrazolo[1,5-a][1,3,5]triazin-4-amine
6	8-(3,4-dimethoxyphenyl)-2,7-dimethyl-N-(4-pyridylmethyl)pyrazolo[1,5-a][1,3,5]triazin-4-amine
7	N-[2-(4-chlorophenyl)ethyl]-8-(3,4-dimethoxyphenyl)-2,7-dimethyl-pyrazolo[1,5-a][1,3,5]triazin-4-amine
8	N-[(4-chlorophenyl)methyl]-8-(3,4-dimethoxyphenyl)-2,7-dimethyl-pyrazolo[1,5-a][1,3,5]triazin-4-amine

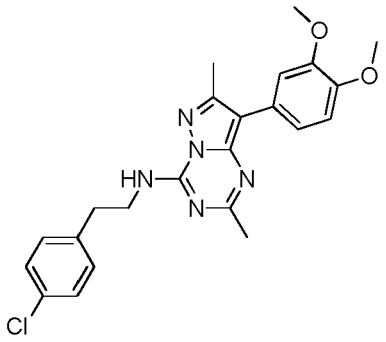
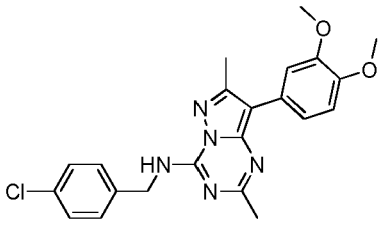
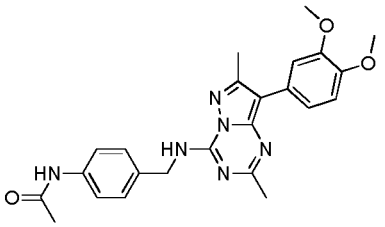
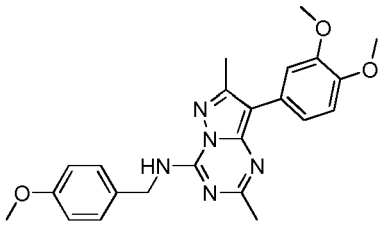
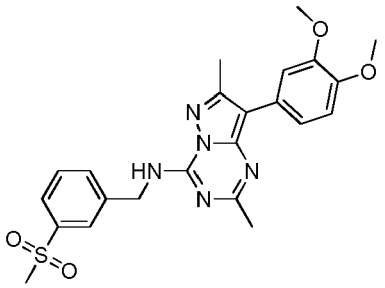
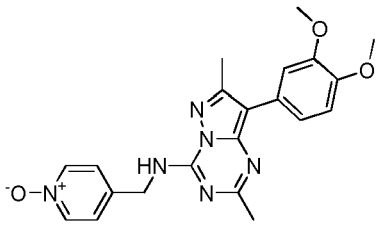
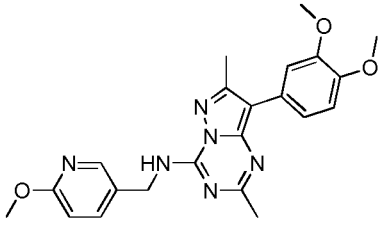
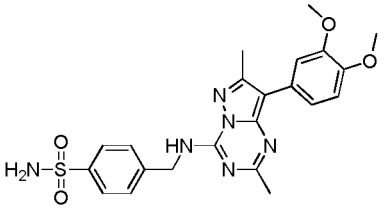
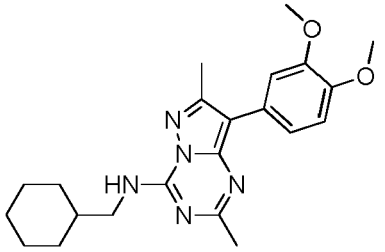
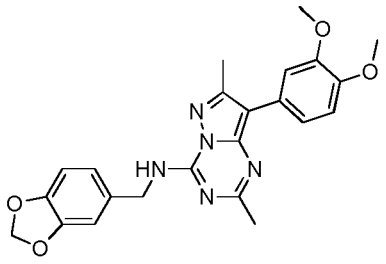
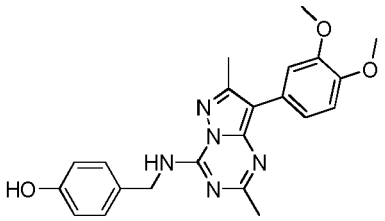
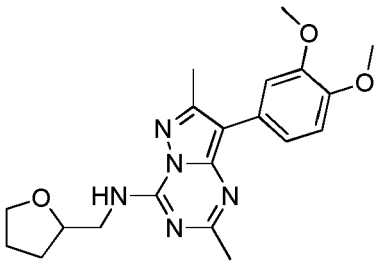
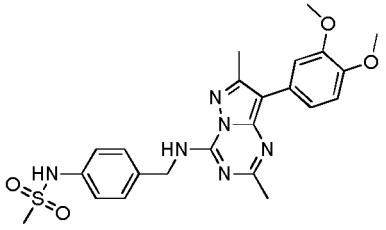
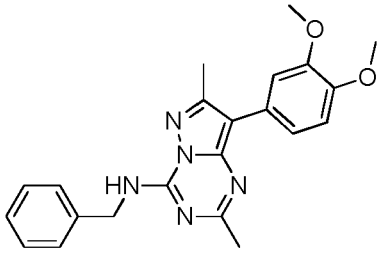
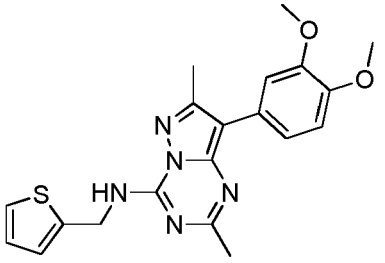
Ex.	Chemical name
9	N-[4-[[[8-(3,4-dimethoxyphenyl)-2,7-dimethyl-pyrazolo[1,5-a][1,3,5]triazin-4-yl]amino]methyl]phenyl]acetamide
10	8-(3,4-dimethoxyphenyl)-N-[(4-methoxyphenyl)methyl]-2,7-dimethyl-pyrazolo[1,5-a][1,3,5]triazin-4-amine
11	8-(3,4-dimethoxyphenyl)-2,7-dimethyl-N-[(3-methylsulfonylphenyl)methyl]pyrazolo[1,5-a][1,3,5]triazin-4-amine
12	8-(3,4-dimethoxyphenyl)-2,7-dimethyl-N-[(1-oxidopyridin-1-ium-4-yl)methyl]pyrazolo[1,5-a][1,3,5]triazin-4-amine
13	8-(3,4-dimethoxyphenyl)-N-[(6-methoxy-3-pyridyl)methyl]-2,7-dimethyl-pyrazolo[1,5-a][1,3,5]triazin-4-amine
14	4-[[[8-(3,4-dimethoxyphenyl)-2,7-dimethyl-pyrazolo[1,5-a][1,3,5]triazin-4-yl]amino]methyl]benzenesulfonamide
15	N-(cyclohexylmethyl)-8-(3,4-dimethoxyphenyl)-2,7-dimethyl-pyrazolo[1,5-a][1,3,5]triazin-4-amine
16	N-(1,3-benzodioxol-5-ylmethyl)-8-(3,4-dimethoxyphenyl)-2,7-dimethyl-pyrazolo[1,5-a][1,3,5]triazin-4-amine
17	4-[[[8-(3,4-dimethoxyphenyl)-2,7-dimethyl-pyrazolo[1,5-a][1,3,5]triazin-4-yl]amino]methyl]phenol
18	8-(3,4-dimethoxyphenyl)-2,7-dimethyl-N-(tetrahydrofuran-2-ylmethyl)pyrazolo[1,5-a][1,3,5]triazin-4-amine
19	N-[4-[[[8-(3,4-dimethoxyphenyl)-2,7-dimethyl-pyrazolo[1,5-a][1,3,5]triazin-4-yl]amino]methyl]phenyl]methanesulfonamide
20	N-benzyl-8-(3,4-dimethoxyphenyl)-2,7-dimethyl-pyrazolo[1,5-a][1,3,5]triazin-4-amine
21	8-(3,4-dimethoxyphenyl)-2,7-dimethyl-N-(2-thienylmethyl)pyrazolo[1,5-a][1,3,5]triazin-4-amine
22	8-(3,4-dimethoxyphenyl)-2,7-dimethyl-N-(3-pyridylmethyl)pyrazolo[1,5-a][1,3,5]triazin-4-amine
23	8-(3,4-dimethoxyphenyl)-2,7-dimethyl-N-[(5-methyl-2-furyl)methyl]pyrazolo[1,5-a][1,3,5]triazin-4-amine
24	methyl N-[4-[[[8-(3,4-dimethoxyphenyl)-2,7-dimethyl-pyrazolo[1,5-a][1,3,5]triazin-4-yl]amino]methyl]phenyl]sulfonylcarbamate

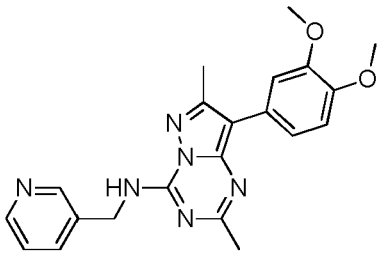
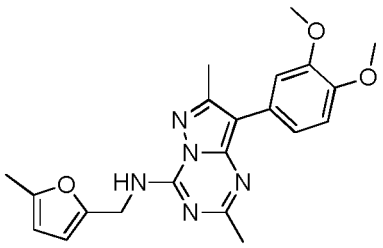
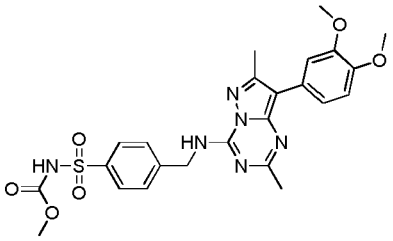
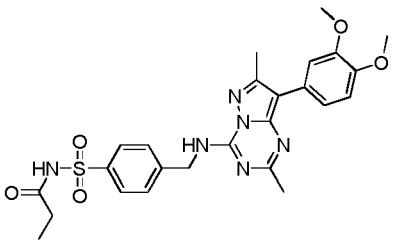
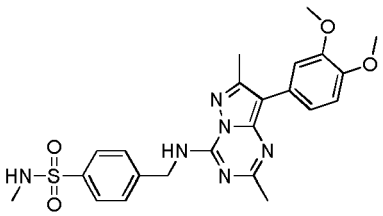
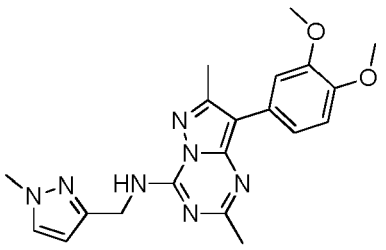
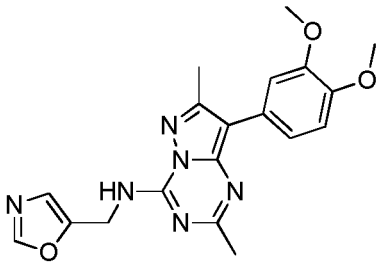
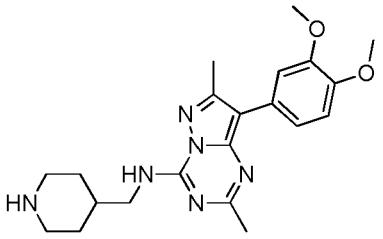
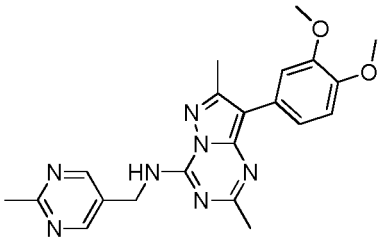
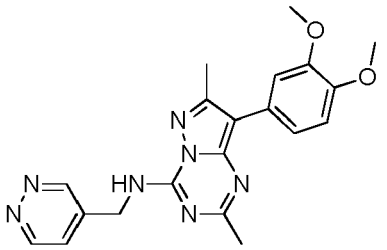
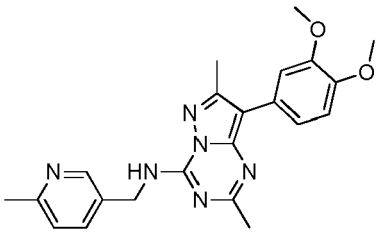
Ex.	Chemical name
25	N-[4-[[[8-(3,4-dimethoxyphenyl)-2,7-dimethyl-pyrazolo[1,5-a][1,3,5]triazin-4-yl]amino]methyl]phenyl]sulfonylpropanamide
26	N-methyl-4-[[[8-(3,4-dimethoxyphenyl)-2,7-dimethyl-pyrazolo[1,5-a][1,3,5]triazin-4-yl]amino]methyl]benzenesulfonamide
27	8-(3,4-dimethoxyphenyl)-2,7-dimethyl-*N*-[(1-methyl-1*H*-pyrazol-3-yl)methyl]pyrazolo[1,5-*a*][1,3,5]triazin-4-amine
28	8-(3,4-dimethoxyphenyl)-2,7-dimethyl-*N*-[(1,3-oxazol-5-yl)methyl]pyrazolo[1,5-a][1,3,5]triazin-4-amine
29	8-(3,4-dimethoxyphenyl)-2,7-dimethyl-*N*-[(piperidin-4-yl)methyl]pyrazolo[1,5-a][1,3,5]triazin-4-amine
30	8-(3,4-dimethoxyphenyl)-2,7-dimethyl-*N*-[(2-methylpyrimidin-5-yl)methyl]pyrazolo[1,5-*a*][1,3,5]triazin-4-amine
31	8-(3,4-dimethoxyphenyl)-2,7-dimethyl-*N*-[(pyridazin-4-yl)methyl]pyrazolo[1,5-a][1,3,5]triazin-4-amine
32	8-(3,4-dimethoxyphenyl)-2,7-dimethyl-*N*-[(6-methylpyridin-3-yl)methyl]pyrazolo[1,5-a][1,3,5]triazin-4-amine

The structural formulas of the compounds of Examples 1-32 are shown in **Table 2**.

Table 2

Ex. 1 	Ex. 2 	Ex. 3 
Ex.4 	Ex. 5 	Ex. 6 

Ex. 7 	Ex. 8 	Ex. 9 
Ex. 10 	Ex. 11 	Ex. 12 
Ex. 13 	Ex. 14 	Ex. 15 
Ex. 16 	Ex. 17 	Ex. 18 
Ex. 19 	Ex. 20 	Ex. 21 

Ex. 22 	Ex. 23 	Ex. 24 
Ex. 25 	Ex. 26 	Ex. 27 
Ex. 28 	Ex. 29 	Ex. 30 
Ex. 31 	Ex. 32 	

Analytical data for the compounds of Examples 1-32 are shown in **Table 3**.

Table 3

Ex.	Analytical Data
1	^{1}H-NMR (DMSO, 300 MHz): δ 8.35 (t, 1 H), 7.42 (t, 2 H), 7.12 (t, 2 H), 7.03 (d, 1 H), 6,93 (d, 1 H), 6.66 (s, 1 H), 4.66 (d, 2 H), 3.78 (d, 6 H), 2.44 (s, 3 H), 2.24 (s, 3 H), LCMS : 407.6 [M+H], HPLC purity: 99.98%

Ex.	Analytical Data
2	^{1}H-NMR (MeOD, 300 MHz): δ 7.31 (d, 2 H), 7.23 (d, 1 H), 7.17 (d, 2 H), 7.10 (d, 1 H), 7.05 (d, 1 H), 4.79 (d, 2 H), 3.89 (d, 6 H), 2.50 (s, 3 H), 2.46 (s, 3 H), 2.33 (s, 3 H), LCMS : 404.6 [M+H], HPLC purity: 99.59%
3	^{1}H-NMR (CDCl3, 300 MHz): δ 7.65 (d, 2 H), 7.55 (d, 2 H), 7.18 (d, 1 H), 6.98 (d, 1 H), 6.81 (d, 1 H), 4.95 (d, 2 H), 3.96 (d, 6 H), 2.57 (s, 3 H), 2.55 (s, 3 H), LCMS : 458.6 [M+H], HPLC purity: 99.89%
4	^{1}H-NMR (MeOD, 300 MHz): δ 7.33 (d, 2 H), 7.22 (t, 3 H), 7.09 (d, 1 H), 7.04 (d, 1 H), 4.79 (s, 2 H), 3.89 (d, 6 H), 2.89 (m, 1 H), 2.49 (s, 3 H), 2.46 (s, 3 H), 1.25 (s, 3 H), 1.29 (s, 3 H), LCMS : 432.7 [M+H], HPLC purity: 99.87%
5	^{1}H-NMR (MeOD, 300 MHz): δ 8.55 (d, 1 H), 7.83 (t, 1 H), 7.50 (d, 1 H), 7.35 (dd, 1 H), 7.25 (d, 1 H), 7.12 (dd, 1 H), 7.05 (d, 1 H), 4.96 (s, 2 H), 3.89 (d, 6 H), 2.53 (s, 3 H), 2.43 (s, 3 H), LCMS : 391.6 [M+H], HPLC purity: 98.99%
6	^{1}H-NMR (MeOD, 300 MHz): δ 8.78 (d, 2 H), 8.06 (d, 2 H), 7.23 (d, 1 H), 7.13 (d, 1 H), 7.06 (d, 1 H), 5.13 (s, 2 H), 3.89 (d, 6 H), 2.54 (s, 3 H), 2.42 (s, 3 H), LCMS : 391.4 [M+H], HPLC purity: 96.53%
7	^{1}H-NMR (MeOD, 300 MHz): δ 7.28 (s, 4 H), 7.22 (d, 1 H), 7.09 (d, 1 H), 7.04 (d, 1 H), 3.89 (d, 6 H), 3.84 (t, 2 H), 3.01 (t, 2 H), 2.49 (s, 3 H), 2.44 (s, 3 H), LCMS : 438.5 [M+H], HPLC purity: 99.45%
8	^{1}H-NMR (DMSO, 300 MHz): δ 7.39 (s, 4 H), 7.30 (d, 1 H), 7.17 (dd, 1 H), 7.04 (d, 1 H), 4.69 (d, 2 H), 3.79 (d, 6 H), 2.49 (s, 3 H), 2.38 (s, 3 H), LCMS : 424.7 [M+H], HPLC purity: 99.94%
9	^{1}H-NMR (MeOD, 300 MHz): δ 7.79 (d, 2 H), 7.63 (d, 2 H), 7.28 (d, 1 H), 7.15 (dd, 1 H), 7.96 (d, 1 H) 3.90 (d, 6 H), 2.57 (s, 3 H), 2.50 (s, 3 H), 2.15 (s, 3 H), LCMS : 433.6 [M+H], HPLC purity: 98.27%
10	^{1}H-NMR (MeOD, 300 MHz): δ 7.35 (d, 2 H), 7.23 (s, 1 H), 7.11 (m, 1 H), 7.05 (d, 1 H), 6.90 (d, 2 H), 4.75 (s, 2 H), 3.89 (d, 6 H), 3.78 (s, 2 H), 2.49 (d, 6 H), LCMS : 420.5 [M+H], HPLC purity: 99.64%
11	^{1}H-NMR (TFA, 300 MHz): δ 11.58, (s, 1 H), 8.25 (s, 1H), 8.03 (d, 1 H), 7.92 (d, 1 H), 7.74 (t, 1 H), 7.14 (d, 1 H), 6.98 (t, 2 H), 5.26 (s, 2 H), 4.01 (s, 3 H), 3.97 (s, 3 H), 3.30 (s, 3 H), 2.77 (s, 3 H), 2.51 (s, 3 H), LCMS : 468.3[M+H], HPLC purity: 99.86%

Ex.	Analytical Data
12	^{1}H-NMR (DMSO, 300 MHz): δ 9.25, (t, 1 H), 8.15 (d, 2H), 7.38 (d, 1 H), 7.30 (d, 1 H), 7.17 (dd, 1 H), 7.02 (d, 1 H), 4.67 (d, 2 H), 3.78 (d, 6 H), 2.52 (s, 3 H), 2.37 (s, 3 H), LCMS : 407.8 [M+H], HPLC purity: 98.86%
13	^{1}H-NMR (DMSO, 300 MHz): δ 9.19, (t, 1 H), 8.20 (d, 2H), 7.76 (dd, 1 H), 7.29 (d, 1 H), 7.17 (dd, 1 H), 7.02 (d, 1 H), 6.78 (d, 1 H), 4.63 (d, 2 H), 3.92 (s, 3 H), 3.78, (s, 3 H), 2.41 (s, 3 H), LCMS : 421.7 [M+H], HPLC purity: 99.54%
14	^{1}H-NMR (DMSO, 300 MHz): δ 9.29, (t, 1 H), 7.78 (d, 2H), 7.54 (d, 2 H), 7.31 (s, 1 H), 7. 29 (d, 2 H), 7.17 (dd, 1 H), 7.03 (d, 1 H), 4.78 (d, 2 H), 3.79 (d, 6 H), 2.53 (s, 3 H), 2.36 (s, 3 H), LCMS : 469.8 [M+H], HPLC purity: 98.53%
15	H-NMR (DMSO, 300 MHz): δ7.22 (s, 1 H), 7. 09 (dd, 1 H), 7.03 (d, 1 H), 3.88 (d, 6 H), 3.48 (d, 2 H), 2.49 (s, 3 H), 2.44 (s, 3 H), 1.78 (m, 6 H), 1.28 (m, 4 H), 1.06 (m, 2 H), LCMS : 396.4 [M+H], HPLC purity: 99.77%
16	^{1}H-NMR (DMSO, 300 MHz): δ 9.12, (t, 1 H), 7.30 (d, 1H), 7.17 (dd, 1 H), 7.02 (d, 1 H), 6.97 (d, 1 H), 6.85 (s, 2 H), 5.97 (s, 2 H), 4.60 (d, 2 H), 3.78 (s, 6 H), 2.50 (s, 3 H), 2.39 (s, 3 H), LCMS : 434.0 [M+H], HPLC purity: 99.84%
17	^{1}H-NMR (MeOD, 300 MHz): δ 7.26, (d, 2 H), 7.22 (d, 1H), 7.10 (dd, 1 H), 7.03 (d, 1 H), 6.76 (d, 2 H), 4.71 (s, 2 H), 3.88 (s, 6 H), 2.47 (d, 6 H), LCMS : 406.4 [M+H], HPLC purity: 97.37%
18	^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.30 (d, 1 H), 7.17 (dd, 1 H), 6.96 (d, 1 H), 6.73 (br, 1 H), 4.18 (m, 1 H), 3.92 (m, 1 H), 3.94 (s, 3 H), 3.90 (s, 3 H), 3.86 (m, 1 H), 3.82 (m, 1 H), 3.61 (m, 1 H), 2.54 (d, 6 H), 2.08 (m, 1 H), 1.96 (m, 1 H), 1.68 (m, 1 H), LCMS : 384.1 [M+H], HPLC purity: 97.65%
19	^{1}H-NMR (MeOD, 300 MHz): δ 9.68 (s, 1 H), 9.16 (t, 1 H), 7.35 (d, 1H), 7.30 (d, 1 H), 7.16 (m, 3 H), 7.02 (d, 1 H), 4.66 (d, 2 H), 3.78 (s, 6 H), 2.67 (s, 3 H), 2.50 (s, 3 H), 2.32 (s, 3 H), LCMS : 483.1 [M+H], HPLC purity: 99.45%
20	^{1}H-NMR (DMSO, 300 MHz): δ 9.20 (t, 1 H), 7.37 (d, 2 H), 7.30 (m, 3 H), 7.25 (d, 1 H), 7.17 (d, 1 H), 7.02 (d, 1 H), 4.72 (d, 2 H), 3.78 (s, 6 H), 2.50 (s, 3 H), 2.38 (s, 3 H), LCMS : 390.1 [M+H], HPLC purity: 99.90%
21	^{1}H-NMR (DMSO, 300 MHz): δ 9.27 (t, 1 H), 7.39 (dd, 1 H), 7.30 (d, 1 H), 7.09 (d, 1 H), 7.02 (d, 1 H), 6.97 (d, 1 H), 4.84 (d, 2 H), 3.78 (d, 6 H), 2.50 (s, 3 H), 2.43 (s, 3 H), LCMS : 396.1 [M+H], HPLC purity: 99.96%

Ex.	Analytical Data
22	^{1}H-NMR (DMSO, 300 MHz): δ 9.26 (t, 1 H), 8.62 (d, 1 H), 8.47 (dd, 1 H), 7.80 (m, 1 H), 7.35 (dd, 1 H), 7.29 (d, 1 H), 7.17 (dd, 1 H), 7.02 (d, 1 H), 4.72 (d, 2 H), 3.78 (d, 6 H), 2.50 (s, 3 H), 2.39 (s, 3 H), LCMS : 391.1 [M+H], HPLC purity: 99.97%
23	^{1}H-NMR (DMSO, 300 MHz): δ 9.26 (bs, 1 H), 7.30 (d, 1 H), 7.17 (dd, 1 H), 7.02 (d, 1 H), 6.18 (d, 1 H), 5.99 (d, 1 H), 4.63 (d, 2 H), 3.78 (d, 6 H), 2.50 (s, 3 H), 2.40 (s, 3 H), 2.20 (s, 3 H), LCMS : 394.1 [M+H], HPLC purity: 99.61%
24	^{1}H-NMR (DMSO, 300 MHz): δ 12.01 (s, 1 H), 9.30 (t, 1 H), 7.85 (d, 2 H), 7.59 (d, 2 H), 7.30 (s, 1 H), 7.18 (d, 1 H), 7.03 (d, 1 H), 4.80 (d, 2 H), 3.98 (q, 2 H), 3.79 (d, 6 H), 2.52 (s, 3 H), 2.36 (s, 3 H), 1.10 (t, 3 H), LCMS : 541.0 [M+H], HPLC purity: 97.51%
25	^{1}H-NMR (DMSO, 300 MHz): δ 12.01 (s, 1 H), 9.29 (t, 1 H), 7.88 (d, 2 H), 7.58 (d, 2 H), 7.30 (s, 1 H), 7.18 (d, 1 H), 7.03 (d, 1 H), 4.80 (d, 2 H), 3.79 (d, 6 H), 2.52 (s, 3 H), 2.34 (s, 3 H), 2.18 (t, 2 H), 0.87 (t, 3 H), LCMS : 525.0 [M+H], HPLC purity: 99.96%
26	^{1}H-NMR (DMSO, 300 MHz): δ 9.30 (t, 1 H), 7.75 (d, 2 H), 7.57 (d, 2 H), 7.42 (dd, 1 H), 7.30 (s, 1 H), 7.18 (d, 1 H), 7.03 (d, 1 H), 4.80 (d, 2 H), 3.79 (d, 6 H), 2.52 (s, 3 H), 2.37 (s, 3 H), 2.33 (t, 2 H), LCMS : 483.2 [M+H], HPLC purity: 97.8%
27	^{1}H-NMR (DMSO, 300 MHz): δ 8.90 (t, 1 H), 7.57 (d, 1 H), 7.30 (d, 1 H), 7.18 (dd, 1 H), 7.02 (d, 1 H), 6.18 (d, 1 H), 4.65 (d, 2 H), 3.79 (d, 9 H), 2.52 (s, 3 H), 2.39 (s, 3 H), LCMS : 394.2 [M+H], HPLC purity: 99.0%
28	^{1}H-NMR (DMSO, 300 MHz): δ 8.16 (s, 1 H), 7.23 (d, 1 H), 7.13 (d, 1 H), 7.09 (dd, 1 H), 7.03 (d, 1 H), 4.91 (d, 2 H), 3.87 (d, 6 H), 2.49 (d, 6 H), LCMS : 381.2 [M+H], HPLC purity: 98.3%
29	^{1}H-NMR (MeOD, 300 MHz): δ 7.12 (d, 1 H), 7.01 (d, 2 H), 3.89 (d, 6 H), 3.74 (d, 2 H), 3.45 (d, 2 H), 3.04 (t, 2 H), 2.63 (s, 3 H), 2.45 (s, 3 H), 2.15 (b, 1 H), 2.05 (d, 2 H), 1.60 (b, 2 H), LCMS : 397.2 [M+H], HPLC purity: 99.9%
30	^{1}H-NMR (MeOH, 300 MHz): δ 8.79 (s, 2 H), 7.22 (d, 1 H), 7.10 (dd, 1 H), 7.03 (d, 1 H), 4.80 (s, 2 H), 3.87 (s, 6 H), 2.67 (s, 3 H), 2.49 (s, 3 H), 2.45 (s, 3 H), LCMS : 406.2 [M+H], HPLC purity: 99.4%
31	^{1}H-NMR (MeOD, 300 MHz): δ 9.28 (d, 1 H), 9.13 (dd, 1 H), 7.75 (d, 1 H), 7.23 (d, 1 H), 7.12 (dd, 1 H), 7.03 (d, 1 H), 4.91 (d, 2 H), 3.88 (s, 6 H), 2.51 (s, 3 H), 2.41 (s, 3 H), LCMS : 392.2 [M+H], HPLC purity: 98.8%

Ex.	Analytical Data
32	^{1}H-NMR (DMSO, 300 MHz): δ 9.22 (t, 1 H), 8.48 (d, 1 H), 7.67 (dd, 1 H), 7.29 (d, 1 H), 7.18 (dd, 1 H), 7.03 (d, 1 H), 4.66 (d, 2 H), 3.78 (s, 6 H), 2.42 (s, 3 H), 2.39 (s, 3 H), LCMS : 405.2 [M+H], HPLC purity: 99.9%

BIOLOGICAL ASSAYS

Phosphatidyl inositol kinase inhibition assay

Inhibition of PI4 kinases was studied using the ADP-Glo™ Kinase Assay which is a luminescent kinase assay that measures ADP formed from a kinase reaction; ADP is converted into ATP, which is converted into light by Ultra-Glo™ Luciferase. The assay is performed in two steps; first, after the kinase reaction, an equal volume of ADP-Glo™ Reagent is added to terminate the kinase reaction and deplete the remaining ATP. In the second step, the Kinase Detection Reagent is added, which simultaneously converts ADP to ATP and allows the newly synthesized ATP to be measured using a coupled luciferase/luciferin reaction. The luminescent signal produced is proportional to the activity of the kinase.

Inhibition of PI3 kinases was studied using the HTRF (homogeneous time-resolved flouorescence) assay which is a universal method for identifying and characterizing the phosphotransferase activity induced by any ATP/ADP dependent target. The formation of ADP is detected by a specific monoclonal antibody labeled with Eu^{3+} cryptate, and directly correlates with the amount of phosphorylated substrate in kinase assays

Table 4 shows test results, expressed as IC_{50} values (in μM) of some compounds of the invention vs. different kinases.

Table 4

Kinase	Example 6 IC_{50} (μM)	Example 14 IC_{50} (μM)
PI4KIIIβ	0.0013	0.0021
PI4KIIIα	3.2	1.3
PI3Kβ	>10	>10
PI3Kα	7.3	>10

In vitro assay in mammalian cell culture

The antiviral activity of compounds of the invention has been evaluated based on the ability of the compounds to prevent virus from causing viral cytopathic effects (CPE) in mammalian cell culture. Incubation time, cell line, cell density and virus titer differed from assay to assay but the general procedure was as follows: Cells were cultivated on 96 well flat bottom plates to approximately 90 % confluence (20 000-90 000 cells/well) in a suitable media. The titer of the virus was determined by the standard method of tissue culture infective dose ($TCID_{50}$) on cells. Briefly, cells were infected with 50 µl of virus suspension, and diluted 10-fold in media. The plates were incubated in 37 °C with 5 % CO_2 for 3-7 days and cells were inspected daily for CPE. After determining CPE, plates were stained with Gram's Crystal Violet solution and optical density was read at 540 nm. The highest virus dilution that resulted in > 95 % CPE was used in the assays. Substances at a final concentration of 2.5-20 µM and the virus were added to the cells and incubated for 3-7 days depending on the virus and cell line used. As controls, uninfected cells and cells infected with virus (no substance) were included on each plate. The cells were stained with crystal violet after determining the CPE on infected controls and the optical density was read at 540 nm. The inhibition capacity was calculated as a % by comparison with non-infected and infected controls.

Table 5 shows the inhibition capacity of compounds of the invention on different enteroviruses. + indicates IC_{50} <1 □M; ++ indicates IC_{50} <100 nM; +++ indicates IC_{50} <10 nM; EV6: Enterovirus 6; EV30: Enterovirus 30; EV68: Enterovirus 68; EV71: Enterovirus 71; B1: coxsackie B1 virus; B2: coxsackie B2 virus; B3: coxsackie B3 virus ; B4: coxsackie B 4 virus ; B5: coxsackie B5virus; Polio1: polio virus Sabin 1.

Table 5

Ex.	EV6	EV30	EV68	EV71	B1	B2	B3	B4	B5	Polio 1
1	+	++	nd	+++	++	+++	+	nd	++	+++
2	+	++	+	+	++	++	+	++	++	++
3	+	++	++	++	++	++	++	++	++	++
4	+	+	+	+	+	+	+	+	+	+
5	+	+	+	+	++	++	+	+	+	++
6	+++	++	+++	+++	+++	+++	+++	+++	+++	+++

Ex.	EV6	EV30	EV68	EV71	B1	B2	B3	B4	B5	Polio 1
7	+	+	+	+	+	+	+	+	+	+
8	+	++	++	+	++	++	++	++	+	++
9	++	++	++	++	+	++	++	++	++	+++
10	+	++	++	+	++	++	+	++	++	++
11	++	+++	++	++	+++	+++	+++	+++	+++	+++
12	nd	+	+	+	+	+	+	+	+	+
13	nd	+++	++	++	+++	++	++	++	++	+++
14	nd	+++	+++	+++	++	++	++	++	+++	+++
15	+	+	+	+	+	+	+	+	+	+
16	+	++	++	++	++	++	++	+++	++	++
17	++	++	++	+++	+++	+++	++	++	+++	+++
18	+	+	+	+	+	+	+	+	+	+
19	+	++	++	+++	++	++	++	+++	+	++
20	++	++	++	++	++	++	++	+++	++	++
21	++	++	++	++	+++	+++	++	++	++	++
22	++	++	++	++	++	++	++	++	++	++
23	++	++	++	++	+++	++	++	+++	++	+++
24	-	-	+	+	-	+	-	+	-	+
25	-	-	+	-	-	-	-	-	-	-
26	+	+	-	+	+	++	+	++	+	++
27	+	++	+++	++	+++	+++	++	+++	++	+++
28	++	-	+++	++	++	++	++	++	+	++
29	-	-	-	-	-	-	-	-	-	-
30	+	++	++	++	+	+	+	++	+	++
31	+	-	++	++	+	+	+	+++	+	+
32	++	+++	++	++	++	++	+++	++	++	++

In **Table 5** the signs have the following meaning:

+ $IC_{50} < 1$ μM

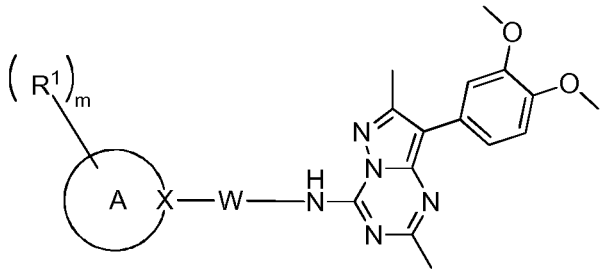
++ $IC_{50} < 100$ nM

+++ $IC_{50} < 10$ nM

- Not determined or $IC_{50} > 1$ μM

CLAIMS

1. A compound of formula (I)



(I)

or a pharmaceutically acceptable salt thereof, wherein

W is CH_2 or CH_2-CH_2;

X is C or CH;

ring A is 5- or 6-membered carbocyclyl or 5- or 6-membered heterocyclyl;

m is an integer of from 0 to 3;

each R^1 is independently selected from C1-C6 alkyl optionally substituted by one or more halogen, R^2O, halogen, $R^3R^4NC(O)$, $R^5C(O)N(R^6)$, $R^7OC(O)$, $R^8C(O)O$, $R^9S(O)_2$, $R^{10}S(O)_2N(H)$, $R^{11}C(O)$, $R^{12}R^{13}N$, ^-O and $R^{14}R^{15}NS(O)_2$; and

when m is at least 2, two R^1 attached to adjacent atoms of ring A may form, together with the atoms to which they are attached, a 5- or 6-membered heterocyclic or carbocyclic ring;

each R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13} and R^{14} is independently selected from H and C1-C6 alkyl, wherein any alkyl is optionally substituted by one or more halogen;

R^{15} is selected from H, C1-C6 alkyl, $R^{16}C(O)$, $R^{17}OC(O)$, and $R^{18}R^{19}NC(O)$; and

each R^{16}, R^{17}, R^{18}, and R^{19} is independently selected from H and C1-C6 alkyl, wherein any alkyl is optionally substituted by one or more halogen.

2. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein ring A is 5- or 6-membered carbocyclyl.

3. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein ring A is phenyl or 5- or 6-membered heteroaryl.

4. The compound of any one of the claims 1 to 3, or a pharmaceutically acceptable salt thereof, wherein ring A is phenyl.

5. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein ring A is 5- or 6-membered heteroaryl.

6. The compound of any one of the claims 1 to 5, or a pharmaceutically acceptable salt thereof, wherein W is CH_2.

7. The compound of any one of the claims 1 to 6, or a pharmaceutically acceptable salt thereof, wherein m is an integer of from 0 to 2.

8. The compound of claim 7, or a pharmaceutically acceptable salt thereof, wherein m is 1 or 2.

9. The compound of any one of the claims 1 to 8, or a pharmaceutically acceptable salt thereof, wherein W is CH_2; X is C; and ring A is phenyl or 5- or 6-membered heteroaryl.

10. A compound according to claim 1, selected from
8-(3,4-dimethoxyphenyl)-N-[(4-fluorophenyl)methyl]-2,7-dimethyl-pyrazolo[1,5-a][1,3,5]triazin-4-amine,
8-(3,4-dimethoxyphenyl)-2,7-dimethyl-N-[[4-(trifluoromethyl)phenyl]methyl]pyrazolo[1,5-a][1,3,5]triazin-4-amine,
8-(3,4-dimethoxyphenyl)-2,7-dimethyl-N-(p-tolylmethyl)pyrazolo[1,5-a][1,3,5]triazin-4-amine,
8-(3,4-dimethoxyphenyl)-N-[(4-isopropylphenyl)methyl]-2,7-dimethyl-pyrazolo[1,5-a][1,3,5]triazin-4-amine,

8-(3,4-dimethoxyphenyl)-2,7-dimethyl-N-(2-pyridylmethyl)pyrazolo[1,5-a][1,3,5]triazin-4-amine,

8-(3,4-dimethoxyphenyl)-2,7-dimethyl-N-(4-pyridylmethyl)pyrazolo[1,5-a][1,3,5]triazin-4-amine,

N-[2-(4-chlorophenyl)ethyl]-8-(3,4-dimethoxyphenyl)-2,7-dimethyl-pyrazolo[1,5-a][1,3,5]triazin-4-amine,

N-[(4-chlorophenyl)methyl]-8-(3,4-dimethoxyphenyl)-2,7-dimethyl-pyrazolo[1,5-a][1,3,5]triazin-4-amine,

N-[4-[[[8-(3,4-dimethoxyphenyl)-2,7-dimethyl-pyrazolo[1,5-a][1,3,5]triazin-4-yl]amino]methyl]phenyl]acetamide,

8-(3,4-dimethoxyphenyl)-N-[(4-methoxyphenyl)methyl]-2,7-dimethyl-pyrazolo[1,5-a][1,3,5]triazin-4-amine,

8-(3,4-dimethoxyphenyl)-2,7-dimethyl-N-[(3-methylsulfonylphenyl)methyl]pyrazolo[1,5-a][1,3,5]triazin-4-amine,

8-(3,4-dimethoxyphenyl)-2,7-dimethyl-N-[(1-oxidopyridin-1-ium-4-yl)methyl]pyrazolo[1,5-a][1,3,5]triazin-4-amine,

8-(3,4-dimethoxyphenyl)-N-[(6-methoxy-3-pyridyl)methyl]-2,7-dimethyl-pyrazolo[1,5-a][1,3,5]triazin-4-amine,

4-[[[8-(3,4-dimethoxyphenyl)-2,7-dimethyl-pyrazolo[1,5-a][1,3,5]triazin-4-yl]amino]methyl]benzenesulfonamide,

N-(cyclohexylmethyl)-8-(3,4-dimethoxyphenyl)-2,7-dimethyl-pyrazolo[1,5-a][1,3,5]triazin-4-amine,

N-(1,3-benzodioxol-5-ylmethyl)-8-(3,4-dimethoxyphenyl)-2,7-dimethyl-pyrazolo[1,5-a][1,3,5]triazin-4-amine,

4-[[[8-(3,4-dimethoxyphenyl)-2,7-dimethyl-pyrazolo[1,5-a][1,3,5]triazin-4-yl]amino]methyl]phenol

8-(3,4-dimethoxyphenyl)-2,7-dimethyl-N-(tetrahydrofuran-2-ylmethyl)pyrazolo[1,5-a][1,3,5]triazin-4-amine,

N-[4-[[[8-(3,4-dimethoxyphenyl)-2,7-dimethyl-pyrazolo[1,5-a][1,3,5]triazin-4-yl]amino]methyl]phenyl]methanesulfonamide,

N-benzyl-8-(3,4-dimethoxyphenyl)-2,7-dimethyl-pyrazolo[1,5-a][1,3,5]triazin-4-amine,

8-(3,4-dimethoxyphenyl)-2,7-dimethyl-N-(2-thienylmethyl)pyrazolo[1,5-a][1,3,5]triazin-4-amine,

8-(3,4-dimethoxyphenyl)-2,7-dimethyl-N-(3-pyridylmethyl)pyrazolo[1,5-a][1,3,5]triazin-4-amine,
8-(3,4-dimethoxyphenyl)-2,7-dimethyl-N-[(5-methyl-2-furyl)methyl]pyrazolo[1,5-a][1,3,5]triazin-4-amine,
methyl N-[4-[[[8-(3,4-dimethoxyphenyl)-2,7-dimethyl-pyrazolo[1,5-a][1,3,5]triazin-4-yl]amino]methyl]phenyl]sulfonylcarbamate,
N-[4-[[[8-(3,4-dimethoxyphenyl)-2,7-dimethyl-pyrazolo[1,5-a][1,3,5]triazin-4-yl]amino]methyl]phenyl]sulfonylpropanamide,
N-methyl-4-[[[8-(3,4-dimethoxyphenyl)-2,7-dimethyl-pyrazolo[1,5-a][1,3,5]triazin-4-yl]amino]methyl]benzenesulfonamide,
8-(3,4-dimethoxyphenyl)-2,7-dimethyl-*N*-[(1-methyl-1*H*-pyrazol-3-yl)methyl]pyrazolo[1,5-a][1,3,5]triazin-4-amine,
8-(3,4-dimethoxyphenyl)-2,7-dimethyl-*N*-[(1,3-oxazol-5-yl)methyl]pyrazolo[1,5-a][1,3,5]triazin-4-amine,
8-(3,4-dimethoxyphenyl)-2,7-dimethyl-*N*-[(piperidin-4-yl)methyl]pyrazolo[1,5-a][1,3,5]triazin-4-amine
8-(3,4-dimethoxyphenyl)-2,7-dimethyl-*N*-[(2-methylpyrimidin-5-yl)methyl]pyrazolo[1,5-a][1,3,5]triazin-4-amine,
8-(3,4-dimethoxyphenyl)-2,7-dimethyl-*N*-[(pyridazin-4-yl)methyl]pyrazolo[1,5-a][1,3,5]triazin-4-amine, and
8-(3,4-dimethoxyphenyl)-2,7-dimethyl-*N*-[(6-methylpyridin-3-yl)methyl]pyrazolo[1,5-a][1,3,5]triazin-4-amine,
or a pharmaceutically acceptable salt thereof.

11. The compound according to any one of the claims 1 to 10 or a pharmaceutically acceptable salt thereof, for use as an inhibitor of phosphatidylinositol 4-kinase IIIβ.

12. The compound according to any one of the claims 1 to 11, or pharmaceutically acceptable salt thereof, for use in therapy.

13. The compound according to any one of the claims 1 to 11, or pharmaceutically acceptable salt thereof, for use in the treatment of a viral infection.

14. The compound or pharmaceutically acceptable salt thereof for use according to claim 13, wherein the viral infection is a non-enveloped single-stranded (+) RNA viral infection.

15. The compound or pharmaceutically acceptable salt thereof for use according to any one of the claims 11 to 14, in the treatment of a disorder selected from neurodegenerative diseases, sepsis, cancer, paralysis, myocarditis, diabetes, common cold, hand-foot-and-mouth disease, herpangina, pleurodynia, diarrhea, mucocutaneous lesions, respiratory illness, conjunctivitis, myositis, and chronic fatigue syndrome.

16. A pharmaceutical composition comprising a compound according to any one of the claims 1 to 10 and optionally a pharmaceutically acceptable excipient.

17. The use of a compound according to any one of the claims 1 to 10, for the manufacturing of a medicament for the treatment of a viral infection.

18. A method of treatment of a viral infection by administering a compound according to any one of the claims 1 to 10 to a mammal in need thereof.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2016/063383

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D487/04 A61K31/53 A61P31/12
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	IVANA MEJDROVÁ ET AL: "Highly Selective Phosphatidylinositol 4-Kinase III[beta] Inhibitors and Structural Insight into Their Mode of Action", JOURNAL OF MEDICINAL CHEMISTRY, vol. 58, no. 9, 14 May 2015 (2015-05-14), pages 3767-3793, XP055206384, ISSN: 0022-2623, DOI: 10.1021/acs.jmedchem.5b00499 cited in the application Whole document, specially compound 18 -----	1-18
A	US 6 191 131 B1 (HE LIQI [US] ET AL) 20 February 2001 (2001-02-20) whole document, specially claim 1 and example 1387 in p. 132 ----- -/--	1-18

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

[X] See patent family annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
14 July 2016	21/07/2016

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	Sahagún Krause, H

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	WO 01/23387 A2 (NEUROGEN CORP [US]; PFIZER [US]; DARROW JAMES W [US]; LOMBAERT STEPHAN) 5 April 2001 (2001-04-05) claim 1 and page 16	1-18
A	US 6 313 124 B1 (HE LIQI [US] ET AL) 6 November 2001 (2001-11-06) formula (1) in column 8 and column 6; examples	1-18

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2016/063383

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 6191131 B1	20-02-2001	US 6191131 B1	20-02-2001
		US 6358950 B1	19-03-2002
WO 0123387 A2	05-04-2001	AU 7738100 A	30-04-2001
		BG 106506 A	29-12-2002
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		US 6372743 B1	16-04-2002
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		WO 0123387 A2	05-04-2001
		YU 23802 A	03-09-2004
		ZA 200202519 A	28-01-2004
US 6313124 B1	06-11-2001	NONE	

PCT

POWER OF ATTORNEY

(for an international application filed under the Patent Cooperation Treaty)

(PCT Rule 90.4)

The undersigned applicant(s) *(Names should be indicated as they appear in the Request Form (PCT/RO/101)):*

CUROVIR AB
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hereby appoints (appoint) the following person as: ☒ agent ☐ common representative

Name and address
(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

BRANN AB
P.O. Box 3690
103 59 STOCKHOLM
Sweden

to represent the undersigned before

☒ all the competent International Authorities

☐ the International Searching Authority only

☐ the Authority specified for supplementary search only: _____
(please indicate the Authority(ies) specified for supplementary search)

☐ the International Preliminary Examining Authority only

in connection with the international application identified below:

Title of the invention: PYRAZOLO[1,5-A]TRIAZIN-4-AMINE DERIVATIVES USEFUL IN THERAPY

Applicant's or agent's file reference: P11049PC00

International application number (if already available): PCT/EP2016/063383

filed with the following Office: European Patent Office as receiving Office and to make or receive payments on behalf of the undersigned.

Signature of the applicant(s) *(where there are several applicants, each of them must sign; next to each signature, indicate the name of the person signing and the capacity in which the person signs, if such capacity is not obvious from reading the request or this power):*

Jonas Claesson, Director of the Board

Date: 30 januari 2017, Stockholm

HEIDI A. BOEHLEFELD , PARTNER

ABOUT HEIDI

Heidi served as the firm's managing partner from 2016 to 2019. Her practice focuses on patent prosecution and counseling, including validity, infringement and due diligence opinions. She has represented clients in patent matters involving a wide range of technologies primarily in the chemical industry, including adhesives, paint, coatings, polymeric films, packaging, composites, lubricants, sealants, electrochemistry, semiconductors, pharmaceuticals, and food science. Heidi's practice also includes trademark prosecution and counseling. She has transactional experience, including drafting and negotiating patent and trademark license agreements.

Prior to joining Renner Otto in 2000, Heidi served as in-house patent and trademark counsel for The Sherwin-Williams Company. She began her career as a research engineer for B.P. America (The Standard Oil Co.); and later joined the Patent and Licensing Department of B.P. America as an attorney. The corporate experience is of significant benefit to Heidi's current practice. She acquired a detailed understanding of in-house intellectual property operations and a familiarity with the issues that often arise in corporations, allowing her to assist her corporate clients with those issues.

EXPERIENCE

BP America (The Standard Oil Company) – Research Engineer

BP America – In-house Counsel, Patent & Licensing Department

The Sherwin-Williams Company – In-house Counsel

PROFESSIONAL MEMBERSHIPS

American Intellectual Property Law Association

American Bar Association

International Trademark Association

Cleveland Intellectual Property Law Association (President 2005-2006, Treasurer 1997-1990, Co-Chair CLE Committee 2008-2011)

Cleveland Metropolitan Bar Association

AWARDS

Heidi has been recognized as an Ohio Super Lawyer—an award presented to no more than 2.5 percent of the lawyers in Ohio.

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EDUCATION

Bachelor of Science, Chemical Engineering, Case Western Reserve University, with honors, 1983

Master of Business Administration, Case Western Reserve University, 1990

Juris Doctorate, Case Western Reserve University, 1990

ADMISSIONS

Ohio

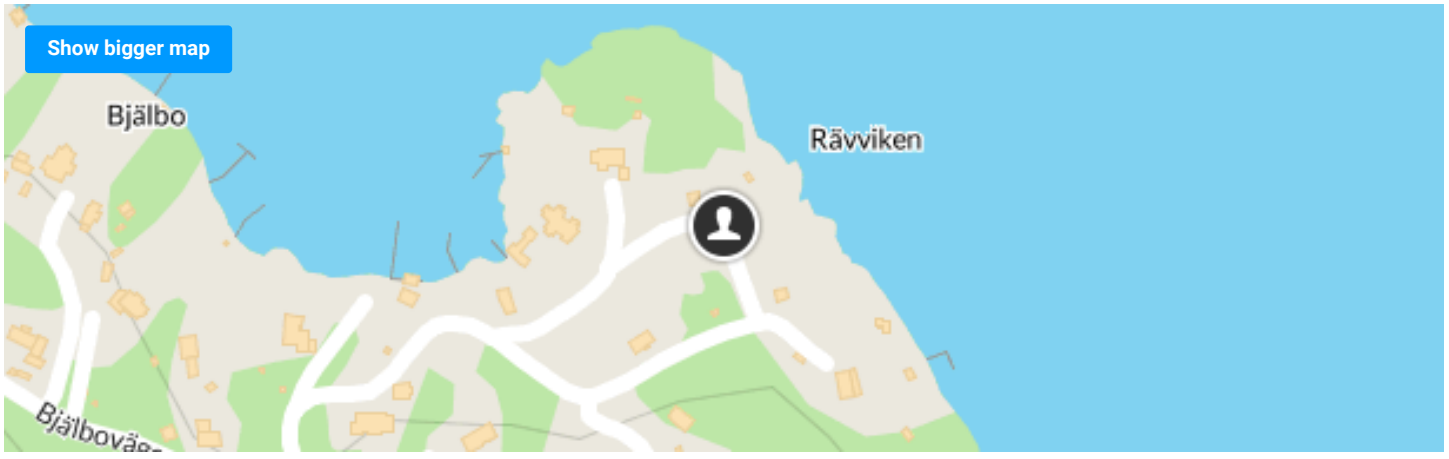
U.S. Patent and Trademark Office

Name street city phone company keywords

[Per Johan Claesson is chariman of the board ob CUROVIR AB, Kalmar, Sweden, Assignee of U.S. Pat. No. 10,407,429]

Per Johan Claesson

1 new message. Read here!



Per Johan Claesson is 69 years old and lives in a house in Elfvik , Lidingö with Greta Marianne Claesson . He turns 70 on March 17 , 2021 . The plot size is about 10497 sqm .

+ Add phone number

Address | population register

Rävviken 9
181 90 Lidingö
directions

More information

- About Per Johan Claesson
- Property Data
- Neighbors and new residents
- The area

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About Per Johan Claesson at Rävviken 9

Per Johan turns 70 in about 10 months

Per Johan's birthday is March 18. Get one SMS reminder a few days before.
He has names day August 1 and December 27.

Per Johan's previous addresses

Previous addresses for Per Johan Claesson are missing.

Per Johan's job & board assignment

Per Johan sits on 125 corporate boards . The largest is BZK Grain Alliance AB, which in 2018 had sales of SEK 146 million.

- BZK Grain Alliance AB , sales SEK 146,067,000, **profit SEK 14,227,000**
- CA Real Estate AB , sales SEK 97,623,000, **loss SEK -39,508,000**
- CA Arabybostäder AB , sales SEK 43,222,000, **profit SEK 1,783,000**
- CA in Skåne AB , sales of SEK 41,253,000, **loss of SEK -2,931,000**
- Catella AB , sales SEK 32,400,000, **loss SEK -73,100,000**
- VARVSHOLMENS FASTIGHETS SHARE COMPANY , turnover SEK 29,747,000, **profit SEK 1,266,000**
- CA I JÖNKÖPING AB , sales SEK 27,423,000, **loss SEK -512,000**
- CA HOUSING IN VÄXJÖ AB , sales SEK 22,636,000, **profit SEK 12,100,000**
- CA I VÄXJÖ SHARE COMPANY , turnover SEK 20,349,000, **profit SEK 5,872,000**
- CA REAL ESTATE SERVICE SHARE COMPANY , sales SEK 19,292,000, **loss SEK -104,000**
- Kalmarsalen Conference & Events AB , sales SEK 15,245,000, **loss SEK -1,226,000**
- Löjtnanten Fastighets AB , sales SEK 14,234,000, **profit SEK 5,969,000**
- BORÅS CITY FASTIGHETS SHARE COMPANY , sales SEK 13,836,000, **profit SEK 1,228,000**
- Sicklaön Fastigheter AB , sales SEK 12,000,000, **profit SEK 1,013,000**
- JÖNKÖPING'S INDUSTRIAL PROPERTIES 1 SHARE COMPANY , sales SEK 11,275,000, **profit SEK 3,540,000**
- CA I HUSKVARNA AB , sales SEK 9,928,000, **loss SEK -3,427,000**
- Green man Fastighets AB , sales SEK 9,615,000, **profit SEK 806,000**
- APODEMUS SHARE COMPANY , sales SEK 8,530,000, **loss SEK -5,079,000**
- JOHAN AND MARIANNE CLAESSON SHARE COMPANY , turnover SEK 7,008,000, **profit SEK 4,993,000**
- Bellvi Real Estate AB , sales SEK 6,192,000, **loss SEK -1,113,000**
- CRAFT CENTER SHARE COMPANY , sales SEK 5,401,000, **profit SEK 2,054,000**
- CA Entreprenad AB , sales SEK 4,532,000, **profit SEK 2,734,000**
- ULVARBOETT SHARE COMPANY , turnover SEK 3,851,000, **profit SEK 2,482,000**
- CA Tremurare AB , sales SEK 3,710,000, **profit SEK 1,042,000**
- H7 Mätarhuset 1 Stockholm AB , turnover SEK 3,535,000, **profit SEK 9,000**
- Movette Fastigheter AB , sales SEK 3,403,000, **loss SEK -29,000**
- CA Elektronen Fastighets AB , sales SEK 2,697,000, **profit SEK 482,000**
- Västregårdsbostäder AB , sales SEK 2,558,000, **loss SEK -917,000**
- JÖNKÖPING INDUSTRIAL PROPERTIES, ÖRONSKYDDET 6 AB , sales SEK 2,521,000, **profit SEK 834,000**
- CA Furnace Fem AB , sales SEK 2,460,000, **profit SEK 1,473,000**

- Rider 29 Borgholm AB , sales SEK 2,308,000, **profit SEK 1,253,000**
- Lomma Hamnallén 1 AB , sales SEK 2,284,000, **profit SEK 2,483,000**
- Svenska Bra AB , sales SEK 2,160,000, **profit SEK 1,185,000**
- Hermoda 2 Fastigheter AB , turnover SEK 2,014,000, **profit SEK 40,000**
- PROPERTY SHARE COMPANY ÅLEN , turnover SEK 1,774,000, **profit SEK 731,000**
- Fastighets AB Storängsbotten , turnover SEK 1,640,000, **profit SEK 1,344,000**
- JÖNKÖPING'S INDUSTRIAL PROPERTIES, JEWEL CORAL 6 A , turnover SEK 1,491,000, **profit SEK 854,000**
- CA INDUSTRIAL PROPERTIES IN JÖNKÖPING AB , turnover SEK 1,420,000, **profit SEK 294,000**
- PROPERTY SHARE COMPANY FUNJUNKAREN , turnover SEK 1,378,000, **profit SEK 419,000**
- PROPERTY SHARE COMPANY JEWELEN , turnover SEK 1,305,000, **loss SEK -884,000**
- FOJOBO FASTIGHETS SHARE COMPANY , turnover SEK 1,073,000, **profit SEK 519,000**
- Lopema Fastighets AB , sales SEK 966 thousand, **loss SEK -4 320 thousand**
- JÖNKÖPING INDUSTRIFASTIGHETER FRIDHEM AB , sales SEK 810 thousand, **profit SEK 507 thousand**
- Bellvi Löjan AB , sales SEK 592 thousand, **profit SEK 60 thousand**
- Curovir AB , sales SEK 400,000, **loss SEK -10,527,000**
- Bellvi Spättan AB , sales SEK 394 thousand, **loss SEK -88 thousand**
- PROPERTY SHARE COMPANY FÖLUNGEN , turnover SEK 352,000, **profit SEK 8,609,000**
- REAL ESTATE SHARE COMPANY BREMIA , turnover SEK 284,000, **profit SEK 6,702,000**
- PHILIPSON CAR CAR COMPANY , sales SEK 13 thousand, **profit SEK 810 thousand**
- PROPERTY SHARE COMPANY ANCHARJARNET , turnover SEK 1 thousand, **profit SEK 6 099 thousand**
- Gasverket Holding 2 AB , sales SEK 1 thousand, **loss SEK -7 thousand**
- PROPERTY SHARE COMPANY SADELTAKET , turnover SEK 1,000, **profit SEK 1,925,000**
- Mastfoten 2 Kalmar AB , sales SEK 0,000, **profit SEK 345,000**
- Bookbox Fastighets AB , sales SEK 0,000, **profit SEK 2,000**
- HALLEFLUNDRAN MANAGEMENT SHARE COMPANY , turnover SEK 0,000, **profit SEK 1,176,000**
- Moveåtta Fastigheter AB , sales SEK 0,000, **loss SEK -1,191,000**
- Movefem Förvaltnings AB , sales SEK 0,000, **loss SEK -47,000**
- Johannes Plan Fastigheter AB , sales SEK 0,000, **loss SEK -158,000**
- EVIDENTIA CONSULT SHARE COMPANY , sales SEK 0,000, **profit SEK 144,000**
- Spantrutan 1 Kalmar AB , sales SEK 0,000, **profit SEK 345,000**
- Saltäng Fastighets AB , sales SEK 0,000, **profit SEK 1,040,000**
- Möllstorp 2: 3 AB , sales SEK 0,000, **profit SEK 7,000**
- H10 Gas Clocks 3 Stockholm AB , sales SEK 0,000, **loss SEK -92,000**
- Bellvi Förvaltnings AB , sales SEK 0,000, **profit SEK 2,839,000**
- Project housing in Kalmar AB , sales SEK 0,000, **loss SEK -2,000**
- Movesex Fastigheter AB , sales SEK 0,000, **loss SEK -4,271,000**
- CA Småland AB , sales SEK 0 thousand, **profit SEK 374 thousand**
- Ernir Holding AB , sales SEK 0,000, **loss SEK -1,316,000**
- CA&DR Holding AB , sales SEK 0 thousand, **loss SEK 0 thousand**
- Malrac Holding AB , sales SEK 0 thousand, **loss SEK -1 thousand**
- PHILIPSON TROLLHÄTTAN CAR SHARE COMPANY , turnover SEK 0,000, **profit SEK 58,000**
- Strandfuruskogen 1 Lomma AB , sales SEK 0,000, **profit SEK 162,000**
- Lomma Hamnallén Fastighets AB , sales SEK 0,000, **loss SEK -1,000**
- Majovation AB , sales SEK 0,000, **profit SEK 634,000**
- CA Progress Kalmar December II AB , sales SEK 0,000, **profit SEK 169,000**
- PHILIPSON SOUTH CAR SHARE COMPANY , sales SEK 0 thousand, **profit SEK 43 thousand**
- CA in Germany AB , sales SEK 0,000, **loss SEK -42,000**
- Strandfuruskogen 2 Lomma AB , sales SEK 0,000, **profit SEK 162,000**
- CA I KARLSKRONA AB , sales SEK 0,000, **loss SEK -1,000**
- Kappi Holding AB , sales SEK 0,000, **profit SEK 63,367,000**
- Strandfuruskogen 3 Lomma AB , sales SEK 0,000, **profit SEK 162,000**
- CA Agroinvest AB , sales SEK 0,000, **loss SEK -4,653,000**
- Movenio Fastigheter AB , sales SEK 0,000, **loss SEK -257,000**
- CLAESSON & ANDERZÉN SHARE COMPANY , sales SEK 0 thousand, **profit SEK 89 588 thousand**
- H 27 Ångpannehuset 1 AB , sales SEK 0 thousand, **loss SEK -4 thousand**
- ULVARBOETT MANAGEMENT SHARE COMPANY , turnover SEK 0,000, **profit SEK 1,000**
- PCH Investment AB , sales SEK 0,000, **loss SEK -848,000**
- CA Plusinvest AB , sales SEK 0,000, **profit SEK 35,575,000**
- Styltenvik Fastighets AB , sales SEK 0,000, **loss SEK -315,000**
- H20 Gasverket AB , sales SEK 0 thousand, **loss SEK -1 thousand**
- CA Progress Kalmar AB , sales SEK 0,000, **profit SEK 261,246,000**
- Nyttab Real Estate Kvarnholmen AB , sales SEK 0,000, **profit SEK 635,000**
- CA Progress Kalmar December I AB , sales SEK 0,000, **loss SEK -700,000**
- Lomma Hamnallén 3 AB , sales SEK 0,000, **profit SEK 2,483,000**
- Gasverket Projektering AB , sales SEK 0 thousand, **loss SEK -1 536 thousand**
- Okolner Kalmar AB , sales SEK 0 thousand, **loss SEK -1 thousand**
- Mastfoten 3 Kalmar AB , sales SEK 0,000, **profit SEK 345,000**
- H8 Reningshuset 1 Stockholm AB , sales SEK 0,000, **loss SEK -16,000**
- CA Property Holding AB , sales SEK 0,000, **profit SEK 2,168,000**

- FASTIGHETS AB GÅSHÖJDEN , turnover SEK 0,000, profit SEK 110,000
- Movetvå Fastigheter AB , sales SEK 0,000, profit SEK 4,312,000
- Gasverket Holding AB , sales SEK 0,000, profit SEK 1,233,000
- Lomma Hamnallén 2 AB , sales SEK 0,000, profit SEK 2,483,000
- PROPERTY SHARE COMPANY SERGEANTEN , sales SEK 0,000, loss SEK -396,000
- TREB PROPERTIES HOLDING AB , sales SEK 0,000, profit SEK 1,561,000
- CA Investment AB , sales SEK 0,000, loss SEK -101,757,000
- VEMO INDUSTRI SHARE COMPANY , sales SEK 0,000, profit SEK 83,123,000
- CA in Estonia AB , sales SEK 0 thousand, profit SEK 6 034 thousand
- CA PROPERTY DEVELOPMENT SHARE COMPANY , turnover SEK 0,000, profit SEK 1,752,000
- Gasverket Holding 3 AB , sales SEK 0 thousand, loss SEK -1 thousand
- LADOGA HOLDING AB , sales SEK 0,000, profit SEK 1,389,000
- ULVARBOETT FASTIGHETS SHARE COMPANY , turnover SEK 0,000, profit SEK 5,000
- GERDÉN'S BUILDING SHARE COMPANY , sales SEK 0,000, profit SEK 11,000
- Movesju Fastigheter AB , sales SEK 0,000, loss SEK -762,000
- Ukrainian Investment AB , sales SEK 0,000, loss SEK -3,114,000
- PROPERTY SHARE COMPANY CORPORAL , turnover SEK 0 thousand, loss SEK -88,252 thousand
- H14 Workshop 1 Stockholm AB , sales SEK 0,000, loss SEK -11,000
- Majoplus AB , sales SEK 0,000, profit SEK 412,000
- Strandfureskogens Fastighets AB , sales SEK 0,000, loss SEK -1,000
- Klara Färdiga Kalmar AB , sales SEK 0,000, profit SEK 1,651,000
- CA in Russia AB , sales SEK 0,000, profit SEK 121,000
- Kattrumpan Fastighets AB , sales SEK 0,000, loss SEK -1,644,000
- SHARE COMPANY CLAESSON & PRESS , sales SEK 0 thousand, loss SEK -160 thousand
- H-INVEST SHARE COMPANY , sales SEK -82,000, profit SEK 958,000
- Specialistklinikerna Stockholm AB

Se om Per Johan finns på LinkedIn.

I Elfvik är medelinkomsten 31 511 kr

Per Johan bor tillsammans med Greta Marianne Claesson

I huset på Rävviken 9 bor även Greta Marianne Claesson.

Om Per Johans bostad på Rävviken 9

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Tomt på ca 10497 kvadratmeter

Tomten, LIDINGÖ 6:127, är större än andra tomter i området.

Se karta med tomtgränser och hur solen rör sig över fastigheten LIDINGÖ 6:127 vid olika klockslag och årstider.

Kolla om någon byggt för nära tomtgränsen.