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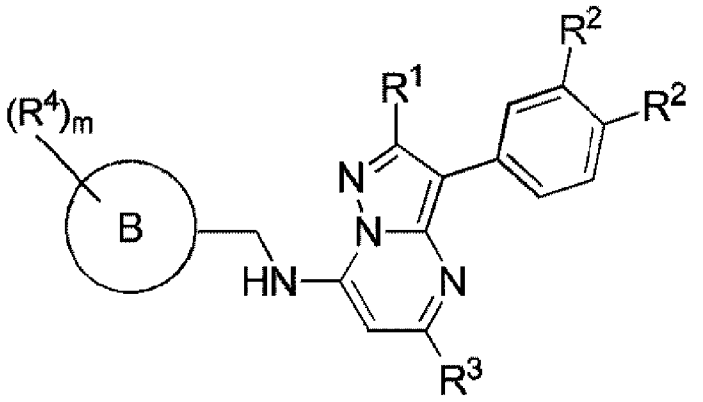
(54) Titre : DERIVES DE PYRAZOLO[1,5-A]PYRIMIDINE-7-AMINE UTILES EN THERAPIE
(54) Title: PYRAZOLO[1,5-A]PYRIMIDIN-7-AMINE DERIVATIVES USEFUL IN THERAPY



(Ie)

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

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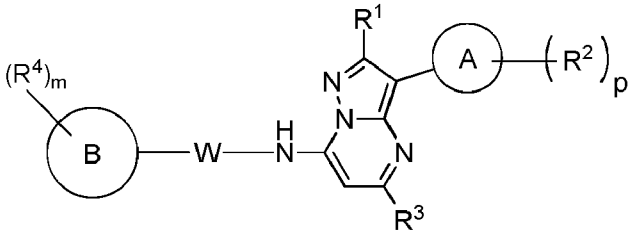


(I)

(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.

WO 2015/110491 A3

PYRAZOLO[1,5-A]PYRIMIDIN-7-AMINE DERIVATIVES USEFUL IN THERAPY

FIELD OF THE INVENTION

The present invention relates generally to 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]pyrimidin-7-amine derivatives for use in therapy.

BACKGROUND OF THE INVENTION

Pyrazolo[1,5-a]pyrimidine is a commonly used scaffold in medicinal chemistry and derivatives thereof are known for their potent utility as analgesics, benzodiazepine receptor antagonists, angiotensin II receptor antagonists, angiogenesis inhibitors, anti-inflammatory agents, neuropeptide Y receptor antagonists, COX2- inhibitor and corticotrophin-releasing hormone receptor type 1 antagonists and as CHK1 inhibitors (e.g. Mayo et al (Adv. Synth. Catal. 2003, 345, 620-624; Tellew et al (Bioorg. Med. Chem. Lett. 2010, 20, 7259-7264); Chen et al (Bioorg. Med. Chem. Lett. 2004, 14, 3669-3673); Labroli et al (Bioorg. Med. Chem. Lett. 2011, 21, 471-474); Griffith et al (Bioorg. Med. Chem. Lett. 2011, 21, 2641-2645); Gilligan et al, (J. Med. Chem. 2009, 52, 3073-3083); He et al. (US Patent No. 6,313,124 B1); and Wren et al. (WO 2010/086040).

The scaffold has also been described in phosphatidylinositol 4-kinase (PI4K) inhibitors. Bianco et al (PLoS Pathogens, 2012, 8(3), 1-17) and LaMarche et al (Antimicr. Agents and Chemother. 2012, 56(10), 5149-5156) have shown that PI4K is important for hepatitis C virus (HCV) replication and Yang et al (J. Biol. Chem. 2012, 287(11), 8547-8467) have shown the same for coronavirus. 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) have shown some imidazopyrazines derivatives inhibiting PI4K that are potent antivirals towards picornavirus.

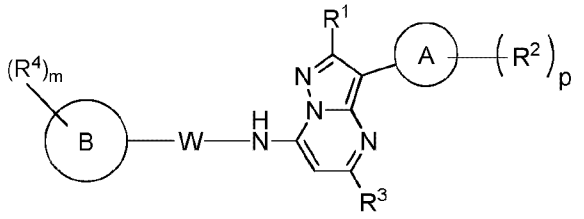
Gudmundsson et al (Bioorg. Med. Chem. Lett. 2009, 19, 5689-5692) have disclosed some 3-arylpyrazolo[1,5-a]pyrimidines with potent activity against herpesviruses.

Hwang et al (Bioorg. Med. Chem. Lett. 2012, 22, 7297-7301) have described 3-arylpyrazolo[1,5-a]pyrimidines as PI4K inhibitors that have anti-HCV effects.

Décor et al (Bioorg Med Chem Lett. 2013, 23, 3841-7) have also shown that PI4K is important for enterovirus replication. However, they have also shown that PI4K inhibitors (non 3-arylpyrazolo[1,5-a]pyrimidines) and the 3-arylpyrazolo[1,5-a]pyrimidine 3-(3,4-dimethoxyphenyl)-2,5-dimethyl-N-(2-morpholinoethyl)pyrazolo[1,5-a]pyrimidin-7-amine (called T-00127-HEV1) when tested in-vivo induced mortality in mice, which raised doubts on the safety of inhibiting PI4K.

SUMMARY OF THE INVENTION

One aspect is a compound of formula (I)



(I)

or a pharmaceutically acceptable salt thereof, wherein

W is  or ;

p is an integer of from 0 to 3;

R^1 is H or C1-C6 alkyl;

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

when ring A is phenyl, said phenyl is not substituted in ortho position;

each R^2 is independently selected from C1-C6 alkyl, R^5O-, $R^6R^7NC(O)$-, $R^9C(O)N(R^8)$-, $R^{10}OC(O)$-, $R^{11}C(O)O$-, and halogen;

R^5, R^6, R^7 and R^8 are independently selected from H and C1-C6 alkyl;

R^9, R^{10} and R^{11} are independently selected from C1-6 alkyl;

any alkyl is optionally substituted by one or more F; or

two R^2 attached to adjacent carbon atoms together form a methylenedioxy or ethylenedioxy biradical;

R^3 is C1-C6 alkyl; and

m is an integer of from 0 to 2;

each R^4 is independently selected from C1-C6 alkyl, $R^{12}O$, halogen, $R^{13}R^{14}NC(O)$-, $R^{16}C(O)N(R^{15})$-, $R^{17}OC(O)$-, $R^{18}C(O)O$-, $R^{19}S(O)_2$-, $R^{20}S(O)_2N(H)$-, $NH_2S(O)_2$-, $R^{21}C(O)$-, $N(R^{22})(R^{23})$-, and ^-O-;

R^{12}, R^{13}, R^{14}, R^{15}, R^{22}, and R^{23} are independently selected from H and C1-C6 alkyl,

R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, and R^{21} are independently selected from C1-6 alkyl;

any alkyl is optionally substituted by one or more F; or

two R^4 attached to adjacent atoms of ring B form, together with the atoms to which they are attached, a 5- or 6-membered heterocyclic or carbocyclic ring;

ring B is 5- or 6-membered saturated or unsaturated carbocyclyl, 5- or 6-membered heteroaryl, or phenyl;

for use in therapy,

provided that the compound is not:

3-(4-chlorophenyl)-N-(4-methoxyphenyl)-5-methylpyrazolo[1,5-a]pyrimidin-7-amine,

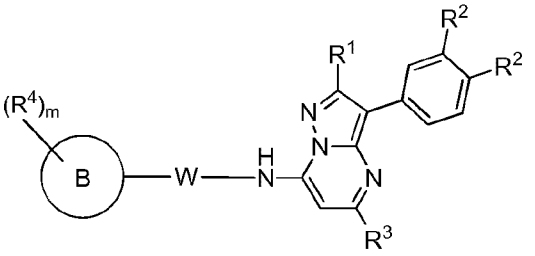
N-(cyclohexylmethyl)-2,5-dimethyl-3-(p-tolyl)pyrazolo[1,5-a]pyrimidin-7-amine,

2,5-dimethyl-N-phenyl-3-(p-tolyl)pyrazolo[1,5-a]pyrimidin-7-amine,

N-benzyl-2,5-dimethyl-3-(p-tolyl)pyrazolo[1,5-a]pyrimidin-7-amine, or

2,5-dimethyl-N-phenethyl-3-(p-tolyl)pyrazolo[1,5-a]pyrimidin-7-amine.

Some of the compounds according to formula (I) as defined herein above are novel. Thus, another aspect is a novel compound of formula (Id)



(Id)

or a pharmaceutically acceptable salt thereof, wherein

W is  or  ;

R^1 is H or C1-C6 alkyl,

each R^2 is independently selected from C1-C6 alkyl, R^5O-, $R^6R^7NC(O)$-, $R^9C(O)N(R^8)$-, $R^{10}OC(O)$-, $R^{11}C(O)O$-, and halogen;

R^5, R^6, R^7 and R^8 are independently selected from H and C1-C6 alkyl;

R^9, R^{10} and R^{11} are independently selected from C1-6 alkyl;

any alkyl is optionally substituted by one or more F; or

two R^2 together form a methylenedioxy or ethylenedioxy biradical;

R^3 is C1-C6 alkyl;

m is an integer of from 0 to 2;

each R^4 is independently selected from C1-C6 alkyl, $R^{12}O$, halogen, $R^{13}R^{14}NC(O)$-, $R^{16}C(O)N(R^{15})$-, $R^{17}OC(O)$-, $R^{18}C(O)O$-, $R^{19}S(O)_2$-, $R^{20}S(O)_2N(H)$-, $NH_2S(O)_2$-, $R^{21}C(O)$-, $N(R^{22})(R^{23})$-, and ^-O-;

R^{12}, R^{13}, R^{14}, R^{15}, R^{22}, and R^{23} are independently selected from H and C1-C6 alkyl,

R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, and R^{21} are independently selected from C1-6 alkyl;

any alkyl is optionally substituted by one or more F; or

two R^4 attached to adjacent atoms of ring B form, together with the atoms to which they are attached, a 5- or 6-membered heterocyclic or carbocyclic ring;

ring B is 5- or 6-membered heteroaryl, or phenyl;

provided that the compound is not:

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

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

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

3-(3,4-dimethoxyphenyl)-2,5-dimethyl-N-(p-tolylmethyl)pyrazolo[1,5-a]pyrimidin-7-amine,

3-(3,4-dimethoxyphenyl)-2,5-dimethyl-N-(3-phenylpropyl)pyrazolo[1,5-a]pyrimidin-7-amine,

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

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

3-(3,4-dimethoxyphenyl)-2,5-dimethyl-N-(2-phenylpropyl)pyrazolo[1,5-a]pyrimidin-7-amine,

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

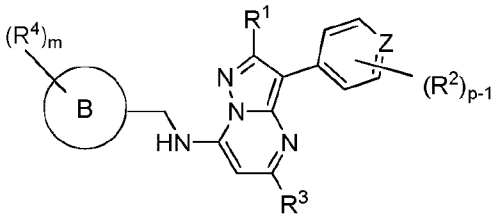
3-(3,4-dimethoxyphenyl)-2,5-dimethyl-N-(2-pyridylmethyl)pyrazolo[1,5-a]pyrimidin-7-amine,

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

N-(4-bromophenyl)-3-(3,4-dimethoxyphenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-amine,

N-(4-chlorophenyl)-3-(3,4-dimethoxyphenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-amine,
3-(3,4-dimethoxyphenyl)-2,5-dimethyl-N-(p-tolyl)pyrazolo[1,5-a]pyrimidin-7-amine,
3-(3,4-dimethoxyphenyl)-N-(4-methoxyphenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-amine,
3-(3,4-dimethoxyphenyl)-2,5-dimethyl-N-(m-tolyl)pyrazolo[1,5-a]pyrimidin-7-amine,
N-(3-chlorophenyl)-3-(3,4-dimethoxyphenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-amine,
3-(3,4-dimethoxyphenyl)-N-(3,4-dimethylphenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-amine,
3-(3,4-dimethoxyphenyl)-N-(4-fluorophenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-amine,
3-(3,4-dimethoxyphenyl)-N-(4-ethoxyphenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-amine,
N-(3-chloro-4-methyl-phenyl)-3-(3,4-dimethoxyphenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-amine,
3-(3,4-dimethoxyphenyl)-N-(3,5-dimethylphenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-amine,
3-(3,4-dimethoxyphenyl)-2,5-dimethyl-N-phenyl-pyrazolo[1,5-a]pyrimidin-7-amine,
N-[4-[[3-(3,4-dimethoxy phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]amino]phenyl]acetamide
N-(3,4-dichlorophenyl)-3-(3,4-dimethoxyphenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-amine,
3-(3,4-dimethoxyphenyl)-N-(4-isopropylphenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-amine,
3-(3,4-dimethoxyphenyl)-N-(3-methoxyphenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-amine
3-(3,4-dimethoxyphenyl)-N-(4-ethylphenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-amine,
N-(4-butylphenyl)-3-(3,4-dimethoxyphenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-amine,
or
N-(3,5-dichlorophenyl)-3-(3,4-dimethoxyphenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-amine.

Still another aspect is a novel compound of formula (Ih)



(Ih)

or a pharmaceutically acceptable salt thereof, wherein

p is an integer of from 1 to 3;

R^1 is H or C1-C6 alkyl;

Z is N or CR^2

each R^2 is independently selected from C1-C6 alkyl, R^5O-, $R^6R^7NC(O)$-, $R^9C(O)N(R^8)$-, $R^{10}OC(O)$-, $R^{11}C(O)O$-, and halogen;

R^5, R^6, R^7 and R^8 are independently selected from H and C1-C6 alkyl;

R^9, R^{10} and R^{11} are independently selected from C1-6 alkyl;

any alkyl is optionally substituted by one or more F; or

two R^2 together form a methylenedioxy or ethylenedioxy biradical;

no R^2 is attached in ortho position on the phenyl ring;

R^3 is C1-C6 alkyl;

m is an integer of from 0 to 2;

each R^4 is independently selected from C1-C6 alkyl, $R^{12}O$, halogen, $R^{13}R^{14}NC(O)$-, $R^{16}C(O)N(R^{15})$-, $R^{17}OC(O)$-, $R^{18}C(O)O$-, $R^{19}S(O)_2$-, $R^{20}S(O)_2N(H)$-, $NH_2S(O)_2$-, $R^{21}C(O)$-, $N(R^{22})(R^{23})$-, and ^-O-;

R^{12}, R^{13}, R^{14}, R^{15}, R^{22}, and R^{23} are independently selected from H and C1-C6 alkyl,

R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, and R^{21} are independently selected from C1-6 alkyl;

any alkyl is optionally substituted by one or more F; or

two R^4 attached to adjacent atoms of ring B form, together with the atoms to which they are attached, a 5- or 6-membered heterocyclic or carbocyclic ring;

ring B is 5- or 6-membered heteroaryl, or phenyl;

provided that the compound is not:

N-benzyl-2,5-dimethyl-3-(p-tolyl)pyrazolo[1,5-a]pyrimidin-7-amine,

3-(4-methoxyphenyl)-2,5-dimethyl-N-(pyridin-3-ylmethyl)pyrazolo[1,5-a]pyrimidin-7-amine,

3-(4-methoxyphenyl)-2,5-dimethyl-N-(pyridin-4-ylmethyl)pyrazolo[1,5-a]pyrimidin-7-amine,

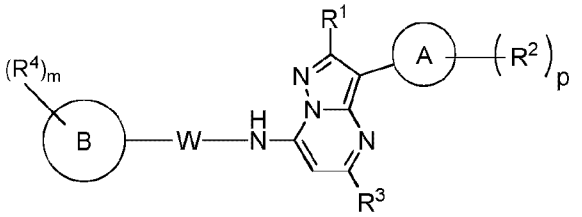
N-[(4-chlorophenyl)methyl]-3-(3,4-dimethoxyphenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-amine,

3-(3,4-dimethoxyphenyl)-N-[(4-methoxyphenyl)methyl]-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-amine,
3-(3,4-dimethoxyphenyl)-2,5-dimethyl-N-(p-tolylmethyl)pyrazolo[1,5-a]pyrimidin-7-amine,
N-(1,3-benzodioxol-5-ylmethyl)-3-(3,4-dimethoxyphenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-amine,
3-(3,4-dimethoxyphenyl)-N-[(4-fluorophenyl)methyl]-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-amine,
N-benzyl-3-(4-fluorophenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-amine,
N-benzyl-3-(4-fluorophenyl)-5-methyl-pyrazolo[1,5-a]pyrimidin-7-amine,
N-benzyl-3-(4-chlorophenyl)-5-methyl-pyrazolo[1,5-a]pyrimidin-7-amine,
2,5-dimethyl-3-(p-tolyl)-N-(2-pyridylmethyl)pyrazolo[1,5-a]pyrimidin-7-amine,
2,5-dimethyl-3-(p-tolyl)-N-(3-pyridylmethyl)pyrazolo[1,5-a]pyrimidin-7-amine,
3-(3,4-dimethoxyphenyl)-2,5-dimethyl-N-(2-pyridylmethyl)pyrazolo[1,5-a]pyrimidin-7-amine,
3-(4-fluorophenyl)-2,5-dimethyl-N-(3-pyridylmethyl)pyrazolo[1,5-a]pyrimidin-7-amine,
3-(4-fluorophenyl)-2,5-dimethyl-N-(2-pyridylmethyl)pyrazolo[1,5-a]pyrimidin-7-amine,
N-benzyl-3-(3,4-dimethoxyphenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-amine,
3-(4-chlorophenyl)-2,5-dimethyl-N-(2-pyridylmethyl)pyrazolo[1,5-a]pyrimidin-7-amine,
3-(4-chlorophenyl)-2,5-dimethyl-N-(3-pyridylmethyl)pyrazolo[1,5-a]pyrimidin-7-amine,
3-(4-methoxyphenyl)-2,5-dimethyl-N-(3-pyridylmethyl)pyrazolo[1,5-a]pyrimidin-7-amine, or
3-(4-methoxyphenyl)-2,5-dimethyl-N-(4-pyridylmethyl)pyrazolo[1,5-a]pyrimidin-7-amine.

Another aspect is a compound of formula (Id) or of formula (Ih) for use in therapy.

Another aspect is a compound of formula (I), as defined herein, or a compound of formula (Id), or a compound of formula (Ih), for use in the treatment of a viral infection, e.g. an RNA viral infection.

Another aspect is a compound of formula (I)



(I)

or a pharmaceutically acceptable salt thereof, wherein

W is  ;

p is an integer of from 0 to 3,

R^1 is H or C1-C6 alkyl,

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

when ring A is phenyl, said phenyl is not substituted in ortho position;

each R^2 is independently selected from C1-C6 alkyl, R^5O-, $R^6R^7NC(O)$-, $R^9C(O)N(R^8)$-, $R^{10}OC(O)$-, $R^{11}C(O)O$-, and halogen;

R^5, R^6, R^7 and R^8 are independently selected from H and C1-C6 alkyl;

R^9, R^{10} and R^{11} are independently selected from C1-6 alkyl;

any alkyl is optionally substituted by one or more F; or

two R^2 attached to adjacent carbon atoms together form a methylenedioxy or ethylenedioxy biradical;

R^3 is C1-C6 alkyl;

m is an integer of from 0 to 2;

each R^4 is independently selected from C1-C6 alkyl, $R^{12}O$, halogen, $R^{13}R^{14}NC(O)$-, $R^{16}C(O)N(R^{15})$-, $R^{17}OC(O)$-, $R^{18}C(O)O$-, $R^{19}S(O)_2$-, $R^{20}S(O)_2N(H)$-, $NH_2S(O)_2$-, $R^{21}C(O)$-, $N(R^{22})(R^{23})$-, and ^-O-;

R^{12}, R^{13}, R^{14}, R^{15}, R^{22}, and R^{23} are independently selected from H and C1-C6 alkyl,

R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, and R^{21} are independently selected from C1-6 alkyl;

any alkyl is optionally substituted by one or more F; or

two R^4 attached to adjacent atoms of ring B form, together with the atoms to which they are attached, a 5- or 6-membered heterocyclic or carbocyclic ring, or a benzene ring;

ring B is 5- or 6-membered saturated or unsaturated carbocyclyl, 5- or 6-membered heteroaryl, or phenyl;

for use in the treatment of a viral infection,

provided that the compound is not:

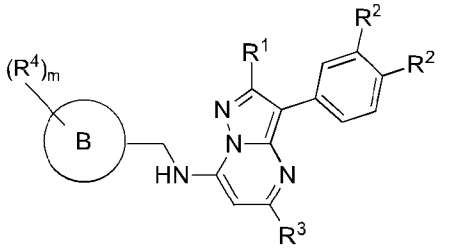
N-(cyclohexylmethyl)-2,5-dimethyl-3-(p-tolyl)pyrazolo[1,5-a]pyrimidin-7-amine,

2,5-dimethyl-N-phenyl-3-(p-tolyl)pyrazolo[1,5-a]pyrimidin-7-amine,

N-benzyl-2,5-dimethyl-3-(p-tolyl)pyrazolo[1,5-a]pyrimidin-7-amine, or

2,5-dimethyl-N-phenethyl-3-(p-tolyl)pyrazolo[1,5-a]pyrimidin-7-amine.

In some embodiments, there is provided a compound of formula (Ie)



(Ie)

or a pharmaceutically acceptable salt thereof, wherein

R^1 is methyl;

each R^2 is methoxy;

R^3 is methyl;

m is an integer of from 0 to 2;

each R^4 is independently selected from C1-C6 alkyl, optionally substituted by one or more F, $R^{12}O$, halogen, $R^{13}R^{14}NC(O)$-, $R^{16}C(O)N(R^{15})$-, $R^{17}OC(O)$-, $R^{18}C(O)O$-, $R^{19}S(O)_2$-, $R^{20}S(O)_2N(H)$-, $NH_2S(O)_2$-, $R^{21}C(O)$-, $N(R^{22})(R^{23})$-, and ^-O-;

R^{12}, R^{13}, R^{14}, R^{15}, R^{22}, and R^{23} are independently selected from H and C1-C6 alkyl;

R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, and R^{21} are independently selected from C1-6 alkyl;

and

in any one of R^{12} to R^{23}, any alkyl is optionally substituted by one or more F;

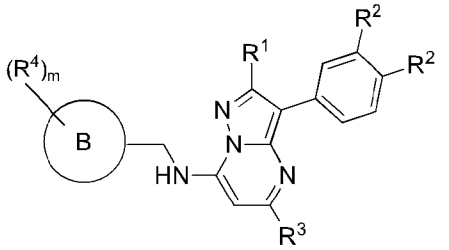
or

two R^4 attached to adjacent atoms of ring B form, together with the atoms to which they are attached, a 5- or 6-membered heterocyclic or carbocyclic ring, or a benzene ring; and

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

for use in therapy.

In some embodiments, there is provided a compound of formula (Ie)



(Ie)

or a pharmaceutically acceptable salt thereof, wherein

R^1 is methyl,

each R^2 is methoxy;

R^3 is methyl;

m is an integer of from 0 to 2;

each R^4 is independently selected from C1-C6 alkyl, optionally substituted by one or more F, $R^{12}O$, halogen, $R^{13}R^{14}NC(O)$-, $R^{16}C(O)N(R^{15})$-, $R^{17}OC(O)$-, $R^{18}C(O)O$-, $R^{19}S(O)_2$-, $R^{20}S(O)_2N(H)$-, $NH_2S(O)_2$-, $R^{21}C(O)$-, $N(R^{22})(R^{23})$-, and ^-O-;

R^{12}, R^{13}, R^{14}, R^{15}, R^{22}, and R^{23} are independently selected from H and C1-C6 alkyl,

R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, and R^{21} are independently selected from C1-6 alkyl; and

in any one of R^{12} to R^{23}, any alkyl is optionally substituted by one or more F;

or

two R^4 attached to adjacent atoms of ring B form, together with the atoms to which they are attached, a 5- or 6-membered heterocyclic or carbocyclic ring, or a benzene ring; and

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

provided that the compound is not:

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

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

3-(3,4-dimethoxyphenyl)-2,5-dimethyl-N-(p-tolylmethyl)pyrazolo[1,5-a]pyrimidin-7-amine,

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

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

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

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

Date Reçue/Date Received 2021-06-03

In some embodiments, the viral infection is a non-enveloped single-stranded (+) RNA viral infection.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a diagram showing the number of surviving animals as a function of the number of days after infections with Coxsackie B3 virus, in mice treated with the compound of Ex. 9, 200 mg/kg once daily per orally starting on day 1 (group 1) or on day 3 (group 2), and in mice treated with vehicle only (0.4% Tween™ 80, 2% glycerol and 15% β-hydroxypropyl cyclodextrin).

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.

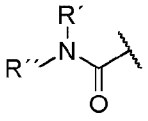
"An effective amount" refers to an amount of a compound that confers a therapeutic effect on the treated subject. The therapeutic effect may be objective (i.e., measurable by some test or marker) or subjective (i.e., subject gives an indication of or feels an effect).

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.

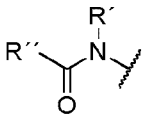
The term "C1-C6 hydroxyalkyl" refers to a C1-C6 alkyl substituted with one OH. An example of a C1-C6 hydroxyalkyl is hydroxymethyl: $-CH_2OH$.

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

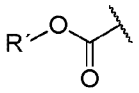
A moiety of the type $R'R''NC(O)$- is a moiety of formula



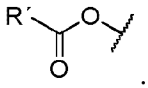
A moiety of the type R´´C(O)N(R´)- is a moiety of formula



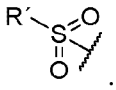
A moiety of the type R´OC(O)- is a moiety of formula



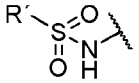
A moiety of the type R´C(O)O- is a moiety of formula



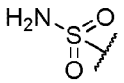
A moiety of the type R´S(O)$_2$- is a moiety of formula



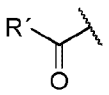
A moiety of the type R´S(O)$_2$N(H)- is a moiety of formula



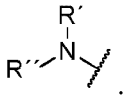
A moiety of the type $NH_2S(O)_2$- is a moiety of formula



A moiety of the type R´C(O)- is a moiety of formula



A moiety of the type N(R′)(R′′)- is a moiety of formula



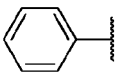
As used herein, the term "carbocyclic ring" refers to a saturated or unsaturated (e.g. monounsaturated or diunsaturated), non-aromatic cyclic moiety containing only carbon atoms in the ring, such as hexyl or hexenyl.

The term "heterocyclic ring" refers to a saturated or unsaturated, 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; such as piperidinyl, or 1,2,3,4-tetrahydropyridinyl. Other examples of heterocyclyl include morpholinyl, pyrrolidinyl, piperazinyl, tetrahydrothienyl, and tetrahydrofuryl.

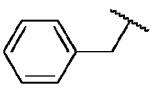
The term "heteroaryl" refers to an aromatic ring containing at least one ring heteroatom, such as furyl, isoxazolyl, isothiazolyl, imidazolyl, pyridyl, pyrrolyl, pyrazolyl, pyrimidinyl, pyridazinyl, pyrazinyl, oxadiazolyl, oxazolyl, thienyl, thiadiazolyl, thiazolyl, triazolyl, and tetrazolyl.

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.

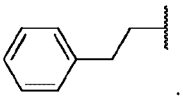
The term "phenyl" refers to a moiety of formula C_6H_5-, i.e.;



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



The term "phenylethyl" refers to a moiety of formula $C_6H_5C_2H_4$-, 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.

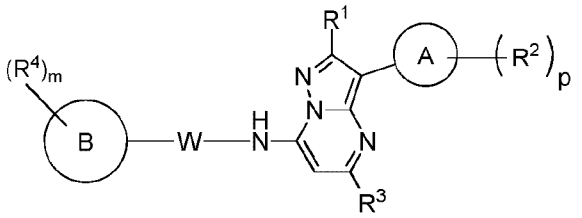
The term "mammal" refers to a human or any mammalian animal, e.g. a primate, a farm animal, a pet animal, or a laboratory animal. Examples of such animals are monkeys, cows, sheep, goats, horses, pigs, dogs, cats, rabbits, mice, rats etc. Preferably, the mammal is a human. In some embodiments, however,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

R^1 is selected from H and C1-C6 alkyl, e.g. from H and C1-C4 alkyl, or from H and C1-C3 alkyl, e.g. from H, methyl and ethyl, or from H and methyl, e.g. R^1 is H.

In some embodiments, R^1 is selected from C1-C6 alkyl, e.g. from C1-C4 alkyl, or from C1-C3 alkyl; e.g. R^1 is CH_3. In some embodiments, R^1 is selected from CH_3 and CH_3CH_2.

In a compound of formula (I), ring A is phenyl or 5- or 6-membered heteroaryl.

When ring A is 5- or 6-membered heteroaryl, it may contain 1-4 heteroatoms, such as 1, 2 or 3 heteroatoms; or 1 or 2 heteroatoms, in particular 1 heteroatom, independently selected from N, O and S.

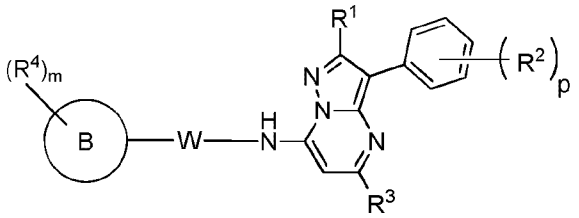
In some embodiments, ring A is 5- membered heteroaryl, containing 1-4 heteroatoms, such as 1, 2 or 3 heteroatoms; or 1 or 2 heteroatoms, in particular 1 heteroatom, independently selected from N, O and S.

In some embodiments, ring A is 6- membered heteroaryl, containing 1-4 heteroatoms, such as 1, 2 or 3 heteroatoms; or 1 or 2 heteroatoms, in particular 1 heteroatom, independently selected from N, O and S.

In some embodiments, ring A is phenyl. In some other embodiments, ring A is phenyl or 6-membered heteroaryl, e.g. ring A is 6-membered heteroaryl, such as pyridyl.

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

In those embodiments where ring A is phenyl, the compound of formula (I) may be represented by formula (Ia)



(Ia)

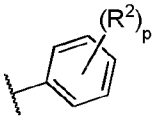
wherein R^1, each R^2, R^3, each R^4, W, m and p are as defined herein.

In a compound of formula (I), the variable p, representing the number of substituents R^2 on ring A, is an integer of from 0 to 3, e.g. from 0 to 2. In some embodiments, ring A is phenyl and p is 0, 1 or 2. In some embodiments, e.g. when ring A is a 6-membered ring, e.g. ring A is phenyl, p is an integer of from 1 to 3, e.g. p is 1 or 2. In some embodiments, e.g. when ring A is a 6-membered ring, e.g. ring A is phenyl, p is 2 or 3, e.g. p is 2. In some other embodiments, e.g. when ring A is a 5-membered or 6-membered heteroaryl, e.g. A is thienyl or pyridyl, p is 0 or 1, e.g. p is 0.

When ring A is pyridyl, it e.g. may be 4-pyridyl.

In some embodiments, when ring A is 6-membered, e.g. in the embodiments when ring A is phenyl, R^2 is not attached to an atom of ring A adjacent to the bond linking ring A to the pyrazolopyrimidine moiety of the compound of formula (I), i.e. R^2 is not attached to a carbon atom in ortho position of ring A. Thus, when ring A is phenyl, any R^2 is attached in meta or para position on ring A.

In some embodiments, when ring A is phenyl, the moiety



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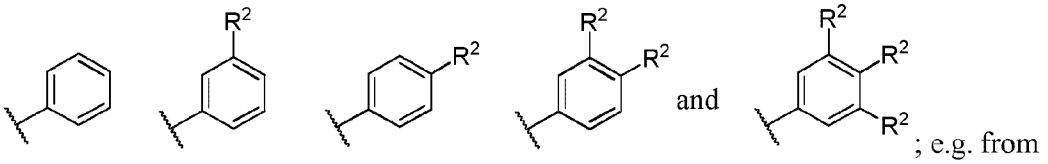
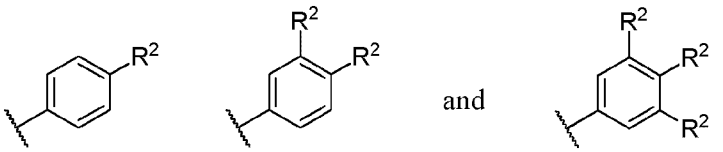
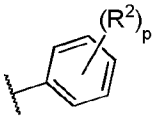


; e.g. from



wherein each R^2 is as defined herein.

In some embodiments, when ring A is phenyl and p is 0, 1 or 2, the moiety



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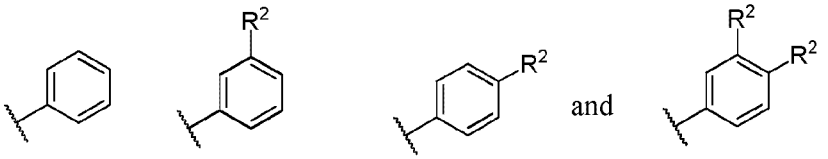
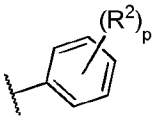


wherein each R^2 is as defined herein.

In some embodiments, when ring A is phenyl and p is 1 or 2, the moiety



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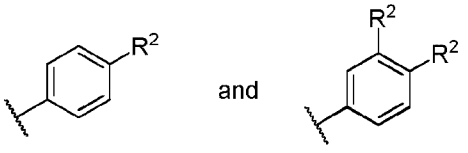
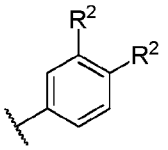


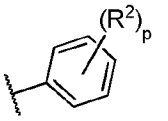
wherein each R^2 is as defined herein.

In some particular embodiments, when ring A is phenyl and p is 2, the moiety is

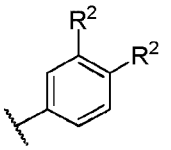
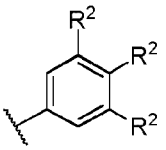


wherein each R^2 is as defined herein.

In some embodiments, when ring A is phenyl and the integer p is 2 or 3, the moiety



is selected from


and


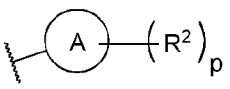
wherein each R^2 is as defined herein.

In some embodiments, ring A is selected from phenyl, said phenyl being substituted with 1-3 groups R^2, e.g. 1 or 2 groups R^2, in particular 2 groups R^2; and pyridyl, e.g. 4-pyridyl, said pyridyl being substituted with 0, 1 or 2 groups R^2, e.g. 0 or 1 group R^2, in particular 0 group R^2; and thienyl, said thienyl being substituted with 0 or 1 group R^2, e.g. 0 group R^2.

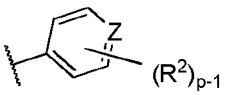
In some embodiments, ring A is selected from phenyl, said phenyl being substituted with 1-3 groups R^2, e.g. 1 or 2 groups R^2, in particular 2 groups R^2; and thienyl, said thienyl being substituted with 0 or 1 group R^2, e.g. 0 group R^2.

In some embodiments, ring A is selected from phenyl, said phenyl being substituted with 1-3 groups R^2, e.g. 1 or 2 groups R^2, in particular 2 groups R^2; and pyridyl, e.g. 4-pyridyl, said pyridyl being substituted with 0, 1 or 2 groups R^2, e.g. 0 or 1 group R^2, in particular 0 group R^2.

In some particular embodiments, the moiety



may be represented by the formula



wherein Z is Z is N or CR^2, R_2 is as defined herein, and p is 1, 2 or 3. In some embodiments, Z is N. In some embodiments, when Z is N, p is 1 (i.e. p-1 is 0). In some other embodiments, Z is CR^2. In some embodiments, when Z is CR^2, p is 2 or 3, i.e. ring A is mono- or disubstituted.

In a compound of formula (I), each R^2 is independently selected from C1-C6 alkyl, R^5O-, $R^6R^7NC(O)$-, $R^9C(O)N(R^8)$-, $R^{10}OC(O)$-, $R^{11}C(O)O$-, and halogen; or two R^2 attached to adjacent carbon atoms form together a methylenedioxy or ethylenedioxy biradical.

In some embodiments, each R^2 is independently selected from C1-C6 alkyl, R^5O-, $R^{10}OC(O)$-, and halogen or two R^2 attached to adjacent carbon atoms form together a methylenedioxy or ethylenedioxy biradical.

In some embodiments, each R^2 is independently selected from C1-C6 alkyl, R^5O-, and halogen; or two R^2 attached to adjacent carbon atoms together form a methylenedioxy or ethylenedioxy biradical.

In some embodiments, each R^2 is independently selected from C1-C6 alkyl, R^5O-, and halogen. In some embodiments, each R^2 is independently selected from R^5O- and halogen. In some other embodiments, each R^2 is independently selected from R^5O- and C1-C6 alkyl. In still other embodiments, each R^2 is R^5O-.

In some embodiments, each R^2 is independently selected from R^5O- and halogen; or two R^2 attached to adjacent carbon atoms together form a methylenedioxy or ethylenedioxy biradical.

In some embodiments, each R^2 is independently selected from C1-C6 alkyl and R^5O-, or two R^2 attached to adjacent carbon atoms together form a methylenedioxy or ethylenedioxy biradical.

In some embodiments, each R^2 is independently selected from R^5O-, or two R^2 attached to adjacent carbon atoms together form a methylenedioxy or ethylenedioxy biradical.

When R^2 is C1-C6 alkyl, it more particularly may be C1-C4 alkyl, or C1-C3 alkyl, such as methyl and ethyl, in particular methyl.

When R^2 is R^5O-, $R^6R^7NC(O)$-, $R^9C(O)N(R^8)$-, or $R^{10}OC(O)$-, the moieties R^5, R^6, R^7, R^8 and R^{10} are independently selected from H and C1-C6 alkyl, e.g. from H and C1-C4 alkyl, e.g. H and C1-C3 alkyl, such as H, methyl and ethyl, in particular H and methyl. In some embodiments, R^5, R^6, R^7, R^8 and R^{10} are independently selected from C1-C6 alkyl, e.g. from C1-C4 alkyl, or C1-C3 alkyl, such as methyl and ethyl, in particular methyl.

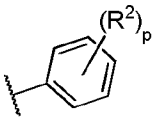
When R^2 is $R^9C(O)N(R^8)$- or $R^{11}C(O)O$-, R^9 and R^{11} are independently selected from C1-6 alkyl; e.g. C1-C4 alkyl, or C1-C3 alkyl, such as methyl and ethyl, in particular methyl.

When R^2 is halogen, said halogen e.g. may be selected from F and Cl.

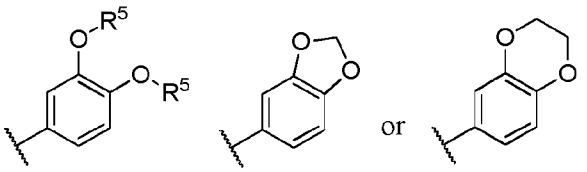
In some embodiments, ring A is phenyl, p is 2, and each R^2 is independently selected from halogen and R^5O-, or the two R^2 are attached to adjacent carbon atoms and form together a methylenedioxy or ethylenedioxy biradical, e.g. ring A is phenyl, p is 2, and each R^2 is R^5O-, or the two R^2 are attached to adjacent carbon atoms and form together a methylenedioxy or ethylenedioxy biradical.

In some embodiments, when two R^2 are attached to adjacent carbon atoms and form together a methylenedioxy or ethylenedioxy biradical, said two R^2 more particularly form a methylenedioxy biradical.

In some embodiments, when p is 2, the moiety

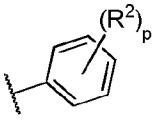


is a moiety of formula

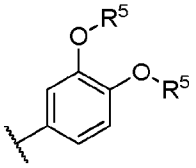
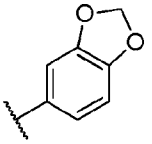


wherein each R^5 is as defined herein, e.g. each R^5 is C1-C6 alkyl, or each R^5 is C1-C3 alkyl, e.g. each R^5 is methyl.

In some embodiments, when p is 2, the moiety

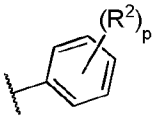


is a moiety of formula

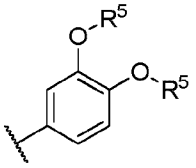
 or 

wherein each R^5 is as defined herein, e.g. each R^5 is methyl.

In some embodiments, when p is 2, the moiety

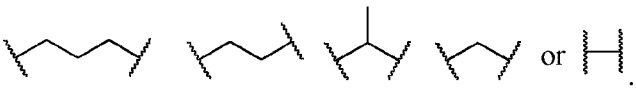
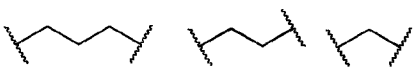
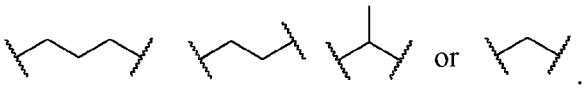


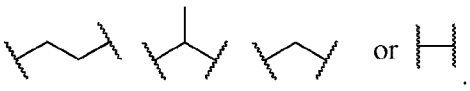
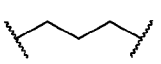
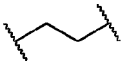
is a moiety of formula



wherein each R^5 is as defined herein, e.g. each R^5 is methyl.

In a compound of formula (I), R^3 is C1-C6 alkyl, e.g. R^3 is selected from C1-C5 alkyl, or R^3 is selected from C1-C4 alkyl. In some embodiments, R^3 is selected from C1-C3 alkyl. In some embodiments, R^3 is CH_3.

The moiety W is  or . In some embodiments, W is  or  . In some embodiments, W is  or . In some other embodiments, W is

 or . In some embodiments, W is  or  . In some other embodiments, W is  or  . In some embodiments, W is  or  . In some other embodiments, W is   or  . In still other embodiments, W is  or  . In still other embodiments, W is  or  . In some particular embodiments, W is  .

In a compound of formula (I), ring B is 5- or 6-membered saturated or unsaturated carbocyclyl, 5- or 6-membered heteroaryl, or phenyl.

In some embodiments, ring B is 5- or 6-membered saturated or unsaturated carbocyclyl. Any such carbocyclyl is non-aromatic and may be saturated (cycloalkyl) or e.g. mono-unsaturated (cycloalkenyl), e.g. selected from cyclopentyl, cyclohexyl and cyclohexenyl. In some embodiments, when ring B is carbocyclyl, said carbocyclyl is saturated. In some embodiments, when ring B is carbocycylcyl, said carbocyclyl is 5-membered. In some embodiments, when ring B is carbocycylcyl, said carbocyclyl is 6-membered. In some embodiments, ring B is cyclopentyl, cyclohexyl or cyclohexenyl. In some embodiments, ring B is cyclopentyl or cyclohexyl, e.g. ring B is cyclopentyl.

In some embodiments, ring B is 5- or 6-membered saturated or unsaturated carbocyclyl, or phenyl. In some embodiments, ring B is 6-membered saturated or unsaturated carbocyclyl, or phenyl, e.g. ring B is phenyl, cyclohexenyl or cyclohexyl.

In some embodiments, ring B is 5- or 6-membered heteroaryl. When ring B is 5- or 6-membered heteroaryl, it e.g. may contain 1-4 heteroatoms, such as 1, 2 or 3 heteroatoms; or 1 or 2 heteroatoms, or 1 heteroatom, independently selected from N, O and S.

In some embodiments, when ring B is 5- or 6-membered heteroaryl, said heteroaryl is selected from pyridinyl and imidazolyl, e.g. pyridin-2-yl, pyridin-3-yl, pyridin-4-yl and 1H-imidazol-

1-yl. In some other embodiments, when ring B is 5- or 6-membered heteroaryl, said heteroaryl is selected from pyridinyl, imidazolyl, pyrimidinyl, thienyl, thiazolyl, isoxazolyl, e.g. pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, 1H-imidazol-1-yl, pyrimidin-4-yl, thien-2-yl, thiazol-2-yl, and isoxazol-3-yl.

In some embodiments, ring B is 5-membered heteroaryl, containing one or more, e.g. 1-4, or 1-3, e.g. 1 or 2 heteroatoms, selected from N, O and S. When ring B is 5-membered heteroaryl, said heteroaryl e.g. may be selected from imidazolyl, thienyl, thiazolyl, isoxazolyl, e.g. 1H-imidazol-1-yl, thien-2-yl, thiazol-2-yl, and isoxazol-3-yl.

In some other particular embodiments, ring B is 6-membered heteroaryl, for example, containing one or more, 1-4, or 1-3, e.g. 1 or 2 heteroatoms, selected from N and O.

When ring B is 6-membered heteroaryl, said heteroaryl e.g. may be selected from pyridinyl, i.e. pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, in particular it may be pyridin-4-yl. In some other embodiments, when ring B is 6-membered heteroaryl, said heteroaryl is selected from pyridinyl and pyrimidinyl e.g. pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, and pyrimidin-4-yl.

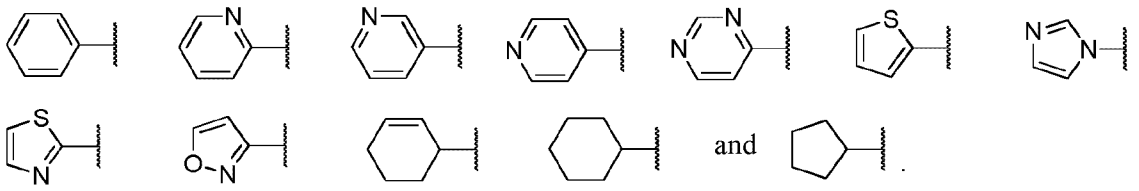
In some embodiments, when ring B is heteroaryl, said heteroaryl is not oxadiazolyl. In some embodiments, when ring B is heteroaryl at least one ring heteroatom is nitrogen, e.g. each ring heteroatom is nitrogen.

In some embodiments, when ring B is 5- or 6-membered heteroaryl, said heteroaryl contains 1 heteroatom. In some embodiments, when ring B is 5- or 6-membered heteroaryl, said heteroaryl contains 2 heteroatoms.

In some embodiments, ring B is 5- or 6-membered heteroaryl containing 1 heteroatom. In some other embodiments, ring B is 5- or 6-membered heteroaryl containing 2 heteroatoms.

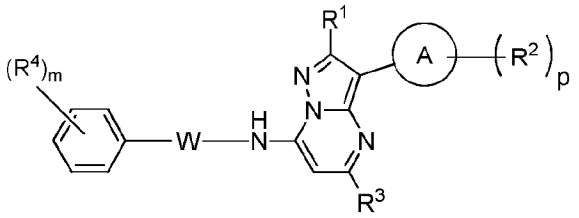
In some embodiments, ring B is 5- or 6-membered heteroaryl or phenyl, e.g. ring B is 6-membered heteroaryl or phenyl. In some other embodiments, ring B is 5-membered heteroaryl or phenyl.

In some embodiments, ring B is selected from



In some embodiments, ring B is phenyl.

When ring B is phenyl, the compound of the invention may be represented by formula (Ib)



(Ib)

wherein ring A, R^1, each R^2, R^3, each R^4, W, m and p are as defined herein.

The integer m represents the number of moieties R^4 attached to ring B and is 0, 1, or 2. In some embodiments, m is 0 or 1, e.g. m is 0. In other embodiments, m is 1 or 2. In some embodiments, m is 1. In some embodiments, m is 2.

For example, in some embodiments, ring B is phenyl or 5- or 6-membered heteroaryl, and ring B is optionally substituted with 1-2 moieties R^4.

In some embodiments, ring B is 5- or 6-membered heteroaryl, said heteroaryl optionally being substituted with 1 or 2 moieties R^4.

In some embodiments, ring B is phenyl, m is 1 or 2, e.g. m is 1, and one R^4 is in para position on the phenyl ring.

When m is 1 or 2, each R^4 is independently selected from C1-C6 alkyl, $R^{12}O$, halogen, $R^{13}R^{14}NC(O)$-, $R^{16}C(O)N(R^{15})$-, $R^{17}OC(O)$-, $R^{18}C(O)O$-, $R^{19}S(O)_2$-, $R^{20}S(O)_2N(H)$-, $NH_2S(O)_2$-, $R^{21}C(O)$-, $N(R^{22})(R^{23})$-, and ^-O-.

In some embodiments, each R^4 is independently selected from C1-C6 alkyl, $R^{12}O$, halogen, $R^{13}R^{14}NC(O)$-, $R^{16}C(O)N(R^{15})$-, $R^{17}OC(O)$- and $R^{18}C(O)O$-.

In some embodiments, each R^4 is independently selected from C1-C6 alkyl, $R^{12}O$, halogen, and $R^{16}C(O)N(R^{15})$-. In some other embodiments, each R^4 is independently selected from C1-C6 alkyl, $R^{12}O$, and halogen. In still other embodiments, each R^4 is independently selected from halogen and $R^{12}O$, e.g. each R^4 is $R^{12}O$.

In some embodiments, two R^4 attached to adjacent atoms of the ring B form, together with the atoms to which they are attached, a 5- or 6-membered heterocyclic or carbocyclic ring, or a benzene ring. In some embodiments, two R^4 attached to adjacent atoms of the ring B form, together with the atoms to which they are attached, a 5- or 6-membered heterocyclic ring or a benzene ring. In some embodiments, two R^4 attached to adjacent atoms of the ring B form, together with the atoms to which they are attached a benzene ring. In some embodiments, two R^4 attached to adjacent atoms of the ring B form, together with the atoms to which they are attached, a 5- or 6-membered heterocyclic ring.

When R^4 is C1-C6 alkyl, said alkyl e.g. may be selected from C1-C4 alkyl, e.g. C1-C3 alkyl, such as methyl and ethyl, in particular methyl.

When R^4 is $R^{12}O$, R^{12} is selected from H and C1-C6 alkyl. In some embodiments, R^{12} is selected from C1-C6 alkyl, e.g. from C1-C4 alkyl, in particular from C1-C3 alkyl, such as methyl and ethyl, in particular methyl.

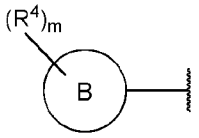
When R^4 is halogen, said halogen e.g. may be selected from F, Cl and Br. In some embodiments, when R^4 is halogen, said halogen is Cl or Br, in particular Cl. In some other embodiments, when R^4 is halogen, said halogen is F or Cl, in particular said halogen is F.

When R^4 is selected from $R^{13}R^{14}NC(O)$-, $R^{16}C(O)N(R^{15})$-, $R^{17}OC(O)$-, $R^{18}C(O)O$-, $R^{19}S(O)_2$-, $R^{20}S(O)_2N(H)$-, $R^{21}C(O)$-, and $N(R^{22})(R^{23})$-, each R^{13}, R^{14}, R^{15}, R^{22} and R^{23} is independently selected from H and C1-C6 alkyl, e.g. from H and C1-C4 alkyl, or from H and C1-C3 alkyl, e.g. from H and methyl; and each R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, and R^{21} is independently selected from C1-6 alkyl, e.g. from C1-C4 alkyl, in particular from C1-C3 alkyl, such as methyl and ethyl, in particular methyl.

When R^4 is an alkyl moiety or comprises an alkyl moiety, any such alkyl moiety may be substituted by one or more F.

When two R^4 attached to adjacent atoms of the ring B form, together with the atoms to which they are attached, a 5- or 6-membered heterocyclic or carbocyclic ring, said ring e.g. may be 5-membered. For example, two R^4 attached to adjacent atoms of the ring B may together with the atoms to which they are attached, a 1,3-dioxolane ring.

In some embodiments, the moiety



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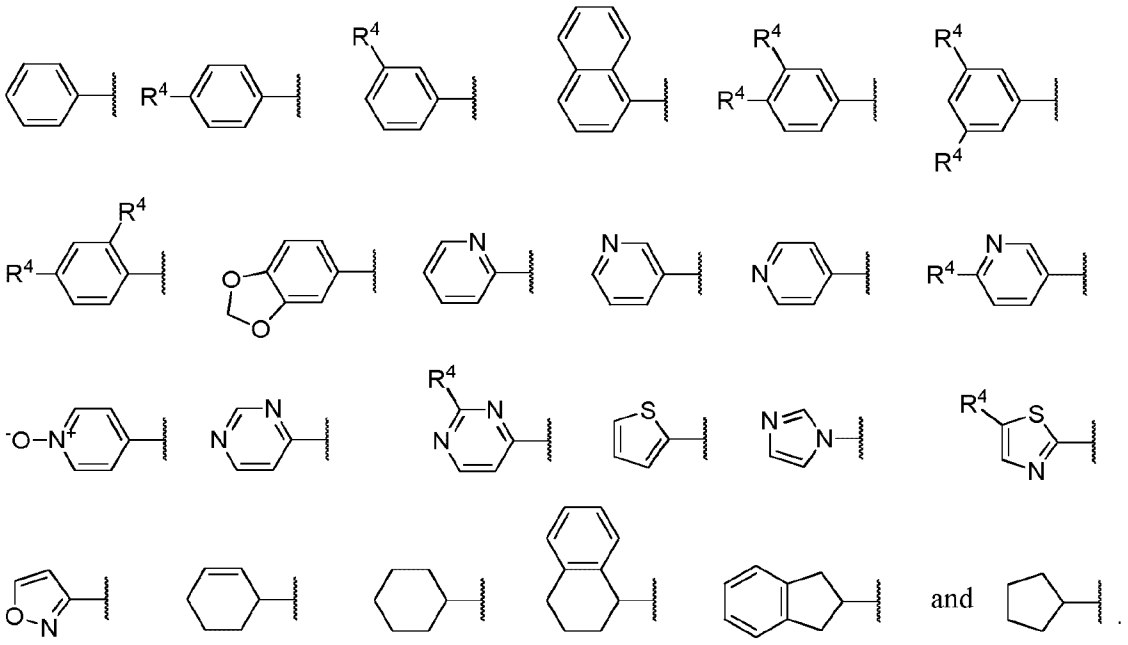
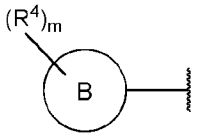


In some embodiments, the moiety



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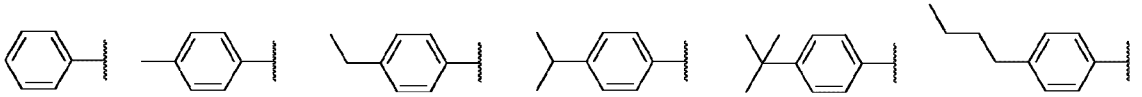
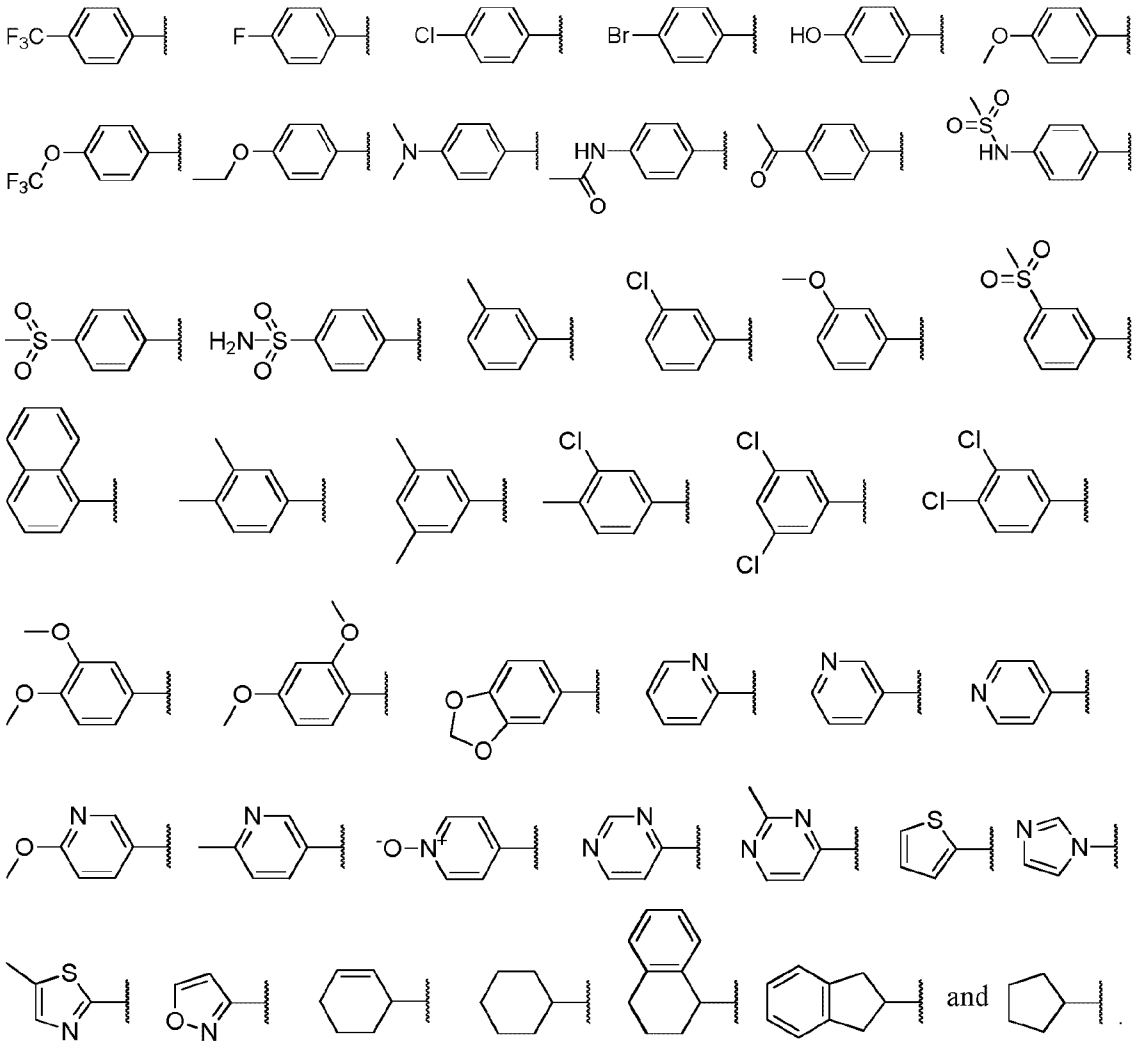
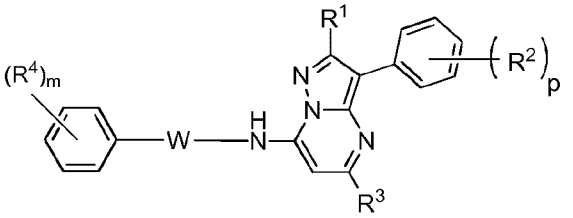




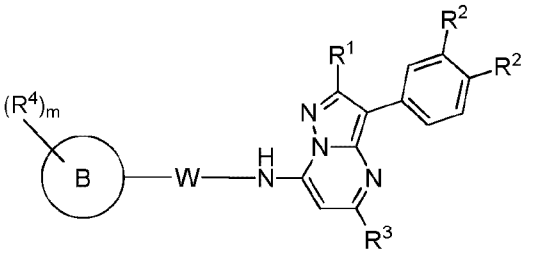
It should be realized that features of the various embodiments described herein may be freely combined within the scope of the present invention, unless mutually incompatible, or unless otherwise specified. For example, in some embodiments of the compound of formula (Ia), ring B is phenyl, as represented in formula (Ib). In these embodiments, the compound may be represented by formula (Ic)



(Ic)

wherein R^1, each R^2, R^3, each R^4, W, m and p are as defined herein.

In some embodiments of the compound of formula (Ia), p is 2. In some embodiments of a compound of formula (Ia), when p is 2, the compound is a compound of formula (Id)



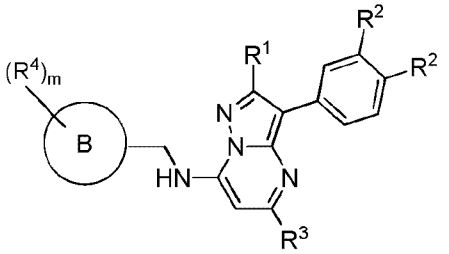
(Id)

wherein R^1, each R^2, R^3, each R^4, W, m and ring B are as defined herein.

In some embodiments of a compound of formula (Id), ring B is phenyl or 5- or 6-membered heteroaryl. In some other embodiments of a compound of formula (Id), ring B is phenyl.

In some embodiments of a compound of formula (Ia), e.g. in some embodiments of a compound of formula (Id), each R^2 is independently selected from C1-C6 alkyl, R^5O- and halogen.

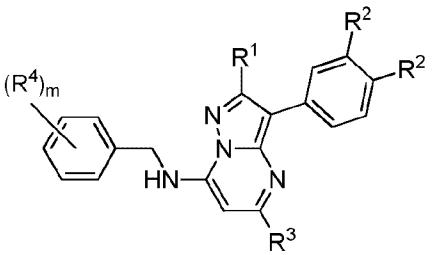
In some particular embodiments of a compound of formula (I), e.g. in a compound of formula (Ia), p is 2 and W is a methylene group. In some embodiments, when p is 2 and W is a methylene group, the compound of formula (Ia) is a compound as represented by formula (Ie)



(Ie)

wherein ring B, R^1, each R^2, R^3, each R^4, and m are as defined herein.

In some particular embodiments of a compound of formula (Ie), ring B is phenyl, i.e. the compound may represented by formula (If)

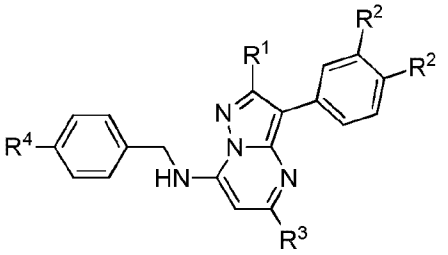


(If)

wherein R^1, each R^2, R^3, each R^4, and m are as defined herein.

In some embodiments of a compound of formula (Ib), i.e. in some embodiments of a compound of formula (Ic), in particular in some embodiments of a compound of formula (If), when m is 1 or 2, one moiety R^4 is in para position on ring B. In some of these embodiments, m is 1.

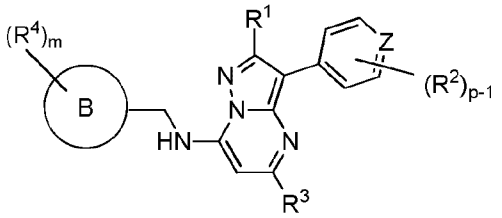
In some embodiments of a compound of formula (If), m is 1 and R^4 is in para position, i.e. the compound may be represented by formula (Ig)



(Ig)

wherein R^1, each R^2, R^3, and R^4 are as defined herein.

In some further embodiments a compound of formula (I) may be represented by formula (Ih)

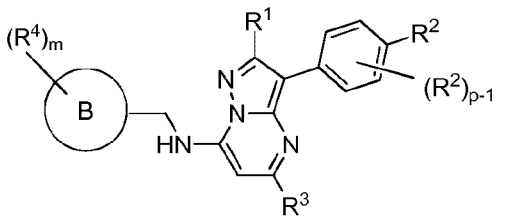


(Ih)

wherein R^1, each R^2, R^3, R^4, m, ring B and Z are as defined herein and p is an integer of from 1 to 3.

In formula (Ih), Z is N or CR^2. In some embodiments, Z is N. In some embodiments, when Z is N, p is 1 (i.e. p-1 is 0).

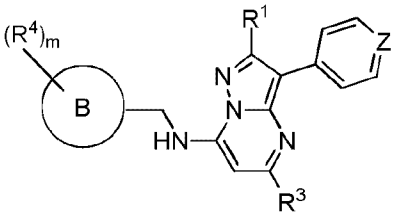
In some embodiments of a compound of formula (Ih), Z is CR^2, in which case the compound may be represented by formula (Ij)



(Ij)

wherein R^1, each R^2, R^3, each R^4, m and ring B are as defined herein and p is an integer of from 1 to 3, e.g. p is 1 or 2, or p is 2.

In some embodiments of a compound of formula (I), e.g. in some embodiments of formula (Ih), or in some embodiments of formula (Ij), p is 1 or 2. In other embodiments of a compound of formula (I), e.g. in embodiments of formula (Ih), or in embodiments of formula (Ij), p is 1. In some particular embodiments, the compound may be represented by formula (Ik)



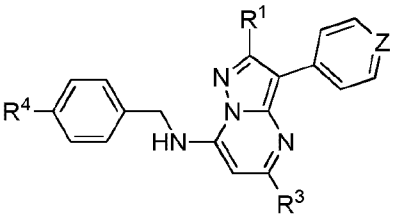
(Ik)

wherein R^1, R^3, each R^4, m, Z and ring B are as defined herein.

In some embodiments of a compound of formula (I), e.g. in embodiments of formula (Ia), or formula (Id), or formula (Ie), or formula (Ih), or formula (Ij), or formula (Ik), ring B is 6-membered heteroaryl, said heteroaryl being substituted by a moiety R^4 in para position or having a heteroatom, such as N, in para position, or ring B is phenyl, said phenyl being substituted by a moiety R^4 in para position.

In some embodiments of a compound of formula (I), e.g. in embodiments of formula (Ia), or formula (Id), or formula (Ie), or formula (Ih), or formula (Ij), or formula (Ik), ring B is 6-membered heteroaryl, said heteroaryl being substituted by a moiety R^4 in para position or having a heteroatom, such as N, in para position.

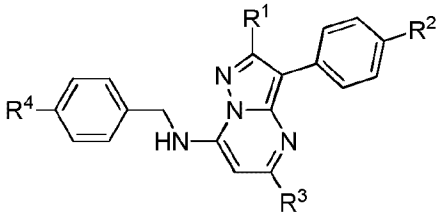
In some embodiments of a compound of formula (I), e.g. in some embodiments of a compound of formula (Ih), or of formula (Ij) or of formula (Ik), ring B is phenyl, said phenyl being substituted by R^4 in para position. In some embodiments, the compound may be represented by formula (Im)



(Im)

wherein R^1, R^3, R^4 and Z are as defined herein.

In some embodiments, in a compound of formula (Im), Z is CR^2, and the compound may be represented by formula (In)



(In)

wherein R^1, R^2, R^3, and R^4 are as defined herein.

It should be realized that, unless the contrary is apparent from the context or specified, any reference herein to a compound of formula (I) also should be construed as a reference to a compound of any of the embodiments thereof, e.g. a compound according to any one of the formulas (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ij), (Ik), (Im) and (In).

As noted herein above, some of the compounds of formula (I) are novel. Thus, with the exceptions listed herein, novel compounds are provided according to formula (Id) or according to formula (Ih).

In some embodiments, the novel compound is as represented by formula (Ie), provided that the compound is not

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

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

3-(3,4-dimethoxyphenyl)-2,5-dimethyl-N-(p-tolylmethyl)pyrazolo[1,5-a]pyrimidin-7-amine,

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

3-(3,4-dimethoxyphenyl)-N-[(4-fluorophenyl)methyl]-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-amine,
3-(3,4-dimethoxyphenyl)-2,5-dimethyl-N-(2-pyridylmethyl)pyrazolo[1,5-a]pyrimidin-7-amine, or
N-benzyl-3-(3,4-dimethoxyphenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-amine.

In some embodiments, the novel compound is as represented by formula (If), provided that the compound is not
N-[(4-chlorophenyl)methyl]-3-(3,4-dimethoxyphenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-amine,
3-(3,4-dimethoxyphenyl)-N-[(4-methoxyphenyl)methyl]-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-amine,
3-(3,4-dimethoxyphenyl)-2,5-dimethyl-N-(p-tolylmethyl)pyrazolo[1,5-a]pyrimidin-7-amine,
N-(1,3-benzodioxol-5-ylmethyl)-3-(3,4-dimethoxyphenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-amine,
3-(3,4-dimethoxyphenyl)-N-[(4-fluorophenyl)methyl]-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-amine, or
N-benzyl-3-(3,4-dimethoxyphenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-amine.

In some embodiments, the novel compound is as represented by formula (Ig), provided that the compound is not
N-[(4-chlorophenyl)methyl]-3-(3,4-dimethoxyphenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-amine,
3-(3,4-dimethoxyphenyl)-N-[(4-methoxyphenyl)methyl]-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-amine,
3-(3,4-dimethoxyphenyl)-2,5-dimethyl-N-(p-tolylmethyl)pyrazolo[1,5-a]pyrimidin-7-amine, or
3-(3,4-dimethoxyphenyl)-N-[(4-fluorophenyl)methyl]-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-amine.

In some embodiments, the novel compound is as represented by formula (Ik), provided that the compound is not
N-benzyl-3-(4-fluorophenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-amine,
N-benzyl-3-(4-fluorophenyl)-5-methyl-pyrazolo[1,5-a]pyrimidin-7-amine,

N-benzyl-3-(4-chlorophenyl)-5-methyl-pyrazolo[1,5-a]pyrimidin-7-amine,
2,5-dimethyl-3-(p-tolyl)-N-(2-pyridylmethyl)pyrazolo[1,5-a]pyrimidin-7-amine,
2,5-dimethyl-3-(p-tolyl)-N-(3-pyridylmethyl)pyrazolo[1,5-a]pyrimidin-7-amine,
3-(4-fluorophenyl)-2,5-dimethyl-N-(3-pyridylmethyl)pyrazolo[1,5-a]pyrimidin-7-amine,
3-(4-fluorophenyl)-2,5-dimethyl-N-(2-pyridylmethyl)pyrazolo[1,5-a]pyrimidin-7-amine,
3-(4-chlorophenyl)-2,5-dimethyl-N-(2-pyridylmethyl)pyrazolo[1,5-a]pyrimidin-7-amine,
3-(4-chlorophenyl)-2,5-dimethyl-N-(3-pyridylmethyl)pyrazolo[1,5-a]pyrimidin-7-amine,
3-(4-methoxyphenyl)-2,5-dimethyl-N-(3-pyridylmethyl)pyrazolo[1,5-a]pyrimidin-7-amine,
3-(4-methoxyphenyl)-2,5-dimethyl-N-(4-pyridylmethyl)pyrazolo[1,5-a]pyrimidin-7-amine,
N-(cyclohexylmethyl)-2,5-dimethyl-3-(p-tolyl)pyrazolo[1,5-a]pyrimidin-7-amine,
N-benzyl-2,5-dimethyl-3-(p-tolyl)pyrazolo[1,5-a]pyrimidin-7-amine,
3-(4-methoxyphenyl)-2,5-dimethyl-N-(pyridin-3-ylmethyl)pyrazolo[1,5-a]pyrimidin-7-amine,
or
3-(4-methoxyphenyl)-2,5-dimethyl-N-(pyridin-4-ylmethyl)pyrazolo[1,5-a]pyrimidin-7-amine.

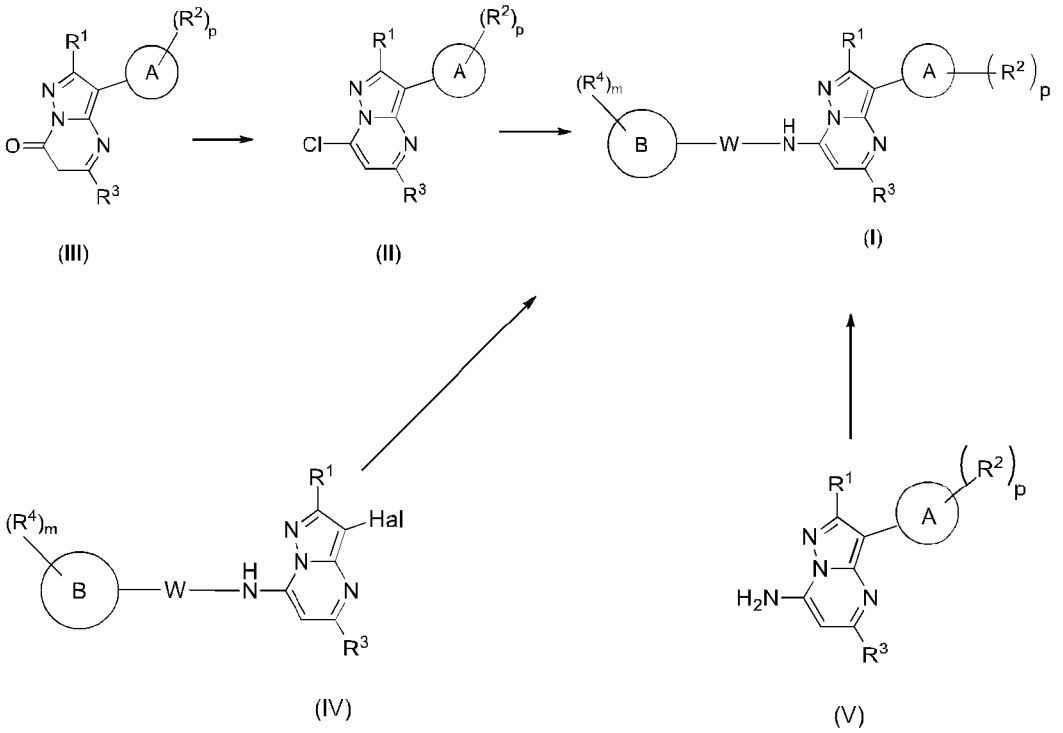
In some embodiments, the novel compound is as represented by formula (Im).

In some embodiments, the novel compound is as represented by formula (In).

Scheme 1 below illustrates suitable ways of synthesizing compounds of formula (I). For example, compounds of formula (I) may be formed from compounds of formula (III) by treatment with $POCl_3$ under reflux conditions to give compounds of formula (II), followed by reaction of amines using methods well-known to the person skilled in the art. Examples illustrating the synthetic methods are described in Griffith et al (Bioorg. Med. Chem. Lett. 2011, 21, 2641-2645); Hwang et al (Bioorg. Med. Chem. Lett. 2012, 22, 7297-7301); Gilligan et al, (J. Med. Chem. 2009, 52, 3073-3083); Chen et al (Bioorg. Med. Chem. Lett. 2004, 14, 3669-3673); Tellew et al (Bioorg. Med. Chem. Lett. 2010, 20, 7259-7264); and Yu et al (Med. Chem. Lett. 2013, 4,230-234).

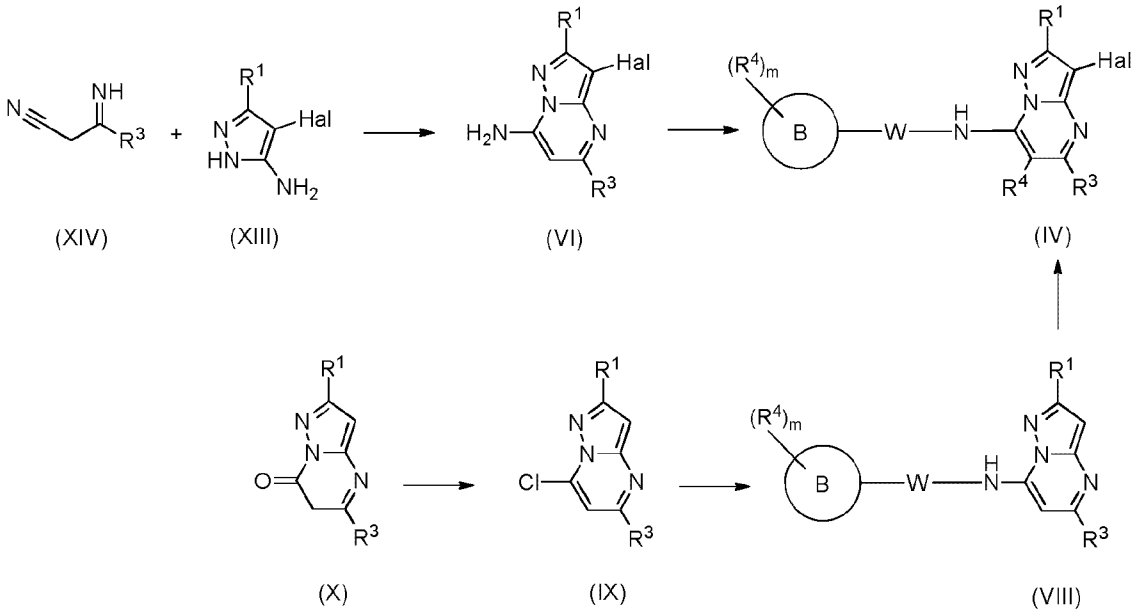
Compounds of formula (I) can also be formed form compounds of formula (IV) via palladium-catalyzed synthetic methods such as Suzuki, Stille or Negishi reactions, depending on the halogen, as for example described in Gudmundsson et al (Bioorg. Med. Chem. Lett. 2009, 19, 5689-5692); Mayo et al (Adv. Synth. Catal. 2003, 345, 620-624); and US2006/0135526. Compounds of formula (I) may also be formed from compounds of

formula (V) by N-alkylations as described by Saito et al (Bioorg. Med. Chem. 2011, 19, 5432-5445.).



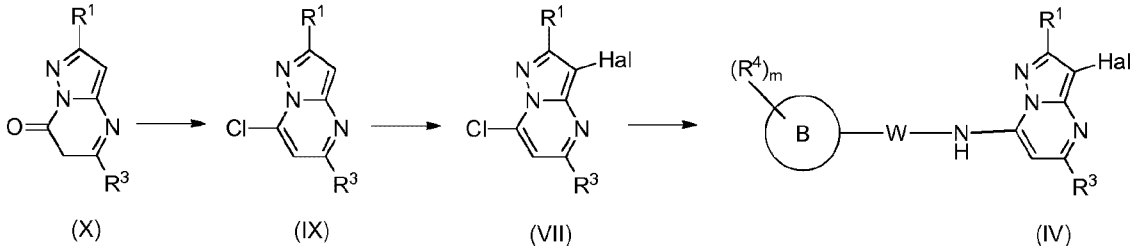
Scheme 1

As illustrated below in **scheme 2,** compounds of formula (IV) can be formed from commercially available starting material (compounds of formula XIII and XIV) followed alkylation of the amine of formula (VI) by a method as described in Majo et al 2003 and references therein. Compounds of formula (IV) can also be formed from compounds of formula (X) by treatment with $POCl_3$ to give compounds of formula (IX) by a method as described previously, followed by amination, as described in US2006/0135526 or Novinson et al (J. Med. Chem. 1977, 20(2), 296-299), to give compounds of formula (VIII). Compounds of formula (VIII) may then be halogenated using NIS or NBr to give compounds of formula (IV) using methods as described in Labroli et al (Bioorg. Med. Chem. Lett. 2011, 21, 471-474), US20050187224 or US2006135526.



Scheme 2

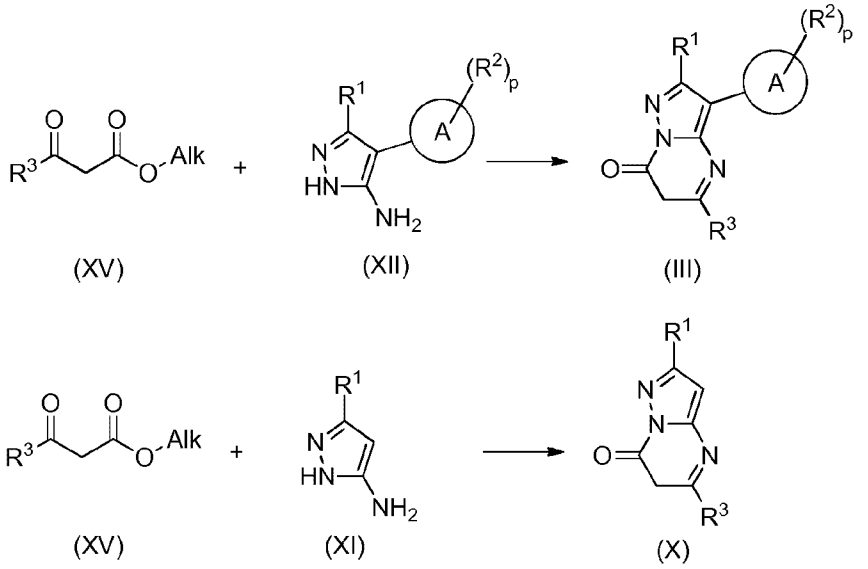
As illustrated below in **scheme 3**, compounds of formula (IV) can also be formed starting from compounds of formula (X), by treatment with a halogenating agent (e.g. $SOCl_2$, $POCl_3$, PCl_3, PBr_3 etc) as described previously, to give compounds of formula (IX), which may then be treated with NBS or NIS to give compounds of formula (VII). Methods useful for synthesizing compounds of formula (VII) from compounds of formula (X) are also described in WO2005103052, WO2012033753 and Gudmundsson et al (Bioorg. Med. Chem. Lett. 2009, 19, 5689-5692). Compounds of formula (VII) can then be reacted with amines to give compounds of formula (IV), by methods as described by Gudmundsson et al (Bioorg. Med. Chem. Lett. 2009, 19, 5689-5692) or Bel Abed (Tetrahedron Lett. 2013, 54(21) 2612-2614)



Scheme 3

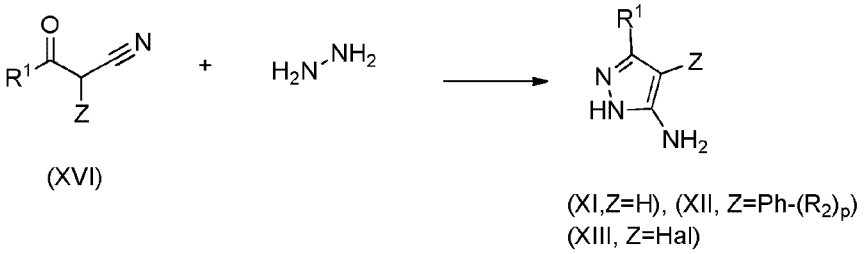
As illustrated below in **scheme 4**, compounds of formula (III) and formula (X) can be formed from commercially available starting material (compounds of formula XV), by reaction with compounds of formula (XI) or (XII) under conditions described in, for example, Griffith et al

(Bioorg. Med. Chem. Lett. 2011, 21, 2641-2645); Hwang et al (Bioorg. Med. Chem. Lett. 2012, 22, 7297-7301); Chen et al (Bioorg. Med. Chem. Lett. 2004, 14, 3669-3673); Yu et al (Med. Chem. Lett. 2013, 4,230-234) or US2006/0135526.



Scheme 4

As illustrated below in **scheme 5**, compounds of formula (XI), formula (XII) and formula (XIII) can be formed from commercially available starting material (compounds of formula XVI), by reaction with hydrazine under conditions described in several of the above-mentioned publications (Labroli, Chen, Hwang, Griffith, Yu, Bel Abed etc).



Scheme 5

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.

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.

The invention also includes 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

In **Table 1**, the chemical name of some exemplifying compounds for use of the invention (Ex. 1 to 71) and of some exemplifying novel compounds of the invention (Ex. 72 to 112) are given.

Table 1

Ex	Chemical name
1	N-[(4-chlorophenyl)methyl]-3-(3,4-dimethoxyphenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-amine
2	3-(3,4-dimethoxyphenyl)-N-[(4-methoxyphenyl)methyl]-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-amine
3	3-(4-fluorophenyl)-2,5-dimethyl-N-(1-phenylethyl)pyrazolo[1,5-a]pyrimidin-7-amine
4	N-benzyl-5-isopropyl-3-phenyl-pyrazolo[1,5-a]pyrimidin-7-amine
5	N-[2-(4-chlorophenyl)ethyl]-3-(3,4-dimethoxyphenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-amine
6	3-(3,4-dimethoxyphenyl)-2,5-dimethyl-N-(p-tolylmethyl)pyrazolo[1,5-a]pyrimidin-7-amine
7	3-(3,4-dimethoxyphenyl)-2,5-dimethyl-N-(3-phenylpropyl)pyrazolo[1,5-a]pyrimidin-7-amine
8	N-(1,3-benzodioxol-5-ylmethyl)-3-(3,4-dimethoxyphenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-amine
9	3-(3,4-dimethoxyphenyl)-N-[(4-fluorophenyl)methyl]-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-amine
10	3-(3,4-dimethoxyphenyl)-2,5-dimethyl-N-(2-phenylpropyl)pyrazolo[1,5-a]pyrimidin-7-amine
11	N-(2-cyclohexen-1-ylethyl)-3-(3,4-dimethoxyphenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-amine
12	3-(3,4-dimethoxyphenyl)-N-[2-(2,4-dimethoxyphenyl)ethyl]-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-amine
13	N-benzyl-3-(4-fluorophenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-amine

Ex	Chemical name
14	3-(4-fluorophenyl)-2,5-dimethyl-N-phenethyl-pyrazolo[1,5-a]pyrimidin-7-amine
15	N-[2-(3,4-dimethoxyphenyl) ethyl]-3-(4-fluorophenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-amine
16	N-(2-cyclohexen-1-ylethyl)-3-(4-fluorophenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-amine
17	3-(4-fluorophenyl)-2,5-dimethyl-N-(1-phenylethyl)pyrazolo[1,5-a]pyrimidin-7-amine
18	N-benzyl-3-(4-fluorophenyl)-5-methyl-pyrazolo[1,5-a]pyrimidin-7-amine
19	N-[2-(3,4-dimethoxyphenyl)ethyl]-3-(4-fluorophenyl)-5-methyl-pyrazolo[1,5-a]pyrimidin-7-amine
20	5-tert-butyl-N-(2-cyclohexen-1-ylethyl)-3-(4-fluorophenyl)-2-methyl-pyrazolo[1,5-a]pyrimidin-7-amine
21	N-benzyl-5-methyl-3-phenyl-pyrazolo[1,5-a]pyrimidin-7-amine
22	N-[2-(3,4-dimethoxyphenyl)ethyl]-5-methyl-3-phenyl-pyrazolo[1,5-a]pyrimidin-7-amine
23	5-tert-butyl-N-(3-imidazol-1-ylpropyl)-3-phenyl-pyrazolo[1,5-a]pyrimidin-7-amine
24	N-(3-imidazol-1-ylpropyl)-2-methyl-3-phenyl-5-propyl-pyrazolo[1,5-a]pyrimidin-7-amine
25	N-benzyl-3-(4-chlorophenyl)-5-methyl-pyrazolo[1,5-a]pyrimidin-7-amine
26	3-(4-chlorophenyl)-5-methyl-N-phenethyl-pyrazolo[1,5-a]pyrimidin-7-amine
27	3-(4-chlorophenyl)-N-[2-(3,4-dimethoxyphenyl)ethyl]-5-methyl-pyrazolo[1,5-a]pyrimidin-7-amine
28	3-(4-chlorophenyl)-N-(3-imidazol-1-ylpropyl)-5-methyl-pyrazolo[1,5-a]pyrimidin-7-amine
29	N-[2-(3,4-dimethoxy phenyl)ethyl]-5-methyl-3-(p-tolyl)pyrazolo[1,5-a]pyrimidin-7-amine
30	N-[2-(3,4-dimethoxyphenyl) ethyl]-2-ethyl-5-methyl-3-phenyl-pyrazolo[1,5-a]pyrimidin-7-amine
31	2-ethyl-N-(3-imidazol-1-ylpropyl)-5-methyl-3-phenyl-pyrazolo[1,5-a]pyrimidin-7-amine
32	3-(4-chlorophenyl)-2,5-dimethyl-N-[2-(p-tolyl)ethyl]pyrazolo[1,5-a]pyrimidin-7-amine
33	2,5-dimethyl-3-(p-tolyl)-N-(2-pyridylmethyl)pyrazolo[1,5-a]pyrimidin-7-amine

Ex	Chemical name
34	2,5-dimethyl-3-(p-tolyl)-N-(3-pyridylmethyl)pyrazolo[1,5-a]pyrimidin-7-amine
35	3-(3,4-dimethoxyphenyl)-2,5-dimethyl-N-(2-pyridylmethyl)pyrazolo[1,5-a]pyrimidin-7-amine
36	3-(4-fluorophenyl)-2,5-dimethyl-N-(3-pyridylmethyl)pyrazolo[1,5-a]pyrimidin-7-amine
37	3-(4-fluorophenyl)-2,5-dimethyl-N-(2-pyridylmethyl)pyrazolo[1,5-a]pyrimidin-7-amine
38	N-cyclopentyl-3-(4-fluorophenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-amine
39	2,5-dimethyl-3-phenyl-N-(3-pyridylmethyl)pyrazolo[1,5-a]pyrimidin-7-amine
40	N-benzyl-3-(3,4-dimethoxyphenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-amine
41	N-cyclopentyl-3-(3,4-dimethoxyphenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-amine
42	3-(4-chlorophenyl)-2,5-dimethyl-N-(2-pyridylmethyl)pyrazolo[1,5-a]pyrimidin-7-amine
43	N-cyclohexyl-3-(3,4-dimethoxyphenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-amine
44	3-(4-chlorophenyl)-N-(3-imidazol-1-ylpropyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-amine
45	3-(4-chlorophenyl)-2,5-dimethyl-N-(3-pyridylmethyl)pyrazolo[1,5-a]pyrimidin-7-amine
46	N-(4-bromophenyl)-3-(3,4-dimethoxyphenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-amine
47	N-(4-chlorophenyl)-3-(3,4-dimethoxyphenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-amine
48	3-(3,4-dimethoxyphenyl)-2,5-dimethyl-N-(p-tolyl)pyrazolo[1,5-a]pyrimidin-7-amine
49	3-(3,4-dimethoxyphenyl)-N-(4-methoxyphenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-amine
50	3-(3,4-dimethoxyphenyl)-2,5-dimethyl-N-(m-tolyl)pyrazolo[1,5-a]pyrimidin-7-amine
51	N-(3-chlorophenyl)-3-(3,4-dimethoxyphenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-amine
52	3-(3,4-dimethoxyphenyl)-N-(3,4-dimethylphenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-amine

Ex	Chemical name
53	3-(3,4-dimethoxyphenyl)-N-(4-fluorophenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-amine
54	3-(3,4-dimethoxyphenyl)-N-(4-ethoxyphenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-amine
55	N-(3-chloro-4-methyl-phenyl)-3-(3,4-dimethoxyphenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-amine
56	3-(3,4-dimethoxyphenyl)-N-(3,5-dimethylphenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-amine
57	3-(3,4-dimethoxyphenyl)-2,5-dimethyl-N-phenyl-pyrazolo[1,5-a]pyrimidin-7-amine
58	N-[4-[[3-(3,4-dimethoxy phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]amino]phenyl]acetamide
59	N-(3,4-dichlorophenyl)-3-(3,4-dimethoxyphenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-amine
60	3-(3,4-dimethoxyphenyl)-N-(4-isopropylphenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-amine
61	3-(3,4-dimethoxyphenyl)-N-(3-methoxyphenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-amine
62	3-(3,4-dimethoxyphenyl)-N-(4-ethylphenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-amine
63	N-(4-butylphenyl)-3-(3,4-dimethoxyphenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-amine
64	N-(3,5-dichlorophenyl)-3-(3,4-dimethoxyphenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-amine
65	3-(4-methoxyphenyl)-2,5-dimethyl-N-(3-pyridylmethyl)pyrazolo[1,5-a]pyrimidin-7-amine
66	3-(4-methoxyphenyl)-2,5-dimethyl-N-(4-pyridylmethyl)pyrazolo[1,5-a]pyrimidin-7-amine
67	N-(3-imidazol-1-ylpropyl)-3-(4-methoxyphenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-amine
68	3-(4-methoxyphenyl)-2,5-dimethyl-N-[2-(2-pyridyl)ethyl]pyrazolo[1,5-a]pyrimidin-7-amine
69	2,5-dimethyl-N-(3-pyridylmethyl)-3-(2-thienyl)pyrazolo[1,5-a]pyrimidin-7-amine

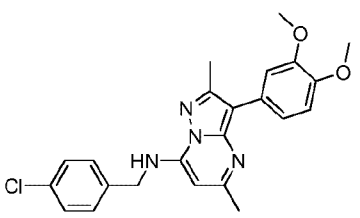
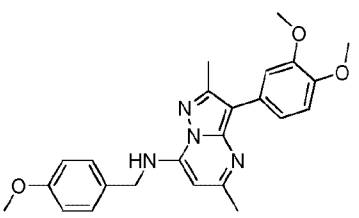
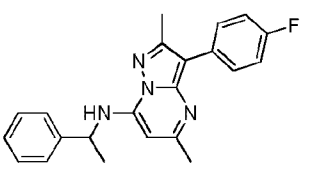
Ex	Chemical name
70	2,5-dimethyl-N-(4-pyridylmethyl)-3-(2-thienyl)pyrazolo[1,5-a]pyrimidin-7-amine
71	N-(3-imidazol-1-ylpropyl)-2,5-dimethyl-3-(2-thienyl)pyrazolo[1,5-a]pyrimidin-7-amine
72	3-(3,4-dimethoxyphenyl)-2,5-dimethyl-N-[[4-(trifluoromethyl)phenyl]methyl]pyrazolo[1,5-a]pyrimidin-7-amine
73	3-(3,4-dimethoxyphenyl)-2,5-dimethyl-N-[4-(trifluoromethyl)phenyl]pyrazolo[1,5-a]pyrimidin-7-amine
74	3-(3,4-dimethoxyphenyl)-2,5-dimethyl-N-(4-pyridyl)pyrazolo[1,5-a]pyrimidin-7-amine
75	3-(3,4-dimethoxyphenyl)-2,5-dimethyl-N-(4-pyridylmethyl)pyrazolo[1,5-a]pyrimidin-7-amine
76	3-(3,4-dimethoxyphenyl)-2,5-dimethyl-N-[[4-(trifluoromethoxy)phenyl]methyl]pyrazolo[1,5-a]pyrimidin-7-amine
77	N-[4-[[[3-(3,4-dimethoxyphenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]amino]methyl]phenyl]acetamide
78	3-(3,4-dimethoxyphenyl)-N-[(4-dimethylaminophenyl)methyl]-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-amine
79	3-(3,4-dimethoxyphenyl)-N-[(6-methoxy-3-pyridyl)methyl]-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-amine
80	N-[4-[[[3-(3,4-dimethoxyphenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]amino]methyl]phenyl]methanesulfonamide
81	4-[[[3-(3,4-dimethoxyphenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]amino]methyl]phenol
82	3-(3,4-dimethoxyphenyl)-2,5-dimethyl-N-[(3-methylsulfonylphenyl)methyl]pyrazolo[1,5-a]pyrimidin-7-amine
83	3-(3,4-dimethoxyphenyl)-2,5-dimethyl-N-[(1-oxidopyridin-1-ium-4-yl)methyl]pyrazolo[1,5-a]pyrimidin-7-amine
84	3-(3,4-dimethoxyphenyl)-2,5-dimethyl-N-[(4-methylsulfonylphenyl)methyl]pyrazolo[1,5-a]pyrimidin-7-amine
85	3-(3,4-dimethoxyphenyl)-2,5-dimethyl-N-[2-(2-pyridyl)ethyl]pyrazolo[1,5-a]pyrimidin-7-amine

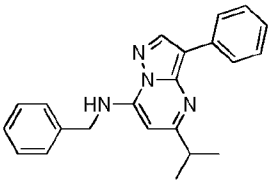
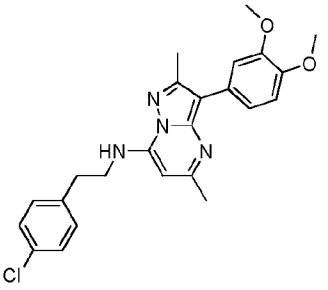
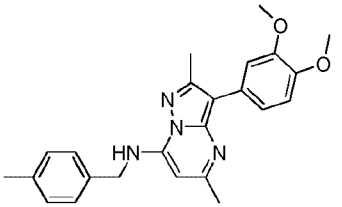
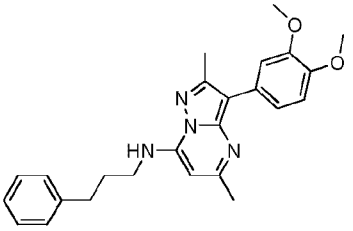
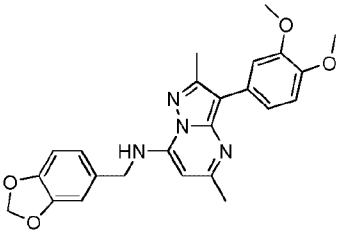
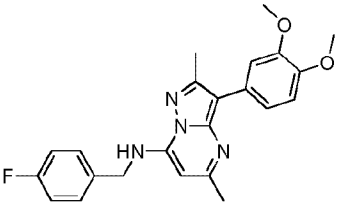
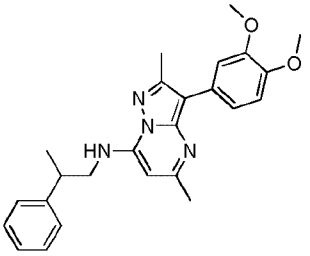
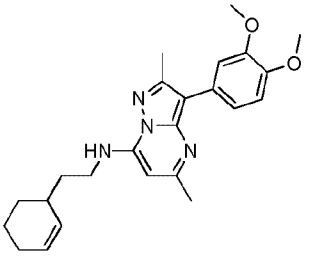
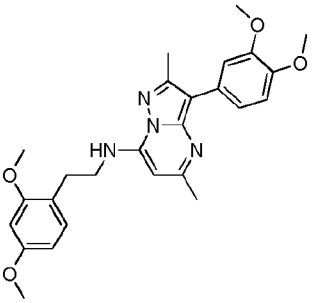
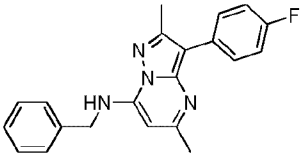
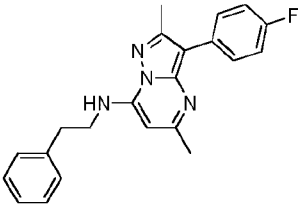
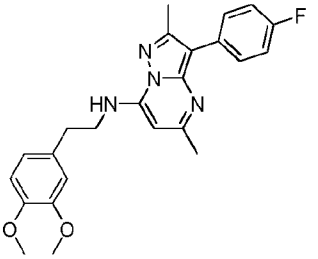
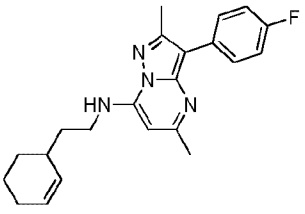
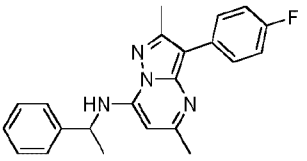
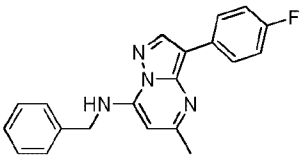
Ex	Chemical name
86	N-[(4-tert-butylphenyl)methyl]-3-(3,4-dimethoxyphenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-amine
87	3-(3,4-dimethoxyphenyl)-2,5-dimethyl-N-[(2-methylpyrimidin-4-yl)methyl]pyrazolo[1,5-a]pyrimidin-7-amine
88	3-(3,4-dimethoxyphenyl)-2,5-dimethyl-N-[2-(2-thienyl)ethyl]pyrazolo[1,5-a]pyrimidin-7-amine
89	3-(3,4-dimethoxyphenyl)-2,5-dimethyl-N-[2-(4-pyridyl)ethyl]pyrazolo[1,5-a]pyrimidin-7-amine
90	3-(3,4-dimethoxyphenyl)-2,5-dimethyl-N-pyrazin-2-yl-pyrazolo[1,5-a]pyrimidin-7-amine
91	3-(3,4-dimethoxyphenyl)-N-indan-2-yl-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-amine
92	3-(3,4-dimethoxyphenyl)-2,5-dimethyl-N-[(6-methyl-3-pyridyl)methyl]pyrazolo[1,5-a]pyrimidin-7-amine
93	N-[3-(3,4-dimethoxyphenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-5-methyl-thiazol-2-amine
94	1-[4-[[[3-(3,4-dimethoxyphenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]amino]methyl]phenyl]ethanone
95	N-[3-(3,4-dimethoxyphenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]isoxazol-3-amine
96	3-(3,4-dimethoxyphenyl)-2,5-dimethyl-N-(1-naphthylmethyl)pyrazolo[1,5-a]pyrimidin-7-amine
97	4-[[[3-(3,4-dimethoxyphenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]amino]methyl]benzenesulfonamide
98	3-(3,4-dimethoxyphenyl)-2,5-dimethyl-N-[1-(4-pyridyl)ethyl]pyrazolo[1,5-a]pyrimidin-7-amine
99	3-(3,4-dimethoxyphenyl)-N-[(4-fluorophenyl)methyl]-5-methyl-pyrazolo[1,5-a]pyrimidin-7-amine
100	3-(3,4-dimethoxyphenyl)-5-methyl-N-(4-pyridylmethyl)pyrazolo[1,5-a]pyrimidin-7-amine
101	3-(3,4-dimethoxyphenyl)-5-methyl-N-[(3-methylsulfonylphenyl)methyl]pyrazolo[1,5-a]pyrimidin-7-amine

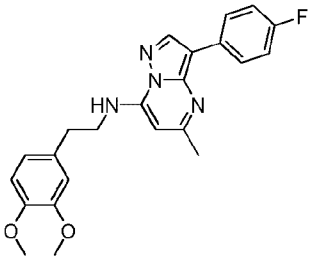
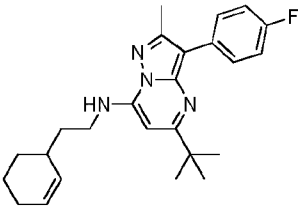
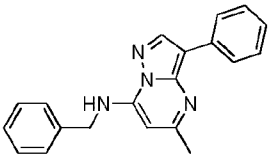
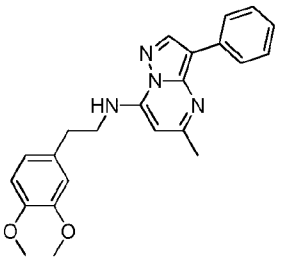
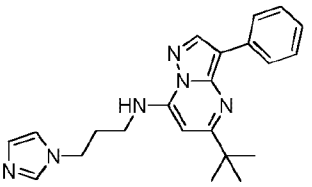
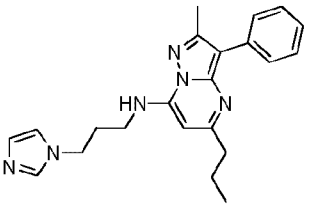
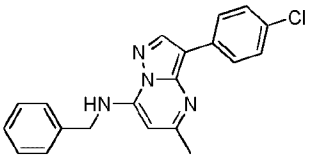
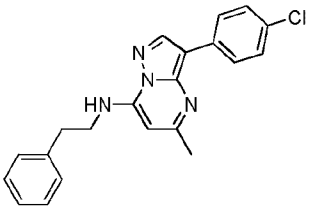
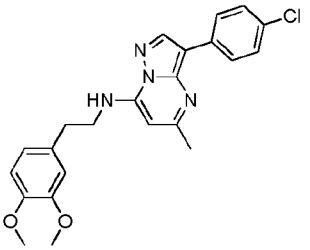
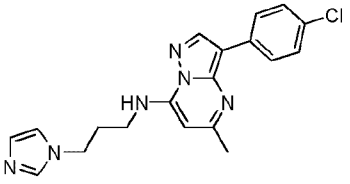
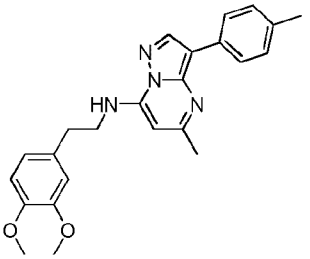
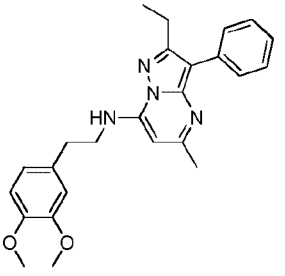
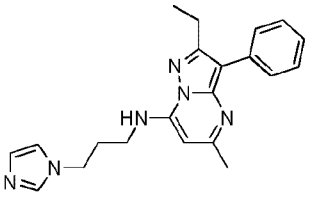
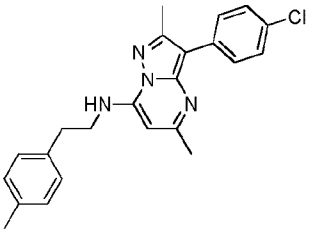
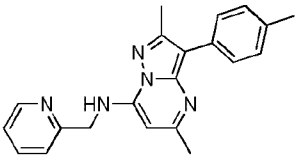
Ex	Chemical name
102	3-(1,3-benzodioxol-5-yl)-N-[(4-fluorophenyl)methyl]-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-amine
103	3-(3,4-dichlorophenyl)-N-[(4-fluorophenyl)methyl]-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-amine
104	N-[(4-fluorophenyl)methyl]-2,5-dimethyl-3-[4-(trifluoromethyl)phenyl]pyrazolo[1,5-a]pyrimidin-7-amine
105	N-[(4-fluorophenyl)methyl]-2,5-dimethyl-3-(3,4,5-trimethoxyphenyl)pyrazolo[1,5-a]pyrimidin-7-amine
106	3-(3,4-difluorophenyl)-N-[(4-fluorophenyl)methyl]-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-amine
107	methyl 4-[7-[(4-fluorophenyl)methylamino]-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-3-yl]benzoate
108	3-(3-fluoro-4-methoxy-phenyl)-2,5-dimethyl-N-(p-tolylmethyl)pyrazolo[1,5-a]pyrimidin-7-amine
109	3-(3,4-diethoxyphenyl)-N-[(4-fluorophenyl)methyl]-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-amine
110	4-[2,5-dimethyl-7-(p-tolylmethylamino)pyrazolo[1,5-a]pyrimidin-3-yl]benzene-1,2-diol
111	3-(3,4-dimethoxyphenyl)-N-[(4-fluorophenyl)methyl]-5-isopropyl-2-methyl-pyrazolo[1,5-a]pyrimidin-7-amine
112	N-[(4-fluorophenyl)methyl]-2,5-dimethyl-3-(4-pyridyl)pyrazolo[1,5-a]pyrimidin-7-amine

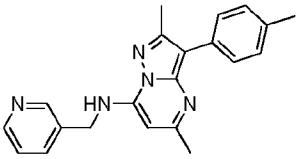
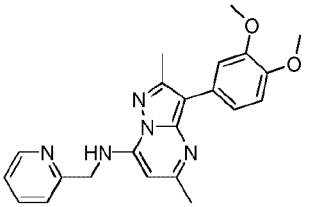
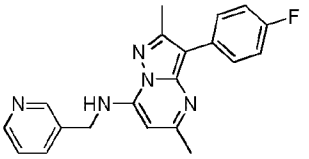
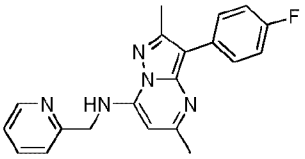
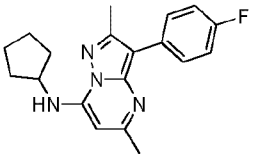
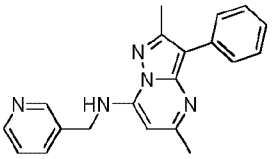
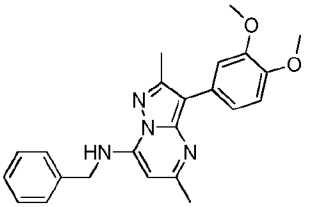
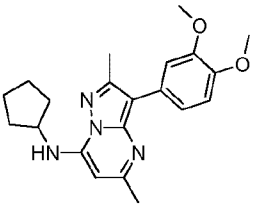
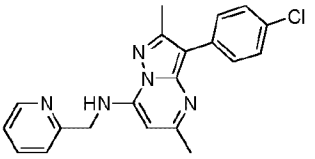
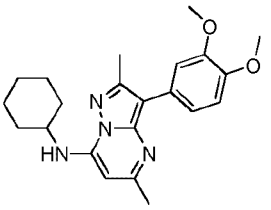
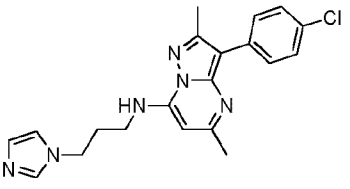
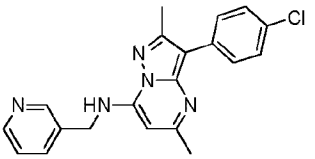
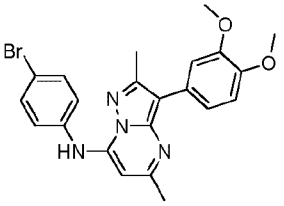
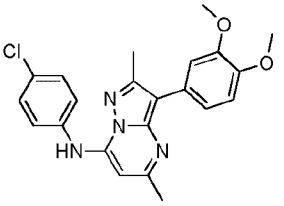
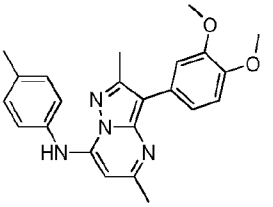
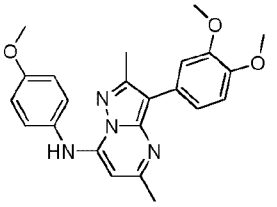
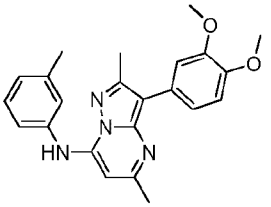
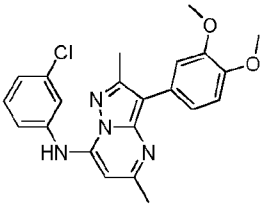
In **Table 2**, the structural formulas of the compounds of Examples 1-112 are given.

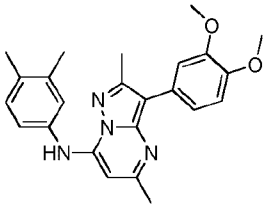
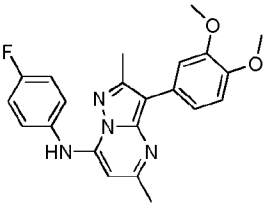
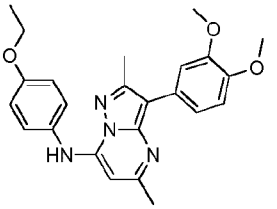
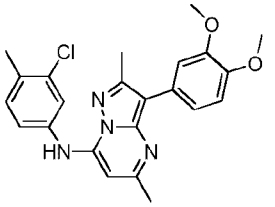
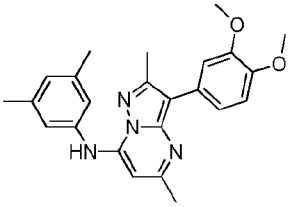
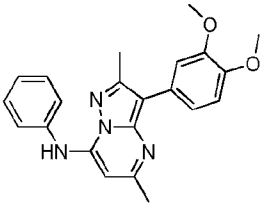
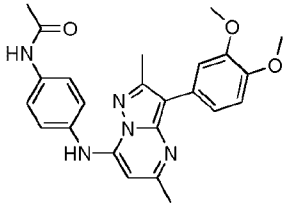
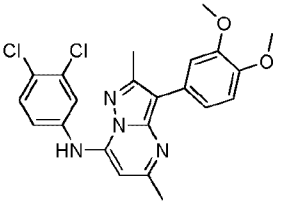
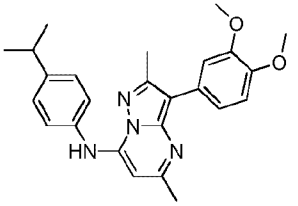
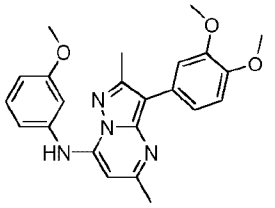
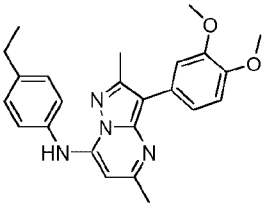
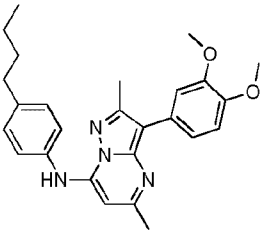
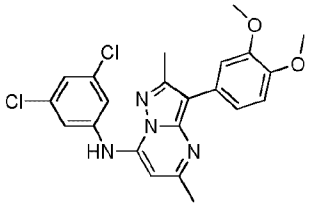
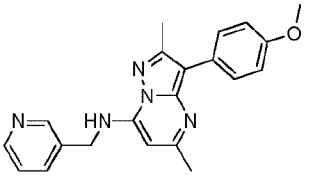
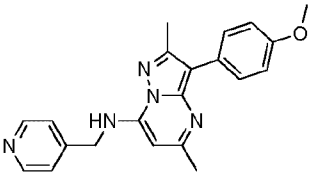
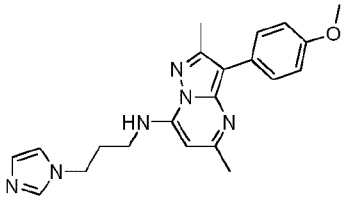
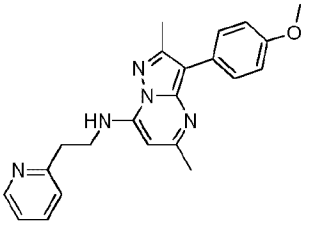
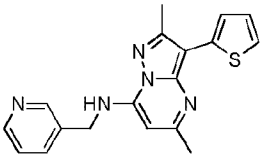
Table 2

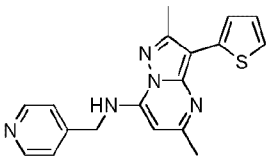
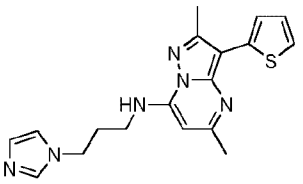
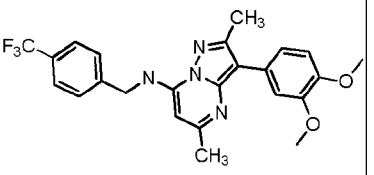
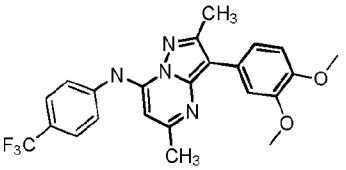
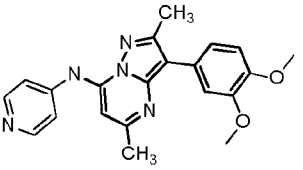
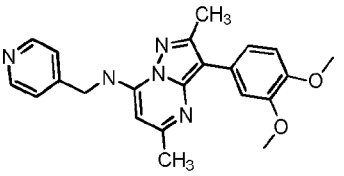
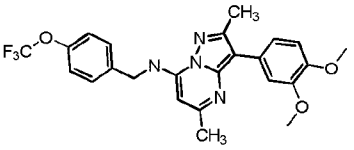
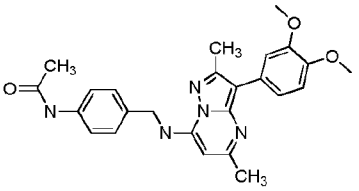
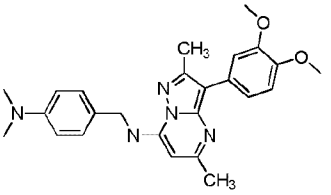
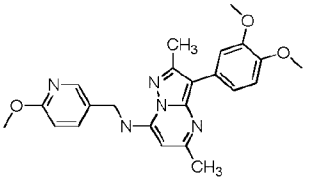
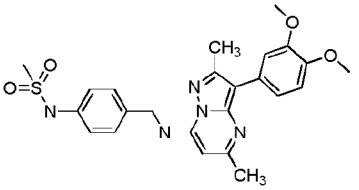
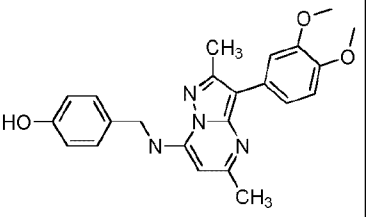
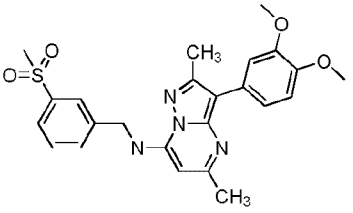
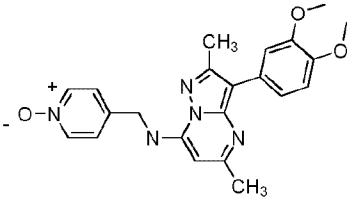
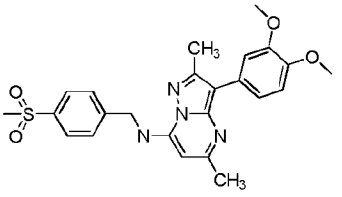
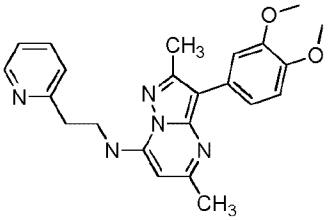
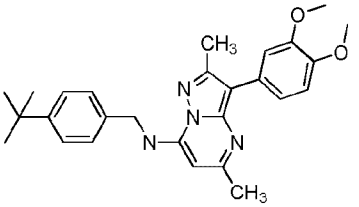
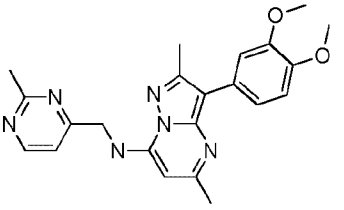
Ex. 1 	Ex. 2 	Ex. 3 

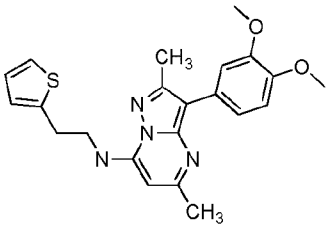
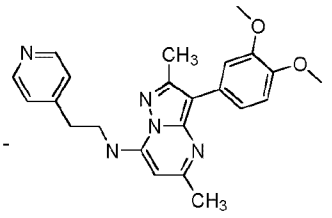
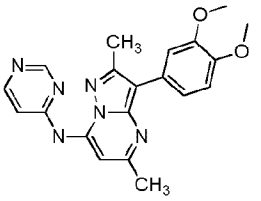
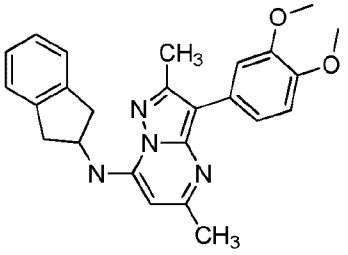
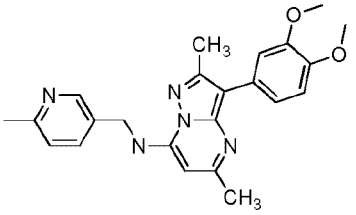
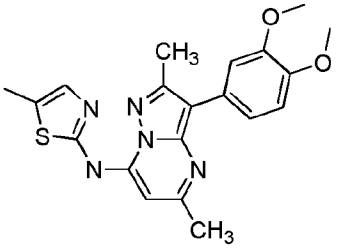
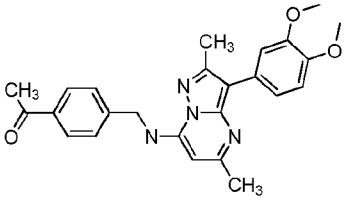
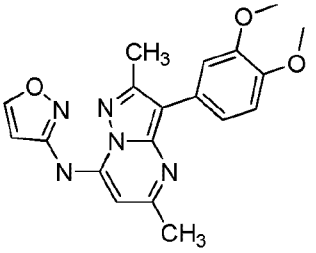
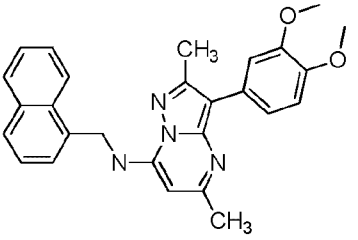
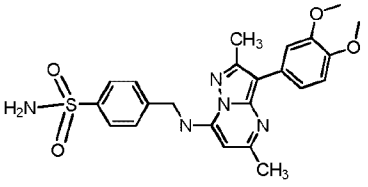
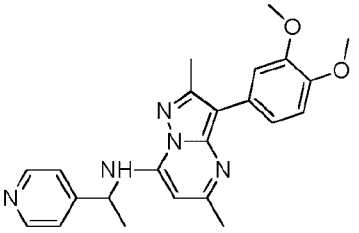
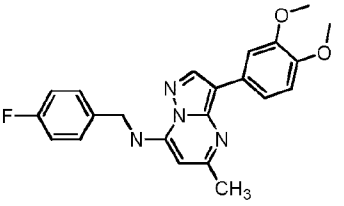
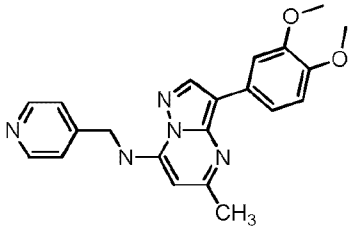
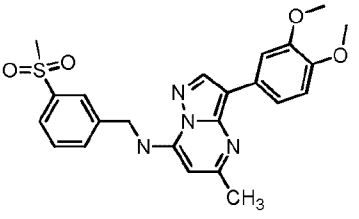
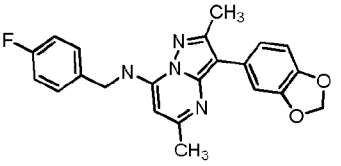
Ex. 4 	Ex. 5 	Ex. 6 
Ex. 7 	Ex. 8 	Ex. 9 
Ex. 10 	Ex. 11 	Ex. 12 
Ex. 13 	Ex. 14 	Ex. 15 
Ex. 16 	Ex. 17 	Ex. 18 

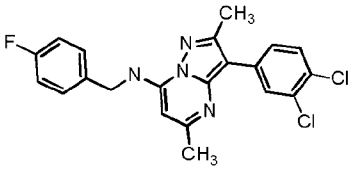
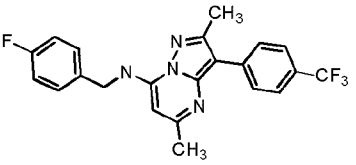
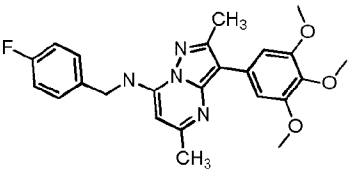
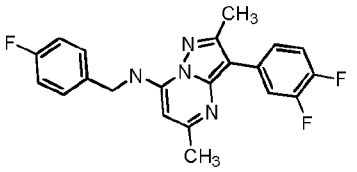
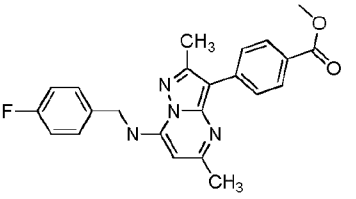
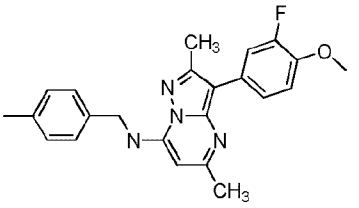
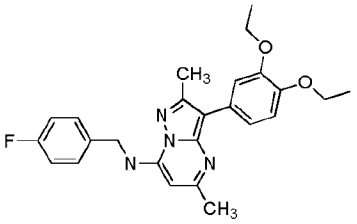
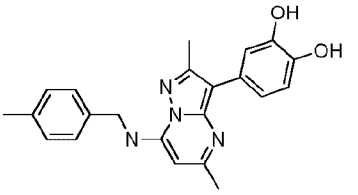
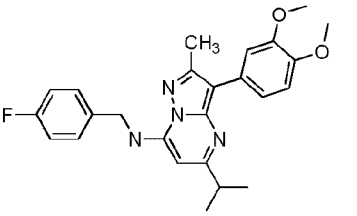
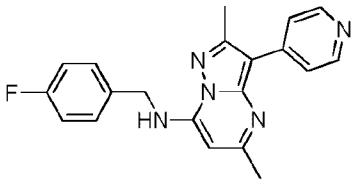
Ex. 19 	Ex. 20 	Ex. 21 
Ex. 22 	Ex. 23 	Ex. 24 
Ex. 25 	Ex. 26 	Ex. 27 
Ex. 28 	Ex. 29 	Ex. 30 
Ex. 31 	Ex. 32 	Ex. 33 

Ex. 34 	Ex. 35 	Ex. 36 
Ex. 37 	Ex. 38 	Ex. 39 
Ex. 40 	Ex. 41 	Ex. 42 
Ex. 43 	Ex. 44 	Ex. 45 
Ex. 46 	Ex. 47 	Ex. 48 
Ex. 49 	Ex. 50 	Ex. 51 

Ex. 52 	Ex. 53 	Ex. 54 
Ex. 55 	Ex. 56 	Ex. 57 
Ex. 58 	Ex. 59 	Ex. 60 
Ex. 61 	Ex. 62 	Ex. 63 
Ex. 64 	Ex. 65 	Ex. 66 
Ex. 67 	Ex. 68 	Ex. 69 

Ex. 70 	Ex. 71 	Ex. 72 
Ex. 73 	Ex. 74 	Ex. 75 
Ex. 76 	Ex. 77 	Ex. 78 
Ex. 79 	Ex. 80 	Ex. 81 
Ex. 82 	Ex. 83 	Ex. 84 
Ex. 85 	Ex. 86 	Ex. 87 

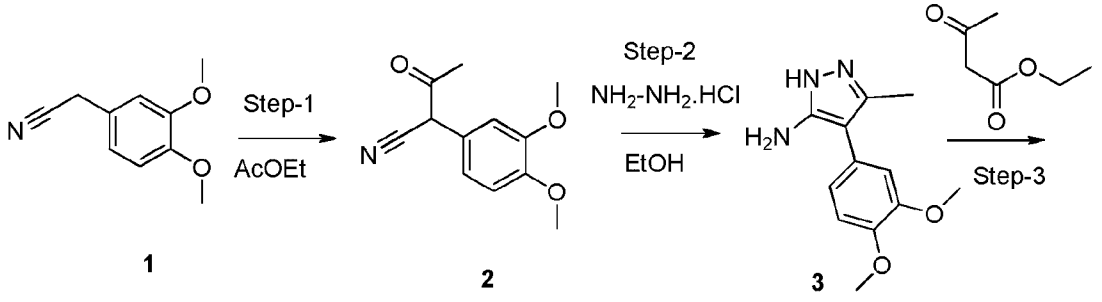
Ex. 88 	Ex. 89 	Ex. 90 
Ex. 91 	Ex. 92 	Ex. 93 
Ex. 94 	Ex. 95 	Ex. 96 
Ex. 97 	Ex. 98 	Ex. 99 
Ex. 100 	Ex. 101 	Ex. 102 

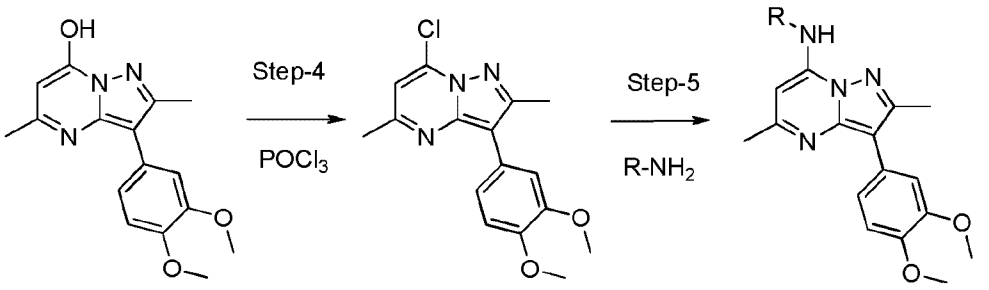
Ex. 103 	Ex. 104 	Ex. 105 
Ex. 106 	Ex. 107 	Ex. 108 
Ex. 109 	Ex. 110 	Ex. 111 
Ex. 112 		

EXAMPLES 72-98

The compounds of Examples 72-98 were synthesized by following the General Procedure A described herein below.

General Procedure A





4 5 Ex. 72-98

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 a pale brown solid.

Step-2

To a solution of **2** (9.0 g, 41.05 mmol) in ethanol (90 mL) were added hydrazine monohydrochloride (4.218 g, 61.57 mmol) and acetic acid (2.7 mL) 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) and 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). 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 solution of **3** (8.0 g, 21.4 mmol) in acetic acid (80 mL) was added ethyl acetoacetate (9 mL, 42.8 mmol) at room temperature and heated to 105 °C for 6 h. The progress of the reaction was monitored by TLC. After completion, the reaction mass was concentrated under high vacuum at 50 °C. The resultant solid was diluted with water and extracted with dichloromethane (3 × 10 mL). The combined organic extract was washed with 10% sodium bicarbonate solution, water and brine. The organic extract was dried over sodium sulphate, filtered and concentrated under vacuum at 50 °C. The residue obtained was treated with dichloromethane (25 mL). The solid was filtered and dried under vacuum to afford pure **4** (9.5 g, 92.54%) as a colorless solid.

Step-4

To a suspension of **4** (2.0 g, 6.68 mmol) in dry toluene (30 mL) were added phosphoryl chloride (6.24 mL, 6.68 mmol) and N,N-diethyl aniline (2.14 mL,13.36 mmol) at room temperature under nitrogen atmosphere. The reaction mass was heated to 105 °C for 16 h. After 16 h, the reaction mass was concentrated under high vacuum at 50-55 °C and co-evaporated with toluene under high vacuum at 50-55 °C. To the residue was added water (40 mL), followed by extraction with dichloromethane (3 × 40 mL), and the combined organic layer was washed with water, brine and dried over sodium sulphate. The organic layer was concentrated under vacuum at 45-50 °C to get crude compound. The crude compound was purified by flash column chromatography using ethyl acetate and hexane as eluant to afford **5** (2.1 g, 98.9%) as a yellow solid.

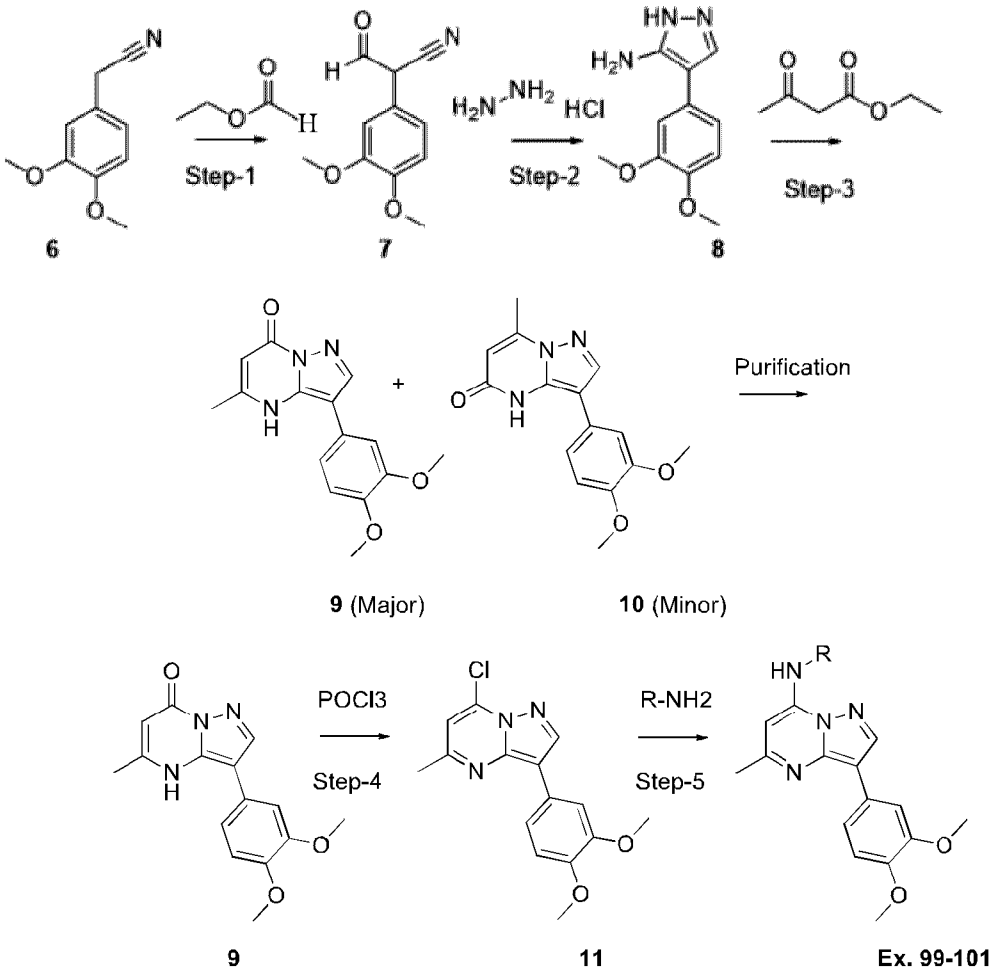
Step-5

To a solution of **5** (1.0 eq.) in toluene or acetonitrile or DMF (10-20 V) were added the respective amines (1.3 eq.) and base [DIPEA (5 V)/ K_2CO_3 / KO^tBu / NaH (2.0 eq.)] sequentially. The reaction mixture was then heated to 90 °C and stirred well 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) and 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 compounds with >95% HPLC purity.

EXAMPLES 99-101

The compounds of Examples 99-101 were synthesized by following the General Procedure B.

General Procedure B



Step-1

To a suspension of **6** (5.0 g, 28.22 mmol) and sodium methoxide (3.81 g, 70.5 mmol) in diethyl ether (75 mL) was added a solution of ethyl formate (2.6 mL, 2.4 g, 32.32 mmol) in diethyl ether (25 mL) slowly at room temperature under nitrogen atmosphere. The suspension was stirred for another 16 h at room temperature. The solid formed was filtered and washed with diethyl ether (25 mL). The solid was then dissolved in minimum amount of water and acidified with acetic acid. The solid formed was filtered, washed with water and dried under vacuum to give pure 7 (4.8 g, 83%) as a pale yellow solid.

Step-2

To a solution of **7** (4.5 g, 21.95 mmol) in ethanol (90 mL) was added hydrazine monohydrochloride (2.25 g, 32.92 mmol) and acetic acid (12 mL) at room temperature under nitrogen atmosphere. The reaction mixture was heated to 85 °C and stirred for 3-4 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 (45 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). Combined organic layer was washed with water, brine, dried over sodium sulphate and concentrated under reduced pressure to afford **8** (3.5 g, 75%) as an off-white solid. The product obtained was used without further purification.

Step-3

To a solution of **8** (4.0 g, 18.25 mmol) in acetic acid (40 mL) was added ethyl acetoacetate (2.55 mL, 18.253 mmol) at room temperature followed by heating to 105 °C for 6 h. The progress of the reaction was monitored by TLC. After completion, the reaction mass was concentrated under high vacuum at 50 °C. The resultant solid was diluted with water and extracted with dichloromethane (3 × 10 mL). The combined organic extract was washed with 10% sodium bicarbonate solution, water and brine. The organic extract was dried over sodium sulphate, filtered and concentrated under vacuum at 50 °C. The residue obtained was triturated with dichloromethane (25 mL) to afford pure **9** (5 g, 96%) as an off-white solid.

Step-4

To a suspension of **9** (5.0 g, 17.525 mmol) in dry toluene (75 mL) were added phosphoryl chloride (16.38 mL, 175.2 mmol) and N,N-diethyl aniline (5.62 mL, 35.05 mmol) at room temperature under nitrogen atmosphere. The reaction mass was heated to 105 °C for 16 h. After 16 h, the reaction mass was concentrated under high vacuum at 50-55 °C and co-evaporated with toluene under high vacuum at 50-55 °C. To the residue was added water (40 mL), extracted with dichloromethane (3 × 40 mL), the combined organic layer were washed with water, brine and dried over sodium sulphate. The organic layer was concentrated under vacuum at 45-50 °C to get crude compound. The crude compound was purified by flash column chromatography using ethyl acetate and hexane as eluent to afford **11** (4.5 g, 84.58%) as a yellow solid.

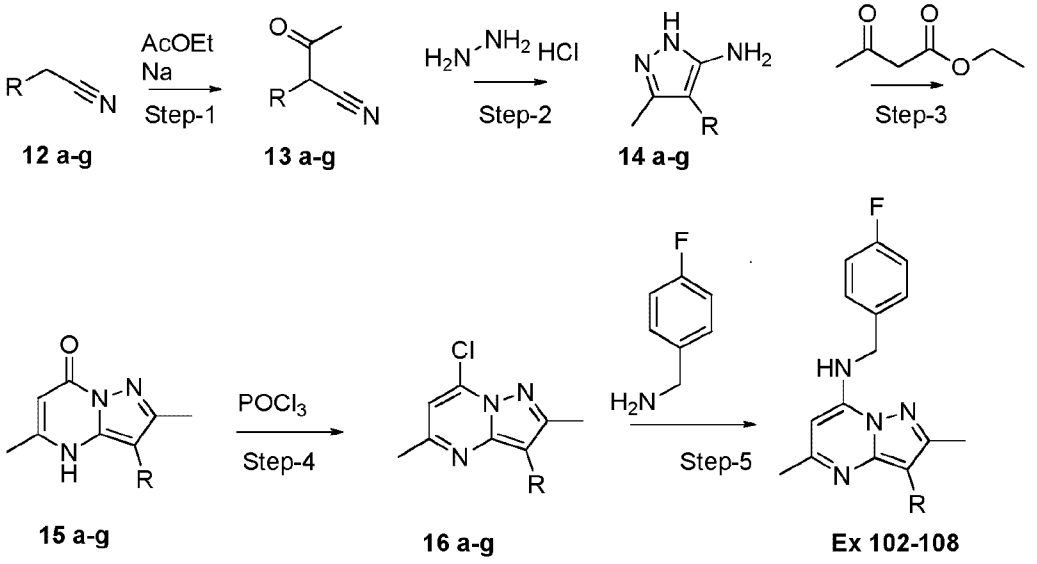
Step-5

To a solution of **11** (1.0 eq.) in toluene or acetonitrile or DMF (10-20 V) were added the respective amines (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, EtOAc in Hexane as eluent) to afford the desired compounds with >95% HPLC purity.

EXAMPLES 102-108

The compounds of Examples 102-108 were synthesized by following the General Procedure E described herein below.

General Procedure E



Step-1

To a solution of nitrile **12a-g** (1.0 eq.) in ethyl acetate (20 Vol.) was added sodium metal (2.0 eq.) 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 followed by quenching with methanol (5 Vol.) and the solvent was evaporated under pressure. The resultant solid was dissolved in water (10 Vol.) and washed with toluene (2 × 10 Vol.). The aqueous solution was acidified with acetic acid (pH: 4 to 5) and extracted with dichloromethane (3 × 10 Vol.). 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 **13a-g**.

Step-2

To a solution of **13a-g** (1.0 eq.) in ethanol (10 Vol.) were added hydrazine monohydrochloride (1.5 eq.) and acetic acid (1.2 eq.) 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 (10 Vol.) and concentrated under reduced pressure. The resultant aqueous layer was washed with toluene (3 × 5 Vol.) and basified with 10% aq. sodium bicarbonate solution (pH: 8-9). The aqueous layer was extracted with dichloromethane (4 × 5 Vol.). Combined organic layer was washed with water, brine, dried over sodium sulphate and concentrated under reduced pressure to afford **14a-g**. The product obtained was used without further purification.

Step-3

To a solution of **14a-g** (1.0 eq.) in acetic acid (10 Vol.) was added ethyl acetoacetate (2.0 eq.) at room temperature and heated to 105 °C for 6 h. The progress of the reaction was monitored by TLC. After completion, the reaction mass was concentrated under high vacuum at 50 °C. The resultant solid was diluted with water and extracted with dichloromethane (3 × 2 Vol.). The combined organic extract was washed with 10% sodium bicarbonate solution, water and brine. The organic extract was dried over sodium sulphate, filtered and concentrated under vacuum at 50 °C. The residue obtained was treated with dichloromethane (25 mL). The solid was filtered and dried under vacuum to afford pure **15a-g**.

Step-4

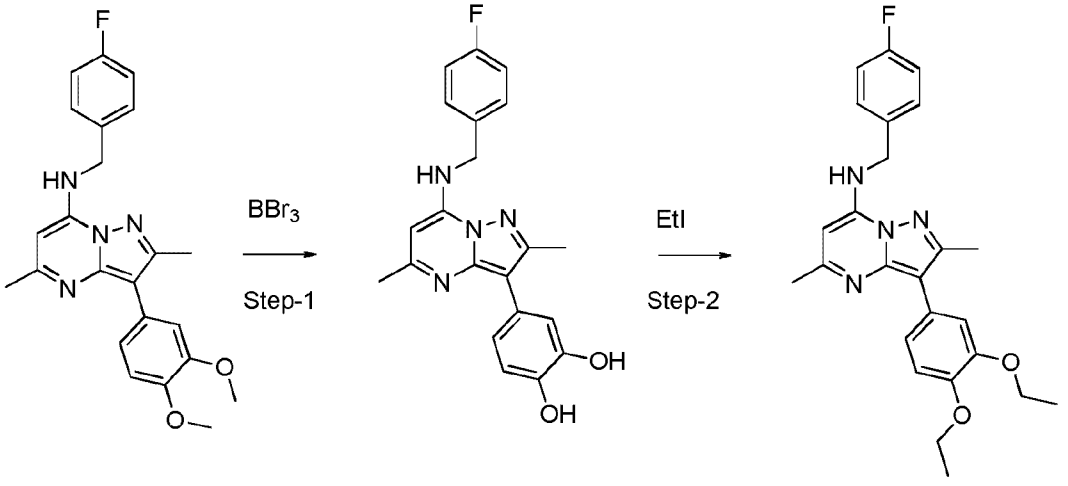
To a suspension of **15a-g** (1.0 eq.) in dry toluene (15 Vol.) were added phosphoryl chloride (1.0 eq.) and N, N-diethyl aniline (2.0 eq.) at room temperature under nitrogen atmosphere. The reaction mass was heated to 105 °C for 16 h. After 16 h, the reaction mass was

concentrated under high vacuum at 50-55 °C and co-evaporated with toluene under high vacuum at 50-55 °C. To the residue was added water (20 Vol.) followed by extraction with dichloromethane (3 × 20 Vol.), and the combined organic layer was washed with water, brine and dried over sodium sulphate. The organic layer was concentrated under vacuum at 45-50 °C to get crude compound. The crude compound was purified by flash column chromatography to afford **16a-g**.

Step-5

To a solution of **16a-g** (1.0 eq.) in toluene (20 V) was added the 4-fluorobenzylamine (1.3 eq.) and DIPEA (5 V) sequentially. The reaction mixture was then heated to 90 °C and stirred well 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) and 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, ethyl acetate in hexane) to afford the desired compounds with >95% HPLC purity.

EXAMPLE 109



Ex 9 **17** **Ex 109**

Step-1

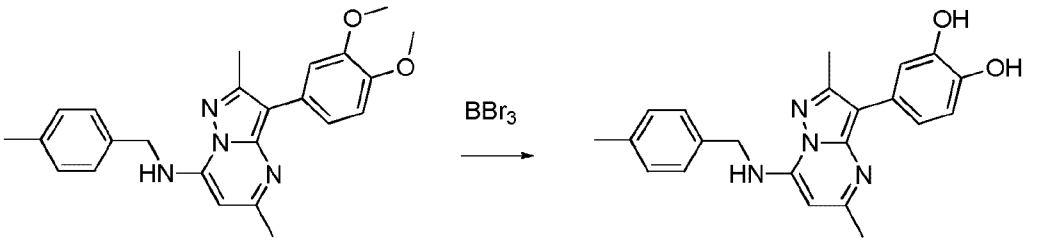
To a solution of **Ex 9** (2.0 g, 4.926 mmol) in dichloromethane (50 mL) was added BBr_3 (1M solution in CH_2Cl_2, 25 mL, 25 mmol) slowly at 0-5 °C. After addition, the reaction mixture was allowed to attain room temperature with stirring. After 4 h, the reaction mixture was quenched with methanol (40 mL). The reaction mixture was concentrated under reduced

pressure. The residue obtained was diluted with water (10 mL) and extracted with CH_2Cl_2 (3 × 20 mL). 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 recrystallization in dichloromethane to afford **17** (1.8 g, 96.77%) as a brown solid.

Step-2

To a solution of **17** (1.8 g, 4.762 mmol) in DMF (36 mL) was added cesium carbonate (3.099 g, 9.51 mmol) at room temperature. To this mixture iodoethane (7.427 g, 3.83 mL, 47.62 mmol) was added at the same temperature and stirred well. After 16 h, the reaction mixture was quenched with ice-cold water (180 mL) and extracted with ethyl acetate (3 × 20 mL). 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, ethyl acetate in hexane as eluent) followed by recrystallization in ethyl acetate to give **Ex 109** (0.9 g, 43.06%) as an off-white solid.

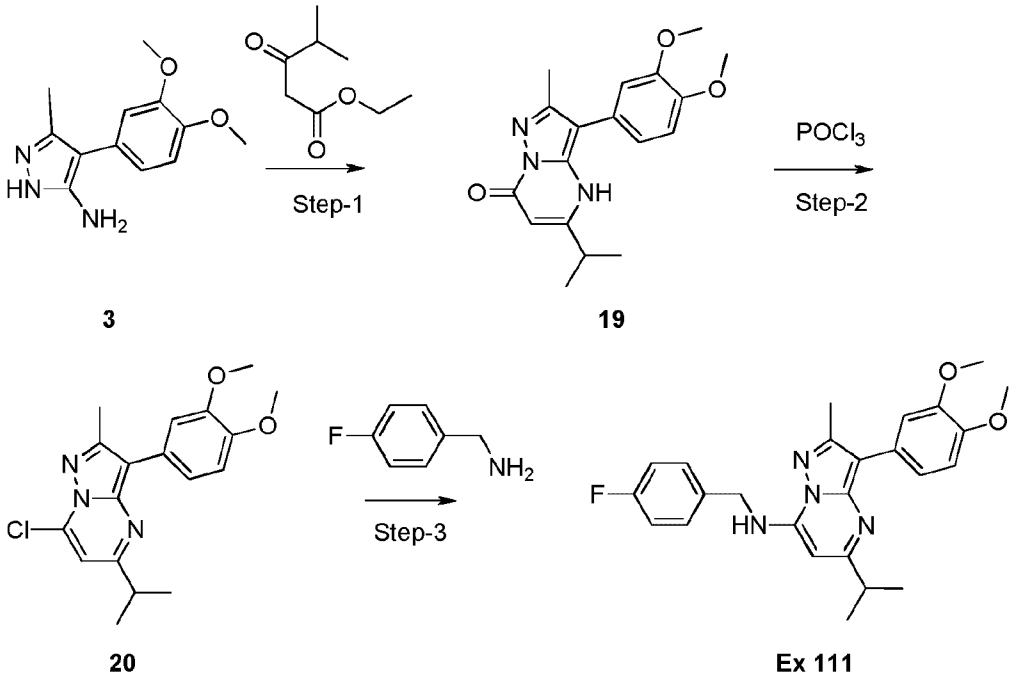
EXAMPLE 110



18 **Ex 110**

To a solution of **18** which was formed as described in General Procedure A (500 mg, 1.242 mmol) in dichloromethane (12.5 mL) was added BBr_3 (1M solution in CH_2Cl_2, 7.86 mL, 7.86 mmol) slowly at 0-5 °C. After addition, the reaction mixture was allowed to attain room temperature with stirring. After 4 h, the reaction mixture was quenched with methanol (10 mL). The reaction mixture was concentrated under reduced pressure. The residue obtained was diluted with water (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). 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, ethyl acetate in hexane) followed by recrystallization in dichloromethane to afford **Ex 110** (110 mg, 23.65%) as an off-white solid.

EXAMPLE 111



Step-1

To a solution of **3** (500 mg, 4.28 mmol) in acetic acid (10 mL) was added methyl isobutyl acetate (0.87 mL, 8.57 mmol) at room temperature and stirred at 105 °C for 16 h. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was concentrated under high vacuum at 50 °C. The resultant solid was diluted with water and extracted with dichloromethane (3 × 10 mL). The combined organic extract was washed with 10% sodium bicarbonate solution, water and brine. The organic extract was dried over sodium sulphate, filtered and concentrated under vacuum to afford **19** (600 mg, 85.71%) as a brown solid.

Step-2

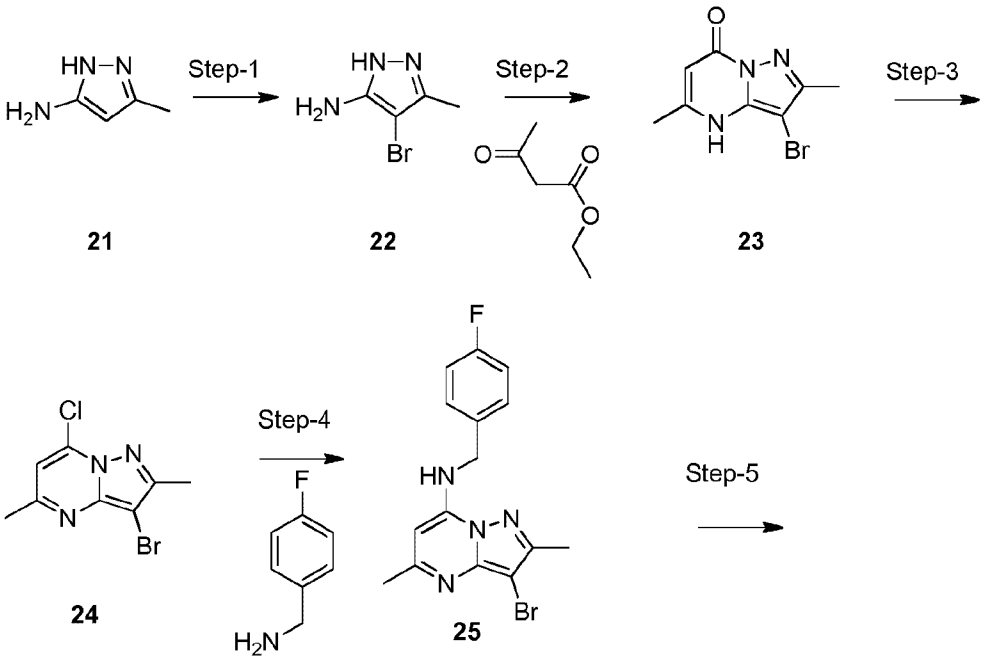
To a suspension of **19** (1.0 g, 3.05 mmol) in dry toluene (15 mL) were added phosphoryl chloride (7.14 mL, 76.36 mmol) and N,N-diethyl aniline (0.98 mL, 6.11 mmol) at room temperature under nitrogen atmosphere. The reaction mass was heated to 105°C for 16 h. After 16 h, the reaction mixture was concentrated under reduced pressure at 50-55 °C and co-evaporated with toluene under reduced pressure. To the resultant solid, was added water (40 mL) and extracted with dichloromethane (3 × 40 mL). The combined organic layer was washed with water, brine, dried over sodium sulphate and concentrated under reduced pressure to get crude compound. The crude compound was purified using flash column

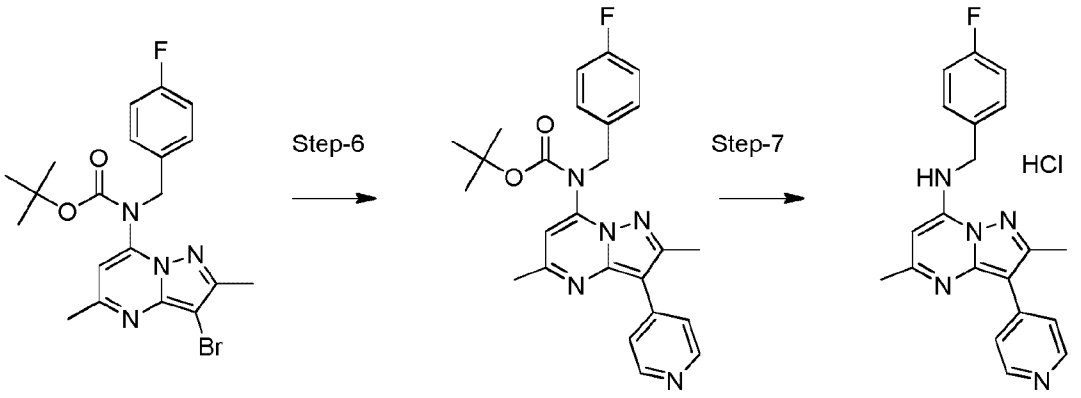
chromatography (silica gel, using ethyl acetate and hexane as eluent) to afford **20** (550 mg, 52.08%) as a yellow solid.

Step-3

To the solution of **20** (500 mg, 1.445 mmol) in toluene (5 mL) were added 4-fluoro benzyl amine (0.215 mL, 1.88 mmol) and DIPEA (4 mL, 22.965 mmol), followed by heating to 90°C for 16 h. The progress of the reaction was monitored by TLC. After completion, the reaction mass was cooled to room temperature and concentrated under reduced pressure. The residue was diluted with water (30 mL) extracted with dichloromethane (3 × 10 mL). The combined organic layer was washed with water, brine, dried over sodium sulphate, filtered and concentrated under high vacuum at 45-50°C. The crude material was purified by flash column chromatography (silica gel, using ethyl acetate in hexane as eluent) to afford **Ex 111** (280 mg, 15.92%) as a yellow solid.

EXAMPLE 112





26 27 Ex. 112

Step-1

To a solution of **21**, (10 g, 102.97 mmol) in acetonitrile (250 mL), was added AIBN (1.65 g, 10.29 mmol) at 0-5 °C. To the reaction mixture was slowly added N-bromosuccinimide (18.33 g, 102.97 mmol) while maintaining temperature between 0-5 °C. After the addition, the reaction mixture was allowed to attain room temperature gradually and stirred for 2 h. The progress of the reaction was monitored with TLC. Starting amine was completely consumed. The reaction mixture was concentrated under reduced pressure. The residue was diluted with water (100 mL) and the insoluble material was filtered. The filtrate was treated with 10% $NaHCO_3$ solution (100 mL) and extracted with dichloromethane (3 × 100 mL). The combined organic extract was washed with water, saturated brine and dried over sodium sulphate. The organic layer was filtered and dried under reduced pressure. The crude material obtained was purified by flash column chromatography (Silica gel, 30% Ethyl acetate in hexane) to afford **22** (14.0 g, 77.25%) as a brown solid.

Step-2

To a solution of **22** (14.0 g, 79.54 mmol) in ethanol (280 mL) were added ethyl acetoacetate (15.15 mL, 15.59 g, 119.79 mmol) and acetic acid (4.55 mL, 79.54 mmol) at room temperature under nitrogen atmosphere. The reaction mixture was then heated to 85 °C and stirred for 16 h. The progress of the reaction was monitored by TLC. After 16 h, the reaction mixture was concentrated completely under reduced pressure. The resultant solid was treated with CH_2Cl_2 (30 mL) and the solid was filtered. The filtered solid was dried under high vacuum at 45-55 °C to afford **23** (10.7 g, 55.57%) as a pale yellow solid.

Step-3

To a suspension of **23** (10.5 g, 43.38 mmol) in toluene (157.5 mL) were added N,N-diethyl aniline (20.63 mL, 130.16 mmol) and phosphorous oxychloride (10.14 mL, 108.47 mmol) at room temperature. The reaction mixture was heated to 105 °C for 16 h. The progress of the reaction was monitored by TLC. After 16 h, the reaction mass was cooled to room temperature and quenched with saturated brine solution, and filtered through Celite™ bed. The layers were separated and the toluene layer was washed with saturated sodium bicarbonate solution and saturated brine solution. The organic layer was dried over sodium sulphate, filtered and concentrated to get crude material. The crude material was purified by flash column chromatography (Silica gel, 5-10% Ethyl acetate in Hexane) to get **24** (10.0 g, 88.49%) as a pale yellow solid.

Step-4

To a solution of **24** (10.0 g, 38.38 mmol) in acetonitrile (100 mL) were added 4-fluoro benzyl amine (5.27 mL, 46.06 mmol) and DIPEA (32.85 mL, 191.9 mmol) at room temperature. The reaction mixture was heated to 80 °C for 16 h. The progress of the reaction was monitored by TLC. After 16 h, the reaction mixture was cooled to room temperature and concentrated under reduced pressure. The resultant solid was diluted with water (100 mL) and extracted with ethyl acetate (3 × 100 mL). The combined organic layer was washed with water, brine, dried over sodium sulphate. The organic layer was filtered and concentrated under reduced pressure to get crude compound. The crude material was purified by flash column chromatography (Silica gel, 5-10% Ethyl acetate in Hexane) to afford **25** (12.0 g, 89.55%) as a colorless solid.

Step-5

To a solution of **25** (2.0 g, 5.727 mmol) in dichloromethane (30 mL) were added DMAP (34.98 mg, 0.286 mmol), Boc-anhydride (1.44 mL, 6.30 mmol) at 10-15 °C under nitrogen atmosphere. The reaction mixture was slowly warmed to room temperature and stirred for 6 h. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was cooled to 0-5°C and quenched with water. The mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layer was washed with brine, dried over sodium sulphate, filtered and concentrated under reduced pressure. The crude compound was purified by recrystallization using CH_2Cl_2 and Hexane solvent combination to afford **26** (2.12 g, 82.38%) as an off-white solid.

Date reçue/ date received 2021-12-22

Step-6

To a solution of **26** (500 mg, 1.113 mmol) in DME : water (5:1, 10 mL) were added 4-pyridine boronic acid (205.23 mg, 1.66 mmol) and cesium carbonate (1.088 mg, 3.339 mmol) at room temperature under argon atmosphere. The reaction mixture was degassed thoroughly with argon. To the reaction mixture was added $Pd(PPh_3)_4$ (258 mg, 0.0445 mmol) under argon atmosphere. The reaction mixture was stirred for 3 h at 100 °C under microwave condition. The progress of the reaction of was monitored by LCMS. The reaction mixture was diluted with water and extracted with ethyl acetate (3 ×10 mL). The combined organic layer was washed with brine and dried over sodium sulphate. The organic layer was concentrated under reduced pressure to get crude material. The crude compound was purified by flash column chromatography to get **27** (0.2 g, 40%) as a brown semi solid.

Step-7

To a solution of **27** (200 mg) in 1,4-dioxane (2 mL) was added HCl solution (15 mL, 4M in dioxane) at 10-15 °C under nitrogen atmosphere. The reaction mixture was stirred for 16 h at room temperature. The solid formed was filtered. The solid was again dissolved in water (4 mL) and the insoluble material was filtered. The filtrate was concentrated under reduced pressure to get **Ex. 112** in the salt form (60 mg, 35%) as a pale yellow solid.

Analytical data for the compounds of Examples 72-112 are shown in **Table 3**.

Table 3

Ex.	Analytical Data
72	^{1}H-NMR (MeOD, 300 MHz): δ 7.65 (dd, 4 H), 7.26 (d, 2 H), 7.13 (d, 1 H), 7.05 (d, 1 H), 5.92 (s, 1 H), 4.79 (s, 2 H), 3.89 (s, 6 H), 2.53 (s, 3 H), 2.37 (s, 3 H), LCMS : 457.2 [M+H], HPLC purity: 98.46%
73	^{1}H-NMR (MeOD, 300 MHz): δ 7.79 (d, 2 H), 7.67 (d, 2 H), 7.30 (d, 1 H), 7.15 (d, 1 H), 7.08 (d, 1H), 6.45 (s, 1 H), 3.90 (s, 6 H), 2.58 (s, 3 H), 2.47 (s, 3 H), LCMS : 443.2 [M+H], HPLC purity: 99.99%
74	^{1}H-NMR (MeOD, 300 MHz): δ 8.53 (d, 2 H), 7.37 (d, 1 H), 7.22 (m, 2 H), 7.09 (m, 3 H), 3.90 (s, 6 H), 2.70 (s, 3 H), 2.58 (s, 3 H), LCMS : 376.5 [M+H], HPLC purity: 95.69%

Ex.	Analytical Data
75	^{1}H-NMR (MeOD, 300 MHz): δ 8.52 (d, 2 H), 7.48 (d, 2 H), 7.26 (d, 1 H), 7.14 (d, 1 H), 7.09 (dd, 1 H) 5.90 (s, 1 H), 4.78 (s, 2 H), 3.89 (s, 6 H), 2.54 (s, 3 H), 2.37 (s, 3 H), LCMS : 390.6 [M+H], HPLC purity: 98.97%
76	^{1}H-NMR (MeOD, 300 MHz): δ 7.51 (d, 2 H), 7.25 (dd, 2 H), 7.12 (d, 1 H), 7.06 (q, 1 H), 5.93 (s, 1 H), 4.70 (s, 2 H), 3.88 (s, 6 H), 2.51 (s, 3 H), 2.37 (s, 3 H), LCMS : 473.7 [M+H], HPLC purity: 100%
77	^{1}H-NMR (MeOD, 300 MHz): δ 7.56 (d, 2 H), 7.38 (d, 2 H), 7.25 (s, 1 H), 7.09 (m, 2 H), 5.95 (s, 1 H), 4.63 (s, 2 H), 3.88 (s, 6 H), 2.52 (s, 3 H), 2.39 (s, 3 H), 2.12 (s, 3 H), LCMS : 446.5 [M+H], HPLC purity: 99.56%
78	^{1}H-NMR (MeOD, 400 MHz): δ 7.23 (q, 3 H), 7.08 (dd, 1 H), 7.02 (d, 1 H), 6.77 (dd, 2 H), 5.97 (s, 1 H), 4.52 (s, 2 H), 3.86 (s, 6 H), 2.91 (s, 3 H), 2.48 (s, 3 H), 2.37 (s, 3 H), LCMS : 432.5 [M+H], HPLC purity: 99.59%
79	^{1}H-NMR (MeOH, 400 MHz): δ 8.19 (s, 1 H), 7.74 (dd, 1 H), 7.23 (s, 1 H), 7.09 (dd, 1 H), 7.02, (d, 1 H), 6.88 (d, 1 H), 6.00 (s, 1 H), 4.60 (s, 2 H), 3.89 (s, 3 H), 3.86 (s, 3 H), 2.48 (s, 3 H), 2.39 (s, 3 H), LCMS : 420.4 [M+H], HPLC purity: 99.86%
80	^{1}H-NMR (MeOH, 400 MHz): δ 7.39 (d, 2 H), 7.23 (m, 3 H), 7.09 (dd, 1 H), 7.02 (d, 1 H), 5.94 (s, 1 H), 4.62 (s, 2 H), 3.86 (s, 6 H), 2.93 (s, 3 H), 2.49 (s, 3 H), 2.36 (s, 3 H), LCMS : 482.5 [M+H], HPLC purity: 99.20%
81	^{1}H-NMR (MeOH, 400 MHz): δ 7.23 (m, 3 H), 7.09 (dd, 1 H), 7.02 (d, 1 H), 6.77 (dd, 2 H), 5.96 (s, 1 H), 4.54 (s, 2 H), 3.86 (s, 6 H), 2.48 (s, 3 H), 2.37 (s, 3 H), LCMS : 405.6 [M+H], HPLC purity: 99.74%
82	^{1}H-NMR (DMSO, 400 MHz): δ 8.57 (t, 1 H), 8.02 (s, 1 H), 7.82 (d, 1 H), 7.76 (d, 1 H), 7.63 (t, 1 H), 7.21 (dd, 1 H), 7.01 (d, 1 H), 6.05 (s, 1 H), 4.70 (d, 2 H), 3.78 (s, 6 H), 3.20 (s, 3 H), 2.55 (s, 3 H), 2.37 (s, 3 H), LCMS : 467.4 [M+H], HPLC purity: 99.78%
83	^{1}H-NMR (MeOH, 400 MHz): δ 8.21 (d, 2 H), 7.47 (d, 2 H), 7.14 (d, 1 H), 7.01 (dd, 1H), 6.94 (d, 1 H), 5.83 (s, 1 H), 4.50 (s, 2 H), 3.78 (s, 6 H), 2.42 (s, 3 H), 2.28 (s, 3 H), LCMS : 406.5 [M+H], HPLC purity: 98.91%
84	^{1}H-NMR (MeOH, 400 MHz): δ 7.97 (dd, 2 H), 7.69 (d, 2 H), 7.26. (d, 1 H), 7.12 (dd, 1H), 7.05 (d, 1 H), 5.93 (s, 1 H), 4.82 (s, 2 H), 3.90 (s, 6 H), 3.13 (s, 3 H), 2.54 (s, 3 H), 2.38 (s, 3 H), LCMS : 467.3 [M+H], HPLC purity: 99.93%

Ex.	Analytical Data
85	^{1}H-NMR (MeOH, 300 MHz): δ 8.83 (d, 1 H), 8.63 (m, 1 H), 8.13 (d, 1 H), 8.04 (t, 1 H), 7.13 (d, 1H), 7.02 (m, 2 H), 6.70 (s, 1H) 4.15 (t, 2 H), 3.92 (d, 6 H), 3.57 (t, 2 H), 2.64 (s, 3 H), 2.43 (s, 3 H), LCMS : 404.3 [M+H], HPLC purity: 99.88%
86	^{1}H-NMR (MeOH, 300 MHz): δ 7.43 (dd, 2 H), 7.35 (d, 2 H), 7.52 (d, 1 H), 7.10 (dd, 1 H), 7.04 (d, 1H), 5.96 (s, 1H) 4.64 (s, 2 H), 3.89 (d, 6 H), 2.51 (s, 3 H), 2.39 (s, 3 H), 1.30 (s, 9 H), LCMS : 445.4 [M+H], HPLC purity: 99.03%
87	^{1}H-NMR (MeOH, 300 MHz): δ 8.60 (d, 1 H), 7.30 (d, 1 H), 7.24 (d, 1 H), 7.10 (dd, 1 H), 7.02 (d, 1H), 5.91 (s, 1H) 4.74 (s, 2 H), 3.87 (d, 6 H), 2.71 (s, 1 H), 2.51 (s, 3 H), 2.37 (s, 3 H), LCMS : 405.4 [M+H], HPLC purity: 98.34%
88	^{1}H-NMR (MeOH, 300 MHz): δ 7.24 (m, 2 H), 7.09 (d, 1 H), 7.04 (d, 1 H), 6.95 (m, 2 H), 5.96 (s, 1H) 3.89 (d, 6 H), 3.73 (t, 2 H), 3.26 (t, 2 H), 2.49 (s, 3 H), 2.41 (s, 3 H), LCMS : 409.3 [M+H], HPLC purity: 98.81%
89	^{1}H-NMR (MeOH, 300 MHz): δ 8.80 (d, 2 H), 8.10 (d, 2 H), 7.11 (d, 1 H), 6.97 (m, 2 H), 6.60 (s, 1H) 4.07 (t, 2 H), 3.87 (d, 6 H), 3.43 (t, 2 H), 2.59 (s, 3 H), 2.41 (s, 3 H), LCMS : 404.4 [M+H], HPLC purity: 99.23%
90	^{1}H-NMR (MeOH, 300 MHz): δ 10.69 (s, 1 H), 9.00 (s, 1 H), 8.45 (dd, 1 H), 8.31 (d, 1 H), 7.77 (s, 1 H), 7.40 (d, 1 H), 7.25 (dd, 1H), 7.06 (d, 1H), 3.81 (d, 6 H), 2.67 (s, 3 H), 2.49 (s, 3 H), LCMS : 377.3 [M+H], HPLC purity: 99.91%
91	^{1}H-NMR (MeOH, 300 MHz): δ 7.27 (dd, 2 H), 7.22 (d, 1 H), 7.17 (dd, 2 H), 7.08 (dd, 1 H), 7.02 (d, 1H), 6.17 (s, 1H) 4.62 (m, 1 H), 3.49 (dd, 2 H), 3.10 (dd, 2 H), 2.46 (s, 3 H), 2.44 (s, 3 H), LCMS : 415.4 [M+H], HPLC purity: 99.94%
92	^{1}H-NMR (MeOH, 300 MHz): δ 8.49 (d, 1 H), 7.80 (dd, 1 H), 7.30 (d, 1 H), 7.25 (d, 1 H), 7.10 (dd, 1H), 7.05 (d, 1H), 5.99 (s, 1H) 4.70 (s, 2 H), 3.89 (d, 6 H), 2.53 (s, 3 H), 2.51 (s, 3 H), 2.39 (s, 3 H), LCMS : 404.3 [M+H], HPLC purity: 99.93%
93	^{1}H-NMR (MeOH, 300 MHz): δ 11.52 (s, 1 H), 7.69 (s, 1 H), 7.40 (d, 1 H), 7.23 (m, 2 H), 7.04 (d, 1H), 3.80 (d, 6 H), 2.54 (s, 3 H), 2.49 (s, 3 H), 2.38 (s, 3 H), LCMS : 396.3 [M+H], HPLC purity: 98.52%
94	^{1}H-NMR (MeOH, 400 MHz): δ 7.96 (dd, 2 H), 7.52 (d, 2 H), 7.20 (d, 1 H), 7.08 (dd, 1 H), 7.00 (d, 1H), 5.86 (s 1 H), 4.72 (s, 2 H), 3.85 (d, 6 H), 2.56 (s, 3 H), 2.49 (s, 3 H), 2.32 (s, 3 H), LCMS : 431.3 [M+H], HPLC purity: 99.66%

Ex.	Analytical Data
95	^{1}H-NMR (MeOH, 300 MHz): δ 8.60 (d, 1 H), 7.37 (s, 1 H), 7.32 (d, 1 H), 7.16 (d, 1 H), 7.07 (d, 1H), 6.61 (s 1 H), 3.91 (d, 6 H), 2.58 (s, 3 H), 2.55 (s, 3 H), LCMS : 366.4 [M+H], HPLC purity: 94.2%
96	^{1}H-NMR (MeOH, 300 MHz): δ 8.13 (d, 1 H), 7.92 (d, 1 H), 7.85 (d, 1 H), 7.56 (m, 3 H), 7.43 (d, 1 H), 7.24 (d, 1 H), 7.11 (dd, 1 H), 7.02 (d, 1 H), 6.01 (s, 1 H), 5.12 (s, 2 H), 3.86 (d, 6 H), 2.47 (s, 3 H), 2.36 (s, 3 H), LCMS : 439.5 [M+H], HPLC purity: 99.94%
97	^{1}H-NMR (DMSO, 400 MHz): δ 8.50 (t, 1 H), 7.78 (d, 2 H), 7.55 (d, 2 H), 7.38 (d, 1 H), 7.30 (s, 2 H), 7.22 (dd, 1H), 7.00 (d, 1H), 5.94 (s, 1 H), 5.12 (s, 2 H), 3.78 (d, 6 H), 2.54 (s, 3 H), 2.32 (s, 3 H), LCMS : 468.3 [M+H], HPLC purity: 98.74%
98	^{1}H-NMR (MeOD, 400 MHz): δ 8.16 (dd, 2 H), 7.19 (dd, 2 H), 7.24 (d, 1 H), 7.10 (d, 1 H), 7.02 (d, 1H), 5.72 (s, 1H), 4.99 (q, 1H), 3.87 (s, 6 H), 2.66 (s, 1 H), 2.50 (s, 3 H), 2.32 (s, 3 H), LCMS : 404.5 [M+H], HPLC purity: 97.3%
99	^{1}H-NMR (DMSO, 400 MHz): δ 8.55 (t, 1 H), 7.77 (d, 1 H), 7.70 (d, 1 H), 7.46 (dd, 2 H), 7.16 (dd, 2 H), 6.97 (d, 1H), 6.08 (s, 1H), 4.58 (d, 1 H), 3.82 (s, 3 H), 3.75 (s, 3 H), 2.39 (s, 3 H), LCMS : 393.4 [M+H], HPLC purity: 99.61%
100	^{1}H-NMR (DMSO, 400 MHz): δ 8.62 (t, 1 H), 8.58 (s, 1 H), 8.51 (dd, 2 H), 7.78 (d, 1 H), 7.72 (dd, 1 H), 7.36 (d, 2 H), 6.97 (d, 1H), 6.02 (s, 1H), 4.65 (d, 2 H), 3.82 (s, 3 H), 3.75 (s, 3 H), 2.38 (s, 3 H), LCMS : 376.4 [M+H], HPLC purity: 96.46%
101	^{1}H-NMR (DMSO, 400 MHz): δ 8.69 (t, 1 H), 8.58 (s, 1 H), 8.03 (s, 1 H), 7.84 (d, 1 H), 7.78 (t, 2 H), 7.71 (dd, 1 H), 7.64 (t, 1H), 6.98 (d, 1 H), 6.14 (s, 1H), 4.73 (d, 2 H), 3.83 (s, 3 H), 3.76 (s, 3 H), 3.21 (s, 3 H), 2.41 (s, 3 H), LCMS : 453.3 [M+H], HPLC purity: 98.50%
102	^{1}H-NMR (MeOD, 300 MHz): δ 7.43 (q, 2 H), 7.09 (m, 3 H), 7.00 (dd, 1 H), 6.89 (d, 1 H), 5.95 (t, 3 H), 4.64 (s, 2 H), 2.47 (s, 3 H), 2.36 (s, 3 H), LCMS : 391.6 [M+H], HPLC purity: 99.74%
103	^{1}H-NMR (MeOD, 300 MHz): δ 7.87 (d, 1 H), 7.59 (m, 2 H), 7.43 (dd, 2 H), 7.08 (t, 2 H), 5.99 (s, 1 H), 4.64 (s, 2 H), 2.54 (s, 3 H), 2.40 (s, 3 H), LCMS : 415.4 [M+H], HPLC purity: 99.90%
104	^{1}H-NMR (MeOD, 300 MHz): δ 7.89 (d, 2 H), 7.72 (d, 2 H), 7.46 (m, 2 H), 7.11 (m, 2 H), 6.01 (s, 1 H), 4.67 (s, 2 H), 2.59 (s, 3 H), 2.41 (s, 3 H), LCMS : 415.1 [M+H], HPLC purity: 99.92%

Ex.	Analytical Data
105	^{1}H-NMR (MeOD, 300 MHz): δ 7.45 (t, 2 H), 7.11 (d, 2 H), 6.91 (s, 2 H), 5.97 (s, 1 H), 4.67 (s, 2 H), 3.90 (s, 6 H), 3.82 (s, 3 H), 2.56 (s, 3 H), 2.39 (s, 3 H), LCMS : 437.2 [M+H], HPLC purity: 99.63%
106	^{1}H-NMR (MeOD, 300 MHz): δ 7.60 (m, 1 H), 7.43 (m, 3 H), 7.31 (m, 1 H), 7.09 (m, 2 H), 5.98 (s, 1 H), 4.65 (s, 2 H), 2.54 (s, 3 H), 2.40 (s, 3 H), LCMS : 383.5 [M+H], HPLC purity: 99.88%
107	^{1}H-NMR (MeOD, 300 MHz): δ 8.09 (d, 2 H), 7.84 (d, 2 H), 7.45 (dd, 2 H), 7.10 (t, 2 H), 6.01 (s, 1 H), 4.67 (s, 2 H), 3.93 (s, 3 H), 2,59 (s, 3H), 2.42 (s, 3 H), LCMS : 404.45 [M+H], HPLC purity: 99.62%
108	^{1}H-NMR (MeOH, 300 MHz): δ 7.42(d, 1 H), 7.34 (m, 3 H), 7.18 (m, 3 H), 5.95 (s, 1 H), 4.62 (s, 2 H), 3.92 (s, 3 H), 2.51 (s, 3 H), 2.39 (s, 3 H), 2.34 (s, 3 H), LCMS : 391.5 [M+H], HPLC purity: 98.09%
109	^{1}H-NMR (MeOD, 300 MHz): δ 8.43 (t, 1 H), 7.44 (m, 2 H), 7.38 (s, 1 H), 7.16 (m, 3 H), 6.99 (d, 1 H), 6.00 (s, 1 H), 4.57 (d, 2 H), 4.04 (m, 4 H), 2.51 (s, 3 H), 2.32 (s, 3 H), 1.35 (q, 6 H), LCMS : 435.3 [M+H], HPLC purity: 99.75%
110	^{1}H-NMR (DMSO, 400 MHz): δ 8.82 (bs, 2 H), 8.33 (bs, 1 H), 7.28 (d, 2 H), 7.14 (t, 3 H), 6.92 (dd, 1 H), 6.77 (d, 1 H), 5.91 (s, 1 H), 4.53 (s, 2 H), 2.48 (s, 3 H), 2.30 (s, 3 H), 2.26 (s, 3 H), LCMS : 375.3 [M+H], HPLC purity: 99.70%
111	^{1}H-NMR (MeOH, 400 MHz): δ 7.40 (s, 1 H), 7.35 (t, 2 H), 7.07. (dd, 1 H), 6.99 (t, 2H), 6.92 (d, 1 H), 5.81 (s, 1 H), 4.55 (s, 2 H), 3.78 (d, 6 H), 2.81 (m, 1 H), 2.45 (s, 3 H), 1.13 (d, 6 H), LCMS : 435.5 [M+H], HPLC purity: 95.7%
112	^{1}H-NMR (MeOD, 400 MHz): δ 8.88 (d, 2 H), 7.57 (d, 2 H), 7.49 (m, 2 H), 7.13 (t, 2 H), 6.65 (s, 1 H), 4.86 (s, 2 H), 2.71 (s, 3 H), 2.67 (s, 3 H), LCMS : 412.4 [M+H], HPLC purity: 99.49%

BIOLOGICAL ASSAYS

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 4 shows the inhibition capacity of compounds of the invention on different picornaviruses at different concentrations. LV012: Ljungan virus strain 012; LV145: Ljungan virus strain 145; EMCV: encephalomyocarditis virus; HPeV-1: Human parechovirus strain 1; HPeV-2: Human parechovirus strain 2; PTV: Porcine Tescho virus; EV6: Enterovirus strain 6; EV30: Enterovirus strain 30; EV71: Enterovirus strain 71; Cox-B1: coxsackie B virus strain 1; Cox-B2: coxsackie B virus strain 2; Cox-B3: coxsackie B virus strain 3; Cox-B4: coxsackie B virus strain 4; Cox-B5: coxsackie B virus strain 5; Polio1: polio virus strain 1.

Table 4

Ex.	Virus	Conc. µM	% inh.	Ex.	Virus	Conc. µM	% inh.
1	EV6	0.25	75	**57**	HPeV-1	10.0	22
2	EV30	0.25	85	**58**	Polio-1	0.1	74
3	EMCV	2.5	92	**59**	Cox-B2	10.0	88
4	EV71	2.5	46	**60**	EV-71	1.0	69
5	Cox-B4	0.25	71	**61**	LV0145	10.0	85
6	LV145	5.0	56	**62**	Polio-1	1.0	97
7	LV145	2.5	54	**63**	Polio-1	1.0	87
8	Cox-B5	0.25	100	**64**	Polio-1	1.0	20
9	EV71	0.25	93	**65**	Cox-B2	1.0	91
10	LV145	2.5	69	**66**	Polio-1	0.01	100
11	PTV	2.5	57	**67**	Polio-1	1.0	63

Ex.	Virus	Conc. µM	% inh.
12	LV012	2.5	60
13	EV71	1	66
14	Polio-1	10.0	73
15	Polio-1	10.0	75
16	LV145	10.0	83
17	LV145	10.0	75
18	Polio-1	10.0	51
19	LV145	10.0	34
20	EV71	1.0	40
21	Polio-1	10.0	78
22	Cox-B2	10.0	44
23	Polio-1	10.0	94
24	Polio-1	10.0	86
25	HPeV-1	10.0	24
26	Cox-B2	10.0	30
27	Polio-1	10.0	35
28	Polio-1	10.0	72
29	Cox-B2	10.0	62
30	LV145	10.0	100
31	LV145	10.0	14
32	Polio-1	10.0	25
33	EV30	1.0	48
34	EV71	1.0	100
35	EV30	0.1	88
36	Cox-B5	1.0	97
37	Cox-B2	10.0	78
38	LV0145	10.0	84
39	Polio-1	1.0	71
40	EV71	0.01	100
41	EMCV	10.0	93
42	Polio-1	1.0	96
43	HPeV-1	10.0	46

Ex.	Virus	Conc. µM	% inh.
68	LV145	10.0	86
69	Cox-B2	10.0	65
70	Polio-1	10.0	89
71	Polio-1	10.0	72
72	Cox-B4	0.1	85
73	Cox-B4	0.1	44
74	LV012	10	55
75	Cox-B3	0.01	85
76	Cox-B3	1	100
77	Cox-B3	0.1	60
78	Cox-B1	0.1	94
79	EV68	1	51
80	EV6	1	93
81	Cox-B1	0.01	76
82	Cox-B3	0.01	82
83	EV71	0.01	82
84	Cox-B3	0.1	84
85	Cox-B1	1	98
86	LV012	10	48
87	Polio-1	0.1	100
88	EV30	1	88
89	Cox-2	1	100
90	LV012	10	71
91	Cox-B5	1	75
92	Cox-B3	0.01	100
93	LV012	100	42
94	Cox-B1	0.01	100
95	HPeV-1	10	55
96	Cox-B1	0.1	100
97	EV71	0.1	94
98	Not tested	-	-
99	Cox-B3	0.1	100

Ex.	Virus	Conc. µM	% inh.
44	Polio-1	1.0	70
45	EV71	1.0	100
46	LV0145	10.0	92
47	HPeV-1	10.0	56
48	Polio-1	1.0	79
49	Cox-B2	1.0	80
50	Polio-1	1.0	81
51	LV0145	10.0	94
52	LV0145	10.0	63
53	Polio-1	10.0	84
54	Polio-1	1.0	89
55	LV145	1.0	41
56	LV145	1.0	61

Ex.	Virus	Conc. µM	% inh.
100	EV30	0.1	78
101	EV71	0.1	99
102	Cox-B3	1	100
103	EMCV	10	74
104	Theiler	10	59
105	EV30	10	67
106	LV145	10	100
107	Polio	1	21
108	Cox-B1	1	100
109	Polio-1	1	88
110	Cox-B5	1	72
111	Cox-B1	0.1	68

Table 5 and **6** show the antiviral effect of certain compounds of the invention at different concentrations against a panel of different picornaviruses. LV012: Ljungan virus strain 012; LV145: Ljungan virus strain 145; EMCV: encephalomyocarditis virus; HPeV-1: Human parechovirus strain 1; HPeV-2: Human parechovirus strain 2; PTV: Porcine Tescho virus; EV6: Enterovirus strain 6; EV30: Enterovirus strain 30; EV71: Enterovirus strain 71; B1: coxsackie B virus strain 1; B2: coxsackie B virus strain 2; B3: coxsackie B virus strain 3; B4: coxsackie B virus strain 4; B5: coxsackie B virus strain 5; Polio1: polio virus strain 1.

Table 5

Ex.	Conc. mM	LV012	LV145	EMCV	HPeV-1	PTV	EV6	EV30
1	5	34	37	14	14	19	90	100
2	5	49	17	0	0	33	83	91
4	10	28	61	81	7	87	0	0
5	5	18	60	0	22	11	80	58
6	10	28	63	0	60	62	58	44
7	2.5	14	54	0	6	29	78	89
8	5	38	28	0	14	22	88	53

Ex.	Conc. mM	LV012	LV145	EMCV	HPeV-1	PTV	EV6	EV30
9	10	18	59	14	19	23	66	35
10	10	0	41	25	3	43	93	88
11	10	18	77	0	8	51	70	80
12	2.5	60	nd	0	8	0	63	84
33	10	nd	69	60	13	nd	nd	85
72	1	0	7	0	4	nd	77	100
75	0.1	0	0	0	0	nd	90	100
79	0.1	0	0	0	0	nd	0	10
80	1	0	0	0	0	nd	80	90
81	0.1	0	0	0	0	nd	62	97
82	0.1	0	0	0	nd	nd	89	94
92	0.1	0	0	0	nd	nd	nd	100
94	0.1	12	0	0	nd	nd	nd	96
100	0.1	0	0	0	nd	nd	88	78
101	0.1	0	0	0	nd	nd	44	89
111	1	0	0	0	nd	nd	89	80

Table 6

Ex.	Conc. mM	EV68	EV71	B1	B2	B3	B4	B5	Polio 1
1	5	nd	44	93	60	95	86	90	31
2	5	nd	73	91	93	97	86	91	90
4	10	nd	69	36	0	0	53	0	17
5	5	nd	77	79	76	nd	97	94	68
6	10	nd	37	35	82	nd	69	54	19
7	2.5	nd	82	77	92	nd	82	68	80
8	5	nd		82	100	nd	89	100	91
9	10	nd	16	53	76	nd	48	73	91
10	10	nd	58	79	97	nd	94	92	94
11	10	nd	47	93	85	nd	100	70	52
12	2.5	nd	80	93	nd	nd	77	82	73

Ex.	Conc. mM	EV68	EV71	B1	B2	B3	B4	B5	Polio 1
33	10	nd	0	nd	81	nd	nd	92	58
72	1	nd	84	100	94	99	91	99	100
75	0.1	31	85	100	100	89	100	98	100
79	0.1	46	88	88	84	87	78	98	79
80	1	30	78	78	96	78	78	97	85
81	0.1	29	86	85	88	87	77	81	89
82	0.1	24	85	95	98	91	100	89	100
92	0.1	nd	100	100	96	100	nd	95	98
94	0.1	nd	100	100	100	100	nd	56	100
100	0.1	nd	81	nd	99	199	nd	90	83
101	0.1	nd	99	nd	99	90	nd	29	100
111	1	40	96	97	96	100	98	99	100

Evaluation of anti-viral efficacy against Coxsackie virus in a neutropenic Mouse model

Test system

Male BALB/c mice, weighing 22-26 grams were used with 4 animals/group.

Neutropenic induction: Cyclophosphamide

Challenge organism: Coxsackie (human origin) virus CVB3

Route of infection: Intraperitoneal

Route of administration: per oral

End point: Cumulative survival

All experimental procedures involving animals were performed according to protocols approved by the Institutional Animal Ethics Committee of Anthem Biosciences. The mice, male BALB/c mice were housed 4 animals per cage and allowed access to feed and water ad libitum under controlled conditions. Mice were acclimatized for 7 days prior to the study. The animals were observed daily for general health during this period.

Neutropenic induction

4 mice/group were treated with intraperitoneal injection of cyclophosphamide (150 mg/kg), 2 days before and, on day "0" 4 hours before infection in order to become neutropenic.

Infection and treatment

Animals were infected by intraperitoneal injection of 0.2 mL of saline containing 10^3 PFU of Coxsackie B3 virus, Nancy strain on day 0. The animals were then treated with the compound of Ex. 9, 200 mg/kg once daily per orally starting on day 1 (group 1) or on day 3 (group 2). The control group was treated with vehicle only (0.4% Tween 80, 2% glycerol and 15% β-hydroxypropyl cyclodextrin)

Clinical observation

The animals were observed daily during the study period for signs of mortality, morbidity (paralysis) and signs of acute toxicity. Abnormal clinical signs were recorded if observed.

Results

The results of the above described assay indicate that the compound of Ex. 9 has an antiviral effect in vivo and can extend the life of the animals, cf. **Figure 1**.

Toxicity Assay

Mouse

Treatment with Ex 9 at 200 and 400 mg/kg body weight/day for 7 days in BALB/C mice did not reveal any adverse clinical signs or mortality in neither sex. The treatment resulted in no adverse effects on body weight, feed consumption, hematology, clinical chemistry and histopathology of the major organs evaluated.

In light of above findings from the present study, the No Observed Adverse Effect Level (NOAEL) of Ex 9 could be determined as 400 mg/kg body weight/day when administered orally to BALB/c mice for 7 consecutive days under the tested dose levels and experimental conditions employed.

Rat

MTD study

Single dose treatment with Ex 9 in doses up to 2000 mg/kg resulted in no adverse effects on clinical signs, mortality, body weight, body weight gain, feed consumption, absolute and relative organ weights. On macroscopic examination, no treatment related gross pathological findings were observed.

In the light of the above findings, the maximum tolerable dose of Ex 9 in female Sprague Dawley rats is found to be >2000 mg/kg body weight under the experimental conditions employed.

7 days toxicity study

Treatment with test item Ex 9 at 250 and 750 mg/kg body weight/day for 7 days in Sprague Dawley rats did reveal adverse clinical signs in both sexes at 750 mg/kg and mortality in one female at 750 mg/kg. The treatment resulted in adverse effects on body weight, feed consumption, hematology, clinical chemistry and histopathology of the major organs evaluated at the 759 mg/kg dose level.

In light of above findings from the present study, the No Observed Adverse Effect Level (NOAEL) of Ex 9 could be determined as 250 mg/kg body weight/day when administered orally to Sprague Dawley rats for 7 consecutive days under the tested dose levels and experimental conditions employed.

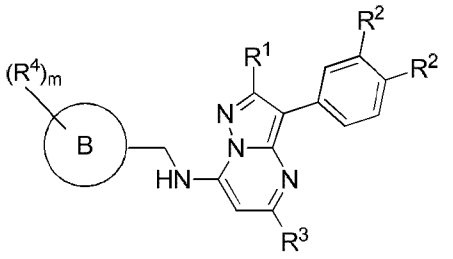
28 days toxicity study

Treatment with the test item Ex 9 at 100 and 200 mg/kg body weight for 28 days in both sexes had no adverse effects on clinical signs, body weight, feed consumption, hematology, clinical chemistry, urinalysis, neurological examination, gross necropsy and histopathological evaluation of the specified tissues. All the animals survived until the scheduled terminal necropsy on Day 29. Serum biochemistry showed an increase in cholesterol, which was correlated with findings of macrovesicular fatty changes in liver at 200 mg/kg body weight in both the sexes.

In light of above findings from the present study, the No Observed Adverse Effect Level (NOAEL) of Ex 9 could be determined as 200 mg/kg body weight when administered orally to Sprague Dawley rats for 28 consecutive days under the tested dose levels and experimental conditions employed.

CLAIMS:

1. A compound of formula (Ie)



(Ie)

or a pharmaceutically acceptable salt thereof, wherein

R^1 is methyl;

each R^2 is methoxy;

R^3 is methyl;

m is an integer of from 0 to 2;

each R^4 is independently selected from C1-C6 alkyl, optionally substituted by one or more F, $R^{12}O$, halogen, $R^{13}R^{14}NC(O)$-, $R^{16}C(O)N(R^{15})$-, $R^{17}OC(O)$-, $R^{18}C(O)O$-, $R^{19}S(O)_2$-, $R^{20}S(O)_2N(H)$-, $NH_2S(O)_2$-, $R^{21}C(O)$-, $N(R^{22})(R^{23})$-, and ^-O-;

R^{12}, R^{13}, R^{14}, R^{15}, R^{22}, and R^{23} are independently selected from H and C1-C6 alkyl;

R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, and R^{21} are independently selected from C1-6 alkyl; and

in any one of R^{12} to R^{23}, any alkyl is optionally substituted by one or more F; or

two R^4 attached to adjacent atoms of ring B form, together with the atoms to which they are attached, a 5- or 6-membered heterocyclic or carbocyclic ring, or a benzene ring; and

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

Date reçue/ date received 2021-12-22

for use in therapy.

2. The compound or the pharmaceutically acceptable salt thereof for use according to claim 1, wherein ring B is phenyl.

3. The compound or the pharmaceutically acceptable salt thereof for use according to claim 1, wherein ring B is 5- or 6-membered heteroaryl.

4. A compound or a pharmaceutically acceptable salt thereof, for use according to claim 1, wherein the compound is selected from

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

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

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

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

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

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

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

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

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

3-(3,4-dimethoxyphenyl)-N-[(4-dimethylaminophenyl)methyl]-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-amine,

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

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

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

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

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

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

N-[(4-tert-butylphenyl)methyl]-3-(3,4-dimethoxyphenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-amine,

3-(3,4-dimethoxyphenyl)-2,5-dimethyl-N-[(2-methylpyrimidin-4-yl)methyl]pyrazolo[1,5-a]pyrimidin-7-amine,

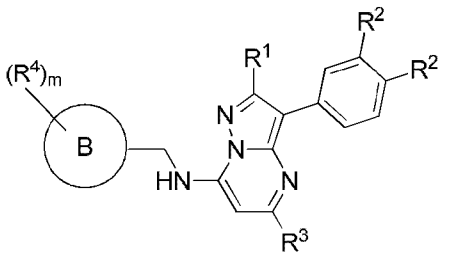
3-(3,4-dimethoxyphenyl)-2,5-dimethyl-N-[(6-methyl-3-pyridyl)methyl]pyrazolo[1,5-a]pyrimidin-7-amine,

1-[4-[[[3-(3,4-dimethoxyphenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]amino]methyl]phenyl]ethanone,

3-(3,4-dimethoxyphenyl)-2,5-dimethyl-N-(1-naphthylmethyl)pyrazolo[1,5-a]pyrimidin-7-amine, and

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

5. A compound of formula (Ie)



(Ie)

or a pharmaceutically acceptable salt thereof, wherein

R^1 is methyl,

each R^2 is methoxy;

R^3 is methyl;

m is an integer of from 0 to 2;

each R^4 is independently selected from C1-C6 alkyl, optionally substituted by one or more F, $R^{12}O$, halogen, $R^{13}R^{14}NC(O)$-, $R^{16}C(O)N(R^{15})$-, $R^{17}OC(O)$-, $R^{18}C(O)O$-, $R^{19}S(O)_2$-, $R^{20}S(O)_2N(H)$-, $NH_2S(O)_2$-, $R^{21}C(O)$-, $N(R^{22})(R^{23})$-, and ^-O-;

R^{12}, R^{13}, R^{14}, R^{15}, R^{22}, and R^{23} are independently selected from H and C1-C6 alkyl,

R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, and R^{21} are independently selected from C1-6 alkyl; and

in any one of R^{12} to R^{23}, any alkyl is optionally substituted by one or more F; or

two R^4 attached to adjacent atoms of ring B form, together with the atoms to which they are attached, a 5- or 6-membered heterocyclic or carbocyclic ring, or a benzene ring; and

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

provided that the compound is not:

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

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

3-(3,4-dimethoxyphenyl)-2,5-dimethyl-N-(p-tolylmethyl)pyrazolo[1,5-a]pyrimidin-7-amine,

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

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

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

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

6. The compound of claim 5, or a pharmaceutically acceptable salt thereof, wherein ring B is 6-membered heteroaryl, said heteroaryl being substituted by a moiety R^4 in para position or having a nitrogen atom in para position; or ring B is phenyl, said phenyl being substituted by a moiety R^4 in para position.

7. The compound of claim 5 or 6, or a pharmaceutically acceptable salt thereof, wherein the ring B is phenyl.

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

9. The compound of claim 8, or a pharmaceutically acceptable salt thereof, wherein ring B is 6-membered heteroaryl.

10. The compound of claim 9, or a pharmaceutically acceptable salt thereof, wherein ring B is 6-membered heteroaryl substituted by a moiety R^4 in para position or ring B is 6-membered heteroaryl having a nitrogen atom in para position.

11. The compound of claim 10, or a pharmaceutically acceptable salt thereof, wherein ring B is 4-pyridyl.

12. The compound of any one of claims 5 to 11, or a pharmaceutically acceptable salt thereof, wherein each R^4 is selected from C1-C6 alkyl, $R^{12}O$, and halogen.

13. A compound according to claim 5, selected from

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

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

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

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

3-(3,4-dimethoxyphenyl)-N-[(4-dimethylaminophenyl)methyl]-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-amine,

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

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

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

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

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

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

N-[(4-tert-butylphenyl)methyl]-3-(3,4-dimethoxyphenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-amine,

3-(3,4-dimethoxyphenyl)-2,5-dimethyl-N-[(2-methylpyrimidin-4-yl)methyl]pyrazolo[1,5-a]pyrimidin-7-amine,

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

1-[4-[[[3-(3,4-dimethoxyphenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]amino]methyl]phenyl]ethanone,

3-(3,4-dimethoxyphenyl)-2,5-dimethyl-N-(1-naphthylmethyl)pyrazolo[1,5-a]pyrimidin-7-amine, and

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

or a pharmaceutically acceptable salt thereof.

14. A compound or pharmaceutically acceptable salt thereof according to any one of the claims 5 to 13, for use in therapy.

15. A pharmaceutical composition comprising a compound or pharmaceutically acceptable salt thereof as defined in any one of the claims 5 to 13, and a pharmaceutically acceptable excipient.

16. A compound or a pharmaceutically acceptable salt thereof according to any one of the claims 5 to 13, for use in the treatment of a viral infection.

17. The compound or pharmaceutically acceptable salt thereof for use according to claim 16, wherein the viral infection is an RNA viral infection.

18. The use of a compound or a pharmaceutically acceptable salt thereof as defined in any one of the claims 5 to 13, in the treatment of a viral infection.

19. The use according to claim 18, wherein the viral infection is an RNA viral infection.

20. The use of a compound or a pharmaceutically acceptable salt thereof as defined in any one of the claims 5 to 13, in the manufacture of a medicament for the treatment of a viral infection.

21. The use according to claim 20, wherein the viral infection is an RNA viral infection.

Date reçue/ date received 2021-12-22

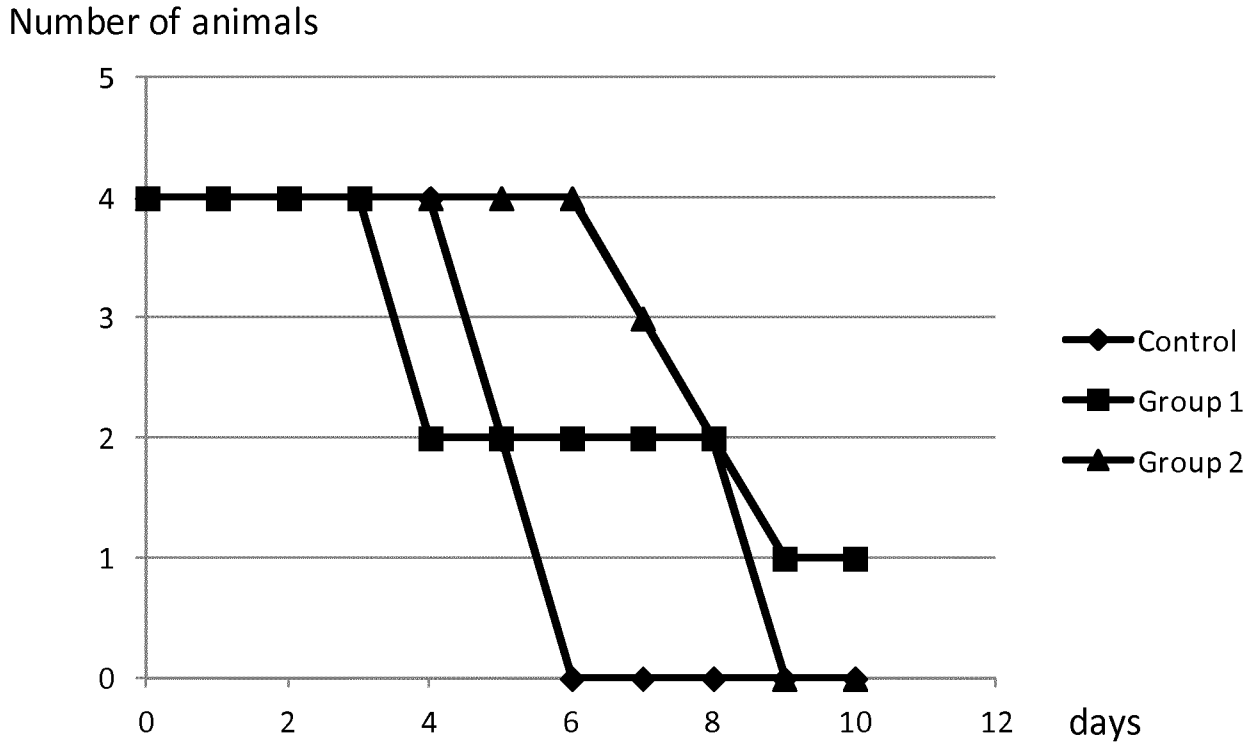
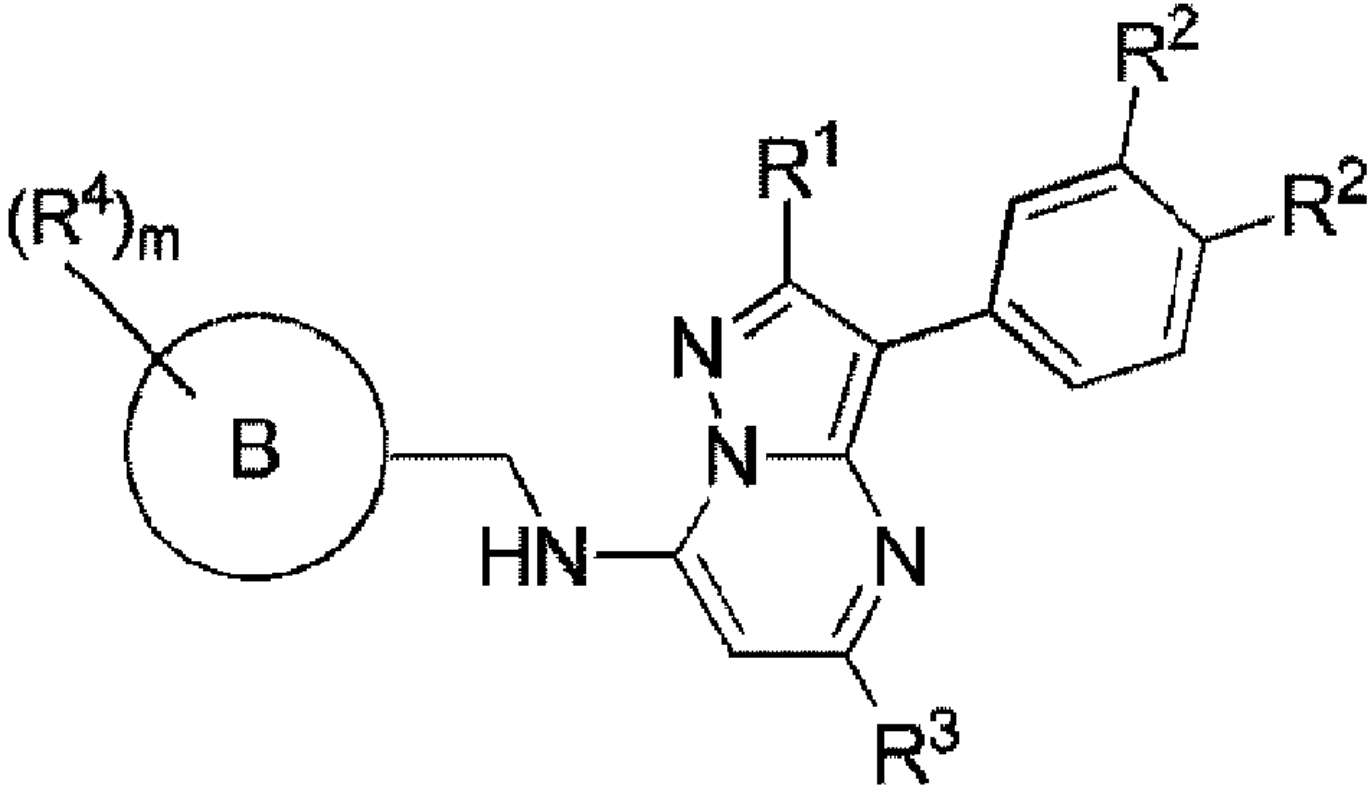

Number of animals
5
4
3
2
1
0
0
2
4
6
8
10
12
days
Control
Group 1
Group 2

FIG. 1



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