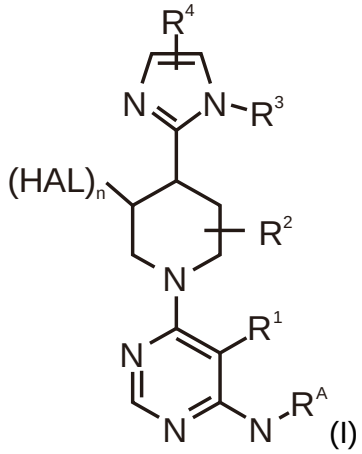
Claims

We claim:

1. A compound of Formula (I)



(I)

wherein:

R^1 is Hal, LA, OH, O(LA), CN, $CONH_2$, CONH(LA), $CON(LA)_2$, NHCO(LA), NHCONH(LA), $NHCONH_2$, $NHSO_2$(LA), CHO, CO(LA), or a mono- or bicyclic, aliphatic or aromatic homo- or heterocycle having 0, 1, 2, 3 or 4 N and/or O atoms and 4, 5 or 6, 7, 8, 9, or 10 skeleton atoms which may be unsubstituted or, independently of one another, mono-, di- or trisubstituted by Hal, LA, OH, O(LA), CN, $CONH_2$, CONH(LA), $CON(LA)_2$, NHCO(LA), NHCONH(LA), $NHCONH_2$, CHO and/or CO(LA) or an unbranched or branched linear or cyclic alkyl having 1, 2, 3, 4, 5, 6, 7 or 8 C atoms, in which one or two CH_2 groups may be replaced by an O atom and/or by an -NH-, NH(LA), -CO-, -NHCO- or –CH=CH– group, and/or in which a CH group may be replaced by -N-;

R^A is H;

R^2 is H, OH or A;

A is unbranched or branched alkyl group having 1, 2, 3, 4, 5 of 6 C atoms in which 1-4 H atoms can be replaced, independently of each other, by Hal;

R^3 H, or an unbranched or branched linear or mono- or bicyclic alkyl group having 1, 2, 3, 4, 5, 6, 7, 8 or 9 C atoms, in which one or two CH_2 groups may be replaced by an -O- or –NH- group, and/or in which one or two CH groups may be replaced by -N- and/or in which 1, 2 or 3 H atoms may be replaced by Hal or OH; or R^3 is unbranched or branched alkyl group

having 1, 2, 3, 4, 5 of 6 C atoms, which is substituted by a 3-6 membered heterocyclic ring, which may be further optionally substituted;

R^4 is $C_{5–10}$ aryl, a 3-8 membered saturated or partially unsaturated carbocyclic ring, a 3-7 membered heterocylic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur; each of which is mono-, di- or trisubstituted by Hal, LA, OH, O(LA), NH_2 and/or NH(LA), $N(LA)_2$, NO_2, CN, OCN, COOH, COO(LA), $CONH_2$, CONH(LA), $CON(LA)_2$, NHCO(LA), NHCONH(LA), $NHCONH_2$, $NHSO_2$(LA), CHO or CO(LA);

LA is an unbranched or branched, saturated or partially unstaturated, linear hydrocarbon chain having 1, 2, 3 or 4 C atoms, wherein 1, 2 or 3 H atoms may be replaced by Hal;

Hal is F, Cl, Br or I; and

n is 0, 1 or 2,

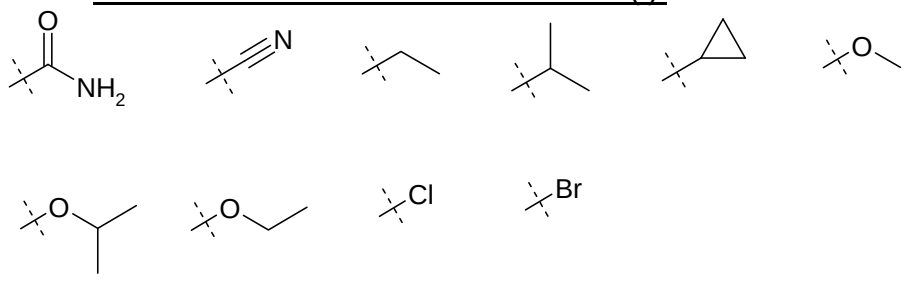
provided that, when n = 0, R^2 cannot be H, and when n $\neq$ 0, R^2 is H;

or a pharmaceutically acceptable salt, solvate or solvate of salt thereof.

2. The compound of claim 1 wherein R^1 is CN, $CONH_2$, Hal, O(LA), or an unbranched or branched linear or cyclic alkyl having 1, 2, 3, 4, 5, 6, 7 or 8 C atoms, in which one or two CH_2 groups may be replaced by an O atom and/or by an -NH-, NH(LA), -CO-, -NHCO- or –CH=CH– group, and/or in which a CH group may be replaced by -N- or a pharmaceutically acceptable salt, solvate, or solvate of salt thereof.

3. The compound of claim 2, wherein R^1 is selected from Table 1.

Table 1: Substituents for R^1 in Formula (I):



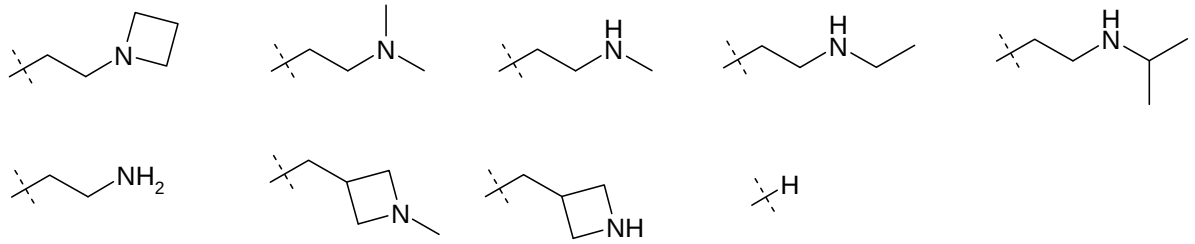
4. The compound of claim 1 wherein each R^2 is independently Hal, OH, methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl, t-butyl, straight chain or branched pentyl, or straight chain or branched hexyl.

5. The compound of claim 4 wherein each R^2 is independently F, OH, or methyl.

6. The compound of claim 1, wherein R^3 is H.

7. The compound of claim 1, wherein R^3 is selected from Table 2:

Table 2: Substituents for R^3 in Formula (I):



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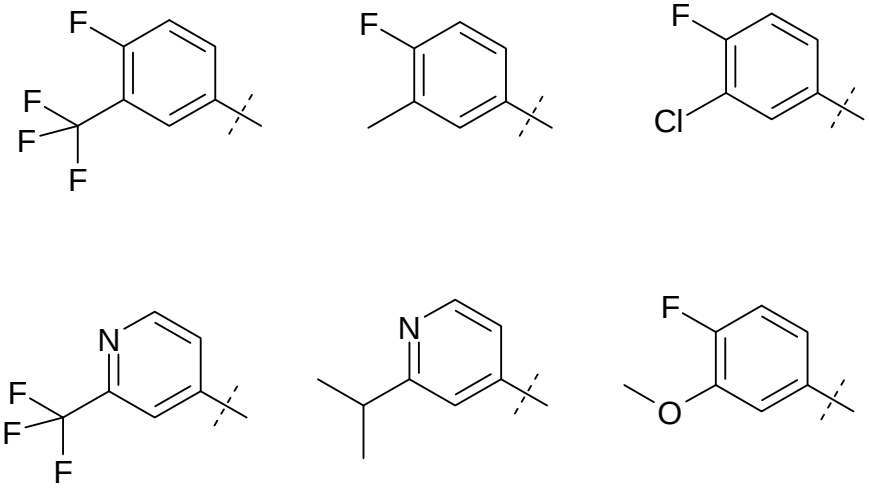
8. The compound of claim 1, wherein R^4 is $C_{5–10}$ aryl or a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur; each of which is mono-, di- or trisubstituted by Hal, LA, OH, O(LA), NH_2 and/or NH(LA), $N(LA)_2$, NO_2, CN, OCN, COOH, COO(LA), $CONH_2$, CONH(LA), $CON(LA)_2$, NHCO(LA), NHCONH(LA), $NHCONH_2$, $NHSO_2$(LA), CHO or CO(LA).

9. The compound of claim 8, wherein R^4 is selected from Table 3.

Table 3: Substituents for R^4 in Formula (I):



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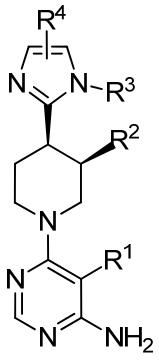
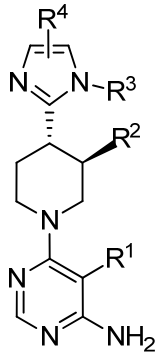
10. The compound of claim 1, of formula (II):


(II)

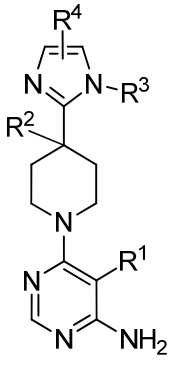
or a pharmaceutically acceptable salt thereof.

11. The compound of claim 1, of formula (III):


(III)

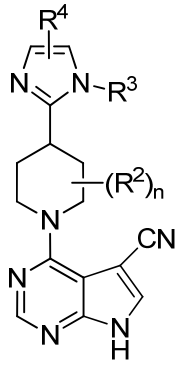
or a pharmaceutically acceptable salt thereof.

12. The compound of claim 1, of formula (IV):


(IV)

or a pharmaceutically acceptable salt thereof.

13. The compound of claim 1, of formula (V):



(V)

or a pharmaceutically acceptable salt thereof.

14. A compound according to claim 1, selected from the group consisting of:

4-Amino-6-{3,4-*cis*-4-[1-(2-azetidin-1-yl-ethyl)-4-(4-fluoro-3-trifluoromethyl-phenyl)-1H-imidazol-2-yl]-3-fluoro-piperidin-1-yl}-pyrimidine-5-carbonitrile (racemic) (“1”);

4-Amino-6-{3,4-*cis*-4-[1-(2-azetidin-1-yl-ethyl)-4-(4-fluoro-3-trifluoromethyl-phenyl)-1H-imidazol-2-yl]-3-fluoro-piperidin-1-yl}-pyrimidine-5-carboxamide (racemic) (“2”);

4-amino-6-[(3R,4S)-4-[1-[2-(azetidin-1-yl)ethyl]-4-[4-fluoro-3-(trifluoromethyl)phenyl]imidazol-2-yl]-3-fluoro-1-piperidyl]pyrimidine-5-carboxamide (chiral) (“3”);

4-amino-6-[(3S,4R)-4-[1-[2-(azetidin-1-yl)ethyl]-4-[4-fluoro-3-(trifluoromethyl)phenyl]imidazol-2-yl]-3-fluoro-1-piperidyl]pyrimidine-5-carboxamide (chiral) (“4”);

4-Amino-6-{3,4-cis-4-[1-(2-azetidin-1-yl-ethyl)-4-(4-fluoro-3-trifluoromethyl-phenyl)-1H-imidazol-2-yl]-3-methyl-piperidin-1-yl}-pyrimidine-5-carbonitrile (racemic) (“5”);

4-Amino-6-{3,4-*cis*-4-[1-(2-azetidin-1-yl-ethyl)-4-(4-fluoro-3-trifluoromethyl-phenyl)-1H-imidazol-2-yl]-3-methyl-piperidin-1-yl}-pyrimidine-5-carboxamide (racemic) (“6”);

4-amino-6-{3,4-*trans*-4-[1-(2-azetidin-1-yl-ethyl)-4-(4-fluoro-3-trifluoromethyl-phenyl)-1H-imidazol-2-yl]-3-fluoro-piperidin-1-yl}-pyrimidine-5-carbonitrile (racemic) (“7”);

4-Amino-6-{3,4-*trans*-4-[1-(2-azetidin-1-yl-ethyl)-4-(4-fluoro-3-trifluoromethyl-phenyl)-1H-imidazol-2-yl]-3-fluoro-piperidin-1-yl}-pyrimidine-5-carboxamide (racemic) (“8”);

4-amino-6-{3,4-*cis*-4-[1-(2-dimethylaminoethyl)-4-(4-fluoro-3-methyl-phenyl)imidazol-2-yl]-3-fluoro-1-piperidyl]}-pyrimidine-5-carbonitrile (racemic) (“9”);

6-{3,4-*cis*-4-[1-(2-Azetidin-1-yl-ethyl)-4-(4-fluoro-3-trifluoromethyl-phenyl)-1H-imidazol-2-yl]-3-fluoro-piperidin-1-yl}-5-chloro-pyrimidin-4-ylamine (racemic) (“10”);

6-{3,4-*trans*-4-[1-(2-Azetidin-1-yl-ethyl)-4-(4-fluoro-3-trifluoromethyl-phenyl)-1H-imidazol-2-yl]-3-fluoro-piperidin-1-yl}-5-chloro-pyrimidin-4-ylamine (racemic) (“11”);

5-chloro-6-{3,4-*cis*--4-[1-(2-dimethylamino-ethyl)-4-(4-fluoro-3-methyl-phenyl)-1H-imidazol-2-yl]-3-fluoro-piperidin-1-yl}-pyrimidin-4-ylamine (racemic) (“12”);

6-{3,4-*cis*-4-[1-(2-Azetidin-1-yl-ethyl)-4-(4-fluoro-3-trifluoromethyl-phenyl)-1H-imidazol-2-yl]-3-fluoro-piperidin-1-yl}-5-ethyl-pyrimidin-4-ylamine (racemic) (“13”);

4-Amino-6-{3,4-*cis*-4-[1-(2-dimethylamino-ethyl)-4-(4-fluoro-3-trifluoromethyl-phenyl)-1H-imidazol-2-yl]-3-fluoro-piperidin-1-yl}-pyrimidine-5-carbonitrile (racemic) (“14”);

4-Amino-6-{3,4-*cis*-4-[1-(2-dimethylamino-ethyl)-4-(4-fluoro-3-trifluoromethyl-phenyl)-1H-imidazol-2-yl]-3-fluoro-piperidin-1-yl}-pyrimidine-5-carbonitrile (racemic) (“15”);

6-{3,4-*cis*-4-[1-(2-Azetidin-1-yl-ethyl)-4-(4-fluoro-3-trifluoromethyl-phenyl)-1H-imidazol-2-yl]-3-fluoro-piperidin-1-yl}-5-ethoxy-pyrimidin-4-ylamine (racemic) (“16”);

6-{*cis*-4-[1-(2-Dimethylamino-ethyl)-4-(4-fluoro-3-trifluoromethyl-phenyl)-1H-imidazol-2-yl]-3-fluoro-piperidin-1-yl}-5-isopropyl-pyrimidin-4-ylamine (racemic) (“17”);

4-Amino-6-{*cis*-4-[1-(2-azetidin-1-yl-ethyl)-4-(4-fluoro-3-methyl-phenyl)-1H-imidazol-2-yl]-3-fluoro-piperidin-1-yl}-pyrimidine-5-carbonitrile (racemic) (“18”);

4-Amino-6-{*cis*-4-[1-(2-azetidin-1-yl-ethyl)-4-(4-fluoro-3-methyl-phenyl)-1H-imidazol-2-yl]-3-fluoro-piperidin-1-yl}-pyrimidine-5-carboxylic acid amide (racamic) (“19”);

4-Amino-6-{(3S, 4R)-4-[1-(2-dimethylamino-ethyl)-4-(4-fluoro-3-trifluoromethyl-phenyl)-1H-imidazol-2-yl]-3-fluoro-piperidin-1-yl}-pyrimidine-5-carboxylic acid amide (chiral) (“20”);

4-Amino-6-{(3R,4S)-4-[1-(2-dimethylamino-ethyl)-4-(4-fluoro-3-trifluoromethyl-phenyl)-1H-imidazol-2-yl]-3-fluoro-piperidin-1-yl}-pyrimidine-5-carboxylic acid amide (chiral) (“21”);

6-{(3R,4S)-4-[1-(2-Azetidin-1-yl-ethyl)-4-(4-fluoro-3-trifluoromethyl-phenyl)-1H-imidazol-2-yl]-3-fluoro-piperidin-1-yl}-5-ethoxy-pyrimidin-4-ylamine (chiral) (“22”);

6-{(3S,4R)-4-[1-(2-Azetidin-1-yl-ethyl)-4-(4-fluoro-3-trifluoromethyl-phenyl)-1H-imidazol-2-yl]-3-fluoro-piperidin-1-yl}-5-ethoxy-pyrimidin-4-ylamine(chiral) (“23”);

6-{*cis*-4-[1-(2-Azetidin-1-yl-ethyl)-4-(4-fluoro-3-methyl-phenyl)-1H-imidazol-2-yl]-3-fluoro-piperidin-1-yl}-5-isopropyl-pyrimidin-4-ylamine (racemic) (“24”);

5-Chloro-6-*cis*-4-[1-(2-dimethylamino-ethyl)-4-(4-fluoro-3-trifluoromethyl-phenyl)-1H-imidazol-2-yl]-3-fluoro-piperidin-1-yl}-pyrimidin-4-ylamine (racemic) (“25”);

6-{*cis*-3-Fluoro-4-[4-(4-fluoro-3-trifluoromethyl-phenyl)-1H-imidazol-2-yl]-piperidin-1-yl}-5-isopropyl-pyrimidin-4-ylamine (racemic) (“26”);

4-Amino-6-{(3R,4S)-4-[1-(2-azetidin-1-yl-ethyl)-4-(4-fluoro-3-methyl-phenyl)-1H-imidazol-2-yl]-3-fluoro-piperidin-1-yl}-pyrimidine-5-carboxylic acid amide (chiral) (“27”);

4-Amino-6-{(3S,4R)-4-[1-(2-azetidin-1-yl-ethyl)-4-(4-fluoro-3-methyl-phenyl)-1H-imidazol-2-yl]-3-fluoro-piperidin-1-yl}-pyrimidine-5-carboxylic acid amide (chiral) (“28”);

5-Chloro-6-{(3R,4S)-4-[1-(2-dimethylamino-ethyl)-4-(4-fluoro-3-trifluoromethyl-phenyl)-1H-imidazol-2-yl]-3-fluoro-piperidin-1-yl}-pyrimidin-4-ylamine (chiral) (“29”);

5-Chloro-6-{(3S,4R)-4-[1-(2-dimethylamino-ethyl)-4-(4-fluoro-3-trifluoromethyl-phenyl)-1H-imidazol-2-yl]-3-fluoro-piperidin-1-yl}-pyrimidin-4-ylamine (chiral) (“30”);

6-{(3S,4R)-4-[1-(2-Dimethylamino-ethyl)-4-(4-fluoro-3-trifluoromethyl-phenyl)-1H-imidazol-2-yl]-3-fluoro-piperidin-1-yl}-5-isopropyl-pyrimidin-4-ylamine (chiral) (“31”);

6-{(3R,4S)-4-[1-(2-Dimethylamino-ethyl)-4-(4-fluoro-3-trifluoromethyl-phenyl)-1H-imidazol-2-yl]-3-fluoro-piperidin-1-yl}-5-isopropyl-pyrimidin-4-ylamine (chiral) (“32”);

6-{*cis*-4-[1-(2-Amino-ethyl)-4-(4-fluoro-3-trifluoromethyl-phenyl)-1H-imidazol-2-yl]-3-fluoro-piperidin-1-yl}-5-isopropyl-pyrimidin-4-ylamine (racemic) (“33”);

6-{(3S,4R)-4-[1-(2-Azetidin-1-yl-ethyl)-4-(4-fluoro-3-methyl-phenyl)-1H-imidazol-2-yl]-3-fluoro-piperidin-1-yl}-5-isopropyl-pyrimidin-4-ylamine (chiral) (“34”);

6-{(3R,4S)-4-[1-(2-Azetidin-1-yl-ethyl)-4-(4-fluoro-3-methyl-phenyl)-1H-imidazol-2-yl]-3-fluoro-piperidin-1-yl}-5-isopropyl-pyrimidin-4-ylamine (chiral) (“35”);

6-{(*cis*-4-[1-(2-Amino-ethyl)-4-(4-fluoro-3-trifluoromethyl-phenyl)-1H-imidazol-2-yl]-3-fluoro-piperidin-1-yl}-5-chloro-pyrimidin-4-ylamine (racemic) (“36”);

6-{*cis*-3-Fluoro-4-[4-(4-fluoro-3-methyl-phenyl)-1-(2-isopropylamino-ethyl)-1H-imidazol-2-yl]-piperidin-1-yl}-5-isopropyl-pyrimidin-4-ylamine (racemic) (“37”);

6-{*cis*-3-Fluoro-4-[4-(4-fluoro-3-methyl-phenyl)-1-(2-methylamino-ethyl)-1H-imidazol-2-yl]-piperidin-1-yl}-5-isopropyl-pyrimidin-4-ylamine (racemic) (“38”);

6-{*cis*-4-[1-(2-Azetidin-1-yl-ethyl)-4-(4-fluoro-3-methyl-phenyl)-1H-imidazol-2-yl]-3-fluoro-piperidin-1-yl}-5-isopropoxy-pyrimidin-4-ylamine (racemic) (“39”);

4-Amino-6-{(3R,4S)-4-[1-(2-azetidin-1-yl-ethyl)-4-(4-fluoro-3-trifluoromethyl-phenyl)-1H-imidazol-2-yl]-3-fluoro-piperidin-1-yl}-pyrimidine-5-carbonitrile (chiral) (“40”);

6-{*cis*-4-[1-Azetidin-3-ylmethyl-4-(4-fluoro-3-methyl-phenyl)-1H-imidazol-2-yl]-3-fluoro-piperidin-1-yl}-5-isopropyl-pyrimidin-4-ylamine (racemic) (“41”);
4-Amino-6-{4-[1-(2-azetidin-1-yl-ethyl)-4-(4-fluoro-3-methyl-phenyl)-1H-imidazol-2-yl]-4-hydroxy-piperidin-1-yl}-pyrimidine-5-carbonitrile (“44”);
1-(6-Amino-5-isopropyl-pyrimidin-4-yl)-4-[1-(2-azetidin-1-yl-ethyl)-4-(4-fluoro-3-methyl-phenyl)-1H-imidazol-2-yl]-piperidin-4-ol (“45”);
1-(6-Amino-5-ethyl-pyrimidin-4-yl)-4-[1-(2-azetidin-1-yl-ethyl)-4-(4-fluoro-3-methyl-phenyl)-1H-imidazol-2-yl]-piperidin-4-ol (“46”);
1-(6-Amino-5-chloro-pyrimidin-4-yl)-4-[1-(2-azetidin-1-yl-ethyl)-4-(4-fluoro-3-methyl-phenyl)-1H-imidazol-2-yl]-piperidin-4-ol (“47”);
4-Amino-6-{4-[1-(2-azetidin-1-yl-ethyl)-4-(4-fluoro-3-methyl-phenyl)-1H-imidazol-2-yl]-3,3-difluoro-piperidin-1-yl}-pyrimidine-5-carbonitrile (“48”);
4-Amino-6-{4-[1-(2-azetidin-1-yl-ethyl)-4-(4-fluoro-3-methyl-phenyl)-1H-imidazol-2-yl]-3,3-difluoro-piperidin-1-yl}-pyrimidine-5-carboxylic acid amide (“49”); and
6-{4-[1-(2-Azetidin-1-yl-ethyl)-4-(4-fluoro-3-methyl-phenyl)-1H-imidazol-2-yl]-3,3-difluoro-piperidin-1-yl}-5-isopropyl-pyrimidin-4-ylamine (“50”);
and pharmaceutically acceptable salts or solvates thereof.

15. A pharmaceutical composition comprising a compound according to claim 1, or a pharmaceutically acceptable salt or solvate thereof, as active ingredient, together with a pharmaceutically acceptable carrier.

16. A kit comprising separate packs of:

a) an effective amount of a compound according to claim 1 or a pharmaceutically acceptable salt or solvate thereof, and

b) an effective amount of a further medicament active ingredient.