

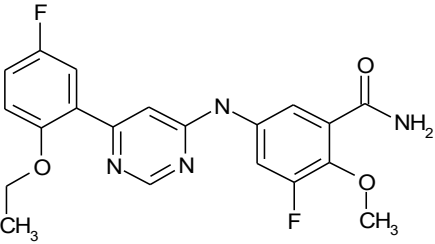
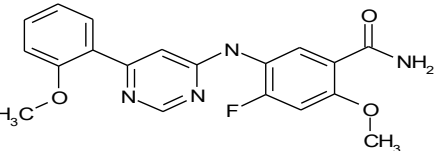
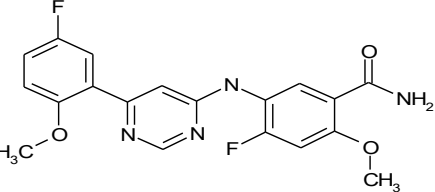
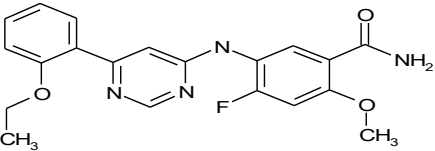
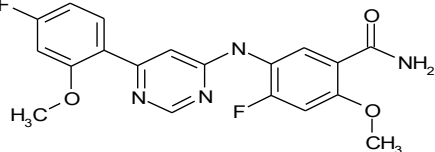
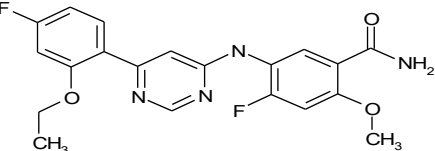
As discussed before, several aminopyrimidine derivatives have been disclosed in the literature, and some of them have been described as potential compounds with applications in the HIV field. However, none of the compounds exemplified therein has been encompassed in the general formula (I) of the present application, nor is the evidence of anti-HIV activity very convincing.

In fact during their research the present inventors surprisingly found that only few compounds with good CDK9 activity exhibited potent anti-HIV activity. This inconsistency suggests that these compounds target a cellular mechanism that is as yet not identified.

The present inventors have now discovered that compounds of formula (I), described below, exert a potent stand alone anti-HIV activity which in the preferred cases is also combined with a potentially attractive antiproliferative activity in the same molecule, irrespective of whether they exhibit a good or bad CDK9 inhibitor activity. Thus, these compounds provide for a potentially new method to treat HIV disease.

Accordingly, a first object of the present invention is to provide novel 4,6-disubstituted aminopyrimidine compounds represented by formula (I), which possess aromatic substituents, which are directly or indirectly attached to two non-adjacent carbons of the pyrimidine ring. The general formula of the compounds is the following:



Example 142		5-[6-(2-Ethoxy-5-fluoro-phenyl)-pyrimidin-4-ylamino]-3-fluoro-2-methoxy-benzamide
Example 143		4-Fluoro-2-methoxy-5-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-benzamide
Example 144		4-Fluoro-5-[6-(5-fluoro-2-methoxy-phenyl)-pyrimidin-4-ylamino]-2-methoxy-benzamide
Example 145		5-[6-(2-Ethoxy-phenyl)-pyrimidin-4-ylamino]-4-fluoro-2-methoxy-benzamide
Example 146		4-Fluoro-5-[6-(4-fluoro-2-methoxy-phenyl)-pyrimidin-4-ylamino]-2-methoxy-benzamide
Example 147		5-[6-(2-Ethoxy-4-fluoro-phenyl)-pyrimidin-4-ylamino]-4-fluoro-2-methoxy-benzamide

It may be advantageous for certain uses to enhance the solubility and/or bioavailability of one or more of the compounds of the present invention.

- Unless otherwise specified, when referring to the compounds of formula (I) *per se* as well as to any pharmaceutical composition thereof or to any therapeutic treatment comprising them, the present disclosure includes all of the isomers, tautomers, hydrates, solvates, complexes, metabolites, pro-drugs, carriers, N-oxides and pharmaceutically acceptable salts of the compounds of this invention.

A metabolite of a compound of formula (I) is any compound into which this same

compound of formula (I) is converted *in vivo*, for instance upon administration to a mammal in need thereof. Typically, without however representing a limiting example, upon administration of a compounds of formula (I), this same derivative may be converted into a variety of compounds, for instance including more soluble derivatives like hydroxylated derivatives, which are easily excreted. Hence, depending upon the metabolic pathway thus occurring, any of these hydroxylated derivatives may be regarded as a metabolite of the compounds of formula (I).

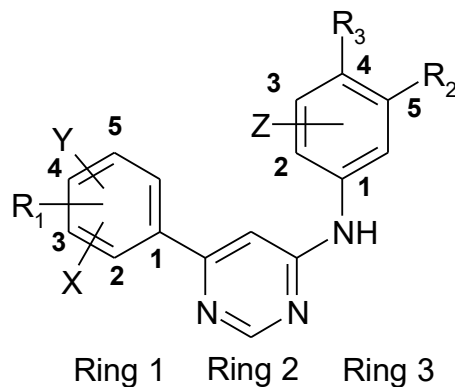
It may be advantageous for certain uses to prepare a compound (or physiologically acceptable salt thereof) as a "prodrug." As used herein, the term "compound" encompasses a prodrug form of the parent compound. "Prodrug" herein refers to a chemical substance, preferably but not only covalently bonded, that is converted into the parent compound (I) *in vivo*. Prodrugs often are useful because, in some situations, they may be easier to administer than the parent compound. They may, for instance, be bioavailable by oral administration whereas the parent compound is not. The prodrug may also have improved solubility in pharmaceutical compositions over the parent compound. An example of a prodrug would be a parent compound of the present invention which is administered as an ester (the "prodrug") to facilitate transmittal across a cell membrane where water solubility is detrimental to mobility. The ester is then metabolically hydrolyzed to the carboxylic acid, the active entity, once inside the cell where water solubility is beneficial. Such a prodrug is generally inactive (or less active) until converted to the active form.

N-oxides are compounds of formula (I) wherein nitrogen and oxygen are tethered through a dative bond.

If a chiral center or another form of an isomeric center is present in a compound of the present invention, all forms of such isomer or isomers, including enantiomers and diastereomers, are intended to be covered herein. Compounds containing a chiral center may be used as a racemic mixture, an enantiomerically enriched mixture, or the racemic mixture may be separated using well-known techniques and an individual enantiomer may be used alone. In cases in which compounds have unsaturated carbon-carbon double bonds, both the cis (Z) and trans (E) isomers are within the scope of this invention.

CLAIMS

1. A compound having formula (I):



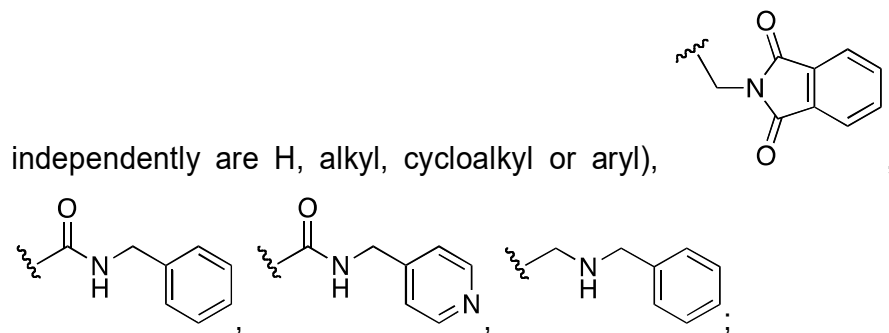
(I)

where X, Y and Z are H, F, or Cl;

R₁ is OR, where R is hydrogen or a group selected from straight or branched C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl, heterocyclyl, CF₃, CCl₃, and aryl in positions 2, 3 or 4;

R₂ is OH, alkoxy, aryloxy, CH₂OR (where R is H, linear or branched aryl, cycloalkyl or alkyl), CH₂NR'R'' (where R' and R'' are independently H, linear or branched aryl, cycloalkyl or alkyl), CHO, OCOW (where W is linear or branched aryl or alkyl or C-(halogen)₃), CONR'R'' (where R' and R'' independently are H, alkyl, cycloalkyl or aryl), COOR (where R is H, alkyl, cycloalkyl or aryl), CH₂NHSO₂R (where R is H, alkyl, cycloalkyl or aryl), Cl, Br, F, CH₂-N-benzimidazole, CONHNR'R'' (where R' and R'' independently are H, alkyl, cycloalkyl or aryl), NR₂COOR' (where R and R' are independently H, alkyl, cycloalkyl or aryl), NH₂, NR'R'' (where R' and R'' independently are alkyl, cycloalkyl or aryl), NHCOR (where R is H, alkyl, cycloalkyl or aryl), nitro, OCH₂CH₂-heterocyclyl, OCOR (where R is H, alkyl, cycloalkyl or aryl), OCONR'R'' (where R' and R'' are independently H, alkyl,

cycloalkyl or aryl), OCOOR (where R is H, alkyl, cycloalkyl or aryl), NHCOOCH₂C-halo₃, NRCONR'R'' (where R, R' and R'' independently are H, alkyl, cycloalkyl or aryl), NHSO₂R (where R is H, alkyl, cycloalkyl or aryl), NHSO₂NR'R'' (where R' and R''



2. A compound according to Claim 1, wherein R₁ is OR, where R is H, methyl, isopropyl or ethyl.
3. A compound according to Claim 1, wherein R₁ is 2'-OR, where R is H, methyl, ethyl or isopropyl.
4. A compound according to Claim 1, wherein Z is H or F.
5. A compound according to Claim 1, wherein R₂ is selected from the group consisting of OH, linear or branched alkoxy, CH₂OR (where R is alkyl), NH₂, CH₂NH₂, OCOC(CH₃)₃, CONH₂, Cl, Br, CH₂-N-benzimidazole, NHSO₂R (where R is alkyl or aryl) and NHSO₂NR'R'' (where R' and R'' independently are H, alkyl, or aryl), OCH₂CH₂-heterocyclyl, OCOR (where R is H, alkyl, cycloalkyl or aryl), OCONR'R'' (where R' and R'' are independently H, alkyl, cycloalkyl or aryl).

6. A compound according to Claim 1, wherein R₃ is OH, linear or branched alkoxy, NR'R'' (where R' and R'' are H), CONR'R'' (where R' and R'' independently are H, alkyl, cycloalkyl or aryl).
7. A compound according to Claim 1, wherein R₂ is selected from the group consisting of OH, linear or branched alkoxy, CONH₂, OCOC(CH₃)₃, Cl, CH₂-*N*-benzimidazole and R₃ is selected from the group consisting of alkoxy.
8. A compound according to Claim 1, wherein X, Y and Z are H or F, R₂ is linear or branched alkoxy, CONH₂, OCOC(CH₃)₃, Cl, CH₂-*N*-benzimidazole and R₃ is alkoxy.
9. A compound according to Claim 1, wherein X, Y and Z are H or F, R₁ is methoxy or ethoxy, R₂ is linear or branched alkoxy, CONH₂, Cl, Br, CH₂-*N*-benzimidazole and R₃ is alkoxy.
10. A compound according to Claim 1, wherein X and Y are 4'-F, 5'-F or H and Z is 2'-F or H, R₁ is 2'-OR, where R is H, methyl, ethyl, or isopropyl, R₂ is linear or branched alkoxy, CONH₂, Cl, Br, CH₂-*N*-benzimidazole and R₃ is OR' (where R' is alkyl).
11. A pharmaceutical composition comprising a pharmaceutically acceptable excipient, diluent or carrier and a therapeutically effective amount of a compound according to any of claims 1 to 10.
12. A compound according to any of claims 1 to 10 selected from:
2-Methoxy-N⁴-[6-(2-methoxy-phenyl)-pyrimidin-4-yl]-benzene-

1,4-diamine (Example 59);

Methyl 2-Methoxy-5-(6-(2-methoxy-phenyl)-pyrimidin-4-ylamino)-benzoate (Example 30);

N¹-[6-(4-Fluoro-2-methoxy-phenyl)-pyrimidin-4-yl]-4-methoxy-benzene-1,3-diamine (Example 64);

4-Fluoro-6-methoxy-N³-[6-(2-methoxy-phenyl)-pyrimidin-4-yl]-benzene-1,3-diamine (Example 92);

4-Fluoro-5-[6-(5-fluoro-2-methoxy-phenyl)-pyrimidin-4-ylamino]-2-methoxy-benzamide (Example 144);

2-methoxy-5-(6-(2-methoxyphenyl)pyrimidin-4-ylamino)phenyl pivalate (Example 26);

5-[6-(4-Fluoro-2-methoxy-phenyl)-pyrimidin-4-ylamino]-2-methoxy-phenol (Example 123);

N-(3-(benzyloxy)-4-methoxyphenyl)-6-(2-methoxyphenyl)-pyrimidin-4-amine (Example 36);

N-(3-fluoro-4-methoxyphenyl)-6-(2-methoxyphenyl)pyrimidin-4-amine (Example 22);

2-methoxy-5-(6-(2-methoxyphenyl)pyrimidin-4-ylamino)-phenol (Example 32);

4-methoxy-N¹-(6-(2-methoxyphenyl)pyrimidin-4-yl)benzene-1,3-diamine (Example 41);

2-methoxy-5-(6-(2-methoxyphenyl)pyrimidin-4-ylamino)benzamide (Example 45);

{2-Methoxy-5-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-carbamic acid methyl ester (Example 51);

(2-methoxy-5-(6-(2-methoxyphenyl)pyrimidin-4-ylamino)-phenyl)(methylsulfamoyl)amine (Example 10);

N-benzyl-2-methoxy-5-(6-(2-methoxyphenyl)pyrimidin-4-ylamino)benzamide (Example 23);

(2-methoxy-5-(6-(2-methoxyphenyl)pyrimidin-4-ylamino)-phenyl)methanol (Example 24);

2-methoxy-5-(6-(2-methoxyphenyl)pyrimidin-4-ylamino)-*N*-methylbenzamide (Example 25);

N-(4-methoxy-3-nitrophenyl)-6-(2-methoxyphenyl)pyrimidin-4-amine (Example 11);

*N*¹-[6-(2-Isopropoxy-phenyl)-pyrimidin-4-yl]-4-methoxybenzene-1,3-diamine (Example 79);

N-(3-((dimethylamino)methyl)-4-methoxyphenyl)-6-(2-methoxyphenyl)pyrimidin-4-amine (Example 35);

N-(4-methoxy-3-((phenylamino)methyl)phenyl)-6-(2-methoxyphenyl)pyrimidin-4-amine (Example 34);

2-(2-methoxy-5-(6-(2-methoxyphenyl)pyrimidin-4-ylamino)-benzyl)isoindoline-1,3-dione (Example 3);

4-Fluoro-5-[6-(4-fluoro-2-methoxy-phenyl)-pyrimidin-4-ylamino]-2-methoxy-benzamide (Example 146);

5-[6-(4-Fluoro-2-methoxy-phenyl)-pyrimidin-4-ylamino]-2-methoxy-benzamide (Example 128);

4-Fluoro-2-methoxy-5-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-benzamide (Example 143);

5-[6-(2-Ethoxy-phenyl)-pyrimidin-4-ylamino]-4-fluoro-2-methoxy-benzamide (Example 145);

5-[6-(2-Ethoxy-4-fluoro-phenyl)-pyrimidin-4-ylamino]-4-fluoro-2-methoxy-benzamide (Example 147);

4-(6-(2-methoxyphenyl)pyrimidin-4-ylamino)-2-nitrophenol (Example 12);

N-(3-((benzylamino)methyl)-4-methoxyphenyl)-6-(2-methoxyphenyl)pyrimidin-4-amine (Example 1);

N-(3-(aminomethyl)-4-methoxyphenyl)-6-(2-methoxyphenyl)pyrimidin-4-amine (Example 43);

3-Fluoro-5-[6-(4-fluoro-2-methoxy-phenyl)-pyrimidin-4-ylamino]-2-methoxy-benzamide (Example 138); and

3-Fluoro-5-[6-(5-fluoro-2-methoxy-phenyl)-pyrimidin-4-

ylamino]-2-methoxy-benzamide (Example 140).

13. Compound selected from
 - 2-Dimethylamino-5-[6-(4-fluoro-2-methoxy-phenyl)-pyrimidin-4-ylamino]-benzamide (Example 113);
 - 2-(2-Chloro-5-(6-(2-methoxyphenyl)pyrimidin-4-ylamino)benzyl)isoindoline-1,3-dione (Example 20);
 - ethyl 2-chloro-5-(6-(2-methoxyphenyl)pyrimidin-4-ylamino)benzoate (Example 14);
 - 2-Fluoro-N⁴-[6-(2-methoxy-phenyl)-pyrimidin-4-yl]-N¹,N¹-dimethyl-benzene-1,4-diamine (Example 106);
 - 2-Dimethylamino-5-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-phenol (Example 108);
 - 2-Dimethylamino-5-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-benzamide (Example 109);
 - ethyl 5-(6-(2-methoxyphenyl)pyrimidin-4-ylamino)-2-morpholinobenzoate (Example 18);
 - 2-chloro-5-(6-(2-methoxyphenyl)pyrimidin-4-ylamino)benzamide (Example 44); and
 - N-(3-((1H-benzo[d]imidazol-1-yl)methyl)-4-(4-methylpiperazin-1-yl)phenyl)-6-(2-methoxyphenyl)pyrimidin-4-amine (Example 2).