Title: NOVEL ANTI-HIV COMPOUNDS

Abstract: The present invention relates to the field of HrV-1 infections, and in particular provides novel compounds containing fluorine on the Central ring. The compounds according to this invention are very suitable for the prevention and/or treatment of HrV-1 infection and in particular show higher activity against NNRTI-resistant strains of HrV-1.
NOVEL ANTI-HIV COMPOUNDS

FIELD OF THE INVENTION
The present invention relates to the field of HIV-1 infections, and in particular provides novel compounds containing fluorine on the Central ring. The compounds according to this invention are very suitable for the prevention and/or treatment of HIV-1 infection and in particular show a higher activity against NNRTI-resistant strains of HIV-1.

BACKGROUND TO THE INVENTION
At the end of 2010, an estimated 34 million people were living with HIV infection worldwide, corresponding to a 17% increase from 2001. The number of people dying of AIDS-related causes fell to 1.8 million in 2010, down from a peak of 2.2 million in the mid-2000s. In the Western world, HIV/AIDS is no longer a fatal disease: life expectancy with adequate anti-retroviral treatment and care is more than 24 years after HIV-infection. Much of that success is due to the introduction of HAART (highly active antiretroviral treatment) by means of combinations of two or three compounds belonging to different classes of anti-HIV compounds. HAART consists of the combination of several active components belonging to different classes of anti-HIV compounds such as protease inhibitors (PI), nucleoside reverse transcriptase inhibitors (NRTI) and non-nucleoside reverse transcriptase inhibitors (NNRTI). A major problem in the HIV treatment remains the emergence of resistance of the virus against the currently available drugs, whatever class of anti-HIV compounds they belong to. Application of HAART for the treatment of HIV infection only in part solves this problem, and HAART may become inefficient once resistance to one or more of the drugs used in combination is developed. Finally, none of the currently available anti-HIV drugs or multi-drug therapies allows for the eradication of the virus, causing the need for life-long treatment which possibly results in multidrug resistance. For this reason, there is a continuous need for the development of new anti-HIV combination therapies. In order to treat drug-resistant HIV infection, new components with novel chemical structures for such combination therapies, possessing new modes of action are necessary.

HIV-1 reverse transcriptase (RT) is one of the most important viral enzymes and plays a unique role in the HIV-1 life cycle. It has two known drug-target sites, the substrate catalytic site and an allosteric site that is distinct from, but located closely to, the substrate site. Non-nucleoside reverse transcriptase inhibitors (NNRTIs) interact with the allosteric site in a non-competitive manner to distort the enzyme's active conformation and thus disrupt the function of the enzyme. It is demonstrated by XRD analysis that many NNRTIs form a hydrogen bond with a K101 amino acid residue in the reverse transcriptase binding site. For example, in the di(arylamino)pyrimidine (DAPY) derivative Etravirine (fig. 1A), which was recently approved as a next-generation NNRTI for AIDS therapy, the NH group of the arylamine and the N atom in the pyrimidine ring of the drug are involved in the hydrogen bonding with the enzyme. Etravirine exhibits high potency against wild-type and a number of mutated viral strains with nanomolar EC50 values and has a high genetic barrier to delay the emergence of drug-resistance. The success of Etravirine greatly encouraged
further research to explore additional novel NNRTIs. The most advanced NNRTI in development is another DAPY derivative Rilpivirine (fig. 1B) which was approved by the FDA in May 2011. It showed better potency and pharmacological profiles than Etravirine, and features the same hydrogen bonding sites as present in the drug Etravirine (WO2002078708).

We have now surprisingly found that a fluorine substituent on the central ring also can participate in the interactions with the protein backbone, by way of action as a hydrogen bond acceptor, and/or other weak forces which are unique for the fluorine atom such as orthogonal C=O…F-C interactions. Compounds according to this invention are thus to be considered non-nucleoside reverse transcriptase inhibitors (NNRTIs) active against HIV virus and therefore suitable as potential medicaments for treatment and/or prevention of HIV infection in patients.

The proposed new compounds, are represented by the general formula (I) as specified herein below; and all contain a central aromatic or azaheteroaromatic ring (Central ring) bearing the two aryl substituents (will be referred to as Eastern and Western rings, according to the terminology used in the literature for analogous compounds) connected to the Central ring by an -NH- or -O- linker. All compounds feature an F atom in the specified position of the Central ring. The novel compounds can be further subdivided into 3 major groups i.e. 2,6-di(arylamino)-3-fluoropyridine (DAFPY) derivatives, DAFPYM (derivatives featuring central pyrimidine) and DAFB (derivatives featuring central benzene); and their analogues where the Western ring is connected with the Central ring by an -O- linker.

FORMULA (I)

A number of NNRTIs with a comparable design, i.e. Central azaheteroaromatic ring decorated with the two arylamino substituents, were already published. For example, in molecules known as DATA [Bioorg. Med. Chem. Lett. 2001, 2229; WO9950256; WO2004074262] or DAPY [WO2000027825; WO9950250; WO200185700; WO2003016306; WO2006079656], triazine and
pyrimidine moieties respectively are used as the Central ring, such as for example in Rilpivirine (TMC 278) (fig. 1B) and Dapivirin (TMC 120) (fig. 1C).

Also compounds containing a central pyridine ring have been published ([WO201 0040275] and [J. Med. Chem., 2010, 8287]), describing di(arylamino) derivatives and reporting their activity against wild type HIV virus. All exemplified compounds of WO201 0040275, however, contain an NO₂ substituent on the central ring, and there are no indications in the applications to support a halogen substituent on the central ring. Even more, the disclosed synthesis method (nucleophilic substitution of Cl) requires an activating strongly electron withdrawing group, and thus said method is not suitable for the preparation of compounds having a halogen substituent on the central ring.

There are some di(arylamino) derivatives of pyridine (WO9628427 - anti-coagulant compounds) and pyrimidine (US201 0/002961 0 - kinase inhibitors) containing a F atom on the central ring, reported in the literature. However, the disclosed compounds of said patent applications differ from the compounds according to the current invention both in terms of structure as well as their utility.

The same applies for a further reference on compounds having a F atom on the central ring. WO20091 32202 discloses macrocyclic compounds having a F atom on the central ring, for the treatment of JAK/ALK associated diseases (including HIV), however, these compounds differ from the compounds according to this invention, in the fact that they are macrocyclic, and in that none of said compounds have actually been shown to be effective against HIV.

The present invention thus discloses compounds which differ from prior art compounds in both structure and/or pharmacological activity.

**BRIEF DESCRIPTION OF THE DRAWINGS**

Figure 1: Prior Art DAPY compounds. A: Etavirine (TMC-1.25), B: Rilpivirine (TMC-278) C: Dapivirin (TMC-1 20)

**SUMMARY OF THE INVENTION**

The invention is based on novel compounds, which contain a halogen atom, in particular an F atom on the central ring, at the position as specified herein below. Surprisingly, the novel compounds of this present invention showed higher activity against NNRTI-resistant viruses of HIV-1.

Viewed from a first aspect, the invention provides a compound of Formula (I) or a stereoisomer, tautomer, racemic, metabolite, pro-or predrug, salt, hydrate, or solvate thereof,
Wherein $R_1$, $R_2$, $R_3$, $R_4$, $R_5$ and $R_6$ are each independently selected from the list comprising -H, -CN, -halo, -(C=0)-$R_7$, and optionally substituted -C$_1$-alkyl, optionally substituted -C$_2$-alkenyl, optionally substituted -C$_2$-alkynyl, or optionally substituted -C$_1$-alkoxy; $X$ and $Y$ are each independently selected from the list comprising N or C; $Z$ is selected from the list comprising -O- and -NH-; $R_7$ is selected from the list comprising -OR$_8$, NR$_9$R$_{10}$; $R_8$, $R_9$ and $R_{10}$ are each independently selected from the list comprising -H and C$_1$-alkyl; and

In a particular embodiment, this invention provides a compound of formula (Ia) or a stereoisomer, tautomer, racemic, metabolite, pro-or predrug, salt, hydrate, or solvate thereof.

Wherein

$R_4$, $R_1$, $R_5$ and $R_6$ are each independently selected from the list comprising -CN, -halo, -(C=0)-$R_7$, and optionally substituted -C$_1$-alkyl, optionally substituted -C$_2$-alkenyl, optionally substituted -C$_2$-alkynyl, or optionally substituted -C$_1$-alkoxy; $X$ and $Y$ are each independently selected from the list comprising N or C; $Z$ is selected from the list comprising -O- and -NH-; $R_7$ is selected from the list comprising -OR$_8$, NR$_9$R$_{10}$; $R_8$, $R_9$ and $R_{10}$ are each independently selected from the list comprising -H and C$_1$-alkyl.
In yet a further embodiment, this invention provides a compound of Formula (lb) or a stereoisomer, tautomer, racemic, metabolite, pro- or predrug, salt, hydrate, or solvate thereof,

[Chemical Structure Image]

5 Wherein
R¹, R², R₃, and R⁴ are each independently selected from the list comprising -CN, -halo, -(C=O)-R⁷, and optionally substituted -Cₘᵦₖyl, optionally substituted -C₂₋₆alkenyl, optionally substituted -C₂₋₆alkynyl, or optionally substituted -C₁₋₆alkoxy;
X and Y are each independently selected from the list comprising N or C;
Z is selected from the list comprising -O- and -NH-;
R⁷ is selected from the list comprising -OR⁸, NR³R⁴⁰;
R⁸, R⁹ and R¹⁰ are each independently selected from the list comprising -H and C₁₋₆alkyl.

10 In a particular embodiment, this invention provides a compound as defined herein above, wherein the optionally substituted -C₁₋₆alkyl, -C₂₋₆alkenyl, -C₂₋₆alkynyl or -C₁₋₆alkoxy as defined in any one of R¹-R⁶ is substituted with one or more substituents selected from the list comprising halo, -CN , and -(C=O)-R¹¹; wherein R¹¹ is selected from the list comprising -OR¹² and -NR¹³R¹⁴; and wherein R¹², R¹³ and R¹⁴ are each independently selected from the list comprising -H and C₁₋₆alkyl.

15 In a particular embodiment, this invention provides a compound as specified above, wherein at least one of the following applies:
X and Y are each N;
X and Y are each C;
X is N and Y is C;

20 In a further specific embodiment, the present invention provides a compound as specified above, wherein R¹ is -CH=CH-CN.

25 In yet a further embodiment, the present invention provides a compound as specified above, wherein R¹ is -CN.
In a further aspect, this invention provides a composition comprising a compound according to this invention.

This invention further provides a compound or a composition according to this invention, for use as a medicament.

This invention in particular provides a compound or composition according to this invention, for use in the prevention and/or treatment of HIV infections in a subject in need thereof.

In yet a further aspect, this invention provides the use of a compound or composition according to this invention as a non-nucleoside reverse transcriptase inhibitor.

In a final aspect this invention provides a method for the prevention and/or treatment of HIV infections; said method comprising administering to a subject in need thereof a compound or a composition according to this invention.

DETAILED DESCRIPTION OF THE INVENTION

The present invention will now be further described. In the following passages, different aspects of the invention are defined in more detail. Each aspect so defined may be combined with any other aspect or aspects unless clearly indicated to the contrary. In particular, any feature indicated as being preferred or advantageous may be combined with any other feature or features indicated as being preferred or advantageous.

Unless a context dictates otherwise, asterisks are used herein to indicate the point at which a mono- or bivalent radical depicted is connected to the structure to which it relates and of which the radical forms part.

As already mentioned hereinbefore, in a first aspect the present invention provides a compound of Formula (I) or a stereoisomer, tautomer, racemic, metabolite, pro-or predrug, salt, hydrate, or solvate thereof,
Wherein
\[R_1, R_2, R_3, R_4, R_5 \text{ and } R_6\] are each independently selected from the list comprising -H, -CN, -halo, -(C=0)-R, optionally substituted -O-alkyl, optionally substituted -C_2-alkenyl, optionally substituted -C_2-alkynyl, and optionally substituted -C_1-alkoxy;

\[X \text{ and } Y\] are each independently selected from the list comprising N or C;
\[Z\] is selected from the list comprising -O- and -NH-
\[R^7\] is selected from the list comprising -OR, NR, R^10;
\[R^8, R^9 \text{ and } R^{10}\] are each independently selected from the list comprising -H and C_1-alkyl; and

Wherein either
\[R^1, R^3 \text{ and } R^6\] are not -H; or
\[R^2, R^3 \text{ and } R^4\] are not -H

When describing the compounds of the invention, the terms used are to be construed in accordance with the following definitions, unless a context dictates otherwise:

The term "alkyl" by itself or as part of another context refers to fully saturated hydrocarbon radicals. Generally, alkyl groups of this invention comprise from 1 to 6 carbon atoms. Alkyl groups may be linear or branched and may be substituted as indicated herein. When a subscript is used herein following a carbon atom, the subscript refers to the number of carbon atoms that the named group may contain. Thus, for example, C_1,alkyl means an alkyl of one to six carbon atoms.

Examples of alkyl groups are methyl, ethyl, n-propyl, i-propyl, butyl, and its isomers (e.g. n-butyl, i-butyl and t-butyl); pentyl and its isomers, hexyl and its isomers. C_1-C_6 alkyl includes all linear, branched, or cyclic alkyl groups with between 1 and 6 carbon atoms, and thus includes methyl, ethyl, n-propyl, i-propyl, butyl and its isomers (e.g. n-butyl, i-butyl and t-butyl); pentyl and its isomers, hexyl and its isomers, cyclopentyl, and cyclohexyl. Optional substituents according to this invention may be selected from the non-limiting list comprising -halo, -CN, -COOH, -C(=0)OC_1.

The term "alkenyl", as used herein, unless otherwise indicated, means straight-chain, cyclic, or branched-chain hydrocarbon radicals containing at least one carbon-carbon double bond. Examples of alkyl radicals include ethenyl, E- and Z-propenyl, isopropenyl, E- and Z-buteny1, E- and Z-isobutenyl, E- and Z-pentenyl, E- and Z-hexenyl, E,E-, E,Z-, Z,E-, Z,Z-hexadienyl, and the like. An optionally substituted alkenyl refers to an alkenyl having optionally one or more substituents (for example 1, 2, 3 or 4), selected from those defined above for substituted alkyl.

The term "alkynyl", as used herein, unless otherwise indicated, means straight-chain or branched-chain hydrocarbon radicals containing at least one carbon-carbon triple bond. Examples of alkynyl radicals include ethynyl, propynyl, isopropynyl, butynyl, pentynyl, hexynyl, and the like. An optionally substituted alkynyl refers to an alkynyl having optionally one or more substituents (for example 1, 2, 3 or 4), selected from those defined above for substituted alkyl.

The term "alkoxy" or "alkyloxy" as used herein refers to a radical having the Formula -OR wherein R^b is alkyl. Preferably, alkoxy is C_1-C_10 alkoxy, C_1-C_6 alkoxy, or C_1-C_4 alkoxy. Non-limiting
examples of suitable alkoxy include methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy, pentyloxy and hexyloxy.

The term "halo" or "halogen" as a group or part of a group is generic for fluoro, chloro, bromo, or iodo, as well as any suitable isotope thereof.

Whenever the term "substituted" is used in the present invention, it is meant to indicate that one or more hydrogens on the atom indicated in the expression using "substituted" is replaced with a selection from the indicated group, provided that the indicated atom's normal valency is not exceeded, and that the substitution results in a chemically stable compound, i.e. a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into a therapeutic and/or diagnostic agent.

Where groups may be optionally substituted, such groups may be substituted once or more, and preferably once, or twice. Substituents may be selected from, those defined above for substituted alky.

As used herein the terms such as "alkyl, aryl, or cycloalkyl, each being optionally substituted with" or "alkyl, aryl, or cycloalkyl, optionally substituted with" refers to optionally substituted alkyl, optionally substituted aryl and optionally substituted cycloalkyl.

More generally, from the above, it will be clear to the skilled person that the compounds of the invention may exist in the form of different isomers and/or tautomers, including but not limited to geometrical isomers, conformational isomers, E/Z-isomers, stereochemical isomers (i.e. enantiomers and diastereoisomers) and isomers that correspond to the presence of the same substituents on different positions of the rings present in the compounds of the invention. All such possible isomers, tautomers and mixtures thereof are included within the scope of the invention.

Whenever used in the present invention the term "compounds of the invention" or a similar term is meant to include the compounds of general Formula I and any subgroup thereof. This term also refers to the compounds as depicted in Tables 2-5, their derivatives, /V-oxides, salts, solvates, hydrates, stereoisomeric forms, racemic mixtures, tautomeric forms, optical isomers, analogues, pro-drugs, esters, and metabolites, as well as their quaternized nitrogen analogues. The /V-oxide forms of said compounds are meant to comprise compounds wherein one or several nitrogen atoms are oxidized to the so-called /V-oxide.

As used in the specification and the appended claims, the singular forms "a", "an", and "the" include plural referents unless the context clearly dictates otherwise. By way of example, "a compound" means one compound or more than one compound.

The terms described above and others used in the specification are well understood to those in the art.
In a particular embodiment, the present invention provides compounds of (la) or a stereoisomer, tautomer, racemic, metabolite, pro-or predrug, salt, hydrate, or solvate thereof,

![Chemical Structure](image)

Wherein

R¹, R⁴, R⁵ and R⁶ are each independently selected from the list comprising -CN, -halo, -(C=0)-R⁷, optionally substituted -C₁₋₅alkyl, optionally substituted -C₂₋₅alkenyl, optionally substituted -C₂₋₅alkynyl, and optionally substituted -d₁₋₅alkoxy;

X and Y are each independently selected from the list comprising N or C;

Z is selected from the list comprising -O- and -NH-;

R⁸ is selected from the list comprising -OR⁹, NR⁹R¹⁰; and

R⁸, R⁹ and R¹⁰ are each independently selected from the list comprising -H and C₁₋₅alkyl.

Exemplary compounds and reaction schemes for synthesis of compounds according to this embodiment are detailed in examples 1 and 6.

In another particular embodiment, the present invention provides compounds compound of Formula (lb) or a stereoisomer, tautomer, racemic, metabolite, pro-or predrug, salt, hydrate, or solvate thereof,

![Chemical Structure](image)

Wherein

R¹, R², R⁴, and R⁸ are each independently selected from the list comprising -CN, -halo, -(C=0)-R⁷, optionally substituted -C₁₋₅alkyl, optionally substituted -C₂₋₅alkenyl, optionally substituted -C₂₋₅alkynyl, and optionally substituted -C₁₋₅alkoxy;

X and Y are each independently selected from the list comprising N or C;
Z is selected from the list comprising -O- and -NH-;
R7 is selected from the list comprising -OR8, NR9R10; and
R8, R9 and R10 are each independently selected from the list comprising -H and Ci$_g$alkyl.

Exemplary compounds and reaction schemes for synthesis of compounds according to this embodiment are detailed in tables 2-5.

In a particular embodiment, this invention provides a compound as defined herein above, wherein the optionally substituted -Ci$_g$alkyl, -C$_2$galkenyl, -C$_2$galkynyl or -Ci$_g$alkoxy as defined in any one of R1-R6 is substituted with one or more substituents selected from the list comprising -halo, -CN , and -(C=O)-R11: wherein R11 is selected from the list comprising -OR12 and -NR13R14; and wherein R12, R13 and R14 are each independently selected from the list comprising -H and Ci$_g$alkyl.

In yet another particular embodiment, the present invention provides compounds as defined herein above wherein X and Y are each N. Exemplary compounds and reaction schemes for synthesis of compounds according to this embodiment are detailed in table 5.

In still another particular embodiment, the present invention provides compounds as defined herein above wherein X and Y are each C. Exemplary compounds and reaction schemes for synthesis of compounds according to this embodiment are detailed in table 4.

In still another particular embodiment, the present invention provides compounds as defined herein above wherein X is N and Y is C. Exemplary compounds and reaction schemes for synthesis of compounds according to this embodiment are detailed in tables 2 and 3.

In a preferred embodiment, the present invention provides compounds as defined herein above wherein R4 is -CH=CH-CN. Exemplary compounds and reaction schemes for synthesis of compounds according to this embodiment are detailed in tables 2, 4 and 5.

In yet a further preferred embodiment, the present invention provides compounds as defined herein above, wherein R1 is -CN. Exemplary compounds and reaction schemes for synthesis of compounds according to this embodiment are detailed in tables 2-5.

In yet a further preferred embodiment, the present invention provides compounds as defined herein above, wherein Z is N. Exemplary compounds and reaction schemes for synthesis of compounds according to this embodiment are detailed in tables 2, 4 and 5.

In yet a further preferred embodiment, the present invention provides compounds as defined herein above, wherein Z is O. Exemplary compounds and reaction schemes for synthesis of compounds according to this embodiment are detailed in table 3.
In yet another embodiment the present invention provides the compounds of formula (I), (la) or (lb) as defined herein above, wherein one or more of the following restrictions apply:
- $R^1$, $R^2$, $R^3$, $R^4$, $R^5$ and $R^6$ are each independently selected from the list comprising hydrogen, -CN, -halo, -(C=0)-R, and optionally substituted -C$_2$H$_5$alkenyl;
- $R^1$, $R^2$, $R^3$, $R^4$, $R^5$ and $R^6$ are each independently selected from the list comprising hydrogen, -CN, -halo, -(C=0)-R, and -C$_2$H$_5$alkenyl, wherein said -C$_2$H$_5$alkenyl is optionally substituted with one or more substituent selected from the group consisting of -CN, -COOH, and -C(O)OC$_1$H$_3$alkyl; in particular a substituent selected from the group consisting of -CN and -C(O)OC$_1$H$_3$alkyl; more in particular -CN and -C(O)OC$_3$H$_7$;
- $R^7$ is -OR with $R^8$ representing -C$_1$H$_3$alkyl, in particular $R^8$ representing -CH$_3$
This invention further provides a composition comprising a compound according to this invention. Furthermore, this invention provides a compound or composition according to this invention for use as a medicament.

This invention also provides a compound or composition according to this invention for use in the prevention and/or treatment of HIV infections in a subject in need thereof. In a particular aspect this invention provides the use of a compound or composition according to this invention as a non-nucleoside reverse transcriptase inhibitor. Finally, this invention provides a method for the prevention and/or treatment of HIV infections; said method comprising administering to a subject in need thereof a compound or composition according to this invention.

**METHOD OF TREATMENT**

Compounds of formula (i), (la) and (lb) a stereoisomer, tautomer, racemic, metabolite, pro- or predrug, salt, hydrate, N-oxide form, or solvate thereof, are inhibitors of non-nucleoside reverse transcriptase inhibitor and are thus believed to be of potential use in the prevention and/or treatment of HIV infections. The methods of the present invention can be utilized in a variety of settings, including, for example, in selecting the optimal treatment course for a patient, in predicting the likelihood of success when treating an individual patient with a particular treatment regimen, in assessing disease progression, in monitoring treatment efficacy, in determining prognosis for individual patients and in assessing predisposition of an individual to benefit from a particular therapy.

For pharmaceutical use, the compounds of the invention may be used as a free acid or base, and/or in the form of a pharmaceutically acceptable acid-addition and/or base-addition salt (e.g. obtained with non-toxic organic or inorganic acid or base), in the form of a hydrate, solvate and/or complex, and/or in the form or a pro-drug or pre-drug, such as an ester. As used herein and unless otherwise stated, the term "solvate" includes any combination which may be formed by a compound of this invention with a suitable inorganic solvent (e.g. hydrates) or organic solvent, such as but not limited to alcohols, ketones, esters and the like. Such salts, hydrates, solvates, etc. and the preparation thereof will be clear to the person skilled in the art; reference is for instance made to the salts, hydrates, solvates, etc. described in US-A-6,372,778, US-A-6,369,086, US-A-6,369,087 and US-A-6,372,733.

The pharmaceutically acceptable salts of the compounds according to the invention, i.e. in the form of water-, oil-soluble, or dispersible products, include the conventional non-toxic salts or the quaternary ammonium salts which are formed, e.g., from inorganic or organic acids or bases. Examples of such acid addition salts include acetate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, methanesulfonate, 2-naphthalene-sulfonate,
nicotinate, oxalate, palmoate, pectinate, persulfate, 3-phenylpropionate, picroate, pivalate, propionate, succinate, tartrate, thiocyanate, tosylate, and undecanoate. Base salts include ammonium salts, alkali metal salts such as sodium and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, salts with organic bases such as dicyclohexylamine salts, N-methyl-D-glucamine, and salts with amino acids such as arginine, lysine, and so forth. In addition, the basic nitrogen-containing groups may be quaternized with such agents as lower alkyl halides, such as methyl, ethyl, propyl, and butyl chloride, bromides and iodides; dialkyl sulfates like dimethyl, diethyl, dibutyl; and diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides, aralkyl halides like benzyl and phenethyl-bromides and others. Other pharmaceutically acceptable salts include the sulfate salt ethanolate and sulfate salts.

Generally, for pharmaceutical use, the compounds of the inventions may be formulated as a pharmaceutical preparation or pharmaceutical composition comprising at least one compound of the invention and at least one pharmaceutically acceptable carrier, diluent or excipient and/or adjuvant, and optionally one or more further pharmaceutically active compounds. By means of non-limiting examples, such a formulation may be in a form suitable for oral administration, for parenteral administration (such as by intravenous, intramuscular or subcutaneous injection or intravenous infusion), for administration by inhalation, by a skin patch, by an implant, by a suppository, etc.. Such suitable administration forms - which may be solid, semi-solid or liquid, depending on the manner of administration - as well as methods and carriers, diluents and excipients for use in the preparation thereof, will be clear to the skilled person; reference is again made to for instance US-A-6,372,778, US-A-6,369,086, US-A-6,369,087 and US-A-6,372,733, as well as to the standard handbooks, such as the latest edition of Remington’s Pharmaceutical Sciences.

Some preferred, but non-limiting examples of such preparations include tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols, ointments, creams, lotions, soft and hard gelatin capsules, suppositories, eye drops, sterile injectable solutions and sterile packaged powders (which are usually reconstituted prior to use) for administration as a bolus and/or for continuous administration, which may be formulated with carriers, excipients, and diluents that are suitable per se for such formulations, such as lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginites, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidione, polyethylene glycol, cellulose, (sterile) water, methylcellulose, methyl- and propylhydroxybenzoates, t alc, magnesium stearate, edible oils, vegetable oils and mineral oils or suitable mixtures thereof. The formulations can optionally contain other pharmaceutically active substances (which may or may not lead to a synergistic effect with the compounds of the invention) and other substances that are commonly used in pharmaceutical formulations, such as lubricating agents, wetting agents, emulsifying and suspending agents, dispersing agents, desintegrants, bulking agents, fillers, preserving agents, sweetening agents, flavoring agents, flow regulators, release agents, etc.. The compositions may also be formulated so as to provide rapid, sustained or delayed release of the
active compound(s) contained therein, for example using liposomes or hydrophilic polymeric matrices based on natural gels or synthetic polymers. In order to enhance the solubility and/or the stability of the compounds of a pharmaceutical composition according to the invention, it can be advantageous to employ α-, β- or γ-cyclodextrins or their derivatives. An interesting way of formulating the compounds in combination with a cyclodextrin or a derivative thereof has been described in EP-A-721,331. In particular, the present invention encompasses a pharmaceutical composition comprising an effective amount of a compound according to the invention with a pharmaceutically acceptable cyclodextrin.

In addition, co-solvents such as alcohols may improve the solubility and/or the stability of the compounds. In the preparation of aqueous compositions, addition of salts of the compounds of the invention can be more suitable due to their increased water solubility.

The preparations may be prepared in a manner known per se, which usually involves mixing at least one compound according to the invention with the one or more pharmaceutically acceptable carriers, and, if desired, in combination with other pharmaceutical active compounds, when necessary under aseptic conditions. Reference is again made to US-A-6,372,778, US-A-6,369,086, US-A-6,369,087 and US-A-6,372,733 and the further prior art mentioned above, as well as to the standard handbooks, such as the latest edition of Remington's Pharmaceutical Sciences. The pharmaceutical preparations of the invention are preferably in a unit dosage form, and may be suitably packaged, for example in a box, blister, vial, bottle, sachet, ampoule or in any other suitable single-dose or multi-dose holder or container (which may be properly labeled); optionally with one or more leaflets containing product information and/or instructions for use. Generally, such unit dosages will contain between 1 and 1000 mg, and usually between 5 and 500 mg, of the at least one compound of the invention, e.g. about 10, 25, 50, 100, 200, 300 or 400 mg per unit dosage.

The compounds can be administered by a variety of routes including the oral, rectal, ocular, transdermal, subcutaneous, intravenous, intramuscular or intranasal routes, depending mainly on the specific preparation used and the condition to be treated or prevented, and with oral and intravenous administration usually being preferred. The at least one compound of the invention will generally be administered in an "effective amount", by which is meant any amount of a compound of Formula or any subgroup thereof that, upon suitable administration, is sufficient to achieve the desired therapeutic or prophylactic effect in the individual to which it is administered. Usually, depending on the condition to be prevented or treated and the route of administration, such an effective amount will usually be between 0.01 to 1000 mg per kilogram body weight day of the patient per day, more often between 0.1 and 500 mg, such as between 1 and 250 mg, for example about 5, 10, 20, 50, 100, 150, 200 or 250 mg, per kilogram body weight day of the patient per day, which may be administered as a single daily dose, divided over one or more daily doses, or essentially continuously, e.g. using a drip infusion. The amount(s) to be administered, the route of administration and the further treatment regimen may be determined by the treating clinician, depending on factors such as the age, gender and general condition of the patient and the nature and severity of the disease/symptoms to be treated. Reference is again made to US-A-6,372,778,

In accordance with the method of the present invention, said pharmaceutical composition can be administered separately at different times during the course of therapy or concurrently in divided or single combination forms. The present invention is therefore to be understood as embracing all such regimes of simultaneous or alternating treatment and the term "administering" is to be interpreted accordingly.

For an oral administration form, the compositions of the present invention can be mixed with suitable additives, such as excipients, stabilizers, or inert diluents, and brought by means of the customary methods into the suitable administration forms, such as tablets, coated tablets, hard capsules, aqueous, alcoholic, or oily solutions. Examples of suitable inert carriers are gum arabic, magnesia, magnesium carbonate, potassium phosphate, lactose, glucose, or starch, in particular, corn starch. In this case, the preparation can be carried out both as dry and as moist granules.

Suitable oily excipients or solvents are vegetable or animal oils, such as sunflower oil or cod liver oil. Suitable solvents for aqueous or alcoholic solutions are water, ethanol, sugar solutions, or mixtures thereof. Polyethylene glycols and polypropylene glycols are also useful as further auxiliaries for other administration forms. As immediate release tablets, these compositions may contain microcrystalline cellulose, dicalcium phosphate, starch, magnesium stearate and lactose and/or other excipients, binders, extenders, disintegrants, diluents and lubricants known in the art.

In preferred embodiments, the compounds and compositions of the invention are used orally or parenterally.

The invention will now be illustrated by means of the following synthetic and biological examples, which do not limit the scope of the invention in any way.

EXAMPLES

Example 1: General synthesis route of DAFPY compounds (DiAminoarvlFluoroPYridines)

DAFPY analogues with -NH- linker at the western ring

Synthesis of compounds from the DAFPY series can be achieved in 2 steps starting from the commercial 2,6-dichloro-3-fluoropyridine (1) and the corresponding anilines (see reaction scheme 1). Our innovative synthesis is based on the regioselective Pd-catalyzed amination reaction (generally known as Buchwald-Hartwig amination) of commercial 2,6-dichloro-3-fluoropyridine (1). In the first step, reaction of 1 with an aniline 2 produced the intermediate 2-arylamino-6-chloro-3-fluoropyridines 3. Optimization of the catalytic system (Pd source, ligand, basic additive) was performed for the reaction between 1 and 2a to give 3a and the results are summarized in the Table 1.
As evident from Table 1, the choice of ligand is crucial, and Xantphos produced the best results in combination with t-BuONa as a base and Pd(OAc)_2 as a metal source. This combination was subsequently applied for the synthesis of other intermediates 2-arylamino-6-chloro-3-fluoropyridines 3b-d (Scheme 1). It is further essential to stress that the reaction proceeds in a perfectly regioselective manner: only substitution at position 2, and no substitution at position 6 is observed (as confirmed by the single crystal XRD structure of 3a (not shown)). Further, also no two-fold substitution (both at position 2 and position 6) is observed.

**Scheme 1. Synthesis of intermediates 3.**

In the second step, another Pd-catalyzed amination reaction of the intermediate 3 with a different aniline 4 provided the target DAFPY compounds (Scheme 2). The second amination step required a choice of different ligands than the first amination. It was found that XPhos ligand provided the best results.
Scheme 2. Synthesis of DAFPY compounds.

3a R¹ = CN
3b R¹ = Cl
3c R¹ = F
3d R¹ = CH=CH-CN

Table 2: DAFPY Compounds according to this invention

<table>
<thead>
<tr>
<th>Cpd</th>
<th>R¹</th>
<th>R²</th>
<th>R³</th>
<th>R⁴</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAFPY-0</td>
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<td>Me</td>
<td>Me</td>
<td>53</td>
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<td>CN</td>
<td>61</td>
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<td>Me</td>
<td>Me</td>
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<td>Cpd</td>
<td>R¹</td>
<td>R²</td>
<td>R³</td>
<td>R⁴</td>
<td>Yield (%)</td>
</tr>
<tr>
<td>----------</td>
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<td>CH=CHCOOMe</td>
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<td>F</td>
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<td>Me</td>
<td>CH=CHCN</td>
<td>72</td>
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</table>

Some anilines used in the synthesis of the DAFPY compounds were commercially available, such as 4-cyano, 4-fluoro and 4-chloro anilines (2a-c). Other anilines were prepared from commercial precursors via a Heck coupling with the corresponding bromo derivatives 5. The latter were commercially available with the exception of 4-bromo-2-fluoro-6-methylaniline 5d, which was prepared by bromination of commercially available 2-fluoro-6-methylaniline (Scheme 3).
Scheme 3. Synthesis of the aniline reagents.

5a \[ \text{R}^2 = \text{R}^3 = \text{Me}, 80\% \]
5b \[ \text{R}^2 = \text{H}, \text{R}^3 = \text{Me}, 74\% \]
5c \[ \text{R}^2 = \text{Cl}, \text{R}^3 = \text{Me}, 72\% \]
5d \[ \text{R}^2 = \text{F}, \text{R}^3 = \text{Me}, 89\% \]
5e \[ \text{R}^2 = \text{R}^3 = \text{H}, 63\% \]
5f \[ \text{R}^2 = \text{R}^3 = \text{F}, 29\% \]

**DAFPY analogues with -O- linker at the western ring**

Similarly to the synthesis of DAFPY compounds described above, DAFPY analogues featuring an O rather than an NH linkage between western and central rings were prepared using a Pd-catalyzed C-O bond formation reaction of 3a with phenol and 2,4,6-trimethylphenol, respectively, instead of an aniline (Scheme 4).
Scheme 4. Synthesis of DAFPY analogues featuring an N linker at the 6 position of the pyridine ring.

3a

Table 3: DAFPY Compounds according to this invention

<table>
<thead>
<tr>
<th>Cpd</th>
<th>R¹</th>
<th>R²</th>
<th>R³</th>
<th>R⁴</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAFPY-11</td>
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<td>H</td>
<td>H</td>
<td>Me</td>
<td>89</td>
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<td>DAFPY-12</td>
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<td>Me</td>
<td>Me</td>
<td>43</td>
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</tbody>
</table>

Example 2: General synthesis route of DAFB compounds (DiAminoarylFluoroBenzenes)

DAFB compounds according to this invention were prepared, starting from commercially available 2-bromo-4-chloro-1-fluorobenzene (6), as shown below (Scheme 5) and is based on the difference in reactivities of a bromine atom and a chlorine atom in Pd-catalyzed amination reactions. In the first step, the bromine atom in 6 was selectively substituted to produce 4-(5-chloro-2-fluorophenylamino)benzonitrile (7). In the second amination reaction, the chlorine in 7 was substituted to produce the DAFB derivatives.
Synthesis of di(arylamino)fluorobenzene derivatives (DAFB).

Scheme 5: Synthesis of di(arylamino)fluorobenzene derivatives (DAFB).

Table 4: DAFB Compounds according to this invention

<table>
<thead>
<tr>
<th>Cpd</th>
<th>R¹</th>
<th>R²</th>
<th>R³</th>
<th>R⁴</th>
<th>Yield (%)</th>
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</thead>
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<td>CN</td>
<td>Me</td>
<td>F</td>
<td>CH=CHCN</td>
<td>59</td>
</tr>
<tr>
<td>DAFB-3</td>
<td>CN</td>
<td>Me</td>
<td>H</td>
<td>CH=CHCN</td>
<td>41</td>
</tr>
</tbody>
</table>

Example 3: General synthesis route of DAFPYM compounds (DiAminoarylFluoroPYriMidines)

In this example, we describe the preparation of DAFPY analogues featuring a pyrimidine as central ring, this series of compounds will be referred to as DAFPYM. Two derivatives have been prepared via a route which is similar to that for the DAFPYs (pyridine series described above). In the first step, reaction of 2,4-dichloro-5-fluoropyrimidine (8) with 4-aminobenzonitrile 2a produced the intermediate 2-arylamino-6-chloro-3-fluoropyridine 9 as a single regioisomer. A second Pd-catalyzed amination reaction with the corresponding aniline provided the target DAFPYM-1 and DAFPYM-2 (Scheme 6).

Example 4: General synthesis route of Defluorinated DAFPY compounds (def-DAFPY)

Synthesis of a reference compounds lacking a fluorine, (e.g. def-DAFPY-2), was performed starting from commercially available 2,6-dichloropyridine as shown in Scheme 7 below. In order to clearly evaluate the benefits of the fluorine atom in the 3-position of the pyridine ring, the synthesis of a few more de-fluorinated analogues of highly active compounds of all 3 series (DAFPY, DAFB and DAFPYM) will be performed.
Scheme 7. Synthesis of the reference "deF-DAFPY" compounds.

Table 6: deF-DAFPY reference Compounds

<table>
<thead>
<tr>
<th>Cpd</th>
<th>R¹</th>
<th>R²</th>
<th>R³</th>
<th>R⁴</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>deF-DAFPY-0</td>
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<td>Me</td>
<td>Me</td>
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<td>deF-DAFPY-1</td>
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<td>Me</td>
<td>Me</td>
<td>CN</td>
<td>20</td>
</tr>
<tr>
<td>deF-DAFPY-2</td>
<td>CN</td>
<td>Me</td>
<td>Me</td>
<td>CH=CHCN</td>
<td>66</td>
</tr>
<tr>
<td>deF-DAFPY-10</td>
<td>CN</td>
<td>Me</td>
<td>F</td>
<td>CH=CHCN</td>
<td>71</td>
</tr>
</tbody>
</table>

Example 5: In vitro screening against wild type and/or mutant HIV and cytotoxicity.

Activity and cytotoxicity of DAFPYs and their analogues.

Antiviral Assay

Cells

The JC53-BL cell line, also known as the TZM-bl cell line (NIH AIDS Research and Reference Reagent Program, Germantown, USA), was used for the evaluation of drug susceptibility of wild type. TZM-bl cells were cultured in Dulbecco's Minimum Essential Medium (DMEM) (Lonza) containing 10% heat-inactivated FBS and 50 μg gentamycin/mL at 37°C in a humidified 5% CO2, 95% air environment. Twice a week the cells were treated with 0.25% trypsin - 1 mM EDTA (Lonza) for 10 minutes. The resulting cell suspension was washed with an equivalent amount of TZM-bl medium and subsequently seeded in a T75 culture flask (Greiner Bio-One, Germany) at 106 cells in 20 mL medium.
**TZM-bl assay**

The antiviral activity of the newly designed compounds was measured by pre-incubating ten thousand TZM-bl cells (at 105 cells/mL in culture medium supplemented with 30μg/mL DEAE dextran) in a 96-well plate for 30 minutes at 37°C, 5% CO2 in the presence or absence of serial dilutions of the respective compound. Subsequently, 200 TCID50 of wild type or NNRTI-resistant HIV-1 was added to each well and cultures were incubated for 48 hours before quantifying luciferase activity. Each condition was evaluated in triplicate wells and in at least three independent experiments. The antiviral activity of the compound was expressed as the percentage of viral inhibition compared to the untreated controls and subsequently plotted against the compound concentration. Non-linear regression analysis was used to calculate the 50% inhibitory concentration (IC50) based on at least three independent measurements and using GraphPad Prism version 5.03 for Windows (GraphPad Software, San Diego, CA, USA).

**WST-1 cytotoxicity assay**

The Water Soluble Tetrazolium-1 (WST-1) Cell Proliferation Assay is a colorimetric assay for the measurement of cell proliferation and viability. The assay is based on the cleavage of the tetrazolium salt WST-1 ((4-[3-(4-iodophenyl)-2-(4-nitrophenyl)-2H-5-tetrazolio]-1,3-benzene disulfonate)) to a formazan dye by a complex cellular mechanism. This bioreduction is largely dependent on the glycolytic production of NAD(P)H in viable cells. Therefore, the amount of formazan dye formed correlates directly to the number of viable cells in the culture, and can be quantified by measuring the absorbance at 450nm in a multiwell plate reader. The greater the number of viable cells, the greater the amount of formazan dye produced following the addition of WST-1. Cytotoxicity of each compound was evaluated using this WST-1 viability assay, according to the manufacturer's instructions (Roche, Vilvoorde, Belgium).

Briefly, ten thousand TZM-bl cells were seeded in a 96-well plate and cultured for 2 days in the presence of a serial dilution of compound. After this 48h exposure, Cell Proliferation Reagent, WST-1, was added and absorbance at 450 nm was quantified after 90 min using a microplate reader (BioRad, Tokio, Japan). Each compound was tested in three replicate wells and in at least three independent experiments. The percentage cell viability, compared to untreated controls, was plotted against the compound concentration and non-linear regression analysis was performed using GraphPad Prism version 5.02 for Windows (GraphPad Software, San Diego, CA, USA) to calculate the 50% cytotoxic concentration (CC50).

**Activity and cytotoxicity results**

The details on the activity against wild type HIV and cytotoxicity are summarized in the table below. Results for structurally related NNRTI Dapivirine (TMC-120) are included for the sake of comparison.
Table 7: Activity and cytotoxicity of DAFPY compounds

<table>
<thead>
<tr>
<th>Name</th>
<th>Z</th>
<th>R¹</th>
<th>R²</th>
<th>R³</th>
<th>R⁴</th>
<th>EC₅₀, nmol</th>
<th>SI *</th>
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<tr>
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<td></td>
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</tr>
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<td>DAFPY-0</td>
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* The selectivity index (SI) is defined as $CC_{50}/EC_{50}$, where $EC_{50}$ is the 50%-effective concentration vs. HIV virus, and $CC_{50}$ is the concentration causing death of 50% of the cells. The $EC_{50}$ value was determined in Ba-L (subtype B, CCR5) cells and the cytotoxicity $CC_{50}$ value in WST-1 cells.

The conclusion is that the best of compounds in the class (DAFPY-2, DAFPY-10) display activity equal to or slightly superior to that of TMC-120, while selectivity index of DAFPY-2 and DAFPY-10 is improved by a factor of 30-50 vs TMC-120.
Activity and cytotoxicity of DAFB Compounds

![Chemical structure of DAFB compounds](image)

Table 8: Activity and cytotoxicity of DAFB compounds

<table>
<thead>
<tr>
<th>Name</th>
<th>Z</th>
<th>R¹</th>
<th>R²</th>
<th>R³</th>
<th>R⁴</th>
<th>EC₅₀</th>
<th>SI</th>
</tr>
</thead>
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<tr>
<td>DAFB-1</td>
<td>NH</td>
<td>CN</td>
<td>Me</td>
<td>Me</td>
<td>CH=CHCN</td>
<td>4.5</td>
<td>7400</td>
</tr>
<tr>
<td>DAFB-2</td>
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<td>Me</td>
<td>F</td>
<td>CH=CHCN</td>
<td>11</td>
<td>6100</td>
</tr>
<tr>
<td>DAFB-3</td>
<td>NH</td>
<td>CN</td>
<td>Me</td>
<td>H</td>
<td>CH=CHCN</td>
<td>58</td>
<td>89</td>
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</table>

Activity and cytotoxicity of DAFPYM Compounds

![Chemical structure of DAFPYM compounds](image)

Table 9: Activity and cytotoxicity of DAFPYM compounds

<table>
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<tr>
<th>Name</th>
<th>Z</th>
<th>R¹</th>
<th>R²</th>
<th>R³</th>
<th>R⁴</th>
<th>EC₅₀</th>
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</tr>
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<tr>
<td>DAFPYM-1</td>
<td>NH</td>
<td>CN</td>
<td>Me</td>
<td>Me</td>
<td>CN</td>
<td>2.8</td>
<td>&gt; 36000</td>
</tr>
<tr>
<td>DAFPYM-2</td>
<td>NH</td>
<td>CN</td>
<td>Me</td>
<td>Me</td>
<td>CH=CHCN</td>
<td>0.9</td>
<td>&gt; 42000</td>
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</tbody>
</table>

Activity and cytotoxicity of deF-DAFPY analogues (lacking the C3 fluorine)

![Chemical structure of deF-DAFPY analogues](image)
In order to evaluate the benefits of the fluorine atom in the 3-position of the pyridine ring, a few reference compounds lacking the fluorine have been synthesized (*vide supra*). In all cases studied so far fluorine does indeed bring advantages, both improving activity (smaller $EC_{50}$ values) and reducing cytotoxicity (larger SI values). In case of DAFPY-10 vs deF-DAFPY-10 this effect is the most pronounced: an increase of activity by ca. a factor of 6 and of the SI by ca. a factor of 20 due to a presence of an F atom.

**Activity and cytotoxicity of DAFPY analogues against mutant strains of HIV-1 virus.**

*The $EC_{50}$ values were determined in V1829 (subtype C, CCR5)*

The data for 4 compounds of the DAFPY series show that the activity of the best of the investigated molecules (DAFPY-2, DAFPY-10) is approximately equal to or higher than that of TMC 120 for all strains (WT, single and double mutant). Further comparison of 3 of compounds with their defluorinated (deF-DAFPY) analogues clearly reveals for every pair of DAFPY/deF-DAFPY compounds higher activity of DAFPY and thus underlines advantages of having an F atom on the Central ring.

**Example 6:** Detailed synthesis schemes of compounds according to this invention

**General Procedure for synthesis of anilines 4 (General Procedure A):** Stock solution of 5 mol% Pd catalyst was prepared. For the preparation of 5 mol% Pd/L, a flask was charged with Pd(OAc)$_2$ (0.2 mmol, 45 mg) and tri(o-tolyl)phosphine (0.4 mmol, 0.122 g). Further, dry DMA (4
mL) was added to the flask. The solution was subsequently stirred for 15 minutes under an argon atmosphere.

Next, a 100 mL round bottomed flask was charged with 4-bromoaniline (4 mmol), acrylonitrile (6.0 mmol, 0.32 g), tetrabutylammoniumchloride (4.0 mmol, 1.12 g) and CH₃COONa.3H₂O (4.0 mmol, 0.54 g). Further, freshly prepared stock solution was added to the round bottomed flask and that flask was rinsed with 4 mL dry DMA and added to the round bottomed flask. The resulting solution was stirred for two minutes under an argon atmosphere. The round bottomed flask was kept in 140 °C preheated oil bath and reaction mixture was refluxed for 48 h. After that round bottomed flask was allowed to cool down to room temperature and reaction mixture was filtered through celite on glass filter and washed with 100 mL toluene and the filtrate was washed with 100 mL water and 50 mL brine solution and dried with MgSO₄. The organic phase was evaporated to dryness under reduced pressure and the residue separated with an automated chromatography system using Silica Flash Cartridges applying a heptane-ethyl acetate gradient (from 100% heptane to 80% ethylacetate in 35 minutes, 35 mL/min).

3-(4-Amino-3-chloro-5-methylphenyl)acrylonitrile (4c): The general procedure A was followed using Pd(OAc)₂ (0.20 mmol, 45 mg), tri(o-tolyl)phosphine (0.40 mmol, 0.12 g), 4-bromo-2-chloro-6-methylaniline (4.0 mmol, 0.88 g), acrylonitrile (6.0 mmol, 0.32 g), tetrabutylammoniumchloride (4.0 mmol, 1.12 g) and CH₃COONa.3H₂O (4.0 mmol, 0.54 g). Obtained as a mixture of geometrical isomers (cis:trans; 1:3.3), light yellow solid; yield 73% (0.56 g); mp 131.1-132 °C; ¹H NMR (400 MHz, CDCl₃): signals of major (E)-isomer: δ 2.20 (s, 3H), 4.39 (brs, 2H), 5.61 (d, J = 16.5 Hz, 1H), 7.05 (d, J = 1.8 Hz, 1H), 7.17 (d, J = 16.5 Hz, 1H), 7.24 (d, J = 1.8 Hz, 1H), signals of minor (Z)-isomer: δ 2.22 (s, 3H), 5.18 (d, J = 12.1 Hz, 1H), 6.86 (d, J = 12.1 Hz, 1H), 7.53 (d, J = 1.8 Hz, 1H), 7.60 (d, J = 1.8 Hz, 1H), signal of NH overlapped with the signal of major isomer;

3-(4-Amino-3-fluoro-5-methylphenyl)acrylonitrile (4d): The general procedure A was followed using Pd(OAc)₂ (0.16 mmol, 36 mg), tri(o-tolyl)phosphine (0.32 mmol, 97 mg), 4-bromo-2-fluoro-6-methylaniline (3.19 mmol, 0.65 g), acrylonitrile (4.78 mmol, 0.25 g), tetrabutylammoniumchloride (3.19 mmol, 0.86 g) and CH₃COONa.3H₂O (3.19 mmol, 0.43 g). Obtained as a mixture of geometrical isomers (cis:trans; 1:3.3), light yellow solid; yield 89% (0.049 g); mp 98.1-00 °C; ¹H NMR (400 MHz, CDCl₃): signals of major (E)-isomer: δ 2.19 (s, 3H), 4.03 (brs, 2H), 5.60 (d, J = 16.5 Hz, 1H), 6.94 (s, 1H), 6.99 (dd, J = 11.4 Hz, 1.6 Hz, 1H), 7.19 (d, J = 16.5 Hz, 1H); signals of minor (Z)-isomer: δ 2.21 (s, 0.72H), 5.19 (d, J = 12.1 Hz, 1H), 6.88 (d, J = 12.1 Hz, 1H), 7.29 (s, 1H), 7.47 (dd, J = 11.8 Hz, 1.6 Hz, 1H), signal of NH overlapped with the signal of major isomer.

3-(4-Amino-3,5-difluorophenyl)acrylonitrile (4l): The general procedure A was followed using Pd(OAc)₂ (0.25 mmol, 56 mg), tri(o-tolyl)phosphine (0.5 mmol, 152 mg), 4-bromo-2,6-difluoroaniline (5.0 mmol, 1.04 g), acrylonitrile (7.5 mmol, 0.398 g), tetrabutylammoniumchloride (5.0 mmol, 1.39 g) and CH₃COONa.3H₂O (5.0 mmol, 0.680 g). Obtained as a mixture of
geometrical isomers (cis:trans; 1:3.1 3), white solid; yield 69% (0.62 g); mp 173-174 °C; 1H NMR (400 MHz, CDCl₃): signals of major (E)-isomer: δ 4.09 (brs, 2H), 5.64 (d, J = 16.5 Hz, 1H), 6.95 (dd, J = 7.0 Hz, 2.2 Hz, 2H), 7.18 (d, J = 16.5 Hz, 1H); signals of minor (Z)-isomer: δ 5.29 (d, J = 12.1 Hz, 1H), 6.87 (d, J = 12.1 Hz, 1H), 7.36 (dd, J = 7.3 Hz, 2.2 Hz, 2H).

(E)-Methyl 3-(4-amino-3,5-dimethylphenyl)acrylate (4g): The general procedure A was followed using Pd(OAc)₂ (0.2 mmol, 45 mg), tri(o-tolyl)phosphene (0.4 mmol, 122 mg), 4-bromo-2,6-dimethylaniline (4.0 mmol, 0.800 g), methylacrylate (6.0 mmol, 0.52 g), tetrabutylammoniumchloride (4.0 mmol, 1.11 g) and CH₂COONa.3H₂O (4.0 mmol, 0.544 g). White solid; yield 61% (0.49 g); mp 83-84 °C; 1H NMR (400 MHz, CDCl₃): δ 2.17 (s, 3H), 3.77 (s, 3H), 3.86 (brs, 2H), 6.23 (d, J = 15.9 Hz, 1H), 7.14 (s, 2H), 7.57 (d, J = 15.9 Hz, 1H).

General Procedure B for the Synthesis of intermediates 3, 7, 9, 11: Stock solution of 5 mol% Pd catalyst in dioxane was prepared as follows. A flask was charged with Pd(OAc)₂ (0.025 mmol, 5.6 mg) and Xantphos (0.03 mmol, 17 mg); dry dioxane (5 mL) was added and the resulting solution was stirred for 15 min under an argon atmosphere. Next, a 50 mL round bottomed flask was charged with 2,5-dichloro-5-fluoropyridine (0.5 mmol, 83 mg), an aniline 2 (0.6 mmol) and t-BuONa (0.7 mmol, 67 mg). Freshly prepared stock solution of Pd catalyst was added and the resulting solution was stirred for 2 min under an argon atmosphere. The round bottomed flask was kept in 110 °C preheated oil bath and reaction mixture was refluxed for 16 h, then allowed to cool down to room temperature and filtered through Celite. Celite cake was washed with 100 mL dichloromethane, combined organic phases were evaporated to dryness under reduced pressure and the residue separated with an automated chromatography system using Silica Flash Cartridges applying a heptane-ethyl acetate gradient (from 100% heptane to 100% ethylacetate in 35 minutes, 35 mL/min).

4-[(6-Chloro-3-fluoropyridin-2-yl)amino]benzonitrile (3a): The general procedure B was followed using Pd(OAc)₂ (0.025 mmol, 5.61 mg) and Xantphos (0.03 mmol, 17 mg), 2,5-dichloro-5-fluoropyridine (0.5 mmol, 83 mg), 4-aminobenzonitrile (0.6 mmol, 71 mg) and i-BuONa (0.7 mmol, 67 mg). Obtained as white solid, yield 89% (0.11 g); mp 171-172 °C; 1H NMR (400 MHz, CDCl₃): δ 6.83 (dd, J = 8.4 Hz, 2.8 Hz, 1H), 6.87 (brs, 1H), 7.31 (dd, J = 10.0 Hz, 8.4 Hz, 1H), 7.57 (d, J = 8.8 Hz, 2H), 7.77 (d, J = 8.8 Hz, 2H).
6-Chloro-3-fluoro-\(V\)-(4-fluorophenyl)pyridin-2-amine (3b): The general procedure B was followed using Pd(OAc)\(_2\) (0.25 mmol, 56 mg), Xantphos (0.30 mmol, 0.17 g), 2,5-dichloro-5-fluoropyridine (5.0 mmol, 0.83 g), 4-fluoroaniline (6.0 mmol, 0.58 mL) and i-BuONa (7.0 mmol, 0.67 g). Obtained as white solid; yield 88% (1.06 g); mp 87-88 °C; \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 6.56 (2H), 6.69 (dd, \(J_1 = 8.2\) Hz, 2.7 Hz, 1H), 7.26 (dd, \(J = 8.6\) Hz, 8.6 Hz, 2H), 7.22 (dd, \(J = 10.2\) Hz, 8.2 Hz, 1H), 7.58 (dd, \(J = 9.1\) Hz, 4.7 Hz, 2H).

6-Chloro-A\(\sim\)-(4-chlorophenyl)-3-fluoropyridin-2-amine (3c): The general procedure B was followed using Pd(OAc)\(_2\) (0.30 mmol, 68 mg), Xantphos (0.36 mmol, 0.21 g), 2,5-dichloro-5-fluoropyridine (6.02 mmol, 1.0 g), 4-chloroaniline (7.23 mmol, 0.92 g) and i-BuONa (8.43 mmol, 0.81 g), white solid; yield 74% (1.12 g); mp 89-90 °C; \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 6.63 (2H), 6.74 (dd, \(J = 8.0\) Hz, 2.7 Hz, 1H), 7.26 (dd, \(J = 10.0\) Hz, 8.0 Hz, 1H), 7.32 (d, \(J = 8.9\) Hz, 2H), 7.61 (d, \(J = 8.9\) Hz, 2H).

3-[4-(6-Chloro-3-fluoropyridin-2-yl)amino]phenyl]acrylonitrile (3d): The general procedure B was followed using Pd(OAc)\(_2\) (0.05 mmol, 11.0 mg) and Xantphos (0.06 mmol, 34 mg), 2,6-dichloro-3-fluoropyridine (1.0 mmol, 166 mg), 3(4-aminophenyl)acrylonitrile (1.0 mmol, 144 mg) and Na/BuO\(\sim\) (1.4 mmol, 135 mg). Obtained as a mixture of geometrical isomers (cis:trans: 1:9), light yellow solid; yield 74% (0.15 g); mp 179-170 °C; \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 6.57 (2H), 6.78 (dd, \(J = 8.2\) Hz, 2.8 Hz, 1H), 6.83 (brs, 1H), 7.28 (dd, \(J = 9.9\) Hz, 8.2 Hz, 1H), 7.34 (d, \(J = 16.6\) Hz, 1H), 7.44 (d, \(J = 8.7\) Hz, 2H), 7.71 (d, \(J = 8.7\) Hz, 2H).

Methyl 4-[6-chloro-3-fluoropyridin-2-yl)amino]benzoate (3e): The general procedure B was followed using Pd(OAc)\(_2\) (0.1 mmol, 22 mg), xantphos (0.120 mmol, 0.069 g), 2,5-dichloro-5-fluoropyridine (2.0 mmol, 0.332 g), methyl 4-aminobenzoate (2.0 mmol, 0.302 g) and Cs\(_2\)CO\(_3\) (10.0 mmol, 3.26 g). white solid; yield 66% (0.367 g); mp 159-160 °C; \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 3.89 (s, 3H), 6.78 (dd, \(J = 8.2\) Hz, 2.8 Hz, 1H), 6.83 (brs, 1H), 7.27 (dd, \(J = 8.2\) Hz, 9.9 Hz, 1H), 7.71 (d, \(J = 8.8\) Hz, 2H), 8.02 (d, \(J = 8.8\) Hz, 2H).

4-[6-Chloro-3-fluoropyridin-2-yl)amino]-3,5-dimethylbenzonitrile (3f): The general procedure B was followed using Pd(OAc)\(_2\) (0.1 mmol, 22 mg), xantphos (0.120 mmol, 0.069 g), 2,5-dichloro-5-fluoropyridine (2.0 mmol, 0.332 g), 4-amino-3,5-dimethylbenzonitrile (2.0 mmol, 0.292 g) and Cs\(_2\)CO\(_3\) (10.0 mmol, 3.26 g). white solid; yield 56% (0.308 g); mp 174-175 °C; \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 2.25 (s, 6H), 6.06 (brs, 1H), 6.66 (dd, \(J = 8.2\) Hz, 2.8 Hz, 1H), 7.24 (dd, \(J = 10.1\) Hz, 8.2 Hz, 1H), 7.39 (s, 2H).

6-Chloro-3-fluoro-A\(\sim\)-mesitylpyridin-2-amine (3g): The general procedure B was followed using Pd(OAc)\(_2\) (0.1 mmol, 22 mg), xantphos (0.120 mmol, 0.069 g), 2,5-dichloro-5-fluoropyridine (2.0 mmol, 0.332 g), 2,4,6-trimethylaniline (2.0 mmol, 0.332 g) and Cs\(_2\)CO\(_3\) (10.0 mmol, 3.26 g). white
solid; yield 78% (0.41 g); mp 126-127 °C; 1H NMR (400 MHz, CDCl₃): δ 2.19 (s, 6H), 2.29 (s, 3H), 5.92 (brs, 1H), 6.54 (dd, J = 8.1 Hz, 2.7 Hz, 1H), 6.92 (s, 2H), 7.15 (dd, J = 10.3 Hz, 8.1 Hz, 1H).

4-[(5-Chloro-2-fluorophenyl)amino]benzonitrile (7): The general procedure B was followed using Pd(OAc)₂ (0.025 mmol, 5.61 mg), Xantphos (0.06 mmol, 17 mg), 2-bromo-4-chloro-1-fluorobenzene (0.5 mmol, 0.11 g), 4-aminobenzonitrile (0.5 mmol, 59 mg) and f-BuONa (0.7 mmol, 67 mg). Obtained as white solid; yield 86% (0.107 g); mp 141-142 °C; 1H NMR (400 MHz, CDCl₃): δ 6.04 (brs, 1H), 6.96 (dd, J = 8.8, 4.3 Hz, 2.5 Hz, 1H), 7.00-7.10 (m, 3H), 7.35 (dd, J = 7.2 Hz, 2.5 Hz, 1H), 7.54 (d, J = 8.8 Hz, 2H).

4-[(2-Chloro-5-fluoropyrimidin-4-yl)amino]benzonitrile (9): Stock solution of 5 mol% Pd catalyst in dioxane was prepared as follows. A flask was charged with Pd(OAc)₂ (0.25 mmol, 56 mg) and Xantphos (0.3 mmol, 0.17 g), dry dioxane (10 mL) was added and the resulting solution was stirred for 15 min under an argon atmosphere.

Next, a 100 mL round bottomed flask was charged with 2,4-dichloro-5-fluoropyrimidine (5 mmol, 0.84 g), 4-aminobenzonitrile (5 mmol, 0.59 g) and Cs₂CO₃ (25 mmol, 0.84 g). The freshly prepared stock solution of Pd catalyst in dioxane was added, the flask containing catalyst was rinsed by dioxane (50 mL) which was also added to the reaction mixture, and the resulting solution was stirred for 2 min under an argon atmosphere. The round bottomed flask was kept in 110 °C preheated oil bath and reaction mixture was refluxed for 16 h, then allowed to cool down to room temperature and filtered through Celite. Celite cake was washed with 100 mL dichloromethane, combined organic phases were evaporated to dryness under reduced pressure and the residue separated with an automated chromatography system using Silica Flash Cartridges applying a heptane-ethyl acetate gradient (from 100% heptane to 100% ethylacetate in 35 minutes, 35 mL/min).

Obtained as white solid; yield 75% (0.93 g); mp 235-236 °C; 1H NMR (400 MHz, CDCl₃): δ 7.12 (s, 1H), 7.69 (d, J = 8.8 Hz, 2H), 7.83 (d, J = 8.8 Hz, 2H), 8.18 (d, J = 2.5 Hz, 1H).

4-[(6-Chloropyridin-2-yl)amino]benzonitrile (11): Stock solution of 2 mol% Pd catalyst in toluene was prepared as follows. A flask was charged with Pd(OAc)₂ (0.1 mmol, 22 mg) and BINAP (0.1 mmol, 62 mg), dry toluene (10 mL) was added and the resulting solution was stirred for 15 min under an argon atmosphere.

Next, a 100 mL round bottomed flask was charged with 2,5-dichloro-pyridine (5 mmol, 0.74 g), 4-aminobenzonitrile (5 mmol, 0.71 g) and K₂CO₃ (0.1 mol, 13.8 g). The freshly prepared stock solution of Pd catalyst in toluene was added, the flask containing catalyst was rinsed with toluene (50 mL) which was also added to the reaction mixture, and the resulting mixture was stirred for 2 min under an argon atmosphere, then placed in the preheated oil bath (120 °C) and refluxed for 16 h, then allowed to cool down to room temperature and filtered through Celite. Celite cake was washed with dichloromethane (100 mL), combined organic phases were evaporated to dryness under reduced pressure and the residue was separated with an automated chromatography system using Silica Flash Cartridges applying a heptane-ethyl acetate gradient (from 100% heptane to 100% ethylacetate in 35 minutes, 35 mL/min).

Obtained as white solid; yield 86% (0.206 g); mp 145-146 °C; 1H NMR (400 MHz, CDCl₃): δ 2.29 (s, 3H), 5.92 (brs, 1H), 6.54 (dd, J = 8.1 Hz, 2.7 Hz, 1H), 6.92 (s, 2H), 7.15 (dd, J = 10.3 Hz, 8.1 Hz, 1H).
system using Silica Flash Cartridges applying a heptane-ethyl acetate gradient (from 100% heptane to 100% ethylacetate in 35 minutes, 35 mL/min). Obtained as white solid; yield 60% (0.28 g); mp 182-183 °C; 1H NMR (400 MHz, DMSO-d6): δ 6.87 (d, J = 8.0 Hz, 1H), 6.91 (d, J = 8.0 Hz, 1H), 7.65 (t, J = 8.0 Hz, 1H), 7.69 (d, J = 8.9 Hz, 2H), 7.77 (d, J = 8.9 Hz, 2H), 9.85 (brs, 1H).

5

General Procedure C for the Synthesis of DAFPY NNRTI: Stock solution of 5 mol% Pd catalyst in dioxane was prepared as follows. A flask was charged with Pd(OAc)2 (0.025 mmol, 5.61 mg) and X-phos (0.03 mmol, 14 mg), dry dioxane (5 mL) was added and the resulting solution was stirred for 15 min under an argon atmosphere.

Next, a 50 mL round bottomed flask was charged with an intermediate 3 (0.5 mmol, 124 mg), an aniline 2 or 4 (0.6 mmol) and Cs2CO3 (1.25 mmol, 0.41 g). Freshly prepared stock solution of Pd catalyst was added and the resulting solution was stirred for 2 min under an argon atmosphere. The round bottomed flask was kept in 110 °C preheated oil bath and reaction mixture was refluxed for 16 h, then allowed to cool down to room temperature and filtered through Celite. Celite cake was washed with 100 mL dichloromethane, combined organic phases were evaporated to dryness under reduced pressure and the residue separated with an automated chromatography system using Silica Flash Cartridges applying a heptane-ethyl acetate gradient (from 100% heptane to 100% ethylacetate in 35 minutes, 35 mL/min).

20 4-[6-(Mesitylamino)-3-fluoropyridin-2-yl]aminobenzonitrile (DAFPY-0): The general procedure C was followed using Pd(OAc)2 (0.025 mmol, 5.6 mg), X-phos (0.03 mmol, 14 mg), 4-(6-chloro-3-fluoropyridin-2-yl-amino)benzonitrile 3a (0.5 mmol, 124 mg), 24,6-trimethylaniline (0.6 mmol, 81 mg) and Cs2CO3 (1.25 mmol, 408 mg). Obtained as white solid; yield 53% (91 mg); mp 201-202 °C; 1H NMR (400 MHz, DMSO-d6): δ 2.07 (s, 6H), 2.67 (s, 3H), 5.86 (br, 1H), 6.93 (s, 2H), 7.31 (dd, J = 10.9 Hz, 8.6 Hz, 1H), 7.34 (d, J = 8.7 Hz, 2H), 7.69 (d, J = 8.7 Hz, 2H), 7.84 (s, 1H), 8.96 (s, 1H).

25 4-[6-(4-Cyanophenyl)amino-5-fluoropyridin-2-yl]amino-3,5-dimethylbenzonitrile (DAFPY-1): The general procedure C was followed using Pd(OAc)2 (0.025 mmol, 5.6 mg), X-phos (0.03 mmol, 14 mg), 4-(6-chloro-3-fluoropyridin-2-yl-amino)benzonitrile 3a (0.5 mmol, 124 mg), 4-amino-3,5-dimethylbenzonitrile (0.6 mmol, 88 mg) and Cs2CO3 (1.25 mmol, 408 mg). Obtained as solid; yield 61% (109 mg); mp 235-236 °C; 1H NMR (400 MHz, CDCl3): δ 2.27 (s, 6H), 5.70 (dd, J = 8.6 Hz, 2.2 Hz, 1H), 5.91 (s, 1H), 6.78 (brs, 1H), 7.19 (dd, J = 10.2 Hz, 8.6 Hz, 1H), 7.45 (s, 2H), 7.49 (d, J = 8.9 Hz, 2H), 7.62 (d, J = 8.9 Hz, 2H).

30 (E)-4-[6-[4-(2-Cyanovinyl)-2,6-dimethylphenyl]amino-3-fluoropyridin-2-yl]amino- benzonitrile (DAFPY-2): The general procedure C was followed using Pd(OAc)2 (0.025 mmol, 5.6 mg), X-phos (0.03 mmol, 14 mg), 4-(6-chloro-3-fluoropyridin-2-yl-amino)benzonitrile 3a (0.5 mmol, 124 mg), 3-(4-amino-3,5-dimethylphenyl)acrylonitrile (0.6 mmol, 103 mg) and Cs2CO3 (1.25 mmol, 408 mg). Obtained as solid; yield 62% (0.119 g); 1H NMR (400 MHz, CDCl3): δ 2.28 (s, 6H), 5.67 (dd, J = 8.6
Hz, 2.2 Hz, 1H), 5.86 (brs, 1H), 5.88 (dd, J = 16.6 Hz, 1H), 6.75 (brs, 1H), 7.18 (dd, J = 10.2 Hz, 8.6 Hz, 1H), 7.26 (s, 2H), 7.39 (d, J = 16.6 Hz, 1H), 7.51 (d, J = 8.9 Hz, 2H), 7.67 (d, J = 8.9 Hz, 2H).

**fC^Methyl-3-[4-[6-(4-cyanophenyl)amino]-5-fluoropyridin-2-yl]amino]-3,5-dimethylphenyl]acrylate (DAFPY-3):** The general procedure C was followed using Pd(OAc)$_2$ (0.025 mmol, 5.6 mg), X-phos (0.03 mmol, 14 mg), 4-(6-chloro-3-fluoropyridin-2-yl)amino)benzonitrile 3a (0.5 mmol, 124 mg), (E)-methyl 3-(4-amino-3,5-dimethylphenyl)acrylate (0.6 mmol, 123 mg) and Cs$_2$CO$_3$ (1.25 mmol, 408 mg). Obtained as white solid; yield 71% (0.15 g); mp 189-190 °C; $^1$H NMR (400 MHz, CDCl$_3$): δ 2.25 (s, 6H), 3.82 (s, 3H), 5.68 (dd, J = 8.6 Hz, 2.2 Hz, 1H), 5.86 (s, 1H), 6.43 (d, J = 16.0 Hz, 1H), 6.76 (d, J = 3.2 Hz, 1H), 7.15 (dd, J = 10.2 Hz, 8.6 Hz, 1H), 7.31 (s, 2H), 7.46 (d, J = 8.8 Hz, 2H), 7.64 (d, J = 8.9 Hz, 2H), 7.67 (d, J = 16.0 Hz, 1H).

**3-[4-[6-[4-(Fluorophenyl)amino]-5-fluoropyridin-2-yl]amino]-3,5-dimethylphenyl]acrylonitrile (DAFPY-4):** The general procedure C was followed using Pd(OAc)$_2$ (0.025 mmol, 5.6 mg), X-phos (0.03 mmol, 14 mg), 6-chloro-N-(4-fluorophenyl)-3-fluopyridin-2-amine (0.5 mmol, 120 mg), 3-[4-amino-3,5-dimethylphenyl]acrylonitrile (0.6 mmol, 103 mg) and Cs$_2$CO$_3$ (1.25 mmol, 408 mg). Obtained as white solid; yield 66% (0.123 g); mp 189-190 °C; $^1$H NMR (400 MHz, CDCl$_3$) of major isomer: δ 2.24 (s, 6H), 5.51 (dd, J = 8.5 Hz, 2.1 Hz, 1H), 5.78 (brs, 1H), 5.84 (d, J = 16.6 Hz, 1H), 6.43 (brs, 1H), 6.09 (t, J = 8.8 Hz, 2H), 7.08 (dd, J = 10.4 Hz, 8.5 Hz, 1H), 7.21 (s, 2H), 7.35 (d, J = 16.6 Hz, 1H), 7.47 (dd, J = 9.1 Hz, 4.7 Hz, 2H).

**3-[4-[6-[4-(2-Cyanovinyl)-2,6-dimethyl(phenyl)amino]-3-fluoropyridin-2-yl]amino]-3,5-dimethylphenyl]acrylonitrile (DAFPY-5):** The general procedure C was followed using Pd(OAc)$_2$ (0.025 mmol, 5.6 mg), X-phos (0.03 mmol, 14 mg), 3-[4-(6-chloro-3-fluoropyridin-2-ylamino)phenyl]acrylonitrile (0.5 mmol, 137 mg), 3-(4-amino-3,5-dimethylphenyl)acrylonitrile (0.6 mmol, 103 mg) and Cs$_2$CO$_3$ (1.25 mmol, 408 mg). Obtained as red solid; yield 63% (0.129 g); mp 269-270 °C; $^1$H NMR (400 MHz, CD$_3$COCD$_3$): δ 2.26 (s, 6H), 2.79 (brs, 1H); 5.97 (d, J = 16.6 Hz, 1H), 6.02 (dd, J = 8.5 Hz, 2.0 Hz, 1H); 6.30 (d, J = 16.7 Hz, 1H); 7.30 (dd, J = 10.9 Hz, 8.5 Hz, 1H), 7.33 (d, J = 8.8 Hz, 2H), 7.41 (d, J = 16.6 Hz, 1H), 7.49 (s, 2H), 7.59 (d, J = 16.7 Hz, 1H), 7.68 (d, J = 8.8 Hz, 2H), 8.16 (brs, 1H).

**4-[6-[4-Fluorophenyl]amino]-5-fluoropyridin-2-yl]amino]-3,5-dimethylbenzonitrile (DAFPY-6):** The general procedure C was followed using Pd(OAc)$_2$ (0.025 mmol, 5.6 mg), X-phos (0.03 mmol, 14 mg), 6-chloro-3-fluoro-N-[(4-fluorophenyl)pyridin-2-amine (0.5 mmol, 137 mg), 4-amino-3,5-dimethylbenzonitrile (0.6 mmol, 88 mg), and Cs$_2$CO$_3$ (1.25 mmol, 408 mg). Obtained as colorless solid; yield 50% (88 mg); mp 135-136 °C; $^1$H NMR (400 MHz, CDCl$_3$): δ 2.23 (s, 6H), 5.58 (dd, J = 8.4 Hz, 2.1 Hz, 1H), 5.86 (brs, 1H), 6.47 (brs, 1H), 6.91 (t, J = 8.7 Hz, 2H), 7.11 (dd, J = 10.4 Hz, 8.4 Hz, 1H), 7.39-7.45 (m, 4H).
4-{6-[4-(2-Cyanovinyl)phenyl]amino-3-fluoropyridin-2-yl]amino}benzonitrile (DAFPY-7): The general procedure C was followed using Pd(OAc)$_2$ (0.025 mmol, 5.6 mg), X-phos (0.03 mmol, 14 mg), 4-(6-chloro-3-fluoropyridin-2-ylamino)benzonitrile 3a (0.5 mmol, 124 mg), 3-(4-aminophenyl)acrylonitrile (0.6 mmol, 87 mg) and Cs$_2$CO$_3$ (1.25 mmol, 408 mg). Obtained as a mixture of geometrical isomers (Z:E 1:2.33), white solid; yield 68% (0.12 g); mp 285-286 °C; $^1$H NMR (400 MHz, DMSO-d$_6$): signals of major (E)-isomer: $\delta$ 6.22 (d, $J$ = 16.6 Hz, 1H), 6.44-6.52 (m, 1H), 7.50-7.60 (m, 2H), 7.69 (d, $J$ = 8.4 Hz, 2H), 7.84 (d, $J$ = 8.4 Hz, 2H), 9.31 (s, 1H), 9.39 (s, 1H), signals of minor (Z)-isomer: $\delta$ 5.60 (d, $J$ = 12.0 Hz, 1H), 7.28 (d, $J$ = 12.0 Hz, 1H), 7.62 (d, $J$ = 8.6 Hz, 2H), 7.75 (d, $J$ = 8.6 Hz, 2H), 9.45 (s, 1H), other signals are overlapped with the signals of major isomer.

4-[6-(4-Chlorophenyl)amino-5-fluoropyridin-2-yl]amino-3,5-dimethylbenzonitrile (DAFPY-8): The general procedure C was followed using Pd(OAc)$_2$ (0.025 mmol, 5.1 mg), X-phos (0.03 mmol, 14 mg), 6-chloro-N-(4-chlorophenyl)-3-fluoropyridin-2-amine 3c (0.5 mmol, 129 mg), 4-amino-3,5-dimethylbenzonitrile (0.6 mmol, 88 mg), and Cs$_2$CO$_3$ (1.25 mmol, 408 mg). Obtained as colorless solid; yield 54% (99 mg); mp 197-198 °C; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 2.25 (s, 6H), 5.60 (dd, $J$ = 8.5 Hz, 2.1 Hz, 1H), 5.85 (brs, 1H), 6.52 (brs, 1H), 7.13 (dd, $J$ = 10.4 Hz, 8.5 Hz, 1H), 7.17 (d, $J$ = 8.8 Hz, 2H), 7.43 (s, 2H), 7.44 (d, $J$ = 8.8 Hz, 2H).

3-{4-[6-(4-Chlorophenyl)amino-5-fluoropyridin-2-yl]amino-3,5-dimethylphenyl} acrylonitrile (DAFPY-9): The general procedure C was followed using Pd(OAc)$_2$ (0.025 mmol, 5.6 mg), X-phos (0.03 mmol, 14 mg), 6-chloro-N-(4-chlorophenyl)-3-fluoropyridin-2-amine (0.5 mmol, 129 mg), 3-(4-amino-3,5-dimethylphenyl)acrylonitrile (0.6 mmol, 103 mg) and Cs$_2$CO$_3$ (1.25 mmol, 408 mg). Obtained as a major trans geometrical isomer, brown solid; yield 65% (128 mg); mp 156-157 °C; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 2.23 (s, 6H), 5.56 (dd, $J$ = 8.5 Hz, 2.1 Hz, 1H), 5.83 (d, $J$ = 16.6 Hz, 1H), 5.84 (brs, 1H), 6.50 (brs, 1H), 7.09 (dd, $J$ = 10.4 Hz, 8.5 Hz, 1H), 7.13 (d, $J$ = 8.9 Hz, 2H), 7.21 (s, 2H), 7.34 (d, $J$ = 16.6 Hz, 1H), 7.45 (d, $J$ = 8.9 Hz, 2H).

(E)-4-[6-(4-Cyanovinyl)-2-fluoro-6-methylphenyl]amino-3-fluoropyridin-2-yl]amino]benzonitrile (DAFPY-10). The general procedure C was followed using Pd(OAc)$_2$ (0.025 mmol, 5.6 mg), X-phos (0.03 mmol, 14 mg), 4-(6-chloro-3-fluoropyridin-2-ylamino)benzonitrile 3a (0.5 mmol, 124 mg), 3-(4-amino-3-fluoro-5-methylphenyl)acrylonitrile (0.6 mmol, 110 mg) and Cs$_2$CO$_3$ (1.25 mmol, 408 mg). Obtained as brown solid; yield 79% (150 mg); mp 235-236 °C; $^1$H NMR (400 MHz, CD$_2$COCD$_3$): $\delta$ 2.29 (s, 3H), 6.26 (dd, $J$ = 8.6 Hz, 2.2 Hz, 1H), 6.34 (d, $J$ = 16.4 Hz, 1H), 7.33-7.38 (m, 1H), 7.37 (d, $J$ = 8.8 Hz, 2H), 7.45-7.48 (m, 2H), 7.59 (d, $J$ = 16.6 Hz, 1H), 7.68 (br s, 1H), 7.75 (d, $J$ = 8.8 Hz, 2H), 8.32 (brs, 1H).
4-[(6-(4-(2-Cyanovinyl)-2,6-difluorophenylamino-3-fluoropyridin-2-yl)amino)benzonitrile (DAFPY-19): The general procedure C was followed using Pd(OAc)$_2$ (0.025 mmol, 5.61 mg), X-phos (0.03 mmol, 14 mg), 4-[(6-chloro-3-fluoropyridin-2-yl)amino]benzonitrile 3a (0.5 mmol, 124 mg), 4-amino-3,5-difluorophenylacrylonitrile (0.6 mmol, 108 mg) and Cs$_2$CO$_3$ (1.25 mmol, 0.41 g). Obtained as dark brown solid; yield 72% (0.14 g); mp 223-224 °C; $^1$H NMR (400 MHz, CD$_2$COCD$_3$) of major isomer: δ 6.38-6.44 (m, 2H), 7.38-7.46 (m, 3H), 7.51 (d, J = 8.8 Hz, 2H), 7.62 (d, J = 16.7 Hz, 1H), 7.79 (d, J = 8.8 Hz, 2H), 7.96 (brs, 1H), 8.38 (brs, 1H).

(E)-Methyl 4-[(3-Fluoro-6-(p-tolyloxy)pyridin-2-yl)amino]benzoate (DAFPY-20): The general procedure C was followed using Pd(OAc)$_2$ (0.025 mmol, 5.61 mg), X-phos (0.03 mmol, 14 mg), methyl 4-(6-chloro-3-fluoropyridin-2-yl)(amino)benzoate (0.5 mmol, 140 mg), 3-[4-amino-3,5-dimethylphenyl]acrylonitrile (0.6 mmol, 103 mg) and Cs$_2$CO$_3$ (1.25 mmol, 0.41 g). Obtained as major trans geometrical isomer, white solid; yield 72% (0.149 g); mp 233-234 °C; $^1$H NMR (400 MHz, CD$_2$COCD$_3$): δ 2.23 (s, 6H), 3.81 (s, 3H), 6.05 (dd, J = 8.5 Hz, 2.0 Hz, 1H), 6.27 (d, J = 16.7 Hz, 1H), 7.27 (dd, J = 10.8 Hz, 8.5 Hz, 1H), 7.45 (brs, 1H), 7.47 (s, 2H), 7.56 (d, J = 16.7 Hz, 1H), 7.61 (d, J = 9.2 Hz, 2H), 7.65 (d, J = 9.2 Hz, 2H), 8.14 (brs, 1H).

4-[(3-Fluoro-6-(p-tolyloxy)pyridin-2-yl)amino]benzonitrile (DAFPY-11): The general procedure C was followed using Pd(OAc)$_2$ (0.025 mmol, 5.61 mg), X-phos (0.03 mmol, 14 mg), 4-(6-chloro-3-fluoropyridin-2-yl) amino)benzonitrile 3a (0.5 mmol, 124 mg), p-cresol (0.6 mmol, 65 mg) and Cs$_2$CO$_3$ (1.25 mmol, 0.41 g). Obtained as white solid; yield 89% (0.142 g); mp 153-154 °C; $^1$H NMR (400 MHz, CDCl$_3$): δ 2.46 (s, 3H), 6.41 (dd, J = 8.5 Hz, 2.0 Hz, 1H), 6.76 (brs, 1H), 7.06 (d, J = 8.4 Hz, 2H), 7.25 (d, J = 8.4 Hz, 2H), 7.36 (d, J = 8.6 Hz, 2H), 7.38 (m, 1H), 7.42 (d, J = 8.6 Hz, 2H).

4-[(3-Fluoro-6-(mesityloxy)pyridin-2-yl)amino]benzonitrile (DAFPY-12): The general procedure C was followed using Pd(OAc)$_2$ (0.025 mmol, 5.61 mg), X-phos (0.03 mmol, 14 mg), 4-(6-chloro-3-fluoropyridin-2-yl) amino)benzonitrile 3a (0.5 mmol, 124 mg), 2,4,6-trimethylphenol (0.6 mmol, 82 mg) and Cs$_2$CO$_3$ (1.25 mmol, 0.41 g). Obtained as yellow solid; yield 43% (0.074 g); mp 201-202 °C; $^1$H NMR (400 MHz, CDCl$_3$): δ 2.08 (s, 6H), 2.38 (s, 3H), 6.39 (dd, J = 8.4 Hz, 2.2 Hz, 1H), 6.70 (brs, 1H), 6.95 (s, 2H), 7.28 (s, 4H), 7.36 (dd, J = 10 Hz, 8.4 Hz, 1H).

3-[4-(6-(4-Chlorophenylamino)-5-fluoropyridin-2-yl)amino-3-methylphenyl]acrylonitrile (DAFPY-13): The general procedure C was followed using Pd(OAc)$_2$ (0.025 mmol, 5.61 mg), X-phos (0.03 mmol, 14 mg), 6-chloro-W-(4-chlorophenyl)-3-fluoropyridin-2-amine 3c (0.5 mmol, 129 mg), 3-[4-amino-3-methylphenyl]acrylonitrile (0.6 mmol, 95 mg) and Cs$_2$CO$_3$ (1.25 mmol, 0.41 g). Obtained as major trans geometrical isomer, yellow solid; yield 73% (0.137 g); mp 189-190 °C; $^1$H NMR (400 MHz, CDCl$_3$): δ 2.30 (s, 3H), 5.74 (d, J = 16.6 Hz, 1H), 6.16 (brs, 1H), 6.24 (dd, J = 8.4
Hz, 2.2 Hz, 1H), 6.54 (brs, 1H), 7.19-7.29 (m, 5H), 7.32 (d, J = 16.6 Hz, 1H), 7.53 (d, J = 8.8 Hz, 2H), 7.67 (d, J = 8.4 Hz, 1H).

(±)-Methyl-3-{4-[6-(4-fluorophenyl)amino]-5-fluoropyridin-2-yl)amino]-3,5-dimethylphenyl]acrylate (DAFPY-14): The general procedure C was followed using Pd(OAc)$_2$ (0.025 mmol, 5.61 mg), X-phos (0.03 mmol, 14 mg), (6-chloro-3-fluoro-/N-(4-fluorophenyl)pyridine-2-amine 3b (0.5 mmol, 120 mg), 3-(4-amino-3,5-dimethylphenyl)acrylate (0.6 mmol, 123 mg) and Cs$_2$CO$_3$ (1.25 mmol, 0.41 g). Obtained as brown solid; yield 55% (0.13 g); mp 162-163 °C; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 2.24 (s, 6H), 3.82 (s, 3H), 5.51 (dd, J = 8.5 Hz, 2.1 Hz, 1H), 5.77 (s, 1H), 6.42 (d, J = 16.0 Hz, 1H), 6.43 (s, 1H), 6.92 (t, J = 8.8 Hz, 2H), 7.07 (dd, J = 10.5 Hz, 8.5 Hz, 1H), 7.30 (s, 2H), 7.49 (dd, J = 9.1 Hz, 4.7 Hz, 2H), 7.66 (d, J = 16.0 Hz, 1H).

(±)-Methyl-3-{4-[6-(4-chlorophenyl)amino]-5-fluoropyridin-2-yl)amino]-3,5-dimethylphenyl]acrylate (DAFPY-15): The general procedure C was followed using Pd(OAc)$_2$ (0.018 mmol, 4.10 mg), X-phos (0.022 mmol, 10.46 mg), (6-chloro-3-(4-chlorophenyl)pyridine-2-amine 3c (0.366 mmol, 94 mg), 3-(4-amino-3,5-dimethylphenyl)acrylate (0.44 mmol, 90 mg) and Cs$_2$CO$_3$ (1.25 mmol, 0.41 g). Obtained as brown solid; yield 71% (0.067 g); mp 162-163 °C; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 2.24 (s, 6H), 3.82 (s, 3H), 5.53 (dd, J = 8.6 Hz, 2.1 Hz, 1H), 5.77 (s, 1H), 6.42 (d, J = 16.0 Hz, 1H), 6.48 (s, 1H), 7.09 (dd, J = 10.5 Hz, 8.5 Hz, 1H), 7.17 (d, J = 8.9 Hz, 2H), 7.30 (s, 2H), 7.49 (d, J = 8.9 Hz, 2H), 7.66 (d, J = 16.0 Hz, 1H).

3-[4-(5-Fluoro-6-(4-fluorophenylamino)pyridin-2-yl)amino]-3-methylphenyl]acrylonitrile (DAFPY-16): The general procedure C was followed using Pd(OAc)$_2$ (0.025 mmol, 5.61 mg), X-phos (0.03 mmol, 14 mg), 6-chloro-N-(4-fluorophenyl)-3-fluoropyridin-2-amine 3b (0.5 mmol, 120 mg), 3-(4-amino-3-methylphenyl)acrylonitrile (0.6 mmol, 95 mg) and Cs$_2$CO$_3$ (1.25 mmol, 0.41 g). Obtained as major trans geometrical isomer, red solid; yield 75% (0.135 g); mp 150-151 °C; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 2.29 (s, 3H), 5.72 (d, J = 16.6 Hz, 1H), 6.16 (brs, 1H), 6.21 (dd, J = 8.4 Hz, 2.2 Hz, 1H), 6.48 (s, 1H), 7.00 (t, J = 8.7 Hz, 2H), 7.19-7.28 (m, 3H), 7.31 (d, J = 16.6 Hz, 1H), 7.50-7.53 (dd, J = 9.0 Hz, 4.7 Hz, 2H), 7.69 (d, J = 8.4 Hz, 1H).

4-[6-[2-Cyanovinyl]-2-methylphenylamino]-3-fluoropyridin-2-yl)amino]benzo-nitrile (DAFPY-17): The general procedure C was followed using Pd(OAc)$_2$ (0.025 mmol, 5.61 mg), X-phos (0.03 mmol, 14 mg), 4-(6-chloro-3-fluoropyridin-2-ylamino)benzonitrile 3c (0.5 mmol, 124 mg), 3-(4-amino-3-methylphenyl)acrylonitrile (0.6 mmol, 95 mg) and Cs$_2$CO$_3$ (1.25 mmol, 0.41 g). Obtained as mixture of geometrical isomers (cis/trans; 1:5.2), yellow solid; yield 70% (0.13 g); mp 239-240 °C; $^1$H NMR (400 MHz, CD$_3$OD) of major isomer: $\delta$ 2.49 (s, 3H), 5.96 (d, J = 16.4 Hz, 1H), 6.52 (d, J = 8.4 Hz, 1H), 7.42-7.47 (m, 2H), 7.49-7.53 (m, 2H), 7.68 (d, J = 8.4 Hz, 2H), 7.84 (d, J = 8.0 Hz, 1H), 7.91 (d, J = 8.4, 2H).
4-[6-(4-cyanophenylamino)-5-fluoropyridin-2-yl]amino-3-fluoro-5-methylbenzonitrile (DAFPY-18): The general procedure C was followed using Pd(OAc)$_2$ (0.025 mmol, 5.61 mg), X-phos (0.03 mmol, 14 mg), 4-(6-chloro-3-fluoropyridin-2-ylamino)benzonitrile 3a (0.5 mmol, 124), 4-aminoo-3-fluoro-5-methylbenzonitrile (0.6 mmol, 90 mg), and Cs$_2$CO$_3$ (1.25 mmol, 0.41 g). Obtained as brown solid; yield 42% (75 mg); mp 253-254 °C; $^1$H NMR (400 MHz, CDCl$_3$): δ 2.36 (s, 3H), 5.63 (d, $J$ = 8.0 Hz, 1H), 5.93 (d, $J$ = 8.5 Hz, 2H), 7.64 (s, 1H), 7.65 (dd, $J$ = 9.2 Hz, 1.7 Hz, 1H), 7.76 (dt, $J$ = 8.9 Hz, 2.2 Hz, 2H), 7.93 (s, 1H), 8.44 (s, 1H).

4,4'-(3-Fluoropyridine-2,6-diyil)bis(azanediyi)|bis(3,5-dimethylbenzonitrile) (DAFPY-21): The general procedure C was followed using Pd(OAc)$_2$ (0.020 mmol, 4.49 mg), X-phos (0.024 mmol, 11 mg), 4-(6-chloro-3-fluoropyridin-2-ylamino)-3,5-dimethylbenzonitrile (0.4 mmol, 110 mg), 4-aminoo-3,5-dimethylbenzonitrile (0.48 mmol, 70 mg), and Cs$_2$CO$_3$ (1.0 mmol, 0.326 g). Obtained as white solid; yield 43% (66 mg); $^1$H NMR (400 MHz, CDCl$_3$): δ 2.15 (s, 6H), 2.25 (s, 6H), 5.38 (dd, $J$ = 8.5 Hz, 2.0 Hz, 1H), 5.63 (brs, 1H), 5.93 (brs, 1H), 7.10 (dd, $J$ = 10.0 Hz, 8.5 Hz, 1H), 7.36 (s, 2H), 7.39 (s, 2H).

4-(5-Fluoro-6-(mesitylamino)pyridin-2-y lamino)benzonitrile (iso-DAFPY-0): The general procedure C was followed using Pd(OAc)$_2$ (0.020 mmol, 4.49 mg), X-phos (0.024 mmol, 11 mg), 4-(6-chloro-3-fluoropyridin-2-ylamino)-3,5-dimethylbenzonitrile (0.4 mmol, 110 mg), 4-aminobenzonitrile (0.6 mmol, 71 mg) and Cs$_2$CO$_3$ (1.0 mmol, 0.326 g). Obtained as white solid. $^1$H NMR (400 MHz, CDCl$_3$): δ 2.19 (s, 6H), 2.38 (s, 3H), 5.85 (brs, 1H), 6.01 (dd, $J$ = 8.4 Hz, 1.9 Hz, 1H), 6.37 (s, 1H), 6.99 (s, 2H), 7.18 (d, $J$ = 8.9 Hz, 2H), 7.16-7.20 (m, 1H), 7.26 (d, $J$ = 8.9 Hz, 2H).

4-(6-(4-Cyanophenylamino)-3-fluoropyridin-2-ylamino)-3,5-dimethylbenzonitrile (iso-DAFPY-1): The general procedure C was followed using Pd(OAc)$_2$ (0.020 mmol, 4.49 mg), X-phos (0.024 mmol, 11 mg), 4-(6-chloro-3-fluoropyridin-2-ylamino)-3,5-dimethylbenzonitrile (0.4 mmol, 110 mg), 4-aminobenzonitrile (0.6 mmol, 71 mg) and Cs$_2$CO$_3$ (1.0 mmol, 0.326 g). Obtained as white solid. $^1$H NMR (400 MHz, CDCl$_3$): δ 2.26 (s, 6H), 5.97 (s, 1H), 6.16 (dd, $J$ = 8.4 Hz, 2.1 Hz, 1H), 6.40 (s, 1H), 7.14 (dd, $J$ = 6.9 Hz, 2.0 Hz, 2H), 7.25 (dd, $J$ = 10.4 Hz, 8.2 Hz, 1H), 7.32 (dd, $J$ = 6.9 Hz, 2.6 Hz, 2H), 7.45 (s, 2H).

4-(6-[4-(2-Cyanovinyl)-2,6-dimethylphenyl]amino)pyridin-2-ylamino)benzonitrile (de-DAFPY-2): The general procedure C was followed using Pd(OAc)$_2$ (0.025 mmol, 5.61 mg), X-phos (0.03 mmol, 14 mg), 4-(6-chloro-3-fluoropyridin-2-yl)amino)benzonitrile (0.5 mmol, 115 mg), 3-(4-aminoo-3,5-dimethylphenyl)acylonitrile (0.6 mmol, 0.10 g) and Cs$_2$CO$_3$ (1.25 mmol, 0.41 g). Obtained as a mixture of geometrical isomers (cis:trans; 1:4.1). Light yellow solid; yield 66% (0.12 g); mp 229-230 °C; $^1$H NMR (400 MHz, CDCl$_3$) of major isomer: δ 2.26 (s, 6H), 5.73 (d, $J$ = 8.0 Hz, 1H), 5.86 (d, $J$ =
16.6 Hz, 1H), 5.96 (s, 1H), 6.26 (d, J = 7.6 Hz, 1H), 6.61 (s, 1H), 7.24 (s, 2H), 7.32-7.38 (m, 2H),
7.42-7.49 (m, 4H).

4-[6-(4-cyanophenylamino-pyridin-2-yl)amino-3,5-dimethylbenzonitrile (deF-DAFPY-1): The
general procedure C was followed using Pd(OAc)$_2$ (0.025 mmol, 5.61 mg), X-phos (0.03 mmol, 14
mg), 4-(6-chloropyridin-2-ylamino)benzonitrile (0.5 mmol, 115 mg), 4-amino-3,5-
dimethylbenzonitrile (0.6 mmol, 88 mg) and Cs$_2$CO$_3$ (1.25 mmol, 0.41 g). Brown solid; yield 20%
(34 mg); mp 223-224 °C; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 2.28 (s, 6H), 5.75 (d, J = 8.1 Hz, 1H), 5.95
(s, 1H), 6.28 (d, J = 7.9 Hz, 1H), 6.56 (s, 1H), 7.37 (t, J = 8.0 Hz, 1H), 7.44 (d, J = 8.9 Hz, 2H), 7.45
(s, 2H), 7.50 (d, J = 8.9 Hz, 2H).

4-[6-(mesitylamino)pyridin-2-ylamino]benzonitrile (deF-DAFPY-0): The general procedure C was
followed using Pd(OAc)$_2$ (0.025 mmol, 5.61 mg), X-phos (0.03 mmol, 14 mg), 4-(6-
chloropyridin-2-ylamino)benzonitrile (0.5 mmol, 115 mg), 2, 4, 6-trimethylaniline (0.6 mmol, 81 mg)
and Cs$_2$CO$_3$ (1.25 mmol, 0.41 g). Obtained as white solid; yield 21% (35 mg); mp 216-217 °C; $^1$H
NMR (400 MHz, CDCl$_3$): $\delta$ 2.20 (s, 6H), 2.33 (s, 3H), 5.67 (d, J = 8.1 Hz, 1H), 5.92 (s, 1H), 6.20 (d,
J = 7.8 Hz, 1H), 6.59 (s, 1H), 6.96 (s, 2H), 7.28 (t, J = 7.8 Hz, 1H), 7.44 (d, J = 8.9 Hz, 2H), 7.50 (d,
J = 8.9 Hz, 2H).

4-[6-(4-(cyanovinyl)-2-fluoro-6-methylphenyl)amino]pyridin-2-ylamino]benzonitrile (deF-
DAFPY-1 0): The general procedure C was followed using Pd(OAc)$_2$ (0.025 mmol, 5.61 mg), X-
phos (0.03 mmol, 14 mg), 4-(6-chloropyridin-2-ylamino)benzonitrile (0.5 mmol, 115 mg), 3-(4-
amino-3-fluoro-5-methylphenyl)acrylonitrile (0.6 mmol, 0.106 g) and Cs$_2$CO$_3$ (1.25 mmol, 0.41 g).
Obtained as a mixture of geometrical isomers (cis:trans; 1:1.08), white solid; yield 71% (0.132 g); 
mp 261-262 °C; $^1$H NMR (400 MHz, CD$_3$COCD$_3$) of major isomer: $\delta$ 2.30 (s, 3H), 6.26 (d, J = 8.0
Hz, 2H), 6.34 (d, J = 16.7 Hz, 1H), 7.32 (d, J = 8.8 Hz, 2H), 7.41 (t, J = 7.9 Hz, 1H), 7.48 (s, 2H),
7.56 (d, J = 17.2 Hz, 1H), 7.61 (d, J = 8.8 Hz, 2H), 7.66 (s, 1H), 8.57 (s, 1H).

4-[5-(4-(cyanovinyl)-2,6-dimethylphenyl)amino]-2-fluorophenylbenzonitrile (DAFB-
1): The general procedure C was followed using Pd(OAc)$_2$ (0.025 mmol, 5.61 mg), X-phos (0.03
mmol, 14 mg), 4-(5-chloro-2-fluorophenylamino)benzonitrile 7 (0.5 mmol, 123 mg), 3-(4-
amino-3,5-
dimethylphenyl)acrylonitrile (0.6 mmol, 103 mg) and Cs$_2$CO$_3$ (2.50 mmol, 0.82 g). Obtained as a
mixture of geometrical isomers (cis:trans; 1:4.2), yellow solid; yield 56% (0.11 g); mp 219-220 °C;
$^1$H NMR (400 MHz, CDCl$_3$) of major isomer: $\delta$ 2.21 (s, 6H), 5.23 (s, 1H), 5.79 (d, J = 16.6 Hz, 1H),
5.95 (s, 1H), 6.15-6.19 (m, 1H), 6.54 (dd, J = 6.7 Hz, 2.5 Hz, 1H), 6.92-6.97 (m, 1H), 6.94 (d, J =
8.5 Hz, 2H), 7.18 (s, 2H), 7.31 (d, J = 16.6 Hz, 1H), 7.48 (d, J = 8.5 Hz, 2H).

4-[5-(4-Cyanovinyl)-2-fluoro-6-methylphenylamino]-2-fluorophenylnitride (DAFB-2): The general
procedure C was followed using Pd(OAc)$_2$ (0.025 mmol, 5.61 mg), X-phos (0.03 mmol, 14 mg), 4-(5-
chloro-2-fluorophenylamino)benzonitrile 7 (0.5 mmol, 123 mg), 3-(4-
amino-3-fluoro-5-methylphenylacrylonitrile (0.6 mmol, 106 mg) and Cs$_2$CO$_3$ (2.50 mmol, 0.82 g). Obtained as a mixture of geometrical isomers (cis:trans; 1:3.13), light yellow solid; yield 59% (0.12 g); mp 173-174 °C; $^1$H NMR (400 MHz, CDCl$_3$) of major isomer: $\delta$ 2.20 (s, 3H), 5.42 (s, 1H), 5.77 (d, $J$ = 16.4 Hz, 1H), 5.98 (s, 1H), 6.35-6.38 (m, 1H), 6.73 (dd, $J$ = 6.8 Hz, 2.4 Hz, 1H), 6.97-7.92 (m, 1H), 6.94 (d, $J$ = 8.5 Hz, 2H), 7.09 (t, $J$ = 4.6 Hz, 1H), 7.25 (s, 1H), 7.27 (d, $J$ = 16.8 Hz, 1H), 7.49 (d, $J$ = 8.8 Hz, 2H).

4-[(4-(2-Cyanovinyl)-2-methylphenylamino)-2-fluorophenylamino]benzonitrile (DAFB-3): The general procedure C was followed using Pd(OAc)$_2$ (0.025 mmol, 5.61 mg), X-phos (0.03 mmol, 14 mg), 4-(5-chloro-2-fluorophenylamino)benzonitrile 7 (0.5 mmol, 123 mg), 3-(4-amino-5-methylphenylacrylonitrile (0.55 mmol, 87 mg) and Cs$_2$CO$_3$ (2.50 mmol, 0.82 g). Obtained as a mixture of geometrical isomers (cis:trans; 1:8.3), light yellow solid; yield 41% (0.076 g); mp 170-171 °C; $^1$H NMR (400 MHz, CDCl$_3$) of major isomer: $\delta$ 2.26 (s, 3H), 5.57 (s, 1H), 5.66 (d, $J$ = 16.8 Hz, 1H), 6.07 (s, 1H), 6.76-6.79 (m, 1H), 7.01-7.04 (m, 1H), 7.02 (d, $J$ = 8.6 Hz, 2H), 7.08-7.12 (m, 2H), 7.18 (d, $J$ = 8.5 Hz, 1H), 7.26 (b, 1H), 7.26 (d, $J$ = 16.8 Hz, 1H), 7.51 (d, $J$ = 8.6 Hz, 2H).

General Procedure D for the Synthesis of NNRTI of DAFPYM series: Stock solution of 5 mol% Pd-catalystindioxane was prepared as follows. A flask was charged with Pd(OAc)$_2$ (0.025 mmol, 5.61 mg) and X-phos (0.03 mmol, 14 mg), dry dioxane (5 mL) was added and the resulting solution was stirred for 15 min under an argon atmosphere.

Next, a 50 mL round bottomed flask was charged with an intermediate 9 (0.5 mmol, 124 mg), an aniline 2 or 4 (0.6 mmol) and Cs$_2$CO$_3$ (1.25 mmol, 0.41 g). Freshly prepared stock solution of Pd catalyst was added and the resulting solution was stirred for 2 min under an argon atmosphere. The round bottomed flask was kept in 110 °C preheated oil bath and reaction mixture was refluxed for 16 h, then allowed to cool down to room temperature and filtered through Celite. Celite cake was washed with 100 mL dichloromethane, combined organic phases were evaporated to dryness under reduced pressure and the residue separated with an automated chromatography system using Silica Flash Cartridges applying a heptane-ethyl acetate gradient (from 100% heptane to 100% ethylacetate in 35 minutes, 35 mL/min).

4-(4-Cyanophenylamino)-5-fluoropyrimidin-2-yl amino)-3,5-dimethylbenzonitrile (DAFPYM-1): The general procedure D was followed using Pd(OAc)$_2$ (0.025 mmol, 5.61 mg), X-phos (0.03 mmol, 14 mg), 4-(2-chloro-5-fluoropyrimidin-4-ylamino)benzonitrile 9 (0.5 mmol, 124 mg), 4-amino-3,5-dimethylbenzonitrile (0.55 mmol, 80 mg) and Cs$_2$CO$_3$ (2.50 mmol, 0.82 g). Obtained as light yellow solid; yield 22% (0.039 g); mp 268-269 °C; $^1$H NMR (400 MHz, CD$_3$COCD$_3$): $\delta$ 2.29 (s, 6H), 7.51 (d, $J$ = 8.8 Hz, 2H), 7.58 (s, 2H), 7.82 (d, $J$ = 8.0 Hz, 2H), 8.00 (d and one singlet merge with doublet, $J$ = 3.1 Hz, 2H), 8.85 (s, 1H).

4-(2-(2-Cyanovinyl)-2,6-dimethylphenylamino)-5-fluoropyrimidin-4-yl]amino)- benzonitrile (DAFPY-2): The general procedure D was followed using Pd(OAc)$_2$ (0.025 mmol, 5.61 mg), X-
phos (0.03 mmol, 14 mg), 4-(2-chloro-5-fluoropyrimidin-4-ylaminobenzonitrile 9 (0.5 mmol, 124 mg), 3-(4-amino-3,5-dimethylphenylacrylonitrile 8 (0.55 mmol, 86 mg) and Cs2CO3 (2.50 mmol, 0.82 g). Obtained as a mixture of geometrical isomers (cis/trans; 1:4.35), light yellow solid; yield 21% (0.040 g); mp 232-233 °C; 1H NMR (400 MHz, CD3COCD3) of major isomer: δ 2.25 (s, 3H), 6.27 (d, $J = 16.7$ Hz, 1H), 7.44 (d, $J = 8.3$ Hz, 2H), 7.48 s, (2H), 7.56 (d, $J = 16.7$ Hz, 1H), 7.82 (d, $J = 7.4$ Hz, 2H), 7.87 s, (1H), 7.99 (d, $J = 2.8$ Hz, 1H), 8.80 (s, 1H).
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Preparation of pyrimidines and triazines as inhibitors of human immunodeficiency virus replication. WO2004074262

Preparation of arylaminopyrimidines as inhibitors of HIV replication. WO2000027825

Preparation of HIV inhibiting pyrimidine derivatives. WO9950250

Preparation of substituted amino pyrimidines and triazines as HIV replication inhibitors. WO200185700

Preparation of pyrimidines as HIV inhibitors. WO2003016306

Preparation of HIV inhibiting 2-(4-cyanophenylamino)pyrimidine derivatives. WO2006079656

Preparation of HIV inhibiting pyrazinones. WO2002078708

Preparation of pyridine derivatives as non-nucleoside reverse transcriptase inhibitors. WO20010040275


Preparation of benzamidine derivatives as anticoagulants. WO9628427

Preparation of pyrimidine derivatives as inhibitors of protein kinases. US2010/0029610

Macrocyclic compounds as kinase inhibitors and their preparation, pharmaceutical compositions and their use in the treatment of JAK/ALK-associated diseases. WO2009132202
CLAIMS

1. A compound of Formula (I) or a stereoisomer, tautomer, racemic, metabolite, pro-or predrug, salt, hydrate, or solvate thereof,

\[ \begin{align*}
\text{R}^1, \text{R}^2, \text{R}^3, \text{R}^4, \text{R}^5 \text{ and } \text{R}^6 \text{ are each independently selected from the list comprising } & - \text{H, } -\text{CN, } -\text{halo, } -\text{(C=0)}-\text{R}^7, \text{optionally substituted } -\text{C}_{1-6}\text{-alkyl, optionally substituted } -\text{C}_{2-6}\text{-alkenyl, optionally substituted } -\text{C}_{2-6}\text{-alkynyl, and optionally substituted } -\text{C}_{1-6}\text{alkoxy;} \\
\text{X and } \text{Y are each independently selected from the list comprising } & \text{N or C;} \\
\text{Z is selected from the list comprising } & -\text{O- and } -\text{NH-;} \\
\text{R}^7 \text{ is selected from the list comprising } & -\text{OR}^8, \text{N}\text{R}^9\text{R}^{10}; \\
\text{R}^8, \text{R}^9 \text{ and } \text{R}^{10} \text{ are each independently selected from the list comprising } & -\text{H and } c_{1-6}\text{alkyl;} \text{ and} \\
\text{Wherein either } & \text{R}^1, \text{R}^5 \text{ and } \text{R}^6 \text{ are not } -\text{H;} \text{ or} \\
\text{R}^2, \text{R}^3 \text{ and } \text{R}^4 \text{ are not } -\text{H} \\
\end{align*} \]

2. A compound of Formula (la) or a stereoisomer, tautomer, racemic, metabolite, pro-or predrug, salt, hydrate, or solvate thereof,

\[ \begin{align*}
\text{R}^4, \text{R}^1, \text{R}^5 \text{ and } \text{R}^6 \text{ are each independently selected from the list comprising } & -\text{CN, } -\text{halo, } -\text{(C=0)}-\text{R}^7, \text{optionally substituted } -\text{C}_{1-6}\text{-alkyl, optionally substituted } -\text{C}_{2-6}\text{-alkenyl, optionally substituted } -\text{C}_{2-6}\text{-alkynyl, and optionally substituted } -\text{C}_{1-6}\text{alkoxy;} \\
\end{align*} \]
X and Y are each independently selected from the list comprising N or C;
Z is selected from the list comprising -O- and -NH-;
R7 is selected from the list comprising -OR8, NR9R10; and
R8, R9 and R10 are each independently selected from the list comprising -H and C-alkyl.

3. A compound of Formula (lb) or a stereoisomer, tautomer, racemic, metabolite, pro-or predrug, salt, hydrate, or solvate thereof,

Wherein
R1, R2, R3, and R4 are each independently selected from the list comprising -CN, -halo, -(C=O)-R7, optionally substituted -C1-alkyl, optionally substituted -C2-alkenyl, optionally substituted -C2-alkynyl, and optionally substituted -alkoxy;
X and Y are each independently selected from the list comprising N or C;
Z is selected from the list comprising -O- and -NH-;
R7 is selected from the list comprising -OR8, NR9R10; and
R8, R9 and R10 are each independently selected from the list comprising -H and C-alkyl.

4. A compound according to anyone of claims 1-3 wherein the optionally substituted -C1-alkyl, -C2-alkenyl, -C2-alkynyl or -alkoxy as defined in any one of R1-R6 is substituted with one or more substituents selected from the list comprising halo, -CN, and -(C=O)-R11:

wherein
R11 is selected from the list comprising -OR12 and -NR13R14; and
R12, R13 and R14 are each independently selected from the list comprising -H and C1-alkyl.

5. A compound according to anyone of claims 1-4 wherein X and Y are each N.

6. A compound according to anyone of claims 1-4 wherein X and Y are each C.

7. A compound according to anyone of claims 1-4 wherein X is N and Y is C.

8. A compound according to anyone of claims 1-7 wherein R4 is -CH=CH-CN.
9. A compound according to anyone of claims 1, or 3-7 wherein R\(^1\) is -CN.

10. A composition comprising a compound according to anyone of claims 1 to 9.

11. A compound according to anyone of claims 1 to 9 or a composition according to claim 10 for use as a medicament.

12. A compound according to anyone of claims 1 to 9 or a composition according to claim 10 for use in the prevention and/or treatment of HIV infections in a subject in need thereof.

13. Use of a compound according to anyone of claims 1 to 9 or a composition according to claim 10 as a non-nucleoside reverse transcriptase inhibitor.

14. Method for the prevention and/or treatment of HIV infections; said method comprising administering to a subject in need thereof a compound according to anyone of claims 1 to 9 or a composition according to claim 10.
### A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D213/74  C07D239/48  C07C255/58  A61K31/277  A61P31/12

### B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

- C07D
- C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

### C. DOCUMENTS CONSIDERED TO BE RELEVANT

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Further documents are listed in the continuation of Box C. See patent family annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier application or patent but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) one of which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

### Date of the actual completion of the international search

15 January 2014

### Date of mailing of the international search report

27/01/2014

Name and mailing address of the ISA:

- European Patent Office, P.B. 5818 Patentlaan 2
- NL - 2280 HV Rijswijk
- Tel. (+31-70) 340-2040,
- Fax: (+31-70) 340-3016

Authorized officer:

- Skulj, Primoz
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