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(54) Title: NOVEL HETEROCYCLIC COMPOUNDS AS ANTIMALARIAL AGENTS

(57) Abstract: The invention relates to novel heterocyclic compounds of the Formula I. The invention also concerns related aspects including processes for the preparation of the compounds, pharmaceutical compositions containing one or more compounds of the Formula I and especially their use as medicaments to treat or prevent malaria infections or to treat or prevent other protozoal diseases like sleeping sickness, Chagas disease, amebiasis, giardiasis, trichomoniasis, toxoplasmosis, and leishmaniasis.



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NOVEL HETEROCYCLIC COMPOUNDS AS ANTIMALARIAL AGENTS

5 The invention relates to novel heterocyclic compounds of the Formula I. The invention also concerns related aspects including processes for the preparation of the compounds, pharmaceutical compositions containing one or more compounds of the Formula I and especially their use as medicaments to treat or prevent malaria infections or to treat or prevent other protozoal diseases like sleeping sickness, Chagas disease, amebiasis, giardiasis, trichomoniasis, toxoplasmosis, and leishmaniasis.

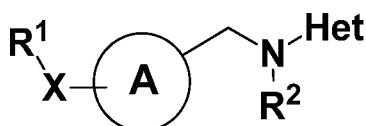
Numerous serious diseases affecting humans as well as domestic and livestock animal are caused by protozoal organisms such as *kinetoplastida*, *apicomplexa*, *anaerobic protozoa*, *microsporidia* and *plasmodium*, for example. The clinically most relevant of these diseases is malaria.

Malaria is one of the most serious and complex health problems affecting humanity in the 21st century. The disease affects about 300 million people worldwide, killing 1 to 1.5 million people every year. Malaria is an infectious disease caused by four species of the protozoan parasite *plasmodium*, *P. falciparum* being the most severe of the four. All attempts to develop vaccines against *P. falciparum* have failed so far. Therefore, therapies and preventive measures against malaria are confined to drugs. Various classes of antimalarial drugs exist. The most widely used are the quinoline antimalarials, e.g. chloroquine which has been an especially effective drug for both prophylaxis and therapy. However, resistance to many of the currently available antimalarial drugs is spreading rapidly, threatening people in areas where malaria is endemic. Reports of multi-drug resistant strains of malaria parasites render the search for new antimalarial agents especially urgent.

P. falciparum enters the human body by way of bites of the female anophelino mosquito (it may also be transmitted by blood transfusion from asymptotic donors; almost all infected blood components including red cells, platelet concentrates, white cells, cryoprecipitates and fresh plasma can transmit malaria). The *plasmodium* parasite initially populates the liver, and during later stages of the infectious cycle reproduces in red blood cells. During this stage, the parasite degrades hemoglobin and uses the degradation products as nutrients for growth.

The limitations of the current antiprotozoal chemotherapeutic arsenal underscore the need for new drugs in this therapeutic area. The present invention relates to the identification of novel heterocyclic compounds of Formula I which are useful in the treatment and/or prevention of protozoal infections, especially in the treatment and/or prevention of malaria, in particular plasmodium falciparum malaria.

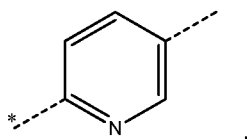
1) A first embodiment of the present invention relates to a compound of the Formula I:



Formula I

wherein

A represents 1,4-phenylene, 1,3-phenylene, pyridin-2,6-diyl, or the following group:



wherein the asterisk indicates the bond that is attached to the group **X-R¹**; or, in case **X** is absent, **A** may also represent piperidin-1,4-diyl, wherein **R¹** is attached to the nitrogen atom of the piperidin-1,4-diyl;

- **X** represents -NR³- wherein **R³** represents hydrogen or (C₁₋₃)alkyl (such as especially hydrogen, methyl or ethyl, preferably hydrogen or methyl), and **R¹** represents a 6-membered heteroaryl ring (especially pyridinyl, pyrimidinyl or pyrazinyl), wherein said heteroaryl ring is optionally mono- or di-substituted (if substituted preferably mono-substituted) wherein the substituents are independently selected from the group consisting of (C₁₋₃)alkyl, (C₁₋₃)alkoxy, halogen, (C₁₋₃)fluoroalkyl, (C₁₋₃)fluoroalkoxy, and pyrrolidinyl; or quinolinyl (especially quinolin-4-yl) optionally mono- or di-substituted wherein the substituents are independently selected from the group consisting of (C₁₋₃)alkyl, (C₁₋₃)alkoxy, halogen, (C₁₋₃)fluoroalkyl, and (C₁₋₃)fluoroalkoxy; or
- **X** is absent, and **R¹** represents pyridinyl optionally mono-substituted with (C₁₋₃)alkyl or, in case **A** is not piperidin-1,4-diyl, **R¹** may also represent piperazinyl (especially piperazin-1-yl) mono-substituted (preferably at a nitrogen atom) with (C₁₋₃)alkyl, such as especially 4-methyl-piperazin-1-yl;

R^2 represents piperidinyl (especially piperidin-4-yl or piperidin-3-yl, preferably piperidin-4-yl), pyrrolidinyl (especially pyrrolidin-3-yl), or (3aR,6aS)-octahydrocyclopenta[c]pyrrol-5-yl, all optionally mono-substituted (preferably at the nitrogen atom) wherein the substituent is selected from the group consisting of (C₁₋₅)alkyl; (C₃₋₆)cycloalkyl (especially cyclopentyl); (C₁₋₃)fluoroalkyl; (C₁₋₅)alkyl (such as especially methyl) mono-substituted with (C₃₋₆)cycloalkyl (especially cyclopropyl), phenyl, imidazolyl (especially 3H-imidazol-4-yl), isoxazolyl (especially isoxazol-4-yl), or imidazo[1,2-a]pyridinyl (especially imidazo[1,2-a]pyridin-7-yl), wherein the phenyl is optionally mono- or di-substituted wherein the substituents are independently selected from the group consisting of (C₁₋₃)alkyl, (C₁₋₃)alkoxy, (C₁₋₃)fluoroalkyl, (C₁₋₃)fluoroalkoxy, halogen, hydroxy and $-(CH_2)_n-NR'R''$, wherein n is 0 or 1 and R' and R'' independently represent (C₁₋₃)alkyl, and wherein imidazolyl, isoxazolyl, and imidazo[1,2-a]pyridinyl are optionally mono- or di-substituted with (C₁₋₃)alkyl; and piperidinyl (especially piperidin-4-yl) or pyrrolidinyl (especially pyrrolidin-3-yl), both optionally mono-substituted (preferably at the nitrogen atom) with (C₁₋₃)alkyl or (C₁₋₃)alkyl-CO-; or R^2 represents $R^4R^5N-(C_{2-4})$ alkyl, wherein R^4 and R^5 independently represent hydrogen or (C₁₋₃)alkyl, with the exception that not both R^4 and R^5 represent hydrogen (preferably both represent methyl), or wherein R^4 and R^5 together with the nitrogen atom to which they are attached form a piperazine ring which is optionally mono-substituted (preferably at the nitrogen atom at position 4) with (C₁₋₃)alkyl (especially methyl); and

Het represents pyridinyl, pyrimidinyl (especially pyrimidin-2-yl), or pyrazinyl (especially pyrazin-2-yl), all optionally mono- or di-substituted (preferably mono-substituted) wherein the substituents are independently selected from the group consisting of (C₁₋₃)alkyl; (C₁₋₃)alkoxy (especially methoxy) optionally mono-substituted with phenyl; (C₁₋₃)fluoroalkyl; phenyl or pyridinyl, both optionally mono-substituted with (C₁₋₄)alkyl, (C₁₋₃)alkoxy, halogen, (C₁₋₃)fluoroalkyl, (C₁₋₃)fluoroalkoxy, cyano, or methylsulfonyl; and $-NR^6R^7$, wherein R^6 and R^7 independently represent (C₁₋₅)alkyl or wherein R^6 and R^7 together with the nitrogen atom to which they are attached form an azetidine, pyrrolidine or piperazine ring wherein the piperazine ring is optionally mono-substituted (preferably at the nitrogen atom at position 4) with (C₁₋₃)alkyl (especially methyl); or **Het** represents benzooxazolyl (especially benzooxazol-2-yl), benzothiazolyl (especially benzothiazol-2-yl), quinolinyl (especially quinolin-4-yl), quinoxalinyl (especially quinoxalin-2-yl), or quinazolinyl (especially quinazolin-2-yl or quinazolin-4-yl), all optionally mono-substituted with (C₁₋₄)alkyl, (C₁₋₃)alkoxy, halogen or (C₁₋₃)fluoroalkyl; or oxadiazolyl (especially 1,2,4-oxadiazol-5-yl or 1,3,4-oxadiazol-2-yl) or thiazolyl (especially thiazol-2-yl), both optionally mono-substituted with phenyl or pyridinyl, wherein phenyl or pyridinyl is optionally mono-substituted with

(C₁₋₄)alkyl, (C₁₋₃)alkoxy, halogen, (C₁₋₃)fluoroalkyl, (C₁₋₃)fluoroalkoxy, cyano, or methylsulfonyl;

with the exception of:

N-(1-isopropylpiperidin-4-yl)-N-(3-(methyl(pyridin-2-yl)amino)benzyl)-4-(4-

5 (trifluoromethyl)phenyl)pyrimidin-2-amine, and

N-(1-isopropylpiperidin-4-yl)-N-((6-(methyl(pyridin-3-yl)amino)pyridin-2-yl)methyl)-4-(4-(trifluoromethyl)phenyl)pyrimidin-2-amine.

The following definitions are intended to apply uniformly to the compounds of Formula I according to embodiment 1) and, *mutatis mutandis*, throughout the description and the claims unless an otherwise expressly set out definition provides a broader or narrower definition. It is well understood that a definition or preferred definition of a term as defined herein below or anywhere else in the description or the claims defines and may replace the respective term independently of (and in combination with) any definition or preferred definition of any or all other terms as defined herein.

The term "halogen" refers to fluorine, chlorine, or bromine, preferably fluorine or chlorine.

The term "(C_{x-y})alkyl" (x and y each being an integer), used alone or in combination, refers to a saturated straight or branched chain alkyl group containing x to y carbon atoms. For example a (C₁₋₅)alkyl group contains from one to five carbon atoms.

The term "(C₁₋₃)alkoxy" refers to a (C₁₋₃)alkyl-O- group wherein the (C₁₋₃)alkyl group is as defined before containing one to three carbon atoms and thus refers to methoxy, ethoxy, n-propoxy, and isopropoxy, preferably methoxy.

The term "(C₁₋₃)fluoroalkyl" refers to a (C₁₋₃)alkyl group as defined before containing one to three carbon atoms in which one or more (and possibly all) hydrogen atoms have been replaced with fluorine. A preferred (C₁₋₃)fluoroalkyl is trifluoromethyl. If **R**² represents piperidin-4-yl mono-substituted at the nitrogen atom with (C₁₋₃)fluoroalkyl, then (C₁₋₃)fluoroalkyl preferably represents 3-fluoro-propyl, 3,3,3-trifluoro-propyl or 2-fluoro-1-(fluoromethyl)-ethyl.

The term "(C₁₋₃)fluoroalkoxy" refers to a (C₁₋₃)alkoxy group as defined before containing one to three carbon atoms in which one or more (and possibly all) hydrogen atoms have been replaced with fluorine. A preferred (C₁₋₃)fluoroalkoxy group is trifluoromethoxy.

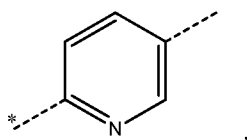
The term “(C₃₋₆)cycloalkyl” refers to a saturated cyclic alkyl group containing three to 6 carbon atoms and thus refers to cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

- 5 The term “6-membered heteroaryl ring” refers to pyridinyl, pyrimidinyl, pyrazinyl and pyridazinyl.

2) Another embodiment of the invention relates to a compound according to embodiment 1), wherein **A** represents 1,4-phenylene.

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3) Another embodiment of the invention relates to a compound according to embodiment 1), wherein **A** represents the following group:



wherein the asterisk indicates the bond that is attached to the group **X-R¹**.

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4) Another embodiment of the invention relates to a compound according to any one of embodiments 1) to 3), wherein

- **X** represents -NR³- wherein **R³** represents hydrogen or (C₁₋₃)alkyl (such as especially hydrogen, methyl or ethyl, preferably hydrogen or methyl), and
- 20 **R¹** represents pyridinyl (especially pyridin-4-yl) optionally mono- or di-substituted (if substituted preferably mono-substituted) wherein the substituents are independently selected from the group consisting of (C₁₋₃)alkyl, (C₁₋₃)alkoxy, halogen, (C₁₋₃)fluoroalkyl, (C₁₋₃)fluoroalkoxy, and pyrrolidinyl; pyrimidinyl optionally mono-substituted with (C₁₋₃)alkyl; pyrazinyl (especially pyrazin-2-yl); or quinolinyl (especially quinolin-4-yl)
- 25 optionally mono- or di-substituted wherein the substituents are independently selected from the group consisting of (C₁₋₃)alkyl, (C₁₋₃)alkoxy, halogen, (C₁₋₃)fluoroalkyl, and (C₁₋₃)fluoroalkoxy.

5) Another embodiment of the invention relates to a compound according to any one of embodiments 1) to 3), wherein

- **X** represents -NR³- wherein **R³** represents hydrogen or (C₁₋₃)alkyl (such as especially hydrogen, methyl or ethyl, preferably hydrogen or methyl), and
- R¹** represents pyridinyl (especially pyridin-4-yl) which is optionally mono- or di-substituted (if substituted preferably mono-substituted) wherein the substituents are

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independently selected from the group consisting of (C₁₋₃)alkyl, (C₁₋₃)alkoxy, halogen, (C₁₋₃)fluoroalkyl, (C₁₋₃)fluoroalkoxy, and pyrrolidinyl.

6) Another embodiment of the invention relates to a compound according to any one of
5 embodiments 1) to 3), wherein

- **X** represents -NR³- wherein **R**³ represents hydrogen or (C₁₋₃)alkyl (such as especially hydrogen, methyl or ethyl, preferably hydrogen or methyl), and
R¹ represents pyridin-4-yl optionally mono-substituted with methyl (if substituted with methyl, especially 2-methyl-pyridin-4-yl) or pyrimidin-4-yl optionally mono-substituted
10 with methyl (especially pyrimidin-4-yl or 2-methyl-pyrimidin-4-yl, preferably pyrimidin-4-yl).

7) Another embodiment of the invention relates to a compound according to any one of
embodiments 1) to 3), wherein

- 15 • **X** represents -NR³- wherein **R**³ represents hydrogen or methyl, and
R¹ represents pyridin-4-yl or 2-methyl-pyridin-4-yl.

8) Another embodiment of the invention relates to a compound according to any one of
embodiments 1) to 3), wherein

- 20 • **X** represents -NR³- wherein **R**³ represents hydrogen or methyl, and
R¹ represents quinolinyl (especially quinolin-4-yl) optionally mono- or di-substituted
wherein the substituents are independently selected from the group consisting of
(C₁₋₃)alkyl, (C₁₋₃)alkoxy, halogen, (C₁₋₃)fluoroalkyl, and (C₁₋₃)fluoroalkoxy.

- 25 9) Another embodiment of the invention relates to a compound according to any one of
embodiments 1) to 8), wherein **R**² represents piperidin-4-yl, piperidin-3-yl, or pyrrolidin-3-yl,
all optionally mono-substituted (preferably at the nitrogen atom) wherein the substituent is
selected from the group consisting of (C₁₋₅)alkyl; (C₃₋₆)cycloalkyl (especially cyclopentyl);
(C₁₋₃)fluoroalkyl; (C₁₋₅)alkyl (such as especially methyl) mono-substituted with
30 (C₃₋₆)cycloalkyl (especially cyclopropyl), phenyl, imidazolyl (especially 3H-imidazol-4-yl),
isoxazolyl (especially isoxazol-4-yl), or imidazo[1,2-a]pyridinyl (especially imidazo[1,2-
a]pyridin-7-yl), wherein the phenyl is optionally mono- or di-substituted wherein the
substituents are independently selected from the group consisting of (C₁₋₃)alkyl,
(C₁₋₃)alkoxy, (C₁₋₃)fluoroalkyl, (C₁₋₃)fluoroalkoxy, halogen, hydroxy and -(CH₂)_n-NR'R'',
35 wherein n is 0 or 1 and R' and R'' independently represent (C₁₋₃)alkyl, and wherein
imidazolyl, isoxazolyl, and imidazo[1,2-a]pyridinyl are optionally mono- or di-substituted with

(C₁₋₃)alkyl; and piperidinyl (especially piperidin-4-yl) or pyrrolidinyl (especially pyrrolidin-3-yl), both optionally mono-substituted (preferably at the nitrogen atom) with (C₁₋₃)alkyl or (C₁₋₃)alkyl-CO-.

5 10) Another embodiment of the invention relates to a compound according to embodiment 9), wherein **R**² represents piperidin-4-yl, piperidin-3-yl, or pyrrolidin-3-yl, all optionally mono-substituted at the nitrogen atom wherein the substituent is selected from the group consisting of (C₁₋₅)alkyl; (C₃₋₆)cycloalkyl (especially cyclopentyl); methyl mono-substituted with (C₃₋₆)cycloalkyl (especially cyclopropyl), phenyl, imidazolyl (especially 3H-imidazol-4-yl), isoxazolyl (especially isoxazol-4-yl), or imidazo[1,2-a]pyridinyl (especially imidazo[1,2-a]pyridin-7-yl), wherein the phenyl is optionally mono-substituted with (C₁₋₃)alkyl, (C₁₋₃)alkoxy, (C₁₋₃)fluoroalkyl, (C₁₋₃)fluoroalkoxy, or halogen, and wherein imidazolyl, isoxazolyl, and imidazo[1,2-a]pyridinyl are optionally mono- or di-substituted with (C₁₋₃)alkyl; and piperidinyl (especially piperidin-4-yl) or pyrrolidinyl (especially pyrrolidin-3-yl), both
10 15 optionally mono-substituted at the nitrogen atom with (C₁₋₃)alkyl or (C₁₋₃)alkyl-CO-.

11) Another embodiment of the invention relates to a compound according to embodiment 10), wherein **R**² represents piperidin-4-yl, piperidin-3-yl, or pyrrolidin-3-yl, all mono-substituted at the nitrogen atom with isopropyl, cyclopentyl, or 1-methyl-piperidin-4-yl.

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12) Another embodiment of the invention relates to a compound according to embodiment 11), wherein **R**² represents piperidin-4-yl or piperidin-3-yl, both mono-substituted at the nitrogen atom with isopropyl, cyclopentyl, or 1-methyl-piperidin-4-yl.

25 13) Another embodiment of the invention relates to a compound according to any one of embodiments 1) to 8), wherein **R**² represents R⁴R⁵N-(C₂₋₄)alkyl, wherein R⁴ and R⁵ independently represent hydrogen or (C₁₋₃)alkyl, with the exception that not both R⁴ and R⁵ represent hydrogen (preferably both represent methyl), or wherein R⁴ and R⁵ together with the nitrogen atom to which they are attached form a piperazine ring which is optionally
30 mono-substituted (preferably at the nitrogen atom at position 4) with (C₁₋₃)alkyl (especially methyl).

14) Another embodiment of the invention relates to a compound according to embodiment 13), wherein **R**² represents R⁴R⁵N-(C₂₋₄)alkyl, wherein R⁴ and R⁵ both represent methyl, or
35 wherein R⁴ and R⁵ together with the nitrogen atom to which they are attached form a piperazine ring which is mono-substituted at the nitrogen atom at position 4 with methyl.

15) Another embodiment of the invention relates to a compound according to any one of
embodiments 1) to 14), wherein **Het** represents mono-substituted pyrimidinyl (especially
mono-substituted pyrimidin-2-yl) wherein the substituent is selected from the group
5 consisting of (C₁₋₃)alkyl; (C₁₋₃)alkoxy (especially methoxy) optionally mono-substituted with
phenyl; (C₁₋₃)fluoroalkyl; phenyl or pyridinyl, both optionally mono-substituted with
(C₁₋₄)alkyl, (C₁₋₃)alkoxy, halogen, (C₁₋₃)fluoroalkyl, (C₁₋₃)fluoroalkoxy, cyano, or
methylsulfonyl; and -NR⁶R⁷, wherein R⁶ and R⁷ independently represent (C₁₋₅)alkyl or
wherein R⁶ and R⁷ together with the nitrogen atom to which they are attached form an
10 azetidine, pyrrolidine or piperazine ring wherein the piperazine ring is optionally mono-
substituted (preferably at the nitrogen atom at position 4) with (C₁₋₃)alkyl (especially methyl).

16) Another embodiment of the invention relates to a compound according to embodiment
15), wherein **Het** represents pyrimidin-2-yl mono-substituted at position 4 wherein the
15 substituent is selected from the group consisting of (C₁₋₃)alkyl; (C₁₋₃)alkoxy (especially
methoxy) optionally mono-substituted with phenyl; (C₁₋₃)fluoroalkyl; phenyl or pyridinyl, both
optionally mono-substituted with (C₁₋₄)alkyl, (C₁₋₃)alkoxy, halogen, (C₁₋₃)fluoroalkyl,
(C₁₋₃)fluoroalkoxy, cyano, or methylsulfonyl; and -NR⁶R⁷, wherein R⁶ and R⁷ independently
represent (C₁₋₅)alkyl or wherein R⁶ and R⁷ together with the nitrogen atom to which they are
20 attached form an azetidine, pyrrolidine or piperazine ring wherein the piperazine ring is
optionally mono-substituted (preferably at the nitrogen atom at position 4) with (C₁₋₃)alkyl
(especially methyl).

17) Another embodiment of the invention relates to a compound according to embodiment
25 16), wherein **Het** represents pyrimidin-2-yl mono-substituted at position 4 with phenyl or
pyridinyl, wherein phenyl or pyridinyl are optionally mono-substituted (preferably mono-
substituted) with (C₁₋₄)alkyl, (C₁₋₃)alkoxy, halogen, (C₁₋₃)fluoroalkyl, (C₁₋₃)fluoroalkoxy,
cyano, or methylsulfonyl.

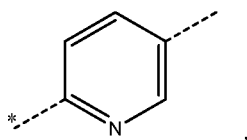
30 18) Another embodiment of the invention relates to a compound according to embodiment
17), wherein **Het** represents pyrimidin-2-yl mono-substituted at position 4 with 4-
(trifluoromethyl)-phenyl or 6-(trifluoromethyl)-pyridin-3-yl.

19) Another embodiment of the invention relates to a compound according to any one of
35 embodiments 1) to 14), wherein **Het** represents quinolinyl (especially quinolin-4-yl)
optionally mono-substituted with (C₁₋₄)alkyl or halogen.

20) Another embodiment of the invention relates to a compound according to embodiment 19), wherein **Het** represents quinolin-4-yl.

5 21) Another embodiment of the invention relates to a compound according to embodiment 1), wherein

A represents 1,4-phenylene, 1,3-phenylene, pyridin-2,6-diyl, or the following group:



wherein the asterisk indicates the bond that is attached to the group **X-R¹**; or, in case **X** is
 10 absent, **A** may also represent piperidin-1,4-diyl, wherein **R¹** is attached to the nitrogen atom of the piperidin-1,4-diyl;

- **X** represents -**NR³**- wherein **R³** represents hydrogen, methyl, or ethyl, and
R¹ represents pyridin-4-yl, 2-methyl-pyridin-4-yl, 2-methoxy-pyridin-4-yl, 2-fluoro-pyridin-4-yl, 3-methyl-pyridin-4-yl, 3-fluoro-pyridin-4-yl, 2-(pyrrolidin-1-yl)-pyridin-4-yl, 3-trifluoromethyl-pyridin-4-yl, 2,6-dimethyl-pyridin-4-yl, pyridin-3-yl, 2-fluoro-pyridin-3-yl, 5-fluoro-pyridin-3-yl, 6-methyl-pyridin-3-yl, pyridin-2-yl, pyrimidin-4-yl, 2-methyl-pyrimidin-4-yl, 6-methyl-pyrimidin-4-yl, pyrimidin-2-yl, pyrazin-2-yl, or 6-methoxy-2-methyl-quinolin-4-yl; or

- **X** is absent and **R¹** represents pyridin-4-yl, pyridin-3-yl or pyridin-2-yl, or, in case **A** is
 20 not piperidin-1,4-diyl, **R¹** may also represent 4-methyl-piperazin-1-yl;

R² represents piperidin-4-yl, piperidin-3-yl, 1-cyclopentyl-piperidin-4-yl, 1-(1-methyl-piperidin-4-yl)-piperidin-4-yl, 1-isopropyl-piperidin-4-yl, 1-(cyclopropylmethyl)-piperidin-4-yl, 1-isopentyl-piperidin-4-yl, 1-((4-methyl-phenyl)-methyl)-piperidin-4-yl, 1-((4-dimethylamino-phenyl)-methyl)-piperidin-4-yl, 1-((4-hydroxy-3-(dimethylaminomethyl)-phenyl)-methyl)-piperidin-4-yl, 1-(imidazo[1,2-a]pyridin-7-ylmethyl)-piperidin-4-yl, 1-(3,5-dimethyl-isoxazol-4-ylmethyl)-piperidin-4-yl, 1-(3-methyl-3H-imidazol-4-ylmethyl)-piperidin-4-yl, 1-isobutyl-piperidin-4-yl, 1-cyclopentyl-piperidin-3-yl, 1-(2-fluoro-1-(fluoromethyl)-ethyl)-piperidin-4-yl, 1-(3,3,3-trifluoro-propyl)-piperidin-4-yl, 1-(1-methylcarbonyl-piperidin-4-yl)-piperidin-4-yl, 1-ethyl-piperidin-4-yl, 1-(1-methyl-piperidin-4-yl)-piperidin-3-yl, 1-cyclopentyl-piperidin-3-yl, 1-isopentyl-piperidin-3-yl, 1-isopropyl-piperidin-3-yl, 1-ethyl-piperidin-3-yl, 1-(1-methyl-pyrrolidin-3-yl)-piperidin-4-yl, 1-(3-fluoro-propyl)-piperidin-4-yl, 1-methyl-piperidin-4-yl, 1-benzyl-piperidin-4-yl, 1-(1-methyl-piperidin-4-yl)-pyrrolidin-3-yl, 1-((4-hydroxy-3-(dimethylaminomethyl)-phenyl)-methyl)-pyrrolidin-3-yl, 1-isopropyl-pyrrolidin-3-yl, 1-isopentyl-pyrrolidin-3-yl, 1-cyclopentyl-pyrrolidin-3-yl, 2-(dimethylamino)-ethyl, 1-methyl-2-

(dimethylamino)-ethyl, 3-(dimethylamino)-propyl, 2-(4-methyl-piperazin-1-yl)-ethyl, 3-(4-methyl-piperazin-1-yl)-propyl, 1-methyl-3-(dimethylamino)-propyl, (3aR,6aS)-2-(1-methyl-piperidin-4-yl)-octahydrocyclopenta[c]pyrrol-5-yl, (3aR,6aS)-2-isopentyl-octahydrocyclopenta[c]pyrrol-5-yl, or (3aR,6aS)-2-cyclopentyl-octahydrocyclopenta[c]pyrrol-5-yl; and

Het represents pyrimidin-2-yl optionally substituted at position 4 by a radical selected from the group consisting of isopropyl, trifluoromethyl, methoxy, pyrrolidin-1-yl, 4-methyl-piperazin-1-yl, phenyl, 2-fluoro-phenyl, 3-fluoro-phenyl, 4-fluoro-phenyl, 3-chloro-phenyl, 4-chloro-phenyl, 3-cyano-phenyl, 4-cyano-phenyl, 4-methoxy-phenyl, 4-methylsulfonyl-phenyl, 2-trifluoromethyl-phenyl, 3-trifluoromethyl-phenyl, 4-trifluoromethyl-phenyl, 4-methyl-phenyl, 4-tert-butyl-phenyl, 4-(trifluoro-methoxy)-phenyl, pyridin-4-yl, 6-trifluoromethyl-pyridin-3-yl, and phenylmethoxy; 5-phenyl-pyrimidin-2-yl; 5-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl; quinolin-4-yl; benzooxazol-2-yl; benzothiazol-2-yl; quinoxalin-2-yl; 3-(4-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl; 5-(4-(trifluoromethyl)phenyl)-1,3,4-oxadiazol-2-yl; 7-chloro-quinazolin-4-yl; 7-isobutyl-quinazolin-4-yl; 6-fluoro-quinazolin-2-yl; 6-(4-trifluoromethyl-phenyl)-pyridin-2-yl; 4-(4-trifluoromethyl-phenyl)-thiazol-2-yl; 2-phenyl-pyrimidin-4-yl; 6-(4-trifluoromethyl-phenyl)-pyrazin-2-yl; 4-(4-trifluoromethyl-phenyl)-pyridin-2-yl; 2-(4-trifluoromethyl-phenyl)-pyridin-4-yl; 4,6-dimethyl-pyrimidin-2-yl; or 6-(4-trifluoromethyl-phenyl)-pyrimidin-4-yl.

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22) The invention, thus, relates to compounds of the Formula I as defined in embodiment 1), or to such compounds further limited by the characteristics of any one of embodiments 2) to 21), under consideration of their respective dependencies; to pharmaceutically acceptable salts thereof; and to such compounds or pharmaceutically acceptable salts thereof for use as medicaments especially for the treatment and/or prevention of protozoal infections, especially malaria. Especially the following embodiments relating to the compounds of Formula I are thus possible and intended and herewith specifically disclosed in individualized form:

1, 2+1, 3+1, 4+1, 4+2+1, 4+3+1, 5+1, 5+2+1, 5+3+1, 6+1, 6+2+1, 6+3+1, 7+1, 7+2+1, 7+3+1, 8+1, 8+2+1, 8+3+1, 9+1, 9+2+1, 9+3+1, 9+4+1, 9+4+2+1, 9+4+3+1, 9+5+1, 9+5+2+1, 9+5+3+1, 9+6+1, 9+6+2+1, 9+6+3+1, 9+7+1, 9+7+2+1, 9+7+3+1, 9+8+1, 9+8+2+1, 9+8+3+1, 10+9+1, 10+9+2+1, 10+9+3+1, 10+9+4+1, 10+9+4+2+1, 10+9+4+3+1, 10+9+5+1, 10+9+5+2+1, 10+9+5+3+1, 10+9+6+1, 10+9+6+2+1, 10+9+6+3+1, 10+9+7+1, 10+9+7+2+1, 10+9+7+3+1, 10+9+8+1, 10+9+8+2+1, 10+9+8+3+1, 11+10+9+1, 11+10+9+2+1, 11+10+9+3+1, 11+10+9+4+1, 11+10+9+4+2+1, 11+10+9+4+3+1, 11+10+9+5+1, 11+10+9+5+2+1, 11+10+9+5+3+1, 11+10+9+6+1, 11+10+9+6+2+1, 11+10+9+6+3+1, 11+10+9+7+1, 11+10+9+7+2+1, 11+10+9+7+3+1, 11+10+9+8+1, 11+10+9+8+2+1, 11+10+9+8+3+1, 12+11+10+9+1, 12+11+10+9+2+1,

- 12+11+10+9+3+1, 12+11+10+9+4+1, 12+11+10+9+4+2+1, 12+11+10+9+4+3+1, 12+11+10+9+5+1,
 12+11+10+9+5+2+1, 12+11+10+9+5+3+1, 12+11+10+9+6+1, 12+11+10+9+6+2+1, 12+11+10+9+6+3+1,
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 12+11+10+9+8+3+1, 13+1, 13+2+1, 13+3+1, 13+4+1, 13+4+2+1, 13+4+3+1, 13+5+1, 13+5+2+1, 13+5+3+1,
 5 13+6+1, 13+6+2+1, 13+6+3+1, 13+7+1, 13+7+2+1, 13+7+3+1, 13+8+1, 13+8+2+1, 13+8+3+1, 14+13+1,
 14+13+2+1, 14+13+3+1, 14+13+4+1, 14+13+4+2+1, 14+13+4+3+1, 14+13+5+1, 14+13+5+2+1, 14+13+5+3+1,
 14+13+6+1, 14+13+6+2+1, 14+13+6+3+1, 14+13+7+1, 14+13+7+2+1, 14+13+7+3+1, 14+13+8+1,
 14+13+8+2+1, 14+13+8+3+1, 15+1, 15+2+1, 15+3+1, 15+4+1, 15+4+2+1, 15+4+3+1, 15+5+1, 15+5+2+1,
 15+5+3+1, 15+6+1, 15+6+2+1, 15+6+3+1, 15+7+1, 15+7+2+1, 15+7+3+1, 15+8+1, 15+8+2+1, 15+8+3+1,
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 15+11+10+9+6+2+1, 15+11+10+9+6+3+1, 15+11+10+9+7+1, 15+11+10+9+7+2+1, 15+11+10+9+7+3+1,
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 15+12+11+10+9+6+2+1, 15+12+11+10+9+6+3+1, 15+12+11+10+9+7+1, 15+12+11+10+9+7+2+1,
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 25 15+13+8+2+1, 15+13+8+3+1, 15+14+13+1, 15+14+13+2+1, 15+14+13+3+1, 15+14+13+4+1,
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 16+15+4+3+1, 16+15+5+1, 16+15+5+2+1, 16+15+5+3+1, 16+15+6+1, 16+15+6+2+1, 16+15+6+3+1,
 30 16+15+7+1, 16+15+7+2+1, 16+15+7+3+1, 16+15+8+1, 16+15+8+2+1, 16+15+8+3+1, 16+15+9+1,
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 16+15+11+10+9+5+2+1, 16+15+11+10+9+5+3+1, 16+15+11+10+9+6+1, 16+15+11+10+9+6+2+1,
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 16+15+12+11+10+9+5+3+1, 16+15+12+11+10+9+6+1, 16+15+12+11+10+9+6+2+1,
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- 30 17+16+15+11+10+9+4+3+1, 17+16+15+11+10+9+5+1, 17+16+15+11+10+9+5+2+1,
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 17+16+15+11+10+9+6+3+1, 17+16+15+11+10+9+7+1, 17+16+15+11+10+9+7+2+1,
 17+16+15+11+10+9+7+3+1, 17+16+15+11+10+9+8+1, 17+16+15+11+10+9+8+2+1,
 17+16+15+11+10+9+8+3+1, 17+16+15+12+11+10+9+1, 17+16+15+12+11+10+9+2+1,
- 35 17+16+15+12+11+10+9+3+1, 17+16+15+12+11+10+9+4+1, 17+16+15+12+11+10+9+4+2+1,
 17+16+15+12+11+10+9+4+3+1, 17+16+15+12+11+10+9+5+1, 17+16+15+12+11+10+9+5+2+1,

- 17+16+15+12+11+10+9+5+3+1, 17+16+15+12+11+10+9+6+1, 17+16+15+12+11+10+9+6+2+1,
 17+16+15+12+11+10+9+6+3+1, 17+16+15+12+11+10+9+7+1, 17+16+15+12+11+10+9+7+2+1,
 17+16+15+12+11+10+9+7+3+1, 17+16+15+12+11+10+9+8+1, 17+16+15+12+11+10+9+8+2+1,
 17+16+15+12+11+10+9+8+3+1, 17+16+15+13+1, 17+16+15+13+2+1, 17+16+15+13+3+1, 17+16+15+13+4+1,
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 17+16+15+14+13+2+1, 17+16+15+14+13+3+1, 17+16+15+14+13+4+1, 17+16+15+14+13+4+2+1,
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 17+16+15+14+13+8+3+1, 18+17+16+15+1, 18+17+16+15+2+1, 18+17+16+15+3+1, 18+17+16+15+4+1,
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 18+17+16+15+9+7+2+1, 18+17+16+15+9+7+3+1, 18+17+16+15+9+8+1, 18+17+16+15+9+8+2+1,
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- In the list above, the numbers refer to the embodiments according to their numbering provided hereinabove whereas "+" indicates the dependency from another embodiment.
- 25 The different individualized embodiments are separated by commas. In other words, "9+6+1" for example refers to embodiment 9) depending on embodiment 6) depending on embodiment 1), i.e. embodiment "9+6+1" corresponds to the compounds of embodiment 1) further limited by the features of the embodiments 6) and 9).
- 30 The compounds of Formula I may contain one or more stereogenic or asymmetric centers, such as one or more asymmetric carbon atoms. The compounds of Formula I may thus be present as mixtures of stereoisomers or preferably as pure stereoisomers. Mixtures of stereoisomers may be separated in a manner known to a person skilled in the art.
- 35 Where the plural form is used for compounds, salts, pharmaceutical compositions, diseases and the like, this is intended to mean also a single compound, salt, or the like.

Any reference hereinbefore or hereinafter to a compound of Formula I is to be understood as referring also to salts, especially pharmaceutically acceptable salts, of a compound of Formula I, as appropriate and expedient.

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The term "pharmaceutically acceptable salts" refers to salts that retain the desired biological activity of the subject compound and exhibit minimal undesired toxicological effects. Such salts include inorganic or organic acid and/or base addition salts depending on the presence of basic and/or acidic groups in the subject compound. For reference see
10 for example 'Handbook of Pharmaceutical Salts. Properties, Selection and Use.', P. Heinrich Stahl, Camille G. Wermuth (Eds.), Wiley-VCH, 2008 and 'Pharmaceutical Salts and Co-crystals', Johan Wouters and Luc Quéré (Eds.), RSC Publishing, 2012.

The present invention also includes isotopically labelled, especially ^2H (deuterium) labelled
15 compounds of Formula I, which compounds are identical to the compounds of Formula I except that one or more atoms have each been replaced by an atom having the same atomic number but an atomic mass different from the atomic mass usually found in nature. Isotopically labelled, especially ^2H (deuterium) labelled compounds of Formula I and salts thereof are within the scope of the present invention. Substitution of hydrogen with the
20 heavier isotope ^2H (deuterium) may lead to greater metabolic stability, resulting e.g. in increased *in vivo* half-life or reduced dosage requirements, or may lead to reduced inhibition of cytochrome P450 enzymes, resulting e.g. in an improved safety profile. In one embodiment of the invention, the compounds of Formula I are not isotopically labelled, or they are labelled only with one or more deuterium atoms. In a sub-embodiment, the
25 compounds of Formula I are not isotopically labelled at all. Isotopically labelled compounds of Formula I may be prepared in analogy to the methods described hereinafter, but using the appropriate isotopic variation of suitable reagents or starting materials.

23) Particular compounds of Formula I are selected from the group consisting of:
30 [4-(Methyl-pyridin-4-yl-amino)-benzyl]-piperidin-4-yl-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
[4-(Methyl-pyridin-4-yl-amino)-benzyl]-(S)-piperidin-3-yl-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
[6-(2-Methyl-pyridin-4-yl-amino)-pyridin-3-ylmethyl]-piperidin-4-yl-quinolin-4-yl-amine,
35 [4-(Methyl-pyridin-4-yl-amino)-benzyl]-piperidin-4-yl-quinolin-4-yl-amine,
[4-(2-Methyl-pyridin-4-yl-amino)-benzyl]-(S)-piperidin-3-yl-quinolin-4-yl-amine,

- (1-Cyclopentyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
(1'-Methyl-[1,4']bipiperidinyl-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
- 5 (1-Isopropyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
(1-Cyclopropylmethyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
[1-(3-Methyl-butyl)-piperidin-4-yl]-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[4-(4-
- 10 trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
[1-(4-Methyl-benzyl)-piperidin-4-yl]-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
[1-(4-Dimethylamino-benzyl)-piperidin-4-yl]-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
- 15 2-Dimethylaminomethyl-4-(4-{[4-(methyl-pyridin-4-yl-amino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amino}-piperidin-1-ylmethyl)-phenol,
(1-Imidazo[1,2-a]pyridin-7-ylmethyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
[1-(3,5-Dimethyl-isoxazol-4-ylmethyl)-piperidin-4-yl]-[4-(methyl-pyridin-4-yl-amino)-benzyl]-
- 20 [4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
[1-(3-Methyl-3H-imidazol-4-ylmethyl)-piperidin-4-yl]-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
[1-(3-Methyl-butyl)-piperidin-4-yl]-[6-(methyl-pyridin-4-yl-amino)-pyridin-3-ylmethyl]-quinolin-4-yl-amine,
- 25 (1-Cyclopropylmethyl-piperidin-4-yl)-[6-(methyl-pyridin-4-yl-amino)-pyridin-3-ylmethyl]-quinolin-4-yl-amine,
[1-(3-Methyl-3H-imidazol-4-ylmethyl)-piperidin-4-yl]-[6-(methyl-pyridin-4-yl-amino)-pyridin-3-ylmethyl]-quinolin-4-yl-amine,
(1-Isobutyl-piperidin-4-yl)-[6-(methyl-pyridin-4-yl-amino)-pyridin-3-ylmethyl]-quinolin-4-yl-
- 30 amine,
((S)-1-Cyclopentyl-piperidin-3-yl)-[4-(2-methyl-pyridin-4-yl-amino)-benzyl]-quinolin-4-yl-amine,
Benzooxazol-2-yl-(1'-methyl-[1,4']bipiperidinyl-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-amine,
- 35 4-(4-{Benzooxazol-2-yl-[4-(methyl-pyridin-4-yl-amino)-benzyl]-amino}-piperidin-1-ylmethyl)-2-dimethylaminomethyl-phenol,

- Benzooxazol-2-yl-(1-isopropyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-amine,
Benzooxazol-2-yl-[1-(3-methyl-butyl)-piperidin-4-yl]-[4-(methyl-pyridin-4-yl-amino)-benzyl]-
amine,
(1'-Methyl-[1,4']bipiperidinyl-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-quinoxalin-2-yl-
amine,
5 2-Dimethylaminomethyl-4-(4-{[4-(methyl-pyridin-4-yl-amino)-benzyl]-quinoxalin-2-yl-amino}-
piperidin-1-ylmethyl)-phenol,
(1-Isopropyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-quinoxalin-2-yl-amine,
[1-(3-Methyl-butyl)-piperidin-4-yl]-[4-(methyl-pyridin-4-yl-amino)-benzyl]-quinoxalin-2-yl-
amine,
10 (1-Cyclopentyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-quinoxalin-2-yl-amine,
Benzooxazol-2-yl-[1-(3-methyl-3H-imidazol-4-ylmethyl)-piperidin-4-yl]-[4-(methyl-pyridin-4-
yl-amino)-benzyl]-amine,
[1-(3-Methyl-3H-imidazol-4-ylmethyl)-piperidin-4-yl]-[4-(methyl-pyridin-4-yl-amino)-benzyl]-
quinoxalin-2-yl-amine,
15 Benzooxazol-2-yl-(1-cyclopentyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-
amine,
[1-(2-Fluoro-1-fluoromethyl-ethyl)-piperidin-4-yl]-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[4-
(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
20 [4-(Methyl-pyridin-4-yl-amino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-[1-(3,3,3-
trifluoro-propyl)-piperidin-4-yl]-amine,
1-(4-{[4-(Methyl-pyridin-4-yl-amino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-
amino}-[1,4']bipiperidinyl-1'-yl)-ethanone,
(1-Ethyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-
pyrimidin-2-yl]-amine,
25 (1'-Methyl-[1,4']bipiperidinyl-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-quinolin-4-yl-amine,
Benzothiazol-2-yl-(1'-methyl-[1,4']bipiperidinyl-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-
amine,
Benzothiazol-2-yl-(1-cyclopentyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-
amine,
30 Benzothiazol-2-yl-[1-(3-methyl-butyl)-piperidin-4-yl]-[4-(methyl-pyridin-4-yl-amino)-benzyl]-
amine,
Benzothiazol-2-yl-[1-(3-methyl-3H-imidazol-4-ylmethyl)-piperidin-4-yl]-[4-(methyl-pyridin-4-
yl-amino)-benzyl]-amine,
35 (S)-1'-methyl-N-(4-(methyl(pyridin-4-yl)amino)benzyl)-N-(4-(4-
(trifluoromethyl)phenyl)pyrimidin-2-yl)-[1,4'-bipiperidin]-3-amine,

- (S)-N-(1-cyclopentylpiperidin-3-yl)-N-(4-(methyl(pyridin-4-yl)amino)benzyl)-4-(4-(trifluoromethyl)phenyl)pyrimidin-2-amine,
- (S)-N-(1-isopentylpiperidin-3-yl)-N-(4-(methyl(pyridin-4-yl)amino)benzyl)-4-(4-(trifluoromethyl)phenyl)pyrimidin-2-amine,
- 5 (3aR,6aS)-N-(4-(methyl(pyridin-4-yl)amino)benzyl)-2-(1-methylpiperidin-4-yl)-N-(4-(4-(trifluoromethyl)phenyl)pyrimidin-2-yl)octahydrocyclopenta[c]pyrrol-5-amine,
- (3aR,6aS)-2-isopentyl-N-(4-(methyl(pyridin-4-yl)amino)benzyl)-N-(4-(4-(trifluoromethyl)phenyl)pyrimidin-2-yl)octahydrocyclopenta[c]pyrrol-5-amine,
- (3aR,6aS)-2-cyclopentyl-N-(4-(methyl(pyridin-4-yl)amino)benzyl)-N-(4-(4-
- 10 (trifluoromethyl)phenyl)pyrimidin-2-yl)octahydrocyclopenta[c]pyrrol-5-amine,
- (S)-N-(4-(Ethyl(pyridin-4-yl)amino)benzyl)-1'-methyl-N-(4-(4-(trifluoromethyl)phenyl)pyrimidin-2-yl)-[1,4'-bipiperidin]-3-amine,
- ((S)-1'-Methyl-[1,4']bipiperidinyl-3-yl)-[4-(methyl-pyridin-3-yl-amino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
- 15 ((S)-1'-Methyl-[1,4']bipiperidinyl-3-yl)-{4-[methyl-(2-methyl-pyridin-4-yl)-amino]-benzyl}-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
- ((S)-1-Isopropyl-piperidin-3-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
- ((S)-1-Ethyl-piperidin-3-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[4-(4-trifluoromethyl-
- 20 phenyl)-pyrimidin-2-yl]-amine,
- N-(4-(Methyl(pyridin-4-yl)amino)benzyl)-N-(1'-methyl-[1,4'-bipiperidin]-4-yl)-3-(4-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-amine,
- N-(4-(Methyl(pyridin-4-yl)amino)benzyl)-N-(1'-methyl-[1,4'-bipiperidin]-4-yl)-5-(4-(trifluoromethyl)phenyl)-1,3,4-oxadiazol-2-amine,
- 25 [(S)-1-(1-Methyl-piperidin-4-yl)-pyrrolidin-3-yl]-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
- 2-Dimethylaminomethyl-4-((S)-3-{[4-(methyl-pyridin-4-yl-amino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amino}-pyrrolidin-1-ylmethyl)-phenol,
- ((S)-1-Isopropyl-pyrrolidin-3-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[4-(4-trifluoromethyl-
- 30 phenyl)-pyrimidin-2-yl]-amine,
- [(R)-1-(1-Methyl-piperidin-4-yl)-pyrrolidin-3-yl]-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
- 2-Dimethylaminomethyl-4-((R)-3-{[4-(methyl-pyridin-4-yl-amino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amino}-pyrrolidin-1-ylmethyl)-phenol,
- 35 [(S)-1-(3-Methyl-butyl)-pyrrolidin-3-yl]-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,

- ((S)-1-Cyclopentyl-pyrrolidin-3-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
((R)-1-Isopropyl-pyrrolidin-3-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
5 [(R)-1-(3-Methyl-butyl)-pyrrolidin-3-yl]-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
((R)-1-Cyclopentyl-pyrrolidin-3-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
[4-(Methyl-pyridin-4-yl-amino)-benzyl]-[1-(1-methyl-pyrrolidin-3-yl)-piperidin-4-yl]-[4-(4-
10 trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
[1-(3-Fluoro-propyl)-piperidin-4-yl]-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
(1-Methyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
15 (1-Benzyl-piperidin-4-yl)-[4-(2-methyl-pyridin-4-yl-amino)-benzyl]-[5-phenyl-pyrimidin-2-yl]-amine,
(1-Benzyl-piperidin-4-yl)-[4-(3-fluoro-phenyl)-pyrimidin-2-yl]-[4-(2-methyl-pyridin-4-yl-amino)-benzyl]-amine,
(1-Benzyl-piperidin-4-yl)-[4-(2-methyl-pyridin-4-yl-amino)-benzyl]-[5-(4-trifluoromethyl-
20 phenyl)-pyrimidin-2-yl]-amine,
(1-Benzyl-piperidin-4-yl)-(7-chloro-quinazolin-4-yl)-[4-(2-methyl-pyridin-4-yl-amino)-benzyl]-amine,
(1-Benzyl-piperidin-4-yl)-(6-fluoro-quinazolin-2-yl)-[4-(2-methyl-pyridin-4-yl-amino)-benzyl]-amine,
25 (1-Benzyl-piperidin-4-yl)-[4-(2-methyl-pyridin-4-yl-amino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
(1-Isopropyl-piperidin-4-yl)-{6-[methyl-(2-methyl-pyridin-4-yl)-amino]-pyridin-3-ylmethyl}-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
(1-Isopropyl-piperidin-4-yl)-[6-(2-methyl-pyridin-4-yl-amino)-pyridin-3-ylmethyl]-[4-(4-
30 trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
(1-Isopropyl-piperidin-4-yl)-[6-(3-methyl-pyridin-4-yl-amino)-pyridin-3-ylmethyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
[6-(3-Fluoro-pyridin-4-yl-amino)-pyridin-3-ylmethyl]-(1-isopropyl-piperidin-4-yl)-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
35 (1-Isopropyl-piperidin-4-yl)-[6-(pyrimidin-4-yl-amino)-pyridin-3-ylmethyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,

- (1-Isopropyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[6-(4-trifluoromethyl-phenyl)-pyridin-2-yl]-amine,
(1-Isopropyl-piperidin-4-yl)-[6-(methyl-pyridin-3-yl-amino)-pyridin-3-ylmethyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
5 (1-Isopropyl-piperidin-4-yl)-[3-(methyl-pyridin-4-yl-amino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
(1-Isopropyl-piperidin-4-yl)-[3-(methyl-pyridin-3-yl-amino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
(1-Isopropyl-piperidin-4-yl)-[3-[methyl-(2-methyl-pyridin-4-yl)-amino]-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
10 (1-Isopropyl-piperidin-4-yl)-[3-(2-methyl-pyridin-4-ylamino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
(1-Isopropyl-piperidin-4-yl)-[3-(3-methyl-pyridin-4-ylamino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
15 [3-(3-Fluoro-pyridin-4-ylamino)-benzyl]-(1-isopropyl-piperidin-4-yl)-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
(1-Isopropyl-piperidin-4-yl)-[3-(pyrimidin-4-ylamino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
[4-(4-Fluoro-phenyl)-pyrimidin-2-yl]-(1-isopropyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-amine,
20 N,N-Dimethyl-N'-[4-(methyl-pyridin-4-yl-amino)-benzyl]-N'-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-ethane-1,2-diamine,
N1,N1-Dimethyl-N2-[4-(methyl-pyridin-4-yl-amino)-benzyl]-N2-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-propane-1,2-diamine,
25 N,N-Dimethyl-N'-[4-(methyl-pyridin-4-yl-amino)-benzyl]-N'-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-propane-1,3-diamine,
[2-(4-Methyl-piperazin-1-yl)-ethyl]-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
[2-(4-Methyl-piperazin-1-yl)-ethyl]-[4-(2-methyl-pyridin-4-ylamino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
30 [3-(4-Methyl-piperazin-1-yl)-propyl]-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
[3-(4-Methyl-piperazin-1-yl)-propyl]-[4-(2-methyl-pyridin-4-ylamino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
35 [3-(4-Methyl-piperazin-1-yl)-propyl]-[4-(3-methyl-pyridin-4-ylamino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,

- [4-((1-Benzyl-piperidin-4-yl)-[4-(4-trifluoromethyl-phenyl)-thiazol-2-yl]-amino)-methyl-phenyl]-(2-methyl-pyridin-4-yl)-amine,
 (1-Isopropyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-(2-phenyl-pyrimidin-4-yl)-amine,
 5 (1-Isopropyl-piperidin-4-yl)-[4-(2-methyl-pyridin-4-yl-amino)-benzyl]-(2-phenyl-pyrimidin-4-yl)-amine,
 (1-Isopropyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[6-(4-trifluoromethyl-phenyl)-pyrazin-2-yl]-amine,
 (1-Isopropyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-quinolin-4-yl-amine,
 10 (4-Benzyloxy-pyrimidin-2-yl)-(1-isopropyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-amine,
 (1-Isopropyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyridin-2-yl]-amine,
 (1-Isopropyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[2-(4-trifluoromethyl-phenyl)-pyridin-4-yl]-amine,
 15 (4,6-Dimethyl-pyrimidin-2-yl)-(1-isopropyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-amine,
 (1-Isopropyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[6-(4-trifluoromethyl-phenyl)-pyrimidin-4-yl]-amine,
 20 (1-Isopropyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-pyrimidin-2-yl-amine,
 (1-Isopropyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[5-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
 (1-Isopropyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-(4-trifluoromethyl-pyrimidin-2-yl)-amine,
 25 N1,N1-Dimethyl-N3-[4-(methyl-pyridin-4-yl-amino)-benzyl]-N3-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-butane-1,3-diamine,
 ((S)-1-Isopropyl-piperidin-3-yl)-[6-(2-methyl-pyridin-4-yl-amino)-pyridin-3-ylmethyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
 (1'-Methyl-[1,4']bipiperidinyl-4-yl)-[6-(2-methyl-pyridin-4-yl-amino)-pyridin-3-ylmethyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
 30 (1'-Methyl-[1,4']bipiperidinyl-4-yl)-[6-(methyl-pyridin-4-yl-amino)-pyridin-3-ylmethyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
 (1-Isopropyl-piperidin-4-yl)-(4-methoxy-pyrimidin-2-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-amine,
 35 1'-Methyl-N-(4-((2-methylpyridin-4-yl)amino)benzyl)-N-(4-(4-(trifluoromethyl)phenyl)pyrimidin-2-yl)-[1,4'-bipiperidin]-4-amine,

- N-(4-((2,6-Dimethylpyridin-4-yl)amino)benzyl)-1'-methyl-N-(4-(4-(trifluoromethyl)phenyl)pyrimidin-2-yl)-[1,4'-bipiperidin]-4-amine,
 1'-Methyl-N-(4-(methyl(pyridin-3-yl)amino)benzyl)-N-(4-(4-(trifluoromethyl)phenyl)pyrimidin-2-yl)-[1,4'-bipiperidin]-4-amine,
 5 1'-Methyl-N-(4-(methyl(pyridin-2-yl)amino)benzyl)-N-(4-(4-(trifluoromethyl)phenyl)pyrimidin-2-yl)-[1,4'-bipiperidin]-4-amine,
 1'-Methyl-N-(4-(methyl(2-methylpyridin-4-yl)amino)benzyl)-N-(4-(4-(trifluoromethyl)phenyl)pyrimidin-2-yl)-[1,4'-bipiperidin]-4-amine,
 1'-Methyl-N-(4-(pyridin-4-ylamino)benzyl)-N-(4-(4-(trifluoromethyl)phenyl)pyrimidin-2-yl)-
 10 [1,4'-bipiperidin]-4-amine,
 1'-Methyl-N-(4-(pyrimidin-4-ylamino)benzyl)-N-(4-(4-(trifluoromethyl)phenyl)pyrimidin-2-yl)-[1,4'-bipiperidin]-4-amine,
 N-(4-((2-Methoxypyridin-4-yl)amino)benzyl)-1'-methyl-N-(4-(4-(trifluoromethyl)phenyl)pyrimidin-2-yl)-[1,4'-bipiperidin]-4-amine,
 15 N-(4-((2-Fluoropyridin-4-yl)amino)benzyl)-1'-methyl-N-(4-(4-(trifluoromethyl)phenyl)pyrimidin-2-yl)-[1,4'-bipiperidin]-4-amine,
 6-Methoxy-2-methyl-N-(4-(((1'-methyl-[1,4'-bipiperidin]-4-yl)(4-(4-(trifluoromethyl)phenyl)pyrimidin-2-yl)amino)methyl)phenyl)quinolin-4-amine,
 N-(4-(Ethyl(pyridin-4-yl)amino)benzyl)-1'-methyl-N-(4-(4-(trifluoromethyl)phenyl)pyrimidin-2-yl)-[1,4'-bipiperidin]-4-amine,
 20 N-(4-((3-Fluoropyridin-4-yl)amino)benzyl)-1'-methyl-N-(4-(4-(trifluoromethyl)phenyl)pyrimidin-2-yl)-[1,4'-bipiperidin]-4-amine,
 1'-Methyl-N-(4-((3-methylpyridin-4-yl)amino)benzyl)-N-(4-(4-(trifluoromethyl)phenyl)pyrimidin-2-yl)-[1,4'-bipiperidin]-4-amine,
 25 1'-Methyl-N-(4-(4-methylpiperazin-1-yl)benzyl)-N-(4-(4-(trifluoromethyl)phenyl)pyrimidin-2-yl)-[1,4'-bipiperidin]-4-amine,
 N-(1-Isopropylpiperidin-4-yl)-N-(4-((2-methylpyridin-4-yl)amino)benzyl)-4-(4-(trifluoromethyl)phenyl)pyrimidin-2-amine,
 N-(1-Isopropylpiperidin-4-yl)-N-(4-((3-methylpyridin-4-yl)amino)benzyl)-4-(4-(trifluoromethyl)phenyl)pyrimidin-2-amine,
 30 N-(4-((3-Fluoropyridin-4-yl)amino)benzyl)-N-(1-isopropylpiperidin-4-yl)-4-(4-(trifluoromethyl)phenyl)pyrimidin-2-amine,
 N-(1-Isopropylpiperidin-4-yl)-4-(4-(trifluoromethyl)phenyl)-N-(4-((3-(trifluoromethyl)pyridin-4-yl)amino)benzyl)pyrimidin-2-amine,
 35 N-(4-((5-Fluoropyridin-3-yl)amino)benzyl)-N-(1-isopropylpiperidin-4-yl)-4-(4-(trifluoromethyl)phenyl)pyrimidin-2-amine,

- N-(1-Isopropylpiperidin-4-yl)-N-(4-(pyridin-3-ylamino)benzyl)-4-(4-(trifluoromethyl)phenyl)pyrimidin-2-amine,
- N-(1-Isopropylpiperidin-4-yl)-N-(4-((2-(pyrrolidin-1-yl)pyridin-4-yl)amino)benzyl)-4-(4-(trifluoromethyl)phenyl)pyrimidin-2-amine,
- 5 N-(1-Isopropylpiperidin-4-yl)-N-(4-((2-methylpyrimidin-4-yl)amino)benzyl)-4-(4-(trifluoromethyl)phenyl)pyrimidin-2-amine,
- N-(1-Isopropylpiperidin-4-yl)-N-(4-(methyl(2-methylpyrimidin-4-yl)amino)benzyl)-4-(4-(trifluoromethyl)phenyl)pyrimidin-2-amine,
- (1-Isopropyl-piperidin-4-yl)-[4-(pyrimidin-4-ylamino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-
- 10 pyrimidin-2-yl]-amine,
- N-(1-Isopropylpiperidin-4-yl)-N-(4-((6-methylpyrimidin-4-yl)amino)benzyl)-4-(4-(trifluoromethyl)phenyl)pyrimidin-2-amine,
- N-(1-Isopropylpiperidin-4-yl)-N-(4-(methyl(6-methylpyrimidin-4-yl)amino)benzyl)-4-(4-(trifluoromethyl)phenyl)pyrimidin-2-amine,
- 15 (1-Isopropyl-piperidin-4-yl)-[4-(pyrimidin-2-ylamino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
- (1-Isopropyl-piperidin-4-yl)-[4-(6-methyl-pyridin-3-ylamino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
- (1-Isopropyl-piperidin-4-yl)-[4-(pyrazin-2-ylamino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-
- 20 pyrimidin-2-yl]-amine,
- (1-Isopropyl-piperidin-4-yl)-[4-(methyl-pyridin-3-yl-amino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
- [4-(2-Fluoro-pyridin-3-ylamino)-benzyl]-(1-isopropyl-piperidin-4-yl)-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
- 25 [2-(4-Methyl-piperazin-1-yl)-ethyl]-[4-(3-methyl-pyridin-4-ylamino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
- {4-[Methyl-(2-methyl-pyridin-4-yl)-amino]-benzyl}-[2-(4-methyl-piperazin-1-yl)-ethyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
- {4-[Methyl-(2-methyl-pyridin-4-yl)-amino]-benzyl}-[3-(4-methyl-piperazin-1-yl)-propyl]-[4-(4-
- 30 trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
- (1-Isopropyl-piperidin-4-yl)-{4-[methyl-(3-methyl-pyridin-4-yl)-amino]-benzyl}-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
- (1-Isopropyl-piperidin-4-yl)-[6-(methyl-pyridin-4-yl-amino)-pyridin-2-ylmethyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
- 35 (1-Isopropyl-piperidin-4-yl)-{6-[methyl-(2-methyl-pyridin-4-yl)-amino]-pyridin-2-ylmethyl}-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,

- (1-Isopropyl-piperidin-4-yl)-[6-(2-methyl-pyridin-4-ylamino)-pyridin-2-ylmethyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
(1-Isopropyl-piperidin-4-yl)-[6-(3-methyl-pyridin-4-ylamino)-pyridin-2-ylmethyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
5 [6-(3-Fluoro-pyridin-4-ylamino)-pyridin-2-ylmethyl]-(1-isopropyl-piperidin-4-yl)-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
(1-Isopropyl-piperidin-4-yl)-[6-(pyrimidin-4-ylamino)-pyridin-2-ylmethyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
(1-Isopropyl-piperidin-4-yl)-[6-(methyl-pyridin-2-yl-amino)-pyridin-2-ylmethyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
10 (1-Isopropyl-piperidin-4-yl)-[4-(4-methyl-piperazin-1-yl)-pyrimidin-2-yl]-[4-(methyl-pyridin-4-yl-amino)-benzyl]-amine,
(1-Isopropyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-(4-pyrrolidin-1-yl-pyrimidin-2-yl)-amine,
15 (1-Isopropyl-piperidin-4-yl)-(3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-ylmethyl)-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
(1-Isopropyl-piperidin-4-yl)-(3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-ylmethyl)-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
(1-Isopropyl-piperidin-4-yl)-(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-ylmethyl)-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
20 (7-Isobutyl-quinazolin-4-yl)-(1-isopropyl-piperidin-4-yl)-[4-(2-methyl-pyridin-4-ylamino)-benzyl]-amine,
[4-(4-Chloro-phenyl)-pyrimidin-2-yl]-(1-isopropyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-amine,
25 [4-(4-tert-Butyl-phenyl)-pyrimidin-2-yl]-(1-isopropyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-amine,
(1-Isopropyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-(4-pyridin-4-yl-pyrimidin-2-yl)-amine,
(1-Isopropyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[4-(4-trifluoromethoxy-phenyl)-pyrimidin-2-yl]-amine,
30 (1-Isopropyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-(4-p-tolyl-pyrimidin-2-yl)-amine,
[4-(2-Fluoro-phenyl)-pyrimidin-2-yl]-(1-isopropyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-amine,
35 4-(2-{(1-Isopropyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-amino}-pyrimidin-4-yl)-benzonitrile,

- (1-Isopropyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[4-(3-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
 (1-Isopropyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[4-(2-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
 5 4-(2-(((S)-1'-Methyl-[1,4']bipiperidinyl-3-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-amino)-pyrimidin-4-yl)-benzonitrile,
 (((S)-1'-Methyl-[1,4']bipiperidinyl-3-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[4-(6-trifluoromethyl-pyridin-3-yl)-pyrimidin-2-yl]-amine,
 [4-(4-Fluoro-phenyl)-pyrimidin-2-yl]-((S)-1'-methyl-[1,4']bipiperidinyl-3-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-amine,
 10 [4-(4-Methanesulfonyl-phenyl)-pyrimidin-2-yl]-((S)-1'-methyl-[1,4']bipiperidinyl-3-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-amine,
 [4-(4-Chloro-phenyl)-pyrimidin-2-yl]-((S)-1'-methyl-[1,4']bipiperidinyl-3-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-amine,
 15 [4-(3-Chloro-phenyl)-pyrimidin-2-yl]-((S)-1'-methyl-[1,4']bipiperidinyl-3-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-amine,
 3-(2-(((S)-1'-Methyl-[1,4']bipiperidinyl-3-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-amino)-pyrimidin-4-yl)-benzonitrile,
 (1-Isopropyl-piperidin-4-yl)-[4-(4-methoxy-phenyl)-pyrimidin-2-yl]-[4-(methyl-pyridin-4-yl-amino)-benzyl]-amine,
 20 (1-Isopropyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[4-(phenyl-pyrimidin-2-yl)-amine,
 (1-Isopropyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[4-(6-trifluoromethyl-pyridin-3-yl)-pyrimidin-2-yl]-amine,
 25 (1-Isopropyl-piperidin-4-yl)-(4-pyridin-3-yl-benzyl)-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
 (1-Isopropyl-piperidin-4-yl)-(4-pyridin-4-yl-benzyl)-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
 (1-Isopropyl-piperidin-4-yl)-(4-pyridin-2-yl-benzyl)-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine, and
 30 (1-Isopropyl-piperidin-4-yl)-(4-isopropyl-pyrimidin-2-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-amine.

- 24) Preferred compounds of Formula I are selected from the group consisting of:
 35 (1'-Methyl-[1,4']bipiperidinyl-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,

- (1-Isopropyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
 (1'-Methyl-[1,4']bipiperidinyl-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-quinolin-4-yl-amine,
 (S)-1'-methyl-N-(4-(methyl(pyridin-4-yl)amino)benzyl)-N-(4-(4-
 5 (trifluoromethyl)phenyl)pyrimidin-2-yl)-[1,4'-bipiperidin]-3-amine,
 (3aR,6aS)-N-(4-(methyl(pyridin-4-yl)amino)benzyl)-2-(1-methylpiperidin-4-yl)-N-(4-(4-
 (trifluoromethyl)phenyl)pyrimidin-2-yl)octahydrocyclopenta[c]pyrrol-5-amine,
 ((S)-1'-Methyl-[1,4']bipiperidinyl-3-yl)-{4-[methyl-(2-methyl-pyridin-4-yl)-amino]-benzyl}-[4-(4-
 trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
 10 (1-Isopropyl-piperidin-4-yl)-[6-(2-methyl-pyridin-4-ylamino)-pyridin-3-ylmethyl]-[4-(4-
 trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
 (1-Isopropyl-piperidin-4-yl)-[3-(2-methyl-pyridin-4-ylamino)-benzyl]-[4-(4-trifluoromethyl-
 phenyl)-pyrimidin-2-yl]-amine,
 (1-Isopropyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-quinolin-4-yl-amine,
 15 (1'-Methyl-[1,4']bipiperidinyl-4-yl)-[6-(methyl-pyridin-4-yl-amino)-pyridin-3-ylmethyl]-[4-(4-
 trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
 ((S)-1'-Methyl-[1,4']bipiperidinyl-3-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[4-(6-
 trifluoromethyl-pyridin-3-yl)-pyrimidin-2-yl]-amine, and
 (1-Isopropyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[4-(6-trifluoromethyl-
 20 pyridin-3-yl)-pyrimidin-2-yl]-amine.

- 25) Particularly preferred compounds of Formula I are selected from the group consisting of:
 (1'-Methyl-[1,4']bipiperidinyl-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-quinolin-4-yl-amine,
 25 (1-Isopropyl-piperidin-4-yl)-[6-(2-methyl-pyridin-4-ylamino)-pyridin-3-ylmethyl]-[4-(4-
 trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
 (1-Isopropyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-quinolin-4-yl-amine, and
 (1-Isopropyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[4-(6-trifluoromethyl-
 pyridin-3-yl)-pyrimidin-2-yl]-amine.

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- The compounds of Formula I according to any one of embodiments 1) to 25) and their pharmaceutically acceptable salts can be used as medicaments, e.g. in the form of pharmaceutical compositions for enteral (such especially oral) or parenteral (including topical application or inhalation) administration, and are suitable for the treatment and/or
 35 prevention of the diseases mentioned herein, such as malaria infections, or other protozoal

diseases like sleeping sickness, Chagas disease, amebiasis, giardiasis, trichomoniasis, toxoplasmosis, and leishmaniasis; especially malaria.

The production of the pharmaceutical compositions can be effected in a manner which will be familiar to any person skilled in the art (see for example Remington, *The Science and Practice of Pharmacy*, 21st Edition (2005), Part 5, "Pharmaceutical Manufacturing" [published by Lippincott Williams & Wilkins]) by bringing the described compounds of Formula I or their pharmaceutically acceptable salts, optionally in combination with other therapeutically valuable substances, into a galenical administration form together with suitable, non-toxic, inert, pharmaceutically acceptable solid or liquid carrier materials and, if desired, usual pharmaceutical adjuvants.

In one embodiment, the invention relates to a method for the treatment or prevention of the diseases mentioned herein, such as especially malaria, said method comprising administering to a subject a pharmaceutically active amount of a compound of Formula I.

In a preferred embodiment of the invention, the administered amount of a compound according to any one of embodiments 1) to 25) is comprised between 1 mg and 2000 mg per day, particularly between 50 mg and 1500 mg per day, more particularly between 100 mg and 1000 mg per day, especially between 250 mg and 1000 mg per day.

For the avoidance of any doubt, if compounds are described as useful for the prevention or treatment of certain diseases, such compounds are likewise suitable for use in the preparation of a medicament for the prevention or treatment of the diseases mentioned herein, such as especially malaria.

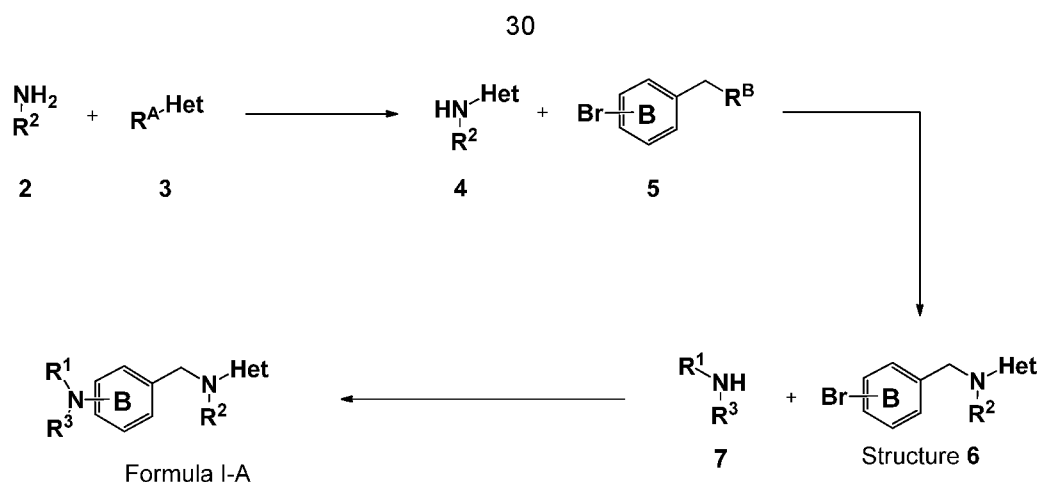
The compounds of Formula I according to any one of embodiments 1) to 25), or the above-mentioned pharmaceutical compositions, may also be used in combination with one or more other therapeutically useful substances e.g. with other antimalarials like quinolines (e.g. quinine, chloroquine, amodiaquine, mefloquine, primaquine, and tafenoquine), peroxide antimalarials (e.g. artemisinin, artemether, and artesunate), pyrimethamine-sulfadoxine antimalarials (e.g. Fansidar®), hydroxynaphtoquinones (e.g. atovaquone), acroline-type antimalarials (e.g. pyronaridine), and other antiprotozoal agents like ethylstilbamidine, hydroxystilbamidine, pentamidine, stilbamidine, quinapyramine, puromycine, propamidine, nifurtimox, melarsoprol, nimorazole, nifuroxime, aminitroazole and the like.

The present invention also relates to the use of a compound of Formula I according to any one of embodiments 1) to 25), or a pharmaceutically acceptable salt thereof, for the preparation of a pharmaceutical composition, optionally for use in combination with one or more other therapeutically useful substances such as those mentioned in the preceding paragraph, for the prevention and/or treatment of the diseases mentioned herein, such as especially malaria.

Preparation of compounds of Formula I

Compounds of Formula I can be manufactured by the methods given below, by the methods given in the examples or by analogous methods. Optimum reaction conditions may vary with the particular reactants or solvents used, but such conditions can be determined by a person skilled in the art by routine optimization procedures. Compounds of Formula I of the present invention can be prepared according to the general sequence of reactions outlined below wherein, if not explicitly stated otherwise, R^1 to R^7 , Het, X, and A are as defined for Formula I.

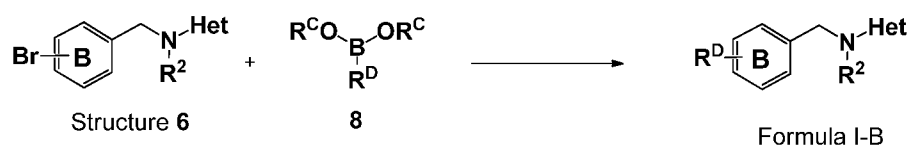
Compounds of Formula I can be prepared following one of the synthetic sequence described in Schemes 1 to 7. Compounds of Formula I-A (wherein X represents $-NR^3-$) are synthesized following the synthetic pathway depicted in Scheme 1. A primary amine **2** can be used in a *Buchwald-Hartwig* cross-coupling with a heterocycle **3** (wherein R^A represents bromo, chloro, or triflate) in the presence of a palladium catalyst like $Pd_2(dba)_3$, a ligand like X-Phos, a base like NaOtBu and a solvent like dioxane to afford a secondary amine **4**. Alternatively, a nucleophilic aromatic substitution between a primary amine **2** and an appropriate heterocycle **3** (wherein R^A represents bromo or chloro) in the presence of a base like NEt_3 or DIPEA in a solvent like EtOH or *i*PrOH can yield a secondary amine **4**. An amine **4** can be alkylated with an electrophile **5** (wherein R^B represents chloro or bromo and ring B represents phenylene or pyridin-diyl) in the presence of a base like NaH to give a bromide of Structure **6**. A compound of Formula I-A (wherein X represents $-NR^3-$) is obtained by a *Buchwald-Hartwig* cross-coupling between a bromide of Structure **6** and an amine **7** in the presence of a palladium catalyst like $Pd_2(dba)_3$, a ligand like X-phos, a base like NaOtBu and a solvent like dioxane.



Scheme 1. Synthesis of a compound of Formula I-A.

In a further aspect, a bromide of Structure 6 can be engaged in a *Suzuki* cross-coupling with an appropriate boronic acid or a boronic ester derivative 8 (wherein R^{C} represents hydrogen or pinacole, and R^{D} represents an optionally mono-substituted pyridinyl) in the presence of a base like Na_2CO_3 or K_3PO_4 , and a palladium catalyst like $\text{Pd}(\text{PPh}_3)_4$, or $\text{Pd}(\text{OAc})_2$ and S-Phos to give a compound of Formula I-B (wherein **X** is absent) (Scheme 2).

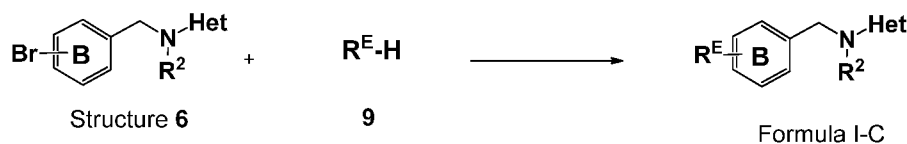
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Scheme 2. Synthesis of a compound of Formula I-B.

In a further aspect, a bromide of Structure 6 can undergo a *Buchwald-Hartwig* cross-coupling with a compound 9 (wherein $\text{R}^{\text{E}}\text{-H}$ represents mono-substituted piperazinyl) in the presence of palladium catalyst like $\text{Pd}_2(\text{dba})_3$, a ligand like X-phos, a base like NaOtBu and a solvent like dioxane to afford a compound of Formula I-C (wherein **X** is absent) (Scheme 3).

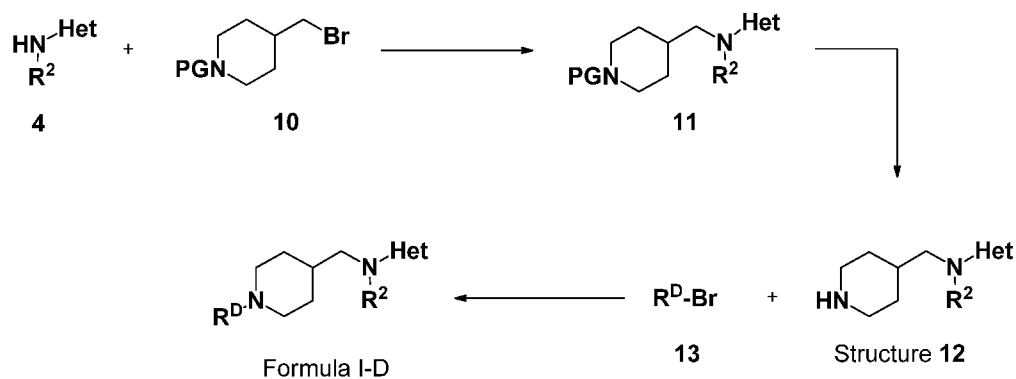
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Scheme 3. Synthesis of a compound of Formula I-C.

In another aspect, a secondary amine **4** can be alkylated with an electrophile **10** in the presence of a base like NaH to give a tertiary amine **11**. An intermediate of Structure **12** is obtained after removal of a protecting group (PG) from a tertiary amine **11**, applying reaction conditions known to a skilled person. Preferably, PG is a group such as *tert*-butoxycarbonyl. A *tert*-butoxycarbonyl group is cleaved under acidic conditions. A compound of Formula I-D is obtained by a *Buchwald-Hartwig* cross-coupling between an intermediate of Structure **12** and a bromide **13** in the presence of palladium catalyst like Pd₂(dba)₃, a ligand like X-phos, a base like NaOtBu and a solvent like dioxane (Scheme 4).

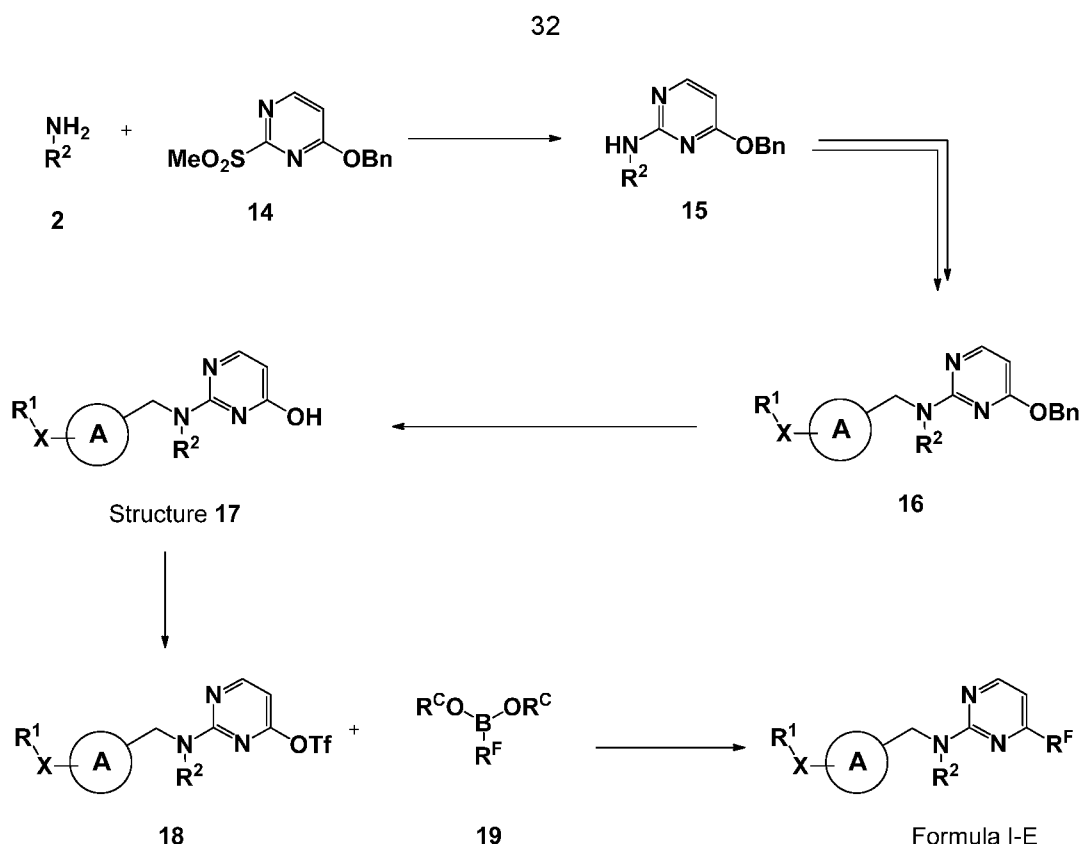
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Scheme 4. Synthesis of a compound of Formula I-D.

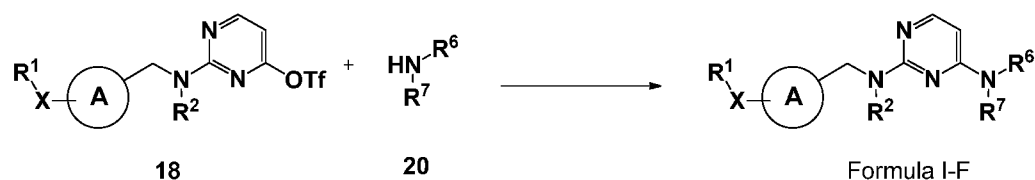
In another aspect, heating an amine **2** in the presence of an electrophile **14** and base like DIPEA in solvent like EtOH or *i*PrOH gives an amine **15**. In analogy to Schemes 1-4, an amine **15** can be converted into an intermediate **16**. Removal of the benzyl protecting group under an H₂-atmosphere in the presence of Pd/C and in a solvent like EtOH affords an alcohol **17**. An intermediate **17** can be converted into a triflate **18** upon treatment with triflic anhydride in the presence of a base like NEt₃ in a solvent like DCM. A triflate **18** can be engaged in a *Suzuki* cross-coupling with an appropriate boronic acid or a boronic ester derivative **19** (wherein R^F represents optionally mono-substituted phenyl or pyridinyl) in the presence of a base like Na₂CO₃ or K₃PO₄, and a palladium catalyst like Pd(PPh₃)₄, or Pd(OAc)₂ and S-Phos to give a compound of Formula I-E (wherein **X** is absent) (Scheme 5).

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Scheme 5. Synthesis of a compound of Formula I-E.

In a further aspect, a triflate **18** can undergo a *Buchwald-Hartwig* cross-coupling with an amine **20** in the presence of palladium catalyst like $\text{Pd}_2(\text{dba})_3$, a ligand like X-phos, a base like NaOtBu and a solvent like dioxane to afford a compound of Formula I-F (Scheme 6).



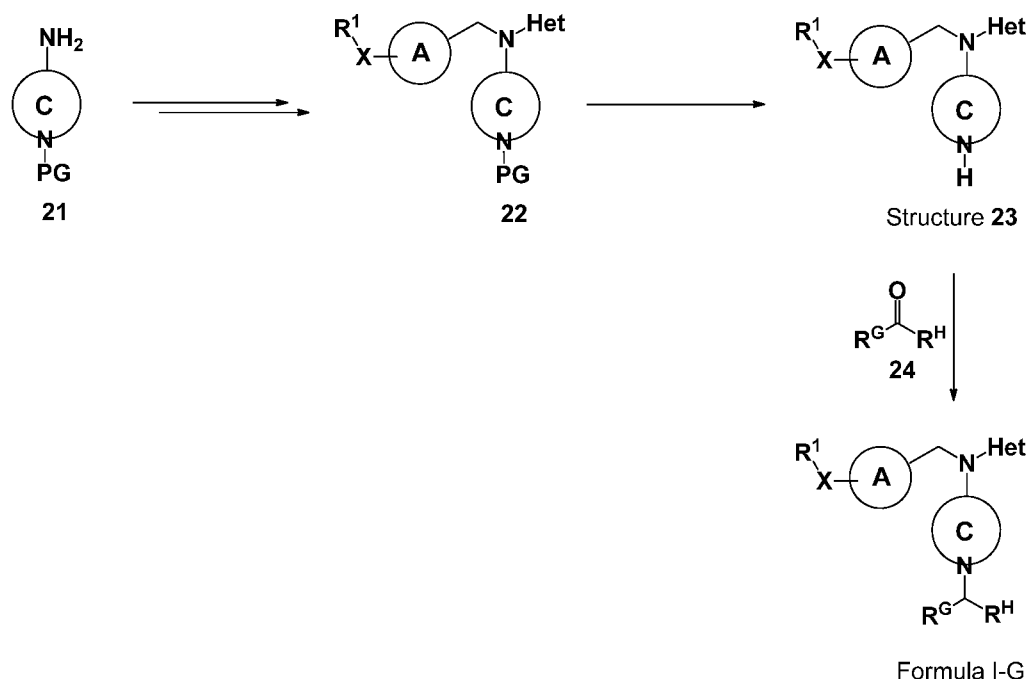
Scheme 6. Synthesis of a compound of Formula I-F.

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In a different aspect, a cyclic amine **21** (wherein ring C represents piperidinyl, pyrrolidinyl, or (3aR,6aS)-octahydrocyclopenta[c]pyrrol-5-yl) is converted to an intermediate **22** according to Schemes 1-4. An intermediate of Structure **23** is obtained after removal of a protecting group (PG) from an intermediate **22**, applying reaction conditions known to a skilled person. Preferably, PG is a group such as *tert*-butoxycarbonyl. A *tert*-butoxycarbonyl group is cleaved under acidic conditions. An cyclic amine of Structure **23** undergoes a

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reductive amination with an appropriate aldehyde or ketone **24** (wherein R^G and R^H together with the carbon atom to which they are attached form a ring C substituent possible according to the present invention) in the presence of a reducing agent like $\text{NaHB}(\text{OAc})_3$ to give a compound of Formula I-G (Scheme 7). If **24** is a ketone, activation with a Lewis acid or AcOH may be required.



Scheme 7. Synthesis of a compound of Formula I-G.

The following examples illustrate the present invention. All solvents and reagents are used as obtained from commercial sources unless otherwise stated. All temperatures are indicated in degrees Celsius and pressures in mbar. Unless mentioned otherwise, the reactions take place at room temperature (r.t.). In mixtures, relations of parts of solvent or eluent or reagent mixtures in liquid form are given as volume relations (v/v), unless indicated otherwise.

Whenever the compounds of Formula I are obtained in the form of mixtures of stereoisomers such as especially enantiomers, the stereoisomers can be separated using methods known to one skilled in the art: e.g. by formation and separation of diastereomeric salts or by HPLC over a chiral stationary phase such as a Daicel ChiralPak AD-H (5 μm) column, a Daicel ChiralCel OD-H (5 μm) column, a Daicel ChiralCel OD (10 μm) column, a Daicel ChiralPak IA (5 μm) column, a Daicel ChiralPak IB (5 μm) column, a Daicel

ChiralPak IC (5 μ m) column, or a (R,R)-Whelk-01 (5 μ m) column. Typical conditions of chiral HPLC are an isocratic mixture of eluent A (EtOH, in presence or absence of a base like triethylamine and/or diethylamine or of an acid like TFA) and eluent B (heptane).

5 **Experimental part**

General conditions:

Analytical HPLC conditions:

10 **LC-MS 1TFA:**

LC-MS-conditions: Analytical. Pump: Waters Acquity Binary, Solvent Manager, MS: Waters SQ Detector, DAD: Acquity UPLC PDA Detector. Column: Acquity UPLC BEH C18 1.7 μ m 2.1x50 mm from Waters, thermostated in the Acquity UPLC Column Manager at 60°C. Eluents: A: H₂O + 0.05% TFA; B: MeCN + 0.045% TFA. Method: Gradient: 2% B 98% B over 2.0 min. Flow: 1.0 mL/min. Detection: UV 214 nm and MS, t_R is given in min.

LC-MS 2 to LC-MS 4:

HPLC/MS analyses are performed on an Ultimate 3000RS Dionex HPLC instrument, equipped with a Dionex Ultimate 3000 RS Photodiode Array Detector, a Dionex Ultimate 3000RS pump and a Dionex MSQ⁺ mass spectrometer.

20 The LC retention times are obtained using the following elution conditions:

- LC-MS 2: Analytical HPLC on a Waters X-Bridge C18 column (4.6x30 mm, 2.5 μ m, Waters); Linear gradient of water/ 0.04% TFA (A) and MeCN (B) from 5% to 95% B over 1.5 min; flow rate 4.5 mL/min, detection at 215 nm.

25 - LC-MS 3: Analytical HPLC on a Waters X-Bridge C18 column (4.6x30 mm, 2.5 μ m, Waters); Linear concentrated NH₃ in water (1.0 mL/L) (A) and MeCN (B) from 5% to 95% B over 1.5 min; flow rate 4.5 mL/min, detection at 215 nm.

- LC-MS 4: Analytical HPLC on a Zorbax[®] SB-AQ column (4.6x50 mm, 3.5 μ m, Agilent); Linear gradient of water/ 0.04% TFA (A) and MeCN (B) from 5% to 95% B over 1.5 min; flow rate 4.5 mL/min, detection at 215 nm.

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Preparative HPLC conditions:

Preparative HPLC/MS purifications are performed on a Gilson HPLC system, equipped with a Gilson 215 autosampler, Gilson 333/334 pumps, Finnigan AQA MS detector system, and a Dionex UV detector, using a Waters Xbridge C18 or an Waters Atlantis T3 column, with a

linear gradient of water/formic acid 0.02% (A) and MeCN (B) (acidic conditions) or water/ammonia 0.02% (A) and MeCN (B) (basic conditions).

Flash chromatography:

Flash chromatography purifications are performed using SiO₂ 60 (230-400 mesh, particle size 40-63 µm) from *Fluka*.

Flashmaster purifications are performed using a Büchi system (Büchi Fraction Collector C-660, Büchi Pump Manager C-615, Büchi Pump Module C-605).

Abbreviations (as used herein below and in the description above):

Ac	acetyl
AcOEt	ethyl acetate
AcOH	acetic acid
aq.	aqueous
Ar	argon
Bn	benzyl
Boc	tert-butyloxycarbonyl
BrettPhos	2-(dicyclohexylphosphino)3,6-dimethoxy-2',4',6'-triisopropyl-1,1'-biphenyl
CC	column chromatography on silica gel
comb.	combined
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
DIPEA	<i>N,N</i> -diisopropylethylamine
DMAP	4-(dimethylamino)-pyridine
DMF	<i>N,N</i> -dimethylformamide
eq.	equivalent(s)
Et ₂ O	diethyl ether
EtOH	ethanol
FC	flash chromatography
Hept	heptane
HPLC	high performance liquid chromatography
<i>i</i> PrOH	isopropanol
LC-MS	liquid chromatography - mass spectroscopy
M	molarity [mol L ⁻¹]
<i>m</i> CPBA	3-chloroperbenzoic acid
Me	methyl

MeCN	acetonitrile
MeOH	methanol
min	minute(s)
MS	mass spectroscopy
N	normality of solution
NaOtBu	sodium tert-butoxide
NEt ₃	triethylamine
NMP	1-methyl-2-pyrrolidone
org.	organic
Pd/C	palladium on carbon
Pd ₂ (dba) ₃	tris(dibenzylideneacetone)dipalladium(0)
Pd(dppf)Cl ₂ CH ₂ Cl ₂	[1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with DCM
Pd(PPh ₃) ₄	tetrakis(triphenylphosphine)palladium(0)
prep.	preparative
r.t.	room temperature
sat.	saturated
soln.	solution
S-Phos	2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl
Tf	trifluoromethyl-sulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
t _R	retention time
UV	ultraviolet
w%	weight percent
X-Phos	2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl

General methods and examples

The following examples illustrate the preparation of compounds of the invention. First the synthesis of compounds of Formula I is described, followed by the description of the synthesis of intermediates and starting materials. Whenever used in the experimental part, generic Structures **1**, **2**, **3** etc. refer to the respective structures described in the preceding general description of the preparation of compounds of Formula I. Compounds denoted with (±) are prepared as racemic mixtures.

General method for the preparation of compounds of Formula I:*Boc deprotection:*

Method A: To an ice-cooled solution of 4-[[4-(methyl-pyridin-4-yl-amino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amino}-piperidine-1-carboxylic acid tert-butyl ester (2.10 g, 3.39 mmol, 1 eq.) in DCM (50 mL), 4M hydrogen chloride in dioxane (12 mL) was added. The reaction mixture was stirred at r.t. for 2 hours. The reaction mixture was concentrated in vacuo. The residue was partitioned between 1M aq. NaOH (100 mL) and DCM (100 mL). The layers were separated. The aq. phase was extracted with DCM (2 x 50 mL). The comb. org. phases were washed with water (2 x 100 mL), sat. aq. NaCl soln. (1 x 100 mL), dried over MgSO₄ and concentrated in vacuo to give the desired product as a pale yellow foam. The product was used without further purification.

Listed in Table 1 below are examples of compounds of Formula I, prepared according to the above-mentioned method with the corresponding Boc-protected amine **22** as starting material.

Table 1

Example	Compound of Formula I	<i>t_R</i> [min] LC-MS Method	MS-data m/z [M+H] ⁺
1	[4-(Methyl-pyridin-4-yl-amino)-benzyl]-piperidin-4-yl-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine	0.79 LC-MS 1TFA	519.4
2	[4-(Methyl-pyridin-4-yl-amino)-benzyl]-(S)-piperidin-3-yl-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine	0.79 LC-MS 1TFA	519.4

Method B: To an ice-cooled solution of tert-butyl 4-(((6-((2-methylpyridin-4-yl)amino)pyridin-3-yl)methyl)(quinolin-4-yl)amino)piperidine-1-carboxylate (1.18 g, 2.25 mmol, 1 eq.) in DCM (15 mL) under N₂, TFA (1.72 mL, 22.5 mmol, 10 eq.) was added. The reaction mixture was stirred at r.t. for 18 hours. The reaction mixture was concentrated in vacuo. The residue was partitioned between 1M aq. NaOH and DCM. The layers were separated. The aq. phase was extracted with DCM. The comb. org. phases were washed with water, sat. aq. NaCl soln., dried over MgSO₄ and concentrated in vacuo to give the desired product as an orange solid. The product was used without further purification.

Listed in Table 2 below are examples of compounds of Formula I, prepared according to the above-mentioned method with the corresponding Boc-protected amine **22** as starting material.

Table 2

Example	Compound of Formula I	t _R [min] LC-MS Method	MS-data m/z [M+H] ⁺
3	[6-(2-Methyl-pyridin-4-ylamino)-pyridin-3-ylmethyl]-piperidin-4-yl-quinolin-4-yl-amine	0.37 LC-MS 1TFA	425.3
4	[4-(Methyl-pyridin-4-yl-amino)-benzyl]-piperidin-4-yl-quinolin-4-yl-amine	0.39 LC-MS 1TFA	424.4
5	[4-(2-Methyl-pyridin-4-ylamino)-benzyl]-(S)-piperidin-3-yl-quinolin-4-yl-amine	0.40 LC-MS 1TFA	424.4

Reductive amination:

Method A: To a solution of cyclopentanone (8.4 mg, 0.10 mmol, 1.3 eq.) and [4-(methylpyridin-4-yl-amino)-benzyl]-piperidin-4-yl-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine (46 mg, 0.08 mmol, 1.0 eq.) in MeOH (1 mL), AcOH (6 µL, 0.09 mmol, 1.1 eq.) was added. The mixture was stirred at 45 °C for 30 min. The mixture was allowed to cool to r.t. and sodium triacetoxyborohydride (16 mg, 0.08 mmol, 1.0 eq.) was added. The mixture was stirred at r.t. for 4 hours. The mixture was partitioned between DCM (3 mL) and sat. aq. NaHCO₃ soln. (2 mL). The layers were separated and the aq. phase was extracted with

DCM (3 x 2 mL). The comb. org. phases were concentrated in vacuo. The residue was purified by prep. HPLC (column: Waters X-bridge, 30x75 mm, 10 μ m, UV/MS, basic conditions), and concentrated in vacuo.

- 5 Listed in Table 3 below are examples of compounds of Formula I, prepared according to the above-mentioned method with the corresponding amine of Structure **23** and the corresponding aldehyde or ketone **24** as starting materials.

Table 3

Example	Compound of Formula I	t_R [min] LC-MS Method	MS-data m/z [M+H] ⁺
6	(1-Cyclopentyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine	0.86 LC-MS 1TFA	587.4
7	(1'-Methyl-[1,4']bipiperidinyl-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine	0.60 LC-MS 4	616.4
8	(1-Isopropyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine	0.83 LC-MS 1TFA	561.4
9	(1-Cyclopropylmethyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine	0.85 LC-MS 1TFA	573.4
10	[1-(3-Methyl-butyl)-piperidin-4-yl]-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine	0.90 LC-MS 1TFA	589.4
11	[1-(4-Methyl-benzyl)-piperidin-4-yl]-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine	0.92 LC-MS 1TFA	623.5
12	[1-(4-Dimethylamino-benzyl)-piperidin-4-yl]-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine	0.89 LC-MS 1TFA	652.5
13	2-Dimethylaminomethyl-4-(4-{[4-(methyl-pyridin-4-yl-amino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amino}-piperidin-1-ylmethyl)-phenol	0.73 LC-MS 1TFA	682.4

14	(1-Imidazo[1,2-a]pyridin-7-ylmethyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine	0.72 LC-MS 1TFA	649.3
15	[1-(3,5-Dimethyl-isoxazol-4-ylmethyl)-piperidin-4-yl]-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine	0.84 LC-MS 1TFA	628.4
16	[1-(3-Methyl-3H-imidazol-4-ylmethyl)-piperidin-4-yl]-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine	0.72 LC-MS 1TFA	613.4
17	[1-(3-Methyl-butyl)-piperidin-4-yl]-[6-(methyl-pyridin-4-yl-amino)-pyridin-3-ylmethyl]-quinolin-4-yl-amine	0.47 LC-MS 1TFA	495.4
18	(1-Cyclopropylmethyl-piperidin-4-yl)-[6-(methyl-pyridin-4-yl-amino)-pyridin-3-ylmethyl]-quinolin-4-yl-amine	0.41 LC-MS 1TFA	479.4
19	[1-(3-Methyl-3H-imidazol-4-ylmethyl)-piperidin-4-yl]-[6-(methyl-pyridin-4-yl-amino)-pyridin-3-ylmethyl]-quinolin-4-yl-amine	0.37 LC-MS 1TFA	519.4
20	(1-Isobutyl-piperidin-4-yl)-[6-(methyl-pyridin-4-yl-amino)-pyridin-3-ylmethyl]-quinolin-4-yl-amine	0.43 LC-MS 1TFA	481.4
21	((S)-1-Cyclopentyl-piperidin-3-yl)-[4-(2-methyl-pyridin-4-ylamino)-benzyl]-quinolin-4-yl-amine	0.45 LC-MS 1TFA	492.4

Method B: To a solution of benzooxazol-2-yl-[4-(methyl-pyridin-4-yl-amino)-benzyl]-piperidin-4-yl-amine (41 mg, 0.1 mmol, 1 eq.) and 1-methyl-4-piperidone (34 mg, 0.3 mmol, 3 eq.) in MeCN (2 mL), sodium triacetoxyborohydride (64 mg, 0.3 mmol, 3 eq.) was added.

- 5 The mixture was stirred at 45 °C for 18 hours. The solution was allowed to cool to r.t. and purified by prep. HPLC (column: Waters X-Bridge, 18x50 mm, 10 μm, UV/MS, basic conditions) and concentrated in vacuo.

- 10 Listed in Table 4 below are examples of compounds of Formula I, prepared according to the above-mentioned method with the corresponding amine of Structure **23** and the corresponding aldehyde or ketone **24** as starting materials.

Table 4

Example	Compound of Formula I	t _R [min] LC-MS Method	MS-data m/z [M+H] ⁺
22	Benzooxazol-2-yl-(1'-methyl-[1,4']bipiperidinyl-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-amine	0.50 LC-MS 4	511.4
23	4-(4-{Benzooxazol-2-yl-[4-(methyl-pyridin-4-yl-amino)-benzyl]-amino}-piperidin-1-ylmethyl)-2-dimethylaminomethyl-phenol	0.57 LC-MS 1TFA	577.4
24	Benzooxazol-2-yl-(1-isopropyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-amine	0.62 LC-MS 1TFA	456.4
25	Benzooxazol-2-yl-[1-(3-methyl-butyl)-piperidin-4-yl]-[4-(methyl-pyridin-4-yl-amino)-benzyl]-amine	0.70 LC-MS 1TFA	484.4
26	(1'-Methyl-[1,4']bipiperidinyl-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-quinoxalin-2-yl-amine	0.55 LC-MS 1TFA	522.4
27	2-Dimethylaminomethyl-4-(4-{[4-(methyl-pyridin-4-yl-amino)-benzyl]-quinoxalin-2-yl-amino}-piperidin-1-ylmethyl)-phenol	0.56 LC-MS 1TFA	588.4
28	(1-Isopropyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-quinoxalin-2-yl-amine	0.63 LC-MS 1TFA	467.4
29	[1-(3-Methyl-butyl)-piperidin-4-yl]-[4-(methyl-pyridin-4-yl-amino)-benzyl]-quinoxalin-2-yl-amine	0.71 LC-MS 1TFA	495.5
30	(1-Cyclopentyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-quinoxalin-2-yl-amine	0.67 LC-MS 1TFA	493.5
31	Benzooxazol-2-yl-[1-(3-methyl-3H-imidazol-4-ylmethyl)-piperidin-4-yl]-[4-(methyl-pyridin-4-yl-amino)-benzyl]-amine	0.55 LC-MS 1TFA	508.4
32	[1-(3-Methyl-3H-imidazol-4-ylmethyl)-piperidin-4-yl]-[4-(methyl-pyridin-4-yl-amino)-benzyl]-quinoxalin-2-yl-amine	0.55 LC-MS 1TFA	519.4

33	Benzooxazol-2-yl-(1-cyclopentyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-amine	0.65 LC-MS 1TFA	482.4
34	[1-(2-Fluoro-1-fluoromethyl-ethyl)-piperidin-4-yl]-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine	0.83 LC-MS 1TFA	597.4
35	[4-(Methyl-pyridin-4-yl-amino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-[1-(3,3,3-trifluoro-propyl)-piperidin-4-yl]-amine	0.86 LC-MS 1TFA	615.4
36	1-(4-{{[4-(Methyl-pyridin-4-yl-amino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amino}-[1,4']bipiperidinyl-1'-yl)-ethanone	0.79 LC-MS 1TFA	644.5
37	(1-Ethyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine	0.81 LC-MS 1TFA	547.4
38	(1'-Methyl-[1,4']bipiperidinyl-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-quinolin-4-yl-amine	0.38 LC-MS 1TFA	521.4
39	Benzothiazol-2-yl-(1'-methyl-[1,4']bipiperidinyl-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-amine	0.57 LC-MS 1TFA	527.5

- Method C: To a solution of benzothiazol-2-yl-[4-(methyl-pyridin-4-yl-amino)-benzyl]-piperidin-4-yl-amine (30 mg, 0.070 mmol, 1.0 eq.) in MeOH (3.5 mL), cyclopentanone (6 mg, 0.070 mmol, 1.0 eq.) and acetic acid (4 μ L, 0.077 mmol, 1.1 eq.) were added in sequence. The mixture was stirred at 45 °C, then cooled to r.t. Sodium triacetoxymethylborohydride (15 mg, 0.070 mmol, 1.0 eq.) was added. The mixture was stirred at r.t. for 18 hours. Cyclopentanone (12 mg, 0.140 mmol, 2.0 eq.) and sodium triacetoxymethylborohydride (30 mg, 0.140 mmol, 2.0 eq.) were added. The mixture was stirred at 45 °C for 24 hours. The mixture was allowed to cool to r.t. and partitioned between sat. aq. NaHCO₃ soln. and DCM. The layers were separated and the aq. phase was extracted with DCM. The comb. org. phases were concentrated in vacuo. The residue was purified by prep. HPLC (column: Waters X-Bridge, 18x50 mm, 10 μ m, UV/MS, basic conditions) and concentrated in vacuo.
- Listed in Table 5 below are examples of compounds of Formula I, prepared according to the above-mentioned method with the corresponding amine of Structure **23** and the corresponding aldehyde or ketone **24** as starting materials.

Table 5

Example	Compound of Formula I	<i>t_R</i> [min] LC-MS Method	MS-data m/z [M+H] ⁺
40	Benzothiazol-2-yl-(1-cyclopentyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-amine	0.69 LC-MS 1TFA	498.4
41	Benzothiazol-2-yl-[1-(3-methyl-butyl)-piperidin-4-yl]-[4-(methyl-pyridin-4-yl-amino)-benzyl]-amine	0.74 LC-MS 1TFA	500.4
42	Benzothiazol-2-yl-[1-(3-methyl-3H-imidazol-4-ylmethyl)-piperidin-4-yl]-[4-(methyl-pyridin-4-yl-amino)-benzyl]-amine	0.59 LC-MS 1TFA	524.3

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Method D: To a solution of [4-(methyl-pyridin-4-yl-amino)-benzyl]-(S)-piperidin-3-yl-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine (25 mg, 0.05 mmol, 1.0 eq.) in MeCN (1 mL), N-methyl-4-piperidone (6 μ L, 0.05 mmol, 1.0 eq.) was added. The reaction mixture was stirred at r.t. for 2 hours. Sodium triacetoxymethylborohydride (15 mg, 0.07 mmol, 1.5 eq.) was

added and the reaction mixture was stirred at r.t. for 18 hours. The mixture was filtered through isolate H-MN and purified by prep. HPLC (column: Waters Xbridge C18, 10 μ m, 30x75mm, acidic conditions) and concentrated in vacuo.

- 5 Listed in Table 6 below are examples of compounds of Formula I, prepared according to the above-mentioned method with the corresponding amine of Structure **23** and the corresponding aldehyde or ketone **24** as starting materials.

Table 6

Example	Compound of Formula I	t_R [min] LC-MS Method	MS-data m/z [M+H] ⁺
43	(S)-1'-methyl-N-(4-(methyl(pyridin-4-yl)amino)benzyl)-N-(4-(4-(trifluoromethyl)phenyl)pyrimidin-2-yl)-[1,4'-bipiperidin]-3-amine	0.69 LC-MS 1TFA	616.4
44	(S)-N-(1-cyclopentylpiperidin-3-yl)-N-(4-(methyl(pyridin-4-yl)amino)benzyl)-4-(4-(trifluoromethyl)phenyl)pyrimidin-2-amine	0.86 LC-MS 1TFA	587.5
45	(S)-N-(1-isopentylpiperidin-3-yl)-N-(4-(methyl(pyridin-4-yl)amino)benzyl)-4-(4-(trifluoromethyl)phenyl)pyrimidin-2-amine	0.90 LC-MS 1TFA	589.5
46	(3aR,6aS)-N-(4-(methyl(pyridin-4-yl)amino)benzyl)-2-(1-methylpiperidin-4-yl)-N-(4-(4-(trifluoromethyl)phenyl)pyrimidin-2-yl)octahydrocyclopenta[c]pyrrol-5-amine (mixture of stereoisomers)	0.74 LC-MS 1TFA	642.5
47	(3aR,6aS)-2-isopentyl-N-(4-(methyl(pyridin-4-yl)amino)benzyl)-N-(4-(4-(trifluoromethyl)phenyl)pyrimidin-2-yl)octahydrocyclopenta[c]pyrrol-5-amine (mixture of stereoisomers)	0.92 LC-MS 1TFA	615.5

48	(3aR,6aS)-2-cyclopentyl-N-(4-(methyl(pyridin-4-yl)amino)benzyl)-N-(4-(4-(trifluoromethyl)phenyl)pyrimidin-2-yl)octahydrocyclopenta[c]pyrrol-5-amine (mixture of stereoisomers)	0.88 LC-MS 1TFA	613.4
49	(S)-N-(4-(Ethyl(pyridin-4-yl)amino)benzyl)-1'-methyl-N-(4-(4-(trifluoromethyl)phenyl)pyrimidin-2-yl)-[1,4'-bipiperidin]-3-amine	0.71 LC-MS 1TFA	630.5
50	((S)-1'-Methyl-[1,4']bipiperidinyl-3-yl)-[4-(methyl-pyridin-3-yl-amino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine	0.70 LC-MS 1TFA	616.5
51	((S)-1'-Methyl-[1,4']bipiperidinyl-3-yl)-{4-[methyl-(2-methyl-pyridin-4-yl)-amino]-benzyl}-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine	0.71 LC-MS 1TFA	630.3
52	((S)-1-Isopropyl-piperidin-3-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine	0.83 LC-MS 1TFA	561.4
53	((S)-1-Ethyl-piperidin-3-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine	0.81 LC-MS 1TFA	547.4
54	N-(4-(Methyl(pyridin-4-yl)amino)benzyl)-N-(1'-methyl-[1,4'-bipiperidin]-4-yl)-3-(4-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-amine	0.69 LC-MS 1TFA	606.5
55	N-(4-(Methyl(pyridin-4-yl)amino)benzyl)-N-(1'-methyl-[1,4'-bipiperidin]-4-yl)-5-(4-(trifluoromethyl)phenyl)-1,3,4-oxadiazol-2-amine	0.63 LC-MS 1TFA	606.4

Method E: To a solution of [4-(methyl-pyridin-4-yl-amino)-benzyl]-(S)-pyrrolidin-3-yl-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine (180 mg, 0.36 mmol, 1 eq.) and 1-methyl-4-piperidone (0.12 mL, 1.07 mmol, 3 eq.) in acetonitrile (4 mL), sodium triacetoxyborohydride (227 mg, 1.07 mmol, 3 eq.) was added. The mixture was stirred at 45 °C for 18 hours. The reaction mixture was quenched with sat. aq. Na₂CO₃ soln. The mixture was extracted with DCM. The comb. org. phases were washed with water, sat. aq. NaCl soln., dried over MgSO₄, and concentrated in vacuo. The residue was purified by prep. HPLC (column: Waters X-Bridge, 18x50 mm, 10 μm, UV/MS, basic conditions) and concentrated in vacuo.

10

Listed in Table 7 below are examples of compounds of Formula I, prepared according to the above-mentioned method with the corresponding amine of Structure **23** and the corresponding aldehyde or ketone **24** as starting materials.

15 **Table 7**

Example	Compound of Formula I	t _R [min] LC-MS Method	MS-data m/z [M+H] ⁺
56	[(S)-1-(1-Methyl-piperidin-4-yl)-pyrrolidin-3-yl]-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine	0.70 LC-MS 1TFA	602.5
57	2-Dimethylaminomethyl-4-((S)-3-{[4-(methyl-pyridin-4-yl-amino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amino}-pyrrolidin-1-ylmethyl)-phenol	0.71 LC-MS 1TFA	668.6
58	((S)-1-Isopropyl-pyrrolidin-3-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine	0.83 LC-MS 1TFA	547.4
59	[(R)-1-(1-Methyl-piperidin-4-yl)-pyrrolidin-3-yl]-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine	0.69 LC-MS 1TFA	602.5
60	2-Dimethylaminomethyl-4-((R)-3-{[4-(methyl-pyridin-4-yl-amino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amino}-pyrrolidin-1-ylmethyl)-phenol	0.71 LC-MS 1TFA	668.5

61	[(S)-1-(3-Methyl-butyl)-pyrrolidin-3-yl]-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine	0.91 LC-MS 1TFA	575.5
62	((S)-1-Cyclopentyl-pyrrolidin-3-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine	0.87 LC-MS 1TFA	573.4
63	((R)-1-Isopropyl-pyrrolidin-3-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine	0.83 LC-MS 1TFA	547.3
64	[(R)-1-(3-Methyl-butyl)-pyrrolidin-3-yl]-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine	0.91 LC-MS 1TFA	575.5
65	((R)-1-Cyclopentyl-pyrrolidin-3-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine	0.86 LC-MS 1TFA	573.4

Example 66: ($\pm$)-[4-(Methyl-pyridin-4-yl-amino)-benzyl]-[1-(1-methyl-pyrrolidin-3-yl)-piperidin-4-yl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine

To a solution of [4-(methyl-pyridin-4-yl-amino)-benzyl]-piperidin-4-yl-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine (38 mg, 0.073 mmol, 1 eq.) in acetonitrile (5 mL), 1-methyl-3-pyrrolidinone (35 μ L, 0.363 mmol, 5 eq.) and sodium triacetoxy borohydride (77 mg, 0.363 mmol, 5 eq.) were added in sequence. The resulting suspension was stirred at 50 °C for 18 hours. The residue was purified by prep. HPLC (column: Waters X-Bridge, 30x75 mm, 10 μ m, UV/MS, basic conditions) and concentrated in vacuo to give the title compound as a white solid.

LC-MS 1TFA: t_R = 0.72 min; $[M+H]^+$ = 602.6

Example 67: [1-(3-Fluoro-propyl)-piperidin-4-yl]-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine

To a mixture of [4-(methyl-pyridin-4-yl-amino)-benzyl]-piperidin-4-yl-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine (18 mg, 0.035 mmol, 1 eq.) and Cs_2CO_3 (11 mg, 0.035 mmol, 1 eq.) in DMF (2 mL), 3-fluoro-1-iodopropane (4 μ L, 0.035 mmol, 1 eq.) was added. The mixture was stirred at r.t. for 18 hours. The reaction mixture was purified by prep. HPLC (column: Waters X-Bridge, 30x75 mm, 10 μ m, UV/MS, acidic conditions) and concentrated in vacuo to give the title compound as a white solid.

LC-MS 1TFA: t_R = 0.82 min; $[M+H]^+$ = 579.4

Example 68: (1-Methyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine

To a solution of [4-(methyl-pyridin-4-yl-amino)-benzyl]-piperidin-4-yl-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine (75 mg, 0.15 mmol, 1.0 eq.) in formic acid (0.55 mL, 14.5 mmol, 100 eq.), 37 w% aq. formaldehyde solution (12 μ L, 0.16 mmol, 1.1 eq.) was added. The mixture was stirred at 90 °C for 3 hours. The mixture was allowed to cool down to r.t. and partitioned between sat. aq. $NaHCO_3$ soln. and DCM. The layers were separated. The aq. phase was extracted with DCM. The comb. org. phases were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by prep. HPLC (column: Waters X-Bridge, 18x50 mm, 10 μ m, UV/MS, basic conditions) and concentrated in vacuo to give the title compound as a white solid.

LC-MS 1TFA: t_R = 0.79 min; $[M+H]^+$ = 533.4

Buchwald cross-coupling:

Method A: A solution of (1-benzyl-piperidin-4-yl)-(4-bromo-benzyl)-(5-phenyl-pyrimidin-2-yl)-amine (189 mg, 0.37 mmol, 1.00 eq.), sodium tert-butoxide (44 mg, 0.46 mmol, 1.25 eq.) and 4-amino-2-picoline (40 mg, 0.37 mmol, 1.00 eq.) in dioxane (2 mL) was degased with N₂ for 15 min before the addition of X-Phos (18 mg, 0.04 mmol, 0.10 eq.) and tris(dibenzylideneacetone)dipalladium(0) (17 mg, 0.02 mmol, 0.05 eq.). The reaction mixture was degased again with N₂ for 15 min and then heated at 105 °C for 18 hours. The reaction was allowed to cool down to r.t. and filtered through Celite. The filtrate was concentrated in vacuo. The residue was purified by prep. HPLC (column: Waters X-Bridge, 30x75 mm, 10 µm, UV/MS, basic conditions) and concentrated in vacuo.

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Listed in Table 8 below are examples of compounds of Formula I, prepared according to the above-mentioned method with the corresponding amine **7** and the corresponding bromide of Structure **6** as starting materials.

15 **Table 8**

Example	Compound of Formula I	t _R [min] LC-MS Method	MS-data m/z [M+H] ⁺
69	(1-Benzyl-piperidin-4-yl)-[4-(2-methyl-pyridin-4-ylamino)-benzyl]-(5-phenyl-pyrimidin-2-yl)-amine	0.80 LC-MS 1TFA	541.5
70	(1-Benzyl-piperidin-4-yl)-[4-(3-fluoro-phenyl)-pyrimidin-2-yl]-[4-(2-methyl-pyridin-4-ylamino)-benzyl]-amine	0.81 LC-MS 1TFA	559.4
71	(1-Benzyl-piperidin-4-yl)-[4-(2-methyl-pyridin-4-ylamino)-benzyl]-[5-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine	0.89 LC-MS 1TFA	609.5
72	(1-Benzyl-piperidin-4-yl)-(7-chloro-quinazolin-4-yl)-[4-(2-methyl-pyridin-4-ylamino)-benzyl]-amine	0.51 LC-MS 1TFA	549.2
73	(1-Benzyl-piperidin-4-yl)-(6-fluoro-quinazolin-2-yl)-[4-(2-methyl-pyridin-4-ylamino)-benzyl]-amine	0.75 LC-MS 1TFA	533.4
74	(1-Benzyl-piperidin-4-yl)-[4-(2-methyl-pyridin-4-ylamino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine	0.88 LC-MS 1TFA	609.5

75	(1-Isopropyl-piperidin-4-yl)-{6-[methyl-(2-methyl-pyridin-4-yl)-amino]-pyridin-3-ylmethyl}-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine	0.79 LC-MS 1TFA	576.4
76	(1-Isopropyl-piperidin-4-yl)-[6-(2-methyl-pyridin-4-ylamino)-pyridin-3-ylmethyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine	0.81 LC-MS 1TFA	562.4
77	(1-Isopropyl-piperidin-4-yl)-[6-(3-methyl-pyridin-4-ylamino)-pyridin-3-ylmethyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine	0.79 LC-MS 1TFA	562.4
78	[6-(3-Fluoro-pyridin-4-ylamino)-pyridin-3-ylmethyl]- (1-isopropyl-piperidin-4-yl)-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine	0.79 LC-MS 1TFA	566.4
79	(1-Isopropyl-piperidin-4-yl)-[6-(pyrimidin-4-ylamino)-pyridin-3-ylmethyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine	0.77 LC-MS 1TFA	549.4
80	(1-Isopropyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[6-(4-trifluoromethyl-phenyl)-pyridin-2-yl]-amine	0.88 LC-MS 1TFA	560.4
81	(1-Isopropyl-piperidin-4-yl)-[6-(methyl-pyridin-3-yl-amino)-pyridin-3-ylmethyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine	0.78 LC-MS 1TFA	562.5
82	(1-Isopropyl-piperidin-4-yl)-[3-(methyl-pyridin-4-yl-amino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine	0.82 LC-MS 1TFA	561.4
83	(1-Isopropyl-piperidin-4-yl)-[3-(methyl-pyridin-3-yl-amino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine	0.83 LC-MS 1TFA	561.4
84	(1-Isopropyl-piperidin-4-yl)-{3-[methyl-(2-methyl-pyridin-4-yl)-amino]-benzyl}-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine	0.83 LC-MS 1TFA	575.5
85	(1-Isopropyl-piperidin-4-yl)-[3-(2-methyl-pyridin-4-ylamino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine	0.82 LC-MS 1TFA	561.5
86	(1-Isopropyl-piperidin-4-yl)-[3-(3-methyl-pyridin-4-ylamino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine	0.81 LC-MS 1TFA	561.4

87	[3-(3-Fluoro-pyridin-4-ylamino)-benzyl]-(1-isopropyl-piperidin-4-yl)-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine	0.80 LC-MS 1TFA	565.4
88	(1-Isopropyl-piperidin-4-yl)-[3-(pyrimidin-4-ylamino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine	0.80 LC-MS 1TFA	548.4
89	[4-(4-Fluoro-phenyl)-pyrimidin-2-yl]-(1-isopropyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-amine	0.74 LC-MS 1TFA	511.4
90	N,N-Dimethyl-N'-[4-(methyl-pyridin-4-yl-amino)-benzyl]-N'-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-ethane-1,2-diamine	0.78 LC-MS 1TFA	507.3
91	(±)-N1,N1-Dimethyl-N2-[4-(methyl-pyridin-4-yl-amino)-benzyl]-N2-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-propane-1,2-diamine	0.78 LC-MS 1TFA	521.4
92	N,N-Dimethyl-N'-[4-(methyl-pyridin-4-yl-amino)-benzyl]-N'-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-propane-1,3-diamine	0.79 LC-MS 1TFA	521.4
93	[2-(4-Methyl-piperazin-1-yl)-ethyl]-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine	0.74 LC-MS 1TFA	562.4
94	[2-(4-Methyl-piperazin-1-yl)-ethyl]-[4-(2-methyl-pyridin-4-ylamino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine	0.74 LC-MS 1TFA	562.4
95	[3-(4-Methyl-piperazin-1-yl)-propyl]-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine	0.73 LC-MS 1TFA	576.5
96	[3-(4-Methyl-piperazin-1-yl)-propyl]-[4-(2-methyl-pyridin-4-ylamino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine	0.72 LC-MS 1TFA	576.3
97	[3-(4-Methyl-piperazin-1-yl)-propyl]-[4-(3-methyl-pyridin-4-ylamino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine	0.72 LC-MS 1TFA	576.5
98	[4-({(1-Benzyl-piperidin-4-yl)-[4-(4-trifluoromethyl-phenyl)-thiazol-2-yl]-amino}-methyl)-phenyl]-(2-methyl-pyridin-4-yl)-amine	0.91 LC-MS 1TFA	614.4

99	(1-Isopropyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-(2-phenyl-pyrimidin-4-yl)-amine	0.72 LC-MS 1TFA	493.4
100	(1-Isopropyl-piperidin-4-yl)-[4-(2-methyl-pyridin-4-ylamino)-benzyl]-(2-phenyl-pyrimidin-4-yl)-amine	0.72 LC-MS 1TFA	493.4
101	(1-Isopropyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[6-(4-trifluoromethyl-phenyl)-pyrazin-2-yl]-amine	0.79 LC-MS 1TFA	561.4
102	(1-Isopropyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-quinolin-4-yl-amine	0.42 LC-MS 1TFA	466.4
103	(4-Benzyloxy-pyrimidin-2-yl)-(1-isopropyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-amine	0.69 LC-MS 1TFA	523.4
104	(1-Isopropyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyridin-2-yl]-amine	0.62 LC-MS 4	560.3
105	(1-Isopropyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[2-(4-trifluoromethyl-phenyl)-pyridin-4-yl]-amine	0.57 LC-MS 1TFA	560.3
106	(4,6-Dimethyl-pyrimidin-2-yl)-(1-isopropyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-amine	0.60 LC-MS 1TFA	445.4
107	(1-Isopropyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[6-(4-trifluoromethyl-phenyl)-pyrimidin-4-yl]-amine	0.66 LC-MS 1TFA	561.5
108	(1-Isopropyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-pyrimidin-2-yl-amine	0.53 LC-MS 1TFA	417.4
109	(1-Isopropyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[5-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine	0.84 LC-MS 1TFA	561.4
110	(1-Isopropyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-(4-trifluoromethyl-pyrimidin-2-yl)-amine	0.69 LC-MS 1TFA	485.4

111	(±)-N1,N1-Dimethyl-N3-[4-(methyl-pyridin-4-yl-amino)-benzyl]-N3-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-butane-1,3-diamine	0.80 LC-MS 1TFA	535.4
112	((S)-1-Isopropyl-piperidin-3-yl)-[6-(2-methyl-pyridin-4-ylamino)-pyridin-3-ylmethyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine	0.80 LC-MS 1TFA	562.4
113	(1'-Methyl-[1,4']bipiperidinyl-4-yl)-[6-(2-methyl-pyridin-4-ylamino)-pyridin-3-ylmethyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine	0.69 LC-MS 1TFA	617.6
114	(1'-Methyl-[1,4']bipiperidinyl-4-yl)-[6-(methyl-pyridin-4-yl-amino)-pyridin-3-ylmethyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine	0.67 LC-MS 1TFA	617.5
115	(1-Isopropyl-piperidin-4-yl)-(4-methoxy-pyrimidin-2-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-amine	0.52 LC-MS 1TFA	447.4

Method B: To a solution under Ar of (4-bromo-benzyl)-(1'-methyl-[1,4']bipiperidinyl-4-yl)-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine (59 mg, 0.10 mmol, 1.00 eq.), 4-amino-2-picoline (13 mg, 0.12 mmol, 1.20 eq.), and sodium tert-butoxide (14 mg, 0.14 mmol, 1.4 eq.) in dioxane (1 mL), X-Phos (5 mg, 0.01 mmol, 0.1 eq.) and tris(dibenzylideneacetone)dipalladium(0) (5 mg, 0.005 mmol, 0.05 eq.) were added. The reaction mixture was stirred at 105 °C for 1 hour. The mixture was allowed to cool down to r.t. and filtered through alumina. The alumina was rinsed with MeOH and the filtrate concentrated in vacuo. The residue was purified by prep. HPLC (column: Waters X-Bridge, 30x75 mm, 10 µm, UV/MS, acidic conditions) and concentrated in vacuo.

Listed in Table 9 below are examples of compounds of Formula I, prepared according to the above-mentioned method with the corresponding amine **7** and the corresponding bromide of Structure **6** as starting materials.

Table 9

Example	Compound of Formula I	t _R [min] LC-MS Method	MS-data m/z [M+H] ⁺
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116	1'-Methyl-N-(4-((2-methylpyridin-4-yl)amino)benzyl)-N-(4-(4-(trifluoromethyl)phenyl)pyrimidin-2-yl)-[1,4'-bipiperidin]-4-amine	0.71 LC-MS 1TFA	616.5
117	N-(4-((2,6-Dimethylpyridin-4-yl)amino)benzyl)-1'-methyl-N-(4-(4-(trifluoromethyl)phenyl)pyrimidin-2-yl)-[1,4'-bipiperidin]-4-amine	0.72 LC-MS 1TFA	630.4
118	1'-Methyl-N-(4-(methyl(pyridin-3-yl)amino)benzyl)-N-(4-(4-(trifluoromethyl)phenyl)pyrimidin-2-yl)-[1,4'-bipiperidin]-4-amine	0.72 LC-MS 1TFA	616.5
119	1'-Methyl-N-(4-(methyl(pyridin-2-yl)amino)benzyl)-N-(4-(4-(trifluoromethyl)phenyl)pyrimidin-2-yl)-[1,4'-bipiperidin]-4-amine	0.71 LC-MS 1TFA	616.4
120	1'-Methyl-N-(4-(methyl(2-methylpyridin-4-yl)amino)benzyl)-N-(4-(4-(trifluoromethyl)phenyl)pyrimidin-2-yl)-[1,4'-bipiperidin]-4-amine	0.72 LC-MS 1TFA	630.6
121	1'-Methyl-N-(4-(pyridin-4-ylamino)benzyl)-N-(4-(4-(trifluoromethyl)phenyl)pyrimidin-2-yl)-[1,4'-bipiperidin]-4-amine	0.69 LC-MS 1TFA	602.5
122	1'-Methyl-N-(4-(pyrimidin-4-ylamino)benzyl)-N-(4-(4-(trifluoromethyl)phenyl)pyrimidin-2-yl)-[1,4'-bipiperidin]-4-amine	0.68 LC-MS 1TFA	603.5
123	N-(4-((2-Methoxypyridin-4-yl)amino)benzyl)-1'-methyl-N-(4-(4-(trifluoromethyl)phenyl)pyrimidin-2-yl)-[1,4'-bipiperidin]-4-amine	0.71 LC-MS 1TFA	632.4
124	N-(4-((2-Fluoropyridin-4-yl)amino)benzyl)-1'-methyl-N-(4-(4-(trifluoromethyl)phenyl)pyrimidin-2-yl)-[1,4'-bipiperidin]-4-amine	0.85 LC-MS 1TFA	620.5
125	6-Methoxy-2-methyl-N-(4-(((1'-methyl-[1,4'-bipiperidin]-4-yl)(4-(4-(trifluoromethyl)phenyl)pyrimidin-2-yl)amino)methyl)phenyl)quinolin-4-amine	0.79 LC-MS 1TFA	696.5
126	N-(4-(Ethyl(pyridin-4-yl)amino)benzyl)-1'-methyl-N-(4-(4-(trifluoromethyl)phenyl)pyrimidin-2-yl)-[1,4'-bipiperidin]-4-amine	0.74 LC-MS 1TFA	630.5

127	N-(4-((3-Fluoropyridin-4-yl)amino)benzyl)-1'-methyl-N-(4-(4-(trifluoromethyl)phenyl)pyrimidin-2-yl)-[1,4'-bipiperidin]-4-amine	0.69 LC-MS 1TFA	620.5
128	1'-Methyl-N-(4-((3-methylpyridin-4-yl)amino)benzyl)-N-(4-(4-(trifluoromethyl)phenyl)pyrimidin-2-yl)-[1,4'-bipiperidin]-4-amine	0.70 LC-MS 1TFA	616.5
129	1'-Methyl-N-(4-(4-methylpiperazin-1-yl)benzyl)-N-(4-(4-(trifluoromethyl)phenyl)pyrimidin-2-yl)-[1,4'-bipiperidin]-4-amine	0.68 LC-MS 1TFA	608.5
130	N-(1-Isopropylpiperidin-4-yl)-N-(4-((2-methylpyridin-4-yl)amino)benzyl)-4-(4-(trifluoromethyl)phenyl)pyrimidin-2-amine	0.82 LC-MS 1TFA	561.4
131	N-(1-Isopropylpiperidin-4-yl)-N-(4-((3-methylpyridin-4-yl)amino)benzyl)-4-(4-(trifluoromethyl)phenyl)pyrimidin-2-amine	0.82 LC-MS 1TFA	561.4
132	N-(4-((3-Fluoropyridin-4-yl)amino)benzyl)-N-(1-isopropylpiperidin-4-yl)-4-(4-(trifluoromethyl)phenyl)pyrimidin-2-amine	0.81 LC-MS 1TFA	565.5
133	N-(1-Isopropylpiperidin-4-yl)-4-(4-(trifluoromethyl)phenyl)-N-(4-((3-(trifluoromethyl)pyridin-4-yl)amino)benzyl)pyrimidin-2-amine	0.84 LC-MS 1TFA	615.5
134	N-(4-((5-Fluoropyridin-3-yl)amino)benzyl)-N-(1-isopropylpiperidin-4-yl)-4-(4-(trifluoromethyl)phenyl)pyrimidin-2-amine	0.95 LC-MS 1TFA	565.4
135	N-(1-Isopropylpiperidin-4-yl)-N-(4-(pyridin-3-ylamino)benzyl)-4-(4-(trifluoromethyl)phenyl)pyrimidin-2-amine	0.81 LC-MS 1TFA	547.4
136	N-(1-Isopropylpiperidin-4-yl)-N-(4-((2-(pyrrolidin-1-yl)pyridin-4-yl)amino)benzyl)-4-(4-(trifluoromethyl)phenyl)pyrimidin-2-amine	0.88 LC-MS 1TFA	616.5
137	N-(1-Isopropylpiperidin-4-yl)-N-(4-((2-methylpyrimidin-4-yl)amino)benzyl)-4-(4-(trifluoromethyl)phenyl)pyrimidin-2-amine	0.81 LC-MS 1TFA	562.4

138	N-(1-Isopropylpiperidin-4-yl)-N-(4-(methyl(2-methylpyrimidin-4-yl)amino)benzyl)-4-(4-(trifluoromethyl)phenyl)pyrimidin-2-amine	0.84 LC-MS 1TFA	576.4
139	(1-Isopropyl-piperidin-4-yl)-[4-(pyrimidin-4-ylamino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine	0.79 LC-MS 1TFA	548.5
140	N-(1-Isopropylpiperidin-4-yl)-N-(4-((6-methylpyrimidin-4-yl)amino)benzyl)-4-(4-(trifluoromethyl)phenyl)pyrimidin-2-amine	0.81 LC-MS 1TFA	562.5
141	N-(1-Isopropylpiperidin-4-yl)-N-(4-(methyl(6-methylpyrimidin-4-yl)amino)benzyl)-4-(4-(trifluoromethyl)phenyl)pyrimidin-2-amine	0.83 LC-MS 1TFA	576.4
142	(1-Isopropyl-piperidin-4-yl)-[4-(pyrimidin-2-ylamino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine	0.99 LC-MS 1TFA	548.4
143	(1-Isopropyl-piperidin-4-yl)-[4-(6-methyl-pyridin-3-ylamino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine	0.83 LC-MS 1TFA	561.4
144	(1-Isopropyl-piperidin-4-yl)-[4-(pyrazin-2-ylamino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine	0.99 LC-MS 1TFA	548.4
145	(1-Isopropyl-piperidin-4-yl)-[4-(methyl-pyridin-3-ylamino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine	0.84 LC-MS 1TFA	561.5
146	[4-(2-Fluoro-pyridin-3-ylamino)-benzyl]-(1-isopropyl-piperidin-4-yl)-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine	1.06 LC-MS 1TFA	565.4

Method C: A solution of N-(4-bromobenzyl)-N-(2-(4-methylpiperazin-1-yl)ethyl)-4-(4-(trifluoromethyl)phenyl)pyrimidin-2-amine (75 mg, 0.14 mmol, 1.00 eq.), sodium tert-butoxide (17 mg, 0.18 mmol, 1.25 eq.) and 4-amino-3-methylpyridine (15 mg, 0.14 mmol, 1.00 eq.) in dioxane (3 mL) was degased with N₂ before the addition of X-Phos (7 mg, 0.01 mmol, 0.1 eq.) and tris(dibenzylideneacetone)dipalladium(0) (6 mg, 0.007 mmol, 0.05 eq.). The reaction mixture was degased again with N₂ and then heated at 100 °C for 18 hours. The reaction was allowed to cool down to r.t. and filtered. The filtrate was concentrated in

vacuo. The residue was purified by prep. HPLC (column: Atlantis, 18x50 mm, 10 μ m, UV/MS, acid conditions) and concentrated in vacuo.

Listed in Table 10 below are examples of compounds of Formula I, prepared according to the above-mentioned method with the corresponding amine **7** and the corresponding bromide of Structure **6** as starting materials.

Table 10

Example	Compound of Formula I	t_R [min] LC-MS Method	MS-data m/z [M+H] ⁺
147	[2-(4-Methyl-piperazin-1-yl)-ethyl]-[4-(3-methyl-pyridin-4-ylamino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine	0.73 LC-MS 1TFA	562.4
148	{4-[Methyl-(2-methyl-pyridin-4-yl)-amino]-benzyl}-[2-(4-methyl-piperazin-1-yl)-ethyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine	0.76 LC-MS 1TFA	576.5
149	{4-[Methyl-(2-methyl-pyridin-4-yl)-amino]-benzyl}-[3-(4-methyl-piperazin-1-yl)-propyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine	0.74 LC-MS 1TFA	590.4
150	(1-Isopropyl-piperidin-4-yl)-{4-[methyl-(3-methyl-pyridin-4-yl)-amino]-benzyl}-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine	0.84 LC-MS 1TFA	575.5

Method D: A solution of N-((6-bromopyridin-2-yl)methyl)-N-(1-isopropylpiperidin-4-yl)-4-(4-(trifluoromethyl)phenyl)pyrimidin-2-amine (50 mg, 94 μ mol, 1.00 eq.), sodium tert-butoxide (11 mg, 117 μ mol, 1.25 eq.) and 4-(methylamino)pyridine (10 mg, 94 μ mol, 1.00 eq.) in dioxane (2 mL) was degased with N₂ before the addition of X-Phos (4.5 mg, 9 μ mol, 0.10 eq.) and tris(dibenzylideneacetone)dipalladium(0) (4.3 mg, 5 μ mol, 0.05 eq.). The reaction mixture was degased again with N₂ and then stirred at 100 °C for 18 hours. The mixture was allowed to cool to r.t. and 4-(methylamino)pyridine (10 mg, 94 μ mol, 1.00 eq.), X-Phos (4.5 mg, 9 μ mol, 0.10 eq.) and tris(dibenzylideneacetone)dipalladium(0) (4.3 mg, 5 μ mol, 0.05 eq.) were added. The reaction mixture was degased again with N₂ and then stirred at 100 °C for 18 hours. The reaction was allowed to cool down to r.t. and filtered through Celite. The filtrate was concentrated in vacuo. The residue was purified by prep. HPLC

(column: Waters X-Bridge, 18x50 mm, 10 μ m, UV/MS, acidic conditions) and concentrated in vacuo.

Listed in Table 11 below are examples of compounds of Formula I, prepared according to the above-mentioned method with the corresponding amine **7** and the corresponding bromide of Structure **6** as starting materials.

Table 11

Example	Compound of Formula I	t_R [min] LC-MS Method	MS-data m/z [M+H] ⁺
151	(1-Isopropyl-piperidin-4-yl)-[6-(methyl-pyridin-4-yl-amino)-pyridin-2-ylmethyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine	0.78 LC-MS 1TFA	562.4
152	(1-Isopropyl-piperidin-4-yl)-{6-[methyl-(2-methyl-pyridin-4-yl)-amino]-pyridin-2-ylmethyl}-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine	0.80 LC-MS 1TFA	576.4
153	(1-Isopropyl-piperidin-4-yl)-[6-(2-methyl-pyridin-4-ylamino)-pyridin-2-ylmethyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine	0.80 LC-MS 1TFA	562.5
154	(1-Isopropyl-piperidin-4-yl)-[6-(3-methyl-pyridin-4-ylamino)-pyridin-2-ylmethyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine	0.80 LC-MS 1TFA	562.4
155	[6-(3-Fluoro-pyridin-4-ylamino)-pyridin-2-ylmethyl]- (1-isopropyl-piperidin-4-yl)-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine	0.79 LC-MS 1TFA	566.4
156	(1-Isopropyl-piperidin-4-yl)-[6-(pyrimidin-4-ylamino)-pyridin-2-ylmethyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine	0.77 LC-MS 1TFA	549.4
157	(1-Isopropyl-piperidin-4-yl)-[6-(methyl-pyridin-2-yl-amino)-pyridin-2-ylmethyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine	0.80 LC-MS 1TFA	562.5

Method E: To an ice-cooled solution of 2-[(1-isopropyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-amino]-pyrimidin-4-ol (50 mg, 0.12 mmol, 1.00 eq.) in DCM (1 mL), triethylamine (48 μ L, 0.35 mmol, 3.00 eq.) and trifluoromethanesulfonic anhydride (30 μ L,

0.17 mmol, 1.50 eq.) were added in sequence. The reaction mixture was stirred at 0 °C for 30 min and further at r.t. for 45 min. The mixture was concentrated in vacuo. To a mixture of the resulting triflate in dioxane (2 mL), sodium tert-butoxide (14 mg, 0.14 mmol, 1.25 eq.) and 1-methylpiperazine (13 µL, 0.12 mmol, 1.00 eq.) were added. The resulting mixture was degased with N₂ before the addition of X-Phos (5.5 mg, 0.01 mmol, 0.10 eq.) and tris(dibenzylideneacetone)dipalladium (0) (5.3 mg, 6 µmol, 0.05 eq.). The reaction mixture was degased again with N₂ and then stirred at 100 °C for 18 hours. The reaction was allowed to cool down to r.t. and filtered through Celite. The filtrate was concentrated in vacuo. The residue was purified by prep. HPLC (column: Waters X-Bridge, 18x50 mm, 10 µm, UV/MS, basic conditions) and concentrated in vacuo.

Listed in Table 12 below are examples of compounds of Formula I, prepared according to the above-mentioned method with the corresponding amine **20** and the corresponding phenol of Structure **17** as starting materials.

15

Table 12

Example	Compound of Formula I	t _R [min] LC-MS Method	MS-data m/z [M+H] ⁺
158	(1-Isopropyl-piperidin-4-yl)-[4-(4-methyl-piperazin-1-yl)-pyrimidin-2-yl]-[4-(methyl-pyridin-4-yl-amino)-benzyl]-amine	0.37 LC-MS 4	515.3
159	(1-Isopropyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-(4-pyrrolidin-1-yl-pyrimidin-2-yl)-amine	0.49 LC-MS 1TFA	486.4

Method F: A solution of N-(1-isopropylpiperidin-4-yl)-N-(piperidin-4-ylmethyl)-4-(4-(trifluoromethyl)phenyl)pyrimidin-2-amine (63 mg, 0.14 mmol, 1.00 eq.), sodium tert-butoxide (16 mg, 0.17 mmol, 1.25 eq.) and 4 bromopyridine (22 mg, 0.14 mmol, 1.00 eq.) in dioxane (2 mL) was degased with N₂ before the addition of X-Phos (6.5 mg, 0.01 mmol, 0.10 eq.) and tris(dibenzylideneacetone)dipalladium (0) (6.2 mg, 7 μmol, 0.05 eq.). The reaction mixture was degased again with N₂ and then stirred at 100 °C for 18 hours. The reaction was allowed to cool down to r.t. and filtered through Celite. The filtrate was concentrated in vacuo. The residue was purified by prep. HPLC (column: Atlantis, 18x50 mm, 10 μm, UV/MS, acid conditions) and concentrated in vacuo.

Listed in Table 13 below are examples of compounds of Formula I, prepared according to the above-mentioned method with the corresponding bromide **13** as starting material and the corresponding amine of Structure **12**.

Table 13

Example	Compound of Formula I	t _R [min] LC-MS Method	MS-data m/z [M+H] ⁺
160	(1-Isopropyl-piperidin-4-yl)-(3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-ylmethyl)-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine	0.81 LC-MS 1TFA	539.4
161	(1-Isopropyl-piperidin-4-yl)-(3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-ylmethyl)-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine	0.81 LC-MS 1TFA	539.4
162	(1-Isopropyl-piperidin-4-yl)-(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-ylmethyl)-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine	0.81 LC-MS 1TFA	539.4

Example 163: (7-Isobutyl-quinazolin-4-yl)-(1-isopropyl-piperidin-4-yl)-[4-(2-methyl-pyridin-4-ylamino)-benzyl]-amine

To a solution under Ar of (4-bromo-benzyl)-(7-isobutyl-quinazolin-4-yl)-(1-isopropyl-piperidin-4-yl)-amine (50 mg, 0.10 mmol, 1.00 eq.), 4-amino-2-methylpyridine (15 mg, 0.14 mmol, 1.38 eq.), and NaOtBu (12 mg, 0.12 mmol, 1.24 eq.) in toluene (1 mL), X-Phos (5 mg, 0.01 mmol, 0.10 eq.) and Pd₂(dba)₃ (5 mg, 5 μmol, 0.05 eq.) were added. The mixture

was stirred at 85 °C for 2 hours. The mixture was allowed to cool to r.t. and 4-amino-2-methylpyridine (33 mg, 0.30 mmol, 3.00 eq.), NaOtBu (12 mg, 0.12 mmol, 1.24 eq.), X-Phos (5 mg, 0.01 mmol, 0.10 eq.) and Pd₂(dba)₃ (5 mg, 5 μmol, 0.05 eq.) were added. The mixture was stirred under Ar at 85 °C for 18 hours. The mixture was allowed to cool to r.t. and diluted with AcOEt. The mixture was washed with water (2 x). The org. layer was dried over MgSO₄ and concentrated in vacuo. The residue was purified by prep. TLC on SiO₂ (0.5 mm, DCM/MeOH/NH₄OH 90:10:1) to give the title compound as a yellow solid.

LC-MS 1TFA: *t_R* = 0.56 min; [M+H]⁺ = 523.5

10 *Suzuki cross-coupling:*

Method A: To an ice-cooled solution of 2-[(1-isopropyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-amino]-pyrimidin-4-ol (50 mg, 0.12 mmol, 1.00 eq.) in DCM (1 mL), triethylamine (48 μL, 0.35 mmol, 3.00 eq.) and trifluoromethanesulfonic anhydride (30 μL, 0.17 mmol, 1.50 eq.) were added in sequence. The reaction mixture was stirred at 0 °C for 30 min and further at r.t. for 45 min. The mixture was concentrated in vacuo. To a mixture under N₂ of the resulting triflate, 4-chlorophenylboronic acid (18 mg, 0.12 mmol, 1.00 eq.), and sodium carbonate (49 mg, 0.46 mmol, 4.00 eq.) in toluene/EtOH/water 20:4:1 (2 mL), tetrakis(triphenylphosphine)palladium (0) (7 mg, 6 μmol, 0.05 eq.) was added. The mixture was stirred at 100 °C for 18 hours. The mixture was allowed to cool to r.t. and concentrated in vacuo. The residue was partitioned between AcOEt and water. The layers were separated. The org. phase was washed with sat. aq. NaCl soln., dried over MgSO₄, and concentrated in vacuo. The residue was purified by prep. HPLC (column: Atlantis, 18x50 mm, 10 μm, UV/MS, acid conditions) and concentrated in vacuo.

25 Listed in Table 14 below are examples of compounds of Formula I, prepared according to the above-mentioned method with the corresponding boronic acid or boronic ester **19** and the corresponding phenol of Structure **17** as starting materials.

Table 14

Example	Compound of Formula I	<i>t_R</i> [min] LC-MS Method	MS-data m/z [M+H] ⁺
164	[4-(4-Chloro-phenyl)-pyrimidin-2-yl]-(1-isopropyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-amine	0.79 LC-MS 1TFA	527.4

165	[4-(4-tert-Butyl-phenyl)-pyrimidin-2-yl]-(1-isopropyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-amine	0.90 LC-MS 1TFA	549.5
166	(1-Isopropyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-(4-pyridin-4-yl-pyrimidin-2-yl)-amine	0.48 LC-MS 1TFA	494.4
167	(1-Isopropyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[4-(4-trifluoromethoxy-phenyl)-pyrimidin-2-yl]-amine	0.85 LC-MS 1TFA	577.5
168	(1-Isopropyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-(4-p-tolyl-pyrimidin-2-yl)-amine	0.77 LC-MS 1TFA	507.5
169	[4-(2-Fluoro-phenyl)-pyrimidin-2-yl]-(1-isopropyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-amine	0.75 LC-MS 1TFA	511.4
170	4-(2-((1-Isopropyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-amino)-pyrimidin-4-yl)-benzonitrile	0.69 LC-MS 1TFA	518.4
171	(1-Isopropyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[4-(3-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine	0.80 LC-MS 1TFA	561.4
172	(1-Isopropyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[4-(2-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine	0.78 LC-MS 1TFA	561.4
173	4-(2-(((S)-1'-Methyl-[1,4']bipiperidinyl-3-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-amino)-pyrimidin-4-yl)-benzonitrile	0.58 LC-MS 1TFA	573.4
174	((S)-1'-Methyl-[1,4']bipiperidinyl-3-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[4-(6-trifluoromethyl-pyridin-3-yl)-pyrimidin-2-yl]-amine	0.61 LC-MS 1TFA	617.5
175	[4-(4-Fluoro-phenyl)-pyrimidin-2-yl]-((S)-1'-methyl-[1,4']bipiperidinyl-3-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-amine	0.61 LC-MS 1TFA	566.2
176	[4-(4-Methanesulfonyl-phenyl)-pyrimidin-2-yl]-((S)-1'-methyl-[1,4']bipiperidinyl-3-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-amine	0.53 LC-MS 1TFA	626.6

177	[4-(4-Chloro-phenyl)-pyrimidin-2-yl]-((S)-1'-methyl-[1,4']bipiperidinyl-3-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-amine	0.65 LC-MS 1TFA	582.4
178	[4-(3-Chloro-phenyl)-pyrimidin-2-yl]-((S)-1'-methyl-[1,4']bipiperidinyl-3-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-amine	0.64 LC-MS 1TFA	582.5
179	3-(2-(((S)-1'-Methyl-[1,4']bipiperidinyl-3-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-amino)-pyrimidin-4-yl)-benzonitrile	0.57 LC-MS 1TFA	573.5
180	(1-Isopropyl-piperidin-4-yl)-[4-(4-methoxy-phenyl)-pyrimidin-2-yl]-[4-(methyl-pyridin-4-yl-amino)-benzyl]-amine	0.71 LC-MS 1TFA	523.5
181	(1-Isopropyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[4-phenyl-pyrimidin-2-yl]-amine	0.72 LC-MS 1TFA	493.4
182	(1-Isopropyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[4-(6-trifluoromethyl-pyridin-3-yl)-pyrimidin-2-yl]-amine	0.73 LC-MS 1TFA	562.4

Method B: A mixture under N₂ of (4-bromo-benzyl)-(1-isopropyl-piperidin-4-yl)-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine (50 mg, 94 μmol, 1.00 eq.), 3-pyridineboronic acid (11.5 mg, 94 μmol, 1.00 eq.), bis(di-tert-butyl(4-dimethylaminophenyl)phosphine)dichloropalladium(II) (3.3 mg, 5 μmol, 0.05 eq.) and K₂CO₃ (39 mg, 0.28 mmol, 3.00 eq.) in acetonitrile (3 mL) was stirred at 100 °C for 18 hours. The mixture was allowed to cool to r.t. and concentrated in vacuo. The residue was partitioned between AcOEt (20 mL) and water (20 mL). The layers were separated. The org. phase was washed with sat. aq. NaCl soln. (1x 10 mL), dried over MgSO₄, and filtered through Celite. The filtrate was concentrated in vacuo. The residue was purified by prep. HPLC (column: Waters X-Bridge, 18x50 mm, 10 μm, UV/MS, basic conditions) and concentrated in vacuo.

Listed in Table 15 below are examples of compounds of Formula I, prepared according to the above-mentioned method with the corresponding boronic acid or boronic ester **19** and the corresponding bromide of Structure **17** as starting materials.

Table 15

Example	Compound of Formula I	t _R [min] LC-MS Method	MS-data m/z [M+H] ⁺
183	(1-Isopropyl-piperidin-4-yl)-(4-pyridin-3-yl-benzyl)-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine	0.83 LC-MS 1TFA	532.4
184	(1-Isopropyl-piperidin-4-yl)-(4-pyridin-4-yl-benzyl)-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine	0.81 LC-MS 1TFA	532.4

Example 185: (1-Isopropyl-piperidin-4-yl)-(4-pyridin-2-yl-benzyl)-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine

To a mixture under N₂ of (4-bromo-benzyl)-(1-isopropyl-piperidin-4-yl)-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine (50 mg, 94 μmol, 1.00 eq.), 2-pyridineboronic acid N-phenyldiethanolamine ester (38 mg, 141 μmol, 1.50 eq.) and (XPhos) palladium(II) phenethylamine chloride (3.5 mg, 5 μmol, 0.05 eq.) in DMF (5 mL), diethanolamine (96 μL, 1.00 mmol, 10.69 eq.), potassium phosphate tribasic (99.5 mg, 0.47 mmol, 5.00 eq.) and copper(II) acetate (8.5 mg, 47 μmol, 0.50 eq.) were added. The mixture was stirred at 100 °C for 18 hours. The reaction mixture was cooled to r.t. 2N aq. HCl soln. (5 mL), then 2N aq. NaOH soln. (5 mL) were added in sequence. The mixture was extracted with Et₂O. The comb. org. phases were washed with sat. aq. NaCl soln., dried over MgSO₄, and concentrated in vacuo. The residue was purified by prep. HPLC (column: Waters X-Bridge, 18x50 mm, 10 μm, UV/MS, basic conditions) and concentrated in vacuo to give the title compound as a white solid.

LC-MS 1TFA: t_R = 0.87 min; [M+H]⁺ = 532.4

Example 186: (1-Isopropyl-piperidin-4-yl)-(4-isopropyl-pyrimidin-2-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-amine

To an ice-cooled solution of 2-[(1-isopropyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-amino]-pyrimidin-4-ol (200 mg, 0.46 mmol, 1.00 eq.) in DCM (2 mL), triethylamine (0.19 mL, 1.39 mmol, 3.00 eq.) and trifluoromethanesulfonic anhydride (0.12 mL, 0.69 mmol, 1.50 eq.) were added in sequence. The reaction mixture was stirred at 0 °C for 30 min and further at r.t. for 45 min. The mixture was concentrated in vacuo. To a solution of the resulting triflate in THF/NMP 5/0.4 (5.4 mL), iron(III)-acetylacetonate (3.4 mg, 9 μmol,

0.02 eq.) was added and the mixture was cooled to 0 °C. 2.9M isopropylmagnesium bromide solution in 2-methyltetrahydrofuran (0.32 mL, 0.93 mmol, 2.00 eq.) was added dropwise. The mixture was stirred at 0 °C for 30 min. A second portion of 2.9M isopropylmagnesium bromide solution in 2-methyltetrahydrofuran (0.32 mL, 0.93 mmol, 2.00 eq.) was added dropwise. The mixture was stirred at 0 °C for 30 min. The reaction was quenched with sat. aq. NH₄Cl soln. and extracted with Et₂O. The comb. org. phases were dried over MgSO₄ and concentrated in vacuo. The residue was purified by prep. HPLC (column: Waters X-Bridge, 18x50 mm, 10 μm, UV/MS, basic conditions) and concentrated in vacuo to give the title compound as a brown solid.

LC-MS 1TFA: t_R = 0.68 min; [M+H]⁺ = 459.5

General methods for the synthesis of precursors and intermediates:

General method for the synthesis of a bromide of Structure 6

Method A: To an ice-cooled solution of (1-isopropyl-piperidin-4-yl)-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine (3.64 g, 10 mmol, 1.0 eq.) in DMF (40 mL), sodium hydride 60% dispersion in mineral oil (520 mg, 13 mmol, 1.3 eq.) was added. The resulting orange mixture was stirred at r.t. for 2 hours. Then a solution of 4-bromobenzyl bromide (2.75 g, 11 mmol, 1.1 eq.) in DMF (20 mL) was added dropwise and the mixture was stirred at r.t. for 18 hours. The reaction mixture was quenched with sat. aq. Na₂CO₃ soln. (200 mL). The mixture was extracted with DCM (3 x 150 mL). The comb. org. phases were washed with water (1 x 150 mL), sat. aq. NaCl soln. (1 x 150 mL), dried over MgSO₄, and concentrated in vacuo. The residue was purified by flashmaster (column: 340 g, flow: 90 mL/min, 90 fractions of 45 mL, Hept/AcOEt-NEt₃ (10% NEt₃) 95:5 to Hept/AcOEt-NEt₃ (10% NEt₃) 1:1) to give the desired product as a yellow foam.

Listed in Table 16 below are bromides of Structure 6, prepared according to the above-mentioned method with the corresponding amine 4 as starting material.

Table 16

Bromide of Structure 6	t _R [min] LC-MS Method	MS-data m/z [M+H] ⁺
(4-Bromo-benzyl)-(1-isopropyl-piperidin-4-yl)-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine	0.87 LC-MS 4	533.2
(1-Benzyl-piperidin-4-yl)-(4-bromo-benzyl)-[4-(4-trifluoromethyl-phenyl)-thiazol-2-yl]-amine	1.35 LC-MS 3	585.6

4-[(4-Bromo-benzyl)-quinoxalin-2-yl-amino]-piperidine-1-carboxylic acid tert-butyl ester	1.10 LC-MS 2	497.1
(4-Bromo-benzyl)-(1-isopropyl-piperidin-4-yl)-(2-phenyl-pyrimidin-4-yl)-amine	0.83 LC-MS 4	464.9
(R)-3-[(4-Bromo-benzyl)-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amino]-pyrrolidine-1-carboxylic acid tert-butyl ester	1.14 LC-MS 4	577.0
(S)-3-[(4-Bromo-benzyl)-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amino]-pyrrolidine-1-carboxylic acid tert-butyl ester	1.14 LC-MS 4	577.0
(4-Bromo-benzyl)-[4-(4-fluoro-phenyl)-pyrimidin-2-yl]-(1-isopropyl-piperidin-4-yl)-amine	0.82 LC-MS 4	483.3
N-(4-Bromo-benzyl)-N',N'-dimethyl-N-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-ethane-1,2-diamine	0.84 LC-MS 4	479.3
(±)-N2-(4-Bromo-benzyl)-N1,N1-dimethyl-N2-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-propane-1,2-diamine	0.86 LC-MS 4	493.3
N-(4-Bromo-benzyl)-N',N'-dimethyl-N-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-propane-1,3-diamine	0.84 LC-MS 4	493.3
(4-Bromo-benzyl)-(1-isopropyl-piperidin-4-yl)-quinolin-4-yl-amine	0.56 LC-MS 4	438.3
(±)-N3-(4-Bromo-benzyl)-N1,N1-dimethyl-N3-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-butane-1,3-diamine	0.86 LC-MS 4	507.1
4-[(4-Bromo-benzyl)-[3-(4-trifluoromethyl-phenyl)-[1,2,4]oxadiazol-5-yl]-amino]-piperidine-1-carboxylic acid tert-butyl ester	1.12 LC-MS 4	581.0
4-[(4-Bromo-benzyl)-[5-(4-trifluoromethyl-phenyl)-[1,3,4]oxadiazol-2-yl]-amino]-piperidine-1-carboxylic acid tert-butyl ester	1.07 LC-MS 4	580.8
4-[Benzooxazol-2-yl-(4-bromo-benzyl)-amino]-piperidine-1-carboxylic acid tert-butyl ester	1.01 LC-MS 4	486.3
(4-Bromo-benzyl)-(1-isopropyl-piperidin-4-yl)-(4-methoxy-pyrimidin-2-yl)-amine	0.65 LC-MS 4	419.0

4-[Benzothiazol-2-yl-(4-bromo-benzyl)-amino]- piperidine-1-carboxylic acid tert-butyl ester	1.03 LC-MS 4	502.3
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Method B: To an ice-cooled solution of 4-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-ylamino]-piperidine-1-carboxylic acid tert-butyl ester (2.59 g, 6.13 mmol, 1.0 eq.) in DMF (30 mL), 95% sodium hydride (201 mg, 7.97 mmol, 1.3 eq.) was added. The resulting red mixture was stirred at r.t. for 45 min. Then a solution of 4-bromobenzyl bromide (1.69 g, 6.74 mmol, 1.1 eq.) in DMF (10 mL) was added dropwise and the orange mixture was stirred at r.t. for 18 hours. The reaction mixture was quenched with sat. aq. Na₂CO₃ soln. The mixture was extracted with DCM. The comb. org. phases were washed with water, sat. aq. NaCl soln., dried over MgSO₄, and concentrated in vacuo. The residue was purified by flashmaster (column: 100 g, flow: 45 mL/min, 45 fractions of 45 mL, Hept/AcOEt-NEt₃ (10% NEt₃) 9:1 to Hept/AcOEt-NEt₃ (10% NEt₃) 4:6) to give the desired product as a pale yellow solid.

Listed in Table 17 below are bromides of Structure 6, prepared according to the above-mentioned method with the corresponding amine 4 as starting material.

15

Table 17

Bromide of Structure 6	t _R [min] LC-MS Method	MS-data m/z [M+H] ⁺
4-[(4-Bromo-benzyl)-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amino]-piperidine-1-carboxylic acid tert-butyl ester	1.15 LC-MS 4	591.1
(S)-3-[(4-Bromo-benzyl)-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amino]-piperidine-1-carboxylic acid tert-butyl ester	1.16 LC-MS 4	590.7
(3aR,6aS)-tert-butyl 5-[(4-bromobenzyl)(4-(4-trifluoromethyl)phenyl)pyrimidin-2-yl]amino)hexahydrocyclopenta[c]pyrrole-2(1H)-carboxylate (mixture of stereoisomers)	1.17 LC-MS 4	616.6
(S)-3-[(4-Benzyloxy-pyrimidin-2-yl)-(4-bromo-benzyl)-amino]-piperidine-1-carboxylic acid tert-butyl ester	1.02 LC-MS 4	553.1
4-[(4-Bromo-benzyl)-quinolin-4-yl-amino]-piperidine-1-carboxylic acid tert-butyl ester	0.80 LC-MS 4	496.3

(S)-3-[(4-Bromo-benzyl)-quinolin-4-yl-amino]-piperidine-1-carboxylic acid tert-butyl ester	0.82 LC-MS 4	496.3
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Method C: To an ice-cooled solution of (4,6-dimethyl-pyrimidin-2-yl)-(1-isopropyl-piperidin-4-yl)-amine (417 mg, 1.68 mmol, 1.0 eq.) in DMF (8 mL), sodium hydride 60% dispersion in mineral oil (87 mg, 2.18 mmol, 1.3 eq.) was added. The resulting orange mixture was stirred at r.t. for 2 hours. Then a solution of 4-bromobenzyl bromide (462 mg, 1.85 mmol, 1.1 eq.) in DMF (2 mL) was added dropwise and the mixture was stirred at 60 °C for 18 hours. The reaction mixture was quenched with sat. aq. Na₂CO₃ soln. The mixture was extracted with DCM. The comb. org. phases were washed with water, sat. aq. NaCl soln., dried over MgSO₄, and concentrated in vacuo. The residue was purified by flashmaster (column: 25 g, flow: 30 mL/min, 25 fractions of 30 mL, Hept 100% to Hept/AcOEt-NEt₃ (10% NEt₃) 8:2) to afford the desired product as a pale yellow solid.

Listed in Table 18 below are bromides of Structure 6, prepared according to the above-mentioned method with the corresponding amine 4 as starting material.

Table 18

Bromide of Structure 6	t _R [min] LC-MS Method	MS-data m/z [M+H] ⁺
(4-Bromo-benzyl)-(4,6-dimethyl-pyrimidin-2-yl)-(1-isopropyl-piperidin-4-yl)-amine	0.74 LC-MS 4	417.2
(4-Bromo-benzyl)-(1-isopropyl-piperidin-4-yl)-(4-trifluoromethyl-pyrimidin-2-yl)-amine	0.79 LC-MS 4	457.2
(4-Bromo-benzyl)-(1-isopropyl-piperidin-4-yl)-[6-(4-trifluoromethyl-phenyl)-pyrimidin-4-yl]-amine	0.75 LC-MS 4	533.2
(4-Bromo-benzyl)-(1-isopropyl-piperidin-4-yl)-[5-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine	0.87 LC-MS 4	533.2
(4-Bromo-benzyl)-(1-isopropyl-piperidin-4-yl)-[6-(4-trifluoromethyl-phenyl)-pyridin-2-yl]-amine	0.91 LC-MS 4	532.2
(4-Benzyloxy-pyrimidin-2-yl)-(4-bromo-benzyl)-(1-isopropyl-piperidin-4-yl)-amine	0.78 LC-MS 4	495.2
(4-Bromo-benzyl)-(1-isopropyl-piperidin-4-yl)-[4-(4-trifluoromethyl-phenyl)-pyridin-2-yl]-amine	0.78 LC-MS 4	532.2

(4-Bromo-benzyl)-(1-isopropyl-piperidin-4-yl)-[2-(4-trifluoromethyl-phenyl)-pyridin-4-yl]-amine	0.66 LC-MS 4	532.2
N-(4-bromobenzyl)-N-(1-isopropylpiperidin-4-yl)pyrimidin-2-amine	0.69 LC-MS 4	389.3
N-(4-bromobenzyl)-N-(3-(4-methylpiperazin-1-yl)propyl)-4-(4-(trifluoromethyl)phenyl)pyrimidin-2-amine	0.76 LC-MS 4	548.2

Method D: To an ice-cooled solution of (1-benzyl-piperidin-4-yl)-(5-phenyl-pyrimidin-2-yl)-amine (206 mg, 0.60 mmol, 1.0 eq.) in DMF (3.5 mL), sodium hydride 60% dispersion in mineral oil (93 mg, 2.32 mmol, 3.9 eq.) was added. The reaction mixture was stirred at r.t. for 2 hours. Then 4-bromobenzyl bromide (164 mg, 0.66 mmol, 1.1 eq.) was added and the mixture was stirred at r.t. for 18 hours. The mixture was cooled to 0 °C and sodium hydride 60% dispersion in mineral oil (43 mg, 1.07 mmol, 1.8 eq.) was added. The mixture was stirred at r.t. for 30 min. 4-Bromobenzyl bromide (268 mg, 1.07 mmol, 1.8 eq.) was added. The reaction mixture was stirred at 70 °C for 18 hours. The mixture was allowed to cool to r.t. and purified by prep. HPLC (column: Waters X-Bridge, 30x75 mm, 10 µm, UV/MS, basic conditions) and concentrated in vacuo to give the desired product.

Listed in Table 19 below are bromides of Structure 6, prepared according to the above-mentioned method with the corresponding amine 4 as starting material.

Table 19

Bromide of Structure 6	t_R [min] LC-MS Method	MS-data m/z [M+H] ⁺
(1-Benzyl-piperidin-4-yl)-(4-bromo-benzyl)-(5-phenyl-pyrimidin-2-yl)-amine	1.29 LC-MS 3	513.0
(1-Benzyl-piperidin-4-yl)-(4-bromo-benzyl)-[4-(3-fluoro-phenyl)-pyrimidin-2-yl]-amine	1.31 LC-MS 3	531.0
(1-Benzyl-piperidin-4-yl)-(4-bromo-benzyl)-[5-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine	1.32 LC-MS 3	580.9
(1-Benzyl-piperidin-4-yl)-(4-bromo-benzyl)-(7-chloro-quinazolin-4-yl)-amine	1.20 LC-MS 3	520.8
(1-Benzyl-piperidin-4-yl)-(4-bromo-benzyl)-(6-fluoro-quinazolin-2-yl)-amine	1.27 LC-MS 3	505.0

(1-Benzyl-piperidin-4-yl)-(4-bromo-benzyl)-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine	1.38 LC-MS 3	581.0
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Method E: To an ice-cooled solution of ((S)-1-isopropyl-piperidin-3-yl)-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine (303 mg, 0.82 mmol, 1.0 eq.) in DMF (4 mL), sodium hydride 95% (25 mg, 1.06 mmol, 1.3 eq.) was added. The resulting mixture was stirred at r.t. for 45 min. Then a solution of 2-bromo-5-(bromomethyl)pyridine (234 mg, 0.90 mmol, 1.1 eq.) in DMF (4 mL) was added dropwise and the mixture was stirred at r.t. for 18 hours. The reaction mixture was concentrated in vacuo and the residue taken up in sat. aq. Na₂CO₃ soln. (10 mL). The mixture was extracted with DCM (3 x 6 mL). The comb. org. phases were washed with water (1 x 6 mL), sat. aq. NaCl soln. (1 x 6 mL), dried over MgSO₄, and concentrated in vacuo. The residue was purified by prep. HPLC (column: Waters X-Bridge, 30x75 mm, 10 µm, UV/MS, basic conditions) and concentrated in vacuo to give the desired product.

Listed in Table 20 below are bromides of Structure 6, prepared according to the above-mentioned method with the corresponding amine 4 as starting material.

Table 20

Bromide of Structure 6	t _R [min] LC-MS Method	MS-data m/z [M+H] ⁺
(6-Bromo-pyridin-3-ylmethyl)-((S)-1-isopropyl-piperidin-3-yl)-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine	0.84 LC-MS 4	534.2
N-((6-bromopyridin-3-yl)methyl)-1'-methyl-N-(4-(4-(trifluoromethyl)phenyl)pyrimidin-2-yl)-[1,4'-bipiperidin]-4-amine	0.68 LC-MS 4	589.2

Synthesis of (6-Bromo-pyridin-3-ylmethyl)-(1-isopropyl-piperidin-4-yl)-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine

To an ice-cooled solution of (1-isopropyl-piperidin-4-yl)-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine (1.09 g, 3.0 mmol, 1.0 eq.) in DMF (15 mL), sodium hydride 60% dispersion in mineral oil (94 mg, 3.9 mmol, 1.3 eq.) was added. The resulting orange mixture was stirred at r.t. for 2 hours. Then a solution of 2-bromo-5-(bromomethyl)pyridine (828 mg, 3.3 mmol, 1.1 eq.) in DMF (5 mL) was added dropwise and the mixture was stirred at 60 °C for 18 hours. The reaction mixture was quenched with sat. aq. Na₂CO₃ soln. (200 mL). The mixture was extracted with DCM (3 x 150 mL). The comb. org. phases were

washed with water (1 x 150 mL), sat. aq. NaCl soln. (1 x 150 mL), dried over MgSO₄, and concentrated in vacuo. The residue was purified by flashmaster (column: 50 g, flow: 40 mL/min, 35 fractions of 45 mL, Hept/AcOEt-NEt₃ (10% NEt₃) 95:5 to Hept/AcOEt-NEt₃ (10% NEt₃) 1:1) to give the title compound as a yellow solid.

5 LC-MS 4: t_R = 0.81 min; $[M+H]^+$ = 534.2

Synthesis of N-((6-Bromopyridin-2-yl)methyl)-N-(1-isopropylpiperidin-4-yl)-4-(4-(trifluoromethyl)phenyl)pyrimidin-2-amine

To an ice-cooled solution of (1-isopropyl-piperidin-4-yl)-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine (1.00 g, 2.74 mmol, 1.0 eq.) in DMF (15 mL), sodium hydride 60% dispersion in mineral oil (154 mg, 3.84 mmol, 1.4 eq.) was added. The resulting orange mixture was stirred at r.t. for 2 hours. Then a solution of 2-bromo-6-(bromomethyl)pyridine (757 mg, 3.02 mmol, 1.1 eq.) in DMF (5 mL) was added dropwise and the mixture was stirred at 60 °C for 18 hours. The mixture was cooled to 0 °C and sodium hydride 60% dispersion in mineral oil (77 mg, 1.92 mmol, 0.7 eq.) was added. The resulting orange mixture was stirred at r.t. for 2 hours. Then a solution of 2-bromo-6-(bromomethyl)pyridine (378 mg, 1.51 mmol, 0.55 eq.) in DMF (2 mL) was added dropwise and the mixture was stirred at 60 °C 4 hours. The reaction mixture was quenched with sat. aq. Na₂CO₃ solution. The mixture was extracted with DCM. The comb. org. phases were washed with water, sat. aq. NaCl soln., dried over MgSO₄, and concentrated in vacuo. The residue was purified by flashmaster (column: 50 g, flow: 40 mL/min, 35 fractions of 45 mL, Hept/AcOEt-NEt₃ (10% NEt₃) 95:5 to Hept/AcOEt-NEt₃ (10% NEt₃) 1:1) to afford the title compound as an orange oil.

LC-MS 4: t_R = 0.82 min; $[M+H]^+$ = 534.2

25

Synthesis of (3-Bromo-benzyl)-(1'-methyl-[1,4']bipiperidiny-4-yl)-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine

To an ice-cooled solution of (1-isopropyl-piperidin-4-yl)-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine (1.00 g, 2.75 mmol, 1.0 eq.) in DMF (15 mL), sodium hydride 60% dispersion in mineral oil (86 mg, 3.57 mmol, 1.3 eq) was added. The resulting orange mixture was stirred at r.t. for 2 hours. Then a solution of 3-bromobenzyl bromide (756 mg, 3.02 mmol, 1.1 eq.) in DMF (5 mL) was added dropwise and the mixture was stirred at 60 °C for 18 hours. The reaction mixture was quenched with sat. aq. Na₂CO₃ solution. The mixture was extracted with DCM. The comb. org. phases were washed with water, sat. aq. NaCl soln., dried over MgSO₄, and concentrated in vacuo. The residue was purified by flashmaster (column: 50 g, flow: 40 mL/min, 35 fractions of 45 mL, Hept/AcOEt-NEt₃ (10%

NEt₃) 95:5 to Hept/AcOEt-NEt₃ (10% NEt₃) 1:1) to afford the title compound as a yellow solid.

LC-MS 4: t_R = 0.86 min; [M+H]⁺ = 533.1

5 *Synthesis of (4-Bromo-benzyl)-piperidin-4-yl-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine*

To an ice-cooled solution of 4-{(4-bromo-benzyl)-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amino}-piperidine-1-carboxylic acid tert-butyl ester (2.50 g, 4.23 mmol, 1 eq.) in DCM (50 mL), 4M HCl in dioxane (12 mL) was added. The reaction mixture was stirred at r.t. for 2
10 hours. The reaction mixture was concentrated in vacuo. The residue was partitioned between 1M aq. NaOH soln. (100 mL) and DCM (100 mL). The layers were separated. The aq. phase was extracted with DCM (2 x 50 mL). The comb. org. phases were washed with water (2 x 100 mL), sat. aq. NaCl soln. (1 x 100 mL), dried over MgSO₄, and concentrated in vacuo to give the title compound as a pale yellow foam. The product was used without
15 further purification.

LC-MS 4: t_R = 0.81 min; [M+H]⁺ = 491.2

Synthesis of (4-Bromo-benzyl)-(1'-methyl-[1,4']bipiperidiny-4-yl)-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine

20 To a solution of (4-bromo-benzyl)-piperidin-4-yl-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine (2.20 g, 4.48 mmol, 1 eq.) in acetonitrile (50 mL), 1-methyl-4-piperidone (1.03 mL, 8.95 mmol, 2 eq.) and sodium triacetoxo borohydride (2.85 g, 13.4 mmol, 3 eq.) were added in sequence. The resulting suspension was stirred at 50 °C for 18 hours. The reaction mixture was poured in water (150 mL). The mixture was extracted with DCM (2x 200 mL).
25 The comb. org. phases were dried over MgSO₄ and concentrated in vacuo. The residue was purified by flashmaster (column: 100 g, flow: 45 mL/min, 40 fractions of 45 mL, from AcOEt-NEt₃ (10% NEt₃) to AcOEt-NEt₃ (10% NEt₃)/MeOH 8:2) to yield the title compound as a white solid.

LC-MS 4: t_R = 0.71 min; [M+H]⁺ = 588.2

30

Synthesis of (4-Bromo-benzyl)-(7-isobutyl-quinazolin-4-yl)-(1-isopropyl-piperidin-4-yl)-amine

Step 1: To a suspension under Ar of 7-bromo-3H-quinazolin-4-one (500 mg, 2.22 mmol, 1.00 eq.) and Pd(dppf)Cl₂ CH₂Cl₂ (181 mg, 0.22 mmol, 0.10 eq.) in THF (1 mL), 0.5N isobutylzinc bromide in THF (9 mL, 4.5 mmol, 2.03 eq.) was added. The purple solution was
35 stirred at r.t. for 18 hours. 0.5N isobutylzinc bromide in THF (4.5 mL, 2.25 mmol, 1.01 eq.) was added and the mixture was stirred at r.t. for 2 hours. The reaction mixture was

concentrated in vacuo. The residue was partitioned between AcOEt and 1N aq. HCl soln. The layers were separated. The org. phase was washed with sat. aq. NaCl soln., dried over MgSO₄, and concentrated in vacuo. The residue was purified by CC (SiO₂, DCM to DCM/MeOH 100:5) to give 7-isobutyl-3H-quinazolin-4-one as a brown solid.

5 LC-MS 4: t_R = 0.73 min; $[M+H]^+$ = 203.3

Step 2: A mixture of 7-isobutyl-3H-quinazolin-4-one (173 mg, 0.86 mmol, 1.0 eq.), N,N-dimethylaniline (0.3 mL, 2.37 mmol, 2.8 eq.), and POCl₃ (0.8 mL, 8.58 mmol, 10.0 eq.) was stirred at 115 °C for 1 hour. Toluene (5 mL) was added and the mixture was concentrated
10 in vacuo. The residue was dissolved in DCM (30 mL) and heptane was added. The DCM was removed in vacuo. The resulting suspension was filtered. The filtrate was concentrated in vacuo to give 4-chloro-7-isobutyl-quinazoline as a yellow oil. The product was used without further purification.

LC-MS 4: t_R = 0.96 min; $[M+H]^+$ = 221.2

15

Step 3: To a solution of 4-amino-1-isopropylpiperidine (5.0 g, 35.2 mmol, 1.00 eq.) in MeOH (80 mL), 4-bromobenzaldehyde (6.8 g, 36.8 mmol, 1.05 eq.) and NEt₃ (5.2 mL, 37.0 mmol, 1.05 eq.) were added. The mixture was refluxed for 2 hours. The solution was allowed to cool down to r.t. and NaBH₄ (1.33 g, 35.2 mmol, 1.00 eq.) was added portionwise. The
20 mixture was stirred at r.t. for 18 hours. The reaction mixture was quenched with sat. aq. NaHCO₃ soln. and the org. solvent was removed in vacuo. The residue was diluted with AcOEt. The layers were separated. The org. phase was washed with sat. NaHCO₃ soln., dried over MgSO₄ and concentrated in vacuo to give (4-bromo-benzyl)-(1-isopropyl-piperidin-4-yl)-amine as a colorless oil that solidified upon standing. The product was used
25 without further purification.

LC-MS 4: t_R = 0.44 min; $[M+H]^+$ = 311.2

Step 4: To a suspension of 4-chloro-7-isobutyl-quinazoline (130 mg, 0.59 mmol, 1.0 eq.) and (4-bromo-benzyl)-(1-isopropyl-piperidin-4-yl)-amine (557 mg, 1.79 mmol, 3.0 eq.) in
30 *tert*-butanol (1 mL), DIPEA (0.2 mL, 1.19 mmol, 2.0 eq.) was added. The mixture was stirred at 125 °C for 4.5 hours. The mixture was concentrated in vacuo. The residue was purified by CC (SiO₂, DCM/MeOH (with 1% of NH₄OH) 99:1 to 90:10) to give the title compound as a pale yellow solid.

LC-MS 4: t_R = 0.44 min; $[M+H]^+$ = 311.2

35

General method for the synthesis of a phenol of Structure 17

To a solution under N₂ of (4-benzyloxy-pyrimidin-2-yl)-(1-isopropyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-amine (2.33 g, 4.46 mmol, 1 eq.) in EtOH (150 mL), palladium on activated carbon (10 w%, 237 mg) was added. The flask was carefully evacuated and backfilled with H₂ (3x). The black suspension was stirred at 40 °C under an H₂-atmosphere for 18 hours. The black suspension was filtered through Celite and the filter cake was rinsed with EtOH. The filtrate was concentrated in vacuo to give the desired phenol. The product was used without further purification.

Listed in Table 21 below are phenol of Structure **17**, prepared according to the above-mentioned method with the corresponding benzyl protected phenol **16** as starting material.

Table 21

Phenol of Structure 17	t _R [min] LC-MS Method	MS-data m/z [M+H] ⁺
2-((1-Isopropyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-amino)-pyrimidin-4-ol	0.44 LC-MS 4	433.3
2-(((S)-1'-Methyl-[1,4']bipiperidinyl-3-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-amino)-pyrimidin-4-ol	0.39 LC-MS 4	488.3

Synthesis of (S)-3-((4-Benzyloxy-pyrimidin-2-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-amino)-piperidine-1-carboxylic acid tert-butyl ester

A solution of (S)-3-[(4-benzyloxy-pyrimidin-2-yl)-(4-bromo-benzyl)-amino]-piperidine-1-carboxylic acid tert-butyl ester (2.36 g, 4.26 mmol, 1.00 eq.), sodium tert-butoxide (512 mg, 5.33 mmol, 1.25 eq.) and 4-(methylamino)pyridine (461 mg, 4.26 mmol, 1.00 eq.) in dioxane (60 mL) was degassed with N₂ for 15 min before the addition of X-Phos (203 mg, 0.43 mmol, 0.10 eq.) and tris(dibenzylideneacetone)dipalladium(0)-chloroform adduct (221 mg, 0.21 mmol, 0.05 eq.). The reaction mixture was degassed again with N₂ for 15 min and then heated at 105 °C for 24 hours. The reaction was allowed to cool to r.t. and filtered through Celite. The filtrate was concentrated in vacuo and the residue was purified by flash chromatography (snap 100 g, from Hept/AcOEt-10%Et₃N 5:5 to Hept/AcOEt-10%Et₃N 3:7) to give the title compound as a pale yellow foam.

LC-MS 4: t_R = 0.81 min; [M+H]⁺ = 581.2

Synthesis of (4-Benzyloxy-pyrimidin-2-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-(S)-piperidin-3-yl-amine

To an ice-cooled solution of (S)-3-[(4-benzyloxy-pyrimidin-2-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-amino]-piperidine-1-carboxylic acid tert-butyl ester (2.00 g, 3.44 mmol, 1 eq.) in DCM (12 mL), 4N HCl in dioxane (12 mL) was added dropwise. The resulting mixture was stirred at r.t. for 30 min. The mixture was concentrated in vacuo. Sat. aq. NaHCO₃ was added and the mixture was extracted with DCM. The comb. org. phases were dried over MgSO₄ and concentrated in vacuo to give the title compound as a pale orange foam.

LC-MS 4: t_R = 0.60 min; [M+H]⁺ = 481.1

10 *Synthesis of (S)-N-(4-(benzyloxy)pyrimidin-2-yl)-1'-methyl-N-(4-(methyl(pyridin-4-yl)amino)benzyl)-[1,4'-bipiperidin]-3-amine*

To a solution of (4-benzyloxy-pyrimidin-2-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-(S)-piperidin-3-yl-amine (1.64 g, 3.34 mmol, 1.0 eq.) in MeCN (15 mL), N-methyl-4-piperidone (0.40 mL, 3.34 mmol, 1.0 eq.) was added. The mixture was stirred at r.t. for 2 hours.

15 Sodium triacetoxyborohydride (1.06 g, 5.02 mmol, 1.5 eq.) was added. The mixture was stirred at r.t. for 1 hour. Sat. aq. NaHCO₃ was added and the mixture was extracted with DCM (3x). The comb. org. layers were dried over MgSO₄ and concentrated in vacuo. The residue was purified by prep. HPLC (column: Waters X-Bridge, 30x75 mm, 10 μm, UV/MS, basic conditions) and concentrated in vacuo to give the title compound as an off-white foam.

20 LC-MS 4: t_R = 0.56 min; [M+H]⁺ = 577.9

General method for the synthesis of an amine of Structure 23

To an ice-cooled solution of 4-[[4-(methyl-pyridin-4-yl-amino)-benzyl]-quinoxalin-2-yl-amino]-piperidine-1-carboxylic acid tert-butyl ester (566 mg, 1.08 mmol, 1 eq.) in DCM (15 mL), 4M HCl in dioxane (6 mL) was added. The reaction mixture was stirred at r.t. for 17 hours. The reaction mixture was concentrated in vacuo. The residue was partitioned between 1M aq. NaOH (50 mL) and DCM (50 mL). The layers were separated. The aq. phase was extracted with DCM (2 x 50 mL). The comb. org. phases were washed with water (2 x 50 mL), sat. aq. NaCl soln. (1 x 50 mL), dried over MgSO₄ and concentrated in vacuo to give the desired amine. The product was used without further purification.

Listed in Table 22 below are amine of Structure 23, prepared according to the above-mentioned method with the corresponding Boc-protected amine 22 as starting material.

35 **Table 22**

Amine of Structure 23	t_R [min] LC-MS Method	MS-data m/z $[M+H]^+$
[4-(Methyl-pyridin-4-yl-amino)-benzyl]-piperidin-4-yl-quinoxalin-2-yl-amine	0.81 LC-MS 3	425.1
Benzooxazol-2-yl-[4-(methyl-pyridin-4-yl-amino)-benzyl]-piperidin-4-yl-amine	0.53 LC-MS 4	414.2
Benzothiazol-2-yl-[4-(methyl-pyridin-4-yl-amino)-benzyl]-piperidin-4-yl-amine	0.55 LC-MS 4	430.2
Methyl-[4-({piperidin-4-yl-[3-(4-trifluoromethyl-phenyl)-[1,2,4]oxadiazol-5-yl]-amino}-methyl)-phenyl]-pyridin-4-yl-amine	0.65 LC-MS 4	508.9
[4-(Ethyl-pyridin-4-yl-amino)-benzyl]-(S)-piperidin-3-yl-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine	0.69 LC-MS 4	533.3
[4-(Methyl-pyridin-3-yl-amino)-benzyl]-(S)-piperidin-3-yl-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine	0.68 LC-MS 4	518.9
{4-[Methyl-(2-methyl-pyridin-4-yl)-amino]-benzyl}-(S)-piperidin-3-yl-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine	0.68 LC-MS 4	533.2
Methyl-[4-({piperidin-4-yl-[5-(4-trifluoromethyl-phenyl)-[1,3,4]oxadiazol-2-yl]-amino}-methyl)-phenyl]-pyridin-4-yl-amine	0.61 LC-MS 4	509.4

Synthesis of [4-(2-Methyl-pyridin-4-ylamino)-benzyl]-(S)-piperidin-3-yl-quinolin-4-yl-amine

To an ice-cooled solution under N_2 of (S)-tert-butyl 3-((4-((2-methylpyridin-4-yl)amino)benzyl)(quinolin-4-yl)amino)piperidine-1-carboxylate (886 mg, 1.69 mmol, 1 eq.) in DCM (10 mL), TFA (1.3 mL, 16.9 mmol, 10 eq.) was added. The reaction mixture was stirred at r.t. for 18 hours. The reaction mixture was concentrated in vacuo. The residue was partitioned between 1M aq. NaOH and DCM. The layers were separated. The aq. phase was extracted with DCM. The comb. org. phases were washed with water, sat. aq. NaCl soln., dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by prep. HPLC (column: Water X-Bridge, 18x50 mm, 10 μm , UV/MS, basic conditions) and concentrated in vacuo to yield the title compound as a white solid.

LC-MS 4: t_R = 0.42 min; $[M+H]^+$ = 424.4

General method for the synthesis of an amine 4

Method A: A mixture of 4-amino-1-benzylpiperidine (0.11 mL, 0.53 mmol, 1.0 eq.), 2-chloro-5-phenyl-pyrimidine (150 mg, 0.79 mmol, 1.5 eq.), and DIPEA (0.37 mL, 2.10 mmol, 4.0 eq.) in MeCN (2.0 mL) was stirred at 190 °C under microwave irradiations for 1 hour. The mixture was allowed to cool to r.t. and concentrated in vacuo. The residue was purified by
 5 flashmaster (column: 50 g, flow: 45 mL/min, 20 fractions of 45 mL, Hept/AcOEt-NEt₃ (10% NEt₃) 9:1 to Hept/AcOEt-NEt₃ (10% NEt₃) 3:7) to yield the desired product as a yellow solid.

Listed in Table 23 below are amine **4**, prepared according to the above-mentioned method with the corresponding amine **2** and the corresponding compound **3** as starting materials.

10

Table 23

Amine 4	<i>t_R</i> [min] LC-MS Method	MS-data m/z [M+H] ⁺
(1-Benzyl-piperidin-4-yl)-(5-phenyl-pyrimidin-2-yl)-amine	0.97 LC-MS 3	345.2
(1-Benzyl-piperidin-4-yl)-[4-(3-fluoro-phenyl)-pyrimidin-2-yl]-amine	1.01 LC-MS 3	362.8
(1-Benzyl-piperidin-4-yl)-[5-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine	1.04 LC-MS 3	412.9
(1-Benzyl-piperidin-4-yl)-(7-chloro-quinazolin-4-yl)-amine	0.88 LC-MS 3	353.1
(1-Benzyl-piperidin-4-yl)-(6-fluoro-quinazolin-2-yl)-amine	0.95 LC-MS 3	337.1
(1-Benzyl-piperidin-4-yl)-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine	1.08 LC-MS 3	412.9
(1-Isopropyl-piperidin-4-yl)-(2-phenyl-pyrimidin-4-yl)-amine	0.56 LC-MS 4	297.2

Method B: To a suspension under N₂ of 2-methanesulfonyl-4-(4-trifluoromethyl-phenyl)-pyrimidine (907 mg, 3.0 mmol, 1.0 eq.) in 2-propanol (6.0 mL), 1-N-Boc-4-aminopiperidine
 15 (601 mg, 3.0 mmol, 1.0 eq.) and triethylamine (0.42 mL, 3.0 mmol, 1.0 eq.) were added. The suspension was stirred at 90 °C for 18 hours. The mixture was allowed to cool to r.t. and concentrated in vacuo. Sat. aq. NaHCO₃ soln. was added and the mixture was extracted with AcOEt. The comb. org. phases were washed with sat. aq. NaCl soln., dried over MgSO₄, filtered, and concentrated in vacuo. The residue was purified by flashmaster

(column: 100 g, flow: 45 mL/min, 36 fractions of 45 mL, from Hept/AcOEt-NEt₃ (10% NEt₃) 8:2 to Hept/AcOEt-NEt₃ (10% NEt₃) 2:8) to yield the desired product as a yellow foam.

Listed in Table 24 below are amine **4**, prepared according to the above-mentioned method
5 with the corresponding amine **2** and the corresponding compound **3** as starting materials.

Table 24

Amine 4	t _R [min] LC-MS Method	MS-data m/z [M+H] ⁺
4-[4-(4-Trifluoromethyl-phenyl)-pyrimidin-2-ylamino]-piperidine-1-carboxylic acid tert-butyl ester	1.05 LC-MS 3	423.1
(1-Benzyl-piperidin-4-yl)-(4-methoxy-pyrimidin-2-yl)-amine	0.88 LC-MS 3	298.9
(1-Isopropyl-piperidin-4-yl)-(4-methoxy-pyrimidin-2-yl)-amine	0.36 LC-MS 4	251.2
(1-Isopropyl-piperidin-4-yl)-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine	0.68 LC-MS 4	365.2
4-(Benzooxazol-2-ylamino)-piperidine-1-carboxylic acid tert-butyl ester	0.87 LC-MS 3	318.2
4-(Benzothiazol-2-ylamino)-piperidine-1-carboxylic acid tert-butyl ester	0.92 LC-MS 3	334.2
4-(Quinoxalin-2-ylamino)-piperidine-1-carboxylic acid tert-butyl ester	0.90 LC-MS 3	329.1
(R)-3-[4-(4-Trifluoromethyl-phenyl)-pyrimidin-2-ylamino]-pyrrolidine-1-carboxylic acid tert-butyl ester	0.95 LC-MS 4	409.2
(S)-3-[4-(4-Trifluoromethyl-phenyl)-pyrimidin-2-ylamino]-pyrrolidine-1-carboxylic acid tert-butyl ester	0.95 LC-MS 4	409.2
N,N-Dimethyl-N'-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-ethane-1,2-diamine	0.64 LC-MS 4	311.1
(±)-N1,N1-Dimethyl-N2-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-propane-1,2-diamine	0.67 LC-MS 4	325.1
N,N-Dimethyl-N'-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-propane-1,3-diamine	0.63 LC-MS 4	325.2
(±)-N1,N1-Dimethyl-N3-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-butane-1,3-diamine	0.65 LC-MS 4	339.1

(4-Benzyloxy-pyrimidin-2-yl)-(1-isopropyl-piperidin-4-yl)-amine	0.53 LC-MS 4	327.3
(S)-3-[4-(4-Trifluoromethyl-phenyl)-pyrimidin-2-ylamino]-piperidine-1-carboxylic acid tert-butyl ester	0.96 LC-MS 4	423.1
(3aR,6aS)-tert-butyl 5-((4-(4-(trifluoromethyl)phenyl)pyrimidin-2-yl)amino)hexahydrocyclopenta[c]pyrrole-2(1H)-carboxylate (mixture of stereoisomers)	0.95 LC-MS 4	449.1
(4,6-Dimethyl-pyrimidin-2-yl)-(1-isopropyl-piperidin-4-yl)-amine	0.39 LC-MS 4	249.3
(1-Isopropyl-piperidin-4-yl)-pyrimidin-2-yl-amine	0.37 LC-MS 4	221.4
(1-Isopropyl-piperidin-4-yl)-[5-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine	0.69 LC-MS 4	365.1
(1-Isopropyl-piperidin-4-yl)-[6-(4-trifluoromethyl-phenyl)-pyrimidin-4-yl]-amine	0.55 LC-MS 4	365.4
(S)-3-(4-Benzyloxy-pyrimidin-2-ylamino)-piperidine-1-carboxylic acid tert-butyl ester	0.76 LC-MS 4	385.0
((S)-1-Isopropyl-piperidin-3-yl)-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine	0.71 LC-MS 4	365.2
[3-(4-Methyl-piperazin-1-yl)-propyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine	0.58 LC-MS 4	380.3
Benzooxazol-2-yl-(1-isopropyl-piperidin-4-yl)-amine	0.51 LC-MS 4	260.4

Method C: A solution of 4-amino-1-isopropylpiperidine (0.16 mL, 1.00 mmol, 1.00 eq.), sodium tert-butoxide (120 mg, 1.25 mmol, 1.25 eq.) and 4-bromoquinoline (208 mg, 1.00 mmol, 1.00 eq.) in dioxane (4 mL) was degassed with N₂ for 15 min before the addition of X-Phos (48 mg, 0.10 mmol, 0.10 eq.) and tris(dibenzylideneacetone)dipalladium(0) (46 mg, 0.05 mmol, 0.05 eq.). The reaction mixture was degassed again with N₂ for 15 min and then stirred at 105 °C for 18 hours. The reaction was allowed to cool down to r.t. and filtered through Celite. The filtrate was concentrated in vacuo. The residue was purified by flashmaster (column: 10 g, flow: 15 mL/min, 40 fractions of 20 mL, from Hept/AcOEt + 10% Et₃N 6:4 to Hept/AcOEt + 10% Et₃N 3:7) to afford the desired product as a yellow solid.

Listed in Table 25 below are amine **4**, prepared according to the above-mentioned method with the corresponding amine **2** and the corresponding compound **3** as starting materials.

Table 25

Amine 4	t_R [min] LC-MS Method	MS-data m/z [M+H]⁺
(1-Isopropyl-piperidin-4-yl)-quinolin-4-yl-amine	0.42 LC-MS 4	270.4
(1-Isopropyl-piperidin-4-yl)-[2-(4-trifluoromethyl-phenyl)-pyridin-4-yl]-amine	0.54 LC-MS 4	364.3
(1-Isopropyl-piperidin-4-yl)-[6-(4-trifluoromethyl-phenyl)-pyridin-2-yl]-amine	0.66 LC-MS 4	364.3
(1-Isopropyl-piperidin-4-yl)-[4-(4-trifluoromethyl-phenyl)-pyridin-2-yl]-amine	0.57 LC-MS 4	364.3
(S)-3-(Quinolin-4-ylamino)-piperidine-1-carboxylic acid tert-butyl ester	0.67 LC-MS 4	328.3
4-(Quinolin-4-ylamino)-piperidine-1-carboxylic acid tert-butyl ester	0.67 LC-MS 4	328.3

5

Synthesis of (1-Isopropyl-piperidin-4-yl)-[6-(4-trifluoromethyl-phenyl)-pyrazin-2-yl]-amine

A solution of 4-amino-1-isopropylpiperidine (142 mg, 1.00 mmol, 1.00 eq.), sodium tert-butoxide (120 mg, 1.25 mmol, 1.25 eq.) and 2-chloro-6-(4-trifluoromethyl-phenyl)-pyrazine (259 mg, 1.00 mmol, 1.00 eq.) in dioxane (4 mL) was degased with N₂ for 15 min before the addition of BrettPhos (54 mg, 0.10 mmol, 0.10 eq.) and tris(dibenzylideneacetone)dipalladium(0) (46 mg, 0.05 mmol, 0.05 eq.). The reaction mixture was degased again with N₂ for 15 min and then stirred at 105 °C for 18 hours. The reaction was allowed to cool down to r.t. and filtered through Celite. The filtrate was concentrated in vacuo. The residue was purified by flashmaster (column: 10 g, flow: 15 mL/min, 40 fractions of 20 mL, from Hept/AcOEt + Et₃N 6:4 to Hept/AcOEt + Et₃N 10% 3:7 to afford the title compound as an orange oil.

LC-MS 4: t_R = 0.71 min; [M+H]⁺ = 365.3

Synthesis of (1-Benzyl-piperidin-4-yl)-[4-(4-trifluoromethyl-phenyl)-thiazol-2-yl]-amine

Step 1: A solution of 4-amino-1-benzylpiperidine (0.32 mL, 1.58 mmol, 1.0 eq.) and 1,1'-thiocarbonyldiimidazol (355 mg, 1.89 mmol, 1.2 eq.) in DCM (16 mL) was stirred at r.t. for 2 hours. 2M ammonia in EtOH (3.3 mL) was added and the mixture was stirred at r.t. for 48

20

hours. 2M ammonia in EtOH (3.3 mL) was added and the mixture was stirred at 40 °C for 18 hours. The mixture was concentrated in vacuo to yield 1-(1-benzylpiperidin-4-yl)thiourea as an orange oil. The product was used crude with no further purification.

LC-MS 3: t_R = 0.71 min; $[M+H]^+$ = 250.2

5

Step 2: A mixture of 1-(1-benzylpiperidin-4-yl)thiourea (860 mg, 1.72 mmol, 1.00 eq.) and 2-bromo-4'-(trifluoromethyl)acetophenone (498 mg, 1.81 mmol, 1.05 eq.) in ethanol (50 mL) was heated at 100 °C for 1 hour. The reaction mixture was allowed to cool to r.t. and concentrated in vacuo. The residue was purified by flashmaster (column: 50 g, flow: 45 mL/min, 20 fractions of 45 mL, Hept/AcOEt-NEt₃ (10% NEt₃) 9:1 to Hept/AcOEt-NEt₃ (10% NEt₃) 4:6) to yield the title compound as an off-white powder.

LC-MS 3: t_R = 1.09 min; $[M+H]^+$ = 418.0

Synthesis of [4-(4-Fluoro-phenyl)-pyrimidin-2-yl]-(1-isopropyl-piperidin-4-yl)-amine

15 Step 1: To a solution 4-amino-1-isopropylpiperidine (1.42 g, 10 mmol, 1.0 eq.) and N,N'-bis-Boc-1-guanylpiprazol (3.10 g, 10 mmol, 1.0 eq.) in MeCN (50 mL), triethylamine (4.18 mL, 30 mmol, 3.0 eq.) and DMAP (122 mg, 1 mmol, 0.1 eq.) were added in sequence. The mixture was stirred at 40 °C for 72 hours. The mixture was concentrated in vacuo. The residue was purified by flashmaster (column: 100 g, flow: 45 mL/min, 50 fractions of 45 mL, from Heptane to Hept/AcOEt-NEt₃ (10% NEt₃) 75:25) to yield carbamic acid [[1-isopropyl-piperidin-4-amino][[(1,1-dimethylethoxy)carbonyl]amino]methylene]-, 1,1-dimethylethyl ester (9CI) as a white solid.

LC-MS 3: t_R = 1.08 min; $[M+H]^+$ = 385.2

25 Step 2: To an ice-cooled solution of carbamic acid [[1-isopropyl-piperidin-4-amino][[(1,1-dimethylethoxy)carbonyl]amino]methylene]-, 1,1-dimethylethyl ester (9CI) (1.50 g, 3.9 mmol, 1.3 eq.) in DCM (50 mL), 4M HCl in dioxane (7.5 mL, 30 mmol, 10.0 eq.) was added. The reaction mixture was stirred at r.t. for 5 hours. 4M HCl in dioxane (7.5 mL, 30 mmol, 10.0 eq.) was added and the mixture was stirred at r.t. for 72 hours. The reaction mixture was concentrated in vacuo. The resulting white solid was suspended in DBU (9 mL, 60 mmol, 20.0 eq.). 3-(Dimethylamino)-1-(4-fluorophenyl)-2-propen-1-one (580 mg, 3 mmol, 1.0 eq.) was added and the mixture was stirred at 120 °C for 2 hours. The mixture was allowed to cool to r.t. and partitioned between AcOEt (100 mL) and water (100 mL). The layers were separated. The org. phase was washed with sat. aq. NaCl soln. (50 mL), dried over MgSO₄, and concentrated in vacuo. The residue was purified by prep. HPLC (column:

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Waters XBridge, 75x30 mm, 10 μ m, UV/MS, acidic conditions) to give the title compound as a pale yellow solid.

LC-MS 4: t_R = 0.57 min; $[M+H]^+$ = 315.2

5 *Synthesis of 4-[3-(4-Trifluoromethyl-phenyl)-[1,2,4]oxadiazol-5-ylamino]-piperidine-1-carboxylic acid tert-butyl ester*

Step 1: To a solution of 4-(trifluoromethyl)benzamidoxime (1.00 g, 4.9 mmol, 1 eq.) in toluene (17 mL), trichloroacetic anhydride (0.9 mL, 4.9 mmol, 1 eq.) was added. The solution was heated at 120 °C for 2.5 hours. The reaction was cooled down to r.t. and
10 poured into water. The aq. layer was extracted with AcOEt. The comb. org. phases were washed with sat. aq. NaHCO₃ soln. and dried over MgSO₄ to yield 5-trichloromethyl-3-(4-trifluoromethyl-phenyl)-[1,2,4]oxadiazole as a yellow solid. The product was used without further purification.

LC-MS 3: t_R = 1.09 min; $[M+H]^+$ = no ionization

15

Step 2: 5-Trichloromethyl-3-(4-trifluoromethyl-phenyl)-[1,2,4]oxadiazole (1.46 g, 4.40 mmol, 1.0 eq.), 1-N-Boc-4-aminopiperidine (990 mg, 4.84 mmol, 1.1 eq.), and NaHCO₃ (740 mg, 8.81 mmol, 2.0 eq.) in 1-methyl-2-pyrrolidone (14.7 mL) was heated at 120 °C under microwave irradiation for 20 min. The mixture was allowed to cool to r.t. and concentrated in
20 vacuo. The residue was partitioned between sat. aq. NaCl soln. and Et₂O. The layers were separated and the aq. phase was extracted with Et₂O. The comb. org. phases were dried over MgSO₄ and concentrated in vacuo. The residue was purified by CC (SiO₂, Hept to Hept/AcOEt 1:1) to give the title compound as a yellow powder.

LC-MS 4: t_R = 1.30 min; $[M+H]^+$ = 413.0

25

Synthesis of 4-[5-(4-Trifluoromethyl-phenyl)-[1,3,4]oxadiazol-2-ylamino]-piperidine-1-carboxylic acid tert-butyl ester

Step 1: To a solution of 4-(trifluoromethyl)benzhydrazide (1.00 g, 4.9 mmol, 1.0 eq.) in EtOH (17 mL), carbon disulfide (0.33 mL, 5.4 mmol, 1.1 eq.) and a solution of KOH (275
30 mg, 4.9 mmol, 1.0 eq.) in water (2.5 mL) were added in sequence. The reaction mixture was refluxed for 24 hours. The reaction mixture was concentrated in vacuo. The residue was dissolved in excess water and acidified with 2M aq. HCl to pH 2-3. The resulting suspension was filtered. The solid was dissolved in AcOEt and the solution was dried over MgSO₄ and evaporated in vacuo to give 5-(4-trifluoromethyl-phenyl)-[1,3,4]oxadiazole-2-
35 thiol as a white solid. The product was used without further purification.

LC-MS 4: t_R = 1.18 min; $[M+H]^+$ = no ionization

Step 2: To a mixture of 5-(4-trifluoromethyl-phenyl)-[1,3,4]oxadiazole-2-thiol (921 mg, 3.74 mmol, 1 eq.) and NEt_3 (1.0 mL, 7.11 mmol, 1.9 eq.) in EtOH (10 mL), benzyl bromide (0.45 mL, 3.74 mmol, 1.0 eq.) was added. The mixture was stirred at r.t. for 2 hours. The resulting suspension was filtered and the solids were washed with EtOH and dried in vacuo to yield

LC-MS 4: $t_R = 1.00$ min; $[\text{M}+\text{H}]^+ = 337.0$

Step 3: To an ice-cooled solution of 2-benzylsulfanyl-5-(4-trifluoromethyl-phenyl)-[1,3,4]oxadiazole (150 mg, 0.45 mmol, 1.0 eq.) in DCM (5 mL), 3-chloroperbenzoic acid (543 mg, 0.98 mmol, 2.2 eq.) was added portionwise. The reaction mixture was warmed up to r.t. and stirred at r.t. for 18 hours. 3-Chloroperbenzoic acid (247 mg, 0.45 mmol, 1.0 eq.) was added and the mixture was stirred at r.t. for 6 hours. DCM (5 mL) and 3-chloroperbenzoic acid (247 mg, 0.45 mmol, 1.0 eq.) were added and the mixture was stirred at r.t. for 18 hours. The suspension was filtered and the solids washed with DCM. The filtrate was washed with a sat. aq. NaHCO_3 soln., dried over MgSO_4 , and concentrated in vacuo to give 2-phenylmethanesulfonyl-5-(4-trifluoromethyl-phenyl)-[1,3,4]oxadiazole as a white solid. The product was used without further purification.

LC-MS 4: $t_R = 0.95$ min; $[\text{M}+\text{H}]^+ = \text{no ionization}$

Step 4: 2-Phenylmethanesulfonyl-5-(4-trifluoromethyl-phenyl)-[1,3,4]oxadiazole (721 mg, 1.57 mmol, 1 eq.) and 1-N-Boc-4-aminopiperidine (320 mg, 1.57 mmol, 1 eq.) were dissolved in dioxane (5 mL) and the mixture was heated at 100 °C under microwave irradiations for 35 min. 1-N-Boc-4-aminopiperidine (320 mg, 1.57 mmol, 1 eq.) was added and the mixture was heated at 150 °C under microwave irradiations for 15 min. The mixture was allowed to cool to r.t. and concentrated in vacuo. The residue was purified by CC (SiO_2 , Hept/AcOEt 8:2 to Hept/AcOEt 4:6) to yield the title compound as a pale yellow powder.

LC-MS 4: $t_R = 0.94$ min; $[\text{M}+\text{H}]^+ = 413.0$

Synthesis of 2-Methanesulfonyl-4-(4-trifluoromethyl-phenyl)-pyrimidine

Step 1: A mixture under N_2 of 4-(trifluoromethyl)phenylboronic acid (3.80 g, 20 mmol, 1.00 eq.), 4-chloro-2-methylthiopyrimidine (2.4 mL, 20 mmol, 1.00 eq.), sodium carbonate (8.48 g, 80 mmol, 4.00 eq.) and tetrakis(triphenylphosphine) palladium (0) (1.16 g, 1 mmol, 0.05 eq.) in toluene/EtOH/water 20:4:1 (75 mL) was stirred at 100 °C for 18 hours. The mixture was allowed to cool to r.t. and partitioned between AcOEt and water. The layers were

separated. The org. phase was washed with sat. aq. NaCl soln., dried over MgSO₄, and concentrated in vacuo. The residue was purified by flashmaster (column: 100 g, flow: 45 mL/min, 45 fractions of 45 mL, Hept to Hept/AcOEt 8:2) to yield 2-methylsulfanyl-4-(4-trifluoromethyl-phenyl)-pyrimidine as a white solid.

5 LC-MS 4: t_R = 0.97 min; $[M+H]^+$ = 271.3

Step 2: To an ice-cooled solution of 2-methylsulfanyl-4-(4-trifluoromethyl-phenyl)-pyrimidine (3.35 g, 12.4 mmol, 1.0 eq.) in DCM (85 mL), 70-75% *m*CPBA (6.54 g, 27.3 mmol, 2.2 eq.) was added portionwise. The reaction mixture was warmed up to r.t. and stirred for 3.5
10 hours. The resulting suspension was filtered and the solids rinsed with DCM. The filtrate was washed with sat. aq. NaHCO₃ soln. and with sat. aq. NaCl soln. The org. phase was dried over MgSO₄ and concentrated in vacuo to give the title compound as a white solid. The product was used without further purification.

LC-MS 4: t_R = 0.82 min; $[M+H]^+$ = 303.2

15

Synthesis of 2-Methanesulfonyl-4-(6-trifluoromethyl-pyridin-3-yl)-pyrimidine

Step 1: A mixture under N₂ of 2-trifluoromethylpyridine-5-boronic acid (2.86 g, 15 mmol, 1.00 eq.), 4-chloro-2-(methylthio)pyrimidine (1.76 mL, 15 mmol, 1.00 eq.), sodium carbonate (6.36 g, 60 mmol, 4.00 eq.) and tetrakis(triphenylphosphine) palladium (0) (867
20 mg, 0.75 mmol, 0.05 eq.) in toluene/EtOH/Water 20:4:1 (50 mL) was stirred at 100 °C for 18 hours. The mixture was allowed to cool to r.t. and partitioned between AcOEt and water. The layers were separated. The org. phase was washed with sat. aq. NaCl soln., dried over MgSO₄, and concentrated in vacuo. The residue was purified by flashmaster (column: 100 g, flow: 45 mL/min, 45 fractions of 45 mL, Hept to Hept/AcOEt 7:3) to yield 2-
25 methylsulfanyl-4-(6-trifluoromethyl-pyridin-3-yl)-pyrimidine as a white solid.

LC-MS 4: t_R = 0.88 min; $[M+H]^+$ = 272.1

Step 2: To an ice-cooled solution of 2-methylsulfanyl-4-(6-trifluoromethyl-pyridin-3-yl)-pyrimidine (2.99 g, 11 mmol, 1 eq.) in THF/MeOH 1:1 (120 mL), a solution of Oxone (27.1
30 g, 44 mmol, 4 eq.) in water (80 mL) was added. After 30 min a sat. NaHCO₃ soln. was added and the mixture was extracted with AcOEt. The layers were separated and the org. phase was washed with sat. aq. NaCl soln., dried over MgSO₄, and concentrated in vacuo to give the title compound as a pale yellow solid. The residue was used without further purification.

35 LC-MS 4: t_R = 0.72 min; $[M+H]^+$ = 304.2

Synthesis of 4-Benzyloxy-2-methanesulfonyl-pyrimidine

Step 1: Benzylalcohol (3 mL, 29.0 mmol, 1.0 eq.) was added dropwise to a suspension of sodium hydride 60% dispersion in mineral oil (1.74 g, 43.4 mmol, 1.5 eq.) in dioxane (30 mL), and the mixture was stirred at 100 °C for 30 min. The mixture was allowed to cool to 50 °C. A solution of 4-chloro-2-(methylthio)pyrimidine (3.4 mL, 29.0 mmol, 1.0 eq.) in dry dioxane (20 mL) was added dropwise and the mixture was stirred at 50 °C for 4.5 hours. The mixture was cooled to r.t. and acidified with glacial acetic acid, diluted with water, and extracted with DCM. The comb. org. phases were dried over MgSO₄ and concentrated in vacuo. The residue was purified by flashmaster (column: 50 g, flow: 40 mL/min, 35 fractions of 40 mL, from Hept/AcOEt 85:15 to Hept/AcOEt 6:4) to afford 4-benzyloxy-2-methylsulfanyl-pyrimidine as a colorless oil.

LC-MS 4: t_R = 0.89 min; $[M+H]^+$ = 233.3

Step 2: To a solution of 4-benzyloxy-2-methylsulfanyl-pyrimidine (3.90 g, 16.8 mmol, 1 eq.) in THF/MeOH 1:1 (150 mL), a solution of Oxone (41.28 g, 67.2 mmol, 4 eq.) in water (100 mL) was added. The mixture was stirred at r.t. for 45 min. Sat. NaHCO₃ soln. was added and the mixture was extracted with AcOEt. The org. phase was washed with sat. aq. NaCl soln., dried over MgSO₄, and concentrated in vacuo. The residue was purified by flashmaster (column: 100 g, flow: 45 mL/min, 45 fractions of 45 mL, from Hept/AcOEt 9:1 to Hept/AcOEt 6:4) to afford the title compound as a white solid.

LC-MS 4: t_R = 0.77 min; $[M+H]^+$ = 265.3

Synthesis of 2-Chloro-6-(4-trifluoromethyl-phenyl)-pyrazine

To a mixture under N₂ of 2,6-dichloropyrazine (1.51 g, 10.0 mmol, 1.00 eq.), sodium carbonate (2.76 g, 26.0 mmol, 2.60 eq.), and 4-(trifluoromethyl)phenylboronic acid (1.90 g, 10.0 mmol, 1.00 eq.) in dimethoxyethane (45 mL) and water (22.5 mL), tetrakis(triphenylphosphine) palladium (0) (231 mg, 0.2 mmol, 0.02 eq.) was added. The reaction mixture was heated at reflux for 2 days. After cooling to r.t., the reaction was diluted with water (50 mL) and extracted with DCM (2 x 75 mL). The comb. org. phases were dried over MgSO₄ and concentrated in vacuo. The residue was purified by flashmaster (column: 50 g, flow: 40 mL/min, 45 fractions of 45 mL, Hept to Hept/AcOEt 8:2) to yield the title compound as a pale yellow solid.

LC-MS 4: t_R = 0.95 min; $[M+H]^+$ = 259.2

Synthesis of 4-Chloro-6-(4-trifluoromethyl-phenyl)-pyrimidine

A mixture under N₂ of 4,6-dichloropyrimidine (447 mg, 3.00 mmol, 1.00 eq.), 4-(trifluoromethyl)phenylboronic acid (188 mg, 0.99 mmol, 0.33 eq.), Na₂CO₃ (1.59 g, 15.00 mmol, 5.00 eq.) and tetrakis(triphenylphosphine)palladium (0) (173 mg, 0.15 mmol, 0.05 eq.) in acetonitrile (5 mL) was stirred at 80 °C for 24 hours and further at 100 °C for 18 hours. The reaction mixture was allowed to cool down to r.t. and concentrated in vacuo. The residue was partitioned between DCM and sat. aq. NaHCO₃ soln. The layers were separated. The aq. phase was extracted with DCM. The comb. org. phases were washed with sat. aq. NaCl soln., dried over MgSO₄, and concentrated in vacuo. The residue was purified by prep. HPLC (column: Waters X-Bridge, 18x50 mm, 10 µm, UV/MS, basic conditions) and concentrated in vacuo to afford the title compound as a white solid.

LC-MS 4: t_R = 0.94 min; [M+H]⁺ = 259.3

Synthesis of 2-Chloro-6-(4-trifluoromethyl-phenyl)-pyridine

To a mixture under N₂ of 2,6-dichloropyridine (740 mg, 5.00 mmol, 1.00 eq.) and tetrakis(triphenylphosphine) palladium (0) (289 mg, 0.25 mmol, 0.05 eq.) in toluene/EtOH/H₂O (7:2:1) (4 mL), 4-(trifluoromethyl)phenylboronic acid (1.04 g, 5.50 mmol, 1.10 eq.) and sodium carbonate (2.12 g, 20.00 mmol, 4.00 eq.) were added. The mixture was stirred at 100 °C for 18 hours. After cooling to r.t., the reaction was partitioned between AcOEt and sat. aq. NaCl soln. The comb. org. layers were dried over MgSO₄ and concentrated in vacuo. The residue was purified by FC (SiO₂, eluent: Hept/AcOEt 99:1 to Hept/AcOEt 95:5) to give the title compound as a white solid.

LC-MS 2: t_R = 0.98 min; [M+H]⁺ = 258.0

Synthesis of 2-Chloro-5-(4-trifluoromethyl-phenyl)-pyrimidine

To a mixture of 5-bromo-2-chloropyrimidine (967 mg, 5 mmol, 1.00 eq.), 4-(trifluoromethyl)phenylboronic acid (997 mg, 5.25 mmol, 1.05 eq.), and sodium carbonate (2.12 g, 20 mmol, 4.00 eq.) in toluene/EtOH/water 20:4:1 (25 mL), tetrakis(triphenylphosphine) palladium (0) (289 mg, 0.25 mmol, 0.05 eq.) was added. The resulting mixture was stirred at 100 °C for 19 hours. The mixture was allowed to cool to r.t. and concentrated in vacuo. The residue was partitioned between AcOEt (40 mL) and water (20 mL). The layers were separated. The org. phase was washed with sat. aq. NaCl soln. (1x 20 mL), dried over MgSO₄, and concentrated in vacuo. The residue was purified by flashmaster (column: 100 g, flow: 45 mL/min, 40 fractions of 45 mL, Hept to Hept + 16% AcOEt) to yield the title compound as a white solid.

LC-MS 2: t_R = 0.83 min; [M+H]⁺ = 259.2

Synthesis of 2-Bromo-4-(4-trifluoromethyl-phenyl)-pyridine

A mixture under N₂ of 4-(trifluoromethyl)phenylboronic acid (950 mg, 5.00 mmol, 1.00 eq.), 2-bromo-4-iodopyridine (1.42 g, 5.00 mmol, 1.00 eq.), sodium carbonate (2.12 g, 20.00 mmol, 4.00 eq.) and tetrakis(triphenylphosphine) palladium (0) (289 mg, 0.25 mmol, 0.05 eq.) in toluene/EtOH/water 20:4:1 (17 mL) was stirred at 100 °C for 17 hours. The mixture was allowed to cool to r.t. and partitioned between AcOEt and water. The layers were separated. The org. phase was washed with sat. aq. NaCl soln., dried over MgSO₄, and concentrated in vacuo. The residue was purified by flashmaster (column: 50 g, flow: 40 mL/min, 45 fractions of 45 mL, Hept/AcOEt 95:5 to Hept/AcOEt 8:2) to afford the title compound as a white solid.

LC-MS 4: t_R = 0.96 min; [M+H]⁺ = 302.1

Synthesis of 4-Chloro-2-(4-trifluoromethyl-phenyl)-pyridine

To a mixture of 2-bromo-4-chloro-pyridine (385 mg, 2 mmol, 1.00 eq.), 4-(trifluoromethyl)phenylboronic acid (380 mg, 2 mmol, 1.00 eq.) and sodium carbonate (848 mg, 8 mmol, 4.00 eq.) in toluene/MeOH/water 25:5:1.5 (32 mL), tetrakis(triphenylphosphine) palladium (0) (116 mg, 0.1 mmol, 0.05 eq.) was added and the mixture was stirred at 100 °C for 18 hours. The mixture was allowed to cool to r.t. and concentrated in vacuo. The residue was partitioned between DCM (50 mL) and water (50 mL). The layers were separated. The org. phase was washed with sat. aq. NaCl soln. (1 x 25 mL), dried over MgSO₄, and concentrated in vacuo. The residue was purified by flashmaster (column: 50 g, flow: 40 mL/min, 30 fractions of 45 mL, from Hept/AcOEt 9:1 to Hept/AcOEt 7:3) to yield the title compound as a viscous oil.

LC-MS 4: t_R = 0.96 min; [M+H]⁺ = 257.9

In vitro antimalarial activity: Plasmodium falciparum in vitro assay:

In vitro activity against erythrocytic stages of P. Falciparum in human red blood cells is determined using a [³H]-hypoxanthine incorporation assay. One strain sensitive to all drugs (P. Falciparum NF54) is used in this assay and all tested compounds are compared for activity with the standard drugs chloroquine (sigma C6628) and artesunate (sigma 36, 159-3). Compounds, tested in duplicates, are serially diluted with screening medium [RPMI1640 medium, supplemented with HEPES (5.94 g/L), NaHCO₃ (2.1 g/L), neomycin (100 U/mL) and human serum (50% final concentration)] in 96-well microtiter plates within an appropriate concentration range. Thereafter, the parasite cultures incubated in screening medium containing washed human red blood cells at 2.5% hematocrit (0.3% parasitemia) are added to the serially diluted compounds and incubated in a humidifying atmosphere at

37°C, 4% CO₂, 3% O₂ and 93% N₂. After 48 hours, [³H]-hypoxanthine (0.5 µCi) is added to each well of a plate. The plates are incubated for a further 24 hours under the same conditions then harvested with a Betaplate cell harvester (Wallac) and washed with distilled water. The dried filters are inserted into a plastic foil with 10 mL of scintillation fluid and counted in a Betaplate liquid scintillation counter. IC₅₀ values are calculated from sigmoidal inhibition curves using Microsoft Excel.

Table 26: IC₅₀ values (nM) for compounds of Formula I:

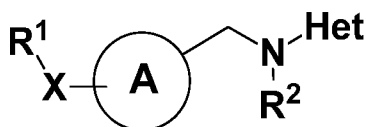
Compound of Example	IC ₅₀ [nM]	Compound of Example	IC ₅₀ [nM]	Compound of Example	IC ₅₀ [nM]
1	10	63	18	125	10
2	17	64	31	126	3.4
3	189	65	38	127	5.7
4	58	66	15	128	3.3
5	120	67	18	129	10
6	19	68	9.4	130	9.9
7	3.3	69	51	131	8.8
8	6.6	70	119	132	44
9	23	71	38	133	38
10	2.9	72	27	134	34
11	43	73	35	135	66
12	32	74	21	136	19
13	0.5	75	21	137	42
14	30	76	13	138	55
15	6.1	77	15	139	95
16	2.0	78	217	140	187
17	11	79	358	141	170
18	28	80	21	142	370
19	57	81	20	143	101
20	15	82	20	144	179
21	26	83	164	145	44
22	21	84	20	146	307
23	<7.8	85	17	147	36
24	277	86	19	148	53

25	76	87	43	149	38
26	17	88	45	150	10
27	<7.8	89	41	151	39
28	86	90	21	152	38
29	49	91	22	153	8.6
30	41	92	17	154	21
31	270	93	50	155	71
32	153	94	17	156	22
33	71	95	31	157	493
34	69	96	18	158	23
35	40	97	20	159	23
36	14	98	46	160	13
37	13	99	33	161	85
38	<7.8	100	27	162	335
39	82	101	22	163	23
40	39	102	15	164	13
41	66	103	328	165	41
42	126	104	22	166	22
43	<7.8	105	12	167	16
44	19	106	286	168	47
45	20	107	88	169	148
46	4.8	108	430	170	9.5
47	20	109	23	171	42
48	20	110	71	172	94
49	3.6	111	13	173	<7.8
50	3.7	112	30	174	<7.8
51	3.3	113	10	175	<7.8
52	13	114	3.2	176	<7.8
53	17	115	160	177	<7.8
54	20	116	4.6	178	<7.8
55	20	117	13	179	<7.8
56	6.5	118	6.3	180	76
57	6.8	119	46	181	42
58	20	120	3.6	182	<7.8
59	5.8	121	3.9	183	103

60	6.7	122	23	184	246
61	39	123	16	185	331
62	42	124	19	186	195
Chloroquine	6.8	Artesunate	0.8		

Claims:

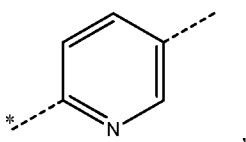
1. A compound of the Formula I:



Formula I

wherein

A represents 1,4-phenylene, 1,3-phenylene, pyridin-2,6-diyl, or the following group:



wherein the asterisk indicates the bond that is attached to the group X-R^1 ; or, in case **X** is absent, **A** may also represent piperidin-1,4-diyl, wherein R^1 is attached to the nitrogen atom of the piperidin-1,4-diyl;

- X** represents $-\text{NR}^3-$ wherein R^3 represents hydrogen or (C_{1-3}) alkyl, and R^1 represents a 6-membered heteroaryl ring, wherein said heteroaryl ring is optionally mono- or di-substituted wherein the substituents are independently selected from the group consisting of (C_{1-3}) alkyl, (C_{1-3}) alkoxy, halogen, (C_{1-3}) fluoroalkyl, (C_{1-3}) fluoroalkoxy, and pyrrolidinyl; or quinolinyl optionally mono- or di-substituted wherein the substituents are independently selected from the group consisting of (C_{1-3}) alkyl, (C_{1-3}) alkoxy, halogen, (C_{1-3}) fluoroalkyl, and (C_{1-3}) fluoroalkoxy; or

- X** is absent, and

R^1 represents pyridinyl optionally mono-substituted with (C_{1-3}) alkyl or, in case **A** is not piperidin-1,4-diyl, R^1 may also represent piperazinyl mono-substituted with (C_{1-3}) alkyl;

R^2 represents piperidinyl, pyrrolidinyl, or (3aR,6aS)-octahydrocyclopenta[c]pyrrol-5-yl, all optionally mono-substituted wherein the substituent is selected from the group consisting of (C_{1-5}) alkyl; (C_{3-6}) cycloalkyl; (C_{1-3}) fluoroalkyl; (C_{1-5}) alkyl mono-substituted with (C_{3-6}) cycloalkyl, phenyl, imidazolyl, isoxazolyl, or imidazo[1,2-a]pyridinyl, wherein the phenyl is optionally mono- or di-substituted wherein the substituents are independently selected from the group consisting of (C_{1-3}) alkyl, (C_{1-3}) alkoxy, (C_{1-3}) fluoroalkyl, (C_{1-3}) fluoroalkoxy, halogen, hydroxy and $-(\text{CH}_2)_n-\text{NR}'\text{R}''$, wherein n is 0 or 1 and R' and R'' independently represent (C_{1-3}) alkyl, and wherein imidazolyl, isoxazolyl, and imidazo[1,2-a]pyridinyl are optionally mono- or di-substituted with (C_{1-3}) alkyl; and piperidinyl or pyrrolidinyl, both optionally mono-substituted with (C_{1-3}) alkyl or (C_{1-3}) alkyl-CO-; or R^2 represents $\text{R}^4\text{R}^5\text{N}-(\text{C}_{2-4})$ alkyl, wherein R^4 and R^5 independently represent hydrogen or (C_{1-3}) alkyl, with the

exception that not both R^4 and R^5 represent hydrogen, or wherein R^4 and R^5 together with the nitrogen atom to which they are attached form a piperazine ring which is optionally mono-substituted with (C_{1-3}) alkyl; and

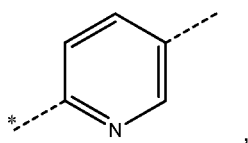
- Het** represents pyridinyl, pyrimidinyl, or pyrazinyl, all optionally mono- or di-substituted wherein the substituents are independently selected from the group consisting of (C_{1-3}) alkyl; (C_{1-3}) alkoxy optionally mono-substituted with phenyl; (C_{1-3}) fluoroalkyl; phenyl or pyridinyl, both optionally mono-substituted with (C_{1-4}) alkyl, (C_{1-3}) alkoxy, halogen, (C_{1-3}) fluoroalkyl, (C_{1-3}) fluoroalkoxy, cyano, or methylsulfonyl; and $-NR^6R^7$, wherein R^6 and R^7 independently represent (C_{1-5}) alkyl or wherein R^6 and R^7 together with the nitrogen atom to which they are attached form an azetidine, pyrrolidine or piperazine ring wherein the piperazine ring is optionally mono-substituted with (C_{1-3}) alkyl; or **Het** represents benzooxazolyl, benzothiazolyl, quinolinyl, quinoxalinyl, or quinazolinyl, all optionally mono-substituted with (C_{1-4}) alkyl, (C_{1-3}) alkoxy, halogen or (C_{1-3}) fluoroalkyl; or oxadiazolyl or thiazolyl, both optionally mono-substituted with phenyl or pyridinyl, wherein phenyl or pyridinyl is optionally mono-substituted with (C_{1-4}) alkyl, (C_{1-3}) alkoxy, halogen, (C_{1-3}) fluoroalkyl, (C_{1-3}) fluoroalkoxy, cyano, or methylsulfonyl;

with the exception of:

- N-(1-isopropylpiperidin-4-yl)-N-(3-(methyl(pyridin-2-yl)amino)benzyl)-4-(4-(trifluoromethyl)phenyl)pyrimidin-2-amine, and
 N-(1-isopropylpiperidin-4-yl)-N-((6-(methyl(pyridin-3-yl)amino)pyridin-2-yl)methyl)-4-(4-(trifluoromethyl)phenyl)pyrimidin-2-amine;
 or a salt of such compound.

2. The compound according to claim 1, wherein **A** represents 1,4-phenylene, or a salt of such compound.

3. The compound according to claim 1, wherein **A** represents the following group:



- wherein the asterisk indicates the bond that is attached to the group $X-R^1$, or a salt of such compound.

4. The compound according to any one of claims 1 to 3, wherein

- X** represents $-NR^3$ - wherein R^3 represents hydrogen or (C_{1-3}) alkyl, and

R¹ represents pyridinyl optionally mono- or di-substituted wherein the substituents are independently selected from the group consisting of (C₁₋₃)alkyl, (C₁₋₃)alkoxy, halogen, (C₁₋₃)fluoroalkyl, (C₁₋₃)fluoroalkoxy, and pyrrolidinyl; pyridimidinyl optionally mono-substituted with (C₁₋₃)alkyl; pyrazinyl; or quinolinyl optionally mono- or di-substituted wherein the substituents are independently selected from the group consisting of (C₁₋₃)alkyl, (C₁₋₃)alkoxy, halogen, (C₁₋₃)fluoroalkyl, and (C₁₋₃)fluoroalkoxy; or a salt of such compound.

5. The compound according to any one of claims 1 to 3, wherein

- **X** represents -NR³- wherein **R**³ represents hydrogen or methyl, and **R**¹ represents pyridin-4-yl or 2-methyl-pyridin-4-yl, or a salt of such compound.

6. The compound according to any one of claims 1 to 5, wherein **R**² represents piperidin-4-yl, piperidin-3-yl, or pyrrolidin-3-yl, all optionally mono-substituted wherein the substituent is selected from the group consisting of (C₁₋₅)alkyl; (C₃₋₆)cycloalkyl; (C₁₋₃)fluoroalkyl; (C₁₋₅)alkyl mono-substituted with (C₃₋₆)cycloalkyl, phenyl, imidazolyl, isoxazolyl, or imidazo[1,2-a]pyridinyl, wherein the phenyl is optionally mono- or di-substituted wherein the substituents are independently selected from the group consisting of (C₁₋₃)alkyl, (C₁₋₃)alkoxy, (C₁₋₃)fluoroalkyl, (C₁₋₃)fluoroalkoxy, halogen, hydroxy and -(CH₂)_n-NR'R'', wherein n is 0 or 1 and R' and R'' independently represent (C₁₋₃)alkyl, and wherein imidazolyl, isoxazolyl, and imidazo[1,2-a]pyridinyl are optionally mono- or di-substituted with (C₁₋₃)alkyl; and piperidinyl or pyrrolidinyl, both optionally mono-substituted with (C₁₋₃)alkyl or (C₁₋₃)alkyl-CO-; or a salt of such compound.

7. The compound according to claim 6, wherein **R**² represents piperidin-4-yl, piperidin-3-yl, or pyrrolidin-3-yl, all mono-substituted at the nitrogen atom with isopropyl, cyclopentyl, or 1-methyl-piperidin-4-yl, or a salt of such compound.

8. The compound according to any one of claims 1 to 5, wherein **R**² represents R⁴R⁵N-(C₂₋₄)alkyl, wherein R⁴ and R⁵ both represent methyl, or wherein R⁴ and R⁵ together with the nitrogen atom to which they are attached form a piperazine ring which is mono-substituted at the nitrogen atom at position 4 with methyl, or a salt of such compound.

9. The compound according to any one of claims 1 to 8, wherein **Het** represents mono-substituted pyrimidinyl wherein the substituent is selected from the group consisting of

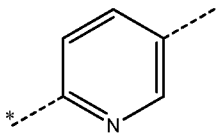
(C₁₋₃)alkyl; (C₁₋₃)alkoxy optionally mono-substituted with phenyl; (C₁₋₃)fluoroalkyl; phenyl or pyridinyl, both optionally mono-substituted with (C₁₋₄)alkyl, (C₁₋₃)alkoxy, halogen, (C₁₋₃)fluoroalkyl, (C₁₋₃)fluoroalkoxy, cyano, or methylsulfonyl; and -NR⁶R⁷, wherein R⁶ and R⁷ independently represent (C₁₋₅)alkyl or wherein R⁶ and R⁷ together with the nitrogen atom to which they are attached form an azetidine, pyrrolidine or piperazine ring wherein the piperazine ring is optionally mono-substituted with (C₁₋₃)alkyl; or a salt of such compound.

10. The compound according to claim 9, wherein **Het** represents pyrimidin-2-yl mono-substituted at position 4 with phenyl or pyridinyl, wherein phenyl or pyridinyl are optionally mono-substituted with (C₁₋₄)alkyl, (C₁₋₃)alkoxy, halogen, (C₁₋₃)fluoroalkyl, (C₁₋₃)fluoroalkoxy, cyano, or methylsulfonyl, or a salt of such compound.

11. The compound according to any one of claims 1 to 8, wherein **Het** represents quinolinyl optionally mono-substituted with (C₁₋₄)alkyl or halogen, or a salt of such compound.

12. The compound according to claim 1, wherein

A represents 1,4-phenylene, 1,3-phenylene, pyridin-2,6-diyl, or the following group:



wherein the asterisk indicates the bond that is attached to the group **X-R¹**; or, in case **X** is absent, **A** may also represent piperidin-1,4-diyl, wherein **R¹** is attached to the nitrogen atom of the piperidin-1,4-diyl;

- **X** represents -NR³- wherein **R³** represents hydrogen, methyl, or ethyl, and **R¹** represents pyridin-4-yl, 2-methyl-pyridin-4-yl, 2-methoxy-pyridin-4-yl, 2-fluoro-pyridin-4-yl, 3-methyl-pyridin-4-yl, 3-fluoro-pyridin-4-yl, 2-(pyrrolidin-1-yl)-pyridin-4-yl, 3-trifluoromethyl-pyridin-4-yl, 2,6-dimethyl-pyridin-4-yl, pyridin-3-yl, 2-fluoro-pyridin-3-yl, 5-fluoro-pyridin-3-yl, 6-methyl-pyridin-3-yl, pyridin-2-yl, pyrimidin-4-yl, 2-methyl-pyrimidin-4-yl, 6-methyl-pyrimidin-4-yl, pyrimidin-2-yl, pyrazin-2-yl, or 6-methoxy-2-methyl-quinolin-4-yl; or
- **X** is absent and **R¹** represents pyridin-4-yl, pyridin-3-yl or pyridin-2-yl, or, in case **A** is not piperidin-1,4-diyl, **R¹** may also represent 4-methyl-piperazin-1-yl; **R²** represents piperidin-4-yl, piperidin-3-yl, 1-cyclopentyl-piperidin-4-yl, 1-(1-methyl-piperidin-4-yl)-piperidin-4-yl, 1-isopropyl-piperidin-4-yl, 1-(cyclopropylmethyl)-piperidin-4-yl, 1-isopentyl-piperidin-4-yl, 1-((4-methyl-phenyl)-methyl)-piperidin-4-yl, 1-((4-dimethylamino-

phenyl)-methyl)-piperidin-4-yl, 1-((4-hydroxy-3-(dimethylaminomethyl)-phenyl)-methyl)-piperidin-4-yl, 1-(imidazo[1,2-a]pyridin-7-ylmethyl)-piperidin-4-yl, 1-(3,5-dimethyl-isoxazol-4-ylmethyl)-piperidin-4-yl, 1-(3-methyl-3H-imidazol-4-ylmethyl)-piperidin-4-yl, 1-isobutyl-piperidin-4-yl, 1-cyclopentyl-piperidin-3-yl, 1-(2-fluoro-1-(fluoromethyl)-ethyl)-piperidin-4-yl, 5 1-(3,3,3-trifluoro-propyl)-piperidin-4-yl, 1-(1-methylcarbonyl-piperidin-4-yl)-piperidin-4-yl, 1-ethyl-piperidin-4-yl, 1-(1-methyl-piperidin-4-yl)-piperidin-3-yl, 1-cyclopentyl-piperidin-3-yl, 1-isopentyl-piperidin-3-yl, 1-isopropyl-piperidin-3-yl, 1-ethyl-piperidin-3-yl, 1-(1-methyl-pyrrolidin-3-yl)-piperidin-4-yl, 1-(3-fluoro-propyl)-piperidin-4-yl, 1-methyl-piperidin-4-yl, 1-benzyl-piperidin-4-yl, 1-(1-methyl-piperidin-4-yl)-pyrrolidin-3-yl, 1-((4-hydroxy-3-10 (dimethylaminomethyl)-phenyl)-methyl)-pyrrolidin-3-yl, 1-isopropyl-pyrrolidin-3-yl, 1-isopentyl-pyrrolidin-3-yl, 1-cyclopentyl-pyrrolidin-3-yl, 2-(dimethylamino)-ethyl, 1-methyl-2-(dimethylamino)-ethyl, 3-(dimethylamino)-propyl, 2-(4-methyl-piperazin-1-yl)-ethyl, 3-(4-methyl-piperazin-1-yl)-propyl, 1-methyl-3-(dimethylamino)-propyl, (3aR,6aS)-2-(1-methyl-piperidin-4-yl)-octahydrocyclopenta[c]pyrrol-5-yl, (3aR,6aS)-2-isopentyl-15 octahydrocyclopenta[c]pyrrol-5-yl, or (3aR,6aS)-2-cyclopentyl-octahydrocyclopenta[c]pyrrol-5-yl; and

Het represents pyrimidin-2-yl optionally substituted at position 4 by a radical selected from the group consisting of isopropyl, trifluoromethyl, methoxy, pyrrolidin-1-yl, 4-methyl-piperazin-1-yl, phenyl, 2-fluoro-phenyl, 3-fluoro-phenyl, 4-fluoro-phenyl, 3-chloro-phenyl, 4-20 chloro-phenyl, 3-cyano-phenyl, 4-cyano-phenyl, 4-methoxy-phenyl, 4-methylsulfonyl-phenyl, 2-trifluoromethyl-phenyl, 3-trifluoromethyl-phenyl, 4-trifluoromethyl-phenyl, 4-methyl-phenyl, 4-tert-butyl-phenyl, 4-(trifluoro-methoxy)-phenyl, pyridin-4-yl, 6-trifluoromethyl-pyridin-3-yl, and phenylmethoxy; 5-phenyl-pyrimidin-2-yl; 5-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl; quinolin-4-yl; benzooxazol-2-yl; benzothiazol-2-yl; 25 quinoxalin-2-yl; 3-(4-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl; 5-(4-(trifluoromethyl)phenyl)-1,3,4-oxadiazol-2-yl; 7-chloro-quinazolin-4-yl; 7-isobutyl-quinazolin-4-yl; 6-fluoro-quinazolin-2-yl; 6-(4-trifluoromethyl-phenyl)-pyridin-2-yl; 4-(4-trifluoromethyl-phenyl)-thiazol-2-yl; 2-phenyl-pyrimidin-4-yl; 6-(4-trifluoromethyl-phenyl)-pyrazin-2-yl; 4-(4-trifluoromethyl-phenyl)-pyridin-2-yl; 2-(4-trifluoromethyl-phenyl)-pyridin-4-yl; 4,6-dimethyl-30 pyrimidin-2-yl; or 6-(4-trifluoromethyl-phenyl)-pyrimidin-4-yl; or a salt of such compound.

13. A compound according to claim 1 selected from the group consisting of:
[4-(Methyl-pyridin-4-yl-amino)-benzyl]-piperidin-4-yl-[4-(4-trifluoromethyl-phenyl)-pyrimidin-35 2-yl]-amine,

- [4-(Methyl-pyridin-4-yl-amino)-benzyl]-(S)-piperidin-3-yl-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
- [6-(2-Methyl-pyridin-4-yl-amino)-pyridin-3-ylmethyl]-piperidin-4-yl-quinolin-4-yl-amine,
- [4-(Methyl-pyridin-4-yl-amino)-benzyl]-piperidin-4-yl-quinolin-4-yl-amine,
- 5 [4-(2-Methyl-pyridin-4-yl-amino)-benzyl]-(S)-piperidin-3-yl-quinolin-4-yl-amine,
- (1-Cyclopentyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
- (1'-Methyl-[1,4']bipiperidinyl-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
- 10 (1-Isopropyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
- (1-Cyclopropylmethyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
- [1-(3-Methyl-butyl)-piperidin-4-yl]-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
- 15 [1-(4-Methyl-benzyl)-piperidin-4-yl]-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
- [1-(4-Dimethylamino-benzyl)-piperidin-4-yl]-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
- 20 2-Dimethylaminomethyl-4-(4-{[4-(methyl-pyridin-4-yl-amino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amino}-piperidin-1-ylmethyl)-phenol,
- (1-Imidazo[1,2-a]pyridin-7-ylmethyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
- [1-(3,5-Dimethyl-isoxazol-4-ylmethyl)-piperidin-4-yl]-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
- 25 [1-(3-Methyl-3H-imidazol-4-ylmethyl)-piperidin-4-yl]-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
- [1-(3-Methyl-butyl)-piperidin-4-yl]-[6-(methyl-pyridin-4-yl-amino)-pyridin-3-ylmethyl]-quinolin-4-yl-amine,
- 30 (1-Cyclopropylmethyl-piperidin-4-yl)-[6-(methyl-pyridin-4-yl-amino)-pyridin-3-ylmethyl]-quinolin-4-yl-amine,
- [1-(3-Methyl-3H-imidazol-4-ylmethyl)-piperidin-4-yl]-[6-(methyl-pyridin-4-yl-amino)-pyridin-3-ylmethyl]-quinolin-4-yl-amine,
- (1-Isobutyl-piperidin-4-yl)-[6-(methyl-pyridin-4-yl-amino)-pyridin-3-ylmethyl]-quinolin-4-yl-amine,
- 35 amine,

- ((S)-1-Cyclopentyl-piperidin-3-yl)-[4-(2-methyl-pyridin-4-yl-amino)-benzyl]-quinolin-4-yl-amine,
 Benzooxazol-2-yl-(1'-methyl-[1,4']bipiperidinyl-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-amine,
 5 4-(4-{Benzooxazol-2-yl-[4-(methyl-pyridin-4-yl-amino)-benzyl]-amino}-piperidin-1-ylmethyl)-2-dimethylaminomethyl-phenol,
 Benzooxazol-2-yl-(1-isopropyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-amine,
 Benzooxazol-2-yl-[1-(3-methyl-butyl)-piperidin-4-yl]-[4-(methyl-pyridin-4-yl-amino)-benzyl]-amine,
 10 (1'-Methyl-[1,4']bipiperidinyl-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-quinoxalin-2-yl-amine,
 2-Dimethylaminomethyl-4-(4-{[4-(methyl-pyridin-4-yl-amino)-benzyl]-quinoxalin-2-yl-amino}-piperidin-1-ylmethyl)-phenol,
 (1-Isopropyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-quinoxalin-2-yl-amine,
 15 [1-(3-Methyl-butyl)-piperidin-4-yl]-[4-(methyl-pyridin-4-yl-amino)-benzyl]-quinoxalin-2-yl-amine,
 (1-Cyclopentyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-quinoxalin-2-yl-amine,
 Benzooxazol-2-yl-[1-(3-methyl-3H-imidazol-4-ylmethyl)-piperidin-4-yl]-[4-(methyl-pyridin-4-yl-amino)-benzyl]-amine,
 20 [1-(3-Methyl-3H-imidazol-4-ylmethyl)-piperidin-4-yl]-[4-(methyl-pyridin-4-yl-amino)-benzyl]-quinoxalin-2-yl-amine,
 Benzooxazol-2-yl-(1-cyclopentyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-amine,
 [1-(2-Fluoro-1-fluoromethyl-ethyl)-piperidin-4-yl]-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
 25 [4-(Methyl-pyridin-4-yl-amino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-[1-(3,3,3-trifluoro-propyl)-piperidin-4-yl]-amine,
 1-(4-{[4-(Methyl-pyridin-4-yl-amino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amino}-[1,4']bipiperidinyl-1'-yl)-ethanone,
 30 (1-Ethyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
 (1'-Methyl-[1,4']bipiperidinyl-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-quinolin-4-yl-amine,
 Benzothiazol-2-yl-(1'-methyl-[1,4']bipiperidinyl-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-amine,
 35 Benzothiazol-2-yl-(1-cyclopentyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-amine,

- Benzothiazol-2-yl-[1-(3-methyl-butyl)-piperidin-4-yl]-[4-(methyl-pyridin-4-yl-amino)-benzyl]-amine,
- Benzothiazol-2-yl-[1-(3-methyl-3H-imidazol-4-ylmethyl)-piperidin-4-yl]-[4-(methyl-pyridin-4-yl-amino)-benzyl]-amine,
- 5 (S)-1'-methyl-N-(4-(methyl(pyridin-4-yl)amino)benzyl)-N-(4-(4-(trifluoromethyl)phenyl)pyrimidin-2-yl)-[1,4'-bipiperidin]-3-amine,
- (S)-N-(1-cyclopentylpiperidin-3-yl)-N-(4-(methyl(pyridin-4-yl)amino)benzyl)-4-(4-(trifluoromethyl)phenyl)pyrimidin-2-amine,
- (S)-N-(1-isopentylpiperidin-3-yl)-N-(4-(methyl(pyridin-4-yl)amino)benzyl)-4-(4-(trifluoromethyl)phenyl)pyrimidin-2-amine,
- 10 (3aR,6aS)-N-(4-(methyl(pyridin-4-yl)amino)benzyl)-2-(1-methylpiperidin-4-yl)-N-(4-(4-(trifluoromethyl)phenyl)pyrimidin-2-yl)octahydrocyclopenta[c]pyrrol-5-amine,
- (3aR,6aS)-2-isopentyl-N-(4-(methyl(pyridin-4-yl)amino)benzyl)-N-(4-(4-(trifluoromethyl)phenyl)pyrimidin-2-yl)octahydrocyclopenta[c]pyrrol-5-amine,
- 15 (3aR,6aS)-2-cyclopentyl-N-(4-(methyl(pyridin-4-yl)amino)benzyl)-N-(4-(4-(trifluoromethyl)phenyl)pyrimidin-2-yl)octahydrocyclopenta[c]pyrrol-5-amine,
- (S)-N-(4-(Ethyl(pyridin-4-yl)amino)benzyl)-1'-methyl-N-(4-(4-(trifluoromethyl)phenyl)pyrimidin-2-yl)-[1,4'-bipiperidin]-3-amine,
- ((S)-1'-Methyl-[1,4']bipiperidiny-3-yl)-[4-(methyl-pyridin-3-yl-amino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
- 20 ((S)-1'-Methyl-[1,4']bipiperidiny-3-yl)-{4-[methyl-(2-methyl-pyridin-4-yl)-amino]-benzyl}-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
- ((S)-1-Isopropyl-piperidin-3-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
- 25 ((S)-1-Ethyl-piperidin-3-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
- N-(4-(Methyl(pyridin-4-yl)amino)benzyl)-N-(1'-methyl-[1,4'-bipiperidin]-4-yl)-3-(4-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-amine,
- N-(4-(Methyl(pyridin-4-yl)amino)benzyl)-N-(1'-methyl-[1,4'-bipiperidin]-4-yl)-5-(4-(trifluoromethyl)phenyl)-1,3,4-oxadiazol-2-amine,
- 30 [(S)-1-(1-Methyl-piperidin-4-yl)-pyrrolidin-3-yl]-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
- 2-Dimethylaminomethyl-4-((S)-3-{[4-(methyl-pyridin-4-yl-amino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amino}-pyrrolidin-1-ylmethyl)-phenol,
- 35 ((S)-1-Isopropyl-pyrrolidin-3-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,

- [(R)-1-(1-Methyl-piperidin-4-yl)-pyrrolidin-3-yl]-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
2-Dimethylaminomethyl-4-((R)-3-{[4-(methyl-pyridin-4-yl-amino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amino}-pyrrolidin-1-ylmethyl)-phenol,
- 5 [(S)-1-(3-Methyl-butyl)-pyrrolidin-3-yl]-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
((S)-1-Cyclopentyl-pyrrolidin-3-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
((R)-1-Isopropyl-pyrrolidin-3-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
- 10 [(R)-1-(3-Methyl-butyl)-pyrrolidin-3-yl]-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
((R)-1-Cyclopentyl-pyrrolidin-3-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
- 15 [4-(Methyl-pyridin-4-yl-amino)-benzyl]-[1-(1-methyl-pyrrolidin-3-yl)-piperidin-4-yl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
[1-(3-Fluoro-propyl)-piperidin-4-yl]-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
(1-Methyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
- 20 (1-Benzyl-piperidin-4-yl)-[4-(2-methyl-pyridin-4-yl-amino)-benzyl]-[5-phenyl-pyrimidin-2-yl]-amine,
(1-Benzyl-piperidin-4-yl)-[4-(3-fluoro-phenyl)-pyrimidin-2-yl]-[4-(2-methyl-pyridin-4-yl-amino)-benzyl]-amine,
- 25 (1-Benzyl-piperidin-4-yl)-[4-(2-methyl-pyridin-4-yl-amino)-benzyl]-[5-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
(1-Benzyl-piperidin-4-yl)-(7-chloro-quinazolin-4-yl)-[4-(2-methyl-pyridin-4-yl-amino)-benzyl]-amine,
(1-Benzyl-piperidin-4-yl)-(6-fluoro-quinazolin-2-yl)-[4-(2-methyl-pyridin-4-yl-amino)-benzyl]-amine,
- 30 (1-Benzyl-piperidin-4-yl)-[4-(2-methyl-pyridin-4-yl-amino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
(1-Isopropyl-piperidin-4-yl)-[6-[methyl-(2-methyl-pyridin-4-yl)-amino]-pyridin-3-ylmethyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
- 35 (1-Isopropyl-piperidin-4-yl)-[6-(2-methyl-pyridin-4-yl-amino)-pyridin-3-ylmethyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,

- (1-Isopropyl-piperidin-4-yl)-[6-(3-methyl-pyridin-4-ylamino)-pyridin-3-ylmethyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
[6-(3-Fluoro-pyridin-4-ylamino)-pyridin-3-ylmethyl]-(1-isopropyl-piperidin-4-yl)-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
- 5 (1-Isopropyl-piperidin-4-yl)-[6-(pyrimidin-4-ylamino)-pyridin-3-ylmethyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
(1-Isopropyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[6-(4-trifluoromethyl-phenyl)-pyridin-2-yl]-amine,
(1-Isopropyl-piperidin-4-yl)-[6-(methyl-pyridin-3-yl-amino)-pyridin-3-ylmethyl]-[4-(4-
- 10 trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
(1-Isopropyl-piperidin-4-yl)-[3-(methyl-pyridin-4-yl-amino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
(1-Isopropyl-piperidin-4-yl)-[3-(methyl-pyridin-3-yl-amino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
- 15 (1-Isopropyl-piperidin-4-yl)-[3-[methyl-(2-methyl-pyridin-4-yl)-amino]-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
(1-Isopropyl-piperidin-4-yl)-[3-(2-methyl-pyridin-4-ylamino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
(1-Isopropyl-piperidin-4-yl)-[3-(3-methyl-pyridin-4-ylamino)-benzyl]-[4-(4-trifluoromethyl-
- 20 phenyl)-pyrimidin-2-yl]-amine,
[3-(3-Fluoro-pyridin-4-ylamino)-benzyl]-(1-isopropyl-piperidin-4-yl)-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
(1-Isopropyl-piperidin-4-yl)-[3-(pyrimidin-4-ylamino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
- 25 [4-(4-Fluoro-phenyl)-pyrimidin-2-yl]-(1-isopropyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-amine,
N,N-Dimethyl-N'-[4-(methyl-pyridin-4-yl-amino)-benzyl]-N'-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-ethane-1,2-diamine,
N1,N1-Dimethyl-N2-[4-(methyl-pyridin-4-yl-amino)-benzyl]-N2-[4-(4-trifluoromethyl-phenyl)-
- 30 pyrimidin-2-yl]-propane-1,2-diamine,
N,N-Dimethyl-N'-[4-(methyl-pyridin-4-yl-amino)-benzyl]-N'-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-propane-1,3-diamine,
[2-(4-Methyl-piperazin-1-yl)-ethyl]-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[4-(4-
- 35 trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
[2-(4-Methyl-piperazin-1-yl)-ethyl]-[4-(2-methyl-pyridin-4-ylamino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,

- [3-(4-Methyl-piperazin-1-yl)-propyl]-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
- [3-(4-Methyl-piperazin-1-yl)-propyl]-[4-(2-methyl-pyridin-4-yl-amino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
- 5 [3-(4-Methyl-piperazin-1-yl)-propyl]-[4-(3-methyl-pyridin-4-yl-amino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
- [4-((1-Benzyl-piperidin-4-yl)-[4-(4-trifluoromethyl-phenyl)-thiazol-2-yl]-amino)-methyl-phenyl]-[2-methyl-pyridin-4-yl]-amine,
- (1-Isopropyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[2-phenyl-pyrimidin-4-yl]-
- 10 amine,
- (1-Isopropyl-piperidin-4-yl)-[4-(2-methyl-pyridin-4-yl-amino)-benzyl]-[2-phenyl-pyrimidin-4-yl]-amine,
- (1-Isopropyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[6-(4-trifluoromethyl-phenyl)-pyrazin-2-yl]-amine,
- 15 (1-Isopropyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-quinolin-4-yl-amine,
- (4-Benzoyloxy-pyrimidin-2-yl)-(1-isopropyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-amine,
- (1-Isopropyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyridin-2-yl]-amine,
- 20 (1-Isopropyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[2-(4-trifluoromethyl-phenyl)-pyridin-4-yl]-amine,
- (4,6-Dimethyl-pyrimidin-2-yl)-(1-isopropyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-amine,
- (1-Isopropyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[6-(4-trifluoromethyl-phenyl)-pyrimidin-4-yl]-amine,
- 25 (1-Isopropyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-pyrimidin-2-yl-amine,
- (1-Isopropyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[5-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
- (1-Isopropyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[4-trifluoromethyl-pyrimidin-2-yl]-amine,
- 30 N1,N1-Dimethyl-N3-[4-(methyl-pyridin-4-yl-amino)-benzyl]-N3-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-butane-1,3-diamine,
- ((S)-1-Isopropyl-piperidin-3-yl)-[6-(2-methyl-pyridin-4-yl-amino)-pyridin-3-ylmethyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
- 35 (1'-Methyl-[1,4']bipiperidinyl-4-yl)-[6-(2-methyl-pyridin-4-yl-amino)-pyridin-3-ylmethyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,

- (1'-Methyl-[1,4']bipiperidinyl-4-yl)-[6-(methyl-pyridin-4-yl-amino)-pyridin-3-ylmethyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
 (1-Isopropyl-piperidin-4-yl)-(4-methoxy-pyrimidin-2-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-amine,
- 5 1'-Methyl-N-(4-((2-methylpyridin-4-yl)amino)benzyl)-N-(4-(4-(trifluoromethyl)phenyl)pyrimidin-2-yl)-[1,4'-bipiperidin]-4-amine,
 N-(4-((2,6-Dimethylpyridin-4-yl)amino)benzyl)-1'-methyl-N-(4-(4-(trifluoromethyl)phenyl)pyrimidin-2-yl)-[1,4'-bipiperidin]-4-amine,
 1'-Methyl-N-(4-(methyl(pyridin-3-yl)amino)benzyl)-N-(4-(4-(trifluoromethyl)phenyl)pyrimidin-2-yl)-[1,4'-bipiperidin]-4-amine,
- 10 1'-Methyl-N-(4-(methyl(pyridin-2-yl)amino)benzyl)-N-(4-(4-(trifluoromethyl)phenyl)pyrimidin-2-yl)-[1,4'-bipiperidin]-4-amine,
 1'-Methyl-N-(4-(methyl(2-methylpyridin-4-yl)amino)benzyl)-N-(4-(4-(trifluoromethyl)phenyl)pyrimidin-2-yl)-[1,4'-bipiperidin]-4-amine,
- 15 1'-Methyl-N-(4-(pyridin-4-ylamino)benzyl)-N-(4-(4-(trifluoromethyl)phenyl)pyrimidin-2-yl)-[1,4'-bipiperidin]-4-amine,
 1'-Methyl-N-(4-(pyrimidin-4-ylamino)benzyl)-N-(4-(4-(trifluoromethyl)phenyl)pyrimidin-2-yl)-[1,4'-bipiperidin]-4-amine,
 N-(4-((2-Methoxypyridin-4-yl)amino)benzyl)-1'-methyl-N-(4-(4-(trifluoromethyl)phenyl)pyrimidin-2-yl)-[1,4'-bipiperidin]-4-amine,
- 20 N-(4-((2-Fluoropyridin-4-yl)amino)benzyl)-1'-methyl-N-(4-(4-(trifluoromethyl)phenyl)pyrimidin-2-yl)-[1,4'-bipiperidin]-4-amine,
 6-Methoxy-2-methyl-N-(4-(((1'-methyl-[1,4'-bipiperidin]-4-yl)(4-(4-(trifluoromethyl)phenyl)pyrimidin-2-yl)amino)methyl)phenyl)quinolin-4-amine,
- 25 N-(4-(Ethyl(pyridin-4-yl)amino)benzyl)-1'-methyl-N-(4-(4-(trifluoromethyl)phenyl)pyrimidin-2-yl)-[1,4'-bipiperidin]-4-amine,
 N-(4-((3-Fluoropyridin-4-yl)amino)benzyl)-1'-methyl-N-(4-(4-(trifluoromethyl)phenyl)pyrimidin-2-yl)-[1,4'-bipiperidin]-4-amine,
 1'-Methyl-N-(4-((3-methylpyridin-4-yl)amino)benzyl)-N-(4-(4-(trifluoromethyl)phenyl)pyrimidin-2-yl)-[1,4'-bipiperidin]-4-amine,
- 30 1'-Methyl-N-(4-(4-methylpiperazin-1-yl)benzyl)-N-(4-(4-(trifluoromethyl)phenyl)pyrimidin-2-yl)-[1,4'-bipiperidin]-4-amine,
 N-(1-Isopropylpiperidin-4-yl)-N-(4-((2-methylpyridin-4-yl)amino)benzyl)-4-(4-(trifluoromethyl)phenyl)pyrimidin-2-amine,
- 35 N-(1-Isopropylpiperidin-4-yl)-N-(4-((3-methylpyridin-4-yl)amino)benzyl)-4-(4-(trifluoromethyl)phenyl)pyrimidin-2-amine,

- N-(4-((3-Fluoropyridin-4-yl)amino)benzyl)-N-(1-isopropylpiperidin-4-yl)-4-(4-(trifluoromethyl)phenyl)pyrimidin-2-amine,
N-(1-Isopropylpiperidin-4-yl)-4-(4-(trifluoromethyl)phenyl)-N-(4-((3-(trifluoromethyl)pyridin-4-yl)amino)benzyl)pyrimidin-2-amine,
- 5 N-(4-((5-Fluoropyridin-3-yl)amino)benzyl)-N-(1-isopropylpiperidin-4-yl)-4-(4-(trifluoromethyl)phenyl)pyrimidin-2-amine,
N-(1-Isopropylpiperidin-4-yl)-N-(4-(pyridin-3-ylamino)benzyl)-4-(4-(trifluoromethyl)phenyl)pyrimidin-2-amine,
N-(1-Isopropylpiperidin-4-yl)-N-(4-((2-(pyrrolidin-1-yl)pyridin-4-yl)amino)benzyl)-4-(4-(trifluoromethyl)phenyl)pyrimidin-2-amine,
- 10 N-(1-Isopropylpiperidin-4-yl)-N-(4-((2-methylpyrimidin-4-yl)amino)benzyl)-4-(4-(trifluoromethyl)phenyl)pyrimidin-2-amine,
N-(1-Isopropylpiperidin-4-yl)-N-(4-(methyl(2-methylpyrimidin-4-yl)amino)benzyl)-4-(4-(trifluoromethyl)phenyl)pyrimidin-2-amine,
- 15 (1-Isopropyl-piperidin-4-yl)-[4-(pyrimidin-4-ylamino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
N-(1-Isopropylpiperidin-4-yl)-N-(4-((6-methylpyrimidin-4-yl)amino)benzyl)-4-(4-(trifluoromethyl)phenyl)pyrimidin-2-amine,
N-(1-Isopropylpiperidin-4-yl)-N-(4-(methyl(6-methylpyrimidin-4-yl)amino)benzyl)-4-(4-(trifluoromethyl)phenyl)pyrimidin-2-amine,
- 20 (1-Isopropyl-piperidin-4-yl)-[4-(pyrimidin-2-ylamino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
(1-Isopropyl-piperidin-4-yl)-[4-(6-methyl-pyridin-3-ylamino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
- 25 (1-Isopropyl-piperidin-4-yl)-[4-(pyrazin-2-ylamino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
(1-Isopropyl-piperidin-4-yl)-[4-(methyl-pyridin-3-yl-amino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
[4-(2-Fluoro-pyridin-3-ylamino)-benzyl]-(1-isopropyl-piperidin-4-yl)-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
- 30 [2-(4-Methyl-piperazin-1-yl)-ethyl]-[4-(3-methyl-pyridin-4-ylamino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
{4-[Methyl-(2-methyl-pyridin-4-yl)-amino]-benzyl}-[2-(4-methyl-piperazin-1-yl)-ethyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
- 35 {4-[Methyl-(2-methyl-pyridin-4-yl)-amino]-benzyl}-[3-(4-methyl-piperazin-1-yl)-propyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,

- (1-Isopropyl-piperidin-4-yl)-{4-[methyl-(3-methyl-pyridin-4-yl)-amino]-benzyl}-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
(1-Isopropyl-piperidin-4-yl)-[6-(methyl-pyridin-4-yl-amino)-pyridin-2-ylmethyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
5 (1-Isopropyl-piperidin-4-yl)-{6-[methyl-(2-methyl-pyridin-4-yl)-amino]-pyridin-2-ylmethyl}-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
(1-Isopropyl-piperidin-4-yl)-[6-(2-methyl-pyridin-4-yl-amino)-pyridin-2-ylmethyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
(1-Isopropyl-piperidin-4-yl)-[6-(3-methyl-pyridin-4-yl-amino)-pyridin-2-ylmethyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
10 [6-(3-Fluoro-pyridin-4-yl-amino)-pyridin-2-ylmethyl]-(1-isopropyl-piperidin-4-yl)-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
(1-Isopropyl-piperidin-4-yl)-[6-(pyrimidin-4-yl-amino)-pyridin-2-ylmethyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
15 (1-Isopropyl-piperidin-4-yl)-[6-(methyl-pyridin-2-yl-amino)-pyridin-2-ylmethyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
(1-Isopropyl-piperidin-4-yl)-[4-(4-methyl-piperazin-1-yl)-pyrimidin-2-yl]-[4-(methyl-pyridin-4-yl-amino)-benzyl]-amine,
(1-Isopropyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-(4-pyrrolidin-1-yl-pyrimidin-2-yl)-amine,
20 (1-Isopropyl-piperidin-4-yl)-(3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-ylmethyl)-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
(1-Isopropyl-piperidin-4-yl)-(3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-ylmethyl)-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
25 (1-Isopropyl-piperidin-4-yl)-(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-ylmethyl)-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
(7-Isobutyl-quinazolin-4-yl)-(1-isopropyl-piperidin-4-yl)-[4-(2-methyl-pyridin-4-yl-amino)-benzyl]-amine,
[4-(4-Chloro-phenyl)-pyrimidin-2-yl]-(1-isopropyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-amine,
30 [4-(4-tert-Butyl-phenyl)-pyrimidin-2-yl]-(1-isopropyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-amine,
(1-Isopropyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-(4-pyridin-4-yl-pyrimidin-2-yl)-amine,
35 (1-Isopropyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[4-(4-trifluoromethoxy-phenyl)-pyrimidin-2-yl]-amine,

- (1-Isopropyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-(4-p-tolyl-pyrimidin-2-yl)-amine,
[4-(2-Fluoro-phenyl)-pyrimidin-2-yl]-(1-isopropyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-amine,
5 4-(2-{{(1-Isopropyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-amino}-pyrimidin-4-yl)-benzonitrile,
(1-Isopropyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[4-(3-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
(1-Isopropyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[4-(2-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
10 4-(2-{{(S)-1'-Methyl-[1,4']bipiperidinyl-3-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-amino}-pyrimidin-4-yl)-benzonitrile,
{{(S)-1'-Methyl-[1,4']bipiperidinyl-3-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[4-(6-trifluoromethyl-pyridin-3-yl)-pyrimidin-2-yl]-amine,
15 [4-(4-Fluoro-phenyl)-pyrimidin-2-yl]-{{(S)-1'-methyl-[1,4']bipiperidinyl-3-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-amine,
[4-(4-Methanesulfonyl-phenyl)-pyrimidin-2-yl]-{{(S)-1'-methyl-[1,4']bipiperidinyl-3-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-amine,
[4-(4-Chloro-phenyl)-pyrimidin-2-yl]-{{(S)-1'-methyl-[1,4']bipiperidinyl-3-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-amine,
20 4-yl-amino)-benzyl]-amine,
[4-(3-Chloro-phenyl)-pyrimidin-2-yl]-{{(S)-1'-methyl-[1,4']bipiperidinyl-3-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-amine,
3-(2-{{(S)-1'-Methyl-[1,4']bipiperidinyl-3-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-amino}-pyrimidin-4-yl)-benzonitrile,
25 (1-Isopropyl-piperidin-4-yl)-[4-(4-methoxy-phenyl)-pyrimidin-2-yl]-[4-(methyl-pyridin-4-yl-amino)-benzyl]-amine,
(1-Isopropyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-(4-phenyl-pyrimidin-2-yl)-amine,
(1-Isopropyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[4-(6-trifluoromethyl-pyridin-3-yl)-pyrimidin-2-yl]-amine,
30 (1-Isopropyl-piperidin-4-yl)-(4-pyridin-3-yl-benzyl)-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
(1-Isopropyl-piperidin-4-yl)-(4-pyridin-4-yl-benzyl)-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
35 (1-Isopropyl-piperidin-4-yl)-(4-pyridin-2-yl-benzyl)-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine, and

(1-Isopropyl-piperidin-4-yl)-(4-isopropyl-pyrimidin-2-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-amine,
or a salt of such compound.

- 5 14. A compound according to claim 1 selected from the group consisting of:
(1'-Methyl-[1,4']bipiperidinyl-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
(1-Isopropyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
10 (1'-Methyl-[1,4']bipiperidinyl-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-quinolin-4-yl-amine,
(S)-1'-methyl-N-(4-(methyl(pyridin-4-yl)amino)benzyl)-N-(4-(4-(trifluoromethyl)phenyl)pyrimidin-2-yl)-[1,4'-bipiperidin]-3-amine,
(3aR,6aS)-N-(4-(methyl(pyridin-4-yl)amino)benzyl)-2-(1-methylpiperidin-4-yl)-N-(4-(4-(trifluoromethyl)phenyl)pyrimidin-2-yl)octahydrocyclopenta[c]pyrrol-5-amine,
15 ((S)-1'-Methyl-[1,4']bipiperidinyl-3-yl)-{4-[methyl-(2-methyl-pyridin-4-yl)-amino]-benzyl}-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
(1-Isopropyl-piperidin-4-yl)-[6-(2-methyl-pyridin-4-ylamino)-pyridin-3-ylmethyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
(1-Isopropyl-piperidin-4-yl)-[3-(2-methyl-pyridin-4-ylamino)-benzyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
20 (1-Isopropyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-quinolin-4-yl-amine,
(1'-Methyl-[1,4']bipiperidinyl-4-yl)-[6-(methyl-pyridin-4-yl-amino)-pyridin-3-ylmethyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
((S)-1'-Methyl-[1,4']bipiperidinyl-3-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[4-(6-trifluoromethyl-pyridin-3-yl)-pyrimidin-2-yl]-amine, and
25 (1-Isopropyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[4-(6-trifluoromethyl-pyridin-3-yl)-pyrimidin-2-yl]-amine,
or a salt of such compound.
- 30 15. A compound according to claim 1 selected from the group consisting of:
(1'-Methyl-[1,4']bipiperidinyl-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-quinolin-4-yl-amine,
(1-Isopropyl-piperidin-4-yl)-[6-(2-methyl-pyridin-4-ylamino)-pyridin-3-ylmethyl]-[4-(4-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine,
(1-Isopropyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-quinolin-4-yl-amine, and
35 (1-Isopropyl-piperidin-4-yl)-[4-(methyl-pyridin-4-yl-amino)-benzyl]-[4-(6-trifluoromethyl-pyridin-3-yl)-pyrimidin-2-yl]-amine,

or a salt of such compound.

16. A pharmaceutical composition comprising a compound according to any one of claims
1 to 15, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable
5 carrier material.

17. A compound according to any one of claims 1 to 15, or a pharmaceutically acceptable
salt thereof, for use as a medicament.

10 18. A compound according to any one of claims 1 to 15, or a pharmaceutically acceptable
salt thereof, for use in the treatment and/or prevention of protozoal infections.

19. A compound according to any one of claims 1 to 15, or a pharmaceutically acceptable
salt thereof, for use in the treatment and/or prevention of malaria.

15

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2014/064166

A. CLASSIFICATION OF SUBJECT MATTER INV. C07D401/12 C07D411/12 C07D413/12 A01N43/56 ADD.		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) C07D A01N		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) EPO-Internal, CHEM ABS Data, WPI Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2010/065932 A1 (DESIGNMEDIX INC [US]; PEYTON DAVID H [US]; BURGESS STEVEN J [US]; LIEB) 10 June 2010 (2010-06-10) paragraph [0002] - paragraph [0010]; claims; examples -----	1-19
☐ 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) or 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 "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family		
Date of the actual completion of the international search 20 October 2014		Date of mailing of the international search report 31/10/2014
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 Schmid, Arnold

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IB2014/064166

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2010065932 A1	10-06-2010	EP 2379505 A1	26-10-2011
		US 2011251210 A1	13-10-2011
		WO 2010065932 A1	10-06-2010
