

WNK1 inhibitors**Technical field**

The present invention relates to novel compounds, pharmaceutical compositions comprising such compounds and their use for treating, alleviating or preventing diseases and disorders related to the activity of WNK1. The invention further relates to methods of treating, alleviating and/or preventing diseases and disorders related to the activity of WNK1.

Background

WNK1 (WNK lysine deficient protein kinase 1) belongs to a subfamily of atypical serine-threonine kinases, characterised by the lack of a conserved catalytic lysine in the kinase subdomain II (WNK1-4).

WNK1 is known to play an important role in ion transport through WNK1-mediated phosphorylation and activation of OSR1 (oxidative-stress response kinase 1) and STK39/SPAK (STE20/SPS1-related proline-alanine-rich protein kinase) kinases. Following activation by WNK1, OSR1 and STK39/SPAK catalyze the phosphorylation of ion cotransporters of the SLC12 family of cation-coupled chloride co-transporters, thereby activating the Na⁺ /K⁺-coupled Cl⁻ importers SLC12A1(NKCC1), SLC12A2 (NKCC2) and SLC12A3 (NCC)11-17, whilst inhibiting the K⁺-coupled Cl⁻ exporters SLC12A4-SLC12A7 (KCC1-KCC4).

WNK1 is known to be involved in various processes, both as ion transport as stated above, but also cell volume regulation, sodium reabsorption, potassium secretion, response to hypertonic stress, autophagy and regulation of blood pressure. Moreover increased WNK1 activity has been associated with different diseases and disorders, including hypertension and cancers such as breast cancer, colon cancer, pancreatic ductal adenocarcinoma and blood cancers, including leukemia and multiple myeloma.

WNK1 and hypertension

Hypertension is a long-term medical condition in which the blood pressure in the arteries is persistently elevated. Hypertension is a risk factor for many disabling and often fatal diseases, including stroke, myocardial infarction, arrhythmia, congestive heart failure, renal failure and retinopathy.

WNK1 has a well-described role in inherited hypertension. Mutations which result in the overexpression of WNK1 have been associated with different types of hypertension, including familial hyperkalemic hypertension (FHHT), an inherited form of hypertension characterized by increased salt reabsorption and impaired K⁺ and H⁺ excretion in the kidney, and pseudohypoaldosteronism type II (PHAII), which is an autosomal dominant disorder featuring hypertension, hyperkalemia and renal tubular acidosis.

WNK1 and cancer

It is known that the WNK1-4 kinases are dysregulated in various types of cancer, and moreover it is has been established that the dysregulation contributes to tumor growth, metastasis, and angiogenesis through complex mechanisms, including phosphorylation of kinase substrates SPS1-related proline/alanine-rich kinase (STK39/SPAK) and oxidative stress-responsive kinase 1 (OSR1).

WNK1 specifically has been associated with different types of cancer, including breast cancer, colon cancer and blood cancers such as leukaemia and multiple myeloma.

US 2008/0286809 A1 discloses that the rate of autophosphorylation of endogenously expressed WNK1 is increased ~ 5-fold by hypertonic stress in kidney epithelial cells and in breast and colon cancer cell lines.

WO 2021/028438 A1 discloses that inhibition of WNK1 is toxic to cells of leukemic and myeloma origin, and moreover it is disclosed that conditional knockdown of WNK1 results in increased lifespan of acute myeloid leukemia (AML) mice.

WNK1 inhibition

Inhibition of WNK1 presents a promising target for treatment of such diseases and disorders, due to the role of WNK1 in various diseases as described above.

An ongoing interest in developing inhibitors to the WNK1-4 kinases, has resulted in a variety of WNK1 inhibitors (Ishigami-Yuasa et al., 2017; Yamada et al., 2017; Yamada et al., 2016a; Yamada et al., 2016b). Nonetheless, there is a need for novel, effective WNK1inhibitors, allowing for effective modulation of WNK1.

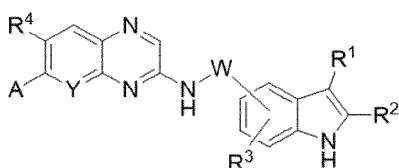
Summary

This invention concerns a series of compounds which are inhibitors of WNK1.

The compounds constitute a new group of potential drugs that can be used to treat or ameliorate diseases and disorder related to dysregulation of WNK1, including hypertension and cancers, such as breast cancer, pancreatic cancer, colon cancer and blood cancers such as leukemia and multiple myeloma.

5

In one major aspect, the present invention concerns a compound of Formula (I):



Formula (I)

10

wherein

Y is C(H) or N;

W is C(H)₂ or C(D)₂;

R¹ is H, C₁₋₃ alkyl or cyclopropyl

R² is H; C₁₋₃ alkyl optionally substituted with OH; or C₃₋₅ cycloalkyl;

15

R³ is H; C₁₋₃ alkyl optionally substituted with OH; -OC₁₋₃ alkyl optionally substituted with one or more F; -C(O)NHCH₃; -NH₂; -N(H)(CH₃); -N(CH₃)₂; or halogen;

R⁴ is H, C₁₋₄ alkyl, or C₃₋₅ cycloalkyl;

A is selected from the group consisting of H, C₁₋₃ alkoxy, CF₃, and a group of

20

formula (II):



Formula (II)

wherein

X is C(H) or N;

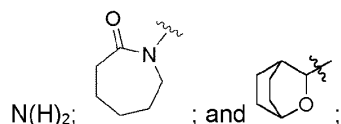
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R⁶ is H or C₁₋₄ alkyl; and

R⁵ is selected from the group consisting of C₁₋₆ alkyl optionally substituted with one or more, identical or different, substituents R⁷, wherein one or more methylene(s) of said C₁₋₆ alkyl is optionally and individually replaced with -O- or

C=O; C₃₋₆ cycloalkyl optionally substituted with one or more, identical or different, substituents R⁷; and tetrahydropyranyl;
wherein two R⁷ are optionally linked together to form a ring together with the intervening atom(s);

5 **R⁷** is individually selected from C₁₋₃ alkoxy optionally substituted with one or more F; -OH; -O-benzyl; C₁₋₃ alkyl optionally substituted with OH; N(CH₃)₂;



or when two R⁷ are linked together to form a ring, then said two R⁷ are individually selected from C₁₋₂ alkanediyl optionally substituted with one or two substituents selected from F and OH, and one of the methylene of said C₁₋₂ alkanediyl is optionally replaced with -O-;

or

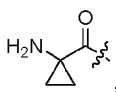
R⁵ and R⁶ are linked together to form a ring and
R⁵ is a bond or C₁₋₅ alkanediyl optionally substituted with one or more, identical or different, substituents R⁸, and one methylene of the C₁₋₅ alkanediyl is optionally replaced with -O- or N(R⁹); and

R⁶ is a bond or C₁₋₅ alkanediyl optionally substituted with one or more, identical or different, substituents R⁸, and one methylene of the C₁₋₅ alkanediyl is optionally replaced with -O- or N(R⁹);

20 wherein two R⁸ are optionally linked together to form a ring together with the intervening atom(s);

R⁸ is individually selected from C₁₋₃ alkyl optionally substituted with OH; -OH; F; N(H)₂; and -OC₁₋₃ alkyl optionally substituted with one or more F;

25 or when two R⁸ are linked together to form a ring, then said two R⁸ are individually selected from C₁₋₃ alkanediyl optionally substituted with one or two substituents selected from F, OH, and NH₂, and one or two methylene(s) of said C₁₋₃ alkanediyl is optionally and individually replaced with -O-, -N(H)- or -N(CH₃)-; and

R⁹ is H, C₁₋₃ alkyl, oxetanyl, or ,

30 or a pharmaceutically acceptable salt thereof,

with the proviso that the compound is not N-[(2,3,5-Trimethyl-1H-indol-7-yl)methyl]-2-quinoxalinamine.

In a second aspect, the invention concerns a composition comprising a compound as defined herein.

5 In a third aspect, the invention concerns a method for treating, alleviating or preventing diseases and disorders related to the activity of WNK1 comprising administration of a compound as herein described to a subject in need thereof.

Detailed description

10 **Definitions**

The term 'WNK1' as used herein refers to 'WNK lysine deficient protein kinase 1'. Other names for WNK1 includes 'With-No-lysine(K) kinase 1',

15 The term 'WNK1 inhibitor' as used herein refers to a chemical compound, which binds to the WNK1 kinase, and which moreover has the ability to reduce, slow, halt or prevent activity the WNK1 kinase. The binding interaction itself, as well as the binding activity can be confirmed by any conventional method for testing binding affinity, known by the skilled person, e.g. those described in the working examples.

20 The terms 'C₁₋₆ alkyl', 'C₁₋₄ alkyl', and 'C₁₋₃ alkyl' refers to a branched or unbranched alkyl group having from one to three, one to four or one to five carbon atoms respectively, including but not limited to methyl, ethyl, prop-1-yl, prop-2-yl, *iso*-propyl, *tert*-butyl, but-1-yl, but-2-yl, pent-1-yl, pent-2-yl, pent-3-yl, 2-methylbut-1-yl, 3-methylbut-1-yl), hex-1-yl or 2,3-dimethylbut-1-yl.

25 The term 'C₃₋₆ cycloalkyl' refers to a group having three to six carbon atoms including a monocyclic or bicyclic carbocycle, including but not limited to cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl.

30 The term 'C₁₋₃ alkoxy' refers to an C₁₋₃ alkyl group, linear or branched, bonded to an oxygen atom. Examples of C₁₋₃ alkoxy groups includes methoxy, ethoxy, n-propoxy, and isopropoxy.

The term 'wherein two R^x are optionally linked together to form a ring together with the intervening atom(s)' refers to an optionally substituted 3-6-membered (hetero)cyclic ring formed by two R^x substituents, together with their intervening atom(s).

The term 'intervening atom(s)' refers to the atom(s) between the two R^x substituents.

5 The intervening atom(s) may for example be carbon, nitrogen, or oxygen.

The terms 'C₁₋₅ alkanediyl', 'C₁₋₃ alkanediyl', and 'C₁₋₂ alkanediyl' refers to branched or unbranched alkanediyl group having from one to two, one to three or one to five carbon atoms. The alkanediyl groups are derived by the removal of two hydrogen atoms from
10 a single carbon atom of a parent alkane. Typical alkanediyl groups include, but are not limited to, methanediyl; ethanediyl; propanediyl, butanediyl, or pentanediyl.

The term "C=O" as well as the term 'C(O)' refers to a carbonyl group.

15 The term "treatment" refers to the combating of a disease or disorder. "Treatment" or "treating," as used herein, includes any desirable effect on the symptoms or pathology of a disease or condition as described herein, and may include even minimal changes or improvements in one or more measurable markers of the disease or condition being treated. "Treatment" or "treating" does not necessarily indicate complete eradication or
20 cure of the disease or condition, or associated symptoms thereof. In some embodiments, the term "treatment" encompasses amelioration and prevention.

The term "alleviating" refers to moderation in the severity of the symptoms of a disease or condition. Improvement in a patient's condition, or the activity of making an effort to
25 correct, or at least make more acceptable, conditions that are difficult to endure related to patient's conditions is considered "ameliorative" treatment.

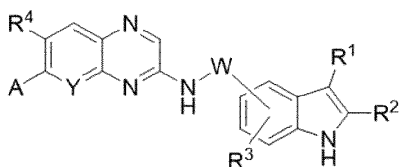
The term "prevent" or "preventing" refers to precluding, alleviating, obviating, forestalling, stopping, or hindering something from happening, especially by advance
30 action.

Compounds

It is within the scope of the present invention to provide a compound for use in treating, alleviating and/or preventing diseases and disorders characterized in that the WNK1

activity is dysregulated. The compounds of the present invention comprise compounds capable of inhibiting WNK1, thereby reducing or normalising the activity of WNK1.

In one aspect, the present invention is a compound of Formula (I):



Formula (I)

wherein

Y is C(H) or N;

W is C(H)₂ or C(D)₂;

R¹ is H, C₁₋₃ alkyl or cyclopropyl

R² is H; C₁₋₃ alkyl optionally substituted with OH; or C₃₋₅ cycloalkyl;

R³ is H; C₁₋₃ alkyl optionally substituted with OH; -OC₁₋₃ alkyl optionally substituted with one or more F; -C(O)NHCH₃; -NH₂; -N(H)(CH₃); -N(CH₃)₂; or halogen;

R⁴ is H, C₁₋₄ alkyl, or C₃₋₅ cycloalkyl;

A is selected from the group consisting of H, C₁₋₃ alkoxy, CF₃, and a group of formula (II):



Formula (II)

wherein

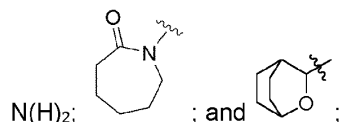
X is C(H) or N;

R⁶ is H or C₁₋₄ alkyl; and

R⁵ is selected from the group consisting of C₁₋₆ alkyl optionally substituted with one or more, identical or different, substituents R⁷, wherein one or more methylene(s) of said C₁₋₆ alkyl is optionally and individually replaced with -O- or C=O; C₃₋₆ cycloalkyl optionally substituted with one or more, identical or different, substituents R⁷; and tetrahydropyranyl;

wherein two R⁷ are optionally linked together to form a ring together with the intervening atom(s);

R^7 is individually selected from C_{1-3} alkoxy optionally substituted with one or more F; -OH; -O-benzyl; C_{1-3} alkyl optionally substituted with OH; $N(CH_3)_2$;



or when two R^7 are linked together to form a ring, then said two R^7 are individually selected from C_{1-2} alkanediyl optionally substituted with one or two substituents selected from F and OH, and one of the methylene of said C_{1-2} alkanediyl is optionally replaced with -O-;

or

R^5 and R^6 are linked together to form a ring and

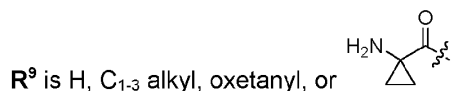
R^5 is a bond or C_{1-5} alkanediyl optionally substituted with one or more, identical or different, substituents R^8 , and one methylene of the C_{1-5} alkanediyl is optionally replaced with -O- or $N(R^9)$; and

R^6 is a bond or C_{1-5} alkanediyl optionally substituted with one or more, identical or different, substituents R^8 , and one methylene of the C_{1-5} alkanediyl is optionally replaced with -O- or $N(R^9)$;

wherein two R^8 are optionally linked together to form a ring together with the intervening atom(s);

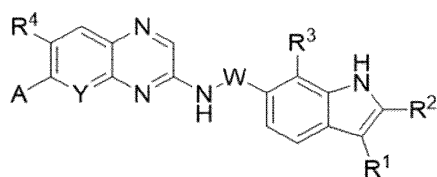
R^8 is individually selected from C_{1-3} alkyl optionally substituted with OH; -OH; F; $N(H)_2$; and -OC $_{1-3}$ alkyl optionally substituted with one or more F;

or when two R^8 are linked together to form a ring, then said two R^8 are individually selected from C_{1-3} alkanediyl optionally substituted with one or two substituents selected from F, OH, and NH_2 , and one or two methylene(s) of said C_{1-3} alkanediyl is optionally and individually replaced with -O-, -N(H)- or - $N(CH_3)$ -; and



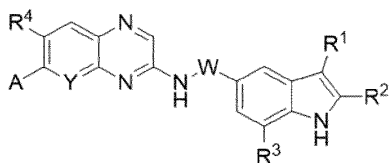
or a pharmaceutically acceptable salt thereof.

In one embodiment the compound of the present invention is of Formula (Ia):



Formula (Ia)

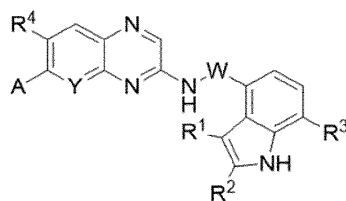
In one embodiment the compound of the present invention is of Formula (Ib):



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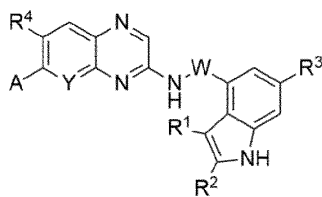
Formula (Ib)

In one embodiment the compound of the present invention is of Formula (Ic):



Formula (Ic)

10 In one embodiment the compound of the present invention is of Formula (Id):



Formula (Id)

In one embodiment Y is C(H). In one embodiment Y is N.

In one embodiment W is C(H)₂. In one embodiment W is C(D)₂.

15 In one embodiment R¹ is H.

In one embodiment R^1 is C_{1-3} alkyl. In one embodiment R^1 is methyl. In one embodiment R^1 is isopropyl. In one embodiment R^1 is cyclopropyl.

In one embodiment R^2 is H.

In one embodiment R^2 is C_{1-3} alkyl. In one embodiment R^2 is methyl.

- 5 In one embodiment R^2 is C_{1-3} alkyl substituted with OH. In one embodiment R^2 is CH_2OH .

In one embodiment R^2 is C_{3-5} cycloalkyl. In one embodiment R^2 is cyclopropyl.

In one embodiment R^3 is H.

- 10 In one embodiment R^3 is C_{1-3} alkyl. In one embodiment R^3 is methyl. In one embodiment R^3 is C_{1-3} alkyl substituted with OH. In one embodiment wherein R^3 is CH_2OH .

In one embodiment R^3 is OC_{1-3} alkyl. In one embodiment R^3 is methoxy.

In one embodiment R^3 is $-OC_{1-3}$ alkyl substituted with one or more F. In one embodiment R^3 is $-OCHF_2$.

- 15 In one embodiment R^3 is $-C(O)NHCH_3$.

In one embodiment R^3 is $-NH_2$. In one embodiment R^3 is $-N(H)(CH_3)$. In one embodiment R^3 is $-N(CH_3)_2$.

In one embodiment R^3 is halogen. In one embodiment R^3 is Cl.

- 20 In one embodiment R^1 is H, and R^2 is H. In one embodiment R^1 is CH_3 , and R^2 is H. In one embodiment R^1 is H, R^2 is H, and R^3 is H. In one embodiment R^1 is H, R^2 is CH_3 , and R^3 is H. In one embodiment R^1 is H, R^2 is cyclopropyl, and R^3 is H. In one embodiment R^1 is H, R^2 is CH_2OH , and R^3 is H. In one embodiment R^1 is CH_3 , R^2 is H, and R^3 is H.

- 25 In one embodiment R^1 is H, R^2 is H, and R^3 is NH_2 . In one embodiment the compound is of Formula (Id) and R^1 is H, R^2 is H, and R^3 is NH_2 .

In one embodiment R^1 is H, R^2 is H, and R^3 is $N(CH_3)_2$. In one embodiment the compound is of Formula (Ic) and R^1 is H, R^2 is H, and R^3 is $N(CH_3)_2$.

In one embodiment R^1 is H, R^2 is H, and R^3 is Cl. In one embodiment the compound is of Formula (Ic) and R^1 is H, R^2 is H, and R^3 is Cl.

In one embodiment R¹ is CH₃, R² is H, and R³ is CH₂OH. In one embodiment the compound is of Formula (Ic) and R¹ is CH₃, R² is H, and R³ is CH₂OH.

In one embodiment R¹ is isopropyl, R² is H, and R³ is OCH₃. In one embodiment the compound is of Formula (Ic) and R¹ is isopropyl, R² is H, and R³ is OCH₃.

5 In one embodiment R¹ is CH₃, R² is H, and R³ is OCH₃. In one embodiment the compound is of Formula (Ic) and R¹ is CH₃, R² is H, and R³ is OCH₃.

In one embodiment R¹ is H, R² is H, and R³ is OCH₃. In one embodiment the compound is of Formula (Ic) and R¹ is H, R² is H, and R³ is OCH₃.

10 In one embodiment R¹ is CH₃, R² is H, and R³ is C(O)NHCH₃. In one embodiment the compound is of Formula (Ic) and R¹ is CH₃, R² is H, and R³ is C(O)NHCH₃.

In one embodiment R¹ is CH₃, R² is H, and R³ is CHF₂. In one embodiment the compound is of Formula (Ic) and R¹ is CH₃, R² is H, and R³ is CHF₂.

In one embodiment R⁴ is H.

15 In one embodiment R⁴ is C₁₋₄ alkyl. In one embodiment R⁴ is methyl. In one embodiment R⁴ is C₃₋₅ cycloalkyl.

In one embodiment A is of Formula (II):



Formula (II)

wherein

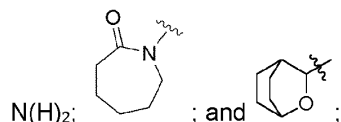
20 X is N;

R⁶ is H or C₁₋₄ alkyl; and

R⁵ is selected from the group consisting of C₁₋₆ alkyl optionally substituted with one or more, identical or different, substituents R⁷, wherein one or more methylene(s) of said C₁₋₆ alkyl is optionally and individually replaced with -O- or C=O; C₃₋₆ cycloalkyl optionally substituted with one or more, identical or different, substituents R⁷; and tetrahydropyranyl;

25 wherein two R⁷ are optionally linked together to form a ring together with the intervening atom(s); and

R^7 is individually selected from C_{1-3} alkoxy optionally substituted with one or more F; -OH; -O-benzyl; C_{1-3} alkyl optionally substituted with OH; $N(CH_3)_2$;



- 5 or when two R^7 are linked together to form a ring, then said two R^7 are individually selected from C_{1-2} alkanediyl optionally substituted with one or two substituents selected from F and OH, and one of the methylene of said C_{1-2} alkanediyl is optionally replaced with -O-.

In one embodiment R^6 is H.

- 10 In one embodiment R^6 is C_{1-4} alkyl. In one embodiment R^6 is CH_3 .

In one embodiment R^5 is C_{1-6} alkyl substituted with one or more, identical or different, substituents R^7 . In one embodiment R^5 is C_1 alkyl substituted with one or more, identical or different, substituents R^7 . In one embodiment R^5 is C_2 alkyl substituted with one or more, identical or different, substituents R^7 . In one embodiment R^5 is C_3 alkyl substituted with one or more, identical or different, substituents R^7 . In one embodiment R^5 is C_5 alkyl, such as neopentanedyl, substituted with one or more, identical or different, substituents R^7 .

- 20 In one embodiment R^5 is C_{3-6} cycloalkyl optionally substituted with one or more, identical or different, substituents R^7 . In one embodiment R^5 is C_3 cycloalkyl substituted with one or more, identical or different, substituents R^7 . In one embodiment R^5 is C_4 cycloalkyl substituted with one or more, identical or different, substituents R^7 . In one embodiment R^5 is C_6 cycloalkyl substituted with one or more, identical or different, substituents R^7 .

In one embodiment R^5 is C_6 cycloalkyl.

- 25 In one embodiment R^5 is tetrahydropyranyl.



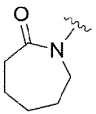
In one embodiment R^7 is OH. In one embodiment R^7 is $N(H)_2$. In one embodiment R^7 is $N(CH_3)_2$.

In one embodiment R^7 is C_{1-3} alkoxy. In one embodiment R^7 is OCH_3 .

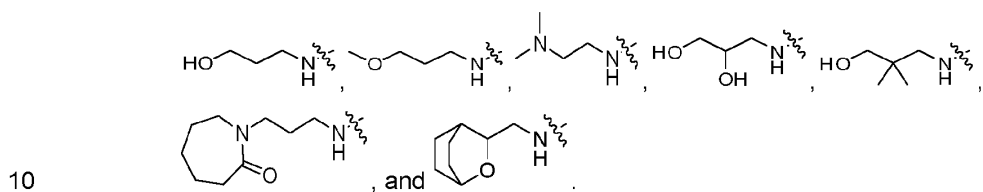
In one embodiment R^7 is C_{1-3} alkoxy substituted with one or more F. In one embodiment R^7 is $OCHF_2$.

In one embodiment R^7 is C_{1-3} alkyl. In one embodiment R^7 is CH_3 .

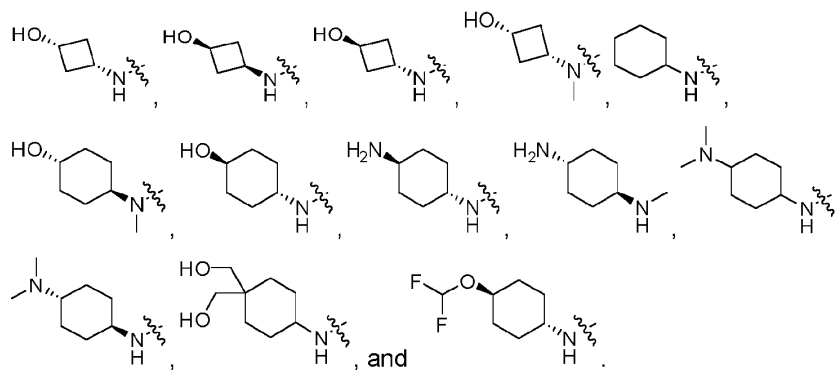
- 5 In one embodiment R^7 is C_{1-3} alkyl substituted with OH. In one embodiment R^7 is CH_2OH .

In one embodiment R^7 is . In one embodiment R^7 is .

In one embodiment A is selected from the group consisting of:



In one embodiment A is selected from the group consisting of:

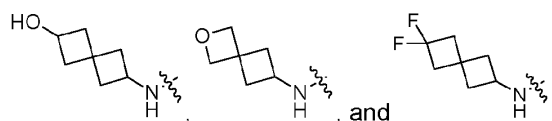


- 15 In one embodiment two R^7 are linked together to form a ring, and said two R^7 are individually selected from C_{1-2} alkanediyl optionally substituted with one or two substituents selected from F and OH, and one of the methylene of said C_{1-2} alkanediyl is optionally replaced with $-O-$.

In one embodiment two R^7 are linked together to form a ring, and said two R^7 are individually selected from C_{1-2} alkanediyl optionally substituted with one or two substituents selected from F and OH.

- 5 In one embodiment two R^7 are linked together to form a ring, and said two R^7 are individually selected from C_{1-2} alkanediyl, and one of the methylene of said C_{1-2} alkanediyl is optionally replaced with -O-.

In one embodiment A is selected from the group consisting of:



- 10 In some embodiments, R^5 and R^6 are linked together to form a ring and
- R^5 is a bond or C_{1-5} alkanediyl optionally substituted with one or more, identical or different, substituents R^8 , and one methylene of the C_{1-5} alkanediyl is optionally replaced with -O- or $N(R^9)$; and
- 15 R^6 is a bond or C_{1-5} alkanediyl optionally substituted with one or more, identical or different, substituents R^8 , and one methylene of the C_{1-5} alkanediyl is optionally replaced with -O- or $N(R^9)$;
- wherein two R^8 are optionally linked together to form a ring together with the intervening atom(s);
- R^8 is individually selected from C_{1-3} alkyl optionally substituted with OH; -OH; F; $N(H)_2$;
- 20 and -OC₁₋₃ alkyl optionally substituted with one or more F;
- or when two R^8 are linked together to form a ring, then said two R^8 are individually selected from C_{1-3} alkanediyl optionally substituted with one or two substituents selected from F OH, and NH_2 , and one or two methylene(s) of said C_{1-3} alkanediyl is optionally and individually replaced with -O-, -N(H)- or -N(CH₃)-; and

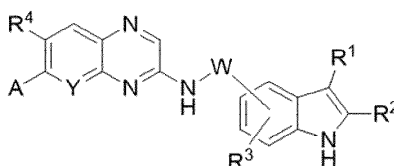
- 25 R^9 is H, C_{1-3} alkyl, oxetanyl, or

In some embodiments, R^8 is individually selected from C_{1-3} alkyl optionally substituted with OH; -OH; -F; -N(H)₂; and -OC₁₋₃ alkyl optionally substituted with one or more F; or when two R^8 are linked together to form a ring, then said two R^8 are individually selected from C_{1-3} alkanediyl optionally substituted with one or two substituents selected from F and OH, and one or two methylene(s) of said C_{1-3} alkanediyl is optionally and individually replaced with -O-, -N(H)- or -N(CH₃)-.

In some embodiments, R^8 is individually selected from C_{1-3} alkyl optionally substituted with OH; -OH; -F; -N(H)₂; and -OC₁₋₃ alkyl optionally substituted with one or more F.

In some embodiments, two R^8 are linked together to form a ring, and said two R^8 are individually selected from C_{1-3} alkanediyl optionally substituted with one or two substituents selected from F, OH, and NH₂, and one or two methylene(s) of said C_{1-3} alkanediyl is optionally and individually replaced with -O-, -N(H)- or -N(CH₃)-.

In one aspect, the present invention relates to a compound of formula (I):



Formula (I)

wherein

Y is C(H) or N;

W is C(H)₂ or C(D)₂;

R^1 is H, C_{1-3} alkyl or cyclopropyl

R^2 is H; C_{1-3} alkyl optionally substituted with OH; or C_{3-5} cycloalkyl;

R^3 is H; C_{1-3} alkyl optionally substituted with OH; -OC₁₋₃ alkyl optionally substituted with one or more F; -C(O)NHCH₃; -NH₂; -N(H)(CH₃); -N(CH₃)₂; or halogen;

R^4 is H, C_{1-4} alkyl, or C_{3-5} cycloalkyl;

A is piperidinyl, pyrrolidinyl, azetidiny, piperazinyl, or morpholinyl,

wherein said piperidinyl, pyrrolidinyl, or azetidiny, is optionally substituted with one or more individually selected R^{18} , wherein two R^{18} are optionally linked together to form a ring together with the intervening atom(s);

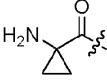
wherein said piperazinyl is optionally substituted with R¹⁴;

wherein said morpholinyl is optionally substituted with one or more, identical or different, substituents R¹⁹;

R¹⁸ is individually selected from C₁₋₃ alkyl optionally substituted with OH; -OH; F; N(H)₂;

5 and -OC₁₋₃ alkyl optionally substituted with one or more F,

or when two R¹⁸ are linked together to form a ring, then said two R¹⁸ are individually selected from C₁₋₃ alkanediyl optionally substituted with one or two substituents selected from F, OH, and NH₂, and one or two methylene(s) of said C₁₋₃ alkanediyl is optionally and individually replaced with -O-, -N(H)- or -N(CH₃)-;

10 R¹⁴ is C₁₋₃ alkyl, oxetanyl or ; and

R¹⁹ is individually selected from C₁₋₃ alkyl and C₁₋₃ alkyl substituted with OH.

In one embodiment A is piperidinyl optionally substituted with one or more individually selected R¹⁸, wherein two R¹⁸ are optionally linked together to form a ring together with the intervening atom(s);

R¹⁸ is individually selected from C₁₋₃ alkyl optionally substituted with OH; -OH; F; N(H)₂; and -OC₁₋₃ alkyl optionally substituted with one or more F;

or when two R¹⁸ are linked together to form a ring, then said two R¹⁸ are individually selected from C₁₋₃ alkanediyl optionally substituted with one or two substituents selected from F, OH, and NH₂, and one or two methylene(s) of said C₁₋₃ alkanediyl is optionally and individually replaced with -O-, -N(H)- or -N(CH₃)-.

In one embodiment piperidinyl is attached to Formula (I) in position 1 of the piperidinyl.

In one embodiment, A is piperidinyl optionally substituted with one R¹⁸, selected from C₁₋₃ alkyl optionally substituted with OH; -OH; F; N(H)₂; and -OC₁₋₃ alkyl optionally substituted with one or more F.

In one embodiment, A is piperidinyl optionally substituted with two R¹⁸, selected from C₁₋₃ alkyl optionally substituted with OH; -OH; F; N(H)₂; and -OC₁₋₃ alkyl optionally substituted with one or more F. In one embodiment A is pyrrolidinyl optionally substituted with one or more individually selected R¹⁸, wherein two R¹⁸ are optionally linked together to form a ring together with the intervening atom(s);

R^{18} is individually selected from C_{1-3} alkyl optionally substituted with OH; -OH; F; $N(H)_2$; and -OC $_{1-3}$ alkyl optionally substituted with one or more F;
 or when two R^{18} are linked together to form a ring, then said two R^{18} are individually
 selected from C_{1-3} alkanediyl optionally substituted with one or two substituents
 5 selected from F, OH, and NH_2 , and one or two methylene(s) of said C_{1-3} alkanediyl is
 optionally and individually replaced with -O-, -N(H)- or -N(CH $_3$)-.

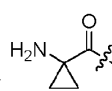
In one embodiment pyrrolidinyl is attached to Formula (I) in position 1 of the pyrrolidinyl.

10 In one embodiment A is azetidiny optionally substituted with one or more individually
 selected R^{18} , wherein two R^{18} are optionally linked together to form a ring together with
 the intervening atom(s);

R^{18} is individually selected from C_{1-3} alkyl optionally substituted with OH; -OH; F;
 $N(H)_2$; and -OC $_{1-3}$ alkyl optionally substituted with one or more F;
 or when two R^{18} are linked together to form a ring, then said two R^{18} are
 15 individually selected from C_{1-3} alkanediyl optionally substituted with one or two
 substituents selected from F, OH, and NH_2 , and one or two methylene(s) of said
 C_{1-3} alkanediyl is optionally and individually replaced with -O-, -N(H)- or -
 N(CH $_3$)-.

20 In one embodiment azetidiny is attached to Formula (I) in position 1 of the azetidiny.

In one embodiment A is piperazinyl optionally substituted with R^{14} at position 4 of the

piperazinyl, and wherein R^{14} is C_{1-3} alkyl, oxetanyl or . In one embodiment
 piperazinyl is attached to Formula (I) in position 1 of the piperazinyl.

25 In one embodiment A is morpholinyl optionally substituted with one or more, identical or
 different, substituents R^{19} , wherein R^{19} is individually selected from C_{1-3} alkyl and C_{1-3}
 alkyl substituted with OH. In one embodiment morpholinyl is attached to Formula (I) in
 position 4 of the morpholinyl.

In one embodiment R^{18} is R^8 .

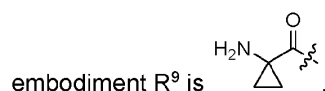
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In one embodiment R^8 is C_{1-3} alkyl. In one embodiment R^8 is -CH $_3$.

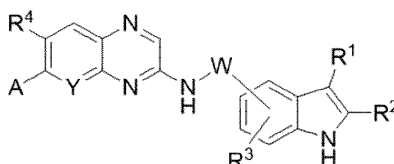
In one embodiment R^8 is C_{1-3} alkyl substituted with OH. In one embodiment R^8 is $-CH_2OH$. In one embodiment R^8 is $-OH$. In one embodiment R^8 is $N(H)_2$. In one embodiment R^8 is $-OC_{1-3}$ alkyl substituted with one or more F. In one embodiment R^8 is $-OCHF_2$.

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In one embodiment R^{19} is R^9 . In one embodiment R^9 is H. In one embodiment R^9 is C_{1-3} alkyl. In one embodiment R^9 is $-CH_3$. In one embodiment R^9 is oxetanyl. In one



10 In one aspect, the present invention relates to a compound of formula (I):



Formula (I)

wherein

Y is C(H) or N;

15 W is C(H)₂ or C(D)₂;

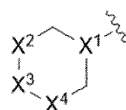
R^1 is H, C_{1-3} alkyl or cyclopropyl

R^2 is H; C_{1-3} alkyl optionally substituted with OH; or C_{3-5} cycloalkyl;

R^3 is H; C_{1-3} alkyl optionally substituted with OH; $-OC_{1-3}$ alkyl optionally substituted with one or more F; $-C(O)NHCH_3$; $-NH_2$; $-N(H)(CH_3)$; $-N(CH_3)_2$; or halogen;

20 R^4 is H, C_{1-4} alkyl, or C_{3-5} cycloalkyl;

A is of Formula (III):



Formula (III)

wherein

25 X^1 is N or C(H);

X^2 is C(R^{10})(R^{11}) or absent;

R^{10} is H or C_{1-3} alkyl;

R^{11} is H or C_{1-3} alkyl;

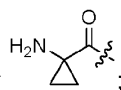
X^3 is $C(R^{12})(R^{13})$, O or $N(R^{14})$;

R^{12} is H, OH, NH_2 or C_{1-3} alkyl optionally substituted with OH; and R^{13} is H or C_{1-3} alkyl optionally substituted with OH; or

- 5 R^{12} and R^{13} are linked together to form a ring together with the intervening atom, and $R^{12}-R^{13}$ is C_{3-5} alkanediyl wherein one or two methylenes of said alkanediyl is optionally replaced with O, $C(H)(NH_2)$ or $N(R^{17})$;

R^{17} is H or C_{1-3} alkyl;

R^{14} is H, C_{1-3} alkyl, oxetanyl or

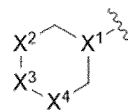


- 10 X^4 is $C(R^{15})(R^{16})$ or absent;

R^{15} is H; OH; C_{1-3} alkyl optionally substituted with OH; or OC_{1-3} alkyl optionally substituted with one or more F; and

R^{16} is H.

- 15 In one embodiment A is of Formula (III):



Formula (III)

wherein

X^1 is N or $C(H)$;

- 20 X^2 is $C(R^{10})(R^{11})$ or absent;

R^{10} is H or C_{1-3} alkyl;

R^{11} is H or C_{1-3} alkyl;

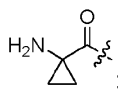
X^3 is $C(R^{12})(R^{13})$, O or $N(R^{14})$;

R^{12} is H, OH, NH_2 or C_{1-3} alkyl optionally substituted with OH; and R^{13} is H or C_{1-3} alkyl optionally substituted with OH; or

- 25 R^{12} and R^{13} are linked together to form a ring together with the intervening atom, and $R^{12}-R^{13}$ is C_{3-5} alkanediyl wherein one or two methylenes of said alkanediyl is optionally replaced with O, $C(H)(NH_2)$ or $N(R^{17})$;

R^{17} is H or C_{1-3} alkyl;

R^{14} is H, C_{1-3} alkyl, oxetanyl or



- 30

X^4 is $C(R^{15})(R^{16})$ or absent;

R^{15} is H; OH; C_{1-3} alkyl optionally substituted with OH; or OC_{1-3} alkyl optionally substituted with one or more F; and

R^{16} is H.

5

In one embodiment X^1 is N, X^2 is $C(R^{10})(R^{11})$, X^3 is $C(R^{12})(R^{13})$, and X^4 is $C(R^{15})(R^{16})$.

In one embodiment X^1 is N, X^2 is absent, X^3 is $C(R^{12})(R^{13})$, and X^4 is $C(R^{15})(R^{16})$.

In one embodiment X^1 is N, X^2 is absent, X^3 is $C(R^{12})(R^{13})$, and X^4 is absent.

In one embodiment X^1 is N, X^2 is $C(R^{10})(R^{11})$, X^3 is O, and X^4 is $C(R^{15})(R^{16})$.

10 In one embodiment X^1 is N, X^2 is $C(R^{10})(R^{11})$, X^3 is $N(R^{14})$, and X^4 is $C(R^{15})(R^{16})$.

In one embodiment X^1 is N.

In one embodiment X^1 is C(H).

In one embodiment X^2 is absent.

15 In one embodiment X^2 is $C(R^{10})(R^{11})$.

In one embodiment R^{10} is H.

In one embodiment R^{10} is C_{1-3} alkyl. In one embodiment R^{10} is CH_3 .

20 In one embodiment R^{11} is H.

In one embodiment R^{11} is C_{1-3} alkyl. In one embodiment R^{11} is CH_3 .

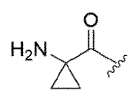
In one embodiment X^2 is $C(H)_2$. In one embodiment X^2 is $C(H)(CH_3)$. In one embodiment X^2 is $C(CH_3)_2$.

In one embodiment X^3 is O. In one embodiment X^3 is $N(R^{14})$.

25 In one embodiment R^{14} is H.

In one embodiment R^{14} is C_{1-3} alkyl. In one embodiment R^{14} is CH_3 .

In one embodiment R^{14} is oxetanyl. In one embodiment R^{14} is . In one

embodiment R^{14} is .

In one embodiment X^3 is N(H). In one embodiment X^3 is $N(CH_3)$. In one embodiment X^3 is $C(R^{12})(R^{13})$.

30

In one embodiment R^{12} is H. In one embodiment R^{12} is OH. In one embodiment R^{12} is NH_2 . In one embodiment R^{12} is C_{1-3} alkyl. In one embodiment R^{12} is C_{1-3} alkyl substituted with OH. In one embodiment R^{12} is CH_2OH .

- 5 In one embodiment R^{13} is H. In one embodiment R^{13} is C_{1-3} alkyl. In one embodiment R^{13} is C_{1-3} alkyl substituted with OH. In one embodiment R^{13} is CH_2OH .

In one embodiment X^3 is $C(H)_2$. In one embodiment X^3 is $C(H)(OH)$. In one embodiment X^3 is $C(H)(CH_2OH)$. In one embodiment X^3 is $C(CH_2OH)_2$.

- 10 In one embodiment X^4 is absent. In one embodiment X^4 is $C(R^{15})(R^{16})$.

In one embodiment R^{15} is H. In one embodiment R^{15} is OH. In one embodiment R^{15} is C_{1-3} alkyl. In one embodiment R^{15} is CH_3 . In one embodiment R^{15} is C_{1-3} alkyl substituted with OH. In one embodiment R^{15} is CH_2OH . In one embodiment R^{15} is OC_{1-3} alkyl substituted with one or more F. In one embodiment R^{15} is $OCHF_2$.

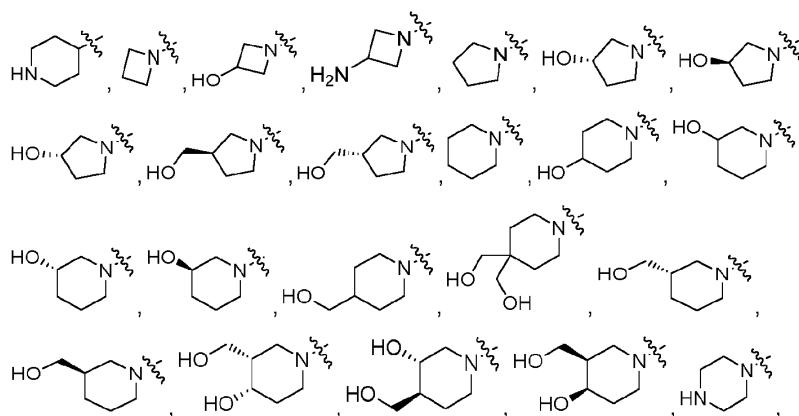
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In one embodiment R^{16} is H.

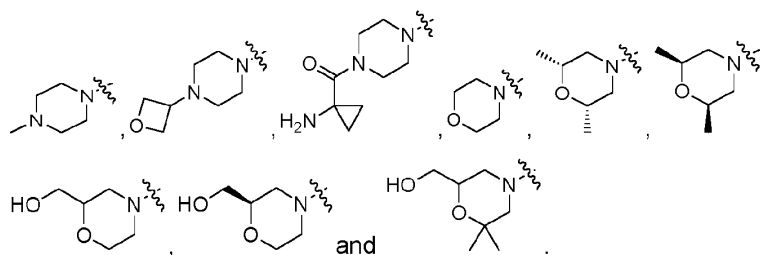
In one embodiment X^4 is $C(H)_2$. In one embodiment X^4 is $C(H)(CH_3)$. In one embodiment X^4 is $C(H)(OH)$. In one embodiment X^4 is $C(H)(CH_2OH)$. In one embodiment X^4 is $C(H)(OCHF_2)$.

20

In one embodiment A is selected from the group consisting of:



25



In one embodiment X^3 is $C(R^{12})(R^{13})$ and R^{12} and R^{13} are linked together to form a ring
5 together with the intervening atom, wherein R^{12} - R^{13} is C_{3-5} alkanediyl wherein one or
two methylenes of said alkanediyl is optionally replaced with O, $C(H)(NH_2)$ or $N(R^{17})$.

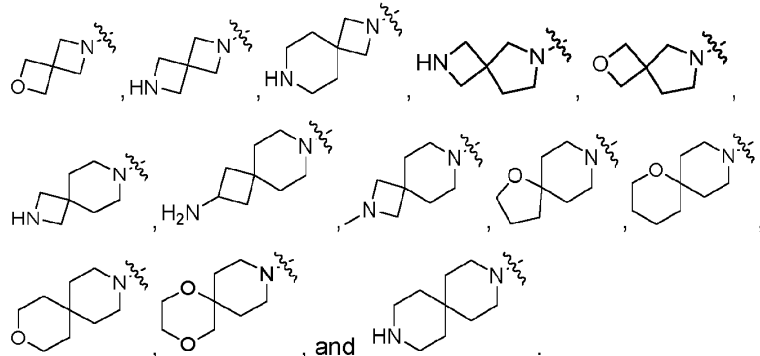
In one embodiment R¹⁷ is H.

In one embodiment R^{17} is C_{1-3} alkyl. In one embodiment R^{17} is CH_3 .

10 In one embodiment R^{12} - R^{13} is $-\text{CH}_2\text{-N}(\text{CH}_3)\text{-CH}_2-$. In one embodiment R^{12} - R^{13} is $-\text{CH}_2\text{-N}(\text{H})\text{-CH}_2-$. In one embodiment R^{12} - R^{13} is $-\text{CH}_2\text{-O-CH}_2-$. In one embodiment R^{12} - R^{13} is $-\text{CH}_2\text{-C}(\text{H})(\text{NH}_2)\text{-CH}_2-$. In one embodiment R^{12} - R^{13} is $-(\text{CH}_2)_3\text{-O-}$. In one embodiment R^{12} - R^{13} is $-(\text{CH}_2)_2\text{-O-}(\text{CH}_2)_2-$. In one embodiment R^{12} - R^{13} is $-(\text{CH}_2)\text{-O-}(\text{CH}_2)_3-$. In one embodiment R^{12} - R^{13} is $-(\text{CH}_2)_2\text{-N}(\text{H})\text{-}(\text{CH}_2)_2-$. In one embodiment R^{12} - R^{13} is $-\text{O-}(\text{CH}_2)_2\text{-O-}(\text{CH}_2)-$.

15

In one embodiment A is selected from the group consisting of:



20

In one embodiment A is H. In one embodiment A is C₁₋₃ alkoxy. In one embodiment A is OCH₃. In one embodiment A is CF₃. In one embodiment A is C₁₋₃ alkyl. In one embodiment A is CH₃. In one embodiment A is CH₂CH₃. In one embodiment A is C₁₋₄ alkyl. In one embodiment A is tert-butyl. In one embodiment A is C₃₋₅ cycloalkyl. In one embodiment A is cyclopropyl.

In one embodiment Y is N; W is C(H)₂; R¹ is H, CH₃, or isopropyl; R² is H, CH₃, cyclopropyl, or CH₂OH; R³ is H, CH₃, CH₂OH, NH₂, N(CH₃)₂, Cl, C(O)NHCH₃, OCHF₂, or OCH₃; R⁴ is H or CH₃; and A is H, CF₃ or of Formula (II):

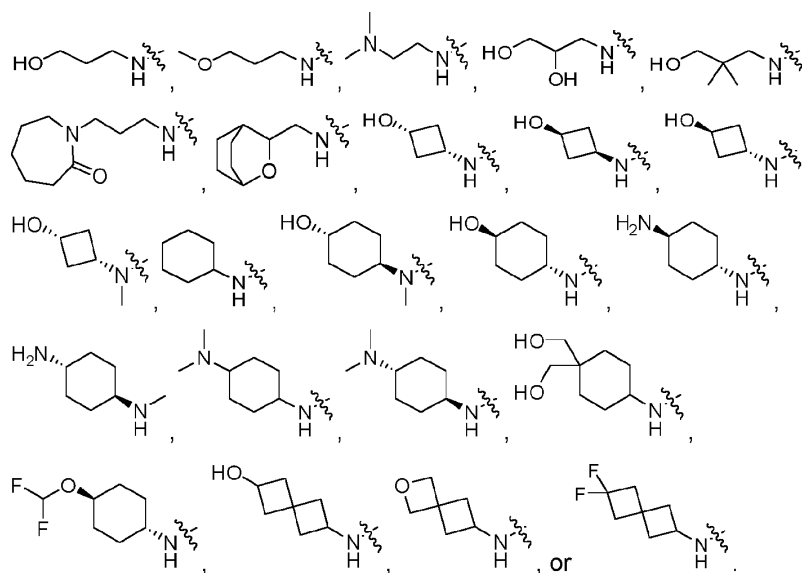


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Formula (II).

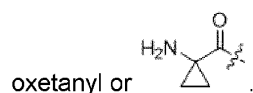
In one embodiment Y is N; W is C(H)₂; R¹ is H, CH₃, or isopropyl; R² is H, CH₃, cyclopropyl, or CH₂OH; R³ is H, CH₃, CH₂OH, NH₂, N(CH₃)₂, Cl, C(O)NHCH₃, OCHF₂, or OCH₃; R⁴ is H or CH₃; and A is H, CF₃,

10



15

In one embodiment A is piperidinyl, pyrrolidinyl, azetidiny, piperazinyl, wherein said piperidinyl, pyrrolidinyl, azetidiny, or piperazinyl is optionally substituted with one or more individually selected R¹⁸, wherein R¹⁸ is -CH₃, -CH₂OH, -OH, N(H)₂, OCHF₂, -F,



20

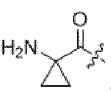
In one embodiment A is piperidinyl, pyrrolidinyl, azetidiny or piperazinyl, wherein said piperidinyl, pyrrolidinyl, azetidiny, or piperazinyl is substituted with two or more R¹⁸, wherein two R¹⁸ are linked together to form a ring together with the intervening atom(s),

and wherein the two R¹⁸ linked together to form a ring are individually selected from C₁₋₃ alkanediyl optionally substituted with one or two substituents selected from F, OH, and NH₂, and wherein one or two methylene(s) of said C₁₋₃ alkanediyl is optionally and individually replaced with -O-, -N(H)- or -N(CH₃)-.

5

In one embodiment A is morpholinyl, wherein said morpholinyl optionally substituted with one or more, identical or different, substituents R¹⁹, wherein R¹⁹ is -CH₃, or -CH₂OH.

- 10 In one embodiment Y is N; W is C(H)₂; R¹ is H, CH₃, or isopropyl; R² is H, CH₃, cyclopropyl, or CH₂OH; R³ is H, CH₃, CH₂OH, NH₂, N(CH₃)₂, Cl, C(O)NHCH₃, OCHF₂, or OCH₃; R⁴ is H or CH₃; and A is piperidinyl, pyrrolidinyl, azetidinyl, piperazinyl, wherein said piperidinyl, pyrrolidinyl, azetidinyl, or piperazinyl is optionally substituted with one or more individually selected R¹⁸, wherein R¹⁸ is -CH₃, -CH₂OH, -OH, N(H)₂,

- 15 OCHF₂, -F, oxetanyl, or .

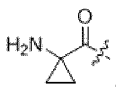
In one embodiment Y is N; W is C(H)₂; R¹ is H, CH₃, or isopropyl; R² is H, CH₃, cyclopropyl, or CH₂OH; R³ is H, CH₃, CH₂OH, NH₂, N(CH₃)₂, Cl, C(O)NHCH₃, OCHF₂, or OCH₃; R⁴ is H or CH₃; and A is piperidinyl, pyrrolidinyl, azetidinyl or piperazinyl, wherein said piperidinyl, pyrrolidinyl, azetidinyl, or piperazinyl is substituted with two or more R¹⁸, wherein two R¹⁸ are linked together to form a ring together with the intervening atom(s), and wherein the two R¹⁸ linked together to form a ring are individually selected from C₁₋₃ alkanediyl optionally substituted with one or two substituents selected from F, OH, and NH₂, and wherein one or two methylene(s) of said C₁₋₃ alkanediyl is optionally and individually replaced with -O-, -N(H)- or -N(CH₃)-.

- 25 In one embodiment Y is N; W is C(H)₂; R¹ is H, CH₃, or isopropyl; R² is H, CH₃, cyclopropyl, or CH₂OH; R³ is H, CH₃, CH₂OH, NH₂, N(CH₃)₂, Cl, C(O)NHCH₃, OCHF₂, or OCH₃; R⁴ is H or CH₃; and A is morpholinyl, wherein said morpholinyl optionally substituted with one or more, identical or different, substituents R¹⁹, wherein R¹⁹ is -CH₃, or -CH₂OH.

30

In one embodiment Y is N; W is C(H)₂; R¹ is H, CH₃, or isopropyl; R² is H, CH₃, cyclopropyl, or CH₂OH; R³ is H, CH₃, CH₂OH, NH₂, N(CH₃)₂, Cl, C(O)NHCH₃, OCHF₂, or OCH₃; R⁴ is H or CH₃; and A is piperidinyl, pyrrolidinyl, azetidinyl, piperazinyl,

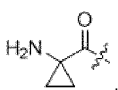
wherein said piperidinyl, pyrrolidinyl, azetidiny, or piperazinyl is optionally substituted with one or more individually selected R^{18} , wherein R^{18} is $-CH_3$, $-CH_2OH$, $-OH$, $N(H)_2$,

OCHF₂, $-F$, oxetanyl, or .

- 5 In one embodiment Y is N; W is C(H)₂; R¹ is H, CH₃, or isopropyl; R² is H, CH₃, cyclopropyl, or CH₂OH; R³ is H, CH₃, CH₂OH, NH₂, N(CH₃)₂, Cl, C(O)NHCH₃, OCHF₂, or OCH₃; R⁴ is H or CH₃; and A is piperidinyl, pyrrolidinyl, azetidiny, or piperazinyl, wherein said piperidinyl, pyrrolidinyl, azetidiny, or piperazinyl is substituted with two or more R^{18} , wherein two R^{18} are linked together to form a ring together with the
- 10 intervening atom(s), and wherein the two R^{18} linked together to form a ring are individually selected from C₁₋₃ alkanediyl optionally substituted with one or two substituents selected from F, OH, and NH₂, and wherein one or two methylene(s) of said C₁₋₃ alkanediyl is optionally and individually replaced with $-O-$, $-N(H)-$ or $-N(CH_3)-$.

- 15 In one embodiment Y is N; W is C(H)₂; R¹ is H, CH₃, or isopropyl; R² is H, CH₃, cyclopropyl, or CH₂OH; R³ is H, CH₃, CH₂OH, NH₂, N(CH₃)₂, Cl, C(O)NHCH₃, OCHF₂, or OCH₃; R⁴ is H or CH₃; and A is morpholinyl, wherein said morpholinyl optionally substituted with one or more, identical or different, substituents R^{19} , wherein R^{19} is $-CH_3$, or $-CH_2OH$.

- 20 In one embodiment Y is N; W is C(H)₂; R¹ CH₃; R² is H; R³ is H, CH₃, OCHF₂, or OCH₃; R⁴ is H; and A is piperidinyl, pyrrolidinyl, azetidiny, piperazinyl, wherein said piperidinyl, pyrrolidinyl, azetidiny, or piperazinyl is optionally substituted with one or more individually selected R^{18} , wherein R^{18} is $-CH_3$, $-CH_2OH$, $-OH$, $N(H)_2$, OCHF₂, $-F$,

- 25 oxetanyl or .

- In one embodiment Y is N; W is C(H)₂; R¹ CH₃; R² is H; R³ is H, CH₃, OCHF₂, or OCH₃; R⁴ is H; and A is piperidinyl, pyrrolidinyl, azetidiny, or piperazinyl, wherein said piperidinyl, pyrrolidinyl, azetidiny, or piperazinyl is substituted with two or more R^{18} ,
- 30 wherein two R^{18} are linked together to form a ring together with the intervening atom(s), and wherein the two R^{18} linked together to form a ring are individually selected from C₁₋₃ alkanediyl optionally substituted with one or two substituents selected from F, OH,

and NH₂, and wherein one or two methylene(s) of said C₁₋₃ alkanediyl is optionally and individually replaced with -O-, -N(H)- or -N(CH₃)-.

5 In one embodiment Y is N; W is C(H)₂; R¹ CH₃; R² is H; R³ is H, CH₃, OCHF₂, or OCH₃; R⁴ is H; and A is morpholinyl, wherein said morpholinyl optionally substituted with one or more, identical or different, substituents R¹⁹, wherein R¹⁹ is -CH₃, or -CH₂OH.

10 In one embodiment the compound is of Formula (Ia); Y is N; W is C(H)₂; R¹ CH₃; R² is H; R³ is H, CH₃, OCHF₂, or OCH₃; and R⁴ is H.

In one embodiment the compound is of Formula (Ib); Y is N; W is C(H)₂; R¹ CH₃; R² is H; R³ is H, CH₃, OCHF₂, or OCH₃; and R⁴ is H.

15 In one embodiment the compound is of Formula (Ic); Y is N; W is C(H)₂; R¹ CH₃; R² is H; R³ is H, CH₃, OCHF₂, or OCH₃; and R⁴ is H.

In one embodiment the compound is of Formula (Id); Y is N; W is C(H)₂; R¹ CH₃; R² is H; R³ is H, CH₃, OCHF₂, or OCH₃; and R⁴ is H.

20 In one embodiment the compound of the present invention is selected from the group consisting of:

7-cyclopropyl-N-(1H-indol-6-ylmethyl)quinoxalin-2-amine,
 N-[(7-methyl-1H-indol-5-yl)methyl]quinoxalin-2-amine,
 N-(1H-indol-6-ylmethyl)-7-(piperidin-1-yl)quinoxalin-2-amine
 25 N-(1H-indol-5-ylmethyl)quinoxalin-2-amine,
 1-(3-[(6-amino-1H-indol-4-yl)methyl]amino)pyrido[2,3-b]pyrazin-6-yl)piperidin-4-ol,
 N-(1H-indol-4-ylmethyl)-6-{2-methyl-2,7-diazaspiro[3.5]nonan-7-yl}pyrido[2,3-b]pyrazin-3-amine
 30 1-[3-({[7-(hydroxymethyl)-3-methyl-1H-indol-4-yl]methyl}amino)pyrido[2,3-b]pyrazin-6-yl]piperidin-4-ol,
 1-(3-[[1H-indol-4-yl(²H₂)methyl]amino]pyrido[2,3-b]pyrazin-6-yl)piperidin-4-ol,
 N-(1H-indol-6-ylmethyl)-6-(piperidin-4-yl)pyrido[2,3-b]pyrazin-3-amine,
 [6-({[6-(piperidin-1-yl)pyrido[2,3-b]pyrazin-3-yl]amino}methyl)-1H-indol-2-yl]MeOH,
 35

- N-[(3-isopropyl-7-methoxy-1H-indol-4-yl)methyl]-6-(pyrrolidin-1-yl)pyrido[2,3-b]pyrazin-3-amine,
6-N-cyclohexyl-3-N-[(7-methoxy-3-methyl-1H-indol-4-yl)methyl]pyrido[2,3-b]pyrazine-3,6-diamine,
5 1-[3-({[7-(dimethylamino)-3-methyl-1H-indol-4-yl]methyl}amino)pyrido[2,3-b]pyrazin-6-yl]piperidin-4-ol,
6-[(2R,6S)-2,6-dimethylmorpholin-4-yl]-N-[(3-methyl-1H-indol-4-yl)methyl]pyrido[2,3-b]pyrazin-3-amine,
N,3-dimethyl-4-[(6-{methyl[(1S,3S)-3-hydroxycyclobutyl]amino}pyrido[2,3-b]pyrazin-3-yl)amino]methyl]-1H-indole-7-carboxamide,
10 1-[3-({[7-(difluoromethoxy)-3-methyl-1H-indol-4-yl]methyl}amino)pyrido[2,3-b]pyrazin-6-yl]piperidin-4-ol,
3-(hydroxymethyl)-1-(3-{[(7-methoxy-3-methyl-1H-indol-4-yl)methyl]amino}pyrido[2,3-b]pyrazin-6-yl)piperidin-4-ol,
15 1-(3-{[(7-chloro-1H-indol-4-yl)methyl]amino}pyrido[2,3-b]pyrazin-6-yl)piperidin-4-ol,
[(3R)-1-(3-{[(1H-indol-6-yl)methyl]amino}pyrido[2,3-b]pyrazin-6-yl)pyrrolidin-3-yl]methanol,
(3R)-1-(3-{[(1H-indol-6-yl)methyl]amino}pyrido[2,3-b]pyrazin-6-yl)pyrrolidin-3-ol,
20 cis-(1S,3S)-3-[3-{[(7-methoxy-3-methyl-1H-indol-4-yl)methyl]amino}pyrido[2,3-b]pyrazin-6-yl)amino]cyclobutan-1-ol,
N-[(1H-indol-6-yl)methyl]-6-{2-oxa-6-azaspiro[3.3]heptan-6-yl}pyrido[2,3-b]pyrazin-3-amine,
6-{2,6-diazaspiro[3.3]heptan-2-yl}-N-(1H-indol-6-ylmethyl)pyrido[2,3-b]pyrazin-3-amine,
25 3-(hydroxymethyl)-1-(3-{[(1H-indol-6-yl)methyl]amino}pyrido[2,3-b]pyrazin-6-yl)piperidin-4-ol,
[(3R)-1-(3-{[(1H-indol-6-yl)methyl]amino}pyrido[2,3-b]pyrazin-6-yl)piperidin-3-yl]methanol,
30 N-[(1H-indol-6-yl)methyl]pyrido[2,3-b]pyrazin-3-amine,
cis-(1R,3R)-3-[3-{[(1H-indol-6-ylmethyl)amino]pyrido[2,3-b]pyrazin-6-yl)amino]cyclobutan-1-ol,
[4-(hydroxymethyl)-1-(3-{[(7-methoxy-3-methyl-1H-indol-4-yl)methyl]amino}pyrido[2,3-b]pyrazin-6-yl)piperidin-4-yl]methanol,

- 3-N-[(7-methoxy-3-methyl-1H-indol-4-yl)methyl]-6-N-[trans-4-aminocyclohexyl]pyrido[2,3-b]pyrazine-3,6-diamine,
7-tert-butyl-N-(1H-indol-6-ylmethyl)quinoxalin-2-amine,
N-[(1H-indol-6-yl)methyl]-6-(piperidin-1-yl)pyrido[2,3-b]pyrazin-3-amine,
5 [4-(hydroxymethyl)-1-{3-[(1H-indol-6-ylmethyl)amino]pyrido[2,3-b]pyrazin-6-yl}piperidin-4-yl]methanol,
N-(1H-indol-6-ylmethyl)-6-[4-(oxetan-3-yl)piperazin-1-yl]pyrido[2,3-b]pyrazin-3-amine,
7-{3-[(1H-indol-6-ylmethyl)amino]pyrido[2,3-b]pyrazin-6-yl}-7-
10 azaspiro[3.5]nonan-2-amine,
1-{3-[(1H-pyrrolo[2,3-b]pyridin-5-yl)methyl]amino}pyrido[2,3-b]pyrazin-6-yl}piperidin-4-ol,
3-N-(1H-indol-6-ylmethyl)-6-N-(oxan-4-yl)pyrido[2,3-b]pyrazine-3,6-diamine,
[(2R)-4-(3-{[(7-methoxy-3-methyl-1H-indol-4-yl)methyl]amino}pyrido[2,3-
15 b]pyrazin-6-yl)morpholin-2-yl]methanol,
N-[(1H-indol-6-yl)methyl]-6-(pyrrolidin-1-yl)pyrido[2,3-b]pyrazin-3-amine,
7-ethyl-N-[(1H-indol-6-yl)methyl]quinoxalin-2-amine,
N-(1H-indol-6-ylmethyl)-6-{2-methyl-2,7-diazaspiro[3.5]nonan-7-yl}pyrido[2,3-
20 b]pyrazin-3-amine,
1-(3-{[(3-hydroxy-4-methoxyphenyl)methyl]amino}pyrido[2,3-b]pyrazin-6-yl)piperidin-4-ol,
1-(3-{[(1H-indol-4-yl)methyl]amino}pyrido[2,3-b]pyrazin-6-yl)piperidin-4-ol,
6-{2,7-diazaspiro[3.5]nonan-7-yl}-N-[(7-methoxy-3-methyl-1H-indol-4-
25 yl)methyl]pyrido[2,3-b]pyrazin-3-amine,
N-[(1H-indol-6-yl)methyl]-7-methylquinoxalin-2-amine,
3-N-(1H-indol-6-ylmethyl)-6-N-{2-oxaspiro[3.3]heptan-6-yl}pyrido[2,3-
b]pyrazine-3,6-diamine,
N-[(2-methyl-1H-indol-5-yl)methyl]quinoxalin-2-amine,
6-{2,6-diazaspiro[3.4]octan-6-yl}-N-(1H-indol-6-ylmethyl)pyrido[2,3-b]pyrazin-3-
30 amine,
N3-[(1H-indol-6-yl)methyl]-N6-[trans-4-(difluoromethoxy)cyclohexyl]pyrido[2,3-
b]pyrazine-3,6-diamine,
N-(1H-indol-6-ylmethyl)-6-(morpholin-4-yl)pyrido[2,3-b]pyrazin-3-amine,
(3R)-1-{3-[(1H-indol-6-ylmethyl)amino]pyrido[2,3-b]pyrazin-6-yl}piperidin-3-ol,

- N-[(1H-indol-6-yl)methyl]-6-{2-oxa-6-azaspiro[3.4]octan-6-yl}pyrido[2,3-b]pyrazin-3-amine,
N-(1H-indol-6-ylmethyl)-6-{1-oxa-9-azaspiro[5.5]undecan-9-yl}pyrido[2,3-b]pyrazin-3-amine,
5 [(2R)-4-[3-({[7-(difluoromethoxy)-3-methyl-1H-indol-4-yl]methyl}amino)pyrido[2,3-b]pyrazin-6-yl]morpholin-2-yl]methanol,
6-N-cyclohexyl-3-N-(1H-indol-6-ylmethyl)pyrido[2,3-b]pyrazine-3,6-diamine,
1-(3-{[(3-isopropyl-7-methoxy-1H-indol-4-yl)methyl]amino}pyrido[2,3-b]pyrazin-6-yl)piperidin-4-ol,
10 (3R,4R)-3-(hydroxymethyl)-1-{3-[(1H-indol-6-ylmethyl)amino]pyrido[2,3-b]pyrazin-6-yl}piperidin-4-ol,
[(2R)-4-{3-[(1H-indol-6-ylmethyl)amino]pyrido[2,3-b]pyrazin-6-yl}morpholin-2-yl]methanol,
N-(1H-indol-6-ylmethyl)-6-{3-oxa-9-azaspiro[5.5]undecan-9-yl}pyrido[2,3-b]pyrazin-3-amine,
15 trans-4-({3-[(1H-indol-6-ylmethyl)amino]pyrido[2,3-b]pyrazin-6-yl}amino)cyclohexan-1-ol,
1-(3-{[(2-cyclopropyl-1H-indol-5-yl)methyl]amino}pyrido[2,3-b]pyrazin-6-yl)piperidin-4-ol,
20 N6-[2-(dimethylamino)ethyl]-N3-[(1H-indol-6-yl)methyl]pyrido[2,3-b]pyrazine-3,6-diamine,
6-{2,7-diazaspiro[3.5]nonan-7-yl}-N-(1H-indol-6-ylmethyl)pyrido[2,3-b]pyrazin-3-amine,
3-[(3-({[(1H-indol-6-yl)methyl]amino}pyrido[2,3-b]pyrazin-6-yl)amino]propane-1,2-diol,
25 [(3S)-1-(3-({[(1H-indol-6-yl)methyl]amino}pyrido[2,3-b]pyrazin-6-yl)piperidin-3-yl]methanol,
1-(3-({[(7-methoxy-3-methyl-1H-indol-4-yl)methyl]amino}pyrido[2,3-b]pyrazin-6-yl)piperidin-4-ol,
30 (1-{3-[(1H-indol-6-ylmethyl)amino]pyrido[2,3-b]pyrazin-6-yl}piperidin-4-yl)methanol,
trans-4-[methyl(3-({[(3-methyl-1H-indol-4-yl)methyl]amino}pyrido[2,3-b]pyrazin-6-yl)amino)cyclohexan-1-ol,
N-[(1H-indol-6-yl)methyl]quinoxalin-2-amine,

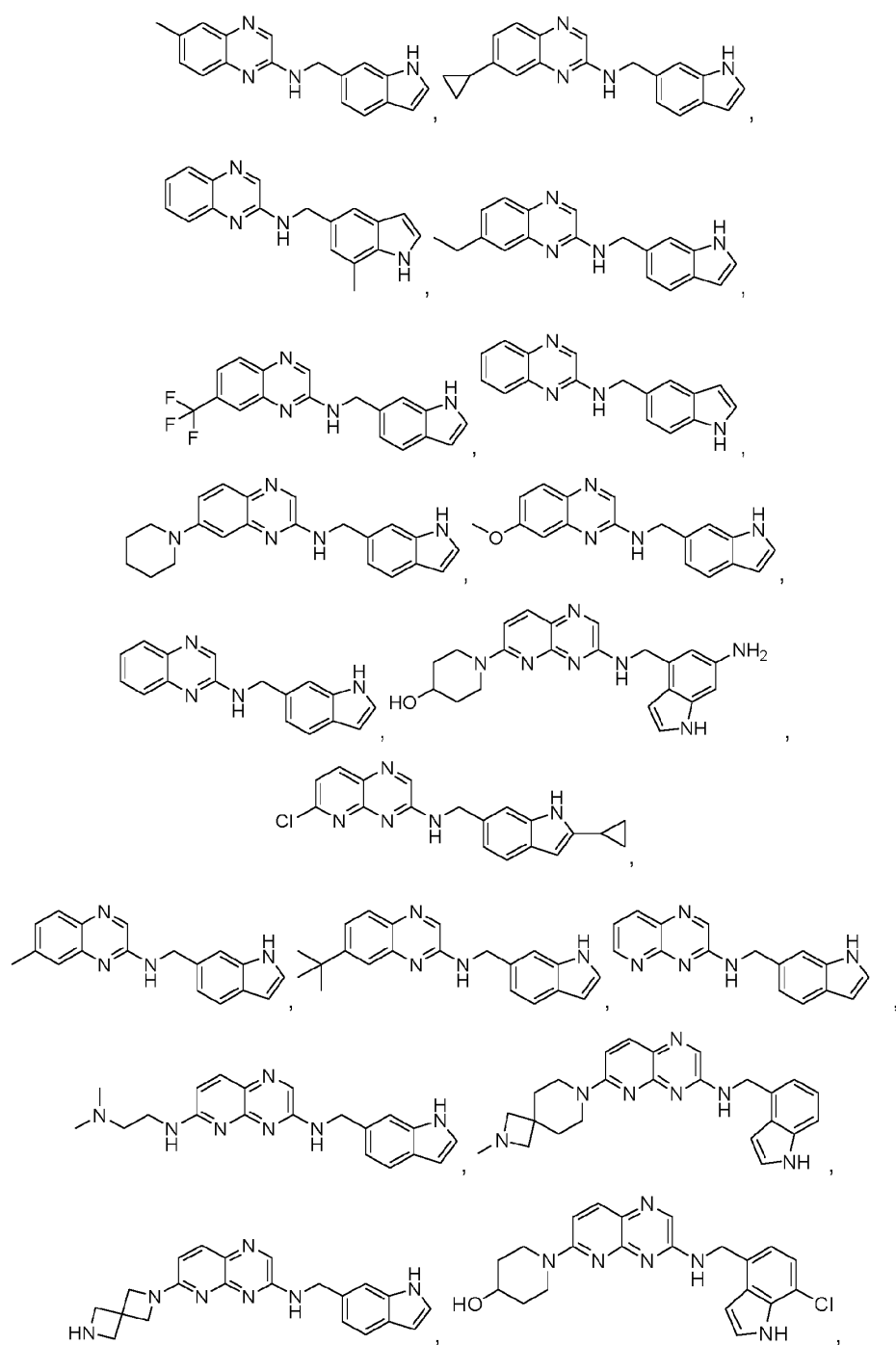
- 1-(3-[[7-methoxy-1H-indol-4-yl)methyl]amino]pyrido[2,3-b]pyrazin-6-yl)piperidin-4-ol,
(3S)-1-(3-[[1H-indol-6-yl)methyl]amino]pyrido[2,3-b]pyrazin-6-yl)piperidin-3-ol,
1-(3-[[1H-indol-6-yl)methyl]amino]pyrido[2,3-b]pyrazin-6-yl)piperidin-4-ol,
5 N3-[(1H-indol-6-yl)methyl]-N6-(3-methoxypropyl)pyrido[2,3-b]pyrazine-3,6-diamine,
trans-3-({3-[(1H-indol-6-yl)methyl]amino}pyrido[2,3-b]pyrazin-6-yl)(methyl)amino)cyclobutan-1-ol,
N-[(7-methoxy-3-methyl-1H-indol-4-yl)methyl]-6-{2-methyl-2,7-
10 diazaspiro[3.5]nonan-7-yl}pyrido[2,3-b]pyrazin-3-amine,
N-(1H-indol-6-ylmethyl)-6-(piperazin-1-yl)pyrido[2,3-b]pyrazin-3-amine,
cis-3-[(3-[(3-methyl-1H-indol-4-yl)methyl]amino]pyrido[2,3-b]pyrazin-6-yl)amino]cyclobutan-1-ol,
(3S,4S)-3-(hydroxymethyl)-1-(3-[[7-methoxy-3-methyl-1H-indol-4-
15 yl)methyl]amino]pyrido[2,3-b]pyrazin-6-yl)piperidin-4-ol,
1-(3-[(2-methyl-1H-indol-5-yl)methyl]amino]pyrido[2,3-b]pyrazin-6-yl)piperidin-4-ol,
N3-[(1H-indol-6-yl)methyl]-N6-[trans-4-aminocyclohexyl]pyrido[2,3-b]pyrazine-3,6-diamine,
20 3-[(3-[(1H-indol-6-yl)methyl]amino]pyrido[2,3-b]pyrazin-6-yl)amino]-2,2-dimethylpropan-1-ol,
6-N-{6,6-difluorospiro[3.3]heptan-2-yl}-3-N-(1H-indol-6-ylmethyl)pyrido[2,3-b]pyrazine-3,6-diamine,
6-{4-[(1-aminocyclopropyl)carbonyl]piperazin-1-yl}-N-(1H-indol-6-ylmethyl)pyrido[2,3-b]pyrazin-3-amine,
25 6-[cis-2,6-dimethylmorpholin-4-yl]-N-(1H-indol-6-ylmethyl)pyrido[2,3-b]pyrazin-3-amine,
[(3S)-1-{3-[(1H-indol-6-ylmethyl)amino]pyrido[2,3-b]pyrazin-6-yl}pyrrolidin-3-yl]methanol,
30 [4-(hydroxymethyl)-1-(3-[(3-methyl-1H-indol-4-yl)methyl]amino]pyrido[2,3-b]pyrazin-6-yl)piperidin-4-yl]methanol,
cis-3-[(3-[(7-methoxy-3-methyl-1H-indol-4-yl)methyl]amino]pyrido[2,3-b]pyrazin-6-yl)(methyl)amino]cyclobutan-1-ol,
4-[(6-[(2R)-2-(hydroxymethyl)morpholin-4-yl]pyrido[2,3-b]pyrazin-3-yl)amino]methyl]-N,3-dimethyl-1H-indole-7-carboxamide,
35

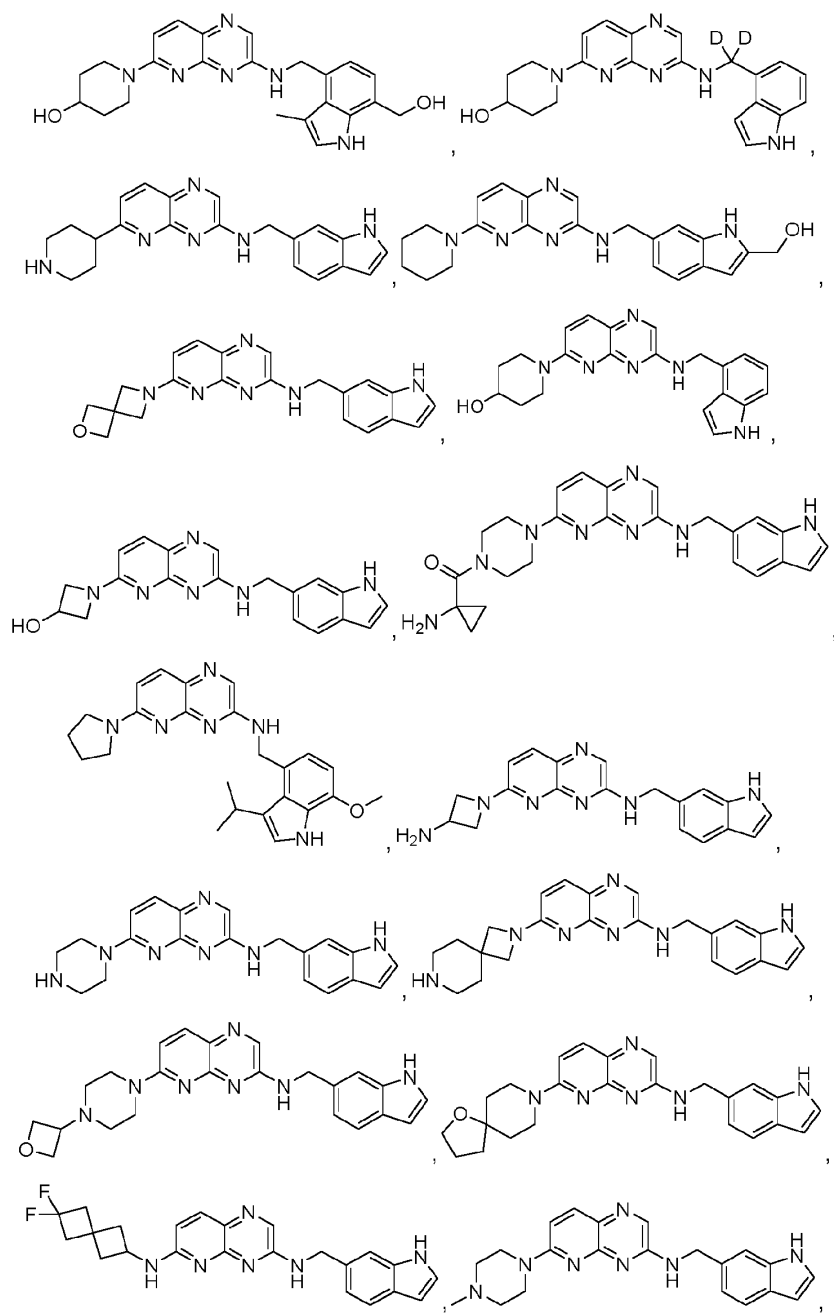
- N-[(1H-indol-6-yl)methyl]-6-methylquinoxalin-2-amine,
1-{3-[(3-{[(7-methoxy-3-methyl-1H-indol-4-yl)methyl]amino}pyrido[2,3-b]pyrazin-6-yl)amino]propyl}azepan-2-one,
1-(3-{[(1H-indol-6-yl)methyl]amino}pyrido[2,3-b]pyrazin-6-yl)piperidin-3-ol,
5 [4-(3-{[(7-methoxy-3-methyl-1H-indol-4-yl)methyl]amino}pyrido[2,3-b]pyrazin-6-yl)morpholin-2-yl]methanol,
N-(1H-indol-6-ylmethyl)-6-(4-methylpiperazin-1-yl)pyrido[2,3-b]pyrazin-3-amine,
trans-3-[methyl(3-{[(3-methyl-1H-indol-4-yl)methyl]amino}pyrido[2,3-b]pyrazin-6-yl)amino]cyclobutan-1-ol,
10 (3S,4S)-3-(hydroxymethyl)-1-{3-[(1H-indol-6-ylmethyl)amino]pyrido[2,3-b]pyrazin-6-yl}piperidin-4-ol,
6-(azetidin-1-yl)-N-[(1H-indol-6-yl)methyl]pyrido[2,3-b]pyrazin-3-amine,
1-(3-{[(3-methyl-1H-indol-4-yl)methyl]amino}pyrido[2,3-b]pyrazin-6-yl)piperidin-4-ol,
15 (3R,4R)-3-(hydroxymethyl)-1-(3-{[(7-methoxy-3-methyl-1H-indol-4-yl)methyl]amino}pyrido[2,3-b]pyrazin-6-yl)piperidin-4-ol,
6-[(3-{[(1H-indol-6-yl)methyl]amino}pyrido[2,3-b]pyrazin-6-yl)amino]spiro[3.3]heptan-2-ol,
3-N-[(7-methoxy-3-methyl-1H-indol-4-yl)methyl]-6-N-[trans-4-(dimethylamino)cyclohexyl]pyrido[2,3-b]pyrazine-3,6-diamine,
20 (3S)-1-(3-{[(7-methoxy-3-methyl-1H-indol-4-yl)methyl]amino}pyrido[2,3-b]pyrazin-6-yl)pyrrolidin-3-ol,
trans-3-({3-[(1H-indol-6-ylmethyl)amino]pyrido[2,3-b]pyrazin-6-yl}amino)cyclobutan-1-ol,
25 (3S)-1-(3-{[(1H-indol-6-yl)methyl]amino}pyrido[2,3-b]pyrazin-6-yl)pyrrolidin-3-ol,
[4-(3-{[(1H-indol-6-yl)methyl]amino}pyrido[2,3-b]pyrazin-6-yl)morpholin-2-yl]methanol,
(3S)-1-(3-{[(3-methyl-1H-indol-4-yl)methyl]amino}pyrido[2,3-b]pyrazin-6-yl)pyrrolidin-3-ol,
30 1-(3-{[(1H-indol-6-yl)methyl]amino}pyrido[2,3-b]pyrazin-6-yl)azetidin-3-ol,
4-({[6-(4-hydroxypiperidin-1-yl)pyrido[2,3-b]pyrazin-3-yl]amino}methyl)-N,3-dimethyl-1H-indole-7-carboxamide,
6-{1,4-dioxo-9-azaspiro[5.5]undecan-9-yl}-N-(1H-indol-6-ylmethyl)pyrido[2,3-b]pyrazin-3-amine,

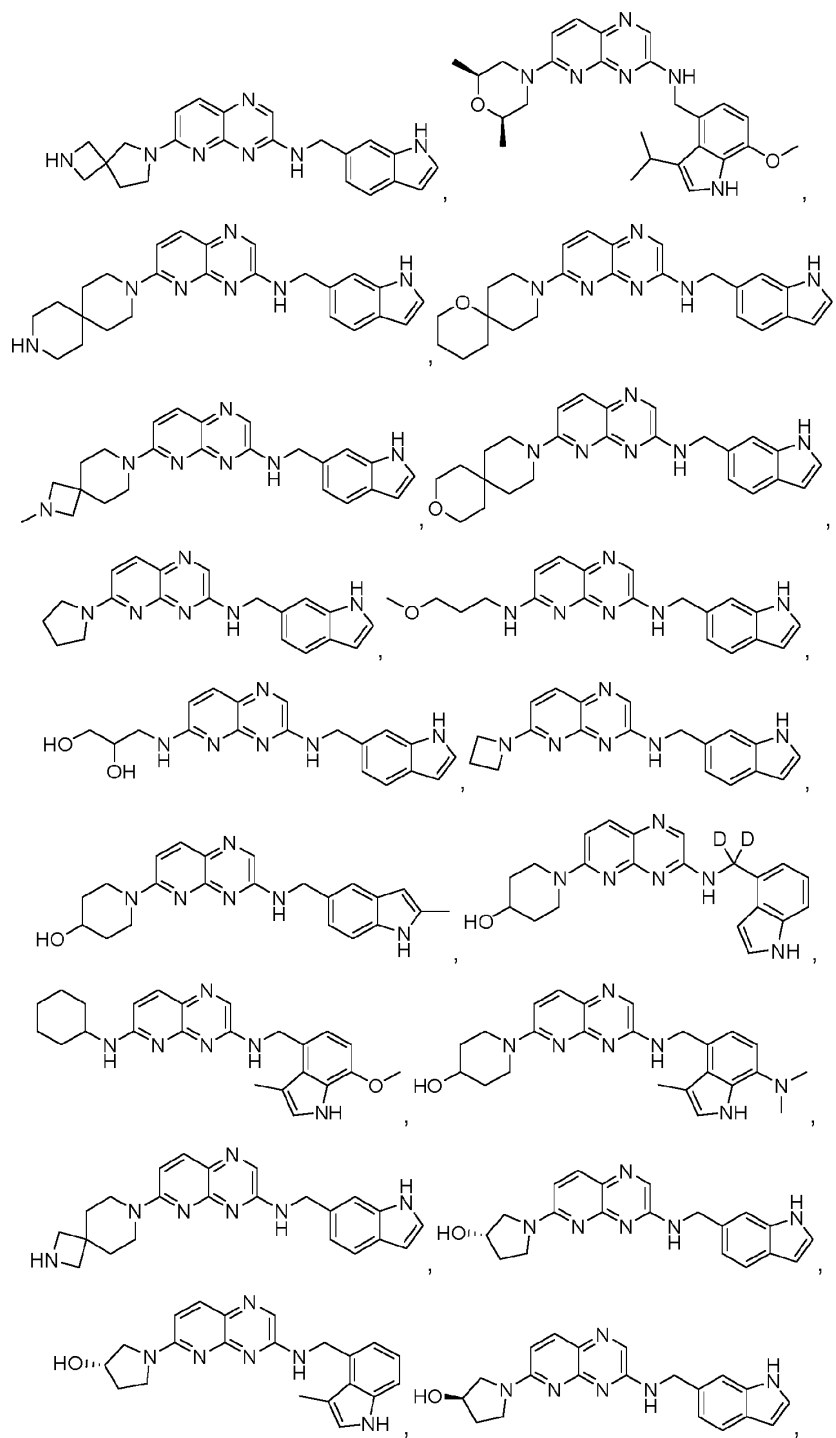
- N-(1H-indol-6-ylmethyl)-6-{1-oxa-8-azaspiro[4.5]decan-8-yl}pyrido[2,3-b]pyrazin-3-amine,
 6-[cis-2,6-dimethylmorpholin-4-yl]-N-[(3-isopropyl-7-methoxy-1H-indol-4-yl)methyl]pyrido[2,3-b]pyrazin-3-amine,
 5 6-[(3-[[[(7-methoxy-3-methyl-1H-indol-4-yl)methyl]amino]pyrido[2,3-b]pyrazin-6-yl)amino]spiro[3.3]heptan-2-ol,
 (3S,4S)-4-(hydroxymethyl)-1-{3-[(1H-indol-6-ylmethyl)amino]pyrido[2,3-b]pyrazin-6-yl}piperidin-3-ol,
 N-[(7-methoxy-3-methyl-1H-indol-4-yl)methyl]-6-(4-methylpiperazin-1-yl)pyrido[2,3-b]pyrazin-3-amine,
 10 N-[(1H-indol-6-yl)methyl]-7-methoxyquinoxalin-2-amine,
 trans-4-[(3-[[[(7-methoxy-3-methyl-1H-indol-4-yl)methyl]amino]pyrido[2,3-b]pyrazin-6-yl)(methyl)amino]cyclohexan-1-ol,
 3-[(3-[(1H-indol-6-yl)methyl]amino]pyrido[2,3-b]pyrazin-6-yl)amino]propan-1-ol,
 15 6-N-[4-(dimethylamino)cyclohexyl]-3-N-(1H-indol-6-ylmethyl)pyrido[2,3-b]pyrazine-3,6-diamine,
 [1-(hydroxymethyl)-4-{3-[[[(7-methoxy-3-methyl-1H-indol-4-yl)methyl]amino]pyrido[2,3-b]pyrazin-6-yl)amino]cyclohexyl]methanol,
 1-{3-[(1H-indol-6-ylmethyl)amino]pyrido[2,3-b]pyrazin-6-yl}azetidin-3-amine,
 20 [(2R)-4-(3-{[(3-methyl-1H-indol-4-yl)methyl]amino}pyrido[2,3-b]pyrazin-6-yl)morpholin-2-yl]methanol,
 [4-(3-[[[(7-methoxy-3-methyl-1H-indol-4-yl)methyl]amino]pyrido[2,3-b]pyrazin-6-yl)-6,6-dimethylmorpholin-2-yl]methanol,
 N3-[(7-methoxy-3-methyl-1H-indol-4-yl)methyl]-N6-({2-oxabicyclo[2.2.2]octan-3-yl)methyl}pyrido[2,3-b]pyrazine-3,6-diamine,
 25 N-[(1H-indol-6-yl)methyl]-7-(trifluoromethyl)quinoxalin-2-amine,
 6-{2,7-diazaspiro[3.5]nonan-2-yl}-N-(1H-indol-6-ylmethyl)pyrido[2,3-b]pyrazin-3-amine,
 N-(1H-indol-5-ylmethyl)-6-(morpholin-4-yl)pyrido[2,3-b]pyrazin-3-amine, and
 30 6-{3,9-diazaspiro[5.5]undecan-3-yl}-N-[(1H-indol-6-yl)methyl]pyrido[2,3-b]pyrazin-3-amine.

In one aspect, the present invention relates to a compound selected from the group consisting of:

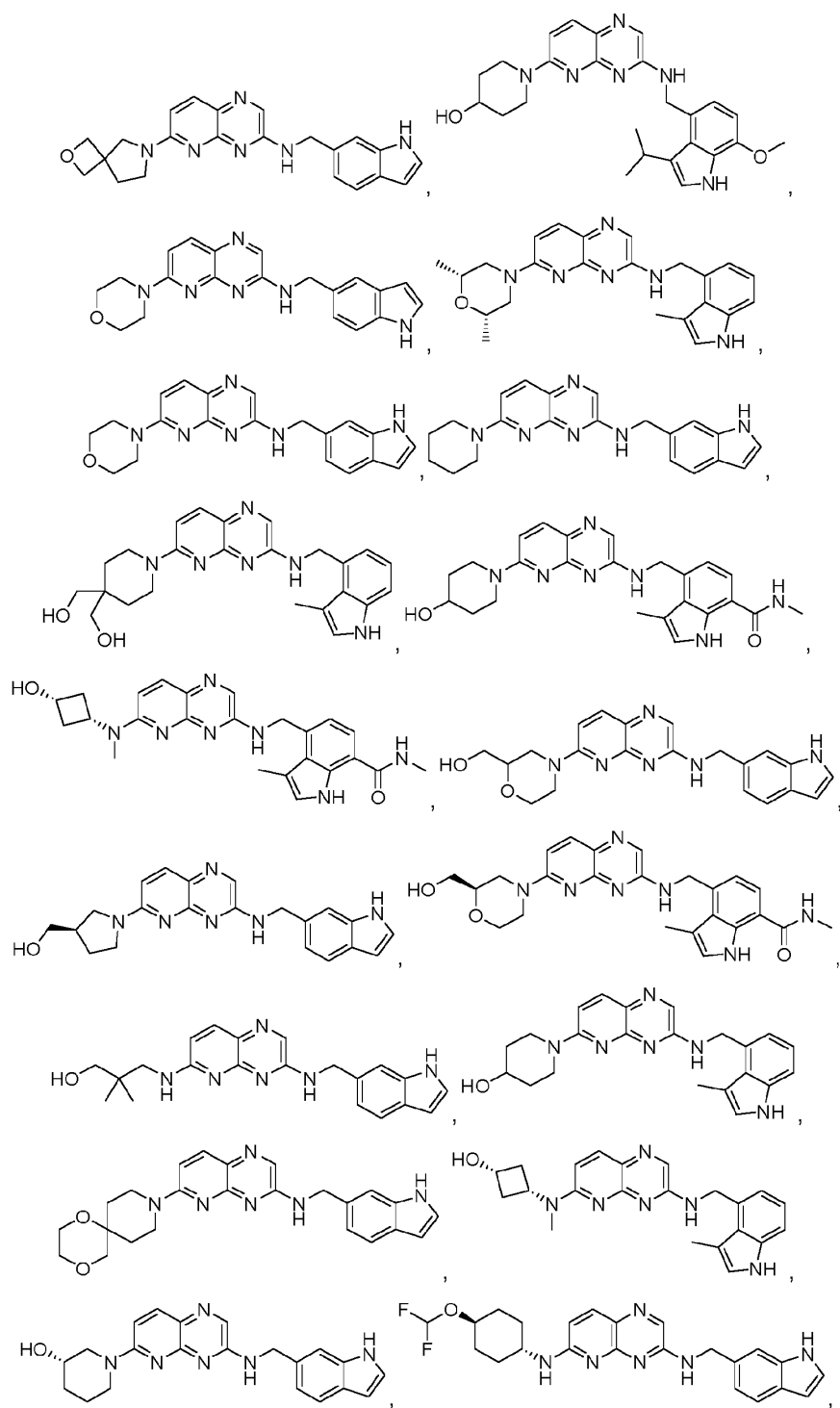
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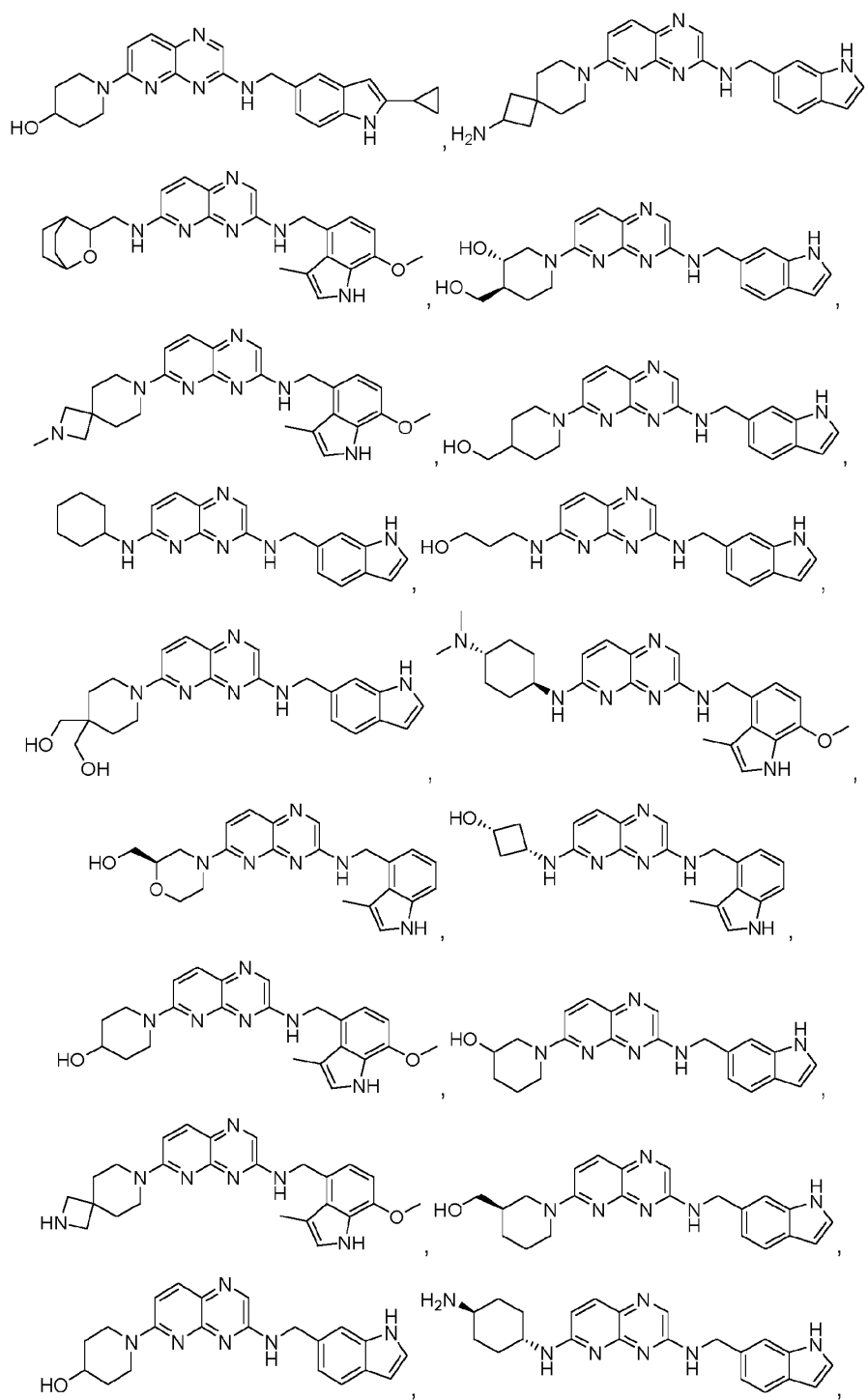


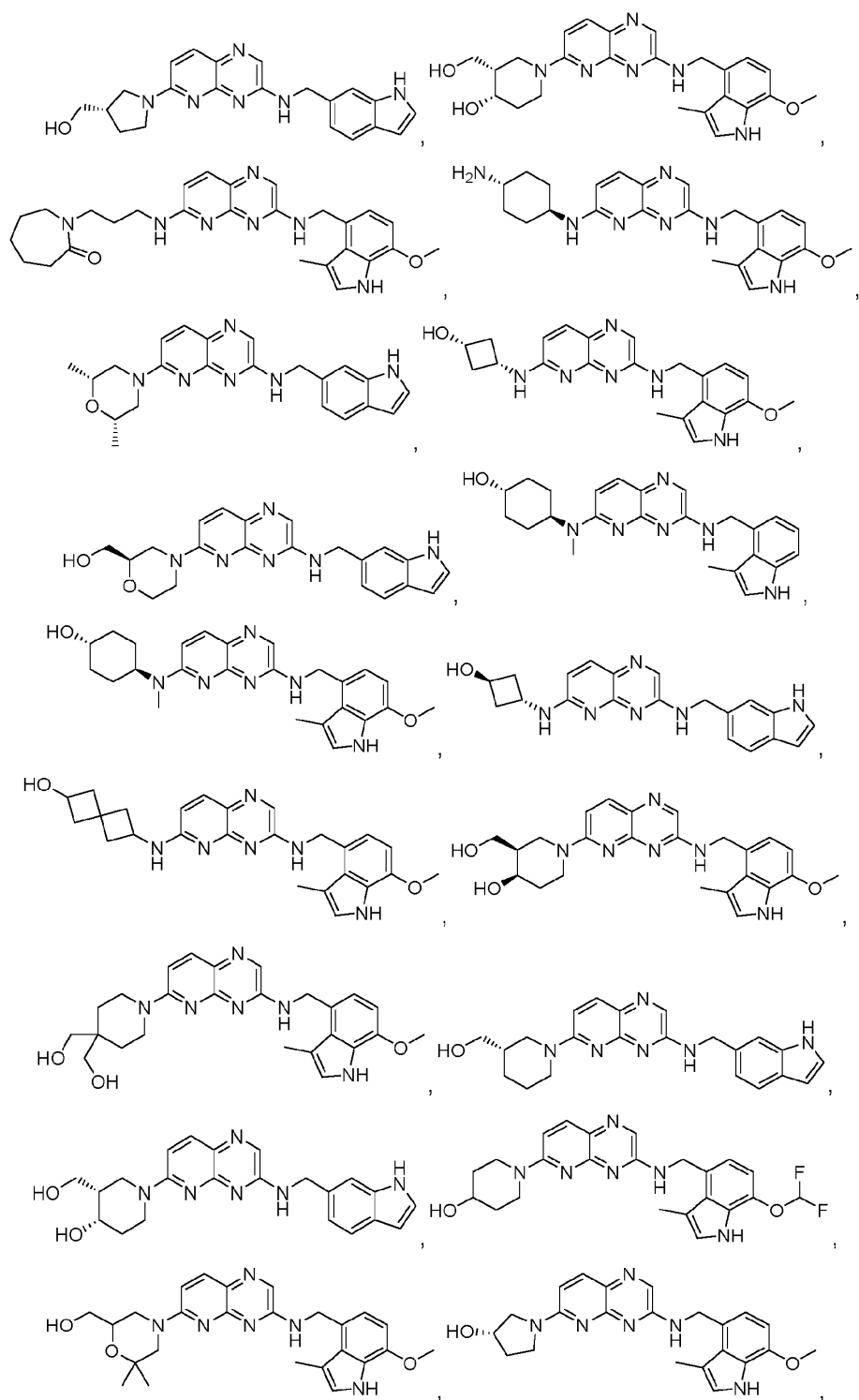


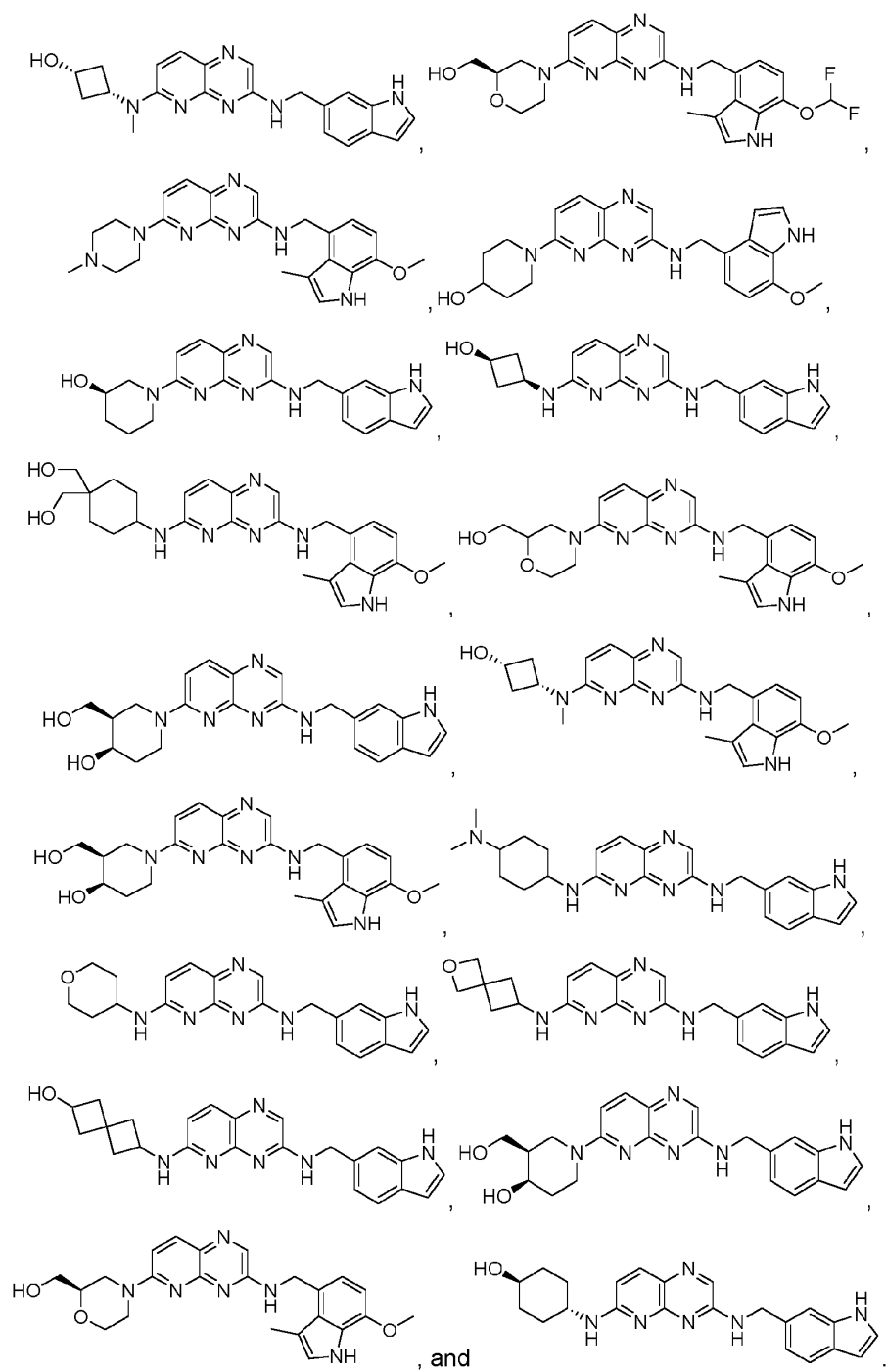


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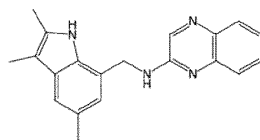








In one embodiment, the compound is not N-[(2,3,5-Trimethyl-1H-indol-7-yl)methyl]-2-quinoxalinamine.



In one embodiment, the compound is not

- 5 Compounds of the invention also include tautomeric forms. Tautomeric forms result from the swapping of a single bond with an adjacent double bond together with the concomitant migration of a proton. Tautomeric forms include prototropic tautomers which are isomeric protonation states having the same empirical formula and total charge. Example prototropic tautomers include ketone – enol pairs, amide - imidic acid
- 10 pairs, lactam – lactim pairs, enamine – imine pairs, and annular forms where a proton can occupy two or more positions of a heterocyclic system, for example, 1H- and 3H-imidazole, 1H-, 2H- and 4H- 1,2,4-triazole, 1H- and 2H- isoindole, and 1H- and 2H-pyrazole. Tautomeric forms can be in equilibrium or sterically locked into one form by appropriate substitution. Tautomeric forms can also include methyltropic tautomers,
- 15 which result from the swapping of a single bond with an adjacent double bond together with the concomitant migration of a methyl group.

All compounds described herein, and pharmaceutically acceptable salts thereof, can be found together with other substances such as water and solvents (e.g., in the form of

20 hydrates and solvates).

In one aspect, the present invention is directed to an intermediate compound, or a pharmaceutically acceptable salt thereof, which can be used in the synthesis of the compounds of the present invention. For example, said intermediate compound is in

25 some embodiments one of the intermediate compounds, or a pharmaceutically acceptable salt thereof, of Example 1 disclosed herein. In some embodiments the compound of the present invention is selected from any of the intermediate compounds, or a pharmaceutically acceptable salt thereof, disclosed in example 1 herein.

30

The compounds of the present invention may contain, for example, one or more asymmetric carbon atoms, and therefore may exist as stereoisomers, enantiomers and

diastereomers. Accordingly, the scope of the instant invention is to be understood to encompass all possible stereoisomers of the illustrated compounds, including the stereoisomerically pure form and stereoisomeric mixtures of any chemical structures disclosed herein, unless the stereochemistry is specifically identified. If the stereochemistry of a structure or a portion of a structure is not indicated with, for example, bold or dashed lines, the structure or portion of the structure is to be interpreted as encompassing all stereoisomers of it. If the stereochemistry of a structure or a portion of a structure is indicated with, for example, bold or dashed lines, the structure or portion of the structure is to be interpreted as encompassing only the stereoisomer indicated.

The term "stereoisomer" or "stereoisomerically pure" compound as used herein refers to one stereoisomer of a compound that is substantially free of other stereoisomers of that compound. For example, a stereoisomerically pure compound having one chiral center will be substantially free of the mirror image enantiomer of the compound and a stereoisomerically pure compound having two chiral centers will be substantially free of the other enantiomer and diastereomers of the compound. A typical stereoisomerically pure compound comprises greater than about 80% by weight of one stereoisomer of the compound and equal or less than about 20% by weight of other stereoisomers of the compound, greater than about 90% by weight of one stereoisomer of the compound and equal or less than about 10% by weight of the other stereoisomers of the compound, greater than about 95% by weight of one stereoisomer of the compound and equal or less than about 5% by weight of the other stereoisomers of the compound, or greater than about 97% by weight of one stereoisomer of the compound and equal or less than about 3% by weight of the other stereoisomers of the compound.

In some embodiments, the compound as defined herein is stereoisomerically pure.

Mixtures of stereoisomers may be resolved using standard techniques, such as chiral columns or chiral resolving agents, for example as outlined in the example section.

Preparation of compounds

Compounds according to the present invention may be prepared according to any conventional methods of chemical synthesis known by the skilled person, e.g. those

described in the working examples. The starting materials for the processes described in the present application are known or may readily be prepared by conventional methods known by the skilled artisan from commercially available chemicals.

- 5 The end products of the reactions described herein may be isolated by conventional technique such as extraction, crystallisation, distillation, chromatography etc.

- 10 The compounds of this invention may exist in unsolvated as well as in solvated forms with pharmaceutically acceptable solvents such as water, ethanol and the like. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of this invention.

Pharmaceutically Acceptable Salts

- 15 The chemical compound of the invention may be provided in any form suitable for the intended administration, including pharmaceutically (i.e. physiologically) acceptable salts. Examples of pharmaceutically acceptable addition salts include, without limitation, non-toxic inorganic and organic acid addition salts such as hydrochloride, hydrobromide, nitrate, perchlorate, phosphate, sulphate, formate, acetate, aconate, ascorbate, benzenesulphonate, benzoate, cinnamate, citrate, embonate, enantate, 20 fumarate, glutamate, glycolate, lactate, maleate, malonate, mandelate, methanesulphonate, naphthalene-2-sulphonate, phthalate, salicylate, sorbate, stearate, succinate, tartrate, toluene-p-sulphonate, and the like. Such salts may be formed by procedures well known and described in the art. Other acids such as oxalic acid, which may not be considered pharmaceutically acceptable, may be useful in the preparation 25 of salts useful as intermediates in obtaining a chemical compound of the invention and its pharmaceutically acceptable acid addition salt.

- 30 Examples of pharmaceutically acceptable cationic salts of a compound of Formula (I) of the invention include, without limitation, the sodium, the potassium, the calcium, the magnesium, the zinc, the aluminium, the lithium, the choline, the lysinium, and the ammonium salt, and the like, of a compound of Formula (I) of the invention containing an anionic group. Such cationic salts may be formed by procedures well known and described in the art. In the context of this invention the "onium salts" of *N*-containing compounds are also contemplated as pharmaceutically acceptable salts. Preferred

"onium salts" include the alkyl-onium salts, the cycloalkyl-onium salts, and the cycloalkylalkyl-onium salts.

Labelled Compounds

5 The chemical compound of the present invention may be used in its labelled or un-labelled form. In the context of this invention the labelled compound has one or more atoms replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. The labelling will allow easy quantitative detection of said compound.

10

The labelled compounds of the invention may be useful as diagnostic tools, radio tracers, or monitoring agents in various diagnostic methods, and for in vivo receptor imaging. The labelled isomer of the invention preferably contains at least one radionuclide as a label. Positron emitting radionuclides are all candidates for usage. In
15 the context of this invention the radionuclide is preferably selected from ^2H (deuterium), ^3H (tritium), ^{13}C , ^{14}C , ^{131}I , ^{125}I , ^{123}I , and ^{18}F .

15

The physical method for detecting the labelled isomer of the present invention may be selected from Position Emission Tomography (PET), Single Photon Imaging Computed
20 Tomography (SPECT), Magnetic Resonance Spectroscopy (MRS), Magnetic Resonance Imaging (MRI), and Computed Axial X-ray Tomography (CAT), or combinations thereof.

20

Pharmaceutical compositions

25 The present invention also relates to a pharmaceutical composition comprising, for example as an active ingredient, a pharmaceutically effective amount of a compound of Formula (I) as defined above. In one embodiment, said pharmaceutical composition comprises a therapeutically effective amount of the compound of Formula (I) or a pharmaceutically acceptable salt thereof, together with at least one pharmaceutically
30 acceptable carrier, excipient, or diluent.

While the compound of Formula (I) of the present invention for use in therapy may be administered in the form of the raw chemical compound, it is preferred to introduce the active ingredient, optionally in the form of a physiologically acceptable salt, in a

pharmaceutical composition together with one or more adjuvants, excipients, carriers, buffers, diluents, and/or other customary pharmaceutical auxiliaries.

5 In a preferred embodiment, the invention provides pharmaceutical compositions comprising the chemical compound of the invention, or a pharmaceutically acceptable salt thereof, together with one or more pharmaceutically acceptable carriers, and, optionally, other therapeutic and/or prophylactic ingredients, known and used in the art. The carrier(s) should be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not harmful to the recipient thereof.

10 A therapeutically effective dose refers to that amount of active ingredient, which ameliorates the symptoms or condition. Therapeutic efficacy and toxicity, e.g. ED₅₀, may be determined by standard pharmacological procedures in cell cultures or experimental animals. The dose ratio between therapeutic and toxic effects is the
15 therapeutic index and may be expressed by ratio between plasma levels resulting in therapeutic effects and plasma ratios resulting in toxic effects. Pharmaceutical compositions exhibiting large therapeutic indexes are preferred.

20 The dose administered may be adjusted to the age, weight and condition of the individual being treated, as well as the route of administration, dosage form and regimen, and the result desired, and the exact dosage can be determined by the practitioner.

25 The actual dosage depends on the nature and severity of the disease being treated, and is within the discretion of the physician, and may be varied by titration of the dosage to the particular circumstances of this invention to produce the desired therapeutic effect. However, it is presently contemplated that pharmaceutical compositions containing of from about 0.1 to about 10.000 mg of active ingredient per individual dose are suitable for therapeutic treatments. In some embodiments, the
30 subject is administered a dose of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in the range of 0.001 – 100 mg/kg.

In one embodiment, a compound of Formula (I) is administered in combination with one or more additional therapeutically active ingredient. In one embodiment, the additional
35 therapeutically active ingredient is known for treating hypertension or cancer.

WNK1 inhibition

The series of compounds of Formula (I) bind to WNK1. By virtue of this binding interaction, the compounds are capable of modulating WNK1.

- 5 WNK463 (*N*-(*tert*-butyl)-1-(1-(5-(5-(trifluoromethyl)-1,3,4-oxadiazol-2-yl)pyridin-2-yl)piperidin-4-yl)-1*H*-imidazole-5-carboxamide) is known to be an inhibitor of WNK1 catalytic activity (Yamada *et al*, 2016). As demonstrated in Example 2, the compounds of the present invention compete for the same site of WNK1 kinase as WNK463. Hence, the compounds of the present invention are inhibitors of WNK1 catalytic
10 activity.

In one embodiment, the compound of Formula (I) is a WNK lysine deficient protein kinase 1 (WNK1) inhibitor.

- To further test that compounds are WNK1 inhibitors, their capability of inhibiting *in vitro* phosphorylation of myelin basic protein (MBP) by purified recombinant human WNK1
15 may be tested as described in Yamada *et al.*, 2016a. Furthermore, the capability of inhibiting phosphorylation of the native substrate OSR1 by purified recombinant WNK1 kinase domain *in vitro*, and exogenously expressed OSR1 in HEK293 cells following sorbitol-induced osmotic stress may also be tested as described in Yamada *et al.*,
20 2016a.

In one aspect, the present invention relates to a method of inhibiting WNK1, said method comprising administering a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

WNK1-4 inhibition

The series of compounds of Formula (I), including the compounds of Formula (Ia) or Formula (Ib), bind to WNK1-4. By virtue of this binding interaction, the compounds are capable of modulating WNK1-4.

- 30 In one embodiment, the compound of Formula (I) is a WNK lysine deficient protein kinase 1-4 (WNK1-4) inhibitor.

In one aspect, the present invention relates to a method of inhibiting WNK1-4, said method comprising administering a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

- 5 In one embodiment, the compound of Formula (I) is a WNK lysine deficient protein kinase 2 (WNK2) inhibitor.

10 In one aspect, the present invention relates to a method of inhibiting WNK2, said method comprising administering a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In one embodiment, the compound of Formula (I) is a WNK lysine deficient protein kinase 3 (WNK3) inhibitor.

- 15 In one aspect, the present invention relates to a method of inhibiting WNK3, said method comprising administering a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

20 In one embodiment, the compound of Formula (I) is a WNK lysine deficient protein kinase 4 (WNK4) inhibitor.

In one aspect, the present invention relates to a method of inhibiting WNK4, said method comprising administering a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

25

Treatment

Being ligands for WNK1, the compounds of Formula (I) are of use in the treatment, prevention, and/or alleviation of disorders of a living body, including human. As used herein, the term "treatment" also includes prevention, and/or alleviation of diseases and disorders. In one aspect, the compound of formula (I) as described herein is for use in medicine.

30

In one aspect, the present invention is a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof, for use as a medicament.

35

5 In one aspect, the present invention is a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof, for use in treating, alleviating or preventing diseases and disorders related to the activity of WNK1.

10 In one aspect, the present invention concerns a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof, for use in treating, alleviating or preventing diseases and disorders related to the activity of WNK1-4, such as WNK1, WNK2, WNK3 and/or WNK4.

15 In one aspect, the present invention concerns a method for treating, alleviating or preventing diseases and disorders related to the activity of WNK1, said method comprising administering a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof, to a subject in need thereof.

20 In another aspect, the present invention concerns a method for treating, alleviating or preventing diseases and disorders related to the activity of WNK1-4, such as WNK1, WNK2, WNK3 and/or WNK4, said method comprising administering a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof, to a subject in need thereof.

25 In one aspect, the present invention concerns the use of a compound of Formula (I), a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof, for the manufacture of a medicament for treating, alleviating or preventing diseases and disorders related to the activity of WNK1.

30 In one aspect, the present invention concerns the use of a compound of Formula (I), a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof, for the manufacture of a medicament for treating, alleviating or preventing diseases and disorders related to the activity of WNK1-4, such as WNK1, WNK2, WNK3 and/or WNK4.

Treatment of hypertension

WNK1 inhibitors have been demonstrated to be effectful in the treatment or prevention of various diseases and disorders associated with increased WNK1 activity, including hypertension. Being ligands for WNK1, the compounds of Formula (I) are of use in the treatment, prevention, and/or alleviation of different types of hypertension, including familial hyperkalemic hypertension (FHHT and pseudohypoaldosteronism type II (PHAII) disorders of a living body, including human.

In one aspect, the present invention relates to a compound of Formula (I) as described herein for use in the treatment, alleviation and/or prevention of hypertension.

In one aspect, the present invention relates to a compound of Formula (I) as described herein for use in the treatment, alleviation and/or prevention of inherited hypertension.

In one aspect, the present invention relates to a method for treating and/or preventing hypertension, the method comprising administering a compound of Formula (I) or a pharmaceutically acceptable salt thereof, to a subject in need thereof.

Preferably, the subject is a mammal, such as a human. In some embodiments, the subject is suffering from hypertension.

In some embodiments, the subject is having, is suspected of having, or at risk of developing hypertension. In some embodiments, the subject is a human subject having, suspected of having, or at risk of developing hypertension.

In one aspect, the present invention concerns a compound of Formula (I), a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof, for use in the treatment of hypertension.

In one aspect, the present invention concerns a method for treatment of hypertension, comprising administering a compound of Formula (I), a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof, to a subject in need thereof.

In one aspect, the present invention concerns the use of a compound of Formula (I), a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof, for the manufacture of a medicament for the treatment of hypertension.

5 ***Treatment of cancer***

WNK1 inhibitors have been demonstrated to be effectful in the treatment or prevention of various diseases and disorders associated with increased WNK1 activity, including cancer. Being ligands for WNK1, the compounds of Formula (I) are of use in the treatment, prevention, and/or alleviation of different types of cancer, including breast
10 cancer, colon cancer, pancreatic cancer such as pancreatic ductal adenocarcinoma and blood cancers, such as leukemia, including acute myeloid leukemia, lymphoma and myeloma, including multiple myeloma.

In one aspect, the present invention relates to a compound of Formula (I) as described
15 herein for use in the treatment, alleviation and/or prevention of cancer.

In one aspect, the present invention relates to a method for treating and/or preventing cancer the method comprising administering a compound of Formula (I) or a pharmaceutically acceptable salt thereof, to a subject in need thereof.
20

Preferably, the subject is a mammal, such as a human. In some embodiments, the subject is suffering from cancer.

In one aspect, the present invention concerns a compound of Formula (I), a
25 pharmaceutically acceptable salt thereof or a pharmaceutical composition thereof, for use in the treatment of cancer.

In one aspect, the present invention concerns a method for treatment of cancer, comprising administering a compound of Formula (I), a pharmaceutically acceptable salt thereof or a pharmaceutical composition thereof, to a subject in need thereof.
30

In one aspect, the present invention concerns the use of a compound of Formula (I), a pharmaceutically acceptable salt thereof or a pharmaceutical composition thereof, for the manufacture of a medicament for the treatment of cancer.
35

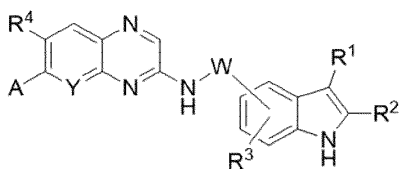
In one embodiment, the cancer is selected from the group consisting of Adenoid cystic carcinoma, Anal cancer, Appendix cancer and PMP, Bile duct cancer (cholangiocarcinoma), Bladder cancer, Blood cancer, Bone cancer (Primary), Bone cancer (Secondary), Bowel cancer, Brain tumours, Breast cancer, Cancer of the
 5 uterus, Cancer of unknown primary, Cervical cancer, Connective tissue cancer, Endocrine cancer, Gall bladder (bile duct) cancer, Head, neck and throat cancers, Kaposi sarcoma, Kidney cancer, Leukaemia, Liver cancer (Primary), Liver cancer (Secondary), Lung cancer, Lymphoma, Melanoma, Mesothelioma, Myeloma, Neuroendocrine tumours (NETs), Ocular (uveal) melanoma, Ovarian cancer,
 10 Pancreatic cancer, Penile cancer, Peritoneal cancer, Prostate cancer, Skin cancer, Small bowel cancer, Soft tissue sarcoma, Stomach and oesophageal cancers, Testicular cancer, Thymus cancer, Thyroid cancer, Upper tract urothelial cancer, Vaginal cancer and Vulvar cancer.

15 In one embodiment, the cancer is selected from the group consisting of Acute Myeloid Leukemia (LAML), Adrenocortical carcinoma (ACC), Bladder Urothelial Carcinoma (BLCA), Brain Lower Grade Glioma (LGG), Breast invasive carcinoma (BRCA), Cervical squamous cell carcinoma and endocervical adenocarcinoma (CESC), Cholangiocarcinoma (CHOL), Chronic Myelogenous Leukemia (LCML), Colon
 20 adenocarcinoma (COAD), Esophageal carcinoma (ESCA), Glioblastoma multiforme (GBM), Head and Neck squamous cell carcinoma (HNSC), Kidney Chromophobe (KICH), Kidney renal clear cell carcinoma (KIRC), Kidney renal papillary cell carcinoma (KIRP), Liver hepatocellular carcinoma (LIHC), Lung adenocarcinoma (LUAD), Lung squamous cell carcinoma (LUSC), Lymphoid Neoplasm Diffuse Large B-cell
 25 Lymphoma (DLBC), Mesothelioma (MESO), Ovarian serous cystadenocarcinoma (OV), Pancreatic adenocarcinoma (PAAD), Pheochromocytoma and Paraganglioma (PCPG), Prostate adenocarcinoma (PRAD), Rectum adenocarcinoma (READ), Sarcoma (SARC), Skin Cutaneous Melanoma (SKCM), Stomach adenocarcinoma (STAD), Testicular Germ Cell Tumors (TGCT), Thymoma (THYM), Thyroid carcinoma
 30 (THCA), Uterine Carcinosarcoma (UCS), Uterine Corpus Endometrial Carcinoma (UCEC), and Uveal Melanoma (UVM).

In one embodiment, the cancer is selected from the group consisting of leukemia, including acute myeloid leukemia, lymphoma and myeloma, including multiple
 35 myeloma.

Items

1. A compound of formula (I):



Formula (I)

5 wherein

Y is C(H) or N;

W is C(H)₂ or C(D)₂;

R¹ is H, C₁₋₃ alkyl or cyclopropyl

R² is H; C₁₋₃ alkyl optionally substituted with OH; or C₃₋₅ cycloalkyl;

10 R³ is H; C₁₋₃ alkyl optionally substituted with OH; -OC₁₋₃ alkyl optionally substituted with one or more F; -C(O)NHCH₃; -NH₂; -N(H)(CH₃); -N(CH₃)₂; or halogen;

R⁴ is H, C₁₋₄ alkyl, or C₃₋₅ cycloalkyl;

15 A is selected from the group consisting of H, C₁₋₃ alkoxy, CF₃, and a group of formula (II):



Formula (II)

wherein

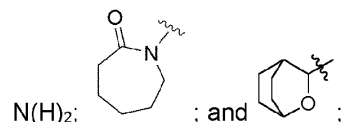
X is C(H) or N;

20 R⁶ is H or C₁₋₄ alkyl; and

R⁵ is selected from the group consisting of C₁₋₆ alkyl optionally substituted with one or more, identical or different, substituents R⁷, wherein one or more methylene(s) of said C₁₋₆ alkyl is optionally and individually replaced with -O- or C=O; C₃₋₆ cycloalkyl optionally substituted with one or more, identical or different, substituents R⁷; and tetrahydropyranyl;

25 wherein two R⁷ are optionally linked together to form a ring together with the intervening atom(s);

R^7 is individually selected from C_{1-3} alkoxy optionally substituted with one or more F; -OH; -O-benzyl; C_{1-3} alkyl optionally substituted with OH; $N(CH_3)_2$;



or when two R^7 are linked together to form a ring, then said two R^7 are individually selected from C_{1-2} alkanediyl optionally substituted with one or two substituents selected from F and OH, and one of the methylene of said C_{1-2} alkanediyl is optionally replaced with -O-;

or

R^5 and R^6 are linked together to form a ring and

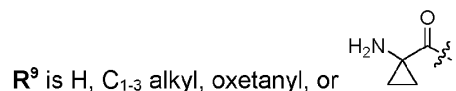
R^5 is a bond or C_{1-5} alkanediyl optionally substituted with one or more, identical or different, substituents R^8 , and one methylene of the C_{1-5} alkanediyl is optionally replaced with -O- or $N(R^9)$; and

R^6 is a bond or C_{1-5} alkanediyl optionally substituted with one or more, identical or different, substituents R^8 , and one methylene of the C_{1-5} alkanediyl is optionally replaced with -O- or $N(R^9)$;

wherein two R^8 are optionally linked together to form a ring together with the intervening atom(s);

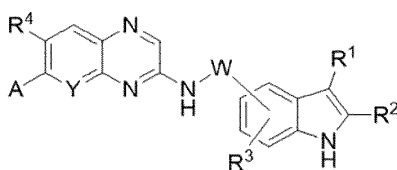
R^8 is individually selected from C_{1-3} alkyl optionally substituted with OH; -OH; F; $N(H)_2$; and -OC $_{1-3}$ alkyl optionally substituted with one or more F;

or when two R^8 are linked together to form a ring, then said two R^8 are individually selected from C_{1-3} alkanediyl optionally substituted with one or two substituents selected from F OH, and NH_2 , and one or two methylene(s) of said C_{1-3} alkanediyl is optionally and individually replaced with -O-, -N(H)- or -N(CH $_3$)-; and



or a pharmaceutically acceptable salt thereof.

2. A compound of formula (I):



Formula (I)

wherein

Y is C(H) or N;

5 W is C(H)₂ or C(D)₂;

R¹ is H, C₁₋₃ alkyl or cyclopropyl

R² is H; C₁₋₃ alkyl optionally substituted with OH; or C₃₋₅ cycloalkyl;

10 R³ is H; C₁₋₃ alkyl optionally substituted with OH; -OC₁₋₃ alkyl optionally substituted with one or more F; -C(O)NHCH₃; -NH₂; -N(H)(CH₃); -N(CH₃)₂; or halogen;

R⁴ is H, C₁₋₄ alkyl, or C₃₋₅ cycloalkyl;

A is selected from the group consisting of H, C₁₋₃ alkoxy, CF₃, and a group of formula (II):



15

Formula (II)

wherein

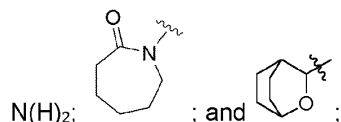
X is C(H) or N;

R⁶ is H or C₁₋₄ alkyl; and

20 R⁵ is selected from the group consisting of C₁₋₆ alkyl optionally substituted with one or more, identical or different, substituents R⁷, wherein one or more methylene(s) of said C₁₋₆ alkyl is optionally and individually replaced with -O- or C=O; C₃₋₆ cycloalkyl optionally substituted with one or more, identical or different, substituents R⁷; and tetrahydropyranyl;

25 wherein two R⁷ are optionally linked together to form a ring together with the intervening atom(s);

R^7 is individually selected from C_{1-3} alkoxy optionally substituted with one or more F; -OH; -O-benzyl; C_{1-3} alkyl optionally substituted with OH; $N(CH_3)_2$;



or when two R^7 are linked together to form a ring, then said two R^7 are individually selected from C_{1-2} alkanediyl optionally substituted with one or two substituents selected from F and OH, and one of the methylene of said C_{1-2} alkanediyl is optionally replaced with -O-;

or

R^5 and R^6 are linked together to form a ring and

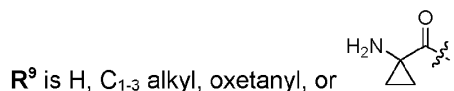
R^5 is a bond or C_{1-5} alkanediyl optionally substituted with one or more, identical or different, substituents R^8 , and one methylene of the C_{1-5} alkanediyl is optionally replaced with -O- or $N(R^9)$; and

R^6 is a bond or C_{1-5} alkanediyl optionally substituted with one or more, identical or different, substituents R^8 , and one methylene of the C_{1-5} alkanediyl is optionally replaced with -O- or $N(R^9)$;

wherein two R^8 are optionally linked together to form a ring together with the intervening atom(s);

R^8 is individually selected from C_{1-3} alkyl optionally substituted with OH; -OH; F; $N(H)_2$; and -OC $_{1-3}$ alkyl optionally substituted with one or more F;

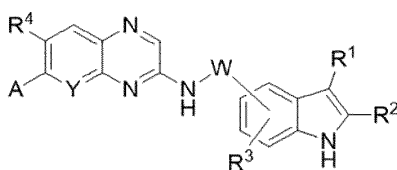
or when two R^8 are linked together to form a ring, then said two R^8 are individually selected from C_{1-3} alkanediyl optionally substituted with one or two substituents selected from F, OH, and NH_2 , and one or two methylene(s) of said C_{1-3} alkanediyl is optionally and individually replaced with -O-, -N(H)- or -N(CH $_3$)-; and



or a pharmaceutically acceptable salt thereof,

with the proviso that the compound is not N-[(2,3,5-Trimethyl-1H-indol-7-yl)methyl]-2-quinoxalinamine.

3. A compound of formula (I):



Formula (I)

wherein

Y is C(H) or N;

5 W is C(H)₂ or C(D)₂;

R¹ is H, C₁₋₃ alkyl or cyclopropyl

R² is H; C₁₋₃ alkyl optionally substituted with OH; or C₃₋₅ cycloalkyl;

R³ is H; C₁₋₃ alkyl optionally substituted with OH; -OC₁₋₃ alkyl optionally substituted with one or more F; -C(O)NHCH₃; -NH₂; -N(H)(CH₃); -N(CH₃)₂; or
10 halogen;

R⁴ is H, C₁₋₄ alkyl, or C₃₋₅ cycloalkyl;

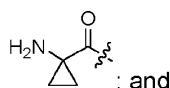
A is piperidinyl, pyrrolidinyl, azetidinyl, piperazinyl, or morpholinyl, wherein said piperidinyl, pyrrolidinyl, or azetidinyl, is optionally substituted with one or more individually selected R¹⁸, wherein two R¹⁸ are optionally linked together to form
15 a ring together with the intervening atom(s); wherein said piperazinyl is optionally substituted with R¹⁴; and wherein said morpholinyl is optionally substituted with one or more, identical or different, substituents R¹⁹;

R¹⁸ is individually selected from C₁₋₃ alkyl optionally substituted with OH; -OH; F; N(H)₂; and -OC₁₋₃ alkyl optionally substituted with one or more F,

20 or when two R¹⁸ are linked together to form a ring, then said two R¹⁸ are individually selected from C₁₋₃ alkanediyl optionally substituted with one or two substituents selected from F, OH, and NH₂, and one or two methylene(s) of said C₁₋₃ alkanediyl is optionally and individually replaced with -O-, -N(H)- or -N(CH₃)-;

25

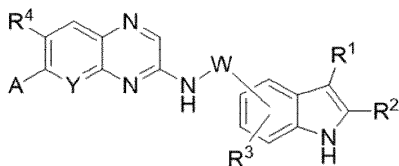
R¹⁴ is C₁₋₃ alkyl, oxetanyl or



; and

R¹⁹ is individually selected from C₁₋₃ alkyl and C₁₋₃ alkyl substituted with OH.

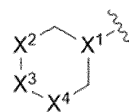
4. A compound of formula (I):



Formula (I)

wherein

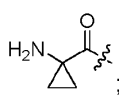
- 5 Y is C(H) or N;
W is C(H)₂ or C(D)₂;
R¹ is H, C₁₋₃ alkyl or cyclopropyl
R² is H; C₁₋₃ alkyl optionally substituted with OH; or C₃₋₅ cycloalkyl;
R³ is H; C₁₋₃ alkyl optionally substituted with OH; -OC₁₋₃ alkyl optionally
10 substituted with one or more F; -C(O)NHCH₃; -NH₂; -N(H)(CH₃); -N(CH₃)₂; or
halogen;
R⁴ is H, C₁₋₄ alkyl, or C₃₋₅ cycloalkyl;
A is of Formula (III):



Formula (III)

wherein

- X¹ is N or C(H);
X² is C(R¹⁰)(R¹¹) or absent;
R¹⁰ is H or C₁₋₃ alkyl;
20 R¹¹ is H or C₁₋₃ alkyl;
X³ is C(R¹²)(R¹³), O or N(R¹⁴);
R¹² is H, OH, NH₂ or C₁₋₃ alkyl optionally substituted with OH; and R¹³ is H or C₁₋₃ alkyl optionally substituted with OH; or
R¹² and R¹³ are linked together to form a ring together with the intervening
25 atom, and R¹²-R¹³ is C₃₋₅ alkanediyl wherein one or two methylenes of said
alkanediyl is optionally replaced with O, C(H)(NH₂) or N(R¹⁷);
R¹⁷ is H or C₁₋₃ alkyl;

- R¹⁴ is H, C₁₋₃ alkyl, oxetanyl or 

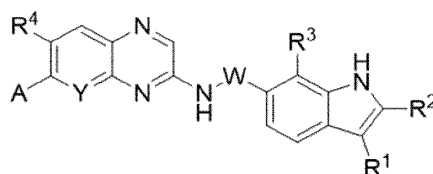
X^4 is $C(R^{15})(R^{16})$ or absent;

R^{15} is H; OH; C_{1-3} alkyl optionally substituted with OH; or OC_{1-3} alkyl optionally substituted with one or more F; and

R^{16} is H.

5

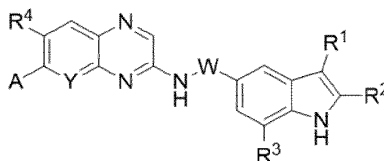
5. The compound according to items 1 to 4, wherein the compound is of formula (Ia):



Formula (Ia)

10

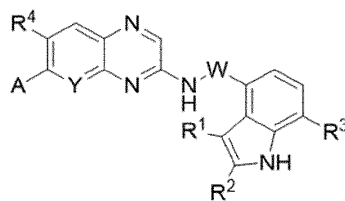
6. The compound according to items 1 to 4, wherein the compound is of formula (Ib):



Formula (Ib)

15

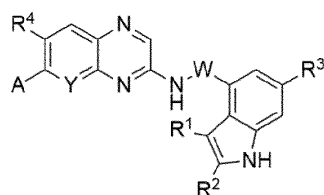
7. The compound according to items 1 to 4, wherein the compound is of formula (Ic):



Formula (Ic)

20

8. The compound according to items 1 to 4, wherein the compound is of formula (Id):



Formula (Id)

9. The compound according to anyone of the preceding items, wherein Y is C(H).
10. The compound according to anyone of the preceding items, wherein Y is N.
- 5 11. The compound according to anyone of the preceding items, wherein W is C(H)₂.
12. The compound according to anyone of the preceding items, wherein W is C(D)₂.
13. The compound according to anyone of the preceding items, wherein R¹ is H.
- 10 14. The compound according to anyone of the preceding items, wherein R¹ is C₁₋₃ alkyl.
15. The compound according to anyone of the preceding items, wherein R¹ is methyl.
- 15 16. The compound according to anyone of the preceding items, wherein R¹ is isopropyl.
17. The compound according to anyone of the preceding items, wherein R¹ is cyclopropyl.
18. The compound according to anyone of the preceding items, wherein R² is H.
- 20 19. The compound according to anyone of the preceding items, wherein R² is C₁₋₃ alkyl.
20. The compound according to anyone of the preceding items, wherein R² is methyl.
21. The compound according to anyone of the preceding items, wherein R² is C₁₋₃ alkyl substituted with OH.
- 25 22. The compound according to anyone of the preceding items, wherein R² is CH₂OH.
23. The compound according to anyone of the preceding items, wherein R² is C₃₋₅ cycloalkyl.
- 30 24. The compound according to anyone of the preceding items, wherein R² is cyclopropyl.

25. The compound according to anyone of the preceding items, wherein R^3 is H.
26. The compound according to anyone of the preceding items, wherein R^3 is C_{1-3} alkyl.
- 5 27. The compound according to anyone of the preceding items, wherein R^3 is methyl.
28. The compound according to anyone of the preceding items, wherein R^3 is C_{1-3} alkyl substituted with OH.
29. The compound according to anyone of the preceding items, wherein R^3 is
10 $-CH_2OH$.
30. The compound according to anyone of the preceding items, wherein R^3 is $-OC_{1-3}$ alkyl.
31. The compound according to anyone of the preceding items, wherein R^3 is methoxy.
- 15 32. The compound according to anyone of the preceding items, wherein R^3 is $-OC_{1-3}$ alkyl substituted with one or more F.
33. The compound according to anyone of the preceding items, wherein R^3 is $-OCHF_2$.
34. The compound according to anyone of the preceding items, wherein R^3 is
20 $-C(O)NHCH_3$.
35. The compound according to anyone of the preceding items, wherein R^3 is $-NH_2$.
36. The compound according to anyone of the preceding items, wherein R^3 is $-N(H)(CH_3)$.
- 25 37. The compound according to anyone of the preceding items, wherein R^3 is $-N(CH_3)_2$.
38. The compound according to anyone of the preceding items, wherein R^3 is halogen.
39. The compound according to anyone of the preceding items, wherein R^3 is Cl.
- 30 40. The compound according to anyone of the preceding items, wherein R^1 is H, and R^2 is H.
41. The compound according to anyone of the preceding items, wherein R^1 is CH_3 , and R^2 is H.

42. The compound according to anyone of the preceding items, wherein R^1 is H, R^2 is H, and R^3 is H.
43. The compound according to anyone of the preceding items, wherein R^1 is H, R^2 is CH_3 , and R^3 is H.
- 5 44. The compound according to anyone of the preceding items, wherein R^1 is H, R^2 is cyclopropyl, and R^3 is H.
45. The compound according to anyone of the preceding items, wherein R^1 is H, R^2 is CH_2OH , and R^3 is H.
46. The compound according to anyone of the preceding items, wherein R^1 is CH_3 ,
10 R^2 is H, and R^3 is H.
47. The compound according to anyone of the preceding items, wherein R^1 is H, R^2 is H, and R^3 is NH_2 .
48. The compound according to anyone of the preceding items, wherein the compound is of Formula (Id) and R^1 is H, R^2 is H, and R^3 is NH_2 .
- 15 49. The compound according to anyone of the preceding items, wherein R^1 is H, R^2 is H, and R^3 is $N(CH_3)_2$.
50. The compound according to anyone of the preceding items, wherein the compound is of Formula (Ic) and R^1 is H, R^2 is H, and R^3 is $N(CH_3)_2$.
51. The compound according to anyone of the preceding items, wherein R^1 is H, R^2 is H, and R^3 is Cl.
20
52. The compound according to anyone of the preceding items, wherein the compound is of Formula (Ic) and R^1 is H, R^2 is H, and R^3 is Cl.
53. The compound according to anyone of the preceding items, wherein R^1 is CH_3 , R^2 is H, and R^3 is CH_2OH .
- 25 54. The compound according to anyone of the preceding items, wherein the compound is of Formula (Ic) and R^1 is CH_3 , R^2 is H, and R^3 is CH_2OH .
55. The compound according to anyone of the preceding items, wherein R^1 is isopropyl, R^2 is H, and R^3 is OCH_3 .
56. The compound according to anyone of the preceding items, wherein the
30 compound is of Formula (Ic) and R^1 is isopropyl, R^2 is H, and R^3 is OCH_3 .
57. The compound according to anyone of the preceding items, wherein R^1 is CH_3 , R^2 is H, and R^3 is OCH_3 .
58. The compound according to anyone of the preceding items, wherein the compound is of Formula (Ic) and R^1 is CH_3 , R^2 is H, and R^3 is OCH_3 .

59. The compound according to anyone of the preceding items, wherein R^1 is H, R^2 is H, and R^3 is OCH_3 .
60. The compound according to anyone of the preceding items, wherein the compound is of Formula (Ic) and R^1 is H, R^2 is H, and R^3 is OCH_3 .
- 5 61. The compound according to anyone of the preceding items, wherein R^1 is CH_3 , R^2 is H, and R^3 is $C(O)NHCH_3$.
62. The compound according to anyone of the preceding items, wherein the compound is of Formula (Ic) and R^1 is CH_3 , R^2 is H, and R^3 is $C(O)NHCH_3$.
63. The compound according to anyone of the preceding items, wherein R^1 is CH_3 ,
10 R^2 is H, and R^3 is CHF_2 .
64. The compound according to anyone of the preceding items, wherein the compound is of Formula (Ic) and R^1 is CH_3 , R^2 is H, and R^3 is CHF_2 .
65. The compound according to anyone of the preceding items, wherein R^4 is H.
- 15 66. The compound according to anyone of the preceding items, wherein R^4 is C_{1-4} alkyl.
67. The compound according to anyone of the preceding items, wherein R^4 is methyl.
68. The compound according to anyone of the preceding items, wherein R^4 is C_{3-5}
20 cycloalkyl.
69. The compound according to anyone of the preceding items, wherein A is of Formula (II):

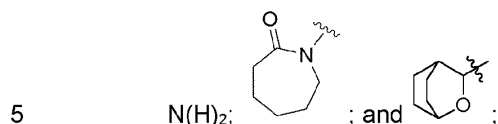


Formula (II)

- 25 wherein
X is N;
 R^6 is H or C_{1-4} alkyl; and
 R^5 is selected from the group consisting of C_{1-6} alkyl optionally substituted with one or more, identical or different, substituents R^7 , wherein one or more
30 methylene(s) of said C_{1-6} alkyl is optionally and individually replaced with -O- or C=O; C_{3-6} cycloalkyl optionally substituted with one or more, identical or different, substituents R^7 ; and tetrahydropyranyl;

wherein two R^7 are optionally linked together to form a ring together with the intervening atom(s); and

R^7 is individually selected from C_{1-3} alkoxy optionally substituted with one or more F; -OH; -O-benzyl; C_{1-3} alkyl optionally substituted with OH; $N(CH_3)_2$;



or when two R^7 are linked together to form a ring, then said two R^7 are individually selected from C_{1-2} alkanediyl optionally substituted with one or two substituents selected from F and OH, and one of the methylene of said C_{1-2} alkanediyl is optionally replaced with -O-.

10 70. The compound according to anyone of the preceding items, wherein R^6 is H.

71. The compound according to anyone of the preceding items, wherein R^6 is C_{1-4} alkyl.

72. The compound according to anyone of the preceding items, wherein R^6 is CH_3 .

15 73. The compound according to anyone of the preceding items, wherein R^5 is C_{1-6} alkyl substituted with one or more, identical or different, substituents R^7 .

74. The compound according to anyone of the preceding items, wherein R^5 is C_1 alkyl substituted with one or more, identical or different, substituents R^7 .

75. The compound according to anyone of the preceding items, wherein R^5 is C_2 alkyl substituted with one or more, identical or different, substituents R^7 .

20 76. The compound according to anyone of the preceding items, wherein R^5 is C_3 alkyl substituted with one or more, identical or different, substituents R^7 .

77. The compound according to anyone of the preceding items, wherein R^5 is C_5 alkyl, such as neopentanedyl, substituted with one or more, identical or different, substituents R^7 .

25 78. The compound according to anyone of the preceding items, wherein R^5 is C_{3-6} cycloalkyl optionally substituted with one or more, identical or different, substituents R^7 .

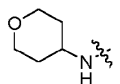
79. The compound according to anyone of the preceding items, wherein R^5 is C_4 cycloalkyl substituted with one or more, identical or different, substituents R^7 .

30 80. The compound according to anyone of the preceding items, wherein R^5 is C_6 cycloalkyl substituted with one or more, identical or different, substituents R^7 .

81. The compound according to anyone of the preceding items, wherein R^5 is C_6 cycloalkyl.

82. The compound according to anyone of the preceding items, wherein R^5 is tetrahydropyranyl.

83. The compound according to any one of the preceding items, wherein A is



5 84. The compound according to anyone of the preceding items, wherein R^7 is OH.

85. The compound according to anyone of the preceding items, wherein R^7 is $N(H)_2$.

86. The compound according to anyone of the preceding items, wherein R^7 is $N(CH_3)_2$.

10 87. The compound according to anyone of the preceding items, wherein R^7 is C_{1-3} alkoxy.

88. The compound according to anyone of the preceding items, wherein R^7 is OCH_3 .

15 89. The compound according to anyone of the preceding items, wherein R^7 is C_{1-3} alkoxy substituted with one or more F.

90. The compound according to anyone of the preceding items, wherein R^7 is $OCHF_2$.

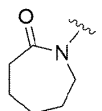
91. The compound according to anyone of the preceding items, wherein R^7 is C_{1-3} alkyl.

20 92. The compound according to anyone of the preceding items, wherein R^7 is CH_3 .

93. The compound according to anyone of the preceding items, wherein R^7 is C_{1-3} alkyl substituted with OH.

94. The compound according to anyone of the preceding items, wherein R^7 is CH_2OH .

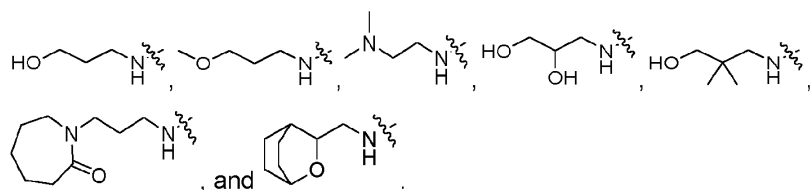
25 95. The compound according to anyone of the preceding items, wherein R^7 is



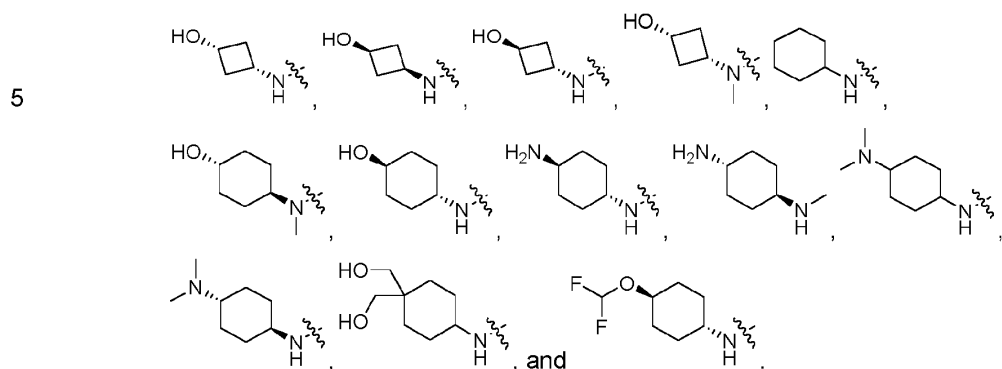
96. The compound according to anyone of the preceding items, wherein R^7 is



30 97. The compound according to anyone of the preceding items, wherein A is selected from the group consisting of:



98. The compound according to anyone of the preceding items, wherein A is selected from the group consisting of:

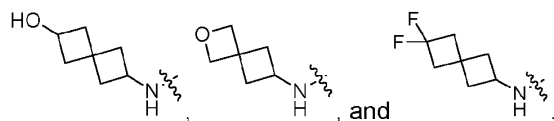


99. The compound according to anyone of the preceding items, wherein two R⁷ are linked together to form a ring, and said two R⁷ are individually selected from C₁₋₂ alkanediyl optionally substituted with one or two substituents selected from F and OH, and one of the methylene of said C₁₋₂ alkanediyl is optionally replaced with -O-.

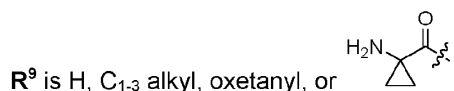
100. The compound according to anyone of the preceding items, wherein two R⁷ are linked together to form a ring, and said two R⁷ are individually selected from C₁₋₂ alkanediyl optionally substituted with one or two substituents selected from F and OH.

101. The compound according to anyone of the preceding items, wherein two R⁷ are linked together to form a ring, and said two R⁷ are individually selected from C₁₋₂ alkanediyl, and one of the methylene of said C₁₋₂ alkanediyl is optionally replaced with -O-.

102. The compound according to anyone of the preceding items, wherein A is selected from the group consisting of:



103. The compound according to any one of the preceding items, wherein R^5 and R^6 are linked together to form a ring and
 R^5 is a bond or C_{1-5} alkanediyl optionally substituted with one or more, identical or different, substituents R^8 , and one methylene of the C_{1-5} alkanediyl is optionally replaced with -O- or $N(R^9)$; and
 R^6 is a bond or C_{1-5} alkanediyl optionally substituted with one or more, identical or different, substituents R^8 , and one methylene of the C_{1-5} alkanediyl is optionally replaced with -O- or $N(R^9)$;
 wherein two R^8 are optionally linked together to form a ring together with the intervening atom(s);
 R^8 is individually selected from C_{1-3} alkyl optionally substituted with OH; -OH; F; $N(H)_2$; and -OC $_{1-3}$ alkyl optionally substituted with one or more F;
 or when two R^8 are linked together to form a ring, then said two R^8 are individually selected from C_{1-3} alkanediyl optionally substituted with one or two substituents selected from F, OH, and NH_2 , and one or two methylene(s) of said C_{1-3} alkanediyl is optionally and individually replaced with -O-, -N(H)- or -N(CH $_3$)-; and



104. The compound according to anyone of the preceding items, wherein A is piperidinyl optionally substituted with one or more individually selected R^{18} , wherein two R^{18} are optionally linked together to form a ring together with the intervening atom(s);
 R^{18} is individually selected from C_{1-3} alkyl optionally substituted with OH; -OH; F; $N(H)_2$; and -OC $_{1-3}$ alkyl optionally substituted with one or more F;
 or when two R^{18} are linked together to form a ring, then said two R^{18} are individually selected from C_{1-3} alkanediyl optionally substituted with one or two substituents selected from F, OH, and NH_2 , and one or two methylene(s) of said C_{1-3} alkanediyl is optionally and individually replaced with -O-, -N(H)- or -N(CH $_3$)-.
105. The compound according to anyone of the preceding items, wherein A is piperidinyl optionally substituted with one R^{18} , selected from C_{1-3} alkyl optionally

substituted with OH; -OH; F; N(H)₂; and -OC₁₋₃ alkyl optionally substituted with one or more F.

5 106. The compound according to anyone of the preceding items, wherein A is piperidinyl optionally substituted with two R¹⁸, selected from C₁₋₃ alkyl optionally substituted with OH; -OH; F; N(H)₂; and -OC₁₋₃ alkyl optionally substituted with one or more F.

10 107. The compound according to anyone of the preceding items, wherein the piperidinyl is attached to Formula (I) in position 1 of the piperidinyl.

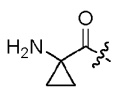
15 108. The compound according to anyone of the preceding items, wherein A is pyrrolidinyl optionally substituted with one or more individually selected R¹⁸, wherein two R¹⁸ are optionally linked together to form a ring together with the intervening atom(s);
R¹⁸ is individually selected from C₁₋₃ alkyl optionally substituted with OH; -OH; F; N(H)₂; and -OC₁₋₃ alkyl optionally substituted with one or more F;
or when two R¹⁸ are linked together to form a ring, then said two R¹⁸ are
20 individually selected from C₁₋₃ alkanediyl optionally substituted with one or two substituents selected from F, OH, and NH₂, and one or two methylene(s) of said C₁₋₃ alkanediyl is optionally and individually replaced with -O-, -N(H)- or -N(CH₃)-.

25 109. The compound according to anyone of the preceding items, wherein the pyrrolidinyl is attached to Formula (I) in position 1 of the pyrrolidinyl.

30 110. The compound according to anyone of the preceding items, wherein A is azetidiny optionally substituted with one or more individually selected R¹⁸, wherein two R¹⁸ are optionally linked together to form a ring together with the intervening atom(s);
R¹⁸ is individually selected from C₁₋₃ alkyl optionally substituted with OH; -OH; F; N(H)₂; and -OC₁₋₃ alkyl optionally substituted with one or more F;
or when two R¹⁸ are linked together to form a ring, then said two R¹⁸ are
35 individually selected from C₁₋₃ alkanediyl optionally substituted with one or two substituents selected from F, OH, and NH₂, and one or two methylene(s) of said C₁₋₃ alkanediyl is optionally and individually replaced with -O-, -N(H)- or -N(CH₃)-.

111. The compound according to anyone of the preceding items, wherein the azetidiny is attached to Formula (I) in position 1 of the azetidiny.

112. The compound according to anyone of the preceding items, wherein A is piperazinyl optionally substituted with R^{14} at position 4 of the piperazinyl, and

5 wherein R^{14} is C_{1-3} alkyl, oxetanyl or .

113. The compound according to anyone of the preceding items, wherein the piperazinyl is attached to Formula (I) in position 1 of the piperazinyl.

114. The compound according to anyone of the preceding items, wherein A is morpholinyl optionally substituted with one or more, identical or different, substituents R^{19} , wherein R^{19} is individually selected from C_{1-3} alkyl and C_{1-3} alkyl substituted with OH.

115. The compound according to anyone of the preceding items, wherein the morpholinyl is attached to Formula (I) in position 4 of the morpholinyl.

116. The compound according to anyone of the preceding items, wherein R^{18} is R^8 .

117. The compound according to anyone of the preceding items, wherein R^8 is individually selected from C_{1-3} alkyl optionally substituted with OH; -OH; -F; -N(H)₂; and -OC₁₋₃ alkyl optionally substituted with one or more F; or when two R^8 are linked together to form a ring, then said two R^8 are individually selected from C_{1-3} alkanediyl optionally substituted with one or two substituents selected from F and OH, and one or two methylene(s) of said C_{1-3} alkanediyl is optionally and individually replaced with -O-, -N(H)- or -N(CH₃)-.

118. The compound according to anyone of the preceding items, wherein R^8 is individually selected from C_{1-3} alkyl optionally substituted with OH; -OH; -F; -N(H)₂; and -OC₁₋₃ alkyl optionally substituted with one or more F.

119. The compound according to anyone of the preceding items, wherein two R^8 are linked together to form a ring, and said two R^8 are individually selected from C_{1-3} alkanediyl optionally substituted with one or two substituents selected from F, OH, and NH₂, and one or two methylene(s) of said C_{1-3} alkanediyl is optionally and individually replaced with -O-, -N(H)- or -N(CH₃)-.

120. The compound according to anyone of the preceding items, wherein R^8 is C_{1-3} alkyl.

121. The compound according to anyone of the preceding items, wherein R^8 is -CH₃.

122. The compound according to anyone of the preceding items, wherein R^8 is C_{1-3} alkyl substituted with OH.

123. The compound according to anyone of the preceding items, wherein R^8 is $-CH_2OH$.

5 124. The compound according to anyone of the preceding items, wherein R^8 is $-OH$.

125. The compound according to anyone of the preceding items, wherein R^8 is $N(H)_2$.

10 126. The compound according to anyone of the preceding items, wherein R^8 is $-OC_{1-3}$ alkyl substituted with one or more F.

127. The compound according to anyone of the preceding items, wherein R^8 is $-OCHF_2$.

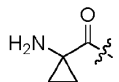
128. The compound according to any one of the preceding items, wherein R^{19} is R^9 .

15 129. The compound according to anyone of the preceding items, wherein R^9 is C_{1-3} alkyl.

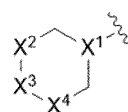
130. The compound according to anyone of the preceding items, wherein R^9 is $-CH_3$.

20 131. The compound according to anyone of the preceding items, wherein R^9 is oxetanyl.

132. The compound according to anyone of the preceding items, wherein R^9 is



133. The compound according to anyone of the preceding items, wherein A is of Formula (III):



Formula (III)

wherein

X^1 is N or C(H);

X^2 is $C(R^{10})(R^{11})$ or absent;

30 R^{10} is H or C_{1-3} alkyl;

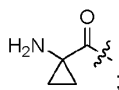
R^{11} is H or C_{1-3} alkyl;

X^3 is $C(R^{12})(R^{13})$, O or $N(R^{14})$;

R^{12} is H, OH, NH_2 or C_{1-3} alkyl optionally substituted with OH; and R^{13} is H or C_{1-3} alkyl optionally substituted with OH; or

5 R^{12} and R^{13} are linked together to form a ring together with the intervening atom, and $R^{12}-R^{13}$ is C_{3-5} alkanediyl wherein one or two methylenes of said alkanediyl is optionally replaced with O, $C(H)(NH_2)$ or $N(R^{17})$;

R^{17} is H or C_{1-3} alkyl;

R^{14} is H, C_{1-3} alkyl, oxetanyl or ;

X^4 is $C(R^{15})(R^{16})$ or absent;

10 R^{15} is H; OH; C_{1-3} alkyl optionally substituted with OH; or OC_{1-3} alkyl optionally substituted with one or more F; and

R^{16} is H.

15 134. The compound according to anyone of the preceding items, wherein X^1 is N, X^2 is $C(R^{10})(R^{11})$, X^3 is $C(R^{12})(R^{13})$, and X^4 is $C(R^{15})(R^{16})$.

135. The compound according to anyone of the preceding items, wherein X^1 is N, X^2 is absent, X^3 is $C(R^{12})(R^{13})$, and X^4 is $C(R^{15})(R^{16})$.

136. The compound according to anyone of the preceding items, wherein X^1 is N, X^2 is absent, X^3 is $C(R^{12})(R^{13})$, and X^4 is absent.

20 137. The compound according to anyone of the preceding items, wherein X^1 is N, X^2 is $C(R^{10})(R^{11})$, X^3 is O, and X^4 is $C(R^{15})(R^{16})$.

138. The compound according to anyone of the preceding items, wherein X^1 is N, X^2 is $C(R^{10})(R^{11})$, X^3 is $N(R^{14})$, and X^4 is $C(R^{15})(R^{16})$.

25 139. The compound according to anyone of the preceding items, wherein X^1 is N.

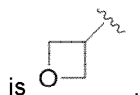
140. The compound according to anyone of the preceding items, wherein X^1 is $C(H)$.

30 141. The compound according to anyone of the preceding items, wherein X^2 is absent.

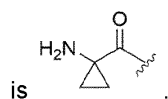
142. The compound according to anyone of the preceding items, wherein X^2 is $C(R^{10})(R^{11})$.

143. The compound according to anyone of the preceding items, wherein R^{10} is H.

144. The compound according to anyone of the preceding items, wherein R^{10} is C_{1-3} alkyl.
145. The compound according to anyone of the preceding items, wherein R^{10} is CH_3 .
- 5 146. The compound according to anyone of the preceding items, wherein R^{11} is H.
147. The compound according to anyone of the preceding items, wherein R^{11} is C_{1-3} alkyl.
148. The compound according to anyone of the preceding items, wherein R^{11} is CH_3 .
- 10 149. The compound according to anyone of the preceding items, wherein X^2 is $C(H)_2$.
150. The compound according to anyone of the preceding items, wherein X^2 is $C(H)(CH_3)$.
- 15 151. The compound according to anyone of the preceding items, wherein X^2 is $C(CH_3)_2$.
152. The compound according to anyone of the preceding items, wherein X^3 is O.
- 20 153. The compound according to anyone of the preceding items, wherein X^3 is $N(R^{14})$.
154. The compound according to anyone of the preceding items, wherein R^{14} is H.
155. The compound according to anyone of the preceding items, wherein R^{14} is C_{1-3} alkyl.
- 25 156. The compound according to anyone of the preceding items, wherein R^{14} is CH_3 .
157. The compound according to anyone of the preceding items, wherein R^{14} is oxetanyl.
- 30 158. The compound according to anyone of the preceding items, wherein R^{14}



159. The compound according to anyone of the preceding items, wherein R^{14}



160. The compound according to anyone of the preceding items, wherein X^3 is $N(H)$.

5 161. The compound according to anyone of the preceding items, wherein X^3 is $N(CH_3)$.

162. The compound according to anyone of the preceding items, wherein X^3 is $C(R^{12})(R^{13})$.

10 163. The compound according to anyone of the preceding items, wherein R^{12} is H .

164. The compound according to anyone of the preceding items, wherein R^{12} is OH .

165. The compound according to anyone of the preceding items, wherein R^{12} is NH_2 .

15 166. The compound according to anyone of the preceding items, wherein R^{12} is C_{1-3} alkyl.

167. The compound according to anyone of the preceding items, wherein R^{12} is C_{1-3} alkyl substituted with OH .

20 168. The compound according to anyone of the preceding items, wherein R^{12} is CH_2OH .

169. The compound according to anyone of the preceding items, wherein R^{13} is H .

170. The compound according to anyone of the preceding items, wherein R^{13} is C_{1-3} alkyl.

25 171. The compound according to anyone of the preceding items, wherein R^{13} is C_{1-3} alkyl substituted with OH .

172. The compound according to anyone of the preceding items, wherein R^{13} is CH_2OH .

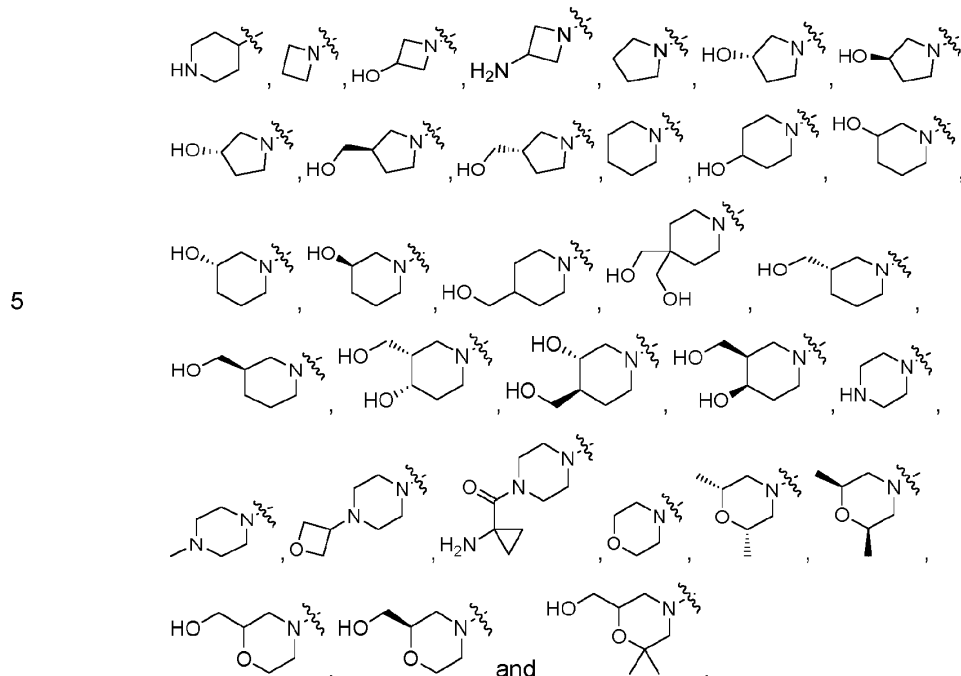
30 173. The compound according to anyone of the preceding items, wherein X^3 is $C(H)_2$.

174. The compound according to anyone of the preceding items, wherein X^3 is $C(H)(OH)$.

175. The compound according to anyone of the preceding items, wherein X^3 is $C(H)(CH_2OH)$.

176. The compound according to anyone of the preceding items, wherein X^3 is $C(CH_2OH)_2$.
177. The compound according to anyone of the preceding items, wherein X^4 is absent.
- 5 178. The compound according to anyone of the preceding items, wherein X^4 is $C(R^{15})(R^{16})$.
179. The compound according to anyone of the preceding items, wherein R^{15} is H.
180. The compound according to anyone of the preceding items, wherein R^{15} is OH.
- 10 181. The compound according to anyone of the preceding items, wherein R^{15} is C_{1-3} alkyl.
182. The compound according to anyone of the preceding items, wherein R^{15} is CH_3 .
- 15 183. The compound according to anyone of the preceding items, wherein R^{15} is C_{1-3} alkyl substituted with OH.
184. The compound according to anyone of the preceding items, wherein R^{15} is CH_2OH .
185. The compound according to anyone of the preceding items, wherein R^{15} is OC_{1-3} alkyl substituted with one or more F.
- 20 186. The compound according to anyone of the preceding items, wherein R^{15} is $OCHF_2$.
187. The compound according to anyone of the preceding items, wherein R^{16} is H.
- 25 188. The compound according to anyone of the preceding items, wherein X^4 is $C(H)_2$.
189. The compound according to anyone of the preceding items, wherein X^4 is $C(H)(CH_3)$.
190. The compound according to anyone of the preceding items, wherein X^4 is $C(H)(OH)$.
- 30 191. The compound according to anyone of the preceding items, wherein X^4 is $C(H)(CH_2OH)$.
192. The compound according to anyone of the preceding items, wherein X^4 is $C(H)(OCHF_2)$.

193. The compound according to anyone of the preceding items, wherein A is selected from the group consisting of:



10 194. The compound according to anyone of the preceding items, wherein X³ is C(R¹²)(R¹³) and R¹² and R¹³ are linked together to form a ring together with the intervening atom, wherein R¹²-R¹³ is C₃₋₅ alkanediyl wherein one or two methylenes of said alkanediyl is optionally replaced with O, C(H)(NH₂) or N(R¹⁷).

15 195. The compound according to anyone of the preceding items, wherein R¹⁷
 is H.

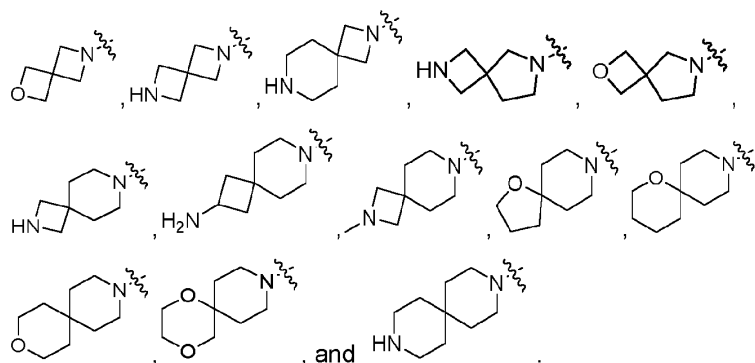
196. The compound according to anyone of the preceding items, wherein R¹⁷ is C₁₋₃ alkyl.

197. The compound according to anyone of the preceding items, wherein R¹⁷
is CH₃.

198. The compound according to anyone of the preceding items, wherein R¹²-R¹³ is -CH₂-N(CH₃)-CH₂-.

199. The compound according to anyone of the preceding items, wherein R¹²-R¹³ is -CH₂-N(H)-CH₂-.

200. The compound according to anyone of the preceding items, wherein R¹²-R¹³ is -CH₂-O-CH₂-.
201. The compound according to anyone of the preceding items, wherein R¹²-R¹³ is -CH₂-C(H)(NH₂)-CH₂-.
- 5 202. The compound according to anyone of the preceding items, wherein R¹²-R¹³ is -(CH₂)₃-O-.
203. The compound according to anyone of the preceding items, wherein R¹²-R¹³ is -(CH₂)₂-O-(CH₂)₂-.
204. The compound according to anyone of the preceding items, wherein R¹²-R¹³ is -(CH₂)-O-(CH₂)₃-.
- 10 205. The compound according to anyone of the preceding items, wherein R¹²-R¹³ is -(CH₂)₂-N(H)-(CH₂)₂-.
206. The compound according to anyone of the preceding items, wherein R¹²-R¹³ is -O-(CH₂)₂-O-(CH₂)₂-.
- 15 207. The compound according to anyone of the preceding items, wherein A is selected from the group consisting of:



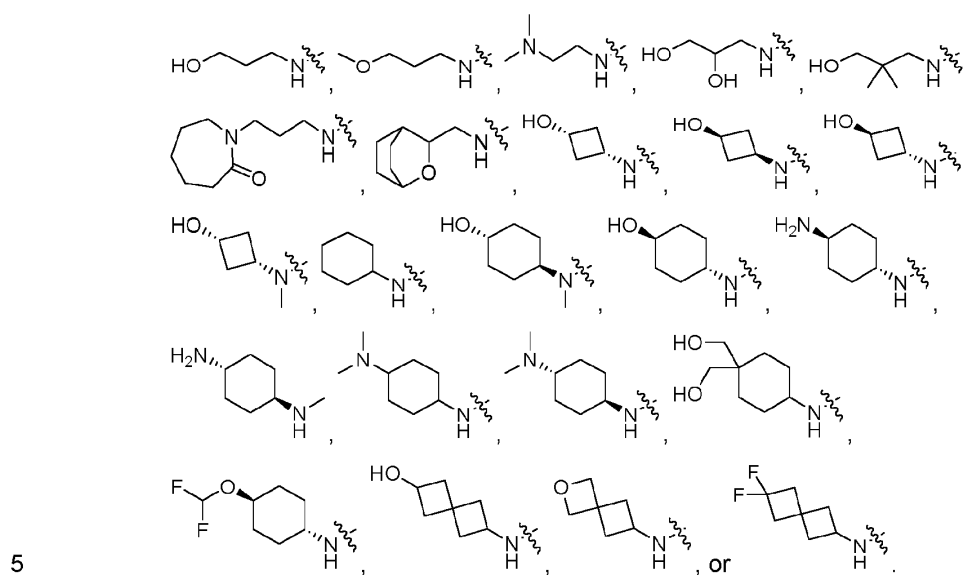
- 20
208. The compound according to anyone of the preceding items, wherein A is H.
209. The compound according to anyone of the preceding items, wherein A is C₁₋₃ alkoxy.
- 25
210. The compound according to anyone of the preceding items, wherein A is OCH₃.
211. The compound according to anyone of the preceding items, wherein A is CF₃.

212. The compound according to anyone of the preceding items, wherein A is C₁₋₃ alkyl.
213. The compound according to anyone of the preceding items, wherein A is CH₃.
- 5 214. The compound according to anyone of the preceding items, wherein A is CH₂CH₃.
215. The compound according to anyone of the preceding items, wherein A is C₃₋₅ cycloalkyl.
- 10 216. The compound according to anyone of the preceding items, wherein A is cyclopropyl.
217. The compound according to anyone of the preceding items, wherein A is tert-butyl.
- 15 218. The compound according to anyone of the preceding items, wherein
Y is N;
W is C(H)₂;
R¹ is H, CH₃, or isopropyl;
R² is H, CH₃, cyclopropyl, or CH₂OH;
20 R³ is H, CH₃, CH₂OH, NH₂, N(CH₃)₂, Cl, C(O)NHCH₃, OCHF₂, or OCH₃;
R⁴ is H or CH₃; and
A is H, CF₃ or of Formula (II):

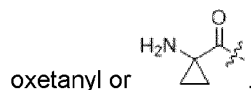


Formula (II).

- 25 219. The compound according to anyone of the preceding items, wherein
Y is N;
W is C(H)₂;
R¹ is H, CH₃, or isopropyl;
R² is H, CH₃, cyclopropyl, or CH₂OH;
30 R³ is H, CH₃, CH₂OH, NH₂, N(CH₃)₂, Cl, C(O)NHCH₃, OCHF₂, or OCH₃;
R⁴ is H or CH₃; and
A is H, CF₃,



220. The compound according to anyone of the preceding items, wherein A is piperidinyl, pyrrolidinyl, azetidiny, piperazinyl, wherein said piperidinyl, pyrrolidinyl, azetidiny, or piperazinyl is optionally substituted with one or more individually selected R^{18} , wherein R^{18} is $-CH_3$, $-CH_2OH$, $-OH$, $N(H)_2$, $OCHF_2$, $-F$,
- 10



221. The compound according to anyone of the preceding items, wherein A is piperidinyl, pyrrolidinyl, azetidiny or piperazinyl, wherein said piperidinyl, pyrrolidinyl, azetidiny, or piperazinyl is substituted with two or more R^{18} , wherein two R^{18} are linked together to form a ring together with the intervening atom(s), and wherein the two R^{18} linked together to form a ring are individually selected from C_{1-3} alkanediyl optionally substituted with one or two substituents selected from F , OH , and NH_2 , and wherein one or two methylene(s) of said C_{1-3} alkanediyl is optionally and individually replaced with $-O-$, $-N(H)-$ or $-N(CH_3)-$.
- 15
- 20

222. The compound according to anyone of the preceding items, wherein A is morpholinyl, wherein said morpholinyl optionally substituted with one or more, identical or different, substituents R^{19} , wherein R^{19} is $-CH_3$, or $-CH_2OH$.
- 25

223. The compound according to anyone of the preceding items, wherein

Y is N;

W is C(H)₂;

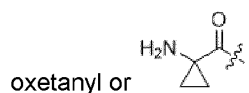
R¹ is H, CH₃, or isopropyl;

5 R² is H, CH₃, cyclopropyl, or CH₂OH;

R³ is H, CH₃, CH₂OH, NH₂, N(CH₃)₂, Cl, C(O)NHCH₃, OCHF₂, or OCH₃;

R⁴ is H or CH₃; and

10 A is piperidinyl, pyrrolidinyl, azetidiny, piperazinyl, wherein said piperidinyl, pyrrolidinyl, azetidiny, or piperazinyl is optionally substituted with one or more individually selected R¹⁸, wherein R¹⁸ is -CH₃, -CH₂OH, -OH, N(H)₂, OCHF₂, -F,



224. The compound according to anyone of the preceding items, wherein

Y is N;

15 W is C(H)₂;

R¹ is H, CH₃, or isopropyl;

R² is H, CH₃, cyclopropyl, or CH₂OH;

R³ is H, CH₃, CH₂OH, NH₂, N(CH₃)₂, Cl, C(O)NHCH₃, OCHF₂, or OCH₃;

R⁴ is H or CH₃; and

20 A is piperidinyl, pyrrolidinyl, azetidiny or piperazinyl, wherein said piperidinyl, pyrrolidinyl, azetidiny, or piperazinyl is substituted with two or more R¹⁸, wherein two R¹⁸ are linked together to form a ring together with the intervening atom(s), and wherein the two R¹⁸ linked together to form a ring are individually selected from C₁₋₃ alkanediyl optionally substituted with one or two substituents
25 selected from F, OH, and NH₂, and wherein one or two methylene(s) of said C₁₋₃ alkanediyl is optionally and individually replaced with -O-, -N(H)- or -N(CH₃)-.

225. The compound according to anyone of the preceding items, wherein

Y is N;

30 W is C(H)₂;

R¹ is H, CH₃, or isopropyl;

R² is H, CH₃, cyclopropyl, or CH₂OH;

R³ is H, CH₃, CH₂OH, NH₂, N(CH₃)₂, Cl, C(O)NHCH₃, OCHF₂, or OCH₃;

R⁴ is H or CH₃; and

A is morpholinyl, wherein said morpholinyl optionally substituted with one or more, identical or different, substituents R¹⁹, wherein R¹⁹ is -CH₃, or -CH₂OH.

5 226. The compound according to anyone of the preceding items, wherein

Y is N;

W is C(H)₂;

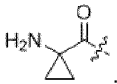
R¹ is H, CH₃, or isopropyl;

R² is H, CH₃, cyclopropyl, or CH₂OH;

10 R³ is H, CH₃, CH₂OH, NH₂, N(CH₃)₂, Cl, C(O)NHCH₃, OCHF₂, or OCH₃;

R⁴ is H or CH₃; and

A is piperidinyl, pyrrolidinyl, azetidiny, piperazinyl, wherein said piperidinyl, pyrrolidinyl, azetidiny, or piperazinyl is optionally substituted with one or more individually selected R¹⁸, wherein R¹⁸ is -CH₃, -CH₂OH, -OH, N(H)₂, OCHF₂, -F,

15 oxetanyl or .

227. The compound according to anyone of the preceding items, wherein

Y is N;

W is C(H)₂;

20 R¹ is H, CH₃, or isopropyl;

R² is H, CH₃, cyclopropyl, or CH₂OH;

R³ is H, CH₃, CH₂OH, NH₂, N(CH₃)₂, Cl, C(O)NHCH₃, OCHF₂, or OCH₃;

R⁴ is H or CH₃; and

25 A is piperidinyl, pyrrolidinyl, azetidiny or piperazinyl, wherein said piperidinyl, pyrrolidinyl, azetidiny, or piperazinyl is substituted with two or more R¹⁸, wherein two R¹⁸ are linked together to form a ring together with the intervening atom(s), and wherein the two R¹⁸ linked together to form a ring are individually selected from C₁₋₃ alkanediyl optionally substituted with one or two substituents selected from F, OH, and NH₂, and wherein one or two methylene(s) of said C₁₋₃ alkanediyl is optionally and individually replaced with -O-, -N(H)- or -N(CH₃)-.

30

228. The compound according to anyone of the preceding items, wherein

Y is N;

W is C(H)₂;

R^1 is H, CH_3 , or isopropyl;

R^2 is H, CH_3 , cyclopropyl, or CH_2OH ;

R^3 is H, CH_3 , CH_2OH , NH_2 , $N(CH_3)_2$, Cl, $C(O)NHCH_3$, $OCHF_2$, or OCH_3 ;

R^4 is H or CH_3 ; and

- 5 A is morpholinyl, wherein said morpholinyl optionally substituted with one or more, identical or different, substituents R^{19} , wherein R^{19} is $-CH_3$, or $-CH_2OH$.

229. The compound according to anyone of the preceding items, wherein

Y is N;

- 10 W is $C(H)_2$;

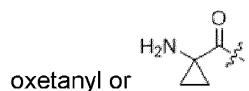
R^1 CH_3 ;

R^2 is H;

R^3 is H, CH_3 , $OCHF_2$, or OCH_3 ;

R^4 is H; and

- 15 A is piperidinyl, pyrrolidinyl, azetidiny, piperazinyl, wherein said piperidinyl, pyrrolidinyl, azetidiny, or piperazinyl is optionally substituted with one or more individually selected R^{18} , wherein R^{18} is $-CH_3$, $-CH_2OH$, $-OH$, $N(H)_2$, $OCHF_2$, $-F$,



- 20 230. The compound according to anyone of the preceding items, wherein

Y is N;

W is $C(H)_2$;

R^1 CH_3 ;

R^2 is H;

- 25 R^3 is H, CH_3 , $OCHF_2$, or OCH_3 ;

R^4 is H; and

- A is piperidinyl, pyrrolidinyl, azetidiny or piperazinyl, wherein said piperidinyl, pyrrolidinyl, azetidiny, or piperazinyl is substituted with two or more R^{18} , wherein two R^{18} are linked together to form a ring together with the intervening atom(s), and wherein the two R^{18} linked together to form a ring are individually selected from C_{1-3} alkanediyl optionally substituted with one or two substituents selected from F, OH, and NH_2 , and wherein one or two methylene(s) of said C_{1-3} alkanediyl is optionally and individually replaced with $-O-$, $-N(H)-$ or $-N(CH_3)-$.
- 30

231. The compound according to anyone of the preceding items, wherein
- Y is N;
W is C(H)₂;
R¹ CH₃;
5 R² is H;
R³ is H, CH₃, OCHF₂, or OCH₃;
R⁴ is H; and
A is morpholinyl, wherein said morpholinyl optionally substituted with one or
more, identical or different, substituents R¹⁹, wherein R¹⁹ is -CH₃, or -CH₂OH.
10
232. The compound according to anyone of the preceding items, wherein the
compound is of Formula (Ia);
Y is N;
W is C(H)₂;
15 R¹ CH₃;
R² is H;
R³ is H, CH₃, OCHF₂, or OCH₃; and
R⁴ is H.
- 20 233. The compound according to anyone of the preceding items, wherein the
compound is of Formula (Ib);
Y is N;
W is C(H)₂;
R¹ CH₃;
25 R² is H;
R³ is H, CH₃, OCHF₂, or OCH₃; and
R⁴ is H.
- 30 234. The compound according to anyone of the preceding items, wherein the
compound is of Formula (Ic);
Y is N;
W is C(H)₂;
R¹ CH₃;
R² is H;
35 R³ is H, CH₃, OCHF₂, or OCH₃; and

R⁴ is H.

227. The compound according to anyone of the preceding items, wherein the compound is of Formula (Id);

5

Y is N;

W is C(H)₂;

R¹ CH₃;

R² is H;

R³ is H, CH₃, OCHF₂, or OCH₃; and

10

R⁴ is H.

235. The compounds according to anyone of the preceding items, wherein the compound is selected from the group consisting of:

15

7-cyclopropyl-N-(1H-indol-6-ylmethyl)quinoxalin-2-amine,

N-[(7-methyl-1H-indol-5-yl)methyl]quinoxalin-2-amine,

N-(1H-indol-6-ylmethyl)-7-(piperidin-1-yl)quinoxalin-2-amine

N-(1H-indol-5-ylmethyl)quinoxalin-2-amine,

20

1-(3-[(6-amino-1H-indol-4-yl)methyl]amino)pyrido[2,3-b]pyrazin-6-yl)piperidin-4-ol,

N-(1H-indol-4-ylmethyl)-6-{2-methyl-2,7-diazaspiro[3.5]nonan-7-yl}pyrido[2,3-b]pyrazin-3-amine

1-[3-({[7-(hydroxymethyl)-3-methyl-1H-indol-4-yl]methyl}amino)pyrido[2,3-b]pyrazin-6-yl]piperidin-4-ol,

25

1-(3-[[1H-indol-4-yl(²H₂)methyl]amino]pyrido[2,3-b]pyrazin-6-yl)piperidin-4-ol,

N-(1H-indol-6-ylmethyl)-6-(piperidin-4-yl)pyrido[2,3-b]pyrazin-3-amine,

[6-({[6-(piperidin-1-yl)pyrido[2,3-b]pyrazin-3-yl]amino}methyl)-1H-indol-2-yl]MeOH,

30

N-[(3-isopropyl-7-methoxy-1H-indol-4-yl)methyl]-6-(pyrrolidin-1-yl)pyrido[2,3-b]pyrazin-3-amine,

6-N-cyclohexyl-3-N-[(7-methoxy-3-methyl-1H-indol-4-yl)methyl]pyrido[2,3-b]pyrazine-3,6-diamine,

1-[3-({[7-(dimethylamino)-3-methyl-1H-indol-4-yl]methyl}amino)pyrido[2,3-b]pyrazin-6-yl]piperidin-4-ol,

- 6-[(2R,6S)-2,6-dimethylmorpholin-4-yl]-N-[(3-methyl-1H-indol-4-yl)methyl]pyrido[2,3-b]pyrazin-3-amine,
N,3-dimethyl-4-[[6-{methyl[(1S,3S)-3-hydroxycyclobutyl]amino}pyrido[2,3-b]pyrazin-3-yl)amino]methyl]-1H-indole-7-carboxamide,
5 1-[3-({[7-(difluoromethoxy)-3-methyl-1H-indol-4-yl]methyl}amino)pyrido[2,3-b]pyrazin-6-yl]piperidin-4-ol,
3-(hydroxymethyl)-1-(3-{{[7-methoxy-3-methyl-1H-indol-4-yl]methyl}amino}pyrido[2,3-b]pyrazin-6-yl)piperidin-4-ol,
1-(3-{{[7-chloro-1H-indol-4-yl]methyl}amino}pyrido[2,3-b]pyrazin-6-yl)piperidin-4-ol,
10 [(3R)-1-(3-{{[1H-indol-6-yl]methyl}amino}pyrido[2,3-b]pyrazin-6-yl)pyrrolidin-3-yl]methanol,
(3R)-1-(3-{{[1H-indol-6-yl]methyl}amino}pyrido[2,3-b]pyrazin-6-yl)pyrrolidin-3-ol,
cis-(1S,3S)-3-[[3-{{[7-methoxy-3-methyl-1H-indol-4-yl]methyl}amino}pyrido[2,3-b]pyrazin-6-yl)amino]cyclobutan-1-ol,
15 N-[(1H-indol-6-yl)methyl]-6-{2-oxa-6-azaspiro[3.3]heptan-6-yl}pyrido[2,3-b]pyrazin-3-amine,
6-{2,6-diazaspiro[3.3]heptan-2-yl}-N-(1H-indol-6-ylmethyl)pyrido[2,3-b]pyrazin-3-amine,
20 3-(hydroxymethyl)-1-(3-{{[1H-indol-6-yl]methyl}amino}pyrido[2,3-b]pyrazin-6-yl)piperidin-4-ol,
[(3R)-1-(3-{{[1H-indol-6-yl]methyl}amino}pyrido[2,3-b]pyrazin-6-yl)piperidin-3-yl]methanol,
N-[(1H-indol-6-yl)methyl]pyrido[2,3-b]pyrazin-3-amine,
25 cis-(1R,3R)-3-({3-[[1H-indol-6-ylmethyl]amino]pyrido[2,3-b]pyrazin-6-yl}amino)cyclobutan-1-ol,
[4-(hydroxymethyl)-1-(3-{{[7-methoxy-3-methyl-1H-indol-4-yl]methyl}amino}pyrido[2,3-b]pyrazin-6-yl)piperidin-4-yl]methanol,
3-N-[(7-methoxy-3-methyl-1H-indol-4-yl)methyl]-6-N-[trans-4-aminocyclohexyl]pyrido[2,3-b]pyrazine-3,6-diamine,
30 7-tert-butyl-N-(1H-indol-6-ylmethyl)quinoxalin-2-amine,
N-[(1H-indol-6-yl)methyl]-6-(piperidin-1-yl)pyrido[2,3-b]pyrazin-3-amine,
[4-(hydroxymethyl)-1-(3-{{[1H-indol-6-ylmethyl]amino}pyrido[2,3-b]pyrazin-6-yl}piperidin-4-yl]methanol,

- N-(1H-indol-6-ylmethyl)-6-[4-(oxetan-3-yl)piperazin-1-yl]pyrido[2,3-b]pyrazin-3-amine,
7-{3-[(1H-indol-6-ylmethyl)amino]pyrido[2,3-b]pyrazin-6-yl}-7-
azaspiro[3.5]nonan-2-amine,
5 1-{3-[(1H-pyrrolo[2,3-b]pyridin-5-yl)methyl]amino}pyrido[2,3-b]pyrazin-6-yl}piperidin-4-ol,
3-N-(1H-indol-6-ylmethyl)-6-N-(oxan-4-yl)pyrido[2,3-b]pyrazine-3,6-diamine,
[(2R)-4-(3-[(7-methoxy-3-methyl-1H-indol-4-yl)methyl]amino)pyrido[2,3-b]pyrazin-6-yl)morpholin-2-yl]methanol,
10 N-[(1H-indol-6-yl)methyl]-6-(pyrrolidin-1-yl)pyrido[2,3-b]pyrazin-3-amine,
7-ethyl-N-[(1H-indol-6-yl)methyl]quinoxalin-2-amine,
N-(1H-indol-6-ylmethyl)-6-{2-methyl-2,7-diazaspiro[3.5]nonan-7-yl}pyrido[2,3-b]pyrazin-3-amine,
1-3-[(3-hydroxy-4-methoxyphenyl)methyl]amino}pyrido[2,3-b]pyrazin-6-yl}piperidin-4-ol,
15 1-(3-[(1H-indol-4-yl)methyl]amino)pyrido[2,3-b]pyrazin-6-yl}piperidin-4-ol,
6-{2,7-diazaspiro[3.5]nonan-7-yl}-N-[(7-methoxy-3-methyl-1H-indol-4-yl)methyl]pyrido[2,3-b]pyrazin-3-amine,
N-[(1H-indol-6-yl)methyl]-7-methylquinoxalin-2-amine,
20 3-N-(1H-indol-6-ylmethyl)-6-N-{2-oxaspiro[3.3]heptan-6-yl}pyrido[2,3-b]pyrazine-3,6-diamine,
N-[(2-methyl-1H-indol-5-yl)methyl]quinoxalin-2-amine,
6-{2,6-diazaspiro[3.4]octan-6-yl}-N-(1H-indol-6-ylmethyl)pyrido[2,3-b]pyrazin-3-amine,
25 N3-[(1H-indol-6-yl)methyl]-N6-[trans-4-(difluoromethoxy)cyclohexyl]pyrido[2,3-b]pyrazine-3,6-diamine,
N-(1H-indol-6-ylmethyl)-6-(morpholin-4-yl)pyrido[2,3-b]pyrazin-3-amine,
(3R)-1-{3-[(1H-indol-6-ylmethyl)amino]pyrido[2,3-b]pyrazin-6-yl}piperidin-3-ol,
N-[(1H-indol-6-yl)methyl]-6-{2-oxa-6-azaspiro[3.4]octan-6-yl}pyrido[2,3-b]pyrazin-3-amine,
30 N-(1H-indol-6-ylmethyl)-6-{1-oxa-9-azaspiro[5.5]undecan-9-yl}pyrido[2,3-b]pyrazin-3-amine,
[(2R)-4-[3-[(7-(difluoromethoxy)-3-methyl-1H-indol-4-yl)methyl]amino]pyrido[2,3-b]pyrazin-6-yl)morpholin-2-yl]methanol,
35 6-N-cyclohexyl-3-N-(1H-indol-6-ylmethyl)pyrido[2,3-b]pyrazine-3,6-diamine,

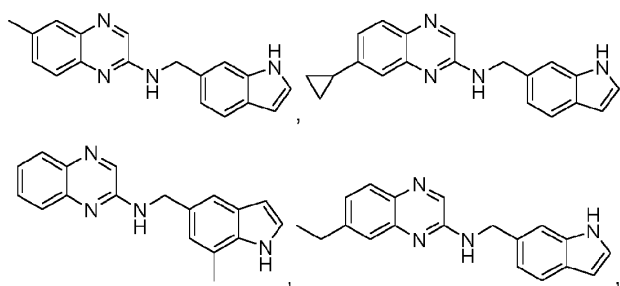
- 1-(3-[(3-isopropyl-7-methoxy-1H-indol-4-yl)methyl]amino)pyrido[2,3-b]pyrazin-6-yl)piperidin-4-ol,
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5 [(2R)-4-{3-[(1H-indol-6-ylmethyl)amino]pyrido[2,3-b]pyrazin-6-yl}morpholin-2-yl)methanol,
N-(1H-indol-6-ylmethyl)-6-{3-oxa-9-azaspiro[5.5]undecan-9-yl}pyrido[2,3-b]pyrazin-3-amine,
trans-4-({3-[(1H-indol-6-ylmethyl)amino]pyrido[2,3-b]pyrazin-6-yl}amino)cyclohexan-1-ol,
10 1-(3-[(2-cyclopropyl-1H-indol-5-yl)methyl]amino)pyrido[2,3-b]pyrazin-6-yl)piperidin-4-ol,
N6-[2-(dimethylamino)ethyl]-N3-[(1H-indol-6-yl)methyl]pyrido[2,3-b]pyrazine-3,6-diamine,
15 6-{2,7-diazaspiro[3.5]nonan-7-yl}-N-(1H-indol-6-ylmethyl)pyrido[2,3-b]pyrazin-3-amine,
3-[(3-[(1H-indol-6-yl)methyl]amino)pyrido[2,3-b]pyrazin-6-yl)amino]propane-1,2-diol,
[(3S)-1-(3-[(1H-indol-6-yl)methyl]amino)pyrido[2,3-b]pyrazin-6-yl)piperidin-3-yl)methanol,
20 1-(3-[(7-methoxy-3-methyl-1H-indol-4-yl)methyl]amino)pyrido[2,3-b]pyrazin-6-yl)piperidin-4-ol,
(1-{3-[(1H-indol-6-ylmethyl)amino]pyrido[2,3-b]pyrazin-6-yl}piperidin-4-yl)methanol,
25 trans-4-[methyl(3-[(3-methyl-1H-indol-4-yl)methyl]amino)pyrido[2,3-b]pyrazin-6-yl)amino]cyclohexan-1-ol,
N-[(1H-indol-6-yl)methyl]quinoxalin-2-amine,
1-(3-[(7-methoxy-1H-indol-4-yl)methyl]amino)pyrido[2,3-b]pyrazin-6-yl)piperidin-4-ol,
30 (3S)-1-(3-[(1H-indol-6-yl)methyl]amino)pyrido[2,3-b]pyrazin-6-yl)piperidin-3-ol,
1-(3-[(1H-indol-6-yl)methyl]amino)pyrido[2,3-b]pyrazin-6-yl)piperidin-4-ol,
N3-[(1H-indol-6-yl)methyl]-N6-(3-methoxypropyl)pyrido[2,3-b]pyrazine-3,6-diamine,
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35

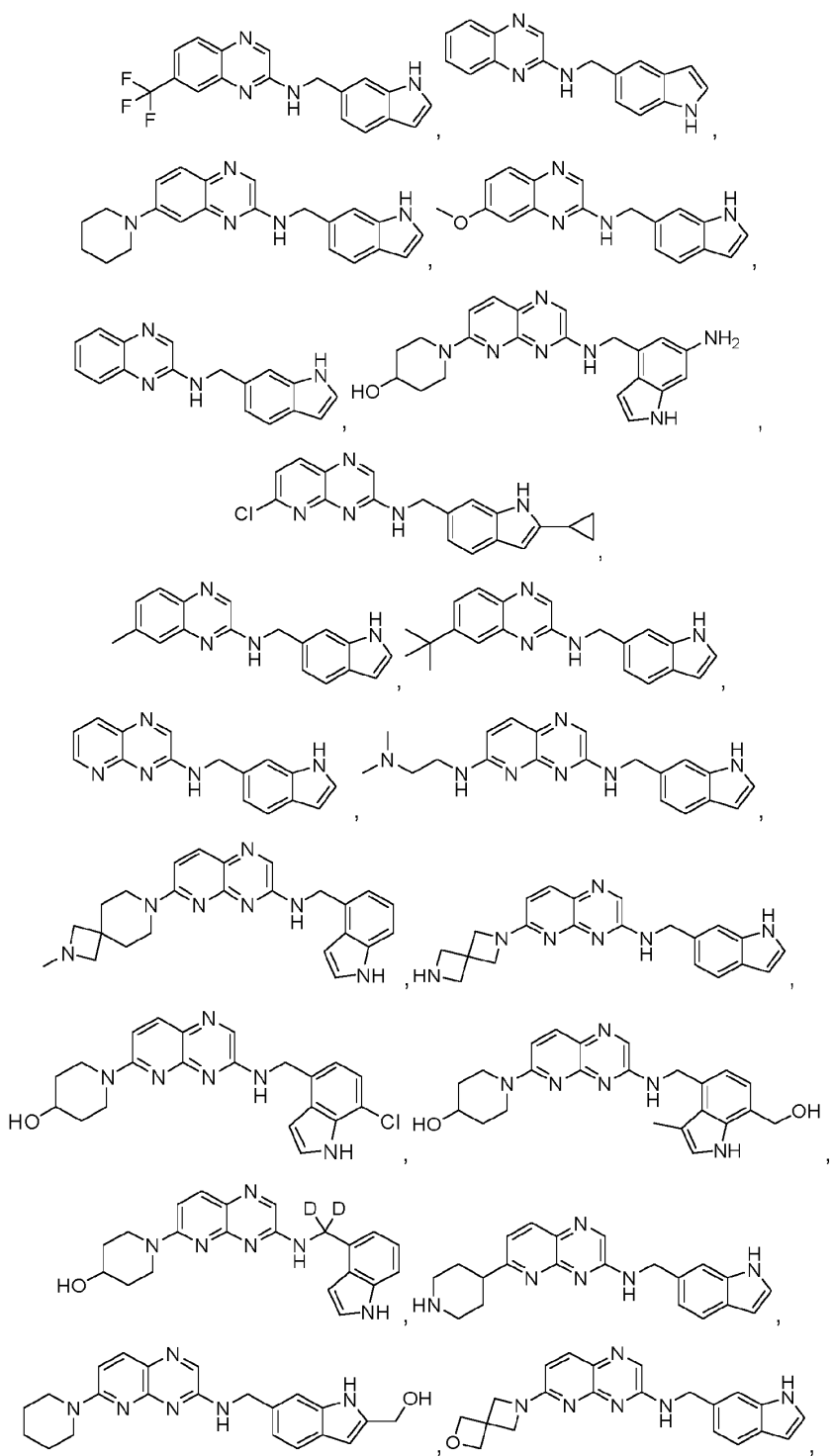
- N-[(7-methoxy-3-methyl-1H-indol-4-yl)methyl]-6-{2-methyl-2,7-diazaspiro[3.5]nonan-7-yl}pyrido[2,3-b]pyrazin-3-amine,
N-(1H-indol-6-ylmethyl)-6-(piperazin-1-yl)pyrido[2,3-b]pyrazin-3-amine,
cis-3-[(3-[(3-methyl-1H-indol-4-yl)methyl]amino)pyrido[2,3-b]pyrazin-6-yl)amino]cyclobutan-1-ol,
5 (3S,4S)-3-(hydroxymethyl)-1-(3-[(7-methoxy-3-methyl-1H-indol-4-yl)methyl]amino)pyrido[2,3-b]pyrazin-6-yl)piperidin-4-ol,
1-(3-[(2-methyl-1H-indol-5-yl)methyl]amino)pyrido[2,3-b]pyrazin-6-yl)piperidin-4-ol,
10 N3-[(1H-indol-6-yl)methyl]-N6-[trans-4-aminocyclohexyl]pyrido[2,3-b]pyrazine-3,6-diamine,
3-[(3-[(1H-indol-6-yl)methyl]amino)pyrido[2,3-b]pyrazin-6-yl)amino]-2,2-dimethylpropan-1-ol,
6-N-{6,6-difluorospiro[3.3]heptan-2-yl}-3-N-(1H-indol-6-ylmethyl)pyrido[2,3-b]pyrazine-3,6-diamine,
15 6-{4-[(1-aminocyclopropyl)carbonyl]piperazin-1-yl}-N-(1H-indol-6-ylmethyl)pyrido[2,3-b]pyrazin-3-amine,
6-[cis-2,6-dimethylmorpholin-4-yl]-N-(1H-indol-6-ylmethyl)pyrido[2,3-b]pyrazin-3-amine,
20 [(3S)-1-{3-[(1H-indol-6-ylmethyl)amino]pyrido[2,3-b]pyrazin-6-yl}pyrrolidin-3-yl]methanol,
[4-(hydroxymethyl)-1-(3-[(3-methyl-1H-indol-4-yl)methyl]amino)pyrido[2,3-b]pyrazin-6-yl)piperidin-4-yl]methanol,
cis-3-[(3-[(7-methoxy-3-methyl-1H-indol-4-yl)methyl]amino)pyrido[2,3-b]pyrazin-6-yl)(methyl)amino]cyclobutan-1-ol,
25 4-[(6-[(2R)-2-(hydroxymethyl)morpholin-4-yl]pyrido[2,3-b]pyrazin-3-yl)amino)methyl]-N,3-dimethyl-1H-indole-7-carboxamide,
N-[(1H-indol-6-yl)methyl]-6-methylquinoxalin-2-amine,
1-{3-[(3-[(7-methoxy-3-methyl-1H-indol-4-yl)methyl]amino)pyrido[2,3-b]pyrazin-6-yl)amino]propyl}azepan-2-one,
30 1-(3-[(1H-indol-6-yl)methyl]amino)pyrido[2,3-b]pyrazin-6-yl)piperidin-3-ol,
[4-(3-[(7-methoxy-3-methyl-1H-indol-4-yl)methyl]amino)pyrido[2,3-b]pyrazin-6-yl)morpholin-2-yl]methanol,
N-(1H-indol-6-ylmethyl)-6-(4-methylpiperazin-1-yl)pyrido[2,3-b]pyrazin-3-amine,

- trans-3-[methyl(3-[(3-methyl-1H-indol-4-yl)methyl]amino)pyrido[2,3-b]pyrazin-6-yl)amino]cyclobutan-1-ol,
(3S,4S)-3-(hydroxymethyl)-1-{3-[(1H-indol-6-ylmethyl)amino]pyrido[2,3-b]pyrazin-6-yl}piperidin-4-ol,
5 6-(azetidin-1-yl)-N-[(1H-indol-6-yl)methyl]pyrido[2,3-b]pyrazin-3-amine,
1-(3-[(3-methyl-1H-indol-4-yl)methyl]amino)pyrido[2,3-b]pyrazin-6-yl)piperidin-4-ol,
(3R,4R)-3-(hydroxymethyl)-1-(3-[(7-methoxy-3-methyl-1H-indol-4-yl)methyl]amino)pyrido[2,3-b]pyrazin-6-yl)piperidin-4-ol,
10 6-[(3-[(1H-indol-6-yl)methyl]amino)pyrido[2,3-b]pyrazin-6-yl)amino]spiro[3.3]heptan-2-ol,
3-N-[(7-methoxy-3-methyl-1H-indol-4-yl)methyl]-6-N-[trans-4-(dimethylamino)cyclohexyl]pyrido[2,3-b]pyrazine-3,6-diamine,
(3S)-1-(3-[(7-methoxy-3-methyl-1H-indol-4-yl)methyl]amino)pyrido[2,3-b]pyrazin-6-yl)pyrrolidin-3-ol,
15 trans-3-({3-[(1H-indol-6-ylmethyl)amino]pyrido[2,3-b]pyrazin-6-yl}amino)cyclobutan-1-ol,
(3S)-1-(3-[(1H-indol-6-yl)methyl]amino)pyrido[2,3-b]pyrazin-6-yl)pyrrolidin-3-ol,
[4-(3-[(1H-indol-6-yl)methyl]amino)pyrido[2,3-b]pyrazin-6-yl)morpholin-2-yl]methanol,
20 (3S)-1-(3-[(3-methyl-1H-indol-4-yl)methyl]amino)pyrido[2,3-b]pyrazin-6-yl)pyrrolidin-3-ol,
1-(3-[(1H-indol-6-yl)methyl]amino)pyrido[2,3-b]pyrazin-6-yl)azetidin-3-ol,
4-({[6-(4-hydroxypiperidin-1-yl)pyrido[2,3-b]pyrazin-3-yl]amino}methyl)-N,3-dimethyl-1H-indole-7-carboxamide,
25 6-{1,4-dioxo-9-azaspiro[5.5]undecan-9-yl}-N-(1H-indol-6-ylmethyl)pyrido[2,3-b]pyrazin-3-amine,
N-(1H-indol-6-ylmethyl)-6-{1-oxa-8-azaspiro[4.5]decan-8-yl}pyrido[2,3-b]pyrazin-3-amine,
30 6-[cis-2,6-dimethylmorpholin-4-yl]-N-[(3-isopropyl-7-methoxy-1H-indol-4-yl)methyl]pyrido[2,3-b]pyrazin-3-amine,
6-[(3-[(7-methoxy-3-methyl-1H-indol-4-yl)methyl]amino)pyrido[2,3-b]pyrazin-6-yl)amino]spiro[3.3]heptan-2-ol,
(3S,4S)-4-(hydroxymethyl)-1-{3-[(1H-indol-6-ylmethyl)amino]pyrido[2,3-b]pyrazin-6-yl}piperidin-3-ol,
35

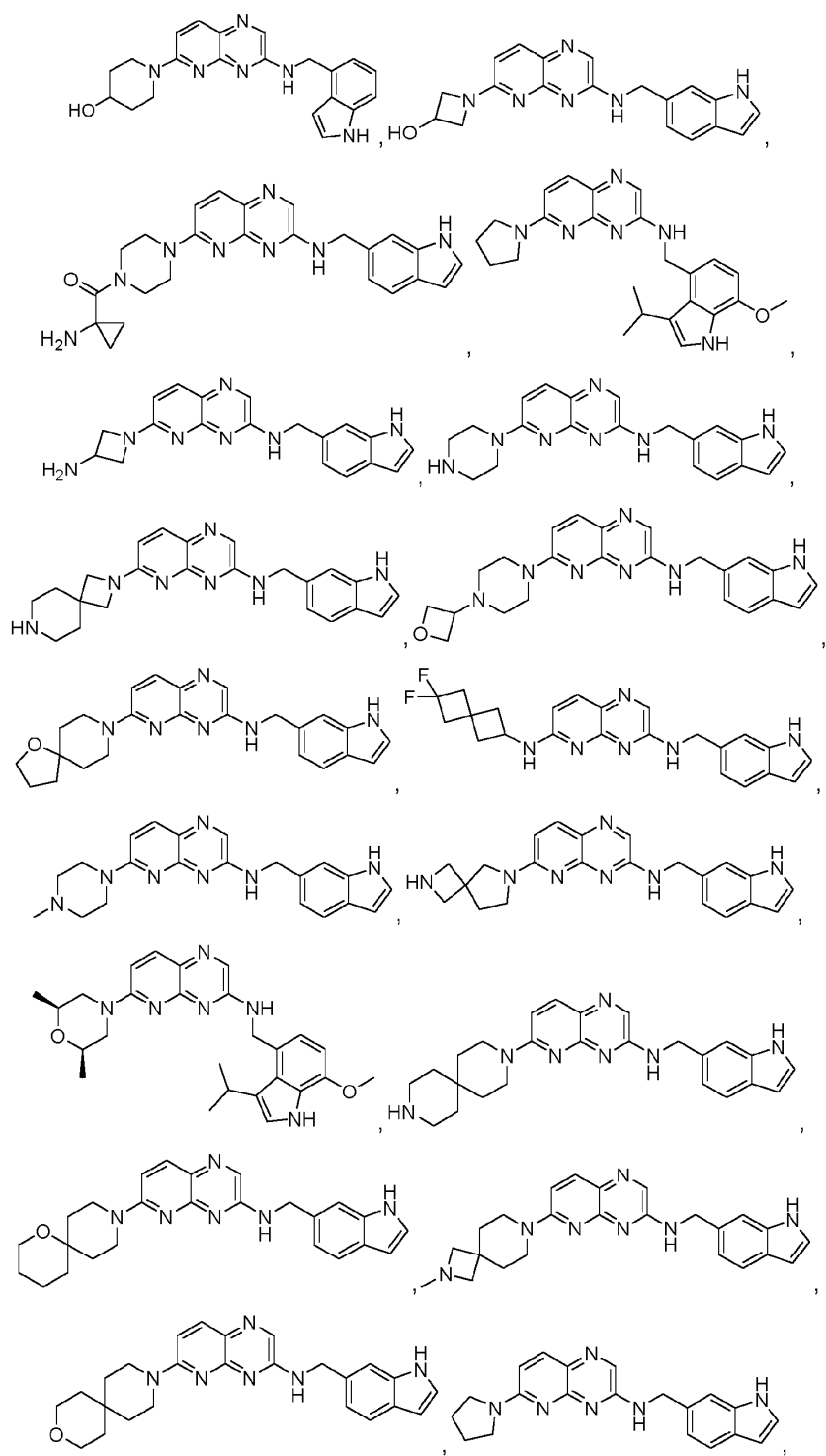
- N-[(7-methoxy-3-methyl-1H-indol-4-yl)methyl]-6-(4-methylpiperazin-1-yl)pyrido[2,3-b]pyrazin-3-amine,
 N-[(1H-indol-6-yl)methyl]-7-methoxyquinoxalin-2-amine,
 trans-4-[(3-[(7-methoxy-3-methyl-1H-indol-4-yl)methyl]amino)pyrido[2,3-b]pyrazin-6-yl)(methyl)amino]cyclohexan-1-ol,
 3-[(3-[(1H-indol-6-yl)methyl]amino)pyrido[2,3-b]pyrazin-6-yl)amino]propan-1-ol,
 6-N-[4-(dimethylamino)cyclohexyl]-3-N-(1H-indol-6-ylmethyl)pyrido[2,3-b]pyrazine-3,6-diamine,
 [1-(hydroxymethyl)-4-[(3-[(7-methoxy-3-methyl-1H-indol-4-yl)methyl]amino)pyrido[2,3-b]pyrazin-6-yl)amino]cyclohexyl]methanol,
 1-[3-[(1H-indol-6-ylmethyl)amino]pyrido[2,3-b]pyrazin-6-yl]azetidin-3-amine,
 [(2R)-4-(3-[(3-methyl-1H-indol-4-yl)methyl]amino)pyrido[2,3-b]pyrazin-6-yl)morpholin-2-yl]methanol,
 [4-(3-[(7-methoxy-3-methyl-1H-indol-4-yl)methyl]amino)pyrido[2,3-b]pyrazin-6-yl)-6,6-dimethylmorpholin-2-yl]methanol,
 N3-[(7-methoxy-3-methyl-1H-indol-4-yl)methyl]-N6-[(2-oxabicyclo[2.2.2]octan-3-yl)methyl]pyrido[2,3-b]pyrazine-3,6-diamine,
 N-[(1H-indol-6-yl)methyl]-7-(trifluoromethyl)quinoxalin-2-amine,
 6-[2,7-diazaspiro[3.5]nonan-2-yl]-N-(1H-indol-6-ylmethyl)pyrido[2,3-b]pyrazin-3-amine,
 N-(1H-indol-5-ylmethyl)-6-(morpholin-4-yl)pyrido[2,3-b]pyrazin-3-amine, and
 6-[3,9-diazaspiro[5.5]undecan-3-yl]-N-[(1H-indol-6-yl)methyl]pyrido[2,3-b]pyrazin-3-amine.

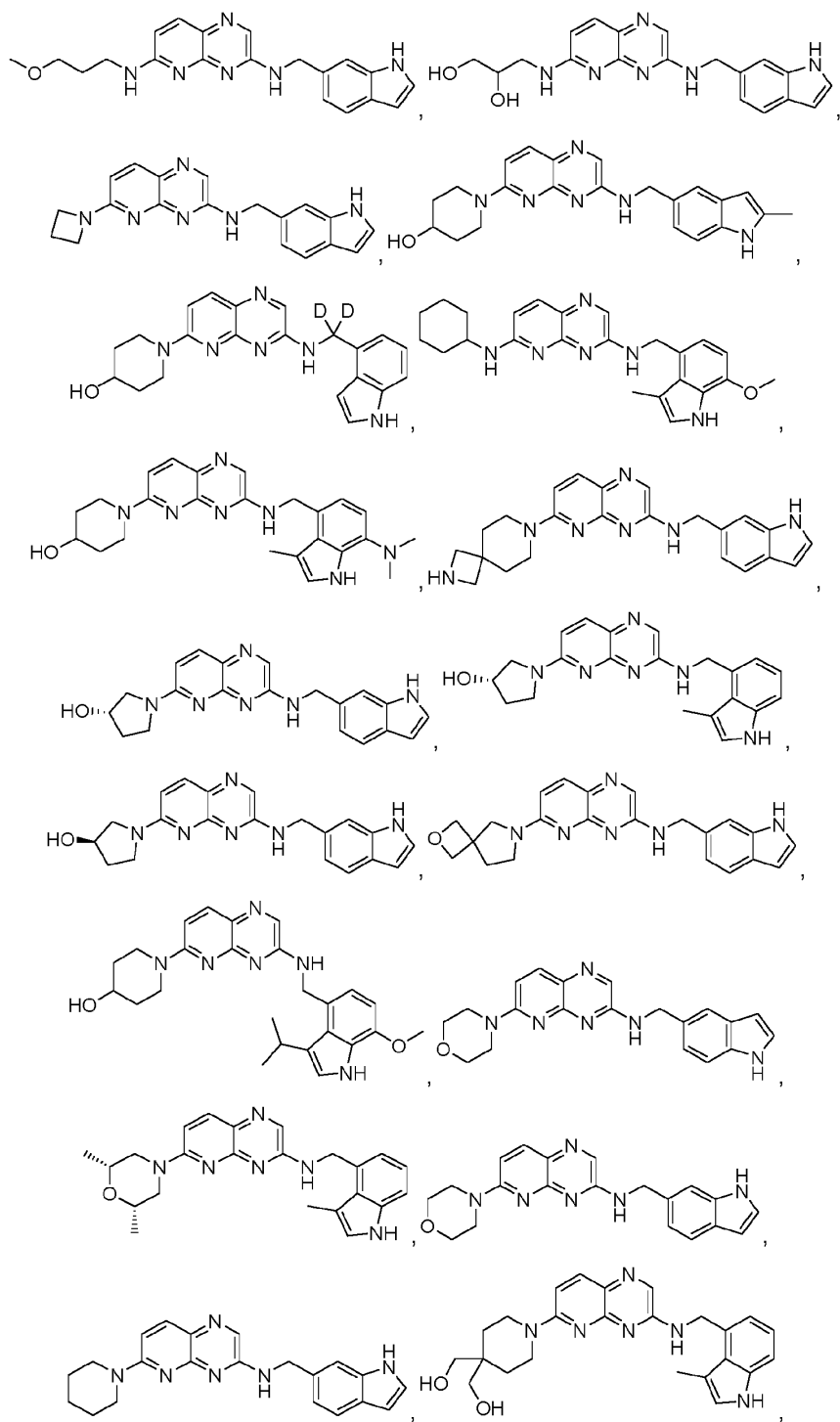
236. A compound selected from the group consisting of:



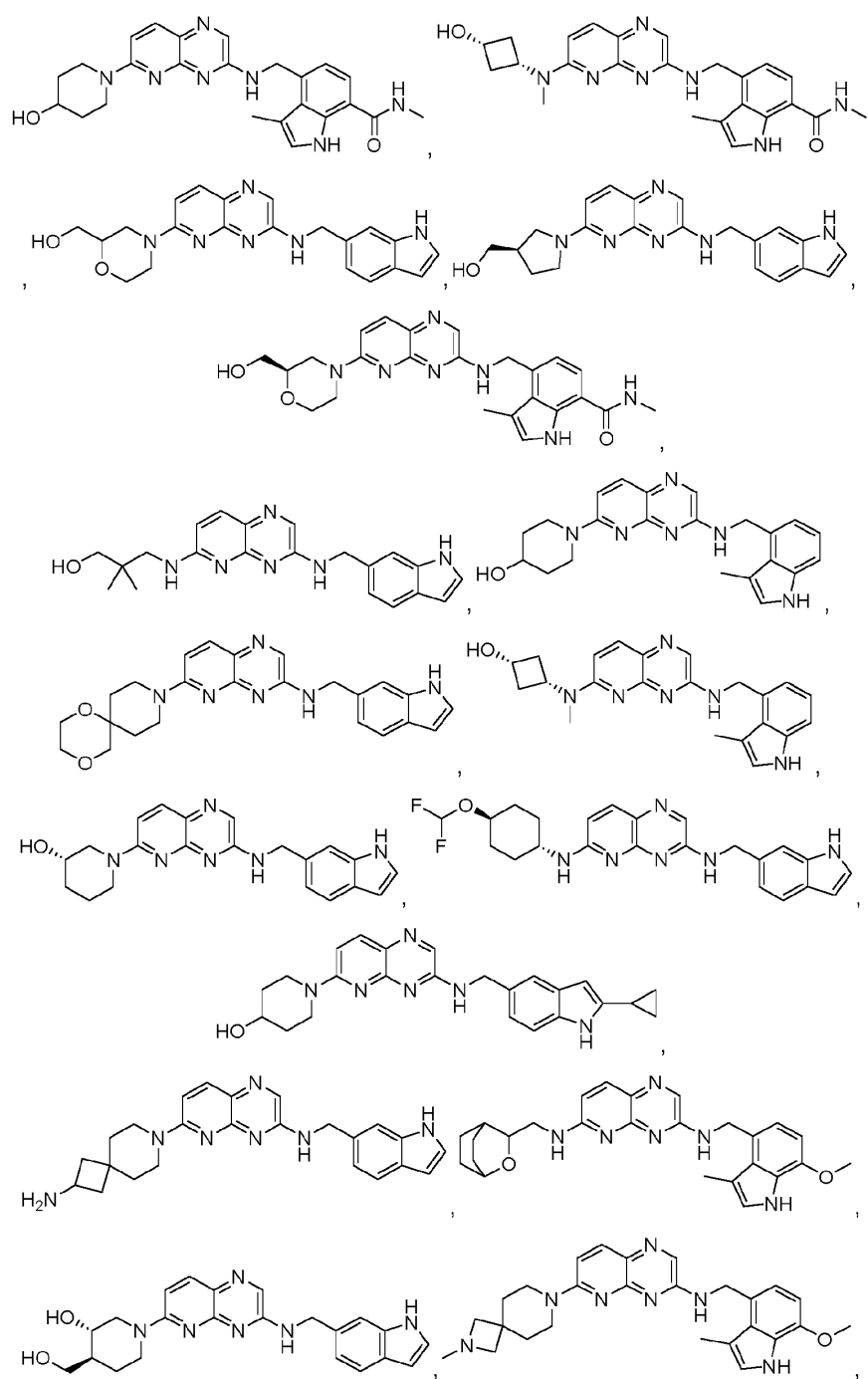


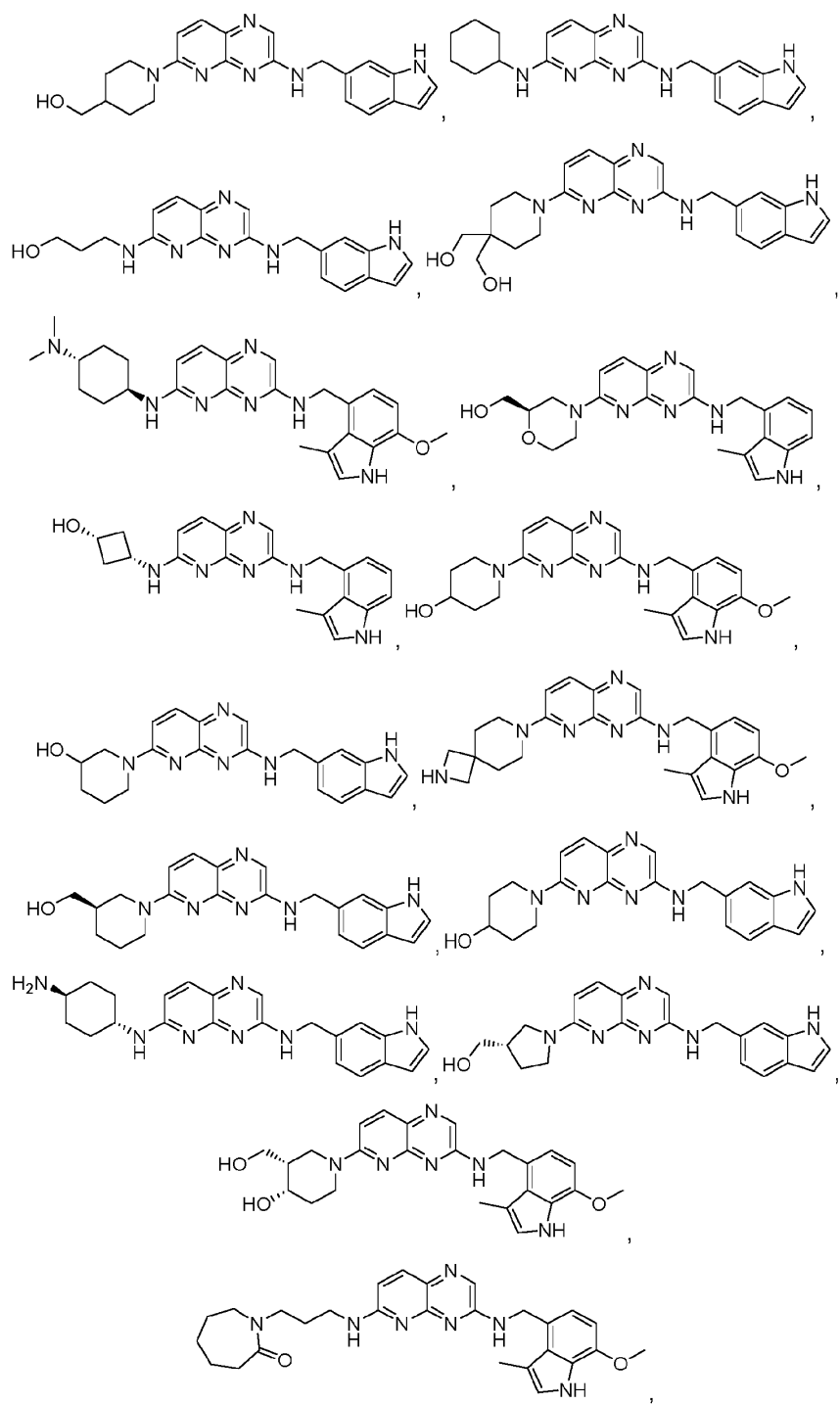
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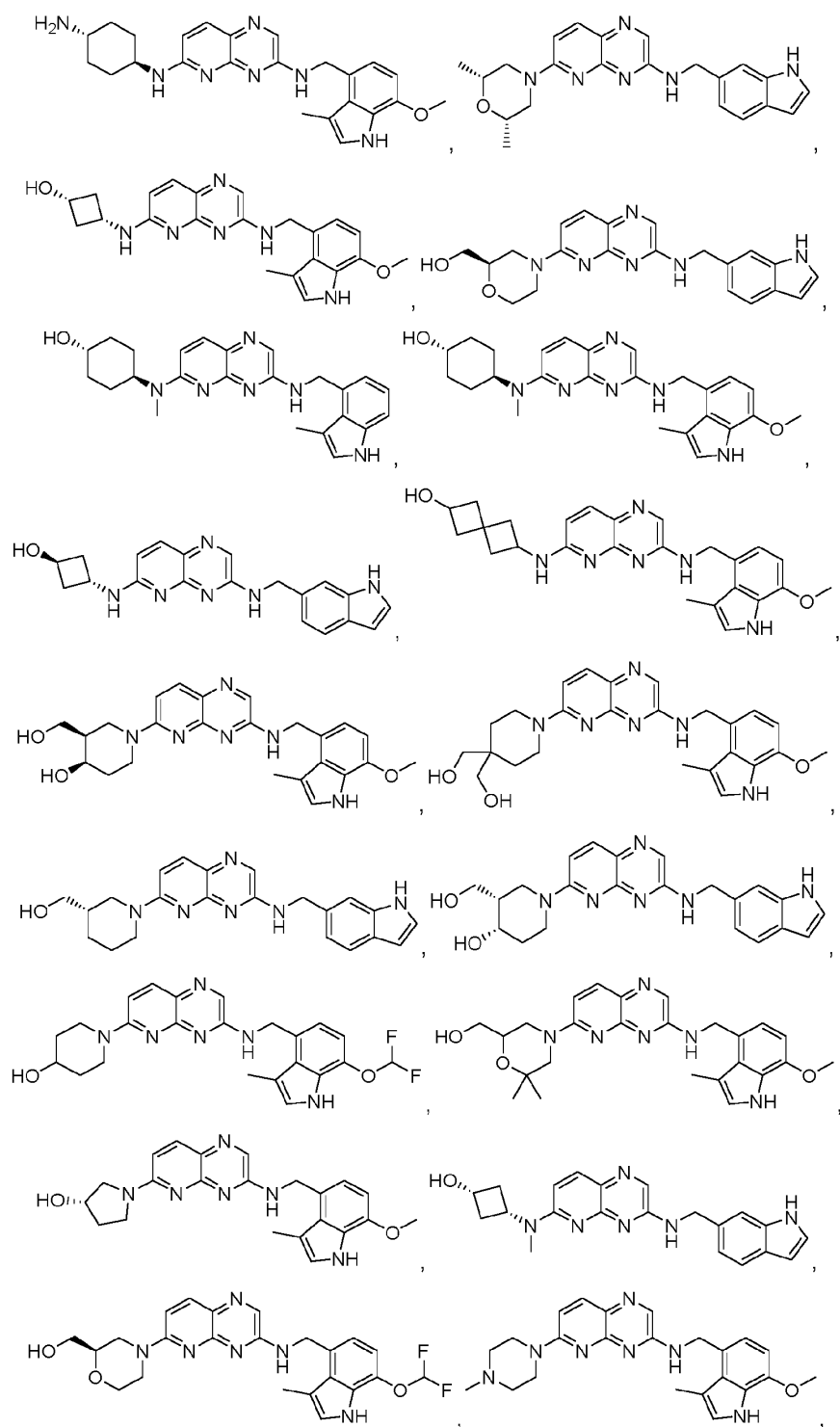


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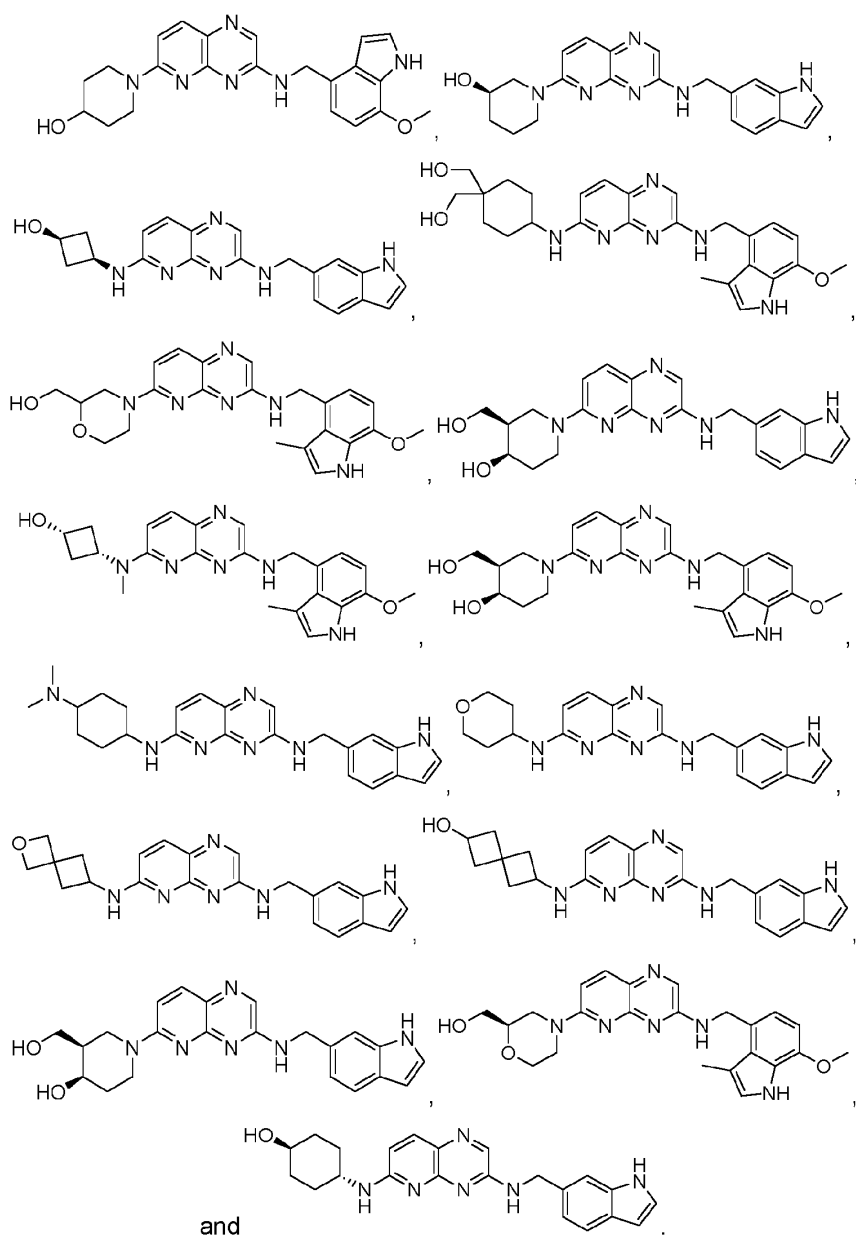




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237. The compound according to any one of the preceding items, wherein the compound is a WNK lysine deficient protein kinase 1 (WNK1) inhibitor.
238. The compound according to any one of the preceding items, wherein the compound is a WNK lysine deficient protein kinase 2 (WNK2) inhibitor.
239. The compound according to any one of the preceding items, wherein the compound is a WNK lysine deficient protein kinase 3 (WNK3) inhibitor.

240. The compound according to any one of the preceding items, wherein the compound is a WNK lysine deficient protein kinase 4 (WNK4) inhibitor.
- 5 241. A pharmaceutical composition comprising a compound according to any one of the preceding items, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable carriers, excipients and/or diluents.
- 10 242. The compound according to any one of items 1 to 240, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition according to item 241, for use as a medicament.
- 15 243. The compound according to any one of items 1 to 240, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition according to item 241, for use in treating, alleviating or preventing diseases and disorders related to the activity of WNK1.
- 20 244. The compound according to any one of items 1 to 240, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition according to item 241, for use in treating, alleviating or preventing diseases and disorders related to the activity of WNK1-4, such as WNK1, WNK2, WNK3 and/or WNK4.
- 25 245. A method for treating, alleviating or preventing diseases and disorders related to the activity of WNK1, said method comprising administering a compound according to any one of items 1 to 240, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition according to item 241, to a subject in need thereof.
- 30 246. A method for treating, alleviating or preventing diseases and disorders related to the activity of WNK1-4, said method comprising administering a compound according to any one of items 1 to 240, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition according to item 241, to a subject in need thereof.

247. Use of a compound according to any one of items 1 to 240, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition according to item 241, for the manufacture of a medicament for treating, alleviating or preventing diseases and disorders related to the activity of WNK1.
- 5
248. Use of a compound according to any one of items 1 to 240, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition according to item 241, for the manufacture of a medicament for treating, alleviating or preventing diseases and disorders related to the activity of WNK1.
- 10
249. The compound according to any one of items 1 to 240, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition according to item 241, for use in the treatment of hypertension.
- 15
250. A method for treatment of hypertension, comprising administering a compound according to any one of items 1 to 240, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition according to item 241, to a subject in need thereof.
- 20
251. Use of a compound according to any one of items 1 to 240, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition according to item 241, for the manufacture of a medicament for the treatment of hypertension.
- 25
252. The compound according to any one of items 1 to 240, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition according to item 241, for use in the treatment of cancer.
- 30
253. A method for treatment of cancer, comprising administering a compound according to any one of items 1 to 240, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition according to item 241, to a subject in need thereof.
- 35
254. Use of a compound according to any one of items 1 to 240, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition

according to item 241, for the manufacture of a medicament for the treatment of cancer.

255. The compound or pharmaceutical composition for use according to item
 5 247, the method according to 250, or the use according to 254, wherein the
 cancer is selected from the group consisting of Adenoid cystic carcinoma, Anal
 cancer, Appendix cancer and PMP, Bile duct cancer (cholangiocarcinoma),
 Bladder cancer, Blood cancer, Bone cancer (Primary), Bone cancer
 (Secondary), Bowel cancer, Brain tumours, Breast cancer, Cancer of the
 10 uterus, Cancer of unknown primary, Cervical cancer, Connective tissue cancer,
 Endocrine cancer, Gall bladder (bile duct) cancer, Head, neck and throat
 cancers, Kaposi sarcoma, Kidney cancer, Leukaemia, Liver cancer (Primary),
 Liver cancer (Secondary), Lung cancer, Lymphoma, Melanoma, Mesothelioma,
 Myeloma, Neuroendocrine tumours (NETs), Ocular (uveal) melanoma, Ovarian
 15 cancer, Pancreatic cancer, Penile cancer, Peritoneal cancer, Prostate cancer,
 Skin cancer, Small bowel cancer, Soft tissue sarcoma, Stomach and
 oesophageal cancers, Testicular cancer, Thymus cancer, Thyroid cancer,
 Upper tract urothelial cancer, Vaginal cancer and Vulvar cancer.
- 20 256. The compound or pharmaceutical composition for use according to item
 247, the method according to 250, or the use according to, wherein the cancer
 is selected from the group consisting of Acute Myeloid Leukemia (LAML),
 Adrenocortical carcinoma (ACC), Bladder Urothelial Carcinoma (BLCA), Brain
 Lower Grade Glioma (LGG), Breast invasive carcinoma (BRCA), Cervical
 25 squamous cell carcinoma and endocervical adenocarcinoma (CESC),
 Cholangiocarcinoma (CHOL), Chronic Myelogenous Leukemia (LCML), Colon
 adenocarcinoma (COAD), Esophageal carcinoma (ESCA), Glioblastoma
 multiforme (GBM), Head and Neck squamous cell carcinoma (HNSC), Kidney
 Chromophobe (KICH), Kidney renal clear cell carcinoma (KIRC), Kidney renal
 30 papillary cell carcinoma (KIRP), Liver hepatocellular carcinoma (LIHC), Lung
 adenocarcinoma (LUAD), Lung squamous cell carcinoma (LUSC), Lymphoid
 Neoplasm Diffuse Large B-cell Lymphoma (DLBC), Mesothelioma (MESO),
 Ovarian serous cystadenocarcinoma (OV), Pancreatic adenocarcinoma
 (PAAD), Pheochromocytoma and Paraganglioma (PCPG), Prostate
 35 adenocarcinoma (PRAD), Rectum adenocarcinoma (READ), Sarcoma (SARC),

Skin Cutaneous Melanoma (SKCM), Stomach adenocarcinoma (STAD), Testicular Germ Cell Tumors (TGCT), Thymoma (THYM), Thyroid carcinoma (THCA), Uterine Carcinosarcoma (UCS), Uterine Corpus Endometrial Carcinoma (UCEC), and Uveal Melanoma (UVM).

5

257. The compound or pharmaceutical composition for use according to item 247, the method according to 250, or the use according to 254, wherein the cancer is selected from the group consisting of leukemia, including acute myeloid leukemia, lymphoma and myeloma, including multiple myeloma.

10

Examples

Example 1: Synthetic protocols

15

General Synthetic Remarks:

Abbreviations

	Ac	acetyl
20	aq	aqueous
	BBBPY	4,4'-di-tert-butyl-2,2'-dipyridyl
	Boc ₂ O	boc anhydride
	BTMG	2-tert-butyl-1,1,3,3-tetramethylguanidine
	cat	catalytic
25	[Cp*IrCl ₂] ₂	Pentamethylcyclopentadienyliridium(III) chloride, dimer
	CV	column volume
	dba	dibenzylideneacetone
	DCM	methylene chloride
	DIPEA	<i>N,N</i> -diisopropylethylamine
30	DMAP	4-dimethylaminopyridine
	DMF	<i>N,N</i> -dimethylformamide
	dppf	1,1'-bis(diphenylphosphino)ferrocene
	eq	equivalent
	Et	ethyl
35	EtOH	ethanol
	HBTU	2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethylaminium
	HFP	hexafluorophosphate
	<i>i</i> Pr	isopropyl
	KO ^t Bu	potassium <i>tert</i> -butoxide
40	LiAlH ₄	lithium aluminiumhydride
	Me	methyl

	MeCN	acetonitrile
	MeOH	MeOH
	N ₂	nitrogen(g)
	NH ₃	ammonia
5	NMP	1methyl-2-pyrrolidinone
	Pd/C	palladium on activated charcoal
	Pd(dppf)Cl ₂	palladium 1,1'-bis(diphenylphosphino)ferrocene dichloride
	Pd ₂ (dba) ₃	tris(dibenzylideneacetone)dipalladium(0)
	Ph	phenyl
10	RBF	round bottom flask
	rt	room temperature
	RT	retention time
	RuPhos	2-dicyclohexylphosphino-2',6'-diisopropoxybiphenyl
	SCX-2	ISOLUTE® SCX-2 catch and release cartridge (sulphonic acid)
15	SPhos	2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl
	TBAF	tetrabutyl ammonium fluoride
	<i>t</i> Bu	<i>tert</i> -butyl
	TBDMS	<i>tert</i> -butyldimethylsilyl
	TBDMS-Cl	<i>tert</i> -butyldimethylsilyl chloride
20	TEA	triethylamine
	TFA	trifluoroacetic acid
	THF	tetrahydrofuran
	ZnCN	zinc cyanide

25

All reagents obtained from commercial sources were used without further purification. Anhydrous solvents were obtained from commercial sources and used without further drying.

The reactions were monitored using LCMS and/or TLC.

30

Thin layer chromatography was conducted with 5 cm × 10 cm plates coated with Merck Type 60 F₂₅₄ silica-gel. Microwave heating was performed in an Anton Parr MonoWave or CEM Discover® instrument. Photochemistry was performed in a Hepatochem Lucent 360™ Advanced Photoreactor. Reductions via hydrogenation were conducted under hydrogen at atmospheric pressure, using an apparatus that includes burettes of hydrogen(g) displaced by water and sealing Rodavis® glassware joints, which were supported and agitated under an atmosphere of hydrogen on a Heidolph shaker. Hydrogen was generated via electrolysis of water using a Domnick Hunter® NITROX™ UHP Hydrogen Generator.

35

Evaporation and drying of compounds were performed using Buchi rotary evaporators and / or Biotage® V-10 Touch Evaporation Systems. Lyophilisation of compounds from

40

aqueous mixtures resultant of preparative reverse phase chromatography were performed using a LABCONCO FreeZone 4.5 Liter -84C freeze drier.

Purification

- 5 Compounds were purified using either flash chromatography or reverse phase preparative chromatography, or a combination of both techniques.

Flash chromatography was performed on ISCO CombiFlash Rf 200, Rf 200i Rf 300+ and Rf+ Lumen™ with pre-packed silica-gel cartridges (RediSep® Rf Normal-phase Silica Flash Columns (35-70µm, 60 Å), RediSep Rf Gold® Normal-phase Silica High
10 Performance Columns (20-40µm, 60 Å), RediSep® Rf Reversed-phase C18 Columns (40-63 µm, 60 Å), or RediSep Rf Gold® Reversed-phase C18 High Performance Columns (20-40 µm, 100 Å).

Reverse phase prep-chromatography was performed by the following methods:

- AccQPrep HP125 (Teledyne ISCO) system, with a Gemini® NX 5 µm C18(2), 150 mm
15 × 21.2 mm i.d. column from Phenomenex, running at a flow rate of 20 mL min⁻¹ or Gemini® NX 5 µm C18(2), 250 mm × 30 mm i.d. column from Phenomenex, running at a flow rate of 40 mL min⁻¹ with UV (214 and 254 nm) and ELS detection. pH4 eluents: Solvent A: water + 0.08% (v/v) formic acid; solvent B: MeCN + 0.08% (v/v) formic acid. pH9 eluents: Solvent A: water + 0.08% (v/v) cc. aq. NH₃ solution; solvent B: MeCN +
20 0.08% (v/v) cc. aq. NH₃ solution. Neutral eluents: Solvent A: water; Solvent B: MeCN.

Analytical methods

- Analytical LC-MS: The compounds of the present invention were characterized by high performance liquid chromatography-mass spectroscopy (HPLC-MS) using the following
25 instruments and methods:

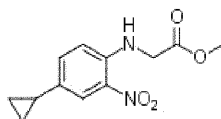
LCMS (method A): Agilent 1260 LC coupled with an Agilent InfinityLab LC/MSD XT single quadrupole, operating in both positive and negative ion electrospray ionisation modes. Molecular weight scan range is 100 to 1350 m/z. Parallel UV detection was
30 performed at 210 nm 254 nm and 270 nm. Samples were supplied as a 1 mM solution in MeCN, or in THF/water (1:1) with 5 µL loop injection. Column specification ZORBAX Eclipse XDB-C18, 1.8 µm, 50 mm × 4.6 mm i.d. operated at 40°C, at a flow rate of 1 mL min⁻¹ using 0.02% V/V aq. Formic acid solution (Solvent A) and 0.02% V/V formic acid

solution in MeCN (Solvent B) with a gradient starting from 100% Solvent A and finishing at 100% Solvent B over various duration of time.

5 **LCMS (method B):** Agilent 1290 Infinity II UHPLC series connected to a TOF 6230 with an ES ionisation source (positive or negative mode ionisation). The LCMS was configured with a buffered mobile phase - polar: Water /10 mM ammonium formate / 0.08% (v/v) formic acid pH = 3.3; apolar: acetonitrile / 5.3 % (v/v) ammonium formate / 0.08% (v/v) formic acid. The mobile phase passed through a Phenomenex Kinetex C18 column, 2.6 microns, 50 x 2 mm, temperature: 55°C at a flow rate of 1.3 mL/min. A 1 µL
10 sample was injected and purified using a 5 to 95% gradient in 1.18 minutes, total run time 1.95 minutes.

¹H-NMR measurements were performed on a Bruker Avance NEO 400 MHz spectrometer, using DMSO-d₆ or CDCl₃ as solvent. ¹H NMR data is in the form of delta
15 values, given in part per million (ppm), using the residual peak of the solvent (2.50 ppm for DMSO-d₆ and 7.26 ppm for CDCl₃) as internal standard. Splitting patterns are designated as: s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), sept (septet), m (multiplet), app s (apparent singlet), br s (broad singlet), br d (broad doublet), br t (broad triplet), br m (broad multiplet), dd (doublet of doublets), td (triplet of doublets), dt
20 (doublet of triplets), qd (quartet of doublets), ddd (doublet of doublet of doublets), dm (doublet of multiplets).

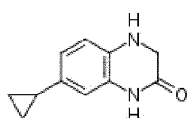
Exemplifications:



25 **Intermediate 1a: methyl 2-[(4-cyclopropyl-2-nitrophenyl)amino]acetate**

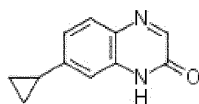
A mixture of 4-cyclopropyl-1-fluoro-2-nitrobenzene, (200 mg, 1.1 mmol, 1 eq); amino-acetic acid methyl ester (98 mg, 1.1 mmol, 1 eq); potassium carbonate (168 mg, 1.21 mmol, 1.1 eq) in ethanol (1 mL) and water (0.2 mL) was heated to 90° C for 18 h. The
30 mixture was cooled and diluted with DMF (1 mL) and treated with methyl iodide, (206.27 µL, 2.28 g/mL, 3.31 mmol, 3 eq) and stirred for 16 h. The crude reaction mixture was partitioned between water and DCM. The aqueous layer was extracted with DCM a further twice. The combined organics were washed with brine and passed through a

phase separator and concentrated to an orange residue gum. The crude material was loaded onto ISOLUTE, HM-N and purified by automated flash chromatography (Combiflash Rf, RediSep silica, 24 g column) eluting a gradient of heptane to 75% ethyl acetate in heptane and concentrated under vacuum to afford the title compound 1a (86 mg, 0.34 mmol, 31%) as a red solid. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 8.26 (t, J = 5.9 Hz, 1H), 7.82 (d, J = 2.3 Hz, 1H), 7.28 (dd, J = 8.9, 2.3 Hz, 1H), 6.85 (d, J = 8.9 Hz, 1H), 4.27 (d, J = 5.9 Hz, 2H), 3.70 (s, 3H), 2.02 – 1.87 (m, 1H), 0.95 – 0.82 (m, 2H), 0.67 – 0.58 (m, 2H).



Intermediate 1b: 7-cyclopropyl-3,4-dihydro-1H-quinoxalin-2-one

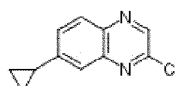
To a solution of (1a) methyl 2-[(4-cyclopropyl-2-nitrophenyl)amino]acetate, (86 mg, 0.34 mmol) in MeOH (2 mL) and acetic acid (0.85 mL) was added iron (reduced), (192 mg, 3.43 mmol, 10 eq). The reaction was heated at 70° C for 2.5 h. The reaction mixture was slowly poured onto a mixture of ice and NaHCO₃(sat) and then extracted three times with ethyl acetate. The combined organics were then washed with brine and dried over anhydrous MgSO₄. The whole was then filtered through a phase separator and concentrated under vacuum. The crude mixture was dry loaded onto ISOLUTE, HM-N and purified by automated flash chromatography (Combiflash Rf, RediSep silica, 12 g column) eluting gradient of heptane to 100% ethyl acetate in heptane and the column the then flushed with 10% MeOH in ethyl acetate to furnish the title compound 1b (25.7 mg, 0.14 mmol, 40%) as a cream solid. LCMS (method A); RT 0.90 min, m/z [M+H]⁺ 189.2. ¹H-NMR (400 MHz, DMSO-d₆) δ ppm 6.73 (d, J = 8.3 Hz, 1H), 6.62 (dd, J = 8.2, 2.1 Hz, 1H), 6.59 – 6.44 (m, 2H), 5.76 (s, 1H), 3.72 – 3.63 (m, 2H), 1.83 – 1.69 (m, 1H), 0.89 – 0.78 (m, 2H), 0.54 – 0.45 (m, 2H).



Intermediate 1c: 7-cyclopropyl-1H-quinoxalin-2-one

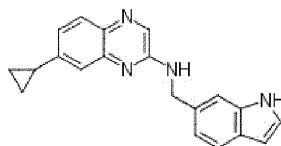
To (1b) 7-cyclopropyl-3,4-dihydro-1H-quinoxalin-2-one, (35 mg, 0.19 mmol) in THF (0.5 mL) was added manganese dioxide (62 mg, 0.71 mmol, 3.8 eq) portion wise at 0° C and then allowed to warm to rt for 16 h. The crude reaction mixture was filtered through celite

and washed with DCM and then ethyl acetate, and the combined organics concentrated under vacuum to afford the title compound 1c (18.2 mg, 0.1 mmol, 52%) as a cream solid. The product material was taken onto the subsequent step without further purification. LCMS (method A); RT 0.89 min, m/z [M+H]⁺ 187.2. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 12.23 (s, 1H), 8.04 (s, 1H), 7.63 (d, J = 8.2 Hz, 1H), 6.99 (d, J = 8.9 Hz, 2H), 2.03 (dd, J = 13.1, 8.3, 4.7 Hz, 1H), 1.09 – 1.01 (m, 2H), 0.74 (t, J = 6.7, 4.4 Hz, 2H).



Intermediate 1d: 2-chloro-7-cyclopropylquinoxaline

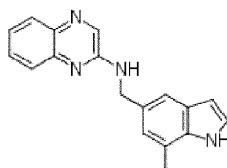
- 10 A mixture of (1c) 7-cyclopropyl-1H-quinoxalin-2-one, (43 mg, 0.23 mmol) and phosphoryl chloride, (370 μL, 1.65 g/mL, 3.93 mmol, 17 eq) was heated to 110° C for 1 h. The mixture was added dropwise to ice and stirred until the reagent was quenched. The aqueous layer was neutralised with 1 M NaOH(aq), whilst stirring in an ice bath, and extracted with ethyl acetate 3x. The combined organics were dried over anhydrous MgSO₄, filtered,
- 15 and concentrated to a crude brown oil. The material was transferred in ethyl acetate (3 mL) and dried on a Biotage V10 evaporator to afford title compound 1d (27.7 mg, 0.14 mmol, 59%) as a brown gum. LCMS (method A); RT 1.25 min, m/z [M+H]⁺ 205.2. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 8.89 (s, 1H), 8.03 (d, J = 8.7 Hz, 1H), 7.74 (d, J = 2.0 Hz, 1H), 7.63 (dd, J = 8.7, 2.0 Hz, 1H), 2.23 (m, 1H), 1.17 – 1.10 (m, 2H), 1.00 – 0.82
- 20 (m, 2H).



Exemplification 1: 7-cyclopropyl-N-(1H-indol-6-ylmethyl)quinoxalin-2-amine

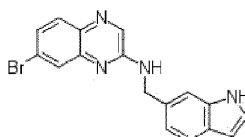
- 25 A mixture of (1d) 2-chloro-7-cyclopropylquinoxaline, (27 mg, 0.13 mmol), (1H-indol-6-yl) methanamine (21 mg, 0.15 mmol, 1.1 eq) and 1,4-dioxane (1 mL) was heated to 90° C for 19 h. The reaction mixture was partitioned between ethyl acetate and water, the aqueous layer was extracted a further twice with ethyl acetate. The combined organics were washed with brine, dried over anhydrous MgSO₄, filtered, and evaporated to dryness. The crude material was dissolved in DMSO (2.5 mL) and purified by reverse
- 30 phase (AccQPrep HP125 prep HPLC) at pH 9 to afford title compound 1 (4.3 mg, 0.01 mmol, 10%) as a dark yellow solid. LC-HRMS (method B); RT 1.18 min; target mass

314.1531; found mass ion $[M+H]^+$ 315.1608; found empirical formula $C_{20}H_{18}N_4$. 1H NMR (400 MHz, DMSO- d_6) δ ppm 11.00 (app s, 1H), 8.27 (s, 1H), 7.97 (t, $J = 5.7$ Hz, 1H), 7.62 (d, $J = 8.4$ Hz, 1H), 7.49 (d, $J = 8.1$ Hz, 1H), 7.42 – 7.38 (m, 1H), 7.31 – 7.27 (m, 1H), 7.22 (d, $J = 2.0$ Hz, 1H), 7.07 – 7.01 (m, 2H), 6.40 – 6.36 (m, 1H), 4.68 (d, $J = 5.7$ Hz, 2H), 2.09 – 1.99 (m, 1H), 1.05 – 0.97 (m, 2H), 0.82 – 0.74 (m, 2H).



Exemplification 2: N-[(7-methyl-1H-indol-5-yl)methyl]quinoxalin-2-amine

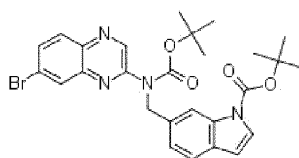
To a mixture of 2-Chloroquinoxaline, (100 mg, 0.61 mmol), (7-methyl-1H-indol-5-yl)methanamine, (117 mg, 0.73 mmol, 1.2 eq) and potassium carbonate (235 mg, 1.7 mmol, 2.8 eq) in 1,4-dioxane (3 mL) was heated to 90° C for 24 h. The reaction mixture was cooled to rt, diluted with water and ethyl acetate. The aqueous layer was extracted a further 2 times with ethyl acetate. The combined organics were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated. The crude material was dry loaded onto ISOLUTE, HM-N and purified by automated flash chromatography (Combiflash Rf 300+, Gold RediSep, 24 g silica column) eluting with gradient heptane to 100% ethyl acetate in heptane to afford 85 mg as a yellow solid. The material was dissolved in DMSO and MeOH and further purified by preparative HPLC pH 9 to afford title compound 2 (40.2 mg, 0.14 mmol, 23%) as a yellow solid. LC-HRMS (method B); RT 1.04 min; target mass 288.1375; found m/z $[M+H]^+$ 289.1455; found empirical formula $C_{18}H_{16}N_4$. 1H NMR (400 MHz, DMSO- d_6) δ ppm 11.01 (app s, 1H), 8.37 (s, 1H), 7.96 (t, $J = 5.5$ Hz, 1H), 7.78 – 7.73 (m, 1H), 7.60 – 7.50 (m, 2H), 7.42 – 7.38 (m, 1H), 7.34 – 7.28 (m, 2H), 6.97 – 6.93 (m, 1H), 6.41 – 6.36 (m, 1H), 4.63 (d, $J = 5.5$ Hz, 2H), 2.46 (s, 3H).



Intermediate 3a: 7-bromo-N-(1H-indol-6-ylmethyl)quinoxalin-2-amine

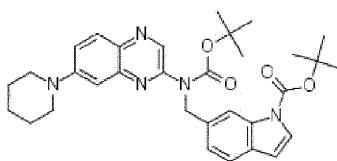
7-bromo-2-chloroquinoxaline (200 mg, 0.82 mmol) was taken up in 1,4-dioxane (8 mL) and (1H-indol-6-yl)methanamine (120 mg, 0.82 mmol, 1 eq) and potassium carbonate

(230 mg, 1.64 mmol, 2 eq) were added. The mixture was heated to 90° C under nitrogen. The reaction mixture was cooled to rt and partitioned between EtOAc/H₂O. The organics were dried over anhydrous MgSO₄, filtered, evaporated onto ISOLUTE, HM-N and purified by automated flash chromatography (Combiflash Rf 300+, RediSep 12 g silica column) eluting heptane to 50% ethyl acetate in heptane to afford title compound 3a (238 mg, 0.67 mmol, 82%) as a colourless gum. LCMS (method A); RT 1.23 min; m/z [M+H]⁺ 353.2. ¹H-NMR (400 MHz, DMSO-d₆) δ ppm 11.02 (s, 1H), 8.38 (s, 1H), 8.29 (t, J = 5.6 Hz, 1H), 7.72 (d, J = 2.1 Hz, 1H), 7.69 (d, J = 8.6 Hz, 1H), 7.50 (dt, J = 8.0, 0.8 Hz, 1H), 7.46 – 7.38 (m, 2H), 7.30 (dd, J = 3.1, 2.4 Hz, 1H), 7.04 (dd, J = 8.1, 1.5 Hz, 1H), 6.39 (ddd, J = 3.0, 2.0, 0.9 Hz, 1H), 4.68 (d, J = 5.6 Hz, 2H).



Intermediate 3b: tert-butyl 6-[[[(7-bromoquinoxalin-2-yl)(tert-butoxycarbonyl)amino]methyl]indole-1-carboxylate

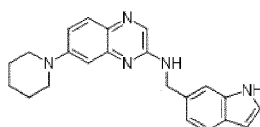
7-bromo-N-(1H-indol-6-ylmethyl)quinoxalin-2-amine 3a (152 mg, 0.43 mmol, 1 eq) was taken up in DCM (6 mL) and treated with DMAP (16 mg, 0.13 mmol, 0.3 eq) and DIPEA, (157 μL, 0.78 g/mL, 0.95 mmol, 2.2 eq), followed by boc-anhydride, (275 mg, 1.29 mmol, 3 eq). The mixture was stirred at rt under nitrogen for 2 h and was partitioned between DCM and (sat) NaHCO₃(aq). The organics passed through a phase separator, evaporated onto ISOLUTE, HM-N and purified by automated flash chromatography (Combiflash 300+, RediSep 12 g silica column) eluting heptane to 15% ethyl acetate heptane to furnish title compound 3b (182 mg, 0.33 mmol, 76%) as a clear gum. LCMS (method A); RT 1.59 min; m/z [M-tBu+H]⁺ 497.



Intermediate 3c: tert-butyl 6-[[[(tert-butoxycarbonyl)[7-(piperidin-1-yl)quinoxalin-2-yl]amino]methyl]indole-1-carboxylate

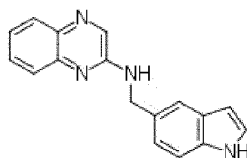
tert-butyl 6-[[[(7-bromoquinoxalin-2-yl)(tert-butoxycarbonyl)amino]methyl]indole-1-carboxylate 3b (90 mg, 0.16 mmol, 1 eq) in toluene (3 mL) was treated with piperidine

(48.3 μ L, 0.49 mmol, 3 eq); sodium tert-butoxide, (18.75 mg, 0.2 mmol, 1.2 eq). The mixture was sparged with nitrogen before adding. Palladium (II) 3-(methylamino)-2-phenylbenzen-1-ide dicyclohexyl[2-(2,6 diisopropoxyphenyl)phenyl]phosphane methanesulfonate, (7 mg, 8.13 μ mol, 0.05 eq) and RuPhos (3.8 mg, 8.13 μ mol, 0.05 eq).
 5 The vessel was sealed and heated to 120° C behind a blast shield for 16 h. The reaction mixture was cooled to rt and was partitioned between EtOAc/sat NaHCO₃(aq). The organics were dried over anhydrous MgSO₄, filtered and evaporated onto ISOLUTE, HM-N before purified by automated flash chromatography (Combiflash Rf 300+, Silica 12 g RediSep column) eluting with heptane to 20% ethyl acetate in heptane to furnish title compound 3c (51 mg, 0.09 mmol, 56%) as a green gum. LCMS (method B); RT 1.56
 10 min; m/z [M+H]⁺ 558.3.



Exemplification 3: N-(1H-indol-6-ylmethyl)-7-(piperidin-1-yl)quinoxalin-2-amine

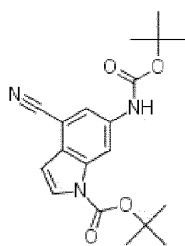
tert-butyl 6-[[[(tert-butoxycarbonyl)[7-(piperidin-1-yl)quinoxalin-2-yl]amino]methyl]indole-1-carboxylate 3c (51 mg, 0.09 mmol) in hexafluoro-2-propanol (2 mL) was heated to 100°
 15 C for 2 h. The reaction was cooled to rt and evaporated before being retaken up in DCM and dry loaded onto ISOLUTE, HM-N and purified by automated flash chromatography (Combiflash Rf 300+, RediSep, 4 g silica column) eluting heptane to 100% ethyl acetate to furnish title compound 3 (19 mg, 0.05 mmol, 58%) as a yellow solid. LC-HRMS
 20 (method B); RT 1.13 min; target mass 357.1965; found m/z [M+H]⁺ 358.2041; found empirical formula C₂₂H₂₃N₅. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 10.99 (app s, 1H), 8.07 (s, 1H), 7.79 (t, J = 5.7 Hz, 1H), 7.53 (d, J = 9.1 Hz, 1H), 7.49 (d, J = 8.1 Hz, 1H), 7.40 – 7.37 (m, 1H), 7.30 – 7.27 (m, 1H), 7.08 (dd, J = 9.1, 2.8 Hz, 1H), 7.03 (dd, J = 8.1, 1.5 Hz, 1H), 6.78 (d, J = 2.8 Hz, 1H), 6.40 – 6.36 (m, 1H), 4.67 (d, J = 5.7 Hz, 2H), 3.31
 25 – 3.24 (m, 4H), 1.67 – 1.52 (m, 6H).



Exemplification 4: N-(1H-indol-5-ylmethyl)quinoxalin-2-amine

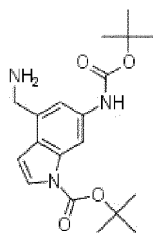
To a mixture of 2-chloroquinoxaline (100 mg, 0.61 mmol), (1H-indol-5-yl)methanamine
 30 (106.58 mg, 0.73 mmol, 1.2 eq) in 1,4-dioxane (3 mL), potassium carbonate (235 mg,

1.7 mmol, 2.8 eq) was added heated to 90° C for 4 days. The reaction mixture was cooled to rt, diluted with water and extracted 3x with ethyl acetate. The combined organics were washed with brine, dried over anhydrous MgSO₄, filtered, and concentrated. The crude liquor was dry loaded onto ISOLUTE, HM-N and purified by automated flash chromatography (Combiflash Rf 300+, Gold RediSep 12 g silica column) eluting with heptane to 100% ethyl acetate and then flushed with 10 % MeOH in DCM. The material was dissolved in DMSO re-purified by preparative HPLC automated chromatography (ISCO AccQPrep HP125) pH 4 and freeze dried to afford title compound 4 (68 mg, 0.25 mmol, 41%) as a yellow solid. LC-HRMS (method B); RT 0.97 min; target mass 274.1221; found m/z [M+H]⁺ 275.1294; found empirical formula C₁₇ H₁₄ N₄. ¹H-NMR (400 MHz, DMSO-d₆) δ ppm 11.03 (app s, 1H), 8.36 (s, 1H), 8.00 (t, J = 5.5 Hz, 1H), 7.78 – 7.73 (m, 1H), 7.59 – 7.50 (m, 3H), 7.38 – 7.34 (m, 1H), 7.34 – 7.29 (m, 2H), 7.15 (dd, J = 8.3, 1.7 Hz, 1H), 6.40 – 6.36 (m, 1H), 4.66 (d, J = 5.5 Hz, 2H).



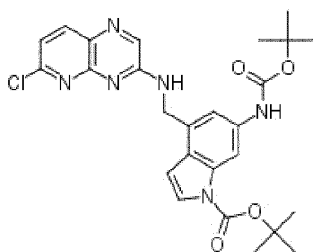
Intermediate 5a: tert-butyl N-(4-cyano-1H-indol-6-yl)carbamate

6-amino-1H-indole-4-carbonitrile [Advanced ChemBlocks Inc, Cat ID Q55346] (250 mg, 1.59 mmol), and DMAP (39 mg, 0.32 mmol, 0.2 eq) in THF (2 mL) and stirred under N₂. To this mixture was added (Boc)₂O (695 mg, 3.2 mmol, 2 eq) in THF (2 mL) followed by TEA (0.46 mL, 3.34 mmol, 2.1 eq) and the reaction was stirred for 1.5 h at rt. The mixture was partitioned between ethyl acetate and sat NaHCO₃ (aq) and the organic layer washed with brine, filtered through a phase separator and concentrated. The crude material was dry loaded onto ISOLUTE, HM-N, HM-N and purified by automated flash chromatography (Combiflash Rf 300+, Gold RediSep, 24 g silica column) eluting heptane/ethyl acetate 0-100% ethyl acetate. The column was further flushed with 10 - 20% MeOH in ethyl acetate to afford 5a (299.7 mg, 0.84 mmol, 53%) which was taken onto the next step without further purification.



Intermediate 5b: tert-butyl 4-(aminomethyl)-6-[(tert-butoxycarbonyl)amino]indole-1-carboxylate

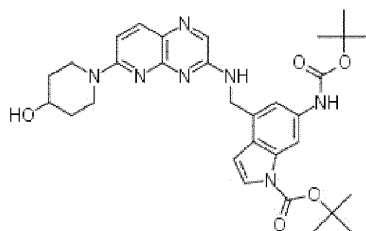
a mixture of 5a tert-butyl 6-[(tert-butoxycarbonyl)amino]-4-cyanoindole-1-carboxylate, (300 mg, 0.84 mmol, 1 eq) in THF (6 mL) and MeOH (6 mL) was cooled to 0° C and cobalt (II) chloride, (217.75 mg, 1.68 mmol, 2 eq) was added and the reaction stirred for 1 min. Sodium borohydride (317.24 mg, 8.39 mmol, 10 eq) was added portion wise over 10 minutes and the reaction warmed to rt for 1 h. The reaction mixture was diluted with ethyl acetate, then filtered through a pad of celite washing with ethyl acetate and 1/10 NH₃OH/water. The organic and aqueous layers were partitioned, and the organic layer dried over MgSO₄, filtered, and concentrated under reduced vacuum. The crude material was dissolved in MeOH/DCM and loaded onto an SCX-2 flash column, washed with 3 column volumes of MeOH/DCM then extracted with 3 column volumes of (1% NH₃/MeOH)/DCM and the concentrated to afford 5b (218 mg, 0.6 mmol) as a crude yellow solid. This material was taken to the subsequent step without further purification.



Intermediate 5c: tert-butyl 6-[(tert-butoxycarbonyl)amino]-4-[(6-chloropyrido[2,3-b]pyrazin-3-yl)amino]methyl]indole-1-carboxylate

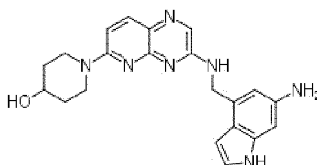
To a mixture of 3,6-dichloropyrido[2,3-b]pyrazine [Combi-Blocks Cat ID JP-8070] (100 mg, 0.5 mmol, 1 eq) and tert-butyl 4-(aminomethyl)-6-[(tert-butoxycarbonyl)amino]indole-1-carboxylate, 5b (216 mg, 0.6 mmol, 1.2 eq) in DCM (5 mL) was added TEA (139 µL, 1 mmol, 2 eq) and the reaction stirred at 0° C for 1 h and then warmed to rt for 24 h. The reaction was quenched with water and the DCM layer was separated, washed with brine, dried over anhydrous MgSO₄ and filtered before was

being dry loaded onto ISOLUTE, HM-N and purified by automated flash chromatography (Combiflash Rf 300+, Gold RediSep, 12 g silica column) eluting with 0-100% ethyl acetate in heptane. The compound was isolated by evaporation under vacuum using Biotage V10 to afford the title compound 5c (57.5 mg, 0.11 mmol, 21.91%) as a yellow solid which was taken to the next step without further purification. LCMS (method A); RT 1.31 min; m/z [M+H]⁺ 1.31.



Intermediate 5e: tert-butyl 6-[(tert-butoxycarbonyl)amino]-4-[(6-{4-hydroxypiperidin-1-yl}pyrido[2,3-b]pyrazin-3-yl)amino)methyl]indole-1-carboxylate

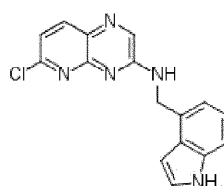
(5f) tert-butyl 6-[(tert-butoxycarbonyl)amino]-4-[(6-chloropyrido[2,3-b]pyrazin-3-yl)amino)methyl]indole-1-carboxylate (57 mg, 0.11 mmol, 1 eq) in 1-propanol (1.1 mL) was treated with 4-hydroxypiperidine (12.08 mg, 0.12 mmol, 1.1 eq) and TEA (30 μ L, 0.22 mmol, 2 eq). The reaction was heated to 100° C for 16 h. The reaction mixture was partitioned between water and ethyl acetate. The aqueous layer was extracted a further twice with ethyl acetate. The combined organic layers were washed with brine, passed through a phase separator and concentrated under vacuum. The crude material was dissolved in DMSO and MeOH, filtered and purified by preparative HPLC automated chromatography (AccQPrep P125, Prep HPLC) and freeze dried to afford the title compound 5e (16.8 mg, 0.03 mmol, 26%) as a yellow solid. LCMS (method A); RT 1.14 min; m/z [M+H]⁺ 590.4



Exemplification 5: 1-(3-[(6-amino-1H-indol-4-yl)methyl]amino)pyrido[2,3-b]pyrazin-6-yl)piperidin-4-ol

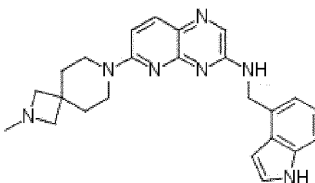
(5e) tert-butyl N-[4-[(6-(4-hydroxypiperidin-1-yl)pyrido[2,3-b]pyrazin-3-yl)amino)methyl]-1H-indol-6-yl]carbamate (5.2 mg, 0.01 mmol, 1 eq) in HFP (300 μ L) was heated to 100° C in a sealed microwave tube (behind a blast shield) for 16 h. The reaction mixture was

concentrated under vacuum and then dissolved in DMSO/MeOH/drop of water and purified by reverse phase automated chromatography (AccQPrep HP125, Prep HPLC) and freeze dried to afford the title compound 5 (2.04 mg, 0.01 mmol, 49%) as a yellow solid. LC-HRMS (method B); RT 1.18 min; target mass 314.1531; found mass ion $[M+H]^+$ 315.1608; found empirical formula C₂₀H₁₈N₄. ¹H-NMR (400 MHz, DMSO-d₆) δ ppm 10.55 – 10.48 (m, 1H), 8.02 (s, 1H), 7.87 (t, J = 5.5 Hz, 1H), 7.77 (d, J = 9.1 Hz, 1H), 6.99 – 6.92 (m, 2H), 6.49 – 6.46 (m, 1H), 6.39 (d, J = 1.9 Hz, 1H), 6.31 – 6.27 (m, 1H), 4.71 (d, J = 5.5 Hz, 2H), 4.22 – 4.10 (m, 2H), 3.79 – 3.68 (m, 1H), 3.29 – 3.18 (m, 2H), 1.86 – 1.74 (m, 2H), 1.43 – 1.29 (m, 2H). NH₂ and OH not observed.



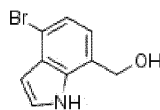
Intermediate 6a: 6-chloro-N-(1H-indol-4-ylmethyl)pyrido[2,3-b]pyrazin-3-amine

A mixture of 3,6-dichloropyrido[2,3-b]pyrazine (100 mg, 0.5 mmol) and 4-aminomethylindole (80 mg, 0.55 mmol, 1.1 eq) in DCM (5 mL) was treated with TEA (140 μ L, 1 mmol, 2 eq) and the reaction stirred at 0° C for 1.5 h and then allowed to warm to rt over 6 h. Water was added and the organic layer was separated, washed with brine, dried over anhydrous MgSO₄ and filtered before being evaporated onto ISOLUTE, HM-N and the purified by automated flash chromatography (Combiflash Rf 300+, Gold RediSep, 12g silica column) eluting with 0-100% ethyl acetate in heptane. The column was the flushed with 10-20% MeOH in ethyl acetate and combined before evaporation. The resultant residue solid was dissolved in DMSO and MeOH and re-purified by preparative automated chromatography (AccQPrep HP125, Prep HPLC) and freeze dried to afford the title compound 6a (41 mg, 0.13 mmol, 26%). LCMS (method A); RT 1.05 min; m/z $[M+H]^+$ 310.2 (chlorine isotopes). ¹H-NMR (400 MHz, DMSO-d₆) δ ppm 11.11 (s, 1H), 8.62 (t, J = 5.6 Hz, 1H), 8.38 (s, 1H), 8.12 (d, J = 8.3 Hz, 1H), 7.34 – 7.24 (m, 3H), 7.04 – 6.91 (m, 2H), 6.53 – 6.45 (m, 1H), 4.82 (d, J = 5.5 Hz, 2H).

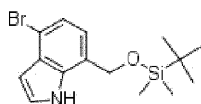


Exemplification 6: N-(1H-indol-4-ylmethyl)-6-{2-methyl-2,7-diazaspiro[3.5]nonan-7-yl}pyrido[2,3-b]pyrazin-3-amine

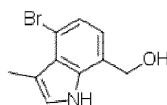
6-chloro-N-(1H-indol-4-ylmethyl)pyrido[2,3-b]pyrazin-3-amine, 6a (87 mg, 0.28 mmol) was taken up in 1-propanol (4 mL) and treated with 2-methyl-2,7-diazaspiro[3.5]nonane dihydrochloride, (89.8 mg, 0.42 mmol, 1.5 eq) and DIPEA (233 μ L, 1.4 mmol, 5 eq). The mixture was heated to 120° C in a sealed tube behind a blast shield for 16 h. After allowing to cool the reaction mixture was partitioned between DCM/brine. The organics were separated via a phase separator and the evaporated to dryness. The residue was re-taken up in DMSO and purified by preparative automated chromatography (AccQPrep HP150, Prep HPLC) and lyophilised on a freeze drier to furnish the title compound 6 (23 mg, 0.05 mmol, 19%) as a yellow solid. LC-HRMS (method B); RT 0.57 min; target mass 413.2328; found mass ion $[M+H]^+$ 413.2332 found empirical formula C₂₄ H₂₇ N₇. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 11.15 (app s, 1H), 8.00 (s, 1H), 7.90 (t, J = 5.5 Hz, 1H), 7.77 (d, J = 8.8 Hz, 1H), 7.37 – 7.29 (m, 2H), 7.04 (t, J = 7.6 Hz, 1H), 7.01 – 6.95 (m, 1H), 6.58 (d, J = 8.8 Hz, 1H), 6.55 – 6.50 (m, 1H), 4.86 (d, J = 5.5 Hz, 2H), 3.65 – 3.35 (br m, 4H), 2.61 – 2.37 (m, 4H), 2.24 (s, 3H), 2.05 – 1.85 (m, 2H), 1.85 – 1.70 (m, 2H).

**Intermediate 7a: (4-bromo-1H-indol-7-yl)methanol**

Methyl 4-bromo-1H-indole-7-carboxylate (500 mg, 1.97 mmol) in THF (20 mL) was cooled to 0° C. LiAlH₄ (2.95 mL (1M), 2.95 mmol, 1.5 eq) was added drop wise and the mixture was allowed to warm to rt for 16 h. The mixture was re-cooled to 0° C and quenched with the addition of water (100 μ L), followed by 15% NaOH(aq) (100 μ L), the whole diluted with EtOAc and dried over anhydrous MgSO₄, before being filtered, and evaporated to furnish title compound 7a (470 mg, 2.08 mmol, quant) as a clear oil. LCMS (method A); RT 1.46 min; m/z $[M+H]^+$ 340. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 11.33 (s, 1H), 7.42 (t, J = 2.8 Hz, 1H), 7.18 (d, J = 7.7 Hz, 1H), 7.01 (dd, J = 7.6, 1.0 Hz, 1H), 6.40 (dd, J = 3.2, 1.8 Hz, 1H), 5.23 (t, J = 5.7 Hz, 1H), 4.75 (dd, J = 5.6, 0.9 Hz, 2H).

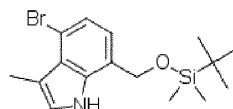
**Intermediate 7b: 4-bromo-7-(((tert-butyldimethylsilyl)oxy)methyl)-1H-indole**

A mixture of (7a) (4-bromo-1H-indol-7-yl)-methanol (470 mg, 2 mmol); TBDMS-Cl (376 mg, 2.5 mmol, 1.2 eq) and imidazole (350 mg, 5.2 mmol, 2.5 eq) in THF (15 mL) was stirred at rt under nitrogen for 16 h. The reaction mixture was partitioned between EtOAc/H₂O, organics were dried over anhydrous MgSO₄, filtered and evaporated to dryness. The compound was purified by automated flash chromatography (Combiflash Rf 300+, RediSep 24 g silica column) eluting heptane to 10% ethyl acetate in heptane to furnish title compound 7b (514 mg, 1.51 mmol, 73%) as a beige solid. LCMS (method A); RT 1.46 min; m/z [M+H]⁺ 341.



Intermediate 7c: (4-bromo-3-methyl-1H-indol-7-yl)methanol

A mixture of 4-bromo-7-[[[(tert-butyldimethylsilyl)oxy]methyl]-1H-indole 7b (514 mg, 1.5 mmol); KO^tBu (170 mg, 1.51 mmol, 1 eq) and [Cp*IrCl₂]₂ (12 mg, 0.02 mmol, 0.01 eq) in MeOH (10 mL) in a sealed tube was heated to 120° C behind a blast shield for 48 h. The reaction mixture was cooled and partitioned between EtOAc/brine. The organics were dried over anhydrous MgSO₄, filtered, evaporated onto ISOLUTE, HM-N and purified by automated flash chromatography (Combiflash Rf, Silica 12 g RediSep column) eluting with heptane to 100% ethyl acetate in heptane to furnish title compound 7c (70 mg, 0.29 mmol, 19%) as a beige solid. LCMS (method A); RT 1.02 min; m/z [M+H]⁺ 238. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 10.94 – 10.83 (m, 1H), 7.17 (dq, J = 2.0, 1.0 Hz, 1H), 7.10 (d, J = 7.6 Hz, 1H), 6.94 (d, J = 7.6, 0.9 Hz, 1H), 5.18 (t, J = 5.7 Hz, 1H), 4.70 (dd, J = 5.7, 0.9 Hz, 2H), 2.46 (d, J = 1.1 Hz, 3H).

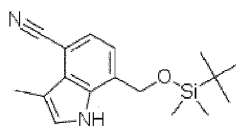


Intermediate 7d: 4-bromo-7-[[[(tert-butyldimethylsilyl)oxy]methyl]-3-methyl-1H-indole

(4-bromo-3-methyl-1H-indol-7-yl)methanol, 7c (70 mg, 0.29 mmol) in THF (4 mL) was treated with TBDMS-Cl (53 mg, 0.35 mmol, 1.2 eq) and imidazole (50 mg 0.73 mmol, 2.5 eq) and stirred at rt under nitrogen for 16 h. The reaction mixture was partitioned between EtOAc/H₂O. The organics were dried over anhydrous MgSO₄, filtered and evaporated onto ISOLUTE, HM-N and purified by automated flash chromatography (Combiflash Rf, RediSep 4 g silica column) eluting with 0-10% ethyl acetate /heptane to

furnish title compound 7d (71 mg, 0.2 mmol, 69%) as a clear oil. LCMS (method A); RT 1.50 min; m/z $[M+H]^+$ 356.2 (bromine isotopes). 1H NMR (400 MHz, DMSO- d_6) δ ppm 10.85 (s, 1H), 7.12 (dd, J = 2.5, 1.2 Hz, 1H), 7.06 (d, J = 7.7 Hz, 1H), 6.88 (d, J = 7.7 Hz, 1H), 4.84 (d, J = 1.0 Hz, 2H), 0.82 (s, 9H), 0.00 (s, 6H).

5



Intermediate 7e: 7-[[tert-butyl(dimethyl)silyl]oxy]methyl]-3-methyl-1H-indole-4-

4-bromo-7-[[tert-butyl(dimethyl)silyl]oxy]methyl]-3-methyl-1H-indole 7d (71 mg, 0.2 mmol) was dissolved in NMP (1.5 mL) and the solution treated with zinc powder (2.6 mg, 0.04 mmol, 0.2 eq) and ZnCN (25 mg, 0.2 mmol, 1 eq), $Pd_2(dba)_3$ (28 mg, 0.03 mmol, 0.15 eq) and $Pd(dppf)Cl_2$ (33 mg, 0.06 mmol, 0.3 eq) were added and the mixture degassed with a stream of nitrogen. The mixture was then heated to 140° C for 24 h. The reaction mixture was cooled to rt, diluted with ethyl acetate and the whole filtered through a pad of celite and rinsed with further EtOAc. The combined organics were washed with brine and dried over anhydrous $MgSO_4$, filtered and onto ISOLUTE, HM-N before being purified by automated flash chromatography (Combiflash Rf 300+, RediSep, 12 g silica column) eluting with 0-40% ethyl Acetate / heptane. Evaporation and drying under vacuum furnished 7e (21 mg, 0.07 mmol, 35%) 3651-SB-033-001 as a colourless solid. LCMS (method A); RT 1.42 min; m/z $[M+H]^+$ 300.2. 1H NMR (400 MHz, DMSO- d_6) δ ppm 11.30 (s, 1H), 7.49 (d, J = 7.5 Hz, 1H), 7.38 (dd, J = 2.5, 1.1 Hz, 1H), 7.23 (dd, J = 7.5, 1.0 Hz, 1H), 5.04 (d, J = 1.0 Hz, 2H), 2.45 (d, J = 1.1 Hz, 3H), 0.92 (s, 9H), 0.10 (s, 6H).

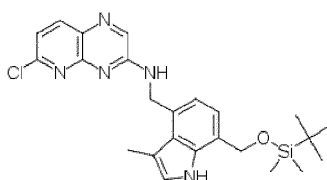


Intermediate 7f: (7-[[tert-butyl(dimethyl)silyl]oxy]methyl]-3-methyl-1H-indol-4-yl)methanamine

7-[[tert-butyl(dimethyl)silyl]oxy]methyl]-3-methyl-1H-indole-4-carbonitrile 7e (21 mg, 0.07 mmol) in MeOH (1.5 mL) and THF (1.5 mL) was cooled to 0° C. The solution was then treated with cobalt (II) chloride (18 mg, 0.14 mmol, 2 eq) was added, after 1 min sodium borohydride (26 mg, 0.7 mmol, 10 eq) was added. Rxn was stirred at rt under N_2 . After

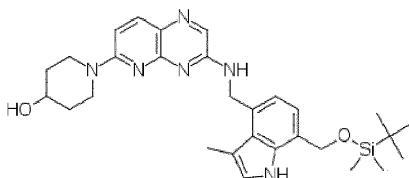
30

15 min, try wk-up. Rxn was diluted with EtOAc and filtered through celite, which was then rinsed with 3% NH₄OH solution. The organics were dried over MgSO₄, filtered and loaded onto ISOLUTE, HM-N and purified by automated flash chromatography (Combiflash Rf 300+, RediSep, 4 g silica column) eluting with 0-12% MeOH in DCM / MeOH (containing 1% 1N NH₃ in MeOH). Evaporation and drying under vacuum furnished title compound 7f (7 mg, 0.02 mmol, 33%) as a colourless solid. LCMS (method A); RT 1.03 min; m/z [M-H]⁻ 303.2. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 10.49 (s, 1H), 7.02 (dd, J = 2.5, 1.2 Hz, 1H), 6.99 (d, J = 7.3 Hz, 1H), 6.90 (d, J = 7.3 Hz, 1H), 4.92 (d, J = 0.9 Hz, 2H), 4.07 (s, 2H), 2.43 (d, J = 1.1 Hz, 3H), 0.90 (s, 9H), 0.07 (s, 6H).



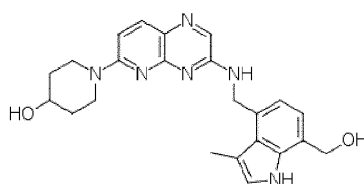
Intermediate 7g: N-[(7-[(tert-butyldimethylsilyl)oxy]methyl)-3-methyl-1H-indol-4-yl)methyl]-6-chloropyrido[2,3-b]pyrazin-3-amine

A mixture of (7-[(tert-butyldimethylsilyl)oxy]methyl)-3-methyl-1H-indol-4-yl)methanamine 7f (7 mg, 0.02 mmol) and 3,6-dichloropyrido[2,3-b]pyrazine (6 mg, 0.03 mmol, 1.2 eq) in DMF (1 mL) was treated with DIPEA (8 μL, 0.05 mmol, 2 eq) and stirred at rt under N₂ for 6 h. The reaction mixture was partitioned between EtOAc and brine. The organics were dried over anhydrous MgSO₄, filtered and evaporated onto ISOLUTE, HM-N before being purified by automated flash chromatography (Combiflash Rf 300+, RediSep, 4 g silica column) eluting with 0-10% ethyl acetate in DCM. Evaporation followed by drying under vacuum furnished title compound 7g (11 mg, 0.02 mmol, quant) as an off white solid. LCMS (method A); RT 1.44 min; m/z [M+H]⁺ 468.2. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 10.60 (d, J = 2.5 Hz, 1H), 8.49 (t, J = 4.8 Hz, 1H), 8.39 (s, 1H), 8.11 (d, J = 8.3 Hz, 1H), 7.30 (d, J = 8.3 Hz, 1H), 7.04 (dd, J = 2.5, 1.2 Hz, 1H), 6.96 (d, 1H), 6.89 (d, J = 7.4 Hz, 1H), 4.88 (s, 2H), 4.84 (d, J = 4.8 Hz, 2H), 2.30 (d, J = 1.0 Hz, 3H), 0.82 (s, 9H), -0.00 (s, 6H).



Intermediate 7h: 1-(3-{[(7-{[(tert-butyldimethylsilyl)oxy]methyl}-3-methyl-1H-indol-4-yl)methyl]amino}pyrido[2,3-b]pyrazin-6-yl)piperidin-4-ol

A mixture of N-[(7-{[(tert-butyldimethylsilyl)oxy]methyl}-3-methyl-1H-indol-4-yl)methyl]-6-chloropyrido[2,3-b]pyrazin-3-amine 7g (11 mg, 0.02 mmol, 1 eq); 4-hydroxypiperidine (7 mg, 0.07 mmol, 3 eq) and DIPEA (20 μ L, 0.78 g/mL, 0.12 mmol, 5 eq) in 1-propanol (1.5 mL) was added to a sealed tube and heated to 120° C behind a blast shield for 16 h. The reaction mixture was cooled to rt before being partitioned between DCM/brine. The organics were passed through a phase separator and evaporated onto ISOLUTE, HM before being purified by automated flash chromatography (Combiflash Rf 300+, RediSep, 4 g silica column) eluting with 0-100% ethyl acetate /heptane. Evaporation and drying under vacuum furnished title compound 7h (10 mg, 0.02 mmol, 80%) as a yellow solid. LCMS (method A); RT 1.26 min; m/z [M+H]⁺ 533.4 ¹H NMR (400 MHz, DMSO-d₆) δ ppm 10.65 (d, J = 2.5 Hz, 1H), 8.04 (s, 1H), 7.83 (t, J = 4.8 Hz, 1H), 7.78 (d, J = 9.0 Hz, 1H), 7.10 (dd, J = 2.4, 1.2 Hz, 1H), 7.02 (d, J = 7.3 Hz, 1H), 6.99–6.86 (m, 2H), 4.95 (s, 2H), 4.88 (d, J = 4.8 Hz, 2H), 4.71 (d, J = 4.3 Hz, 1H), 4.27–4.11 (m, 1H), 3.74 (td, J = 8.6, 4.3 Hz, 1H), 3.24 (td, J = 10.1, 4.9 Hz, 2H), 2.39 (d, J = 1.0 Hz, 3H), 1.87–1.74 (m, 2H), 1.41–1.29 (m, 2H), 0.91 (s, 9H), 0.09 (s, 6H).

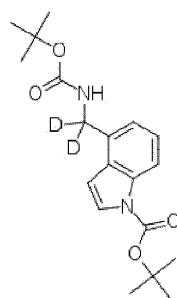


Exemplification 7: 1-[3-{[7-(hydroxymethyl)-3-methyl-1H-indol-4-yl)methyl]amino}pyrido[2,3-b]pyrazin-6-yl]piperidin-4-ol

1-(3-{[(7-{[(tert-butyldimethylsilyl)oxy]methyl}-3-methyl-1H-indol-4-yl)methyl]amino}pyrido[2,3-b]pyrazin-6-yl)piperidin-4-ol 7h (10 mg, 0.02 mmol) in THF (1 mL) was treated with TBAF (1M in THF) (56 μ L 0.06 mmol, 3 eq). After 2.5 h, the whole was partitioned between EtOAc /H₂O. The organics were dried over anhydrous MgSO₄, filtered and evaporated onto ISOLUTE HM-N before being purified by automated flash chromatography (Combiflash Rf 300+, RediSep 4 g silica column) eluting with 2-10% MeOH in DCM to furnish title compound 7 (3 mg, 0.01 mmol, 38%) as a yellow solid. LC-HRMS (method B); RT 0.64 min; target mass 418.2117; found mass ion [M+H]⁺ 419.2198; found empirical formula C₂₃ H₂₆ N₆ O₂. ¹H-NMR (400 MHz, DMSO-d₆) δ ppm 10.65 (d, J = 2.5 Hz, 1H), 8.05 (s, 1H), 7.83 (t, J = 4.9 Hz, 1H), 7.78 (d, J = 9.1 Hz,

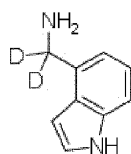
1H), 7.08 (dd, J = 2.4, 1.2 Hz, 1H), 7.02 – 6.93 (m, 2H), 6.90 (d, J = 7.3 Hz, 1H), 5.09 (t, J = 5.6 Hz, 1H), 4.88 (d, J = 4.7 Hz, 2H), 4.73 (dd, J = 9.9, 4.9 Hz, 3H), 4.17 (dt, J = 13.3, 4.6 Hz, 2H), 3.74 (tq, J = 8.6, 4.1 Hz, 1H), 3.32 – 3.18 (m, 2H), 2.39 (d, J = 1.1 Hz, 3H), 1.84 – 1.76 (m, 2H), 1.43 – 1.30 (m, 2H).

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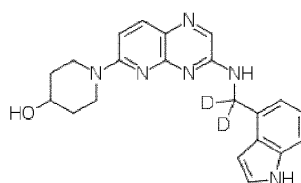
Intermediate 8a: tert-butyl 4-[[[(tert-butoxycarbonyl)amino](²H₂)methyl]indole-1-carboxylate

To a solution of 1-boc-4-bromoindole (500 mg, 1.7 mmol) in dry DMF (15 mL) was added
 10 nickel (II) chloride ethylene glycol dimethyl ether complex (20 mg, 0.08 mmol, 0.05 eq);
 boc-Gly-OH-2,2-d₂ (0.45 mL, 1 g/mL, 2.53 mmol, 1.5 eq); BTMG (0.5 mL, 2.5 mmol, 1.5
 eq); (4,4'-di-*t*-butyl-2,2'-bipyridine)bis[3,5-difluoro-2-[5-trifluoromethyl-2-pyridinyl-
 kN)phenyl-kC]iridium (III) hexafluorophosphate (99%) [CAS:870987-63-6] (20 mg, 17
 15 μmol, 0.01 eq) and BBBPY (23 mg, 0.08 mmol, 0.05 eq) and then the whole degassed
 with a stream of nitrogen for 5 min. The reaction was then irradiated under a blue LED
 (450 nm, 50 W at 75% intensity) at 25° C (cooled via an auxiliary circulating chiller) in a
 Lucent 360 for 16 h. The reaction was then quenched with water and product was
 extracted with EtOAc (x3). The combined organics were washed with brine, dried with
 anhydrous MgSO₄, filtered and dry loaded onto ISOLUTE, HM-N before being purified
 20 by automated flash chromatography (Combiflash Rf 300+, RediSep, 12 g silica column)
 eluting with 0-100% ethyl acetate / heptane. Evaporation and drying furnished the titled
 compound 8a (240 mg, 0.69 mmol, 40%) as a colourless oil. LCMS (method A); RT 1.36
 min; m/z [M-H]⁻ 347.2. ¹H-NMR (400 MHz, DMSO-d₆) δ 7.96 (dt, J = 8.3, 0.9 Hz, 1H),
 7.69 (d, J = 3.8 Hz, 1H), 7.42 (s, 1H), 7.27 (dd, J = 8.3, 7.3 Hz, 1H), 7.10 (dd, J = 7.4,
 25 0.9 Hz, 1H), 6.89 – 6.83 (m, 1H), 1.63 (s, 9H), 1.40 (s, 9H).

**Intermediate 8b: 1H-indol-4-yl(²H₂)methanamine**

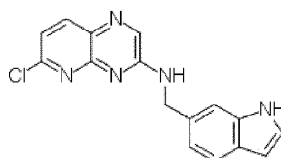
tert-butyl 4-[[[(tert-butoxycarbonyl)amino](²H₂)methyl]indole-1-carboxylate 8a (100 mg, 0.29 mmol, 1 eq) was taken in HPF (3 mL, 28 mmol, 100 eq) sealed and heated to 110° C behind a blast shield for 16 h. The reaction mixture was cooled then concentrated and the crude residue then dissolved in DCM/MeOH and loaded onto an SCX cartridge and loaded with DCM/MeOH. The product was extracted with DCM/ 7N NH₃ in MeOH and evaporated to furnish title compound 8b (45 mg, 0.3 mmol, 105.8%) as a brown gum.

¹H-NMR (400 MHz, DMSO-d₆) δ ppm 11.35 (s, 1H), 7.49 – 7.39 (m, 2H), 7.40 – 7.20 (m, 2H), 7.18 – 7.09 (m, 2H), 6.67 (ddd, J = 3.0, 1.9, 0.9 Hz, 1H).

**Exemplification 8: 1-(3-{[1H-indol-4-yl(²H₂)methyl]amino}pyrido[2,3-b]pyrazin-6-yl)piperidin-4-ol**

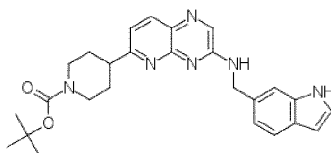
DIPEA (0.11 mL, 0.61 mmol, 1.2 eq) was added to a solution of 3,6-dichloropyrido[2,3-b]pyrazine (121.47 mg, 0.61 mmol, 1.2 eq) and 1H-indol-4-yl(²H₂)methanamine (75 mg, 0.51 mmol, 1 eq) in NMP (3 mL) and stirred for 1 h. 4-hydroxypiperidine (155 mg, 1.52 mmol, 3 eq) and further DIPEA (0.26 mL, 1.52 mmol, 3 eq) were added before the reaction was sealed, and heated in a microwave to 150° C for 2 h. The cooled reaction mixture was quenched with water and extracted with EtOAc (x3). The combined organics were washed with brine, dried over anhydrous MgSO₄, filtered and concentrated. The resultant residue was redissolved in DMSO (1.5 mL) and purified by preparative HPLC automated chromatography (ISCO AccQPrep HP125, Prep HPLC) and solvent was removed via freeze drying for 16 h to furnish the titled compound 8 (7 mg, 0.02 mmol, 4%) was obtained as a yellow solid. LC-HRMS (method B); RT 0.67 min; target mass 376.1981; found m/z [M+H]⁺ 377.2058; found empirical formula C₂₁ H₂₀ D₂ N₆ O. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 11.15 (app s, 1H), 8.02 (s, 1H), 7.91 (s, 1H), 7.78 (d, J = 9.0 Hz, 1H), 7.36 – 7.30 (m, 2H), 7.04 (dd, J = 8.0, 7.1 Hz, 1H), 7.00 – 6.93 (m, 2H),

6.55 – 6.51 (m, 1H), 4.71 (d, J = 4.2 Hz, 1H), 4.21 – 4.11 (m, 2H), 3.78 – 3.68 (m, 1H), 3.29 – 3.19 (m, 2H), 1.86 – 1.74 (m, 2H), 1.42 – 1.30 (m, 2H).



5 **Intermediate 9a: 6-chloro-N-(1H-indol-6-ylmethyl)pyrido[2,3-b]pyrazin-3-amine**

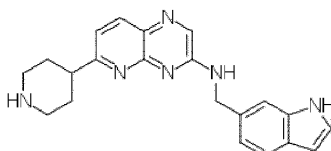
To a mixture of 3,6-Dichloropyrido[2,3-b]pyrazine (1.3 g, 6.5 mmol, 1 eq) and 1H-indole-6-methanamine (855 mg, 5.85 mmol, 0.9 eq) in DCM (60 mL) was added TEA (1.81 mL, 13 mmol, 2 eq) and the reaction stirred at 0° C for 1 h then warmed to rt for 3 h. The reaction was quenched with water and the organic layer was washed with brine, dried over anhydrous MgSO₄ and filtered, before evaporating onto ISOLUTE, HM-N and then purified by automated flash chromatography (Combiflash Rf 300+, Silica 40 g Gold RediSep 40 g silica column) eluting with 0-100% (3:1 EtOAc/EtOH) heptane. Evaporation on a Biotage V10 afforded the title compound 9a (1.37 g, 4.42 mmol, 76%) as a yellow solid. LCMS (method A); RT 0.938 min; m/z [M+H]⁺ 310.1 (chlorine isotopes). ¹H NMR (400 MHz, DMSO-d₆) δ ppm 11.05 (s, 1H), 8.76 – 8.66 (m, 1H), 8.44 (s, 1H), 8.19 (d, J = 8.3 Hz, 1H), 7.52 (d, J = 8.1 Hz, 1H), 7.47 – 7.41 (m, 1H), 7.38 (d, J = 8.3 Hz, 1H), 7.35 – 7.27 (m, 1H), 7.06 (dd, J = 8.1, 1.5 Hz, 1H), 6.43 – 6.37 (m, 1H), 4.73 (d, J = 5.7 Hz, 2H).



20 **Intermediate 9b: tert-butyl 4-(3-(((1H-indol-6-yl)methyl)amino)pyrido[2,3-b]pyrazin-6-yl)piperidine-1-carboxylate**

In a rodavis RBF, a mixture of 6-chloro-N-(1H-indol-6-ylmethyl)pyrido[2,3-b]pyrazin-3-amine 9a (100 mg, 0.32 mmol); Pd(dppf)Cl₂:DCM complex (2.6 mg, 0.01 eq); potassium carbonate (133.85 mg, 0.97 mmol, 3 eq) and N-Boc-1,2,3,6-tetrahydropyridine-4-boronic acid pinacol ester (110 mg, 0.36 mmol, 1.1 eq) in THF (5 mL) and water (1 mL) was sparged with a stream of nitrogen for 5 min and stirred under nitrogen 70° C for 16 h under N₂. The reaction was cooled to rt then 10%Pd/C (30 mg cat) in propan-2-ol (1 mL) was added and the mixture further diluted with MeOH (5 mL). The flask was evacuated and backfilled with N₂ three times followed by a final evacuation and

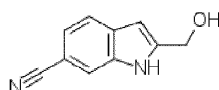
backfilling with H₂(g). The flask was shaken at rt under 1 atm of H₂ for 16 h and uptake of H₂ measured by volume. The mixture was then filtered through celite under N₂, washing with aliquots of DCM. The combined organics were washed with sat NaHCO₃(aq) before being dried over anhydrous MgSO₄. The whole was re-filtered and
 5 evaporated onto ISOLUTE, HM-N and purified by automated flash chromatography (Combiflash Rf 300+, Gold RediSep, 12 g silica column) eluting with 0-100% ethyl acetate/heptane to afford title compound 9b (123 mg, 0.27 mmol, 83%) as a yellow solid. LCMS (method A); RT 1.12 min; m/z [M-tBu+H]⁺ 459.4. ¹H NMR (400 MHz, DMSO-d₆)
 10 δ ppm 11.05 – 10.98 (m, 1H), 8.38 (s, 1H), 8.07 (d, J = 8.2 Hz, 1H), 7.51 (d, J = 8.1 Hz, 1H), 7.41 (s, 1H), 7.30 (t, 1H), 7.28 (d, J = 8.2 Hz, 1H), 7.05 (dd, J = 8.1, 1.5 Hz, 1H), 6.39 (dd, J = 3.0, 1.9, 0.9 Hz, 1H), 4.73 (d, J = 5.5 Hz, 2H), 4.09 (d, J = 11.9 Hz, 2H), 3.04 – 2.92 (m, 1H), 1.91 – 1.81 (m, 2H), 1.65 (qd, J = 12.5, 4.3 Hz, 2H), 1.42 (s, 9H).



15 **Exemplification 9: N-(1H-indol-6-ylmethyl)-6-(piperidin-4-yl)pyrido[2,3-b]pyrazin-3-amine**

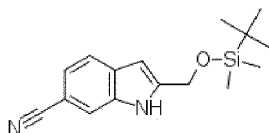
tert-butyl 4-{3-[(1H-indol-6-ylmethyl)amino]pyrido[2,3-b]pyrazin-6-yl}piperidine-1-carboxylate, 3614-CAM-015-002 (123 mg, 0.27 mmol, 1 eq) in HFP (3 mL) was heated to 110° C in a sealed tube behind a blast shield for 16 h. The reaction mixture was
 20 concentrated under vacuum then re-dissolved in DMSO/MeOH/drop of water and purified by preparative HPLC automated chromatography (ISCO AccQPrep HP125, Prep HPLC) and freeze dried to afford N-(1H-indol-6-ylmethyl)-6-(piperidin-4-yl)pyrido[2,3-b]pyrazin-3-amine (6.8 mg, 0.02 mmol, 7%) as a cream solid. LC-HRMS (method B); RT 0.66, target mass 358.1906, found m/z 359.1982, found formula C₂₁
 25 H₂₂ N₆. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 11.04 (app s, 1H), 8.42 – 8.34 (m, 2H), 8.09 (d, J = 8.2 Hz, 1H), 7.51 (d, J = 8.1 Hz, 1H), 7.42 – 7.39 (m, 1H), 7.32 – 7.29 (m, 1H), 7.26 (d, J = 8.2 Hz, 1H), 7.05 (dd, J = 8.1, 1.5 Hz, 1H), 6.42 – 6.36 (m, 1H), 4.73 (d, J = 5.5 Hz, 2H), 3.26 – 3.16 (m, 2H), 3.04 – 2.93 (m, 1H), 2.87 – 2.75 (m, 2H), 1.96 – 1.76 (m, 4H). Piperidine NH not observed.

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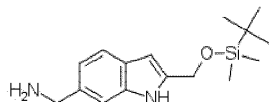


Intermediate 10a: 2-(hydroxymethyl)-1H-indole-6-carbonitrile

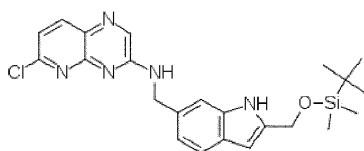
Methyl 6-cyano-1H-indole-2-carboxylate (525 mg, 2.62 mmol) was taken up in THF (20 mL) and cooled to 0° C. LiAlH₄ (2.62 mL (1M in THF), 2.62 mmol, 1 eq) was added dropwise and the mixture allowed to warm to rt. After 15 min, the whole was cooled to 0° C and quenched with 0.1ml H₂O was added, followed by 0.3ml of 15% NaOH(aq) and a further 0.3ml H₂O. The whole was then diluted with EtOAc and dried with the addition of anhydrous MgSO₄. The mixture was filtered and evaporated onto ISOLUTE, HM-N and purified by automated flash chromatography (Combiflash Rf 300+, RediSep, 12 g silica column) eluting with 0-80% ethyl acetate/heptane to furnish title compound 10a (293 mg, 1.7 mmol, 65%) as a yellow solid. LCMS (method A); RT 0.84 min; m/z [M-H]⁻ 172.2. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 11.60 (s, 1H), 7.77 (dt, J = 1.6, 0.8 Hz, 1H), 7.70 – 7.48 (m, 1H), 7.28 (dd, J = 8.2, 1.5 Hz, 1H), 6.43 (dd, J = 2.1, 1.0 Hz, 1H), 5.43 (t, J = 5.6 Hz, 1H), 4.66 (dd, J = 5.5, 0.8 Hz, 2H).

**Intermediate 10b: 2-[[[(tert-butyldimethylsilyl)oxy]methyl]-1H-indole-6-carbonitrile**

2-(hydroxymethyl)-1H-indole-6-carbonitrile 10a (330 mg, 1.92 mmol) in DMF (12 mL) was cooled to 0° C and treated with TBDMS-Cl (477 mg, 3.2 mmol, 1.7 eq) followed by imidazole (390 mg, 3.84 mmol, 5.8 eq) and the mixture stirred at rt for 5 h under N₂. The reaction mixture was partitioned between EtOAc/ sat NH₄Cl(aq) and the organics were dried over anhydrous MgSO₄, filtered and evaporated onto ISOLUTE, HM-N before being purified by automated flash chromatography (Combiflash Rf 300+, RediSep, 12 g silica column) eluting with 0-70% ethyl acetate/heptane to furnish title compound 10b (400 mg, 1.41 mmol, 73%) as a colourless solid. LCMS (method A); RT 1.42 min; m/z [M+H]⁺ 287.2. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 11.64 – 11.51 (m, 1H), 7.80 (dt, J = 1.6, 0.8 Hz, 1H), 7.65 (d, J = 8.2 Hz, 1H), 7.29 (dd, J = 8.2, 1.5 Hz, 1H), 6.47 (dd, J = 2.1, 0.9 Hz, 1H), 4.85 (d, J = 0.9 Hz, 2H), 0.89 (s, 9H), 0.09 (s, 6H).

**Intermediate 10c: (2-[[[(tert-butyldimethylsilyl)oxy]methyl]-1H-indol-6-yl)methanamine**

2-[[[(tert-butyldimethylsilyl)oxy]methyl]-1H-indole-6-carbonitrile 10b (100 mg, 0.35 mmol) in MeOH (2.5 mL) and THF (2.5 mL) was cooled to 0° C and treated with cobalt (II) chloride (90 mg, 0.7 mmol, 2 eq) followed by portion wise addition of sodium borohydride (132 mg, 3.49 mmol, 10 eq) and the mixture stirred at rt under N₂. After 15 min the reaction mixture was partitioned between EtOAc/H₂O (with 2ml NH₄OH(aq) hydroxide solution pre added) and the organics were filtered through celite then dried over anhydrous MgSO₄. The whole was re-filtered and evaporated onto ISOLUTE, HM-N and purified by automated flash chromatography (Combiflash Rf 300+, RediSep, 4 g silica column) eluting with 0-20% MeOH(1% 1N NH₃ in MeOH)/DCM to furnish title compound 10c (53 mg, 0.18 mmol, 52%) as an off-white solid. LCMS (method A); RT 1.07 min; m/z [M-H]⁻ 289.2. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 10.90 (s, 1H), 7.37 (d, J = 8.0 Hz, 1H), 7.29 (s, 1H), 6.92 (dd, J = 8.1, 1.5 Hz, 1H), 6.30 – 6.22 (m, 1H), 4.76 (s, 2H), 3.77 (s, 2H), 2.20 (s, broad 2H), 0.88 (s, 9H), 0.06 (s, 6H).

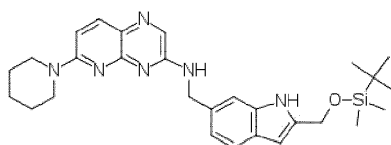


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Intermediate 10d: N-[(2-[[[(tert-butyldimethylsilyl)oxy]methyl]-1H-indol-6-yl)methyl]-6-chloropyrido[2,3-b]pyrazin-3-amine

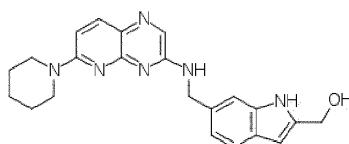
(2-[[[(tert-butyldimethylsilyl)oxy]methyl]-1H-indol-6-yl)methanamine 10c (130.7 mg, 0.45 mmol) in DCM (5 mL) was cooled to 0° C and treated with TEA (125 μL, 0.9 mmol, 2 eq) followed by 3,6-Dichloropyrido[2,3-b]pyrazine (90 mg, 0.45 mmol, 1 eq) and the mixture stirred at 0° C for 1 h. The reaction mixture was then partitioned between DCM and brine. The organics were separated via a phase separator and the organics evaporated onto ISOLUTE, HM-N before purification by automated flash chromatography (Combiflash Rf 300+, RediSep, 12 g silica column) eluting 0-100% ethyl acetate/heptane to furnish title compound 10d (116 mg, 0.26 mmol, 57%) as an off-white solid. LCMS (method A); RT 1.42 min; m/z 454.4 (chlorine isotopes) [M+H]⁺ 454.4 (chlorine isotopes). ¹H NMR (400 MHz, DMSO-d₆) δ ppm 10.98 (d, J = 1.9 Hz, 1H), 8.71 (t, J = 5.8 Hz, 1H), 8.43 (s, 1H), 8.18 (d, J = 8.3 Hz, 1H), 7.45 (d, J = 8.1 Hz, 1H), 7.40 – 7.33 (m, 2H), 7.02 (dd, J = 8.1, 1.5 Hz, 1H), 6.28 (dd, J = 2.1, 0.9 Hz, 1H), 4.76 (d, J = 0.7 Hz, 2H), 4.70 (d, J = 5.6 Hz, 2H), 0.87 (s, 9H), 0.05 (s, 6H).

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Intermediate 10e: N-[(2-[[tert-butyl(dimethyl)silyl]oxy]methyl)-1H-indol-6-yl)methyl]-6-(piperidin-1-yl)pyrido[2,3-b]pyrazin-3-amine

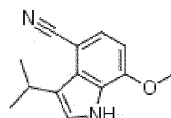
N-[(2-[[tert-butyl(dimethyl)silyl]oxy]methyl)-1H-indol-6-yl)methyl]-6-chloropyrido[2,3-b]pyrazin-3-amine 10d (116 mg, 0.26 mmol) in 1-propanol (5 mL) was treated with piperidine (30 μ L, 0.31 mmol, 1.2 eq) and TEA (70 μ L, 0.51 mmol, 2 eq) and was heated to 100° C under N₂. The reaction mixture was partitioned between DCM and brine and the organics were separated using a phase separator. The organics were evaporated onto ISOLUTE, HM-N and purified by automated flash chromatography (Combiflash Rf 300+, RediSep, 4 g silica column) eluting 0-60% ethyl acetate/ heptane to furnish 10e (39 mg, 0.08 mmol, 30%) as a yellow solid. LCMS (method A); RT 1.42 min; m/z [M+H]⁺ 503.4. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 10.94 (d, J = 2.1 Hz, 1H), 8.01 (s, 1H), 7.94 (t, J = 5.7 Hz, 1H), 7.77 (d, J = 9.0 Hz, 1H), 7.43 (d, J = 8.1 Hz, 1H), 7.33 (s, 1H), 6.99 (dd, J = 8.1, 1.5 Hz, 1H), 6.94 (d, J = 9.1 Hz, 1H), 6.27 (dd, J = 2.1, 0.9 Hz, 1H), 4.76 (s, 2H), 4.68 (d, J = 5.6 Hz, 2H), 3.68 (t, J = 5.4 Hz, 4H), 1.64 (q, J = 5.1, 4.2 Hz, 2H), 1.59 – 1.49 (m, 4H), 0.87 (s, 9H), 0.05 (s, 6H).



Exemplification 10: [6-({[6-(piperidin-1-yl)pyrido[2,3-b]pyrazin-3-yl]amino}methyl)-1H-indol-2-yl]MeOH

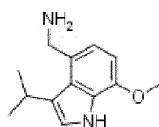
N-[(2-[[tert-butyl(dimethyl)silyl]oxy]methyl)-1H-indol-6-yl)methyl]-6-(piperidin-1-yl)pyrido[2,3-b]pyrazin-3-amine 10e (39 mg, 0.08 mmol) in THF (3 mL) was treated with TBAF (1M in THF) (120 μ L 0.12 mmol, 1.5 eq) and stirred at rt under N₂. After 90 min the reaction mixture was partitioned between EtOAc/H₂O. The organics were dried over anhydrous MgSO₄, filtered, and evaporated onto ISOLUTE, HM-N before being purified by automated flash chromatography (Combiflash Rf 300+, RediSep, 4 g silica column) eluting with 0-100% ethyl acetate/heptane. The residue from evaporation was triturated with diethyl ether and collected via filtration. The solid filter cake was dried *in vacuo* at 40° C to furnish title compound 10 (22 mg, 0.06 mmol, 72%) as a yellow solid. LC-HRMS (method B): rt 0.84, target mass 388.2012, found m/z 389.2093, found formula C₂₂ H₂₄

N6 O. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 10.93 (app s, 1H), 8.00 (s, 1H), 7.93 (t, J = 5.7 Hz, 1H), 7.77 (d, J = 9.1 Hz, 1H), 7.41 (d, J = 8.1 Hz, 1H), 7.33 – 7.29 (m, 1H), 6.98 (dd, J = 8.1, 1.4 Hz, 1H), 6.94 (d, J = 9.1 Hz, 1H), 6.25 – 6.21 (m, 1H), 5.19 (t, J = 5.6 Hz, 1H), 4.67 (d, J = 5.7 Hz, 2H), 4.57 (d, J = 5.6 Hz, 2H), 3.74 – 3.61 (m, 4H), 1.69 – 1.50 (m, 6H).



Intermediate 11a: 3-isopropyl-7-methoxy-1H-indole-4-carbonitrile

To toluene (12 mL) in a sealed tube was added TFA 99% (0.39 mL 5.23 mmol, 1.5 eq) and triethylsilane, (1.67 mL 10 mmol, 3 eq). 7-Methoxy-1H-indole-4-carbonitrile was added (600 mg, 3.48 mmol) portion wise followed by acetone (2.56 mL 35 mmol, 10 eq). The mixture was degassed with a stream of nitrogen for 5 min and then sealed and heated to 130° C behind a blast shield for 24 h. The whole was partitioned between DCM/ sat NaHCO₃ (aq). The organics were separated and evaporated onto ISOLUTE, HM-N and purified by automated flash chromatography (Combiflash Rf 300+, RediSep, 24 g silica column) eluting with heptane to 25% ethyl acetate/heptane to furnish the title compound 11a (62 mg, 0.29 mmol, 8%) as a colourless solid. LCMS (method A); RT 1.12 min; m/z [M+H]⁺ 215.2. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 11.56 (s, 1H), 7.47 (d, J = 8.2 Hz, 1H), 7.26 (dd, J = 2.6, 0.8 Hz, 1H), 6.81 (d, J = 8.2 Hz, 1H), 3.99 (s, 3H), 3.54 - 3.39 (m, 1H), 1.30 (d, J = 6.8 Hz, 6H).

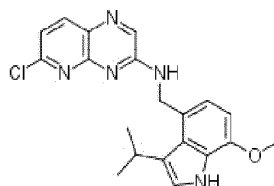


Intermediate 11b: (3-isopropyl-7-methoxy-1H-indol-4-yl)methanamine

3-isopropyl-7-methoxy-1H-indole-4-carbonitrile 11a (96 mg, 0.45 mmol) was dissolved in THF (3 mL) and MeOH (3 mL), and cooled to 0° C. cobalt (II) chloride (116 mg, 0.9 mmol, 2 eq) was added, followed by sodium borohydride (170 mg, 4.48 mmol, 10 eq) portion wise. The reaction mixture was stirred at rt under N₂ for 15 min. The whole was filtered through celite and the celite pad washed with 3% ammonium hydroxide(aq). The combined filtrate was extracted with ethyl acetate and the organics were dried over anhydrous MgSO₄, filtered, evaporated onto ISOLUTE, HM-N and purified by automated flash chromatography (Combiflash 300+, Silica 4 g RediSep column) eluting with 1-10%

MeOH (contains 1% 1N NH₃ in MeOH) in DCM to furnish title compound 11b (57 mg, 0.26 mmol, 58%) as an off-white solid. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 10.82 (s, 1H), 7.00 (dd, J = 2.6, 0.7 Hz, 1H), 6.86 (d, J = 7.9 Hz, 1H), 6.55 (d, J = 7.8 Hz, 1H), 4.02 (d, J = 0.8 Hz, 2H), 3.87 (s, 3H), 3.42 – 3.28 (m, 1H), 1.99 (s, broad 2H), 1.26 (d, J = 6.8 Hz, 6H).

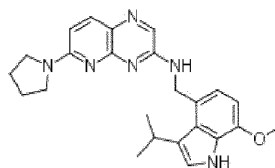
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Intermediate 11c: 6-chloro-N-[(3-isopropyl-7-methoxy-1H-indol-4-yl)methyl]pyrido[2,3-b]pyrazin-3-amine

(3-isopropyl-7-methoxy-1H-indol-4-yl)methanamine 11b (57 mg, 0.26 mmol) in DMF (2.5 mL) was treated with 3,6-dichloropyrido[2,3-b]pyrazine (57mg, 0.29 mmol, 1.1 eq) followed by DIPEA (87 μL, 0.52 mmol, 2 eq) and stirred at rt under N₂ for 16 h. The reaction mixture was partitioned between DCM/brine. The organics were separated via a phase separator and subsequently evaporated onto ISOLUTE, HM-N and purified by automated flash chromatography (Combiflash Rf 300+, RediSep, 4 g silica column) eluting with 0-40% ethyl acetate/heptane to furnish 11c (88 mg, 0.23 mmol, 88%) as a yellow solid. LCMS (method A); RT 1.19 min; m/z [M+H]⁺ 382.2 (chlorine isotopes). ¹H NMR (400 MHz, DMSO-d₆) δ ppm 11.02 (s, 1H), 8.54 (t, J = 4.8 Hz, 1H), 8.47 (s, 1H), 8.20 (d, J = 8.3 Hz, 1H), 7.39 (d, J = 8.3 Hz, 1H), 7.10 (d, J = 2.6 Hz, 1H), 6.92 (d, J = 7.9 Hz, 1H), 6.61 (d, J = 7.9 Hz, 1H), 4.86 (d, J = 4.7 Hz, 2H), 3.90 (s, 3H), 3.28 – 3.17 (m, 1H), 1.23 (d, J = 6.7 Hz, 6H).

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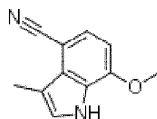


Exemplification 11: N-[(3-isopropyl-7-methoxy-1H-indol-4-yl)methyl]-6-(pyrrolidin-1-yl)pyrido[2,3-b]pyrazin-3-amine

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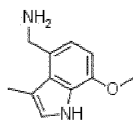
6-chloro-N-[(3-isopropyl-7-methoxy-1H-indol-4-yl)methyl]pyrido[2,3-b]pyrazin-3-amine 11c (44 mg, 0.12 mmol) in 1-propanol (3.5 mL) and treated with pyrrolidine, (20 μL, 0.23 mmol, 2 eq) followed by DIPEA (57 μL, 0.35 mmol, 3 eq) and the mixture heated to 120°

C in a sealed tube behind a blast shield for 16 h. The mixture was partitioned between DCM and brine. The organics were separated via a phase separator and evaporated onto ISOLUTE, HM-N before being purified by automated flash chromatography (Combiflash Rf 300+, RediSep, 4 g silica column) eluting with 0-60% ethyl acetate/heptane to furnish the title compound 11 (33 mg, 0.08 mmol, 70%) as a yellow solid. LC-HRMS (method B): rt 0.89, target mass 416.2325, found m/z 417.2422, found formula C₂₄H₂₈N₆O. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 10.97 (d, J = 2.6 Hz, 1H), 7.99 (s, 1H), 7.77 (d, J = 8.9 Hz, 1H), 7.73 (t, J = 4.7 Hz, 1H), 7.08 (d, J = 2.6 Hz, 1H), 6.87 (d, J = 7.9 Hz, 1H), 6.62 – 6.56 (m, 2H), 4.80 (d, J = 4.7 Hz, 2H), 3.88 (s, 3H), 3.56 – 3.45 (m, 4H), 3.32 – 3.21 (m, 1H), 2.01 – 1.91 (m, 4H), 1.23 (d, J = 6.8 Hz, 6H).



Intermediate 12a: 7-methoxy-3-methyl-1H-indole-4-carbonitrile

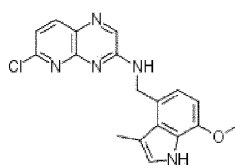
7-Methoxy-1H-indole-4-carbonitrile (900 mg, 5.23 mmol) in MeOH, (25 mL) was treated with KOtBu (587 mg, 5.23 mmol, 1 eq) and [Cp*IrCl₂]₂ (42 mg, 0.05 mmol, 0.01 eq) was degassed with a stream of N₂, sealed and heated to 140° C behind a blast shield for 16 h. The reaction mixture was partitioned between EtOAc/brine. The organics were dried over anhydrous MgSO₄, filtered and evaporated onto ISOLUTE, HM-N and purified by automated flash chromatography (Combiflash Rf 300+, Silica 12 g RediSep, 12 g silica column) eluting with 0-40% ethyl acetate/heptane to furnish title compound 12a (139 mg, 0.74 mmol, 14%) as a colourless solid. LCMS (method A); RT 0.98 min; m/z [M+H]⁺ 187.2. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 11.50 (s, 1H), 7.46 (d, J = 8.1 Hz, 1H), 7.25 (dd, J = 2.5, 1.1 Hz, 1H), 6.80 (d, J = 8.1 Hz, 1H), 3.99 (s, 3H), 2.42 (d, J = 1.0 Hz, 3H).



Intermediate 12b:(7-methoxy-3-methyl-1H-indol-4-yl)methanamine

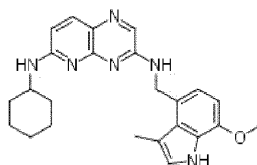
7-methoxy-3-methyl-1H-indole-4-carbonitrile 12a (314 mg, 1.69 mmol) in THF (11 mL) and MeOH (11 mL) was stirred under N₂ at 0° C. The solution was treated with cobalt (II) chloride (440 mg, 3.37 mmol, 2 eq), followed by portion wise, sodium borohydride (640 mg, 17 mmol, 10 eq) and stirred at rt for 15 min. The reaction mixture was diluted

with EtOAc, filtered through celite, which was rinsed with 3% NH₄OH(aq) and organics separated and dried over anhydrous MgSO₄. The whole was re-filtered and evaporated onto ISOLUTE, HM-N before being purified by automated flash chromatography (Combiflash Rf 300+, RediSep, 12 g silica column) eluting with 0-10% MeOH (containing 1% 1N NH₃ in MeOH) /DCM to furnish title compound 12b (176 mg, 0.93 mmol, 54.86%) as a colourless solid. ¹H-NMR (400 MHz, DMSO-d₆) δ ppm 10.74 (s, 1H), 6.95 (dd, J = 2.5, 1.1 Hz, 1H), 6.80 (d, J = 7.8 Hz, 1H), 6.53 (d, J = 7.8 Hz, 1H), 4.02 (s, 2H), 3.87 (s, 3H), 2.41 (d, J = 1.0 Hz, 3H).



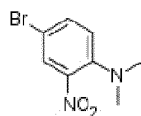
Intermediate 12c: 6-chloro-N-[(7-methoxy-3-methyl-1H-indol-4-yl)methyl]pyrido[2,3-b]pyrazin-3-amine

(7-methoxy-3-methyl-1H-indol-4-yl)methanamine 12b (114 mg, 0.6 mmol) in DCM (10 mL) was treated with TEA (170 μL, 1.2 mmol, 2 eq) and the solution cooled to 0° C. The mixture was then treated with 3,6-dichloropyrido[2,3-b]pyrazine (120 mg, 0.6 mmol, 1 eq) and stirred at 0° C for 1 h, and then at rt for a further 16 h under N₂. The reaction mixture was partitioned between DCM/brine. The organics were separated via a phase separator and evaporated onto ISOLUTE, HM-N before being purified by automated flash chromatography (Combiflash Rf 300+, RediSep, 12 g silica column) eluting with 0-50% ethyl acetate/heptane to furnish title compound 12c (53 mg, 0.15 mmol, 25%) as a yellow solid. LCMS (method A); RT 1.06 min; m/z [M+H]⁺ 354.2 (chlorine isotopes). ¹H NMR (400 MHz, DMSO-d₆) δ ppm 10.92 (d, J = 2.3 Hz, 1H), 8.52 (t, J = 4.8 Hz, 1H), 8.47 (s, 1H), 8.20 (d, J = 8.3 Hz, 1H), 7.39 (d, J = 8.3 Hz, 1H), 7.03 (dd, J = 2.5, 1.2 Hz, 1H), 6.91 (d, J = 7.8 Hz, 1H), 6.60 (d, J = 7.9 Hz, 1H), 5.76 (s, 1H), 4.84 (d, J = 4.6 Hz, 2H), 3.90 (s, 3H), 2.34 (d, J = 1.1 Hz, 3H).

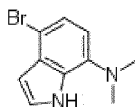


Exemplification 12: 6-N-cyclohexyl-3-N-[(7-methoxy-3-methyl-1H-indol-4-yl)methyl]pyrido[2,3-b]pyrazine-3,6-diamine

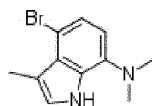
6-chloro-N-[(7-methoxy-3-methyl-1H-indol-4-yl)methyl]pyrido[2,3-b]pyrazin-3-amine 12c (53 mg, 0.15 mmol) in 1-propanol (5 mL) was treated with cyclohexylamine (150 μ L, 1.65 mmol, 9 eq) and DIPEA (125 μ L 0.75 mmol, 5 eq) and the mixture heated to 120° C N₂. After 40 h the reaction was cooled and then was partitioned between DCM/brine. The organics were separated via a phase separator and evaporated onto ISOLUTE, HM-N before being purified by automated flash chromatography (Combiflash Rf 300+, RediSep, 4 g silica column) eluting with 0-70% ethyl acetate/heptane and dried at 40° C under vacuum to furnish title compound 12 (14 mg, 0.03 mmol, 22%) as a beige solid. LC-HRMS (method B): rt 0.93, target mass 416.2325, found m/z 417.2332, found formula C₂₄ H₂₈ N₆ O. ¹H-NMR (400 MHz, DMSO-d₆) δ ppm 10.87 (d, J = 2.4 Hz, 1H), 7.95 (s, 1H), 7.64 – 7.58 (m, 2H), 7.04 – 6.97 (m, 2H), 6.84 (d, J = 7.8 Hz, 1H), 6.57 (d, J = 7.8 Hz, 1H), 6.53 (d, J = 8.9 Hz, 1H), 4.77 (d, J = 4.6 Hz, 2H), 4.03 – 3.89 (br m, 1H), 3.88 (s, 3H), 2.35 (d, J = 1.0 Hz, 3H), 1.97 – 1.87 (m, 2H), 1.78 – 1.67 (m, 2H), 1.66 – 1.55 (m, 1H), 1.45 – 1.29 (m, 2H), 1.28 – 1.11 (m, 3H).

**Intermediate 13a: 4-bromo-N,N-dimethyl-2-nitroaniline**

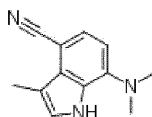
4-Bromo-2-nitroaniline (8 g, 37 mmol) in DMF (180 mL) was cooled to 0° C under N₂ and then treated portion wise with sodium hydride (4.42 g (60% suspension in mineral oil), 111 mmol, 3 eq) and stirred for 30 min. The mixture was treated with methyl iodide (6.9 mL, 111 mmol, 3 eq) dropwise and the mixture stirred at rt for 1 h. The reaction mixture was reduced to half volume and then was partitioned between EtOAc and water. The organics were dried over anhydrous MgSO₄, filtered and evaporated onto ISOLUTE, HM-N before being purified by automated flash chromatography (Combiflash Rf 300+, RediSep, 220 g silica column) eluting as gradient 0-20% ethyl acetate/heptane. Evaporation and drying under vacuum furnished the title compound 13a (8.7 g, 36 mmol, 97%) as an orange oil. LCMS (method A); RT 1.18 min; m/z [M+H]⁺ 245 & 247 (bromine isotopes). ¹H-NMR (400 MHz, DMSO-d₆) δ ppm 7.94 (d, J = 2.5 Hz, 1H), 7.63 (dd, J = 9.1, 2.5 Hz, 1H), 7.15 (d, J = 9.1 Hz, 1H), 2.82 (s, 6H).

**Intermediate 13b: 4-bromo-N,N-dimethyl-1H-indol-7-amine**

4-bromo-N,N-dimethyl-2-nitroaniline 13a (4.52 g, 18.4 mmol) in THF (130 mL) was degassed with a stream of nitrogen and cooled to -78° C (using acetone/CO₂ bath). The solution was then treated with vinylmagnesium bromide (55 mL, 1M in THF, 3 eq) and stirring continued under N₂ at -78° C for 2 h. continued. The reaction was then allowed to warm to 0 C by transfer to an iced bath and stirring continued for a further hour. The reaction mixture was partitioned between EtOAc/sat NH₃Cl(aq) and the organics were dried over anhydrous MgSO₄, filtered and evaporated onto ISOLUTE, HM-N before being purified by automated flash chromatography (Combiflash Rf 300+, RediSep 220 g silica column) eluting with 0-20% ethyl acetate/heptane to furnish title compound 13b (2.1 g, 8.8 mmol, 48%) as a beige solid. LCMS (method A); RT 1.18 min; m/z [M+H]⁺ 247 (bromine isotopes).

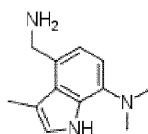
**Intermediate 13c: 4-bromo-N,N,3-trimethyl-1H-indol-7-amine**

4-bromo-N,N-dimethyl-1H-indol-7-amine 13b (700 mg, 2.93 mmol) in MeOH (15mL) was treated with KO^tBu (330 mg, 2.93 mmol, 1 eq) and [Cp*IrCl₂]₂ (23 mg, 0.03 mmol, 0.01 eq). The mixture was sealed and heated to 120° C behind a blast shield for 16 h. The cooled reaction mixture was partitioned between EtOAc/brine. The organics were then dried over anhydrous MgSO₄, filtered and evaporated onto ISOLUTE, HM-N before being purified by automated flash chromatography (Combiflash Rf 300+, Gold RediSep, 40 g silica column) eluting with 0-15% ethyl acetate/heptane to furnish title compound 13c (324 mg, 1.28 mmol, 44%) as a beige solid. LCMS (method A); RT 1.22 min; m/z [M+H]⁺ 253.2 (bromine isotopes). ¹H-NMR (400 MHz, DMSO-d₆) δ ppm 10.87 (s, 1H), 7.10 (dd, J = 2.5, 1.2 Hz, 1H), 7.02 (d, J = 8.1 Hz, 1H), 6.51 (d, J = 8.0 Hz, 1H), 2.75 (s, 6H), 2.44 (d, J = 1.0 Hz, 3H).

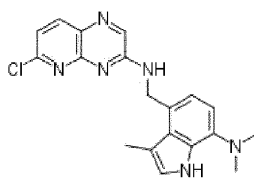


Intermediate 13d: 7-(dimethylamino)-3-methyl-1H-indole-4-carbonitrile

4-bromo-N,N,3-trimethyl-1H-indol-7-amine 13c (324 mg, 1.28 mmol) in NMP (3 mL) was treated with zinc cyanide (150.3 mg, 1.28 mmol, 1 eq) and zinc powder (17 mg, 0.26 mmol, 0.2 eq) and the mixture degassed with a stream of N₂. Pd₂(dba)₃ (176 mg, 0.19 mmol, 0.15 eq) and Pd(dppf)Cl₂ (212.87 mg, 0.38 mmol, 0.3 eq) were added and then heated to 140° C under N₂ for 16 h. The reaction mixture was cooled, diluted with EtOAc, filtered through a pad of celite and then dried over anhydrous MgSO₄. The whole was filtered and evaporated onto ISOLUTE, HM-N before being purified by automated flash chromatography (Combiflash Rf 300+, RediSep 40 g silica column) eluting with 0-50% ethyl acetate/heptane to furnish title compound 13d (223 mg, 1.12 mmol, 87%) as a beige solid. LCMS (method A); RT 1.05 min; m/z [M+H]⁺ 200.2. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 11.06 (s, 1H), 7.36 (d, J = 8.0 Hz, 1H), 7.24 (dd, J = 2.5, 1.2 Hz, 1H), 6.60 (d, J = 8.1 Hz, 1H), 2.94 (s, 6H), 2.42 (d, J = 1.0 Hz, 3H).

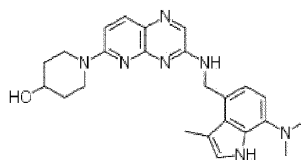
**Intermediate 13e: 4-(aminomethyl)-N,N,3-trimethyl-1H-indol-7-amine**

7-(dimethylamino)-3-methyl-1H-indole-4-carbonitrile 13d (223 mg, 1.12 mmol) in THF (5 mL) and MeOH (5 mL) was cooled to 0° C in an ice bath. The solution was treated with cobalt (II) chloride (290 mg, 2.24 mmol, 2 eq) followed after a couple of minutes by sodium borohydride (425 mg, 11.2 mmol, 10 eq) which was added portion wise. The ice bath was removed, and the reaction allowed to warm to rt for 15 min. The reaction mixture was diluted with ethyl acetate, then filtered through a pad of celite washing with ethyl acetate and 3% NH₃OH/water. The organic and aqueous layers were partitioned, and the organic layer dried over anhydrous MgSO₄. The whole was filtered and concentrated under reduced vacuum. The crude residue was dissolved in MeOH/DCM mixture and loaded onto an SCX-2 cartridge, washed with 3 x CV MeOH/DCM then 3 x CV (1N NH₃/MeOH)/DCM. Evaporation and to drying on a Biotage V10 to afforded title compound 13e (184 mg, 0.91 mmol, 81%) as a dark yellow solid. LCMS (method A); RT 0.39 min; m/z [M+H]⁺ no mass ion. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 10.49 (s, 1H), 6.98 – 6.94 (m, 1H), 6.79 (dd, J = 7.6, 0.8 Hz, 1H), 6.55 (d, J = 7.6 Hz, 1H), 4.01 (d, J = 0.7 Hz, 2H), 2.74 (s, 6H), 2.42 (d, J = 1.1 Hz, 3H).



Intermediate 13f: 4-[(6-chloropyrido[2,3-b]pyrazin-3-yl)amino)methyl]-N,N,3-trimethyl-1H-indol-7-amine

4-(aminomethyl)-N,N,3-trimethyl-1H-indol-7-amine 13e (183 mg, 0.9 mmol) in DMF (5 mL) was treated with DIPEA (0.39 mL, 2.25 mmol, 2.5 eq) followed by portion wise addition of 3,6-dichloropyrido[2,3-b]pyrazine (180 mg, 0.9 mmol, 1 eq) and the mixture was stirred at rt for 30 minutes to ensure a homogenous solution. The reaction was then subsequently heated to 40° C for 1 h. The reaction was then cooled to rt and quenched with sat NH₄Cl(aq) before being extracted with EtOAc twice. The combined organics were washed with brine and dried over anhydrous MgSO₄. The whole was then filtered and evaporated onto ISOLUTE, HM-N before being purified by automated flash chromatography (Combiflash Rf 300+, Gold RediSep, 24 g silica column) eluting with 0-30% EtOAc/DCM, evaporation and drying on a Biotage V10 to afford the title compound 13f (202 mg, 0.55 mmol, 61%) as a yellow solid. LCMS (method A); RT 1.02 min; m/z [M+Na]⁺ 389.2 (chlorine isotopes). ¹H NMR (400 MHz, DMSO-d₆) δ ppm 10.68 (d, J = 2.5 Hz, 1H), 8.53 (t, J = 4.6 Hz, 1H), 8.47 (s, 1H), 8.20 (d, J = 8.3 Hz, 1H), 7.39 (d, J = 8.3 Hz, 1H), 7.05 (dd, J = 2.5, 1.2 Hz, 1H), 6.90 (d, J = 7.6 Hz, 1H), 6.60 (d, J = 7.7 Hz, 1H), 4.83 (d, J = 4.6 Hz, 2H), 2.77 (s, 6H), 2.34 (d, J = 1.1 Hz, 3H).

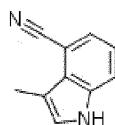


Exemplification 13: 1-[3-({[7-(dimethylamino)-3-methyl-1H-indol-4-yl]methyl}amino)pyrido[2,3-b]pyrazin-6-yl]piperidin-4-ol

4-[(6-chloropyrido[2,3-b]pyrazin-3-yl)amino)methyl]-N,N,3-trimethyl-1H-indol-7-amine 13f (50 mg, 0.14 mmol) in 1-propanol (1.4 mL) was treated with 4-hydroxypiperidine (15 mg, 0.15 mmol, 1.1 eq) followed by TEA (40 μL, 0.27 mmol, 2 eq) and the mixture heated to 100° C for 16 h. The reaction mixture was cooled to rt and partitioned between water and EtOAc. The aqueous layer was extracted twice with further EtOAc and the combined organics washed with brine before being concentrated under vacuum. The residue material was then dissolved in DMSO and MeOH and purified by preparative HPLC

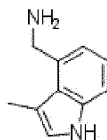
automated chromatography (AccQPrep HP125, Prep HPLC) freeze dried to afford the title compound 13 (14.7 mg, 0.03 mmol, 25%) as a cream solid. LC-HRMS (method B): rt 0.66, target mass 431.2434, found m/z 432.251, found formula C₂₄ H₂₉ N₇ O. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 10.64 (d, J = 2.5 Hz, 1H), 8.03 (s, 1H), 7.81 – 7.74 (m, 2H), 7.05 – 7.00 (m, 1H), 6.95 (d, J = 9.1 Hz, 1H), 6.85 (d, J = 7.7 Hz, 1H), 6.58 (d, J = 7.7 Hz, 1H), 4.77 (d, J = 4.6 Hz, 2H), 4.71 (d, J = 4.3 Hz, 1H), 4.23 – 4.12 (m, 2H), 3.79 – 3.69 (m, 1H), 3.30 – 3.20 (m, 2H), 2.76 (s, 6H), 2.34 (d, J = 1.1 Hz, 3H), 1.86 – 1.75 (m, 2H), 1.43 – 1.31 (m, 2H).

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**Intermediate 14a: 3-methyl-1H-indole-4-carbonitrile**

To a stirred solution of 4-Bromo-3-methyl-1H-indole (1 g, 4.76 mmol) in NMP (10 mL) was treated with zinc cyanide (560 mg, 4.76 mmol, 1 eq) followed by zinc powder (62 mg, 0.95 mmol, 0.2 eq); Pd(dppf)Cl₂ (396 mg, 0.71 mmol, 0.15 eq) and Pd₂(dba)₃ (327 mg, 0.36 mmol, 0.08 eq) under a nitrogen atmosphere. The mixture was heated to 140° C for 16 h. The reaction was cooled to rt then diluted with EtOAc and a small amount of water. The mixture was filtered through celite (10 g column, pre-washed with EtOAc), eluting with further EtOAc. The combined organic extracts were evaporated on to ISOLUTE, HM-N before being purified by automated flash chromatography (Combiflash Rf 300+, RediSep, 40 g silica column) eluting with 0-30% ethyl acetate/heptane to furnish the title compound (616 mg, 3.94 mmol, 83%) as a beige solid. LCMS (method A); RT 0.98 min; m/z 157 [M+H]⁺ ¹H NMR (400 MHz, DMSO-d₆) δ ppm 11.40 (s, 1H), 7.69 (dd, J = 8.2, 0.9 Hz, 1H), 7.47 (dd, J = 7.4, 1.0 Hz, 1H), 7.43 – 7.37 (m, 1H), 7.20 (dd, J = 8.2, 7.4 Hz, 1H), 2.46 (d, J = 1.0 Hz, 3H).

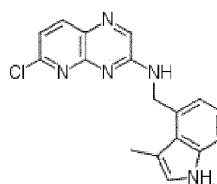
25

**Intermediate 14b: (3-methyl-1H-indol-4-yl)methanamine**

A solution of 3-methyl-1H-indole-4-carbonitrile 14a (616 mg, 3.94 mmol, 1 eq) in THF (20 mL) / MeOH (20 mL) was cooled in an ice bath and treated with cobalt (II) chloride

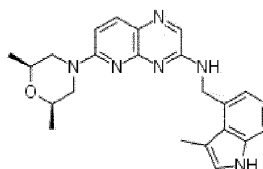
30

(1.02 g, 7.89 mmol, 2 eq). After 2 min then sodium borohydride (1.49 g, 39 mmol, 10 eq) was added portion wise, cooling removed, and the mixture stirred at rt for 15 min. The reaction mixture was the diluted with EtOAc then filtered through celite (10g, pre-washed with EtOAc), eluting with further EtOAc followed by 3% NH₄OH(aq). The filtrate layers were separated then the aqueous layer extracted with further EtOAc. The organic extracts were combined, dried over anhydrous MgSO₄ and then evaporated. The residue was triturated in diethyl ether then collected by filtration to afford title compound 14b (391 mg, 2.44 mmol, 62%) as a peach solid. LCMS (method A); RT 0.322 min; m/z no mass ion. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 10.69 (s, 1H), 7.17 (d, J = 8.0 Hz, 1H), 7.08 – 6.87 (m, 3H), 4.09 (s, 2H), 2.43 (s, 3H), 1.93 – 1.80 (m, broad 2H).



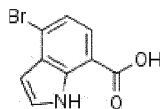
Intermediate 14c: 6-chloro-N-[(3-methyl-1H-indol-4-yl)methyl]pyrido[2,3-b]pyrazin-3-amine

(3-methyl-1H-indol-4-yl)methanamine 14b (391 mg, 2.44 mmol) in DMF (22 mL) and treated with 3,6-dichloropyrido[2,3-b]pyrazine (537 mg, 2.68 mmol, 1.1 eq) followed by DIPEA (810 μL, 4.88 mmol, 2 eq) and the mixture stirred at rt under N₂ for 16 h. The reaction mixture was partitioned between EtOAc/brine and the organics were dried over anhydrous MgSO₄. The whole was filtered and evaporated to a residue slurry. The residue was the triturated with dry MeOH, collected by filtration and dried under vacuum to furnish title compound 14c (664 mg, 2.05 mmol, 84%) as a beige solid. LCMS (method A); RT 1.09 min; m/z [M+H]⁺ 324.2 (chlorine isotopes). ¹H NMR (400 MHz, DMSO-d₆) δ ppm 10.86 (s, 1H), 8.62 (t, J = 4.9 Hz, 1H), 8.49 (s, 1H), 8.20 (d, J = 8.3 Hz, 1H), 7.39 (d, J = 8.3 Hz, 1H), 7.31 (dd, J = 8.0, 1.2 Hz, 1H), 7.13 (dd, J = 2.4, 1.2 Hz, 1H), 7.03 (dd, J = 8.0, 7.2 Hz, 1H), 6.97 (dd, J = 7.1, 1.2 Hz, 1H), 4.95 (d, J = 4.9 Hz, 2H), 2.40 (d, J = 1.1 Hz, 3H).

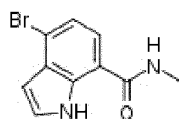


Exemplification 14: 6-[(2R,6S)-2,6-dimethylmorpholin-4-yl]-N-[(3-methyl-1H-indol-4-yl)methyl]pyrido[2,3-b]pyrazin-3-amine

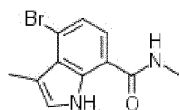
6-chloro-N-[(3-methyl-1H-indol-4-yl)methyl]pyrido[2,3-b]pyrazin-3-amine 14c (50 mg, 0.15 mmol, 1 eq) in 1-propanol (5 mL) was treated with cis-2,6-dimethylmorpholine (40 μ L, 0.31 mmol, 2 eq) and DIPEA (80 μ L, 0.46 mmol, 3 eq). The reaction mixture was sealed and heated to 120° C behind a blast shield for 16 h. The reaction mixture as cooled to rt and partitioned between DCM/brine. The organics were separated via a phase separator and evaporated onto ISOLUTE, HM-N and purified by automated flash chromatography (Combiflash Rf 300+, RediSep, 4 g silica column) eluting with 0-5% MeOH/DCM. The residue was then further purified by preparative HPLC automated chromatography (AccQPrep HP150, Prep HPLC) and isolated as a freeze dried solid, the title compound 14 (23 mg, 0.06 mmol, 37%) as a yellow solid. LC-HRMS (method B): RT 0.94, target mass 402.2168, found m/z 403.2257, found formula C₂₃ H₂₆ N₆ O. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 10.83 (app s, 1H), 8.10 (s, 1H), 7.93 (t, J = 4.9 Hz, 1H), 7.84 (d, J = 9.0 Hz, 1H), 7.28 (d, J = 7.9 Hz, 1H), 7.13 – 7.08 (m, 1H), 7.03 – 6.94 (m, 2H), 6.91 (d, J = 7.1 Hz, 1H), 4.90 (d, J = 4.9 Hz, 2H), 4.43 – 4.30 (m, 2H), 3.66 – 3.53 (m, 2H), 2.56 – 2.44 (m, 2H), 2.39 (s, 3H), 1.17 (d, J = 6.2 Hz, 6H).

**Intermediate 15a: 4-bromo-1H-indole-7-carboxylic acid**

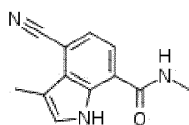
Methyl 4-bromo-1H-indole-7-carboxylate (300 mg, 1.18 mmol) in 1,4-Dioxane (8 mL) was treated with lithium hydroxide monohydrate (247.74 mg, 5.9 mmol, 5 eq) and water (2 mL) and the mixture heated in a microwave at 100° C for 1 h. The cooled reaction mixture was partitioned between EtOAc and 0.5 N HCl(aq) and the organics dried over anhydrous MgSO₄, filtered and evaporated to furnish title compound 15a (285 mg, 1.19 mmol, quant) as a colourless solid. LCMS (method A): RT, 0.98 min; m/z [M+H]⁺ 240 (bromine isotopes). ¹H NMR (400 MHz, DMSO-d₆) δ ppm 13.19 (s, 1H), 11.42 (s, 1H), 7.66 (d, J = 8.0 Hz, 1H), 7.48 (t, J = 2.9 Hz, 1H), 7.35 (d, J = 8.0 Hz, 1H), 6.51 (dd, J = 3.2, 2.0 Hz, 1H).

**Intermediate 15b: 4-bromo-N-methyl-1H-indole-7-carboxamide**

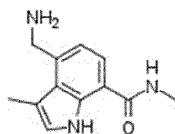
4-bromo-1H-indole-7-carboxylic acid (661 mg, 2.75 mmol) in DMF (18 mL) was treated with HBTU (1.25 g, 3.3 mmol, 1.2 eq) and DIPEA (0.96 mL, 5.51 mmol, 2 eq) followed by methylamine (0.3 mL, 2M in THF, 8.26 mmol, 3 eq) and the mixture stirred at rt under N₂ for 2.5 h. The reaction mixture was taken up in EtOAc, then washed with bicarb, followed by brine and the organics dried over anhydrous MgSO₄, filtered and evaporated onto ISOLUTE, HM-N before being purified by automated flash chromatography (Combiflash Rf 300+, RediSep, 24 g silica column) eluting with 0-60% ethyl acetate/heptane to furnish title compound 15b (516 mg, 2.04 mmol, 74%) as a colourless solid. LCMS (method A); RT 0.98 min; m/z [M+H]⁺ 255 (bromine isotopes). ¹H NMR (400 MHz, DMSO-d₆) δ ppm 11.48 (s, 1H), 8.58 (d, J = 4.8 Hz, 1H), 7.54 (d, J = 8.0 Hz, 1H), 7.45 (t, J = 2.8 Hz, 1H), 7.31 (d, J = 8.0 Hz, 1H), 6.45 (dd, J = 3.2, 2.1 Hz, 1H), 2.84 (d, J = 4.5 Hz, 3H).

**Intermediate 15c: 4-bromo-N,3-dimethyl-1H-indole-7-carboxamide**

Methyl 4-bromo-1H-indole-7-carboxylate 15b (279 mg, 1.1 mmol) in MeOH (10 mL) was treated with KO^tBu (125 mg, 1.1 mmol, 1 eq), followed by [Cp*IrCl₂]₂ (9 mg, 0.01 mmol, 0.01 eq) and then sealed and heated at 120°C for 16 h behind a blast shield. The cooled reaction mixture was partitioned between EtOAc/brine and the organics dried over anhydrous MgSO₄, filtered and evaporated onto ISOLUTE, HM-N. Purification by automated flash chromatography (Combiflash Rf 300+, RediSep, 12 g silica column) eluting with 0-100% ethyl acetate/heptane furnished title compound 15c. (91 mg, 0.34 mmol, 31%) as an off-white solid. LCMS (method A); RT 1.07 min; m/z [M+H]⁺ 267 (bromine isotopes). ¹H NMR (400 MHz, DMSO-d₆) δ ppm 11.11 (s, 1H), 8.53 (d, J = 4.6 Hz, 1H), 7.45 (d, J = 8.1 Hz, 1H), 7.25 - 7.19 (m, 2H), 2.83 (d, J = 4.5 Hz, 3H), 2.47 (d, J = 1.1 Hz, 3H).

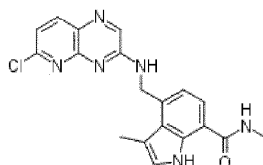
**Intermediate 15d: 4-cyano-N,3-dimethyl-1H-indole-7-carboxamide**

4-bromo-N,3-dimethyl-1H-indole-7-carboxamide 15c (91 mg, 0.34 mmol) in NMP (5 mL) was treated with zinc powder (5 mg, 0.07 mmol, 0.2 eq); zinc cyanide (40 mg, 0.34 mmol, 1 eq); Pd₂(dba)₃ (50 mg, 0.05 mmol, 0.15 eq) and Pd(dppf)Cl₂ (57 mg, 0.1 mmol, 0.3 eq). The mixture was degassed with a stream of N₂ and then heated to 140° C for 24 h. The reaction mixture was cooled before being partitioned between EtOAc/brine. The aqueous fraction was filtered through celite and extracted with further EtOAc. The combined organics were dried over anhydrous MgSO₄, filtered, and evaporated onto ISOLUTE, HM-N. Purified was performed by automated flash chromatography (Combiflash Rf 300+, RediSep, 24 g silica column) eluting with 0-80% ethyl acetate/heptane to furnish title compound 15d (56 mg, 0.26 mmol, 77%) as an off-white solid. LCMS (method A); RT 0.89 min; m/z [M+H]⁺ 212.2. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 11.38 (s, 1H), 8.73 (d, J = 4.8 Hz, 1H), 7.64 (d, J = 7.7 Hz, 1H), 7.56 (d, J = 7.8 Hz, 1H), 7.39 (dd, J = 2.5, 1.2 Hz, 1H), 2.86 (d, J = 4.6 Hz, 3H), 2.47 (d, J = 1.0 Hz, 3H).

**Intermediate 15e: 4-(aminomethyl)-N,3-dimethyl-1H-indole-7-carboxamide**

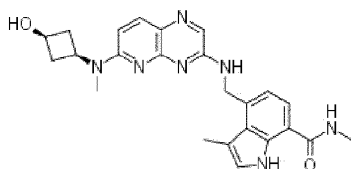
4-cyano-N,3-dimethyl-1H-indole-7-carboxamide 15d (115 mg, 0.54 mmol) in MeOH (4 mL) and THF (4 mL) was cooled to 0° C and treated with cobalt (II) chloride (140 mg, 1.08 mmol, 2 eq). After 2 min sodium borohydride (200 mg, 5.39 mmol, 10 eq) was added and the mixture stirred at rt for 15 min. The reaction mixture was diluted with EtOAc and passed through a pad of celite. The celite was rinsed with 3% ammonium hydroxide solution and then further extracted with EtOAc. The combined organics were dried over anhydrous MgSO₄, filtered and evaporated onto ISOLUTE, HM-N. Purification was achieved by automated flash chromatography (Combiflash Rf 300+, RediSep, 4 g silica column) eluting with 0-15% MeOH (containing 1% 1N NH₃ in MeOH)/DCM to furnish title compound 15e (75 mg, 0.35 mmol, 64%) as a colourless solid. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 10.77 (s, 1H), 8.39 (q, J = 4.6 Hz, 1H), 7.54 (d, J = 7.6 Hz, 1H), 7.07

(dd, J = 2.4, 1.2 Hz, 1H), 7.02 (d, J = 7.6 Hz, 1H), 4.16 (s, 2H), 2.82 (d, J = 4.6 Hz, 3H), 2.44 (d, J = 1.1 Hz, 3H), 1.90 (s, broad 2H).



Intermediate 15f: 4-[(6-chloropyrido[2,3-b]pyrazin-3-yl)amino)methyl]-N,3-dimethyl-1H-indole-7-carboxamide

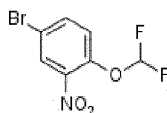
4-(aminomethyl)-N,3-dimethyl-1H-indole-7-carboxamide 15e (75 mg, 0.35 mmol) in DMF (3 mL) was treated with 3,6-Dichloropyrido[2,3-b]pyrazine (76 mg, 0.38 mmol, 1.1 eq) and DIPEA (115 μ L, 0.69 mmol, 2 eq) and the mixture was stirred at rt under N₂ for 16 h. The reaction mixture was partitioned between EtOAc/brine. The organics were dried over anhydrous MgSO₄, filtered and evaporated onto ISOLUTE, HM-N. Purification by automated flash chromatography (Combiflash Rf 300+, RediSep 12 g silica column) eluting with 0-100% ethyl acetate/DCM afforded the title compound 15f (70 mg, 0.18 mmol, 53%) as an off-white solid. LCMS (method A); RT 0.99 min; m/z [M+H]⁺ 381.2 (chlorine isotopes). ¹H NMR (400 MHz, DMSO-d₆) δ ppm 10.92 (d, J = 2.3 Hz, 1H), 8.69 (t, J = 5.1 Hz, 1H), 8.51 (s, 1H), 8.45 (d, J = 4.7 Hz, 1H), 8.22 (d, J = 8.3 Hz, 1H), 7.54 (d, J = 7.7 Hz, 1H), 7.40 (d, J = 8.3 Hz, 1H), 7.17 (dd, J = 2.4, 1.2 Hz, 1H), 7.03 (d, J = 7.6 Hz, 1H), 5.03 (d, J = 5.0 Hz, 2H), 2.83 (d, J = 4.5 Hz, 3H), 2.44 (d, J = 1.1 Hz, 3H).



Exemplification 15: N,3-dimethyl-4-[(6-{methyl[(1s,3s)-3-hydroxycyclobutyl]amino}pyrido[2,3-b]pyrazin-3-yl)amino)methyl]-1H-indole-7-carboxamide

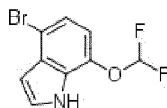
4-[(6-chloropyrido[2,3-b]pyrazin-3-yl)amino)methyl]-N,3-dimethyl-1H-indole-7-carboxamide 15f (35 mg, 0.09 mmol) in 1-propanol (5 mL) was treated with cis-3-(methylamino)cyclobutan-1-ol hydrochloride (50 mg, 0.36 mmol, 4 eq) and DIPEA (100 μ L, 0.55 mmol, 6 eq) and the mixture sealed in a tube and heated at 120° C behind a blast shield. After 3 days the reaction was cooled and partitioned between EtOAc/brine. The organics were dried over anhydrous MgSO₄, filtered before evaporating to

dryness. The residue re-taken up in DMSO and purified by preparative HPLC automated chromatography (AccQPrep HP150, Prep HPLC) and lyophilised on a freeze drier to furnish target compound 15 (5 mg, 0.01 mmol, 13%) as a yellow solid. LC-HRMS (method B): RT 0.72, target mass 445.2226, found m/z 446.2304, found formula C₂₄H₂₇N₇O₂. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 10.89 (d, J = 2.4 Hz, 1H), 8.43 (q, J = 4.6 Hz, 1H), 8.07 (s, 1H), 7.95 (t, J = 5.1 Hz, 1H), 7.80 (d, J = 9.0 Hz, 1H), 7.53 (d, J = 7.7 Hz, 1H), 7.17 – 7.12 (m, 1H), 6.96 (d, J = 7.7 Hz, 1H), 6.77 (d, J = 9.0 Hz, 1H), 5.11 (br s, 1H), 4.98 (d, J = 5.1 Hz, 2H), 4.62 – 4.49 (m, 1H), 3.93 – 3.81 (m, 1H), 3.05 (s, 3H), 2.82 (d, J = 4.6 Hz, 3H), 2.57 – 2.48 (m, 2H), 2.44 (d, J = 1.0 Hz, 3H), 2.07 – 1.96 (m, 2H).



Intermediate 16a: 4-bromo-1-(difluoromethoxy)-2-nitrobenzene

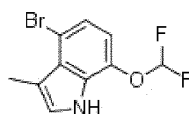
4-Bromo-2-nitrophenol (1 g, 4.59 mmol) in MeCN (10 mL) was treated with potassium hydroxide (10 mL, 6M, 60 mmol, 13 eq) followed by difluoromethyl trifluoromethanesulfonate (1.16 mL, 9.2 mmol, 2 eq) and the mixture stirred for 1 h. The reaction mixture was partitioned between EtOAc/H₂O and the organics were dried over anhydrous MgSO₄, filtered and evaporated onto ISOLUTE, HM-N. Purification by automated flash chromatography (Combiflash Rf 300+, Silica 40g RediSep 40 g silica column) eluting with heptane to 7% ethyl acetate in heptane furnished the title compound 16a (1.15 g, 4.29 mmol, 94%) as a yellow oil. LCMS (method A); RT 1.12 min; m/z mass ion not detected. ¹H-NMR (400 MHz, DMSO-d₆) δ ppm 8.34 (d, J = 2.4 Hz, 1H), 8.01 (dd, J = 8.9, 2.5 Hz, 1H), 7.50 (d, J = 8.9 Hz, 1H), 7.38 (t, J = 72.4 Hz, 1H). ¹⁹F NMR (376 MHz, DMSO) δ ppm -83.20 (s, 2F).



Intermediate 16b: 4-bromo-7-(difluoromethoxy)-1H-indole

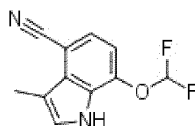
4-bromo-1-(difluoromethoxy)-2-nitrobenzene 16a (1.15 g, 4.29 mmol) in THF (22 mL) was cooled to -78° C under N₂. The solution was treated with vinyl magnesium bromide (13 mL, 1M in THF, 13 mmol, 3 eq) dropwise whilst stirring at -78° C. After 2.5 h, the

reaction mixture was partitioned between EtOAc/sat NH₄Cl(aq). The organics were dried over anhydrous MgSO₄, filtered and evaporated onto ISOLUTE, HM-N. Purification by automated flash chromatography (Combiflash Rf 300+, RediSep, 24 g silica column) eluting with 0-15% ethyl acetate/heptane afforded title compound 16b (231 mg, 0.88 mmol, 21%) as a yellow oil. LCMS (method A); RT 1.16 min; m/z [M-H]⁻ 260. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 11.88 (s, 1H), 7.55 – 7.46 (m, 1H), 7.32 (t, J = 74 Hz, 1H) 7.22 (d, J = 8.2 Hz, 1H), 6.89 (dt, J = 8.3, 1.0 Hz, 1H), 6.46 (dd, J = 3.1, 2.0 Hz, 1H).



Intermediate 16c: 4-bromo-7-(difluoromethoxy)-3-methyl-1H-indole

4-bromo-7-(difluoromethoxy)-1H-indole 16b (231 mg, 0.88 mmol) in MeOH (5 mL) was treated with KO^tBu (100 mg, 0.88 mmol, 1 eq) and [Cp*IrCl₂]₂ (7 mg, 0.01 mmol, 0.01 eq), the mixture then sealed in a tube and heated to 120° C for 16 h behind a blast shield. The cooled reaction mixture partitioned between EtOAc/brine and the organics were dried over anhydrous MgSO₄, filtered and evaporated onto ISOLUTE, HM-N. Purification by automated flash chromatography (Combiflash Rf 300+, RediSep 12 g silica column) eluting with 0-15% ethyl acetate/heptane furnished the title compound 16c (38 mg, 0.14 mmol, 16%) as a beige oil. LCMS (method A); RT 1.33 min; m/z [M+H]⁺ 276. ¹H-NMR (400 MHz, DMSO-d₆) δ ppm 11.44 (s, 1H), 7.29 (t, J = 74.0 Hz, 1H), 7.24 (d, J = 1.2 Hz, 1H), 7.14 (d, J = 8.2 Hz, 1H), 6.85 – 6.76 (m, 1H), 2.46 (d, J = 1.1 Hz, 3H).

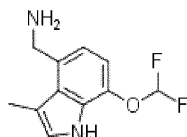


Intermediate 16d: 7-(difluoromethoxy)-3-methyl-1H-indole-4-carbonitrile

4-bromo-7-(difluoromethoxy)-3-methyl-1H-indole 16c (38 mg, 0.14 mmol) in NMP (2 mL) was treated with zinc powder (2 mg, 0.03 mmol, 0.2 eq); zinc cyanide (20 mg, 0.14 mmol, 1 eq); Pd₂(dba)₃ (20 mg, 0.02 mmol, 0.15 eq) and Pd(dppf)Cl₂ (23 mg, 0.04 mmol, 0.3 eq) and the mixture degassed with a stream of nitrogen before being heated to 140° C under N₂. After 16 h the cooled reaction mixture was partition between EtOAc/brine. The aq was filtered through celite and rinsed with further EtOAc. The combined organics were dried over anhydrous MgSO₄, filtered and evaporated onto ISOLUTE, HM-N. Purification by automated flash chromatography (Combiflash Rf 300+, RediSep, 12 g silica column)

eluting with 0-60% ethyl acetate/heptane to furnish title compound 16d (7 mg, 0.03 mmol, 23%) as a colourless solid. LCMS (method A); RT 1.06 min; m/z [M-H]⁻ 221. ¹H-NMR (400 MHz, DMSO-d₆) δ ppm 11.82 (s, 1H), 7.54 (d, J = 8.1 Hz, 1H), 7.49 (t, J = 73.3 Hz, 1H), 7.42 (dd, J = 2.5, 1.1 Hz, 1H), 7.04 (dt, J = 8.1, 1.0 Hz, 1H), 2.45 (d, J = 1.0 Hz, 3H).

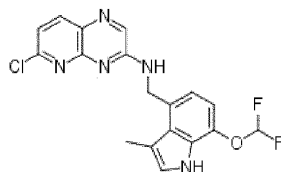
5



Intermediate 16e: [7-(difluoromethoxy)-3-methyl-1H-indol-4-yl]methanamine

7-(difluoromethoxy)-3-methyl-1H-indole-4-carbonitrile 16d (39 mg, 0.18 mmol) in THF (1.5 mL) and MeOH (1.5 mL) was cooled to 0° C and treated with cobalt (II) chloride (45.58 mg, 0.35 mmol, 2 eq) followed after 2 min by sodium borohydride (70 mg, 1.76 mmol, 10 eq) and the mixture stirred at rt under N₂. After 15min, EtOAc was added, followed by 3% NH₄OH(aq) with stirring and the whole filtered through celite and rinsed with further EtOAc. The organics were separated and dried over anhydrous MgSO₄, filtered and evaporated onto ISOLUTE, HM-N. Purification by automated flash chromatography (Combiflash Rf 300+, RediSep, 4 g silica column) eluting with 0-15% MeOH (containing 1% 1N NH₃ in MeOH)/DCM furnished title compound 16e (27 mg, 0.12 mmol, 68%) as an off-white solid. LCMS (method A); RT 0.54 min; m/z [M-H]⁻ 225. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 11.00 (s, 1H), 7.21 (t, J = 74.7 Hz, 1H), 7.07 (dd, J = 2.4, 1.2 Hz, 1H), 6.90 (d, J = 7.9 Hz, 1H), 6.84 – 6.77 (m, 1H), 4.08 (s, 2H), 2.44 (d, J = 1.1 Hz, 3H), 1.87 (s, 2H).

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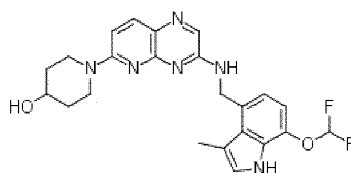


Intermediate 16f: 6-chloro-N-([7-(difluoromethoxy)-3-methyl-1H-indol-4-yl]methyl)pyrido[2,3-b]pyrazin-3-amine

[7-(difluoromethoxy)-3-methyl-1H-indol-4-yl]methanamine 16e (27 mg, 0.12 mmol) in DMF (1.2 mL) was treated with and 3,6-dichloropyrido[2,3-b]pyrazine (26 mg, 0.13 mmol, 1.1 eq) followed by DIPEA (40 μL, 0.24 mmol, 2 eq) and the mixture was stirred at rt under N₂ for 16 h. The reaction mixture was partitioned between EtOAc/brine and the organics were dried over anhydrous MgSO₄, filtered and evaporated onto ISOLUTE, HM-

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N. Purification by automated flash chromatography (Combiflash Rf 300+, RediSep, 4 g silica column) eluting with 0-40% ethyl acetate/heptane afforded title compound 16f (34 mg, 0.09 mmol, 73%) as a yellow solid. LCMS (method A); RT 1.13 min; m/z [M+H]⁺ 390.2 (chlorine isotopes). ¹H NMR (400 MHz, DMSO-d₆) δ ppm 11.20 (s, 1H), 8.63 (t, J = 4.9 Hz, 1H), 8.48 (s, 1H), 8.21 (d, J = 8.3 Hz, 1H), 7.40 (d, J = 8.3 Hz, 1H), 7.26 (t, J = 74.4 Hz, 1H), 7.17 (dd, J = 2.5, 1.2 Hz, 1H), 6.97 (d, J = 7.9 Hz, 1H), 6.87 (d, J = 7.8 Hz, 1H), 4.93 (d, J = 4.8 Hz, 2H), 4.09 (q, J = 5.3 Hz, 1H), 2.39 (d, J = 1.1 Hz, 3H).



Exemplification 16: 1-[3-({[7-(difluoromethoxy)-3-methyl-1H-indol-4-yl]methyl}amino)pyrido[2,3-b]pyrazin-6-yl]piperidin-4-ol

6-chloro-N-([7-(difluoromethoxy)-3-methyl-1H-indol-4-yl]methyl)pyrido[2,3-b]pyrazin-3-amine 16f (34 mg, 0.09 mmol) in 1-propanol (5 mL) was treated with 4-hydroxypiperidine (18 mg, 0.17 mmol, 2 eq) and DIPEA (45 μL, 0.26 mmol, 3 eq). The mixture was sealed in a tube and heated to 120° C behind a blast shield for 16 h. The cooled reaction mixture was partitioned between DCM/brine. The organics were separated via a phase separator and evaporated onto ISOLUTE, HM-N. Purification by automated flash chromatography (Combiflash Rf 300+, RediSep 4 g silica column) eluting with 0-100% ethyl acetate/heptane to furnish the title compound 16 (27.6 mg, 0.06 mmol, 70%) as a yellow solid LC-HRMS (method B): RT 0.81, target mass 454.1929, found m/z 455.2011, found formula C₂₃H₂₄F₂N₆O₂. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 11.15 (d, J = 2.4 Hz, 1H), 8.04 (s, 1H), 7.87 (t, J = 4.9 Hz, 1H), 7.78 (d, J = 9.1 Hz, 1H), 7.24 (t, J_{HF} = 74.4 Hz, 1H), 7.16 – 7.13 (m, 1H), 6.96 (d, J = 9.1 Hz, 1H), 6.91 (d, J = 7.9 Hz, 1H), 6.87 – 6.82 (m, 1H), 4.87 (d, J = 4.9 Hz, 2H), 4.71 (d, J = 4.2 Hz, 1H), 4.22 – 4.11 (m, 2H), 3.79 – 3.69 (m, 1H), 3.29– 3.19 (m, 2H), 2.39 (d, J = 1.1 Hz, 3H), 1.85 – 1.75 (m, 2H), 1.43 – 1.30 (m, 2H). ¹⁹F NMR (376 MHz, DMSO) δ -80.76 (s, 2F).

Exemplifications 17 - 125:

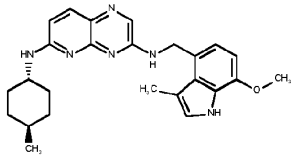
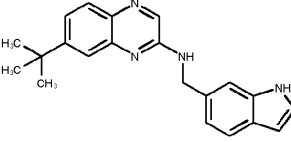
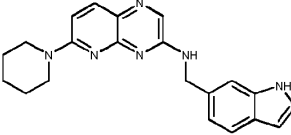
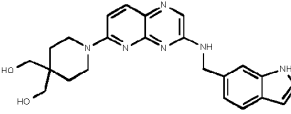
The following example compounds in Table 1 were made by similar methods.

Table 1.

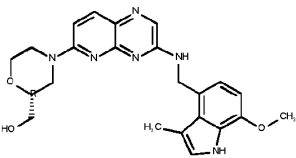
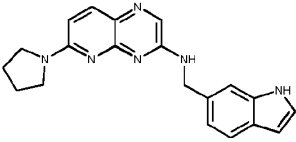
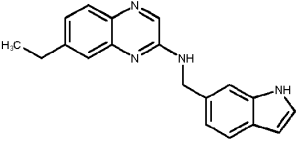
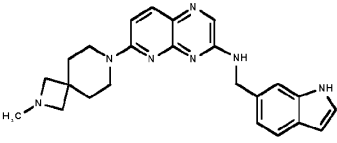
Exemplification Number	Structure	IUPAC Name / Analytical Data LC-HRMS
17		3-(hydroxymethyl)-1-(3-(((7-methoxy-3-methyl-1H-indol-4-yl)methyl)amino)pyrido[2,3-b]pyrazin-6-yl)piperidin-4-ol LC-HRMS (method B): RT 0.7 min, target mass 448.2223, found m/z 449.2301; found empirical formula C ₂₄ H ₂₈ N ₆ O ₃
18		1-(3-(((7-chloro-1H-indol-4-yl)methyl)amino)pyrido[2,3-b]pyrazin-6-yl)piperidin-4-ol LC-HRMS (method B): RT 0.8 min, target mass 408.1465, found m/z 409.1542; found empirical formula C ₂₁ H ₂₁ ClN ₆ O
19		[(3R)-1-(3-(((1H-indol-6-yl)methyl)amino)pyrido[2,3-b]pyrazin-6-yl)pyrrolidin-3-yl]methanol LC-HRMS (method B): RT 0.68 min, target mass 374.1855, found m/z 375.1932; found empirical formula C ₂₁ H ₂₂ N ₆ O
20		(3R)-1-(3-(((1H-indol-6-yl)methyl)amino)pyrido[2,3-b]pyrazin-6-yl)pyrrolidin-3-ol LC-HRMS (method B): RT 0.66 min, target mass 360.1699, found m/z 361.1777; found empirical formula C ₂₀ H ₂₀ N ₆ O

Exemplification Number	Structure	IUPAC Name / Analytical Data LC-HRMS
21		cis-(1s,3s)-3-[(3-[[[(7-methoxy-3-methyl-1H-indol-4-yl)methyl]amino]pyrido[2,3-b]pyrazin-6-yl)amino]cyclobutan-1-ol LC-HRMS (method B): RT 0.69 min, target mass 404.1961, found m/z 405.2039; found empirical formula C ₂₂ H ₂₄ N ₆ O ₂
22		N-[(1H-indol-6-yl)methyl]-6-{2-oxa-6-azaspiro[3.3]heptan-6-yl}pyrido[2,3-b]pyrazin-3-amine LC-HRMS (method B): RT 0.71 min, target mass 372.1699, found m/z 373.1798; found empirical formula C ₂₁ H ₂₀ N ₆ O
23		6-{2,6-diazaspiro[3.3]heptan-2-yl}-N-(1H-indol-6-ylmethyl)pyrido[2,3-b]pyrazin-3-amine LC-HRMS (method B): RT 0.6 min, target mass 371.1858, found m/z 372.1929; found empirical formula C ₂₁ H ₂₁ N ₇
24		3-(hydroxymethyl)-1-(3-[[[(1H-indol-6-yl)methyl]amino]pyrido[2,3-b]pyrazin-6-yl]piperidin-4-ol LC-HRMS (method B): RT 0.67 min, target mass 404.1961, found m/z 405.2037; found empirical formula C ₂₂ H ₂₄ N ₆ O ₂

Exemplification Number	Structure	IUPAC Name / Analytical Data LC-HRMS
25		[(3R)-1-(3-[(1H-indol-6-yl)methyl]amino)pyrido[2,3-b]pyrazin-6-yl]piperidin-3-yl]methanol LC-HRMS (method B): RT 0.74 min, target mass 388.2012, found m/z 389.2097; found empirical formula C ₂₂ H ₂₄ N ₆ O
26		N-[(1H-indol-6-yl)methyl]pyrido[2,3-b]pyrazin-3-amine LC-HRMS (method B): RT 0.75 min, target mass 275.1171, found m/z 276.1252; found empirical formula C ₁₆ H ₁₃ N ₅
27		cis-(1R,3R)-3-({3-[(1H-indol-6-yl)methyl]amino}pyrido[2,3-b]pyrazin-6-yl)amino)cyclobutan-1-ol LC-HRMS (method B): RT 0.68 min, target mass 360.1699, found m/z 361.1777; found empirical formula C ₂₀ H ₂₀ N ₆ O
28		[4-(hydroxymethyl)-1-(3-[(7-methoxy-3-methyl-1H-indol-4-yl)methyl]amino)pyrido[2,3-b]pyrazin-6-yl]piperidin-4-yl]methanol LC-HRMS (method B): RT 0.71 min, target mass 462.2379, found m/z 463.2459; found empirical formula C ₂₅ H ₃₀ N ₆ O ₃

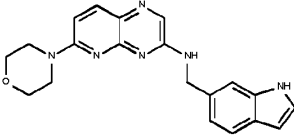
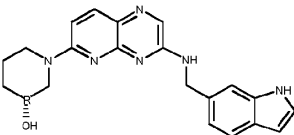
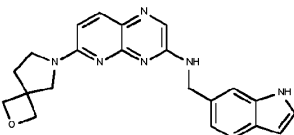
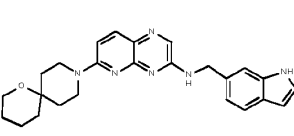
Exemplification Number	Structure	IUPAC Name / Analytical Data LC-HRMS
29		3-N-[(7-methoxy-3-methyl-1H-indol-4-yl)methyl]-6-N-[trans-4-aminocyclohexyl]pyrido[2,3-b]pyrazine-3,6-diamine LC-HRMS (method B): RT 0.62 min, target mass 431.2434, found m/z 432.2508; found empirical formula C ₂₄ H ₂₉ N ₇ O
30		7-tert-butyl-N-(1H-indol-6-ylmethyl)quinoxalin-2-amine LC-HRMS (method B): RT 1.28 min, target mass 330.1844, found m/z 331.1993; found empirical formula C ₂₁ H ₂₂ N ₄
31		N-[(1H-indol-6-yl)methyl]-6-(piperidin-1-yl)pyrido[2,3-b]pyrazin-3-amine LC-HRMS (method B): RT 0.88 min, target mass 358.1906, found m/z 359.2003; found empirical formula C ₂₁ H ₂₂ N ₆
32		[4-(hydroxymethyl)-1-{3-[(1H-indol-6-yl)methyl]amino}pyrido[2,3-b]pyrazin-6-yl]piperidin-4-yl]methanol LC-HRMS (method B): RT 0.7 min, target mass 418.2117, found m/z 419.2188; found empirical formula C ₂₃ H ₂₆ N ₆ O ₂

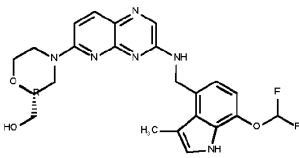
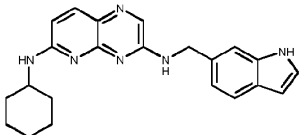
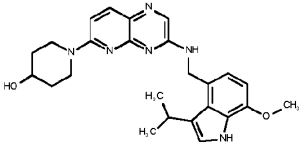
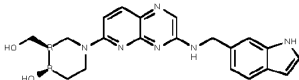
Exemplification Number	Structure	IUPAC Name / Analytical Data LC-HRMS
33		N-(1H-indol-6-ylmethyl)-6-[4-(oxetan-3-yl)piperazin-1-yl]pyrido[2,3-b]pyrazin-3-amine LC-HRMS (method B): RT 0.71 min, target mass 415.2121, found m/z 416.2191; found empirical formula C ₂₃ H ₂₅ N ₇ O
34		7-{3-[(1H-indol-6-ylmethyl)amino]pyrido[2,3-b]pyrazin-6-yl}-7-azaspiro[3.5]nonan-2-amine LC-HRMS (method B): RT 0.63 min, target mass 413.2328, found m/z 414.2402; found empirical formula C ₂₄ H ₂₇ N ₇
35		1-{3-[(1H-pyrrolo[2,3-b]pyridin-5-yl)methyl]amino}pyrido[2,3-b]pyrazin-6-yl}piperidin-4-ol LC-HRMS (method B): RT 0.59 min, target mass 375.1808, found m/z 376.1882; found empirical formula C ₂₀ H ₂₁ N ₇ O
36		3-N-(1H-indol-6-ylmethyl)-6-N-(oxan-4-yl)pyrido[2,3-b]pyrazine-3,6-diamine LC-HRMS (method B): RT 0.72 min, target mass 374.1855, found m/z 375.1934; found empirical formula C ₂₁ H ₂₂ N ₆ O

Exemplification Number	Structure	IUPAC Name / Analytical Data LC-HRMS
37		[(2R)-4-(3-[[7-methoxy-3-methyl-1H-indol-4-yl)methyl]amino]pyrido[2,3-b]pyrazin-6-yl)morpholin-2-yl]methanol LC-HRMS (method B): RT 0.74 min, target mass 434.2066, found m/z 435.2134; found empirical formula C ₂₃ H ₂₆ N ₆ O ₃
38		N-[(1H-indol-6-yl)methyl]-6-(pyrrolidin-1-yl)pyrido[2,3-b]pyrazin-3-amine LC-HRMS (method B): RT 0.84 min, target mass 344.1749, found m/z 345.1833; found empirical formula C ₂₀ H ₂₀ N ₆
39		7-ethyl-N-[(1H-indol-6-yl)methyl]quinoxalin-2-amine LC-HRMS (method B): RT 1.18 min, target mass 302.1531, found m/z 303.1612; found empirical formula C ₁₉ H ₁₈ N ₄
40		N-(1H-indol-6-ylmethyl)-6-{2-methyl-2,7-diazaspiro[3.5]nonan-7-yl}pyrido[2,3-b]pyrazin-3-amine LC-HRMS (method B): RT 0.61 min, target mass 413.2328, found m/z 414.2406; found empirical formula C ₂₄ H ₂₇ N ₇

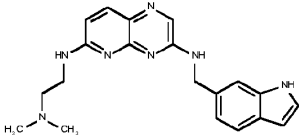
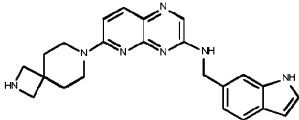
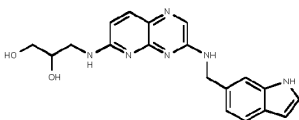
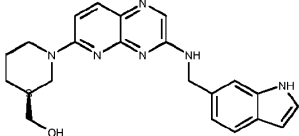
Exemplification Number	Structure	IUPAC Name / Analytical Data LC-HRMS
41		1-(3-((3-hydroxy-4-methoxyphenyl)methyl)amino)pyrido[2,3-b]pyrazin-6-yl)piperidin-4-ol LC-HRMS (method B): RT 0.63 min, target mass 381.1801, found m/z 382.1883; found empirical formula C ₂₀ H ₂₃ N ₅ O ₃
42		1-(3-((1H-indol-4-yl)methyl)amino)pyrido[2,3-b]pyrazin-6-yl)piperidin-4-ol LC-HRMS (method B): RT 0.68 min, target mass 374.1855, found m/z 375.1952; found empirical formula C ₂₁ H ₂₂ N ₆ O
43		6-(2,7-diazaspiro[3.5]nonan-7-yl)-N-((7-methoxy-3-methyl-1H-indol-4-yl)methyl)pyrido[2,3-b]pyrazin-3-amine LC-HRMS (method B): RT 0.66 min, target mass 443.2434, found m/z 444.2508; found empirical formula C ₂₅ H ₂₉ N ₇ O
44		N-((1H-indol-6-yl)methyl)-7-methylquinoxalin-2-amine LC-HRMS (method B): RT 1.04 min, target mass 288.1375, found m/z 289.1455; found empirical formula C ₁₈ H ₁₆ N ₄

Exemplification Number	Structure	IUPAC Name / Analytical Data LC-HRMS
45		3-N-(1H-indol-6-ylmethyl)-6-N-{2-oxaspiro[3.3]heptan-6-yl}pyrido[2,3-b]pyrazine-3,6-diamine LC-HRMS (method B): RT 0.7 min, target mass 386.1855, found m/z 387.1946; found empirical formula C ₂₂ H ₂₂ N ₆ O
46		N-[(2-methyl-1H-indol-5-yl)methyl]quinoxalin-2-amine LC-HRMS (method B): RT 1.02 min, target mass 288.1375, found m/z 289.1453; found empirical formula C ₁₈ H ₁₆ N ₄
47		6-{2,6-diazaspiro[3.4]octan-6-yl}-N-(1H-indol-6-ylmethyl)pyrido[2,3-b]pyrazin-3-amine LC-HRMS (method B): RT 0.6 min, target mass 385.2015, found m/z 386.2089; found empirical formula C ₂₂ H ₂₃ N ₇
48		N3-[(1H-indol-6-yl)methyl]-N6-[trans-4-(difluoromethoxy)cyclohexyl]pyrido[2,3-b]pyrazine-3,6-diamine LC-HRMS (method B): RT 0.89 min, target mass 438.198, found m/z 439.2057; found empirical formula C ₂₃ H ₂₄ F ₂ N ₆ O

Exemplification Number	Structure	IUPAC Name / Analytical Data LC-HRMS
49		N-(1H-indol-6-ylmethyl)-6-(morpholin-4-yl)pyrido[2,3-b]pyrazin-3-amine LC-HRMS (method B): RT 0.76 min, target mass 360.1699, found m/z 361.1784; found empirical formula C ₂₀ H ₂₀ N ₆ O
50		(3R)-1-{3-[(1H-indol-6-ylmethyl)amino]pyrido[2,3-b]pyrazin-6-yl}piperidin-3-ol LC-HRMS (method B): RT 0.72 min, target mass 374.1855, found m/z 375.1934; found empirical formula C ₂₁ H ₂₂ N ₆ O
51		N-[(1H-indol-6-yl)methyl]-6-{2-oxa-6-azaspiro[3.4]octan-6-yl}pyrido[2,3-b]pyrazin-3-amine LC-HRMS (method B): RT 0.73 min, target mass 386.1855, found m/z 387.1929; found empirical formula C ₂₂ H ₂₂ N ₆ O
52		N-(1H-indol-6-ylmethyl)-6-{1-oxa-9-azaspiro[5.5]undecan-9-yl}pyrido[2,3-b]pyrazin-3-amine LC-HRMS (method B): RT 0.96 min, target mass 428.2325, found m/z 429.2418; found empirical formula C ₂₅ H ₂₈ N ₆ O

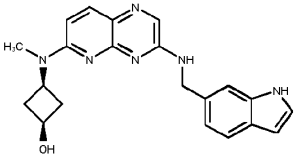
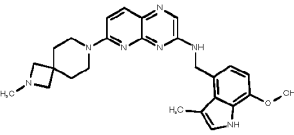
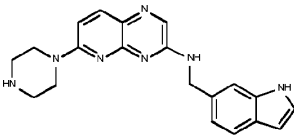
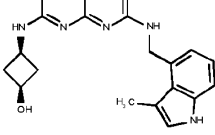
Exemplification Number	Structure	IUPAC Name / Analytical Data LC-HRMS
53		[(2R)-4-[3-({[7-(difluoromethoxy)-3-methyl-1H-indol-4-yl]methyl}amino)pyrido[2,3-b]pyrazin-6-yl]morpholin-2-yl)methanol LC-HRMS (method B): RT 0.89 min, target mass 470.1878, found m/z 471.1956; found empirical formula C ₂₃ H ₂₄ F ₂ N ₆ O ₃
54		6-N-cyclohexyl-3-N-(1H-indol-6-ylmethyl)pyrido[2,3-b]pyrazine-3,6-diamine LC-HRMS (method B): RT 0.91 min, target mass 372.2062, found m/z 395.1983; found empirical formula C ₂₂ H ₂₄ N ₆
55		1-(3-({[3-isopropyl-7-methoxy-1H-indol-4-yl]methyl}amino)pyrido[2,3-b]pyrazin-6-yl)piperidin-4-ol LC-HRMS (method B): RT 0.82 min, target mass 446.243, found m/z 447.2511; found empirical formula C ₂₅ H ₃₀ N ₆ O ₂
56		(3R,4R)-3-(hydroxymethyl)-1-{3-[(1H-indol-6-ylmethyl)amino]pyrido[2,3-b]pyrazin-6-yl}piperidin-4-ol LC-HRMS (method B): RT 0.73 min, target mass 404.1961, found m/z 405.2037; found empirical formula C ₂₂ H ₂₄ N ₆ O ₂

Exemplification Number	Structure	IUPAC Name / Analytical Data LC-HRMS
57		[(2R)-4-{3-[(1H-indol-6-ylmethyl)amino]pyrido[2,3-b]pyrazin-6-yl}morpholin-2-yl]methanol LC-HRMS (method B): RT 0.73 min, target mass 390.1804, found m/z 391.188; found empirical formula C ₂₁ H ₂₂ N ₆ O ₂
58		N-(1H-indol-6-ylmethyl)-6-{3-oxa-9-azaspiro[5.5]undecan-9-yl}pyrido[2,3-b]pyrazin-3-amine LC-HRMS (method B): RT 0.86 min, target mass 428.2325, found m/z 429.2398; found empirical formula C ₂₅ H ₂₈ N ₆ O
59		trans-4-({3-[(1H-indol-6-ylmethyl)amino]pyrido[2,3-b]pyrazin-6-yl}amino)cyclohexan-1-ol LC-HRMS (method B): RT 0.72 min, target mass 388.2012, found m/z 389.2081; found empirical formula C ₂₂ H ₂₄ N ₆ O
60		1-(3-[[2-(cyclopropyl-1H-indol-5-yl)methyl]amino]pyrido[2,3-b]pyrazin-6-yl)piperidin-4-ol LC-HRMS (method B): RT 0.87 min, target mass 414.2168, found m/z 415.2241; found empirical formula C ₂₄ H ₂₆ N ₆ O

Exemplification Number	Structure	IUPAC Name / Analytical Data LC-HRMS
61		N6-[2-(dimethylamino)ethyl]-N3-[(1H-indol-6-yl)methyl]pyrido[2,3-b]pyrazine-3,6-diamine LC-HRMS (method B): RT 0.69 min, target mass 361.2015, found m/z 362.21; found empirical formula C ₂₀ H ₂₃ N ₇
62		6-{2,7-diazaspiro[3.5]nonan-7-yl}-N-(1H-indol-6-ylmethyl)pyrido[2,3-b]pyrazin-3-amine LC-HRMS (method B): RT 0.66 min, target mass 399.2171, found m/z 400.2241; found empirical formula C ₂₃ H ₂₅ N ₇
63		3-[(3-[(1H-indol-6-yl)methyl]amino)pyrido[2,3-b]pyrazin-6-yl)amino]propane-1,2-diol LC-HRMS (method B): RT 0.62 min, target mass 364.1648, found m/z 365.1723; found empirical formula C ₁₉ H ₂₀ N ₆ O ₂
64		[(3S)-1-(3-[(1H-indol-6-yl)methyl]amino)pyrido[2,3-b]pyrazin-6-yl]piperidin-3-yl]methanol LC-HRMS (method B): RT 0.75 min, target mass 388.2012, found m/z 389.2099; found empirical formula C ₂₂ H ₂₄ N ₆ O

Exemplification Number	Structure	IUPAC Name / Analytical Data LC-HRMS
65		1-(3-((7-methoxy-3-methyl-1H-indol-4-yl)methyl)amino)pyrido[2,3-b]pyrazin-6-yl)piperidin-4-ol LC-HRMS (method B): RT 0.73 min, target mass 418.2117, found m/z 419.2195; found empirical formula C ₂₃ H ₂₆ N ₆ O ₂
66		(1-{3-[(1H-indol-6-yl)methyl]amino}pyrido[2,3-b]pyrazin-6-yl)piperidin-4-yl)methanol LC-HRMS (method B): RT 0.7 min, target mass 388.2012, found m/z 389.2092; found empirical formula C ₂₂ H ₂₄ N ₆ O
67		trans-4-[methyl(3-((3-methyl-1H-indol-4-yl)methyl)amino)pyrido[2,3-b]pyrazin-6-yl)amino]cyclohexan-1-ol LC-HRMS (method B): RT 0.7 min, target mass 416.2325, found m/z 417.2426; found empirical formula C ₂₄ H ₂₈ N ₆ O
68		N-[(1H-indol-6-yl)methyl]quinoxalin-2-amine LC-HRMS (method B): RT 1 min, target mass 274.1218, found m/z 275.1294; found empirical formula C ₁₇ H ₁₄ N ₄

Exemplification Number	Structure	IUPAC Name / Analytical Data LC-HRMS
69		1-(3-((7-methoxy-1H-indol-4-yl)methyl)amino)pyrido[2,3-b]pyrazin-6-yl)piperidin-4-ol LC-HRMS (method B): RT 0.69 min, target mass 404.1961, found m/z 405.204; found empirical formula C ₂₂ H ₂₄ N ₆ O ₂
70		(3S)-1-(3-((1H-indol-6-yl)methyl)amino)pyrido[2,3-b]pyrazin-6-yl)piperidin-3-ol LC-HRMS (method B): RT 0.72 min, target mass 374.1855, found m/z 375.1933; found empirical formula C ₂₁ H ₂₂ N ₆ O
71		1-(3-((1H-indol-6-yl)methyl)amino)pyrido[2,3-b]pyrazin-6-yl)piperidin-4-ol LC-HRMS (method B): RT 0.73 min, target mass 374.1855, found m/z 375.194; found empirical formula C ₂₁ H ₂₂ N ₆ O
72		N3-((1H-indol-6-yl)methyl)-N6-(3-methoxypropyl)pyrido[2,3-b]pyrazine-3,6-diamine LC-HRMS (method B): RT 0.78 min, target mass 362.1855, found m/z 363.1964; found empirical formula C ₂₀ H ₂₂ N ₆ O

Exemplification Number	Structure	IUPAC Name / Analytical Data LC-HRMS
73		trans-3-({3-[(1H-indol-6-ylmethyl)amino]pyrido[2,3-b]pyrazin-6-yl}(methyl)amino)cyclobutan-1-ol LC-HRMS (method B): RT 0.69 min, target mass 374.1855, found m/z 375.1934; found empirical formula C ₂₁ H ₂₂ N ₆ O
74		N-[(7-methoxy-3-methyl-1H-indol-4-yl)methyl]-6-{2-methyl-2,7-diazaspiro[3.5]nonan-7-yl}pyrido[2,3-b]pyrazin-3-amine LC-HRMS (method B): RT 0.67 min, target mass 457.259, found m/z 458.2654; found empirical formula C ₂₆ H ₃₁ N ₇ O
75		N-(1H-indol-6-ylmethyl)-6-(piperazin-1-yl)pyrido[2,3-b]pyrazin-3-amine LC-HRMS (method B): RT 0.64 min, target mass 359.1858, found m/z 360.1933; found empirical formula C ₂₀ H ₂₁ N ₇
76		cis-3-[(3-[(3-methyl-1H-indol-4-yl)methyl]amino)pyrido[2,3-b]pyrazin-6-yl]amino]cyclobutan-1-ol LC-HRMS (method B): RT 0.68 min, target mass 374.1855, found m/z 375.1932; found empirical formula C ₂₁ H ₂₂ N ₆ O

Exemplification Number	Structure	IUPAC Name / Analytical Data LC-HRMS
77		(3S,4S)-3-(hydroxymethyl)-1-(3-((7-methoxy-3-methyl-1H-indol-4-yl)methyl)amino)pyrido[2,3-b]pyrazin-6-yl)piperidin-4-ol LC-HRMS (method B): RT 0.7 min, target mass 448.2223, found m/z 449.2302; found empirical formula C ₂₄ H ₂₈ N ₆ O ₃
78		1-(3-((2-methyl-1H-indol-5-yl)methyl)amino)pyrido[2,3-b]pyrazin-6-yl)piperidin-4-ol LC-HRMS (method B): RT 0.71 min, target mass 388.2012, found m/z 389.2096; found empirical formula C ₂₂ H ₂₄ N ₆ O
79		N3-[(1H-indol-6-yl)methyl]-N6-[trans-4-aminocyclohexyl]pyrido[2,3-b]pyrazine-3,6-diamine LC-HRMS (method B): RT 0.53 min, target mass 387.2171, found m/z 388.2249; found empirical formula C ₂₂ H ₂₅ N ₇
80		3-[(3-((1H-indol-6-yl)methyl)amino)pyrido[2,3-b]pyrazin-6-yl)amino]-2,2-dimethylpropan-1-ol LC-HRMS (method B): RT 0.78 min, target mass 376.2012, found m/z 377.2096; found empirical formula C ₂₁ H ₂₄ N ₆ O

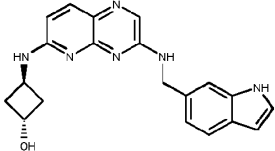
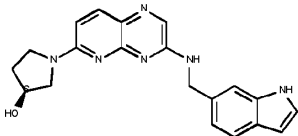
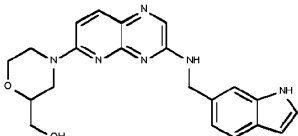
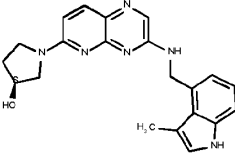
Exemplification Number	Structure	IUPAC Name / Analytical Data LC-HRMS
81		6-N-{6,6-difluorospiro[3.3]heptan-2-yl}-3-N-(1H-indol-6-ylmethyl)pyrido[2,3-b]pyrazine-3,6-diamine LC-HRMS (method B): RT 0.91 min, target mass 420.1874, found m/z 421.195; found empirical formula C ₂₃ H ₂₂ F ₂ N ₆
82		6-{4-[(1-aminocyclopropyl)carbonyl]piperazin-1-yl}-N-(1H-indol-6-ylmethyl)pyrido[2,3-b]pyrazin-3-amine LC-HRMS (method B): RT 0.67 min, target mass 442.223, found m/z 443.2305; found empirical formula C ₂₄ H ₂₆ N ₈ O
83		6-[cis-2,6-dimethylmorpholin-4-yl]-N-(1H-indol-6-ylmethyl)pyrido[2,3-b]pyrazin-3-amine LC-HRMS (method B): RT 0.9 min, target mass 388.2012, found m/z 389.2095; found empirical formula C ₂₂ H ₂₄ N ₆ O
84		[(3S)-1-{3-[(1H-indol-6-ylmethyl)amino]pyrido[2,3-b]pyrazin-6-yl}pyrrolidin-3-yl]methanol LC-HRMS (method B): RT 0.67 min, target mass 374.1855, found m/z 375.1935; found empirical formula C ₂₁ H ₂₂ N ₆ O

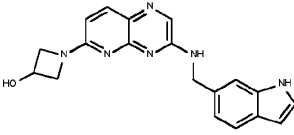
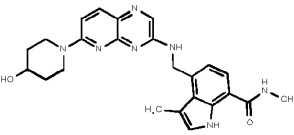
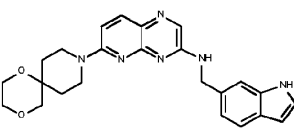
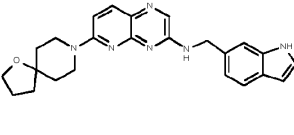
Exemplification Number	Structure	IUPAC Name / Analytical Data LC-HRMS
85		[4-(hydroxymethyl)-1-(3-[(3-methyl-1H-indol-4-yl)methyl]amino)pyrido[2,3-b]pyrazin-6-yl)piperidin-4-yl]methanol LC-HRMS (method B): RT 0.67 min, target mass 432.2274, found m/z 433.2351; found empirical formula C ₂₄ H ₂₈ N ₆ O ₂
86		cis-3-[(3-[(7-methoxy-3-methyl-1H-indol-4-yl)methyl]amino)pyrido[2,3-b]pyrazin-6-yl)(methyl)amino]cyclobutan-1-ol LC-HRMS (method B): RT 0.76 min, target mass 418.2117, found m/z 419.2202; found empirical formula C ₂₃ H ₂₆ N ₆ O ₂
87		4-[(6-[(2R)-2-(hydroxymethyl)morpholin-4-yl]pyrido[2,3-b]pyrazin-3-yl)amino)methyl]-N,3-dimethyl-1H-indole-7-carboxamide LC-HRMS (method B): RT 0.7 min, target mass 461.2175, found m/z 462.2251; found empirical formula C ₂₄ H ₂₇ N ₇ O ₃
88		N-[(1H-indol-6-yl)methyl]-6-methylquinoxalin-2-amine LC-HRMS (method B): RT 1.11 min, target mass 288.1375, found m/z 289.1452; found empirical formula C ₁₈ H ₁₆ N ₄

Exemplification Number	Structure	IUPAC Name / Analytical Data LC-HRMS
89		1-((3-((7-methoxy-3-methyl-1H-indol-4-yl)methyl)amino)pyrido[2,3-b]pyrazin-6-yl)azepan-2-one LC-HRMS (method B): RT 0.81 min, target mass 487.2696, found m/z 488.2783; found empirical formula C ₂₇ H ₃₃ N ₇ O ₂
90		1-((3-((1H-indol-6-yl)methyl)amino)pyrido[2,3-b]pyrazin-6-yl)piperidin-3-ol LC-HRMS (method B): RT 0.71 min, target mass 374.1855, found m/z 375.1935; found empirical formula C ₂₁ H ₂₂ N ₆ O
91		4-((3-((7-methoxy-3-methyl-1H-indol-4-yl)methyl)amino)pyrido[2,3-b]pyrazin-6-yl)morpholin-2-yl)methanol LC-HRMS (method B): RT 0.79 min, target mass 434.2066, found m/z 435.2142; found empirical formula C ₂₃ H ₂₆ N ₆ O ₃
92		N-((1H-indol-6-yl)methyl)-6-((4-methylpiperazin-1-yl)pyrido[2,3-b]pyrazin-3-amine LC-HRMS (method B): RT 0.67 min, target mass 373.2015, found m/z 374.2125; found empirical formula C ₂₁ H ₂₃ N ₇

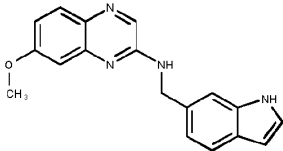
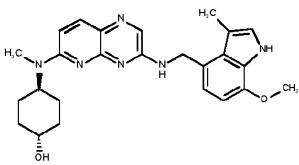
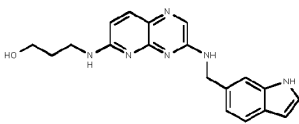
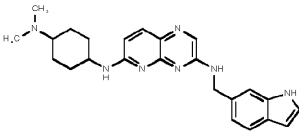
Exemplification Number	Structure	IUPAC Name / Analytical Data LC-HRMS
93		trans-3-[methyl(3-[(3-methyl-1H-indol-4-yl)methyl]amino)pyrido[2,3-b]pyrazin-6-yl)amino]cyclobutan-1-ol LC-HRMS (method B): RT 0.69 min, target mass 388.2012, found m/z 389.2093; found empirical formula C ₂₂ H ₂₄ N ₆ O
94		(3S,4S)-3-(hydroxymethyl)-1-{3-[(1H-indol-6-ylmethyl)amino]pyrido[2,3-b]pyrazin-6-yl}piperidin-4-ol LC-HRMS (method B): RT 0.68 min, target mass 404.1961, found m/z 405.2038; found empirical formula C ₂₂ H ₂₄ N ₆ O ₂
95		6-(azetidin-1-yl)-N-[(1H-indol-6-yl)methyl]pyrido[2,3-b]pyrazin-3-amine LC-HRMS (method B): RT 0.81 min, target mass 330.1593, found m/z 331.1675; found empirical formula C ₁₉ H ₁₈ N ₆
96		1-(3-[(3-methyl-1H-indol-4-yl)methyl]amino)pyrido[2,3-b]pyrazin-6-yl)piperidin-4-ol LC-HRMS (method B): RT 0.71 min, target mass 388.2012, found m/z 389.2085; found empirical formula C ₂₂ H ₂₄ N ₆ O

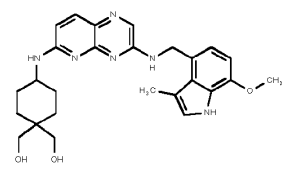
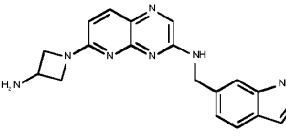
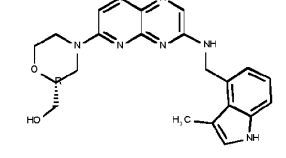
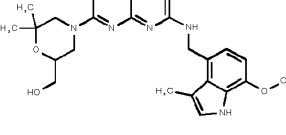
Exemplification Number	Structure	IUPAC Name / Analytical Data LC-HRMS
97		(3R,4R)-3-(hydroxymethyl)-1-(3-(((7-methoxy-3-methyl-1H-indol-4-yl)methyl)amino)pyrido[2,3-b]pyrazin-6-yl)piperidin-4-ol LC-HRMS (method B): RT 0.78 min, target mass 448.2223, found m/z 449.2302; found empirical formula C ₂₄ H ₂₈ N ₆ O ₃
98		6-(((3-(((1H-indol-6-yl)methyl)amino)pyrido[2,3-b]pyrazin-6-yl)amino)spiro[3.3]heptan-2-ol LC-HRMS (method B): RT 0.72 min, target mass 400.2012, found m/z 401.2087; found empirical formula C ₂₃ H ₂₄ N ₆ O
99		3-N-(((7-methoxy-3-methyl-1H-indol-4-yl)methyl)amino)-6-N-([trans-4-(dimethylamino)cyclohexyl]pyrido[2,3-b]pyrazine-3,6-diamine LC-HRMS (method B): RT 0.63 min, target mass 459.2747, found m/z 460.2823; found empirical formula C ₂₆ H ₃₃ N ₇ O
100		(3S)-1-(3-(((7-methoxy-3-methyl-1H-indol-4-yl)methyl)amino)pyrido[2,3-b]pyrazin-6-yl)pyrrolidin-3-ol LC-HRMS (method B): RT 0.68 min, target mass 404.1961, found m/z 405.2041; found empirical formula C ₂₂ H ₂₄ N ₆ O ₂

Exemplification Number	Structure	IUPAC Name / Analytical Data LC-HRMS
101		trans-3-({3-[(1H-indol-6-yl)methyl]amino}pyrido[2,3-b]pyrazin-6-yl)amino)cyclobutan-1-ol LC-HRMS (method B): RT 0.67 min, target mass 360.1699, found m/z 361.1776; found empirical formula C ₂₀ H ₂₀ N ₆ O
102		(3S)-1-(3-[(1H-indol-6-yl)methyl]amino)pyrido[2,3-b]pyrazin-6-yl)pyrrolidin-3-ol LC-HRMS (method B): RT 0.94 min, target mass 360.1699, found m/z 361.1778; found empirical formula C ₂₀ H ₂₀ N ₆ O
103		[4-(3-[(1H-indol-6-yl)methyl]amino)pyrido[2,3-b]pyrazin-6-yl)morpholin-2-yl]methanol LC-HRMS (method B): RT 0.74 min, target mass 390.1804, found m/z 391.1875; found empirical formula C ₂₁ H ₂₂ N ₆ O ₂
104		(3S)-1-(3-[(3-methyl-1H-indol-4-yl)methyl]amino)pyrido[2,3-b]pyrazin-6-yl)pyrrolidin-3-ol LC-HRMS (method B): RT 0.67 min, target mass 374.1855, found m/z 375.1934; found empirical formula C ₂₁ H ₂₂ N ₆ O

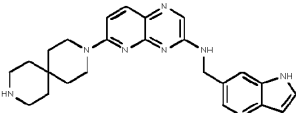
Exemplification Number	Structure	IUPAC Name / Analytical Data LC-HRMS
105		1-(3-((1H-indol-6-yl)methyl)amino)pyrido[2,3-b]pyrazin-6-yl)azetidin-3-ol LC-HRMS (method B): RT 0.68 min, target mass 346.1542, found m/z 347.1619; found empirical formula C ₁₉ H ₁₈ N ₆ O
106		4-((6-(4-hydroxypiperidin-1-yl)pyrido[2,3-b]pyrazin-3-yl)amino)methyl)-N,3-dimethyl-1H-indole-7-carboxamide LC-HRMS (method B): RT 0.66 min, target mass 445.2226, found m/z 446.2304; found empirical formula C ₂₄ H ₂₇ N ₇ O ₂
107		6-(1,4-dioxo-9-azaspiro[5.5]undecan-9-yl)-N-(1H-indol-6-ylmethyl)pyrido[2,3-b]pyrazin-3-amine LC-HRMS (method B): RT 0.79 min, target mass 430.2117, found m/z 431.2197; found empirical formula C ₂₄ H ₂₆ N ₆ O ₂
108		N-(1H-indol-6-ylmethyl)-6-(1-oxa-8-azaspiro[4.5]decan-8-yl)pyrido[2,3-b]pyrazin-3-amine LC-HRMS (method B): RT 0.91 min, target mass 414.2168, found m/z 415.2268; found empirical formula C ₂₄ H ₂₆ N ₆ O

Exemplification Number	Structure	IUPAC Name / Analytical Data LC-HRMS
109		6-[cis-2,6-dimethylmorpholin-4-yl]-N-[(3-isopropyl-7-methoxy-1H-indol-4-yl)methyl]pyrido[2,3-b]pyrazin-3-amine LC-HRMS (method B): RT 1.13 min, target mass 460.2587, found m/z 461.2675; found empirical formula C ₂₆ H ₃₂ N ₆ O ₂
110		6-[(3-[(7-methoxy-3-methyl-1H-indol-4-yl)methyl]amino)pyrido[2,3-b]pyrazin-6-yl)amino]spiro[3.3]heptan-2-ol LC-HRMS (method B): RT 0.82 min, target mass 444.2274, found m/z 445.2353; found empirical formula C ₂₅ H ₂₈ N ₆ O ₂
111		(3S,4S)-4-(hydroxymethyl)-1-{3-[(1H-indol-6-ylmethyl)amino]pyrido[2,3-b]pyrazin-6-yl}piperidin-3-ol LC-HRMS (method B): RT 0.68 min, target mass 404.1961, found m/z 405.2032; found empirical formula C ₂₂ H ₂₄ N ₆ O ₂
112		N-[(7-methoxy-3-methyl-1H-indol-4-yl)methyl]-6-(4-methylpiperazin-1-yl)pyrido[2,3-b]pyrazin-3-amine LC-HRMS (method B): RT 0.67 min, target mass 417.2277, found m/z 418.2353; found empirical formula C ₂₃ H ₂₇ N ₇ O

Exemplification Number	Structure	IUPAC Name / Analytical Data LC-HRMS
113		N-[(1H-indol-6-yl)methyl]-7-methoxyquinoxalin-2-amine LC-HRMS (method B): RT 0.99 min, target mass 304.1324, found m/z 305.1403; found empirical formula C ₁₈ H ₁₆ N ₄ O
114		trans-4-[(3-[[[(7-methoxy-3-methyl-1H-indol-4-yl)methyl]amino]pyrido[2,3-b]pyrazin-6-yl)(methyl)amino]cyclohexan-1-ol LC-HRMS (method B): RT 0.82 min, target mass 446.243, found m/z 447.2514; found empirical formula C ₂₅ H ₃₀ N ₆ O ₂
115		3-[(3-[[[(1H-indol-6-yl)methyl]amino]pyrido[2,3-b]pyrazin-6-yl)amino]propan-1-ol LC-HRMS (method B): RT 0.66 min, target mass 348.1699, found m/z 349.1778; found empirical formula C ₁₉ H ₂₀ N ₆ O
116		6-N-[4-(dimethylamino)cyclohexyl]-3-N-(1H-indol-6-ylmethyl)pyrido[2,3-b]pyrazine-3,6-diamine LC-HRMS (method B): RT 0.63 min, target mass 415.2484, found m/z 416.2565; found empirical formula C ₂₄ H ₂₉ N ₇

Exemplification Number	Structure	IUPAC Name / Analytical Data LC-HRMS
117		[1-(hydroxymethyl)-4-[(3-[(7-methoxy-3-methyl-1H-indol-4-yl)methyl]amino]pyrido[2,3-b]pyrazin-6-yl)amino]cyclohexyl)methanol LC-HRMS (method B): RT 0.72 min, target mass 476.2536, found m/z 477.2611; found empirical formula C ₂₆ H ₃₂ N ₆ O ₃
118		1-{3-[(1H-indol-6-yl)methyl]amino}pyrido[2,3-b]pyrazin-6-yl}azetidin-3-amine LC-HRMS (method B): RT 0.58 min, target mass 345.1702, found m/z 346.1777; found empirical formula C ₁₉ H ₁₉ N ₇
119		[(2R)-4-(3-[(3-methyl-1H-indol-4-yl)methyl]amino]pyrido[2,3-b]pyrazin-6-yl)morpholin-2-yl)methanol LC-HRMS (method B): RT 0.81 min, target mass 404.1961, found m/z 405.2038; found empirical formula C ₂₂ H ₂₄ N ₆ O ₂
120		[4-(3-[(7-methoxy-3-methyl-1H-indol-4-yl)methyl]amino]pyrido[2,3-b]pyrazin-6-yl)-6,6-dimethylmorpholin-2-yl)methanol LC-HRMS (method B): RT 0.87 min, target mass 462.2379, found m/z 463.2463; found empirical formula C ₂₅ H ₃₀ N ₆ O ₃

Exemplification Number	Structure	IUPAC Name / Analytical Data LC-HRMS
121		N3-[(7-methoxy-3-methyl-1H-indol-4-yl)methyl]-N6-({2-oxabicyclo[2.2.2]octan-3-yl)methyl}pyrido[2,3-b]pyrazine-3,6-diamine LC-HRMS (method B): RT 0.88 min, target mass 458.243, found m/z 459.252; found empirical formula C ₂₆ H ₃₀ N ₆ O ₂
122		N-[(1H-indol-6-yl)methyl]-7-(trifluoromethyl)quinoxalin-2-amine LC-HRMS (method B): RT 1.18 min, target mass 342.1092, found m/z 343.1166; found empirical formula C ₁₈ H ₁₃ F ₃ N ₄
123		6-{2,7-diazaspiro[3.5]nonan-2-yl}-N-(1H-indol-6-ylmethyl)pyrido[2,3-b]pyrazin-3-amine LC-HRMS (method B): RT 0.6 min, target mass 399.2171, found m/z 400.2241; found empirical formula C ₂₃ H ₂₅ N ₇
124		N-(1H-indol-5-ylmethyl)-6-(morpholin-4-yl)pyrido[2,3-b]pyrazin-3-amine LC-HRMS (method B): RT 0.81 min, target mass 360.1699, found m/z 361.1783; found empirical formula C ₂₀ H ₂₀ N ₆ O

Exemplification Number	Structure	IUPAC Name / Analytical Data LC-HRMS
125		6-{3,9-diazaspiro[5.5]undecan-3-yl}-N-[(1H-indol-6-yl)methyl]pyrido[2,3-b]pyrazin-3-amine LC-HRMS (method B): RT 0.64 min, target mass 427.2484, found m/z 428.256; found empirical formula C ₂₅ H ₂₉ N ₇

Example 2: WNK1 TR-FRET binding assay

- 5 The binding activity of compounds was determined by in-vitro assay plates (corning #3574) using in-house Terbium labelled phosphorylated or dephosphorylated WNK1 protein, Tb-8His-Halo-TEV-WNK1 (210-482) (UniProtKB® primary accession number Q9H4A3) having an amino acid sequence:
- 10 MHHHHHHHHAEIGTGFPDPHYEVLGERMHYVDVGPRDGPVLFLHGNPTSSYVW
RNIIPHVAPTHRCIAPDLIGMGKSDKPD LGYFFDDHVRFM DAFIEALGLEEVVLVIHDW
GSALGFHWAKRNP ERVKGI AFMEFIRPIPTWDEWPEFA RETFQAFRTT DVGRKLIIDQ
NVFIEGTLPMGVVRPLTEVEMDHYREPFLNPVDREPLWRFPNELPIAGEPANIVALVE
EYMDWLHQSPVPKLLFWGTPGVLIPPAEAA RLAKSLPNCKAVDIGPGLNLLQEDNPDL
15 IGSEIARWLSTLEISGGGSENLYFQCKAVGMSNDGRFLKFDIEIGRGSFKTVYKGLDTE
TTVEVAWC ELQDRKLT KSERQRFKEEA EMLKGLQHPNIVRFYDSWESTVKGKKCIVL
VTELM TSGTLKTYLKR FKMVKIKVLR SWCRQILKGLQLHTRTPPIIHRDLKCDNIFITG
PTGSVKIGDLGLATLKRASF AKSVIGTPEFMAPEMYEEKYDESVDVYA FGMCMLEMA
TSEYPYSECQNAAQIYRRVTSGVKPASFDKVAIPEVKEIIEGCIRQNKDERYSIKDLLNH
20 AFFQEE (SEQ ID NO. 1).

The Terbium labelled WNK1 proteins were coupled with a fluorescein labelled ATP competitive probe, VER-00540269. The design of VER-00540269 was based on literature inhibitor WNK463 (Yamada *et al.*, 2016a), replacing the t-butyl amide with a flexible linker to tether a fluorescein label. The addition of WNK463 (MCE® Cat. No.: HY-100626), competitively to the same site as the inhibitor probe, results in a decrease in the TR-FRET signal due to displacement of the probe. WNK463 was demonstrated to dose dependently inhibit the phosphorylation of OSR1 in HEK293 cells (Yamada *et al* 2016).

Compounds were screened in n=2 11 point 3-fold titrations. The assay consisted of 1nM Terbium labelled WNK1, 2 nM or 150 nM VER-00540269 probe, 50 mM HEPES (4-(2-hydroxyethyl)-1-piperazine-ethanesulfonic acid) pH 7.5, 150 mM NaCl, 0.01% Tween-20, 1 mM dithiothreitol and 5% DMSO. Assays were incubated for 2 h at 23°C.

5

TR-FRET measurements were performed on a BioTek Synergy Neo2 plate reader. TR-FRET was measured by excitation of the terbium-donor with 340 nm light and then, after a delay time 100 µs, measurement of terbium and fluorescein emission at 495 nm and 520 nm, using a time window of 300 µs. This measurement was repeated 20 times for both emissions (495 nm and 520 nm) with a 300 µs time window between repeat reads. The TR-FRET signal was calculated as an emission ratio of 520 nm over 495 nm signals.

The TR-FRET signal for test compound was normalized against 0% inhibition control wells and 100% inhibition control wells and % inhibition of test compound calculated. Test compound potency (IC₅₀) was estimated by nonlinear regression using the sigmoidal dose-response (variable slope) using Xlfit 4 (IDBS, Guildford, Surrey, UK, model 205).

15

$$y = (A + ((B - A) / (1 + ((C/x)^D))))$$

where y is the normalized TR-FRET signal measurement for a given concentration of test compound, x is the concentration of test compound, A is the estimated efficacy (% inhibition) at infinite compound dilution, and B is the maximal efficacy (% inhibition). C is the IC₅₀ value and D is the Hill slope coefficient.

20

The K_i values were determined from the IC₅₀ values according to Cer *et al*, Nucleic Acids Res, 2009, 37(WebServer issue): W441-W445. Inhibition constants (K_i) are determined from complete binding inhibition curves (cK_i).

25

The cK_i values were determined from the IC₅₀ values as follows;

30

$$cK_i = K_M \times \frac{I_{50}}{L_{50}} \times \frac{PL_{50}}{PI_{50}}$$

Where $I_{50} = IC_{50} - PI_{50}$, $L_{50} = L_T - \frac{PL_0}{2}$, $PL_{50} = \frac{PL_0}{2}$, $PI_{50} = P_T - \left(\frac{K_M \times PL_{50}}{L_{50}} \right) - PL_{50}$ with

$$PL_0 = P_T - \frac{-(K_M + L_T - P_T) \pm \sqrt{(K_M + L_T - P_T)^2 + 4P_T K_M}}{2}.$$

And P_T is total protein, L_T is total probe, IC_{50} is concentration giving 50% inhibition and K_M (probe K_d) is determined experimentally. I_{50} is the free inhibitor concentration at the IC_{50} , L_{50} is the free probe concentration at the IC_{50}

- 5 The compounds of the invention were screened in the above-mentioned assay and the cK_i values of the compounds are set forth in Table 2 below wherein "A" refers to a cK_i of less than 1 nM, "B" refers to cK_i value in the range of 1 nM to 100 nM and "C" refers to cK_i value in the range of greater than 100 nM to 1000 nM.

10 Table 2. cK_i values

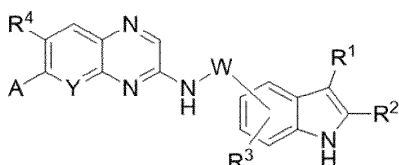
Group	Compound No.
A	12, 13, 14, 15, 16, 17, 19, 20, 21, 24, 25, 27, 28, 29, 32, 34, 36, 37, 38, 43, 45, 48, 49, 50, 51, 53, 54, 55, 56, 57, 59, 60, 62, 63, 65, 66, 67, 69, 70, 71, 72, 73, 74, 76, 77, 78, 79, 80, 83, 84, 85, 86, 87, 89, 90, 91, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 106, 107, 110, 111, 112, 114, 115, 116, 117, 119, 120, 121, 124
B	5, 6, 7, 8, 9, 10, 11, 18, 22, 23, 26, 30, 33, 35, 40, 41, 42, 44, 47, 52, 58, 61, 68, 75, 81, 82, 92, 105, 108, 109, 118, 123, 125
C	1, 2, 3, 4, 39, 46, 88, 113, 122

References

- Ishigami-Yuasa M et al.: Development of WNK signaling inhibitors as a new class of antihypertensive drugs. *Bioorg Med Chem.* 2017, 25(14):3845-3852.
- 5 Yamada K et al.: Small-molecule WNK inhibition regulates cardiovascular and renal function. *Nat Chem Biol.* 2016, 12:896-898. (Yamada et al., 2016a)
- 10 Yamada K, et al.: Discovery and Characterization of Allosteric WNK Kinase Inhibitors. *ACS Chem Biol.* 2016, 11(12):3338-3346. (Yamada et al., 2016b)
- 15 Yamada K et al.: Optimization of Allosteric With-No-Lysine (WNK) Kinase Inhibitors and Efficacy in Rodent Hypertension Models. *J Med Chem.* 2017 Aug 24;60(16):7099-7107.
- Xiu, M., Li, L., Li, Y. *et al.* An update regarding the role of WNK kinases in cancer. *Cell Death Dis* 13, 795 (2022).

Claims

1. A compound of formula (I):



Formula (I)

wherein

Y is C(H) or N;

W is C(H)₂ or C(D)₂;

R¹ is H, C₁₋₃ alkyl or cyclopropyl

R² is H; C₁₋₃ alkyl optionally substituted with OH; or C₃₋₅ cycloalkyl;

R³ is H; C₁₋₃ alkyl optionally substituted with OH; -OC₁₋₃ alkyl optionally substituted with one or more F; -C(O)NHCH₃; -NH₂; -N(H)(CH₃); -N(CH₃)₂; or halogen;

R⁴ is H, C₁₋₄ alkyl, or C₃₋₅ cycloalkyl;

A is selected from the group consisting of H, C₁₋₃ alkoxy, CF₃, and a group of formula (II):



Formula (II)

wherein

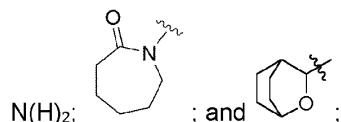
X is C(H) or N;

R⁶ is H or C₁₋₄ alkyl; and

R⁵ is selected from the group consisting of C₁₋₆ alkyl optionally substituted with one or more, identical or different, substituents R⁷, wherein one or more methylene(s) of said C₁₋₆ alkyl is optionally and individually replaced with -O- or C=O; C₃₋₆ cycloalkyl optionally substituted with one or more, identical or different, substituents R⁷; and tetrahydropyranyl;

wherein two R⁷ are optionally linked together to form a ring together with the intervening atom(s);

R^7 is individually selected from C_{1-3} alkoxy optionally substituted with one or more F; -OH; -O-benzyl; C_{1-3} alkyl optionally substituted with OH; $N(CH_3)_2$;



or when two R^7 are linked together to form a ring, then said two R^7 are individually selected from C_{1-2} alkanediyl optionally substituted with one or two substituents selected from F and OH, and one of the methylene of said C_{1-2} alkanediyl is optionally replaced with -O-;

or

R^5 and R^6 are linked together to form a ring and

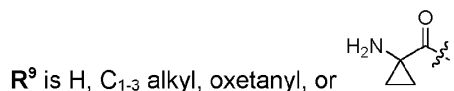
R^5 is a bond or C_{1-5} alkanediyl optionally substituted with one or more, identical or different, substituents R^8 , and one methylene of the C_{1-5} alkanediyl is optionally replaced with -O- or $N(R^9)$; and

R^6 is a bond or C_{1-5} alkanediyl optionally substituted with one or more, identical or different, substituents R^8 , and one methylene of the C_{1-5} alkanediyl is optionally replaced with -O- or $N(R^9)$;

wherein two R^8 are optionally linked together to form a ring together with the intervening atom(s);

R^8 is individually selected from C_{1-3} alkyl optionally substituted with OH; -OH; -F; - $N(H)_2$; and - OC_{1-3} alkyl optionally substituted with one or more F;

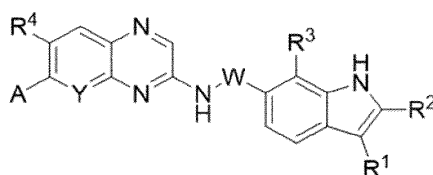
or when two R^8 are linked together to form a ring, then said two R^8 are individually selected from C_{1-3} alkanediyl optionally substituted with one or two substituents selected from F, OH, and NH_2 , and one or two methylene(s) of said C_{1-3} alkanediyl is optionally and individually replaced with -O-, -N(H)- or - $N(CH_3)$ -; and



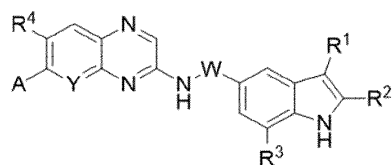
or a pharmaceutically acceptable salt thereof,

with the proviso that the compound is not N-[(2,3,5-Trimethyl-1H-indol-7-yl)methyl]-2-quinoxalinamine.

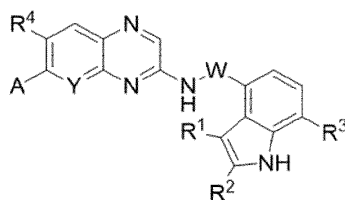
2. The compound according to claim 1, wherein the compound is of Formula (Ia), Formula (Ib), Formula (Ic), or Formula (Id):



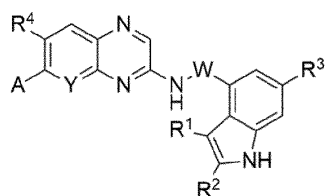
Formula (Ia)



Formula (Ib)



Formula (Ic),



Formula (Id).

5

- 10 3. The compound according to anyone of the preceding claims, wherein R¹ is H, CH₃, or isopropyl, R² is H, CH₃, cyclopropyl, or CH₂OH and R³ is H, CH₃, CH₂OH, NH₂, N(CH₃)₂, Cl, C(O)NHCH₃, OCHF₂, or OCH₃.
- 15 4. The compound according to anyone of the preceding claims, wherein the compound is of Formula (Ib), and wherein R¹ is H, R² is H, and R³ is H, CH₃, or OCH₃.

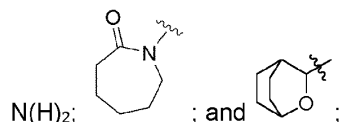
5. The compound according to anyone of the preceding claims, wherein the compound is of Formula (Ic), and wherein R¹ is CH₃, R² is H, and R³ is H, N(CH₃)₂, Cl, CH₂OH, OCHF₂, C(O)NHCH₃ or OCH₃.
- 5 6. The compound according to anyone of the preceding claims, wherein the compound is of Formula (Ib), and wherein R¹ is H, R² is CH₃, cyclopropyl, or CH₂OH, and R³ is H.
- 10 7. The compound according to anyone of the preceding claims, wherein the compound is of Formula (Ic), and wherein R¹ is isopropyl, R² is H, and R³ is H or OCH₃.
8. The compound according to anyone of the preceding claims, wherein R⁴ is H or CH₃.
- 15 9. The compound according to anyone of the preceding claims, wherein A is H, CF₃ or of Formula (II):



Formula (II)

- 20 wherein
X is N;
R⁶ is H or C₁₋₄ alkyl; and
R⁵ is selected from the group consisting of C₁₋₆ alkyl optionally substituted with one or more, identical or different, substituents R⁷, wherein one or more methylene(s) of said C₁₋₆ alkyl is optionally and individually replaced with -O- or C=O; C₃₋₆ cycloalkyl optionally substituted with one or more, identical or different, substituents R⁷; and tetrahydropyranyl;
25 wherein two R⁷ are optionally linked together to form a ring together with the intervening atom(s); and

R^7 is individually selected from C_{1-3} alkoxy optionally substituted with one or more F; -OH; -O-benzyl; C_{1-3} alkyl optionally substituted with OH; $N(CH_3)_2$;

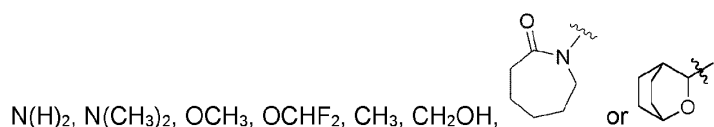


or when two R^7 are linked together to form a ring, then said two R^7 are individually selected from C_{1-2} alkanediyl optionally substituted with one or two substituents selected from F and OH, and one of the methylene of said C_{1-2} alkanediyl is optionally replaced with -O-.

10. The compound according to anyone of the preceding claims, wherein R^6 is H or CH_3 .

11. The compound according to anyone of the preceding claims, wherein R^5 is C_1 alkyl substituted with one or more, identical or different, substituents R^7 , C_2 alkyl substituted with one or more, identical or different, substituents R^7 , C_3 alkyl substituted with one or more, identical or different, substituents R^7 , C_4 alkyl substituted with one or more, identical or different, substituents R^7 , C_5 alkyl substituted with one or more, identical or different, substituents R^7 , C_6 alkyl substituted with one or more, identical or different, substituents R^7 , is C_4 cycloalkyl substituted with one or more, identical or different, substituents R^7 , C_6 cycloalkyl, or C_6 cycloalkyl substituted with one or more, identical or different, substituents R^7 .

12. The compound according to anyone of the preceding claims, wherein R^7 is OH,



13. The compound according to anyone of the preceding claims, wherein A is piperidinyl, pyrrolidinyl, azetidiny, piperazinyl, or morpholinyl, wherein said piperidinyl, pyrrolidinyl, azetidiny, or piperazinyl is optionally substituted with one or more individually selected R^{18} , wherein two R^{18} are optionally linked together to form a ring together with the intervening atom(s); and wherein said morpholinyl optionally substituted with one or more, identical or different,

substituents R^{19} , wherein R^{19} is individually selected from C_{1-3} alkyl and C_{1-3} alkyl substituted with OH;

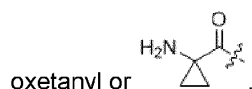
R^{18} is individually selected from C_{1-3} alkyl optionally substituted with OH; -OH; F; $N(H)_2$; and -OC $_{1-3}$ alkyl optionally substituted with one or more F;

5 or when two R^{18} are linked together to form a ring, then said two R^{18} are individually selected from C_{1-3} alkanediyl optionally substituted with one or two substituents selected from F, OH, and NH_2 , and one or two methylene(s) of said C_{1-3} alkanediyl is optionally and individually replaced with -O-, -N(H)- or -N(CH $_3$)-.

10

14. The compound according to anyone of the preceding claims, wherein A is piperidinyl, pyrrolidinyl, azetidiny, or piperazinyl, wherein said piperidinyl, pyrrolidinyl, azetidiny, or piperazinyl is optionally substituted with one or more individually selected R^{18} , wherein R^{18} is -CH $_3$, -CH $_2$ OH, -OH, $N(H)_2$, OCHF $_2$, -F,

15



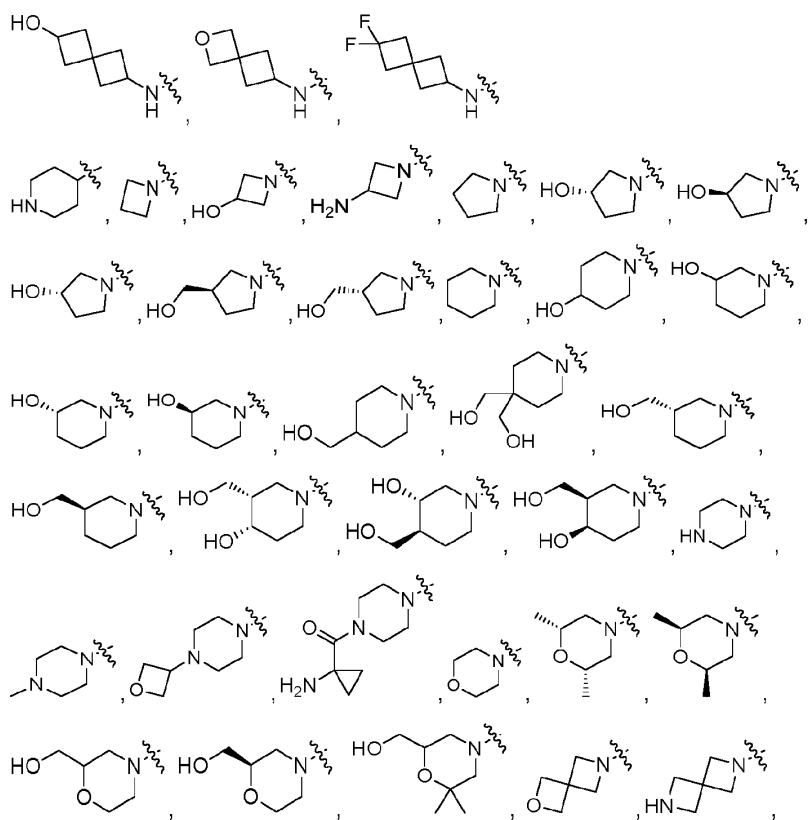
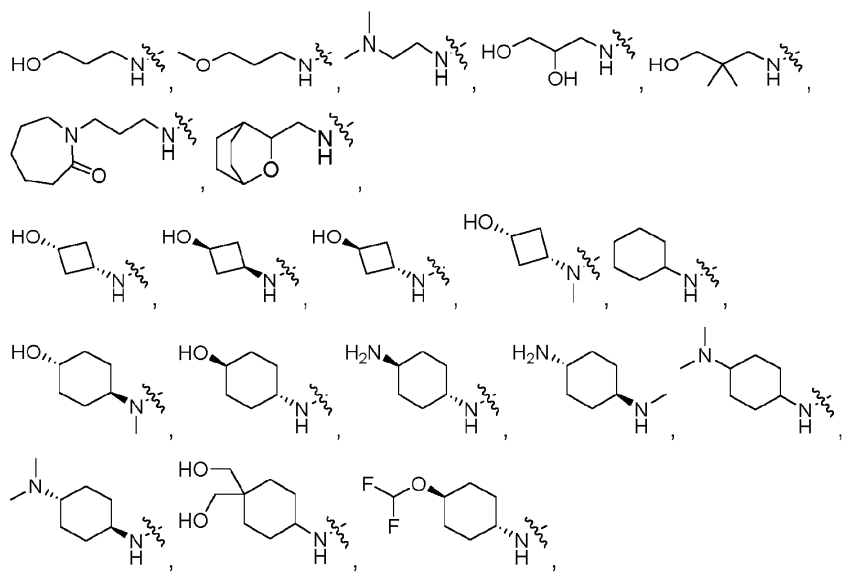
15. The compound according to anyone of the preceding claims, wherein A is piperidinyl, pyrrolidinyl, azetidiny or piperazinyl, wherein said piperidinyl, pyrrolidinyl, azetidiny, or piperazinyl is substituted with two or more R^{18} , wherein two R^{18} are linked together to form a ring together with the intervening atom(s), and wherein the two R^{18} linked together to form a ring are individually selected from C_{1-3} alkanediyl optionally substituted with one or two substituents selected from F, OH and -NH $_2$, and wherein one or two methylene(s) of said C_{1-3} alkanediyl is optionally and individually replaced with -O-, -N(H)- or -N(CH $_3$)-.

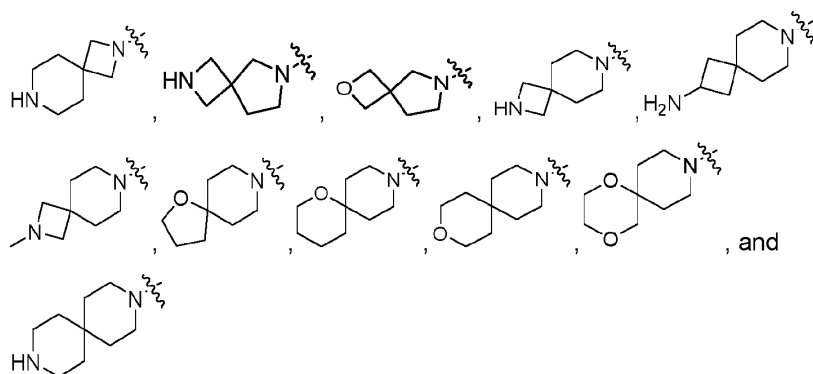
25

16. The compound according to anyone of the preceding claims, wherein A is morpholinyl, wherein said morpholinyl optionally substituted with one or more, identical or different, substituents R^{19} , wherein R^{19} is -CH $_3$, or -CH $_2$ OH.

30

17. The compound according to anyone of the preceding claims, wherein A is selected from the group consisting of: H, CF $_3$,





- 5 18. The compound according to anyone of the preceding claims, wherein the compound is selected from the group consisting of:

- 7-cyclopropyl-N-(1H-indol-6-ylmethyl)quinoxalin-2-amine,
 N-[(7-methyl-1H-indol-5-yl)methyl]quinoxalin-2-amine,
 10 N-(1H-indol-6-ylmethyl)-7-(piperidin-1-yl)quinoxalin-2-amine
 N-(1H-indol-5-ylmethyl)quinoxalin-2-amine,
 1-(3-[(6-amino-1H-indol-4-yl)methyl]amino)pyrido[2,3-b]pyrazin-6-yl)piperidin-4-ol,
 N-(1H-indol-4-ylmethyl)-6-{2-methyl-2,7-diazaspiro[3.5]nonan-7-yl}pyrido[2,3-
 15 b]pyrazin-3-amine
 1-[3-({[7-(hydroxymethyl)-3-methyl-1H-indol-4-yl]methyl}amino)pyrido[2,3-b]pyrazin-6-yl]piperidin-4-ol,
 1-(3-[[1H-indol-4-yl(²H₂)methyl]amino]pyrido[2,3-b]pyrazin-6-yl)piperidin-4-ol,
 N-(1H-indol-6-ylmethyl)-6-(piperidin-4-yl)pyrido[2,3-b]pyrazin-3-amine,
 20 [6-({[6-(piperidin-1-yl)pyrido[2,3-b]pyrazin-3-yl]amino}methyl)-1H-indol-2-yl]MeOH,
 N-[(3-isopropyl-7-methoxy-1H-indol-4-yl)methyl]-6-(pyrrolidin-1-yl)pyrido[2,3-b]pyrazin-3-amine,
 6-N-cyclohexyl-3-N-[(7-methoxy-3-methyl-1H-indol-4-yl)methyl]pyrido[2,3-
 25 b]pyrazine-3,6-diamine,
 1-[3-({[7-(dimethylamino)-3-methyl-1H-indol-4-yl]methyl}amino)pyrido[2,3-b]pyrazin-6-yl]piperidin-4-ol,
 6-[(2R,6S)-2,6-dimethylmorpholin-4-yl]-N-[(3-methyl-1H-indol-4-yl)methyl]pyrido[2,3-b]pyrazin-3-amine,

- N,3-dimethyl-4-[[6-{methyl[(1s,3s)-3-hydroxycyclobutyl]amino}pyrido[2,3-b]pyrazin-3-yl]amino]methyl]-1H-indole-7-carboxamide,
1-[3-({[7-(difluoromethoxy)-3-methyl-1H-indol-4-yl]methyl}amino)pyrido[2,3-b]pyrazin-6-yl]piperidin-4-ol,
5 3-(hydroxymethyl)-1-(3-{{[7-methoxy-3-methyl-1H-indol-4-yl]methyl}amino}pyrido[2,3-b]pyrazin-6-yl)piperidin-4-ol,
1-(3-{{[7-chloro-1H-indol-4-yl]methyl}amino}pyrido[2,3-b]pyrazin-6-yl)piperidin-4-ol,
[(3R)-1-(3-{{[1H-indol-6-yl]methyl}amino}pyrido[2,3-b]pyrazin-6-yl)pyrrolidin-3-yl]methanol,
10 (3R)-1-(3-{{[1H-indol-6-yl]methyl}amino}pyrido[2,3-b]pyrazin-6-yl)pyrrolidin-3-ol,
cis-(1s,3s)-3-[[3-{{[7-methoxy-3-methyl-1H-indol-4-yl]methyl}amino}pyrido[2,3-b]pyrazin-6-yl]amino]cyclobutan-1-ol,
N-[(1H-indol-6-yl)methyl]-6-{2-oxa-6-azaspiro[3.3]heptan-6-yl}pyrido[2,3-b]pyrazin-3-amine,
15 6-{2,6-diazaspiro[3.3]heptan-2-yl}-N-(1H-indol-6-ylmethyl)pyrido[2,3-b]pyrazin-3-amine,
3-(hydroxymethyl)-1-(3-{{[1H-indol-6-yl]methyl}amino}pyrido[2,3-b]pyrazin-6-yl)piperidin-4-ol,
20 [(3R)-1-(3-{{[1H-indol-6-yl]methyl}amino}pyrido[2,3-b]pyrazin-6-yl)piperidin-3-yl]methanol,
N-[(1H-indol-6-yl)methyl]pyrido[2,3-b]pyrazin-3-amine,
cis-(1R,3R)-3-{{[3-{{[1H-indol-6-ylmethyl]amino}pyrido[2,3-b]pyrazin-6-yl}amino]cyclobutan-1-ol},
25 [4-(hydroxymethyl)-1-(3-{{[7-methoxy-3-methyl-1H-indol-4-yl]methyl}amino}pyrido[2,3-b]pyrazin-6-yl)piperidin-4-yl]methanol,
3-N-[[7-methoxy-3-methyl-1H-indol-4-yl]methyl]-6-N-[trans-4-aminocyclohexyl]pyrido[2,3-b]pyrazine-3,6-diamine,
7-tert-butyl-N-(1H-indol-6-ylmethyl)quinoxalin-2-amine,
30 N-[(1H-indol-6-yl)methyl]-6-(piperidin-1-yl)pyrido[2,3-b]pyrazin-3-amine,
[4-(hydroxymethyl)-1-{3-{{[1H-indol-6-ylmethyl]amino}pyrido[2,3-b]pyrazin-6-yl}piperidin-4-yl]methanol,
N-(1H-indol-6-ylmethyl)-6-[4-(oxetan-3-yl)piperazin-1-yl]pyrido[2,3-b]pyrazin-3-amine,

- 7-{3-[(1H-indol-6-ylmethyl)amino]pyrido[2,3-b]pyrazin-6-yl}-7-azaspiro[3.5]nonan-2-amine,
1-{3-[(1H-pyrrolo[2,3-b]pyridin-5-yl)methyl]amino}pyrido[2,3-b]pyrazin-6-yl}piperidin-4-ol,
5 3-N-(1H-indol-6-ylmethyl)-6-N-(oxan-4-yl)pyrido[2,3-b]pyrazine-3,6-diamine,
[(2R)-4-(3-[(7-methoxy-3-methyl-1H-indol-4-yl)methyl]amino)pyrido[2,3-b]pyrazin-6-yl)morpholin-2-yl]methanol,
N-[(1H-indol-6-yl)methyl]-6-(pyrrolidin-1-yl)pyrido[2,3-b]pyrazin-3-amine,
7-ethyl-N-[(1H-indol-6-yl)methyl]quinoxalin-2-amine,
10 N-(1H-indol-6-ylmethyl)-6-{2-methyl-2,7-diazaspiro[3.5]nonan-7-yl}pyrido[2,3-b]pyrazin-3-amine,
1-(3-[(3-hydroxy-4-methoxyphenyl)methyl]amino)pyrido[2,3-b]pyrazin-6-yl}piperidin-4-ol,
1-(3-[(1H-indol-4-yl)methyl]amino)pyrido[2,3-b]pyrazin-6-yl}piperidin-4-ol,
15 6-{2,7-diazaspiro[3.5]nonan-7-yl}-N-[(7-methoxy-3-methyl-1H-indol-4-yl)methyl]pyrido[2,3-b]pyrazin-3-amine,
N-[(1H-indol-6-yl)methyl]-7-methylquinoxalin-2-amine,
3-N-(1H-indol-6-ylmethyl)-6-N-{2-oxaspiro[3.3]heptan-6-yl}pyrido[2,3-b]pyrazine-3,6-diamine,
20 N-[(2-methyl-1H-indol-5-yl)methyl]quinoxalin-2-amine,
6-{2,6-diazaspiro[3.4]octan-6-yl}-N-(1H-indol-6-ylmethyl)pyrido[2,3-b]pyrazin-3-amine,
N3-[(1H-indol-6-yl)methyl]-N6-[trans-4-(difluoromethoxy)cyclohexyl]pyrido[2,3-b]pyrazine-3,6-diamine,
25 N-(1H-indol-6-ylmethyl)-6-(morpholin-4-yl)pyrido[2,3-b]pyrazin-3-amine,
(3R)-1-{3-[(1H-indol-6-ylmethyl)amino]pyrido[2,3-b]pyrazin-6-yl}piperidin-3-ol,
N-[(1H-indol-6-yl)methyl]-6-{2-oxa-6-azaspiro[3.4]octan-6-yl}pyrido[2,3-b]pyrazin-3-amine,
N-(1H-indol-6-ylmethyl)-6-{1-oxa-9-azaspiro[5.5]undecan-9-yl}pyrido[2,3-b]pyrazin-3-amine,
30 [(2R)-4-[3-[(7-(difluoromethoxy)-3-methyl-1H-indol-4-yl)methyl]amino]pyrido[2,3-b]pyrazin-6-yl)morpholin-2-yl]methanol,
6-N-cyclohexyl-3-N-(1H-indol-6-ylmethyl)pyrido[2,3-b]pyrazine-3,6-diamine,
1-(3-[(3-isopropyl-7-methoxy-1H-indol-4-yl)methyl]amino)pyrido[2,3-b]pyrazin-6-yl}piperidin-4-ol,
35

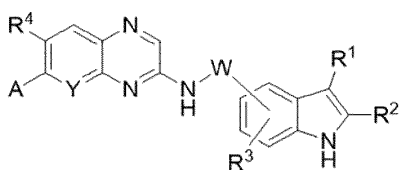
- (3R,4R)-3-(hydroxymethyl)-1-{3-[(1H-indol-6-ylmethyl)amino]pyrido[2,3-b]pyrazin-6-yl}piperidin-4-ol,
[(2R)-4-{3-[(1H-indol-6-ylmethyl)amino]pyrido[2,3-b]pyrazin-6-yl}morpholin-2-yl]methanol,
5 N-(1H-indol-6-ylmethyl)-6-{3-oxa-9-azaspiro[5.5]undecan-9-yl}pyrido[2,3-b]pyrazin-3-amine,
trans-4-({3-[(1H-indol-6-ylmethyl)amino]pyrido[2,3-b]pyrazin-6-yl}amino)cyclohexan-1-ol,
1-(3-{[(2-cyclopropyl-1H-indol-5-yl)methyl]amino}pyrido[2,3-b]pyrazin-6-yl)piperidin-4-ol,
10 N6-[2-(dimethylamino)ethyl]-N3-[(1H-indol-6-yl)methyl]pyrido[2,3-b]pyrazine-3,6-diamine,
6-[2,7-diazaspiro[3.5]nonan-7-yl]-N-(1H-indol-6-ylmethyl)pyrido[2,3-b]pyrazin-3-amine,
15 3-[(3-{[(1H-indol-6-yl)methyl]amino}pyrido[2,3-b]pyrazin-6-yl)amino]propane-1,2-diol,
[(3S)-1-(3-{[(1H-indol-6-yl)methyl]amino}pyrido[2,3-b]pyrazin-6-yl)piperidin-3-yl]methanol,
1-(3-{[(7-methoxy-3-methyl-1H-indol-4-yl)methyl]amino}pyrido[2,3-b]pyrazin-6-yl)piperidin-4-ol,
20 (1-{3-[(1H-indol-6-ylmethyl)amino]pyrido[2,3-b]pyrazin-6-yl}piperidin-4-yl)methanol,
trans-4-[methyl(3-{[(3-methyl-1H-indol-4-yl)methyl]amino}pyrido[2,3-b]pyrazin-6-yl)amino]cyclohexan-1-ol,
25 N-[(1H-indol-6-yl)methyl]quinoxalin-2-amine,
1-(3-{[(7-methoxy-1H-indol-4-yl)methyl]amino}pyrido[2,3-b]pyrazin-6-yl)piperidin-4-ol,
(3S)-1-(3-{[(1H-indol-6-yl)methyl]amino}pyrido[2,3-b]pyrazin-6-yl)piperidin-3-ol,
1-(3-{[(1H-indol-6-yl)methyl]amino}pyrido[2,3-b]pyrazin-6-yl)piperidin-4-ol,
30 N3-[(1H-indol-6-yl)methyl]-N6-(3-methoxypropyl)pyrido[2,3-b]pyrazine-3,6-diamine,
trans-3-({3-[(1H-indol-6-ylmethyl)amino]pyrido[2,3-b]pyrazin-6-yl}(methyl)amino)cyclobutan-1-ol,
N-[(7-methoxy-3-methyl-1H-indol-4-yl)methyl]-6-{2-methyl-2,7-diazaspiro[3.5]nonan-7-yl}pyrido[2,3-b]pyrazin-3-amine,
35

- N-(1H-indol-6-ylmethyl)-6-(piperazin-1-yl)pyrido[2,3-b]pyrazin-3-amine,
cis-3-[(3-[(3-methyl-1H-indol-4-yl)methyl]amino)pyrido[2,3-b]pyrazin-6-
yl)amino]cyclobutan-1-ol,
(3S,4S)-3-(hydroxymethyl)-1-(3-[(7-methoxy-3-methyl-1H-indol-4-
5 yl)methyl]amino)pyrido[2,3-b]pyrazin-6-yl)piperidin-4-ol,
1-(3-[(2-methyl-1H-indol-5-yl)methyl]amino)pyrido[2,3-b]pyrazin-6-yl)piperidin-
4-ol,
N3-[(1H-indol-6-yl)methyl]-N6-[trans-4-aminocyclohexyl]pyrido[2,3-b]pyrazine-
3,6-diamine,
10 3-[(3-[(1H-indol-6-yl)methyl]amino)pyrido[2,3-b]pyrazin-6-yl)amino]-2,2-
dimethylpropan-1-ol,
6-N-{6,6-difluorospiro[3.3]heptan-2-yl}-3-N-(1H-indol-6-ylmethyl)pyrido[2,3-
b]pyrazine-3,6-diamine,
6-{4-[(1-aminocyclopropyl)carbonyl]piperazin-1-yl}-N-(1H-indol-6-
15 ylmethyl)pyrido[2,3-b]pyrazin-3-amine,
6-[cis-2,6-dimethylmorpholin-4-yl]-N-(1H-indol-6-ylmethyl)pyrido[2,3-b]pyrazin-
3-amine,
[(3S)-1-{3-[(1H-indol-6-ylmethyl)amino]pyrido[2,3-b]pyrazin-6-yl}pyrrolidin-3-
yl]methanol,
20 [4-(hydroxymethyl)-1-(3-[(3-methyl-1H-indol-4-yl)methyl]amino)pyrido[2,3-
b]pyrazin-6-yl)piperidin-4-yl]methanol,
cis-3-[(3-[(7-methoxy-3-methyl-1H-indol-4-yl)methyl]amino)pyrido[2,3-
b]pyrazin-6-yl)(methyl)amino]cyclobutan-1-ol,
4-[(6-[(2R)-2-(hydroxymethyl)morpholin-4-yl]pyrido[2,3-b]pyrazin-3-
25 yl)amino)methyl]-N,3-dimethyl-1H-indole-7-carboxamide,
N-[(1H-indol-6-yl)methyl]-6-methylquinoxalin-2-amine,
1-{3-[(3-[(7-methoxy-3-methyl-1H-indol-4-yl)methyl]amino)pyrido[2,3-b]pyrazin-
6-yl)amino]propyl}azepan-2-one,
1-(3-[(1H-indol-6-yl)methyl]amino)pyrido[2,3-b]pyrazin-6-yl)piperidin-3-ol,
30 [4-(3-[(7-methoxy-3-methyl-1H-indol-4-yl)methyl]amino)pyrido[2,3-b]pyrazin-6-
yl)morpholin-2-yl]methanol,
N-(1H-indol-6-ylmethyl)-6-(4-methylpiperazin-1-yl)pyrido[2,3-b]pyrazin-3-amine,
trans-3-[methyl(3-[(3-methyl-1H-indol-4-yl)methyl]amino)pyrido[2,3-b]pyrazin-6-
yl)amino]cyclobutan-1-ol,

- (3S,4S)-3-(hydroxymethyl)-1-{3-[(1H-indol-6-ylmethyl)amino]pyrido[2,3-b]pyrazin-6-yl}piperidin-4-ol,
6-(azetidin-1-yl)-N-[(1H-indol-6-yl)methyl]pyrido[2,3-b]pyrazin-3-amine,
1-(3-{[(3-methyl-1H-indol-4-yl)methyl]amino}pyrido[2,3-b]pyrazin-6-yl)piperidin-
5 4-ol,
(3R,4R)-3-(hydroxymethyl)-1-(3-{[(7-methoxy-3-methyl-1H-indol-4-yl)methyl]amino}pyrido[2,3-b]pyrazin-6-yl)piperidin-4-ol,
6-{3-{[(1H-indol-6-yl)methyl]amino}pyrido[2,3-b]pyrazin-6-yl}amino]spiro[3.3]heptan-2-ol,
10 3-N-[(7-methoxy-3-methyl-1H-indol-4-yl)methyl]-6-N-[trans-4-(dimethylamino)cyclohexyl]pyrido[2,3-b]pyrazine-3,6-diamine,
(3S)-1-(3-{[(7-methoxy-3-methyl-1H-indol-4-yl)methyl]amino}pyrido[2,3-b]pyrazin-6-yl)pyrrolidin-3-ol,
trans-3-{3-[(1H-indol-6-ylmethyl)amino]pyrido[2,3-b]pyrazin-6-yl}amino)cyclobutan-1-ol,
15 (3S)-1-(3-{[(1H-indol-6-yl)methyl]amino}pyrido[2,3-b]pyrazin-6-yl)pyrrolidin-3-ol,
[4-(3-{[(1H-indol-6-yl)methyl]amino}pyrido[2,3-b]pyrazin-6-yl)morpholin-2-yl]methanol,
(3S)-1-(3-{[(3-methyl-1H-indol-4-yl)methyl]amino}pyrido[2,3-b]pyrazin-6-yl)pyrrolidin-3-ol,
20 1-(3-{[(1H-indol-6-yl)methyl]amino}pyrido[2,3-b]pyrazin-6-yl)azetidin-3-ol,
4-{[6-(4-hydroxypiperidin-1-yl)pyrido[2,3-b]pyrazin-3-yl]amino}methyl)-N,3-dimethyl-1H-indole-7-carboxamide,
6-{1,4-dioxo-9-azaspiro[5.5]undecan-9-yl}-N-(1H-indol-6-ylmethyl)pyrido[2,3-b]pyrazin-3-amine,
25 N-(1H-indol-6-ylmethyl)-6-{1-oxa-8-azaspiro[4.5]decan-8-yl}pyrido[2,3-b]pyrazin-3-amine,
6-[cis-2,6-dimethylmorpholin-4-yl]-N-[(3-isopropyl-7-methoxy-1H-indol-4-yl)methyl]pyrido[2,3-b]pyrazin-3-amine,
30 6-{3-{[(7-methoxy-3-methyl-1H-indol-4-yl)methyl]amino}pyrido[2,3-b]pyrazin-6-yl}amino]spiro[3.3]heptan-2-ol,
(3S,4S)-4-(hydroxymethyl)-1-{3-[(1H-indol-6-ylmethyl)amino]pyrido[2,3-b]pyrazin-6-yl}piperidin-3-ol,
N-[(7-methoxy-3-methyl-1H-indol-4-yl)methyl]-6-(4-methylpiperazin-1-yl)pyrido[2,3-b]pyrazin-3-amine,
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N-[(1H-indol-6-yl)methyl]-7-methoxyquinoxalin-2-amine,
trans-4-[(3-[[[(7-methoxy-3-methyl-1H-indol-4-yl)methyl]amino]pyrido[2,3-
b]pyrazin-6-yl)(methyl)amino]cyclohexan-1-ol,
3-[(3-[[[(1H-indol-6-yl)methyl]amino]pyrido[2,3-b]pyrazin-6-yl)amino]propan-1-ol,
5 6-N-[4-(dimethylamino)cyclohexyl]-3-N-(1H-indol-6-ylmethyl)pyrido[2,3-
b]pyrazine-3,6-diamine,
[1-(hydroxymethyl)-4-[(3-[[[(7-methoxy-3-methyl-1H-indol-4-
yl)methyl]amino]pyrido[2,3-b]pyrazin-6-yl)amino]cyclohexyl]methanol,
1-[(3-[(1H-indol-6-ylmethyl)amino]pyrido[2,3-b]pyrazin-6-yl)azetidin-3-amine,
10 [(2R)-4-(3-[(3-methyl-1H-indol-4-yl)methyl]amino]pyrido[2,3-b]pyrazin-6-
yl)morpholin-2-yl]methanol,
[4-(3-[[[(7-methoxy-3-methyl-1H-indol-4-yl)methyl]amino]pyrido[2,3-b]pyrazin-6-
yl)-6,6-dimethylmorpholin-2-yl]methanol,
N3-[(7-methoxy-3-methyl-1H-indol-4-yl)methyl]-N6-({2-oxabicyclo[2.2.2]octan-3-
yl)methyl)pyrido[2,3-b]pyrazine-3,6-diamine,
15 N-[(1H-indol-6-yl)methyl]-7-(trifluoromethyl)quinoxalin-2-amine,
6-{2,7-diazaspiro[3.5]nonan-2-yl}-N-(1H-indol-6-ylmethyl)pyrido[2,3-b]pyrazin-3-
amine,
N-(1H-indol-5-ylmethyl)-6-(morpholin-4-yl)pyrido[2,3-b]pyrazin-3-amine, and
20 6-{3,9-diazaspiro[5.5]undecan-3-yl}-N-[(1H-indol-6-yl)methyl]pyrido[2,3-
b]pyrazin-3-amine.

19. The compound according to anyone of the preceding claims, wherein the
compound of Formula (I) is a WNK lysine deficient protein kinase 1 (WNK1)
25 inhibitor.
20. A pharmaceutical composition comprising a compound according to claims 1-
19, or a pharmaceutically acceptable salt thereof, and one or more
pharmaceutically acceptable carriers, excipients and/or diluents.
- 30 21. The compound according to any one of claims 1-19, or a pharmaceutically
acceptable salt thereof, or the pharmaceutical composition according to claim
20, for use as a medicament.
- 35 22. A compound of formula (I):



Formula (I)

wherein

Y is C(H) or N;

5 W is C(H)₂ or C(D)₂;

R¹ is H, C₁₋₃ alkyl or cyclopropyl

R² is H; C₁₋₃ alkyl optionally substituted with OH; or C₃₋₅ cycloalkyl;

10 R³ is H; C₁₋₃ alkyl optionally substituted with OH; -OC₁₋₃ alkyl optionally substituted with one or more F; -C(O)NHCH₃; -NH₂; -N(H)(CH₃); -N(CH₃)₂; or halogen;

R⁴ is H, C₁₋₄ alkyl, or C₃₋₅ cycloalkyl;

A is selected from the group consisting of H, C₁₋₃ alkoxy, CF₃, and a group of formula (II):



15

Formula (II)

wherein

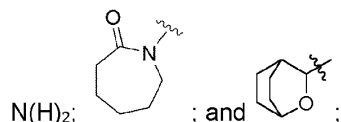
X is C(H) or N;

R⁶ is H or C₁₋₄ alkyl; and

20 R⁵ is selected from the group consisting of C₁₋₆ alkyl optionally substituted with one or more, identical or different, substituents R⁷, wherein one or more methylene(s) of said C₁₋₆ alkyl is optionally and individually replaced with -O- or C=O; C₃₋₆ cycloalkyl optionally substituted with one or more, identical or different, substituents R⁷; and tetrahydropyranyl;

25 wherein two R⁷ are optionally linked together to form a ring together with the intervening atom(s);

R^7 is individually selected from C_{1-3} alkoxy optionally substituted with one or more F; -OH; -O-benzyl; C_{1-3} alkyl optionally substituted with OH; $N(CH_3)_2$;



or when two R^7 are linked together to form a ring, then said two R^7 are individually selected from C_{1-2} alkanediyl optionally substituted with one or two substituents selected from F and OH, and one of the methylene of said C_{1-2} alkanediyl is optionally replaced with -O-;

or

R^5 and R^6 are linked together to form a ring and

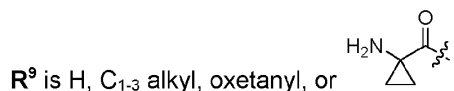
R^5 is a bond or C_{1-5} alkanediyl optionally substituted with one or more, identical or different, substituents R^8 , and one methylene of the C_{1-5} alkanediyl is optionally replaced with -O- or $N(R^9)$; and

R^6 is a bond or C_{1-5} alkanediyl optionally substituted with one or more, identical or different, substituents R^8 , and one methylene of the C_{1-5} alkanediyl is optionally replaced with -O- or $N(R^9)$;

wherein two R^8 are optionally linked together to form a ring together with the intervening atom(s);

R^8 is individually selected from C_{1-3} alkyl optionally substituted with OH; -OH; F; $N(H)_2$; and -OC $_{1-3}$ alkyl optionally substituted with one or more F;

or when two R^8 are linked together to form a ring, then said two R^8 are individually selected from C_{1-3} alkanediyl optionally substituted with one or two substituents selected from F, OH, and NH_2 , and one or two methylene(s) of said C_{1-3} alkanediyl is optionally and individually replaced with -O-, -N(H)- or -N(CH $_3$)-; and



or a pharmaceutically acceptable salt thereof, for use in treating, alleviating or preventing diseases and disorders related to the activity of WNK1.

23. The compound according to any one of claims 1-19, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition according to claim

20, for use in treating, alleviating or preventing diseases and disorders related to the activity of WNK1.

5 24. The compound for use according to claim 21 or 22, wherein the disease or disorder related to the activity of WNK1 is hypertension.

25. The compound for use according to claim 21 or 22, wherein the disease or disorder related to the activity of WNK1 is cancer.

10 26. The compound for use according to claim 24, wherein the cancer is selected from leukemia, lymphoma and myeloma.

15 27. Use of a compound according to any one of claims 1-19, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition according to claim 20, for the manufacture of a medicament for treating, alleviating or preventing diseases and disorders related to the activity of WNK1.

20 28. A method for treating, alleviating or preventing diseases and disorders related to the activity of WNK1, said method comprising administering a compound according to any one of claims 1-19, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition according to claim 20, to a subject in need thereof.

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