

**PIPERIDINYLPYRIDINYLCARBONITRILE DERIVATIVES AS INHIBITORS
OF GLUTAMINYL-PEPTIDE CYCLOTRANSFERASE AND GLUTAMINYL-
PEPTIDE CYCLOTRANSFERASE LIKE PROTEIN**

5 TECHNICAL FIELD

The present disclosure provides certain piperidinylpyridinylcarbonitrile derivatives, and pharmaceutically acceptable salts thereof, that are inhibitors of Glutaminyl-peptide cyclotransferase (QPCT) and glutaminyl-peptide cyclotransferase-like protein (QPCTL), and are therefore useful for the treatment of diseases treatable by inhibition of QPCT/L. Also
10 provided are pharmaceutical compositions containing the same, and processes for preparing said compounds.

BACKGROUND INFORMATION

Glutaminyl-peptide cyclotransferase (QPCT) and glutaminyl-peptide cyclotransferase-like
15 protein (QPCTL) catalyze the intramolecular cyclization of N-terminal glutamine (Q) residues into pyroglutamic acid (pE) liberating ammonia [Stephan Schilling et al., "Identification of Human Glutaminyl Cyclase as a Metalloenzyme POTENT INHIBITION BY IMID-AZOLE DERIVATIVES AND HETEROCYCLIC CHELATORS," *Journal of Biological Chemistry* 278, no. 50 (2003): 49773–79, <https://doi.org/10.1074/jbc.m309077200>; Holger
20 Cynis et al., "Isolation of an Isoenzyme of Human Glutaminyl Cyclase: Retention in the Golgi Complex Suggests Involvement in the Protein Maturation Machinery," *Journal of Molecular Biology* 379, no. 5 (2008): 966–80, <https://doi.org/10.1016/j.jmb.2008.03.078>; Anett Stephan et al., "Mammalian Glutaminyl Cyclases and Their Isoenzymes Have Identical Enzymatic Characteristics," *FEBS Journal* 276, no. 22 (2009): 6522–36,
25 <https://doi.org/10.1111/j.1742-4658.2009.07337.x>]. While QPCT is a secreted protein, QPCTL is retained within the Golgi complex. Both enzymes share a high homology in the active site and similar catalytic specificity. Because of the high homology in the active site, inhibition of the active site blocks the enzymatic activity of both enzymes: QPCT and QPCTL. Hence the term "QPCT/L" describes both enzymes at once. Due to their different
30 cellular localisation, differences in their relevance for modification of biological substrates have been reported. Known substrates of the intracellular QPCTL and/or extracellular QPCT are CD47 [Meike E. W. Logtenberg et al., "Glutaminyl Cyclase Is an Enzymatic Modifier of the CD47- SIRPα Axis and a Target for Cancer Immunotherapy," *Nature Medicine* 25,

no. 4 (2019): 612–19, <https://doi.org/10.1038/s41591-019-0356-z>], different chemokines (like for example CCL2 and 7 or CX3CL1) [Rosa Barreira da Silva et al., “Loss of the Intracellular Enzyme QPCTL Limits Chemokine Function and Reshapes Myeloid Infiltration to Augment Tumor Immunity,” *Nature Immunology* 23, no. 4 (2022): 568–80, <https://doi.org/10.1038/s41590-022-01153-x>; Astrid Kehlen et al., “N-Terminal Pyroglutamate Formation in CX3CL1 Is Essential for Its Full Biologic Activity,” *Bioscience Reports* 37, no. 4 (2017): BSR20170712, <https://doi.org/10.1042/bsr20170712>], Amyloid-b peptides [Cynis et al., “Isolation of an Isoenzyme of Human Glutaminyl Cyclase: Retention in the Golgi Complex Suggests Involvement in the Protein Maturation Machinery.”] or hormones like TRH [Andreas Becker et al., “IsoQC (QPCTL) Knock-out Mice Suggest Differential Substrate Conversion by Glutaminyl Cyclase Isoenzymes,” *Biological Chemistry* 397, no. 1 (2016): 45–55, <https://doi.org/10.1515/hsz-2015-0192>]. The modification of N-terminal glutamine to pyroglutamate on the substrates has functional consequences for the proteins and could impact different pathomechanisms in several diseases. CD47 is expressed on the cell surface of virtually all cells of the body, including apoptotic cells, senescent cells or cancer cells. [Meike E.W. Logtenberg, Ferenc A. Scheeren, and Ton N. Schumacher, “The CD47-SIRP α Immune Checkpoint,” *Immunity* 52, no. 5 (2020): 742–52, <https://doi.org/10.1016/j.immuni.2020.04.011>]. The main ligand for CD47 is signal-regulatory protein alpha (SIRP α), an inhibitory transmembrane receptor present on myeloid cells, such as macrophages, monocytes, neutrophils, dendritic cells and others. QPCTL mediated N-terminal pyroglutamate modification on CD47 is required for SIRP α binding [Deborah Hatherley et al., “Paired Receptor Specificity Explained by Structures of Signal Regulatory Proteins Alone and Complexed with CD47,” *Molecular Cell* 31, no. 2 (2008): 266–77, <https://doi.org/10.1016/j.molcel.2008.05.026>; Meike E. W. Logtenberg et al., “Glutaminyl Cyclase Is an Enzymatic Modifier of the CD47- SIRP α Axis and a Target for Cancer Immunotherapy,” *Nature Medicine* 25, no. 4 (2019): 612–19, <https://doi.org/10.1038/s41591-019-0356-z>] This signaling axis induces a “Don’t Eat Me Signal”, preventing engulfment of CD47 expressing cells by macrophages. Thus, high expression of CD47 is connected to the pathogenesis of cancer [Logtenberg et al., “Glutaminyl Cyclase Is an Enzymatic Modifier of the CD47- SIRP α Axis and a Target for Cancer Immunotherapy,” 2019; Meike E.W. Logtenberg, Ferenc A. Scheeren, and Ton N. Schumacher, “The CD47-SIRP α Immune Checkpoint,” *Immunity* 52, no. 5 (2020): 742–52, <https://doi.org/10.1016/j.immuni.2020.04.011>], COVID-19 [Katie-May McLaughlin et al., “A Potential Role of the CD47/SIRPalpha Axis

in COVID-19 Pathogenesis,” *Current Issues in Molecular Biology* 43, no. 3 (2021): 1212–25, <https://doi.org/10.3390/cimb43030086>], lung fibrosis [Gerlinde Wernig et al., “Unifying Mechanism for Different Fibrotic Diseases,” *Proceedings of the National Academy of Sciences* 114, no. 18 (2017): 4757–62, <https://doi.org/10.1073/pnas.1621375114>; Lu Cui et al., “Activation of JUN in Fibroblasts Promotes Pro-Fibrotic Programme and Modulates Protective Immunity,” *Nature Communications* 11, no. 1 (2020): 2795, <https://doi.org/10.1038/s41467-020-16466-4>], systemic sclerosis [Wernig et al., “Unifying Mechanism for Different Fibrotic Diseases”; Tristan Lerbs et al., “CD47 Prevents the Elimination of Diseased Fibroblasts in Scleroderma,” *JCI Insight* 5, no. 16 (2020): e140458, <https://doi.org/10.1172/jci.insight.140458>] and liver fibrosis [Taesik Gwag et al., “Anti-CD47 Antibody Treatment Attenuates Liver Inflammation and Fibrosis in Experimental Non-alcoholic Steatohepatitis Models,” *Liver International* 42, no. 4 (2022): 829–41, <https://doi.org/10.1111/liv.15182>]. Since enhanced CD47 expression blocks the clearance of apoptotic cells, there is an accrual of apoptotic lung epithelial cells, leading to a pro-fibrotic stimulus and accelerating lung inflammation and -scarring [Alexandra L. McCubrey and Jeffrey L. Curtis, “Efferocytosis and Lung Disease,” *Chest* 143, no. 6 (2013): 1750–57, <https://doi.org/10.1378/chest.12-2413>; Brennan D. Gerlach et al., “Efferocytosis Induces Macrophage Proliferation to Help Resolve Tissue Injury,” *Cell Metabolism*, 2021, <https://doi.org/10.1016/j.cmet.2021.10.015>]. Since CD47 half-life and function is majorly dependent on QPCTL enzyme activity, QPCT and QPCTL inhibition could be a suitable mechanism as a treatment in lung fibrosis such as IPF or SSC-ILD [Lerbs et al., “CD47 Prevents the Elimination of Diseased Fibroblasts in Scleroderma.”], alone or together with current standard of care in pulmonary fibrosis like Nintedanib [Luca Richeldi et al., “Efficacy and Safety of Nintedanib in Idiopathic Pulmonary Fibrosis,” *The New England Journal of Medicine* 370, no. 22 (2014): 2071–82, <https://doi.org/10.1056/nejmoa1402584>; Kevin R Flaherty et al., “Nintedanib in Progressive Fibrosing Interstitial Lung Diseases,” *New England Journal of Medicine* 381, no. 18 (2019): 1718–27, <https://doi.org/10.1056/nejmoa1908681>] or future treatments like a PDE4 inhibitor [Luca Richeldi et al., “Trial of a Preferential Phosphodiesterase 4B Inhibitor for Idiopathic Pulmonary Fibrosis,” *New England Journal of Medicine* 386, no. 23 (2022): 2178–87, <https://doi.org/10.1056/nejmoa2201737>].

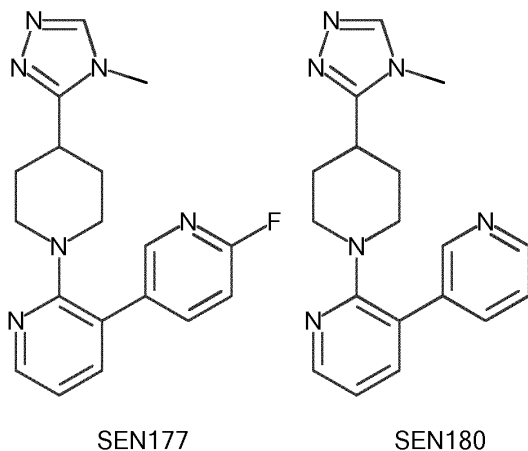
By expression of CD47, cancer cells can evade destruction by the immune system or evade immune surveillance, e.g. by evading phagocytosis by immune cells [Stephen B. Willingham

et al., “The CD47-Signal Regulatory Protein Alpha (SIRPa) Interaction Is a Therapeutic Target for Human Solid Tumors,” *Proceedings of the National Academy of Sciences* 109, no. 17 (2012): 6662–67, <https://doi.org/10.1073/pnas.1121623109>].

In addition to CD47, chemokines, such as CCL2 and CX3CL1, have been identified as
5 QPCTL and/or QPCT substrates [Holger Cynis et al., “The Isoenzyme of Glutaminyl
Cyclase Is an Important Regulator of Monocyte Infiltration under Inflammatory Condi-
tions,” *EMBO Molecular Medicine* 3, no. 9 (2011): 545–58,
<https://doi.org/10.1002/emmm.201100158>]. The formation of the N-terminal pGlu was
shown to increase in vivo activity, both by conferring resistance to aminopeptidases and by
10 increasing its capacity to induce chemokine receptor signaling. Two main monocyte chem-
oattractants CCL2 and CCL7 are insensitive to DPP4-inactivation in vivo because of an in-
tracellular mechanism of N-terminal cyclization mediated by the Golgi-associated enzyme
QPCTL. It has been shown that QPCTL is a critical regulator of monocyte migration into
solid tumors [Kaspar Bresser et al., “QPCTL Regulates Macrophage and Monocyte Abun-
15 dance and Inflammatory Signatures in the Tumor Microenvironment,” *Oncoimmunology*
11, no. 1 (2022): 2049486, <https://doi.org/10.1080/2162402x.2022.2049486>; Rosa Barreira
da Silva et al., “Loss of the Intracellular Enzyme QPCTL Limits Chemokine Function and
Reshapes Myeloid Infiltration to Augment Tumor Immunity,” *Nature Immunology*, 2022,
1–13, <https://doi.org/10.1038/s41590-022-01153-x>]. Targeting of chemokines has long
20 been pursued as a potential strategy for modulating cellular trafficking in different disease
settings.

It is therefore desirable to provide potent QPCTL inhibitors.

25 Jimenez-Sanchez, et al., *Nature Chemical Biology*, 2015, 11, 347-357, (hereinafter “J-S,
NCB 2015”) discloses the human glutaminyl cyclase (hQC) inhibitors SEN177 and
SEN180:

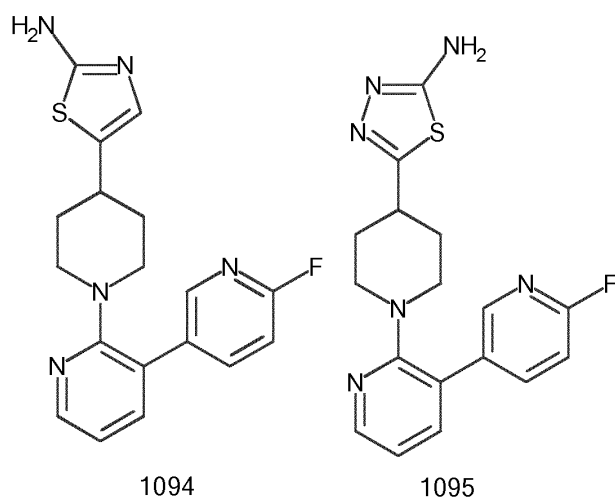


SEN177 is disclosed therein (supplementary information) as having a IC_{50} on isolated hQC of 53 nM and on isolated QPCTL of 13 nM. SEN180 is disclosed therein (supplementary information) as having a IC_{50} on hQC of 170 nM and on QPCTL of 58 nM.

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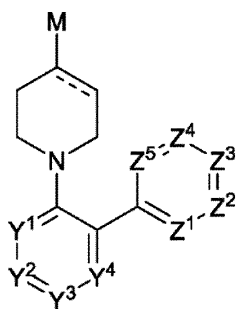
Pozzi, C, et al, Journal of Biological Inorganic Chemistry, 2018, 23, (8), 1219-1226, (hereinafter “P, JBIC 2018”), further discloses SEN177 and its binding mode within the hQC cavity. SEN177 is disclosed therein as having a K_i on isolated hQC of 20 nM.

- 10 WO 2018/178384 discloses QPCTL inhibitors of the general formula A-B-D-E, which include examples 1094 and 1095 (Formula (XIIa) on page 123 and table on page 125):

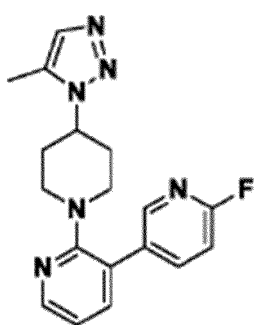


WO 2018/178384 does not disclose any biological data for examples 1094 or 1095.

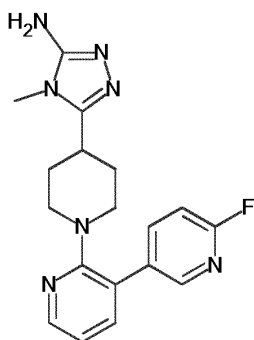
WO 2022/086920 discloses QPCTL inhibitors of the general formula



which include compounds 3 and 6:

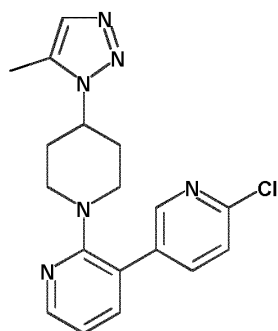


Compound 3



Compound 6

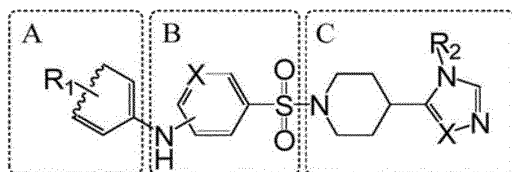
The chemical name of Compound 3 is disclosed in WO 2022/086920 as “1-(1-(6'-chloro-
 5 [3,3'-bipyridin]-2-yl)piperidin-4-yl)-1H-1,2,3-triazol-4-amine” which does not correspond to the chemical structure disclosed therein, but to an alternative structure in which the fluorine atom is replaced with chlorine:



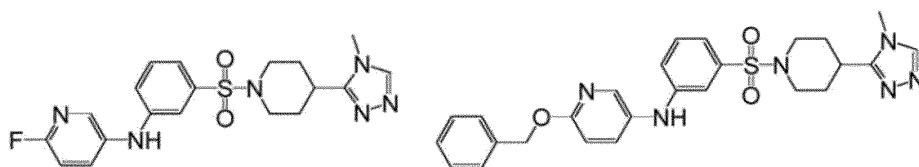
Alternative Compound 3

Compounds 3 (including alternative compound 3) and 6 in WO 2022/086920 are disclosed
 10 therein [00343] as having inhibitory activity on isolated QPCTL of $IC_{50} < 1\mu M$.

CN 114874186 discloses glutamine acyl cyclase isoenzyme inhibitors of the general formula



which include examples 21 and 23 (table on page 17):



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Example 21

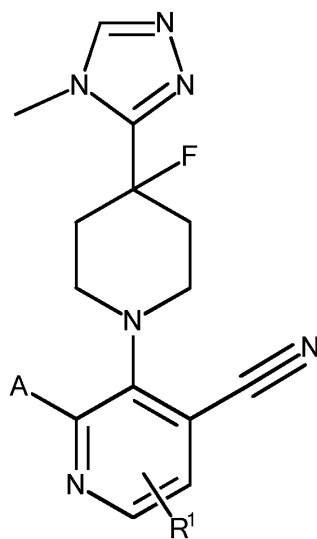
Example 23

IC₅₀'s are given in CN 114874186 for examples 21 and 23 as 29.22 nM and 11.26 nM respectively.

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DETAILED DESCRIPTION OF THE INVENTION

The present invention discloses novel piperidinylpyridinylcarbonitrile derivatives of formula (I)



(I)

15

that are inhibitors of Glutaminyl-peptide cyclotransferase (QPCT) and glutaminyl-peptide cyclotransferase-like protein (QPCTL), possessing appropriate pharmacological and pharmacokinetic properties enabling their use as medicaments for the treatment of conditions and/or diseases treatable by inhibition of QPCT/L.

- 5 The compounds of the present invention may provide several advantages, such as enhanced potency, cellular potency, high metabolic and/or chemical stability, high selectivity, safety and tolerability, enhanced solubility, enhanced permeability, desirable plasma protein binding, enhanced bioavailability, suitable pharmacokinetic profiles, and the possibility to form stable salts.

10

Compounds of the invention

The present invention provides novel piperidinylpyridinylcarbonitrile derivatives that surprisingly, are potent inhibitors of QPCT and QPCTL (Assay A), as well as potent inhibitors of QPCT/L in cells relevant for, but not limited to, lung diseases or cancer, (Assay B).

- 15 Furthermore, the present novel piperidinylpyridinylcarbonitrile derivatives have appropriate membrane permeability and a low *in vitro* efflux (Assay C).

Consequently, compounds of the present invention are more viable for human use.

- 20 Compounds of the present invention differ structurally from SEN177 and SEN180 in J-S, NCB 2015, in that a carbonitrile substituent is attached at the ortho-position to the piperidinyl ring attachment position of the pyridyl ring. Furthermore, the pyridyl ring - including the piperidinyl ring to which it is attached - is in total, tri- or tetra-substituted. Still further, **R¹** is not limited to hydrogen, and **A** represents substituted heterocyclic ring systems beyond pyridinyl.
- 25

- Compounds of the present invention differ structurally from examples 1094 and 1095 in WO 2018/178384 in that a carbonitrile substituent is attached at the ortho-position to the piperidinyl ring attachment position of the pyridyl ring. Furthermore, the pyridyl ring - including the piperidinyl ring to which it is attached - is in total, tri- or tetra-substituted. Still further, **R¹** is not limited to hydrogen and **A** represents heterocyclic ring systems beyond pyridinyl. Still further, the 5-membered heterocyclic ring attached to the piperidinyl ring at the 4-position relative to the piperidinyl nitrogen is in example 1094 an aminothiazolyl ring and in
- 30

example 1095 an aminothiadiazoxy ring whereas in compounds of the present invention it is a 3-substituted-4-methyl-4H-1,2,4-triazolyl ring.

Compounds of the present invention differ structurally from compounds 3 (including alternative compound 3) and 6 in WO 2022/086920 in that a carbonitrile substituent is attached at the ortho-position to the piperidinyl ring attachment position of the pyridyl ring. Furthermore, the pyridyl ring - including the piperidinyl ring to which it is attached - is in total, tri- or tetra-substituted. Still further, **R**¹ is not limited to hydrogen, and **A** represents heterocyclic ring systems beyond pyridinyl. Still further, the 5-membered heterocyclic ring “M” in the general formula of WO 2022/086920 is in compound 3 a regioisomer of the 3-substituted 4-methyl-4H-1,2,4-triazolyl ring in compounds of the present invention, and the 5-membered heterocyclic ring “M” in the general formula of WO 2022/086920 in compound 4 is a 3-substituted 4-methyl-4H-1,2,4-triazolyl ring as in compounds of the present invention but that it bears an amino group.

Compounds of the present invention differ structurally from compounds 21 and 23 in CN114874186 in that the central sulfonamide moiety linking the piperidinyl ring to the phenyl ring is replaced by a direct bond and the phenyl ring is replaced by a pyridyl ring. Furthermore, a carbonitrile substituent is attached at the ortho-position to the piperidinyl ring attachment position of said pyridyl ring. Furthermore, the pyridyl ring - including the piperidinyl ring to which it is attached - is in total, tri- or tetra-substituted. Still further, compounds of the present invention do not contain an amino linker between said phenyl ring and a further cyclic ring.

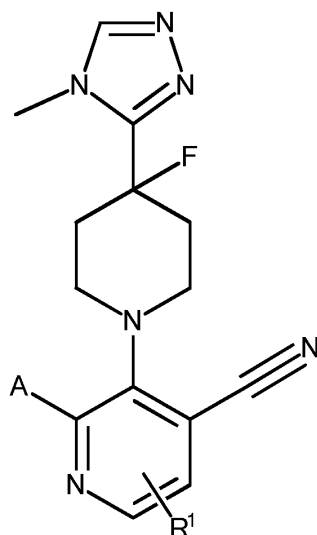
These structural differences between compounds of the present invention and the prior art unexpectedly lead to a favourable combination of (i) potent inhibition of QPCT and QPCTL, (ii) potent inhibition of QPCT/L in cells relevant for, but not limited to, lung diseases or cancer, and (iii) appropriate membrane permeability and a low *in vitro* efflux.

Compounds of the invention are thus superior to those disclosed in the prior art in terms of the combination of the following parameters:

- potent inhibition of QPCT and QPCTL (Assay A)

- potent inhibition of QPCT/L in cells relevant for, but not limited to, lung diseases or cancer (Assay B)
- appropriate membrane permeability and a low *in vitro* efflux (Assay C)

5 The present invention provides novel compounds according to formula (I)



(I)

wherein

- A** is **A1a** which is a 5- or 6-membered mono-heteroaryl ring containing one or two heteroatom members selected from the group consisting of nitrogen and oxygen;
 10 wherein at least one of the heteroatom members is nitrogen;
 or **A** is **A1b** which is a 9- or 10-membered fused bicyclic-heteroaryl ring containing one to four heteroatom members selected from the group consisting of nitrogen and oxygen,
 wherein at least one of the heteroatom members is nitrogen;
 15 and wherein **A** is independently optionally substituted with one or two **R²**;

R¹ is selected from the group **R1a**, consisting of H, C₁₋₄-alkyl, C₁₋₄-alkyloxy, hydroxy-C₁₋₄-alkyl, F₁₋₉-fluoro-C₁₋₄-alkyl and F₁₋₈-fluoro-C₃₋₅-cycloalkyl;

- 20 **R²** is selected from the group **R2a**, consisting of halo, NH₂, C₁₋₆-alkyl, F₁₋₉-fluoro-C₁₋₆-alkyl, C₁₋₄-alkyl-O-H₂CH₂C-O-, F₁₋₉-fluoro-C₁₋₄-alkyloxy and CH₃S(O);

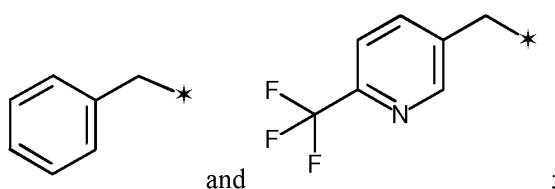
or

R² is selected from the group **R2b**, consisting of phenyl, pyridinyl, isoxazolyl, oxazolyl, pyrazolyl and thiophenyl;

wherein **R2b** is optionally substituted independently by one or two **R³**;

or

5 **R²** is selected from the group **R2c**, consisting of



R³ is **R3a**, selected from halo, C₁₋₄-alkyl, C₁₋₄-alkyloxy, HO-C₁₋₄-alkyl or CN;

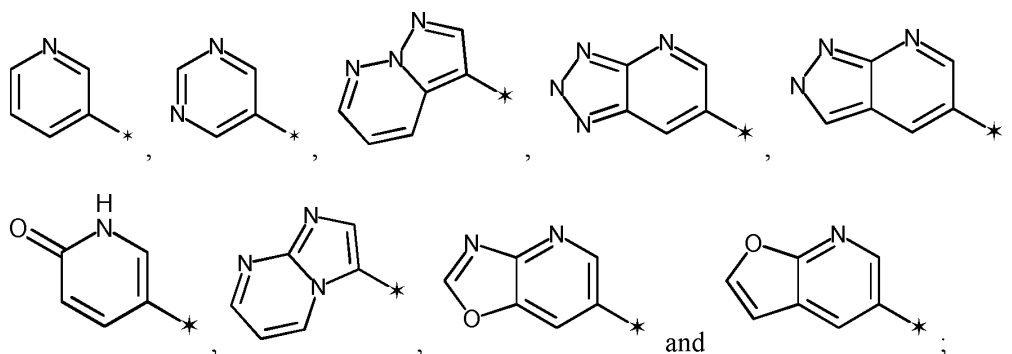
10 or a salt thereof, particularly a pharmaceutically acceptable salt thereof.

Another embodiment of the present invention relates to a compound of formula (I), wherein **A** is **A2** which is a 6-membered mono-heteroaryl ring containing one or two heteroatom members selected from nitrogen;

15 wherein **A** is independently optionally substituted with one or two **R²**; and substituent **R¹**, **R²** and **R³** are defined as in any of the preceding embodiments.

Another embodiment of the present invention relates to a compound of formula (I), wherein **A** is the group **A3** consisting of pyridinyl, pyrimidinyl, pyrazolo[1,5-b]pyridazinyl, 2H-[1,2,3]triazolo[4,5-b]pyridinyl, pyrazolo[3,4-b]pyridinyl, 1,2-dihydropyridin-2-onyl, imidazo[1,2-a]pyrimidinyl, [1,3]oxazolo[4,5-b]pyridinyl and furo[2,3-b]pyridinyl; and wherein **A** is independently optionally substituted with one or two **R²**; and substituent **R¹**, **R²** and **R³** are defined as in any of the preceding embodiments.

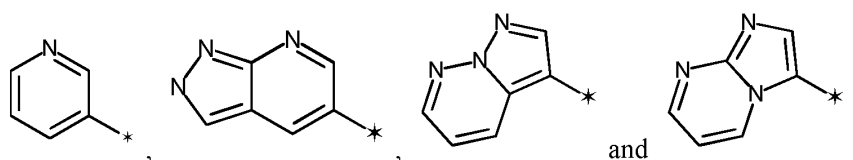
25 Another embodiment of the present invention relates to a compound of formula (I), wherein **A** is selected from the group **A4** consisting of



and wherein **A** is independently optionally substituted with one or two **R**²;
and substituent **R**¹, **R**² and **R**³ are defined as in any of the preceding embodiments.

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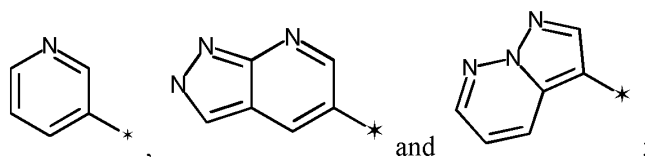
Another embodiment of the present invention relates to a compound of formula (I),
wherein **A** is selected from the group **A5** consisting of



and wherein **A** is independently optionally substituted with one or two **R**²;
and substituent **R**¹, **R**² and **R**³ are defined as in any of the preceding embodiments.

10

Another embodiment of the present invention relates to a compound of formula (I),
wherein **A** is selected from the group **A6** consisting of



and wherein **A** is independently optionally substituted with one or two **R**²;
and substituent **R**¹, **R**² and **R**³ are defined as in any of the preceding embodiments.

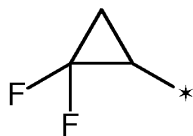
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R¹ is selected from the group **R1b**, consisting of H, C₁₋₄-alkyl, C₁₋₄-alkyloxy, hydroxy-C₁₋₄-alkyl, F₁₋₃-fluoro-C₁₋₄-alkyl and F₁₋₃-fluoro-C₃₋₅-cycloalkyl;

and substituents **A**, **R**² and **R**³ are defined as in any of the preceding embodiments.

20

Another embodiment of the present invention relates to a compound of formula (I), wherein **R**¹ is selected from the group **R1c**, consisting of H, H₃C-O-, F₃C-, HO-C(H₃C)₂-



and ;

and substituents **A**, **R**² and **R**³ are defined as in any of the preceding embodiments.

5

Another embodiment of the present invention relates to a compound of formula (I), wherein **R**² is selected from the group **R2d**, consisting of F, Cl, NH₂, C₁₋₆-alkyl, C₁₋₄-alkyl-O-H₂CH₂C-O- and CH₃S(O);

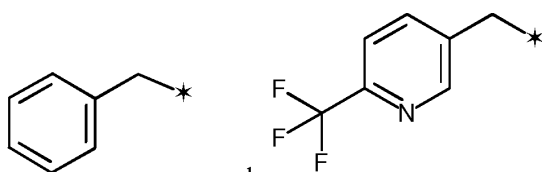
or

10 **R**² is selected from the group **R2e**, consisting of phenyl, pyridinyl, isoxazolyl, oxazolyl, pyrazolyl and thiophenyl;

wherein **R2e** is optionally substituted independently by one or two **R**³;

or

R² is selected from the group **R2c**, consisting of



15

and ;

and substituents **A**, **R**¹ and **R**³ are defined as in any of the preceding embodiments.

Another embodiment of the present invention relates to a compound of formula (I), wherein **R**² is selected from the group **R2f**, consisting of F, Cl, NH₂, H₃C-O-H₂CH₂C-O- and CH₃S(O);

20

or

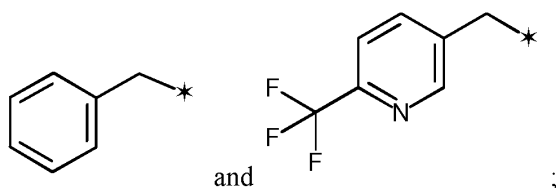
R² is selected from the group **R2e**, consisting of phenyl, pyridinyl, isoxazolyl, oxazolyl, pyrazolyl and thiophenyl;

wherein **R2e** is optionally substituted independently by one or two **R**³;

25

or

R² is selected from the group **R2c**, consisting of

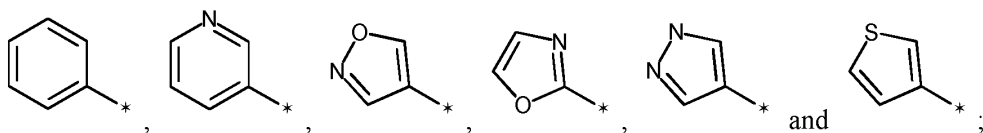


and substituents **A**, **R¹** and **R³** are defined as in any of the preceding embodiments.

Another embodiment of the present invention relates to a compound of formula (**I**),
 5 wherein **R²** is selected from the group **R2f**, consisting of F, Cl, NH₂, H₃C-O-H₂CH₂C-O- and CH₃S(O);

or

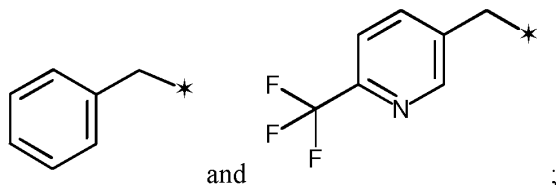
R² is selected from the group **R2g**, consisting of



10 wherein **R2g** is optionally substituted independently by one or two **R³**;

or

R² is selected from the group **R2c**, consisting of



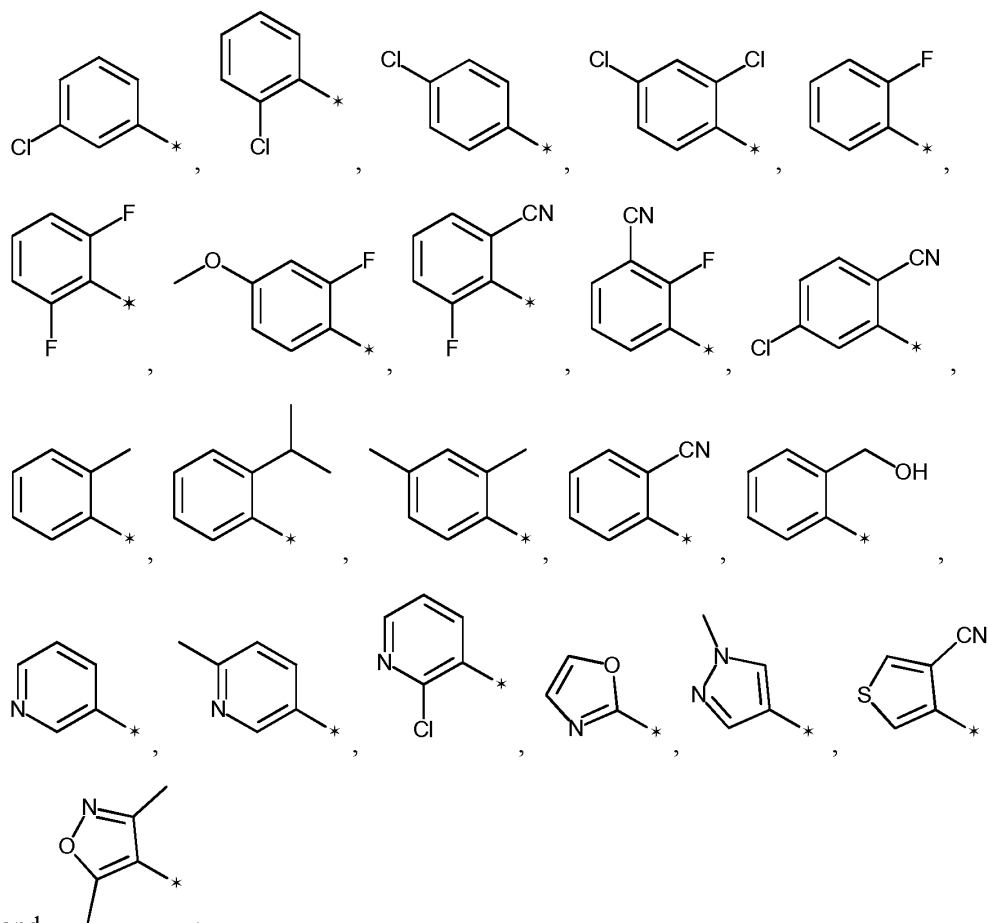
and substituents **A**, **R¹** and **R³** are defined as in any of the preceding embodiments.

15

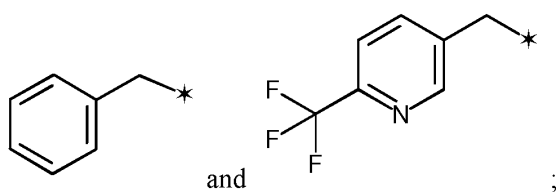
Another embodiment of the present invention relates to a compound of formula (**I**),
 wherein **R²** is selected from the group **R2f**, consisting of F, Cl, NH₂, H₃C-O-H₂CH₂C-O- and CH₃S(O);

or

20 **R²** is selected from the group **R2h**, consisting of



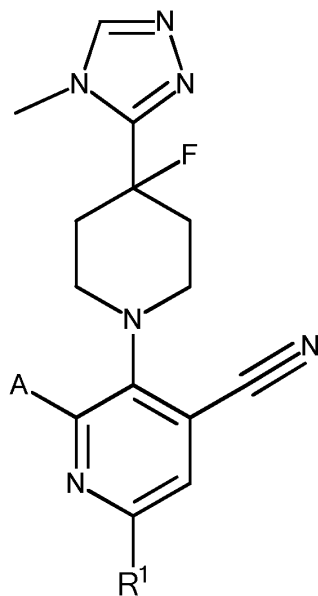
or

 R^2 is selected from the group **R2c**, consisting ofand substituents **A** and R^1 are defined as in any of the preceding embodiments.

10

Another embodiment of the present invention relates to a compound of formula (I), wherein R^3 is **R3b**, selected from F, Cl, H_3C , isopropyl, H_3C-O- , $HO-H_2C$ or CN; and substituents **A**, R^1 , and R^2 are defined as in any of the preceding embodiments.

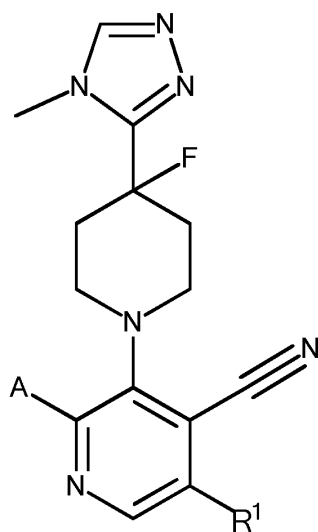
Another embodiment of the present invention relates to a compound of formula (I), having formula (1-a)



(1-a)

5 and substituents A, R² and R³ are defined as in any of the preceding embodiments.

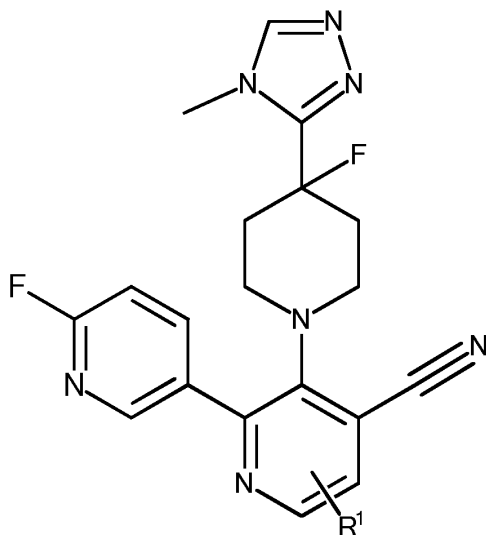
Another embodiment of the present invention relates to a compound of formula (I), having formula (1-b)



(1-b)

and substituents **A**, **R²** and **R³** are defined as in any of the preceding embodiments.

Another embodiment of the present invention relates to a compound of formula (**I**), having formula (**1-c**)

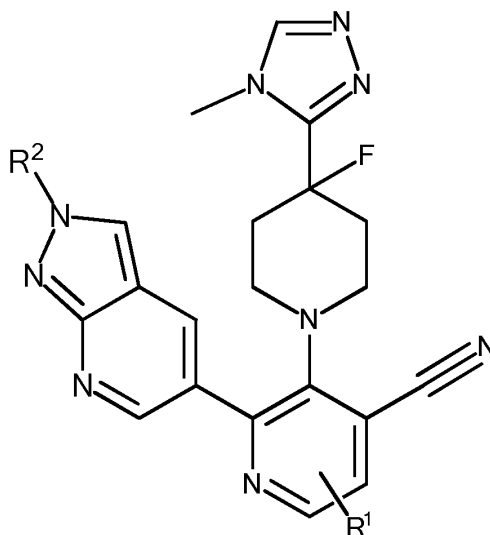


5

(1-c)

wherein substituent **R¹** is defined as in any of the preceding embodiments.

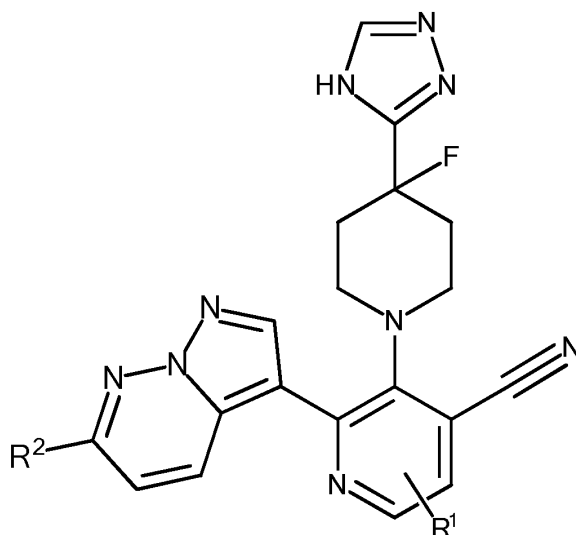
Another embodiment of the present invention relates to a compound of formula (**I**), having
10 formula (**1-d**)



(1-d)

and substituents R^1 , R^2 and R^3 are defined as in any of the preceding embodiments.

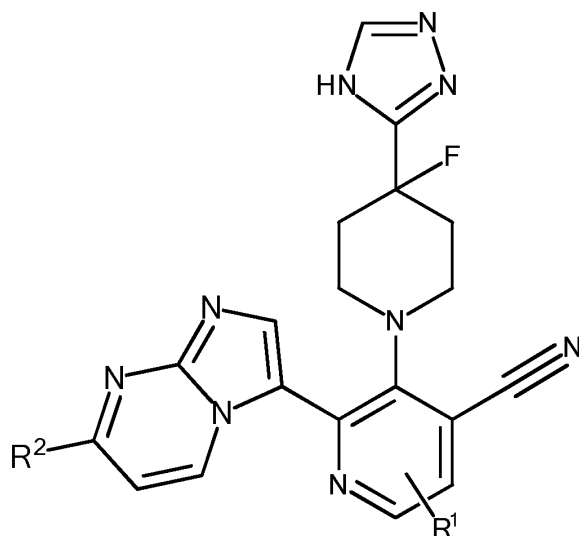
Another embodiment of the present invention relates to a compound of formula (I), having
5 formula (1-e)



(1-e)

and substituents R^1 , R^2 and R^3 are defined as in any of the preceding embodiments.

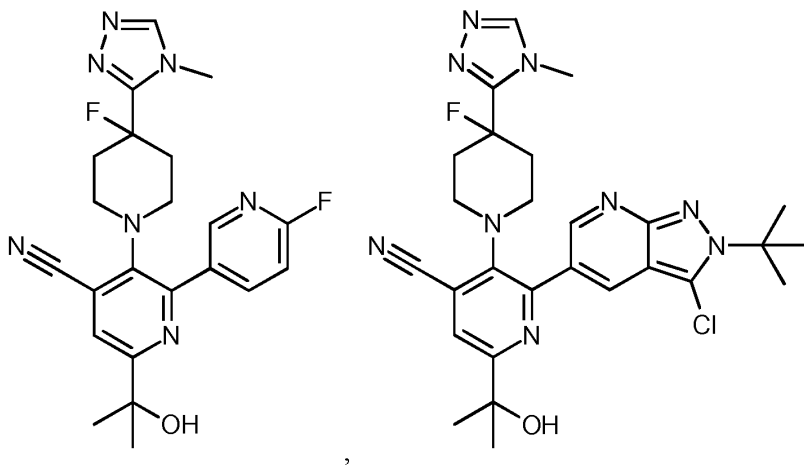
10 Another embodiment of the present invention relates to a compound of formula (I), having
formula (1-f)

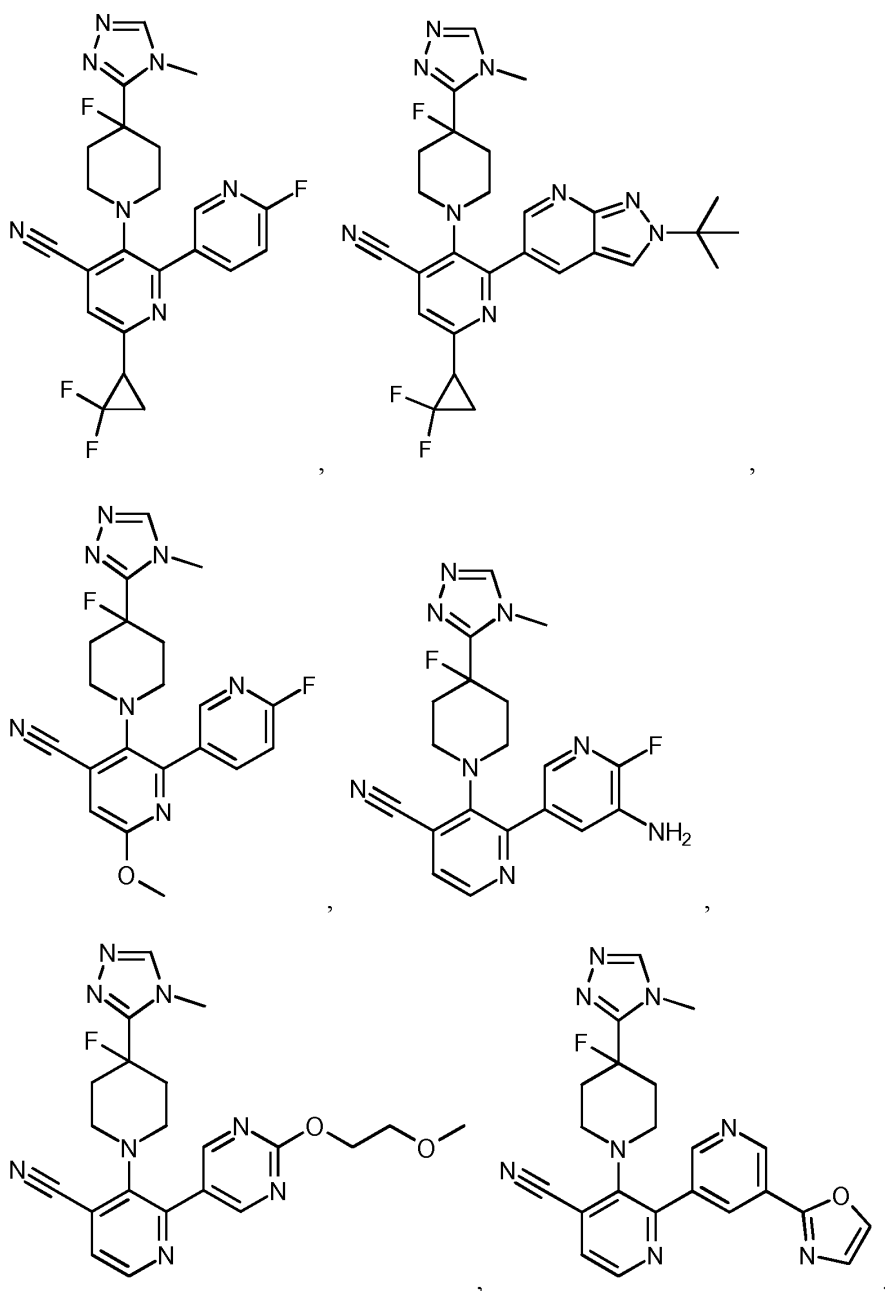


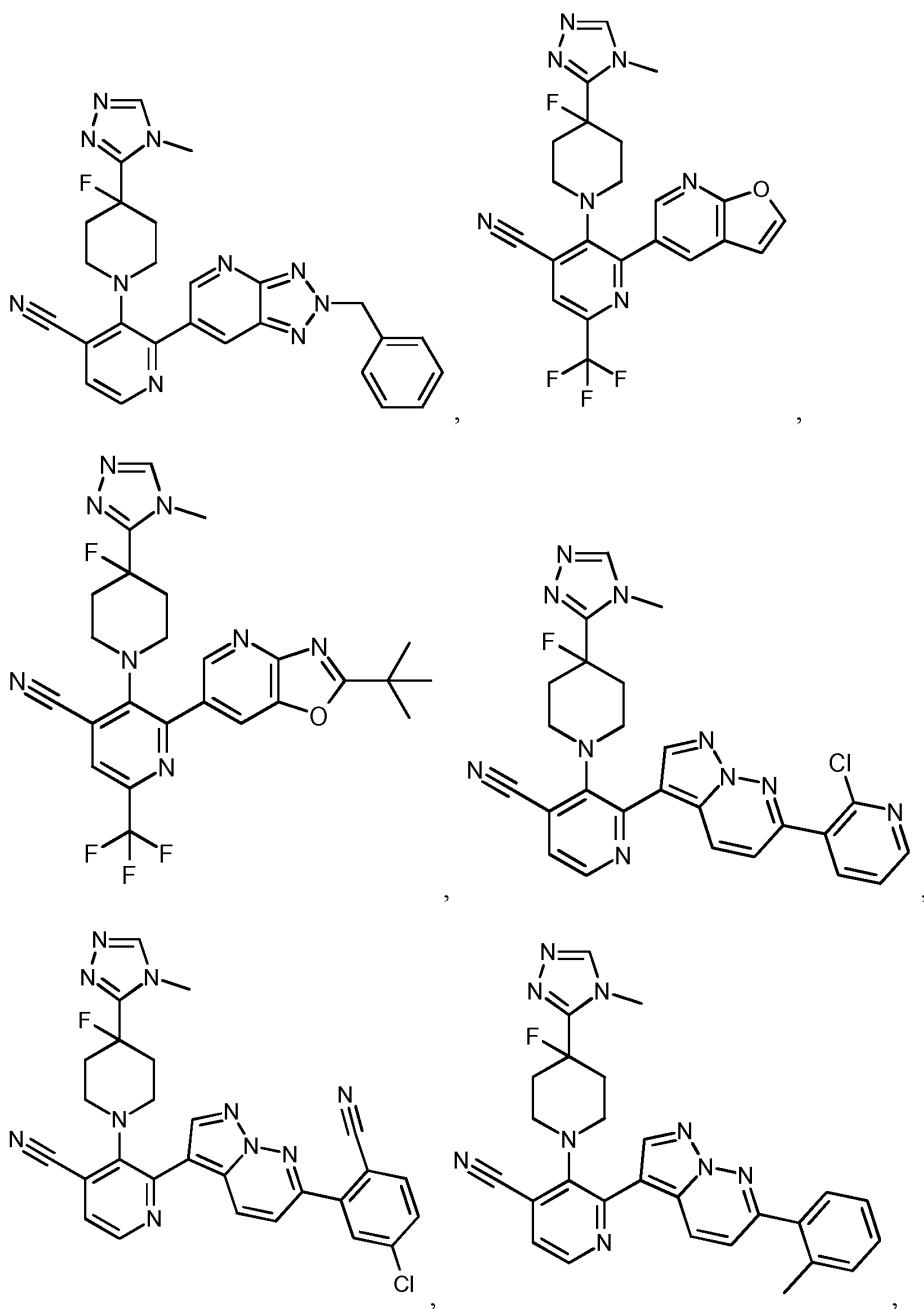
(1-f)

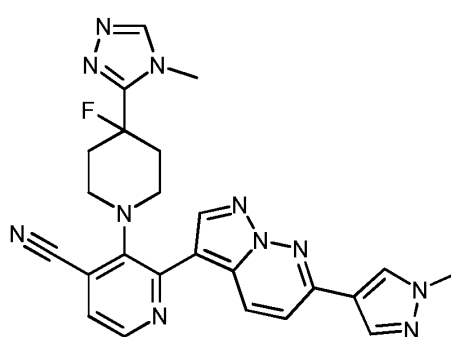
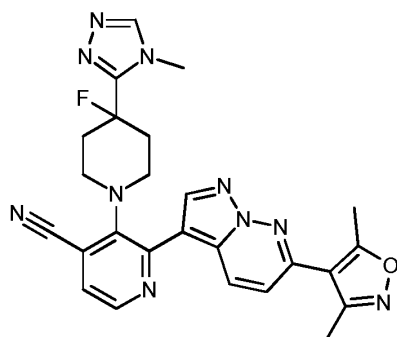
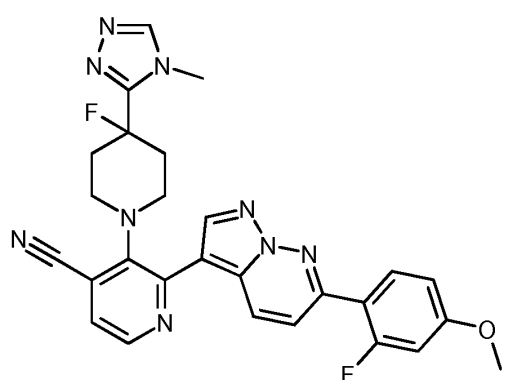
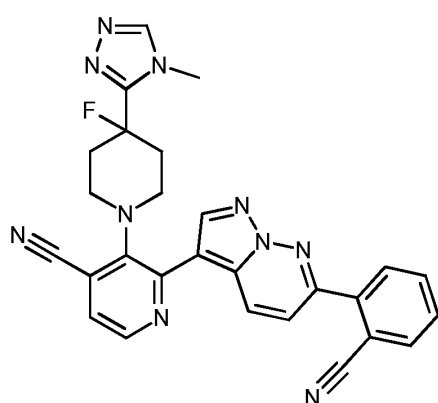
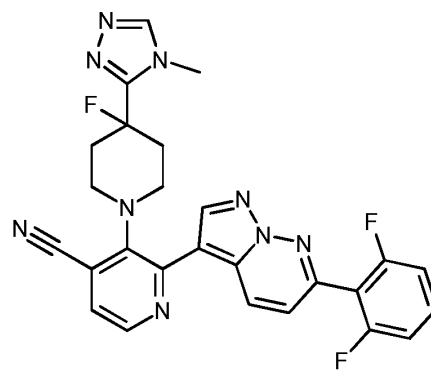
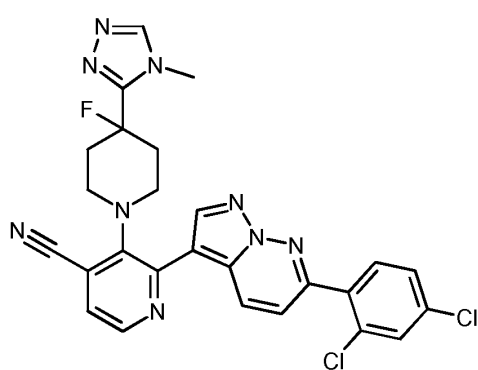
and substituents **R¹**, **R²** and **R³** are defined as in any of the preceding embodiments.

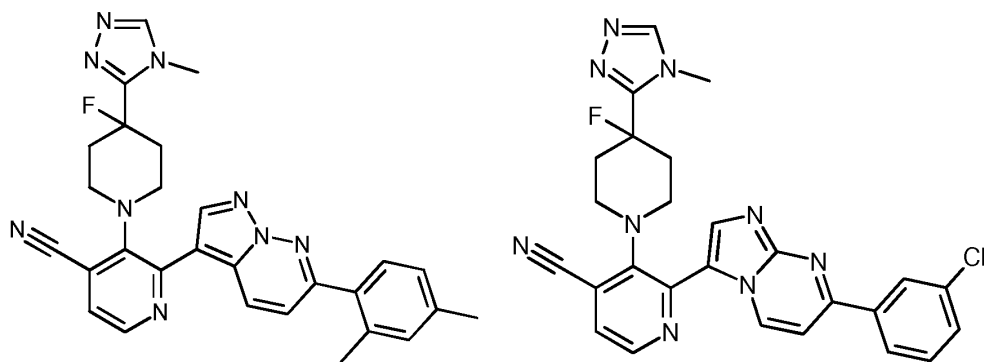
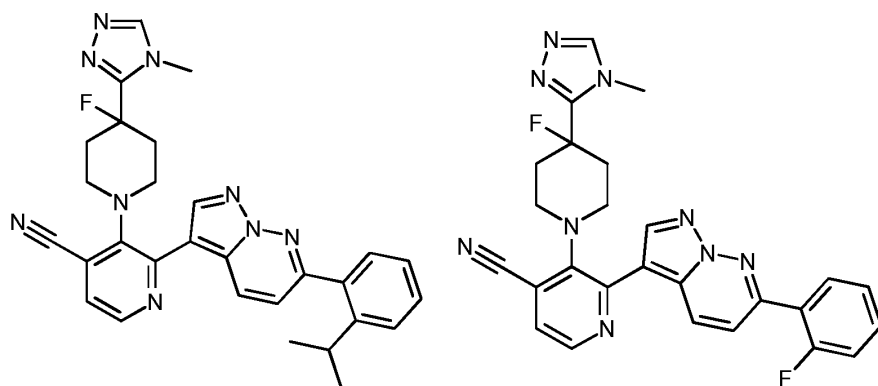
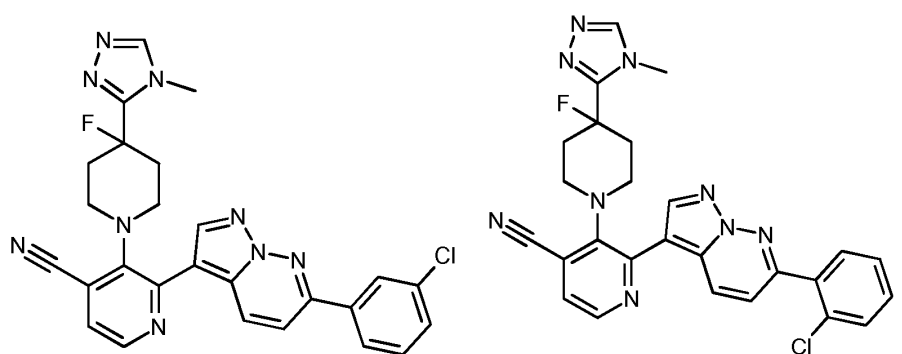
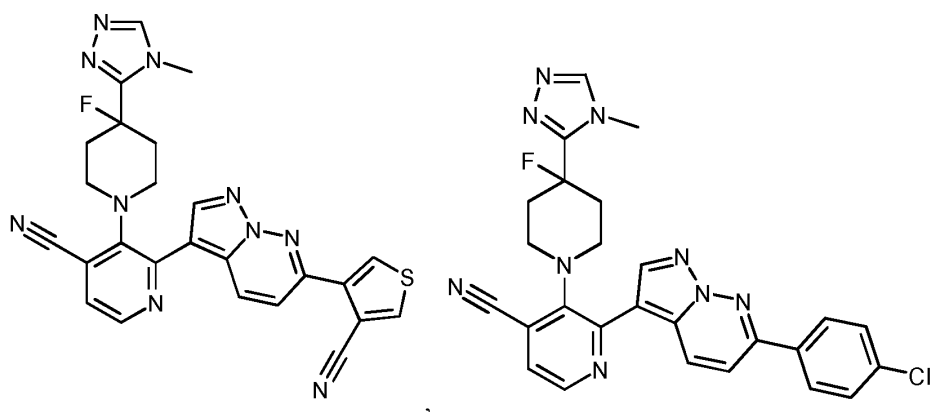
- 5 Particularly preferred is the compound according to formula (I) selected from the group consisting of

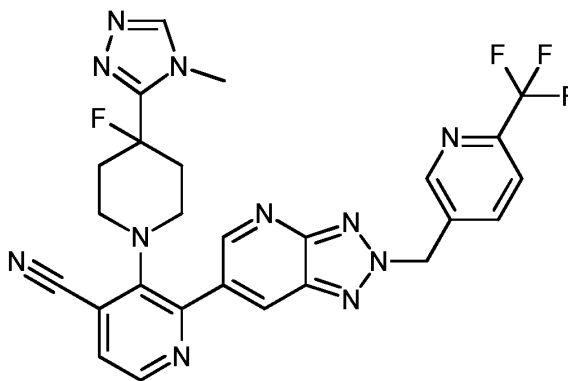
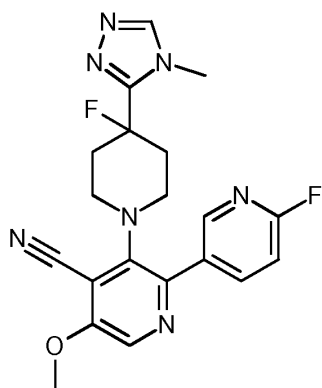




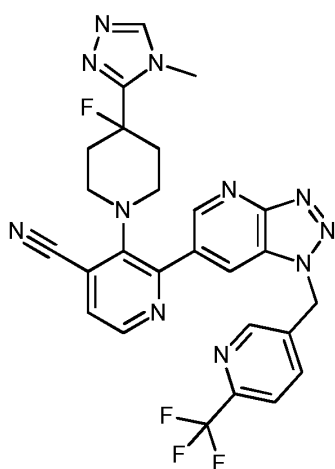








and



Particularly preferred is the compound according to formula (I) selected from the group
 5 consisting of example 1, example 3, example 4, example 5, example 26, example 32, example 38 and example 40, as described hereinafter in EXAMPLES.

Particularly preferred is the compound according to formula (I) selected from the group
 consisting of example 1, example 2, example 3, example 4, example 5, example 7, example
 10 9, example 12, example 16, example 24, example 25, example 26, example 27, example 28, example 29, example 30 and example 31, as described hereinafter in EXAMPLES.

The present invention provides novel piperidinylpyridinylcarbonitrile derivatives of formula (I) that are surprisingly potent QPCT/L inhibitors.

15

Another aspect of the invention refers to compounds according to formula (I) as surprisingly having potent inhibition of QPCT/L in cells relevant for, but not limited to, lung diseases or cancer.

- 5 Another aspect of the invention refers to compounds according to formula (I) as surprisingly cellular potent QPCT/L inhibitors having appropriate membrane permeability and low *in vitro* efflux.

Another aspect of the invention refers to pharmaceutical compositions, containing at least
10 one compound according to formula (I) optionally together with one or more inert carriers and/or diluents.

A further aspect of the present invention refers to compounds according to formula (I), for the use in the prevention and/or treatment of disorders associated with QPCT/L inhibition.

15

Another aspect of the invention refers to processes of manufacture of the compounds of the present invention.

Further aspects of the present invention will become apparent to the skilled artisan directly
20 from the foregoing and following description and the examples.

USED TERMS AND DEFINITIONS

25 General Definitions

Terms not specifically defined herein should be given the meanings that would be given to them by one of skill in the art in light of the disclosure and the context. As used in the specification, however, unless specified to the contrary, the following terms have the
30 meaning indicated and the following conventions are adhered to.

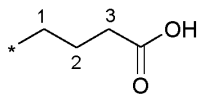
In the groups, radicals, or moieties defined below, the number of carbon atoms is often specified preceding the group, for example, C₁₋₆-alkyl means an alkyl group or radical

having 1 to 6 carbon atoms. In general in groups like HO, H₂N, (O)S, (O)₂S, NC (cyano), HOOC, F₃C or the like, the skilled artisan can see the radical attachment point(s) to the molecule from the free valences of the group itself. For combined groups comprising two or more subgroups, the last named subgroup is the radical attachment point, for example, the substituent "aryl-C₁₋₃-alkylene" means an aryl group which is bound to a C₁₋₃-alkyl-group, the latter of which is bound to the core or to the group to which the substituent is attached.

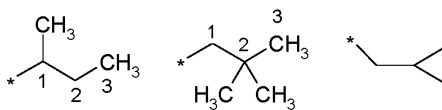
In case a compound of the present invention is depicted in the form of a chemical name and as a formula, in case of any discrepancy the formula shall prevail. An asterisk may be used in sub-formulas to indicate the bond which is connected to the core molecule as defined.

The numeration of the atoms of a substituent starts with the atom which is closest to the core or to the group to which the substituent is attached.

For example, the term "3-carboxypropyl-group" represents the following substituent:



wherein the carboxy group is attached to the third carbon atom of the propyl group. The terms "1-methylpropyl-", "2,2-dimethylpropyl-" or "cyclopropylmethyl-" group represent the following groups:



The asterisk may be used in sub-formulas to indicate the bond which is connected to the core molecule as defined.

The term "substituted" as used herein, means that one or more hydrogens on the designated atom are replaced by a group selected from a defined group of substituents, provided that the designated atom's normal valence is not exceeded, and that the substitution results in a stable compound. Likewise, the term "substituted" may be used in connection with a

chemical moiety instead of a single atom, e.g. “substituted alkyl”, “substituted aryl” or the like.

Unless specifically indicated, throughout the specification and the appended claims, a given chemical formula or name shall encompass tautomers and all stereo, optical and geometrical isomers (e.g. enantiomers, diastereomers, E/Z isomers etc...) and racemates
5 thereof as well as mixtures in different proportions of the separate enantiomers, mixtures of diastereomers, or mixtures of any of the foregoing forms where such isomers and enantiomers exist, as well as solvates thereof such as for instance hydrates.

Unless specifically indicated, also “pharmaceutically acceptable salts” as defined in more
10 detail below shall encompass solvates thereof such as for instance hydrates.

In general, substantially pure stereoisomers can be obtained according to synthetic principles known to a person skilled in the field, e.g. by separation of corresponding mixtures, by using stereochemically pure starting materials and/or by stereoselective synthesis. It is
15 known in the art how to prepare optically active forms, such as by resolution of racemic forms or by synthesis, e.g. starting from optically active starting materials and/or by using chiral reagents.

Enantiomerically pure compounds of this invention or intermediates may be prepared via
20 asymmetric synthesis, for example by preparation and subsequent separation of appropriate diastereomeric compounds or intermediates which can be separated by known methods (e.g. by chromatographic separation or crystallization) and/or by using chiral reagents, such as chiral starting materials, chiral catalysts or chiral auxiliaries.

25 Further, it is known to the person skilled in the art how to prepare enantiomerically pure compounds from the corresponding racemic mixtures, such as by chromatographic separation of the corresponding racemic mixtures on chiral stationary phases; or by resolution of a racemic mixture using an appropriate resolving agent, e.g. by means of diastereomeric salt formation of the racemic compound with optically active acids or bases, subsequent
30 resolution of the salts and release of the desired compound from the salt; or by derivatization of the corresponding racemic compounds with optically active chiral auxiliary reagents, subsequent diastereomer separation and removal of the chiral auxiliary group; or by kinetic resolution of a racemate (e.g. by enzymatic resolution); by enantioselective

crystallization from a conglomerate of enantiomorphous crystals under suitable conditions; or by (fractional) crystallization from a suitable solvent in the presence of an optically active chiral auxiliary.

- 5 The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings without excessive toxicity, irritation, allergic response, or other problem or complication, and commensurate with a reasonable benefit/risk ratio.

10

As used herein, "pharmaceutically acceptable salt" refers to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues
15 such as carboxylic acids; and the like.

For example, such salts include salts from benzenesulfonic acid, benzoic acid, citric acid, ethanesulfonic acid, fumaric acid, gentisic acid, hydrobromic acid, hydrochloric acid, maleic acid, malic acid, malonic acid, mandelic acid, methanesulfonic acid, 4-methyl-ben-
20 zenesulfonic acid, phosphoric acid, salicylic acid, succinic acid, sulfuric acid and tartaric acid. Further pharmaceutically acceptable salts can be formed with cations from ammonia, L-arginine, calcium, 2,2'-iminobisethanol, L-lysine, magnesium, *N*-methyl-D-glucamine, potassium, sodium and tris(hydroxymethyl)-aminomethane.

- 25 The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a sufficient amount of the appropriate base or acid in water or in an organic diluent such as ether, ethyl acetate, ethanol, isopropanol, or acetonitrile, or a mixture
30 thereof.

Salts of other acids than those mentioned above which for example are useful for purifying or isolating the compounds of the present invention (e.g. trifluoro acetate salts,) also comprise a part of the invention.

- 5 The term halogen denotes fluorine, chlorine, bromine and iodine.

The term "C_{1-n}-alkyl", wherein n is an integer selected from 2, 3, 4, 5 or 6, preferably 4, 5, or 6, either alone or in combination with another radical, denotes an acyclic, saturated, branched or linear hydrocarbon radical with 1 to n C atoms. For example the term C₁₋₅-alkyl embraces the radicals H₃C-, H₃C-CH₂-, H₃C-CH₂-CH₂-, H₃C-CH(CH₃)-,
 10 H₃C-CH₂-CH₂-CH₂-, H₃C-CH₂-CH(CH₃)-, H₃C-CH(CH₃)-CH₂-, H₃C-C(CH₃)₂-,
 H₃C-CH₂-CH₂-CH₂-CH₂-, H₃C-CH₂-CH₂-CH(CH₃)-, H₃C-CH₂-CH(CH₃)-CH₂-,
 H₃C-CH(CH₃)-CH₂-CH₂-, H₃C-CH₂-C(CH₃)₂-, H₃C-C(CH₃)₂-CH₂-,
 H₃C-CH(CH₃)-CH(CH₃)- and H₃C-CH₂-CH(CH₂CH₃)-.
 15

The term "C_{2-m}-alkynyl" is used for a group "C_{2-m}-alkyl" wherein m is an integer selected from 3, 4, 5 or 6, preferably 4, 5 or 6, if at least two carbon atoms of said group are bonded to each other by a triple bond.

- 20 The term "C_{3-k}-cycloalkyl", wherein k is an integer selected from 3, 4, 5, 7 or 8, preferably 4, 5 or 6, either alone or in combination with another radical, denotes a cyclic, saturated, unbranched hydrocarbon radical with 3 to k C atoms. For example the term C₃₋₇-cycloalkyl includes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

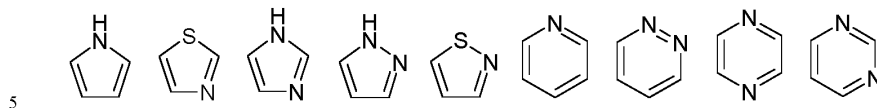
- 25 The term "halo" added to an "alkyl", "alkylene" or "cycloalkyl" group (saturated or unsaturated) defines an alkyl, alkylene or cycloalkyl group wherein one or more hydrogen atoms are replaced by a halogen atom selected from among fluorine, chlorine or bromine, preferably fluorine and chlorine, particularly preferred is fluorine. Examples include: H₂FC-, HF₂C-, F₃C-.

30

The term "mono-heteroaryl ring" means a monocyclic aromatic ring system, containing one or more heteroatoms selected from N, O or S, consisting of 5 to 6 ring atoms.

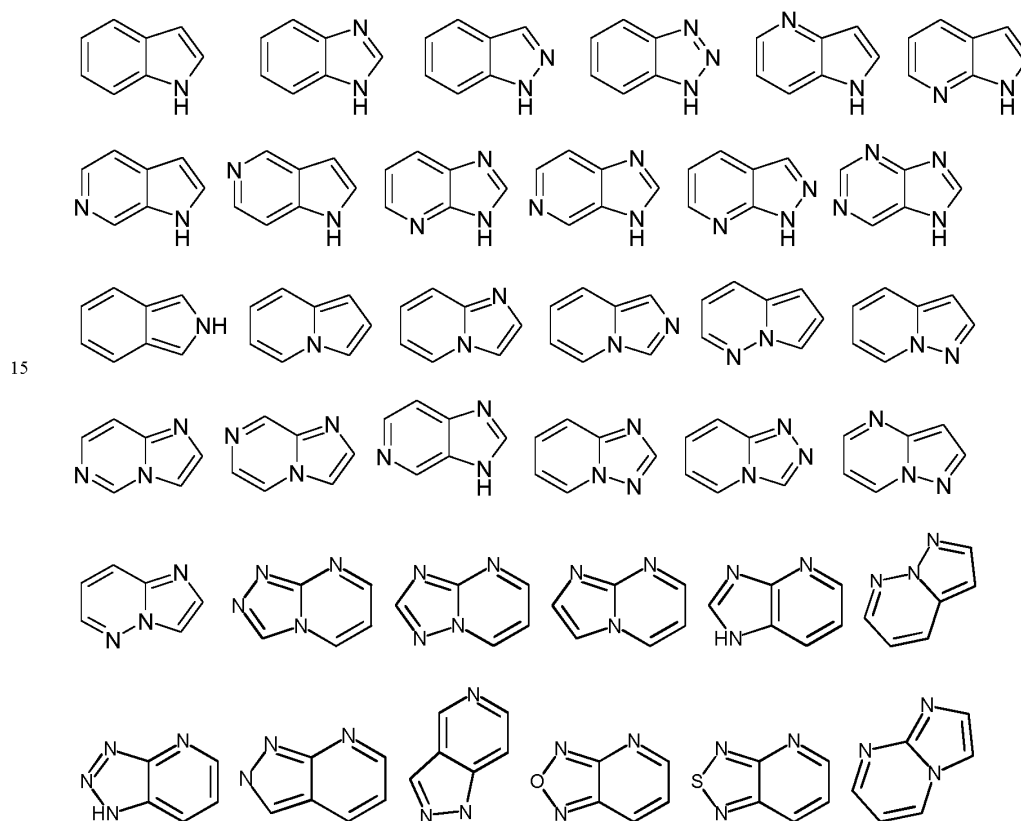
The term "mono-heteroaryl ring" is intended to include all the possible isomeric forms.

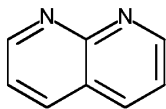
Thus, the term "mono-heteroaryl ring" includes the following exemplary structures (not depicted as radicals as each form is optionally attached through a covalent bond to any atom so long as appropriate valences are maintained):



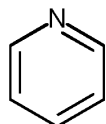
The term "fused bicyclic-heteroaryl ring" means a bicyclic aromatic ring system, containing one or more heteroatoms selected from N, O or S, consisting of 9 to 10 ring atoms. The term "fused bicyclic-heteroaryl ring" is intended to include all the possible isomeric forms.

10 Thus, the term "bicyclic-heteroaryl ring" includes the following exemplary structures (not depicted as radicals as each form is optionally attached through a covalent bond to any atom so long as appropriate valences are maintained):

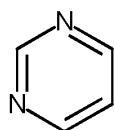




The term pyridyl refers to the radical of the following ring:

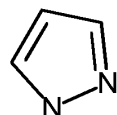


The term pyrimidyl refers to the radical of the following ring:

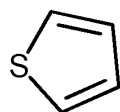


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The term pyrazolyl refers to the radical of the following ring:

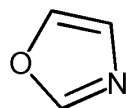


The term thiophenyl refers to the radical of the following ring:

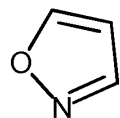


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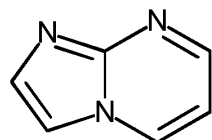
The term oxazolyl refers to the radical of the following ring:



The term isoxazolyl refers to the radical of the following ring:

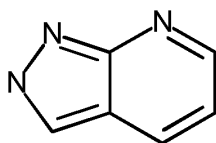


The term imidazo[1,2-a]pyrimidinyl refers to the radical of the following ring:

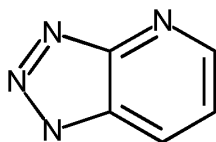


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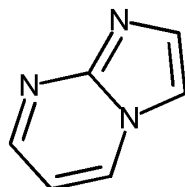
The term 2H-pyrazolo[3,4-b]pyridyl refers to the radical of the following ring:



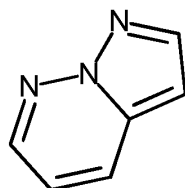
The term 1H-[1,2,3]triazolo[4,5-b]pyridyl refers to the radical of the following ring:



- 5 The term imidazo[1,2-a]pyrimidinyl refers to the radical of the following ring:



The term pyrazolo[1,5-b]pyridazinyl refers to the radical of the following ring:



- 10 Many of the terms given above may be used repeatedly in the definition of a formula or group and in each case have one of the meanings given above, independently of one another.

15

BIOLOGICAL ASSAYS

Evaluation of inhibitory activity on QPCT and QPCTL

Assay A: Biochemical QPCT and QPCTL Activity Assay

- 20 The activity of the compounds of the invention may be demonstrated using the following biochemical enzyme activity assay:

QPCT or QPCTL dependent conversion of N-terminal glutamine to pyroglutamate of CD47 was monitored via MALDI-TOF MS. Test compounds were dissolved in 100 %

DMSO and serially diluted into clear 1,536-well microtiter plates. Enzymatic reactions were set up in assay buffer containing 20 mM Tris pH 7.5, 0.1 mM TCEP, 0.01% BSA, and 0.001% Tween20. 2.5 µL of 2x concentrated QPCTL (in-house) or QPCT (Origine #TP700028) enzyme in assay buffer (0.5 nM final concentration, columns 1-23) or plain assay buffer (columns 24) were added to each well. The plates were incubated for 10 min in a humidified incubator at 24°C. Subsequently, 2.5 µL of CD47 peptide substrate surrogate (¹⁹QLLFNKTKSVEFTFC³³) was added to each well (final concentration: 10 µM for QPCTL / 20 µM for QPCT). The plates were mixed for 30 sec at 1,000 rpm and subsequently incubated for 40 min in a humidified incubator at 24°C. After incubation, the enzymatic reaction was stopped by adding 1 µL containing stable isotope labeled internal standard peptide ¹⁹[Pyr]LLFN(K)TKSVEFTFC³³ (final concentration 4.0 µM) as well as SEN177 (final concentration 10 µM). The plates were sealed with an adhesive foil, mixed for 30 s at 1,000 rpm and stored at room temperature until preparation of the MALDI target plates. MALDI target plates were prepared as described previously. Mass spectra were acquired with a rapifleX MALDI-TOF/TOF instrument tracking the signals of the product (¹⁹[Pyr]LLFNKTKSVEFTFC³³, m/z 1,787.9037) as well as internal standard (¹⁹[Pyr]LLFN(K)TKSVEFTFC³³, m/z 1,795.9179) peptide. QPCT or QPCTL activity was monitored by calculating the ratio between product and internal standard signals followed by normalization to high (100% activity) and low (0% activity) controls. Determination of compound potencies was obtained by fitting the dose-response data to a four-parameter logistical equation.

Table 2: Biological data for compounds of the invention as obtained in Assay A.

Example	Inhibition of QPCTL: IC ₅₀ [nM]	Inhibition of QPCT: IC ₅₀ [nM]
1	2	3
2	1	1
3	1	4
4	1	1
5	4	9
7	8	12
9	2	4

10	8	30
11	13	48
12	3	4
13	8	24
14	3	11
15	15	58
16	1	1
17	5	5
18	2	1
19	1	1
20	2	3
21	2	1
22	2	2
23	4	4
24	14	8
25	1	6
26	3	2
27	4	3
28	1	1
29	2	1
30	2	1
31	3	3
32	1	1
33	1	2

Table 3: Biological data for prior art compounds as obtained in Assay A.

Prior art Compound	Reference	Inhibition of QPCTL: IC ₅₀ [nM]	Inhibition of QPCT: IC ₅₀ [nM]
SEN177	J-S, NCB 2015; P, JBIC 2018	17	79
SEN180	J-S, NCB 2015	39	176
1094	WO 2018/178384	111	1707
1095	WO 2018/178384	13	260
3	WO 2022/086920	52	482
alternative 3	WO 2022/086920	837	4691
6	WO 2022/086920	1	1
21	CN 114874186	5493	1398
23	CN 114874186	4772	1845

Assay B: SIRP α signalling assay (using either Raji or A549 cells)

- 5 The activity of the compounds of the invention may be demonstrated using the following SIRP α signalling assay that measures SIRP α engagement induced by CD47 presented via cell-cell interaction. Two cell types are independently used: the Raji cell line (lymphoblast-like human cell line derived from B lymphocytes from a Burkitt's lymphoma patient in 1963) and A549 cells (adenocarcinomic human alveolar basal epithelial cells).

10

- Test compounds were dissolved in 100 % DMSO and serially diluted into a white 384-well microtiter cell culture plate (PerkinElmer #60076780 in case of Raji assay; PDL-coated plates Greiner #781945 in case of A549 assay). 5000 Raji cells (ATCC #CC86) or 5000 A549 cells (ATCC #CCL-185) in Assay Complete Cell Plating reagent 30 (DiscoverX 93-0563R30B) were added per well. The assay plate was incubated for 48 h at 37 °C, 95% humidity and 5 % CO₂. 15000 reporter cells (Jurkat PathHunter SIRP α V1, DiscoverX #93-1135C19) were added to each well, and the plate was incubated for 5 h at 37 °C, 95 % humidity and 5 % CO₂. Bioassay reagent 1 of the PathHunter Bioassay detection kit (DiscoverX 93-0001) was added to each well of the plate using a multichannel pipette followed

by a 15 min incubation at room temperature. Afterwards bioassay reagent 2 was added followed by 60 min incubation at room temperature (incubation in the dark).

The analysis of the data was performed using the luminescence signal generated by beta-galactosidase in the PathHunter reporter cell line. The luminescence measurement was done
 5 using a Pherastar Multi-Mode Reader. Dose-response curves & IC₅₀ data were calculated with 4-parameter sigmoidal dose response formula.

Table 4: Biological data for compounds of the invention as obtained in Assay B.

Example	Inhibition of SIRPα signalling induced by Raji cells: IC₅₀ [nM]	Inhibition of SIRPα signalling induced by A549 cells: IC₅₀ [nM]
1	77	41
2	20	40
3	131	40
4	15	17
5	617	60
7	568	200
9	103	39
10	536	283
11	1167	419
12	150	45
13	596	358
14	673	202
15	296	410
16	27	32
17	274	71
18	44	16
19	20	6
20	83	29
21	16	11

22	117	51
23	158	46
24	981	184
25	150	78
26	148	101
27	106	52
28	70	53
29	64	27
30	87	17
31	54	31
32	72	21
33	53	30

Table 5: Biological data for prior art compounds as obtained in Assay B.

Prior art Compound	Reference	Inhibition of SIRPα signalling induced by Raji cells: IC₅₀ [nM]	Inhibition of SIRPα signalling induced by A549 cells: IC₅₀ [nM]
SEN177	J-S, NCB 2015; P, JBIC 2018	1365	214
SEN180	J-S, NCB 2015	2973	868
1094	WO 2018/178384	3240	3059
1095	WO 2018/178384	2203	161
3	WO 2022/086920	2736	921
alternative 3	WO 2022/086920	>10000	>10000
6	WO 2022/086920	8	12
21	CN 114874186	>10000	>10000
23	CN 114874186	>10000	>10000

Evaluation of permeability

Assay C: Permeability in CACO-2 cells

Caco-2 cells ($1 - 2 \times 10^5$ cells/ 1 cm^2 area) are seeded on filter inserts (Costar transwell polycarbonate or PET filters, $0.4 \text{ }\mu\text{m}$ pore size) and cultured (DMEM) for 10 to 25 days.

- 5 Compounds are dissolved in appropriate solvent (like DMSO, 1 - 20 mM stock solutions). Stock solutions are diluted with HTP-4 buffer (128.13 mM NaCl, 5.36 mM KCl, 1 mM MgSO_4 , 1.8 mM CaCl_2 , 4.17 mM NaHCO_3 , 1.19 mM $\text{Na}_2\text{HPO}_4 \times 7\text{H}_2\text{O}$, 0.41 mM $\text{NaH}_2\text{PO}_4 \times \text{H}_2\text{O}$, 15 mM HEPES, 20 mM glucose, 0.25% BSA, pH 7.2) to prepare the transport solutions ($0.1 - 300 \text{ }\mu\text{M}$ compound, final DMSO $\leq 0.5 \%$). The transport solution
- 10 (TL) is applied to the apical or basolateral donor side for measuring A-B or B-A permeability (3 filter replicates), respectively. Samples are collected at the start and end of experiment from the donor and at various time intervals for up to 2 hours also from the receiver side for concentration measurement by HPLC-MS/MS or scintillation counting. Sampled receiver volumes are replaced with fresh receiver solution.
- 15 Efflux ratio (ER) = permeability B-A / permeability A-B

Table 7: Biological data for compounds of the invention as obtained in Assay C.

Example	Permeability A-B [10^{-6} cm/s]	Efflux Ratio
1	8.7	6.3
2	4.5	15.3
3	47.0	1.3
4	8.8	7.5
5	27.0	1.6
7	15.0	5.5
9	5.8	4.5
10	1.6	13.1
11	13.0	5.0
12	9.4	9.9
13	6.2	9.0
14	0.7	32.8
15	47.0	1.6
16	33.0	2.5

17		
18		
19		
20		
21		
22		
23		
24	16.0	4.6
25	5.3	7.7
26	7.2	11.5
27	16.0	2.2
28	28.0	0.8
29	39.0	1.7
30	46.0	0.7
31	54.0	1.2
32	60.0	0.7
33	13.0	6.2

Table 8: Biological data for prior art compounds as obtained in Assay C.

Prior art Compound	Reference	Permeability A-B [10⁻⁶ cm/s]	Efflux Ratio
SEN177	J-S, NCB 2015; P, JBIC 2018	11.0	3.3
SEN180	J-S, NCB 2015	4.2	7.1
1094	WO 2018/178384	73	1.0
1095	WO 2018/178384	68	0.5
3	WO 2022/086920	93.0	0.8
alternative 3	WO 2022/086920	97.0	0.7
6	WO 2022/086920	0.2	65.0
21	CN 114874186	0.7	27.3
23	CN 114874186	3.5	17.6

Evaluation of Microsomal Clearance

Microsomal clearance:

The metabolic degradation of the test compound was assayed at 37 °C with pooled liver microsomes from various species. The final incubation volume of 60 µl per time point contains TRIS buffer pH 7.6 at room temperature (0.1 M), magnesium chloride (5 mM), micro-
 5 somal protein (1 mg/mL for human and dog, 0.5 mg/mL for other species) and the test compound at a final concentration of 1 µM. Following a short preincubation period at 37°C, the reactions were initiated by addition of betanicotinamide adenine dinucleotide phosphate, reduced form (NADPH, 1 mM), and terminated by transferring an aliquot into solvent after
 10 different time points. After centrifugation (10000 g, 5 min), an aliquot of the supernatant was assayed by LC-MS/MS for the amount of parent compound. The half-life was determined by the slope of the semi-logarithmic plot of the concentration-time profile.

The intrinsic clearance (CL_INTRINSIC) is calculated by considering the amount of protein in the incubation:

$$15 \quad \text{CL_INTRINSIC} [\mu\text{l}/\text{min}/\text{mg protein}] = (\text{Ln } 2 / (\text{half-life} [\text{min}] * \text{protein content} [\text{mg}/\text{ml}])) * 1000$$

$$\text{CL_INTRINSIC_INVIVO} [\text{ml}/\text{min}/\text{kg}] = (\text{CL_INTRINSIC} [\mu\text{L}/\text{min}/\text{mg protein}] \times \text{MPPGL} [\text{mg protein}/\text{g liver}] \times \text{liver factor} [\text{g}/\text{kg bodyweight}]) / 1000$$

$$\text{Qh} [\%] = \text{CL} [\text{ml}/\text{min}/\text{kg}] / \text{hepatic blood flow} [\text{ml}/\text{min}/\text{kg}]$$

$$20 \quad \text{Hepatocellularity, human: } 120 \times 10^6 \text{ cells / g liver}$$

$$\text{Liver factor, human: } 25.7 \text{ g / kg bodyweight}$$

$$\text{Blood flow, human: } 21 \text{ ml}/(\text{min} \times \text{kg})$$

Evaluation of Hepatocyte Clearance

Hepatocyte clearance

The metabolic degradation of a test compound is assayed in a human hepatocyte suspension. After recovery from cryopreservation, human hepatocytes are diluted in Dulbecco's modified eagle medium (supplemented with 3.5 µg glucagon/500 mL, 2.5 mg insulin/500 mL, 3.75 mg hydrocortisone/500 mL, 5% human serum) to obtain a final cell density of
 30 1.0×10^6 cells/mL.

Following a 30 minutes preincubation in a cell culture incubator (37 °C, 10 % CO₂), test compound solution is spiked into the hepatocyte suspension, resulting in a final test compound concentration of 1 µM and a final DMSO concentration of 0.05 %.

The cell suspension is incubated at 37 °C (cell culture incubator, horizontal shaker) and samples are removed from the incubation after 0, 0.5, 1, 2, 4 and 6 hours. Samples are quenched with acetonitrile (containing internal standard) and pelleted by centrifugation. The supernatant is transferred to a 96-deepwell plate, and prepared for analysis of decline of parent compound by HPLC-MS/MS.

The percentage of remaining test compound is calculated using the peak area ratio (test compound/internal standard) of each incubation time point relative to the time point 0 peak area ratio. The log-transformed data are plotted versus incubation time, and the absolute value of the slope obtained by linear regression analysis is used to estimate in vitro half-life (T_{1/2}).

In vitro intrinsic clearance (CL_{int}) is calculated from in vitro T_{1/2} and scaled to whole liver using a hepatocellularity of 120x10⁶ cells/g liver, a human liver per body weight of 25.7 g liver/kg as well as in vitro incubation parameters, applying the following equation:

$$CL_INTRINSIC_IN\ VIVO\ [mL/min/kg] = (CL_INTRINSIC\ [\mu L/min/10^6\ cells] \times hepatocellularity\ [10^6\ cells/g\ liver] \times liver\ factor\ [g/kg\ body\ weight]) / 1000$$

Hepatic in vivo blood clearance (CL) is predicted according to the well-stirred liver model considering an average liver blood flow (QH) of 20.7 mL/min/kg:

$$CL\ [mL/min/kg] = CL_INTRINSIC_IN\ VIVO\ [mL/min/kg] \times hepatic\ blood\ flow\ [mL/min/kg] / (CL_INTRINSIC_IN\ VIVO\ [mL/min/kg] + hepatic\ blood\ flow\ [mL/min/kg])$$

Results are expressed as percentage of hepatic blood flow:

$$QH\ [\%] = CL\ [mL/min/kg] / hepatic\ blood\ flow\ [mL/min/kg]$$

Evaluation of plasma protein binding

Equilibrium dialysis technique is used to determine the approximate in vitro fractional binding of test compounds to plasma proteins applying Dianorm Teflon dialysis cells (micro

0.2). Each dialysis cell consists of a donor and an acceptor chamber, separated by an ultrathin semipermeable membrane with a 5 kDa molecular weight cutoff. Stock solutions for each test compound are prepared in DMSO at 1 mM and serially diluted to obtain a final test concentration of 1 μ M. The subsequent dialysis solutions are prepared in plasma (supplemented with NaEDTA as anticoagulant), and aliquots of 200 μ l test compound dialysis solution in plasma are dispensed into the donor (plasma) chambers. Aliquots of 200 μ l dialysis buffer (100 mM potassium phosphate, pH 7.4, supplemented with up to 4.7 % Dextran) are dispensed into the buffer (acceptor) chamber. Incubation is carried out for 2 hours under rotation at 37°C for establishing equilibrium.

At the end of the dialysis period, aliquots obtained from donor and acceptor chambers, respectively, are transferred into reaction tubes and processed for HPLC-MS/MS analysis. Analyte concentrations are quantified in aliquots of samples by HPLC-MS/MS against calibration curves.

Percent bound is calculated using the formula:

$$\% \text{bound} = (\text{plasma concentration} - \text{buffer concentration} / \text{plasma concentration}) \times 100$$

Evaluation of solubility

Saturated solutions are prepared in well plates (format depends on robot) by adding an appropriate volume of selected aqueous media (typically in the range of 0.25 - 1.5 ml) into each well which contains a known quantity of solid drug substance (typically in the range 0.5 - 5.0 mg). The wells are shaken or stirred for a predefined time period (typically in a range of 2 - 24 h) and then filtered using appropriate filter membranes (typically PTFE-filters with 0.45 μ m pore size). Filter absorption is avoided by discarding the first few drops of filtrate. The amount of dissolved drug substance is determined by UV spectroscopy. In addition, the pH of the aqueous saturated solution is measured using a glass-electrode pH meter.

Evaluation of Metabolism in human hepatocytes *in vitro*

The metabolic pathway of a test compound is investigated using primary human hepatocytes in suspension. After recovery from cryopreservation, human hepatocytes are incubated in Dulbecco's modified eagle medium containing 5% human serum and supplemented with 3.5 μ g glucagon/500ml, 2.5mg insulin/500ml and 3.75mg/500ml hydrocortisone.

Following a 30 min preincubation in a cell culture incubator (37°C, 10% CO₂), test compound solution is spiked into the hepatocyte suspension to obtain a final cell density of 1.0*10⁶ to 4.0*10⁶ cells/ml (depending on the metabolic turnover rate of the compound observed with primary human hepatocytes), a final test compound concentration of 10 µM, and
5 a final DMSO concentration of 0.05%.

The cells are incubated for six hours in a cell culture incubator on a horizontal shaker, and samples are removed from the incubation after 0, 0.5, 1, 2, 4 or 6 hours, depending on the metabolic turnover rate. Samples are quenched with acetonitrile and pelleted by centrifugation. The supernatant is transferred to a 96-deepwell plate, evaporated under nitrogen and
10 resuspended prior to bioanalysis by liquid chromatography-high resolution mass spectrometry for identification of putative metabolites.

The structures are assigned tentatively based on Fourier-Transform-MSⁿ data. Metabolites are reported as percentage of the parent in human hepatocyte incubation with a threshold of ≥ 4%.

15

Evaluation of pharmacokinetic characteristics

The test compound is administered either intravenously or orally to the respective test species. Blood samples are taken at several time points post application of the test compound, anticoagulated and centrifuged.

20 The concentration of analytes - the administered compound and/or metabolites - are quantified in the plasma samples. PK parameters are calculated using non compartment methods. AUC and Cmax are normalized to a dose of 1 µmol/kg.

METHOD OF TREATMENT

25

The present invention is directed to compounds of general formula (I) which are useful in the prevention and/or treatment of a disease and/or condition associated with or modulated by QPCT/L activity, including but not limited to the treatment and/or prevention of cancer, fibrotic diseases, neurodegenerative diseases, atherosclerosis, infectious diseases, chronic
30 kidney diseases.

The compounds of general formula (I) are useful for the prevention and/or treatment of:

(1) Pulmonary fibrotic diseases such as pneumonitis or interstitial pneumonitis associated with collagenosis, e.g. lupus erythematoses, systemic scleroderma, rheumatoid arthritis,

polymyositis and dermatomyositis, idiopathic interstitial pneumonias, such as pulmonary lung fibrosis (IPF), non-specific interstitial pneumonia, respiratory bronchiolitis associated interstitial lung disease, desquamative interstitial pneumonia, cryptogenic organizing pneumonia, acute interstitial pneumonia and lymphocytic interstitial pneumonia, lymphangi-
 5 oleiomyomatosis, pulmonary alveolar proteinosis, Langerhan's cell histiocytosis, pleural parenchymal fibroelastosis, interstitial lung diseases of known cause, such as interstitial pneumonitis as a result of occupational exposures such as asbestosis, silicosis, miners lung (coal dust), farmers lung (hay and mould), Pidgeon fanciers lung (birds) or other occupational airbourne triggers such as metal dust or mycobacteria, or as a result of treatment
 10 such as radiation, methotrexate, amiodarone, nitrofurantoin or chemotherapeutics, or for granulomatous disease, such as granulomatosis with polyangitis, Churg-Strauss syndrome, sarcoidosis, hypersensitivity pneumonitis, or interstitial pneumonitis caused by different origins, e.g. aspiration, inhalation of toxic gases, vapors, bronchitis or pneumonitis or interstitial pneumonitis caused by heart failure, X-rays, radiation, chemotherapy, M. boeck or
 15 sarcoidosis, granulomatosis, cystic fibrosis or mucoviscidosis, or alpha-1-antitrypsin deficiency.

(2) Other fibrotic diseases such as hepatic bridging fibrosis, liver cirrhosis, non-alcoholic steatohepatitis (NASH), atrial fibrosis, endomyocardial fibrosis, old myocardial infarction, glial scar, arterial stiffness, arthrofibrosis, Dupuytren's contracture, keloid, scleroderma/
 20 systemic sclerosis, mediastinal fibrosis, myelofibrosis, Peyronie's disease, nephrogenic systemic fibrosis, retroperitoneal fibrosis, adhesive capsulitis; spontaneous acute exacerbations in pulmonary fibrosis and progressive pulmonary fibrosis or induced by infection, microaspiration, surgical lung biopsy, surgical resection, bronchoscopy (BAL, cryobiopsy), air pollution, prior exacerbation and medications.

(3) Leukemia, acute myeloid leukemia (AML), acute promyelocytic leukemia (APL), chronic myeloid leukemia (CML), acute lymphoblastic leukemia (ALL), T-cell acute lymphoblastic leukemia (T-ALL), lymphoma, B-cell lymphoma, T-cell lymphoma, Hodgkin's disease, non-Hodgkin's lymphoma (NHL), hairy cell lymphoma, Burkett's lymphoma, multiple myeloma (MM), myelodysplastic syndrome, solid cancer, lung cancer, adenocarcinoma, small cell lung cancer (SCLC), non-small cell lung cancer (NSCLC), mediastinum
 30 cancer, peritoneal cancer, mesothelioma, gastrointestinal cancer, gastric cancer, stomach cancer, bowel cancer, small bowel cancer, large bowel cancer, colon cancer, colon adenocarcinoma, colon adenoma, rectal cancer, colorectal cancer, leiomyosarcoma, breast

cancer, gynaecological cancer, genito-urinary cancer, ovarian cancer, endometrial cancer, cervical cancer, prostate cancer, testicular cancer, seminoma, teratocarcinoma, liver cancer, kidney cancer, bladder cancer, urothelial cancer, biliary tract cancer, pancreatic cancer, exocrine pancreatic carcinoma, esophageal cancer, nasopharyngeal cancer, head and neck squamous cell carcinoma (HNSCC), skin cancer, squamous cancer, squamous cell carcinoma, Kaposi's sarcoma, melanoma, malignant melanoma, xeroderma pigmentosum, keratoacanthoma, bone cancer, bone sarcoma, osteosarcoma, rhabdomyosarcoma, fibrosarcoma, thyroid gland cancer, thyroid follicular cancer, adrenal gland cancer, nervous system cancer, brain cancer, astrocytoma, neuroblastoma, glioma, schwannoma, glioblastoma, or sarcoma, gastrointestinal cancer, gastric cancer, stomach cancer, esophageal cancer, head and neck squamous cell carcinoma (HNSCC), breast cancer, colorectal cancer, bowel cancer, large bowel cancer, colon cancer, colon adenocarcinoma, colon adenoma, rectal cancer, ovarian cancer, pancreatic cancer, exocrine pancreatic carcinoma, leukemia, acute myeloid leukemia (AML), myelodysplastic syndrome, lymphoma, B-cell lymphoma, non-Hodgkin's lymphoma (NHL), urothelial cancer, or peritoneal cancer.

(4) Inflammatory, auto-immune or allergic diseases and conditions such as asthma, pediatric asthma, allergic bronchitis, alveolitis, hyperreactive airways, allergic conjunctivitis, bronchiectasis, adult respiratory distress syndrome, bronchial and pulmonary edema, bronchitis or pneumonitis, non-allergic asthma, chronic obstructive pulmonary disease (COPD), acute bronchitis, chronic bronchitis, pulmonary emphysema; autoimmune diseases, such as rheumatoid arthritis, Graves' disease, Sjogren's syndrome psoriatic arthritis, multiple sclerosis, systemic lupus erythematosus, inflammatory bowel diseases, such as Crohn's disease and ulcerative colitis, scleroderma; psoriasis (including T-cell mediated psoriasis) and inflammatory dermatoses such as an dermatitis, eczema, atopic dermatitis, allergic contact dermatitis, urticaria; vasculitis (e.g., necrotizing, cutaneous, and hypersensitivity vasculitis), or erythema nodosum.

(5) Neurodegenerative disorders such as amyotrophic lateral sclerosis, multiple sclerosis, Parkinson's disease, Alzheimer's disease, Huntington's disease, multiple system atrophy, or prion diseases.

30

Accordingly, the present invention relates to a compound of general formula (I) or a pharmaceutically acceptable salt thereof for use as a medicament.

Furthermore, the present invention relates to the use of a compound of general formula (I) for the treatment and/or prevention of a disease and/or condition associated with or modulated by QPCT/L activity.

- 5 Furthermore, the present invention relates to the use of a compound of general formula (I) or a pharmaceutically acceptable salt thereof or a pharmaceutical composition thereof for the treatment and/or prevention of cancer, fibrotic diseases, neurodegenerative diseases, atherosclerosis, infectious diseases, chronic kidney diseases.
- 10 Furthermore, the present invention relates to the use of a compound of general formula (I) or a pharmaceutically acceptable salt thereof or a pharmaceutical composition thereof for the treatment and/or prevention of: (1) Pulmonary fibrotic diseases such as pneumonitis or interstitial pneumonitis associated with collagenosis, e.g. lupus erythematoses, systemic scleroderma, rheumatoid arthritis, polymyositis and dermatomyositis, idiopathic interstitial
- 15 pneumonias, such as pulmonary lung fibrosis (IPF), non-specific interstitial pneumonia, respiratory bronchiolitis associated interstitial lung disease, desquamative interstitial pneumonia, cryptogenic organizing pneumonia, acute interstitial pneumonia and lymphocytic interstitial pneumonia, lymphangioleiomyomatosis, pulmonary alveolar proteinosis, Langerhan's cell histiocytosis, pleural parenchymal fibroelastosis, interstitial lung diseases of
- 20 known cause, such as interstitial pneumonitis as a result of occupational exposures such as asbestosis, silicosis, miners lung (coal dust), farmers lung (hay and mould), Pidgeon fanciers lung (birds) or other occupational airborne triggers such as metal dust or mycobacteria, or as a result of treatment such as radiation, methotrexate, amiodarone, nitrofurantoin or chemotherapeutics, or for granulomatous disease, such as granulomatosis with polyangiitis, Churg-Strauss syndrome, sarcoidosis, hypersensitivity pneumonitis, or interstitial pneumonitis caused by different origins, e.g. aspiration, inhalation of toxic gases, vapors, bronchitis or pneumonitis or interstitial pneumonitis caused by heart failure, X-rays, radiation, chemotherapy, M. boeck or sarcoidosis, granulomatosis, cystic fibrosis or mucoviscidosis, or alpha-I-antitrypsin deficiency.
- 25 (2) Other fibrotic diseases such as hepatic bridging fibrosis, liver cirrhosis, non-alcoholic steatohepatitis (NASH), atrial fibrosis, endomyocardial fibrosis, old myocardial infarction, glial scar, arterial stiffness, arthrofibrosis, Dupuytren's contracture, keloid, scleroderma/systemic sclerosis, mediastinal fibrosis, myelofibrosis, Peyronie's disease, nephrogenic
- 30

systemic fibrosis, retroperitoneal fibrosis, adhesive capsulitis; spontaneous acute exacerbations in pulmonary fibrosis and progressive pulmonary fibrosis or induced by infection, microaspiration, surgical lung biopsy, surgical resection, bronchoscopy (BAL, cryobiopsy), air pollution, prior exacerbation and medications.

- 5 (3) Leukemia, acute myeloid leukemia (AML), acute promyelocytic leukemia (APL), chronic myeloid leukemia (CML), acute lymphoblastic leukemia (ALL), T-cell acute lymphoblastic leukemia (T-ALL), lymphoma, B-cell lymphoma, T-cell lymphoma, Hodgkin's disease, non-Hodgkin's lymphoma (NHL), hairy cell lymphoma, Burkett's lymphoma, multiple myeloma (MM), myelodysplastic syndrome, solid cancer, lung cancer, adenocarcinoma, small cell lung cancer (SCLC), non-small cell lung cancer (NSCLC), mediastinum
10 cancer, peritoneal cancer, mesothelioma, gastrointestinal cancer, gastric cancer, stomach cancer, bowel cancer, small bowel cancer, large bowel cancer, colon cancer, colon adenocarcinoma, colon adenoma, rectal cancer, colorectal cancer, leiomyosarcoma, breast cancer, gynaecological cancer, genito-urinary cancer, ovarian cancer, endometrial cancer, cervical cancer, prostate cancer, testicular cancer, seminoma, teratocarcinoma, liver cancer,
15 kidney cancer, bladder cancer, urothelial cancer, biliary tract cancer, pancreatic cancer, exocrine pancreatic carcinoma, esophageal cancer, nasopharyngeal cancer, head and neck squamous cell carcinoma (HNSCC), skin cancer, squamous cancer, squamous cell carcinoma, Kaposi's sarcoma, melanoma, malignant melanoma, xeroderma pigmentosum, keratoacanthoma, bone cancer, bone sarcoma, osteosarcoma, rhabdomyosarcoma, fibrosarcoma, thyroid gland cancer, thyroid follicular cancer, adrenal gland cancer, nervous system
20 cancer, brain cancer, astrocytoma, neuroblastoma, glioma, schwannoma, glioblastoma, or sarcoma, gastrointestinal cancer, gastric cancer, stomach cancer, esophageal cancer, head and neck squamous cell carcinoma (HNSCC), breast cancer, colorectal cancer, bowel cancer, large bowel cancer, colon cancer, colon adenocarcinoma, colon adenoma, rectal cancer,
25 cancer, ovarian cancer, pancreatic cancer, exocrine pancreatic carcinoma, leukemia, acute myeloid leukemia (AML), myelodysplastic syndrome, lymphoma, B-cell lymphoma, non-Hodgkin's lymphoma (NHL), urothelial cancer, or peritoneal cancer.

- (4) Inflammatory, auto-immune or allergic diseases and conditions such as asthma, pediatric
30 asthma, allergic bronchitis, alveolitis, hyperreactive airways, allergic conjunctivitis, bronchiectasis, adult respiratory distress syndrome, bronchial and pulmonary edema, bronchitis or pneumonitis, non-allergic asthma, chronic obstructive pulmonary disease (COPD), acute bronchitis, chronic bronchitis, pulmonary emphysema; autoimmune diseases, such as

rheumatoid arthritis, Graves' disease, Sjogren's syndrome psoriatic arthritis, multiple sclerosis, systemic lupus Erythematosus, inflammatory bowel diseases, such as Crohn's disease and ulcerative colitis, scleroderma; psoriasis (including T-cell mediated psoriasis) and inflammatory dermatoses such as an dermatitis, eczema, atopic dermatitis, allergic contact dermatitis, urticaria; vasculitis (e g, necrotizing, cutaneous, and hypersensitivity vasculitis), or erythemanodosum.

(5) Neurodegenerative disorders such as amyotrophic lateral sclerosis, multiple sclerosis, Parkinson's disease, Alzheimer's disease, Huntington's disease, multiple system atrophy, or prion diseases.

10

In a further aspect the present invention relates to a compound of general formula (I) or a pharmaceutically acceptable salt thereof or a pharmaceutical composition thereof for use in the treatment and/or prevention of above-mentioned diseases and conditions.

15 In a further aspect the present invention relates to the use of a compound of general formula (I) or a pharmaceutically acceptable salt thereof or a pharmaceutical composition thereof for the preparation of a medicament for the treatment and/or prevention of above-mentioned diseases and conditions.

20 In a further aspect of the present invention the present invention relates to methods for the treatment or prevention of above-mentioned diseases and conditions, which method comprises the administration of an effective amount of a compound of general formula (I) or a pharmaceutically acceptable salt thereof or a pharmaceutical composition thereof to a human being.

25

COMBINATION THERAPY

The compounds of the invention may further be combined with one or more, preferably one additional therapeutic agent. According to one embodiment the additional therapeutic agent is selected from the group of therapeutic agents useful in the treatment of diseases or conditions described hereinbefore, in particular associated with cancer, fibrotic diseases, Alzheimer's diseases, atherosclerosis, infectious diseases, chronic kidney diseases and auto-immune disease.

Additional therapeutic agents that are suitable for such combinations include in particular those, which, for example, potentiate the therapeutic effect of one or more active substances with respect to one of the indications mentioned and/or allow the dosage of one or more active substances to be reduced.

5 Therefore, a compound of the invention may be combined with one or more additional therapeutic agents selected from the group consisting of chemotherapy, targeted cancer therapy, cancer immunotherapy, irradiation, antifibrotic agents, anti-tussive agents, anti-inflammatory agents, anti-atopic dermatitis, and broncho dilators.

Chemotherapy is a type of cancer therapy that uses one or more chemical anti-cancer
10 drugs, such as cytostatic or cytotoxic substances, cell proliferation inhibitors, anti-angiogenic substances and the like. Examples include folic acid (Leucovorin), 5-Fluorouracil, Irinotecan, Oxaliplatin, cis-platin Azacytidine, gemcitabine, alkylation agents, antimitotic agents, taxanes and further state-of-the-art or standard-of-care compounds.

Targeted therapy is a type of cancer treatment that uses drugs to target specific genes and
15 proteins that help cancer cells survive and grow. Targeted therapy includes agents such as inhibitors of growth factors (e.g. platelet derived growth factor (PDGF), fibroblast growth factor (FGF), vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), insulin-like growth factors (IGF), human epidermal growth factor (HER, e.g. HER2, HER3, HER4) and hepatocyte growth factor), tyrosine-kinases, KRAS, BRAF, BCR-ABL,
20 mTOR, cyclin-dependent kinases, or MDM2.

Cancer immunotherapy is a type of therapy that uses substances to stimulate or suppress the immune system to help the body fight cancer. Cancer immunotherapy includes a therapeutic antibody, such as: anti-Her2 antibody, an anti-EGFR antibody, and an anti-PDGFR antibody; an anti-GD2 (Ganglioside G2) antibody. Examples include Dinutuximab, Olara-
25 tumab, Trastuzumab, Pertuzumab, Ertumaxomab, Cetuximab, Necitumumab,

Nimotuzumab, Panitumumab, or rituximab. Cancer immunotherapy also includes a therapeutic antibody which is a checkpoint inhibitor, such as an anti PD1, anti PD-L1 antibody or CTLA4 inhibitor. Examples include Atezolizumab, Avelumab, and Durvalumab, Ipilimumab, nivolumab, or pembrolizumab. Cancer immunotherapy also includes agents which
30 target (inhibit) the CD47-SIRP α signaling axis, such as agents which bind to CD47 or SIRP α . Non-limiting examples include antibodies such as anti-CD47 antibodies and anti-SIRP α antibodies, and recombinant Fc-fusion proteins such as CD47-Fc and SIRP α -Fc.

Cancer immunotherapy also includes STING-targeting agent, or T cell engagers, such as blinatumomab.

Antifibrotic agents are for example nintedanib, pirfenidone, phosphodiesterase-IV (PDE4) inhibitors such as roflumilast or specific PDE4b inhibitors like BI 1015550, autotaxin inhibitors such as GLPG-1690 or BBT-877; connective tissue growth factor (CTGF) blocking antibodies such as Pamrevlumab; B-cell activating factor receptor (BAFF-R) blocking antibodies such as Lanalumab, alpha-V/beta-6 blocking inhibitors such as BG-00011/STX-100, recombinant pentraxin-2 (PTX-2) such as PRM-151; c-Jun-N-terminal kinase (JNK) inhibitors such as CC-90001; galectin-3 inhibitors such as TD-139; G-protein coupled receptor 84 (GPR84) inhibitors ; G-protein coupled receptor 84/ G-protein coupled receptor 40 dual inhibitors such as PBI-4050, Rho Associated Coiled-Coil Containing Protein Kinase 2 (ROCK2) inhibitors such as KD-025, heat shock protein 47 (HSP47) small interfering RNA such as BMS-986263/ND-L02-s0201; Wnt pathway inhibitor such as SM-04646; LD4/ PDE3/4 inhibitors such as Tipelukast; recombinant immuno-modulatory domains of histidyl tRNA synthetase (HARS) such as ATYR-1923, prostaglandin synthase inhibitors such as ZL-2102 /SAR-191801; 15-hydroxy-eicosapentaenoic acid (15-HEPE e.g. DS-102); Lysyl Oxidase Like 2 (LOXL2) inhibitors such as PAT-1251, PXS-5382/PXS-5338; phosphoinositide 3-kinases (PI3K)/ mammalian target of rapamycin (mTOR) dual inhibitors such as HEC-68498; calpain inhibitors such as BLD-2660; mitogen-activated protein kinase kinase kinase (MAP3K19) inhibitors such as MG-S-2525; chitinase inhibitors such as OATD-01, mitogen-activated protein kinase-activated protein kinase 2 (MAPKAPK2) inhibitors such as MMI-0100; transforming growth factor beta I (TGF-beta I) small interfering RNA such as TRKZSO/BNC-1021; or lysophosphatidic acid receptor antagonists such as BMS986278.

The dosage for the combination partners mentioned above is usually 1/5 of the lowest dose normally recommended up to 1/1 of the normally recommended dose.

Therefore, in another aspect, this invention relates to the use of a compound according to the invention in combination with one or more additional therapeutic agents described hereinbefore and hereinafter for the treatment of diseases or conditions which may be affected or which are mediated by QPCT/L, in particular diseases or conditions as described hereinbefore and hereinafter.

In a further aspect this invention relates to a method for treating a disease or condition which can be influenced by the inhibition of QPCT/L in a patient that includes the step of administering to the patient in need of such treatment a therapeutically effective amount of
5 a compound of formula (I) or a pharmaceutically acceptable salt thereof in combination with a therapeutically effective amount of one or more additional therapeutic agents.

In a further aspect this invention relates to the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof in combination with one or more additional therapeutic
10 agents for the treatment of diseases or conditions which can be influenced by the inhibition of QPCT/L in a patient in need thereof.

In yet another aspect the present invention relates to a method for the treatment of a disease or condition mediated by QPCT/L activity in a patient that includes the step of administering to the patient, preferably a human, in need of such treatment a therapeutically effective
15 amount of a compound of the present invention in combination with a therapeutically effective amount of one or more additional therapeutic agents described in hereinbefore and hereinafter.

20 The use of the compound according to the invention in combination with the additional therapeutic agent may take place simultaneously or at staggered times.
The compound according to the invention and the one or more additional therapeutic agents may both be present together in one formulation, for example a tablet or capsule, or separately in two identical or different formulations, for example as a so-called kit-of-parts.

25 Consequently, in another aspect, this invention relates to a pharmaceutical composition that comprises a compound according to the invention and one or more additional therapeutic agents described hereinbefore and hereinafter, optionally together with one or more inert carriers and/or diluents.

30 Other features and advantages of the present invention will become apparent from the following more detailed examples which illustrate, by way of example, the principles of the invention.

PREPARATION

The compounds according to the present invention and their intermediates may be obtained using methods of synthesis which are known to the one skilled in the art and described in the literature of organic synthesis. Preferably, the compounds are obtained in analogous fashion to the methods of preparation explained more fully hereinafter, in particular as described in the experimental section. In some cases, the order in carrying out the reaction steps may be varied. Variants of the reaction methods that are known to the one skilled in the art but not described in detail here may also be used.

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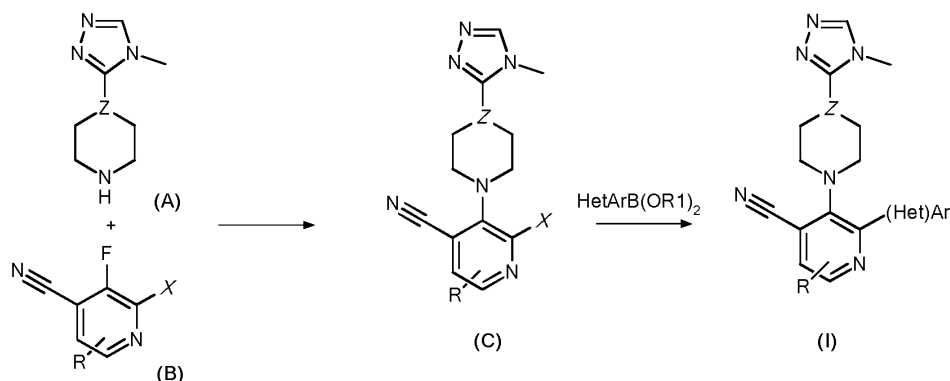
The general processes for preparing the compounds according to the invention will become apparent to the one skilled in the art studying the following schemes. Any functional groups in the starting materials or intermediates may be protected using conventional protecting groups. These protecting groups may be cleaved again at a suitable stage within the reaction sequence using methods familiar to the one skilled in the art.

The compounds according to the invention are prepared by the methods of synthesis described hereinafter in which the substituents of the general formulae have the meanings given herein before. These methods are intended as an illustration of the invention without restricting its subject matter and the scope of the compounds claimed to these examples.

Where the preparation of starting compounds is not described, they are commercially obtainable or may be prepared analogously to known compounds or methods described herein. Substances described in the literature are prepared according to the published methods of synthesis. Abbreviations are as defined in the Examples section.

Examples may be prepared as shown in Scheme I below.

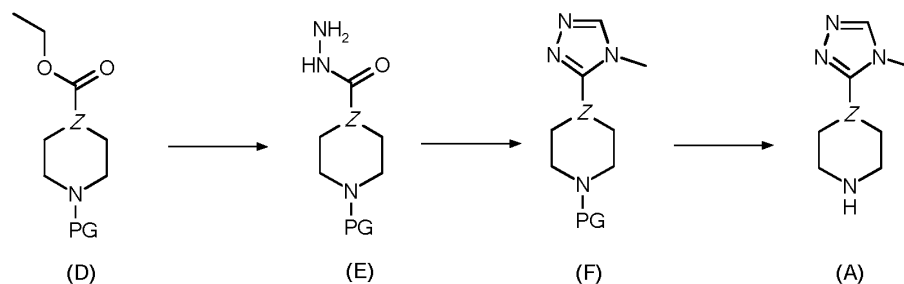
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Scheme I:

In scheme I, N-Methyl triazolyl piperidine (Z=C-H, C-F) (A) undergo a nucleophilic aromatic substitution with heteroaryl fluoride (X= Cl, Br) (B). The reaction can typically be run at ambient temperature or at elevated temperature (up to 110 °C) in the presence of a base (e.g. diisopropylethylamine). The intermediate (C) is then subjected to a Suzuki-cross coupling with a hetero-aryl boronic acid derivative in the presence of a suitable catalyst (e.g. Pd(dppf)Cl₂) and a suitable base at elevated temperature (e.g. 100 °C) to afford compounds of general formula (I).

10

Intermediates I may be prepared as shown in Scheme II below:

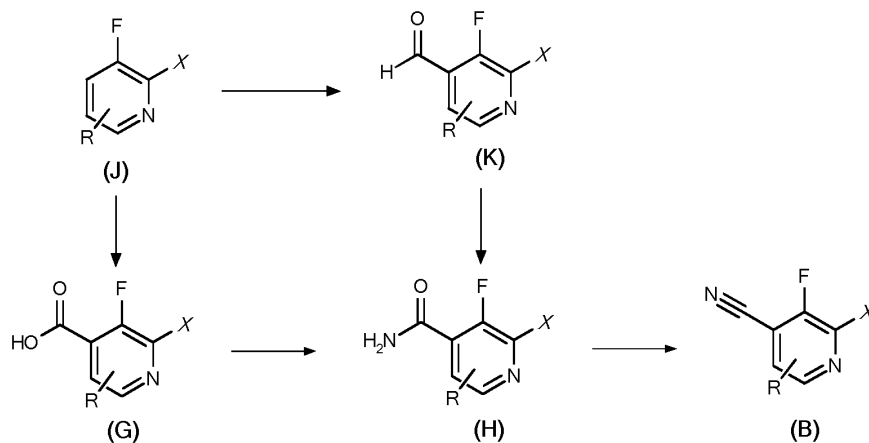
Scheme II:

Compounds of formula (A) with Z = C-F can be prepared from the corresponding piperidinyl esters (D) equipped with a suitable protecting group (PG, e.g. Benzyl) by treatment with a suitable hydrazine source (e.g. N₂H₄*H₂O) at elevated temperature (e.g. 50 °C). The obtained hydrazide (E) is then activated with DMF/DMA at elevated temperature (e.g. 50 °C) and subsequently treated with methyl amine at elevated temperature (e.g. 90 °C) to yield the triazole derivative (F). Compounds of formula (A) can be obtained by cleaving the protecting group under suitable conditions (e.g. H₂, Pd/C 10 %, EtOH).

20

Intermediates II.2 – II.6 may be prepared as shown in Scheme III below:

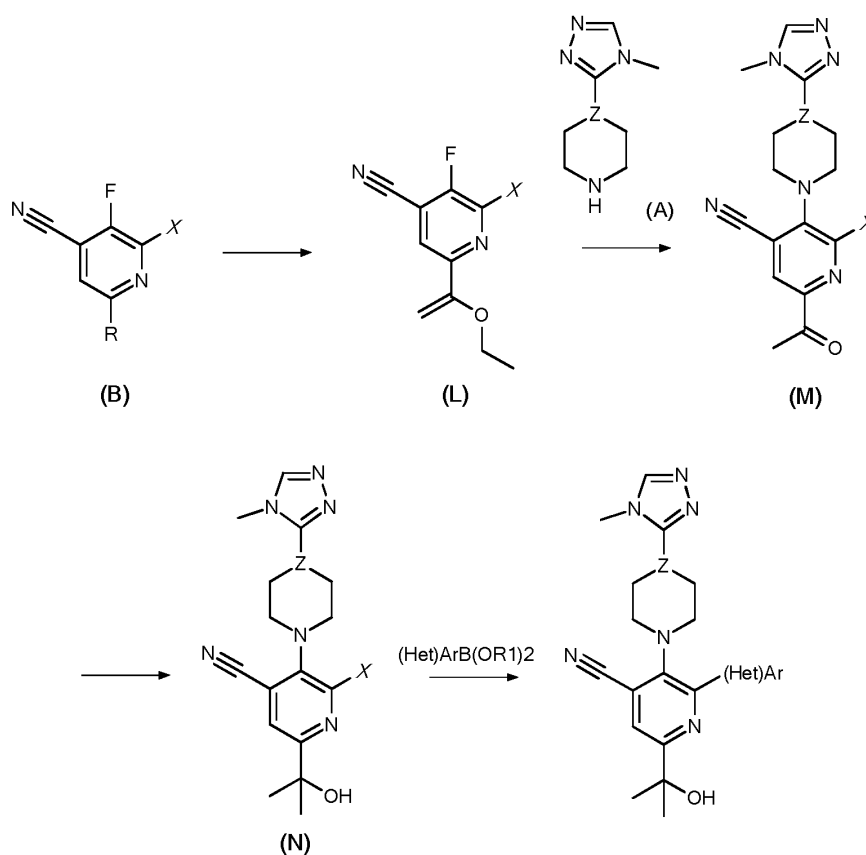
Scheme III:



- 5 In case of R=H, intermediates of formula (B) can be prepared starting from the corresponding carboxylic acids (G). In the case of R=Cl, the carboxylic acid (G) can be prepared from the corresponding pyridine (J) via deprotonation with a strong base (e.g. LDA) at low temperature (e.g. -70°C) and quenching with a suitable reagent (e.g. carbon dioxide). The carboxylic acid moiety is transformed into the corresponding amide (H) using a suitable combination of reagents, e.g. 1,1'-carbonyldiimidazole and ammonia at ambient temperature.
- 10 Compounds of formula (B) are subsequently obtained by treatment of (H) with a suitable dehydrating agent, e.g. Burgess reagent at ambient temperature. In case of R = Me or CF₃, deprotonation of pyridine (J) at low temperature (e.g. -65 °C) and quenching with DMF yields the corresponding aldehydes (K). In case of R = CF₃, aldehyde (K) can be transformed into the amide (H) using a suitable reagent, e.g. phenyltrimethylammonium tribromide, at ambient temperature and further into the nitrile (B) as described above for R=H.
- 15

Examples 1 and 2 may be prepared as shown in Scheme IV below:

Scheme IV:



- Pyridonitrile Intermediates (B) with R=Br and X=Cl may be prepared according to Scheme
- 5 III and may be further converted into enol ether (L) using a suitable coupling reagent (e.g. tributyl(1-ethoxyethenyl) stannane) and a suitable catalyst (e.g. Pd(dppf)Cl₂) at elevated temperature (e.g. 70 °C). Upon reaction with piperidine (A) at a suitable temperature (e.g. 15 °C) followed acidic workup by using a suitable acid (e.g. HCl in dioxane), ketone (M) may be obtained. This may be further converted into tertiary alcohol (N) upon reaction
- 10 with a suitable organometallic reagent (e.g. MeMgBr). The intermediate (N) is then subjected to a Suzuki-cross coupling with a hetero-aryl boronic acid derivative in the presence of a suitable catalyst (e.g. Pd(dppf)Cl₂) and a suitable base at elevated temperature (e.g. 100 °C) to afford examples 1 or 2.

EXAMPLES

Preparation

The compounds according to the invention and their intermediates may be obtained using methods of synthesis which are known to the one skilled in the art and described in the literature of organic synthesis for example using methods described in "Comprehensive Organic Transformations", 2nd Edition, Richard C. Larock, John Wiley & Sons, 2010, and "March's Advanced Organic Chemistry", 7th Edition, Michael B. Smith, John Wiley & Sons, 2013. Preferably the compounds are obtained analogously to the methods of preparation explained more fully hereinafter, in particular as described in the experimental section. In some cases the sequence adopted in carrying out the reaction schemes may be varied. Variants of these reactions that are known to the skilled artisan but are not described in detail herein may also be used. The general processes for preparing the compounds according to the invention will become apparent to the skilled man on studying the schemes that follow. Starting compounds are commercially available or may be prepared by methods that are described in the literature or herein, or may be prepared in an analogous or similar manner. Before the reaction is carried out, any corresponding functional groups in the starting compounds may be protected using conventional protecting groups. These protecting groups may be cleaved again at a suitable stage within the reaction sequence using methods familiar to the skilled man and described in the literature for example in "Protecting Groups", 3rd Edition, Philip J. Kocienski, Thieme, 2005, and "Protective Groups in Organic Synthesis", 4th Edition, Peter G. M. Wuts, Theodora W. Greene, John Wiley & Sons, 2006. The terms "ambient temperature" and "room temperature" are used interchangeably and designate a temperature of about 20 °C, e.g. between 19 and 24 °C.

Abbreviations:

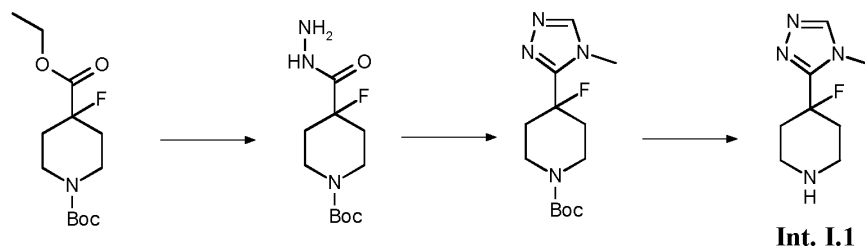
ACN	acetonitrile
Aq.	aqueous
brine	saturated aqueous NaCl solution
°C	degree celsius
CyH/CH	cyclohexane
CO ₂	carbon dioxide
conc.	concentrated

Cs ₂ CO ₃	cesium carbonate
DCM	dichloromethane
DIPA	<i>N,N</i> -diisopropylamine
DIPEA	<i>N,N</i> -diisopropylethylamine
DMF	<i>N,N</i> -dimethylformamide
DMSO	dimethyl sulfoxide
ESI-MS	Electrospray ionisation mass spectrometry
EtOAc/EA	ethyl acetate
EtOH	ethanol
ex	example
eq	equivalent
FA	formic acid
h	hour
H ₂ O	water
HCl	hydrochloric acid
HPLC	high performance liquid chromatography
Int.	intermediate
K ₂ CO ₃	potassium carbonate
K ₃ PO ₄	tripotassium phosphate
KOAc	potassium acetate
KOH	potassium hydroxide
L	liter
LDA	lithium diisopropylamide
LiOH	lithium hydroxide
M	Molar (mol/L)
MeOH	methanol
MeTHF	methyl tetrahydrofuran
MgSO ₄	magnesium sulfate
min	minute
mL	milliliter
MTBE	Methyl-tert-butylether
μL	microliter

N ₂	nitrogen
n-BuLi	n-Butyllithium
NBS	N-Bromosuccinimide
NCS	N-Chlorosuccinimide
Na ₂ CO ₃	sodium carbonate
NaHCO ₃	sodium bicarbonate
NH ₃	ammonia
NH ₄ Cl	ammonium chloride
NaOH	sodium hydroxide
Na ₂ SO ₄	sodium sulfate
PdCl ₂ (PPh ₃) ₂	Bis(triphenylphosphine)palladium(II) dichloride
Pd(dppf)Cl ₂	1,1'-Bis(diphenylphosphino)ferrocene palladium(II)dichloride
Pd(PPh ₃) ₄	Tetrakis(triphenylphosphine)palladium(0)
PE	petroleum ether
Prep.	preparative
RP	reversed phase
RT/rt	room temperature (about 20°C)
sat.	saturated
SFC	Supercritical Fluid Chromatography
SiO ₂	silica
TEA	triethylamine
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
Xphos Pd G3	(2-Dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II) methanesulfonate

Preparation of intermediates

Synthesis of Intermediate I.1

5 ***tert*-Butyl 4-fluoro-4-(hydrazinecarbonyl)piperidine-1-carboxylate**

1-*tert*-Butyl 4-ethyl 4-fluoropiperidine-1,4-dicarboxylate (160 g, 0.58 mol) is suspended in ethanol (640 mL) in a round-bottom flask. Hydrazine hydrate (70.6 mL, 1.16 mol) is added to the mixture at ambient temperature. The reaction mixture is heated to 50 °C and stirred for 12 h. After cooling to ambient temperature, the mixture is concentrated under reduced pressure to yield *tert*-butyl 4-fluoro-4-(hydrazinecarbonyl)piperidine-1-carboxylate in 80% purity.

$C_{11}H_{20}FN_3O_3$ (M = 261.3 g/mol)

ESI-MS: 284 [M+Na]⁺

Rt (HPLC): 0.62 min (method A)

15

***tert*-Butyl 4-fluoro-4-(4-methyl-4H-1,2,4-triazol-3-yl)piperidine-1-carboxylate**

tert-Butyl 4-fluoro-4-(hydrazinecarbonyl)piperidine-1-carboxylate (135 g, 0.413 mol, 80% purity) is mixed with dioxane (945 mL) in a round-bottom-flask. *N,N*-Dimethylformamid-dimethylacetal (137 mL, 1.03 mol) is added to the mixture at ambient temperature. The reaction mixture is heated to 50 °C and stirred for 1 h. A solution of methylamine (299 g, 30% in EtOH, 2.89 mol) and acetic acid (165 mL, 2.89 mol) are added into the mixture. The resulting reaction mixture is heated to 90 °C and stirred for 11 h. After cooling to ambient temperature, the mixture is concentrated under reduced pressure. The residue is purified by column chromatography (SiO₂, PE/EtOAc gradient 20:1 to 0:1) to obtain *tert*-butyl 4-fluoro-4-(4-methyl-4H-1,2,4-triazol-3-yl)piperidine-1-carboxylate.

$C_{13}H_{21}FN_4O_2$ (M=284.3 g/mol)

ESI-MS: 285 [M+H]⁺

Rt (HPLC): 0.77 min (method A)

25

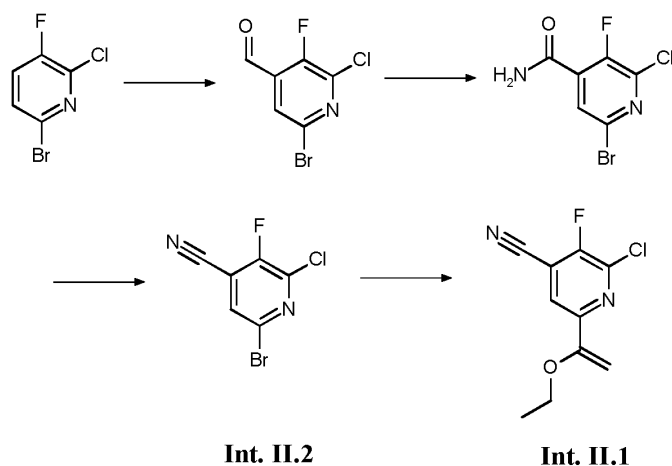
Intermediate I.1: 4-fluoro-4-(4-methyl-4H-1,2,4-triazol-3-yl)piperidine

tert-Butyl 4-fluoro-4-(4-methyl-4H-1,2,4-triazol-3-yl)piperidine-1-carboxylate (90 g, 0.32 mol) is combined with methanol (90 mL) in a round-bottom flask. A solution of HCl (4 M in MeOH, 450 mL, 1.8 mol) is added slowly at ambient temperature. The resulting reaction mixture is stirred at ambient temperature for 12 h. The desired product is collected by filtration, washed with methanol, and dried to yield 4-fluoro-4-(4-methyl-4H-1,2,4-triazol-3-yl)piperidine hydrochloride salt.

The hydrochloride salt (13.5 g) is added to a solution of ammonia in methanol (7 M, 150 mL) and purified by column chromatography (Biotage SNAP Cartridge KP-NH 110 g, gradient DCM/MeOH 4:1 to 7:3) to afford the title compound.

$C_8H_{13}FN_4$ (M=184.2 g/mol)
ESI-MS: 185 [M+H]⁺
Rt (HPLC): 0.20 min (method B)

4-(4-Methyl-4H-1,2,4-triazol-3-yl)piperidine (MFCD09055373, CAS: 297172-18-0) is obtained from a commercial vendor.

Synthesis of Intermediate II.1 and II.2**6-Bromo-2-chloro-3-fluoropyridine-4-carbaldehyde**

Under an argon atmosphere, 6-bromo-2-chloro-3-fluoropyridine (6.80 g, 30.7 mmol) is added to THF (30 mL), and the resulting mixture is cooled to -75 °C. A solution of lithium diisopropylamide (1 M in THF, 30.7 mL, 30.7 mmol) is added dropwise, and the mixture is stirred for 1 h at -75 °C. DMF (2.83 mL, 36.8 mmol) is added dropwise. The mixture is

stirred for additional 2 h at -78°C . The reaction is quenched by addition of acetic acid (2.64 mL) and diluted with water/brine 1/1 and ethyl acetate and allowed to warm to ambient temperature. The organic phase is separated, dried over Na_2SO_4 , and concentrated. The residue is purified by column chromatography (SiO_2 , CyH/EtOAc gradient 1:0 to 1:1) to yield 6-bromo-2-chloro-3-fluoropyridine-4-carbaldehyde.

$\text{C}_6\text{H}_2\text{BrClFNO}$ (M=238.4 g/mol)
ESI-MS: mass not detected
Rt (HPLC): 0.44 min (method B)

10 **6-Bromo-2-chloro-3-fluoropyridine-4-carboxamide**

Ammonium acetate (12.0 g, 15.5 mmol) and 6-Bromo-2-chloro-3-fluoropyridine-4-carbaldehyde (3.70 g, 15.5 mmol) are mixed, and acetonitrile (50 mL) is added. Phenyltrimethylammonium tribromide (12.0 g, 31.0 mmol) is added in small portions, and the resulting reaction mixture is stirred for 16 h at ambient temperature. The mixture is filtered, and the residue is washed with acetonitrile, purified by column chromatography (dry load, SiO_2 , CyH/EtOAc gradient 1:0 to 1:1) to yield the desired product.

$\text{C}_6\text{H}_3\text{BrClFN}_2\text{O}$ (M=253.5 g/mol)
ESI-MS: 251 / 253 $[\text{M}-\text{H}]^-$
Rt (HPLC): 0.41 min (method B)

20

Intermediate II.2: 6-Bromo-2-chloro-3-fluoropyridine-4-carbonitrile

6-Bromo-2-chloro-3-fluoropyridine-4-carboxamide (510 mg, 2.01 mmol) is suspended in dichloromethane (10 mL), and Burgess reagent (CAS: 29684-56-8, 742 mg, 3.02 mmol) is added at ambient temperature. The resulting reaction mixture is stirred for 16 h and then directly purified by column chromatography (SiO_2 , CyH/EtOAc gradient 1:0 to 9:1) to yield the title compound.

$\text{C}_6\text{HBrClFN}_2$ (M=235.4 g/mol)
ESI-MS: no mass detected
Rt (HPLC): 0.61 min (method B)

30 ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 8.45 (d, $J=3.8$ Hz, 1 H).

Intermediate II.1: 2-Chloro-6-(1-ethoxyethenyl)-3-fluoropyridine-4-carbonitrile

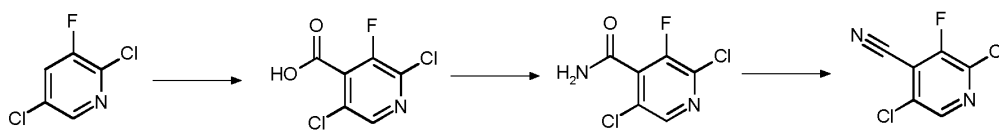
Under an argon atmosphere, Int. II.3 (50.0 mg, 0.21 mmol) and tributyl(1-ethoxyethenyl)stannane (87.9 μ L, 0.23 mmol) are suspended in 1,4-dioxane (0.5 mL). Then, [1,1'-Bis-(diphenylphosphino)-ferrocen]-dichloro-palladium(II) (Pd(dppf)Cl₂, CAS: 72287-26-4) (15.5 mg, 0.02 mmol) is added, and the mixture is further degassed for 5 min. The reaction mixture is heated at 70 °C for 10 h. The mixture is concentrated and the residue is purified by column chromatography (dry load, SiO₂, CyH/EtOAc gradient 1:0 to 9:1) to yield the title compound.

C₁₀H₈ClFN₂O (M=226.6 g/mol)

ESI-MS: no mass detected

Rt (HPLC): 0.80 min (method B)

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.08 (d, *J*=4.1 Hz, 1 H), 5.31 (d, *J*=2.3 Hz, 1 H), 4.62 (d, *J*=2.3 Hz, 1 H), 3.97 (q, *J*=6.8 Hz, 2 H), 1.38 (t, *J*=7.0 Hz, 3 H).

Synthesis of Intermediate II.4**Int. II.4****2,5-Dichloro-3-fluoropyridine-4-carboxylic acid**

To a mixture of 2,5-dichloro-3-fluoropyridine (10.00 g, 60.2 mmol) and DIPA (7.5 mL, 66.3 mmol) in THF (100 mL) is added *n*-BuLi (5.7 mL, 60.2 mmol) at -70 °C under N₂. The mixture is stirred at -70 °C for 2 h. Then freshly crushed solid CO₂ (13.3 g, 301 mmol) is added portion wise at -70 °C. The resulting mixture is stirred at 25 °C for 12 h. The reaction mixture is quenched by addition of NH₄Cl (500 mL), diluted with H₂O (500 mL), and extracted with EtOAc (2 x 500 mL). The combined organic layers are washed with brine (200 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue is purified by column chromatography (SiO₂, PE/EtOAc gradient 1:0 to 0:1) to afford 2,5-dichloro-3-fluoropyridine-4-carboxylic acid.

C₆H₂Cl₂FNO₂ (M=210.0 g/mol)

ESI-MS: 210 [M+H]⁺

Rt (HPLC): 0.26 min (method D)

2,5-Dichloro-3-fluoropyridine-4-carboxamide

To a mixture of 2,5-dichloro-3-fluoropyridine-4-carboxylic acid (6.00 g, 28.6 mmol) in DCM (60 mL) is added oxalyl chloride (21.8 g, 171 mmol) under N₂ at 0 °C. After 2 h, the reaction mixture is concentrated under reduced pressure, and the residue is suspended in DCM (60 mL). Then the reaction mixture is poured slowly into NH₃/H₂O (50 mL) and stirred at 25 °C for 12 h. The reaction mixture is filtered and concentrated under reduced pressure to afford 2,5-dichloro-3-fluoropyridine-4-carboxamide.

C₆H₃Cl₂FN₂O (M=209.0 g/mol)

ESI-MS: no mass detected

Rt (HPLC): 0.40 min (method D)

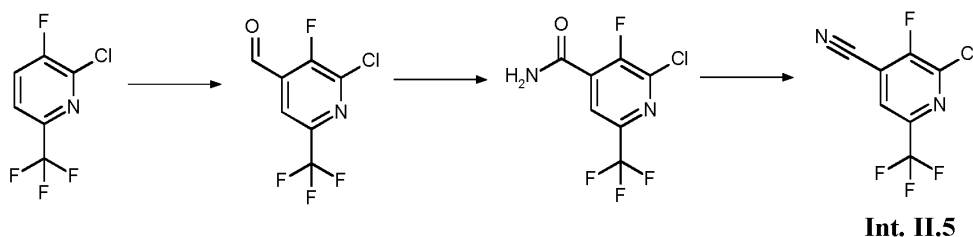
Intermediate II.4: 2,5-dichloro-3-fluoropyridine-4-carbonitrile

To a mixture of 2,5-dichloro-3-fluoropyridine-4-carboxamide (3.00 g, 14.4 mmol) in DCM (30 mL) is added TEA (3.19 g, 31.6 mmol) and TFAA (3.32 g, 15.8 mmol) under N₂ at 0 °C. The mixture is stirred at 10 °C for 2 h. The reaction mixture is diluted with H₂O (100 mL) and extracted with EtOAc (2 x 100 mL). The combined organic layers are washed with brine (100 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue is purified by column chromatography (SiO₂, PE/EtOAc gradient 1:0 to 3:1) to afford the title compound.

C₆HCl₂FN₂ (M=191.0 g/mol)

ESI-MS: 190 [M-H]-

Rt (GCMS): 6.40 min (method E)

Synthesis of Intermediate II.5**2-Chloro-3-fluoro-6-(trifluoromethyl)pyridine-4-carbaldehyde**

Under an argon atmosphere, 2-chloro-3-fluoro-6-(trifluoromethyl)pyridine (14.2 g, 69.7 mmol) is added to THF (330 mL), and the resulting mixture is cooled to -75 °C. A solution of lithium diisopropylamide (1 M in THF, 77.0 mL, 77.0 mmol) is added dropwise in a

period of 90 min, and the mixture is stirred for 60 min at -75°C . DMF (6.44 mL, 83.7 mmol) is added dropwise. The mixture is stirred for additional 30 min at -75°C . The reaction is quenched by addition of a half concentrated acetic acid (40 mL) and diluted with water and EtOAc. The organic phase is separated, washed with brine, dried, and concentrated. The residue is purified by column chromatography (SiO_2 , CyH/EtOAc gradient 100:0 to 85:15) to yield the desired compound.

$\text{C}_7\text{H}_2\text{ClF}_4\text{NO}$ (M=227.5 g/mol)
EI-MS: 227 M^{*+}
Rt (HPLC): 0.48 min (method B)

10

2-Chloro-3-fluoro-6-(trifluoromethyl)pyridine-4-carboxamide

Ammonium acetate (47.1 g, 611 mmol) and 2-chloro-3-fluoro-6-(trifluoromethyl)pyridine-4-carbaldehyde (13.9 g, 61.1 mmol) are mixed, and acetonitrile (300 mL) is added. Phenyltrimethylammonium tribromide (47.4 g, 122 mmol) is added in small portions, and the resulting reaction mixture is stirred at ambient temperature for 16 h. The mixture is filtered through a pad of silica, and the residue is washed with acetonitrile, purified by column chromatography (SiO_2 , CyH/EtOAc gradient 1:0 to 7:3) to yield the desired product.

$\text{C}_7\text{H}_3\text{ClF}_4\text{N}_2\text{O}$ (M=242.6 g/mol)
ESI-MS: 241 $[\text{M}-\text{H}]^-$
Rt (HPLC): 0.47 min (method B)

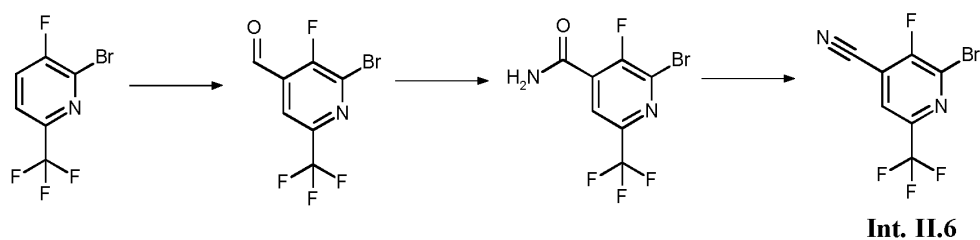
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Intermediate II.6: 2-chloro-3-fluoro-6-(trifluoromethyl)pyridine-4-carbonitrile

The product of the previous step, 2-chloro-3-fluoro-6-(trifluoromethyl)pyridine-4-carboxamide (5.10 g, 21.0 mmol) is suspended in dichloromethane (400 mL), and Burgess reagent (CAS: 29684-56-8, 8.75 g, 35.6 mmol) is added at ambient temperature. The resulting reaction mixture is stirred for 40 h and then directly purified by column chromatography (SiO_2 , CyH/EtOAc gradient 100:0 to 95:5) to yield the title compound.

$\text{C}_7\text{HClF}_4\text{N}_2$ (M=224.5 g/mol)
ESI-MS: 225 $[\text{M}+\text{H}]^+$
Rt (HPLC): 0.57 min (method F)

30

Synthesis of Intermediate II.6**2-Bromo-3-fluoro-6-(trifluoromethyl)pyridine-4-carbaldehyde**

Under an argon atmosphere, 2-bromo-3-fluoro-6-(trifluoromethyl)pyridine (3.08 g, 12.6 mmol) is added to THF (75 mL), and the resulting mixture is cooled to -70°C . A solution of lithium diisopropylamide (1 M in THF, 13.9 mL, 13.9 mmol) is added dropwise, and the mixture is stirred for 90 min at -70°C . DMF (1.17 mL, 15.1 mmol) is added dropwise. The mixture is stirred for additional 30 min at -70°C . The reaction is quenched by addition of a half concentrated acetic acid (800 μL) and diluted with water and EtOAc. The organic phase is separated, dried over MgSO_4 , and concentrated. The residue is purified by column chromatography (SiO_2 , CyH/EtOAc gradient 1:0 to 4:1) to yield 2-bromo-3-fluoro-6-(trifluoromethyl)pyridine-4-carbaldehyde.

$\text{C}_7\text{H}_2\text{BrF}_4\text{NO}$ (M=272.0 g/mol)

ESI-MS: no mass detected

Rt (HPLC): 0.51 min (method B)

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 10.19 (s, 1 H), 8.26 (d, $J=4.3$ Hz, 1 H).

2-Bromo-3-fluoro-6-(trifluoromethyl)pyridine-4-carboxamide

Ammonium acetate (5.53 g, 71.8 mmol) and 2-bromo-3-fluoro-6-(trifluoromethyl)pyridine-4-carbaldehyde (2.17 g, 7.18 mmol) are mixed, and acetonitrile (44 mL) is added. Phenyltrimethylammonium tribromide (5.57 g, 14.4 mmol) is added in small portions, and the resulting reaction mixture is stirred for 72 h at ambient temperature. The mixture is filtered, and the residue is washed with acetonitrile, purified by column chromatography (dry load with Celite®, SiO_2 , CyH/EtOAc gradient 1:0 to 7:3) to yield the desired product.

$\text{C}_7\text{H}_3\text{BrF}_4\text{N}_2\text{O}$ (M=287.0 g/mol)

ESI-MS: 285 / 287 $[\text{M}-\text{H}]^-$

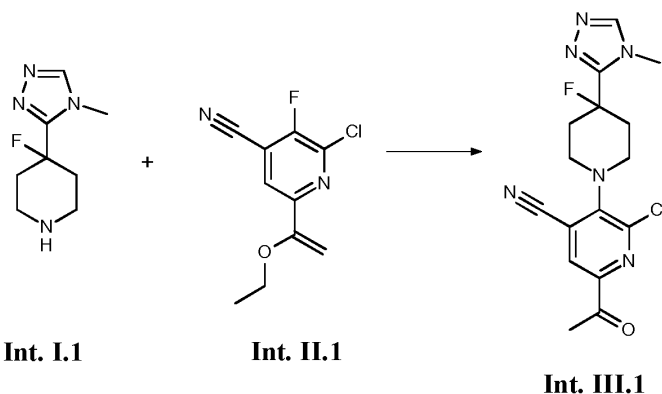
Rt (HPLC): 0.50 min (method B)

Intermediate II.6: 2-bromo-3-fluoro-6-(trifluoromethyl)pyridine-4-carbonitrile

Product of the previous step, 2-bromo-3-fluoro-6-(trifluoromethyl)pyridine-4-carboxamide (975 mg, 3.40 mmol) is suspended in dichloromethane (80 mL), and Burgess reagent (CAS: 29684-56-8, 1.25 g, 5.10 mmol) is added at ambient temperature. The resulting reaction mixture is stirred for 40 h and then directly purified by column chromatography (dry load, SiO₂, CyH/EtOAc gradient 1:0 to 9:1) to yield the title compound.

C₇HBrF₄N₂ (M=268.9 g/mol)
ESI-MS: 268 / 270 [M+H]⁺
Rt (HPLC): 0.59 min (method C)

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Intermediate III.1: 6-acetyl-2-chloro-3-[4-fluoro-4-(4-methyl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]pyridine-4-carbonitrile

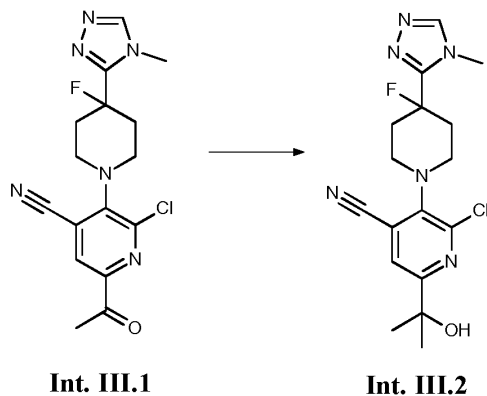
Int. II.1 (481 mg, 2.12 mmol) is suspended in DMSO (2.4 mL) and DIPEA (734 μL, 4.25 mmol). At 15 °C, Int. I.1 (586 mg, 3.18 mmol) is added, and the resulting mixture is stirred at 15 °C for 18 h. The mixture is diluted with water and the formed precipitate is filtered. The residue is diluted with 1,4-dioxane and 4 M HCl in 1,4-dioxane (2.0 mL) and stirred at rt for 3 h. The reaction mixture is concentrated and triturated with a half saturated aqueous K₂CO₃ solution. The formed precipitate is filtered, washed with water and MTBE, and dried to yield the title compound.

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C₁₆H₁₆ClFN₆O (M=362.8 g/mol)
ESI-MS: 363 [M+H]⁺
Rt (HPLC): 0.66 min (method G)

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Intermediate III.2: 2-chloro-3-[4-fluoro-4-(4-methyl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]-6-(2-hydroxypropan-2-yl)pyridine-4-carbonitrile



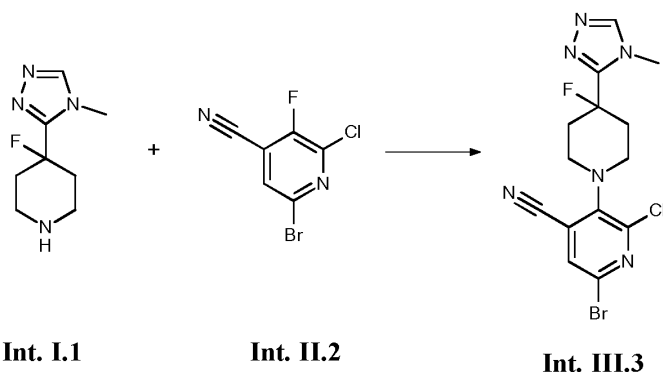
Under an argon atmosphere, Int. III.1 (265 mg, 0.73 mmol) is suspended in THF (4.0 mL).

- 5 Methyl magnesium bromide (3.2 M in MeTHF, 274 μ L, 0.88 mmol) is added dropwise at ambient temperature and the reaction mixture is stirred at rt for 3 h. The reaction mixture is quenched by the addition of water (100 μ L), concentrated, and purified by preparative HPLC (XBridge C18, acetonitrile/water gradient containing 0.1% TFA) to afford the desired compound.

- 10 $C_{17}H_{20}ClFN_6O$ (M=378.8 g/mol)
ESI-MS: 379 [M+H]⁺
Rt (HPLC): 0.56 min (method B)

Intermediate III.3: 6-bromo-2-chloro-3-[4-fluoro-4-(4-methyl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]pyridine-4-carbonitrile

- 15



Int. II.2 (1.00 g, 4.25 mmol) is suspended in DMSO (4.0 mL) and DIPEA (1.47 mL, 8.50 mmol). At 15 °C, Int. I.1 (900 mg, 4.89 mmol) is added, and the resulting mixture is stirred

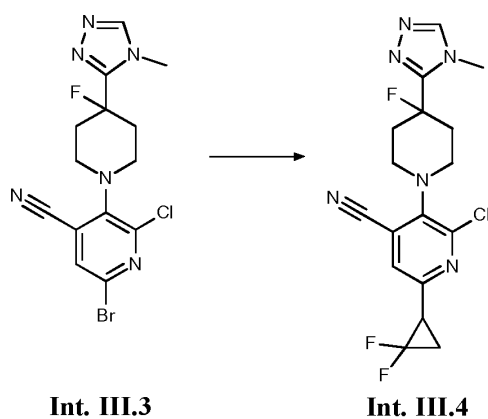
at 15 °C for 2 h. The mixture is diluted with ACN/water and purified by preparative HPLC (Sunfire C18, acetonitrile/water gradient containing 0.1% TFA) to afford the desired compound.

$C_{14}H_{13}BrClFN_6$ (M=399.6 g/mol)

5 ESI-MS: 399 / 401 $[M+H]^+$

Rt (HPLC): 0.75 min (method G)

Intermediate III.4: 2-chloro-6-(2,2-difluorocyclopropyl)-3-[4-fluoro-4-(4-methyl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]pyridine-4-carbonitrile



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Under an argon atmosphere, Int. III.3 (150 mg, 0.36 mmol, 95 % purity) and (2,2-difluorocyclopropyl)boronic acid (200 mg, 1.59 mmol, 97 % purity) are suspended in 1,4-dioxane (3 mL). K_2CO_3 (aq. 2 M, 535 μ L, 1.07 mmol) is added, and the resulting mixture is degassed for 10 min by passing an argon stream through the mixture. [1,1'-Bis-

15 (diphenylphosphino)-ferrocen]-dichloro-palladium(II) ($Pd(dppf)Cl_2$) (26.1 mg, 0.04 mmol) is added, and the mixture is degassed again for 5 min. The mixture is then heated to 70 °C for 12 h. After cooling to ambient temperature, the mixture is purified by preparative HPLC (Sunfire C18, ACN/water gradient containing 0.1% TFA) to yield the title compound.

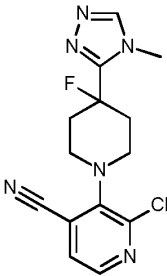
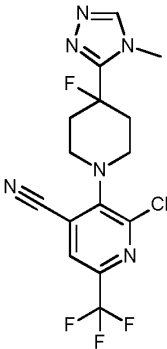
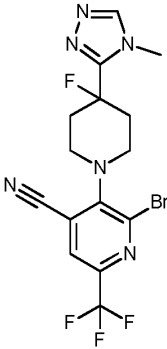
$C_{17}H_{16}ClF_3N_6$ (M=396.8 g/mol)

20 ESI-MS: 397 $[M+H]^+$

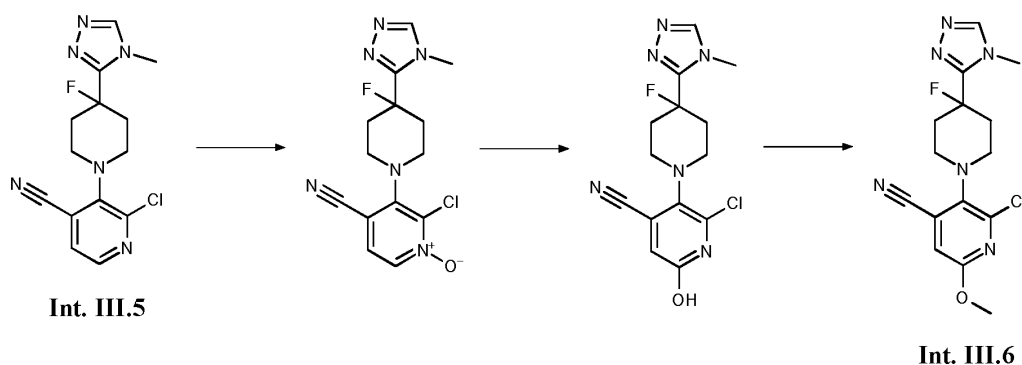
Rt (HPLC): 0.56 min (method F)

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Intermediates synthesized analogous to the procedure described for Int. III.3

Int.	Starting material	Structure	Deviation from general procedure	Molecular Formula (MW) ESI-MS HPLC retention time (method)
III.5	Int. I.1 + 2-chloro-3-fluoropyridine-4-carbonitrile		3 h @ 10 °C 20 h @ rt	C ₁₄ H ₁₄ ClFN ₆ (M=320.8 g/mol) ESI-MS: 321 [M+H] ⁺ Rt (HPLC): 0.43 min (method F)
III.9	Int. I.1 + Int. II.5		15 min @ rt purification by preparative HPLC (XBridge C18, acetonitrile/water gradient containing 0.1% NH ₃)	C ₁₅ H ₁₃ ClF ₄ N ₆ (M=388.8 g/mol) ESI-MS: 389 / 391 [M+H] ⁺ Rt (HPLC): 0.59 min (method B)
III.10	Int. I.1 + Int. II.6		1.5 h @ 15 °C purification by preparative HPLC (XBridge C18, acetonitrile/water gradient containing 0.1% NH ₃)	C ₁₅ H ₁₃ BrF ₄ N ₆ (M=433.2 g/mol) ESI-MS: 433 / 435 [M+H] ⁺ Rt (HPLC): 0.54 min (method F)

Synthesis of Intermediate III.6



2-Chloro-4-cyano-3-[4-fluoro-4-(4-methyl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]pyridin-1-ium-1-olate

- 5 Int. III.5 (500 mg, 1.56 mmol) is suspended in DCM (25 mL). H₂O₂ (30 %, 530 mg, 4.68 mmol) and TFA (355 mg, 3.12 mmol) are added, and the reaction mixture is stirred at rt for 18 h. Still starting material left. Three times the same amounts of H₂O₂ and TFA are added and the reaction mixture is stirred at rt for 90 h. The reaction mixture is diluted with water (5 mL) and the DCM is concentrated. The residue is purified by preparative HPLC (XBridge
- 10 C18, ACN/water gradient containing 0.1% TFA). The desired fractions are combined, the ACN is concentrated, and the aqueous residue is basified with K₂CO₃. The formed precipitate is filtered, washed with water, and dried to afford the desired compound.

C₁₄H₁₄ClFN₆O (M=336.8 g/mol)

ESI-MS: 337 / 339 [M+H]⁺

- 15 Rt (HPLC): 0.33 min (method B)

2-Chloro-3-[4-fluoro-4-(4-methyl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]-6-hydroxypyridine-4-carbonitrile

- 2-Chloro-4-cyano-3-[4-fluoro-4-(4-methyl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]pyridin-1-ium-1-olate (100 mg, 0.30 mmol) is suspended in THF (4 mL). Trifluoroacetic anhydride (124 μL, 0.89 mmol) is added, and the reaction mixture is stirred at 60 °C for 18 h. The reaction mixture is quenched by the addition of a saturated aqueous solution of K₂CO₃. The THF is concentrated, and the aqueous residue is stirred at rt for 0.5 h. The reaction mixture is concentrated, and the residue is purified by preparative HPLC (XBridge C18, ACN/water
- 20 gradient containing 0.1% NH₃) to afford the desired compound.
- 25

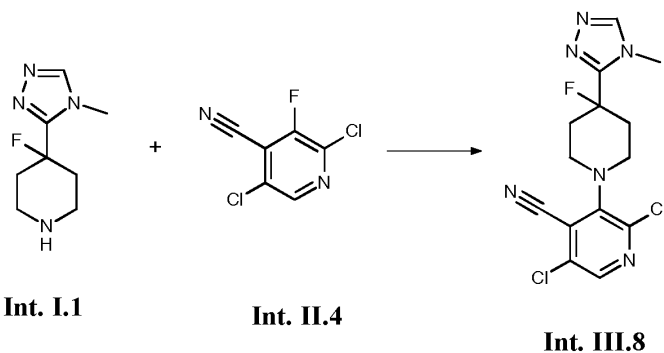
$C_{14}H_{14}ClFN_6O$ (M=336.8 g/mol)
 ESI-MS: 337 $[M+H]^+$
 Rt (HPLC): 0.22 min (method B)

5 **Intermediate III.6: 2-chloro-3-[4-fluoro-4-(4-methyl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]-6-methoxypyridine-4-carbonitrile**

2-Chloro-3-[4-fluoro-4-(4-methyl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]-6-hydroxypyridine-4-carbonitrile (63.0 mg, 0.19 mmol) is suspended in chloroform (5 mL), silver carbonate (77.4 mg, 0.28 mmol) and methyl iodide (115 mg, 0.81 mmol) are added, and the reaction mixture is stirred at rt for 2 d. The reaction mixture is concentrated, diluted with ACN, filtered, and purified by preparative HPLC (XBridge C18, ACN/water gradient containing 0.1% NH_3) to afford the desired compound.

$C_{15}H_{16}ClFN_6O$ (M=350.8 g/mol)
 ESI-MS: 351 / 353 $[M+H]^+$
 15 Rt (HPLC): 0.56 min (method B)

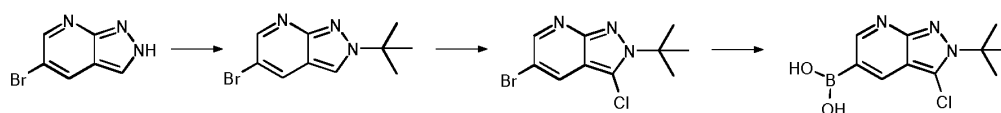
Intermediate III.8: 2,5-dichloro-3-[4-fluoro-4-(4-methyl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]pyridine-4-carbonitrile



20 Int. II.7 (0.17 g, 0.89 mmol) in DMF (5 mL) is added Int. I.1 (0.96 g, 5.21 mmol) and K_2CO_3 (2.40 g, 22.7 mmol). The mixture is stirred at 100 °C for 10 h. The reaction mixture is diluted with H_2O (100 mL) and extracted with EtOAc (2 x 200 mL). The combined organic layers are washed with brine (100 mL), dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. The residue is purified by column chromatography (SiO_2 , PE/EtOAc gradient 1:0 to 0:1) and by preparative HPLC (Agela DuraShell C18, ACN/water gradient containing 10 mM NH_4HCO_3) to yield the title compound.

$C_{14}H_{13}Cl_2FN_6$ (M=355.2 g/mol)
 ESI-MS: 355 / 357 [M+H]⁺
 Rt (HPLC): 2.27 min (method H)

5 Synthesis of Intermediate IV.1



Int. IV.1

5-Bromo-2-tert-butyl-2H-pyrazolo[3,4-b]pyridine

5-Bromo-2H-pyrazolo[3,4-b]pyridine (8.00 g, 39.6 mmol) is suspended in toluene (50 mL), and *tert*-butyl acetate (53.1 mL, 396 mmol). Methanesulfonic acid (2.60 mL, 39.6 mmol) is added. The resulting reaction mixture is heated to 80 °C and stirred for 1 h. After cooling to ambient temperature, additional methanesulfonic acid (2.60 mL, 39.6 mmol) is added, and the reaction mixture is heated to 80 °C and stirred for 1 h. After cooling to ambient temperature, the reaction mixture is concentrated, and the residue is diluted with DCM. The mixture is basified by the addition of 1 M NaOH. The layers are separated, and the aq. layer is extracted with DCM. The combined organic layers are washed with H₂O, dried over Na₂SO₄, filtered, and concentrated. The residue is purified by column chromatography (SiO₂, CyH/EtOAc gradient 9:1 to 0:10) to afford the desired compound.

$C_{10}H_{12}BrN_3$ (M=254.1 g/mol)
 ESI-MS: 254 / 256 [M+H]⁺
 Rt (HPLC): 0.85 min (method C)

5-Bromo-2-tert-butyl-3-chloro-2H-pyrazolo[3,4-b]pyridine

To a mixture of 5-bromo-2-tert-butyl-2H-pyrazolo[3,4-b]pyridine (4.00 g, 14.2 mmol) in ACN (40 mL) is added NCS (2.08 g, 15.6 mmol) at 20 °C under N₂. The mixture is stirred at 85 °C for 12 h. The reaction mixture is concentrated under reduced pressure to remove solvent. The residue is diluted with H₂O (20 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layers are dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue is purified by column chromatography (SiO₂, PE/EtOAc gradient 1:0 to 0:1) to afford the desired compound.

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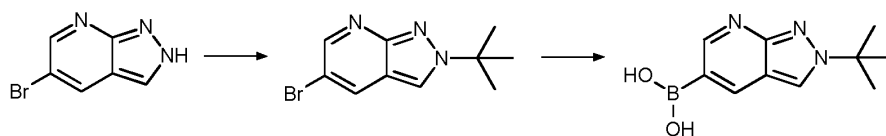
$C_{10}H_{11}BrClN_3$ (M=288.6 g/mol)
 ESI-MS: 288 / 290 $[M+H]^+$
 Rt (HPLC): 0.55 min (method I)

5 **Intermediate IV.1: {2-Tert-butyl-3-chloro-2H-pyrazolo[3,4-b]pyridin-5-yl}boronic acid**

To a mixture of 5-bromo-2-tert-butyl-3-chloro-2H-pyrazolo[3,4-b]pyridine (3.00 g, 9.36 mmol) in 1,4-dioxane (60 mL) is added 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (3.09 g, 12.2 mmol), KOAc (2.75 g, 28.1 mmol) and Pd(dppf)Cl₂ (0.68 g, 0.94 mmol) under N₂. The mixture is stirred at 100 °C under N₂ for 12 h. The reaction mixture is diluted with H₂O (40 mL) and extracted with EtOAc (2 x 40 mL). The combined organic layers are washed with brine (20 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue is purified by column chromatography (SiO₂, PE/EtOAc gradient 1:0 to 1:1) to afford the title compound.

15 $C_{10}H_{13}BClN_3O_3$ (M=253.5 g/mol)
 ESI-MS: 254 / 256 $[M+H]^+$
 Rt (HPLC): 0.33 min (method I)

Synthesis of Intermediate IV.2



Int. IV.2

20 **5-Bromo-2-tert-butyl-2H-pyrazolo[3,4-b]pyridine**

5-Bromo-2H-pyrazolo[3,4-b]pyridine (4.0 g, 19.8 mmol) is suspended in toluene (23 mL), and *tert*-butyl acetate (26.6 mL, 198 mmol) is added. Methanesulfonic acid (1.3 mL, 19.8 mmol) is added slowly. The resulting reaction mixture is heated to 80 °C and stirred for 1 h. After cooling to ambient temperature, additional methanesulfonic acid (1.3 mL, 19.8 mmol) is added, and the reaction mixture is heated to 80 °C and stirred for 1 h. After cooling to ambient temperature, the reaction mixture is concentrated and purified by preparative HPLC (XBridge C18, ACN/water gradient containing 0.1% TFA) to yield the 5-bromo-2-*tert*-butyl-2H-pyrazolo[3,4-b]pyridine.

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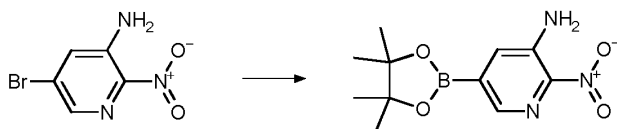
$C_{10}H_{12}BrN_3$ (M=254.1 g/mol)
 ESI-MS: 254 / 256 $[M+H]^+$
 Rt (HPLC): 0.50 min (method F)

5 **Intermediate IV.2: {2-tert-butyl-2H-pyrazolo[3,4-b]pyridin-5-yl}boronic acid**

5-Bromo-2-*tert*-butyl-2H-pyrazolo[3,4-b]pyridine (1.50 g, 3.87 mmol), bis(pinacolato)diborane (1.21 g, 4.78 mmol), and potassium acetate (763 mg, 7.77 mmol) are added to 1,4-dioxane (15 mL), and the resulting mixture is degassed by passing an argon stream through the mixture for 10 min. [1,1'-Bis-(diphenylphosphino)-ferrocen]-dichloro-
 10 palladium(II) dichloromethane complex ($Pd(dppf)Cl_2 \cdot CH_2Cl_2$, CAS: 95464-05-4) (190 mg, 0.232 mmol) is added, and the mixture is degassed for additional 3 min. The mixture is then heated to 110 °C and stirred at this temperature for 4 h. After cooling to ambient temperature, the mixture is concentrated, and the residue is suspended in an ACN/water mixture, filtered, and purified by preparative HPLC (XBridge C18, ACN/water gradient containing 0.1%
 15 TFA) to yield the title compound.

$C_{10}H_{14}BN_3O_2$ (M=219.1 g/mol)
 ESI-MS: 220 $[M+H]^+$
 Rt (HPLC): 0.27 min (method F)

20 **Intermediate IV.3: 2-nitro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-amine**

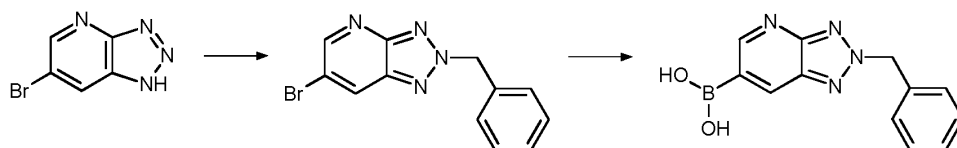


Int. IV.3

Under an argon atmosphere, 5-bromo-2-nitropyridin-3-amine (200 mg, 0.88 mmol, 96 % purity), bis(pinacolato)diborane (300 mg, 1.18 mmol), and potassium acetate (259 mg, 2.64
 25 mmol) are added to 1,4-dioxane (4 mL), and the resulting mixture is degassed by passing an argon stream through the mixture for 15 min. $PdCl_2(PPh_3)_2$ (61.2 mg, 0.09 mmol) is added, and the mixture is heated to 60 °C and stirred at this temperature for 4.5 h. After cooling to ambient temperature, the mixture is diluted with EtOAc, filtered through a pad of Celite, and concentrated. The residue is triturated with MTBE, the formed precipitate is filtered, washed
 30 with MTBE, and dried to yield the title compound.

$C_{11}H_{16}BN_3O_4$ (M=265.1 g/mol)
 ESI-MS: 266 [M+H]⁺
 Rt (HPLC): 0.20 min (method F)

5 Synthesis of Intermediate IV.4



Int. IV.4

2-Benzyl-6-bromo-2H-[1,2,3]triazolo[4,5-b]pyridine

6-Bromo-1H-[1,2,3]triazolo[4,5-b]pyridine (600 mg, 2.96 mmol) is suspended in DMSO (5 mL) and DIPEA (1.00 mL, 5.91 mmol). Benzyl bromide (359 μ L, 2.96 mmol) is added and the resulting reaction mixture is heated to 90 °C and stirred for 16 h. After cooling to ambient temperature the reaction mixture is purified by preparative HPLC (XBridge C18, ACN/water gradient containing 0.1% NH₃) to yield the desired compound.

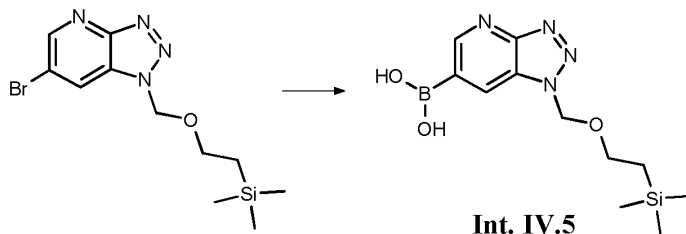
$C_{12}H_9BrN_4$ (M=289.1 g/mol)
 ESI-MS: 289 / 291 [M+H]⁺
 Rt (HPLC): 0.59 min (method F)

Intermediate IV.4: {2-benzyl-2H-[1,2,3]triazolo[4,5-b]pyridin-6-yl}boronic acid

2-Benzyl-6-bromo-2H-[1,2,3]triazolo[4,5-b]pyridine (310 mg, 1.07 mmol), bis(pinacolato)diborane (407 g, 1.61 mmol), and potassium acetate (315 mg, 3.22 mmol) are added to 1,4-dioxane (2 mL), and the resulting mixture is degassed by passing an argon stream through the mixture. PdCl₂(PPh₃)₂ (75.3 mg, 0.11 mmol) is added, and the mixture is heated to 100 °C and stirred at this temperature for 3 h. After cooling to ambient temperature, the mixture is diluted with EtOAc, filtered through a pad of celite, and concentrated. The residue is suspended in an ACN/water mixture, and purified by preparative HPLC (XBridge C18, ACN/water gradient containing 0.1% TFA) to yield the title compound.

$C_{12}H_{11}BN_4O_2$ (M=254.1 g/mol)
 ESI-MS: 255 [M+H]⁺
 Rt (HPLC): 0.41 min (method F)

Intermediate IV.5: (1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-[1,2,3]triazolo[4,5-b]pyridin-6-yl)boronic acid



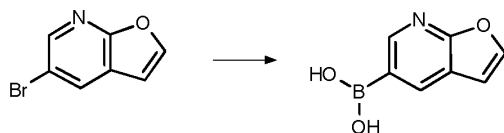
Under an argon atmosphere, 6-bromo-1-([2-(trimethylsilyl)ethoxy]methyl)-1H-[1,2,3]triazolo[4,5-b]pyridine (100 mg, 0.30 mmol), bis(pinacolato)diborane (231 mg, 0.91 mmol), and potassium acetate (116 mg, 1.18 mmol) are added to 1,4-dioxane (2 mL), and the resulting mixture is degassed by passing an argon stream through the mixture for 15 min. $\text{PdCl}_2(\text{PPh}_3)_2$ (21.3 mg, 0.03 mmol) is added, and the mixture is heated to 60 °C and stirred at this temperature for 16 h. After cooling to ambient temperature, the mixture is concentrated, and the residue is suspended in an ACN/water mixture, filtered, and purified by preparative HPLC (XBridge C18, ACN/water gradient containing 0.1% TFA) to yield the title compound.

$\text{C}_{11}\text{H}_{19}\text{BN}_4\text{O}_3\text{Si}$ (M=294.2 g/mol)

ESI-MS: 295 $[\text{M}+\text{H}]^+$

Rt (HPLC): 0.51 min (method F)

Intermediate IV.6: {furo[2,3-b]pyridin-5-yl}boronic acid



Under an argon atmosphere, 5-bromofuro[2,3-b]pyridine (250 mg, 1.20 mmol, 95 % purity), bis(pinacolato)diborane (487 mg, 1.92 mmol), and potassium acetate (459 mg, 4.68 mmol) are added to 1,4-dioxane (5 mL), and the resulting mixture is degassed by passing an argon stream through the mixture for 15 min. $\text{PdCl}_2(\text{PPh}_3)_2$ (105 mg, 0.15 mmol) is added, and the mixture is heated to 60 °C and stirred at this temperature for 16 h. After cooling to ambient temperature, the mixture is diluted with EtOAc, filtered, and concentrated. The residue is

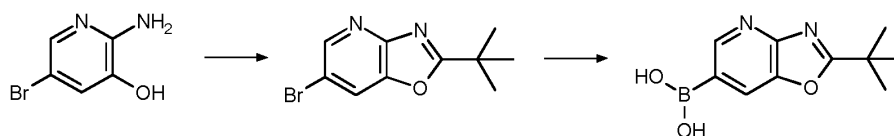
suspended in an ACN/water mixture, and purified by preparative HPLC (Sunfire C18, ACN/water gradient containing 0.1% TFA) to yield the title compound.

$C_7H_6BNO_3$ (M=162.9 g/mol)

ESI-MS: 164 $[M+H]^+$

5 Rt (HPLC): 0.39 min (method G)

Synthesis of Intermediate IV.7



Int. IV.7

6-Bromo-2-tert-butyl-[1,3]oxazolo[4,5-b]pyridine

10 2-Amino-5-bromopyridin-3-ol (200 mg, 1.04 mmol) and pivaloyl chloride (1.48 g, 12.1 mmol) are added in a microwave vial and the resulting reaction mixture is heated to 120 °C in a closed vial and stirred at this temperature for 40 h. After cooling to ambient temperature, the reaction mixture is diluted with DCM and washed with $NaHCO_3$. The organic layer is dried, filtered and concentrated to yield the desired compound.

15 $C_{10}H_{11}BrN_2O$ (M=255.1 g/mol)

ESI-MS: 255 / 257 $[M+H]^+$

Rt (HPLC): 0.59 min (method F)

Intermediate IV.7: {2-tert-butyl-[1,3]oxazolo[4,5-b]pyridin-6-yl}boronic acid

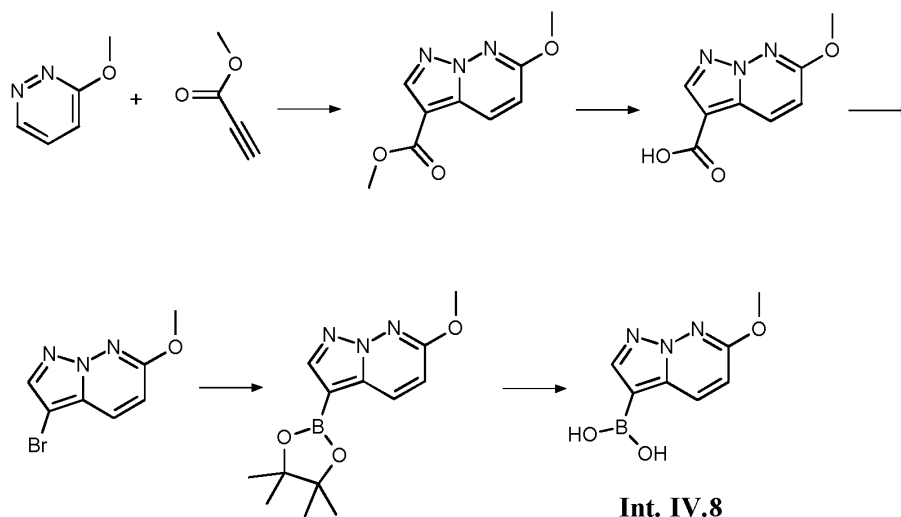
20 Under an argon atmosphere, 6-bromo-2-tert-butyl-[1,3]oxazolo[4,5-b]pyridine (210 mg, 0.82 mmol), bis(pinacolato)diborane (334 mg, 1.32 mmol), and potassium acetate (315 mg, 3.21 mmol) are added to 1,4-dioxane (4 mL), and the resulting mixture is degassed by passing an argon stream through the mixture for 15 min. $PdCl_2(PPh_3)_2$ (72.2 mg, 0.10 mmol) is added, and the mixture is heated to 60 °C and stirred at this temperature for 90 h. After
25 cooling to ambient temperature, the mixture is diluted with EtOAc, filtered, and concentrated. The residue is suspended in an ACN/water mixture, and purified by preparative HPLC (Sunfire C18, ACN/water gradient containing 0.1% TFA) to yield the title compound.

$C_{10}H_{13}BN_2O_3$ (M=220.0 g/mol)

30 ESI-MS: 221 $[M+H]^+$

Rt (HPLC): 0.39 min (method F)

Synthesis of Intermediate IV.8



5 Methyl 6-methoxypyrazolo[1,5-b]pyridazine-3-carboxylate

To a mixture of hydroxylamine-O-sulfonic acid (17.0 g, 150 mmol) in H₂O (50 mL) is added NaHCO₃ aq. (100 mL) to adjust pH to 6 and heated the temperature up to 70 °C. Then 3-methoxypyridazine (5.00 g, 45.4 mmol) is added to the mixture. The mixture is stirred at 70 °C for 2 h. After cooling the reaction to 25 °C, the pH is adjusted to 8. A suspension of methyl prop-2-ynoate (6.30 g, 74.9 mmol) and KOH (10.0 g, 178 mmol) in DCM (50 mL) is added to the mixture. The resulting mixture is stirred at 25 °C for 12 h. The reaction mixture is diluted with H₂O (200 mL) and extracted with EtOAc (2 x 200 mL). The combined organic layers are washed with brine (100 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue is purified by column chromatography (SiO₂, PE/EtOAc gradient 1:0 to 1:1) to afford the desired compound.

C₉H₉N₃O₃ (M=207.2 g/mol)

ESI-MS: 208 [M+H]⁺

Rt (HPLC): 0.53 min (method D)

20 6-Methoxypyrazolo[1,5-b]pyridazine-3-carboxylic acid

To a mixture of methyl 6-methoxypyrazolo[1,5-b]pyridazine-3-carboxylate (10.0 g, 48.3 mmol) in THF (20 mL) is added LiOH (4.05 g, 96.5 mmol) and H₂O (10 mL). The mixture is stirred at 25 °C for 12 h. The reaction mixture is diluted with H₂O (100 mL) and extracted

with EtOAc (2 x 200 mL). The aqueous phase is adjusted to pH 1, the formed precipitate is filtered and concentrated to yield the titled compound.

$C_8H_7N_3O_3$ (M=193.2 g/mol)

ESI-MS: 194 $[M+H]^+$

5 Rt (HPLC): 0.41 min (method D)

3-Bromo-6-methoxypyrazolo[1,5-b]pyridazine

To a mixture of 6-methoxypyrazolo[1,5-b]pyridazine-3-carboxylic acid (8.00 g, 41.4 mmol) in DMF (80 mL) is added NBS (14.7 g, 82.8 mmol). The mixture is stirred at 25 °C for 16

10 h. The reaction mixture is diluted with H₂O (200 mL) and extracted with EtOAc (2 x 200 mL). The combined organic layers are washed with brine (100 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue is purified by column chromatography (SiO₂, PE/EtOAc gradient 1:0 to 3:1) to afford the desired compound.

$C_7H_6BrN_3O$ (M=228.0 g/mol)

15 ESI-MS: 228 / 230 $[M+H]^+$

Rt (HPLC): 0.63 min (method D)

6-Methoxy-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazolo[1,5-b]pyridazine

To a mixture of 3-bromo-6-methoxy-pyrazolo[1,5-b]pyridazine (8.00 g, 29.8 mmol, 85 %
20 purity) in 1,4-dioxane (80 mL) is added bis(pinacolato)diborane (11.4 g, 44.7 mmol), potassium acetate (17.8 g, 107 mmol) and Pd(PPh₃)₄ (3.45 g, 2.98 mmol) under N₂. The mixture is stirred at 100 °C for 12 h. After cooling to ambient temperature, the reaction mixture is diluted with H₂O (100 mL) and extracted with EtOAc (2 x 200 mL). The combined organic layers are washed with brine (100 mL), dried over Na₂SO₄, filtered, and
25 concentrated under reduced pressure. The residue is purified by column chromatography (SiO₂, PE/EtOAc gradient 1:0 to 3:1) to afford the desired compound.

$C_{13}H_{18}BN_3O_3$ (M=275.1 g/mol)

ESI-MS: 276 $[M+H]^+$

Rt (HPLC): 0.73 min (method D)

30

Intermediate IV.8: {6-methoxypyrazolo[1,5-b]pyridazin-3-yl}boronic acid

To a mixture of 6-methoxy-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazolo[1,5-b]pyridazine (7.00 g, 10.2 mmol, 40 % purity) in MeOH (50 mL) is added HCl (5 mL). The

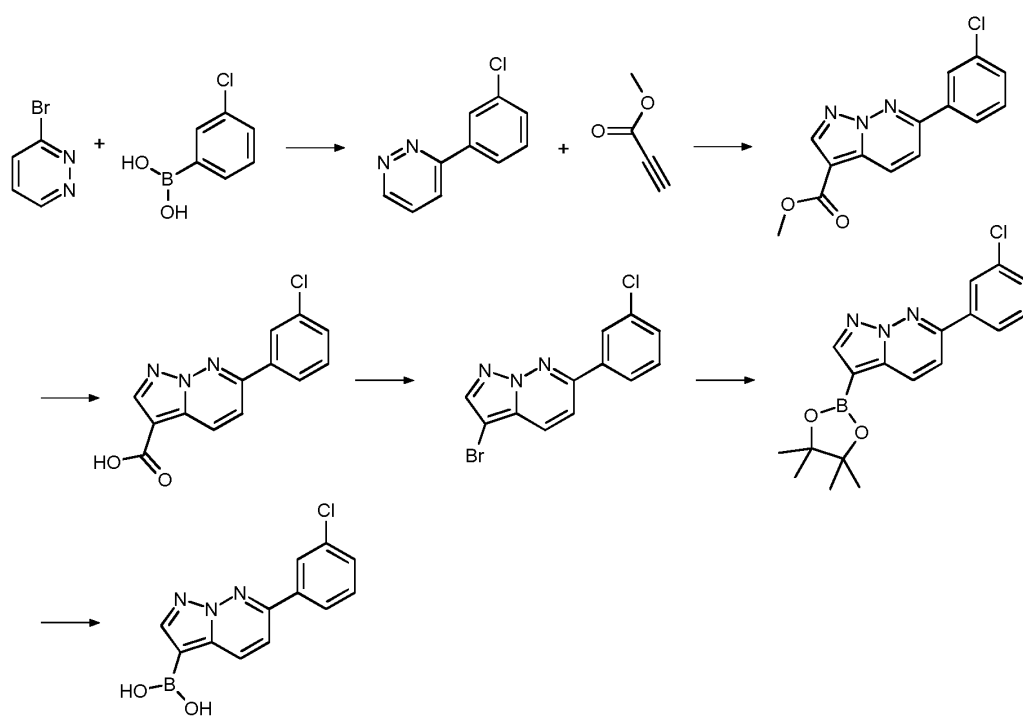
mixture is stirred at 25 °C for 5 h. The reaction mixture is filtered and concentrated under reduced pressure to afford the desired compound.

$C_7H_8BN_3O_3$ (M=193.0 g/mol)

ESI-MS: 194 $[M+H]^+$

5 Rt (HPLC): 1.47 min (method J)

Synthesis of Intermediate IV.9



Int. IV.9

3-(3-Chlorophenyl)pyridazine

10 To a mixture of 3-bromopyridazine (30.0 g, 147 mmol, 78 % purity) in 1,4-dioxane (300 mL) and H₂O (30 mL) is added (3-chlorophenyl)boronic acid (29.9 g, 191 mmol), KOAc (43.3 g, 442 mmol) and Pd(dppf)Cl₂ * DCM (6.01 g, 7.36 mmol) under N₂. The mixture is stirred at 100 °C for 12 h. After cooling to ambient temperature, the reaction mixture is diluted with H₂O (200 mL) and extracted with EtOAc (2 x 300 mL). The combined organic

15 layers are washed with brine (100 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue is purified by column chromatography (SiO₂, PE/EtOAc gradient 1:0 to 3:1) to afford the desired compound.

$C_{10}H_7ClN_2$ (M=190.6 g/mol)

ESI-MS: 191 [M+H]⁺
Rt (HPLC): 0.53 min (method D)

Methyl 6-(3-chlorophenyl)pyrazolo[1,5-b]pyridazine-3-carboxylate

5 To a mixture of hydroxylamine-O-sulfonic acid (32.3 g, 285 mmol) in H₂O (200 mL) is added NaHCO₃ (200 mL) to adjust pH to 6 and heated the temperature up to 70 °C. Then 3-(3-chlorophenyl)pyridazine (35.0 g, 184 mmol) is added to the mixture. The mixture is stirred at 70 °C for 2 h. After cooling the reaction to 25 °C, the pH is adjusted to 7. Methyl prop-2-ynoate (4.00 g, 47.6 mmol) in DCM (100 mL) is added to the mixture. The
10 resulting mixture is stirred at 25 °C for 12 h. The reaction mixture is diluted with H₂O (500 mL) and extracted with EtOAc (2 x 1000 mL). The combined organic layers are washed with brine (500 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue is purified by column chromatography (SiO₂, PE/EtOAc gradient 1:0 to 2:1) to afford the desired compound.

15 C₁₄H₁₀ClN₃O₂ (M=287.7 g/mol)
ESI-MS: 288 [M+H]⁺
Rt (HPLC): 0.78 min (method D)

6-(3-Chlorophenyl)pyrazolo[1,5-b]pyridazine-3-carboxylic acid

20 To a mixture of methyl 6-(3-chlorophenyl)pyrazolo[1,5-b]pyridazine-3-carboxylate (5.00 g, 10.4 mmol, 60 % purity) in THF (50 mL) is added LiOH (0.88 g, 20.9 mmol) and H₂O (30 mL). The mixture is stirred at 25 °C for 5 h. The reaction mixture is diluted with H₂O (100 mL) and extracted with EtOAc (2 x 200 mL). The aqueous phase is adjusted to pH 1. Then the aqueous phase is extracted with EtOAc (2 x 200 mL). The combined organic
25 layers are washed with brine (200 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to afford the desired compound.

C₁₃H₈ClN₃O₂ (M=273.7 g/mol)
ESI-MS: 274 [M+H]⁺
Rt (HPLC): 0.64 min (method D)

30

3-Bromo-6-(3-chlorophenyl)pyrazolo[1,5-b]pyridazine

To a mixture of 6-(3-chlorophenyl)pyrazolo[1,5-b]pyridazine-3-carboxylic acid (1.60 g, 5.44 mmol, 93 % purity) in DMF (15 mL) is added NBS (1.94 g, 10.9 mmol). The mixture

is stirred at 25 °C for 12 h. The reaction mixture is diluted with H₂O (50 mL) and extracted with EtOAc (2 x 100 mL). The combined organic layers are washed with brine (50 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue is purified by column chromatography (SiO₂, PE/EtOAc gradient 1:0 to 1:1) to afford the
5 desired compound.

C₁₃H₈ClN₃O₂ (M=273.7 g/mol)
ESI-MS: 274 [M+H]⁺
Rt (HPLC): 0.64 min (method D)

10 **6-(3-Chlorophenyl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazolo[1,5-b]pyridazine**

To a mixture of 3-bromo-6-(3-chlorophenyl)pyrazolo[1,5-b]pyridazine (1.00 g, 2.59 mmol, 80 % purity) in 1,4-dioxane (10 mL) is added bis(pinacolato)diborane (3.95 g, 15.6 mmol), potassium acetate (0.91 g, 9.33 mmol) and Pd(PPh₃)₄ (0.60 g, 0.519 mmol) under N₂. The
15 mixture is stirred at 100 °C for 12 h. After cooling to ambient temperature, the reaction mixture is diluted with H₂O (100 mL) and extracted with EtOAc (2 x 100 mL). The combined organic layers are washed with brine (100 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue is purified by column chromatography (SiO₂, PE/EtOAc gradient 1:0 to 3:1) to afford the desired compound.

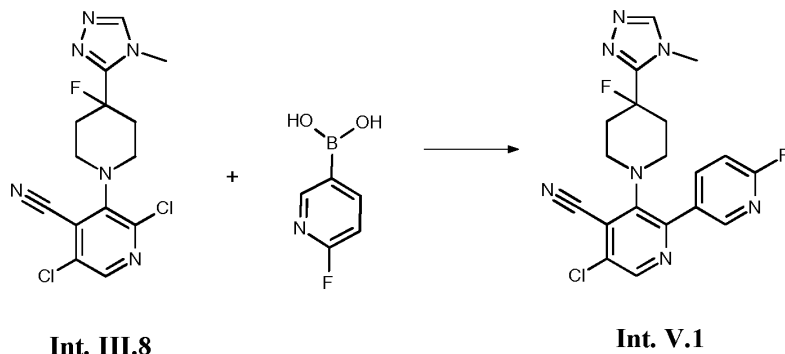
20 C₁₈H₁₉BClN₃O₂ (M=355.6 g/mol)
ESI-MS: 356 [M+H]⁺
Rt (HPLC): 0.90 min (method D)

Intermediate IV.9: [6-(3-chlorophenyl)pyrazolo[1,5-b]pyridazin-3-yl]boronic acid

25 Purification of 6-(3-Chlorophenyl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazolo[1,5-b]pyridazine by preparative HPLC (Instrument: Shimadzu LC-8A preparative HPLC; Column: Welch Xtimate C18 250 * 70 mm, 10 µm; Mobile phase: A for H₂O (10 mM NH₄HCO₃) and B for ACN; Gradient: B from 53 % to 83 % in 20 min; Flow rate: 130 mL/min; Wavelength: 220 & 254 nm) to afford the titled compound.

30 C₁₂H₉BClN₃O₂ (M=273.5 g/mol)
ESI-MS: 274 [M+H]⁺
Rt (HPLC): 2.57 min (method K)

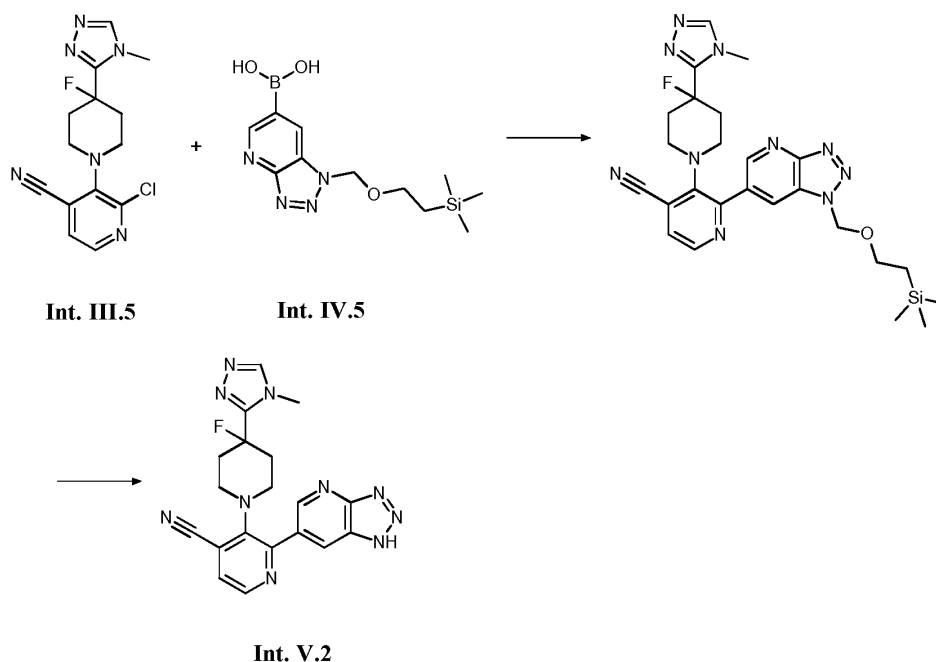
Intermediate V.1: 5-chloro-6'-fluoro-3-[4-fluoro-4-(4-methyl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]-[2,3'-bipyridine]-4-carbonitrile



Under an argon atmosphere, Int. III.8 (20.0 mg, 0.06 mmol) and (6-fluoropyridin-3-yl)boronic acid (7.90 mg, 0.06 mmol) are suspended in 1,4-dioxane (3 mL). K₂CO₃ (aq. 2 M, 110 µL, 0.22 mmol) is added, and the resulting mixture is degassed by passing an argon stream through the mixture. [1,1'-Bis-(diphenylphosphino)-ferrocen]-dichloro-palladium(II) (Pd(dppf)Cl₂) (4.02 mg, 0.005 mmol) is added, and the mixture is degassed again. The mixture is then heated to 70 °C for 1 h. After cooling to ambient temperature, the mixture is diluted with H₂O, filtered, washed with DMF, and purified by preparative SFC (Torus_1AA; MeOH/CO₂; 40 °C; BPR: 120bar) to yield the title compound.

C₁₉H₁₆ClF₂N₇ (M=415.8 g/mol)
 ESI-MS: 416 [M+H]⁺
 Rt (HPLC): 0.68 min (method L)

Synthesis of Intermediate V.2



3-[4-Fluoro-4-(4-methyl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]-2-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-[1,2,3]triazolo[4,5-b]pyridin-6-yl)pyridine-4-carbonitrile

Under an argon atmosphere, Int. III.5 (96.4 mg, 0.30 mmol) and Int. IV.5 (88.4 mg, 0.30 mmol) are suspended in 1,4-dioxane (3 mL). K_2CO_3 (aq. 2 M, 300 μ L, 0.60 mmol) is added, and the resulting mixture is degassed by passing an argon stream through the mixture. [1,1'-Bis-(diphenylphosphino)-ferrocen]-dichloro-palladium(II) ($Pd(dppf)Cl_2$) (22.0 mg, 0.03 mmol) is added, and the mixture is degassed again. The mixture is then heated to 100 $^{\circ}C$ for 3.5 h. After cooling to ambient temperature, the mixture is diluted with ACN, filtered, and purified by preparative HPLC (Sunfire C18, ACN/water gradient containing 0.1% TFA) to afford the desired compound.

$C_{25}H_{31}FN_{10}OSi$ (M=534.7 g/mol)

ESI-MS: 535 $[M+H]^+$

Rt (HPLC): 0.83 min (method G)

Intermediate V.2: 3-[4-fluoro-4-(4-methyl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]-2-{1H-[1,2,3]triazolo[4,5-b]pyridin-6-yl}pyridine-4-carbonitrile

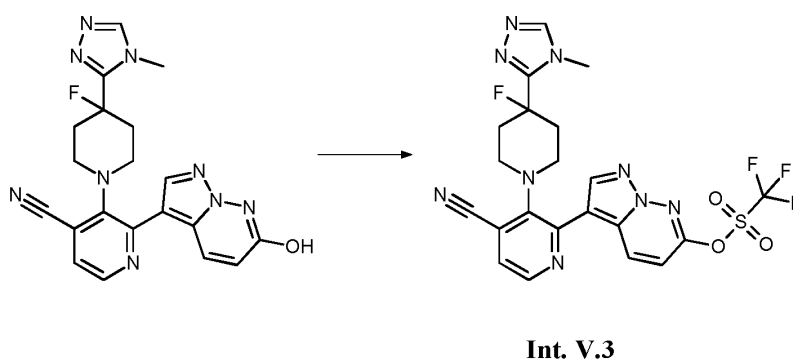
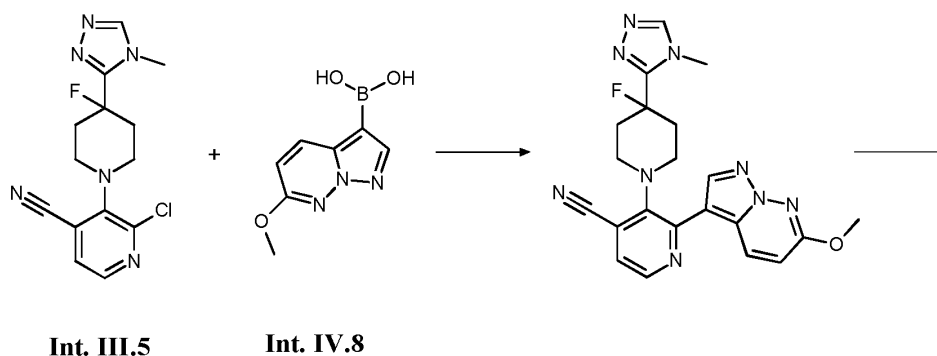
3-[4-Fluoro-4-(4-methyl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]-2-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-[1,2,3]triazolo[4,5-b]pyridin-6-yl)pyridine-4-carbonitrile (129 mg, 0.24 mmol) is suspended in DCM (1.76 mL). TFA (0.88 mL, 11.4 mmol) is added, and the reaction mixture is stirred at rt for 5 h. The reaction mixture is concentrated, and the residue is purified by preparative HPLC (Sunfire C18, ACN/water gradient containing 0.1% TFA) to afford the desired compound.

$C_{19}H_{17}FN_{10}$ (M=404.4 g/mol)

ESI-MS: 405 $[M+H]^+$

Rt (HPLC): 0.46 min (method G)

Synthesis of Intermediate V.3



3-[4-Fluoro-4-(4-methyl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]-2-{6-methoxypyrazolo[1,5-b]pyridazin-3-yl}pyridine-4-carbonitrile

Under an argon atmosphere, Int. III.5 (1.00 g, 3.12 mmol) and Int. IV.8 (663 mg, 3.27 mmol) are suspended in 1,4-dioxane (12 mL). Na₂CO₃ (aq. 2 M, 4.68 mL, 9.35 mmol) is added, and the resulting mixture is degassed by passing an argon stream through the mixture. Pd(dppf)Cl₂ * DCM (50.9 mg, 0.06 mmol) is added, and the mixture is degassed again. The mixture is then heated to 100 °C for 2 h. After cooling to ambient temperature, the mixture is diluted with water and extracted with DCM (2 x). The combined organic layers are dried over Na₂SO₄, filtered, and concentrated. The residue is purified by column chromatography (SiO₂, EtOAc/MeOH gradient 1:0 to 8:2) to yield the title compound.

C₂₁H₂₀FN₉O (M=433.4 g/mol)
ESI-MS: 434 [M+H]⁺
Rt (HPLC): 0.81 min (method C)

3-[4-Fluoro-4-(4-methyl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]-2-{6-hydroxypyrazolo[1,5-b]pyridazin-3-yl}pyridine-4-carbonitrile

3-[4-Fluoro-4-(4-methyl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]-2-{6-methoxypyrazolo[1,5-b]pyridazin-3-yl}pyridine-4-carbonitrile (850 mg, 1.96 mmol) is suspended in DMF (8 mL). Sodium thiomethoxide (687 mg, 8.83 mmol, 90 % purity) is added, and the reaction mixture is stirred at 130 °C for 1 h. After cooling to ambient temperature, The reaction mixture is purified by column chromatography (SiO₂, EtOAc/MeOH gradient 1:0 to 1:1) and repurified by preparative HPLC (Sunfire C18, ACN/water gradient containing 0.1% TFA) to afford the desired compound.

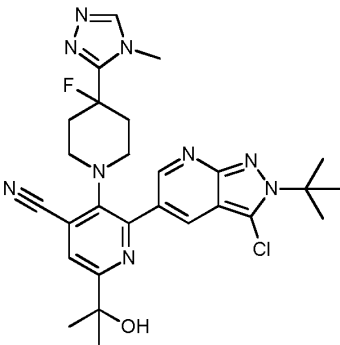
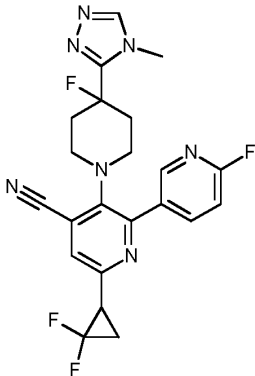
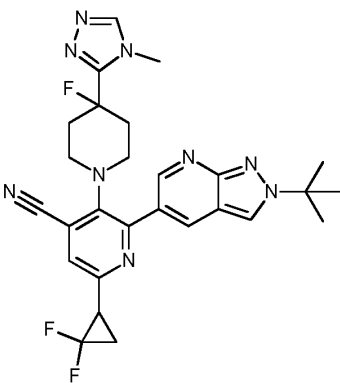
C₂₀H₁₈FN₉O (M=419.4 g/mol)
ESI-MS: 420 [M+H]⁺
Rt (HPLC): 0.74 min (method C)

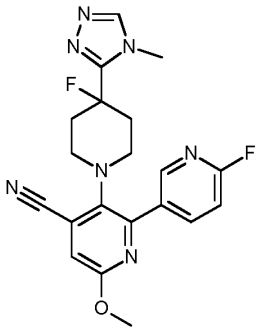
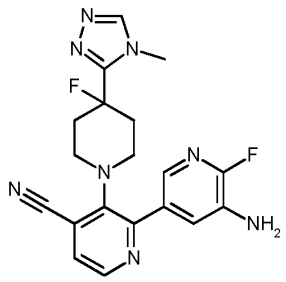
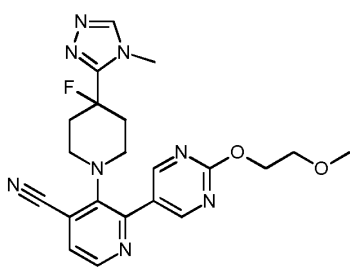
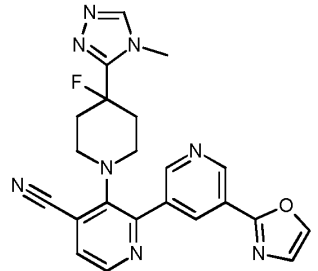
Intermediate V.3: 3-{4-cyano-3-[4-fluoro-4-(4-methyl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]pyridin-2-yl}pyrazolo[1,5-b]pyridazin-6-yl trifluoromethanesulfonate

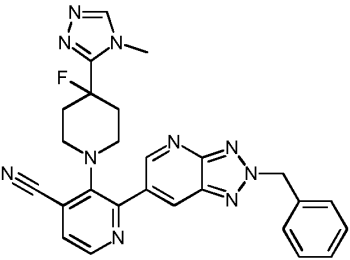
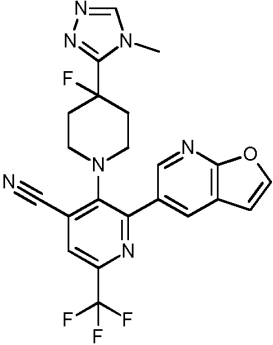
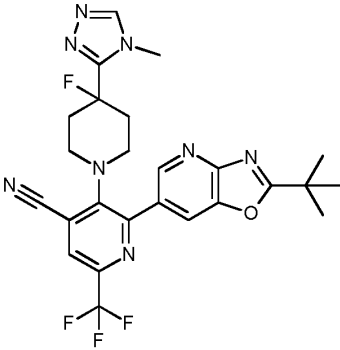
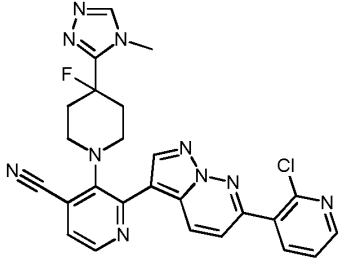
3-[4-Fluoro-4-(4-methyl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]-2-{6-hydroxypyrazolo[1,5-b]pyridazin-3-yl}pyridine-4-carbonitrile (540 mg, 1.29 mmol) is suspended in DCM (20 mL) and TEA (0.29 mL, 2.06 mmol). At -10 °C, trifluoromethanesulfonic anhydride (1 M in DCM, 2.58 mL, 2.58 mmol) is added dropwise, and the reaction mixture is stirred at -10 °C

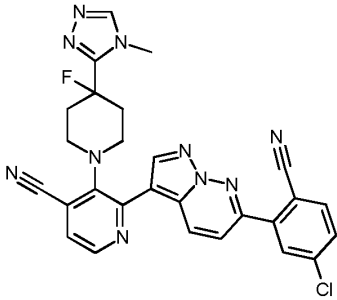
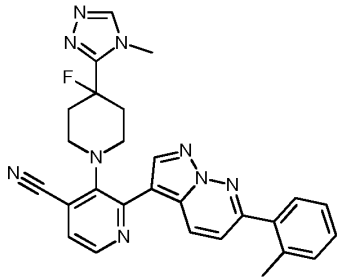
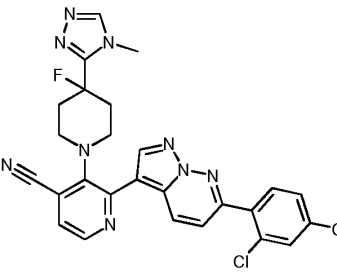
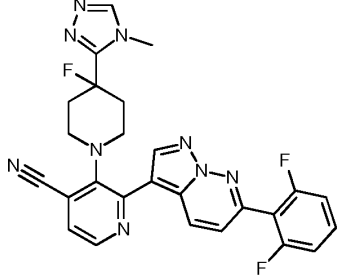
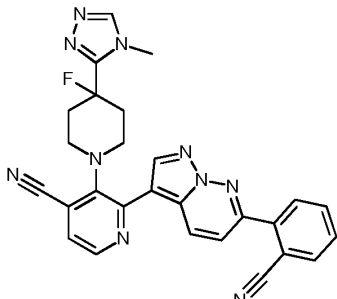
$J=1.5$ Hz, 3 H), 3.22 - 3.29 (m, 2 H), 3.12 - 3.19 (m, 2 H), 2.10 - 2.27 (m, 4 H), 1.46 (s, 6 H).

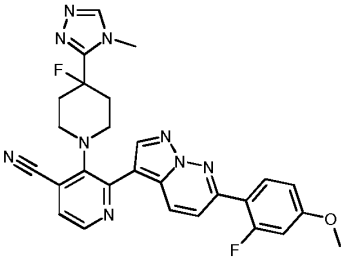
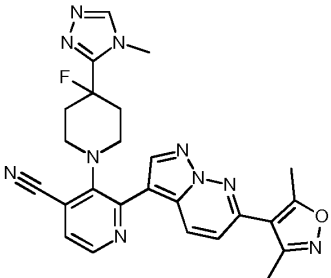
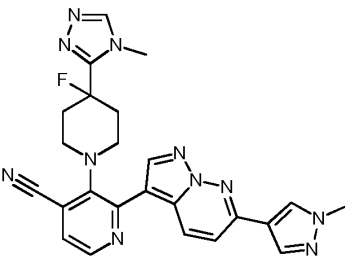
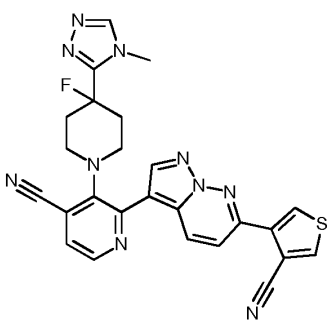
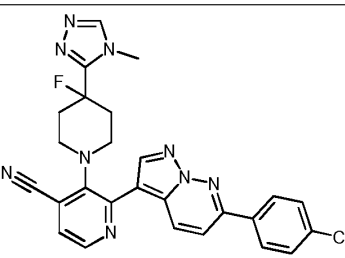
Examples synthesized analogous to the procedure described for Example 1

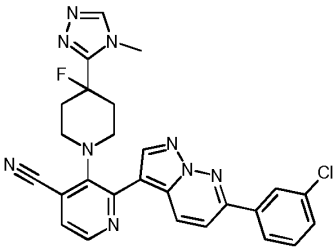
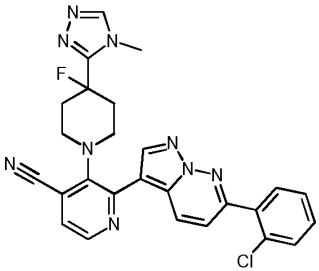
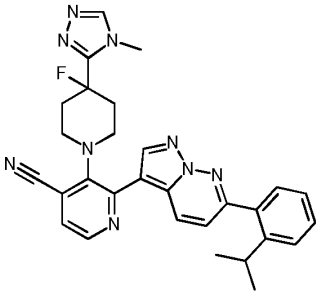
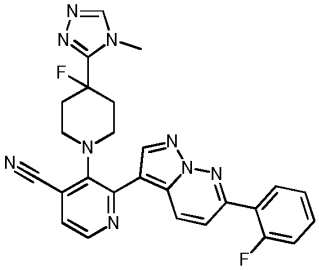
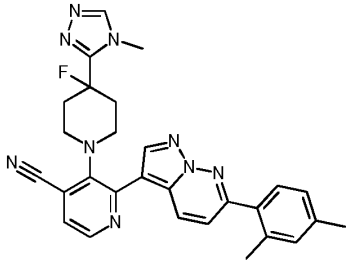
example	Starting materials	Structure	Deviation from general procedure
2	Int. III.2 + Int. IV.1		3.0 eq. Na ₂ CO ₃ solution; 3 h at 100 °C; purification by preparative HPLC (XBridge C18, ACN/water gradient containing 0.1% TFA)
3	Int. III.4 + 2-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine		10 h at 100 °C; purification by preparative SFC (Torus_1AA; MeOH/CO ₂ ; 40°C; BPR: 120bar)
4	Int. III.4 + Int. IV.2		3.0 eq. K ₂ CO ₃ solution; 10 h at 100 °C; purification by preparative SFC (Torus_1AA; MeOH/CO ₂ ; 40°C; BPR: 120bar)

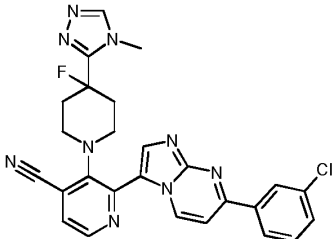
5	Int. III.6 + 2-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine		1.2 eq. 2-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine; 3.0 eq. K ₂ CO ₃ solution; 10 h at 95 °C; purification by preparative HPLC (XBridge C18, ACN/water gradient containing 0.1% TFA)
9	Int. III.5 + 2-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-amine		1.2 eq. boronic acid or ester; 2.5 eq. 2 M K ₃ PO ₄ solution; Xphos Pd G3; 16 h at 100 °C; purification by preparative HPLC (C18, ACN/water gradient containing 0.1% NH ₃ or TFA)
10	Int. III.5 + 2-(2-methoxyethoxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidine		1.2 eq. boronic acid or ester; 2.5 eq. 2 M K ₃ PO ₄ solution; Xphos Pd G3; 16 h at 100 °C; purification by preparative HPLC (C18, ACN/water gradient containing 0.1% NH ₃ or TFA)
11	Int. III.5 + 3-(1,3-oxazol-2-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine		1.2 eq. boronic acid or ester; 2.5 eq. 2 M K ₃ PO ₄ solution; Xphos Pd G3; 16 h at 100 °C; purification by preparative HPLC (C18, ACN/water gradient containing 0.1% NH ₃ or TFA)

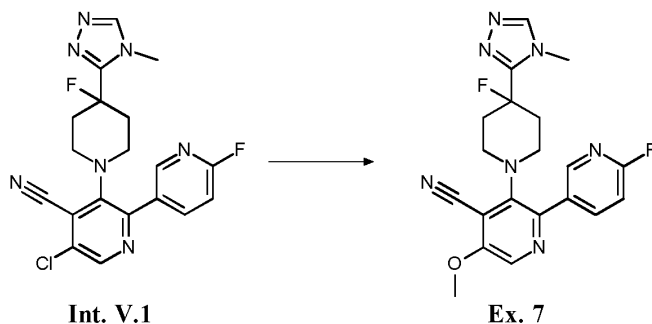
12	Int. III.5 + Int. IV.4		1.0 eq. Int. IV.4; 3 h at 100 °C; purification by preparative SFC (BEH; MeOH/CO ₂ ; 40°C; BPR: 120bar)
15	Int. III.9 + Int. IV.6		1.2 eq. Int. IV.6; 3.0 eq. K ₂ CO ₃ solution; 4 h at 95 °C
16	Int. III.10 + Int. IV.7		1.2 eq. Int. IV.7; 3.5 eq. K ₂ CO ₃ solution; 4.5 h at 95 °C
17	Int. V.3 + (2-chloropyridin-3-yl)boronic acid		1.2 eq. boronic acid; 2 h at 90 °C; purification by preparative HPLC (Sunfire C18, ACN/water gradient containing 0.1% TFA)

18	Int. V.3 + (5-chloro-2-cyanophenyl)boronic acid		1.2 eq. boronic acid; 2 h at 90 °C; purification by preparative HPLC (Sunfire C18, ACN/water gradient containing 0.1% TFA)
19	Int. V.3 + (2-methylphenyl)boronic acid		1.2 eq. boronic acid; 2 h at 90 °C; purification by preparative HPLC (Sunfire C18, ACN/water gradient containing 0.1% TFA)
20	Int. V.3 + (2,4-dichlorophenyl)boronic acid		1.2 eq. boronic acid; 2 h at 90 °C; purification by preparative HPLC (Sunfire C18, ACN/water gradient containing 0.1% TFA)
21	Int. V.3 + (2,6-difluorophenyl)boronic acid		1.2 eq. boronic acid; 2 h at 90 °C; purification by preparative HPLC (Sunfire C18, ACN/water gradient containing 0.1% TFA)
22	Int. V.3 + (2-cyanophenyl)boronic acid		1.2 eq. boronic acid; 2 h at 90 °C; purification by preparative HPLC (Sunfire C18, ACN/water gradient containing 0.1% TFA)

23	Int. V.3 + (2-fluoro-4-methoxyphenyl) boronic acid		1.2 eq. boronic acid; 2 h at 90 °C; purification by preparative HPLC (Sunfire C18, ACN/water gradient containing 0.1% TFA)
24	Int. V.3 + (3,5-dimethyl-1,2-oxazol-4-yl)boronic acid		1.2 eq. boronic acid; 2 h at 90 °C; purification by preparative HPLC (Sunfire C18, ACN/water gradient containing 0.1% TFA)
25	Int. V.3 + (1-methyl-1H-pyrazol-4-yl)boronic acid		1.2 eq. boronic acid; 2 h at 90 °C; purification by preparative HPLC (Sunfire C18, ACN/water gradient containing 0.1% TFA)
26	Int. V.3 + 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophene-3-carbonitrile		1.2 eq. boronic ester; 2 h at 90 °C; purification by preparative HPLC (Sunfire C18, ACN/water gradient containing 0.1% TFA)
27	Int. V.3 + (4-chlorophenyl)boronic acid		2 h at 90 °C; purification by preparative HPLC (Sunfire C18, ACN/water gradient containing 0.1% TFA)

28	Int. III.5 + Int. IV.9		1.2 eq. Int. IV.9; 4.0 eq. K ₂ CO ₃ solution; 1 h at 70 °C; purification by preparative HPLC (Sunfire C18, ACN/water gradient containing 0.1% TFA)
29	Int. V.3 + (2-chlorophenyl)boronic acid		1.2 eq. boronic acid; 2 h at 90 °C; purification by preparative HPLC (Sunfire C18, ACN/water gradient containing 0.1% TFA)
30	Int. V.3 + [2-(propan-2-yl)phenyl]boronic acid		1.2 eq. boronic acid; 2 h at 90 °C; purification by preparative HPLC (Sunfire C18, ACN/water gradient containing 0.1% TFA)
31	Int. V.3 + (2-fluorophenyl)boronic acid		1.2 eq. boronic acid; 2 h at 90 °C; purification by preparative HPLC (Sunfire C18, ACN/water gradient containing 0.1% TFA)
32	Int. V.3 + (2,4-dimethylphenyl)boronic acid		1.2 eq. boronic acid; 2 h at 90 °C; purification by preparative HPLC (Sunfire C18, ACN/water gradient containing 0.1% TFA)

33	Int. III.5 + Int. IV.10		1.0 eq. Int. IV.10; 1.5 h at 100 °C; purification by preparative SFC (Torus_DIOL; MeOH/CO ₂ ; 40°C; BPR: 120bar)
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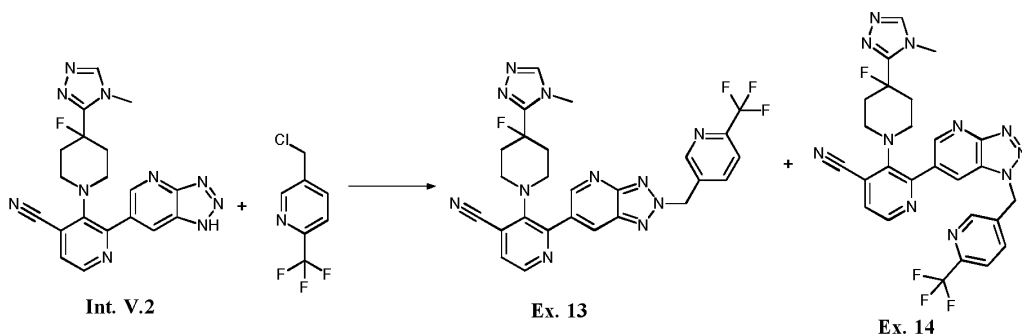
Example 7

Int. V.1 (16.0 mg, 0.04 mmol) is suspended in MeOH (0.50 mL). Sodium methanolate (25
5 % in MeOH, 26.4 μ L, 0.12 mmol) is added, and the reaction mixture is stirred at rt for 16 h.
The reaction is diluted with water, filtered, and purified by preparative HPLC (Zorbax
StableBond C18 column, ACN/water gradient containing 0.1% TFA) to yield the title
compound.

$C_{20}H_{19}F_2N_7O$ (M=411.4 g/mol)

10 ESI-MS: 412 [M+H]⁺

Rt (HPLC): 0.77 min (method N)

Synthesis of Example 13 and 14

Int. V.2 x TFA (86.6 mg, 0.16 mmol) is suspended in DMF (1.0 mL). At – 10 °C, K₂CO₃ (45.3 mg, 0.33 mmol) and 5-(chloromethyl)-2-(trifluoromethyl)pyridine (32.7 mg, 0.16 mmol) are added, and the reaction mixture is stirred at rt for 28 h. Still starting material left. More K₂CO₃ (20 mg, 0.14 mmol) and 5-(chloromethyl)-2-(trifluoromethyl)pyridine (15 mg, 0.08 mmol) are added, and the reaction mixture is stirred at rt for 60 h. The reaction mixture is diluted with water and extracted with EtOAc. The organic layer is washed with brine, dried over MgSO₄, filtered, and concentrated. The residue is purified by preparative HPLC (Sunfire C18 column, ACN/water gradient containing 0.1% TFA) to yield example 13 and 14.

10

Example 13

C₂₆H₂₁F₄N₁₁ (M=563.5 g/mol)

ESI-MS: 564 [M+H]⁺

Rt (HPLC): 0.74 min (method G)

15 ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 9.06 (d, *J*=2.0 Hz, 1 H), 8.95 (d, *J*=1.7 Hz, 1 H), 8.65 (d, *J*=2.0 Hz, 1 H), 8.59 (d, *J*=4.9 Hz, 1 H), 8.52 (s, 1 H), 8.19 (dd, *J*=8.1, 1.7 Hz, 1 H), 7.98 (d, *J*=8.2 Hz, 1 H), 7.87 (d, *J*=4.9 Hz, 1 H), 6.28 (s, 2 H), 3.70 (d, *J*=1.5 Hz, 3 H), 3.19 - 3.28 (m, 4 H), 2.05 - 2.21 (m, 4 H).

20 **Example 14**

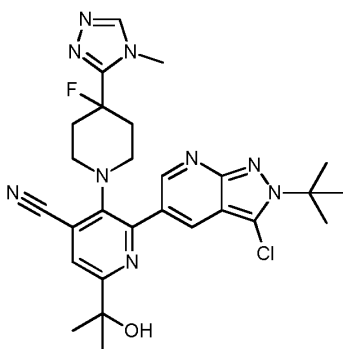
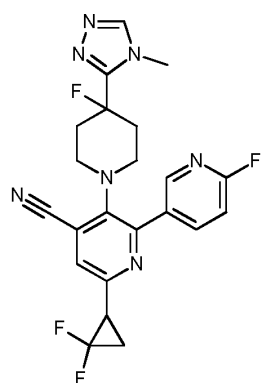
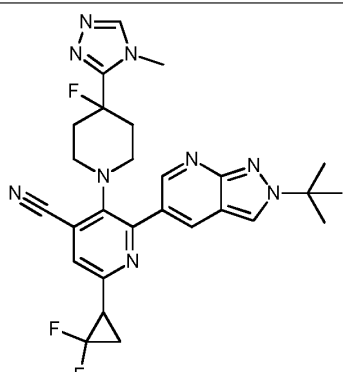
C₂₆H₂₁F₄N₁₁ (M=563.5 g/mol)

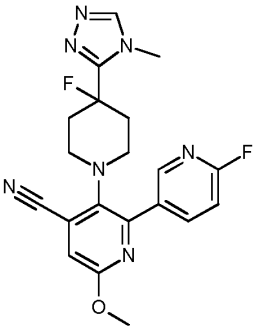
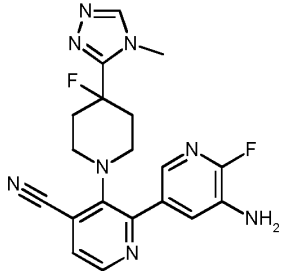
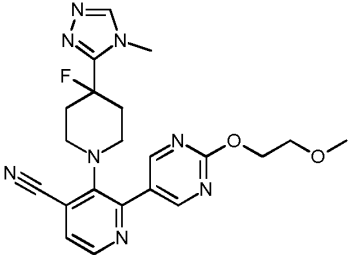
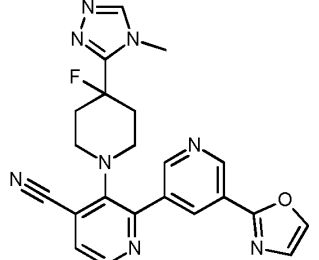
ESI-MS: 564 [M+H]⁺

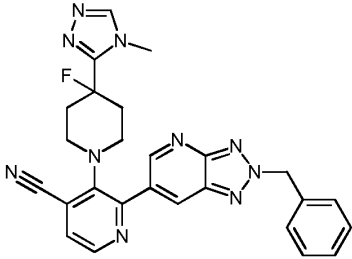
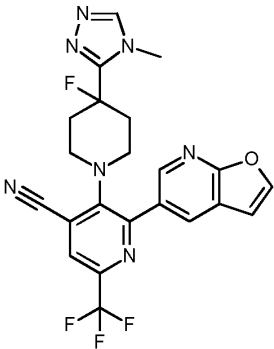
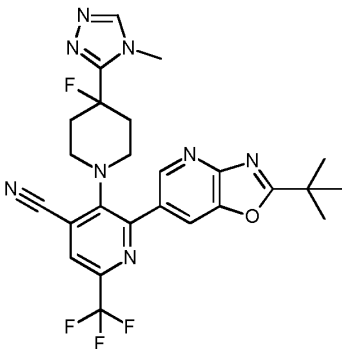
Rt (HPLC): 0.69 min (method G)

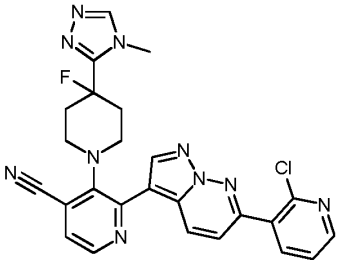
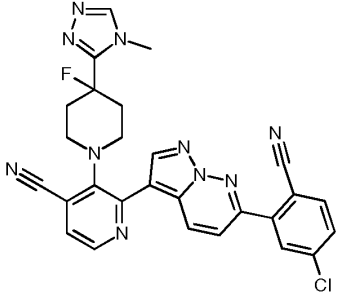
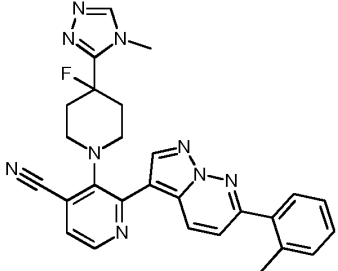
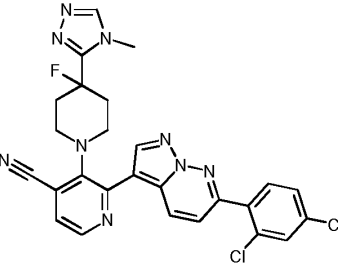
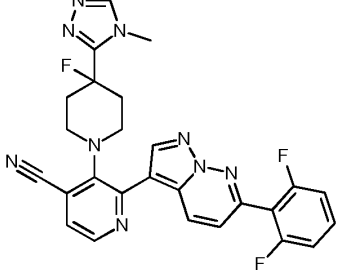
25 ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.99 (d, *J*=1.9 Hz, 1 H), 8.91 (d, *J*=1.7 Hz, 1 H), 8.70 (d, *J*=1.9 Hz, 1 H), 8.57 - 8.60 (m, 1 H), 8.52 - 8.55 (m, 1 H), 8.03 (dd, *J*=8.1, 1.7 Hz, 1 H), 7.87 - 7.93 (m, 2 H), 6.25 (s, 2 H), 3.70 (d, *J*=1.5 Hz, 3 H), 3.10 - 3.23 (m, 4 H), 2.04 - 2.20 (m, 4 H).

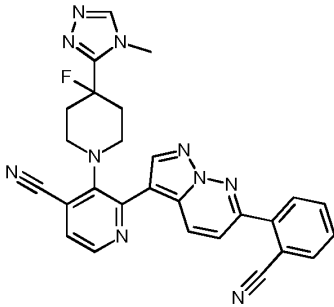
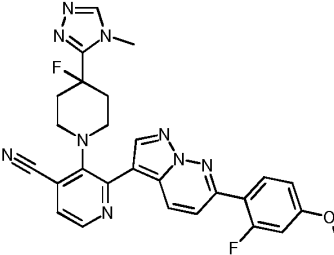
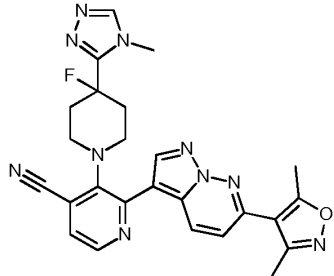
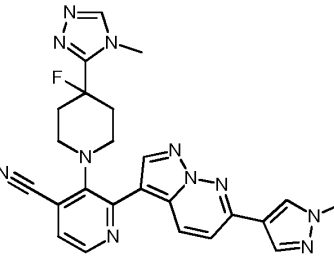
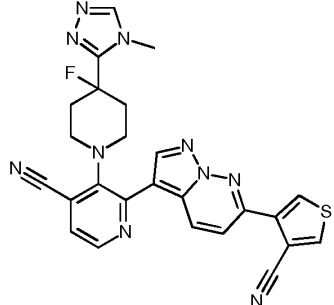
Analytical data of synthesized examples

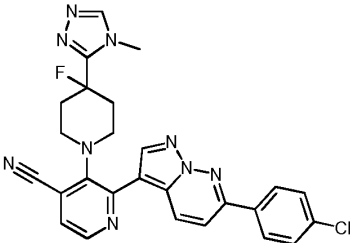
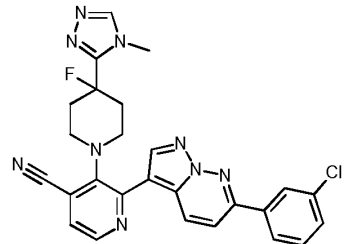
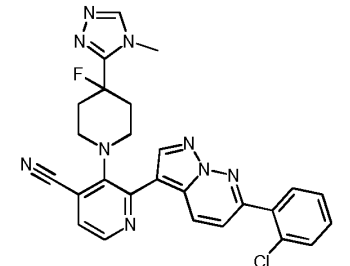
example	Structure	Molecular Formula (MW) ESI-MS HPLC retention time (method)	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ in ppm
2		$C_{27}H_{31}ClFN_9O$ (M=552.0 g/mol) ESI-MS: 553 [M+H] ⁺ Rt (HPLC): 0.55 min (method F)	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.98 (d, <i>J</i> =2.2 Hz, 1 H), 8.54 (s, 1 H), 8.31 (d, <i>J</i> =2.2 Hz, 1 H), 7.88 (s, 1 H), 3.73 (d, <i>J</i> =1.4 Hz, 4 H), 3.19 - 3.35 (m, 4 H), 2.10 - 2.26 (m, 4 H), 1.84 (s, 9 H), 1.47 (s, 6 H); OH signal not detected
3		$C_{22}H_{19}F_4N_7$ (M=457.4 g/mol) ESI-MS: 458 [M+H] ⁺ Rt (HPLC): 0.54 min (method F)	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.50 (d, <i>J</i> = 2.4 Hz, 1 H), 8.48 (s, 1 H), 8.24 (td, <i>J</i> =8.2, 2.53 Hz, 1 H), 7.90 (s, 1 H), 7.33 (dd, <i>J</i> =8.4, 2.60 Hz, 1 H), 3.73 (d, <i>J</i> =1.5 Hz, 3 H), 3.13 - 3.27 (m, 5 H), 2.27 - 2.35 (m, 1 H), 2.11 - 2.25 (m, 4 H), 2.00 - 2.08 (m, 1 H)
4		$C_{27}H_{28}F_3N_9$ (M=535.6 g/mol) ESI-MS: 536 [M+H] ⁺ Rt (HPLC): 0.53 min (method F)	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.83 (d, <i>J</i> =2.3 Hz, 1 H), 8.65 (s, 1 H), 8.46 (s, 1 H), 8.35 (d, <i>J</i> =2.2 Hz, 1 H), 7.87 (s, 1 H), 3.70 (d, <i>J</i> =1.5 Hz, 3 H), 3.18 - 3.28 (m, 5 H), 2.15 - 2.35 (m, 5 H), 1.99 -

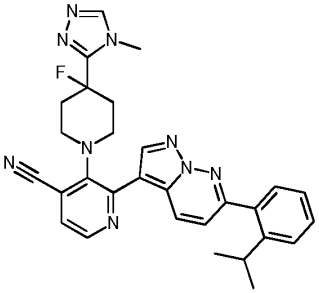
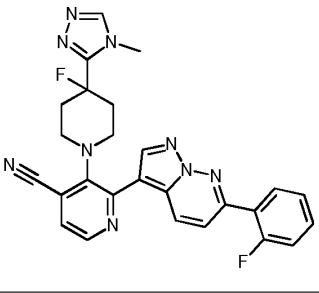
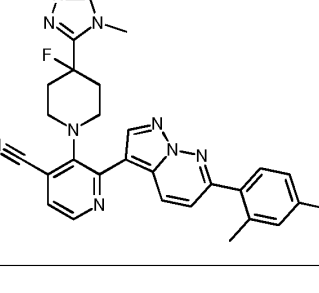
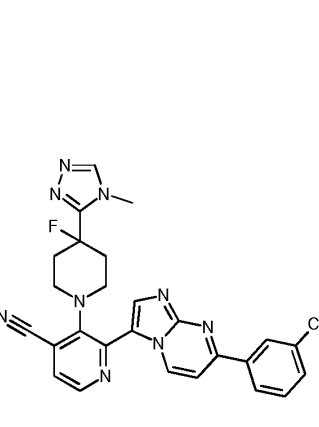
			2.10 (m, 1 H), 1.71 (s, 9 H)
5		$C_{20}H_{19}F_2N_7O$ (M=411.4 g/mol) ESI-MS: 412 [M+H] ⁺ Rt (HPLC): 0.52 min (method F)	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.52 - 8.57 (m, 2 H), 8.28 (td, <i>J</i> =8.2, 2.1 Hz, 1 H), 7.43 (s, 1 H), 7.33 (dd, <i>J</i> =8.5, 2.5 Hz, 1 H), 3.90 (s, 3 H), 3.75 (d, <i>J</i> =1.5 Hz, 3 H), 3.19 - 3.37 (m, 2 H), 3.00 - 3.08 (m, 2 H), 2.06 - 2.27 (m, 4 H)
9		$C_{19}H_{18}F_2N_8$ (M=396.4 g/mol) ESI-MS: 397.2 [M+H] ⁺ Rt (HPLC): 0.52 min (method P)	-
10		$C_{21}H_{23}FN_8O_2$ (M=438.5 g/mol) ESI-MS: 439 [M+H] ⁺ Rt (HPLC): 0.53 min (method Q)	-
11		$C_{22}H_{19}FN_8O$ (M=430.4 g/mol) ESI-MS: 431 [M+H] ⁺ Rt (HPLC): 0.55 min (method P)	-

12		$C_{26}H_{23}FN_{10}$ (M=494.5 g/mol) ESI-MS: 495 [M+H] ⁺ Rt (HPLC): 0.72 min (method M)	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 9.04 (d, <i>J</i> = 2.0 Hz, 1 H), 8.63 (d, <i>J</i> = 2.0 Hz, 1 H), 8.58 (d, <i>J</i> =4.9 Hz, 1 H), 8.46 (s, 1 H), 7.86 (d, <i>J</i> = 4.9 Hz, 1 H), 7.46 - 7.51 (m, 2 H), 7.34 - 7.44 (m, 3 H), 6.05 (s, 2 H), 3.69 (d, <i>J</i> = 1.5 Hz, 3 H), 3.20 - 3.27 (m, 4 H), 2.04 - 2.21 (m, 4 H)
15		$C_{22}H_{17}F_4N_7O$ (M=471.4 g/mol) ESI-MS: 472 [M+H] ⁺ Rt (HPLC): 0.64 min (method B)	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.56 (d, <i>J</i> =2.2 Hz, 1 H), 8.47 (s, 1 H), 8.36 - 8.40 (m, 2 H), 8.20 (d, <i>J</i> =2.5 Hz, 1 H), 7.14 (d, <i>J</i> =2.5 Hz, 1 H), 3.70 (d, <i>J</i> =1.5 Hz, 3 H), 3.35 (br d, <i>J</i> =4.6 Hz, 1 H), 3.18 - 3.27 (m, 3 H), 2.14 - 2.30 (m, 4 H)
16		$C_{25}H_{24}F_4N_8O$ (M=528.5 g/mol) ESI-MS: 529 [M+H] ⁺ Rt (HPLC): 0.72 min (method B)	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.74 (d, <i>J</i> =1.8 Hz, 1 H), 8.47 (s, 1 H), 8.35 - 8.42 (m, 2 H), 7.45 - 7.59 (m, 1 H), 3.71 (d, <i>J</i> =1.3 Hz, 3 H), 3.31 - 3.39 (m, 2 H), 3.21 - 3.27 (m, 1 H), 2.13 - 2.31 (m, 4 H), 1.49 (s, 9 H)

17		$C_{25}H_{20}ClFN_{10}$ (M=515.0 g/mol) ESI-MS: 515 [M+H] ⁺ Rt (HPLC): 0.70 min (method P)	-
18		$C_{27}H_{20}ClFN_{10}$ (M=539.0 g/mol) ESI-MS: 539 [M+H] ⁺ Rt (HPLC): 0.79 min (method P)	-
19		$C_{27}H_{24}FN_9$ (M=493.6 g/mol) ESI-MS: 494 [M+H] ⁺ Rt (HPLC): 0.82 min (method L)	-
20		$C_{26}H_{20}Cl_2FN_9$ (M=548.4 g/mol) ESI-MS: 548 [M+H] ⁺ Rt (HPLC): 0.91 min (method L)	-
21		$C_{26}H_{20}F_3N_9$ (M=515.5 g/mol) ESI-MS: 516 [M+H] ⁺ Rt (HPLC): 0.78 min (method P)	-

22		$C_{27}H_{21}FN_{10}$ (M=504.5 g/mol) ESI-MS: 505 [M+H] ⁺ Rt (HPLC): 0.72 min (method L)	-
23		$C_{27}H_{23}F_2N_9O$ (M=527.5 g/mol) ESI-MS: 528 [M+H] ⁺ Rt (HPLC): 0.82 min (method P)	-
24		$C_{25}H_{23}FN_{10}O$ (M=498.5 g/mol) ESI-MS: 499 [M+H] ⁺ Rt (HPLC): 0.69 min (method P)	-
25		$C_{24}H_{22}FN_{11}$ (M=483.5 g/mol) ESI-MS: 484 [M+H] ⁺ Rt (HPLC): 0.62 min (method P)	-
26		$C_{25}H_{19}FN_{10}S$ (M=510.6 g/mol) ESI-MS: 511 [M+H] ⁺ Rt (HPLC): 0.70 min (method P)	-

27		$C_{26}H_{21}ClFN_9$ (M=514.0 g/mol) ESI-MS: 514 [M+H] ⁺ Rt (HPLC): 0.85 min (method M)	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.79 (s, 1 H), 8.71 (d, <i>J</i> =9.5 Hz, 1 H), 8.60 (d, <i>J</i> =4.9 Hz, 1 H), 8.52 (s, 1 H), 8.14 - 8.19 (m, 2 H), 7.97 (d, <i>J</i> =9.5 Hz, 1 H), 7.69 - 7.72 (m, 1 H), 7.64 - 7.69 (m, 2 H), 3.77 (d, <i>J</i> =1.7 Hz, 3 H), 3.48 - 3.57 (m, 2 H), 3.23 - 3.30 (m, 2 H), 2.27 - 2.44 (m, 4 H)
28		$C_{26}H_{21}ClFN_9$ (M=514.0 g/mol) ESI-MS: 514 [M+H] ⁺ Rt (HPLC): 0.85 min (method M)	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.80 (s, 1 H), 8.71 (d, <i>J</i> =9.4 Hz, 1 H), 8.57 - 8.62 (m, 2 H), 8.16 - 8.20 (m, 1 H), 8.08 - 8.14 (m, 1 H), 8.01 (d, <i>J</i> =9.4 Hz, 1 H), 7.71 (d, <i>J</i> =4.9 Hz, 1 H), 7.62 - 7.67 (m, 2 H), 3.78 (d, <i>J</i> =1.5 Hz, 3 H), 3.49 - 3.57 (m, 2 H), 3.24 - 3.31 (m, 2 H), 2.29 - 2.44 (m, 4 H),
29		$C_{26}H_{21}ClFN_9$ (M=514.0 g/mol) ESI-MS: 514 [M+H] ⁺ Rt (HPLC): 0.83 min (method L)	-

30		$C_{29}H_{28}FN_9$ (M=521.6 g/mol) ESI-MS: 522 [M+H] ⁺ Rt (HPLC): 0.92 min (method L)	
31		$C_{26}H_{21}F_2N_9$ (M=497.5 g/mol) ESI-MS: 498 [M+H] ⁺ Rt (HPLC): 0.81 min (method L)	
32		$C_{28}H_{26}FN_9$ (M=507.6 g/mol) ESI-MS: 508 [M+H] ⁺ Rt (HPLC): 0.88 min (method L)	
33		$C_{26}H_{21}ClFN_9$ (M=514.0 g/mol) ESI-MS: 514 [M+H] ⁺ Rt (HPLC): 0.52 min (method F)	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 9.44 (d, <i>J</i> =7.4 Hz, 1 H), 8.60 (d, <i>J</i> =4.8 Hz, 1 H), 8.45 - 8.51 (m, 2 H), 8.30 (d, <i>J</i> =2.0 Hz, 1 H), 8.21 - 8.26 (m, 1 H), 7.89 (d, <i>J</i> =7.4 Hz, 1 H), 7.79 (d, <i>J</i> =4.8 Hz, 1 H), 7.61 - 7.65 (m, 2 H), 3.75 (d, <i>J</i> =1.5 Hz, 3 H), 3.41 - 3.51 (m, 2 H), 2.25 - 2.40 (m, 4 H) 2H missing (under water peak)

Analytical HPLC methods**Method A**

time (min)	Vol% water (incl. 0.04% TFA)	Vol% ACN (incl. 0.02% TFA)	Flow [mL/min]
0.00	95	5	1.5
0.70	5	95	1.5
1.16	5	95	1.5
1.50	95	5	1.5

Analytical column: Kinetex EVO C18_2.1 x 30 mm_5 µm; column temperature: 40°C

Method B

time (min)	Vol% water (incl. 0.1% NH ₃)	Vol% ACN	Flow [mL/min]
0.00	95	5	1.3
0.02	95	5	1.3
1.00	0	100	1.3
1.30	0	100	1.3

Device description: Waters Acquity; Analytical column: XBridge (Waters) BEH C18_2.1 x 30 mm_2.5µm; column temperature: 60°C

Method C

time (min)	Vol% water (incl. 0.1% FA)	Vol% ACN	Flow [mL/min]
0.00	97	3	2.2
0.20	97	3	2.2
1.20	0	100	2.2
1.25	0	100	3.0
1.40	0	100	3.0

Device description: Agilent 1200; Analytical column: Sunfire C18_3.0 x 30 mm_2.5µm;
column temperature: 60°C

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Method D

time (min)	Vol% water (incl. 0.1% FA)	Vol% ACN	Flow [mL/min]
0.01	90	10	1.5
0.80	0	100	1.5
1.30	0	100	1.5

Device description: Shimadzu LC-20ADXR; Analytical column: Halo C18_3.0 x 30 mm_5µm; column temperature: 40°C

Method E

hold time (min)	rate (°C/min)	Temperature (°C)	Flow [mL/min]
1		40	1.5
0	30	100	1.5
1	10	270	1.5

Device description: Shimadzu GCMS-QP2020; Analytical column: Agilent J&W HP-5MS 30M*0.25mmID*0.25µm film thickness; injector temperature: 200 °C; split ratio: 100:1; carrier gas: He, ionization mode: EI; ion source temperature: 230 °C; interface temperature: 250 °C; solvent cut time: 2 min (Start time – End time: 2 – 21 min); run time: 21.00 min

Method F

time (min)	Vol% water (incl. 0.1% TFA)	Vol% ACN	Flow [mL/min]
0.00	99	1	1.6
0.02	99	1	1.6
1.00	0	100	1.6
1.10	0	100	1.6

Device description: Waters Acquity; Analytical column: Xbridge (Waters) BEH C18_2.1 x 30 mm_1.7µm; column temperature: 60°C

Method G

time (min)	Vol% water (incl. 0.1% TFA)	Vol% ACN	Flow [mL/min]
0.00	95	5	1.5
1.30	0	100	1.5
1.50	0	100	1.5

Device description: Waters Acquity; Analytical column: Sunfire (Waters) C18_3.0 x 30 mm_2.5 µm; column temperature: 60°C

Method H

time (min)	Vol% water (incl. 0.04% TFA)	Vol% ACN (incl. 0.02% TFA)	Flow [mL/min]
0.01	95	5	1.0
0.40	95	5	1.0
3.00	5	95	1.0
4.00	5	95	1.0
4.01	95	5	1.0
4.50	95	5	1.0

Device description: Agilent 1260; Analytical column: Luna C18_2.0 x 50 mm_5µm; column temperature: 40°C

Method I

time (min)	Vol% water (incl. 0.04% TFA)	Vol% ACN (incl. 0.02% TFA)	Flow [mL/min]
0.00	90	10	2.0
0.50	0	100	2.0
0.90	0	100	2.0

Device description: Shimadzu LC-20ADXR; Analytical column: Halo C18_3.0 x 30 mm_5µm; column temperature: 40°C

Method J

time (min)	Vol% water (incl. 0.04% TFA)	Vol% ACN (incl. 0.02% TFA)	Flow [mL/min]
0.01	95	5	0.8
0.40	95	5	0.8
3.00	5	95	0.8
4.00	5	95	0.8
4.01	95	5	0.8
4.50	95	5	0.8

Device description: Agilent 1260; Analytical column: Luna C18_2.0 x 50 mm_5µm;
column temperature: 40°C

Method K

time (min)	Vol% water (incl. 10mM NH ₄ CO ₃)	Vol% ACN	Flow [mL/min]
0.00	95	5	0.8
0.40	95	5	0.8
3.40	5	95	0.8
3.85	5	95	0.8
3.86	95	5	0.8
4.50	95	5	0.8

Device description: Agilent 1260; Analytical column: XBridge C18_2.1 x 50 mm_5µm;
column temperature: 40°C

Method L

time (min)	Vol.% water (incl. 0.1 % NH ₃)	Vol. % ACN	Flow [mL/min]
0.00	95	5	1.5
1.30	0	100	1.5
1.50	0	100	1.5
1.60	95	5	1.5

Device description: Waters Acquity; Analytical column: Xbridge (Waters) C18_3.0 x 30 mm_2.5 μ m; column temperature: 60°C

Method M

time (min)	Vol.% water (incl. 0.1 % TFA)	Vol% ACN (incl. 0.08% TFA)	Flow [mL/min]
0.00	95	5	1.5
1.30	0	100	1.5
1.50	0	100	1.5
1.60	95	5	1.5

Device description: Waters Acquity; Analytical column: Sunfire (Waters) C18_3.0 x 30 mm_2.5 μ m; column temperature: 60°C

Method N

time (min)	Vol% water (incl. 0.1% TFA)	Vol% ACN	Flow [mL/min]
0.00	97	3	2.2
0.20	97	3	2.2
1.20	0	100	2.2
1.25	0	100	3.0
1.40	0	100	3.0

Device description: Agilent 1200; Analytical column: Zorbax (Agilent) StableBond C18_3.0 x 30 mm_1.8 μ m; column temperature: 60 °C

Method O

time (min)	Vol.% water (incl. 0.1 % NH ₃)	Vol. % ACN	Flow [mL/min]
0.00	95	5	1.5
1.30	0	100	1.5
1.50	0	100	1.5
1.60	95	5	1.5

Device description: Waters Acquity; Analytical column: XBridge (Waters) C18_3.0 x 30 mm_2.5 µm; column temperature: 60 °C

Method P

time (min)	Vol% water (incl. 0.1%TFA)	Vol% ACN (incl. 0.08% TFA)	Flow [mL/min]
0.00	95	5	1.5
1.30	0	100	1.5
1.50	0	100	1.5
1.60	95	5	1.5

Device description: Waters Acquity; Analytical column: Sunfire (Waters) C18_3.0 x 30 mm_2.5 µm; column temperature: 60°C

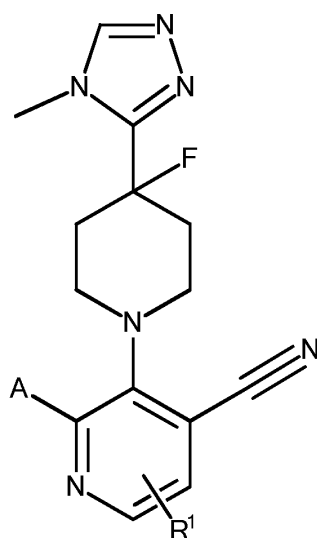
Method Q

time (min)	Vol.% water (incl. 0.1 % NH ₃)	Vol. % ACN	Flow [mL/min]
0.00	95	5	1.5
1.30	0	100	1.5
1.50	0	100	1.5
1.60	95	5	1.5

Device description: Waters Acquity; Analytical column: XBridge (Waters) C18_3.0 x 30 mm_2.5 µm; column temperature: 60 °C

WHAT IS CLAIMED

1. A compound of formula (I)



(I)

wherein

A is **A1a** which is a 5- or 6-membered mono-heteroaryl ring containing one or two heteroatom members selected from the group consisting of nitrogen and oxygen;

wherein at least one of the heteroatom members is nitrogen;

or **A** is **A1b** which is a 9- or 10-membered fused bicyclic-heteroaryl ring containing one to four heteroatom members selected from the group consisting of nitrogen and oxygen, wherein at least one of the heteroatom members is nitrogen;

and wherein **A** is independently optionally substituted with one or two **R²**;

R¹ is selected from the group **R1a**, consisting of H, C₁₋₄-alkyl, C₁₋₄-alkyloxy, hydroxy-C₁₋₄-alkyl, F₁₋₉-fluoro-C₁₋₄-alkyl and F₁₋₈-fluoro-C₃₋₅-cycloalkyl;

R² is selected from the group **R2a**, consisting of halo, NH₂, C₁₋₆-alkyl, F₁₋₉-fluoro-C₁₋₆-alkyl, C₁₋₄-alkyl-O-H₂CH₂C-O-, F₁₋₉-fluoro-C₁₋₄-alkyloxy and CH₃S(O);

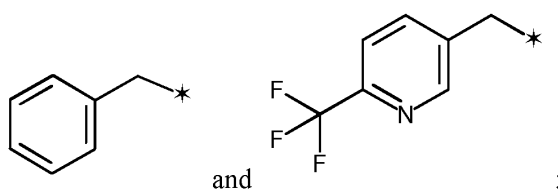
or

R² is selected from the group **R^{2b}**, consisting of phenyl, pyridinyl, isoxazolyl, oxazolyl, pyrazolyl and thiophenyl;

wherein **R2b** is optionally substituted independently by one or two **R³**;

or

5 $\mathbf{R}^2$ is selected from the group $\mathbf{R2c}$, consisting of

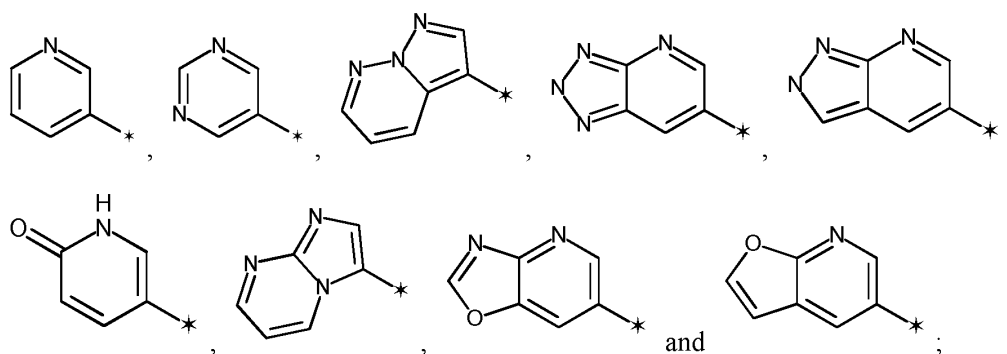


R³ is **R3a**, selected from halo, C₁₋₄-alkyl, C₁₋₄-alkyloxy, HO-C₁₋₄-alkyl or CN;

10 or a salt thereof, particularly a pharmaceutically acceptable salt thereof.

2. The compound of formula (I) according to claim 1, wherein **A** is the group **A3** consisting of pyridinyl, pyrimidinyl, pyrazolo[1,5-b]pyridazinyl, 2H-[1,2,3]triazolo[4,5-b]pyridinyl, pyrazolo[3,4-b]pyridinyl, 1,2-dihydropyridin-2-onyl, imidazo[1,2-a]pyrimidinyl, [1,3]oxazolo[4,5-b]pyridinyl and furo[2,3-b]pyridinyl;
and wherein **A** is independently optionally substituted with one or two **R²**;
or a salt thereof.

20 **3.** The compound of formula (I) according to claim 1, wherein **A** is selected from the group **A4** consisting of

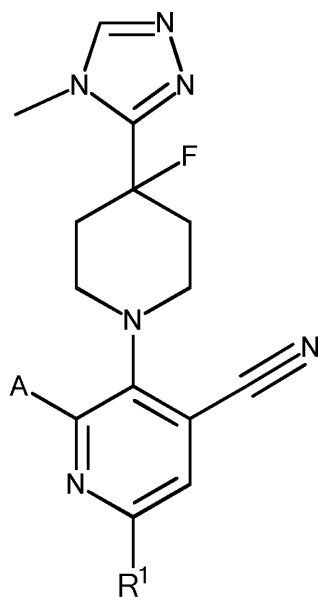


or a salt thereof.

4. The compound of formula (I) according to any of claims 1 to 3, wherein **R¹** is selected from the group **R1b**, consisting of H, C₁₋₄-alkyl, C₁₋₄-alkyloxy, hydroxy-C₁₋₄-alkyl, F₁₋₃-fluoro-C₁₋₄-alkyl and F₁₋₃-fluoro-C₃₋₅-cycloalkyl;
or a salt thereof.

5

5. The compound of formula (I) according to any of claims 1 to 4 having formula (I-a)

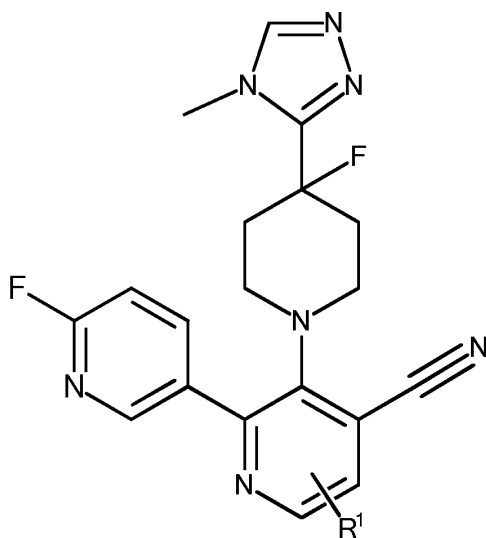


(I-a)

or a salt thereof.

10

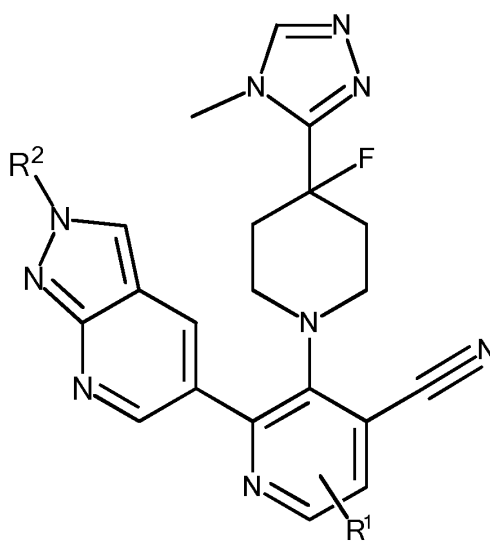
6. The compound of formula (I) according to claim 1 or claim 4 having formula (I-c)



(I-c)

or a salt thereof.

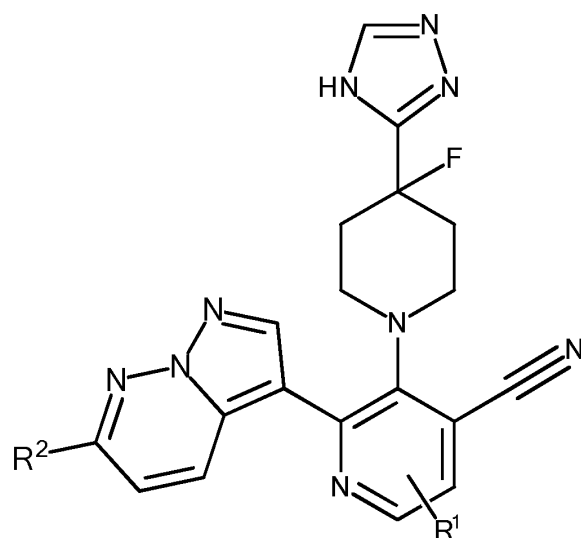
- 5 7. The compound of formula (I) according to claim 1 or claim 4 having formula (I-d)



(I-d)

or a salt thereof.

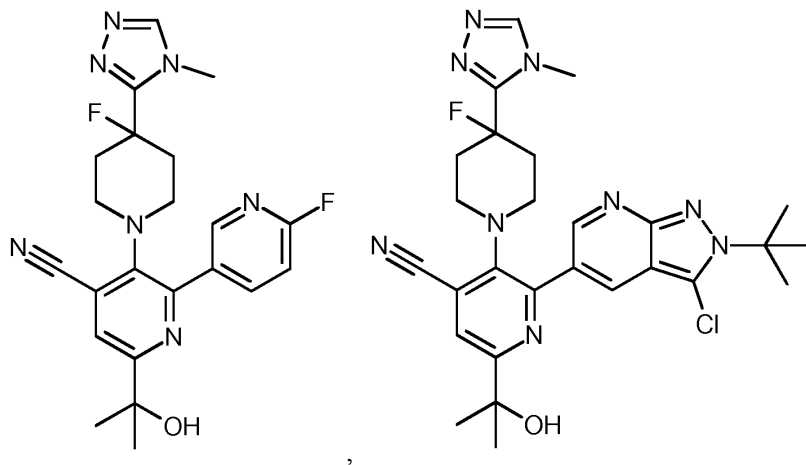
- 10 8. The compound of formula (I) according to claim 1 or claim 4 having formula (I-e)

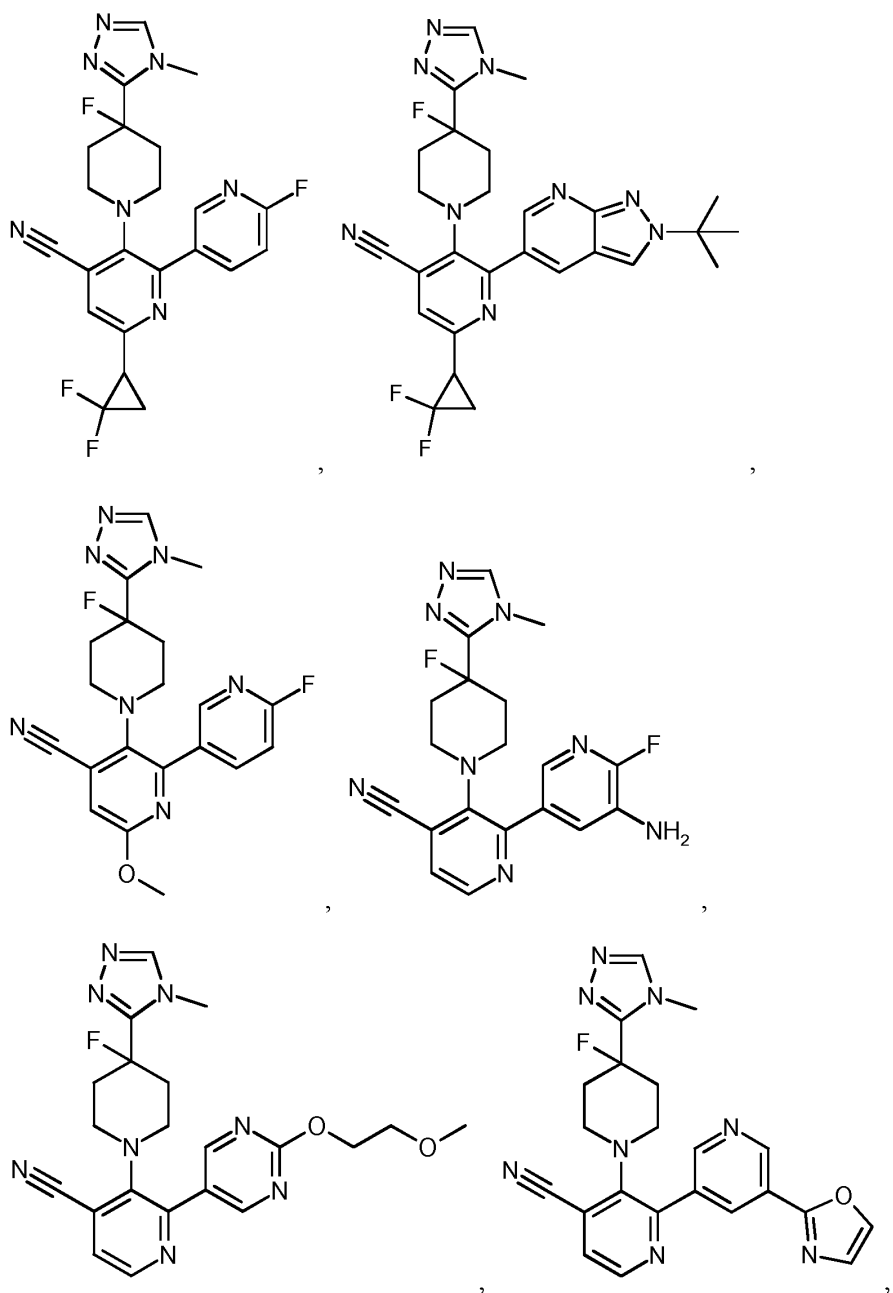


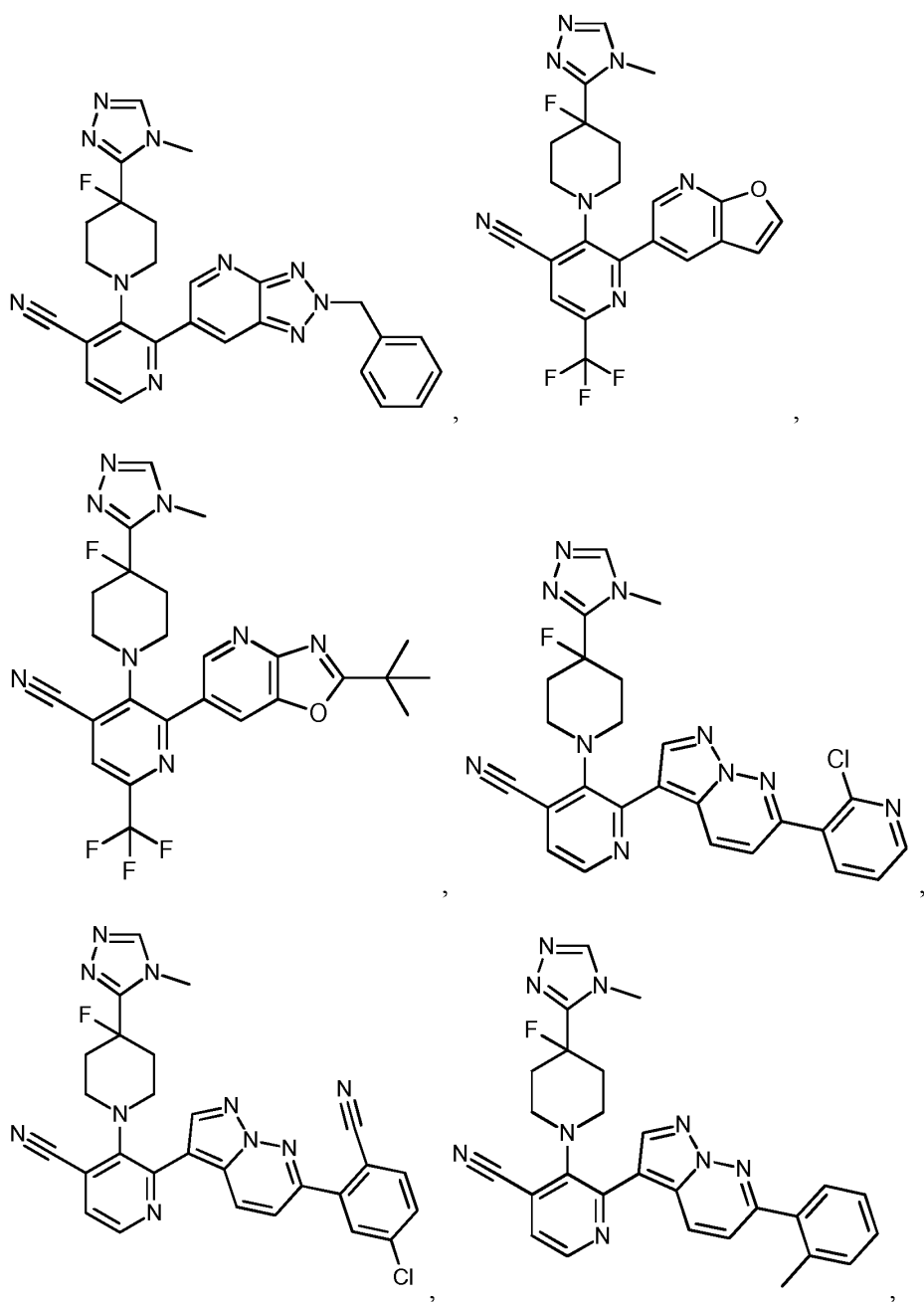
(I-e)

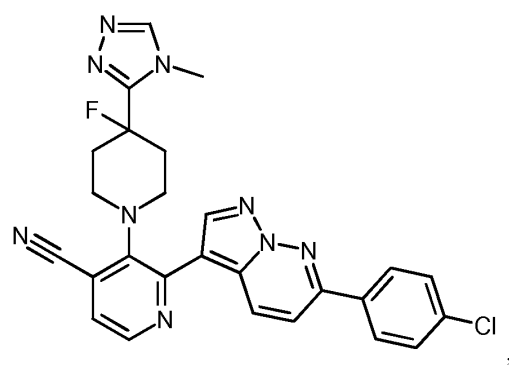
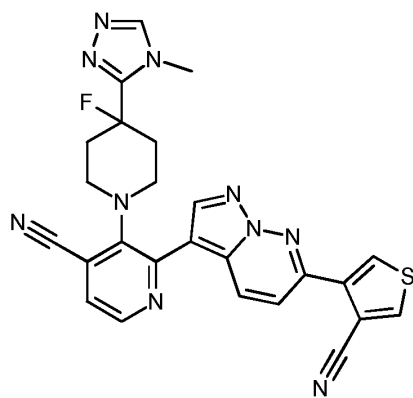
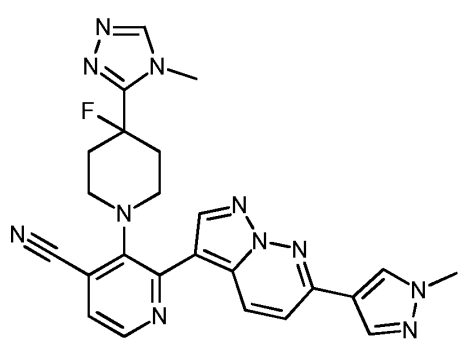
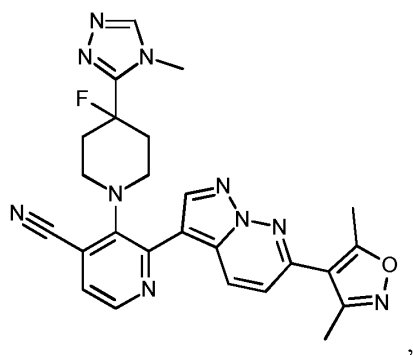
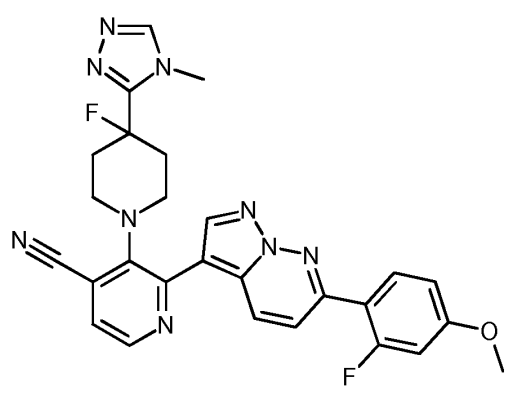
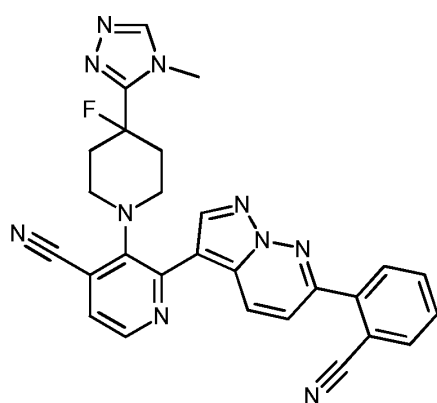
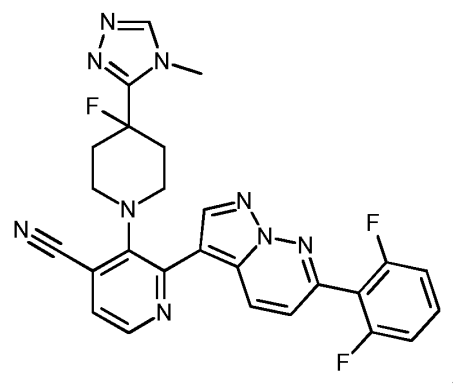
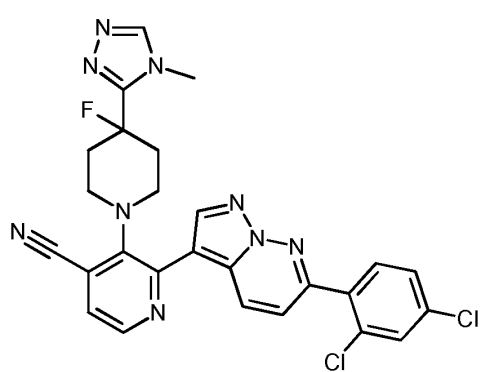
or a salt thereof.

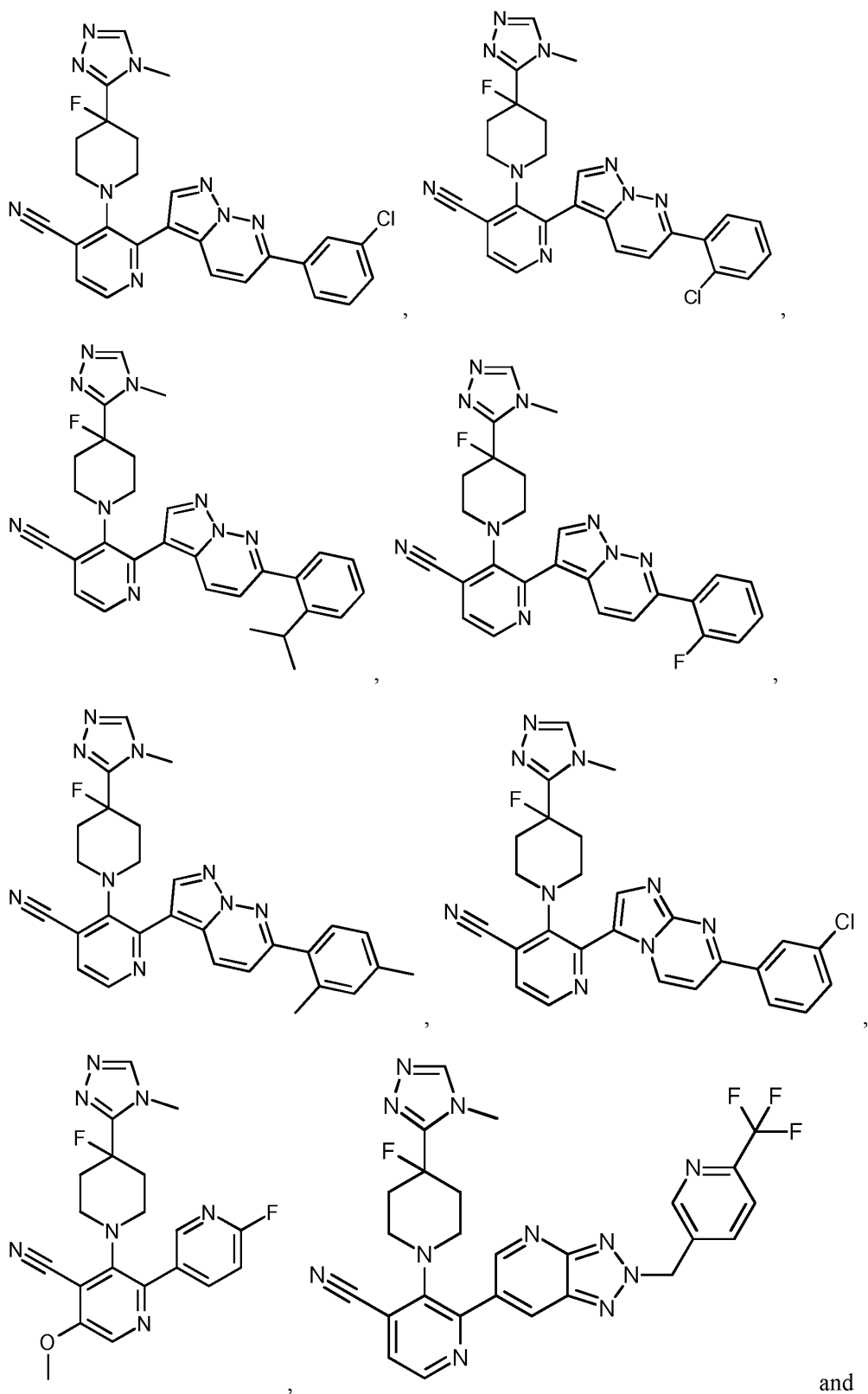
- 5 **9.** The compound of formula (I) according to claim 1, selected from the group consisting of

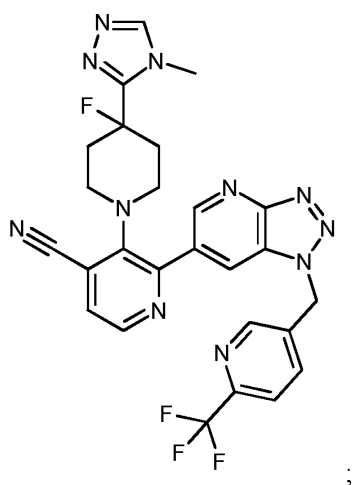












or a salt thereof.

5 **10.** A pharmaceutically acceptable salt of a compound according to one or more of claims 1 to 9.

10 **11.** A pharmaceutical composition comprising one or more compounds according to one or more of claims 1 to 9, or pharmaceutically acceptable salts thereof, optionally together with one or more inert carriers and/or diluents.

15 **12.** A pharmaceutical composition comprising one or more compounds according to one or more of the claims 1 to 9, or pharmaceutically acceptable salts thereof, and one or more additional therapeutic agents, optionally together with one or more inert carriers and/or diluents.

20 **13.** The pharmaceutical composition according to claim 12 wherein the one or more additional therapeutic agents are selected from the group consisting of anticancer agents and antifibrotic agents.

14. The compound according to one or more of claims 1 to 9 or a pharmaceutically acceptable salt thereof for use as a medicament.

15. A method for the treatment of diseases, such as cancer or fibrotic diseases, and conditions associated with these diseases, in a patient in need thereof, the method being characterized in that one or more compounds according to one or more of claims 1 to 9 or pharmaceutically acceptable salts thereof are administered to the patient.

5

16. A compound according to one or more of claims 1 to 9 or a pharmaceutically acceptable salt thereof for use in a method for the treatment of cancer, fibrotic diseases, neurodegenerative diseases, atherosclerosis, infectious diseases, or chronic kidney diseases.