

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

5 TECHNICAL FIELD

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

BACKGROUND INFORMATION

Glutaminy-peptide cyclotransferase (QPCT) and glutaminy-peptide cyclotransferase-like 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 Glutaminy 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 Cynis et al., "Isolation of an Isoenzyme of Human Glutaminy 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 Glutaminy Cyclases and Their Isoenzymes Have Identical Enzymatic Characteristics," *FEBS Journal* 276, no. 22 (2009): 6522–36, <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 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., "Glutaminy 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>], 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-SIRPα 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 (SIRPα), 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 SIRPα 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- 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>.] 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- SIRPα Axis and a Target for Cancer Immunotherapy,” 2019; Meike E.W. Logtenberg, Ferenc A. Scheeren, and Ton N. Schumacher, “The CD47-SIRPα 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/SIRPα 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

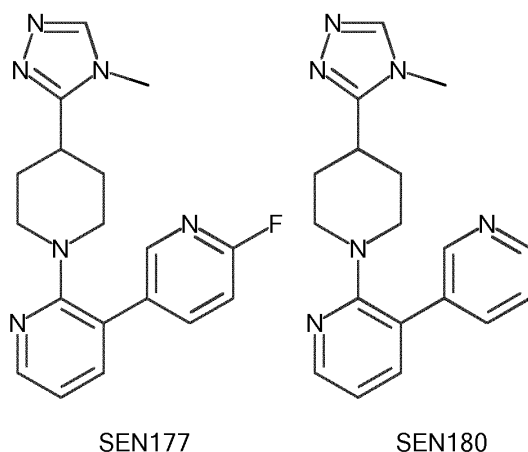
et al., “The CD47-Signal Regulatory Protein Alpha (SIRPa) Interaction Is a Therapeutic Target for Human Solid Tumors,” *Proceedings of the National Academy of Sciences* 109, no. 17 (2012): 6662–67, <https://doi.org/10.1073/pnas.1121623109>].

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 Conditions,” *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 chemoattractants CCL2 and CCL7 are insensitive to DPP4-inactivation in vivo because of an intracellular 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 dence 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:

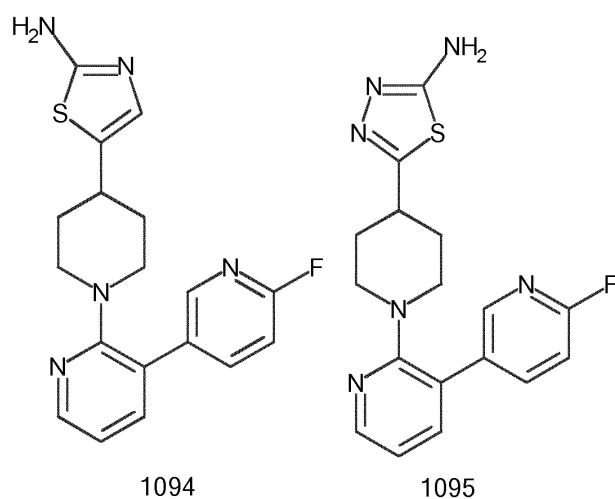


SEN177 is disclosed therein (supplementary information) as having a IC_{50} on isolated hQC of 53 nM and on isolated QPCTL of 13 nM. SEN180 is disclosed therein (supplementary information) as having a IC_{50} on hQC of 170 nM and on QPCTL of 58 nM.

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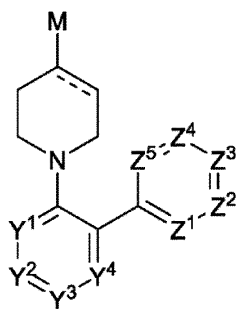
Pozzi, C, et al, Journal of Biological Inorganic Chemistry, 2018, 23, (8), 1219-1226, (hereinafter “P, JBIC 2018”), further discloses SEN177 and its binding mode within the hQC cavity. SEN177 is disclosed therein as having a K_i on isolated hQC of 20 nM.

- 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):

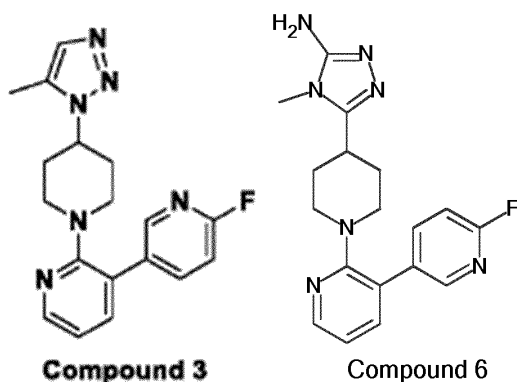


WO 2018/178384 does not disclose any biological data for examples 1094 or 1095.

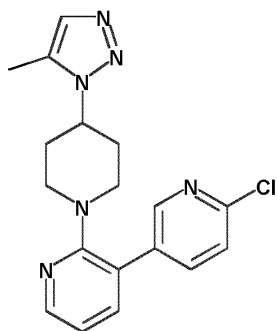
WO 2022/086920 discloses QPCTL inhibitors of the general formula



which include compounds 3 and 6:



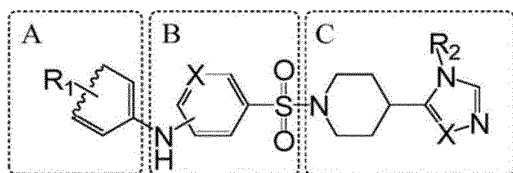
The chemical name of Compound 3 is disclosed in WO 2022/086920 as “1-(1-(6'-chloro-
5 [3,3'-bipyridin]-2-yl)piperidin-4-yl)-1H-1,2,3-triazol-4-amine” which does not correspond to the chemical structure disclosed therein, but to an alternative structure in which the fluorine atom is replaced with chlorine:



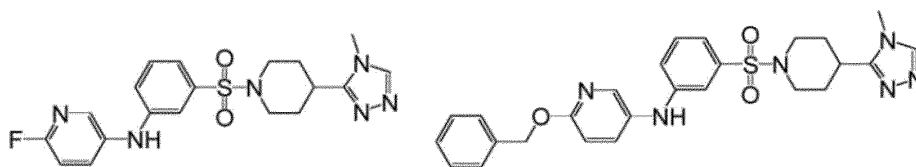
Alternative Compound 3

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

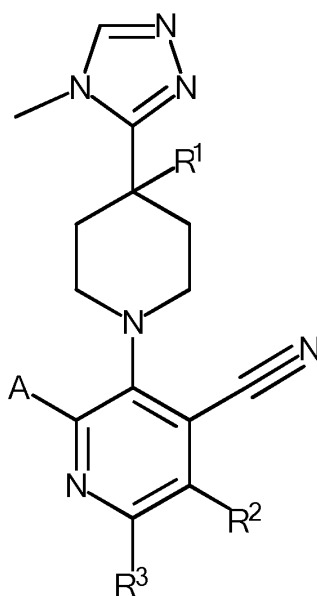
Example 23

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)



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(I)

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.

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.

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). 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.

Compounds of the present invention differ structurally from SEN177 and SEN180 in J-S, NCB 2015, in that the pyridinyl ring attached to the piperidinyl ring contains a ring-nitrogen which is in a meta-position relative to the piperidinyl ring attachment position. Furthermore, a carbonitrile substituent is attached at the ortho-position to the piperidinyl ring attachment position of said pyridinyl ring. Still further, **R¹**, **R²** and **R³** are not limited to hydrogen or methyl and **A** represents heterocyclic ring systems beyond pyridinyl.

Compounds of the present invention differ structurally from examples 1094 and 1095 in WO 2018/178384 in that the pyridinyl ring attached to the piperidinyl ring contains a ring-nitrogen which is in a meta-position relative to the piperidinyl ring attachment position. Furthermore, a carbonitrile substituent is attached at the ortho-position to the piperidinyl ring attachment position of said pyridinyl ring. Still further, **R¹**, **R²** and **R³** are 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 example 1095 an aminothiadiazolyl 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 the pyridinyl ring attached to the piperidinyl ring contains a ring-nitrogen which is in a meta-position relative to the piperidinyl ring attachment position. Furthermore, a carbonitrile substituent is attached at the ortho-position to the piperidinyl ring attachment position of said phenyl ring. Further, **R¹**, **R²** and **R³** are 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. Furthermore, a carbonitrile substituent is attached at the ortho-position to the piperidinyl ring attachment position of said phenyl ring.

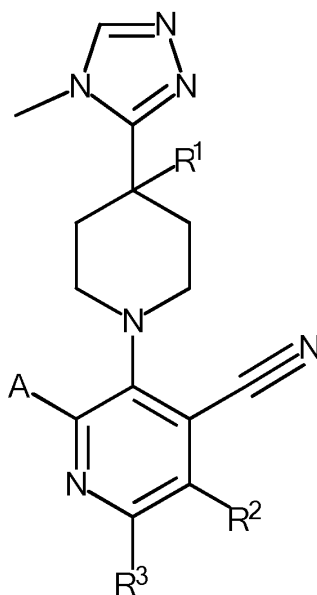
These structural differences between compounds of the present invention and the prior art unexpectedly lead to a favourable combination of (i) potent inhibition of QPCT and QPCTL, (ii) potent inhibition of QPCT/L in cells relevant for, but not limited to, lung diseases or cancer, and (iii) appropriate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

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 nitrogens;

or **A** is **A1b** which is a 9- or 10-membered fused bicyclic-heteroaryl ring containing one to four nitrogens;

wherein **A** is optionally substituted by one or two **R⁴**;

R¹ is selected from the group **R1a**, consisting of H and F;

R² is selected from the group **R2a**, consisting of H, halo, C₁₋₆-alkyl and F₁₋₉-fluoro-C₁₋₆-alkyl;

R³ is selected from the group **R3a**, consisting of H, halo, C₁₋₄-alkyl, F₁₋₉-fluoro-C₁₋₄-alkyl and C₃₋₆-cycloalkyl;

R^4 is selected from the group **R4a**, consisting of halo, C₁₋₆-alkyl, F₁₋₉-fluoro-C₁₋₆-alkyl and C₃₋₆-cycloalkyl;

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

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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 nitrogens;

wherein **A2** is independently substituted with one or two R^4 ;

10 and substituents R^1 , R^2 , R^3 and R^4 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 selected from the group **A3** consisting of 1H-[1,2,3]triazolo[4,5-b]pyridinyl, pyridinyl, 2H-pyrazolo[3,4-b]pyridinyl, [1,2,4]triazolo[1,5-a]pyrimidinyl and 1H-imid-

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azo[4,5-b]pyridinyl;

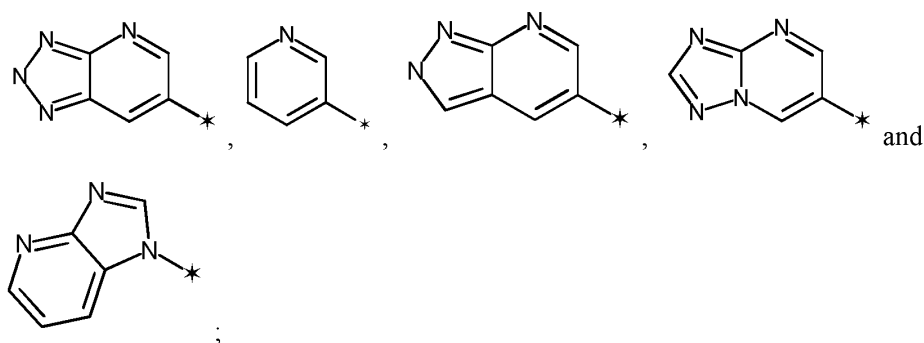
wherein **A3** is independently substituted with one or two R^4 ;

and substituents R^1 , R^2 , R^3 and R^4 are defined as in any of the preceding embodiments.

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

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wherein **A** is selected from the group **A4** consisting of



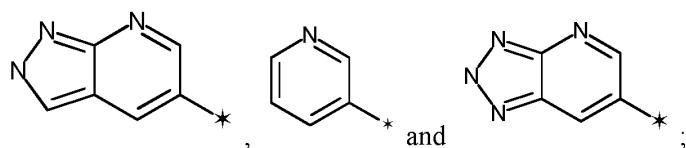
wherein **A4** is independently substituted with one or two R^4 ;

and substituents R^1 , R^2 , R^3 and R^4 are defined as in any of the preceding embodiments.

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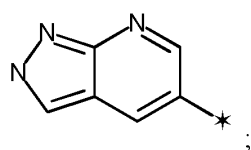
Another embodiment of the present invention relates to a compound of formula (I),

wherein **A** is selected from the group **A5** consisting of



wherein **A5** is independently substituted with one or two **R⁴**;
and substituents **R¹**, **R²**, **R³** and **R⁴** are defined as in any of the preceding embodiments.

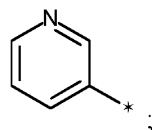
- 5 Another embodiment of the present invention relates to a compound of formula (I),
wherein **A** is selected from the group **A6** consisting of



wherein **A6** is independently substituted with one or two **R⁴**;
and substituents **R¹**, **R²**, **R³** and **R⁴** are defined as in any of the preceding embodiments.

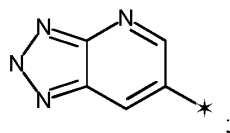
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Another embodiment of the present invention relates to a compound of formula (I),
wherein **A** is selected from the group **A7** consisting of



wherein **A7** is independently substituted with one or two **R⁴**;
15 and substituents **R¹**, **R²**, **R³** and **R⁴** 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 selected from the group **A8** consisting of



- 20 wherein **A8** is independently substituted with one or two **R⁴**;
and substituents **R¹**, **R²**, **R³** and **R⁴** 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 **A9** which is a 9-membered fused bicyclic-heteroaryl ring containing one to four nitrogens;

wherein **A** is optionally substituted by one or two **R⁴**;

5 and substituents **R¹**, **R²**, **R³** and **R⁴** are defined as in any of the preceding embodiments.

Another embodiment of the present invention relates to a compound of formula (I), wherein **R¹** is **R1b** selected from F;

and substituents **R²**, **R³** and **R⁴** 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 **R²** is **R2b** selected from H, halo, C₁₋₄-alkyl and F₁₋₃-fluoro-C₁₋₄-alkyl;

and substituents **R¹**, **R³** and **R⁴** 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 **R2c** selected from H, Cl, H₃C and F₃C;

and substituents **R¹**, **R³** and **R⁴** are defined as in any of the preceding embodiments.

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

20 wherein **R³** is **R3b** selected from of H, chloro, fluoro, C₁₋₄-alkyl, F₁₋₉-fluoro-C₁₋₄-alkyl and cyclopropyl;

and substituents **R¹**, **R²** and **R⁴** are defined as in any of the preceding embodiments.

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

25 wherein **R³** is **R3c** selected from of H, chloro, fluoro, H₃C, F₃C, F₂HC, H₃CF₂C and cyclopropyl;

and substituents **R¹**, **R²** and **R⁴** are defined as in any of the preceding embodiments.

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

30 wherein **R³** is **R3d** selected from of H, chloro, H₃C, F₃C, F₂HC, H₃CF₂C and cyclopropyl;

and substituents **R¹**, **R²** and **R⁴** are defined as in any of the preceding embodiments.

Another embodiment of the present invention relates to a compound of formula (I), wherein **R**³ is selected from the group **R3e**, consisting of halo, C₁₋₄-alkyl, F₁₋₉-fluoro-C₁₋₄-alkyl and C₃₋₆-cycloalkyl; and substituents **R**¹, **R**² and **R**⁴ 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 **R**⁴ is selected from the group **R4b**, consisting of halo, C₁₋₄-alkyl, F₁₋₉-fluoro-C₁₋₄-alkyl and C₃₋₆-cycloalkyl; and substituents **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 **R**⁴ is selected from the group **R4c** consisting of halo, C₁₋₄-alkyl and F₁₋₃-fluoro-C₁₋₄-alkyl; and substituents **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 **R**⁴ is selected from the group **R4d** consisting of chloro, fluoro, C₁₋₄-alkyl and F₁₋₃-fluoro-C₁₋₄-alkyl; and substituents **R**¹, **R**² and **R**³ are defined as in any of the preceding embodiments.

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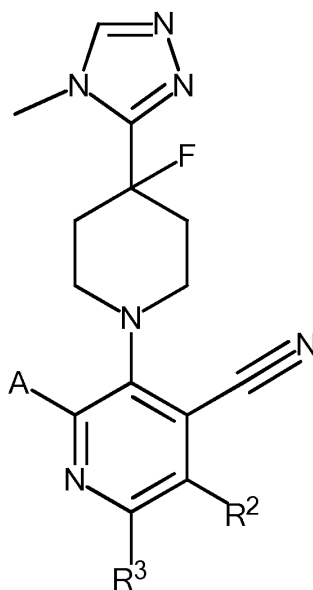
Another embodiment of the present invention relates to a compound of formula (I), wherein **R**⁴ is selected from the group **R4e** consisting of chloro, fluoro, H₃C, F₃C, (H₃C)₃C, (H₃C)₂HC and F₃C(H₃C)₂C; and substituents **R**¹, **R**² and **R**³ are defined as in any of the preceding embodiments.

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Another embodiment of the present invention relates to a compound of formula (I), wherein **A** is **A9** and **R**³ is **R3e**; and substituents **R**¹, **R**² and **R**⁴ are defined as in any of the preceding embodiments.

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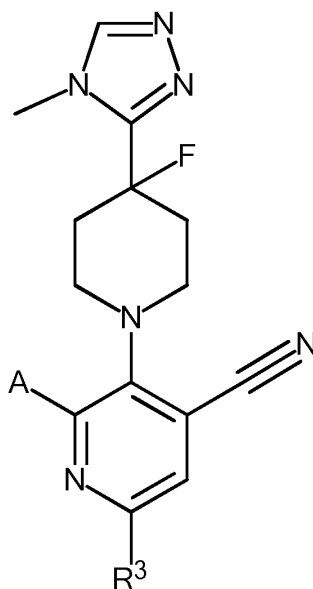
Another embodiment of the present invention relates to a compound of formula (I) above, having formula (I-a)



(I-a)

wherein substituents A, R², R³ and R⁴ are defined as in any of the preceding embodiments.

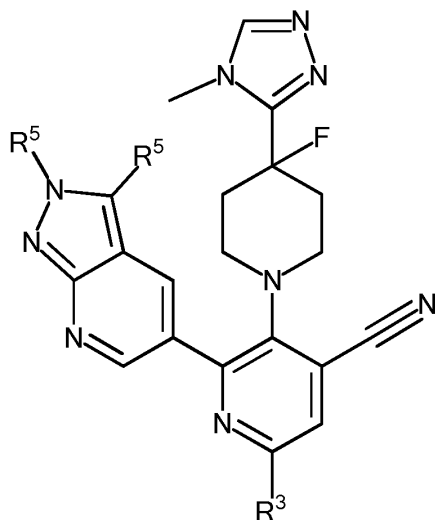
- 5 Another embodiment of the present invention relates to a compound of formula (I) above, having formula (I-b)



(I-b)

wherein substituents A, R³ and R⁴ are defined as in any of the preceding embodiments.

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



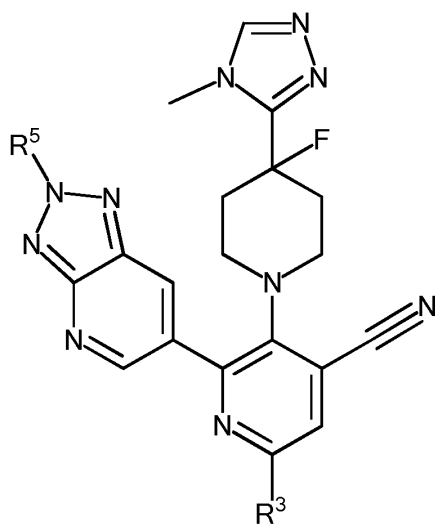
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(I-c)

wherein substituent **R**⁵ is H or **R**⁴, and substituents **R**³ and **R**⁴ are defined as in any of the preceding embodiments.

10

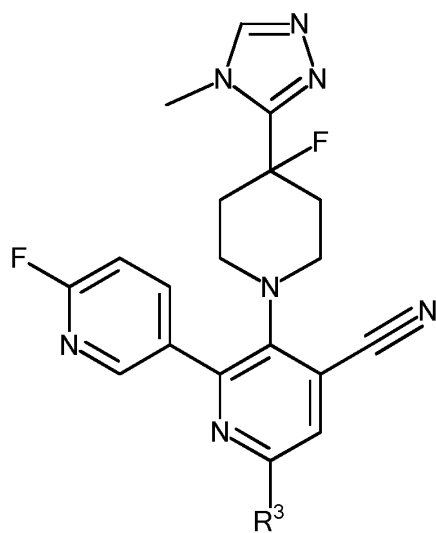
Another embodiment of the present invention relates to a compound of formula (I) above,
having formula (I-d)

**(I-d)**

wherein substituent **R**⁵ is H or **R**⁴, and substituents **R**³ and **R**⁴ are defined as in any of the preceding embodiments.

5

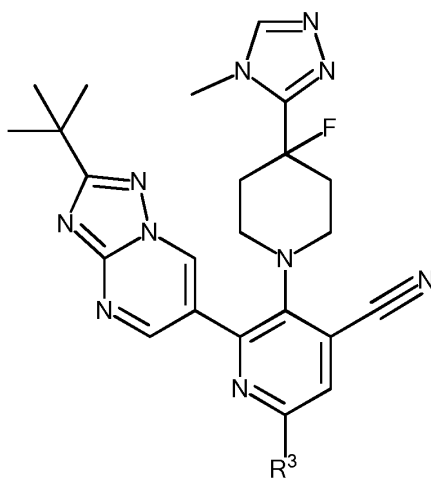
Another embodiment of the present invention relates to a compound of formula (I) above, having formula **(I-e)**



(I-e)

wherein substituent **R³** is defined as in any of the preceding embodiments.

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

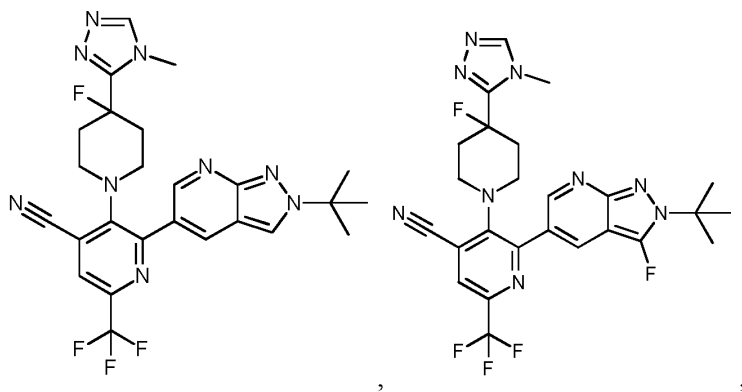


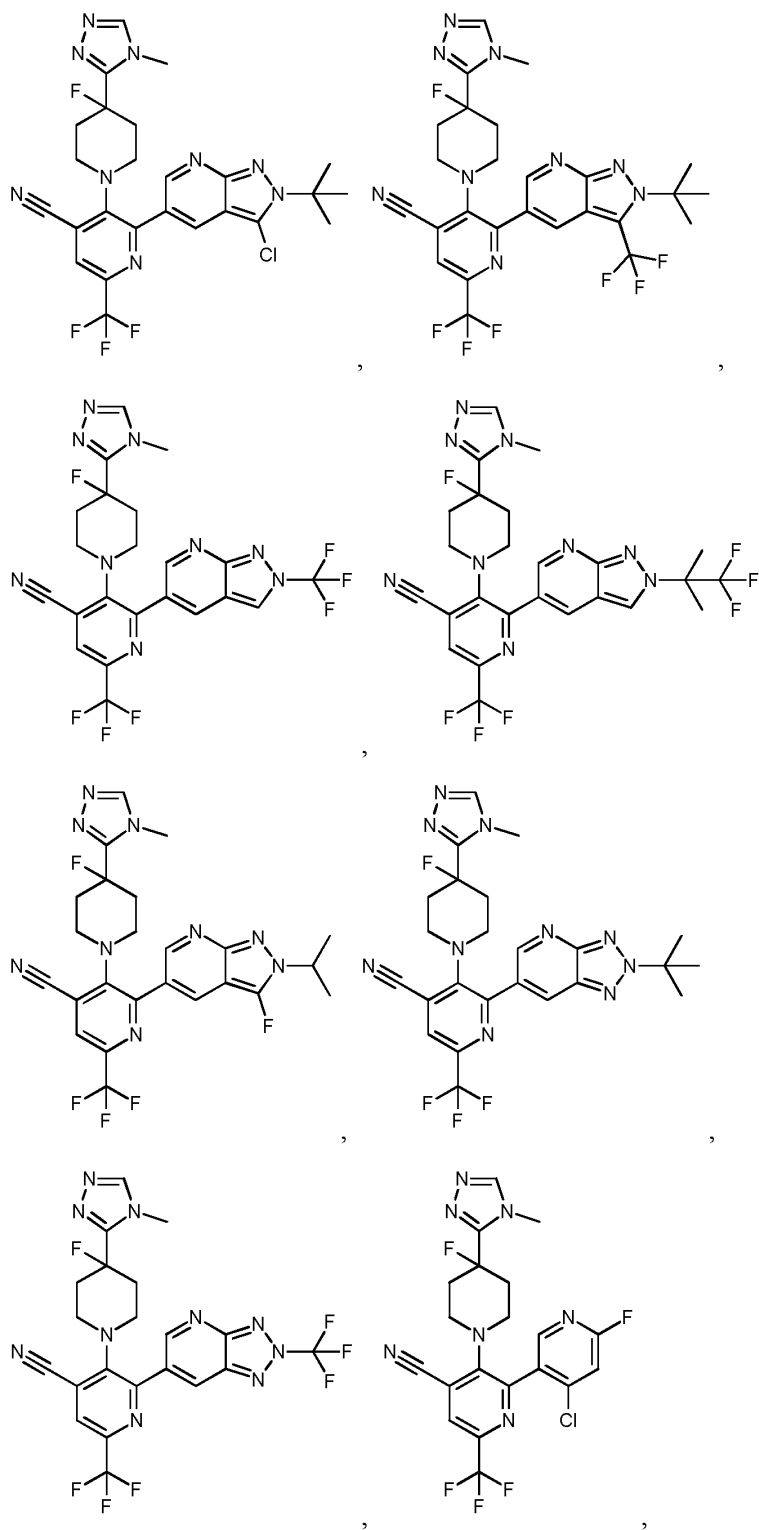
(I-f)

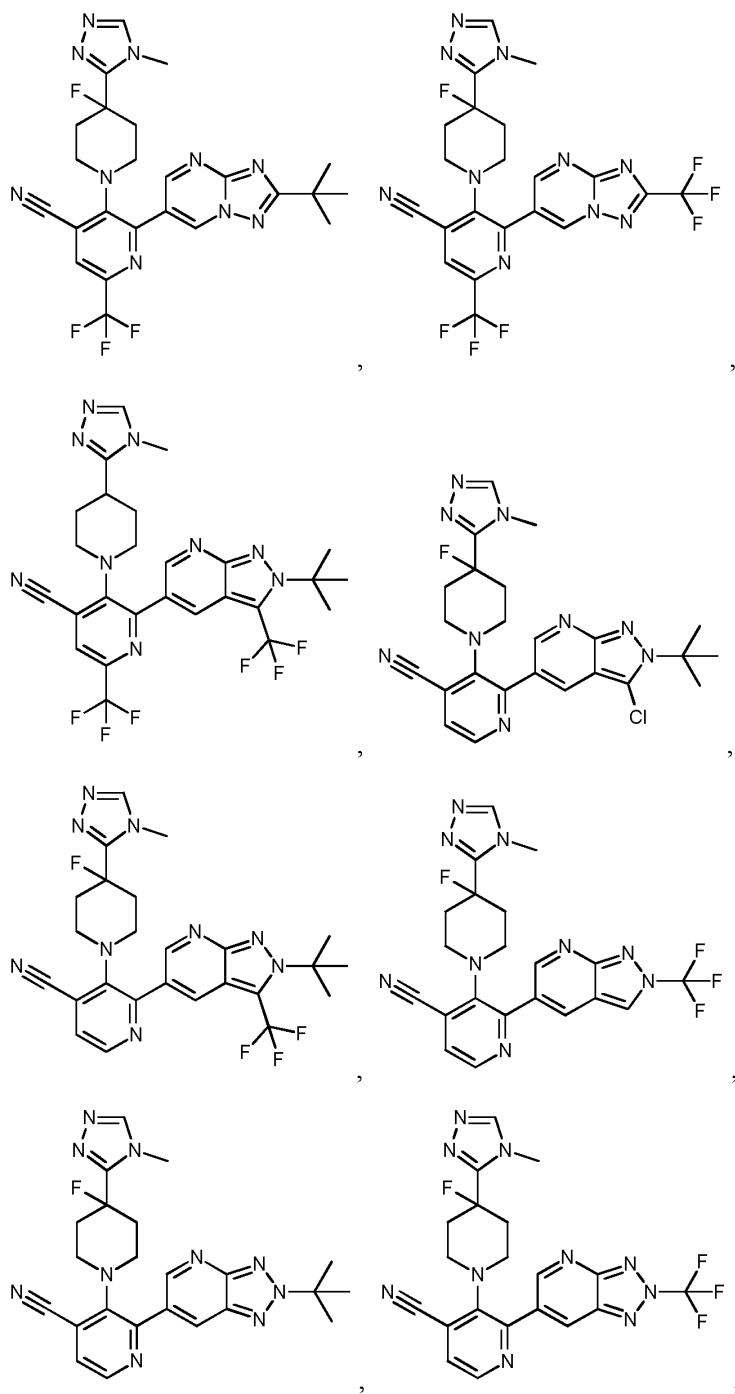
wherein substituent **R³** is defined as in any of the preceding embodiments.

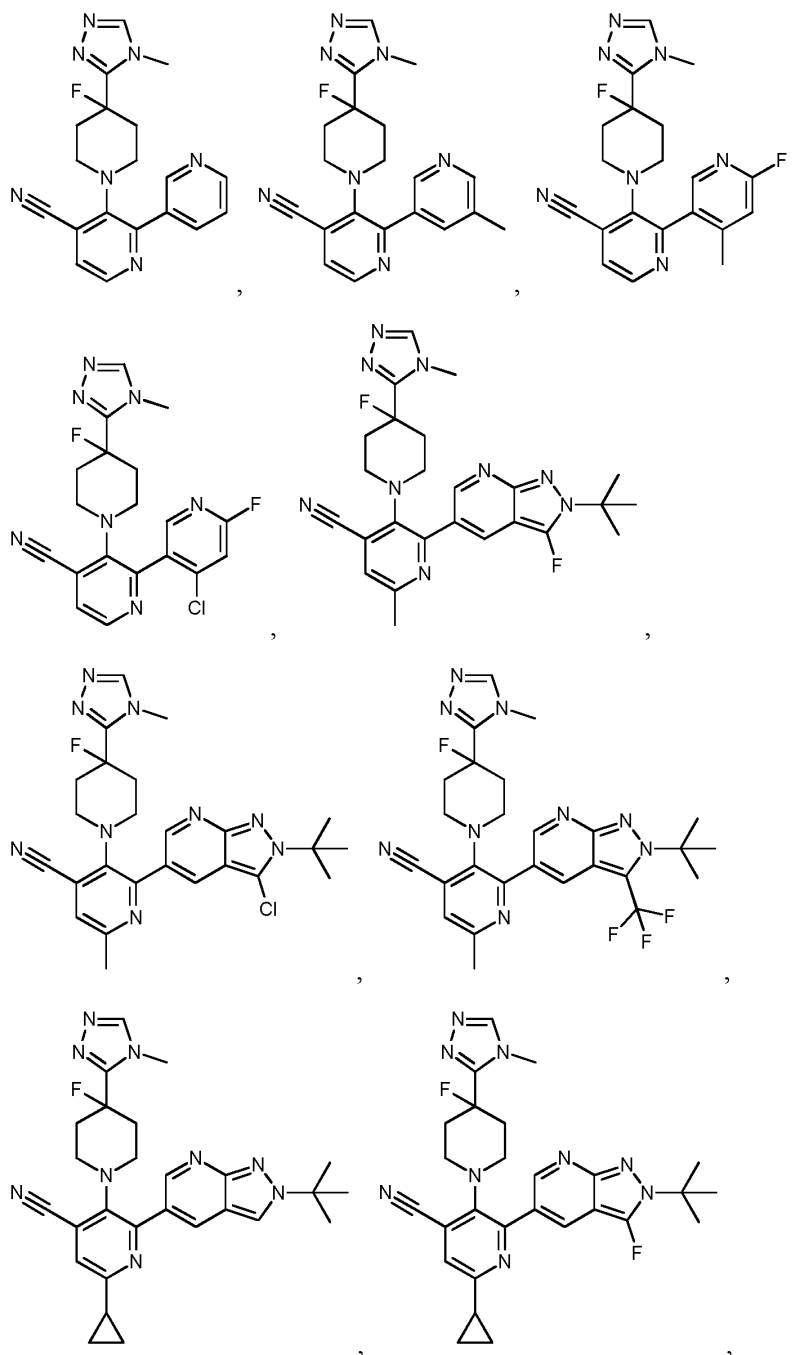
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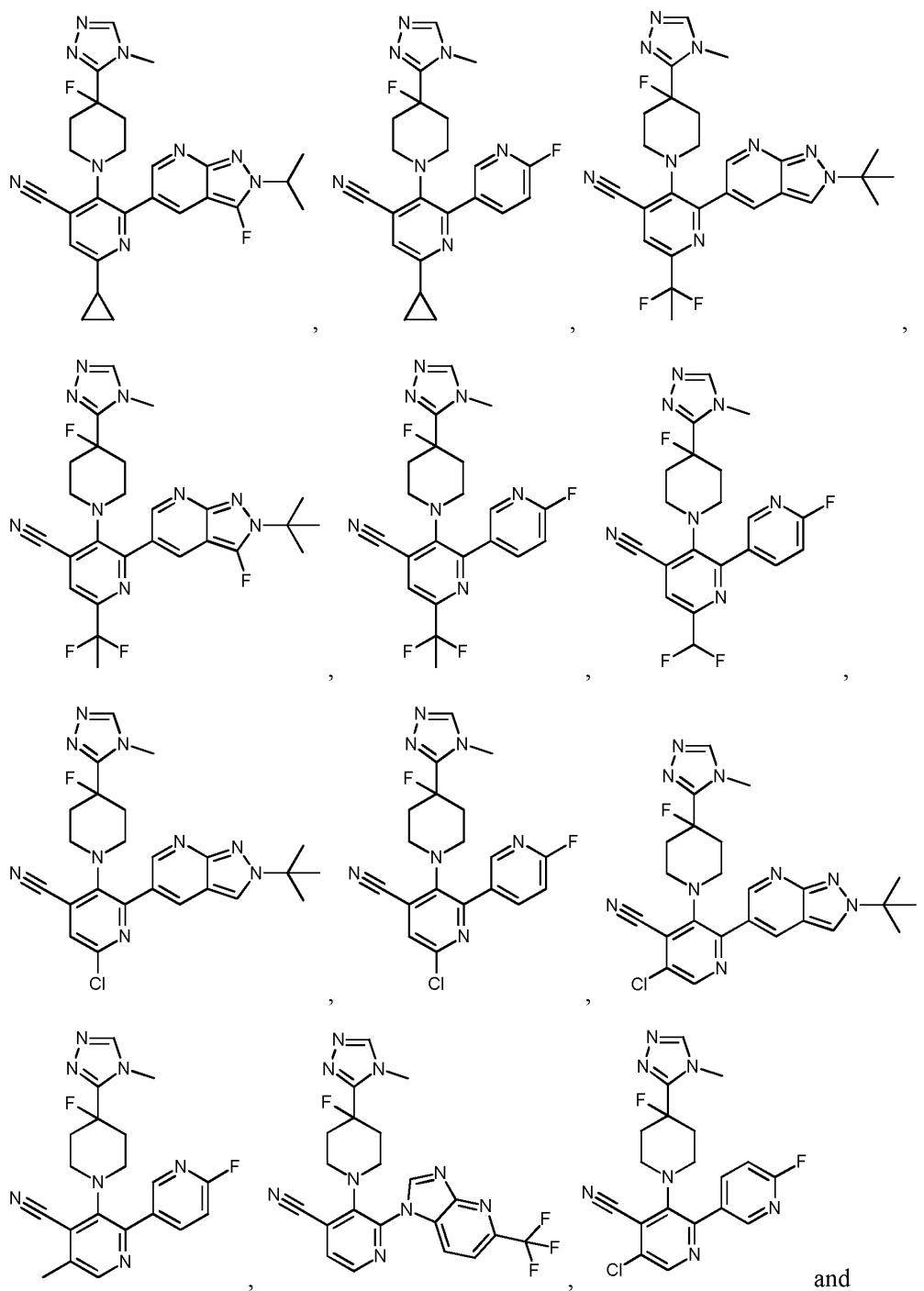
Particularly preferred is the compound according to formula (I) selected from the group consisting of

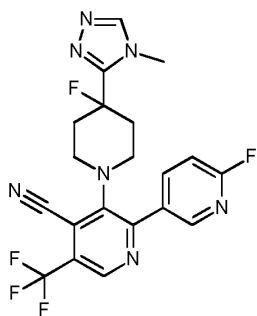












Particularly preferred is the compound according to formula (I) selected from the group consisting of example 1, example 2, example 5, example 28, example 29, example 31, example 32, example 33, example 34 and example 36 as described hereinafter in EXAM-
 5 PLES.

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

10

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.

15

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.

20

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

25

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.

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 from the foregoing and following description and the examples.

USED TERMS AND DEFINITIONS

5

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
10 specification, however, unless specified to the contrary, the following terms have the meaning indicated and the following conventions are adhered to.

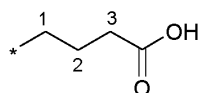
In the groups, radicals, or moieties defined below, the number of carbon atoms is often specified preceding the group, for example, C₁₋₆-alkyl means an alkyl group or radical hav-
15 ing 1 to 6 carbon atoms. In general in groups like HO, H₂N, (O)S, (O)₂S, NC (cyano), HOOC, F₃C or the like, the skilled 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-
20 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
25 used in sub-formulas to indicate the bond which is connected to the core molecule as defined.

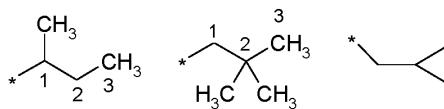
The numeration of the atoms of a substituent starts with the atom which is closest to the core or to the group to which the substituent is attached.

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

30



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:



5

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
10 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
15 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 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.

20 Unless specifically indicated, also "pharmaceutically acceptable salts" as defined in more 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
25 using stereochemically pure starting materials and/or by stereoselective synthesis. It is 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.

30 Enantiomerically pure compounds of this invention or intermediates may be prepared via 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.

- 5 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
10 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
15 (fractional) crystallization from a suitable solvent in the presence of an optically active chiral auxiliary.

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
20 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.

As used herein, "pharmaceutically acceptable salt" refers to derivatives of the disclosed
25 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 such as carboxylic acids; and the like.

30 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-benzenesulfonic 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.

5 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 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.

15

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 C_{1-5} -alkyl embraces the radicals H_3C- , H_3C-CH_2- , $H_3C-CH_2-CH_2-$, $H_3C-CH(CH_3)-$, $H_3C-CH_2-CH_2-CH_2-$, $H_3C-CH_2-CH(CH_3)-$, $H_3C-CH(CH_3)-CH_2-$, $H_3C-C(CH_3)_2-$, $H_3C-CH_2-CH_2-CH_2-CH_2-$, $H_3C-CH_2-CH_2-CH(CH_3)-$, $H_3C-CH_2-CH(CH_3)-CH_2-$, $H_3C-CH(CH_3)-CH_2-CH_2-$, $H_3C-CH_2-C(CH_3)_2-$, $H_3C-C(CH_3)_2-CH_2-$, $H_3C-CH(CH_3)-CH(CH_3)-$ and $H_3C-CH_2-CH(CH_2CH_3)-$.

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.

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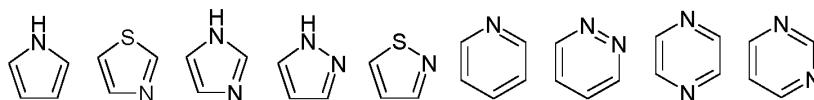
The term " C_{3-k} -cycloalkyl", wherein k is an integer selected from 3, 4, 5, 7 or 8, preferably 4, 5 or 6, either alone or in combination with another radical, denotes a cyclic, saturated,

unbranched hydrocarbon radical with 3 to k C atoms. For example the term C₃₋₇-cycloalkyl includes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

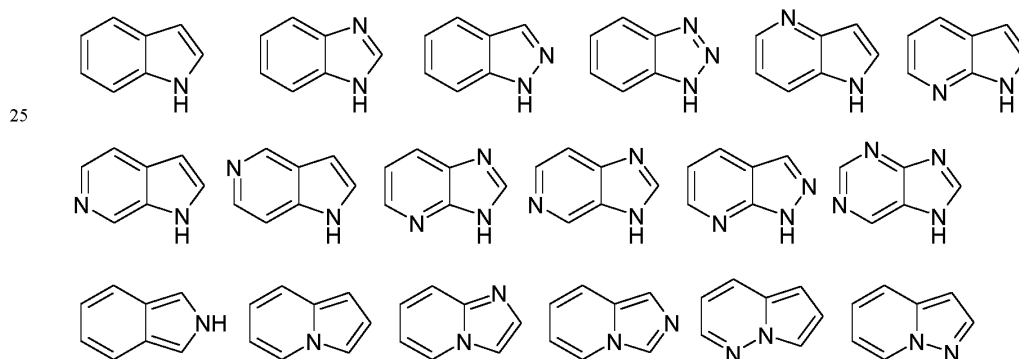
The term "halo" added to an "alkyl", "alkylene" or "cycloalkyl" group (saturated or unsaturated) defines an alkyl, alkylene or cycloalkyl group wherein one or more hydrogen atoms are replaced by a halogen atom selected from among fluorine, chlorine or bromine, preferably fluorine and chlorine, particularly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

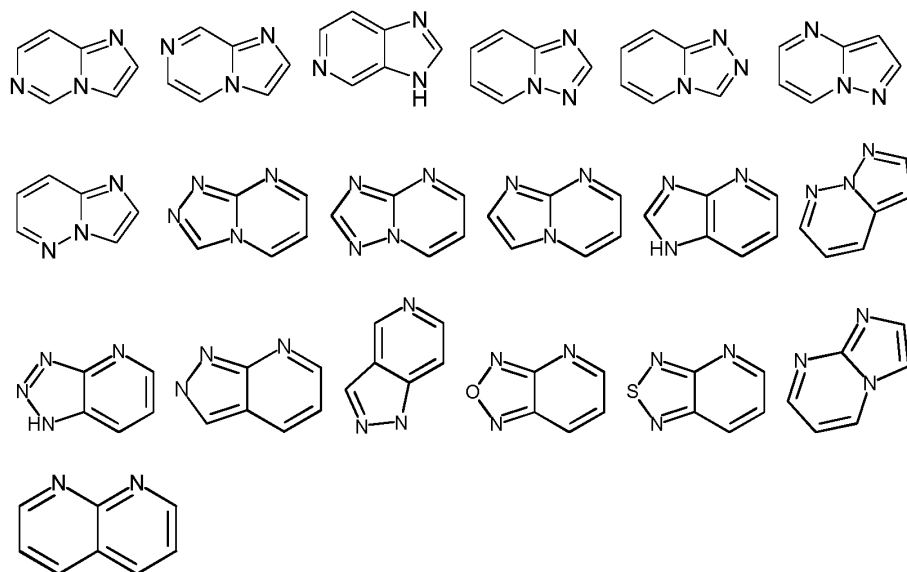
The term "mono-heteroaryl ring" means a monocyclic aromatic ring system, containing one or more heteroatoms selected from N, O or S, consisting of 5 to 6 ring atoms.

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):

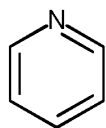


The term "fused bicyclic-heteroaryl ring" means a bicyclic aromatic ring system, containing one or more heteroatoms selected from N, O or S, consisting of 9 to 10 ring atoms. The term "fused bicyclic-heteroaryl ring" is intended to include all the possible isomeric forms. Thus, the term "bicyclic-heteroaryl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

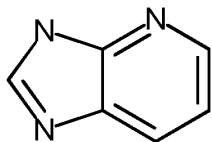




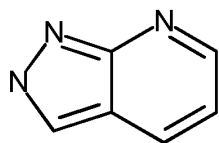
- 5 The term pyridyl refers to the radical of the following ring:



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

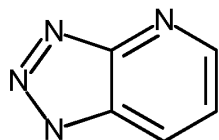


The term 2H-pyrazolo[3,4-b]pyridyl refers to the radical of the following ring:

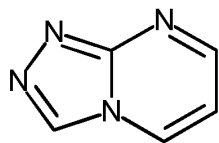


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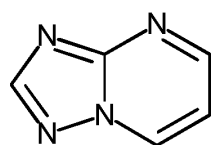
The term 1H-[1,2,3]triazolo[4,5-b]pyridyl refers to the radical of the following ring:



The term [1,2,4]triazolo[4,3-a]pyrimidinyl refers to the radical of the following ring:



The term [1,2,4]triazolo[1,5-a]pyrimidinyl refers to the radical of the following ring:



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.

BIOLOGICAL ASSAYS

10 Evaluation of inhibitory activity on QPCT and QPCTL

Assay A: Biochemical QPCT and QPCTL Activity Assay

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 μ L 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 μ L of CD47 peptide substrate surrogate (19 QLLFNKTKSVEFTFC 33) was added to each well (final concentration: 10 μ M for QPCTL / 20 μ M 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 μ L containing stable isotope labeled internal standard peptide 19 [Pyr]LLFN(K)TKSVEFTFC 33 (final concentration 4.0 μ M) as well as SEN177 (final concentration 10 μ M). 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.1 Mass spectra

were acquired with a rapifleX MALDI-TOF/TOF instrument tracking the signals of the product ($^{19}\text{[Pyr]LLFNKTKSVEFTFC}^{33}$, m/z 1,787.9037) as well as internal standard ($^{19}\text{[Pyr]LLFN(K)TKSVEFTFC}^{33}$, 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	1	1
2	1	1
3	1	1
4	9	5
5	2	4
6	2	2
7	2	2
8	5	4
9	56	100
10	10	27
11	3	3
12	24	29
13	8	16
14	1	<1
15	4	3
16	1	1
17	2	2
18	33	52
19	18	62
20	13	35

21	1	6
22	5	15
24	7	11
25	1	1
26	<1	<1
27	2	2
28	1	<1
29	1	1
30	1	1
31	2	4
32	1	1
33	1	1
34	2	6
35	3	10
36	1	<1
37	2	6
38	1	<1
39	3	6
40	4	5
41	1	2

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

Prior art Compound	Reference	Inhibition of QPCTL: IC₅₀ [nM]	Inhibition of QPCT: IC₅₀ [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)

The activity of the compounds of the invention may be demonstrated using the following
 5 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%
 15 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 fol-
 20 lowed 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 using a Pherastar Multi-Mode Reader. Dose-response curves & IC₅₀ data were calculated with 4-parameter sigmoidal dose response formula.

25

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	9	17
2	17	53
3	14	28
4	31	46
5	41	67
6	26	50
7	26	39
8	67	29
9	869	365
10	352	201
11	47	29
12	860	599
13	54	70
14	21	12
15	69	66
16	37	9
17	102	40
18	942	292
19	2192	410
20	1371	615
21	187	115
22	435	218
24	321	349
25	9	7
26	6	13
27	26	34

28	7	12
29	17	45
30	25	20
31	87	41
32	4	21
33	13	26
34	37	20
35	154	43
36	9	13
37	95	35
38	21	6
39	247	106
40	258	115
41	71	16

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 x 10⁵ cells/1 cm² area) are seeded on filter inserts (Costar transwell polycarbonate or PET filters, 0.4 µm 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 MgSO₄, 1.8 mM CaCl₂, 4.17 mM NaHCO₃, 1.19 mM Na₂HPO₄ x 7H₂O, 0.41 mM NaH₂PO₄xH₂O, 15 mM HEPES, 20 mM glucose, 0.25% BSA, pH 7.2) to prepare the transport solutions (0.1 - 300 µM compound, final DMSO <= 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	5.3	6.4
2	16.0	4.9
3	47.0	1.0
4	99.5	0.6
5	6.1	8.2
6	7.2	10.1
7	5.8	11.9
8	31.0	2.6
9	45.0	1.4
10	58.0	1.2
11	4.3	14.9
12	4.9	6.9
13	3.7	5.7
14	12.0	6.9

15	35.0	1.6
16	3.1	7.7
17	7.2	13.9
18	27.0	2.8
19	11.0	2.6
20	14.0	4.5
21	18.0	2.4
22	34.0	1.6
24	1.0	14.1
25	7.6	9.9
26	20.0	4.2
27	38.0	2.4
28	19.0	3.8
29	29.0	2.7
30	9.4	9.4
31	62.0	1.4
32	8.2	8.2
33	31.0	2.2
34	23.0	1.7
35	17.0	3.6
36	5.8	13.3
37	23.0	2.2
38	6.6	10.9
39	16.0	2.9
40	18.0	2.8
41	28.0	2.6

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:

- 5 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), microsomal 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 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.

- 15 The intrinsic clearance (CL_{INTRINSIC}) is calculated by considering the amount of protein in the incubation:

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

- CL_{INTRINSIC_INVIVO} [ml/min/kg] = (CL_{INTRINSIC} [µL/min/mg protein] x MPPGL [mg protein/g liver] x liver factor [g/kg bodyweight]) / 1000

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

Hepatocellularity, human: 120×10^6 cells / g liver

Liver factor, human: 25.7 g / kg bodyweight

Blood flow, human: 21 ml/(min x kg)

5 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 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 120×10^6 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:

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

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:

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

Results are expressed as percentage of hepatic blood flow:

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

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 µM. The subsequent dialysis solutions are prepared in plasma (supplemented with NaEDTA as anticoagulant), and aliquots of 200 µl test compound dialysis solution in plasma are dispensed into the donor (plasma) chambers. Aliquots of 200 µl 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 µm 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 µg 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 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 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%.

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.

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 C_{max} are normalized to a dose of 1 µmol/kg.

METHOD OF TREATMENT

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 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, lymphangioma, leiomyomatosis, 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), Pigeon 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.

(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 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 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 erythemanodosum.

- 5 (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.

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.

15 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.

20 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 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, lymphangiomyomatosis, pulmonary alveolar proteinosis, Langerhan's cell histiocytosis, pleural parenchymal fibroelastosis, interstitial lung diseases of
25 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
30

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
5 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.

(2) Other fibrotic diseases such as hepatic bridging fibrosis, liver cirrhosis, non-alcoholic steatohepatitis (NASH), atrial fibrosis, endomyocardial fibrosis, old myocardial infarction,
10 glial scar, arterial stiffness, arthrofibrosis, Dupuytren's contracture, keloid, scleroderma/ systemic sclerosis, mediastinal fibrosis, myelotibrosis, 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, cryobi-
15 opsy), 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,
20 multiple myeloma (MM), myelodysplastic syndrome, solid cancer, lung cancer, adenocarcinoma, small cell lung cancer (SCLC), non-small cell lung cancer (NSCLC), mediastinum 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,
25 cervical cancer, gynaecological cancer, genito-urinary cancer, ovarian cancer, endometrial 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, kera-
30 toacanthoma, 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 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.

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.

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.

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.

COMBINATION THERAPY

5

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

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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

15

more active substances to be reduced.

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.

20

Chemotherapy is a type of cancer therapy that uses one or more chemical anti-cancer 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, antimetabolic agents, taxanes and further state-of-the-art or standard-of-care compounds.

25

Targeted therapy is a type of cancer treatment that uses drugs to target specific genes and 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,

30

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, Olaratumab, 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 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 asPBI-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.

5 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
10 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
15 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
20 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
25 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.

30 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.

5 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.

10 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

15 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
20 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.

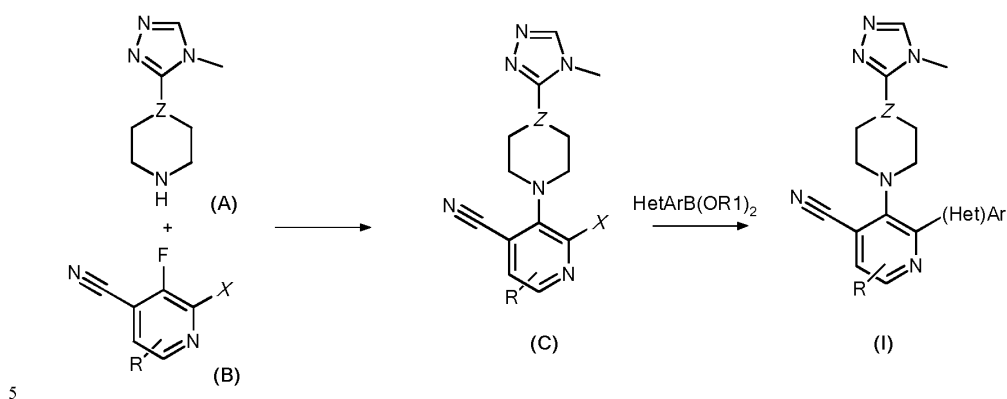
The general processes for preparing the compounds according to the invention will become apparent to the one skilled in the art studying the following schemes. Any functional
25 groups in the starting materials or intermediates may be protected using conventional protecting groups. These protecting groups 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
30 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 1 - 41 may be prepared as shown in Scheme I below.

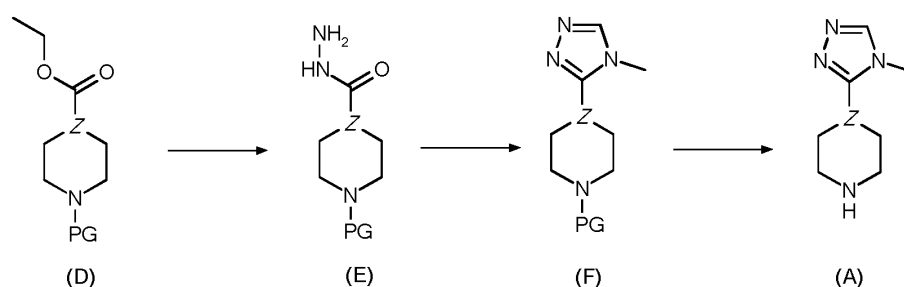
Scheme I:



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).

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

Scheme II:

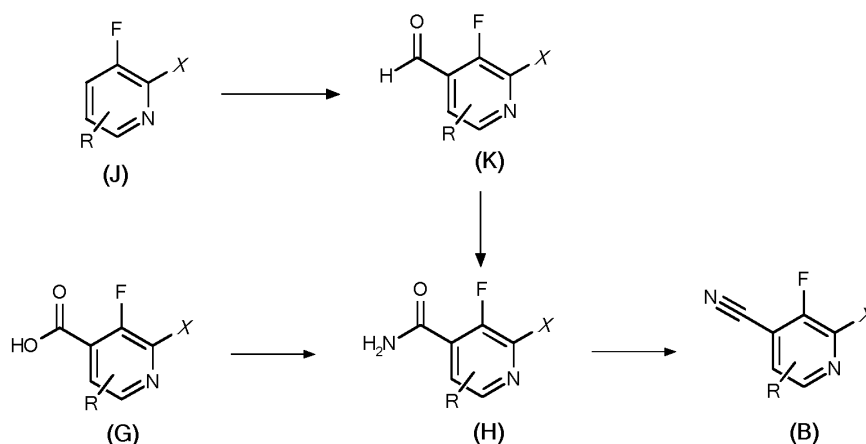


Compounds of formula (A) with Z = C-F, C-H can be prepared from the corresponding piperidinyl esters (D) equipped with a suitable protecting group (PG, e.g. Benzyl) by treatment with a suitable hydrazine source (e.g. N₂H₄*H₂O) at elevated temperature (e.g. 50 °C).

°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). The compound of formula (A) with Z = C-H can also be obtained from commercial sources.

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

Scheme III:



In case of R=H, intermediates of formula (B) can be prepared from the corresponding carboxylic acids (G). 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. 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.

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.

20

Abbreviations:

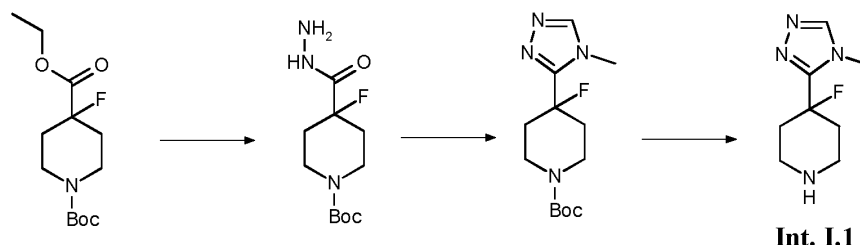
ACN	acetonitrile
Aq.	aqueous
BOC	<i>tert</i> -butoxycarbonyl
brine	saturated aqueous NaCl solution
°C	degree celsius
CDI	carbonyl diimidazole
CyH/CH	cyclohexane
CO ₂	carbon dioxide
conc.	concentrated
Cs ₂ CO ₃	cesium carbonate
Cu(OAc) ₂	copper (II) acetate
DAST	(diethylamino)sulfur trifluoride

DCE	dichloroethane
DCM	dichloromethane
DIPA	<i>N,N</i> -diisopropylamine
DIPEA	<i>N,N</i> -diisopropylethylamine
DMF	<i>N,N</i> -dimethylformamide
DMSO	dimethyl sulfoxide
Dppf	1,1'-Bis(diphenylphosphino)ferrocene
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
HATU	1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate
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
L	liter
LDA	lithium diisopropylamide
LiOH	lithium hydroxide
M	Molar (mol/L)
MeOH	methanol
MgSO ₄	magnesium sulfate
min	minute
mL	milliliter
μL	microliter

N ₂	nitrogen
n-BuLi	n-Butyllithium
NCS	N-Chlorosuccinimide
Na ₂ CO ₃	sodium carbonate
NaH	sodium hydride
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
PE	petroleum ether
Prep.	preparative
RP	reversed phase
RT/rt	room temperature (about 20°C)
sat.	saturated
Selectfluor	1-Chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetra-fluoroborate)
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: 284.2 [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. 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.

25

$C_{13}H_{21}FN_4O_2$ (M=284.3 g/mol)
ESI-MS: 285.1 [M+H]⁺
Rt (HPLC): 0.77 min (method A)

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.

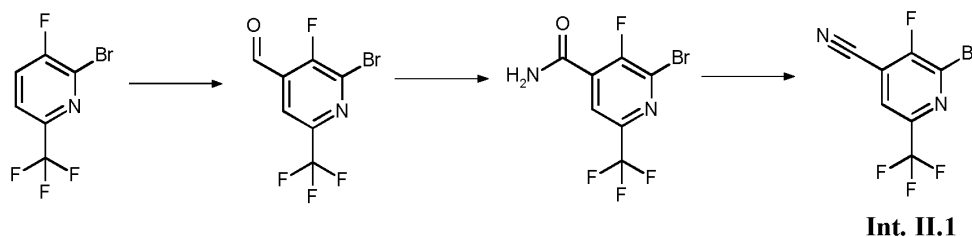
The hydrochloride salt (13.5 g) is added to a solution of ammonia in methanol (7 M, 150 mL) and purified by column chromatography (Biotage SNAP Cartridge KP-NH 110 g, gradient DCM/MeOH 4:1 to 7:3) to afford the title compound.

$C_8H_{13}FN_4$ (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**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.

$C_7H_2BrF_4NO$ (M=272.0 g/mol)

ESI-MS: no mass detected

Rt (HPLC): 0.51 min (method B)

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

5

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®, SiO₂, CyH/EtOAc gradient 1:0 to 7:3) to yield the desired product.

10

$C_7H_3BrF_4N_2O$ (M=287.0 g/mol)

ESI-MS: 285 / 287 $[M-H]^-$

15

Rt (HPLC): 0.50 min (method B)

Intermediate II.1: 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.

20

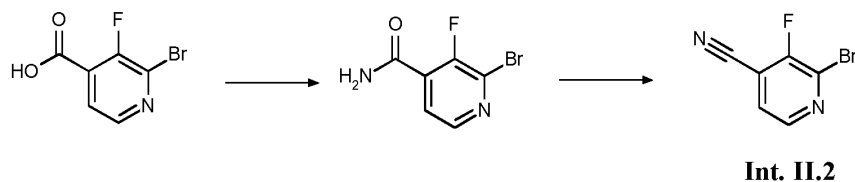
$C_7HBrF_4N_2$ (M=268.9 g/mol)

ESI-MS: 268 / 270 $[M+H]^+$

25

Rt (HPLC): 0.59 min (method C)

Synthesis of Intermediate II.2



30

2-Bromo-3-fluoropyridine-4-carboxamide

2-Bromo-3-fluoropyridine-4-carboxylic acid (25.0 g, 0.114 mol) is suspended in THF (250 mL), and 1,1'-carbonyldiimidazole (22.1 g, 0.136 mol) is added in several smaller portions. The reaction mixture is stirred for 3 h at ambient temperature, before a solution of ammonia (32% in H₂O, 64.8 mL, 0.938 mol) is added slowly. The resulting reaction mixture is stirred for additional 3h at ambient temperature. The mixture is concentrated, the residue loaded onto Extrelut® and purified by column chromatography (SiO₂, DCM/MeOH 9:1) to yield 2-bromo-3-fluoropyridine-4-carboxamide.

C₆H₄BrFN₂O (M=219.0 g/mol)

ESI-MS: 219 / 221 [M+H]⁺

Rt (HPLC): 0.28 min (method C)

Intermediate II.2: 2-bromo-3-fluoropyridine-4-carbonitrile

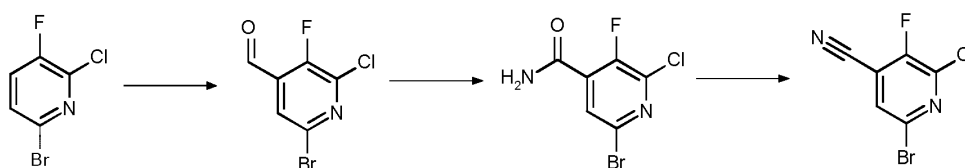
2-Bromo-3-fluoropyridine-4-carboxamide (17.4 g, 79.5 mmol) is added to dichloromethane (250 mL). Burgess reagent (CAS: 29684-56-8, 22.0 g, 89.5 mmol) is added, and the resulting reaction mixture is stirred for 16 h at ambient temperature. The mixture is concentrated to half of the original volume and purified by column chromatography (SiO₂, DCM) to yield the title compound.

C₆H₂BrFN₂ (M=201.0 g/mol)

ESI-MS: no mass detected

Rt (HPLC): 0.41 min (method D)

¹H NMR (400 MHz, DMSO-d₆) δ = 8.52 (d, *J* = 4.9 Hz, 1H), 8.05 (t, *J* = 4.8 Hz, 1H)

Synthesis of Intermediate II.3**Int. II.3****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. 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: 234 / 236 $[\text{M}+\text{H}]^+$

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 $[\text{M}-\text{H}]^-$

20 Rt (HPLC): 0.41 min (method B)

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

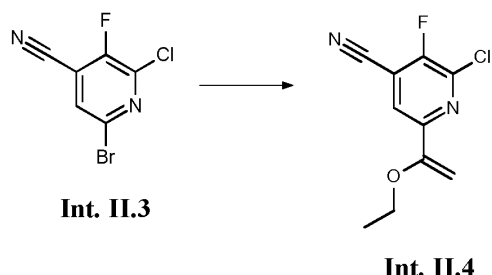
6-Bromo-2-chloro-3-fluoropyridine-4-carboxamide (510 mg, 2.01 mmol) is dissolved in dichloromethane (10 mL), and Burgess reagent (CAS: 29684-56-8, 742 mg, 3.02 mmol) is added at ambient temperature. The resulting reaction mixture is stirred for 16 h and then directly purified by column chromatography (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

30 Rt (HPLC): 0.61 min (method B)

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

Intermediate II.4: 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 dissolved 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.

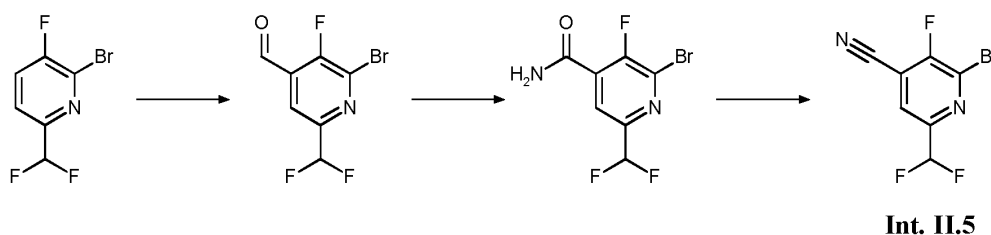
10 C₁₀H₈ClFN₂O (M=226.6 g/mol)

ESI-MS: no mass detected

Rt (HPLC): 0.80 min (method B)

¹H NMR (400 MHz, DMSO-d₆) δ = 8.08 (d, J = 4.1 Hz, 1H), 5.31 (d, J = 2.3 Hz, 1H), 4.62 (d, J = 2.4 Hz, 1H), 3.97 (d, J = 7.0 Hz, 2H), 1.38 (s, 3H)

15

Synthesis of Intermediate II.5**2-Bromo-6-(difluoromethyl)-3-fluoropyridine-4-carbaldehyde**

Under an argon atmosphere, 2-bromo-6-(difluoromethyl)-3-fluoropyridine (1.00 g, 4.12 mmol) is dissolved in THF (25 mL), and the resulting mixture is cooled to -70 °C. A solution of lithium diisopropylamide (1 M in THF, 4.33 mL, 4.33 mmol) is added dropwise, and the mixture is stirred for 1 h at -70 °C. DMF (381 μ L, 4.95 mmol) dissolved in THF (2 mL) is added dropwise. The mixture is stirred for additional 1 h at -70 °C. The reaction is quenched by the addition of a saturated solution of NH₄Cl and diluted with Me-THF. After extraction,

the organic phase is separated, washed with water, dried, and concentrated. The residue is purified by column chromatography (SiO₂, CyH/EtOAc gradient 1:0 to 7:3) to yield 2-bromo-6-(difluoromethyl)-3-fluoropyridine-4-carbaldehyde.

C₇H₃BrF₃NO (M=254.0 g/mol)

5 ESI-MS: no mass detected

Rt (HPLC): 0.47 min (method C)

¹H NMR (400 MHz, DMSO-d₆) δ = 10.19 (s, 1H), 8.04 (d, *J* = 4.4 Hz, 1H), 7.10 (t, *J* = 54.3 Hz, 1H)

10 **2-Bromo-6-(difluoromethyl)-3-fluoropyridine-4-carboxamide**

Ammonium acetate (2.05 g, 26.6 mmol) and 2-bromo-6-(difluoromethyl)-3-fluoropyridine-4-carbaldehyde (675 mg, 2.66 mmol) are mixed, and acetonitrile (15 mL) is added. Phenyltrimethylammonium tribromide (2.06 g, 5.32 mmol) is added in small portions, and the resulting reaction mixture is stirred for 18 h at ambient temperature. The mixture is
15 filtered, and the residue is washed with acetonitrile, purified by column chromatography (dry load, SiO₂, CyH/EtOAc gradient 1:0 to 7:3) to yield the desired product.

C₇H₄BrF₃N₂O (M=269.0 g/mol)

ESI-MS: 270 / 272 [M+H]⁺

Rt (HPLC): 0.57 min (method C)

20

Intermediate II.5: 2-bromo-6-(difluoromethyl)-3-fluoropyridine-4-carbonitrile

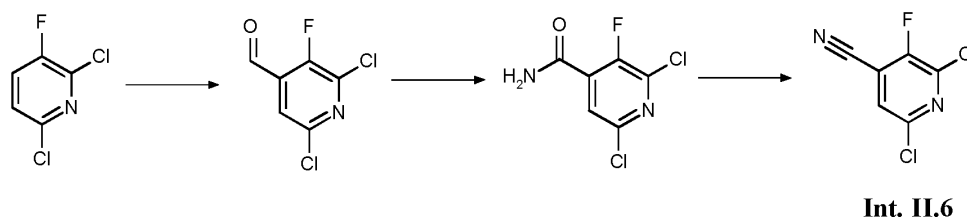
2-Bromo-6-(difluoromethyl)-3-fluoropyridine-4-carboxamide (290 mg, 1.08 mmol) is dissolved in dichloromethane (4 mL), and Burgess reagent (CAS: 29684-56-8, 318 mg, 1.29 mmol) is added at ambient temperature. The resulting reaction mixture is stirred for 48 h and
25 then directly purified by column chromatography (SiO₂, CyH/EtOAc gradient 1:0 to 85:15) to yield the title compound.

C₇H₂BrF₃N₂ (M=251.0 g/mol)

ESI-MS: no mass detected

Rt (HPLC): 0.40 min (method C)

30

Synthesis of Intermediate II.6**2,6-Dichloro-3-fluoropyridine-4-carbaldehyde**

Under an argon atmosphere, 2,6-dichloro-3-fluoropyridine (5.00 g, 28.6 mmol) is added to THF (80 mL), and the resulting mixture is cooled to -70°C . A solution of lithium diisopropylamide (1 M in THF, 31.5 mL, 31.5 mmol) is added dropwise, and the mixture is stirred for 1.5 h at -70°C . DMF (2.64 mL, 34.3 mmol) is added dropwise. The mixture is stirred for additional 0.5 h at -70°C . The reaction is quenched by addition of acetic acid (0.5 mL), warmed to rt, and diluted with water and EtOAc. The organic phase is separated, dried, and concentrated. The residue is purified by column chromatography (SiO_2 , CyH/EtOAc gradient 95:5 to 60:40) to yield the desired product.

$\text{C}_6\text{H}_2\text{Cl}_2\text{FNO}$ (M=194.0 g/mol)

ESI-MS: 212 / 214 $[\text{M}+\text{H}_2\text{O}]^+$

Rt (HPLC): 0.70 min (method F)

2,6-Dichloro-3-fluoropyridine-4-carboxamide

Ammonium acetate (7.82 g, 101 mmol) and 2,6-dichloro-3-fluoropyridine-4-carbaldehyde (2.46 g, 10.1 mmol, 80 % purity) are mixed, and acetonitrile (30 mL) is added. Phenyltrimethylammonium tribromide (7.86 g, 20.3 mmol) is added in small portions, and the resulting reaction mixture is stirred over the weekend at ambient temperature. The mixture is filtered, and the residue is washed with acetonitrile, purified by column chromatography (SiO_2 , CyH/EtOAc gradient 92:8 to 34:66) to yield the desired product.

$\text{C}_6\text{H}_3\text{Cl}_2\text{FN}_2\text{O}$ (M=209.0 g/mol)

ESI-MS: 207 $[\text{M}-\text{H}]^-$

Rt (HPLC): 0.71 min (method F)

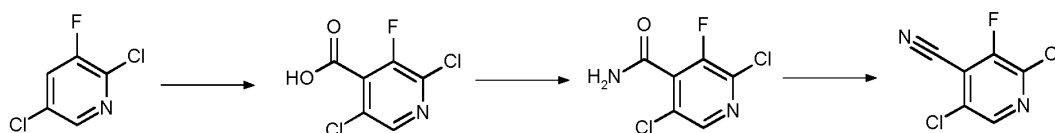
Intermediate II.6: 2,6-dichloro-3-fluoropyridine-4-carbonitrile

2,6-Dichloro-3-fluoropyridine-4-carboxamide (460 mg, 2.20 mmol) is dissolved in dichloromethane (20 mL), and Burgess reagent (CAS: 29684-56-8, 1.08 g, 4.40 mmol) is

added at ambient temperature. The resulting reaction mixture is stirred for 18 h at ambient temperature. The mixture is diluted with DCM and washed with water (2 x). The organic layer is dried, filtered, and concentrated. The residue is purified by column chromatography (SiO₂, CyH/EtOAc gradient 95:5 to 70:30) to yield the title compound.

- 5 C₆HCl₂FN₂ (M=191.0 g/mol)
 ESI-MS: no mass detected
 Rt (HPLC): 0.91 min (method F)
 ¹H NMR (400 MHz, DMSO-d₆) δ = 8.36 (d, *J* = 3.7 Hz, 1H)

10 **Synthesis of Intermediate II.7**



Int. II.7

2,5-Dichloro-3-fluoropyridine-4-carboxylic acid

- To a solution 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/z
 Rt (HPLC): 0.26 min (method G)

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

- To a solution 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 dissolved in DCM (60mL). 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.

$C_6H_3Cl_2FN_2O$ (M=209.0 g/mol)

ESI-MS: no mass detected

5 Rt (HPLC): 0.40 min (method G)

Intermediate II.7: 2,5-dichloro-3-fluoropyridine-4-carbonitrile

To a solution of 2,5-dichloro-3-fluoropyridine-4-carboxamide (3.00 g, 14.4 mmol) in DCM (30mL) is added TEA (3.19 g, 31.6 mmol) and TFAA (3.32 g, 15.8 mmol) under N_2 at 0 °C.

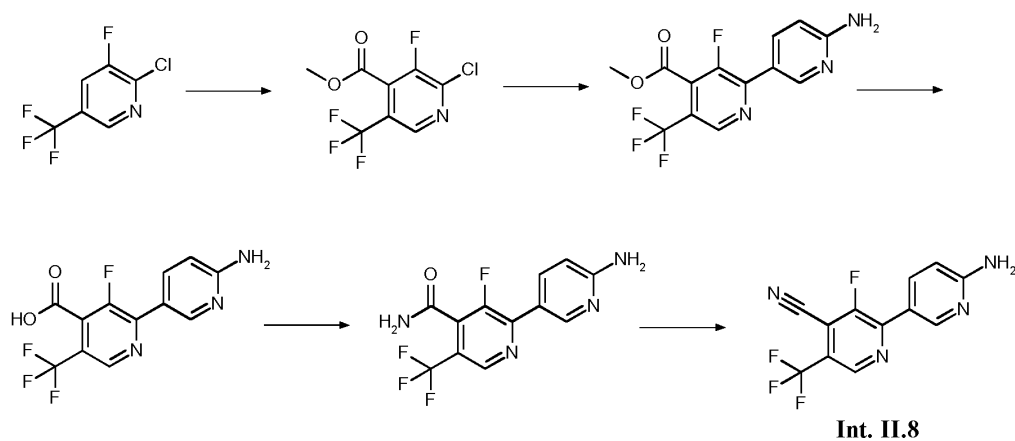
10 The mixture is stirred at 10 °C for 2 h. The reaction mixture is diluted with H_2O (100 mL) and extracted with EtOAc (2 x 100 mL). The combined organic layers are washed with brine (100 mL), dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. The residue is purified by column chromatography (SiO_2 , PE/EtOAc gradient 1:0 to 3:1) to afford the title compound.

15 $C_6HCl_2FN_2$ (M=191.0 g/mol)

ESI-MS: 190 m/z

Rt (GCMS): 6.40 min (method H 200.qgm, instrument: GCMS-005)

Synthesis of Intermediate II.8



20

Methyl 2-chloro-3-fluoro-5-(trifluoromethyl)pyridine-4-carboxylate

Under an argon atmosphere, 2-chloro-3-fluoro-5-(trifluoromethyl)pyridine (500 mg, 2.43 mmol) is dissolved in THF (10 mL), and the resulting mixture is cooled to -70 °C. A solution of lithium diisopropylamide (1 M in THF, 2.67 mL, 2.67 mmol) is added dropwise, and the mixture is stirred for 80 min at -70 °C. Methyl chloroformate (225 μ L, 2.92 mmol) is added

25

dropwise. The mixture is stirred for additional 15 min at -70°C . The reaction is quenched by addition of a half concentrated acetic acid (1 mL), warmed to rt, and diluted with water and EtOAc. The organic phase is separated, dried, and concentrated. The residue is purified by column chromatography (SiO_2 , CyH/EtOAc gradient 1:0 to 95:5) to yield the desired product.

$\text{C}_8\text{H}_4\text{ClF}_4\text{NO}_2$ (M=257.6 g/mol)
ESI-MS: 258 / 260 $[\text{M}+\text{H}]^+$
Rt (HPLC): 0.60 min (method C)

10 **Methyl 6'-amino-3-fluoro-5-(trifluoromethyl)-[2,3'-bipyridine]-4-carboxylate**

Under an argon atmosphere, methyl 2-chloro-3-fluoro-5-(trifluoromethyl)pyridine-4-carboxylate (130 mg, 0.51 mmol), 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-amine (133 mg, 0.61 mmol) and K_2CO_3 (2 M in water, 505 μL , 1.01 mmol) are dissolved in 1,4-dioxane (2 mL) and the resulting mixture is degassed by passing an argon stream through the mixture. [1,1'-Bis-(diphenylphosphino)-ferrocen]-dichloro-palladium(II) dichloromethane complex ($\text{Pd}(\text{dppf})\text{Cl}_2 \cdot \text{CH}_2\text{Cl}_2$, CAS: 95464-05-4) (36.9 mg, 0.05 mmol) is added, and the mixture is degassed. The mixture is then heated to 90°C and stirred at this temperature for 3 h. After cooling to ambient temperature, the mixture is concentrated, and the residue is dissolved in ACN, filtered, and purified by preparative HPLC (XBridge C18, ACN/water gradient containing 0.1% NH_3) to yield methyl 6'-amino-3-fluoro-5-(trifluoromethyl)-[2,3'-bipyridine]-4-carboxylate.

$\text{C}_{13}\text{H}_9\text{F}_4\text{N}_3\text{O}_2$ (M=315.2 g/mol)
ESI-MS: 316 $[\text{M}+\text{H}]^+$
Rt (HPLC): 0.41 min (method C)

25 **6'-Amino-3-fluoro-5-(trifluoromethyl)-[2,3'-bipyridine]-4-carboxylic acid**

Methyl 6'-amino-3-fluoro-5-(trifluoromethyl)-[2,3'-bipyridine]-4-carboxylate (115 mg, 0.37 mmol) is dissolved in 1,4-dioxane (3 mL) and LiOH (26.2 mg, 1.09 mmol), dissolved in water (1 mL), is added, and the reaction mixture is stirred at ambient temperature overnight. The reaction mixture is acidified with acidic acid to pH 5 and diluted with water (3 mL). The formed precipitate is filtered, washed with water and dried to afford the desired compound.

$C_{12}H_7F_4N_3O_2$ (M=301.2 g/mol)
 ESI-MS: 302 $[M+H]^+$
 Rt (HPLC): 0.24 min (method C)

5 **6'-Amino-3-fluoro-5-(trifluoromethyl)-[2,3'-bipyridine]-4-carboxamide**

6'-Amino-3-fluoro-5-(trifluoromethyl)-[2,3'-bipyridine]-4-carboxylic acid (70.0 mg, 0.23 mmol) and HATU (155 mg, 0.41 mmol) are dissolved in DMF (1 mL) and ammonia (0.5 M in THF, 2.50 mL, 1.25 mmol) is added. The reaction mixture is stirred at ambient temperature for 20 h and purified by preparative HPLC (XBridge C18, ACN/water gradient
 10 containing 0.1% NH_3) to yield the desired compound.

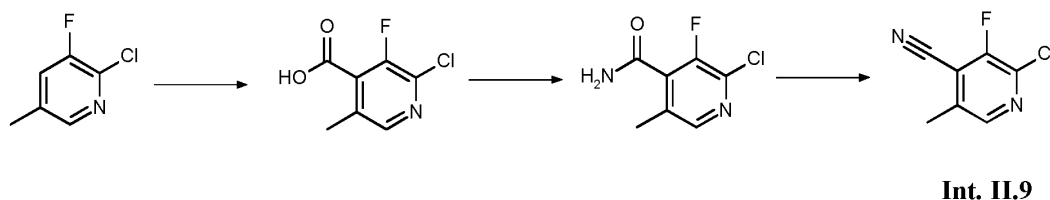
$C_{12}H_8F_4N_4O$ (M=300.2 g/mol)
 ESI-MS: 301 $[M+H]^+$
 Rt (HPLC): 0.35 min (method B)

15 **Intermediate II.8: 6'-amino-3-fluoro-5-(trifluoromethyl)-[2,3'-bipyridine]-4-carbonitrile**

6'-Amino-3-fluoro-5-(trifluoromethyl)-[2,3'-bipyridine]-4-carboxamide * trifluoroacetic acid (50.0 mg, 0.12 mmol) is dissolved in DCM (4 mL). TEA (234 μ L, 1.69 mmol) and trifluoroacetic anhydride (101 μ L, 0.72 mmol) are added and the reaction mixture is stirred
 20 at ambient temperature for 30 h. The reaction mixture is concentrated, and the residue is dissolved 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.

$C_{12}H_6F_4N_4$ (M=282.2 g/mol)
 ESI-MS: 283 $[M+H]^+$
 25 Rt (HPLC): 0.39 min (method C)

Synthesis of Intermediate II.9



2-Chloro-3-fluoro-5-methylpyridine-4-carboxylic acid

To a solution of 2-chloro-3-fluoro-5-methylpyridine (5.00 g, 34.4 mmol) and DIPA (3.82 g, 37.8 mmol) in THF (50 mL) is added n-BuLi (2.20 g, 34.4 mmol) at -78 °C under N₂. The mixture is stirred at -78 °C for 2 h. Then fresh dry ice CO₂ (7.56 g, 172 mmol) is added at -78 °C. The resulting mixture is stirred at 25 °C for 10 h. The reaction mixture is diluted with H₂O (100 mL) and extracted with EtOAc (2 x 100 mL). The aqueous phase is acidified to pH 1 and the mixture is filtered and concentrated under reduced pressure to yield 2-chloro-3-fluoro-5-methylpyridine-4-carboxylic acid.

C₇H₅ClFNO₂ (M=189.6 g/mol)

ESI-MS: 190 m/z

Rt (HPLC): 0.34 min (method G)

2-Chloro-3-fluoro-5-methylpyridine-4-carboxamide

To a solution of 2-chloro-3-fluoro-5-methylpyridine-4-carboxylic acid (2.50 g, 13.1 mmol) in DCM (30 mL) is added oxalyl chloride (8.29 g, 65.3 mmol) and DMF (9.5 mg, 0.13 mmol). The mixture is stirred at 25 °C for 2 h. The reaction mixture is concentrated and poured into NH₃/H₂O (30 mL). The resulting mixture is stirred at 25 °C for 12 h. The reaction mixture is filtered and concentrated under reduced pressure to yield crude 2-chloro-3-fluoro-5-methylpyridine-4-carboxamide, which is used without further purification

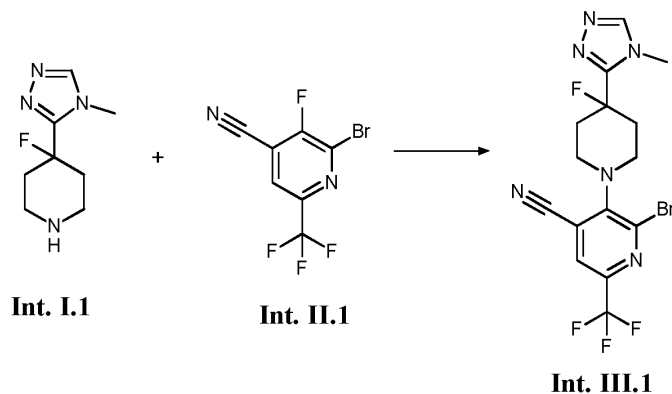
Intermediate II.9: 2-chloro-3-fluoro-5-methylpyridine-4-carbonitrile

To a solution of 2-chloro-3-fluoro-5-methylpyridine-4-carboxamide (1.50 g, 7.95 mmol) in DCM (20 mL) is added TFAA (1.67 g, 7.95 mmol) and TEA (0.80 g, 7.95 mmol) 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 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 title compound.

C₇H₄ClFN₂ (M=170.6 g/mol)

¹H NMR (400 MHz, CDCl₃) δ = 8.27 (s, 1H), 2.56 (s, 3H)

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



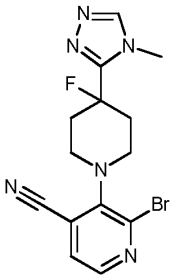
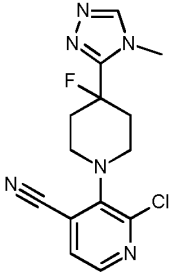
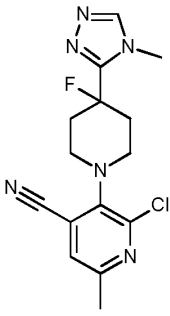
Int. II.1 (30 mg, 0.11 mmol) is dissolved in DMSO (0.5 mL) and DIPEA (38.6 μ L, 0.22 mmol). At 10 °C and Int. I.1 (24.7 mg, 0.13 mmol) is added and the resulting mixture is stirred for 1.5 h at 10 °C. The mixture is purified by preparative HPLC (Xbridge C18, acetonitrile/water gradient containing 0.1% NH_3) to yield the title compound.

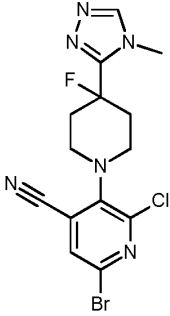
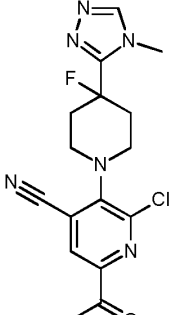
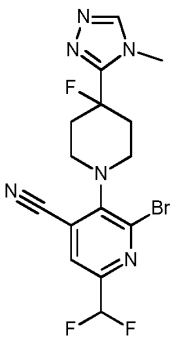
$\text{C}_{15}\text{H}_{13}\text{BrF}_4\text{N}_6$ (M=433.2 g/mol)

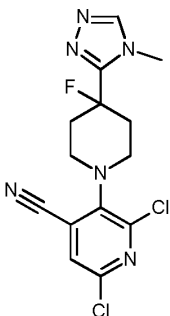
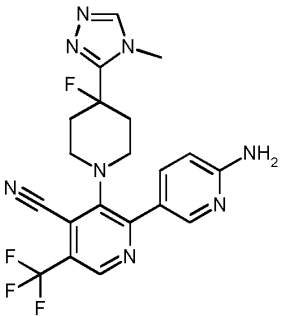
ESI-MS: 433 / 435 $[\text{M}+\text{H}]^+$

Rt (HPLC): 0.54 min (method C)

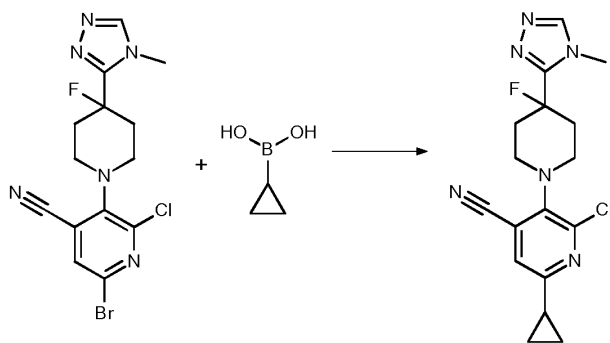
Int.	Starting material	Structure	Deviation from general procedure	Molecular Formula (MW) ESI-MS HPLC retention time (method)
III.2	4-(4-methyl-4H-1,2,4-triazol-3-yl)piperidine + Int. II.1		0.5 h @ rt purification by trituration with water	$\text{C}_{15}\text{H}_{14}\text{BrF}_3\text{N}_6$ (M=415.2 g/mol) ESI-MS: 415 / 417 $[\text{M}+\text{H}]^+$ Rt (HPLC): 0.83 min (method I)

III.3	Int. I.1 + Int. II.2		1.2 equiv. of Int. I.1; 16 h @ 10 °C 16 h @ rt purification by preparative HPLC (Xbridge C18, acetonitrile/wat er gradient containing 0.1% TFA)	$C_{14}H_{14}BrFN_6$ (M=365.2 g/mol) ESI-MS: 365 / 367 [M+H] ⁺ Rt (HPLC): 0.42 min (method C)
III.4	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 C)
III.5	Int. I.1 + 2-chloro-3- fluoro-6- methylpyridine -4-carbonitrile		10 °C → rt 18 h @ rt trituration with water and purification by SiO ₂ chromatograph y (DCM/MeOH 100:0 to 88:12)	$C_{15}H_{16}ClFN_6$ (M=334.8 g/mol) ESI-MS: 335 [M+H] ⁺ Rt (HPLC): 0.80 min (method F)

III.6	Int. I.1 + Int. II.3		2 h @ 15 °C purification by preparative HPLC (Sunfire C18, acetonitrile/wat er gradient containing 0.1% TFA)	C ₁₄ H ₁₃ BrClFN ₆ (M=399.6 g/mol) ESI-MS: 339 / 401 / 403 [M+H] ⁺ Rt (HPLC): 0.75 min (method J)
III.8	Int. I.1 + Int. II.4		1.5 equiv. of Int. I.1 16 h @ 15 °C; crude product treated with 4M HCl in 1,4- dioxane for 3 h at ambient temperature, concentrated, and basified with aq. K ₂ CO ₃	C ₁₆ H ₁₆ ClFN ₆ O (M=362.8 g/mol) ESI-MS: 363 [M+H] ⁺ Rt (HPLC): 0.66 min (method J)
III.10	Int. I.1 + Int. II.5		64 h @ rt purification by preparative HPLC (Xbridge C18, acetonitrile/wat er gradient containing 0.1% TFA)	C ₁₅ H ₁₄ BrF ₃ N ₆ (M=415.2 g/mol) ESI-MS: 415 / 417 [M+H] ⁺ Rt (HPLC): 0.48 min (method C)

III.11	Int. I.1 + Int. II.6		2 h @ 15 °C purification by preparative HPLC (Sunfire C18, acetonitrile/wat er gradient containing 0.1% TFA)	C ₁₄ H ₁₃ Cl ₂ FN ₆ (M=355.2 g/mol) ESI-MS: 355 / 357 / 359 [M+H] ⁺ Rt (HPLC): 0.85 min (method F)
III.13	Int. I.1 + Int. II.8		2.0 equiv. of Int. I.1; 40 h @ 100 °C	C ₂₀ H ₁₈ F ₄ N ₈ (M=446.4 g/mol) ESI-MS: 447 [M+H] ⁺ Rt (HPLC): 0.53 min (method B)

Intermediate III.7: 2-chloro-6-cyclopropyl-3-[4-fluoro-4-(4-methyl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]pyridine-4-carbonitrile



Int. III.6

Int. III.7

- 5 Int. III.6 (150 mg, 0.36 mmol), cyclopropylboronic acid (153 mg, 1.78 mmol), and potassium carbonate (aq. 2 M, 357 μ L, 0.71 mmol) are added to 1,4-dioxane (3 mL), and the resulting mixture is degassed by passing an argon stream through the mixture for 10 min. [1,1'-Bis-(diphenylphosphino)-ferrocen]-dichloro-palladium(II) (Pd(dppf)Cl₂) (26.1 mg, 0.04 mmol) is added, and the mixture is degassed for additional 5 min. The mixture is then heated in the
- 10 microwave to 70 °C for 15 h. After cooling to ambient temperature, the mixture is purified

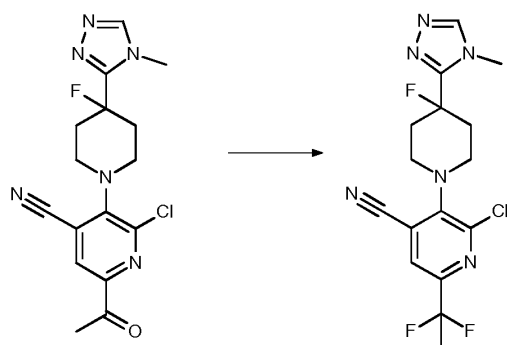
by preparative HPLC (Sunfire C18, ACN/water gradient containing 0.1% TFA) to yield the title compound.

$C_{17}H_{18}ClFN_6$ (M=360.8 g/mol)

ESI-MS: 361 $[M+H]^+$

5 Rt (HPLC): 0.80 min (method J)

Intermediate III.9: 2-chloro-6-(1,1-difluoroethyl)-3-[4-fluoro-4-(4-methyl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]pyridine-4-carbonitrile



Int. III.8

Int. III.9

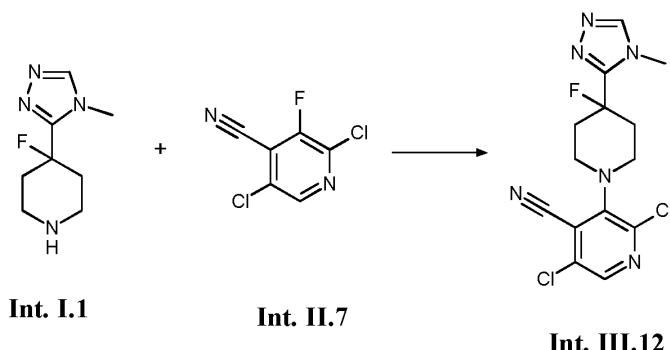
10 Int. III.8 (300 mg, 0.83 mmol) is suspended in DCM (2 mL). DAST (400 μ L, 3.03 mmol) is added and the resulting reaction mixture is stirred at rt for 2 days. The reaction is basified with an aqueous ammonia solution and the organic layer is separated, dried, and concentrated. The residue is purified by preparative HPLC (Xbridge C18, ACN/water gradient containing 0.1% NH_3) to yield the title compound.

15 $C_{16}H_{16}ClF_3N_6$ (M=384.8 g/mol)

ESI-MS: 385 $[M+H]^+$

Rt (HPLC): 0.65 min (method B)

Intermediate III.12: 2,5-dichloro-3-[4-fluoro-4-(4-methyl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]pyridine-4-carbonitrile

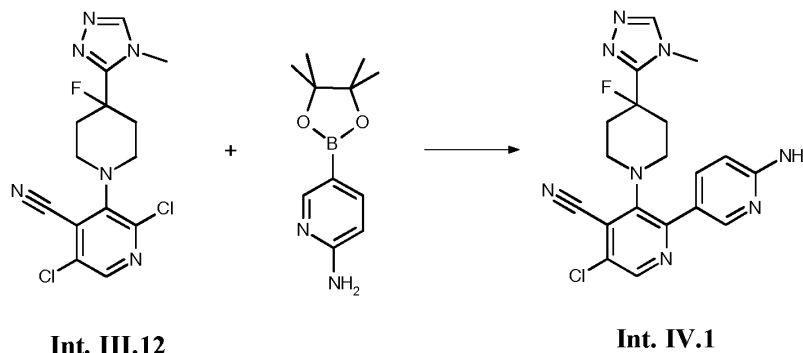


Int. II.7 (0.17 g, 0.89 mmol) in DMF (5 mL) is added Int. I.1 (0.96 g, 5.21 mmol) and K₂CO₃ (2.40 g, 22.7 mmol). The mixture is stirred at 100 °C for 10 h. The reaction mixture is diluted with H₂O (100 mL) and extracted with EtOAc (2 x 200 mL). The combined organic layers are washed with brine (100 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue is purified by column chromatography (SiO₂, PE/EtOAc gradient 1:0 to 0:1) and by preparative HPLC (Agela DuraShell C18, ACN/water gradient containing 10 mM NH₄HCO₃) to yield the title compound.

C₁₄H₁₃Cl₂FN₆ (M=355.2 g/mol)
 ESI-MS: 355 / 357 [M+H]⁺
 Rt (HPLC): 2.27 min (method K)

Int.	Starting material	Structure	Deviation from general procedure	Molecular Formula (MW) ESI-MS HPLC retention time (method)
III.14	Int. I.1 + Int. II.9		12 h @ 100 °C	C ₁₅ H ₁₆ ClFN ₆ (M=334.8 g/mol) ESI-MS: 335 [M+H] ⁺ Rt (HPLC): 2.16 min (method E)

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



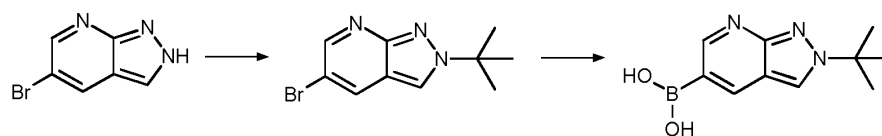
Under an argon atmosphere, Int. III.12 (50.0 mg, 0.14 mmol) and 5-(4,4,5,5-tetramethyl-
 1,3,2-dioxaborolan-2-yl)pyridin-2-amine (34.3 mg, 0.15 mmol) are dissolved in 1,4-dioxane
 (3 mL). K_2CO_3 (aq. 2 M, 275 μ L, 0.55 mmol) is added, and the resulting mixture is degassed
 by passing an argon stream through the mixture. [1,1'-Bis-(diphenylphosphino)-ferrocen]-
 dichloro-palladium(II) ($Pd(dppf)Cl_2$) (10.1 mg, 0.01 mmol) is added, and the mixture is
 degassed again. The mixture is then heated to 70 $^{\circ}C$ for 1 h. After cooling to ambient
 temperature, the mixture is diluted with H_2O , filtered, washed with DMF, and purified by
 preparative HPLC (StableBond C18, ACN/water gradient containing 0.1% TFA) to yield the
 title compound.

$C_{19}H_{18}ClFN_8$ (M=412.9 g/mol)

ESI-MS: 413 $[M+H]^+$

Rt (HPLC): 0.57 min (method L)

Synthesis of Intermediate V.1



Int. V.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 $^{\circ}C$ 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.

C₁₀H₁₂BrN₃ (M=254.1 g/mol)

ESI-MS: 254 / 256 [M+H]⁺

Rt (HPLC): 0.85 min (method F)

10

Intermediate V.1: {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]-dichloropalladium(II) dichloromethane complex (Pd(dppf)Cl₂*CH₂Cl₂, 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 dissolved 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.

20

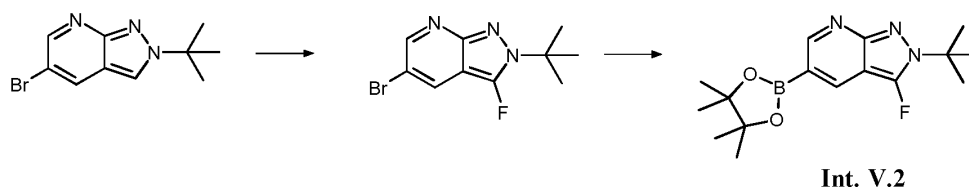
C₁₀H₁₄BN₃O₂ (M=219.1 g/mol)

ESI-MS: 220 [M+H]⁺

Rt (HPLC): 0.27 min (method C)

25

Synthesis of Intermediate V.2



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

To a solution of 5-bromo-2-tert-butyl-2H-pyrazolo[3,4-b]pyridine (4.70 g, 18.5 mmol) in ACN (47mL) is added Selectfluor (13.1 g, 37.0 mmol) at 20 °C under N₂. The mixture is stirred at 40 °C for 12 h. The reaction mixture is quenched by the addition of H₂O (50 mL) and extracted with EtOAc (3 x 50 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.

C₁₀H₁₁BrFN₃ (M=272.1 g/mol)

ESI-MS: 272 / 274 [M+H]⁺

10 Rt (HPLC): 0.53 min (method M)

Intermediate V.2: 2-tert-butyl-3-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2H-pyrazolo[3,4-b]pyridine

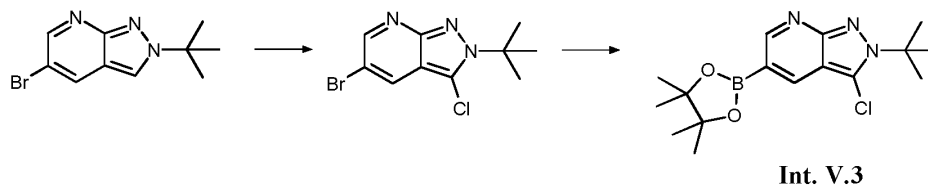
To a solution of 5-bromo-2-tert-butyl-3-fluoro-2H-pyrazolo[3,4-b]pyridine (2.30 g, 8.45 mmol) in 1,4-dioxane (23 mL) is added 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (2.36 g, 9.30 mmol), KOAc (2.48 g, 25.4 mmol) and Pd(dppf)Cl₂ (0.62 g, 0.85 mmol) at 20 °C under N₂. The mixture is stirred at 100 °C for 12 h. The residue is diluted with H₂O (30 mL) and extracted with EtOAc (3 x 30 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 title compound.

C₁₆H₂₃BFN₃O₂ (M=319.2 g/mol)

ESI-MS: 320 [M+H]⁺

Rt (HPLC): 2.94 min (method N)

25 R_f (TLC) 0.4 (PE/EtOAc 2:1)

Synthesis of Intermediate V.3

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

To a solution 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.

C₁₀H₁₁BrClN₃ (M=288.6 g/mol)

ESI-MS: 288 / 290 [M+H]⁺

Rt (HPLC): 0.55 min (method M)

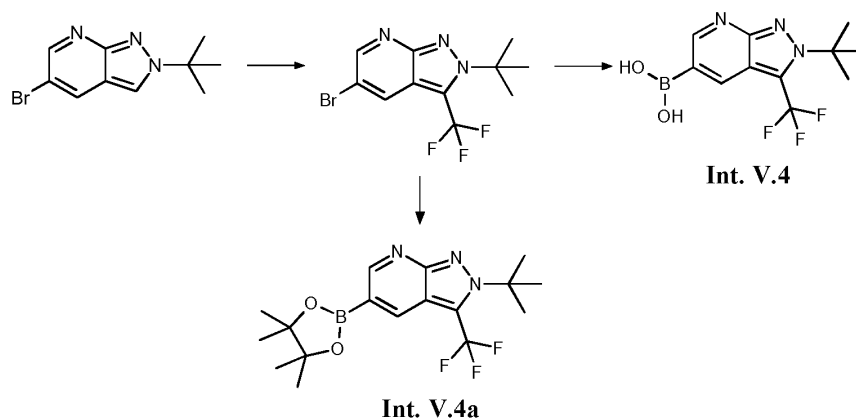
Intermediate V.3: {2-Tert-butyl-3-chloro-2H-pyrazolo[3,4-b]pyridin-5-yl}boronic acid

To a solution 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.

C₁₀H₁₃BClN₃O₃ (M=253.5 g/mol)

ESI-MS: 254 / 256 [M+H]⁺

Rt (HPLC): 0.33 min (method M)

Synthesis of Intermediate V.4**5-Bromo-2-tert-butyl-3-(trifluoromethyl)-2H-pyrazolo[3,4-b]pyridine**

To a solution of 5-bromo-2-tert-butyl-2H-pyrazolo[3,4-b]pyridine (1.51 g, 5.94 mmol) in MeOH (30 mL) is added 1-(trifluoromethyl)-3H-1λ³,2-benziodaxol-3-one (2.44 g, 7.72 mmol) and Cu(OAc)₂ (1.62 g, 8.91 mmol) at 20 °C under N₂. The mixture is stirred at 20 °C for 12 h. Then the mixture is stirred at 80 °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.

C₁₁H₁₁BrF₃N₃ (M=322.1 g/mol)

ESI-MS: 322 / 324 [M+H]⁺

Rt (HPLC): 0.89 min (method G)

Intermediate V.4: [2-tert-butyl-3-(trifluoromethyl)-2H-pyrazolo[3,4-b]pyridin-5-yl]boronic acid

To a solution of 5-bromo-2-tert-butyl-3-(trifluoromethyl)-2H-pyrazolo[3,4-b]pyridine (0.28 g, 0.87 mmol) in 1,4-dioxane (6 mL) is added 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (0.26 g, 1.04 mmol), KOAc (0.26 g, 2.61 mmol) and Pd(dppf)Cl₂ (0.06 g, 0.09 mmol) at 20 °C under N₂. The mixture is heated to 100 °C and stirred for 12 h. The reaction mixture is diluted with H₂O (15 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 preparative HPLC (XBridge C18, ACN/water gradient containing 10 mM NH₄HCO₃) to yield the title compound.

C₁₁H₁₃BF₃N₃O₂ (M=287.0 g/mol)

ESI-MS: 288 [M+H]⁺

5 Rt (HPLC): 0.68 min (method O)

Intermediate V.4a: 2-tert-butyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(trifluoromethyl)-2H-pyrazolo[3,4-b]pyridine

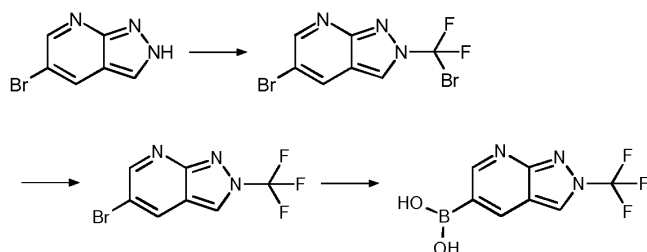
Analogous procedure as for Intermediate V.4 is used with 5-bromo-2-tert-butyl-3-(trifluoromethyl)-2H-pyrazolo[3,4-b]pyridine (4.5 g, 14.0 mmol) in 1,4-dioxane (100 mL) is added 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (4.3 g, 16.8 mmol), KOAc (4.1 g, 41.9 mmol), and Pd(dppf)Cl₂ (0.06 g, 0.09 mmol). Crude product is purified by column chromatography (SiO₂, PE/EtOAc gradient 1:0 to 1:1) to afford the desired compound.

15 C₁₇H₂₃BF₃N₃O₂ (M=369.2 g/mol)

ESI-MS: 370 [M+H]⁺

Rt (HPLC): 3.54 min (method N)

Synthesis of Intermediate V.5



Int. V.5

20

5-Bromo-2-(bromodifluoromethyl)-2H-pyrazolo[3,4-b]pyridine

5-Bromo-2H-pyrazolo[3,4-b]pyridine (6.00 g, 28.8 mmol) is dissolved in DMF (200 mL). At 0 °C, NaH (55 %, 1.51 g, 34.5 mmol) is added, and the reaction mixture is stirred at 0 °C for 30 min. Then dibromodifluoromethane (8.30 mL, 86.4 mmol) is added, and the reaction mixture is stirred at rt overnight. The reaction mixture is diluted with ACN/H₂O and purified by preparative HPLC (XBridge C18, ACN/water gradient containing 0.1 % TFA) to yield the desired compound.

25

$C_7H_3Br_2F_2N_3$ (M=326.9 g/mol)
ESI-MS: 326 / 328 / 330 $[M+H]^+$
Rt (HPLC): 0.56 min (method C)

5 **5-Bromo-2-(trifluoromethyl)-2H-pyrazolo[3,4-b]pyridine**

5-Bromo-2-(bromodifluoromethyl)-2H-pyrazolo[3,4-b]pyridine (2.10 g, 6.42 mmol) and silver tetrafluoroborate (2.53 g, 12.8 mmol) are dissolved in DCE (40 mL) and stirred at 80 °C overnight. After cooling to ambient temperature, the reaction mixture is concentrated and purified by column chromatography (SiO₂, DCM/MeOH gradient 1:0 to 1:1) to afford the
10 desired compound.

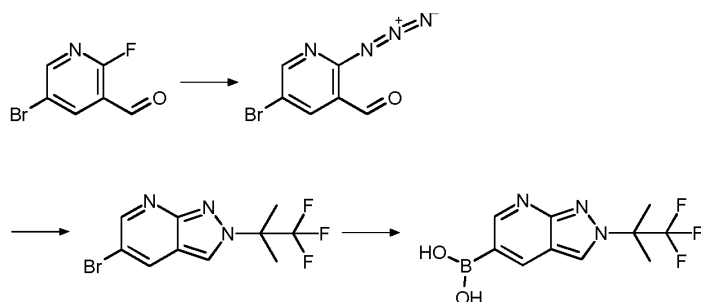
$C_7H_3BrF_3N_3$ (M=266.0 g/mol)
ESI-MS: 266 / 268 $[M+H]^+$
Rt (HPLC): 0.47 min (method C)

15 **Intermediate V.5: [2-(trifluoromethyl)-2H-pyrazolo[3,4-b]pyridin-5-yl]boronic acid**

5-Bromo-2-(trifluoromethyl)-2H-pyrazolo[3,4-b]pyridine (324 mg, 0.61 mmol, 50 % purity), bis(pinacolato)diborane (231 mg, 0.91 mmol), and potassium acetate (179 mg, 1.83 mmol) are added to 1,4-dioxane (3 mL), and the resulting mixture is degassed by passing an argon stream through the mixture for 10 min. [1,1'-Bis-(diphenylphosphino)-ferrocen]-
20 dichloro-palladium(II) dichloromethane complex (Pd(dppf)Cl₂*CH₂Cl₂, CAS: 95464-05-4) (49.7 mg, 0.06 mmol) is added, and the mixture is then heated to 90 °C and stirred at this temperature for 5 h. After cooling to ambient temperature, the mixture is concentrated, and the residue is dissolved 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.

25 $C_7H_5BF_3N_3O_2$ (M=230.9 g/mol)
ESI-MS: 232 $[M+H]^+$
Rt (HPLC): 0.30 min (method C)

Synthesis of Intermediate V.6



Int. V.6

2-Azido-5-bromopyridine-3-carbaldehyde

5-Bromo-2-fluoropyridine-3-carbaldehyde (1.00 g, 4.66 mmol) and tetrabutylammonium iodide (172 mg, 0.47 mmol) are dissolved in DMSO (6 mL). Sodium azide (367 mg, 5.59 mmol) is added, and the reaction mixture is stirred at rt for 45 min. The reaction is quenched by the addition of water and the formed precipitate is filtered, washed with water, and dried to afford the desired compound.

$C_6H_3BrN_4O$ (M=227.0 g/mol)

ESI-MS: 227 / 229 $[M+H]^+$

Rt (HPLC): 0.25 min (method C)

5-Bromo-2-(1,1,1-trifluoro-2-methylpropan-2-yl)-2H-pyrazolo[3,4-b]pyridine

2-Azido-5-bromopyridine-3-carbaldehyde (400 mg, 1.76 mmol) and 1,1,1-trifluoro-2-methylpropan-2-amine hydrochloride (432 mg, 2.64 mmol) are dissolved in EtOH (20 mL) and stirred at 100 °C for 4 h. The reaction mixture is concentrated. The residue is dissolved in toluene (20 mL) and stirred at rt overnight. The reaction mixture is concentrated, dissolved in ACN/water, filtered, and purified by preparative HPLC (XBridge C18, ACN/water gradient containing 0.1% NH_3) to yield the desired compound.

$C_{10}H_9BrF_3N_3$ (M=308.1 g/mol)

ESI-MS: 308 / 310 $[M+H]^+$

Rt (HPLC): 0.62 min (method B)

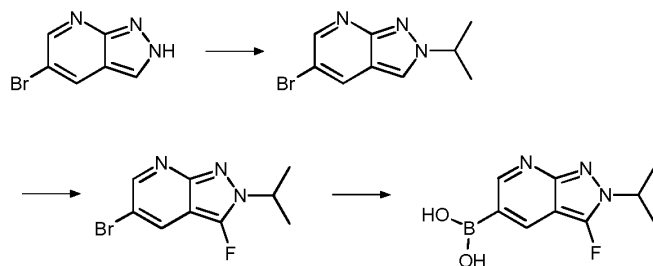
Intermediate V.6: [2-(1,1,1-trifluoro-2-methylpropan-2-yl)-2H-pyrazolo[3,4-b]pyridin-5-yl]boronic acid

5-Bromo-2-(1,1,1-trifluoro-2-methylpropan-2-yl)-2H-pyrazolo[3,4-b]pyridine (643 mg, 1.67 mmol, 80 % purity), bis(pinacolato)diborane (678 mg, 2.67 mmol), and potassium acetate (639 mg, 6.51 mmol) are added to 1,4-dioxane (6 mL), and the resulting mixture is degassed by passing an argon stream through the mixture for 15 min. PdCl₂(PPh₃)₂ (141 mg, 0.20 mmol) is added, and the mixture is then heated to 60 °C and stirred at this temperature for 10 h. After cooling to ambient temperature, the mixture is concentrated, and the residue is dissolved 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.

C₁₀H₁₁BF₃N₃O₂ (M=273.0 g/mol)

ESI-MS: 274 [M+H]⁺

Rt (HPLC): 0.32 min (method C)

Synthesis of Intermediate V.7**Int. V.7****5-Bromo-2-(propan-2-yl)-2H-pyrazolo[3,4-b]pyridine**

To a solution of 5-bromo-2H-pyrazolo[3,4-b]pyridine (5.00 g, 25.2 mmol) in DMF (50mL) is added K₂CO₃ (8.54 g, 30.3 mmol) at 0 °C under N₂. The mixture is stirred at 0 °C for 1 h. Then 2-bromopropane (3.73 g, 30.3 mmol) is added to the above solution at 20 °C under N₂. The mixture is stirred at 70 °C for 12 h. The reaction is diluted with H₂O (50 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layers are dried over Na₂SO₄, filtered, and concentrated under reduced pressure to afford the desired compound, which is used directly without further purification.

C₉H₁₀BrN₃ (M=240.1 g/mol)

ESI-MS: 240 / 242 [M+H]⁺

Rt (HPLC): 0.39 min (method M)

5-Bromo-3-fluoro-2-(propan-2-yl)-2H-pyrazolo[3,4-b]pyridine

To a solution of 5-bromo-2-(propan-2-yl)-2H-pyrazolo[3,4-b]pyridine (0.95 g, 3.96 mmol) in ACN (10 mL) is added Selectfluor (2.80 g, 7.91 mmol) at 20 °C under N₂. The mixture is stirred at 20 °C for 12 h and at 40 °C for 12 h. After cooling to ambient temperature, the reaction mixture is diluted with H₂O (10 mL) and extracted with EtOAc (3 x 10 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.

C₉H₉BrFN₃ (M=258.1 g/mol)

ESI-MS: 258 / 260 [M+H]⁺

Rt (HPLC): 0.46 min (method M)

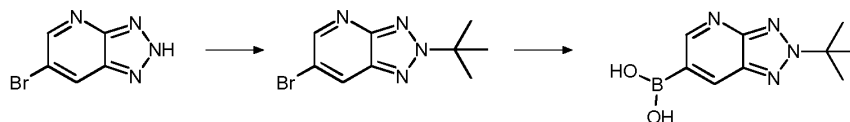
Intermediate V.7: [3-fluoro-2-(propan-2-yl)-2H-pyrazolo[3,4-b]pyridin-5-yl]boronic acid

To a solution of 5-bromo-3-fluoro-2-(propan-2-yl)-2H-pyrazolo[3,4-b]pyridine (0.50 g, 1.94 mmol) in 1,4-dioxane (5 mL) is added 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (0.54 g, 2.13 mmol), KOAc (0.57 g, 5.81 mmol) and Pd(dppf)Cl₂ (0.14 g, 0.194 mmol) at 20 °C under N₂. The mixture is stirred at 100 °C for 12 h. After cooling to ambient temperature, the reaction mixture is diluted with H₂O (10 mL) and extracted with EtOAc (3 x 10 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 title compound.

C₉H₁₁BFN₃O₂ (M=223.0 g/mol)

ESI-MS: 224 [M+H]⁺

Rt (HPLC): 0.28 min (method M)

Synthesis of Intermediate V.8**Int. V.8**

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

6-Bromo-2H-[1,2,3]triazolo[4,5-b]pyridine (500 mg, 2.46 mmol) is suspended in toluene (1 mL), and *tert*-butyl acetate (3.30 mL, 24.6 mmol). Methanesulfonic acid (161 μ L, 2.46 mmol) is added. The resulting reaction mixture is heated to 80 °C and stirred for 2 h. After cooling to ambient temperature, the reaction mixture is concentrated, and the residue is dissolved in an ACN/water mixture, filtered, and purified by preparative HPLC (XBridge C18, ACN/water gradient containing 0.1% TFA) to yield the desired compound.

$C_9H_{11}BrN_4$ (M=255.1 g/mol)

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

Rt (HPLC): 0.96 min (method J)

Intermediate V.8: {2-tert-butyl-2H-[1,2,3]triazolo[4,5-b]pyridin-6-yl}boronic acid

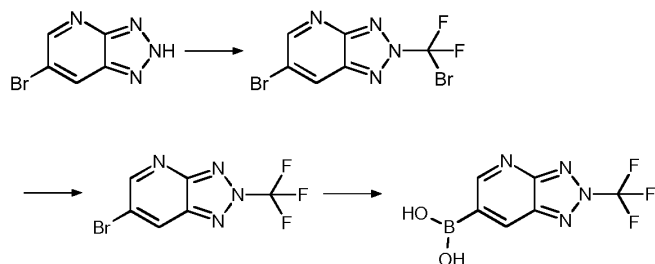
6-Bromo-2-tert-butyl-2H-[1,2,3]triazolo[4,5-b]pyridine (369 mg, 0.72 mmol, 50 % purity), bis(pinacolato)diborane (274 mg, 1.09 mmol), and potassium acetate (213 mg, 2.17 mmol) are added to 1,4-dioxane (5 mL), and the resulting mixture is degassed by passing an argon stream through the mixture for 5 min. $PdCl_2(PPh_3)_2$ (50.8 mg, 0.07 mmol) is added, and the mixture is then heated to 100 °C and stirred at this temperature for 3 h. After cooling to ambient temperature, the mixture is diluted with EtOAc and filtered through Celite. The filtrate is concentrated, and the residue is dissolved in an ACN/water mixture, and purified by preparative HPLC (XBridge C18, ACN/water gradient containing 0.1% TFA) to yield the title compound.

$C_9H_{13}BN_4O_2$ (M=220.0 g/mol)

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

Rt (HPLC): 0.36 min (method C)

25

Synthesis of Intermediate V.9**Int. V.9****6-Bromo-2-(bromodifluoromethyl)-2H-[1,2,3]triazolo[4,5-b]pyridine**

At 0 °C, NaH (0.48 g, 20.1 mmol) is added to 6-bromo-2H-[1,2,3]triazolo[4,5-b]pyridine
 5 (2.00 g, 10.0 mmol) in DMF (20 mL) under N₂ and stirred for 30 min. Dibromodifluoromethane (5.85 g, 30.1 mmol) is added and the mixture stirred at 25 °C for 12 h. The reaction mixture is quenched by the addition of NH₄Cl (50 mL), and then diluted with H₂O (50 mL) and extracted with EtOAc (100 mL). The organic layer is washed with brine (50 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The
 10 residue is purified by column chromatography (SiO₂, PE/EtOAc gradient 1:0 to 3:1) to afford the desired compound.

C₆H₂Br₂F₂N₄ (M=327.9 g/mol)
 ESI-MS: 329 [M+H]⁺
 Rt (HPLC): 2.64 min (method K)

15

6-Bromo-2-(trifluoromethyl)-2H-[1,2,3]triazolo[4,5-b]pyridine

6-Bromo-2-(bromodifluoromethyl)-2H-[1,2,3]triazolo[4,5-b]pyridine (500 mg, 1.53 mmol) and silver tetrafluoroborate (1.00 g, 5.09 mmol) are dissolved in DCE (40 mL) and stirred at 80 °C for 48 h. The reaction mixture is concentrated, diluted with an ACN/water mixture, and purified by preparative HPLC (XBridge C18, ACN/water gradient containing 0.1% TFA) to yield the desired compound.
 20

C₆H₂BrF₃N₄ (M=267.0 g/mol)
 ESI-MS: 267 / 269 [M+H]⁺
 Rt (HPLC): 0.57 min (method C)

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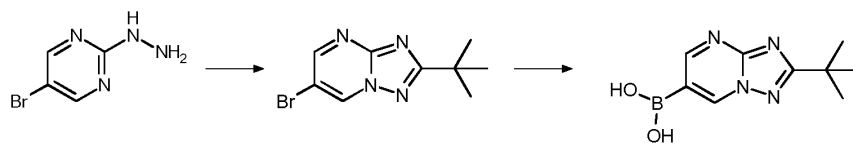
Intermediate V.9: [2-(trifluoromethyl)-2H-[1,2,3]triazolo[4,5-b]pyridin-6-yl]boronic acid

6-Bromo-2-(trifluoromethyl)-2H-[1,2,3]triazolo[4,5-b]pyridine (319 mg, 0.60 mmol, 50 % purity), bis(pinacolato)diborane (227 mg, 0.90 mmol), and potassium acetate (176 mg, 1.79 mmol) are added to 1,4-dioxane (3 mL), and the resulting mixture is degassed by passing an argon stream through the mixture for 10 min. Pd(dppf)Cl₂ (43.7 mg, 0.06 mmol) is added, and the mixture is then heated to 90 °C and stirred at this temperature for 5 h. After cooling to ambient temperature, the mixture is concentrated, and the residue is dissolved 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.

C₆H₄BF₃N₄O₂ (M=231.9 g/mol)

ESI-MS: 233 [M+H]⁺

Rt (HPLC): 0.38 min (method C)

Synthesis of Intermediate V.10

Int. V.10

6-Bromo-2-tert-butyl-[1,2,4]triazolo[1,5-a]pyrimidine

5-Bromo-2-hydrazinylpyrimidine (500 mg, 2.51 mmol) and pivaloyl chloride are mixed in a microwave vial and stirred at 120 °C for 22 h. After cooling to ambient temperature, the mixture is concentrated, and the residue is dissolved in MeOH and stirred for some minutes. Then it is diluted with an ACN/water mixture, filtered, and purified by preparative HPLC (XBridge C18, ACN/water gradient containing 0.1% TFA) to yield the desired compound.

C₉H₁₁BrN₄ (M=255.1 g/mol)

ESI-MS: 255 / 257 [M+H]⁺

Rt (HPLC): 0.46 min (method C)

Intermediate V.10: {2-tert-butyl-[1,2,4]triazolo[1,5-a]pyrimidin-6-yl}boronic acid

6-Bromo-2-tert-butyl-[1,2,4]triazolo[1,5-a]pyrimidine (200 mg, 0.63 mmol, 80 % purity), bis(pinacolato)diborane (260 mg, 1.02 mmol), and potassium acetate (240 mg, 2.45 mmol) are added to 1,4-dioxane (4 mL), and the resulting mixture is degassed by passing an argon

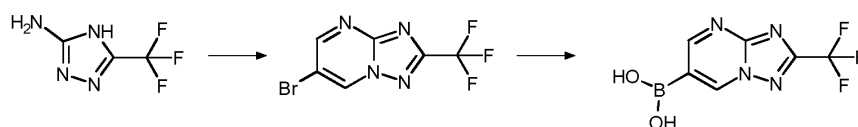
stream through the mixture for 15 min. $\text{PdCl}_2(\text{PPh}_3)_2$ (55.0 mg, 0.08 mmol) is added, and the mixture is then heated to 60 °C and stirred at this temperature for 24 h. After cooling to ambient temperature, the mixture is diluted with EtOAc, filtered, and concentrated. The residue is dissolved in an ACN/water mixture, and purified by preparative HPLC (Sunfire
5 C18, ACN/water gradient containing 0.1% TFA) to yield the title compound.

$\text{C}_9\text{H}_{13}\text{BN}_4\text{O}_2$ (M=220.0 g/mol)

ESI-MS: 221 $[\text{M}+\text{H}]^+$

Rt (HPLC): 0.34 min (method C)

10 Synthesis of Intermediate V.11



Int. V.11

6-Bromo-2-(trifluoromethyl)-[1,2,4]triazolo[1,5-a]pyrimidine

5-(Trifluoromethyl)-4H-1,2,4-triazol-3-amine (500 mg, 3.12 mmol) is dissolved in glacial acetic acid (5 mL). 2-Bromopropanedial (744 mg, 4.69 mmol) is added, and the reaction
15 mixture is stirred at 60 °C for 3 h. The reaction is concentrated, the residue is neutralized with a saturated solution of NaHCO_3 and extracted with DCM (3x). The combined organic layers are dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. The residue is purified by column chromatography (SiO_2 , CyH/EtOAc gradient 94:6 to 34:66) to afford the desired compound.

20 $\text{C}_6\text{H}_2\text{BrF}_3\text{N}_4$ (M=267.0 g/mol)

ESI-MS: 267 / 269 $[\text{M}+\text{H}]^+$

Rt (HPLC): 0.78 min (method F)

25 Intermediate V.11: [2-(trifluoromethyl)-[1,2,4]triazolo[1,5-a]pyrimidin-6-yl]boronic acid

6-Bromo-2-(trifluoromethyl)-[1,2,4]triazolo[1,5-a]pyrimidine (650 mg, 2.43 mmol), bis(pinacolato)diborane (0.93 g, 3.65 mmol), and potassium acetate (597 mg, 6.09 mmol) are added to 1,4-dioxane (10 mL), and the resulting mixture is degassed by passing an argon
30 stream through the mixture. $\text{Pd}(\text{dppf})\text{Cl}_2 \cdot \text{DCM}$ (199 mg, 0.24 mmol) is added, and the mixture is then heated to 100 °C and stirred at this temperature for 6 h. After cooling to

ambient temperature, the mixture is diluted with an ACN/water mixture, filtered, and purified by preparative HPLC (Sunfire C18, ACN/water gradient containing 0.1% TFA) to yield the title compound.

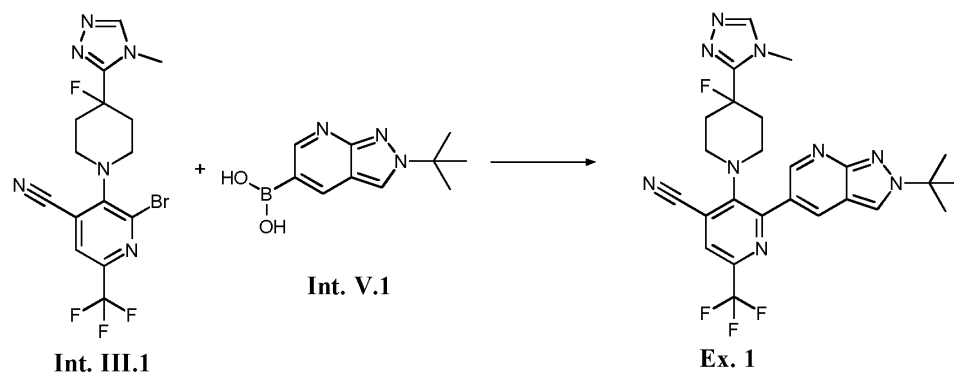
$C_6H_4BF_3N_4O_2$ (M=231.9 g/mol)

5 ESI-MS: 233 [M+H]⁺

Rt (HPLC): 0.65 min (method F)

Preparation of Final Compounds

10 Example 1



To a solution of Int. III.1 (50.0 mg, 0.12 mmol) and Int. V.1 (46.1 mg, 0.14 mmol) in 1,4-dioxane (2 mL) is added potassium carbonate (2 M in water, 0.17 mL, 0.35 mmol). The resulting mixture is purged by passing an argon stream through the solution. [1,1'-Bis-

15 (diphenylphosphino)-ferrocen]-dichloro-palladium(II) (Pd(dppf)Cl₂, CAS: 72287-26-4) (8.5 mg, 11.5 μmol) is added, and the mixture is further purged with argon. The reaction mixture is stirred at 95 °C for 4.5 h. After cooling to ambient temperature, the mixture is diluted with an ACN/water mixture and purified by preparative HPLC (XBridge C18 column, ACN/water gradient containing 0.1% NH₃) to yield the title compound.

20 $C_{25}H_{25}F_4N_9$ (M=527.5 g/mol)

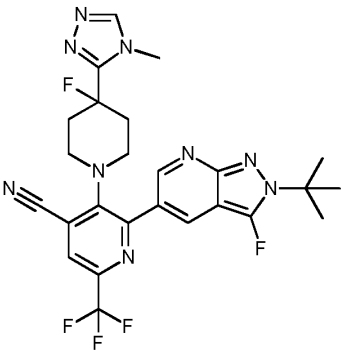
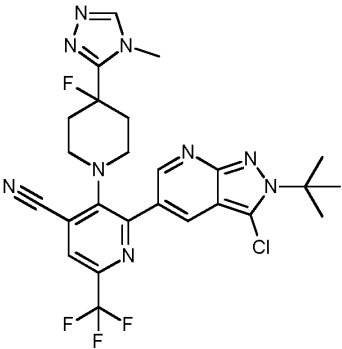
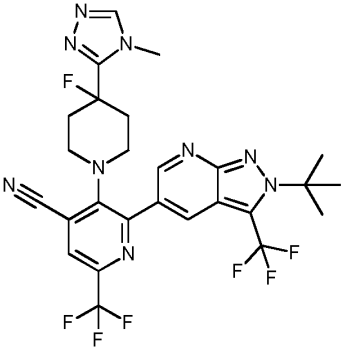
ESI-MS: 528 [M+H]⁺

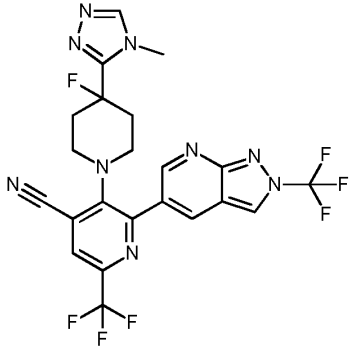
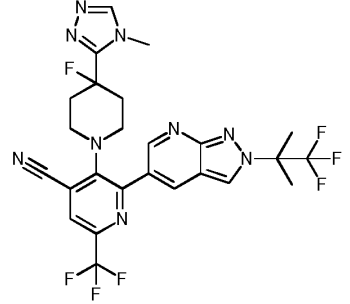
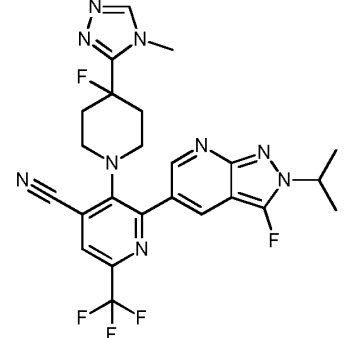
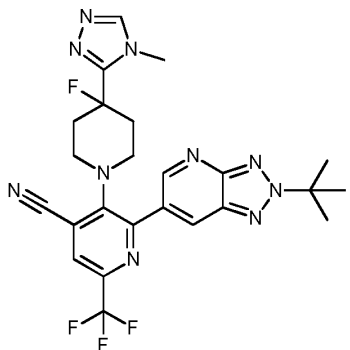
Rt (HPLC): 0.65 min (method B)

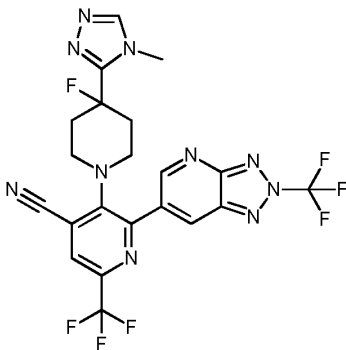
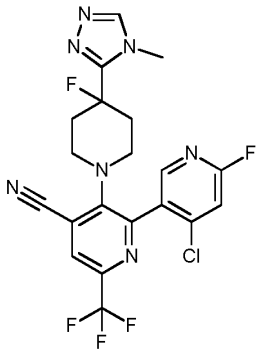
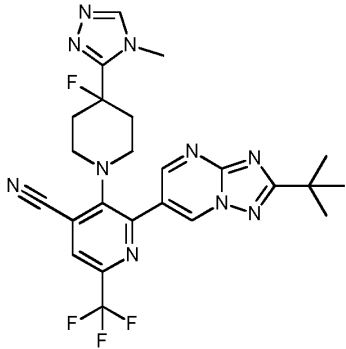
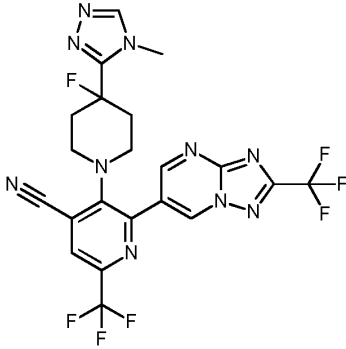
¹H NMR (400 MHz, DMSO-d₆) δ = 8.84 (d, *J* = 2.3 Hz, 1H), 8.68 (s, 1H), 8.47 (s, 1H), 8.41 (d, *J* = 2.3 Hz, 1H), 8.34 (s, 1H), 3.70 (d, *J* = 1.5 Hz, 3H), 3.43 - 3.35 (m, 2H), 3.29 -

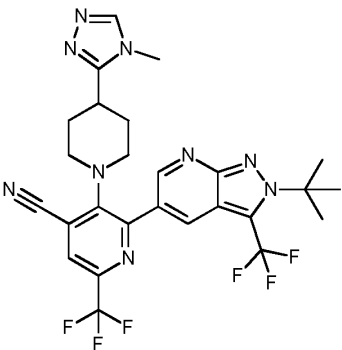
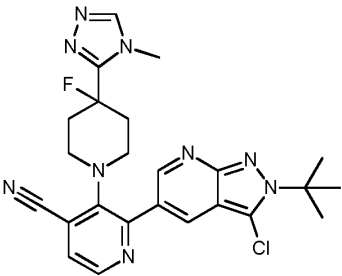
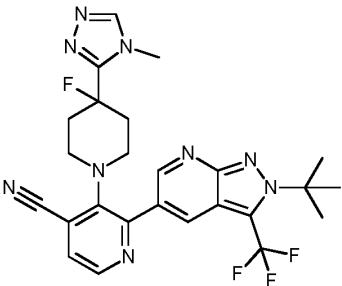
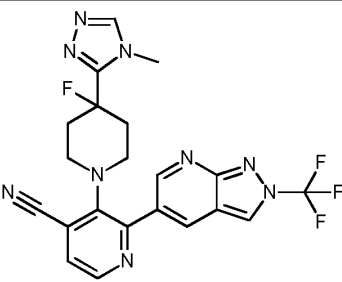
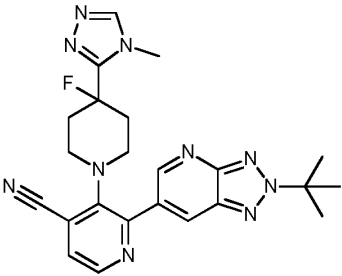
25 3.23 (m, 2H), 2.36 - 2.18 (m, 4H), 1.72 (s, 9H).

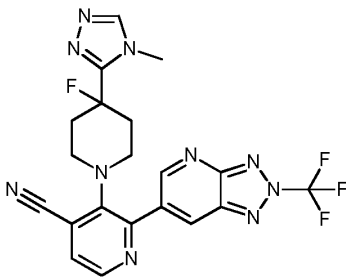
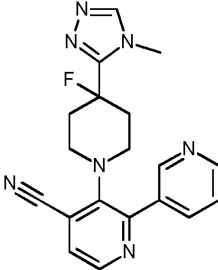
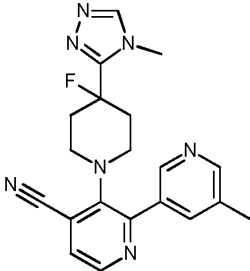
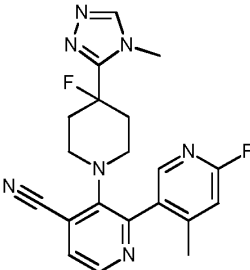
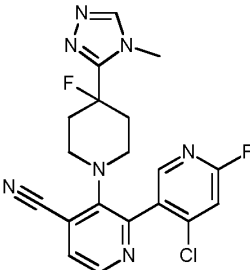
Examples synthesized analogous to the procedure described for Example 1

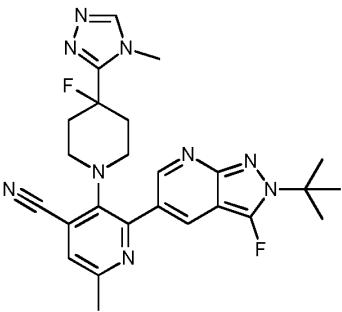
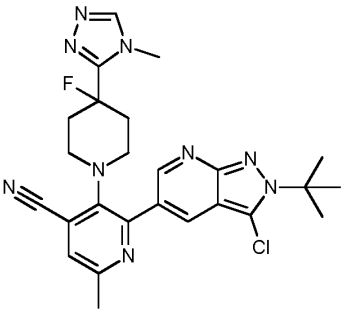
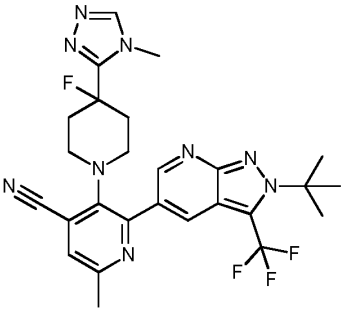
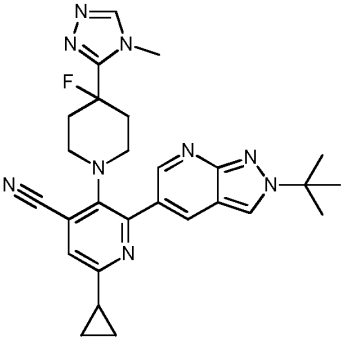
example	Starting materials	Structure	Deviation from general procedure
2	Int. III.1 + Int. V.2		2.0 eq. K ₂ CO ₃ solution; 5 h at 100 °C; purification by preparative HPLC (XBridge C18, ACN/water gradient containing 0.1% TFA)
3	Int. III.1 + Int. V.3		1.5 eq. of Int. V.3; Na ₂ CO ₃ was used instead of K ₂ CO ₃ ; 2 h at 100 °C
4	Int. III.1 + Int. V.4		1.5 eq. of Int. V.4; Na ₂ CO ₃ was used instead of K ₂ CO ₃ ; 2 h at 100 °C

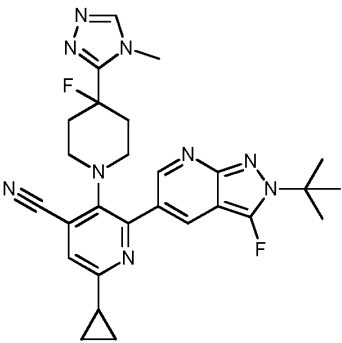
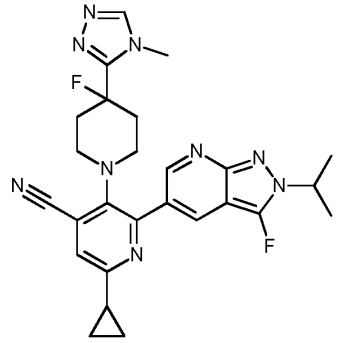
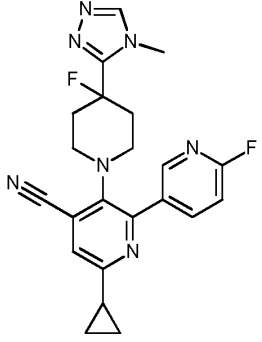
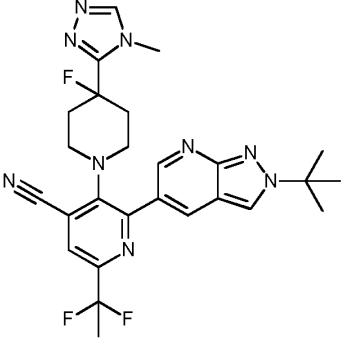
5	Int. III.1 + Int. V.5		1.5 eq. of Int. V.5; 15 h at 100 °C; purified by preparative HPLC (XBridge C18, ACN/water gradient containing 0.1% TFA)
6	Int. III.1 + Int. V.6		1.7 eq. of Int. V.6; 5.5 h at 95 °C
7	Int. III.1 + Int. V.7		2.0 eq. K ₂ CO ₃ solution; 5 h at 100 °C; purification by preparative HPLC (XBridge C18, ACN/water gradient containing 0.1% TFA)
8	Int. III.1 + Int. V.8		1.5 eq. of Int. V.8; 2.0 eq. K ₂ CO ₃ solution; 4 h at 100 °C; purification by preparative HPLC (XBridge C18, ACN/water gradient containing 0.1% TFA)

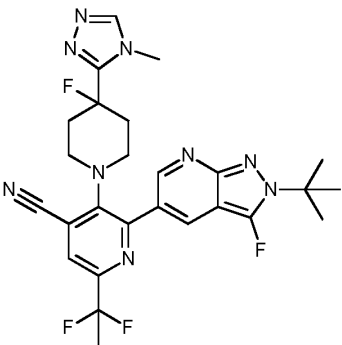
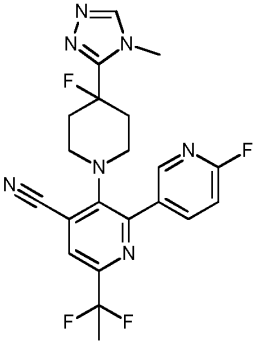
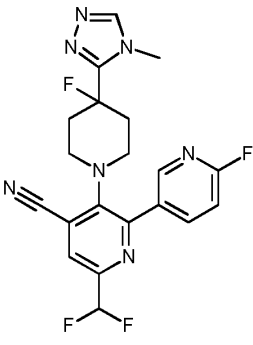
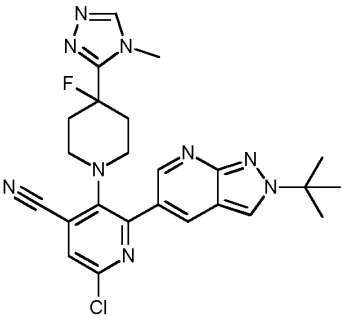
9	Int. III.1 + Int. V.9		1.1 eq. of Int. V.9; 1.5 h at 100 °C; purification by preparative HPLC (XBridge C18, ACN/water gradient containing 0.1% TFA)
10	Int. III.1 + (4-chloro-6-fluoropyridin-3-yl)boronic acid		1.1 eq. of (4-chloro-6-fluoropyridin-3-yl)boronic acid; 4.0 eq. K ₂ CO ₃ solution 1 h at 70 °C
11	Int. III.1 + Int. V.10		None
12	Int. III.1 + Int. V.11		1.1 eq. of Int. V.11; Na ₂ CO ₃ was used instead of K ₂ CO ₃ ; 4 h at 100 °C; purification by preparative HPLC (Sunfire C18, ACN/water gradient containing 0.1% TFA)

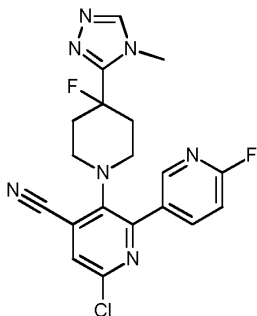
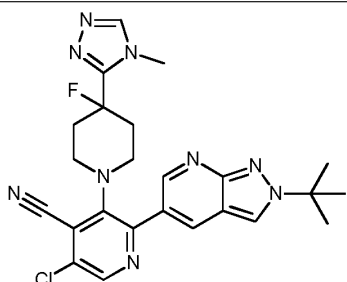
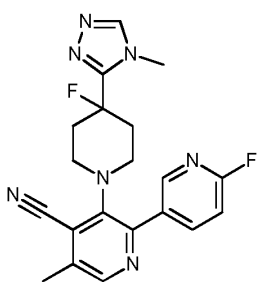
13	Int. III.2 + Int. V.4		2.0 eq. Na ₂ CO ₃ was used instead of K ₂ CO ₃ ; 1.5 h at 100 °C
14	Int. III.3 + Int. V.3		1.5 eq. of Int. V.3; Na ₂ CO ₃ was used instead of K ₂ CO ₃ ; 2 h at 100 °C
15	Int. III.3 + Int. V.4		1.5 eq. of Int. V.4; Na ₂ CO ₃ was used instead of K ₂ CO ₃ ; 2 h at 100 °C
16	Int. III.3 + Int. V.5		1.04 eq. of Int. V.4; 2.0 eq. K ₂ CO ₃ solution; 5 h at 100 °C; purification by preparative SFC (BEH; MeOH/CO ₂ ; 40°C; BPR: 120bar)
17	Int. III.3 + Int. V.8		1.5 eq. of Int. V.8; 2.0 eq. K ₂ CO ₃ solution; 4 h at 100 °C; purification by preparative HPLC (XBridge C18, ACN/water gradient containing 0.1% TFA)

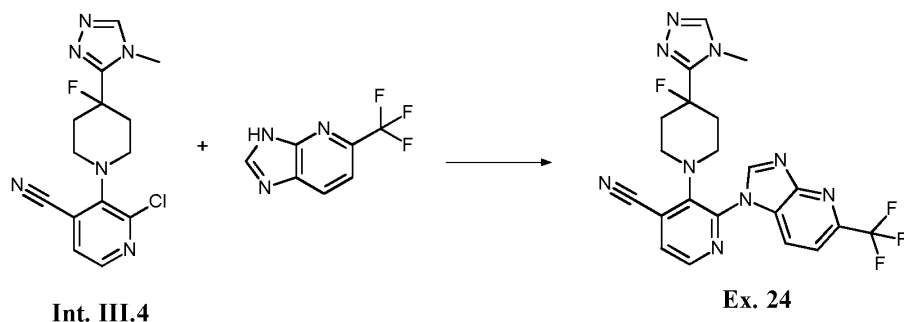
18	Int. III.3 + Int. V.9		1.1 eq. of Int. V.9; 1.5 h at 100 °C; purification by preparative HPLC (XBridge C18, ACN/water gradient containing 0.1% TFA)
19	Int. III.4 + (pyridin-3-yl)boronic acid		0.05 eq. Xphos Pd G3; 2.5 eq. aq. 2M K ₃ PO ₄ solution; 16 h at 100 °C; purification by preparative HPLC (C18, ACN/water gradient containing 0.1% TFA)
20	Int. III.4 + (5-methylpyridin-3-yl)boronic acid		0.05 eq. Xphos Pd G3; 2.5 eq. aq. 2M K ₃ PO ₄ solution; 16 h at 100 °C; purification by preparative HPLC (C18, ACN/water gradient containing 0.1% TFA)
21	Int. III.4 + (6-fluoro-4-methylpyridin-3-yl)boronic acid		0.05 eq. Xphos Pd G3; 2.5 eq. aq. 2M K ₃ PO ₄ solution; 16 h at 100 °C; purification by preparative HPLC (C18, ACN/water gradient containing 0.1% TFA)
22	Int. III.4 + (4-chloro-6-fluoropyridin-3-yl)boronic acid		1.1 eq. of (4-chloro-6-fluoropyridin-3-yl)boronic acid; 4.0 eq. K ₂ CO ₃ solution; 1 h at 70 °C

25	Int. III.5 + Int. V.2		1.0 eq. of Int. V.2; 2.0 eq. K ₂ CO ₃ solution; 1.5 h at 100 °C
26	Int. III.5 + Int. V.3		1.0 eq. of Int. V.3; 2.0 eq. K ₂ CO ₃ solution; 1.5 h at 100 °C
27	Int. III.5 + Int. V.4a		1.0 eq. of Int. V.4; 2.0 eq. K ₂ CO ₃ solution; 1.5 h at 100 °C; purification by preparative HPLC (C18, ACN/water gradient containing 0.1% TFA)
28	Int. III.7 + Int. V.1		1.5 eq. of Int. V.1; 3 h at 100 °C; purification by preparative HPLC (XBridge C18, ACN/water gradient containing 0.1% TFA)

29	Int. III.7 + Int. V.2		2 h at 100 °C; purification by preparative HPLC (XBridge C18, ACN/water gradient containing 0.1% TFA)
30	Int. III.7 + Int. V.7		2.0 eq. K ₂ CO ₃ solution; 2 h at 100 °C; purification by preparative HPLC (XBridge C18, ACN/water gradient containing 0.1% TFA)
31	Int. III.7 + 2-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine		2.0 eq. K ₂ CO ₃ solution; 10 h at 100 °C; purification by preparative HPLC (Sunfire C18, ACN/water gradient containing 0.1% TFA)
32	Int. III.9 + Int. V.1		1.5 eq. of Int. V.1; 1.5 h at 95 °C; purification by preparative HPLC (XBridge C18, ACN/water gradient containing 0.1% TFA)

33	Int. III.9 + Int. V.2		1.5 eq. of Int. V.2; 1.5 h at 95 °C; purification by preparative HPLC (XBridge C18, ACN/water gradient containing 0.1% TFA)
34	Int. III.9 + 2-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine		1.5 eq of 2-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine; 2.0 eq. K ₂ CO ₃ solution; 15 h at 95 °C; purification by preparative HPLC (XBridge C18, ACN/water gradient containing 0.1% TFA)
35	Int. III.10 + 2-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine		2.0 eq. K ₂ CO ₃ solution; 12 h at 100 °C; purification by preparative HPLC (C18, ACN/water gradient containing 0.1% TFA)
36	Int. III.11 + Int. V.1		1.1 eq. of Int. V.1; 20 min at 50 °C; purification by preparative SFC (Torus_2-PIC; MeOH/CO ₂ ; 40°C; BPR: 120bar)

37	Int. III.11 + 2-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine		1.0 eq of 2-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine; 16 h at rt °C and 1 h at 40 °C; purification by preparative SFC (Torus_2-PIC; MeOH/CO ₂ ; 40°C; BPR: 120bar)
38	Int. III.12 + Int. V.1		1.0 eq of Int. V.1; 4.0 eq. K ₂ CO ₃ solution; 1 h at 70 °C; purification by preparative HPLC (C18, ACN/water gradient containing 0.1% TFA)
41	Int. III.14 + 2-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine		2 h at 95 °C

Example 24

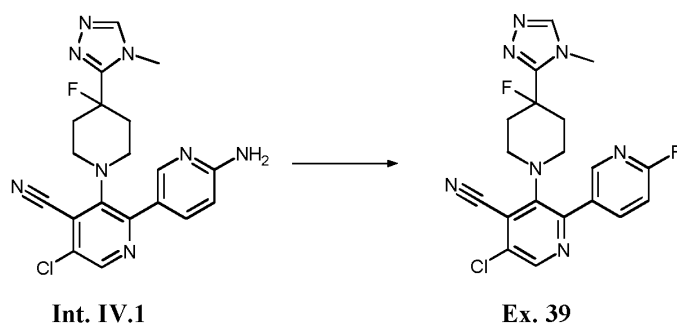
Int. III.4 (70.0 mg, 0.22 mmol), 5-(trifluoromethyl)-3H-imidazo[4,5-b]pyridine (61.3 mg, 0.33 mmol) and Cs_2CO_3 (237 mg, 0.44 mmol) are suspended in DMSO (1 mL), and the resulting mixture is heated to 100 °C and stirred for 24 h. After cooling to ambient temperature, it is diluted with an ACN/water mixture and purified by preparative HPLC (XBridge C18 column, ACN/water gradient containing 0.1% NH_3) and repurified by column chromatography (SiO_2 , EtOAc/MeOH gradient 10:0 to 8:2) to yield the title compound.

$\text{C}_{21}\text{H}_{17}\text{F}_4\text{N}_9$ (M=471.4 g/mol)

ESI-MS: 472 $[\text{M}+\text{H}]^+$

Rt (HPLC): 0.79 min (method F)

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 9.20 (s, 1 H), 8.50 (d, $J=4.9$ Hz, 1 H), 8.45 (s, 1 H), 8.33 (d, $J=8.2$ Hz, 1 H), 8.04 (d, $J=4.9$ Hz, 1 H), 7.89 (d, $J=8.4$ Hz, 1 H), 3.68 (d, $J=1.7$ Hz, 3 H), 3.15 - 3.26 (m, 4 H), 2.00 - 2.20 (m, 4 H)

Example 39

To a stirred solution of pyridine hydrofluoride (166 μL , 1.85 mmol) in pyridine (166 μL) is added Int. IV.1 (22.0 mg, 0.05 mmol) at 0 °C. After being stirred at 0 °C for 45 min, the reaction is treated with sodium nitrite (4.78 mg, 0.07 mmol), warmed to ambient temperature, and stirred for 2 h. The reaction mixture is quenched by the addition of a sat.

solution of NaHCO₃, diluted with ACN, filtered, and purified by preparative HPLC (C18 column, ACN/water gradient containing 0.1% TFA) to yield the title compound.

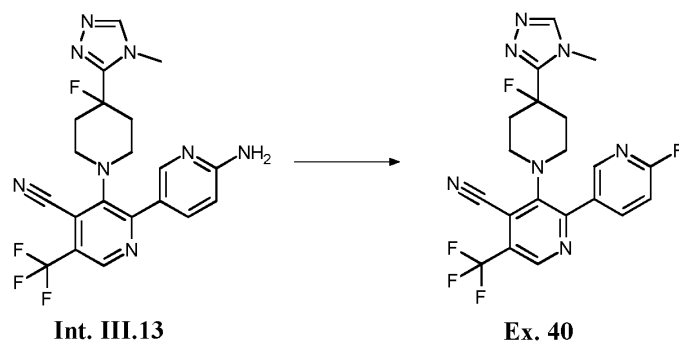
C₁₉H₁₆ClF₂N₇ (M=415.8 g/mol)

ESI-MS: 416 [M+H]⁺

5 Rt (HPLC): 0.70 min (method P)

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.69 (s, 1 H), 8.55 (s, 1 H), 8.47 (d, *J*=2.4 Hz, 1 H), 8.21 (td, *J*= 8.2, 2.5 Hz, 1 H), 7.35 (dd, *J*=8.5, 2.7 Hz, 1 H), 3.74 (d, *J*=1.5 Hz, 3 H), 3.21 – 3.27 (m, 4 H), 2.11 – 2.27 (m, 4 H).

10 Example 40



Int. III.13 (10.0 mg, 0.02 mmol) is dissolved in pyridine (210 μL), and pyridine hydrofluoride (70.6 μL, 0.78 mmol) is added at 0 °C. After being stirred at 0 °C for 1 h, the reaction is treated with sodium nitrite (2.01 mg, 0.03 mmol), warmed to ambient temperature, and stirred overnight. The reaction mixture is diluted with ACN/water, filtered, and purified by preparative HPLC (XBridge C18 column, ACN/water gradient containing 0.1% TFA) to yield the title compound.

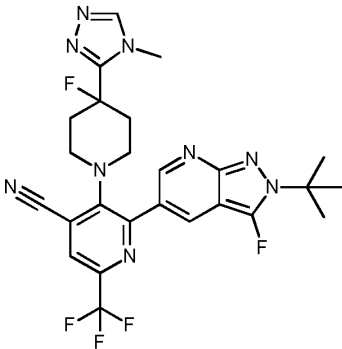
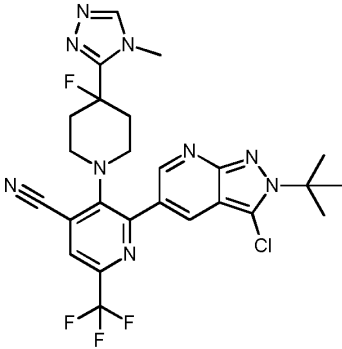
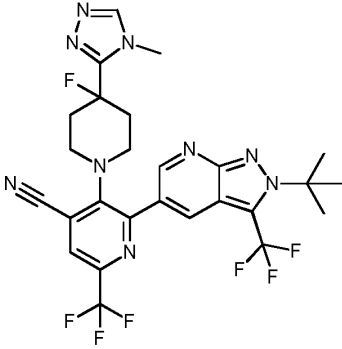
C₂₀H₁₆F₅N₇ (M=449.4 g/mol)

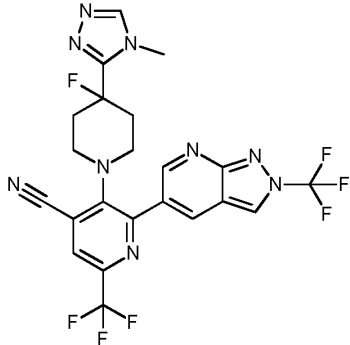
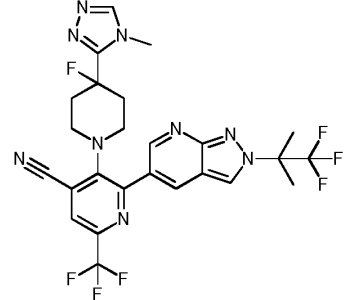
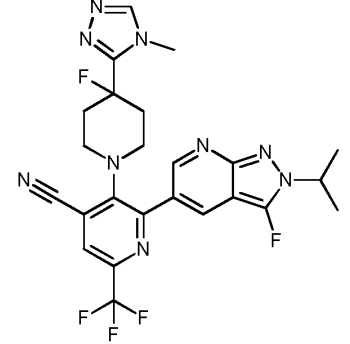
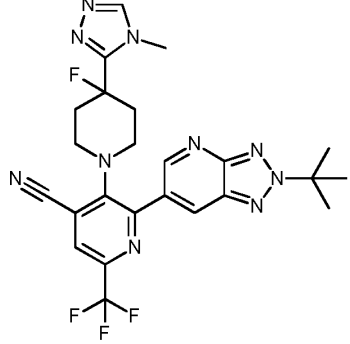
ESI-MS: 450 [M+H]⁺

20 Rt (HPLC): 0.52 min (method C)

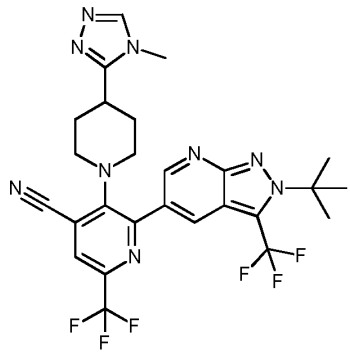
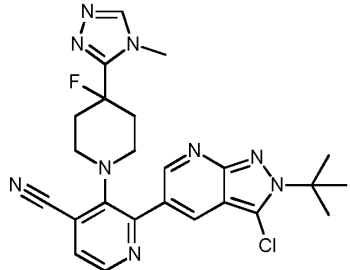
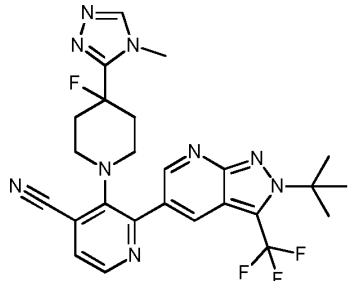
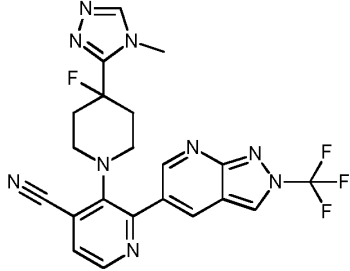
¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.92 (d, *J*=0.6 Hz, 1 H), 8.53 (s, 1 H), 8.51 (d, *J*=2.4 Hz, 1 H), 8.25 (td, *J*=8.2, 2.4 Hz, 1 H), 7.40 (dd, *J*=8.5, 2.5 Hz, 1 H), 3.74 (d, *J*=1.7 Hz, 3 H), 3.21 – 3.31 (m, 4 H), 2.14 – 2.30 (m, 4 H).

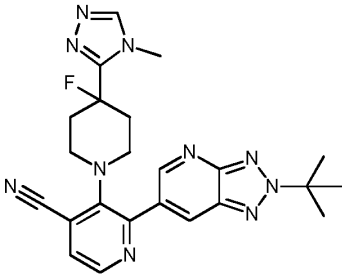
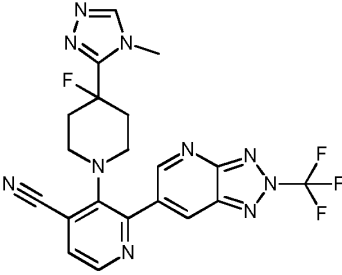
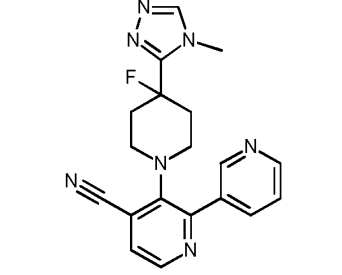
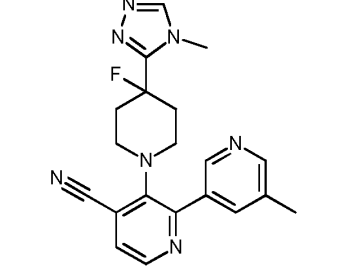
Analytical data of synthesized examples

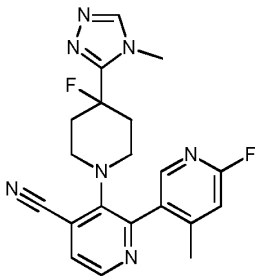
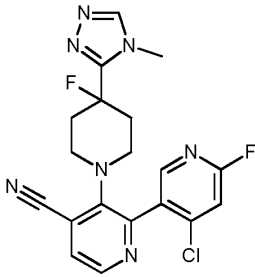
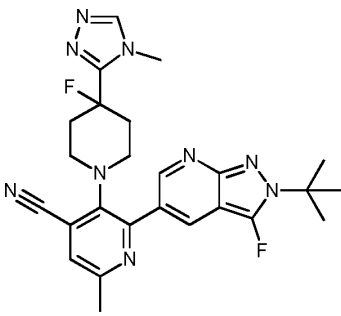
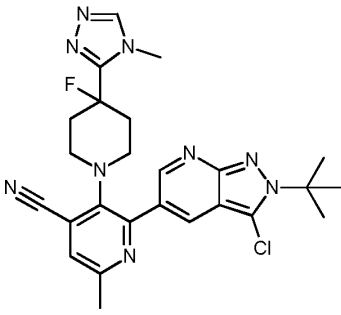
example	Structure	Molecular Formula (MW) ESI-MS HPLC retention time (method)	¹ H NMR (400 MHz, DMSO-d ₆): δ in ppm
2		$C_{25}H_{24}F_5N_9$ (M=545.5 g/mol) ESI-MS: 546 [M+H] ⁺ Rt (HPLC): 0.87 min (method J)	8.85 (d, <i>J</i> =2.2 Hz, 1 H), 8.52 (s, 1 H), 8.34 - 8.39 (m, 2 H), 3.72 (d, <i>J</i> =1.4 Hz, 3 H), 3.35 - 3.43 (m, 2 H), 3.24 - 3.34 (m, 2 H), 2.13 - 2.34 (m, 4 H), 1.74 (d, <i>J</i> =1.3 Hz, 9 H)
3		$C_{25}H_{24}ClF_4N_9$ (M=562.0 g/mol) ESI-MS: 562 [M+H] ⁺ Rt (HPLC): 0.99 min (method Q)	8.93 (d, <i>J</i> = 2.2 Hz, 1H), 8.47 (s, 1H), 8.38 (s, 1H), 8.33 (d, <i>J</i> = 2.0 Hz, 1H), 3.71 (d, <i>J</i> = 0.8 Hz, 3H), 3.44 - 3.24 (m, 4H), 2.32 - 2.13 (m, 4H), 1.84 (s, 9H)
4		$C_{26}H_{24}F_7N_9$ (M=595.5 g/mol) ESI-MS: 596 [M+H] ⁺ Rt (HPLC): 1.03 min (method Q)	9.01 (d, <i>J</i> = 2.0 Hz, 1H), 8.50 - 8.45 (m, 2H), 8.40 (s, 1H), 3.71 (d, <i>J</i> = 1.4 Hz, 3H), 3.45 - 3.22 (m, 4H), 2.28 - 2.14 (m, 4H), 1.82 (s, 9H)

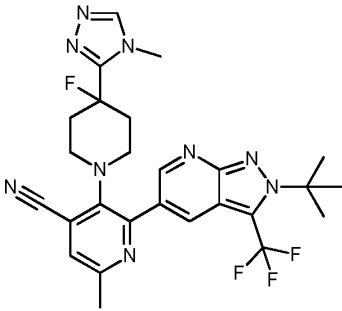
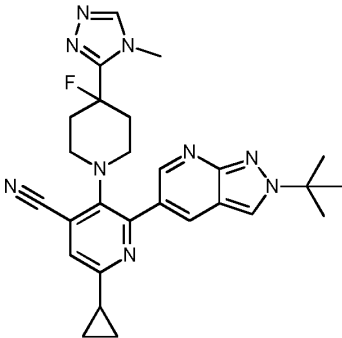
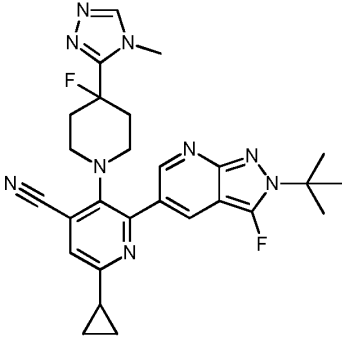
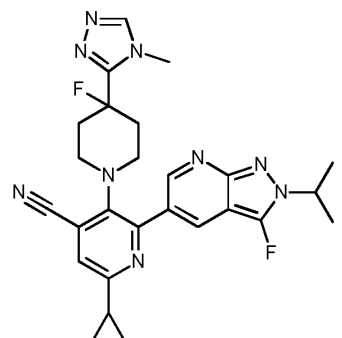
5		$C_{22}H_{16}F_7N_9$ (M=539.4 g/mol) ESI-MS: 540 [M+H] ⁺ Rt (HPLC): 0.57 min (method C)	9.36 (s, 1 H), 9.09 (d, $J=2.2$ Hz, 1 H), 8.57 (d, $J=2.3$ Hz, 1 H), 8.52 (s, 1 H), 8.42 (s, 1 H), 3.71 (d, $J=1.4$ Hz, 3 H), 3.37 - 3.45 (m, 2 H), 3.27 - 3.36 (m, 2 H), 2.13 - 2.31 (m, 4 H)
6		$C_{25}H_{22}F_7N_9$ (M=581.5 g/mol) ESI-MS: 582 [M+H] ⁺ Rt (HPLC): 0.59 min (method C)	8.98 (s, 1H), 8.92 (d, $J=2.3$ Hz, 1H), 8.49 - 8.45 (m, 2H), 8.37 (s, 1H), 3.71 (d, $J=1.4$ Hz, 3H), 3.45 - 3.23 (m, 4H), 2.36 - 2.17 (m, 4H), 2.04 (s, 6 H)
7		$C_{24}H_{22}F_5N_9$ (M=531.5 g/mol) ESI-MS: 532 [M+H] ⁺ Rt (HPLC): 0.81 min (method J)	8.85 (d, $J=2.3$ Hz, 1 H), 8.53 (s, 1 H), 8.35 - 8.40 (m, 2 H), 4.91 - 5.03 (m, 1 H), 3.72 (d, $J=1.4$ Hz, 3 H), 3.24 - 3.43 (m, 4 H), 2.14 - 2.31 (m, 4 H), 1.57 (d, $J=6.6$ Hz, 6 H)
8		$C_{24}H_{24}F_4N_{10}$ (M=528.5 g/mol) ESI-MS: 529 [M+H] ⁺ Rt (HPLC): 0.62 min (method C)	9.03 (d, $J=2.2$ Hz, 1H), 8.66 (d, $J=2.0$ Hz, 1H), 8.53 (s, 1H), 8.43 (s, 1H), 3.71 (br d, $J=1.3$ Hz, 3H), 3.45 - 3.23 (m, 4H), 2.27 - 2.11 (m, 4H), 1.82 (s, 9H)

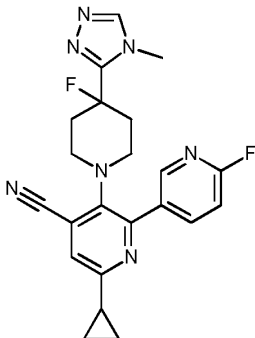
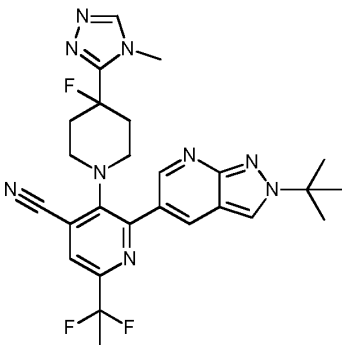
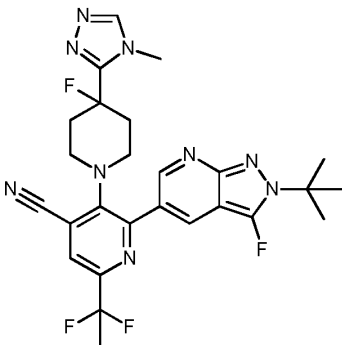
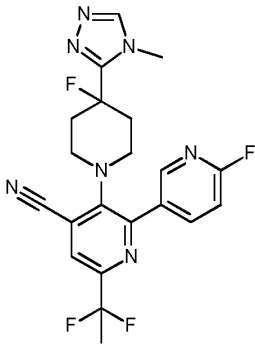
9		$C_{21}H_{15}F_7N_{10}$ (M=540.4 g/mol) ESI-MS: 541 [M+H] ⁺ Rt (HPLC): 0.66 min (method C)	9.31 (d, J = 2.0 Hz, 1H), 8.87 (d, J = 2.0 Hz, 1H), 8.52 (s, 1H), 8.49 (s, 1H), 3.71 (d, J = 1.4 Hz, 3H), 3.50 - 3.29 (m, 4H), 2.29 - 2.09 (m, 4H)
10		$C_{20}H_{15}ClF_5N_7$ (M=483.8 g/mol) ESI-MS: 484 [M+H] ⁺ Rt (HPLC): 0.79 min (method R)	8.50 - 8.53 (m, 2 H), 8.48 (s, 1 H), 7.79 (d, J =2.2 Hz, 1 H), 3.72 (d, J =1.5 Hz, 3 H), 3.22 - 3.40 (m, 4H), 2.02 - 2.27 (m, 4 H)
11		$C_{24}H_{24}F_4N_{10}$ (M=528.5 g/mol) ESI-MS: 529 [M+H] ⁺ Rt (HPLC): 0.69 min (method B)	9.58 (d, J =2.3 Hz, 1 H), 9.14 (d, J =2.3 Hz, 1 H), 8.49 (s, 1 H), 8.45 (s, 1 H), 3.73 (d, J =1.4 Hz, 3 H), 3.35 - 3.50 (m, 4 H), 2.16 - 2.35 (m, 4 H), 1.44 (s, 9 H)
12		$C_{21}H_{15}F_7N_{10}$ (M=540.4 g/mol) ESI-MS: 541 [M+H] ⁺ Rt (HPLC): 0.93 min (method F)	9.82 (d, J =2.3 Hz, 1 H), 9.38 (d, J =2.3 Hz, 1 H), 8.57 (s, 1 H), 8.50 (s, 1 H), 3.74 (d, J =1.4 Hz, 3 H), 3.37 - 3.49 (m, 4 H), 2.19 - 2.32 (m, 4 H)

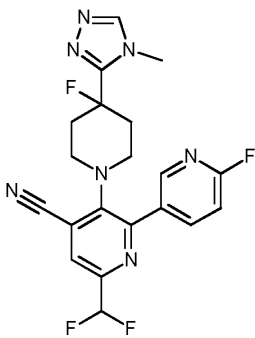
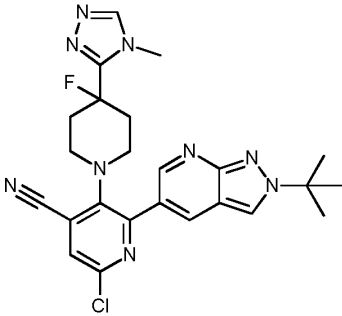
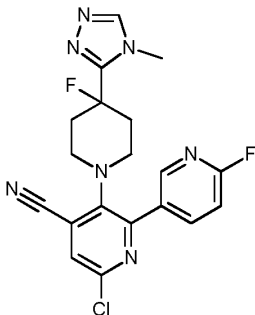
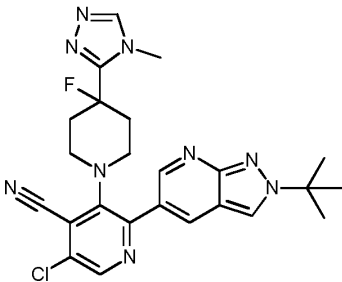
13		$C_{26}H_{25}F_6N_9$ (M=577.5 g/mol) ESI-MS: 578 [M+H] ⁺ Rt (HPLC): 1.01 min (method I)	8.99 (d, J = 2.2 Hz, 1H), 8.47 (t, J = 1.7 Hz, 1H), 8.35 (s, 1H), 8.29 (s, 1H), 3.56 (s, 3H), 3.51 (br d, J = 12.8 Hz, 2H), 3.08 (br t, J = 11.1 Hz, 2H), 3.01 - 2.91 (m, 1H), 1.84 - 1.63 (m, 4H), 1.83 (s, 9H)
14		$C_{24}H_{25}ClF_3N_9$ (M=494.0 g/mol) ESI-MS: 495 [M+H] ⁺ Rt (HPLC): 0.86 min (method Q)	8.95 (d, J =2.2 Hz, 1 H), 8.57 (d, J =4.8 Hz, 1 H), 8.48 (s, 1 H), 8.30 (d, J =2.2 Hz, 1 H), 7.82 (d, J =4.9 Hz, 1 H), 3.72 (d, J =1.4 Hz, 3 H), 3.21 - 3.30 (m, 4 H), 2.11 - 2.26 (m, 4 H), 1.85 (s, 9 H)
15		$C_{25}H_{25}F_4N_9$ (M=527.5 g/mol) ESI-MS: 528 [M+H] ⁺ Rt (HPLC): 0.92 min (method Q)	9.05 (d, J =2.0 Hz, 1 H), 8.59 (d, J =4.8 Hz, 1 H), 8.43 - 8.49 (m, 2 H), 7.85 (d, J =4.9 Hz, 1 H), 3.72 (d, J =1.5 Hz, 3 H), 3.23 - 3.30 (m, 4 H), 2.10 - 2.26 (m, 4 H), 1.83 (s, 9 H)
16		$C_{21}H_{17}F_4N_9$ (M=471.4 g/mol) ESI-MS: 472 [M+H] ⁺ Rt (HPLC): 0.46 min (method C)	9.33 (s, 1 H), 9.10 (d, J =2.2 Hz, 1 H), 8.58 (d, J =4.8 Hz, 1 H), 8.49 - 8.52 (m, 1 H), 8.47 (s, 1 H), 7.85 (d, J =4.9 Hz, 1 H), 3.71 (d, J =1.4 Hz, 3 H), 3.22 - 3.35 (m, 4 H), 2.10 - 2.25 (m, 4 H)

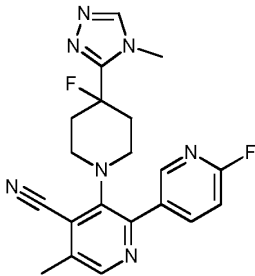
17		$C_{23}H_{25}FN_{10}$ (M=460.5 g/mol) ESI-MS: 461 [M+H] ⁺ Rt (HPLC): 0.49 min (method C)	9.03 (d, $J=2.0$ Hz, 1 H), 8.61 (d, $J=2.0$ Hz, 1 H), 8.59 (d, $J=4.8$ Hz, 1 H), 8.55 (s, 1 H), 7.87 (d, $J=4.9$ Hz, 1 H), 3.71 (d, $J=1.5$ Hz, 3 H), 3.25 (br d, $J=5.5$ Hz, 4 H), 2.07 - 2.23 (m, 4 H), 1.82 (s, 9 H)
18		$C_{20}H_{16}F_4N_{10}$ (M=472.4 g/mol) ESI-MS: 473 [M+H] ⁺ Rt (HPLC): 0.53 min (method C)	9.33 (d, $J=2.2$ Hz, 1 H), 8.82 (d, $J=2.0$ Hz, 1 H), 8.63 (d, $J=4.8$ Hz, 1 H), 8.56 (s, 1 H), 7.91 - 7.95 (m, 1 H), 3.72 (d, $J=1.5$ Hz, 3 H), 3.24 - 3.40 (m, 4 H), 2.05 - 2.23 (m, 4 H)
19		$C_{19}H_{18}FN_7$ (M=363.4 g/mol) ESI-MS: 364 [M+H] ⁺ Rt (HPLC): 0.49 min (method S)	8.84 (d, $J=1.6$ Hz, 1H), 8.68 (dd, $J=1.6, 4.9$ Hz, 1H), 8.55 (d, $J=4.9$ Hz, 1H), 8.50 (s, 1H), 8.10 (td, $J=1.8, 7.9$ Hz, 1H), 7.83 (d, $J=4.8$ Hz, 1H), 7.60 (dd, $J=5.0,$ 7.9 Hz, 1H), 3.73 (d, $J=$ 1.6 Hz, 3H), 3.28 - 3.15 (m, 4H), 2.25 - 2.12 (m, 4H)
20		$C_{20}H_{20}FN_7$ (M=377.4 g/mol) ESI-MS: 378 [M+H] ⁺ Rt (HPLC): 0.41 min (method P)	8.82 (d, $J=1.5$ Hz, 1H), 8.67 (d, $J=1.4$ Hz, 1H), 8.60 - 8.54 (m, 2H), 8.27 (s, 1H), 7.87 (d, $J=$ 4.8 Hz, 1H), 3.75 (d, $J=$ 1.8 Hz, 3H), 3.35 - 3.15 (m, 4H), 2.46 (s, 3H), 2.25 - 2.06 (m, 4H)

21		$C_{20}H_{19}F_2N_7$ (M=395.4 g/mol) ESI-MS: 396 [M+H] ⁺ Rt (HPLC): 0.56 min (method S)	8.60 (s, 1H), 8.54 (d, J = 4.9 Hz, 1H), 8.15 (s, 1H), 7.85 (d, J = 4.8 Hz, 1H), 7.25 (s, 1H), 3.73 (d, J = 1.6 Hz, 3H), 3.22 - 3.04 (m, 4H), 2.24 (s, 3H), 2.22 - 1.96 (m, 4H)
22		$C_{19}H_{16}ClF_2N_7$ (M=415.8 g/mol) ESI-MS: 416 [M+H] ⁺ Rt (HPLC): 0.59 min (method L)	8.57 (d, J =4.9 Hz, 1 H), 8.47 (s, 1 H), 8.43 - 8.45 (m, 1 H), 7.90 - 7.93 (m, 1 H), 7.73 - 7.75 (m, 1 H), 3.71 (d, J =1.5 Hz, 3 H), 3.13 - 3.26 (m, 4 H), 1.95 - 2.23 (m, 4 H)
25		$C_{25}H_{27}F_2N_9$ (M=491.5 g/mol) ESI-MS: 492 [M+H] ⁺ Rt (HPLC): 0.75 min (method R)	8.85 (d, J =2.2 Hz, 1 H), 8.46 (s, 1 H), 8.28 (d, J =2.2 Hz, 1 H), 7.70 (s, 1 H), 3.71 (d, J =1.5 Hz, 3 H), 3.12 - 3.28 (m, 4 H), 2.52 (s, 3 H), 2.05 - 2.23 (m, 4 H), 1.74 (d, J =1.4 Hz, 9 H)
26		$C_{25}H_{27}ClFN_9$ (M=508.0 g/mol) ESI-MS: 508 [M+H] ⁺ Rt (HPLC): 0.80 min (method R)	8.93 (d, J = 2.0 Hz, 1H), 8.46 (s, 1H), 8.27 (d, J = 2.2 Hz, 1H), 7.70 (s, 1H), 3.71 (d, J = 1.5 Hz, 3H), 3.28 - 3.14 (m, 4H), 2.53 (s, 3H), 2.24 - 2.07 (m, 4H), 1.84 (s, 9H)

27		$C_{26}H_{27}F_4N_9$ (M=541.5 g/mol) ESI-MS: 542 [M+H] ⁺ Rt (HPLC): 0.86 min (method T)	9.02 (d, $J=2.0$ Hz, 1 H), 8.55 (s, 1 H), 8.42 (t, $J=1.7$ Hz, 1 H), 7.73 (s, 1 H), 3.72 (d, $J=1.5$ Hz, 3 H), 3.13 - 3.34 (m, 4 H), 2.54 (s, 3 H), 2.04 - 2.25 (m, 4 H), 1.82 (s, 9 H)
28		$C_{27}H_{30}FN_9$ (M=499.6 g/mol) ESI-MS: 500 [M+H] ⁺ Rt (HPLC): 0.53 min (method C)	8.84 (d, $J=2.2$ Hz, 1 H), 8.65 (s, 1 H), 8.54 (s, 1 H), 8.37 (d, $J=2.2$ Hz, 1 H), 7.72 (s, 1 H), 3.72 (d, $J=1.5$ Hz, 3 H), 3.11 - 3.30 (m, 4 H), 2.12 - 2.26 (m, 5 H), 1.71 (s, 9 H), 0.92 - 1.03 (m, 4 H)
29		$C_{27}H_{29}F_2N_9$ (M=517.6 g/mol) ESI-MS: 518 [M+H] ⁺ Rt (HPLC): 0.63 min (method C)	8.84 (d, $J=2.2$ Hz, 1 H), 8.54 (s, 1 H), 8.27 (d, $J=2.0$ Hz, 1 H), 7.73 (s, 1 H), 3.72 (d, $J=1.5$ Hz, 3 H), 3.10 - 3.32 (m, 4 H), 2.05 - 2.24 (m, 5 H), 1.73 (d, $J=1.4$ Hz, 9 H), 0.92 - 1.03 (m, 4 H)
30		$C_{26}H_{27}F_2N_9$ (M=503.6 g/mol) ESI-MS: 504 [M+H] ⁺ Rt (HPLC): 0.59 min (method C)	8.84 (d, $J=2.2$ Hz, 1 H), 8.54 (s, 1 H), 8.30 (d, $J=2.0$ Hz, 1 H), 7.73 (s, 1 H), 4.95 (spt, $J=6.7$ Hz, 1 H), 3.72 (d, $J=1.5$ Hz, 3 H), 3.09 - 3.34 (m, 4 H), 2.05 - 2.25 (m, 5 H), 1.56 (d, $J=6.6$ Hz, 6 H), 0.91 - 1.04 (m, 4 H)

31		$C_{22}H_{21}F_2N_7$ (M=421.4 g/mol) ESI-MS: 422 [M+H] ⁺ Rt (HPLC): 0.78 min (method J)	8.55 (s, 1 H), 8.47 (d, <i>J</i> =2.3 Hz, 1 H), 8.22 (td, <i>J</i> =8.2, 2.5 Hz, 1 H), 7.75 (s, 1 H), 7.31 (dd, <i>J</i> =8.4, 2.5 Hz, 1 H), 3.74 (d, <i>J</i> =1.7 Hz, 3 H), 3.05 - 3.30 (m, 4 H), 2.06 - 2.25 (m, 5 H), 0.91 - 1.03 (m, 4 H)
32		$C_{26}H_{28}F_3N_9$ (M=523.6 g/mol) ESI-MS: 524 [M+H] ⁺ Rt (HPLC): 0.54 min (method C)	8.88 (d, <i>J</i> =2.3 Hz, 1 H), 8.68 - 8.69 (m, 1 H), 8.56 (s, 1 H), 8.43 (d, <i>J</i> =2.3 Hz, 1 H), 8.06 (s, 1 H), 3.72 (d, <i>J</i> =1.7 Hz, 3 H), 3.21 - 3.36 (m, 4 H), 2.17 - 2.34 (m, 4 H), 2.02 (t, <i>J</i> =19.0 Hz, 3 H), 1.72 (s, 9 H)
33		$C_{26}H_{27}F_4N_9$ (M=541.5 g/mol) ESI-MS: 542 [M+H] ⁺ Rt (HPLC): 0.67 min (method B)	8.88 (d, <i>J</i> =2.2 Hz, 1 H), 8.47 (s, 1 H), 8.36 (d, <i>J</i> =2.0 Hz, 1 H), 8.07 (s, 1 H), 3.72 (d, <i>J</i> =1.4 Hz, 3 H), 3.23 - 3.36 (m, 4 H), 2.11 - 2.31 (m, 4 H), 2.02 (t, <i>J</i> =19.1 Hz, 3 H), 1.74 (d, <i>J</i> =1.1 Hz, 9 H)
34		$C_{21}H_{19}F_4N_7$ (M=445.4 g/mol) ESI-MS: 446 [M+H] ⁺ Rt (HPLC): 0.55 min (method C)	8.52 - 8.56 (m, 2 H), 8.24 - 8.30 (m, 1 H), 8.10 (s, 1 H), 7.37 (dd, <i>J</i> =8.5, 2.5 Hz, 1 H), 3.74 (d, <i>J</i> =1.7 Hz, 3 H), 3.26 (br dd, <i>J</i> =6.6, 4.1 Hz, 4 H), 2.11 - 2.29 (m, 4 H), 2.00 (t, <i>J</i> =19.0 Hz, 3 H)

35		$C_{20}H_{17}F_4N_7$ (M=431.4 g/mol) ESI-MS: 432 [M+H] ⁺ Rt (HPLC): 0.49 min (method C)	8.56 (s, 1 H), 8.51 (d, <i>J</i> =2.4 Hz, 1 H), 8.25 (td, <i>J</i> =8.2, 2.5 Hz, 1 H) (m, 1 H), 8.13 (s, 1 H), 7.37 (dd, <i>J</i> =8.4, 2.6 Hz, 1 H), 7.00 (t, <i>J</i> =54.6 Hz, 1 H), 3.74 (d, <i>J</i> =1.5 Hz, 3 H), 3.21 - 3.33 (m, 4 H), 2.11 - 2.28 (m, 4 H)
36		$C_{24}H_{25}ClFN_9$ (M=494.0 g/mol) ESI-MS: 494 [M+H] ⁺ Rt (HPLC): 0.71 min (method T)	8.80 (d, <i>J</i> =2.2 Hz, 1 H), 8.66 (s, 1 H), 8.46 (s, 1 H), 8.37 (d, <i>J</i> =2.2 Hz, 1 H), 8.04 - 8.06 (m, 1 H), 3.70 (d, <i>J</i> =1.5 Hz, 3 H), 3.18 - 3.26 (m, 4 H), 2.15 - 2.31 (m, 4 H), 1.72 (s, 9 H)
37		$C_{19}H_{16}ClF_2N_7$ (M=415.8 g/mol) ESI-MS: 416 [M+H] ⁺ Rt (HPLC): 0.72 min (method T)	8.47 - 8.50 (m, 2 H), 8.23 (td, <i>J</i> =8.2, 2.5 Hz, 1 H), 8.10 (s, 1 H), 7.34 - 7.38 (m, 1 H), 3.73 (d, <i>J</i> =1.5 Hz, 3 H), 3.14 - 3.24 (m, 4 H), 2.09 - 2.26 (m, 4 H)
38		$C_{24}H_{25}ClFN_9$ (M=494.0 g/mol) ESI-MS: 494 [M+H] ⁺ Rt (HPLC): 0.68 min (method P)	8.81 (d, <i>J</i> =2.2 Hz, 1 H), 8.68 (d, <i>J</i> =6.3 Hz, 2 H), 8.56 (s, 1 H), 8.37 (d, <i>J</i> =2.3 Hz, 1 H), 3.72 (d, <i>J</i> =1.5 Hz, 3 H), 3.18 - 3.33 (m, 4 H), 2.17 - 2.30 (m, 4 H), 1.72 (s, 9 H)

41		$C_{20}H_{19}F_2N_7$ (M=395.4 g/mol) ESI-MS: 396 [M+H] ⁺ Rt (HPLC): 0.50 min (method B)	8.50 (d, J = 0.6 Hz, 1H), 8.48 (s, 1H), 8.44 (d, J = 2.4 Hz, 1H), 8.19 (dt, J = 2.4, 8.2 Hz, 1H), 7.32 (dd, J = 2.6, 8.4 Hz, 1H), 3.73 (d, J = 1.5 Hz, 3H), 3.28 - 3.12 (m, 4H), 2.30 - 2.09 (m, 4H); 3 H's missing (Me peak overlaps with DMSO-d6 signal)
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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 μ m; 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_2.5 μ m; column temperature: 60°C

Method C

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 D

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

Method E

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 1200; Analytical column: Luna C18_2.0 x 50 mm_5µm;
column temperature: 40°C

Method F

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

Method G

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 H

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 I

time (min)	Vol% water (incl. 0.1% NH ₃)	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: Xbridge (Waters) C18_3.0 x 30 mm_2.5 µm; column temperature: 60°C

Method J

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 K

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 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 µm; column temperature: 60 °C

Method M

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 N

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 O

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 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% 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 µm; column temperature: 60 °C

Method R

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
5 mm_2.5 µm; column temperature: 60 °C

Method S

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

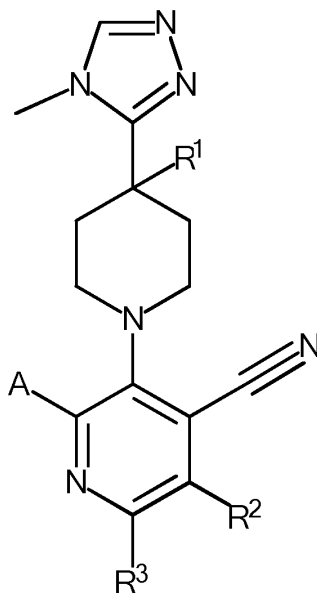
Method T

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

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 nitrogens;

or **A** is **A1b** which is a 9- or 10-membered fused bicyclic-heteroaryl ring containing one to four nitrogens;

wherein **A** is optionally substituted by one or two **R⁴**;

R¹ is selected from the group **R1a**, consisting of H and F;

R² is selected from the group **R2a**, consisting of H, halo, C₁₋₆-alkyl and F₁₋₉-fluoro-C₁₋₆-alkyl;

R³ is selected from the group **R3a**, consisting of H, halo, C₁₋₄-alkyl, F₁₋₉-fluoro-C₁₋₄-alkyl and C₃₋₆-cycloalkyl;

R⁴ is selected from the group **R4a**, consisting of halo, C₁₋₆-alkyl, F₁₋₉-fluoro-C₁₋₆-alkyl and C₃₋₆-cycloalkyl;

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

5

2. The compound of formula (**I**) according to claim 1, wherein **A** is selected from the group **A3** consisting of 1H-[1,2,3]triazolo[4,5-b]pyridinyl, pyridinyl, 2H-pyrazolo[3,4-b]pyridinyl, [1,2,4]triazolo[1,5-a]pyrimidinyl and 1H-imidazo[4,5-b]pyridinyl; wherein **A2** is independently substituted with one or two **R⁴**;

10

or a salt thereof.

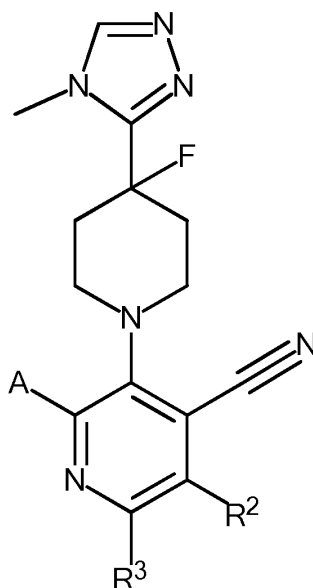
3. The compound of formula (**I**) according to any of claims 1 to 2, wherein **R²** is **R2b**, selected from H, halo, C₁₋₄-alkyl and F₁₋₃-fluoro-C₁₋₄-alkyl; or a salt thereof.

15

4. The compound of formula (**I**) according to any of claims 1 to 3, wherein **R³** is **R3b** selected from of H, chloro, fluoro, C₁₋₄-alkyl, F₁₋₉-fluoro-C₁₋₄-alkyl and cyclopropyl; or a salt thereof.

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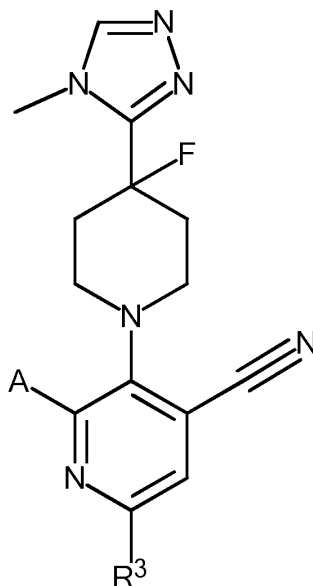
5. The compound of formula (**I**) according to any of claims 1 to 4 having formula (**1-a**)



(I-a)

or a salt thereof.

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

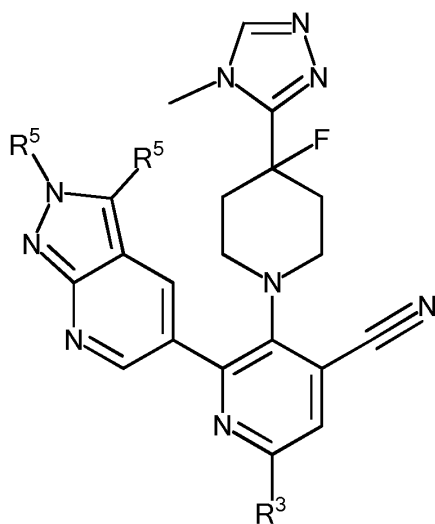


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(I-b)

or a salt thereof.

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

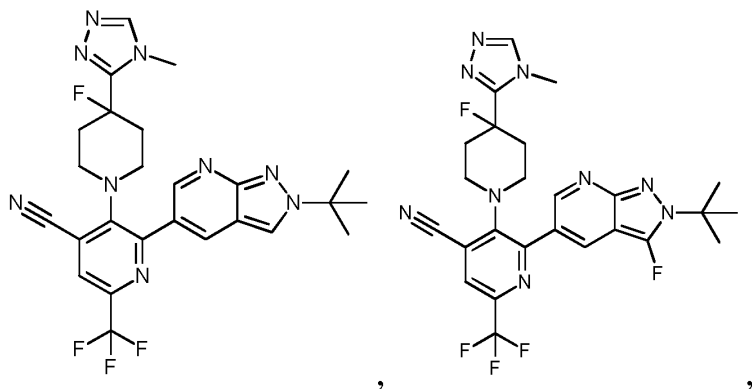


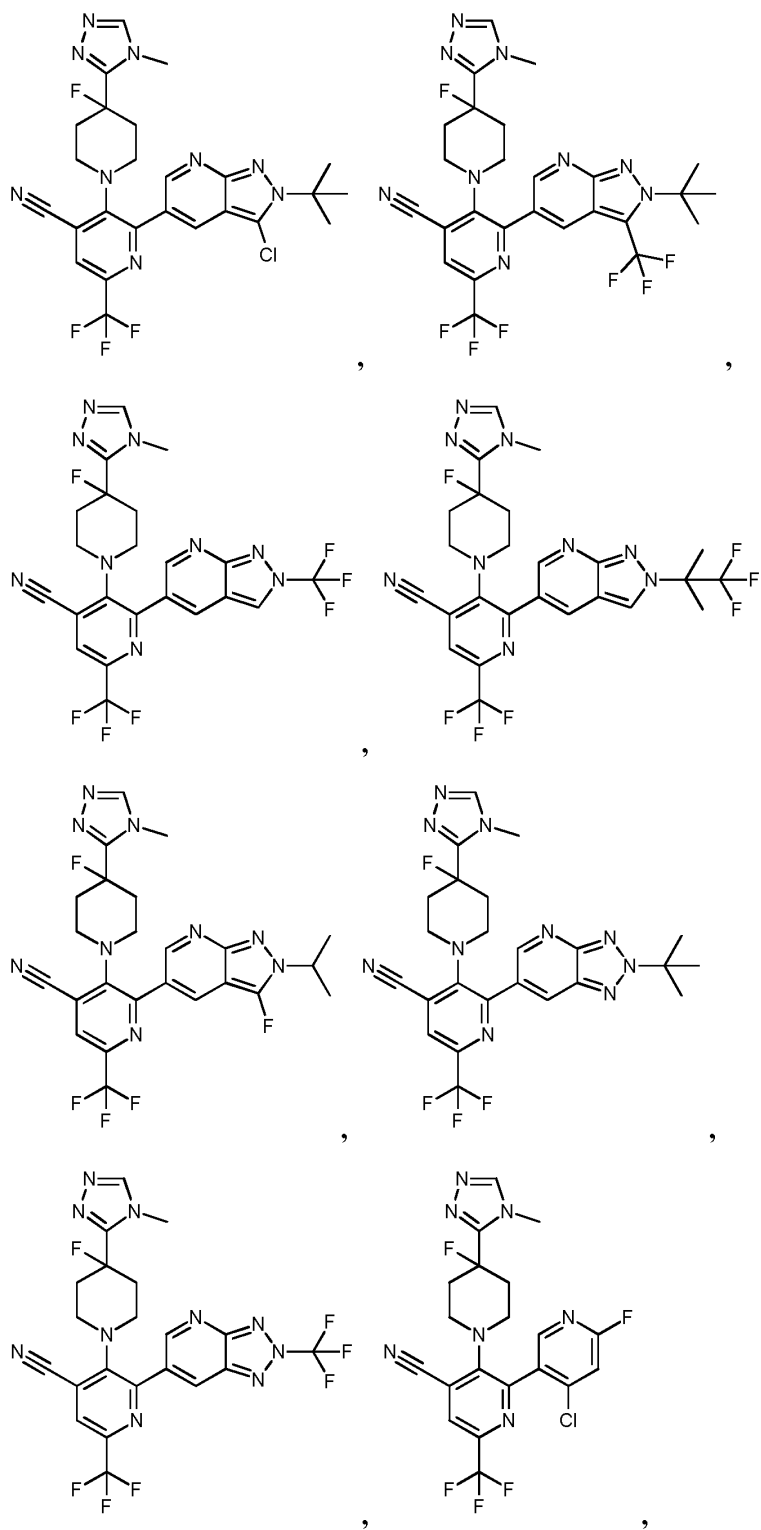
(I-c)

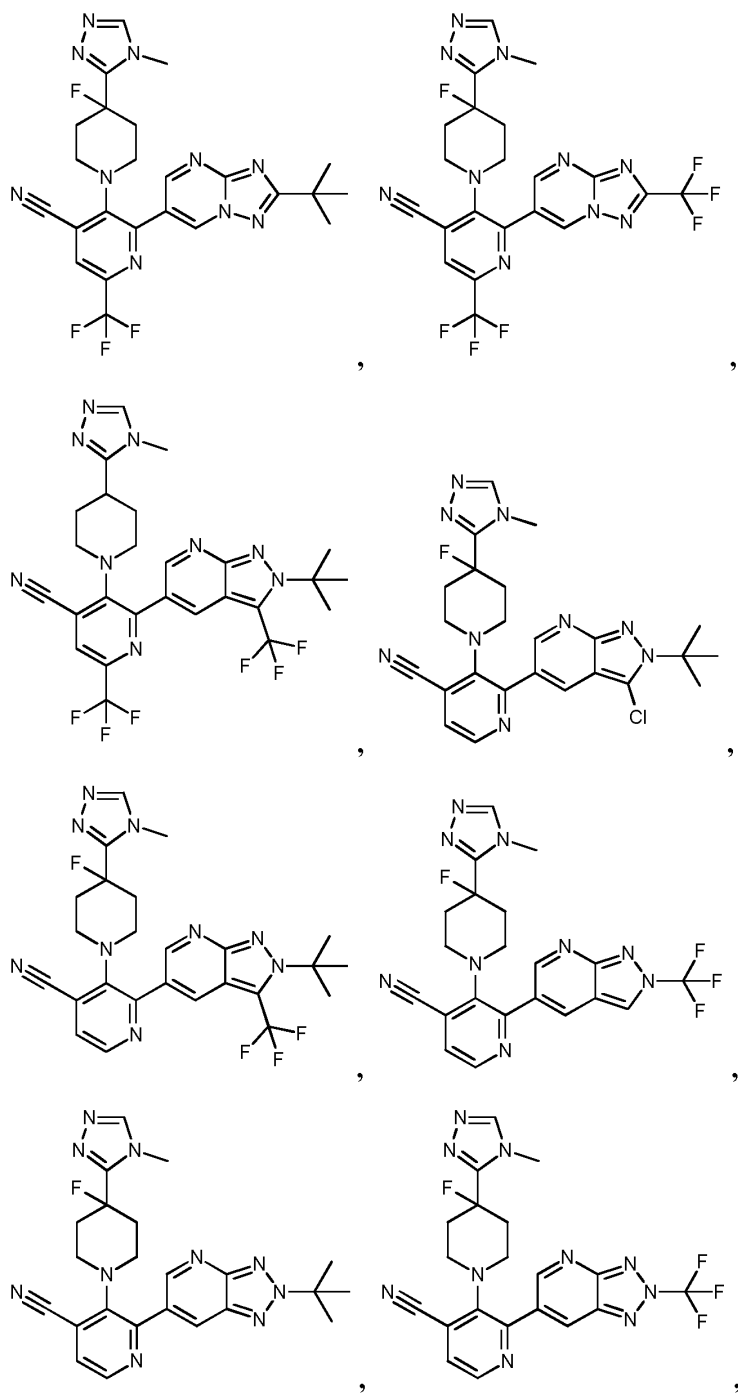
wherein substituent **R**⁵ is H or **R**⁴,
or a salt thereof.

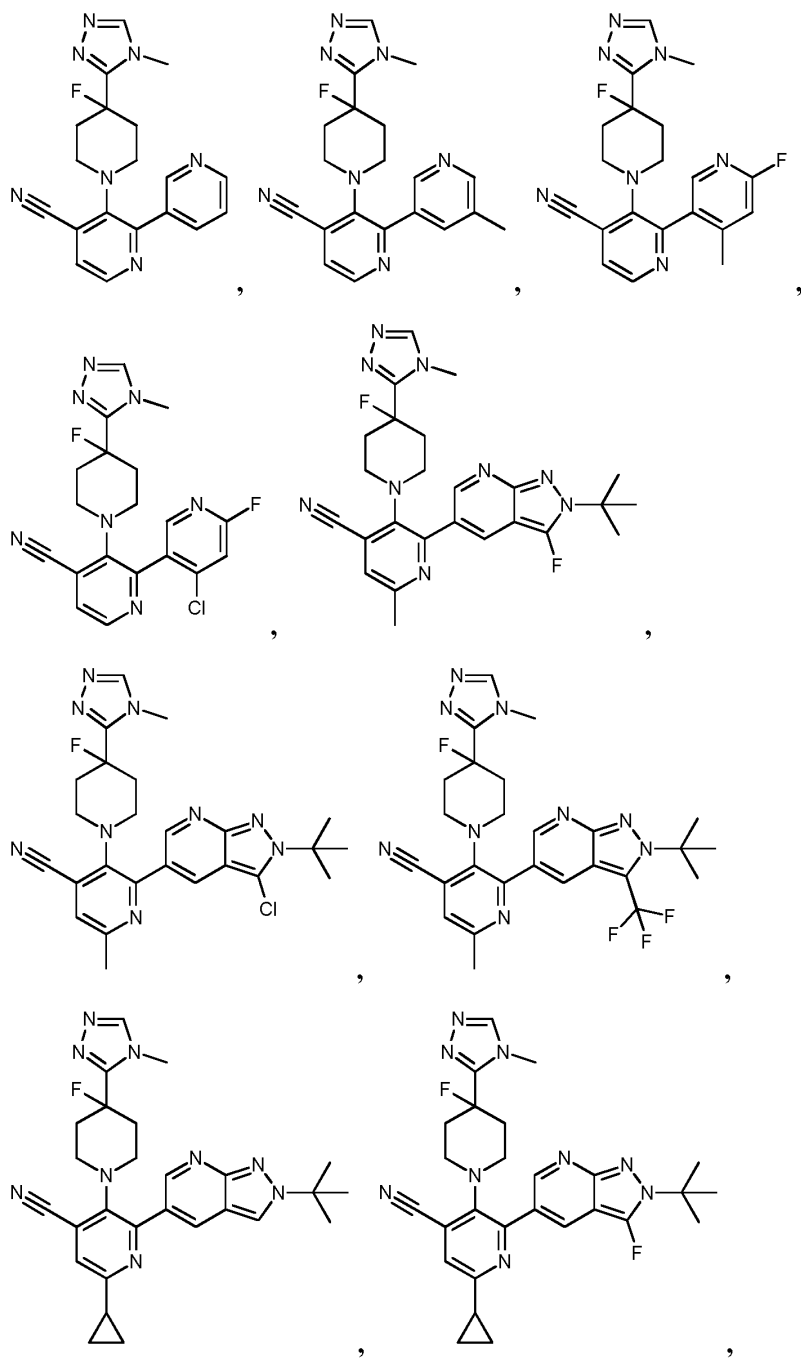
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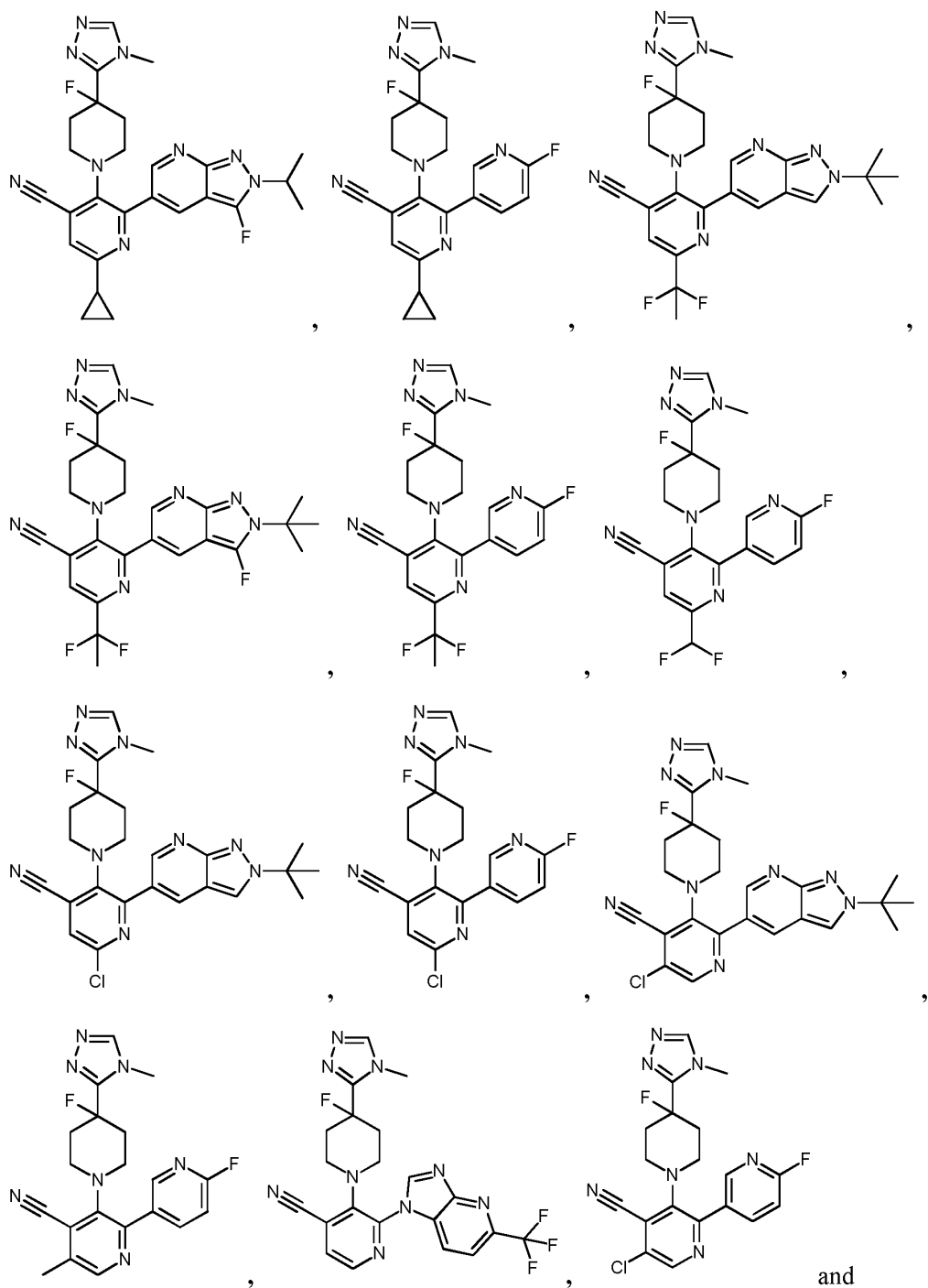
8. The compound of formula **(I)** according to claim 1, selected from the group consisting of

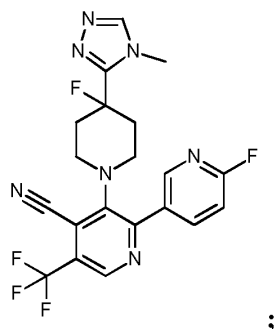












or a salt thereof.

9. A pharmaceutically acceptable salt of a compound according to one or more of claims 1
5 to 8.

10. A pharmaceutical composition comprising one or more compounds according to one or
more of claims 1 to 8, or pharmaceutically acceptable salts thereof, optionally together
with one or more inert carriers and/or diluents.

10

11. A pharmaceutical composition comprising one or more compounds according to one or
more of the claims 1 to 8, or pharmaceutically acceptable salts thereof, and one or more
additional therapeutic agents, optionally together with one or more inert carriers and/or
diluents.

15

12. The pharmaceutical composition according to claim 11 wherein the one or more
additional therapeutic agents are selected from the group consisting of anticancer agents
and antifibrotic agents.

20 13. The compound according to one or more of claims 1 to 8 or a pharmaceutically
acceptable salt thereof for use as a medicament.

14. 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
25 characterized in that one or more compounds according to one or more of claims 1 to 8 or
pharmaceutically acceptable salts thereof are administered to the patient.

15. A compound according to one or more of claims 1 to 8 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.

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