

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

5 TECHNICAL FIELD

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

BACKGROUND INFORMATION

Glutaminyl-peptide cyclotransferase (QPCT) and glutaminyl-peptide cyclotransferase-like protein (QPCTL) catalyze the intramolecular cyclization of N-terminal glutamine (Q) resi-
15 dues into pyroglutamic acid (pE) liberating ammonia [Stephan Schilling et al., "Identification of Human Glutaminyl Cyclase as a Metalloenzyme POTENT INHIBITION BY IMID-
AZOLE DERIVATIVES AND HETEROCYCLIC CHELATORS," *Journal of Biological Chemistry* 278, no. 50 (2003): 49773–79, <https://doi.org/10.1074/jbc.m309077200>; Holger Cynis et al., "Isolation of an Isoenzyme of Human Glutaminyl Cyclase: Retention in the
20 Golgi Complex Suggests Involvement in the Protein Maturation Machinery," *Journal of Molecular Biology* 379, no. 5 (2008): 966–80, <https://doi.org/10.1016/j.jmb.2008.03.078>; Anett Stephan et al., "Mammalian Glutaminyl Cyclases and Their Isoenzymes Have Identical Enzymatic Characteristics," *FEBS Journal* 276, no. 22 (2009): 6522–36, <https://doi.org/10.1111/j.1742-4658.2009.07337.x>]. While QPCT is a secreted protein,
25 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
30 have been reported. Known substrates of the intracellular QPCTL and/or extracellular QPCT are CD47 [Meike E. W. Logtenberg et al., "Glutaminyl Cyclase Is an Enzymatic Modifier of the CD47- SIRPα Axis and a Target for Cancer Immunotherapy," *Nature Medicine* 25, no. 4 (2019): 612–19, <https://doi.org/10.1038/s41591-019-0356-z>], different chemokines

(like for example CCL2 and 7 or CX3CL1) [Rosa Barreira da Silva et al., “Loss of the Intracellular Enzyme QPCTL Limits Chemokine Function and Reshapes Myeloid Infiltration to Augment Tumor Immunity,” *Nature Immunology* 23, no. 4 (2022): 568–80, <https://doi.org/10.1038/s41590-022-01153-x>; Astrid Kehlen et al., “N-Terminal Pyroglutamate Formation in CX3CL1 Is Essential for Its Full Biologic Activity,” *Bioscience Reports* 37, no. 4 (2017): BSR20170712, <https://doi.org/10.1042/bsr20170712>.], Amyloid-b peptides [Cynis et al., “Isolation of an Isoenzyme of Human Glutaminy 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 Glutaminy 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., “Glutaminy 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., “Glutaminy 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/SIRPalpha Axis in COVID-19 Pathogenesis,” *Current Issues in Molecular Biology* 43, no. 3 (2021): 1212–

25, <https://doi.org/10.3390/cimb43030086>], lung fibrosis [Gerlinde Wernig et al., “Unifying Mechanism for Different Fibrotic Diseases,” *Proceedings of the National Academy of Sciences* 114, no. 18 (2017): 4757–62, <https://doi.org/10.1073/pnas.1621375114>; Lu Cui et al., “Activation of JUN in Fibroblasts Promotes Pro-Fibrotic Programme and Modulates Protective Immunity,” *Nature Communications* 11, no. 1 (2020): 2795, <https://doi.org/10.1038/s41467-020-16466-4>], systemic sclerosis [Wernig et al., “Unifying Mechanism for Different Fibrotic Diseases”; Tristan Lerbs et al., “CD47 Prevents the Elimination of Diseased Fibroblasts in Scleroderma,” *JCI Insight* 5, no. 16 (2020): e140458, <https://doi.org/10.1172/jci.insight.140458>] and liver fibrosis [Taesik Gwag et al., “Anti-CD47 Antibody Treatment Attenuates Liver Inflammation and Fibrosis in Experimental Non-alcoholic Steatohepatitis Models,” *Liver International* 42, no. 4 (2022): 829–41, <https://doi.org/10.1111/liv.15182>]. Since enhanced CD47 expression blocks the clearance of apoptotic cells, there is an accrual of apoptotic lung epithelial cells, leading to a profibrotic 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 (SIRPα) Interaction Is a Therapeutic

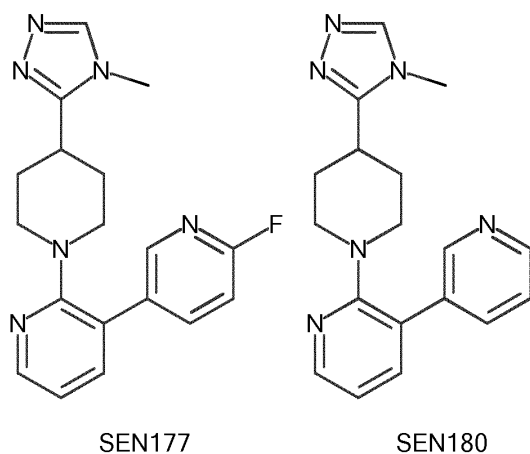
Target for Human Solid Tumors,” *Proceedings of the National Academy of Sciences* 109, no. 17 (2012): 6662–67, <https://doi.org/10.1073/pnas.1121623109>].

In addition to CD47, chemokines, such as CCL2 and CX3CL1, have been identified as QPCTL and/or QPCT substrates [Holger Cynis et al., “The Isoenzyme of Glutaminyl

5 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 increasing its capacity to induce chemokine receptor signaling. Two main monocyte chem-
10 oattractants 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 Abundance and Inflammatory Signatures in the Tumor Microenvironment,” *Oncoimmunology*
15 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 QPCT/L inhibitors.

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

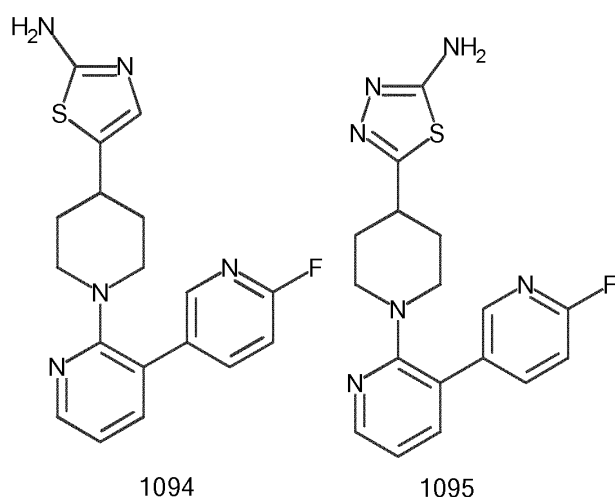


SEN177 is disclosed therein (supplementary information) as having a IC_{50} on isolated hQC of 53 nM and on isolated QPCTL of 13 nM. SEN180 is disclosed therein (supplementary information) as having a IC_{50} on hQC of 170 nM and on QPCTL of 58 nM.

5

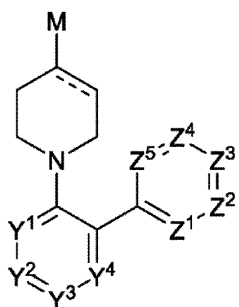
Pozzi, C, et al, Journal of Biological Inorganic Chemistry, 2018, 23, (8), 1219-1226, (hereinafter “P, JBIC 2018”), further discloses SEN177 and its binding mode within the hQC cavity. SEN177 is disclosed therein as having a K_i on isolated hQC of 20 nM.

- 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):

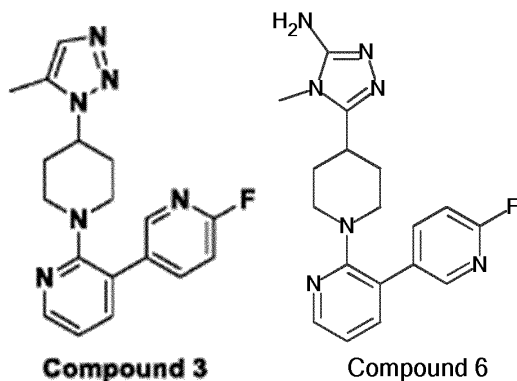


WO 2018/178384 does not disclose any biological data for examples 1094 or 1095.

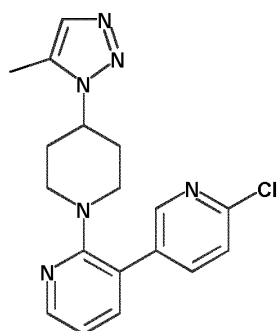
WO 2022/086920 discloses QPCTL inhibitors of the general formula



which include compounds 3 and 6:



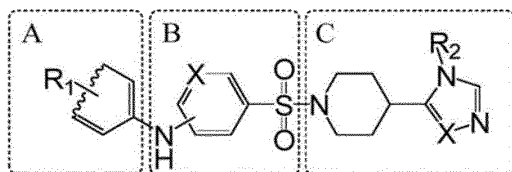
The chemical name of Compound 3 is disclosed in WO 2022/086920 as “1-(1-(6'-chloro-
5 [3,3'-bipyridin]-2-yl)piperidin-4-yl)-1H-1,2,3-triazol-4-amine” which does not correspond to the chemical structure disclosed therein, but to an alternative structure in which the fluorine atom is replaced with chlorine:



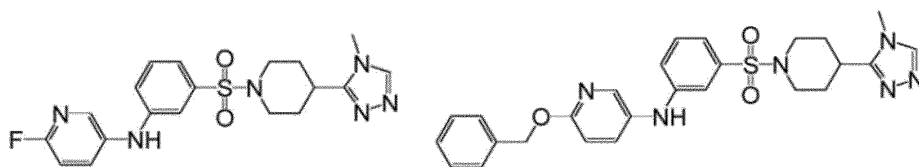
Alternative Compound 3

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):



5

Example 21

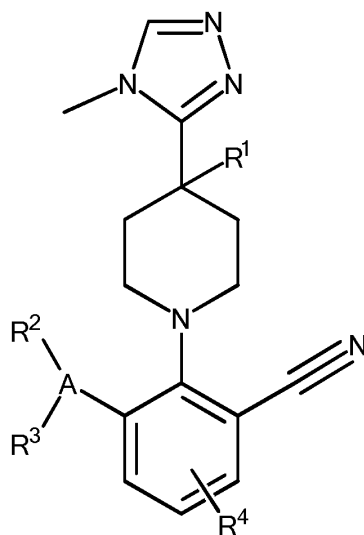
Example 23

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

10

DETAILED DESCRIPTION OF THE INVENTION

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



15

(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.

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

10

Compounds of the invention

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

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

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

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

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

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.

5 Compounds of the present invention differ structurally from compounds 3 (including alternative compound 3) and 6 in WO 2022/086920 in that a phenyl ring instead of a pyridinyl ring, is attached to the piperidinyl ring. Furthermore, a carbonitrile substituent is attached at the ortho-position to the piperidinyl ring attachment position of said phenyl ring. Furthermore, the phenyl ring - including the piperidinyl ring to which it is attached - is in total, tetra-
10 substituted. Still further, **R¹** is not limited to hydrogen, and **A** represents heterocyclic ring systems beyond pyridinyl. Still further, the 5-membered heterocyclic ring “M” in the general formula of WO 2022/086920 is in compound 3 a regioisomer of the 3-substituted 4-methyl-4H-1,2,4-triazolyl ring in compounds of the present invention, and the 5-membered heterocyclic ring “M” in the general formula of WO 2022/086920 in compound 4 is a 3-substituted
15 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
20 the ortho-position to the piperidinyl ring attachment position of said phenyl ring. Furthermore, the phenyl ring - including the piperidinyl ring to which it is attached - is in total, tetra-substituted. Still further, compounds of the present invention do not contain an amino linker between said phenyl ring and a further cyclic ring.

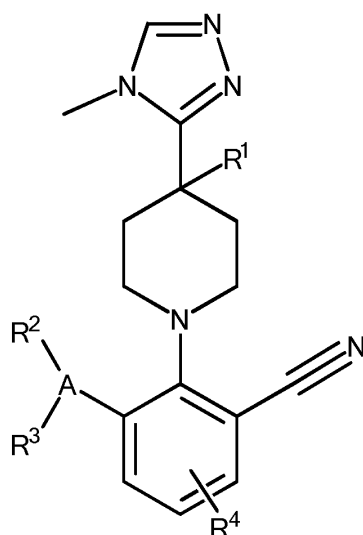
25 These structural differences between compounds of the present invention and the prior art unexpectedly lead to a favourable combination of (i) potent inhibition of QPCT and QPCTL, (ii) potent inhibition of QPCT/L in cells relevant for, but not limited to, lung diseases or cancer, and (iii) appropriate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

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

- potent inhibition of QPCT and QPCTL (Assay A)

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

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



(I)

wherein

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

15

R¹ is selected from the group **R1a**, consisting of H, C₁₋₄-alkyl and halo;

R² is selected from the group **R2a**, consisting of H, halo, hydroxy, C₁₋₆-alkyl, C₂₋₆-alkynyl, C₃₋₆-cycloalkyl, 1-methyl-C₃₋₆-cycloalkyl, F₁₋₉-fluoro-C₁₋₆-alkyl, HO-C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₄-alkyl-O-H₂CH₂C-O-, C₃₋₆-cycloalkyloxy, C₃₋₆-cycloalkyl-H₂C-O-, F₁₋₉-fluoro-C₁₋₄-alkyloxy, C₁₋₆-alkyl-O-C(O)-, H₂N-C(O)- and C₁₋₆-alkyl-NH-C(O)-;
 20

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

R⁴ is selected from the group **R4a**, consisting of halo, C₁₋₄-alkyl, C₃₋₆-cycloalkyl, -CN, C₁₋₆-alkyloxy, C₁₋₆-alkyl-O-C(O)-, F₁₋₉-fluoro-C₁₋₄-alkyl, F₁₋₉-fluoro-C₁₋₄-alkyloxy, C₃₋₆-cycloalkyloxy, C₃₋₆-cycloalkyl-H₂C-O-, benzyloxy, (HO)(H₃C)₂-C- and HO-C(H₃C)₂H₂CH₂C-O-;
or a salt thereof, particularly a pharmaceutically acceptable salt thereof.

Another embodiment of the present invention relates to a compound of formula (**I**), wherein **A** is **A2** which is a 5- or 6-membered mono-heteroaryl ring containing one or two heteroatom members selected from nitrogen; 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 **A3** which is a 6-membered mono-heteroaryl ring containing one or two heteroatom members selected from nitrogen; 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 **A4** which is a 9- or 10-membered fused bicyclic-heteroaryl ring containing two to four heteroatom members selected from nitrogen; and substituents **R¹**, **R²**, **R³** and **R⁴** are defined as in any of the preceding embodiments.

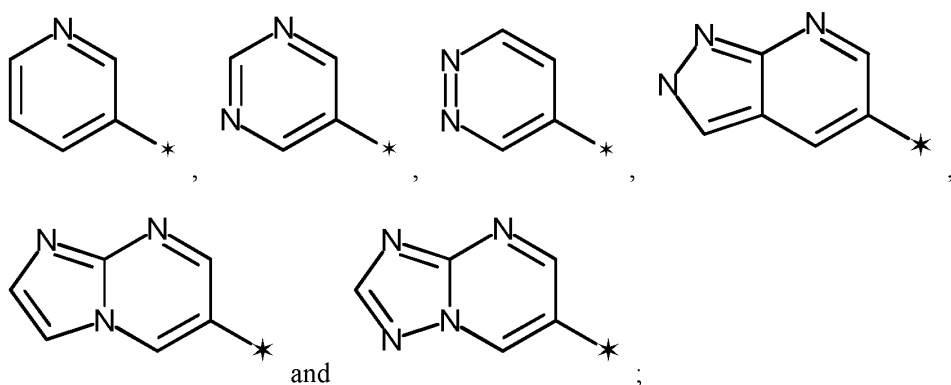
Another embodiment of the present invention relates to a compound of formula (**I**), wherein **A** is selected from the group **A5** consisting of pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, [1,2,4]triazolo[1,5-a]pyrimidinyl, 2H-pyrazolo[3,4-b]pyridinyl and imidazo[1,2-a]pyrimidinyl; and substituents **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 **A6** consisting of pyridinyl, pyridazinyl, [1,2,4]triazolo[1,5-a]pyrimidinyl, 2H-pyrazolo[3,4-b]pyridinyl and imidazo[1,2-a]pyrimidinyl;

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

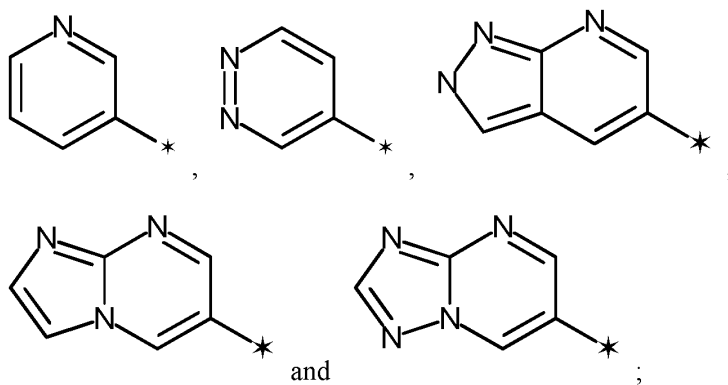
Another embodiment of the present invention relates to a compound of formula (I), wherein **A** is selected from the group **A7** consisting of

5



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

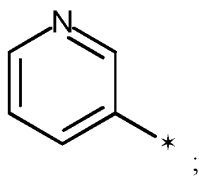
10 Another embodiment of the present invention relates to a compound of formula (I), wherein **A** is selected from the group **A8** consisting of



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

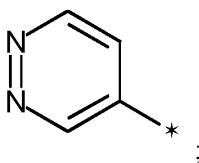
15

Another embodiment of the present invention relates to a compound of formula (I), wherein **A** is selected from the group **A9** consisting of



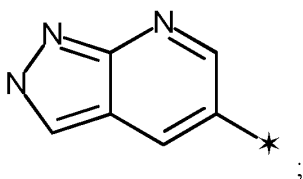
and substituents **R¹**, **R²**, **R³** and **R⁴** are defined as in any of the preceding embodiments.

Another embodiment of the present invention relates to a compound of formula (**I**),
5 wherein **A** is selected from the group **A10** consisting of



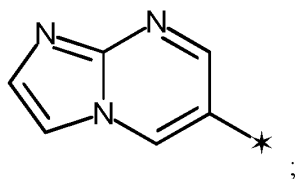
and substituents **R¹**, **R²**, **R³** and **R⁴** are defined as in any of the preceding embodiments.

Another embodiment of the present invention relates to a compound of formula (**I**),
10 wherein **A** is selected from the group **A11** consisting of



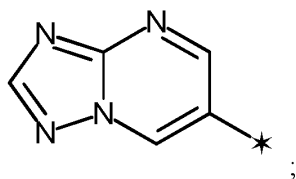
and substituents **R¹**, **R²**, **R³** and **R⁴** are defined as in any of the preceding embodiments.

Another embodiment of the present invention relates to a compound of formula (**I**),
15 wherein **A** is selected from the group **A12** consisting of



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**),
20 wherein **A** is selected from the group **A13** consisting of



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**),
 5 wherein **R¹** is selected from the group **R1b**, consisting of H, H₃C-, Cl and F;
 and substituents **A**, **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 selected from the group **R1c**, consisting of H and F;
 10 and substituents **A**, **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 selected from the group **R1d**, consisting of H;
 and substituents **A**, **R²**, **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 **R¹** is selected from the group **R1e**, consisting of F;
 and substituents **A**, **R²**, **R³** and **R⁴** are defined as in any of the preceding embodiments.

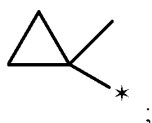
20 Another embodiment of the present invention relates to a compound of formula (**I**),
 wherein **R²** is **R2b**, consisting of H, halo, C₁₋₄-alkyl, C₃₋₄-cycloalkyl, F₁₋₉-fluoro-C₁₋₆-alkyl,
 1-methyl-C₃₋₆-cycloalkyl, C₁₋₄-alkyloxy and C₃₋₄-cycloalkyloxy;
 and substituents **A**, **R¹**, **R³** and **R⁴** are defined as in any of the preceding embodiments.

25 Another embodiment of the present invention relates to a compound of formula (**I**),
 wherein **R²** is **R2c**, consisting of H, Cl, F, methyl, i-propyl, t-butyl, cyclopropyl, trifluoro-
 methyl, 1-methyl-cyclopropyl, methyloxy and cyclopropyloxy;
 and substituents **A**, **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), wherein **R**² is **R2d**, consisting of H, Cl, F, methyl, t-butyl, cyclopropyl, trifluoromethyl, 1-methyl-cyclopropyl, methyloxy and cyclopropyloxy; and substituents **A**, **R**¹, **R**³ and **R**⁴ are defined as in any of the preceding embodiments.

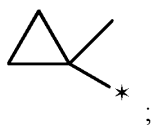
5

Another embodiment of the present invention relates to a compound of formula (I), wherein **R**² is **R2e**, consisting of H, Cl, F, i-propyl, t-butyl, trifluoromethyl, methyloxy and



10 and substituents **A**, **R**¹, **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 **R**² is **R2f**, consisting of H, Cl, F, t-butyl, trifluoromethyl, methyloxy and



15 and substituents **A**, **R**¹, **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 **R**² is **R2g**, consisting of H, F, i-propyl, t-butyl and trifluoromethyl; and substituents **A**, **R**¹, **R**³ and **R**⁴ are defined as in any of the preceding embodiments.

20

Another embodiment of the present invention relates to a compound of formula (I), wherein **R**² is **R2h**, consisting of H, F, t-butyl and trifluoromethyl; and substituents **A**, **R**¹, **R**³ and **R**⁴ are defined as in any of the preceding embodiments.

25 Another embodiment of the present invention relates to a compound of formula (I), wherein **R**² is **R2j**, consisting of i-propyl, t-butyl and trifluoromethyl; and substituents **A**, **R**¹, **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 **R**² is **R2k**, consisting of t-butyl and trifluoromethyl; and substituents **A**, **R**¹, **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), wherein **R**² is **R2m**, selected from i-propyl and t-butyl; and substituents **A**, **R**¹, **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),
10 wherein **R**² is **R2n**, selected from t-butyl; and substituents **A**, **R**¹, **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 **R**³ is selected from the group **R3b**, consisting of H, methyl, trifluoromethyl, F and
15 Cl; and substituents **A**, **R**¹, **R**² 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 **R**³ is selected from the group **R3c**, consisting of H, methyl, F and Cl;
20 and substituents **A**, **R**¹, **R**² 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 **R**³ is selected from the group **R3d**, consisting of H, methyl and Cl; and substituents **A**, **R**¹, **R**² and **R**⁴ are defined as in any of the preceding embodiments.
25

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

- 30 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, -CN, C₁₋₄-alkyl, C₃₋₆-cyclo-alkyl, C₁₋₆-alkyloxy, C₁₋₆-alkyl-O-C(O)-, F₁₋₉-fluoro-C₁₋₄-alkyl, F₁₋₉-fluoro-C₁₋₄-alkyloxy,

C₃₋₆-cycloalkyloxy, C₃₋₆-cycloalkyl-H₂C-O-, benzyloxy, (HO)(H₃C)₂-C- and HO-C(H₃C)₂H₂CH₂C-O-;

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

- 5 Another embodiment of the present invention relates to a compound of formula (**I**), wherein **R⁴** is selected from the group **R4c**, consisting of halo, -CN, C₁₋₄-alkyl, C₃₋₆-cycloalkyl, C₁₋₆-alkyloxy, C₁₋₆-alkyl-O-C(O)-, F₁₋₉-fluoro-C₁₋₄-alkyl, F₁₋₉-fluoro-C₁₋₄-alkyloxy, C₃₋₆-cycloalkyloxy, C₃₋₆-cycloalkyl-H₂C-O-, benzyloxy and HO-C(H₃C)₂H₂CH₂C-O-; and substituents **A**, **R¹**, **R²** and **R³** are defined as in any of the preceding embodiments.

10

Another embodiment of the present invention relates to a compound of formula (**I**), wherein **R⁴** is selected from the group **R4d**, consisting of fluoro, chloro, -CN, C₁₋₄-alkyl, C₃₋₆-cycloalkyl, methoxy, (H₃C)₂HC-O-, H₃CO-C(O)-, F₂HC-, H₃C-F₂C-, trifluoromethyl, F₂HC-O-, cyclopropyl-H₂C-O-, benzyloxy, (HO)(H₃C)₂-C- and HO-C(H₃C)₂H₂CH₂C-O-;

15

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

Another embodiment of the present invention relates to a compound of formula (**I**), wherein **R⁴** is selected from the group **R4e**, consisting of fluoro, chloro, -CN, C₁₋₄-alkyl, C₃₋₆-cycloalkyl, methoxy, (H₃C)₂HC-O-, H₃CO-C(O)-, F₂HC-, H₃C-F₂C-, trifluoromethyl, F₂HC-O-, cyclopropyl-H₂C-O-, benzyloxy, and HO-C(H₃C)₂H₂CH₂C-O-;

20

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

Another embodiment of the present invention relates to a compound of formula (**I**), wherein **R⁴** is selected from the group **R4f**, consisting of fluoro, chloro, -CN, methyl, cyclopropyl, methoxy, (H₃C)₂HC-O-, H₃CO-C(O)-, F₂HC-, H₃C-F₂C-, trifluoromethyl, F₂HC-O-, cyclopropyl-H₂C-O-, benzyloxy, (H₃C)₂HC-O- and HO-C(H₃C)₂H₂CH₂C-O-;

25

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

Another embodiment of the present invention relates to a compound of formula (**I**), wherein **R⁴** is selected from the group **R4g**, consisting of fluoro, chloro, -CN, methyl, cyclopropyl, methoxy, (H₃C)₂HC-O-, H₃CO-C(O)-, F₂HC-, H₃C-F₂C-, trifluoromethyl, F₂HC-O-, cyclopropyl-H₂C-O-, benzyloxy and HO-C(H₃C)₂H₂CH₂C-O-;

30

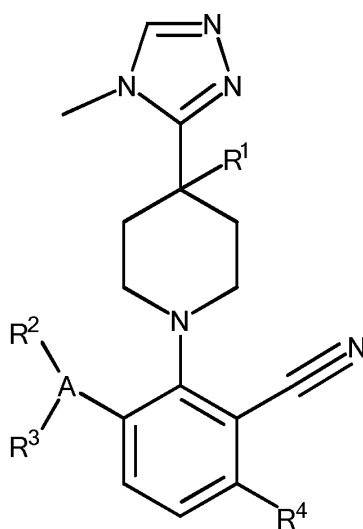
and substituents **A**, **R¹**, **R²** and **R³** are defined as in any of the preceding embodiments.

Another embodiment of the present invention relates to a compound of formula (I), wherein R^4 is selected from the group **R4h**, consisting of fluoro, chloro, -CN, methyl, cyclopropyl, methoxy, F_2HC- , H_3C-F_2C- , trifluoromethyl and F_2HC-O- ;
 5 and substituents **A**, R^1 , R^2 and R^3 are defined as in any of the preceding embodiments.

Another embodiment of the present invention relates to a compound of formula (I), wherein R^4 is selected from the group **R4j**, consisting of fluoro, chloro, methyl, cyclopropyl, methoxy and trifluoromethyl;
 10 and substituents **A**, R^1 , R^2 and R^3 are defined as in any of the preceding embodiments.

Another embodiment of the present invention relates to a compound of formula (I), wherein R^4 is selected from the group **R4k**, consisting of fluoro, chloro, methoxy and trifluoromethyl;
 15 and substituents **A**, R^1 , R^2 and R^3 are defined as in any of the preceding embodiments.

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

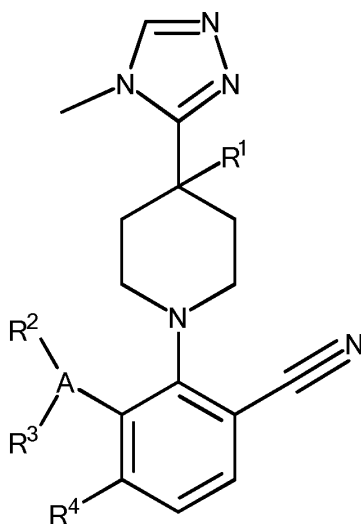


(I-a)

20

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

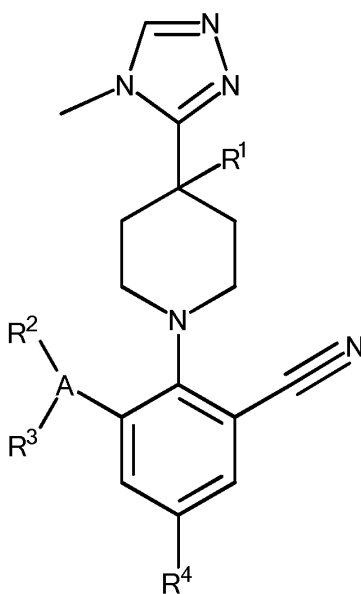
Another embodiment of the present invention relates to a compound of formula (I) above, having formula (I-b)



(I-b)

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

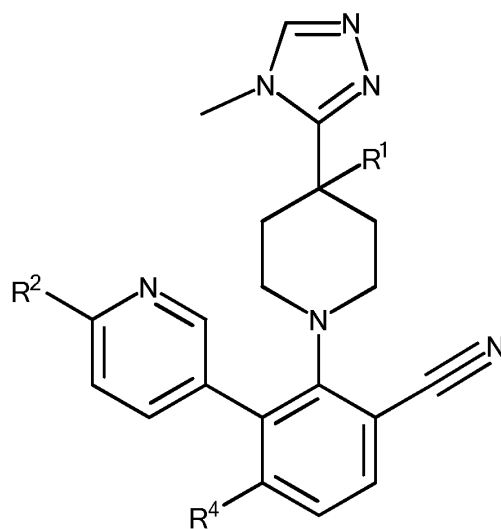
Another embodiment of the present invention relates to a compound of formula (I) above, having formula (I-c)



(I-c)

wherein substituents R^1 , R^2 , 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-d)

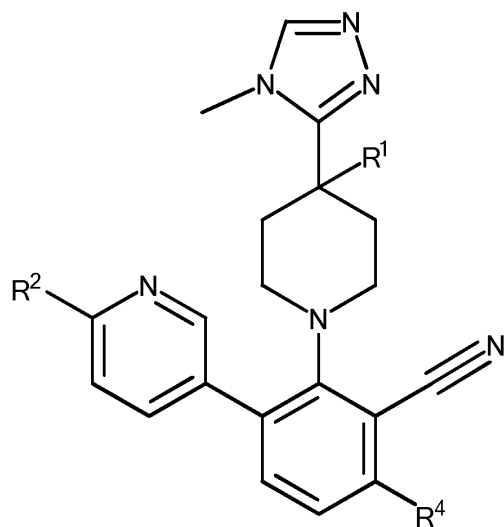


(I-d)

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

10

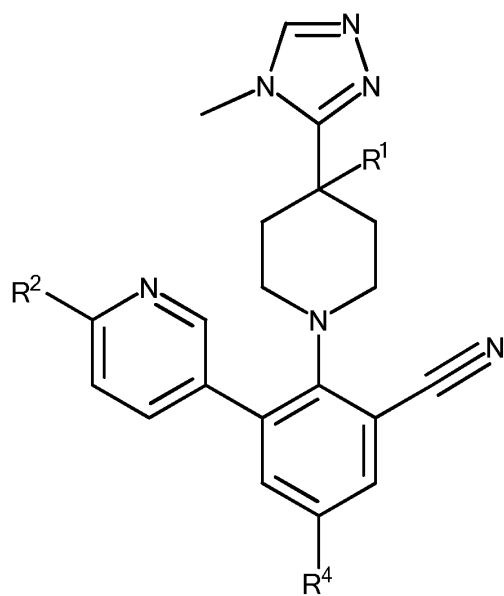
Another embodiment of the present invention relates to a compound of formula (I) above, having formula (I-e)



(I-e)

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

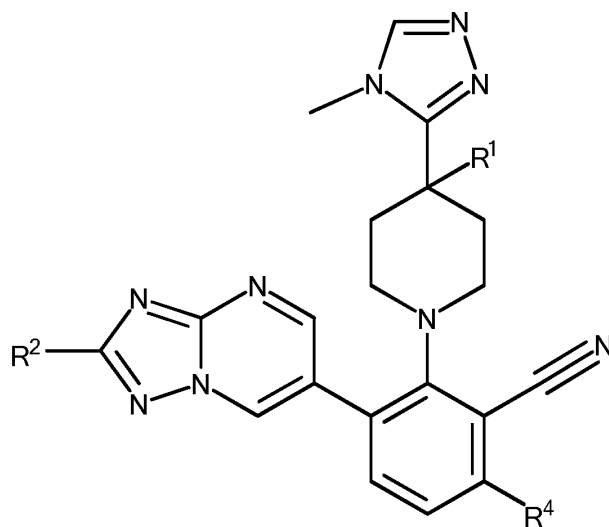
- 5 Another embodiment of the present invention relates to a compound of formula (I) above, having formula (I-f)



(I-f)

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

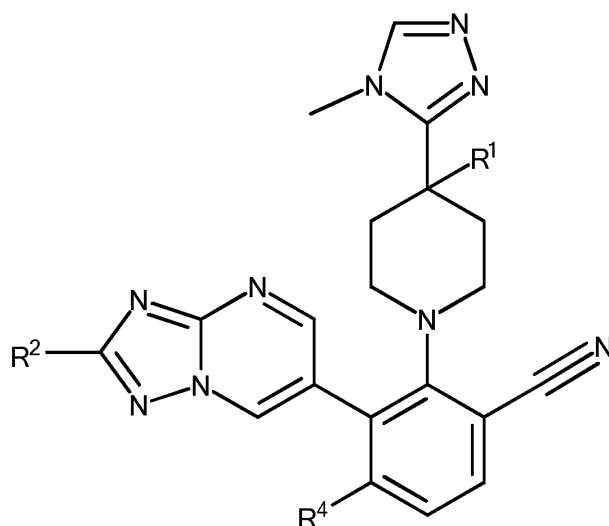
Another embodiment of the present invention relates to a compound of formula (I) above, having formula (I-g)



(I-g)

5 wherein 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) above, having formula (I-h)

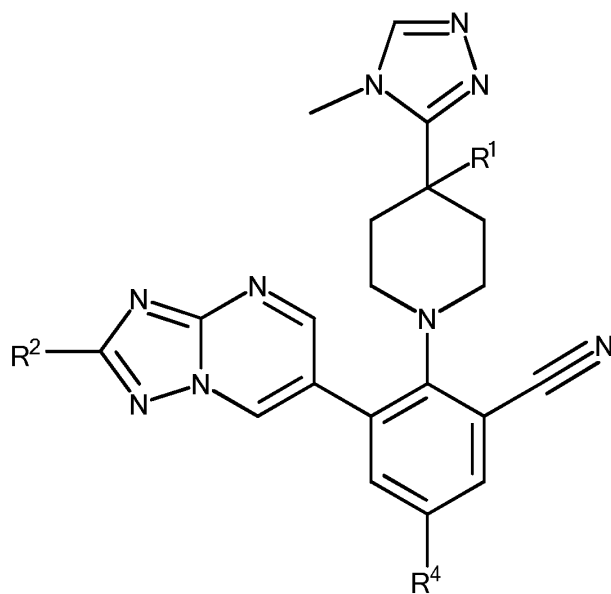


(I-h)

10

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

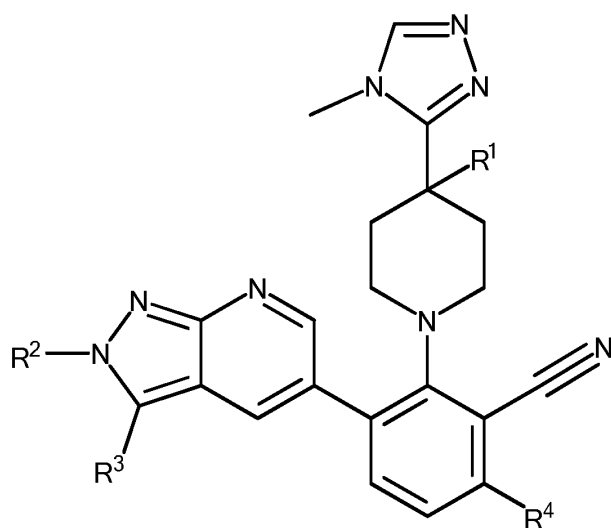
Another embodiment of the present invention relates to a compound of formula (I) above, having formula (I-j)



(I-j)

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

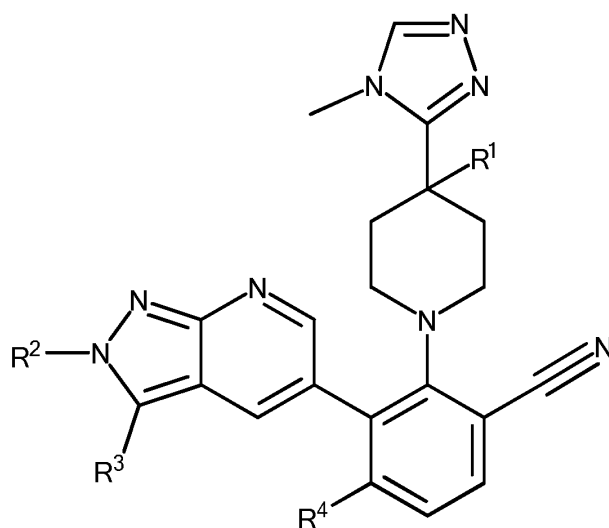
Another embodiment of the present invention relates to a compound of formula (I) above, having formula (I-k)



(I-k)

wherein 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) above,
5 having formula (I-m)

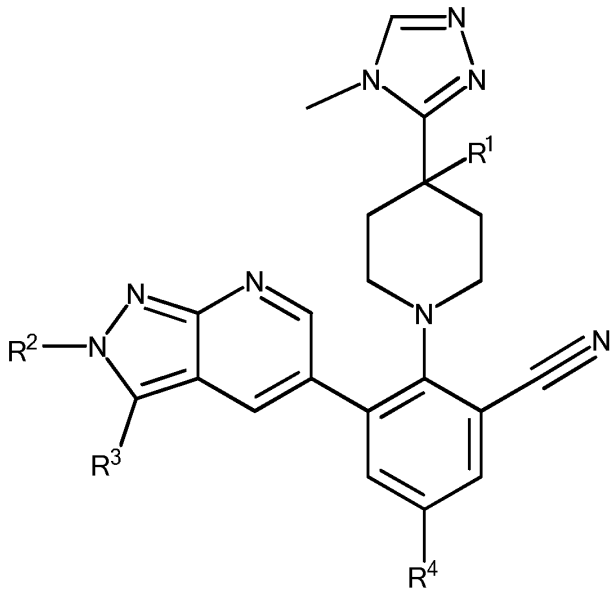


(I-m)

wherein substituents **R¹**, **R²**, **R³** and **R⁴** 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-n)



(I-n)

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

5

Further preferred embodiments of the compounds of formula (I) are encompassed as embodiments (EMB-1) to (EMB-10) in the following Table 1, wherein the substituent definitions above are employed.

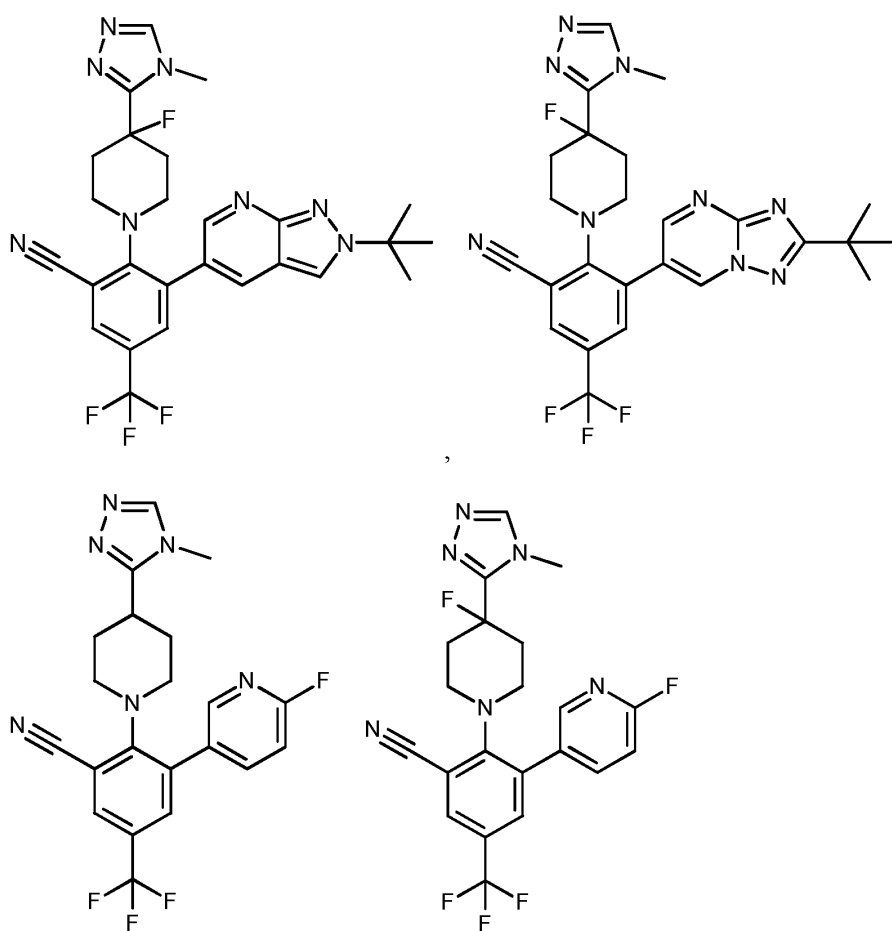
10 Table 1: further preferred embodiments

Embodiment	Substituent					
	formula	A	R ¹	R ²	R ³	R ⁴
EMB-1	I-c	A2	F	R2c	R3c	R4e
EMB-2	I-c	A2	H	R2c	R3c	R4e
EMB-3	I-c	A4	H	R2c	R3c	R4e
EMB-4	I-c	A4	H	R2c	R3c	R4e
EMB-5	I-f	-	F	F	-	R4e
EMB-6	I-f	-	H	F	-	R4e
EMB-7	I-j	-	F	R2h	-	R4e
EMB-8	I-j	-	H	R2h	-	R4e
EMB-9	I-n	-	F	R2g	R3c	R4e

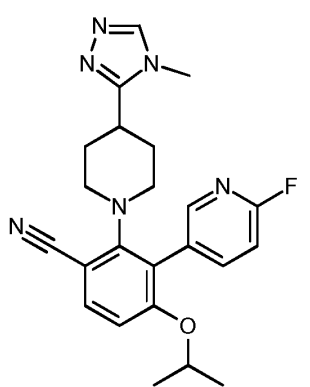
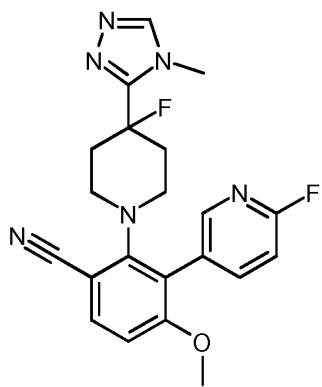
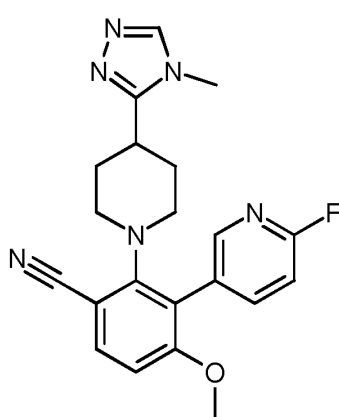
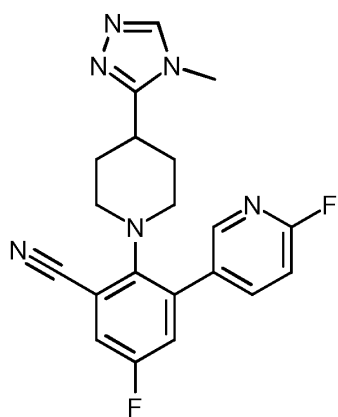
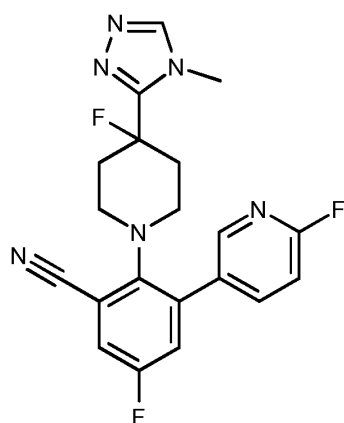
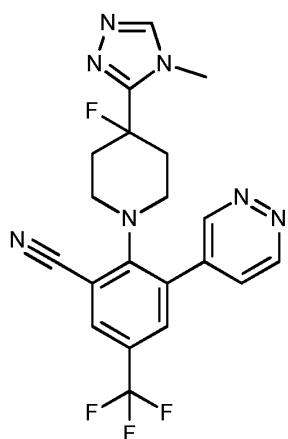
EMB-10	I-n	-	H	R2g	R3c	R4e
---------------	-----	---	---	-----	-----	-----

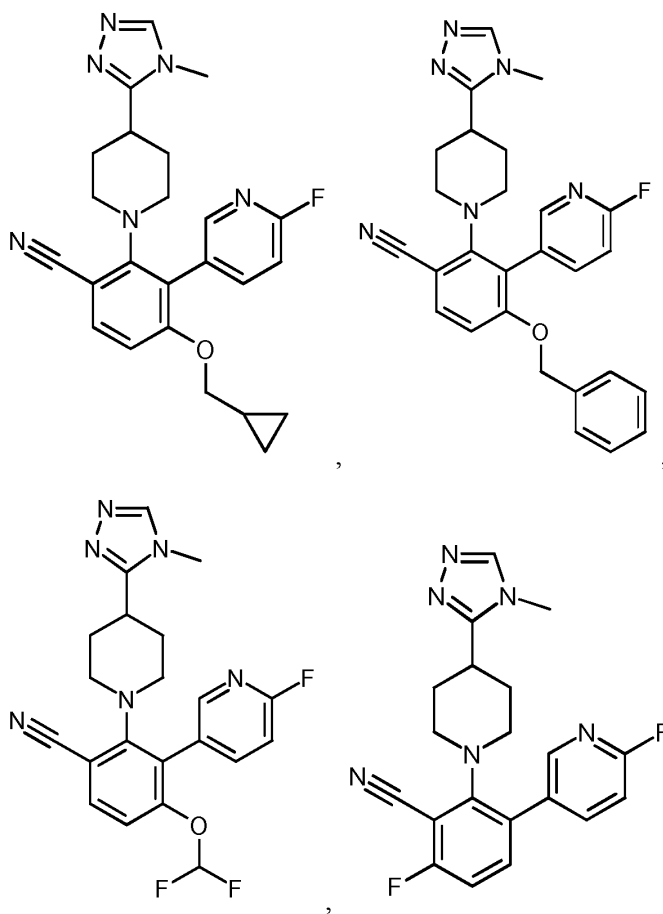
For example, compounds of the embodiment **EMB-1** have for **R²** the genus group **R2c** as defined above, in combination with the other genus groups for the other substituents in formula (**I**) as defined within the same row of the table. The same applies analogously to the
 5 other variables incorporated in the general formulae.

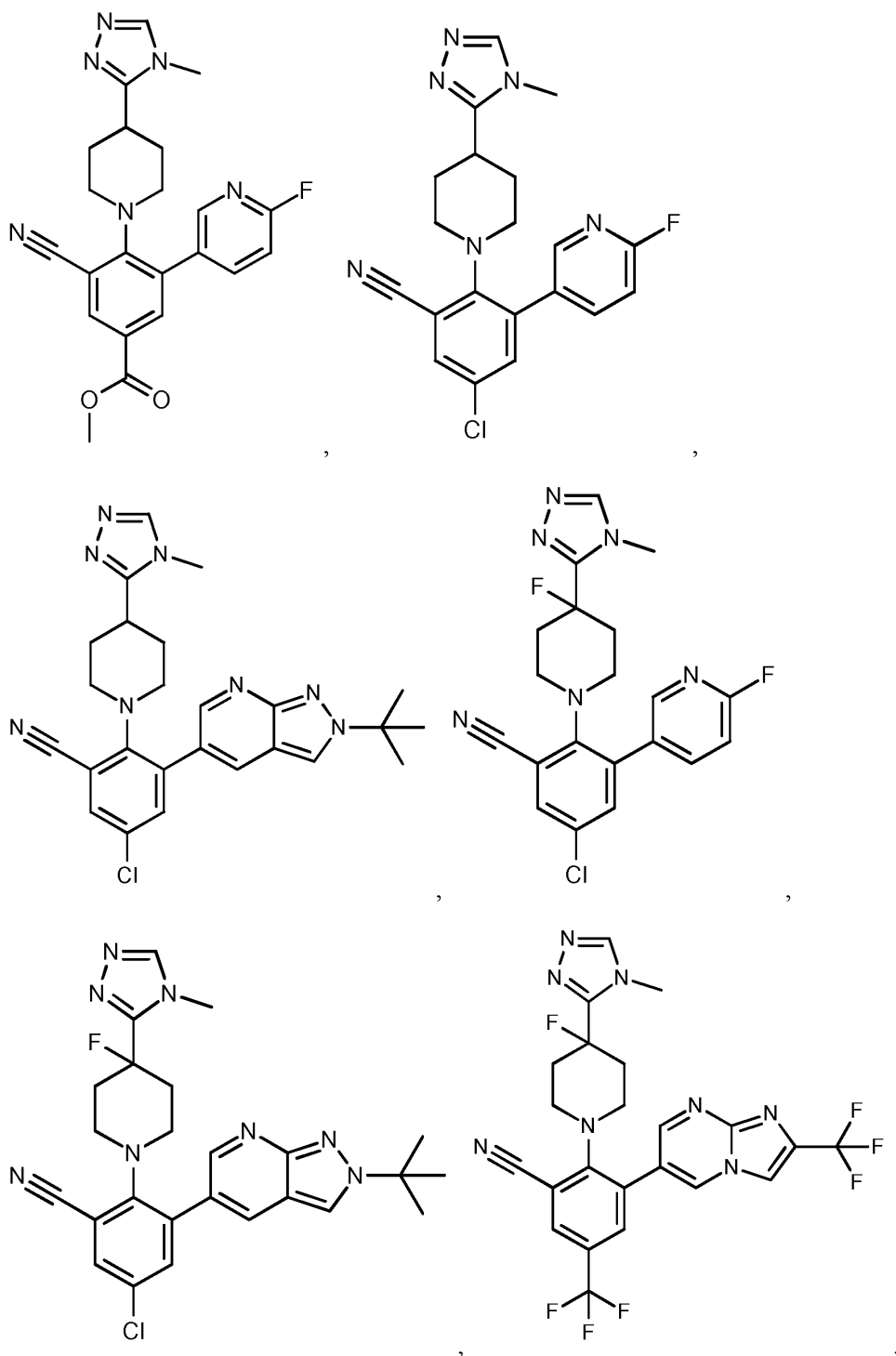
Particularly preferred is the compound according to formula (**I**) selected from the group consisting of

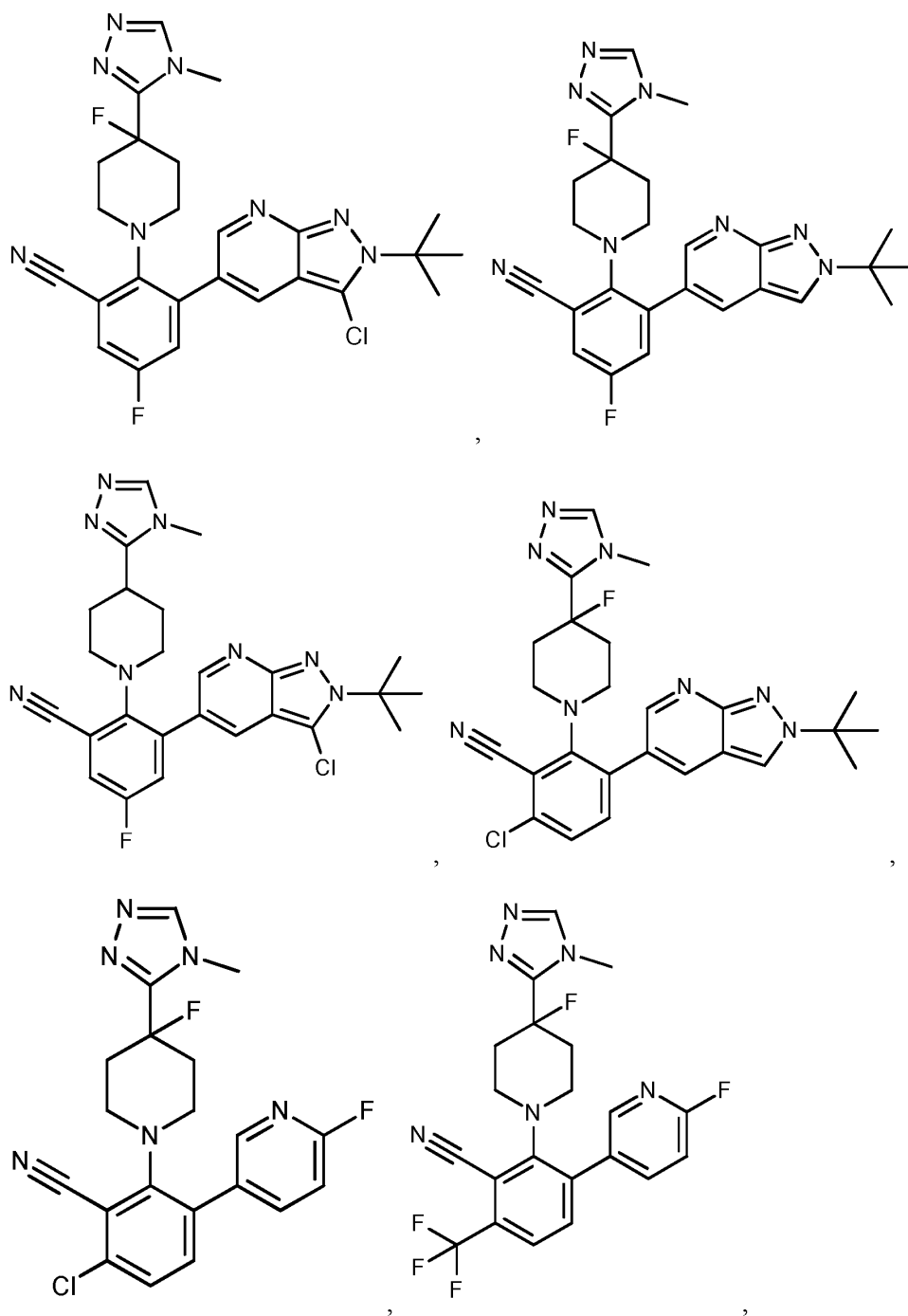


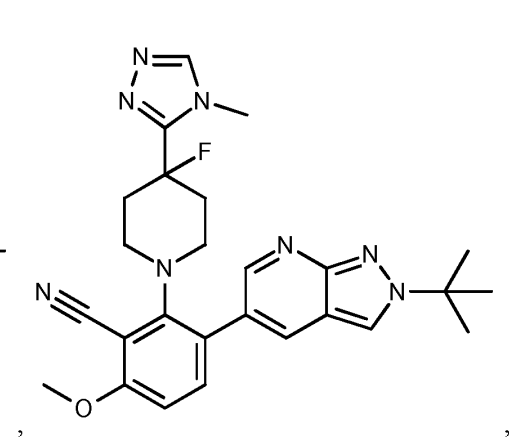
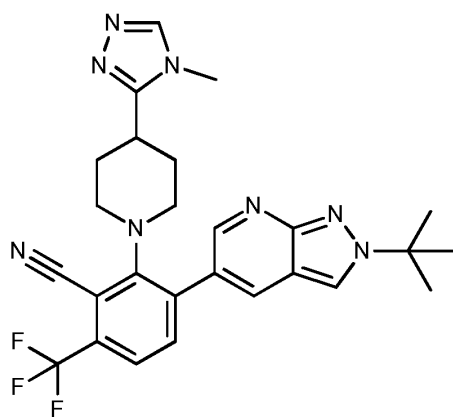
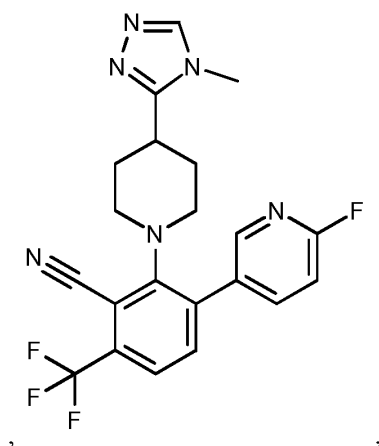
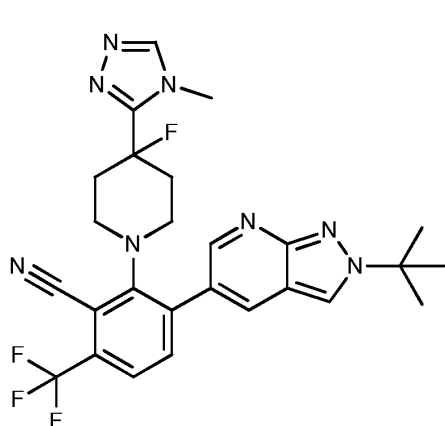
10













Particularly preferred is the compound according to formula (I) selected from the group consisting of example 1, example 2, example 3, example 4, example 5, example 6, example 7, example 8, example 9, example 16, example 18, example 19, example 22, example 24, example 25, example 29, example 31 and example 36 as described hereinafter in EXAMPLES.

Particularly preferred is the compound according to formula (I) selected from the group consisting of example 1, example 2, example 4, example 7, example 16, example 18, example 19, example 25, example 31 and example 36 as described hereinafter in EXAMPLES.

Particularly preferred is the compound according to formula (I) selected from the group consisting of example 1, example 4, example 7, example 16 and example 18 as described hereinafter in EXAMPLES.

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

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.

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

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

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

Another aspect of the invention refers to processes of manufacture of the compounds of
5 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.

10

USED TERMS AND DEFINITIONS

General Definitions

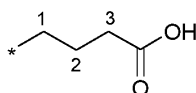
15 Terms not specifically defined herein should be given the meanings that would be given to them by one of skill in the art in light of the disclosure and the context. As used in the specification, however, unless specified to the contrary, the following terms have the meaning indicated and the following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

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

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

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

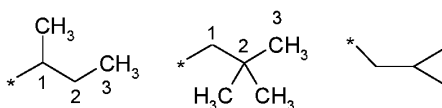
For example, the term "3-carboxypropyl-group" represents the following substituent:



5

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:

10



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

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

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

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

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

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

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 resolution of the salts and release of the desired compound from the salt; or by derivatization of the corresponding racemic compounds with optically active chiral auxiliary reagents, subsequent diastereomer separation and removal of the chiral auxiliary group; or by kinetic resolution of a racemate (e.g. by enzymatic resolution); by enantioselective crystallization from a conglomerate of enantiomorphous crystals under suitable conditions; or by (fractional) crystallization from a suitable solvent in the presence of an optically active chiral auxiliary.

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

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

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

15 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
20 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.

25

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,
30 branched or linear hydrocarbon radical with 1 to n C atoms. For example the term C₁₋₅-alkyl embraces the radicals H₃C-, H₃C-CH₂-, H₃C-CH₂-CH₂-, H₃C-CH(CH₃)-, H₃C-CH₂-CH₂-CH₂-, H₃C-CH₂-CH(CH₃)-, H₃C-CH(CH₃)-CH₂-, H₃C-C(CH₃)₂-, H₃C-CH₂-CH₂-CH₂-CH₂-, H₃C-CH₂-CH₂-CH(CH₃)-, H₃C-CH₂-CH(CH₃)-CH₂-,

$\text{H}_3\text{C}-\text{CH}(\text{CH}_3)-\text{CH}_2-\text{CH}_2-$, $\text{H}_3\text{C}-\text{CH}_2-\text{C}(\text{CH}_3)_2-$, $\text{H}_3\text{C}-\text{C}(\text{CH}_3)_2-\text{CH}_2-$,
 $\text{H}_3\text{C}-\text{CH}(\text{CH}_3)-\text{CH}(\text{CH}_3)-$ and $\text{H}_3\text{C}-\text{CH}_2-\text{CH}(\text{CH}_2\text{CH}_3)-$.

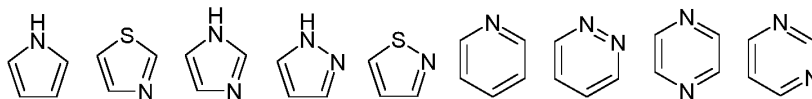
The term " C_{2-m} -alkynyl" is used for a group " C_{2-m} -alkyl" wherein m is an integer selected
 5 from 3, 4, 5 or 6, preferably 4, 5 or 6, if at least two carbon atoms of said group are bonded
 to each other by a triple bond.

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

The term "halo" added to an "alkyl", "alkylene" or "cycloalkyl" group (saturated or unsatu-
 rated) defines an alkyl, alkylene or cycloalkyl group wherein one or more hydrogen atoms
 15 are replaced by a halogen atom selected from among fluorine, chlorine or bromine, prefer-
 ably fluorine and chlorine, particularly preferred is fluorine. Examples include: $\text{H}_2\text{FC}-$,
 $\text{HF}_2\text{C}-$, $\text{F}_3\text{C}-$.

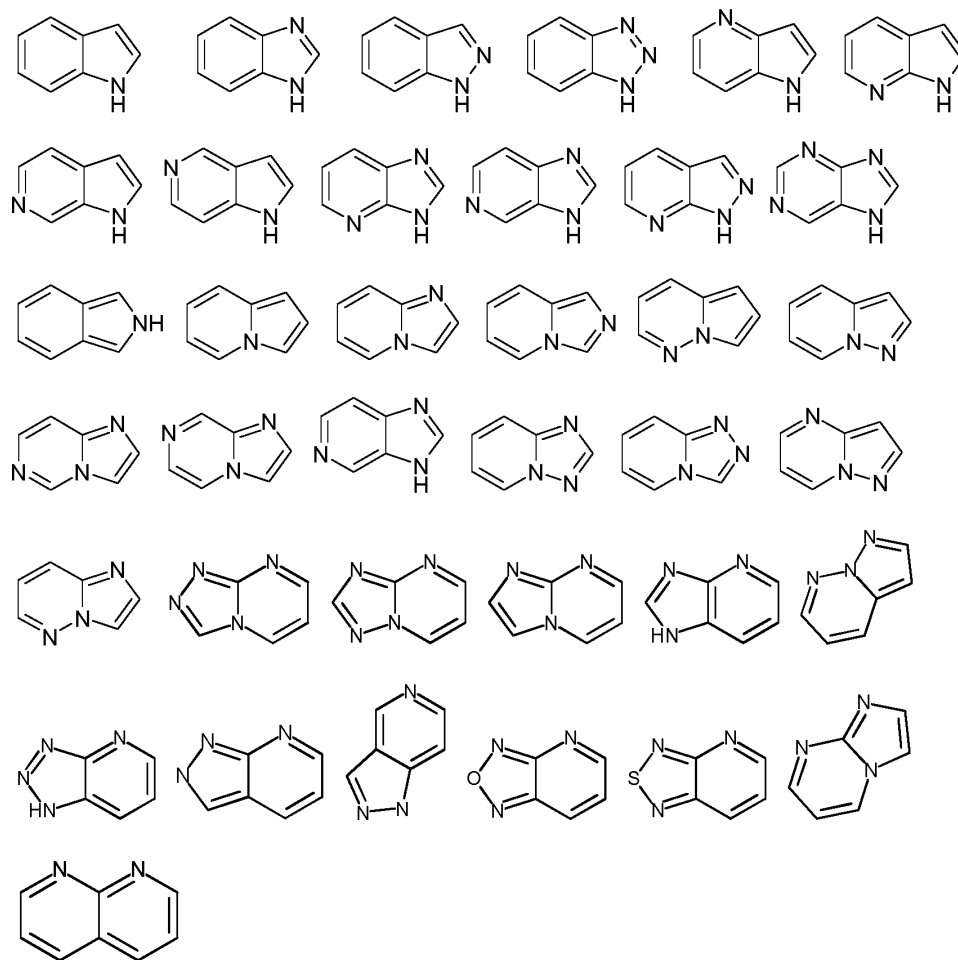
The term "mono-heteroaryl ring" means a monocyclic aromatic ring system, containing
 20 one or more heteroatoms selected from N, O or S, consisting of 5 to 6 ring atoms.

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 de-
 picted as radicals as each form is optionally attached through a covalent bond to any atom
 25 so long as appropriate valences are maintained):

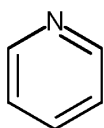


The term "fused bicyclic-heteroaryl ring" means a bicyclic aromatic ring system, contain-
 ing one or more heteroatoms selected from N, O or S, consisting of 9 to 10 ring atoms. The
 30 term "fused bicyclic-heteroaryl ring" is intended to include all the possible isomeric forms.
 Thus, the term "bicyclic-heteroaryl ring" includes the following exemplary structures (not

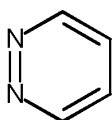
depicted as radicals as each form is optionally attached through a covalent bond to any atom so long as appropriate valences are maintained):



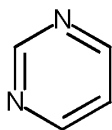
- 10 The term pyridyl refers to the radical of the following ring:



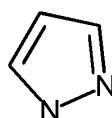
The term pyridazinyl refers to the radical of the following ring:



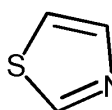
The term pyrimidyl refers to the radical of the following ring:



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

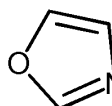


The term thiazolyl refers to the radical of the following ring:

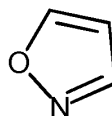


5

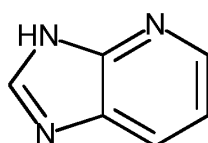
The term oxazolyl refers to the radical of the following ring:



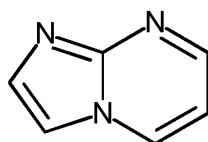
The term isoxazolyl refers to the radical of the following ring:



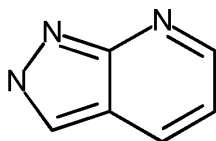
10 The term 3H-imidazo[4,5-b]pyridyl refers to the radical of the following ring:



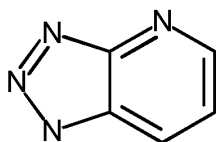
The term imidazo[1,2-a]pyrimidinyl refers to the radical of the following ring:



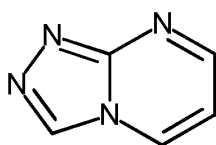
The term 2H-pyrazolo[3,4-b]pyridyl refers to the radical of the following ring:



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

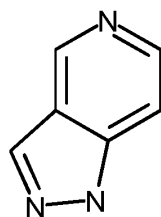


The term [1,2,4]triazolo[4,3-a]pyrimidinyl refers to the radical of the following ring:

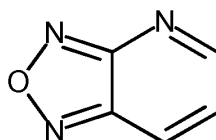


5

The term 1H-pyrazolo[4,3-c]pyridyl refers to the radical of the following ring:

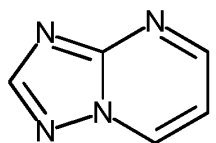


The term [1,2,5]oxadiazolo[3,4-b]pyridyl refers to the radical of the following ring:

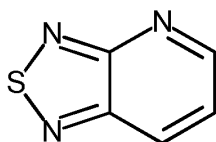


10

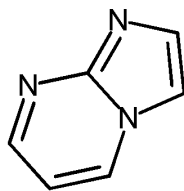
The term [1,2,4]triazolo[1,5-a]pyrimidinyl refers to the radical of the following ring:



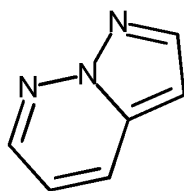
The term [1,2,5]thiadiazolo[3,4-b]pyridyl refers to the radical of the following ring:



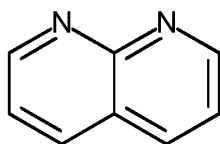
The term imidazo[1,2-a]pyrimidinyl refers to the radical of the following ring:



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



The term 1,8-naphthyridinyl refers to the radical of the following ring:



5

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.

10

BIOLOGICAL ASSAYS

Evaluation of inhibitory activity on QPCT and QPCTL

15 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 %
 20 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 µL of CD47 peptide substrate surrogate (¹⁹QLLFNKTKSVEFTFC³³) was added to each well (final concentration: 10 µM for QPCTL / 20 µM for QPCT). The plates were mixed for 30 sec at 1,000 rpm and subsequently incubated for 40 min in a humidified incubator at 24°C. After incubation, the enzymatic reaction was stopped by adding 1 µL containing stable isotope labeled internal standard peptide ¹⁹[Pyr]LLFN(K)TKSVEFTFC³³ (final concentration 4.0 µM) as well as SEN177 (final concentration 10 µM). The plates were sealed with an adhesive foil, mixed for 30 s at 1,000 rpm and stored at room temperature until preparation of the MALDI target plates. MALDI target plates were prepared as described previously. 1 Mass spectra were acquired with a rapifleX MALDI-TOF/TOF instrument tracking the signals of the product (¹⁹[Pyr]LLFNKTKSVEFTFC³³, m/z 1,787.9037) as well as internal standard (¹⁹[Pyr]LLFN(K)TKSVEFTFC³³, m/z 1,795.9179) peptide. QPCT or QPCTL activity was monitored by calculating the ratio between product and internal standard signals followed by normalization to high (100% activity) and low (0% activity) controls. Determination of compound potencies was obtained by fitting the dose-response data to a four-parameter logistical equation.

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

Example	Inhibition of QPCTL: IC ₅₀ [nM]	Inhibition of QPCT: IC ₅₀ [nM]
1	1	1
2	2	1
3	3	12
4	2	4
5	2	3
6	3	4
7	2	10
8	1	3
9	1	1
10	1	1
11	1	2
12	1	1

13	2	2
14	2	11
15	3	12
16	2	8
17	1	1
18	2	4
19	1	1
20	1	4
21	5	25
22	1	1
23	21	14
24	2	1
25	2	1
26	1	1
27	1	1
28	2	2
29	1	2
30	1	1
31	1	4
32	2	2
33	1	1
34	1	0
35	1	2
36	1	1

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	5	11
2	14	7
3	19	12
4	17	12
5	19	21
6	47	16
7	48	18
8	44	11
9	35	6
10	52	9
11	44	43
12	20	14
13	96	27
14	124	24
15	312	218
16	30	18
17	17	5
18	36	24
19	9	9
20	102	24
21	324	280
22	17	39
23	278	145
24	16	13
25	23	10
26	16	8
27	19	7

28	93	12
29	78	19
30	19	8
31	77	19
32	70	36
33	20	11
34	36	73
35	16	6
36	8	9

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 permeability5 **Assay C: Permeability in CACO-2 cells**

Caco-2 cells ($1 - 2 \times 10^5$ cells/1 cm² area) are seeded on filter inserts (Costar transwell polycarbonate or PET filters, 0.4 μ m pore size) and cultured (DMEM) for 10 to 25 days.

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 μ M compound, final DMSO $\leq$ 0.5 %). The transport solution (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.

Efflux ratio (ER) = permeability B-A / permeability A-B

10

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	25.0	3.2
2	8.9	6.9
3	9.0	10.4
4	40.5	1.3
5	3.3	10.3
6	44.0	1.6
7	24.0	2.1
8	8.5	4.4
9	28.0	1.9
10	30.0	2.4
11	28.0	3.2
12	19.0	2.6
13	9.1	3.6
14	9.6	6.7
15	5.3	9.2
16	23.0	3.3
17	2.5	21.2
18	66.0	1.0
19	18.0	4.5

20	5.6	12.5
21	1.1	39.1
22	2.1	10.5
23	13.0	4.3
24	46.0	1.7
25	7.5	9.7
26	14.0	3.9
27	2.2	19.1
28	34.0	1.7
29	53.0	1.4
30	1.7	22.9
31	22.0	3.5
32	0.2	145.8
33	0.8	51.9
34	-	-
35	4.8	17.1
36	5.7	6.7

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

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

Evaluation of Microsomal Clearance

Microsomal clearance:

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

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

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

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

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

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

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

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

Evaluation of Hepatocyte Clearance

Hepatocyte clearance

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

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

5 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.

10 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}).

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

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

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

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

Results are expressed as percentage of hepatic blood flow:

25 $QH\ [\%] = CL\ [mL/min/kg] / hepatic\ blood\ flow\ [mL/min/kg]$

Evaluation of plasma protein binding

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

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

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

Percent bound is calculated using the formula:

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

Evaluation of solubility

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

Evaluation of Metabolism in human hepatocytes *in vitro*

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

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

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

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

15

Evaluation of pharmacokinetic characteristics

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

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

METHOD OF TREATMENT

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

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

(1) Pulmonary fibrotic diseases such as pneumonitis or interstitial pneumonitis associated

with collagenosis, e.g. lupus erythematoses, systemic scleroderma, rheumatoid arthritis, polymyositis and dermatomyositis, idiopathic interstitial pneumonias, such as pulmonary lung fibrosis (IPF), non-specific interstitial pneumonia, respiratory bronchiolitis associated interstitial lung disease, desquamative interstitial pneumonia, cryptogenic organizing

5 pneumonia, acute interstitial pneumonia and lymphocytic interstitial pneumonia, lymphangioma, pulmonary alveolar proteinosis, Langerhan's cell histiocytosis, pleural parenchymal fibroelastosis, interstitial lung diseases of known cause, such as interstitial pneumonitis as a result of occupational exposures such as asbestosis, silicosis, miners lung (coal dust), farmers lung (hay and mould), Pidgeon fanciers lung (birds) or other occupa-

10 tional 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 inter-

15 stitial pneumonitis caused by heart failure, X-rays, radiation, chemotherapy, M. boeck or sarcoidosis, granulomatosis, cystic fibrosis or mucoviscidosis, or alpha-1-antitrypsin deficiency.

(2) Other fibrotic diseases such as hepatic bridging fibrosis, liver cirrhosis, non-alcoholic steatohepatitis (NASH), atrial fibrosis, endomyocardial fibrosis, old myocardial infarction,

20 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, cryobi-

25 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,

30 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) 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.

5

Furthermore, the present invention relates to the use of a compound of general formula (I) or a pharmaceutically acceptable salt thereof or a pharmaceutical composition thereof for the treatment and/or prevention of cancer, fibrotic diseases, neurodegenerative diseases, atherosclerosis, infectious diseases, chronic kidney diseases.

10

Furthermore, the present invention relates to the use of a compound of general formula (I) or a pharmaceutically acceptable salt thereof or a pharmaceutical composition thereof for the treatment and/or prevention of: (1) Pulmonary fibrotic diseases such as pneumonitis or interstitial pneumonitis associated with collagenosis, e.g. lupus erythematoses, systemic
15 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, Langer-
20 han's cell histiocytosis, pleural parenchymal fibroelastosis, interstitial lung diseases of known cause, such as interstitial pneumonitis as a result of occupational exposures such as asbestosis, silicosis, miners lung (coal dust), farmers lung (hay and mould), Pidgeon fanciers lung (birds) or other occupational airborne triggers such as metal dust or mycobacteria, or as a result of treatment such as radiation, methotrexate, amiodarone, nitrofurantoin
25 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,
30 or alpha-1-antitrypsin deficiency.

(2) Other fibrotic diseases such as hepatic bridging fibrosis, liver cirrhosis, non-alcoholic steatohepatitis (NASH), atrial fibrosis, endomyocardial fibrosis, old myocardial infarction, glial scar, arterial stiffness, arthrofibrosis, Dupuytren's contracture, keloid, scleroderma/

- 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, 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) 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

The compounds of the invention may further be combined with one or more, preferably one additional therapeutic agent. According to one embodiment the additional therapeutic agent is selected from the group of therapeutic agents useful in the treatment of diseases or conditions described hereinbefore, in particular associated with cancer, fibrotic diseases,

Alzheimer's diseases, atherosclerosis, infectious diseases, chronic kidney diseases and auto-immune disease.

Additional therapeutic agents that are suitable for such combinations include in particular those, which, for example, potentiate the therapeutic effect of one or more active sub-
5 stances with respect to one of the indications mentioned and/or allow the dosage of one or 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-
10 inflammatory agents, anti-atopic dermatitis, and broncho dilators.

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, antimitotic
15 agents, taxanes and further state-of-the-art or standard-of-care compounds.

Targeted therapy is a type of cancer treatment that uses drugs to target specific genes and 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),
20 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, 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
25 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
30 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.

- 5 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; 20 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 25 such as BMS986278.

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

- 30 Therefore, in another aspect, this invention relates to the use of a compound according to the invention in combination with one or more additional therapeutic agents described hereinbefore and hereinafter for the treatment of diseases or conditions which may be

affected or which are mediated by QPCT/L, in particular diseases or conditions as described hereinbefore and hereinafter.

- In a further aspect this invention relates to a method for treating a disease or condition which can be influenced by the inhibition of QPCT/L in a patient that includes the step of administering to the patient in need of such treatment a therapeutically effective amount of 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 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 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.

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.

- 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.

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.

5

PREPARATION

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

15

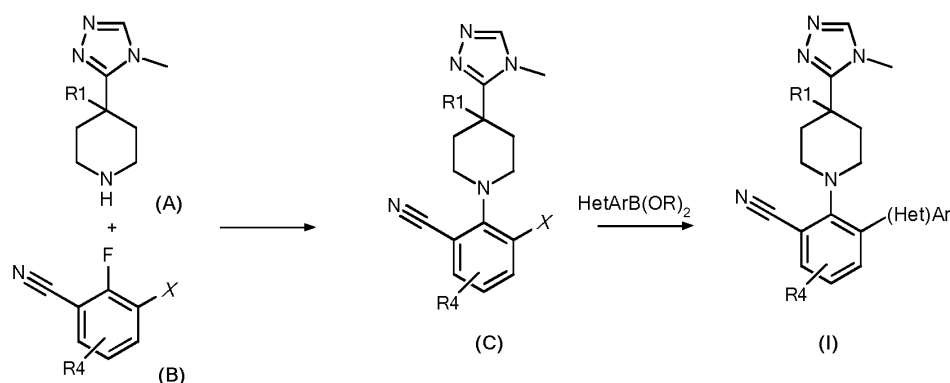
The general processes for preparing the compounds according to the invention will become apparent to the one skilled in the art studying the following schemes. Any functional groups in the starting materials or intermediates may be protected using conventional protecting groups. These protecting groups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

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

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

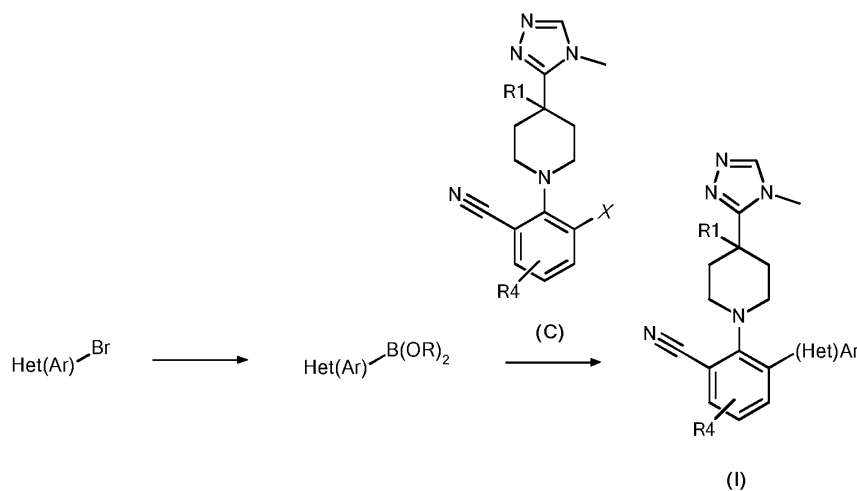
Compounds of formula (I) may be prepared as shown in Scheme I below.

30 **Scheme I:**



In scheme I, N-methyl triazolyl piperidine (R1=H, F) (A) undergoes a nucleophilic aromatic substitution with aryl fluoride (B with X=Cl, Br). The reaction is typically run at elevated temperature (100 – 130 °C). 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 (e.g. an aqueous K₂CO₃ solution) at elevated temperature (e.g. 100 °C) to afford compounds of general formula (I).

Scheme II:

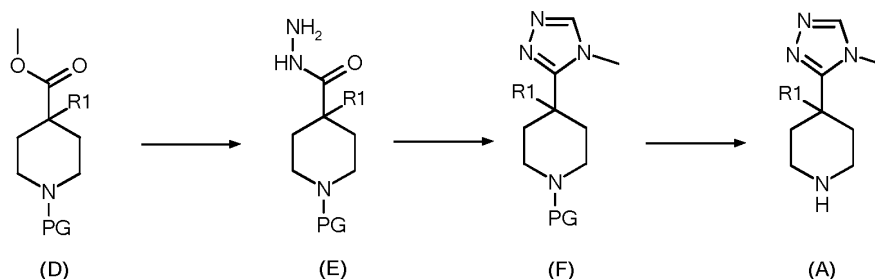


Alternatively as described in scheme II, the hetero-aryl boronic acid derivative can be prepared from the corresponding bromide (Het(Ar)-Br) with a suitable borylating agent (e.g. bis(pinacolato)diboron) in the presence of a suitable catalyst (e.g. Pd(dppf)Cl₂*CH₂Cl₂) and a suitable base (e.g. KOAc) at elevated temperatures (e.g. 100 °C). The hetero-aryl boronic acid derivative (Het(Ar)-B(OR)₂) is either isolated as pinacolate boronic acid ester (R = CMe₂ and both R forming a five membered ring together with O, B, O) or boronic acid (R=H) depending on the stability of the boronic acid ester or it can be used in the subsequent

Suzuki coupling upon addition of (C with X=Cl, Br), a suitable catalyst (e.g. Pd(dppf)Cl₂*CH₂Cl₂) and a suitable base (e.g. aqueous Na₂CO₃ solution). If isolated, the boronic acid derivative can be transformed into examples of general formula I as describe in scheme I.

5 **Scheme III:**

for R1 = F



Compounds of formula (A) with R1=F can be prepared from the corresponding piperidiny esters (D) equipped with a suitable protecting group (PG, e.g. BOC) by treatment with a suitable hydrazine source (e.g. N₂H₄*H₂O) at elevated temperature (e.g. 50 °C). The obtained hydrazide (E) is then activated with DMF/DMA at elevated temperature (e.g. 50 °C) and subsequently treated with methyl amine at elevated temperature (e.g. 90 °C) to yield the triazole derivative (F). Compounds of formula (A) with R1=F can be obtained by cleaving the protecting group under suitable conditions (e.g. 4N HCl in dioxane for PG=BOC). Compound of formula (A) with R1=H is obtained from commercial sources (R1=H: CAS No: 297172-18-0).

EXAMPLES

Preparation

20 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. 25 In some cases the sequence adopted in carrying out the reaction schemes may be varied.

Variants of these reactions that are known to the skilled artisan but are not described in detail herein may also be used. The general processes for preparing the compounds according to the invention will become apparent to the skilled man on studying the schemes that follow. Starting compounds are commercially available or may be prepared by methods that are described in the literature or herein, or may be prepared in an analogous or similar manner. Before the reaction is carried out, any corresponding functional groups in the starting compounds may be protected using conventional protecting groups. These protecting groups may be cleaved again at a suitable stage within the reaction sequence using methods familiar to the skilled man and described in the literature for example in "Protecting Groups", 3rd Edition, Philip J. Kocienski, Thieme, 2005, and "Protective Groups in Organic Synthesis", 4th Edition, Peter G. M. Wuts, Theodora W. Greene, John Wiley & Sons, 2006. The terms "ambient temperature" and "room temperature" are used interchangeably and designate a temperature of about 20 °C, e.g. between 19 and 24 °C.

Abbreviations:

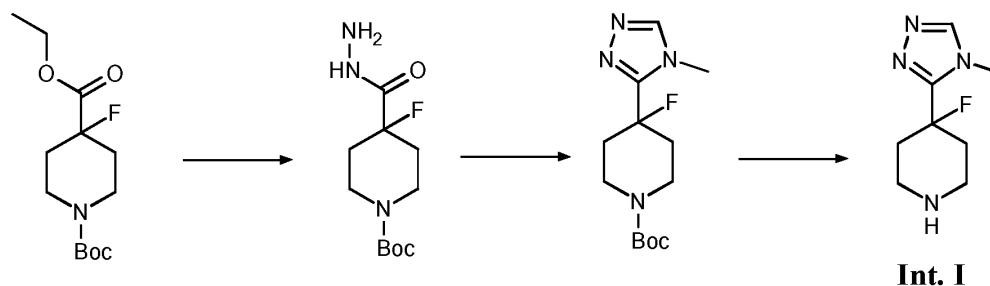
ACN	acetonitrile
Aq.	Aqueous
°C	Degree celsius
CDI	Carbonyl diimidazole
CyH/CH	cyclohexane
conc.	Concentrated
DCM	dichloro methane
DIPEA	<i>N,N</i> -diisopropylethylamine
DMA	<i>N,N</i> -dimethylacetamide
DMF	<i>N,N</i> -dimethylformamide
DMSO	dimethyl sulfoxide
ESI-MS	Electrospray ionisation mass spectrometry
EtOAc	ethyl acetate
EtOH	ethanol
ex	example
eq	equivalent

FA	formic acid
h	hour
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(OtBu)	Potassium <i>tert.</i> butoxide
L	liter
LiOH·H ₂ O	Lithium hydroxide monohydrate
M	molar
MeOH	methanol
MgSO ₄	magnesium sulphate
min	minute
mL	milliliter
MTBE	<i>tert</i> -butylmethylether
NaOEt	Sodium ethanolate
NH ₃	ammonia
PMB	Para-methoxy benzyl
Prep.	preparative
RP	Reversed phase
RT	room temperature (about 20°C)
sat.	saturated
TBTU	Benzotriazolyl tetramethyluronium tetrafluoroborate
TEA	triethylamine
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	Tetrahydrofuran

TMS-Cl	Trimethylsilyl chloride
--------	-------------------------

Preparation of intermediates

Synthesis of Intermediate I



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): 0.615 min (Method I)

***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 (135g, 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.

$C_{13}H_{21}FN_4O_2$ (M=284.3 g/mol)
 ESI-MS: 285.1 [M+H]⁺
 Rt (HPLC): 0.766 min (Method I)

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

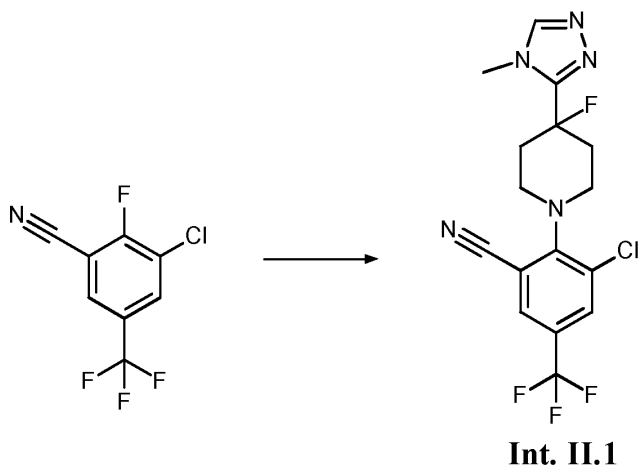
tert-Butyl 4-fluoro-4-(4-methyl-4H-1,2,4-triazol-3-yl)piperidine-1-carboxylate (90 g, 0.316 mol) is combined with methanol (90 mL) in a round-bottom flask. A solution of HCl (4 M in MeOH, 450 mL, 1.79 mol) is added slowly at ambient temperature. The resulting reaction mixture is stirred at ambient temperature for 12 h. The desired product is collected by
 10 filtration, washed with methanol and dried to yield 4-fluoro-4-(4-methyl-4H-1,2,4-triazol-3-yl)piperidine hydrochloride salt.

Hydrochloride salt (13.5 g) is added to a solution of ammonia in methanol (7 N, 150 mL) and purified by chromatography (Biotage SNAP Cartridge KP-NH, gradient DCM/MeOH 4:1 to 7:3)

15 $C_8H_{13}FN_4$ (M=184.2 g/mol)
 ESI-MS: 185 [M+H]⁺
 Rt (HPLC): 0.20 min (Method D)

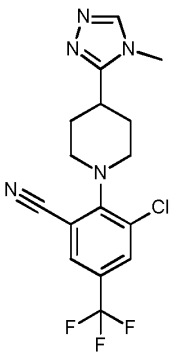
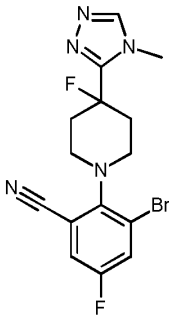
4-(4-Methyl-4H-1,2,4-triazol-3-yl)piperidine (MFCD09055373, CAS: 297172-18-0) is obtained from commercial vendors. Hydrochloride salt is converted into the free piperidine or
 20 piperazine according to the procedure described for Int. I

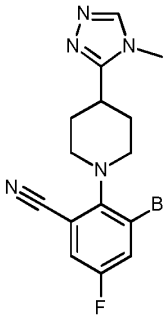
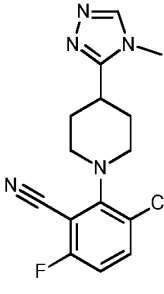
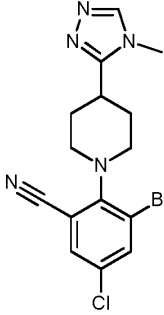
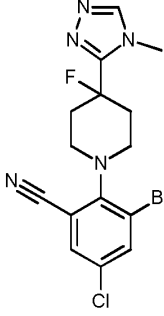
Intermediate II.1

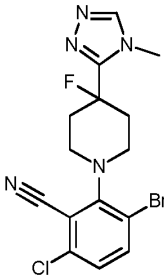
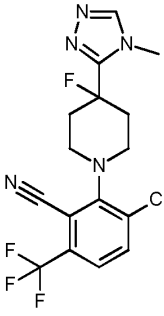
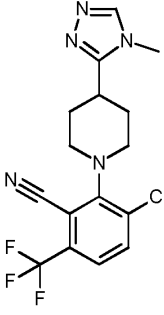


A solution of 3-chloro-2-fluorobenzonitrile (100 mg, 0.43 mmol) and Intermediate I (80 mg, 0.43 mmol) in DMSO (1 mL) is stirred at 100 °C for 18 h. The reaction mixture is diluted with acetonitrile and water and directly subjected to purification via preparative HPLC (Xbridge C18, acetonitrile/water gradient containing 0.1% TFA) to give intermediate II.1

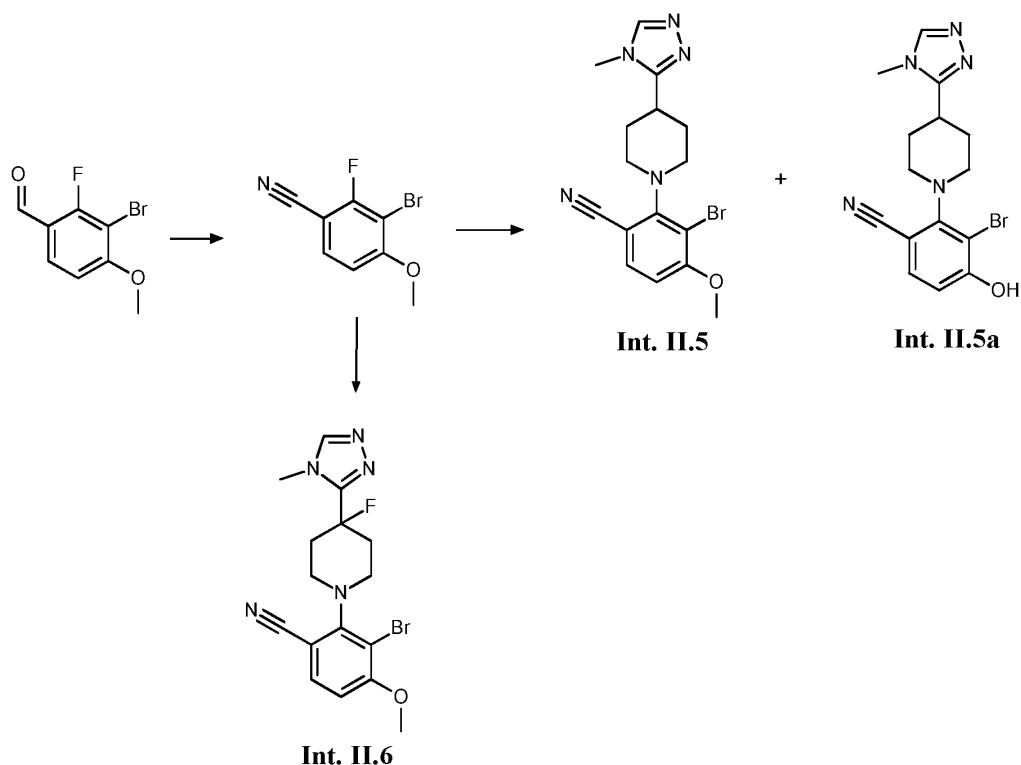
$C_{16}H_{14}ClF_4N_5$ (M= 387.8 g/mol)
ESI-MS: 389 [M+H]⁺
Rt (HPLC): 0.58 min (Method A)

Int.	Starting material	Structure	Deviation from general procedure	Molecular Formula (MW) ESI-MS HPLC retention time (method)
II.2	4-(4-methyl-4H-1,2,4-triazol-3-yl)piperidine + 3-chloro-2-fluoro-5-(trifluoromethyl)benzonitrile		18 h at 100 °C	$C_{16}H_{15}ClF_3N_5$ (M= 369.8 g/mol) ESI-MS: 371 [M+H] ⁺ Rt (HPLC): 0.50 min (Method A)
II.3	Int. I + 3-bromo-2,5-difluorobenzonitrile		6 h at 130 °C; purification by preparative HPLC (Sunfire C18, water/acetonitrile gradient containing 0.1% TFA)	$C_{15}H_{14}BrF_2N_5$ (M= 382.2 g/mol) ESI-MS: 382/384 [M+H] ⁺ Rt (HPLC): 0.86 min (Method B)

II.4	4-(4-methyl-4H-1,2,4-triazol-3-yl)piperidine + 3-bromo-2,5-difluorobenzonitrile		6 h at 130 °C; purification by preparative HPLC (Sunfire C18, water/ace- tonitrile gradient containing 0.1% TFA)	$C_{15}H_{15}BrFN_5$ (M= 364.2 g/mol) ESI-MS: 364/366 [M+H] ⁺ Rt (HPLC): 0.77 min (Method B)
II.11	4-(4-methyl-4H-1,2,4-triazol-3-yl)piperidine + 3-chloro-2,6-difluorobenzonitrile		18 h at 130 °C	$C_{15}H_{15}ClFN_5$ (M= 319.8 g/mol) ESI-MS: 319/321 [M+H] ⁺ Rt (HPLC): 0.48 min (Method A)
II.13	4-(4-methyl-4H-1,2,4-triazol-3-yl)piperidine + Int. IV		N,N-Diisopropylethylamine (2.0 eq) is added to the reaction mixture prior to heating 18 h at 100 °C; 48 h at 120 °C	$C_{15}H_{15}BrClN_5$ (M= 380.7 g/mol) ESI-MS: 380 / 382 [M+H] ⁺ Rt (HPLC): 0.80 min (Method B)
II.14	Int. I + Int. IV		N,N-Diisopropylethylamine (2.0 eq) is added to the reaction mixture prior to heating 18 h at 100 °C; 48 h at 120 °C	$C_{15}H_{14}BrClFN_5$ (M= 398.7 g/mol) ESI-MS: 398 / 400 [M+H] ⁺ Rt (HPLC): 0.90 min (Method B)

II.15	Int. I + 3-bromo-6-chloro-2-fluorobenzonitrile		1.5 eq. of Int. I; <i>N,N</i> -Diisopropylethylamine (2.5 eq) is added to the reaction mixture prior to heating 18 h at 100 °C	$C_{15}H_{14}BrClFN_5$ (M= 398.7 g/mol) ESI-MS: 398 / 400 [M+H] ⁺ Rt (HPLC): 0.73 min (Method G)
II.16	Int. I + 3-chloro-2-fluoro-6-(trifluoromethyl)benzonitrile		1.5 eq. of Int. I; <i>N,N</i> -Diisopropylethylamine (2.0 eq) is added to the reaction mixture prior to heating 6 h at 100 °C	$C_{16}H_{14}ClF_4N_5$ (M= 387.8 g/mol) ESI-MS: 388 [M+H] ⁺ Rt (HPLC): 0.88 min (Method B)
II.17	4-(4-methyl-4H-1,2,4-triazol-3-yl)piperidine + 3-chloro-2-fluoro-6-(trifluoromethyl)benzonitrile		1.5 eq. of Int. I; <i>N,N</i> -Diisopropylethylamine (2.0 eq) is added to the reaction mixture prior to heating 6 h at 100 °C	$C_{16}H_{15}ClF_3N_5$ (M= 369.8 g/mol) ESI-MS: 370 [M+H] ⁺ Rt (HPLC): 0.79 min (Method B)

Synthesis of Intermediate II.5 and II.6



3-Bromo-2-fluoro-4-methoxybenzonitrile

3-Bromo-2-fluoro-4-methoxybenzaldehyde (500 mg, 2.06 mmol), sodium formate (303 mg, 4.41 mmol) and hydroxylamine hydrochloride (168 mg, 2.37 mmol) are added to formic acid (2.5 mL). The resulting mixture is stirred and heated to reflux for 30 h. After cooling to ambient temperature, it is diluted with half-saturated sodium chloride solution. The resulting precipitate is collected by filtration, washed with water and dried to yield the desired product.

C_8H_5BrFO (M= 230.0 g/mol)

ESI-MS: 229 / 231 (M^{*+})

Rt (HPLC): 0.61 min (Method A)

Intermediate II.5

3-Bromo-2-fluoro-4-methoxybenzonitrile (2.00 g, 8.69 mmol) is added to DMSO (20 mL) and 4-(4-methyl-4H-1,2,4-triazol-3-yl)piperidine (3.47 g, 20.9 mmol) is added. The resulting mixture is heated to 100 °C for 30 h. After cooling to ambient temperature, the mixture is concentrated, the residue is purified by preparative HPLC (Sunfire C18, MeCN/water gradient containing 0.1% TFA) to yield the desired product along with the demethylated analogue Int. II.5a.

Intermediate II.5:

$C_{16}H_{18}BrN_5O$ (M= 376.3 g/mol)
ESI-MS: 376 / 378 [M+H]⁺
Rt (HPLC): 0.72 min (Method C)

5 Intermediate II.5a:

$C_{15}H_{16}BrN_5O$ (M= 362.2 g/mol)
ESI-MS: 362 / 364 [M+H]⁺
Rt (HPLC): 0.64 min (Method C)

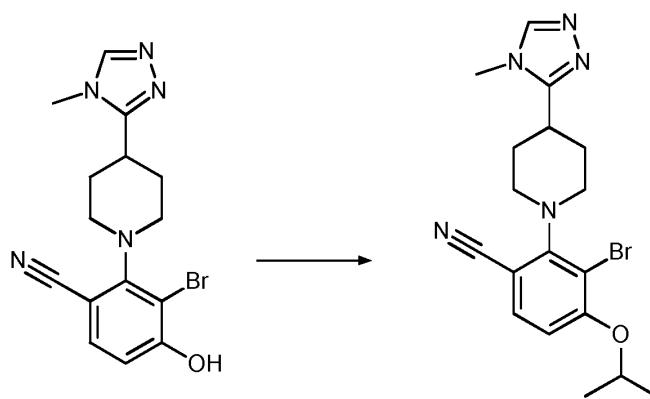
10 **Intermediate II.6**

3-Bromo-2-fluoro-4-methoxybenzonitrile (200 mg, 869 μ mol) is added to DMSO (4 mL) and intermediate I (384 mg, 2.09 mmol) is added. The resulting mixture is heated to 100 °C for 22 h. After cooling to ambient temperature, the mixture is concentrated, the residue is purified by preparative HPLC (XBridge C18, MeCN/water gradient containing 0.1% TFA; then X-Bridge C18, MeCN/water gradient containing 0.1% NH₃) to yield the desired product.

$C_{16}H_{17}BrFN_5O$ (M= 394.2 g/mol)
ESI-MS: 394 / 396 [M+H]⁺
Rt (HPLC): 0.53 min (Method D)

20

Intermediate II.7



Int. II.5a

Int. II.7

Intermediate II.5a (70.0 mg, 0.193 mmol) and cyclopropanol (17.4 μ L, 0.290 mmol) are added to degassed THF (1.0 mL). Triphenylphosphine (102 mg, 0.387 mmol) and

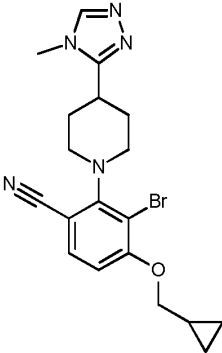
diisopropyl azodicarboxylate (81.0 μ L, 0.387 mmol) are added. The mixture is stirred at 70 °C for 2 h. Another batch of triphenylphosphine (102 mg, 0.387 mmol), diisopropyl azodicarboxylate (81.0 μ L, 0.387 mmol) and cyclopropanol (17.4 μ L, 0.290 mmol) are added and the mixture is again stirred at 70 °C for 4 h. After cooling to ambient temperature, it is diluted with MeCN and water, acidified with TFA and purified by preparative HPLC (Sunfire C18, MeCN/water gradient containing 0.1% TFA) to yield the desired product.

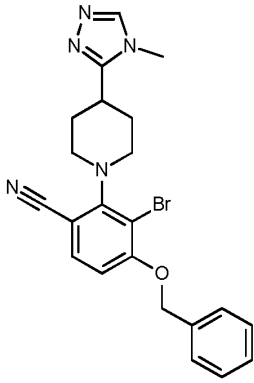
$C_{18}H_{22}BrN_5O$ (M= 404.3 g/mol)

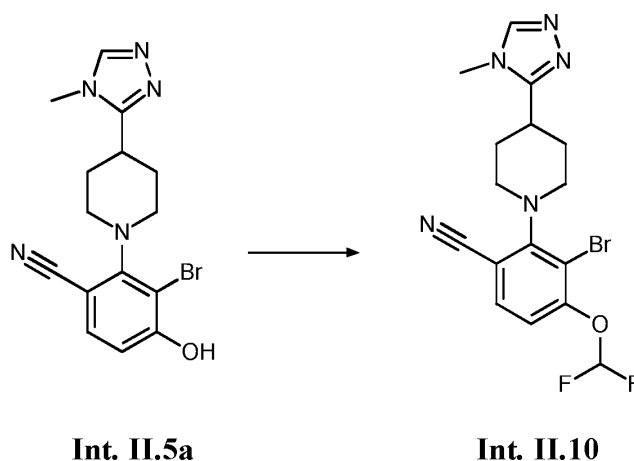
ESI-MS: 404 / 406 [M+H]⁺

Rt (HPLC): 0.78 min (Method C)

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm: 8.98 (s, 1 H), 7.69 (d, *J*=8.7 Hz, 1 H), 7.04 (d, *J*=9.0 Hz, 1 H), 4.80 (spt, *J*=6.0 Hz, 1 H), 3.79 (s, 3 H), 3.38 - 3.51 (m, 2 H), 3.27 - 3.36 (m, 2 H), 3.16 - 3.27 (m, 1 H), 1.89 - 2.07 (m, 4 H), 1.32 (d, *J*=6.0 Hz, 6 H).

Int.	Starting material	Structure	Deviation from procedure of Int. II.12	Molecular Formula (MW) ESI-MS HPLC retention time (method)
II.8	II.5a + cyclopropanemethanol		3 h at 70 °C; no second addition of alcohol and reagents	$C_{19}H_{22}BrN_5O$ (M= 416.3 g/mol) ESI-MS: 416 / 418 [M+H] ⁺ Rt (HPLC): 0.82 min (Method C)

II.9	II.5a + Benzyl alcohol		4 h at 70 °C; no second addition of alcohol and reagents	C ₂₇ H ₂₅ BrN ₅ O (M= 452.4 g/mol) ESI-MS: 452 / 454 [M+H] ⁺ Rt (HPLC): 0.83 min (Method C)
------	------------------------------	---	---	--

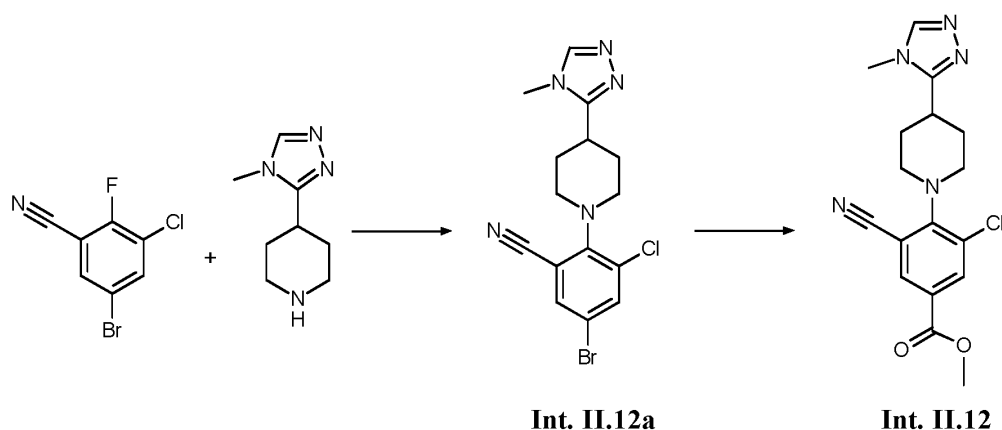
Intermediate II.10

Intermediate II.5a (75 mg, 0.207 mmol) is added to a mixture of DMF and water (9:1, 1.0 mL). Potassium carbonate (143 mg, 1.04 mmol) and sodium chlorodifluoroacetate (189 mg, 1.24 mmol) are added and the mixture is stirred and heated to 90 °C for 10 h. After cooling to ambient temperature, the addition of potassium carbonate (143 mg, 1.04 mmol) and sodium chlorodifluoroacetate (189 mg, 1.24 mmol) is repeated. The mixture is then stirred again for 10 h at 90 °C. After cooling to ambient temperature, it is concentrated and the residue purified by preparative HPLC (Sunfire C18, MeCN/water gradient containing 0.1% TFA) to yield the desired product.

C₁₆H₁₆BrF₂N₅O (M= 412.2 g/mol)
ESI-MS: 412 / 414 [M+H]⁺
Rt (HPLC): 0.53 min (Method C)

15

Synthesis of Intermediate II.12

**Intermediate II.12a**

5-Bromo-3-chloro-2-fluorobenzonitrile (1.20 g, 4.96 mmol) and 4-(4-methyl-4H-1,2,4-triazol-3-yl)piperidine (956 mg, 5.46 mmol) are suspended in DMF (10 mL) and diisopropylethylamine (954 μ L, 5.46 mmol) is added. The resulting reaction mixture is stirred at ambient temperature for 18 h. It is then added dropwise to water and the precipitated solid collected by filtration and subsequently purified by column chromatography (SiO₂, EtOAc/MeOH gradient) to yield the desired product.

C₁₅H₁₅BrClN₅ (M=380.7 g/mol)

ESI-MS: 380 / 382 [M+H]⁺

Rt (HPLC): 0.77 min (Method C)

Intermediate II.12

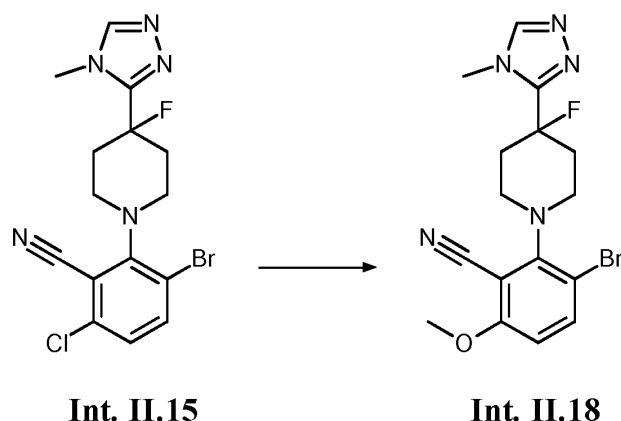
Intermediate II.12a (700 mg, 1.84 mmol), palladium(II)-acetate (64.8 mg, 0.288 mmol), 1,1'-bis(diphenylphosphino)ferrocene (80.0 mg, 0.144 mmol) and sodium acetate (400 mg, 4.88 mmol) are suspended in a mixture of methanol (20 mL) and 1,4-dioxane (20 mL). The mixture is subjected to three cycles of vacuum and purged with carbon monoxide. After the third purging cycle, a pressure of 8 bar is applied and the mixture stirred at 60 °C for 18 h. The mixture is then concentrated and the residue is purified by column chromatography (SiO₂, EtOAc/MeOH gradient) to yield the desired product.

C₁₇H₁₈ClN₅O₂ (M=359.8 g/mol)

ESI-MS: 360 [M+H]⁺

Rt (HPLC): 0.74 min (Method C)

Synthesis of Intermediate II.18

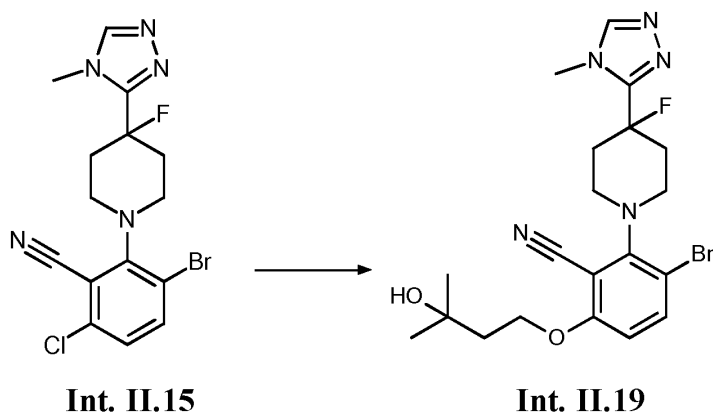


Intermediate II.18

To a mixture of intermediate II.15 (40.0 mg, 0.100 mmol) in acetonitrile (1.0 mL) is added a solution of sodium methoxide in MeOH (30%, 28.2 μ L, 0.151 mmol). The resulting mixture is stirred at ambient temperature for 1 h and additionally at 50 °C for 18 h. A second crop of sodium methoxide solution in MeOH (30%, 28.2 μ L, 0.151 mmol) is added. The resulting mixture is stirred at 50 °C for 4 h. After cooling to ambient temperature, the mixture is neutralized by addition of acetic acid and diluted with water. It is purified by preparative HPLC (Sunfire C18, acetonitrile/water gradient containing 0.1% TFA) to yield the desired product.

C ₁₆ H ₁₇ BrFN ₅ O	(M=394.2 g/mol)
ESI-MS:	394 / 396 [M+H] ⁺
Rt (HPLC):	0.92 min (Method E)

15 Synthesis of Intermediate II.19



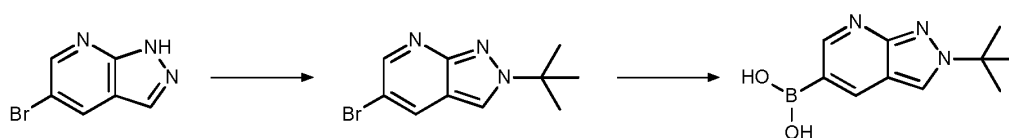
Intermediate II.19

To a mixture of 3-methyl-1,3-butanediol (52.2 mg, 0.502 mmol) in THF (1 mL) is added sodium hydride (55%, 17.5 mg, 0.401 mmol) and the resulting mixture is stirred at ambient temperature for 1 h. A solution of intermediate II.15 (40.0 mg, 0.100 mmol) in acetonitrile (1 mL) is added and the resulting reaction mixture is heated to 50°C. After stirring for 18 at
 5 this temperature, the mixture is cooled to ambient temperature, neutralized by addition of acetic acid and diluted with water. It is purified by preparative HPLC (Sunfire C18, acetonitrile/water gradient containing 0.1% TFA) to yield the desired product.

$C_{20}H_{25}BrFN_5O_2$ (M=466.3 g/mol)

10 ESI-MS: 466 / 468 [M+H]⁺

Rt (HPLC): 0.71 min (Method J)

Synthesis of Intermediate III.1**Int. III.1****5-Bromo-2-tert-butyl-2H-pyrazolo[3,4-b]pyridine**

To a mixture of 5-bromo-1H-pyrazolo[3,4-b]pyridine (4.00 g, 19.8 mmol) in toluene (23 mL) are added *tert*-butyl acetate (26.6 mL, 198 mmol) and methanesulfonic acid (1.3 mL, 19.8 mmol). After being stirred at 80 °C for 1 h, the reaction is treated with additional methanesulfonic acid (1.3 mL, 19.8 mmol). The reaction mixture is cooled to ambient temperature, concentrated, redissolved in MeCN/H₂O, and purified via preparative HPLC (Xbridge C18, acetonitrile/water gradient containing 0.1% TFA) to give 5-bromo-2-*tert*-butyl-2H-pyrazolo[3,4-b]pyridine.
 20

$C_{10}H_{12}BrN_3$ (M=254.1 g/mol)

ESI-MS: 254 / 256 [M+H]⁺

25 Rt (HPLC): 0.50 min (Method A)

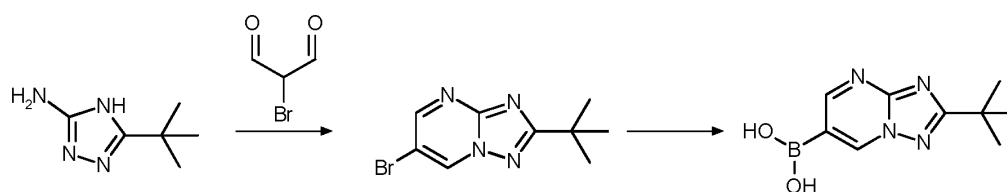
Intermediate III.1

A solution of 5-bromo-2-*tert*-butyl-2H-pyrazolo[3,4-b]pyridine (1.50 g, 3.87 mmol), bis(pinacolato)diboron (1.20 g, 4.78 mmol), and potassium acetate (763 mg, 7.77 mmol) in
 30 1,4-dioxane (15 mL) is purged with Ar for 10 min, followed by addition of [1,1'-bis-

(diphenylphosphino)-ferrocen]-dichloro-palladium(II) (Pd(dppf)Cl₂, CAS: 72287-26-4) (190 mg, 0.23 mmol). After being stirred at 110 °C for 4 h, the mixture is cooled to ambient temperature, concentrated, redissolved in MeCN/H₂O, and purified via preparative HPLC (Xbridge C18, acetonitrile/water gradient containing 0.1% TFA) to give Int. III.1.

5 C₁₀H₁₄BN₃O₂ (M=219.0 g/mol)
ESI-MS: 220 [M+H]⁺
Rt (HPLC): 0.27 min (Method A)

Synthesis of Intermediate III.2



Int. III.2

10

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

5-*tert*-Butyl-4H-1,2,4-triazol-3-amine (400 mg, 2.71 mmol) and 2-bromopropanedial (646 mg, 4.07 mmol) are added to acetic acid (5 mL). After being stirred at 60 °C for 3 h, the reaction mixture is concentrated, neutralized with aqueous saturated solution of NaHCO₃,
15 and extracted three times with DCM. The combined organic phases are dried (Na₂SO₄), concentrated, and purified by column chromatography (SiO₂, cyclohexane/EtOAc gradient) to yield the title compound.

C₉H₁₁BrN₄ (M=255.1 g/mol)
ESI-MS: 255 / 257 [M+H]⁺
20 Rt (HPLC): 0.84 min (Method C)

Intermediate III.2

A solution of 6-bromo-2-*tert*-butyl-[1,2,4]triazolo[1,5-*a*]pyrimidine (200 mg, 0.63 mmol), bis(pinacolato)diboron (260 mg, 1.02 mmol), and potassium acetate (240 mg, 2.45 mmol) in
25 1,4-dioxane (4 mL) is purged with Ar for 15 min, followed by addition of bis(triphenylphosphine)palladium chloride (CAS: 13965-03-2) (55 mg, 0.08 mmol). After being stirred at 60 °C for 24 h, the mixture is cooled to ambient temperature, diluted with EtOAc, and filtered through a silica plug. Filtrate is concentrated, redissolved in MeCN/H₂O/TFA,

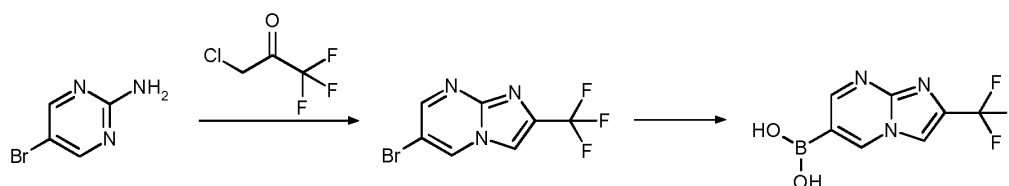
and purified by preparative HPLC (SunFire C18, MeCN/H₂O gradient containing 0.1% TFA) to give intermediate III.2.

C₉H₁₃BN₄O₂ (M=220.0 g/mol)

ESI-MS: 221 [M+H]⁺

5 Rt (HPLC): 0.34 min (Method A)

Synthesis of Intermediate III.3



6-bromo-2-trifluoromethylimidazo[1,2-a]pyrimidine

10 Ethanol (2 mL) is added to a mixture of 2-amino-5-bromopyrimidine (1.00 g, 5.63 mmol) and 1-chloro-3,3,3-trifluoroacetone (889 μ L, 8.45 mmol). The resulting mixture is stirred at 90 °C for 5 days. After cooling to ambient temperature, the mixture is loaded onto EX-trelut® and purified by column chromatography (SiO₂, DCM/MeOH gradient) to yield the desired product.

15 C₇H₃BrF₃N₃ (M=266.1 g/mol)

ESI-MS: 266 / 268 [M+H]⁺

Rt (HPLC): 0.38 min (Method A)

Intermediate III.3

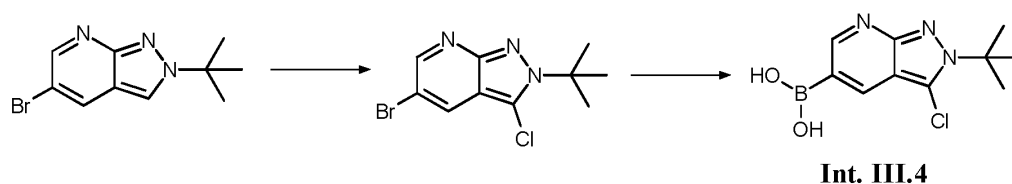
20 6-Bromo-2-trifluoromethylimidazo[1,2-a]pyrimidine (82 mg, 0.308 mmol) is added to 1,4-dioxane (1.0 mL). Bis(pinacolato)diborane (117 mg, 462 μ mol) and potassium acetate (90.6 mg, 0.925 mmol) is added and the resulting mixture is degassed by passing an Argon flow through the mixture. Pd(PPh₃)₂Cl₂ (21.6 mg, 0.031 mmol) is added and the reaction mixture is heated to 90 °C and stirred for 5 h. After cooling to ambient temperature, the mixture is concentrated, resuspended in a mixture of water and ACN and purified by preparative HPLC (XBridge C18, ACN/water gradient containing 0.1% TFA) to yield the desired product.

25 C₇H₅BF₃N₃O₂ (M=230.9 g/mol)

ESI-MS: 232 [M+H]⁺

Rt (HPLC): 0.29 min (Method A)

30

Synthesis of Intermediate III.4**5-Bromo-2-tert-butyl-3-chloro-2H-pyrazolo[3,4-b]pyridine**

5-Bromo-2-*tert*-butyl-2H-pyrazolo[3,4-b]pyridine (1.00 g, 3.93 mmol) is added to acetonitrile (15 mL) and *N*-chlorosuccinimide (0.58 g, 4.33 mmol) is added at ambient temperature. The resulting reacting mixture is stirred at 85 °C for 12 h. After cooling to ambient temperature, the mixture is concentrated and resuspended in water. It is extracted with EtOAc (3x). The combined organic extracts are dried over Na₂SO₄, filtered and concentrated. The residue is purified by column chromatography (SiO₂, PE/EtOAc gradient) to yield the desired product.

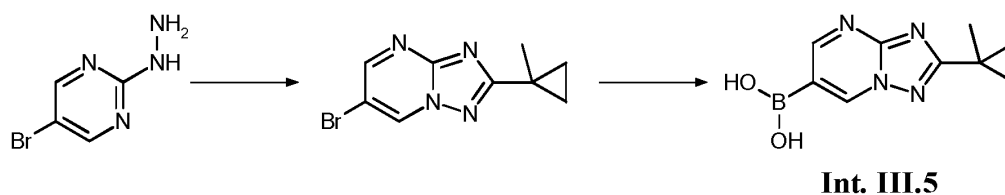
C₁₀H₁₁BrClN₃ (M=288.6 g/mol)
 ESI-MS: 288 / 290 [M+H]⁺
 Rt (HPLC): 0.80 min (Method L)

Intermediate III.4

A solution of 5-bromo-2-*tert*-butyl-3-chloro-pyrazolo[3,4-b]pyridine (0.80 g, 2.77 mmol), bis(pinacolato)diboron (0.92 g, 3.61 mmol), and potassium acetate (815 mg, 8.32 mmol) in 1,4-dioxane (16 mL) is purged with N₂ for 10 min, followed by addition of [1,1'-bis-(diphenylphosphino)-ferrocen]-dichloro-palladium(II) (Pd(dppf)Cl₂, CAS: 72287-26-4) (202 mg, 0.23 mmol). After being stirred at 100 °C for 12 h, the mixture is cooled to ambient temperature, concentrated and resuspended in water. It is extracted with EtOAc (3x), dried over Na₂SO₄ and concentrated. The residue is purified via preparative HPLC (Welch Xtimate C18, acetonitrile/water gradient containing 10 mM NH₄HCO₃) to give Int. III.4.

C₁₀H₁₃BClN₃O₂ (M=253.5 g/mol)
 ESI-MS: 254 [M+H]⁺
 Rt (HPLC): 0.71 min (Method M)

Synthesis of Intermediate III.5



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

A solution of 5-bromo-2-hydrazinopyrimidine (2.0 g, 2.1 mmol) and 1-methylcyclopropane-carboxylic acid (1.1 g, 2.1 mmol) in phosphoryl chloride (20 mL) is stirred at 100 °C for 12 h. After cooling to ambient temperature, the mixture is concentrated, resuspended in saturated aqueous solution of Na₂CO₃, and extracted with EtOAc (3x). The combined organic extracts are dried over Na₂SO₄, filtered, and concentrated. The obtained crude product is used without further purification.

C₉H₉BrN₄ (M=253.1 g/mol)

ESI-MS: 253 / 255 [M+H]⁺

Rt (HPLC): 0.56 min (Method L)

Intermediate III.5

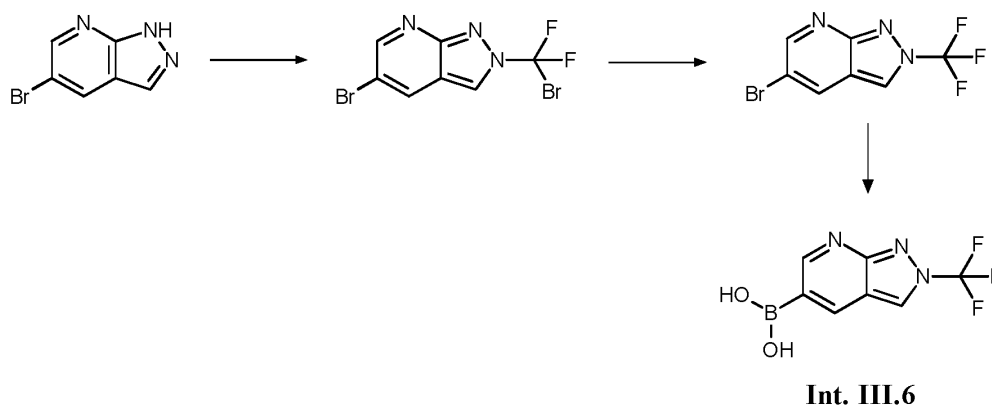
To a solution of 6-bromo-2-(1-methylcyclopropyl)-[1,2,4]triazolo[1,5-a]pyrimidine (0.50 g, 2.0 mmol) in 1,4-dioxane (5 mL) are added bis(pinacolato)diboron (0.60 g, 2.4 mmol), potassium acetate (0.58 g, 3.5 mmol), and [1,1'-bis-(diphenylphosphino)-ferrocen]-dichloropalladium(II) (Pd(dppf)Cl₂, CAS: 72287-26-4) (0.14 g, 0.19 mmol). After being stirred at 100 °C for 12 h, the mixture is cooled to ambient temperature, diluted with water, and extracted with EtOAc (3x). The combined organic layers are dried over Na₂SO₄ and concentrated. Further purification by column chromatography (SiO₂, PE/EtOAc gradient, followed by DCM/MeOH gradient) yields Int. III.5.

C₉H₁₁BN₄O₂ (M=218.0 g/mol)

ESI-MS: 219 [M+H]⁺

Rt (HPLC): 0.42 min (Method L)

Synthesis of Intermediate III.6



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

To a stirred solution of 5-bromo-1H-pyrazolo[3,4-b]pyridine (6.00 g, 28.8 mmol) in DMF (200 mL) is added sodium hydride (1.50 g, 34.5 mmol; 55% in mineral oil) at 0 °C. After being stirred for 30 min, the reaction mixture is treated with dibromodifluoromethane (8.3 mL, 86.3 mmol) and warmed to ambient temperature. The resulting mixture is stirred for 18 h, diluted with MeCN/H₂O, and directly purified via preparative HPLC (Xbridge C18, MeCN/water gradient containing 0.1% TFA) to give 5-bromo-2-(bromodifluoromethyl)-2H-pyrazolo[3,4-b]pyridine.

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

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

A solution of 5-bromo-2-(bromodifluoromethyl)-2H-pyrazolo[3,4-b]pyridine (2.1 g, 6.4 mmol) and silver tetrafluoroborate (2.5 g, 12 mmol) in DCM (40 mL) is stirred at 50 °C for 18 h. The reaction mixture is concentrated, redissolved in DCE (40 mL), and stirred at 80 °C for 18 h. The resulting mixture is concentrated, loaded onto EXtrelut®, and purified by column chromatography (SiO₂, DCM/MeOH gradient 100/0 to 1/1) to yield the title compound.

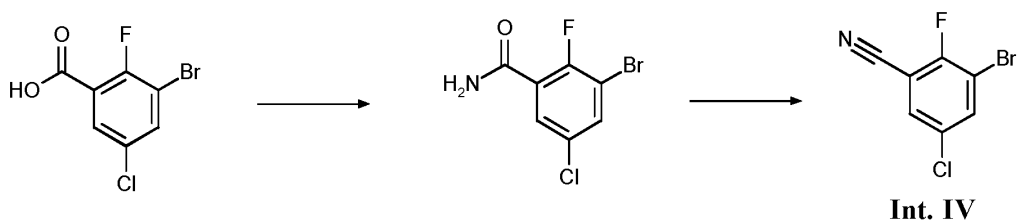
$C_7H_3BrF_3N_3$ (M=266.0 g/mol)
ESI-MS: 266 / 268 [M+H]⁺
Rt (HPLC): 0.47 min (Method A)

Intermediate III.6

To a stirred solution of 5-bromo-2-(trifluoromethyl)-2H-pyrazolo[3,4-b]pyridine (741 mg, 1.39 mmol) in 1,4-dioxane (10 mL) are added bis(pinacolato)diboron (529 mg, 2.09 mmol) and potassium acetate (409 mg, 4.18 mmol). The resulting mixture is purged with Ar for 10 min, followed by addition of [1,1'-bis-(diphenylphosphino)-ferrocen]-dichloro-palladium(II) (Pd(dppf)Cl₂; CAS: 72287-26-4) (102 mg, 0.14 mmol). After being stirred at 90 °C for 5 h, the mixture is cooled to ambient temperature, concentrated, redissolved in H₂O/MeCN, and purified via preparative HPLC (Xbridge C18, MeCN/water gradient containing 0.1% TFA) to give Int. III.6.

10 C7H5BF3N3O2 (M=230.9 g/mol)
ESI-MS: 232 [M+H]⁺
Rt (HPLC): 0.30 min (Method A)

15

Synthesis of Intermediate IV**3-Bromo-5-chloro-2-fluorobenzamide**

3-Bromo-5-chloro-2-fluorobenzoic acid (1.00 g, 3.75 mmol) and HATU (1.49 g, 3.94 mmol) are suspended in DMF (10 mL) and a solution of ammonia in THF (0.5 M, 37.5 mL, 18.7 mmol) is added. The resulting mixture is stirred for 18 h at ambient temperature. Another aliquot of the ammonia solution in THF (0.5 M, 37.5 mL, 18.7 mmol) is added and the mixture stirred for another 4 h. After completion, it is diluted with ethyl acetate and half-saturated NH₄Cl solution. The organic phase is further washed with aqueous sat. NaHCO₃ solution and aqueous sat. NaCl solution, dried over Na₂SO₄ and concentrated to yield the desired product.

25 C7H4BrClFNO (M=252.5 g/mol)
ESI-MS: not detected
Rt (HPLC): 0.76 min (Method B)

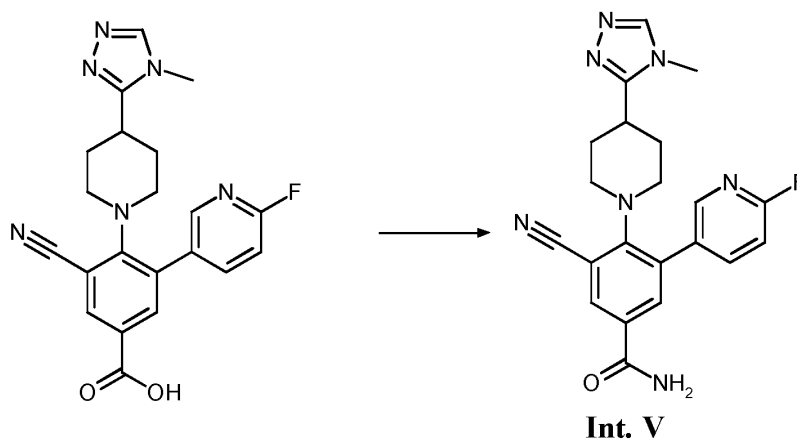
¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.00 (dd, *J*=5.6, 2.7 Hz, 1 H), 7.92 - 7.98 (m, 1 H), 7.83 (br s, 1 H), 7.64 (dd, *J*=5.4, 2.7 Hz, 1 H)

Intermediate IV

- 3-Bromo-5-chloro-2-fluorobenzamide (850 mg, 3.37 mmol) is added to dichloromethane (20 mL) and burgess reagent (1.61 g, 6.73 mmol) is added. The resulting mixture is stirred at ambient temperature for 1.5 h and a second batch of burgess reagent (1.61 g, 6.73 mmol) is added. The mixture is stirred for another 4 h at ambient temperature. It is then washed with aqueous sat. NaCl solution, the organic phase is dried over Na₂SO₄ and concentrated to yield the desired product.

C₇H₂BrClFN (M=234.4 g/mol)
 EI-MS: 233 / 235 [M*]⁺
 Rt (HPLC): 0.97 min (Method B)

Intermediate V



3-Cyano-5-(6-fluoropyridin-3-yl)-4-[4-(4-methyl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]benzoic acid

This compound is obtained as a by-product during the synthesis of example 15.

- C₂₁H₁₉FN₆O₂ (M=406.4 g/mol)
 ESI-MS: 405 (M-H)⁻
 Rt (HPLC): 0.63 min (Method C)

Intermediate V

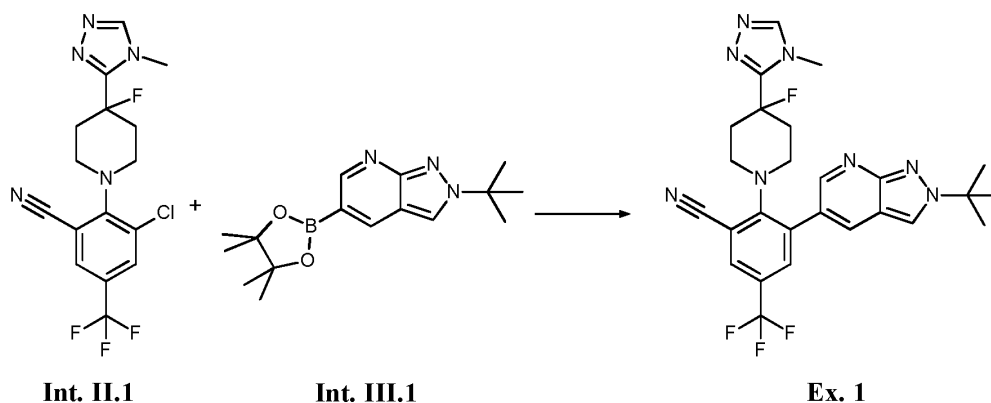
3-Cyano-5-(6-fluoropyridin-3-yl)-4-[4-(4-methyl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]benzoic acid (60.0 mg, 0.140 mmol), HATU (56.0 mg, 0.148 mmol) are added to DMF (1.0 mL) and a solution of ammonia in THF (0.5 M, 1.40 mL, 0.701 mmol) is added. The resulting reaction mixture is stirred for 18 h at ambient temperature. It is concentrated and the residue is purified by preparative HPLC (XBridge C18, acetonitrile/water gradient containing 0.1% NH₃) to yield the desired product.

C₂₁H₂₀FN₇O (M=405.4 g/mol)
ESI-MS: 406 [M+H]⁺
Rt (HPLC): 0.60 min (Method C)

10

Preparation of Final Compounds

Example 1



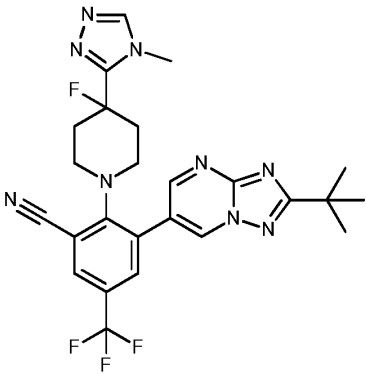
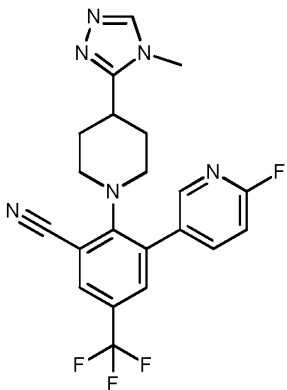
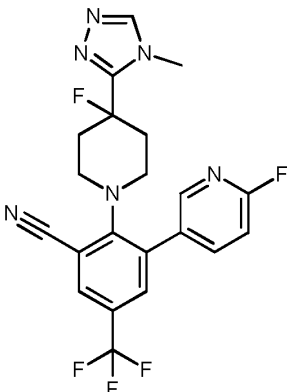
To a mixture of intermediate II.1 (50 mg, 0.13 mmol) and intermediate III.1 (33 mg, 0.15 mmol) in 1,4-dioxane (2 mL) is added potassium carbonate (2 M in H₂O, 0.13 mL, 0.25 mmol). The resulting mixture is purged with argon for 15 min, [1,1'-Bis-(diphenylphosphino)-ferrocen]-dichloro-palladium(II) (Pd(dppf)Cl₂, CAS: 72287-26-4) (9.2 mg, 0.01 mmol) is added, and the mixture is further purged with argon for 3 min. The reaction mixture is heated to 100 °C and stirred for 15 h. After cooling to ambient temperature, the reaction mixture is diluted with MeCN/H₂O and filtered. Direct purification via preparative HPLC (XBridge C18, acetonitrile/water gradient containing 0.1% TFA) yields Example 1.

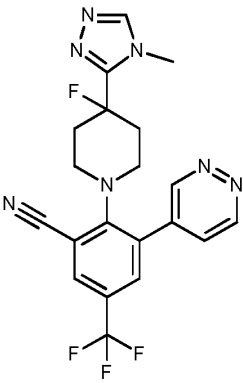
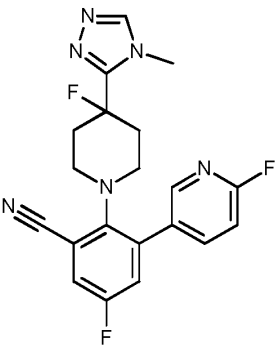
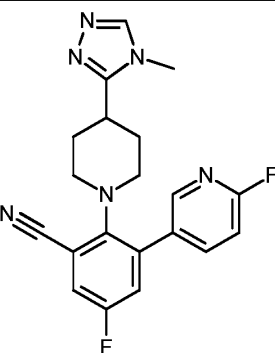
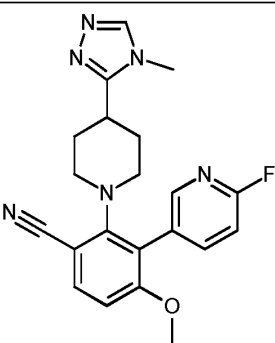
C₂₆H₂₆F₄N₈ (M= 526.5 g/mol)
ESI-MS: 527 [M+H]⁺
Rt (HPLC): 0.59 min (Method A)

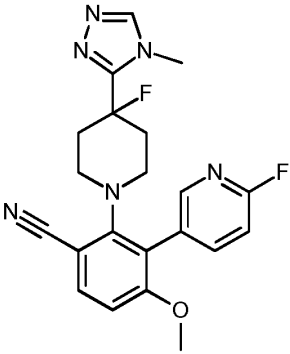
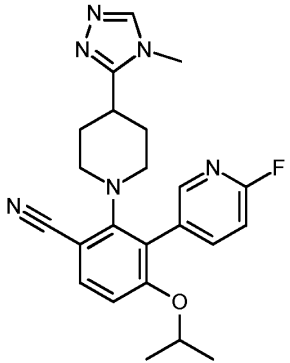
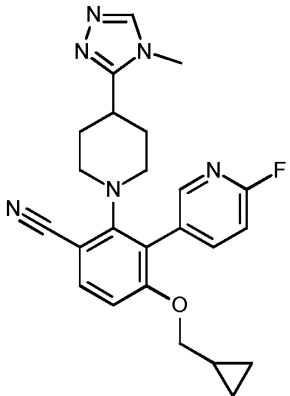
25

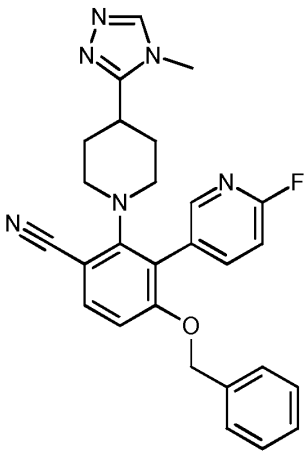
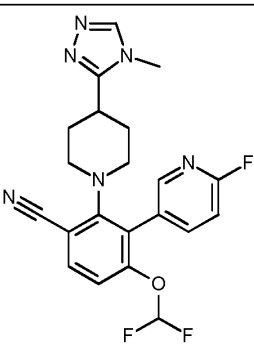
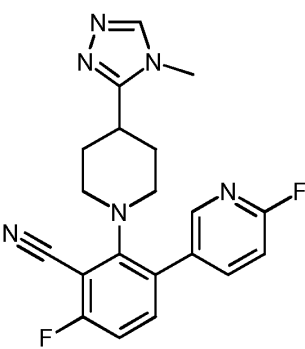
^1H NMR (400 MHz, DMSO- d_6) δ = 8.66 (d, J =2.3 Hz, 1 H), 8.63 (s, 1 H), 8.51 (s, 1 H), 8.29 (d, J =2.3 Hz, 1 H), 8.24 (dd, J =2.3, 0.6 Hz, 1 H), 7.85 - 7.88 (m, 1 H), 3.70 (d, J =1.6 Hz, 4 H), 3.25 - 3.34 (m, 2 H), 3.11 - 3.22 (m, 2 H), 2.12 - 2.29 (m, 4 H), 1.72 (s, 9 H)

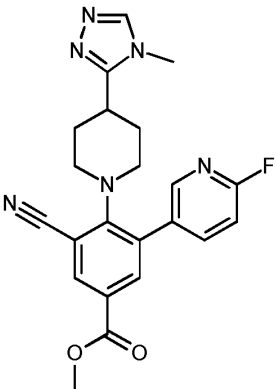
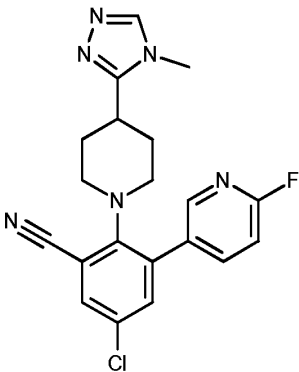
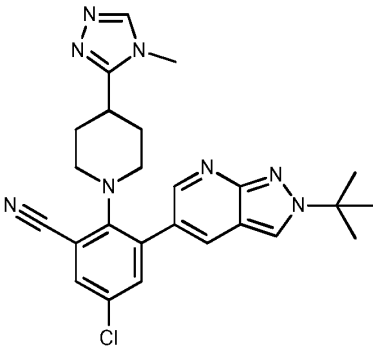
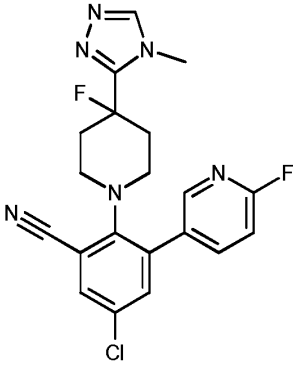
The following examples are prepared with minor modifications of the procedure of example 1:

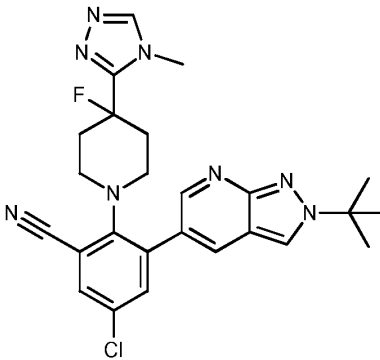
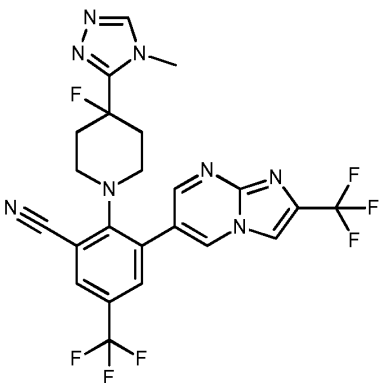
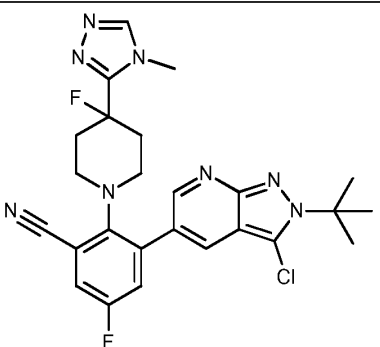
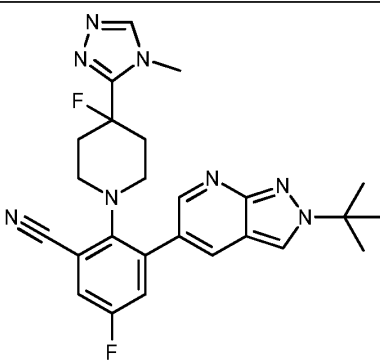
Ex.	Starting material	Structure	Deviation from general procedure
2	Int. II.1 + Int. III.2		3.0 eq. of K ₂ CO ₃ solution; purified by preparative HPLC (XBridge C18, acetonitrile/water gradient containing 0.1% NH ₃)
3	Int. II.2 + 2-fluoro-pyridine-5-boronic acid pinacol ester		15 h at 95 °C; purified by preparative SFC (Torus Diol, MeOH/CO ₂ , 40 °C), followed by preparative HPLC (XBridge C18, acetonitrile/water gradient containing 0.1% TFA)
4	Int. II.1 + 2-fluoro-pyridine-5-boronic acid pinacol ester		12 h at 100 °C; purified by preparative HPLC (XBridge C18, acetonitrile/water gradient containing 0.1% NH ₃), followed by preparative SFC (Torus Diol, MeOH/CO ₂ , 40 °C)

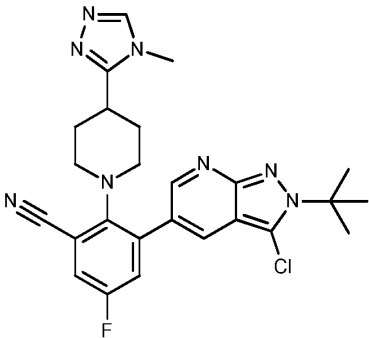
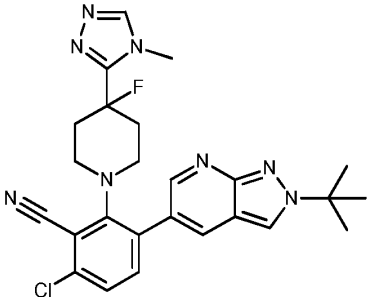
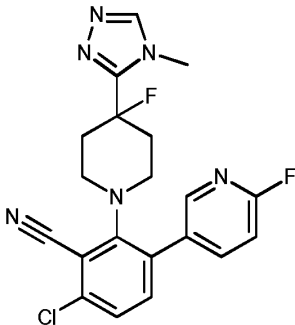
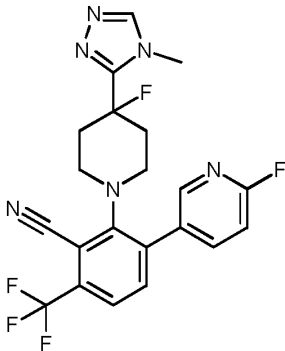
5	Int. II.1 + 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridazine		1.5 eq. of 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridazine; 3.0 eq. of Na ₂ CO ₃ solution; 0.1 eq. of Pd(PPh ₃) ₄ ; 15 h at 100 °C, followed by 5 h at 120 °C
6	Int. II.3 + 2-fluoropyridine-5-boronic acid pinacol ester		1.5 eq 2-fluoropyridine-5-boronic acid pinacol ester; 2.2 eq Na ₂ CO ₃ solution; 0.1 eq XPhos Pd G3 (CAS: 1445085-55-1); 5 h at 80 °C; purification by column chromatography (SiO ₂ , EtOAc/MeOH gradient)
7	Int. II.4 + 2-fluoropyridine-5-boronic acid pinacol ester		2.2 eq. of Na ₂ CO ₃ solution is used, 0.1 eq XPhos Pd G3 (CAS: 1445085-55-1); 5 h at 80 °C; purified by column chromatography (SiO ₂ , EtOAc/MeOH gradient)
8	Int. II.5 + 2-fluoropyridine-5-boronic acid pinacol ester		4 eq. of K ₂ CO ₃ solution; 0.05 eq Pd(dppf)Cl ₂ ; 3 h at 95 °C; purified by preparative HPLC (XBridge C18, acetonitrile/water gradient containing 0.1% NH ₃)

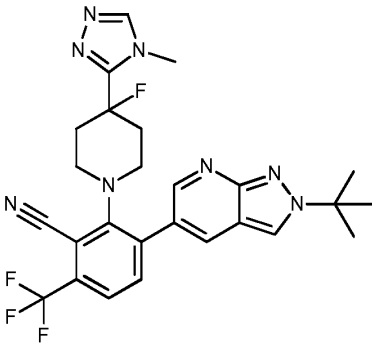
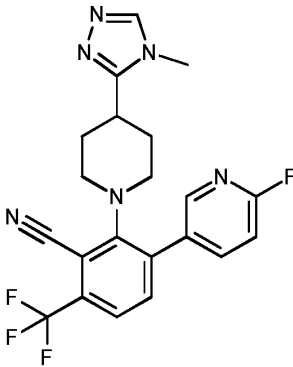
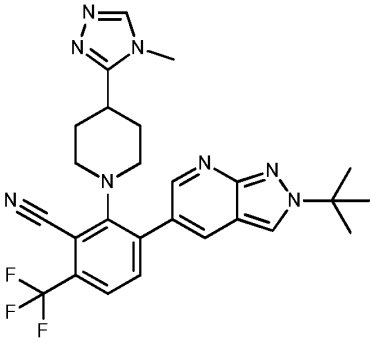
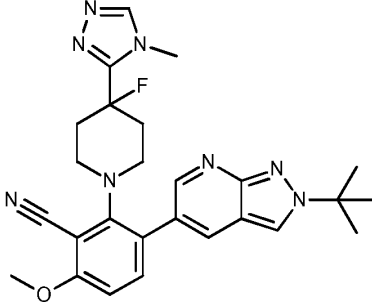
9	Int. II.6 + 2-fluoro- pyridine-5-bo- ronic acid pina- col ester		3 eq. of K ₂ CO ₃ solution; 0.05 eq Pd(dppf)Cl ₂ ; 3 h at 95 °C; purified by preparative HPLC (XBridge C18, acetonitrile/water gradient containing 0.1% NH ₃)
10	Int. II.7 + 2-fluoro- pyridine-5-bo- ronic acid		1.5 eq. of 2-fluoropyridine-5-boronic acid; 4 eq. of K ₂ CO ₃ solution; 4 h at 100 °C; purified by preparative HPLC (Sunfire C18, acetonitrile/water gradient containing 0.1% TFA)
11	Int. II.8 + 2-fluoro- pyridine-5-bo- ronic acid		1.5 eq. of 2-fluoropyridine-5-boronic acid; 4 eq. of K ₂ CO ₃ solution; 4 h at 100 °C; purified by preparative HPLC (Sunfire C18, acetonitrile/water gradient containing 0.1% TFA), followed by preparative HPLC (XBridge C18, acetonitrile/water gradient containing 0.1% TFA)

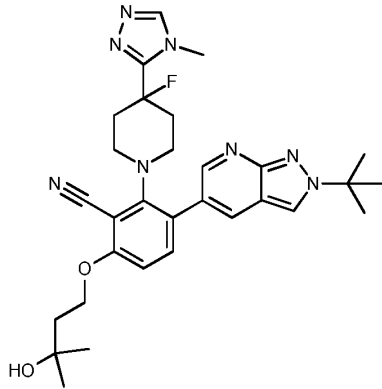
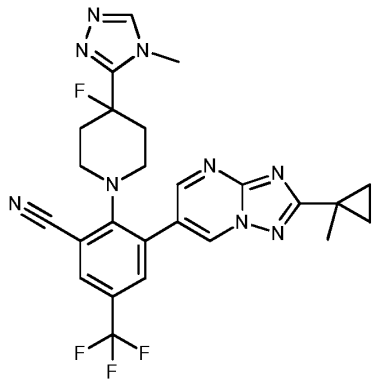
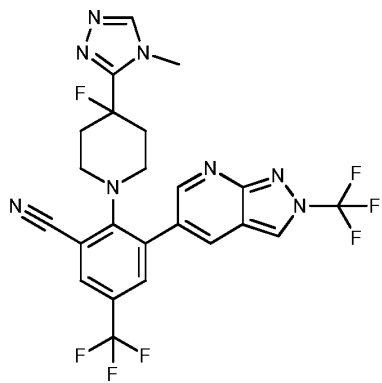
12	Int. II.9 + 2-fluoro- pyridine-5-bo- ronic acid		1.5 eq. of 2-fluoropyridine-5-bo- ronic acid; 4 eq. of K ₂ CO ₃ solu- tion; 4 h at 100 °C; purified by preparative HPLC (Sunfire C18, acetonitrile/water gradient con- taining 0.1% TFA)
13	Int. II.10 + 2-fluoro- pyridine-5-bo- ronic acid		1.5 eq. of 2-fluoropyridine-5-bo- ronic acid; 4 eq. of K ₂ CO ₃ solu- tion; 4 h at 100 °C; purified by preparative HPLC (Sunfire C18, acetonitrile/water gradient con- taining 0.1% TFA)
14	Int. II.11 + 2-fluoro- pyridine-5-bo- ronic acid pina- col ester		3.2 eq. of Na ₂ CO ₃ solution; 0.05 eq XPhos Pd G3 (CAS: 1445085-55-1); 36 h at 100 °C; purified by preparative HPLC (XBridge C18, acetonitrile/water gradient containing 0.1% NH ₃), followed by preparative HPLC (Sunfire C18, acetonitrile/water gradient containing 0.1% TFA)

15	Int. II.12 + 2-fluoro- pyridine-5-bo- ronic acid pina- col ester		1.8 eq. of 2-fluoropyridine-5-bo- ronic acid pinacol ester; 2.2. eq. of Na ₂ CO ₃ solution; 0.05 eq. of XPhos Pd G4 (1599466-81-5); 10 h at 80 °C; purified by column chromatog- raphy (SiO ₂ , EtOAc / MeOH gradient)
16	Int. II.13 + 2-fluoro- pyridine-5-bo- ronic acid		1.0 eq of 2-fluoropyridine-5-bo- ronic acid; 4.0 eq. of K ₂ CO ₃ so- lution; 1 h at 70 °C; purified by preparative HPLC (XBridge C18, acetonitrile/water gradient containing 0.1% NH ₃)
17	Int. II.13 + Int. III.1		1.0 eq of Int. III.1; 4.0 eq. of K ₂ CO ₃ solution; 1 h at 70 °C; purified by pre- parative HPLC (XBridge C18, acetonitrile/water gradient con- taining 0.1% NH ₃)
18	Int. II.14 + 2-fluoro- pyridine-5-bo- ronic acid		1.0 eq of 2-fluoropyridine-5-bo- ronic acid; 4.0 eq. of K ₂ CO ₃ solution; 1 h at 70 °C; purified by pre- parative HPLC (XBridge C18, acetonitrile/water gradient con- taining 0.1% NH ₃)

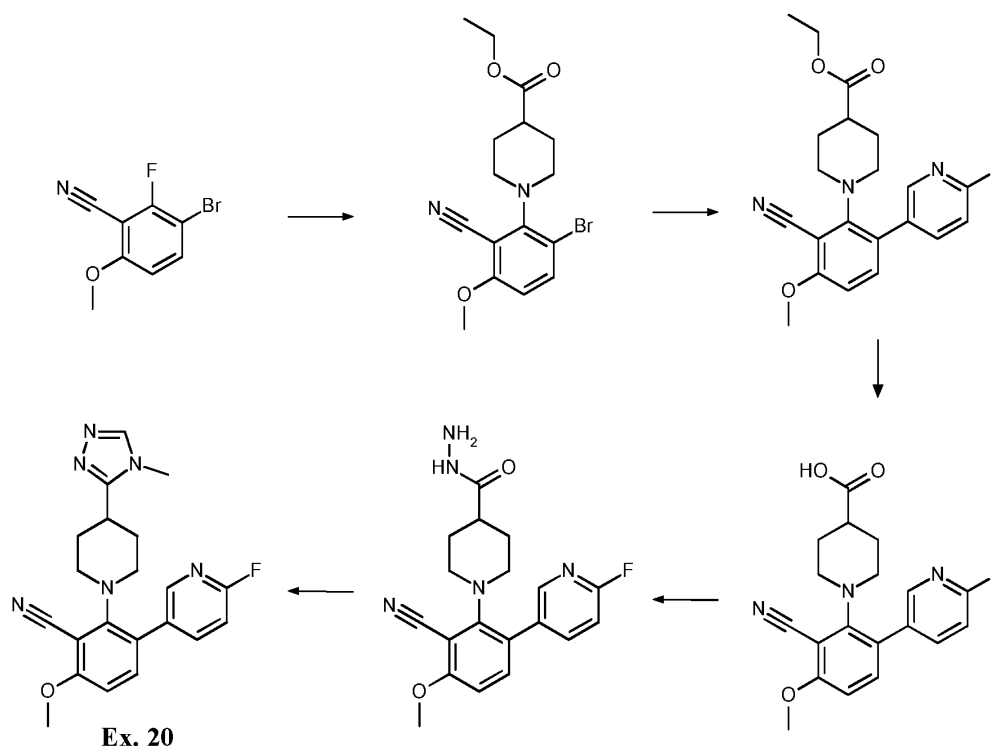
19	Int. II.14 + Int. III.1		1.0 eq. of Int. III.1; 4.0 eq. of K ₂ CO ₃ solution; 1 h at 70 °C; purified by pre- parative HPLC (XBridge C18, acetonitrile/water gradient con- taining 0.1% NH ₃)
22	Int. II.1 + Int. III.3		3.0 eq. of K ₂ CO ₃ solution; 1 h at 100 °C; purified by col- umn chromatography (SiO ₂ , EtOAc / MeOH gradient)
24	Int. II.3 + Int. III.4		1.3 eq. of Int. III.4; 3.0 eq. of Na ₂ CO ₃ solution; 2 h at 100 °C; by preparative HPLC (Sunfire C18, acetonitrile/water gradient containing 0.1% TFA)
25	Int. II.3 + Int. III.1		1.0 eq. of Int. III.1; 4.0 eq. of K ₂ CO ₃ solution; 1 h at 70 °C; purified by pre- parative HPLC (Sunfire C18, ac- etonitrile/water gradient contain- ing 0.1% TFA)

26	Int. II.4 + Int. III.4		2.0 eq. of Na ₂ CO ₃ solution; 2 h at 100 °C; purified by preparative HPLC (Sunfire C18, acetonitrile/water gradient containing 0.1% TFA), followed by preparative SFC (Torus DIOL, MeOH/CO ₂ , 40 °C)
27	Int. II.15 + Int. III.1		0.71 eq. of Int. III.1; 2.9 eq. of K ₃ PO ₄ solution; 0.04 eq. of XPhos Pd G3; 2 h at 50 °C; purified by preparative HPLC (Sunfire C18, acetonitrile/water gradient containing 0.1% TFA)
28	Int. II.15 + 2-fluoropyridine-5-boronic acid		1.0 eq. of 2-fluoropyridine-5-boronic acid; 4.0 eq. of K ₃ PO ₄ solution; 0.05 eq. of XPhos Pd G3; 2 h at 40 °C; purified by preparative HPLC (Sunfire C18, acetonitrile/water gradient containing 0.1% TFA)
29	Int. II.16 + 2-fluoropyridine-5-boronic acid		3.0 eq. of K ₂ CO ₃ solution; 1 h at 100 °C; purified by column chromatography (SiO ₂ , EtOAc / MeOH gradient)

30	Int. II.16 + Int. III.1		1.0 eq. of Int. III.1; 4.0 eq. of K ₂ CO ₃ solution; 1 h at 70 °C; purified by pre- parative HPLC (Sunfire C18, ac- etonitrile/water gradient contain- ing 0.1% TFA)
31	Int. II.17 + 2-fluoro- pyridine-5-bo- ronic acid		3.0 eq. of K ₂ CO ₃ solution; 1 h at 100 °C; purified by col- umn chromatography (SiO ₂ , EtOAc / MeOH gradient)
32	Int. II.17 + Int. III.1		4.0 eq. of K ₂ CO ₃ solution; 1 h at 70 °C; purified by pre- parative HPLC (XBridge C18, acetonitrile/water gradient con- taining 0.1% NH ₃)
33	Int. II.18 + Int. III.1		1.3 eq. of Int. III.1; 3.0 eq. of K ₃ PO ₄ solution; 0.05 eq. of XPhos Pd G3; 2 h at 85 °C; pu- rified by preparative HPLC (Sunfire C18, acetonitrile/water gradient containing 0.1% TFA)

34	Int. II.19 + Int. III.1		1.5 eq. of Int. III.1; 4.0 eq. of K_3PO_4 solution; 0.05 eq. of XPhos Pd G3; 2 h at 85 °C; purified by preparative HPLC (Sunfire C18, acetonitrile/water gradient containing 0.1% TFA)
35	Int. II.1 + Int. III.5		1.1, 1.2, and 1.2 eq. of Int. III.5 added at 0, 4, and 8 h, respectively; 3.0, 3.0, and 3.0 eq. of Na_2CO_3 solution added at 0, 4, and 8 h, respectively; 0.08, 0.08, and 0.08 eq. of XPhos Pd G3 (CAS: 1445085-55-1) added at 0, 4, and 8 h, respectively; 48 h at 90 °C; purified by preparative HPLC (Sunfire C18, MeOH/water gradient containing 0.1% TFA)
36	Int. II.1 + Int. III.6		3.5 eq. of Na_2CO_3 solution; 0.08 eq. of XPhos Pd G3; 4 h at 95 °C; purified by preparative HPLC (XBridge C18, acetonitrile/water gradient containing 0.1% NH_3)

Synthesis of Example 20



Ethyl 1-(6-bromo-2-cyano-3-methoxyphenyl)piperidine-4-carboxylate

A solution of 3-bromo-2-fluoro-6-methoxybenzonitrile (726 mg, 3.00 mmol), ethyl piperidine-4-carboxylate (1.2 mL, 7.5 mmol), and DIPEA (2.6 mL, 15 mmol) in DMSO (10 mL) is stirred at 100 °C for 18 h, followed by addition of further ethyl piperidine-4-carboxylate (1.2 mL, 7.5 mmol). After being stirred at 100 °C for 72 h, the resulting mixture is diluted with H₂O and purified by preparative HPLC (XBridge C18, acetonitrile/water gradient containing 0.1% NH₃) to yield the title compound.

$C_{16}H_{19}BrN_2O_3$ (M= 367.2 g/mol)
ESI-MS: 367 [M+H]⁺
Rt (HPLC): 1.13 min (Method E)

Ethyl 1-[2-cyano-6-(6-fluoropyridin-3-yl)-3-methoxyphenyl]piperidine-4-carboxylate

A solution of ethyl 1-(6-bromo-2-cyano-3-methoxyphenyl)piperidine-4-carboxylate (310 mg, 0.84 mmol), 2-fluoropyridine-5-boronic acid pinacol ester (CAS: 329214-79-1) (297 mg, 1.3 mmol), XPhos Pd G3 (40 mg, 0.08 mmol), and 2 M aqueous solution of potassium phosphate (1.3 mL, 2.5 mmol) in 1,4-dioxane (10 mL) is purged with argon for 2 min and

then stirred at 90 °C for 18 h. After being cooled to ambient temperature, the resulting mixture is filtered and directly subjected to preparative HPLC (XBridge C18, acetonitrile/water gradient containing 0.1% NH₃) to yield the title compound.

C₂₁H₂₂FN₃O₃ (M= 383.4 g/mol)

5 ESI-MS: 384 [M+H]⁺

Rt (HPLC): 1.07 min (Method E)

1-[2-Cyano-6-(6-fluoropyridin-3-yl)-3-methoxyphenyl]piperidine-4-carboxylic acid

To a solution of ethyl 1-[2-cyano-6-(6-fluoropyridin-3-yl)-3-methoxyphenyl]piperidine-4-
10 carboxylate (240 mg, 0.63 mmol) in EtOH (10 mL) is added 1 M aqueous solution of sodium hydroxide (0.75 mL, 0.75 mmol). After being stirred for 1 h, the reaction is treated with additional 1 M aqueous solution of sodium hydroxide (0.75 mL, 0.75 mmol) and further stirred for 1 h, followed by addition of further 1 M aqueous solution of sodium hydroxide (0.75 mL, 0.75 mmol). After being stirred for 1 h, the reaction mixture is acidified with
15 acetic acid, and diluted with H₂O/EtOAc. The aqueous phase is further extracted twice with EtOAc. The combined organic phases are dried (Na₂SO₄) and concentrated to give the title compound, which is used without further purification.

C₁₉H₁₈FN₃O₃ (M= 355.4 g/mol)

ESI-MS: 356 [M+H]⁺

20 Rt (HPLC): 0.96 min (Method C)

1-[2-Cyano-6-(6-fluoropyridin-3-yl)-3-methoxyphenyl]piperidine-4-carbohydrazide

To a stirred solution of 1-[2-cyano-6-(6-fluoropyridin-3-yl)-3-methoxyphenyl]piperidine-4-
carboxylic acid (210 mg, 0.59 mmol) in DMF (10 mL) are added hydrazine hydrate (44 mg,
25 0.89 mmol) and DIPEA (0.2 mL, 1.2 mmol). The resulting mixture is stirred for 2 min, treated with HATU (292 mg, 0.77 mmol), and further stirred for 18 h. The reaction is directly purified by preparative HPLC (XBridge C18, acetonitrile/water gradient containing 0.1% NH₃) to yield the title compound.

C₁₉H₂₀FN₅O₂ (M= 369.4 g/mol)

30 ESI-MS: 370 [M+H]⁺

Rt (HPLC): 0.81 min (Method C)

Example 20

To a solution of 1-[2-cyano-6-(6-fluoropyridin-3-yl)-3-methoxyphenyl]piperidine-4-carbohydrazide (55 mg, 0.15 mmol) in 1,4-dioxane (1 mL) is added N,N-dimethylformamide dimethyl acetal (49 μ L, 0.37 mmol). After being stirred at 50 °C for 45 min, the mixture is treated with 2 M solution of methylamine in THF (0.37 mL, 0.74 mmol) and acetic acid (43 μ L, 0.74 mmol) and further stirred at 90 °C for 18 h. Direct purification by preparative HPLC (XBridge C18, acetonitrile/water gradient containing 0.1% TFA) yields Example 20.

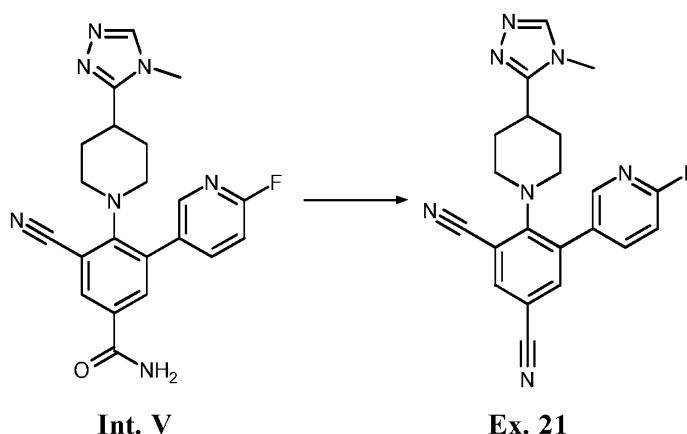
$C_{21}H_{21}FN_6O$ (M= 392.4 g/mol)

ESI-MS: 393 [M+H]⁺

Rt (HPLC): 0.81 min (Method C)

¹H NMR (400 MHz, DMSO-d₆) δ = 8.98 (s, 1 H), 8.23 (d, *J*=2.4 Hz, 1 H), 8.00 (td, *J*=8.2, 2.4 Hz, 1 H), 7.49 (d, *J*=8.6 Hz, 1 H), 7.28 (dd, *J*=8.5, 2.7 Hz, 1 H), 7.01 (d, *J*=8.7 Hz, 1 H), 3.94 (s, 3 H), 3.72 (s, 3 H), 3.15 - 3.25 (m, 2 H), 2.92 - 3.09 (m, 3 H), 1.78 - 1.87 (m, 2 H), 1.57 - 1.73 (m, 2 H)

Synthesis of Example 21



Example 21

Intermediate V (18 mg, 44 μ mol) is added to pyridine (0.4 mL) and phosphoroxchloride (4.1 μ L, 44 μ mol) is added. The resulting reaction mixture is stirred at 60 °C for 1 h. After cooling to ambient temperature, it is concentrated and the residue is purified by column chromatography (SiO₂, EtOAc/MeOH gradient) and preparative HPLC (XBridge C18, acetonitrile/water gradient containing 0.1% NH₃) to yield the desired product.

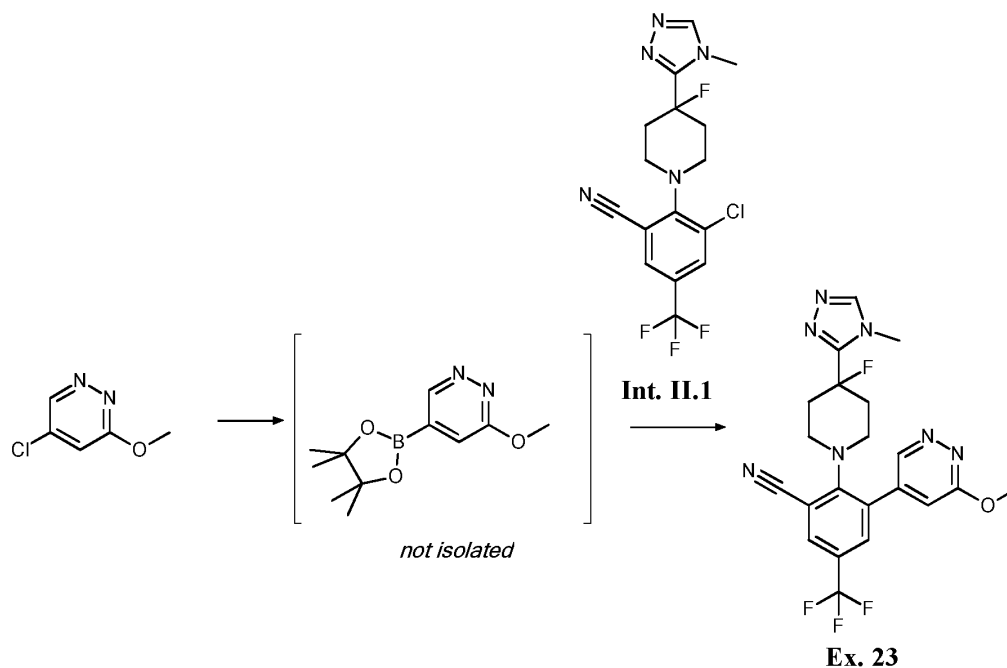
$C_{21}H_{18}FN_7$ (M=387.4 g/mol)

ESI-MS: 388 [M+H]⁺

Rt (HPLC): 0.60 min (Method F)

^1H NMR (400 MHz, DMSO- d_6) δ = 8.37 (d, J =2.0 Hz, 1 H), 8.32 (d, J =2.4 Hz, 1 H), 8.31 (s, 1 H), 8.08 (td, J =8.2, 2.5 Hz, 1 H), 7.97 (d, J =2.2 Hz, 1 H), 7.35 (dd, J =8.5, 2.7 Hz, 1 H), 3.58 (s, 3 H), 3.32 - 3.38 (m, 2 H), 2.88 - 3.01 (m, 3 H), 1.63 - 1.84 (m, 4 H)

5 Example 23



5-Chloro-3-methoxypyridazine (34.6 mg, 0.23 mmol), potassium acetate (30.4 mg, 0.31 mmol) and bis(pinacolato)diboron (58.9 mg, 0.23 mmol) are suspended in 1,4-dioxane (2 mL), and the resulting mixture is purged with argon for 15 min. [1,1'-Bis-(diphenylphosphino)-ferrocen]-dichloro-palladium(II) dichloride DCM complex (Pd(dppf)Cl₂*CH₂Cl₂, CAS: 95464-05-4) (12.6 mg, 0.015 mmol) is added. The reaction mixture is heated to 100 °C and stirred for 4 h. After being cooled to ambient temperature, intermediate II.1 (60.0 mg, 0.15 mmol), Na₂CO₃ solution (2 M in H₂O, 232 μ L, 0.46 mmol), and (Pd(dppf)Cl₂*CH₂Cl₂, CAS: 95464-05-4) (12.6 mg, 0.015 mmol) are added. The mixture is purged again with argon for 3 min and heated to and stirred at 100 °C for 4 h. After being cooled to ambient temperature, the reaction is diluted with a mixture of water/ACN, acidified with TFA, filtered and purified by preparative HPLC (Sunfire C18, ACN/water gradient containing 0.1% TFA) to yield the desired compound.

C₂₁H₁₉F₄N₇O (M=461.4 g/mol)

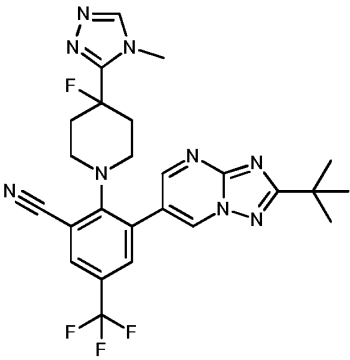
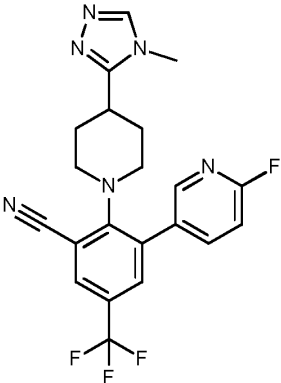
ESI-MS: 462 [M+H]⁺

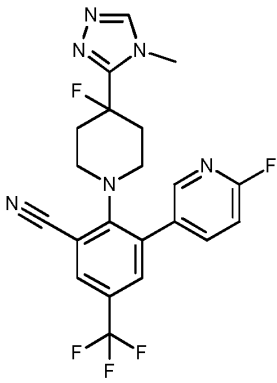
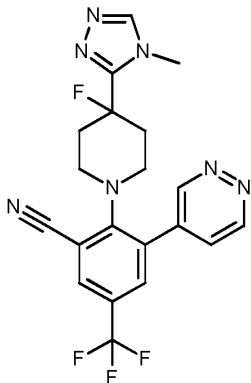
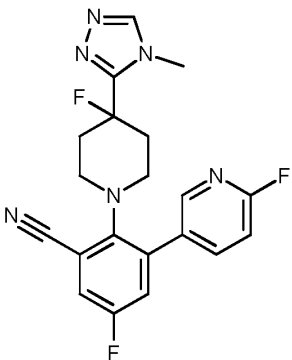
Rt (HPLC): 0.87 min (Method C)

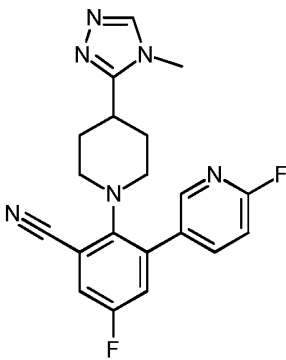
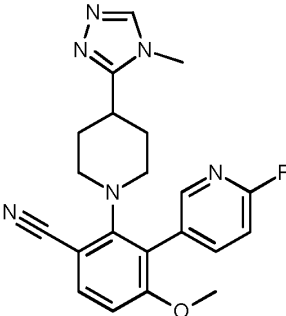
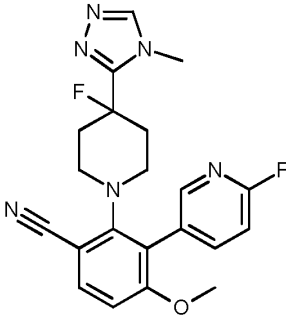
¹H NMR (400 MHz, DMSO-d₆) δ = 9.02 (d, *J* = 1.6 Hz, 1H), 8.56 (s, 1H), 8.33 (d, *J* = 1.8 Hz, 1H), 7.98 (d, *J* = 2.0 Hz, 1H), 7.41 (d, *J* = 1.8 Hz, 1H), 4.09 (s, 3H), 3.74 (d, *J* = 1.1 Hz, 3H), 3.32 - 3.16 (m, 4H), 2.26 - 2.08 (m, 4H)

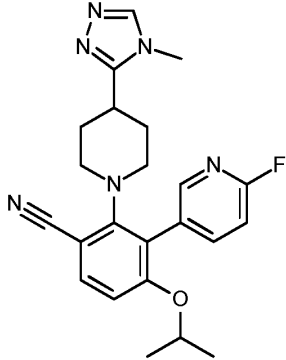
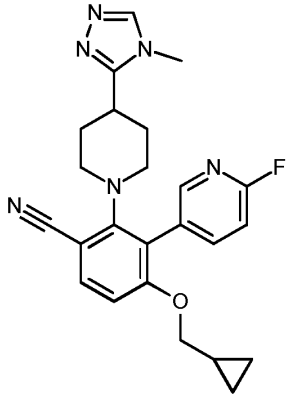
5

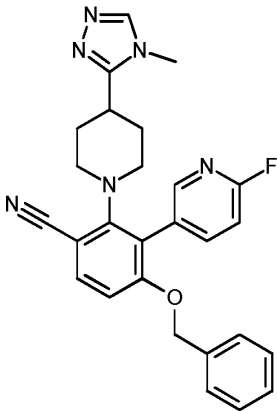
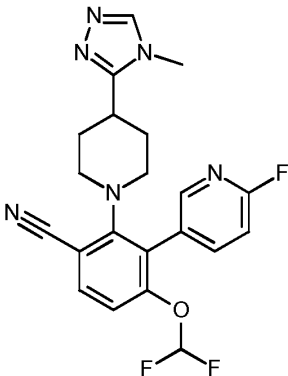
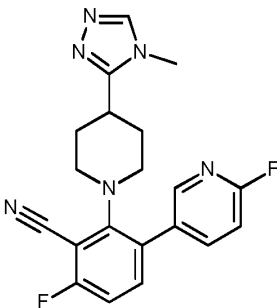
Analytical data of synthesized examples

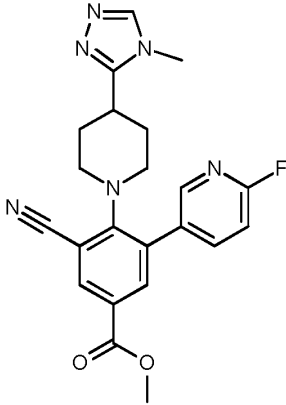
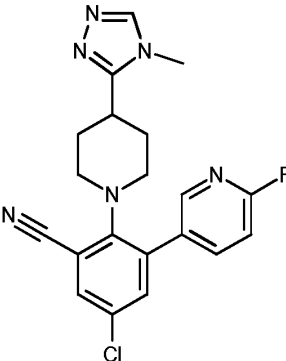
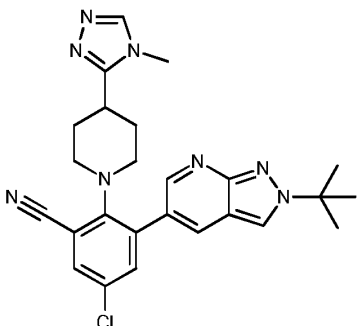
ex- am- ple	Structure	Molecular Formula (MW) ESI-MS HPLC retention time (method)	¹ H NMR (400 MHz, DMSO-d ₆): δ in ppm
2		C ₂₅ H ₂₅ F ₄ N ₉ (M= 527.5 g/mol) ESI-MS: 528 [M+H] ⁺ Rt (HPLC): 0.60 min (Method A)	9.53 (d, <i>J</i> =2.3 Hz, 1 H), 8.95 (d, <i>J</i> =2.3 Hz, 1 H), 8.47 (s, 1 H), 8.30 - 8.34 (m, 1 H), 8.11 (d, <i>J</i> =1.9 Hz, 1 H), 3.71 (d, <i>J</i> =1.4 Hz, 3 H), 3.30 - 3.40 (m, 4 H), 2.07 - 2.25 (m, 4 H), 1.44 (s, 9 H)
3		C ₂₁ H ₁₈ F ₄ N ₆ (M= 430.4 g/mol) ESI-MS: 431 [M+H] ⁺ Rt (HPLC): 0.51 min (Method A)	8.91 (s, 1 H), 8.34 (d, <i>J</i> =2.3 Hz, 1 H), 8.24 (d, <i>J</i> =1.9 Hz, 1 H), 8.11 (td, <i>J</i> =8.2, 2.5 Hz, 1 H), 7.85 (d, <i>J</i> =2.0 Hz, 1 H), 7.34 (dd, <i>J</i> =8.4, 2.7 Hz, 1 H), 3.70 (s, 3 H), 3.29 - 3.37 (m, 2 H), 3.08 (tt, <i>J</i> =11.6, 3.3 Hz, 1 H), 2.96 (br t, <i>J</i> =11.5 Hz, 2 H), 1.80 - 1.88 (m, 2 H), 1.67 (qd, <i>J</i> =11.9, 3.4 Hz, 2 H)

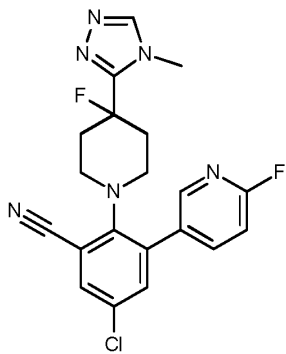
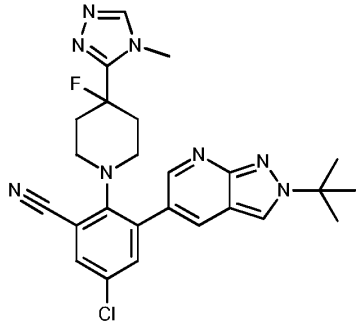
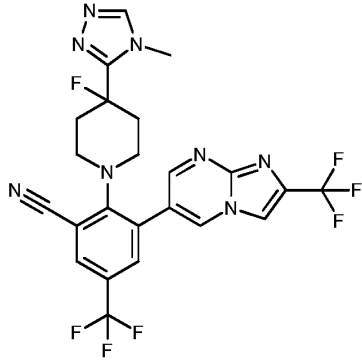
4		$C_{21}H_{17}F_5N_6$ (M= 448.4 g/mol) ESI-MS: 449 [M+H]⁺ Rt (HPLC): 0.58 min (Method A)	8.47 (s, 1 H), 8.36 (d, $J=2.3$ Hz, 1 H), 8.27 (d, $J=1.8$ Hz, 1 H), 8.13 (td, $J=8.2, 2.4$ Hz, 1 H), 7.88 (d, $J=2.2$ Hz, 1 H), 7.34 (dd, $J=8.5, 2.7$ Hz, 1 H), 3.72 (d, $J=1.5$ Hz, 3 H), 3.11 - 3.26 (m, 4 H), 2.09 - 2.24 (m, 4 H)
5		$C_{20}H_{17}F_4N_7$ (M= 431.4 g/mol) ESI-MS: 432 [M+H]⁺ Rt (HPLC): 0.88 min (Method G)	9.37 - 9.41 (m, 2 H), 8.55 (s, 1 H), 8.34 (dd, $J=2.3, 0.6$ Hz, 1 H), 7.99 (dd, $J=1.9, 0.4$ Hz, 1 H), 7.86 (dd, $J=5.3, 2.4$ Hz, 1 H), 3.73 (d, $J=1.6$ Hz, 3 H), 3.18 - 3.29 (m, 4 H), 2.04 - 2.24 (m, 4 H)
6		$C_{20}H_{17}F_3N_6$ (M= 398.4 g/mol) ESI-MS: 399 [M+H]⁺ Rt (HPLC): 0.83 min (Method B)	8.47 (s, 1H), 8.33 (d, $J=2.4$ Hz, 1H), 8.10 (dt, $J=2.5, 8.2$ Hz, 1H), 7.84 (dd, $J=3.1, 8.0$ Hz, 1H), 7.60 (dd, $J=3.1, 8.9$ Hz, 1H), 7.32 (dd, $J=2.7, 8.5$ Hz, 1H), 3.72 (d, $J=1.5$ Hz, 3H), 3.19 (br s, 2H), 3.10 - 3.01 (m, 2H), 2.19 - 1.98 (m, 4H)

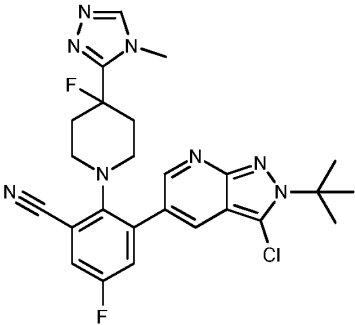
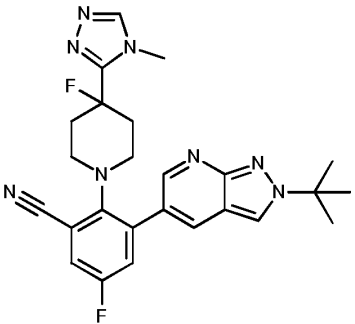
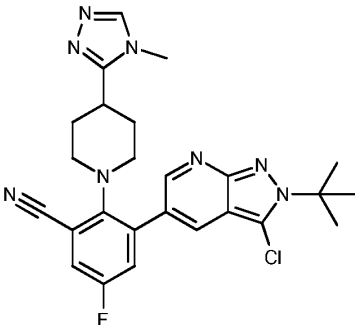
7		$C_{20}H_{18}F_2N_6$ (M= 380.4 g/mol) ESI-MS: 381 [M+H] ⁺ Rt (HPLC): 0.74 min (Method C)	8.31 (d, $J=2.3$ Hz, 1 H), 8.29 (s, 1 H), 8.08 (td, $J=8.2, 2.4$ Hz, 1 H), 7.81 (dd, $J=8.0, 3.1$ Hz, 1 H), 7.57 (dd, $J=8.9, 3.1$ Hz, 1 H), 7.32 (dd, $J=8.4, 2.7$ Hz, 1 H), 3.57 (s, 3 H), 3.09 - 3.16 (m, 2 H), 2.90 - 3.06 (m, 2 H), 2.82 (s, 1 H), 1.70 - 1.80 (m, 2 H), 1.51 - 1.69 (m, 2 H)
8		$C_{21}H_{21}FN_6O$ (M= 392.4 g/mol) ESI-MS: 393 [M+H] ⁺ Rt (HPLC): 0.43 min (Method A)	8.28 (s, 1 H), 8.10 (d, $J=2.4$ Hz, 1 H), 7.90 (td, $J=8.2, 2.5$ Hz, 1 H), 7.79 (d, $J=8.7$ Hz, 1 H), 7.27 (dd, $J=8.4, 2.7$ Hz, 1 H), 7.02 (d, $J=8.9$ Hz, 1 H), 3.75 (s, 3 H), 3.55 (s, 3 H), 3.09 - 3.18 (m, 2 H), 2.70 - 2.92 (m, 3 H), 1.66 - 1.75 (m, 2 H), 1.44 - 1.62 (m, 2 H)
9		$C_{21}H_{20}F_2N_6O$ (M= 410.4 g/mol) ESI-MS: 411 [M+H] ⁺ Rt (HPLC): 0.53 min (Method D)	8.45 (s, 1 H), 8.13 (d, $J=2.4$ Hz, 1 H), 7.93 (td, $J=8.2, 2.4$ Hz, 1 H), 7.82 (d, $J=8.7$ Hz, 1 H), 7.27 (dd, $J=8.4, 2.7$ Hz, 1 H), 7.05 (d, $J=8.7$ Hz, 1 H), 3.76 (s, 3 H), 3.70 (d, $J=1.6$ Hz, 3 H), 2.93 - 3.14 (m, 4 H), 1.88 - 2.15 (m, 4 H)

10		$C_{23}H_{25}FN_6O$ (M= 420.5 g/mol) ESI-MS: 421 [M+H]⁺ Rt (HPLC): 0.80 min (Method C)	8.94 (s, 1 H), 8.09 (d, $J=2.0$ Hz, 1 H), 7.89 (td, $J=8.2, 2.3$ Hz, 1 H), 7.74 (d, $J=8.7$ Hz, 1 H), 7.26 (dd, $J=8.4, 2.7$ Hz, 1 H), 7.03 (d, $J=8.9$ Hz, 1 H), 4.67 (spt, $J=6.0$ Hz, 1 H), 3.70 (s, 3 H), 3.15 (br d, $J=11.5$ Hz, 2 H), 2.95 (tt, $J=11.7, 3.2$ Hz, 1 H), 2.73 - 2.90 (m, 2 H), 1.71 - 1.81 (m, 2 H), 1.44 - 1.64 (m, 2 H), 1.14 (d, $J=6.0$ Hz, 6 H)
11		$C_{24}H_{25}FN_6O$ (M= 432.5 g/mol) ESI-MS: 433 [M+H]⁺ Rt (HPLC): 0.79 min (Method C)	8.99 (s, 1 H), 8.12 (d, $J=2.3$ Hz, 1 H), 7.93 (td, $J=8.2, 2.4$ Hz, 1 H), 7.75 (d, $J=8.6$ Hz, 1 H), 7.28 (dd, $J=8.5, 2.7$ Hz, 1 H), 7.00 (d, $J=8.7$ Hz, 1 H), 3.90 (d, $J=6.6$ Hz, 2 H), 3.71 (s, 3 H), 3.11 - 3.20 (m, 2 H), 2.92 - 3.04 (m, 1 H), 2.75 - 2.92 (m, 2 H), 1.73 - 1.83 (m, 2 H), 1.45 - 1.63 (m, 2 H), 0.97 - 1.11 (m, 1 H), 0.40 - 0.47 (m, 2 H), 0.14 - 0.21 (m, 2 H)

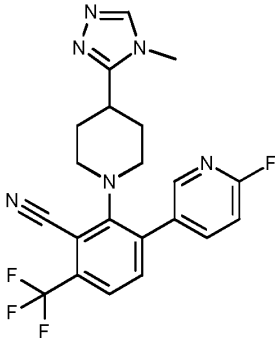
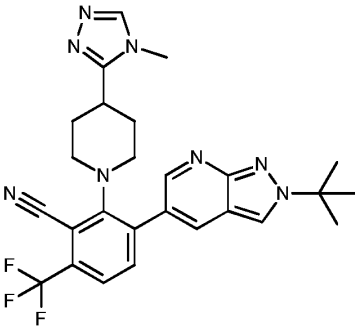
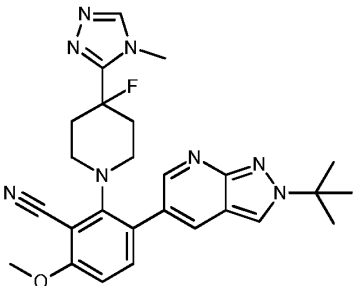
12		$C_{27}H_{25}FN_6O$ (M= 468.5 g/mol) ESI-MS: 469 [M+H]⁺ Rt (HPLC): 0.83 min (Method C)	8.92 (s, 1 H), 8.16 (d, $J=2.2$ Hz, 1 H), 7.97 (td, $J=8.2, 2.3$ Hz, 1 H), 7.78 (d, $J=8.7$ Hz, 1 H), 7.25 - 7.36 (m, 5 H), 7.19 - 7.24 (m, 2 H), 7.08 (d, $J=8.7$ Hz, 1 H), 5.17 (s, 2 H), 3.69 (s, 3 H), 3.11 - 3.24 (m, 2 H), 2.90 - 3.02 (m, 1 H), 2.77 - 2.89 (m, 1 H), 1.72 - 1.81 (m, 2 H), 1.44 - 1.63 (m, 2 H)
13		$C_{21}H_{19}F_3N_6O$ (M= 428.4 g/mol) ESI-MS: 429 [M+H]⁺ Rt (HPLC): 0.75 min (Method C)	8.99 (s, 1 H), 8.18 (d, $J=2.3$ Hz, 1 H), 7.99 (td, $J=8.2, 2.4$ Hz, 1 H), 7.92 (d, $J=8.7$ Hz, 1 H), 7.34 (dd, $J=8.5, 2.7$ Hz, 1 H), 7.18 (d, $J=8.7$ Hz, 1 H), 7.26 (t, $J=72.9$ Hz, 1 H), 3.71 (s, 3 H), 3.14 - 3.30 (m, 2 H), 3.00 (tt, $J=11.5, 3.2$ Hz, 1 H), 2.74 - 2.94 (m, 2 H), 1.78 (br d, $J=11.5$ Hz, 2 H), 1.45 - 1.63 (m, 2 H)
14		$C_{20}H_{18}F_2N_6$ (M= 380.4 g/mol) ESI-MS: 381 [M+H]⁺ Rt (HPLC): 0.81 min (Method C)	9.05 (s, 1 H), 8.27 (d, $J=2.4$ Hz, 1 H), 8.04 (td, $J=8.2, 2.5$ Hz, 1 H), 7.60 (dd, $J=8.7, 6.9$ Hz, 1 H), 7.31 (dd, $J=8.5, 2.7$ Hz, 1 H), 7.25 (t, $J=8.6$ Hz, 1 H), 3.73 (s, 3 H), 3.23 - 3.32 (m, 2 H), 3.09 (tt, $J=11.6, 3.4$ Hz, 1 H), 2.98 (br t,

			<i>J</i> =11.6 Hz, 2 H), 1.80 - 1.90 (m, 2 H), 1.63 (qd, <i>J</i> =11.9, 3.3 Hz, 2 H)
15		$C_{22}H_{21}FN_6O_2$ (M= 420.4 g/mol) ESI-MS: 421 [M+H] ⁺ Rt (HPLC): 0.73 min (Method C)	9.03 (s, 1 H), 8.32 (d, <i>J</i> =2.5 Hz, 1 H), 8.25 (d, <i>J</i> =2.2 Hz, 1 H), 8.10 (td, <i>J</i> =8.2, 2.5 Hz, 1 H), 7.93 (d, <i>J</i> =2.2 Hz, 1 H), 7.34 (dd, <i>J</i> =8.4, 2.6 Hz, 1 H), 3.86 (s, 3 H), 3.73 (s, 3 H), 3.30 - 3.39 (m, 2 H), 3.08 - 3.17 (m, 1 H), 2.97 (s, 2 H), 1.81 - 1.90 (m, 2 H), 1.68 (qd, <i>J</i> =12.1, 3.7 Hz, 3 H)
16		$C_{20}H_{18}ClFN_6$ (M= 396.8 g/mol) ESI-MS: 397 [M+H] ⁺ Rt (HPLC): 0.73 min (Method H)	8.33 (s, 1 H), 8.30 (d, <i>J</i> =2.4 Hz, 1 H), 8.08 (td, <i>J</i> =8.2, 2.5 Hz, 1 H), 7.95 (d, <i>J</i> =2.7 Hz, 1 H), 7.66 (d, <i>J</i> =2.7 Hz, 1 H), 7.32 (dd, <i>J</i> =8.4, 2.6 Hz, 1 H), 3.58 (s, 3 H), 3.14 - 3.21 (m, 2 H), 2.94 (br t, <i>J</i> =11.1 Hz, 2 H), 2.85 (tt, <i>J</i> =11.5, 3.8 Hz, 1 H), 1.71 - 1.79 (m, 2 H), 1.56 - 1.69 (m, 2 H)
17		$C_{25}H_{27}ClN_8$ (M= 475.0 g/mol) ESI-MS: 476 [M+H] ⁺ Rt (HPLC): 0.78 min (Method H)	8.58 - 8.61 (m, 2 H), 8.34 (s, 1 H), 8.20 (d, <i>J</i> =2.3 Hz, 1 H), 7.93 (d, <i>J</i> =2.7 Hz, 1 H), 7.63 (d, <i>J</i> =2.7 Hz, 1 H), 3.55 (s, 3 H), 3.21 - 3.29 (m, 2 H), 2.93 (br t, <i>J</i> =10.6 Hz, 1 H), 2.82 (tt,

			$J=11.1, 3.9 \text{ Hz, 1 H)}$, 1.61 - 1.78 (m, 13 H)
18		$\text{C}_{20}\text{H}_{17}\text{ClF}_2\text{N}_6$ (M= 414.8 g/mol) ESI-MS: 415 [M+H] ⁺ Rt (HPLC): 0.77 min (Method H)	8.47 (s, 1 H), 8.33 (d, $J=2.4 \text{ Hz, 1 H)}$, 8.10 (td, $J=8.2, 2.5 \text{ Hz, 1 H)}$, 7.99 (d, $J=2.7 \text{ Hz, 1 H)}$, 7.69 (d, $J=2.5 \text{ Hz, 1 H)}$, 7.32 (dd, $J=8.5, 2.7 \text{ Hz, 1 H)}$, 3.71 (d, $J=1.6 \text{ Hz, 3 H)}$, 3.04 - 3.21 (m, 4 H), 2.02 - 2.20 (m, 4 H)
19		$\text{C}_{25}\text{H}_{26}\text{ClFN}_8$ (M= 493.0 g/mol) ESI-MS: 494 [M+H] ⁺ Rt (HPLC): 0.80 min (Method H)	8.63 (d, $J=2.2 \text{ Hz, 1 H)}$, 8.61 (s, 1 H), 8.46 (s, 1 H), 8.22 (d, $J=2.3 \text{ Hz, 1 H)}$, 7.97 (d, $J=2.7 \text{ Hz, 1 H)}$, 7.67 (d, $J=2.5 \text{ Hz, 1 H)}$, 3.68 (d, $J=1.5 \text{ Hz, 3 H)}$, 3.10 - 3.21 (m, 4 H), 2.07 - 2.23 (m, 4 H), 1.71 (s, 9 H)
22		$\text{C}_{23}\text{H}_{17}\text{F}_7\text{N}_8$ (M= 538.4 g/mol) ESI-MS: 539 [M+H] ⁺ Rt (HPLC): 0.78 min (Method H)	9.18 (d, $J=2.4 \text{ Hz, 1 H)}$, 8.88 (d, $J=2.4 \text{ Hz, 1 H)}$, 8.56 (d, $J=1.0 \text{ Hz, 1 H)}$, 8.47 (s, 1 H), 8.33 (d, $J=1.6 \text{ Hz, 1 H)}$, 8.05 (d, $J=1.9 \text{ Hz, 1 H)}$, 3.70 (d, $J=1.5 \text{ Hz, 3 H)}$, 3.34 - 3.39 (m, 4 H), 2.26 - 2.13 (m, 4 H)

24		$C_{25}H_{25}ClF_2N_8$ (M= 511.0 g/mol) ESI-MS: 511 [M+H] ⁺ Rt (HPLC): 0.99 min (Method E)	8.74 (s, 1 H), 8.54 (s, 1 H), 8.15 (d, <i>J</i> = 2.2 Hz, 1 H), 7.83 (dd, <i>J</i> = 3.0, 8.0 Hz, 1 H), 7.66 (dd, <i>J</i> = 2.9, 8.9 Hz, 1 H), 3.70 (s, 3 H), 3.38 - 3.03 (m, 4 H), 2.20 - 1.96 (m, 4 H), 1.83 (s, 9 H)
25		$C_{25}H_{26}F_2N_8$ (M= 476.5 g/mol) ESI-MS: 477 [M+H] ⁺ Rt (HPLC): 0.70 min (Method J)	8.69 (s, 1 H), 8.66 (s, 1 H), 8.61 (s, 1 H), 8.27 (d, <i>J</i> = 2.2 Hz, 1 H), 7.82 (dd, <i>J</i> = 3.0, 8.0 Hz, 1 H), 7.58 (dd, <i>J</i> = 3.0, 8.9 Hz, 1 H), 3.71 (d, <i>J</i> = 1.4 Hz, 3 H), 3.29 - 3.04 (m, 4 H), 2.20 - 1.99 (m, 4 H), 1.71 (s, 9 H)
26		$C_{25}H_{26}ClFN_8$ (M= 493.0 g/mol) ESI-MS: 493 [M+H] ⁺ Rt (HPLC): 0.95 min (Method E)	8.71 (s, 1 H), 8.59 (s, 1 H), 8.13 (d, <i>J</i> = 2.2 Hz, 1 H), 7.80 (dd, <i>J</i> = 3.1, 8.0 Hz, 1 H), 7.63 (dd, <i>J</i> = 3.0, 8.9 Hz, 1 H), 3.62 (s, 3 H), 3.21 (br d, <i>J</i> = 11.5 Hz, 2 H), 3.13 - 2.95 (m, 2 H), 2.94 - 2.83 (m, 1 H), 1.84 (s, 9 H), 1.77 (br d, <i>J</i> = 10.5 Hz, 2 H), 1.69 - 1.51 (m, 2 H)

27		$C_{25}H_{26}ClFN_8$ (M= 493.0 g/mol) ESI-MS: 493/495 [M+H] ⁺ Rt (HPLC): 0.93 min (Method C)	8.64 - 8.61 (m, 2 H), 8.55 (s, 1 H), 8.20 (d, <i>J</i> = 2.2 Hz, 1 H), 7.60 - 7.57 (m, 1 H), 7.52 - 7.49 (m, 1 H), 3.70 (d, <i>J</i> = 1.6 Hz, 3 H), 3.25 - 3.07 (m, 4 H), 2.26 - 2.07 (m, 4 H), 1.71 (s, 9 H)
28		$C_{20}H_{17}ClF_2N_6$ (M= 414.8 g/mol) ESI-MS: 415/417 [M+H] ⁺ Rt (HPLC): 1.42 min (Method N)	
29		$C_{21}H_{17}F_5N_6$ (M= 448.4 g/mol) ESI-MS: 449 [M+H] ⁺ Rt (HPLC): 0.77 min (Method G)	8.47 (s, 1 H), 8.34 (d, <i>J</i> = 2.4 Hz, 1 H), 8.10 (dt, <i>J</i> = 2.5, 8.2 Hz, 1 H), 7.80 - 7.70 (m, 2 H), 7.37 (dd, <i>J</i> = 2.6, 8.4 Hz, 1 H), 3.72 (d, <i>J</i> = 1.6 Hz, 3 H), 3.23 - 3.08 (m, 4 H), 2.17 (br d, <i>J</i> = 17.7 Hz, 4 H)
30		$C_{26}H_{26}F_4N_8$ (M= 526.5 g/mol) ESI-MS: 527 [M+H] ⁺ Rt (HPLC): 0.75 min (Method K)	8.69 - 8.62 (m, 2 H), 8.57 (s, 1 H), 8.26 (d, <i>J</i> = 2.2 Hz, 1 H), 7.79 - 7.75 (m, 1 H), 7.75 - 7.71 (m, 1 H), 3.73 - 3.67 (m, 3 H), 3.30 - 3.05 (m, 4 H), 2.31 -

			2.11 (m, 4 H), 1.72 (s, 9 H)
31		$C_{21}H_{18}F_4N_6$ (M= 430.4 g/mol) ESI-MS: 431 [M+H] ⁺ Rt (HPLC): 0.73 min (Method G)	8.33 - 8.28 (m, 2H), 8.09 (dt, $J = 2.5$, 8.2 Hz, 1H), 7.76 - 7.67 (m, 2H), 7.36 (dd, $J =$ 2.6, 8.4 Hz, 1H), 3.58 (s, 3H), 3.26 (br d, $J =$ 12.7 Hz, 2H), 3.01 - 2.80 (m, 3H), 1.82 - 1.63 (m, 4H)
32		$C_{26}H_{27}F_3N_8$ (M= 508.5 g/mol) ESI-MS: 509 [M+H] ⁺ Rt (HPLC): 0.77 min (Method F)	8.63 (s, 1H), 8.61 - 8.58 (m, 1H), 8.27 (s, 1H), 8.22 (d, $J = 2.3$ Hz, 1H), 7.76 - 7.64 (m, 2H), 3.54 (s, 3H), 3.37 - 3.29 (m, 2H), 3.00 - 2.76 (m, 3H), 1.83 - 1.67 (m, 13H)
33		$C_{26}H_{29}FN_8O$ (M= 488.6 g/mol) ESI-MS: 489 [M+H] ⁺ Rt (HPLC): 0.61 min (Method K)	8.62 - 8.59 (m, 2H), 8.53 (s, 1H), 8.15 (d, J = 2.2 Hz, 1H), 7.51 (d, $J = 8.7$ Hz, 1H), 7.03 (d, $J = 8.7$ Hz, 1H), 3.94 (s, 3H), 3.69 (d, J = 1.5 Hz, 3H), 3.16 (br s, 4H), 2.13 (br d, $J = 17.6$ Hz, 4H), 1.71 (s, 9H)

34		$C_{30}H_{37}FN_8O_2$ (M= 560.7 g/mol) ESI-MS: 561 [M+H] ⁺ Rt (HPLC): 0.88 min (Method C)	8.62 - 8.57 (m, 2H), 8.52 (s, 1H), 8.14 (d, <i>J</i> = 2.2 Hz, 1H), 7.49 (d, <i>J</i> = 8.6 Hz, 1H), 7.05 (d, <i>J</i> = 8.7 Hz, 1H), 4.28 (br t, <i>J</i> = 6.9 Hz, 2H), 3.69 (d, <i>J</i> = 1.5 Hz, 3H), 3.16 (br s, 4H), 2.13 (br d, <i>J</i> = 17.7 Hz, 4H), 1.91 (t, <i>J</i> = 6.9 Hz, 2H), 1.71 (s, 9H), 1.20 (s, 6H)
35		$C_{25}H_{23}F_4N_9$ (M= 525.5 g/mol) ESI-MS: 526 [M+H] ⁺ Rt (HPLC): 0.83 min (Method O)	9.50 (d, <i>J</i> = 2.3 Hz, 1H), 8.91 (d, <i>J</i> = 2.3 Hz, 1H), 8.53 (s, 1H), 8.32 (d, <i>J</i> = 1.8 Hz, 1H), 8.07 (d, <i>J</i> = 1.9 Hz, 1H), 3.71 (s, 3H), 3.38 - 3.24 (m, 4H), 2.23 - 2.05 (m, 4H), 1.57 (s, 3H), 1.30 - 1.25 (m, 2H), 0.99 - 0.95 (m, 2H)
36		$C_{23}H_{17}F_7N_8$ (M= 538.4 g/mol) ESI-MS: 539 [M+H] ⁺ Rt (HPLC): 0.67 min (Method D)	9.34 (s, 1H), 8.92 (d, <i>J</i> = 2.2 Hz, 1H), 8.46 - 8.43 (m, 2H), 8.29 (d, <i>J</i> = 1.8 Hz, 1H), 7.97 (d, <i>J</i> = 2.2 Hz, 1H), 3.71 - 3.67 (m, 3H), 3.31 - 3.18 (m, 4H), 2.23 - 2.05 (m, 4H)

Analytical HPLC methods**Method A**

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 B

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

5 C18_3.0 x 30 mm_1.8 µm; column temperature: 60 °C

Method C

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

Method D

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

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

Method E

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 F

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 G

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

5 Method H

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 I

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

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

Method J

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 K

time (min)	Vol.% water (incl. 0.1 % TFA)	Vol% ACN (incl. 0.1% FA)	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 L

time (min)	Vol% water (incl. 0.04% TFA)	Vol% CAN (incl. 0.02% TFA)	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_5 µm; column temperature: 40°C

Method M

time (min)	Vol% water (incl. 0.04% TFA)	Vol% CAN (incl. 0.02% TFA)	Flow [mL/min]
------------	---------------------------------	-------------------------------	------------------

0.01	95	5	1.5
0.70	5	95	1.5
1.16	5	95	1.5
1.50	95	5	
1.51	95	5	

Device description: Agilent 1200 HPLC; Analytical column: Halo C18_3.0 x 30 mm_5 µm; column temperature: 40°C

Method N

time (min)	Vol% water (incl. 0.1% TFA)	Vol% MeOH	Flow [mL/min]
0.00	95	5	1.8
0.25	95	5	1.8
1.7	0	100	1.8
1.75	0	100	2.5
1.9	0	100	2.5

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

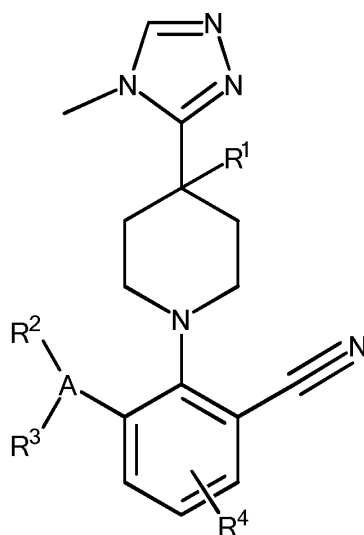
Method O

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

WHAT IS CLAIMED

1. A compound of formula (I)



(I)

wherein

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

wherein at least one of the heteroatom members is nitrogen;

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

R¹ is selected from the group **R1a**, consisting of H, C₁₋₄-alkyl and halo;

R² is selected from the group **R2a**, consisting of H, halo, hydroxy, C₁₋₆-alkyl, C₂₋₆-alkynyl, C₃₋₆-cycloalkyl, 1-methyl-C₃₋₆-cycloalkyl, F₁₋₉-fluoro-C₁₋₆-alkyl, HO-C₁₋₆-alkyl, C₁₋₆-alkyloxy, C₁₋₄-alkyl-O-H₂CH₂C-O-, C₃₋₆-cycloalkyloxy, C₃₋₆-cycloalkyl-H₂C-O-, F₁₋₉-fluoro-C₁₋₄-alkyloxy, C₁₋₆-alkyl-O-C(O)-, H₂N-C(O)- and C₁₋₆-alkyl-NH-C(O)-;

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

R⁴ is selected from the group **R4a**, consisting of halo, C₁₋₄-alkyl, C₃₋₆-cycloalkyl, -CN, C₁₋₆-alkyloxy, C₁₋₆-alkyl-O-C(O)-, F₁₋₉-fluoro-C₁₋₄-alkyl, F₁₋₉-fluoro-C₁₋₄-alkyloxy, C₃₋₆-cycloalkyloxy, C₃₋₆-cycloalkyl-H₂C-O-, benzyloxy, (HO)(H₃C)₂-C- and HO-C(H₃C)₂H₂CH₂C-O-;

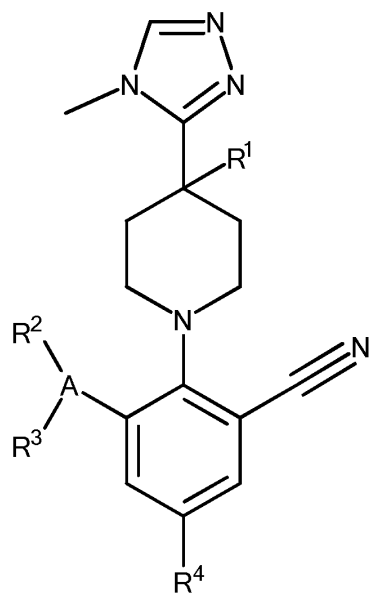
or a salt thereof, particularly a pharmaceutically acceptable salt thereof.

2. The compound of formula (I) according to claim 1, wherein **A** is selected from the group **A5** consisting of pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, [1,2,4]triazolo[1,5-a]pyrimidinyl, 2H-pyrazolo[3,4-b]pyridinyl and imidazo[1,2-a]pyrimidinyl; or a salt thereof.

3. The compound of formula (I) according to any of claims 1 to 2, wherein **R²** is **R2b**, consisting of H, halo, C₁₋₄-alkyl, C₃₋₄-cycloalkyl, F₁₋₉-fluoro-C₁₋₆-alkyl, 1-methyl-C₃₋₆-cycloalkyl, C₁₋₄-alkyloxy and C₃₋₄-cycloalkyloxy; or a salt thereof.

4. The compound of formula (I) according to any of claims 1 to 3, wherein **R⁴** is selected from the group **R4b**, consisting of halo, -CN, C₁₋₄-alkyl, C₃₋₆-cycloalkyl, C₁₋₆-alkyloxy, C₁₋₆-alkyl-O-C(O)-, F₁₋₉-fluoro-C₁₋₄-alkyl, F₁₋₉-fluoro-C₁₋₄-alkyloxy, C₃₋₆-cycloalkyloxy, C₃₋₆-cycloalkyl-H₂C-O-, benzyloxy, (HO)(H₃C)₂-C- and HO-C(H₃C)₂H₂CH₂C-O-; or a salt thereof.

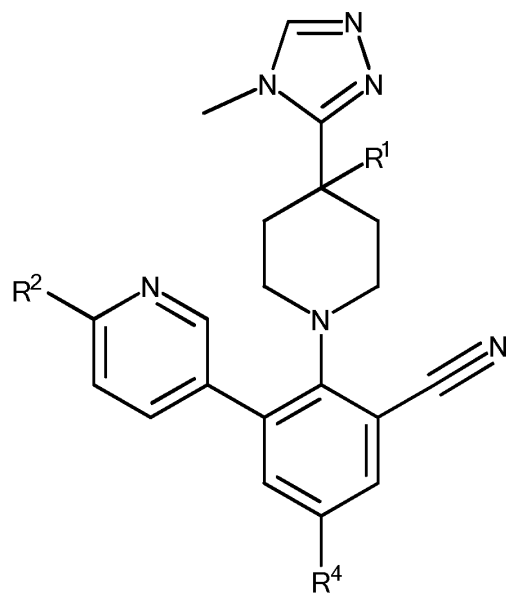
5. The compound of formula (I) according to any of claims 1 to 4 having formula (1-c)



(I-c)

or a salt thereof.

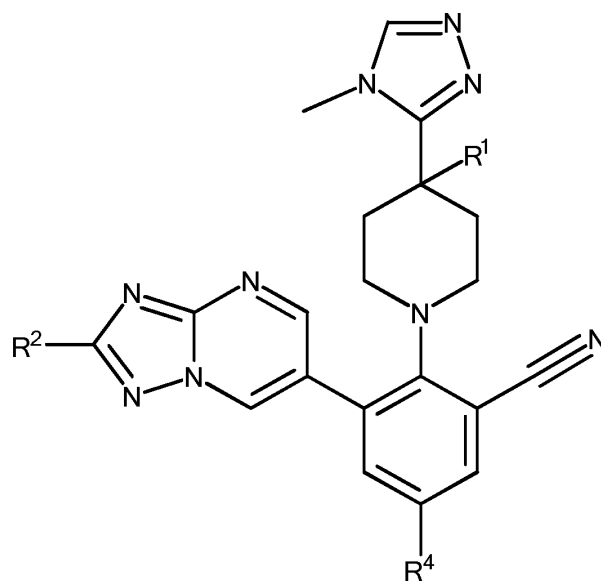
- 5 6. The compound of formula (I) according to any of claims 1 to 4 having formula (I-f)



(I-f)

or a salt thereof.

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

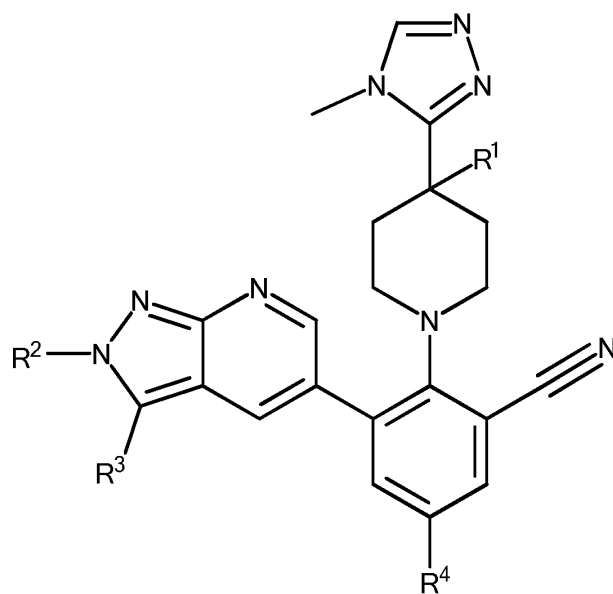


(I-j)

or a salt thereof.

5

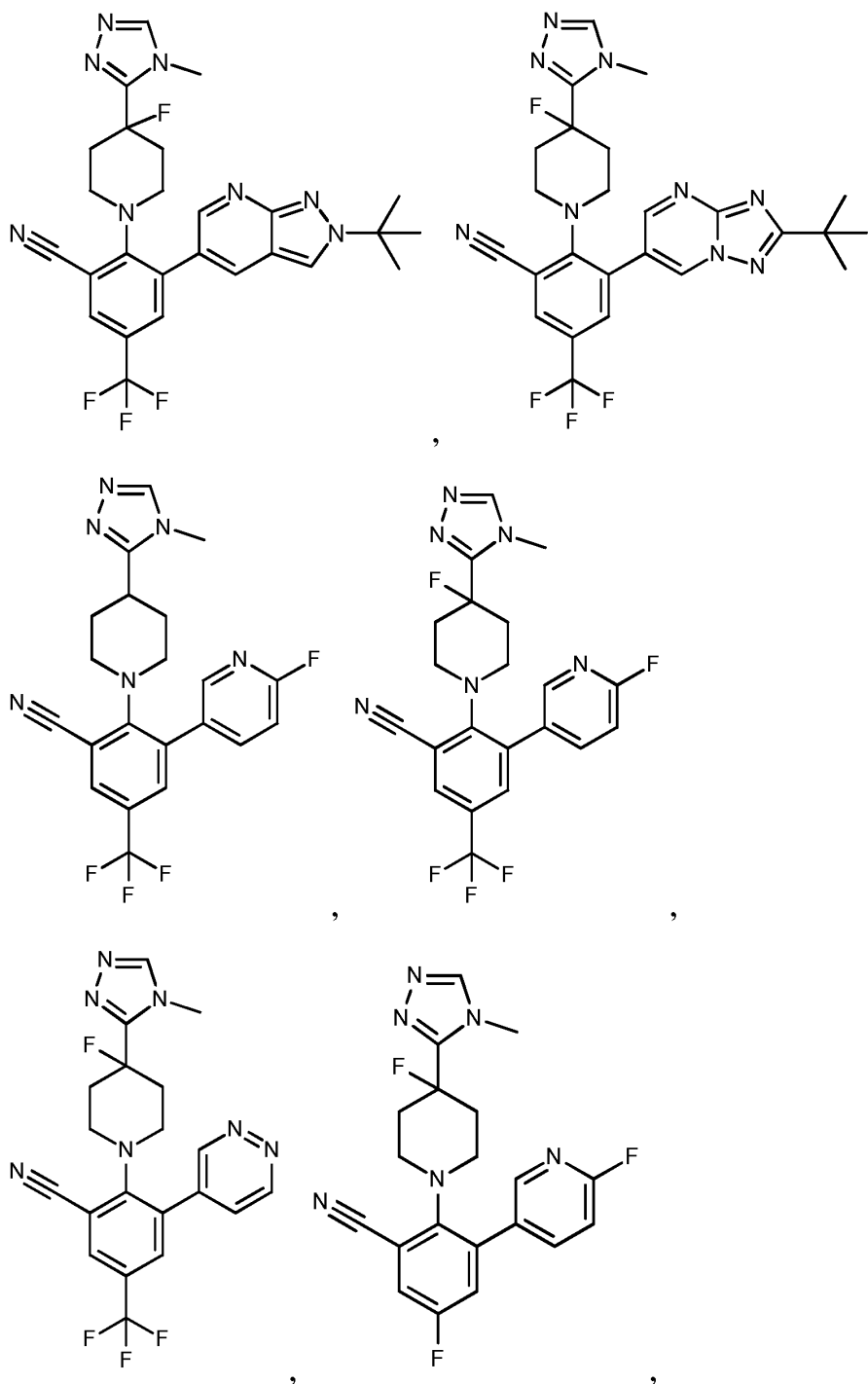
8. The compound of formula (I) according to any of claims 1 to 4 having formula (1-n)

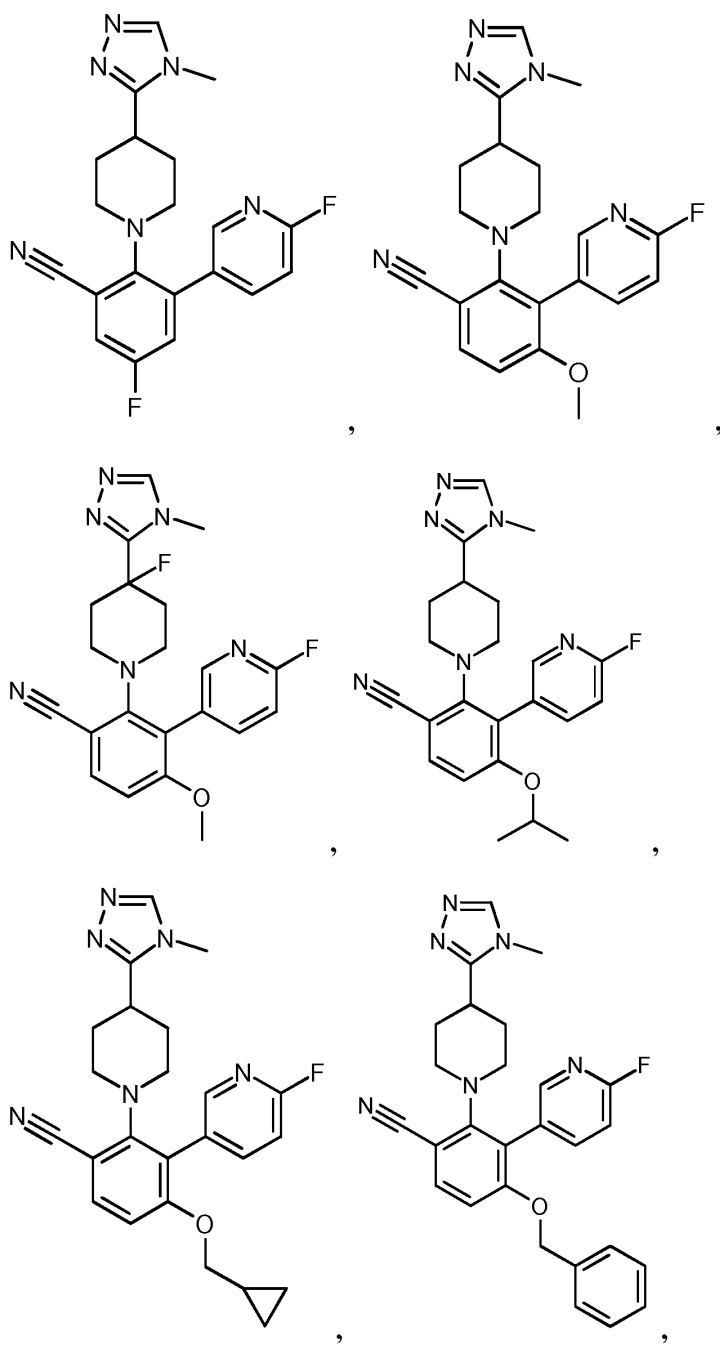


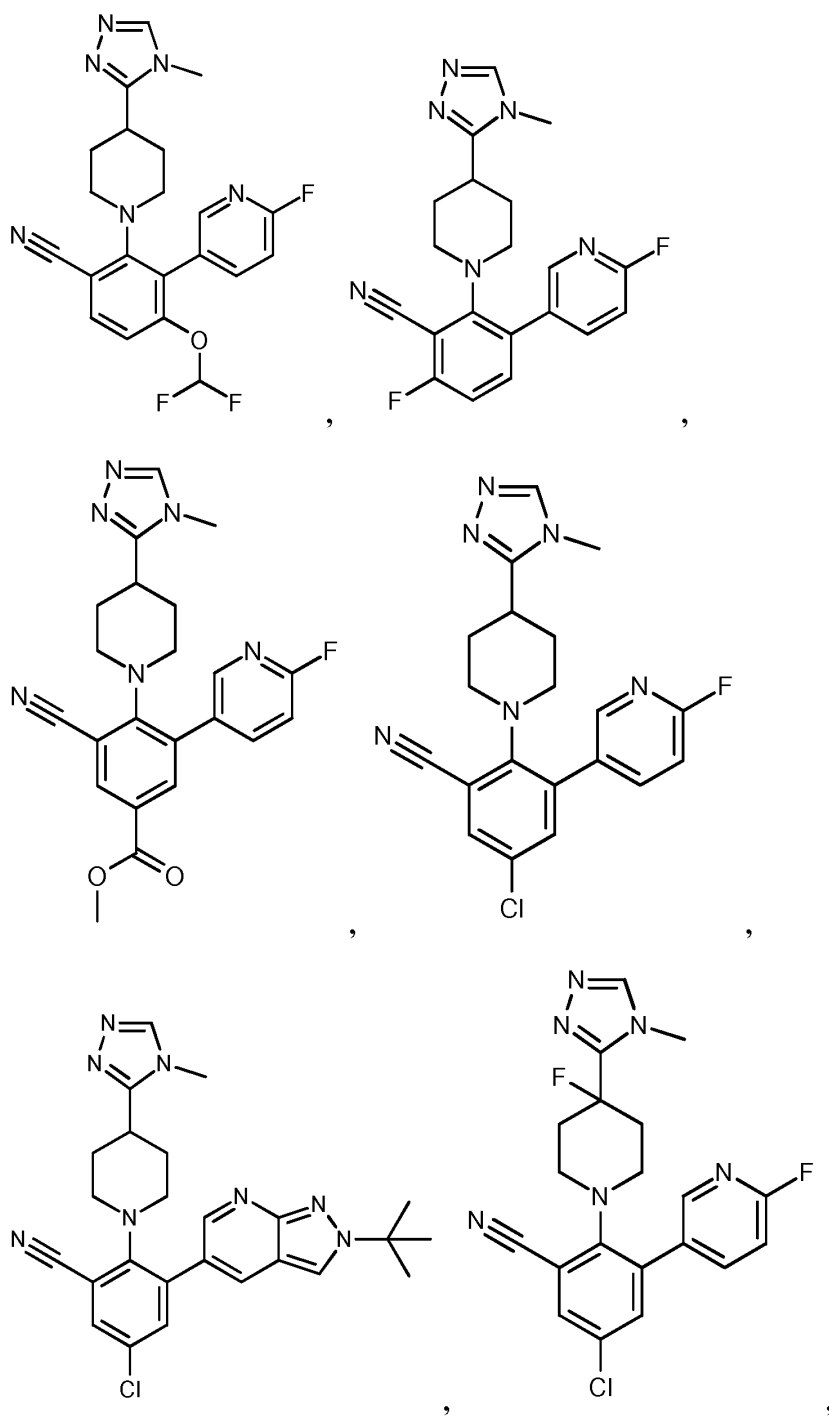
(I-n)

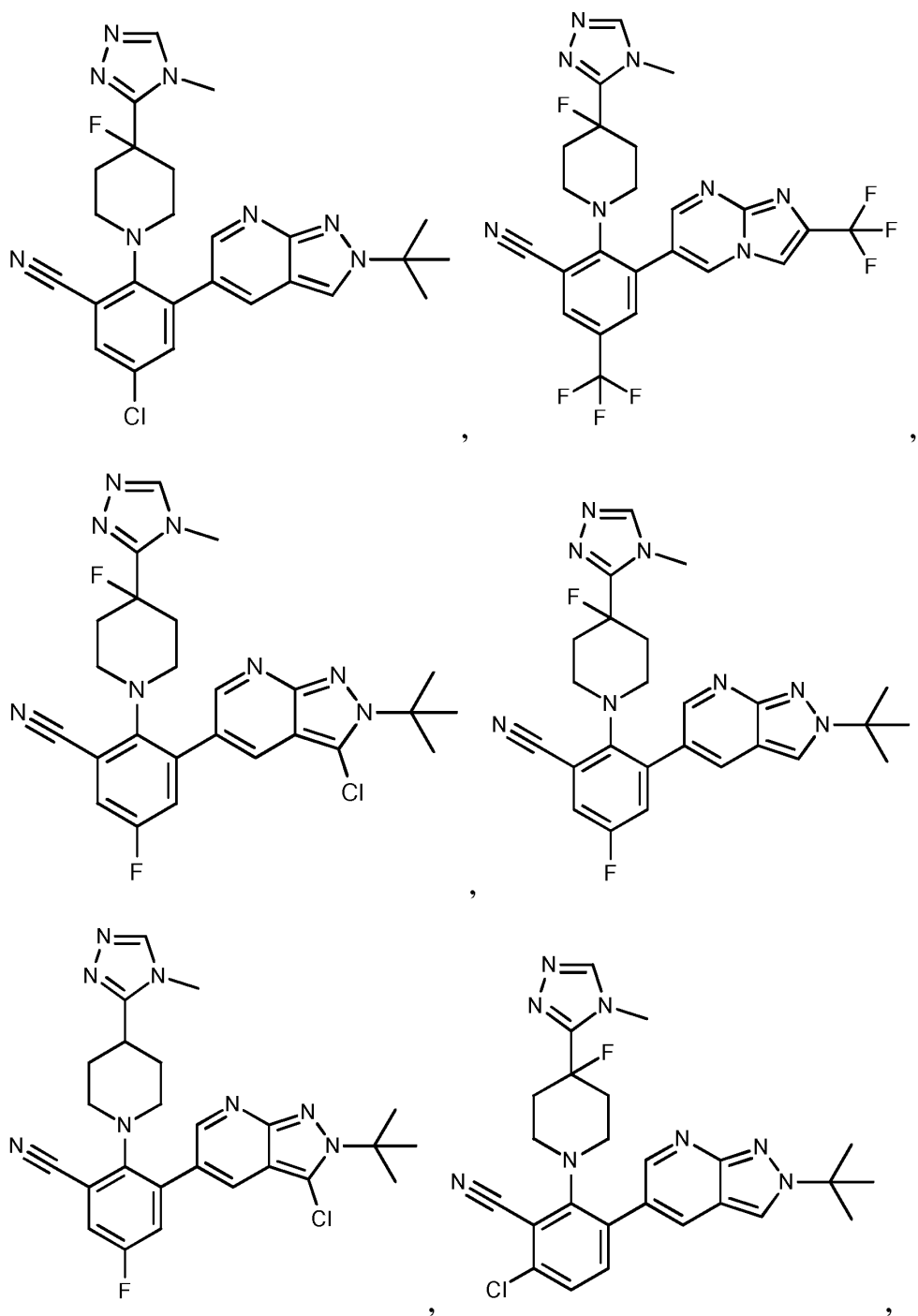
or a salt thereof.

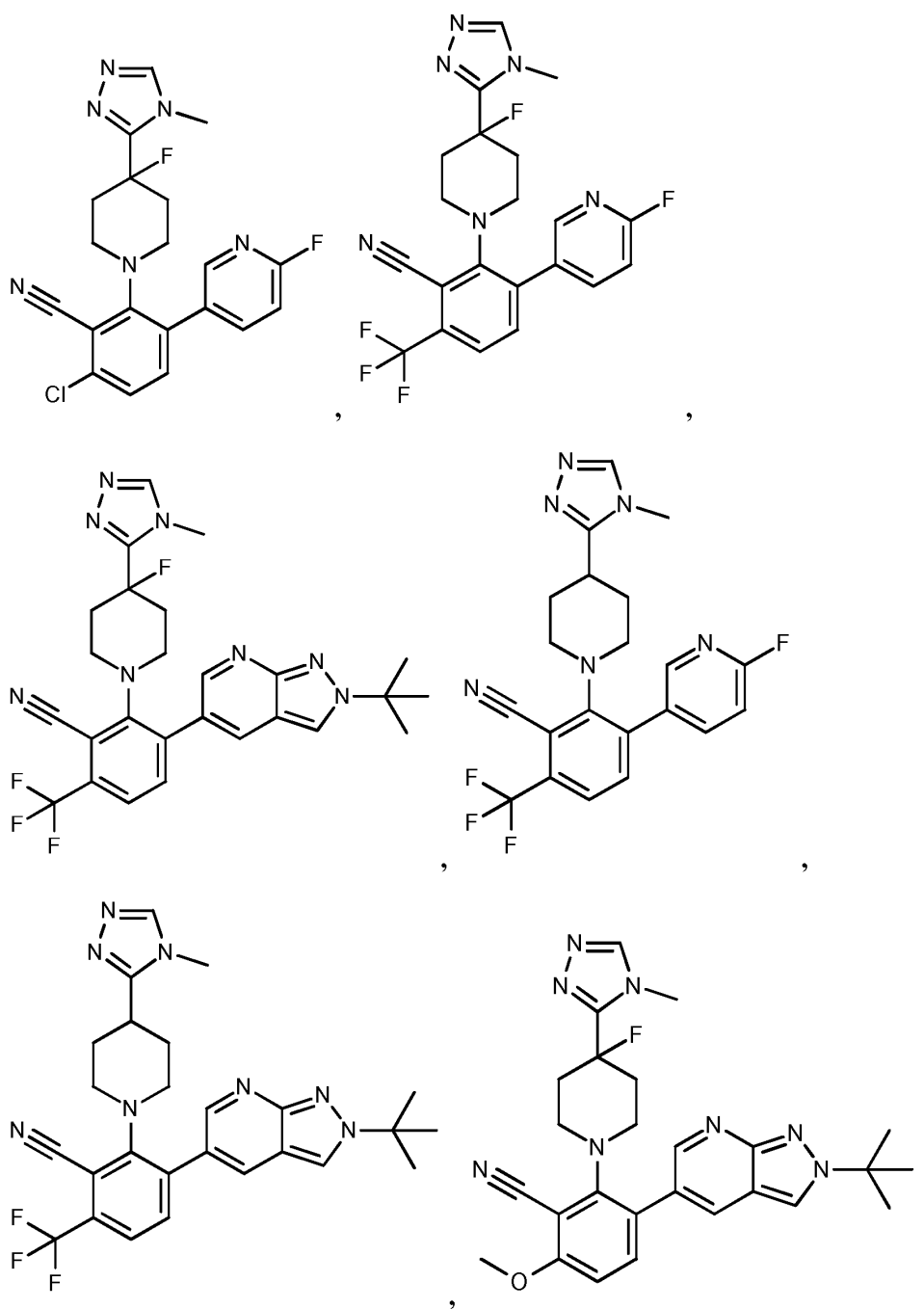
9. The compound of formula (I) according to claim 1, selected from the group consisting of

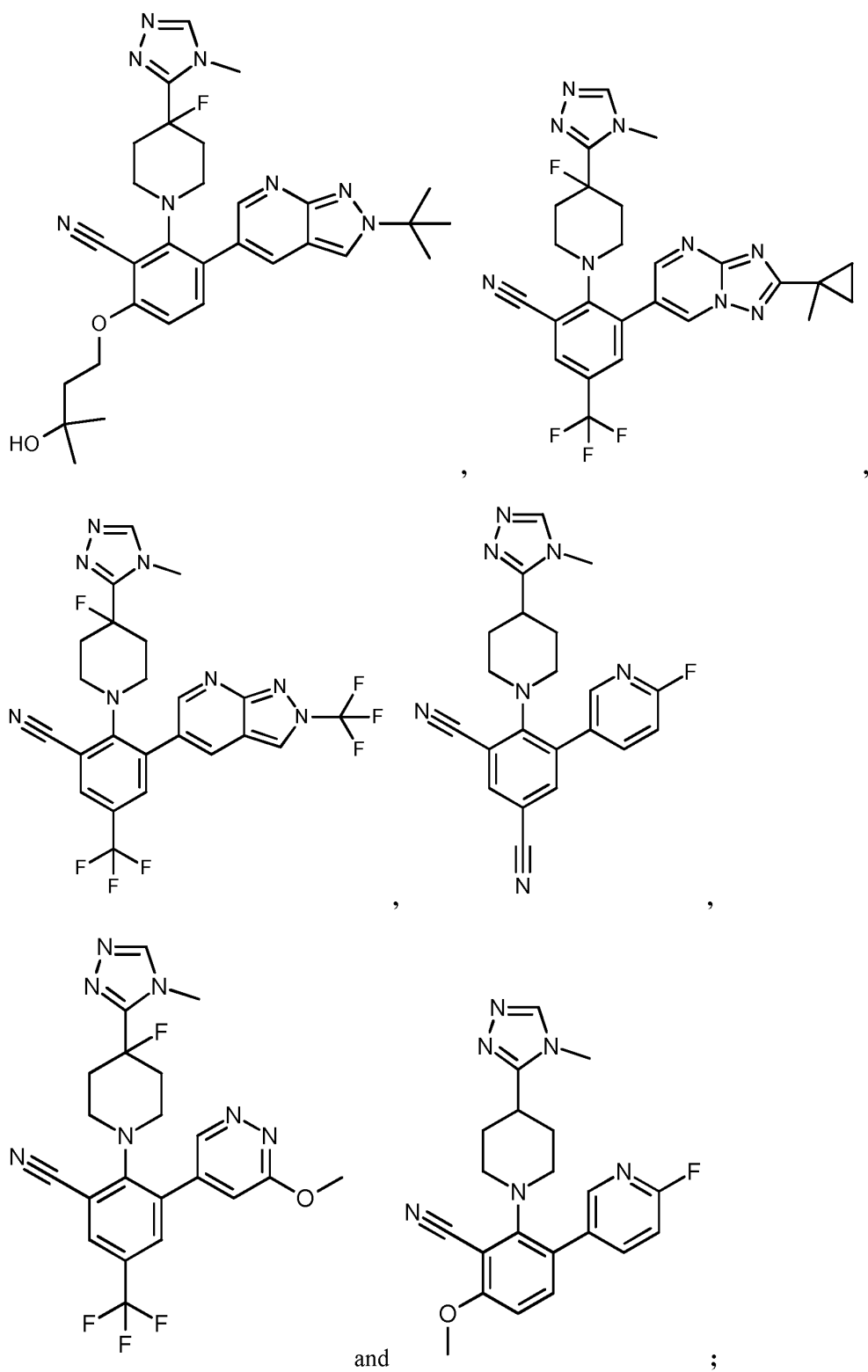












or a salt thereof.

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

5

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

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

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

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

20

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

25

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

30