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(54) Title: SUBSTITUTED BICYCLIC COMPOUNDS AS MODULATORS OF THE ARYL HYDROCARBON RECEPTOR (AHR)

(57) Abstract: The present invention relates to bicyclic compounds which can act as aryl hydrocarbon receptor (AhR) modulators and, in particular, as AhR antagonists. The invention further relates to the use of the compounds for the treatment and/or prophylaxis of diseases and/or conditions through binding of said aryl hydrocarbon receptor by said compounds. A-B-L-C (I)



WO 2020/021024 A1

Substituted Bicyclic Compounds as Modulators of the Aryl Hydrocarbon Receptor (AhR)

The present invention relates to compounds which can act as aryl hydrocarbon receptor (AhR) modulators and, in particular, as AhR antagonists. The invention further relates to the use of the compounds for the treatment and/or prophylaxis of diseases and/or conditions through binding of said aryl hydrocarbon receptor by said compounds.

The aryl hydrocarbon receptor (AhR) is a ligand-modulated transcription factor, belonging to the basic helix-loop-helix PAS (Per-Arnt-Sim homology domain) family, that is expressed in most tissues in mice and humans and known to mediate many of the toxicities of 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) in mice. The AhR protein is localized in the cytoplasm of eukaryotic cells in complexes with HSP90 and other proteins. Binding of agonistic ligands, such as TCDD, leads to dissociation of AhR from the HSP90 containing complex, transport to the nucleus and association with its heterodimeric partner ARNT. This heterodimeric complex can bind to AhR response elements located in promoter regions of genes such as CYP1A1, CYP1B1, ALDH3A1, NQO1, UGT1A1 etc. and induces the transcription of such genes in case of very potent and efficacious AhR agonists, such as TCDD.

By regulating the expression of genes involved in xenobiotic transformation (e.g. CYP1A1), the AhR plays a significant role in the detoxification of xenobiotic substances in liver and intestine, which are prominent locations of AhR expression. This activity might be underlying some of the described chemoprevention and tumor suppression effects exerted by AhR. On the other hand, CYP1A1 is known to metabolize some pro-cancerogens, such as benzo(a)pyrene into DNA reactive intermediates leading to mutagenesis and tumor formation (Murray et al. Nat Rev Cancer. 2014 Dec; 14(12):801-14; Safe et al Toxicol Sci. 2013 Sep; 135(1):1-16).

In mouse cancer models, knock-down of AhR typically resulted in decreased proliferation and/or invasion and migration of cancer cell lines and overexpression of constitutive active AhR results in vivo in enhanced stomach and liver cancers (Safe et al Toxicol Sci. 2013 Sep;135(1):1-16).

The AhR is relatively strongly expressed in intestinal epithelial tissues, lung epithelium and skin. In these tissues the AhR expression is particularly high in cells of lymphoid origin such as T-cells, Dendritic Cells, Langerhans Cells, Macrophages, Mast cells etc. One possible function in these compartments is to integrate signals from the commensal

microbiomes in the intestine, the lung and the skin, which are known to produce diverse mixtures of indolic AhR modulators that are thought to balance the responses of the immune system towards the microbiome (Bessede et al., Nature. 2014 Jul 10; 511(7508):184-90, Zelante et al. Immunity. 2013 Aug 22;39(2):372-85, Romani et al., Eur J Immunol. 2014 Nov;44(11):3192-200).

The expression of AhR has been found to be constitutive active in advanced human prostate cancer (Richmond et al., 2014, PLoS ONE 9(4): e95058), overexpressed in breast cancer (Li et al., Int J Clin Exp Pathol. 2014 Oct 15;7(11):7931) and pancreas cancer (Koliopanos et al., Oncogene. 2002 Sep 5;21(39):6059-70). Modulation of the AhR pathway activity by small molecule modulators might be beneficial for some of these devastating diseases with very limited treatment options.

In a recently published Patent Application US 2016/01752278 by the Trustees of Boston University, novel small molecule agents characterized as AhR modulators are being claimed for inhibiting cancer cell proliferation, tumor cell invasion and metastasis.

AhR modulators and in particular modulators with primarily antagonistic activities might be useful as medicaments for the treatment of solid tumors (e.g. pancreatic cancer, prostate cancer, breast cancer, colon cancer).

The problem underlying the present invention is to provide compounds which have a AhR-antagonistic activity and can be used in the treatment and/or prophylaxis of AhR-mediated diseases.

Said problem has been solved by a compound according to the following Formula (I), an enantiomer, diastereomer, tautomer, solvate, N-oxide, prodrug or pharmaceutical acceptable salt thereof

A-B-L-C (I)

wherein

A represents a 6- to 10-membered mono- or bicyclic aryl or a 5- to 10-membered mono- or bicyclic heteroaryl containing 1 to 4 heteroatoms independently selected from N, O and S,

wherein aryl and heteroaryl are unsubstituted or substituted with 1 to 7 substituents independently selected from the group consisting of halogen, OH, CN, C₁₋₆-alkyl, O-C₁₋₆-alkyl, oxo, C(O)OR^a, OC(O)R^a, S-C₁₋₆-alkyl, S(O)-C₁₋₆-alkyl, S(O)₂-C₁₋₆-alkyl, N(R^a)₂, C(O)N(R^a)₂, NR^aC(O)-C₁₋₆-alkyl, S(O)₂N(R^a)₂, NR^aS(O)₂-C₁₋₆-alkyl and C₃₋₆-cycloalkyl, wherein alkyl and cycloalkyl are unsubstituted or substituted with 1 to 3 substituents

independently selected from the group consisting of halogen, C₁₋₃-alkyl, halo-C₁₋₃-alkyl, OH, CN and oxo, or

wherein two substituents on the aryl or heteroaryl group together with the atoms they are attached to may form a 5- to 7-membered saturated or partially unsaturated carbocyclic ring or heterocyclic ring containing 1 to 3 heteroatoms independently selected from O, N and S, wherein the carbocyclic or heterocyclic ring is unsubstituted or substituted with 1 to 5 substituents independently selected from the group consisting of halogen, oxo, OH, C₁₋₆-alkyl and halo-C₁₋₆-alkyl;

R^a is independently selected from hydrogen and C₁₋₆-alkyl;

B represents a 8- to 10- membered bicyclic aryl or heteroaryl ring, wherein the heteroaryl ring contains up to 6 heteroatoms independently selected from N, O and S,

wherein the bicyclic aryl or heteroaryl ring is unsubstituted or substituted with 1 to 5 substituents independently selected from the group consisting of halogen, C₁₋₆-alkyl, halo-C₁₋₃-alkyl, OH, C₃₋₆-cycloalkyl, OH, O-C₁₋₃-alkyl, oxo and CN, wherein cycloalkyl or alkyl is unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of halogen, OH, oxo, C₁₋₃-alkyl and halo-C₁₋₃-alkyl;

L represents -NR^bC(O)C(O)NR^b-, -NR^bC(=NR^c)-, -NR^bSO₂-, -C(O)NR^b-, -NR^b-C₁₋₂-alkylene-, -S(O)_x-C₁₋₂-alkylene- or -C₀₋₂-alkylene-NR^bC(O)-,

wherein alkylene is unsubstituted or substituted with 1 to 4 substituents independently selected from halogen, C₁₋₃-alkyl and halo-C₁₋₃-alkyl;

R^b is independently selected from hydrogen and C₁₋₆-alkyl;

R^c is hydrogen, OH, C₁₋₆-alkyl, O-C₁₋₆-alkyl, CN or SO₂-C₁₋₆-alkyl;

C represents a C₁₋₆-alkyl, C₃₋₁₀-cycloalkyl, 3- to 10-membered heterocycloalkyl containing 1 to 4 heteroatoms independently selected from N, O and S, 6- to 10-membered mono- or bicyclic aryl or a 5- to 10-membered mono- or bicyclic heteroaryl containing 1 to 4 heteroatoms independently selected from N, O and S,

wherein cycloalkyl, heterocycloalkyl, aryl and heteroaryl are unsubstituted or substituted with 1 to 7 substituents independently selected from the group consisting of halogen, OH, CN, C₁₋₆-alkyl, O-C₁₋₆-alkyl, C(O)OR^a, OC(O)R^a, S(O)-C₁₋₆-alkyl, S(O)₂-C₁₋₆-alkyl, N(R^a)₂, C(O)N(R^a)₂, NR^aC(O)-C₁₋₆-alkyl, S(O)₂N(R^a)₂, NR^aS(O)₂-C₁₋₆-alkyl and C₃₋₆-cycloalkyl, wherein alkyl and cycloalkyl are unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of halogen, C₁₋₃-alkyl, halo-C₁₋₃-alkyl, OH, CN and oxo, or

wherein two substituents on the cycloalkyl, heterocycloalkyl, aryl or heteroaryl group together with the atoms they are attached to may form a 5- to 7-membered saturated or partially unsaturated carbocyclic ring or heterocyclic ring containing 1 to 3 heteroatoms independently selected from O, N and S, wherein the carbocyclic or heterocyclic ring is unsubstituted or substituted with 1 to 5 substituents independently selected from the group consisting of halogen, C₁₋₆-alkyl and halo-C₁₋₆-alkyl; and
 5 x is 0, 1 or 2;

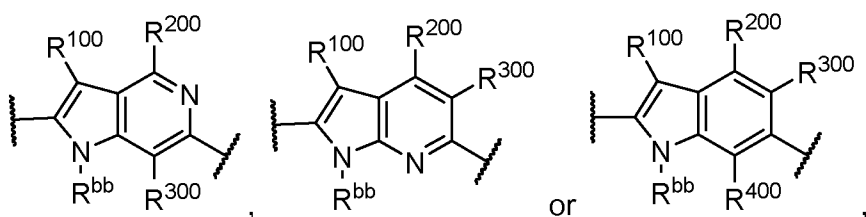
and with the proviso that if L represents a -NR^{bb}C(O)- group, wherein R^{bb} is hydrogen or C₁₋₆-alkyl, and C is 6- to 10-membered mono- or bicyclic aryl and 5- to 10-membered
 10 mono- or bicyclic heteroaryl containing 1 to 4 heteroatoms independently selected from N, O and S,

wherein aryl and heteroaryl are unsubstituted or substituted with 1 to 7 substituents independently selected from the group consisting of halogen, OH, CN, C₁₋₆-alkyl, O-C₁₋₆-alkyl, C(O)OR^{aa}, OC(O)R^{aa}, S(O)-C₁₋₆-alkyl, S(O)₂-C₁₋₆-alkyl, N(R^{aa})₂, C(O)N(R^{aa})₂,
 15 NR^{aa}C(O)-C₁₋₆-alkyl, S(O)₂N(R^{aa})₂, NR^{aa}S(O)₂-C₁₋₆-alkyl and C₃₋₆-cycloalkyl, wherein the alkyl and cycloalkyl are unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of halogen, C₁₋₃-alkyl, halo-C₁₋₃-alkyl, OH, CN and oxo, or

wherein two substituents on the aryl or heteroaryl group together with the atoms they are attached to may form a 5- to 7-membered saturated or partially unsaturated carbocyclic ring or heterocyclic ring containing 1 to 3 heteroatoms independently selected from O, N and S, wherein the carbocyclic or heterocyclic ring is unsubstituted or substituted with 1 to 5 substituents independently selected from the group consisting of halogen, C₁₋₆-alkyl and halo-C₁₋₆-alkyl, and
 20

25 wherein R^{aa} is hydrogen or C₁₋₆-alkyl,

then B is not



wherein R¹⁰⁰ to R⁴⁰⁰ is independently selected from the group consisting of hydrogen, halogen, C₁₋₄-alkyl, halo-C₁₋₃-alkyl, OH, O-C₁₋₃-alkyl, and CN, and R^{bb} is hydrogen or
 30 C₁₋₆-alkyl.

In a preferred embodiment in combination with any of the above or below embodiments, the compound and an enantiomer, diastereomer, tautomer, solvate, prodrug or pharmaceutical acceptable salt thereof is represented by Formula (I)

A-B-L-C (I)

5 wherein

A represents a 6- to 10-membered mono- or bicyclic aryl or a 5- to 10-membered mono- or bicyclic heteroaryl containing 1 to 4 heteroatoms independently selected from N, O and S,

10 wherein aryl and heteroaryl are unsubstituted or substituted with 1 to 7 substituents independently selected from the group consisting of halogen, OH, CN, C₁₋₆-alkyl, O-C₁₋₆-alkyl, C(O)OR^a, OC(O)R^a, S(O)-C₁₋₆-alkyl, S(O)₂-C₁₋₆-alkyl, N(R^a)₂, C(O)N(R^a)₂, NR^aC(O)-C₁₋₆-alkyl, S(O)₂N(R^a)₂, NR^aS(O)₂-C₁₋₆-alkyl and C₃₋₆-cycloalkyl, wherein alkyl and cycloalkyl are unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of halogen, C₁₋₃-alkyl, halo-C₁₋₃-alkyl, OH, CN and
15 oxo, or

wherein two substituents on the aryl or heteroaryl group together with the atoms they are attached to may form a 5- to 7-membered saturated or partially unsaturated carbocyclic ring or heterocyclic ring containing 1 to 3 heteroatoms independently selected from O, N and S, wherein the carbocyclic or heterocyclic ring is unsubstituted or substituted with 1
20 to 5 substituents independently selected from the group consisting of halogen, C₁₋₆-alkyl and halo-C₁₋₆-alkyl;

R^a is independently selected from hydrogen and C₁₋₆-alkyl;

B represents a 8- to 10- membered bicyclic aryl or heteroaryl ring, wherein the heteroaryl ring contains up to 6 heteroatoms independently selected from N, O and S,

25 wherein the bicyclic aryl or heteroaryl ring is unsubstituted or substituted with 1 to 5 substituents independently selected from halogen, C₁₋₆-alkyl, halo-C₁₋₃-alkyl, C₃₋₆-cycloalkyl, OH, O-C₁₋₃-alkyl and CN, wherein cycloalkyl or alkyl is unsubstituted or substituted with 1 to 3 substituents independently selected from halogen, OH, C₁₋₃-alkyl and halo-C₁₋₃-alkyl;

30 L represents -NR^bC(O)C(O)NR^b-, -NR^bC(=NR^c)-, -NR^bSO₂-, -C(O)NR^b-, -NR^b-C₁₋₂-alkylene-, -S(O)_x-C₁₋₂-alkylene- or -C₀₋₂-alkylene-NR^bC(O)-, wherein alkylene is unsubstituted or substituted with 1 to 4 substituents independently selected from halogen, C₁₋₃-alkyl and halo-C₁₋₃-alkyl;

R^b is independently selected from hydrogen and C₁₋₆-alkyl;

35 R^c is hydrogen, OH, C₁₋₆-alkyl, O-C₁₋₆-alkyl, CN or SO₂-C₁₋₆-alkyl;

C represents a C₁₋₆-alkyl, C₃₋₁₀-cycloalkyl, 3- to 10-membered heterocycloalkyl containing 1 to 4 heteroatoms independently selected from N, O and S, 6- to 10-membered mono- or bicyclic aryl or a 5- to 10-membered mono- or bicyclic heteroaryl containing 1 to 4 heteroatoms independently selected from N, O and S,

wherein cycloalkyl, heterocycloalkyl, aryl and heteroaryl are unsubstituted or substituted with 1 to 7 substituents independently selected from the group consisting of halogen, OH, CN, C₁₋₆-alkyl, O-C₁₋₆-alkyl, C(O)OR^a, OC(O)R^a, S(O)-C₁₋₆-alkyl, S(O)₂-C₁₋₆-alkyl, N(R^a)₂, C(O)N(R^a)₂, NR^aC(O)-C₁₋₆-alkyl, S(O)₂N(R^a)₂, NR^aS(O)₂-C₁₋₆-alkyl and C₃₋₆-cycloalkyl, wherein the alkyl and cycloalkyl are unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of halogen, C₁₋₃-alkyl, halo-C₁₋₃-alkyl, OH, CN and oxo, or

wherein two substituents on the cycloalkyl, heterocycloalkyl, aryl or heteroaryl group together with the atoms they are attached to may form a 5- to 7-membered saturated or partially unsaturated carbocyclic ring or heterocyclic ring containing 1 to 3 heteroatoms independently selected from O, N and S, wherein the carbocyclic or heterocyclic ring is unsubstituted or substituted with 1 to 5 substituents independently selected from the group consisting of halogen, C₁₋₆-alkyl and halo-C₁₋₆-alkyl;

and

x is 0, 1 or 2;

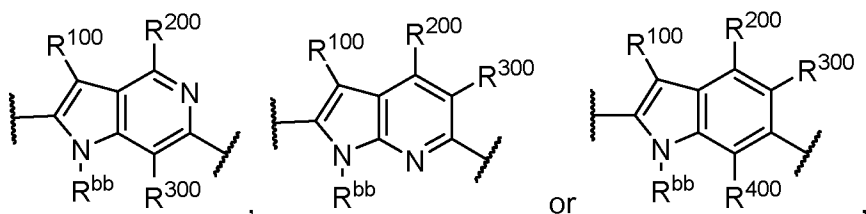
with the proviso that if L represents a -NR^{bb}C(O)- group, wherein R^{bb} is hydrogen or C₁₋₆-alkyl, and C is 6- to 10-membered mono- or bicyclic aryl and 5- to 10-membered mono- or bicyclic heteroaryl containing 1 to 4 heteroatoms independently selected from N, O and S,

wherein aryl and heteroaryl are unsubstituted or substituted with 1 to 7 substituents independently selected from the group consisting of halogen, OH, CN, C₁₋₆-alkyl, O-C₁₋₆-alkyl, C(O)OR^{aa}, OC(O)R^{aa}, S(O)-C₁₋₆-alkyl, S(O)₂-C₁₋₆-alkyl, N(R^a)₂, C(O)N(R^{aa})₂, NR^{aa}C(O)-C₁₋₆-alkyl, S(O)₂N(R^{aa})₂, NR^{aa}S(O)₂-C₁₋₆-alkyl and C₃₋₆-cycloalkyl, wherein alkyl and cycloalkyl are unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of halogen, C₁₋₃-alkyl, halo-C₁₋₃-alkyl, OH, CN and oxo, or

wherein two substituents on the aryl or heteroaryl group together with the atoms they are attached to may form a 5- to 7-membered saturated or partially unsaturated carbocyclic ring or heterocyclic ring containing 1 to 3 heteroatoms independently selected from O, N and S, wherein the carbocyclic or heterocyclic ring is unsubstituted or substituted with 1 to 5 substituents independently selected from the group consisting of halogen, C₁₋₆-alkyl and halo-C₁₋₆-alkyl, and

wherein R^{aa} is hydrogen or C_{1-6} -alkyl,

then B is not



wherein R^{100} to R^{400} is independently hydrogen, halogen, C_{1-4} -alkyl, halo- C_{1-3} -alkyl, OH, O- C_{1-3} -alkyl and CN, and R^{bb} is hydrogen or C_{1-6} -alkyl.

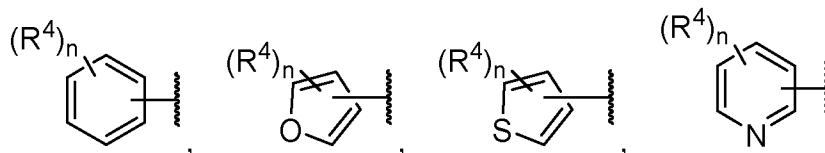
In a further preferred embodiment in combination with any of the above or below embodiments, A represents a 6- to 10-membered mono- or bicyclic aryl or a 5- to 10-membered mono- or bicyclic heteroaryl containing 1 to 4 heteroatoms independently selected from N, O and S,

wherein aryl and heteroaryl are unsubstituted or substituted with 1 to 7 substituents independently selected from the group consisting of halogen, OH, CN, C_{1-6} -alkyl, O- C_{1-6} -alkyl, $C(O)OR^a$, $OC(O)R^a$, $S(O)-C_{1-6}$ -alkyl, $S(O)_2-C_{1-6}$ -alkyl, $N(R^a)_2$, $C(O)N(R^a)_2$, $S(O)_2N(R^a)_2$, $NR^aS(O)_2-C_{1-6}$ -alkyl and C_{3-6} -cycloalkyl, wherein alkyl and cycloalkyl are unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of halogen, C_{1-3} -alkyl, halo- C_{1-3} -alkyl, OH, CN and oxo, or

wherein two substituents on the aryl or heteroaryl group together with the atoms they are attached to may form a 5- to 7-membered saturated or partially unsaturated carbocyclic ring or heterocyclic ring containing 1 to 3 heteroatoms independently selected from O, N and S, wherein the carbocyclic or heterocyclic ring is unsubstituted or substituted with 1 to 5 substituents independently selected from the group consisting of halogen, C_{1-6} -alkyl and halo- C_{1-6} -alkyl; and

R^a is independently selected from hydrogen and C_{1-6} -alkyl.

In a more preferred embodiment in combination with any of the above or below embodiments, A is



wherein

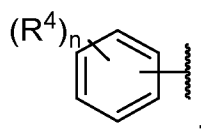
R^4 is independently selected from halogen, OH, CN, C_{1-6} -alkyl, $O-C_{1-6}$ -alkyl, $C(O)OR^a$, $OC(O)R^a$, $S(O)-C_{1-6}$ -alkyl, $S(O)_2-C_{1-6}$ -alkyl, $N(R^a)_2$, $C(O)N(R^a)_2$, $S(O)_2N(R^a)_2$, $NR^aS(O)_2-$, C_{1-6} -alkyl and C_{3-6} -cycloalkyl,

wherein alkyl and cycloalkyl are unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of halogen, C_{1-3} -alkyl, halo- C_{1-3} -alkyl, OH, CN and oxo;

R^a is independently selected from hydrogen and C_{1-6} -alkyl; and

n is 0 to 5.

In an even more preferred embodiment in combination with any of the above or below embodiments, A is



wherein

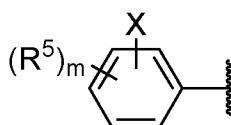
R^4 is independently selected from halogen, OH, CN, C_{1-6} -alkyl, $O-C_{1-6}$ -alkyl, $C(O)OR^a$, $OC(O)R^a$, $S(O)-C_{1-6}$ -alkyl, $S(O)_2-C_{1-6}$ -alkyl, $N(R^a)_2$, $C(O)N(R^a)_2$, $S(O)_2N(R^a)_2$, $NR^aS(O)_2-$, C_{1-6} -alkyl and C_{3-6} -cycloalkyl,

wherein alkyl and cycloalkyl are unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of halogen, C_{1-3} -alkyl, halo- C_{1-3} -alkyl, OH, CN and oxo;

R^a is independently selected from hydrogen and C_{1-6} -alkyl; and

n is 0 to 5.

In a more preferred embodiment in combination with any of the above or below embodiments, A is



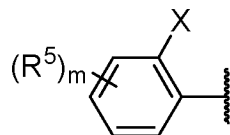
wherein

X is halogen, C_{1-6} -alkyl or C_{3-6} -cycloalkyl, wherein alkyl and cycloalkyl are unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of halogen, C_{1-3} -alkyl and halo- C_{1-3} -alkyl;

R^5 is independently selected from halogen and CN; and

m is 0 to 4.

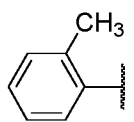
In another more preferred embodiment in combination with any of the above or below embodiments, A is



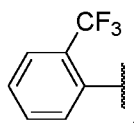
wherein X is F, Cl, CH₃, CH₂CH₃, CHF₂ or CF₃;

- 5 R⁵ is independently selected from halogen and CN; and
m is 0 to 4.

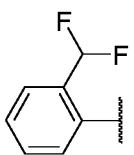
In a most preferred embodiment in combination with any of the above or below embodiments, A is



- 10 In an equally most preferred embodiment in combination with any of the above or below embodiments, A is

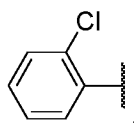


In a further equally most preferred embodiment in combination with any of the above or below embodiments, A is

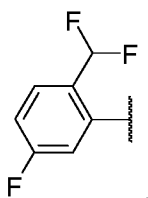


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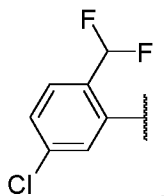
In a further equally most preferred embodiment in combination with any of the above or below embodiments, A is



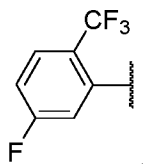
- 20 In a further equally most preferred embodiment in combination with any of the above or below embodiments, A is



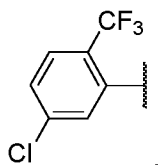
In a further equally most preferred embodiment in combination with any of the above or below embodiments, A is



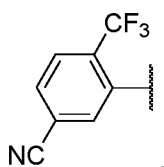
5 In a further equally most preferred embodiment in combination with any of the above or below embodiments, A is



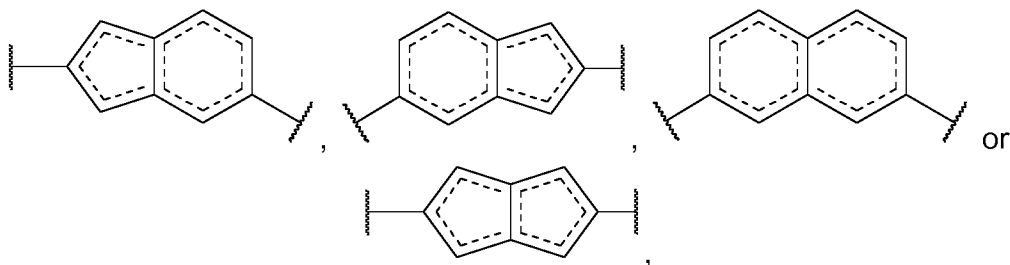
In a further equally most preferred embodiment in combination with any of the above or below embodiments, A is



10 In a further equally most preferred embodiment in combination with any of the above or below embodiments, A is



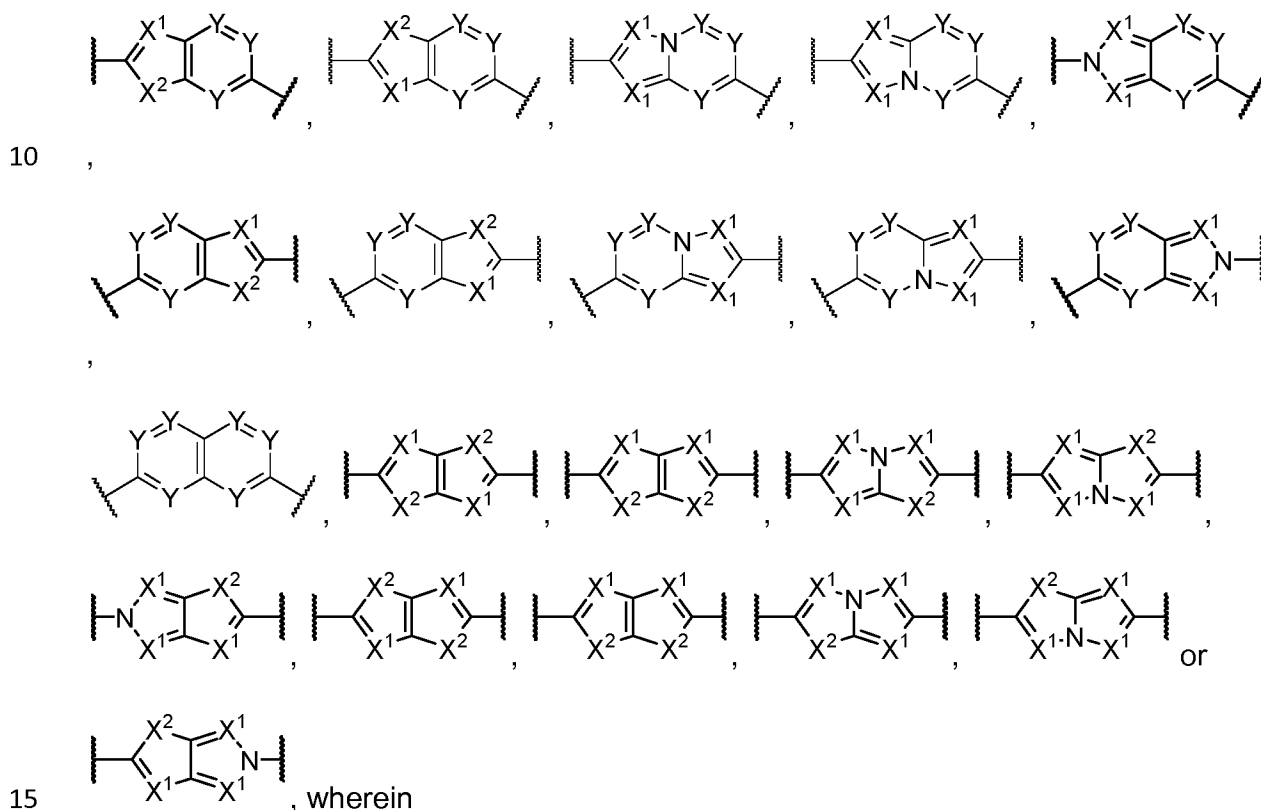
15 In a preferred embodiment in combination with any of the above or below embodiments, B represents a 8- to 10-membered bicyclic aryl or heteroaryl ring, wherein the heteroaryl ring contains up to 6 heteroatoms independently selected from N, O and S, and wherein the bicyclic ring is connected to A and L-C in the following configurations



wherein the bicyclic aryl or heteroaryl ring is unsubstituted or substituted with 1 to 5 substituents independently selected from the group consisting of halogen, C₁₋₆-alkyl, halo-C₁₋₃-alkyl, OH, C₃₋₆-cycloalkyl, O-C₁₋₃-alkyl and CN,

wherein cycloalkyl or alkyl is unsubstituted or substituted with 1 to 3 substituents
 5 independently selected from the group consisting of halogen, OH, C₁₋₃-alkyl and halo-C₁₋₃-alkyl.

In a more preferred embodiment in combination with any of the above or below embodiments, B is



X¹ is independently selected from N and CR¹;

X² is independently selected from NR², O and S;

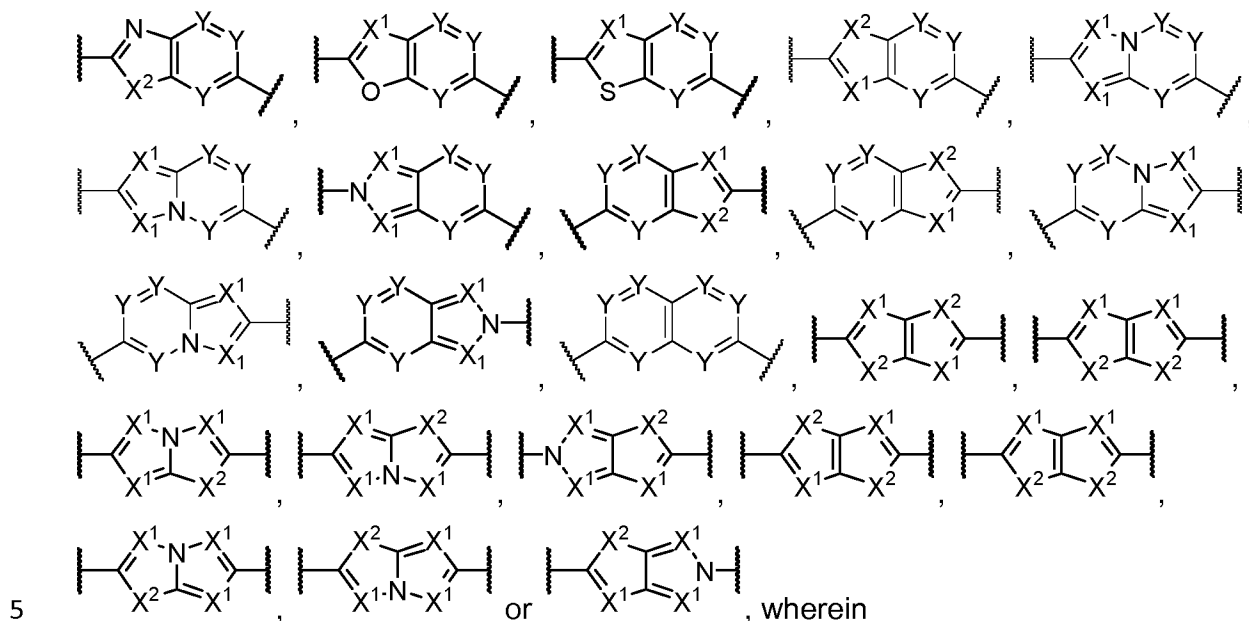
Y is independently selected from N and CR¹;

R¹ is independently selected from hydrogen, halogen, C₁₋₆-alkyl, halo-C₁₋₃-alkyl, OH, C₃₋₆-cycloalkyl, O-C₁₋₃-alkyl and CN,
 20

wherein cycloalkyl or alkyl is unsubstituted or substituted with 1 to 3 substituents independently selected from halogen, OH, C₁₋₃-alkyl and halo-C₁₋₃-alkyl; and

R² is independently selected from hydrogen and C₁₋₆-alkyl.

In an even more preferred embodiment in combination with any of the above or below
 25 embodiments, B is



X^1 is independently selected from N and CR^1 ;

X^2 is independently selected from NR^2 , O and S;

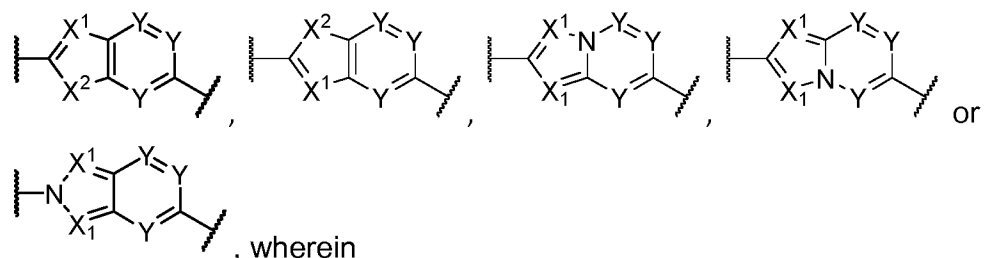
Y is independently selected from N and CR^1 ;

10 R^1 is independently selected from hydrogen, halogen, C_{1-3} -alkyl, halo- C_{1-3} -alkyl, C_{3-6} -cycloalkyl, OH, O- C_{1-3} -alkyl and CN,

wherein cycloalkyl or alkyl is unsubstituted or substituted with 1 to 3 substituents independently selected from halogen, OH, C_{1-3} -alkyl and halo- C_{1-3} -alkyl; and

R^2 is independently selected from hydrogen and C_{1-6} -alkyl.

15 In a further more preferred embodiment in combination with any of the above or below embodiments, B is



X^1 is independently selected from N and CR^1 ;

X^2 is independently selected from NR^2 , O and S;

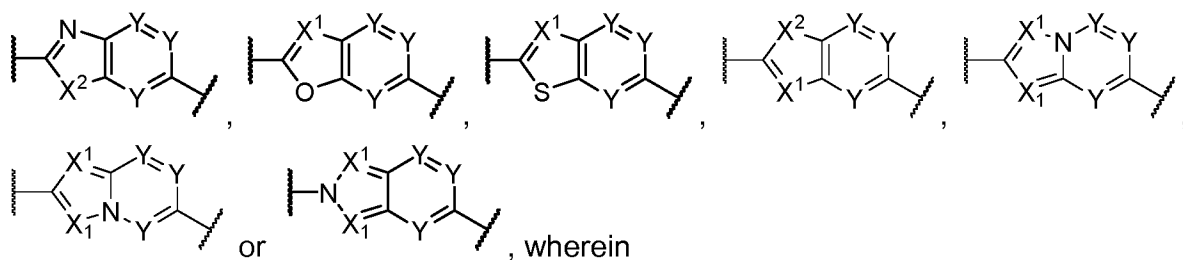
20 Y is independently selected from N and CR^1 ;

R^1 is independently selected from hydrogen, halogen, C_{1-3} -alkyl, halo- C_{1-3} -alkyl, OH, C_{3-6} -cycloalkyl, O- C_{1-3} -alkyl and CN,

wherein cycloalkyl or alkyl is unsubstituted or substituted with 1 to 3 substituents independently selected from halogen, OH, C_{1-3} -alkyl and halo- C_{1-3} -alkyl; and

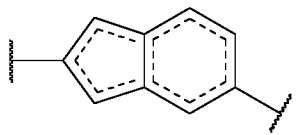
25 R^2 is independently selected from hydrogen and C_{1-6} -alkyl.

In an even more preferred embodiment in combination with any of the above or below embodiments, B is



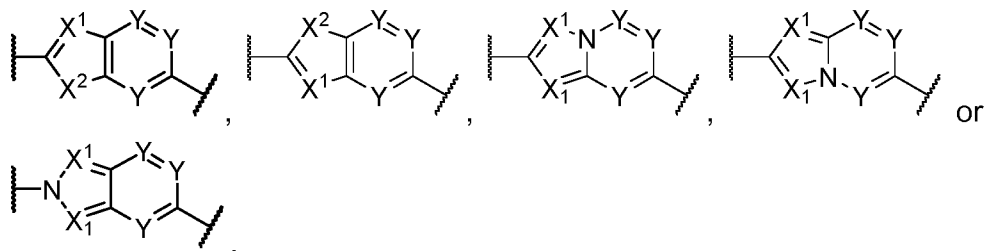
- 5 X¹ is independently selected from N and CR¹;
 X² is independently selected from NR², O and S;
 Y is independently selected from N and CR¹;
 R¹ is independently selected from hydrogen, halogen, C₁₋₃-alkyl, halo-C₁₋₃-alkyl, OH, C₃₋₆-cycloalkyl, O-C₁₋₃-alkyl, and CN,
 10 wherein cycloalkyl or alkyl is unsubstituted or substituted with 1 to 3 substituents independently selected from halogen, OH, C₁₋₃-alkyl and halo-C₁₋₃-alkyl; and
 R² is independently selected from hydrogen and C₁₋₆-alkyl.

In a preferred embodiment in combination with any of the above or below embodiments, B is

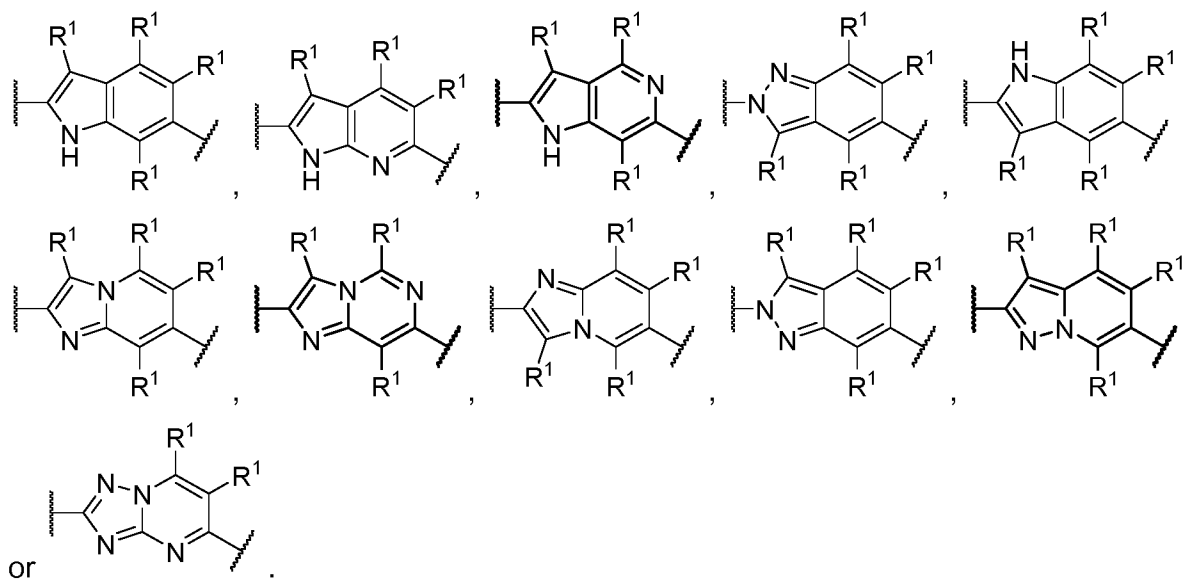


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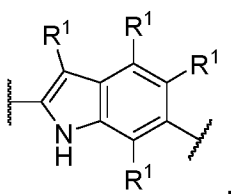
In a more preferred embodiment in combination with any of the above or below embodiments, B is



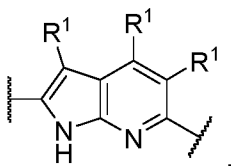
- 20 In an even more preferred embodiment in combination with any of the above or below embodiments, B is



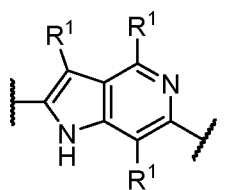
In a most preferred embodiment in combination with any of the above or below
 5 embodiments, B is



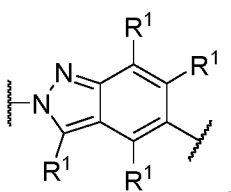
In an equally most preferred embodiment in combination with any of the above or below
 embodiments, B is



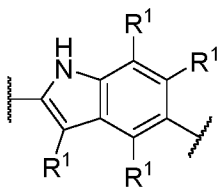
10 In an equally most preferred embodiment in combination with any of the above or below
 embodiments, B is



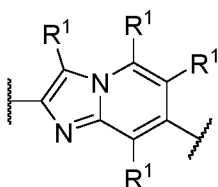
In an equally most preferred embodiment in combination with any of the above or below
 embodiments, B is



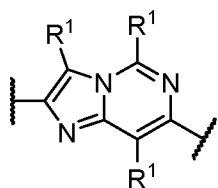
In an equally most preferred embodiment in combination with any of the above or below embodiments, B is



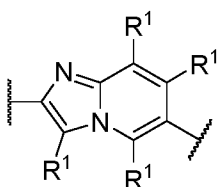
5 In an equally most preferred embodiment in combination with any of the above or below embodiments, B is



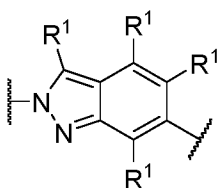
In an equally most preferred embodiment in combination with any of the above or below embodiments, B is



10 In an equally most preferred embodiment in combination with any of the above or below embodiments, B is

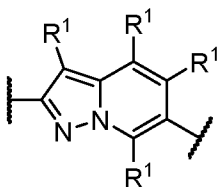


In an equally most preferred embodiment in combination with any of the above or below embodiments, B is

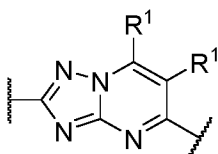


15

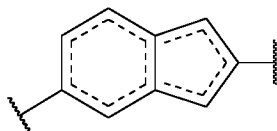
In an equally most preferred embodiment in combination with any of the above or below embodiments, B is



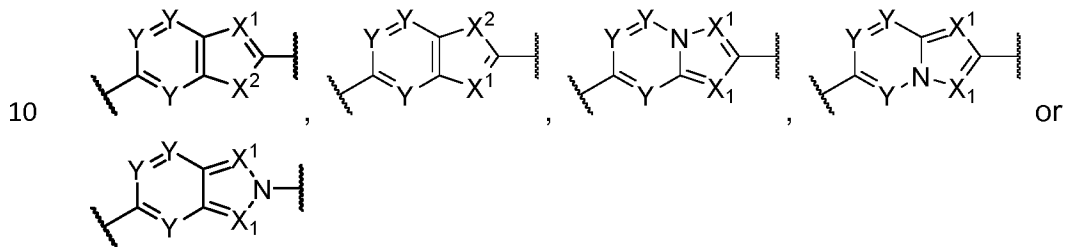
In an equally most preferred embodiment in combination with any of the above or below embodiments, B is



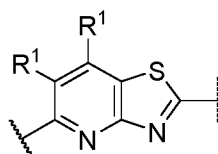
- 5 In an equally preferred embodiment in combination with any of the above or below embodiments, B is



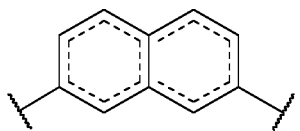
In a more preferred embodiment in combination with any of the above or below embodiments, B is



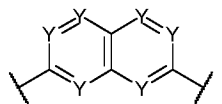
In an even more preferred embodiment in combination with any of the above or below embodiments, B is



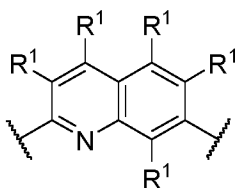
- 15 In a further equally preferred embodiment in combination with any of the above or below embodiments, B is



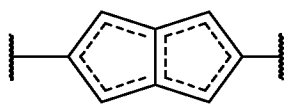
In a more preferred embodiment in combination with any of the above or below embodiments, B is



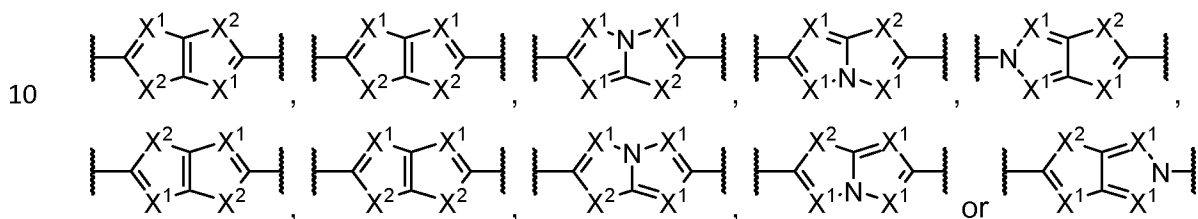
In an even more preferred embodiment in combination with any of the above or below embodiments, B is



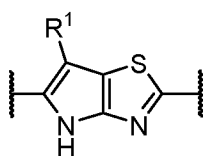
- 5 In a further equally preferred embodiment in combination with any of the above or below embodiments, B is



In a more preferred embodiment in combination with any of the above or below embodiments, B is



In an even more preferred embodiment in combination with any of the above or below embodiments, B is



- 15 In a preferred embodiment in combination with any of the above or below embodiments, R¹ is hydrogen or C₁₋₃-alkyl.

In a more preferred embodiment in combination with any of the above or below embodiments, R¹ is hydrogen or methyl, most preferably R¹ is hydrogen.

- In a preferred embodiment in combination with any of the above or below embodiments,
- 20 C represents a 6-membered heteroaryl containing 1 to 4 heteroatoms independently selected from N, O and S, more preferably the 6-membered heteroaryl is pyridine, wherein the heteroaryl is unsubstituted or substituted with 1 to 5 substituents independently selected from the group consisting of OH, halogen, CN, C₁₋₆-alkyl, O-C₁₋₆-alkyl, OC(O)R^a, S(O)-C₁₋₆-alkyl, S(O)₂-C₁₋₆-alkyl, N(R^a)₂, NR^aC(O)-C₁₋₆-alkyl,

$S(O)_2N(R^a)_2$, $NR^aS(O)_2-C_{1-6}$ -alkyl and C_{3-6} -cycloalkyl, wherein alkyl and cycloalkyl are unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of halogen, C_{1-3} -alkyl, halo- C_{1-3} -alkyl, OH, CN and oxo, or

wherein two substituents on the heteroaryl group together with the atoms they are attached to may form a 5- to 7-membered saturated or partially unsaturated carbocyclic ring or heterocyclic ring containing 1 to 3 heteroatoms independently selected from O, N and S, wherein the carbocyclic or heterocyclic ring is unsubstituted or substituted with 1 to 5 substituents independently selected from the group consisting of halogen, C_{1-6} -alkyl and halo- C_{1-6} -alkyl.

In a further preferred embodiment in combination with any of the above or below embodiments, C represents a C_{1-6} -alkyl, C_{3-10} -cycloalkyl, 3- to 10-membered heterocycloalkyl containing 1 to 4 heteroatoms independently selected from N, O and S, 6- to 10-membered mono- or bicyclic aryl or a 5- to 10-membered mono- or bicyclic heteroaryl containing 1 to 4 heteroatoms independently selected from N, O and S,

wherein cycloalkyl, heterocycloalkyl, aryl and heteroaryl are unsubstituted or substituted with 1 to 7 substituents independently selected from the group consisting of OH, CN, C_{1-6} -alkyl, O- C_{1-6} -alkyl, $OC(O)R^a$, $S(O)-C_{1-6}$ -alkyl, $S(O)_2-C_{1-6}$ -alkyl, $N(R^a)_2$, $NR^aC(O)-C_{1-6}$ -alkyl, $S(O)_2N(R^a)_2$, $NR^aS(O)_2-C_{1-6}$ -alkyl and C_{3-6} -cycloalkyl, wherein alkyl and cycloalkyl are unsubstituted or substituted with 1 to 3 substituents independently selected from the

group consisting of halogen, C_{1-3} -alkyl, halo- C_{1-3} -alkyl, OH, CN and oxo, or wherein two substituents on the cycloalkyl, heterocycloalkyl, aryl or heteroaryl group together with the atoms they are attached to may form a 5- to 7-membered saturated or partially unsaturated carbocyclic ring or heterocyclic ring containing 1 to 3 heteroatoms independently selected from O, N and S, wherein the carbocyclic or heterocyclic ring is unsubstituted or substituted with 1 to 5 substituents independently selected from the group consisting of halogen, C_{1-6} -alkyl and halo- C_{1-6} -alkyl.

In a more preferred embodiment in combination with any of the above or below embodiments, C represents a 6- to 10-membered mono- or bicyclic aryl or a 5- to 6-membered heteroaryl containing 1 to 4 heteroatoms independently selected from N, O

and S, wherein aryl and heteroaryl are unsubstituted or substituted with 1 to 7 substituents independently selected from the group consisting of OH, CN, C_{1-6} -alkyl, O- C_{1-6} -alkyl, $OC(O)R^a$, $S(O)-C_{1-6}$ -alkyl, $S(O)_2-C_{1-6}$ -alkyl, $N(R^a)_2$, $NR^aC(O)-C_{1-6}$ -alkyl, $S(O)_2N(R^a)_2$, $NR^aS(O)_2-C_{1-6}$ -alkyl and C_{3-6} -cycloalkyl, wherein alkyl and cycloalkyl are unsubstituted or substituted with 1 to 3 substituents independently selected from the

group consisting of halogen, C_{1-3} -alkyl, halo- C_{1-3} -alkyl, OH, CN and oxo, or

wherein two substituents on the aryl or heteroaryl group together with the atoms they are attached to may form a 5- to 7-membered saturated or partially unsaturated carbocyclic ring or heterocyclic ring containing 1 to 3 heteroatoms independently selected from O, N and S, wherein the carbocyclic or heterocyclic ring is unsubstituted or substituted with 1 to 5 substituents independently selected from the group consisting of halogen, C₁₋₆-alkyl and halo-C₁₋₆-alkyl.

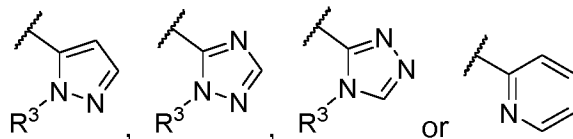
In an even more preferred embodiment in combination with any of the above or below embodiments, C represents a 5-membered heteroaryl containing 2 to 4 nitrogen atoms, which is unsubstituted or substituted with 1 or 2 substituents independently selected from the group consisting of OH, CN, C₁₋₆-alkyl, O-C₁₋₆-alkyl, OC(O)R^a, S(O)-C₁₋₆-alkyl, S(O)₂-C₁₋₆-alkyl, N(R^a)₂, NR^aC(O)-C₁₋₆-alkyl, S(O)₂N(R^a)₂, NR^aS(O)₂-C₁₋₆-alkyl and C₃₋₆-cycloalkyl, wherein alkyl and cycloalkyl are unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of halogen, C₁₋₃-alkyl, halo-C₁₋₃-alkyl, OH, CN and oxo, or

wherein two substituents on the heteroaryl group together with the atoms they are attached to may form a 5- to 7-membered saturated or partially unsaturated carbocyclic ring or heterocyclic ring containing 1 to 3 heteroatoms independently selected from O, N and S, wherein the carbocyclic or heterocyclic ring is unsubstituted or substituted with 1 to 5 substituents independently selected from the group consisting of halogen, C₁₋₆-alkyl and halo-C₁₋₆-alkyl.

In an equally more preferred embodiment in combination with any of the above or below embodiments, C represents a 5-membered heteroaryl containing 2 or 3 nitrogen atoms, which is unsubstituted or substituted with 1 or 2 substituents independently selected from the group consisting of OH, CN, C₁₋₆-alkyl, O-C₁₋₆-alkyl, OC(O)R^a, S(O)-C₁₋₆-alkyl, S(O)₂-C₁₋₆-alkyl, N(R^a)₂, NR^aC(O)-C₁₋₆-alkyl, S(O)₂N(R^a)₂, NR^aS(O)₂-C₁₋₆-alkyl and C₃₋₆-cycloalkyl, wherein the alkyl and cycloalkyl are unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of halogen, C₁₋₃-alkyl, halo-C₁₋₃-alkyl, OH, CN and oxo, or

wherein two substituents on the heteroaryl group together with the atoms they are attached to may form a 5- to 7-membered saturated or partially unsaturated carbocyclic ring or heterocyclic ring containing 1 to 3 heteroatoms independently selected from O, N and S, wherein the carbocyclic or heterocyclic ring is unsubstituted or substituted with 1 to 5 substituents independently selected from the group consisting of halogen, C₁₋₆-alkyl and halo-C₁₋₆-alkyl.

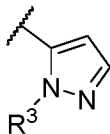
In a further preferred embodiment in combination with any of the above or below embodiments, C is



which is not further substituted or substituted with 1 or 2 substituents independently selected from the group consisting of OH, CN, C₁₋₆-alkyl, O-C₁₋₆-alkyl, OC(O)R^a, S(O)-C₁₋₆-alkyl, S(O)₂-C₁₋₆-alkyl, N(R^a)₂, NR^aC(O)-C₁₋₆-alkyl, S(O)₂N(R^a)₂, NR^aS(O)₂-C₁₋₆-alkyl and C₃₋₆-cycloalkyl, wherein the alkyl and cycloalkyl are unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of halogen, C₁₋₃-alkyl, halo-C₁₋₃-alkyl, OH, CN and oxo; and

- 10 wherein R³ is C₁₋₆-alkyl which is unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of OH, halogen and CN.

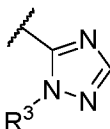
In a preferred embodiment in combination with any of the above or below embodiments, C is



- 15 which is not further substituted or substituted with 1 or 2 substituents independently selected from the group consisting of OH, CN, C₁₋₆-alkyl, O-C₁₋₆-alkyl, OC(O)R^a, S(O)-C₁₋₆-alkyl, S(O)₂-C₁₋₆-alkyl, N(R^a)₂, NR^aC(O)-C₁₋₆-alkyl, S(O)₂N(R^a)₂, NR^aS(O)₂-C₁₋₆-alkyl and C₃₋₆-cycloalkyl, wherein the alkyl and cycloalkyl are unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of halogen, C₁₋₃-alkyl, halo-C₁₋₃-alkyl, OH, CN and oxo; and
- 20

wherein R³ is C₁₋₆-alkyl which is unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of OH, halogen and CN.

In a further preferred embodiment in combination with any of the above or below embodiments, C is



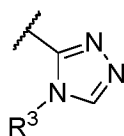
25

which is not further substituted or substituted with 1 substituent selected from the group consisting of OH, CN, C₁₋₆-alkyl, O-C₁₋₆-alkyl, OC(O)R^a, S(O)-C₁₋₆-alkyl, S(O)₂-C₁₋₆-alkyl,

$N(R^a)_2$, $NR^aC(O)-C_{1-6}\text{-alkyl}$, $S(O)_2N(R^a)_2$, $NR^aS(O)_2-C_{1-6}\text{-alkyl}$ and $C_{3-6}\text{-cycloalkyl}$, wherein the alkyl and cycloalkyl are unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of halogen, $C_{1-3}\text{-alkyl}$, halo- $C_{1-3}\text{-alkyl}$, OH, CN and oxo; and

- 5 wherein R^3 is $C_{1-6}\text{-alkyl}$ which is unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of OH, halogen and CN.

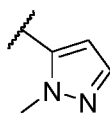
In a further preferred embodiment in combination with any of the above or below embodiments, C is



- 10 which is not further substituted or substituted with 1 substituent selected from the group consisting of OH, CN, $C_{1-6}\text{-alkyl}$, $O-C_{1-6}\text{-alkyl}$, $OC(O)R^a$, $S(O)-C_{1-6}\text{-alkyl}$, $S(O)_2-C_{1-6}\text{-alkyl}$, $N(R^a)_2$, $NR^aC(O)-C_{1-6}\text{-alkyl}$, $S(O)_2N(R^a)_2$, $NR^aS(O)_2-C_{1-6}\text{-alkyl}$ and $C_{3-6}\text{-cycloalkyl}$, wherein the alkyl and cycloalkyl are unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of halogen, $C_{1-3}\text{-alkyl}$, halo- $C_{1-3}\text{-alkyl}$, OH, CN and oxo; and

15 wherein R^3 is $C_{1-6}\text{-alkyl}$ which is unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of OH, halogen and CN.

In a most preferred embodiment in combination with any of the above or below embodiments, C is

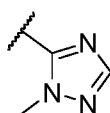


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which is not further substituted or substituted with 1 or 2 substituents independently selected from the group consisting of OH, CN, $C_{1-6}\text{-alkyl}$, $O-C_{1-6}\text{-alkyl}$, $OC(O)R^a$, $S(O)-C_{1-6}\text{-alkyl}$, $S(O)_2-C_{1-6}\text{-alkyl}$, $N(R^a)_2$, $NR^aC(O)-C_{1-6}\text{-alkyl}$, $S(O)_2N(R^a)_2$, $NR^aS(O)_2-C_{1-6}\text{-alkyl}$ and $C_{3-6}\text{-cycloalkyl}$, wherein the alkyl and cycloalkyl are unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of halogen, $C_{1-3}\text{-alkyl}$, halo- $C_{1-3}\text{-alkyl}$, OH, CN and oxo.

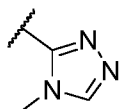
25

In a further most preferred embodiment in combination with any of the above or below embodiments, C is



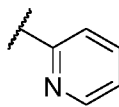
which is not further substituted or substituted with 1 substituent selected from the group consisting of OH, CN, C₁₋₆-alkyl, O-C₁₋₆-alkyl, OC(O)R^a, S(O)-C₁₋₆-alkyl, S(O)₂-C₁₋₆-alkyl, N(R^a)₂, NR^aC(O)-C₁₋₆-alkyl, S(O)₂N(R^a)₂, NR^aS(O)₂-C₁₋₆-alkyl and C₃₋₆-cycloalkyl, wherein the alkyl and cycloalkyl are unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of halogen, C₁₋₃-alkyl, halo-C₁₋₃-alkyl, OH, CN and oxo.

In a further most preferred embodiment in combination with any of the above or below embodiments, C is



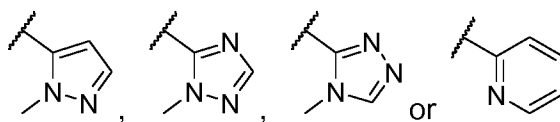
which is not further substituted or substituted with 1 substituent selected from the group consisting of OH, CN, C₁₋₆-alkyl, O-C₁₋₆-alkyl, OC(O)R^a, S(O)-C₁₋₆-alkyl, S(O)₂-C₁₋₆-alkyl, N(R^a)₂, NR^aC(O)-C₁₋₆-alkyl, S(O)₂N(R^a)₂, NR^aS(O)₂-C₁₋₆-alkyl and C₃₋₆-cycloalkyl, wherein the alkyl and cycloalkyl are unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of halogen, C₁₋₃-alkyl, halo-C₁₋₃-alkyl, OH, CN and oxo.

In a further most preferred embodiment in combination with any of the above or below embodiments, C is



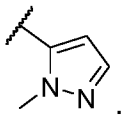
which is not further substituted or substituted with 1 substituent selected from the group consisting of OH, CN, C₁₋₆-alkyl, O-C₁₋₆-alkyl, OC(O)R^a, S(O)-C₁₋₆-alkyl, S(O)₂-C₁₋₆-alkyl, N(R^a)₂, NR^aC(O)-C₁₋₆-alkyl, S(O)₂N(R^a)₂, NR^aS(O)₂-C₁₋₆-alkyl and C₃₋₆-cycloalkyl, wherein the alkyl and cycloalkyl are unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of halogen, C₁₋₃-alkyl, halo-C₁₋₃-alkyl, OH, CN and oxo.

In an utmost preferred embodiment in combination with any of the above or below embodiments, C is

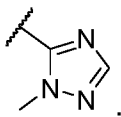


In a further utmost preferred embodiment in combination with any of the above or below embodiments, C is

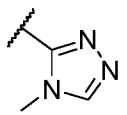
23



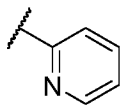
In an equally utmost preferred embodiment in combination with any of the above or below embodiments, C is



- 5 In a further equally utmost preferred embodiment in combination with any of the above or below embodiments, C is

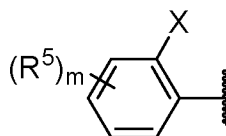


In a further utmost preferred embodiment in combination with any of the above or below embodiments, C is



10

In a preferred embodiment in combination with any of the above or below embodiments, A is



wherein X is F, Cl, CH₃, CH₂CH₃, CHF₂ or CF₃;

- 15 R⁵ is independently halogen or CN; and

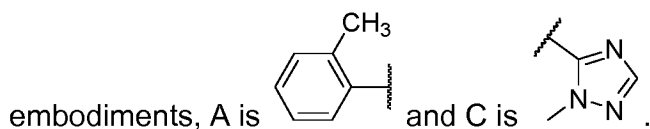
m is 0 or 1, and

C is , , or , wherein the ring is not further substituted

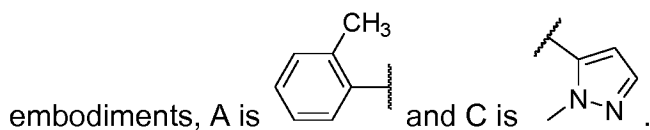
or substituted with 1 or 2 substituents independently selected from the group consisting of OH, CN, C₁₋₆-alkyl, O-C₁₋₆-alkyl, OC(O)R^a, S(O)-C₁₋₆-alkyl, S(O)₂-C₁₋₆-alkyl, N(R^a)₂,

- 20 NR^aC(O)-C₁₋₆-alkyl, S(O)₂N(R^a)₂, NR^aS(O)₂-C₁₋₆-alkyl and C₃₋₆-cycloalkyl, wherein alkyl and cycloalkyl are unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of halogen, C₁₋₃-alkyl, halo-C₁₋₃-alkyl, OH, CN and oxo.

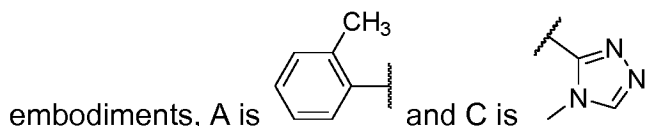
In a more preferred embodiment in combination with any of the above or below



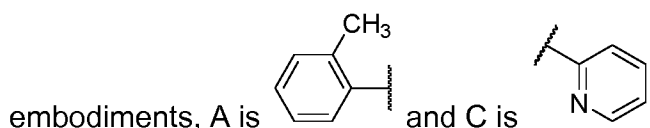
In a further more preferred embodiment in combination with any of the above or below



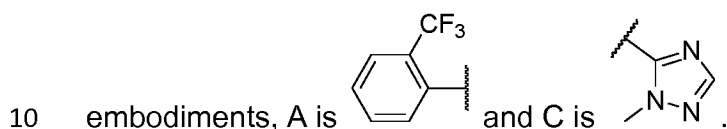
5 In a further more preferred embodiment in combination with any of the above or below



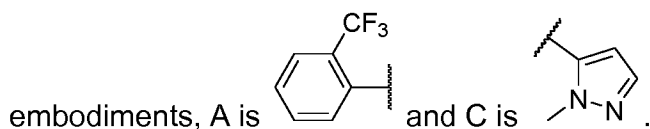
In a further more preferred embodiment in combination with any of the above or below



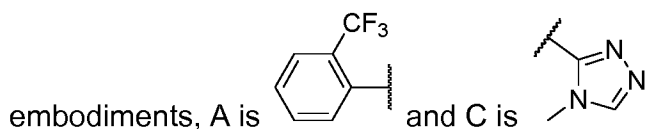
In a further more preferred embodiment in combination with any of the above or below



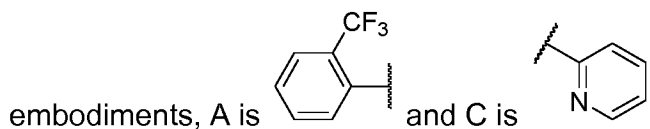
In a further more preferred embodiment in combination with any of the above or below



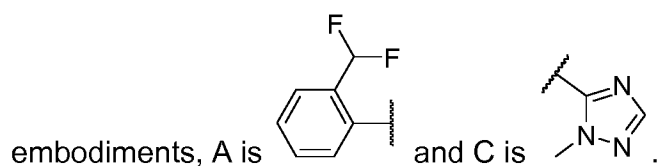
In a further more preferred embodiment in combination with any of the above or below



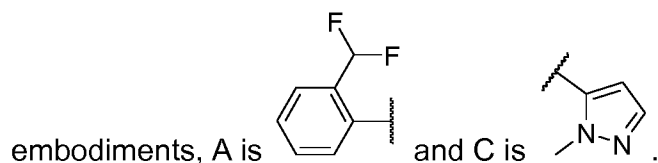
15 In a further more preferred embodiment in combination with any of the above or below



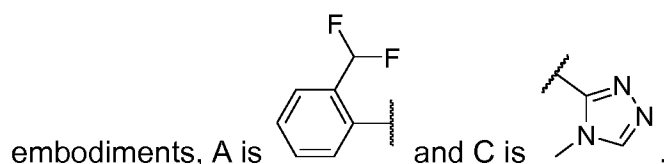
In a further more preferred embodiment in combination with any of the above or below



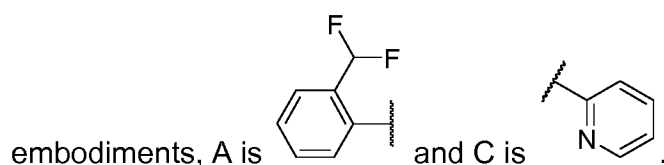
In a further more preferred embodiment in combination with any of the above or below



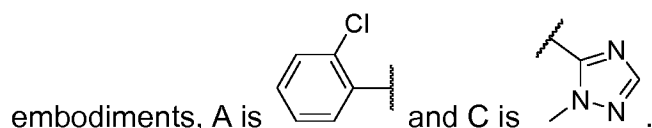
5 In a further more preferred embodiment in combination with any of the above or below



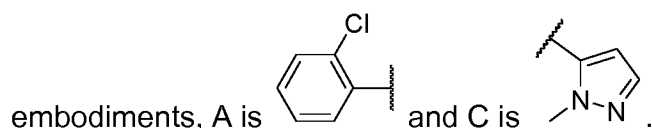
In a further more preferred embodiment in combination with any of the above or below



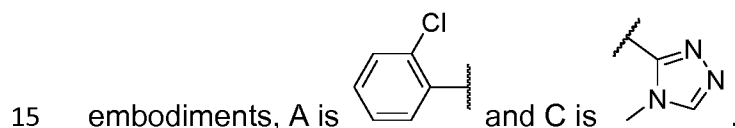
10 In a further more preferred embodiment in combination with any of the above or below



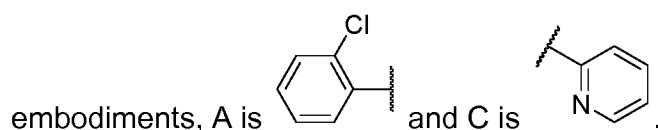
In a further more preferred embodiment in combination with any of the above or below



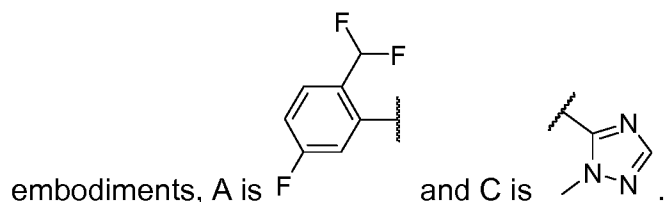
In a further more preferred embodiment in combination with any of the above or below



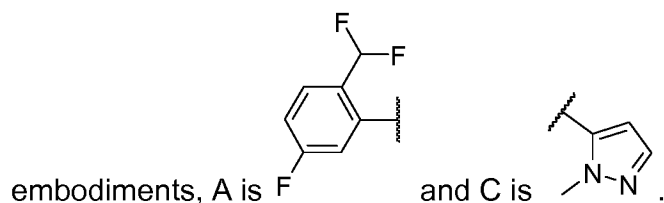
In a further more preferred embodiment in combination with any of the above or below



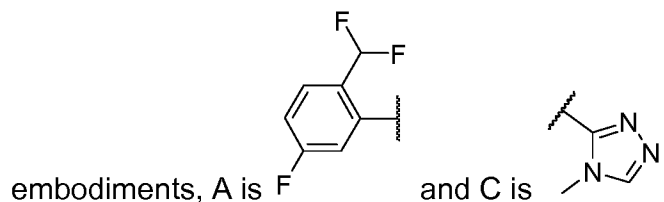
In a further more preferred embodiment in combination with any of the above or below



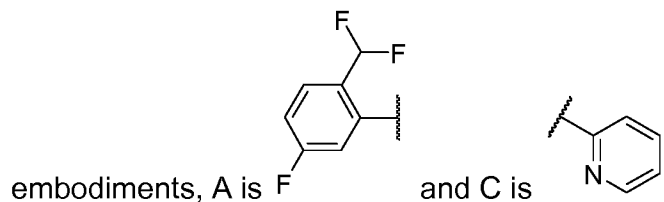
In a further more preferred embodiment in combination with any of the above or below



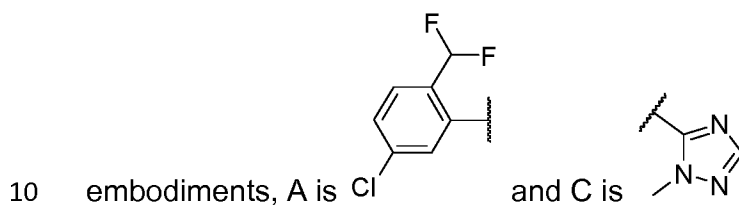
5 In a further more preferred embodiment in combination with any of the above or below



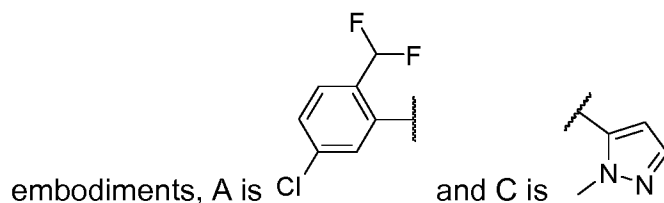
In a further more preferred embodiment in combination with any of the above or below



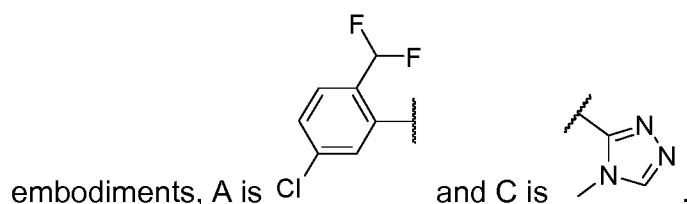
In a further more preferred embodiment in combination with any of the above or below



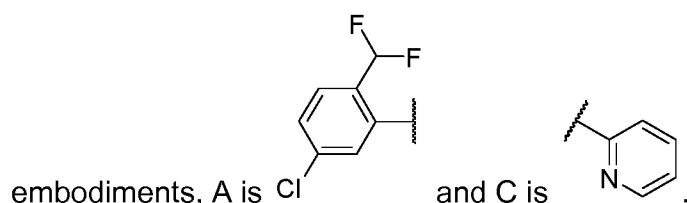
In a further more preferred embodiment in combination with any of the above or below



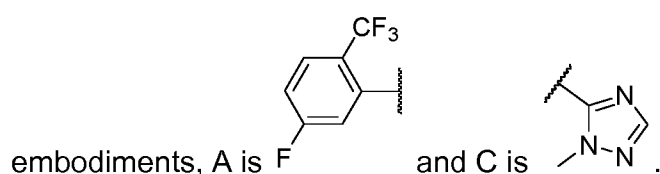
In a further more preferred embodiment in combination with any of the above or below



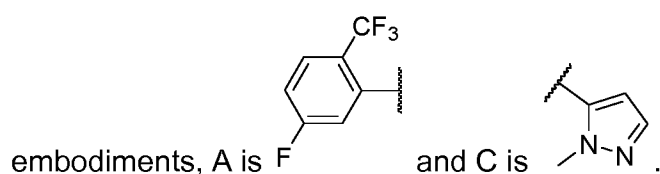
In a further more preferred embodiment in combination with any of the above or below



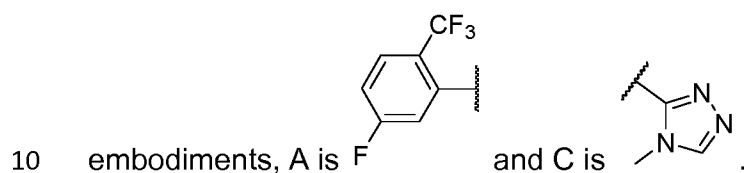
5 In a further more preferred embodiment in combination with any of the above or below



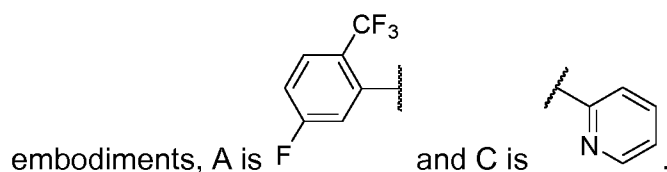
In a further more preferred embodiment in combination with any of the above or below



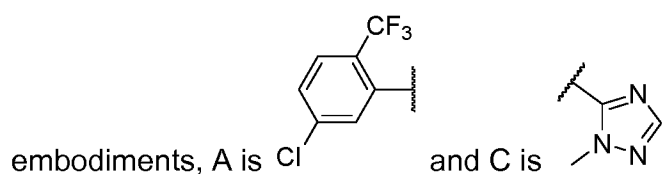
In a further more preferred embodiment in combination with any of the above or below



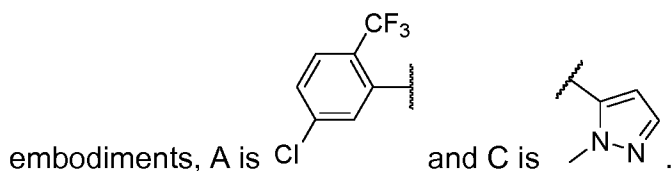
In a further more preferred embodiment in combination with any of the above or below



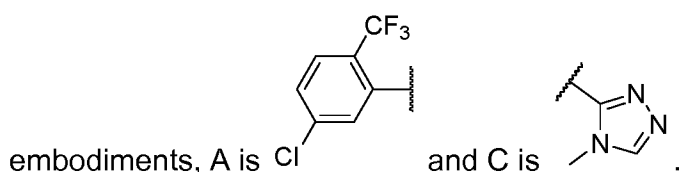
In a further more preferred embodiment in combination with any of the above or below



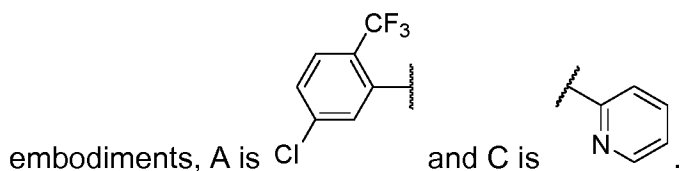
In a further more preferred embodiment in combination with any of the above or below



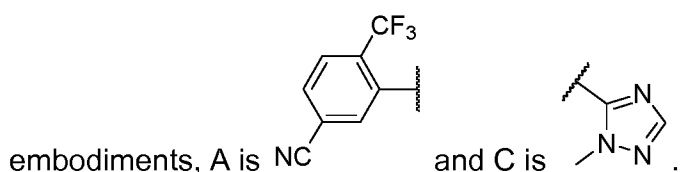
In a further more preferred embodiment in combination with any of the above or below



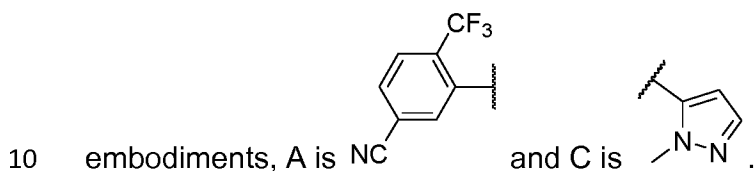
5 In a further more preferred embodiment in combination with any of the above or below



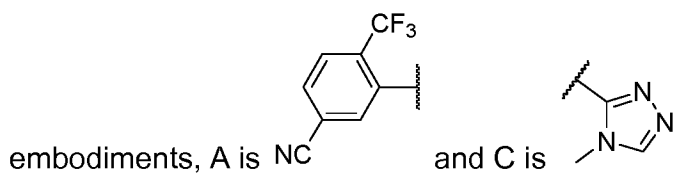
In a further more preferred embodiment in combination with any of the above or below



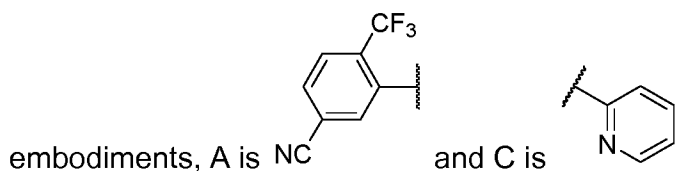
In a further more preferred embodiment in combination with any of the above or below



In a further more preferred embodiment in combination with any of the above or below



In a further more preferred embodiment in combination with any of the above or below



15 In a preferred embodiment in combination with any of the above or below embodiments, L is -NR^bC(O)C(O)NR^b-, -NR^bC(=NR^c)-, -NR^bSO₂-, -C(O)NR^b-, -NR^b-C₁₋₂-alkylene- or

-C₀₋₂-alkylene-NR^bC(O)-, wherein alkylene is unsubstituted or substituted with 1 to 4 substituents independently selected from halogen, C₁₋₃-alkyl and halo-C₁₋₃-alkyl;
 R^b is independently selected from hydrogen and C₁₋₆-alkyl; and
 R^c is hydrogen, OH, C₁₋₆-alkyl, O-C₁₋₆-alkyl or CN.

- 5 In a more preferred embodiment in combination with any of the above or below embodiments, L is -NR^bC(O)-.

In a further more preferred embodiment in combination with any of the above or below embodiments, L is -NR^bC(O)C(O)NR^b-.

- 10 In a further more preferred embodiment in combination with any of the above or below embodiments, L is -NR^bC(=NR^c)-.

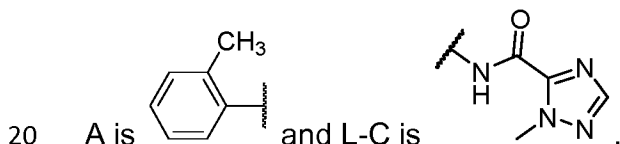
In a further more preferred embodiment in combination with any of the above or below embodiments, L is -NR^bSO₂-.

In a further more preferred embodiment in combination with any of the above or below embodiments, L is -C(O)NR^b-.

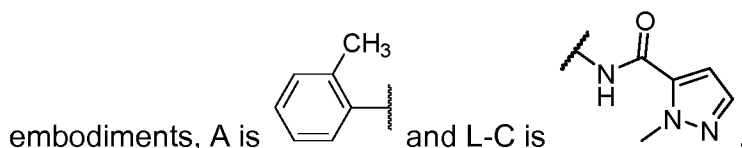
- 15 In a further more preferred embodiment in combination with any of the above or below embodiments, L is -NR^b-C₁₋₂-alkylene-.

In a most preferred embodiment in combination with any of the above or below embodiments, L is -NR^bC(O)-, wherein R^b is hydrogen or C₁₋₆-alkyl, more R^b is hydrogen.

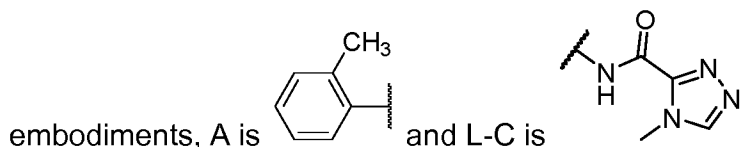
In a preferred embodiment in combination with any of the above or below embodiments,



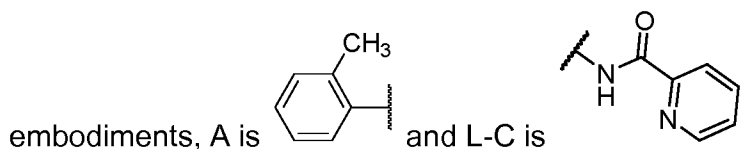
In a further preferred embodiment in combination with any of the above or below



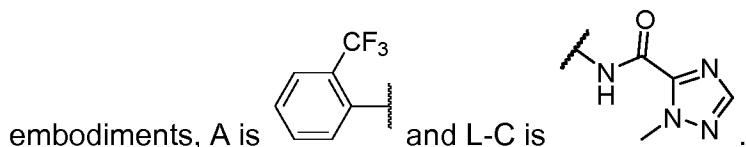
In a further preferred embodiment in combination with any of the above or below



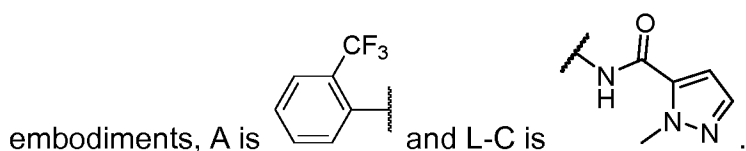
In a further preferred embodiment in combination with any of the above or below



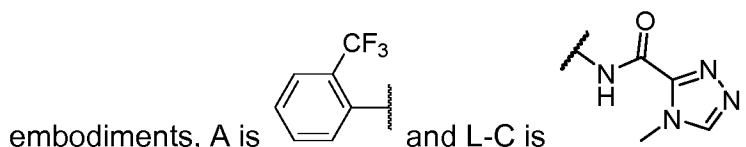
In a further preferred embodiment in combination with any of the above or below



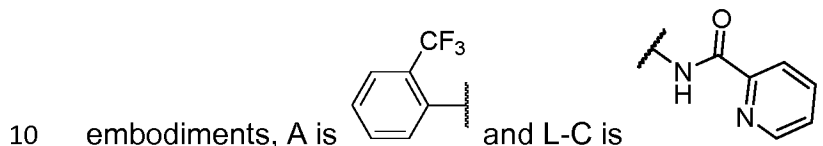
5 In a further preferred embodiment in combination with any of the above or below



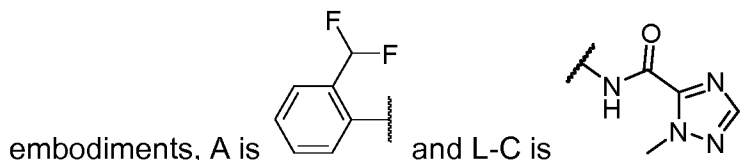
In a further preferred embodiment in combination with any of the above or below



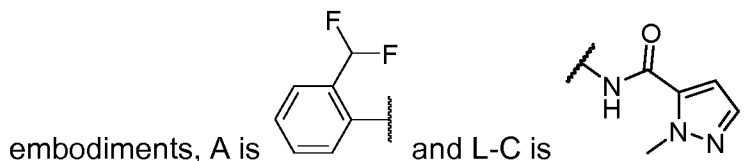
In a further preferred embodiment in combination with any of the above or below



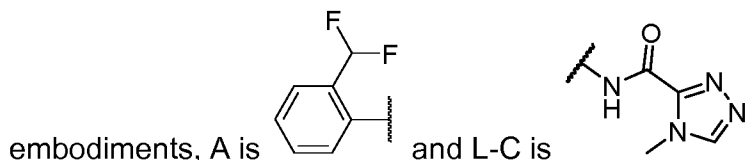
In a further preferred embodiment in combination with any of the above or below



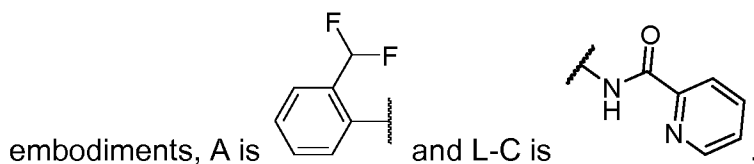
In a further preferred embodiment in combination with any of the above or below



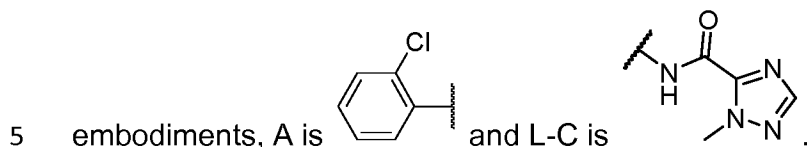
15 In a further preferred embodiment in combination with any of the above or below



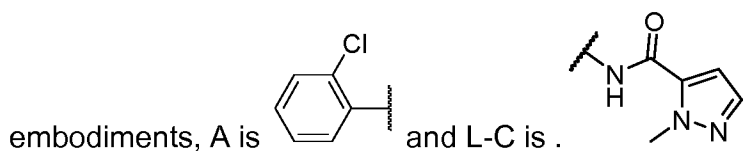
In a further preferred embodiment in combination with any of the above or below



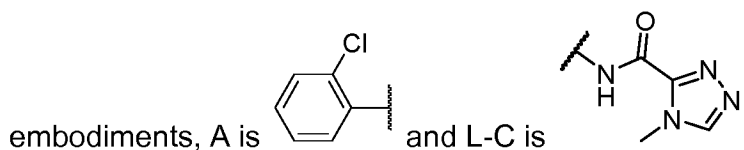
In a further preferred embodiment in combination with any of the above or below



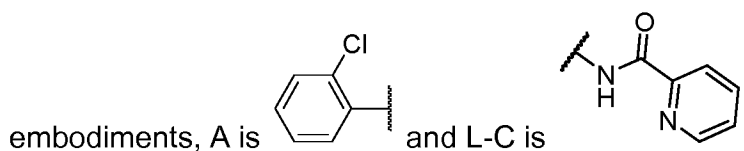
In a further preferred embodiment in combination with any of the above or below



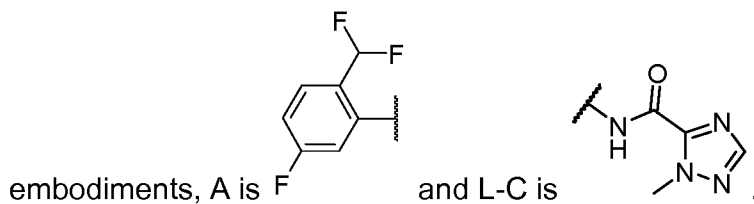
In a further preferred embodiment in combination with any of the above or below



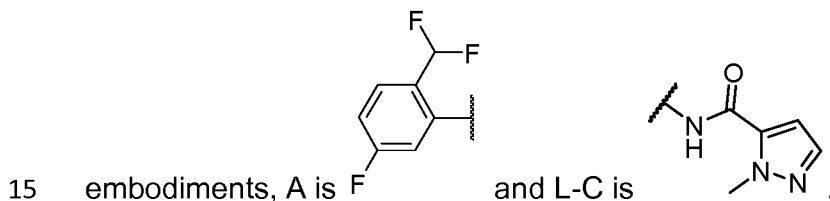
10 In a further preferred embodiment in combination with any of the above or below



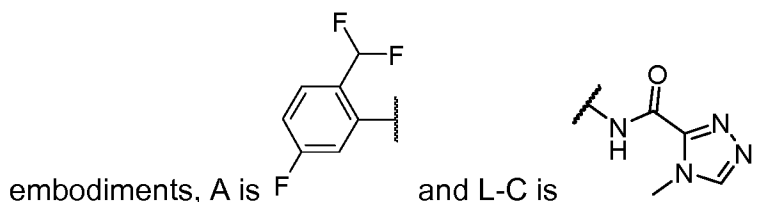
In a further preferred embodiment in combination with any of the above or below



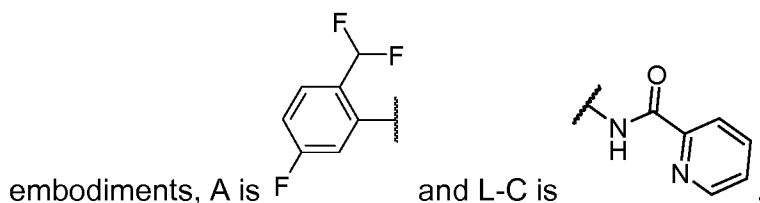
In a further preferred embodiment in combination with any of the above or below



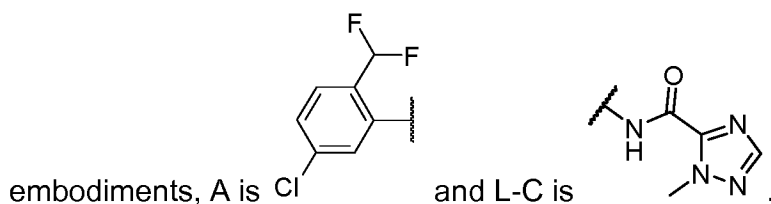
In a further preferred embodiment in combination with any of the above or below



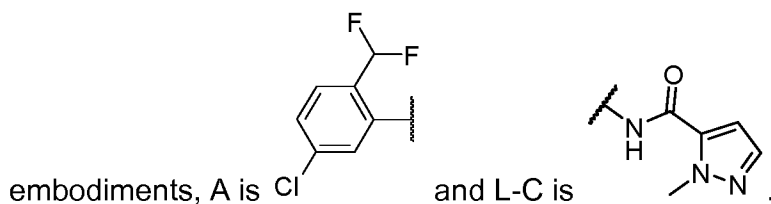
In a further preferred embodiment in combination with any of the above or below



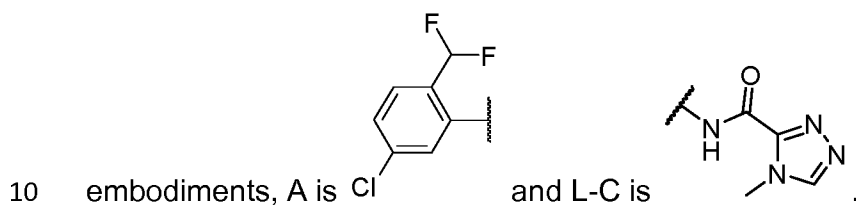
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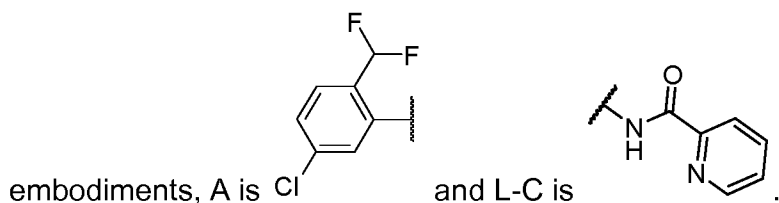
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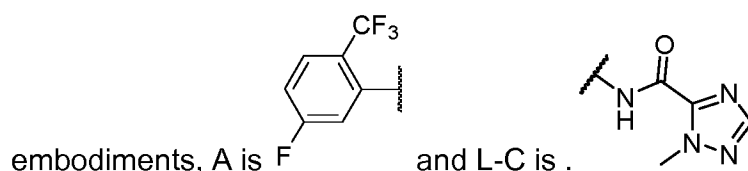
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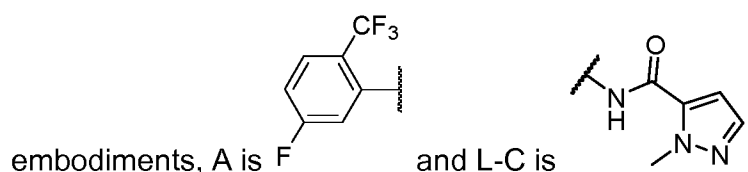
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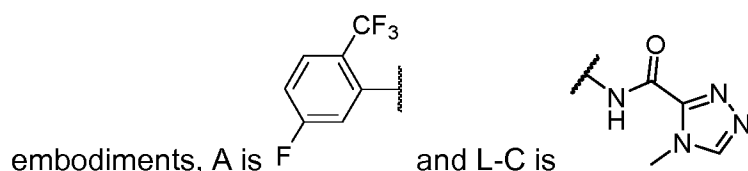
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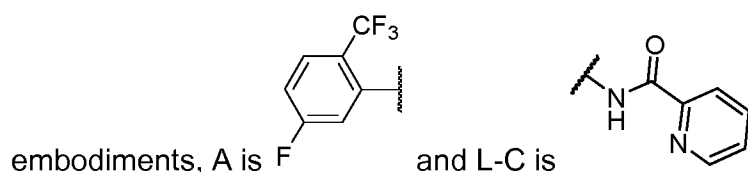
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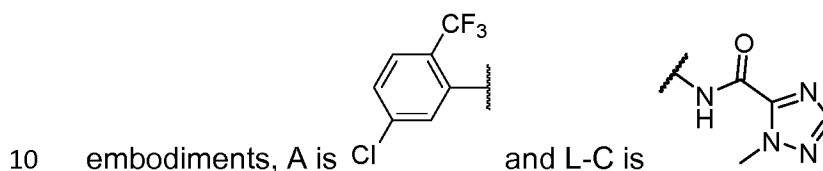
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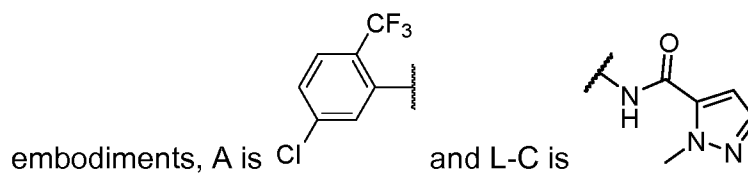
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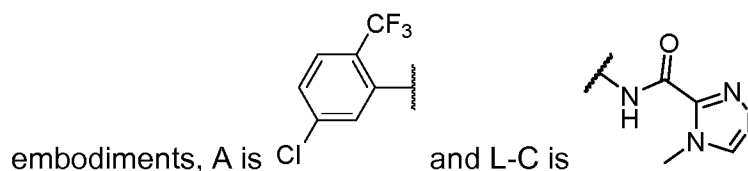
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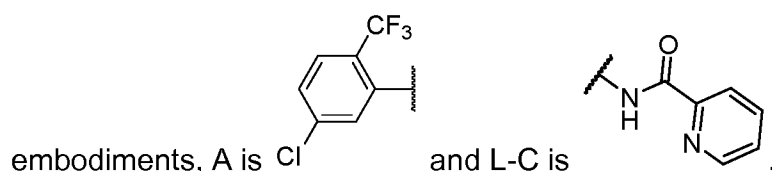
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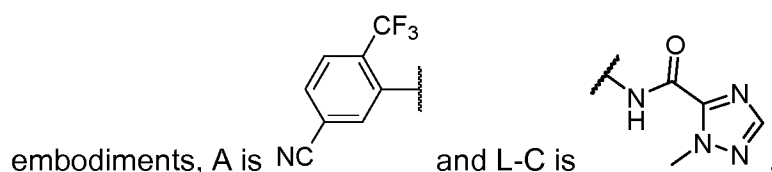
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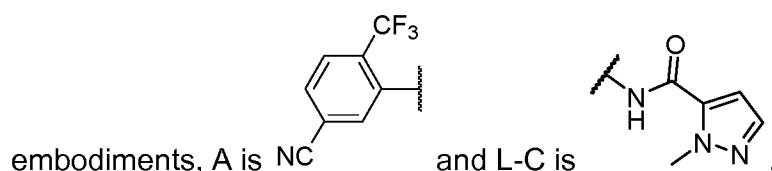
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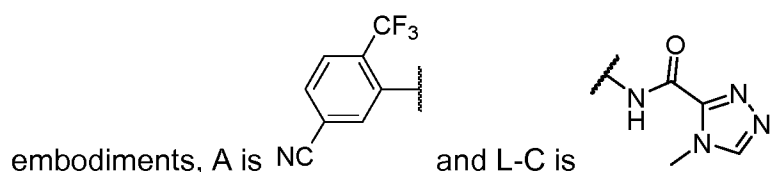
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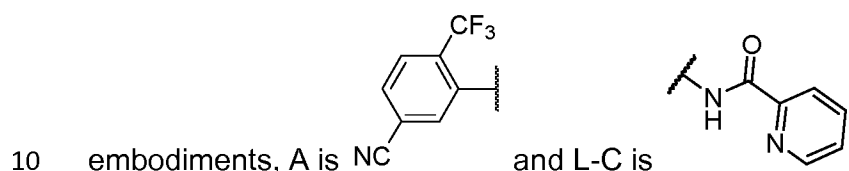
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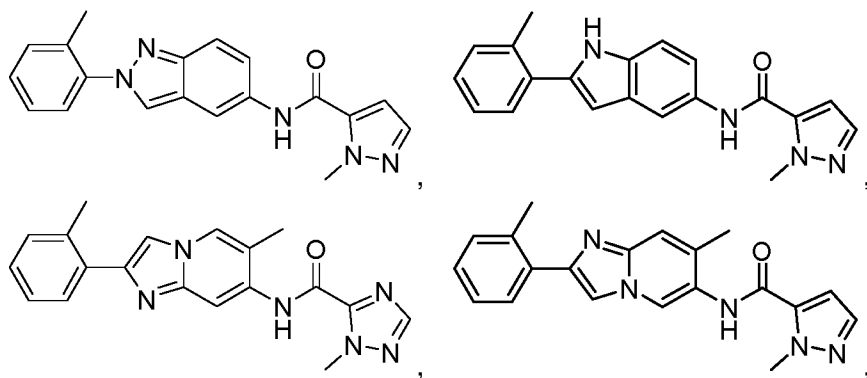
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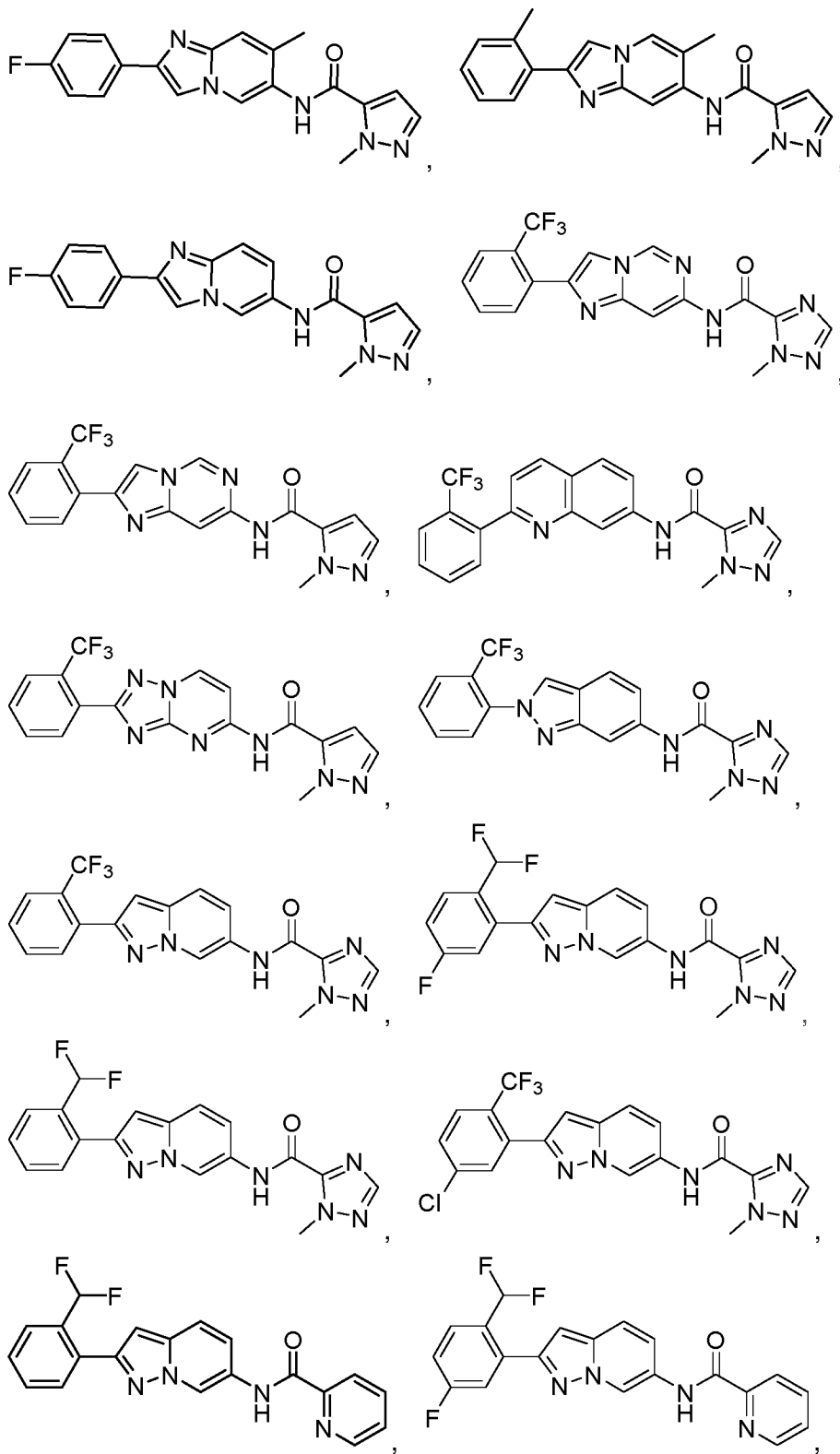


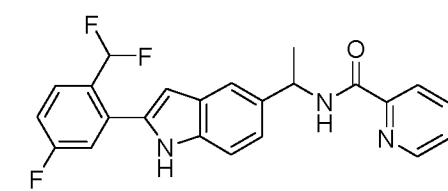
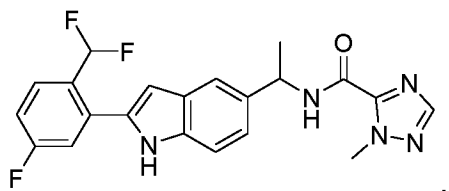
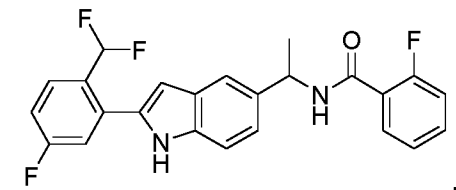
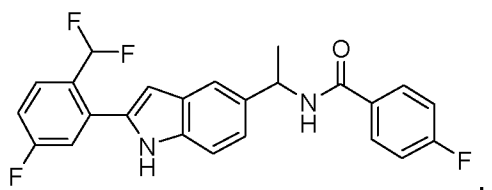
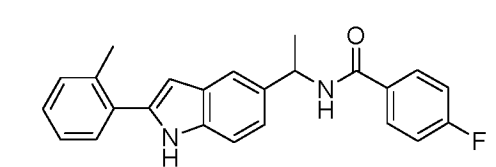
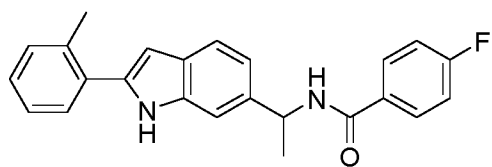
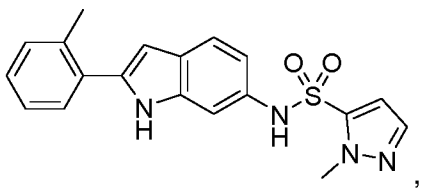
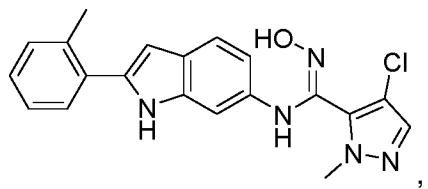
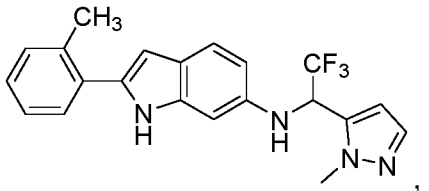
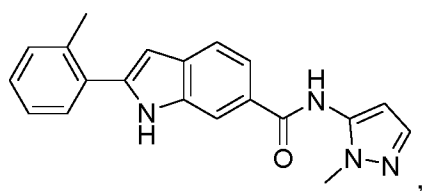
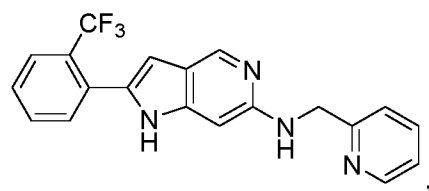
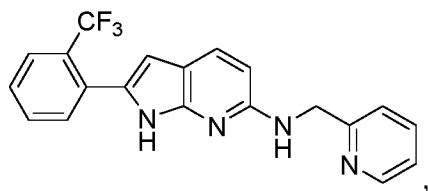
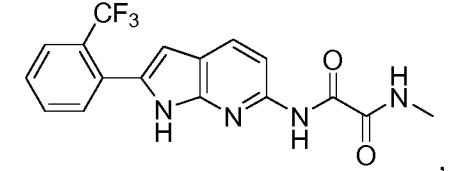
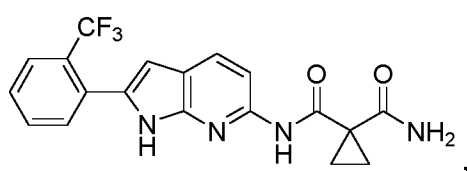
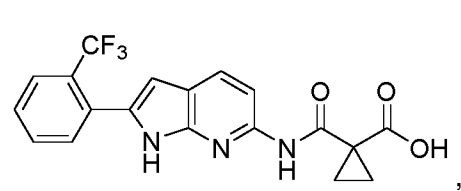
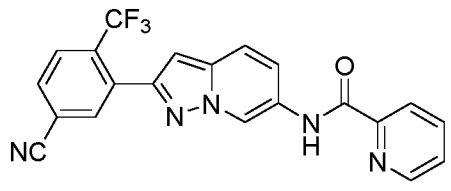
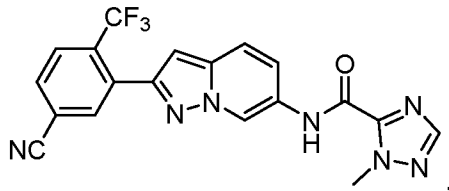
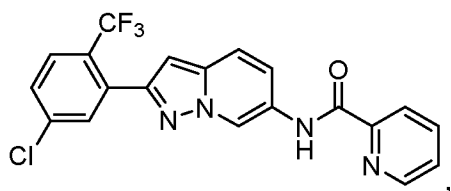
In a further preferred embodiment in combination with any of the above or below

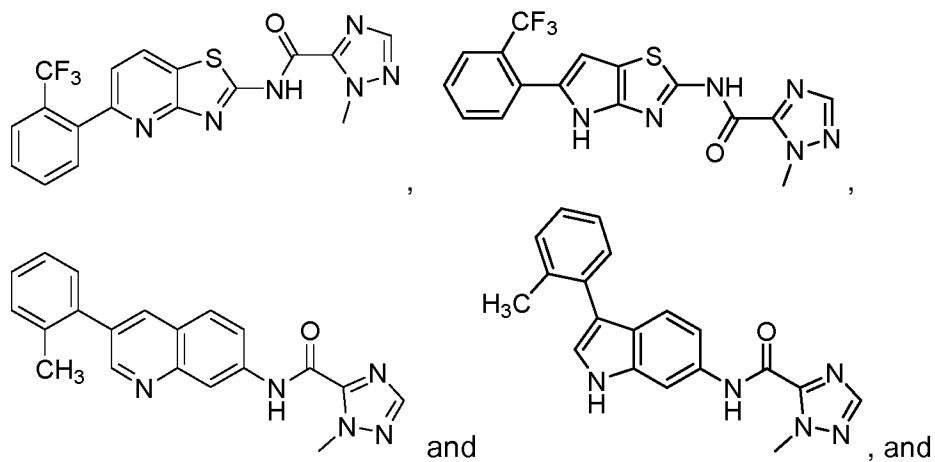


In another embodiment in combination with any of the above or below embodiments, the compound according to Formula (I) is selected from



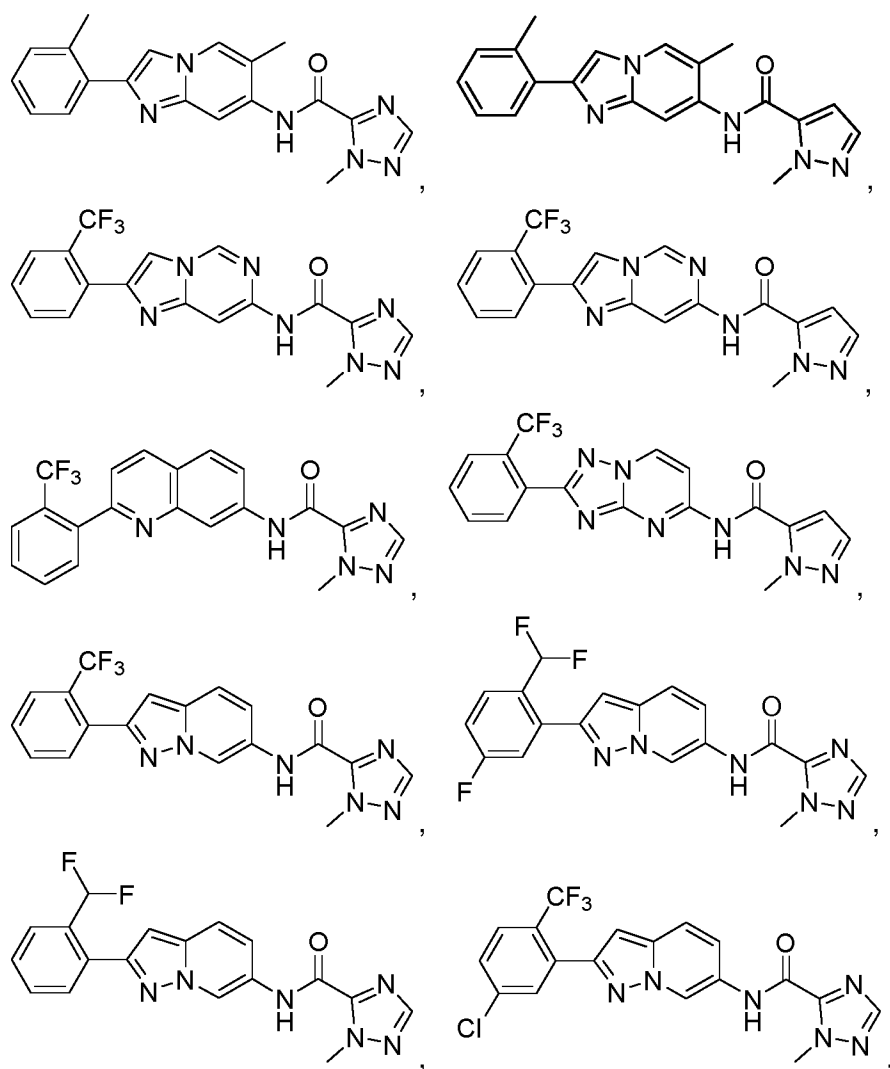


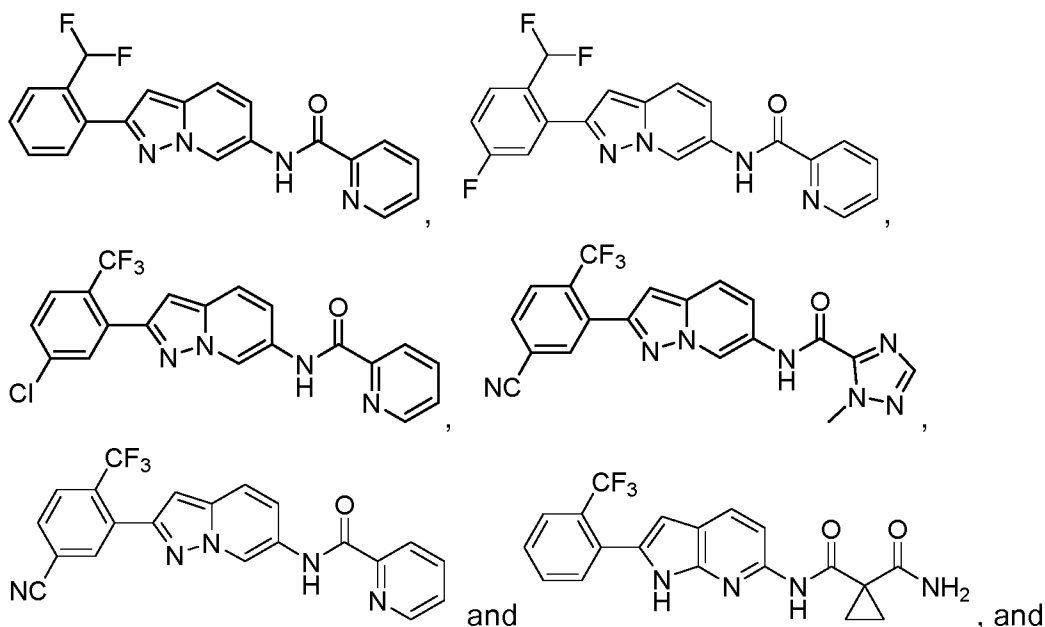




an enantiomer, diastereomer, tautomer, solvate, N-oxide, prodrug or pharmaceutical acceptable salt thereof.

- 5 In a preferred embodiment in combination with any of the above and below embodiments, the compound according to Formula (I) is selected from





an enantiomer, diastereomer, tautomer, solvate, N-oxide, prodrug or pharmaceutical acceptable salt thereof.

In another embodiment, the present invention is directed to a pharmaceutical composition comprising the compound according to Formula (I) and a physiologically acceptable excipient.

In another embodiment, the present invention is directed to the compound according to Formula (I) for use as a medicament.

In another embodiment, the present invention is directed to the compound according to Formula (I) or a pharmaceutical composition containing same and a physiologically acceptable excipient for use in the prophylaxis and/or treatment of a disease or condition mediated by aryl hydrocarbon receptor (AhR).

In another embodiment in combination with any of the above or below embodiments, the disease or condition mediated by aryl hydrocarbon receptor (AhR) is cancer.

In another embodiment in combination with any of the above or below embodiments, the compound according to Formula (I) is administered with one or more therapeutic agents for cancer selected from the group consisting of PD-1 agent, PD-L1 agent, CTLA-4 agent, IDO1 inhibitor, chemotherapeutic agent, anticancer vaccine, Toll like receptor agonist, oncolytic virus, STING agonist and cytokine therapy, or wherein the compound is administered under irradiation therapy.

In the context of the present invention "C₁₋₆-alkyl" means a saturated alkyl chain having 1 to 6 carbon atoms which may be straight chained or branched. Examples thereof

include methyl, ethyl, propyl, isopropyl, *n*-butyl, isobutyl, *tert*-butyl, *n*-pentyl, isopentyl, neopentyl, and hexyl.

A "C₀₋₂-alkylene" means that the respective group is divalent and connects the attached residue with the remaining part of the molecule. Moreover, in the context of the present invention, "C₀-alkylene" is meant to represent a bond, whereas C₁-alkylene means a methylene linker, C₂-alkylene means an ethylene linker or a methyl-substituted methylene linker and so on. In the context of the present invention, a C₀₋₂-alkylene preferably represents a bond or a methylene group.

The term "O-C₁₋₆-alkyl" means that the alkyl chain is connected via an oxygen atom with the remainder of the molecule.

The term "halo-C₁₋₆-alkyl" means that one or more hydrogen atoms in the alkyl chain are replaced by a halogen. A preferred example thereof is CF₃.

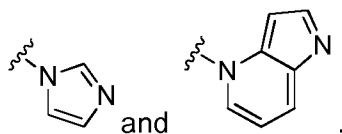
A C₃₋₆-cycloalkyl group means a saturated or partially unsaturated mono- or bicyclic ring system comprising 3 to 6 carbon atoms. Examples include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cyclohexenyl.

A 3- to 10-membered heterocycloalkyl group means a saturated or partially unsaturated 3 to 10 membered carbon mono-, bi-, spiro- or multicyclic ring wherein 1, 2, 3 or 4 carbon atoms are replaced by 1, 2, 3 or 4 heteroatoms, respectively, wherein the heteroatoms are independently selected from N, O, S, SO and SO₂. Examples thereof include epoxidyl, oxetanyl, pyrrolidinyl, tetrahydrofuranyl, piperidinyl, piperazinyl, tetrahydropyranyl, 1,4-dioxanyl, morpholinyl, 4-quinuclidinyl, 1,4-dihydropyridinyl and 6-azabicyclo[3.2.1]octanyl. The heterocycloalkyl group can be connected with the remaining part of the molecule via a carbon, nitrogen (e.g. in morpholine or piperidine) or sulfur atom.

A 5-10-membered mono- or bicyclic heteroaromatic ring system (within the application also referred to as heteroaryl) containing up to 6 heteroatoms means a monocyclic heteroaromatic ring such as pyrrolyl, imidazolyl, furanyl, thiophenyl, pyridinyl, pyrimidinyl, pyrazinyl, pyrazolyl, oxazolyl, isoxazolyl, triazolyl, oxadiazolyl and thiadiazolyl. It further means a bicyclic ring system wherein the heteroatom(s) may be present in one or both rings including the bridgehead atoms. Examples thereof include, benzimidazolyl, benzisoxazolyl, benzodioxanyl, benzofuranyl, benzoxazolyl, imidazo[1,2-*a*]pyridinyl, imidazo[1,2-*c*]pyrimidinyl, indazolyl, indolizinyl, indolyl, isoquinolinyl, pyrazolo[1,5-*a*]pyridinyl, pyrrolo[2,3-*b*]pyridinyl, pyrrolo[3,2-*c*]pyridinyl, pyrrolo[2,3-*d*]thiazolyl,

quinolinyl, quinoxaliny, pyrazolo[1,5-a]pyrimidinyl, thiazolo[4,5-b]pyridinyl and [1,2,4]triazolo[1,5-a]pyrimidinyl.

The nitrogen or sulphur atom of the heteroaryl system may also be optionally oxidized to the corresponding *N*-oxide, *S*-oxide or *S,S*-dioxide. If not stated otherwise, the heteroaryl system can be connected via a carbon or nitrogen atom. Examples for *N*-linked heterocycles are



Moreover, where not explicitly defined, heteroaryl contains 1 to 6 heteroatoms independently selected from the group consisting of N, O and S.

- 10 A 6-10-membered mono- or bicyclic aromatic ring system (within the application also referred to as aryl) means an aromatic carbon cycle such as phenyl or naphthyl.

The term “halogen” comprises the specific halogen atoms fluorine, bromine, chlorine and iodine.

- Any formula or structure given herein, is also intended to represent unlabeled forms as well as isotopically labeled forms of the compounds. Isotopically labeled compounds have structures depicted by the formulas given herein except that one or more atoms are replaced by an atom having a selected atomic mass or mass number. Examples of isotopes that can be incorporated into compounds of the disclosure include isotopes of hydrogen, carbon, nitrogen, oxygen, fluorine and chlorine, such as, but not limited to ^2H (deuterium, D), ^3H (tritium), ^{11}C , ^{13}C , ^{14}C , ^{15}N , ^{18}F , ^{35}S , ^{36}Cl and ^{125}I . Various isotopically labeled compounds of the present disclosure, for example those into which radioactive isotopes such as ^3H , ^{13}C and ^{14}C are incorporated. Such isotopically labelled compounds may be useful in metabolic studies, reaction kinetic studies, detection or imaging techniques, such as positron emission tomography (PET) or single-photon emission computed tomography (SPECT) including drug or substrate tissue distribution assays or in radioactive treatment of patients. Isotopically labeled compounds of this disclosure and prodrugs thereof can generally be prepared by carrying out the procedures disclosed in the schemes or in the examples and preparations described below by substituting a readily available isotopically labeled reagent for a non-isotopically labeled reagent.

- 30 The disclosure also includes “deuterated analogs” of compounds of Formula (I) in which from 1 to n hydrogens attached to a carbon atom is/are replaced by deuterium, in which n is the number of hydrogens in the molecule. Such compounds may exhibit increased

resistance to metabolism and thus be useful for increasing the half-life of any compound of Formula (I) when administered to a mammal, e.g. a human. See, for example, Foster in Trends Pharmacol. Sci. 1984:5;524. Such compounds are synthesized by means well known in the art, for example by employing starting materials in which one or more
5 hydrogens have been replaced by deuterium.

Deuterium labelled or substituted therapeutic compounds of the disclosure may have improved DMPK (drug metabolism and pharmacokinetics) properties, relating to distribution, metabolism and excretion (ADME). Substitution with heavier isotopes such as deuterium may afford certain therapeutic advantages resulting from greater metabolic
10 stability, for example increased *in vivo* half-life, reduced dosage requirements and/or an improvement in therapeutic index. An ¹⁸F labeled compound may be useful for PET or SPECT studies.

The concentration of such a heavier isotope, specifically deuterium, may be defined by an isotopic enrichment factor. In the compounds of this disclosure any atom not
15 specifically designated as a particular isotope is meant to represent any stable isotope of that atom. Unless otherwise stated, when a position is designated specifically as "H" or "hydrogen", the position is understood to have hydrogen at its natural abundance isotopic composition.

The compounds of the present invention can be in the form of a prodrug compound.
20 "Prodrug compound" means a derivative that is converted into a compound according to the present invention by a reaction with an enzyme, gastric acid or the like under a physiological condition in the living body, e.g. by oxidation, reduction, hydrolysis or the like, each of which is carried out enzymatically. Examples of the prodrug are compounds, wherein the amino group in a compound of the present invention is acylated, alkylated
25 or phosphorylated to form, e.g., eicosanoylamino, alanylamino, pivaloyloxymethylamino or wherein the hydroxyl group is acylated, alkylated, phosphorylated or converted into the borate, e.g. acetyloxy, palmitoyloxy, pivaloyloxy, succinyloxy, fumaryloxy, alanyloxy or wherein the carboxyl group is esterified or amidated. These compounds can be produced from compounds of the present invention according to well-known methods.
30 Other examples of the prodrug are compounds, wherein the carboxylate in a compound of the present invention is, for example, converted into an alkyl-, aryl-, choline-, amino, acyloxymethylester, linolenylester.

Metabolites of compounds of the present invention are also within the scope of the present invention.

Where tautomerism, like e.g. keto-enol tautomerism, of compounds of the present invention or their prodrugs may occur, the individual forms, like e.g. the keto and enol form, are each within the scope of the invention as well as their mixtures in any ratio. Same applies for stereoisomers, like e.g. enantiomers, cis/trans isomers, conformers and the like.

If desired, isomers can be separated by methods well known in the art, e.g. by liquid chromatography. Same applies for enantiomers by using e.g. chiral stationary phases. Additionally, enantiomers may be isolated by converting them into diastereomers, i.e. coupling with an enantiomerically pure auxiliary compound, subsequent separation of the resulting diastereomers and cleavage of the auxiliary residue. Alternatively, any enantiomer of a compound of the present invention may be obtained from stereoselective synthesis using optically pure starting materials. Another way to obtain pure enantiomers from racemic mixtures would use enantioselective crystallization with chiral counterions.

The compounds of the present invention can be in the form of a pharmaceutically acceptable salt or a solvate. The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids, including inorganic bases or acids and organic bases or acids. In case the compounds of the present invention contain one or more acidic or basic groups, the invention also comprises their corresponding pharmaceutically or toxicologically acceptable salts, in particular their pharmaceutically utilizable salts. Thus, the compounds of the present invention which contain acidic groups can be present on these groups and can be used according to the invention, for example, as alkali metal salts, alkaline earth metal salts or ammonium salts. More precise examples of such salts include sodium salts, potassium salts, calcium salts, magnesium salts or salts with ammonia or organic amines such as, for example, ethylamine, ethanolamine, triethanolamine or amino acids. The compounds of the present invention which contain one or more basic groups, i.e. groups which can be protonated, can be present and can be used according to the invention in the form of their addition salts with inorganic or organic acids. Examples of suitable acids include hydrogen chloride, hydrogen bromide, phosphoric acid, sulfuric acid, nitric acid, methanesulfonic acid, p-toluenesulfonic acid, naphthalenedisulfonic acids, oxalic acid, acetic acid, tartaric acid, lactic acid, salicylic acid, benzoic acid, formic acid, propionic acid, pivalic acid, diethylacetic acid, malonic acid, succinic acid, pimelic acid, fumaric acid, maleic acid, malic acid, sulfaminic acid, phenylpropionic acid, gluconic acid, ascorbic acid, isonicotinic acid, citric acid, adipic acid, and other acids known to the person skilled in the art. If the compounds of the present invention simultaneously contain

acidic and basic groups in the molecule, the invention also includes, in addition to the salt forms mentioned, inner salts or betaines (zwitterions). The respective salts can be obtained by customary methods which are known to the person skilled in the art like, for example, by contacting these with an organic or inorganic acid or base in a solvent or dispersant, or by anion exchange or cation exchange with other salts. The present invention also includes all salts of the compounds of the present invention which, owing to low physiological compatibility, are not directly suitable for use in pharmaceuticals but which can be used, for example, as intermediates for chemical reactions or for the preparation of pharmaceutically acceptable salts.

- Further the compounds of the present invention may be present in the form of solvates, such as those which include as solvate water, or pharmaceutically acceptable solvates, such as alcohols, in particular ethanol.

Furthermore, the present invention provides pharmaceutical compositions comprising at least one compound of the present invention, or a prodrug compound thereof, or a pharmaceutically acceptable salt or solvate thereof as active ingredient together with a pharmaceutically acceptable carrier.

"Pharmaceutical composition" means one or more active ingredients, and one or more inert ingredients that make up the carrier, as well as any product which results, directly or indirectly, from combination, complexation or aggregation of any two or more of the ingredients, or from dissociation of one or more of the ingredients, or from other types of reactions or interactions of one or more of the ingredients. Accordingly, the pharmaceutical compositions of the present invention encompass any composition made by admixing at least one compound of the present invention and a pharmaceutically acceptable carrier.

- The pharmaceutical composition of the present invention may additionally comprise one or more other compounds as active ingredients like a prodrug compound or other nuclear receptor modulators.

Specifically, the compound of the present invention can be administered with one or more therapeutic agents for cancer selected from the group consisting of PD-1 agent, PD-L1 agent, CTLA-4 agent, IDO1 inhibitor, chemotherapeutic agent, anticancer vaccine, Toll like receptor agonist, oncolytic virus, STING agonist and cytokine therapy, or the compound is administered under irradiation therapy.

Examples of PD-1 agents include, but are not limited to, Pembrolizumab and Nivolumab.

Examples of PD-L1 agents include, but are not limited to, Atezolizumab, Avelumab and Durvalumab.

Examples of CTLA-4 agents include, but are not limited to, Ipilimumab.

Examples of IDO1 inhibitors include, but are not limited to, Epacadostat, Navoximod and BMS-986205.

Examples of chemotherapeutic agents include, but are not limited to, Cyclophosphamide, Busulfan, Carmustin, Temozolimide, Procarbazine, Trabectedin, Cisplatin, Carboplatin, Methotrexate, Pemetrexed, 6-Mercaptopurine, 6-Thioguanine, Cladribine, Clofarabine, Nelarabine, Pentostatin, 5-Fluorouracil, Cytarabine, Gemcitabine, Azacitidine, Vincristine, Vinblastine, Vindesine, Paclitaxel, Docetaxel, Cabazitaxel, Ixabepilone, Eribulin, Estramustine phosphate, Topotecan, Irinotecan, Etoposide, Teniposide, Dactinomycin, Bleomycin, Doxorubicin, Daunorubicin, Epirubicin, Idarubicin, Mitoxantrone, all-trans retinoic acid, Bexarotene, As₂O₃, Imatinib, Nilotinib, Dasatinib, Bosutinib, Ponatinib, Erlotinib, Gefitinib, Afatinib, Osimertinib, Lapatinib, Crizotinib, Ceritinib, Axitinib, Cabozantinib, Larvatinib, Nintedanib, Pazopanib, Regorafenib, Sorafenib, Sunitinib, Ruxolitinib, Dovitinib, Ibrutinib, Idelalisib, Vemurafenib, Dabrafenib, Trametinib, Cobimetinib, Palbociclib, Temsirolimus, Everolimus, Bortezomib, Carfilzomib, Vismodegib, Panobinostat, Olaparib, Venetoclax, Rituximab, Trastuzumab, Pertuzumab, Cetuximab, Panitumumab, Necitumumab, Bevacizumab, Ramucirumab, Olaratumab, Mifamurtide, Elotuzumab, Catumaxomab, Blinatumomab, Rituximab, Daratumumab, Alemtuzumab, Prednisone, Buserelin, Goserelin, Leuporelin, Histrelin, Triptorelin, Degarelix, Abarelix, Flutamide, Bicalutamide, Enzalutamide, Arbiraterone, Tamoxifen, Toremifen, Exemestane, Letrozole, Anastrozole, Fulvestrant, Thalidomide, Lenalidomide and Pomalidomide.

Examples of anticancer vaccines include, but are not limited to, Hepa-VAC-101 and Sipuleucel-T.

Examples of Toll like receptor agonists include, but are not limited to Imiquimod, Resiquimod, monophosphoryl lipid A, BCG, CpG ODNs and Motolimod.

Examples of oncolytic viruses include, but are not limited to H101, Talimogene laherparepvec.

Examples of STING agonists include, but are not limited to, ADU-S100 and MK-1454.

Examples of cytokine therapy include, but are not limited to IL-2, GM-CSF, IL-12 and IL-10.

Examples of other Immune-Oncology therapeutics that can be used in combination with the compounds of the present invention include, but are not limited to Chimeric antigen receptor, or *CAR T-cell therapy*, such as Tisagenlecleucel, Axicabtagen Ciloleucel and immune response modifying enzymes such as Asparaginase or Kynureninase.

5 In practical use, the compounds used in the present invention can be combined as the active ingredient in intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g., oral or parenteral (including intravenous). In preparing the compositions for oral dosage
10 form, any of the usual pharmaceutical media may be employed, such as, for example, water, glycols, oils, alcohols, flavouring agents, preservatives, colouring agents and the like in the case of oral liquid preparations, such as, for example, suspensions, elixirs and solutions; or carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents and the like in the case of
15 oral solid preparations such as, for example, powders, hard and soft capsules and tablets, with the solid oral preparations being preferred over the liquid preparations.

Because of their ease of administration, tablets and capsules represent the most advantageous oral dosage unit form in which case solid pharmaceutical carriers are obviously employed. If desired, tablets may be coated by standard aqueous or non-
20 aqueous techniques. Such compositions and preparations should contain at least 0.1 percent of active compound. The percentage of active compound in these compositions may, of course, be varied and may conveniently be between about 2 percent to about 60 percent of the weight of the unit. The amount of active compound in such therapeutically useful compositions is such that an effective dosage will be obtained. The active
25 compounds can also be administered intranasally as, for example, liquid drops or spray.

The tablets, pills, capsules, and the like may also contain a binder such as gum tragacanth, acacia, corn starch or gelatine; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, lactose or saccharin.
30 When a dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier such as a fatty oil.

Various other materials may be present as coatings or to modify the physical form of the dosage unit. For instance, tablets may be coated with shellac, sugar or both. A syrup or elixir may contain, in addition to the active ingredient, sucrose as a sweetening agent,

methyl and propylparabens as preservatives, a dye and a flavouring such as cherry or orange flavour.

The compounds used in the present invention may also be administered parenterally. Solutions or suspensions of these active compounds can be prepared in water suitably mixed with a surfactant such as hydroxy-propylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols and mixtures thereof in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases, the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g., glycerol, propylene glycol and liquid polyethylene glycol), suitable mixtures thereof, and vegetable oils.

Any suitable route of administration may be employed for providing a mammal, especially a human, with an effective dose of a compound of the present invention. For example, oral, rectal, topical, parenteral (including intravenous, intramuscular and subcutaneous), ocular (ophthalmic), pulmonary (nasal or buccal inhalation), nasal and the like may be employed. Dosage forms include tablets, troches, dispersions, suspensions, solutions, capsules, creams, ointments, aerosols, and the like. Preferably, compounds of the present invention are administered orally.

The effective dosage of active ingredient employed may vary depending on the particular compound employed, the mode of administration, the condition being treated and the severity of the condition being treated. Such dosage may be ascertained readily by a person skilled in the art.

When treating or preventing AhR-mediated conditions for which compounds of Formula (I) are indicated, generally satisfactory results are obtained when the compounds are administered at a daily dosage of from about 0.1 mg to about 100 mg per kilogram of mammal body weight, preferably given as a single daily dose or in divided doses two to six times a day, or in sustained release form. For most large mammals, the total daily dosage is from about 1 mg to about 1000 mg, preferably from about 1 mg to about 50 mg. In the case of a 70 kg adult human, the total daily dose will generally be from about

7 mg to about 350 mg. This dosage regimen may be adjusted to provide the optimal therapeutic response.

Abbreviations

5 Herein and throughout the application, the following abbreviations may be used.

	Ac	acetyl
	Boc	<i>tert</i> -butyloxycarbonyl
	br	broad
	Bz	benzoyl
10	CDI	1,1'-carbonyldiimidazole
	d	doublet
	DAST	(diethylamino)sulfur trifluoride
	dba	dibenzylideneacetone
	DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
15	DCM	dichloromethane
	DIBAL-H	diisobutylaluminum hydride
	DIPEA	<i>N,N</i> -diisopropylethylamine
	DMA	<i>N,N</i> -dimethylacetamide
	DMAP	4-(dimethylamino)pyridine
20	DMF	<i>N,N</i> -dimethylformamide
	DMSO	dimethyl sulfoxide
	dppf	1,1'- bis(diphenylphosphino)ferrocene
	dtbpf	1,1'- bis(di- <i>tert</i> -butylphosphino)ferrocene
	EDC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
25	Et	ethyl
	Et ₂ O	diethyl ether
	EtOAc	ethyl acetate
	HAUT	O-(7-azabenzotriazol-1-yl)- <i>N,N,N',N'</i> -tetramethyluronium hexafluorophosphate
30	HPLC	high performance liquid chromatography
	m	multiplet
	LHMDS	lithium hexamethyldisilazide
	MCPBA	3-chloroperoxybenzoic acid
	Me	methyl
35	min	minutes

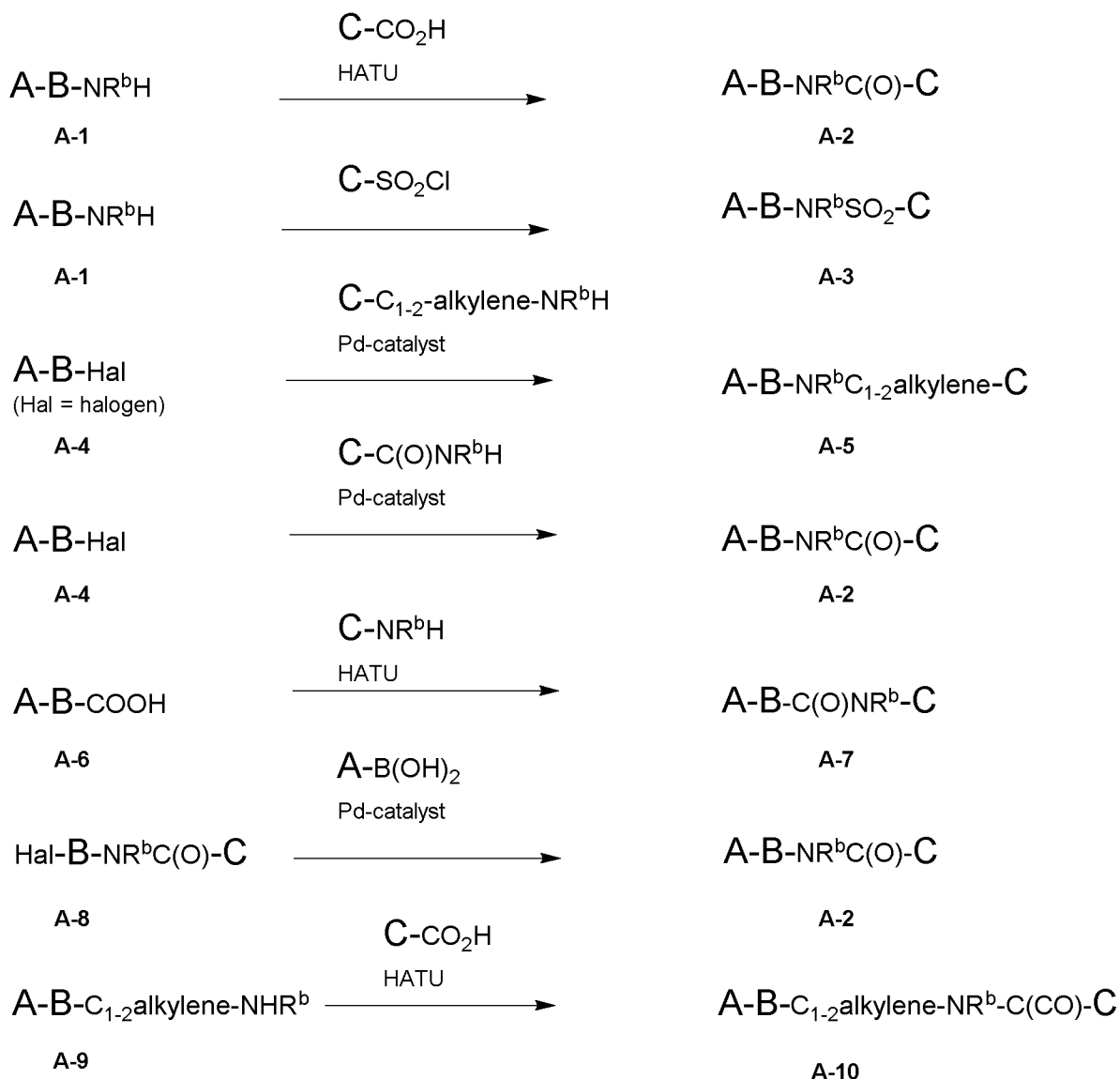
	Ms	methanesulfonyl
	NBS	<i>N</i> -bromosuccinimide
	NCS	<i>N</i> -chlorosuccinimide
	NIS	<i>N</i> -iodosuccinimide
5	PE	petroleum ether
	PyBOP	(benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate
	rt	room temperature
	s	singlet
10	SEM	2-(trimethylsilyl)ethoxymethyl
	t	triplet
	TBTU	2-(1 <i>H</i> -benzotriazole-1-yl)-1,1,3,3-tetramethylaminium tetrafluoroborate
	TFA	trifluoroacetic acid
15	TFAA	trifluoroacetic acid anhydride
	TEA	triethylamine
	THF	tetrahydrofuran
	tBuXPhos	2-di- <i>tert</i> -butylphosphino-2',4',6'-triisopropylbiphenyl
	Xantphos	4,5-bis(diphenylphosphino)-9,9-dimethylxanthene
20		

General Schemes

The compounds of the present invention can be prepared by a combination of methods known in the art including the procedures described in schemes **1** to **14** below. The following reaction schemes are only meant to represent examples of the invention and are in no way meant to be a limit of the invention.

Scheme **1** describes the preparation of examples of the present invention from bicyclic scaffold intermediates. In the case where these intermediates contain an amino functional group (**A-1**) amide coupling with a carboxylic acid and for example HATU affords compounds of structure **A-2**. Coupling of **A-1** with a sulfonylchloride affords sulfonamide compounds of structure **A-3**. Intermediates containing a halogen (**A-4**) can be transformed into **A-5** by Pd-catalysed coupling with an amine. Intermediate **A-4** can also be transformed into **A-2** by Pd-catalysed coupling with a carboxylic acid amide as an alternative synthesis route. Intermediates containing a carboxylic acid (**A-6**) can be converted to compounds of structure **A-7** by amide coupling with an amine using for example HATU as reagent. Intermediates with a halogen substituent at B (**A-8**) can be converted to compounds of structure **A-2** by Suzuki coupling as a third alternative

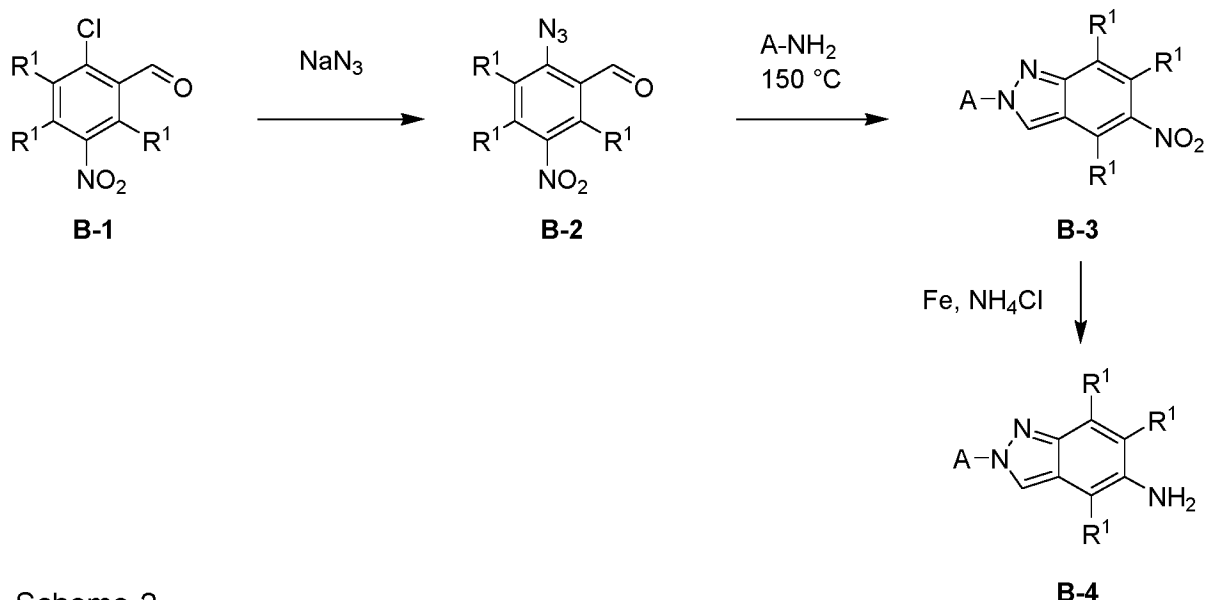
synthesis route for **A-2**. Intermediates with an alkylene linker between the bicyclic scaffold and an amino group (**A-9**) can be converted to compounds of structure **A-10** by amide coupling.



Scheme 1

- 5 Scheme **2** describes the preparation of *2H*-indazole derived intermediates used in the coupling reactions described in Scheme **1**. A substituted or unsubstituted chloro nitrobenzaldehyde intermediate **B-1** can be converted into azide **B-2** using sodium azide. Cyclocondensation reaction of **B-2** with an amine at high temperature leads to the nitro intermediate **B-3**. Reduction of the nitro group with for example iron powder and
- 10 ammoniumchloride affords intermediate **B-4**.

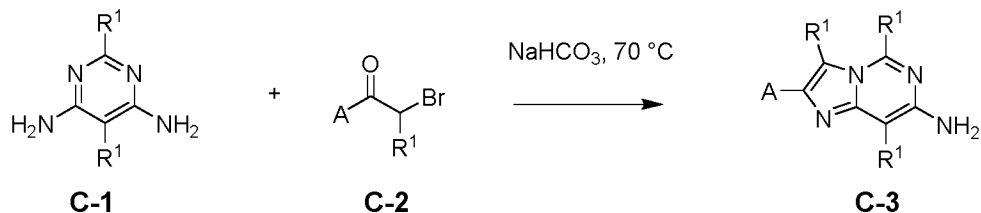
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Scheme 2

Scheme 3 describes the preparation of imidazo[1,2-c]pyrimidine derived intermediates used in the coupling reactions described in Scheme 1. A substituted or unsubstituted

5 diaminopyrimidine **C-1** can react with an α -bromo ketone **C-2** in the presence of sodium bicarbonate at higher temperature to give a bicyclic intermediate of structure **C-3**.

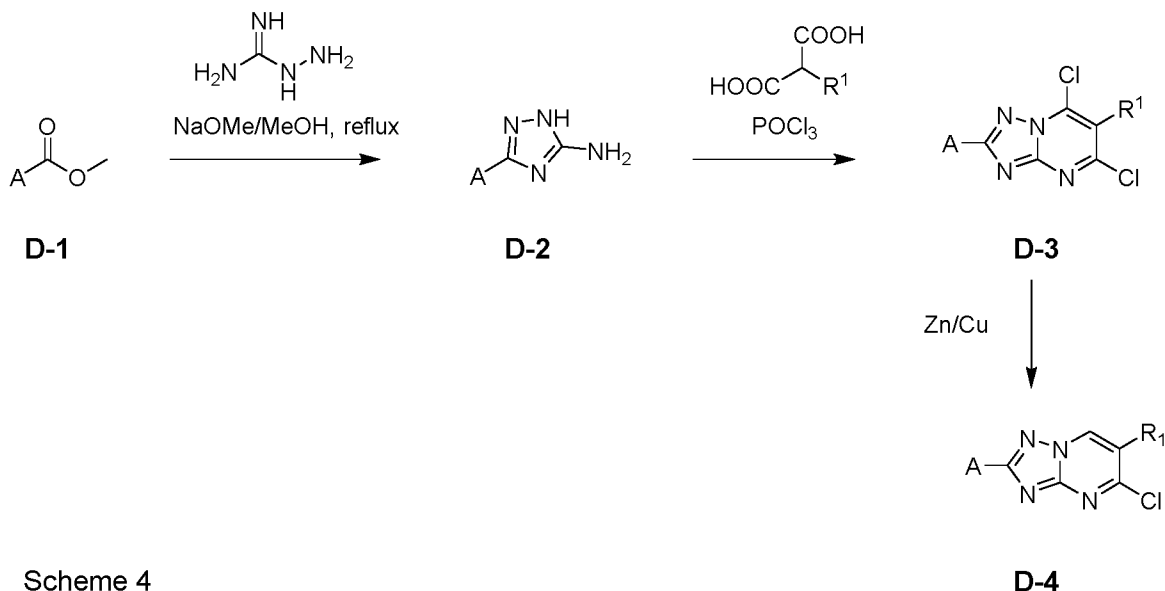


Scheme 3

Scheme 4 describes the preparation of [1,2,4]triazolo[1,5-a]pyrimidine derived

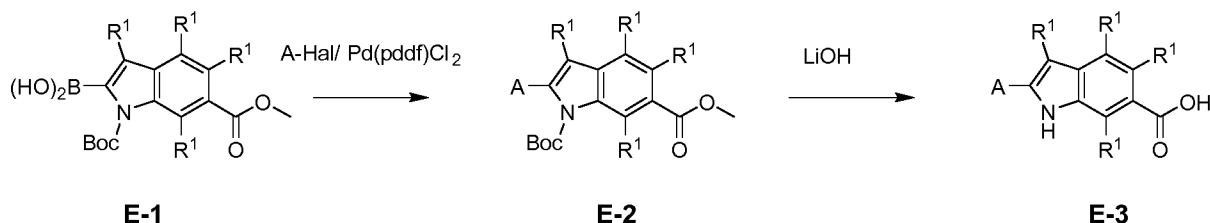
10 intermediates used in the coupling reactions described in Scheme 1. Treatment of ester **D-1** with hydrazinecarboximidamide in the presence of sodium methoxide at elevated temperature affords the amino triazole intermediate **D-2**. Cyclocondensation of **D-2** with a malonic acid derivative in the presence of phosphoryl chloride affords bicyclic intermediate **D-3**. Treatment of intermediate **D-3** with Zn-Cu couple affords a bicyclic

15 intermediate of structure **D-4**.



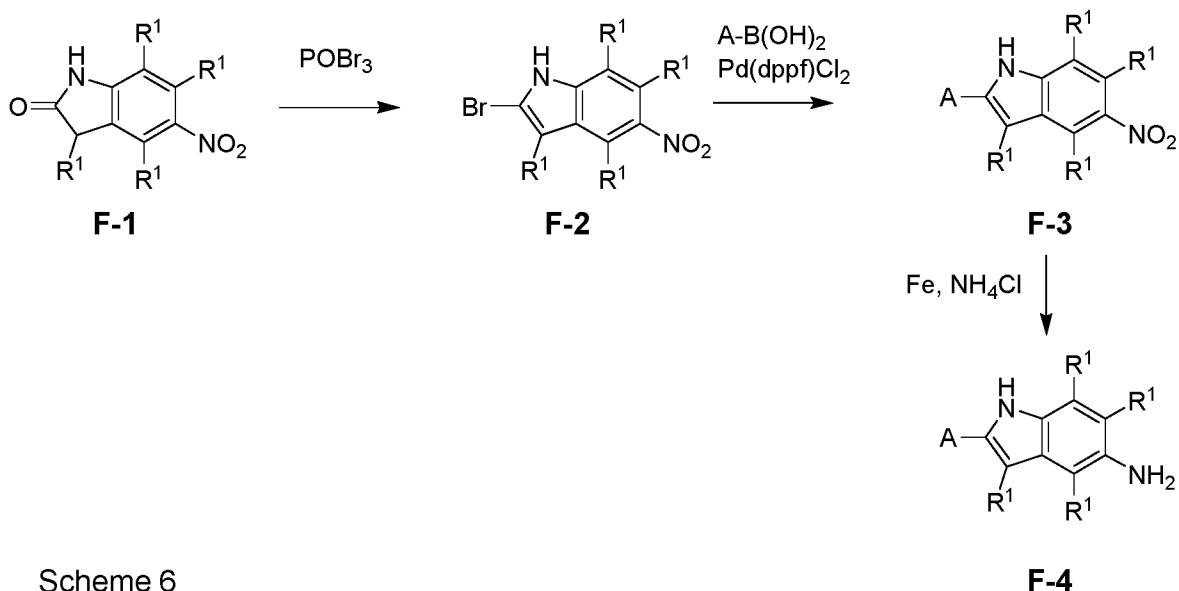
Scheme 4

Scheme 5 describes the preparation of indole-derived intermediates used in the coupling reactions described in Scheme 1. A substituted or unsubstituted indole boronic acid **E-1** can be coupled with an aryl halide in a Suzuki reaction to afford intermediate **E-2**. Ester saponification and deprotection affords the corresponding carboxylic acid **E-3**.



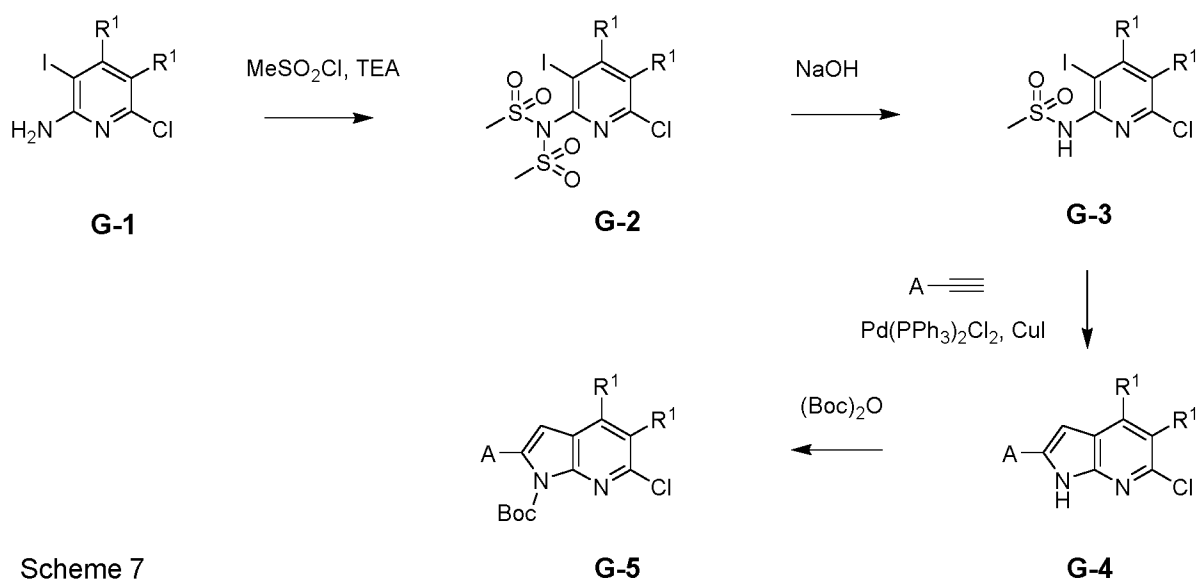
Scheme 5

Scheme 6 describes the preparation of indole-derived intermediates used in the coupling reactions described in Scheme 1. A substituted or unsubstituted 5-nitroindolin-2-one **F-1** can be converted to the corresponding 2-bromo-5-nitro-1*H*-indole **F-2** with phosphoryl bromide. Suzuki coupling affords intermediate **F-3**, which can be reduced with iron powder and ammoniumchloride to give intermediate **F-4**.



Scheme 6

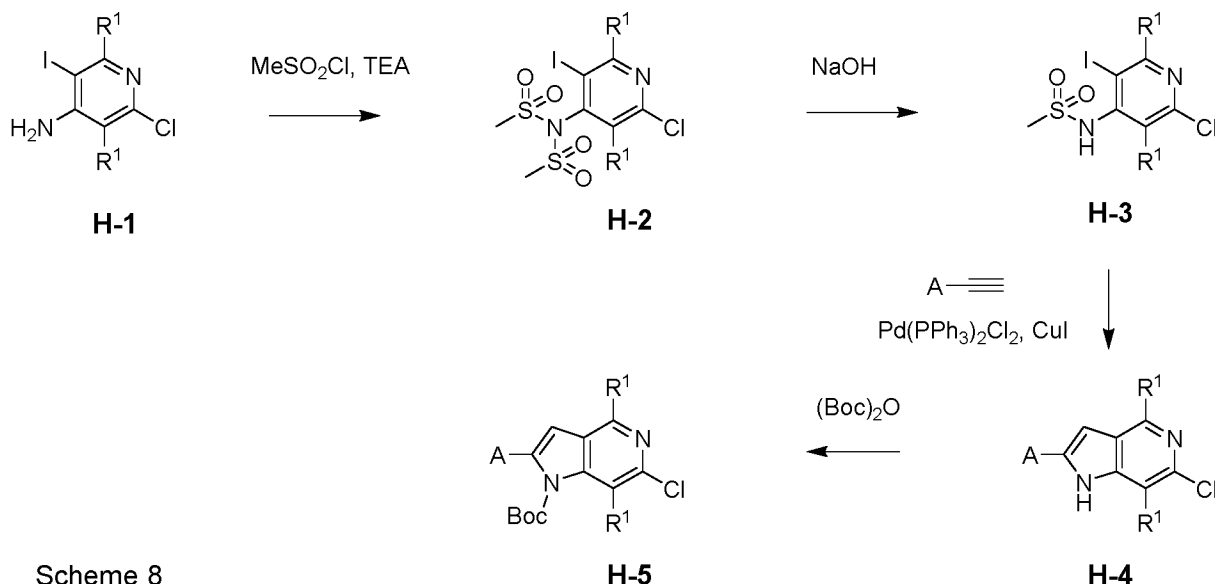
Scheme 7 describes the preparation of 1*H*-pyrrolo[2,3-*b*]pyridine derived intermediates used in the coupling reactions described in Scheme 1. A substituted or unsubstituted 6-chloro-3-iodopyridin-2-amine **G-1** is converted to the corresponding bis-methylsulfonamide **G-2** with methylsulfonylchloride in the presence of triethylamine. Treatment of **G-2** with NaOH affords the corresponding mono-methylsulfonamide **G-3** which is converted to azaindole **G-4** via Pd/Cu(I) catalysed coupling/cyclisation reaction with an appropriately substituted alkyne. Boc-protection using di-*tert*-butyl dicarbonate affords the corresponding intermediate **G-5**.



Scheme 7

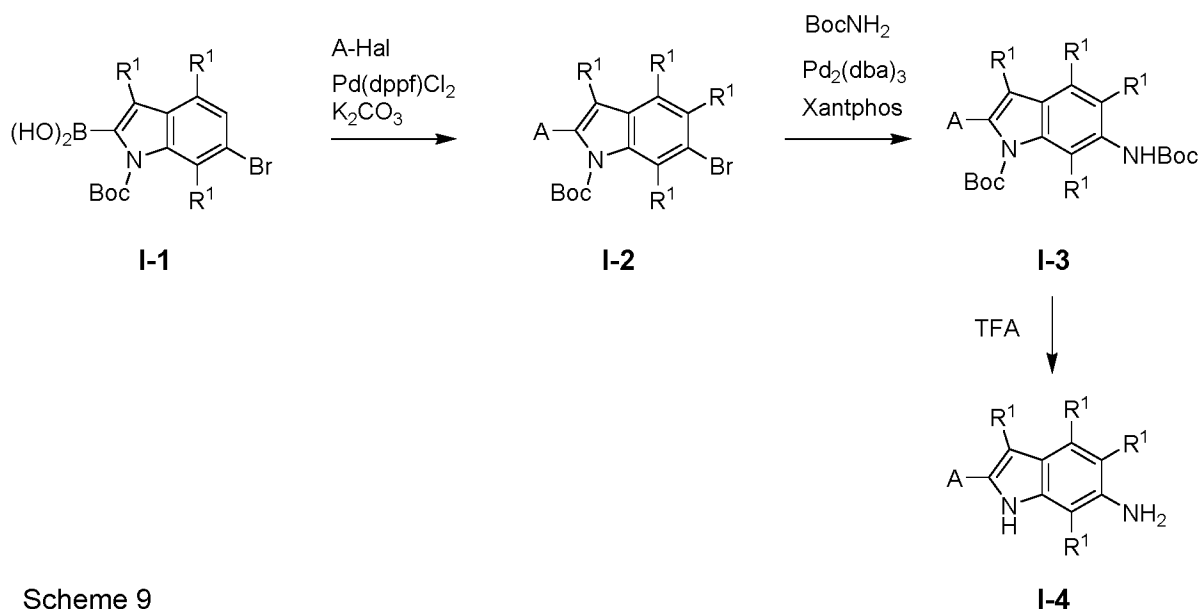
Scheme 8 describes the preparation of 1*H*-pyrrolo[3,2-*c*]pyridine derived intermediates used in the coupling reactions described in Scheme 1. A substituted or unsubstituted 2-chloro-5-iodopyridin-4-amine **H-1** is converted to the corresponding bis-

methanesulfonamide **H-2** with methanesulfonylchloride in the presence of triethylamine. Treatment of **H-2** with NaOH affords the corresponding mono methanesulfonamide **H-3** which is converted to azaindole **H-4** via Pd/Cu(I) catalysed coupling/cyclisation reaction with an appropriately substituted alkyne. Boc-protection using di-*tert*-butyl dicarbonate affords the corresponding intermediate **H-5**.



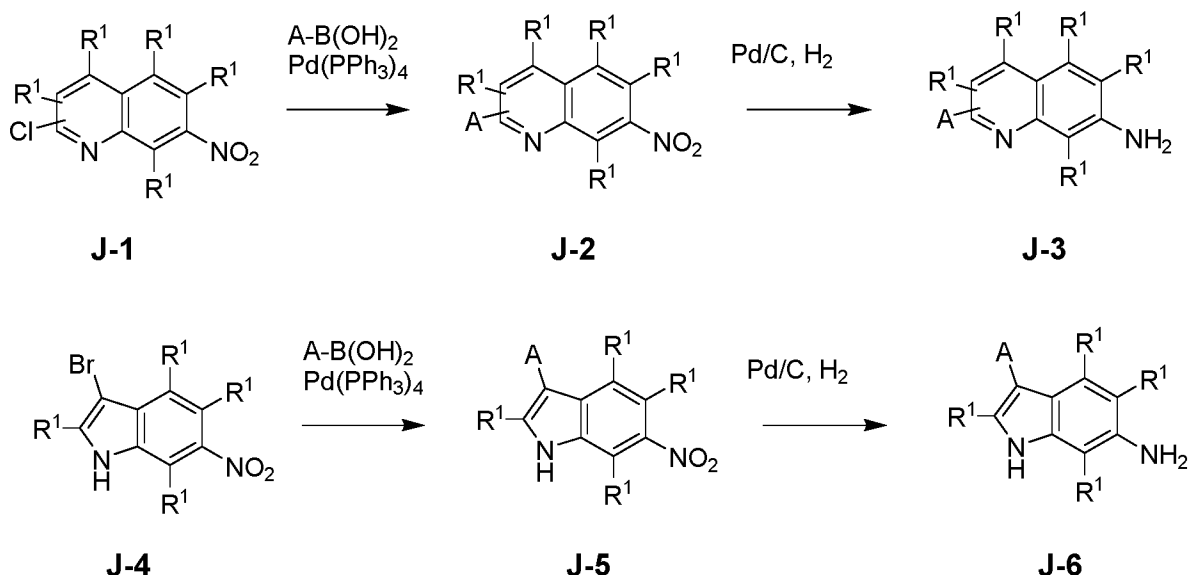
Scheme 8

Scheme 9 describes the preparation of indole-derived intermediates used in the coupling reactions described in Scheme 1. A substituted or unsubstituted (6-bromo-1-(*tert*-butoxycarbonyl)-1*H*-indol-2-yl)boronic acid **I-1** is submitted to a Suzuki coupling with an aryl halide to give intermediate **I-2**. Intermediate **I-2** can be coupled with *tert*-butyl carbamate under Pd catalysis to give a Boc-protected aryl amine **I-3**, which is converted to intermediate **I-4** through deprotection with for example TFA.



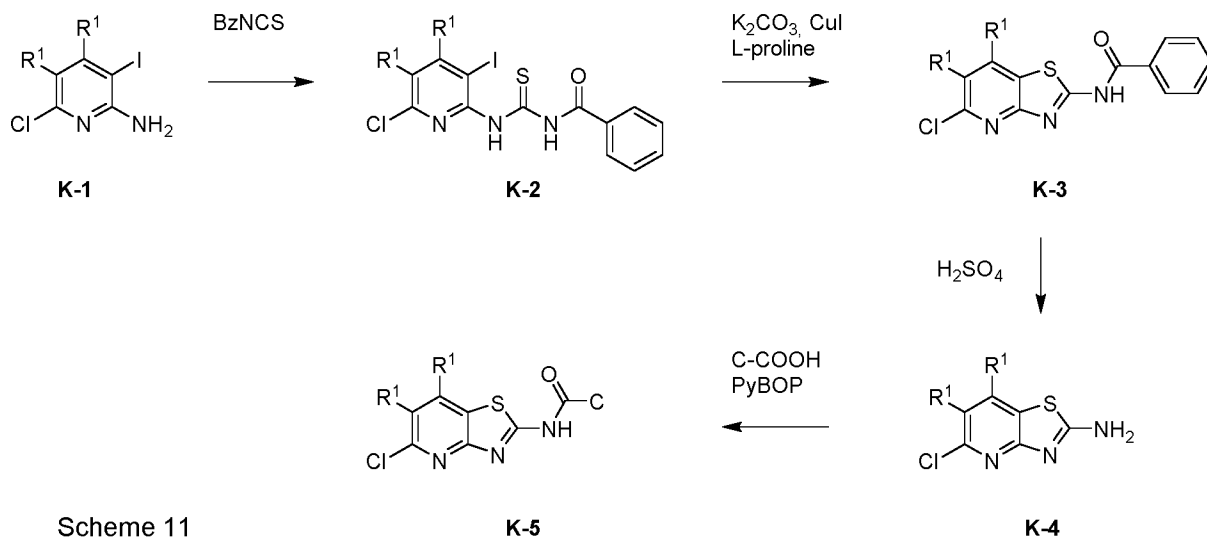
Scheme 9

Scheme 10 describes the preparation of quinoline-derived intermediates used in the coupling reactions described in Scheme 1. Substituted or unsubstituted quinoline **J-1** is submitted to a Suzuki coupling with an aryl boronic acid to give intermediate **J-2**. Pd catalyzed hydrogenation of the nitro group affords intermediate **J-3**. In a similar procedure substituted or unsubstituted indole **J-4** is converted into intermediate **J-6**.



Scheme 10

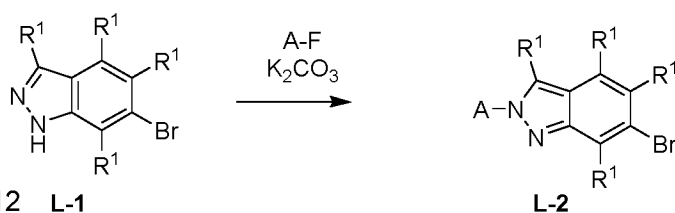
Scheme 11 describes the preparation of thiazolo[4,5-b]pyridine derived intermediates used in the coupling reactions described in Scheme 1. A substituted or unsubstituted 6-chloro-3-iodopyridin-2-amine is treated with benzoyl isothiocyanate to afford intermediate **K-2**. Cyclisation of **K-2** with potassium carbonate and catalytic amounts of L-proline and copper(I) iodide at elevated temperatures leads to intermediate **K-3**. Amide cleavage of **K-3** using sulfuric acid at high temperatures affords the amino intermediate **K-4** which can be coupled to a carboxylic acid using for example PyBOP.



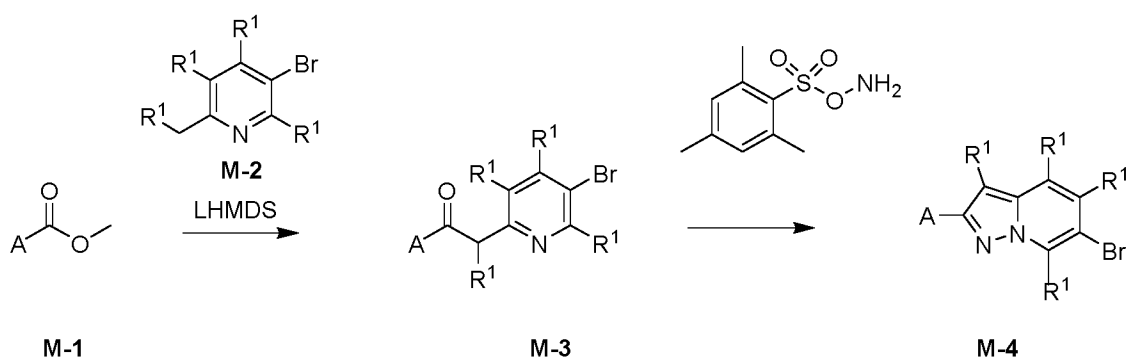
Scheme 11

K-5**K-4**

Scheme **12** describes the preparation of 1*H*-indazole derived intermediates used in the coupling reactions described in Scheme **1**. A substituted or unsubstituted 6-bromo-1*H*-indazole (**L-1**) is treated with an aryl-fluoride in the presence of a base to afford intermediate **L-2**.

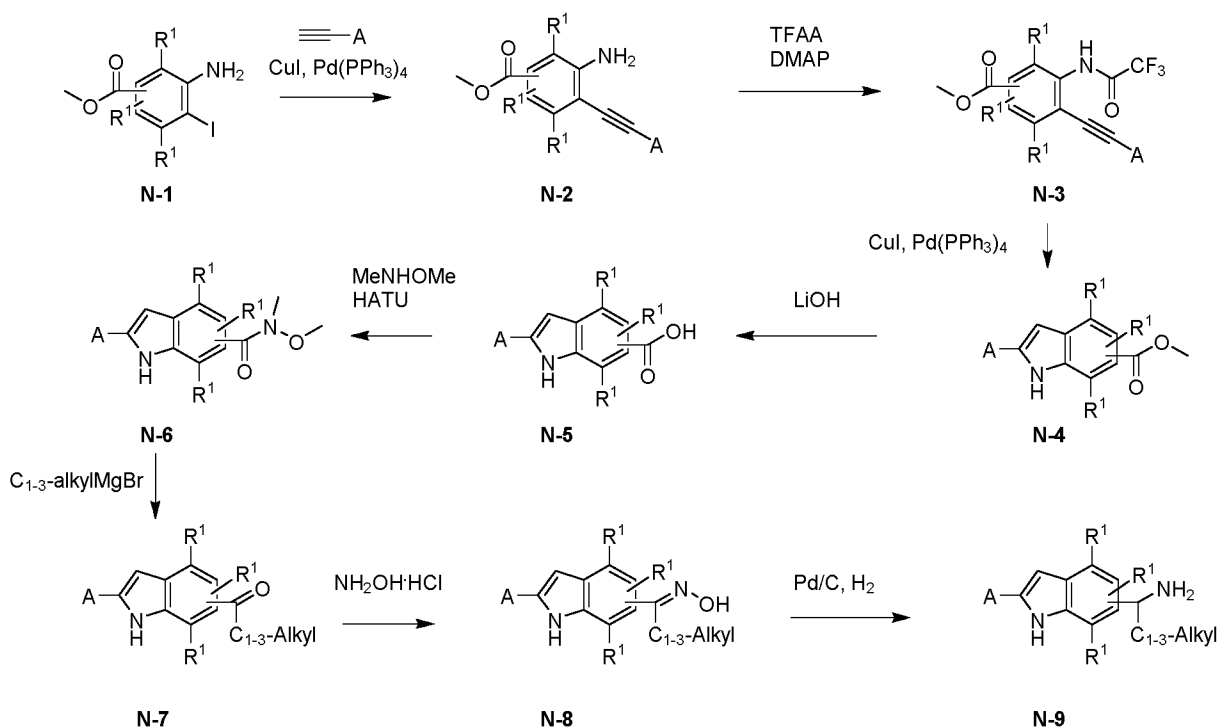
Scheme 12 **L-1****L-2**

Scheme **13** describes the preparation of pyrazolo[1,5-*a*]pyridine derived intermediates used in the coupling reactions described in Scheme **1**. A substituted or unsubstituted 5-bromo-2-methylpyridine (**M-2**) is deprotonated with lithium hexamethyldisilazide and the resulting metallated intermediate is treated with an ester intermediate **M-1** to afford the intermediate **M-3**. Treatment of **M-3** with *O*-(mesitylsulfonyl)hydroxylamine affords intermediates of structure **M-4**.

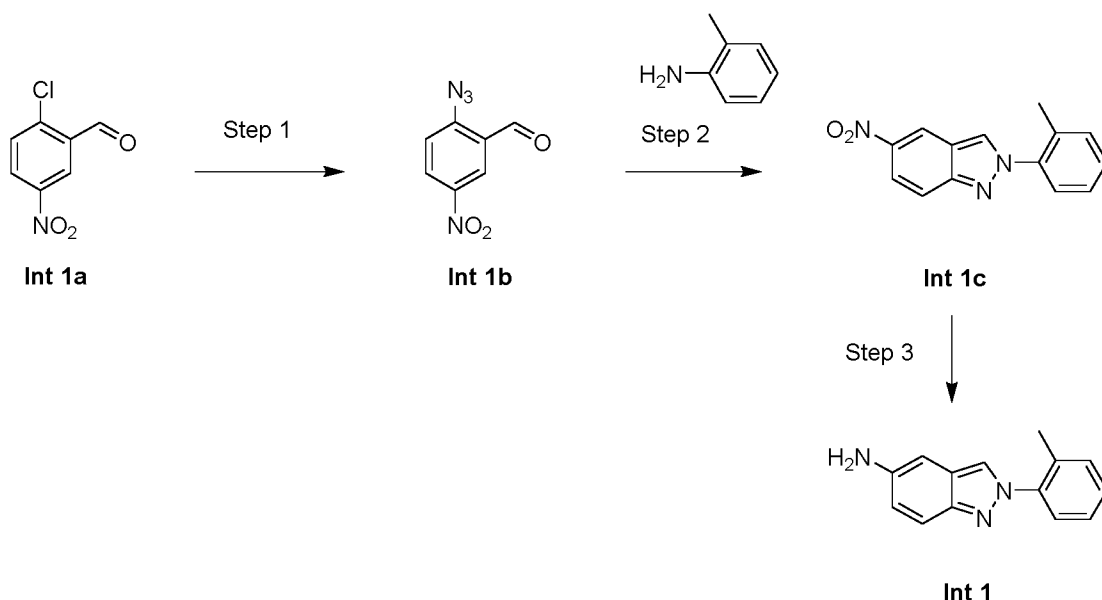
**M-1****M-3****M-4**

Scheme 13

Scheme 14 describes the preparation of indole derived intermediates bearing a methylene linker united L in 5- or 6-position of the indole used in the coupling reactions described in Scheme 1. The iodoaniline intermediate **N-1** is converted into **N-2** by Sonogashira reaction. Treatment with TFAA and DMAP affords the corresponding trifluoroacetamide derivative **N-3**, which is cyclized to the indole intermediate **N-4** under Pd catalysis. Ester saponification using for example LiOH is followed by amide coupling with *N,O*-dimethylhydroxylamine to afford intermediate **N-6**. Grignard reaction is followed by condensation reaction with hydroxylamine to afford oxime intermediate **N-8**. Reduction of **N-8** with Pd on charcoal under an atmosphere of hydrogen affords intermediates of structure **N-9**.



Scheme 14

Intermediate 1: 2-(o-Tolyl)-2H-indazol-5-amine (Int 1)**Step 1: 2-Azido-5-nitrobenzaldehyde (Int 1b)**

- 5 To a solution of 2-chloro-5-nitrobenzaldehyde (**Int 1a**) (960 mg, 5.17 mmol) in ethanol (15 mL), sodium azide (670 mg, 10.3 mmol) in water (2 mL) was added. The mixture was stirred at reflux for 2 h. The mixture was cooled to rt and diluted with water (50 mL). A solid precipitated, which was filtered off and washed with PE to afford the title compound as a yellow solid.

10

Step 2: 5-Nitro-2-(o-tolyl)-2H-indazole (Int 1c)

- A mixture of 2-azido-5-nitrobenzaldehyde (**Int 1b**) (610 mg, 3.17 mmol) and o-toluidine (680 mg, 6.34 mmol) in DMF (3 mL) was stirred at 150 °C for 1 h. Water and aqueous sodium bicarbonate were added and the mixture was extracted with DCM. The combined organic layers were washed with water and brine, dried over anhydrous Na₂SO₄ and concentrated to dryness. The residue was purified by silica gel chromatography (gradient PE to PE/EtOAc 3:1) to afford the title compound as a yellow solid.

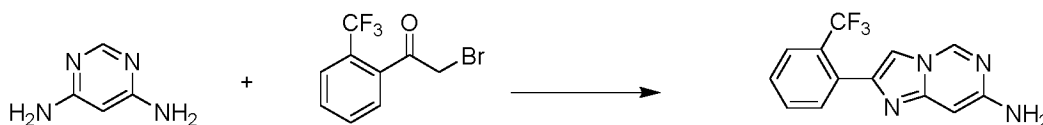
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Step 3: 2-(o-Tolyl)-2H-indazol-5-amine (Int 1)

- 20 To a mixture of 5-nitro-2-o-tolyl-2H-indazole (**Int 1c**) (680 mg, 2.68 mmol), iron powder (2.99 g, 53.6 mmol) and ammonium chloride (2.87 g, 53.6 mmol) in ethanol (20 mL) was added water (4 mL) and the mixture was stirred at reflux for 2 h. The mixture was filtered through celite and the filtrate was concentrated to dryness. The residue was dissolved in EtOAc (30 mL) and the combined organic layers were washed with water and brine, dried

over anhydrous Na₂SO₄, filtered and concentrated to dryness to afford the title compound as a brownish solid.

Intermediate 2: 2-(2-(Trifluoromethyl)phenyl)imidazo[1,2-c]pyrimidin-7-amine (**Int 2**)



5

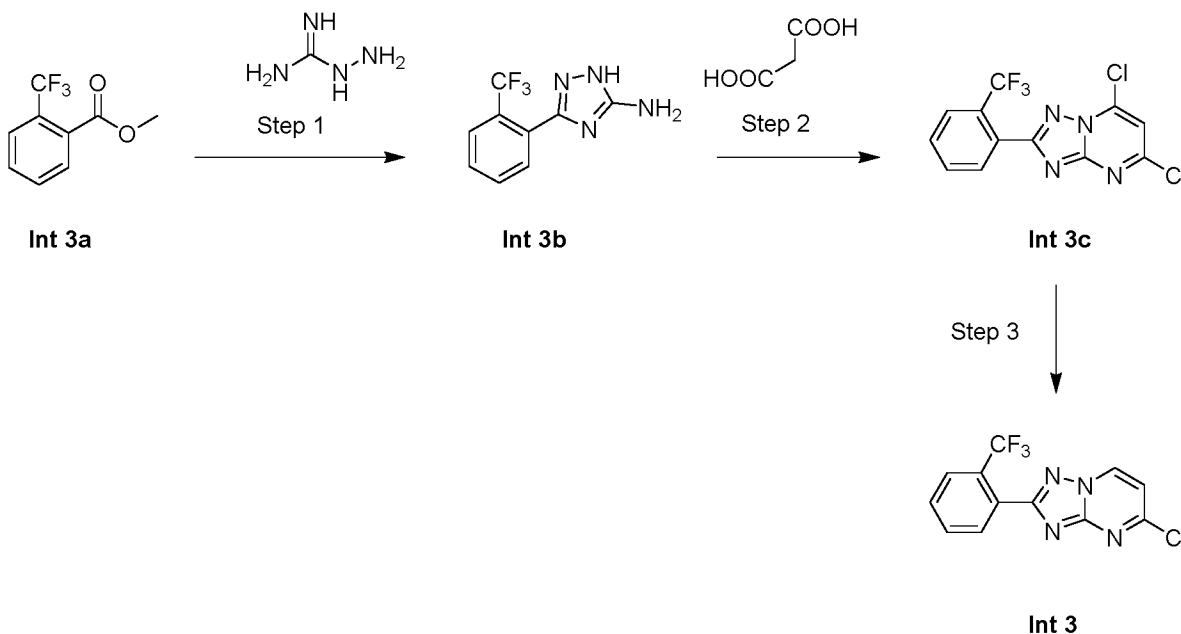
Int 2a**Int 2b****Int 2**

To a mixture of pyrimidine-4,6-diamine (**Int 2a**) (3.3 g, 30 mmol) and 2-bromo-1-(2-(trifluoromethyl)phenyl)ethan-1-one (**Int 2b**) (8.0 g, 30 mmol) in DMF (60 mL), NaHCO₃ (3.0 g, 36 mmol) was added at rt. The mixture was stirred at 70 °C overnight. Water was added and the mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated to dryness. The residue was purified by silica gel chromatography (gradient PE/EtOAc 2:1 to 1:1) to give the title compound as a yellow solid.

10

Intermediate 3: 5-Chloro-2-(2-(trifluoromethyl)phenyl)-[1,2,4]triazolo[1,5-a]pyrimidine (**Int 3**)

15



Step 1: 3-(2-(Trifluoromethyl)phenyl)-1H-1,2,4-triazol-5-amine (**Int 3b**)

To a cooled solution of NaOMe (10.5 g, 196 mmol) in MeOH (100 mL) was added hydrazinecarboximidamide (14.5 g, 196 mmol) and methyl 2-(trifluoromethyl)benzoate (10.0 g, 49 mmol) (**Int 3a**) at 0 °C. The mixture was stirred at reflux for 24 h and poured into ice-water (100 mL). The pH of the mixture was adjusted to pH 3 - 4 with 1M HCl.

5 The mixture was concentrated to dryness and MeOH was added to the residue for extraction. The mixture was filtered and the filtrate was concentrated to dryness. The residue was suspended in 5% aqueous NaOH (140 mL) and heated at reflux overnight. The mixture was filtered. The filtrate was acidified with 1M HCl to pH = 3 - 4. The formed precipitate was filtered off and the filtrate was concentrated to dryness to give the title compound as a white solid.

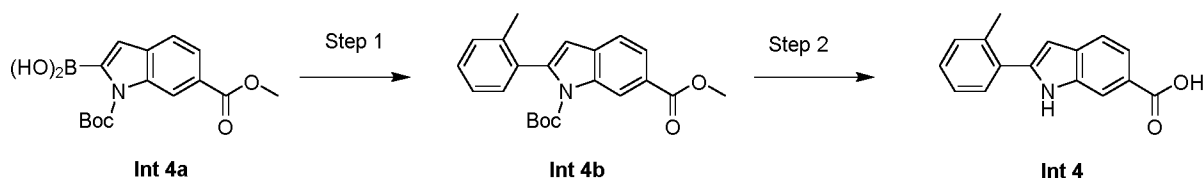
Step 2: 5,7-Dichloro-2-(2-(trifluoromethyl)phenyl)-[1,2,4]triazolo[1,5-a]pyrimidine (Int 3c**)**

A mixture of 3-(2-(trifluoromethyl)phenyl)-1*H*-1,2,4-triazol-5-amine (**Int 3b**) (9.0 g, 19.7 mmol) and malonic acid (6.2 g, 29.6 mmol) in POCl₃ (20 mL) was stirred at 110 °C for 2 h. The mixture was concentrated to dryness. Toluene (10 mL) was added and the mixture was concentrated to dryness. Toluene (10 mL) was added a second time and the mixture was concentrated to dryness. The residue was poured into water (40 mL), diluted with DCM (50 mL) and the mixture was washed with saturated NaHCO₃ (2 x 50 mL). The organic layer was concentrated to dryness. The residue was purified by flash chromatography on silica gel (PE/EtOAc = 10:1) to give the title compound as a white solid.

Step 3: 5-Chloro-2-(2-(trifluoromethyl)phenyl)-[1,2,4]triazolo[1,5-a]pyrimidine (Int 3**)**

To a solution of 5,7-dichloro-2-(2-(trifluoromethyl)phenyl)-[1,2,4]triazolo[1,5-a]pyrimidine (**Int 3c**) (166 mg) in AcOH/MeOH/THF (0.5 mL/2 mL/12 mL), Zn-Cu couple (300 mg) was added. The mixture was stirred at rt for 4 h and filtered. The filtrate was concentrated to dryness. The residue was purified by flash chromatography on silica gel (PE/EtOAc = 5:1) to give the title compound as a white solid.

Intermediate 4: 1-(*tert*-Butoxycarbonyl)-2-(*o*-tolyl)-1*H*-indole-6-carboxylic acid (Int 4**)**

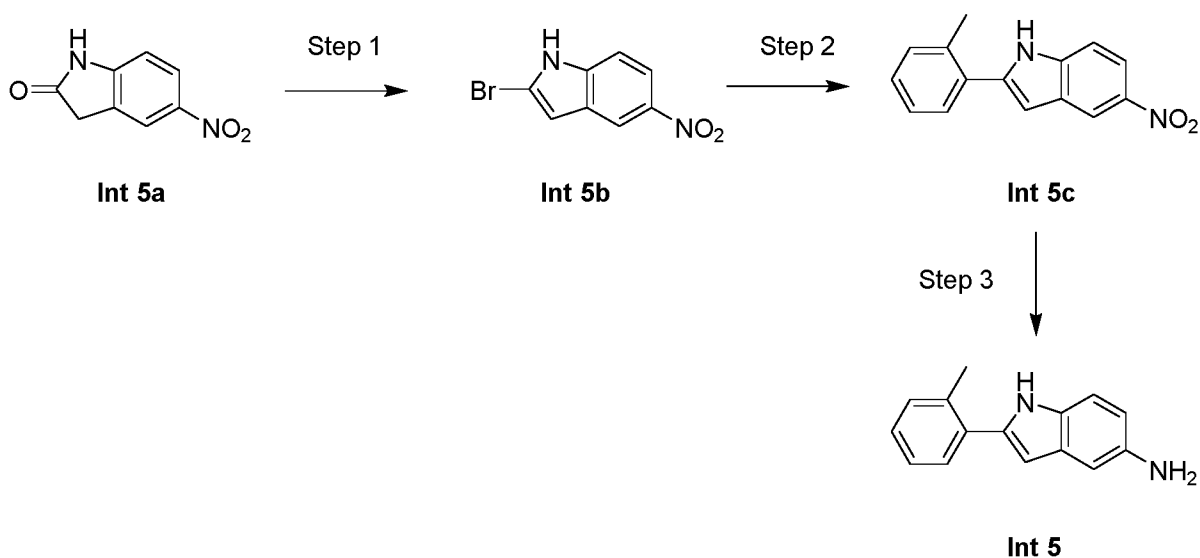


Step 1: 1-(*tert*-Butyl) 6-methyl 2-(*o*-tolyl)-1*H*-indole-1,6-dicarboxylate (Int 4b)

A mixture of (1-(*tert*-butoxycarbonyl)-6-(methoxycarbonyl)-1*H*-indol-2-yl)boronic acid (500 mg, 1.57 mmol) (**Int 4a**), 1-iodo-2-methylbenzene (512 mg, 2.35 mmol), Pd(dppf)Cl₂ (118 mg, 0.15 mmol) and K₂CO₃ (433 mg, 3.14 mmol) in 1,4-dioxane (10 mL) and H₂O (2 mL) was stirred at 110 °C under N₂ atmosphere for 2 h. The layers were separated and the organic layer was concentrated to dryness. The residue was purified by flash silica chromatography (PE/EtOAc = 10:1) to give the title compound as a white solid.

Step 2: 2-(*o*-Tolyl)-1*H*-indole-6-carboxylic acid (Int 4)

A mixture of 1-(*tert*-butyl) 6-methyl 2-(*o*-tolyl)-1*H*-indole-1,6-dicarboxylate (**Int 4b**) (340 mg, 0.93 mmol) and LiOH·H₂O (195 mg, 5.74 mmol) in THF (10 mL) and H₂O (10 mL) was stirred at 60 °C overnight. The mixture was concentrated, acidified to pH 5 using 1M aqueous HCl and extracted with EtOAc. The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated to dryness to give the title compound as a light yellow solid.

Intermediate 5: 2-(*o*-Tolyl)-1*H*-indol-5-amine (Int 5)**Step 1: 2-Bromo-5-nitro-1*H*-indole (Int 5b)**

To a mixture of 5-nitroindolin-2-one (**Int 5a**) (3.00 g, 16.8 mmol) in 1,2-dichloroethane (60 mL) was added phosphorus(V) oxybromide (4.59 g, 16.0 mmol). The mixture was heated to 90 °C for 0.5 h. The mixture was cooled to just below reflux temperature. Imidazole (1.26 g, 18.5 mmol) was added and the mixture was heated to 90 °C for 2 h. The mixture was cooled to rt and diluted with ice-water and sodium bicarbonate (solid).

The mixture was extracted with DCM (4 x 100 mL). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated to dryness. The residue was purified by silica gel column chromatography (gradient PE to PE/EtOAc = 3:1) to afford the title compound as a yellow solid.

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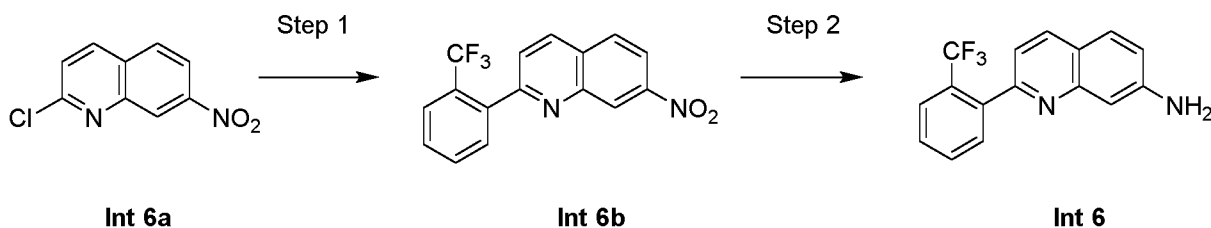
Step 2: 5-Nitro-2-(o-tolyl)-1H-indole (Int 5c)

To a mixture of 2-bromo-5-nitro-1H-indole (**Int 5b**) (375 mg, 1.56 mmol), o-tolylboronic acid (850 mg, 6.24 mmol), Pd(dppf)Cl₂ (225 mg, 0.31 mmol) and potassium carbonate (580 mg, 4.68 mmol) in 1,4-dioxane (15 mL) was added water (3 mL). The mixture was stirred at 100 °C overnight. The mixture was concentrated to dryness and the residue was dissolved in EtOAc (15 mL). The organic layer was washed with water and brine, dried over anhydrous Na₂SO₄, filtered and concentrated to dryness. The residue was purified by silica gel column chromatography (gradient PE to PE/EtOAc = 3:1) to afford the title compound as a yellow solid.

10

Step 3: 2-(o-Tolyl)-1H-indol-5-amine (Int 5)

To a mixture of 5-nitro-2-(o-tolyl)-1H-indole (**Int 5c**) (355 mg, 1.41 mmol), iron powder (1.57 g, 28.2 mmol) and ammonium chloride (1.51 g, 28.2 mmol) in ethanol (15 mL) was added water (3 mL) and the mixture was stirred at reflux for 2 h. The mixture was filtered through a pad of celite. The filtrate was concentrated to dryness and the residue was dissolved in EtOAc (30 mL). The organic layer was washed with water and brine, dried over anhydrous Na₂SO₄, filtered and concentrated to dryness to afford the title compound as a brownish solid.

Intermediate 6: 2-(2-(Trifluoromethyl)phenyl)quinolin-7-amine (Int 6)**Step 1: 7-Nitro-2-(2-(trifluoromethyl)phenyl)quinoline (Int 6b)**

A mixture of 2-chloro-7-nitroquinoline (**Int 6a**) (270 mg, 1.29 mmol), (2-(trifluoromethyl)phenyl)boronic acid (366 mg, 1.93 mmol), Pd(PPh₃)₄ (74 mg, 0.064 mmol) and K₂CO₃ (532 mg, 3.86 mmol) in acetonitrile (30 mL) and water (10 mL) was

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stirred at 80 °C under N₂ overnight. After cooling to rt, the mixture was filtered and the filtrate was concentrated to dryness. The residue was purified by column chromatography on silica gel (PE/EtOAc = 10:1) to afford the title compound as a white solid.

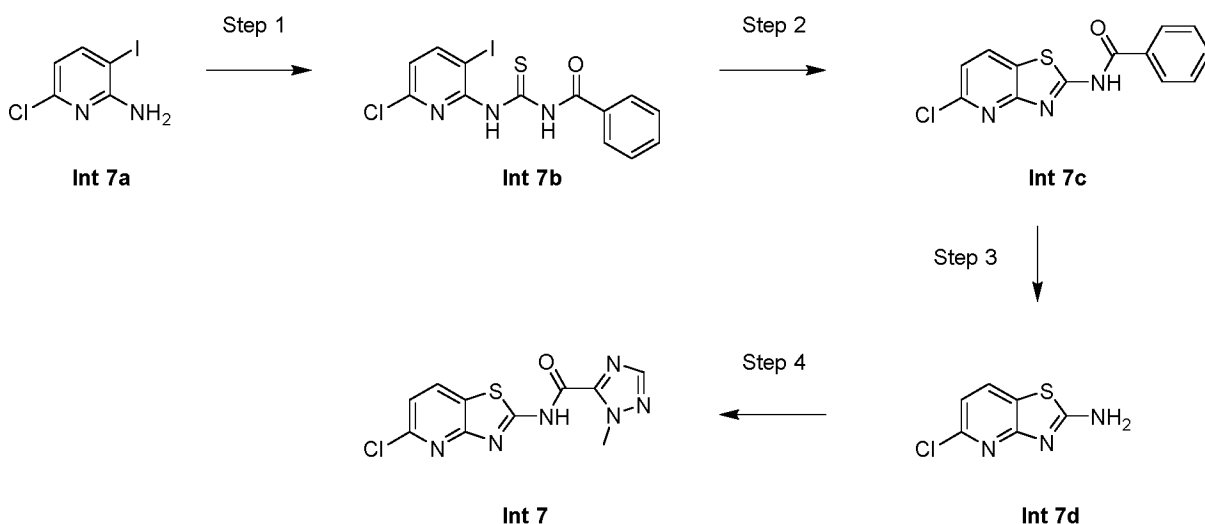
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Step 2: 2-(2-(Trifluoromethyl)phenyl)quinolin-7-amine (**Int 6**)

A mixture of 7-nitro-2-(2-(trifluoromethyl)phenyl)quinoline (**Int 6b**) (420 mg, 1.32 mmol) and Pd/C (42 mg) in MeOH (20 mL) was stirred at rt under H₂ atmosphere for 2 h. The mixture was filtered and the filtrate was concentrated to dryness to obtain the title compound as a gray solid.

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Intermediate 7: *N*-(5-Chlorothiazolo[4,5-*b*]pyridin-2-yl)-1-methyl-1*H*-1,2,4-triazole-5-carboxamide (**Int 7**)



15 **Step 1:** *N*-(6-Chloro-3-iodopyridin-2-yl)carbamothioylbenzamide (**Int 7b**)

A solution of 6-chloro-3-iodopyridin-2-amine (1.00 g, 3.92 mmol) and benzoyl isothiocyanate (0.67 mL, 5.09 mmol) in acetone (10 mL) was stirred at rt for 18 h. The precipitated solid was filtered off, washed with PE and dried to give the title compound as a yellow solid.

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Step 2: *N*-(5-Chlorothiazolo[4,5-*b*]pyridin-2-yl)benzamide (**Int 7c**)

To a solution of *N*-(6-chloro-3-iodopyridin-2-yl)carbamothioylbenzamide (**Int 7b**) (1.05 g, 2.51 mmol) in 1,4-dioxane (25 mL) was added potassium carbonate (694 mg, 5.03 mmol), *L*-proline (57 mg, 0.50 mmol) and copper(I) iodide (47 mg, 0.25 mmol). The

mixture was stirred at 80 °C for 6 h. After cooling to rt, the mixture was poured into 50 mL of water and 50 mL of saturated NH₄Cl aqueous solution and the mixture was stirred at rt for 1 h. The precipitated solid was filtered, washed with saturated NH₄Cl aqueous solution (2 x 25 mL), water (2 x 25 mL) and dried under vacuum to give the title compound as a brown solid.

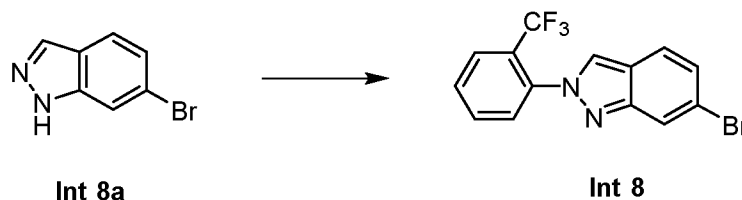
Step 3: 5-Chlorothiazolo[4,5-b]pyridin-2-amine (Int 7d)

A mixture of *N*-(5-chlorothiazolo[4,5-b]pyridin-2-yl)benzamide (**Int 7c**) (700 mg, 2.41 mmol) in 70 % H₂SO₄ (5 mL) was heated at 120 °C for 4 h. After cooling to rt, the mixture was poured slowly into 50 mL of ice cold water and the mixture was basified to pH 8 - 9 with solid NaOH. The mixture was filtered. The filter cake was washed with 1M aqueous NaOH (2 x 25 mL), saturated aqueous NH₄Cl solution (25 mL), water (2 x 25 mL) and dried under vacuum to a crude product. The crude product was dissolved in DCM/MeOH (5 mL, 25:1) and filtered through a plug of silica. The plug was extracted with DCM/MeOH (6:4) and the combined organic layers were concentrated to dryness to give the title compound as a brown solid.

Step 4: *N*-(5-Chlorothiazolo[4,5-b]pyridin-2-yl)-1-methyl-1*H*-1,2,4-triazole-5-carboxamide (Int 7)

To a solution of 5-chlorothiazolo[4,5-b]pyridin-2-amine (**Int 7d**) (700 mg, 3.76 mmol), 1-methyl-1*H*-1,2,4-triazole-5-carboxylic acid (762 mg, 5.64 mmol) and PyBOP (3.91 mg, 7.53 mmol) in DMF (20 mL) was added DIPEA (1.45 g, 11.2 mmol). The solution was stirred at rt overnight. The mixture was concentrated, diluted with H₂O (50 mL) and filtered. The filter cake was dried under vacuum to give the title compound as a brown solid.

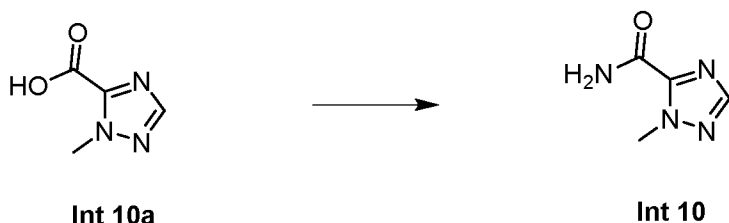
Intermediate 8: 6-Bromo-2-(2-(trifluoromethyl)phenyl)-2*H*-indazole (Int 8)



To a solution of 6-bromo-1*H*-indazole (**Int 8a**) (500 mg, 2.55 mmol), and 1-fluoro-2-(trifluoromethyl)benzene (627 mg, 3.83 mmol) in DMF (5 mL) was added K₂CO₃ (1.06 g, 7.25 mmol) and the mixture was stirred at rt overnight. EtOAc (10 mL) and water (10 mL)

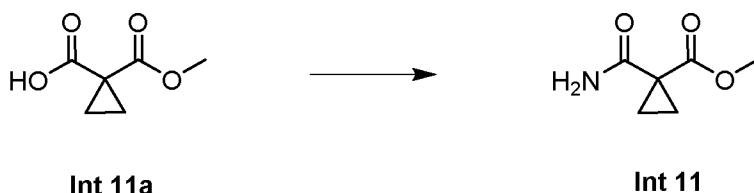
were added to the mixture. The aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na₂SO₄, filtered and concentrated to dryness. The residue was purified by column chromatography on silica gel (PE/EtOAc = 3:1) to give the title compound as a yellow oil.

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Intermediate 10: 1-Methyl-1H-1,2,4-triazole-5-carboxamide (Int 10)

A mixture of 1-methyl-1H-1,2,4-triazole-5-carboxylic acid (7.0 g, 55 mmol) in SOCl₂ (20 mL) was heated to 70 °C for 2 h. The mixture was concentrated to dryness. The residue was dissolved in NH₃/MeOH (7M, 40 mL) and stirred at rt overnight. The precipitated solid was filtered off, extracted with Et₂O and dried under reduced pressure to give the title compound.

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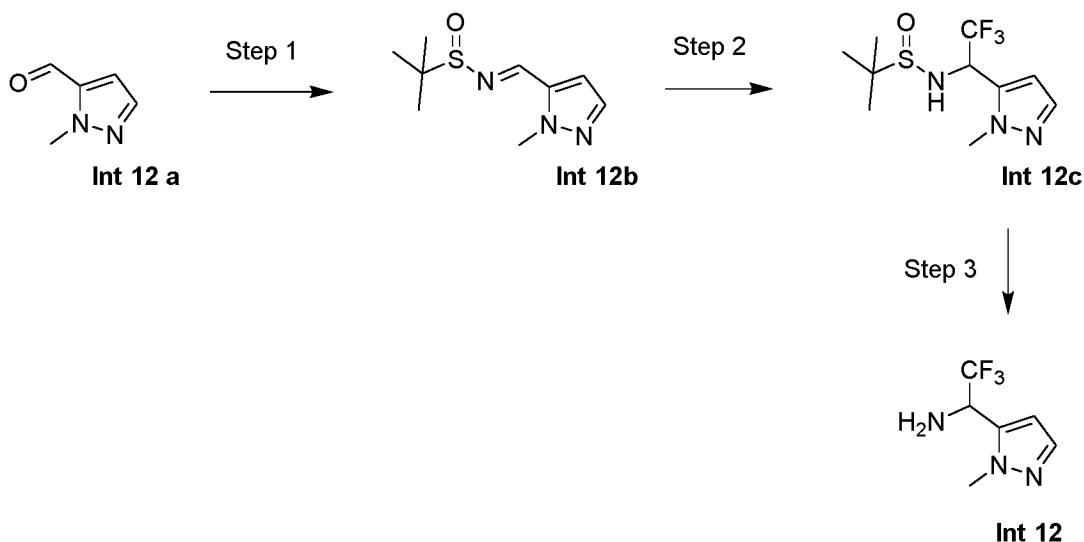
Intermediate 11: Methyl 1-carbamoylcyclopropane-1-carboxylate (Int 11)

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To a mixture of 1-(methoxycarbonyl)cyclopropane-1-carboxylic acid (**Int 11a**) (1.00 g, 6.94 mmol) in THF (20 mL) was added SOCl₂ (1.24 g, 10.4 mmol) followed by 3 drops of DMF at 0 °C. The mixture was heated to 65 °C for 2 h. The mixture was concentrated to dryness, dissolved in DCM and concentrated to dryness for a second time. The residue was added portion wise to a mixture of concentrated aqueous NH₄OH (5 mL) and THF (20 mL) at 0 °C. The precipitated solid was filtered off, washed with water and dried under reduced pressure to give the title compound.

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Intermediate 12: 2,2,2-Trifluoro-1-(1-methyl-1H-pyrazol-5-yl)ethan-1-amine (Int 12)



Step 1: 2-Methyl-N-((1-methyl-1H-pyrazol-5-yl)methylene)propane-2-sulfinamide (**Int 12b**)

To a mixture of 1-methyl-1H-pyrazole-5-carbaldehyde (**Int 12a**) (1.00 g, 9.09 mmol) and 2-methyl-propane-2-sulfinamide (1.10 g, 10.9 mmol) in THF (30 mL) was added titanium tetraethoxide (4.14 g, 18.2 mmol). The mixture was stirred at rt overnight. The mixture was concentrated to dryness and the residue was purified by silica gel chromatography (PE/EtOAc = 8:2) to give the title compound as a white solid.

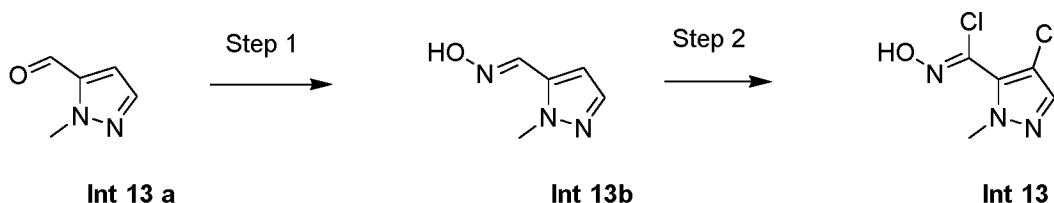
Step 2: 2-Methyl-N-(2,2,2-trifluoro-1-(1-methyl-1H-pyrazol-5-yl)ethyl)propane-2-sulfinamide (**Int 12c**)

To a mixture of 2-methyl-N-((1-methyl-1H-pyrazol-5-yl)methylene)propane-2-sulfinamide (**Int 12b**) (600 mg, 2.81 mmol) and tetrabutylammonium acetate (851 mg, 2.81 mmol) in DMF (10 mL) was added drop wise trifluoromethyltrimethylsilane (997 mg, 7.02 mmol). The mixture was stirred at rt for 1.5 h. Water and EtOAc were added. The organic layer was separated, washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated to dryness to give the title compound as a grey solid.

Step 3: 2,2,2-Trifluoro-1-(1-methyl-1H-pyrazol-5-yl)ethan-1-amine (**Int 12**)

To a mixture of 2-methyl-N-(2,2,2-trifluoro-1-(1-methyl-1H-pyrazol-5-yl)ethyl)propane-2-sulfinamide (**Int 12c**) (600 mg, 2.13 mmol) in MeOH (10 mL) was added HCl/MeOH (10 mL). The mixture was stirred at rt for 1.5 h. The mixture was concentrated to dryness to afford the title compounds as a grey solid.

Intermediate 13: 4-Chloro-*N*-hydroxy-1-methyl-1*H*-pyrazole-5-carbimidoyl chloride (**Int 13**)



5 **Step 1:** 1-Methyl-1*H*-pyrazole-5-carbaldehyde oxime (**Int 13b**)

To a solution of 1-methyl-1*H*-pyrazole-5-carbaldehyde (**Int 13a**) (275 mg, 2.50 mmol) and hydroxylamine hydrochloride (350 mg, 5.00 mmol) in EtOH (5 mL), pyridine (0.5 mL) was added. The mixture was stirred at rt for 1 h. The mixture was concentrated and EtOAc (20 mL) was added. The organic layer was washed with water (3 x 20 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated to dryness. The residue was purified by column chromatography (EtOAc/PE = 1:1) to give the title compound as a white solid.

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Step 2: 4-Chloro-*N*-hydroxy-1-methyl-1*H*-pyrazole-5-carbimidoyl chloride (**Int 13**)

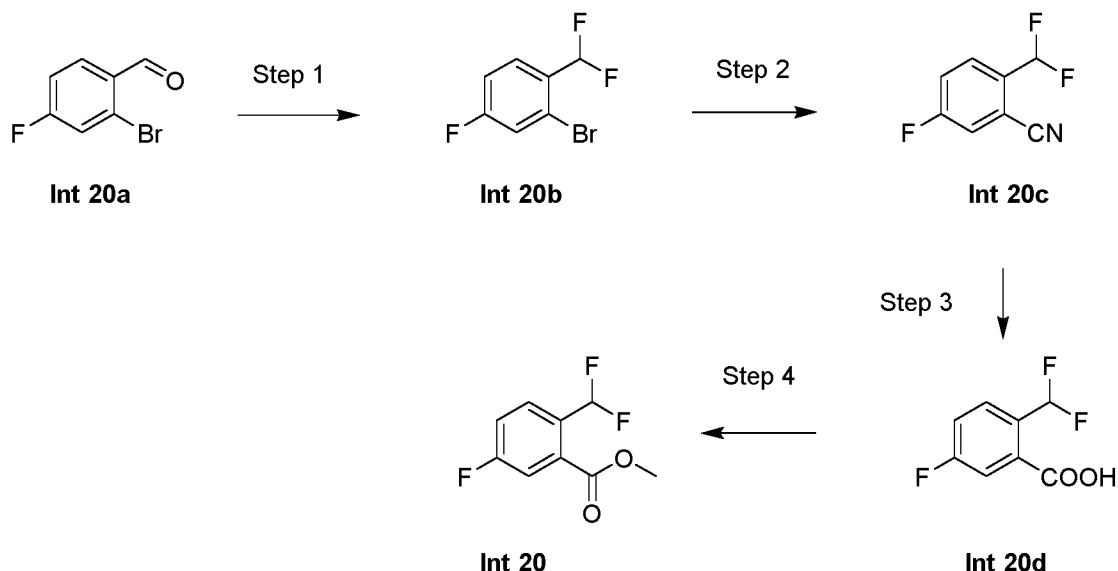
To a stirred solution of 1-methyl-1*H*-pyrazole-5-carbaldehyde oxime (**Int 13b**) (160 mg, 1.00 mmol) in DMF (3 mL) was added NCS (401 mg, 3.00 mmol) at 0 °C. The mixture was warmed to rt and stirred for 3 h. EtOAc (10 mL) was added and the mixture was washed with water (3 x 10 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated to dryness. The residue was purified by column chromatography (EtOAc/PE = 1:2) to give the title compound as a white solid.

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Intermediate 20: Methyl 2-(difluoromethyl)-5-fluorobenzoate (**Int 20**)

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**Step 1: 2-Bromo-1-(difluoromethyl)-4-fluorobenzene (Int 20b)**

To a solution of 2-bromo-4-fluorobenzaldehyde (3.00 g, 14.9 mmol) in DCM (30 mL) at 0 °C was added DAST (5.98 g, 37.1 mmol) and the mixture was stirred at rt overnight.

- 5 Aqueous NaHCO₃ was added and the aqueous layer was extracted with DCM (3 x 50 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated to dryness. The residue was purified by column chromatography on silica gel (PE/EtOAc = 10:1) to give the title compound as a yellow oil.

10 **Step 2: 2-(Difluoromethyl)-5-fluorobenzonitrile (Int 20c)**

To a solution of 2-bromo-1-(difluoromethyl)-4-fluorobenzene (Int 20b) (2.89 g, 12.9 mmol) in DMF (30 mL) was added CuCN (6.61 g, 38.8 mmol) and the mixture was stirred at 110 °C for 2 d. The mixture was filtered. To the filtrate was added water (50 mL) and the mixture was extracted with EtOAc (3 x 40 mL). The combined organic layers were

15 dried over anhydrous Na₂SO₄, filtered and concentrated to dryness. The residue was purified by column chromatography on silica gel (PE/EtOAc = 10:1) to give the title compound as a yellow oil.

Step 3: 2-(Difluoromethyl)-5-fluorobenzoic acid (Int 20d)

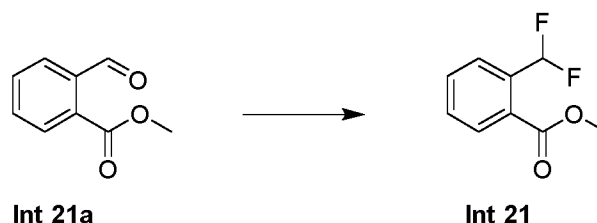
- 20 To a solution of 2-(difluoromethyl)-5-fluorobenzonitrile (Int 20c) (1.51 g, 8.92 mmol) in MeOH (20 mL) was added NaOH (5 mL, 4M) and the mixture was stirred at 60 °C overnight. The mixture was concentrated and the pH was adjust to pH < 2 with 2M HCl. The mixture was extracted with EtOAc (3 x 40 mL). The combined organic layers were

dried over anhydrous Na₂SO₄, filtered and concentrated to dryness to give the title compound as a yellow oil.

Step 4: Methyl 2-(difluoromethyl)-5-fluorobenzoate (Int 20)

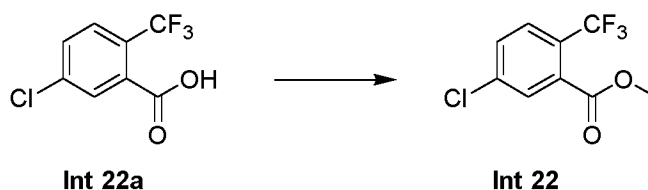
- 5 To a solution of 2-(difluoromethyl)-5-fluorobenzoic acid (**Int 20d**) (1.43 g, 7.52 mmol) in DCM (20 mL) was added SOCl₂ (8 mL) and the mixture was stirred at 40 °C for 2 h. The mixture was concentrated and MeOH (10 mL) was added at 0 °C. The mixture was stirred at rt overnight. Water (40 mL) was added and the mixture was extracted with EtOAc (3 x 40 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and
10 concentrated to dryness. The residue was purified by column chromatography on silica gel (PE/EtOAc = 8:1) to give the title compound as a yellow oil.

Intermediate 21: Methyl 2-(difluoromethyl)benzoate (Int 21)

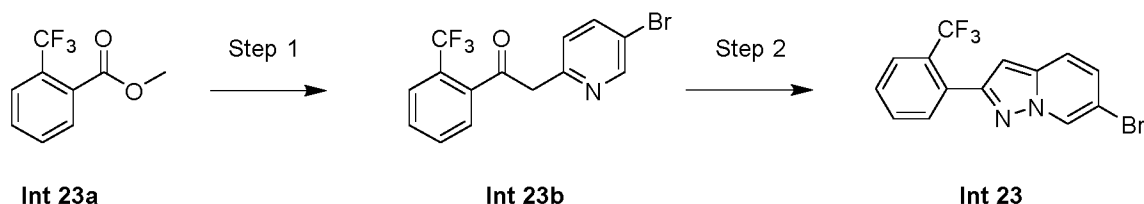


- 15 The title compound was prepared similar as described for intermediate **20**, step 1 (**Int 20b**) using methyl 2-formylbenzoate in place of 2-bromo-4-fluorobenzaldehyde.

Intermediate 22: Methyl 5-chloro-2-(trifluoromethyl)benzoate (Int 22)



- 20 To a solution of 5-chloro-2-(trifluoromethyl)benzoic acid (**Int 22a**) (3.00 g, 13.4 mmol) in DCM (30 mL) was added SOCl₂ (10 mL) and the mixture was stirred at 40 °C for 2 h. The mixture was concentrated and MeOH (30 mL) was added at 0 °C. The mixture was stirred at rt overnight. Water (50 mL) was added and the mixture was extracted with EtOAc (3 x 40 mL). The combined organic layers were dried over anhydrous Na₂SO₄,
25 filtered and concentrated to dryness. The residue was purified by column chromatography on silica gel (PE/EtOAc = 8:1) to give the title compound as a yellow oil.

Intermediate 23: 6-Bromo-2-(2-(trifluoromethyl)phenyl)pyrazolo[1,5-a]pyridine (**Int 23**)**Step 1:** 2-(5-Bromopyridin-2-yl)-1-(2-(trifluoromethyl)phenyl)ethan-1-one (**Int 23b**)

To a solution of 5-bromo-2-methylpyridine (3.81 g, 22.3 mmol) in THF (100 mL) at -78 °C was added LHMDS (67 mL, 1M in THF, 66.8 mmol) under Ar. The mixture was stirred at rt for 2 h. Then methyl 2-(trifluoromethyl)benzoate (**Int 23a**) (5.00 g, 24.5 mmol) was added and the mixture was stirred at rt overnight. Aqueous NH₄Cl was added and the aqueous layer was extracted with EtOAc (3 x 40 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated to dryness. The residue was purified by column chromatography on silica gel (PE/EtOAc = 3:1) to give the title compound as a yellow solid.

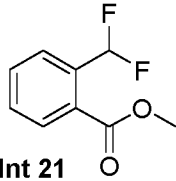
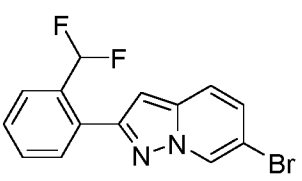
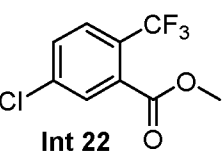
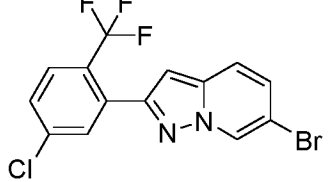
Step 2: 6-Bromo-2-(2-(trifluoromethyl)phenyl)pyrazolo[1,5-a]pyridine (**Int 23**)

To a solution of 2-(5-bromopyridin-2-yl)-1-(2-(trifluoromethyl)phenyl)ethan-1-one (**Int 23b**) (2.00 g, 5.83 mmol) in MeCN (10 mL) was added O-(mesitylsulfonyl)hydroxylamine (3.13 g, 14.6 mmol). The mixture was stirred at rt for 5 h. EtOAc (30 mL) and water (30 mL) were added. The aqueous layer was extracted with EtOAc (3 x 30 mL) and the combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated to dryness. The residue was purified by column chromatography on silica gel (PE/EtOAc = 4:1) to give the title compound as a yellow solid.

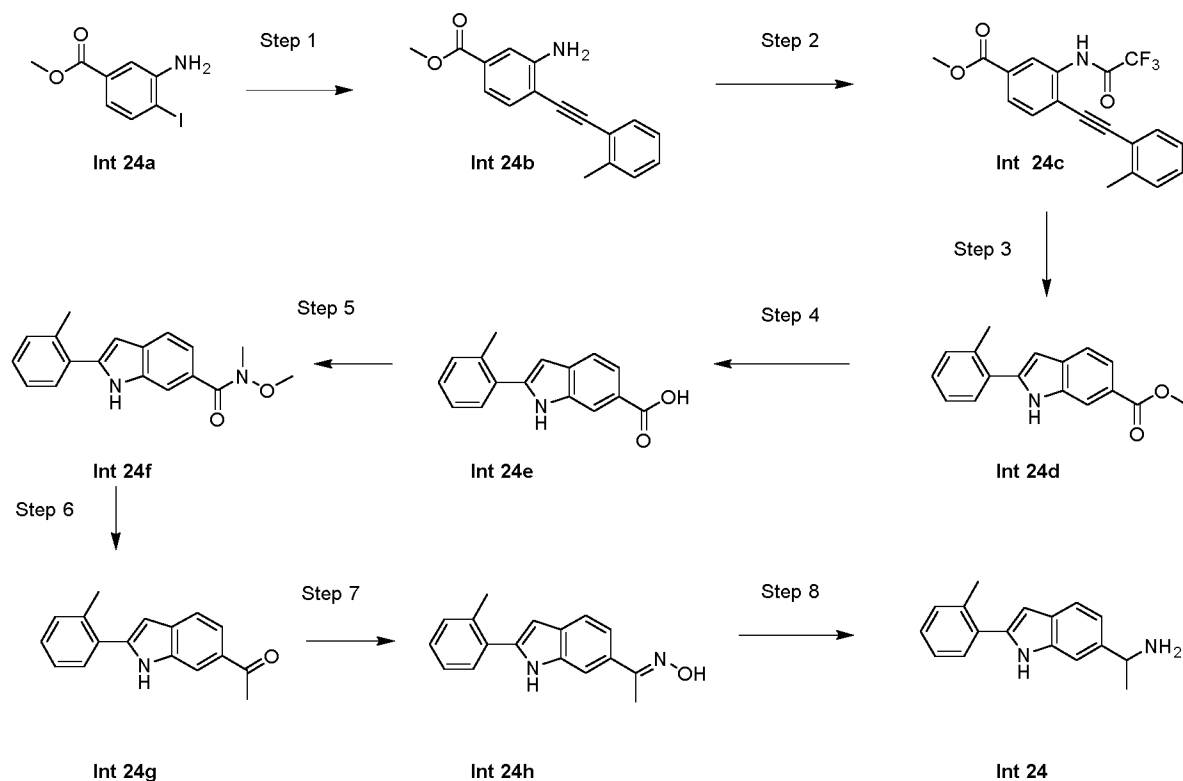
Intermediates 23/1 to 23/3

The following intermediates were prepared similar as described for intermediate **23** using the appropriate building blocks.

#	Building Block	Structure
23/1	Int 20	

23/2	 Int 21	
23/3	 Int 22	

Intermediate 24: 1-(2-(o-Tolyl)-1H-indol-6-yl)ethan-1-amine (Int 24)



Step 1: Methyl 3-amino-4-(o-tolyethynyl)benzoate (Int 24b)

- 5 To a solution of methyl 3-amino-4-iodobenzoate (**Int 24a**) (1.10 g, 4.03 mmol) in Et₃N (15 mL) was added Pd(PPh₃)₄ (185 mg, 0.16 mmol), CuI (46 mg, 0.24 mmol), PPh₃ (63 mg, 0.24 mmol) and 1-ethynyl-2-methylbenzene (604 mg, 5.21 mmol). The mixture was stirred at 60 °C under N₂ overnight. The mixture was filtered and concentrated to dryness. The residue was purified by silica gel column chromatography (PE/EtOAc = 5:1) to give
- 10 the title compound as yellow solid.

Step 2: Methyl 4-(o-tolyethynyl)-3-(2,2,2-trifluoroacetamido)benzoate (Int 24c)

To a solution of methyl 3-amino-4-(*o*-tolylethynyl)benzoate (**Int 24b**) (900 mg, 3.40 mmol) in DCM (20 mL) was added TFAA (785 mg, 3.70 mmol), pyridine (1.10 g, 13.60 mmol) and DMAP (50 mg). The mixture was stirred at 40 °C overnight. DCM (50 mL) was added and the mixture was washed with 1M HCl (2 x 30 mL) and brine (1 x 40 mL).

- 5 The combined organic layers were dried over Na₂SO₄, filtered and concentrated to dryness. The residue was purified by silica gel column chromatography (PE/EtOAc = 4:1) to give the title compound as a yellow solid.

Step 3: Methyl 2-(*o*-tolyl)-1*H*-indole-6-carboxylate (Int 24d**)**

- 10 To a solution of methyl 4-(*o*-tolylethynyl)-3-(2,2,2-trifluoroacetamido)benzoate (**Int 24c**) (950 mg, 2.6 mmol) in DMF (15 mL) was added CuI (50 mg, 0.26 mmol), TEA (525 mg, 5.20 mmol) and Pd(PPh₃)₂Cl₂ (100 mg) under N₂ and the mixture was stirred at 60 °C for 3 h. The mixture was cooled to rt, poured into H₂O (150 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (40 mL), dried over
15 Na₂SO₄ and filtered. The mixture was concentrated to dryness and the residue was purified by silica gel column chromatography (PE/EtOAc = 4:1) to give the title compound as a yellow solid.

Step 4: 2-(*o*-Tolyl)-1*H*-indole-6-carboxylic acid (Int 24e**)**

- 20 To a solution of methyl 2-(*o*-tolyl)-1*H*-indole-6-carboxylate (**Int 24d**) (470 mg, 1.80 mmol) in MeOH/THF (5 mL/5 mL) was added LiOH (5 mL, 2M aqueous solution). The mixture was stirred at 40 °C overnight and the pH was adjusted to pH = 7 with 1M HCl. The mixture was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (40 mL), dried over sodium sulfate, filtered and concentrated to
25 dryness to give the title compound as a yellow solid.

Step 5: *N*-Methoxy-*N*-methyl-2-(*o*-tolyl)-1*H*-indole-6-carboxamide (Int 24f**)**

- To a solution of 2-(*o*-tolyl)-1*H*-indole-6-carboxylic acid (**Int 24e**) (400 mg, 1.60 mmol) in DMF (10 mL) was added HATU (912 mg, 2.40 mmol) and DIPEA (619 mg, 4.80 mmol)
30 and the mixture was stirred at rt for 1 h. Then *N,O*-dimethylhydroxylamine hydrochloride (186 mg, 1.90 mmol) was added and the mixture was stirred at rt overnight. Water (100 mL) was added and the mixture was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (80 mL), dried over sodium sulfate and filtered. The mixture was concentrated to dryness and the residue was purified by silica-gel column
35 chromatography (PE/EtOAc = 4:1) to give the title compound as a white solid.

Step 6: 1-(2-(o-Tolyl)-1H-indol-6-yl)ethan-1-one (Int 24g)

To a solution of *N*-methoxy-*N*-methyl-2-(o-tolyl)-1*H*-indole-6-carboxamide (**Int 24f**) (410 mg, 1.40 mmol) in THF (10 mL) was added MeMgBr (1 mL, 3 M solution in Et₂O) and the mixture was stirred at rt for 3 h. Water (30 mL) was added and the mixture was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (30 mL), dried over Na₂SO₄ and filtered. The filtrate was concentrated to dryness and the residue was purified by silica gel column (PE/EtOAc = 4:1) to give the title compound as a white solid.

Step 7: 1-(2-(o-Tolyl)-1H-indol-6-yl)ethan-1-one oxime (Int 24h)

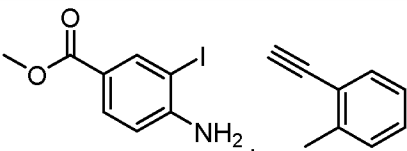
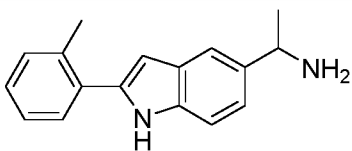
To a solution of 1-(2-(o-tolyl)-1*H*-indol-6-yl)ethan-1-one (**Int 24g**) (250 mg, 1.00 mmol) in ethanol (10 mL) was added hydroxylamine hydrochloride (172 mg, 2.50 mmol) and pyridine (158 mg, 2.00 mmol) and the mixture was stirred at 60 °C for 3 h. The mixture was concentrated to dryness and the residue was purified by silica gel column (PE/EtOAc = 2:1) to give the title compound as a white solid.

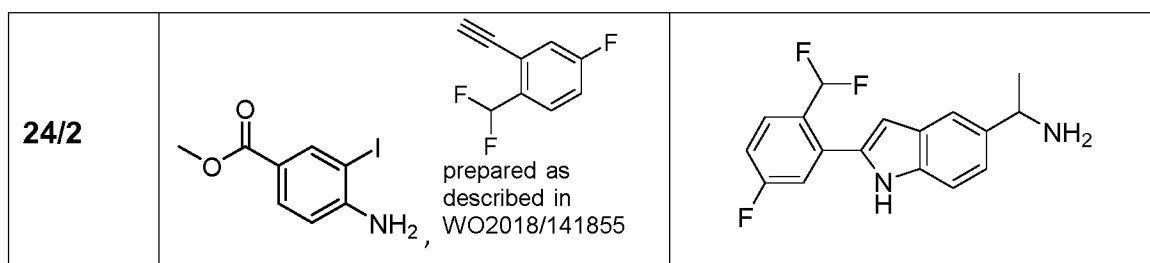
Step 8: 1-(2-(o-Tolyl)-1H-indol-6-yl)ethan-1-amine (Int 24)

To a mixture of 1-(2-(o-tolyl)-1*H*-indol-6-yl)ethan-1-one oxime (**Int 24h**) (132 mg, 0.50 mmol) in methanol (10 mL) was added Pd/C (50 mg) and the mixture was stirred overnight at rt under H₂ atmosphere. The mixture was filtered and the filtrate was concentrated to dryness to give the title compound as a colorless oil.

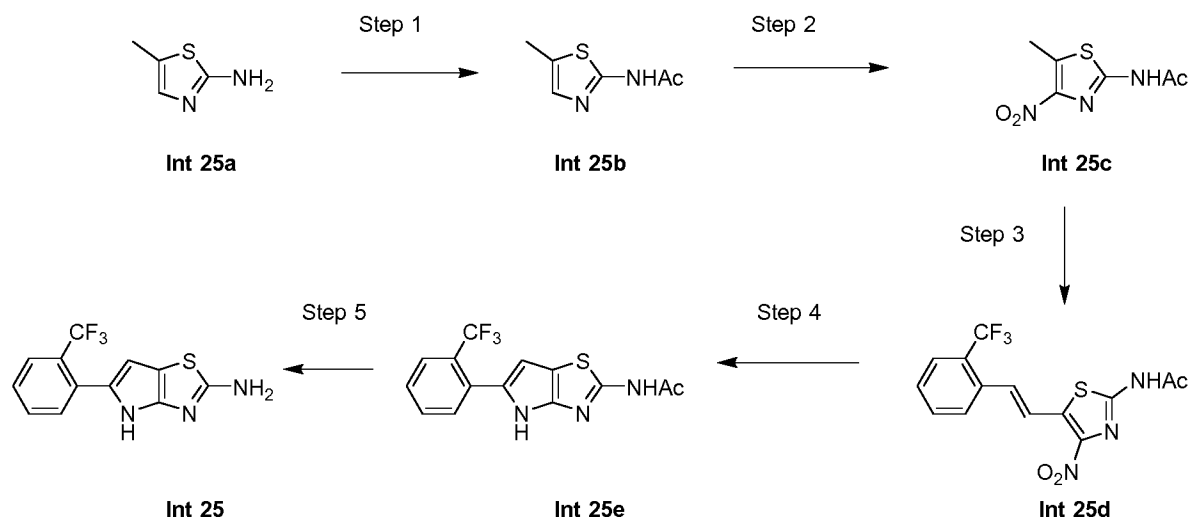
Intermediates 24/1 to 24/2

The following intermediates were prepared similar as described for intermediate **24** using the appropriate building blocks in step 1.

#	Building Blocks	Structure
24/1		



Intermediate 25: 5-(2-(Trifluoromethyl)phenyl)-4*H*-pyrrolo[2,3-*d*]thiazol-2-amine (**Int 25**)



Step 1: *N*-(5-Methylthiazol-2-yl)acetamide (**Int 25b**)

- 5 To a solution of 5-methylthiazol-2-amine (**Int 25a**) (20.00 g, 175.40 mmol), DIPEA (45.30 g, 350.0 mmol) in MeCN (200 mL) was added AcCl at 0 °C. The mixture was stirred at rt overnight. H₂O was added and the mixture was extracted with EtOAc (2 x 100 mL). The combined organic layers were washed with brine (100 mL), dried over Na₂SO₄, filtered and concentrated to dryness. The residue was purified by column chromatography on silica gel (PE/EtOAc = 5:1) to give the title compound as a yellow solid.
- 10

Step 2: *N*-(5-Methyl-4-nitrothiazol-2-yl)acetamide (**Int 25c**)

- To a solution of *N*-(5-Methylthiazol-2-yl)acetamide (**Int 25b**) (8.00 g, 51.3 mmol), KNO₃ (15.5 g, 153.8 mmol) in dichloroethane (150 mL) was added trifluoromethanesulfonic acid (15.4 g, 102.6 mmol). The mixture was stirred at rt for 1 h and then at 50 °C for 2 h.
- 15 After cooling to rt, KNO₃ (26.0 g, 256.5 mmol) and trifluoromethanesulfonic acid anhydride (4.75 g, 16.8 mmol) were added under Ar. The mixture was stirred at 50 °C for 2 h. Then the mixture was stirred at rt overnight. Ice-water was added and the mixture was extracted with DCM (2 x 150 mL). The combined organic layers were washed with
- 20 brine (150 mL), dried over Na₂SO₄, filtered and concentrated to dryness. The residue

was purified by column chromatography on silica gel (PE/EtOAc = 3:1) to give the title compound as a yellow solid.

Step 3: (*E*)-*N*-(4-Nitro-5-(2-(trifluoromethyl)styryl)thiazol-2-yl)acetamide (Int 25d)

- 5 To a solution of *N*-(5-methyl-4-nitrothiazol-2-yl)acetamide (**Int 25c**) 3.80 g, 18.9 mmol) in DMSO (60 mL) were added DBU (5.75 g, 37.8 mmol), 2-(trifluoromethyl)benzaldehyde (3.29 g, 18.9 mmol), then the mixture was stirred at rt overnight. Water was added and the mixture was extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over Na₂SO₄, concentrated, filtered and the residue
- 10 was purified by column chromatography on silica gel (PE/EtOAc = 3:1) to give the title compound as a yellow solid.

Step 4: *N*-(5-(2-(Trifluoromethyl)phenyl)-4*H*-pyrrolo[2,3-*d*]thiazol-2-yl)acetamide (Int 25e)

- 15 A mixture of (*E*)-*N*-(4-nitro-5-(2-(trifluoromethyl)styryl)thiazol-2-yl)acetamide (**Int 25d**) (2.50 g, 7.00 mmol) in P(OEt)₃ (30 mL) was stirred at 155 °C for 2 h. After cooling to rt, H₂O was added and the mixture was extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over Na₂SO₄, filtered and concentrated to dryness. The residue was purified by column chromatography on silica
- 20 gel (PE/EtOAc = 3:1) to give the title compound as a yellow solid.

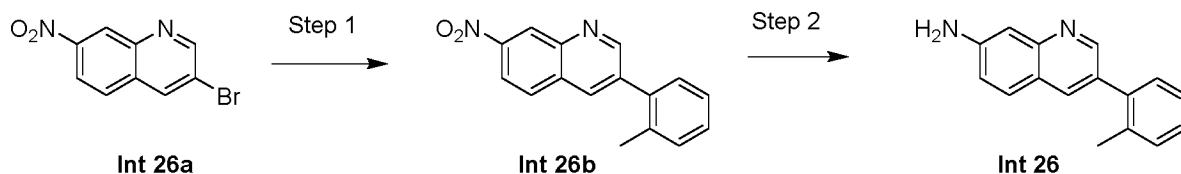
Step 5: 5-(2-(Trifluoromethyl)phenyl)-4*H*-pyrrolo[2,3-*d*]thiazol-2-amine (Int 25)

- To a solution of *N*-(5-(2-(trifluoromethyl)phenyl)-4*H*-pyrrolo[2,3-*d*]thiazol-2-yl)acetamide (**Int 25e**) (1.50 g, 4.60 mmol) in EtOH (40 mL) was added concentrated HCl (20 mL) and
- 25 the mixture was stirred at 60 °C for 6 h. The mixture was then stirred at rt overnight. The mixture was filtered and the filter residue was added to saturated NaHCO₃ (30 mL). The aqueous layer was extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over Na₂SO₄, filtered and concentrated to dryness to give the title compound as a white solid.

30

Intermediate 26: 3-(*o*-Tolyl)quinolin-7-amine (Int 26)

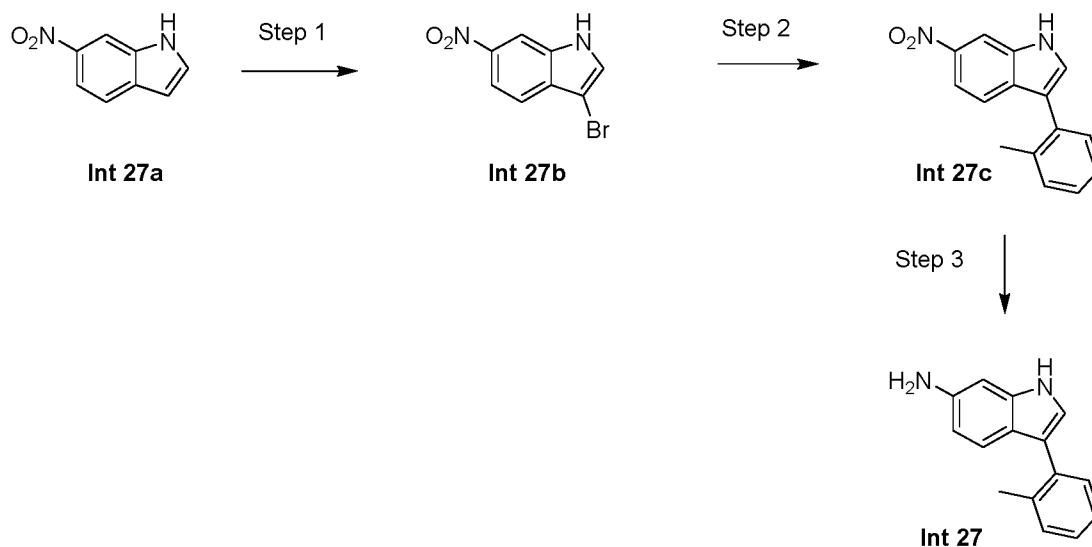
75

**Step 1: 7-Nitro-3-(o-tolyl)quinoline (Int 26b)**

To a solution of 3-bromo-7-nitroquinoline (**Int 26a**) (500 mg, 2.00 mmol), o-tolylboronic acid (400 mg, 3.00 mmol) and Na₂CO₃ (420 mg, 4.00 mmol) in 1,4-dioxane (50 mL) and water (5 mL) was added Pd(dppf)Cl₂ (50 mg, 0.05 mmol) and the mixture was stirred at 90 °C overnight. The mixture was filtered and the filtrate was extracted with EtOAc (3 x 150 mL). The combined organic layers were concentrated to dryness and the residue was purified by column chromatography (PE/EtOAc = 10:1) to give the title compound as a white solid.

Step 2: 3-(o-Tolyl)quinolin-7-amine (Int 26)

A mixture of 7-nitro-3-(o-tolyl)quinoline (**Int 26b**) (456 mg, 1.70 mmol), NH₄Cl (901 mg, 17.0 mmol) and Zn (1.10 g, 17.0 mmol) in THF (50 mL) and water (5 mL) was stirred at rt overnight. The mixture was filtered and the filtrate was extracted with EtOAc (3 x 150 mL). The combined organic layers were concentrated to dryness and the residue was purified by column chromatography (PE/EtOAc = 10:1) to give the title compound as a white solid.

Intermediate 27: 3-(o-Tolyl)-1H-indol-6-amine (Int 27)

Step 1: 3-Bromo-6-nitro-1*H*-indole (Int 27b)

To a solution of 6-nitro-1*H*-indole (**Int 27a**) (1.00 g, 6.17 mmol) in THF (50 mL) was added NBS (1.00 g, 6.18 mmol) and the mixture was stirred at rt for 2 h. The mixture was extracted with EtOAc (3 x 150 mL). The combined organic layers were concentrated to dryness to give the title compound as a yellow solid.

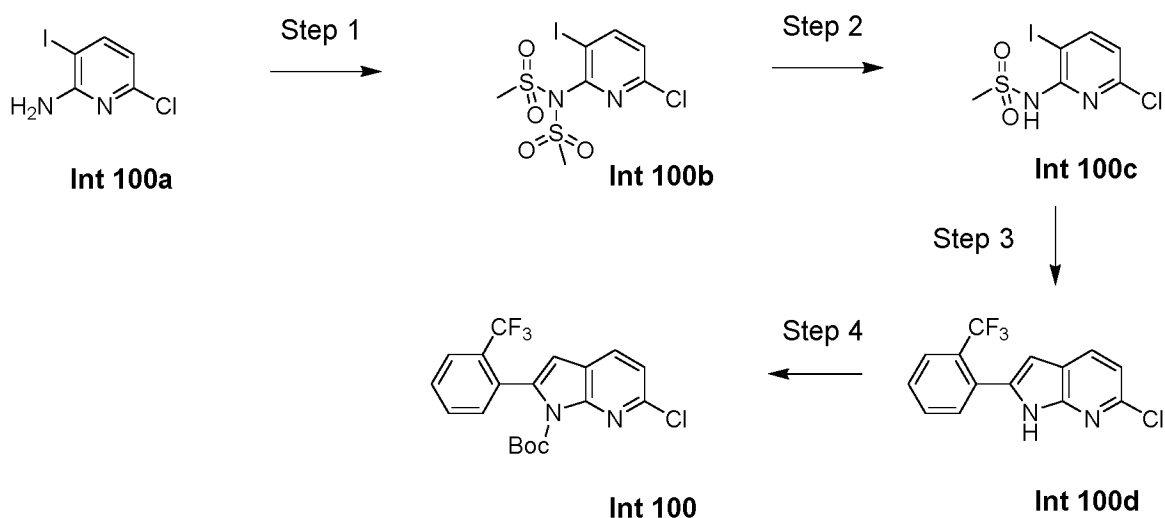
Step 2: 6-Nitro-3-(*o*-tolyl)-1*H*-indole (Int 27c)

To a solution of 3-bromo-6-nitro-1*H*-indole (**Int 27b**) (1.00 g, 4.10 mmol), *o*-tolylboronic acid (846 mg, 6.20 mmol) and Na₂CO₃ (880 mg, 8.20 mmol) in 1,4-dioxane (50 mL) and water (5 mL) was added Pd(dppf)Cl₂ (100 mg, 0.10 mmol) under N₂ and the mixture was stirred at 90 °C overnight. The mixture was filtered and the filtrate was extracted with EtOAc (3 x 150 mL). The combined organic layers were concentrated to dryness and the residue was purified by column chromatography (PE/EtOAc = 10:1) to give the title compound as a white solid.

Step 3: 3-(*o*-Tolyl)-1*H*-indol-6-amine (Int 27)

A solution of 6-nitro-3-(*o*-tolyl)-1*H*-indole (**Int 27c**) (800 mg, 3.20 mmol), NH₄Cl (1.60 g, 31.70 mmol) and Zn (2.00 g, 31.70 mmol) in THF (50 mL) and water (5 mL) was stirred at rt overnight. The mixture was filtered and extracted with EtOAc (3 x 150 mL). The combined organic layers were concentrated to dryness and the residue was purified by column chromatography (PE/EtOAc = 10:1) to give the title compound as a white solid.

Intermediate 100: *tert*-Butyl 6-chloro-2-(2-(trifluoromethyl)phenyl)-1*H*-pyrrolo[2,3-*b*]pyridine-1-carboxylate (**Int 100**)



Step 1: *N*-(6-Chloro-3-iodopyridin-2-yl)-*N*-(methylsulfonyl)methanesulfonamide (**Int 100b**)

Methanesulfonyl chloride (26.7 mL, 345 mmol) was added dropwise to a solution of 6-chloro-3-iodopyridin-2-amine (**Int 100a**) (25.0 g, 98.4 mmol) in pyridine (200 mL) at 0 °C.

- 5 The mixture was allowed to warm to rt and stirred overnight. The mixture was concentrated to dryness and the residue was purified by column chromatography (gradient 5-100% EtOAc in DCM) to give the title compound as a yellow solid.

Step 2: *N*-(6-Chloro-3-iodopyridin-2-yl)methanesulfonamide (**Int 100c**)

- 10 *N*-(6-Chloro-3-iodopyridin-2-yl)-*N*-(methylsulfonyl)methanesulfonamide (**Int 100b**) (15.0 g, 36.6 mmol) was dissolved in a mixture of aqueous NaOH (10 w/w %, 100 mL) and THF (100 mL). The mixture was stirred at rt for 16 h. The mixture was concentrated, water was added and the pH was adjusted to pH 4 using aqueous citric acid. The precipitated solid was filtered and dried under vacuum to give the title compound as a
15 yellow solid.

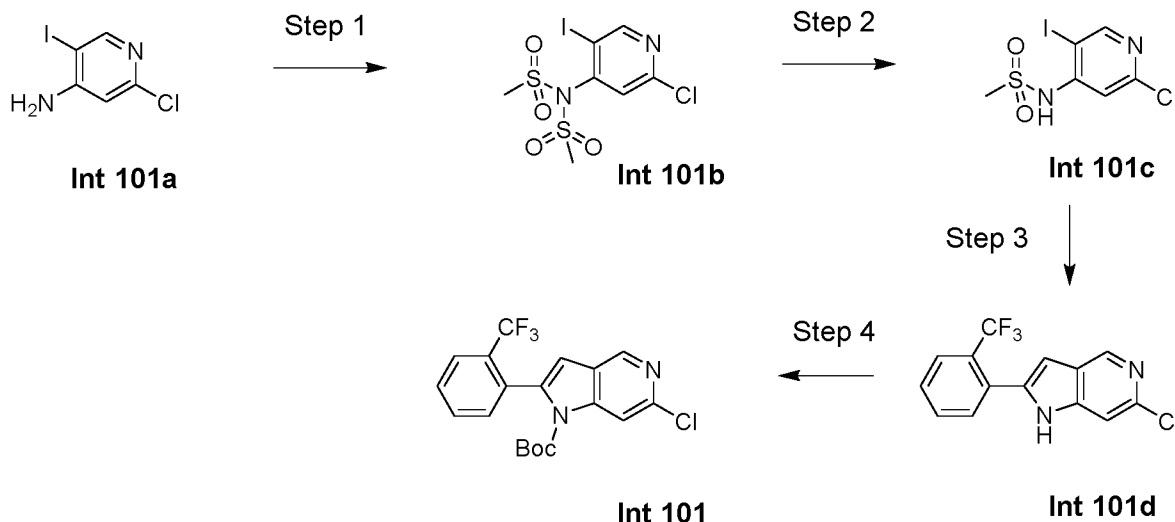
Step 3: 6-Chloro-2-(2-(trifluoromethyl)phenyl)-1*H*-pyrrolo[2,3-*b*]pyridine (**Int 100d**)

- A mixture of *N*-(6-chloro-3-iodopyridin-2-yl)methanesulfonamide (**Int 100c**) (7.50 g, 22.60 mmol), 1-ethynyl-2-(trifluoromethyl)benzene (5.76 g, 33.9 mmol), Pd(PPh₃)₂Cl₂ (793 mg, 1.13 mmol), copper (I) iodide (215 mg, 1.13 mmol) and TEA (6.20 g, 61.50 mmol) in DMF (100 mL) was stirred under nitrogen at 100 °C for 3 h. DBU (10.0 mL) was added and the mixture was stirred at 100 °C overnight. The mixture was cooled to rt. Aqueous NH₄Cl was added and the mixture was extracted with EtOAc. The combined organic layers were dried over anhydrous MgSO₄, filtered and concentrated to dryness.
20 The residue was purified by silica gel chromatography (gradient 5-100% EtOAc in PE) to give the title compound as a yellow solid.

Step 4: *tert*-Butyl 6-chloro-2-(2-(trifluoromethyl)phenyl)-1*H*-pyrrolo[2,3-*b*]pyridine-1-carboxylate (**Int 100**)

- 30 To a mixture of 6-chloro-2-(2-(trifluoromethyl)phenyl)-1*H*-pyrrolo[2,3-*b*]pyridine (**Int 100d**) (2.50 g, 8.40 mmol) in DCM (40 mL) was added a solution of Boc₂O (2.10 g, 9.60 mmol) in DCM (15 mL), followed by DMAP (100 mg, 0.82 mmol). The mixture was stirred at rt for 2 h. The mixture was absorbed onto silica and purified by column chromatography (DCM/EtOAc = 9:1) to give the title compound as a white solid.

Intermediate 101: *tert*-Butyl 6-chloro-2-(2-(trifluoromethyl)phenyl)-1*H*-pyrrolo[3,2-*c*]pyridine-1-carboxylate (**Int 101**)



Step 1: *N*-(2-Chloro-5-iodopyridin-4-yl)-*N*-(methanesulfonyl)methanesulfonamide (**Int 101b**)

Methanesulfonyl chloride (2.34 mL, 30.1 mmol) in dichloromethane (5 mL) was added dropwise to a solution of 2-chloro-5-iodopyridin-4-amine (**Int 101a**) (1.01 g, 3.97 mmol) and triethylamine (3.73 mL, 26.4 mmol) in dichloromethane (10 mL). The mixture was allowed to warm to rt and stirred overnight. The mixture was concentrated to dryness and the residue was purified by column chromatography (gradient 5-100% EtOAc in DCM) to give the title compound as a yellow solid.

Step 2: *N*-(2-Chloro-5-iodopyridin-4-yl)methanesulfonamide (**Int 101c**)

N-(2-Chloro-5-iodopyridin-4-yl)-*N*-(methanesulfonyl)methanesulfonamide (**Int 101b**) (571 mg, 1.39 mmol) was dissolved in a mixture of aqueous NaOH solution (10 w/w%, 3.5 mL) and THF (3.5 mL) and the mixture was stirred at rt for 16 h. The mixture was concentrated to dryness. Water was added and the mixture was acidified to pH 4 using aqueous citric acid solution. The precipitated solid was filtered and dried to give the title compound as a yellow solid.

Step 3: 6-Chloro-2-(2-(trifluoromethyl)phenyl)-1*H*-pyrrolo[3,2-*c*]pyridine (**Int 101d**)

A mixture of *N*-(2-chloro-5-iodopyridin-4-yl)methanesulfonamide (**Int 101c**) (4.10 g, 12.3 mmol), 1-ethynyl-2-(trifluoromethyl)benzene (3.10 g, 18.5 mmol), Pd(PPh₃)₂Cl₂ (862 mg, 1.23 mmol), copper(I) iodide (23.4 mg, 1.23 mmol) and TEA (6.20 g, 61.5 mmol) in DMF (60 mL) was stirred under nitrogen and heated to 100 °C for 2 h. DBU (6.0 mL) was added and the mixture was stirred at 100 °C overnight. The mixture was cooled to rt. The

mixture was diluted with aqueous NH_4Cl and extracted with EtOAc. The combined organic layers were dried over anhydrous MgSO_4 , filtered and concentrated to dryness. The residue was purified by silica gel chromatography (EtOAc/PE = 1: 8) to give the title compound as a yellow solid.

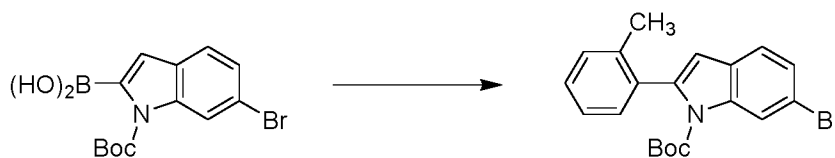
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Step 4: *tert*-Butyl 6-chloro-2-(2-(trifluoromethyl)phenyl)-1*H*-pyrrolo[3,2-*c*]pyridine-1-carboxylate (**Int 101**)

To a mixture of 6-chloro-2-(2-(trifluoromethyl)phenyl)-1*H*-pyrrolo[3,2-*c*]pyridine (**Int 101d**) (2.50 g, 8.40 mmol) in DCM (10 mL) was added a solution of $(\text{Boc})_2\text{O}$ (2.10 g, 9.60 mmol) in DCM (40 mL), followed by DMAP (108 mg, 0.89 mmol). The mixture was stirred at rt for 2 h. The mixture was absorbed onto silica and purified by column chromatography (DCM/EtOAc = 10:1) to give the title compound as a white solid.

10

Intermediate 102: *tert*-Butyl 6-bromo-2-(*o*-tolyl)-1*H*-indole-1-carboxylate (**Int 102**)



Int 102a

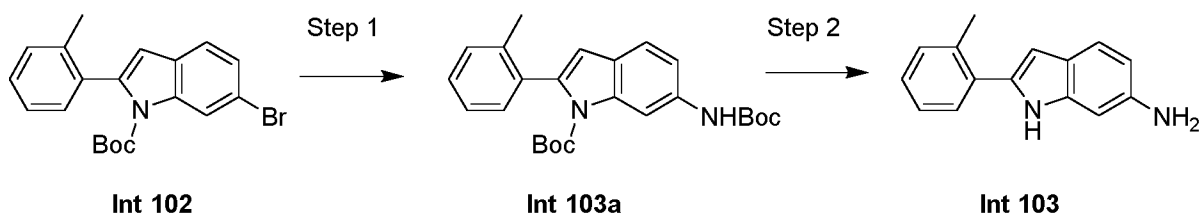
Int 102

15

A mixture of (6-bromo-1-(*tert*-butoxycarbonyl)-1*H*-indol-2-yl)boronic acid (850 mg, 2.5 mmol), 1-iodo-2-methylbenzene (1.6 g, 7.5 mmol), $\text{Pd}(\text{dppf})\text{Cl}_2$ (178 mg, 0.25 mmol) and K_2CO_3 (690 mg, 5.0 mmol) in 1,4-dioxane/water (40 mL, 3/1) was stirred at 110 °C under N_2 atmosphere for 2 h. The layers were separated and the organic layer was concentrated to dryness. The residue was purified by column chromatography (PE/EtOAc = 97:3) to give the title compound as a white solid.

20

Intermediate 103: 2-(*o*-Tolyl)-1*H*-indol-6-amine (**Int 103**)



Int 102

Int 103a

Int 103

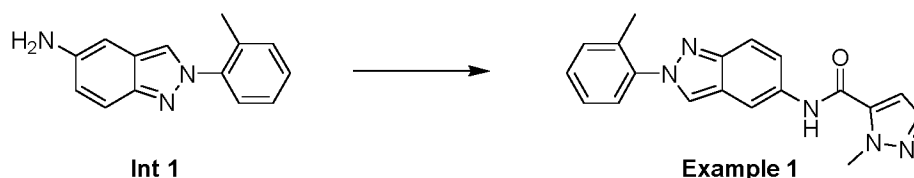
25

Step 1: *tert*-Butyl 6-((*tert*-butoxycarbonyl)amino)-2-(*o*-tolyl)-1*H*-indole-1-carboxylate (Int 103a)

To a mixture of *tert*-butyl 6-bromo-2-(*o*-tolyl)-1*H*-indole-1-carboxylate (**Int 102**) (3.85 g, 10.0 mmol) in 1,4-dioxane (40 mL) and water (4 mL) was added *tert*-butyl carbamate (1.41 g, 12.0 mmol), Cs₂CO₃ (4.88 g, 15.0 mmol), Xantphos (385 mg, 0.66 mmol) and Pd₂(dba)₃ (385 mg, 0.42 mmol). The mixture was stirred at 110 °C for 2 h under N₂. Water (80 mL) was added and the mixture was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and filtered. The filtrate was concentrated to dryness and the residue was purified by column chromatography (PE/EtOAc = 5:1) to give the title compound as a yellow solid.

Step 2: 2-(*o*-Tolyl)-1*H*-indol-6-amine (Int 103)

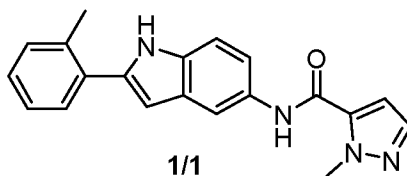
A mixture of *tert*-butyl 6-((*tert*-butoxycarbonyl)amino)-2-(*o*-tolyl)-1*H*-indole-1-carboxylate (**Int 103a**) (2.45 g, 5.81 mmol), TFA (8 mL) and DCM (25 mL) was stirred at rt for 2 h. Water (30 mL) was added and the pH was adjusted to pH = 7 by adding NaHCO₃. The mixture was extracted with DCM (3 x 30 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated to dryness to give the title compound as a solid.

Example 1: 1-Methyl-*N*-(2-(*o*-tolyl)-2*H*-indazol-5-yl)-1*H*-pyrazole-5-carboxamide (1)

A mixture of 2-*o*-tolyl-2*H*-indazol-5-amine (**Int 1**) (225 mg, 1.0 mmol), DIPEA (640 mg, 5.0 mmol), HATU (570 mg, 1.5 mmol) and 1-methyl-1*H*-pyrazole-5-carboxylic acid (189 mg, 1.5 mmol) in DMF (8 mL) was stirred at 35 °C overnight. The mixture was purified by reverse phase chromatography (c18, gradient 25-55 % acetonitrile in 10 mmol/L aqueous ammonium bicarbonate) to afford the title compound as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆): δ ppm 10.25 (s, 1H), 8.63 (s, 1H), 8.32 (s, 1H), 7.73-7.71 (d, *J* = 9.2 Hz, 1H), 7.56-7.39 (m, 6H), 7.10-7.09 (d, *J* = 1.6 Hz, 1H), 4.12 (s, 3H), 2.22 (s, 3H). MS (ESI): *m/z* 332.2 [*M*+1]⁺.

Example 1/1: 1-Methyl-*N*-(2-(*o*-tolyl)-1*H*-indol-5-yl)-1*H*-pyrazole-5-carboxamide (1/1)

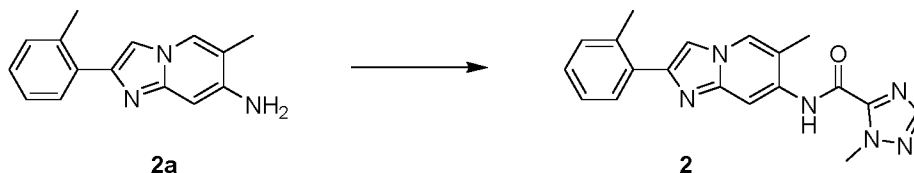
81



1/1

The title compound was prepared similar as described for Example 1 using 2-(o-tolyl)-1H-indol-5-amine (**Int 5**) in place of 2-o-tolyl-2H-indazol-5-amine. ¹H NMR (400 MHz, DMSO-d₆): δ ppm 11.29 (s, 1H), 10.10 (s, 1H), 7.96 (s, 1H), 7.56-7.53 (m, 2H), 7.36-7.27 (m, 5H), 7.07 (d, J = 1.6 Hz, 1H), 6.59 (d, J = 1.2 Hz, 1H), 4.11 (s, 3H), 2.49 (s, 3H). MS (ESI): m/z 331.2 [M+1]⁺.

Example 2: 1-Methyl-N-(6-methyl-2-(o-tolyl)imidazo[1,2-a]pyridin-7-yl)-1H-1,2,4-triazole-5-carboxamide (**2**)



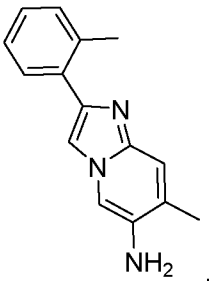
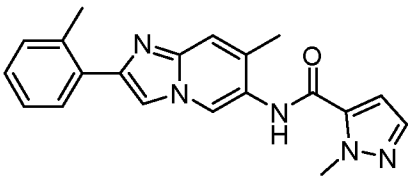
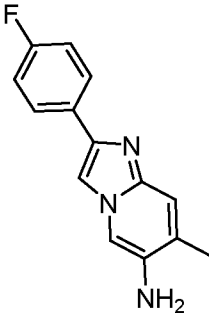
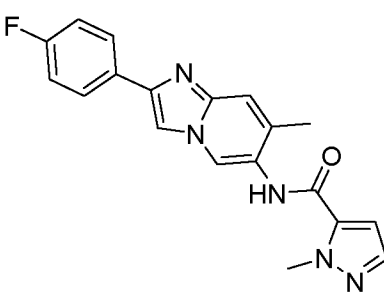
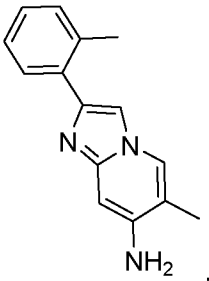
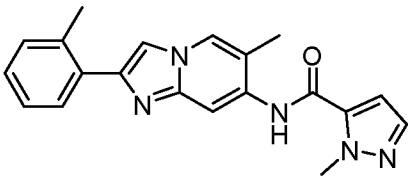
2a

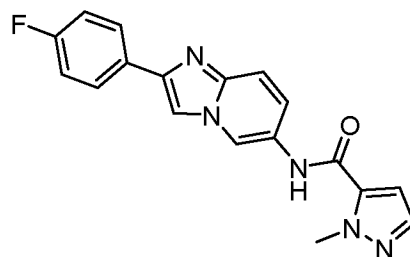
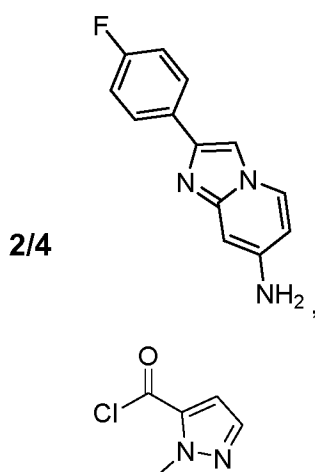
2

To a mixture of 6-methyl-2-(o-tolyl)imidazo[1,2-a]pyridin-7-amine (**2a**) (300 mg, 1.27 mmol) and TEA (191 mg, 1.90 mmol) in THF (10 mL), 1-methyl-1H-pyrazole-5-carbonyl chloride (181 mg, 1.28 mmol) was added. The mixture was stirred at rt overnight. The mixture was filtered and concentrated to dryness. The residue was purified by silica gel chromatography (gradient 5-25% EtOAc in PE) to give the title compound as a yellow solid. ¹H NMR (400 MHz, CD₃OD): δ ppm 8.84 (s, 1H), 8.70 (s, 1H), 8.20 (s, 1H), 8.09 (s, 1H), 7.64-7.62 (m, 1H), 7.50-7.43 (m, 3H), 4.35 (s, 3H), 2.60 (s, 3H), 2.55 (s, 3H). MS (ESI): m/z 347.1 [M+1]⁺.

Examples 2/1 to 2/4

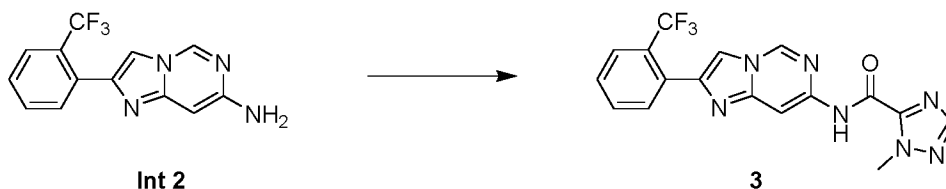
The following Examples were prepared similar as described for Example 2 using the appropriate intermediates.

#	Int.	Structure	Analytical data
2/1			¹ H NMR (500 MHz, CD ₃ OD): δ ppm 9.08 (s, 1H), 8.32 (s, 1H), 7.85 (s, 1H), 7.65-7.61 (m, 2H), 7.51-7.44 (m, 3H), 7.10 (s, 1H), 4.21 (s, 3H), 2.61 (s, 3H), 2.55 (s, 3H). MS (ESI): m/z 346.0 [M+1] ⁺ .
2/2			¹ H NMR (500 MHz, DMSO-d ₆): δ ppm 10.18 (s, 1H), 8.95 (s, 1H), 8.62 (s, 1H), 8.00 (dd, J = 8.7, 5.3 Hz, 2H), 7.77 (s, 1H), 7.60 (d, J = 1.9 Hz, 1H), 7.46-7.41 (m, 2H), 7.13 (s, 1H), 4.11 (s, 3H), 2.45 (s, 3H). MS (ESI): m/z 350.0 [M+1] ⁺ .
2/3			¹ H NMR (400 MHz, DMSO-d ₆): δ ppm 9.94 (s, 1H), 8.46 (s, 1H), 8.11 (s, 1H), 7.93-7.91 (m, 1H), 7.67 (s, 1H), 7.57 (d, J = 2.0 Hz, 1H), 7.30-7.24 (m, 3H), 7.10 (d, J = 2.0 Hz, 1H), 4.11 (s, 3H), 2.55 (s, 3H), 2.25 (s, 3H). MS (ESI): m/z 346.2 [M+1] ⁺ .



^1H NMR (500 MHz, DMSO- d_6): δ ppm 10.64 (s, 1H), 9.52 (s, 1H), 8.75 (s, 1H), 7.97 (dd, J = 8.7, 5.4 Hz, 2H), 7.89-7.79 (m, 2H), 7.60 (d, J = 2.0 Hz, 1H), 7.45-7.40 (m, 2H), 7.14 (d, J = 1.8 Hz, 1H), 4.15 (s, 3H). MS (ESI): m/z 336.0 $[\text{M}+1]^+$.

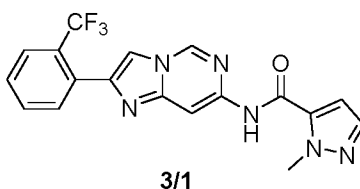
Example 3: 1-Methyl-*N*-(2-(2-(trifluoromethyl)phenyl)imidazo[1,2-*c*]pyrimidin-7-yl)-1*H*-pyrazole-5-carboxamide (**3**)



- 5 To a suspension of 2-(2-(trifluoromethyl)phenyl)imidazo[1,2-*c*]pyrimidin-7-amine (**Int 2**) (556 mg, 2.00 mmol), 1-methyl-1*H*-1,2,4-triazole-5-carboxylic acid (254 mg, 2.00 mmol) and TBTU (770 mg, 2.40 mmol) in DMF (10 mL), DIPEA (516 mg, 4.00 mmol) was added at rt. The mixture was stirred at rt for 12 h. Water was added and the mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated to dryness. The residue was purified by silica gel chromatography (gradient PE/EtOAc 2:1 to 1:1) to give the title compound as a white solid. ^1H NMR (DMSO- d_6 , 400 MHz): δ ppm 10.39 (s, 1H), 9.45 (s, 1H), 8.22-8.19 (m, 2H), 8.14 (s, 1H), 7.97-7.92 (m, 1H), 7.91-7.85 (m, 1H), 7.81-7.76 (m, 1H), 7.69-7.61 (m, 1H), 4.22 (s, 3H). MS (ESI): m/z 388.0 $[\text{M}+1]^+$.
- 10

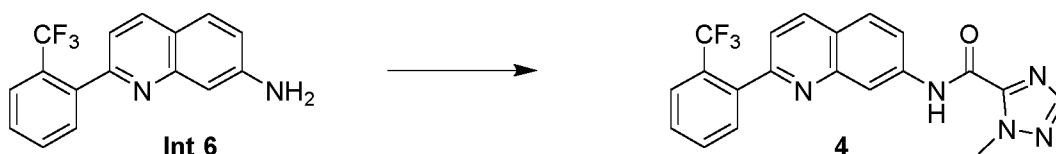
15

Example 3/1: 1-Methyl-*N*-(2-(2-(trifluoromethyl)phenyl)imidazo[1,2-*c*]pyrimidin-7-yl)-1*H*-pyrazole-5-carboxamide (**3/1**)



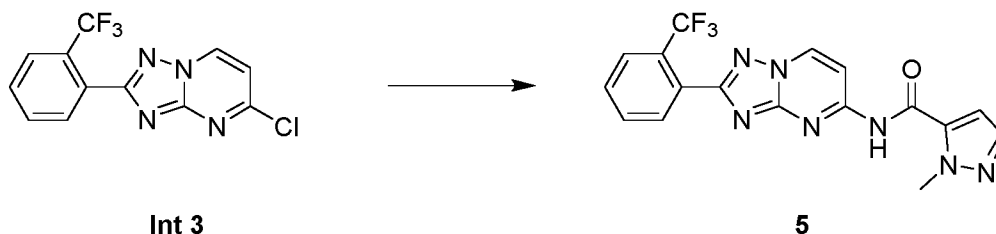
The title compound was prepared similar as described for Example 3 using 1-methyl-1*H*-pyrazole-5-carboxylic acid in place of 1-methyl-1*H*-1,2,4-triazole-5-carboxylic acid. ¹H NMR (DMSO-*d*₆, 400 MHz): δ ppm 9.44 (s, 1H), 8.23 (s, 1H), 8.18 (s, 1H), 7.95 (d, *J* = 8.0 Hz, 1H), 7.88 (d, *J* = 7.6 Hz, 1H), 7.81-7.77 (m, 1H), 7.66-7.63 (m, 1H), 7.55 (d, *J* = 2.0 Hz, 1H), 7.33 (d, *J* = 2.0 Hz, 1H), 4.14 (s, 3H). MS (ESI): *m/z* 387.0 [*M*+1]⁺.

Example 4: 1-Methyl-*N*-(2-(2-(trifluoromethyl)phenyl)quinolin-7-yl)-1*H*-1,2,4-triazole-5-carboxamide (**4**)



To a solution of 2-(2-(trifluoromethyl)phenyl)quinolin-7-amine (**Int 6**) (200 mg, 0.692 mmol), 1-methyl-1*H*-1,2,4-triazole-5-carboxylic acid (139 mg, 1.04 mmol) and PyBOP (720 mg, 1.38 mmol) in DMF (10 mL) was added DIPEA (269 mg, 2.08 mmol). The solution was stirred at rt overnight. The mixture was diluted in H₂O (20 mL) and extracted with EtOAc (20 mL). The combined organic layers were washed with water (3 x 20 mL) and brine, dried over anhydrous Na₂SO₄ and filtered. The filtrate was concentrated to dryness. The residue was purified by preparative HPLC to afford the title compound as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆): δ ppm 11.18 (s, 1H), 8.63 (s, 1H), 8.42 (d, *J* = 8.4 Hz, 1H), 8.22 (s, 1H), 8.09 (dd, *J*₁ = 2.0, *J*₂ = 8.8 Hz, 1H), 8.04 (d, *J* = 9.2 Hz, 1H), 7.92 (d, *J* = 8.0 Hz, 1H), 7.82 (dd, *J*₁ = *J*₂ = 7.6 Hz, 1H), 7.73 (dd, *J*₁ = *J*₂ = 8.0 Hz, 1H), 7.67 (d, *J* = 7.6 Hz, 1H), 7.58 (d, *J* = 8.4 Hz, 1H), 4.22 (s, 3H). MS (ESI): *m/z* 398.0 [*M*+1]⁺.

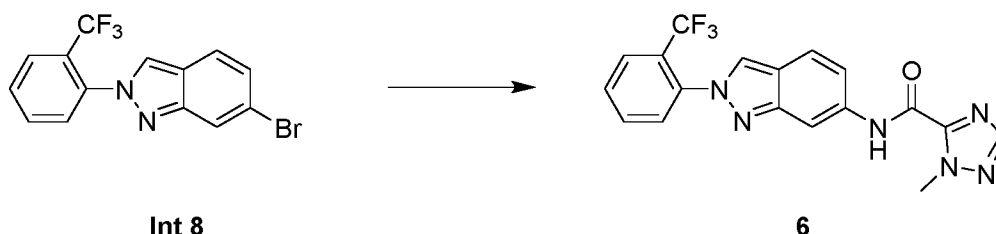
Example 5: 1-Methyl-*N*-(2-(2-(trifluoromethyl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyrimidin-5-yl)-1*H*-pyrazole-5-carboxamide (**5**)



A mixture of 5-chloro-2-(2-(trifluoromethyl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyrimidine (**Int 3**) (20 mg, 0.067 mmol), 1-methyl-1*H*-pyrazole-5-carboxamide (16 mg, 0.134 mmol),

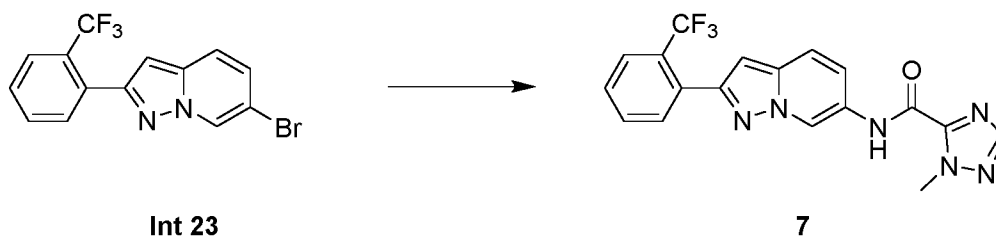
Pd₂(dba)₃ (20 mg, 0.022 mmol), tBuXphos (8 mg, 0.013 mmol) and K₂CO₃ (40 mg, 0.27 mmol) in DMF (8 mL) was stirred at 110 °C in a sealed tube overnight. The mixture was concentrated to dryness. The residue was purified by preparative TLC on silica gel (PE/EtOAc = 2:1) to give a crude product which was further purified by preparative HPLC to give the title compound as a white solid. ¹H NMR (CD₃OD, 400 MHz): δ ppm 9.13 (d, 1H, J = 7.6 Hz), 8.36 (d, 1H, J = 7.6 Hz), 7.91-7.86 (m, 2H), 7.78-7.73 (m, 2H), 7.57-7.56 (m, 1H), 7.16-7.15 (m, 1H), 4.21 (s, 3H). MS (ESI): m/z 388.0 [M+1]⁺.

Example 6: 1-Methyl-*N*-(2-(2-(trifluoromethyl)phenyl)-2*H*-indazol-6-yl)-1*H*-1,2,4-triazole-5-carboxamide (**6**)



To a solution of 6-bromo-2-(2-(trifluoromethyl)phenyl)-2*H*-indazole (**Int 8**) (150 mg, 0.44 mmol), 1-methyl-1*H*-1,2,4-triazole-5-carboxamide (**Int 10**) (67 mg, 0.53 mmol) and K₂CO₃ (183 mg, 1.32 mmol) in *t*-BuOH (5 mL) and water (0.5 mL) was added Pd₂(dba)₃ (202 mg, 0.22 mmol) and tBuXPhos (141 mg, 0.33 mmol) under Ar. The mixture was stirred at 90 °C overnight. EtOAc (10 mL) and water (10 mL) were added. The aqueous layer was extracted with EtOAc (3 x 10 mL) and the combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by preparative HPLC to give the title compound as a white solid. ¹H NMR (400 MHz, MeOD): δ ppm 8.14 (d, J = 0.9 Hz, 1H), 7.94–7.85 (m, 3H), 7.82–7.68 (m, 3H), 7.51 (d, J = 7.8 Hz, 1H), 7.34 (dd, J = 8.7, 1.7 Hz, 1H), 4.12 (s, 3H). MS (ESI): m/z 387.1 [M+1]⁺.

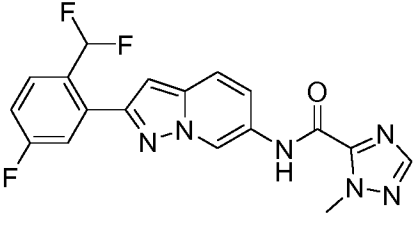
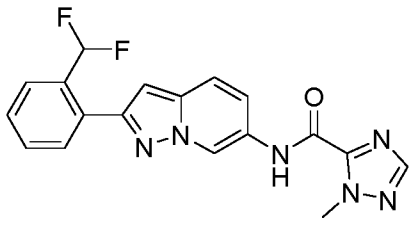
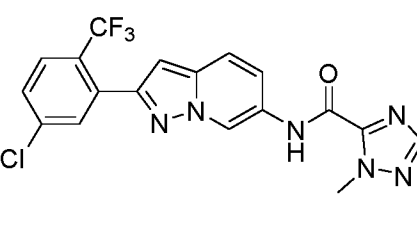
Example 7: 1-Methyl-*N*-(2-(2-(trifluoromethyl)phenyl)pyrazolo[1,5-*a*]pyridin-6-yl)-1*H*-1,2,4-triazole-5-carboxamide (**7**)

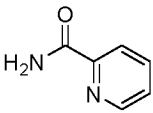
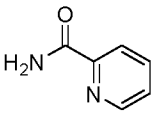
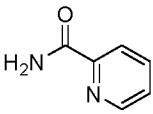
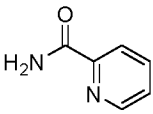


To a solution of 6-bromo-2-(2-(trifluoromethyl)phenyl)pyrazolo[1,5-a]pyridine (**Int 23**) (300 mg, 0.88 mmol), 1-methyl-1*H*-1,2,4-triazole-5-carboxamide (**Int 10**) (134 mg, 1.06 mmol) and K₂CO₃ (365 mg, 2.65 mmol) in *t*-BuOH (6 mL) and water (0.6 mL), was added Pd₂(dba)₃ (404 mg, 0.44 mmol) and tBuXPhos (282 mg, 0.66 mmol) under Ar. The mixture was heated at 90 °C overnight. EtOAc (20 mL) and water (20 mL) were added. The aqueous layers was extracted with EtOAc (3 x 20 mL) and the combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by preparative HPLC to give the title compound as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆): δ ppm 11.08 (s, 1H), 9.38 (s, 1H), 8.21 (s, 1H), 7.89 (d, *J* = 7.8 Hz, 1H), 7.82–7.72 (m, 3H), 7.73–7.60 (m, 2H), 6.79 (s, 1H), 4.21 (s, 3H). MS (ESI): *m/z* 387.2 [M+1]⁺.

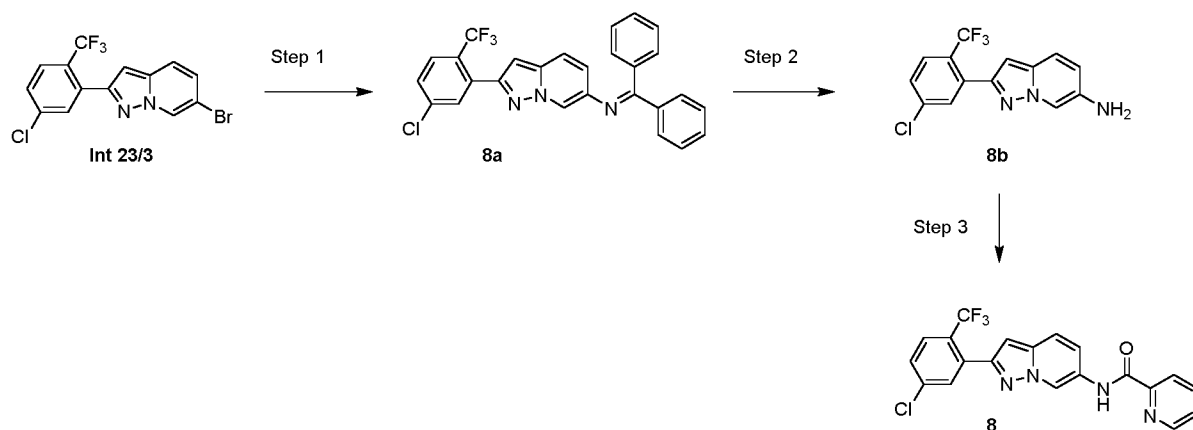
Examples 7/1 to 7/5

The following Examples were prepared similar as described for Example 7 using the appropriate intermediates.

#	Int.	Structure	Analytical data
7/1	Int 10 Int 23/1		¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ ppm 11.13 (s, 1H), 9.45 (s, 1H), 8.21 (s, 1H), 7.87 (dd, <i>J</i> = 8.7, 5.8 Hz, 1H), 7.83–7.51 (m, 4H), 7.47–7.38 (m, 1H), 7.06 (s, 1H), 4.22 (s, 3H). MS (ESI): <i>m/z</i> 387.1 [M+1] ⁺ .
7/2	Int 10 Int 23/2		¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ: 11.13 (s, 1H), 9.44 (s, 1H), 8.22 (s, 1H), 7.86 (d, <i>J</i> = 7.6 Hz, 1H), 7.83–7.46 (m, 6H), 6.97 (s, 1H), 4.22 (s, 3H). MS (ESI): <i>m/z</i> 369.1 [M+1] ⁺ .
7/3	Int 10 Int 23/3		¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ ppm 11.09 (s, 1H), 9.40 (s, 1H), 8.21 (s, 1H), 7.93 (d, <i>J</i> = 8.6 Hz, 1H), 7.86 (d, <i>J</i> = 1.6 Hz, 1H), 7.86–7.68 (m, 3H), 6.87 (s, 1H), 4.22 (s, 3H). MS (ESI): <i>m/z</i> 421.0 [M+1] ⁺ .

7/4	Int 23/2 		¹ H NMR (400 MHz, DMSO-d ₆): δ ppm 11.01 (s, 1H), 9.57 (s, 1H), 8.79 (d, J = 4.7 Hz, 1H), 8.22-8.19 (m, 1H), 8.15-8.08 (m, 1H), 7.92-7.43 (m, 8H), 6.95 (s, 1H). MS (ESI): m/z 365.1 [M+1] ⁺ .
7/5	Int 23/1 		¹ H NMR (400 MHz, DMSO-d ₆): δ: 11.03 (s, 1H), 9.57 (s, 1H), 8.79 (d, J = 4.5 Hz, 1H), 8.22-8.19 (m, 1H), 8.14-8.10 (m, 1H), 7.92-7.48 (m, 6H), 7.46-7.41 (m, 1H), 7.04 (s, 1H). MS (ESI): m/z 383.0 [M+1] ⁺ .

Example 8: *N*-(2-(5-Chloro-2-(trifluoromethyl)phenyl)pyrazolo[1,5-a]pyridin-6-yl)picolinamide (**8**)



Step 1: *N*-(2-(5-Chloro-2-(trifluoromethyl)phenyl)pyrazolo[1,5-a]pyridin-6-yl)-1,1-diphenylmethanimine (**8a**)

To a solution of 6-bromo-2-(5-chloro-2-(trifluoromethyl)phenyl)pyrazolo[1,5-a]pyridine (**Int 23/3**) (2.00 g, 5.35 mmol), diphenylmethanimine (1.16 g, 6.42 mmol) and Cs₂CO₃ (2.61 g, 8.03 mmol) in toluene (20 mL) were added Pd₂(dba)₃ (200 mg) and Xantphos (200 mg) under Ar. The mixture was heated at 90 °C overnight. EtOAc (30 mL) and water (30 mL) were added. The aqueous layer was extracted with EtOAc (3 x 30 mL) and the combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated to dryness. The residue was purified by column chromatography on silica gel (PE/EtOAc = 10:1) to give the title compound as a yellow solid.

Step 2: 2-(5-Chloro-2-(trifluoromethyl)phenyl)pyrazolo[1,5-a]pyridin-6-amine (**8b**)

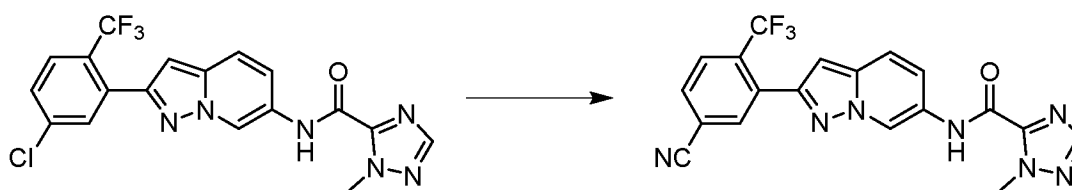
To a solution of *N*-(2-(5-chloro-2-(trifluoromethyl)phenyl)pyrazolo[1,5-a]pyridin-6-yl)-1,1-diphenylmethanimine (**8a**) (1.14 g, 2.40 mmol) in THF (15 mL) was added HCl (2M, 5

mL) and the mixture was stirred at rt for 2 h. Water (30 mL) was added and the mixture was extracted with EtOAc (3 x 30 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated to dryness. The residue was purified by column chromatography on silica gel (PE/EtOAc = 8:1) to give the title compound as a yellow solid.

Step 3: *N*-(2-(5-Chloro-2-(trifluoromethyl)phenyl)pyrazolo[1,5-*a*]pyridin-6-yl)picolinamide (**8**)

To a solution of picolinic acid (317 mg, 2.58 mmol) in DCM (5 mL) was added SOCl₂ (2 mL) and the mixture was stirred at 40 °C for 1 h. The mixture was concentrated to dryness and the residue was dissolved in DCM (8 mL). 2-(5-Chloro-2-(trifluoromethyl)phenyl)pyrazolo[1,5-*a*]pyridin-6-amine (**8b**) (670 mg, 2.15 mmol) and TEA (326 mg, 3.23 mmol) were added and the mixture was stirred at rt overnight. Water (30 mL) was added and the mixture was extracted with DCM (3 x 30 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated to dryness to give a brown solid. MeOH (5 mL) was added and the mixture was stirred at rt for 30 min. The mixture was filtered. The filter residue was washed with MeOH (3 mL) and dried to give the title compound as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆): δ ppm 11.02 (s, 1H), 9.54 (s, 1H), 8.79 (d, *J* = 4.6 Hz, 1H), 8.21 (d, *J* = 7.7 Hz, 1H), 8.11 (dd, *J*₁ = *J*₂ = 7.3 Hz, 1H), 7.93 (d, *J* = 8.6 Hz, 1H), 7.86 (s, 1H), 7.83-7.67 (m, 4H), 6.85 (s, 1H). MS (ESI): *m/z* 417.0 [*M*+1]⁺.

Example 9: *N*-(2-(5-Cyano-2-(trifluoromethyl)phenyl)pyrazolo[1,5-*a*]pyridin-6-yl)-1-methyl-1*H*-1,2,4-triazole-5-carboxamide (**9**)



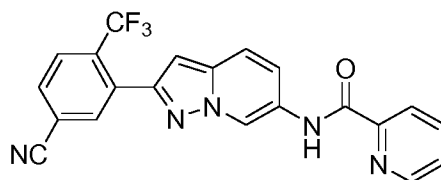
Example 7/3

9

To a solution of *N*-(2-(5-chloro-2-(trifluoromethyl)phenyl)pyrazolo[1,5-*a*]pyridin-6-yl)-1-methyl-1*H*-1,2,4-triazole-5-carboxamide (Example 7/3) (60 mg, 0.14 mmol), Zn(CN)₂ (24 mg, 0.20 mmol) and Zn (10 mg, 0.15 mmol) in DMA (3 mL) was added bis(tri-*tert*-butylphosphino)palladium (6 mg, 0.01 mmol). The mixture was heated at 95 °C for 2 d. The mixture was filtered. EtOAc (20 mL) and water (20 mL) were added to the filtrate.

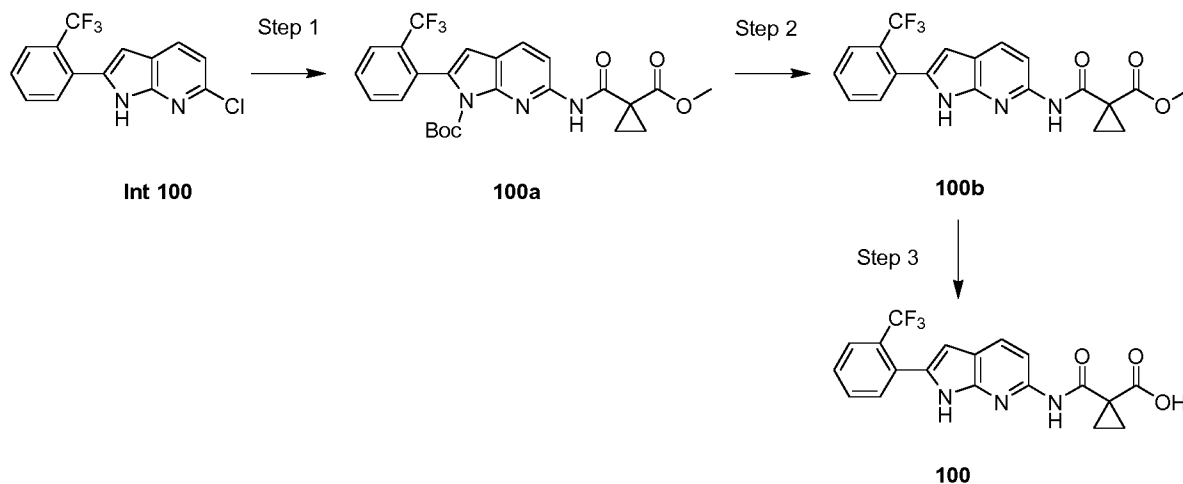
The aqueous layer was extracted with EtOAc (3 x 20 mL) and the combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated to dryness. The residue was purified by preparative HPLC to give the title compound as a white solid. ¹H NMR (400 MHz, DMSO-d₆): δ ppm 11.13 (s, 1H), 9.41 (s, 1H), 8.27 (s, 1H), 8.21 (s, 1H), 8.19-8.10 (m, 2H), 7.82 (d, J = 9.6 Hz, 1H), 7.71 (dd, J = 9.6, 1.5 Hz, 1H), 6.90 (s, 1H), 4.22 (s, 3H). MS (ESI): m/z 412.1 [M+1]⁺.

Example 9/1: *N*-(2-(5-Cyano-2-(trifluoromethyl)phenyl)pyrazolo[1,5-a]pyridin-6-yl)picolinamide (**9/1**)



The title compound was prepared similar as described for Example 9 using Example 8 instead of example 7/3. ¹H NMR (400 MHz, DMSO-d₆): δ ppm 11.02 (s, 1H), 9.55 (s, 1H), 8.79 (d, J = 4.2 Hz, 1H), 8.30–8.08 (m, 5H), 7.89-7.66 (m, 3H), 6.89 (s, 1H). MS (ESI): m/z 408.1 [M+1]⁺.

Example 100: 1-((2-(2-(Trifluoromethyl)phenyl)-1*H*-pyrrolo[2,3-*b*]pyridin-6-yl)carbamoyl)cyclopropane-1-carboxylic acid (**100**)



Step 1: *tert*-Butyl 6-(1-(methoxycarbonyl)cyclopropane-1-carboxamido)-2-(2-(trifluoromethyl)phenyl)-1*H*-pyrrolo[2,3-*b*]pyridine-1-carboxylate (**100a**)

Pd₂(dba)₃ (463 mg, 0.50 mmol) was added to a mixture of 6-chloro-2-(2-(trifluoromethyl)phenyl)-1*H*-pyrrolo[2,3-*b*]pyridine (**Int 100**) (400 mg, 1.01 mmol), K₂CO₃ (419 mg, 3.03 mmol), methyl 1-carbamoylcyclopropane-1-carboxylate (**Int 11**) (159 mg,

1.11 mmol) and tBuXPhos (322 mg, 0.785 mmol) in *t*-BuOH (10 mL) containing water (0.5 mL). The mixture was heated at 90 °C for 5 h. The mixture was cooled to rt, filtered and the filter residue was rinsed with DCM (30 mL). The filtrate was concentrated to dryness and the residue was purified by silica gel chromatography (gradient 5-25% EtOAc in PE) to give the title compound as a yellow solid.

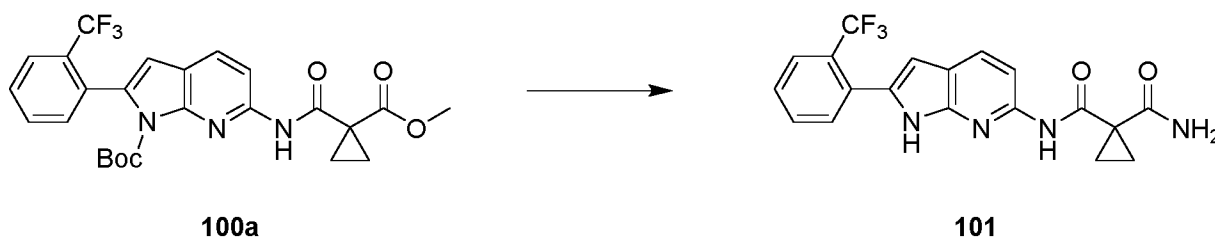
Step 2: Methyl 1-((2-(2-(trifluoromethyl)phenyl)-1*H*-pyrrolo[2,3-*b*]pyridin-6-yl)carbamoyl)cyclopropane-1-carboxylate (**100b**)

To a mixture of *tert*-butyl 6-(1-(methoxycarbonyl)cyclopropane-1-carboxamido)-2-(2-(trifluoromethyl)phenyl)-1*H*-pyrrolo[2,3-*b*]pyridine-1-carboxylate (**100a**) (150 mg, 0.30 mmol) in DCM (5 mL) was added TFA (5 mL) and the mixture was stirred at rt overnight. The mixture was concentrated to dryness and the residue was purified by preparative HPLC to give the title compound as a white solid.

Step 3: 1-((2-(2-(Trifluoromethyl)phenyl)-1*H*-pyrrolo[2,3-*b*]pyridin-6-yl)carbamoyl)cyclopropane-1-carboxylic acid (**100**)

A mixture of methyl 1-((2-(2-(trifluoromethyl)phenyl)-1*H*-pyrrolo[2,3-*b*]pyridin-6-yl)carbamoyl)cyclopropane-1-carboxylate (**100b**) (109 mg, 0.27 mmol) in 10 w/w% aqueous NaOH/THF 1:1 (4 mL) was stirred at rt for 1 h. The mixture was concentrated and water was added to the residue. The aqueous layer was acidified to pH 4 using aqueous citric acid. A solid precipitated, which was filtered and dried under vacuum to give the title compound. ¹H NMR (500 MHz, DMSO-*d*₆): δ ppm 13.46 (br s, 1H), 11.88 (s, 1H), 11.43 (s, 1H), 8.00-7.77 (m, 4H), 7.70-7.66 (m, 2H), 6.52 (s, 1H), 1.55 (s, 4H). MS (ESI): *m/z* 390.1 [*M*+1]⁺.

Example 101: *N*-(2-(2-(trifluoromethyl)phenyl)-1*H*-pyrrolo[2,3-*b*]pyridin-6-yl)cyclopropane-1,1-dicarboxamide (**101**)

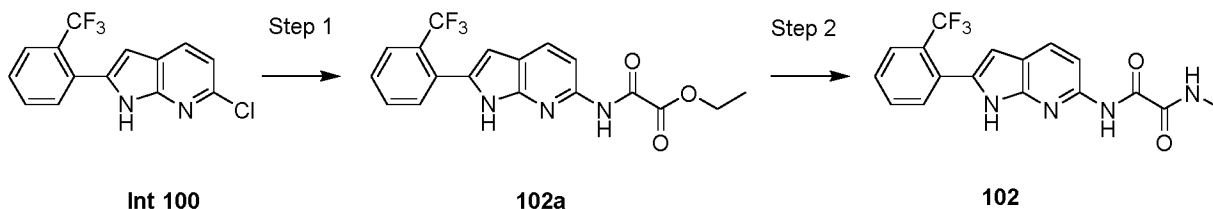


A mixture of *tert*-butyl 6-(1-(methoxycarbonyl)cyclopropane-1-carboxamido)-2-(2-(trifluoromethyl)phenyl)-1*H*-pyrrolo[2,3-*b*]pyridine-1-carboxylate (**100a**) (160 mg, 0.32 mmol) in NH₃/MeOH (7M) (15 mL) was stirred at 50 °C overnight. The mixture was

concentrated to dryness and the residue was purified by preparative HPLC to give the title compound as a white solid. ^1H NMR (500 MHz, DMSO- d_6): δ ppm 12.19 (s, 1H), 11.88 (s, 1H), 7.98-7.88 (m, 3H), 7.80-7.77 (m, 1H), 7.70-7.64 (m, 2H), 7.48 (s, 1H), 7.32 (s, 1H), 6.51 (s, 1H), 1.57-1.49 (m, 4H). MS (ESI): m/z 389.1 $[\text{M}+1]^+$.

5

Example 102: N^1 -Methyl- N^2 -(2-(2-(trifluoromethyl)phenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)oxalamide (**102**)



Step 1: Ethyl 2-oxo-2-((2-(2-(trifluoromethyl)phenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)amino)acetate (**102a**)

$\text{Pd}_2(\text{dba})_3$ (463 mg, 0.50 mmol) was added to a mixture of 6-chloro-2-(2-(trifluoromethyl)phenyl)-1H-pyrrolo[2,3-b]pyridine (**Int 100**) (400 mg, 1.01 mmol), K_2CO_3 (419 mg, 3.03 mmol), ethyl 2-amino-2-oxoacetate (130 mg, 1.11 mmol) and tBuXPhos (322 mg, 0.78 mmol) in 10 mL *t*-BuOH/water (20:1). The mixture was heated at 90 °C for 5 h. The mixture was filtered and the filter residue was rinsed with DCM (30 mL). The filtrate was concentrated to dryness and the residue was purified by silica gel chromatography (gradient 5-25% EtOAc in PE) to give the title compound as a yellow solid.

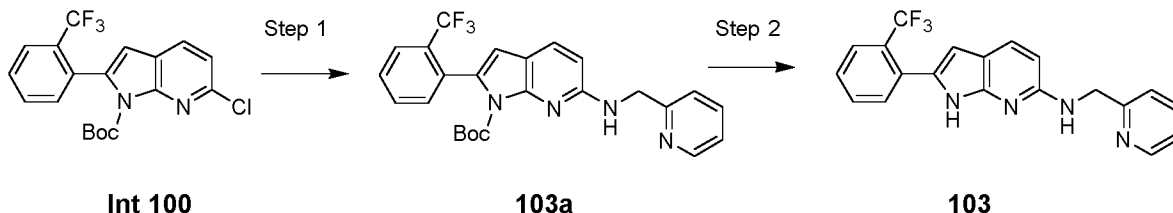
20

Step 2: N^1 -Methyl- N^2 -(2-(2-(trifluoromethyl)phenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)oxalamide (**102**)

The title compound was prepared similar as described for Example **101** using ethyl 2-oxo-2-((2-(2-(trifluoromethyl)phenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)amino)acetate (**102a**) in place of *tert*-butyl 6-(1-(methoxycarbonyl)cyclopropane-1-carboxamido)-2-(2-(trifluoromethyl)phenyl)-1H-pyrrolo[2,3-b]pyridine-1-carboxylate and $\text{MeNH}_2/\text{MeOH}$ (2M) in place of NH_3/MeOH (7M). ^1H NMR (500 MHz, DMSO- d_6): δ ppm 12.01 (s, 1H), 9.90 (s, 1H), 9.11-9.08 (m, 1H), 8.08 (d, $J = 8.0$ Hz, 1H), 7.91-7.78 (m, 3H), 7.70-7.66 (m, 2H), 6.56 (s, 1H), 2.77 (s, 3H). MS (ESI): m/z 363.1 $[\text{M}+1]^+$.

30

Example 103: *N*-(Pyridin-2-ylmethyl)-2-(2-(trifluoromethyl)phenyl)-1*H*-pyrrolo[2,3-*b*]pyridin-6-amine (**103**)



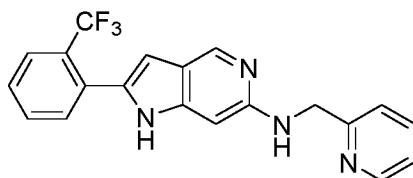
Step 1: *tert*-Butyl 6-((pyridin-2-ylmethyl)amino)-2-(2-(trifluoromethyl)phenyl)-1*H*-pyrrolo[2,3-*b*]pyridine-1-carboxylate (**103a**)

$\text{Pd}_2(\text{dba})_3$ (348 mg, 0.38 mmol) was added to a mixture of *tert*-butyl 6-chloro-2-(2-(trifluoromethyl)phenyl)-1*H*-pyrrolo[2,3-*b*]pyridine-1-carboxylate (**Int 100**) (300 mg, 0.76 mmol), potassium carbonate (349 mg, 2.28 mmol), pyridin-2-ylmethanamine (164 mg, 1.52 mmol) and *t*BuXPhos (273 mg, 0.57 mmol) in 6 mL *t*-BuOH/water (30:1). The mixture was heated at 90 °C for 5 h under microwave irradiation. The mixture was filtered using DCM (20 mL) to rinse the filter residue. The filtrate was concentrated to dryness and the residue was purified by silica gel chromatography (gradient 5-100% EtOAc in PE) to give the title compound as a yellow solid.

Step 2: *N*-(Pyridin-2-ylmethyl)-2-(2-(trifluoromethyl)phenyl)-1*H*-pyrrolo[2,3-*b*]pyridin-6-amine (**103**)

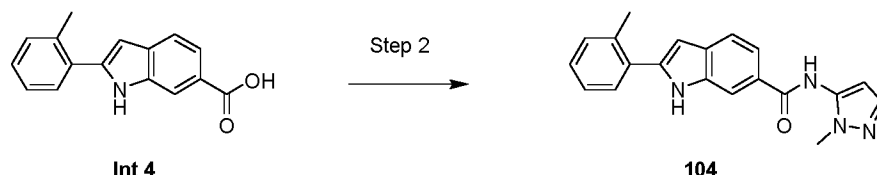
To a mixture of *tert*-butyl 6-((pyridin-2-ylmethyl)amino)-2-(2-(trifluoromethyl)phenyl)-1*H*-pyrrolo[2,3-*b*]pyridine-1-carboxylate (**103a**) (159 mg, 0.34 mmol) in DCM (5 mL) was added TFA (2.5 mL) and the mixture was stirred at rt overnight. The mixture was concentrated to dryness and the residue was purified by reverse phase chromatography (c18, gradient 25 - 55 % acetonitrile in 10 mmol/L aqueous ammonium bicarbonate) to give the title compound as a white solid. ^1H NMR (500 MHz, $\text{DMSO}-d_6$): δ ppm 11.37 (s, 1H), 8.51 (d, $J = 4.5$ Hz, 1H), 7.81-7.79 (m, 1H), 7.73-7.60 (m, 4H), 7.53-7.50 (m, 1H), 7.35 (d, $J = 7.7$ Hz, 1H), 7.24-7.23 (m, 1H), 7.11-7.10 (m, 1H), 6.47-6.45 (m, 1H), 6.34 (s, 1H), 4.64 (d, $J = 6.1$ Hz, 2H). MS (ESI): m/z 369.2 $[\text{M}+1]^+$.

Example 103/1: *N*-(Pyridin-2-ylmethyl)-2-(2-(trifluoromethyl)phenyl)-1*H*-pyrrolo[3,2-*c*]pyridin-6-amine (**103/1**)



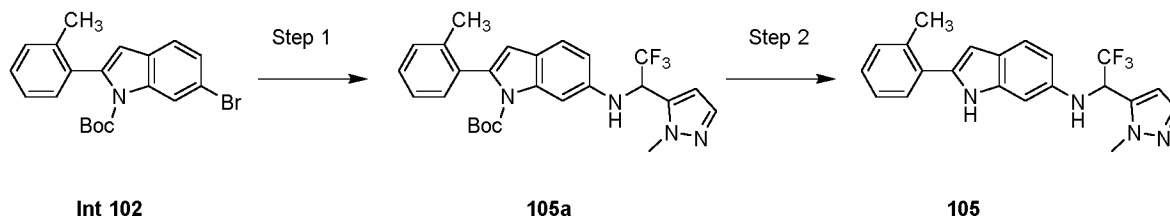
The title compound was prepared similar as described for Example **103** using in Step 1 *tert*-butyl 6-chloro-2-(2-(trifluoromethyl)phenyl)-1*H*-pyrrolo[3,2-*c*]pyridine-1-carboxylate (**Int 101**) in place of *tert*-butyl 6-chloro-2-(2-(trifluoromethyl)phenyl)-1*H*-pyrrolo[2,3-*b*]pyridine-1-carboxylate (**Int 100**). ¹H NMR (500 MHz, DMSO-*d*₆): δ ppm 11.10 (s, 1H), 8.52 (d, *J* = 4.5 Hz, 1H), 8.34 (s, 1H), 7.86-7.84 (m, 1H), 7.75-7.61 (m, 4H), 7.36 (d, *J* = 7.7 Hz, 1H), 7.28 – 7.12 (m, 1H), 6.66-6.64 (m, 1H), 6.44 (s, 1H), 6.32 (s, 1H), 4.54 (d, *J* = 6.1 Hz, 2H). MS (ESI): *m/z* 369.2 [*M*+1]⁺.

Example 104: *N*-(1-Methyl-1*H*-pyrazol-5-yl)-2-(*o*-tolyl)-1*H*-indole-6-carboxamide (**104**)



A mixture of 2-(*o*-Tolyl)-1*H*-indole-6-carboxylic acid (**Int 4**) (200 mg, 0.79 mmol), 1-methyl-1*H*-pyrazol-5-amine (92 mg, 0.95 mmol), HATU (448 mg, 1.18 mmol) and Et₃N (239 mg, 2.37 mmol) in DMF (5 mL) was stirred at 40 °C overnight. The mixture was concentrated to dryness and the residue was purified by preparative HPLC to give the title compound as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆): δ ppm 11.70 (s, 1H), 10.24 (s, 1H), 8.09 (s, 1H), 7.67-7.66 (m, 2H), 7.59-7.57 (m, 1H), 7.40-7.33 (m, 4H), 6.69 (s, 1H), 6.24 (s, 1H), 3.72 (s, 3H), 2.48 (s, 3H). MS (ESI): *m/z* 331 [*M*+H]⁺.

Example 105: 2-(*o*-Tolyl)-*N*-(2,2,2-trifluoro-1-(1-methyl-1*H*-pyrazol-5-yl)ethyl)-1*H*-indol-6-amine (**105**)



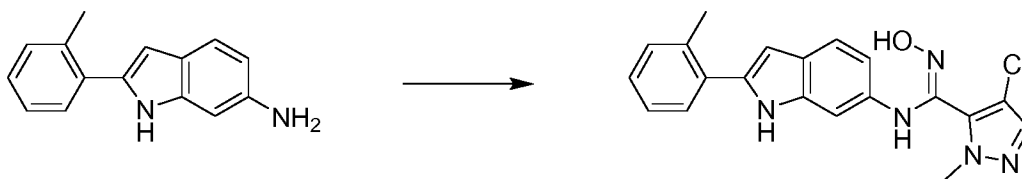
Step 1: *tert*-Butyl 2-(*o*-tolyl)-6-((2,2,2-trifluoro-1-(1-methyl-1*H*-pyrazol-5-yl)ethyl)amino)-1*H*-indole-1-carboxylate (**105a**)

A mixture of *tert*-butyl 6-bromo-2-(*o*-tolyl)-1*H*-indole-1-carboxylate (**Int 102**) (500 mg, 1.30 mmol), 2,2,2-trifluoro-1-(1-methyl-1*H*-pyrazol-5-yl)ethan-1-amine (**Int 12**) (419 mg, 1.95 mmol), chloro[2-(dicyclohexylphosphino)-3,6-dimethoxy-2',4',6'-triisopropyl-1,1'-biphenyl][2-(2-aminoethyl)phenyl]palladium(II) (BrettPhos Palladacycle) (310 mg, 0.39 mmol) and Cs₂CO₃ (1.30 g, 3.90 mmol) in 1,4-dioxane (30 mL) was stirred at 110 °C under N₂ atmosphere for 5 h. The mixture was concentrated to dryness and the residue was purified by flash silica chromatography (PE/EtOAc = 7:3) to give the title compound as a brown solid.

Step 2: 2-(*o*-Tolyl)-*N*-(2,2,2-trifluoro-1-(1-methyl-1*H*-pyrazol-5-yl)ethyl)-1*H*-indol-6-amine (**105**)

To a mixture of *tert*-butyl 2-(*o*-tolyl)-6-((2,2,2-trifluoro-1-(1-methyl-1*H*-pyrazol-5-yl)ethyl)amino)-1*H*-indole-1-carboxylate (**105a**) (120 mg, 0.25 mmol) in DCM (10 mL), TFA (2 mL) was added dropwise. The mixture was stirred at rt overnight. Aqueous NaHCO₃ (10 mL) was added. The mixture was extracted with EtOAc. The combined organic layers were concentrated to dryness and the residue was purified by preparative HPLC to give the title compound as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆): δ ppm 10.88 (s, 1H), 7.49 (d, *J* = 7.6 Hz, 1H), 7.40 (d, *J* = 1.6 Hz, 1H), 7.31-7.19 (m, 4H), 6.82 (s, 1H), 6.75 (dd, *J*₁ = 8.0, *J*₂ = 2.0 Hz, 1H), 6.47 (s, 1H), 6.40 (d, *J* = 1.6 Hz, 1H), 6.19 (d, *J* = 10.0 Hz, 1H), 5.81-5.71 (m, 1H), 3.85 (s, 3H), 2.45 (s, 3H). MS (ESI): *m/z* 385.1 [M+H]⁺.

Example 106: 4-Chloro-*N'*-hydroxy-1-methyl-*N*-(2-(*o*-tolyl)-1*H*-indol-6-yl)-1*H*-pyrazole-5-carboximidamide (**106**)



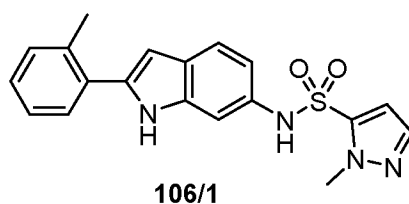
Int 103

106

To a mixture of 4-chloro-*N*-hydroxy-1-methyl-1*H*-pyrazole-5-carboximidoyl chloride (**Int 13**) (100 mg, 0.34 mmol) and 2-(*o*-tolyl)-1*H*-indol-6-amine (**Int 103**) (92 mg, 0.41 mmol) in DMF (2 mL) was added DIPEA (220 mg, 1.70 mmol). The mixture was stirred at rt for 3 h. EtOAc (10 mL) was added to the mixture. The organic layer was washed with water (3 x 10 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated to dryness. The residue was purified by preparative HPLC to give the title

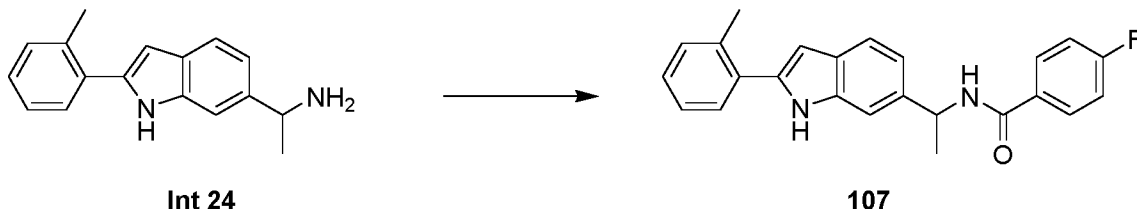
compound as a white solid. ^1H NMR (400 MHz, DMSO- d_6): δ ppm 11.09 (s, 1H), 10.68 (s, 1H), 8.61 (s, 1H), 7.51-7.47 (m, 2H), 7.31-7.23 (m, 4H), 6.74 (s, 1H), 6.45-6.51 (m, 2H), 3.67 (s, 3H), 2.45 (s, 3H). MS (ESI): m/z 380.0 $[\text{M}+1]^+$.

5 **Example 106/1:** 1-Methyl-*N*-(2-(*o*-tolyl)-1*H*-indol-6-yl)-1*H*-pyrazole-5-sulfonamide (106/1)



The title compound was prepared similar as described for Example **106** using 1-methyl-1*H*-pyrazole-5-sulfonyl chloride in place of 4-chloro-*N*-hydroxy-1-methyl-1*H*-pyrazole-5-carbimidoyl chloride (**Int 13**). ^1H NMR (400 MHz, DMSO- d_6): δ ppm 11.28 (s, 1H), 10.53 (s, 1H), 7.53-7.42 (m, 3H), 7.35-7.26 (m, 3H), 7.21 (s, 1H), 6.79 (d, $J = 8.8$ Hz, 1H), 6.67 (d, $J = 2.0$ Hz, 1H), 6.53 (s, 1H), 3.94 (s, 3H), 2.45 (s, 3H). MS (ESI): m/z 367.1 $[\text{M}+1]^+$.

Example 107: 4-Fluoro-*N*-(1-(2-(*o*-tolyl)-1*H*-indol-6-yl)ethyl)benzamide (**107**)



15

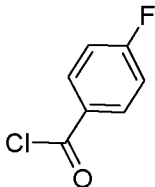
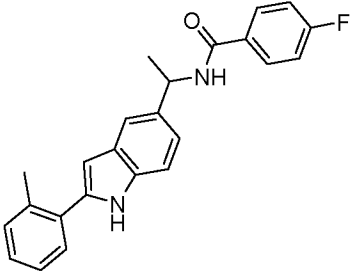
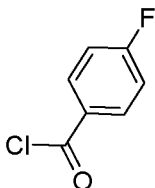
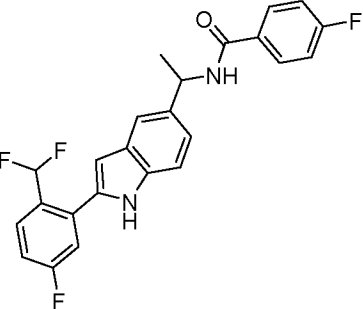
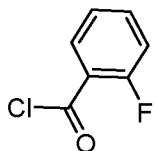
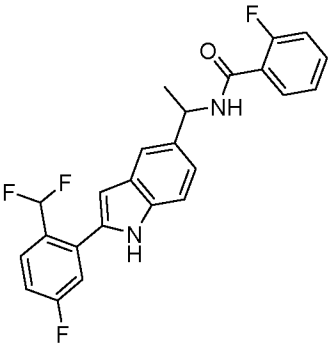
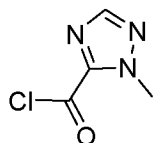
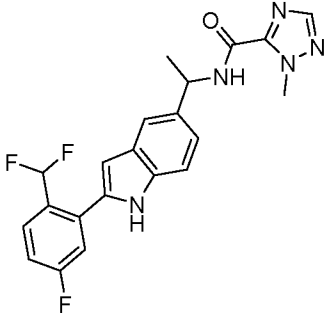
To the mixture of 1-(2-(*o*-tolyl)-1*H*-indol-6-yl)ethan-1-amine (**Int 24**) (122 mg, 0.50 mmol) in DCM (5 mL) was added 4-fluorobenzoyl chloride (79 mg, 0.50 mmol) and Et_3N (152 mg, 1.50 mmol) and the mixture was stirred at rt for 1 h. Water (30 mL) was added and the mixture was extracted with DCM (3 x 30 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4 and filtered. The mixture was concentrated to dryness and the residue was purified by preparative HPLC to give the title compound as a white solid. ^1H NMR (500 MHz, DMSO- d_6): δ ppm 11.19 (s, 1H), 8.85 (d, $J = 8.0$ Hz, 1H), 8.02-7.93 (m, 2H), 7.52-7.48 (m, 2H), 7.39 (s, 1H), 7.36-7.23 (m, 5H), 7.08 (dd, $J = 8.2, 1.2$ Hz, 1H), 6.52 (d, $J = 1.4$ Hz, 1H), 5.29-5.23 (m, 1H), 2.45 (s, 3H), 1.55 (d, $J = 7.0$ Hz, 3H). MS (ESI): m/z 373.3 $[\text{M}+1]^+$.

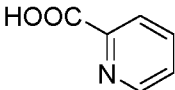
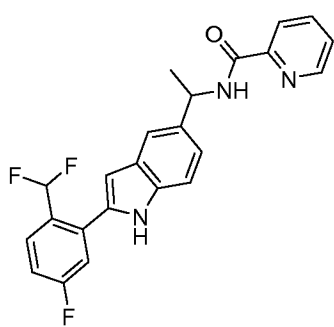
20

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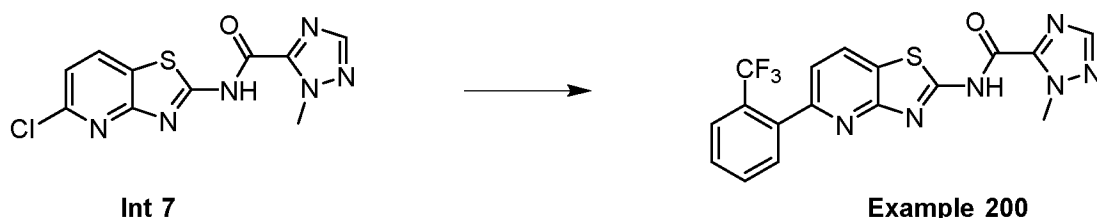
Examples 107/1 to 107/5

The following Examples were prepared similar as described for Example **107** using the appropriate building blocks.

#	Int.	Structure	Analytical data
107/1	Int 24/1 		¹ H NMR (500 MHz, DMSO-d ₆): δ ppm 11.21 (s, 1H), 8.80 (d, J = 8.1 Hz, 1H), 8.02-7.91 (m, 2H), 7.56 (s, 1H), 7.53-7.50 (m, 1H), 7.36-7.25 (m, 6H), 7.17 (dd, J = 8.4, 1.5 Hz, 1H), 6.54 (d, J = 1.5 Hz, 1H), 5.29-5.23 (m, 1H), 2.45 (s, 3H), 1.54 (d, J = 7.0 Hz, 3H). MS (ESI): m/z 373.3 [M+1] ⁺ .
107/2	Int 24/2 		¹ H NMR (500 MHz, DMSO-d ₆): δ ppm 11.53 (s, 1H), 8.80 (d, J = 8.1 Hz, 1H), 8.01-7.94 (m, 2H), 7.85 (dd, J = 8.7, 5.8 Hz, 1H), 7.62 (s, 1H), 7.55-7.48 (m, 1H), 7.45-7.36 (m, 2H), 7.32-6.99 (m, 4H), 6.62 (d, J = 1.5 Hz, 1H), 5.29-5.23 (m, 1H), 1.54 (d, J = 7.0 Hz, 3H). MS (ESI): m/z 427.2 [M+1] ⁺ .
107/3	Int 24/2 		¹ H NMR (400 MHz, DMSO-d ₆): δ ppm 11.55 (s, 1H), 8.75 (d, J = 7.9 Hz, 1H), 7.86 (dd, J = 8.7, 5.9 Hz, 1H), 7.63 (s, 1H), 7.60-7.46 (m, 3H), 7.46-7.37 (m, 2H), 7.30-6.96 (m, 4H), 6.63 (d, J = 1.3 Hz, 1H), 5.25-5.19 (m, 1H), 1.50 (d, J = 7.0 Hz, 3H). MS (ESI): m/z 427.1 [M+1] ⁺ .
107/4	Int 24/2 		¹ H NMR (400 MHz, DMSO-d ₆): δ ppm 11.55 (s, 1H), 9.16 (d, J = 8.4 Hz, 1H), 8.07 (s, 1H), 7.86 (dd, J = 8.7, 5.8 Hz, 1H), 7.64 (s, 1H), 7.52 (d, J = 10.0 Hz, 1H), 7.45-7.35 (m, 2H), 7.31-6.95 (m, 2H), 6.62 (d, J = 1.5 Hz, 1H), 5.25-5.19 (m, 1H), 4.11 (s, 3H), 1.56 (d, J = 7.0 Hz, 3H). MS (ESI): m/z 414.2 [M+1] ⁺ .

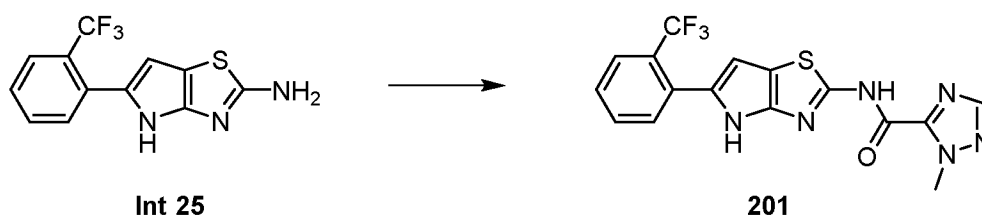
107/5	Int 24/2  HOOC HATU, DIPEA		¹H NMR (400 MHz, DMSO-d₆): δ ppm 11.55 (s, 1H), 8.92 (d, J = 8.5 Hz, 1H), 8.66 (d, J = 4.6 Hz, 1H), 8.07-7.92 (m, 2H), 7.86 (dd, J = 8.7, 5.9 Hz, 1H), 7.66 (s, 1H), 7.62-7.58 (m, 1H), 7.52 (d, J = 9.9 Hz, 1H), 7.44-7.34 (m, 2H), 7.33 – 6.94 (m, 2H), 6.62 (s, 1H), 5.29-5.23 (m, 1H), 1.59 (d, J = 7.0 Hz, 3H). MS (ESI): m/z 408.1 [M-1]⁻.
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Example 200: 1-Methyl-*N*-(5-(2-(trifluoromethyl)phenyl)thiazolo[4,5-*b*]pyridin-2-yl)-1*H*-1,2,4-triazole-5-carboxamide (**200**)



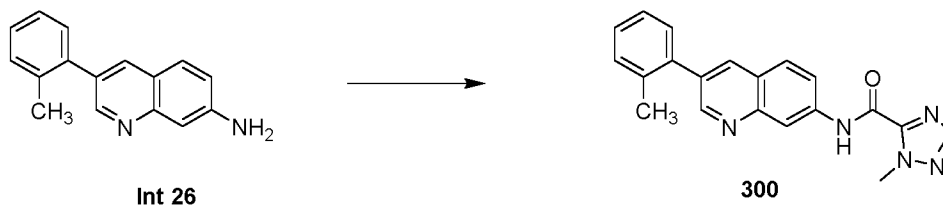
- 5 A mixture of *N*-(5-chlorothiazolo[4,5-*b*]pyridin-2-yl)-1-methyl-1*H*-1,2,4-triazole-5-carboxamide (**Int 7**) (160 mg, 0.544 mmol), (2-(trifluoromethyl)phenyl)boronic acid (310 mg, 1.63 mmol), Pd(dtbpf)Cl₂ (35 mg, 0.054 mmol) and Cs₂CO₃ (532 mg, 1.63 mmol) in 1,4-dioxane/H₂O (16 mL, 3:1) was stirred at 100 °C under N₂ overnight. After cooling to
- 10 rt the mixture was concentrated and diluted with H₂O (20 mL). The mixture was extracted with EtOAc (2 x 20 mL). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and filtered. The filtrate was concentrated to dryness and the residue was purified by preparative HPLC to afford the title compound as a white solid. ¹H NMR (400 MHz, DMSO-d₆): δ ppm 13.33 (br s, 1H), 8.61 (d, J = 8.0 Hz, 1H), 8.24 (s, 1H), 7.89 (d, J = 7.6 Hz, 1H), 7.80 (dd, J₁ = J₂ = 7.6 Hz, 1H), 7.71 (dd, J₁ = J₂ = 7.6 Hz, 1H), 7.62
- 15 (d, J = 7.6 Hz, 1H), 7.47 (d, J = 8.0 Hz, 1H), 4.23 (s, 3H). MS (ESI): m/z = 405.0 [M+1]⁺.

Example 201: 1-Methyl-*N*-(5-(2-(trifluoromethyl)phenyl)-4*H*-pyrrolo[2,3-*d*]thiazol-2-yl)-1*H*-1,2,4-triazole-5-carboxamide (**201**)



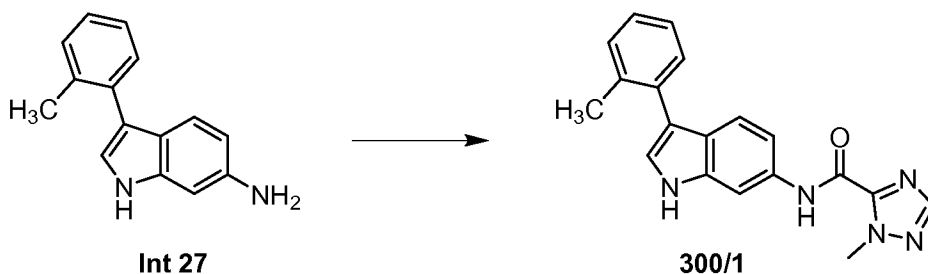
A mixture of compound 5-(2-(trifluoromethyl)phenyl)-4*H*-pyrrolo[2,3-*d*]thiazol-2-amine (**Int 25**) (100 mg, 0.35 mmol), 1-methyl-1*H*-1,2,4-triazole-5-carboxylic acid (47 mg, 0.37 mmol), HATU (199 mg, 0.53 mmol) and DIPEA (135 mg, 1.05 mmol) in DMF (15 mL) was stirred at rt overnight. Water was added and the mixture was extracted with EtOAc (2 x 30 mL). The combined organic layers were washed with brine (50 mL), dried over Na₂SO₄, filtered and concentrated to dryness. The residue was purified by preparative HPLC to give the title compound as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆): δ ppm 12.01 (br s, 1H), 10.88 (br s, 1H), 8.21 (s, 1H), 7.85 (d, *J* = 7.8 Hz, 1H), 7.75 (dd, *J*₁ = *J*₂ = 7.5 Hz, 1H), 7.62-7.54 (m, 2H), 6.49 (s, 1H), 4.20 (s, 3H). MS (ESI): *m/z* 393.3 [*M*+1]⁺.

Example 300: 1-Methyl-*N*-(3-(*o*-tolyl)quinolin-7-yl)-1*H*-1,2,4-triazole-5-carboxamide (**300**)



A mixture of 3-(*o*-tolyl)quinolin-7-amine (**Int 26**) (312 mg, 1.30 mmol), 1-methyl-1*H*-1,2,4-triazole-5-carboxylic acid (181 mg, 1.40 mmol), HATU (988 mg, 2.60 mmol) and DIPEA (33 mg, 2.60 mmol) in DMF (10 mL) was stirred at rt overnight. The mixture was filtered and the filter residue was rinsed with EtOAc. The combined organic layers were concentrated to dryness and the residue was purified by preparative HPLC to give the title compound as a white solid. ¹H NMR (500 MHz, DMSO-*d*₆): δ ppm 11.15 (s, 1H), 8.89 (s, 1H), 8.68 (s, 1H), 8.31 (s, 1H), 8.22 (s, 1H), 8.10-8.08 (m, 1H), 8.03-8.01 (s, 1H), 7.38-7.36 (m, 4H), 4.24 (s, 3H), 2.32 (s, 3H). MS (ESI): *m/z* = 344.3 [*M*+1]⁺.

Example 300/1: 1-Methyl-*N*-(3-(*o*-tolyl)-1*H*-indol-6-yl)-1*H*-1,2,4-triazole-5-carboxamide (**300/1**)



A mixture of 3-(o-tolyl)-1*H*-indol-6-amine (**Int 27**) (578 mg, 2.50 mmol), 1-methyl-1*H*-1,2,4-triazole-5-carboxylic acid (348 mg, 2.70 mmol), HATU (1.90 g, 5.00 mmol), DIPEA (882 mg, 5.00 mmol) in DMF (20 mL) was stirred at rt overnight. The mixture was filtered and the residue was rinsed with EtOAc. The combined organic layers were concentrated to dryness and the residue was purified by preparative HPLC to give the title compound as a white solid. ¹H NMR (500 MHz, DMSO-*d*₆): δ ppm 11.33 (s, 1H), 10.66 (s, 1H), 8.16 (s, 1H), 8.12 (s, 1H), 7.42-7.31 (m, 5H), 7.25-7.21 (m, 2H), 4.21 (s, 3H), 2.30 (s, 3H). MS (ESI): *m/z* = 332.3 [*M*+1]⁺.

10 Biological Assay

AhR direct luciferase reporter assay in HepG2 cells.

A stable cell line (HepG2 CYP1A1-LUC) was used in which part of the promoter region of the human CYP1A1 gene is stably integrated into the genome of human HepG2 hepatocytes (DSZM#ACC 180) in front of a *Photinus pyralis* Firefly Luciferase gene. A 1210 bp fragment comprising part of the human CYP1A1 promoter was isolated via SacI and BglII restriction digestion from Lightswitch Clone S714555 (SwitchGearGenomics) and inserted between the SacI and BglII sites in pGL4.30 (Promega # E8481) in front of the Firefly Luciferase gene. The resulting vector was linearized with NotI, transfected into HepG2 cells (DSMZ#ACC 180) and stably transfected clones selected with 250µg/ml Hygromycin B. After repetitive rounds of subcloning and testing for robustly regulated luciferase activity after AhR agonist stimulation, a stable clonal HepG2 CYP1A1-Luc cell line was selected.

The HepG2 CYP1A1-Luc cells do express basal luciferase activity that can be increased via potent AhR agonists or decreased via potent AhR antagonists, added to the growth medium of the cells.

In typical reporter assays performed with this cell line, cells are grown in 96-well plates and AhR modulators are titrated into the growth medium in serial dilutions in RPMI-1640 Medium (Sigma # R7509) supplemented with 8,6% fetal calf serum (Sigma # F7524) and containing either no exogenous AhR agonist or 10nM of the potent AhR agonist VAF347 (Calbiochem #182690). Cells are further cultivated for 18 hours and luciferase activities are determined from extracts of cells in buffers containing D-Luciferine and ATP using a LUMIstar Optima microplate Luminometer from BMG Labtech.

The AhR antagonistic potency of the example compounds is shown in Table 1 below (A = IC₅₀ < 100 nM, B = IC₅₀ 100 nM – 1 µM, C = IC₅₀ > 1 µM)

Table 1

Example #	AhR potency
1	C
1/1	C
2	A
2/1	C
2/2	C
2/3	A
3	B
3/1	C
4	A
5	C
7	A
7/1	A
7/2	B
7/3	A
7/4	B
7/5	B
8	A
9	A
9/1	A
100	C
101	B
102	B
103	B
103/1	C
104	C
105	C
200	C
201	C
300	A
300/1	A

Claims:

1. A compound represented by Formula (I), an enantiomer, diastereomer, tautomer, solvate, N-oxide, prodrug or pharmaceutical acceptable salt thereof

5 A-B-L-C (I)

wherein

A represents a 6- to 10-membered mono- or bicyclic aryl or a 5- to 10-membered mono- or bicyclic heteroaryl containing 1 to 4 heteroatoms independently selected from N, O and S,

10 wherein aryl and heteroaryl are unsubstituted or substituted with 1 to 7 substituents independently selected from the group consisting of halogen, OH, CN, C₁₋₆-alkyl, O-C₁₋₆-alkyl, oxo, C(O)OR^a, OC(O)R^a, S-C₁₋₆-alkyl, S(O)-C₁₋₆-alkyl, S(O)₂-C₁₋₆-alkyl, N(R^a)₂, C(O)N(R^a)₂, NR^aC(O)-C₁₋₆-alkyl, S(O)₂N(R^a)₂, NR^aS(O)₂-C₁₋₆-alkyl and C₃₋₆-cycloalkyl,

15 wherein alkyl and cycloalkyl are unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of halogen, C₁₋₃-alkyl, halo-C₁₋₃-alkyl, OH, CN and oxo, or

wherein two substituents on the aryl or heteroaryl group together with the atoms they are attached to may form a 5- to 7-membered saturated or partially unsaturated carbocyclic ring or heterocyclic ring containing 1 to 3 heteroatoms independently selected from O, N and S,

20 wherein the carbocyclic or heterocyclic ring is unsubstituted or substituted with 1 to 5 substituents independently selected from the group consisting of halogen, oxo, OH, C₁₋₆-alkyl and halo-C₁₋₆-alkyl;

25 R^a is independently selected from hydrogen and C₁₋₆-alkyl;

B represents a 8- to 10- membered bicyclic aryl or heteroaryl ring, wherein the heteroaryl ring contains up to 6 heteroatoms independently selected from N, O and S,

wherein the bicyclic aryl or heteroaryl ring is unsubstituted or substituted with 1 to 5 substituents independently selected from the group consisting of halogen, C₁₋₆-alkyl, halo-C₁₋₃-alkyl, C₃₋₆-cycloalkyl, OH, O-C₁₋₃-alkyl, oxo and CN,

30

wherein cycloalkyl or alkyl is unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of halogen, oxo, OH, C₁₋₃-alkyl and halo-C₁₋₃-alkyl;

L represents -NR^bC(O)C(O)NR^b-, -NR^bC(=NR^c)-, -NR^bSO₂-, -C(O)NR^b-, -NR^b-C₁₋₂-alkylene-, -S(O)_x-C₁₋₂-alkylene- or -C₀₋₂-alkylene-NR^bC(O)-,

wherein alkylene is unsubstituted or substituted with 1 to 4 substituents independently selected from the group consisting of halogen, C₁₋₃-alkyl and halo-C₁₋₃-alkyl;

R^b is independently selected from hydrogen and C₁₋₆-alkyl;

R^c is hydrogen, OH, C₁₋₆-alkyl, O-C₁₋₆-alkyl, CN or SO₂-C₁₋₆-alkyl;

C represents a C₁₋₆-alkyl, C₃₋₁₀-cycloalkyl, 3- to 10-membered heterocycloalkyl containing 1 to 4 heteroatoms independently selected from N, O and S, 6- to 10-membered mono- or bicyclic aryl or a 5- to 10-membered mono- or bicyclic heteroaryl containing 1 to 4 heteroatoms independently selected from N, O and S,

wherein cycloalkyl, heterocycloalkyl, aryl and heteroaryl are unsubstituted or substituted with 1 to 7 substituents independently selected from the group consisting of halogen, OH, CN, C₁₋₆-alkyl, O-C₁₋₆-alkyl, C(O)OR^a, OC(O)R^a, S(O)-C₁₋₆-alkyl, S(O)₂-C₁₋₆-alkyl, N(R^a)₂, C(O)N(R^a)₂, NR^aC(O)-C₁₋₆-alkyl, S(O)₂N(R^a)₂, NR^aS(O)₂-C₁₋₆-alkyl and C₃₋₆-cycloalkyl,

wherein the alkyl and cycloalkyl are unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of halogen, C₁₋₃-alkyl, halo-C₁₋₃-alkyl, OH, CN and oxo, or

wherein two substituents on the cycloalkyl, heterocycloalkyl, aryl or heteroaryl group together with the atoms they are attached to may form a 5- to 7-membered saturated or partially unsaturated carbocyclic ring or heterocyclic ring containing 1 to 3 heteroatoms independently selected from O, N and S,

wherein the carbocyclic or heterocyclic ring is unsubstituted or substituted with 1 to 5 substituents independently selected from the group consisting of halogen, C₁₋₆-alkyl and halo-C₁₋₆-alkyl;

and

x is 0, 1 or 2;

with the proviso that if L represents a $-\text{NR}^{\text{bb}}\text{C}(\text{O})-$ group, wherein R^{bb} is hydrogen or C_{1-6} -alkyl, and C is 6- to 10-membered mono- or bicyclic aryl and 5- to 10-membered mono- or bicyclic heteroaryl containing 1 to 4 heteroatoms independently selected from N, O and S,

wherein aryl and heteroaryl are unsubstituted or substituted with 1 to 7 substituents independently selected from the group consisting of halogen, OH, CN, C_{1-6} -alkyl, O- C_{1-6} -alkyl, $\text{C}(\text{O})\text{OR}^{\text{aa}}$, $\text{OC}(\text{O})\text{R}^{\text{aa}}$, $\text{S}(\text{O})-\text{C}_{1-6}$ -alkyl, $\text{S}(\text{O})_2-\text{C}_{1-6}$ -alkyl, $\text{N}(\text{R}^{\text{a}})_2$, $\text{C}(\text{O})\text{N}(\text{R}^{\text{aa}})_2$, $\text{NR}^{\text{aa}}\text{C}(\text{O})-\text{C}_{1-6}$ -alkyl, $\text{S}(\text{O})_2\text{N}(\text{R}^{\text{aa}})_2$, $\text{NR}^{\text{aa}}\text{S}(\text{O})_2-\text{C}_{1-6}$ -alkyl and C_{3-6} -cycloalkyl,

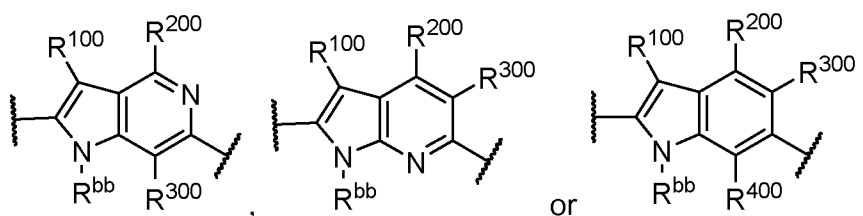
wherein the alkyl and cycloalkyl are unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of halogen, C_{1-3} -alkyl, halo- C_{1-3} -alkyl, OH, CN and oxo, or

wherein two substituents on the aryl or heteroaryl group together with the atoms they are attached to may form a 5- to 7-membered saturated or partially unsaturated carbocyclic ring or heterocyclic ring containing 1 to 3 heteroatoms independently selected from O, N and S,

wherein the carbocyclic or heterocyclic ring is unsubstituted or substituted with 1 to 5 substituents independently selected from the group consisting of halogen, C_{1-6} -alkyl and halo- C_{1-6} -alkyl, and

wherein R^{aa} is hydrogen or C_{1-6} -alkyl,

then B is not



wherein R^{100} to R^{400} is independently selected from the group consisting of hydrogen, halogen, C_{1-4} -alkyl, halo- C_{1-3} -alkyl, OH, O- C_{1-3} -alkyl and CN, and R^{bb} is hydrogen or C_{1-6} -alkyl.

2. The compound and an enantiomer, diastereomer, tautomer, solvate, prodrug or pharmaceutical acceptable salt thereof according to claim 1, wherein the compound is represented by Formula (I)

A-B-L-C (I)

wherein

A represents a 6- to 10-membered mono- or bicyclic aryl or a 5- to 10-membered mono- or bicyclic heteroaryl containing 1 to 4 heteroatoms independently selected from N, O and S,

5 wherein aryl and heteroaryl are unsubstituted or substituted with 1 to 7 substituents independently selected from the group consisting of halogen, OH, CN, C₁₋₆-alkyl, O-C₁₋₆-alkyl, C(O)OR^a, OC(O)R^a, S(O)-C₁₋₆-alkyl, S(O)₂-C₁₋₆-alkyl, N(R^a)₂, C(O)N(R^a)₂, NR^aC(O)-C₁₋₆-alkyl, S(O)₂N(R^a)₂, NR^aS(O)₂-C₁₋₆-alkyl and C₃₋₆-cycloalkyl,

10 wherein alkyl and cycloalkyl are unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of halogen, C₁₋₃-alkyl, halo-C₁₋₃-alkyl, OH, CN and oxo, or

15 wherein two substituents on the aryl or heteroaryl group together with the atoms they are attached to may form a 5- to 7-membered saturated or partially unsaturated carbocyclic ring or heterocyclic ring containing 1 to 3 heteroatoms independently selected from O, N and S,

wherein the carbocyclic or heterocyclic ring is unsubstituted or substituted with 1 to 5 substituents independently selected from the group consisting of halogen, C₁₋₆-alkyl and halo-C₁₋₆-alkyl;

R^a is independently selected from hydrogen and C₁₋₆-alkyl;

20 B represents a 8- to 10- membered bicyclic aryl or heteroaryl ring, wherein the heteroaryl ring contains up to 6 heteroatoms independently selected from N, O and S,

wherein the bicyclic aryl or heteroaryl ring is unsubstituted or substituted with 1 to 5 substituents independently selected from halogen, C₁₋₆-alkyl, halo-C₁₋₃-alkyl, C₃₋₆-cycloalkyl, OH, O-C₁₋₃-alkyl and CN,

25 wherein cycloalkyl or alkyl is unsubstituted or substituted with 1 to 3 substituents independently selected from halogen, OH, C₁₋₃-alkyl and halo-C₁₋₃-alkyl;

L represents -NR^bC(O)C(O)NR^b-, -NR^bC(=NR^c)-, -NR^bSO₂-, -C(O)NR^b-, -NR^b-C₁₋₂-alkylene-, -S(O)_x-C₁₋₂-alkylene- or -C₀₋₂-alkylene-NR^bC(O)-,

30 wherein alkylene is unsubstituted or substituted with 1 to 4 substituents independently selected from halogen, C₁₋₃-alkyl and halo-C₁₋₃-alkyl;

R^b is independently selected from hydrogen and C₁₋₆-alkyl;

R^c is hydrogen, OH, C₁₋₆-alkyl, O-C₁₋₆-alkyl, CN or SO₂-C₁₋₆-alkyl;

C represents a C₁₋₆-alkyl, C₃₋₁₀-cycloalkyl, 3- to 10-membered heterocycloalkyl containing 1 to 4 heteroatoms independently selected from N, O and S, 6- to 10-membered mono- or bicyclic aryl or a 5- to 10-membered mono- or bicyclic heteroaryl containing 1 to 4 heteroatoms independently selected from N, O and S,

wherein cycloalkyl, heterocycloalkyl, aryl and heteroaryl are unsubstituted or substituted with 1 to 7 substituents independently selected from the group consisting of halogen, OH, CN, C₁₋₆-alkyl, O-C₁₋₆-alkyl, C(O)OR^a, OC(O)R^a, S(O)-C₁₋₆-alkyl, S(O)₂-C₁₋₆-alkyl, N(R^a)₂, C(O)N(R^a)₂, NR^aC(O)-C₁₋₆-alkyl, S(O)₂N(R^a)₂, NR^aS(O)₂-C₁₋₆-alkyl and C₃₋₆-cycloalkyl,

wherein the alkyl and cycloalkyl are unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of halogen, C₁₋₃-alkyl, halo-C₁₋₃-alkyl, OH, CN and oxo, or

wherein two substituents on the cycloalkyl, heterocycloalkyl, aryl or heteroaryl group together with the atoms they are attached to may form a 5- to 7-membered saturated or partially unsaturated carbocyclic ring or heterocyclic ring containing 1 to 3 heteroatoms independently selected from O, N and S,

wherein the carbocyclic or heterocyclic ring is unsubstituted or substituted with 1 to 5 substituents independently selected from the group consisting of halogen, C₁₋₆-alkyl and halo-C₁₋₆-alkyl;

and

x is 0, 1 or 2;

with the proviso that if L represents a -NR^{bb}C(O)- group, wherein R^{bb} is hydrogen or C₁₋₆-alkyl, and C is 6- to 10-membered mono- or bicyclic aryl and 5- to 10-membered mono- or bicyclic heteroaryl containing 1 to 4 heteroatoms independently selected from N, O and S,

wherein aryl and heteroaryl are unsubstituted or substituted with 1 to 7 substituents independently selected from the group consisting of halogen, OH, CN, C₁₋₆-alkyl, O-C₁₋₆-alkyl, C(O)OR^{aa}, OC(O)R^{aa}, S(O)-C₁₋₆-alkyl, S(O)₂-C₁₋₆-alkyl, N(R^a)₂, C(O)N(R^{aa})₂, NR^{aa}C(O)-C₁₋₆-alkyl, S(O)₂N(R^{aa})₂, NR^{aa}S(O)₂-C₁₋₆-alkyl and C₃₋₆-cycloalkyl,

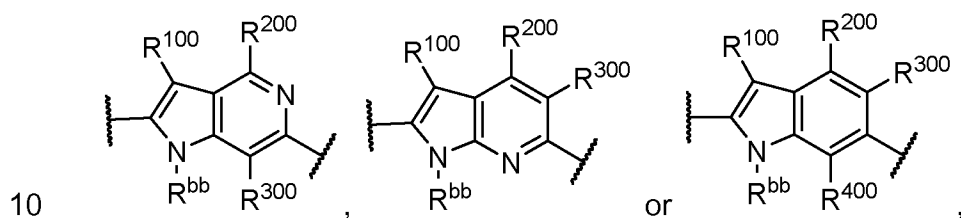
wherein alkyl and cycloalkyl are unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of halogen, C₁₋₃-alkyl, halo-C₁₋₃-alkyl, OH, CN and oxo, or

wherein two substituents on the aryl or heteroaryl group together with the atoms they are attached to may form a 5- to 7-membered saturated or partially unsaturated carbocyclic ring or heterocyclic ring containing 1 to 3 heteroatoms independently selected from O, N and S,

- 5 wherein the carbocyclic or heterocyclic ring is unsubstituted or substituted with 1 to 5 substituents independently selected from the group consisting of halogen, C₁₋₆-alkyl and halo-C₁₋₆-alkyl, and

wherein R^{aa} is hydrogen or C₁₋₆-alkyl,

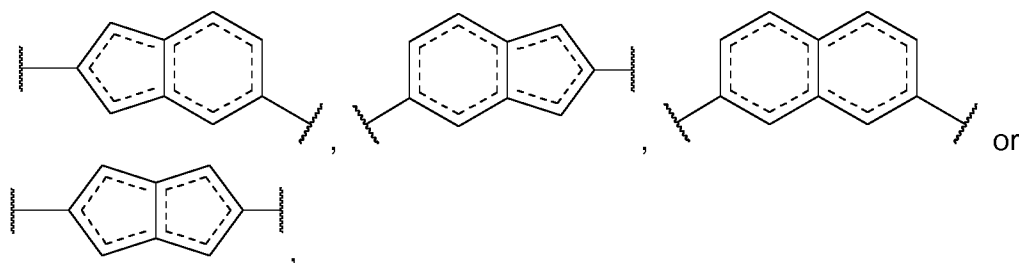
then B is not



wherein R¹⁰⁰ to R⁴⁰⁰ is independently hydrogen, halogen, C₁₋₄-alkyl, halo-C₁₋₃-alkyl, OH, O-C₁₋₃-alkyl and CN, and R^{bb} is hydrogen or C₁₋₆-alkyl.

3. The compound according to claim 1 or 2, wherein

- 15 B represents a 8- to 10-membered bicyclic aryl or heteroaryl ring, wherein the heteroaryl ring contains up to 6 heteroatoms independently selected from N, O and S, and wherein the bicyclic ring is connected to A and L-C in the following configurations



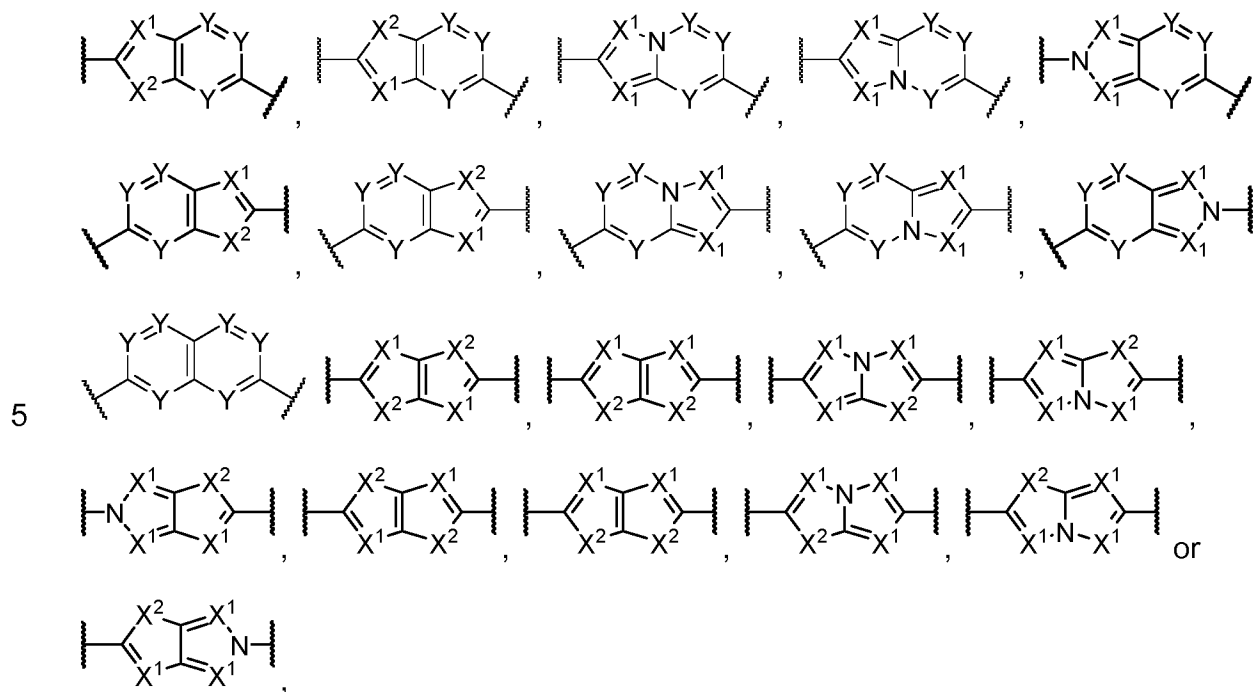
- 20 wherein the bicyclic aryl or heteroaryl ring is unsubstituted or substituted with 1 to 5 substituents independently selected from halogen, C₁₋₆-alkyl, halo-C₁₋₃-alkyl, OH, C₃₋₆-cycloalkyl, O-C₁₋₃-alkyl and CN,

wherein cycloalkyl and alkyl is unsubstituted or substituted with 1 to 3 substituents independently selected from halogen, OH, C₁₋₃-alkyl and halo-C₁₋₃-alkyl.

25

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

B is



X^1 is independently selected from N and CR^1 ;

10 X^2 is independently selected from NR^2 , O and S;

Y is independently selected from N and CR^1 ;

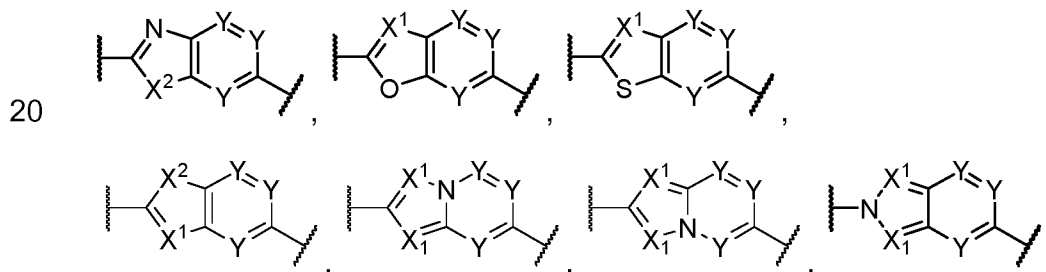
R^1 is independently selected from hydrogen, halogen, C_{1-6} -alkyl, halo- C_{1-3} -alkyl, OH, C_{3-6} -cycloalkyl, O- C_{1-3} -alkyl and CN,

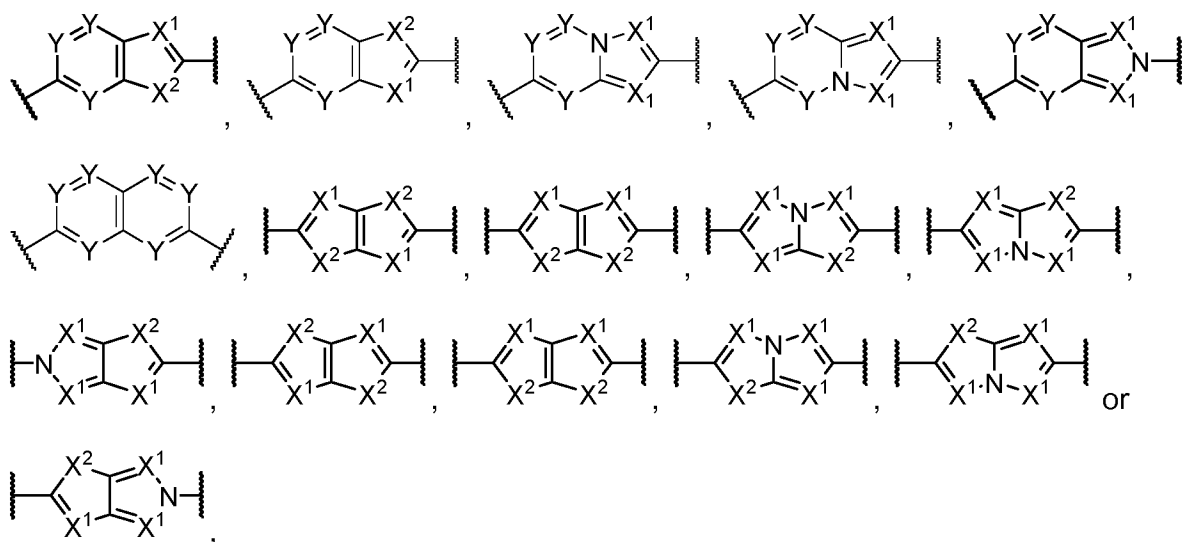
15 wherein cycloalkyl or alkyl is unsubstituted or substituted with 1 to 3 substituents independently selected from halogen, OH, C_{1-3} -alkyl and halo- C_{1-3} -alkyl; and

R^2 is independently selected from hydrogen and C_{1-6} -alkyl.

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

B is





5 wherein

X¹ is independently selected from N and CR¹;

X² is independently selected from NR², O and S;

Y is independently selected from N and CR¹;

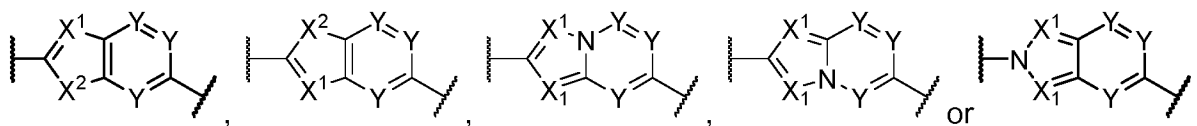
10 R¹ is independently selected from hydrogen, halogen, C₁₋₃-alkyl, halo-C₁₋₃-alkyl, C₃₋₆-cycloalkyl, OH, O-C₁₋₃-alkyl and CN,

wherein cycloalkyl or alkyl is unsubstituted or substituted with 1 to 3 substituents independently selected from halogen, OH, C₁₋₃-alkyl and halo-C₁₋₃-alkyl; and

R² is independently selected from hydrogen and C₁₋₆-alkyl.

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

B is



wherein

X¹ is independently selected from N and CR¹;

20 X² is independently selected from NR², O and S;

Y is independently selected from N and CR¹;

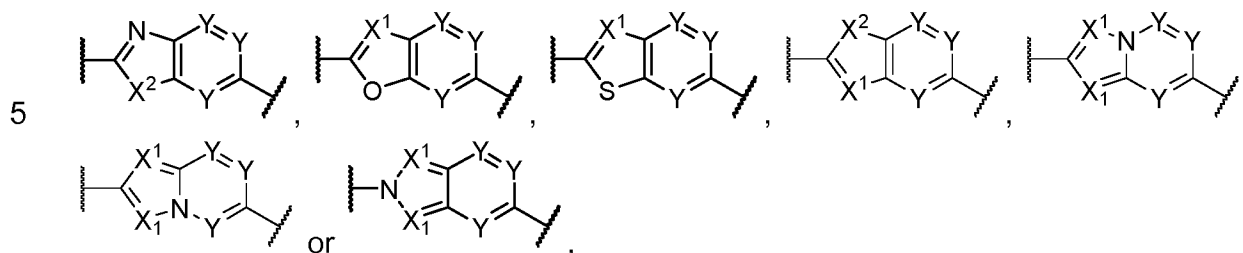
R¹ is independently selected from hydrogen, halogen, C₁₋₃-alkyl, halo-C₁₋₃-alkyl, OH, C₃₋₆-cycloalkyl, O-C₁₋₃-alkyl and CN,

25 wherein cycloalkyl or alkyl is unsubstituted or substituted with 1 to 3 substituents independently selected from halogen, OH, C₁₋₃-alkyl and halo-C₁₋₃-alkyl; and

R^2 is independently selected from hydrogen and C_{1-6} -alkyl.

7. The compound according to any one of claims 1 to 6, wherein

B is



wherein

X^1 is independently selected from N and CR^1 ;

X^2 is independently selected from NR^2 , O and S;

10 Y is independently selected from N and CR^1 ;

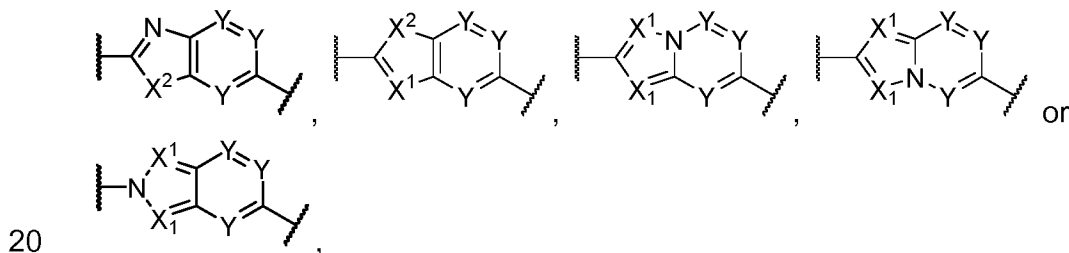
R^1 is independently selected from hydrogen, halogen, C_{1-3} -alkyl, halo- C_{1-3} -alkyl, OH, C_{3-6} -cycloalkyl, O- C_{1-3} -alkyl and CN,

wherein cycloalkyl or alkyl is unsubstituted or substituted with 1 to 3 substituents independently selected from halogen, OH, C_{1-3} -alkyl and halo- C_{1-3} -alkyl; and

15 R^2 is independently selected from hydrogen and C_{1-6} -alkyl.

8. The compound according to any one of claims 1 to 7, wherein

B is



wherein

X^1 is independently selected from N and CR^1 ;

X^2 is independently selected from NR^2 , O and S;

Y is independently selected from N and CR^1 ;

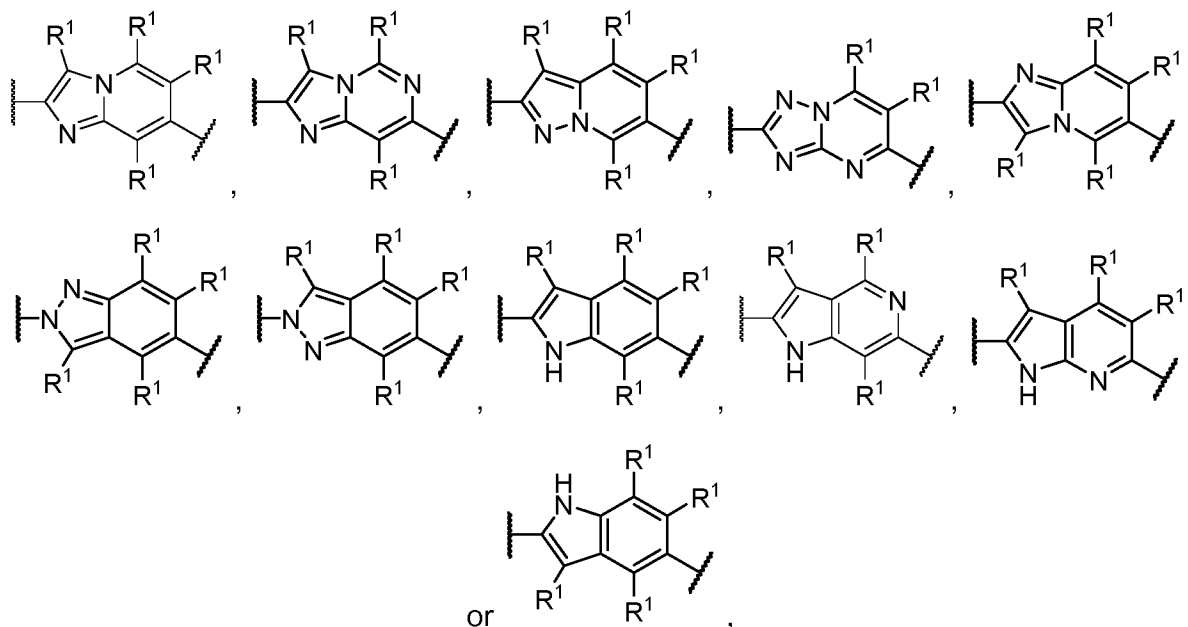
25 R^1 is independently selected from hydrogen, halogen, C_{1-3} -alkyl, halo- C_{1-3} -alkyl, OH, C_{3-6} -cycloalkyl, O- C_{1-3} -alkyl and CN,

wherein cycloalkyl or alkyl is unsubstituted or substituted with 1 to 3 substituents independently selected from halogen, OH, C₁₋₃-alkyl and halo-C₁₋₃-alkyl; and

R² is independently selected from hydrogen and C₁₋₆-alkyl.

5 9. The compound according to any one of claims 1 to 8, wherein

B is



10 wherein

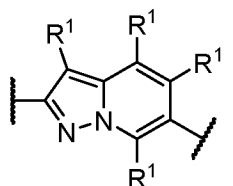
R¹ is independently selected from hydrogen, halogen, C₁₋₃-alkyl, halo-C₁₋₃-alkyl, OH, C₃₋₆-cycloalkyl, O-C₁₋₃-alkyl and CN,

wherein cycloalkyl or alkyl is unsubstituted or substituted with 1 to 3 substituents independently selected from halogen, OH, C₁₋₃-alkyl and halo-C₁₋₃-alkyl.

15

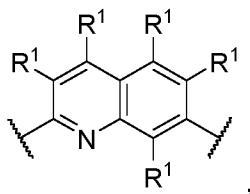
10. The compound according to any one of claims 1 to 9, wherein

B is



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

B is



wherein

- 5 R^1 is independently selected from hydrogen, halogen, C_{1-3} -alkyl, halo- C_{1-3} -alkyl, OH, C_{3-6} -cycloalkyl, O- C_{1-3} -alkyl and CN,

wherein cycloalkyl or alkyl is unsubstituted or substituted with 1 to 3 substituents independently selected from halogen, OH, C_{1-3} -alkyl and halo- C_{1-3} -alkyl.

- 10 12. The compound according to any one of claims 1 to 11, wherein

C represents a C_{1-6} -alkyl, C_{3-10} -cycloalkyl, 3- to 10-membered heterocycloalkyl containing 1 to 4 heteroatoms independently selected from N, O and S, 6- to 10-membered mono- or bicyclic aryl or a 5- to 10-membered mono- or bicyclic heteroaryl containing 1 to 4 heteroatoms independently selected from N, O and S,

- 15 wherein cycloalkyl, heterocycloalkyl, aryl and heteroaryl are unsubstituted or substituted with 1 to 7 substituents independently selected from the group consisting of OH, CN, C_{1-6} -alkyl, O- C_{1-6} -alkyl, $OC(O)R^a$, $S(O)-C_{1-6}$ -alkyl, $S(O)_2-C_{1-6}$ -alkyl, $N(R^a)_2$, $NR^aC(O)-C_{1-6}$ -alkyl, $S(O)_2N(R^a)_2$, $NR^aS(O)_2-C_{1-6}$ -alkyl and C_{3-6} -cycloalkyl,

- 20 wherein the alkyl and cycloalkyl are unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of halogen, C_{1-3} -alkyl, halo- C_{1-3} -alkyl, OH, CN and oxo, or

- wherein two substituents on the cycloalkyl, heterocycloalkyl, aryl or heteroaryl group together with the atoms they are attached to may form a 5- to 7-membered saturated or partially unsaturated carbocyclic ring or heterocyclic ring containing 1 to 3
25 heteroatoms independently selected from O, N and S,

wherein the carbocyclic or heterocyclic ring is unsubstituted or substituted with 1 to 5 substituents independently selected from the group consisting of halogen, C_{1-6} -alkyl and halo- C_{1-6} -alkyl.

13. The compound according to any one of claims 1 to 12, wherein

C represents a 6- to 10-membered mono- or bicyclic aryl or a 5- to 6-membered heteroaryl containing 1 to 4 heteroatoms independently selected from N, O and S,

wherein aryl and heteroaryl are unsubstituted or substituted with 1 to 7 substituents independently selected from the group consisting of OH, CN, C₁₋₆-alkyl, O-C₁₋₆-alkyl, OC(O)R^a, S(O)-C₁₋₆-alkyl, S(O)₂-C₁₋₆-alkyl, N(R^a)₂, NR^aC(O)-C₁₋₆-alkyl, S(O)₂N(R^a)₂, NR^aS(O)₂-C₁₋₆-alkyl and C₃₋₆-cycloalkyl,

wherein the alkyl and cycloalkyl are unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of halogen, C₁₋₃-alkyl, halo-C₁₋₃-alkyl, OH, CN and oxo, or

wherein two substituents on the aryl or heteroaryl group together with the atoms they are attached to may form a 5- to 7-membered saturated or partially unsaturated carbocyclic ring or heterocyclic ring containing 1 to 3 heteroatoms independently selected from O, N and S,

wherein the carbocyclic or heterocyclic ring is unsubstituted or substituted with 1 to 5 substituents independently selected from the group consisting of halogen, C₁₋₆-alkyl and halo-C₁₋₆-alkyl.

14. The compound according to any one of claims 1 to 13, wherein

C represents a 5-membered heteroaryl containing 2 to 4 nitrogen atoms,

which is unsubstituted or substituted with 1 or 2 substituents independently selected from the group consisting of OH, CN, C₁₋₆-alkyl, O-C₁₋₆-alkyl, OC(O)R^a, S(O)-C₁₋₆-alkyl, S(O)₂-C₁₋₆-alkyl, N(R^a)₂, NR^aC(O)-C₁₋₆-alkyl, S(O)₂N(R^a)₂, NR^aS(O)₂-C₁₋₆-alkyl and C₃₋₆-cycloalkyl,

wherein alkyl and cycloalkyl are unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of halogen, C₁₋₃-alkyl, halo-C₁₋₃-alkyl, OH, CN and oxo, or

wherein two substituents on the heteroaryl group together with the atoms they are attached to may form a 5- to 7-membered saturated or partially unsaturated carbocyclic ring or heterocyclic ring containing 1 to 3 heteroatoms independently selected from O, N and S,

wherein the carbocyclic or heterocyclic ring is unsubstituted or substituted with 1 to 5 substituents independently selected from the group consisting of halogen, C₁₋₆-alkyl and halo-C₁₋₆-alkyl.

5 15. The compound according to any one of claims 1 to 14, wherein

A represents a 6- to 10-membered mono- or bicyclic aryl or a 5- to 10-membered mono- or bicyclic heteroaryl containing 1 to 4 heteroatoms independently selected from N, O and S,

10 wherein aryl and heteroaryl are unsubstituted or substituted with 1 to 7 substituents independently selected from the group consisting of halogen, OH, CN, C₁₋₆-alkyl, O-C₁₋₆-alkyl, C(O)OR^a, OC(O)R^a, S(O)-C₁₋₆-alkyl, S(O)₂-C₁₋₆-alkyl, N(R^a)₂, C(O)N(R^a)₂, S(O)₂N(R^a)₂, NR^aS(O)₂-C₁₋₆-alkyl and C₃₋₆-cycloalkyl,

15 wherein alkyl and cycloalkyl are unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of halogen, C₁₋₃-alkyl, halo-C₁₋₃-alkyl, OH, CN and oxo, or

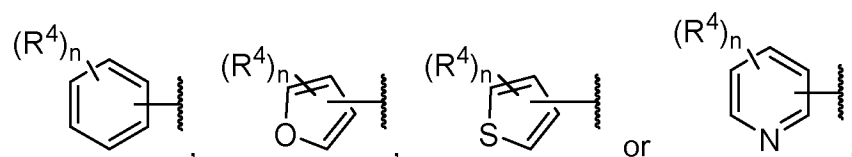
wherein two substituents on the aryl or heteroaryl group together with the atoms they are attached to may form a 5- to 7-membered saturated or partially unsaturated carbocyclic ring or heterocyclic ring containing 1 to 3 heteroatoms independently selected from O, N and S,

20 wherein the carbocyclic or heterocyclic ring is unsubstituted or substituted with 1 to 5 substituents independently selected from the group consisting of halogen, C₁₋₆-alkyl and halo-C₁₋₆-alkyl; and

R^a is independently selected from hydrogen and C₁₋₆-alkyl.

25 16. The compounds according to any one of claims 1 to 15, wherein

A is



wherein

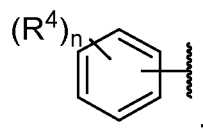
R^4 is independently selected from halogen, OH, CN, C_{1-6} -alkyl, $O-C_{1-6}$ -alkyl, $C(O)OR^a$, $OC(O)R^a$, $S(O)-C_{1-6}$ -alkyl, $S(O)_2-C_{1-6}$ -alkyl, $N(R^a)_2$, $C(O)N(R^a)_2$, $S(O)_2N(R^a)_2$, $NR^aS(O)_2-C_{1-6}$ -alkyl and C_{3-6} -cycloalkyl,

wherein alkyl and cycloalkyl are unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of halogen, C_{1-3} -alkyl, halo- C_{1-3} -alkyl, OH, CN and oxo;

R^a is independently selected from hydrogen and C_{1-6} -alkyl; and

n is 0 to 5.

17. The compound according to any one of claims 1 to 16, wherein A is



wherein

R^4 is independently selected from halogen, OH, CN, C_{1-6} -alkyl, $O-C_{1-6}$ -alkyl, $C(O)OR^a$, $OC(O)R^a$, $S(O)-C_{1-6}$ -alkyl, $S(O)_2-C_{1-6}$ -alkyl, $N(R^a)_2$, $C(O)N(R^a)_2$, $S(O)_2N(R^a)_2$, $NR^aS(O)_2-C_{1-6}$ -alkyl and C_{3-6} -cycloalkyl,

wherein alkyl and cycloalkyl are unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of halogen, C_{1-3} -alkyl, halo- C_{1-3} -alkyl, OH, CN and oxo;

R^a is independently selected from hydrogen and C_{1-6} -alkyl; and

n is 0 to 5.

18. The compound according to any one of claims 1 to 17, wherein

L represents $-NR^bC(O)-$.

19. A pharmaceutical composition comprising the compound according to any one of claims 1 to 18 and a physiologically acceptable excipient.

20. The compound according to any one of claims 1 to 18 for use as a medicament.

21. The compound according to any one of claims 1 to 18 or the pharmaceutical composition according to claim 19 for use in the prophylaxis and/or treatment of a disease or condition mediated by aryl hydrocarbon receptor (AhR).

22. The compound or pharmaceutical composition for use according to claim 21,
5 wherein the disease or condition mediated by aryl hydrocarbon receptor (AhR) is cancer.

23. The compound for use according to claim 22, wherein the compound is administered with one or more therapeutic agents for cancer selected from the group consisting of PD-1 agent, PD-L1 agent, CTLA-4 agent, IDO1 inhibitor, chemotherapeutic agent, anticancer vaccine, Toll like receptor agonist, oncolytic virus, STING agonist and
10 cytokine therapy, or wherein the compound is administered under irradiation therapy.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference PCT118948KG030	FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, item 5 below.	
International application No. PCT/EP2019/070066	International filing date (<i>day/month/year</i>) 25 July 2019 (25-07-2019)	(Earliest) Priority Date (<i>day/month/year</i>) 26 July 2018 (26-07-2018)
Applicant PHENEX PHARMACEUTICALS AG		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 6 sheets.

☒

It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the **language**, the international search was carried out on the basis of:

☒

the international application in the language in which it was filed

☐

a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))

b. ☐

This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6**bis**(a)).

c. ☐

With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☐

Certain claims were found unsearchable (See Box No. II)

3. ☐

Unity of invention is lacking (see Box No III)

4. With regard to the **title**,

☒

the text is approved as submitted by the applicant

☐

the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

☐

the text is approved as submitted by the applicant

☒

the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the **drawings**,

a. the figure of the **drawings** to be published with the abstract is Figure No. _____

☐

as suggested by the applicant

☐

as selected by this Authority, because the applicant failed to suggest a figure

☐

as selected by this Authority, because this figure better characterizes the invention

b. ☐

none of the figures is to be published with the abstract

Box No. IV Text of the abstract (Continuation of item 5 of the first sheet)

The present invention relates to bicyclic compounds which can act as aryl hydrocarbon receptor (AhR) modulators and, in particular, as AhR antagonists. The invention further relates to the use of the compounds for the treatment and/or prophylaxis of diseases and/or conditions through binding of said aryl hydrocarbon receptor by said compounds.

A-B-L-C (I)

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2019/070066

A. CLASSIFICATION OF SUBJECT MATTER		
INV.	C07D403/12 A61K31/437	C07D401/12 A61P35/00
	C07D471/04	C07D487/04
		C07D513/04
ADD.		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED		
Minimum documentation searched (classification system followed by classification symbols) C07D A61K A61P		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) EPO-Internal, CHEM ABS Data, WPI Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2014/100620 A2 (PLEXXIKON INC [US]) 26 June 2014 (2014-06-26) abstract page 127 - page 199; examples claims	1-23
X	WO 2014/177493 A1 (HOFFMANN LA ROCHE [CH]; HOFFMANN LA ROCHE [US]) 6 November 2014 (2014-11-06) abstract page 12 - page 22; examples claims	1-19
	----- -/-	
☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.		
* Special categories of cited documents : "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier application or patent but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family		
Date of the actual completion of the international search 19 August 2019		Date of mailing of the international search report 29/08/2019
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016		Authorized officer Stix-Malaun, Elke

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2019/070066

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2012/076430 A1 (HOFFMANN LA ROCHE [CH]; FLOHR ALEXANDER [DE]; GOBBI LUCA [CH]; GROEBKE) 14 June 2012 (2012-06-14) abstract page 43 - page 196; examples claims -----	1-23
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