

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.

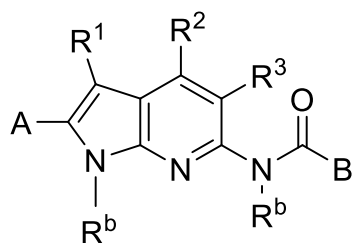
In a recently published Patent Application US 2016/01752278 by the Trustees of Boston University, novel small molecule agents characterized as AhR modulators are being claimed for inhibiting cancer cell proliferation and tumor cell invasion and metastasis.

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.

Summary

In a first aspect, the present disclosure refers to a compound represented by Formula (I), an enantiomer, diastereomer, tautomer, solvate, or pharmaceutical acceptable salt thereof



(I)

wherein

A and B are independently selected from 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^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 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;

R¹, R², R³ are each independently selected from hydrogen, halogen, C₁₋₃-alkyl, halo-C₁₋₃-alkyl, OH, O-C₁₋₃-alkyl, and CN;

R^a is hydrogen or C₁₋₆-alkyl; and

R^b is hydrogen or C₁₋₆-alkyl.

In another aspect, the present disclosure refers to a pharmaceutical composition comprising the compound disclosed herein and a physiologically acceptable excipient.

In yet another aspect, the present disclosure refers to the compound disclosed herein for use as a medicament.

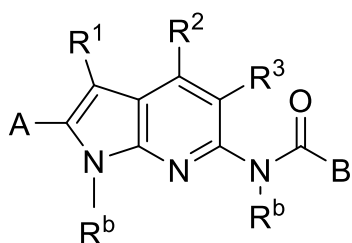
In a further aspect, the present disclosure refers to the compound disclosed herein or the pharmaceutical composition disclosed herein for use in the prophylaxis and/or treatment of a disease or condition mediated by aryl hydrocarbon receptor (AhR), wherein the disease or condition is cancer.

In another aspect, the present disclosure refers to a use of a compound disclosed herein in the manufacture of a medicament for the prophylaxis and/or treatment of a disease or condition mediated by aryl hydrocarbon receptor (AhR).

5 In yet another aspect, the present disclosure refers to a use of a compound disclosed herein or the pharmaceutical composition disclosed herein in the manufacture of a medicament for the prophylaxis and/or treatment of a disease or condition mediated by aryl hydrocarbon receptor (AhR).

Description

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

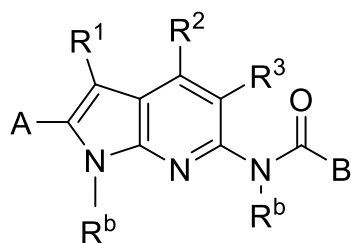


(I)

wherein

Claims

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



(I)

wherein

A and B are independently selected from 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^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 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;

R¹, R², R³ are each independently selected from hydrogen, halogen, C₁₋₃-alkyl, halo-C₁₋₃-alkyl, OH, O-C₁₋₃-alkyl, and CN;

R^a is hydrogen or C₁₋₆-alkyl; and

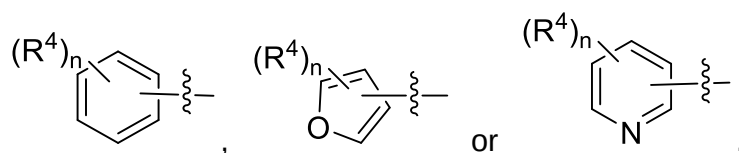
R^b is hydrogen or C_{1-6} -alkyl.

2. The compound of claim 1, wherein R^b is hydrogen.

3. The compound of at least one of claims 1 and 2, wherein A is substituted with 1 to 5 substituents independently selected from halogen, C_{1-6} -alkyl, halo- C_{1-6} -alkyl, CN, SO_2CH_3 , $C(O)OR^a$, $C(O)N(R^a)_2$ and C_{3-6} -cycloalkyl which is unsubstituted or substituted with C_{1-3} -alkyl or halo- C_{1-3} -alkyl.

4. The compound of at least one of claims 1 and 2, wherein

A is



10 wherein

R^4 is independently 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, $N(R^a)_2$, $C(O)N(R^a)_2$, $NR^aC(O)-C_{1-6}$ -alkyl, $S(O)_2N(R^a)_2$, $NR^aS(O)_2-C_{1-6}$ -alkyl and C_{3-6} -cycloalkyl,

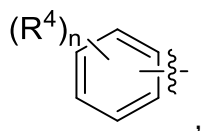
15 wherein the alkyl and cycloalkyl are unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of halogen, C_{1-3} -alkyl, halo- C_{1-3} -alkyl, OH, CN and oxo;

R^a is hydrogen or C_{1-6} -alkyl; and

n is 0 to 5.

5. The compound of claim 4, wherein n is 1 to 5 and R^4 is independently selected from halogen, C_{1-6} -alkyl, halo- C_{1-6} -alkyl, CN and C_{3-6} -cycloalkyl which is unsubstituted or substituted with 1 or 2 substituents independently selected from the group consisting of halogen, C_{1-3} -alkyl and halo- C_{1-3} -alkyl.

6. The compound of claim 4, wherein A is



wherein

R^4 is independently 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, $N(R^a)_2$, $C(O)N(R^a)_2$, $NR^aC(O)$ - C_{1-6} -alkyl, $S(O)_2N(R^a)_2$, $NR^aS(O)_2$ - C_{1-6} -alkyl and C_{3-6} -cycloalkyl,

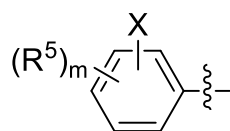
- 5 wherein the alkyl and cycloalkyl are unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of halogen, C_{1-3} -alkyl, halo- C_{1-3} -alkyl, OH, CN and oxo;

R^a is hydrogen or C_{1-6} -alkyl; and

n is 0 to 5.

- 10 7. The compound of at least one of claims 1, 2, 4 and 6, wherein

A is



wherein

X is halogen, C_{1-6} -alkyl or C_{3-6} -cycloalkyl,

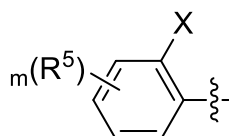
- 15 wherein the alkyl and cycloalkyl are unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of halogen, C_{1-3} -alkyl and halo- C_{1-3} -alkyl;

R^5 is independently halogen or CN; and

m is 0 to 4.

- 20 8. The compound of at least one of claims 1, 2 and 4 to 7, wherein

A is



wherein

X is CH_3 , CH_2CH_3 , CHF_2 or CF_3 ;

- 25 R^5 is independently halogen or CN; and

m is 0 to 4.

9. The compound of at least one of claims 1 to 8, wherein B is a 5- or 6-membered heteroaryl containing 1 to 4 heteroatoms independently selected from N, O and S, which is unsubstituted or substituted with 1 to 5 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; and

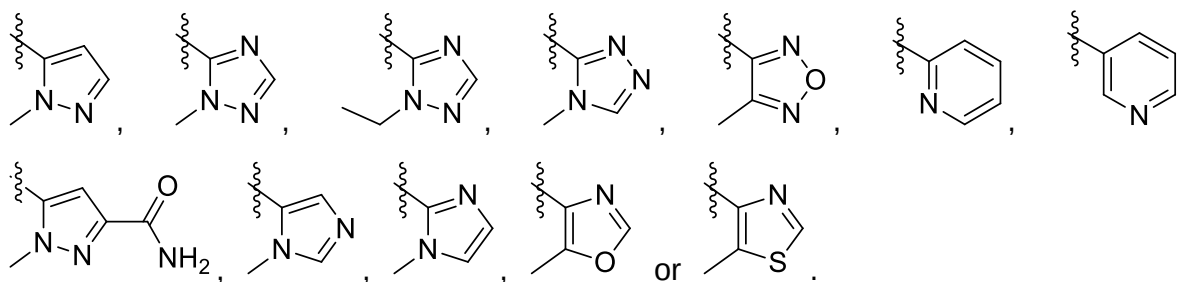
R^a is hydrogen or C₁₋₆-alkyl.

10. The compound of at least one of claims 1 to 9, wherein B is a 5- or 6-membered heteroaryl containing 1 to 3 heteroatoms independently selected from N, O and S, which is unsubstituted or substituted with 1 to 2 substituents independently selected from the group consisting of C₁₋₆-alkyl, halo-C₁₋₆-alkyl, C(O)OR^a, C(O)N(R^a)₂ and C₃₋₆-cycloalkyl.

11. The compound of at least one of claims 1 to 8, wherein B is a 9- or 10-membered heteroaryl containing 1 to 4 heteroatoms independently selected from N, O and S, which is unsubstituted or substituted with 1 to 2 substituents independently selected from the group consisting of C₁₋₆-alkyl, halo-C₁₋₆-alkyl, and C₃₋₆-cycloalkyl or wherein B is a 6- or 10-membered aryl, which is unsubstituted or substituted with 1 to 2 substituents independently selected from the group consisting of halogen and C₁₋₆-alkyl.

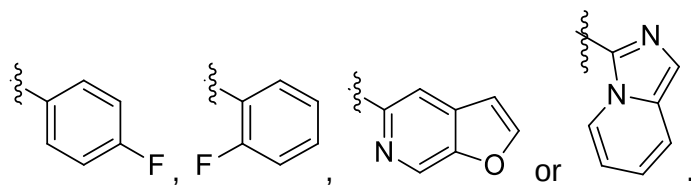
12. The compound of at least one of claims 1 to 10, wherein

B is



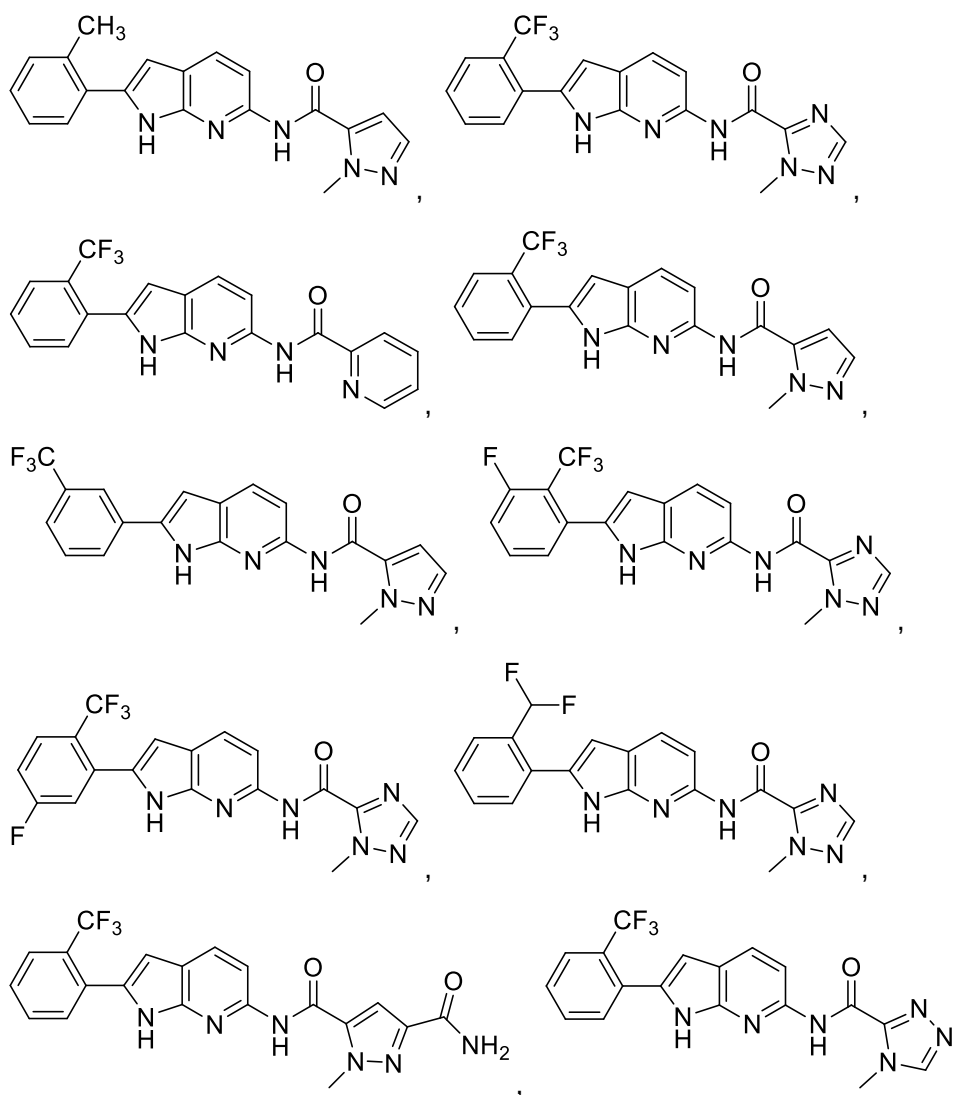
13. The compound of at least one of claims 1 to 8 and 11, wherein

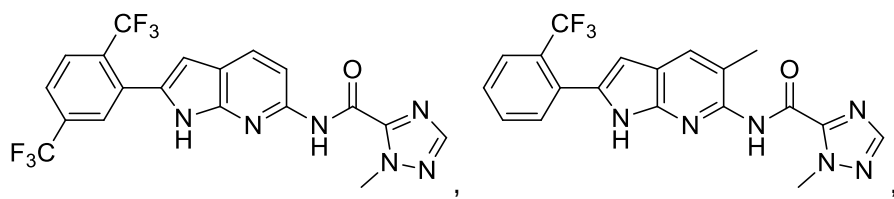
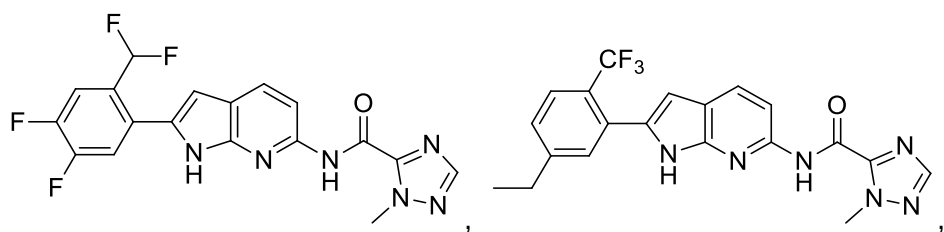
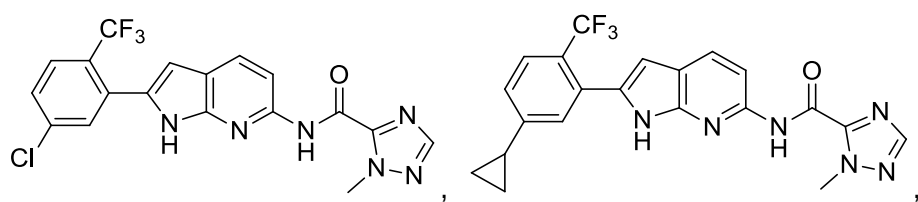
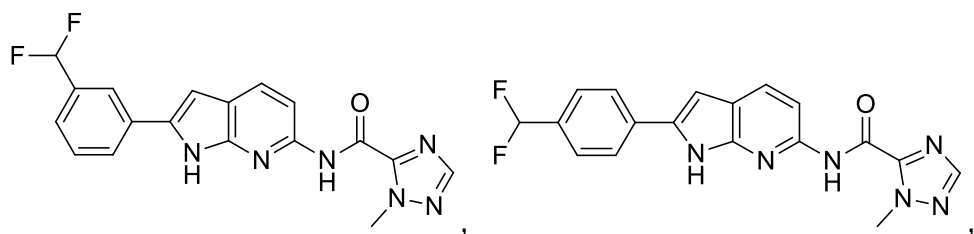
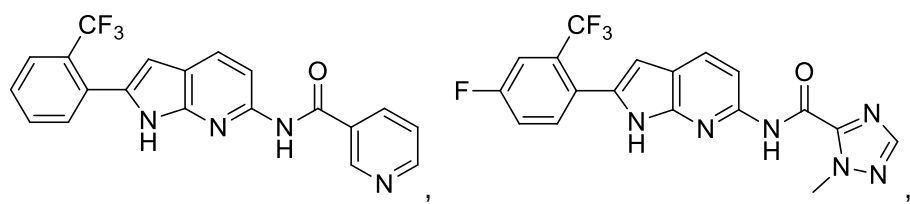
B is



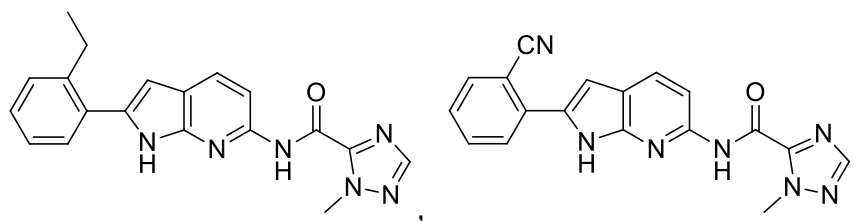
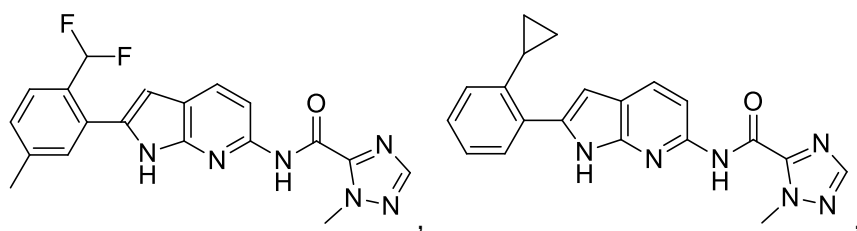
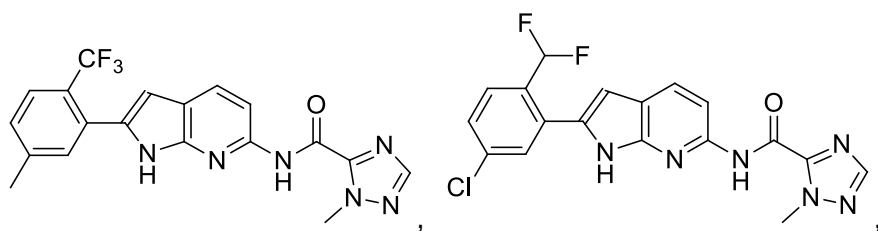
14. The compound of at least one of claims 1 to 13, wherein each of R¹, R², R³ are
5 hydrogen.

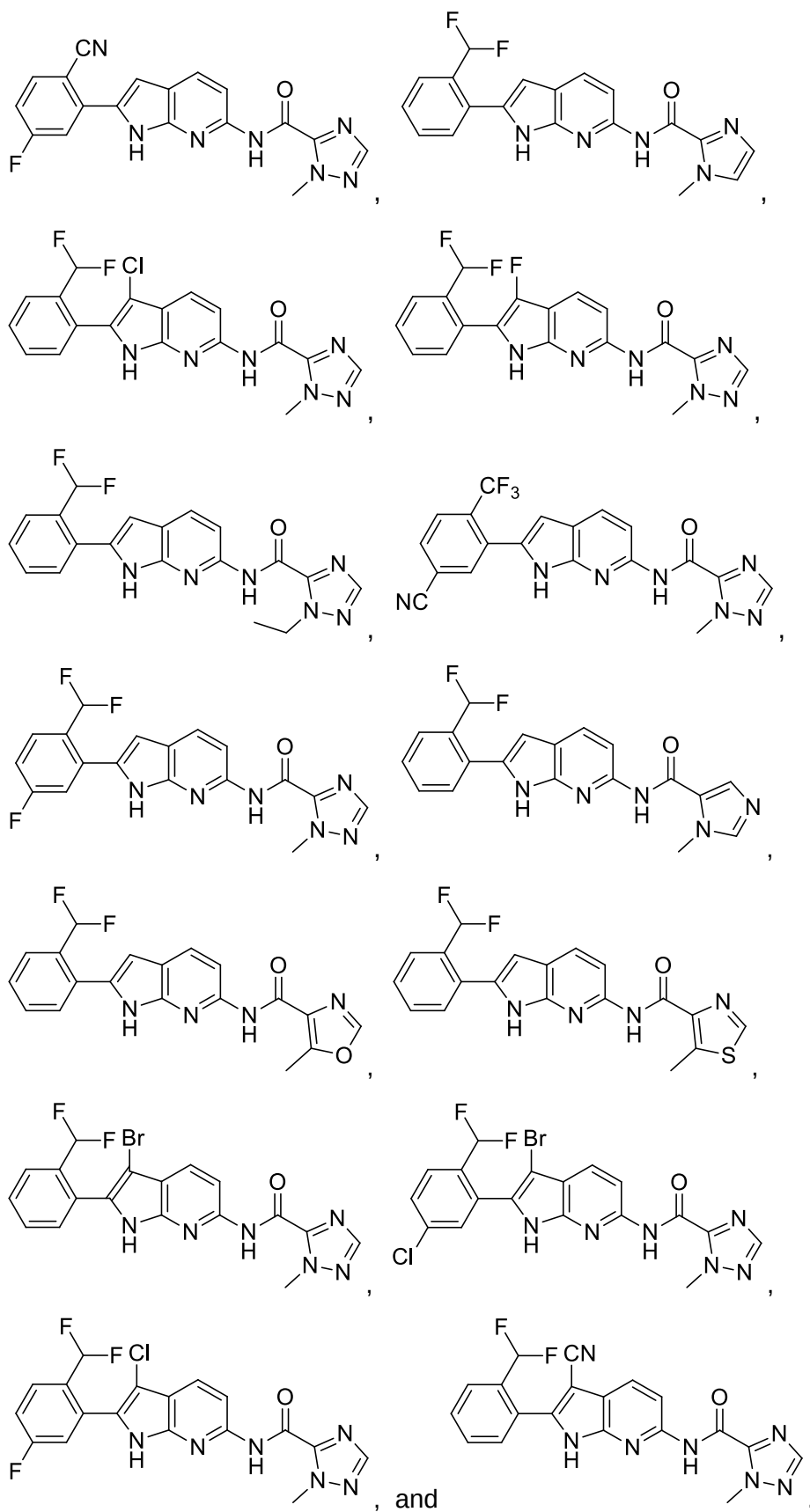
15. The compound of claim 1 which is selected from





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16. A pharmaceutical composition comprising the compound of at least one of claims 1 to 15 and a physiologically acceptable excipient.

17. The compound of at least one of claims 1 to 15 for use as a medicament.

18. The compound of at least one of claims 1 to 15 or the pharmaceutical composition according to claim 16 for use in the prophylaxis and/or treatment of a disease or condition mediated by aryl hydrocarbon receptor (AhR), wherein the disease or condition is cancer.

5 19. The compound for use according to claim 18, wherein the compound is to 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, and cytokine therapy, or wherein the compound is to be administered under irradiation therapy.

10 20. Use of a compound of at least one of claims 1 to 15 in the manufacture of a medicament for the prophylaxis and/or treatment of a disease or condition mediated by aryl hydrocarbon receptor (AhR).

15 21. Use of a compound of at least one of claims 1 to 15 or the pharmaceutical composition according to claim 16 in the manufacture of a medicament for the prophylaxis and/or treatment of a disease or condition mediated by aryl hydrocarbon receptor (AhR).

22. The use of claim 21, wherein the disease or condition mediated by aryl hydrocarbon receptor (AhR) is cancer.

20 23. The use of claim 22, wherein the compound is to 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, and cytokine therapy, or wherein the compound is to be administered under irradiation therapy.