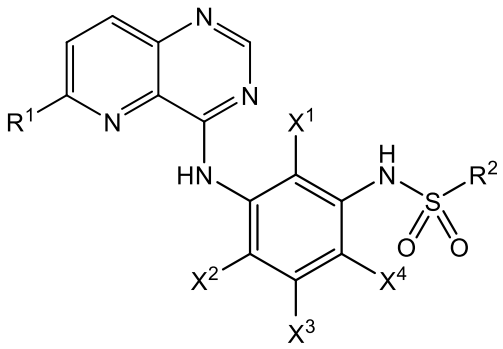
generations of RAF inhibitors. Although this class of compounds show improved properties, they were recently showed to mostly spare the ARAF isoform, which leads to paradoxical pathway activation and primary resistance as well as to the emergence of acquired resistance in vitro and in clinical settings (Clin Cancer Res. 2021, 27, 2061; Nature 2021, 594, 418). The second strategy consisted in designing compounds that conformationally bias the BRAF kinase domain in the inactive state and thus do not paradoxically induce ERK signaling. This has given rise to the "Paradox Breaker" (PB) molecule PLX8394, a derivative of PLX4032/vemurafenib (*Nature* 2015, *526*, 583). These molecules retained high potency against $BRAF^{V600E}$ and therefore should prove useful for treating $BRAF^{V600E}$-dependent melanomas. However, while PLX8394 does not induce ERK signaling in RAS-mutant cell lines that have been tested, it remains ineffective and is not useful against RAS-mutant tumors.

There remains a need for inhibitors that potently and consistently block RAS-ERK signaling and cellular proliferation in human tumor cells bearing a variety of RAS and RAF genotypes. The development of such inhibitors importantly being also devoid of paradoxical pathway induction in a variety of RAS-mutant tumor cell lines is highly desirable.

SUMMARY

According to one example, the present technology relates to a compound of Formula I:



Formula I

wherein:

R^1 is selected from substituted or unsubstituted OR^3, SR^3, NH_2, NHR^3, $N(R^3)_2$, C_{3-8}cycloalkyl, C_{4-8}heterocycloalkyl, C_{6-10}aryl and C_{5-10}heteroaryl, for example, selected from substituted or unsubstituted C_{6-10}aryl and C_{5-10}heteroaryl;

R^2 is selected from substituted C_6aryl or C_{5-10}heteroaryl, substituted or unsubstituted C_{4-8}heterocycloalkyl, and $N(R^3)_2$;

R^3 is independently in each occurrence selected from substituted or unsubstituted C_{1-8}alkyl, C_{3-8}cycloalkyl, C_{4-8}heterocycloalkyl, C_{6-10}aryl and C_{5-10}heteroaryl;

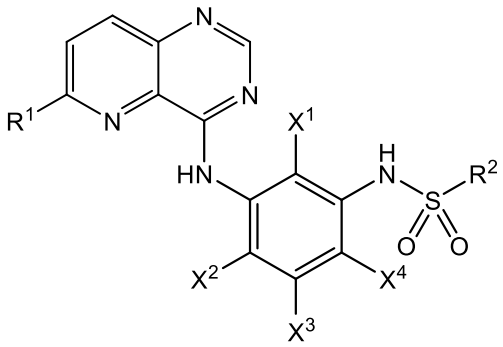
X^1 is halo or an electron-withdrawing group;

X^2 is selected from H, halo, and an electron-withdrawing group;

X^3 and X^4 are each selected from H, halo, an electron-withdrawing group, C_{1-3}alkyl, C_{3-4}cycloalkyl, and OC_{1-3}alkyl ;

or a pharmaceutically acceptable salt or solvate thereof.

In one aspect, the present disclosure refers to a compound of Formula I:



Formula I

wherein:

R^1 is selected from substituted or unsubstituted OR^3, SR^3, NH_2, NHR^3, $N(R^3)_2$, C_{3-8}cycloalkyl, C_{4-8}heterocycloalkyl, C_{6-10}aryl and C_{5-10}heteroaryl, for example, selected from substituted or unsubstituted C_{6-10}aryl and C_{5-10}heteroaryl;

R^2 is selected from substituted C_6aryl or C_{5-10}heteroaryl, substituted or unsubstituted C_{4-8}heterocycloalkyl, and $N(R^3)_2$;

R^3 is independently in each occurrence selected from substituted or unsubstituted C_{1-8}alkyl, C_{3-8}cycloalkyl, C_{4-8}heterocycloalkyl, C_{6-10}aryl and C_{5-10}heteroaryl;

X^1 is halo, perhaloalkyl, CN, NO_2, sulfonate, alkylsulfonyl, alkylcarbonyl, carboxylate, alkoxycarbonyl, or aminocarbonyl;

X^2 is selected from H, halo, perhaloalkyl, CN, NO_2, sulfonate, alkylsulfonyl, alkylcarbonyl, carboxylate, alkoxycarbonyl, and aminocarbonyl;

X^3 and X^4 are each selected from H, halo, perhaloalkyl, CN, NO_2, sulfonate, alkylsulfonyl, alkylcarbonyl, carboxylate, alkoxycarbonyl, aminocarbonyl, $C_{1\text{-}3}$alkyl, $C_{3\text{-}4}$cycloalkyl, and $OC_{1\text{-}3}$alkyl;

or a pharmaceutically acceptable salt or solvate thereof.

The compounds of Formula I are also defined according to any of the examples, alone or in combination, and examples described throughout the present document.

In another aspect, there is provided a pharmaceutical composition comprising a compound as defined above, together with a pharmaceutically acceptable carrier, diluent or excipient.

According to another example, the present technology relates to a pharmaceutical composition for a use as defined in any one of the aforementioned examples, the composition comprising a compound as herein defined together with a pharmaceutically acceptable carrier, diluent or excipient.

In a further example, the present technology relates to the use of a compound as herein defined for the treatment of a disease or disorder selected from a proliferative disease or disorder, a developmental anomaly caused by dysregulation of the RAS-ERK signaling cascade (RASopathies), or an inflammatory disease or an immune system disorder.

In another aspect, there is provided the use of a compound as defined above in the manufacture of a medicament for the treatment of a disease or disorder selected from a proliferative disease or disorder, a developmental anomaly caused by dysregulation of the RAS-ERK signaling cascade (RASopathies), or an inflammatory disease or an immune system disorder.

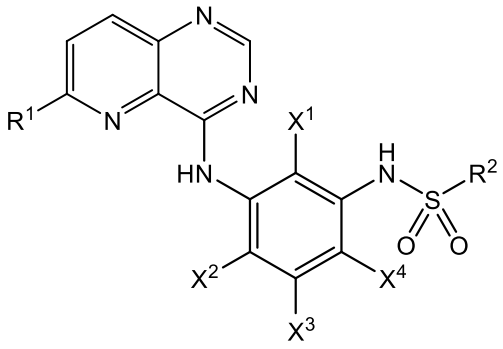
The present technology also further relates to a method for the treatment of a disease or disorder selected from a proliferative disease or disorder, a developmental anomaly caused by dysregulation of the RAS-ERK signaling cascade (RASopathies), or an inflammatory disease or an immune system disorder, comprising administering a compound as herein defined to a subject in need thereof. A method for inhibiting abnormal proliferation of cells, comprising contacting the cells with a compound as defined herein is also contemplated.

In one example of the above uses and methods, the disease or disorder is selected from a neoplasm and a developmental anomaly, for instance, a disease or disorder associated with a RAF gene mutation (e.g. ARAF, BRAF, or CRAF), a disease or disorder associated with a RAS gene mutation (e.g. KRAS), or a disease or disorder associated with both a RAF gene mutation and a RAS gene mutation. In one example, the disease or disorder is associated with a receptor

tyrosine kinase mutation or amplification (e.g. EGFR, HER2) or a mutation in a regulator of RAS downstream of the receptor (e.g. SOS1 gain of function, NF1 loss of function).

CLAIMS

1. A compound of Formula I:



Formula I

wherein:

R^1 is selected from substituted or unsubstituted OR^3, SR^3, NH_2, NHR^3, $N(R^3)_2$, C_{3-8}cycloalkyl, C_{4-8}heterocycloalkyl, C_{6-10}aryl and C_{5-10}heteroaryl, for example, selected from substituted or unsubstituted C_{6-10}aryl and C_{5-10}heteroaryl;

R^2 is selected from substituted C_6aryl or C_{5-10}heteroaryl, substituted or unsubstituted C_{4-8}heterocycloalkyl, and $N(R^3)_2$;

R^3 is independently in each occurrence selected from substituted or unsubstituted C_{1-8}alkyl, C_{3-8}cycloalkyl, C_{4-8}heterocycloalkyl, C_{6-10}aryl and C_{5-10}heteroaryl;

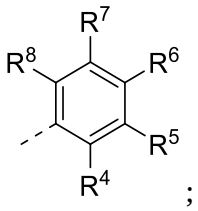
X^1 is halo, perhaloalkyl, CN, NO_2, sulfonate, alkylsulfonyl, alkylcarbonyl, carboxylate, alkoxycarbonyl, or aminocarbonyl;

X^2 is selected from H, halo, perhaloalkyl, CN, NO_2, sulfonate, alkylsulfonyl, alkylcarbonyl, carboxylate, alkoxycarbonyl, and aminocarbonyl;

X^3 and X^4 are each selected from H, halo, perhaloalkyl, CN, NO_2, sulfonate, alkylsulfonyl, alkylcarbonyl, carboxylate, alkoxycarbonyl, aminocarbonyl, C_{1-3}alkyl, C_{3-4}cycloalkyl, and OC_{1-3}alkyl;

or a pharmaceutically acceptable salt or solvate thereof.

2. The compound of claim 1, wherein R^2 is a group of the formula:



;

wherein:

R^4 is selected from H, F, Cl, Br, CN, and a substituted or unsubstituted C_{1-3}alkyl, C_{3-4}cycloalkyl or OC_{1-3}alkyl;

R^5 is selected from H, F, Cl, CN, and a substituted or unsubstituted C_{1-3}alkyl, C_{3-4}cycloalkyl or OC_{1-3}alkyl;

R^6 is selected from H, F, Cl, Br, NO_2, NH_2, and a substituted or unsubstituted C_{1-3}alkyl, C_{3-4}cycloalkyl or OC_{1-3}alkyl;

R^7 is selected from H, F, Cl, and a substituted or unsubstituted C_{1-3}alkyl;

R^8 is selected from H, F, and a substituted or unsubstituted C_{1-3}alkyl;

or R^4 and R^5 or R^5 and R^6 are taken together with their adjacent carbon atoms to form a substituted or unsubstituted carbocycle or heterocycle provided that the heterocycle is not a benzoxazolinone; and

(---) represents a bond;

wherein when R^4 is H or F, then at least one of R^5, R^6, R^7 or R^8 is other than H or F; and

wherein when R^5 is CN, then at least one of R^4, R^6, R^7 or R^8 is other than H.

3. The compound of claim 2, wherein:

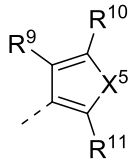
R^4 is selected from Cl and a substituted or unsubstituted C_{1-3}alkyl;

R^5 is selected from H, F, Cl, and a substituted or unsubstituted C_{1-3}alkyl;

R^6 is selected from H, F, Cl, a substituted or unsubstituted C_{1-3}alkyl, and a substituted or unsubstituted OC_{1-3}alkyl; and

R^7 and R^8 are each H.

4. The compound of claim 1, wherein R^2 is a group of the formula:



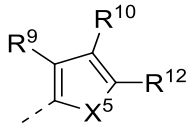
wherein:

X^5 is selected from NH, NC_{1-3}alkyl, NC_{3-4}cycloalkyl, O and S;

R^9, R^{10}, R^{11} are each independently selected from H, F, Cl, CN, and a substituted or unsubstituted C_{1-3}alkyl, C_{3-4}cycloalkyl, $C(O)OC_{1-3}$alkyl or OC_{1-3}alkyl, provided that one of R^9 and R^{11} is H and the other is different from H; and

(---) represents a bond.

5. The compound of claim 1, wherein R^2 is a group of the formula:



wherein:

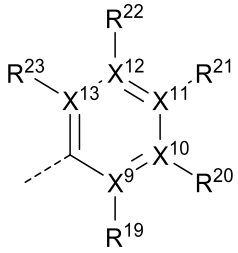
X^5 is selected from NH, NC_{1-3}alkyl, NC_{3-4}cycloalkyl, O and S;

R^9 is selected from F, Cl, CN, and a substituted or unsubstituted C_{1-3}alkyl, C_{3-4}cycloalkyl, $C(O)OC_{1-3}$alkyl or OC_{1-3}alkyl;

R^{10} and R^{12} are each independently selected from H, F, Cl, CN, and a substituted or unsubstituted C_{1-3}alkyl, C_{3-4}cycloalkyl, $C(O)OC_{1-3}$alkyl or OC_{1-3}alkyl; and

(---) represents a bond.

6. The compound of claim 1, wherein R^2 is a group of the formula:



wherein:

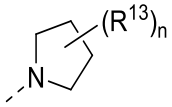
X^9, X^{10}, X^{11}, X^{12}, and X^{13} are independently selected from N and C, wherein at least one and at most two of X^9, X^{10}, X^{11}, X^{12}, and X^{13} are N; and

R^{19}, R^{20}, R^{21}, R^{22} and R^{23} are selected from H, F, Cl, Br, CN, NO_2, NH_2, and a substituted or unsubstituted $C_{1\text{-}3}$alkyl, $C_{3\text{-}4}$cycloalkyl or $OC_{1\text{-}3}$alkyl, or are absent when their attached X^9, X^{10}, X^{11}, X^{12}, or X^{13} is N;

wherein at least one of X^9 and X^{13} is not N; and

wherein when one of X^9 and X^{13} is N, then the other is not N or CH.

7. The compound of claim 1, wherein R^2 is a group of the formula:



wherein:

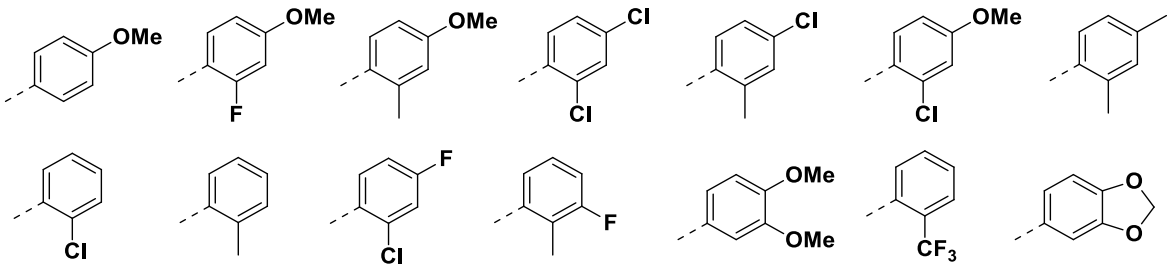
R^{13} is independently in each occurrence selected from F, Cl, and a substituted or unsubstituted $C_{1\text{-}3}$alkyl, $C_{3\text{-}4}$cycloalkyl, or $C_{1\text{-}3}$alkoxy;

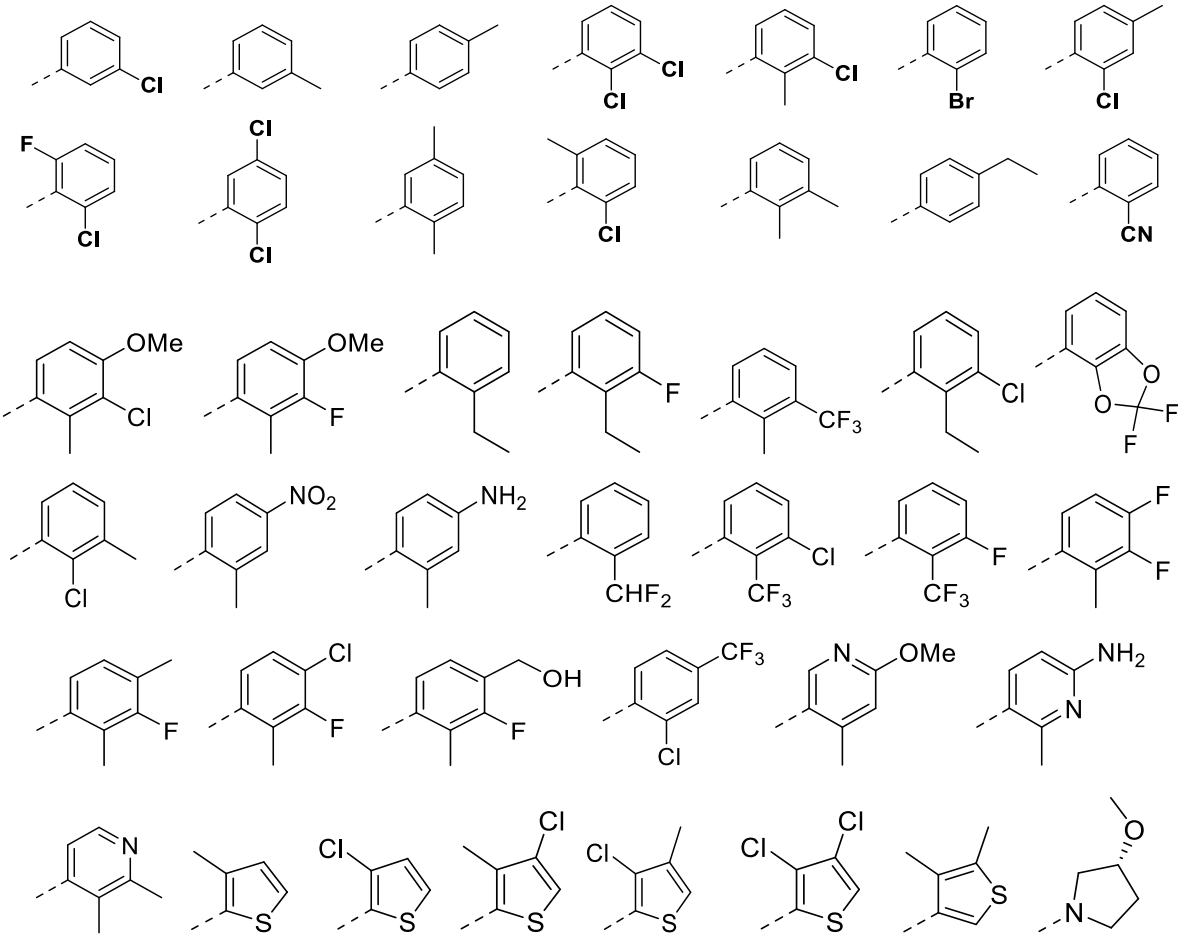
n is an integer selected from 0 to 8; or

n is between 2 and 8 and two R^{13} are taken together with their adjacent carbon atoms to form a $C_{3\text{-}4}$cycloalkyl;

(---) represents a bond.

8. The compound of claim 1, wherein R^2 is a group selected from:

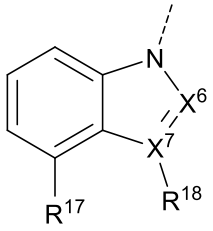




wherein (---) represents a bond.

9. The compound of any one of claims 1 to 8, wherein R^1 is a substituted or unsubstituted group selected from thienyl, imidazolyl, pyrazolyl, triazolyl, thiazolyl, pyridyl, pyrimidinyl, indolyl, indazolyl, benzimidazolyl, benzotriazolyl, pyrrolopyridinyl (e.g. pyrrolo[3,2-b]pyridinyl or pyrrolo[3,2-c]pyridinyl), pyrazolopyridinyl (e.g. pyrazolo[1,5-a]pyridinyl), purinyl, imidazopyrazinyl (e.g. imidazo[4,5-b]pyrazinyl), and quinolyl (quinolinyl).

10. The compound of any one of claims 1 to 8, wherein R^1 is a group of the formula:



wherein:

R^{17} is selected from H, OH, halo, CN, NO_2, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, OC_{1-6}alkyl, C_{5-10}heteroaryl, C_{3-10}cycloalkyl, C_{4-10}heterocycloalkyl, $C(O)R^{15}$, $C(O)N(R^{14})_2$, SO_2R^{15}, $SO_2N(R^{14})_2$, $N(R^{16})C(O)R^{15}$, $N(R^{16})SO_2R^{15}$, $N(R^{16})C(O)N(R^{14})_2$, $N(R^{16})SO_2N(R^{14})_2$, $N(R^{14})_2$, $P(O)(R^{15})_2$, $CH_2C(O)R^{15}$, $CH_2C(O)N(R^{14})_2$, $CH_2SO_2R^{15}$, $CH_2SO_2N(R^{14})_2$, $CH_2N(R^{16})C(O)R^{15}$, $CH_2N(R^{16})SO_2R^{15}$, $CH_2N(R^{16})C(O)N(R^{14})_2$, $CH_2N(R^{16})SO_2N(R^{14})_2$, and $CH_2N(R^{14})_2$;

X^6 is N or CH; and

X^7 is N and R^{18} is absent; or

X^7 is C and R^{18} is selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, OC_{1-6}alkyl, C_{5-10}heteroaryl, C_{3-10}cycloalkyl, C_{4-10}heterocycloalkyl, $C(O)R^{15}$, $C(O)N(R^{14})_2$, SO_2R^{15}, $SO_2N(R^{14})_2$, $N(R^{16})C(O)R^{15}$, $N(R^{16})SO_2R^{15}$, $N(R^{16})C(O)N(R^{14})_2$, $N(R^{16})SO_2N(R^{14})_2$, $N(R^{14})_2$, $P(O)(R^{15})_2$, $CH_2C(O)R^{15}$, $CH_2C(O)N(R^{14})_2$, $CH_2SO_2R^{15}$, $CH_2SO_2N(R^{14})_2$, $CH_2N(R^{16})C(O)R^{15}$, $CH_2N(R^{16})SO_2R^{15}$, $CH_2N(R^{16})C(O)N(R^{14})_2$, $CH_2N(R^{16})SO_2N(R^{14})_2$, and $CH_2N(R^{14})_2$;

wherein ;

R^{14} is independently in each occurrence selected from H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{4-10}heterocycloalkyl, C_6aryl, and C_{5-10}heteroaryl, or two R^{14} are taken together with their adjacent nitrogen atom to form a C_{4-10}heterocycloalkyl group;

R^{15} is independently in each occurrence selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_6aryl, and C_{5-10}heteroaryl; and

R^{16} is independently in each occurrence selected from H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_6aryl, and C_{5-10}heteroaryl;

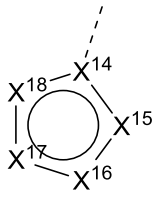
wherein said alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl group is optionally further substituted; and

wherein (---) represents a bond.

11. The compound of claim 10, wherein X^7 is N, R^{17} is selected from H, OH, CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, OC_{1-6}alkyl, C_{5-10}heteroaryl, C_{3-10}cycloalkyl, C_{4-10}heterocycloalkyl, $C(O)R^{15}$, $C(O)N(R^{14})_2$, SO_2R^{15}, $SO_2N(R^{14})_2$, $N(R^{16})C(O)R^{15}$, $N(R^{16})SO_2R^{15}$, $N(R^{16})C(O)N(R^{14})_2$, $N(R^{16})SO_2N(R^{14})_2$, $N(R^{14})_2$, $P(O)(R^{15})_2$, $CH_2C(O)R^{15}$, $CH_2C(O)N(R^{14})_2$, $CH_2SO_2R^{15}$, $CH_2SO_2N(R^{14})_2$, $CH_2N(R^{16})C(O)R^{15}$, $CH_2N(R^{16})SO_2R^{15}$,

$CH_2N(R^{16})C(O)N(R^{14})_2$, $CH_2N(R^{16})SO_2N(R^{14})_2$, and $CH_2N(R^{14})_2$, and R^{18} is absent, wherein said alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, or heteroaryl is optionally further substituted.

12. The compound of any one of claims 1 to 8, wherein R^1 is a group of the formula:



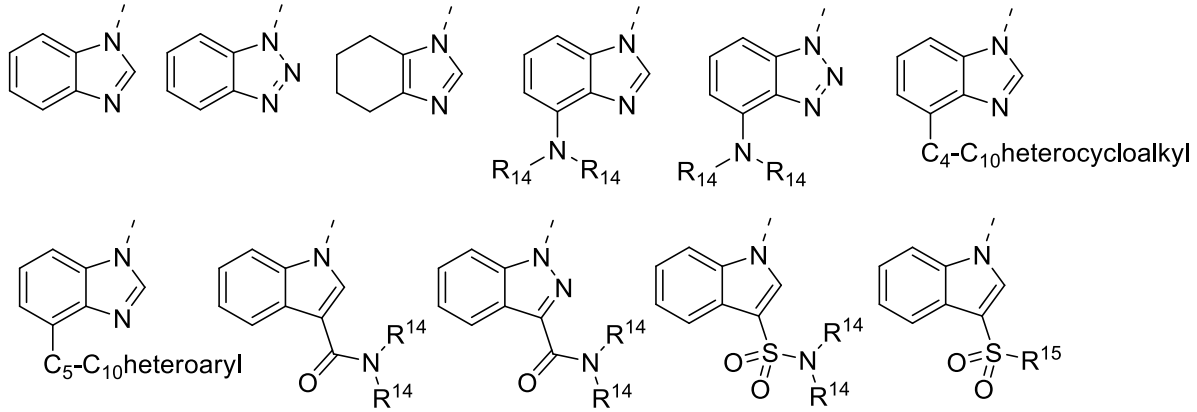
wherein:

X^{14} is selected from C and N;

X^{15}, X^{16}, X^{17}, and X^{18} are independently selected from O, N, S, and CR^{17}, wherein R^{17} is as previously defined;

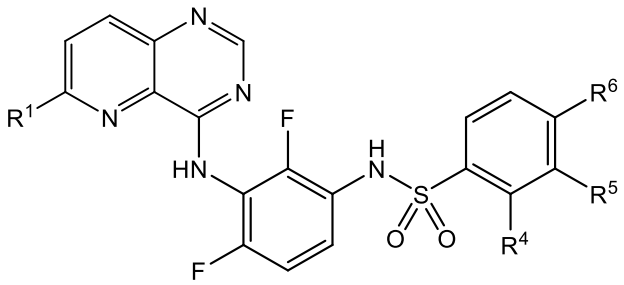
wherein at least one and at most three of X^{14}, X^{15}, X^{16}, X^{17}, and X^{18} are O, N, or S, and two double bonds and present in the cycle in order for aromaticity to be maintained.

13. The compound of any one of claims 1 to 8, wherein R^1 is selected from:



wherein R^{14} is as previously defined herein and (---) represents a bond.

14. The compound of claim 1, wherein said compound is of Formula II:

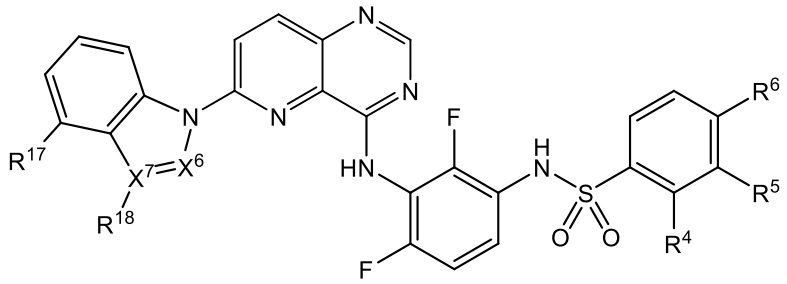


Formula II

wherein R^1, R^4, R^5, and R^6 are each independently as defined herein, preferably R^4 is selected from Cl, Br and Me, R^5 is selected from H, F, Cl or methyl, and R^6 is selected from H, F, Cl, Me and OMe;

or a pharmaceutically acceptable salt or solvate thereof.

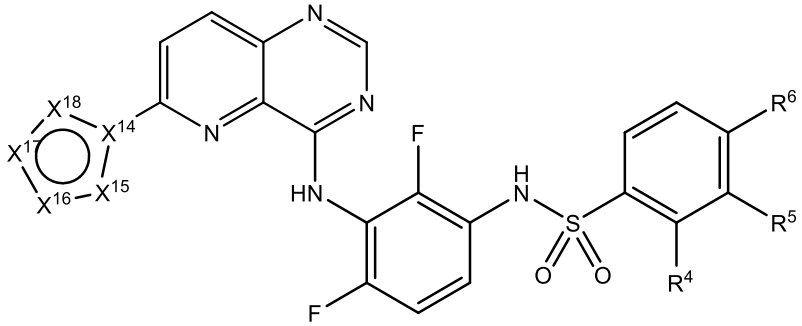
15. The compound of claim 14, wherein said compound if a compound of Formula IV:



Formula IV

wherein X^6, X^7, R^4, R^5, R^6, R^{17}, and R^{18} are each independently as previously defined.

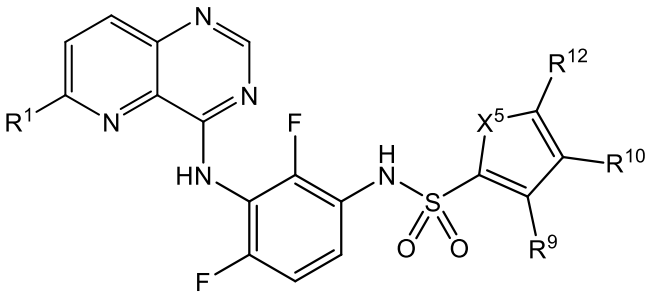
16. The compound of claim 14, wherein said compound if a compound of Formula V:



Formula V

wherein R^4, R^5, R^6, X^{14}, X^{15}, X^{16}, X^{17}, and X^{18} are each independently as previously defined.

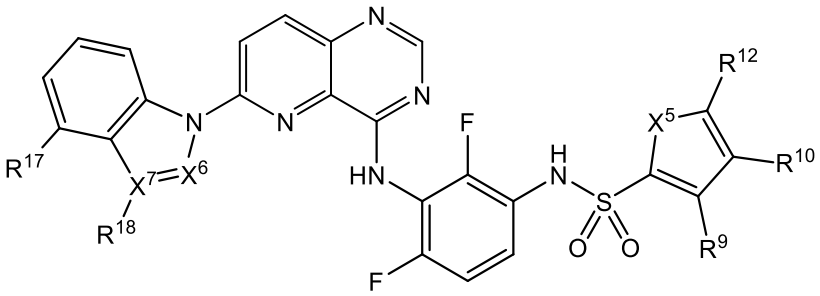
17. The compound of claim 1, wherein said compound is of Formula III:



Formula III

wherein R^1, R^9, R^{10}, R^{12}, and X^5 are each independently as previously defined.

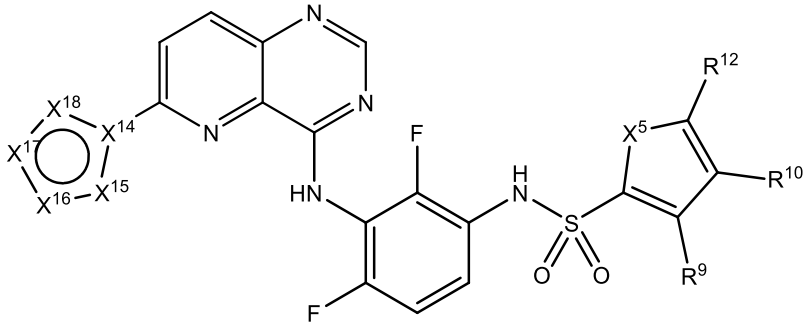
18. The compound of claim 17, wherein said compound is of Formula VI:



Formula VI

wherein R^9, R^{10}, R^{12}, R^{17}, R^{18}, X^5, X^6, and X^7, are each independently as previously defined.

19. The compound of claim 17, wherein said compound is of Formula VII:

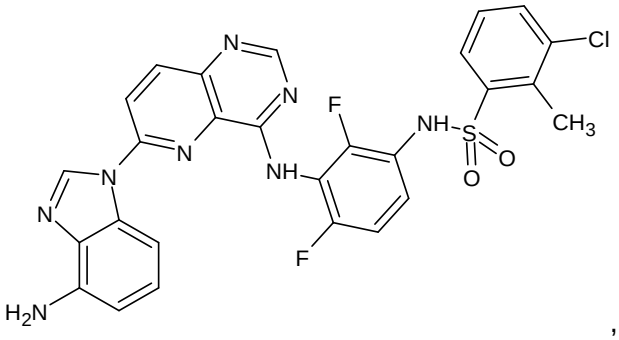
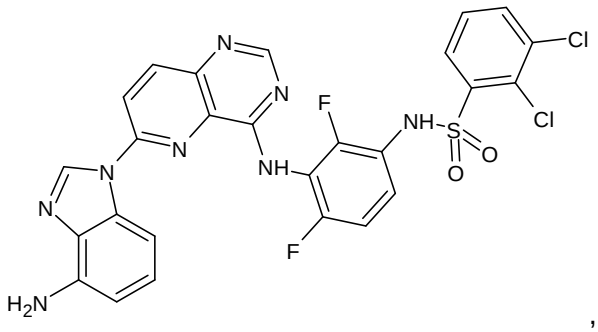
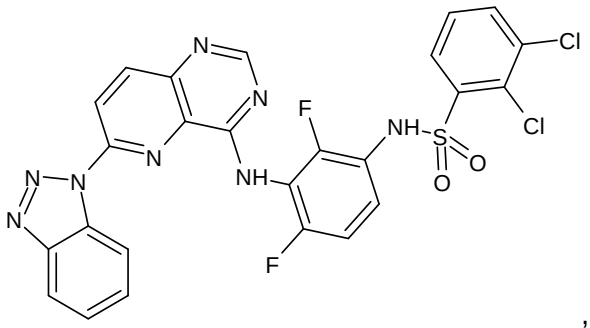
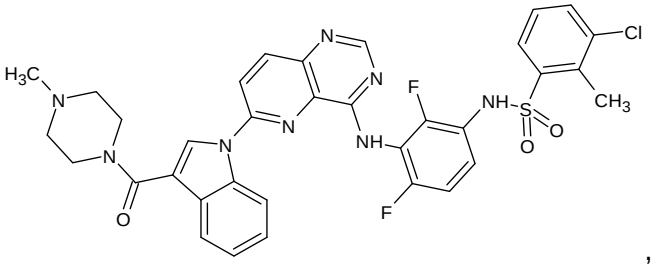
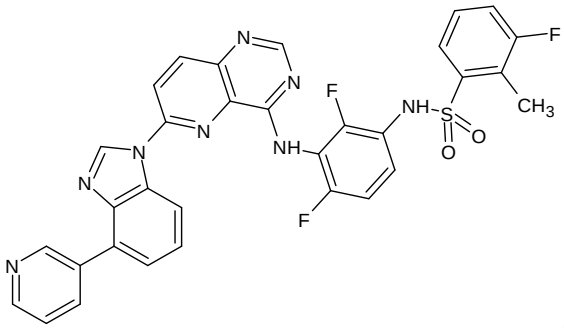
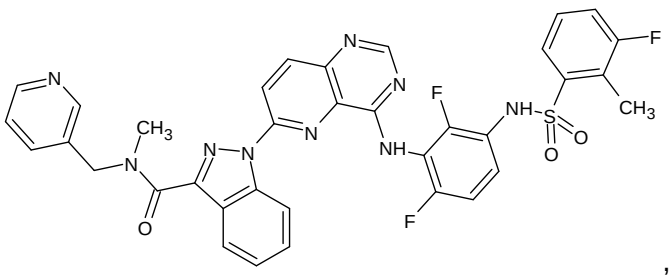
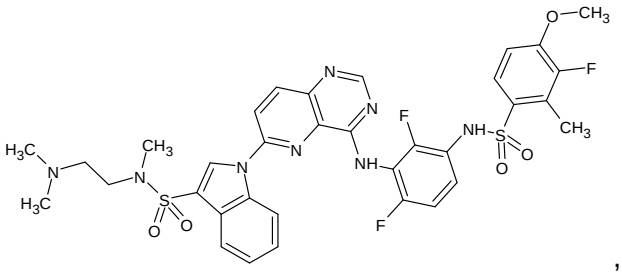
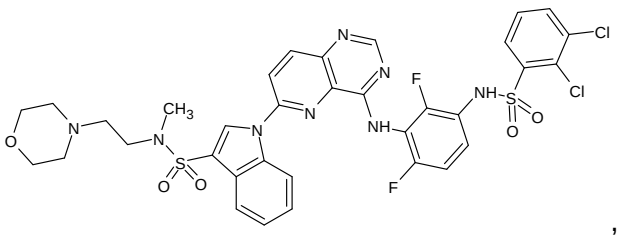


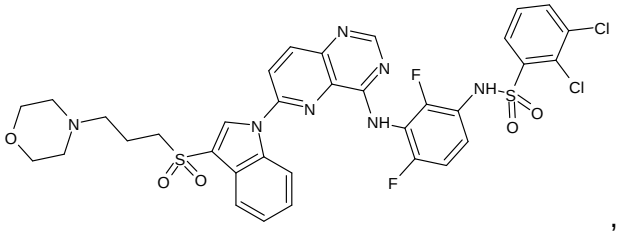
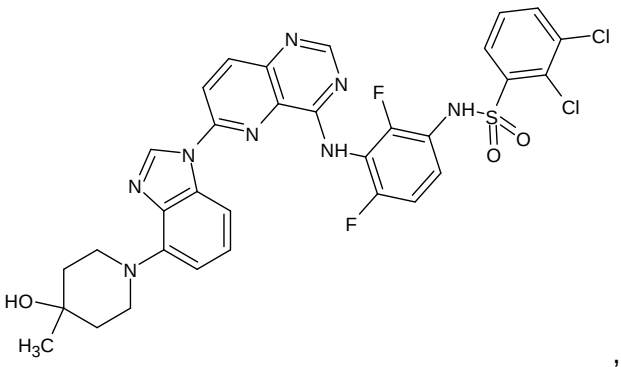
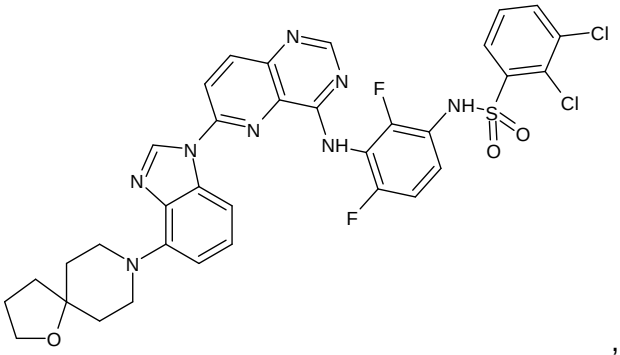
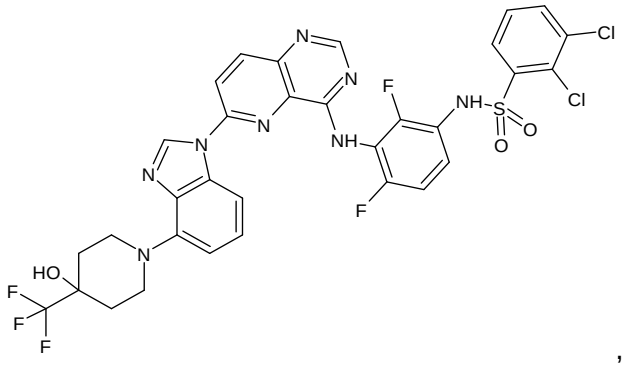
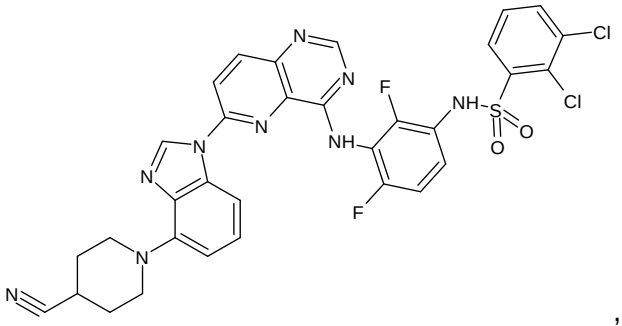
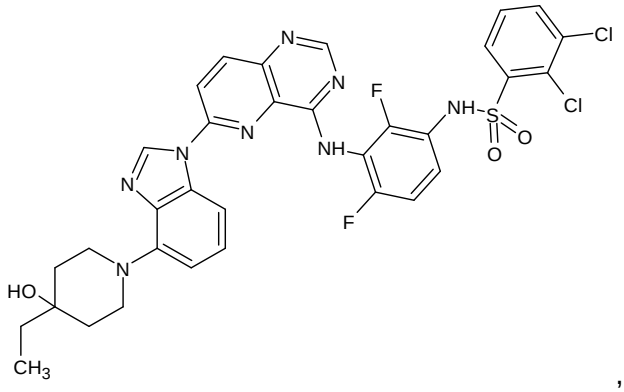
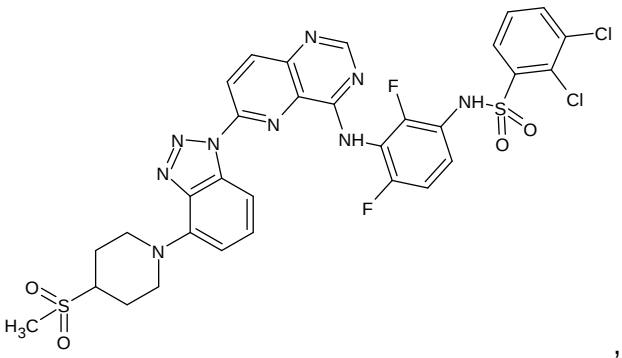
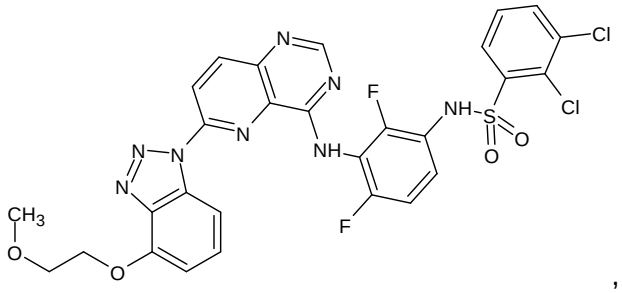
Formula VII

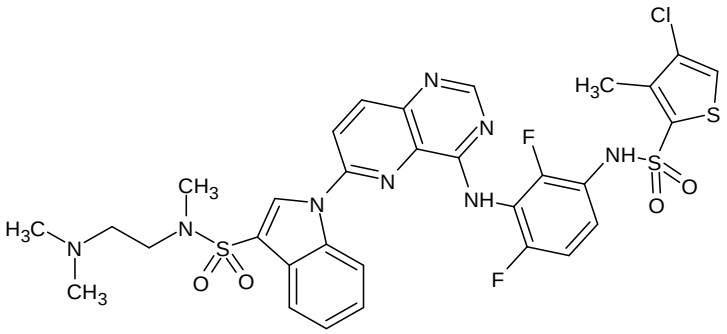
wherein R^9, R^{10}, R^{12}, X^5, X^{14}, X^{15}, X^{16}, X^{17} and X^{18} are each independently as previously defined.

20. The compound of claim 1, wherein said compound is selected from Examples 1 to 691 as defined herein, or a salt and/or solvate thereof.

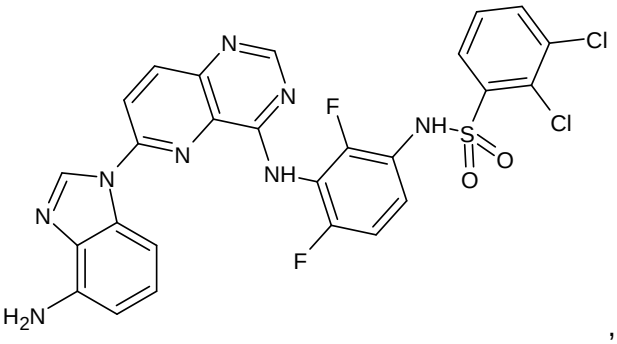
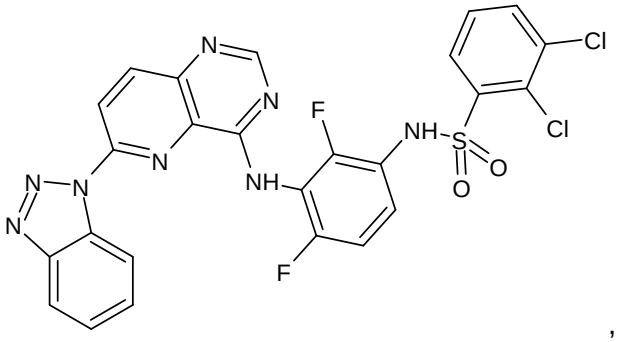
21. The compound of claim 1, or a pharmaceutically acceptable salt or solvate thereof, wherein said compound is selected from:

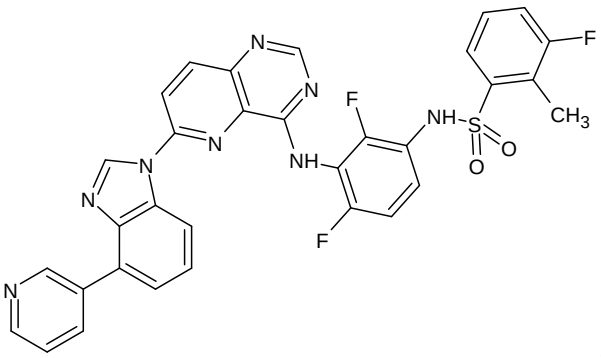
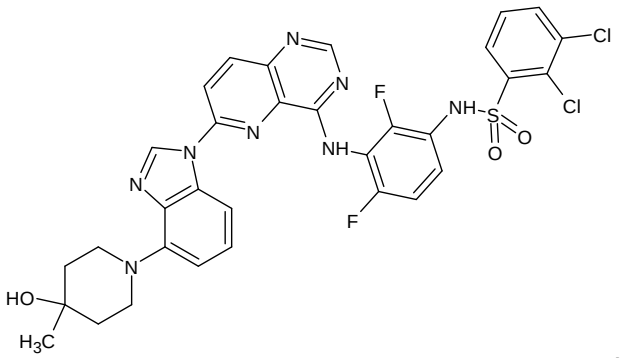

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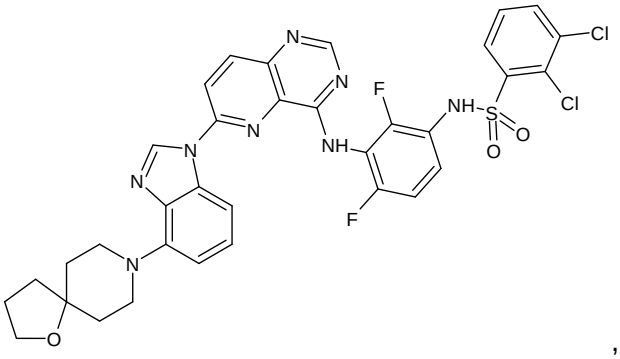
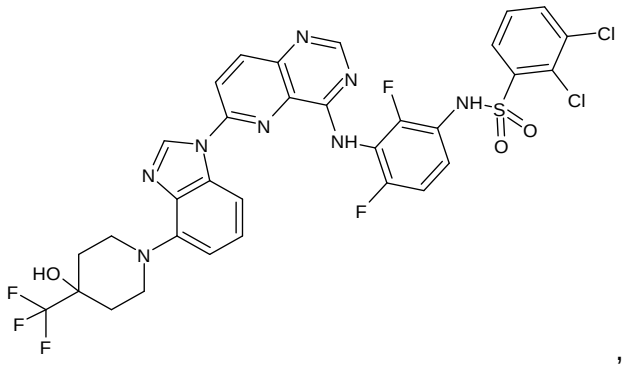

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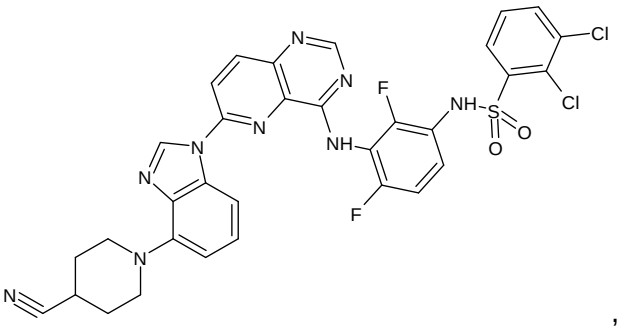
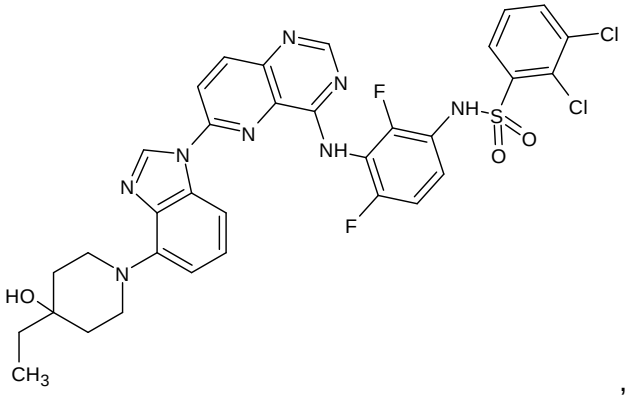
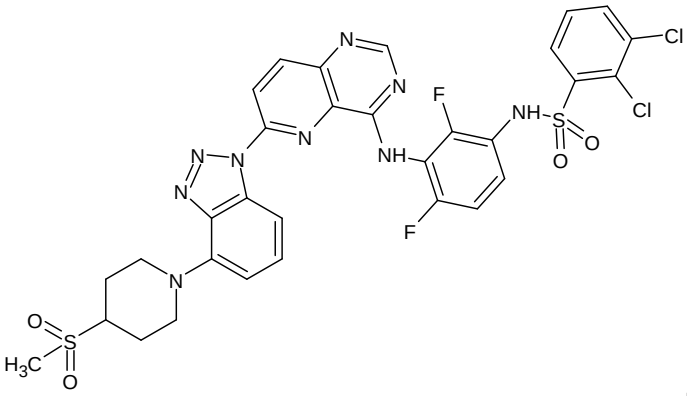
and  .

22. The compound of claim 1, or a pharmaceutically acceptable salt or solvate thereof, wherein said compound is selected from:

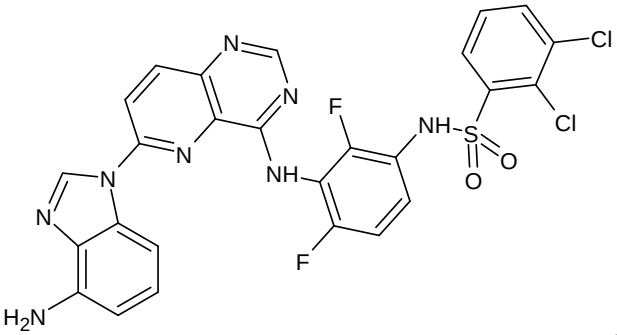
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and .

23. The compound of claim 1, or a pharmaceutically acceptable salt or solvate thereof, wherein said compound is:


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24. A pharmaceutical composition comprising a compound as defined in any one of claims 1 to 23, together with a pharmaceutically acceptable carrier, diluent or excipient.

25. Use of a compound as defined in any one of claims 1 to 23 in the manufacture of a medicament for the treatment of a disease or disorder selected from a proliferative disease or disorder, a developmental anomaly caused by dysregulation of the RAS-ERK signaling cascade (RASopathies), or an inflammatory disease or an immune system disorder.

26. The use of claim 25, wherein said disease or disorder is associated with a RAF gene mutation (e.g. ARAF, BRAF, or CRAF).

27. The use of claim 26, wherein said disease is a neoplasm selected from melanoma, thyroid carcinoma (e.g. papillary thyroid carcinoma), colorectal, ovarian, breast cancer, endometrial cancer, liver cancer, sarcoma, stomach cancer, pancreatic carcinoma, Barret's adenocarcinoma, glioma (e.g. ependymoma), lung cancer (e.g. non-small cell lung cancer), head and neck cancer, acute lymphoblastic leukemia, acute myelogenous leukemia, non-Hodgkin's lymphoma, and hairy-cell leukemia.