HETERO-ATOM CONTAINING COMPOUNDS AND USES THEREOF

CROSS-REFERENCE

[0001] This application claims the benefit of U.S. Provisional Patent Application Nos. 63/282,614 filed on November 23, 2021 and 63/406,215 filed on September 13, 2022, each of which is incorporated by reference in its entirety.

BACKGROUND

[0002] PTPN2 encodes a protein tyrosine phosphatase that has been implicated in a number of intracellular signaling pathways of immune cells. PTPN2 can negatively regulate αβ TCR T cell receptor (TCR) signaling by dephosphorylating and inactivating, e.g., the Src family kinase including LCK. In addition, PTPN2 can antagonize growth factor or cytokine-mediated signaling required for T cell function, homeostasis, and/or differentiation by dephosphorylating and inactivating JAK family kinases, e.g., JAK-1 and JAK-3, and/or target substrates of the JAK family kinases, e.g., STAT-1, STAT-3, and STAT-5.

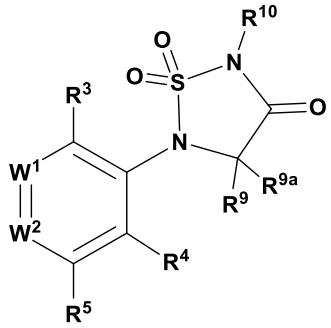
[0003] Based on genome-wide association studies, PTPN2 single nucleotide polymorphisms (SNPs) have been linked with the development of several human autoimmune diseases including, but not limited to, type 1 diabetes, rheumatoid arthritis, Crohn's disease, and celiac disease. For example, a PTPN2 variant, rs1893217(C), has been associated with about a 40% decrease in PTPN2 mRNA expression in CD4+ T cells, as well as the development of type 1 diabetes. In addition, PTPN2 mRNA expression levels in lung cancer tissues have been shown to be higher than those in normal lung tissues or adjacent normal tissues, such overexpression of PTPN2 promoting proliferation of lung cancer cells. Furthermore, two PTPN2 SNPs, rs2847297 and rs2847282, have been associated with a decrease in both PTPN2 mRNA expression and lung cancer risk, especially squamous cell lung carcinoma risk.

[0004] Cancer is the second leading cause of human death. There were close to 10 million deaths from cancer worldwide in 2018 and 17 million new cases were diagnosed. In the United States alone, cancer causes the death of over a half-million people annually, with some 1.7 million new cases diagnosed per year (excluding basal cell and squamous cell skin cancers). Lung, liver, stomach, and bowel cancers account for more than four in ten of all cancer deaths worldwide.

[0005] Adoptive transfer of gene modified lymphoid cells, particularly T cells (i.e., ACT), is an emerging treatment for cancer. While efficacy has been demonstrated in a range of hematological cancers including ALL, CLL, DLBCL, FL, and multiple myeloma, its efficacy in treating solid tumors is still yet to be established. Current immune cell therapy (e.g., CAR-T therapy) suffers from a number of profound deficiencies. T cell manufacturing and clonal expansion are highly inefficient and costly. When introduced in to a patient, T cell’s anti-tumor activity and numbers can be reduced in the immunosuppressive microenvironment often found in a tumor. In addition, CAR-T therapy has been limited by life threatening toxicities in over 30% of patients. Toxicities primarily manifest as cytokine release syndrome (CRS) characterized by an early phase with fever, hypotension and elevations of various cytokines, and a later phase associated with life-ending neurologic events.

BRIEF SUMMARY

[0005a] In an aspect of the present disclosure, there is provided a compound of Formula (IIa), or a pharmaceutically acceptable salt or solvate thereof:



Formula (IIa);

wherein:

W^1 is $C(R^1)$, and W^2 is $C(R^{2a})$ or N;

R^1 is selected from C_{5-12}cycloalkyl, 5 to 12 membered heterocycloalkyl, C_{6-12}aryl, and 5 to 12 membered heteroaryl, wherein C_{5-12}cycloalkyl, 5 to 12 membered heterocycloalkyl, C_{6-12}aryl, and 5 to 12 membered heteroaryl are substituted with one or more substituents independently selected from R^6 and $R^{6'}$, wherein ring heteroatoms of the 5 to 12 membered heterocycloalkyl and 5 to 12 membered heteroaryl are independently selected from N, O, and S;

R^{2a} are independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, $-OR^{12}$, $-SR^{12}$, $-N(R^{12})(R^{13})$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)OR^{12}$, $-N(R^{14})S(O)_2R^{15}$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})$, $-S(=O)(=NH)N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, and $-CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, and C_{2-6}alkynyl are optionally substituted with one, two, or three R^{20b};

R^3 is halogen;

R^4 is OH;

R^5 is hydrogen;

each R^6 is independently selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12}$, $-SR^{12}$, $-N(R^{12})(R^{13})$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)OR^{12}$, $-N(R^{14})S(O)_2R^{15}$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})$, $-S(=O)(=NH)N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, and $-CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{26};

each $R^{6'}$ is independently selected from -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12}$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-C(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, and $-CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{26};

R^9 and R^{9a} are independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12}$, $-SR^{12}$, $-N(R^{12})(R^{13})$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)OR^{12}$, $-N(R^{14})S(O)_2R^{15}$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})$, $-S(=O)(=NH)N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, and -

$CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20i}; or R^9 and R^{9a} are combined to form a C_{3-6}cycloalkyl or a C_{2-9}heterocycloalkyl, wherein the C_{3-6}cycloalkyl and C_{2-9}heterocycloalkyl are optionally substituted with one, two, or three R^{20i};

R^{10} is independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-R^{16}$, $-OR^{16}$, $-N(R^{12})(R^{16})$, $-OR^{12}$, $-SR^{12}$, $-N(R^{12})(R^{13})$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)OR^{12}$, $-N(R^{14})S(O)_2R^{15}$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})$, $-S(=O)(=NH)N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, and $-CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20j};

each R^{12} is independently selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, $-CH_2$-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, $-CH_2$-C_{2-9}heterocycloalkyl, C_{6-10}aryl, $-CH_2$-C_{6-10}aryl, and C_{1-9}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, $-CH_2$-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, $-CH_2$-C_{2-9}heterocycloalkyl, C_{6-10}aryl, $-CH_2$-C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20k};

each R^{13} is independently selected from hydrogen, C_{1-6}alkyl, and C_{1-6}haloalkyl; or R^{12} and R^{13}, together with the nitrogen to which they are attached, form a C_{2-9}heterocycloalkyl ring optionally substituted with one, two, or three R^{20l};

each R^{14} is independently selected from hydrogen, C_{1-6}alkyl, and C_{1-6}haloalkyl;

each R^{15} is independently selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{1-6}heteroalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{1-6}heteroalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20m};

each R^{16} is independently selected from $-C_{1-6}$alkylene-$OP(O)(OR^{16a})(OR^{16b})$ and $-P(O)(OR^{16a})(OR^{16b})$; wherein the C_{1-6}alkylene is optionally substituted with one, two, or three R^{20n}; or $-C_{1-6}$alkylene-$OC(O)$-R^{16c} wherein C_{1-6}alkylene is optionally substituted with one, two, or three R^{20n};

each R^{16a} and R^{16b} is independently selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, $-CH_2$-C_{3-10}cycloalkyl, $-CH_2$-C_{2-9}heterocycloalkyl, C_{6-10}aryl, $-CH_2$-C_{6-10}aryl, and C_{1-9}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, $-CH_2$-C_{3-10}cycloalkyl, $-CH_2$-C_{2-9}heterocycloalkyl, C_{6-10}aryl, $-CH_2$-C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20o};

R^{16c} is selected from halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, $-CH_2$-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, $-CH_2$-C_{2-9}heterocycloalkyl, C_{6-10}aryl, $-CH_2$-C_{6-10}aryl, C_{1-9}heteroaryl, $-CH_2$-C_{1-9}heteroaryl, $-OR^{21}$, $-SR^{21}$, $-N(R^{22})(R^{23})$, $-C(O)OR^{22}$, $-C(O)N(R^{22})(R^{23})$, $-C(O)C(O)N(R^{22})(R^{23})$, $-OC(O)N(R^{22})(R^{23})$, $-N(R^{24})C(O)N(R^{22})(R^{23})$, $-N(R^{24})C(O)OR^{25}$, $-N(R^{24})C(O)R^{25}$, $-N(R^{24})S(O)_2R^{25}$, $-C(O)R^{25}$, $-S(O)_2R^{25}$, $-S(O)_2N(R^{22})(R^{23})$, $-OCH_2C(O)OR^{22}$, and $-OC(O)R^{25}$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, $-CH_2$-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, $-CH_2$-C_{2-9}heterocycloalkyl, C_{6-10}aryl, $-CH_2$-C_{6-10}aryl, $-CH_2$-C_{1-9}heteroaryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three of R^{20o};

each R^{20b}, R^{20i}, R^{20j}, R^{20k}, R^{20l}, R^{20m}, R^{20n}, and R^{20o} are each independently selected from oxo, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, $-CH_2$-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, $-CH_2$-C_{2-9}heterocycloalkyl, C_{6-10}aryl, $-CH_2$-C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{21}$, $-SR^{21}$, $-N(R^{22})(R^{23})$, $-C(O)OR^{22}$, -

$C(O)N(R^{22})(R^{23})$, $-C(O)C(O)N(R^{22})(R^{23})$, $-OC(O)N(R^{22})(R^{23})$, $-N(R^{24})C(O)N(R^{22})(R^{23})$, $-N(R^{24})C(O)OR^{22}$, $-N(R^{24})C(O)R^{25}$, $-N(R^{24})S(O)_2R^{25}$, $-C(O)R^{25}$, $-S(O)_2R^{25}$, $-S(O)_2N(R^{22})(R^{23})$, $-OCH_2C(O)OR^{22}$, and $-OC(O)R^{25}$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, $-CH_2-C_{3-10}$cycloalkyl, C_{2-9}heterocycloalkyl, $-CH_2-C_{2-9}$heterocycloalkyl, C_{6-10}aryl, $-CH_2-C_{6-10}$aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three groups independently selected from halogen, oxo, -CN, C_{1-6}alkyl optionally substituted with one or more R^{26}, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy, $-OR^{21}$, $-SR^{21}$, $-N(R^{22})(R^{23})$, $-C(O)OR^{22}$, $-C(O)N(R^{22})(R^{23})$, $-C(O)C(O)N(R^{22})(R^{23})$, $-OC(O)N(R^{22})(R^{23})$, $-N(R^{24})C(O)N(R^{22})(R^{23})$, $-N(R^{24})C(O)OR^{25}$, $-N(R^{24})C(O)R^{25}$, $-N(R^{24})S(O)_2R^{25}$, $-C(O)R^{25}$, $-S(O)_2R^{25}$, $-S(O)_2N(R^{22})(R^{23})$, and $-OC(O)R^{25}$;

each R^{21} is independently selected from H, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl;

each R^{22} is independently selected from H, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl;

each R^{23} is independently selected from H and C_{1-6}alkyl;

each R^{24} is independently selected from H and C_{1-6}alkyl;

each R^{25} is selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{1-6}heteroalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl;

each R^{26} is independently selected from oxo, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12}$, $-SR^{12}$, $-N(R^{12})(R^{13})$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)OR^{12}$, $-N(R^{14})S(O)_2R^{15}$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})$, $-S(=O)(=NH)N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, and $-CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{27};

each R^{27} is independently selected from oxo, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12}$, $-SR^{12}$, $-N(R^{12})(R^{13})$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)OR^{12}$, $-N(R^{14})S(O)_2R^{15}$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})$, $-S(=O)(=NH)N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, and $-CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20f}; and

each R^{20f} is independently selected from oxo, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, $-CH_2-C_{3-10}$cycloalkyl, C_{2-9}heterocycloalkyl, $-CH_2-C_{2-9}$heterocycloalkyl, C_{6-10}aryl, $-CH_2-C_{6-10}$aryl, C_{1-9}heteroaryl, $-OR^{21}$, $-SR^{21}$, $-N(R^{22})(R^{23})$, $-C(O)OR^{22}$, $-C(O)N(R^{22})(R^{23})$, $-C(O)C(O)N(R^{22})(R^{23})$, $-OC(O)N(R^{22})(R^{23})$, $-N(R^{24})C(O)N(R^{22})(R^{23})$, $-N(R^{24})C(O)OR^{22}$, $-N(R^{24})C(O)R^{25}$, $-N(R^{24})S(O)_2R^{25}$, $-C(O)R^{25}$, $-S(O)_2R^{25}$, $-S(O)_2N(R^{22})(R^{23})$, $-OCH_2C(O)OR^{22}$, and $-OC(O)R^{25}$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, $-CH_2-C_{3-10}$cycloalkyl, C_{2-9}heterocycloalkyl, $-CH_2-C_{2-9}$heterocycloalkyl, C_{6-10}aryl, $-CH_2-C_{6-10}$aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three groups independently selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy, $-OR^{21}$, $-SR^{21}$, $-N(R^{22})(R^{23})$, $-C(O)OR^{22}$, $-C(O)N(R^{22})(R^{23})$, $-C(O)C(O)N(R^{22})(R^{23})$, $-OC(O)N(R^{22})(R^{23})$, $-N(R^{24})C(O)N(R^{22})(R^{23})$, $-N(R^{24})C(O)OR^{25}$, $-N(R^{24})C(O)R^{25}$, $-N(R^{24})S(O)_2R^{25}$, $-C(O)R^{25}$, $-S(O)_2R^{25}$, $-S(O)_2N(R^{22})(R^{23})$, and $-OC(O)R^{25}$.

[0005b] In a further aspect of the present disclosure, there is provided a pharmaceutical composition comprising a

compound disclosed herein, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable excipient.

[0005c] In another aspect of the present disclosure, there is provided a use of a compound disclosed herein, or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for treating cancer.

[0005d] In a further aspect of the present disclosure, there is provided a use of a compound disclosed herein, in the manufacture of a medicament for potentiating immunity of a subject in need thereof, wherein:

(a) a subject that exhibits expression or activity of PTPN2 and/or PTP1B is selected; and

(b) the compound downregulates expression or activity of PTPN2 and/or PTP1B in a cell of the subject, thereby potentiating immunity of the subject.

[0005e] In another aspect of the present disclosure, there is provided a compound disclosed herein, for use in therapy.

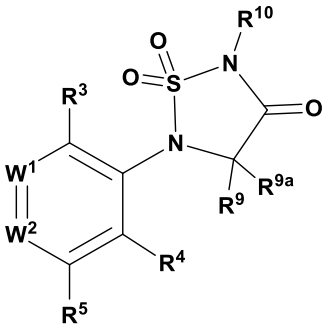
SUMMARY

[0006] In view of the foregoing, there exists a considerable need for alternative compositions and methods to treat cancer, and/or carry out immunotherapy. The compositions and methods of the present disclosure address this need and provide additional advantages as well. The ability of PTPN2 to act as a negative regulator of immunoreceptor-related pathways (e.g., TCR signaling) and promote cancer cell proliferation can be exploited for cancer and tumor

CLAIMS

WHAT IS CLAIMED IS:

1. A compound of Formula (IIa), or a pharmaceutically acceptable salt or solvate thereof:



Formula (IIa);

wherein:

W^1 is $C(R^1)$, and W^2 is $C(R^{2a})$ or N;

R^1 is selected from C_{5-12}cycloalkyl, 5 to 12 membered heterocycloalkyl, C_{6-12}aryl, and 5 to 12 membered heteroaryl, wherein C_{5-12}cycloalkyl, 5 to 12 membered heterocycloalkyl, C_{6-12}aryl, and 5 to 12 membered heteroaryl are substituted with one or more substituents independently selected from R^6 and $R^{6'}$, wherein ring heteroatoms of the 5 to 12 membered heterocycloalkyl and 5 to 12 membered heteroaryl are independently selected from N, O, and S;

R^{2a} are independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, $-OR^{12}$, $-SR^{12}$, $-N(R^{12})(R^{13})$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)OR^{12}$, $-N(R^{14})S(O)_2R^{15}$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})$, $-S(=O)(=NH)N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, and $-CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, and C_{2-6}alkynyl are optionally substituted with one, two, or three R^{20b};

R^3 is halogen;

R^4 is -OH;

R^5 is hydrogen;

each R^6 is independently selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12}$, $-SR^{12}$, $-N(R^{12})(R^{13})$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)OR^{12}$, $-N(R^{14})S(O)_2R^{15}$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})$, $-S(=O)(=NH)N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, and $-CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{26};

each $R^{6'}$ is independently selected from -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12}$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-C(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, and $-CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{26};

R^9 and R^{9a} are independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12}$, $-SR^{12}$, $-N(R^{12})(R^{13})$, $-C(O)OR^{12}$, -

$OC(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)OR^{12}$, $-N(R^{14})S(O)_2R^{15}$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})$, $-S(=O)(=NH)N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, and $-CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20i}; or R^9 and R^{9a} are combined to form a C_{3-6}cycloalkyl or a C_{2-9}heterocycloalkyl, wherein the C_{3-6}cycloalkyl and C_{2-9}heterocycloalkyl are optionally substituted with one, two, or three R^{20i};

R^{10} is independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-R^{16}$, $-OR^{16}$, $-N(R^{12})(R^{16})$, $-OR^{12}$, $-SR^{12}$, $-N(R^{12})(R^{13})$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)OR^{12}$, $-N(R^{14})S(O)_2R^{15}$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})$, $-S(=O)(=NH)N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, and $-CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20j};

each R^{12} is independently selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, $-CH_2-C_{3-10}$cycloalkyl, C_{2-9}heterocycloalkyl, $-CH_2-C_{2-9}$heterocycloalkyl, C_{6-10}aryl, $-CH_2-C_{6-10}$aryl, and C_{1-9}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, $-CH_2-C_{3-10}$cycloalkyl, C_{2-9}heterocycloalkyl, $-CH_2-C_{2-9}$heterocycloalkyl, C_{6-10}aryl, $-CH_2-C_{6-10}$aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20k};

each R^{13} is independently selected from hydrogen, C_{1-6}alkyl, and C_{1-6}haloalkyl; or R^{12} and R^{13}, together with the nitrogen to which they are attached, form a C_{2-9}heterocycloalkyl ring optionally substituted with one, two, or three R^{20l};

each R^{14} is independently selected from hydrogen, C_{1-6}alkyl, and C_{1-6}haloalkyl;

each R^{15} is independently selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{1-6}heteroalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{1-6}heteroalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20m};

each R^{16} is independently selected from $-C_{1-6}$alkylene-$OP(O)(OR^{16a})(OR^{16b})$ and $-P(O)(OR^{16a})(OR^{16b})$; wherein the C_{1-6}alkylene is optionally substituted with one, two, or three R^{20n}; or $-C_{1-6}$alkylene-$OC(O)-R^{16c}$ wherein C_{1-6}alkylene is optionally substituted with one, two, or three R^{20n};

each R^{16a} and R^{16b} is independently selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, $-CH_2-C_{3-10}$cycloalkyl, $-CH_2-C_{2-9}$heterocycloalkyl, C_{6-10}aryl, $-CH_2-C_{6-10}$aryl, and C_{1-9}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, $-CH_2-C_{3-10}$cycloalkyl, $-CH_2-C_{2-9}$heterocycloalkyl, C_{6-10}aryl, $-CH_2-C_{6-10}$aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20o};

R^{16c} is selected from halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, $-CH_2-C_{3-10}$cycloalkyl, C_{2-9}heterocycloalkyl, $-CH_2-C_{2-9}$heterocycloalkyl, C_{6-10}aryl, $-CH_2-C_{6-10}$aryl, C_{1-9}heteroaryl, $-CH_2-C_{1-9}$heteroaryl, $-OR^{21}$, $-SR^{21}$, $-N(R^{22})(R^{23})$, $-C(O)OR^{22}$, $-C(O)N(R^{22})(R^{23})$, $-C(O)C(O)N(R^{22})(R^{23})$, $-OC(O)N(R^{22})(R^{23})$, $-N(R^{24})C(O)N(R^{22})(R^{23})$, $-N(R^{24})C(O)OR^{25}$, $-N(R^{24})C(O)R^{25}$, $-N(R^{24})S(O)_2R^{25}$, $-C(O)R^{25}$, $-S(O)_2R^{25}$, $-S(O)_2N(R^{22})(R^{23})$, $-OCH_2C(O)OR^{22}$, and $-OC(O)R^{25}$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, $-CH_2-C_{3-10}$cycloalkyl, C_{2-9}heterocycloalkyl, $-CH_2-C_{2-9}$heterocycloalkyl, C_{6-10}aryl, $-CH_2-C_{6-10}$aryl, $-CH_2-C_{1-9}$heteroaryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three of R^{20o}**;**

each R^{20b}, R^{20i}, R^{20j}, R^{20k}, R^{20l}, R^{20m}, R^{20n}, and R^{20o} are each independently selected from oxo, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -CH_2-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -CH_2-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -CH_2-C_{6-10}aryl, C_{1-9}heteroaryl, -OR^{21}, -SR^{21}, -$N(R^{22})(R^{23})$, -$C(O)OR^{22}$, -$C(O)N(R^{22})(R^{23})$, -$C(O)C(O)N(R^{22})(R^{23})$, -$OC(O)N(R^{22})(R^{23})$, -$N(R^{24})C(O)N(R^{22})(R^{23})$, -$N(R^{24})C(O)OR^{22}$, -$N(R^{24})C(O)R^{25}$, -$N(R^{24})S(O)_2R^{25}$, -$C(O)R^{25}$, -$S(O)_2R^{25}$, -$S(O)_2N(R^{22})(R^{23})$, -$OCH_2C(O)OR^{22}$, and -$OC(O)R^{25}$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -CH_2-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -CH_2-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -CH_2-C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three groups independently selected from halogen, oxo, -CN, C_{1-6}alkyl optionally substituted with one or more R^{26}, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy, -OR^{21}, -SR^{21}, -$N(R^{22})(R^{23})$, -$C(O)OR^{22}$, -$C(O)N(R^{22})(R^{23})$, -$C(O)C(O)N(R^{22})(R^{23})$, -$OC(O)N(R^{22})(R^{23})$, -$N(R^{24})C(O)N(R^{22})(R^{23})$, -$N(R^{24})C(O)OR^{25}$, -$N(R^{24})C(O)R^{25}$, -$N(R^{24})S(O)_2R^{25}$, -$C(O)R^{25}$, -$S(O)_2R^{25}$, -$S(O)_2N(R^{22})(R^{23})$, and -$OC(O)R^{25}$;

each R^{21} is independently selected from H, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl;

each R^{22} is independently selected from H, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl;

each R^{23} is independently selected from H and C_{1-6}alkyl;

each R^{24} is independently selected from H and C_{1-6}alkyl;

each R^{25} is selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{1-6}heteroalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl;

each R^{26} is independently selected from oxo, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, -OR^{12}, -SR^{12}, -$N(R^{12})(R^{13})$, -$C(O)OR^{12}$, -$OC(O)N(R^{12})(R^{13})$, -$N(R^{14})C(O)N(R^{12})(R^{13})$, -$N(R^{14})C(O)OR^{12}$, -$N(R^{14})S(O)_2R^{15}$, -$C(O)R^{15}$, -$S(O)R^{15}$, -$OC(O)R^{15}$, -$C(O)N(R^{12})(R^{13})$, -$C(O)C(O)N(R^{12})(R^{13})$, -$N(R^{14})C(O)R^{15}$, -$S(O)_2R^{15}$, -$S(O)_2N(R^{12})(R^{13})$, -$S(=O)(=NH)N(R^{12})(R^{13})$, -$CH_2C(O)N(R^{12})(R^{13})$, -$CH_2N(R^{14})C(O)R^{15}$, -$CH_2S(O)_2R^{15}$, and -$CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{27};

each R^{27} is independently selected from oxo, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, -OR^{12}, -SR^{12}, -$N(R^{12})(R^{13})$, -$C(O)OR^{12}$, -$OC(O)N(R^{12})(R^{13})$, -$N(R^{14})C(O)N(R^{12})(R^{13})$, -$N(R^{14})C(O)OR^{12}$, -$N(R^{14})S(O)_2R^{15}$, -$C(O)R^{15}$, -$S(O)R^{15}$, -$OC(O)R^{15}$, -$C(O)N(R^{12})(R^{13})$, -$C(O)C(O)N(R^{12})(R^{13})$, -$N(R^{14})C(O)R^{15}$, -$S(O)_2R^{15}$, -$S(O)_2N(R^{12})(R^{13})$, -$S(=O)(=NH)N(R^{12})(R^{13})$, -$CH_2C(O)N(R^{12})(R^{13})$, -$CH_2N(R^{14})C(O)R^{15}$, -$CH_2S(O)_2R^{15}$, and -$CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20f}; and

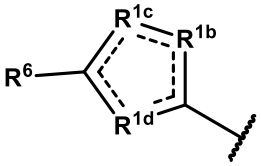
each R^{20f} is independently selected from oxo, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -CH_2-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -CH_2-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -CH_2-C_{6-10}aryl, C_{1-9}heteroaryl, -OR^{21}, -SR^{21}, -$N(R^{22})(R^{23})$, -$C(O)OR^{22}$, -$C(O)N(R^{22})(R^{23})$, -$C(O)C(O)N(R^{22})(R^{23})$, -$OC(O)N(R^{22})(R^{23})$, -$N(R^{24})C(O)N(R^{22})(R^{23})$, -$N(R^{24})C(O)OR^{22}$, -$N(R^{24})C(O)R^{25}$, -$N(R^{24})S(O)_2R^{25}$, -$C(O)R^{25}$, -$S(O)_2R^{25}$, -$S(O)_2N(R^{22})(R^{23})$, -$OCH_2C(O)OR^{22}$, and -$OC(O)R^{25}$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -CH_2-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -CH_2-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -CH_2-C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three groups independently selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy, -OR^{21}, -SR^{21}, -$N(R^{22})(R^{23})$, -$C(O)OR^{22}$,

-C(O)N(R^{22})(R^{23}), -C(O)C(O)N(R^{22})(R^{23}), -OC(O)N(R^{22})(R^{23}), -N(R^{24})C(O)N(R^{22})(R^{23}), -N(R^{24})C(O)OR^{25}, -N(R^{24})C(O)R^{25}, -N(R^{24})S(O)$_2$$R^{25}$, -C(O)$R^{25}$, -S(O)$_2$$R^{25}$, -S(O)$_2$N($R^{22}$)($R^{23}$), and -OC(O)$R^{25}$.

2. The compound of claim 1, or a pharmaceutically acceptable salt or solvate thereof, wherein R^3 is F.

3. The compound of claim 1 or claim 2, or a pharmaceutically acceptable salt or solvate thereof, wherein R^1 is selected from C_{5-12}cycloalkyl, 5 to 12 membered partially unsaturated heterocycloalkyl, 6 to 12 membered saturated heterocycloalkyl, and 5 to 12 membered heteroaryl, wherein C_{5-12}cycloalkyl, 5 to 12 membered partially unsaturated heterocycloalkyl, 6 to 12 membered saturated heterocycloalkyl, and 5 to 12 membered heteroaryl are substituted with one or more substituents independently selected from R^6 and $R^{6'}$, wherein ring heteroatoms of the 5 to 12 membered partially unsaturated heterocycloalkyl, 6 to 12 membered saturated heterocycloalkyl, and 5 to 12 membered heteroaryl are independently selected from C, N, O, and S.

4. The compound of claim 1 or claim 2, or a pharmaceutically acceptable salt or solvate thereof, wherein R^1 is



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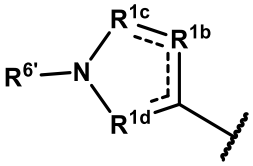
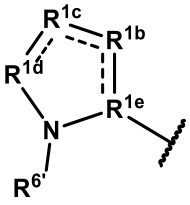
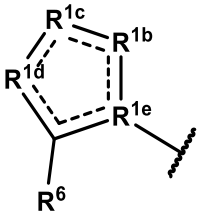


wherein R^{1c} is not N or N($R^{6c''}$) when R^{1b} is C(R^{6b}) and R^{1d} is C(R^{6d});



wherein R^1 is not a substituted pyrrolyl;



wherein R^1 is not a substituted imidazolyl wherein R^{1d} and R^{1e} are N; or fluoro-substituted pyrazolyl optionally further substituted with one, two, or three substituents independently selected from R^6 and $R^{6'}$;

R^{1b} is O, S, N, N($R^{6b''}$), C(R^{6b}), or C(R^{6b})($R^{6b'}$);

R^{1c} is O, S, N, N($R^{6c''}$), C(R^{6c}), or C(R^{6c})($R^{6c'}$);

R^{1d} is O, S, N, N($R^{6d''}$), C(R^{6d}), or C(R^{6d})($R^{6d'}$);

R^{1e} is N or C(R^{6e});

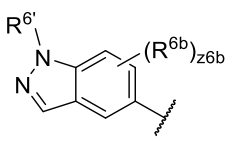
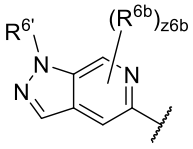
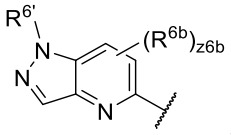
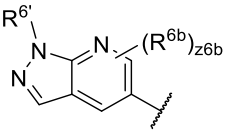
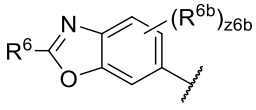
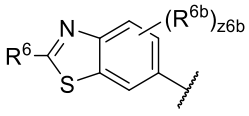
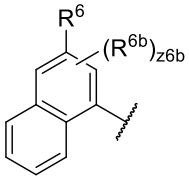
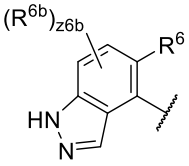
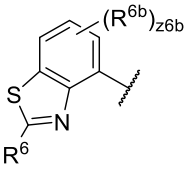
R^{6b}, $R^{6b'}$, R^{6c}, $R^{6c'}$, R^{6d}, $R^{6d'}$, and R^{6e} are independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl -OR^{12}, -SR^{12}, -N(R^{12})(R^{13}), -C(O)OR^{12}, -OC(O)N(R^{12})(R^{13}), -N(R^{14})C(O)N(R^{12})(R^{13}), -N(R^{14})C(O)OR^{12}, -N(R^{14})S(O)$_2$$R^{15}$, -C(O)$R^{15}$, -S(O)$R^{15}$, -OC(O)$R^{15}$, -C(O)N($R^{12}$)($R^{13}$), -C(O)C(O)N($R^{12}$)($R^{13}$), -N($R^{14}$)C(O)$R^{15}$, -S(O)$_2$$R^{15}$, -S(O)$_2$N($R^{12}$)($R^{13}$), -S(=O)(=NH)N($R^{12}$)($R^{13}$), -CH$_2$C(O)N($R^{12}$)($R^{13}$), -CH$_2$N($R^{14}$)C(O)$R^{15}$, -CH$_2$S(O)$_2$$R^{15}$, and -

$CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{26};

$R^{6b''}$, $R^{6c''}$, and $R^{6d''}$ are independently selected from hydrogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl $-OR^{12}$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-C(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, and $-CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{26}; and

indicates a single or double bond such that all valences are satisfied.

5. The compound of claim 1 or claim 2, or a pharmaceutically acceptable salt or solvate thereof, wherein R^1 is

;

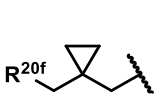
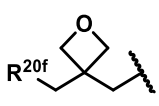
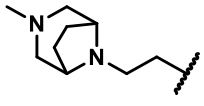
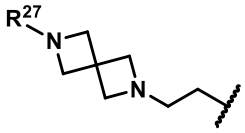
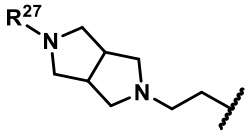
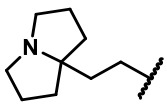
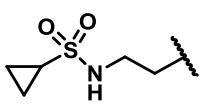
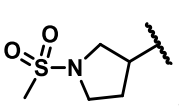
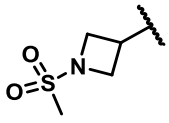
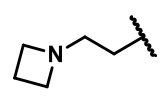
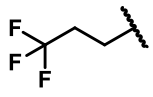
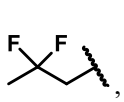
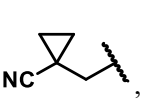
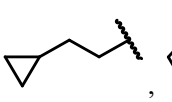
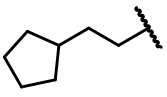
R^{6b} is independently selected from halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl $-OR^{12}$, $-SR^{12}$, $-N(R^{12})(R^{13})$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)OR^{12}$, $-N(R^{14})S(O)_2R^{15}$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})$, $-S(=O)(=NH)N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, and $-CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{26}; and

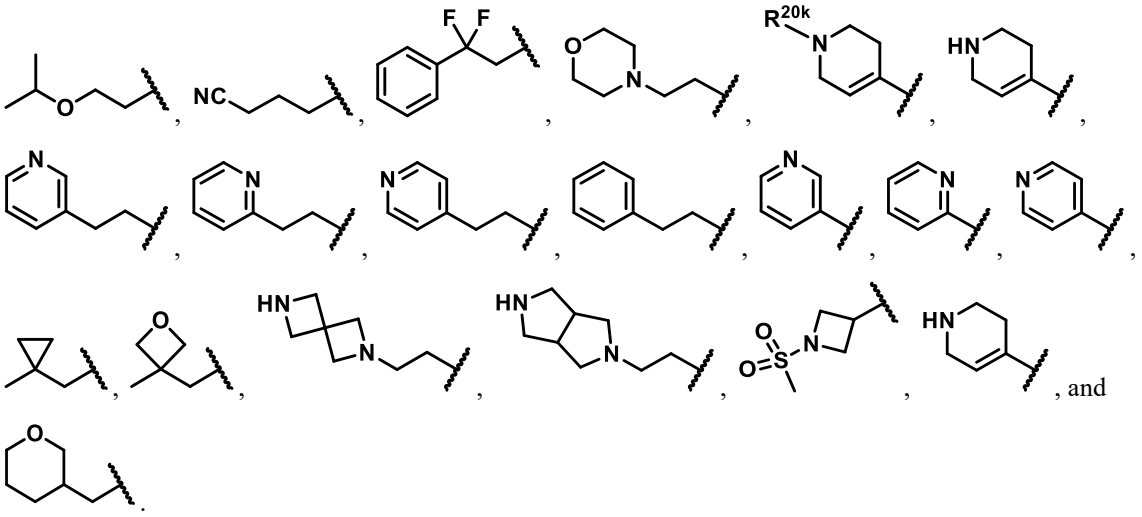
z6b is an integer from 0 to 4.

6. The compound of claim 2, or a pharmaceutically acceptable salt or solvate thereof, wherein R^1 is pyrazolyl substituted with one or more substituents independently selected from R^6 and $R^{6'}$.

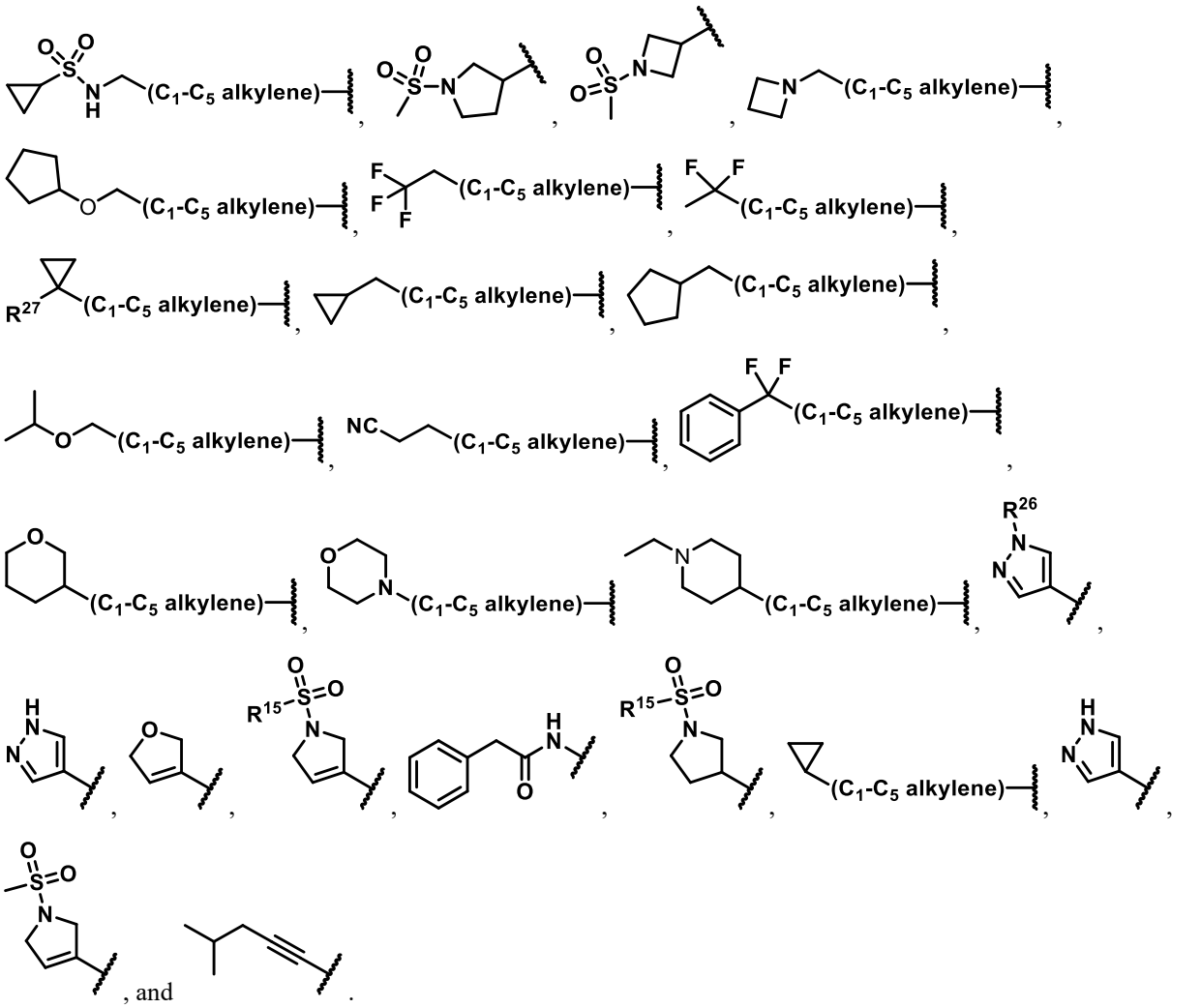
7. The compound of any one of claims 1 to 6, or a pharmaceutically acceptable salt or solvate thereof, wherein R^6 is independently selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, , wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{26}.

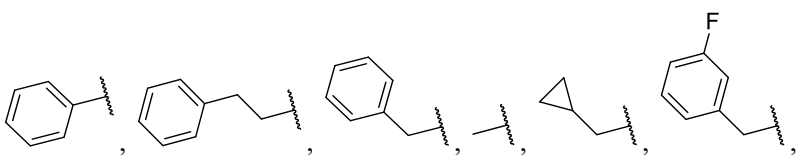
8. The compound of any one of claims 1 to 6, or a pharmaceutically acceptable salt or solvate thereof, wherein R^6 is independently selected from C_{1-6}alkyl,

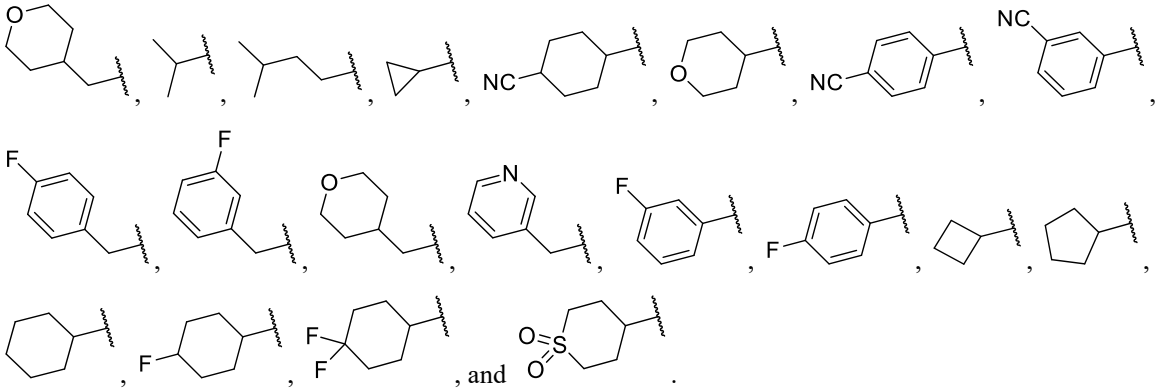


















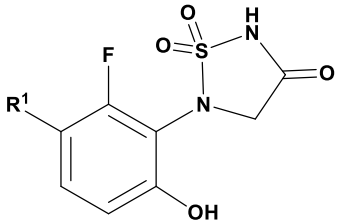
9. The compound of any one of claims 1 to 6, or a pharmaceutically acceptable salt or solvate thereof, wherein R^6 is independently selected from



10. The compound of any one of claims 1 to 6, or a pharmaceutically acceptable salt or solvate thereof, wherein R^6 is independently selected from 

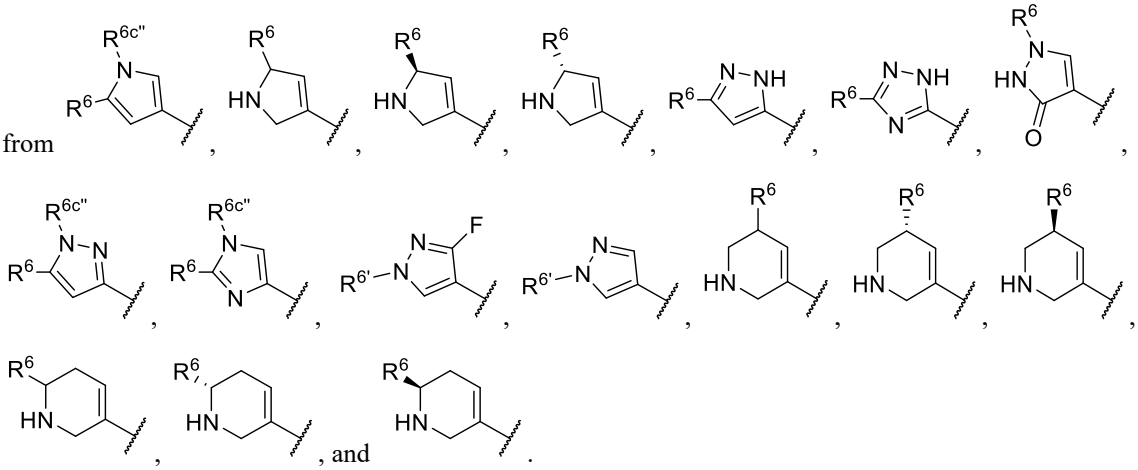


11. The compound of any one of claims 1 to 10, or a pharmaceutically acceptable salt or solvate thereof, wherein W^2 is CH, R^9 is hydrogen, R^{9a} is hydrogen, and R^{10} is hydrogen.
12. The compound of claim 1, or a pharmaceutically acceptable salt or solvate thereof, having the structure of Formula (IId-1):

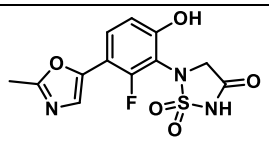
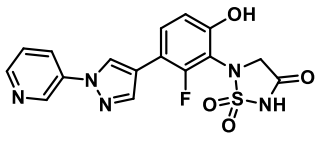
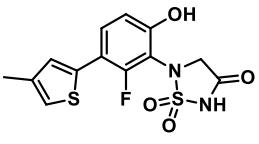


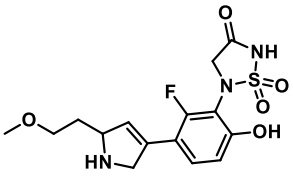
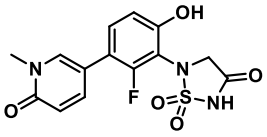
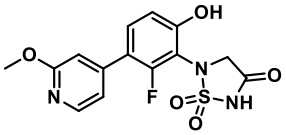
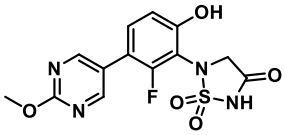
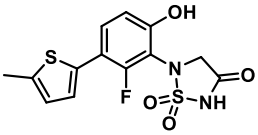
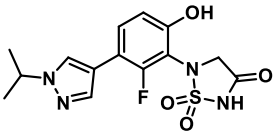
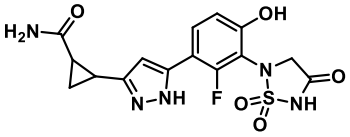
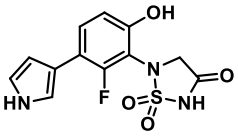
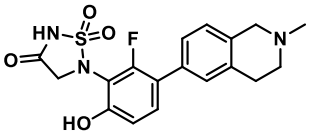
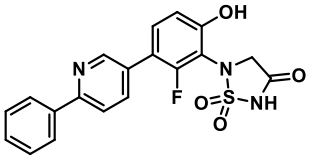
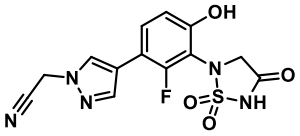
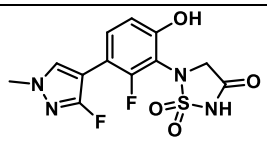
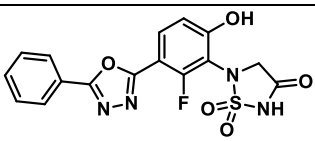
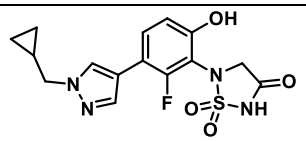
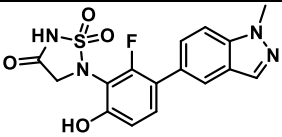
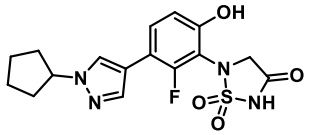
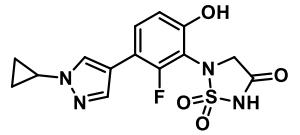
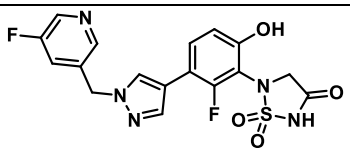
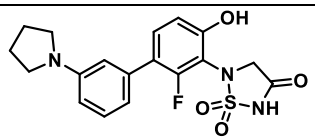
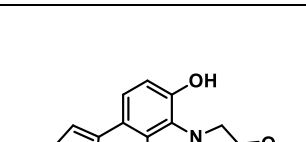
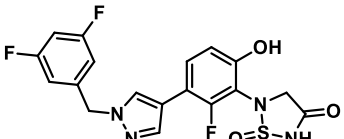
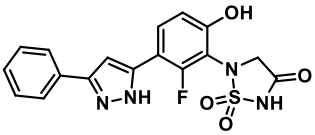
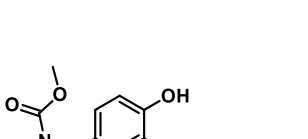
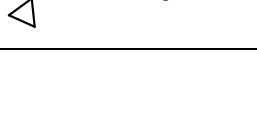
Formula (IId-1).

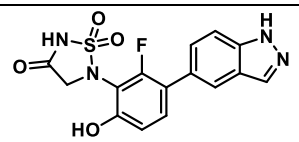
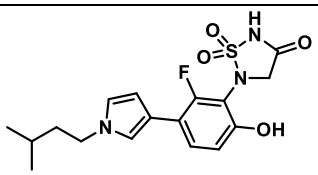
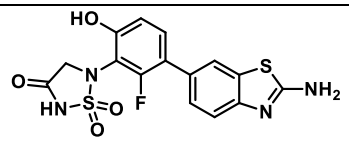
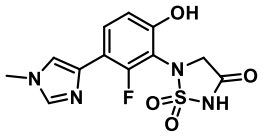
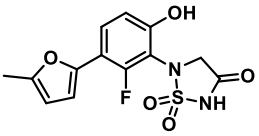
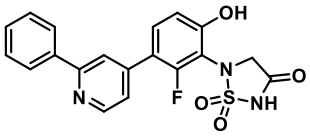
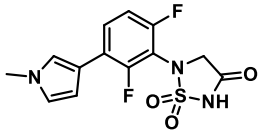
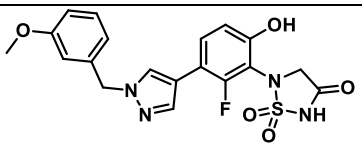
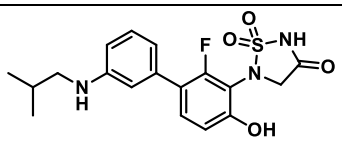
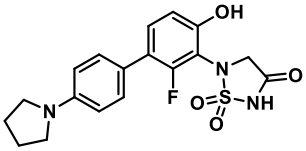
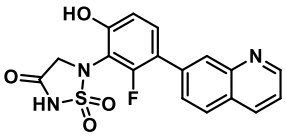
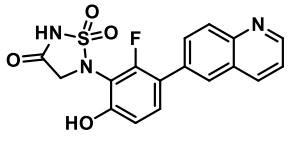
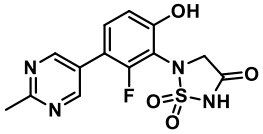
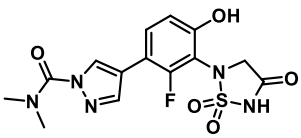
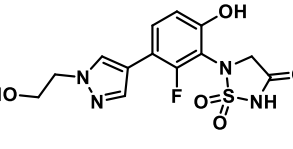
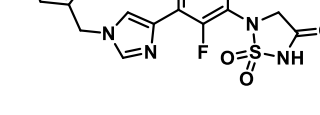
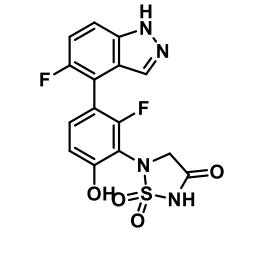
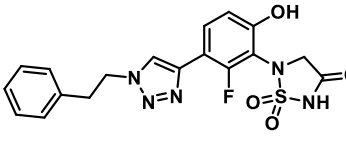
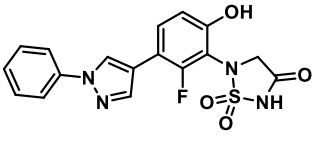
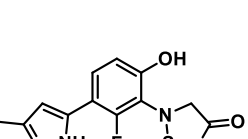
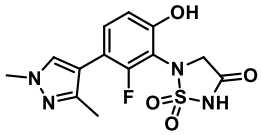
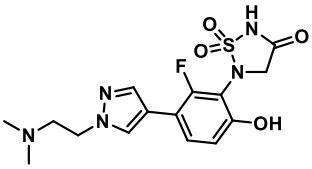
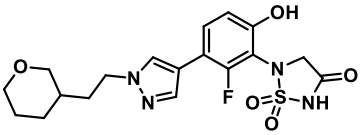
13. The compound of claim 12, or a pharmaceutically acceptable salt or solvate thereof, wherein R^1 is selected from pyrrolyl, pyrazolyl, imidazolyl, triazolyl, pyrrolinyl, pyridinyl, tetrahydropyridinyl, piperidinyl, and piperazinyl, each of which is substituted with one or more R^6.
14. The compound of claim 12, or a pharmaceutically acceptable salt or solvate thereof, wherein R^1 is selected from

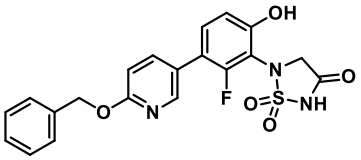
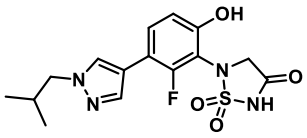
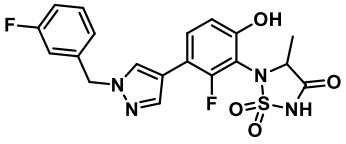
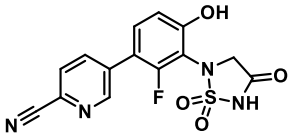
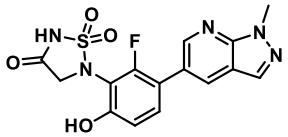
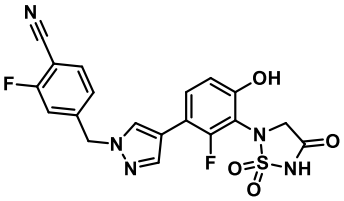
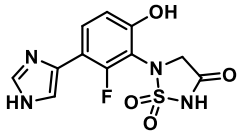
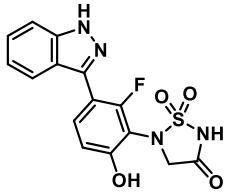
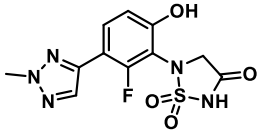
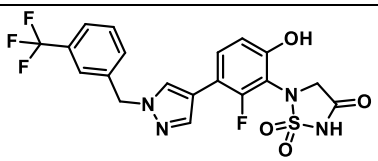
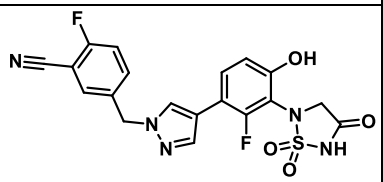
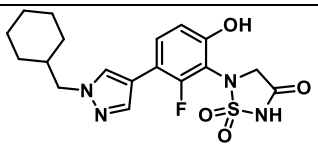
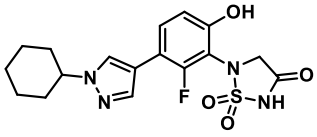
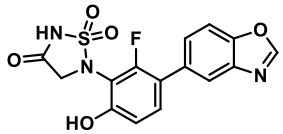
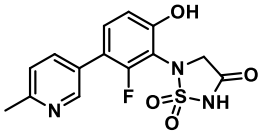
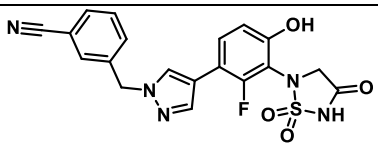
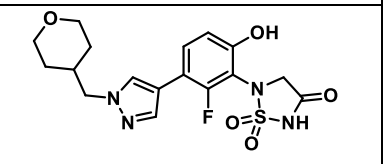
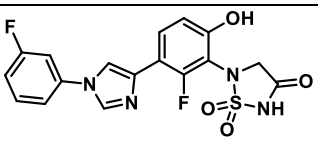
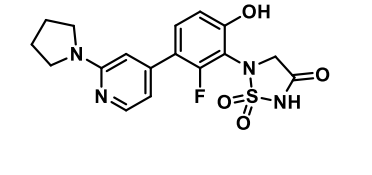
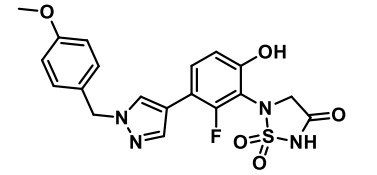
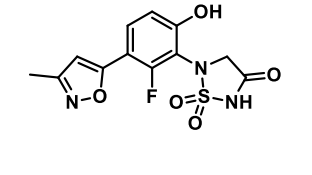
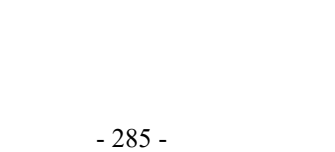


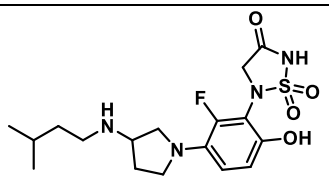
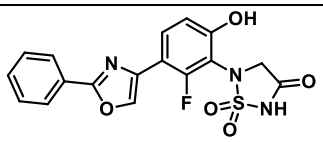
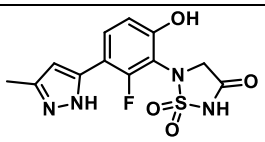
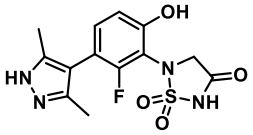
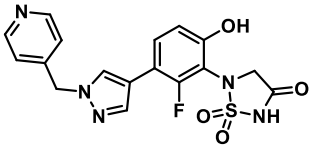
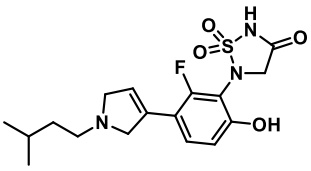
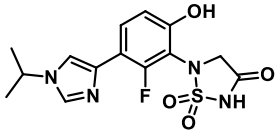
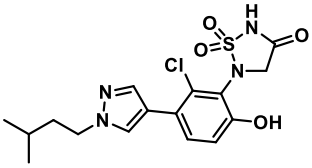
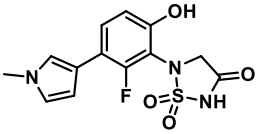
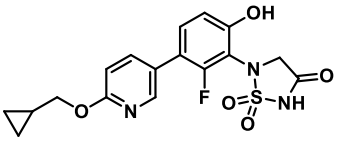
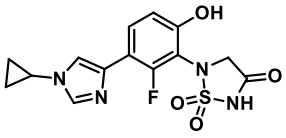
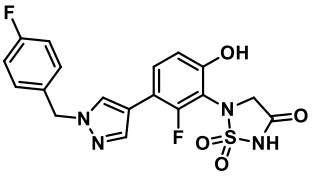
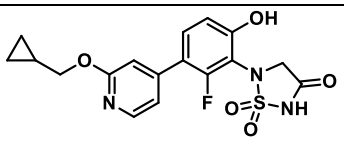
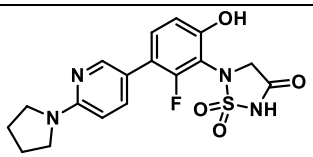
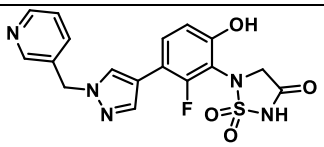
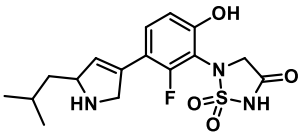
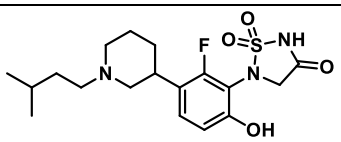
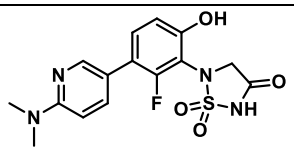
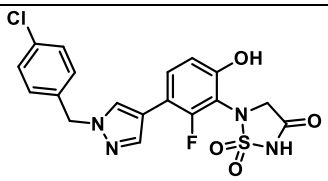
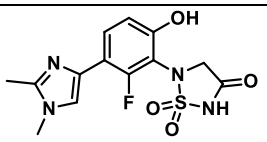
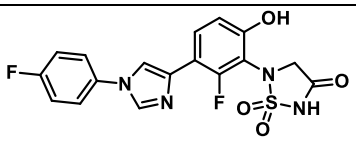
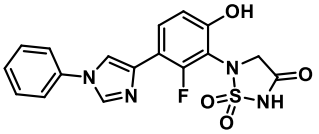
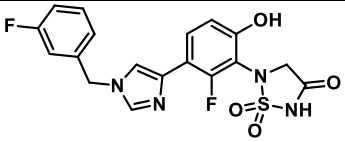
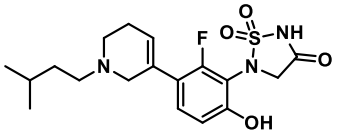
15. The compound of claim 1, or a pharmaceutically acceptable salt or solvate thereof, wherein the compound is selected from:

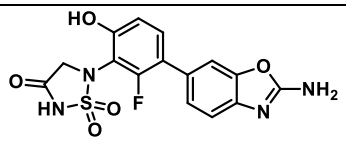
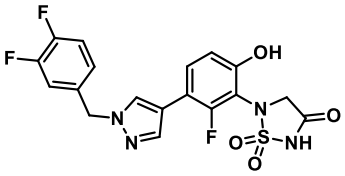
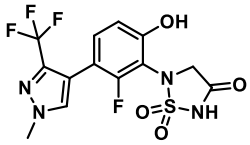
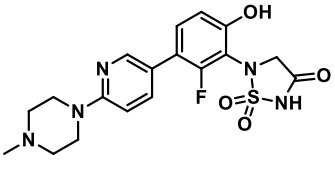
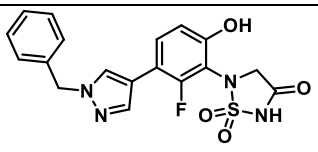
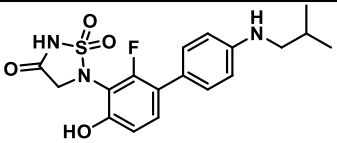
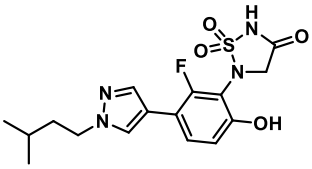
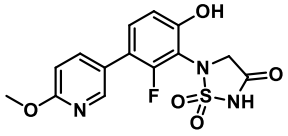
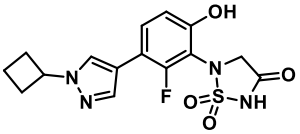
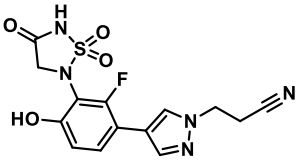
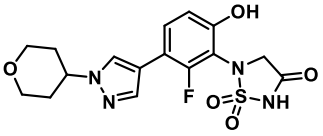
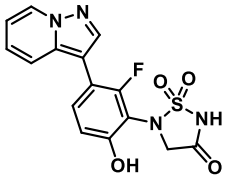
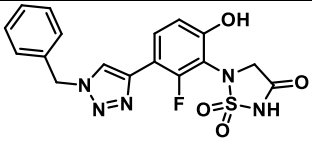
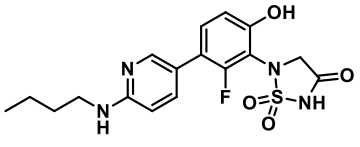
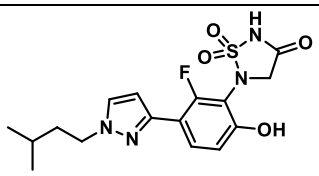
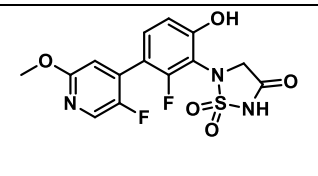
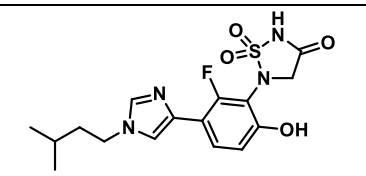
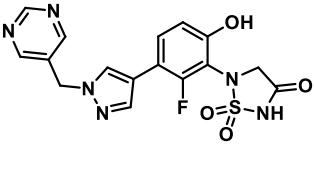
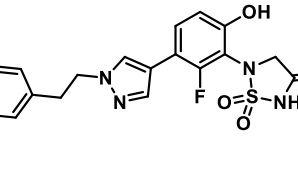
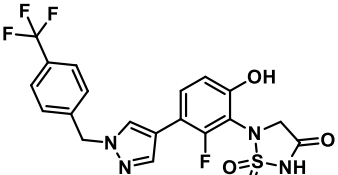
		

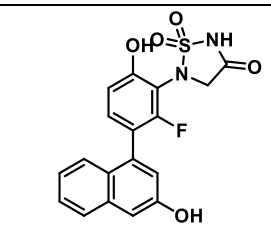
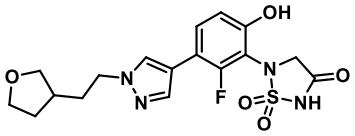
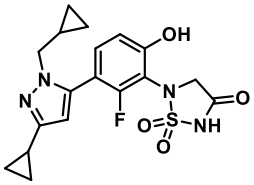
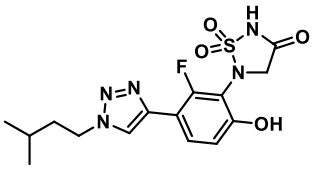
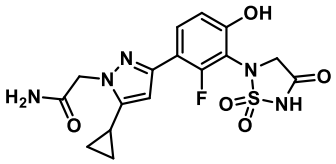
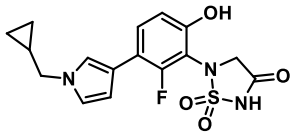
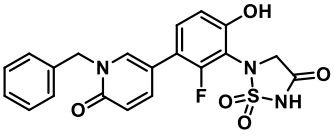
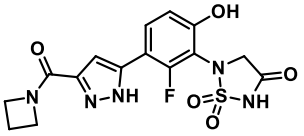
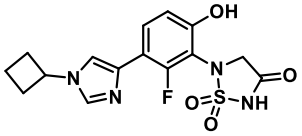
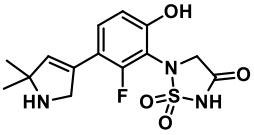
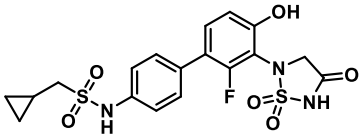
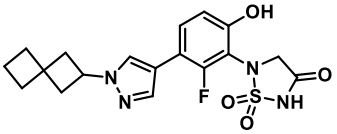
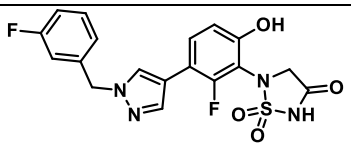
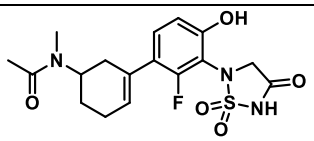
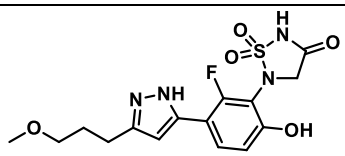
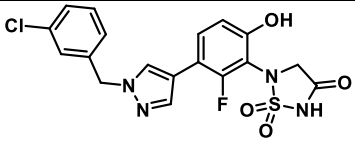
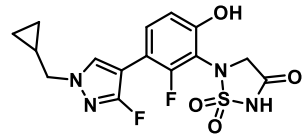
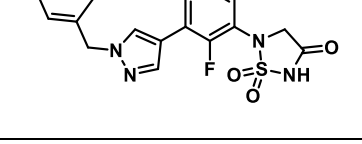
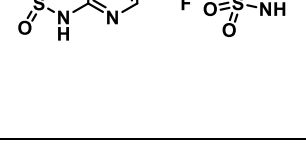
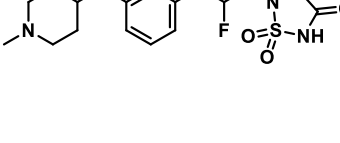
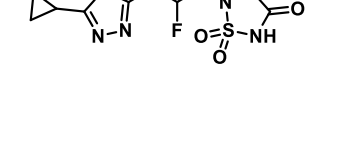
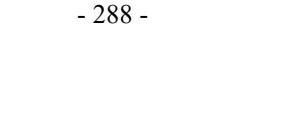
		
		
		
		
		
		
		
		
		

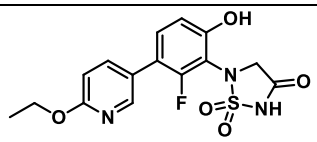
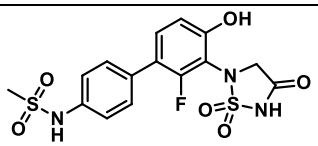
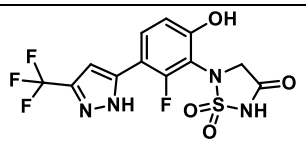
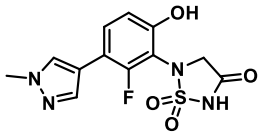
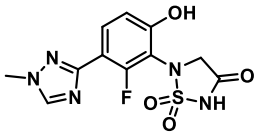
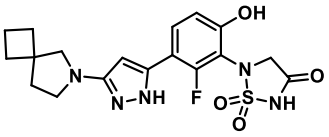
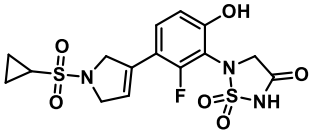
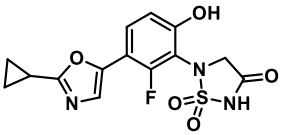
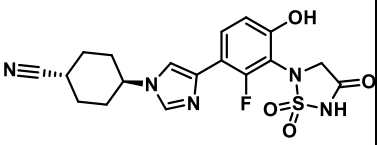
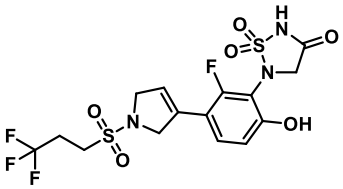
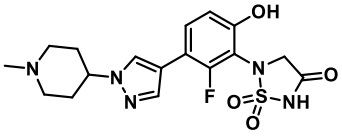
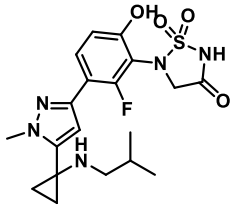
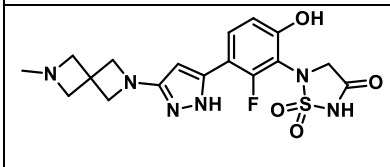
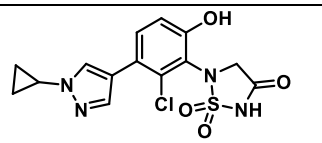
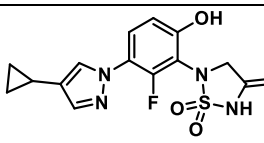
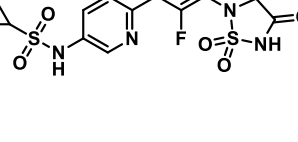
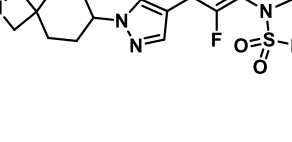
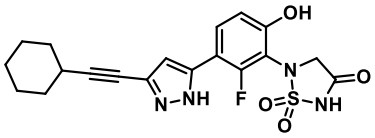
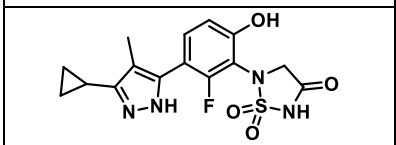
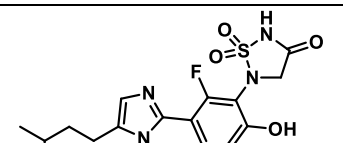
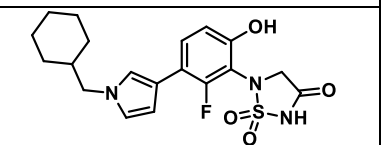
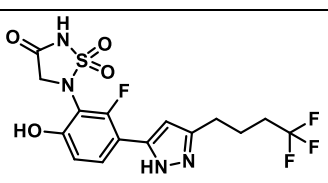
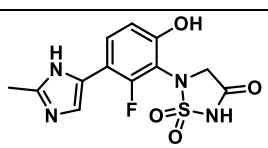
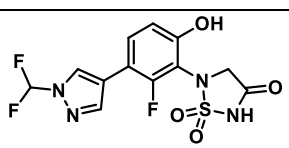
		
		
		
		
		
		
		
		

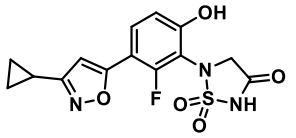
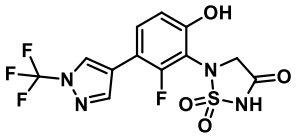
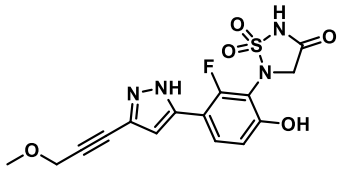
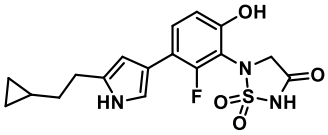
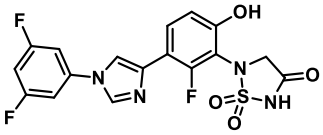
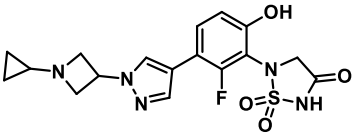
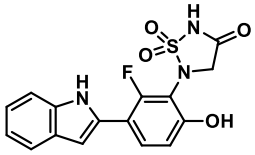
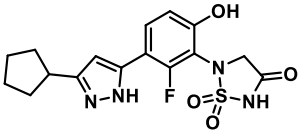
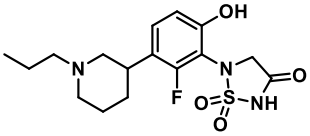
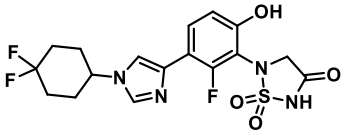
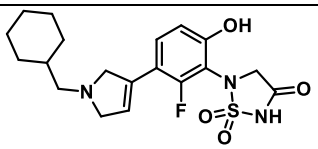
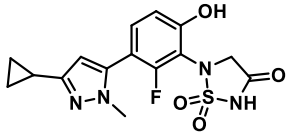
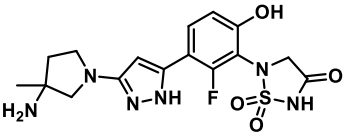
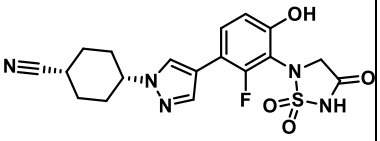
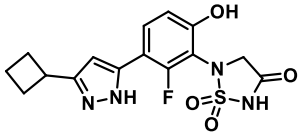
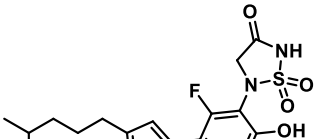
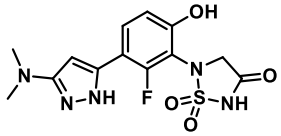
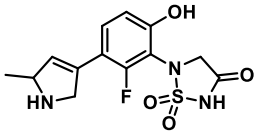
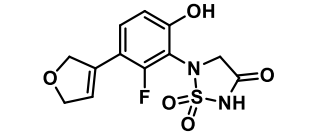
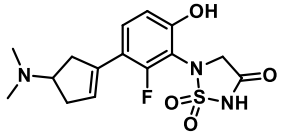
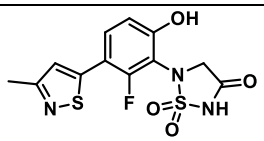
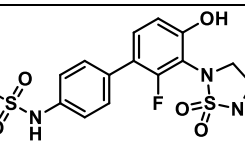
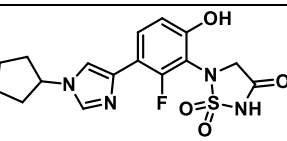
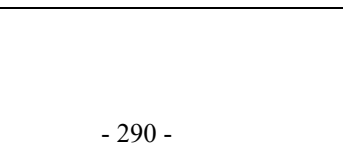
		
		
		
		
		
		
		
		

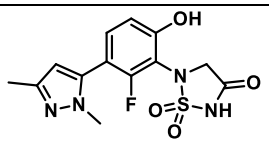
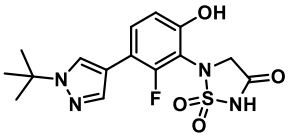
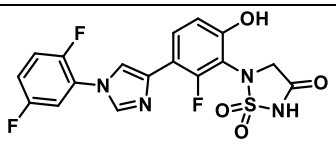
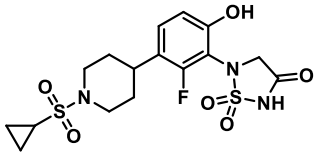
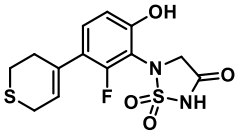
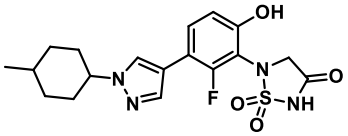
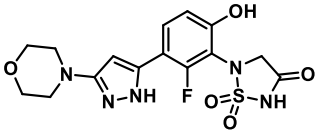
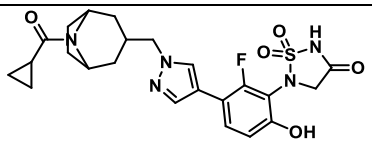
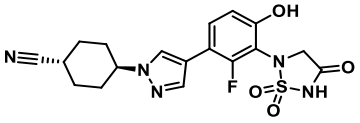
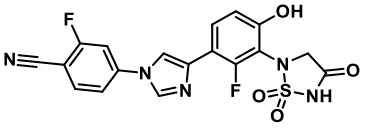
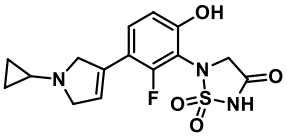
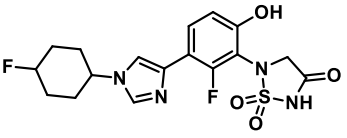
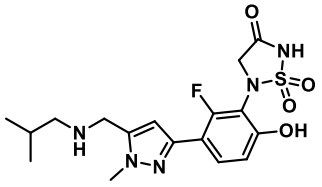
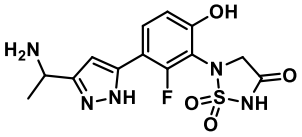
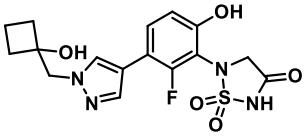
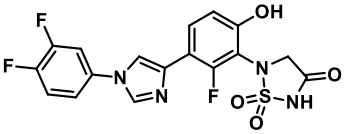
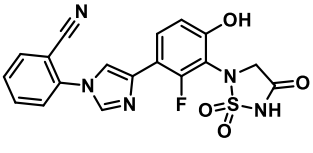
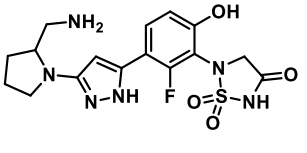
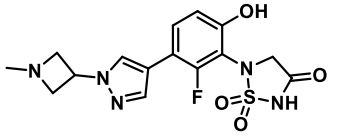
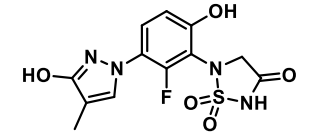
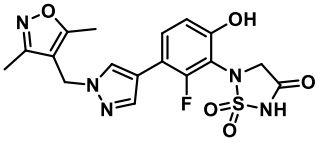
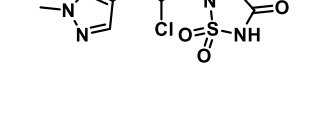
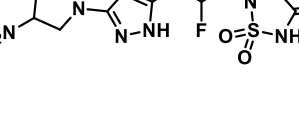
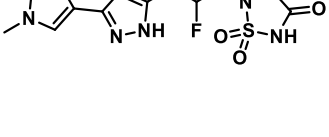
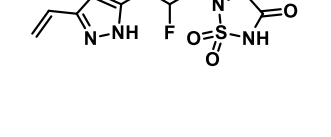
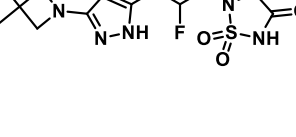
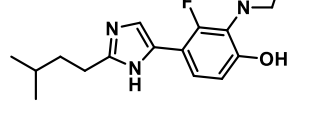
		
		
		
		
		
		
		
		

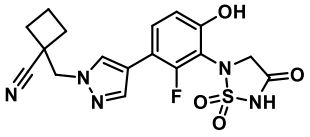
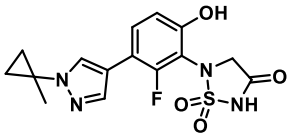
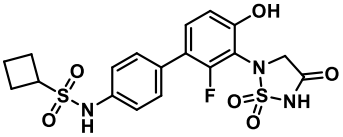
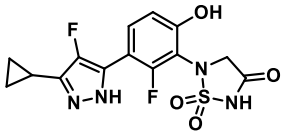
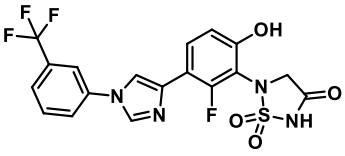
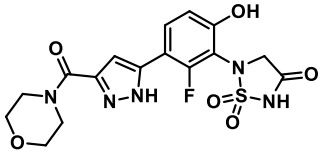
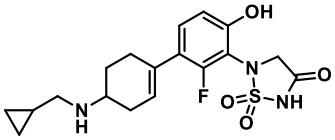
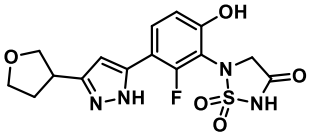
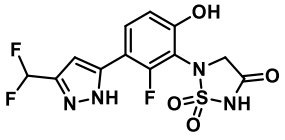
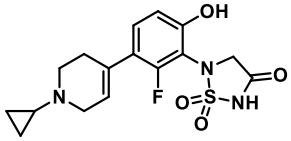
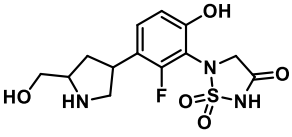
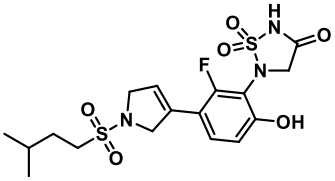
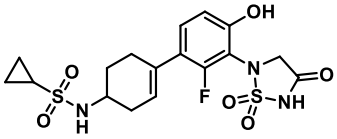
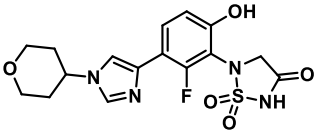
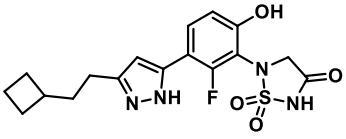
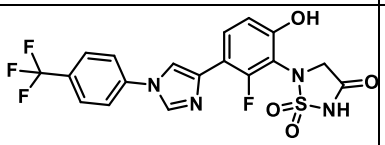
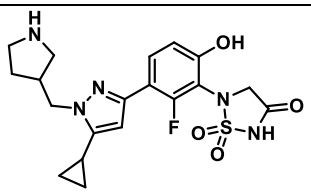
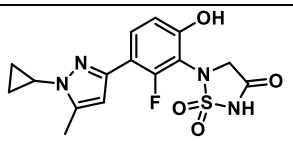
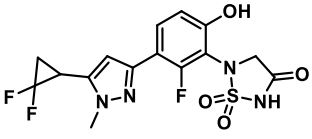
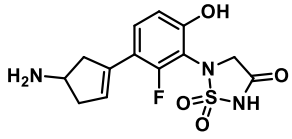
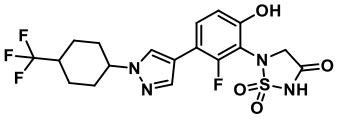
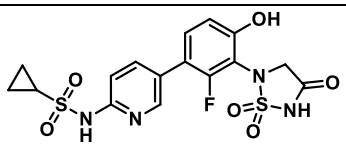
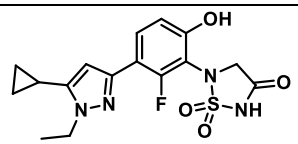
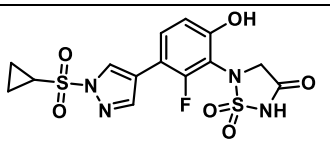
		
		
		
		
		
		
		

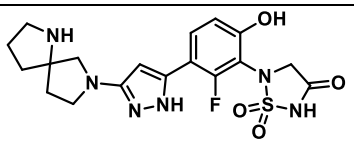
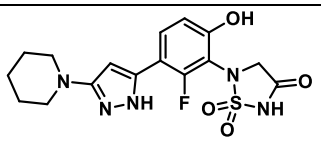
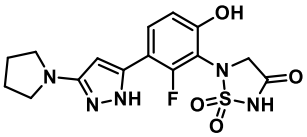
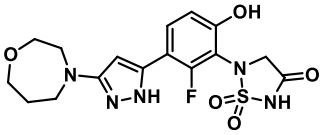
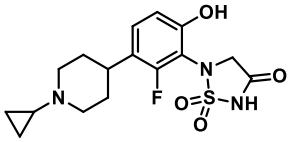
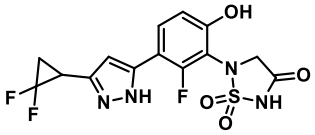
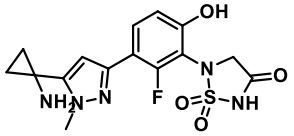
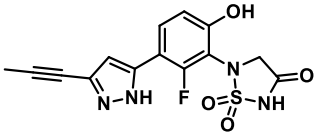
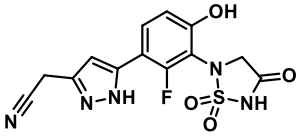
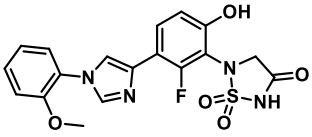
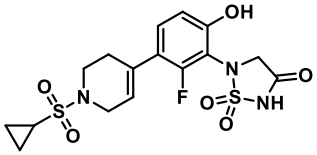
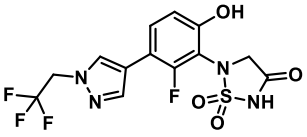
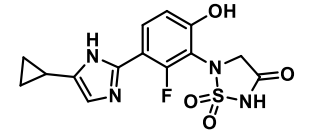
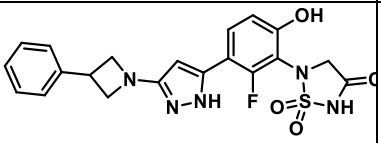
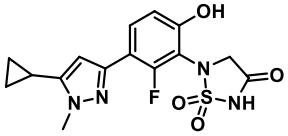
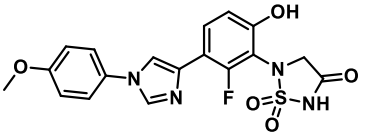
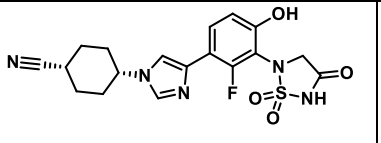
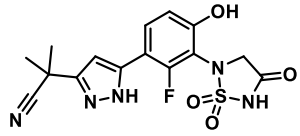
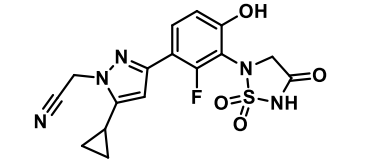
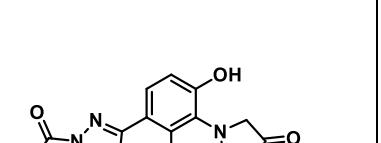
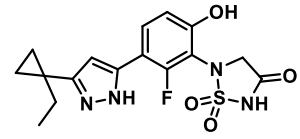
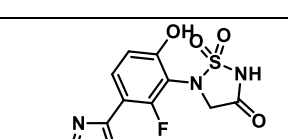
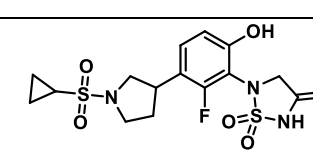
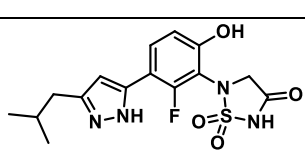
		
		
		
		
		
		
		
		
		

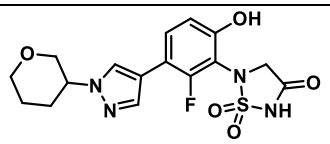
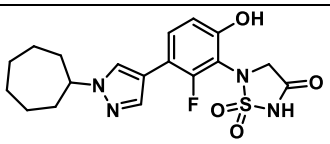
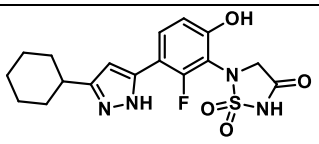
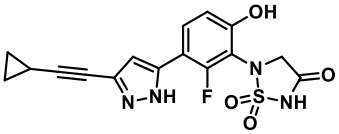
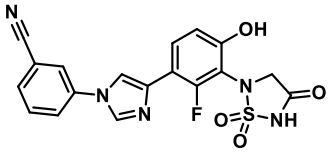
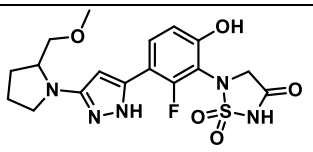
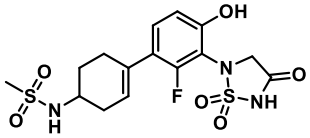
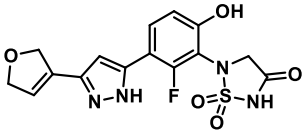
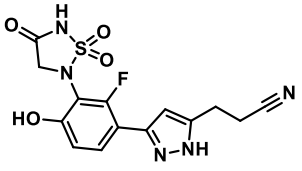
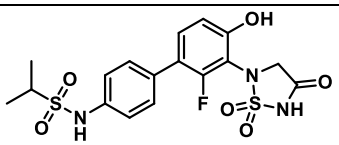
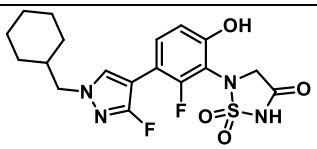
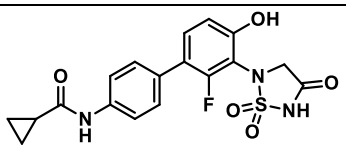
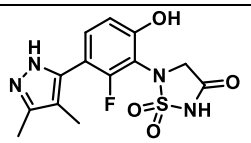
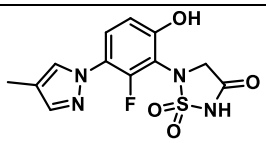
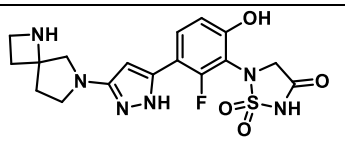
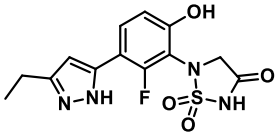
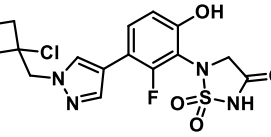
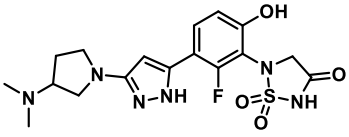
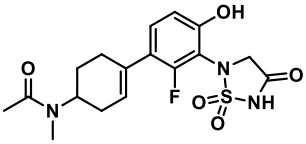
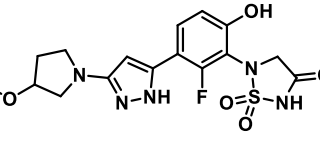
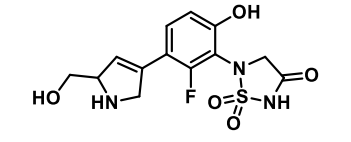
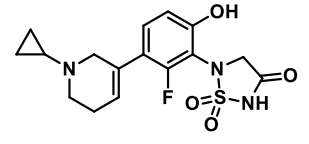
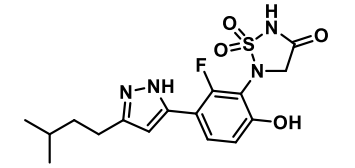
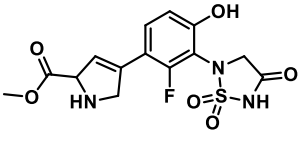
		
		
		
		
		
		
		
		
		
		

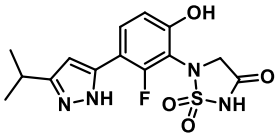
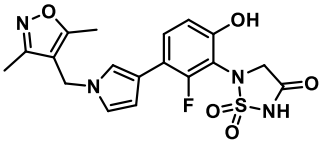
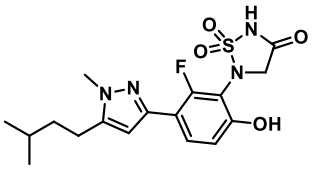
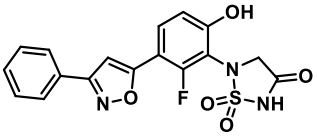
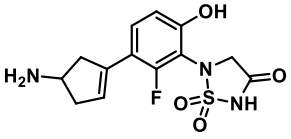
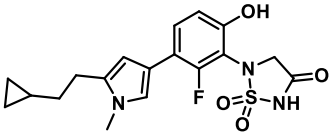
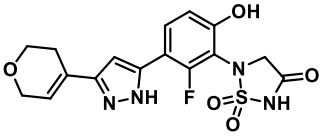
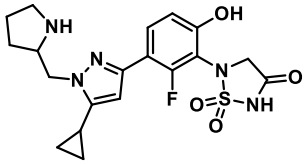
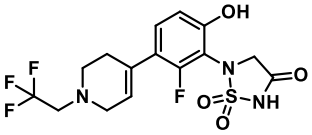
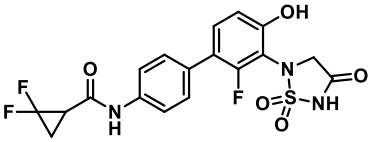
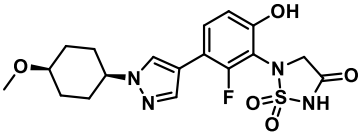
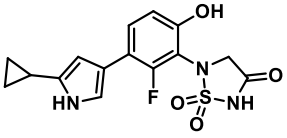
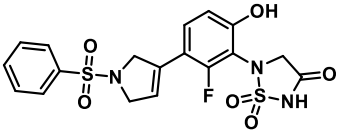
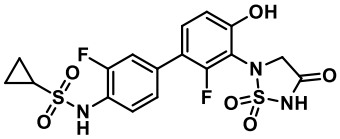
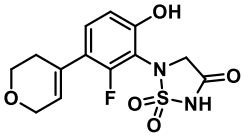
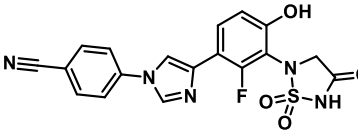
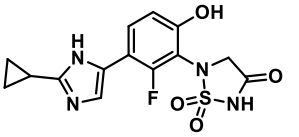
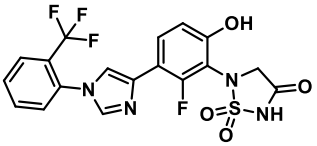
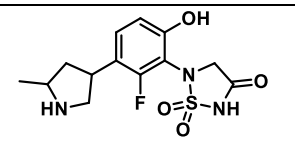
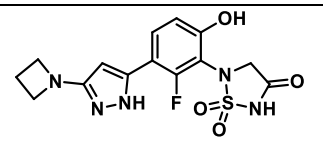
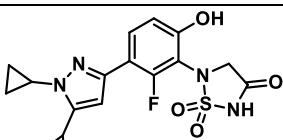
		
		
		
		
		
		
		
		
		

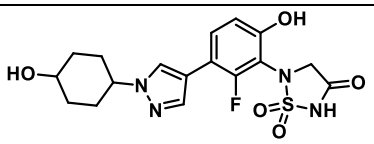
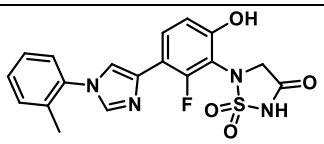
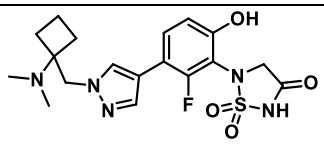
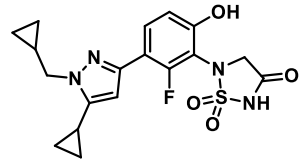
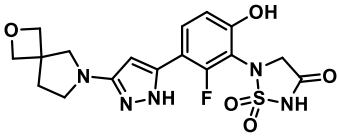
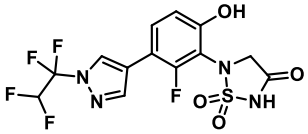
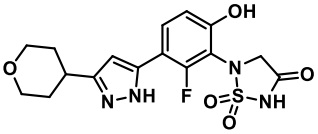
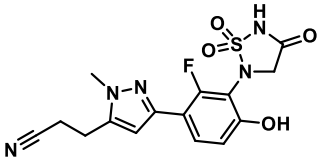
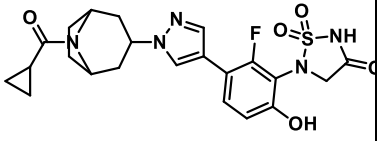
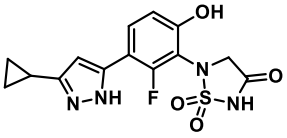
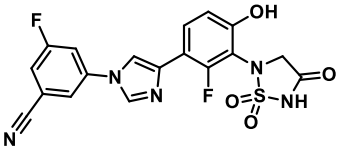
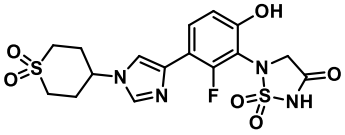
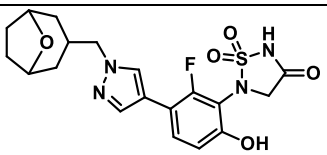
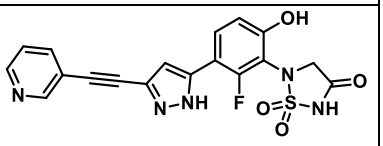
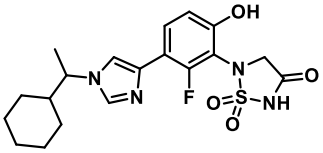
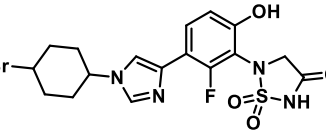
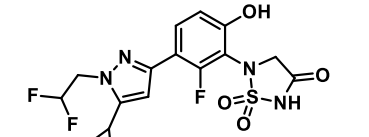
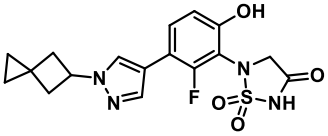
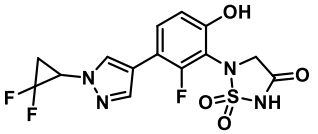
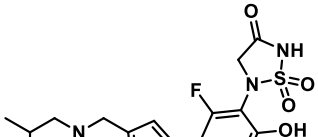
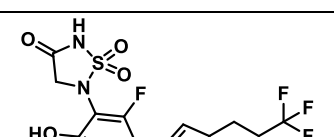
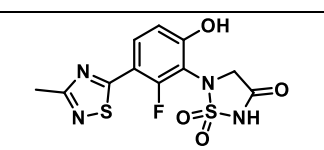
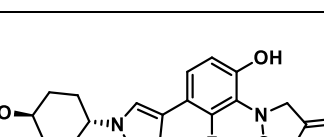
		
		
		
		
		
		
		
		
		

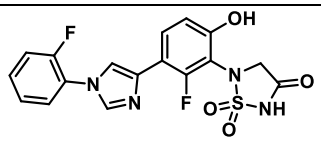
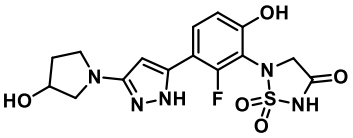
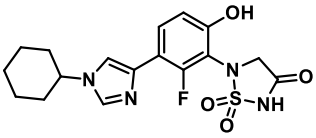
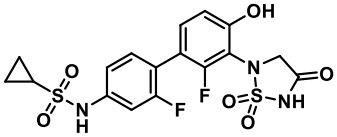
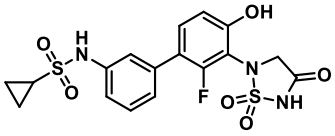
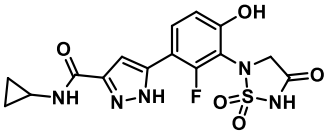
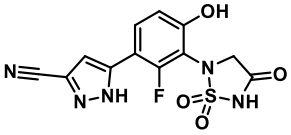
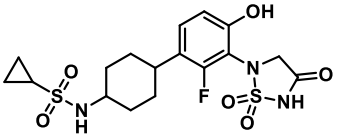
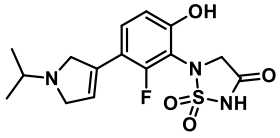
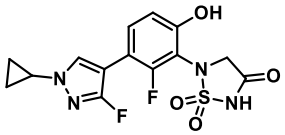
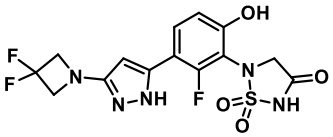
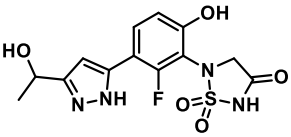
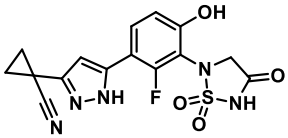
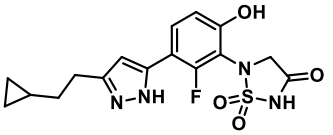
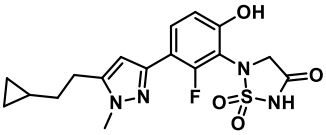
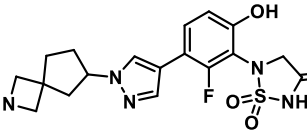
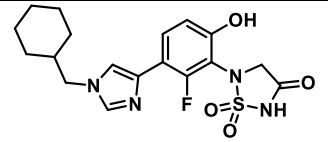
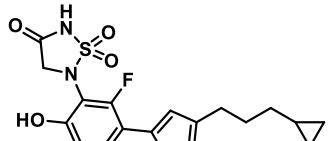
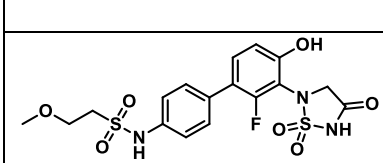
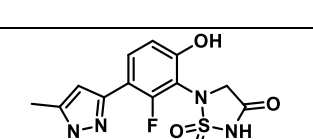
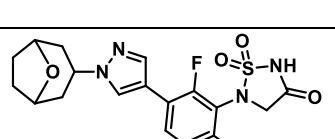
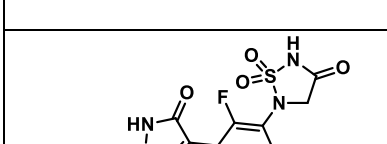
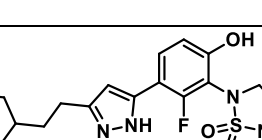
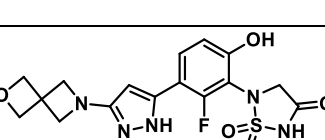
		
		
		
		
		
		
		
		

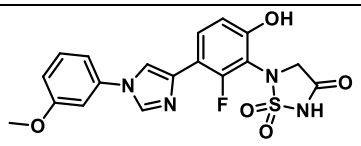
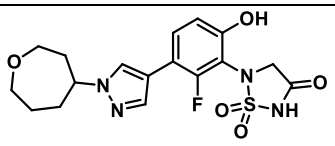
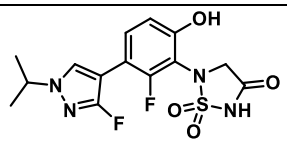
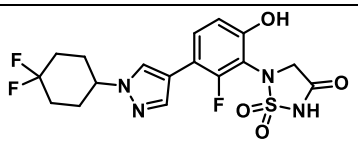
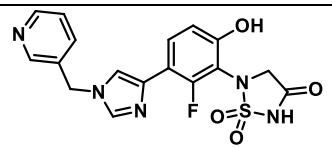
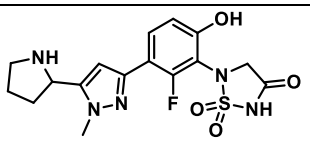
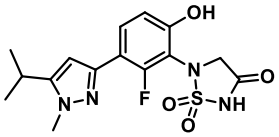
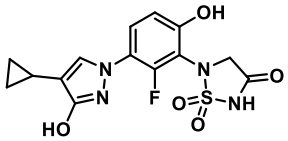
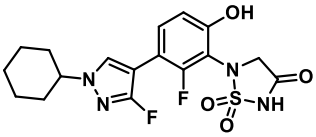
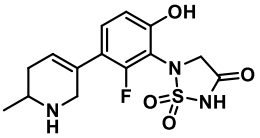
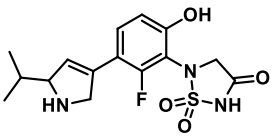
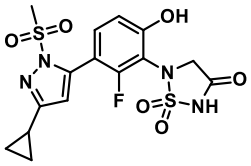
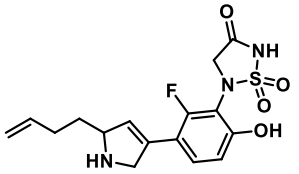
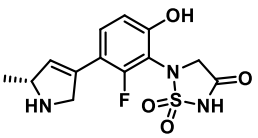
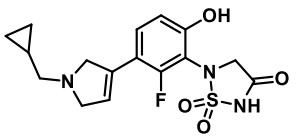
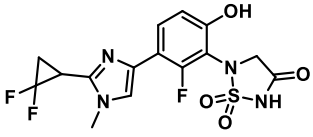
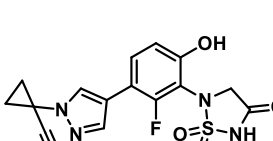
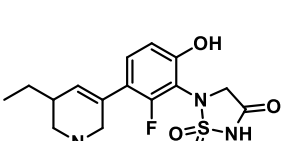
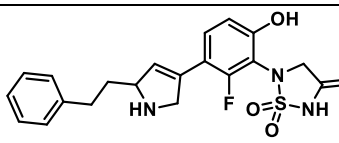
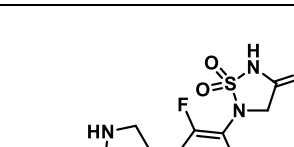
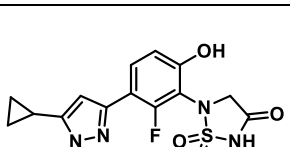
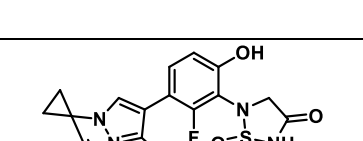
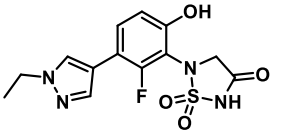
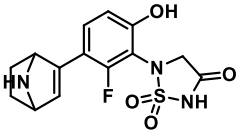
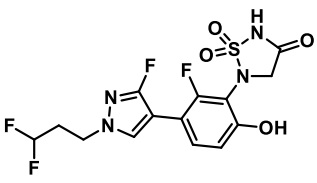
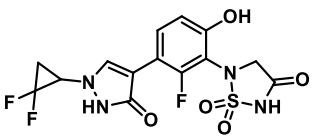
		
		
		
		
		
		
		
		
		

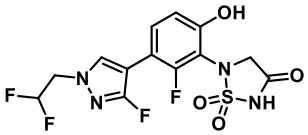
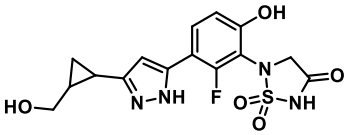
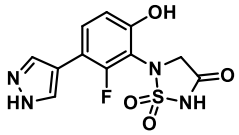
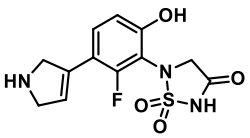
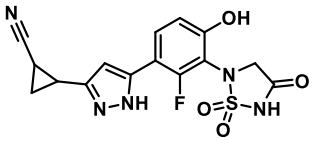
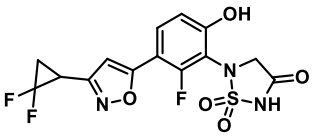
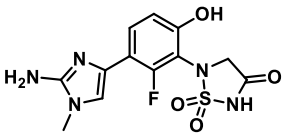
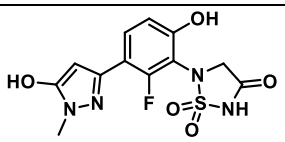
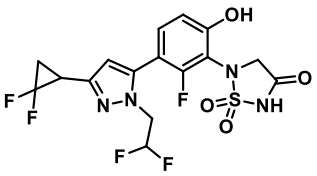
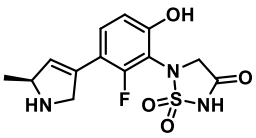
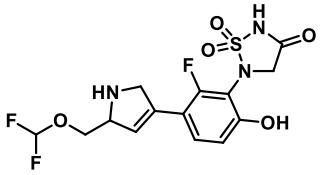
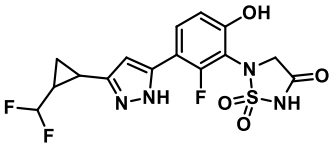
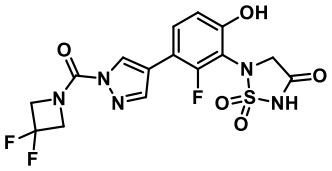
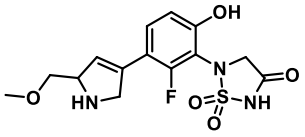
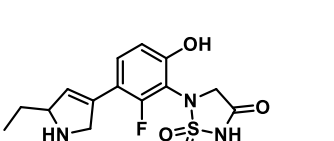
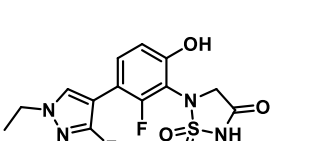
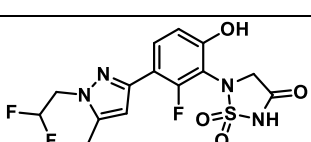
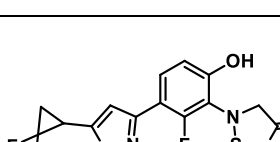
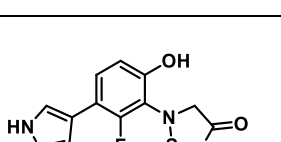
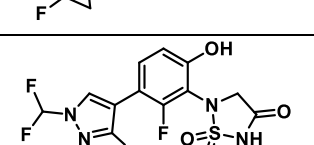
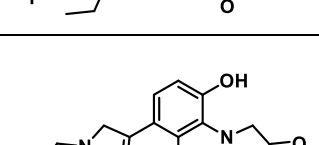
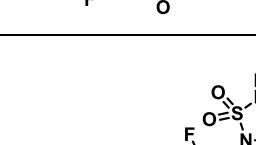
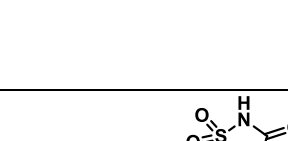
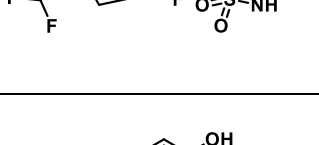
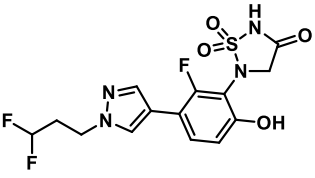
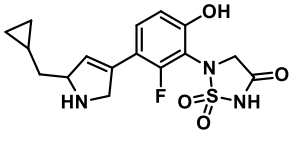
		
		
		
		
		
		
		
		

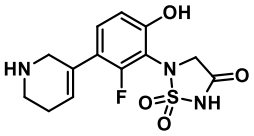
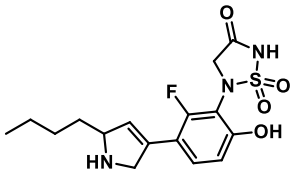
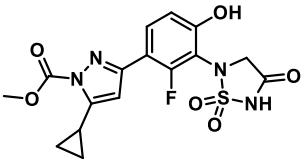
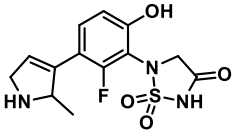
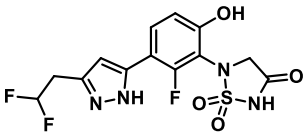
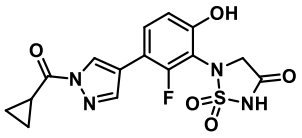
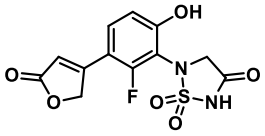
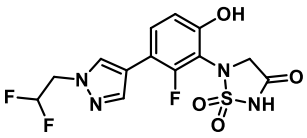
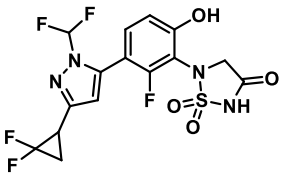
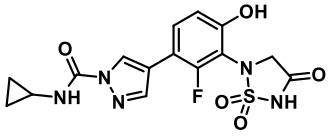
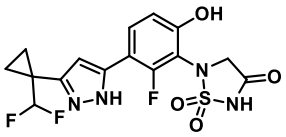
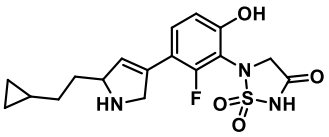
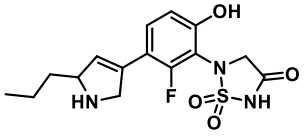
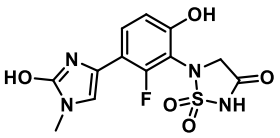
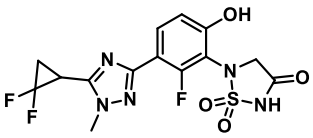
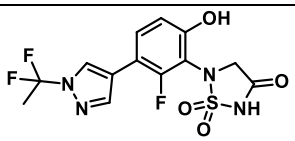
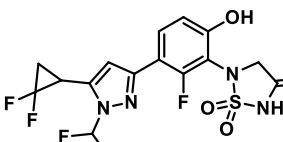
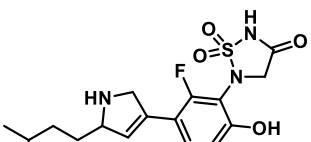
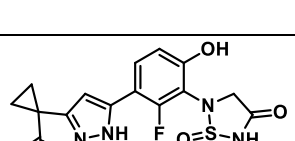
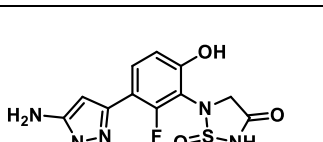
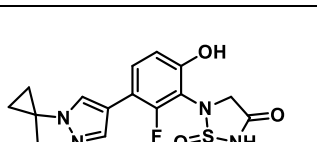
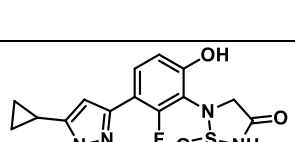
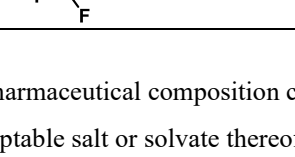
		
		
		
		
		
		
		
		

16. A pharmaceutical composition comprising a compound of any one of claims 1 to 15, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable excipient.
17. Use of a compound of any one of claims 1 to 15, or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for treating cancer.
18. Use of a compound of any one of claims 1 to 15, in the manufacture of a medicament for potentiating immunity of a subject in need thereof, wherein:

(a) a subject that exhibits expression or activity of PTPN2 and/or PTP1B is selected; and

(b) the compound downregulates expression or activity of PTPN2 and/or PTP1B in a cell of the subject, thereby potentiating immunity of the subject.

19. The use of claim 18, wherein another agent or therapy is to be administered to the subject, and the downregulation of the expression or activity of PTPN2 and/or PTP1B in the cell of the subject is performed prior to, concurrent with, or subsequent to the administration of the another agent or therapy to the subject.
20. A compound of any one of claims 1 to 15, for use in therapy.