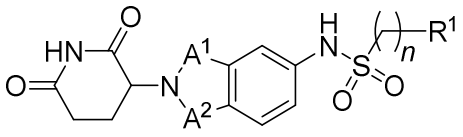
CLAIMS

What is claimed is:

1. A compound having a structure represented by a formula:



,

wherein *n* is an integer selected from 0, 1 and 2;

wherein each of A^1 and A^2 is independently selected from —(C=O)— and —CH_2—, provided that at least one of A^1 and A^2 is —(C=O)—;

wherein R^1 is selected from:

(a) a 5- to 10-membered aryl or heteroaryl optionally substituted with a group selected from halogen, —SF_5, —CN, —N_3, —NH_2, —OH, —CN, —SCF_3, C_1-C_3 alkoxy, C_1-C_3 haloalkyl, C_1-C_3 aminoalkyl, C_1-C_3 alkylamino, C_1-C_3 hydroxyalkyl, —O—(C_1-C_3 haloalkyl), C_3-C_8 cycloalkyl, C_1-C_6 alkyl, and phenyl; and

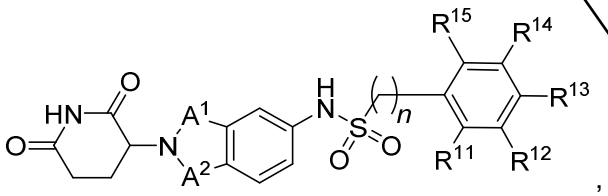
(b) a 5- to 10-membered cycloalkyl optionally substituted with a group selected from halogen, —SF_5, —CN, —N_3, —NH_2, —OH, —CN, —SCF_3, C_1-C_3 alkoxy, C_1-C_3 haloalkyl, C_1-C_3 aminoalkyl, C_1-C_3 alkylamino, C_1-C_3 hydroxyalkyl, —O—(C_1-C_3 haloalkyl), C_3-C_8 cycloalkyl, C_1-C_6 alkyl, and phenyl;

or a pharmaceutically acceptable salt thereof.

2. The compound of claim 1, wherein n is selected from 0 and 1.

3. The compound of claim 1, wherein each of A^1 and A^2 is —(C=O)—.

4. The compound of claim 1, wherein the compound has a structure represented by a formula



,

wherein n is an integer selected from 0, 1 and 2;

wherein each of A^1 and A^2 is independently selected from —(C=O)— and —CH_2—, provided that at least one of A^1 and A^2 is —(C=O)—;

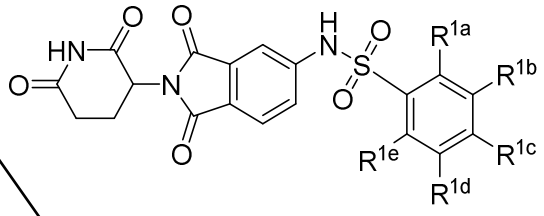
wherein each of R^{11}, R^{12}, R^{13}, R^{14}, and R^{15} is independently selected from hydrogen, halogen, —SF_5, —CN, —N_3, —NH_2, —OH, —CN, —SCF_3, C_1-C_3 alkoxy, C_1-C_3 haloalkyl,

C_1-C_3 aminoalkyl, C_1-C_3 alkylamino, C_1-C_3 hydroxyalkyl, ─O─(C_1-C_3 haloalkyl), C_3-C_8 cycloalkyl, C_1-C_6 alkyl, and phenyl;

or a pharmaceutically acceptable salt thereof.

5. The compound of claim 4, wherein at least one of R^{11}, R^{12}, R^{13}, R^{14}, and R^{15} is not hydrogen.

6. The compound of claim 1, the compound has a structure represented by a formula:



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wherein R^{1a} is selected from bromo, methyl, ─CF_3, and ─OCF_3;

wherein each of R^{1b}, R^{1d}, and R^{1e} is independently selected from hydrogen, halogen, and methyl; and

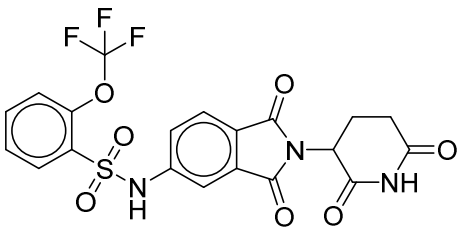
wherein R^{1c} is selected from hydrogen, halogen, methyl, and phenyl;

or a pharmaceutically acceptable salt thereof.

7. The compound of claim 6, wherein R^{1a} is selected from ─CF_3 and ─OCF_3.

8. The compound of claim 6, wherein each of R^{1b}, R^{1c}, R^{1d}, and R^{1e} is hydrogen.

9. The compound of claim 1, having a structure represented by a formula:



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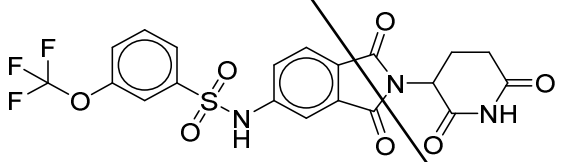

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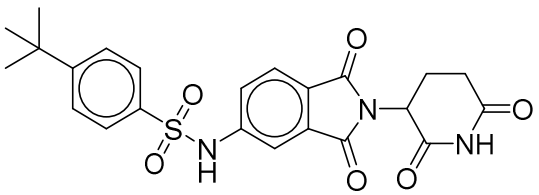

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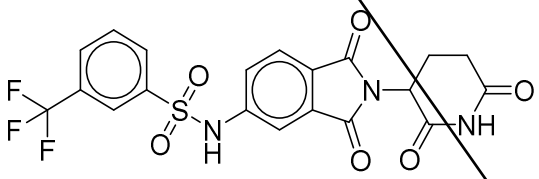

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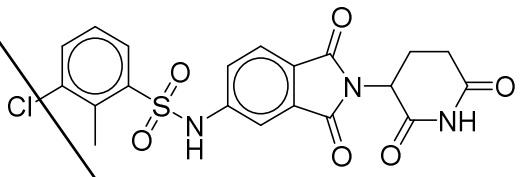
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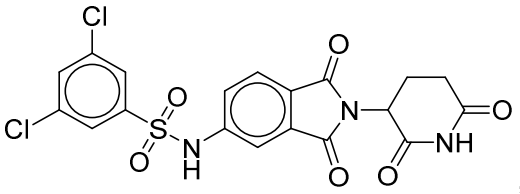
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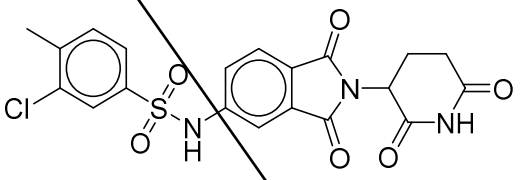
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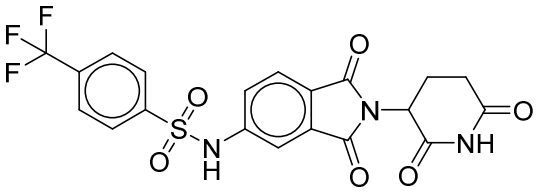
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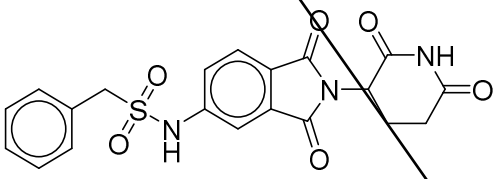
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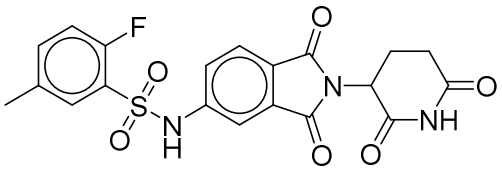
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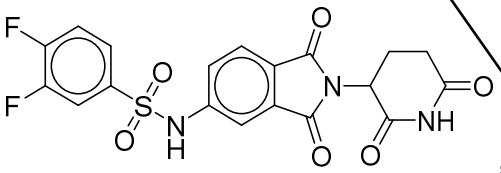
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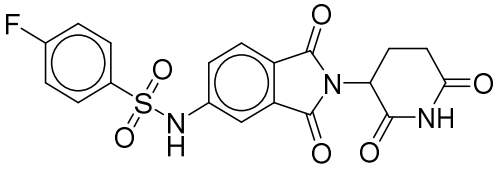
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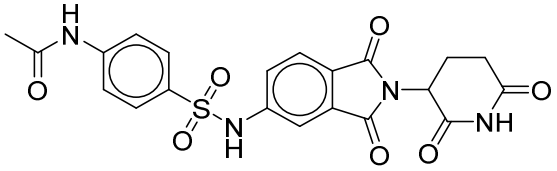
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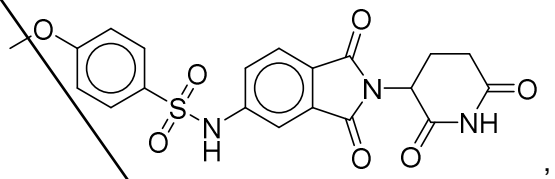
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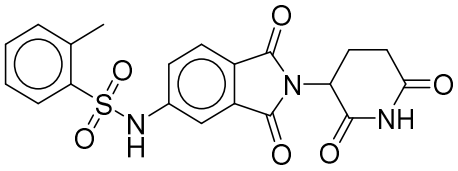
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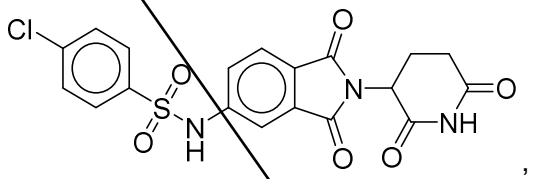
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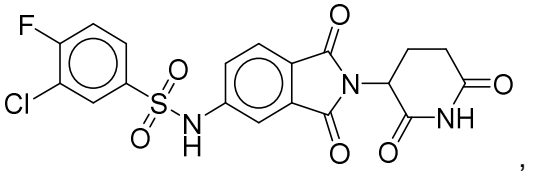
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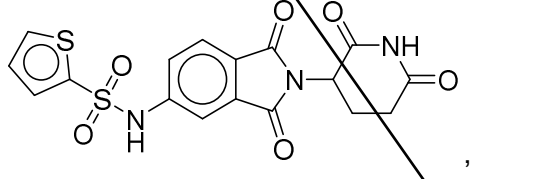
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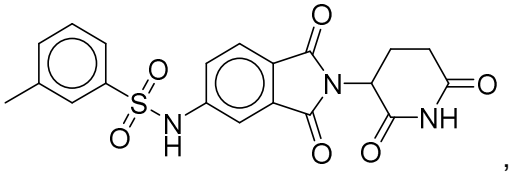
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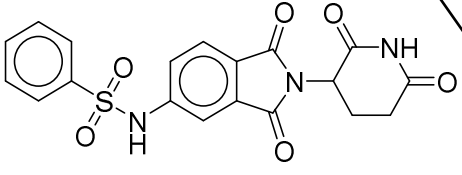
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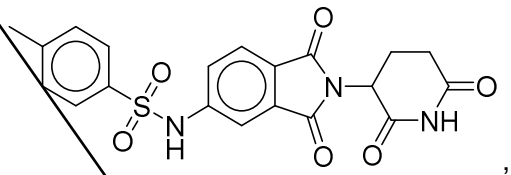
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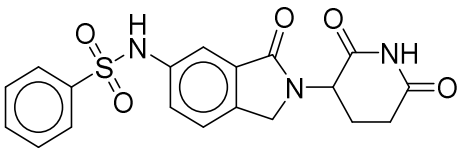
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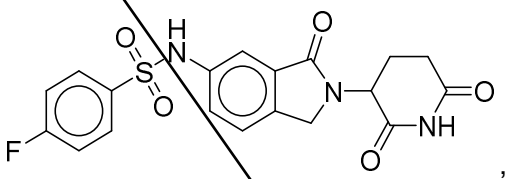
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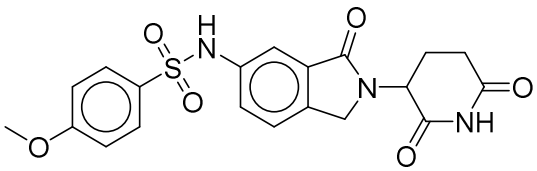
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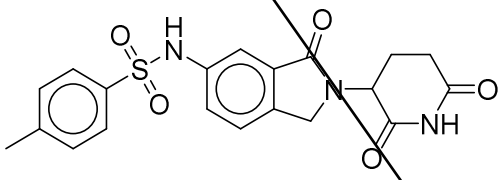
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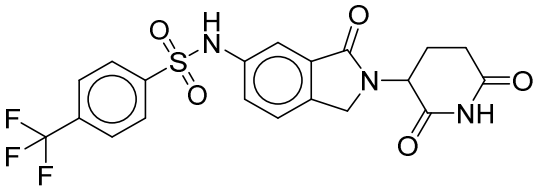
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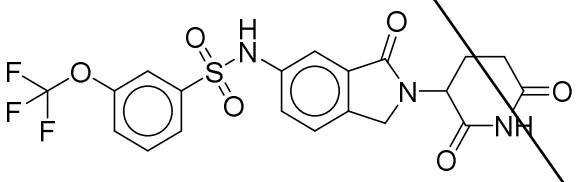
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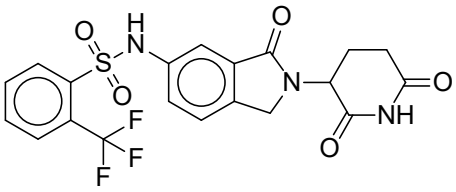
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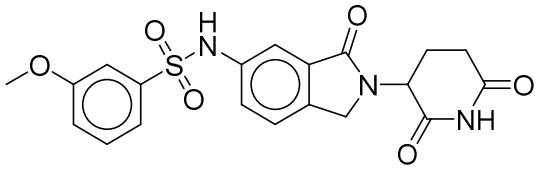
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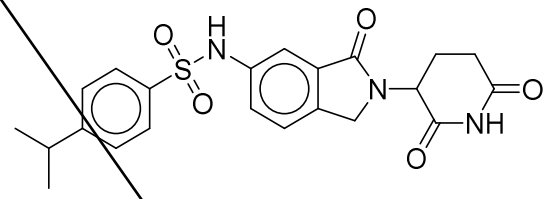
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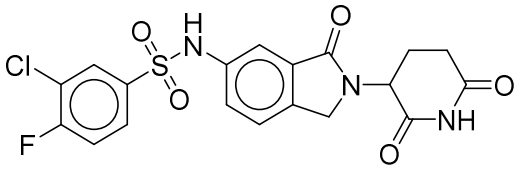
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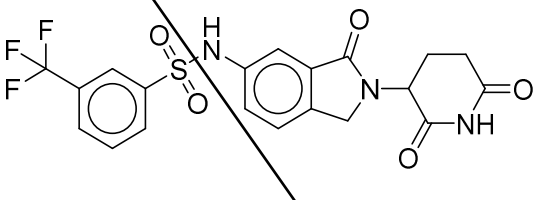
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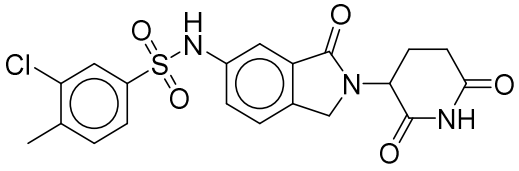
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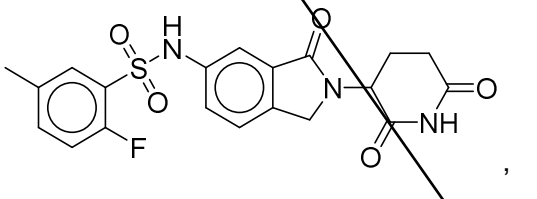
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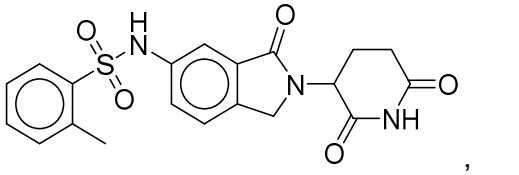
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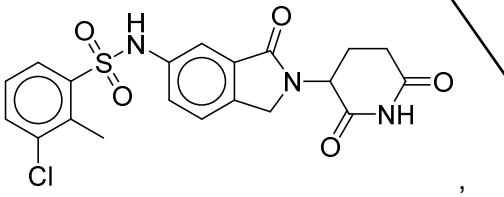
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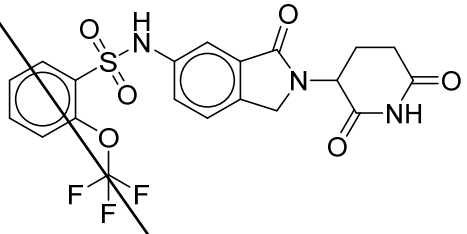
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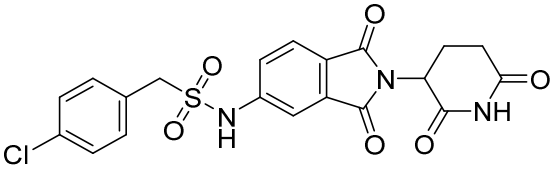
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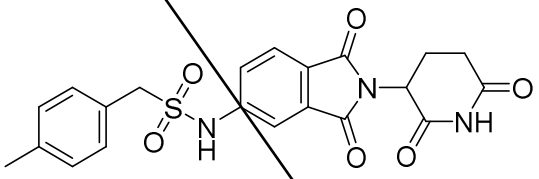
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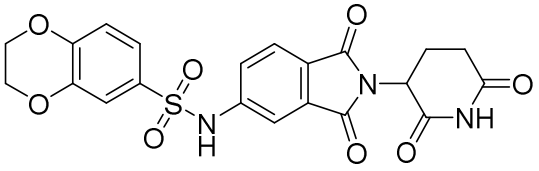
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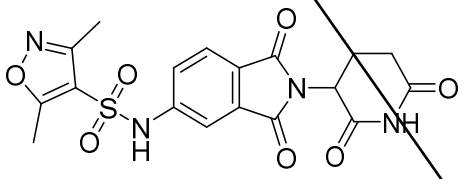
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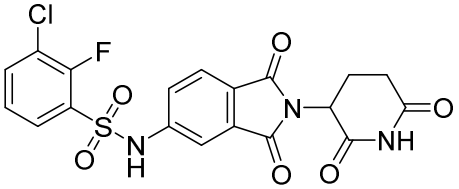
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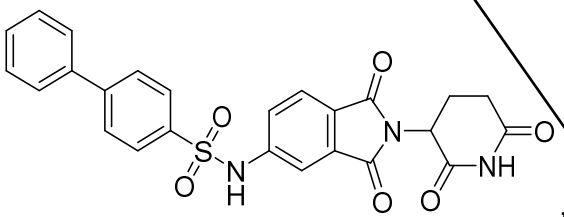
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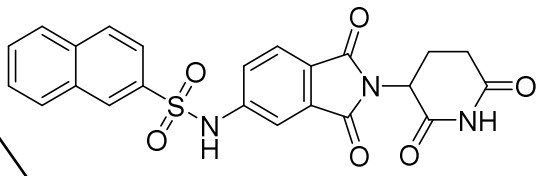
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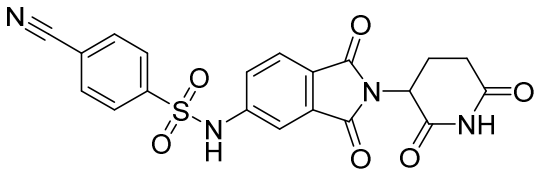
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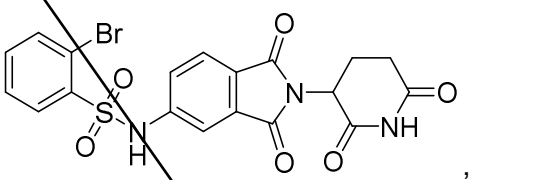
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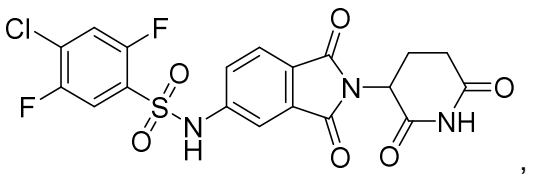
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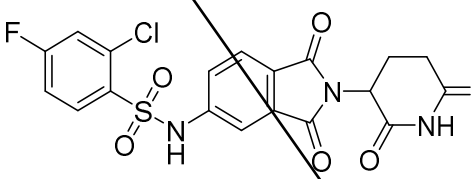
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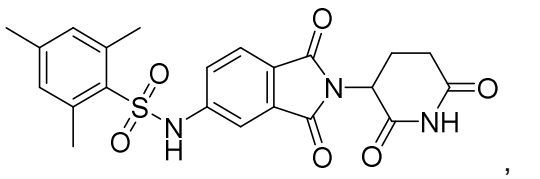
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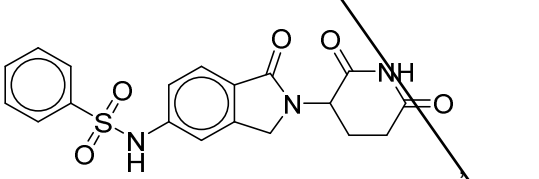
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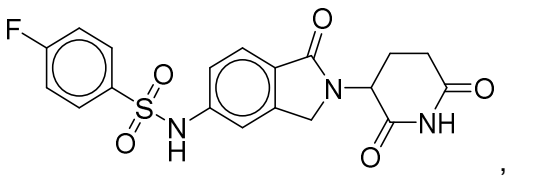
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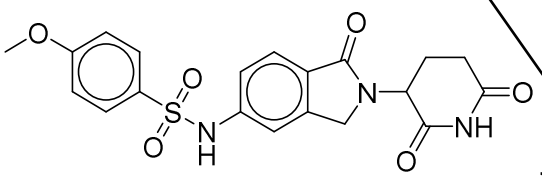
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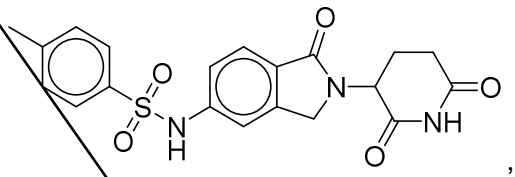
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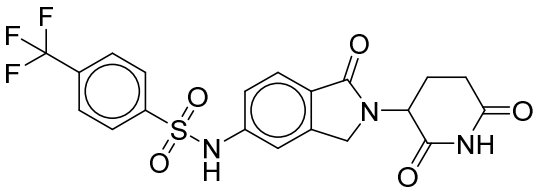
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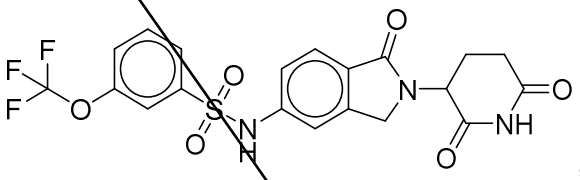
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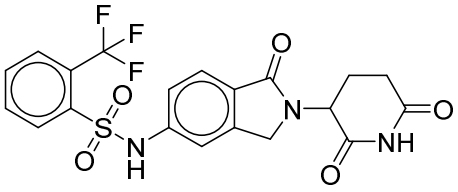
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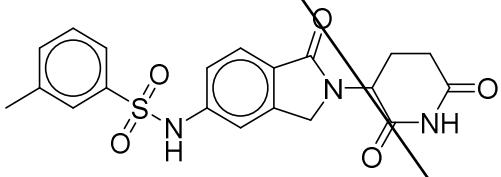
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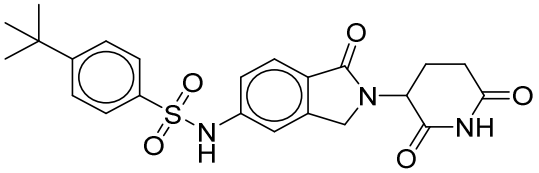
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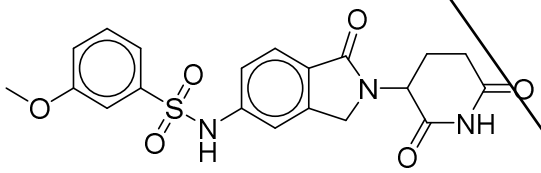
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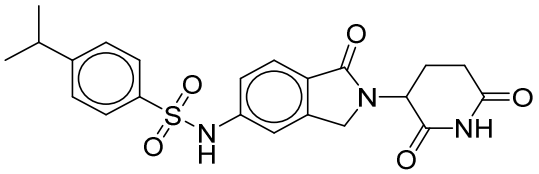
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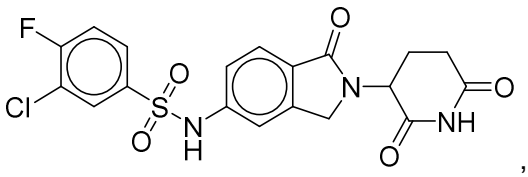
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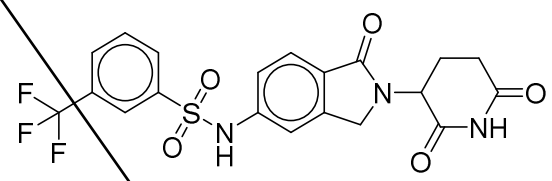
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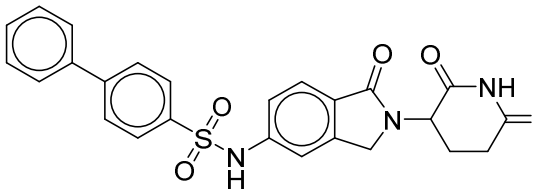
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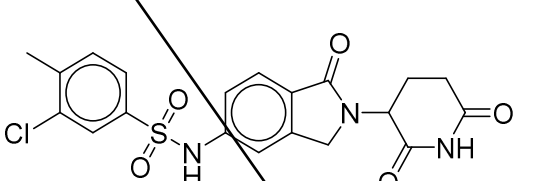
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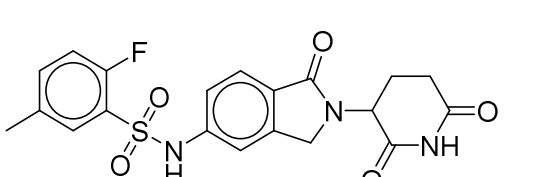
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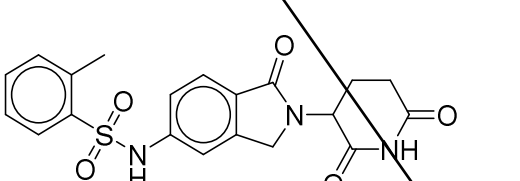
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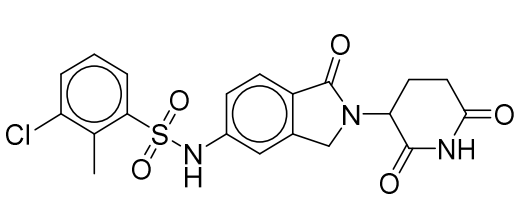
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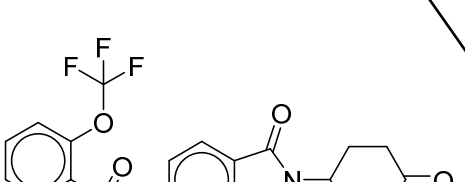
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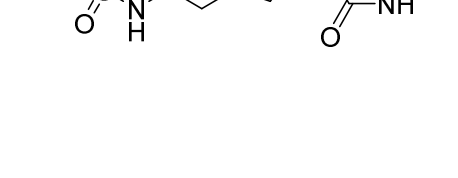
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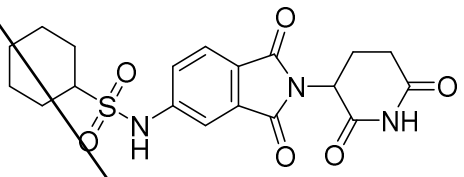
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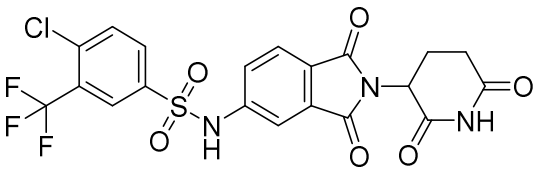
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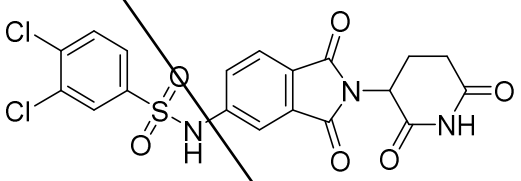
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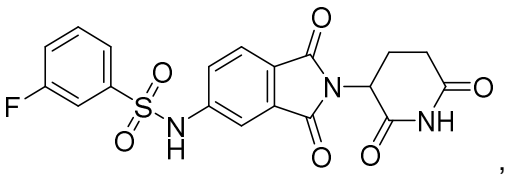
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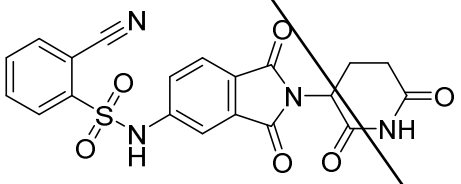
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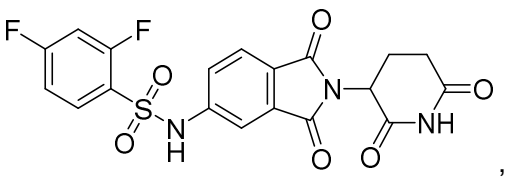
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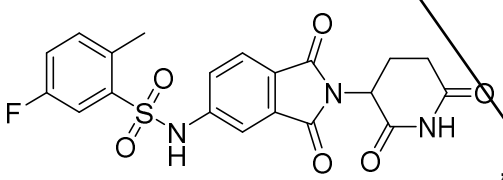
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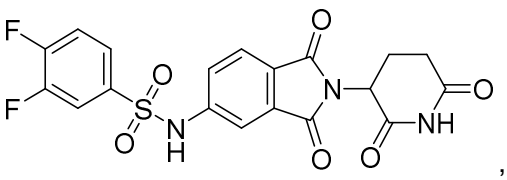
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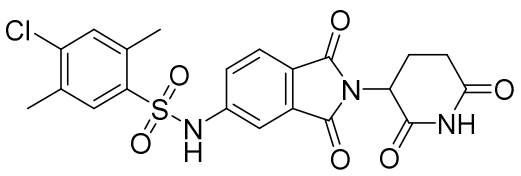
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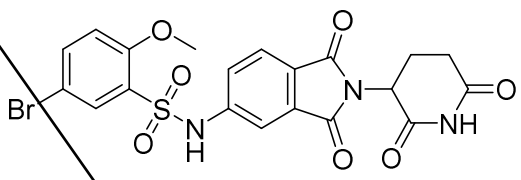
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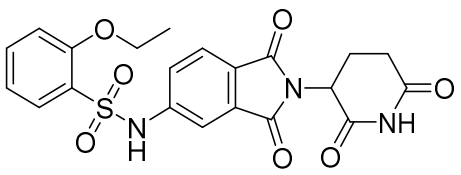
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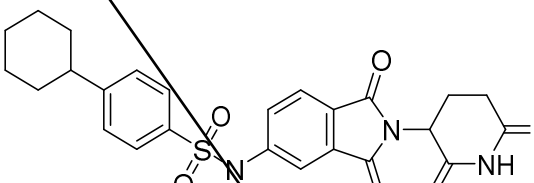
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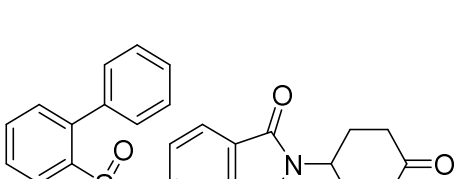
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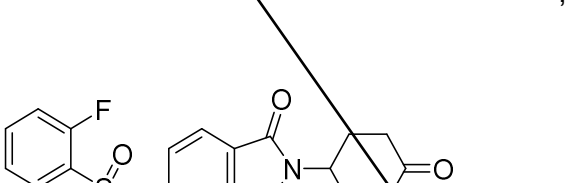
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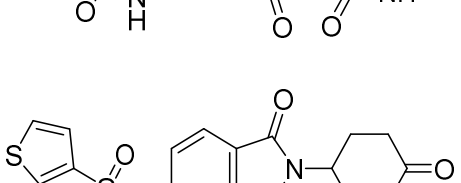
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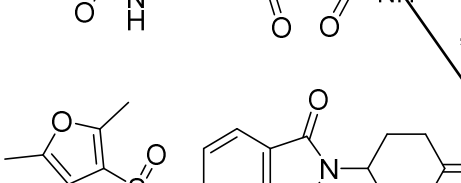
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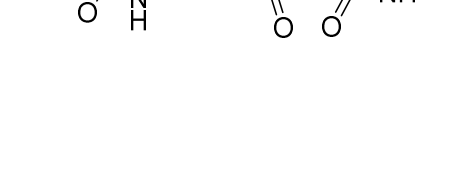
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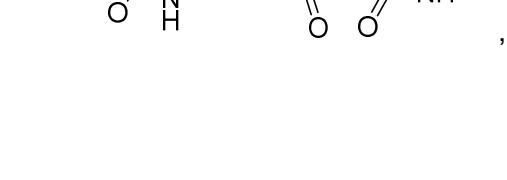
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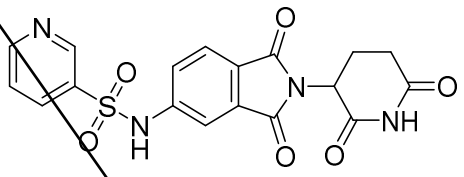
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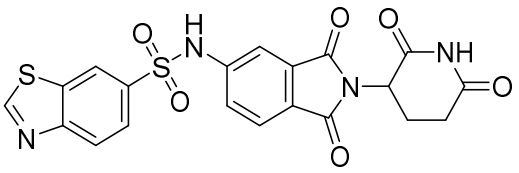
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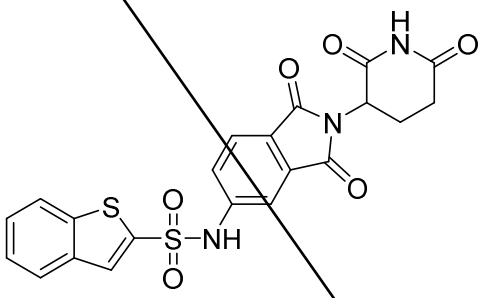
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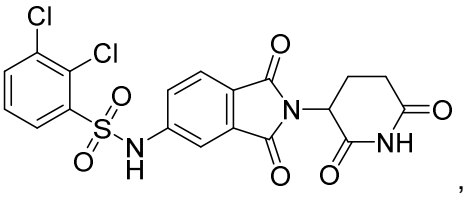
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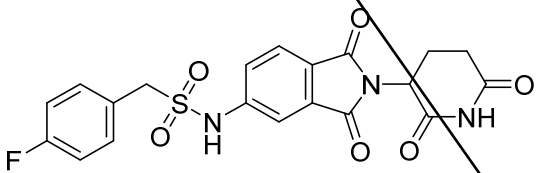
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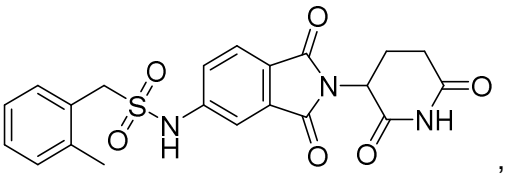
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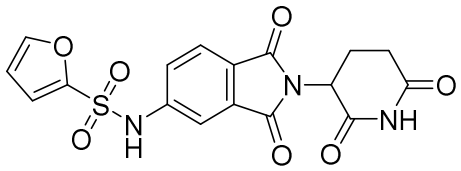
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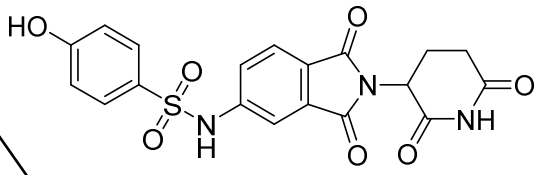
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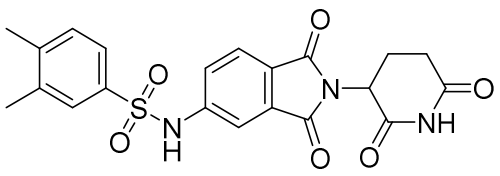
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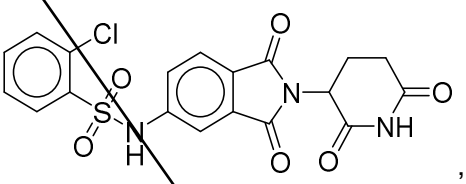
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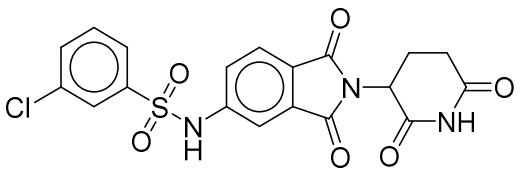
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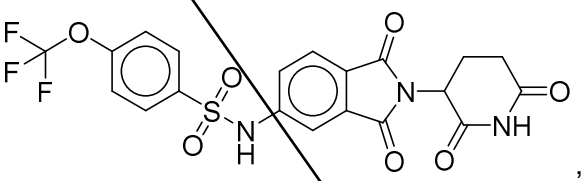
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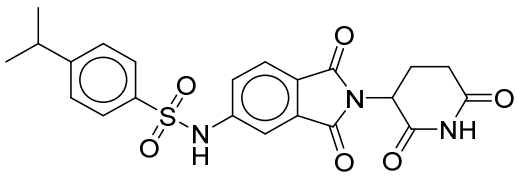
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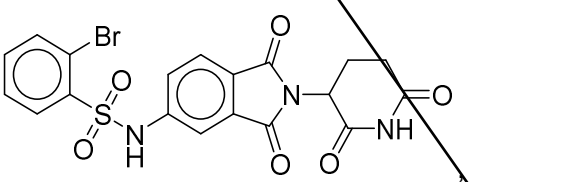
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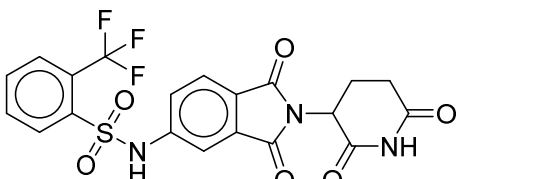
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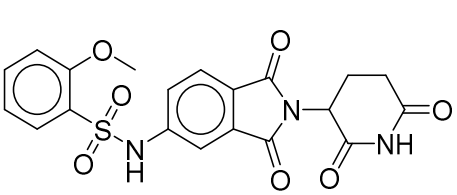
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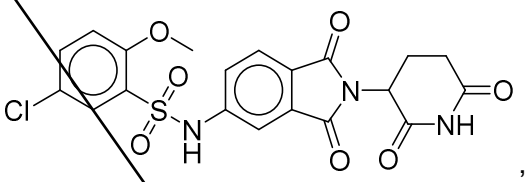
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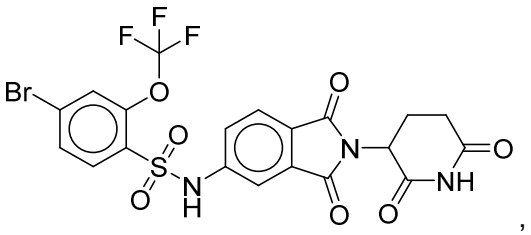
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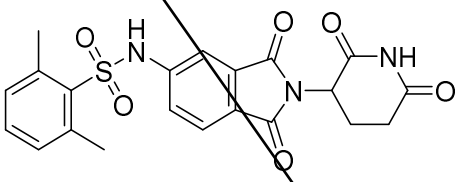
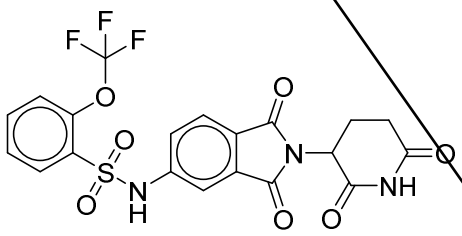

, or a subgroup thereof.

10. The compound of claim 8, having a structure represented by a formula: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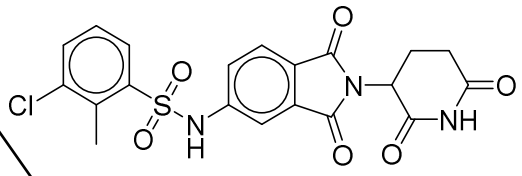
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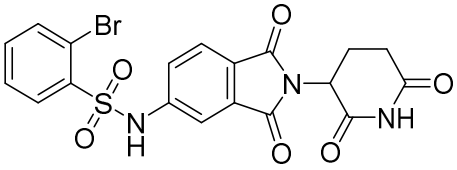
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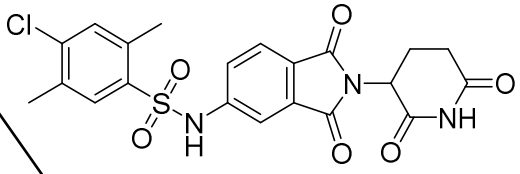
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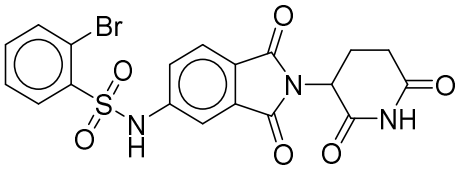
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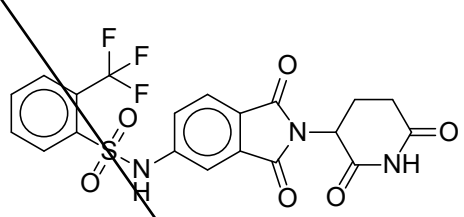
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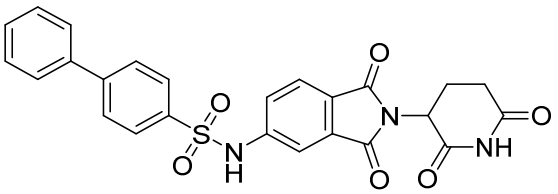

; or a subgroup thereof.

11. A pharmaceutical composition comprising a therapeutically effective amount of a compound of claim 1, and a pharmaceutically acceptable carrier.

12. The pharmaceutical composition of claim 11, further comprising at least one agent known to treat a cancer.

13. A method for the treatment of a disorder of uncontrolled cellular proliferation in a mammal comprising the step of administering to the mammal a therapeutically effective amount of at least one compound of claim 1, or a pharmaceutically acceptable salt thereof.

14. The method of claim 13, wherein the mammal has been diagnosed with a need for treatment of the disorder of uncontrolled cellular proliferation prior to the administering step.

15. The method of claim 13, further comprising the step of identifying a mammal in need of treatment of the disorder of uncontrolled cellular proliferation.

16. The method of claim 13, wherein the disorder of uncontrolled cellular proliferation is associated with cereblon (CRBN) dysfunction.

17. The method of claim 13, wherein the disorder of uncontrolled cellular proliferation is a cancer.

18. The method of claim 17, wherein the cancer is selected from a brain cancer, lung cancer, hematological cancer, bladder cancer, colon cancer, cervical cancer, ovarian cancer, squamous cell cancer, kidney cancer, peritoneal cancer, breast cancer, gastric cancer, colorectal cancer, prostate cancer, pancreatic cancer, genitourinary tract cancer, lymphatic system cancer, stomach cancer, larynx cancer, malignant melanoma, colorectal cancer, endometrial carcinoma, thyroid cancer, rhabdosarcoma, and combinations thereof.

19. The method of claim 18, wherein the lung cancer is selected from small-cell lung cancer, non-small cell lung cancer, and combinations thereof;

    wherein the kidney cancer is a kidney clear cell carcinoma;

    wherein the brain cancer is selected from glioblastoma, medullablastoma, glioma, and combination thereof;

    wherein the bladder cancer is a bladder urothelia carcinoma;

    the liver cancer is a hepatic carcinoma; and

    the hematological cancer is selected from a childhood acute leukemia (AL), chronic myeloid leukemia (CML), acute myeloid leukemia (AML), chronic lymphoid leukemia (CLL), acute lymphoid leukemia (ALL), hairy cell leukemia, chronic myelomonocytic leukemia (CMML), juvenile myelomonocyte leukemia (JMML), large granular lymphocytic leukemia (LGL), acute lymphocytic leukemia, acute lymphoblastic leukemia, B-cell lymphoma, T-cell-lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, hairy cell lymphoma, Burkett's lymphoma, Hodgkin lymphoma, non-Hodgkin lymphoma, and combinations thereof.

20. The method of claim 13, further comprising the step of administering a therapeutically effective amount of at least one agent known to treat a cancer.

21. The method of claim 20, wherein the at least one agent is selected from uracil mustard, chlormethine, cyclophosphamide, ifosfamide, melphalan, chlorambucil, pipobroman, triethylenemelamine, triethylenethiophosphoramine, busulfan, carmustine, lomustine, streptozocin, dacarbazine, temozolomide, thiotepa, altretamine, methotrexate, 5-fluorouracil, floxuridine, cytarabine, 6-mercaptopurine, 6-thioguanine, fludarabine phosphate, pentostatin, bortezomib, vinblastine, vincristine, vinorelbine, vindesine, bleomycin, dactinomycin, daunorubicin, doxorubicin, epirubicin, dexamethasone, clofarabine, cladribine, pemextresed, idarubicin, paclitaxel, docetaxel, ixabepilone, mithramycin, topotecan, irinotecan, deoxycoformycin, mitomycin-C, L-asparaginase, interferons, etoposide, teniposide 17α-ethinylestradiol, diethylstilbestrol, testosterone, prednisone, fluoxymesterone, dromostanolone propionate, testolactone, megestrolacetate, tamoxifen, methylprednisolone, methyltestosterone, prednisolone, triamcinolone, chlorotrianisene, hydroxyprogesterone, aminoglutethimide, estramustine, medroxyprogesteroneacetate, leuprolide, flutamide, toremifene, goserelin, cisplatin, carboplatin, hydroxyurea, amsacrine, procarbazine, mitotane, mitoxantrone, levamisole, navelbene, anastrazole, letrazole, capecitabine, reloxafine, droloxafine, hexamethylmelamine, oxaliplatin, gefinitib, capecitabine, erlotinib, azacitidine, temozolomide, gemcitabine, vasostatin, and combinations thereof.

22. The method of claim 20, wherein the at least one agent is a DNA methyltransferase inhibitor, an HDAC-inhibitor, a glucocorticoid, an mTOR inhibitor, a cytotoxic agent, or combinations thereof.

23. The method of claim 22, wherein the DNA methyltransferase inhibitor is 5-aza-2′-deoxycytidine, 5-azacytidine, zebularin, epigallocatechin-3-gallate, procaine, or combinations thereof;

    wherein the HDAC-inhibitor is vorinostat, entinostat, panbinostat, trichostatin A, mocetinostat, belinostat, dacinostat, givinostat, tubastatin A, pracinostat, droxinostat, quisinostat, romidepsin, valproic acid, AR-42 (OSU-HDAC42), tacedinaline, rocilinostat, apicidin, or combinations thereof;

    wherein the glucocorticoid is dexamethasone, prednisolone, methylprednisolone, betamethasone, triamicinolone, fludrocortisone, beclomethasone, or combinations thereof;

    wherein the mTor inhibitor is BEZ235, everolimus, temsirolimus, rapamycin, AZD8055, or combinations thereof; and

    wherein the cytotoxic agent is an alkylating agent, an antimetabolite agent, an antineoplastic antibiotic agent, a mitotic inhibitor agent, a mTor inhibitor agent, or other

chemotherapeutic agent.

24. The method of claim 23, wherein the antineoplastic antibiotic agent is selected from one or more of the group consisting of doxorubicin, mitoxantrone, bleomycin, daunorubicin, dactinomycin, epirubicin, idarubicin, plicamycin, mitomycin, pentostatin, and valrubicin, or a pharmaceutically acceptable salt, hydrate, solvate, or polymorph thereof;

    wherein the antimetabolite agent is selected from one or more of the group consisting of gemcitabine, 5-fluorouracil, capecitabine, hydroxyurea, mercaptopurine, pemetrexed, fludarabine, nelarabine, cladribine, clofarabine, cytarabine, decitabine, pralatrexate, floxuridine, methotrexate, and thioguanine, or a pharmaceutically acceptable salt, hydrate, solvate, or polymorph thereof;

    wherein the alkylating agent is selected from one or more of the group consisting of carboplatin, cisplatin, cyclophosphamide, chlorambucil, melphalan, carmustine, busulfan, lomustine, dacarbazine, oxaliplatin, ifosfamide, mechlorethamine, temozolomide, thiotepa, bendamustine, and streptozocin, or a pharmaceutically acceptable salt, hydrate, solvate, or polymorph thereof;

    wherein the mitotic inhibitor agent is selected from one or more of the group consisting of irinotecan, topotecan, rubitecan, cabazitaxel, docetaxel, paclitaxel, etopside, vincristine, ixabepilone, vinorelbine, vinblastine, and teniposide, or a pharmaceutically acceptable salt, hydrate, solvate, or polymorph thereof;

    wherein the mTor inhibitor is everolimus, sirolimus, temsirolimus, or combinations thereof; and

    wherein the other chemotherapeutic agent is an anthracycline, cytarabine, a purine analog, sorafenib, gemtuzumab ozogamicin, rituximab, or combinations thereof.

25. The method of claim 20, wherein the at least one agent is administered sequentially or simultaneously.

26. The method of claim 20, wherein the at least one agent is co-formulated or co-packaged.

27. A method for modulating of cereblon activity or GSPT1 activity in at least one cell, comprising the step of contacting the at least one cell with an effective amount of at least one compound of claim 1, or a pharmaceutically acceptable salt thereof.

28. The method of claim 27, wherein contacting is via administration to a mammal.

29. The method of claim 28, wherein the mammal has been diagnosed with a need for modulating of cereblon activity or for treatment of a disorder related to cereblon activity prior to the administering step.

30. The method of claim 28, wherein the compound inhibits cell proliferation with an IC_{50} of less than about 10 μM when determined in a cell viability assay using MV4-11 cells as described herein;

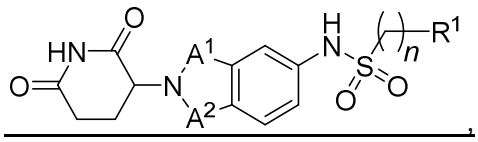
wherein the compound exhibits cereblon binding with an IC_{50} of less than about 10 μM using a fluorescence polarization assay as described herein; or

wherein the compound inhibits cell proliferation with an IC_{50} of less than about 20 μM when determined in a cell viability assay using GSPT1 HiBit tagged cells.

CLAIMS

What is claimed is:

1. A compound having a structure represented by a formula:



wherein *n* is an integer selected from 0, 1 and 2;

wherein each of A^1 and A^2 is independently selected from —(C=O)— and —CH_2—, provided that at least one of A^1 and A^2 is —(C=O)—;

wherein R^1 is selected from:

(a) a 5- to 10-membered aryl or heteroaryl optionally substituted with a group selected from halogen, —SF_5, —CN, —N_3, —NH_2, —OH, —CN, —SCF_3, C_1-C_3 alkoxy, C_1-C_3 haloalkyl, C_1-C_3 aminoalkyl, C_1-C_3 alkylamino, C_1-C_3 hydroxyalkyl, —O—(C_1-C_3 haloalkyl), C_3-C_8 cycloalkyl, C_1-C_6 alkyl, and phenyl; and

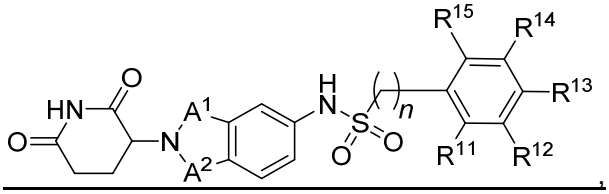
(b) a 5- to 10-membered cycloalkyl optionally substituted with a group selected from halogen, —SF_5, —CN, —N_3, —NH_2, —OH, —CN, —SCF_3, C_1-C_3 alkoxy, C_1-C_3 haloalkyl, C_1-C_3 aminoalkyl, C_1-C_3 alkylamino, C_1-C_3 hydroxyalkyl, —O—(C_1-C_3 haloalkyl), C_3-C_8 cycloalkyl, C_1-C_6 alkyl, and phenyl;

or a pharmaceutically acceptable salt thereof.

2. The compound of claim 1, wherein n is selected from 0 and 1.

3. The compound of claim 1, wherein each of A^1 and A^2 is —(C=O)—.

4. The compound of claim 1, wherein the compound has a structure represented by a formula



wherein n is an integer selected from 0, 1 and 2;

wherein each of A^1 and A^2 is independently selected from —(C=O)— and —CH_2—, provided that at least one of A^1 and A^2 is —(C=O)—;

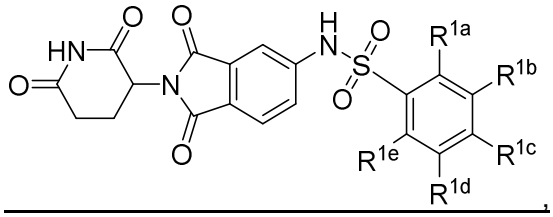
wherein each of R^{11}, R^{12}, R^{13}, R^{14}, and R^{15} is independently selected from hydrogen, halogen, —SF_5, —CN, —N_3, —NH_2, —OH, —CN, —SCF_3, C_1-C_3 alkoxy, C_1-C_3 haloalkyl,

C_1-C_3 aminoalkyl, C_1-C_3 alkylamino, C_1-C_3 hydroxyalkyl, —O—(C_1-C_3 haloalkyl), C_3-C_8 cycloalkyl, C_1-C_6 alkyl, and phenyl;

or a pharmaceutically acceptable salt thereof.

5. The compound of claim 4, wherein at least one of R^{11}, R^{12}, R^{13}, R^{14}, and R^{15} is not hydrogen.

6. The compound of claim 1, the compound has a structure represented by a formula:



wherein R^{1a} is selected from bromo, methyl, —CF_3, and —OCF_3;

wherein each of R^{1b}, R^{1d}, and R^{1e} is independently selected from hydrogen, halogen, and methyl; and

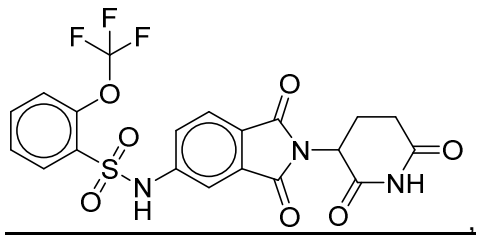
wherein R^{1c} is selected from hydrogen, halogen, methyl, and phenyl;

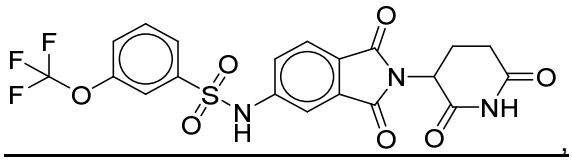
or a pharmaceutically acceptable salt thereof.

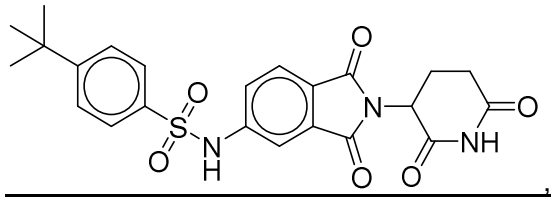
7. The compound of claim 6, wherein R^{1a} is selected from —CF_3 and —OCF_3.

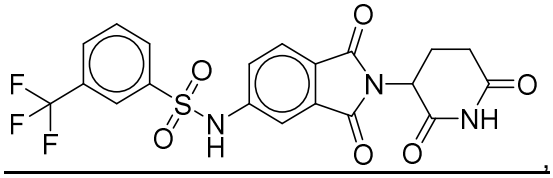
8. The compound of claim 6, wherein each of R^{1b}, R^{1c}, R^{1d}, and R^{1e} is hydrogen.

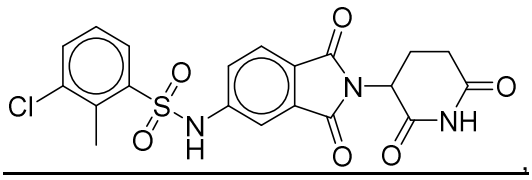
9. The compound of claim 1, having a structure represented by a formula:

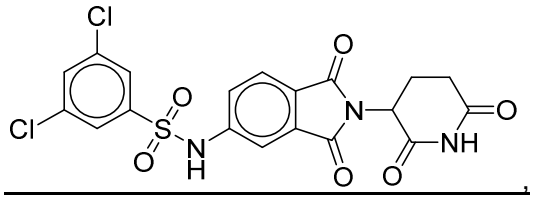


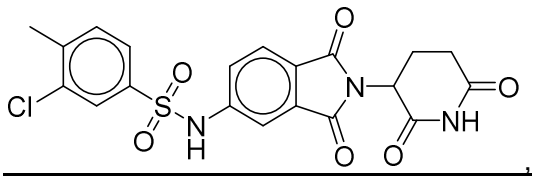


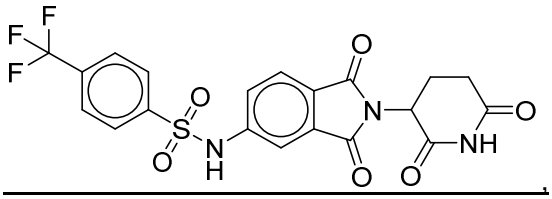


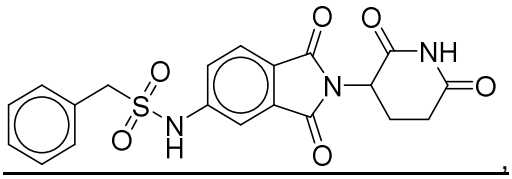


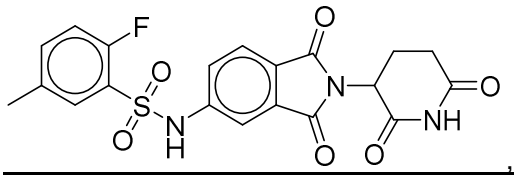


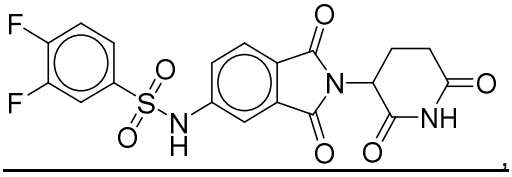


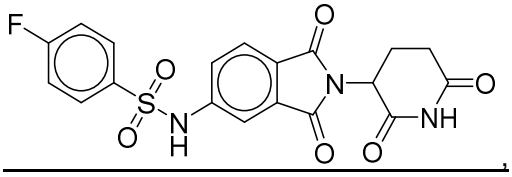


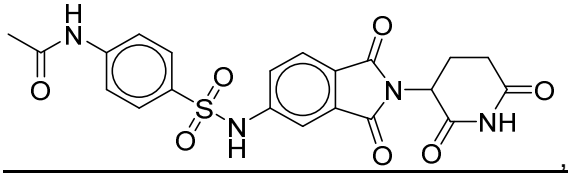


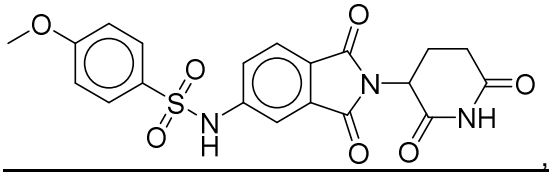


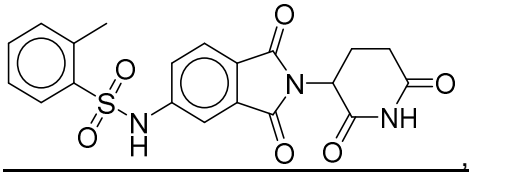


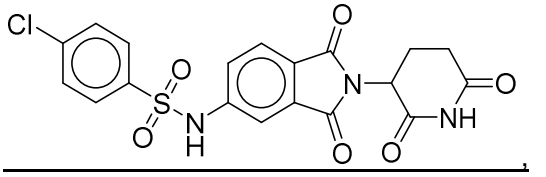


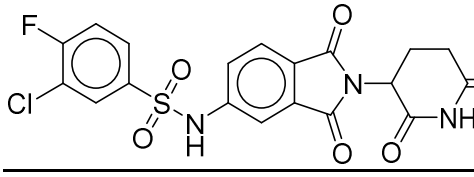


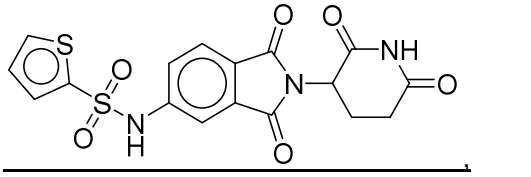


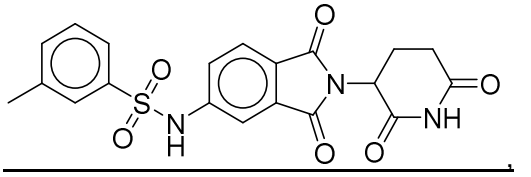


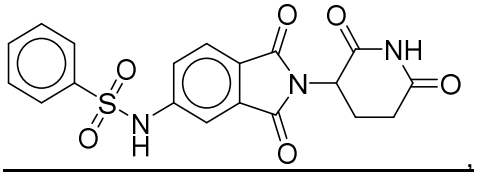


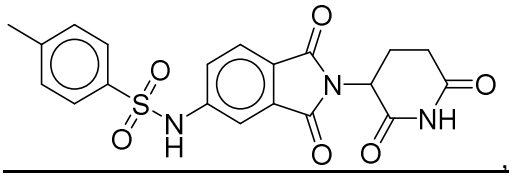


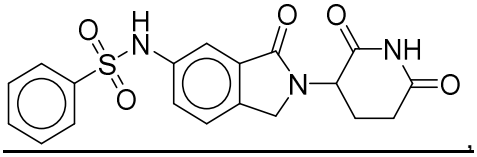


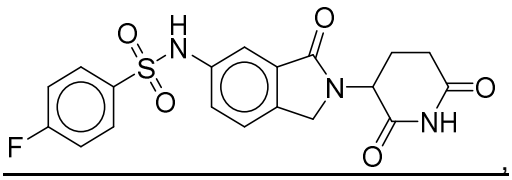


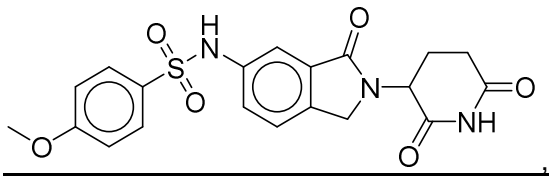


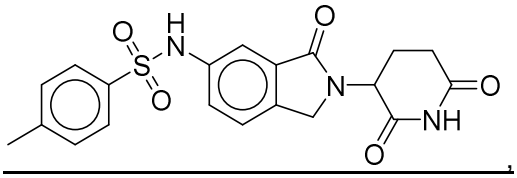


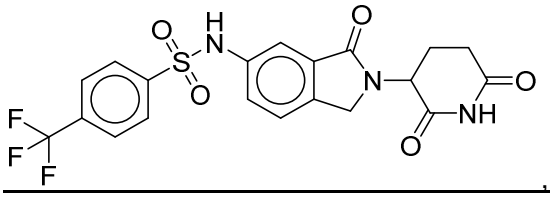


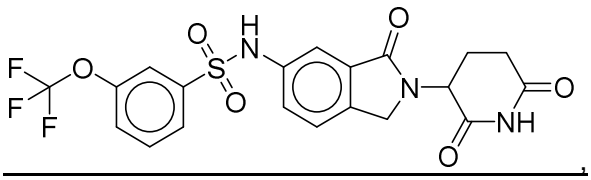


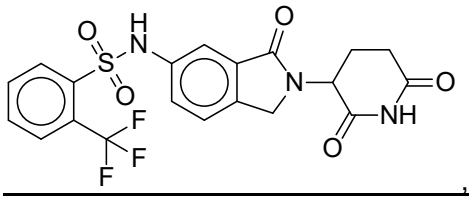


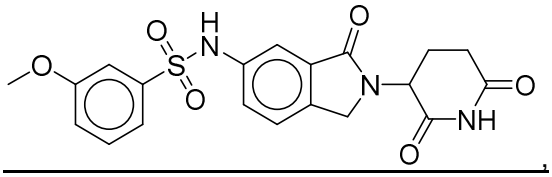


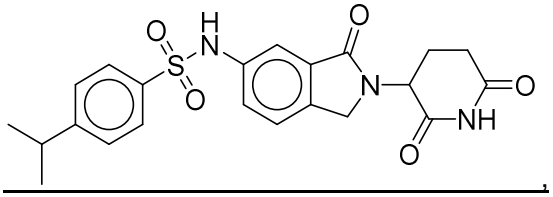


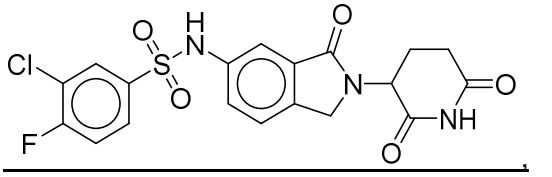


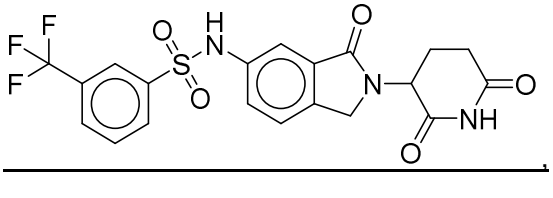


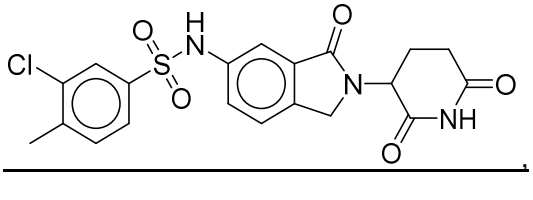


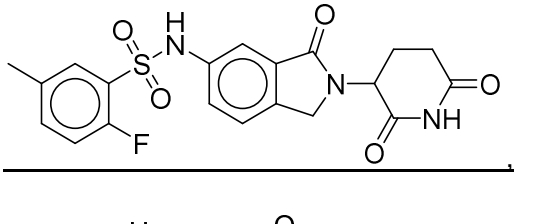


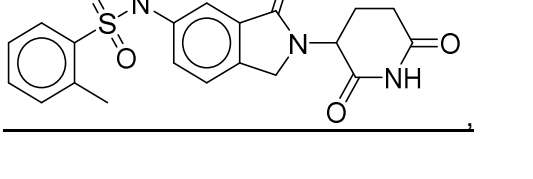


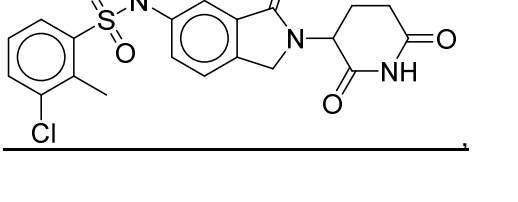




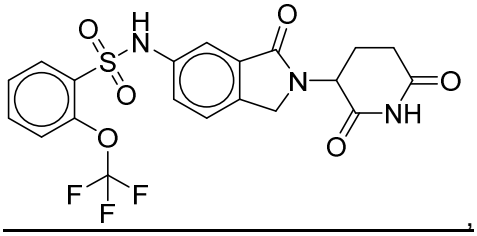


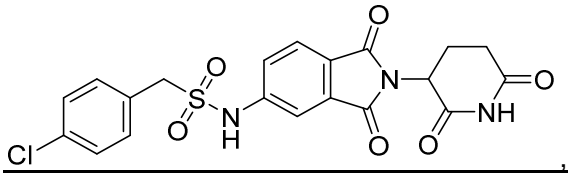


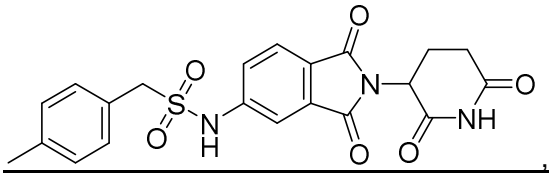


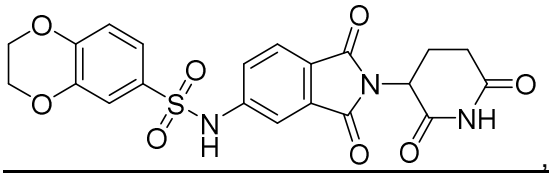


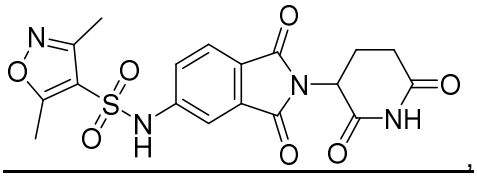


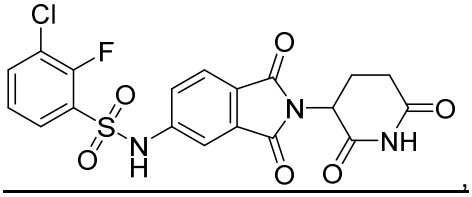


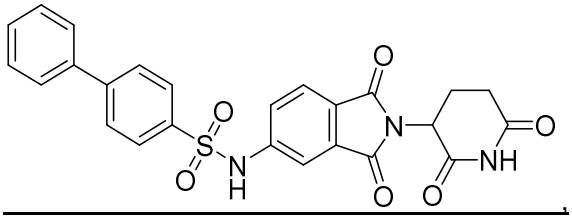


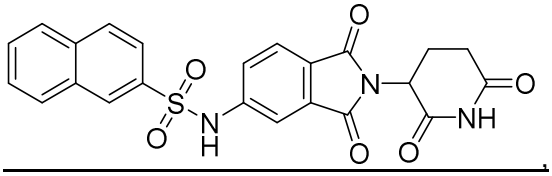


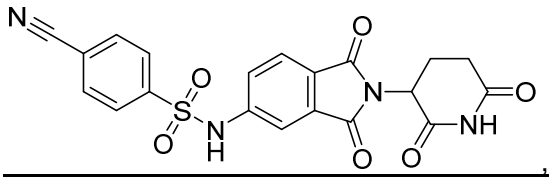


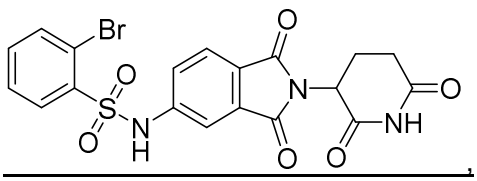


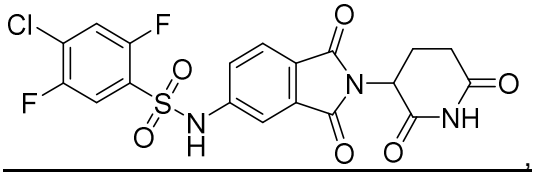


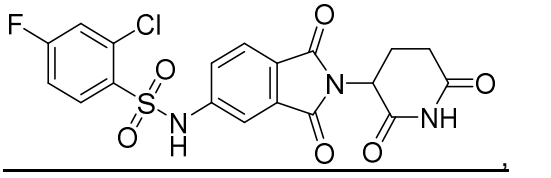


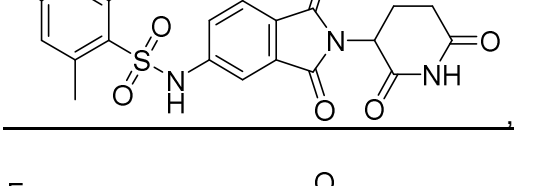


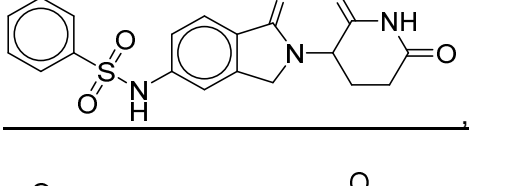


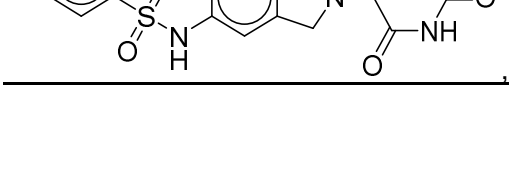


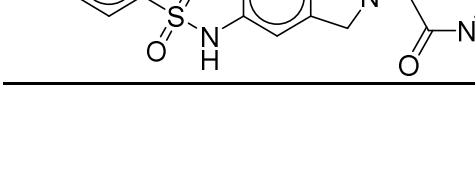


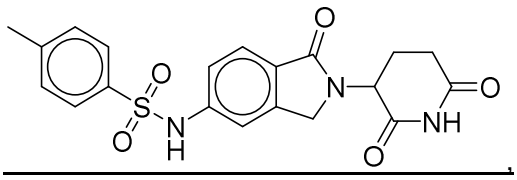


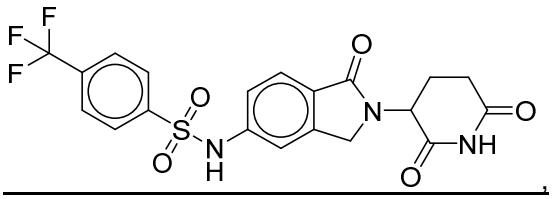


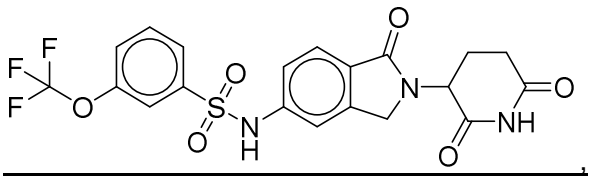


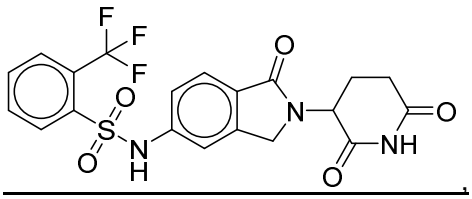


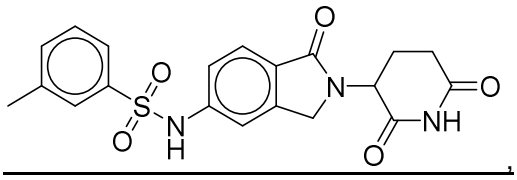


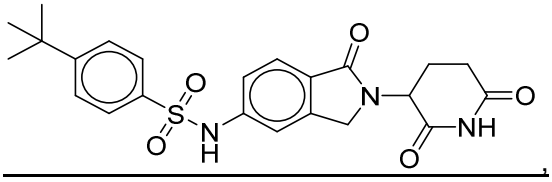


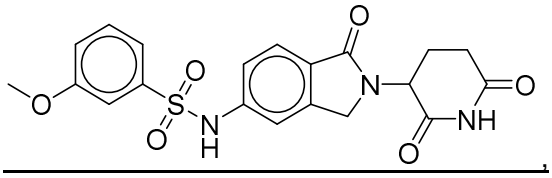


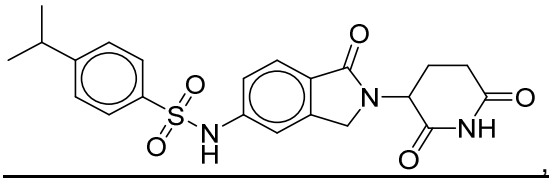


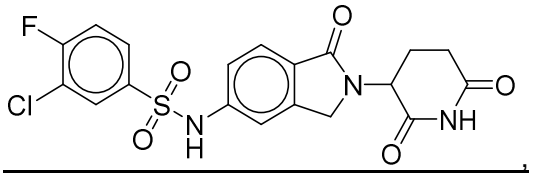


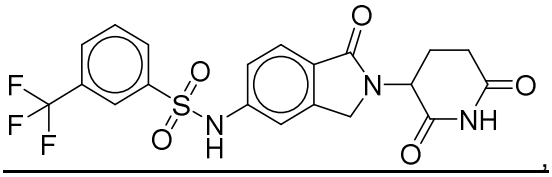


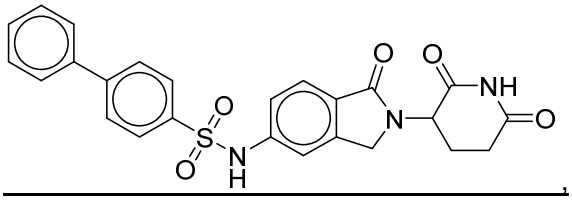


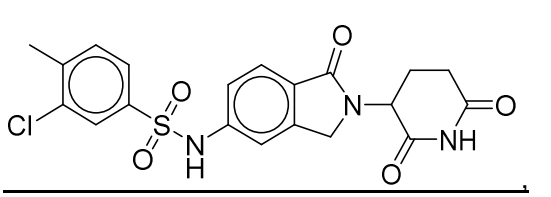


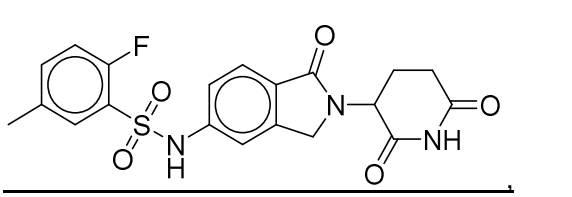


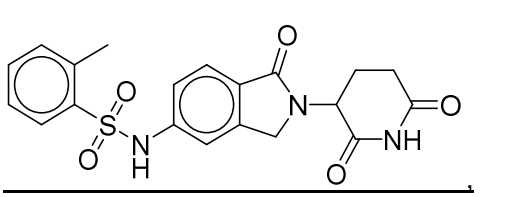


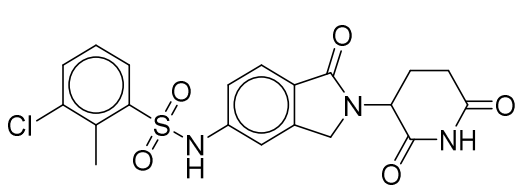


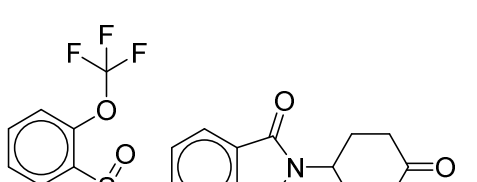


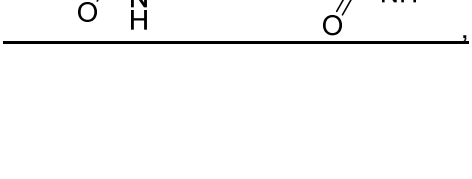


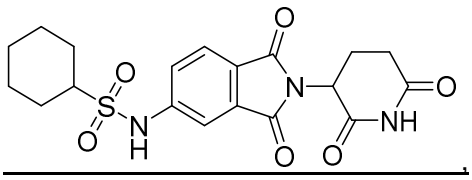


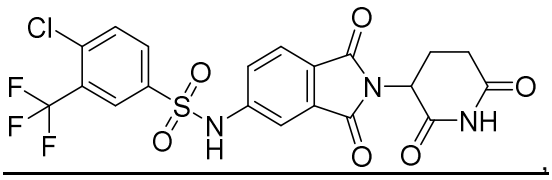


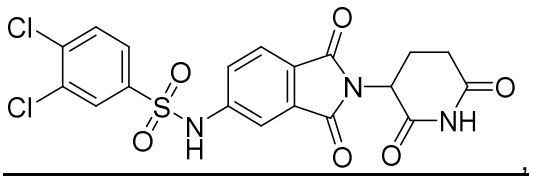


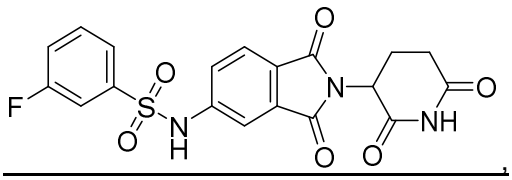


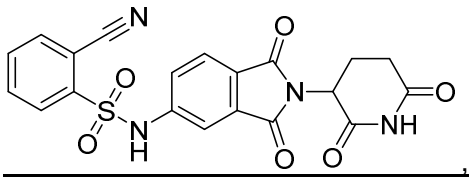


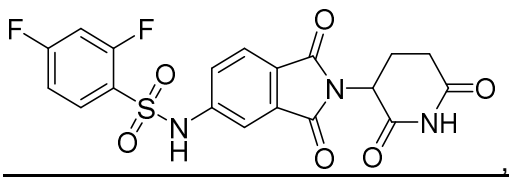


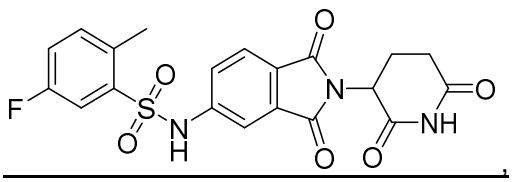


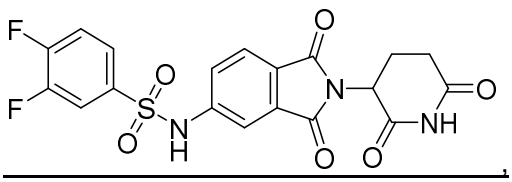


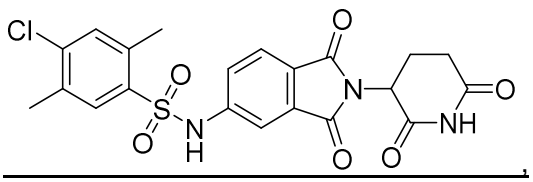


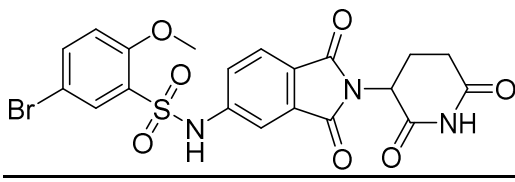


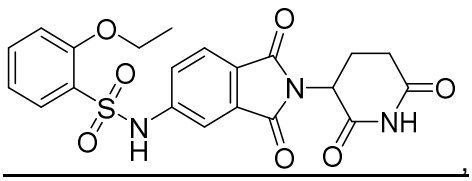


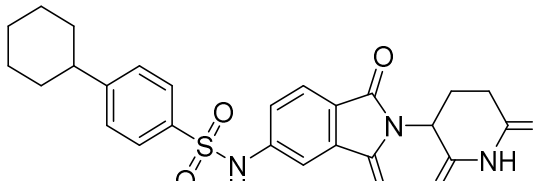


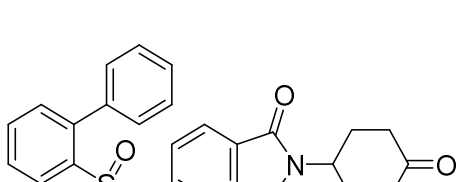


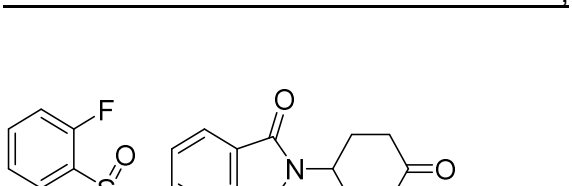


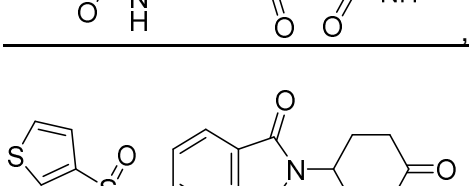


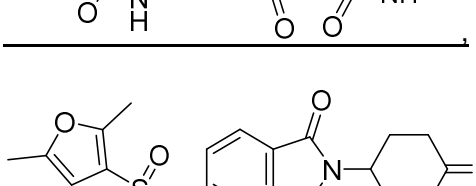


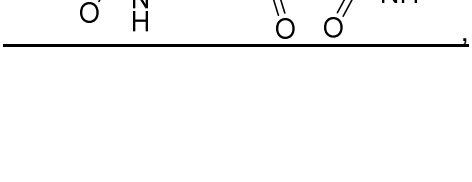


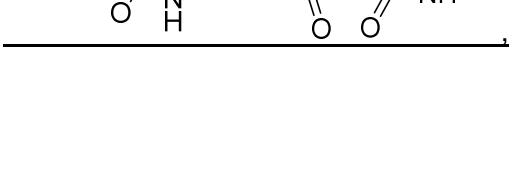


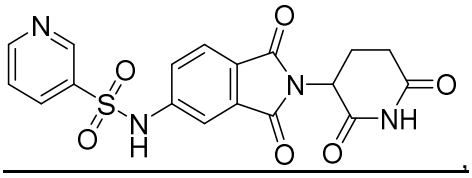


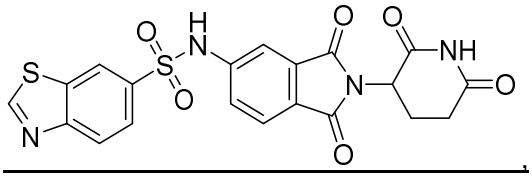


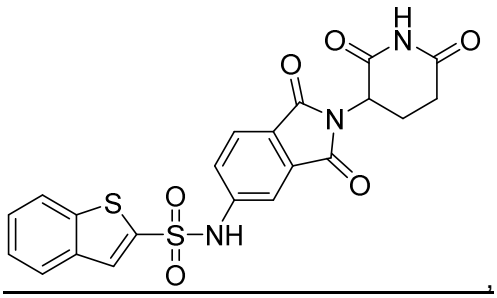


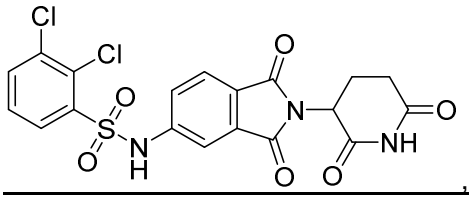


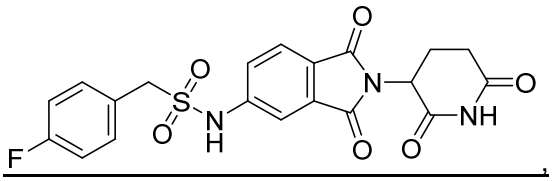


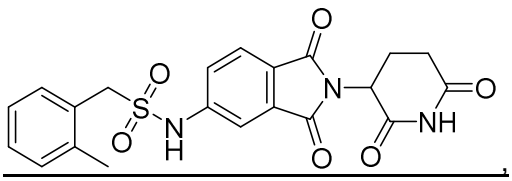


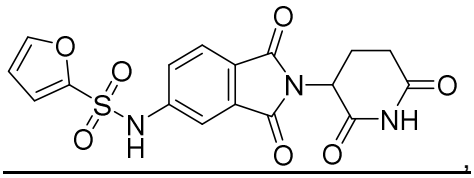


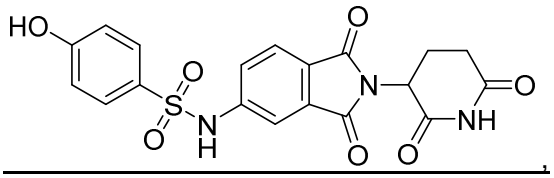


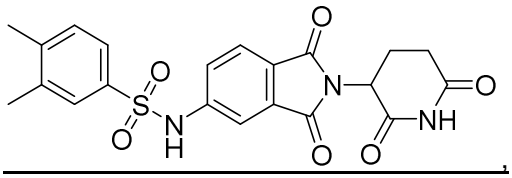


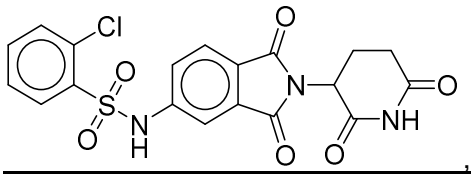


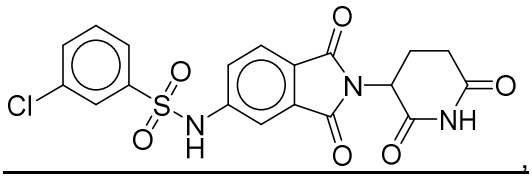


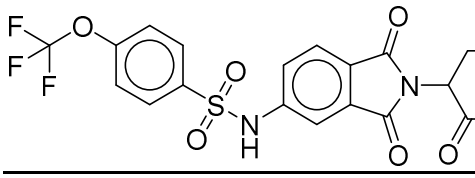


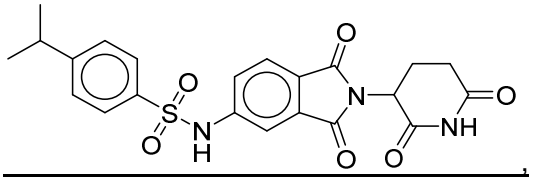


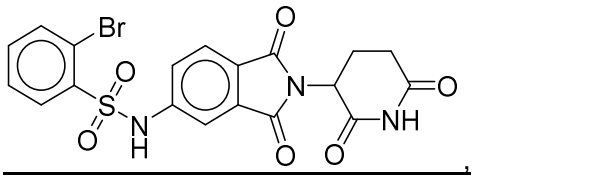


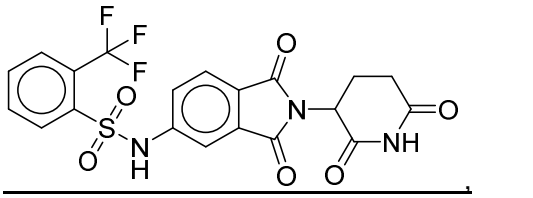


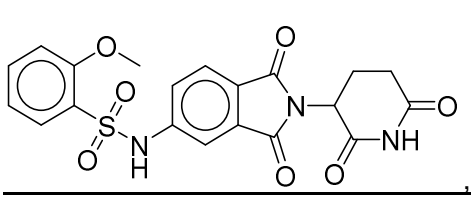




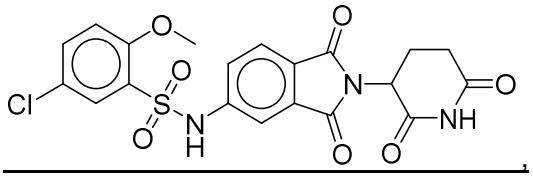








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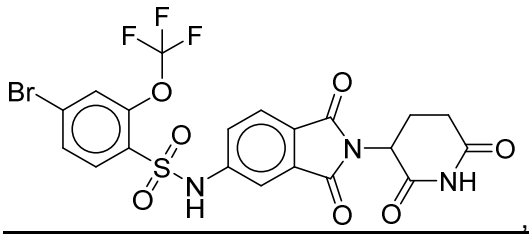
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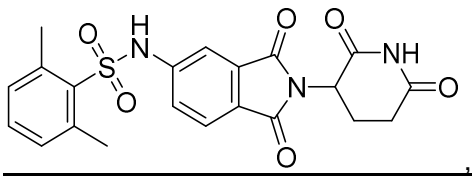
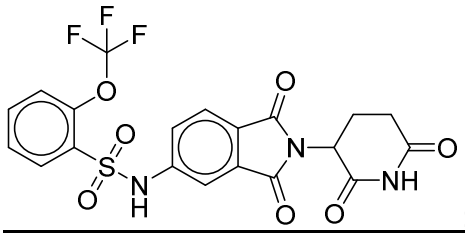

, and combinations thereof.

10. The compound of claim 8, having a structure represented by a formula: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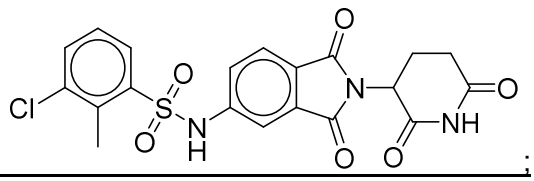
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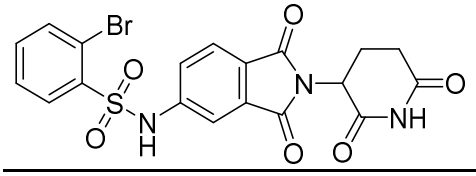
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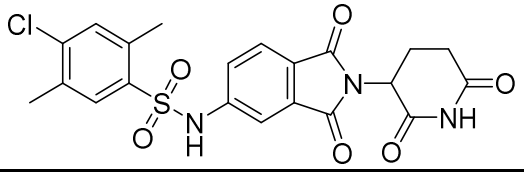
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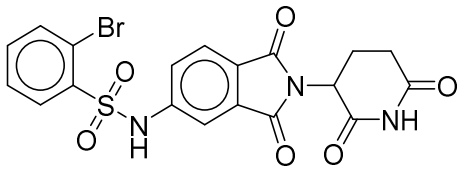
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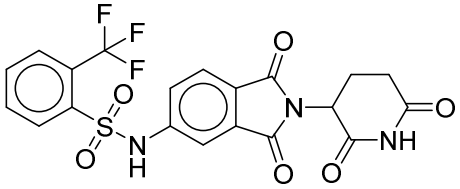
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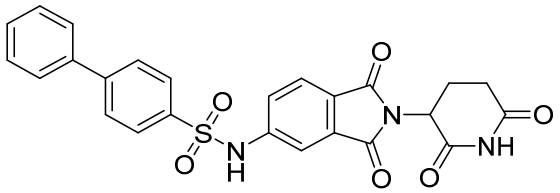
; and combinations thereof.

11. A pharmaceutical composition comprising a therapeutically effective amount of a compound of claim 1, and a pharmaceutically acceptable carrier.

12. The pharmaceutical composition of claim 11, further comprising at least one agent known to treat a cancer.

13. Use of at least one compound of claim 1, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for amelioration or alleviation of a cancer characterized by GSPT1 activity.

14. The use of claim 13, wherein the cancer is selected from a group consisting of brain cancer, lung cancer, hematological cancer, bladder cancer, colon cancer, cervical cancer, ovarian cancer, squamous cell cancer, kidney cancer, peritoneal cancer, breast cancer, gastric cancer, colorectal cancer, prostate cancer, pancreatic cancer, genitourinary tract cancer, lymphatic system cancer, stomach cancer, larynx cancer, malignant melanoma, endometrial carcinoma, thyroid cancer, rhabdosarcoma, and combinations thereof.

15. The use of claim 13, wherein the cancer is selexted from a group consisting of leukemia, lung cancer hematological cancer, bladder cancer, ovarian cancer, squamous cell cancer, breast cancer, prostate cancer, pancreatic cancer, genitourinary tract cancer, malignant melanoma, endometrial carcinoma, and combinations therof

16. The use of claim 13, wherein the lung cancer is selected from a group consisting of small-cell lung cancer, non-small cell lung cancer, and combinations thereof;

    wherein the bladder cancer is a bladder urothelia carcinoma; and

    wherein the hematological cancer is selected from a group consisting of a childhood acute leukemia (AL), chronic myeloid leukemia (CML), acute myeloid leukemia (AML), chronic lymphoid leukemia (CLL), acute lymphoid leukemia (ALL), hairy cell leukemia, chronic myelomonocytic leukemia (CMML), juvenile myelomonocyte leukemia (JMML), large granular lymphocytic leukemia (LGL), acute lymphocytic leukemia, acute lymphoblastic leukemia, B-cell lymphoma, T-cell-lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, hairy cell lymphoma, Burkett's lymphoma, Hodgkin lymphoma, non-Hodgkin lymphoma, and combinations thereof.

17. The use of claim 13, wherein the medicament further comprises at least one agent known to alleviate a cancer.

18. The use of claim 17, wherein the at least one agent is selected from a group consisiting of uracil mustard, chlormethine, cyclophosphamide, ifosfamide, melphalan, chlorambucil, pipobroman, triethylenemelamine, triethylenethiophosphoramine, busulfan, carmustine, lomustine, streptozocin, dacarbazine, temozolomide, thiotepa, altretamine, methotrexate, 5-fluorouracil, floxuridine, cytarabine, 6-mercaptopurine, 6-thioguanine, fludarabine phosphate, pentostatin, bortezomib, vinblastine, vincristine, vinorelbine, vindesine, bleomycin, dactinomycin, daunorubicin, doxorubicin, epirubicin, dexamethasone, clofarabine, cladribine, pemextresed, idarubicin, paclitaxel, docetaxel, ixabepilone, mithramycin, topotecan, irinotecan, deoxycoformycin, mitomycin-C, L-asparaginase, interferons, etoposide, teniposide 17α-ethinylestradiol, diethylstilbestrol, testosterone, prednisone, fluoxymesterone, dromostanolone propionate, testolactone, megestrolacetate, tamoxifen, methylprednisolone, methyltestosterone, prednisolone,

triamcinolone, chlorotrianisene, hydroxyprogesterone, aminoglutethimide, estramustine, medroxyprogesteroneacetate, leuprolide, flutamide, toremifene, goserelin, cisplatin, carboplatin, hydroxyurea, amsacrine, procarbazine, mitotane, mitoxantrone, levamisole, navelbene, anastrazole, letrazole, capecitabine, reloxafine, droloxafine, hexamethylmelamine, oxaliplatin, gefinitib, capecitabine, erlotinib, azacitidine, temozolomide, gemcitabine, vasostatin, and combinations thereof.

19. The use of claim 17, wherein the at least one agent is selected from a group consisting of a DNA methyltransferase inhibitor, an HDAC-inhibitor, a glucocorticoid, an mTOR inhibitor, a cytotoxic agent, and combinations thereof.

20. The use of claim 19, wherein the DNA methyltransferase inhibitor is selected from a group consisiting of 5-aza-2′-deoxycytidine, 5-azacytidine, zebularin, epigallocatechin-3-gallate, procaine, and combinations thereof;

    wherein the HDAC-inhibitor is selected from a group consisting of vorinostat, entinostat, panbinostat, trichostatin A, mocetinostat, belinostat, dacinostat, givinostat, tubastatin A, pracinostat, droxinostat, quisinostat, romidepsin, valproic acid, AR-42 (OSU-HDAC42), tacedinaline, rocilinostat, apicidin, and combinations thereof;

    wherein the glucocorticoid is selected from a group consisting of dexamethasone, prednisolone, methylprednisolone, betamethasone, triamicinolone, fludrocortisone, beclomethasone, and combinations thereof;

    wherein the mTor inhibitor is selected from a group consisting of BEZ235, everolimus, temsirolimus, rapamycin, AZD8055, and combinations thereof; and

    wherein the cytotoxic agent is selected from a group consisting of an alkylating agent, an antimetabolite agent, an antineoplastic antibiotic agent, a mitotic inhibitor agent, a mTor inhibitor agent, and other chemotherapeutic agent.

21. The use of claim 20, wherein the antineoplastic antibiotic agent is selected from one or more of the group consisting of doxorubicin, mitoxantrone, bleomycin, daunorubicin, dactinomycin, epirubicin, idarubicin, plicamycin, mitomycin, pentostatin, valrubicin, and combinations thereof, or a pharmaceutically acceptable salt, hydrate, solvate, or polymorph thereof;

    wherein the antimetabolite agent is selected from a group consisting of gemcitabine, 5-fluorouracil, capecitabine, hydroxyurea, mercaptopurine, pemetrexed, fludarabine, nelarabine, cladribine, clofarabine, cytarabine, decitabine, pralatrexate, floxuridine, methotrexate, thioguanine, and combinations thereof, or a pharmaceutically acceptable salt, hydrate, solvate, or polymorph thereof;

wherein the alkylating agent is selected from a group consisting of carboplatin, cisplatin, cyclophosphamide, chlorambucil, melphalan, carmustine, busulfan, lomustine, dacarbazine, oxaliplatin, ifosfamide, mechlorethamine, temozolomide, thiotepa, bendamustine, streptozocin, and combinations thereof, or a pharmaceutically acceptable salt, hydrate, solvate, or polymorph thereof;

wherein the mitotic inhibitor agent is selected from a group consisting of irinotecan, topotecan, rubitecan, cabazitaxel, docetaxel, paclitaxel, etopside, vincristine, ixabepilone, vinorelbine, vinblastine, teniposide, and combinations thereof, or a pharmaceutically acceptable salt, hydrate, solvate, or polymorph thereof;

wherein the mTor inhibitor is selected from a group consisting of everolimus, sirolimus, temsirolimus, and combinations thereof; and

wherein the other chemotherapeutic agent is selected from a group consisting of an anthracycline, cytarabine, a purine analog, sorafenib, gemtuzumab ozogamicin, rituximab, and combinations thereof.

22. Use of at least one compound of claim 1, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for modulating GSPT1 activity in at least one cell in a mammal.

23. The use of claim 22, wherein the mammal has been diagnosed with a need for modulating GSPT1 activity or for amelioration or alleviation of a cancer characterized by GSPT1 activity.

24. The use of claim 22, wherein the compound inhibits cell proliferation with an IC_{50} of less than about 10 μM when determined in a cell viability assay using MV4-11 cells as described herein;

wherein the compound exhibits cereblon binding with an IC_{50} of less than about 10 μM using a fluorescence polarization assay as described herein; or

wherein the compound inhibits cell proliferation with an IC_{50} of less than about 20 μM when determined in a cell viability assay using GSPT1 HiBit tagged cells.