inhibitors of the menin-MLL interaction in the treatment of diabetes (Yang *et al*., 2010, Proc Natl Acad Sci U S A., 107:20358-20363). The interaction between menin and MLL or MLL fusion proteins is an attractive target for therapeutic intervention, and there is a need for novel combination therapeutics that inhibit the menin-MLL interaction for the treatment of various diseases and conditions, including leukemia, other cancers and diabetes.

SUMMARY

In an aspect of the present disclosure, there is provided a use of a menin inhibitor in the manufacture of a medicament for treating an individual in need thereof, wherein the medicament and a CYP3A4 inhibitor are to be administered to the individual in need thereof.

In another aspect of the present disclosure, there is provided a use of a pharmaceutical composition comprising a menin inhibitor in the manufacture of a medicament for treating an individual in need thereof, wherein the medicament and a pharmaceutical composition comprising a CYP3A4 inhibitor are to be administered to the individual in need thereof.

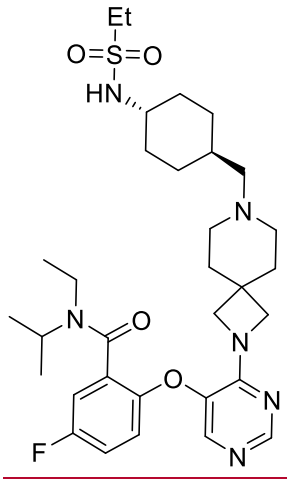
In a further aspect of the present disclosure, there is provided a kit for use in treating cancer in an individual comprising a combination of a menin inhibitor and a CYP3A4 inhibitor.

In another aspect of the present disclosure, there is provided a composition of a menin inhibitor and a CYP3A4 inhibitor, wherein the composition is to be administered to a human, and wherein the menin inhibitor and the CYP3A4 inhibitor come into contact with each other in the human body (e.g., only in the human body).

In a further aspect of the present disclosure, there is provided a method of preparing a composition by bringing a menin inhibitor and a CYP3A4 inhibitor into contact with each other at a locus.

In another aspect of the present disclosure, there is provided a use of a menin inhibitor for the manufacture of a medicament for treating cancer, wherein the medicament is to be administered with a CYP3A4 inhibitor.

In a further aspect of the present disclosure, there is provided a use of a pharmaceutical composition comprising the menin inhibitor of Formula (II)



Formula (II),

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating cancer in a patient, wherein the medicament and a pharmaceutical composition comprising posaconazole are to be administered to the patient.

In another aspect of the present disclosure, there is provided a menin inhibitor for use in therapy, wherein the menin inhibitor is to be administered with a CYP3A4 inhibitor.

The present ~~invention~~disclosure provides a combination therapy comprising a menin inhibitor and a CYP3A inhibitor. In certain ~~embodiment~~examples, the ~~invention~~present disclosure provides for a pharmaceutical composition comprising: (a) a menin inhibitor, and (b) a CYP3A inhibitor. In some ~~embodiment~~examples, the ~~invention~~present disclosure is directed to a method for treating a patient comprising (a) administering a menin inhibitor, and (b) administering a CYP3A inhibitor.

Some ~~embodiment~~examples of this ~~invention~~present disclosure are directed to combination therapies designed to treat or manage cancer in a subject, wherein the combination therapies comprise administering a menin inhibitor in combination with a CYP3A inhibitor. In particular, some ~~embodiment~~examples of this ~~invention~~present disclosure are directed to methods of treating or managing cancer in a subject, comprising administering a menin inhibitor in combination with a therapeutically effective amount of a CYP3A inhibitor administered simultaneously, separately or sequentially.

In some ~~embodiment~~examples, the ~~invention~~present disclosure provides a combination therapy comprising a menin inhibitor and a CYP3A4 inhibitor. In certain ~~embodiment~~examples, the ~~invention~~present disclosure provides for a pharmaceutical composition comprising: (a) a menin inhibitor, and (b) a CYP3A4 inhibitor. In some ~~embodiment~~examples, the ~~invention~~present

disclosure is directed to a method for treating a patient comprising (a) administering a menin inhibitor, and (b) administering a CYP3A4 inhibitor.

Some ~~embodiment~~examples of this ~~invention~~present disclosure are directed to combination therapies designed to treat or manage cancer in a subject, wherein the combination therapies comprise administering a menin inhibitor in combination with a CYP3A4 inhibitor. In particular, some ~~embodiment~~examples of this ~~invention~~present disclosure are directed to methods of treating or managing cancer in a subject, comprising administering a menin inhibitor in combination with a therapeutically effective amount of a CYP3A4 inhibitor administered simultaneously, separately or sequentially.

In some ~~embodiment~~examples, the CYP3A inhibitor is: an antiarrhythmic; an antihistamine; an azole antifungal; a benzodiazepine; a calcium channel blocker; a HIV antiviral; a HMG CoA

Reductase inhibitor; a macrolide antibiotic; a prokinetic; a protease inhibitor; or any combinations thereof. In some ~~embodiment~~examples, the CYP3A inhibitor is: posaconazole, alprazolam; amiodarone; amlodipine; aprepitant; aripiprazole; astemizole; atorvastatin; boceprevir; buspirone; chloramphenicol; chlorpheniramine; cimetidine; ciprofloxacin; cisapride; clarithromycin; cobicistat (GS-9350); analogs or derivatives of cobicistat (GS-9350); cyclosporine; delaviridine; diazepam→3-OH; diethyl-dithiocarbamate; diltiazem; erythromycin; felodipine; fluconazole; fluvoxamine; gestodene; gleevec; grapefruit juice; haloperidol; imatinib; indinavir; itraconazole; ketoconazole; lovastatin; methadone; mibefradil; midazolam; mifepristone; nefazodone; nelfinavir; nifedipine; nisoldipine; nitrendipine; norfloxacin; norfluoxetine; pimozide; quinine; quinidine→3-OH; ritonavir; saquinavir; sildenafil; simvastatin; starfruit; tacrolimus (FK506); tamoxifen; telaprevir; telithromycin; trazodone; triazolam; verapamil; telaprevir; vincristine; voriconazole; or any combinations thereof.

In some ~~embodiment~~examples, the CYP3A4 inhibitor is posaconazole, cobicistat (GS-9350) or analogs or derivatives of cobicistat (GS-9350). In some ~~embodiment~~examples, the CYP3A4 inhibitor is ketoconazole. In some ~~embodiment~~examples, the CYP3A4 inhibitor is ritonavir. In some ~~embodiment~~examples, the menin inhibitor and the CYP3A4 inhibitor are in separate dosage forms. In some ~~embodiment~~examples, the pharmaceutical composition is in a combined dosage form. In some ~~embodiment~~examples, the CYP3A4 inhibitor is posaconazole.

In some ~~embodiment~~examples, the pharmaceutical composition comprises an amount of the CYP3A4 inhibitor that is effective to increase the oral bioavailability of the menin inhibitor. In some ~~embodiment~~examples, the pharmaceutical composition comprises an amount of the CYP3A4 inhibitor that is effective to increase the C_{max} of the menin inhibitor. In some ~~embodiment~~examples, the pharmaceutical composition comprises an amount of the CYP3A4 inhibitor that is effective to increase the C_{max} of the menin inhibitor by about 20X to about 40X the C_{max} of the menin inhibitor administered without a CYP3A4 inhibitor, or about 25X to about 35X. In some ~~embodiment~~examples, the pharmaceutical composition comprises an amount of the CYP3A4 inhibitor that is effective to increase the AUC of the menin inhibitor. In some ~~embodiment~~examples, the pharmaceutical composition comprises an amount of the CYP3A4 inhibitor that is effective to increase the AUC of the menin inhibitor by about 15X to about 35X the AUC of the menin inhibitor administered without a CYP3A4 inhibitor, or about 20X to about 30X. In some ~~embodiment~~examples, the pharmaceutical composition comprises an amount of the CYP3A4 inhibitor that

is effective to increase the AUC of the menin inhibitor by about 2X to about 35X the AUC of the menin inhibitor administered without a CYP3A4 inhibitor. In some ~~embodiment~~examples, the pharmaceutical composition comprises an amount of the CYP3A4 inhibitor that is effective to increase the AUC of the menin inhibitor by about 2X to about 30X the AUC of the menin inhibitor administered without a CYP3A4 inhibitor. In some ~~embodiment~~examples, the pharmaceutical composition comprises an amount of the CYP3A4 inhibitor that is effective to increase the AUC of the menin inhibitor by about 2X to about 25X the AUC of the menin inhibitor administered without a CYP3A4 inhibitor. In some ~~embodiment~~examples, the pharmaceutical composition comprises an amount of the CYP3A4 inhibitor that is effective to increase the AUC of the menin inhibitor by about 2X to about 20X the AUC of the menin inhibitor administered without a CYP3A4 inhibitor. In some ~~embodiment~~examples, the pharmaceutical composition comprises an amount of the CYP3A4 inhibitor that is effective to increase the AUC of the menin inhibitor by about 2X to about 15X the AUC of the menin inhibitor administered without a CYP3A4 inhibitor. In some ~~embodiment~~examples, the pharmaceutical composition comprises an amount of the CYP3A4 inhibitor that is effective to increase the AUC of the menin inhibitor by about 2X to about 10X the AUC of the menin inhibitor administered without a CYP3A4 inhibitor. In some ~~embodiment~~examples, the pharmaceutical composition comprises an amount of the CYP3A4 inhibitor that is effective to increase the AUC of the menin inhibitor by about 2X to about 5X the AUC of the menin inhibitor administered without a CYP3A4 inhibitor. In some ~~embodiment~~examples, the pharmaceutical composition comprises an amount of the CYP3A4 inhibitor that is effective to increase the AUC of the menin inhibitor by about 2X to about 4X the AUC of the menin inhibitor administered without a CYP3A4 inhibitor.

In some ~~embodiment~~examples, the pharmaceutical composition further comprises chlorambucil, ifosphamide, doxorubicin, mesalazine, thalidomide, lenalidomide, temsirolimus, everolimus, fludarabine, fostamatinib, paclitaxel, docetaxel, ofatumumab, rituximab, dexamethasone, prednisone, CAL-101, ibritumomab, tositumomab, bortezomib, pentostatin, endostatin, or a combination thereof. In some ~~embodiment~~examples, the pharmaceutical composition further comprises cyclophosphamide, hydroxydaunorubicin, vincristine, and prednisone, and optionally, rituximab. In some ~~embodiment~~examples, the pharmaceutical composition further comprises bendamustine, and rituximab. In some ~~embodiment~~examples, the pharmaceutical composition further comprises fludarabine,

cyclophosphamide, and rituximab. In some ~~embodiment~~examples, the pharmaceutical composition further comprises cyclophosphamide, vincristine, and prednisone, and optionally, rituximab. In some ~~embodiment~~examples, the pharmaceutical composition further comprises etoposide, doxorubicin, vincristine, cyclophosphamide, prednisolone, and optionally, rituximab. In some ~~embodiment~~examples, the pharmaceutical composition further comprises dexamethasone and lenalidomide.

Disclosed herein, in certain ~~embodiment~~examples, is a pharmaceutical combination comprising a therapeutically-effective amount of the menin inhibitor and a CYP3A4 inhibitor. In some ~~embodiment~~examples, the combination is in a combined dosage form. In some ~~embodiment~~examples, the combination is in separate dosage forms. In some ~~embodiment~~examples, the menin inhibitor and the CYP3A4 inhibitor are administered concurrently. In some ~~embodiment~~examples, the menin inhibitor and the CYP3A4 inhibitor are administered simultaneously, essentially simultaneously or within the same treatment protocol. In some ~~embodiment~~examples, the menin inhibitor and the CYP3A4 inhibitor are administered sequentially. In some ~~embodiment~~examples, the CYP3A4 inhibitor is: an anti-arrhythmic; an antihistamine; an azole antifungal; a benzodiazepine; a calcium channel blocker; a HIV antiviral; a HMG CoA Reductase inhibitor; a macrolide antibiotic; a prokinetic; a protease inhibitor; or any combinations thereof. In some ~~embodiment~~examples, the CYP3A4 inhibitor is: alprazolam; amiodarone; amlodipine; aprepitant; aripiprazole; astemizole; atorvastatin; boceprevir; buspirone; chloramphenicol; chlorpheniramine; cimetidine; ciprofloxacin; cisapride; clarithromycin; cobicistat (GS-9350); analogs or derivatives of cobicistat (GS-9350); cyclosporine; delaviridine; diazepam→3-OH; diethyl-dithiocarbamate; diltiazem; erythromycin; felodipine; fluconazole; fluvoxamine; gestodene; gleevec; grapefruit juice; haloperidol; imatinib; indinavir; itraconazole; ketoconazole; lovastatin; methadone; mibefradil; midazolam; mifepristone; nefazodone; nelfmavir; nifedipine; nisoldipine; nitrendipine; norfloxacin; norfluoxetine; pimozide; quinine; quinidine→3-OH; ritonavir; saquinavir; sildenafil; simvastatin; starfruit; tacrolimus (FK506); tamoxifen; telaprevir; telithromycin; trazodone; triazolam; verapamil; troleandromycin; vincristine; voriconazole; or any combinations thereof.

In some ~~embodiment~~examples, the CYP3A4 inhibitor is cobicistat (GS-9350) or analogs or derivatives of cobicistat (GS-9350). In some ~~embodiment~~examples, the CYP3A4 inhibitor is ketoconazole. In some ~~embodiment~~examples, the CYP3A4 inhibitor is ritonavir.

In some ~~embodiment~~examples, the pharmaceutical combination comprises an amount of the CYP3A4 inhibitor that is effective to increase the oral bioavailability of the menin inhibitor. In some ~~embodiment~~examples, the pharmaceutical combination comprises an amount of the CYP3A4 inhibitor that is effective to increase the C_{max} of the menin inhibitor. In some ~~embodiment~~examples, the pharmaceutical combination comprises an amount of the CYP3A4 inhibitor that is effective to increase the C_{max} of the menin inhibitor by about 20X to about 40X the C_{max} of the menin inhibitor administered without a CYP3A4 inhibitor, or about 25X to about 35X. In some ~~embodiment~~examples, the pharmaceutical combination comprises an amount of the CYP3A4 inhibitor that is effective to increase the AUC of the menin inhibitor. In some ~~embodiment~~examples, the pharmaceutical combination comprises an amount of the CYP3A4 inhibitor that is effective to increase the AUC of the menin inhibitor by about 15X to about 35X the AUC of the menin inhibitor administered without a CYP3A4 inhibitor, or about 20X to about 30X. In some ~~embodiment~~examples, the pharmaceutical combination comprises an amount of the CYP3A4 inhibitor that is effective to increase the AUC of the menin inhibitor by about 2X to about 30X the AUC of the menin inhibitor administered without a CYP3A4 inhibitor. In some ~~embodiment~~examples, the pharmaceutical combination comprises an amount of the CYP3A4 inhibitor that is effective to increase the AUC of the menin inhibitor by about 2X to about 25X the AUC of the menin inhibitor administered without a C YP3A4 inhibitor. In some ~~embodiment~~examples, the pharmaceutical combination comprises an amount of the CYP3A4 inhibitor that is effective to increase the AUC of the menin inhibitor by about 2X to about 20X the AUC of the menin inhibitor administered without a CYP3A4 inhibitor. In some ~~embodiment~~examples, the pharmaceutical combination comprises an amount of the CYP3A4 inhibitor that is effective to increase the AUC of the menin inhibitor by about 2X to about 15X the AUC of the menin inhibitor administered without a CYP3A4 inhibitor. In some ~~embodiment~~examples, the pharmaceutical combination comprises an amount of the CYP3A4 inhibitor that is effective to increase the AUC of the menin inhibitor by about 2X to about 10X the AUC of the menin inhibitor administered without a CYP3A4 inhibitor. In some ~~embodiment~~examples, the pharmaceutical combination comprises an amount of the CYP3A4 inhibitor that is effective to increase the AUC of the menin inhibitor by about 2X to about 5X the AUC of the menin inhibitor administered without a CYP3A4 inhibitor. In some ~~embodiment~~examples, the pharmaceutical combination comprises an amount of the CYP3A4 inhibitor that

is effective to increase the AUC of the menin inhibitor by about 2X to about 4X the AUC of the menin inhibitor administered without a CYP3A4 inhibitor.

In some ~~embodiment~~examples, the pharmaceutical combination further comprises chlorambucil, ifosphamide, doxorubicin, mesalazine, thalidomide, lenalidomide, temsirolimus, everolimus, fludarabine, fostamatinib, paclitaxel, docetaxel, ofatumumab, rituximab, dexamethasone, prednisone, CAL-101, ibritumomab, tositumomab, bortezomib, pentostatin, endostatin, or a combination thereof. In some ~~embodiment~~examples, the pharmaceutical combination further comprises cyclophosphamide, hydroxydaunorubicin, vincristine, and prednisone, and optionally, rituximab. In some ~~embodiment~~examples, the pharmaceutical combination further comprises bendamustine, and rituximab. In some ~~embodiment~~examples, the pharmaceutical combination further comprises fludarabine, cyclophosphamide, and rituximab. In some ~~embodiment~~examples, the pharmaceutical combination further comprises cyclophosphamide, vincristine, and prednisone, and optionally, rituximab. In some ~~embodiment~~examples, the pharmaceutical combination further comprises etoposide, doxorubicin, vincristine, cyclophosphamide, prednisolone, and optionally, rituximab. In some ~~embodiment~~examples, the pharmaceutical combination further comprises dexamethasone and lenalidomide.

In some ~~embodiment~~examples, the CYP3A4 inhibitor is: an anti-arrhythmic; an antihistamine; an azole antifungal; a benzodiazepine; a calcium channel blocker; a HIV antiviral; a HMG CoA Reductase inhibitor; a macrolide antibiotic; a prokinetic; a protease inhibitor; or any combinations thereof. In some ~~embodiment~~examples, the CYP3A4 inhibitor is: alprazolam; amiodarone; amlodipine; aprepitant; aripiprazole; astemizole; atorvastatin; boceprevir; buspirone; chloramphenicol; chlorpheniramine; cimetidine; ciprofloxacin; cisapride; clarithromycin; cobicistat (GS-9350); analogs or derivatives of cobicistat (GS-9350); cyclosporine; delaviridine; diazepam→3-OH; diethyl-dithiocarbamate; diltiazem; erythromycin; felodipine; fluconazole; fluvoxamine; gestodene; gleevec; grapefruit juice; haloperidol; imatinib; indinavir; itraconazole; ketoconazole; lovastatin; methadone; mibefradil; midazolam; mifepristone; nefazodone; nelfmavir; nifedipine; nisoldipine; nitrendipine; norfloxacin; norfluoxetine; pimozide; quinine; quinidine→3-OH; ritonavir; saquinavir; sildenafil; simvastatin; starfruit; tacrolimus (FK506); tamoxifen; telaprevir; telithromycin; trazodone; triazolam; troleandromycin; verapamil; telaprevir; vincristine; voriconazole; or any combinations thereof.

In some ~~embodiment~~examples, the CYP3A4 inhibitor is posaconazole. In some ~~embodiment~~examples, the CYP3A4 inhibitor is cobicistat (GS-9350) or analogs or derivatives of cobicistat (GS-9350).

In some ~~embodiment~~examples, the CYP3A4 inhibitor is ketoconazole. In some ~~embodiment~~examples, the CYP3A4 inhibitor is ritonavir.

In some ~~embodiment~~examples, the daily dosage of the menin inhibitor is between about 10 mg to about 500 mg. In some ~~embodiment~~examples, the daily dosage of the menin inhibitor is between about 200 mg and about 500 mg. In some ~~embodiment~~examples, the daily dosage of the menin inhibitor is between about 250 mg and about 460 mg. In some ~~embodiment~~examples, the daily dosage amount of the menin inhibitor is about 226 mg. In some ~~embodiment~~examples, the daily dosage of the menin inhibitor is 452 mg.

In some ~~embodiment~~examples, the method comprises an amount of the CYP3A4 inhibitor that is effective to increase the oral bioavailability of the menin inhibitor. In some ~~embodiment~~examples, the method comprises an amount of the CYP3A4 inhibitor that is effective to increase the C_{max} of the menin inhibitor. In some ~~embodiment~~examples, the method comprises an amount of the CYP3A4 inhibitor that is effective to increase the C_{max} of the menin inhibitor by about 20X to about 40X the C_{max} of the menin inhibitor administered without a CYP3A4 inhibitor, or about 25X to about 35X. In some ~~embodiment~~examples, the method comprises an amount of the CYP3A4 inhibitor that is effective to increase the AUC of the menin inhibitor. In some ~~embodiment~~examples, the method comprises an amount of the CYP3A4 inhibitor that is effective to increase the AUC of the menin inhibitor by about 15X to about 35X the AUC of the menin inhibitor administered without a CYP3A4 inhibitor, or about 20X to about 30X. In some ~~embodiment~~examples, the method comprises an amount of the CYP3A4 inhibitor that is effective to increase the AUC of the menin inhibitor by about 2X to about 35X the AUC of the menin inhibitor administered without a CYP3A4 inhibitor. In some ~~embodiment~~examples, the method comprises an amount of the CYP3A4 inhibitor that is effective to increase the AUC of the menin inhibitor by about 2X to about 30X the AUC of the menin inhibitor administered without a CYP3A4 inhibitor. In some ~~embodiment~~examples, the method comprises an amount of the CYP3A4 inhibitor that is effective to increase the AUC of the menin inhibitor by about 2X to about 25X the AUC of the menin inhibitor administered without a CYP3A4 inhibitor. In some ~~embodiment~~examples, the method comprises an amount of the CYP3A4 inhibitor that is effective to increase the AUC of the menin inhibitor by about 2X to about 20X the AUC of the menin inhibitor administered without a CYP3A4 inhibitor. In some ~~embodiment~~examples, the method comprises an amount of the CYP3A4 inhibitor that is effective to increase the AUC of the menin inhibitor by about 2X to

about 15X the AUC of the menin inhibitor administered without a CYP3A4 inhibitor. In some ~~embodiment~~examples, the method comprises an amount of the CYP3A4 inhibitor that is effective to increase the AUC of the menin inhibitor by about 2X to about 10X the AUC of the menin inhibitor administered without a CYP3A4 inhibitor. In some ~~embodiment~~examples, the method comprises an amount of the CYP3A4 inhibitor that is effective to increase the AUC of the menin inhibitor by about 2X to about 5X the AUC of the menin inhibitor administered without a CYP3A4 inhibitor. In some ~~embodiment~~examples, the method comprises an amount of the CYP3A4 inhibitor that is effective to increase the AUC of the menin inhibitor by about 2X to about 4X the AUC of the menin inhibitor administered without a CYP3A4 inhibitor. In some ~~embodiment~~examples, the method comprises the pharmaceutical combination does not significantly affect the T_{max} or T 1/2 of the menin inhibitor as compared to the T_{max} and $T_{1/2}$ of the menin inhibitor administered without a CYP3A4 inhibitor. In some ~~embodiment~~examples, the menin inhibitor and the CYP3A4 inhibitor are in a combined dosage form. In some ~~embodiment~~examples, the menin inhibitor and the CYP3A4 inhibitor are in separate dosage forms. In some ~~embodiment~~examples, the menin inhibitor and the CYP3A4 inhibitor are administered concurrently. In some ~~embodiment~~examples, the menin inhibitor and the CYP3A4 inhibitor are administered simultaneously, essentially simultaneously or within the same treatment protocol. In some ~~embodiment~~examples, the menin inhibitor and the CYP3A4 inhibitor are administered sequentially.

BRIEF DESCRIPTION OF THE FIGURES

FIGURE 1 illustrates the change in steady state AUC following oral administration of the menin inhibitor of Formula II with and without CYP3A4 inhibitor, posaconazole.

DETAILED DESCRIPTION OF THE INVENTION

Small molecule menin inhibitors administered in combination with CYP3A4 inhibitors act together to treat a variety of diseases affected by or affecting many cell types.

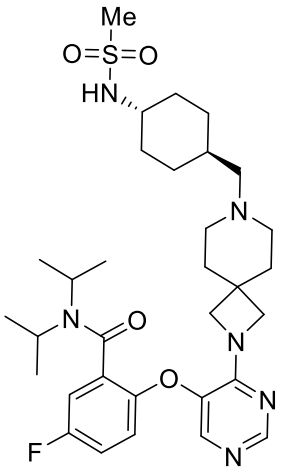
In some embodiments, the invention provides a combination therapy comprising a menin inhibitor and a CYP3A4 inhibitor. In some embodiments, the invention provides for a pharmaceutical composition comprising: (a) a menin inhibitor, and (b) a CYP3A4 inhibitor. In some embodiments, the invention is directed to a method for treating a patient comprising (a) administering a menin inhibitor, and (b) administering a CYP3A4 inhibitor. In some embodiments,

CLAIMS

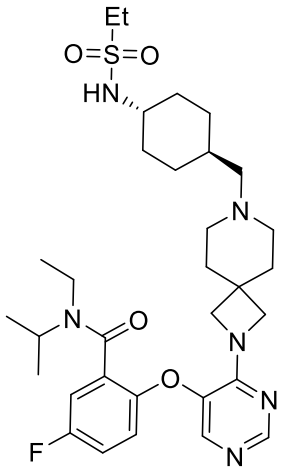
1. Use of a menin inhibitor in the manufacture of a medicament for ~~A method of~~ treating an individual in need thereof ~~comprising administering a combination of a menin inhibitor~~ , wherein the medicament and a CYP3A4 inhibitor are to be administered to the individual in need thereof.

2. Use of a pharmaceutical composition comprising a menin inhibitor in the manufacture of a medicament for ~~A method of~~ treating an individual in need thereof, wherein the medicament ~~comprising administering a pharmaceutical composition comprising a menin inhibitor~~ and a pharmaceutical composition comprising a CYP3A4 inhibitor are to be administered to the individual in need thereof.

3. The ~~method~~use of any preceding claim, wherein the menin inhibitor is selected from Formula (I) and Formula (II)



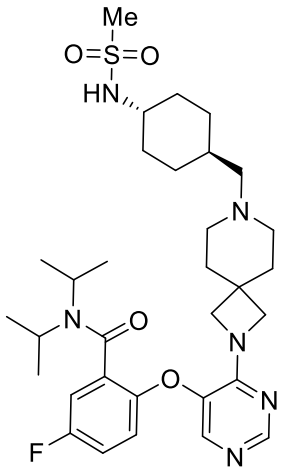
Formula (I),



Formula (II)

or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, geometric isomer or tautomer thereof.

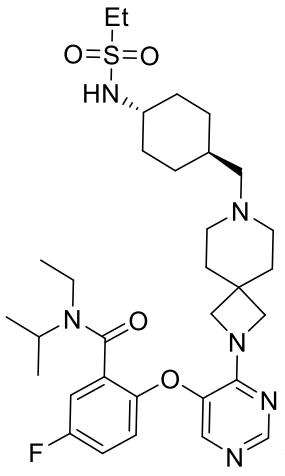
4. The ~~method~~use of any preceding claim, wherein the menin inhibitor is a compound of Formula (I)



Formula (I),

or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, geometric isomer, or tautomer thereof.

5. The ~~method~~use of any one of ~~preceding~~ claims 1-3, wherein the menin inhibitor ~~is inhibitor~~ is a compound of Formula (II)



Formula (II),

or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, geometric isomer, or tautomer thereof.

6. The ~~method~~use of any preceding claim, wherein the CYP3A4 inhibitor is selected from the group consisting of boceprevir, nefazodone, clarithromycin, nelfinavir, conivaptan, posaconazole, grapefruit juice, ritonavir, indinavir, saquinavir, itraconazole, telaprevir, ketoconazole, telithromycin, lopinavir, voriconazole, cobicistat, mibefradil.

7. The ~~method~~use of any preceding claim, wherein the CYP3A4 inhibitor is an azole antifungal.

8. The ~~method~~use of any preceding claim, wherein the CYP3A4 inhibitor is posaconazole.

9. The ~~method~~use of any preceding claim, wherein the CYP3A4 inhibitor is cobicistat.

10. The ~~method~~use of any preceding claim, wherein the CYP3A4 inhibitor is ketoconazole.

11. The ~~method~~use of any preceding claim, wherein the CYP3A4 inhibitor is ritonavir.

12. The ~~method~~use of any preceding claim, wherein the menin inhibitor and the CYP3A4 inhibitor are in a combined dosage form.

13. The ~~method~~use of any one of claims 1-11, wherein the menin inhibitor and the CYP3A4 inhibitor are in separate dosage forms.

14. The ~~method~~use of any preceding claim, wherein the menin inhibitor is to be administered in a sub-therapeutically-effective amount.

15. The ~~method~~use of any preceding claim, wherein the CYP3A4 inhibitor is to be administered in a therapeutically-effective amount.

16. The ~~method~~use of any one of claims 1-14, wherein the CYP3A4 inhibitor is to be administered in a sub-therapeutically-effective amount.

17. The ~~method~~use of any preceding claim, wherein the menin inhibitor and the CYP3A4 inhibitor are to be administered concurrently.

18. The ~~method~~use of any preceding claim, wherein the menin inhibitor and the CYP3A4 inhibitor are to be administered simultaneously, essentially simultaneously or within the same treatment protocol.

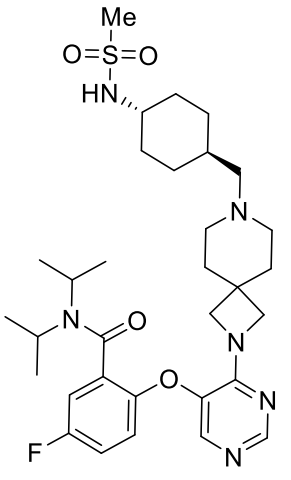
19. The ~~method~~use of any preceding claim, wherein the menin inhibitor and the CYP3A4 inhibitor are to be administered sequentially.

20. The ~~method~~use of any preceding claim, wherein the menin inhibitor and the CYP3A4 inhibitor ~~combination is~~ are to be administered for an initial treatment period, ~~followed by continued administration of~~ and wherein the menin inhibitor is to be further administered thereafter.

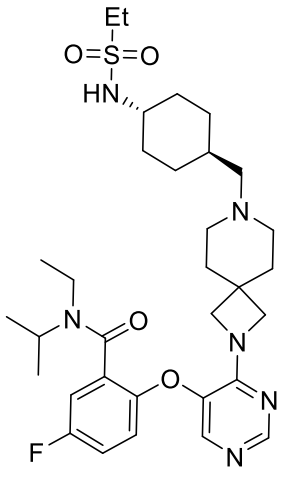
21. The ~~method~~use of any preceding claim, wherein ~~administration of~~ the CYP3A4 inhibitor ~~occurs~~ is to be administered before ~~the administration of~~ the menin inhibitor is to be administered.

22. A kit for use in treating cancer in an individual comprising a combination of a menin inhibitor and a CYP3A4 inhibitor.

23. The kit for use of claim 22, wherein the menin inhibitor is selected from Formula (I) and Formula (II)



Formula (I),



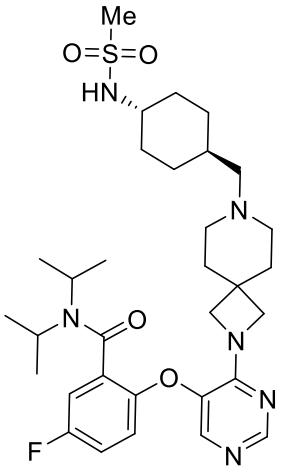
Formula (II)

or a pharmaceutically acceptable salt, stereoisomer, geometric isomer or tautomer thereof.

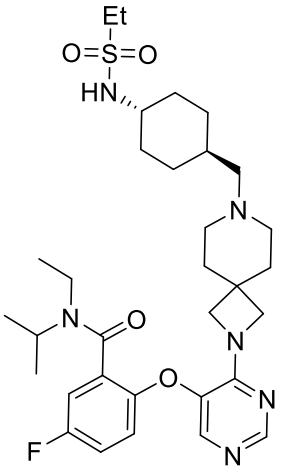
24. The kit for use of any one of claims 22-23, further comprising instructions on how to use the kit.

25. A composition of a menin inhibitor and a CYP3A4 inhibitor, wherein the composition is to be administered to a human, and wherein the menin inhibitor and the CYP3A4 inhibitor come into contact with each other in the human body (e.g., only in the human body).

26. The composition of claim 25, wherein the menin inhibitor is selected from Formula (I) and Formula (II)



Formula (I),

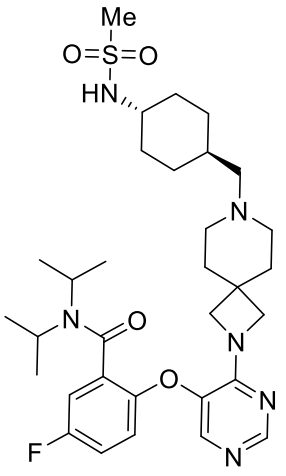


Formula (II)

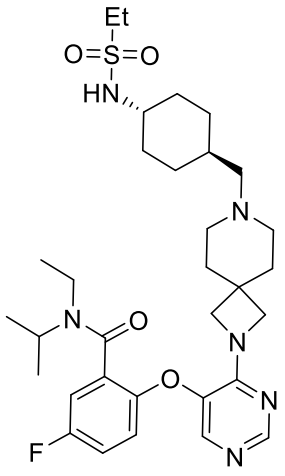
or a pharmaceutically acceptable salt, stereoisomer, geometric isomer or tautomer thereof..

27. A method of preparing a composition by bringing a menin inhibitor and a CYP3A4 inhibitor into contact with each other at a locus.

28. The method of claim 27, wherein the menin inhibitor is selected from Formula (I) and Formula (II)



Formula (I),



Formula (II)

or a pharmaceutically acceptable salt, stereoisomer, geometric isomer, or tautomer thereof.

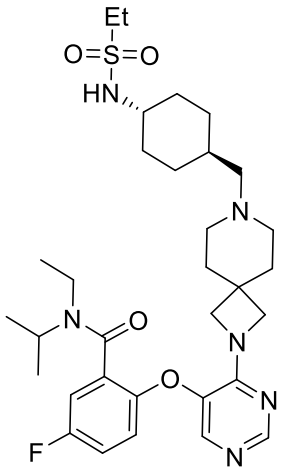
29. Use ~~A combination~~ of a menin inhibitor ~~and a CYP3A4 inhibitor used~~ for the manufacture of a medicament for treating cancer, wherein the medicament is to be administered with a CYP3A4 inhibitor.

30. The ~~method~~use of any one of claims 1-21, wherein the CYP3A4 inhibitor is a strong CYP3A4 inhibitor.

31. Use of a pharmaceutical composition comprising the menin inhibitor of Formula (II)~~A method for treating cancer in a patient comprising the steps of~~

~~a) administering a pharmaceutical composition comprising posaconazole, and~~

~~b) administering a pharmaceutical composition comprising the menin inhibitor of Formula (II)~~



Formula (II),

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating cancer in a patient, wherein the medicament and a pharmaceutical composition comprising posaconazole are to be administered to the patient.

32. The ~~method~~use of any one of claims 1-21 or 31, wherein the menin inhibitor is a fumarate salt.

33. The ~~method~~use of any one of claims 1-21 or 31-32, wherein the menin inhibitor is a sesquifumarate salt.

34. A menin inhibitor for use in therapy, wherein the menin inhibitor is to be administered with a CYP3A4 inhibitor.