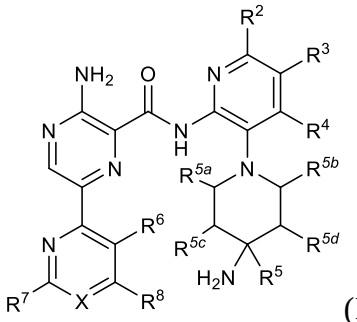
CLAIMS

1. A protein kinase C inhibitor for use in a method of treating a patient having uveal melanoma, a tumor having a *GNAQ* or *GNA11* mutation ("*GNAQ/11* tumor"), or both, wherein the method comprises:

co-administering to the patient a cMET inhibitor and the protein kinase C inhibitor, wherein the protein kinase C inhibitor is represented by Formula II:



(II),

or a pharmaceutically acceptable salt thereof, wherein:

X is N or CR;

R, R^2, R^3 and R^4 are each independently selected from the group consisting of H, ^2H, halogen, hydroxyl, C_{1-3} alkoxy and C_{1-3} alkyl; wherein C_{1-3} alkoxy may optionally be substituted by one, two, three or more halogens; and wherein C_{1-3} alkyl may optionally be substituted by one, two, three or more substituents, each independently selected from the group consisting of hydroxyl, halogen and C_{1-3} alkoxy (optionally substituted by one or more halogens);

R^5 is selected from the group consisting of H, ^2H, $-CH_3$, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CH_2OH$ and C_{2-3} alkyl; wherein C_{2-3} alkyl may optionally be substituted by one, two, three or more substituents, each independently selected from the group consisting of fluorine, hydroxyl and C_{1-3} alkoxy (optionally substituted by one or more halogens);

R^{5a} and R^{5b} are each independently selected from the group consisting of H, ^2H and C_{1-3}alkyl; wherein C_{1-3} alkyl may optionally be substituted by one, two, three or more substituents, each independently selected from the group consisting of fluorine, hydroxyl and C_{1-3} alkoxy; or R^{5a} and R^{5b} are taken together to form a methylene or ethylene bridging group;

R^{5c} and R^{5d} are each independently selected from the group consisting of H, ^2H, fluorine, hydroxyl, C_{1-3} alkoxy and C_{1-3} alkyl; wherein C_{1-3} alkyl may optionally be substituted by one, two, three or more substituents, each independently selected from the

group consisting of fluorine, hydroxyl and C_{1-3} alkoxy; or R^{5c} and R^{5d} taken together form a methylene, ethylene or -CH_2-O- bridging group;

R^6, R^7 and R^8 are each independently selected from the group consisting of H, ^2H, halogen, C_{1-3} alkyl, C_{1-3} alkoxy, C_{3-7} cycloalkyl and a 4-7 membered heterocyclyl having one, two or three heteroatoms each independently selected from the group consisting of N, O and S; wherein C_{1-3} alkoxy may optionally be substituted by one, two, three or more halogens; and wherein C_{1-3} alkyl may optionally be substituted by one, two, three or more substituents, each independently selected from the group consisting of hydroxyl, halogen and C_{1-3} alkoxy (optionally substituted by one or more halogens); or

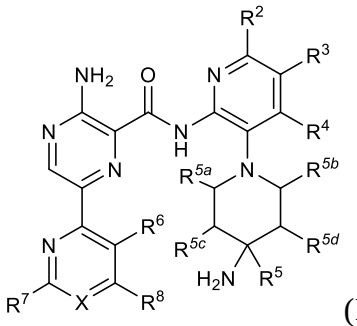
wherein R^6 and R^8 optionally forms a partially unsaturated carbobicyclic or heterobicyclic ring with the heteroaryl ring to which they are attached, wherein the carbobicyclic or heterobicyclic ring may optionally be substituted by one, two or three groups, each independently selected from the group consisting of ^2H, halogen, C_{1-3} alkyl, C_{1-3} alkoxy, C_{3-7} cycloalkyl and a 4-7 membered heterocyclyl having one, two or three heteroatoms each independently selected from the group consisting of N, O and S; and

wherein C_{1-3} alkyl and C_{1-3} alkoxy may optionally be substituted by one, two, three or more halogens.

2. A protein kinase C inhibitor for use in a method of treating a patient having uveal melanoma, wherein the method comprises:

selecting a patient with uveal melanoma having an elevated cMET presence determined by assessing a biopsy of the uveal melanoma; and

co-administering to the patient a cMET inhibitor and a protein kinase C inhibitor, wherein the protein kinase C inhibitor is represented by Formula II:



(II),

or a pharmaceutically acceptable salt thereof, wherein:

X is N or CR;

R, R^2, R^3 and R^4 are each independently selected from the group consisting of H, ^2H, halogen, hydroxyl, C_{1-3} alkoxy and C_{1-3} alkyl; wherein C_{1-3} alkoxy may optionally be substituted by one, two, three or more halogens; and wherein C_{1-3} alkyl may optionally be substituted by one, two, three or more substituents, each independently selected from the group consisting of hydroxyl, halogen and C_{1-3} alkoxy (optionally substituted by one or more halogens);

R^5 is selected from the group consisting of H, ^2H, $-CH_3$, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CH_2OH$ and C_{2-3} alkyl; wherein C_{2-3} alkyl may optionally be substituted by one, two, three or more substituents, each independently selected from the group consisting of fluorine, hydroxyl and C_{1-3} alkoxy (optionally substituted by one or more halogens);

R^{5a} and R^{5b} are each independently selected from the group consisting of H, ^2H and C_{1-3} alkyl; wherein C_{1-3} alkyl may optionally be substituted by one, two, three or more substituents, each independently selected from the group consisting of fluorine, hydroxyl and C_{1-3} alkoxy; or R^{5a} and R^{5b} are taken together to form a methylene or ethylene bridging group;

R^{5c} and R^{5d} are each independently selected from the group consisting of H, ^2H, fluorine, hydroxyl, C_{1-3} alkoxy and C_{1-3} alkyl; wherein C_{1-3} alkyl may optionally be substituted by one, two, three or more substituents, each independently selected from the group consisting of fluorine, hydroxyl and C_{1-3} alkoxy; or R^{5c} and R^{5d} taken together form a methylene, ethylene or $-CH_2-O-$ bridging group;

R^6, R^7 and R^8 are each independently selected from the group consisting of H, ^2H, halogen, C_{1-3}alkyl, C_{1-3} alkoxy, C_{3-7} cycloalkyl and a 4-7 membered heterocyclyl having one, two or three heteroatoms each independently selected from the group consisting of N, O and S; wherein C_{1-3}alkoxy may optionally be substituted by one, two, three or more halogens; and wherein C_{1-3}alkyl may optionally be substituted by one, two, three or more substituents, each independently selected from the group consisting of hydroxyl, halogen and C_{1-3} alkoxy (optionally substituted by one or more halogens); or

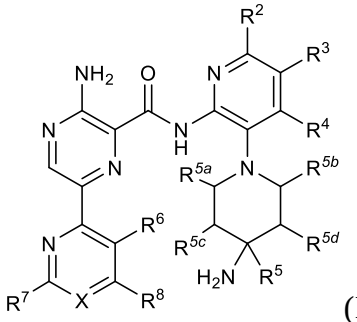
wherein R^6 and R^8 optionally forms a partially unsaturated carbobicyclic or heterobicyclic ring with the heteroaryl ring to which they are attached, wherein the carbobicyclic or heterobicyclic ring may optionally be substituted by one, two or three groups, each independently selected from the group consisting of ^2H, halogen, C_{1-3}alkyl, C_{1-3}alkoxy, C_{3-7}cycloalkyl and a 4-7 membered heterocyclyl having one, two or three heteroatoms each independently selected from the group consisting of N, O and S; and

wherein C_{1-3} alkyl and C_{1-3} alkoxy may optionally be substituted by one, two, three or more halogens.

3. A protein kinase C inhibitor for use in a method of treating a patient having a tumor having a *GNAQ* or *GNA11* mutation ("*GNAQ/11* tumor"), wherein the method comprises:

selecting a patient with a *GNAQ/11* tumor having an elevated cMET presence determined by assessing a biopsy of the *GNAQ/11* tumor; and

co-administering to the patient a cMET inhibitor and the protein kinase C inhibitor, wherein the protein kinase C inhibitor is represented by Formula II:



(II),

or a pharmaceutically acceptable salt thereof, wherein:

X is N or CR;

R, R^2, R^3 and R^4 are each independently selected from the group consisting of H, ^2H, halogen, hydroxyl, C_{1-3} alkoxy and C_{1-3} alkyl; wherein C_{1-3} alkoxy may optionally be substituted by one, two, three or more halogens; and wherein C_{1-3} alkyl may optionally be substituted by one, two, three or more substituents, each independently selected from the group consisting of hydroxyl, halogen and C_{1-3}alkoxy (optionally substituted by one or more halogens);

R^5 is selected from the group consisting of H, ^2H, $-CH_3$, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CH_2OH$ and C_{2-3} alkyl; wherein C_{2-3} alkyl may optionally be substituted by one, two, three or more substituents, each independently selected from the group consisting of fluorine, hydroxyl and C_{1-3} alkoxy (optionally substituted by one or more halogens);

R^{5a} and R^{5b} are each independently selected from the group consisting of H, ^2H and C_{1-3}alkyl; wherein C_{1-3} alkyl may optionally be substituted by one, two, three or more substituents, each independently selected from the group consisting of fluorine, hydroxyl and C_{1-3} alkoxy; or R^{5a} and R^{5b} are taken together to form a methylene or ethylene bridging group;

R^{5c} and R^{5d} are each independently selected from the group consisting of H, ^2H, fluorine, hydroxyl, C_{1-3} alkoxy and C_{1-3} alkyl; wherein C_{1-3} alkyl may optionally be substituted by one, two, three or more substituents, each independently selected from the

group consisting of fluorine, hydroxyl and C_{1-3} alkoxy; or R^{5c} and R^{5d} taken together form a methylene, ethylene or -CH_2-O- bridging group;

R^6, R^7 and R^8 are each independently selected from the group consisting of H, ^2H, halogen, C_{1-3} alkyl, C_{1-3} alkoxy, C_{3-7} cycloalkyl and a 4-7 membered heterocyclyl having one, two or three heteroatoms each independently selected from the group consisting of N, O and S; wherein C_{1-3} alkoxy may optionally be substituted by one, two, three or more halogens; and wherein C_{1-3} alkyl may optionally be substituted by one, two, three or more substituents, each independently selected from the group consisting of hydroxyl, halogen and C_{1-3} alkoxy (optionally substituted by one or more halogens); or

wherein R^6 and R^8 optionally forms a partially unsaturated carbobicyclic or heterobicyclic ring with the heteroaryl ring to which they are attached, wherein the carbobicyclic or heterobicyclic ring may optionally be substituted by one, two or three groups, each independently selected from the group consisting of ^2H, halogen, C_{1-3} alkyl, C_{1-3} alkoxy, C_{3-7} cycloalkyl and a 4-7 membered heterocyclyl having one, two or three heteroatoms each independently selected from the group consisting of N, O and S; and

wherein C_{1-3} alkyl and C_{1-3} alkoxy may optionally be substituted by one, two, three or more halogens.

4. The protein kinase C inhibitor for use in a method of claim 1, wherein the method comprises obtaining a biopsy, or obtaining information about a biopsy, of the uveal melanoma.

5. The protein kinase C inhibitor for use in a method of claim 1, wherein the method comprises obtaining a biopsy, or obtaining information about a biopsy, of the *GNAQ/11* tumor.

6. The protein kinase C inhibitor for use in a method of any one of claims 4 or 5, wherein the method comprises assessing cMET presence in the biopsy.

7. The protein kinase C inhibitor for use in a method of claim 6, further comprising selecting the patient having an elevated cMET presence as determined by assessing the biopsy.

8. The protein kinase C inhibitor for use in a method of any one of claims 2-7, wherein the method comprises qualitatively, or quantitatively, measuring total cMET, phosphorylated cMET, non-phosphorylated cMET, or a combination thereof, in the biopsy.

9. The protein kinase C inhibitor for use in a method of any one of claims 2-8, wherein the method comprises determining elevated cMET presence in the biopsy by performing ELISA, western blotting, IHC-F, IHC-P, immunocytochemistry, immunofluorescence, flow cytometry, mass cytometry, immunoprecipitation or cMET RNA transcriptome analysis.

10. The protein kinase C inhibitor for use in a method of any one of claims 1-9, wherein the method comprises:

obtaining the biopsy from the patient;

determining a concentration level of cMET in the biopsy; and

evaluating whether the determined level of cMET in the biopsy is equal to or greater than a predetermined level of cMET.

11. The protein kinase C inhibitor for use in a method of any one of claims 1-10, wherein the method comprises assessing genetic mutation in the patient.

12. The protein kinase C inhibitor for use in a method of any one of claims 1-11 wherein the *GNAQ/11* tumor is pancreatic, stomach, colorectal, uterine, cervical, bladder, hepatocellular carcinoma, head and neck, prostate, breast, lung adenocarcinoma, or cutaneous melanoma.

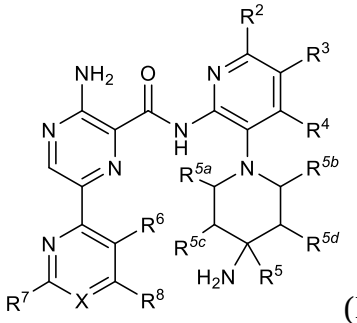
13. A protein kinase C inhibitor for use in a method of treating a patient having a tumor having a *GNAQ* or *GNA11* mutation ("*GNAQ/11* tumor"), or both wherein the method comprises:

assessing cMET presence, or activity, in a biopsy of the uveal melanoma or the *GNAQ/11* tumor;

if the cMET presence, or activity, is elevated in the uveal melanoma or the *GNAQ/11* tumor, then co-administering to the patient a cMET inhibitor and a protein kinase C inhibitor; and

if cMET presence is not elevated in the uveal melanoma or the *GNAQ/11* tumor, then administering to the patient the protein kinase C inhibitor without the cMET inhibitor,

wherein the protein kinase C inhibitor is represented by Formula II:



(II),

or a pharmaceutically acceptable salt thereof, wherein:

X is N or CR;

R, R^2, R^3 and R^4 are each independently selected from the group consisting of H, ^2H, halogen, hydroxyl, C_{1-3} alkoxy and C_{1-3} alkyl; wherein C_{1-3} alkoxy may optionally be substituted by one, two, three or more halogens; and wherein C_{1-3} alkyl may optionally be substituted by one, two, three or more substituents, each independently selected from the group consisting of hydroxyl, halogen and C_{1-3}alkoxy (optionally substituted by one or more halogens);

R^5 is selected from the group consisting of H, ^2H, $-CH_3$, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CH_2OH$ and C_{2-3} alkyl; wherein C_{2-3} alkyl may optionally be substituted by one, two, three or more substituents, each independently selected from the group consisting of fluorine, hydroxyl and C_{1-3} alkoxy (optionally substituted by one or more halogens);

R^{5a} and R^{5b} are each independently selected from the group consisting of H, ^2H and C_{1-3}alkyl; wherein C_{1-3} alkyl may optionally be substituted by one, two, three or more substituents, each independently selected from the group consisting of fluorine, hydroxyl and C_{1-3} alkoxy; or R^{5a} and R^{5b} are taken together to form a methylene or ethylene bridging group;

R^{5c} and R^{5d} are each independently selected from the group consisting of H, ^2H, fluorine, hydroxyl, C_{1-3} alkoxy and C_{1-3} alkyl; wherein C_{1-3} alkyl may optionally be substituted by one, two, three or more substituents, each independently selected from the group consisting of fluorine, hydroxyl and C_{1-3} alkoxy; or R^{5c} and R^{5d} taken together form a methylene, ethylene or $-CH_2-O-$ bridging group;

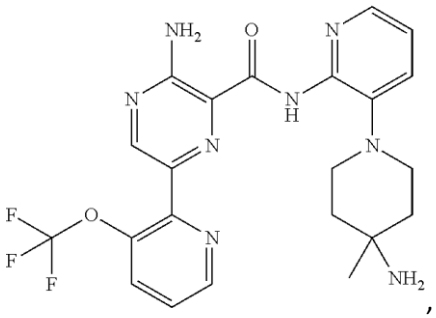
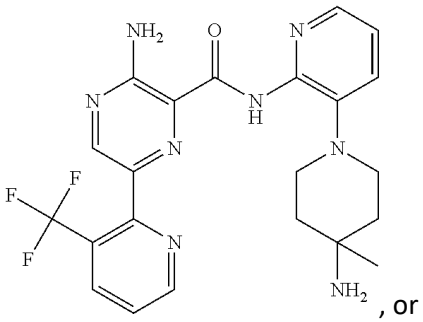
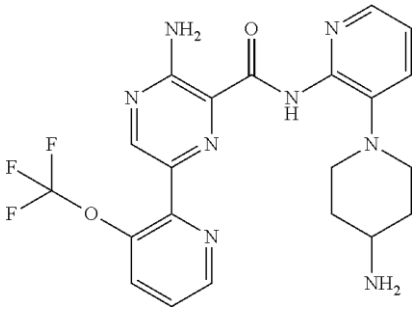
R^6, R^7 and R^8 are each independently selected from the group consisting of H, ^2H, halogen, C_{1-3} alkyl, C_{1-3} alkoxy, C_{3-7} cycloalkyl and a 4-7 membered heterocyclyl having one, two or three heteroatoms each independently selected from the group consisting of N, O and

S; wherein C_{1-3} alkoxy may optionally be substituted by one, two, three or more halogens; and wherein C_{1-3} alkyl may optionally be substituted by one, two, three or more substituents, each independently selected from the group consisting of hydroxyl, halogen and C_{1-3}alkoxy (optionally substituted by one or more halogens); or

wherein R^6 and R^8 optionally forms a partially unsaturated carbobicyclic or heterobicyclic ring with the heteroaryl ring to which they are attached, wherein the carbobicyclic or heterobicyclic ring may optionally be substituted by one, two or three groups, each independently selected from the group consisting of ^2H, halogen, C_{1-3} alkyl, C_{1-3} alkoxy, C_{3-7} cycloalkyl and a 4-7 membered heterocyclyl having one, two or three heteroatoms each independently selected from the group consisting of N, O and S; and

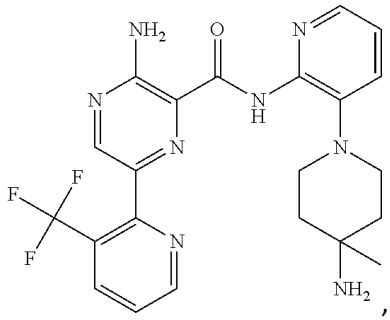
wherein C_{1-3} alkyl and C_{1-3} alkoxy may optionally be substituted by one, two, three or more halogens.

14. The protein kinase C inhibitor for use in a method of any one of claims 1-13, wherein the protein kinase C inhibitor is:


,

, or


or a pharmaceutically acceptable salt thereof.

15. The protein kinase C inhibitor for use in a method of claim 14, wherein the protein kinase C inhibitor is:


, or a pharmaceutically acceptable salt thereof.

16. The protein kinase C inhibitor for use in a method of any one of claims 1-15, wherein the cMET inhibitor is selected from the group consisting of crizotinib, capmatinib, cabozantinib, tivantinib, and any combination thereof.

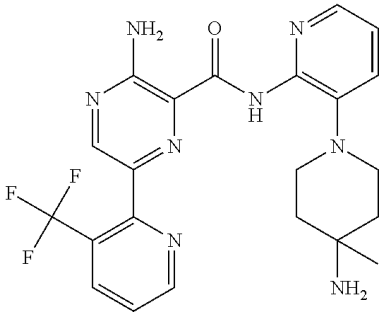
17. The protein kinase C inhibitor for use in a method of claim 16, wherein the cMET inhibitor is crizotinib.

18. The protein kinase C inhibitor for use in a method of any one of claims 1-17, wherein the uveal melanoma is metastatic uveal melanoma.

19. The protein kinase C inhibitor for use in a method of any one of claims 1-18, which is for simultaneous or sequential co-administration with the cMET inhibitor in separate compositions to the patient.

20. A protein kinase C inhibitor for use in a method of treating a patient having uveal melanoma, a tumor having a GNAQ or GNA11 mutation ("GNAQ/11 tumor"), or both, wherein the method comprises:

co-administering to the patient crizotinib and the protein kinase C inhibitor, wherein the protein kinase C inhibitor is


or a pharmaceutically acceptable salt thereof.