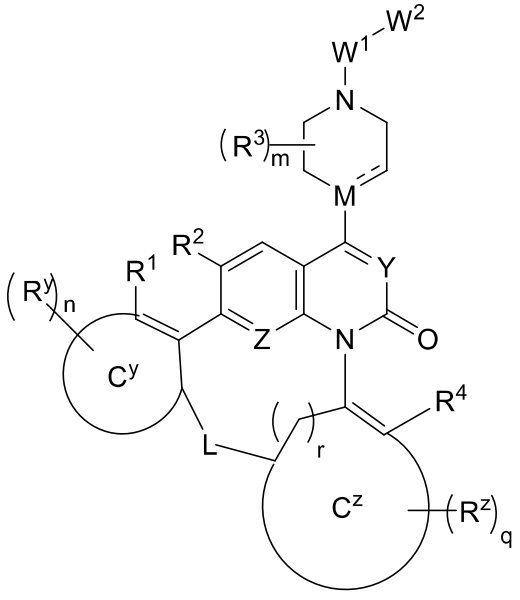
most, 70-75%, to cancer cases having the KRAS G12C mutation. *See* Lindsay, C.R., *et al.*, *Br J Cancer* 121, 197–198 (2019).

Accordingly, while progress has been made in this field, there remains a need in the art for improved compounds and methods for treatment of cancer, for example, by inhibition of a mutant KRAS, HRAS or NRAS protein (*e.g.*, KRAS G12C). Embodiments of the present disclosure fulfill this need and provide further related advantages.

SUMMARY OF THE DISCLOSURE

The present disclosure provides compounds which modulate mutant KRAS, HRAS, and/or NRAS proteins and may be valuable pharmaceutically active compounds for the treatment of cancer. In some embodiments the disclosed compounds selectively inhibit the KRAS (G12C) protein. The compounds of Formula (I)



(I)

and their pharmaceutically acceptable salts, can modulate the activity of KRAS, HRAS and/or NRAS activity and thereby effect the signaling pathway which regulates cell growth, differentiation, and proliferation associated with oncological disorders. In certain embodiments, the compounds of Formula (I) can inhibit the KRAS (G12C) protein. The disclosure furthermore provides processes for preparing compounds of Formula (I), methods for using such compounds to treat oncological disorders, and pharmaceutical compositions which comprise compounds of Formula (I).

In an aspect, there is provided a compound selected from the group consisting of:

2-[(2*S*,5*R*)-2,5-dimethyl-4-(prop-2-enoyl)piperazin-1-yl]-18,21-difluoro-6-(propan-2-yl)-10,11,12,13-tetrahydro-4*H*-1,19-ethenopyrido[4,3-*f*]pyrimido[1,6-*h*][1,8,10]benzoxadiazacyclotridecin-4-one;

(5aS_a,17aR_a)-20-chloro-2-[(2*S*,5*R*)-2,5-dimethyl-4-(prop-2-enoyl)piperazin-1-yl]-14,17-difluoro-6-(propan-2-yl)-11,12-dihydro-4*H*-1,18-(ethanediylidene)pyrido[4,3-*e*]pyrimido[1,6-*g*][1,4,7,9]benzodioxadiazacyclododecin-4-one;

(5aS_a,17aR_a)-20-Chloro-2-[(2*S*,5*R*)-2,5-dimethyl-4-(prop-2-enoyl)piperazin-1-yl]-14,17-difluoro-6-(propan-2-yl)-11,12-di[(^{2}H)hydro](11,12-$^2H_2$)-4*H*-1,18-(ethanediylidene)pyrido[4,3-*e*]pyrimido[1,6-*g*][1,4,7,9]benzodioxadiazacyclododecin-4-one;

(5aR_a,18aR_a)-2-[(2*S*,5*R*)-2,5-dimethyl-4-(prop-2-enoyl)piperazin-1-yl]-12,12,18,21-tetrafluoro-6-(propan-2-yl)-10,11,12,13-tetrahydro-4*H*-1,19-(ethanediylidene)pyrido[4,3-*f*]pyrimido[1,6-*h*][1,8,10]benzoxadiazacyclotridecin-4-one;

(5aR_a,18aR_a)-2-[(2*S*,5*R*)-2,5-dimethyl-4-(prop-2-enoyl)piperazin-1-yl]-12,12,17,18,21-pentafluoro-6-(propan-2-yl)-10,11,12,13-tetrahydro-4*H*-1,19-(ethanediylidene)pyrido[4,3-*f*]pyrimido[1,6-*h*][1,8,10]benzoxadiazacyclotridecin-4-one**;**

(5aR_a,18aR_a)-2-[(2*S*,5*R*)-2,5-dimethyl-4-(prop-2-enoyl)piperazin-1-yl]-12,12,15,18,21-pentafluoro-6-(propan-2-yl)-10,11,12,13-tetrahydro-4*H*-1,19-(ethanediylidene)pyrido[4,3-*f*]pyrimido[1,6-*h*][1,8,10]benzoxadiazacyclotridecin-4-one;

(5aR_a,18aR_a)-2-[(2*S*,5*R*)-2,5-dimethyl-4-(prop-2-enoyl)piperazin-1-yl]-12,12,16,18,21-pentafluoro-6-(propan-2-yl)-10,11,12,13-tetrahydro-4*H*-1,19-(ethanediylidene)pyrido[4,3-*f*]pyrimido[1,6-*h*][1,8,10]benzoxadiazacyclotridecin-4-one;

(5aS_a,17aR_a)-20-chloro-2-[(2*S*,5*R*)-2,5-dimethyl-4-(prop-2-enoyl)piperazin-1-yl]-16,17-difluoro-6-(propan-2-yl)-11,12-di[(^{2}H)hydro](11,12-$^2H_2$)-4*H*-1,18-(ethanediylidene)pyrido[4,3-*e*]pyrimido[1,6-*g*][1,4,7,9]benzodioxadiazacyclododecin-4-one;

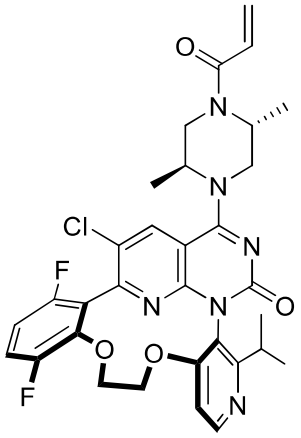
2-[(2*S*,5*R*)-2,5-dimethyl-4-(prop-2-enoyl)piperazin-1-yl]-12,12,17,18,21-pentafluoro-6-(propan-2-yl)-10,11,12,13-tetrahydro-4*H*-1,19-(ethanediylidene)dipyrimido[4,5-*f*:1',6'-*h*][1,8,10]benzoxadiazacyclotridecin-4-one;

21-chloro-2-[(2*S*,5*R*)-2,5-dimethyl-4-(prop-2-enoyl)piperazin-1-yl]-12,12,18-trifluoro-6-(propan-2-yl)-12,13-dihydro-4*H*,11*H*-1,19-(ethanediylidene)pyrido[4,3-*f*]pyrimido[1,6-*h*][1,5,8,10]benzodioxadiazacyclotridecin-4-one;

20-chloro-2-[(2*S*,5*R*)-2,5-dimethyl-4-(prop-2-enoyl)piperazin-1-yl]-17-fluoro-6-(propan-2-yl)-11,12-dihydro-4*H*,10*H*-1,18-(ethanediylidene)pyrido[4,3-*e*]pyrimido[1,6-*g*][1,7,9]benzoxadiazacyclododecin-4-one; or

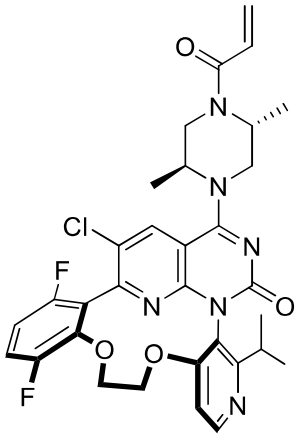
a pharmaceutically acceptable salt thereof.

In another aspect, there is provided a compound having the formula:



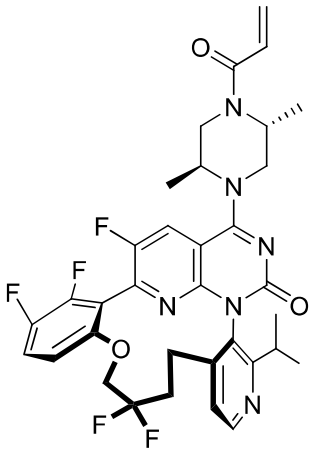
or a pharmaceutically acceptable salt thereof.

In another aspect, there is provided a compound having the formula:



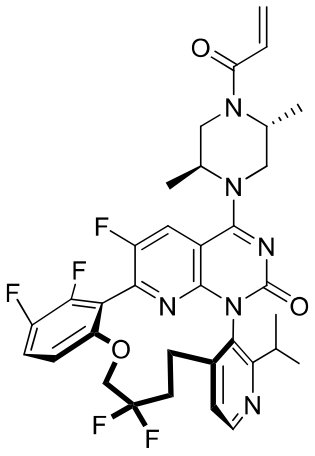
.

In another aspect, there is provided a compound having the formula:



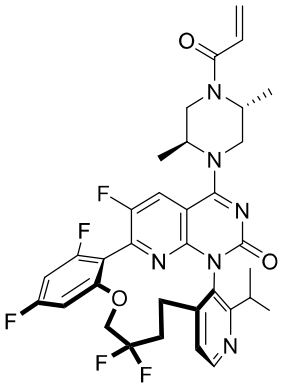
or a pharmaceutically acceptable salt thereof.

In another aspect, there is provided a compound having the formula:



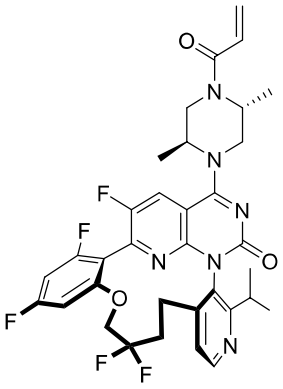
.

In another aspect, there is provided a compound having the formula:

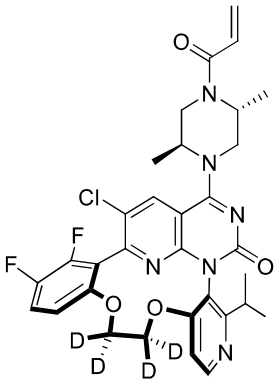


or a pharmaceutically acceptable salt thereof.

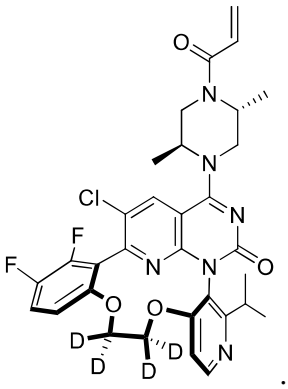
In another aspect, there is provided a compound having the formula:


.

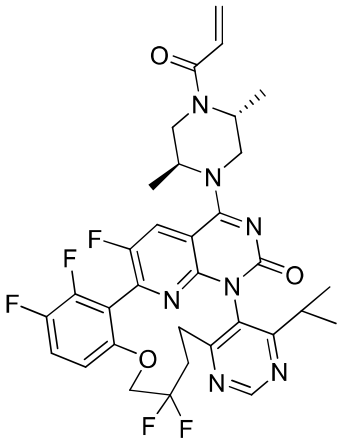
In another aspect, there is provided a compound having the formula:


or a pharmaceutically acceptable salt thereof.

In another aspect, there is provided a compound having the formula:

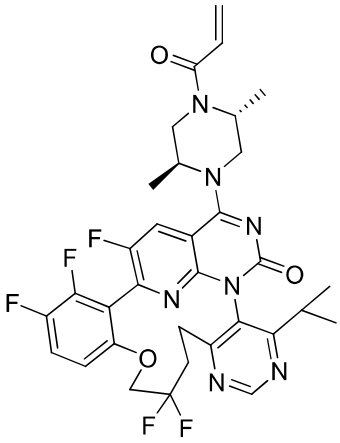

.

In another aspect, there is provided a compound having the formula:



or a pharmaceutically acceptable salt thereof.

In another aspect, there is provided a compound having the formula:



.

In one aspect, provided herein is a pharmaceutical composition comprising the compound or the pharmaceutically acceptable salt thereof as described herein, and a pharmaceutically acceptable carrier.

In one aspect, provided herein is the compound or the pharmaceutically acceptable salt thereof as described herein, for use in the treatment of cancer mediated by a KRAS G12C protein.

In another aspect, there is provided the use of the compound or the pharmaceutically acceptable salt thereof as described herein, in the manufacture of a medicament for use in the treatment of cancer mediated by a KRAS G12C protein.

In one aspect, provided herein is a use of the compound or the pharmaceutically acceptable salt thereof as described herein, in the manufacture of a medicament for treating cancer, wherein the medicament is to be administered to a subject in need of such treatment.

In one aspect, provided herein is a compound or the pharmaceutically acceptable salt thereof as described herein, for use in therapy.

In one aspect, provided herein is a compound or the pharmaceutically acceptable salt thereof as described herein, for use in treating cancer.

In one aspect, provided herein is a use of the compound or the pharmaceutically acceptable salt thereof as described herein, for the preparation of a medicament for the treatment of cancer.

In one aspect, provided herein is the compound or the pharmaceutically acceptable salt thereof as described herein, and an additional anti-cancer agent, for use in therapy or for use in the treatment of cancer.

In one aspect, provided herein is a use of the compound or the pharmaceutically acceptable salt thereof as described herein,, and an additional anti-cancer agent, for the preparation of a medicament for the treatment of cancer.

In one aspect, provided herein is a pharmaceutical composition comprising the compound or the pharmaceutically acceptable salt thereof as described herein, for use in the treatment of cancer, or use of the pharmaceutical composition comprising the compound as described herein, or the pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating cancer.

In one aspect, provided herein is a pharmaceutical composition comprising the compound or the pharmaceutically acceptable salt thereof as described herein, and an additional anti-cancer agent, for use in therapy or for use in the treatment of cancer, or use of the pharmaceutical composition comprising the compound as described herein, or the pharmaceutically acceptable salt thereof, and an additional anti-cancer agent in the manufacture of a medicament, for treating cancer.

DETAILED DESCRIPTION OF THE INVENTION

CLAIMS

We claim:

1. A compound selected from the group consisting of:

2-[(2*S*,5*R*)-2,5-dimethyl-4-(prop-2-enoyl)piperazin-1-yl]-18,21-difluoro-6-(propan-2-yl)-10,11,12,13-tetrahydro-4*H*-1,19-ethenopyrido[4,3-*f*]pyrimido[1,6-*h*][1,8,10]benzoxadiazacyclotridecin-4-one;

(5aS_a,17aR_a)-20-chloro-2-[(2*S*,5*R*)-2,5-dimethyl-4-(prop-2-enoyl)piperazin-1-yl]-14,17-difluoro-6-(propan-2-yl)-11,12-dihydro-4*H*-1,18-(ethanediylidene)pyrido[4,3-*e*]pyrimido[1,6-*g*][1,4,7,9]benzodioxadiazacyclododecin-4-one;

(5aS_a,17aR_a)-20-Chloro-2-[(2*S*,5*R*)-2,5-dimethyl-4-(prop-2-enoyl)piperazin-1-yl]-14,17-difluoro-6-(propan-2-yl)-11,12-di[(^{2}H)hydro](11,12-$^2H_2$)-4*H*-1,18-(ethanediylidene)pyrido[4,3-*e*]pyrimido[1,6-*g*][1,4,7,9]benzodioxadiazacyclododecin-4-one;

(5aR_a,18aR_a)-2-[(2*S*,5*R*)-2,5-dimethyl-4-(prop-2-enoyl)piperazin-1-yl]-12,12,18,21-tetrafluoro-6-(propan-2-yl)-10,11,12,13-tetrahydro-4*H*-1,19-(ethanediylidene)pyrido[4,3-*f*]pyrimido[1,6-*h*][1,8,10]benzoxadiazacyclotridecin-4-one;

(5aR_a,18aR_a)-2-[(2*S*,5*R*)-2,5-dimethyl-4-(prop-2-enoyl)piperazin-1-yl]-12,12,17,18,21-pentafluoro-6-(propan-2-yl)-10,11,12,13-tetrahydro-4*H*-1,19-(ethanediylidene)pyrido[4,3-*f*]pyrimido[1,6-*h*][1,8,10]benzoxadiazacyclotridecin-4-one**;**

(5aR_a,18aR_a)-2-[(2*S*,5*R*)-2,5-dimethyl-4-(prop-2-enoyl)piperazin-1-yl]-12,12,15,18,21-pentafluoro-6-(propan-2-yl)-10,11,12,13-tetrahydro-4*H*-1,19-(ethanediylidene)pyrido[4,3-*f*]pyrimido[1,6-*h*][1,8,10]benzoxadiazacyclotridecin-4-one;

(5aR_a,18aR_a)-2-[(2*S*,5*R*)-2,5-dimethyl-4-(prop-2-enoyl)piperazin-1-yl]-12,12,16,18,21-pentafluoro-6-(propan-2-yl)-10,11,12,13-tetrahydro-4*H*-1,19-(ethanediylidene)pyrido[4,3-*f*]pyrimido[1,6-*h*][1,8,10]benzoxadiazacyclotridecin-4-one;

(5aS_a,17aR_a)-20-chloro-2-[(2*S*,5*R*)-2,5-dimethyl-4-(prop-2-enoyl)piperazin-1-yl]-16,17-difluoro-6-(propan-2-yl)-11,12-di[(^{2}H)hydro](11,12-$^2H_2$)-4*H*-1,18-(ethanediylidene)pyrido[4,3-*e*]pyrimido[1,6-*g*][1,4,7,9]benzodioxadiazacyclododecin-4-one;

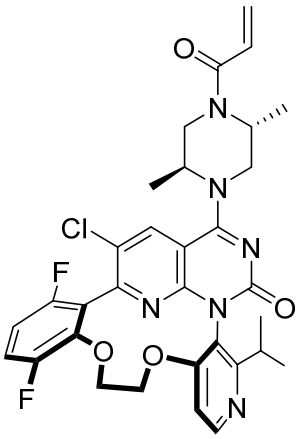
2-[(2*S*,5*R*)-2,5-dimethyl-4-(prop-2-enoyl)piperazin-1-yl]-12,12,17,18,21-pentafluoro-6-(propan-2-yl)-10,11,12,13-tetrahydro-4*H*-1,19-(ethanediylidene)dipyrimido[4,5-*f*:1',6'-*h*][1,8,10]benzoxadiazacyclotridecin-4-one;

21-chloro-2-[(2*S*,5*R*)-2,5-dimethyl-4-(prop-2-enoyl)piperazin-1-yl]-12,12,18-trifluoro-6-(propan-2-yl)-12,13-dihydro-4*H*,11*H*-1,19-(ethanediylidene)pyrido[4,3-*f*]pyrimido[1,6-*h*][1,5,8,10]benzodioxadiazacyclotridecin-4-one;

20-chloro-2-[(2*S*,5*R*)-2,5-dimethyl-4-(prop-2-enoyl)piperazin-1-yl]-17-fluoro-6-(propan-2-yl)-11,12-dihydro-4*H*,10*H*-1,18-(ethanediylidene)pyrido[4,3-*e*]pyrimido[1,6-*g*][1,7,9]benzoxadiazacyclododecin-4-one; or

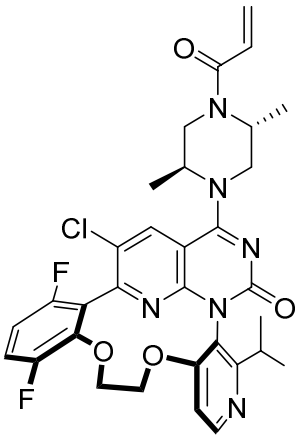
a pharmaceutically acceptable salt thereof.

2. A compound having the formula:



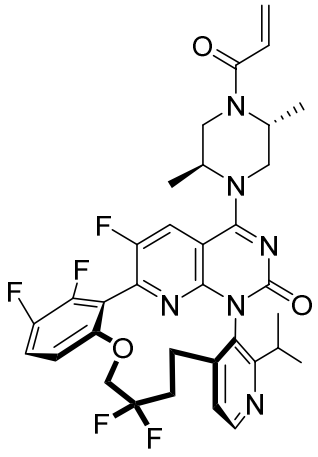
or a pharmaceutically acceptable salt thereof.

3. A compound having the formula:



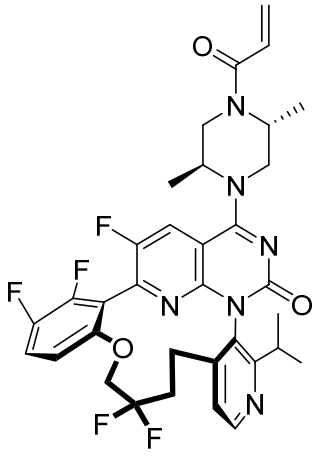
.

4. A compound having the formula:



or a pharmaceutically acceptable salt thereof.

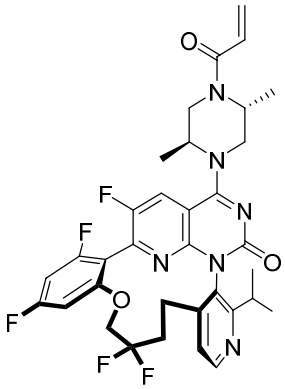
5. A compound having the formula:



.

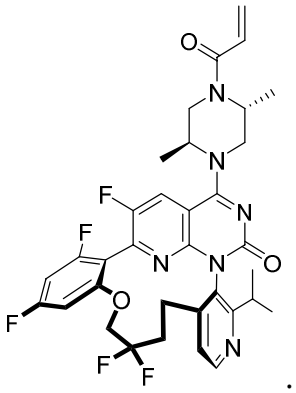
5

6. A compound having the formula:



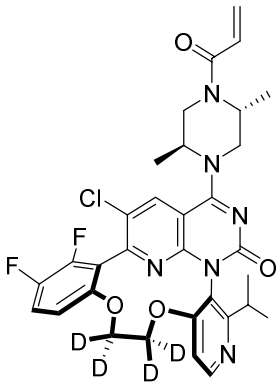
or a pharmaceutically acceptable salt thereof.

7. A compound having the formula:



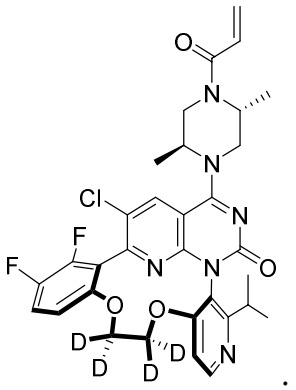
.

8. A compound having the formula:



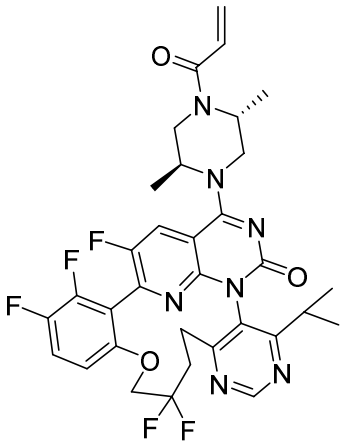
or a pharmaceutically acceptable salt thereof.

9. A compound having the formula:

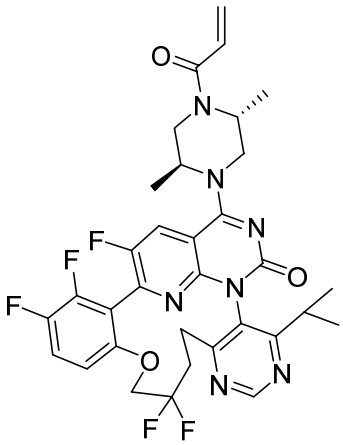


.

10. A compound having the formula:


or a pharmaceutically acceptable salt thereof.

11. A compound having the formula:


.

12. A pharmaceutical composition comprising the compound or the pharmaceutically acceptable salt thereof of any one of claims 1 to 11, and a pharmaceutically acceptable carrier.

13. The compound or the pharmaceutically acceptable salt thereof of any one of claims 1 to 11, for use in the treatment of cancer mediated by a KRAS G12C protein.

14. Use of the compound or the pharmaceutically acceptable salt thereof of any one of claims 1 to 11, in the manufacture of a medicament for use in the treatment of cancer mediated by a KRAS G12C protein.

15. Use of the compound, or the pharmaceutically acceptable salt thereof of any one of claims 1 to 11, in the manufacture of a medicament for treating cancer, wherein the medicament is to be administered to a subject in need of such treatment.

16. The use of claim 15, wherein an additional active agent is to be administered to the subject, wherein the additional active agent is an anti-cancer agent.

17. The use of claim 16, wherein the anti-cancer agent is selected from an EGFR inhibitor, an anti-PD-1 agent, a SHP2 inhibitor, and an ERK inhibitor.

18. The compound or the pharmaceutically acceptable salt thereof of any one of claims 1 to 11 for use in therapy.

19. The compound or the pharmaceutically acceptable salt thereof of any one of claims 1 to 11, for use in treating cancer.

20. Use of the compound or the pharmaceutically acceptable salt thereof of any one of claims 1 to 11, for the preparation of a medicament for the treatment of cancer.

21. The compound or the pharmaceutically acceptable salt thereof of any one of claims 1 to 11, and an additional anti-cancer agent, for use in therapy or for use in the treatment of cancer.

22. Use of the compound, or the pharmaceutically acceptable salt thereof of any one of claims 1 to 11, and an additional anti-cancer agent, for the preparation of a medicament for the treatment of cancer.

23. A pharmaceutical composition comprising the compound, or the pharmaceutically acceptable salt thereof of any one of claims 1 to 11, for use in the treatment of cancer, or use of the pharmaceutical composition comprising the compound, or the pharmaceutically acceptable salt thereof of any one of claims 1 to 11, in the manufacture of a medicament for treating cancer.

24. A pharmaceutical composition comprising the compound, or the pharmaceutically acceptable salt thereof of any one of claims 1 to 11, and an additional anti-cancer agent, for use in therapy or for use in the treatment of cancer, or use of the pharmaceutical composition

comprising the compound, or the pharmaceutically acceptable salt thereof of any one of claims 1 to 11, and an additional anti-cancer agent in the manufacture of a medicament, for treating cancer.