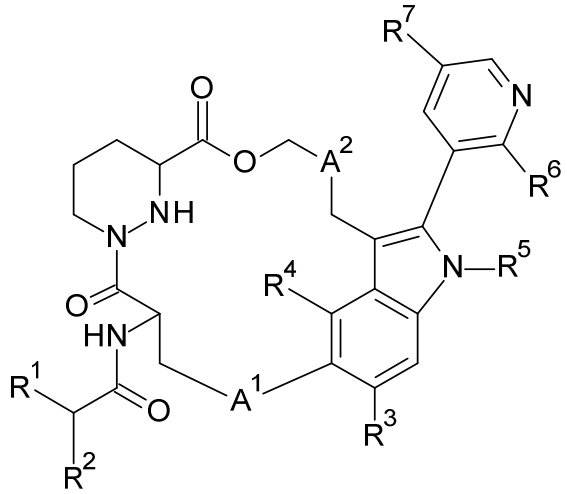
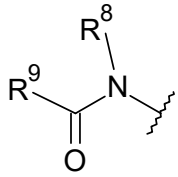
CLAIMS

1. A compound of formula (I),



(I),

wherein



R^1 is , 3-oxo-5,6,8,8a-tetrahydro-1H-imidazo[5,1-c][1,4]oxazinyl or (C_{1-6}alkyl)oxoimidazolidinyl;

wherein R^8 is C_{1-6}alkyl;

R^9 is ((C_{1-6}alkyl)$_2$amino)azetidinyl, C_{1-6}alkylpiperazinyl, haloazetidinyl, haloC_{1-6}alkylamino, haloC_{1-6}alkylaminoazetidinyl, haloC_{1-6}alkylpiperazinyl, hydroxy(C_{1-6}alkyl)piperidinyl or morpholinyl;

R^2 is C_{1-6}alkyl;

R^3 is H or halogen;

R^4 is H or halogen;

R^5 is C_{1-6}alkyl or haloC_{1-6}alkyl;

R^6 is C_{1-6}alkoxyC_{1-6}alkyl;

R^7 is morpholinyl, (haloC_{1-6}alkyl)piperazinyl or C_{1-6}alkylpiperazinyl;

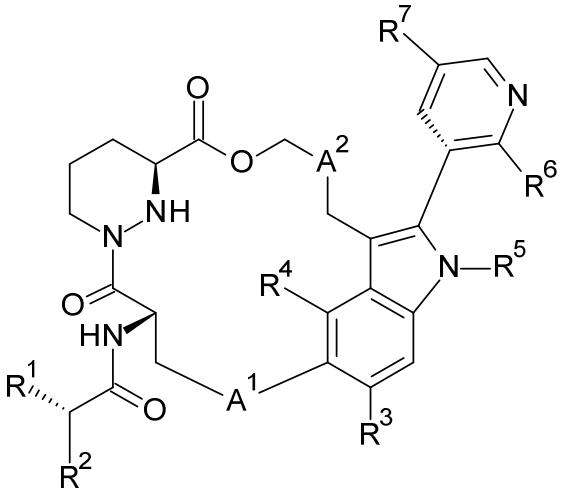
A^1 is thiazolylene;

A^2 is C_{1-6}alkylene;

with the proviso that R^3 and R^4 are not H simultaneously;

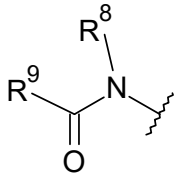
or a pharmaceutically acceptable salt thereof.

2. A compound of formula (Ia),



(Ia),

wherein



R^1 is , 3-oxo-5,6,8,8a-tetrahydro-1H-imidazo[5,1-c][1,4]oxazinyl or (C_{1-6}alkyl)oxoimidazolidinyl;

wherein R^8 is C_{1-6}alkyl;

R^9 is ((C_{1-6}alkyl)$_2$amino)azetidinyl, C_{1-6}alkylpiperazinyl, haloazetidinyl, haloC_{1-6}alkylamino, haloC_{1-6}alkylaminoazetidinyl, haloC_{1-6}alkylpiperazinyl, hydroxy(C_{1-6}alkyl)piperidinyl or morpholinyl;

R^2 is C_{1-6}alkyl;

R^3 is H or halogen;

R^4 is H or halogen;

R^5 is C_{1-6}alkyl or haloC_{1-6}alkyl;

R^6 is C_{1-6}alkoxyC_{1-6}alkyl;

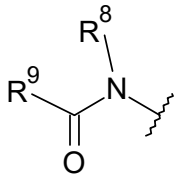
R^7 is morpholinyl, (haloC_{1-6}alkyl)piperazinyl or C_{1-6}alkylpiperazinyl;

A^1 is thiazolylene;

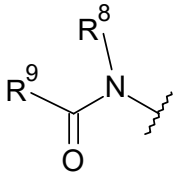
A^2 is C_{1-6}alkylene;

with the proviso that R^3 and R^4 are not H simultaneously;

or a pharmaceutically acceptable salt thereof.



3. A compound according to claim 1 or 2, wherein R^1 is ; wherein R^8 is C_{1-6}alkyl; R^9 is C_{1-6}alkylpiperazinyl, haloC_{1-6}alkylpiperazinyl or morpholinyl.



4. A compound according to any one of claims 1-3, wherein R^1 is ; wherein R^8 is methyl; R^9 is 4-methylpiperazin-1-yl, 4-(2,2,2-trifluoroethyl)piperazin-1-yl or morpholinyl.

5. A compound according to any one of claims 1-4, wherein R^1 is methyl-(4-methylpiperazine-1-carbonyl)amino, methyl-[4-(2,2,2-trifluoroethyl)piperazine-1-carbonyl]amino or methyl(morpholine-4-carbonyl)amino.

6. A compound according to any one of claims 1-5, wherein R^2 is isopropyl.

7. A compound according to any one of claims 1-6, wherein R^3 is H or fluoro.

8. A compound according to any one of claims 1-7, wherein R^3 is fluoro.

9. A compound according to any one of claims 1-8, wherein R^4 is H or fluoro.

10. A compound according to any one of claims 1-9, wherein R^4 is H.

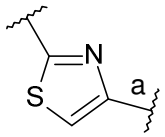
11. A compound according to any one of claims 1-10, wherein R^5 is haloC_{1-6}alkyl.

12. A compound according to any one of claims 1-11, wherein R^5 is 2,2,2-trifluoroethyl.

13. A compound according to any one of claims 1-12, wherein R^6 is 1-methoxyethyl.

14. A compound according to any one of claims 1-13, wherein R^7 is (haloC_{1-6}alkyl)piperazinyl.

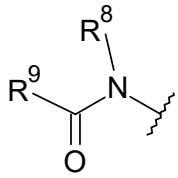
15. A compound according to any one of claims 1-14, wherein R^7 is 4-(2,2,2-trifluoroethyl)piperazin-1-yl.

16. A compound according to any one of claims 1-15, wherein A^1 is 

, wherein bond "a" connects to indole ring.

17. A compound according to any one of claims 1-16, wherein A^2 is dimethylmethylene.

18. A compound according to claim 1 or 2, wherein

R^1 is 

; wherein R^8 is C_{1-6}alkyl; R^9 is C_{1-6}alkylpiperazinyl, haloC_{1-6}alkylpiperazinyl or morpholinyl;

R^2 is C_{1-6}alkyl;

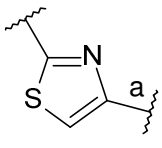
R^3 is halogen;

R^4 is H;

R^5 is haloC_{1-6}alkyl;

R^6 is C_{1-6}alkoxyC_{1-6}alkyl;

R^7 is (haloC_{1-6}alkyl)piperazinyl;

A^1 is 

, wherein bond "a" connects to indole ring;

A^2 is C_{1-6}alkylene;

or a pharmaceutically acceptable salt thereof.

19. A compound according to claim 18, wherein

R^1 is methyl-(4-methylpiperazine-1-carbonyl)amino, methyl-[4-(2,2,2-trifluoroethyl)piperazine-1-carbonyl]amino or methyl(morpholine-4-carbonyl)amino;

R^2 is isopropyl;

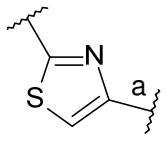
R^3 is fluoro;

R^4 is H;

R^5 is 2,2,2-trifluoroethyl;

R^6 is (1S)-1-methoxyethyl;

R^7 is 4-(2,2,2-trifluoroethyl)piperazin-1-yl;

A^1 is 

, wherein bond "a" connects to indole ring;

A^2 is dimethylmethylene;

or a pharmaceutically acceptable salt thereof.

20. A compound selected from:

3-(dimethylamino)-*N*-[(1*S*)-1-[[(7*S*,13*S*)-24-fluoro-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-(4-methylpiperazin-1-yl)-3-pyridyl]-17,17-dimethyl-8,14-dioxo-21-(2,2,2-trifluoroethyl)-15-oxa-4-thia-9,21,27,28-tetrazapentacyclo[17.5.2.$1^{2,5}$.$1^{9,13}$.$0^{22,26}$]octacosa-1(25),2,5(28),19,22(26),23-hexaen-7-yl]carbamoyl]-2-methyl-propyl]-*N*-methyl-azetidine-1-carboxamide;

3-(dimethylamino)-*N*-[(1*S*)-1-[[(7*S*,13*S*)-25-fluoro-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-(4-methylpiperazin-1-yl)-3-pyridyl]-17,17-dimethyl-8,14-dioxo-21-(2,2,2-trifluoroethyl)-15-oxa-4-thia-9,21,27,28-tetrazapentacyclo[17.5.2.$1^{2,5}$.$1^{9,13}$.$0^{22,26}$]octacosa-1(25),2,5(28),19,22(26),23-hexaen-7-yl]carbamoyl]-2-methyl-propyl]-*N*-methyl-azetidine-1-carboxamide;

N-[(1*S*)-1-[[(7*S*,13*S*)-24-fluoro-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-(4-methylpiperazin-1-yl)-3-pyridyl]-17,17-dimethyl-8,14-dioxo-21-(2,2,2-trifluoroethyl)-15-oxa-4-thia-9,21,27,28-tetrazapentacyclo[17.5.2.$1^{2,5}$.$1^{9,13}$.$0^{22,26}$]octacosa-1(25),2,5(28),19,22(26),23-hexaen-7-yl]carbamoyl]-2-methyl-propyl]-*N*-methyl-morpholine-4-carboxamide;

3-(dimethylamino)-*N*-[(1*S*)-1-[[(7*S*,13*S*)-24-fluoro-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-morpholino-3-pyridyl]-17,17-dimethyl-8,14-dioxo-21-(2,2,2-trifluoroethyl)-15-oxa-4-thia-9,21,27,28-tetrazapentacyclo[17.5.2.$1^{2,5}$.$1^{9,13}$.$0^{22,26}$]octacosa-1(25),2,5(28),19,22(26),23-hexaen-7-yl]carbamoyl]-2-methyl-propyl]-*N*-methyl-azetidine-1-carboxamide;

N-[(1*S*)-1-[[(7*S*,13*S*)-21-ethyl-24-fluoro-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-morpholino-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,27,28-

tetrazapentacyclo[17.5.2.1^{2,5}.1^{9,13}.0^{22,26}]octacosa-1(25),2,5(28),19,22(26),23-hexaen-7-yl]carbamoyl]-2-methyl-propyl]-*N*-methyl-morpholine-4-carboxamide;

N-[(1*S*)-1-[[(7*S*,13*S*)-24-fluoro-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-[4-(2,2,2-trifluoroethyl)piperazin-1-yl]-3-pyridyl]-17,17-dimethyl-8,14-dioxo-21-(2,2,2-trifluoroethyl)-15-oxa-4-thia-9,21,27,28-tetrazapentacyclo[17.5.2.1^{2,5}.1^{9,13}.0^{22,26}]octacosa-1(25),2,5(28),19,22(26),23-hexaen-7-yl]carbamoyl]-2-methyl-propyl]-*N*-methyl-morpholine-4-carboxamide;

N-[(1*S*)-1-[[(7*S*,13*S*)-21-ethyl-24-fluoro-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-morpholino-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,27,28-tetrazapentacyclo[17.5.2.1^{2,5}.1^{9,13}.0^{22,26}]octacosa-1(25),2,5(28),19,22(26),23-hexaen-7-yl]carbamoyl]-2-methyl-propyl]-3,3-difluoro-*N*-methyl-azetidine-1-carboxamide;

(2*S*)-*N*-[(7*S*,13*S*)-21-ethyl-24-fluoro-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-morpholino-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,27,28-tetrazapentacyclo[17.5.2.1^{2,5}.1^{9,13}.0^{22,26}]octacosa-1(25),2,5(28),19,22(26),23-hexaen-7-yl]-3-methyl-2-(3-methyl-2-oxo-imidazolidin-1-yl)butanamide;

N-[(1*S*)-1-[[(7*S*,13*S*)-21-ethyl-24-fluoro-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-[4-(2,2,2-trifluoroethyl)piperazin-1-yl]-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,27,28-tetrazapentacyclo[17.5.2.1^{2,5}.1^{9,13}.0^{22,26}]octacosa-1(25),2,5(28),19,22(26),23-hexaen-7-yl]carbamoyl]-2-methyl-propyl]-*N*-methyl-morpholine-4-carboxamide;

N-[(1*S*)-1-[[(7*S*,13*S*)-21-ethyl-24-fluoro-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-(4-methylpiperazin-1-yl)-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,27,28-tetrazapentacyclo[17.5.2.1^{2,5}.1^{9,13}.0^{22,26}]octacosa-1(25),2,5(28),19,22(26),23-hexaen-7-yl]carbamoyl]-2-methyl-propyl]-*N*-methyl-morpholine-4-carboxamide;

N-[(1*S*)-1-[[(7*S*,13*S*)-24-fluoro-20-(20*M*)-[2-[(1*S*)-1-methoxyethyl]-5-morpholino-3-pyridyl]-17,17-dimethyl-8,14-dioxo-21-(2,2,2-trifluoroethyl)-15-oxa-4-thia-9,21,27,28-tetrazapentacyclo[17.5.2.1^{2,5}.1^{9,13}.0^{22,26}]octacosa-1(25),2,5(28),19,22(26),23-hexaen-7-yl]carbamoyl]-2-methyl-propyl]-*N*-methyl-morpholine-4-carboxamide;

3-(dimethylamino)-*N*-[(1*S*)-1-[[(7*S*,13*S*)-24-fluoro-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-[4-(2,2,2-trifluoroethyl)piperazin-1-yl]-3-pyridyl]-17,17-dimethyl-8,14-dioxo-21-(2,2,2-trifluoroethyl)-15-oxa-4-thia-9,21,27,28-tetrazapentacyclo[17.5.2.1^{2,5}.1^{9,13}.0^{22,26}]octacosa-1(25),2,5(28),19,22(26),23-hexaen-7-yl]carbamoyl]-2-methyl-propyl]-*N*-methyl-azetidine-1-carboxamide;

(2*S*)-*N*-[(7*S*,13*S*)-21-ethyl-24-fluoro-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-morpholino-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,27,28-tetrazapentacyclo[17.5.2.1^{2,5}.1^{9,13}.0^{22,26}]octacosa-1(25),2,5(28),19,22(26),23-hexaen-7-yl]-3-methyl-2-[methyl(2,2,2-trifluoroethylcarbamoyl)amino]butanamide;

N-[(1*S*)-1-[[(7*S*,13*S*)-21-ethyl-24-fluoro-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-morpholino-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,27,28-tetrazapentacyclo[17.5.2.1^{2,5}.1^{9,13}.0^{22,26}]octacosa-1(25),2,5(28),19,22(26),23-hexaen-7-yl]carbamoyl]-2-methyl-propyl]-*N*-methyl-3-(trifluoromethyl)azetidine-1-carboxamide;

(2*S*)-*N*-[(7*S*,13*S*)-21-ethyl-24-fluoro-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-morpholino-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,27,28-tetrazapentacyclo[17.5.2.1^{2,5}.1^{9,13}.0^{22,26}]octacosa-1(25),2,5(28),19,22(26),23-hexaen-7-yl]-3-methyl-2-(3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[5,1-c][1,4]oxazin-2-yl)butanamide;

(3*R*)-*N*-[(1*S*)-1-[[(7*S*,13*S*)-24-fluoro-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-morpholino-3-pyridyl]-17,17-dimethyl-8,14-dioxo-21-(2,2,2-trifluoroethyl)-15-oxa-4-thia-9,21,27,28-tetrazapentacyclo[17.5.2.1^{2,5}.1^{9,13}.0^{22,26}]octacosa-1(25),2,5(28),19,22(26),23-hexaen-7-yl]carbamoyl]-2-methyl-propyl]-3-hydroxy-*N*,3-dimethyl-piperidine-1-carboxamide;

N-[(1*S*)-1-[[(7*S*,13*S*)-25-fluoro-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-[4-(2,2,2-trifluoroethyl)piperazin-1-yl]-3-pyridyl]-17,17-dimethyl-8,14-dioxo-21-(2,2,2-trifluoroethyl)-15-oxa-4-thia-9,21,27,28-tetrazapentacyclo[17.5.2.1^{2,5}.1^{9,13}.0^{22,26}]octacosa-1(25),2,5(28),19,22(26),23-hexaen-7-yl]carbamoyl]-2-methyl-propyl]-*N*-methyl-morpholine-4-carboxamide;

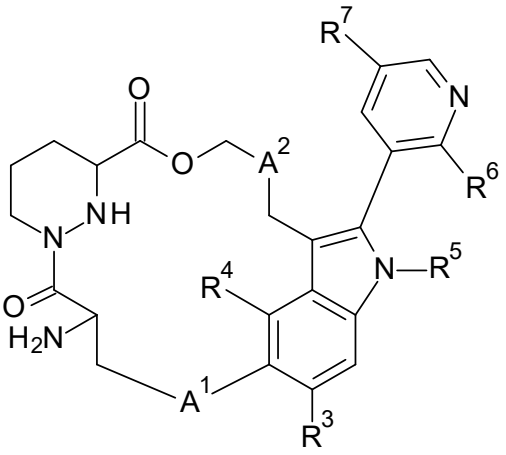
N-[(1*S*)-1-[[(7*S*,13*S*)-24-fluoro-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-[4-(2,2,2-trifluoroethyl)piperazin-1-yl]-3-pyridyl]-17,17-dimethyl-8,14-dioxo-21-(2,2,2-trifluoroethyl)-15-oxa-4-thia-9,21,27,28-tetrazapentacyclo[17.5.2.1^{2,5}.1^{9,13}.0^{22,26}]octacosa-1(25),2,5(28),19,22(26),23-hexaen-7-yl]carbamoyl]-2-methyl-propyl]-*N*,4-dimethyl-piperazine-1-carboxamide; and

N-[(1*S*)-1-[[(7*S*,13*S*)-24-fluoro-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-[4-(2,2,2-trifluoroethyl)piperazin-1-yl]-3-pyridyl]-17,17-dimethyl-8,14-dioxo-21-(2,2,2-trifluoroethyl)-15-oxa-4-thia-9,21,27,28-tetrazapentacyclo[17.5.2.1^{2,5}.1^{9,13}.0^{22,26}]octacosa-1(25),2,5(28),19,22(26),23-hexaen-7-yl]carbamoyl]-2-methyl-propyl]-*N*-methyl-4-(2,2,2-trifluoroethyl)piperazine-1-carboxamide;

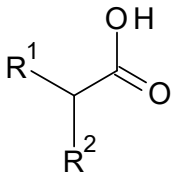
or a pharmaceutically acceptable salt thereof.

21. A process for the preparation of a compound according to any one of claims 1 to 20 comprising the following step:

a) coupling reaction between compound of formula (II),



(II), and acid (III),



(III),

in the presence of a coupling reagent and a base to form the compound of formula (I);

wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, A^1 and A^2 are defined as in any one of claims 1 to 19; the coupling reagent is T_3P, HATU, PyBOP or EDCI/HOBt; the base is TEA, DIEPA or DMAP.

22. A compound or pharmaceutically acceptable salt according to any one of claims 1 to 20 for use as therapeutically active substance.

23. A pharmaceutical composition comprising a compound in accordance with any one of claims 1 to 20 and a pharmaceutically acceptable excipient.

24. The use of a compound according to any one of claims 1 to 20 for treating a KRAS G12C protein-related disease.

25. The use of a compound according to any one of claims 1 to 20 for treating a KRAS G12C, G12D and G12V protein-related disease.

26. The use of a compound according to any one of claims 1 to 20 for inhibiting RAS interaction with downstream effectors, wherein the downstream effectors are RAF and PI3K.

27. The use of a compound according to any one of claims 1 to 20 for inhibiting the propagating oncogenic MAPK and PI3K signaling.

28. The use of a compound according to any one of claims 1 to 20 for the treatment or prophylaxis of KRAS mutation driven cancers, wherein the cancer is selected from pancreatic cancer, colorectal cancer, lung cancer, esophageal cancer, gallbladder cancer, melanoma ovarian cancer and endometrial cancer.

29. The use of a compound according to any one of claims 1 to 20 for the treatment or prophylaxis of KRAS mutation driven cancers, wherein the cancer is selected from pancreatic adenocarcinoma, colorectal cancer and non-small cell lung cancer.

30. A compound or pharmaceutically acceptable salt according to any one of claims 1 to 20 for the treatment or prophylaxis of KRAS mutation driven cancers, wherein the cancer is selected from pancreatic adenocarcinoma, colorectal cancer and non-small cell lung cancer.

31. The use a compound according to any one of claims 1 to 20 for the treatment or prophylaxis of KRAS mutation driven cancers, wherein the cancer comprises a first mutation that is G12C, and a second mutation at a position selected from V8A, V9Y, S17E, T58I, A59T, S65W, R68S, D69P, M72I, D92R, H95N, Y96D, Q99F, Q99W, Y96H, and F156L.

32. The use of a compound according to any one of claims 1 to 20 for the preparation of a medicament for the treatment or prophylaxis of KRAS mutation driven cancers, wherein the cancer is selected from pancreatic adenocarcinoma, colorectal cancer and non-small cell lung cancer.

33. The use of a compound according to any one of claims 1 to 18 for the preparation of a medicament for the treatment or prophylaxis of KRAS mutation driven cancers, wherein the cancer comprises a first mutation that is G12C, and a second mutation at a position selected from V8A, V9Y, S17E, T58I, A59T, S65W, R68S, D69P, M72I, D92R, H95N, Y96D, Q99F, Q99W, Y96H, and F156L.

34. A method for the treatment or prophylaxis of KRAS mutation driven cancers, wherein the

cancer is selected from pancreatic adenocarcinoma, colorectal cancer and non-small cell lung cancer, which method comprises administering a therapeutically effective amount of a compound as defined in any one of claims 1 to 20.

35. A method for the treatment or prophylaxis of KRAS mutation driven cancers, wherein the cancer comprises a first mutation that is G12C, and a second mutation at a position selected from V8A, V9Y, S17E, T58I, A59T, S65W, R68S, D69P, M72I, D92R, H95N, Y96D, Q99F, Q99W, Y96H, and F156L.

36. A compound or pharmaceutically acceptable salt according to any one of claims 1 to 20, when manufactured according to a process of claim 21.