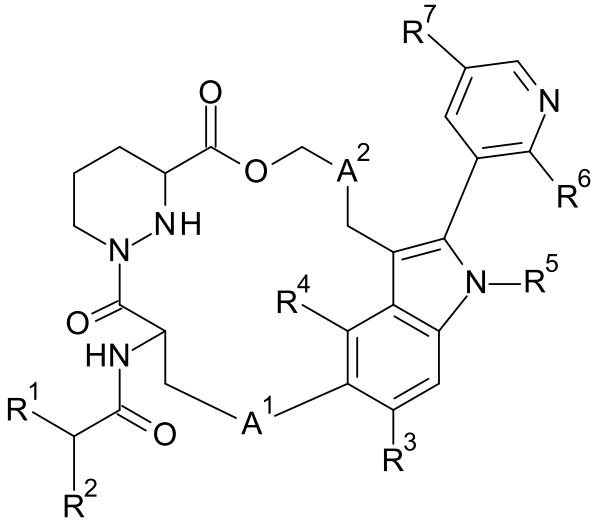
Despite its well-recognized importance in cancer malignancy, continuous efforts in the past failed to develop approved therapies for KRAS mutant cancer until recently, the first selective drug AMG510 has fast approval as second line treatment in KRAS G12C driven non-small cell lung cancer (NSCLC). Nevertheless, the clinical acquired resistance to KRAS G12C inhibitors emerge rigorously with disease progresses after around 6 month of treatment. All of the mutations converge to reactivate RAS–MAPK signaling, with secondary RAS mutants at oncogenic hotspots (e.g. G12/G13/Q61) and within the switch II pocket (e.g. H95, R68, and Y96) have been observed; moreover, over 85% of all KRAS-mutated or wild-type amplified driven cancers still lack novel agents. Altogether, both the myriad of escape mechanism and various oncogenic alleles, highlight the urgent medical need for additional KRAS therapies. As such, we invented oral compounds that target and inhibit KRAS alleles for the treatment of KRAS mutant driven cancers.

First generation KRAS G12C inhibitors like Sotorosib, Adagrasib targeting on 'GDP bound off' form (RASOFF) of KRAS G12C mutation have demonstrated promising efficacy. While this treatment has benefited many patients with activating KRAS mutations, almost all who initially benefited will eventually acquire resistance via various mechanism. Increasing cases of *KRAS G12C* second mutations have been identified either from patients' samples such as Y96D, R68S, H95D, H95Q, H95R, V8L (Tanaka et al., Cancer Discovery (2021), Awad et al., NEJM (2021), Ho et al., EJC (2021), Zhao et al., Nature (2021), Tsai et al., JCI (2022)), or discovered from saturation mutagenesis (Siyu et al, PNAS (2022)) and ENU mutagenesis (Takamasa et al, J Thorac Oncol (2021)) that demonstrated resistance to KRAS(OFF) G12C inhibitors. Therefore, there are unmet needs to prevent the acquisition of one or more mutations in RAS that confer resistance to the RAS(OFF) inhibitor.

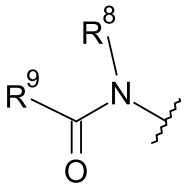
SUMMARY

In one aspect, the present disclosure relates to 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;

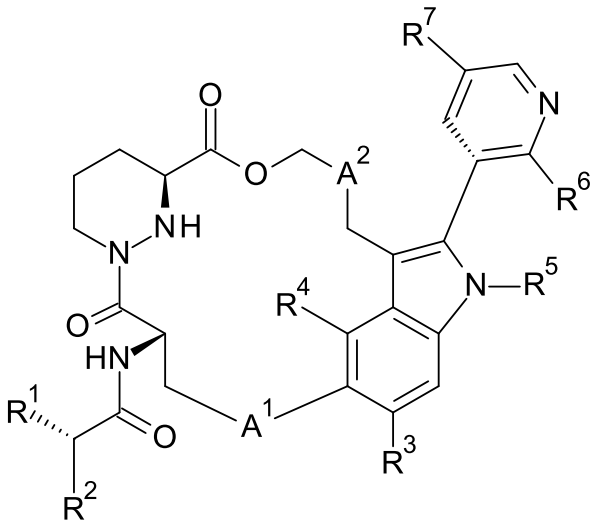
A^1 is thiazolylene;

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

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

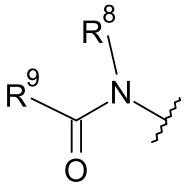
or a pharmaceutically acceptable salt thereof.

In another aspect, the present disclosure relates to 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.

In another aspect, the present disclosure relates to 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

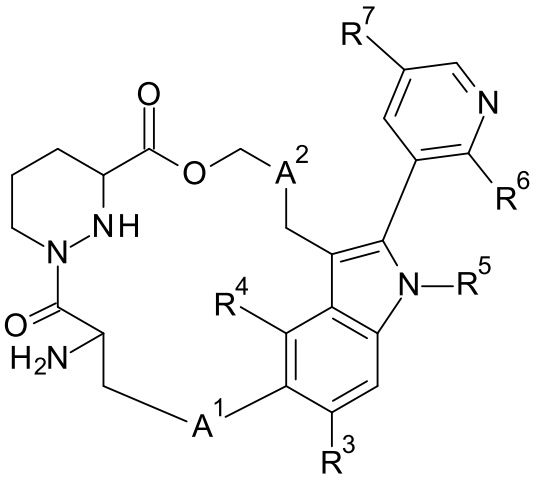
N-[(1*S*)-1-[[(7*S*,13*S*)-24-fluoro-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-[4-(2,2,2-trifluoroethyl)piperazin-1-yl]-3-pyridyl]-17,17-dimethyl-8,14-dioxo-21-(2,2,2-trifluoroethyl)-15-oxa-4-thia-9,21,27,28-tetrazapentacyclo[17.5.2.1^{2,5}.1^{9,13}.0^{22,26}]octacosa-1(25),2,5(28),19,22(26),23-hexaen-7-yl]carbamoyl]-2-methyl-propyl]-*N*-methyl-4-(2,2,2-trifluoroe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

or a pharmaceutically acceptable salt thereof.

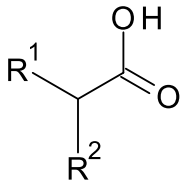
The disclosure also relates to their manufacture, medicaments based on a compound in accordance with the disclosure and their production as well as the use of compounds of formula (I) or (Ia) thereof as inhibitor of KRAS.

In another aspect, the present disclosure relates to a process for the preparation of a compound as described herein 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 as described herein; the coupling reagent is T_3P, HATU, PyBOP or EDCI/HOBt; the base is TEA, DIEPA or DMAP.

In another aspect, the present disclosure provides a compound or pharmaceutically acceptable salt as described herein for use as therapeutically active substance.

In another aspect, the present disclosure provides a pharmaceutical composition comprising a compound as described herein and a pharmaceutically acceptable excipient.

In another aspect, the present disclosure provides a compound as described herein for use in treating a KRAS G12C protein-related disease.

In another aspect, the present disclosure provides a compound as described herein for use in treating a KRAS G12C, G12D and G12V protein-related disease.

In another aspect, the present disclosure provides a compound as described herein for use in inhibiting RAS interaction with downstream effectors, wherein the downstream effectors are RAF and PI3K.

In another aspect, the present disclosure provides a compound as described herein for use in inhibiting the propagating oncogenic MAPK and PI3K signaling.

In another aspect, the present disclosure provides the use of a compound as described herein in the preparation of a medicament 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.

In another aspect, the present disclosure provides a compound as described herein for use in 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.

In another aspect, the present disclosure provides a compound or pharmaceutically acceptable salt as described herein for use in 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.

In another aspect, the present disclosure provides a compound as described herein for use in 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.

In another aspect, the present disclosure provides the use of a compound as described herein in 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.

In another aspect, the present disclosure provides the use of a compound as described herein in 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.

In another aspect, the present disclosure provides a compound or pharmaceutically acceptable salt as described herein, when manufactured according to a process as described herein.

The compounds of formula (I) or (Ia) show good KRAS inhibition for G12C, G12D and G12V. In another example, the compounds of this disclosure showed superior cancer cell inhibition and human hepatocyte stability. In addition, the compounds of formula (I) or (Ia) also show good or improved cytotoxicity and solubility profiles. Furthermore, the compound of current disclosure had excellent pharmacokinetic properties comparing with the reference compounds.

BRIEF DESCRIPTION OF THE FIGURE

Figure 1. X-ray crystallographic analysis of compound G5.

DETAILED DESCRIPTION OF THE INVENTION

DEFINITIONS

The term "C_{1-6}alkyl" denotes a saturated, linear or branched chain alkyl group containing 1 to 6, particularly 1 to 4 carbon atoms, for example methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *tert*-butyl and the like. Particular "C_{1-6}alkyl" groups are methyl, ethyl and *n*-propyl.

The term "C_{1-6}alkoxy" denotes C_{1-6}alkyl-O-.

The term "C_{1-6}alkylene" denotes a linear or branched saturated divalent hydrocarbon group of 1 to 6 carbon atoms or a divalent branched saturated divalent hydrocarbon group of 3 to 6 carbon atoms. Examples of C_{1-6}alkylene groups include methylene, ethylene, propylene, 2-methylpropylene, butylene, 2-ethylbutylene, pentylene, hexylene.

The term "halogen" and "halo" are used interchangeably herein and denote fluoro, chloro, bromo, or iodo.

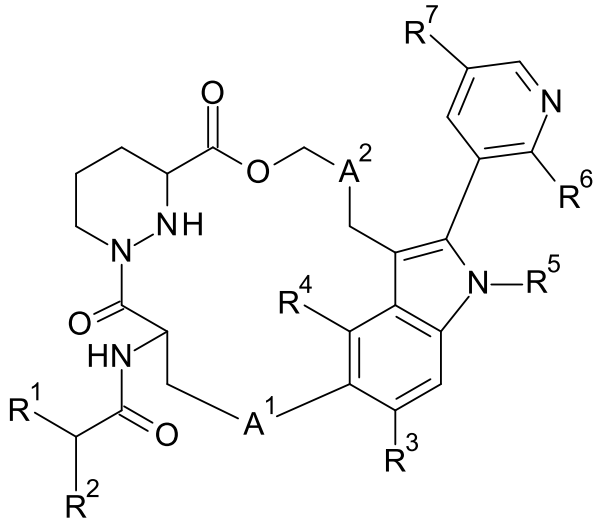
The term "haloC_{1-6}alkyl" denotes a C_{1-6}alkyl group wherein at least one of the hydrogen atoms of the C_{1-6}alkyl group has been replaced by same or different halogen atoms, particularly fluoro atoms. Examples of haloalkyl include monofluoro-, difluoro- or trifluoro-methyl, -ethyl or -propyl, for example 3,3,3-trifluoropropyl, 2-fluoroethyl, 2,2,2-trifluoroethyl, fluoromethyl, or trifluoromethyl.

The term "C_{3-7}cycloalkyl" denotes a monovalent saturated monocyclic or bicyclic hydrocarbon group of 3 to 7 ring carbon atoms. Bicyclic means consisting of two saturated carbocycles having one or more carbon atoms in common. Examples for monocyclic cycloalkyl are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl. Examples for bicyclic cycloalkyl are bicyclo[1.1.0]butyl, bicyclo[2.2.1]heptanyl, bicyclo[1.1.1]pentanyl, or bicyclo[2.2.2]octanyl.

The term "thiazolylene" denotes a divalent thiazolyl group.

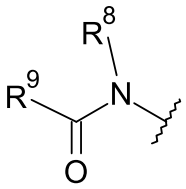
CLAIMS

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;

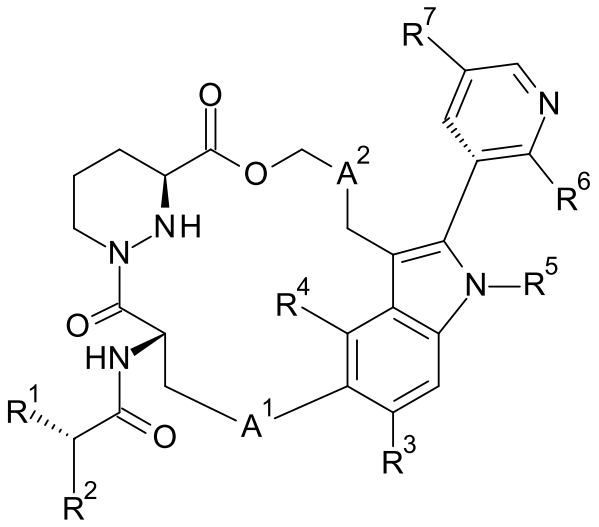
A^1 is thiazolylene;

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

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

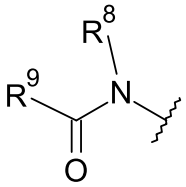
or a pharmaceutically acceptable salt thereof.

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;

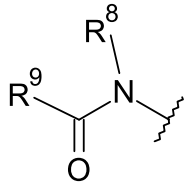
R^7 is morpholinyl, (haloC_{1-6}alkyl)piperazinyl or C_{1-6}alkylpiperazinyl;

A^1 is thiazolylene;

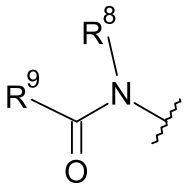
A^2 is C_{1-6}alkylene;

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.

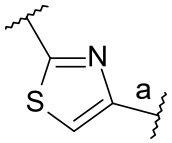
11. A compound according to any one of claims 1-10, wherein R^5 is haloC_{1-6}alkyl.

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.

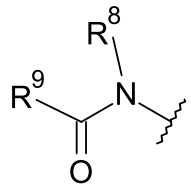
15. A compound according to any one of claims 1-14, wherein R^7 is 4-(2,2,2-trifluoroethyl)piperazin-1-yl.

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;

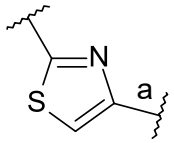
R^3 is halogen;

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;

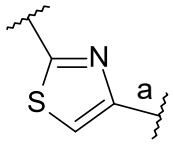
R^3 is fluoro;

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;

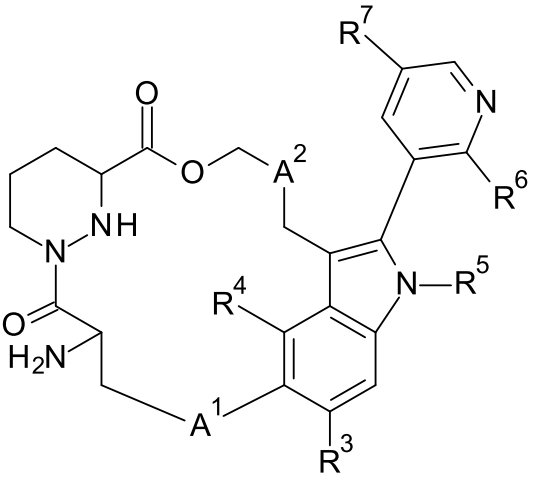
N-[(1*S*)-1-[[(7*S*,13*S*)-24-fluoro-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-[4-(2,2,2-trifluoroethyl)piperazin-1-yl]-3-pyridyl]-17,17-dimethyl-8,14-dioxo-21-(2,2,2-trifluoroethyl)-15-oxa-4-thia-9,21,27,28-tetrazapentacyclo[17.5.2.1^{2,5}.1^{9,13}.0^{22,26}]octacosa-1(25),2,5(28),19,22(26),23-hexaen-7-yl]carbamoyl]-2-methyl-propyl]-*N*,4-dimethyl-piperazine-1-ca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

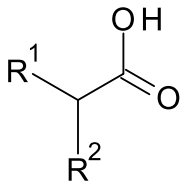
or a pharmaceutically acceptable salt thereof.

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

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

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

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

28. The use of a compound according to any one of claims 1 to 20 in the preparation of a medicament 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. A compound according to any one of claims 1 to 20 for use in 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.

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