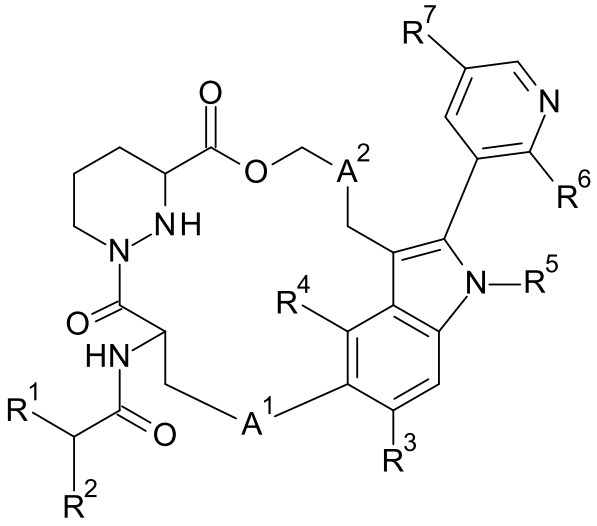
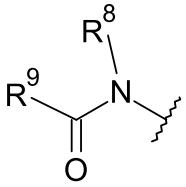
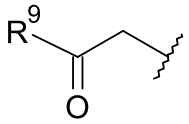
**SUMMARY**

In one aspect, the present disclosure relates to a compound of formula (I),



(I),

wherein

$R^1$ is  or ,

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

$R^9$ is $C_{3-7}$cycloalkyl, azetidinyl or phenyl, said $C_{3-7}$cycloalkyl, azetidinyl and phenyl being substituted by halo$C_{3-6}$alkynyl, (halo$C_{3-6}$alkylpyrimidinyl)$C_{2-6}$alkynyl or pyrimidinyl$C_{2-6}$alkynyl;

$R^2$ 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 halo$C_{1-6}$alkyl;

$R^6$ is $C_{1-6}$alkoxy$C_{1-6}$alkyl;

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

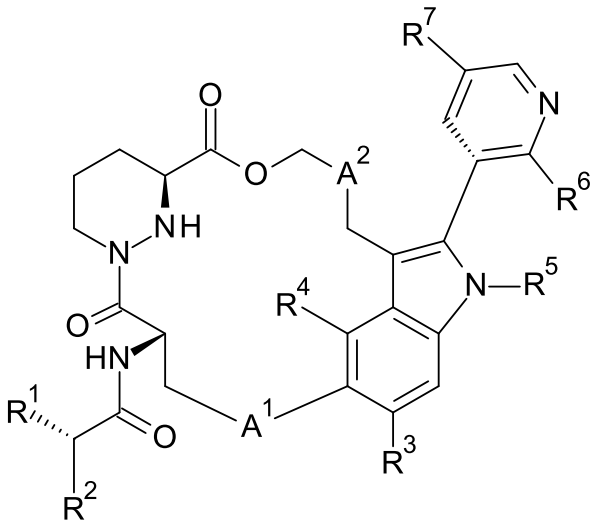
$A^1$ is thiazolylene;

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

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

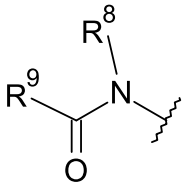
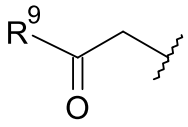
or a pharmaceutically acceptable salt thereof.

In another aspect, the present disclosure relates to a compound of formula (Ia),



(Ia),

wherein

$R^1$ is  or ,

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

$R^9$ is $C_{3-7}$cycloalkyl, azetidinyl or phenyl, said $C_{3-7}$cycloalkyl, azetidinyl and phenyl being substituted by halo$C_{3-6}$alkynyl, (halo$C_{3-6}$alkylpyrimidinyl)$C_{2-6}$alkynyl or pyrimidinyl$C_{2-6}$alkynyl;

$R^2$ 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 halo$C_{1-6}$alkyl;

$R^6$ is $C_{1-6}$alkoxy$C_{1-6}$alkyl;

$R^7$ is morpholinyl, (halo$C_{1-6}$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:

*trans*-*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-3-(3,3,3-trifluoroprop-1-ynyl)cyclobutanecarboxamide;

*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-3-(3,3,3-trifluoroprop-1-ynyl)azetidine-1-carboxamide;

*cis*-*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-3-(3,3,3-trifluoroprop-1-ynyl)cyclobutanecarboxamide;

*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-4-(3,3,3-trifluoroprop-1-ynyl)benzamide;

*cis*-*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-3-(2-pyrimidin-2-ylethynyl)cyclobutanecarboxamide;

*cis*-*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-3-(3,3,3-trifluoroprop-1-ynyl)cyclobutanecarboxamide;

*cis*-*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-3-(3,3,3-trifluoroprop-1-ynyl)cyclobutanecarboxamide;

*cis*-*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-3-(3,3,3-trifluoroprop-1-ynyl)cyclobutanecarboxamide;

*trans*-*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-4-(3,3,3-trifluoroprop-1-ynyl)cyclohexanecarboxamide;

*cis*-*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-4-(3,3,3-trifluoroprop-1-ynyl)cyclohexanecarboxamide;

*cis*-*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-(3,3,3-trifluoroprop-1-ynyl)cyclobutanecarboxamide;

*cis*-*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-3-(3,3,3-trifluoroprop-1-ynyl)cyclobutanecarboxamide;

*cis*-*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-3-[2-[5-(trifluoromethyl)pyrimidin-2-yl]ethynyl]cyclobutanecarboxamide;

*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-3-(3,3,3-trifluoroprop-1-ynyl)azetidine-1-carboxamide;

*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-3-(3,3,3-trifluoroprop-1-ynyl)azetidine-1-carboxamide;

*cis*-*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-3-[2-[4-(trifluoromethyl)pyrimidin-2-yl]ethynyl]cyclobutanecarboxamide;

*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-3-(3,3,3-trifluoroprop-1-ynyl)azetidine-1-carboxamide;

(2*S*)-*N*-[(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]-2-isopropyl-4-oxo-4-[3-(3,3,3-trifluoroprop-1-ynyl)azetidin-1-yl]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-(3,3,3-trifluoroprop-1-ynyl)azetidine-1-carboxamide;

*cis*-*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-[2-[4-(trifluoromethyl)pyrimidin-2-yl]ethynyl]cyclobutanecarboxamide; and

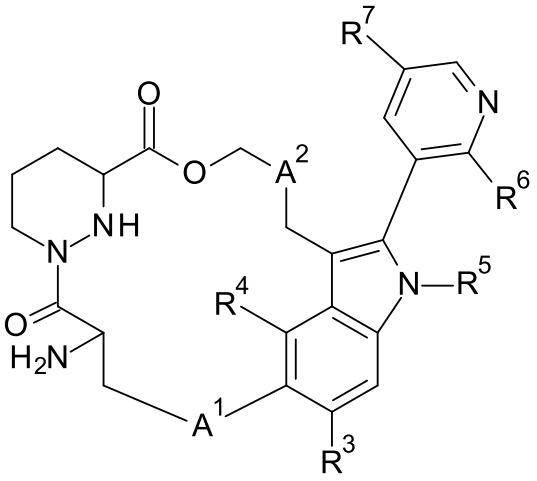
*cis*-*N*-[(1*S*)-1-[[(7*S*,13*S*)-24-fluoro-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-morpholino-3-pyridyl]-17,17-dimethyl-8,14-dioxo-21-(2,2,2-trifluoroethyl)-15-oxa-4-thia-9,21,27,28-tetrazapentacyclo[17.5.2.$1^{2,5}$.$1^{9,13}$.$0^{22,26}$]octacosa-1(25),2,5(28),19,22(26),23-hexaen-7-yl]carbamoyl]-2-methyl-propyl]-*N*-methyl-3-(3,3,3-trifluoroprop-1-ynyl)cyclo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

or a pharmaceutically acceptable salt thereof.

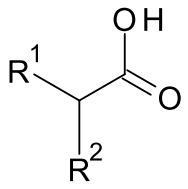
The disclosure also relates to their manufacture, medicaments based on a compound in accordance with the disclosure and their production as well as the use of compounds of formula (I) or (Ia) thereof as inhibitor of KRAS.

In another aspect, the present disclosure relates to a process for the preparation of a compound as described herein comprising any of the following steps:

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 relates to a compound or pharmaceutically acceptable salt as described herein for use as therapeutically active substance.

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

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

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

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

In another aspect, the present disclosure relates to 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 relates to 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, non-small cell lung cancer, esophageal cancer, gallbladder cancer, melanoma ovarian cancer and endometrial cancer.

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

The compound of current disclosure addressed GSH toxicity issue comparing with the reference compounds. 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, solubility, and single dose pharmacokinetics (SDPK) profiles. Furthermore, the compound of current disclosure demonstrated good efficacy towards a second mutation as mentioned in this application.

## 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.

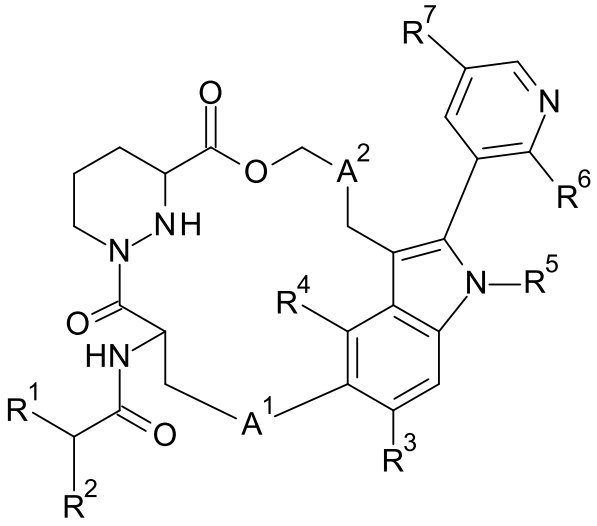
The term "halogen" and "halo" are used interchangeably herein and denote fluoro, chloro, bromo, or iodo.

The term "$C_{2-6}$alkynyl" denotes a monovalent linear or branched hydrocarbon group of 2 to 6 carbon atoms with at least one triple bond. In particular embodiments, alkynyl has 2 to 4 carbon atoms with at least one triple bond. Examples of $C_{2-6}$alkynyl include ethynyl (–C≡CH), prop-1-ynyl (–C≡C$CH_3$), prop-2-ynyl (propargyl, –$CH_2$C≡CH), but-1-ynyl, but-2-ynyl, and but-3-ynyl.

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

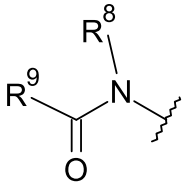
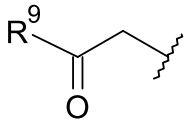
## CLAIMS

1. A compound of formula (I),



(I),

wherein

$R^1$ is  or ,

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

$R^9$ is $C_{3-7}$cycloalkyl, azetidinyl or phenyl, said $C_{3-7}$cycloalkyl, azetidinyl and phenyl being substituted by halo$C_{3-6}$alkynyl, (halo$C_{3-6}$alkylpyrimidinyl)$C_{2-6}$alkynyl or pyrimidinyl$C_{2-6}$alkynyl;

$R^2$ 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 halo$C_{1-6}$alkyl;

$R^6$ is $C_{1-6}$alkoxy$C_{1-6}$alkyl;

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

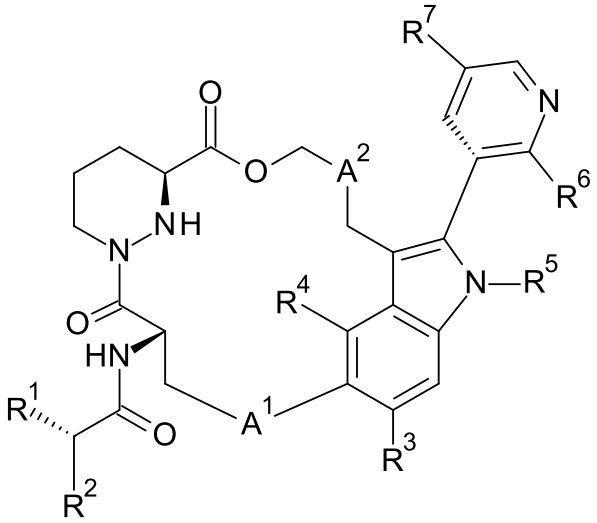
$A^1$ is thiazolylene;

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

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

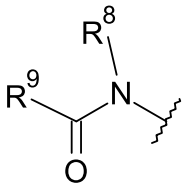
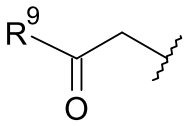
or a pharmaceutically acceptable salt thereof.

2. A compound of formula (Ia),



(Ia),

wherein

$R^1$ is  or ,

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

$R^9$ is $C_{3-7}$cycloalkyl, azetidinyl or phenyl, said $C_{3-7}$cycloalkyl, azetidinyl and phenyl being substituted by halo$C_{3-6}$alkynyl, (halo$C_{3-6}$alkylpyrimidinyl)$C_{2-6}$alkynyl or pyrimidinyl$C_{2-6}$alkynyl;

$R^2$ 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 halo$C_{1-6}$alkyl;

$R^6$ is $C_{1-6}$alkoxy$C_{1-6}$alkyl;

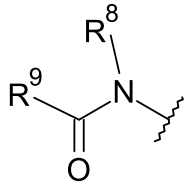
$R^7$ is morpholinyl, (halo$C_{1-6}$alkyl)piperazinyl or $C_{1-6}$alkylpiperazinyl;

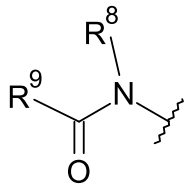
$A^1$ is thiazolylene;

$A^2$ 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 $C_{3-7}$cycloalkyl substituted by halo$C_{3-6}$alkynyl.

4. A compound according to claim 1 or 2, wherein $R^1$ is , wherein $R^8$ is methyl; $R^9$ is cyclobutyl substituted by 3,3,3-trifluoroprop-1-ynyl.

5. A compound according to any one of claims 1-4, wherein $R^9$ is 3-(3,3,3-trifluoroprop-1-ynyl)cyclobutyl.

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 halogen.

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

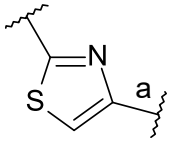
9. A compound according to any one of claims 1-8, wherein $R^4$ is H or fluoro.

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 ethyl or 2,2,2-trifluoroethyl.

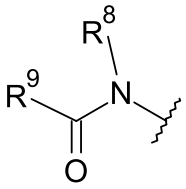
12. A compound according to any one of claims 1-11, wherein $R^6$ is 1-methoxyethyl.

13. A compound according to any one of claims 1-12, wherein $R^7$ is morpholinyl, 4-(2,2,2-trifluoroethyl)piperazin-1-yl or 4-methylpiperazin-1-yl.

14. A compound according to any one of claims 1-13, wherein $A^1$ is , wherein bond "a" connects to indole ring.

15. A compound according to any one of claims 1-14, wherein $A^2$ is dimethylmethylene.

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

$R^1$ is , wherein $R^8$ is $C_{1-6}$alkyl; $R^9$ is $C_{3-7}$cycloalkyl substituted by halo$C_{3-6}$alkynyl;

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

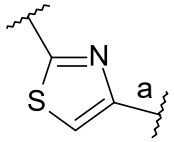
$R^3$ is halogen;

$R^4$ is H;

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

$R^6$ is $C_{1-6}$alkoxy$C_{1-6}$alkyl;

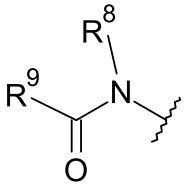
$R^7$ is morpholinyl, (halo$C_{1-6}$alkyl)piperazinyl or $C_{1-6}$alkylpiperazinyl;

$A^1$ is , wherein bond "a" connects to indole ring;

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

or a pharmaceutically acceptable salt thereof.

17. A compound according to claim 16, wherein

$R^1$ is , wherein $R^8$ is methyl; $R^9$ is 3-(3,3,3-trifluoroprop-1-ynyl)cyclobutyl;

$R^2$ is isopropyl;

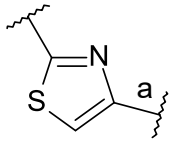
$R^3$ is fluoro;

$R^4$ is H;

$R^5$ is ethyl or 2,2,2-trifluoroethyl;

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

$R^7$ is morpholinyl, 4-(2,2,2-trifluoroethyl)piperazin-1-yl or 4-methylpiperazin-1-yl;

$A^1$ is 

, wherein bond "a" connects to indole ring;

$A^2$ is dimethylmethylene;

or a pharmaceutically acceptable salt thereof.

18. A compound selected from:

*trans*-*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-3-(3,3,3-trifluoroprop-1-ynyl)cyclobutanecarboxamide;

*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-3-(3,3,3-trifluoroprop-1-ynyl)azetidine-1-carboxamide;

*cis*-*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-3-(3,3,3-trifluoroprop-1-ynyl)cyclobutanecarboxamide;

*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-4-(3,3,3-trifluoroprop-1-ynyl)benzamide;

*cis*-*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-3-(2-pyrimidin-2-ylethynyl)cyclobutanecarboxamide;

*cis*-*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-3-(3,3,3-trifluoroprop-1-ynyl)cyclobutanecarboxamide;

*cis*-*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-3-(3,3,3-trifluoroprop-1-ynyl)cyclobutanecarboxamide;

*cis*-*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-3-(3,3,3-trifluoroprop-1-ynyl)cyclobutanecarboxamide;

*trans*-*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-4-(3,3,3-trifluoroprop-1-ynyl)cyclohexanecarboxamide;

*cis*-*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-4-(3,3,3-trifluoroprop-1-ynyl)cyclohexanecarboxamide;

*cis*-*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-(3,3,3-trifluoroprop-1-ynyl)cyclobutanecarboxamide;

*cis*-*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-3-(3,3,3-trifluoroprop-1-ynyl)cyclobutanecarboxamide;

*cis*-*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-3-[2-[5-(trifluoromethyl)pyrimidin-2-yl]ethynyl]cyclobutanecarboxamide;

*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-3-(3,3,3-trifluoroprop-1-ynyl)azetidine-1-carboxamide;

*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-3-(3,3,3-trifluoroprop-1-ynyl)azetidine-1-carboxamide;

*cis*-*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-3-[2-[4-(trifluoromethyl)pyrimidin-2-yl]ethynyl]cyclobutanecarboxamide;

*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-3-(3,3,3-trifluoroprop-1-ynyl)azetidine-1-carboxamide;

(2*S*)-*N*-[(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]-2-isopropyl-4-oxo-4-[3-(3,3,3-trifluoroprop-1-ynyl)azetidin-1-yl]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-(3,3,3-trifluoroprop-1-ynyl)azetidine-1-carboxamide;

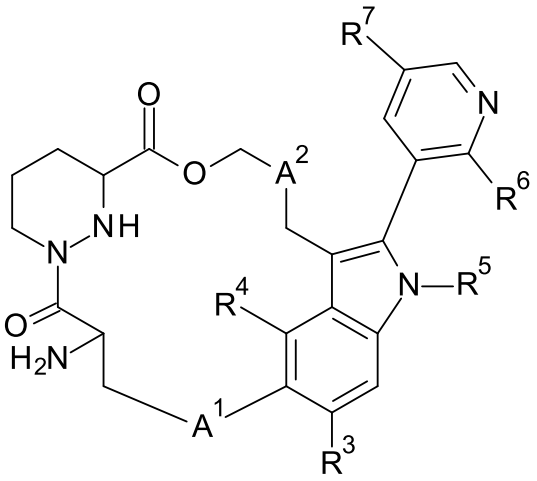
*cis*-*N*-[(1*S*)-1-[[(7*S*,13*S*)-21-ethyl-24-fluoro-(20*M*)-20-[2-[(1*S*)-1-methoxyethyl]-5-morpholino-3-pyridyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,27,28-tetrazapentacyclo[17.5.2.1$^{2,5}$.1$^{9,13}$.0$^{22,26}$]octacosa-1(25),2,5(28),19,22(26),23-hexaen-7-yl]carbamoyl]-2-methyl-propyl]-*N*-methyl-3-[2-[4-(trifluoromethyl)pyrimidin-2-yl]ethynyl]cycl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

*cis*-*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-3-(3,3,3-trifluoroprop-1-ynyl)cyclobutanecarboxamide;

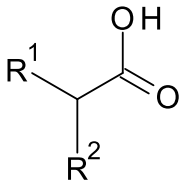
or a pharmaceutically acceptable salt thereof.

19. A process for the preparation of a compound according to any one of claims 1 to 18 comprising any of the following steps:

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 17; the coupling reagent is $T_3P$, HATU, PyBOP or EDCI/HOBt; the base is TEA, DIEPA or DMAP.

20. A compound or pharmaceutically acceptable salt according to any one of claims 1 to 18 for use as therapeutically active substance.

21. A pharmaceutical composition comprising a compound in accordance with any one of claims 1 to 18 and a pharmaceutically acceptable excipient.

22. A compound according to any one of claims 1 to 18 for use in treating a KRAS G12C protein-related disease.

23. A compound according to any one of claims 1 to 18 for use in treating a KRAS G12C, G12D and G12V protein-related disease.

24. A compound according to any one of claims 1 to 18 for use in inhibiting RAS interaction with downstream effectors, wherein the downstream effectors are RAF and PI3K.

25. A compound according to any one of claims 1 to 18 for use in inhibiting the propagating oncogenic MAPK and PI3K signaling.

26. The use of a compound according to any one of claims 1 to 18 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.

27. A compound or pharmaceutically acceptable salt according to any one of claims 1 to 18 for use in the treatment or prophylaxis of KRAS mutation driven cancers, wherein the cancer is selected from pancreatic adenocarcinoma, colorectal cancer, non-small cell lung cancer, esophageal cancer, gallbladder cancer, melanoma ovarian cancer and endometrial cancer.

28. A compound according to any one of claims 1 to 18 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.

29. The use of a compound according to any one of claims 1 to 18 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.

30. The use of a compound according to any one of claims 1 to 18 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.

31. A compound or pharmaceutically acceptable salt according to any one of claims 1 to 18, when manufactured according to a process of claim 19.