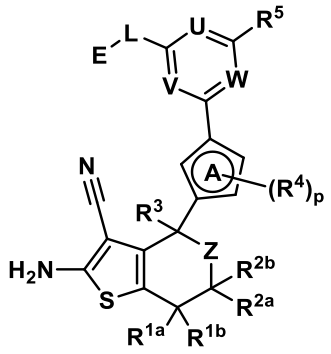
expected to inhibit signaling in cells downstream of Ras family proteins (*e.g.* ERK phosphorylation). In cancer cells associated with dependence on mutant Ras family proteins (*e.g.* KRAS mutant cancer cell lines), such binders/inhibitors are expected to deliver anti-cancer efficacy (*e.g.* inhibition of proliferation, survival, metastasis *etc.*).

To date there have been no inhibitors of G12C mutant Ras family proteins which have been approved for therapeutic use. Recently the first selective drugs against KRAS G12C have moved into clinical development with sotorasib and adagrasib already in advanced stage for the treatment of KRAS G12C driven lung cancers (see corresponding patent applications WO 2018/217651, WO 2017/201161, WO 2019/099524, WO 2020/102730). There is a need for new or even improved inhibitors of G12C mutant Ras family proteins to be suitable for clinical use.

Summary

In one aspect, the present disclosure provides a compound of the formula **(I)**



(I)

, wherein

R^{1a} and **R^{1b}** are both independently selected from the group consisting of hydrogen, $C_{1\text{-}4}$alkyl, $C_{1\text{-}4}$haloalkyl, $C_{1\text{-}4}$alkoxy, $C_{1\text{-}4}$haloalkoxy, halogen, -NH_2, -NH($C_{1\text{-}4}$alkyl), -N($C_{1\text{-}4}$alkyl)$_2$, $C_{3\text{-}5}$cycloalkyl and 3-5 membered heterocyclyl;

R^{2a} and **R^{2b}** are both independently selected from the group consisting of hydrogen, $C_{1\text{-}4}$alkyl, $C_{1\text{-}4}$haloalkyl, $C_{1\text{-}4}$alkoxy, $C_{1\text{-}4}$haloalkoxy, halogen, -NH_2, -NH($C_{1\text{-}4}$alkyl), -N($C_{1\text{-}4}$alkyl)$_2$, $C_{3\text{-}5}$cycloalkyl and 3-5 membered heterocyclyl;

and/or, optionally, one of **R^{1a}** or **R^{1b}** and one of **R^{2a}** or **R^{2b}** together with the carbon atoms they are attached form a cyclopropane ring;

Z is -$(CR^{6a}R^{6b})_n$-;

each **R^{6a}** and **R^{6b}** is independently selected from the group consisting of hydrogen, C_{1-4}alkyl, C_{1-4}haloalkyl, C_{1-4}alkoxy, C_{1-4}haloalkoxy, halogen, -NH_2, -NH(C_{1-4}alkyl), -N(C_{1-4}alkyl)$_2$, C_{3-5}cycloalkyl and 3-5 membered heterocyclyl;

n is selected from the group consisting 0, 1 and 2;

R^3 is selected from the group consisting of hydrogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy, cyano-C_{1-6}alkyl, halogen, -OH, -NH_2, -NH(C_{1-4}alkyl), -N(C_{1-4}alkyl)$_2$, -CN, C_{3-5}cycloalkyl and 3-5 membered heterocyclyl;

ring **A** is a ring selected from the group consisting of pyrrole, furan, thiophene, imidazole, pyrazole, oxazole, isoxazole, thiazole, isothiazole and triazole;

each **R^4**, if present, is independently selected from the group consisting of C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy, cyano-C_{1-6}alkyl, halogen, -OH, -NH_2, -NH(C_{1-4}alkyl), -N(C_{1-4}alkyl)$_2$, -CN, C_{3-5}cycloalkyl and 3-5 membered heterocyclyl;

p is selected from the group consisting 0, 1, 2 and 3;

U is selected from the group consisting of nitrogen (=N–) and carbon substituted with **R^A** (=C(R^A)-);

V is selected from the group consisting of nitrogen (=N–) and carbon substituted with **R^B** (=C(R^B)-);

W is selected from the group consisting of nitrogen (=N–) and carbon substituted with **R^C** (=C(R^C)-);

R^A, **R^B** and **R^C** is each independently selected from the group consisting of hydrogen, C_{1-6}haloalkyl, C_{2-6}alkynyl optionally substituted with C_{3-5}cycloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy, halogen, -CN, -OH, -NH_2, -NH(C_{1-4}alkyl), -N(C_{1-4}alkyl)$_2$, -C(=O)NH_2, -C(=O)NH(C_{1-4}alkyl), -C(=O)N(C_{1-4}alkyl)$_2$, -S-C_{1-6}alkyl, -S(=O)$_2$-C_{1-6}alkyl, C_{3-5}cycloalkyl, 3-5 membered heterocyclyl and C_{1-6}alkyl optionally substituted with a substituent selected from

the group consisting of C_{1-6}alkoxy, -CN, -OH, $-NH_2$, $-NH(C_{1-4}alkyl)$, $-N(C_{1-4}alkyl)_2$, $-C(=O)NH_2$, $-C(=O)NH(C_{1-4}alkyl)$ and $-C(=O)N(C_{1-4}alkyl)_2$;

R^5 is selected from the group consisting of **R^{a1}** and **R^{b1}**;

R^{a1} is selected from the group consisting of C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{4-10}cycloalkenyl, 3-11 membered heterocyclyl, C_{6-10}aryl and 5-10 membered heteroaryl, wherein the C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{4-10}cycloalkenyl, 3-11 membered heterocyclyl, C_{6-10}aryl and 5-10 membered heteroaryl are all optionally substituted with one or more, identical or different **R^{b1}** and/or **R^{c1}**;

each **R^{b1}** is independently selected from the group consisting of $-OR^{c1}$, $-NR^{c1}R^{c1}$, halogen, -CN, $-C(=O)R^{c1}$, $-C(=O)OR^{c1}$, $-C(=O)NR^{c1}R^{c1}$, $-S(=O)_2R^{c1}$, $-S(=O)_2NR^{c1}R^{c1}$, $-NHC(=O)R^{c1}$, $-N(C_{1-4}alkyl)C(=O)R^{c1}$, $-NHS(=O)_2R^{c1}$, $-N(C_{1-4}alkyl)S(=O)_2R^{c1}$, $-NHC(=O)OR^{c1}$, $-N(C_{1-4}alkyl)C(=O)OR^{c1}$ and the bivalent substituent =O;

each **R^{c1}** is independently selected from the group consisting of hydrogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{4-10}cycloalkenyl, 3-11 membered heterocyclyl, C_{6-10}aryl and 5-10 membered heteroaryl, wherein the C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{4-10}cycloalkenyl, 3-11 membered heterocyclyl, C_{6-10}aryl and 5-10 membered heteroaryl are all optionally substituted with one or more, identical or different **R^{d1}** and/or **R^{e1}**;

each **R^{d1}** is independently selected from the group consisting of $-OR^{e1}$, $-NR^{e1}R^{e1}$, halogen, -CN, $-C(=O)R^{e1}$, $-C(=O)OR^{e1}$, $-C(=O)NR^{e1}R^{e1}$, $-S(=O)_2R^{e1}$, $-S(=O)_2NR^{e1}R^{e1}$, $-NHC(=O)R^{e1}$, $-N(C_{1-4}alkyl)C(=O)R^{e1}$, $-NHS(=O)_2R^{c1}$, $-N(C_{1-4}alkyl)S(=O)_2R^{c1}$, $-NHC(=O)OR^{e1}$, $-N(C_{1-4}alkyl)C(=O)OR^{e1}$ and the bivalent substituent =O;

each **R^{e1}** is independently selected from the group consisting of hydrogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{4-10}cycloalkenyl, 3-11 membered heterocyclyl, C_{6-10}aryl and 5-10 membered heteroaryl, wherein the C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{4-10}cycloalkenyl, 3-11 membered heterocyclyl, C_{6-10}aryl and 5-10 membered heteroaryl are all optionally substituted with one or more, identical or different substituent(s) selected from the group consisting of

C_{1-6}alkyl, C_{1-6}haloalkyl, C_{3-10}cycloalkyl, 3-11 membered heterocyclyl optionally substituted with one or more, identical or different C_{1-4}alkyl, C_{6-10}aryl, 5-10 membered heteroaryl, -OH, C_{1-6}alkoxy, C_{1-4}alkoxy-C_{1-4}alkyl, hydroxy-C_{1-4}alkyl, halogen, -CN, -NH_2, -C(=O)C_{1-4}alkyl, -NH(C_{1-4}alkyl), -N(C_{1-4}alkyl)$_2$ and the bivalent substituent =O;

L is **-L^1-L^2-L^3-**, wherein **L^1** is linked to **E**;

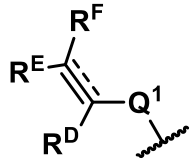
L^1 is selected from the group consisting of a bond, -NH-, -N(C_{1-4}alkyl)-, -O-, -C(=O)-, -NH-C(=O)-, -N(C_{1-4}alkyl)-C(=O)-, -C(=O)-NH-, -C(=O)-N(C_{1-4}alkyl)-, -C(=O)-, C_{1-6}alkylen, C_{3-7}cycloalkylene, phenylene, 4-12 membered heterocyclylene and 5-10 membered heteroarylene;

L^2 is selected from the group consisting of C_{1-6}alkylen, C_{3-7}cycloalkylene, phenylene, 4-12 membered heterocyclylene and 5-10 membered heteroarylene;

L^3 is selected from the group consisting of a bond, -NH-, -N(C_{1-4}alkyl)-, -O-, -C(=O)-, -NH-C(=O)-, -N(C_{1-4}alkyl)-C(=O)-, -C(=O)-NH-, -C(=O)-N(C_{1-4}alkyl)-, -C(=O)-, C_{1-6}alkylen, C_{3-7}cycloalkylene, phenylene, 4-12 membered heterocyclylene and 5-10 membered heteroarylene;

wherein each C_{1-6}alkylen, C_{3-7}cycloalkylene, phenylene, 4-12 membered heterocyclylene and 5-10 membered heteroarylene in **L^1**, **L^2** and **L^3** is optionally and independently substituted with one or more, identical or different substituent(s) selected from the group consisting of C_{2-6}alkinyl, C_{1-6}haloalkyl, C_{3-7}cycloalkyl, phenyl, 5-6 membered heteroaryl, halogen, -OH, -CN, C_{1-6}alkoxy, -NH_2, -NH(C_{1-4}alkyl), -N(C_{1-4}alkyl)$_2$, -C(=O)OH, -C(=O)-OC_{1-6}alkyl, -C(=O)NH_2, -C(=O)NH(C_{1-4}alkyl), -C(=O)N(C_{1-4}alkyl)$_2$, the bivalent substituent =O and C_{1-6}alkyl optionally substituted with one or more, identical or different substituent(s) selected from the group consisting of halogen, -OH, -CN, C_{1-4}alkoxy, -NH_2, -NH(C_{1-4}alkyl), -N(C_{1-4}alkyl)$_2$, -C(=O)OH, -C(=O)-OC_{1-6}alkyl, -C(=O)NH_2, -C(=O)NH(C_{1-4}alkyl) and -C(=O)N(C_{1-4}alkyl)$_2$;

E is



(i)

 represents a double or a triple bond;

Q^1 is selected from the group consisting of a bond, -CH_2-, -CH(OH)-, -C(=O)-, -C(=O)N(R^{G1})-, -C(=O)O-, -$S(=O)_2$-, -$S(=O)_2$N(R^{G1})- and -C(=NR^{H1})-;

each **R^{G1}** is independently selected from the group consisting of hydrogen, C_{1-6}alkyl, C_{1-6}haloalkyl, hydroxy-C_{1-6}alkyl, H_2N-C_{1-6}alkyl, cyano-C_{1-6}alkyl, (C_{1-4}alkyl)HN-C_{1-6}alkyl, (C_{1-4}alkyl)$_2$N-C_{1-6}alkyl, C_{1-6}alkoxy-C_{1-6}alkyl, C_{3-7}cycloalkyl and 3-11 membered heterocyclyl;

each **R^{H1}** is independently selected from the group consisting of hydrogen, -OH, C_{1-6}alkoxy, -CN and C_{1-6}alkyl;

if  represents a double bond then

R^D is selected from the group consisting of hydrogen, C_{3-7}cycloalkyl, phenyl, halogen, -CN, C_{1-6}alkoxy, -C(=O)O-C_{1-6}alkyl, -NHC(=O)-C_{1-6}alkyl and C_{1-6}alkyl optionally substituted with one or more, identical or different substituent(s) selected from the group consisting of phenyl, 3-11 membered heterocyclyl, C_{1-6}alkoxy, halogen, -OH, -NH_2, -NH(C_{1-6}alkyl), -N(C_{1-6}alkyl)$_2$, -C(=O)OH, -C(=O)O-C_{1-6}alkyl,-C(=O)NH(C_{1-6}alkyl), -NHC(=O)-C_{1-6}alkyl, -OC(=O)-C_{1-6}alkyl and phenyl-C_{1-6}alkoxy;

R^E and **R^F** is each independently selected from the group consisting of **R^{a2}** and **R^{b2}**;

R^{a2} is selected from the group consisting of hydrogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{3-10}cycloalkyl, 3-11 membered heterocyclyl, C_{6-10}aryl and 5-10 membered heteroaryl, wherein the C_{1-6}alkyl, C_{1-6}haloalkyl, C_{3-10}cycloalkyl, 3-11 membered heterocyclyl, C_{6-10}aryl and 5-10 membered heteroaryl are all optionally substituted with one or more, identical or different **R^{b2}** and/or **R^{c2}**;

each $\mathbf{R^{b2}}$ is independently selected from the group consisting of -OR^{c2}, -$NR^{c2}R^{c2}$, halogen, -CN, -$C(=O)R^{c2}$, -$C(=O)OR^{c2}$, -$C(=O)NR^{c2}R^{c2}$, -$S(=O)_2R^{c2}$, -$S(=O)_2NR^{c2}R^{c2}$, -$NHC(=O)R^{c2}$, -$N(C_{1\text{-}4}alkyl)C(=O)R^{c2}$, -$NHC(=O)OR^{c2}$, -$N(C_{1\text{-}4}alkyl)C(=O)OR^{c2}$ and the bivalent substituent =O;

each $\mathbf{R^{c2}}$ is independently selected from the group consisting of hydrogen, $C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$haloalkyl, $C_{2\text{-}6}$alkenyl, $C_{2\text{-}6}$alkynyl, $C_{3\text{-}10}$cycloalkyl, $C_{4\text{-}10}$cycloalkenyl, 3-11 membered heterocyclyl, $C_{6\text{-}10}$aryl and 5-10 membered heteroaryl, wherein the $C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$haloalkyl, $C_{2\text{-}6}$alkenyl, $C_{2\text{-}6}$alkynyl, $C_{3\text{-}10}$cycloalkyl, $C_{4\text{-}10}$cycloalkenyl, 3-11 membered heterocyclyl, $C_{6\text{-}10}$aryl and 5-10 membered heteroaryl are all optionally substituted with one or more, identical or different substituent(s) selected from the group consisting of $C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$alkoxy, halogen, -OH, -C(=O)OH, -$C(=O)O$-$C_{1\text{-}6}$alkyl, -$C(=O)C_{1\text{-}6}$alkyl, -$C(=O)NH_2$, -$C(=O)NH(C_{1\text{-}6}alkyl)$, -$C(=O)N(C_{1\text{-}6}alkyl)_2$, and the bivalent substituent =O;

or

$\mathbf{R^D}$ and $\mathbf{R^E}$ taken together with the carbon atoms they are attached form a 4-7 membered unsaturated alicycle or 4-7 membered unsaturated heterocycle, wherein this 4-7 membered unsaturated alicycle or 4-7 membered unsaturated heterocycle is optionally, in addition to $\mathbf{R^F}$, substituted with one or more identical or different substituent(s) selected from the group consisting of $C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$haloalkyl, -OH, $C_{1\text{-}6}$alkoxy, $C_{1\text{-}4}$alkoxy-$C_{1\text{-}4}$alkyl, -NH_2, -CN, -$NH(C_{1\text{-}4}alkyl)$, -$N(C_{1\text{-}4}alkyl)_2$, halogen, -$C(=O)O$-$C_{1\text{-}6}$alkyl and the bivalent substituent =O;

or

if $\mathbf{Q^1}$ is -$C(=O)N(R^{G1})$-, then $\mathbf{R^{G1}}$ of -$C(=O)N(R^{G1})$- and $\mathbf{R^F}$ together form a linker selected from the group consisting of -C(=O)-, -CH_2-, -CH_2-C(=O)-, -C(=O)-CH_2- and -C_2H_4-;

if  represents a triple bond then

$\mathbf{R^D}$ and $\mathbf{R^E}$ are both absent;

$\mathbf{R^F}$ is $\mathbf{R^{a2}}$;

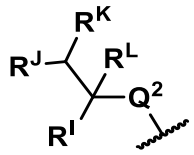
R^{a2} is selected from the group consisting of hydrogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{3-10}cycloalkyl, 3-11 membered heterocyclyl, C_{6-10}aryl and 5-10 membered heteroaryl, wherein the C_{1-6}alkyl, C_{1-6}haloalkyl, C_{3-10}cycloalkyl, 3-11 membered heterocyclyl, C_{6-10}aryl and 5-10 membered heteroaryl are all optionally substituted with one or more, identical or different **R^{b2}** and/or **R^{c2}**;

each **R^{b2}** is independently selected from the group consisting of $-OR^{c2}$, $-NR^{c2}R^{c2}$, halogen, -CN, $-C(=O)R^{c2}$, $-C(=O)OR^{c2}$, $-C(=O)NR^{c2}R^{c2}$, $-S(=O)_2R^{c2}$, $-S(=O)_2NR^{c2}R^{c2}$, $-NHC(=O)R^{c2}$, $-N(C_{1-4}alkyl)C(=O)R^{c2}$, $-NHC(=O)OR^{c2}$, $-N(C_{1-4}alkyl)C(=O)OR^{c2}$ and the bivalent substituent =O;

each **R^{c2}** is independently selected from the group consisting of hydrogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{3-10}cycloalkyl, 3-11 membered heterocyclyl, C_{6-10}aryl and 5-10 membered heteroaryl;

or

E is



(ii)

Q^2 is selected from the group consisting of a bond, $-CH_2-$, -CH(OH)-, -C(=O)-, $-C(=O)N(R^{G2})-$, -C(=O)O-, $-S(=O)_2-$, $-S(=O)_2N(R^{G2})-$ and $-C(=NR^{H2})-$;

each **R^{G2}** is independently selected from the group consisting of hydrogen, C_{1-6}alkyl, C_{1-6}haloalkyl, hydroxy-C_{1-6}alkyl, H_2N-C_{1-6}alkyl, cyano-C_{1-6}alkyl, $(C_{1-4}alkyl)HN$-C_{1-6}alkyl, $(C_{1-4}alkyl)_2N$-C_{1-6}alkyl, C_{1-6}alkoxy-C_{1-6}alkyl, C_{3-7}cycloalkyl and 3-11 membered heterocyclyl;

each **R^{H2}** is independently selected from the group consisting of hydrogen, -OH, C_{1-6}alkoxy, -CN and C_{1-6}alkyl;

R^I is selected from the group consisting of hydrogen and halogen;

R^J is hydrogen; or

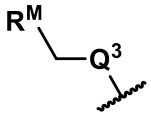
$\mathbf{R^I}$ and $\mathbf{R^J}$ together with the carbon atoms they are attached form a cyclopropane or oxirane ring;

$\mathbf{R^K}$ is selected from the group consisting of hydrogen, C_{1-6}alkyl, -CN and halogen;

$\mathbf{R^L}$ is selected from the group consisting of hydrogen, C_{1-6}alkyl, -CN, halogen and -C(=O)-C_{1-6}alkyl;

or

E is



(iii)

$\mathbf{Q^3}$ is selected from the group consisting of -C(=O)-, -C(=O)N(R^{G3})-, -C(=O)O-, -S(=O)$_2$-, -S(=O)$_2$N(R^{G3})- and -C(=NR^{H3})-;

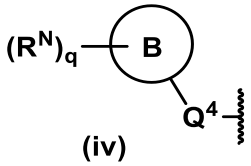
each $\mathbf{R^{G3}}$ is independently selected from the group consisting of hydrogen, C_{1-6}alkyl, C_{1-6}haloalkyl, hydroxy-C_{1-6}alkyl, H_2N-C_{1-6}alkyl, cyano-C_{1-6}alkyl, (C_{1-4}alkyl)HN-C_{1-6}alkyl, (C_{1-4}alkyl)$_2$N-C_{1-6}alkyl, C_{1-6}alkoxy-C_{1-6}alkyl, C_{3-7}cycloalkyl and 3-11 membered heterocyclyl;

each $\mathbf{R^{H3}}$ is independently selected from the group consisting of hydrogen, -OH, C_{1-6}alkoxy, -CN and C_{1-6}alkyl;

$\mathbf{R^M}$ is selected from the group consisting of halogen, -CN and -O-C(=O)-C_{1-6}alkyl;

or

E is



(iv)

$\mathbf{Q^4}$ is selected from the group consisting of a bond, -C(=O)-, -C(=O)O-, -C(=O)NH-, -C(=O)N(C_{1-4}alkyl)-, -S(=O)$_2$- and -S(=O)$_2$NH-;

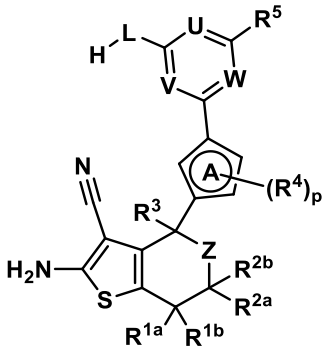
ring **B** is selected from the group consisting of phenyl, pyridyl, pyrimidyl, pyridazinyl, pyrazinyl and 5-membered heteroaryl;

q is selected from the group consisting 1, 2, 3 and 4;

each $\mathbf{R^N}$ is independently selected from the group consisting of $C_{1\text{-}4}$alkyl, $C_{1\text{-}4}$haloalkyl, vinyl, ethinyl, halogen, -CN, nitro and $C_{1\text{-}4}$alkoxy;

or a salt thereof.

In another aspect, the present disclosure provides a compound of the formula **(II)**



(II)

, wherein

$\mathbf{R^{1a}}$, $\mathbf{R^{1b}}$, $\mathbf{R^{2a}}$, $\mathbf{R^{2b}}$, **Z**, $\mathbf{R^3}$, ring **A**, $\mathbf{R^4}$, **p**, **U**, **V**, **W**, $\mathbf{R^5}$ and **L** are defined as in formula **(I)** as described herein, or a salt thereof.

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

In another aspect, the present disclosure provides use of a compound as described herein – or a pharmaceutically acceptable salt thereof – in the manufacture of a medicament for the treatment and/or prevention of cancer.

In another aspect, the present disclosure provides a pharmaceutical composition comprising a compound as described herein – or a pharmaceutically acceptable salt thereof – and one or more pharmaceutically acceptable excipient(s).

In another aspect, the present disclosure provides a pharmaceutical composition comprising a compound as described herein – or a pharmaceutically acceptable salt thereof – and one or more other pharmacologically active substance(s).

Detailed description of the invention

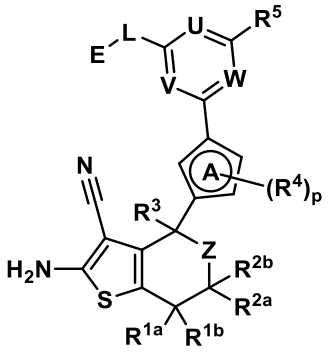
Compounds

It has now been found that, surprisingly, compounds of formula **(I)** wherein $\mathbf{R^{1a}}$, $\mathbf{R^{1b}}$, $\mathbf{R^{2a}}$, $\mathbf{R^{2b}}$, **Z**, $\mathbf{R^{3}}$ to $\mathbf{R^{5}}$, **A**, **p**, **U**, **V**, **W**, **L** and **E** have the meanings given hereinafter act as inhibitors of G12C mutant Ras family proteins which are involved in controlling cell proliferation and possess anti-tumor activity, being useful in inhibiting the uncontrolled cellular proliferation which arises from malignant disease. It is believed that this anti-tumor activity is derived from inhibition of G12C mutant Ras family proteins, in particular KRAS G12C, that are key mediators of proliferation and survival in certain tumor cells. It is further believed that the compounds according to the invention interact with, and then covalently bind to, G12C mutant Ras family proteins, in particular KRAS G12C, *via* an electrophilic moiety (*e.g.* a MICHAEL acceptor) present in compounds of formula **(I)** (confirmed by means of crystallography for KRAS G12C). In covalently binding to G12C mutant Ras family proteins, in particular KRAS G12C, which most probably occurs at position 12 of the Ras family proteins, the compounds impair or substantially eliminate the ability of the G12C Ras family proteins to access their active, pro-proliferative/pro-survival conformation.

Indeed, the binding of the compounds of formula **(I)** according to the invention may lead to selective and very strong antiproliferative cellular effects in G12C mutant KRAS cell lines and large selectivity windows compared to KRAS wild type cells. This excellent potency can potentially lead to lower systemic exposures and/or doses needed for full efficacy in humans and therefore to good/better tolerability (*e.g.* a lower risk of idiosyncratic toxicities), may

Claims

1. A compound of the formula **(I)**



(I) , wherein

R^{1a} and **R^{1b}** are both independently selected from the group consisting of hydrogen, C_{1-4}alkyl, C_{1-4}haloalkyl, C_{1-4}alkoxy, C_{1-4}haloalkoxy, halogen, $-NH_2$, $-NH(C_{1-4}alkyl)$, $-N(C_{1-4}alkyl)_2$, C_{3-5}cycloalkyl and 3-5 membered heterocyclyl;

R^{2a} and **R^{2b}** are both independently selected from the group consisting of hydrogen, C_{1-4}alkyl, C_{1-4}haloalkyl, C_{1-4}alkoxy, C_{1-4}haloalkoxy, halogen, $-NH_2$, $-NH(C_{1-4}alkyl)$, $-N(C_{1-4}alkyl)_2$, C_{3-5}cycloalkyl and 3-5 membered heterocyclyl;

and/or, optionally, one of **R^{1a}** or **R^{1b}** and one of **R^{2a}** or **R^{2b}** together with the carbon atoms they are attached form a cyclopropane ring;

Z is $-(CR^{6a}R^{6b})_n-$;

each **R^{6a}** and **R^{6b}** is independently selected from the group consisting of hydrogen, C_{1-4}alkyl, C_{1-4}haloalkyl, C_{1-4}alkoxy, C_{1-4}haloalkoxy, halogen, $-NH_2$, $-NH(C_{1-4}alkyl)$, $-N(C_{1-4}alkyl)_2$, C_{3-5}cycloalkyl and 3-5 membered heterocyclyl;

n is selected from the group consisting 0, 1 and 2;

R^3 is selected from the group consisting of hydrogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy, cyano-C_{1-6}alkyl, halogen, -OH, $-NH_2$, $-NH(C_{1-4}alkyl)$, $-N(C_{1-4}alkyl)_2$, -CN, C_{3-5}cycloalkyl and 3-5 membered heterocyclyl;

ring **A** is a ring selected from the group consisting of pyrrole, furan, thiophene, imidazole, pyrazole, oxazole, isoxazole, thiazole, isothiazole and triazole;

each **R^4**, if present, is independently selected from the group consisting of C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy, cyano-C_{1-6}alkyl, halogen, -OH, $-NH_2$,

-NH(C_{1-4}alkyl), -N(C_{1-4}alkyl)$_2$, -CN, C_{3-5}cycloalkyl and 3-5 membered heterocyclyl;

p is selected from the group consisting 0, 1, 2 and 3;

U is selected from the group consisting of nitrogen (=N–) and carbon substituted with $\mathbf{R^A}$ (=C(R^A)-);

V is selected from the group consisting of nitrogen (=N–) and carbon substituted with $\mathbf{R^B}$ (=C(R^B)-);

W is selected from the group consisting of nitrogen (=N–) and carbon substituted with $\mathbf{R^C}$ (=C(R^C)-);

$\mathbf{R^A}$, $\mathbf{R^B}$ and $\mathbf{R^C}$ is each independently selected from the group consisting of hydrogen, C_{1-6}haloalkyl, C_{2-6}alkynyl optionally substituted with C_{3-5}cycloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy, halogen, -CN, -OH, -NH_2, -NH(C_{1-4}alkyl), -N(C_{1-4}alkyl)$_2$, -C(=O)NH_2, -C(=O)NH(C_{1-4}alkyl), -C(=O)N(C_{1-4}alkyl)$_2$, -S-C_{1-6}alkyl, -S(=O)$_2$-C_{1-6}alkyl, C_{3-5}cycloalkyl, 3-5 membered heterocyclyl and C_{1-6}alkyl optionally substituted with a substituent selected from the group consisting of C_{1-6}alkoxy, -CN, -OH, -NH_2, -NH(C_{1-4}alkyl), -N(C_{1-4}alkyl)$_2$, -C(=O)NH_2, -C(=O)NH(C_{1-4}alkyl) and -C(=O)N(C_{1-4}alkyl)$_2$;

$\mathbf{R^5}$ is selected from the group consisting of $\mathbf{R^{a1}}$ and $\mathbf{R^{b1}}$;

$\mathbf{R^{a1}}$ is selected from the group consisting of C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{4-10}cycloalkenyl, 3-11 membered heterocyclyl, C_{6-10}aryl and 5-10 membered heteroaryl, wherein the C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{4-10}cycloalkenyl, 3-11 membered heterocyclyl, C_{6-10}aryl and 5-10 membered heteroaryl are all optionally substituted with one or more, identical or different $\mathbf{R^{b1}}$ and/or $\mathbf{R^{c1}}$;

each $\mathbf{R^{b1}}$ is independently selected from the group consisting of -OR^{c1}, -N$R^{c1}R^{c1}$, halogen, -CN, -C(=O)R^{c1}, -C(=O)OR^{c1}, -C(=O)N$R^{c1}R^{c1}$, -S(=O)$_2R^{c1}$, -S(=O)$_2$N$R^{c1}R^{c1}$, -NHC(=O)R^{c1}, -N(C_{1-4}alkyl)C(=O)R^{c1}, -NHS(=O)$_2R^{c1}$, -N(C_{1-4}alkyl)S(=O)$_2R^{c1}$, -NHC(=O)OR^{c1}, -N(C_{1-4}alkyl)C(=O)OR^{c1} and the bivalent substituent =O;

each $\mathbf{R^{c1}}$ is independently selected from the group consisting of hydrogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{4-10}cycloalkenyl, 3-11 membered heterocyclyl, C_{6-10}aryl and 5-10 membered heteroaryl, wherein the C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{4-10}cycloalkenyl, 3-11 membered heterocyclyl, C_{6-10}aryl and 5-10 membered heteroaryl are all optionally substituted with

one or more, identical or different **R^{d1}** and/or **R^{e1}**;

each **R^{d1}** is independently selected from the group consisting of -OR^{e1}, -$NR^{e1}R^{e1}$, halogen, -CN, -$C(=O)R^{e1}$, -$C(=O)OR^{e1}$, -$C(=O)NR^{e1}R^{e1}$, -$S(=O)_2R^{e1}$, -$S(=O)_2NR^{e1}R^{e1}$, -$NHC(=O)R^{e1}$, -$N(C_{1-4}alkyl)C(=O)R^{e1}$, -$NHS(=O)_2R^{c1}$, -$N(C_{1-4}alkyl)S(=O)_2R^{c1}$, -$NHC(=O)OR^{e1}$, -$N(C_{1-4}alkyl)C(=O)OR^{e1}$ and the bivalent substituent =O;

each **R^{e1}** is independently selected from the group consisting of hydrogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{4-10}cycloalkenyl, 3-11 membered heterocyclyl, C_{6-10}aryl and 5-10 membered heteroaryl, wherein the C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{4-10}cycloalkenyl, 3-11 membered heterocyclyl, C_{6-10}aryl and 5-10 membered heteroaryl are all optionally substituted with one or more, identical or different substituent(s) selected from the group consisting of C_{1-6}alkyl, C_{1-6}haloalkyl, C_{3-10}cycloalkyl, 3-11 membered heterocyclyl optionally substituted with one or more, identical or different C_{1-4}alkyl, C_{6-10}aryl, 5-10 membered heteroaryl, -OH, C_{1-6}alkoxy, C_{1-4}alkoxy-C_{1-4}alkyl, hydroxy-C_{1-4}alkyl, halogen, -CN, -NH_2, -$C(=O)C_{1-4}$alkyl, -$NH(C_{1-4}alkyl)$, -$N(C_{1-4}alkyl)_2$ and the bivalent substituent =O;

L is **-L^1-L^2-L^3-**, wherein **L^1** is linked to **E**;

L^1 is selected from the group consisting of a bond, -NH-, -$N(C_{1-4}alkyl)$-, -O-, -C(=O)-, -NH-C(=O)-, -$N(C_{1-4}alkyl)$-C(=O)-, -C(=O)-NH-, -C(=O)-$N(C_{1-4}alkyl)$-, -C(=O)-, C_{1-6}alkylen, C_{3-7}cycloalkylene, phenylene, 4-12 membered heterocyclylene and 5-10 membered heteroarylene;

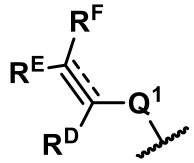
L^2 is selected from the group consisting of C_{1-6}alkylen, C_{3-7}cycloalkylene, phenylene, 4-12 membered heterocyclylene and 5-10 membered heteroarylene;

L^3 is selected from the group consisting of a bond, -NH-, -$N(C_{1-4}alkyl)$-, -O-, -C(=O)-, -NH-C(=O)-, -$N(C_{1-4}alkyl)$-C(=O)-, -C(=O)-NH-, -C(=O)-$N(C_{1-4}alkyl)$-, -C(=O)-, C_{1-6}alkylen, C_{3-7}cycloalkylene, phenylene, 4-12 membered heterocyclylene and 5-10 membered heteroarylene;

wherein each C_{1-6}alkylen, C_{3-7}cycloalkylene, phenylene, 4-12 membered heterocyclylene and 5-10 membered heteroarylene in **L^1**, **L^2** and **L^3** is optionally and independently substituted with one or more, identical or different substituent(s) selected from the group consisting of C_{2-6}alkinyl, C_{1-6}haloalkyl, C_{3-7}cycloalkyl, phenyl, 5-6 membered heteroaryl, halogen, -OH, -CN, C_{1-6}alkoxy, -NH_2, -$NH(C_{1-4}alkyl)$, -$N(C_{1-4}alkyl)_2$, -C(=O)OH, -C(=O)-OC_{1-6}alkyl, -$C(=O)NH_2$, -$C(=O)NH(C_{1-4}alkyl)$, -$C(=O)N(C_{1-4}alkyl)_2$, the bivalent

substituent =O and C_{1-6}alkyl optionally substituted with one or more, identical or different substituent(s) selected from the group consisting of halogen, -OH, -CN, C_{1-4}alkoxy, $-NH_2$, $-NH(C_{1-4}alkyl)$, $-N(C_{1-4}alkyl)_2$, -C(=O)OH, $-C(=O)-OC_{1-6}alkyl$, $-C(=O)NH_2$, $-C(=O)NH(C_{1-4}alkyl)$ and $-C(=O)N(C_{1-4}alkyl)_2$;

E is



(i)

 represents a double or a triple bond;

Q^1 is selected from the group consisting of a bond, $-CH_2-$, -CH(OH)-, -C(=O)-, $-C(=O)N(R^{G1})-$, -C(=O)O-, $-S(=O)_2-$, $-S(=O)_2N(R^{G1})-$ and $-C(=NR^{H1})-$;

each **R^{G1}** is independently selected from the group consisting of hydrogen, C_{1-6}alkyl, C_{1-6}haloalkyl, hydroxy-C_{1-6}alkyl, H_2N-C_{1-6}alkyl, cyano-C_{1-6}alkyl, $(C_{1-4}alkyl)HN-C_{1-6}alkyl$, $(C_{1-4}alkyl)_2N-C_{1-6}alkyl$, C_{1-6}alkoxy-C_{1-6}alkyl, C_{3-7}cycloalkyl and 3-11 membered heterocyclyl;

each **R^{H1}** is independently selected from the group consisting of hydrogen, -OH, C_{1-6}alkoxy, -CN and C_{1-6}alkyl;

if  represents a double bond then

R^D is selected from the group consisting of hydrogen, C_{3-7}cycloalkyl, phenyl, halogen, -CN, C_{1-6}alkoxy, $-C(=O)O-C_{1-6}alkyl$, $-NHC(=O)-C_{1-6}alkyl$ and C_{1-6}alkyl optionally substituted with one or more, identical or different substituent(s) selected from the group consisting of phenyl, 3-11 membered heterocyclyl, C_{1-6}alkoxy, halogen, -OH, $-NH_2$, $-NH(C_{1-6}alkyl)$, $-N(C_{1-6}alkyl)_2$, -C(=O)OH, $-C(=O)O-C_{1-6}alkyl$,$-C(=O)NH(C_{1-6}alkyl)$, $-NHC(=O)-C_{1-6}alkyl$, $-OC(=O)-C_{1-6}alkyl$ and phenyl-C_{1-6}alkoxy;

R^E and **R^F** is each independently selected from the group consisting of **R^{a2}** and **R^{b2}**;

R^{a2} is selected from the group consisting of hydrogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{3-10}cycloalkyl, 3-11 membered heterocyclyl, C_{6-10}aryl and 5-10 membered heteroaryl, wherein the C_{1-6}alkyl, C_{1-6}haloalkyl, C_{3-10}cycloalkyl, 3-11 membered heterocyclyl, C_{6-10}aryl and 5-10 membered heteroaryl are all optionally substituted with one or more,

identical or different $\mathbf{R^{b2}}$ and/or $\mathbf{R^{c2}}$;

each $\mathbf{R^{b2}}$ is independently selected from the group consisting of $-OR^{c2}$, $-NR^{c2}R^{c2}$, halogen, -CN, $-C(=O)R^{c2}$, $-C(=O)OR^{c2}$, $-C(=O)NR^{c2}R^{c2}$, $-S(=O)_2R^{c2}$, $-S(=O)_2NR^{c2}R^{c2}$, $-NHC(=O)R^{c2}$, $-N(C_{1\text{-}4}alkyl)C(=O)R^{c2}$, $-NHC(=O)OR^{c2}$, $-N(C_{1\text{-}4}alkyl)C(=O)OR^{c2}$ and the bivalent substituent =O;

each $\mathbf{R^{c2}}$ is independently selected from the group consisting of hydrogen, $C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$haloalkyl, $C_{2\text{-}6}$alkenyl, $C_{2\text{-}6}$alkynyl, $C_{3\text{-}10}$cycloalkyl, $C_{4\text{-}10}$cycloalkenyl, 3-11 membered heterocyclyl, $C_{6\text{-}10}$aryl and 5-10 membered heteroaryl, wherein the $C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$haloalkyl, $C_{2\text{-}6}$alkenyl, $C_{2\text{-}6}$alkynyl, $C_{3\text{-}10}$cycloalkyl, $C_{4\text{-}10}$cycloalkenyl, 3-11 membered heterocyclyl, $C_{6\text{-}10}$aryl and 5-10 membered heteroaryl are all optionally substituted with one or more, identical or different substituent(s) selected from the group consisting of $C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$alkoxy, halogen, -OH, -C(=O)OH, $-C(=O)O\text{-}C_{1\text{-}6}$alkyl, $-C(=O)C_{1\text{-}6}$alkyl, $-C(=O)NH_2$, $-C(=O)NH(C_{1\text{-}6}alkyl)$, $-C(=O)N(C_{1\text{-}6}alkyl)_2$, and the bivalent substituent =O;

or

$\mathbf{R^D}$ and $\mathbf{R^E}$ taken together with the carbon atoms they are attached form a 4-7 membered unsaturated alicycle or 4-7 membered unsaturated heterocycle, wherein this 4-7 membered unsaturated alicycle or 4-7 membered unsaturated heterocycle is optionally, in addition to $\mathbf{R^F}$, substituted with one or more identical or different substituent(s) selected from the group consisting of $C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$haloalkyl, -OH, $C_{1\text{-}6}$alkoxy, $C_{1\text{-}4}$alkoxy-$C_{1\text{-}4}$alkyl, $-NH_2$, -CN, $-NH(C_{1\text{-}4}alkyl)$, $-N(C_{1\text{-}4}alkyl)_2$, halogen, $-C(=O)O\text{-}C_{1\text{-}6}$alkyl and the bivalent substituent =O;

or

if $\mathbf{Q^1}$ is $-C(=O)N(R^{G1})-$, then $\mathbf{R^{G1}}$ of $-C(=O)N(R^{G1})-$ and $\mathbf{R^F}$ together form a linker selected from the group consisting of $-C(=O)-$, $-CH_2-$, $-CH_2-C(=O)-$, $-C(=O)-CH_2-$ and $-C_2H_4-$;

if  represents a triple bond then

$\mathbf{R^D}$ and $\mathbf{R^E}$ are both absent;

$\mathbf{R^F}$ is $\mathbf{R^{a2}}$;

$\mathbf{R^{a2}}$ is selected from the group consisting of hydrogen, $C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$haloalkyl, $C_{3\text{-}10}$cycloalkyl, 3-11 membered heterocyclyl, $C_{6\text{-}10}$aryl and 5-10 membered heteroaryl, wherein the $C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$haloalkyl, $C_{3\text{-}10}$cycloalkyl, 3-11 membered heterocyclyl,

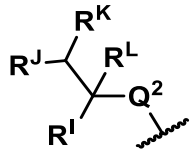
C_{6-10}aryl and 5-10 membered heteroaryl are all optionally substituted with one or more, identical or different $\mathbf{R^{b2}}$ and/or $\mathbf{R^{c2}}$;

each $\mathbf{R^{b2}}$ is independently selected from the group consisting of $-OR^{c2}$, $-NR^{c2}R^{c2}$, halogen, -CN, $-C(=O)R^{c2}$, $-C(=O)OR^{c2}$, $-C(=O)NR^{c2}R^{c2}$, $-S(=O)_2R^{c2}$, $-S(=O)_2NR^{c2}R^{c2}$, $-NHC(=O)R^{c2}$, $-N(C_{1-4}alkyl)C(=O)R^{c2}$, $-NHC(=O)OR^{c2}$, $-N(C_{1-4}alkyl)C(=O)OR^{c2}$ and the bivalent substituent =O;

each $\mathbf{R^{c2}}$ is independently selected from the group consisting of hydrogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{3-10}cycloalkyl, 3-11 membered heterocyclyl, C_{6-10}aryl and 5-10 membered heteroaryl;

or

E is



(ii)

$\mathbf{Q^2}$ is selected from the group consisting of a bond, $-CH_2-$, -CH(OH)-, -C(=O)-, $-C(=O)N(R^{G2})-$, -C(=O)O-, $-S(=O)_2-$, $-S(=O)_2N(R^{G2})-$ and $-C(=NR^{H2})-$;

each $\mathbf{R^{G2}}$ is independently selected from the group consisting of hydrogen, C_{1-6}alkyl, C_{1-6}haloalkyl, hydroxy-C_{1-6}alkyl, H_2N-C_{1-6}alkyl, cyano-C_{1-6}alkyl, $(C_{1-4}alkyl)HN$-C_{1-6}alkyl, $(C_{1-4}alkyl)_2N$-C_{1-6}alkyl, C_{1-6}alkoxy-C_{1-6}alkyl, C_{3-7}cycloalkyl and 3-11 membered heterocyclyl;

each $\mathbf{R^{H2}}$ is independently selected from the group consisting of hydrogen, -OH, C_{1-6}alkoxy, -CN and C_{1-6}alkyl;

$\mathbf{R^I}$ is selected from the group consisting of hydrogen and halogen;

$\mathbf{R^J}$ is hydrogen; or

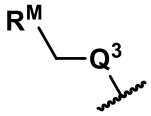
$\mathbf{R^I}$ and $\mathbf{R^J}$ together with the carbon atoms they are attached form a cyclopropane or oxirane ring;

$\mathbf{R^K}$ is selected from the group consisting of hydrogen, C_{1-6}alkyl, -CN and halogen;

$\mathbf{R^L}$ is selected from the group consisting of hydrogen, C_{1-6}alkyl, -CN, halogen and $-C(=O)-C_{1-6}$alkyl;

or

E is



(iii)

Q^3 is selected from the group consisting of -C(=O)-, -C(=O)N(R^{G3})-, -C(=O)O-, -S(=O)$_2$-, -S(=O)$_2$N(R^{G3})- and -C(=NR^{H3})-;

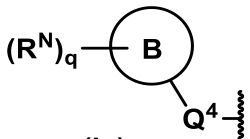
each **R^{G3}** is independently selected from the group consisting of hydrogen, C_{1-6}alkyl, C_{1-6}haloalkyl, hydroxy-C_{1-6}alkyl, H_2N-C_{1-6}alkyl, cyano-C_{1-6}alkyl, (C_{1-4}alkyl)HN-C_{1-6}alkyl, (C_{1-4}alkyl)$_2$N-C_{1-6}alkyl, C_{1-6}alkoxy-C_{1-6}alkyl, C_{3-7}cycloalkyl and 3-11 membered heterocyclyl;

each **R^{H3}** is independently selected from the group consisting of hydrogen, -OH, C_{1-6}alkoxy, -CN and C_{1-6}alkyl;

R^M is selected from the group consisting of halogen, -CN and -O-C(=O)-C_{1-6}alkyl;

or

E is



(iv)

Q^4 is selected from the group consisting of a bond, -C(=O)-, -C(=O)O-, -C(=O)NH-, -C(=O)N(C_{1-4}alkyl)-, -S(=O)$_2$- and -S(=O)$_2$NH-;

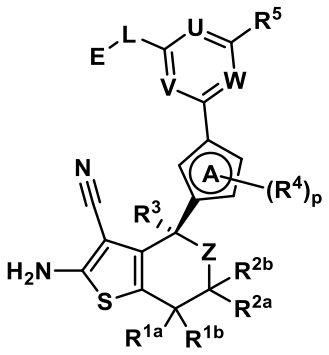
ring **B** is selected from the group consisting of phenyl, pyridyl, pyrimidyl, pyridazinyl, pyrazinyl and 5-membered heteroaryl;

q is selected from the group consisting 1, 2, 3 and 4;

each **R^N** is independently selected from the group consisting of C_{1-4}alkyl, C_{1-4}haloalkyl, vinyl, ethinyl, halogen, -CN, nitro and C_{1-4}alkoxy;

or a salt thereof.

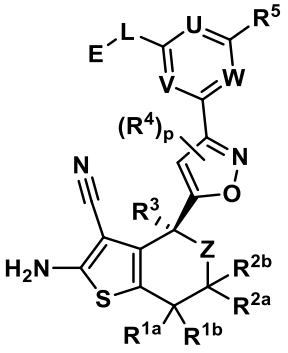
2. The compound or salt according to claim 1 of the formula **(I*)**



(I*) , wherein

R^{1a}, R^{1b}, R^{2a}, R^{2b}, **Z**, R^3, ring **A**, R^4, **p**, **U**, **V**, **W**, R^5, **L** and **E** are defined as in in claim 1.

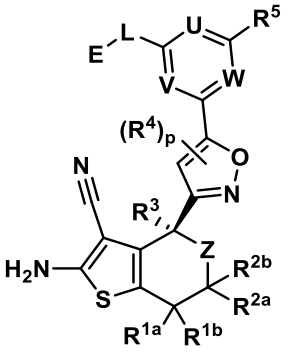
3. The compound or salt according to claim 1 of the formula **(Ib*)**



(Ib*) , wherein

R^{1a}, R^{1b}, R^{2a}, R^{2b}, **Z**, R^3, R^4, **p**, **U**, **V**, **W**, R^5, **L** and **E** are defined as in in claim 1.

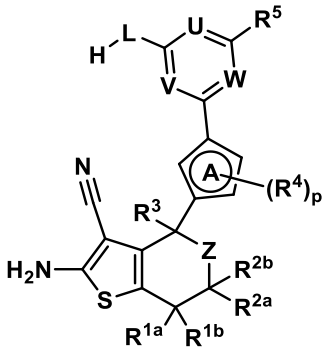
4. The compound or salt according to claim 1 of the formula **(Ic*)**



(Ic*) , wherein

R^{1a}, R^{1b}, R^{2a}, R^{2b}, **Z**, R^3, R^4, **p**, **U**, **V**, **W**, R^5, **L** and **E** are defined as in in claim 1.

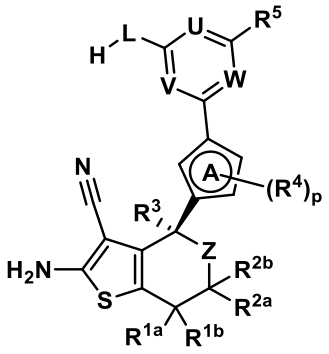
5. A compound of the formula **(II)**



(II) , wherein

R^{1a}, **R^{1b}**, **R^{2a}**, **R^{2b}**, **Z**, **R^3**, ring **A**, **R^4**, **p**, **U**, **V**, **W**, **R^5** and **L** are defined as in formula **(I)** in claim 1, or a salt thereof.

6. The compound or salt according to claim 5 of the formula **(II*)**



(II*) , wherein

R^{1a}, **R^{1b}**, **R^{2a}**, **R^{2b}**, **Z**, **R^3**, ring **A**, **R^4**, **p**, **U**, **V**, **W**, **R^5** and **L** are defined as in formula **(I)** in claim 1.

7. The compound or salt according to any one of claim 1 to 6, wherein

R^{1a} and **R^{1b}** are both independently selected from the group consisting of hydrogen and $C_{1\text{-}4}$alkyl;

R^{2a} and **R^{2b}** are both independently selected from the group consisting of hydrogen and halogen.

8. The compound or salt according to any one of claim 1 to 7, wherein

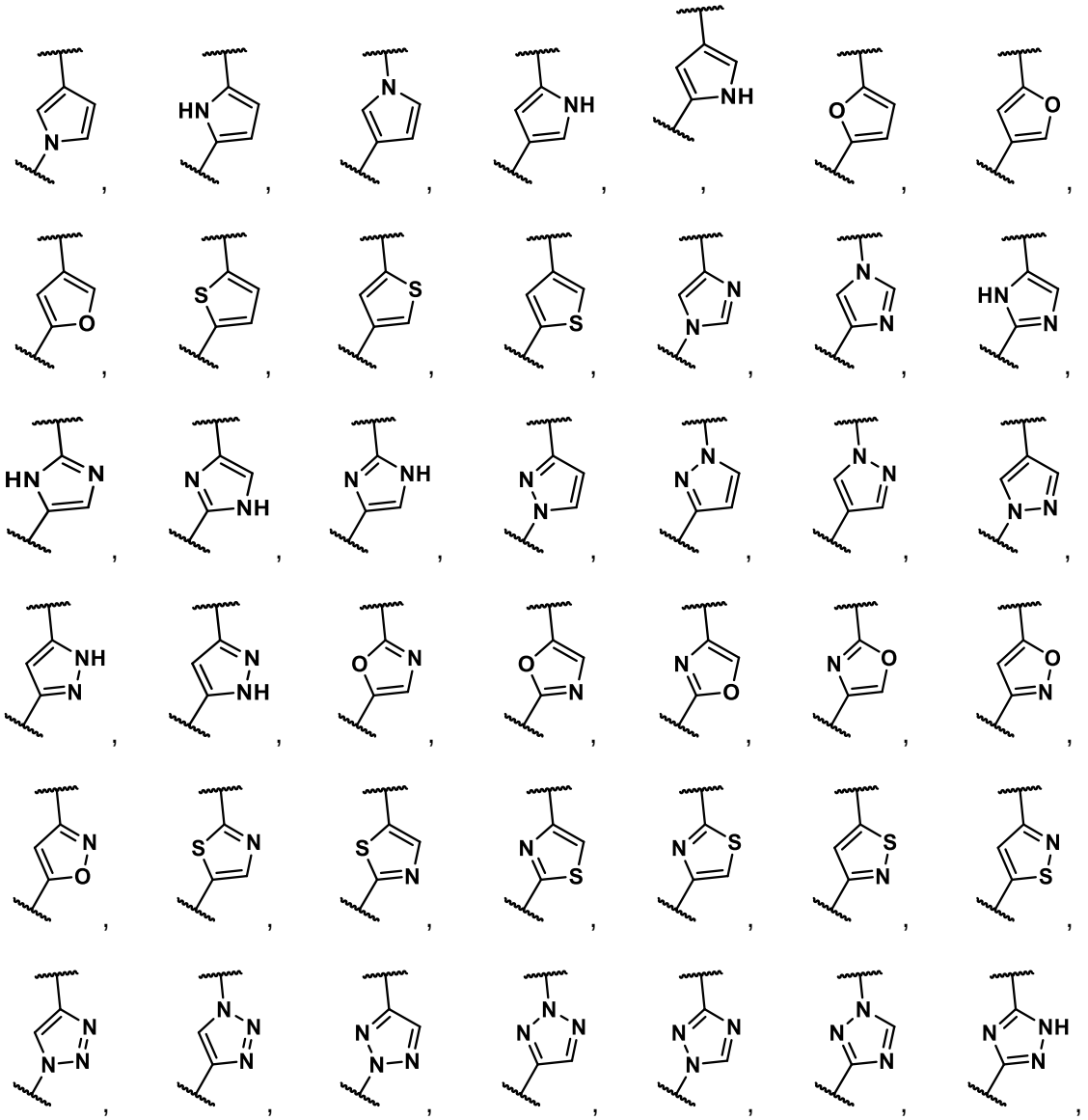
Z is -CH_2-.

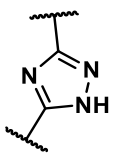
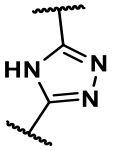
9. The compound or salt according to any one of claim 1 to 8, wherein

R^3 is selected from the group consisting of hydrogen, C_{1-4}alkyl, C_{1-4}haloalkyl, C_{1-4}alkoxy, C_{1-4}haloalkoxy, cyano-C_{1-4}alkyl, halogen, -OH, -NH_2, -NH(C_{1-4}alkyl), -N(C_{1-4}alkyl)$_2$ and -CN.

10. The compound or salt according to any one of claim 1, 2 and 5 to 9, wherein

ring **A** is selected from the group consisting of



 and .

11. The compound or salt according to any one of claim 1 to 10, wherein

p is 0.

12. The compound or salt according to any one of claim 1 to 11, wherein

U is carbon substituted with $\mathbf{R^A}$ (=C(R^A)-);

V is nitrogen (=N–);

W is nitrogen (=N–);

$\mathbf{R^A}$ is selected from the group consisting of hydrogen, C_{1-6}haloalkyl, C_{2-6}alkynyl optionally substituted with C_{3-5}cycloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy, halogen, -CN, -OH, -NH_2, -NH(C_{1-4}alkyl), -N(C_{1-4}alkyl)$_2$, -C(=O)NH_2, -C(=O)NH(C_{1-4}alkyl), -C(=O)N(C_{1-4}alkyl)$_2$, C_{3-5}cycloalkyl, 3-5 membered heterocyclyl and C_{1-6}alkyl optionally substituted with a substituent selected from the group consisting of C_{1-6}alkoxy, -CN, -OH, -NH_2, -NH(C_{1-4}alkyl), -N(C_{1-4}alkyl)$_2$, -C(=O)NH_2,-C(=O)NH(C_{1-4}alkyl) and -C(=O)N(C_{1-4}alkyl)$_2$.

13. The compound or salt according to any one of claim 1 to 12, wherein

$\mathbf{R^5}$ is selected from the group consisting of $\mathbf{R^{a1}}$ and $\mathbf{R^{b1}}$;

$\mathbf{R^{a1}}$ is selected from the group consisting of C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, 3-11 membered heterocyclyl, C_{6-10}aryl and 5-10 membered heteroaryl, wherein the C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, 3-11 membered heterocyclyl, C_{6-10}aryl and 5-10 membered heteroaryl are all optionally substituted with one or more, identical or different $\mathbf{R^{b1}}$ and/or $\mathbf{R^{c1}}$;

each $\mathbf{R^{b1}}$ is independently selected from the group consisting of -OR^{c1}, -$NR^{c1}R^{c1}$, halogen, -CN, -C(=O)R^{c1}, -C(=O)OR^{c1}, -C(=O)$NR^{c1}R^{c1}$, -S(=O)$_2R^{c1}$, -S(=O)$_2NR^{c1}R^{c1}$, -NHC(=O)R^{c1}, -N(C_{1-4}alkyl)C(=O)R^{c1} and the bivalent substituent =O;

each $\mathbf{R^{c1}}$ is independently selected from the group consisting of hydrogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{3-10}cycloalkyl, 3-11 membered heterocyclyl, C_{6-10}aryl and 5-10 membered

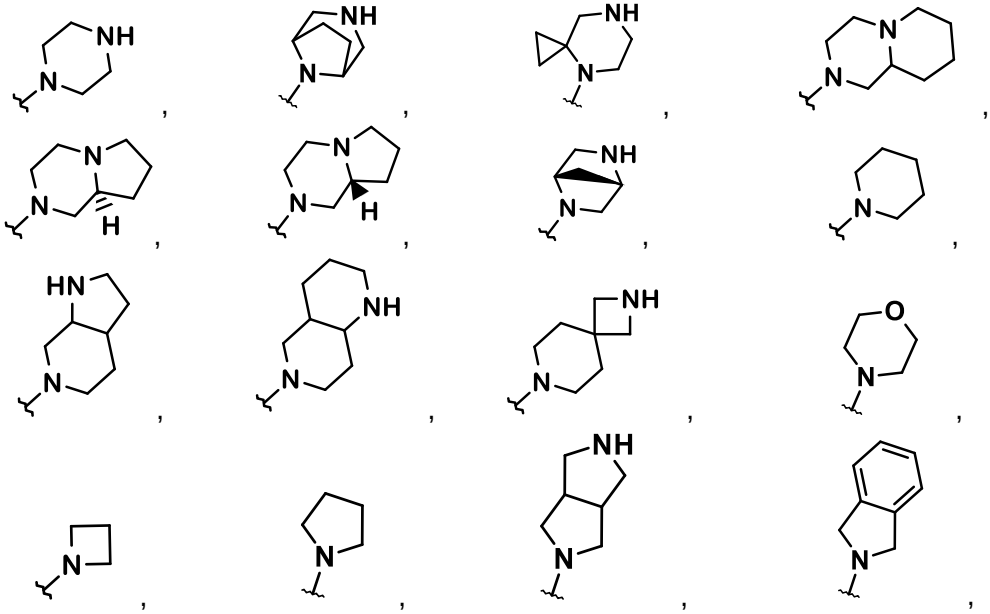
heteroaryl, wherein the C_{1-6}alkyl, C_{1-6}haloalkyl, C_{3-10}cycloalkyl, 3-11 membered heterocyclyl, C_{6-10}aryl and 5-10 membered heteroaryl are all optionally substituted with one or more, identical or different **R^{d1}** and/or **R^{e1}**;

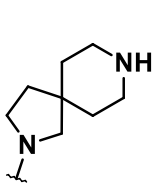
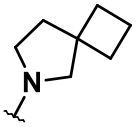
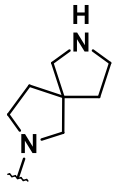
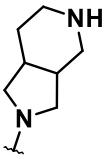
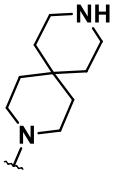
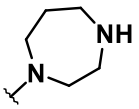
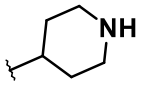
each **R^{d1}** is independently selected from the group consisting of -OR^{e1}, -$NR^{e1}R^{e1}$, halogen, -CN, -$C(=O)R^{e1}$, -$C(=O)NR^{e1}R^{e1}$ and the bivalent substituent =O;

each **R^{e1}** is independently selected from the group consisting of hydrogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{3-10}cycloalkyl, 3-11 membered heterocyclyl, C_{6-10}aryl and 5-10 membered heteroaryl, wherein the C_{1-6}alkyl, C_{1-6}haloalkyl, C_{3-10}cycloalkyl, 3-11 membered heterocyclyl, C_{6-10}aryl and 5-10 membered heteroaryl are all optionally substituted with one or more, identical or different substituent(s) selected from the group consisting of C_{1-6}alkyl, C_{1-6}haloalkyl, C_{3-10}cycloalkyl, 3-11 membered heterocyclyl optionally substituted with one or more, identical or different C_{1-4}alkyl, C_{6-10}aryl, 5-10 membered heteroaryl, -OH, C_{1-6}alkoxy, C_{1-4}alkoxy-C_{1-4}alkyl, hydroxy-C_{1-4}alkyl, halogen, -CN, -NH_2, -$C(=O)C_{1-4}$alkyl, -$NH(C_{1-4}$alkyl), -$N(C_{1-4}$alkyl$)_2$ and the bivalent substituent =O.

14. The compound or salt according to any one of claim 1 to 12, wherein

R^5 is **R^{a1}** selected from the group consisting of









and

, wherein

each **R^{a1}** is optionally substituted with one or more, identical or different **R^{b1}** and/or **R^{c1}**;

each **R^{b1}** is independently selected from the group consisting of -OR^{c1}, -NR^{c1}R^{c1}, halogen, -C(=O)OR^{c1} and the bivalent substituent =O;

each **R^{c1}** is independently selected from the group consisting of hydrogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{3-10}cycloalkyl and 3-11 membered heterocyclyl, wherein the C_{1-6}alkyl, C_{1-6}haloalkyl, C_{3-10}cycloalkyl and 3-11 membered heterocyclyl are all optionally substituted with one or more, identical or different **R^{d1}** and/or **R^{e1}**;

each **R^{d1}** is independently selected from the group consisting of -OR^{e1}, -NR^{e1}R^{e1} and halogen;

each **R^{e1}** is independently selected from the group consisting of hydrogen, C_{1-6}alkyl, C_{3-10}cycloalkyl and 3-11 membered heterocyclyl, wherein the C_{1-6}alkyl, C_{3-10}cycloalkyl and 3-11 membered heterocyclyl are all optionally substituted with one or more, identical or different substituent(s) selected from the group consisting of C_{1-6}alkyl and 3-11 membered heterocyclyl optionally substituted with one or more, identical or different C_{1-4}alkyl.

15. The compound or salt according to any one of claim 1 to 13, wherein

R^{5} is **R^{b1}**;

R^{b1} is -OR^{c1};

each **R^{c1}** is independently selected from the group consisting of C_{1-6}alkyl, C_{3-10}cycloalkyl, and 3-11 membered heterocyclyl, wherein the C_{1-6}alkyl, C_{3-10}cycloalkyl and 3-11 membered heterocyclyl are all optionally substituted with one or more, identical or different **R^{d1}** and/or **R^{e1}**;

each **R^{d1}** is independently selected from the group consisting of -NR^{e1}R^{e1} and halogen;

each **R^{e1}** is independently selected from the group consisting of hydrogen, C_{1-6}alkyl and 3-11 membered heterocyclyl, wherein the C_{1-6}alkyl and 3-11 membered heterocyclyl are all optionally substituted with one or more, identical or different substituent(s) selected from the group consisting of C_{1-6}alkyl and 3-11 membered heterocyclyl optionally substituted with one or more, identical or different C_{1-4}alkyl.

16. The compound or salt according to any one of claim 1 to 15, wherein

L is **-L^1-L^2-L^3-**, wherein **L^1** is linked to **E**;

L^1 is selected from the group consisting of a bond, C_{1-6}alkylen and 4-12 membered heterocyclylene;

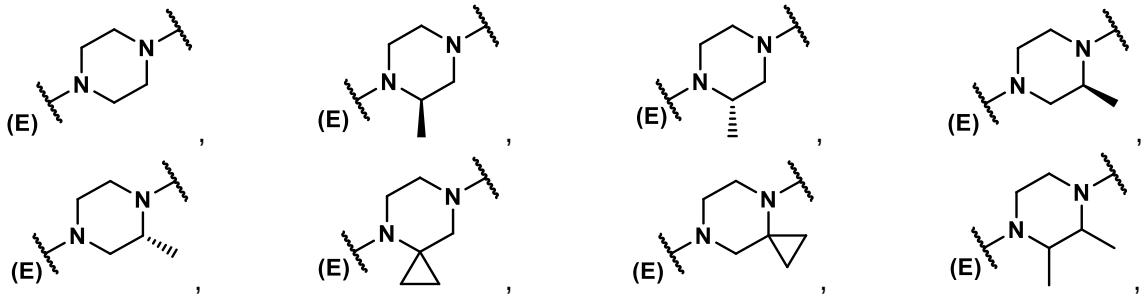
L^2 is selected from the group consisting of C_{1-6}alkylen, phenylene and 4-12 membered heterocyclylene;

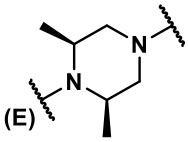
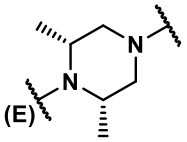
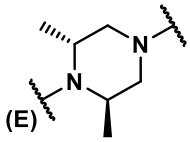
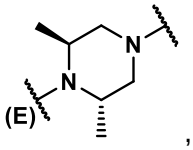
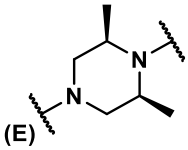
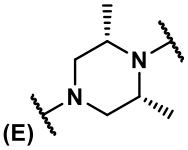
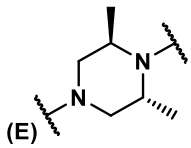
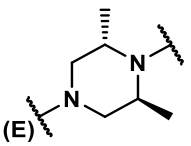
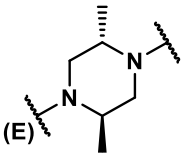
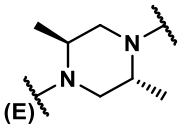
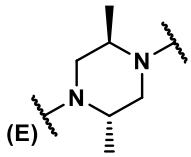
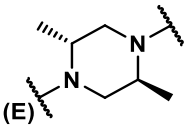
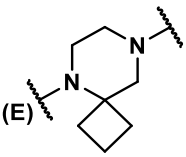
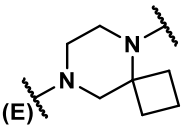
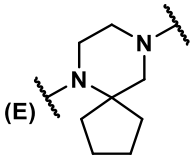
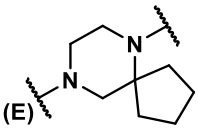
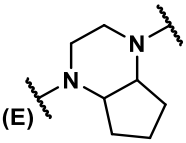
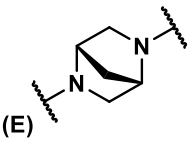
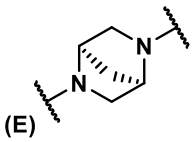
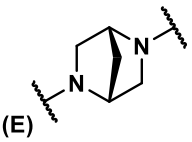
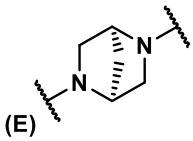
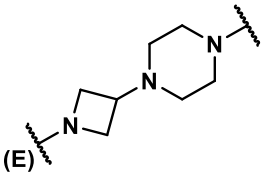
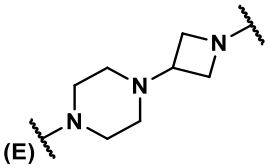
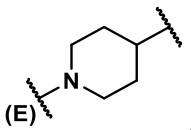
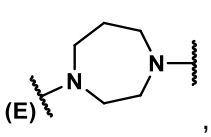
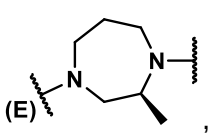
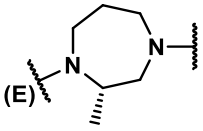
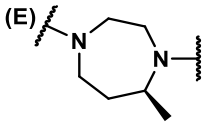
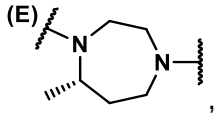
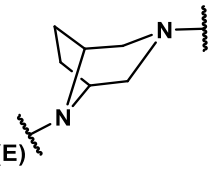
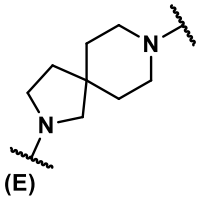
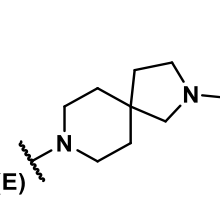
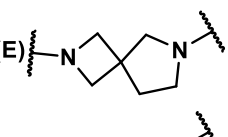
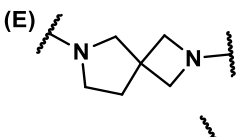
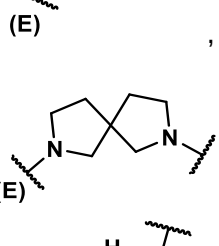
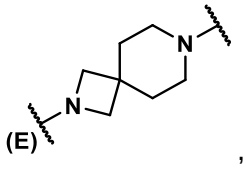
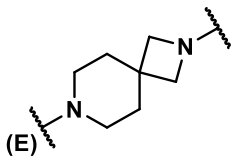
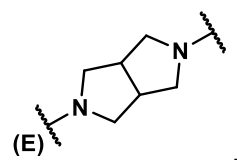
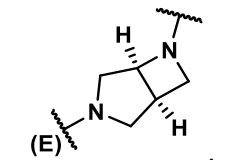
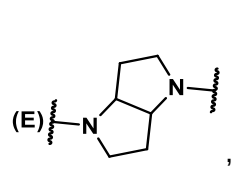
L^3 is selected from the group consisting of a bond, -NH-, -N(C_{1-4}alkyl)- and -O-;

wherein each C_{1-6}alkylen, phenylene and 4-12 membered heterocyclylene in **L^1** and **L^2** is optionally and independently substituted with one or more, identical or different substituent(s) selected from the group consisting of C_{2-6}alkinyl, C_{1-6}haloalkyl, C_{3-7}cycloalkyl, phenyl, 5-6 membered heteroaryl, halogen, -OH, -CN, C_{1-6}alkoxy, -NH_2, -NH(C_{1-4}alkyl), -N(C_{1-4}alkyl)$_2$, -C(=O)OH, -C(=O)-OC_{1-6}alkyl, -C(=O)NH_2, -C(=O)NH(C_{1-4}alkyl), -C(=O)N(C_{1-4}alkyl)$_2$, the bivalent substituent =O and C_{1-6}alkyl optionally substituted with one or more, identical or different substituent(s) selected from the group consisting of halogen, -OH, -CN, -NH_2, C_{1-4}alkoxy, -NH(C_{1-4}alkyl), -N(C_{1-4}alkyl)$_2$, -C(=O)OH, -C(=O)-OC_{1-6}alkyl, -C(=O)NH_2, -C(=O)NH(C_{1-4}alkyl) and -C(=O)N(C_{1-4}alkyl)$_2$.

17. The compound or salt according to claim 16, wherein

L is selected from the group consisting of



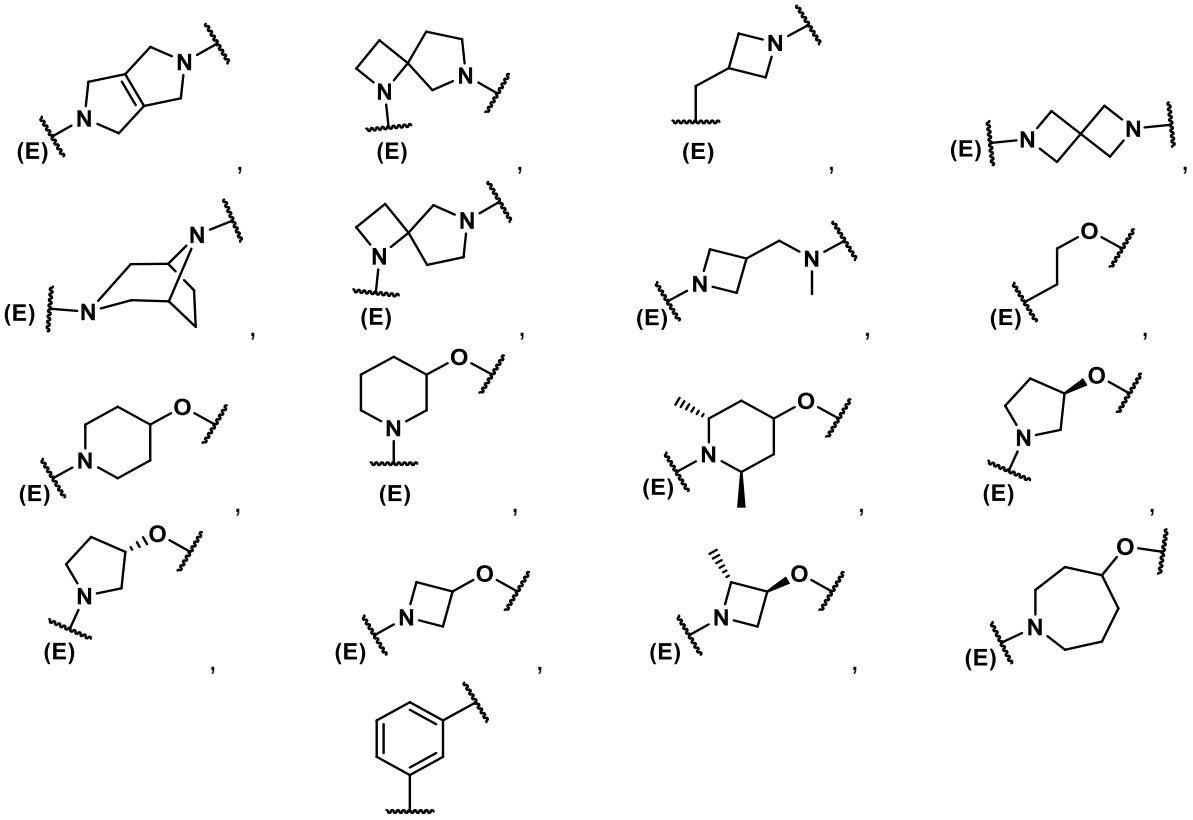

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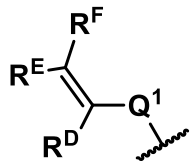
(E)
N
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,



and .

18. The compound or salt according to any one of claim 1 to 4 and 7 to 17, wherein

E is



(i) ;

Q^1 is selected from the group consisting of -CH_2-, -C(=O)-, -C(=O)N(R^{G1})-, -C(=O)O-, -$S(=O)_2$-, -$S(=O)_2$N(R^{G1})- and -C(=NR^{H1})-;

each **R^{G1}** is independently selected from the group consisting of hydrogen, C_{1-6}alkyl, C_{1-6}haloalkyl and hydroxy-C_{1-6}alkyl;

each **R^{H1}** is independently selected from the group consisting of hydrogen, -OH, C_{1-6}alkoxy, -CN and C_{1-6}alkyl;

R^D is selected from the group consisting of hydrogen, C_{3-7}cycloalkyl, phenyl, halogen,

-CN, C_{1-6}alkoxy, -C(=O)O-C_{1-6}alkyl and C_{1-6}alkyl optionally substituted with one or more, identical or different substituent(s) selected from the group consisting of phenyl, 3-11 membered heterocyclyl, C_{1-6}alkoxy, halogen, -OH, -N(C_{1-6}alkyl)$_2$, -C(=O)OH, -C(=O)O-C_{1-6}alkyl, -C(=O)NH(C_{1-6}alkyl), -NHC(=O)-C_{1-6}alkyl, -OC(=O)-C_{1-6}alkyl and phenyl-C_{1-6}alkoxy;

R^E and **R^F** is each independently selected from the group consisting of **R^{a2}** and **R^{b2}**;

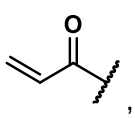
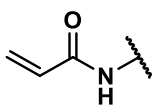
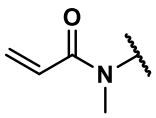
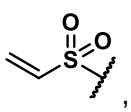
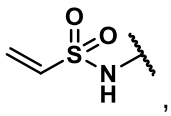
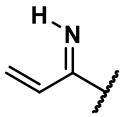
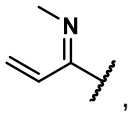
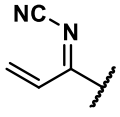
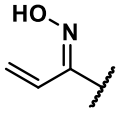
R^{a2} is selected from the group consisting of hydrogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{3-10}cycloalkyl, 3-11 membered heterocyclyl, C_{6-10}aryl and 5-10 membered heteroaryl, wherein the C_{1-6}alkyl, C_{1-6}haloalkyl, C_{3-10}cycloalkyl, 3-11 membered heterocyclyl, C_{6-10}aryl and 5-10 membered heteroaryl are all optionally substituted with one or more, identical or different **R^{b2}** and/or **R^{c2}**;

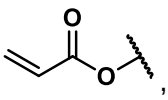
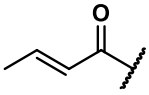
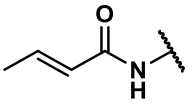
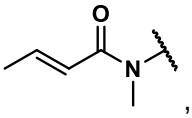
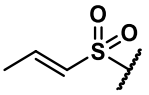
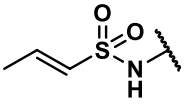
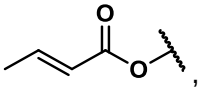
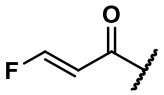
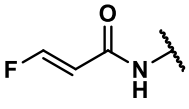
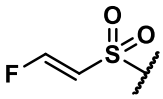
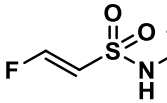
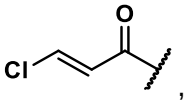
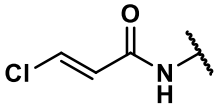
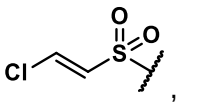
each **R^{b2}** is independently selected from the group consisting of -OR^{c2}, -$NR^{c2}R^{c2}$, halogen, -CN, -C(=O)OR^{c2}, -C(=O)$NR^{c2}R^{c2}$, -NHC(=O)R^{c2}, -N(C_{1-4}alkyl)C(=O)R^{c2}, -NHC(=O)OR^{c2} and -N(C_{1-4}alkyl)C(=O)OR^{c2};

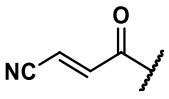
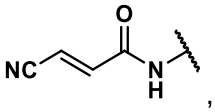
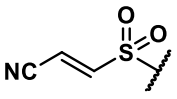
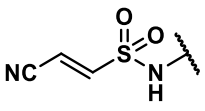
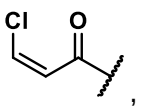
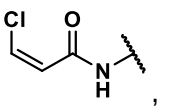
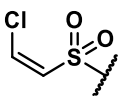
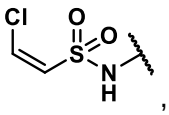
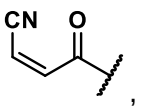
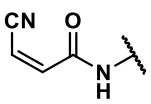
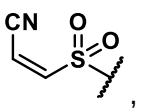
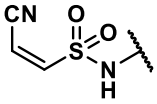
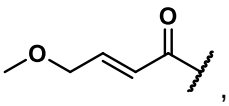
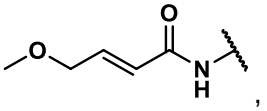
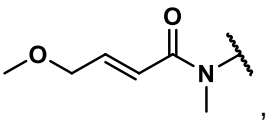
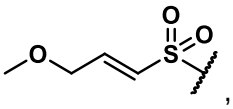
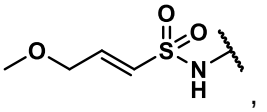
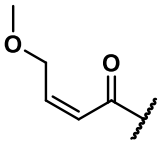
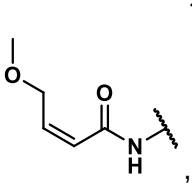
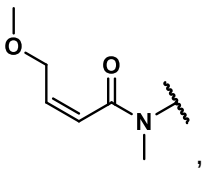
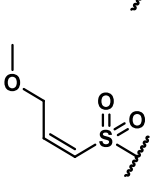
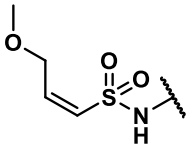
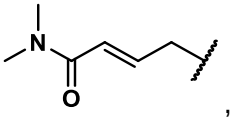
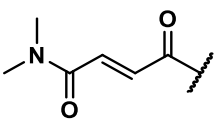
each **R^{c2}** is independently selected from the group consisting of hydrogen, C_{1-6}alkyl, C_{1-6}haloalkyl, 3-11 membered heterocyclyl, C_{6-10}aryl and 5-10 membered heteroaryl, wherein the C_{1-6}alkyl, C_{1-6}haloalkyl, 3-11 membered heterocyclyl, C_{6-10}aryl and 5-10 membered heteroaryl are all optionally substituted with one or more, identical or different substituent(s) selected from the group consisting of C_{1-6}alkyl, C_{1-6}alkoxy, halogen, -OH, -C(=O)OH, -C(=O)O-C_{1-6}alkyl, -C(=O)C_{1-6}alkyl,-C(=O)NH_2, -C(=O)NH(C_{1-6}alkyl), -C(=O)N(C_{1-6}alkyl)$_2$, and the bivalent substituent =O.

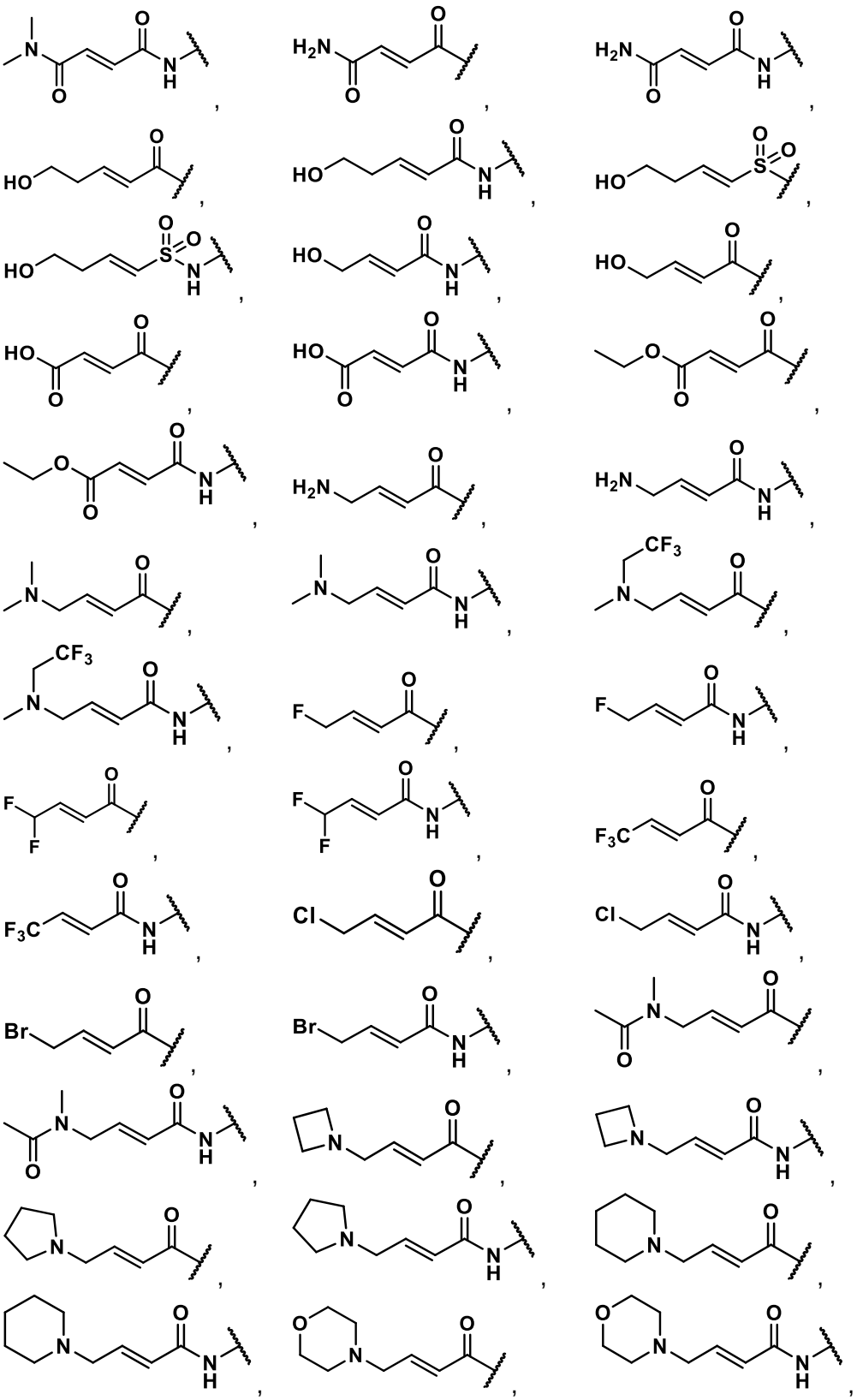
19. The compound or salt according to claim 18, wherein

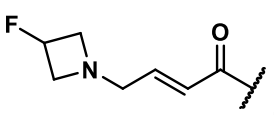
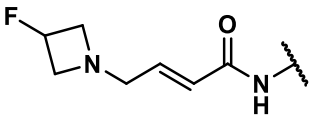
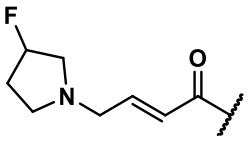
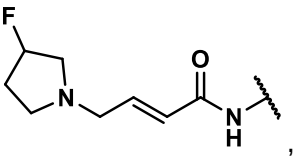
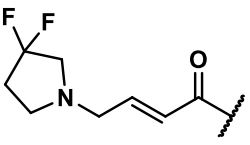
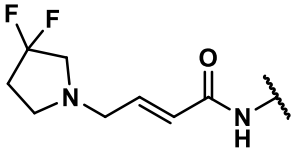
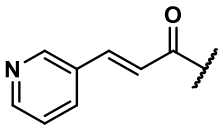
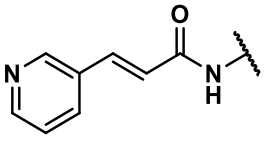
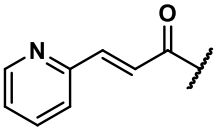
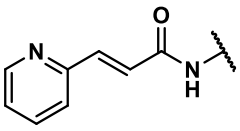
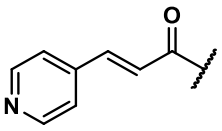
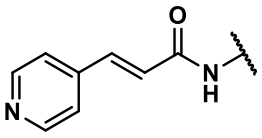
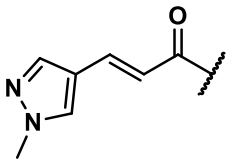
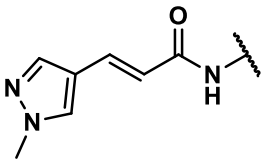
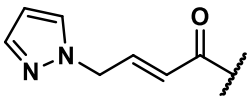
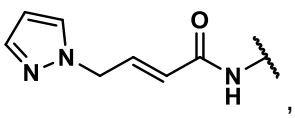
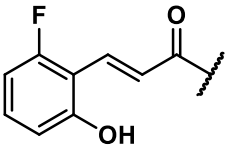
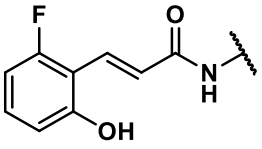
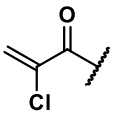
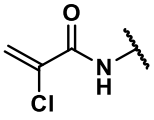
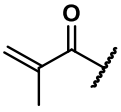
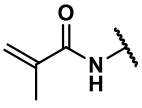
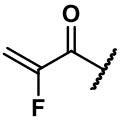
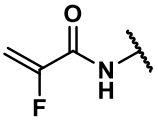
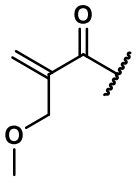
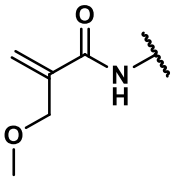
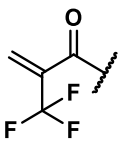
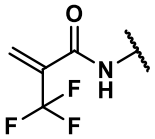
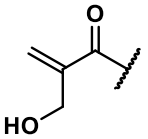
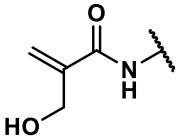
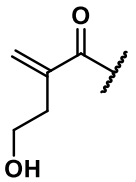
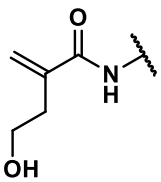
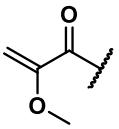
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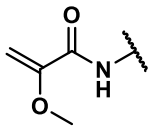
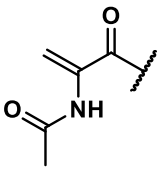
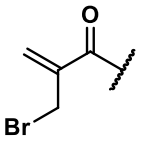
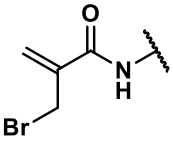
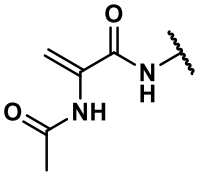
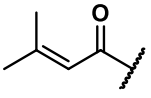
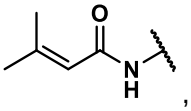
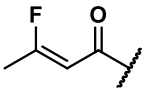
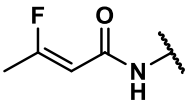
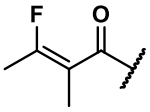
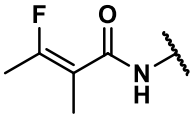
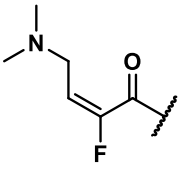
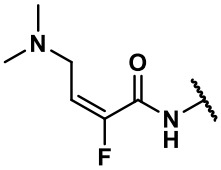
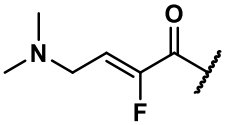
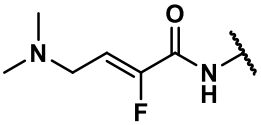
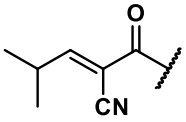
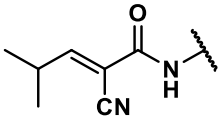
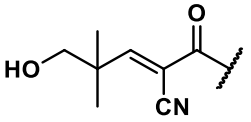
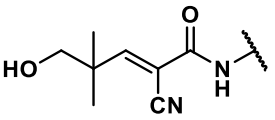
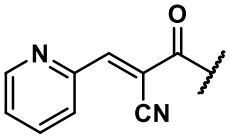
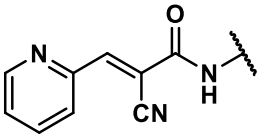
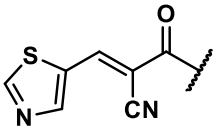
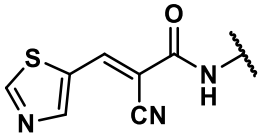
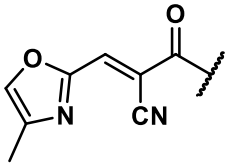
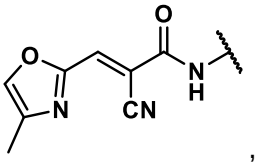
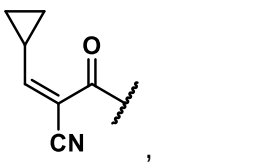
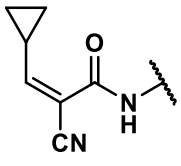
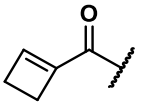
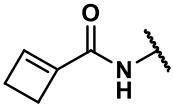
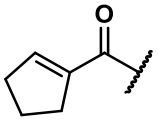










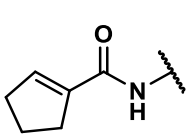
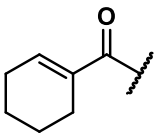
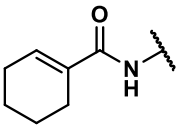
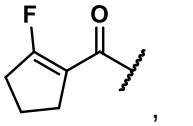
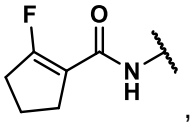
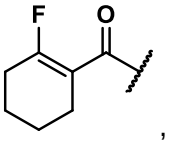
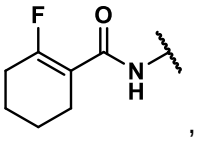
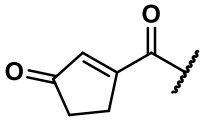
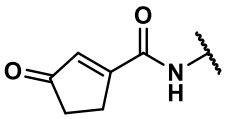
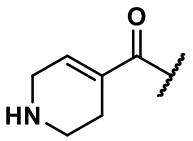
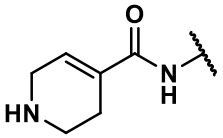

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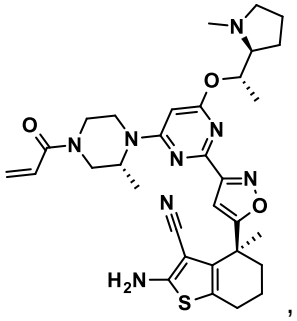


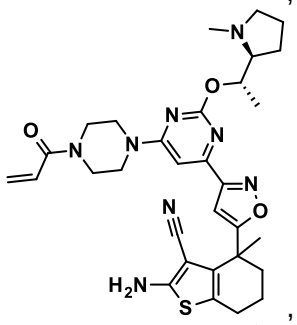

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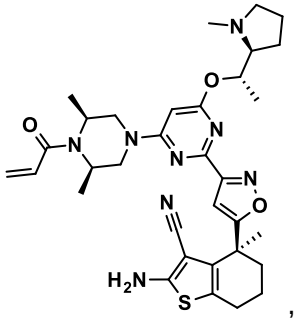

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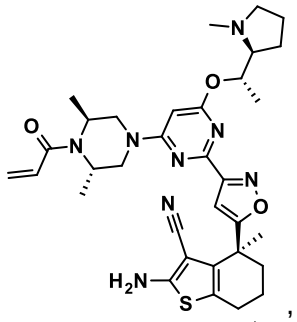

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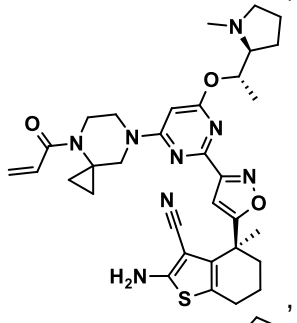
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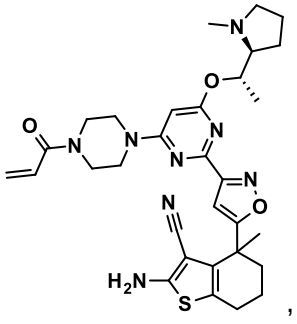
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Ib-2

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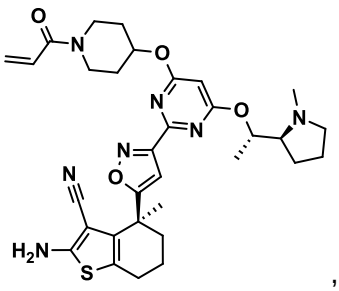
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Ib-4

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Ib-5

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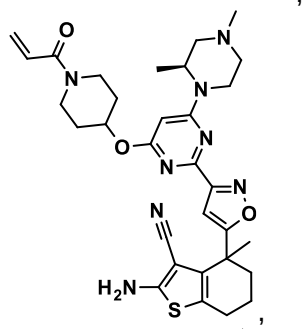
Ib-6

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Ib-7



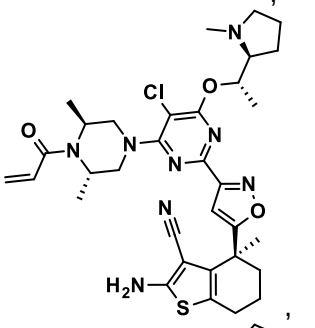
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Ib-8



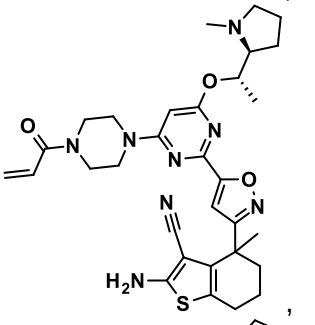
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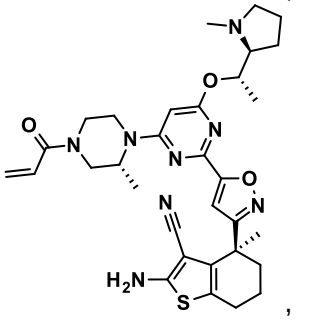
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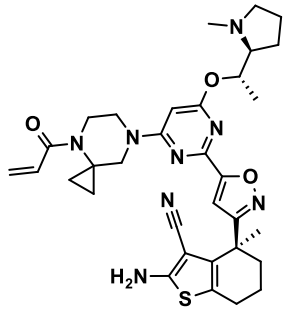
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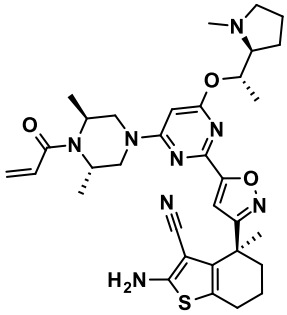
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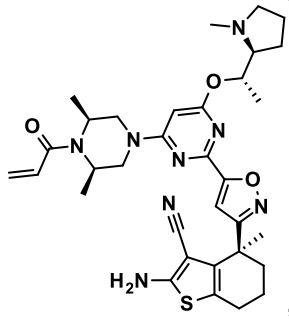
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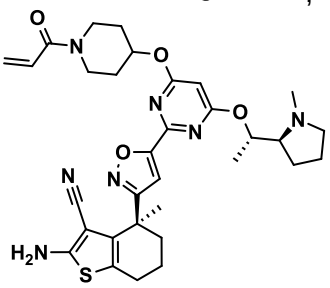
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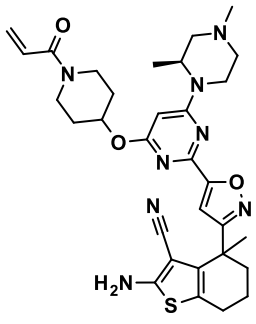
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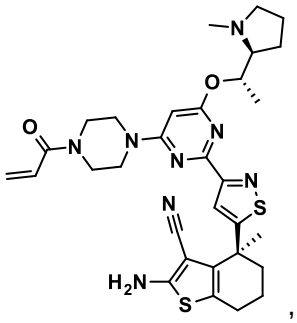
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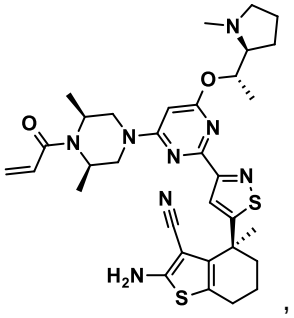
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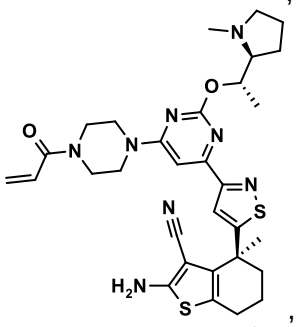
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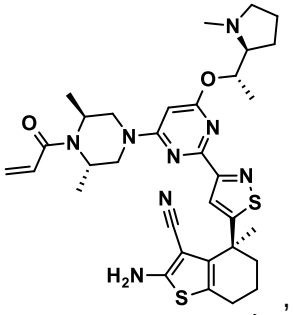
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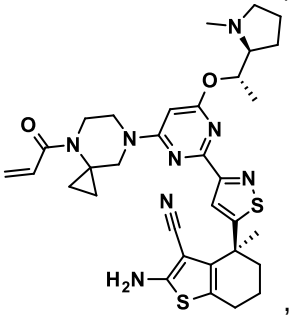
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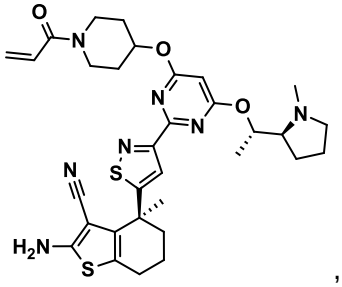
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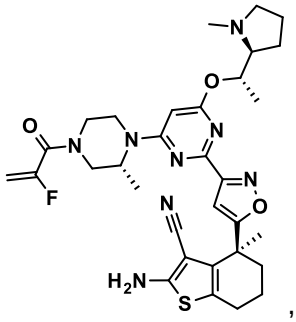
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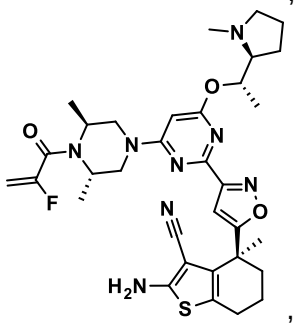
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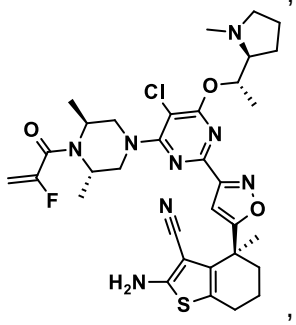
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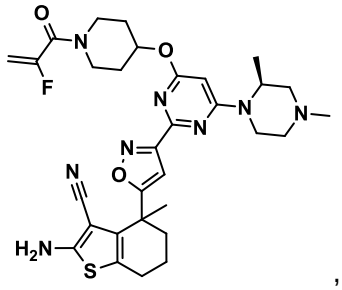
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Ib-12

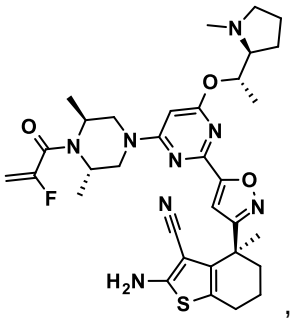


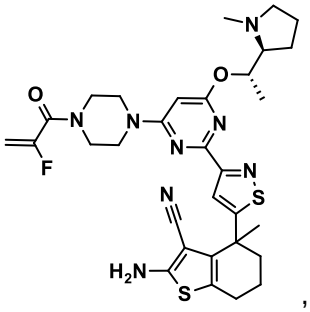
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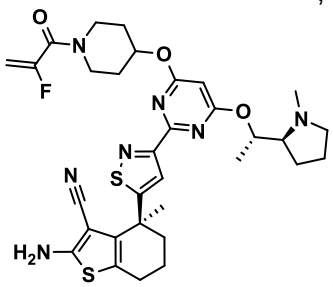
Ib-13

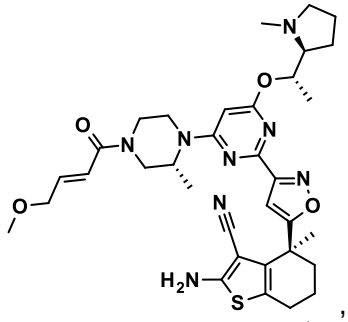


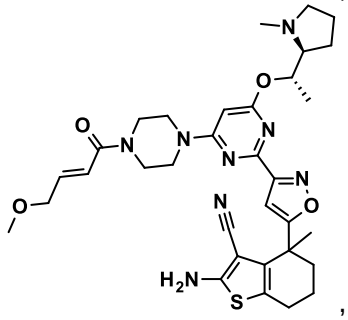
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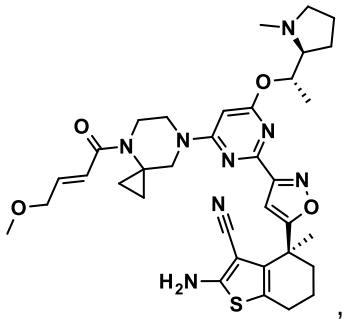
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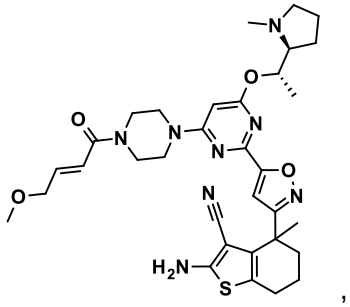
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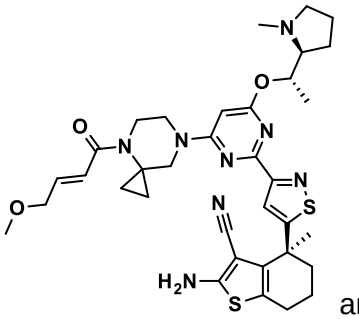
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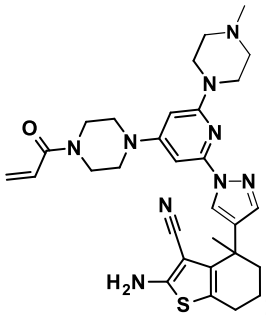
Ib-14 ,

Ib-15 ,

Ib-16 ,

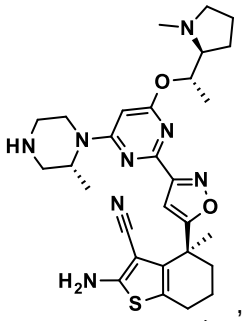
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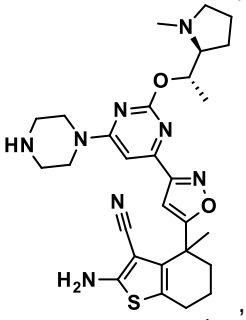
Id-9 and

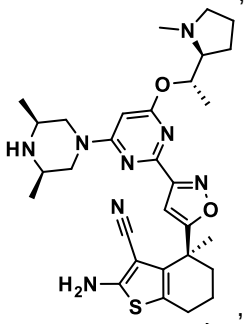
Ie-1 ;

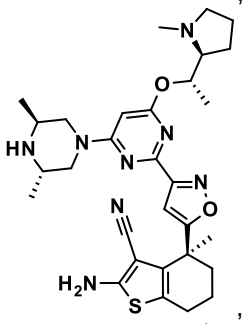
or a salt thereof.

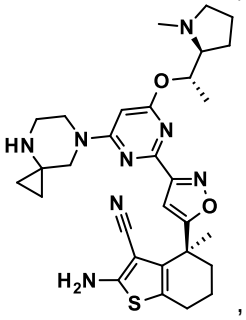
21. A compound according to claim 5 selected from the group consisting of

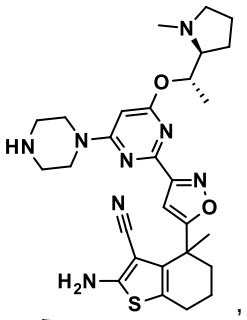
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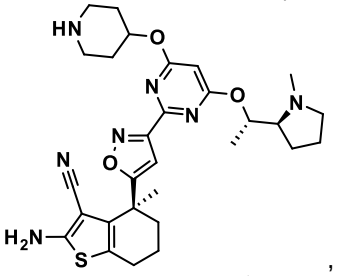
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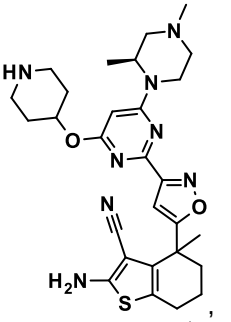
C-4c ,

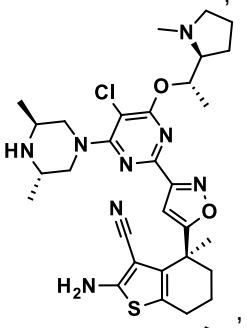
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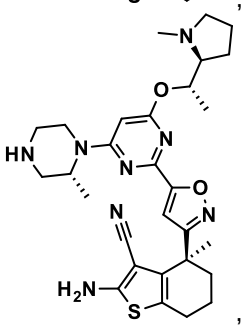
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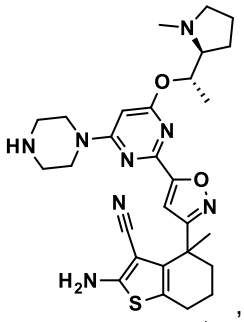
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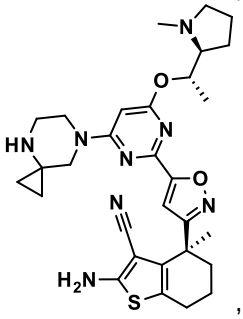
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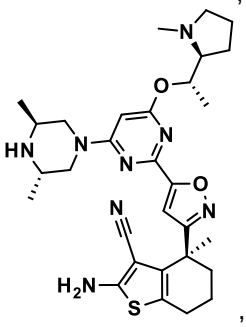
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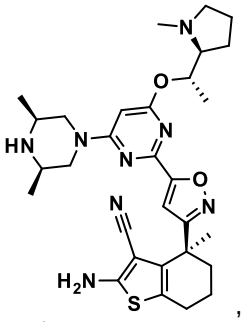
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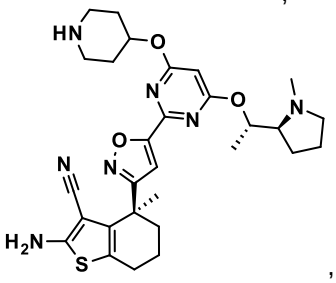
C-5a ,

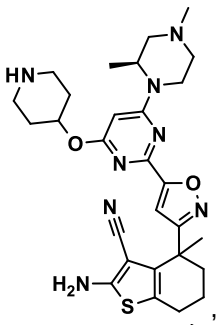
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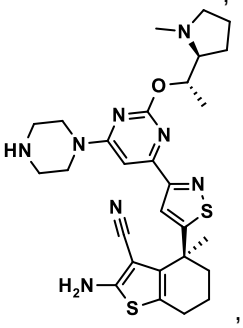
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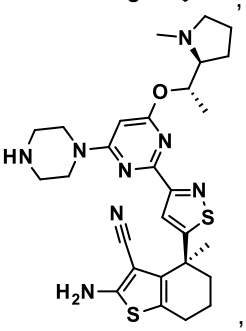
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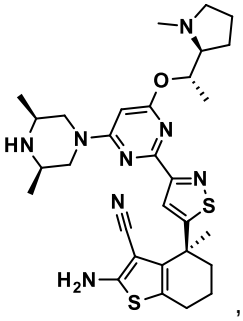
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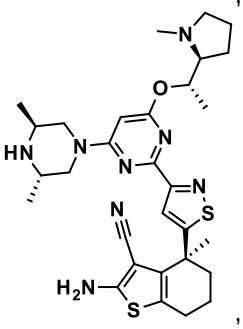
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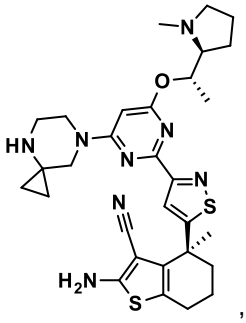
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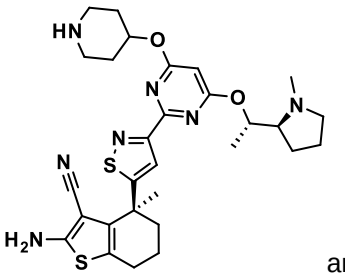
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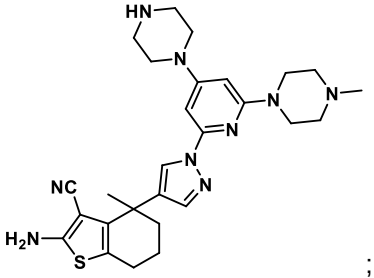
C-7b ,

C-7c ,

C-7d ,

C-7e ,

C-7f  and

D-7a ;

or a salt thereof.

22. A compound according to any one of claim 1 to 21 – or a pharmaceutically acceptable salt thereof – for use as a medicament.

23. Use of a compound according to any one of claim 1 to 21 – or a pharmaceutically acceptable salt thereof –in the manufacture of a medicament for the treatment and/or prevention of cancer.

24. The use according to claim 23, wherein said compound or salt is to be administered before, after or together with one or more other pharmacologically active substance(s).

25. The use according to claim 23 or 24, wherein the cancer is selected from the group consisting of pancreatic cancer, lung cancer, colorectal cancer, cholangiocarcinoma, appendiceal cancer, multiple myeloma, melanoma, uterine cancer, endometrial cancer, thyroid cancer, acute myeloid leukaemia, bladder cancer, urothelial cancer, gastric cancer, cervical cancer, head and neck squamous cell carcinoma, diffuse large B cell lymphoma, oesophageal cancer, chronic lymphocytic leukaemia, hepatocellular cancer, breast cancer, ovarian cancer, prostate cancer, glioblastoma, renal cancer and sarcoma.

26. A pharmaceutical composition comprising a compound according to any one of claim 1 to 21 – or a pharmaceutically acceptable salt thereof – and one or more pharmaceutically

acceptable excipient(s).

27. A pharmaceutical composition comprising a compound according to any one of claim 1 to 21 – or a pharmaceutically acceptable salt thereof – and one or more other pharmacologically active substance(s).