Pan-TEAD Inhibitors and Methods Thereof

Technical Field

The present disclosure relates, in general terms, to pan-TEAD inhibitors and methods thereof.

Background

Non-Small Cell Lung Cancer (NSCLC) is a form of lung cancer, including adenocarcinoma, squamous cell carcinoma, and large cell carcinoma. NSCLC is a highly prevalent and challenging form of lung cancer, with smoking being a leading risk factor. It accounts for approximately 85% of all lung cancer cases. The EGFR mutation is one of the most common mutations in NSCLC, posing challenges despite available anti-EGFR treatments.

NSCLC is a critical and challenging disease that requires a multidisciplinary approach for diagnosis and treatment. Various genetic mutations also characterize NSCLC that play a significant role in development and progression. For instance, EGFR mutations by exon 19 deletion and L858R point mutation, are common in NSCLC and responsive to targeted therapies only.

Researchers have been constantly trying to come up with newly designed molecules as well as repurposing the already existing treatment options to curb this menace. There are multiple inhibitors being used to treat various forms of mutations. For example: FDA has approved Dacomitinib, Erlotinib, Gefitinib, and Osimertinib to target EGFR exon 19 deletion mutation. Amivantamab-vmjw, mobocertinib to target EGFR exon 20 insertion mutation, Osimertinib to target EGFR exon T790M mutation as well as afatinib as an oral medication for certain metastatic tumors.

Despite multiple mutant specific targeted therapy, majority of these drugs do not improve the progression free survival rate to a greater extent. Osimertinib is a third generation EGFR-tyrosine kinase inhibitor (TKI) that potently and selectively inhibits both EGFR 19 deletion and T790M resistance mutations and enhance the PFA up to 20.5 months, which was almost two-fold higher than results achieved with erlotinib or gefitinib.

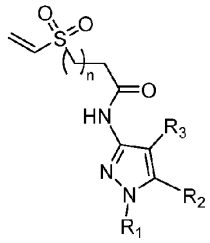
The major challenges of these drugs are the development of drug resistance either by

harbouring allele specific additional mutation or by modulation of oncogenic signalling and reliance on other signalling pathways, actively involved in the process of tumorigenesis and development of drug resistance. Indeed, overexpression of TEADs can lead to genetic mutations and alterations as well as activating the EGFR-RAS-RAF-MAPK pathway, leading to oncogenesis. Growing body evidence suggest a strong potential of targeting TEAD driven YAP/TAZ signalling complex as the possible option to regress EGFR and other tumors as well as to break the stemness of carcinogenesis and development of drug resistance.

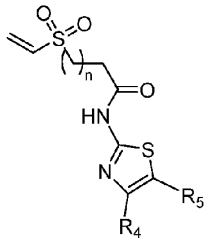
It would be desirable to overcome or ameliorate at least one of the above-described problems.

Summary

The present disclosure provides a method of treating NF2, EGFR and/or KRAS/G12C mutated cancer and/or tumor in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of Formula (I) or (II) or a pharmaceutically acceptable salt, solvate or prodrug thereof:



(I)



(II)

wherein

n is an integer selected from 1 to 5;

R_1 is selected from optionally substituted aryl, optionally substituted heteroaryl or optionally substituted cycloalkyl;

R_2 is selected from H, or optionally substituted alkyl;

R_3 is selected from optionally substituted aryl, optionally substituted heteroaryl, optionally substituted alkyl;

R_4 is selected from optionally substituted aryl, optionally substituted heteroaryl or optionally substituted cycloalkyl; and

R_5 is selected from optionally substituted aryl, optionally substituted heteroaryl, optionally substituted alkyl.

The present disclosure also provides a compound of Formula (I) or (II) or a pharmaceutically acceptable salt, solvate or prodrug thereof for use in treating NF2, EGFR and/or KRAS/G12C mutated cancer and/or tumor.

The present disclosure also provides a use of compound of Formula (I) or (II) or a pharmaceutically acceptable salt, solvate or prodrug thereof in the manufacture of a medicament for the treatment of NF2, EGFR and/or KRAS/G12C mutated cancer and/or tumor.

The present disclosure also provides a method of treating NF2, EGFR and/or KRAS/G12C mutated cancer and/or tumor in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of Formula (I) in combination with a EGFR inhibitor and/or a KRAS/G12C inhibitor.

The present disclosure a compound of Formula (I) or (II) or a pharmaceutically acceptable salt, solvate or prodrug thereof in combination with a EGFR inhibitor and/or a KRAS/G12C inhibitor for use in treating NF2, EGFR and/or KRAS/G12C mutated cancer and/or tumor.

The present disclosure also provides a use of compound of Formula (I) or (II) or a pharmaceutically acceptable salt, solvate or prodrug thereof and a EGFR inhibitor and/or a KRAS/G12C inhibitor in the manufacture of a medicament for the treatment of NF2, EGFR and/or KRAS/G12C mutated cancer and/or tumor.

The present disclosure also provides a use of compound of Formula (I) or (II) or a pharmaceutically acceptable salt, solvate or prodrug thereof in the manufacture of a medicament for the treatment of NF2, EGFR and/or KRAS/G12C mutated cancer and/or tumor to be used in combination with a EGFR inhibitor and/or a KRAS/G12C inhibitor.

In some embodiments, the NF2 and/or EGFR mutated cancer and/or tumor is selected

from solid tumor, gastric cancer (mesenchymal- subtype GC), non-small cell lung cancer (NSCLC), glioblastoma and mesothelioma, and NF2 deficient mesothelioma.

In some embodiments, the EGFR inhibitor is selected from amivantamab-vmjw, mobocertinib, osimertinib, afatinib, erlotinib, gefitinib, BI-8128, tarloxin-TKI or a combination thereof. In some embodiments, the EGFR inhibitor is osimertinib.

In some embodiments, the NF2 and/or EGFR mutated cancer and/or tumor is characterised by a resistance to a EGFR inhibitor.

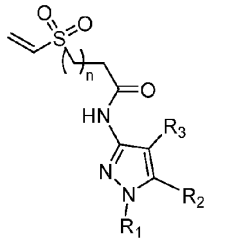
In some embodiments, the KRAS/G12C mutated cancer and/or tumor is selected from colorectal cancer (CRC), pancreatic ductal adenocarcinoma (PDAC), and non-small cell lung cancer (NSCLC).

In some embodiments, the KRAS/G12C inhibitor is selected from Sotorasib and/or Adagrasib.

In some embodiments, the KRAS/G12C mutated cancer and/or tumor is characterised by a resistance to a KRAS/G12C inhibitor.

In some embodiments, R_1 is selected from optionally substituted phenyl, optionally substituted naphthalenyl, or optionally substituted heteroaryl.

The present disclosure also provides a compound of Formula (Ia) or a salt, or solvate thereof:



(Ia)

wherein

n is an integer selected from 1 to 5;

R_1 is selected from optionally substituted aryl, optionally substituted heteroaryl;

R_2 is selected from H, or optionally substituted alkyl; and
R_3 is selected from optionally substituted aryl, optionally substituted heteroaryl, optionally substituted alkyl.

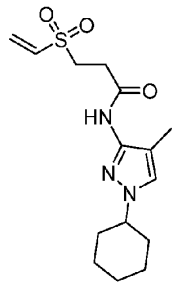
In some embodiments, R_1 is selected from phenyl substituted with haloalkyl, optionally substituted naphthalenyl, or optionally substituted heteroaryl.

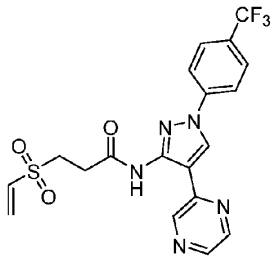
In some embodiments, R_2 is H.

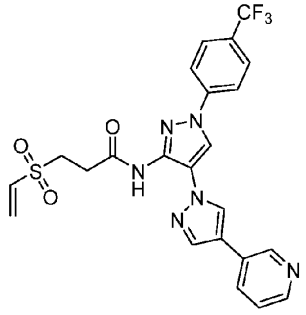
In some embodiments, R_3 is selected from optionally substituted phenyl, optionally substituted N-heteroaryl.

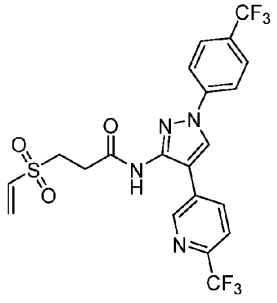
In some embodiments, n is 1.

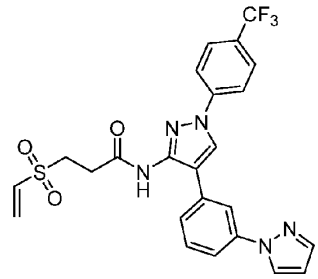
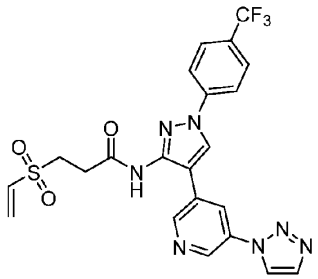
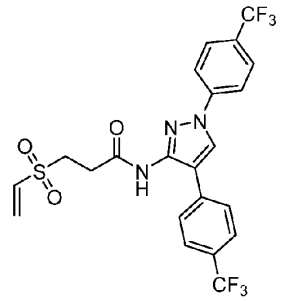
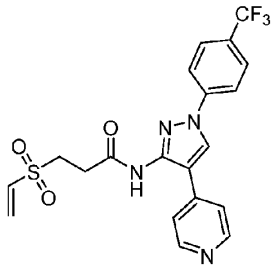
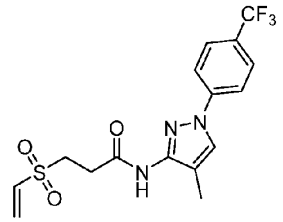
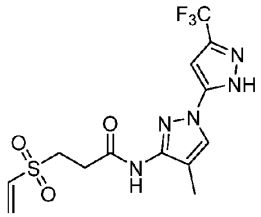
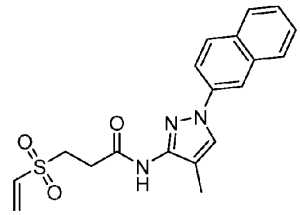
The compound of Formula (I) may be selected from:





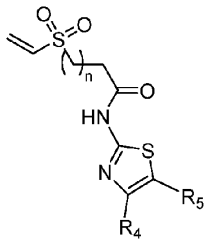




.

The present disclosure also provides a compound of Formula (II) or a salt, or solvate thereof:



(II)

wherein

n is an integer selected from 1 to 5;

R_4 is selected from optionally substituted aryl, optionally substituted heteroaryl or optionally substituted cycloalkyl; and

R_5 is selected from optionally substituted aryl, optionally substituted heteroaryl, optionally substituted alkyl.

In some embodiments, R_4 is selected from phenyl substituted with haloalkyl, optionally substituted naphthalenyl, or optionally substituted heteroaryl.

In some embodiments, R_5 is selected from optionally substituted phenyl, optionally substituted N-heteroaryl.

The present disclosure also concerns a pharmaceutical composition comprising an effective amount of a compound of Formula (I) or (II) or a pharmaceutically acceptable salt, solvate or prodrug thereof, optionally in combination with a pharmaceutically acceptable carrier, excipient or diluent.

Brief description of the drawings

Embodiments of the present invention will now be described, by way of non-limiting example, with reference to the drawings in which:

Figure 1 shows the generation of stable cell lines.

Figure 2 shows Compound B (CPD10) and Compound C (CPD13) significantly downregulate phospho-EGFR in mutant cells.

Figure 3 shows Compound B (CPD10) and Compound C (CPD13) inhibit cellular proliferation in EGFR mutant cancer cell line.

Figure 4 shows Compound B (CPD10) in combination with Osimertinib acts synergistically

to inhibit cellular proliferation in EGFR mutant cancer cell lines.

Figure 5 shows Compound B (CPD10) and Compound C (CPD13) sensitizes mutant EGFR cancer cell lines and act synergistically in combination with EGFR inhibitors.

Figure 6 shows Compound B (CPD10) evaluation across EGFR mutant BBM cell lines

Figure 7 shows Compound D (CPD21) evaluation across EGFR mutant BBM cell lines.

Figure 8 shows Compound F (CPD23) evaluation across EGFR mutant BBM cell lines.

Figure 9 shows evaluation of compounds in combination with osimertinib (OSM).

Figure 10 shows evaluation of compounds in combination with osimertinib (OSM).

Figure 11 shows evaluation of compounds in combination with osimertinib (OSM).

Figure 12 shows evaluation of compounds in combination with osimertinib (OSM).

Figure 13 shows evaluation of compounds in EGFR mutant BBM lung cancer cell lines.

Figure 14 shows evaluation of 2μM compounds in combination with Osimertinib in EGFR mutant BBM lung cancer cell lines.

Figure 15 shows that the compounds target H1975 cells with EGFR-L858R/T790M mutation.

Figure 16 shows the compounds may overcome drug resistance and sensitize EGFR mutant NSCLC.

Figure 17 shows that the compounds target KRAS/G12C mutant cancer cells and synergise with sotorasib in targeting resistant cancer cells.

Figure 18 shows that the compounds synergize with the sotorasib in targeting resistant KRAS-G12C mutant cancer cells.

Detailed description

"Alkyl" refers to monovalent alkyl groups which may be straight chained or branched and preferably have from 1 to 10 carbon atoms or more preferably 1 to 6 carbon atoms. Examples of such alkyl groups include methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *n*-hexyl, and the like.

"Alkenyl" refers to a monovalent alkenyl group which may be straight chained or branched and preferably have from 2 to 10 carbon atoms and more preferably 2 to 6 carbon atoms and have at least 1 and preferably from 1-2, carbon to carbon, double bonds. Examples include ethenyl (-CH=CH_2), *n*-propenyl (-CH_2CH=CH_2), *iso*-propenyl (-C(CH_3)=CH_2), but-2-enyl (-CH_2CH=CHCH_3), and the like.

"Halo" or "halogen" refers to fluoro, chloro, bromo and iodo.

"Oxo/hydroxy" refers to groups =O, HO-.

"Aryl" refers to an unsaturated aromatic carbocyclic group having a single ring (eg. phenyl) or multiple condensed rings (eg. naphthyl or anthryl), preferably having from 6 to 14 carbon atoms. Examples of aryl groups include phenyl, naphthyl and the like.

"Heteroaryl" refers to a monovalent aromatic heterocyclic group which fulfils the Hückel criteria for aromaticity (ie. contains 4n + 2 π electrons) and preferably has from 2 to 10 carbon atoms and 1 to 4 heteroatoms selected from oxygen, nitrogen, selenium, and sulfur within the ring (and includes oxides of sulfur, selenium and nitrogen). Such heteroaryl groups can have a single ring (eg. pyridyl, pyrrolyl or N-oxides thereof or furyl) or multiple condensed rings (eg. indolizinyl, benzoimidazolyl, coumarinyl, quinolinyl, isoquinolinyl or benzothienyl).

Examples of heteroaryl groups include, but are not limited to, oxazole, pyrrole, imidazole, pyrazole, pyridine, pyrazine, pyrimidine, pyridazine, indolizine, isoindole, indole, indazole, purine, isoquinoline, quinoline, phthalazine, naphthylpyridine, quinoxaline, quinazoline, cinnoline, pteridine, carbazole, carboline, phenanthridine, acridine, phenanthroline, isothiazole, phenazine, isoxazole, isothiazole, phenoxazine, phenothiazine, thiazole, thiadiazoles, oxadiazole, oxatriazole, tetrazole, thiophene, benzo[b]thiophene, triazole, imidazopyridine and the like.

"Heterocyclyl" refers to a monovalent saturated or unsaturated group having a single ring or multiple condensed rings, preferably from 1 to 8 carbon atoms and from 1 to 4 hetero atoms selected from nitrogen, sulfur, oxygen, selenium or phosphorous within the ring. The most preferred heteroatom is nitrogen. It will be understood that where, for instance, R_2 or R' is an optionally substituted heterocyclyl which has one or more ring heteroatoms, the heterocyclyl group can be connected to the core molecule of the compounds of the present invention, through a C-C or C-heteroatom bond, in particular a C-N bond.

Examples of heterocyclyl and heteroaryl groups include, but are not limited to, oxazole, pyrrole, imidazole, pyrazole, pyridine, pyrazine, pyrimidine, pyridazine, indolizine, isoindole, indole, indazole, purine, quinolizine, isoquinoline, quinoline, phthalazine, naphthylpyridine, quinoxaline, quinazoline, cinnoline, pteridine, carbazole, carboline,

phenanthridine, acridine, phenanthroline, isothiazole, phenazine, isoxazole, isothiazole, phenoxazine, phenothiazine, imidazolidine, imidazoline, piperidine, piperazine, indoline, phthalimide, 1,2,3,4-tetrahydroisoquinoline, 4,5,6,7-tetrahydrobenzo[b]thiophene, thiazole, thiadiazoles, oxadiazole, oxatriazole, tetrazole, thiazolidine, thiophene, benzo[b]thiophene, morpholino, piperidinyl, pyrrolidine, tetrahydrofuranyl, triazole, and the like.

"Amino" refers to the group –NR"R" where each R" is independently hydrogen, alkyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl and where each of alkyl, cycloalkyl, aryl, heteroaryl and heterocyclyl is as described herein.

In this specification "optionally substituted" is taken to mean that a group may or may not be further substituted or fused (so as to form a condensed polycyclic group) with one or more groups selected from hydroxyl, acyl, alkyl, alkoxy, alkenyl, alkenyloxy, alkynyl, alkynyloxy, amino, aminoacyl, thio, arylalkyl, arylalkoxy, aryl, aryloxy, carboxyl, acylamino, cyano, halogen, nitro, phosphono, sulfo, phosphorylamino, phosphinyl, heteroaryl, heteroarylalkyl, heteroaryloxy, heterocyclyl, heterocyclylalkyl, heterocyclyloxy, oxyacyl, oxime, oxime ether, hydrazone, oxyacylamino, oxysulfonylamino, aminoacyloxy, trihalomethyl, trialkylsilyl, pentafluoroethyl, trifluoromethoxy, difluoromethoxy, trifluoromethanethio, trifluoroethenyl, mono- and di-alkylamino, mono-and di-(substituted alkyl)amino, mono- and di-arylamino, mono- and di-heteroarylamino, mono- and di-heterocyclyl amino, and unsymmetric di-substituted amines having different substituents selected from alkyl, aryl, heteroaryl and heterocyclyl, and the like, and may also include a bond to a solid support material, (for example, substituted onto a polymer resin). For instance, an "optionally substituted amino" group may include amino acid and peptide residues.

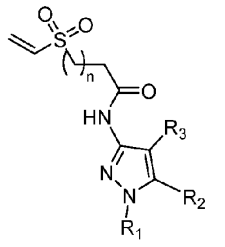
Up-regulation of the Hippo pathway effector TAZ renders lung adenocarcinoma cells harbouring EGFR-T790M mutation resistant to gefitinib. Study have shown that TAZ is a novel gene mediating tumorigenesis and EMT correlated with gefitinib sensitivity of lung adenocarcinoma cells harbouring EGFR T790M mutation.

The present disclosure is predicated on the understanding that patients may be sensitized for treatment of EGFR-TKI-resistant lung cancers. This may be done using Pan-TEAD inhibitors which hijack the conserved cysteine of the TEAD and disrupting oncogenic phospho-EGFR, disrupting mutant specific oncogenic EGFR signaling, and sensitizing EGFR

mutant cancer cell lines. The Pan-TEAD inhibitor may be combined with EGFR inhibitor (such as osimertinib), which shows a massive synergistic effect on cellular sensitization. By docking studies, a library of small molecule inhibitors were designed and synthesized.

In siRNA depletion experiments, it was found that the TEAD1 and TEAD4 are the key regulator of the phosphorylated EGFR in mutant overexpressing cells. Further, TEAD3 and TEAD4 has some role in regulating phosphorylated EGFR in wild type EGFR overexpressing cells. Thus, it is believed that Pan-TEAD inhibitors may be used reliably as a therapeutic approach.

The present disclosure provides a method of treating neurofibromatosis type 2 (NF2), epidermal growth factor receptor (EGFR) and/or KRAS/G12C mutated cancer and/or tumor in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt, solvate or prodrug thereof:



(I)

wherein

n is an integer selected from 1 to 5;

R_1 is selected from optionally substituted aryl, optionally substituted heteroaryl or optionally substituted cycloalkyl;

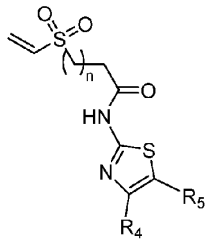
R_2 is selected from H, or optionally substituted alkyl; and

R_3 is selected from optionally substituted aryl, optionally substituted heteroaryl, optionally substituted alkyl.

In some embodiments, the method is for treating neurofibromatosis type 2 (NF2), and/or epidermal growth factor receptor (EGFR) mutated cancer and/or tumor.

The present disclosure provides a method of treating NF2, EGFR and/or KRAS/G12C mutated cancer and/or tumor in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of Formula (II) or a

pharmaceutically acceptable salt, solvate or prodrug thereof:



(II)

wherein

n is an integer selected from 1 to 5;

R_4 is selected from optionally substituted aryl, optionally substituted heteroaryl or optionally substituted cycloalkyl; and

R_5 is selected from optionally substituted aryl, optionally substituted heteroaryl, optionally substituted alkyl.

In some embodiments, the method is for treating neurofibromatosis type 2 (NF2), and/or epidermal growth factor receptor (EGFR) mutated cancer and/or tumor.

EGFR mutant is one of the major contributors of more aggressive forms of tumour. Upon exposure to therapeutic agents, cancer cells acquire allele specific mutations and adaptation to develop resistance. Hippo pathway components at the heart of the oncogenic signaling fuel to process of tumorigenesis. The compounds of Formula (I) and (II) are found to bind to all TEADs (TEAD1, TEAD2, TEAD3 and TEAD4) to a great extent. This binding leads to disruption of TEAD driven YAP/TAZ signaling and repression of transcriptional target genes such as AXL, CYR61 and CTGF. Drug induced downregulation of phospho-EGFR, phospho-AXL, YAP, and TAZ protein leads to cellular sensitization in EGFR mutant tumors.

Expression of AXL has been known to be highly upregulated in EGFR mutant cancer cell lines and fuel the process of carcinogenesis. In lung cancer, AXL interacts with EGFR and HER3 to maintain the activations status of downstream signal pathway, which confers intrinsic resistance to osmertinib in NSCLC.

The compounds may be used for treating cancer and/or tumor with drug resistance due to either loss of NF2 and/or hyperactivation of hippo singaling components. The NF2 tumor suppressor gene is a frequent somatically mutated gene in mesothelioma, with 30%–40%

mesotheliomas showing NF2 inactivation. NF2 encodes merlin, a member of the ezrin, radixin, and moesin (ERM) family of proteins that regulate cytoskeleton and cell signaling. Recent genome analysis revealed that NF2 alteration may be a late event in mesothelioma development, suggesting that NF2 mutation confers a more aggressive phenotype to mesothelioma cells and may not be directly caused by asbestos exposure. The Hippo tumor-suppressive and mTOR prooncogenic signaling pathways are crucial cell-signaling cascades regulated by merlin.

TEAD inhibitors may be used as an effective therapy to target neurofibromin 2 (NF2) mutant cancers. This is based on cell line data from 2 NF2 mutant cancer cell lines (as the monotherapy). Mutations in NF2 have been noted in EGFR TKI-resistant NSCLC. In this regard, TEAD inhibitors may be used to sensitize any similar drug resistant NSCLC.

Kirsten rat sarcoma (KRAS) gene belongs to a member of the RAS family and its mutations are genetic drivers of multiple cancer types, especially colorectal cancer (CRC), pancreatic ductal adenocarcinoma (PDAC), and non-small cell lung cancer (NSCLC). KRAS-G12 mutations (89%) predominate in human cancers, followed by G13 (9%) and Q61 (1%) mutations [6]. Furthermore, the G12D mutation is the most common mutation among three common G12C (14%), G12D (36%), and G12V (23%) mutations. Compared with G12D which plays a major role in PDAC, G12C is the most common mutation subtype in NSCLC (13%).

KRAS protein is a signaling GTPase that switches between the active GTP-bound and inactive GDP-bound conformations. Guanine nucleotide exchange factors (GEF) promote the exchange of GDP to GTP on KRAS, whereas GTPase-activating proteins (GAP) favor the exchange of GTP to GDP. The activation of receptor tyrosine kinases (RTKs) on the plasma membrane, such as epidermal growth factor receptor (EGFR) family, initiates KRAS activation and subsequent multiple effector pathways, especially mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3-kinase (PI3K) pathways. As the downstream of RTKs, SOS Ras/Rac guanine nucleotide exchange factor 1 (SOS1) and protein tyrosine phosphatase non-receptor type 11 (PTPN11, best known as SHP2) promote the ratio of GDP-GTP exchange, leading to KRAS activation. Comparing the GTP- and GDP-bound structures of KRAS identified two regions, called switch-I and switch-II. The mutant cysteine 12 is located next to the pocket (P2) in the switch-II region. Compared with the wild-type, the KRAS mutation disrupts the guanine exchange cycle, thereby locking it in an active GDP-bound form that drives pro-tumorigenic signals.

The present disclosure also provides a compound of Formula (I), (II) or a pharmaceutically acceptable salt, solvate or prodrug thereof for use in treating NF2, EGFR and/or KRAS/G12C mutated cancer and/or tumor.

The present disclosure also provides a use of compound of Formula (I), (II) or a pharmaceutically acceptable salt, solvate or prodrug thereof in the manufacture of a medicament for the treatment of NF2, EGFR and/or KRAS/G12C mutated cancer and/or tumor.

The present disclosure also provides a method of treating NF2, EGFR and/or KRAS/G12C mutated cancer and/or tumor in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of Formula (I), (II) in combination with a EGFR inhibitor and/or a KRAS/G12C inhibitor.

Data presented in a recent finding have shown that the synergistic effect of AXL and EGFR inhibitors is attenuated by LATS1/2 KO-mediated YAP hyperactivation, thus providing evidence that YAP inhibition represents a necessary downstream target of AXL/EGFR co-inhibition. These findings support the approach of targeting both EGFR and AXL simultaneously may effectively suppress tumour growth and prevent resistance and relapse in patients with EGFR-altered cancers, including HNSCC and lung adeno-carcinoma.

The present disclosure a compound of Formula (I), (II) or a pharmaceutically acceptable salt, solvate or prodrug thereof in combination with a EGFR inhibitor and/or a KRAS/G12C inhibitor for use in treating NF2, EGFR and/or KRAS/G12C mutated cancer and/or tumor.

The present disclosure also provides a use of compound of Formula (I), (II) or a pharmaceutically acceptable salt, solvate or prodrug thereof and a EGFR inhibitor and/or a KRAS/G12C inhibitor in the manufacture of a medicament for the treatment of NF2, EGFR and/or KRAS/G12C mutated cancer and/or tumor.

The present disclosure also provides a use of compound of Formula (I), (II) or a pharmaceutically acceptable salt, solvate or prodrug thereof in the manufacture of a medicament for the treatment of NF2, EGFR and/or KRAS/G12C mutated cancer and/or tumor to be used in combination with a EGFR inhibitor and/or a KRAS/G12C inhibitor.

The present disclosure also provides a use of EGFR inhibitor and/or a KRAS/G12C inhibitor in the manufacture of a medicament for the treatment of NF2, EGFR and/or KRAS/G12C mutated cancer and/or tumor to be used in combination with a compound of Formula (I), (II) or a pharmaceutically acceptable salt, solvate or prodrug thereof.

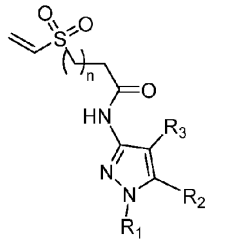
In some embodiments, the NF2 and/or EGFR mutated cancer and/or tumor is selected from solid tumor, gastric cancer (mesenchymal- subtype GC), non-small cell lung cancer (NSCLC), glioblastoma and mesothelioma, and NF2 deficient mesothelioma. In some embodiments, the KRAS/G12C mutated cancer and/or tumor is selected from colorectal cancer (CRC), pancreatic ductal adenocarcinoma (PDAC), and non-small cell lung cancer (NSCLC).

In some embodiments, the EGFR inhibitor is selected from amivantamab-vmjw, mobocertinib, osimertinib, afatinib, erlotinib, gefitinib, BI-8128, tarloxin-TKI or a combination thereof. In some embodiments, the EGFR inhibitor is osimertinib.

In some embodiments, the KRAS/G12C inhibitor is selected from Sotorasib and/or Adagrasib.

In some embodiments, the NF2 and/or EGFR mutated cancer and/or tumor is characterised by a resistance to a EGFR inhibitor. In some embodiments, the KRAS/G12C mutated cancer and/or tumor is characterised by a resistance to a KRAS/G12C inhibitor.

In some embodiments, the compound of Formula (I) is



(I)

wherein

n is an integer selected from 1 to 5;

R_1 is selected from optionally substituted aryl, optionally substituted heteroaryl or optionally substituted cycloalkyl;

R_2 is selected from H, or optionally substituted alkyl; and
R_3 is selected from optionally substituted aryl, optionally substituted heteroaryl, optionally substituted alkyl.

Based on structure-activity relationship (SAR) studies, the inventors have found that certain moieties when present allows for a strong inhibitory effect against protein-protein interactions between YAP1/TAZ and TEAD. The compound of Formula (I) has a cysteine warhead (vinyl sulfone) that targets TEAD cysteine (Cys359) located in the palmitate-binding pocket of TEAD. The compounds are optimised to interact with the polar residues near the entrance of the pocket. The compounds were identified via in-house systematic rational analysis of available TEAD crystal structures, and the insights from the analysis were derived and matured in-house. These compounds were found to be Pan-TEAd inhibitor so can be used in a broad range of tumors either as a mono therapy or combination therapy.

Further, the hydrophobic pocket of TEAD may be targeted. For example, it was found that the large pocket of TEAD offers the possibility of a Y-shaped inhibitor. In this regard, the pyrazole moiety was found to be appropriately sized with good electron distribution density. By having R_1 as an electron rich and/or hydrophobic moiety, and/or R_3 as a bulky and/or hydrophobic moiety, the complexation of the inhibitor to TEAD is improved. With improved binding, the potency of compounds of Formula (I) is enhanced.

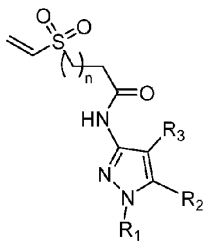
In some embodiments, R_1 is selected from optionally substituted aryl, optionally substituted cycloalkyl, optionally substituted heterocyclyl, and optionally substituted heteroaryl. In some embodiments, R_1 is selected from optionally substituted cycloalkyl, or optionally substituted aryl. In some embodiments, R_1 is selected from optionally substituted phenyl and optionally substituted cyclohexyl. In some embodiments, R_1 is selected from phenyl and cyclohexyl. In some embodiments, R_1 is selected from optionally substituted aryl, optionally substituted heteroaryl. In some embodiments, R_1 is selected from optionally substituted phenyl, optionally substituted naphthalenyl, or optionally substituted heteroaryl. In some embodiments, R_1 is selected from optionally substituted phenyl, optionally substituted naphthalenyl, or optionally substituted N-heteroaryl. In some embodiments, R_1 is selected from optionally substituted phenyl, optionally substituted naphthalenyl, or optionally substituted pyrazolyl.

In some embodiments, the optional substituent is selected from halo, oxo, optionally

substituted alkyl, optionally substituted alkoxy, optionally substituted alkyenyl and optionally substituted amino. In some embodiments, the optional substituent is selected from optionally substituted C_1-C_5 alkyl, optionally substituted C_1-C_5 alkoxy and optionally substituted C_2-C_5 alkyenyl. In some embodiments, the optional substituent is selected from C_1-C_5 alkyl, C_1-C_5 alkoxy and C_2-C_5 alkyenyl.

In some embodiments, the optional substituent on R_1 is selected from alkyl or haloalkyl. In some embodiments, the optional substituent on R_1 is selected from C_1-C_5 alkyl or C_1-C_5 haloalkyl.

Accordingly, the present disclosure provides a compound of Formula (Ia) or a salt, solvate or prodrug thereof:



(Ia)

wherein

n is an integer selected from 1 to 5;

R_1 is selected from optionally substituted aryl, optionally substituted heteroaryl;

R_2 is selected from H, or optionally substituted alkyl; and

R_3 is selected from optionally substituted aryl, optionally substituted heteroaryl, optionally substituted alkyl.

In some embodiments, R_2 is selected from H, or optionally substituted alkyl. In some embodiments, R_2 is H. In some embodiments, R_2 is optionally substituted C_1-C_5 alkyl. In some embodiments, R_2 is C_1-C_5 alkyl. In some embodiments, the alkyl is methyl, ethyl, n-propyl or iso-propyl. In some embodiments, the alkyl is methyl.

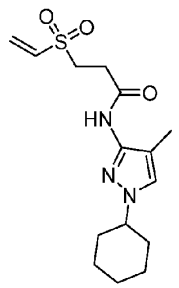
In some embodiments, R_3 is selected from optionally substituted aryl, optionally substituted heteroaryl. In some embodiments, R_3 is selected from optionally substituted phenyl, optionally substituted N-heteroaryl. In some embodiments, R_3 is selected from

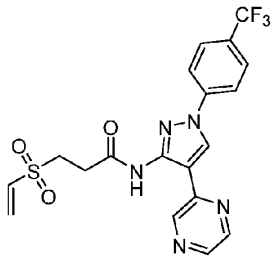
optionally substituted phenyl, optionally substituted pyrimidinyl, optionally substituted pyrazolyl, optionally substituted pyridinyl.

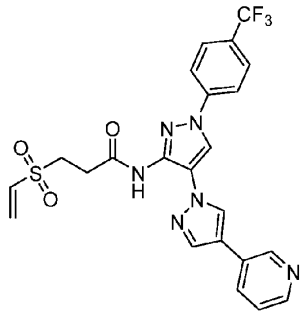
In some embodiments, the optional substituent is selected from halo, oxo, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted alkyenyl, optionally substituted amino, optionally substituted heteroaryl optionally substituted heterocyclyl. In some embodiments, the optional substituent is selected from C_1-C_5 alkyl, C_1-C_5 haloalkyl, N-heteroaryl, and N-heterocyclyl. In some embodiments, the optional substituent is selected from C_1-C_5 alkyl, C_1-C_5 haloalkyl, pyridinyl, pyrazolyl, and triazolyl.

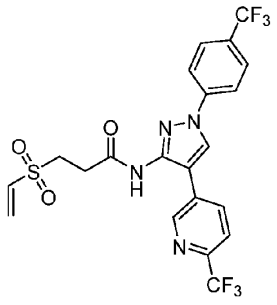
In some embodiments, n is an integer selected from 2 to 5, 3 to 5, or 4 to 5. In some embodiments, n is an integer selected from 1 to 4, 1 to 3, or 1 to 2. In some embodiments, n is 1.

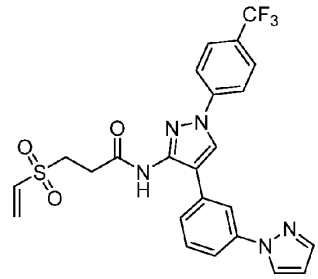
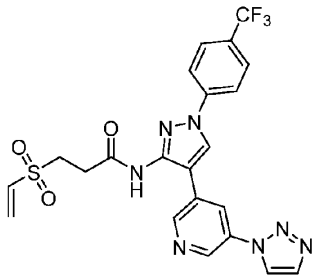
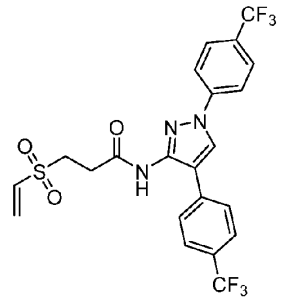
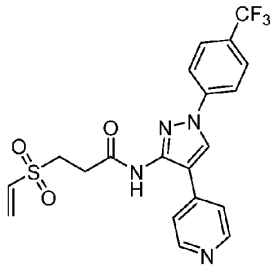
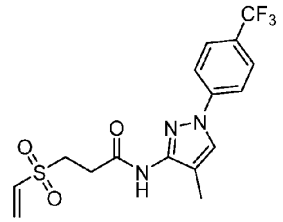
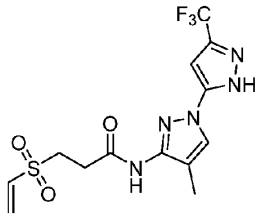
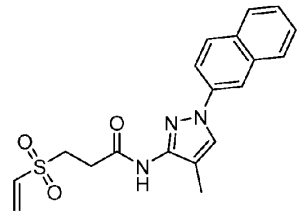
The compound of Formula (I) may be selected from:





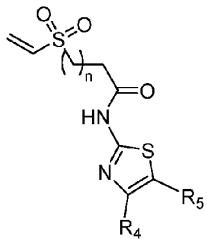




.

In some embodiments, the compound of Formula (II) is:



(II)

wherein

n is an integer selected from 1 to 5;

R_4 is selected from optionally substituted aryl, optionally substituted heteroaryl or optionally substituted cycloalkyl; and

R_5 is selected from optionally substituted aryl, optionally substituted heteroaryl, optionally substituted alkyl.

Based on structure-activity relationship (SAR) studies, the inventors have found that certain moieties when present allows for a strong inhibitory effect against protein-protein interactions between YAP1/TAZ and TEAD. The compound of Formula (II) has a cysteine warhead (vinyl sulfone) that targets TEAD cysteine (Cys359) located in the palmitate-binding pocket of TEAD. The compounds are optimised to interact with the polar residues near the entrance of the pocket. The compounds were identified via in-house systematic rational analysis of available TEAD crystal structures, and the insights from the analysis were derived and matured in-house. These compounds were found to be Pan-TEAD inhibitor so can be used in a broad range of tumors either as a mono therapy or combination therapy.

Further, the hydrophobic pocket of TEAD may be targeted. For example, it was found that the large pocket of TEAD offers the possibility of a Y-shaped inhibitor. In this regard, the thiazole moiety was found to be appropriately sized with good electron distribution density. By having R_4 as an electron rich and/or hydrophobic moiety, and/or R_5 as a bulky and/or hydrophobic moiety, the complexation of the inhibitor to TEAD is improved. With improved binding, the potency of compounds of Formula (II) is enhanced.

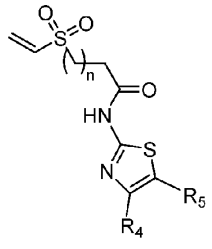
In some embodiments, R_4 is selected from optionally substituted aryl, optionally substituted cycloalkyl, optionally substituted heterocyclyl, and optionally substituted heteroaryl. In some embodiments, R_4 is selected from optionally substituted cycloalkyl, or optionally substituted aryl. In some embodiments, R_4 is selected from optionally

substituted phenyl and optionally substituted cyclohexyl. In some embodiments, R_4 is selected from phenyl and cyclohexyl. In some embodiments, R_4 is selected from optionally substituted aryl, optionally substituted heteroaryl. In some embodiments, R_4 is selected from optionally substituted phenyl, optionally substituted naphthalenyl, or optionally substituted heteroaryl. In some embodiments, R_4 is selected from optionally substituted phenyl, optionally substituted naphthalenyl, or optionally substituted N-heteroaryl. In some embodiments, R_4 is selected from optionally substituted phenyl, optionally substituted naphthalenyl, or optionally substituted pyrazolyl.

In some embodiments, the optional substituent is selected from halo, oxo, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted alkyenyl and optionally substituted amino. In some embodiments, the optional substituent is selected from optionally substituted C_1-C_5 alkyl, optionally substituted C_1-C_5 alkoxy and optionally substituted C_2-C_5 alkyenyl. In some embodiments, the optional substituent is selected from C_1-C_5 alkyl, C_1-C_5 alkoxy and C_2-C_5 alkyenyl.

In some embodiments, the optional substituent on R_4 is selected from alkyl or haloalkyl. In some embodiments, the optional substituent on R_4 is selected from C_1-C_5 alkyl or C_1-C_5 haloalkyl.

In some embodiments, the compound of Formula (II) is a compound of Formula (IIa) is:



(IIa)

wherein

n is an integer selected from 1 to 5;

R_4 is selected from optionally substituted aryl, optionally substituted heteroaryl; and

R_5 is selected from optionally substituted aryl, optionally substituted heteroaryl, optionally substituted alkyl.

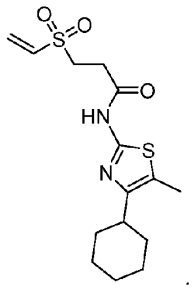
In some embodiments, R_5 is selected from optionally substituted aryl, optionally substituted heteroaryl. In some embodiments, R_5 is selected from optionally substituted

phenyl, optionally substituted N-heteroaryl. In some embodiments, R_5 is selected from optionally substituted phenyl, optionally substituted pyrimidinyl, optionally substituted pyrazolyl, optionally substituted pyridinyl.

In some embodiments, the optional substituent is selected from halo, oxo, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted alkyenyl, optionally substituted amino, optionally substituted heteroaryl optionally substituted heterocyclyl. In some embodiments, the optional substituent is selected from C_1-C_5 alkyl, C_1-C_5 haloalkyl, N-heteroaryl, and N-heterocyclyl. In some embodiments, the optional substituent is selected from C_1-C_5 alkyl, C_1-C_5 haloalkyl, pyridinyl, pyrazolyl, and triazolyl.

In some embodiments, n is an integer selected from 2 to 5, 3 to 5, or 4 to 5. In some embodiments, n is an integer selected from 1 to 4, 1 to 3, or 1 to 2. In some embodiments, n is 1.

The compound of Formula (II) may be selected from:



The present disclosure concerns a modulator of Hippo pathway, comprising a compound of Formula (I) or (II). The compound of Formula (I) or (II) is a modulator of YAP/TAZ-TEAD.

In some embodiments, the modulator is for use *in vitro*. For example, the modulators may be used to treat a cancer cell line, or a tumour excised from an organism. In other embodiments, the modulator is for use *in vivo*.

The present disclosure also concerns a pharmaceutical composition comprising an effective amount of a compound of Formula (I), (Ia), (II), (IIa) or a pharmaceutically acceptable salt, solvate or prodrug thereof, optionally in combination with a pharmaceutically

acceptable carrier, excipient or diluent.

In some embodiments, the pharmaceutical composition further comprises a EGFR inhibitor and/or KRAS/G12C inhibitor.

The compound of the invention can be administered to a subject as a pharmaceutically acceptable salt thereof. Suitable pharmaceutically acceptable salts include, but are not limited to salts of pharmaceutically acceptable inorganic acids such as hydrochloric, sulphuric, phosphoric, nitric, carbonic, boric, sulfamic, and hydrobromic acids, or salts of pharmaceutically acceptable organic acids such as acetic, propionic, butyric, tartaric, maleic, hydroxymaleic, fumaric, maleic, citric, lactic, mucic, gluconic, benzoic, succinic, oxalic, phenylacetic, methanesulphonic, toluenesulphonic, benezenesulphonic, salicyclic sulphanilic, aspartic, glutamic, edetic, stearic, palmitic, oleic, lauric, pantothenic, tannic, ascorbic and valeric acids.

Base salts include, but are not limited to, those formed with pharmaceutically acceptable cations, such as sodium, potassium, lithium, calcium, magnesium, ammonium and alkylammonium. In particular, the present invention includes within its scope cationic salts eg sodium or potassium salts, or alkyl esters (eg methyl, ethyl) of the phosphate group.

Basic nitrogen-containing groups may be quarternised with such agents as lower alkyl halide, such as methyl, ethyl, propyl, and butyl chlorides, bromides and iodides; dialkyl sulfates like dimethyl and diethyl sulfate; and others.

It will be appreciated that any compound that is a prodrug of the compound of formula (I) is also within the scope and spirit of the invention. Thus the compound of the invention can be administered to a subject in the form of a pharmaceutically acceptable pro-drug. The term "pro-drug" is used in its broadest sense and encompasses those derivatives that are converted in vivo to the compound of the invention. Such derivatives would readily occur to those skilled in the art. Other texts which generally describe prodrugs (and the preparation thereof) include: Design of Prodrugs, 1985, H. Bundgaard (Elsevier); The Practice of Medicinal Chemistry, 1996, Camille G. Wermuth et al., Chapter 31 (Academic Press); and A Textbook of Drug Design and Development, 1991, Bundgaard et al., Chapter 5, (Harwood Academic Publishers).

The compound of the invention may be in crystalline form either as the free compound or

as a solvate (e.g. hydrate) and it is intended that both forms are within the scope of the present invention. Methods of solvation are generally known within the art.

The compound of the invention, or a pharmaceutically acceptable salt, solvate or prodrug thereof is administered to the patient in a therapeutically effective amount. As used herein, a therapeutically effective amount is intended to include at least partially attaining the desired effect, or delaying the onset of, or inhibiting the progression of, or halting or reversing altogether the onset or progression of macular degeneration.

As used herein, the term "effective amount" relates to an amount of compound which, when administered according to a desired dosing regimen, provides the desired therapeutic activity. Dosing may occur at intervals of minutes, hours, days, weeks, months or years or continuously over any one of these periods. Suitable dosages may lie within the range of about 0.1 ng per kg of body weight to 1 g per kg of body weight per dosage, such as is in the range of 1 mg to 1 g per kg of body weight per dosage. In one embodiment, the dosage may be in the range of 1 mg to 500 mg per kg of body weight per dosage. In another embodiment, the dosage may be in the range of 1 mg to 250 mg per kg of body weight per dosage. In yet another embodiment, the dosage may be in the range of 1 mg to 100 mg per kg of body weight per dosage, such as up to 50 mg per body weight per dosage.

Suitable dosage amounts and dosing regimens can be determined by the attending physician and may depend on the severity of the condition as well as the general age, health and weight of the patient to be treated.

The compound of the invention may be administered in a single dose or a series of doses. While it is possible for the active ingredient to be administered alone, it is preferable to present it as a composition, preferably as a pharmaceutical composition. The formulation of such compositions is well known to those skilled in the art. The composition may contain any suitable carriers, diluents or excipients. These include all conventional solvents, dispersion media, fillers, solid carriers, coatings, antifungal and antibacterial agents, dermal penetration agents, surfactants, isotonic and absorption agents and the like. It will be understood that the compositions of the invention may also include other supplementary physiologically active agents.

The carrier must be pharmaceutically "acceptable" in the sense of being compatible with

the other ingredients of the composition and not injurious to the patient. The compositions may conveniently be presented in unit dosage form and may be prepared by any methods well known in the art of pharmacy. Such methods include the step of bringing into association the active ingredient with the carrier which constitutes one or more accessory ingredients. In general, the compositions are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both, and then if necessary shaping the product.

Injectables for such use can be prepared in conventional forms, either as a liquid solution or suspension or in a solid form suitable for preparation as a solution or suspension in a liquid prior to injection, or as an emulsion. Carriers can include, for example, water, saline (e.g., normal saline (NS), phosphate-buffered saline (PBS), balanced saline solution (BSS)), sodium lactate Ringer's solution, dextrose, glycerol, ethanol, and the like; and if desired, minor amounts of auxiliary substances, such as wetting or emulsifying agents, buffers, and the like can be added. Proper fluidity can be maintained, for example, by using a coating such as lecithin, by maintaining the required particle size in the case of dispersion and by using surfactants. By way of example, the compound, composition or combination can be dissolved in a pharmaceutically effective carrier and be injected into the vitreous of the eye with a fine gauge hollow bore needle (e.g., 30 gauge, 1/2 or 3/8 inch needle) using a temporal approach (e.g., about 3 to about 4 mm posterior to the limbus for human eye to avoid damaging the lens).

A person skilled in the art will appreciate that other means for injecting and/or administering the compound, composition or combinations to the vitreous of the eye can also be used. These other means can include, for example, intravitreal medical delivery devices. These devices and methods can include, for example, intravitreal medicine delivery devices, and biodegradable polymer delivery members that are inserted in the eye for long term delivery of medicaments. These devices and methods can further include transscleral delivery devices.

Other modes of administration including topical or intravenous administration may also be possible. For example, solutions or suspensions of the compound, composition or combinations of the invention may be formulated as eye drops, or as a membranous ocular patch, which is applied directly to the surface of the eye. Topical application typically involves administering the compound of the invention in an amount between 0.1 ng and 10 mg.

The compound, composition or combinations of the invention may also be suitable for intravenous administration. For example, a compound of formula (I), (II) or a pharmaceutically acceptable salt, solvate or prodrug thereof may be administered intravenously at a dose of up to 16 mg/m^2.

The compound, composition or combinations of the invention may also be suitable for oral administration and may be presented as discrete units such as capsules, sachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary or paste. In another embodiment, the compound of formula (I), (II) or a pharmaceutically acceptable salt, solvate or prodrug is orally administerable.

A tablet may be made by compression or moulding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder (e.g inert diluent, preservative disintegrant (e.g. sodium starch glycolate, cross-linked polyvinyl pyrrolidone, cross-linked sodium carboxymethyl cellulose) surface-active or dispersing agent. Moulded tablets may be made by moulding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredient therein using, for example, hydroxypropylmethyl cellulose in varying proportions to provide the desired release profile. Tablets may optionally be provided with an enteric coating, to provide release in parts of the gut other than the stomach.

The compound, composition or combinations of the invention may be suitable for topical administration in the mouth including lozenges comprising the active ingredient in a flavoured base, usually sucrose and acacia or tragacanth gum; pastilles comprising the active ingredient in an inert basis such as gelatine and glycerin, or sucrose and acacia gum; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

The compound, composition or combinations of the invention may be suitable for topical administration to the skin may comprise the compounds dissolved or suspended in any

suitable carrier or base and may be in the form of lotions, gel, creams, pastes, ointments and the like. Suitable carriers include mineral oil, propylene glycol, polyoxyethylene, polyoxypropylene, emulsifying wax, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water. Transdermal patches may also be used to administer the compounds of the invention.

The compound, composition or combination of the invention may be suitable for parenteral administration include aqueous and non-aqueous isotonic sterile injection solutions which may contain anti-oxidants, buffers, bactericides and solutes which render the compound, composition or combination isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The compound, composition or combination may be presented in unit-dose or multi-dose sealed containers, for example, ampoules and vials, and may be stored in a freeze-dried (lyophilised) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

Preferred unit dosage composition or combinations are those containing a daily dose or unit, daily sub-dose, as herein above described, or an appropriate fraction thereof, of the active ingredient.

It should be understood that in addition to the active ingredients particularly mentioned above, the composition or combination of this invention may include other agents conventional in the art having regard to the type of composition or combination in question, for example, those suitable for oral administration may include such further agents as binders, sweeteners, thickeners, flavouring agents disintegrating agents, coating agents, preservatives, lubricants and/or time delay agents. Suitable sweeteners include sucrose, lactose, glucose, aspartame or saccharine. Suitable disintegrating agents include cornstarch, methylcellulose, polyvinylpyrrolidone, xanthan gum, bentonite, alginic acid or agar. Suitable flavouring agents include peppermint oil, oil of wintergreen, cherry, orange or raspberry flavouring. Suitable coating agents include polymers or copolymers of acrylic acid and/or methacrylic acid and/or their esters, waxes, fatty alcohols, zein, shellac or gluten. Suitable preservatives include sodium benzoate, vitamin E, alpha-tocopherol, ascorbic acid, methyl paraben, propyl paraben or sodium bisulphite. Suitable lubricants include magnesium stearate, stearic acid, sodium oleate, sodium chloride or

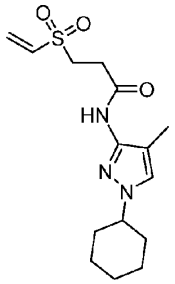
talc. Suitable time delay agents include glyceryl monostearate or glyceryl distearate.

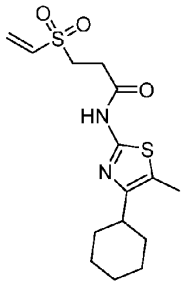
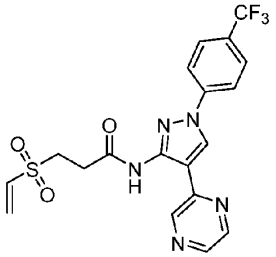
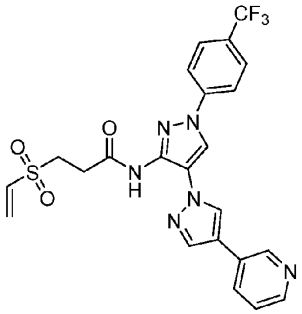
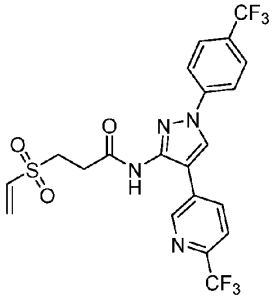
As used herein, the term "combination" relates to the co-administration of the combination partners to a single patient, and are intended to include treatment regimens in which the agents are not necessarily administered by the same route of administration or at the same time. The therapeutic compounds or treatments used in such combination therapies may be administered together with a compound of formula (I) or a pharmaceutically acceptable salt, solvate or prodrug, one after the other, separately in one combined unit dosage or in separate unit dosage forms.

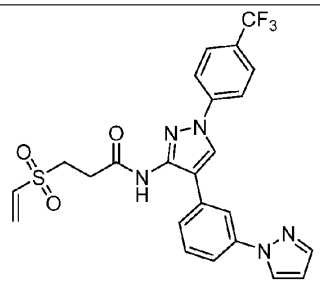
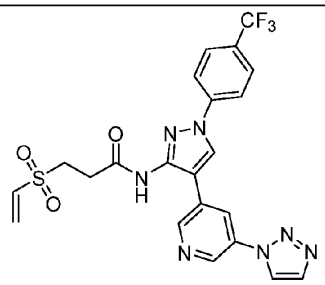
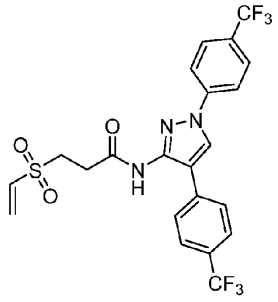
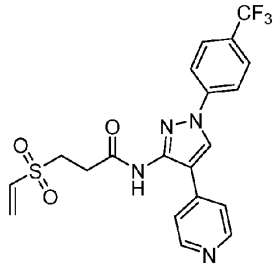
Examples

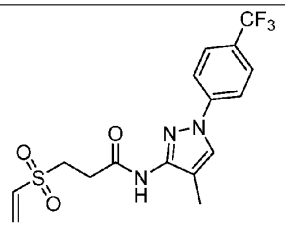
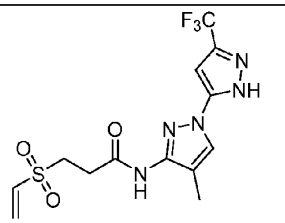
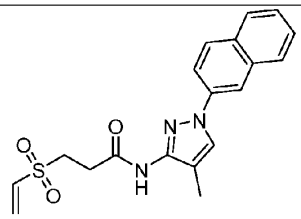
Modeling TEAD-Compound B and Compound C using in silico docking resulted in multiple Y-shaped compounds:

Vinyl sulfone warhead forms covalent bond with conserved Cysteine. Sulfone forms H - bond interactions with side chain of Lysine (Lys336) or backbone of Cystine (Cys359). Docking study suggest that the parent compound strongly binds into the palmitoylation pocket. CPD13 also binds into palmitoylation pocket. Rest of the molecule occupies the hydrophobic pocket. Y-shaped compounds occupy the large pocket including the hydrophobic pocket and retains interaction with the backbone of Cysteine. These compounds also form additional interactions with residues from the extended pocket. Ten compounds shortlisted for synthesis and validation.

Compound		LogP
B/CPD10		

C/CPD13		
D/CPD21		2.9
E/CPD22		4.3
F/CPD23		4.9

G/CPD24		5.1
H/CPD25		3.3
I/CPD26		5.5
J/CPD27		4.9

K/CPD28		3.2
L/CPD29		1.8
M/CPD30		3.2

Generation of stable cell lines

EGFR wild type and EGFR mutant cells generated in HEK293 and A549 cell lines under puro selection. The expression of indicated mutant EGFR were detected by anti-EGFR antibody. Immunoblotting data suggest the expression of indicated proteins (Figure 1).

Work flow:

Day 1: Transient transfection of 3 indicated plasmid DNS constructs in H293FT cells with optimal ratio of helper plasmid DNA

Day 2: Change into fresh medium

Day 4: Virus collection and transduction into HEK293 and A549 cell lines

Day 5: Change medium (DMEM+/+)

Day 7: Change medium supplemented with 1µg/ml of puromycin.

Day 15 onwards: Expansion of puro-resistant EGGFR WT and EGFR mutant cell lines.

Cell lines:

HEK293-EGFR_WT

HEK293-EGFR_19Δ

HEK293-EGFR_19Δ_T790M
HEK293-EGFR_19Δ_T790M_C797S

BBM-EGFR_WT
BBM-EGFR_19Δ
BBM-EGFR_19Δ_T790M
BBM-EGFR_19Δ_T790M_C797S

A549-EGFR_WT
A549-EGFR_19Δ
A549-EGFR_19Δ_T790M (T)
A549-EGFR_19Δ_T790M_C797S

Compound B (CPD10) and Compound C (CPD13) significantly downregulate phosphorylated EGFR in mutant cells.

To determine the role of Compound B (CPD10) and Compound C (CPD13) in the regulation of phosphorylated EGFR, 4 indicated cell lines were either mock treated or treated with 10μM of compound B, C and MGH-CP1, 2 μM of Tarlox-TKI and Osimertinib (OSM) for 24 hrs in a serum starved medium (OPTIMEM). Cells were lysed and protein samples were prepared, quantified, and resolved in 8% SDS-PAGE. After transferring into nitrocellulose membranes, probed with indicated primary antibodies and subsequently re-probed with respective secondary antibodies. Membranes were washed and developed under Chemidoc (BioRad).

Figure 2A shows phosphorylated EGFR protein was significantly reduced in response to Tarlox-TKI and OSM treatment. Compound B, C and MGH-CP1 treatment also resulted in reduction of phosphorylated EGFR protein. A small reduction in total EGFR was noticed in response to Compound C treatment (Upper panel). A significant reduction in phospho-YAP and YAP/TAZ protein were observed in response to Compound B treatment (Lower Panel).

Figure 2B shows phosphorylated EGFR and phosphor-ERC was significantly reduced in response to Compound B, C Tarlox-TKI, OSM and MGH-CP1 treatment. A minor reduction in total EGFR was also observed in responses to Compound C, Tarlox-TKI, OSM and MGH-CP1 treatment (upper panel). Phosphorylated AXL protein was significantly reduced in responses to all indicated treatments. Phosphorylated YAP and YAP/TAZ protein was significantly reduced in responses to Compound B treatment (lower panel).

Figure 2C shows phosphorylated EGFR and phosphor-ERC protein was significantly reduced in response to Compound B and C treatment. Total EGFR was reduced in responses to Tarlox-TKI and OSM treatments (upper panel). Phosphorylated AXL, YAP and total YAP/TAZ level was significantly reduced in responses to Compound B and C treatment (lower panel).

Figure 2D shows phosphorylated EGFR was significantly reduced in responses to Compound B and C treatment. Total EGFR was also reduced in response to Tarlox-TKI and OSM treatment (upper panel). Phosphorylated AXL, YAP and total YAP/TAZ was significantly reduced in responses to Compound B and C treatment (lower panel).

Compound B (CPD10) and Compound C (CPD13) inhibit proliferation in EGFR mutant expressing cell lines

HEK293 cell stably expressing either EGFR WT or EGFR mutant proteins, were plated in 96 well plate at 1200 cell density. Next day, treated with indicated concentrations of small molecules and incubated for 96 hours. Cells were added with WST reagent and incubated for 3 hrs and absorbances measured in plate reader.

Figure 3A shows in response to Compound B (CPD10) treatment, HEK293-EGFR_19Δ, HEK293-EGFR_19Δ_T790M, HEK293-EGFR_19Δ_T790M_C797S cells were sensitive in a dose dependent manner.

Figure 3B shows in response to Compound C (CPD13) treatment, a minor reduction in cellular proliferations observed.

Figure 3C shows in response to OSM treatment, a minor reduction in cellular proliferation was observed.

Figure 3D shows in response to Tarlox-TKI treatment a significant reduction in cellular proliferation was observed in HEK293-EGFR_19Δ_T790M and HEK293-EGFR_19Δ_T790M_C797S mutant cells.

Compound B (CPD10) in combination with OSM acts synergistically to inhibit cellular-proliferation in EGFR mutant cancer cell lines.

Figure 4A shows Compound B inhibit cellular proliferation in EGFR mutant expressing cells in a dose dependent manner.

Figure 4B shows EGFR wild type expressing cell lines, Compound B in combination with OSM, doesn't add any significant effect of inhibition of proliferation.

Figure 4C shows in EGFR 19 delta mutant expressing cells, Compound B in combination with OSM inhibit cell proliferation.

Figure 4D shows in EGFR_19Δ_T790M mutant expressing cells, Compound B in combination with OSM inhibit cell proliferation.

Figure 4E shows in EGFR_19Δ_T790M_C797S mutant expressing cells, Compound B in combination with OSM inhibit cell proliferation.

Compound B (CPD10) and Compound C (CPD13) sensitizes mutant EGFR cancer cell lines and act synergistically in combination with EGFR inhibitors.

Figure 5A shows Compound B and C inhibit colony formation in a dose dependent manner in EGFR L858R/T790M (H1975) double mutation cancer cell line.

Figure 5B shows Compound B and C in combination with Sapotinib, suppresses colony formation significantly in H1975 cancer cell line.

Figure 5C shows indicated concentrations of Compound B and C in combination with Osimertinib, suppresses colony formation significantly in H1975 cancer cells.

To determine the cellular sensitivity of CPDB across multiple EGFR mutants in lung cancer cell, we used BBM cells overexpressing the GFP (control), WT-EGFR, EGFR_19Δ, EGFR_19Δ_T790M and EGFR_19Δ_T790M_C797S) and performed colony forming assay (CFA). CFA data indicate that CPDB sensitizes EGFR mutant-expressing cells in a dose-dependent manner (**Figure 6**). In a similar CFA experiment, we evaluated the CPD-D-induced sensitivity in EGFR mutant expressing cells. CFA data indicate that CPD-D sensitizes EGFR mutant-expressing cells in a dose-dependent manner **(Figure 7**). In a similar CFA experiment, we evaluated the CPD-F-induced sensitivity in EGFR mutant expressing cells. CFA data indicate that CPD-F sensitizes EGFR mutant-expressing cells in at 7.5 and 10μM **(Figure 8**). EGFR wild-type over-expressing BBM cells were treated with increasing concentrations of Osimertinib and combined either with CPD-D or K-975. In combination with CPD-D, we noticed sensitivity at high concentrations, while low concentrations of Osimertinib do not display any sensitivity (**Figure 9**). BBM cells over-expressing EGFR_19Δ mutation treated with increasing concentrations of Osimertinib, combined with CPD-D (2μM) displayed strong sensitivity (**Figure 10**). BBM cells over-expressing EGFR_19Δ/T790M mutation treated with increasing concentrations of

Osimertinib, combined with CPD-D (1 and 2μM) displayed strong sensitivity (**Figure 11**). We noticed a similar synergy with osimertinib combined with CPD-D in EGFR_19Δ/T790M/C797S mutant over-expressing BBM cells (**Figure 12**). We further evaluated our key compounds and compared sensitivity with IK-930 (Phase-I molecules), K-975 and VT-107 in a proliferation assay in EGFR WT overexpressing cells (**Figure 13A**), EGFR_19Δ over-expressing cells (**Figure 13B),** EGFR_19Δ/T790M over-expressing cells (**Figure 13 C**) and EGFR_19Δ/T790M/C797S over-expressing cells (**Figure 13D**).

Next, we treated EGFR wild over-expressing cells with increasing concentrations of Osimertinib and combined with 2μM of indicated compounds. We noticed a synergy in EGFR WT over-expressing cells (**Figure 14A**). We noticed a strong synergy of our compounds CPD B, CPD F, and CPD D in EGFR_19Δ (**Figure 14B**), EGFR_19Δ/T790M (**Figure 14C**), and EGFR_19Δ/T790M/C797S mutant over-expressing BBM cells ((**Figure 14D**). Notably, CPD D drives a very strong synergy with a very low concentration of the osimerinib (**Figure 14 B-D)** across all mutant cells.

As shown in Figure 15, other compounds of the present disclosure also target H1975 cells with EGFR-L858R/T790M mutation, and further acts in synergy with Osmertinib. Colony-forming assay data indicate the dose-dependent sensitivity of the Osimertinib in H1975 cells. (Figure 15a). Upon combination with Compound D (CPD21) (Figure 15b), Compound F (CPD23) (Figure 15c), Compound J (CPD27) (Figure 15d), Compound K (CPD28) (Figure 15e), and Compound M (CPD30) (Figure 15f), the sensitivity was enhanced significantly. This data suggests that the compounds target EGFR mutant H1975 cells and synergize with osimertinib.

As shown in Figure 16, the compounds overcome drug resistance and sensitize EGFR mutant NSCLC. An illustration of the development of OSM resistant (3μM) H1975 and BBM lung cancer cells, stably expressing EGFR-19Δ_T790M (and EGFR-19Δ_T790M/C797S mutants is shown in Figure 16A. In Figure 16B, colony-forming assay data indicate that the newly generated OSM-resistant H1975 cells can tolerate the Osimertinib concentrations up to 3μM. Compounds D (CPD21), F (CPD23), J (CPD27), K (CPD28), and M (CPD30), upon combining with Osimertinib, significantly enhance the sensitivity and inhibit colony formation. This data suggests that the compounds synergize with osimertinib in targeting drug-resistant EGFR mutant lung cells. In Figure 16C, colony-forming assay data indicate that Osimiertinib-resistant EGFR_19ΔT790M mutant cells, upon treatment with IK930, displayed minor sensitivity and inhibition of colony formation in combination

with Osimertinib. Combination with the compounds (CPD21, CPD23, CPD28, and CPD30) strongly sensitizes resistant cells and inhibits colony formation. This data indicates that the compounds efficiently target drug-resistant EGFR_T790M/C797S mutant cells. In Figure 16D, colony-forming assay data indicate that Osimertinib-resistant EGFR_19Δ/T790M/C797S mutant cells, upon treatment with IK930, displayed minor sensitivity and inhibition of colony formation in combination with Osimertinib. The compounds (CPD21, CPD23, CPD28, and CPD30) strongly sensitize resistant cells and inhibit colony formation. This data indicates that our newly developed compounds efficiently target drug-resistant EGFR_19Δ/T790M/C797S mutant cells.

Collectively, the results show that the presently disclosed compounds target difficult-to-treat drug-resistant EGFR mutant NSCLC cells and demonstrate synergy with Osimertinib when administered in combination.

The compounds sensitize KRAS/G12C mutant lung cancer cells and overcome drug resistance.

Among all KRAS mutations, G12C is the most common mutation subtype (12–14%) in NSCLC. The FDA's approval of two highly potent small-molecule inhibitors, AMG510 (Sotorasib) and MRTX840 (Adagrasib), targeting KRAS-G12C inhibitors (G12Ci), has made a substantial difference in the field. The emergence of drug resistance is one of the biggest hurdles to improving progression-free and overall survival among cancer patients. YAP/TAZ-TEAD signaling and MAPK reactivation fuel the process of adaptive resistance in the presence of KRAS G12Ci. In line with YAP/TAZ oncogenic signaling convergence, the compounds as panTEAD inhibitors were evaluated in NCI-H23 and NCI-H358 cells with KRAS/G12C mutant cell lines.

H23 cells were treated with indicated concentrations of CPD10 and CPD13 for 6 days, and a colony-forming assay (CFA) was performed with crystal violet (CV) staining. CPD10 and CPD13 displayed sensitivity and inhibited colony formation of H358 and H23 (KRAS/G12C) mutant cells (Figure 17A). H23 cells were treated with indicated concentrations of adagrasib (upper panel) and sotorasib (lower panel), combined with 2.5 μM of Cpd10. CV Staining was performed after 6 days (Figure 17B). Cell Titer-Glo (CTG)-based luminescence signal was recorded after 72 hrs. H23 cells treated with sotorasib and combined with the indicated concentration of CPD10 resulted in inhibition of cell proliferation (Figure 17C). H23 cells treated with adagrasib, combined with the indicated

concentrations of CPD10, resulted in the inhibition of cell proliferation (Figure 17D). An illustration of the generation of sotorasib-resistant H23 cell line (Figure 17E). Sotorasib-resistant H23 cells treated with indicated concentrations of commercially available TEAD inhibitors (IK930, K975, VT-107, GNE-7883, IAG-933), CPD10, and CPD13. CTG-based proliferation data indicate the inhibition of cellular proliferation upon treatment with CPD10 and CPD13. (Figure 17F). Sotorasib-resistant H23 cells treated with indicated concentrations of commercially available TEAD inhibitors, CPD21, CPD28 and CPD30. CTG-based proliferation data indicate the inhibition of cellular proliferation upon treatment with CPD21, CPD28, and CPD30 (Figure 17G). Sotorasib-resistant H23 cells were treated with indicated concentrations of commercially available TEAD inhibitors, CPD10 and CPD13, and cotreated with 4μM of sotorasib. CTG-based proliferation data indicate the inhibition of cellular proliferation when CPD10 was combined with the sotorasib (Figure 17H). Sotorasib-resistant H23 cells were treated with indicated concentrations of commercially available TEAD inhibitors, IMCB compounds (CPD21, CPD23, CPD28, and CPD30) and cotreated with 4μM of sotorasib. CTG-based proliferation data indicate a significant reduction in luminance signal in CPD21, CPD23, CPD28, and CPD30 treated cells (Figure 17I). This data indicates that the presently disclosed compounds targeting KRASG12C mutant cancer cells and synergistic with the sotorasib in targeting resistant cancer cells.

Sotorasib-resistant H23 cells were treated with increasing concentrations of CPD21, CPD23, CPD28, and CPD30, and colony forming assay was performed after 6 days of the treatments. A dose-dependent inhibition of colony formation was noticed in responses to indicated treatments (Figure 18A). Sotorasib-resistant H23 cells are either treated with increasing concentrations of sotorasib or combined with the 1μM of CPD21, CPD23, CPD28, and CPD30. Upon combination, a significant reduction in colony formation was observed in co-treated cells (Figure 18B). This data indicates that the compounds synergize with the sotorasib in targeting resistant KRAS-G12C mutant cancer cells.

Collectively, the results show that the presently disclosed compounds target KRAS/G12C mutant lung cancer cells, demonstrating synergy with the FDA-approved compounds Sotorasib and/or Adagrasib.

It will be appreciated that many further modifications and permutations of various aspects of the described embodiments are possible. Accordingly, the described aspects are intended to embrace all such alterations, modifications, and variations that fall within the spirit and scope of the appended claims.

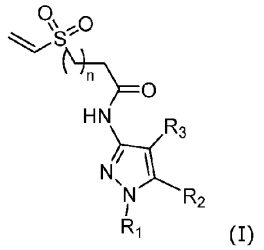
Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" and "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

Throughout this specification and the claims which follow, unless the context requires otherwise, the phrase "consisting essentially of", and variations such as "consists essentially of" will be understood to indicate that the recited element(s) is/are essential i.e. necessary elements of the invention. The phrase allows for the presence of other non-recited elements which do not materially affect the characteristics of the invention but excludes additional unspecified elements which would affect the basic and novel characteristics of the method defined.

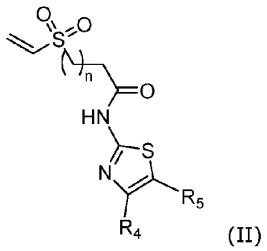
The reference in this specification to any prior publication (or information derived from it), or to any matter which is known, is not, and should not be taken as an acknowledgment or admission or any form of suggestion that that prior publication (or information derived from it) or known matter forms part of the common general knowledge in the field of endeavour to which this specification relates.

Claims

1. A method of treating NF2, EGFR and/or KRAS/G12C mutated cancer and/or tumor in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of Formula (I) or (II) or a pharmaceutically acceptable salt, solvate or prodrug thereof:



(I)



(II)

wherein

n is an integer selected from 1 to 5;

R_1 is selected from optionally substituted aryl, optionally substituted heteroaryl or optionally substituted cycloalkyl;

R_2 is selected from H, or optionally substituted alkyl;

R_3 is selected from optionally substituted aryl, optionally substituted heteroaryl, optionally substituted alkyl;

R_4 is selected from optionally substituted aryl, optionally substituted heteroaryl or optionally substituted cycloalkyl; and

R_5 is selected from optionally substituted aryl, optionally substituted heteroaryl, optionally substituted alkyl.

2. A compound of Formula (I) or (II) or a pharmaceutically acceptable salt, solvate or prodrug thereof for use in treating NF2, EGFR and/or KRAS/G12C mutated cancer and/or tumor.

3. Use of compound of Formula (I) or (II) or a pharmaceutically acceptable salt,

solvate or prodrug thereof in the manufacture of a medicament for the treatment of NF2, EGFR and/or KRAS/G12C mutated cancer and/or tumor.

4. A method of treating NF2 and/or EGFR mutated cancer and/or tumor in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of Formula (I) or (II) in combination with a EGFR inhibitor.

5. A compound of Formula (I) or (II) or a pharmaceutically acceptable salt, solvate or prodrug thereof in combination with a EGFR inhibitor for use in treating NF2 and/or EGFR mutated cancer and/or tumor.

6. Use of compound of Formula (I) or (II) or a pharmaceutically acceptable salt, solvate or prodrug thereof and a EGFR inhibitor in the manufacture of a medicament for the treatment of NF2 and/or EGFR mutated cancer and/or tumor.

7. Use of compound of Formula (I) or (II) or a pharmaceutically acceptable salt, solvate or prodrug thereof in the manufacture of a medicament for the treatment of NF2 and/or EGFR mutated cancer and/or tumor to be used in combination with a EGFR inhibitor.

8. The method, compound for use or use according to any one of claims 1 to 7, wherein the NF2 and/or EGFR mutated cancer and/or tumor is selected from solid tumor, gastric cancer (mesenchymal- subtype GC), non-small cell lung cancer (NSCLC), glioblastoma and mesothelioma, and NF2 deficient mesothelioma.

9. The method, compound for use or use according to any one of claims 4 to 8, wherein the EGFR inhibitor is selected from amivantamab-vmjw, mobocertinib, osimertinib, afatinib, erlotinib, gefitinib, BI-8128, tarloxin-TKI or a combination thereof.

10. The method, compound for use or use according to any one of claims 1 to 9, wherein the NF2 and/or EGFR mutated cancer and/or tumor is characterised by a resistance to a EGFR inhibitor.

11. A method of treating KRAS/G12C mutated cancer and/or tumor in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of Formula (I) or (II) in combination with a KRAS/G12C inhibitor.

12. A compound of Formula (I) or (II) or a pharmaceutically acceptable salt, solvate or prodrug thereof in combination with a KRAS/G12C inhibitor for use in treating KRAS/G12C mutated cancer and/or tumor.

13. Use of compound of Formula (I) or (II) or a pharmaceutically acceptable salt, solvate or prodrug thereof and a KRAS/G12C inhibitor in the manufacture of a medicament for the treatment of KRAS/G12C mutated cancer and/or tumor.

14. Use of compound of Formula (I) or (II) or a pharmaceutically acceptable salt, solvate or prodrug thereof in the manufacture of a medicament for the treatment of KRAS/G12C mutated cancer and/or tumor to be used in combination with a KRAS/G12C inhibitor.

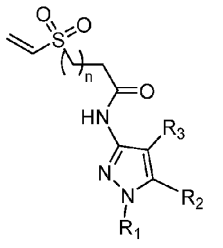
15. The method, compound for use or use according to any one of claims 11 to 14, wherein the KRAS/G12C mutated cancer and/or tumor is selected from colorectal cancer (CRC), pancreatic ductal adenocarcinoma (PDAC), and non-small cell lung cancer (NSCLC).

16. The method, compound for use or use according to any one of claims 11 to 15, wherein the KRAS/G12C inhibitor is selected from Sotorasib and/or Adagrasib.

17. The method, compound for use or use according to any one of claims 1 to 3 and 11 to 14, wherein the KRAS/G12C mutated cancer and/or tumor is characterised by a resistance to a KRAS/G12C inhibitor.

18. The method, compound for use or use according to any one of claims 1 to 17, wherein R_1 is selected from optionally substituted phenyl, optionally substituted naphthalenyl, or optionally substituted heteroaryl.

19. A compound of Formula (Ia) or a salt, or solvate thereof:



(Ia)

wherein

n is an integer selected from 1 to 5;

R_1 is selected from optionally substituted aryl, optionally substituted heteroaryl;

R_2 is selected from H, or optionally substituted alkyl; and

R_3 is selected from optionally substituted aryl, optionally substituted heteroaryl, optionally substituted alkyl.

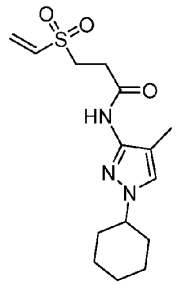
20. The compound according to claim 19, wherein R_1 is selected from phenyl substituted with haloalkyl, optionally substituted naphthalenyl, or optionally substituted heteroaryl.

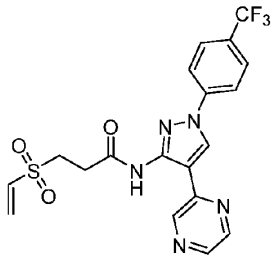
21. The compound according to claim 19 or 20, wherein R_2 is H.

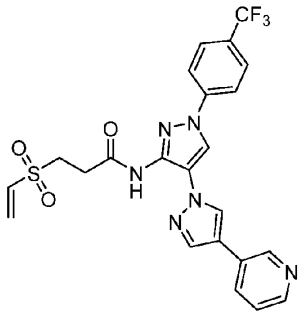
22. The compound according to any one of claims 19 to 21, wherein R_3 is selected from optionally substituted phenyl, optionally substituted N-heteroaryl.

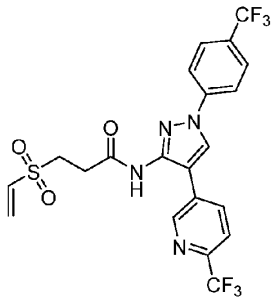
23. The compound according to any one of claims 19 to 22, wherein n is 1.

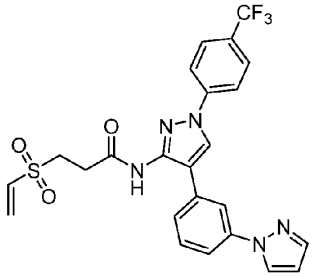
24. The compound according to any one of claims 19 to 23, wherein compound of Formula (I) is selected from:

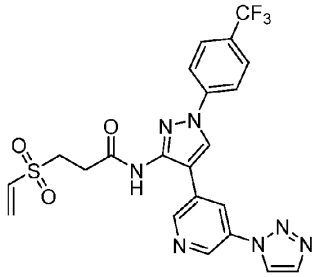


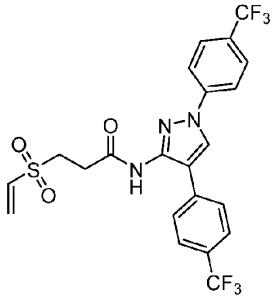


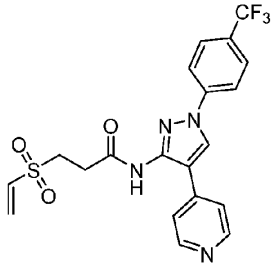


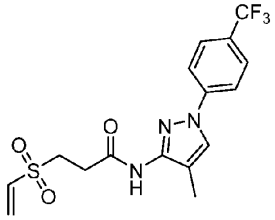


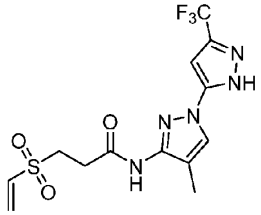


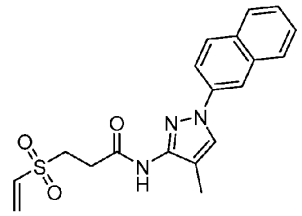






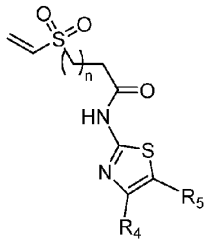






.

25. A compound of Formula (II) or a salt, or solvate thereof:



(II)

wherein

n is an integer selected from 1 to 5;

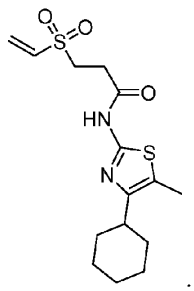
R_4 is selected from optionally substituted aryl, optionally substituted heteroaryl or optionally substituted cycloalkyl; and

R_5 is selected from optionally substituted aryl, optionally substituted heteroaryl, optionally substituted alkyl.

26. The compound according to claim 25, wherein R_4 is selected from phenyl substituted with haloalkyl, optionally substituted naphthalenyl, or optionally substituted heteroaryl.

27. The compound according to claim 25 or 26, wherein R_5 is selected from optionally substituted phenyl, optionally substituted N-heteroaryl.

28. The compound according to any one of claims 25 to 27, wherein the compound is



29. A pharmaceutical composition comprising an effective amount of a compound of Formula (I) or (II) or a pharmaceutically acceptable salt, solvate or prodrug thereof, optionally in combination with a pharmaceutically acceptable carrier, excipient or diluent.