

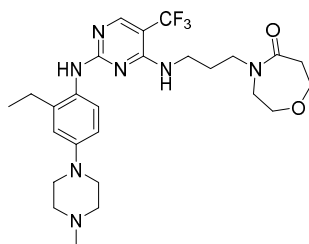
[0007] Mutant Ras cancers are addicted to autophagy. In pancreatic cancer, mutant Ras signals predominantly through the MAPKAP pathway. Mutant Ras activates RAF kinases, which in turn activate MEK kinases, which finally activate ERK kinases: mutant Ras → RAF → MEK → ERK. Despite mutant Ras signaling through the MAPKAP pathway, inhibitors of this pathway have provided no or little clinical benefit in clinical trials when used as single agents. It has been recently reported that inhibition of the MAPKAP pathway induces autophagy as a compensatory adaptive stress response resistance mechanism. When MEK inhibitors were combined with the autophagy inhibitor hydroxychloroquine, there was synergistic activity leading to regression of a number of mutant Ras or mutant BRAF cancers. Similarly, when ERK inhibitors were combined with the autophagy inhibitor hydroxychloroquine or chloroquine, there was synergistic activity leading to inhibition of mutant Ras pancreatic cancers. It has been demonstrated that genetic depletion of RAF kinases (CRAF and BRAF) led to synergistic anti-tumor activity in mutant Ras cancer cell lines when autophagy was also genetically depleted. In composite, recent publications highlight that dual inhibition of the RAS/MAPK pathway and the autophagy pathway in mutant Ras cancers is a promising treatment regimen for patients with mutant Ras cancers. It has also been demonstrated that other targeted therapies and chemotherapeutic agents activate tumor autophagy as a resistance mechanism; hence there is rationale for combining such targeted therapeutics or chemotherapeutic agents with inhibitors of autophagy.

[0008] It has also been demonstrated that tumor driver receptor tyrosine kinases (RTKs) can modulate autophagy, and that inhibitors of RTKs also activate autophagy through the same mTORC1 and AMP kinase pathways as do inhibitors of mutant RAS or RAF.

[0009] There is a need for new targeted therapies which inhibit autophagy and can be used in combination with RTK/RAS/MAPK pathway inhibitors, chemotherapeutic agents, and/or other targeted therapeutics.

SUMMARY

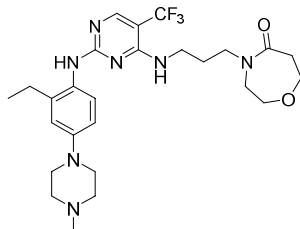
[00010] The present disclosure provides, in part, methods of treating disorders with ULK inhibitors in combination therapies. Described herein, in an example, is a method of treating cancer in a patient in need thereof, comprising: (i) administering to the patient about 20 mg to about 600 mg, once or twice daily, of a compound represented by Formula (I):



Formula (I)

or a pharmaceutically acceptable salt thereof; and (ii) administering to the patient a therapeutically effective amount of one or more additional therapeutic agents.

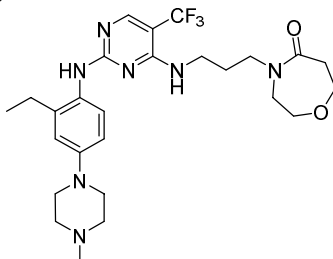
[00010a] In one aspect, the present disclosure refers to use of a compound represented by Formula (I):



Formula (I)

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a cancer in a patient in need thereof, wherein: (i) about 20 mg to about 600 mg of the compound represented by Formula (I), or a pharmaceutically acceptable salt thereof is to be administered to the patient once or twice daily; and (ii) one or more additional therapeutic agents is to be administered to the patient.

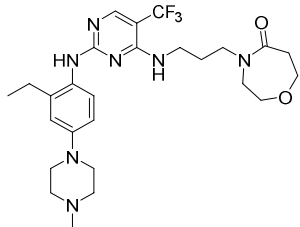
[00011] In another example, described herein is a method of treating cancer in a patient in need thereof, comprising: (i) administering to the patient about 20 mg to about 600 mg, once or twice daily, of a compound represented by Formula (I):



Formula (I)

or a pharmaceutically acceptable salt thereof; and (ii) orally administering to the patient a therapeutically effective amount of trametinib.

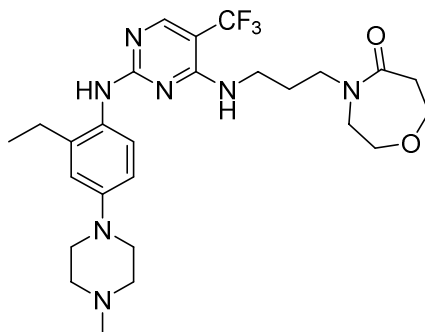
[00011a] In one aspect, the present disclosure refers to use of a compound represented by Formula (I):



Formula (I)

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of cancer in a patient in need thereof, wherein: (i) about 20 mg to about 600 mg, of the compound represented by Formula (I), or a pharmaceutically acceptable salt thereof is to be orally administered to the patient once or twice daily; and (ii) a therapeutically effective amount of trametinib is to be orally administered to the patient.

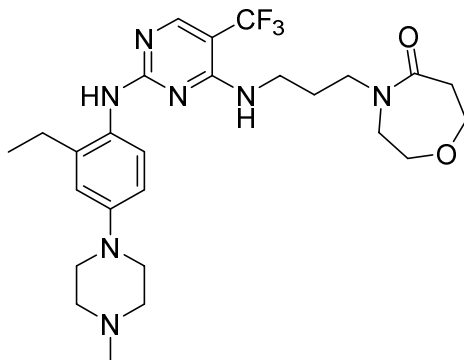
[00012] In an example, described herein is a method of treating cancer in a patient in need thereof, comprising: (i) administering to the patient about 20 mg to about 600 mg, once or twice daily, of a compound represented by Formula (I):



Formula (I)

or a pharmaceutically acceptable salt thereof; and (ii) orally administering to the patient a therapeutically effective amount of binimetinib.

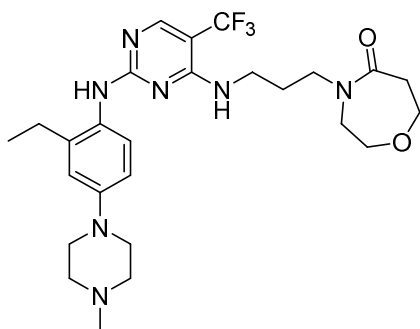
[00012a] In one aspect, the present disclosure refers to use of a compound represented by Formula (I):



Formula (I)

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of cancer in a patient in need thereof, wherein: (i) about 20 mg to about 600 mg of the compound represented by Formula (I), or a pharmaceutically acceptable salt thereof is to be orally administered to the patient once or twice daily; and (ii) a therapeutically effective amount of binimetinib is to be orally administered to the patient.

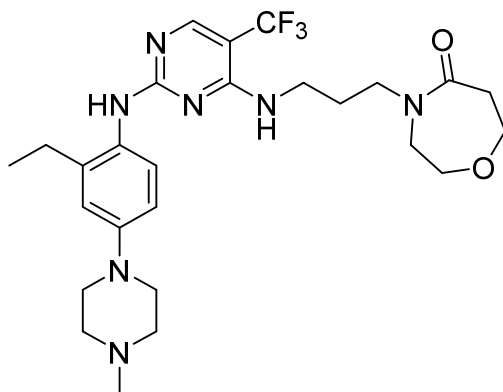
[00013] In another example, described herein is a method of treating cancer in a patient in need thereof, comprising administering to the patient: (i) administering to the patient about 20 mg to about 600 mg, once or twice daily, of a compound represented by Formula (I):



Formula (I)

or a pharmaceutically acceptable salt thereof; and (ii) orally administering to the patient a therapeutically effective amount of a KRAS G12C inhibitor.

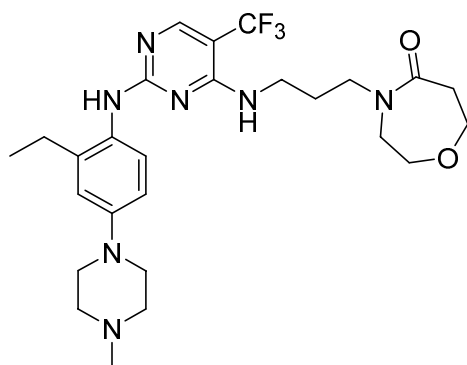
[00013a] In one aspect, the present disclosure refers to use of a compound represented by Formula (I):



Formula (I)

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a cancer in a patient in need thereof, wherein: (i) about 20 mg to about 600 mg of the compound represented by Formula (I), or a pharmaceutically acceptable salt thereof is to be orally administered to the patient once or twice daily; and (ii) a therapeutically effective amount of a KRAS G12C inhibitor is to be orally administered to the patient.

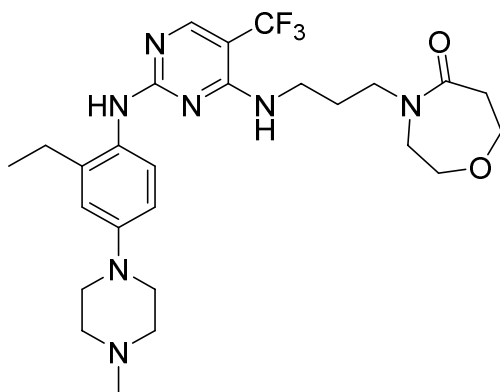
[00014] In another example, described herein is a method of treating cancer in a patient in need thereof, comprising administering to the patient: (i) orally administering to the patient about 20 mg to about 600 mg, once or twice daily, of a compound represented by Formula (I):



Formula (I)

or a pharmaceutically acceptable salt thereof; and (ii) administering to the patient a therapeutically effective amount of sotorasib.

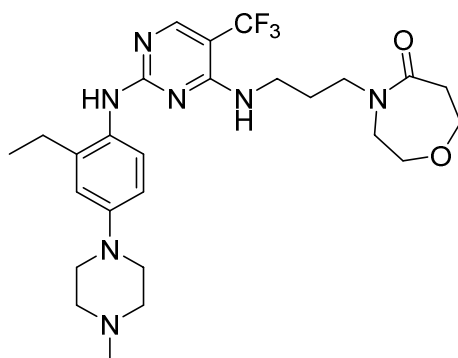
[00014a] In one aspect, the present disclosure refers to use of a compound represented by Formula (I):



Formula (I)

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of cancer in a patient in need thereof, wherein: (i) about 20 mg to about 600 mg of the compound represented by Formula (I), or a pharmaceutically acceptable salt thereof is to be orally administered to the patient once or twice daily; and (ii) a therapeutically effective amount of sotorasib is to be orally administered to the patient.

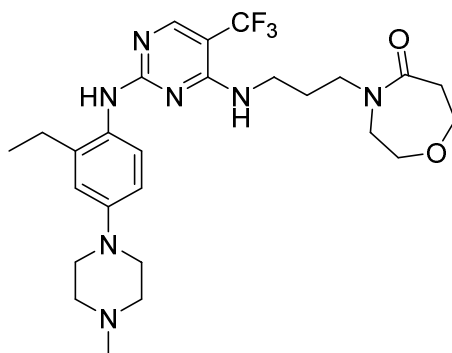
[00015] In another example, described herein is a method of treating colorectal cancer in a patient in need thereof, comprising: (i) administering to the patient a therapeutically effective amount of a compound represented by Formula (I):



Formula (I)

or a pharmaceutically acceptable salt thereof; and (ii) administering to the patient a therapeutically effective amount of encorafenib.

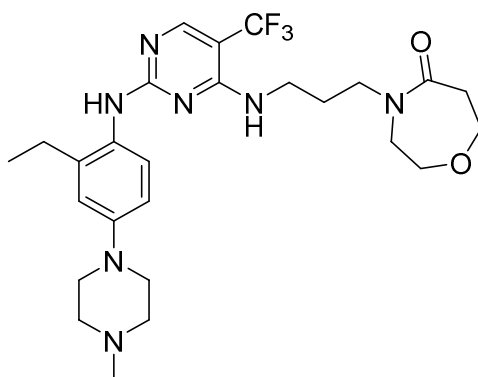
[00015a] In one aspect, the present disclosure refers to use of a compound represented by Formula (I):



Formula (I)

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of colorectal cancer in a patient in need thereof, wherein: (i) a therapeutically effective amount of the compound represented by Formula (I), or a pharmaceutically acceptable salt thereof is to be orally administered to the patient; and (ii) a therapeutically effective amount of encorafenib is to be administered to the patient.

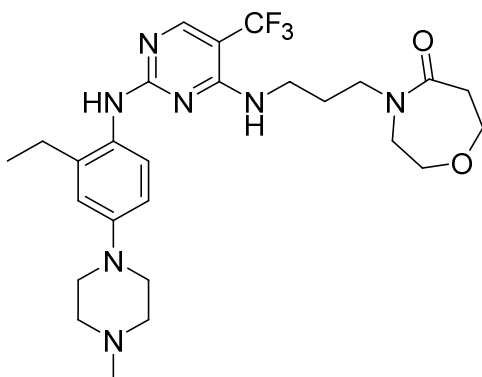
[00016] In another example, described herein is a method of treating colorectal cancer in a patient in need thereof, comprising: (i) administering to the patient a therapeutically effective amount of a compound represented by Formula (I):



Formula (I)

or a pharmaceutically acceptable salt thereof; and (ii) administering to the patient a therapeutically effective amount of encorafenib, and (iii) administering to the patient a therapeutically effective amount of cetuximab.

[00016a] In one aspect, the present disclosure refers to use of a compound represented by Formula (I):



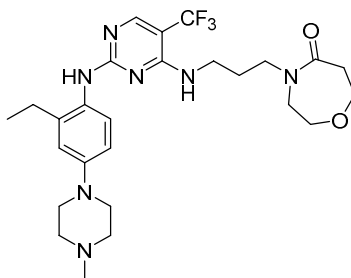
Formula (I)

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of colorectal cancer in a patient in need thereof, wherein: (i) a therapeutically effective amount of the compound represented by Formula (I), or a pharmaceutically acceptable salt thereof is to be orally administered to the patient; and (ii) a therapeutically effective amount of encorafenib is to be administered to the patient, and (iii) a therapeutically effective amount of cetuximab is to be administered to the patient.

[00017] In another example, described herein a method of treating in a gastrointestinal stromal tumor in a patient in need thereof, comprising administering to the patient: (i) a therapeutically effective amount of an inhibitor of ULK1 kinase, an inhibitor of an ULK2 kinase, or an inhibitor of ULK1 and ULK2 kinases; and (ii) a therapeutically effective amount of ripretinib.

[00017a] In one aspect, the present disclosure refers to use of an inhibitor of ULK1 kinase, an inhibitor of ULK2 kinase, or an inhibitor of ULK1 kinase and ULK2 kinase, in the manufacture of a medicament for the treatment of a gastrointestinal stromal tumor in a patient in need thereof, wherein: (i) a therapeutically effective amount of the inhibitor of ULK1 kinase, the inhibitor of ULK2 kinase, or the inhibitor of ULK1 kinase and ULK2 kinase; and (ii) a therapeutically effective amount of ripretinib, are to be administered to the patient.

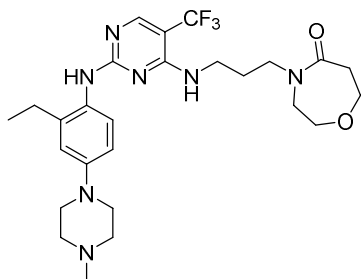
[00018] In another example, described herein is a method of treating in an advanced gastrointestinal stromal tumor in a patient in need thereof, comprising: (i) administering to the patient a therapeutically effective amount of a compound represented by Formula (I):



Formula (I)

or a pharmaceutically acceptable salt thereof; and (ii) orally administering to the patient a therapeutically effective amount of ripretinib.

[00018a] In one aspect, the present disclosure refers to use of a compound represented by Formula (I):



Formula (I)

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of an advanced gastrointestinal stromal tumor in a patient in need thereof, wherein: (i) a therapeutically effective amount of the compound represented by Formula (I), or a pharmaceutically acceptable salt thereof; and (ii) a therapeutically effective amount of ripretinib are to be orally administered to the patient.