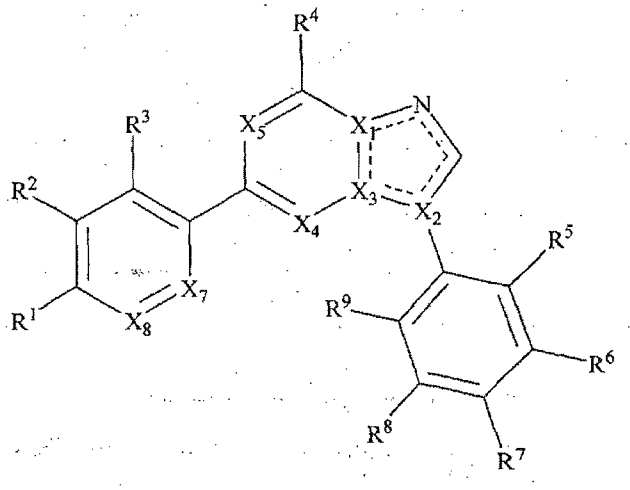


(Ia)

or a pharmaceutically acceptable form thereof, wherein

X_1, X_2, and X_3 are independently N or C;

X_4 and X_5 are independently N or CR^4;

wherein at least one of X_1, X_2, X_3, X_4, and X_5 is N;

X_7 is N or CR^{10};

X_8 is N or CR^{11};

----- is a single or double bond, as valency allows;

R^1 is an optionally substituted aryl, optionally substituted carbocyclyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, -CN, -SR, $-N(R)_2$, -C(O)R, $-CO_2R$, $-C(O)N(R)_2$, -C(O)NROR, -S(O)R, $-SO_2R$, $-SO_2N(R)_2$, -OC(O)R, -NRC(O)R, $-NRSO_2R$, or $-NRC(O)N(R)_2$; each R is independently hydrogen, optionally substituted C_{1-6} aliphatic, optionally substituted aryl, optionally substituted carbocyclyl, optionally substituted heteroaryl, or optionally substituted heterocyclyl; or two R groups on the same nitrogen may be taken together to form an optionally substituted heterocycle;

R^2, R^3, R^5, R^6, R^7, R^8, R^9, R^{10}, and R^{11} are independently hydrogen, halogen, optionally substituted aliphatic, optionally substituted aryl, optionally substituted carbocyclyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, -CN, -OR, -SR, $-N(R)_2$, $-NO_2$, -C(O)R, $-CO_2R$, $-C(O)N(R)_2$, -C(O)NROR, -S(O)R, $-SO_2R$, $-SO_2N(R)_2$, -OC(O)R, -NRC(O)R, $-NRSO_2R$, or $-NRC(O)N(R)_2$;

each R is independently hydrogen, optionally substituted C_{1-6} aliphatic, optionally substituted aryl, optionally substituted carbocyclyl, optionally substituted heteroaryl, or optionally substituted heterocyclyl; or two R groups on the same nitrogen may be taken together to form an optionally substituted heterocycle;

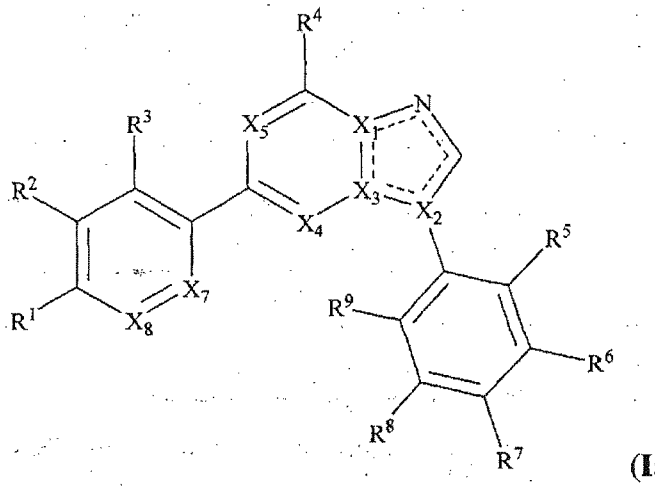
kinase pathway), such as but not limited to, cancer (blood and solid tumors), inflammatory conditions, Alzheimer's disease, metabolic disorders (obesity, diabetes) as well as methods of treatment of these disorders using compounds described herein as single agents or in combination with one or more additional agents. In some embodiments, an additional agent is a kinase inhibitor. In some embodiments, an additional agent is an mTOR inhibitor. Exemplary mTOR inhibitors include sirolimus, temsirolimus, everolimus, and ridaforolimus. In some embodiments, an additional agent is a PI3-kinase inhibitor. Exemplary PI3-kinase inhibitors include wortmannin, demethoxyviridin, LY294002, perifosine, CAL101, PX-886, BEZ235, SF1126, INK1117, INK1197, IPI-145, GDC-0941, BKM120, XL147, XL765, palomid 529, GSK1059615, ZSTK474, PWT33597, IC87114, TG100-115, CAL263, PI-103, GNE-477, CUDC-907, GSK 2126458, GDC-0980, PF-46915032, CAL263, SF1126 and PX-886. In some embodiments, the PI3-kinase inhibitor inhibits PI3K-α, PI3K-β, PI3K-γ, and/or PI3K-δ.

In a third aspect, there is provided a composition comprising a compound as defined above or a pharmaceutically acceptable form thereof, and a pharmaceutically acceptable excipient.

In a fourth aspect, there is provided a method of inhibiting MNK1 and/or MNK2 in a cell comprising administering to a cell a compound as defined above, or a pharmaceutically acceptable form thereof, wherein the cell is in vitro.

In a fifth aspect, there is provided a use of a compound as defined above, or a pharmaceutically acceptable form thereof, or a composition as defined above, in the manufacture of a medicament for treating a MNK1 – or MNK2 –related disorder, wherein the disorder is cancer (e.g., blood and solid tumors), an inflammatory conditions, Alzheimer's disease, or a metabolic disorder (e.g., obesity, diabetes).

In a sixth aspect, there is provided a use of a compound of Formula (Ia):



(Ia)

or a pharmaceutically acceptable form thereof, wherein

X_1, X_2, and X_3 are independently N or C;

X_4 and X_5 are independently N or CR^4;

wherein at least one of X_1, X_2, X_3, X_4, and X_5 is N;

X_7 is N or CR^{10};

X_8 is N or CR^{11};

$\overline{\text{-----}}$ is a single or double bond, as valency allows;

R^1 is an optionally substituted aryl, optionally substituted carbocyclyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, -CN, -SR, $-N(R)_2$, -C(O)R, $-CO_2R$, $-C(O)N(R)_2$, -C(O)NROR, -S(O)R, $-SO_2R$, $-SO_2N(R)_2$, -OC(O)R, -NRC(O)R, $-NRSO_2R$, or $-NRC(O)N(R)_2$; each R is independently hydrogen, optionally substituted C_{1-6} aliphatic, optionally substituted aryl, optionally substituted carbocyclyl, optionally substituted heteroaryl, or optionally substituted heterocyclyl; or two R groups on the same nitrogen may be taken together to form an optionally substituted heterocycle;

R^2, R^3, R^5, R^6, R^7, R^8, R^9, R^{10}, and R^{11} are independently hydrogen, halogen, optionally substituted aliphatic, optionally substituted aryl, optionally substituted carbocyclyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, -CN, -OR, -SR, $-N(R)_2$, $-NO_2$, -C(O)R, $-CO_2R$, $-C(O)N(R)_2$, -C(O)NROR, -S(O)R, $-SO_2R$, $-SO_2N(R)_2$, -OC(O)R, -NRC(O)R, $-NRSO_2R$, or $-NRC(O)N(R)_2$;

each R is independently hydrogen, optionally substituted C_{1-6} aliphatic, optionally substituted aryl, optionally substituted carbocyclyl, optionally substituted heteroaryl, or optionally substituted heterocyclyl; or two R groups on the same nitrogen may be taken together to form an optionally substituted heterocycle; each R^4 is independently hydrogen,

halogen, or optionally substituted C_{1-6} aliphatic; and R^1 and R^2, R^2 and R^3, R^3 and R^4, R^1 and R^{11}, R^{10} and R^{11}, R^5 and R^6, R^6 and R^7, R^7 and R^8, or R^8 and R^9 may be optionally taken together to form an optionally substituted 5-6 membered carbocyclic, aryl, heterocyclic, or heteroaryl ring;

or a pharmaceutically acceptable form thereof, in the manufacture of a medicament for treating a MNK1 - or MNK2 -related disorder, wherein the disorder is cancer (e.g., blood and solid tumors), an inflammatory conditions, Alzheimer's disease, or a metabolic disorder (e.g., obesity, diabetes).

In yet another embodiment, the present disclosure describes methods for the synthesis and isolation of a compound of Formula (**I**), such as, for example, substituted 3,6-diphenylimidazo[1,2-a]pyridine; 3,6-diphenylimidazo[1,2-a]pyrazine; 3,6-diphenylimidazo[1,2-b]pyridazine; 3,5-diphenylpyrazolo[1,5-a]pyrimidine; 1,6-diphenyl-1H-imidazo[4,5-c]pyridine; 1,6-diphenyl-1H-benzo[d]imidazole.

BRIEF DESCRIPTION OF THE DRAWINGS

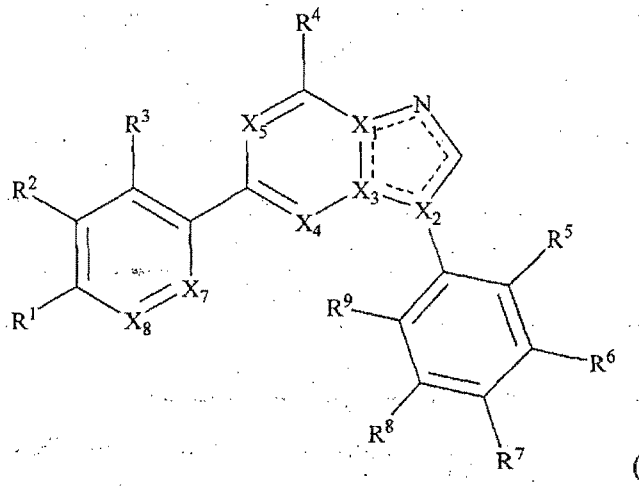
Figure 1 demonstrates that Example 6 (ETC-10445-3), Example 1 (ETC-5336) and Example 2 (ETC-6740) prevent eIF4E phosphorylation in BC-CML cell lines and primary cells. (A) Western blot analysis of K562 cell lines treated with various concentrations of compounds for 24 h. (B-D) BC-CML cells were treated with various compounds for 48 h. 48 hours post drug treatment, cells were harvested for immunofluorescence analysis for nuclear active β-catenin and phosphor-eIF4E level.

Figure 2 shows the effects of Example 6 (ETC-0445-3), Example 1 (ETC-5336), and Example 2 (ETC-6740) on serial replating efficiency of BC-CML primary cells. Colony forming and serial replating assays were performed on normal and BC-CML primary samples. CD34+ cells from (A) cord blood and (B-D) BC CML cells were treated with compounds for 48 hr. Forty-eight hours post drug treatmnent, 1 x 10^4 cells were plated for

CLAIMS

What is claimed is:

1. A compound of Formula (Ia):



(Ia)

or a pharmaceutically acceptable form thereof, wherein

X_1, X_2, and X_3 are independently N or C;

X_4 and X_5 are independently N or CR^4;

wherein at least one of X_1, X_2, X_3, X_4, and X_5 is N;

X_7 is N or CR^{10};

X_8 is N or CR^{11};

----- is a single or double bond, as valency allows;

R^1 is an optionally substituted aryl, optionally substituted carbocyclyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, -CN, -SR, $-N(R)_2$, -C(O)R, $-CO_2R$, $-C(O)N(R)_2$, -C(O)NROR, -S(O)R, $-SO_2R$, $-SO_2N(R)_2$, -OC(O)R, -NRC(O)R, $-NRSO_2R$, or $-NRC(O)N(R)_2$; each R is independently hydrogen, optionally substituted C_{1-6} aliphatic,

9. A compound of any one of claims 1-8, wherein the compound is an MNK1 and/or MNK2 inhibitor.

10. A composition comprising a compound of any one of claims 1-9, or a pharmaceutically acceptable form thereof, and a pharmaceutically acceptable excipient.

11. The composition of claim 10, wherein the composition comprises an additional therapeutic agent.

12. The composition of claim 11, wherein the additional therapeutic agent is a kinase inhibitor.

13. The composition of claim 12, wherein the kinase inhibitor is a PI3K inhibitor.

14. The composition of claim 12, wherein the kinase inhibitor is an mTOR inhibitor.

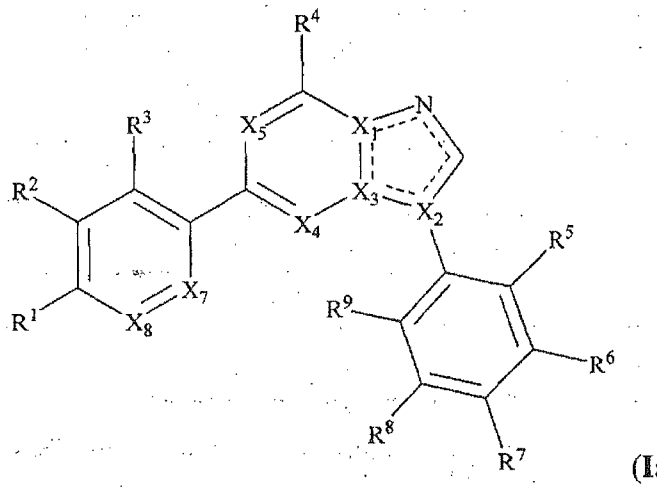
15. A method of inhibiting MNK1 and/or MNK2 in a cell comprising administering to a cell a compound of any one of claims 1-9, or a pharmaceutically acceptable form thereof, wherein the cell is in vitro.

~~16. The method of claim 15, wherein the cell is in vitro.~~

~~17. The method of claim 15, wherein the cell is in a subject.~~

186. A use of a compound of any one of claims 1-9, or a pharmaceutically acceptable form thereof, or a composition of any one of claims 10-14, in the manufacture of a medicament for treating a MNK1 - or MNK2 -related disorder,
wherein the disorder is cancer (e.g., blood and solid tumors), an inflammatory conditions, Alzheimer's disease, or a metabolic disorder (e.g., obesity, diabetes).

17. Use of a compound of Formula (Ia):



(Ia)

or a pharmaceutically acceptable form thereof, wherein

X_1, X_2, and X_3 are independently N or C;

X_4 and X_5 are independently N or CR^4;

wherein at least one of X_1, X_2, X_3, X_4, and X_5 is N;

X_7 is N or CR^{10};

X_8 is N or CR^{11};

----- is a single or double bond, as valency allows;

R^1 is an optionally substituted aryl, optionally substituted carbocyclyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, -CN, -SR, $-N(R)_2$, -C(O)R, $-CO_2R$, $-C(O)N(R)_2$, -C(O)NROR, -S(O)R, $-SO_2R$, $-SO_2N(R)_2$, -OC(O)R, -NRC(O)R, $-NRSO_2R$, or $-NRC(O)N(R)_2$; each R is independently hydrogen, optionally substituted C_{1-6} aliphatic, optionally substituted aryl, optionally substituted carbocyclyl, optionally substituted heteroaryl, or optionally substituted heterocyclyl; or two R groups on the same nitrogen may be taken together to form an optionally substituted heterocycle;

R^2, R^3, R^5, R^6, R^7, R^8, R^9, R^{10}, and R^{11} are independently hydrogen, halogen, optionally substituted aliphatic, optionally substituted aryl, optionally substituted carbocyclyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, -CN, -OR, -SR, $-N(R)_2$, $-NO_2$, -C(O)R, $-CO_2R$, $-C(O)N(R)_2$, -C(O)NROR, -S(O)R, $-SO_2R$, $-SO_2N(R)_2$, -OC(O)R, -NRC(O)R, $-NRSO_2R$, or $-NRC(O)N(R)_2$;

each R is independently hydrogen, optionally substituted C_{1-6} aliphatic, optionally substituted aryl, optionally substituted carbocyclyl, optionally substituted heteroaryl, or optionally substituted heterocyclyl; or two R groups on the same nitrogen may be taken together to form an optionally substituted heterocycle;

each R^4 is independently hydrogen, halogen, or optionally substituted C_{1-6} aliphatic; and R^1 and R^2, R^2 and R^3, R^3 and R^4, R^1 and R^{11}, R^{10} and R^{11}, R^5 and R^6, R^6 and R^7, R^7 and R^8, or R^8 and R^9 may be optionally taken together to form an optionally substituted 5-6 membered carbocyclic, aryl, heterocyclic, or heteroaryl ring;
or a pharmaceutically acceptable form thereof, in the manufacture of a medicament for treating a MNK1 - or MNK2 -related disorder, wherein the disorder is cancer (e.g., blood and solid tumors), an inflammatory conditions, Alzheimer's disease, or a metabolic disorder (e.g., obesity, diabetes).

189. The use of claim 16 or 1718, wherein the compound is administered in combination with an additional therapeutic agent.

~~20~~19. The use of claim ~~19~~18, wherein the additional therapeutic agent is a kinase inhibitor.

~~20~~21. The use of claim 19~~20~~, wherein the kinase inhibitor is a PI3K inhibitor.

~~21~~22. The use of claim 19~~20~~, wherein the kinase inhibitor is an mTOR inhibitor.

~~22~~23. The use of claim 16 or 17~~18~~, wherein the disorder is cancer.

~~23~~24. The use of any one of claims ~~18-23~~16 to 22, wherein the compound or composition is administered at a dosage level sufficient to deliver from about 0.001 mg/kg to about 100 mg/kg to a subject in need thereof.