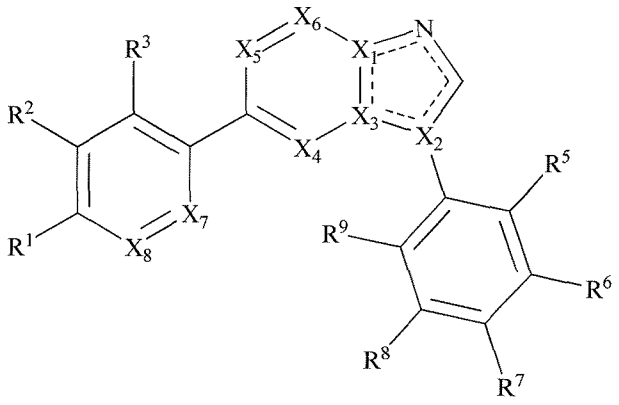
It has been shown that CGP57380, a Mnk inhibitor, inhibits the release of TNF alpha by macrophage[61] (and not eIF4E). According to WO2005/003785 MNK kinases are promising targets for anti-inflammatory therapy.

MNK1/2 were also reported to phosphorylate a number of different proteins in addition to eIF4E. Three of these are hnRNPA1,[60] cPLA2 and Sprouty2.[62;63] Their role and function is still being investigated. Among these substrates, hnRNPA1 is overexpressed in colorectal cancer and it could contribute to maintenance of telomere repeats in cancer cells with enhanced cell proliferation.[64] It is also reported that the expression levels of hnRNPA/B is deregulated in non small cell lung cancer.[65]

MNK inhibitors are potentially useful in the treatment of cancers including breast,[66] protate,[11] hematological malignancies (*e.g.*, CML, AML), head and neck, colon,[67] bladder, prostatic adenocarcinoma, lung, cervical, and lymphomas.[68;68;69]

SUMMARY

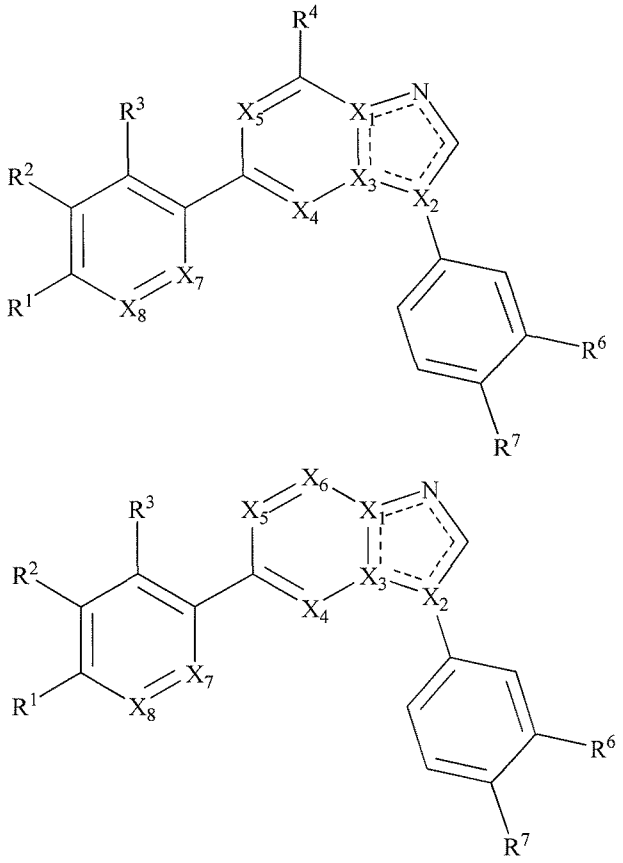
In an embodiment, the present disclosure relates to compounds that act as kinase inhibitors, in particular as inhibitors of the MAP kinase interacting kinases 1 and 2 (MNK1 and MNK2). In certain embodiments, a compound of the present disclosure is of Formula (**I**):



(**I**)

or a pharmaceutically acceptable form thereof, wherein R^1, R^2, R^3, R^5, R^6, R^7, R^8, R^9, X_1, X_2, X_3, X_4, X_5, X_6, X_7, and X_8 are as described herein.

In a first aspect, there is provided a compound of Formula (Ib):



(Ib)

or a pharmaceutically acceptable form thereof, wherein

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

X_4, X_5 and X_6 are independently N or CR^4;

wherein at least one of X_1, X_2, X_3, X_4, X_5 and X_6 is N;

X_7 is N or CH;

X_8 is N or CH;

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

R^1 is -C(O)R, wherein R is an optionally substituted 5-6 membered heterocyclyl non-aromatic ring system having ring carbon atoms and 1-4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen and sulfur; wherein the optionally substituted 5-6 membered heterocyclyl non-aromatic ring system is unsubstituted or substituted with;

halogen, –CN, –NO_2, –N_3, –SO_2H, –SO_3H, –OH, –OR^{aa}, –$ON(R^{bb})_2$, –$N(R^{bb})_2$, –$N(R^{bb})_3^+X^-$, –$N(OR^{cc})R^{bb}$, –SH, –SR^{aa}, –SSR^{cc}, –$C(=O)R^{aa}$, –CO_2H, –CHO, –$C(OR^{cc})_2$, –CO_2R^{aa}, –$OC(=O)R^{aa}$, –OCO_2R^{aa}, –$C(=O)N(R^{bb})_2$, –$OC(=O)N(R^{bb})_2$, –$NR^{bb}C(=O)R^{aa}$, –$NR^{bb}CO_2R^{aa}$, –$NR^{bb}C(=O)N(R^{bb})_2$, –$C(=NR^{bb})R^{aa}$, –$C(=NR^{bb})OR^{aa}$, –$OC(=NR^{bb})R^{aa}$, –$OC(=NR^{bb})OR^{aa}$, –$C(=NR^{bb})N(R^{bb})_2$, –$OC(=NR^{bb})N(R^{bb})_2$, –$NR^{bb}C(=NR^{bb})N(R^{bb})_2$, –$C(=O)NR^{bb}SO_2R^{aa}$, –$NR^{bb}SO_2R^{aa}$, –$SO_2N(R^{bb})_2$, –$SO_2R^{aa}$, –$SO_2OR^{aa}$, –$OSO_2R^{aa}$, –$S(=O)R^{aa}$, –$OS(=O)R^{aa}$, –$Si(R^{aa})_3$, –$OSi(R^{aa})_3$ –$C(=S)N(R^{bb})_2$, –$C(=O)SR^{aa}$, –$C(=S)SR^{aa}$, –$SC(=S)SR^{aa}$, –$SC(=O)SR^{aa}$, –$OC(=O)SR^{aa}$, –$SC(=O)OR^{aa}$, –$SC(=O)R^{aa}$, –$P(=O)_2R^{aa}$, –$OP(=O)_2R^{aa}$, –$P(=O)(R^{aa})_2$, –$OP(=O)(R^{aa})_2$, –$OP(=O)(OR^{cc})_2$, –$P(=O)_2N(R^{bb})_2$, –$OP(=O)_2N(R^{bb})_2$, –$P(=O)(NR^{bb})_2$, –$OP(=O)(NR^{bb})_2$, –$NR^{bb}P(=O)(OR^{cc})_2$, –$NR^{bb}P(=O)(NR^{bb})_2$, –$P(R^{cc})_2$, –$P(R^{cc})_3$, –$OP(R^{cc})_2$, –$OP(R^{cc})_3$, –$B(R^{aa})_2$, –$B(OR^{cc})_2$, –$BR^{aa}(OR^{cc})$, C_{1-10} alkyl, C_{1-10} perhaloalkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} carbocyclyl, 3–14 membered heterocyclyl, C_{6-14} aryl, and 5–14 membered heteroaryl, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups;

or two geminal hydrogens on a carbon atom are replaced with the group =O, =S, $=NN(R^{bb})_2$, $=NNR^{bb}C(=O)R^{aa}$, $=NNR^{bb}C(=O)OR^{aa}$, $=NNR^{bb}S(=O)_2R^{aa}$, $=NR^{bb}$, or $=NOR^{cc}$;

each instance of R^{aa} is, independently, selected from C_{1-10} alkyl, C_{1-10} perhaloalkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} carbocyclyl, 3–14 membered heterocyclyl, C_{6-14} aryl, and 5–14 membered heteroaryl, or two R^{aa} groups are joined to form a 3–14 membered heterocyclyl or 5–14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups;

each instance of R^{bb} is, independently, selected from hydrogen, –OH, –OR^{aa}, –$N(R^{cc})_2$, –CN, –$C(=O)R^{aa}$, –$C(=O)N(R^{cc})_2$, –CO_2R^{aa}, –SO_2R^{aa}, –$C(=NR^{cc})OR^{aa}$, –$C(=NR^{cc})N(R^{cc})_2$, –$SO_2N(R^{cc})_2$, –SO_2R^{cc}, –SO_2OR^{cc}, –SOR^{aa}, –$C(=S)N(R^{cc})_2$, –$C(=O)SR^{cc}$, –$C(=S)SR^{cc}$, –$P(=O)_2R^{aa}$, –$P(=O)(R^{aa})_2$, –$P(=O)_2N(R^{cc})_2$, –$P(=O)(NR^{cc})_2$, C_{1-10} alkyl, C_{1-10} perhaloalkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} carbocyclyl, 3–14 membered heterocyclyl, C_{6-14} aryl, and 5–14 membered heteroaryl, or two R^{bb} groups are joined to form a 3–14 membered heterocyclyl or 5–14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups;

each instance of R^{cc} is, independently, selected from hydrogen, C_{1-10} alkyl, C_{1-10} perhaloalkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} carbocyclyl, 3–14 membered heterocyclyl, C_{6-14} aryl, and 5–14 membered heteroaryl, or two R^{cc} groups are joined to form a 3–14

membered heterocyclyl or 5–14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups;

each instance of R^{dd} is, independently, selected from halogen, $-CN$, $-NO_2$, $-N_3$, $-SO_2H$, $-SO_3H$, $-OH$, $-OR^{ee}$, $-ON(R^{ff})_2$, $-N(R^{ff})_2$, $-N(R^{ff})_3^+X^-$, $-N(OR^{ee})R^{ff}$, $-SH$, $-SR^{ee}$, $-SSR^{ee}$, $-C(=O)R^{ee}$, $-CO_2H$, $-CO_2R^{ee}$, $-OC(=O)R^{ee}$, $-OCO_2R^{ee}$, $-C(=O)N(R^{ff})_2$, $-OC(=O)N(R^{ff})_2$, $-NR^{ff}C(=O)R^{ee}$, $-NR^{ff}CO_2R^{ee}$, $-NR^{ff}C(=O)N(R^{ff})_2$, $-C(=NR^{ff})OR^{ee}$, $-OC(=NR^{ff})R^{ee}$, $-OC(=NR^{ff})OR^{ee}$, $-C(=NR^{ff})N(R^{ff})_2$, $-OC(=NR^{ff})N(R^{ff})_2$, $-NR^{ff}C(=NR^{ff})N(R^{ff})_2$, $-NR^{ff}SO_2R^{ee}$, $-SO_2N(R^{ff})_2$, $-SO_2R^{ee}$, $-SO_2OR^{ee}$, $-OSO_2R^{ee}$, $-S(=O)R^{ee}$, $-Si(R^{ee})_3$, $-OSi(R^{ee})_3$, $-C(=S)N(R^{ff})_2$, $-C(=O)SR^{ee}$, $-C(=S)SR^{ee}$, $-SC(=S)SR^{ee}$, $-P(=O)_2R^{ee}$, $-P(=O)(R^{ee})_2$, $-OP(=O)(R^{ee})_2$, $-OP(=O)(OR^{ee})_2$, C_{1-6} alkyl, C_{1-6} perhaloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocyclyl, 3–10 membered heterocyclyl, C_{6-10} aryl, 5–10 membered heteroaryl, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{gg} groups, or two geminal R^{dd} substituents can be joined to form =O or =S;

each instance of R^{ee} is, independently, selected from C_{1-6} alkyl, C_{1-6} perhaloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocyclyl, C_{6-10} aryl, 3–10 membered heterocyclyl, and 3–10 membered heteroaryl, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{gg} groups;

each instance of R^{ff} is, independently, selected from hydrogen, C_{1-6} alkyl, C_{1-6} perhaloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocyclyl, 3–10 membered heterocyclyl, C_{6-10} aryl and 5–10 membered heteroaryl, or two R^{ff} groups are joined to form a 3–14 membered heterocyclyl or 5–14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{gg} groups; and

each instance of R^{gg} is, independently, halogen, $-CN$, $-NO_2$, $-N_3$, $-SO_2H$, $-SO_3H$, $-OH$, $-OC_{1-6}$ alkyl, $-ON(C_{1-6}$ alkyl$)_2$, $-N(C_{1-6}$ alkyl$)_2$, $-N(C_{1-6}$ alkyl$)_3^+X^-$, $-NH(C_{1-6}$ alkyl$)_2^+X^-$, $-NH_2(C_{1-6}$ alkyl$)^+X^-$, $-NH_3^+X^-$, $-N(OC_{1-6}$ alkyl$)(C_{1-6}$ alkyl$)$, $-N(OH)(C_{1-6}$ alkyl$)$, $-NH(OH)$, $-SH$, $-SC_{1-6}$ alkyl, $-SS(C_{1-6}$ alkyl$)$, $-C(=O)(C_{1-6}$ alkyl$)$, $-CO_2H$, $-CO_2(C_{1-6}$ alkyl$)$, $-OC(=O)(C_{1-6}$ alkyl$)$, $-OCO_2(C_{1-6}$ alkyl$)$, $-C(=O)NH_2$, $-C(=O)N(C_{1-6}$ alkyl$)_2$, $-OC(=O)NH(C_{1-6}$ alkyl$)$, $-NHC(=O)($ C_{1-6} alkyl$)$, $-N(C_{1-6}$ alkyl$)C(=O)($ C_{1-6} alkyl$)$, $-NHCO_2(C_{1-6}$ alkyl$)$, $-NHC(=O)N(C_{1-6}$ alkyl$)_2$, $-NHC(=O)NH(C_{1-6}$ alkyl$)$, $-NHC(=O)NH_2$, $-C(=NH)O(C_{1-6}$ alkyl$)$, $-OC(=NH)(C_{1-6}$ alkyl$)$, $-OC(=NH)OC_{1-6}$ alkyl, $-C(=NH)N(C_{1-6}$ alkyl$)_2$, $-C(=NH)NH(C_{1-6}$ alkyl$)$, $-C(=NH)NH_2$, $-OC(=NH)N(C_{1-6}$ alkyl$)_2$,

–OC(NH)NH(C_{1-6} alkyl), –OC(NH)NH_2, –NHC(NH)N(C_{1-6} alkyl)$_2$, –NHC(=NH)NH_2, –NHSO_2(C_{1-6} alkyl), –SO_2N(C_{1-6} alkyl)$_2$, –SO_2NH(C_{1-6} alkyl), –SO_2NH_2,–SO_2C_{1-6} alkyl, –SO_2OC_{1-6} alkyl, –OSO_2C_{1-6} alkyl, –SOC_{1-6} alkyl, –Si(C_{1-6} alkyl)$_3$, –OSi(C_{1-6} alkyl)$_3$ – C(=S)N(C_{1-6} alkyl)$_2$, C(=S)NH(C_{1-6} alkyl), C(=S)NH_2, –C(=O)S(C_{1-6} alkyl), –C(=S)SC_{1-6} alkyl, –SC(=S)SC_{1-6} alkyl, –P(=O)$_2$(C_{1-6} alkyl), –P(=O)(C_{1-6} alkyl)$_2$, –OP(=O)(C_{1-6} alkyl)$_2$, –OP(=O)(OC_{1-6} alkyl)$_2$, C_{1-6} alkyl, C_{1-6} perhaloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocyclyl, C_{6-10} aryl, 3–10 membered heterocyclyl, 5–10 membered heteroaryl; or two geminal R^{gg} substituents can be joined to form =O or =S; wherein X^- is a counterion;

R^2, R^3, $R^6$and R^7 are independently –H, -F, -Cl, -CN, CH_3, -CF_3, CHF_2, -C(O)NH_2, -OH, -OC_{1-4}alkyl, or –OCF_3; or R^6 and R^7 are taken together to form a 5-6 membered fused heterocyclcly or heteroaryl;

each R^4 is independently hydrogen, or C_{1-6} alkyl.

In an embodiment, there is provided a compound as defined above, wherein the compound is an MNK1 and/or MNK2 inhibitor.

In another embodiment, the present disclosure relates to pharmaceutical compositions comprising these compounds and to their use for the preparation of a medicament for the prophylaxis and treatment diseases associated with a dysfunction linked to MNK1 and MNK2 pathway, where MNK1 and MNK2 play a role (MNK overexpression, eIF4E overexpression, P38 MAPK

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

In another aspect, there is provided an in vitro 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, or a composition as defined above.

In another 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, Alzheimer's disease, obesity, diabetes or inflammation associated with acne, asthma, arteritis, polyarteritis, temporal arteritis, periarteritis nodosa, Takayasu's arteritis, arthritis, crystalline arthritis, osteoarthritis, psoriatic arthritis, gouty arthritis, reactive arthritis, rheumatoid arthritis, and Reiter's arthritis, ankylosing spondylitis, amylosis, amyotrophic lateral sclerosis, autoimmune diseases, allergies or allergic reactions, atherosclerosis, bronchitis, bursitis, chronic prostatitis, conjunctivitis, Chagas disease, chronic obstructive pulmonary disease, cermatomyositis, dry eye syndrome, diverticulitis, diabetes, type I diabetes mellitus, type 2 diabetes mellitus, a skin condition, psoriasis, eczema, burns, dermatitis, pruritus, endometriosis, Guillain-Barre syndrome, infection, ischaemic heart disease, Kawasaki disease, glomerulonephritis, gingivitis, hypersensitivity, headaches, migraine headaches, tension headaches, ileus, postoperative ileus and ileus during sepsis, idiopathic thrombocytopenic purpura, interstitial cystitis, prostatitis, appendicitis, Blau

syndrome, blepharitis, bronchiolitis, cervicitis, cholangitis, cholecystitis, chronic recurrent multifocal osteomyelitis (CRMO), cryopyrin associated periodic syndrome (CAPS), dacryoadenitis, dermatomyositis, dry eye syndrome, encephalitis, endocarditis, endometritis, enterocolitis, epicondylitis, epididymitis, familial cold-induced autoinflammatory syndrome, familial Mediterranean fever (FMF), fasciitis, fibrositis, hepatitis, hidradenitis suppurativa, laryngitis, mastitis, meningitis, mevalonate kinase deficiency (MKD), Muckle-Well syndrome, myelitis, myocarditis, myositis, nephritis, oophoritis, orchitis, osteitis, inflammatory osteolysis, otitis, pancreatitis, parotitis, pericarditis, peritonitis, pharyngitis, pleuritis, phlebitis, pneumonitis, pneumonia, proctitis, pulmonary fibrosis, pyelonephritis, pyoderma gangrenosum and acne syndrome (PAPA), pyogenic sterile arthritis, rhinitis, salpingitis, sinusitis, stomatitis, synovitis, TNF receptor associated periodic syndrome (TRAPS), tonsillitis, undifferentiated arthropathy, uveitis, vaginitis and vulvitis, gastrointestinal disorder, peptic ulcers, regional enteritis, diverticulitis, gastrointestinal bleeding, eosinophilic gastrointestinal disorders, eosinophilic esophagitis, eosinophilic gastritis, eosinophilic gastroenteritis, eosinophilic colitis, gastritis, diarrhea, gastroesophageal reflux disease (GERD), inflammatory bowel disease (IBD), Crohn's disease, ulcerative colitis, collagenous colitis, lymphocytic colitis, ischaemic colitis, diversion colitis, Behcet's syndrome, indeterminate colitis, inflammatory bowel syndrome (IBS), lupus, multiple sclerosis, morphea, myeasthenia gravis, myocardial ischemia, nephrotic syndrome, pemphigus vulgaris, pernicious aneaemia, peptic ulcers, polymyositis, primary biliary cirrhosis, neuroinflammation associated with brain disorders, Parkinson's disease, Huntington's disease, progressive supranuclear palsy, corticobasal degeneration, frontotemporal lobar degeneration, Pick's disease , Lewy body disease, oamyotropic lateral sclerosis (ALS), Alzheimer's disease, prostatitis, chronic inflammation associated with cranial radiation injury, pelvic inflammatory disease, reperfusion injury, regional enteritis, rheumatic fever, systemic lupus erythematosus, schleroderma, scierodoma, sarcoidosis, spondyloarthopathies, Sjogren's syndrome, thyroiditis, transplantation rejection, tendonitis, trauma or injury, frostbite, chemical irritants, toxins, scarring, burns, physical injury, vasculitis, vitiligo and Wegener's granulomatosis, acute inflammatory condition, chronic inflammatory condition, trauma, non-inflammatory myalgia or cancer.

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

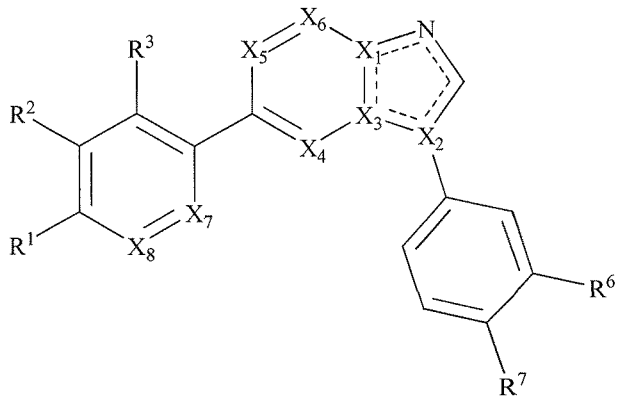
Figure 1 demonstrates that Example 6 (ETC-10445-3), Example 1 (ETC-5336) and Example 2 (ETC-6740) prevent eIF4E phosphorylation in BC-CML cell lines and primary cells. (A) Western blot analysis of K562 cell lines treated with various concentrations of compounds for 24 h. (B-D) BC-CML cells were treated 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 (Ib):



(Ib)

or a pharmaceutically acceptable form thereof, wherein

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

X_4, X_5 and X_6 are independently N or CR^4;

wherein at least one of X_1, X_2, X_3, X_4, X_5 and X_6 is N;

X_7 is N or CH;

X_8 is N or CH;

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

R^1 is -C(O)R, wherein R is

an optionally substituted 5-6 membered heterocyclyl non-aromatic ring system having ring carbon atoms and 1-4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen and sulfur; wherein the optionally substituted 5-6 membered heterocyclyl non-aromatic ring system is unsubstituted or substituted with halogen, $-CN$, $-NO_2$, $-N_3$, $-SO_2H$, $-SO_3H$, $-OH$, $-OR^{aa}$, $-ON(R^{bb})_2$, $-N(R^{bb})_2$, $-N(R^{bb})_3^+X^-$, $-N(OR^{cc})R^{bb}$, $-SH$, $-SR^{aa}$, $-SSR^{cc}$, $-C(=O)R^{aa}$, $-CO_2H$, $-CHO$, $-C(OR^{cc})_2$, $-CO_2R^{aa}$, $-OC(=O)R^{aa}$, $-OCO_2R^{aa}$, $-C(=O)N(R^{bb})_2$, $-OC(=O)N(R^{bb})_2$, $-NR^{bb}C(=O)R^{aa}$, $-NR^{bb}CO_2R^{aa}$, $-NR^{bb}C(=O)N(R^{bb})_2$, $-C(=NR^{bb})R^{aa}$, $-C(=NR^{bb})OR^{aa}$, $-OC(=NR^{bb})R^{aa}$, $-OC(=NR^{bb})OR^{aa}$, $-C(=NR^{bb})N(R^{bb})_2$, $-OC(=NR^{bb})N(R^{bb})_2$, $-NR^{bb}C(=NR^{bb})N(R^{bb})_2$, $-C(=O)NR^{bb}SO_2R^{aa}$, $-NR^{bb}SO_2R^{aa}$, $-SO_2N(R^{bb})_2$, $-SO_2R^{aa}$, $-SO_2OR^{aa}$, $-OSO_2R^{aa}$, $-S(=O)R^{aa}$, $-OS(=O)R^{aa}$, $-Si(R^{aa})_3$, $-OSi(R^{aa})_3$ $-C(=S)N(R^{bb})_2$, $-C(=O)SR^{aa}$, $-C(=S)SR^{aa}$, $-SC(=S)SR^{aa}$, $-SC(=O)SR^{aa}$, $-OC(=O)SR^{aa}$, $-SC(=O)OR^{aa}$, $-SC(=O)R^{aa}$, $-P(=O)_2R^{aa}$, $-OP(=O)_2R^{aa}$, $-P(=O)(R^{aa})_2$, $-OP(=O)(R^{aa})_2$, $-OP(=O)(OR^{cc})_2$, $-P(=O)_2N(R^{bb})_2$, $-OP(=O)_2N(R^{bb})_2$, $-P(=O)(NR^{bb})_2$, $-OP(=O)(NR^{bb})_2$, $-NR^{bb}P(=O)(OR^{cc})_2$, $-NR^{bb}P(=O)(NR^{bb})_2$, $-P(R^{cc})_2$, $-P(R^{cc})_3$, $-OP(R^{cc})_2$, $-OP(R^{cc})_3$, $-B(R^{aa})_2$, $-B(OR^{cc})_2$, $-BR^{aa}(OR^{cc})$, C_{1-10} alkyl, C_{1-10} perhaloalkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} carbocyclyl, 3–14 membered heterocyclyl, C_{6-14} aryl, and 5–14 membered heteroaryl, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups;

or two geminal hydrogens on a carbon atom are replaced with the group =O, =S, $=NN(R^{bb})_2$, $=NNR^{bb}C(=O)R^{aa}$, $=NNR^{bb}C(=O)OR^{aa}$, $=NNR^{bb}S(=O)_2R^{aa}$, $=NR^{bb}$, or $=NOR^{cc}$;

each instance of R^{aa} is, independently, selected from C_{1-10} alkyl, C_{1-10} perhaloalkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} carbocyclyl, 3–14 membered heterocyclyl, C_{6-14} aryl, and 5–14 membered heteroaryl, or two R^{aa} groups are joined to form a 3–14 membered heterocyclyl or 5–14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups;

each instance of R^{bb} is, independently, selected from hydrogen, $-OH$, $-OR^{aa}$, $-N(R^{cc})_2$, $-CN$, $-C(=O)R^{aa}$, $-C(=O)N(R^{cc})_2$, $-CO_2R^{aa}$, $-SO_2R^{aa}$, $-C(=NR^{cc})OR^{aa}$, $-C(=NR^{cc})N(R^{cc})_2$, $-SO_2N(R^{cc})_2$, $-SO_2R^{cc}$, $-SO_2OR^{cc}$, $-SOR^{aa}$, $-C(=S)N(R^{cc})_2$, $-C(=O)SR^{cc}$, $-C(=S)SR^{cc}$, $-P(=O)_2R^{aa}$, $-P(=O)(R^{aa})_2$, $-P(=O)_2N(R^{cc})_2$, $-P(=O)(NR^{cc})_2$, C_{1-10} alkyl, C_{1-10} perhaloalkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} carbocyclyl, 3–14 membered heterocyclyl, C_{6-14} aryl, and 5–14 membered heteroaryl, or two R^{bb} groups are joined to form a 3–14 membered heterocyclyl or 5–14 membered heteroaryl ring, wherein each alkyl, alkenyl,

alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups;

each instance of R^{cc} is, independently, selected from hydrogen, C_{1-10} alkyl, C_{1-10} perhaloalkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} carbocyclyl, 3–14 membered heterocyclyl, C_{6-14} aryl, and 5–14 membered heteroaryl, or two R^{cc} groups are joined to form a 3–14 membered heterocyclyl or 5–14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups;

each instance of R^{dd} is, independently, selected from halogen, $-CN$, $-NO_2$, $-N_3$, $-SO_2H$, $-SO_3H$, $-OH$, $-OR^{ee}$, $-ON(R^{ff})_2$, $-N(R^{ff})_2$, $-N(R^{ff})_3^+X^-$, $-N(OR^{ee})R^{ff}$, $-SH$, $-SR^{ee}$, $-SSR^{ee}$, $-C(=O)R^{ee}$, $-CO_2H$, $-CO_2R^{ee}$, $-OC(=O)R^{ee}$, $-OCO_2R^{ee}$, $-C(=O)N(R^{ff})_2$, $-OC(=O)N(R^{ff})_2$, $-NR^{ff}C(=O)R^{ee}$, $-NR^{ff}CO_2R^{ee}$, $-NR^{ff}C(=O)N(R^{ff})_2$, $-C(=NR^{ff})OR^{ee}$, $-OC(=NR^{ff})R^{ee}$, $-OC(=NR^{ff})OR^{ee}$, $-C(=NR^{ff})N(R^{ff})_2$, $-OC(=NR^{ff})N(R^{ff})_2$, $-NR^{ff}C(=NR^{ff})N(R^{ff})_2$, $-NR^{ff}SO_2R^{ee}$, $-SO_2N(R^{ff})_2$, $-SO_2R^{ee}$, $-SO_2OR^{ee}$, $-OSO_2R^{ee}$, $-S(=O)R^{ee}$, $-Si(R^{ee})_3$, $-OSi(R^{ee})_3$, $-C(=S)N(R^{ff})_2$, $-C(=O)SR^{ee}$, $-C(=S)SR^{ee}$, $-SC(=S)SR^{ee}$, $-P(=O)_2R^{ee}$, $-P(=O)(R^{ee})_2$, $-OP(=O)(R^{ee})_2$, $-OP(=O)(OR^{ee})_2$, C_{1-6} alkyl, C_{1-6} perhaloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocyclyl, 3–10 membered heterocyclyl, C_{6-10} aryl, 5–10 membered heteroaryl, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{gg} groups, or two geminal R^{dd} substituents can be joined to form =O or =S;

each instance of R^{ee} is, independently, selected from C_{1-6} alkyl, C_{1-6} perhaloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocyclyl, C_{6-10} aryl, 3–10 membered heterocyclyl, and 3–10 membered heteroaryl, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{gg} groups;

each instance of R^{ff} is, independently, selected from hydrogen, C_{1-6} alkyl, C_{1-6} perhaloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocyclyl, 3–10 membered heterocyclyl, C_{6-10} aryl and 5–10 membered heteroaryl, or two R^{ff} groups are joined to form a 3–14 membered heterocyclyl or 5–14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{gg} groups; and

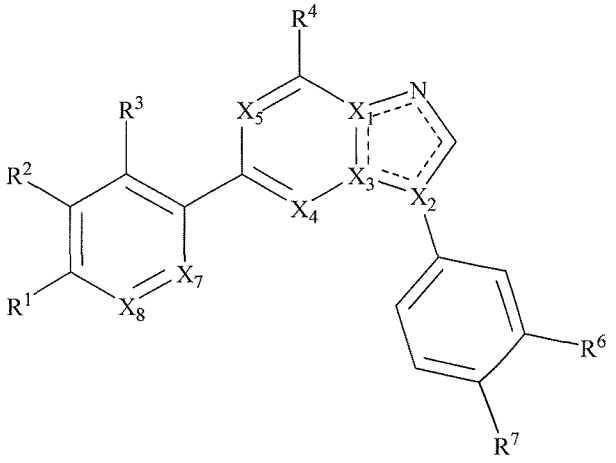
each instance of R^{gg} is, independently, halogen, $-CN$, $-NO_2$, $-N_3$, $-SO_2H$, $-SO_3H$, $-OH$, $-OC_{1-6}$ alkyl, $-ON(C_{1-6}$ alkyl$)_2$, $-N(C_{1-6}$ alkyl$)_2$, $-N(C_{1-6}$ alkyl$)_3^+X^-$, $-NH(C_{1-6}$ alkyl$)_2^+X^-$, $-NH_2(C_{1-6}$ alkyl$)^+X^-$, $-NH_3^+X^-$, $-N(OC_{1-6}$ alkyl$)(C_{1-6}$ alkyl$)$, $-N(OH)(C_{1-6}$ alkyl$)$,

–NH(OH), –SH, –SC_{1-6} alkyl, –$SS(C_{1-6}$ alkyl), –$C(=O)(C_{1-6}$ alkyl), –CO_2H, –$CO_2(C_{1-6}$ alkyl), –$OC(=O)(C_{1-6}$ alkyl), –$OCO_2(C_{1-6}$ alkyl), –$C(=O)NH_2$, –$C(=O)N(C_{1-6}$ alkyl)$_2$, –$OC(=O)NH(C_{1-6}$ alkyl), –$NHC(=O)(C_{1-6}$ alkyl), –$N(C_{1-6}$ alkyl)$C(=O)(C_{1-6}$ alkyl), –$NHCO_2(C_{1-6}$ alkyl), –$NHC(=O)N(C_{1-6}$ alkyl)$_2$, –$NHC(=O)NH(C_{1-6}$ alkyl), –$NHC(=O)NH_2$, –$C(=NH)O(C_{1-6}$ alkyl),–$OC(=NH)(C_{1-6}$ alkyl), –$OC(=NH)OC_{1-6}$ alkyl, –$C(=NH)N(C_{1-6}$ alkyl)$_2$, –$C(=NH)NH(C_{1-6}$ alkyl), –$C(=NH)NH_2$, –$OC(=NH)N(C_{1-6}$ alkyl)$_2$, –$OC(NH)NH(C_{1-6}$ alkyl), –$OC(NH)NH_2$, –$NHC(NH)N(C_{1-6}$ alkyl)$_2$, –$NHC(=NH)NH_2$, –$NHSO_2(C_{1-6}$ alkyl), –$SO_2N(C_{1-6}$ alkyl)$_2$, –$SO_2NH(C_{1-6}$ alkyl), –SO_2NH_2,–SO_2C_{1-6} alkyl, –SO_2OC_{1-6} alkyl, –OSO_2C_{1-6} alkyl, –SOC_{1-6} alkyl, –$Si(C_{1-6}$ alkyl)$_3$, –$OSi(C_{1-6}$ alkyl)$_3$ –$C(=S)N(C_{1-6}$ alkyl)$_2$, $C(=S)NH(C_{1-6}$ alkyl), $C(=S)NH_2$, –$C(=O)S(C_{1-6}$ alkyl), –$C(=S)SC_{1-6}$ alkyl, –$SC(=S)SC_{1-6}$ alkyl, –$P(=O)_2(C_{1-6}$ alkyl), –$P(=O)(C_{1-6}$ alkyl)$_2$, –$OP(=O)(C_{1-6}$ alkyl)$_2$, –$OP(=O)(OC_{1-6}$ alkyl)$_2$, C_{1-6} alkyl, C_{1-6} perhaloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocyclyl, C_{6-10} aryl, 3–10 membered heterocyclyl, 5–10 membered heteroaryl; or two geminal R^{gg} substituents can be joined to form =O or =S; wherein X^- is a counterion;

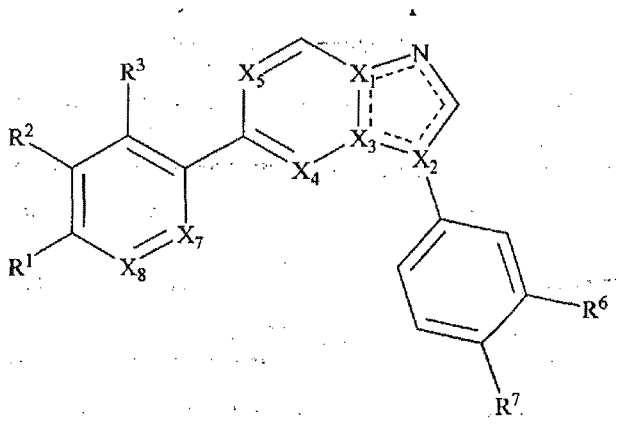
R^2, R^3, R^6, and R^7 are independently –H, -F, -Cl, -CN, $-CH_3$, $-CF_3$, CHF_2, $-C(O)NH_2$, -OH, $-OC_{1-4}$alkyl, or $-OCF_3$; or R^6 and R^7 are taken together to form a 5-6 membered fused heterocyclcly or heteroaryl;

each R^4 is independently hydrogen, or C_{1-6} alkyl.

2. The compound of claim 1, wherein the compound is of Formula (Ib-i) or (Ib-ii):



(Ib-i)



(Ib-ii)

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 CH;

X_8 is N or CH;

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

R^1 is -C(O)R, wherein R is optionally substituted heterocyclyl;

R^2, R^3, R^6, and R^7 are independently –H, -F, -Cl, -CN, $-CH_3$, $-CF_3$, CHF_2, $-C(O)NH_2$, -OH, $-OC_{1-4}$alkyl, or $-OCF_3$; or R^6 and R^7 are taken together to form a 5-6 membered fused heterocyclcly or heteroaryl moiety; and

each R^4 is independently hydrogen, or C_{1-6} alkyl.

3. The compound of claim 1 or 2, wherein R^7 is -CN.

4. The compound of any one of claims 1-3, wherein R^1 is -C(O)R, wherein R is one of the following:

myocarditis, myositis, nephritis, oophoritis, orchitis, osteitis, inflammatory osteolysis, otitis, pancreatitis, parotitis, pericarditis, peritonitis, pharyngitis, pleuritis, phlebitis, pneumonitis, pneumonia, proctitis, pulmonary fibrosis, pyelonephritis, pyoderma gangrenosum and acne syndrome (PAPA), pyogenic sterile arthritis, rhinitis, salpingitis, sinusitis, stomatitis, synovitis, TNF receptor associated periodic syndrome (TRAPS), tonsillitis, undifferentiated arthropathy, uveitis, vaginitis and vulvitis, gastrointestinal disorder, peptic ulcers, regional enteritis, diverticulitis, gastrointestinal bleeding, eosinophilic gastrointestinal disorders, eosinophilic esophagitis, eosinophilic gastritis, eosinophilic gastroenteritis, eosinophilic colitis, gastritis, diarrhea, gastroesophageal reflux disease (GERD), inflammatory bowel disease (IBD), Crohn's disease, ulcerative colitis, collagenous colitis, lymphocytic colitis, ischaemic colitis, diversion colitis, Behcet's syndrome, indeterminate colitis, inflammatory bowel syndrome (IBS), lupus, multiple sclerosis, morphea, myeasthenia gravis, myocardial ischemia, nephrotic syndrome, pemphigus vulgaris, pernicious aneaemia, peptic ulcers, polymyositis, primary biliary cirrhosis, neuroinflammation associated with brain disorders, Parkinson's disease, Huntington's disease, progressive supranuclear palsy, corticobasal degeneration, frontotemporal lobar degeneration, Pick's disease , Lewy body disease, oamyotropic lateral sclerosis (ALS), Alzheimer's disease, prostatitis, chronic inflammation associated with cranial radiation injury, pelvic inflammatory disease, reperfusion injury, regional enteritis, rheumatic fever, systemic lupus erythematosus, schleroderma, scierodoma, sarcoidosis, spondyloarthopathies, Sjogren's syndrome, thyroiditis, transplantation rejection, tendonitis, trauma or injury, frostbite, chemical irritants, toxins, scarring, burns, physical injury, vasculitis, vitiligo and Wegener's granulomatosis, acute inflammatory condition, chronic inflammatory condition, trauma, non-inflammatory myalgia or cancer.

14. Use of a compound of claims 1 to 9, or a pharmaceutically acceptable form thereof, or a composition of claim 10 or 11, in the manufacture of a medicament for treating a MNK1 and/or MNK2 -related disorder in accordance with claim 13, wherein the MNK1 and/or MNK2 -related disorder is cancer.

15. Use of a compound of claims 1 to 9, or a pharmaceutically acceptable form thereof, or a composition of claim 10 or 11, in the manufacture of a medicament for treating a MNK1 and/or MNK2 -related disorder in accordance with claim 13, wherein the MNK1 and/or MNK2 -related disorder is Huntington's disease, progressive supranuclear palsy, corticobasal

degeneration, frontotemporal lobar degeneration, Pick's disease, Parkinson's disease, Lewy body disease, or amyotropic lateral sclerosis (ALS).

16. Use of a compound of claims 1 to 9, or a pharmaceutically acceptable form thereof, or a composition of claim 10 or 11 in the manufacture of a medicament for treating a MNK1 and/or MNK2 -related disorder in accordance with claim 14, wherein the cancer is blood or solid tumours.

17. Use of a compound of claims 1 to 9, or a pharmaceutically acceptable form thereof, or a composition of claim 10 or 11, in the manufacture of a medicament for treating a MNK1 and/or MNK2 -related disorder in accordance with claim 13, wherein the MNK1 and/or MNK2 -related disorder is obesity or diabetes.

18. Use of a compound of claims 1 to 9, or a pharmaceutically acceptable form thereof, or a composition of claim 10 or 11 in the manufacture of a medicament for treating a MNK1 and/or MNK2 -related disorder in accordance with claim 13, wherein the compound or composition is to be administered in combination with a kinase inhibitor selected from a PI3K inhibitor or a mTOR inhibitor.

19. Use of a compound of claims 1 to 9, or a pharmaceutically acceptable form thereof, or a composition of claim 10 or 11 in accordance with any one of claims 13 to 17, wherein the compound or composition is to be 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.