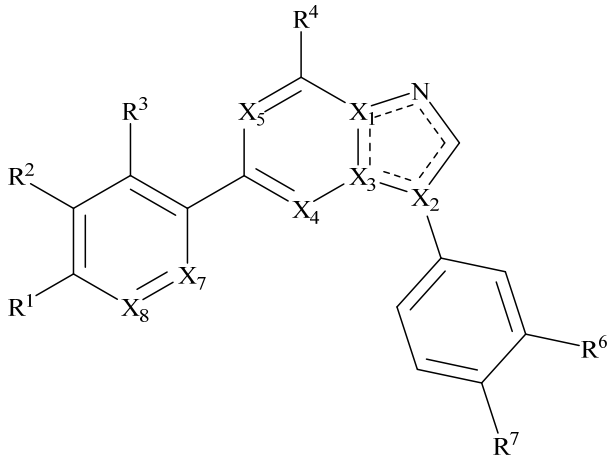
CLAIMS

1. A compound of Formula (**Ib-i**):



(**Ib-i**).

or a pharmaceutically acceptable salt 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 an 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,–$OC_{1\text{-}4}$alkyl, or $–OCF_3$; or R^6 and R^7 are taken together to form a 5-6 membered fused heterocyclyl or heteroaryl; and

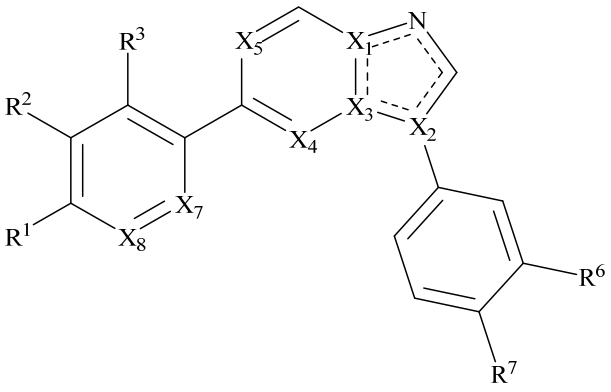
each R^4 is independently hydrogen or $C_{1\text{-}6}$ alkyl.

2. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein X_2 is C.

3. The compound of claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein X_3 is N.

4. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein X_7 and X_8 are each CH.

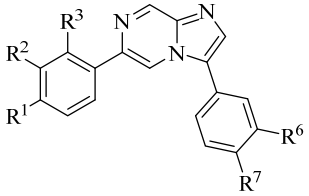
5. The compound of any one of the preceding claims, wherein the compound is of Formula (**Ib-ii**):



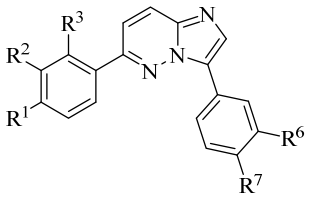
(**Ib-ii**)

or a pharmaceutically acceptable salt thereof.

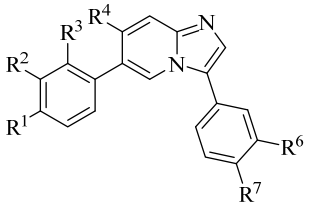
6. The compound of claim 1, wherein the compound is of Formula (**IIa**), (**IIIa**), (**IVa**), (**Va**), (**VIa**), or (**VIIa**):



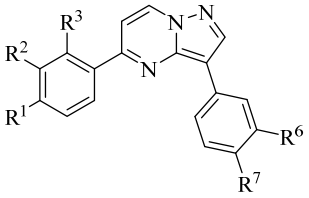
Formula IIa



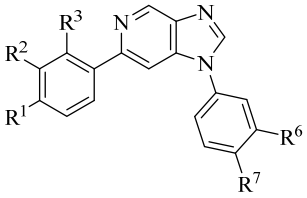
Formula IIIa



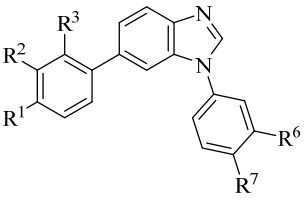
Formula IVa



Formula Va



Formula VIa



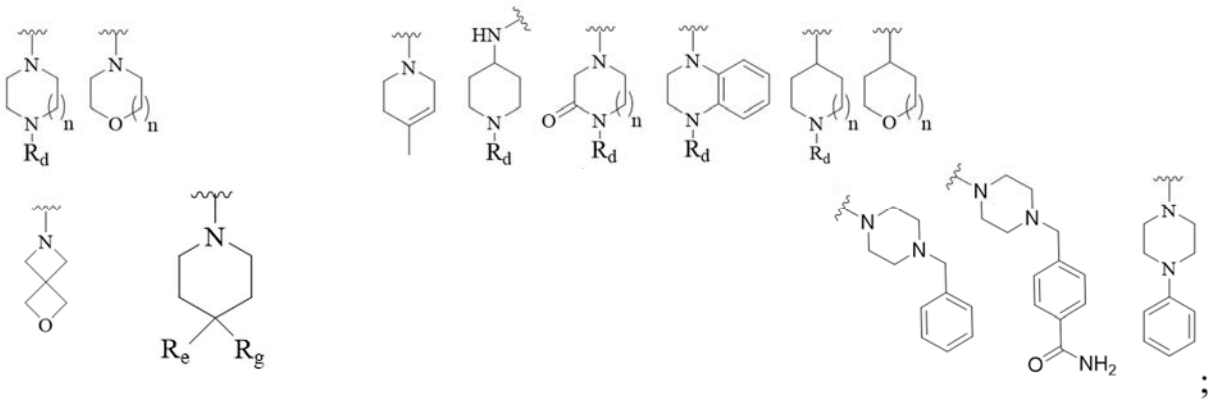
Formula VIIa

,

or a pharmaceutically acceptable salt thereof.

7. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein R^1 is –C(O)R, wherein:

R is of the formula:



each R_C is independently optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

each Rd is independently optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, -COR_C, $S(O)R_C$, $S(O)_2R_C$, optionally substituted alkylaryl, or optionally substituted aryl;

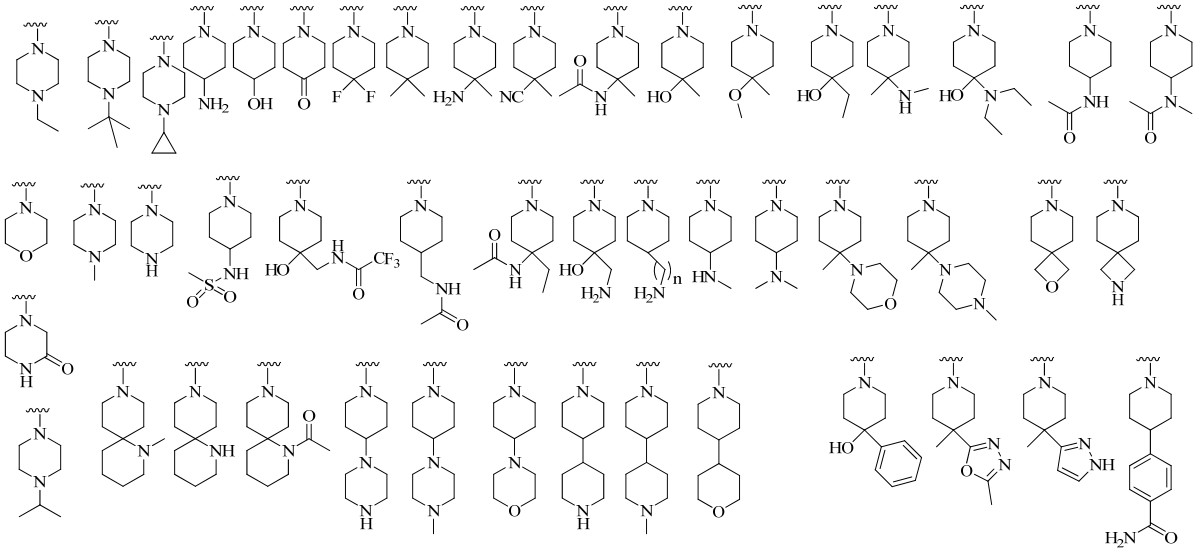
each R_e is independently hydrogen, halo, -OH, -OR_C, -NH_2, -NHR_C, -$NHSO_2R_C$, -$NR_fSO_2R_C$, -NR_CR_f, -CN, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclyl, -COR_C, or -$NHCOR_C$;

each R_f is independently -H or C_{1-6} alkyl;

each R_g is independently hydrogen, halo, -OH, -OR_C, -NH_2, -NHR_C, -$NHSO_2R_C$, -$NR_fSO_2R_C$, -NR_CR_f, -CN, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclyl, -COR_C, or -$NHCOR_C$; and

n is 1, or 2.

8. The compound of Claim 1, or a pharmaceutically acceptable salt thereof, wherein R^1 is –C(O)R, wherein R is one of the following:



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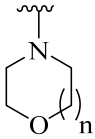
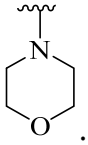
9. The compound of claim 7, or a pharmaceutically acceptable salt thereof,

wherein R is of the formula: , and n is 1 or 2.

10. The compound of claim 7, or a pharmaceutically acceptable salt thereof,

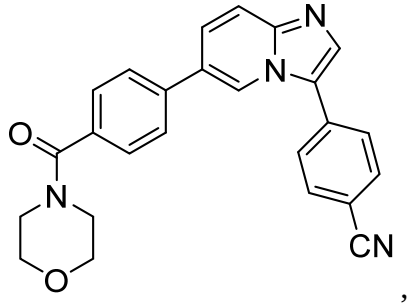
wherein R is of the formula: .

11. The compound of claim 2, or a pharmaceutically acceptable salt thereof, wherein both R^2 and R^3 are hydrogen.

12. The compound of claim 2, or a pharmaceutically acceptable salt thereof, wherein R^6 is -H.

13. The compound of claim 2, or a pharmaceutically acceptable salt thereof, wherein R^7 is -F, -Cl, or -CN.

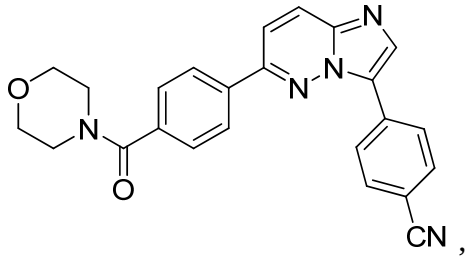
14. A compound of formula:



,

or a pharmaceutically acceptable salt thereof.

15. A compound of formula:



,

or a pharmaceutically acceptable salt thereof.

16. A pharmaceutical composition comprising a compound of any one of claims 1 to 15, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

17. Use of a compound of any one of claims 1 to 15, or a pharmaceutically acceptable salt thereof, or a composition of claim 16 in the manufacture of a medicament for treating a MNK1-related disorder or MNK2-related disorder, where the disorder is selected from the group consisting of:

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, and non-inflammatory myalgia.

18. The use of claim 17, wherein the MNK1-related disorder or MNK2-related disorder is cancer, or Alzheimer’s disease, optionally wherein the cancer is a hematological cancer or solid tumor.

19. The use of claim 17 or 18, wherein the compound is to be administered in combination with an additional therapeutic agent.

20. A kit comprising a compound of any one of claims 1 to 15, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 16; and instructions for administering the compound or the composition to a subject.