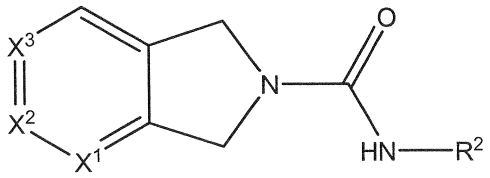
WHAT IS CLAIMED IS:

1. A compound of Formula (Ic), and pharmaceutically acceptable salts thereof



Formula (Ic);

wherein

X^1, X^2, and X^3 are CH; or

X^1 and X^3 are CH; and X^2 is N; or

X^1 and X^3 are CH; and X^2 is CR^1; or

X^2 and X^3 are CH; and X^1 is CR^1; or

X^1 is CH; and X^2 and X^3 are CR^1; or

X^2 is CH; and X^1 and X^3 are N; or

X^2 and X^3 are CH; and X^1 is N; or

X^1 is CH; X^2 is N; and X^3 is CR^1; or

X^1 is CR^1; X^2 is N; and X^3 is CH; or

X^1 is N; X^2 is CR^1; and X^3 is CH; or

X^1 is N; X^2 is CR^1; and X^3 is N;

R^1 is R^3, OR^3, SR^3, $S(O)R^3$, SO_2R^3, $C(O)R^3$, $C(O)OR^3$, $OC(O)R^3$, NHR^3, $N(R^3)_2$, $C(O)NH_2$, $C(O)NHR^3$, $C(O)N(R^3)_2$, $NHC(O)R^3$, $NR^3C(O)R^3$, $NHC(O)OR^3$, $NR^3C(O)OR^3$, SO_2NH_2, SO_2NHR^3, $SO_2N(R^3)_2$, $NHSO_2R^3$, $NR^3SO_2R^3$, $NHSO_2NHR^3$, $NHSO_2N(R^3)_2$, $NR^3SO_2NHR^3$, $NR^3SO_2N(R^3)_2$, $C(O)NHSO_2R^3$, $NHSO_2NHR^3$, F, Cl, Br, I, CN, NH_2, NO_2, N_3, OH, C(O)H, CF_3, C(O)OH, or $C(O)NH_2$;

R^2 is alkyl, alkenyl, alkynyl, phenyl, heterocyclyl, cycloalkyl, or cycloalkenyl; wherein each R^2 alkyl, alkenyl, and alkynyl is ~~optionally~~ substituted with one, two, three or four independently selected R^4, OR^4, SR^4, $S(O)R^4$, SO_2R^4, $C(O)R^4$, $CO(O)R^4$, $OC(O)R^4$, $OC(O)OR^4$, $NHC(O)R^4$, $NR^4C(O)R^4$, $NHS(O)_2R^4$, $NR^4S(O)_2R^4$, $NHC(O)OR^4$, $NR^4C(O)OR^4$, $NHC(O)NH_2$, $NHC(O)NHR^4$, $NHC(O)N(R^4)_2$, $NR^4C(O)NHR^4$, $NR^4C(O)N(R^4)_2$, $C(O)NH_2$, $C(O)NHR^4$, $C(O)N(R^4)_2$, C(O)NHOH, $C(O)NHOR^4$, $C(O)NHSO_2R^4$, $C(O)NR^4SO_2R^4$, SO_2NH_2, SO_2NHR^4, $SO_2N(R^4)_2$, C(O)H, (O), CN, N_3, NO_2, CF_3, CF_2CF_3, OCF_3, OCF_2CF_3, F, Cl, Br or I; wherein each R^2 phenyl is ~~optionally~~ substituted at the para position with one independently selected R^5, OR^5, SR^5, $S(O)R^5$, SO_2R^5, $C(O)R^5$, $CO(O)R^5$, $OC(O)R^5$, $OC(O)OR^5$, NH_2, NHR^5, $N(R^5)_2$, $NHC(O)R^5$, $NR^5C(O)R^5$, $NHS(O)_2R^5$, $NR^5S(O)_2R^5$, $NHC(O)OR^5$, $NR^5C(O)OR^5$, $NHC(O)NH_2$, $NHC(O)NHR^5$, $NHC(O)N(R^5)_2$, $NR^5C(O)NHR^5$, $NR^5C(O)N(R^5)_2$, $C(O)NH_2$, $C(O)NHR^5$, $C(O)N(R^5)_2$, $CHNOR^5$, C(O)NHOH, $C(O)NHOR^5$,

$C(O)NHSO_2R^5$, $C(O)NR^5SO_2R^5$, SO_2NH_2, SO_2NHR^5, $SO_2N(R^5)_2$, C(O)H, C(O)OH, OH, CN, N_3, NO_2, CF_3, CF_2CF_3, OCF_3, OCF_2CF_3, Br or I; wherein each R^2 phenyl is optionally additionally substituted with one F; wherein each R^2 heterocyclyl, cycloalkyl, and cycloalkenyl is ~~optionally~~ substituted with one, two, three or four independently selected R^5, OR^5, SR^5, $S(O)R^5$, SO_2R^5, $C(O)R^5$, $CO(O)R^5$, $OC(O)R^5$, $OC(O)OR^5$, NH_2, NHR^5, $N(R^5)_2$, $NHC(O)R^5$, $NR^5C(O)R^5$, $NHS(O)_2R^5$, $NR^5S(O)_2R^5$, $NHC(O)OR^5$, $NR^5C(O)OR^5$, $NHC(O)NH_2$, $NHC(O)NHR^5$, $NHC(O)N(R^5)_2$, $NR^5C(O)NHR^5$, $NR^5C(O)N(R^5)_2$, $C(O)NH_2$, $C(O)NHR^5$, $C(O)N(R^5)_2$, C(O)NHOH, $C(O)NHOR^5$, $C(O)NHSO_2R^5$, $C(O)NR^5SO_2R^5$, SO_2NH_2, SO_2NHR^5, $SO_2N(R^5)_2$, C(O)H, C(O)OH, OH, CN, N_3, CF_3, CF_2CF_3, OCF_3, OCF_2CF_3, F, Cl, Br or I;

R^3, at each occurrence, is independently selected alkyl, alkenyl, alkynyl, aryl, or heterocyclyl; wherein each R^3 alkyl, alkenyl, and alkynyl is optionally substituted with one, two, three or four independently selected R^6, OR^6, SR^6, $S(O)R^6$, SO_2R^6, $C(O)R^6$, $CO(O)R^6$, $OC(O)R^6$, $OC(O)OR^6$, NH_2, NHR^6, $N(R^6)_2$, $NHC(O)R^6$, $NR^6C(O)R^6$, $NHS(O)_2R^6$, $NR^6S(O)_2R^6$, $NHC(O)OR^6$, $NR^6C(O)OR^6$, $NHC(O)NH_2$, $NHC(O)NHR^6$, $NHC(O)N(R^6)_2$, $NR^6C(O)NHR^6$, $NR^6C(O)N(R^6)_2$, $C(O)NH_2$, $C(O)NHR^6$, $C(O)N(R^6)_2$, C(O)NHOH, $C(O)NHOR^6$, $C(O)NHSO_2R^6$, $C(O)NR^6SO_2R^6$, SO_2NH_2, SO_2NHR^6, $SO_2N(R^6)_2$, C(O)H, C(O)OH, OH, (O), CN, N_3, NO_2, CF_3, CF_2CF_3, OCF_3, OCF_2CF_3, F, Cl, Br or I;

R^4, at each occurrence, is independently selected alkyl, alkenyl, alkynyl, aryl, cycloalkyl, or heterocyclyl; wherein each R^4 alkyl, alkenyl, and alkynyl is optionally substituted with one, two, three or four independently selected R^7, OR^7, SR^7, $S(O)R^7$, SO_2R^7, $C(O)R^7$, $OC(O)R^7$, $OC(O)OR^7$, NH_2, NHR^7, $NHC(O)R^7$, $NR^7C(O)R^7$, $NHS(O)_2R^7$, $NR^7S(O)_2R^7$, $NHC(O)OR^7$, $NR^7C(O)OR^7$, $NHC(O)NH_2$, $NHC(O)NHR^7$, $NHC(O)N(R^7)_2$, $NR^7C(O)NHR^7$, $NR^7C(O)N(R^7)_2$, $C(O)NH_2$, $C(O)NHR^7$, $C(O)N(R^7)_2$, C(O)NHOH, $C(O)NHOR^7$, $C(O)NHSO_2R^7$, $C(O)NR^7SO_2R^7$, SO_2NH_2, SO_2NHR^7, $SO_2N(R^7)_2$, C(O)H, OH, (O), CN, N_3, NO_2, CF_3, CF_2CF_3, OCF_3, OCF_2CF_3, F, Cl, Br or I; wherein each R^4 aryl and heterocycyl is optionally substituted with one, two, three or four independently selected R^8, OR^8, SR^8, $S(O)R^8$, SO_2R^8, $C(O)R^8$, $CO(O)R^8$, $OC(O)R^8$, $OC(O)OR^8$, NH_2, NHR^8, $NHC(O)R^8$, $NR^8C(O)R^8$, $NHS(O)_2R^8$, $NR^8S(O)_2R^8$, $NHC(O)OR^8$, $NR^8C(O)OR^8$, $NHC(O)NH_2$, $NHC(O)NHR^8$, $NHC(O)N(R^8)_2$, $NR^8C(O)NHR^8$, $NR^8C(O)N(R^8)_2$, $C(O)NH_2$, $C(O)NHR^8$, $C(O)N(R^8)_2$, C(O)NHOH, $C(O)NHOR^8$, $C(O)NHSO_2R^8$, $C(O)NR^8SO_2R^8$, SO_2NH_2, SO_2NHR^8, $SO_2N(R^8)_2$, C(O)H, C(O)OH, OH, CN, N_3, NO_2, CF_3, CF_2CF_3, OCF_3, OCF_2CF_3, F, Cl, Br or I;

R^5, at each occurrence, is independently selected alkyl, alkenyl, alkynyl, aryl, heterocyclyl, cycloalkyl, or cycloalkenyl; wherein each R^5 alkyl, alkenyl, and alkynyl is optionally substituted with one, two, three or four independently selected R^9, OR^9, SR^9, $S(O)R^9$, SO_2R^9, $C(O)R^9$, $CO(O)R^9$, $OC(O)R^9$, $OC(O)OR^9$, NH_2, NHR^9, $N(R^9)_2$, $NHC(O)R^9$,

R^{15}, at each occurrence, is independently selected alkyl; wherein the R^{15} alkyl is optionally substituted with one, two, three or four alkoxy;

R^{16}, at each occurrence, is independently selected alkyl, wherein the R^{16} alkyl is optionally substituted with one, two, three or four alkoxy;

with the proviso that when X^1, X^2, and X^3 are CH and R^2 is phenyl; R^5 is not methyl;

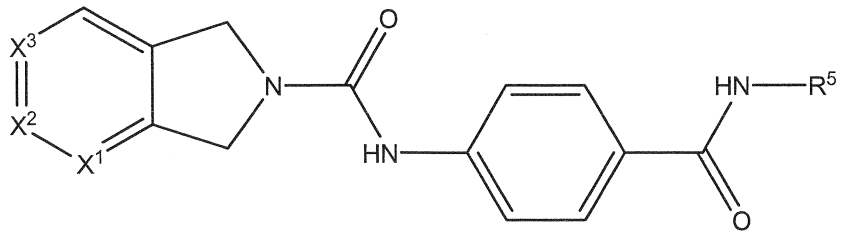
with the proviso that when X^1, X^2, and X^3 are CH, and R^2 is phenyl substituted with OR^5; R^5 is not methyl;

with the proviso that when R^2 is ~~unsubstituted alkyl or optionally~~ substituted alkyl; R^2 is C_4-C_6-alkyl;

with the proviso that when R^{13} is piperidinyl, it is substituted piperidinyl; and

with the proviso that when R^{13} is pyrrolinyl, at least one of X^1, X^2, and X^3 is N.

2. A compound having Formula (Vc), or pharmaceutically acceptable salts thereof



(Vc);

wherein

X^1, X^2, and X^3 are CH; or

X^1 and X^3 are CH; and X^2 is N; or

X^1 and X^3 are CH; and X^2 is CR^1; or

X^2 and X^3 are CH; and X^1 is CR^1; or

X^1 is CH; and X^2 and X^3 are CR^1; or

X^2 is CH; and X^1 and X^3 are N; or

X^2 and X^3 are CH; and X^1 is N; or

X^1 is CH; X^2 is N; and X^3 is CR^1; or

X^1 is CR^1; X^2 is N; and X^3 is CH; or

X^1 is N; X^2 is CR^1; and X^3 is CH; or

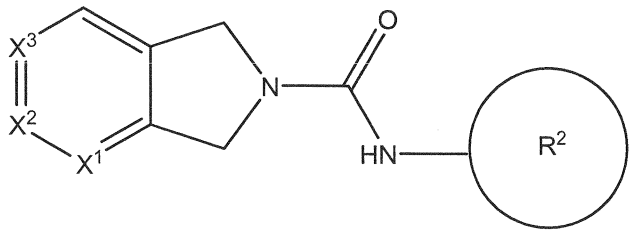
X^1 is N; X^2 is CR^1; and X^3 is N;

R^1 is R^3, OR^3, SR^3, $S(O)R^3$, SO_2R^3, $C(O)R^3$, $C(O)OR^3$, $OC(O)R^3$, NHR^3, $N(R^3)_2$, $C(O)NH_2$, $C(O)NHR^3$, $C(O)N(R^3)_2$, $NHC(O)R^3$, $NR^3C(O)R^3$, $NHC(O)OR^3$, $NR^3C(O)OR^3$, SO_2NH_2, SO_2NHR^3, $SO_2N(R^3)_2$, $NHSO_2R^3$, $NR^3SO_2R^3$, $NHSO_2NHR^3$, $NHSO_2N(R^3)_2$,

19. Use of a therapeutically effective amount of one additional therapeutic agent or more than one additional therapeutic agent, in the manufacture of a medicament for treating hypertension, chronic and congestive heart failure, cardiac hypertrophy, restenosis, chronic renal failure, cerebral vasospasm after subarachnoid bleeding, pulmonary hypertension, atherosclerosis, asthma, male erectile dysfunctions, female sexual dysfunction, over-active bladder syndrome, spinal-cord injury, traumatic brain injury, stroke, inflammatory and demyelinating diseases, Alzheimer's disease, pain, multiple sclerosis, amyotrophic lateral sclerosis, Huntington's disease, Parkinson's disease, inflammatory pain, rheumatoid arthritis, osteoarthritis, irritable bowel syndrome, Crohn's disease, psoriasis, ulcerative colitis, lupus, inflammatory bowel disease, cancer, tumor metastasis, viral infections, bacterial infections, insulin resistance, diabetes, ocular hypertension, preterm labor, atherosclerosis, spinal muscular atrophy, encephalomyelitis, osteoporosis, HIV-1, encephalitis, ischemic CNS disorders, vascular or AD type dementia, glaucoma, retinopathy, benign prostatic hypertrophy, psychiatric disorders, including depression, schizophrenia, obsessive compulsive disorder and bipolar disorder, epilepsy and seizure disorders, for decreasing ischemia-reperfusion injury, myocardial infarct size and myocardial fibrosis, for the prevention of graft failure, and cystic fibrosis in a patient.

20. Use of a therapeutically effective amount of the compound of claim 1, or pharmaceutically acceptable salts thereof; and a therapeutically effective amount of one additional therapeutic agent or more than one additional therapeutic agent, in the manufacture of a medicament for treating inflammatory and tissue repair disorders including rheumatoid arthritis, inflammatory bowel disease, asthma and COPD (chronic obstructive pulmonary disease), osteoarthritis, osteoporosis and fibrotic diseases; dermatosis, including psoriasis, atopic dermatitis and ultra-violet induced skin damage; autoimmune diseases including systemic lupus erythematosis, multiple sclerosis, psoriatic arthritis, ankylosing spondylitis, tissue and organ rejection, Alzheimer's disease, stroke, atherosclerosis, restenosis, diabetes, glomerulonephritis, cancer, including breast cancer, prostate cancer, lung cancer, colon cancer, cervix cancer, ovarian cancer, skin cancer, CNS cancer, bladder cancer, pancreatic cancer, leukemia, lymphoma or Hodgkin's disease, cachexia, inflammation associated with infection and certain viral infections, including Acquired Immune Deficiency Syndrome (AIDS), adult respiratory distress syndrome, and ataxia telengiectasia or spleen cancer in a patient.

21. A compound of claim 1 having Formula (IIc), or pharmaceutically acceptable salts thereof



(IIc);

wherein

X^1, X^2, and X^3 are CH; or

X^1 and X^3 are CH; and X^2 is N; or

X^1 and X^3 are CH; and X^2 is CR^1; or

X^2 and X^3 are CH; and X^1 is CR^1; or

X^1 is CH; and X^2 and X^3 are CR^1; or

X^2 is CH; and X^1 and X^3 are N; or

X^2 and X^3 are CH; and X^1 is N; or

X^1 is CH; X^2 is N; and X^3 is CR^1; or

X^1 is CR^1; X^2 is N; and X^3 is CH; or

X^1 is N; X^2 is CR^1; and X^3 is CH; or

X^1 is N; X^2 is CR^1; and X^3 is N;

R^1 is R^3, OR^3, SR^3, $S(O)R^3$, SO_2R^3, $C(O)R^3$, $C(O)OR^3$, $OC(O)R^3$, NHR^3, $N(R^3)_2$, $C(O)NH_2$, $C(O)NHR^3$, $C(O)N(R^3)_2$, $NHC(O)R^3$, $NR^3C(O)R^3$, $NHC(O)OR^3$, $NR^3C(O)OR^3$, SO_2NH_2, SO_2NHR^3, $SO_2N(R^3)_2$, $NHSO_2R^3$, $NR^3SO_2R^3$, $NHSO_2NHR^3$, $NHSO_2N(R^3)_2$, $NR^3SO_2NHR^3$, $NR^3SO_2N(R^3)_2$, $C(O)NHSO_2R^3$, $NHSO_2NHR^3$, F, Cl, Br, I, CN, NO_2, N_3, OH, C(O)H, CF_3, C(O)OH, or $C(O)NH_2$;

R^2 is phenyl, heterocyclyl, cycloalkyl, or cycloalkenyl; wherein each R^2 phenyl is substituted at the para position with one independently selected R^5, OR^5, SR^5, $S(O)R^5$, SO_2R^5, $C(O)R^5$, $CO(O)R^5$, $OC(O)R^5$, $OC(O)OR^5$, NH_2, NHR^5, $N(R^5)_2$, $NHC(O)R^5$, $NR^5C(O)R^5$, $NHS(O)_2R^5$, $NR^5S(O)_2R^5$, $NHC(O)OR^5$, $NR^5C(O)OR^5$, $NHC(O)NH_2$, $NHC(O)NHR^5$, $NHC(O)N(R^5)_2$, $NR^5C(O)NHR^5$, $NR^5C(O)N(R^5)_2$, $C(O)NH_2$, $C(O)NHR^5$, $C(O)N(R^5)_2$, $CHNOR^5$, $C(O)NHOH$, $C(O)NHOR^5$, $C(O)NHSO_2R^5$, $C(O)NR^5SO_2R^5$, SO_2NH_2, SO_2NHR^5, $SO_2N(R^5)_2$, C(O)H, C(O)OH, OH, CN, N_3, CF_3, CF_2CF_3, OCF_3, OCF_2CF_3, Br or I; wherein each R^2 phenyl is optionally additionally substituted with one F; wherein each R^2 heterocyclyl, cycloalkyl, and cycloalkenyl is substituted with one, two, three or four independently selected R^5, OR^5, SR^5, $S(O)R^5$, SO_2R^5, $C(O)R^5$, $CO(O)R^5$, $OC(O)R^5$, $OC(O)OR^5$, NH_2, NHR^5, $N(R^5)_2$, $NHC(O)R^5$, $NR^5C(O)R^5$, $NHS(O)_2R^5$, $NR^5S(O)_2R^5$, $NHC(O)OR^5$, $NR^5C(O)OR^5$, $NHC(O)NH_2$, $NHC(O)NHR^5$, $NHC(O)N(R^5)_2$, $NR^5C(O)NHR^5$, $NR^5C(O)N(R^5)_2$, $C(O)NH_2$, $C(O)NHR^5$, $C(O)N(R^5)_2$, $C(O)NHOH$, $C(O)NHOR^5$, $C(O)NHSO_2R^5$, $C(O)NR^5SO_2R^5$, SO_2NH_2, SO_2NHR^5, $SO_2N(R^5)_2$, C(O)H, C(O)OH, OH, CN, N_3, CF_3, CF_2CF_3, OCF_3, OCF_2CF_3, F, Cl, Br or I;

R^3, at each occurrence, is independently selected alkyl, alkenyl, alkynyl, aryl, or heterocyclyl; wherein each R^3 alkyl, alkenyl, and alkynyl is optionally substituted with one, two, three or four independently selected R^6, OR^6, SR^6, $S(O)R^6$, SO_2R^6, $C(O)R^6$, $CO(O)R^6$, $OC(O)R^6$, $OC(O)OR^6$, NH_2, NHR^6, $N(R^6)_2$, $NHC(O)R^6$, $NR^6C(O)R^6$, $NHS(O)_2R^6$, $NR^6S(O)_2R^6$, $NHC(O)OR^6$, $NR^6C(O)OR^6$, $NHC(O)NH_2$, $NHC(O)NHR^6$, $NHC(O)N(R^6)_2$, $NR^6C(O)NHR^6$, $NR^6C(O)N(R^6)_2$, $C(O)NH_2$, $C(O)NHR^6$, $C(O)N(R^6)_2$, $C(O)NHOH$, $C(O)NHOR^6$, $C(O)NHSO_2R^6$, $C(O)NR^6SO_2R^6$, SO_2NH_2, SO_2NHR^6, $SO_2N(R^6)_2$, C(O)H, C(O)OH, OH, (O), CN, N_3, NO_2, CF_3, CF_2CF_3, OCF_3, OCF_2CF_3, F, Cl, Br or I;

R^5, at each occurrence, is independently selected alkyl, alkenyl, alkynyl, aryl, heterocyclyl, cycloalkyl, or cycloalkenyl; wherein each R^5 alkyl, alkenyl, and alkynyl is optionally substituted with one, two, three or four independently selected R^9, OR^9, SR^9, $S(O)R^9$, SO_2R^9, $C(O)R^9$, $CO(O)R^9$, $OC(O)R^9$, $OC(O)OR^9$, NH_2, NHR^9, $N(R^9)_2$, $NHC(O)R^9$, $NR^9C(O)R^9$, $NHS(O)_2R^9$, $NR^9S(O)_2R^9$, $NHC(O)OR^9$, $NR^9C(O)OR^9$, $NHC(O)NH_2$, $NHC(O)NHR^9$, $NHC(O)N(R^9)_2$, $NR^9C(O)NHR^9$, $NR^9C(O)N(R^9)_2$, $C(O)NH_2$, $C(O)NHR^9$, $C(O)N(R^9)_2$, $C(O)NHOH$, $C(O)NHOR^9$, $C(O)NHSO_2R^9$, $C(O)NR^9SO_2R^9$, SO_2NH_2, SO_2NHR^9, $SO_2N(R^9)_2$, C(O)H, C(O)OH, OH, (O), CN, N_3, NO_2, CF_3, CF_2CF_3, OCF_3, OCF_2CF_3, F, Cl, Br or I;

R^6, at each occurrence, is independently selected alkyl, alkenyl, alkynyl, aryl, heterocyclyl, cycloalkyl, or cycloalkenyl; wherein each R^6 alkyl, alkenyl, and alkynyl is optionally substituted with one, two, three or four independently selected R^{10}, OR^{10}, SR^{10}, $S(O)R^{10}$, SO_2R^{10}, NHR^{10}, $N(R^{10})_2$, $C(O)R^{10}$, $C(O)NH_2$, $C(O)NHR^{10}$, $C(O)N(R^{10})_2$, $NHC(O)R^{10}$, $NR^{10}C(O)R^{10}$, $NHSO_2R^{10}$, $NHC(O)OR^{10}$, SO_2NH_2, SO_2NHR^{10}, $SO_2N(R^{10})_2$, $NHC(O)NH_2$, $NHC(O)NHR^{10}$, OH, (O), C(O)OH, N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br or I;

R^9, at each occurrence, is independently selected alkyl, alkenyl, alkynyl, aryl, heterocyclyl, cycloalkyl, or cycloalkenyl; wherein each R^9 alkyl, alkenyl, and alkynyl is optionally substituted with one, two, three or four independently selected alkoxy, OH, cycloalkyl, aryl, or heterocyclyl;

R^{10}, at each occurrence, is independently selected alkyl, alkenyl, alkynyl, aryl, heterocyclyl, cycloalkyl, or cycloalkenyl;

wherein the cyclic moieties represented by R^3, R^5, R^6, R^9, and R^{10} are optionally substituted with one, two, three, four, five, or six independently selected R^{13}, OR^{13}, SR^{13}, $S(O)R^{13}$, SO_2R^{13}, $C(O)R^{13}$, $CO(O)R^{13}$, $OC(O)R^{13}$, $OC(O)OR^{13}$, NH_2, NHR^{13}, $N(R^{13})_2$, $NHC(O)R^{13}$, $NR^{13}C(O)R^{13}$, $NHS(O)_2R^{13}$, $NR^{13}S(O)_2R^{13}$, $NHC(O)OR^{13}$, $NR^{13}C(O)OR^{13}$, $NHC(O)NH_2$, $NHC(O)NHR^{13}$, $NHC(O)N(R^{13})_2$, $NR^{13}C(O)NHR^{13}$, $NR^{13}C(O)N(R^{13})_2$, $C(O)NH_2$, $C(O)NHR^{13}$, $C(O)N(R^{13})_2$, C(O)NHOH, $C(O)NHOR^{13}$, $C(O)NHSO_2R^{13}$, $C(O)NR^{13}SO_2R^{13}$, SO_2NH_2, SO_2NHR^{13}, $SO_2N(R^{13})_2$, C(O)H, C(O)OH, OH, CN, N_3, NO_2, CF_3, CF_2CF_3, OCF_3, OCF_2CF_3, SCF_3, F, Cl, Br or I;

R^{13}, at each occurrence, is independently selected alkyl, alkenyl, alkynyl, aryl, tetrahydrofuranyl, pyridazinyl, pyrazinyl, pyrimidinyl, pyridinyl, thieno[3,2-c]pyridinyl, furo[3,2-c]pyridinyl, pyrrolidin-2-onyl, 1,1-dioxidotetrahydrothien-3-yl, 1,1-dioxidotetrahydro-2*H*-thiopyran-3-yl, dioxanyl, tetrahydropyranyl, piperidinyl, pyrimidinyl, oxazolyl, pyrazolyl, thiazolyl, pyrrolidinyl, pyrrolyl, thienyl, furanyl, morpholinyl, isooxazolyl, cycloalkyl, or cycloalkenyl; wherein each R^{13} alkyl, alkenyl, and alkynyl is optionally substituted with one, two, three or four independently selected R^{14}, OR^{14}, SR^{14}, $S(O)R^{14}$, SO_2R^{14}, $C(O)R^{14}$, $OC(O)R^{14}$, $OC(O)OR^{14}$, NH_2, NHR^{14}, $N(R^{14})_2$, $NHC(O)R^{14}$, $NR^{14}C(O)R^{14}$, $NHS(O)_2R^{14}$, $NR^{14}S(O)_2R^{14}$, $NHC(O)OR^{14}$, $NR^{14}C(O)OR^{14}$, $NHC(O)NH_2$, $NHC(O)NHR^{14}$, $NHC(O)N(R^{14})_2$, $NR^{14}C(O)NHR^{14}$, $NR^{14}C(O)N(R^{14})_2$, $C(O)NH_2$, $C(O)NHR^{14}$, $C(O)N(R^{14})_2$, C(O)NHOH, $C(O)NHOR^{14}$, $C(O)NHSO_2R^{14}$, $C(O)NR^{14}SO_2R^{14}$, SO_2NH_2, SO_2NHR^{14}, $SO_2N(R^{14})_2$, C(O)H, C(O)OH, OH, (O), CN, N_3, NO_2, CF_3, CF_2CF_3, OCF_3, OCF_2CF_3, F, Cl, Br or I; wherein each R^{13} aryl, tetrahydrofuranyl, pyridazinyl, pyrazinyl, pyrimidinyl, pyridinyl, thieno[3,2-c]pyridinyl, furo[3,2-c]pyridinyl, pyrrolidin-2-onyl, 1,1-dioxidotetrahydrothien-3-yl, 1,1-dioxidotetrahydro-2*H*-thiopyran-3-yl, dioxanyl, tetrahydropyranyl, piperidinyl, pyrimidinyl, oxazolyl, pyrazolyl, thiazolyl, pyrrolidinyl, pyrrolyl, thienyl, furanyl, morpholinyl, isooxazolyl, cycloalkyl, and cycloalkenyl is optionally substituted with one, two, three or four independently selected R^{15}, OR^{15}, SR^{15}, $S(O)R^{15}$, SO_2R^{15}, $C(O)R^{15}$, $CO(O)R^{15}$, $OC(O)R^{15}$, $OC(O)OR^{15}$, NH_2, NHR^{15}, $N(R^{15})_2$, $NHC(O)R^{15}$, $NR^{15}C(O)R^{15}$, $NHS(O)_2R^{15}$, $NR^{15}S(O)_2R^{15}$, $NHC(O)OR^{15}$, $NR^{15}C(O)OR^{15}$, $NHC(O)NH_2$, $NHC(O)NHR^{15}$, $NHC(O)N(R^{15})_2$, $NR^{15}C(O)NHR^{15}$, $NR^{15}C(O)N(R^{15})_2$, $C(O)NH_2$, $C(O)NHR^{15}$, $C(O)N(R^{15})_2$, C(O)NHOH, $C(O)NHOR^{15}$, $C(O)NHSO_2R^{15}$, $C(O)NR^{15}SO_2R^{15}$, SO_2NH_2,

SO_2NHR^{15}, $SO_2N(R^{15})_2$, C(O)H, C(O)OH, OH, CN, N_3, NO_2, CF_3, CF_2CF_3, OCF_3, OCF_2CF_3, F, Cl, Br or I;

R^{14}, at each occurrence, is independently selected alkyl, alkenyl, alkynyl, aryl, heterocyclyl, cycloalkyl, or cycloalkenyl; wherein each R^{14} alkyl, alkenyl, and alkynyl is optionally substituted with one, two, three or four independently selected heterocyclyl, alkoxy, NH_2, SO_2NH_2, C(O)H, C(O)OH, OH, (O), CN, N_3, NO_2, CF_3, CF_2CF_3, OCF_3, OCF_2CF_3, F, Cl, Br or I; wherein each R^{14} aryl, heterocyclyl, cycloalkyl, and cycloalkenyl is optionally substituted with one, two, three or four independently selected R^{16}, OR^{16}, OH, F, Cl, Br, or I;

R^{15}, at each occurrence, is independently selected alkyl; wherein the R^{15} alkyl is optionally substituted with one, two, three or four alkoxy; and

R^{16}, at each occurrence, is independently selected alkyl, wherein the R^{16} alkyl is optionally substituted with one, two, three or four alkoxy;

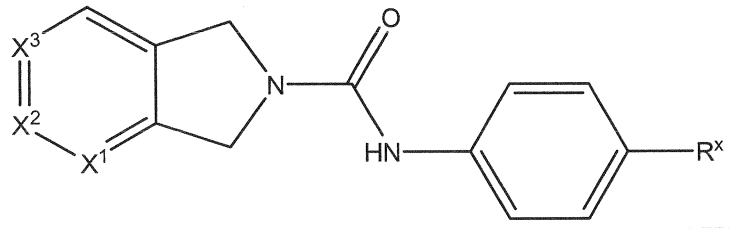
with the proviso that when X^1, X^2, and X^3 are CH and R^2 is phenyl; R^5 is not methyl;

with the proviso that when X^1, X^2, and X^3 are CH, and R^2 is phenyl substituted with OR^5; R^5 is not methyl;

with the proviso that when R^{13} is piperidinyl, it is substituted piperidinyl; and

with the proviso that when R^{13} is pyrrolinyl, at least one of X^1, X^2, and X^3 is N.

22. A compound of claim 1 having Formula (IIIc), or pharmaceutically acceptable salts thereof



(IIIc);

wherein

X^1, X^2, and X^3 are CH; or

X^1 and X^3 are CH; and X^2 is N; or

X^1 and X^3 are CH; and X^2 is CR^1; or

X^2 and X^3 are CH; and X^1 is CR^1; or

X^1 is CH; and X^2 and X^3 are CR^1; or

X^2 is CH; and X^1 and X^3 are N; or

X^2 and X^3 are CH; and X^1 is N; or

X^1 is CH; X^2 is N; and X^3 is CR^1; or

X^1 is CR^1; X^2 is N; and X^3 is CH; or

X^1 is N; X^2 is CR^1; and X^3 is CH; or

X^1 is N; X^2 is CR^1; and X^3 is N;

R^1 is R^3, OR^3, SR^3, $S(O)R^3$, SO_2R^3, $C(O)R^3$, $C(O)OR^3$, $OC(O)R^3$, NHR^3, $N(R^3)_2$, $C(O)NH_2$, $C(O)NHR^3$, $C(O)N(R^3)_2$, $NHC(O)R^3$, $NR^3C(O)R^3$, $NHC(O)OR^3$, $NR^3C(O)OR^3$, SO_2NH_2, SO_2NHR^3, $SO_2N(R^3)_2$, $NHSO_2R^3$, $NR^3SO_2R^3$, $NHSO_2NHR^3$, $NHSO_2N(R^3)_2$, $NR^3SO_2NHR^3$, $NR^3SO_2N(R^3)_2$, $C(O)NHSO_2R^3$, $NHSO_2NHR^3$, F, Cl, Br, I, CN, NH_2, NO_2, N_3, OH, C(O)H, CF_3, C(O)OH, or $C(O)NH_2$;

R^x is R^5, OR^5, SR^5, $S(O)R^5$, SO_2R^5, $C(O)R^5$, $CO(O)R^5$, $OC(O)R^5$, $OC(O)OR^5$, NH_2, NHR^5, $N(R^5)_2$, $NHC(O)R^5$, $NR^5C(O)R^5$, $NHS(O)_2R^5$, $NR^5S(O)_2R^5$, $NHC(O)OR^5$, $NR^5C(O)OR^5$, $NHC(O)NH_2$, $NHC(O)NHR^5$, $NHC(O)N(R^5)_2$, $NR^5C(O)NHR^5$, $NR^5C(O)N(R^5)_2$, $C(O)NH_2$, $C(O)NHR^5$, $C(O)N(R^5)_2$, $CHNOR^5$, C(O)NHOH, $C(O)NHOR^5$, $C(O)NHSO_2R^5$, $C(O)NR^5SO_2R^5$, SO_2NH_2, SO_2NHR^5, $SO_2N(R^5)_2$, C(O)H, C(O)OH, OH, CN, N_3, CF_3, CF_2CF_3, OCF_3, OCF_2CF_3, Br or I;

R^3, at each occurrence, is independently selected alkyl, alkenyl, alkynyl, aryl, or heterocyclyl; wherein each R^3 alkyl, alkenyl, and alkynyl is optionally substituted with one, two, three or four independently selected R^6, OR^6, SR^6, $S(O)R^6$, SO_2R^6, $C(O)R^6$, $CO(O)R^6$, $OC(O)R^6$, $OC(O)OR^6$, NH_2, NHR^6, $N(R^6)_2$, $NHC(O)R^6$, $NR^6C(O)R^6$, $NHS(O)_2R^6$, $NR^6S(O)_2R^6$, $NHC(O)OR^6$, $NR^6C(O)OR^6$, $NHC(O)NH_2$, $NHC(O)NHR^6$, $NHC(O)N(R^6)_2$, $NR^6C(O)NHR^6$, $NR^6C(O)N(R^6)_2$, $C(O)NH_2$, $C(O)NHR^6$, $C(O)N(R^6)_2$, C(O)NHOH, $C(O)NHOR^6$, $C(O)NHSO_2R^6$, $C(O)NR^6SO_2R^6$, SO_2NH_2, SO_2NHR^6, $SO_2N(R^6)_2$, C(O)H, C(O)OH, OH, (O), CN, N_3, NO_2, CF_3, CF_2CF_3, OCF_3, OCF_2CF_3, F, Cl, Br or I;

R^5, at each occurrence, is independently selected alkyl, alkenyl, alkynyl, aryl, heterocyclyl, cycloalkyl, or cycloalkenyl; wherein each R^5 alkyl, alkenyl, and alkynyl is optionally substituted with one, two, three or four independently selected R^9, OR^9, SR^9, $S(O)R^9$, SO_2R^9, $C(O)R^9$, $CO(O)R^9$, $OC(O)R^9$, $OC(O)OR^9$, NH_2, NHR^9, $N(R^9)_2$, $NHC(O)R^9$, $NR^9C(O)R^9$, $NHS(O)_2R^9$, $NR^9S(O)_2R^9$, $NHC(O)OR^9$, $NR^9C(O)OR^9$, $NHC(O)NH_2$, $NHC(O)NHR^9$, $NHC(O)N(R^9)_2$, $NR^9C(O)NHR^9$, $NR^9C(O)N(R^9)_2$, $C(O)NH_2$, $C(O)NHR^9$, $C(O)N(R^9)_2$, C(O)NHOH, $C(O)NHOR^9$, $C(O)NHSO_2R^9$, $C(O)NR^9SO_2R^9$, SO_2NH_2, SO_2NHR^9, $SO_2N(R^9)_2$, C(O)H, C(O)OH, OH, (O), CN, N_3, NO_2, CF_3, CF_2CF_3, OCF_3, OCF_2CF_3, F, Cl, Br or I;

R^6, at each occurrence, is independently selected alkyl, alkenyl, alkynyl, aryl, heterocyclyl, cycloalkyl, or cycloalkenyl; wherein each R^6 alkyl, alkenyl, and alkynyl is optionally substituted with one, two, three or four independently selected R^{10}, OR^{10}, SR^{10}, $S(O)R^{10}$, SO_2R^{10}, NHR^{10}, $N(R^{10})_2$, $C(O)R^{10}$, $C(O)NH_2$, $C(O)NHR^{10}$, $C(O)N(R^{10})_2$, $NHC(O)R^{10}$, $NR^{10}C(O)R^{10}$, $NHSO_2R^{10}$, $NHC(O)OR^{10}$, SO_2NH_2, SO_2NHR^{10}, $SO_2N(R^{10})_2$, $NHC(O)NH_2$, $NHC(O)NHR^{10}$, OH, (O), C(O)OH, N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br or I;

R^9, at each occurrence, is independently selected alkyl, alkenyl, alkynyl, aryl, heterocyclyl, cycloalkyl, or cycloalkenyl; wherein each R^9 alkyl, alkenyl, and alkynyl is optionally substituted with one, two, three or four independently selected alkoxy, OH, cycloalkyl, aryl, or heterocyclyl;

R^{10}, at each occurrence, is independently selected alkyl, alkenyl, alkynyl, aryl, heterocyclyl, cycloalkyl, or cycloalkenyl;

wherein the cyclic moieties represented by R^3, R^5, R^6, R^9, and R^{10} are optionally substituted with one, two, three, four, five, or six independently selected R^{13}, OR^{13}, SR^{13}, $S(O)R^{13}$, SO_2R^{13}, $C(O)R^{13}$, $CO(O)R^{13}$, $OC(O)R^{13}$, $OC(O)OR^{13}$, NH_2, NHR^{13}, $N(R^{13})_2$, $NHC(O)R^{13}$, $NR^{13}C(O)R^{13}$, $NHS(O)_2R^{13}$, $NR^{13}S(O)_2R^{13}$, $NHC(O)OR^{13}$, $NR^{13}C(O)OR^{13}$, $NHC(O)NH_2$, $NHC(O)NHR^{13}$, $NHC(O)N(R^{13})_2$, $NR^{13}C(O)NHR^{13}$, $NR^{13}C(O)N(R^{13})_2$, $C(O)NH_2$, $C(O)NHR^{13}$, $C(O)N(R^{13})_2$, C(O)NHOH, $C(O)NHOR^{13}$, $C(O)NHSO_2R^{13}$, $C(O)NR^{13}SO_2R^{13}$, SO_2NH_2, SO_2NHR^{13}, $SO_2N(R^{13})_2$, C(O)H, C(O)OH, OH, CN, N_3, NO_2, CF_3, CF_2CF_3, OCF_3, OCF_2CF_3, SCF_3, F, Cl, Br or I;

R^{13}, at each occurrence, is independently selected alkyl, alkenyl, alkynyl, aryl, tetrahydrofuranyl, pyridazinyl, pyrazinyl, pyrimidinyl, pyridinyl, thieno[3,2-c]pyridinyl, furo[3,2-c]pyridinyl, pyrrolidin-2-onyl, 1,1-dioxidotetrahydrothien-3-yl, 1,1-dioxidotetrahydro-2*H*-thiopyran-3-yl, dioxanyl, tetrahydropyranyl, piperidinyl, pyrimidinyl, oxazolyl, pyrazolyl, thiazolyl, pyrrolidinyl, pyrrolyl, thienyl, furanyl, morpholinyl, isooxazolyl, cycloalkyl, or cycloalkenyl; wherein each R^{13} alkyl, alkenyl, and alkynyl is optionally substituted with one, two, three or four independently selected R^{14}, OR^{14}, SR^{14}, $S(O)R^{14}$, SO_2R^{14}, $C(O)R^{14}$, $OC(O)R^{14}$, $OC(O)OR^{14}$, NH_2, NHR^{14}, $N(R^{14})_2$, $NHC(O)R^{14}$, $NR^{14}C(O)R^{14}$, $NHS(O)_2R^{14}$, $NR^{14}S(O)_2R^{14}$, $NHC(O)OR^{14}$, $NR^{14}C(O)OR^{14}$, $NHC(O)NH_2$, $NHC(O)NHR^{14}$, $NHC(O)N(R^{14})_2$, $NR^{14}C(O)NHR^{14}$, $NR^{14}C(O)N(R^{14})_2$, $C(O)NH_2$, $C(O)NHR^{14}$, $C(O)N(R^{14})_2$, C(O)NHOH, $C(O)NHOR^{14}$, $C(O)NHSO_2R^{14}$, $C(O)NR^{14}SO_2R^{14}$, SO_2NH_2, SO_2NHR^{14}, $SO_2N(R^{14})_2$, C(O)H, C(O)OH, OH, (O), CN, N_3, NO_2, CF_3, CF_2CF_3, OCF_3, OCF_2CF_3, F, Cl, Br or I; wherein each R^{13} aryl, tetrahydrofuranyl, pyridazinyl, pyrazinyl, pyrimidinyl, pyridinyl, thieno[3,2-c]pyridinyl, furo[3,2-c]pyridinyl, pyrrolidin-2-onyl, 1,1-dioxidotetrahydrothien-3-yl, 1,1-dioxidotetrahydro-2*H*-thiopyran-3-yl, dioxanyl, tetrahydropyranyl, piperidinyl, pyrimidinyl, oxazolyl, pyrazolyl, thiazolyl, pyrrolidinyl, pyrrolyl, thienyl, furanyl, morpholinyl, isooxazolyl, cycloalkyl, and cycloalkenyl is optionally substituted with one, two, three or four independently selected R^{15}, OR^{15}, SR^{15}, $S(O)R^{15}$, SO_2R^{15}, $C(O)R^{15}$, $CO(O)R^{15}$, $OC(O)R^{15}$, $OC(O)OR^{15}$, NH_2, NHR^{15}, $N(R^{15})_2$, $NHC(O)R^{15}$, $NR^{15}C(O)R^{15}$, $NHS(O)_2R^{15}$, $NR^{15}S(O)_2R^{15}$, $NHC(O)OR^{15}$, $NR^{15}C(O)OR^{15}$, $NHC(O)NH_2$, $NHC(O)NHR^{15}$, $NHC(O)N(R^{15})_2$, $NR^{15}C(O)NHR^{15}$, $NR^{15}C(O)N(R^{15})_2$, $C(O)NH_2$, $C(O)NHR^{15}$, $C(O)N(R^{15})_2$, C(O)NHOH, $C(O)NHOR^{15}$, $C(O)NHSO_2R^{15}$, $C(O)NR^{15}SO_2R^{15}$, SO_2NH_2, SO_2NHR^{15}, $SO_2N(R^{15})_2$, C(O)H, C(O)OH, OH, CN, N_3, NO_2, CF_3, CF_2CF_3, OCF_3, OCF_2CF_3, F, Cl, Br or I;

R^{14}, at each occurrence, is independently selected alkyl, alkenyl, alkynyl, aryl, heterocyclyl, cycloalkyl, or cycloalkenyl; wherein each R^{14} alkyl, alkenyl, and alkynyl is optionally substituted with one, two, three or four independently selected heterocyclyl, alkoxy, NH_2, SO_2NH_2, C(O)H, C(O)OH, OH, (O), CN, N_3, NO_2, CF_3, CF_2CF_3, OCF_3, OCF_2CF_3, F, Cl, Br or I; wherein each R^{14} aryl, heterocyclyl, cycloalkyl, and cycloalkenyl is optionally substituted with one, two, three or four independently selected R^{16}, OR^{16}, OH, F, Cl, Br, or I;

R^{15}, at each occurrence, is independently selected alkyl, wherein the R^{15} alkyl is optionally substituted with one, two, three or four alkoxy; and

R^{16}, at each occurrence, is independently selected alkyl, wherein the R^{16} alkyl is optionally substituted with one, two, three or four alkoxy;

with the proviso that when X^1, X^2, and X^3 are CH; R^x is not methyl;

with the proviso that when X^1, X^2, and X^3 are CH; R^x is not methoxy;

with the proviso that when R^{13} is piperidinyl, it is substituted piperidinyl; and

with the proviso that when R^{13} is pyrrolinyl, at least one of X^1, X^2, and X^3 is N.