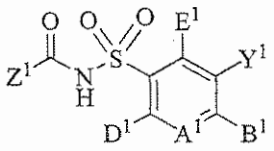
Accordingly, the inventors have discovered that while compounds taught in the art have utility for the treatment of various cancers and immune diseases, they are not selective for anti-apoptotic Bcl-2 proteins over anti-apoptotic Bcl-X_L proteins and thereby result in a higher probability of side effects characterized by inhibition of anti-apoptotic Bcl-X_L proteins such as, thrombocytopenia.

This invention therefore comprises a series of compounds that demonstrate unexpected properties with respect to their selectivity for binding to, and inhibiting the activity of anti-apoptotic Bcl-2 protein over anti-apoptotic Bcl-X_L protein as significantly higher than those of the compounds taught in PCT/US/2004/36770 and PCT/US/2004/367911.

SUMMARY OF THE INVENTION

In one embodiment, there is provided a compound having formula I



(I),

or a therapeutically acceptable salt thereof,

wherein A^1 is N or $C(A^2)$;

one or two or three or each of A^2, B^1, D^1 and E^1 are independently selected from R^1, OR^1, SR^1, $S(O)R^1$, SO_2R^1, $C(O)R^1$, $C(O)OR^1$, $OC(O)R^1$, NHR^1, $N(R^1)_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$, $NHC(O)OR^1$, $NR^1C(O)NHR^1$, $NR^1C(O)N(R^1)_2$, SO_2NHR^1, $SO_2N(R^1)_2$, $NHSO_2R^1$, $NHSO_2NHR^1$ and $N(CH_3)SO_2N(CH_3)R^1$, and the remainder of A^2, B^1, D^1 and E^1 are independently selected from H, F, Cl, Br, I, CN, CF_3, C(O)OH, $C(O)NH_2$ and $C(O)OR^{1A}$;

Y^1 is H, CN, NO_2, C(O)OH, F, Cl, Br, I, CF_3, OCF_3, CF_2CF_3, OCF_2CF_3, R^{17}, OR^{17}, $C(O)R^{17}$, $C(O)OR^{17}$, SR^{17}, NH_2, NHR^{17}, $N(R^{17})_2$, $NHC(O)R^{17}$, $C(O)NH_2$, $C(O)NHR^{17}$, $C(O)N(R^{17})_2$, $NHS(O)R^{17}$ or $NHSO_2R^{17}$;

R^1 is R^2, R^3, R^4 or R^5;

R^{1A} is C_1-C_6-alkyl, C_3-C_6-alkenyl or C_3-C_6-alkynyl;

R^2 is phenyl which is unfused or fused with C_5-C_6-arene, C_5-C_6-heteroarene or R^{2A};

R^{2A} is C_3-C_{10}-cycloalkane or C_2-C_8-heterocycloalkane;

R^3 is C_2-C_6-heteroaryl which is unfused or fused with benzene, C_2-C_6-heteroarene or R^{3A}; R^{3A} is C_3-C_{10}-cycloalkane or C_2-C_8-heterocycloalkane;

R^4 is C_3-C_{10}-cycloalkyl, C_4-C_{10}-cycloalkenyl, C_2-C_8-heterocycloalkyl or C_2-C_8-heterocycloalkenyl, each of which is unfused or fused with C_5-C_6-arene, C_2-C_6-heteroarene or R^{4A}; R^{4A} is C_3-C_{10}-cycloalkane, C_4-C_{10}-cycloalkene, C_2-C_8-heterocycloalkane or C_2-C_8-heterocycloalkene;

R^5 is C_1-C_{10}-alkyl, C_1-C_{10}-alkenyl or C_2-C_{10}-alkynyl, each of which is unsubstituted or substituted with one or two or three independently selected R^6, R^7, OR^7, SR^7, $S(O)R^7$, SO_2R^7, NHR^7, $N(R^7)_2$, $C(O)R^7$, $C(O)NH_2$, $C(O)NHR^7$, $NHC(O)R^7$, $NHSO_2R^7$, $NHC(O)OR^7$, SO_2NH_2, SO_2NHR^7, $SO_2N(R^7)_2$, $NHC(O)NH_2$, $NHC(O)NHR^7$, $NHC(O)CH(CH_3)NHC(O)CH(CH_3)NH_2$, $NHC(O)CH(CH_3)NHC(O)CH(CH_3)NHR^1$, OH, (O), C(O)OH, N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br or I substituents;

R^6 is C_2-C_5-spiroalkyl, each of which is unsubstituted or substituted with OH, (O), N_3, CN, CF_3, CF_2CF_3, F, Cl, Br, I, NH_2, $NH(CH_3)$ or $N(CH_3)_2$;

R^7 is R^8, R^9, R^{10} or R^{11};

R^8 is phenyl which is unfused or fused with C_5-C_6-arene, C_2-C_6-heteroarene or R^{8A};

R^{8A} is C_3-C_{10}-cycloalkane, C_4-C_{10}-cycloalkene, C_2-C_8-heterocycloalkane or C_2-C_8-heterocycloalkene;

R^9 is C_2-C_6-heteroaryl which is unfused or fused with C_5-C_6-arene, C_5-C_6-heteroarene or R^{9A}; R^{9A} is C_3-C_{10}-cycloalkane, C_4-C_{10}-cycloalkene, C_2-C_8-heterocycloalkane or C_2-C_8-heterocycloalkene;

R^{10} is C_3-C_{10}-cycloalkyl or C_4-C_{10}-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with C_5-C_6-arene, C_2-C_6-heteroarene or R^{10A}; R^{10A} is C_3-C_{10}-cycloalkane, C_4-C_{10}-cycloalkene, C_2-C_8-heterocycloalkane or C_2-C_8-heterocycloalkene;

R^{11} is C_1-C_{10}-alkyl, C_1-C_{10}-alkenyl or C_2-C_{10}-alkynyl, each of which is unsubstituted or substituted with one or two or three independently selected R^{12}, OR^{12}, NHR^{12}, $N(R^{12})_2$, $C(O)NH_2$, $C(O)NHR^{12}$, $C(O)N(R^{12})_2$, OH, (O), C(O)OH, N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br or I substituents;

R^{12} is R^{13}, R^{14}, R^{15} or R^{16};

R^{13} is phenyl which is unfused or fused with C_5-C_6-arene, C_2-C_6-heteroarene or R^{13A}; R^{13A} is C_3-C_{10}-cycloalkane, C_4-C_{10}-cycloalkene, C_2-C_8-heterocycloalkane or C_2-C_8-heterocycloalkene;

R^{14} is C_2-C_6-heteroaryl, each of which is unfused or fused with C_5-C_6-arene, C_2-C_6-heteroarene or R^{14A}; R^{14A} is C_3-C_{10}-cycloalkane, C_4-C_{10}-cycloalkene, C_2-C_8-heterocycloalkane or C_2-C_8-heterocycloalkene;

R^{15} is C_3-C_{10}-cycloalkane, C_4-C_{10}-cycloalkene, C_2-C_8-heterocycloalkane or C_2-C_8-heterocycloalkene, each of which is unfused or fused with C_5-C_6-arene, C_2-C_6-heteroarene or R^{15A}; R^{15A} is C_3-C_{10}-cycloalkane, C_4-C_{10}-cycloalkene, C_2-C_8-heterocycloalkane or C_2-C_8-heterocycloalkene;

R^{16} is C_1-C_{10}-alkyl, C_1-C_{10}-alkenyl or C_2-C_{10}-alkynyl;

R^{17} is R^{18}, R^{19}, R^{20} or R^{21};

R^{18} is phenyl which is unfused or fused with C_5-C_6-arene, C_2-C_6-heteroarene or R^{18A}; R^{18A} is C_3-C_{10}-cycloalkane, C_4-C_{10}-cycloalkene, C_2-C_8-heterocycloalkane or C_2-C_8-heterocycloalkene;

R^{19} is C_2-C_6-heteroaryl which is unfused or fused with C_5-C_6-arene, C_2-C_6-heteroarene or R^{19A}; R^{19A} is C_3-C_{10}-cycloalkane, C_4-C_{10}-cycloalkene, C_2-C_8-heterocycloalkane or C_2-C_8-heterocycloalkene;

R^{20} is C_3-C_{10}-cycloalkyl or C_4-C_{10}-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with C_5-C_6-arene, C_2-C_6-heteroarene or R^{20A}; R^{20A} is C_3-C_{10}-cycloalkane, C_4-C_{10}-cycloalkene, C_2-C_8-heterocycloalkane or C_2-C_8-heterocycloalkene;

R^{21} is C_1-C_{10}-alkyl, C_1-C_{10}-alkenyl or C_2-C_{10}-alkynyl, each of which is unsubstituted or substituted with one or two or three independently selected R^{22}, OR^{22}, NHR^{22}, $N(R^{22})_2$, $C(O)NH_2$, $C(O)NHR^{22}$, $C(O)N(R^{22})_2$, OH, (O), C(O)OH, N_3, CN, NH_2, CF_3, CF_2CF_3, F, Cl, Br or I substituents;

R^{22} is R^{23}, R^{24} or R^{25};

R^{23} is phenyl which is unfused or fused with C_5-C_6-arene, C_2-C_6-heteroarene or R^{23A}; R^{23A} is C_3-C_{10}-cycloalkane, C_4-C_{10}-cycloalkene, C_2-C_8-heterocycloalkane or C_2-C_8-heterocycloalkene;

R^{24} is C_2-C_6-heteroarene which is unfused or fused with C_5-C_6-arene, C_2-C_6-heteroarene or R^{24A}; R^{24A} is C_3-C_{10}-cycloalkane, C_4-C_{10}-cycloalkene, C_2-C_8-heterocycloalkane or C_2-C_8-heterocycloalkene;

R^{25} is C_3-C_6-cycloalkyl or C_4-C_6-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with C_5-C_6-arene, C_2-C_6-heteroarene or R^{25A}; R^{25A} is C_3-C_{10}-cycloalkane, C_4-C_{10}-cycloalkene, C_2-C_8-heterocycloalkane or C_2-C_8-heterocycloalkene;

Z^1 is R^{26} substituted with R^{30}, which is substituted with CH_2R^{37} or $CH(R^{31})(R^{37})$;

R^{30} is C_3-C_{10}-cycloalkyl having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N; R^{31} is F, Cl, Br or alkyl;

R^{37} is R^{38} or R^{40}, each of which is substituted with R^{41}

R^{38} is phenyl;

R^{40} is C_3-C_8-cycloalkyl or C_4-C_8-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N;

R^{41} is R^{42}

R^{42} is phenyl substituted with one or two or three or four or five independently selected R^{50}, OR^{50}, SR^{50}, $S(O)R^{50}$, SO_2R^{50}, $C(O)R^{50}$, $CO(O)R^{50}$, $OC(O)R^{50}$, $OC(O)OR^{50}$, NH_2, NHR^{50}, $N(R^{50})_2$, $C(O)NH_2$, $C(O)NHR^{50}$, $C(O)N(R^{50})_2$, C(O)NHOH, $C(O)NHOR^{50}$, $C(O)NHSO_2R^{50}$, $C(O)NR^{55}SO_2R^{50}$, SO_2NH_2, SO_2NHR^{50}, $SO_2N(R^{50})_2$, CF_3, CF_2CF_3, C(O)H, C(O)OH, $C(N)NH_2$, $C(N)NHR^{50}$, $C(N)N(R^{50})_2$, OH, (O), CN, N_3, NO_2, CF_3, CF_2CF_3, OCF_3, OCF_2CF_3, F, Cl, Br or I substituents;

wherein the phenyl represented by R^{26} is further substituted by one or two or three substituents independently selected from OR^{50A}, SR^{50A}, $S(O)R^{50A}$, SO_2R^{50A} ~~or~~ and NHR^{50A},

R^{50A} is R^{51A}, R^{52A}, or R^{53A};

R^{51A} is phenyl which is unfused or fused with benzene, C_5-C_6-heteroarene or R^{51AA},

wherein R^{51AA} is C_3-C_{10}-cycloalkane, C_4-C_{10}-cycloalkene, C_2-C_8-heterocycloalkane or C_2-C_8-heterocycloalkene,

R^{52A} is C_2-C_6-heteroaryl;

R^{53A} is C_3-C_6-cycloalkyl or C_4-C_6-cycloalkenyl; each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with C_5-C_6-arene, C_5-C_6-heteroarene or R^{53AA};

wherein R^{53AA} is C_3-C_{10}-cycloalkane, C_4-C_{10}-cycloalkene, C_2-C_8-heterocycloalkane or C_2-C_8-heterocycloalkene;

wherein moieties represented by R^2, R^3, R^4, R^6, R^8, R^{8A}, R^9, R^{10}, R^{13}, R^{14}, R^{15}, R^{18}, R^{19}, R^{20}, R^{23}, R^{24}, R^{25}, R^{30}, R^{38}, and R^{40} are independently optionally substituted with one or two or three or four or five independently selected R^{50}, OR^{50}, SR^{50}, $S(O)R^{50}$, SO_2R^{50}, $C(O)R^{50}$, $CO(O)R^{50}$, $OC(O)R^{50}$, $OC(O)OR^{50}$, NH_2, NHR^{50}, $N(R^{50})_2$, $C(O)NH_2$, $C(O)NHR^{50}$, $C(O)N(R^{50})_2$, C(O)NHOH, $C(O)NHOR^{50}$, $C(O)NHSO_2R^{50}$, $C(O)NR^{55}SO_2R^{50}$, SO_2NH_2, SO_2NHR^{50}, $SO_2N(R^{50})_2$, CF_3, CF_2CF_3, C(O)H, C(O)OH, $C(N)NH_2$, $C(N)NHR^{50}$, $C(N)N(R^{50})_2$, OH, (O), CN, N_3, NO_2, CF_3, CF_2CF_3, OCF_3, OCF_2CF_3, F, Cl, Br or I substituents;

R^{50} is R^{51}, R^{52}, R^{53} or R^{54};

R^{51} is phenyl which is unfused or fused with C_5-C_6-arene, C_5-C_6-heteroarene or R^{51B};

R^{51B} is C_3-C_{10}-cycloalkane, C_4-C_{10}-cycloalkene, C_2-C_8-heterocycloalkane or C_2-C_8-heterocycloalkene;

R^{52} is C_2-C_6-heteroaryl;

R^{53} is C_3-C_6-cycloalkyl or C_4-C_6-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N, and each of which is unfused or fused with C_5-C_6-arene, C_2-C_6-heteroarene or R^{53B};

wherein R^{53B} is C_3-C_{10}-cycloalkane, C_4-C_{10}-cycloalkene, C_2-C_8-heterocycloalkane or C_2-C_8-heterocycloalkene;

R^{54} is C_1-C_{10}-alkyl, C_1-C_{10}-alkenyl or C_2-C_{10}-alkynyl, each of which is unsubstituted or substituted with one or two or three independently selected R^{55}, OR^{55}, SR^{55}, $S(O)R^{55}$, SO_2R^{55}, NHR^{55}, $N(R^{55})_2$, $C(O)R^{55}$, $C(O)NH_2$, $C(O)NHR^{55}$, $NHC(O)R^{55}$, $NHSO_2R^{55}$, $NHC(O)OR^{55}$, SO_2NH_2, SO_2NHR^{55}, $SO_2N(R^{55})_2$, $NHC(O)NH_2$, $NHC(O)NHR^{55}$, OH, (O), C(O)OH, N_3, CN, NH_2, CF_3, OCF_3, CF_2CF_3, OCF_2CF_3, F, Cl, Br or I substituents;

R^{55} is C_1-C_{10}-alkyl, C_1-C_{10}-alkenyl, C_2-C_{10}-alkynyl, phenyl, C_2-C_6-heteroaryl or R^{56};

wherein the C_1-C_{10}-alkyl, C_1-C_{10}-alkenyl and C_2-C_{10}-alkynyl are unsubstituted or substituted with OCH_3; and

R^{56} is C_3-C_8-cycloalkyl or C_4-C_6-cycloalkenyl, each having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N.

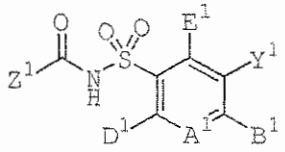
In one embodiment, there is provided a composition for treating bladder cancer, brain cancer, breast cancer, bone marrow cancer, cervical cancer, chronic lymphocytic leukemia, colorectal cancer, esophageal cancer, hepatocellular cancer, lymphoblastic leukemia, follicular lymphoma, a lymphoid malignancy of T-cell or B-cell origin, melanoma, myelogenous leukemia, myeloma, oral cancer, ovarian cancer, non-small cell lung cancer, prostate cancer, small cell lung cancer or spleen cancer, said composition comprising an excipient and a therapeutically effective amount of the compound or therapeutically acceptable salt as defined herein.

In one embodiment, there is provided the use of the compound or therapeutically acceptable salt as defined herein for the manufacture of a medicament for treating bladder cancer, brain cancer, breast cancer, bone marrow cancer, cervical cancer, chronic lymphocytic leukemia, colorectal cancer, esophageal cancer, hepatocellular cancer, lymphoblastic leukemia, follicular lymphoma, a lymphoid malignancy of T-cell or B-cell origin, melanoma, myelogenous leukemia, myeloma, oral cancer, ovarian cancer, non-small cell lung cancer, prostate cancer, small cell lung cancer or spleen cancer in a patient.

In one embodiment, there is provided the use of the compound or therapeutically acceptable salt as defined herein, and one additional therapeutic agent or more than one additional therapeutic agent, for the manufacture of a medicament for treating bladder cancer, brain cancer, breast cancer, bone marrow cancer, cervical cancer, chronic lymphocytic leukemia, colorectal cancer, esophageal cancer, hepatocellular cancer, lymphoblastic leukemia, follicular lymphoma, a lymphoid malignancy of T-cell or B-cell origin, melanoma, myelogenous leukemia, myeloma, oral cancer, ovarian cancer, non-small cell lung cancer, prostate cancer, small cell lung cancer or spleen cancer in a patient.

In one embodiment, there is provided 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-chloro-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl}-2-(1H-indazol-4-yloxy)benzamide or a therapeutically acceptable salt thereof.

One embodiment of this invention, therefore, pertains to compounds or therapeutically acceptable salts, prodrugs or salts of prodrugs thereof, which are useful as selective inhibitors one or more than one anti-apoptotic protein family member, the compounds having Formula (I)



(I),

wherein A^1 is N or $C(A^2)$;

one or two or three or each of A^2, B^1, D^1 and E^1 are independently selected R^1, OR^1, SR^1, $S(O)R^1$, SO_2R^1, $C(O)R^1$, $C(O)OR^1$, $OC(O)R^1$, NHR^1, $N(R^1)_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$, $NHC(O)OR^1$, $NR^1C(O)NHR^1$, $NR^1C(O)N(R^1)_2$, SO_2NHR^1, $SO_2N(R^1)_2$, $NHSO_2R^1$, $NHSO_2NHR^1$ or $N(CH_3)SO_2N(CH_3)R^1$, and the remainder are independently selected H, F, Cl, Br, I, CN, CF_3, C(O)OH, $C(O)NH_2$ or $C(O)OR^{1A}$; and

Y^1 is H, CN, NO_2, C(O)OH, F, Cl, Br, I, CF_3, OCF_3, CF_2CF_3, OCF_2CF_3, R^{17}, OR^{17}, $C(O)R^{17}$, $C(O)OR^{17}$, SR^{17}, NH_2, NHR^{17}, $N(R^{17})_2$, $NHC(O)R^{17}$, $C(O)NH_2$, $C(O)NHR^{17}$, $C(O)N(R^{17})_2$, $NHS(O)R^{17}$ or $NHSO_2R^{17}$;

or

B^1 and Y^1, together with the atoms to which they are attached, are imidazole or triazole; and