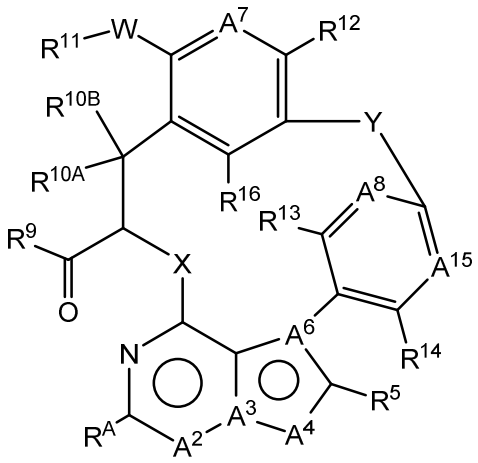
et al. Nature 2011, 471, 110). Accordingly, there is a need in the therapeutic arts for compounds which inhibit the activity of the MCL-1 protein.

SUMMARY

[0005] In examples the present disclosure provides for compounds of formula (I) or a pharmaceutically acceptable salt thereof,



(I)

wherein

A^2 is CR^2, A^3 is N, A^4 is CR^{4a}, and A^6 is C; or

A^2 is CR^2, A^3 is N, A^4 is O or S, and A^6 is C; or

A^2 is CR^2, A^3 is C, A^4 is O or S and A^6 is C; or

A^2 is N, A^3 is C, A^4 is O or S and A^6 is C; or

A^2 is N, A^3 is C, A^4 is CR^{4a}, and A^6 is N;

R^A is hydrogen, CH_3, halogen, CN, CH_2F, CHF_2, or CF_3;

X is O, or $N(R^{x2})$; wherein R^{x2} is hydrogen, C_1-C_3 alkyl, or unsubstituted cyclopropyl;

Y is $(CH_2)_m$, $-CH=CH-(CH_2)_n-$, $-(CH_2)_p-CH=CH-$, or $-(CH_2)_q-CH=CH-(CH_2)_r-$; wherein 0, 1, 2, or 3 CH_2 groups are each independently replaced by O, $N(R^{ya})$, $C(R^{ya})(R^{yb})$, C(O), $NC(O)R^{ya}$, or $S(O)_2$;

m is 2, 3, 4, or 5;

n is 1, 2, or 3;

p is 1, 2, or 3;

q is 1 or 2; and

r is 1 or 2; wherein the sum of q and r is 2 or 3;

R^{ya}, at each occurrence, is independently hydrogen, C_2-C_6 alkenyl, C_2-C_6 alkynyl, G^1, C_1-C_6 alkyl, or C_1-C_6 haloalkyl; wherein the C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkyl, and C_1-C_6 haloalkyl are optionally substituted with 1 or 2 substituents independently selected from the group consisting of oxo, $-N(R^{yd})(R^{ye})$, G^1, $-OR^{yf}$, $-SR^{yg}$, $-S(O)_2N(R^{yd})(R^{ye})$, and $-S(O)_2-G^1$; and

R^{yb} is C_2-C_6 alkenyl, C_2-C_6 alkynyl, G^1, C_1-C_6 alkyl, or C_1-C_6 haloalkyl; wherein the C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkyl, and C_1-C_6 haloalkyl are optionally substituted with 1 or 2 substituents independently selected from the group consisting of oxo, $-N(R^{yd})(R^{ye})$, G^1, $-OR^{yf}$, $-SR^{yg}$, $-S(O)_2N(R^{yd})(R^{ye})$, and $-S(O)_2-G^1$; or

R^{ya} and R^{yb}, together with the carbon atom to which they are attached, form a C_3-C_7 monocyclic cycloalkyl, C_4-C_7 monocyclic cycloalkenyl, or a 4-7 membered monocyclic heterocycle; wherein the C_3-C_7 monocyclic cycloalkyl, C_4-C_7 monocyclic cycloalkenyl, and the 4-7 membered monocyclic heterocycle are each optionally substituted with 1 $-OR^m$ and 0, 1, 2, or 3 independently selected R^s groups;

R^{yd}, R^{ye}, R^{yf}, and R^{yg}, at each occurrence, are each independently hydrogen, G^1, C_1-C_6 alkyl, or C_1-C_6 haloalkyl; wherein the C_1-C_6 alkyl and the C_1-C_6 haloalkyl are optionally substituted with one substituent selected from the group consisting of G^1, $-OR^{yh}$, $-SR^{yh}$, $-SO_2R^{yh}$, and $-N(R^{yi})(R^{yk})$;

G^1, at each occurrence, is piperazinyl, piperidinyl, pyrrolidinyl, thiomorpholinyl, tetrahydropyranyl, morpholinyl, oxetanyl, 1,3-dioxolanyl, 1,3-dioxanyl, 1,4-dioxanyl, 1,3-dioxepanyl, or 1,4-dioxepanyl; wherein each G^1 is optionally substituted with 1 $-OR^m$ and 0, 1, 2, or 3 substituents independently selected from the group consisting of G^2, $-(C_1$-C_6 alkylenyl)-G^2, and R^s;

G^2, at each occurrence, is a C_3-C_7 monocyclic cycloalkyl, C_4-C_7 monocyclic cycloalkenyl, oxetanyl, morpholinyl, 1,3-dioxolanyl, 1,3-dioxanyl, 1,4-dioxanyl, 1,3-dioxepanyl, or 1,4-dioxepanyl; wherein each G^2 is optionally substituted with 1 $-OR^m$ and 0, 1, or 2 independently selected R^t groups;

R^2 is independently hydrogen, halogen, CH_3, or CN;

R^{4a}, at each occurrence, is independently hydrogen, halogen, CN, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_1-C_4 alkyl, C_1-C_4 haloalkyl, G^A, C_1-C_4 alkyl-G^A, or C_1-C_4 alkyl-O-G^A; wherein each G^A is independently C_6-C_{10} aryl, C_3-C_7 monocyclic cycloalkyl, C_4-C_7 monocyclic cycloalkenyl, or 4-7 membered heterocycle; wherein each G^A is optionally substituted with 1, 2, or 3 R^u groups;

R^5 is independently hydrogen, halogen, G^3, C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl; wherein the C_1-C_6 alkyl, C_2-C_6 alkenyl, and C_2-C_6 alkynyl are each optionally substituted with one G^3;

G^3, at each occurrence, is independently C_6-C_{10} aryl, 5-11 membered heteroaryl, C_3-C_{11} cycloalkyl, C_4-C_{11} cycloalkenyl, oxetanyl, 2-oxaspiro[3.3]heptanyl, 1,3-dioxolanyl, 1,3-dioxanyl, 1,4-dioxanyl, 1,3-dioxepanyl, 2,3-dihydro-1,4-dioxinyl, or 1,4-dioxepanyl; wherein each G^3 is optionally substituted with 1, 2, or 3 R^v groups;

A^7 is N or CR^7;

A^8 is N or CR^8;

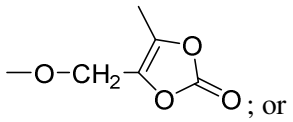
A^{15} is N or CR^{15};

R^7, R^{12} and R^{16} are each independently hydrogen, halogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, -CN, -OR^{7a}, -SR^{7a}, or -$N(R^{7b})(R^{7c})$;

R^8, R^{13}, R^{14}, and R^{15}, are each independently hydrogen, halogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, -CN, -OR^{8a}, -SR^{8a}, -$N(R^{8b})(R^{8c})$, or C_3-C_4 monocyclic cycloalkyl; wherein the C_3-C_4 monocyclic cycloalkyl is optionally substituted with one or two substituents independently selected from the group consisting of halogen, C_1-C_3 alkyl, and C_1-C_3 haloalkyl; or

R^8 and R^{13} are each independently hydrogen, halogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, -CN, -OR^{8a}, -SR^{8a}, -$N(R^{8b})(R^{8c})$, or C_3-C_4 monocyclic cycloalkyl; wherein the C_3-C_4 monocyclic cycloalkyl is optionally substituted with one or two substituents independently selected from the group consisting of halogen, C_1-C_3 alkyl, and C_1-C_3 haloalkyl; and

R^{14} and R^{15}, together with the carbon atoms to which they are attached, form a monocyclic ring selected from the group consisting of benzene, cyclobutane, cyclopentane, and pyridine; wherein the monocyclic ring is optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, -CN, -OR^{8a}, -SR^{8a}, and -$N(R^{8b})(R^{8c})$;

R^9 is -OH, -O-C_1-C_4 alkyl, -O-CH_2-OC(O)(C_1-C_6 alkyl), -NHOH, ; or -N(H)$S(O)_2$-(C_1-C_6 alkyl);

R^{10A} and R^{10B}, are each independently hydrogen, C_1-C_3 alkyl, or C_1-C_3 haloalkyl; or R^{10A} and R^{10B}, together with the carbon atom to which they are attached, form a cyclopropyl; wherein the cyclopropyl is optionally substituted with one or two substituents independently selected from the group consisting of halogen and CH_3;

W is -CH=CH-, C_1-C_4 alkyl, -O-CHF-, -L^1-CH_2-, or -CH_2-L^1-; wherein L^1 at each occurrence, is independently O, S, S(O), $S(O)_2$, $S(O)_2N(H)$, N(H), or N(C_1-C_3 alkyl);

R^{11} is a C_6-C_{10} aryl or a 5-11 membered heteroaryl; wherein each R^{11} is optionally substituted with 1, 2, or 3 independently selected R^w groups;

R^w, at each occurrence, is independently C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen, C_1-C_6 haloalkyl, -CN, NO_2, -OR^{11a}, -SR^{11b}, -$S(O)_2R^{11b}$, -$S(O)_2N(R^{11c})_2$, -$C(O)R^{11a}$, -$C(O)N(R^{11c})_2$, -$N(R^{11c})_2$, -$N(R^{11c})C(O)R^{11b}$, -$N(R^{11c})S(O)_2R^{11b}$, -$N(R^{11c})C(O)O(R^{11b})$, -$N(R^{11c})C(O)N(R^{11c})_2$, G^4, -(C_1-C_6 alkylenyl)-OR^{11a}, -(C_1-C_6 alkylenyl)-$OC(O)N(R^{11c})_2$, -(C_1-C_6 alkylenyl)-SR^{11a}, -(C_1-C_6 alkylenyl)-$S(O)_2R^{11b}$, -(C_1-C_6 alkylenyl)-$S(O)_2N(R^{11c})_2$, -(C_1-C_6 alkylenyl)-$C(O)R^{11a}$, -(C_1-C_6 alkylenyl)-$C(O)N(R^{11c})_2$, -(C_1-C_6 alkylenyl)-$N(R^{11c})_2$, -(C_1-C_6 alkylenyl)-$N(R^{11c})C(O)R^{11b}$, -(C_1-C_6 alkylenyl)-$N(R^{11c})S(O)_2R^{11b}$, -(C_1-C_6 alkylenyl)-$N(R^{11c})C(O)O(R^{11b})$, -(C_1-C_6 alkylenyl)-$N(R^{11c})C(O)N(R^{11c})_2$, -($C_1$-$C_6$ alkylenyl)-CN, or -(C_1-C_6 alkylenyl)-G^4;

R^{11a} and R^{11c}, at each occurrence, are each independently hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_1-C_6 haloalkyl, G^4, -(C_2-C_6 alkylenyl)-OR^{11d}, -(C_2-C_6 alkylenyl)-$N(R^{11e})_2$, or -(C_2-C_6 alkylenyl)-G^4;

R^{11b}, at each occurrence, is independently C_1-C_6 alkyl, C_2-C_6 alkenyl, C_1-C_6 haloalkyl, G^4, -(C_2-C_6 alkylenyl)-OR^{11d}, -(C_2-C_6 alkylenyl)-$N(R^{11e})_2$, or -(C_2-C_6 alkylenyl)-G^4;

G^4, at each occurrence, is independently phenyl, monocyclic heteroaryl, C_3-C_{11} cycloalkyl, C_4-C_{11} cycloalkenyl, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, 2,6-dioxa-9-azaspiro[4.5]decanyl, 2-oxa-5-azabicyclo[2.2.1]heptanyl, 3-oxa-8-azabicyclo[3.2.1]octanyl, piperidinyl, piperazinyl, azetidinyl, morpholinyl, dihydropyranyl, tetrahydropyridinyl, dihydropyrrolyl, pyrrolidinyl, 2,3-dihydrodioxinyl, 1,3-dioxolanyl, 1,3-dioxanyl, 1,4-dioxanyl, 1,3-dioxepanyl, or 1,4-dioxepanyl; wherein each G^4 is optionally substituted with 1 -OR^m and 0, 1, 2, or 3 substituents independently selected from the group consisting of G^5, R^y, -(C_1-C_6 alkylenyl)-G^5, -(C_1-C_6 alkylenyl)-L^2-(C_1-C_6 alkylenyl)-G^5, and -L^2-(C_1-C_6 alkylenyl)$_s$-G^5;

L^2 is O, C(O), N(H), N(C_1-C_6 alkyl), NHC(O), C(O)O, S, S(O), or $S(O)_2$;

s is 0 or 1;

G^5, at each occurrence, is independently phenyl, monocyclic heteroaryl, C_3-C_7 monocyclic cycloalkyl, C_4-C_7 monocyclic cycloalkenyl, piperazine, 1,3-dioxolanyl, 1,3-dioxanyl, 1,4-dioxanyl, 1,3-dioxepanyl, or 1,4-dioxepanyl; wherein each G^5 is optionally substituted with 1 independently selected -OR^m or 0, 1, 2, or 3 R^z groups;

R^s, R^t, R^u, R^v, R^y, and R^z, at each occurrence, are each independently C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen, C_1-C_6 haloalkyl, -CN, oxo, NO_2, $P(O)(R^k)_2$, -$OC(O)R^k$, -$OC(O)N(R^j)_2$, -SR^j, -$S(O)_2R^k$, -$S(O)_2N(R^j)_2$, -$C(O)R^j$, -$C(O)N(R^j)_2$, -$N(R^j)_2$, -$N(R^j)C(O)R^k$, -$N(R^j)S(O)_2R^k$, -$N(R^j)C(O)O(R^k)$, -$N(R^j)C(O)N(R^j)_2$, -(C_1-C_6 alkylenyl)-OR^j, (C_1-C_6 alkylenyl)-$OC(O)N(R^j)_2$, -(C_1-C_6 alkylenyl)-SR^j, -(C_1-C_6 alkylenyl)-$S(O)_2R^k$, -(C_1-C_6 alkylenyl)-$S(O)_2N(R^j)_2$, -(C_1-C_6 alkylenyl)-$C(O)R^j$, -(C_1-C_6 alkylenyl)-$C(O)N(R^j)_2$, -(C_1-C_6 alkylenyl)-$N(R^j)_2$, -(C_1-C_6 alkylenyl)-$N(R^j)C(O)R^k$, -(C_1-C_6 alkylenyl)-$N(R^j)S(O)_2R^k$, -(C_1-C_6 alkylenyl)-$N(R^j)C(O)O(R^k)$, -(C_1-C_6 alkylenyl)-$N(R^j)C(O)N(R^j)_2$, or -(C_1-C_6 alkylenyl)-CN;

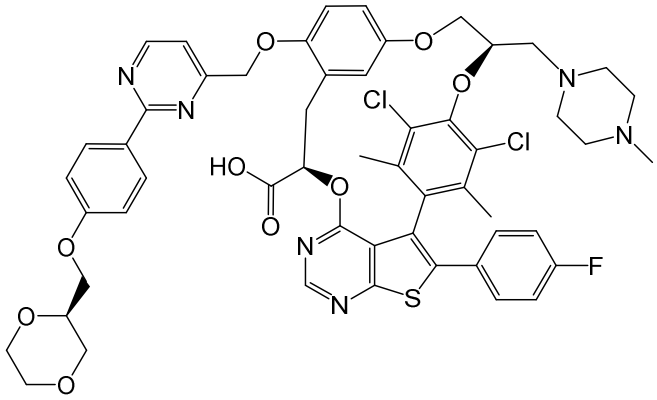
R^m is hydrogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, -(C_2-C_6 alkylenyl)-OR^j, or -(C_2-C_6 alkylenyl)-$N(R^j)_2$;

R^{yh}, R^{yi}, R^{yk}, R^{7a}, R^{7b}, R^{7c}, R^{8a}, R^{8b}, R^{8c}, R^{11d}, R^{11e}, and R^j, at each occurrence, are each independently hydrogen, C_1-C_6 alkyl, or C_1-C_6 haloalkyl; and

R^k, at each occurrence, is independently C_1-C_6 alkyl or C_1-C_6 haloalkyl;

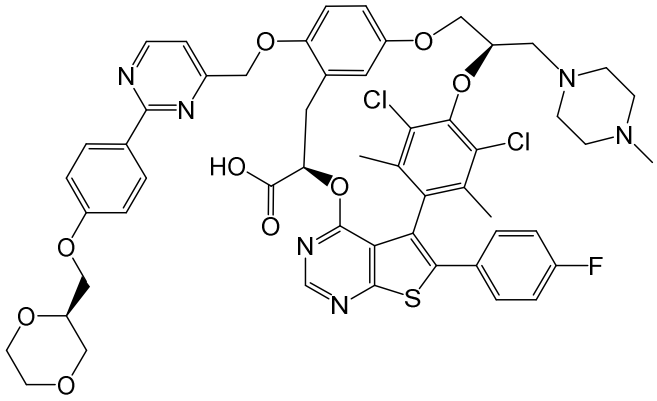
wherein at least one of G^1, G^2, G^3, G^4, and G^5 is 2,2-dimethyl-1,3-dioxolanyl, 2,3-dihydro-1,4-dioxinyl, 1,3-dioxolanyl, 1,3-dioxanyl, 1,4-dioxanyl, 1,3-dioxepanyl, or 1,4-dioxepanyl.

[0005a] In one aspect, the present disclosure provides for a compound having the structure:



or a pharmaceutically acceptable salt thereof.

[0005b] In one aspect, the present disclosure provides for a compound having the structure:



.

[0006] In examples, the present disclosure provides for methods of treating or preventing disorders that are amenable to inhibition of MCL-1. Such methods comprise administering to the subject a therapeutically effective amount of a compound of formula (I), alone, or in combination with a pharmaceutically acceptable carrier.

[0007] In examples, some methods are directed to treating or preventing cancer. That is, in examples, the present disclosure provides for methods for treating or preventing cancer, wherein such methods comprise administering to the subject a therapeutically effective amount of a compound of formula (I), alone, or in combination with a pharmaceutically acceptable carrier.

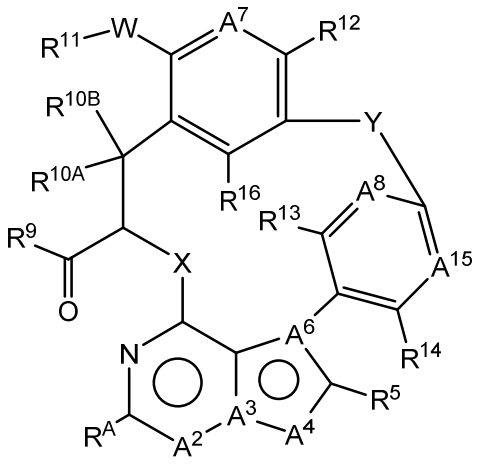
[0008] In examples, the present disclosure relates to methods of treating cancer in a subject comprising administering a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, to a subject in need thereof. In certain examples, the cancer is multiple myeloma. In certain examples, the methods further comprise administering a therapeutically effective amount of at least one additional therapeutic agent.

[0009] In examples, the present disclosure provides the use of a compound of formula (I), alone or in combination with at least one additional therapeutic agent, in the manufacture of a medicament for treating or preventing conditions and disorders disclosed herein, with or without a pharmaceutically acceptable carrier.

[0010] Pharmaceutical compositions comprising a compound of formula (I), or a pharmaceutically acceptable salt, alone or in combination with at least one additional therapeutic agent, are also provided.

DETAILED DESCRIPTION

[0011] In embodiments, the present disclosure provides for compounds of Formula (I), or a pharmaceutically acceptable salt thereof,



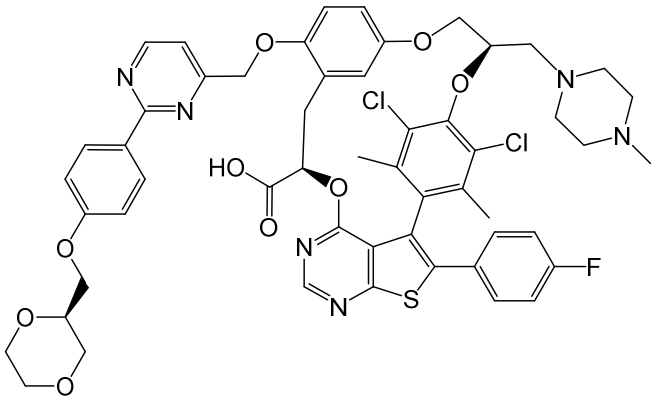
(I),

wherein A^2, A^3, A^4, A^6, A^7, A^8, A^{15}, R^A, R^5, R^9, R^{10A}, R^{10B}, R^{11}, R^{12}, R^{13}, R^{14}, R^{16}, W, X, and Y are defined above in the Summary and below in the Detailed Description. Further, compositions comprising such compounds and methods for treating conditions and disorders using such compounds and compositions are also included.

[0012] Compounds included herein may contain one or more variable(s) that occur more than one time in any substituent or in the formulae herein. Definition of a variable on each occurrence is independent

WE CLAIM:

1. A compound having the structure:



or a pharmaceutically acceptable salt thereof.

2. A compound having the structure:

