(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
9 September 2016 (09.09.2016)

WIPO | PCT

(10) International Publication Number
WO 2016/141042 A4

(51) International Patent Classification:
C07D 471/14 (2006.01) *A61K 31/4375* (2006.01)
C07D 487/14 (2006.01) *A61K 31/519* (2006.01)
C07D 403/04 (2006.01) *A61K 31/4985* (2006.01)
C07D 403/14 (2006.01) *A61K 31/5025* (2006.01)

(21) International Application Number:
PCT/US2016/020418

(22) International Filing Date:
2 March 2016 (02.03.2016)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/128,208 4 March 2015 (04.03.2015) US

(71) Applicant: **PIMERA, INC.** [US/US]; 3210 Merryfield Row, San Diego, California 92121 (US).

(72) Inventor: **HADDACH, Mustapha**; 3210 Merryfield Row, San Diego, California 92121 (US).

(74) Agent: **HADDACH, Aubrey, A.**; VENABLE LLP., P.O. Box 34385, Washington, District of Columbia 20043-9998 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

— *of inventorship (Rule 4.17(iv))*

Published:

— *with international search report (Art. 21(3))*

— *with amended claims (Art. 19(1))*

(88) Date of publication of the international search report:
3 November 2016

Date of publication of the amended claims: 15 December 2016

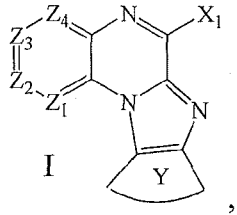
WO 2016/141042 A4

(54) Title: NOVEL COMPOSITIONS, USES AND METHODS FOR MAKING THEM

(57) Abstract: Generally, the present invention provides novel quinolone compounds and pharmaceutical composition thereof which may inhibit cell proliferation and/or induce cell apoptosis. The present invention also provides methods of preparing such compounds and compositions, and methods of making and using the same.

AMENDED CLAIMS
received by the International Bureau on 27 September 2016 (27.09.2016)

WHAT IS CLAIMED IS:



I

1. A compound of Formula I: , or a pharmaceutically acceptable salt, esters prodrug, hydrate, or tautomer thereof; wherein:

each Z_1, Z_2, Z_3, and Z_4 is N, CH, or CR_1, provided any three N are non-adjacent; and further provided that one or more of Z_1, Z_2, Z_3, and Z_4 is CR_1;

each R_1 is independently an optionally substituted C_1-C_8 alkyl, C_2-C_8 heteroalkyl, C_2-C_8 alkenyl, C_2-C_8 heteroalkenyl, C_2-C_8 alkynyl, C_2-C_8 heteroalkynyl, C_1-C_8 acyl, C_2-C_8 heteroacyl, C_6-C_{10} aryl, C_5-C_{12} heteroaryl, C_7-C_{12} arylalkyl, or C_6-C_{12} heteroarylalkyl group, or each R_1 is independently H, halo, CF_3, OR_2, NR_2R_3, NR_2OR_3, $NR_2NR_2R_3$, SR_2, SOR_2, SO_2R_2, $SO_2NR_2R_3$, $NR_2SO_2R_3$, $NR_2CONR_2R_3$, NR_2COOR_3, NR_2COR_3, CN, $COOR_2$, COOH, $CONR_2R_3$, $OOCR_2$, COR_2, or NO_2;

and wherein R_2 and R_3 groups on the same atom or on adjacent atoms can be linked to form a 3-8 membered ring, optionally containing one or more N, O or S atoms; and each R_2 and R_3 groups, and each ring formed by linking R_2 and R_3 groups together, is optionally substituted with one or more substituents selected from halo, =O, =N-CN, =N-OR', =NR', OR', $N(R')_2$, SR', SO_2R', $SO_2NR'_2$, $NR'SO_2R'$, $NR'CONR'_2$, NR'COOR', NR'COR', CN, COOR', $CON(R')_2$, OOCR', COR', and NO_2, wherein each R' is independently H, C_1-C_6 alkyl, C_2-C_6 heteroalkyl, C_1-C_6 acyl, C_2-C_6 heteroacyl, C_6-C_{10} aryl, C_5-C_{10} heteroaryl, C_7-C_{12} arylalkyl, or C_6-C_{12} heteroarylalkyl, each of which is optionally substituted with one or more groups selected from halo, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_1-C_6 acyl, C_1-C_6 heteroacyl, hydroxy, amino, and =O; wherein two R' can be linked to form a 3-7 membered ring optionally containing up to three heteroatoms selected from N, O and S;

or each R_1 is independently -W, -L-W, -X-L-A; wherein X is NR_6, O, or S; W is an optionally substituted 4-7 membered azacyclic ring, optionally containing an additional heteroatom selected from N, O and S as a ring member; L is a C_1-C_{10} alkylene, C_1-C_{10} heteroalkylene, C_2-C_{10} alkenylene or C_2-C_{10} heteroalkenylene linker, each of which may be optionally substituted with one or more substituents selected from the group consisting of halogen, oxo (=O), or C1-C6 alkyl; and A is heterocycloalkyl, heteroaryl or NR_4R_5 where R_4 and R_5 are

independently H, optionally substituted C_1-C_8 alkyl, C_2-C_8 heteroalkyl, C_2-C_8 alkenyl, C_2-C_8 heteroalkenyl, C_2-C_8 alkynyl, C_2-C_8 heteroalkynyl, C_1-C_8 acyl, C_2-C_8 heteroacyl, C_6-C_{10} aryl, C_5-C_{12} heteroaryl, C_7-C_{12} arylalkyl, or C_6-C_{12} heteroarylalkyl group;

R_4 and R_5 can be linked to form a 3-8 membered ring, optionally containing one or more N, O or S; and each R_4 and R_5 groups, and each ring formed by linking R_4 and R_5 groups together, is optionally substituted with one or more substituents selected from halo, =O, =N-CN, =N-OR', =NR', OR', $N(R')_2$, SR', SO_2R', $SO_2NR'_2$, $NR'SO_2R'$, $NR'CONR'_2$, NR'COOR', NR'COR', CN, COOR', $CON(R')_2$, OOCR', COR', and NO_2, wherein each R' is independently H, C_1-C_6 alkyl, C_2-C_6 heteroalkyl, C_1-C_6 acyl, C_2-C_6 heteroacyl, C_6-C_{10} aryl, C_5-C_{10} heteroaryl, C_7-C_{12} arylalkyl, or C_6-C_{12} heteroarylalkyl, each of which is optionally substituted with one or more groups selected from halo, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_1-C_6 acyl, C_1-C_6 heteroacyl, hydroxy, amino, and =O; wherein two R' can be linked to form a 3-7 membered ring optionally containing up to three heteroatoms selected from N, O and S;

R_6 is H, optionally substituted C_1-C_8 alkyl, C_2-C_8 heteroalkyl, C_2-C_8 alkenyl, C_2-C_8 heteroalkenyl, C_2-C_8 alkynyl, C_2-C_8 heteroalkynyl, C_1-C_8 acyl, C_2-C_8 heteroacyl, C_6-C_{10} aryl, C_5-C_{12} heteroaryl, C_7-C_{12} arylalkyl, or C_6-C_{12} heteroarylalkyl group,

R_6 can be linked to R_4 or R_5 to form a 3-8 membered ring; and R_4 or R_5 is optionally substituted with one or more substituents selected from halo, =O, =N-CN, =N-OR', =NR', OR', $N(R')_2$, SR', SO_2R', $SO_2NR'_2$, $NR'SO_2R'$, $NR'CONR'_2$, NR'COOR', NR'COR', CN, COOR', $CON(R')_2$, OOCR', COR', and NO_2, wherein each R' is independently H, C_1-C_6 alkyl, C_2-C_6 heteroalkyl, C_1-C_6 acyl, C_2-C_6 heteroacyl, C_6-C_{10} aryl, C_5-C_{10} heteroaryl, C_7-C_{12} arylalkyl, or C_6-C_{12} heteroarylalkyl, each of which is optionally substituted with one or more groups selected from halo, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_1-C_6 acyl, C_1-C_6 heteroacyl, hydroxy, amino, and =O; wherein two R' can be linked to form a 3-7 membered ring optionally containing up to three heteroatoms selected from N, O and S;

Y is an optionally substituted 5-6 membered carbocyclic or heterocyclic ring; and

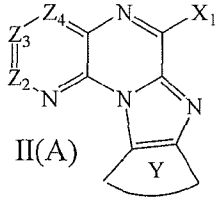
X_1 is an optionally substituted C_1-C_8 alkyl, C_2-C_8 heteroalkyl, C_2-C_8 alkenyl, C_2-C_8 heteroalkenyl, C_2-C_8 alkynyl, C_2-C_8 heteroalkynyl, C_1-C_8 acyl, C_2-C_8 heteroacyl, C_6-C_{10} aryl, C_5-C_{12} heteroaryl, C_7-C_{12} arylalkyl, or C_6-C_{12} heteroarylalkyl group, optionally substituted with one or more halogens, =O, CF_3, CN, OR_7, NR_8R_9, SR_7, $SO_2NR_8R_9$, C_1-C_8 alkyl, C_2-C_8 heteroalkyl, C_2-C_8 alkenyl, C_2-C_8 heteroalkenyl, C_2-C_8 alkynyl, C_2-C_8 heteroalkynyl, C_1-C_8

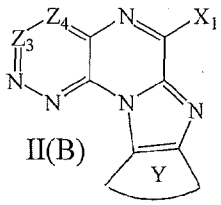
acyl, C_2-C_8 heteroacyl, C_6-C_{10} aryl, C_5-C_{12} heteroaryl, C_7-C_{12} arylalkyl, or C_6-C_{12} heteroarylalkyl group;

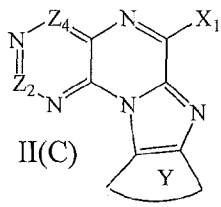
wherein each R_7, R_8 and R_9 is independently selected from H, C_1-C_6 alkyl, C_2-C_6 heteroalkyl, C_1-C_6 acyl, C_2-C_6 heteroacyl, C_6-C_{10} aryl, C_5-C_{10} heteroaryl, C_7-C_{12} arylalkyl, or C_6-C_{12} heteroarylalkyl, each of which is optionally substituted with one or more groups selected from halo, =O, =N-CN, =N-OR', =NR', OR', $N(R')_2$, SR', SO_2R', $SO_2NR'_2$, NR'SO_2R', NR'CONR'$_2$, NR'COOR', NR'COR', CN, COOR', $CON(R')_2$, OOCR', COR', and NO_2; wherein each R' is independently H, C_1-C_6 alkyl, C_2-C_6 heteroalkyl, C_1-C_6 acyl, C_2-C_6 heteroacyl, C_6-C_{10} aryl, C_5-C_{10} heteroaryl, C_7-C_{12} arylalkyl, or C_6-C_{12} heteroarylalkyl, each of which is optionally substituted with one or more groups selected from halo, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_1-C_6 acyl, C_1-C_6 heteroacyl, hydroxy, amino, and =O; wherein two R' can be linked to form a 3-7 membered ring optionally containing up to three heteroatoms selected from N, O and S; or

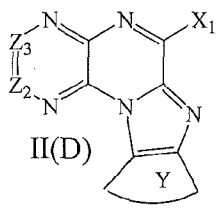
X_1 is NR_2R_3, SOR_2, SO_2R_2, $SO_2NR_2R_3$, $NR_2SO_2R_3$, $NR_2CONR_2R_3$, NR_2COOR_3, NR_2COR_3, CN, $COOR_2$, ester bioisostere, COOH, carboxy bioisostere, $CONR_2R_3$, amide bioisostere, $OOCR_2$, COR_2, or NO_2.

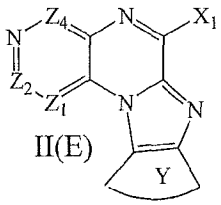
2. A compound of Formula II(A), II(B), II(C), II(D) and II(E),


II(A)


II(B)


II(C)


II(D)


II(E)

, or

a pharmaceutically acceptable salt, esters prodrug, hydrate, or tautomer thereof; wherein:

Z_1, Z_2, Z_3 and Z_4 are independently CH or CR_1;

each R_1 is independently an optionally substituted C_1-C_8 alkyl, C_2-C_8 heteroalkyl, C_2-C_8 alkenyl, C_2-C_8 heteroalkenyl, C_2-C_8 alkynyl, C_2-C_8 heteroalkynyl, C_1-C_8 acyl, C_2-C_8 heteroacyl, C_6-C_{10} aryl, C_5-C_{12} heteroaryl, C_7-C_{12} arylalkyl, or C_6-C_{12} heteroarylalkyl group, or each R_1 is independently halo, CF_3, OR_2, NR_2R_3, NR_2OR_3, $NR_2NR_2R_3$, SR_2, SOR_2, SO_2R_2, $SO_2NR_2R_3$, $NR_2SO_2R_3$, $NR_2CONR_2R_3$, NR_2COOR_3, NR_2COR_3, CN, $COOR_2$, COOH, $CONR_2R_3$, $OOCR_2$, COR_2, or NO_2;

or each R_1 is independently -W, -L-W, -X-L-A; wherein X is NR_6, O, or S; W is an optionally substituted 4-7 membered azacyclic ring, optionally containing an additional heteroatom selected from N, O and S as a ring member; L is a C_1-C_{10} alkylene, C_1-C_{10} heteroalkylene, C_2-C_{10} alkenylene or C_2-C_{10} heteroalkenylene linker, each of which may be optionally substituted with one or more substituents selected from the group consisting of halogen, oxo (=O), or C1-C6 alkyl; and A is heterocycloalkyl, heteroaryl or NR_4R_5 where R_4 and R_5 are independently H, optionally substituted C_1-C_8 alkyl, C_2-C_8 heteroalkyl, C_2-C_8 alkenyl, C_2-C_8 heteroalkenyl, C_2-C_8 alkynyl, C_2-C_8 heteroalkynyl, C_1-C_8 acyl, C_2-C_8 heteroacyl, C_6-C_{10} aryl, C_5-C_{12} heteroaryl, C_7-C_{12} arylalkyl, or C_6-C_{12} heteroarylalkyl group;

R_4 and R_5 can be linked to form a 3-8 membered ring, optionally containing one or more N, O or S; and each R_4 and R_5 groups, and each ring formed by linking R_4 and R_5 groups together, is optionally substituted with one or more substituents selected from halo, =O, =N-CN, =N-OR', =NR', OR', $N(R')_2$, SR', SO_2R', $SO_2NR'_2$, $NR'SO_2R'$, $NR'CONR'_2$, NR'COOR', NR'COR', CN, COOR', $CON(R')_2$, OOCR', COR', and NO_2, wherein each R' is independently H, C_1-C_6 alkyl, C_2-C_6 heteroalkyl, C_1-C_6 acyl, C_2-C_6 heteroacyl, C_6-C_{10} aryl, C_5-C_{10} heteroaryl, C_7-C_{12} arylalkyl, or C_6-C_{12} heteroarylalkyl, each of which is optionally substituted with one or more groups selected from halo, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_1-C_6 acyl, C_1-C_6 heteroacyl, hydroxy, amino, and =O; wherein two R' can be linked to form a 3-7 membered ring optionally containing up to three heteroatoms selected from N, O and S;

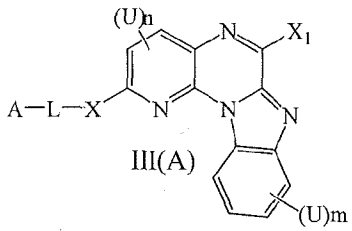
R_6 is H, optionally substituted C_1-C_8 alkyl, C_2-C_8 heteroalkyl, C_2-C_8 alkenyl, C_2-C_8 heteroalkenyl, C_2-C_8 alkynyl, C_2-C_8 heteroalkynyl, C_1-C_8 acyl, C_2-C_8 heteroacyl, C_6-C_{10} aryl, C_5-C_{12} heteroaryl, C_7-C_{12} arylalkyl, or C_6-C_{12} heteroarylalkyl group; or R_6 can be linked to R_4 or R_5 to form a 3-8 membered ring; and R_4 or R_5 is optionally substituted with one or more substituents selected from halo, =O, =N-CN, =N-OR', =NR', OR', $N(R')_2$, SR', SO_2R', $SO_2NR'_2$, $NR'SO_2R'$, $NR'CONR'_2$, NR'COOR', NR'COR', CN, COOR', $CON(R')_2$, OOCR', COR', and NO_2, wherein each R' is independently H, C_1-C_6 alkyl, C_2-C_6 heteroalkyl, C_1-C_6 acyl, C_2-C_6 heteroacyl, C_6-C_{10} aryl, C_5-C_{10} heteroaryl, C_7-C_{12} arylalkyl, or C_6-C_{12} heteroarylalkyl, each of which is optionally substituted with one or more groups selected from halo, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_1-C_6 acyl, C_1-C_6 heteroacyl, hydroxy, amino, and =O; wherein two R' can be linked to form a 3-7 membered ring optionally containing up to three heteroatoms selected from N, O and S;

Y is an optionally substituted 5-6 membered carbocyclic or heterocyclic ring;

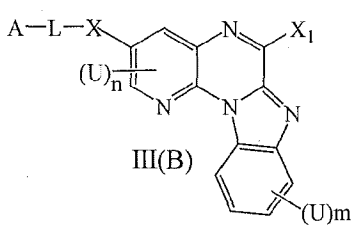
X_1 is an optionally substituted C_1-C_8 alkyl, C_2-C_8 heteroalkyl, C_2-C_8 alkenyl, C_2-C_8 heteroalkenyl, C_2-C_8 alkynyl, C_2-C_8 heteroalkynyl, C_1-C_8 acyl, C_2-C_8 heteroacyl, C_6-C_{10} aryl, C_5-C_{12} heteroaryl, C_7-C_{12} arylalkyl, or C_6-C_{12} heteroarylalkyl group, or ~~X_1 is H,~~ NR_2R_3, SOR_2, SO_2R_2, $SO_2NR_2R_3$, $NR_2SO_2R_3$, $NR_2CONR_2R_3$, NR_2COOR_3, NR_2COR_3, CN, $COOR_2$, COOH, polar substituent, carboxy bioisostere, $CONR_2R_3$, $OOCR_2$, COR_2, or NO_2;

wherein R_2 and R_3 groups on the same atom or on adjacent atoms can be linked to form a 3-8 membered ring, optionally containing one or more N, O or S; and each R_2 and R_3 groups, and each ring formed by linking R_2 and R_3 groups together, is optionally substituted with one or more substituents selected from halo, =O, =N-CN, =N-OR', =NR', OR', $N(R')_2$, SR', SO_2R', $SO_2NR'_2$, NR'SO_2R', NR'CONR'$_2$, NR'COOR', NR'COR', CN, COOR', $CON(R')_2$, OOCR', COR', and NO_2, wherein each R' is independently H, C_1-C_6 alkyl, C_2-C_6 heteroalkyl, C_1-C_6 acyl, C_2-C_6 heteroacyl, C_6-C_{10} aryl, C_5-C_{10} heteroaryl, C_7-C_{12} arylalkyl, or C_6-C_{12} heteroarylalkyl, each of which is optionally substituted with one or more groups selected from halo, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_1-C_6 acyl, C_1-C_6 heteroacyl, hydroxy, amino, and =O; wherein two R' can be linked to form a 3-7 membered ring optionally containing up to three heteroatoms selected from N, O and S.

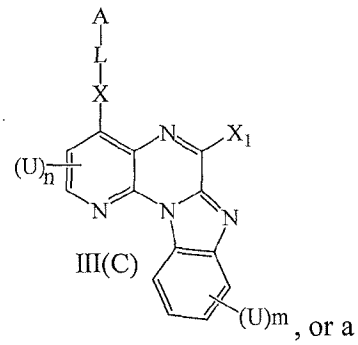
3. A compound of Formula III(A), III(B) and III(C):



III(A)



III(B)



III(C)

, or a pharmaceutically acceptable salt, esters prodrug, hydrate, or tautomer thereof; wherein:

L is a C_1-C_{10} alkylene, C_1-C_{10} heteroalkylene, C_2-C_{10} alkenylene or C_2-C_{10} heteroalkenylene linker, each of which may be optionally substituted with one or more substituents selected from the group consisting of halogen, oxo (=O), or C_1-C_6 alkyl;

A is heterocycloalkyl, heteroaryl or NR_4R_5 where R_4 and R_5 are independently H, optionally substituted C_1-C_8 alkyl, C_2-C_8 heteroalkyl, C_2-C_8 alkenyl, C_2-C_8 heteroalkenyl, C_2-C_8 alkynyl,

C_2-C_8 heteroalkynyl, C_1-C_8 acyl, C_2-C_8 heteroacyl, C_6-C_{10} aryl, C_5-C_{12} heteroaryl, C_7-C_{12} arylalkyl, or C_6-C_{12} heteroarylalkyl group;

R_4 and R_5 can be linked to form a 3-8 membered ring, optionally containing one or more N, O or S; and each R_4 and R_5 groups, and each ring formed by linking R_4 and R_5 groups together, is optionally substituted with one or more substituents selected from halo, =O, =N-CN, =N-OR', =NR', OR', $N(R')_2$, SR', SO_2R', $SO_2NR'_2$, $NR'SO_2R'$, $NR'CONR'_2$, NR'COOR', NR'COR', CN, COOR', $CON(R')_2$, OOCR', COR', and NO_2, wherein each R' is independently H, C_1-C_6 alkyl, C_2-C_6 heteroalkyl, C_1-C_6 acyl, C_2-C_6 heteroacyl, C_6-C_{10} aryl, C_5-C_{10} heteroaryl, C_7-C_{12} arylalkyl or C_6-C_{12} heteroarylalkyl, each of which is optionally substituted with one or more groups selected from halo, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_1-C_6 acyl, C_1-C_6 heteroacyl, hydroxy, amino, and =O; wherein two R' can be linked to form a 3-7 membered ring optionally containing up to three heteroatoms selected from N, O and S;

X is NR_6, O, or S;

R_6 is H, optionally substituted C_1-C_8 alkyl, C_2-C_8 heteroalkyl, C_2-C_8 alkenyl, C_2-C_8 heteroalkenyl, C_2-C_8 alkynyl, C_2-C_8 heteroalkynyl, C_1-C_8 acyl, C_2-C_8 heteroacyl, C_6-C_{10} aryl, C_5-C_{12} heteroaryl C_7-C_{12} arylalkyl, or C_6-C_{12} heteroarylalkyl group;

R_6 can be linked to R_4 or R_5 to form a 3-8 membered ring; and R_4 or R_5 is optionally substituted with one or more substituents selected from halo, =O, =N-CN, =N-OR', =NR', OR', $N(R')_2$, SR', SO_2R', $SO_2NR'_2$, $NR'SO_2R'$, $NR'CONR'_2$, NR'COOR', NR'COR', CN, COOR', $CON(R')_2$, OOCR', COR', and NO_2, wherein each R' is independently H, C_1-C_6 alkyl, C_2-C_6 heteroalkyl, C_1-C_6 acyl, C_2-C_6 heteroacyl, C_6-C_{10} aryl, C_5-C_{10} heteroaryl, C_7-C_{12} arylalkyl, or C_6-C_{12} heteroarylalkyl, each of which is optionally substituted with one or more groups selected from halo, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_1-C_6 acyl, C_1-C_6 heteroacyl, hydroxy, amino, and =O; wherein two R' can be linked to form a 3-7 membered ring optionally containing up to three heteroatoms selected from N, O and S;

X_1 is an optionally substituted C_1-C_8 alkyl, C_2-C_8 heteroalkyl, C_2-C_8 alkenyl, C_2-C_8 heteroalkenyl, C_2-C_8 alkynyl, C_2-C_8 heteroalkynyl, C_1-C_8 acyl, C_2-C_8 heteroacyl, C_6-C_{10} aryl, C_5-C_{12} heteroaryl C_7-C_{12} arylalkyl, or C_6-C_{12} heteroarylalkyl group, or X_1 is ~~H,~~ NR_2R_3, SOR_2, SO_2R_2, $SO_2NR_2R_3$, $NR_2SO_2R_3$, $NR_2CONR_2R_3$, NR_2COOR_3, NR_2COR_3, CN, $COOR_2$, ester bioisostere, COOH, carboxy bioisostere, $CONR_2R_3$, amide bioisostere, $OOCR_2$, COR_2, or NO_2;

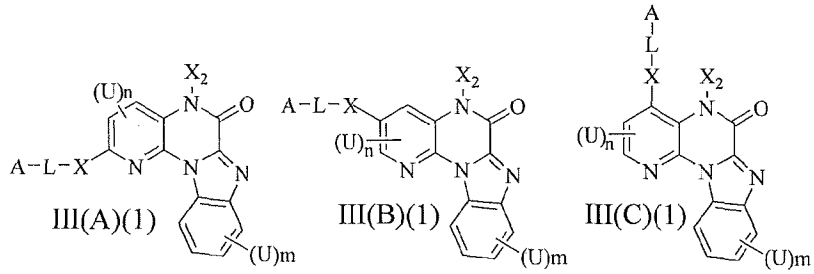
AMENDED SHEET (ARTICLE 19)

wherein R_2 and R_3 groups on the same atom or on adjacent atoms can be linked to form a 3-8 membered ring, optionally containing one or more N, O or S; and each R_2 and R_3 groups, and each ring formed by linking R_2 and R_3 groups together, is optionally substituted with one or more substituents selected from halo, =O, =N-CN, =N-OR', =NR', OR', $N(R')_2$, SR', SO_2R', $SO_2NR'_2$, $NR'SO_2R'$, $NR'CONR'_2$, NR'COOR', NR'COR', CN, COOR', $CON(R')_2$, OOCR', COR', and NO_2, wherein each R' is independently H, C_1-C_6 alkyl, C_2-C_6 heteroalkyl C_1-C_6 acyl, C_2-C_6 heteroacyl, C_6-C_{10} aryl, C_5-C_{10} heteroaryl, C_7-C_{12} arylalkyl, or C_6-C_{12} heteroarylalkyl, each of which is optionally substituted with one or more groups selected from halo, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_1-C_6 acyl, C_1-C_6 heteroacyl, hydroxy, amino, and =O; wherein two R' can be linked to form a 3-7 membered ring optionally containing up to three heteroatoms selected from N, O and S; and

$(U)_n$ and $(U)_m$ are independently H, halogen, CF_3, CN, OR_7, NR_8R_9, SR_7, $SO_2NR_8R_9$, C_1-C_{10} alkyl, C_1-C_{10} heteroalkyl, C_2-C_{10} alkenyl, or C_2-C_{10} heteroalkenyl, each of which may be optionally substituted with one or more halogens, =O, or an optionally substituted 3-7 membered carbocyclic or heterocyclic ring;

wherein each R_7, R_8 and R_9 is independently selected from H, C_1-C_6 alkyl, C_2-C_6 heteroalkyl, C_1-C_6 acyl, C_2-C_6 heteroacyl, C_6-C_{10} aryl, C_5-C_{10} heteroaryl, C_7-C_{12} arylalkyl, or C_6-C_{12} heteroarylalkyl, each of which is optionally substituted with one or more groups selected from halo, =O, =N-CN, =N-OR', =NR', OR', $N(R')_2$, SR', SO_2R', $SO_2NR'_2$, $NR'SO_2R'$, $NR'CONR'_2$, NR'COOR', NR'COR', CN, COOR', $CON(R')_2$, OOCR', COR', and NO_2; wherein each R' is independently H, C_1-C_6 alkyl, C_2-C_6 heteroalkyl, C_1-C_6 acyl, C_2-C_6 heteroacyl, C_6-C_{10} aryl, C_5-C_{10} heteroaryl, C_7-C_{12} arylalkyl, or C_6-C_{12} heteroarylalkyl, each of which is optionally substituted with one or more groups selected from halo, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_1-C_6 acyl, C_1-C_6 heteroacyl, hydroxy, amino, and =O; wherein two R' can be linked to form a 3-7 membered ring optionally containing up to three heteroatoms selected from N, O and S.

4. A compound of Claim 3, wherein the compound has the following structure:



, or a pharmaceutically acceptable salt, esters prodrug, hydrate, or tautomer thereof; wherein:

L is a C_1-C_{10} alkylene, C_1-C_{10} heteroalkylene, C_2-C_{10} alkenylene or C_2-C_{10} heteroalkenylene linker, each of which may be optionally substituted with one or more substituents selected from the group consisting of halogen, oxo (=O), or C_1-C_6 alkyl;

A is heterocycloalkyl, heteroaryl, or NR_4R_5 where R_4 and R_5 are independently H, optionally substituted C_1-C_8 alkyl, C_2-C_8 heteroalkyl, C_2-C_8 alkenyl, C_2-C_8 heteroalkenyl, C_2-C_8 alkynyl, C_2-C_8 heteroalkynyl, C_1-C_8 acyl, C_2-C_8 heteroacyl, C_6-C_{10} aryl, C_5-C_{12} heteroaryl, C_7-C_{12} arylalkyl, or C_6-C_{12} heteroarylalkyl groupl;

R_4 and R_5 can be linked to form a 3-8 membered ring, optionally containing one or more N, O or S; and each R_4 and R_5 groups, and each ring formed by linking R_4 and R_5 groups together, is optionally substituted with one or more substituents selected from halo, =O, =N-CN, =N-OR', =NR', OR', $N(R')_2$, SR', SO_2R', $SO_2NR'_2$, NR'SO_2R', NR'CONR'$_2$, NR'COOR', NR'COR', CN, COOR', $CON(R')_2$, OOCR', COR', and NO_2, wherein each R' is independently H, C_1-C_6 alkyl, C_2-C_6 heteroalkyl, C_1-C_6 acyl, C_2-C_6 heteroacyl, C_6-C_{10} aryl, C_5-C_{10} heteroaryl, C_7-C_{12} arylalkyl, or C_6-C_{12} heteroarylalkyl, each of which is optionally substituted with one or more groups selected from halo, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_1-C_6 acyl, C_1-C_6 heteroacyl, hydroxy, amino, and =O; wherein two R' can be linked to form a 3-7 membered ring optionally containing up to three heteroatoms selected from N, O and S;

X is NR_6, O, or S;

R_6 is H, optionally substituted C_1-C_8 alkyl, C_2-C_8 heteroalkyl, C_2-C_8 alkenyl, C_2-C_8 heteroalkenyl, C_2-C_8 alkynyl, C_2-C_8 heteroalkynyl, C_1-C_8 acyl, C_2-C_8 heteroacyl, C_6-C_{10} aryl, C_5-C_{12} heteroaryl, C_7-C_{12} arylalkyl, or C_6-C_{12} heteroarylalkyl group;

R_6 can be linked to R_4 or R_5 to form a 3-8 membered ring; and R_4 or R_5 is optionally substituted with one or more substituents selected from halo, =O, =N-CN, =N-OR', =NR', OR', $N(R')_2$,

SR', SO_2R', $SO_2NR'_2$, NR'SO_2R', NR'CONR'$_2$, NR'COOR', NR'COR', CN, COOR', CON(R')$_2$, OOCR', COR', and NO_2, wherein each R' is independently H, C_1-C_6 alkyl, C_2-C_6 heteroalkyl, C_1-C_6 acyl, C_2-C_6 heteroacyl, C_6-C_{10} aryl, C_5-C_{10} heteroaryl, C_7-C_{12} arylalkyl, or C_6-C_{12} heteroarylalkyl, each of which is optionally substituted with one or more groups selected from halo, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_1-C_6 acyl, C_1-C_6 heteroacyl, hydroxy, amino, and =O; wherein two R' can be linked to form a 3-7 membered ring optionally containing up to three heteroatoms selected from N, O and S;

X_2 is hydrogen, or an optionally substituted C_1-C_8 alkyl, C_2-C_8 heteroalkyl, C_2-C_8 alkenyl, C_2-C_8 heteroalkenyl, C_2-C_8 alkynyl, C_2-C_8 heteroalkynyl, C_1-C_8 acyl, C_2-C_8 heteroacyl, C_6-C_{10} aryl, C_5-C_{12} heteroaryl, C_7-C_{12} arylalkyl, or C_6-C_{12} heteroarylalkyl group;

wherein R_2 and R_3 groups on the same atom or on adjacent atoms can be linked to form a 3-8 membered ring, optionally containing one or more N, O or S; and each R_2 and R_3 groups, and each ring formed by linking R_2 and R_3 groups together, is optionally substituted with one or more substituents selected from halo, =O, =N-CN, =N-OR', =NR', OR', N(R')$_2$, SR', SO_2R', $SO_2NR'_2$, NR'SO_2R', NR'CONR'$_2$, NR'COOR', NR'COR', CN, COOR', CON(R')$_2$, OOCR', COR', and NO_2, wherein each R' is independently H, C_1-C_6 alkyl, C_2-C_6 heteroalkyl, C_1-C_6 acyl, C_2-C_6 heteroacyl, C_6-C_{10} aryl, C_5-C_{10} heteroaryl, C_7-C_{12} arylalkyl, or C_6-C_{12} heteroarylalkyl, each of which is optionally substituted with one or more groups selected from halo, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_1-C_6 acyl, C_1-C_6 heteroacyl, hydroxy, amino, and =O; wherein two R' can be linked to form a 3-7 membered ring optionally containing up to three heteroatoms selected from N, O and S; and

$(U)_n$ and $(U)_m$ are independently H, halogen, CF_3, CN, OR_7, NR_8R_9, SR_7, $SO_2NR_8R_9$, C_1-C_{10} alkyl, C_1-C_{10} heteroalkyl, C_2-C_{10} alkenyl, or C_2-C_{10} heteroalkenyl, each of which may be optionally substituted with one or more halogens, =O, or an optionally substituted 3-7 membered carbocyclic or heterocyclic ring;

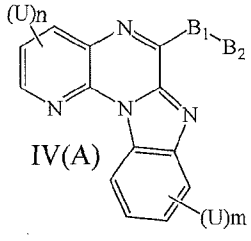
wherein each R_7, R_8 and R_9 is independently selected from H, C_1-C_6 alkyl, C_2-C_6 heteroalkyl, C_1-C_6 acyl, C_2-C_6 heteroacyl, C_6-C_{10} aryl, C_5-C_{10} heteroaryl, C_7-C_{12} arylalkyl, or C_6-C_{12} heteroarylalkyl, each of which is optionally substituted with one or more groups selected from halo, =O, =N-CN, =N-OR', =NR', OR', N(R')$_2$, SR', SO_2R', $SO_2NR'_2$, NR'SO_2R', NR'CONR'$_2$, NR'COOR', NR'COR', CN, COOR', CON(R')$_2$, OOCR', COR', and NO_2; wherein each R' is independently H, C_1-C_6 alkyl, C_2-C_6 heteroalkyl, C_1-C_6 acyl, C_2-C_6

heteroacyl, C_6-C_{10} aryl, C_5-C_{10} heteroaryl, C_7-C_{12} arylalkyl, or C_6-C_{12} heteroarylalkyl, each of which is optionally substituted with one or more groups selected from halo, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_1-C_6 acyl, C_1-C_6 heteroacyl, hydroxy, amino, and =O; wherein two R' can be linked to form a 3-7 membered ring optionally containing up to three heteroatoms selected from N, O and S.

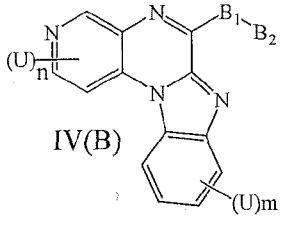
5. The compound of Claim 4, wherein L is a C_1-C_{10} alkylene, C_1-C_{10} heteroalkylene, C_2-C_{10} alkenylene or C_2-C_{10} heteroalkenylene linker, each of which is optionally substituted with one or more substituents selected from the group consisting of halogen, oxo (=O), or C_1-C_6 alkyl.
6. The compound of Claim 4, wherein A is heterocycloalkyl, heteroaryl, or NR_4R_5 where R_4 and R_5 are independently H, optionally substituted C_1-C_8 alkyl, C_2-C_8 heteroalkyl, C_2-C_8 alkenyl, C_2-C_8 heteroalkenyl, C_2-C_8 alkynyl, C_2-C_8 heteroalkynyl, C_1-C_8 acyl, C_2-C_8 heteroacyl, C_6-C_{10} aryl, C_5-C_{12} heteroaryl, C_7-C_{12} arylalkyl, or C_6-C_{12} heteroarylalkyl group.
7. The compound of Claim 4, wherein R_4 and R_5 can be linked to form a 3-8 membered ring, optionally containing one or more N, O or S; and each R_4 and R_5 groups, and each ring formed by linking R_4 and R_5 groups together, is optionally substituted with one or more substituents selected from halo, =O, =N-CN, =N-OR', =NR', OR', $N(R')_2$, SR', SO_2R', $SO_2NR'_2$, NR'SO_2R', NR'$CONR'_2$, NR'COOR', NR'COR', CN, COOR', $CON(R')_2$, OOCR', COR', and NO_2, wherein each R' is independently H, C_1-C_6 alkyl, C_2-C_6 heteroalkyl, C_1-C_6 acyl, C_2-C_6 heteroacyl, C_6-C_{10} aryl, C_5-C_{10} heteroaryl, C_7-C_{12} arylalkyl, or C_6-C_{12} heteroarylalkyl, each of which is optionally substituted with one or more groups selected from halo, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_1-C_6 acyl, C_1-C_6 heteroacyl, hydroxy, amino, and =O; wherein two R' can be linked to form a 3-7 membered ring optionally containing up to three heteroatoms selected from N, O and S.
8. The compound of Claim 4, whereiun X is NR_6, O, or S.
9. The compound of Claim 4, whereiun R_6 is H, optionally substituted C_1-C_8 alkyl, C_2-C_8 heteroalkyl, C_2-C_8 alkenyl, C_2-C_8 heteroalkenyl, C_2-C_8 alkynyl, C_2-C_8 heteroalkynyl, C_1-C_8 acyl, C_2-C_8 heteroacyl, C_6-C_{10} aryl, C_5-C_{12} heteroaryl, C_7-C_{12} arylalkyl, or C_6-C_{12} heteroarylalkyl group.
10. The compound of Claim 4, whereiun R_6 is linked to R_4 or R_5 to form a 3-8 membered ring; and R_4 or R_5 are optionally substituted with one or more substituents selected from halo, =O, =N-CN, =N-OR', =NR', OR', $N(R')_2$, SR', SO_2R', $SO_2NR'_2$, NR'SO_2R', NR'$CONR'_2$, NR'COOR', NR'COR', CN, COOR', $CON(R')_2$, OOCR', COR', and NO_2, wherein each R' is independently H,

C_1-C_6 alkyl, C_2-C_6 heteroalkyl, C_1-C_6 acyl, C_2-C_6 heteroacyl, C_6-C_{10} aryl, C_5-C_{10} heteroaryl, C_7-C_{12} arylalkyl, or C_6-C_{12} heteroarylalkyl, each of which is optionally substituted with one or more groups selected from halo, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_1-C_6 acyl, C_1-C_6 heteroacyl, hydroxy, amino, and =O; wherein two R' can be linked to form a 3-7 membered ring optionally containing up to three heteroatoms selected from N, O and S.

11. The compound of Claim 4, wherein X_2 is H, C_1-C_{10} alkyl, C_1-C_{10} heteroalkyl, C_2-C_{10} alkenyl, or C_2-C_{10} heteroalkenyl, each of which is optionally substituted with one or more halogens, =O, or an optionally substituted 3-7 membered carbocyclic or heterocyclic ring.
12. The compound of Claim 4, wherein $(U)_n$ and $(U)_m$ are independently H, halogen, CF_3, CN, OR_7, NR_8R_9, SR_7, $SO_2NR_8R_9$, C_1-C_{10} alkyl, C_1-C_{10} heteroalkyl, C_2-C_{10} alkenyl, or C_2-C_{10} heteroalkenyl, each of which is optionally substituted with one or more halogens, =O, or an optionally substituted 3-7 membered carbocyclic or heterocyclic ring.
13. The compound of Claim 4, wherein R_2 and R_3 groups on the same atom or on adjacent atoms are linked to form a 3-8 membered ring, optionally containing one or more N, O or S; and each R_2 and R_3 groups, and each ring formed by linking R_2 and R_3 groups together, is optionally substituted with one or more substituents selected from halo, =O, =N-CN, =N-OR', =NR', OR', $N(R')_2$, SR', SO_2R', $SO_2NR'_2$, NR'SO_2R', NR'CONR'$_2$, NR'COOR', NR'COR', CN, COOR', $CON(R')_2$, OOCR', COR', and NO_2, wherein each R' is independently H, C_1-C_6 alkyl, C_2-C_6 heteroalkyl, C_1-C_6 acyl, C_2-C_6 heteroacyl, C_6-C_{10} aryl, C_5-C_{10} heteroaryl, C_7-C_{12} arylalkyl, or C_6-C_{12} heteroarylalkyl, each of which is optionally substituted with one or more groups selected from halo, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_1-C_6 acyl, C_1-C_6 heteroacyl, hydroxy, amino, and =O; wherein two R' can be linked to form a 3-7 membered ring optionally containing up to three heteroatoms selected from N, O and S.
14. The compound of Claim 4, wherein X_2 is H.
15. A compound of Formula IV(A) and IV(B):



IV(A)



IV(B)

, or a pharmaceutically acceptable salt, esters prodrug, hydrate, or tautomer thereof; wherein:
B_1 is a bond or C=O, B_2 is X-L-A;

L is a C_1-C_{10} alkylene, C_1-C_{10} heteroalkylene, C_2-C_{10} alkenylene or C_2-C_{10} heteroalkenylene linker, each of which may be optionally substituted with one or more substituents selected from the group consisting of halogen, oxo (=O), or C1-C6 alkyl;

A is heterocycloalkyl, heteroaryl or NR_4R_5 wherein R_4 and R_5 are independently H, optionally substituted C_1-C_8 alkyl, C_2-C_8 heteroalkyl, C_2-C_8 alkenyl, C_2-C_8 heteroalkenyl, C_2-C_8 alkynyl, C_2-C_8 heteroalkynyl, C_1-C_8 acyl, C_2-C_8 heteroacyl, C_6-C_{10} aryl, C_5-C_{12} heteroaryl, C_7-C_{12} arylalkyl, or C_6-C_{12} heteroarylalkyl group, or R_4 and R_5 can be linked to form a 3-8 membered ring, optionally containing one or more N, O or S; and each R_4 and R_5 groups, and each ring formed by linking R_4 and R_5 groups together, is optionally substituted with one or more substituents selected from halo, =O, =N-CN, =N-OR', =NR', OR', $N(R')_2$, SR', SO_2R', $SO_2NR'_2$, $NR'SO_2R'$, $NR'CONR'_2$, NR'COOR', NR'COR', CN, COOR', $CON(R')_2$, OOCR', COR', and NO_2, wherein each R' is independently H, C_1-C_6 alkyl, C_2-C_6 heteroalkyl, C_1-C_6 acyl, C_2-C_6 heteroacyl, C_6-C_{10} aryl, C_5-C_{10} heteroaryl, C_7-C_{12} arylalkyl, or C_6-C_{12} heteroarylalkyl, each of which is optionally substituted with one or more groups selected from halo, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_1-C_6 acyl, C_1-C_6 heteroacyl, hydroxy, amino, and =O; wherein two R' can be linked to form a 3-7 membered ring optionally containing up to three heteroatoms selected from N, O and S;

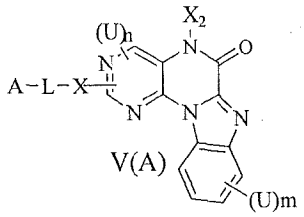
X is CR_6R_6, NR_6, O, or S; wherein R_6 is H, optionally substituted C_1-C_8 alkyl, C_2-C_8 heteroalkyl, C_2-C_8 alkenyl, C_2-C_8 heteroalkenyl, C_2-C_8 alkynyl, C_2-C_8 heteroalkynyl, C_1-C_8 acyl, C_2-C_8 heteroacyl, C_6-C_{10} aryl, C_5-C_{12} heteroaryl, C_7-C_{12} arylalkyl, or C_6-C_{12} heteroarylalkyl group; or R_6 can be linked to R_4 or R_5 to form a 3-8 membered ring; and

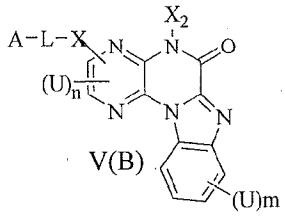
$(U)_n$ and $(U)_m$ are each independently H, halogen, CF_3, CN, OR_7, NR_8R_9, SR_7, $SO_2NR_8R_9$, C_1-C_{10} alkyl, C_1-C_{10} heteroalkyl, C_2-C_{10} alkenyl, or C_2-C_{10} heteroalkenyl, each of which may be optionally substituted with one or more halogens, =O, or an optionally substituted 3-7 membered carbocyclic or heterocyclic ring;

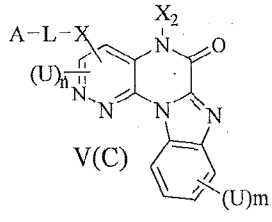
wherein each R_7, R_8 and R_9 is independently selected from H, C_1-C_6 alkyl, C_2-C_6 heteroalkyl, C_1-C_6 acyl, C_2-C_6 heteroacyl, C_6-C_{10} aryl, C_5-C_{10} heteroaryl, C_7-C_{12} arylalkyl, or C_6-C_{12} heteroarylalkyl, each of which is optionally substituted with one or more groups selected from halo, =O, =N-CN, =N-OR', =NR', OR', $N(R')_2$, SR', SO_2R', $SO_2NR'_2$, $NR'SO_2R'$, $NR'CONR'_2$, NR'COOR', NR'COR', CN, COOR', $CON(R')_2$, OOCR', COR', and NO_2; wherein each R' is independently H, C_1-C_6 alkyl, C_2-C_6 heteroalkyl, C_1-C_6 acyl, C_2-C_6

heteroacyl, C_6-C_{10} aryl, C_5-C_{10} heteroaryl, C_7-C_{12} arylalkyl, or C_6-C_{12} heteroarylalkyl, each of which is optionally substituted with one or more groups selected from halo, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_1-C_6 acyl, C_1-C_6 heteroacyl.

16. A compound of Formula V(A), Formula V(B), and Formula V(C):


V(A)


V(B)


V(C)

, or a pharmaceutically acceptable salt, esters prodrug, hydrate, or tautomer thereof; wherein:

L is a bond, C_1-C_{10} alkylene, C_1-C_{10} heteroalkylene, C_2-C_{10} alkenylene or C_2-C_{10} heteroalkenylene linker, each of which is optionally substituted with one or more substituents selected from the group consisting of halogen, oxo (=O), or C_1-C_6 alkyl;

A is heterocycloalkyl, heteroaryl or NR_4R_5 where R_4 and R_5 are independently H, optionally substituted C_1-C_8 alkyl, C_2-C_8 heteroalkyl, C_2-C_8 alkenyl, C_2-C_8 heteroalkenyl, C_2-C_8 alkynyl, C_2-C_8 heteroalkynyl, C_1-C_8 acyl, C_2-C_8 heteroacyl, C_6-C_{10} aryl, C_5-C_{12} heteroaryl, C_7-C_{12} arylalkyl, or C_6-C_{12} heteroarylalkyl group;

R_4 and R_5 can be linked to form a 3-8 membered ring, optionally containing one or more N, O or S; and each R_4 and R_5 groups, and each ring formed by linking R_4 and R_5 groups together, is optionally substituted with one or more substituents selected from halo, =O, =N-CN, =N-OR', =NR', OR', $N(R')_2$, SR', SO_2R', $SO_2NR'_2$, NR'SO_2R', NR'CONR'_2, NR'COOR', NR'COR', CN, COOR', $CON(R')_2$, OOCR', COR', and NO_2, wherein each R' is independently H, C_1-C_6 alkyl, C_2-C_6 heteroalkyl, C_1-C_6 acyl, C_2-C_6 heteroacyl, C_6-C_{10} aryl, C_5-C_{10} heteroaryl, C_7-C_{12} arylalkyl, or C_6-C_{12} heteroarylalkyl, each of which is optionally substituted with one or more groups selected from halo, C_1-C_4 alkyl, C_1-C_4 hetcroalkyl, C_1-C_6 acyl, C_1-C_6 heteroacyl, hydroxy, amino, and =O; wherein two R' can be linked to form a 3-7 membered ring optionally containing up to three heteroatoms selected from N, O and S;

X is NR_6, O, or S;

R_6 is H, optionally substituted C_1-C_8 alkyl, C_2-C_8 heteroalkyl, C_2-C_8 alkenyl, C_2-C_8 heteroalkenyl, C_2-C_8 alkynyl, C_2-C_8 heteroalkynyl, C_1-C_8 acyl, C_2-C_8 heteroacyl, C_6-C_{10} aryl, C_5-C_{12} heteroaryl, C_7-C_{12} arylalkyl, or C_6-C_{12} heteroarylalkyl group;

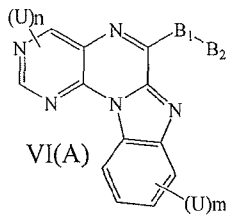
R_6 can be linked to R_4 or R_5 to form a 3-8 membered ring; and R_4 or R_5 is optionally substituted with one or more substituents selected from halo, =O, =N-CN, =N-OR', =NR', OR', $N(R')_2$, SR', SO_2R', $SO_2NR'_2$, NR'SO_2R', NR'CONR'$_2$, NR'COOR', NR'COR', CN, COOR', $CON(R')_2$, OOCR', COR', and NO_2, wherein each R' is independently H, C_1-C_6 alkyl, C_2-C_6 heteroalkyl, C_1-C_6 acyl, C_2-C_6 heteroacyl, C_6-C_{10} aryl, C_5-C_{10} heteroaryl, C_7-C_{12} arylalkyl, or C_6-C_{12} heteroarylalkyl, each of which is optionally substituted with one or more groups selected from halo, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_1-C_6 acyl, C_1-C_6 heteroacyl, hydroxy, amino, and =O; wherein two R' can be linked to form a 3-7 membered ring optionally containing up to three heteroatoms selected from N, O and S;

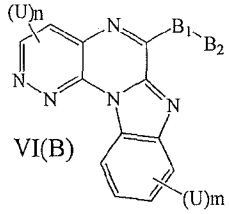
X_2 is H, C_1-C_{10} alkyl, C_1-C_{10} heteroalkyl, C_2-C_{10} alkenyl, or C_2-C_{10} heteroalkenyl, each of which is optionally substituted with one or more halogens, =O, or an optionally substituted 3-7 membered carbocyclic or heterocyclic ring; and

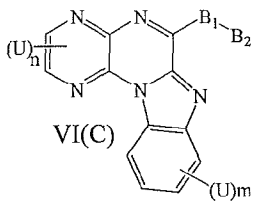
$(U)_n$ and $(U)_m$ are independently H, halogen, CF_3, CN, OR_7, NR_8R_9, SR_7, $SO_2NR_8R_9$, C_1-C_{10} alkyl, C_1-C_{10} heteroalkyl, C_2-C_{10} alkenyl, or C_2-C_{10} heteroalkenyl, each of which is optionally substituted with one or more halogens, =O, or an optionally substituted 3-7 membered carbocyclic or heterocyclic ring;

wherein each R_7, R_8 and R_9 is independently selected from H, C_1-C_6 alkyl, C_2-C_6 heteroalkyl, C_1-C_6 acyl, C_2-C_6 heteroacyl, C_6-C_{10} aryl, C_5-C_{10} heteroaryl, C_7-C_{12} arylalkyl, or C_6-C_{12} heteroarylalkyl, each of which is optionally substituted with one or more groups selected from halo, =O, =N-CN, =N-OR', =NR', OR', $N(R')_2$, SR', SO_2R', $SO_2NR'_2$, NR'SO_2R', NR'CONR'$_2$, NR'COOR', NR'COR', CN, COOR', $CON(R')_2$, OOCR', COR', and NO_2; wherein each R' is independently H, C_1-C_6 alkyl, C_2-C_6 heteroalkyl, C_1-C_6 acyl, C_2-C_6 heteroacyl, C_6-C_{10} aryl, C_5-C_{10} heteroaryl, C_7-C_{12} arylalkyl, or C_6-C_{12} heteroarylalkyl, each of which is optionally substituted with one or more groups selected from halo, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_1-C_6 acyl, C_1-C_6 heteroacyl.

17. A compound of Formula VI(A), VI(B) and VI(C):







, or a pharmaceutically acceptable salt, esters prodrug, hydrate, or tautomer thereof; wherein:

B_1 is a bond or C=O;

B_2 is X-L-A;

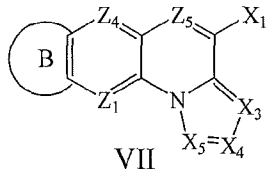
L is a C_1-C_{10} alkylene, C_1-C_{10} heteroalkylene, C_2-C_{10} alkenylene or C_2-C_{10} heteroalkenylene linker, each of which may be optionally substituted with one or more substituents selected from the group consisting of halogen, oxo (=O), or C_1-C_6 alkyl;

A is heterocycloalkyl, heteroaryl or NR_4R_5 wherein R_4 and R_5 are independently H, optionally substituted C_1-C_8 alkyl, C_2-C_8 heteroalkyl, C_2-C_8 alkenyl, C_2-C_8 heteroalkenyl, C_2-C_8 alkynyl, C_2-C_8 heteroalkynyl, C_1-C_8 acyl, C_2-C_8 heteroacyl, C_6-C_{10} aryl, C_5-C_{12} heteroaryl, C_7-C_{12} arylalkyl, or C_6-C_{12} heteroarylalkyl group, or R_4 and R_5 can be linked to form a 3-8 membered ring, optionally containing one or more N, O or S; and each R_4 and R_5 groups, and each ring formed by linking R_4 and R_5 groups together, is optionally substituted with one or more substituents selected from halo, =O, =N-CN, =N-OR', =NR', OR', N(R')$_2$, SR', SO_2R', SO_2NR'$_2$, NR'SO_2R', NR'CONR'$_2$, NR'COOR', NR'COR', CN, COOR', CON(R')$_2$, OOCR', COR', and NO_2, wherein each R' is independently H, C_1-C_6 alkyl, C_2-C_6 heteroalkyl, C_1-C_6 acyl, C_2-C_6 heteroacyl, C_6-C_{10} aryl, C_5-C_{10} heteroaryl, C_7-C_{12} arylalkyl, or C_6-C_{12} heteroarylalkyl, each of which is optionally substituted with one or more groups selected from halo, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_1-C_6 acyl, C_1-C_6 heteroacyl, hydroxy, amino, and =O; wherein two R' can be linked to form a 3-7 membered ring optionally containing up to three heteroatoms selected from N, O and S;

X is CR_6R_6, NR_6, O, or S; wherein R_6 is H, optionally substituted C_1-C_8 alkyl, C_2-C_8 heteroalkyl, C_2-C_8 alkenyl, C_2-C_8 heteroalkenyl, C_2-C_8 alkynyl, C_2-C_8 heteroalkynyl, C_1-C_8 acyl, C_2-C_8 heteroacyl, C_6-C_{10} aryl, C_5-C_{12} heteroaryl, C_7-C_{12} arylalkyl, or C_6-C_{12} heteroarylalkyl group; or R_6 can be linked to R_4 or R_5 to form a 3-8 membered ring; and

$(U)_n$ and $(U)_m$ are independently H, halogen, CF_3, CN, OR_7, NR_8R_9, SR_7, $SO_2NR_8R_9$, C_1-C_{10} alkyl, C_1-C_{10} heteroalkyl, C_2-C_{10} alkenyl, or C_2-C_{10} heteroalkenyl, each of which may be optionally substituted with one or more halogens, =O, or an optionally substituted 3-7 membered carbocyclic or heterocyclic ring

wherein each R_7, R_8 and R_9 is independently selected from H, C_1-C_6 alkyl, C_2-C_6 heteroalkyl, C_1-C_6 acyl, C_2-C_6 heteroacyl, C_6-C_{10} aryl, C_5-C_{10} heteroaryl, C_7-C_{12} arylalkyl, or C_6-C_{12} heteroarylalkyl, each of which is optionally substituted with one or more groups selected from halo, =O, =N-CN, =N-OR', =NR', OR', $N(R')_2$, SR', SO_2R', $SO_2NR'_2$, $NR'SO_2R'$, $NR'CONR'_2$, NR'COOR', NR'COR', CN, COOR', $CON(R')_2$, OOCR', COR', and NO_2; wherein each R' is independently H, C_1-C_6 alkyl, C_2-C_6 heteroalkyl, C_1-C_6 acyl, C_2-C_6 heteroacyl, C_6-C_{10} aryl, C_5-C_{10} heteroaryl, C_7-C_{12} arylalkyl, or C_6-C_{12} heteroarylalkyl, each of which is optionally substituted with one or more groups selected from halo, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_1-C_6 acyl, C_1-C_6 heteroacyl.



VII

18. A compound of Formula VII: , or a pharmaceutically acceptable salt, esters prodrug, hydrate, or tautomer thereof; wherein:

B is an optionally substituted 5-6 membered carbocyclic or heterocyclic ring;

Z_5 is N or CX_2;

each Z_1 and Z_4 is N, CH, or CR_1, provided any three N are non-adjacent; and further provided that one or more of Z_1, Z_2, Z_3, and Z_4 is CR_1;

each R_1 is independently an optionally substituted C_1-C_8 alkyl, C_2-C_8 heteroalkyl, C_2-C_8 alkenyl, C_2-C_8 heteroalkenyl, C_2-C_8 alkynyl, C_2-C_8 heteroalkynyl, C_1-C_8 acyl, C_2-C_8 heteroacyl, C_6-C_{10} aryl, C_5-C_{12} heteroaryl, C_7-C_{12} arylalkyl, or C_6-C_{12} heteroarylalkyl group, or each R_1 is independently H, halo, CF_3, OR_2, NR_2R_3, NR_2OR_3, $NR_2NR_2R_3$, SR_2, SOR_2, SO_2R_2, $SO_2NR_2R_3$, $NR_2SO_2R_3$, $NR_2CONR_2R_3$, NR_2COOR_3, NR_2COR_3, CN, $COOR_2$, COOH, $CONR_2R_3$, $OOCR_2$, COR_2, or NO_2; and

wherein R_2 and R_3 groups on the same atom or on adjacent atoms can be linked to form a 3-8 membered ring, optionally containing one or more N, O or S atoms; and each R_2 and R_3 groups, and each ring formed by linking R_2 and R_3 groups together, is optionally substituted

with one or more substituents selected from halo, =O, =N-CN, =N-OR', =NR', OR', $N(R')_2$, SR', SO_2R', $SO_2NR'_2$, NR'SO_2R', NR'CONR'$_2$, NR'C_OOR', NR'COR', CN, COOR', $CON(R')_2$, OOCR', COR', and NO_2, wherein each R' is independently H, C_1-C_6 alkyl, C_2-C_6 heteroalkyl, C_1-C_6 acyl, C_2-C_6 heteroacyl, C_6-C_{10} aryl, C_5-C_{10} heteroaryl, C_7-C_{12} arylalkyl, or C_6-C_{12} heteroarylalkyl, each of which is optionally substituted with one or more groups selected from halo, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_1-C_6 acyl, C_1-C_6 heteroacyl, hydroxy, amino, and =O; wherein two R' can be linked to form a 3-7 membered ring optionally containing up to three heteroatoms selected from N, O and S;

two R_1 groups on adjacent atoms may form a carboxylic ring, heterocyclic ring, aryl or heteroaryl, each of which may be optionally substituted and/or fused with a cyclic ring;

or each R_1 is independently -W, -L-W, -X-L-A; wherein X is NR_6, O, or S; W is an optionally substituted 4-7 membered azacyclic ring, optionally containing an additional heteroatom selected from N, O and S as a ring member; L is a C_1-C_{10} alkylene, C_1-C_{10} heteroalkylene, C_2-C_{10} alkenylene or C_2-C_{10} heteroalkenylene linker, each of which may be optionally substituted with one or more substituents selected from the group consisting of halogen, oxo (=O), or C_1-C_6 alkyl; and A is heterocycloalkyl, heteroaryl or NR_4R_5 where R_4 and R_5 are independently H, optionally substituted C_1-C_8 alkyl, C_2-C_8 heteroalkyl, C_2-C_8 alkenyl, C_2-C_8 heteroalkenyl, C_2-C_8 alkynyl, C_2-C_8 heteroalkynyl, C_1-C_8 acyl, C_2-C_8 heteroacyl, C_6-C_{10} aryl, C_5-C_{12} heteroaryl, C_7-C_{12} arylalkyl, or C_6-C_{12} heteroarylalkyl group;

R_4 and R_5 can be linked to form a 3-8 membered ring, optionally containing one or more N, O or S; and each R_4 and R_5 groups, and each ring formed by linking R_4 and R_5 groups together, is optionally substituted with one or more substituents selected from halo, =O, =N-CN, =N-OR', =NR', OR', $N(R')_2$, SR', SO_2R', $SO_2NR'_2$, NR'SO_2R', NR'CONR'$_2$, NR'COOR', NR'COR', CN, COOR', $CON(R')_2$, OOCR', COR', and NO_2, wherein each R' is independently H, C_1-C_6 alkyl, C_2-C_6 heteroalkyl, C_1-C_6 acyl, C_2-C_6 heteroacyl, C_6-C_{10} aryl, C_5-C_{10} heteroaryl, C_7-C_{12} arylalkyl, or C_6-C_{12} heteroarylalkyl, each of which is optionally substituted with one or more groups selected from halo, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_1-C_6 acyl, C_1-C_6 heteroacyl, hydroxy, amino, and =O; wherein two R' can be linked to form a 3-7 membered ring optionally containing up to three heteroatoms selected from N, O and S;

R_6 is H, optionally substituted C_1-C_8 alkyl, C_2-C_8 heteroalkyl, C_2-C_8 alkenyl, C_2-C_8 heteroalkenyl, C_2-C_8 alkynyl, C_2-C_8 heteroalkynyl, C_1-C_8 acyl, C_2-C_8 heteroacyl, C_6-C_{10} aryl, C_5-C_{12} heteroaryl, C_7-C_{12} arylalkyl, or C_6-C_{12} heteroarylalkyl group;

R_6 can be linked to R_4 or R_5 to form a 3-8 membered ring; and R_4 or R_5 is optionally substituted with one or more substituents selected from halo, =O, =N-CN, =N-OR', =NR', OR', $N(R')_2$, SR', SO_2R', $SO_2NR'_2$, $NR'SO_2R'$, $NR'CONR'_2$, NR'COOR', NR'COR', CN, COOR', $CON(R')_2$, OOCR', COR', and NO_2, wherein each R' is independently H, C_1-C_6 alkyl, C_2-C_6 heteroalkyl, C_1-C_6 acyl, C_2-C_6 heteroacyl, C_6-C_{10} aryl, C_5-C_{10} heteroaryl, C_7-C_{12} arylalkyl, or C_6-C_{12} heteroarylalkyl, each of which is optionally substituted with one or more groups selected from halo, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_1-C_6 acyl, C_1-C_6 heteroacyl, hydroxy, amino, and =O; wherein two R' can be linked to form a 3-7 membered ring optionally containing up to three heteroatoms selected from N, O and S;

X_1 is an optionally substituted C_1-C_8 alkyl, C_2-C_8 heteroalkyl, C_2-C_8 alkenyl, C_2-C_8 heteroalkenyl, C_2-C_8 alkynyl, C_2-C_8 heteroalkynyl, C_1-C_8 acyl, C_2-C_8 heteroacyl, C_6-C_{10} aryl, C_5-C_{12} heteroaryl, C_7-C_{12} arylalkyl, or C_6-C_{12} heteroarylalkyl group, optionally substituted with one or more halogens, =O, CF_3, CN, OR_7, NR_8R_9, SR_7, $SO_2NR_8R_9$, C_1-C_8 alkyl, C_2-C_8 heteroalkyl, C_2-C_8 alkenyl, C_2-C_8 heteroalkenyl, C_2-C_8 alkynyl, C_2-C_8 heteroalkynyl, C_1-C_8 acyl, C_2-C_8 heteroacyl, C_6-C_{10} aryl, C_5-C_{12} heteroaryl, C_7-C_{12} arylalkyl, or C_6-C_{12} heteroarylalkyl group, or;

X_1 is NR_2R_3, SOR_2, SO_2R_2, $SO_2NR_2R_3$, $NR_2SO_2R_3$, $NR_2CONR_2R_3$, NR_2COOR_3, NR_2COR_3, CN, $COOR_2$, ester bioisostere, COOH, carboxy bioisostere, $CONR_2R_3$, amide bioisostere, $OOCR_2$, COR_2, or NO_2;

X_2 is, H, halogen, CF_3, CN, OR_7, NR_8R_9, SR_7, $SO_2NR_8R_9$, C_1-C_{10} alkyl, C_1-C_{10} heteroalkyl, C_2-C_{10} alkenyl, or C_2-C_{10} heteroalkenyl, each of which may be optionally substituted with one or more halogens, =O, or an optionally substituted 3-7 membered carbocyclic or heterocyclic ring;

wherein each R_7, R_8 and R_9 is independently selected from H, C_1-C_6 alkyl, C_2-C_6 heteroalkyl, C_1-C_6 acyl, C_2-C_6 heteroacyl, C_6-C_{10} aryl, C_5-C_{10} heteroaryl, C_7-C_{12} arylalkyl, or C_6-C_{12} heteroarylalkyl, each of which is optionally substituted with one or more groups selected from halo, =O, =N-CN, =N-OR', =NR', OR', $N(R')_2$, SR', SO_2R', $SO_2NR'_2$, $NR'SO_2R'$, $NR'CONR'_2$, NR'COOR', NR'COR', CN, COOR', $CON(R')_2$, OOCR', COR', and NO_2;

AMENDED SHEET (ARTICLE 19)

wherein each R' is independently H, C_1-C_6 alkyl, C_2-C_6 heteroalkyl, C_1-C_6 acyl, C_2-C_6 heteroacyl, C_6-C_{10} aryl, C_5-C_{10} heteroaryl, C_7-C_{12} arylalkyl, or C_6-C_{12} heteroarylalkyl, each of which is optionally substituted with one or more groups selected from halo, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_1-C_6 acyl, C_1-C_6 heteroacyl,

each X_3, X_4 and X_5 is N or CR_{10};

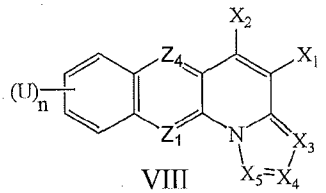
each R_{10} is independently an optionally substituted C_1-C_8 alkyl, C_2-C_8 heteroalkyl, C_2-C_8 alkenyl, C_2-C_8 heteroalkenyl, C_2-C_8 alkynyl, C_2-C_8 heteroalkynyl, C_1-C_8 acyl, C_2-C_8 heteroacyl, C_6-C_{10} aryl, C_5-C_{12} heteroaryl, C_7-C_{12} arylalkyl, or C_6-C_{12} heteroarylalkyl group, or each R_1 is independently H, halo, CF_3, OR_2, NR_2R_3, NR_2OR_3, $NR_2NR_2R_3$, SR_2, SOR_2, SO_2R_2, $SO_2NR_2R_3$, $NR_2SO_2R_3$, $NR_2CONR_2R_3$, NR_2COOR_3, NR_2COR_3, CN, $COOR_2$, COOH, $CONR_2R_3$, $OOCR_2$, COR_2, or NO_2;

and wherein R_2 and R_3 groups on the same atom or on adjacent atoms can be linked to form a 3-8 membered ring, optionally containing one or more N, O or S atoms; and each R_2 and R_3 groups, and each ring formed by linking R_2 and R_3 groups together, is optionally substituted with one or more substituents selected from halo, =O, =N-CN, =N-OR', =NR', OR', $N(R')_2$, SR', SO_2R', $SO_2NR'_2$, NR'SO_2R', NR'CONR'$_2$, NR'CO_OR', NR'COR', CN, COOR', $_CON(R')_2$, OOCR', COR', and NO_2, wherein each R' is independently H, C_1-C_6 alkyl, C_2-C_6 heteroalkyl, C_1-C_6 acyl, C_2-C_6 heteroacyl, C_6-C_{10} aryl, C_5-C_{10} heteroaryl, C_7-C_{12} arylalkyl, or C_6-C_{12} heteroarylalkyl, each of $_{wh}$ich $_{is}$ optionally substituted with one or more groups selected from halo, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_1-C_6 acyl, C_1-C_6 heteroacyl, hydroxy, amino, and =O; wherein two R' can be linked to form a 3-7 membered ring optionally containing up to three heteroatoms selected from N, O and S;

two R_{10} groups on adjacent atoms may form a carboxylic ring, heterocyclic ring, aryl or heteroaryl, each of which may be optionally substituted and/or fused with a cyclic ring;

or each R_{10} is independently -W, -L-W, -X-L-A; wherein X is NR_6, O, or S; W is an optionally substituted 4-7 membered azacyclic ring, optionally containing an additional heteroatom selected from N, O and S as a ring member; L is a C_1-C_{10} alkylene, C_1-C_{10} heteroalkylene, C_2-C_{10} alkenylene or C_2-C_{10} heteroalkenylene linker, each of which may be optionally substituted with one or more substituents selected from the group consisting of halogen, oxo (=O), or C1-C_6 alkyl; and A is heterocycloalkyl, heteroaryl or NR_4R_5 where R_4 and R_5 are independently H, optionally substituted C_1-C_8 alkyl, C_2-C_8 heteroalkyl, C_2-C_8 alkenyl, C_2-C_8

heteroalkenyl, C_2-C_8 alkynyl, C_2-C_8 heteroalkynyl, C_1-C_8 acyl, C_2-C_8 heteroacyl, C_6-C_{10} aryl, C_5-C_{12} heteroaryl, C_7-C_{12} arylalkyl, or C_6-C_{12} heteroarylalkyl group.



VIII

19. A a compound of Formula VIII: , or a pharmaceutically acceptable salt, esters prodrug, hydrate, or tautomer thereof; wherein:

each Z_1 and Z_4 is N, CH, or CR_1; wherein each R_1 is independently an optionally substituted C_1-C_8 alkyl, C_2-C_8 heteroalkyl, C_2-C_8 alkenyl, C_2-C_8 heteroalkenyl, C_2-C_8 alkynyl, C_2-C_8 heteroalkynyl, C_1-C_8 acyl, C_2-C_8 heteroacyl, C_6-C_{10} aryl, C_5-C_{12} heteroaryl, C_7-C_{12} arylalkyl, or C_6-C_{12} heteroarylalkyl group, or each R_1 is independently H, halo, CF_3, OR_2, NR_2R_3, NR_2OR_3, $NR_2NR_2R_3$, SR_2, SOR_2, SO_2R_2, $SO_2NR_2R_3$, $NR_2SO_2R_3$, $NR_2CONR_2R_3$, NR_2COOR_3, NR_2COR_3, CN, $COOR_2$, COOH, $CONR_2R_3$, $OOCR_2$, COR_2, or NO_2;

and wherein R_2 and R_3 groups on the same atom or on adjacent atoms can be linked to form a 3-8 membered ring, optionally containing one or more N, O or S atoms; and each R_2 and R_3 groups, and each ring formed by linking R_2 and R_3 groups together, is optionally substituted with one or more substituents selected from halo, =O, =N-CN, =N-OR', =NR', OR', $N(R')_2$, SR', SO_2R', $SO_2NR'_2$, NR'SO_2R', NR'CONR'$_2$, NR'COOR', NR'COR', CN, COOR', $CON(R')_2$, OOCR', COR', and NO_2, wherein each R' is independently H, C_1-C_6 alkyl, C_2-C_6 heteroalkyl, C_1-C_6 acyl, C_2-C_6 heteroacyl, C_6-C_{10} aryl, C_5-C_{10} heteroaryl, C_7-C_{12} arylalkyl, or C_6-C_{12} heteroarylalkyl, each of which is optionally substituted with one or more groups selected from halo, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_1-C_6 acyl, C_1-C_6 heteroacyl, hydroxy, amino, and =O; wherein two R' can be linked to form a 3-7 membered ring optionally containing up to three heteroatoms selected from N, O and S;

or each R_1 is independently -W, -L-W, -X-L-A; wherein X is NR_6, O, or S; W is an optionally substituted 4-7 membered azacyclic ring, optionally containing an additional heteroatom selected from N, O and S as a ring member; L is a C_1-C_{10} alkylene, C_1-C_{10} heteroalkylene, C_2-C_{10} alkenylene or C_2-C_{10} heteroalkenylene linker, each of which may be optionally substituted with one or more substituents selected from the group consisting of halogen, oxo (=O), or C1-C_6 alkyl; and A is heterocycloalkyl, heteroaryl or NR_4R_5 where R_4 and R_5 are independently H, optionally substituted C_1-C_8 alkyl, C_2-C_8 heteroalkyl, C_2-C_8 alkenyl, C_2-C_8

heteroalkenyl, C_2-C_8 alkynyl, C_2-C_8 heteroalkynyl, C_1-C_8 acyl, C_2-C_8 heteroacyl, C_6-C_{10} aryl, C_5-C_{12} heteroaryl, C_7-C_{12} arylalkyl, or C_6-C_{12} heteroarylalkyl group;

R_4 and R_5 can be linked to form a 3-8 membered ring, optionally containing one or more N, O or S; and each R_4 and R_5 groups, and each ring formed by linking R_4 and R_5 groups together, is optionally substituted with one or more substituents selected from halo, =O, =N-CN, =N-OR', =NR', OR', $N(R')_2$, SR', SO_2R', $SO_2NR'_2$, $NR'SO_2R'$, $NR'CONR'_2$, NR'COOR', NR'COR', CN, COOR', $CON(R')_2$, OOCR', COR', and NO_2, wherein each R' is independently H, C_1-C_6 alkyl, C_2-C_6 heteroalkyl, C_1-C_6 acyl, C_2-C_6 heteroacyl, C_6-C_{10} aryl, C_5-C_{10} heteroaryl, C_7-C_{12} arylalkyl, or C_6-C_{12} heteroarylalkyl, each of which is optionally substituted with one or more groups selected from halo, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_1-C_6 acyl, C_1-C_6 heteroacyl, hydroxy, amino, and =O; wherein two R' can be linked to form a 3-7 membered ring optionally containing up to three heteroatoms selected from N, O and S;

R_6 is H, optionally substituted C_1-C_8 alkyl, C_2-C_8 heteroalkyl, C_2-C_8 alkenyl, C_2-C_8 heteroalkenyl, C_2-C_8 alkynyl, C_2-C_8 heteroalkynyl, C_1-C_8 acyl, C_2-C_8 heteroacyl, C_6-C_{10} aryl, C_5-C_{12} heteroaryl, C_7-C_{12} arylalkyl, or C_6-C_{12} heteroarylalkyl group; or R_6 can be linked to R_4 or R_5 to form a 3-8 membered ring; and R_4 or R_5 is optionally substituted with one or more substituents selected from halo, =O, =N-CN, =N-OR', =NR', OR', $N(R')_2$, SR', SO_2R', $SO_2NR'_2$, $NR'SO_2R'$, $NR'CONR'_2$, NR'COOR', NR'COR', CN, COOR', $CON(R')_2$, OOCR', COR', and NO_2, wherein each R' is independently H, C_1-C_6 alkyl, C_2-C_6 heteroalkyl, C_1-C_6 acyl, C_2-C_6 heteroacyl, C_6-C_{10} aryl, C_5-C_{10} heteroaryl, C_7-C_{12} arylalkyl, or C_6-C_{12} heteroarylalkyl, each of which is optionally substituted with one or more groups selected from halo, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_1-C_6 acyl, C_1-C_6 heteroacyl, hydroxy, amino, and =O; wherein two R' can be linked to form a 3-7 membered ring optionally containing up to three heteroatoms selected from N, O and S;

X_1 is an optionally substituted C_1-C_8 alkyl, C_2-C_8 heteroalkyl, C_2-C_8 alkenyl, C_2-C_8 heteroalkenyl, C_2-C_8 alkynyl, C_2-C_8 heteroalkynyl, C_1-C_8 acyl, C_2-C_8 heteroacyl, C_6-C_{10} aryl, C_5-C_{12} heteroaryl, C_7-C_{12} arylalkyl, or C_6-C_{12} heteroarylalkyl group, optionally substituted with one or more halogens, =O, CF_3, CN, OR_7, NR_8R_9, SR_7, $SO_2NR_8R_9$, C_1-C_8 alkyl, C_2-C_8 heteroalkyl, C_2-C_8 alkenyl, C_2-C_8 heteroalkenyl, C_2-C_8 alkynyl, C_2-C_8 heteroalkynyl, C_1-C_8 acyl, C_2-C_8 heteroacyl, C_6-C_{10} aryl, C_5-C_{12} heteroaryl, C_7-C_{12} arylalkyl, or C_6-C_{12} heteroarylalkyl group; or

X_1 is NR_2R_3, SOR_2, SO_2R_2, $SO_2NR_2R_3$, $NR_2SO_2R_3$, $NR_2CONR_2R_3$, NR_2COOR_3, NR_2COR_3, CN, $COOR_2$, ester bioisostere, COOH, carboxy bioisostere, $CONR_2R_3$, amide bioisostere, $OOCR_2$, COR_2, or NO_2;

X_2 is, H, halogen, CF_3, CN, OR_7, NR_8R_9, SR_7, $SO_2NR_8R_9$, C_1-C_{10} alkyl, C_1-C_{10} heteroalkyl, C_2-C_{10} alkenyl, or C_2-C_{10} heteroalkenyl, each of which may be optionally substituted with one or more halogens, =O, or an optionally substituted 3-7 membered carbocyclic or heterocyclic ring;

wherein each R_7, R_8 and R_9 is independently selected from H, C_1-C_6 alkyl, C_2-C_6 heteroalkyl, C_1-C_6 acyl, C_2-C_6 heteroacyl, C_6-C_{10} aryl, C_5-C_{10} heteroaryl, C_7-C_{12} arylalkyl, or C_6-C_{12} heteroarylalkyl, each of which is optionally substituted with one or more groups selected from halo, =O, =N-CN, =N-OR', =NR', OR', $N(R')_2$, SR', SO_2R', $SO_2NR'_2$, NR'SO_2R', NR'$CONR'_2$, NR'COOR', NR'COR', CN, COOR', $CON(R')_2$, OOCR', COR', and NO_2; wherein each R' is independently H, C_1-C_6 alkyl, C_2-C_6 heteroalkyl, C_1-C_6 acyl, C_2-C_6 heteroacyl, C_6-C_{10} aryl, C_5-C_{10} heteroaryl, C_7-C_{12} arylalkyl, or C_6-C_{12} heteroarylalkyl, each of which is optionally substituted with one or more groups selected from halo, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_1-C_6 acyl, C_1-C_6 heteroacyl;

each X_3, X_4 and X_5 is N or CR_{10};

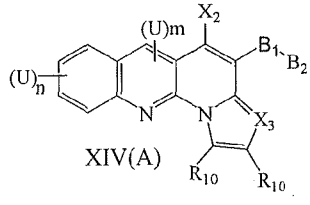
each R_{10} is independently an optionally substituted C_1-C_8 alkyl, C_2-C_8 heteroalkyl, C_2-C_8 alkenyl, C_2-C_8 heteroalkenyl, C_2-C_8 alkynyl, C_2-C_8 heteroalkynyl, C_1-C_8 acyl, C_2-C_8 heteroacyl, C_6-C_{10} aryl, C_5-C_{12} heteroaryl, C_7-C_{12} arylalkyl, or C_6-C_{12} heteroarylalkyl group, or each R_1 is independently H, halo, CF_3, OR_2, NR_2R_3, NR_2OR_3, $NR_2NR_2R_3$, SR_2, SOR_2, SO_2R_2, $SO_2NR_2R_3$, $NR_2SO_2R_3$, $NR_2CONR_2R_3$, NR_2COOR_3, NR_2COR_3, CN, $COOR_2$, COOH, $CONR_2R_3$, $OOCR_2$, COR_2, or NO_2; and wherein R_2 and R_3 groups on the same atom or on adjacent atoms can be linked to form a 3-8 membered ring, optionally containing one or more N, O or S atoms; and each R_2 and R_3 groups, and each ring formed by linking R_2 and R_3 groups together, is optionally substituted with one or more substituents selected from halo, =O, =N-CN, =N-OR', =NR', OR', $N(R')_2$, SR', SO_2R', $SO_2NR'_2$, NR'SO_2R', NR'$CONR'_2$, NR'COOR', NR'COR', CN, COOR', $CON(R')_2$, OOCR', COR', and NO_2, wherein each R' is independently H, C_1-C_6 alkyl, C_2-C_6 heteroalkyl, C_1-C_6 acyl, C_2-C_6 heteroacyl, C_6-C_{10} aryl, C_5-C_{10} heteroaryl, C_7-C_{12} arylalkyl, or C_6-C_{12} heteroarylalkyl, each of which is optionally substituted with one or more groups selected from halo, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_1-

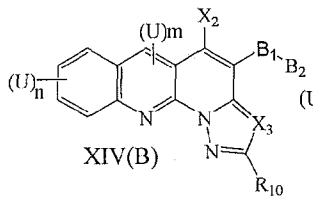
C_6 acyl, C_1-C_6 heteroacyl, hydroxy, amino, and =O; wherein two R' can be linked to form a 3-7 membered ring optionally containing up to three heteroatoms selected from N, O and S;

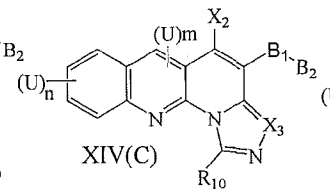
two R_{10} groups on adjacent atoms may form a carboxylic ring, heterocyclic ring, aryl or heteroaryl, each of which may be optionally substituted and/or fused with a cyclic ring; or

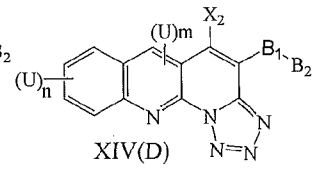
each R_{10} is independently -W, -L-W, -X-L-A; wherein: X is NR_6, O, or S; W is an optionally substituted 4-7 membered azacyclic ring, optionally containing an additional heteroatom selected from N, O and S as a ring member; L is a C_1-C_{10} alkylene, C_1-C_{10} heteroalkylene, C_2-C_{10} alkenylene or C_2-C_{10} heteroalkenylene linker, each of which may be optionally substituted with one or more substituents selected from the group consisting of halogen, oxo (=O), or C1-C_6 alkyl; and A is heterocycloalkyl, heteroaryl or NR_4R_5 where R_4 and R_5 are independently H, optionally substituted C_1-C_8 alkyl, C_2-C_8 heteroalkyl, C_2-C_8 alkenyl, C_2-C_8 heteroalkenyl, C_2-C_8 alkynyl, C_2-C_8 heteroalkynyl, C_1-C_8 acyl, C_2-C_8 heteroacyl, C_6-C_{10} aryl, C_5-C_{12} heteroaryl, C_7-C_{12} arylalkyl, or C_6-C_{12} heteroarylalkyl group.

20. A compound of Formula XIV(A), XIV(B), XIV (C) and XIV (D):


XIV(A)


XIV(B)


XIV(C)


XIV(D)

or a pharmaceutically acceptable salt, esters prodrug, hydrate, or tautomer thereof; wherein:

B_1 is a bond or C=O and B_2 is X-L-A;

L is a C_1-C_{10} alkylene, C_1-C_{10} heteroalkylene, C_2-C_{10} alkenylene or C_2-C_{10} heteroalkenylene linker, each of which may be optionally substituted with one or more substituents selected from the group consisting of halogen, oxo (=O), or C1-C6 alkyl;

A is heterocycloalkyl, heteroaryl or NR_4R_5 wherein R_4 and R_5 are independently H, optionally substituted C_1-C_8 alkyl, C_2-C_8 heteroalkyl, C_2-C_8 alkenyl, C_2-C_8 heteroalkenyl, C_2-C_8 alkynyl, C_2-C_8 heteroalkynyl, C_1-C_8 acyl, C_2-C_8 heteroacyl, C_6-C_{10} aryl, C_5-C_{12} heteroaryl, C_7-C_{12} arylalkyl, or C_6-C_{12} heteroarylalkyl group, or R_4 and R_5 can be linked to form a 3-8 membered ring, optionally containing one or more N, O or S; and each R_4 and R_5 groups, and each ring formed by linking R_4 and R_5 groups together, is optionally substituted with one or more substituents selected from halo, =O, =N-CN, =N-OR', =NR', OR', $N(R')_2$, SR', SO_2R',

$SO_2NR'_2$, $NR'SO_2R'$, $NR'CONR'_2$, NR'COOR', NR'COR', CN, COOR', $CON(R')_2$, OOCR', COR', and NO_2, wherein each R' is independently H, C_1-C_6 alkyl, C_2-C_6 heteroalkyl, C_1-C_6 acyl, C_2-C_6 heteroacyl, C_6-C_{10} aryl, C_5-C_{10} heteroaryl, C_7-C_{12} arylalkyl, or C_6-C_{12} heteroarylalkyl, each of which is optionally substituted with one or more groups selected from halo, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_1-C_6 acyl, C_1-C_6 heteroacyl, hydroxy, amino, and =O; wherein two R' can be linked to form a 3-7 membered ring optionally containing up to three heteroatoms selected from N, O and S;

X is CR_6R_6, NR_6, O, or S; wherein R_6 is H, optionally substituted C_1-C_8 alkyl, C_2-C_8 heteroalkyl, C_2-C_8 alkenyl, C_2-C_8 heteroalkenyl, C_2-C_8 alkynyl, C_2-C_8 heteroalkynyl, C_1-C_8 acyl, C_2-C_8 heteroacyl, C_6-C_{10} aryl, C_5-C_{12} heteroaryl, C_7-C_{12} arylalkyl, or C_6-C_{12} heteroarylalkyl group; or R_6 can be linked to R_4 or R_5 to form a 3-8 membered ring;

X_2 is H, halogen, CF_3, CN, OR_7, NR_8R_9, SR_7, $SO_2NR_8R_9$, C_1-C_{10} alkyl, C_1-C_{10} heteroalkyl, C_2-C_{10} alkenyl, or C_2-C_{10} heteroalkenyl, each of which may be optionally substituted with one or more halogens, =O, or an optionally substituted 3-7 membered carbocyclic or heterocyclic ring;

$(U)_n$ and $(U)_m$ are independently H, halogen, CF_3, CN, OR_7, NR_8R_9, SR_7, $SO_2NR_8R_9$, C_1-C_{10} alkyl, C_1-C_{10} heteroalkyl, C_2-C_{10} alkenyl, or C_2-C_{10} heteroalkenyl, each of which may be optionally substituted with one or more halogens, =O, or an optionally substituted 3-7 membered carbocyclic or heterocyclic ring;

wherein each R_7, R_8 and R_9 is independently selected from H, C_1-C_6 alkyl, C_2-C_6 heteroalkyl, C_1-C_6 acyl, C_2-C_6 heteroacyl, C_6-C_{10} aryl, C_5-C_{10} heteroaryl, C_7-C_{12} arylalkyl, or C_6-C_{12} heteroarylalkyl, each of which is optionally substituted with one or more groups selected from halo, =O, =N-CN, =N-OR', =NR', OR', $N(R')_2$, SR', SO_2R', $SO_2NR'_2$, $NR'SO_2R'$, $NR'CONR'_2$, NR'COOR', NR'COR', CN, COOR', $CON(R')_2$, OOCR', COR', and NO_2; wherein each R' is independently H, C_1-C_6 alkyl, C_2-C_6 heteroalkyl, C_1-C_6 acyl, C_2-C_6 heteroacyl, C_6-C_{10} aryl, C_5-C_{10} heteroaryl, C_7-C_{12} arylalkyl, or C_6-C_{12} heteroarylalkyl, each of which is optionally substituted with one or more groups selected from halo, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_1-C_6 acyl, C_1-C_6 heteroacyl;

each X_3 is N or CR_{10};

each R_{10} is independently an optionally substituted C_1-C_8 alkyl, C_2-C_8 heteroalkyl, C_2-C_8 alkenyl, C_2-C_8 heteroalkenyl, C_2-C_8 alkynyl, C_2-C_8 heteroalkynyl, C_1-C_8 acyl, C_2-C_8

heteroacyl, C_6-C_{10} aryl, C_5-C_{12} heteroaryl, C_7-C_{12} arylalkyl, or C_6-C_{12} heteroarylalkyl group, or each R_1 is independently H, halo, CF_3, OR_2, NR_2R_3, NR_2OR_3, $NR_2NR_2R_3$, SR_2, SOR_2, SO_2R_2, $SO_2NR_2R_3$, $NR_2SO_2R_3$, $NR_2CONR_2R_3$, NR_2COOR_3, NR_2COR_3, CN, $COOR_2$, COOH, $CONR_2R_3$, $OOCR_2$, COR_2, or NO_2;

and wherein R_2 and R_3 groups on the same atom or on adjacent atoms can be linked to form a 3-8 membered ring, optionally containing one or more N, O or S atoms; and each R_2 and R_3 groups, and each ring formed by linking R_2 and R_3 groups together, is optionally substituted with one or more substituents selected from halo, =O, =N-CN, =N-OR', =NR', OR', $N(R')_2$, SR', SO_2R', $SO_2NR'_2$, $NR'SO_2R'$, NR'CONR'$_2$, NR'COOR', NR'COR', CN, COOR', $CON(R')_2$, OOCR', COR', and NO_2, wherein each R' is independently H, C_1-C_6 alkyl, C_2-C_6 heteroalkyl, C_1-C_6 acyl, C_2-C_6 heteroacyl, C_6-C_{10} aryl, C_5-C_{10} heteroaryl, C_7-C_{12} arylalkyl, or C_6-C_{12} heteroarylalkyl, each of which is optionally substituted with one or more groups selected from halo, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_1-C_6 acyl, C_1-C_6 heteroacyl, hydroxy, amino, and =O; wherein two R' can be linked to form a 3-7 membered ring optionally containing up to three heteroatoms selected from N, O and S;

two R_{10} groups on adjacent atoms may form a carboxylic ring, heterocyclic ring, aryl or heteroaryl, each of which may be optionally substituted and/or fused with a cyclic ring; or each R_{10} is independently -W, -L-W, -X-L-A; wherein X is NR_6, O, or S; W is an optionally substituted 4-7 membered azacyclic ring, optionally containing an additional heteroatom selected from N, O and S as a ring member; L is a C_1-C_{10} alkylene, C_1-C_{10} heteroalkylene, C_2-C_{10} alkenylene or C_2-C_{10} heteroalkenylene linker, each of which may be optionally substituted with one or more substituents selected from the group consisting of halogen, oxo (=O), or C1-C6 alkyl; and A is heterocycloalkyl, heteroaryl or NR_4R_5 where R_4 and R_5 are independently H, optionally substituted C_1-C_8 alkyl, C_2-C_8 heteroalkyl, C_2-C_8 alkenyl, C_2-C_8 heteroalkenyl, C_2-C_8 alkynyl, C_2-C_8 heteroalkynyl, C_1-C_8 acyl, C_2-C_8 heteroacyl, C_6-C_{10} aryl, C_5-C_{12} heteroaryl, C_7-C_{12} arylalkyl, or C_6-C_{12} heteroarylalkyl group.

21. A method for treating cancer in a subject comprising administering a therapeutically effective amount of a compound of any of Claims 1-21.

22. The method of Claim 22, wherein the cancer is of the breast, lung, colorectum, liver, pancreas, lymph node, colon, prostate, brain, head and neck, skin, liver, kidney, blood or heart.