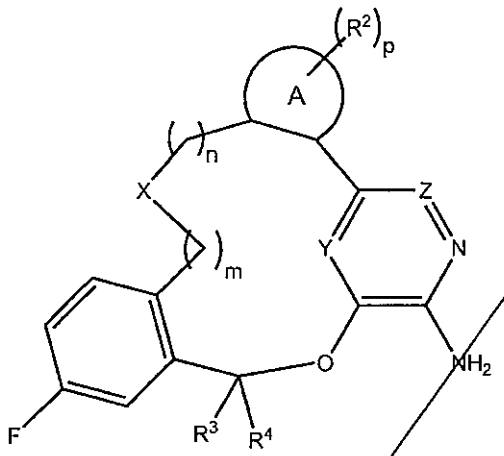
Claims

We Claim:

1. A compound of the formula (I)



(I)

wherein:

X is selected from the group consisting of $-(CR^5R^6)_qO(CR^5R^6)_r-$, $-(CR^5R^6)_qN(R^1)(CR^5R^6)_r-$, $-(CR^5R^6)_qC(O)N(R^1)(CR^5R^6)_r-$ and $-(CR^5R^6)_qN(R^1)C(O)(CR^5R^6)_r-$;

Y and Z are each independently N or CH, with the proviso that when Y is N, Z is CH and when Z is N, Y is CH;

A is a ring selected from C_6-C_{12} aryl and 5-6 membered heteroaryl;

R^1 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic and 5-6 membered heteroaryl, wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^2 is independently selected from the group consisting of halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, 5-6 membered heteroaryl, $-S(O)_tR^7$, $-S(O)_2NR^7R^8$, $-S(O)_2OR^7$, $-NO_2$, $-(CR^5R^6)_qNR^7R^8$, $-N(CR^5R^6)(CR^5R^6)_qNR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$, -CN, $-C(O)R^7$, $-OC(O)R^7$, $-O(CR^5R^6)_qR^7$, $-NR^7C(O)R^8$, $-(CR^5R^6)_qC(O)OR^7$, $-(CR^5R^6)_qNR^7R^8$, $-C(=NR^7)NR^7R^8$, $-NR^7C(O)NR^7R^8$, $-NR^7S(O)_2R^8$ and $-(CR^5R^6)_qC(O)NR^7R^8$; wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, -

NH_2, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, -CN, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

R^3 and R^4 are each independently selected from hydrogen, C_1-C_6 alkyl and C_3-C_6 cycloalkyl, wherein each hydrogen on C_1-C_6 alkyl and C_3-C_6 cycloalkyl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^5 and R^6 is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, 5-6 membered heteroaryl, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ and $-C(O)NR^9R^{10}$; wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^7 and R^8 is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl, wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, -CN, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^9 and R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl;

m is 0, 1, 2 or 3;

n is 0, 1, 2 or 3;

p is 0, 1, 2, 3 or 4;

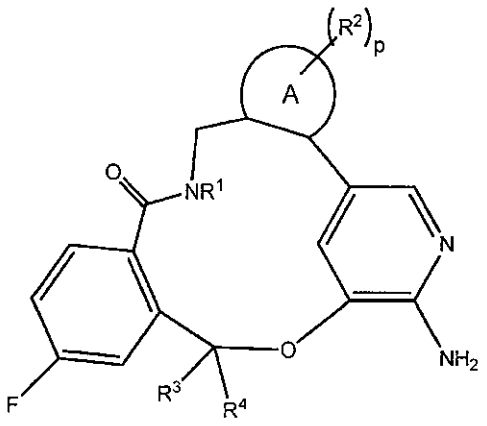
each q is independently 0, 1, 2 or 3;

each r is independently 0, 1, 2 or 3; and

each t is independently 0, 1 or 2;

or a pharmaceutically acceptable salt thereof.

2. A compound of the formula (V)



(V)

wherein:

A is a ring selected from C_6-C_{12} aryl and 5-6 membered heteroaryl;

R^1 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic and 5-6 membered heteroaryl, wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $--C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^2 is independently selected from the group consisting of halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, 5-6 membered heteroaryl, $-S(O)_tR^7$, $-S(O)_2NR^7R^8$, $-S(O)_2OR^7$, $-NO_2$, $-(CR^5R^6)_qNR^7R^8$, $-N(CR^5R^6)(CR^5R^6)_qNR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$, -CN, $-C(O)R^7$, $-OC(O)R^7$, $-O(CR^5R^6)_qR^7$, $-NR^7C(O)R^8$, $-(CR^5R^6)_qC(O)OR^7$, $-(CR^5R^6)_qNR^7R^8$, $-C(=NR^7)NR^7R^8$, $-NR^7C(O)NR^7R^8$, $-NR^7S(O)_2R^8$ and $-(CR^5R^6)_qC(O)NR^7R^8$; wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, -CN, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

R^3 and R^4 are each independently selected from hydrogen, C_1-C_6 alkyl and C_3-C_6 cycloalkyl, wherein each hydrogen on C_1-C_6 alkyl and C_3-C_6 cycloalkyl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^5 and R^6 is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, 5-6 membered heteroaryl, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ and $-C(O)NR^9R^{10}$; wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^7 and R^8 is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl, wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, -CN, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^9 and R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl;

p is 0, 1, 2, 3 or 4;

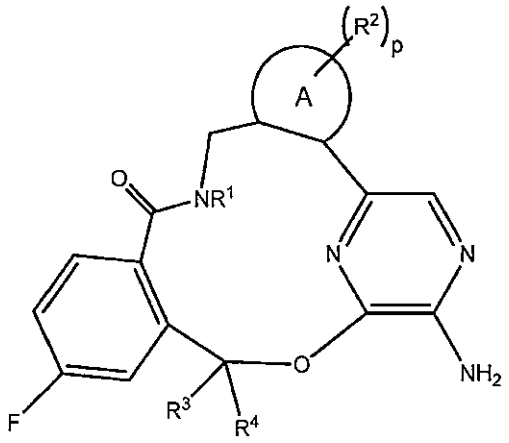
each q is independently 0, 1, 2 or 3;

each r is independently 0, 1, 2 or 3; and

each t is independently 0, 1 or 2;

or a pharmaceutically acceptable salt thereof.

3. A compound of the formula (VI)



(VI)

wherein:

A is a ring selected from C_6-C_{12} aryl and 5-6 membered heteroaryl;

R^1 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic and 5-6 membered heteroaryl, wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^2 is independently selected from the group consisting of halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, 5-6 membered heteroaryl, $-S(O)_tR^7$, $-S(O)_2NR^7R^8$, $-S(O)_2OR^7$, $-NO_2$, $-(CR^5R^6)_qNR^7R^8$, $-N(CR^5R^6)(CR^5R^6)_qNR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$, -CN, $-C(O)R^7$, $-OC(O)R^7$, $-O(CR^5R^6)_qR^7$, $-NR^7C(O)R^8$, $-(CR^5R^6)_qC(O)OR^7$, $-(CR^5R^6)_qNR^7R^8$, $-C(=NR^7)NR^7R^8$, $-NR^7C(O)NR^7R^8$, $-NR^7S(O)_2R^8$ and $-(CR^5R^6)_qC(O)NR^7R^8$; wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, -CN, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

R^3 and R^4 are each independently selected from hydrogen, C_1-C_6 alkyl and C_3-C_6 cycloalkyl, wherein each hydrogen on C_1-C_6 alkyl and C_3-C_6 cycloalkyl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^5 and R^6 is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, 5-6 membered heteroaryl, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ and $-C(O)NR^9R^{10}$; wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^7 and R^8 is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl, wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, -CN, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^9 and R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl;

p is 0, 1, 2, 3 or 4;

each q is independently 0, 1, 2 or 3;

each r is independently 0, 1, 2 or 3; and

each t is independently 0, 1 or 2;

or a pharmaceutically acceptable salt thereof.

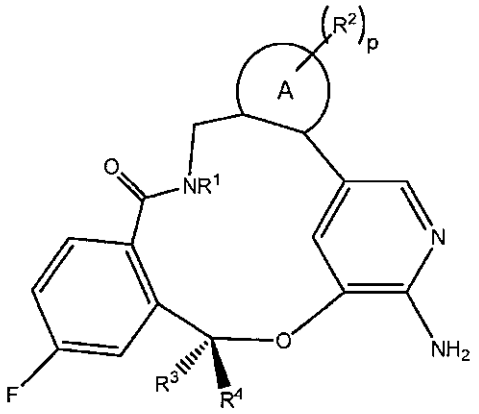
4. The compound of claim 1, 2 or 3, wherein R^1 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, and C_3-C_6 cycloalkyl, or a pharmaceutically acceptable salt thereof.

5. The compound of any one of claims 1 to 4, wherein each R^2 is independently selected from the group consisting of C_1-C_6 alkyl, C_3-C_6 cycloalkyl, $-S(O)_rR^7$, $-S(O)_2NR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$ and -CN; wherein each hydrogen on said C_1-C_6 alkyl and C_3-C_6 cycloalkyl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, -CN, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$, or a pharmaceutically acceptable salt thereof.

6. The compound of any one of claims 1 to 5, wherein A is a ring selected from the group consisting of phenyl, pyridine, pyrimidine, pyridazine, pyrazine, triazine, pyrazole, imidazole, triazole, tetrazole, thiazole, isothiazole, oxazole and isoxazole, or a pharmaceutically acceptable salt thereof.

7. The compound of any one of claims 1 to 6, wherein R^3 and R^4 are each independently selected from the group consisting of hydrogen and C_1-C_6 alkyl, or a pharmaceutically acceptable salt thereof.

8. A compound of the formula (XV)



(XV)

wherein:

A is a ring selected from C_6-C_{12} aryl and 5-6 membered heteroaryl;

R^1 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic and 5-6 membered heteroaryl, wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $--C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^2 is independently selected from the group consisting of halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, 5-6 membered heteroaryl, $-S(O)_tR^7$, $-S(O)_2NR^7R^8$, $-S(O)_2OR^7$, $-NO_2$, $-(CR^5R^6)_qNR^7R^8$, $-N(CR^5R^6)(CR^5R^6)_qNR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$, -CN, $-C(O)R^7$, $-OC(O)R^7$, $-O(CR^5R^6)_qR^7$, $-NR^7C(O)R^8$, $-(CR^5R^6)_qC(O)OR^7$, $-(CR^5R^6)_qNR^7R^8$, $-C(=NR^7)NR^7R^8$, $-NR^7C(O)NR^7R^8$, $-NR^7S(O)_2R^8$ and $-(CR^5R^6)_qC(O)NR^7R^8$; wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, -CN, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

R^3 is C_1-C_6 alkyl or C_3-C_6 cycloalkyl and R^4 is hydrogen, wherein each hydrogen on said C_1-C_6 alkyl or C_3-C_6 cycloalkyl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^5 and R^6 is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic,

5-6 membered heteroaryl, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ and $-C(O)NR^9R^{10}$; wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^7 and R^8 is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl, wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, -CN, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^9 and R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl;

p is 0, 1, 2, 3 or 4;

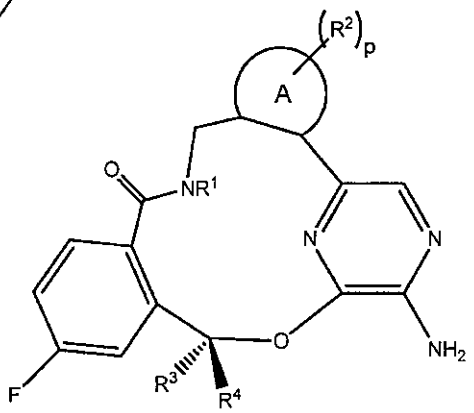
each q is independently 0, 1, 2 or 3;

each r is independently 0, 1, 2 or 3; and

each t is independently 0, 1 or 2;

or a pharmaceutically acceptable salt thereof.

9. A compound of the formula (XVI)



(XVI)

wherein:

A is a ring selected from C_6-C_{12} aryl and 5-6 membered heteroaryl;

R^1 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic and 5-6 membered heteroaryl, wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^2 is independently selected from the group consisting of halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, 5-6 membered heteroaryl, $-S(O)_tR^7$, $-S(O)_2NR^7R^8$, $-S(O)_2OR^7$, $-NO_2$, $-(CR^5R^6)_qNR^7R^8$, $-N(CR^5R^6)(CR^5R^6)_qNR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$, -CN, $-C(O)R^7$, $-OC(O)R^7$, $-O(CR^5R^6)_qR^7$, $-NR^7C(O)R^8$, $-(CR^5R^6)_qC(O)OR^7$, $-(CR^5R^6)_qNR^7R^8$, $-C(=NR^7)NR^7R^8$, $-NR^7C(O)NR^7R^8$, $-NR^7S(O)_2R^8$ and $-(CR^5R^6)_qC(O)NR^7R^8$; wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, -CN, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

R^3 is C_1-C_6 alkyl or C_3-C_6 cycloalkyl and R^4 is hydrogen, wherein each hydrogen on said C_1-C_6 alkyl or C_3-C_6 cycloalkyl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^5 and R^6 is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, 5-6 membered heteroaryl, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ and $-C(O)NR^9R^{10}$; wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^7 and R^8 is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl, wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$,

$-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, -CN, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^9 and R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl;

p is 0, 1, 2, 3 or 4;

each q is independently 0, 1, 2 or 3;

each r is independently 0, 1, 2 or 3; and

each t is independently 0, 1 or 2;

or a pharmaceutically acceptable salt thereof.

10. The compound of claim 7, 8 or 9, wherein R^1 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, and C_3-C_6 cycloalkyl, or a pharmaceutically acceptable salt thereof.

11. The compound of any one of claims 7 to 10, wherein each R^2 is independently selected from the group consisting of C_1-C_6 alkyl, C_3-C_6 cycloalkyl, $-S(O)_rR^7$, $-S(O)_2NR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$ and -CN; wherein each hydrogen on said C_1-C_6 alkyl and C_3-C_6 cycloalkyl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, -CN, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ and $-C(O)NR^9R^{10}$, or a pharmaceutically acceptable salt thereof.

12. The compound of any one of claims 7 to 11, wherein A is a ring selected from the group consisting of phenyl, pyridine, pyrimidine, pyridazine, pyrazine, triazine, pyrazole, imidazole, triazole, tetrazole, thiazole, isothiazole, oxazole and isoxazole, or a pharmaceutically acceptable salt thereof.

13. The compound of any one of claims 7 to 12, wherein R^3 is methyl and R^4 is hydrogen, or a pharmaceutically acceptable salt thereof.

14. A pharmaceutical composition comprising a compound of any one of claims 1 to 13, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or excipient.

15. A method of treating abnormal cell proliferation in a mammal, comprising administering to said mammal a therapeutically effective amount of a compound of any one of claims 1 to 13, or a pharmaceutically acceptable salt thereof.

16. The method of claim 15, wherein the abnormal cell proliferation is cancer.

17. The method of claim 16, wherein the cancer is mediated by anaplastic lymphoma kinase (ALK).

18. The method of claim 16, wherein the cancer is mediated by an EML4-ALK fusion protein.

19. The method of claim 16, wherein the cancer is mediated by an EML4-ALK fusion protein having at least one mutation.

20. The method of claim 19, wherein said mutation is L1196M or C1156Y.

21. The method of any one of claims 16 to 20, wherein the wherein the cancer is selected from the group consisting of non-small cell lung cancer (NSCLC), squamous cell carcinoma, hormone-refractory prostate cancer, papillary renal cell carcinoma, colorectal adenocarcinoma, neuroblastomas, anaplastic large cell lymphoma (ALCL) and gastric cancer.

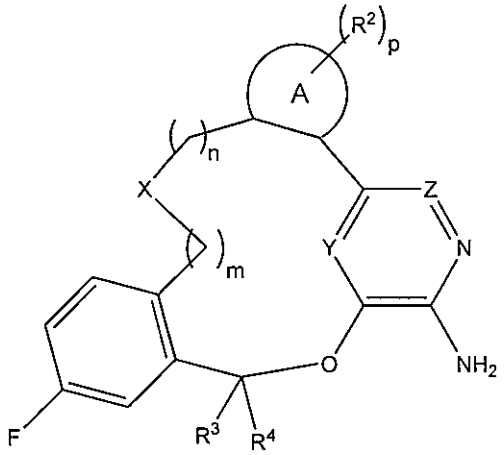
22. The method of any one of claims 15 to 21, wherein the mammal is a human.

23. The method of any one of claims 15 to 21, wherein the mammal is a dog.

Claims

We Claim:

1. A compound of the formula (I)



(I)

wherein:

X is selected from the group consisting of $-(CR^5R^6)_qO(CR^5R^6)_r-$, $-(CR^5R^6)_qN(R^1)(CR^5R^6)_r-$, $-(CR^5R^6)_qC(O)N(R^1)(CR^5R^6)_r-$ and $-(CR^5R^6)_qN(R^1)C(O)(CR^5R^6)_r-$;

Y and Z are each independently N or CH, with the proviso that when Y is N, Z is CH and when Z is N, Y is CH;

A is a ring selected from C_6-C_{12} aryl and 5-6 membered heteroaryl;

R^1 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic and 5-6 membered heteroaryl, wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^2 is independently selected from the group consisting of halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, 5-6 membered heteroaryl, $-S(O)_tR^7$, $-S(O)_2NR^7R^8$, $-S(O)_2OR^7$, $-NO_2$, $-(CR^5R^6)_qNR^7R^8$, $-N(CR^5R^6)(CR^5R^6)_qNR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$, -CN, $-C(O)R^7$, $-OC(O)R^7$, $-O(CR^5R^6)_qR^7$, $-NR^7C(O)R^8$, $-(CR^5R^6)_qC(O)OR^7$, $-(CR^5R^6)_qNR^7R^8$, $-C(=NR^7)NR^7R^8$, $-NR^7C(O)NR^7R^8$, $-NR^7S(O)_2R^8$ and $-(CR^5R^6)_qC(O)NR^7R^8$; wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic,

and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -OR^9, -CN, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ or -$C(O)NR^9R^{10}$;

R^3 and R^4 are each independently selected from hydrogen, C_1-C_6 alkyl and C_3-C_6 cycloalkyl, wherein each hydrogen on C_1-C_6 alkyl and C_3-C_6 cycloalkyl may be independently optionally substituted by halogen, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -CN, -OR^9, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ or -$C(O)NR^9R^{10}$;

each R^5 and R^6 is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, 5-6 membered heteroaryl, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -CN, -OR^9, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ and -$C(O)NR^9R^{10}$; wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -CN, -OR^9, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ or -$C(O)NR^9R^{10}$;

each R^7 and R^8 is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl, wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -OR^9, -CN, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ or -$C(O)NR^9R^{10}$;

each R^9 and R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl;

m is 0, 1, 2 or 3;

n is 0, 1, 2 or 3;

p is 0, 1, 2, 3 or 4;

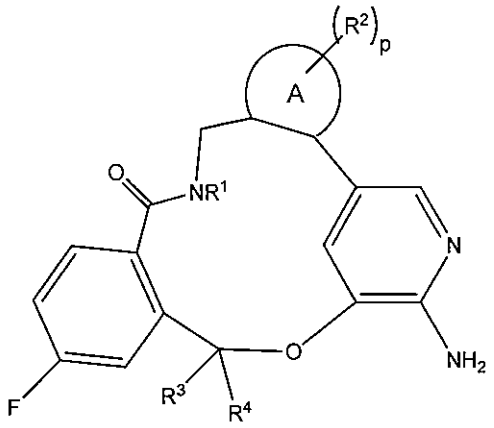
each q is independently 0, 1, 2 or 3;

each r is independently 0, 1, 2 or 3; and

each t is independently 0, 1 or 2;

or a pharmaceutically acceptable salt thereof.

2. A compound as claimed in claim 1 of the formula (V)



(V)

wherein:

A is a ring selected from C_6-C_{12} aryl and 5-6 membered heteroaryl;

R^1 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic and 5-6 membered heteroaryl, wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $--C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^2 is independently selected from the group consisting of halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, 5-6 membered heteroaryl, $-S(O)_tR^7$, $-S(O)_2NR^7R^8$, $-S(O)_2OR^7$, $-NO_2$, $-(CR^5R^6)_qNR^7R^8$, $-N(CR^5R^6)(CR^5R^6)_qNR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$, -CN, $-C(O)R^7$, $-OC(O)R^7$, $-O(CR^5R^6)_qR^7$, $-NR^7C(O)R^8$, $-(CR^5R^6)_qC(O)OR^7$, $-(CR^5R^6)_qNR^7R^8$, $-C(=NR^7)NR^7R^8$, $-NR^7C(O)NR^7R^8$, $-NR^7S(O)_2R^8$ and $-(CR^5R^6)_qC(O)NR^7R^8$; wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, -CN, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

R^3 and R^4 are each independently selected from hydrogen, C_1-C_6 alkyl and C_3-C_6 cycloalkyl, wherein each hydrogen on C_1-C_6 alkyl and C_3-C_6 cycloalkyl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN,

$-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^5 and R^6 is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, 5-6 membered heteroaryl, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ and $-C(O)NR^9R^{10}$; wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^7 and R^8 is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl, wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, -CN, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^9 and R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl;

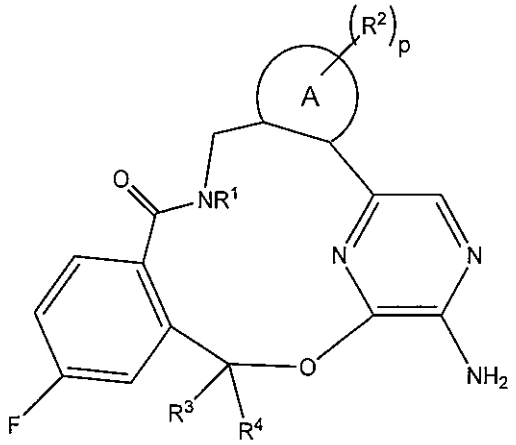
p is 0, 1, 2, 3 or 4;

each q is independently 0, 1, 2 or 3; and

each t is independently 0, 1 or 2;

or a pharmaceutically acceptable salt thereof.

3. A compound as claimed in claim 1 of the formula (VI)



(VI)

wherein:

A is a ring selected from C_6-C_{12} aryl and 5-6 membered heteroaryl;

R^1 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic and 5-6 membered heteroaryl, wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $--C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^2 is independently selected from the group consisting of halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, 5-6 membered heteroaryl, $-S(O)_tR^7$, $-S(O)_2NR^7R^8$, $-S(O)_2OR^7$, $-NO_2$, $-(CR^5R^6)_qNR^7R^8$, $-N(CR^5R^6)(CR^5R^6)_qNR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$, -CN, $-C(O)R^7$, $-OC(O)R^7$, $-O(CR^5R^6)_qR^7$, $-NR^7C(O)R^8$, $-(CR^5R^6)_qC(O)OR^7$, $-(CR^5R^6)_qNR^7R^8$, $-C(=NR^7)NR^7R^8$, $-NR^7C(O)NR^7R^8$, $-NR^7S(O)_2R^8$ and $-(CR^5R^6)_qC(O)NR^7R^8$; wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, -CN, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

R^3 and R^4 are each independently selected from hydrogen, C_1-C_6 alkyl and C_3-C_6 cycloalkyl, wherein each hydrogen on C_1-C_6 alkyl and C_3-C_6 cycloalkyl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^5 and R^6 is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, 5-6 membered heteroaryl, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ and $-C(O)NR^9R^{10}$; wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^7 and R^8 is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl, wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, -CN, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^9 and R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl;

p is 0, 1, 2, 3 or 4;

each q is independently 0, 1, 2 or 3; and

each t is independently 0, 1 or 2;

or a pharmaceutically acceptable salt thereof.

4. The compound of claim 1, 2 or 3, wherein R^1 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, and C_3-C_6 cycloalkyl, or a pharmaceutically acceptable salt thereof.

5. The compound of any one of claims 1 to 4, wherein each R^2 is independently selected from the group consisting of C_1-C_6 alkyl, C_3-C_6 cycloalkyl, $-S(O)_rR^7$, $-S(O)_2NR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$ and -CN; wherein each hydrogen on said C_1-C_6 alkyl and C_3-C_6 cycloalkyl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, -CN, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$, or a pharmaceutically acceptable salt thereof.

6. The compound of any one of claims 1 to 5, wherein A is a ring selected from the group consisting of phenyl, pyridine, pyrimidine, pyridazine, pyrazine, triazine, pyrazole, imidazole, triazole, tetrazole, thiazole, isothiazole, oxazole and isoxazole, or a pharmaceutically acceptable salt thereof.

7. The compound of any one of claims 1 to 6, wherein R^3 and R^4 are each independently selected from the group consisting of hydrogen and C_1-C_6 alkyl, or a pharmaceutically acceptable salt thereof.

8. A compound which is (10*R*)-7-amino-12-fluoro-2,10,16-trimethyl-15-oxo-10,15,16,17-tetrahydro-2*H*-8,4-(metheno)pyrazolo[4,3-*h*][2,5,11]benzoxadiazacyclo-tetradecine-3-carbonitrile, or a pharmaceutically acceptable salt thereof.

9. A pharmaceutical composition comprising a compound of any one of claims 1 to 8, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or excipient.

10. A compound of any one of claims 1 to 8, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer in a mammal.

11 The compound of claim 10, wherein the cancer is mediated by anaplastic lymphoma kinase (ALK).

12. The compound of claim 10, wherein the cancer is mediated by an EML4-ALK fusion protein.

13. The compound of claim 10, wherein the cancer is mediated by an EML4-ALK fusion protein having at least one mutation.

14. The compound of claim 13, wherein said mutation is L1196M or C1156Y.

15. The compound of any one of claims 10 to 14, wherein the cancer is selected from the group consisting of non-small cell lung cancer (NSCLC), squamous cell carcinoma, hormone-refractory prostate cancer, papillary renal cell carcinoma, colorectal adenocarcinoma, neuroblastomas, anaplastic large cell lymphoma (ALCL) and gastric cancer.

16. A combination of a compound of any one of claims 1 to 8, or a pharmaceutically acceptable salt thereof, and an additional anti-cancer agent.