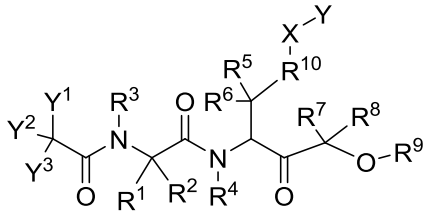
WHAT IS CLAIMED IS:

1. A compound having formula I:



I

or an enantiomer or a mixture of enantiomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, wherein

X and Y are selected as follows:

i) X is C=O; and Y is alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, -R^aOR^b, or -$R^aN(R^c)(R^d)$; or

ii) X is -O-, or -$N(R^c)$-; Y is hydrogen, -$C(O)R^d$, alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl;

Y is optionally substituted with one to three groups Q^1;

R^3, Y^1, Y^2 and Y^3 are selected as follows:

i) Y^1 together with R^3 forms an optionally substituted saturated or unsaturated bicyclic ring B, where substituents on ring B, when present, are selected from one to three groups Q^1;

Y^2 is absent, hydrogen or alkyl; and

Y^3 is absent, hydrogen or alkyl; or

ii) R^3 is hydrogen or alkyl; Y^1 and Y^2 together are =O; and Y^3 is $–N(Z^1)(Z^2)$;

X, Y, R^3 and Y^1 are selected such that when X is O, then Y^1 and R^3 cannot form ring B;

each Q^1 is independently alkyl, halo, haloalkyl, hydroxyl, alkoxy, cycloalkyl, heterocyclyl, aryl or heteroaryl; each Q^1 is optionally substituted with one to three groups Q^2; each Q^2 is independently alkyl, halo, haloalkyl, aryl or haloaryl;

each R^a is independently alkylene or a direct bond;

R^b is hydrogen, alkyl, haloalkyl, hydroxyalkyl, alkoxyalkyl, cycloalkyl, aryl, heteroaryl or heterocyclyl;

each R^c is independently hydrogen or alkyl;

each R^d is independently alkyl, aryl, cycloalkyl, heteroaryl, heterocyclyl or -R^aOR^b;

each R^d is optionally substituted with one to three groups Q^1;

R^1 and R^2 are selected as follows:

i) R^1 and R^2 are each independently hydrogen, alkyl or cycloalkyl; or

ii) R^1 and R^2 together with the carbon atom on which they are substituted form an optionally substituted saturated or unsaturated ring A, where the substituents on ring A, when present, are selected from one to three groups Q^1;

R^4, R^5, R^6, R^7 and R^8 are each independently hydrogen or alkyl;

R^9 is aryl or heteroaryl, each optionally substituted with one to four substituents Q^1;

R^{10} is alkylene;

Z^1 and Z^2 are selected as follows:

i) Z^1 is hydrogen or alkyl; and Z^2 is aryl, cycloalkyl, heteroaryl or heterocyclyl, each optionally substituted with one to four substituents Q^3; or

ii) Z^1 and Z^2 together with the nitrogen atom on which they are substituted form an optionally substituted saturated or unsaturated ring C, where the substituents on ring C, when present, are selected from one to three groups Q^3;

each Q^3 is independently selected from alkyl, halo, cyano, cycloalkyl, heterocyclyl, aryl, heteroaryl, $-R^{11}OR^{12}$, $-R^{11}OR^{11}OR^{12}$, $-R^{11}N(R^{13})(R^{14})$, $-R^{11}SR^{12}$, $-R^{11}OR^{11}N(R^{13})(R^{14})$, $-R^{11}C(J)N(R^{13})(R^{14})$, $-R^{11}OR^{11}C(J)N(R^{13})(R^{14})$, $-C(J)R^{15}$ and $R^{11}S(O)_tR^{16}$; where each Q^3 is optionally substituted with one to three groups Q^4, where each Q^4 is independently alkyl, halo, haloalkyl, hydroxyl, alkoxy or cycloalkyl;

each R^{11} is independently alkylene, alkenylene or a direct bond;

each R^{12} is independently hydrogen, alkyl, haloalkyl, hydroxyalkyl, alkoxyalkyl, cycloalkyl, aryl, heteroaryl or heterocyclyl;

R^{13} and R^{14} are selected as follows:

i) R^{13} and R^{14} are each independently hydrogen, alkyl, haloalkyl, hydroxyalkyl, alkoxyalkyl, cycloalkyl, aryl, heteroaryl or heterocyclyl; or

ii) R^{13} and R^{14} together with the nitrogen atom on which they are substituted form a 5 or 6-membered heterocyclyl or heteroaryl ring, optionally substituted with one or two alkyl, halo, haloalkyl, hydroxyl, alkoxy or cycloalkyl;

each R^{15} is independently hydroxy, alkyl, haloalkyl, alkoxy, cycloalkyl, aryl, heteroaryl, heterocyclyl or heterocyclyl;

each R^{16} is independently hydrogen, alkyl, haloalkyl, hydroxyalkyl, alkoxyalkyl, cycloalkyl, aryl, heteroaryl or heterocyclyl;

J is O or S; and

t is 0-2.

2. The compound of claim 1, wherein X and Y are selected as follows:

i) X is C=O; and Y is -R^aOR^b; or

ii) X is -O-; Y is hydrogen, alkyl, aryl, arylalkyl, heteroarylalkyl or -C(O)R^d; where the alkyl and aryl groups are optionally substituted with one or two groups selected from alkyl and halo;

R^3, Y^1, Y^2 and Y^3 are selected as follows:

i) Y^1 together with R^3 forms an optionally substituted saturated or unsaturated ring B, where substituents on ring B, when present, are selected from one to three groups Q^3;

Y^2 is absent, hydrogen or alkyl; and

Y^3 is absent, hydrogen or alkyl; or

ii) R^3 is hydrogen or alkyl; Y^1 and Y^2 together are =O; and Y^3 is –N(Z^1)(Z^2);

X, Y, R^3 and Y^1 are selected such that when X is O, then Y^1 and R^3 cannot form ring B;

R^a is alkylene or a direct bond;

R^b is hydrogen, alkyl or aryl;

R^d is aryl or aryloxy;

R^1 and R^2 are selected as follows:

i) R^1 and R^2 are each independently hydrogen or alkyl; or

ii) R^1 and R^2 together with the carbon atom on which they are substituted form a cycloalkyl ring;

R^4, R^5, R^6, R^7 and R^8 are each independently hydrogen or alkyl;

R^9 is aryl or heteroaryl, each optionally substituted with one to four substituents selected from halo, alkyl and haloalkyl;

R^{10} is alkylene;

Z^1 is hydrogen or alkyl;

Z^2 is aryl or heteroaryl, each optionally substituted with one to four substituents Q^3;

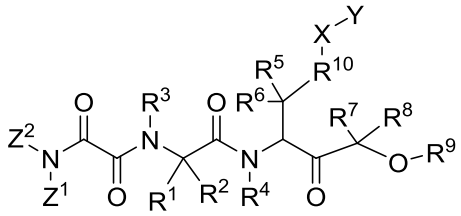
each Q^3 is independently selected from alkyl, haloalkyl, haloalkoxy, halo, cyano, aryl, heteroaryl, -R^{11}OR^{12}, -C(O)R^{15} and -C(O)NH_2;

R^{11} is alkylene or a direct bond;

R^{12} is hydrogen, alkyl or haloalkyl; and

R^{15} is hydroxyl or alkyl.

3. The compound of claim 1 or claim 2, having formula II



II

or an enantiomer or a mixture of enantiomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof.

4. The compound of any one of claims 1-3, wherein

X and Y are selected as follows:

i) X is C=O; and Y is $-R^aOR^b$; or

ii) X is -O-; Y is hydrogen, alkyl, aryl, arylalkyl, heteroarylalkyl or $-C(O)R^d$; where the alkyl and aryl groups are optionally substituted with one or two groups selected from alkyl and halo;

R^a is alkylene or a direct bond;

R^b is hydrogen, alkyl or aryl;

R^d is aryl or aryloxy;

R^1 and R^2 are selected as follows:

i) R^1 and R^2 are each independently hydrogen or alkyl; or

ii) R^1 and R^2 together with the carbon atom on which they are substituted form a cycloalkyl ring;

R^3, R^4, R^5, R^6, R^7 and R^8 are each independently hydrogen or alkyl;

R^9 is aryl or heteroaryl, each optionally substituted with one to four substituents selected from halo, alkyl and haloalkyl;

R^{10} is alkylene;

Z^1 is hydrogen or alkyl;

Z^2 is aryl or heteroaryl, each optionally substituted with one to four substituents Q^3;

each Q^3 is independently selected from alkyl, haloalkyl, haloalkoxy, halo, cyano, aryl, heteroaryl, $-R^{11}OR^{12}$, $-C(O)R^{15}$ and $-C(O)NH_2$;

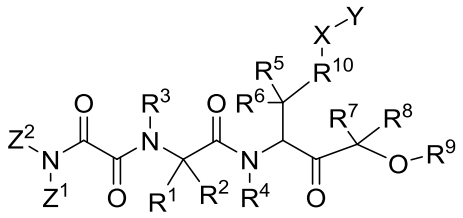
each R^{11} is independently alkylene or a direct bond;

R^{12} is hydrogen, alkyl or haloalkyl; and

R^{15} is hydroxyl or alkyl.

5. The compound of any one of claims 1-4, wherein R^9 is phenyl or pyrimidinyl, each optionally substituted with one to four substituents selected from halo, alkyl and haloalkyl.

6. The compound of any one of claims 1-3, having formula II



II

or an enantiomer or a mixture of enantiomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, wherein

X and Y are selected as follows:

i) X is C=O; and Y is alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, $-R^aOR^b$, or $-R^aN(R^c)(R^d)$; or

ii) X is -O-, or $-N(R^c)-$; Y is hydrogen, $-C(O)R^d$, alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl;

Y is optionally substituted with one to three groups Q^1;

each Q^1 is independently alkyl, halo, haloalkyl, hydroxyl, alkoxy, cycloalkyl, heterocyclyl, aryl or heteroaryl; each Q^1 is optionally substituted with one to three groups Q^2; each Q^2 is independently alkyl, halo, haloalkyl, aryl or haloaryl;

each R^a is independently alkylene or a direct bond;

R^b is hydrogen, alkyl, haloalkyl, hydroxyalkyl, alkoxyalkyl, cycloalkyl, aryl, heteroaryl or heterocyclyl;

each R^c is independently hydrogen or alkyl;

each R^d is independently alkyl, aryl, cycloalkyl, heteroaryl, heterocyclyl or $-R^aOR^b$;

each R^d is optionally substituted with one to three groups Q^1;

R^1 and R^2 are selected as follows:

i) R^1 and R^2 are each independently hydrogen, alkyl or cycloalkyl; or

ii) R^1 and R^2 together with the carbon atom on which they are substituted form an optionally substituted saturated or unsaturated ring A, where substituents on ring A, when present, are selected from one to three groups Q^1;

R^3, R^4, R^5, R^6, R^7 and R^8 are each independently hydrogen or alkyl;

R^{10} is alkylene;

each Q^5 is independently alkyl, halo or haloalkyl;

Z^1 is hydrogen or alkyl;

Z^2 is aryl, cycloalkyl, heteroaryl or heterocyclyl, each optionally substituted with one to four substituents Q^3;

each Q^3 is independently selected from alkyl, halo, cyano, cycloalkyl, heterocyclyl, aryl, heteroaryl, $-R^{11}OR^{12}$, $-R^{11}OR^{11}OR^{12}$, $-R^{11}N(R^{13})(R^{14})$, $-R^{11}SR^{12}$, $-R^{11}OR^{11}N(R^{13})(R^{14})$, $-R^{11}C(J)N(R^{13})(R^{14})$, $-R^{11}OR^{11}C(J)N(R^{13})(R^{14})$, $-C(J)R^{15}$ and $R^{11}S(O)_tR^{16}$; where each Q^3 is optionally substituted with one to three groups Q^4, where each Q^4 is independently alkyl, halo, haloalkyl, hydroxyl, alkoxy or cycloalkyl;

each R^{11} is independently alkylene, alkenylene or a direct bond;

each R^{12} is independently hydrogen, alkyl, haloalkyl, hydroxyalkyl, alkoxyalkyl, cycloalkyl, aryl, heteroaryl or heterocyclyl;

R^{13} and R^{14} are selected as follows:

i) R^{13} and R^{14} are each independently hydrogen, alkyl, haloalkyl, hydroxyalkyl, alkoxyalkyl, cycloalkyl, aryl, heteroaryl or heterocyclyl; or

ii) R^{13} and R^{14} together with the nitrogen atom on which they are substituted form a 5 or 6-membered heterocyclyl or heteroaryl ring, optionally substituted with one or two alkyl, halo, haloalkyl, hydroxyl, alkoxy or cycloalkyl;

each R^{15} is independently hydroxy, alkyl, haloalkyl, alkoxy, cycloalkyl, aryl, heteroaryl, heterocyclyl or heterocyclyl;

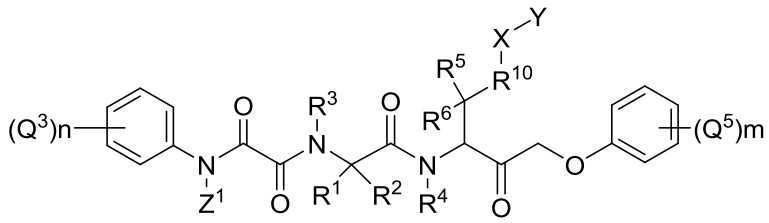
each R^{16} is independently hydrogen, alkyl, haloalkyl, hydroxyalkyl, alkoxyalkyl, cycloalkyl, aryl, heteroaryl or heterocyclyl;

J is O or S;

t is 0-2; and

m is 0-4.

7. The compound of claim 6, having formula V



V

or an enantiomer or a mixture of enantiomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof.

8. The compound of claim 7, wherein

X and Y are selected as follows:

i) X is C=O; and Y is $-R^aOR^b$; or

ii) X is -O-; Y is hydrogen, alkyl, aryl, arylalkyl, heteroarylalkyl or $-C(O)R^d$; where the alkyl and aryl groups are optionally substituted with one or two groups selected from

alkyl and halo;

R^a is alkylene or a direct bond;

R^b is hydrogen, alkyl or aryl;

R^d is aryl or aryloxy;

R^1 and R^2 are selected as follows:

i) R^1 and R^2 are each independently hydrogen or alkyl; or

ii) R^1 and R^2 together with the carbon atom on which they are substituted form a cycloalkyl ring;

R^3, R^4, R^5 and R^6 are each independently hydrogen or alkyl;

R^{10} is alkylene;

Z^1 is hydrogen or alkyl;

each Q^3 is independently selected from alkyl, haloalkyl, haloalkoxy, halo, cyano, aryl, heteroaryl, $-R^{11}OR^{12}$, $-C(O)R^{15}$ and $-C(O)NH_2$;

each R^{11} is independently alkylene or a direct bond;

R^{12} is hydrogen, alkyl or haloalkyl;

R^{15} is hydroxyl or alkyl;

each Q^5 is independently alkyl, halo or haloalkyl;

m is 0-4; and

n is 0- 2.

9. The compound of any one of claims 1-4, wherein

X and Y are selected as follows:

i) X is C=O; and Y is $-R^aOR^b$; or

ii) X is -O-; Y is hydrogen, alkyl, aryl, arylalkyl, heteroarylalkyl or $-C(O)R^d$; where the alkyl and aryl groups are optionally substituted with one or two groups selected from alkyl and halo;

R^a is alkylene or a direct bond;

R^b is hydrogen, alkyl or aryl;

R^d is aryl or aryloxy;

R^1 and R^2 are selected as follows:

i) R^1 and R^2 are each independently hydrogen or alkyl; or

ii) R^1 and R^2 together with the carbon atom on which they are substituted form a cycloalkyl ring;

R^3, R^4, R^5, R^6, R^7 and R^8 are each independently hydrogen or alkyl;

R^9 is aryl or heteroaryl, each optionally substituted with one to four substituents selected from halo, alkyl and haloalkyl;

R^{10} is alkylene;

Z^1 is hydrogen or alkyl;

each Q^3 is independently selected from alkyl, haloalkyl, haloalkoxy, halo, cyano, aryl, heteroaryl, $-R^{11}OR^{12}$, $-C(O)R^{15}$ and $-C(O)NH_2$;

R^{11} is alkylene or a direct bond;

R^{12} is hydrogen, alkyl or haloalkyl;

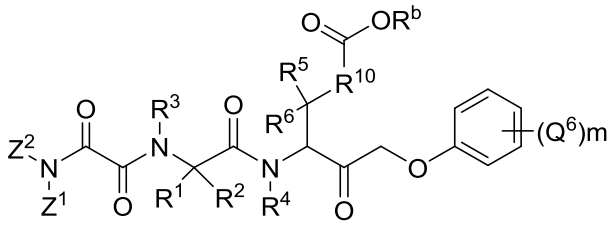
R^{15} is hydroxyl or alkyl;

each Q^5 is independently alkyl, halo or haloalkyl;

m is 0-4; and

n is 0- 2.

10. The compound of any one of claims 1-4, having formula VIII



VIII

or an enantiomer or a mixture of enantiomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, wherein

each Q^6 is independently alkyl, halo or haloalkyl; and

m is 0-4.

11. The compound of claim 10, wherein

R^b is hydrogen;

R^1 and R^2 are selected as follows:

i) R^1 and R^2 are each independently hydrogen or alkyl; or

ii) R^1 and R^2 together with the carbon atom on which they are substituted form a 3-5 membered cycloalkyl ring;

R^3, R^4, R^5 and R^6 are each independently hydrogen or alkyl;

Z^1 is hydrogen or alkyl;

Z^2 is aryl or heteroaryl, each optionally substituted with one to four substituents Q^3;

each Q^3 is independently selected from alkyl, haloalkyl, haloalkoxy, halo, cyano, aryl, heteroaryl, $-R^{11}OR^{12}$, $-C(O)R^{15}$ and $-C(O)NH_2$;

R^{10} is $–CH_2–$ or $–CH_2-CH_2–$;

R^{11} is alkylene or a direct bond;

R^{12} is hydrogen, alkyl or haloalkyl;

R^{15} is hydroxyl or alkyl;

Q^6 is independently alkyl, halo or haloalkyl; and

m is 0-4.

12. The compound of any of claims 1-11, wherein R^{10} is lower alkylene.

13. The compound of claim 12, wherein R^{10} is methylene or ethylene.

14. The compound of any one of claims 1-13, wherein

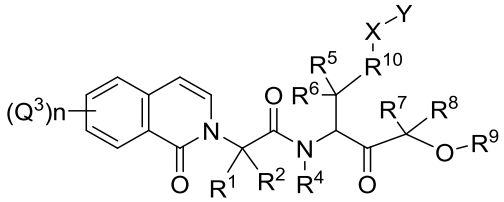
i) R^1 and R^2 are each independently hydrogen or methyl; or

ii) R^1 and R^2 together with the carbon atom on which they are substituted form a cyclopentyl ring.

15. The compound of any one of claims 1-6 and 10, wherein

Z^2 is selected from phenyl, pyridinyl, pyrimidyl, naphthyl, indazolyl, quinolinyl, isoquinolynyl and benzoisothiazolyl; each optionally substituted with one or two Q^3 groups, and each Q^3 is independently selected from halo, alkyl, haloalkyl, arylalkyl, alkoxy, alkylcarbonyl, haloalkoxy, cyano, aryl, heteroaryl and aminocarbonyl.

16. The compound of any one of claims 1-4, having formula XIV



XIV

or an enantiomer or a mixture of enantiomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof;

wherein

X is C=O;

Y is alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, $-R^aOR^b$, or $-R^aN(R^c)(R^d)$; each optionally substituted with one to three groups Q^1;

each Q^1 is independently alkyl, halo, haloalkyl, hydroxyl, alkoxy, cycloalkyl, heterocyclyl, aryl or heteroaryl; each Q^1 is optionally substituted with one to three groups Q^2; each Q^2 is independently alkyl, halo, haloalkyl, aryl or haloaryl;

each R^a is independently alkylene or a direct bond;

R^b is hydrogen, alkyl, haloalkyl, hydroxyalkyl, alkoxyalkyl, cycloalkyl, aryl, heteroaryl or heterocyclyl;

R^c is hydrogen or alkyl;

R^d is alkyl, aryl, cycloalkyl, heteroaryl, heterocyclyl or $-R^aOR^b$;

each R^d is optionally substituted with one to three groups Q^1;

R^1 and R^2 are selected as follows:

i) R^1 and R^2 are each independently hydrogen, alkyl or cycloalkyl; or

ii) R^1 and R^2 together with the carbon atom on which they are substituted form an optionally substituted saturated or unsaturated ring A, where the substituents on ring A, when present, are selected from one to three groups Q^1;

R^4, R^5, R^6, R^7 and R^8 are each independently hydrogen or alkyl;

R^9 is aryl or heteroaryl, each optionally substituted with one to four substituents Q^1;

R^{10} is alkylene;

each Q^3 is independently selected from alkyl, halo, cyano, cycloalkyl, heterocyclyl, aryl, heteroaryl, $-R^{11}OR^{12}$, $-R^{11}OR^{11}OR^{12}$, $-R^{11}N(R^{13})(R^{14})$, $-R^{11}SR^{12}$, $-R^{11}OR^{11}N(R^{13})(R^{14})$, $-R^{11}C(J)N(R^{13})(R^{14})$, $-R^{11}OR^{11}C(J)N(R^{13})(R^{14})$, $-C(J)R^{15}$ and $R^{11}S(O)_tR^{16}$; where each Q^3 is optionally substituted with one to three groups Q^4, where each Q^4 is independently alkyl, halo, haloalkyl, hydroxyl, alkoxy or cycloalkyl;

each R^{11} is independently alkylene, alkenylene or a direct bond;

each R^{12} is independently hydrogen, alkyl, haloalkyl, hydroxyalkyl, alkoxyalkyl, cycloalkyl, aryl, heteroaryl or heterocyclyl;

R^{13} and R^{14} are selected as follows:

i) R^{13} and R^{14} are each independently hydrogen, alkyl, haloalkyl, hydroxyalkyl, alkoxyalkyl, cycloalkyl, aryl, heteroaryl or heterocyclyl; or

ii) R^{13} and R^{14} together with the nitrogen atom on which they are substituted form a 5 or 6-membered heterocyclyl or heteroaryl ring, optionally substituted with one or two alkyl, halo, haloalkyl, hydroxyl, alkoxy or cycloalkyl;

each R^{15} is independently hydroxy, alkyl, haloalkyl, alkoxy, cycloalkyl, aryl, heteroaryl, heterocyclyl or heterocyclyl;

each R^{16} is independently hydrogen, alkyl, haloalkyl, hydroxyalkyl, alkoxyalkyl, cycloalkyl, aryl, heteroaryl or heterocyclyl;

J is O or S;

t is 0-2; and

n is 0-3.

17. The compound of claim 16, wherein

X is C=O; and Y is $-R^aOR^b$;

R^a is alkylene or a direct bond;

R^b is hydrogen or alkyl;

R^1 and R^2 are each hydrogen;

R^4, R^5, R^6, R^7 and R^8 are each independently hydrogen or alkyl;

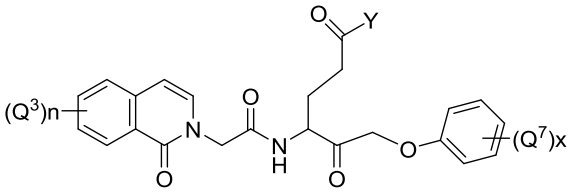
R^9 is aryl or heteroaryl, each optionally substituted with one to four halo;

R^{10} is alkylene;

each Q^3 is halo; and

n is 0-3.

18. The compound of any one of claims 1 and 16-17, having formula XVII



XVII

or an enantiomer or a mixture of enantiomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, wherein each Q^3 is halo; n is 0-2; each Q^7 is halo, and x is 0-4.

19. The compound of claim 17 , wherein Q^3 is chloro; n is 1; each Q^7 is fluoro and x is 4.

20. A pharmaceutical composition, comprising the compound of any one of claims 1-19 and a pharmaceutically acceptable carrier.

21. Use of the the compound of any one of claims 1-19 or the pharmaceutical composition of claim 20 in the manufacture of a medicament for treating a disease, wherein the disease is selected from gastrointestinal disease, respiratory disease, cardiovascular disease, dermatological disease, rheumatological diseases, kidney disease, autoimmune disease, CNS disease, inflammatory disease, liver disease, cancer and ophthalmological disease.