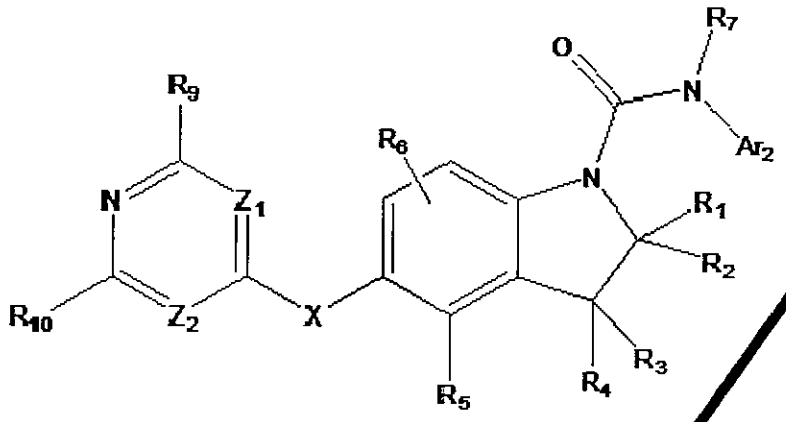
Claims

1. A compound of Formula I:



I

or a pharmaceutically acceptable salt thereof

R_1 is hydrogen or C_1-C_6alkyl;

R_2 is hydrogen or C_1-C_6alkyl;

R_3 is hydrogen or C_1-C_6alkyl;

R_4 is hydrogen or C_1-C_6alkyl; or

R_2 and R_4, taken in combination form a bond;

R_5 is hydrogen, C_1-C_6alkyl, or halogen;

R_6 represents 0, 1 or 2 groups independently selected at each occurrence from halogen or C_1-C_6alkyl;

R_7 is hydrogen or C_1-C_6alkyl;

X is O or S;

Z_1 and Z_2 are independently selected from the group consisting of N and CR_8;

R_8 and R_{10} are independently selected from the group consisting of hydrogen and C_1-C_6alkyl;

R_9 is selected from the group consisting of $(CR_{11}R_{12})_nNR_{13}R_{14}$, $(CR_{11}R_{12})_n$heterocycle, $(CR_{11}R_{12})_nOR_{15}$, $(CR_{11}R_{12})_nC(O)ER_{13}$, $(CH_2)_nS(O)_mN(R_{18})_2$ and $(CR_{11}R_{12})_nS(O)_mR_{17}$, wherein the heterocycle is a 4-, 5-, 6-, or 7-membered monocyclic heterocycle which contains at least one heteroatom selected from O, S and N and which is substituted with

0, 1 or 2 groups independently selected from C_1-C_4alkyl, C_1-C_4alkoxy, halogen, hydroxyl, amino, and mono- and di- C_1-C_6alkylamino;

R_8 and R_9, taken in combination, together with the atoms to which they are attached, form a saturated 4-7 membered heterocyclic ring having 1 or 2 ring heteroatoms selected from N, O or S, which heterocyclic ring is substituted with 0, 1 or 2 groups independently selected from the group consisting of oxo, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, halogen, hydroxyl, amino, hydroxyC_1-C_6alkyl, aminoC_1-C_6alkyl, mono- and di-C_1-C_6alkylaminoC_1-C_6alkyl, C_3-C_7cycloalkylC_1-C_4alkyl, heterocycleC_1-C_4alkyl, C_1-C_6alkanoyl, mono- and di-C_1-C_6alkylamino, aminocarbonyl, mono- and di-C_1-C_6alkylaminocarbonyl, C_1-C_6alkoxycarbonyl, C_1-C_6alkylsulfonyl, aminosulfonyl, and mono- and di-C_1-C_6alkylaminosulfonyl, wherein the heterocycle is a 4-, 5-, 6-, or 7-membered monocyclic heterocycle which contains at least one heteroatom selected from O, S and N and which is substituted with 0, 1 or 2 groups independently selected from C_1-C_4alkyl, C_1-C_4alkoxy, halogen, hydroxyl, amino, and mono- and di- C_1-C_6alkylamino;

Ar_2 is selected from the group consisting of phenyl, naphthyl, a monocyclic or bicyclic heteroaryl, and bicyclic or tricyclic heterocycle wherein each heteroaryl or heterocycle group has 1, 2, 3 or 4 ring heteroatoms selected from N, O or S and wherein the phenyl, naphthyl, heteroaryl or heterocycle group is unsubstituted or substituted by 1, 2, or 3 groups independently selected from C_1-C_8alkyl, C_1-C_8haloalkyl, hydroxyC_1-C_6alkyl, C_1-C_8alkoxy, C_1-C_8haloalkoxy, halogen, hydroxy, amino, aminoC_1-C_6alkyl, mono- and di-C_1-C_6alkylaminoC_1-C_6alkyl, mono- and di-C_1-C_6alkylamino, CO_2C_1-C_6alkyl, phenylC_0-C_4alkyl, C_3-C_7cycloalkylC_0-C_4alkyl, spirocyclic C_3-C_7cycloalkyl, aminosulfonyl, and mono- and di-C_1-C_6alkylaminosulfonyl;

m is 0, 1, or 2;

n is 1, 2, or 3;

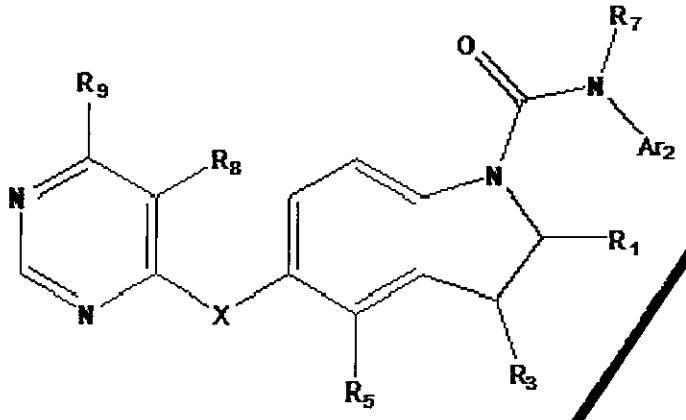
E is absent, O or NR_{18};

R_{11}, R_{12} and R_{18} are the same or different and are independently selected at each occurrence from the group consisting of hydrogen and C_1-C_4alkyl; and

R_{13}, R_{14}, R_{15} and R_{17} are independently selected at each occurrence from the group consisting of hydrogen, C_1-C_6alkyl, C_1-C_6alkanoyl, C_3-C_6cycloalkyl, phenyl and

heterocycle, each of which is substituted with 0, 1 or 2 groups independently selected from C_1-C_4alkyl, C_1-C_4alkoxy, halogen, hydroxyl, amino, and mono- and di- C_1-C_6alkylamino, and wherein the heterocycle is a 4-, 5-, 6-, or 7-membered monocyclic heterocycle which contains at least one heteroatom selected from O, S and N and which is substituted with 0, 1 or 2 groups independently selected from C_1-C_4alkyl, C_1-C_4alkoxy, halogen, hydroxyl, amino, and mono- and di- C_1-C_6alkylamino.

2. The compound of claim 1 according to Formula II:



II

or a pharmaceutically acceptable salt thereof wherein

R_1 is hydrogen or C_1-C_6alkyl;

R_3 is hydrogen or C_1-C_6alkyl;

R_5 is hydrogen or halogen;

R_7 is hydrogen or C_1-C_6alkyl;

X is O or S;

R_8 is selected from the group consisting of hydrogen and C_1-C_4alkyl;

R_9 is selected from the group consisting of $(CR_{11}R_{12})_nNR_{13}R_{14}$, $(CR_{11}R_{12})_n$heterocycle, $(CR_{11}R_{12})_nOR_{15}$, $(CR_{11}R_{12})_nC(O)ER_{13}$, and $(CR_{11}R_{12})_nS(O)_mR_{17}$; or

R_8 and R_9, taken in combination with the atoms to which they are attached form a saturated 4-7 membered heterocyclic ring having 1 or 2 ring heteroatoms selected from N, O or S, which heterocyclic ring is substituted with 0, 1, or 2 groups independently selected from the group consisting of C_1-C_6alkyl, C_1-C_6haloalkyl, halogen, hydroxyC_1-C_6alkyl, aminoC_1-C_6alkyl, C_3-C_7cycloalkylC_1-C_4alkyl, heterocycleC_1-C_4alkyl, C_1-

C_6alkanoyl, mono- and di-C_1-C_6alkylaminocarbonyl, C_1-C_6alkoxycarbonyl, and C_1-C_6alkylsulfonyl.

Ar_2 is phenyl, naphthyl, 5 or 6 membered monocyclic heteroaryl, wherein each heteroaryl has 1, 2, or 3 ring heteroatoms selected from N, O or S and wherein the phenyl, naphthyl, or heteroaryl group is unsubstituted or substituted by 1, 2, or 3 groups independently selected from the group consisting of C_1-C_6alkyl, C_1-C_6haloalkyl, halo, hydroxyl, CO_2C_1-C_6alkyl, phenyl, and C_3-C_7cycloalkyl;

m is 0, 1, or 2;

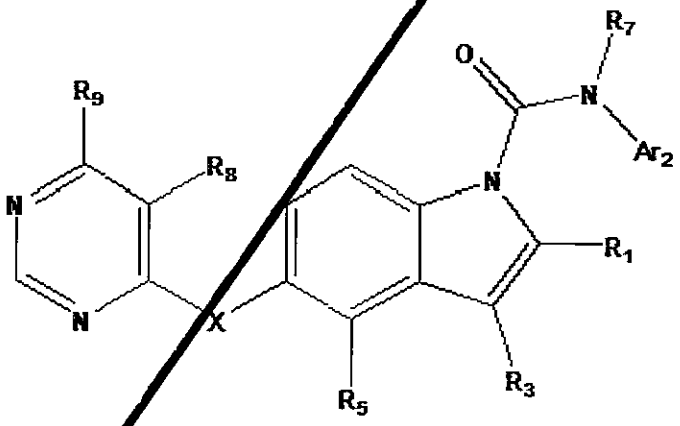
n is 1, 2, or 3;

E is O or NR_{18};

R_{11}, R_{12} and R_{18} are the same or different and are independently selected at each occurrence from the group consisting of hydrogen and C_1-C_4alkyl; and

R_{13}, R_{14}, R_{15} and R_{17} are independently selected at each occurrence from the group consisting of hydrogen, C_1-C_6alkyl, C_3-C_6cycloalkyl, phenyl and heterocycle, each of which is substituted with 0, 1 or 2 groups independently selected from hydroxyl, amino, and mono- and di- C_1-C_6alkylamino.

3. The compound of claim 1 according to Formula III:



III

or a pharmaceutically acceptable salt thereof

R_1 is hydrogen or C_1-C_6alkyl;

R_3 is hydrogen or C_1-C_6alkyl;

R_5 is hydrogen or halogen;

R_7 is hydrogen or C_1-C_6alkyl;

X is O or S;

R_8 is selected from the group consisting of hydrogen and C_1-C_4alkyl;

R_9 is selected from the group consisting of $(CR_{11}R_{12})_nNR_{13}R_{14}$, $(CR_{11}R_{12})_n$heterocycle, $(CR_{11}R_{12})_nOR_{15}$, $(CR_{11}R_{12})_nC(O)ER_{13}$, and $(CR_{11}R_{12})_nS(O)_mR_{17}$; or

R_8 and R_9, taken in combination together with the atoms to which they are attached form a saturated 4-7 membered heterocyclic ring having 1 or 2 ring heteroatoms selected from N, O or S, which heterocyclic ring is substituted with 0, 1, or 2 groups independently selected from the group consisting of C_1-C_6alkyl, C_1-C_6haloalkyl, halogen, hydroxyC_1-C_6alkyl, aminoC_1-C_6alkyl, C_3-C_7cycloalkylC_1-C_4alkyl, heterocycleC_1-C_4alkyl, C_1-C_6alkanoyl, mono- and di-C_1-C_6alkylaminocarbonyl, C_1-C_6alkoxycarbonyl, and C_1-C_6alkylsulfonyl;

Ar_2 is phenyl, naphthyl, 5 or 6 membered monocyclic heteroaryl, wherein each heteroaryl has 1, 2, or 3 ring heteroatoms selected from N, O or S and wherein the phenyl, naphthyl, or heteroaryl group is unsubstituted or substituted by 1, 2, or 3 groups independently selected from the group consisting of C_1-C_6alkyl, C_1-C_6haloalkyl, halo, hydroxyl, CO_2C_1-C_6alkyl, phenyl, and C_3-C_7cycloalkyl;

m is 0, 1, or 2;

n is 1, 2, or 3;

E is O or NR_{18};

R_{11}, R_{12} and R_{18} are the same or different and are independently selected at each occurrence from the group consisting of hydrogen and C_1-C_4alkyl; and

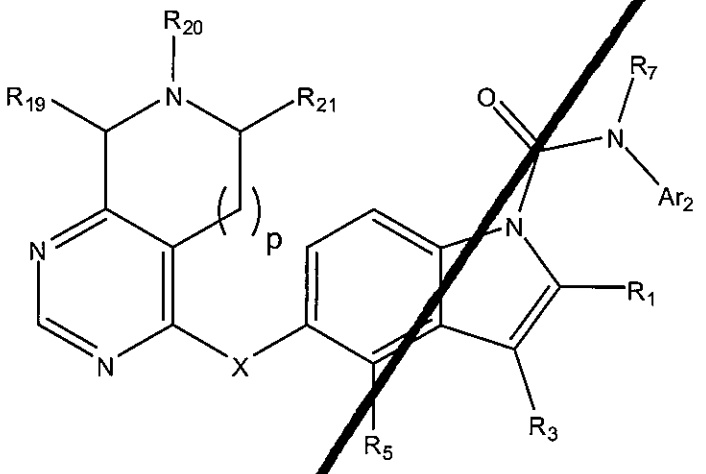
R_{13}, R_{14}, R_{15}, R_{16} and R_{17} are independently selected at each occurrence from the group consisting of hydrogen, C_1-C_6alkyl, C_3-C_6cycloalkyl, phenyl and heterocycle, each of which is substituted with 0, 1 or 2 groups independently selected from hydroxyl, amino, and mono- and di- C_1-C_6alkylamino.

4. The compound of claim 1, or a salt thereof, wherein R_{10} is hydrogen and R_8 and R_9, taken in combination, form a saturated 5 or 6 membered heterocyclic ring having 1 ring nitrogen atoms, which heterocyclic ring is substituted with 0, 1, or 2 groups independently selected from the group consisting of C_1-C_4alkyl, C_1-C_4haloalkyl, hydroxyC_1-C_4alkyl, aminoC_1-C_4alkyl, heterocycleC_1-C_4alkyl, C_1-C_4alkanoyl, mono- and

di-C_1-C_4alkylaminocarbonyl, mono- and di-C_1-C_4alkylaminocarbonylC_1-C_4alkyl, aminocarbonylC_1-C_4alkyl, C_1-C_4alkoxycarbonyl, and C_1-C_4alkylsulfonyl.

5. The compound of claim 1, or a salt thereof, wherein R_8 and R_9, taken in combination form a saturated 5 or 6 membered heterocyclic ring having 1 ring nitrogen atom beta to the pyrimidine ring, which heterocyclic ring is substituted with 0, 1, or 2 groups independently selected from the group consisting of C_1-C_4alkyl, C_1-C_4haloalkyl, hydroxyC_1-C_4alkyl, aminoC_1-C_4alkyl, heterocycleC_1-C_4alkyl, C_1-C_4alkanoyl, mono- and di-C_1-C_4alkylaminocarbonyl, mono- and di-C_1-C_4alkylaminoC_1-C_4alkanoyl, mono- and di-C_1-C_4alkylaminocarbonylC_1-C_4alkyl, aminocarbonylC_1-C_4alkyl, C_1-C_4alkoxycarbonyl, and C_1-C_4alkylsulfonyl.

6. The compound of claim 5, according to Formula IV:



IV

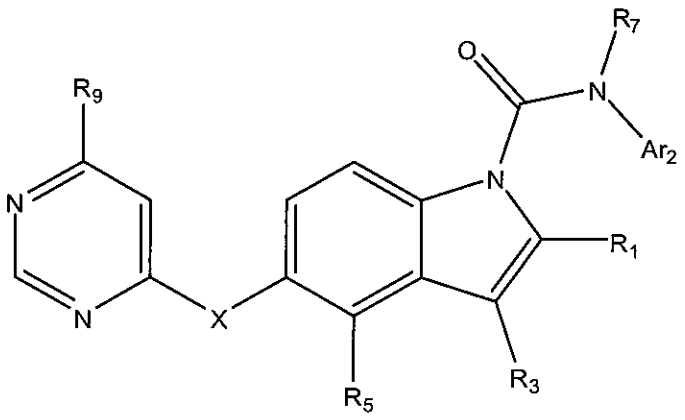
and pharmaceutically acceptable salts thereof, wherein

p is 0 or 1; and

R_{19}, R_{20}, and R_{21} are independently selected from the group consisting of hydrogen, C_1-C_4alkyl, hydroxyC_1-C_4alkyl, $NH_2C(O)CH_2$, and $NHMeC(O)CH_2$.

7. The compound of claim 6, wherein two of variables R_{19}, R_{20} or R_{21} are hydrogen and other is selected from the group consisting of hydrogen, methyl, ethyl, or hydroxyethyl.

8. The compound of claim 1, according to Formula V:



V

or a pharmaceutically acceptable salt thereof

R_9 is selected from the group consisting of $CH_2NR_{13}R_{14}$, CH_2OR_{15}, $CH_2C(O)ER_{13}$, $(CH_2)_nS(O)_mN(R_{18})_2$ and $CH_2S(O)_2R_{17}$;

E is absent, O or NR_{18};

R_{18} is hydrogen, methyl or ethyl; and

R_{13}, R_{14}, R_{15}, R_{16} and R_{17} are independently selected at each occurrence from the group consisting of hydrogen, C_1-C_4alkyl, and hydroxyC_1-C_4alkyl.

9. The compound of claim 1, wherein the R_8 is hydrogen; and

R_9 is selected from the group consisting of $(CH_2)_nNHR_{13}$, $(CR_{11}R_{12})_n$heterocycle, $(CR_{11}R_{12})_nOR_{15}$, $(CH_2)_nS(O)_mR_{17}$ and $(CH_2)_nS(O)_mN(R_{18})_2$;

n is 1 or 2;

R_{13} is hydrogen, C_1-C_4alkyl, hydroxyC_1-C_4alkyl, or C_3-C_6cycloalkyl;

R_{15} is hydrogen or C_1-C_4alkyl;

R_{17} is C_1-C_4alkyl; and

R_{18} is independently selected at each occurrence from the group consisting of hydrogen, methyl or ethyl.

10. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein

R_1 is hydrogen, methyl or ethyl;

R_3 is hydrogen;

R_5 is hydrogen, fluoro or chloro;

X is O or S;

R_8 is selected from the group consisting of hydrogen and C_1-C_4alkyl;

R_9 is selected from the group consisting of $CH_2NR_{13}R_{14}$, CH_2heterocycle, CH_2OR_{15}, $CH_2C(O)ER_{13}$, and $CH_2S(O)_2R_{17}$; or

R_8 and R_9, taken in combination form a saturated 4-7 membered heterocyclic ring having one ring nitrogen atom, which heterocyclic ring is substituted with 0, 1, or 2 groups independently selected from the group consisting of C_1-C_6alkyl, C_1-C_6haloalkyl, halogen, C_1-C_6alkanoyl, and C_1-C_6alkylsulfonyl;

Ar_2 is phenyl, 5 membered monocyclic heteroaryl, wherein each heteroaryl has one ring nitrogen and 0 or 1 additional ring heteroatoms selected from N, O or S and wherein the phenyl or heteroaryl group is unsubstituted or substituted by 1, 2, or 3 groups independently selected from the group consisting of C_1-C_6alkyl, C_1-C_6haloalkyl, halo, hydroxyl, CO_2C_1-C_6alkyl, phenyl, and C_3-C_7cycloalkyl;

m is 0, 1, or 2;

E is O or NR_{18};

R_{18} is selected from the group consisting of hydrogen and C_1-C_4alkyl; and

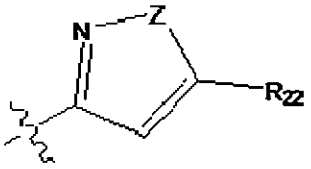
R_{13}, R_{14}, R_{15}, R_{16} and R_{17} are independently selected at each occurrence from the group consisting of hydrogen, C_1-C_6alkyl, C_3-C_6cycloalkyl, phenyl and heterocycle, each of which is substituted with 0, 1 or 2 groups independently selected from hydroxyl, amino, and mono- and di- C_1-C_4alkylamino.

11. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein Ar_2 is phenyl which unsubstituted or substituted with 1 or 2 groups independently selected from halogen, C_1-C_4alkyl, C_1-C_4alkoxy, C_1-C_4haloalkyl, and C_1-C_4haloalkoxy.

12. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein Ar_2 is a five membered heteroaryl having 1 ring nitrogen atom and 0 or 1 additional ring heteroatoms selected from N and O and wherein said heteroaryl group is unsubstituted or substituted with 1 or 2 groups independently selected from the group consisting of C_1-C_4alkyl, C_1-C_4haloalkyl, C_1-C_4alkoxy, C_1-C_4haloalkoxy, halogen, amino, aminoC_1-C_4alkyl, mono- and di-C_1-C_4alkylaminoC_1-C_4alkyl, mono- and di-C_1-C_4alkylamino,

hydroxyl, CO_2C_1-C_4alkyl, phenylC_0-C_4alkyl, C_3-C_6cycloalkylC_0-C_2alkyl, aminosulfonyl, and mono- and di-C_1-C_4alkylaminosulfonyl.

13. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein Ar_2 is a group of the formula:



wherein

R_{22} is selected from C_1-C_4alkyl, C_3-C_6cycloalkyl, C_3-C_6cycloalkylC_1-C_4alkyl, C_1-C_4haloalkyl, hydroxyC_1-C_4alkyl, phenyl, 5 and 6 membered heterocycle, wherein the heterocycle is a 4-, 5-, 6-, or 7-membered monocyclic heterocycle which contains at least one heteroatom selected from O, S and N and which is substituted with 0, 1 or 2 groups independently selected from C_1-C_4alkyl, C_1-C_4alkoxy, halogen, hydroxyl, amino, and mono- and di- C_1-C_6alkylamino; and Z is O, NH or N(C_1-C_4alkyl).

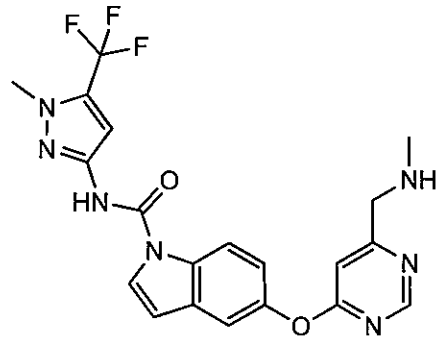
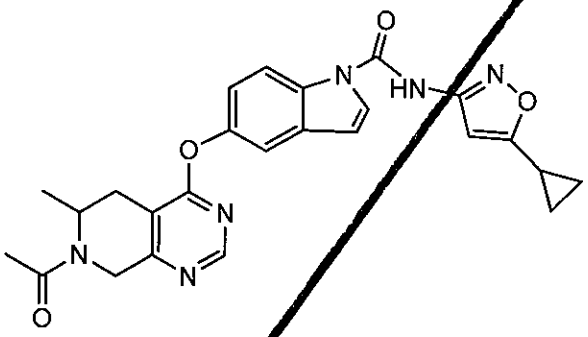
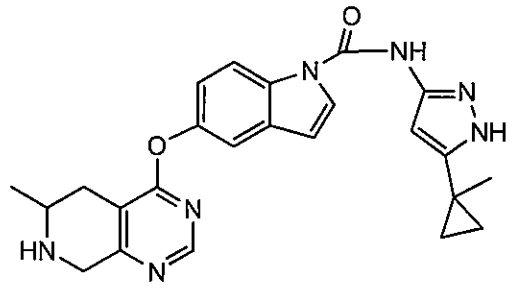
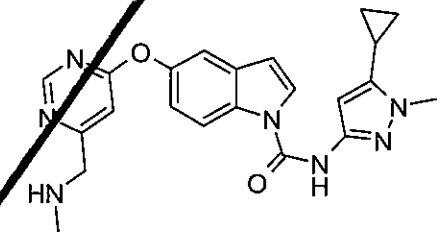
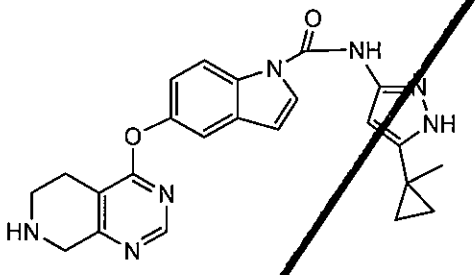
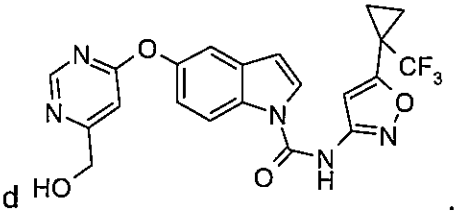
14. The compound of claim 13, wherein R_{22} is selected from C_1-C_4alkyl, C_3-C_6cycloalkyl, 1-methyl-C_3-C_6cycloalkyl, C_{1-2}haloalkyl, and hydroxyC_1-C_4alkyl; and
Z is O or NH.

15. The compound of claim 13, wherein R_{22} is selected from isopropyl, tert-butyl, cyclopropyl, cyclobutyl, 1-methyl-cyclopropyl, 1-trifluoromethyl-cyclopropyl, 1-ethyl-cyclopropyl, 1-methylcyclobutyl, 1-ethylcyclobutyl, hydroxyl-tert-butyl, and trifluoromethyl; and
Z is O.

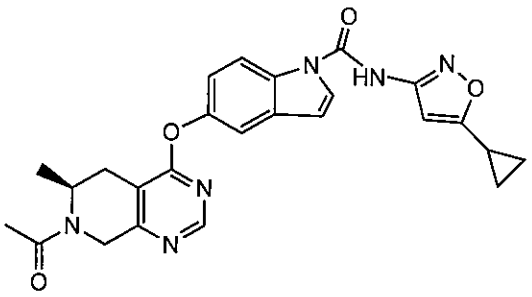
16. The compound of claim 1 in which R_7 is hydrogen.

17. A pharmaceutical composition comprising at least one compound of claim 1 and at least one pharmaceutically acceptable carrier.

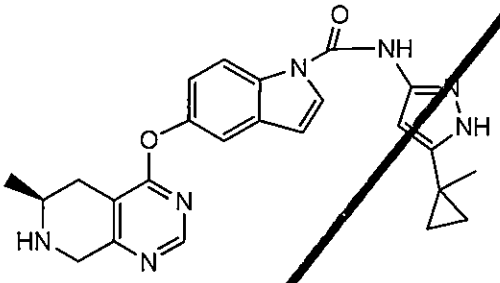
18. A compound, or pharmaceutically acceptable salt thereof, selected from the group consisting of:


,

,

,

,

and

.

19. The compound of claim 18, or a pharmaceutically acceptable salt thereof, selected from the group consisting of



and



20. A pharmaceutical composition comprising at least one compound of claim 18 or claim 19 and at least one pharmaceutically acceptable carrier.

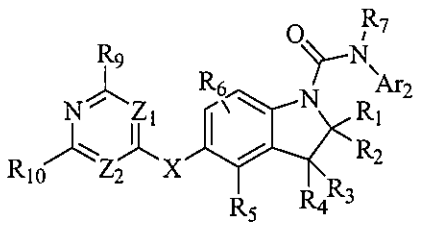
21. A pharmaceutical combination, comprising a therapeutically effective amount of the compound according to claim 18 or claim 19 and one or more additional therapeutically active agents.

22. Use of a compound according to claim 18 or claim 19 in the manufacture of a medicament for the treatment of inhibiting VEGF-R activity in a subject.

23. Use of a compound according to claim 18 or claim 19 in the manufacture of a medicament for the treatment of a disorder or disease in a subject medicated by VEGF-R, wherein the disease or disorder is selected from age related macular degeneration, diabetic retinopathy, retinitis pigmentosa and retinopathy, geographic atrophy.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A compound of Formula I:



I

or a pharmaceutically acceptable salt thereof, wherein

R_1 is hydrogen or C_1-C_6alkyl;

R_3 is hydrogen or C_1-C_6alkyl;

R_2 and R_4, taken in combination form a bond;

R_5 is hydrogen, C_1-C_6alkyl, or halogen;

R_6 represents 0, 1, or 2 groups independently selected at each occurrence from halogen or C_1-C_6alkyl;

R_7 is hydrogen or C_1-C_6alkyl;

X is O or S;

Z_1 and Z_2 are independently selected from the group consisting of N and CR_8;

R_8 and R_{10} are independently selected from the group consisting of hydrogen and C_1-C_6alkyl;

R_9 is selected from the group consisting of $(CR_{11}R_{12})_nNR_{13}R_{14}$, $(CR_{11}R_{12})_n$heterocycle, $(CR_{11}R_{12})_nOR_{15}$, $(CR_{11}R_{12})_nC(O)ER_{13}$, $(CH_2)_nS(O)_mN(R_{18})_2$ and $(CR_{11}R_{12})_nS(O)_mR_{17}$, wherein the heterocycle is a 4-, 5-, 6-, or 7-membered monocyclic heterocyle which contains at least one heteroatom selected from O, S and N and which is substituted with 0, 1 or 2 groups independently selected from C_1-C_4alkyl, C_1-C_4alkoxy, halogen, hydroxyl, amino, and mono- and di-C_1-C_6alkylamino; or

R_8 and R_9, taken in combination, together with the atoms to which they are attached, form a saturated 4-7 membered heterocyclic ring having 1 or 2 ring heteroatoms selected from N, O or S, which heterocyclic ring is substituted with 0, 1, or 2 groups independently selected from the group consisting of oxo, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_1-C_6haloakoxy, halogen, hydroxyl, amino, hydroxyC_1-C_6alkyl, aminoC_1-C_6alkyl, mono- and

di-C_1-C_6alkylaminoC_1-C_6alkyl, C_3-C_7cycloalkylC_1-C_4alkyl, heterocycleC_1-C_4alkyl, C_1-C_6alkanoyl, mono- and di-C_1-C_6alkylamino, aminocarbonyl, mono- and di-C_1-C_6alkylaminocarbonyl, C_1-C_6alkoxycarbonyl, C_1-C_6alkylsulfonyl, aminosulfonyl, and mono- and di-C_1-C_6alkylaminosulfonyl, wherein the heterocycle is a 4-, 5-, 6-, or 7-membered monocyclic heterocycle which contains at least one heteroatom selected from O, S and N and which is substituted with 0, 1 or 2 groups independently selected from C_1-C_4alkyl, C_1-C_4alkoxy, halogen, hydroxyl, amino, and mono- and di-C_1-C_6alkylamino;

Ar_2 is selected from the group consisting of phenyl, naphthyl, a monocyclic or bicyclic heteroaryl, and bicyclic or tricyclic heterocycle wherein each heteroaryl or heterocycle group has 1, 2, 3 or 4 ring heteroatoms selected from N, O or S and wherein the phenyl, naphthyl, heteroaryl or heterocycle group is unsubstituted or substituted by 1, 2, or 3 groups independently selected from C_1-C_8alkyl, C_1-C_8haloalkyl, hydroxyC_1-C_6alkyl, C_1-C_8alkoxy, C_1-C_8haloalkoxy, halogen, hydroxy, amino, aminoC_1-C_6alkyl, mono- and di-C_1-C_6alkylaminoC_1-C_6alkyl, mono- and di-C_1-C_6alkylamino, CO_2C_1-C_6alkyl, phenylC_0-C_4alkyl, C_3-C_7cycloalkylC_0-C_4alkyl, spirocyclic C_3-C_7cycloalkyl, aminosulfonyl, C_5-C_6heterocycle and mono- and di-C_1-C_6alkylaminosulfonyl;

m is 0, 1, or 2;

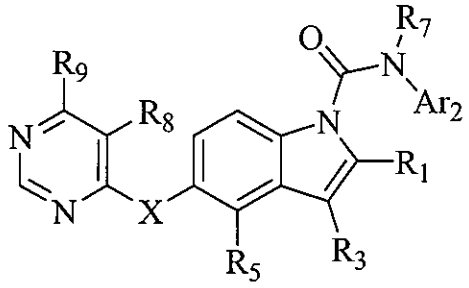
n is 1, 2, or 3;

E is absent, O or NR_{18};

R_{11}, R_{12} and R_{18} are the same or different and are independently selected at each occurrence from the group consisting of hydrogen and C_1-C_4alkyl; and

R_{13}, R_{14}, R_{15} and R_{17} are independently selected at each occurrence from the group consisting of hydrogen, C_1-C_6alkyl, C_1-C_6alkanoyl, C_3-C_6cycloalkyl, phenyl and heterocycle, each of which is substituted with 0, 1 or 2 groups independently selected from C_1-C_4alkyl, C_1-C_4alkoxy, halogen, hydroxyl, amino, and mono- and di-C_1-C_6alkylamino, and wherein the heterocycle is a 4-, 5-, 6-, or 7-membered monocyclic heterocycle which contains at least one heteroatom selected from O, S and N and which is substituted with 0, 1 or 2 groups independently selected from C_1-C_4alkyl, C_1-C_4alkoxy, halogen, hydroxyl, amino, and mono- and di-C_1-C_6alkylamino.

2. The compound of claim 1 according to Formula III:



III

or a pharmaceutically acceptable salt thereof, wherein

R_1 is hydrogen or C_1-C_6alkyl;

R_3 is hydrogen or C_1-C_6alkyl;

R_5 is hydrogen or halogen;

R_7 is hydrogen or C_1-C_6alkyl;

X is O or S;

R_8 is selected from the group consisting of hydrogen and C_1-C_4alkyl;

R_9 is selected from the group consisting of $(CR_{11}R_{12})_nNR_{13}R_{14}$, $(CR_{11}R_{12})_n$heterocycle, $(CR_{11}R_{12})_nOR_{15}$, $(CR_{11}R_{12})_nC(O)ER_{13}$, $(CH_2)_nS(O)_mN(R_{18})_2$ and $(CR_{11}R_{12})_nS(O)_mR_{17}$;

Ar_2 is phenyl, naphthyl, 5 or 6 membered monocyclic heteroaryl, wherein each heteroaryl has 1, 2, or 3 ring heteroatoms selected from N, O or S and wherein the phenyl, naphthyl, or heteroaryl group is unsubstituted or substituted by 1, 2, or 3 groups independently selected from the group consisting of C_1-C_6alkyl, C_1-C_8alkoxy, C_1-C_8haloalkoxy, C_1-C_6haloalkyl, hydroxyC_1-C_6alkyl, halogen, hydroxyl, CO_2C_1-C_6alkyl, amino, aminoC_1-C_6alkyl, mono- and di-C_1-C_6alkylaminoC_1-C_6alkyl, mono- and di-C_1-C_6alkylamino, CO_2C_1-C_6alkyl, phenylC_0-C_4alkyl, C_3-C_7cycloalkylC_0-C_4alkyl, aminosulfonyl, mono- and di-C_1-C_6alkylaminosulfonyl, phenyl, C_5-C_6heterocycle and C_3-C_7cycloalkyl;

m is 0, 1, or 2;

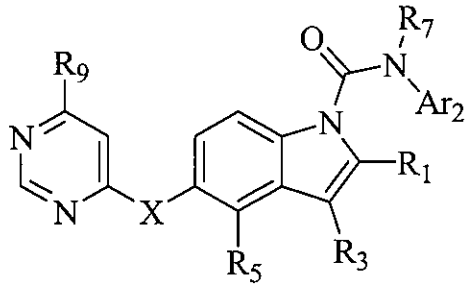
n is 1, 2, or 3;

E is O or NR_{18};

R_{11}, R_{12} and R_{18} are the same or different and are independently selected at each occurrence from the group consisting of hydrogen and C_1-C_4alkyl; and

R_{13}, R_{14}, R_{15} and R_{17} are independently selected at each occurrence from the group consisting of hydrogen, C_1-C_6alkyl, C_3-C_6cycloalkyl, phenyl and heterocycle, each of which is substituted with 0, 1 or 2 groups independently selected from hydroxyl, amino, and mono- and di- C_1-C_6alkylamino.

3. The compound of claim 1 or 2, according to Formula V:



V

or a pharmaceutically acceptable salt thereof, wherein

R_9 is selected from the group consisting of $CH_2NR_{13}R_{14}$, CH_2OR_{15}, $CH_2C(O)ER_{13}$, $(CH_2)_nS(O)_mN(R_{18})_2$ and $CH_2S(O)_2R_{17}$;

E is absent, O or NR_{18};

R_{18} is hydrogen, methyl or ethyl; and

R_{13}, R_{14}, R_{15} and R_{17} are independently selected at each occurrence from the group consisting of hydrogen, C_1-C_4alkyl, and hydroxyC_1-C_4alkyl.

4. The compound of claim 1 or 2, wherein the R_8 is hydrogen; and

R_9 is selected from the group consisting of $(CH_2)_nNHR_{13}$, $(CR_{11}R_{12})_n$heterocycle, $(CR_{11}R_{12})_nOR_{15}$, $(CH_2)_nS(O)_mR_{17}$ and $(CH_2)_nS(O)_mN(R_{18})_2$;

n is 1 or 2;

R_{13} is hydrogen, C_1-C_4alkyl, hydroxyC_1-C_4alkyl, or C_3-C_6cycloalkyl;

R_{15} is hydrogen or C_1-C_4alkyl;

R_{17} is C_1-C_4alkyl; and

R_{18} is independently selected at each occurrence from the group consisting of hydrogen, methyl or ethyl.

5. The compound of claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein

R_1 is hydrogen, methyl or ethyl;

R_3 is hydrogen;

R_5 is hydrogen, fluoro or chloro;

X is O or S;

R_8 is selected from the group consisting of hydrogen and C_1-C_4alkyl;

R_9 is selected from the group consisting of $CH_2NR_{13}R_{14}$, CH_2heterocycle, CH_2OR_{15}, $CH_2C(O)ER_{13}$, and $CH_2S(O)_2R_{17}$;

Ar_2 is phenyl, or a 5 membered monocyclic heteroaryl, wherein each heteroaryl has one ring nitrogen and 0 or 1 additional ring heteroatoms selected from N, O or S and wherein the phenyl or heteroaryl group is unsubstituted or substituted by 1, 2, or 3 groups independently selected from the group consisting of C_1-C_6alkyl, C_1-C_6haloalkyl, halo, hydroxyl, CO_2C_1-C_6alkyl, phenyl, and C_3-C_7cycloalkyl;

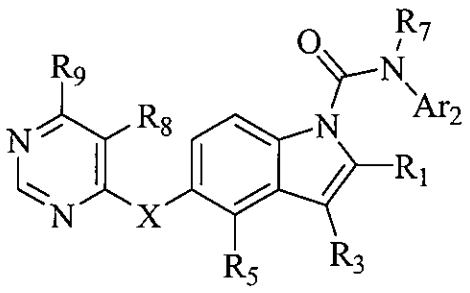
m is 0, 1, or 2;

E is O or NR_{18};

R_{18} is selected from the group consisting of hydrogen and C_1-C_4alkyl; and

R_{13}, R_{14}, R_{15} and R_{17} are independently selected at each occurrence from the group consisting of hydrogen, C_1-C_6alkyl, C_3-C_6cycloalkyl, phenyl and heterocycle, each of which is substituted with 0, 1 or 2 groups independently selected from hydroxyl, amino, and mono- and di- C_1-C_6alkylamino.

6. The compound of claim 1, according to Formula III:



III

or a pharmaceutically acceptable salt thereof, wherein

R_1 is hydrogen or C_1-C_6alkyl;

R_3 is hydrogen or C_1-C_6alkyl;

R_5 is hydrogen or halogen;

R_7 is hydrogen or C_1-C_6alkyl;

X is O or S;

R_8 and R_9, taken in combination together with the atoms to which they are attached form a saturated 4-7 membered heterocyclic ring having 1 or 2 ring heteroatoms selected from N, O or S, which heterocyclic ring is substituted with 0, 1, or 2 groups independently selected from the group consisting of C_1-C_6alkyl, C_1-C_6haloalkyl, halogen, hydroxyC_1-C_6alkyl, aminoC_1-C_6alkyl, C_3-C_7cycloalkylC_1-C_4alkyl, heterocycleC_1-C_4alkyl, C_1-C_6alkanoyl, mono- and di-C_1-C_6alkylaminocarbonyl, C_1-C_6alkoxycarbonyl, and C_1-C_6alkylsulfonyl;

Ar_2 is phenyl, naphthyl, 5 or 6 membered monocyclic heteroaryl, wherein each heteroaryl has 1, 2, or 3 ring heteroatoms selected from N, O or S and wherein the phenyl, naphthyl, or heteroaryl group is unsubstituted or substituted by 1, 2, or 3 groups independently selected from the group consisting of C_1-C_6alkyl, C_1-C_8alkoxy, C_1-C_8haloalkoxy, C_1-C_6haloalkyl, hydroxyC_1-C_6alkyl, halogen, hydroxyl, CO_2C_1-C_6alkyl, amino, aminoC_1-C_6alkyl, mono- and di-C_1-C_6alkylaminoC_1-C_6alkyl, mono- and di-C_1-C_6alkylamino, CO_2C_1-C_6alkyl, phenylC_0-C_4alkyl, C_3-C_7cycloalkylC_0-C_4alkyl, aminosulfonyl, mono- and di-C_1-C_6alkylaminosulfonyl, phenyl, C_5-C_6heterocycle and C_3-C_7cycloalkyl;

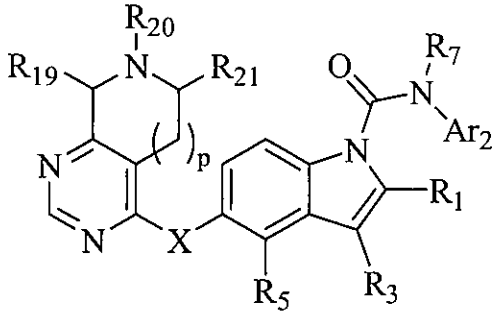
m is 0, 1, or 2; and

n is 1, 2, or 3.

7. The compound of claim 1 or 6, or a pharmaceutically acceptable salt thereof, wherein R_8 and R_9, taken in combination, form a saturated 5 or 6 membered heterocyclic ring having 1 ring nitrogen atom, which heterocyclic ring is substituted with 0, 1, or 2 groups independently selected from the group consisting of C_1-C_4alkyl, C_1-C_4haloalkyl, hydroxyC_1-C_4alkyl, aminoC_1-C_4alkyl, heterocycleC_1-C_4alkyl, C_1-C_4alkanoyl, mono- and di-C_1-C_4alkylaminocarbonyl, mono- and di-C_1-C_4alkylaminocarbonylC_1-C_4alkyl, aminocarbonylC_1-C_4alkyl, C_1-C_4alkoxycarbonyl, and C_1-C_4alkylsulfonyl.

8. The compound of claim 1 or 6, or a pharmaceutically acceptable salt thereof, wherein R_8 and R_9, taken in combination form a saturated 5 or 6 membered heterocyclic ring having 1 ring nitrogen atom beta to the pyrimidine ring, which heterocyclic ring is substituted with 0, 1, or 2 groups independently selected from the group consisting of C_1-C_4alkyl, C_1-C_4haloalkyl, hydroxyC_1-C_4alkyl, aminoC_1-C_4alkyl, heterocycleC_1-C_4alkyl, C_1-C_4alkanoyl, mono- and di-C_1-C_4alkylaminocarbonyl, mono- and di-C_1-C_4alkylaminoC_1-C_4alkanoyl, mono- and di-C_1-C_4alkylaminocarbonylC_1-C_4alkyl, aminocarbonylC_1-C_4alkyl, C_1-C_4alkoxycarbonyl, and C_1-C_4alkylsulfonyl.

9. The compound of any one of claims 1, 6 or 9, according to Formula IV:



IV

and pharmaceutically acceptable salts thereof, wherein

p is 0 or 1; and

R_{19}, R_{20}, and R_{21} are independently selected from the group consisting of hydrogen, C_1-C_4alkyl, hydroxyC_1-C_4alkyl, $NH_2C(O)CH_2$, and $NHMeC(O)CH_2$.

10. The compound of claim 9, wherein two of variables R_{19}, R_{20} or R_{21} are hydrogen and other is selected from the group consisting of hydrogen, methyl, ethyl, or hydroxyethyl.

11. The compound of claim 1 or 6, or a pharmaceutically acceptable salt thereof, wherein

R_1 is hydrogen, methyl or ethyl;

R_3 is hydrogen;

R_5 is hydrogen, fluoro or chloro;

X is O or S;

R_8 and R_9, taken in combination form a saturated 4-7 membered heterocyclic ring having one ring nitrogen atom, which heterocyclic ring is substituted with 0, 1, or 2 groups independently selected from the group consisting of C_1-C_6alkyl, C_1-C_6haloalkyl, halogen, C_1-C_6alkanoyl, and C_1-C_6alkylsulfonyl;

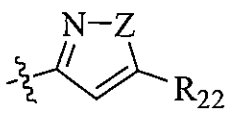
Ar_2 is phenyl, 5 membered monocyclic heteroaryl, wherein each heteroaryl has one ring nitrogen and 0 or 1 additional ring heteroatoms selected from N, O or S and wherein the phenyl or heteroaryl group is unsubstituted or substituted by 1, 2, or 3 groups independently selected from the group consisting of C_1-C_6alkyl, C_1-C_6haloalkyl, halo, hydroxyl, CO_2C_1-C_6alkyl, phenyl, and C_3-C_7cycloalkyl;

m is 0, 1, or 2.

12. The compound of any one of claims 1 to 3, 6 or 9, or a pharmaceutically acceptable salt thereof, wherein Ar_2 is phenyl which is unsubstituted or substituted with 1 or 2 groups independently selected from halogen, C_1-C_4alkyl, C_1-C_4alkoxy, C_1-C_4haloalkyl, and C_1-C_4haloalkoxy.

13. The compound of any one of claims 1 to 3, 6 or 9, or a pharmaceutically acceptable salt thereof, wherein Ar_2 is a five membered heteroaryl having 1 ring nitrogen atom and 0 or 1 additional ring heteroatoms selected from N and O and wherein said heteroaryl group is unsubstituted or substituted with 1 or 2 groups independently selected from the group consisting of C_1-C_4alkyl, C_1-C_4haloalkyl, C_1-C_4alkoxy, C_1-C_4haloalkoxy, halogen, amino, aminoC_1-C_4alkyl, mono- and di-C_1-C_4alkylaminoC_1-C_4alkyl, mono- and di-C_1-C_4alkylamino, hydroxyl, CO_2C_1-C_4alkyl, phenylC_0-C_4alkyl, C_3-C_6cycloalkylC_0-C_2alkyl, aminosulfonyl, and mono- and di-C_1-C_4alkylaminosulfonyl.

14. The compound of any one of claims 1 to 3, 6 or 9, or a pharmaceutically acceptable salt thereof, wherein Ar_2 is a group of the formula:



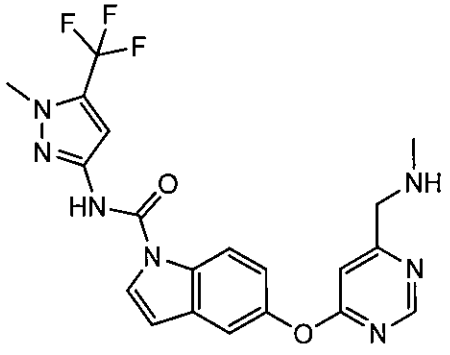
wherein

R_{22} is selected from C_1-C_4alkyl, C_3-C_6cycloalkyl, C_3-C_6cycloalkylC_1-C_4alkyl, C_1-C_4haloalkyl, hydroxyC_1-C_4alkyl, phenyl, 5 and 6 membered heterocycle, wherein the heterocycle contains at least one heteroatom selected from O, S and N and is substituted with 0, 1 or 2 groups independently selected from C_1-C_4alkyl, C_1-C_4alkoxy, halogen, hydroxyl, amino, and mono- and di- C_1-C_6alkylamino; and Z is O, NH or N(C_1-C_4alkyl).

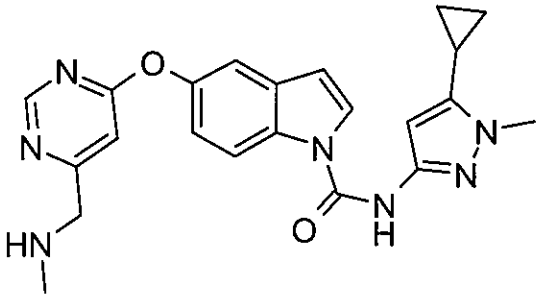
15. The compound of claim 14, wherein R_{22} is selected from isopropyl, tert-butyl, cyclopropyl, cyclobutyl, 1-methyl-cyclopropyl, 1-trifluoromethyl-cyclopropyl, 1-ethyl-cyclopropyl, 1-methylcyclobutyl, 1-ethylcyclobutyl, hydroxyl-tert-butyl, and trifluoromethyl; and
Z is O.

16. The compound of any one of the preceding claims in which R_7 is hydrogen.

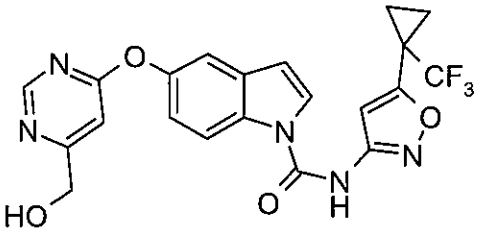
17. A compound, or pharmaceutically acceptable salt thereof, according to the formula:



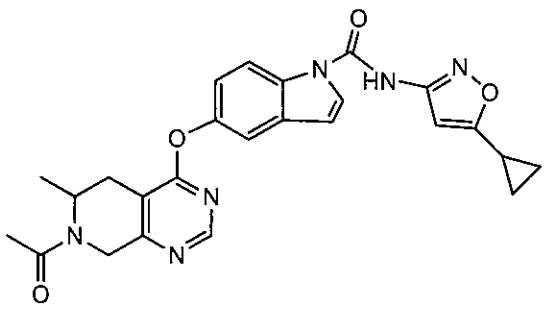
18. A compound, or salt thereof, according to the formula:



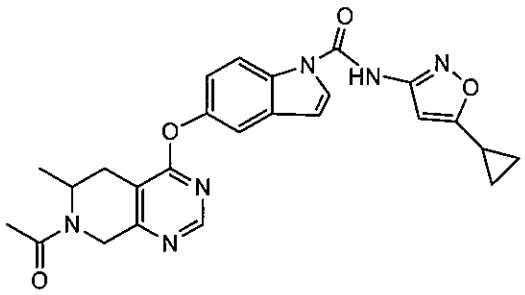
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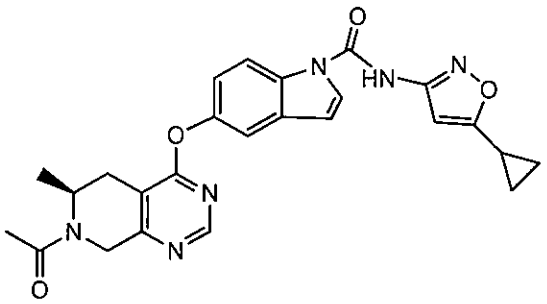
19. A compound, or salt thereof, according to the formula:



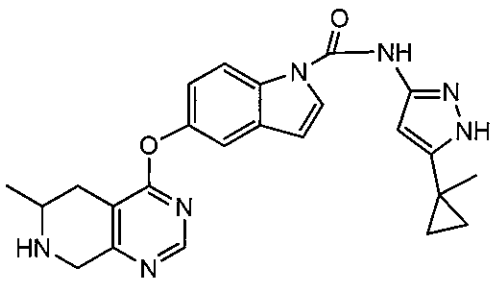
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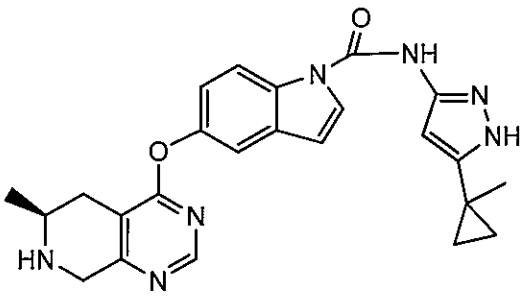
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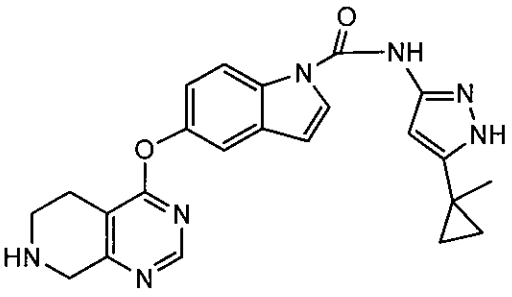
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,and



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20. A pharmaceutical combination, comprising a therapeutically effective amount of the compound according to any one of claims 1 to 19 and one or more additional therapeutically active agents.

21. A pharmaceutical composition comprising at least one compound of any one of claims 1 to 19, and at least one pharmaceutically acceptable carrier.

22. Use of a compound according to any one of claims 1 to 19 in the manufacture of a medicament for inhibiting VEGF-R activity in a subject.

23. Use of a compound according to any one of claims 1 to 19 in the manufacture of a medicament for the treatment of a disorder or disease in a subject mediated by VEGF-R, wherein the disease or disorder is selected from age related macular degeneration, diabetic retinopathy, retinitis pigmentosa and retinopathy, geographic atrophy.

24. Use according to claims 22 or 23 wherein the compound is selected from any one of claims 17 to 19.