CLAIMS

1. A compound selected from the group consisting of:

1-(2-fluoro-5-((4-oxo-3,4,5,6,7,8-hexahydrophthalazin-1-yl)methyl)phenyl)pyrrolidine-2,5-dione, or a pharmaceutically acceptable salt thereof;

4-(3-(1,4-diazepan-1-ylcarbonyl)-4-fluorobenzyl)-5,6,7,8-tetrahydrophthalazin-1(2H)-one, or a pharmaceutically acceptable salt thereof.

2. A pharmaceutical composition comprising a compound of claim 1 and a pharmaceutically acceptable excipient.

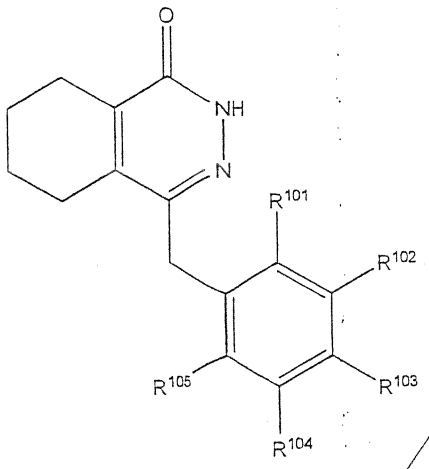
3. A compound of claim 1 for use in treating cancer in a mammal by administering thereto a therapeutically acceptable amount of said compound.

4. The compound of claim 3 for use in combination with radiotherapy.

5. The compound of claim 3 for use in combination with a chemotherapeutic agent selected from temozolomide, dacarbazine, cyclophosphamide, carmustine, melphalan, lomustine, carboplatin, cisplatin, 5-FU +/- leucovorin, gemcitabine, methotrexate, bleomycin, irinotecan, camptothecin, or topotecan.

WE CLAIM:

1. A compound having formula (Ik),



(Ik),

or a pharmaceutically acceptable salt thereof, wherein

R^{101}, R^{104}, and R^{105} are H;

R^{103} is F;

R^{102} is $NHC(O)R^{11}$;

R^{11} is R^{12}, R^{13}, R^{14} or R^{15};

R^{12} is phenyl which is unfused or fused with benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene; each of which is unfused or fused with benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{13} is heteroaryl which is unfused or fused with benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene; each of which is unfused or fused with benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{14} is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl; each of which is unfused or fused with benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene; each of which is unfused or fused with benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{15} is alkyl, alkenyl or alkynyl; each of which is unsubstituted or substituted with one or two of independently selected R^{16}, OR^{16}, SR^{16}, $S(O)_2R^{16}$, C(O)OH, NH_2,

$NHR^{16}N(R^{16})_2$, $C(O)R^{16}$, $C(O)NH_2$, $C(O)NHR^{16}$, $C(O)N(R^{16})_2$, $NHC(O)R^{16}$, $NR^{16}C(O)R^{16}$, $NHC(O)OR^{16}$, $NR^{16}C(O)OR^{16}$, OH, F, Cl, Br or I;

wherein each R^{16} is R^{17} or R^{17A};

R^{17} is alkyl, alkenyl or alkynyl; each of which is unsubstituted or substituted with one or two of independently selected R^{18}, $C(O)OH$, NH_2, NHR^{18} or $N(R^{18})_2$, $C(O)R^{18}$, $C(O)NH_2$, $C(O)NHR^{18}$, $C(O)N(R^{18})_2$, $NHC(O)R^{18}$, $NR^{18}C(O)R^{18}$, F, Cl, Br or I;

R^{17A} is phenyl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl each of which is unfused or fused with benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

wherein each R^{18} is phenyl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl;

wherein each of the moieties represented by R^{12}, R^{13}, R^{14}, R^{17A}, and R^{18} are independently unsubstituted or substituted with one or two or three or four of independently selected R^{19}, OR^{19}, SR^{19}, $S(O)R^{19}$, SO_2R^{19}, $C(O)R^{19}$, $CO(O)R^{19}$, $OC(O)R^{19}$, $OC(O)OR^{19}$, NH_2, NHR^{19}, $N(R^{19})_2$, $NHC(O)R^{19}$, $NR^{19}C(O)R^{19}$, $NHS(O)_2R^{19}$, $NR^{19}S(O)_2R^{19}$, $NHC(O)OR^{19}$, $NR^{19}C(O)OR^{19}$, $NHC(O)NH_2$, $NHC(O)NHR^{19}$, $NHC(O)N(R^{19})_2$, $NR^{19}C(O)NHR^{19}$, $NR^{19}C(O)N(R^{19})_2$, $C(O)NH_2$, $C(O)NHR^{19}$, $C(O)N(R^{19})_2$, $C(O)NHOH$, $C(O)NHOR^{19}$, $C(O)NHSO_2R^{19}$, $C(O)NR^{19}SO_2R^{19}$, SO_2NH_2, SO_2NHR^{19}, $SO_2N(R^{19})_2$, C(O)H, $C(O)OH$, $C(N)NH_2$, $C(N)NHR^{19}$, $C(N)N(R^{19})_2$, CNOH, $CNOCH_3$, OH, (O), CN, N_3, NO_2, CF_3, CF_2CF_3, OCF_3, OCF_2CF_3, F, Cl, Br or I;

wherein each R^{19} is R^{20}, R^{21}, R^{22} or R^{23};

R^{20} is phenyl which is unfused or fused with benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene; each of which is unfused or fused with benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{21} is heteroaryl which is unfused or fused with benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene; each of which is unfused or fused with benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{22} is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl; each of which is unfused or fused with benzene, heteroarene, cycloalkane, cycloalkene,

heterocycloalkane or heterocycloalkene; each of which is unfused or fused with benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{23} is alkyl, alkenyl or alkynyl; each of which is unsubstituted or substituted with one or two of independently selected R^{24}, OR^{24}, SR^{24}, $S(O)_2R^{24}$, C(O)OH, NH_2, $NHR^{24}N(R^{24})_2$, $C(O)R^{24}$, $C(O)NH_2$, $C(O)NHR^{24}$, $C(O)N(R^{24})_2$, $NHC(O)R^{24}$, $NR^{24}C(O)R^{24}$, $NHC(O)OR^{24}$, $NR^{24}C(O)OR^{24}$, $NHS(O)_2R^{24}$, $NR^{24}S(O)_2R^{24}$, OH, F, Cl, Br or I;

wherein each R^{24} is R^{24A} or R^{24B};

R^{24A} is phenyl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl each of which is unfused or fused with benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{24B} is alkyl, alkenyl or alkynyl each of which is unsubstituted or substituted with one or two of independently selected R^{25}, OR^{25}, SR^{25}, $S(O)_2R^{25}$, C(O)OH, NH_2, $NHR^{25}N(R^{25})_2$, $C(O)R^{25}$, $C(O)NH_2$, $C(O)NHR^{25}$, $C(O)N(R^{25})_2$, $NHC(O)R^{25}$, $NR^{25}C(O)R^{25}$, $NHC(O)OR^{25}$, $NR^{25}C(O)OR^{25}$, OH, F, Cl, Br or I;

wherein each R^{25} is alkyl, phenyl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl; each of which is unsubstituted or substituted with NH_2, $NH(CH_3)$, $N(CH_3)_2$, OH or OCH_3;

wherein each of the moieties represented by R^{20}, R^{21}, R^{22}, and R^{24A} are independently unsubstituted or substituted with one or two of independently selected R^{26}, OR^{26}, alkenyl, alkynyl, phenyl, OH, (O), C(O)OH, CN, CF_3, OCF_3, CF_2CF_3, F, Cl, Br or I; and

R^{26} is alkyl.

2. The compound of claim 1, wherein R^{11} is R^{15}, wherein R^{15} is alkyl, unsubstituted or substituted with one or two of independently selected R^{16}, OR^{16}, SR^{16}, $S(O)_2R^{16}$, C(O)OH, NH_2, $NHR^{16}N(R^{16})_2$, $C(O)R^{16}$, $C(O)NHR^{16}$, $NHC(O)R^{16}$, $NHC(O)OR^{16}$, OH or Cl;

wherein each R^{16} is R^{17} or R^{17A};

R^{17} is alkyl, which is unsubstituted or substituted with one or two of independently selected R^{18};

R^{17A} is phenyl, heteroaryl, cycloalkyl, heterocycloalkyl, heterocycloalkenyl each of which is unfused or fused with benzene or heterocycloalkane;

wherein each R^{18} is phenyl or heterocycloalkyl;

wherein each of the moieties represented by R^{17A} and R^{18} are independently unsubstituted or substituted with one or two or three or four of independently selected R^{19}, OR^{19}, SR^{19}, SO_2R^{19}, $C(O)R^{19}$, $CO(O)R^{19}$, NHR^{19}, $N(R^{19})_2$, $NHC(O)R^{19}$, $NHS(O)_2R^{19}$, $C(O)NH_2$, $C(O)NHR^{19}$, $C(O)N(R^{19})_2$, C(O)H, OH, (O), CN, CF_3, F, Cl, Br or I;

wherein each R^{19} is R^{20}, R^{21}, R^{22} or R^{23};

R^{20} is phenyl which is unfused;

R^{21} is heteroaryl which is unfused;

R^{22} is cycloalkyl or heterocycloalkyl; each of which are unfused or fused with benzene;

R^{23} is alkyl, which is unsubstituted or substituted with one or two of independently selected R^{24}, OR^{24}, $NHR^{24}N(R^{24})_2$, $NHS(O)_2R^{24}$ or OH;

wherein each R^{24} is R^{24A} or R^{24B};

R^{24A} is unsubstituted phenyl, cycloalkyl, heterocycloalkyl or heterocycloalkenyl each of which is unfused or fused with heterocycloalkane;

R^{24B} is alkyl, which is unsubstituted or substituted with one or two of independently selected OR^{25} or OH;

wherein each R^{25} is alkyl unsubstituted or substituted with NH_2;

wherein each R^{20} is unsubstituted or substituted with one or two of independently selected R^{26}, OR^{26} (O), F or Cl; and

R^{26} is alkyl; or a pharmaceutically acceptable salt thereof.

3. The compound according to claim 1 selected from

4-((2-fluoro-5-((4-oxo-3,4,5,6,7,8-hexahydrophthalazin-1-yl)methyl)phenyl)amino)-4-oxobutanoic acid;

4-(3-(1,4-diazepan-1-ylcarbonyl)-4-fluorobenzyl)-5,6,7,8-tetrahydrophthalazin-1(2H)-one;

N-(2-fluoro-5-((4-oxo-3,4,5,6,7,8-hexahydrophthalazin-1-yl)methyl)phenyl)-3-piperidin-1-ylpropanamide;

N-(2-fluoro-5-((4-oxo-3,4,5,6,7,8-hexahydrophthalazin-1-yl)methyl)phenyl)-3-(4-methylpiperazin-1-yl)propanamide;

2-amino-N-(2-fluoro-5-((4-oxo-3,4,5,6,7,8-hexahydrophthalazin-1-yl)methyl)phenyl)acetamide;

3-cyclohexyl-N-(2-uoro-5-((4-oxo-3,4,5,6,7,8-hexahydrophthalazin-1-yl)methyl)phenyl)propanamide;

N-(2-fluoro-5-((4-oxo-3,4,5,6,7,8-hexahydrophthalazin-1-yl)methyl)phenyl)-piperidine-3-carboxamide;

N-(2-fluoro-5-((4-oxo-3,4,5,6,7,8-hexahydrophihalazin-1-yl)methyl)phenyl)azetidine-3-carboxamide;

N-(2-fluoro-5-((4-oxo-3,4,5,6,7,8-hexahydrophthalazin-1-yl)methyl)phenyl)-2-morpholin-4-ylacetamide;

N-(2-fluoro-5-((4-oxo-3,4,5,6,7,8-hexahydrophthalazin-1-yl)methyl)phenyl)-4-(4-methoxyphenyl)-4-oxobutanamide;

N-(2-fluoro-5-((4-oxo-3,4,5,6,7,8-hexahydrophthalazin-1-yl)methyl)phenyl)-2-hydroxy-2-methylpropanamide;

N-(2-fluoro-5-((4-oxo-3,4,5,6,7,8-hexahydrophthalazin-1-yl)methyl)phenyl)-2-(2-oxopyrrolidin-1-yl)acetamide;

N-(2-fluoro-5-((4-oxo-3,4,5,6,7,8-hexahydrophthalazin-1-yl)methyl)phenyl)-5-methyl-1-phenyl-1H-pyrazole-4-carboxamide;

N-(2-fluoro-5-((4-oxo-3,4,5,6,7,8-hexahydrophthalazin-1-yl)methyl)phenyl)-5-oxohexanamide;

N-(2-fluoro-5-((4-oxo-3,4,5,6,7,8-hexahydrophihalazin-1-yl)methyl)phenyl)-3-methoxypropanamide;

N-(2-fluoro-5-((4-oxo-3,4,5,6,7,8-hexahydrophthalazin-1-yl)methyl)phenyl)-N'-phenylpentanediamide;

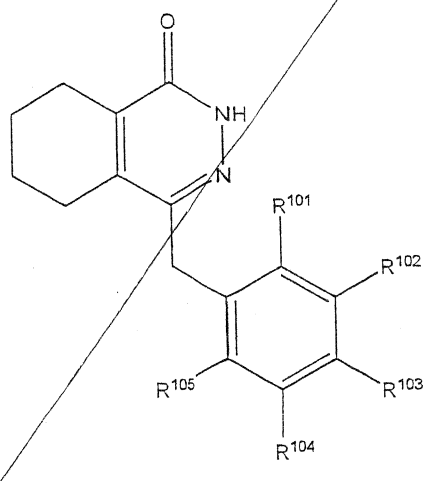
4-(4-fluoro-3-((4-pyrimidin-2-ylpiperazin-1-yl)carbonyl)benzyl)-5,6,7,8-tetrahydrophthalazin-1(2H)-one; or

4-((2-fluoro-5-((4-oxo-3,4,5,6,7,8-hexahydrophihalazin-1-yl)methyl)phenyl)amino)-4-oxobutanoic acid.

4. The compound of claim 1 which is 4-(3-(1,4-diazepan-1-ylcarbonyl)-4-fluorobenzyl)-5,6,7,8-tetrahydrophthalazin-1(2h)-one; or a pharmaceutically acceptable salt thereof.

5. The compound of claim 1 which is 4-((2-fluoro-5-((4-oxo-3,4,5,6,7,8-hexahydrophthalazin-1-yl)methyl)phenyl)amino)-4-oxobutanoic acid; or a pharmaceutically acceptable salt thereof.

6. A compound having formula (Ik),



(Ik),

or a pharmaceutically acceptable salt thereof, wherein

R^{101}, R^{104}, and R^{105} are H;

R^{103} is F;

R^{102} is R^{11} wherein R^{11} is selected from pyrrolidinyl, oxazolyl, imidazolidinyl, isothiazolidinyl, piperidinyl, piperazinyl and azepanyl, wherein R^{102} is substituted with one or two (O) substituents.

7. The compound of claim 6, wherein R^{11} is pyrrolidinyl; or a pharmaceutically acceptable salt thereof.

8. The compound of claim 6 selected from

1-(2-fluoro-5-((4-oxo-3,4,5,6,7,8-hexahydrophthalazin-1-yl)methyl)phenyl)pyrrolidine-2,5-dione;

4-(4-fluoro-3-(2-oxopyrrolidin-1-yl)benzyl)-5,6,7,8-tetrahydrophthalazin-1(2H)-one;

4-(4-fluoro-3-(2-oxo-1,3-oxazolidin-3-yl)benzyl)-5,6,7,8-tetrahydrophthalazin-1(2H)-one;

4-(4-fluoro-3-(2-oxoazepan-1-yl)benzyl)-5,6,7,8-tetrahydrophthalazin-1(2H)-one;

1-(2-fluoro-5-((4-oxo-3,4,5,6,7,8-hexahydrophthalazin-1-yl)methyl)phenyl)piperidine-2,6-dione;

4-(4-fluoro-3-(2-oxoimidazolidin-1-yl)benzyl)-5,6,7,8-tetrahydrophthalazin-1(2H)-one;

4-(4-fluoro-3-(2-oxopiperidin-1-yl)benzyl)-5,6,7,8-tetrahydrophthalazin-1(2H)-one; or

4-(4-fluoro-3-(2-oxopyrrolidin-1-yl)phenyl)-5,6,7,8-tetrahydrophthalazin-1(2H)-one; or a pharmaceutically acceptable salt thereof.

9. The compound of claim 6 which is 1-(2-fluoro-5-((4-oxo-3,4,5,6,7,8-hexahydrophthalazin-1-yl)methyl)phenyl)pyrrolidine-2,5-dione; or a pharmaceutically acceptable salt thereof.