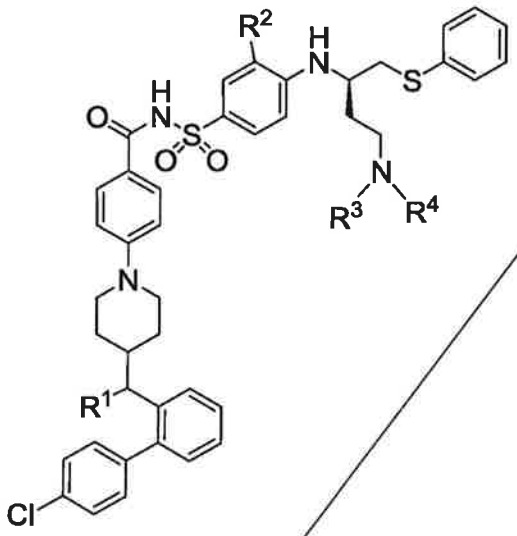
CLAIMS

What is claimed is:

1. A compound of Formula (I):



Formula (I)

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from -CN, -OR^{1a}, and -$N(R^{1a})_2$;

R^{1a} in each occurrence is independently selected from H, C_{1-4}alkyl, -$C(O)CH_2NH_2$, -$C(O)CH_2NHCH_3$, and when **R^1** is -OR^{1a}, then **R^{1a}** is additionally selected from -$P(=O)(OH)(OCH_3)$, -$P(=O)(OCH_2CH_3)_2$, -$CH_2OP(=O)(OH)[OC(CH_3)_3]$ and -$CH_2OP(=O)[OC(CH_3)_3]_2$;

R^2 is selected from -$N(O)_2$ and -$S(O)_2CF_3$;

R^3 is selected from H and C_{1-4}alkyl, wherein said C_{1-4}alkyl is optionally substituted with one or more R^{40};

R^4 is selected from H and C_{1-4}alkyl, wherein said C_{1-4}alkyl is optionally substituted with one or more R^{40};

or **R^3** and **R^4** together with the nitrogen to which they are attached form a 5- or 6-membered heterocyclic ring, wherein

i) said 5- or 6-membered heterocyclic ring is optionally substituted on carbon with one or more R^{40}; and

ii) if said 5- or 6-membered heterocyclic ring contains a nitrogen, that nitrogen is

optionally substituted with R^{40*} to form a tertiary amine;

R^{40*} is selected from C_{1-4}alkyl and $-(CH_2)_2OP(=O)(OH)_2$, wherein said C_{1-4}alkyl is optionally substituted with one or more R^a;

R^{40} in each occurrence is selected from $-OR^{40a}$, $-N(R^{40a})_2$, $-CH_2OR^{5a}$, $-CH_2N(R^{5a})_2$, $-OP(=O)(OH)_2$, and $-OP(=O)[OC(CH_3)_3]_2$;

R^{5a} in each occurrence is selected from H and C_{1-3}alkyl;

R^{40a} in each occurrence is independently selected from H and C_{1-4}alkyl; and

R^a is selected from halo, $-OR^m$, and $-N(R^m)_2$; and

R^m in each occurrence is independently selected from H and C_{1-4}alkyl.

2. A compound of Formula (I), or a pharmaceutically acceptable salt thereof, as claimed in claim 1, wherein,

R^1 is –OH;

R^2 is $-S(O)_2CF_3$;

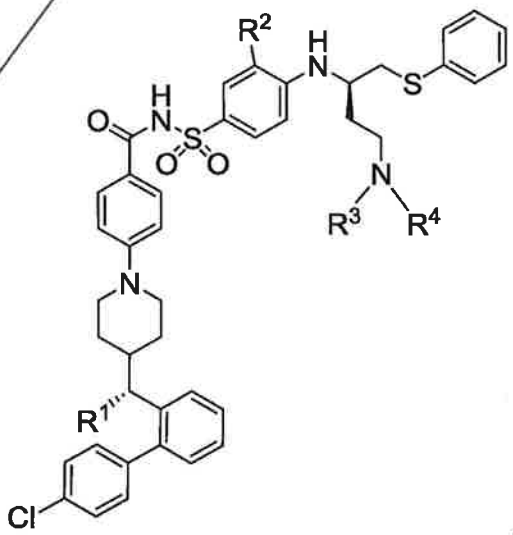
R^3 is C_{1-2}alkyl, wherein said C_{1-2}alkyl is optionally substituted with one or more R^{40};

R^4 is C_{1-2}alkyl, wherein said C_{1-2}alkyl is optionally substituted with one or more R^{40};

R^{40} in each occurrence is selected from $-OR^{40a}$ and $-OP(=O)(OH)_2$; and

R^{40a} is H.

3. The compound of claim 1 or 2 wherein the compound has the following stereochemistry:



4. A compound of Formula (I), or a pharmaceutically acceptable salt thereof, as claimed in claim 3, wherein the compound is 4-(4-((*R*)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)-*N*-(4-((*R*)-4-((2-hydroxyethyl)(methyl)amino)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)benzamide.

5. A compound of Formula (I), or a pharmaceutically acceptable salt thereof, as claimed in claim 3, wherein the compound is 2-(((*R*)-3-(4-(*N*-(4-(4-((*R*)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)benzoyl)sulfamoyl)-2-(trifluoromethylsulfonyl)phenylamino)-4-(phenylthio)butyl)(methyl)amino)ethyl dihydrogen phosphate.

6. A compound of Formula (I), or a pharmaceutically acceptable salt thereof, as claimed in claim 3, wherein the compound is 4-(4-((R)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)-N-(4-((R)-4-(ethyl(2-hydroxyethyl)amino)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)benzamide.

7. A compound of Formula (I), or a pharmaceutically acceptable salt thereof, as claimed in claim 3, wherein the compound is 2-(((*R*)-3-(4-(*N*-(4-(4-((*R*)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)benzoyl)sulfamoyl)-2-(trifluoromethylsulfonyl)phenylamino)-4-(phenylthio)butyl)(ethyl)amino)ethyl dihydrogen phosphate.

8. A compound of Formula (I), or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 7, for use as a medicament.

9. The use of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 7, in the manufacture of a medicament for use in the production of an anti-proliferation and/or pro-apoptotic effect in a warm-blooded animal.

10. The use according to claim 9 for use in the treatment of bladder cancer, breast cancer, colon cancer, ovarian cancer, AML, diffuse large B-cell lymphoma (DLBCL), CLL; small cell lung cancer (SCLC), non-small cell lung cancer (NSCLC), including the non-squamous and squamous subtypes, pancreatic cancer, prostate cancer, non-Hodgkin's lymphomas, Follicular Lymphoma (FL), Mantle Cell Lymphoma (MCL), Mantle Zone Lymphoma (MZL), Hairy Cell Leukemia (HCL), and Peripheral T-cell Lymphoma (PTCL).

11. A method for producing an anti-proliferation and/or pro-apoptotic effect in a warm-blooded animal, said method comprising administering to said animal an effective amount of a compound of Formula (I), as claimed in any one of claims 1 to 7, or a pharmaceutically acceptable salt thereof.

12. The method according to claim 11 for treating bladder cancer, breast cancer, colon cancer, ovarian cancer, AML, diffuse large B-cell lymphoma (DLBCL), CLL; small cell lung cancer (SCLC), non-small cell lung cancer (NSCLC), including the non-squamous and squamous subtypes, pancreatic cancer, prostate cancer, non-Hodgkin's lymphomas, Follicular Lymphoma (FL), Mantle Cell Lymphoma (MCL), Mantle Zone Lymphoma (MZL), Hairy Cell Leukemia (HCL), and Peripheral T-cell Lymphoma (PTCL), in a warm-blooded animal, said method comprising administering to said animal an effective amount of a compound of Formula (I), as claimed in any one of claims 1 to 7, or a pharmaceutically acceptable salt thereof.

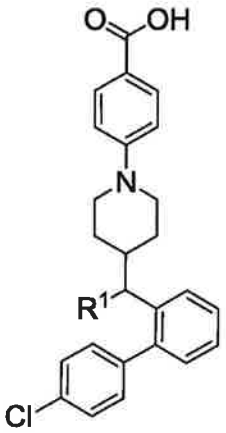
13. A compound of Formula (I), or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 7, for use in producing an anti-proliferation and/or pro-apoptotic effect in a warm-blooded animal.

14. The compound of Formula (I) according to claim 13, for use in treating bladder cancer, breast cancer, colon cancer, ovarian cancer, AML, diffuse large B-cell lymphoma (DLBCL), CLL; small cell lung cancer (SCLC), non-small cell lung cancer (NSCLC), including the non-squamous and squamous subtypes, pancreatic cancer, prostate cancer, non-Hodgkin's lymphomas, Follicular Lymphoma (FL), Mantle Cell Lymphoma (MCL), Mantle Zone Lymphoma (MZL), Hairy Cell Leukemia (HCL), and Peripheral T-cell Lymphoma (PTCL), in a warm-blooded animal.

15. A pharmaceutical composition comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 7, and at least one pharmaceutically acceptable carrier, diluent, or excipient.

16. A process for preparing a compound of Formula (I), or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 7, said process comprising:

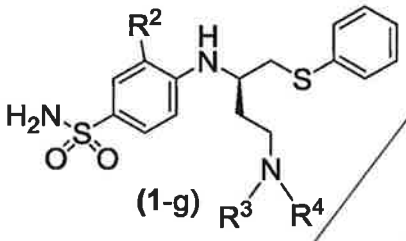
(i) providing a carboxylic acid compound of formula (1-f):



(1-f)

;

(ii) providing a sulfonamide compound of formula (1-g):

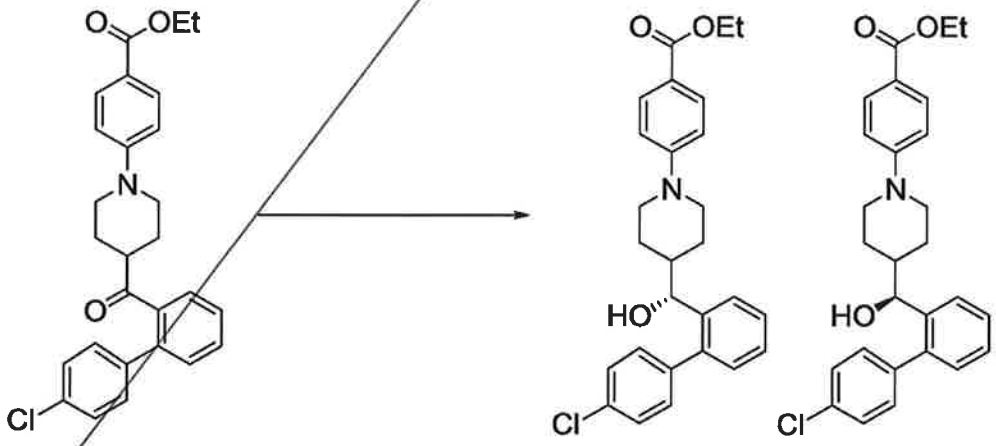


(1-g)

; and

(iii) coupling the carboxylic acid compound of formula (1-f) with the sulfonamide compound of formula (1-g).

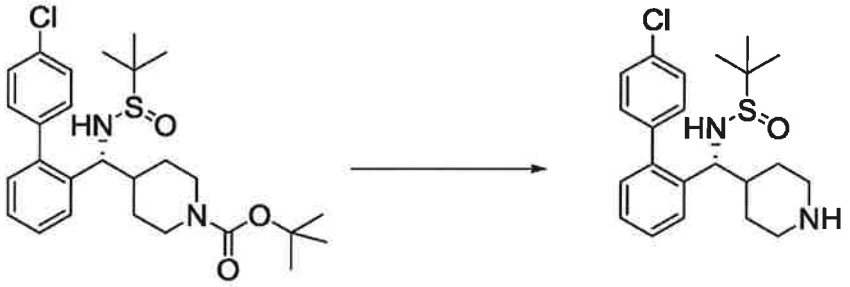
17. A process for preparing a compound of formula (2-g) and (2-h), said process comprising:



3-c 2-g 2-h

performing enantioselective reduction to a compound of formula (3-c).

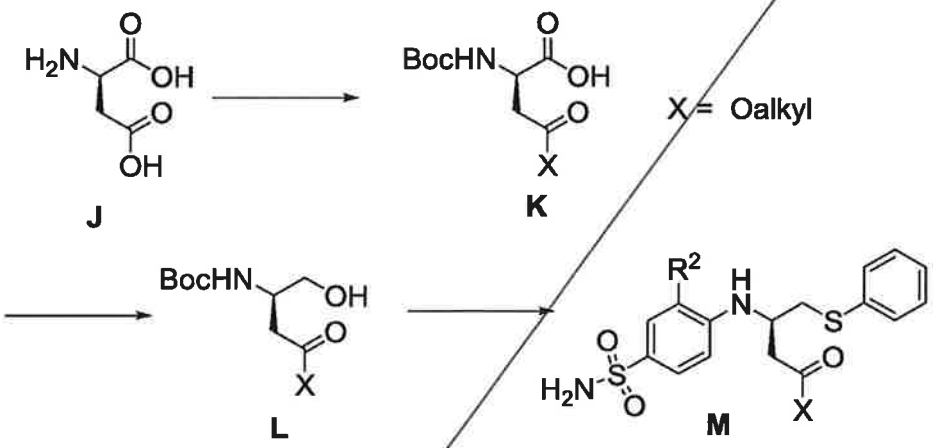
18. A process for preparing a compound of formula (5-f), said process comprising:



(5-e) (5-f)

selectively deprotecting a compound of formula (5-e).

19. A process for preparing a compound of formula (M), said process comprising:



(i) converting a compound of formula (J) to a compound of formula (K);

(ii) reducing a compound of formula (K) to form a compound of formula (L);

(iii) performing a substitution reaction on a compound of formula (L) to form a corresponding thioether;

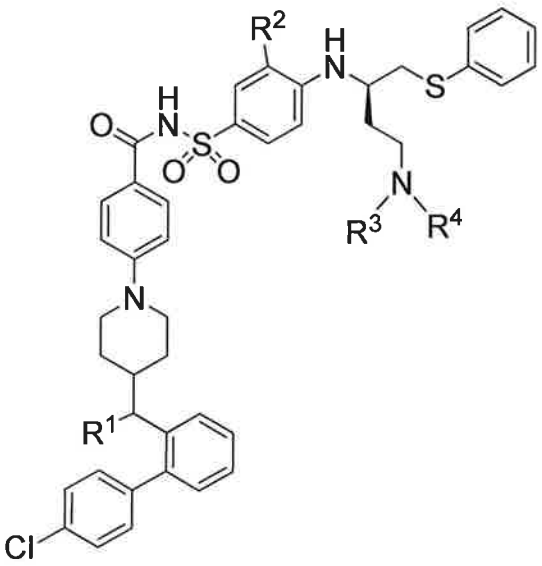
(iv) performing a deprotection on the thioether to form a corresponding amine; and

(v) performing an aromatic substitution reaction on the corresponding amine to form a compound of formula (M).

CLAIMS

What is claimed is:

1. A compound of Formula (I):



Formula (I)

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from -CN, -OR^{1a}, and -$N(R^{1a})_2$;

R^{1a} in each occurrence is independently selected from H, C_{1-4}alkyl, -$C(O)CH_2NH_2$, -$C(O)CH_2NHCH_3$, and when **R^1** is -OR^{1a}, then **R^{1a}** is additionally selected from -$P(=O)(OH)(OCH_3)$, -$P(=O)(OCH_2CH_3)_2$, -$CH_2OP(=O)(OH)[OC(CH_3)_3]$ and -$CH_2OP(=O)[OC(CH_3)_3]_2$;

R^2 is selected from -$N(O)_2$ and -$S(O)_2CF_3$;

R^3 is selected from H and C_{1-4}alkyl, wherein said C_{1-4}alkyl is optionally substituted with one or more R^{40};

R^4 is selected from H and C_{1-4}alkyl, wherein said C_{1-4}alkyl is optionally substituted with one or more R^{40};

or **R^3** and **R^4** together with the nitrogen to which they are attached form a 5- or 6-membered heterocyclic ring, wherein

i) said 5- or 6-membered heterocyclic ring is optionally substituted on carbon with one or more R^{40}; and

ii) if said 5- or 6-membered heterocyclic ring contains a nitrogen, that nitrogen is optionally substituted with R^{40*} to form a tertiary amine;

R^{40*} is selected from C_{1-4}alkyl and $-(CH_2)_2OP(=O)(OH)_2$, wherein said C_{1-4}alkyl is optionally substituted with one or more R^a;

R^{40} in each occurrence is selected from $-OR^{40a}$, $-N(R^{40a})_2$, $-CH_2OR^{5a}$, $-CH_2N(R^{5a})_2$, $-OP(=O)(OH)_2$, and $-OP(=O)[OC(CH_3)_3]_2$;

R^{5a} in each occurrence is selected from H and C_{1-3}alkyl;

R^{40a} in each occurrence is independently selected from H and C_{1-4}alkyl; and

R^a is selected from halo, $-OR^m$, and $-N(R^m)_2$; and

R^m in each occurrence is independently selected from H and C_{1-4}alkyl.

2. The compound of Formula (I), or a pharmaceutically acceptable salt thereof, as claimed in claim 1, wherein,

R^1 is –OH;

R^2 is $-S(O)_2CF_3$;

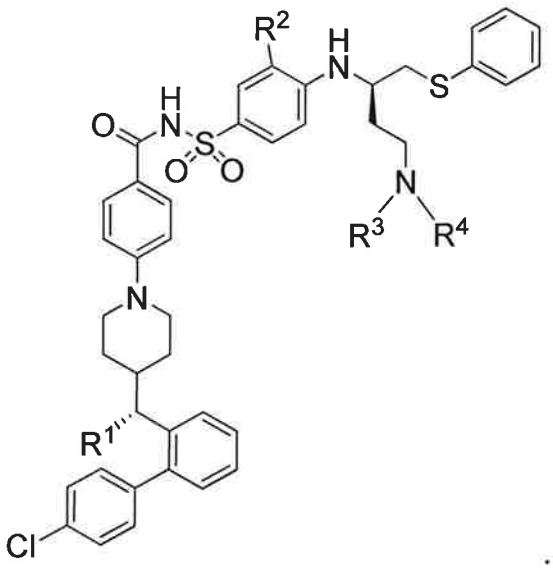
R^3 is C_{1-2}alkyl, wherein said C_{1-2}alkyl is optionally substituted with one or more R^{40};

R^4 is C_{1-2}alkyl, wherein said C_{1-2}alkyl is optionally substituted with one or more R^{40};

R^{40} in each occurrence is selected from $-OR^{40a}$ and $-OP(=O)(OH)_2$; and

R^{40a} is H.

3. The compound of claim 1 wherein the compound has the following stereochemistry:



4. The compound of Formula (I), or a pharmaceutically acceptable salt thereof, as claimed in claim 3, wherein the compound is 4-(4-((*R*)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)-*N*-(4-((*R*)-4-((2-hydroxyethyl)(methyl)amino)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)benzamide.

5. The compound of Formula (I), or a pharmaceutically acceptable salt thereof, as claimed in claim 3, wherein the compound is 2-(((*R*)-3-(4-(*N*-(4-(4-((*R*)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)benzoyl)sulfamoyl)-2-(trifluoromethylsulfonyl)phenylamino)-4-(phenylthio)butyl)(methyl)amino)ethyl dihydrogen phosphate.

6. The compound of Formula (I), or a pharmaceutically acceptable salt thereof, as claimed in claim 3, wherein the compound is 4-(4-((R)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)-N-(4-((R)-4-(ethyl(2-hydroxyethyl)amino)-1-(phenylthio)butan-2-ylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)benzamide.

7. The compound of Formula (I), or a pharmaceutically acceptable salt thereof, as claimed in claim 3, wherein the compound is 2-(((*R*)-3-(4-(*N*-(4-(4-((*R*)-(4'-chlorobiphenyl-2-yl)(hydroxy)methyl)piperidin-1-yl)benzoyl)sulfamoyl)-2-(trifluoromethylsulfonyl)phenylamino)-4-(phenylthio)butyl)(ethyl)amino)ethyl dihydrogen phosphate.

8. A pharmaceutical composition comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof, as claimed in claim 1, and at least one pharmaceutically acceptable carrier, diluent, or excipient.