CLAIMS:

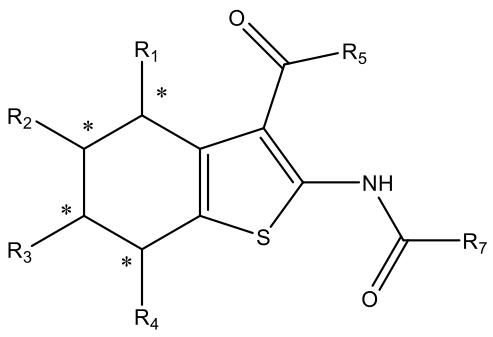
1. Use of a ROR inverse agonist, its pharmaceutically acceptable salt or stereoisomers thereof for reducing neutrophils to lymphocytes ratio (NLR) in the peripheral blood of a patient suffering from a disease or a condition characterized by an elevated neutrophil to lymphocyte ratio.

2. Use of a ROR inverse agonist, its pharmaceutically acceptable salt or stereoisomers thereof for preventing or treating a disease or a condition characterized by an elevated neutrophil to lymphocyte ratio in a patient in need thereof, which comprises administering to said patient a therapeutically effective amount of a ROR inverse agonist, its pharmaceutically acceptable salt or stereoisomers thereof.

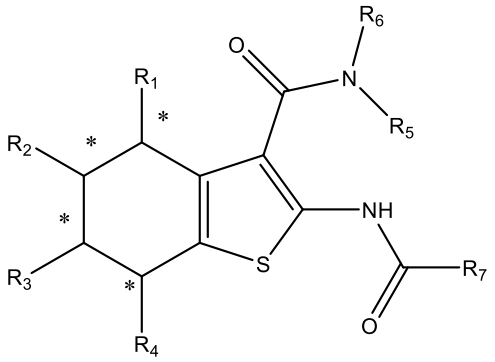
3. The use of claim 1 or claim 2, wherein said neutrophils express nuclear receptors (RORs) alpha (RORα or RORA) or gamma (RORC, RORγ or RORγt).

4. The use of claim 3, wherein the RORs mediated disease or autoimmune disease. is HIV, celiac disease, diabetes mellitus type 1, Graves' disease, inflammatory bowel disease, psoriasis, rheumatoid arthritis, systemic lupus erythematosus, asthma, dermatitis, fatty liver disease, Crohn’s disease, cardiovascular disease, inflammatory diseases, neurological disorder, multiple sclerosis, acute respiratory distress syndrome, arteriosclerosis, cancer stemness, cancer stem cells, metastatic cancer, prostate cancer, breast cancer, ovarian cancer, multiple myeloma, brain cancer, glioma, lung cancer, salivary cancer, stomach cancer, thymic epithelial cancer, thyroid cancer, leukemia, melanoma, lymphoma, gastric cancer, pancreatic cancer, kidney cancer, bladder cancer, colon cancer, gastroesophageal adenocarcinoma or liver cancer.

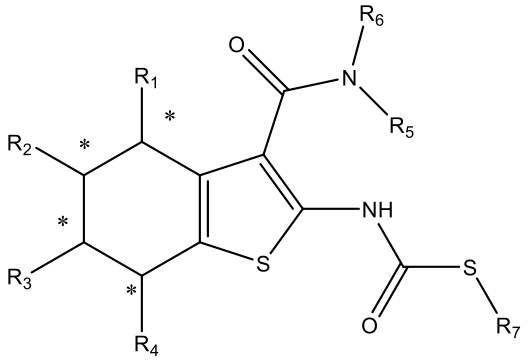
5. The use of any one of claims 1 to 4, wherein the inverse agonist of RORs is a compound of Formula (I), (II), (III), or (IV), a pharmaceutically acceptable salts thereof, or stereoisomers thereof:



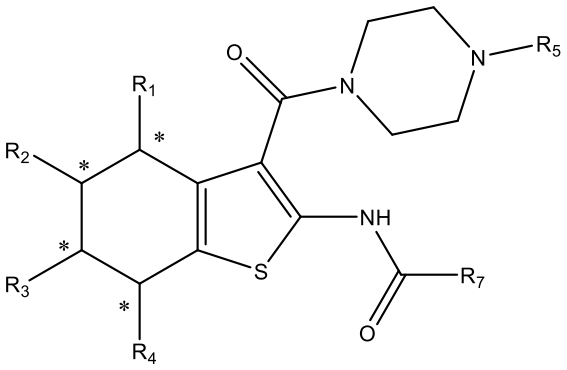
(I)



(II)



(III)



(IV)

wherein,

R_1, R_2, R_3, and/or R_4 group(s) is/are H, halogen, NO_2, 1-6 alkoxy, OH, NH_2, 1-6 alkyl, 1-6 alkenyl, 1-6 haloalkyl, N-dialkyl, haloalkoxy, 1-6 hydroxyalkyl, and/or -CO_2(1-6 alkyl);

R_5 is a substituted or unsubstituted five or six membered saturated or unsaturated heterocycle, aryl, alkylarene, halo aryl, ring substituted alkylarene, ring substituted alkylhexane, ring substituted alkylcyclopentane, haloaryl, benzene, phenyl, benzyl, pyridine, pyrimidine, pyridine, imidazole, diazole, triazole, thiadiazole, imidazolidine,

thizolidine, pyrrolidine, piperazine, piperidine, pyridazine, pyrazine, triazine, 1H pyrrole, 2H pyrrole, pyrroline, pyrazolidine, pyrazoline, thiazole, isothiazole, isoxazole, haloalkyl, cyanoalkyl, methylpyrimidine, toluene, methylpyridine, methylimidazole, methyldiazole, methyltriazole, methylthiadiazole, methylimidazolidine, methylthizolidine, methylpyrrolidine, methylpiperazine, methylpiperidine, methylpyridazine, methylpyrazine, methyltriazine, methylpyrrole, methylpyrroline, methylpyrazolidine, methylpyrazoline, methylthiazole, methylisothiazole, methylisoxazole, or arylalkyl.

R_6 is H, 1-6 alkyl, or may form a five or six ring structure with R_5; and

R_7 is a substituted or unsubstituted five or six membered saturated or unsaturated heterocycle, ring substituted alkylarene, ring substituted alkylhexane, ring substituted alkylcyclopentane, substituted haloaryl, substituted benzene, substituted phenyl, benzyl, pyrimidine, pyridine, imidazole, diazole, triazole, thiadiazole, imidazolidine, thizolidine, pyrrolidine, piperazine, aryl, halo aryl, alkylarene, piperidine, pyridazine, pyrazine, triazine, 1H pyrrole, 2H pyrrole, pyrroline, pyrazolidine, pyrazoline, thiazole, isothiazole, isoxazole, cyanoalkyl, methylpyrimidine, toluene, methylpyridine, methylimidazole, methyldiazole, methyltriazole, methylthiadiazole, methylimidazolidine, methylthizolidine, methylpyrrolidine, methylpiperazine, methylpiperidine, methylpyridazine, methylpyrazine, methyltriazine, methylpyrrole, methylpyrroline, methylpyrazolidine, methylpyrazoline, methylthiazole, methylisothiazole, methylisoxazole, or arylalkyl.

6. The use of any one of claims 1 to 5, wherein the inverse agonist of RORs is a compound or pharmaceutically acceptable salts thereof, or stereoisomers thereof selected from the group consisting of:

N-(3-(4-benzylpiperazine-1-carbonyl)-4,5,6,7-tetrahydro-benzo[b]thiophen-2-yl)-2-fluorobenzamide;

N-(3-(benzylcarbamoyl)-4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl)-5-chloro-2-(methylthio)pyrimidine-4-carboxamide;

5-chloro-N-(3-{[(1,1-dioxidotetrahydro-3-thienyl)amino]-carbonyl}-6-methyl-4,5,6,7-tetrahydro-1-benzothien-2-yl)-2-(methylthio)-4-pyrimidine-carboxamide;

N-(6-ethyl-3-{[(2-methylphenyl)amino]carbonyl}-4,5,6,7-tetrahydro-1-benzothien-2-yl)-1-methyl-1H-pyrazole-5-carboxamide;

N-{6-tert-butyl-3-[(4-methyl-1-piperazinyl)carbonyl]-4,5,6,7-tetrahydro-1-benzothien-2-yl}-2-fluorobenzamide;

2-fluoro-N-{6-methyl-3-[(4-methyl-1-piperazinyl)carbonyl]-4,5,6,7-tetrahydro-1-benzothien-2-yl}benzamide;

N-benzyl-2-[(trifluoroacetyl)amino]-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxamide;

N-benzyl-2-({[(4-methyl-2-pyrimidinyl)thio]acetyl}amino)-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxamide;

N-benzyl-2-[(1-piperidinylacetyl)amino]-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxamide;

N-benzyl-2-{[(4-methyl-1-piperazinyl)acetyl]amino}-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxamide;

N-benzyl-2-{[(4-methyl-1-piperidinyl)acetyl]amino}-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxamide;

N-(3-(2-methylpyrrolidine-1-carbonyl)-4,5,6,7-tetrahydro-benzo[b]thiophen-2-yl)nicotinamide;

N-(3-((2R,4R)-2,4-dimethylpiperidine-1-carbonyl)-4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl)nicotinamide;

N-(3-(((1r,4r)-4-hydroxycyclohexyl)carbamoyl)-4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl)nicotinamide;

N-(3-(3-ethylpyrrolidine-1-carbonyl)-4,5,6,7-tetrahydro-benzo[b]thiophen-2-yl)nicotinamide;

N-benzyl-2-(2-((1-methyl-1H-imidazol-2-yl)thio)acetamido)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide;

N-(3-(3-(hydroxymethyl)pyrrolidine-1-carbonyl)-4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl)nicotinamide;

N-(6,6-dimethyl-3-(morpholine-4-carbonyl)-4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl)pyrazine-2-carboxamide;

N-(3-(((1-methyl-1H-1,2,4-triazol-3-yl)methyl)carbamoyl)-4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl)nicotinamide;

(S)-N-(3-((1-cyanoethyl)carbamoyl)-4,5,6,7-tetrahydro-benzo[b]thiophen-2-yl)nicotinamide;

N-(3-((piperidin-4-ylmethyl)carbamoyl)-4,5,6,7-tetrahydro-benzo[b]thiophen-2-yl)nicotinamide;

N-(3-benzoyl-4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl)pyrazine-2-carboxamide;

N-(3-benzoyl-4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl)-5-methyl-2-(methylsulfonyl)pyrimidine-4-carboxamide;

N-(4-ethylphenyl)-3-(hydroxymethyl)-N-isobutyl-4-((tetrahydro-2H-pyran-4-yl)methoxy)benzenesulfonamide;

(7S)-N-{[5-(Ethylsulfonyl)-2-pyridinyl]methyl}-7-isopropyl-6-{[trans-4-(trifluoromethyl)cyclohexyl]methyl}-6,7-dihydro-5H-pyrrolo[3,4-b]pyridine-3-carboxamide;

N-{3-[(3-methylbut-2-en-1-yl){methyl[trans-4-(pyridin-4-yl)cyclohexyl]carbamoyl}amino]phenyl}benzamide;

2-(1-(2,4-dichloro-3-((7-chloro-5-(trifluoromethyl)-1H-indol-1-yl)methyl)benzoyl)piperidin-4-yl)acetic acid;

(S)-2-(4-cyclopropyl-6-methylpyrimidin-5-yl)-8-(1-cyclopropylethyl)-6-(((5-(methylsulfonyl)pyridin-2-yl)methyl)amino)pteridin-7(8H)-one;

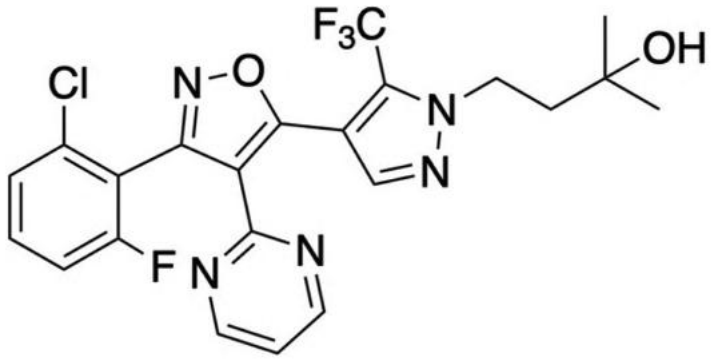
(S)-6-(2,6-dimethylpyrimidin-4-yl)-N-(4-(ethylsulfonyl)benzyl)-6-methyl-5-oxo-5,6,7,8-tetrahydroquinoline-2-carboxamide;

2-(2-((S)-(3,5-dimethylisoxazol-4-yl)(hydroxy)methyl)benzofuran-5-yl)-N-((S)-(2,4-dimethylphenyl)(phenyl)methyl)acetamide;

N-(4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)phenyl)-N-(2,2,2-trifluoroethyl)benzenesulfonamide;

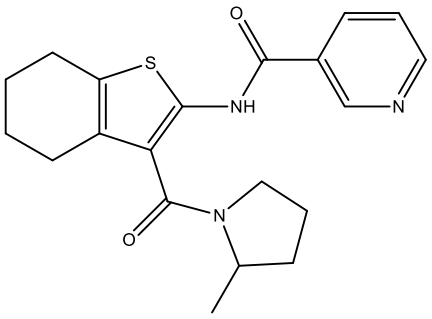
1,1,1,3,3,3-hexafluoro-2-(2-fluoro-4'-((4-(pyridin-4-ylmethyl)piperazin-1-yl)methyl)-[1,1'-biphenyl]-4-yl)propan-2-ol;

(1R,3aS,5aR,5bR,7aR,9S,11aR,11bR,13aR,13bR)-N-(3-(dimethylamino)propyl)-9-hydroxy-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)icosahydro-3aH-cyclopenta[a]chrysene-3a-carboxamide; and



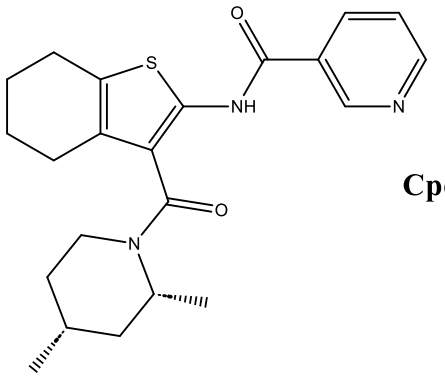
.

7. The use of claim 6, wherein the inverse agonist of RORs is a compound or pharmaceutically acceptable salts thereof, or stereoisomers thereof selected from the group consisting of:



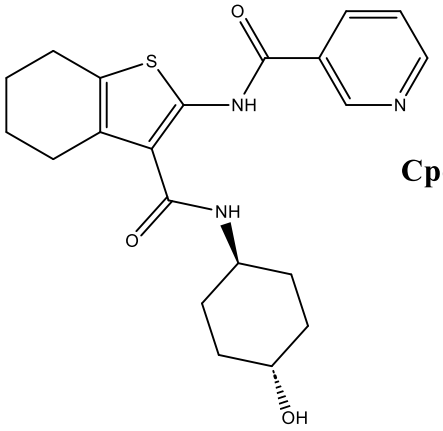
Cpd 12

N-(3-(2-methylpyrrolidine-1-carbonyl)-4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl)nicotinamide



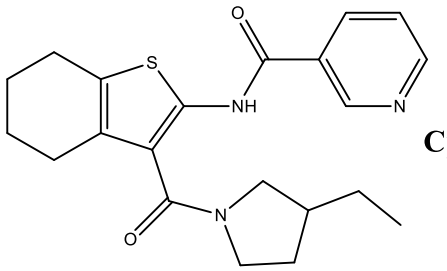
Cpd 13

N-(3-((2*R*,4*R*)-2,4-dimethylpiperidine-1-carbonyl)-4,5,6,7-tetrahydrobenzo[*b*]thiophen-2-yl)nicotinamide



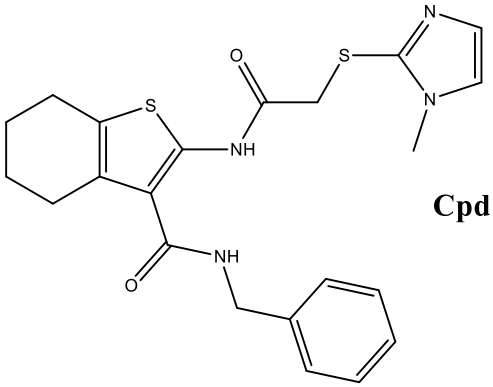
Cpd 14

N-(3-(((1*r*,4*r*)-4-hydroxycyclohexyl)carbamoyl)-4,5,6,7-tetrahydrobenzo[*b*]thiophen-2-yl)nicotinamide



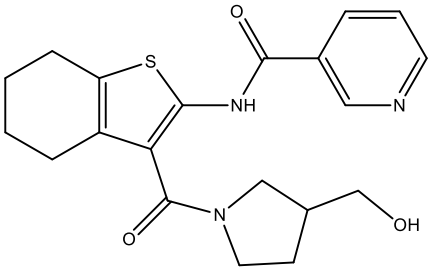
Cpd 15

N-(3-(3-ethylpyrrolidine-1-carbonyl)-4,5,6,7-tetrahydrobenzo[*b*]thiophen-2-yl)nicotinamide



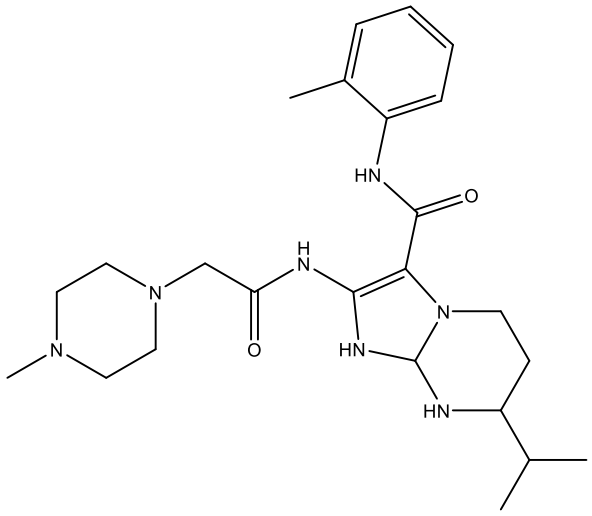
Cpd 16

N-benzyl-2-(2-((1-methyl-1*H*-imidazol-2-yl)thio)acetamido)-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide

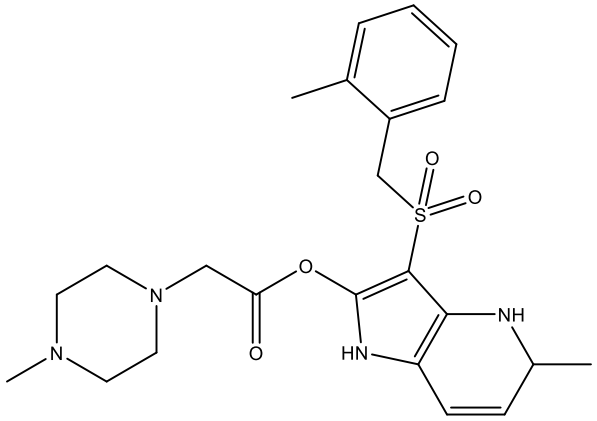


Cpd 17

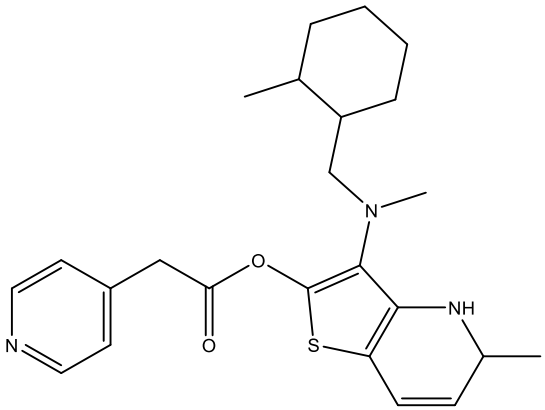
N-(3-(3-(hydroxymethyl)pyrrolidine-1-carbonyl)-4,5,6,7-tetrahydrobenzo[*b*]thiophen-2-yl)nicotinamide



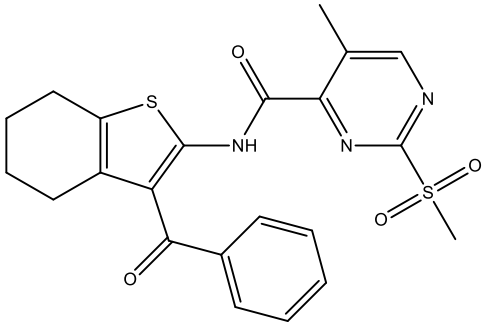
7-isopropyl-2-(2-(4-methylpiperazin-1-yl)acetamido)-*N*-(*o*-tolyl)-1,5,6,7,8,8a-hexahydroimidazo[1,2-*a*]pyrimidine-3-carboxamide



5-methyl-3-((2-methylbenzyl)sulfonyl)-4,5-dihydro-1*H*-pyrrolo[3,2-*b*]pyridin-2-yl 2-(4-methylpiperazin-1-yl)acetate

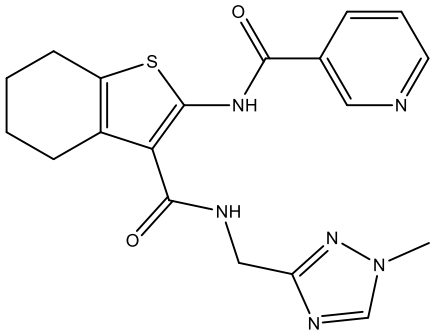


5-methyl-3-(methyl((2-methylcyclohexyl)methyl)amino)-4,5-dihydrothieno[3,2-*b*]pyridin-2-yl 2-(pyridin-4-yl)acetate



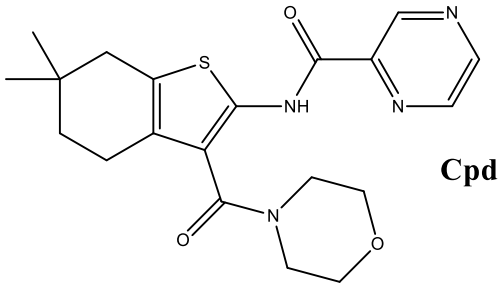
Cpd 23

N-(3-benzoyl-4,5,6,7-tetrahydrobenzo[*b*]thiophen-2-yl)-5-methyl-2-(methylsulfonyl)pyrimidine-4-carboxamide



Cpd 19

N-(3-(((1-methyl-1*H*-1,2,4-triazol-3-yl)methyl)carbamoyl)-4,5,6,7-tetrahydrobenzo[*b*]thiophen-2-yl)nicotinamide



Cpd 18

N-(6,6-dimethyl-3-(morpholine-4-carbonyl)-4,5,6,7-tetrahydrobenzo[*b*]thiophen-2-yl)pyrazine-2-carboxamide

8. The use of any one of claims 1 to 7, further comprising one or more additional compounds selected from the group consisting of :

(a) a cytotoxic agent selected from the group consisting of: taxol, cytochalasin B, gramicidin D, ethidium bromide, emetine, mitomycin, etoposide, tenoposide, vincristine, vinblastine, colchicin, doxorubicin, daunorubicin, dihydroxy anthracin dione, mitoxantrone, mithramycin, actinomycin D, 1-dehydrotestosterone, glucocorticoids, procaine, tetracaine, lidocaine, propranolol, puromycin, Gemcitabine, Paclitaxel and Folfirinox, or is a combination thereof;

(b) an antimetabolite selected from the group consisting of methotrexate, 6-mercaptopurine, 6-thioguanine, cytarabine, and 5-fluorouracil decarbazine, or is a combination thereof;

(c) an alkylating agent selected from the group consisting of mechlorethamine, thioepa chlorambucil, melphalan, carmustine (BSNU), lomustine (CCNU), cyclothosphamide, busulfan, dibromomannitol, streptozotocin, mitomycin C, and cis-dichlorodiamine platinum (II) (DDP) cisplatin, or is a combination thereof;

(d) an anthracycline consisting of daunorubicin, doxorubicin, or a combination thereof;

(e) an antibiotic consisting of dactinomycin, bleomycin, mithramycin, anthramycin (AMC), or a combination thereof;

(f) an anti-mitotic agent consisting of vincristine, vinblastine, or a combination thereof;

(g) an hormone therapy consisting of imatinib, trastuzumab, or a combination thereof;

(h) a signal transduction inhibitor consisting of a siRNA, a shRNA, an antisense oligonucleotide, an HDAC inhibitor, or a combination thereof;

(i) a gene expression modulator consisting of an Immune Checkpoint Inhibitors, a monoclonal antibody, a chimeric antigen receptors (CARs) -T-Cell, or a combination thereof;

(j) an apoptosis inducer;

(k) an angiogenesis inhibitor

(l) an immunotherapy agent

(m) an Immune Checkpoint Inhibitor

and

a pharmaceutically acceptable carrier.

9. The use of any one of claims 11 to 20, wherein said hormone therapy is an luteinizing hormone-releasing hormone (LHRH) antagonist, said apoptosis inducers is a recombinant human TNF-related apoptosis-inducing ligand (TRAIL), and/or said angiogenesis inhibitors is sorafenib, sunitinib, pazopanib, everolimus or a combination thereof.

10. A whole blood diagnostic test to monitor a patient's response to a treatment and help predict patient outcomes; which comprises reagents for measuring total neutrophils, total lymphocytes and ratio of total neutrophils versus total lymphocytes in a blood sample before and after treatment with a ROR inverse agonist according to the use in any one of claims 1 to 9; wherein an increase in the ratio is indicative of a poor response to the treatment.

11. A whole blood diagnostic test to monitor a patient's response to treatment and help predict patient outcomes; which comprises measuring RORC+ neutrophils, total lymphocytes and ratio of ROC+ neutrophils versus total lymphocytes in a blood sample before and after treatment with a ROR inverse agonist according to the use in any one of claims 1 to 9; wherein an increase in the ratio is indicative of a poor response to the treatment.

12. A whole blood diagnostic test to monitor a patient's response to treatment and help predict patient outcomes; which comprises measuring RORC+ neutrophils and FOXP3+ Treg lymphocytes and ratio of RORC+ neutrophils versus FOXP3+ Treg lymphocytes in a blood sample before and after treatment with a ROR inverse agonist according to the

use in any one of claims 1 to 11; wherein an increase in the ratio is indicative of a poor response to the treatment.

13. A whole blood diagnostic test to monitor a patient's response to treatment and help predict patient outcomes; which comprises measuring RORC+ neutrophils and CD8+ Treg lymphocytes and ratio of RORC+ neutrophils versus CD8+ Treg lymphocytes in a blood sample before and after treatment with a ROR inverse agonist according to the use in any one of claims 1 to 11; wherein increased in the ratio is indicative of a poor response to the treatment.

14. A whole blood diagnostic test to monitor a patient's response to treatment and help predict patient outcomes; which comprises measuring ratio of RORC+ neutrophils versus FOXP3+ Treg lymphocytes, and ratio of RORC+ neutrophils versus CD8+ Treg lymphocytes in a blood sample before and after treatment with a ROR inverse agonist according to the use in any one of claims 1 to 11; wherein an increase in the ratio is indicative of a poor response to the treatment.

15. A whole blood diagnostic test to monitor a patient's response to treatment and help predict patient outcomes; which comprises measuring ratio of RORC+ neutrophils, to ratio of FOXP3+ Treg lymphocytes to CD8+ Treg lymphocytes in a blood sample before and after treatment with a ROR inverse agonist according to the use in any one of claims 1 to 11; wherein an increase in the ratio is indicative of a poor response to the treatment.