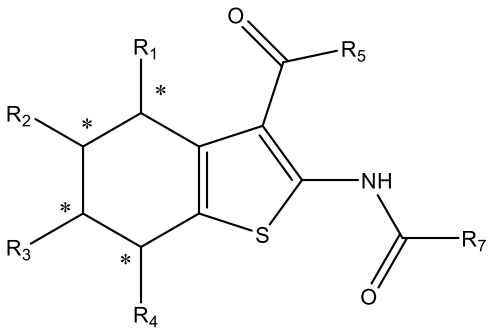
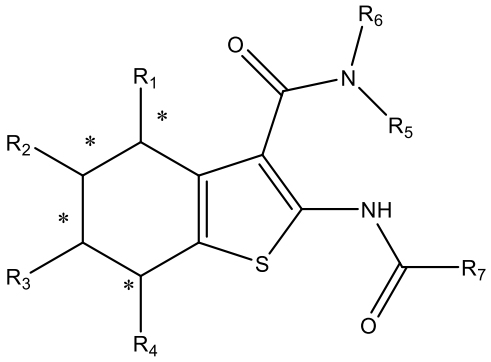
CLAIMS:

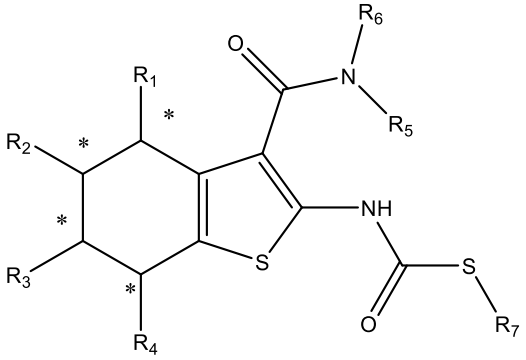
1. A pharmaceutical composition for modulating RORs and/or controlling autoimmune diseases and antibody mediated rejection in a patient comprising at least one compound of Formula (I), (II), (III), or (IV) pharmaceutically acceptable salts thereof, or stereoisomers thereof selected from the group consisting of:



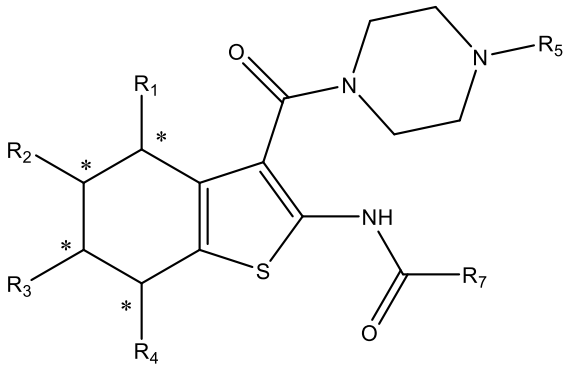
(I)



(II)



(III)



(IV)

wherein,

R_1, R_2, R_3, or R_4 groups 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,or -CO_2(1-6 alkyl);

R_5 is a five or six membered saturated or unsaturated heterocycle, -NH-aryl, alkylarene, -NH-aryl, alkylarene, alkylcyclohexane, alkylcyclopentane, -NH-phenyl, -NH-phenyl, benzyl, , pyrimidine, imidazole, diazole, triazole, thiadiazole, imidazolidine, thiazolidine, pyrrolidine, piperazine, piperidine, pyridazine, pyrazine, triazine, 1H pyrrole, 2H pyrrole, pyrroline, pyrazolidine, pyrazoline, thiazole, isothiazole, isoxazole, haloalkyl, cyanoalkyl, methylpyrimidine, methylpyridine, methylimidazole, methyldiazole, methyltriazole, methylthiadiazole, methylimidazolidine, methylthiazolidine, methylpyrrolidine, methylpiperazine, methylpiperidine, methylpyridazine, methylpyrazine, methyltriazine, methylpyrrole, methylpyrroline, methylpyrazolidine, methylpyrazoline, methylthiazole, methylisothiazole, methylisoxazole, morpholine, -NH-arylalkyl or cyclohexane;

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

R_7 is a five or six membered saturated or unsaturated heterocycle, alkylarene, alkylcyclohexane, alkylcyclopentane, fluoroaryl, fluorophenyl, benzyl, pyrimidine, pyridine, imidazole, diazole, triazole, thiadiazole, imidazolidine, thiazolidine, pyrrolidine, piperazine, fluoroaryl, alkylarene, piperidine, pyridazine, pyrazine, triazine, 1H pyrrole, 2H pyrrole, pyrroline, pyrazolidine, pyrazoline, thiazole, isothiazole, isoxazole, methylpyrimidine, toluene, methylpyridine, methylimidazole, methyldiazole, methyltriazole, methylthiadiazole, methylimidazolidine, methylthiazolidine, methylpyrrolidine, methylpiperazine, methylpiperidine, methylpyridazine, methylpyrazine, methyltriazine, methylpyrrole, methylpyrroline, methylpyrazolidine, methylpyrazoline, methylthiazole, methylisothiazole, methylisoxazole, arylalkyl, trifluoromethyl, or pyrazole;

with the proviso that the compound is not a compound of Formula (II) wherein R_1, R_3, R_4 and R_6 are H, R_5 is 1,1-dioxidotetrahydro-3-thienyl, and R_7 is 5-chloro-2-(methylthio)pyrimidin-4-yl; and

with the proviso that the compound is not a compound of Formula (II), pharmaceutically acceptable salts thereof, or stereoisomers thereof, wherein R5 is a six membered unsaturated heterocycle, and R7 is fluorophenyl.

or

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;

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; and

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

and a pharmaceutically acceptable carrier;

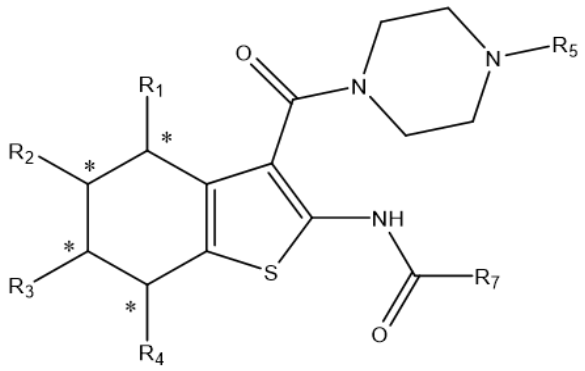
wherein the compound inhibits the activity of RORs.

2. The pharmaceutical composition according to claim 1, wherein modulating RORs is for preventing or treating a RORs mediated disease or autoimmune disease in a patient in need of treatment or antibody mediated rejection in a patient.

3. The pharmaceutical composition of claim 2, wherein said RORs mediated disease or autoimmune disease is selected from the group consisting of cancer, celiac disease, diabetes mellitus type 1, Graves' disease, inflammatory bowel disease, multiple sclerosis, psoriasis, rheumatoid arthritis, systemic lupus erythematosus, asthma, dermatitis, fatty liver disease, Crohn’s disease, cardiovascular disease, inflammatory diseases, neurological disorder, multiple sclerosis and arteriosclerosis.

4. The pharmaceutical composition of claim 3, wherein said cancer is selected from the group consisting of 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 and liver cancer.

5. A pharmaceutical composition comprising at least one compound of Formula (IV) or a pharmaceutically acceptable salt thereof, or stereoisomers thereof comrising:



(IV)

wherein,

R_1, R_2, R_3, or R_4 groups 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,or -CO_2(1-6 alkyl);

R_5 is a substituted five or six membered saturated or unsaturated heterocycle, -NH-aryl, alkylarene, substituted -NH-aryl, ring substituted alkylarene, ring substituted alkylcyclohexane, ring substituted alkylcyclopentane, -NH-phenyl, substituted -NH-phenyl, benzyl, , pyrimidine, imidazole, diazole, triazole, thiadiazole, imidazolidine, thiazolidine, pyrrolidine, piperazine, piperidine, pyridazine, pyrazine, triazine, 1H pyrrole, 2H pyrrole, pyrroline, pyrazolidine, pyrazoline, thiazole, isothiazole, isoxazole, haloalkyl, cyanoalkyl, methylpyrimidine, methylpyridine, methylimidazole, methyldiazole, methyltriazole, methylthiadiazole, methylimidazolidine, methylthiazolidine, methylpyrrolidine, methylpiperazine, methylpiperidine, methylpyridazine, methylpyrazine, methyltriazine, methylpyrrole, methylpyrroline, methylpyrazolidine, methylpyrazoline, methylthiazole, methylisothiazole, methylisoxazole, morpholine, -NH-arylalkyl or substituted cyclohexane; and

R_7 is a substituted five or six membered saturated or unsaturated heterocycle, ring substituted alkylarene, ring substituted alkylcyclohexane, ring substituted alkylcyclopentane, substituted fluoroaryl, substituted fluorophenyl, benzyl, pyrimidine, , imidazole, diazole, triazole, thiadiazole, imidazolidine, thiazolidine, pyrrolidine, piperazine, fluoroaryl, alkylarene, piperidine, pyridazine, pyrazine, triazine, 1H pyrrole, 2H pyrrole, pyrroline, pyrazolidine, pyrazoline, thiazole, isothiazole, isoxazole, methylpyrimidine, , methylpyridine, methylimidazole, methyldiazole, methyltriazole, methylthiadiazole, methylimidazolidine, methylthiazolidine, methylpyrrolidine, methylpiperazine, methylpiperidine, methylpyridazine, methylpyrazine, methyltriazine, methylpyrrole, methylpyrroline, methylpyrazolidine, methylpyrazoline, methylthiazole, methylisothiazole, methylisoxazole, arylalkyl, trifluoromethyl, or pyrazole; and

a pharmaceutically acceptable carrier,

wherein the compound is N-(3-(4-benzylpiperazine-1-carbonyl)-4,5,6,7-tetrahydro-benzo[b]thiophen-2-yl)-2-fluorobenzamide.

6. Use of the compound of Formula (IV) or a pharmaceutically acceptable salt thereof, or a stereoisomer thereof according to claim 5 in the manufacture of a medicament for modulating RORs and/or controlling autoimmune diseases and antibody mediated rejection in a patient.

7. The use of any one of the compounds of Formula (IV) or a pharmaceutically acceptable salts thereof, or stereoisomers thereof according to claim 5 in the manufacture of a medicament for preventing or treating a RORs mediated disease or autoimmune disease, or for preventing or treatingantibody mediated rejection in a patient.

8. The use of the composition of claim 5 in the manufacture of a medicament for modulating RORs and/or controlling autoimmune diseases and antibody mediated rejection in a patient.

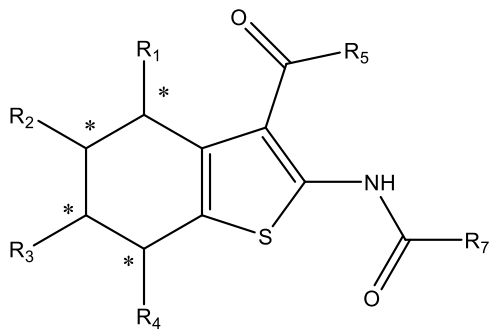
9. The use of the composition of claim 5 in the manufacture of a medicament for preventing or treating a RORs mediated disease or autoimmune disease or for preventing or treating antibody mediated rejection in a patient.

10. The use of any one of claims 6 to 9, wherein said RORs mediated disease or autoimmune disease is selected from the group consisting of cancer, celiac disease, diabetes mellitus type 1, Graves' disease, inflammatory bowel disease, multiple sclerosis, psoriasis, rheumatoid arthritis, systemic lupus erythematosus, asthma, dermatitis, fatty liver disease, Crohn’s disease, cardiovascular disease, inflammatory diseases, neurological disorder, multiple sclerosis and arteriosclerosis.

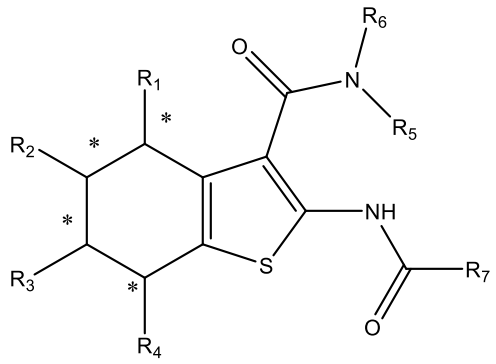
11. The use of claim 10, wherein said cancer is selected from the group consisting of prostate cancer, breast cancer, ovarian cancer, multiple myeloma, brain cancer, glioma, lung cancer, salivary cancer, stomach cancer, thymic epithelial cancer, thyroid cancer, leukemia, melanoma, lymphoma, gastric cancer, pancreatic cancer, kidney cancer, bladder cancer, colon cancer and liver cancer.

12. A pharmaceutical composition comprising:

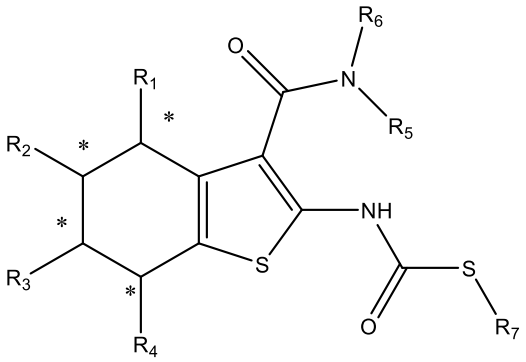
(1) a first compound of Formula (I), (II), (III), or a pharmaceutically acceptable salt thereof, or a stereoisomer thereof selected from the group consisting of:



(I)



(II)



(III)

wherein, R_1, R_2, R_3, or R_4 groups 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,or -CO_2(1-6 alkyl);

R_5 is a five or six membered saturated or unsaturated heterocycle, -NH-aryl, alkylarene, -NH-aryl, alkylarene, ring alkylcyclohexane, alkylcyclopentane, -NH-phenyl, -NH-phenyl, benzyl, , pyrimidine, imidazole, diazole, triazole, thiadiazole, imidazolidine, thiazolidine, pyrrolidine, piperazine, piperidine, pyridazine, pyrazine, triazine, 1H pyrrole, 2H pyrrole, pyrroline, pyrazolidine, pyrazoline, thiazole, isothiazole, isoxazole, haloalkyl, cyanoalkyl, methylpyrimidine, methylpyridine, methylimidazole, methyldiazole, methyltriazole, methylthiadiazole, methylimidazolidine, methylthiazolidine, methylpyrrolidine, methylpiperazine, methylpiperidine, methylpyridazine, methylpyrazine, methyltriazine, methylpyrrole, methylpyrroline, methylpyrazolidine, methylpyrazoline, methylthiazole, methylisothiazole, methylisoxazole, morpholine, -NH-arylalkyl or substituted cyclohexane;

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 five or six membered saturated or unsaturated heterocycle, ring substituted alkylarene, ring substituted alkylcyclohexane, ring substituted alkylcyclopentane, substituted fluoroaryl, substituted fluorophenyl, benzyl, pyrimidine, pyridine, imidazole, diazole, triazole, thiadiazole, imidazolidine, thiazolidine, pyrrolidine, piperazine, fluoroaryl, alkylarene, piperidine, pyridazine, pyrazine, triazine, 1H pyrrole, 2H pyrrole, pyrroline, pyrazolidine, pyrazoline, thiazole, isothiazole, isoxazole, methylpyrimidine, toluene, methylpyridine, methylimidazole, methyldiazole, methyltriazole, methylthiadiazole, methylimidazolidine, methylthiazolidine, methylpyrrolidine, methylpiperazine,

methylpiperidine, methylpyridazine, methylpyrazine, methyltriazine, methylpyrrole, methylpyrroline, methylpyrazolidine, methylpyrazoline, methylthiazole, methylisothiazole, methylisoxazole, arylalkyl, trifluoromethyl, or pyrazole

or

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; and

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

(2) 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, analogs or homologs thereof, or a combination thereof;

(b) an antimetabolite;

(c) an alkylating agent;

(d) an anthracycline;

(e) an antibiotic;

(f) an anti-mitotic agent;

(g) a hormone therapy;

(h) a signal transduction inhibitor;

(i) a gene expression modulator;

(j) an apoptosis inducer;

(k) an angiogenesis inhibitor;and

(l) an immunotherapy agent;

and

(3) a pharmaceutically acceptable carrier

wherein the compound inhibits the activity of RORs.

13. The pharmaceutical composition of claim 12, wherein said antimetabolite is methotrexate, 6-mercaptopurine, 6-thioguanine, cytarabine, 5-fluorouracil decarbazine, or a combination thereof.

14. The pharmaceutical composition of claim 12, wherein said alkylating agent is mechlorethamine, thiotepa chlorambucil, melphalan, carmustine (BSNU), lomustine (CCNU), cyclothosphamide, busulfan, dibromomannitol, streptozotocin, mitomycin C, cis-dichlorodiamine platinum (II) (DDP) cisplatin, or a combination thereof.

15. The pharmaceutical composition of claim 12, wherein said anthracycline is daunorubicin, doxorubicin, or a combination thereof.

16. The pharmaceutical composition of claim 12, wherein said antibiotic is dactinomycin, bleomycin, mithramycin, anthramycin (AMC), or a combination thereof.

17. The pharmaceutical composition of claim 12, wherein said anti-mitotic agent is vincristine, vinblastine, or a combination thereof.

18. The pharmaceutical composition of claim 12, wherein said signal transduction inhibitor is imatinib, trastuzumab, or a combination thereof.

19. The pharmaceutical composition of claim 12, wherein said gene expression modulator is a siRNA, a shRNA, an antisense oligonucleotide, an HDAC inhibitor, or a combination thereof.

20. The pharmaceutical composition of claim 12, wherein said immunotherapy agent is a monoclonal antibody, a chimeric antigen receptors (CARs) T-Cell, or a combination thereof.