CLAIMS

1. A method of treating a disease in a subject in need thereof comprising administering to the subject a composition comprising an Akt3 modulator in an amount effective to modulate Akt3 signaling and treat or delay the progression of the disease.

2. The method of claim 1, wherein the disease is selected from the group consisting of neurodegenerative disease, cachexia, anorexia, obesity's complication, inflammatory disease, viral-induced inflammatory reaction, Gulf War Syndrome, tuberous sclerosis, retinitis pigmentosa, transplant rejection, cancer, ischemic tissue injury, traumatic tissue injury, and a combination thereof.

3. The method of claim 2, wherein the disease is the neurodegenerative disease.

4. The method of claim 3, wherein the neurodegenerative disease is selected from the group consisting of Parkinson's disease, Alzheimer's disease, amyotrophic lateral sclerosis, Motor Neuron Disease, Huntington's disease, HIV-induced neurodegeneration, Lewy Body Disease, spinal muscular atrophy, prion disease, spinocerebellar ataxia, familial amyloid polyneuropathy, and a combination thereof.

5. The method of claim 2, wherein the disease is cachexia or anorexia.

6. The method of claim 2, wherein the disease is obesity's complication.

7. The method of claim 6, wherein the obesity's complication is selected from the group consisting of glucose intolerance, hepatic steatosis, dyslipidemia, and a combination thereof.

8. The method of claim 2, wherein the disease is inflammatory disease.

9. The method of claim 8, wherein the inflammatory disease is selected from the group consisting of atopic dermatitis, allergy, asthma, and a combination thereof.

10. The method of claim 2, wherein the disease is viral-induced inflammatory reaction.

11. The method of claim 10, wherein the viral-induced inflammatory reaction is SARS-induced inflammatory pneumonitis, coronavirus disease 2019, or a combination thereof.

12. The method of claim 2, wherein the disease is Gulf War Syndrome or tuberous sclerosis.

13. The method of claim 2, wherein the disease is retinitis pigmentosa or transplant rejection.

14. The method of claim 2, wherein the disease is ischemic tissue injury or traumatic tissue injury.

15. The method of claim 2, wherein the disease is cancer.

16. The method of claim 15, wherein the cancer is selected from the group consisting of adult T-cell leukemia/lymphoma, bladder, brain, breast, cervical, colorectal, esophageal, kidney, liver, lung, nasopharyngeal, pancreatic, prostate, skin, stomach, uterine, ovarian, and testicular cancer.

17. The method of claim 15, wherein the cancer is leukemia.

18. The method of claim 17, wherein the leukemia is adult T-cell leukemia/lymphoma.

19. The method of claim 18, wherein the adult T-cell leukemia/lymphoma is caused by human T-cell lymphotropic virus.

20. The method of any one of claims 1-19, wherein Akt3 is modulated in immune cells.

21. The method of claim 20, wherein the immune cells are selected from the group consisting of T cells, B cells, macrophages, and glial cells.

22. The method of claim 21, wherein the glial cells are astrocytes, microglia, or oligodendrocytes.

23. The method of claim 21, wherein the T cells are T regulatory cells.

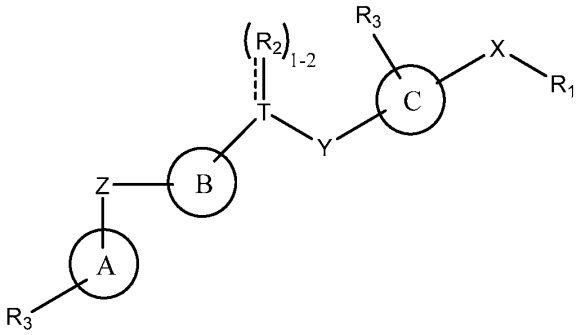
24. The method of claim 1 or 2, wherein the Akt3 modulator activates Akt3 signaling.

25. The method of claim 1 or 2, wherein the Akt3 modulator inhibits Akt3 signaling.

26. The method of claim 1 or 2, wherein the Akt3 modulator increases T regulatory cell activity or production.

27. The method of claim 1 or 2, wherein the Akt3 modulator decreases T regulatory cell activity or production.

28. The method of any one of claims 1-27, wherein the modulator of Akt3 is a compound according to Formula I:



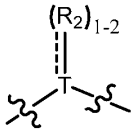
Formula I

or a pharmaceutically acceptable enantiomer, salt, or solvate thereof, wherein:

rings A, B, and C are independently six-membered aryl or N-containing heteroaryl mono- or bicyclic ring systems containing zero or more N-atoms selected from the group consisting of phenyl, pyridine, pyrimidine, pyridazine, pyrazine, triazine, quinoline, quinazoline, isoquinoline, naphthalene, naphthyridine, indole, isoindole, cinnoline, phthalazine, quinoxaline, pteridine, purine, and benzimidazole;

R_1 is -(C_1-C_{30})-alkyl, -(C_3-C_{12})-cycloalkyl, -(C_3-C_{12})-heterocycloalkyl, -(C_6-C_{20})-aryl, or -(C_3-C_{20})-heteroaryl groups optionally substituted by one or more substituents selected from -(C_1-C_{12})-alkyl, -(C_3-C_{12})-cycloalkyl, -(C_3-C_{12})-heterocycloalkyl, -O-(C_1-C_{12})-alkyl, -O-(C_1-C_{12})-alkyl-(C_6-C_{20})-aryl, -O-(C_3-C_{12})-cycloalkyl, -S-(C_1-C_{12})-alkyl, -S-(C_3-C_{12})-cycloalkyl, -COO-(C_1-C_{12})-alkyl, -COO-(C_3-C_{12})-cycloalkyl, -CONH-(C_1-C_{12})-alkyl, -CONH-(C_3-C_{12})-cycloalkyl, -CO-(C_1-C_{12})-alkyl, -CO-(C_3-C_{12})-cycloalkyl, -N-[(C_1-C_{12})-alkyl]$_2$, -(C_6-C_{20})-aryl, -(C_6-C_{20})-aryl-(C_1-C_{12})-alkyl, -(C_6-C_{20})-aryl-O-(C_1-C_{12})-alkyl, -(C_3-C_{20})-heteroaryl, -(C_3-C_{20})-heteroaryl-(C_1-C_{12})-alkyl, -(C_3-C_{20})-heteroaryl-O-(C_1-C_{12})-alkyl, -COOH, -OH, -SH, -SO_3H, -CN, -NH_2, or a halogen;

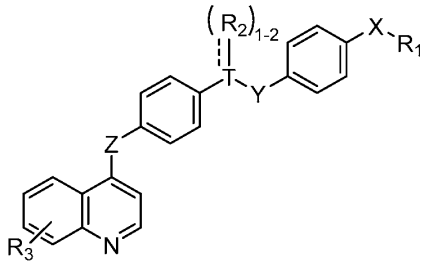
X, Y, and Z are independently =O, -NH, -S, -N-(C_1-C_{30})-alkyl, or -(C_1-C_{30})-aryl;



is -CH((C_1-C_{30})-alkyl))-, -(C=O)-, -CH(OH), -SO_2-, -SO-, or -CH($SOCH_3$)-; and

R_3 is -(C_1-C_{30})-alkyl, -(C_3-C_{12})-cycloalkyl, -(C_3-C_{12})-heterocycloalkyl, -(C_6-C_{20})-aryl, or -(C_3-C_{20})-heteroaryl groups optionally substituted by one or more substituents selected from -(C_1-C_{12})-alkyl, -(C_3-C_{12})-cycloalkyl, -(C_3-C_{12})-heterocycloalkyl, -O-(C_1-C_{12})-alkyl, -O-(C_1-C_{12})-alkyl-(C_6-C_{20})-aryl, -O-(C_3-C_{12})-cycloalkyl, -S-(C_1-C_{12})-alkyl, -S-(C_3-C_{12})-cycloalkyl, -COO-(C_1-C_{12})-alkyl, -COO-(C_3-C_{12})-cycloalkyl, -CONH-(C_1-C_{12})-alkyl, -CONH-(C_3-C_{12})-cycloalkyl, -CO-(C_1-C_{12})-alkyl, -CO-(C_3-C_{12})-cycloalkyl, -N-[(C_1-C_{12})-alkyl]$_2$, -(C_6-C_{20})-aryl, -(C_6-C_{20})-aryl-(C_1-C_{12})-alkyl, -(C_6-C_{20})-aryl-O-(C_1-C_{12})-alkyl, -(C_3-C_{20})-heteroaryl, -(C_3-C_{20})-heteroaryl-(C_1-C_{12})-alkyl, -(C_3-C_{20})-heteroaryl-O-(C_1-C_{12})-alkyl, -COOH, -OH, -SH, -SO_3H, -CN, -NH_2, or a halogen.

29. The method of any one of claims 1-28, wherein the Akt3 modulator is a compound according to Formula II:

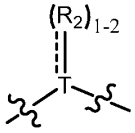


Formula II

or a pharmaceutically acceptable enantiomer, salt, or solvate thereof, wherein:

R_1 is -(C_1-C_{30})-alkyl, -(C_3-C_{12})-cycloalkyl, -(C_3-C_{12})-heterocycloalkyl, -(C_6-C_{20})-aryl, or -(C_3-C_{20})-heteroaryl groups optionally substituted by one or more substituents selected from -(C_1-C_{12})-alkyl, -(C_3-C_{12})-cycloalkyl, -(C_3-C_{12})-heterocycloalkyl, -O-(C_1-C_{12})-alkyl, -O-(C_1-C_{12})-alkyl-(C_6-C_{20})-aryl, -O-(C_3-C_{12})-cycloalkyl, -S-(C_1-C_{12})-alkyl, -S-(C_3-C_{12})-cycloalkyl, -COO-(C_1-C_{12})-alkyl, -COO-(C_3-C_{12})-cycloalkyl, -CONH-(C_1-C_{12})-alkyl, -CONH-(C_3-C_{12})-cycloalkyl, -CO-(C_1-C_{12})-alkyl, -CO-(C_3-C_{12})-cycloalkyl, -N-[(C_1-C_{12})-alkyl]$_2$, -(C_6-C_{20})-aryl, -(C_6-C_{20})-aryl-(C_1-C_{12})-alkyl, -(C_6-C_{20})-aryl-O-(C_1-C_{12})-alkyl, -(C_3-C_{20})-heteroaryl, -(C_3-C_{20})-heteroaryl-(C_1-C_{12})-alkyl, -(C_3-C_{20})-heteroaryl-O-(C_1-C_{12})-alkyl, -COOH, -OH, -SH, -SO_3H, -CN, -NH_2, or a halogen;

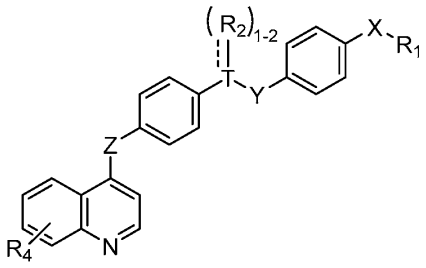
X, Y, and Z are independently -O, -NH, -S, -N-(C_1-C_{30})-alkyl, or -(C_1-C_{30})-aryl;



is -CH((C1-C30)-alkyl))-, -(C=O)-, -CH(OH), -SO2-, -SO-, or -CH(SOCH3)-; and

R3 is -(C1-C30)-alkyl, -(C3-C12)-cycloalkyl, -(C3-C12)-heterocycloalkyl, -(C6-C20)-aryl, or -(C3-C20)-heteroaryl groups optionally substituted by one or more substituents selected from -(C1-C12)-alkyl, -(C3-C12)-cycloalkyl, -(C3-C12)-heterocycloalkyl, -O-(C1-C12)-alkyl, -O-(C1-C12)-alkyl-(C6-C20)-aryl, -O-(C3-C12)-cycloalkyl, -S-(C1-C12)-alkyl, -S-(C3-C12)-cycloalkyl, -COO-(C1-C12)-alkyl, -COO-(C3-C12)-cycloalkyl, -CONH-(C1-C12)-alkyl, -CONH-(C3-C12)-cycloalkyl, -CO-(C1-C12)-alkyl, -CO-(C3-C12)-cycloalkyl, -N-[(C1-C12)-alkyl]2, -(C6-C20)-aryl, -(C6-C20)-aryl-(C1-C12)-alkyl, -(C6-C20)-aryl-O-(C1-C12)-alkyl, -(C3-C20)-heteroaryl, -(C3-C20)-heteroaryl-(C1-C12)-alkyl, -(C3-C20)-heteroaryl-O-(C1-C12)-alkyl, -COOH, -OH, -SH, -SO3H, -CN, -NH2, or a halogen.

30. The method of any one of claims 1-28, wherein the Akt3 modulator is a compound according to Formula III:

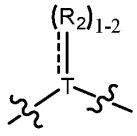


Formula III

or a pharmaceutically acceptable enantiomer, salt, or solvate thereof, wherein:

R1 is -(C1-C30)-alkyl, -(C3-C12)-cycloalkyl, -(C3-C12)-heterocycloalkyl, -(C6-C20)-aryl, or -(C3-C20)-heteroaryl groups optionally substituted by one or more substituents selected from -(C1-C12)-alkyl, -(C3-C12)-cycloalkyl, -(C3-C12)-heterocycloalkyl, -O-(C1-C12)-alkyl, -O-(C1-C12)-alkyl-(C6-C20)-aryl, -O-(C3-C12)-cycloalkyl, -S-(C1-C12)-alkyl, -S-(C3-C12)-cycloalkyl, -COO-(C1-C12)-alkyl, -COO-(C3-C12)-cycloalkyl, -CONH-(C1-C12)-alkyl, -CONH-(C3-C12)-cycloalkyl, -CO-(C1-C12)-alkyl, -CO-(C3-C12)-cycloalkyl, -N-[(C1-C12)-alkyl]2, -(C6-C20)-aryl, -(C6-C20)-aryl-(C1-C12)-alkyl, -(C6-C20)-aryl-O-(C1-C12)-alkyl, -(C3-C20)-heteroaryl, -(C3-C20)-heteroaryl-(C1-C12)-alkyl, -(C3-C20)-heteroaryl-O-(C1-C12)-alkyl, -COOH, -OH, -SH, -SO3H, -CN, -NH2, or a halogen;

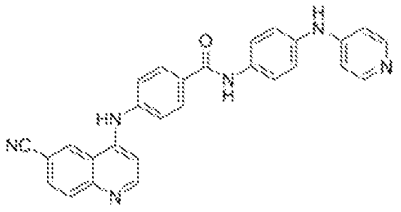
X, Y, and Z are independently -O, -NH, -S, -N-(C_1-C_{30})-alkyl, or -(C_1-C_{30})-aryl;



is -CH((C_1-C_{30})-alkyl))-, -(C=O)-, -CH(OH), -SO_2-, -SO-, or -CH($SOCH_3$)-; and

R_4 is -(C_1-C_{12})-alkyl, -(C_3-C_{12})-cycloalkyl, -(C_3-C_{12})-heterocycloalkyl, -O-(C_1-C_{12})-alkyl, -O-(C_1-C_{12})-alkyl-(C_6-C_{20})-aryl, -O-(C_3-C_{12})-cycloalkyl, -S-(C_1-C_{12})-alkyl, -S-(C_3-C_{12})-cycloalkyl, -COO-(C_1-C_{12})-alkyl, -COO-(C_3-C_{12})-cycloalkyl, -CONH-(C_1-C_{12})-alkyl, -CONH-(C_3-C_{12})-cycloalkyl, -CO-(C_1-C_{12})-alkyl, -CO-(C_3-C_{12})-cycloalkyl, -N-[(C_1-C_{12})-alkyl]$_2$, -(C_6-C_{20})-aryl, -(C_6-C_{20})-aryl-(C_1-C_{12})-alkyl, -(C_6-C_{20})-aryl-O-(C_1-C_{12})-alkyl, -(C_3-C_{20})-heteroaryl, -(C_3-C_{20})-heteroaryl-(C_1-C_{12})-alkyl, -(C_3-C_{20})-heteroaryl-O-(C_1-C_{12})-alkyl, -COOH, -OH, -SH, -SO_3H, -CN, -NH_2, or a halogen.

31. The method of any one of claims 1-28, wherein the Akt3 modulator is a compound according to Formula IV:



Formula IV

or a pharmaceutically acceptable enantiomer, salt, or solvate thereof.

32. The method of any one of claims 1-31, further comprising administering a second therapeutic agent to the subject.

33. The method of claim 32, wherein the second therapeutic agent is selected from the group consisting of a nutrient supplementation, a chemotherapeutic, an anti-inflammatory, an immunosuppressant, a cholinesterase inhibitor, an antidepressant, an anxiolytic, an antipsychotic, riluzole, edavarone, a dopamine agonist, a MAO B inhibitor, a catechol O-methyltransferase inhibitor, an anticholinergic, an anticonvulsant, tetrabenazine, carbidopa-levodopa, an antispastic, an antibody, a fusion protein, an enzyme, a nucleic acid, a ribonucleic acid, an anti-proliferative, a cytotoxic agent, an appetite stimulant, a 5-HT3 antagonist, a Cox-2 inhibitor, and a combination thereof.

34. A method of treating cachexia in a subject in need thereof comprising administering a composition comprising a selective inhibitor of Akt3 to the subject in an amount effective to inhibit Akt3 signaling in adipocytes and activate adipogenesis.

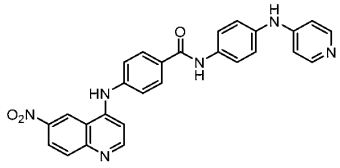
35. The method of claim 34, further comprising administering a second therapeutic agent to the subject.

36. The method of claim 35, wherein the second therapeutic agent is selected from the group consisting of an appetite stimulant, a nutrient supplementation, a 5-HT3 antagonist, a Cox-2 inhibitor, a chemotherapeutic, an anti-inflammatory, an immunosuppressant, a cholinesterase inhibitor, an antidepressant, an anxiolytic, an antipsychotic, riluzole, edavarone, a dopamine agonist, a MAO B inhibitor, a catechol O-methyltransferase inhibitor, an anticholinergic, an anticonvulsant, tetrabenazine, carbidopa-levodopa, an antispastic, an antibody, a fusion protein, an enzyme, a nucleic acid, a ribonucleic acid, an anti-proliferative, a cytotoxic agent, and a combination thereof.

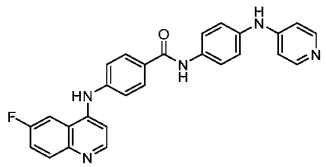
37. The method of claim 36, wherein the second therapeutic agent is an appetite stimulant, a nutrient supplementation, a 5-HT3 antagonist, or a Cox-2 inhibitor.

38. The method of any one of claims 34-37, wherein the subject has neurodegenerative disease, cachexia, anorexia, obesity's complication, inflammatory disease, viral-induced inflammatory reaction, Gulf War Syndrome, tuberous sclerosis, retinitis pigmentosa, transplant rejection, cancer, and a combination thereof.

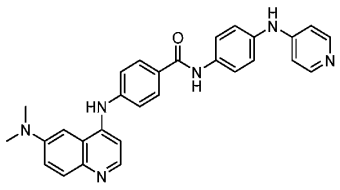
39. The method of any one of claims 1-38, wherein the Akt3 inhibitor is a compound selected from the group consisting of:



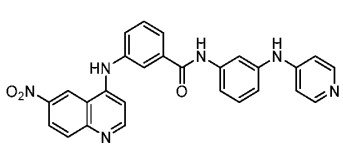
Formula VI,



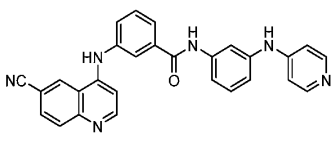
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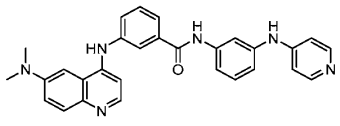
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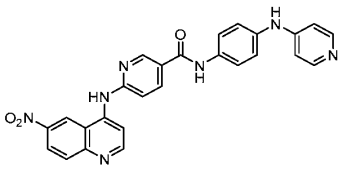
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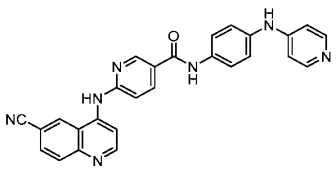
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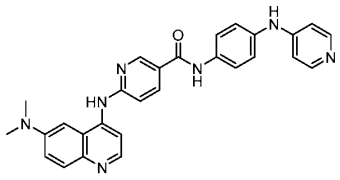
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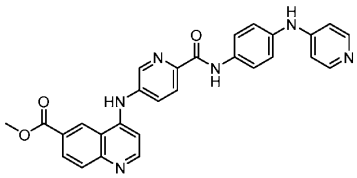
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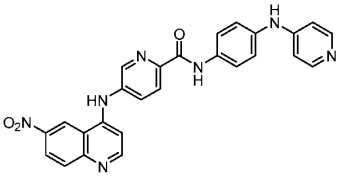
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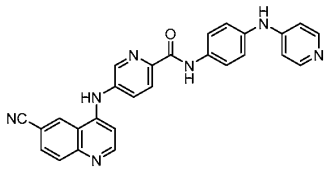
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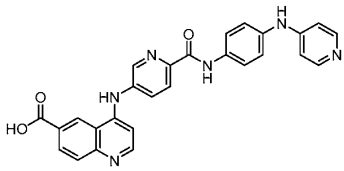
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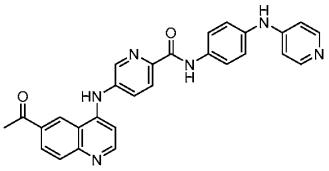
Formula XVI,



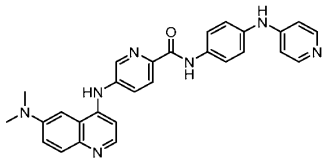
Formula XVII,



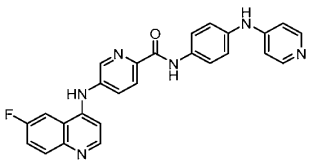
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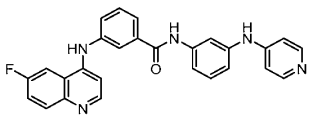
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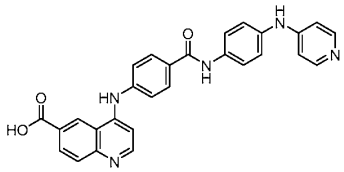
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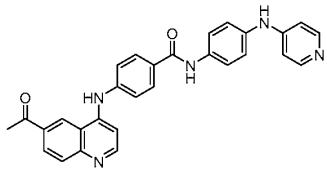
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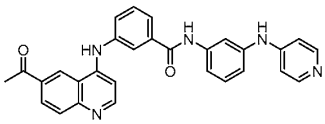
Formula XXII,



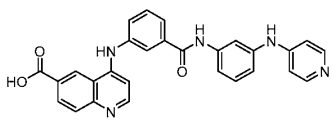
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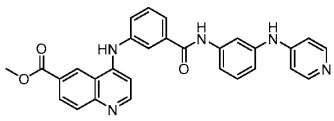
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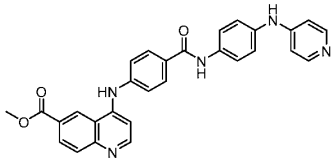
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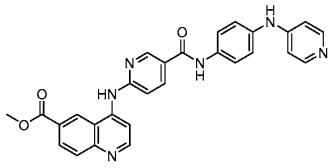
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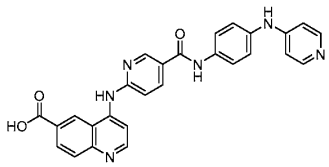
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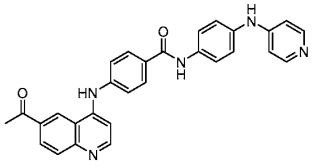
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Formula XXIX,

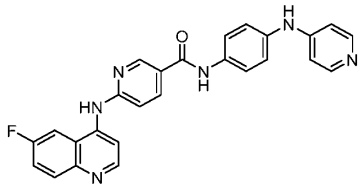


Formula XXX,



Formula XXXI,

and



Formula XXXII.