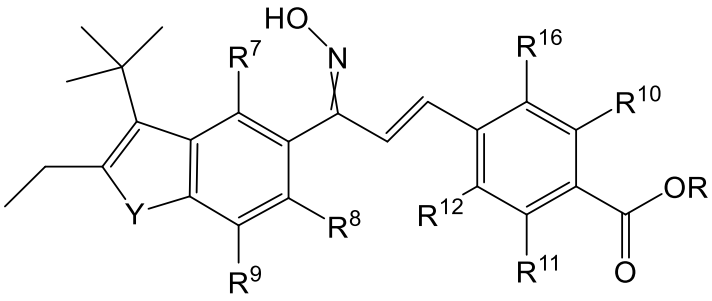
CLAIMS

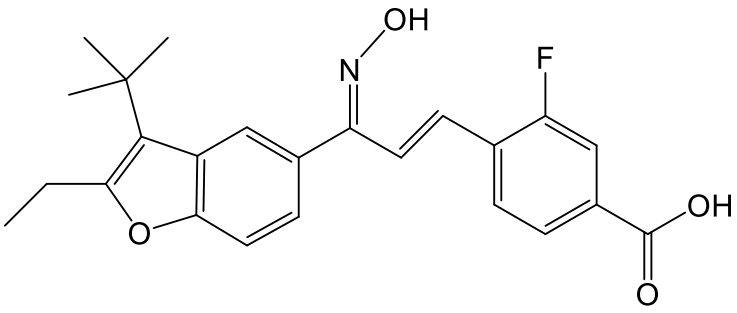
1. Use of a RARγ-selective agonist, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating cancer, wherein the RARγ-selective agonist has the structure



(GAG1),

wherein R is H or C_{1-6} alkyl; the crossed double bond to the =N-OH group indicates that stereochemistry is not specified; R^7 to R^{12} are independently, C_{1-6} alkyl, a hydrogen atom, an alkoxy group, a halogen atom, a nitro group, a hydroxy group, OCF_3, or COR^{13}, where R^{13} is C_{1-6} alkyl or CF_3; Y is oxygen, sulfur, or NR^{14}, where R^{14} is C_{1-6} alkyl; and R^{16} is H or F, wherein an effective amount of the RARγ-selective agonist, or a pharmaceutically acceptable salt thereof, is to be administered to a patient in need thereof.

2. The use of claim 1, wherein the RARγ-selective agonist has the structure



(GA1E).

3. The use of claim 1 or 2, wherein the cancer is a solid tumor.

4. The use of claim 3, wherein the cancer is breast cancer.

5. The use of claim 4, wherein the breast cancer is triple negative breast cancer.

6. The use of claim 4, wherein the breast cancer is $Her2^+$ breast cancer.

7. The use of claim 3, wherein the cancer is lung cancer.

8. The use of any one of claims 1-7, wherein the effective amount is about 1 to about 100 mg/day.

9. The use of any one of claims 1-8, wherein a CAR-T cell is to be further administered to the patient.

10. The use of any one of claims 1-8, wherein an immune checkpoint inhibitor is to be

further administered to the patient.

11. A method of generating or expanding tumor infiltrating lymphocytes (TIL) by contacting the TIL with a RARγ selective agonist.

12. The method of claim 11, wherein the RARγ selective agonist is to be administered to a subject having cancer.

13. The method of claim 11, wherein contacting comprises culturing the TIL *in vitro* in a media supplemented with the RARγ selective agonist.

14. The method of claim 13, comprising isolating TIL from a tumor explant.

15. The method of claim 13, comprising culturing peripheral blood mononuclear cells (PBMC) *in vitro,* in the presence of irradiated tumor cells, in a media supplemented with the RARγ selective agonist.

16. The method of claim 15, wherein the PBMC and the irradiated tumor cells are obtained from the same individual.

17. The method of any one of claims 13-16, wherein the media is further supplemented with IL-2.

18. The method of any one of claims 13-17, further comprising supplementing the culture media with an anti-PD-1 or anti-PD-L1 antibody.

19. Use of the TIL generated or expanded according to any one of claims 11-18 in the manufacture of a medicament for treating cancer, wherein the TIL is to be infused to a patient in need thereof.

20. Use of a RARγ selective agonist-expanded TIL in the manufacture of a medicament for treating cancer, wherein the RARγ selective agonist-expanded TIL is to be provided to a patient in need thereof.

21. The use of claim 20, wherein the TIL cultured *in vitro* in a media supplemented with the RARγ selective agonist is to be administered to the patient.

22. The use of claim 20 or 21, wherein the RARγ selective agonist is to be administered to the patient.

23. The use of any one of claims 20-22, wherein the cancer is a solid tumor.

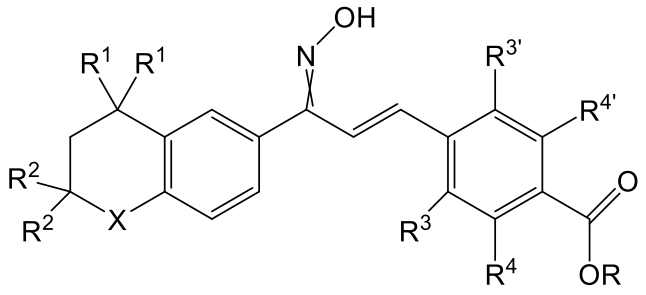
24. The use of claim 23 wherein the cancer is breast cancer.

25. The use of claim 24, wherein the breast cancer is triple negative breast cancer.

26. The use of claim 24, wherein the breast cancer is $Her2^{+}$ breast cancer.

27. The use of claim 24, wherein the cancer is lung cancer.

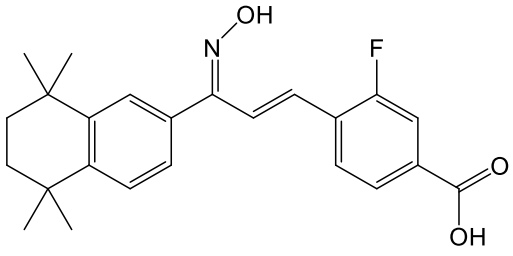
28. The use of any one of claims 11-27, wherein the RARγ selective agonist is a compound of structure



(GAG3p),

or a pharmaceutically acceptable salt thereof, wherein R is H or C_{1-6} alkyl; each R^1 and R^2 are independently H or C_{1-6} alkyl; R^3, $R^{3'}$, R^4, and $R^{4'}$ are independently, H or F; X is O, S, CH_2, $C(R^5)_2$, or NR^6, wherein each R^5 and R^6 are independently H or C_{1-6} alkyl; the crossed double bond to the =N-OH group indicates that stereochemistry is not specified.

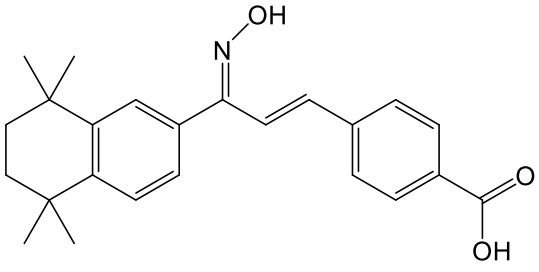
29. The use of claim 28, wherein the RARγ selective agonist is a compound of structure



(GA2E),

or a pharmaceutically acceptable salt thereof.

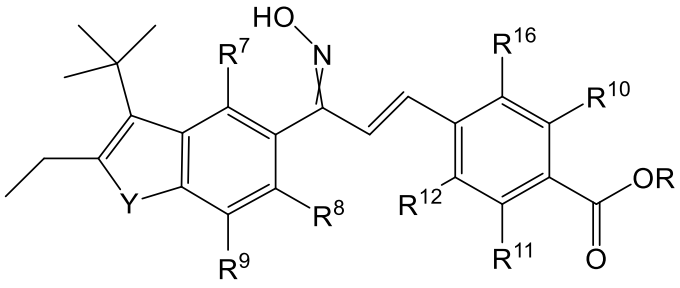
30. The use of claim 28, wherein the RARγ selective agonist is a compound of structure



(GA3Ep),

or a pharmaceutically acceptable salt thereof.

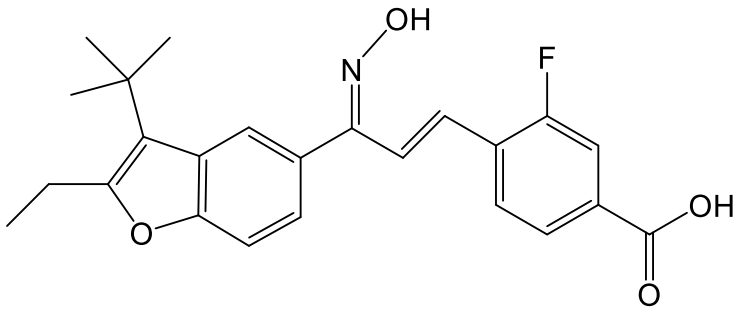
31. The use of any one of claims 19-30, wherein the RARγ selective agonist is a compound of structure



(GAG1),

or a pharmaceutically acceptable salt thereof, wherein R is H or C_{1-6} alkyl; the crossed double bond to the =N-OH group indicates that stereochemistry is not specified; R^7 to R^{12} are independently, C_{1-6} alkyl, a hydrogen atom, an alkoxy group, a halogen atom, a nitro group, a hydroxy group, OCF_3, or COR^{13}, where R^{13} is C_{1-6} alkyl or CF_3; Y is oxygen, sulfur, or NR^{14}, where R^{14} is C_{1-6} alkyl; and R^{16} is H or F.

32. The use of claim 31, wherein the RARγ-selective agonist has the structure



(GA1E).

33. The use of any one of claims 1-10, or 19-32, wherein the RARγ selective agonist is to be administered to a subject, wherein the administration occurs periodically throughout an interval of treatment.

34. The use of any one of claims 1-10, or 19-32, wherein the RARγ selective agonist is to be administered to a subject, wherein the administration occurs in repeated cycles throughout an interval of treatment.

35. The use of claim 34, wherein one cycle of treatment comprises the following:

1) the RARγ selective agonist is to be administered periodically over a first span of time and

2) the administration of the RARγ selective agonist is to be suspended over a second span of time, after which a new cycle may be initiated.

36. The use of claim 35, wherein the first span of time is 10-15 days or any integer number of days therein.

37. The use of claim 35 or 36, wherein the second span of time is two weeks to one month or any integer number of days therein.

38. The use of any one of claims 33-37, wherein periodically is daily.

39. The use of any one of claims 33-37, wherein periodically is twice daily.

40. The use of any one of claims 33-37, wherein periodically is every other day.

41. The use of any one of claims 33-40, wherein the interval of treatment extends from a first administration until a complete response is achieved.

42. The use of any one of claims 33-40, wherein the interval of treatment extends from a first administration until the cancer again progresses after stable disease or regression.

43. The use of any one of claims 1-10, or 19-42, wherein an inhibitor of Treg cells is to be further administered to the patient.

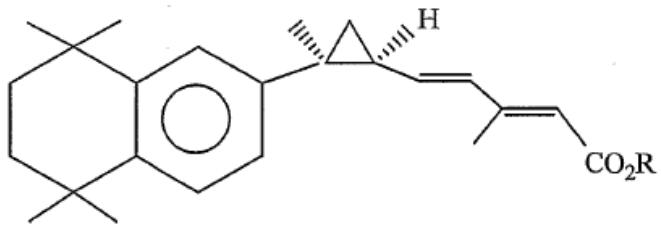
44. The use of claim 43, wherein the inhibitor of Treg cells comprises a RARα antagonist.

45. The use of claim 43, wherein the inhibitor of Treg cells comprises a Treg-depleting antibody.

46. The use of claim 45, wherein the Treg-depleting antibody comprises an anti-CD25 antibody, an anti-GITR antibody, an anti-FoxP3 antibody, an anti-CCR_4 antibody, or an anti-folate receptor 4 antibody.

47. The use of any one of claims 1-8, or 19-46, wherein an anti-PD-1 or anti-PD-L1 antibody is to be further administered to the patient.

48. The use of any one of claims 1-10, or 19-46, wherein a RXR agonist, or a pharmaceutically acceptable salt thereof, is to be further administered to the patient, wherein the RXR agonist has the structure

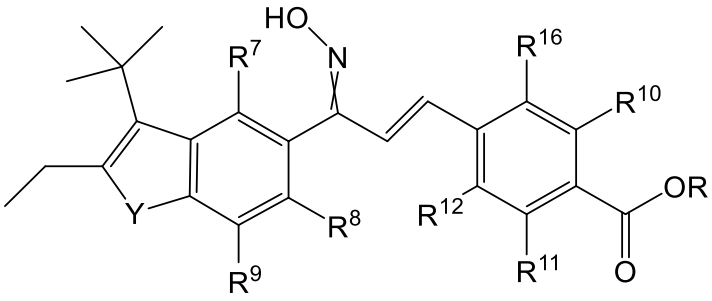


(XAG),

where R is H or C_{1-6} alkyl.

49. The use of claim 48, wherein the RXR agonist is 3,7-dimethyl-6(S),7(S)-methano,7-[1,1,4,4-tetramethyl-1,2,3,4-tetrahydron-aphth-7-yl]2(E), 4(E) heptadienoic acid (IRX4204).

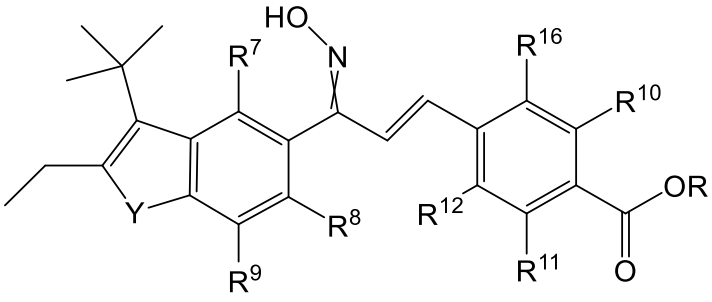
50. Use of a RARγ-selective agonist, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for potentiating chimeric antigen receptor-T (CAR-T) cancer immunotherapy, wherein the RARγ-selective agonist has the structure



(GAG1),

wherein R is H or C_{1-6} alkyl; the crossed double bond to the =N-OH group indicates that stereochemistry is not specified; R^7 to R^{12} are independently, C_{1-6} alkyl, a hydrogen atom, an alkoxy group, a halogen atom, a nitro group, a hydroxy group, OCF_3, or COR^{13}, where R^{13} is C_{1-6} alkyl or CF_3; Y is oxygen, sulfur, or NR^{14}, where R^{14} is C_{1-6} alkyl; and R^{16} is H or F, wherein an effective amount of the RARγ-selective agonist, or a pharmaceutically acceptable salt thereof, is to be administered to a cancer patient who is receiving, has received, or is scheduled to receive, CAR-T cells.

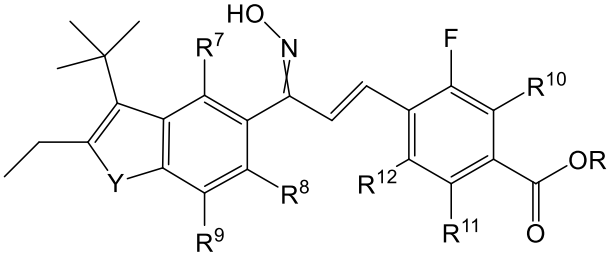
51. Use of a RARγ-selective agonist, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for potentiating immune checkpoint inhibitor cancer immunotherapy, wherein the RARγ-selective agonist has the structure



(GAG1),

wherein R is H or C_{1-6} alkyl; the crossed double bond to the =N-OH group indicates that stereochemistry is not specified; R^7 to R^{12} are independently, C_{1-6} alkyl, a hydrogen atom, an alkoxy group, a halogen atom, a nitro group, a hydroxy group, OCF_3, or COR^{13}, where R^{13} is C_{1-6} alkyl or CF_3; Y is oxygen, sulfur, or NR^{14}, where R^{14} is C_{1-6} alkyl; and R^{16} is H or F, wherein an effective amount of the RARγ-selective agonist, or a pharmaceutically acceptable salt thereof, is to be administered to a cancer patient who is receiving, has received, or is scheduled to receive, an immune checkpoint inhibitor.

52. A RARγ-selective agonist of the structure:



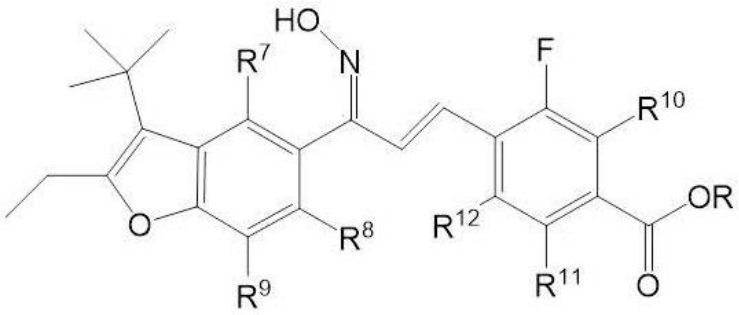
(GAG1),

or a pharmaceutically acceptable salt thereof, wherein R is H or C_{1-6} alkyl; R^7 to R^{12} are independently: C_{1-6} alkyl, a hydrogen atom, an alkoxy group, a halogen atom, a nitro group, a hydroxy group, OCF_3, or COR^{13}, where R^{13} is C_{1-6} alkyl or CF_3. Y is oxygen, sulfur, or NR^{14}, where R^{14} is C_{1-6} alkyl.

53. The RARγ-selective agonist of claim 52, wherein R is H, methyl, or ethyl.

54. The RARγ-selective agonist of claim 52, wherein Y is O.

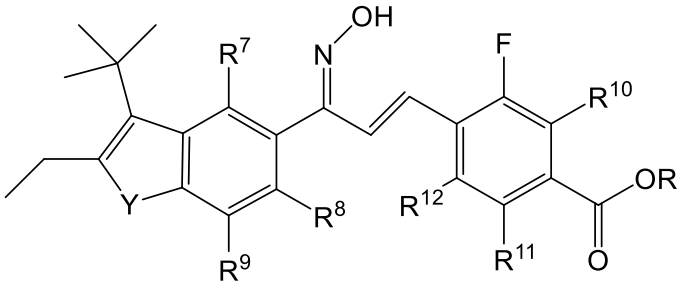
55. The RARγ-selective agonist of claim 54 having the following structure:



(GAG1-1).

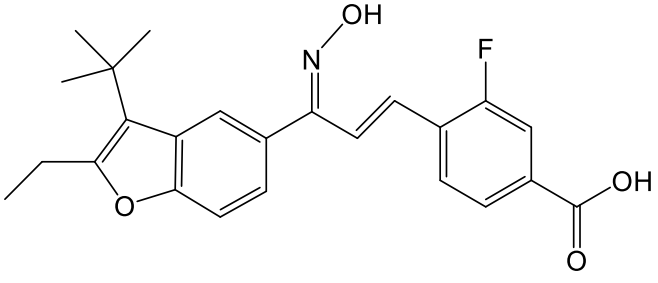
56. The RARγ-selective agonist of claim 52, wherein the =N-OH group is in the E configuration.

57. The RARγ-selective agonist of claim 56 having the following structure:



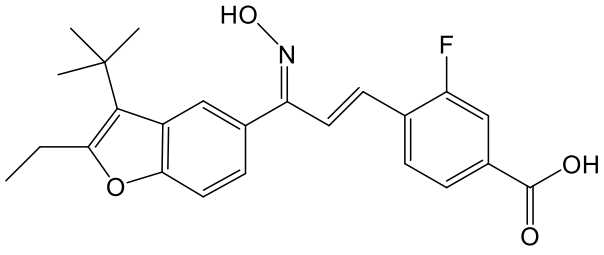
(GAG1-2).

58. The RARγ-selective agonist of claim 52, wherein the RARγ selective agonist is 4-((1*E*,3*E*)-3-(3-(*tert*-butyl)-2-ethyl-benzofuran-5-yl)-3-(hydroxyimino)prop-1-en-1-yl)-3-fluorobenzoic acid (GA1E), having the structure



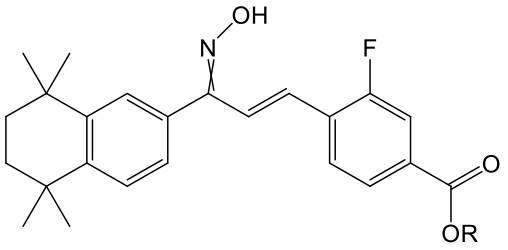
(GA1E).

59. The RARγ-selective agonist of claim 52, wherein the RARγ selective agonist is 4-((1E,3Z)-3-(3-(tert-butyl)-2-ethyl=benzofuran-5-yl)-3-(hydroxyimino)prop-1-en-1-yl)-3-fluorobenzoic acid (GA1Z), having the structure



(GA1Z).

60. A RARγ-selective agonist having the structure



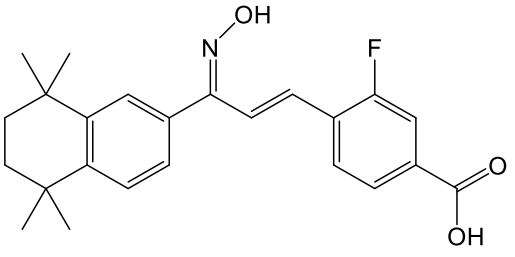
GAG2,

or a pharmaceutically acceptable salt thereof, wherein R is H or C_{1-6} alkyl, and the crossed double bond to the =N-OH group indicates that stereochemistry is not specified.

61. The RARγ-selective agonist of claim 60, wherein R is H, methyl, or ethyl.

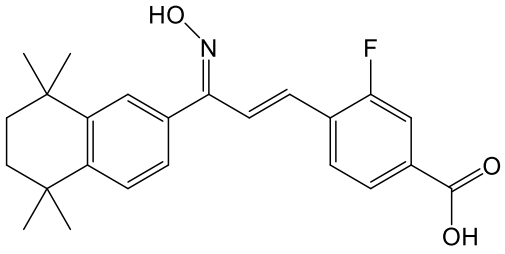
62. The RARγ-selective agonist of claim 60, wherein the =N-OH group is in the E configuration.

63. The RARγ-selective agonist of claim 60, wherein the RARγ selective agonist is 3-fluoro-4-((1E,3E)-3-(hydroxyimino)-3-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)prop-1-en-1-yl)benzoic acid (GA2E), having the structure



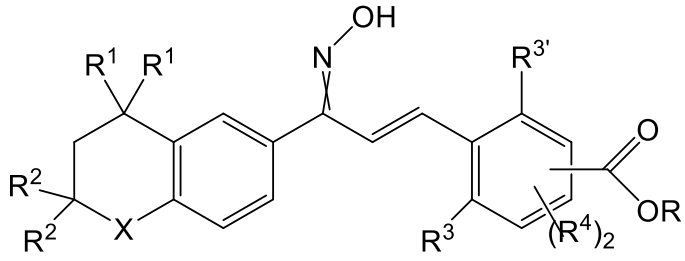
(GA2E).

64. The RARγ-selective agonist of claim 60, wherein the RARγ selective agonist is 3-fluoro-4-((1E,3Z)-3-(hydroxyimino)-3-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)prop-1-en-1-yl)benzoic acid (GA2Z), having the structure



(GA2Z).

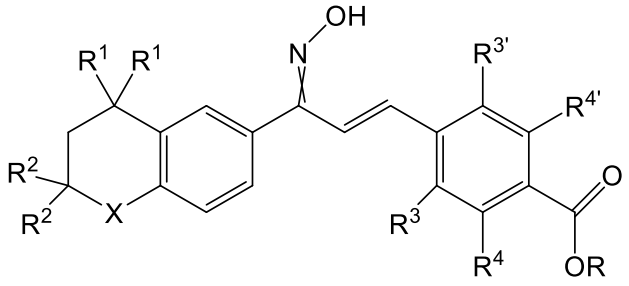
65. A RARγ-selective agonist having the structure



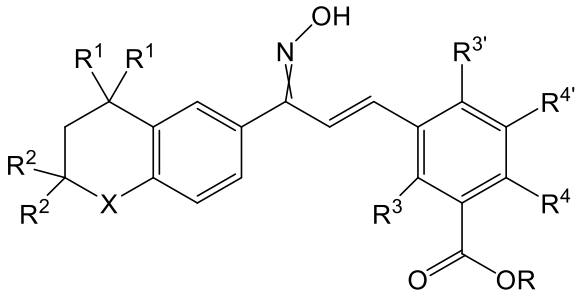
GAG3,

or a pharmaceutically acceptable salt thereof, wherein R is H or C_{1-6} alkyl; each R^1 and R^2 are independently H or C_{1-6} alkyl; R^3 and $R^{3'}$ are independently H, or halogen; $(R^4)_2$ comprises R^4 and $R^{4'}$ which are independently H, halogen, C_{1-6} alkyl or C_{1-6} alkoxy; X is O, S, CH_2, $C(R^5)_2$, or NR^6, wherein each R^5 and R^6 are independently H or C_{1-6} alkyl; the crossed double bond to the =N-OH group indicates that stereochemistry is not specified; and the COOR group is in the meta or para position and the two R^4 groups occupy the remaining positions on the ring.

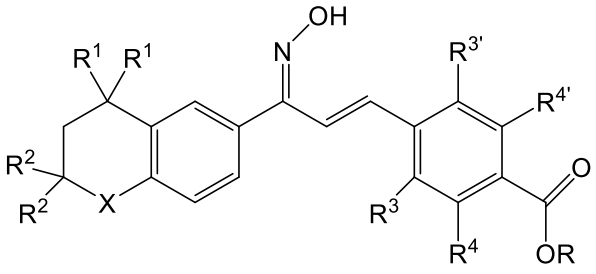
66. The RARγ-selective agonist of claim 65, having the structure



GAG3p,

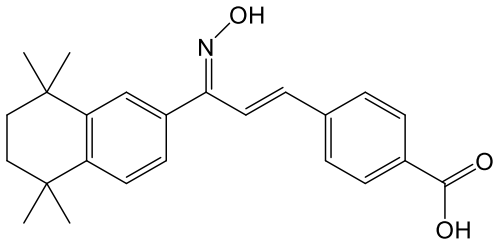


GAG3m, or

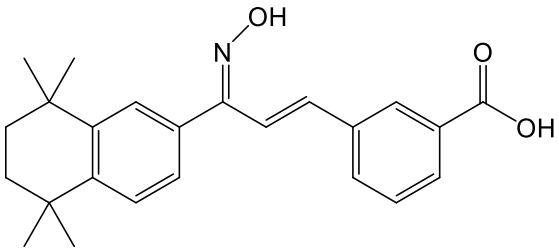


(GAG3Ep).

67. The RARγ-selective agonist of claim 65, having the structure



GA3Ep, or



GA3Em.