[0009] In some embodiments, the CAR-modified immune cells are, or comprise, CAR-modified T cells. In some embodiments, the CAR-modified immune cells are, or comprise, CAR-modified NK cells. In some embodiments, the CAR-modified immune cells are, or comprise, CAR-modified NKT cells. In some embodiments, the CAR-modified immune cells are, or comprise, CAR-modified macrophages. Further embodiments can comprise mixtures of these cell types. Most typically such cellular preparations are administered by infusion, for example intravenous infusion. In contrast, the retinoid and rexinoids are small molecules that can be administered orally, for example as pills or capsules and the like. Thus the retinoids and rexinoids, and the CAR-modified immune cells, may be administered on independent schedules.

Combinations of CAR-MIC with immunomodulatory retinoids and rexinoids

[0010] Thus in one aspect, provided herein are methods of treating cancer, the methods comprising administering CAR-modified immune cells and at least one retinoid active agent and/or rexinoid active agent (collectively RAR/RXR active agents). In some embodiments, the retinoid active agent is a Retinoic Acid Receptor (RAR) active agent. In some embodiments, the rexinoid active agent is a Retinoid X Receptor (RXR) active agent. In some embodiments, two RAR/RXR active agents are used; they can be two RAR active agents, two RXR active agents, or a RAR active agent and a RXR active agent. In some embodiments the RAR/RXR active agent acts as an agonist of its receptor while in other embodiments the RAR/RXR active agent acts as an antagonist of its receptor. In some embodiments utilizing multiple RAR/RXR active agents, the multiple RAR/RXR active agents are formulated and administered separately. In some aspects of these embodiments, the RAR/RXR active agents are administered separately, but during the same treatment session. In other aspects of these embodiments, the RAR/RXR active agents are administered in different treatment sessions. In other embodiments, the multiple RAR/RXR active agents are formulated separately, but co-administered (that is, administered during the same treatment session). In still other embodiments, the multiple RAR/RXR active agents are formulated together as a single, common medicament.

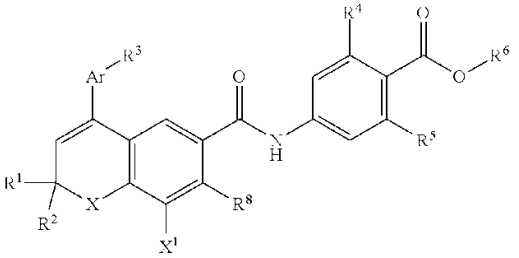
[0010a] In another aspect, provided herein is a use of an immunomodulatory retinoid active agent and/or rexinoid active agent (RAR/RXR active agent) in the manufacture of a medicament for cancer immunotherapy, wherein the RAR/RXR active agent is to be administered to a subject in need thereof, and wherein the RAR/RXR active agent is to be administered with chimeric antigen receptor-modified immune cells (CAR-MIC) and a differentiating RAR active agent,

wherein the immunomodulatory RAR/RXR active agent is:

a) a RARα antagonist, wherein the RARα antagonist is:

i) a compound of general formula (I)

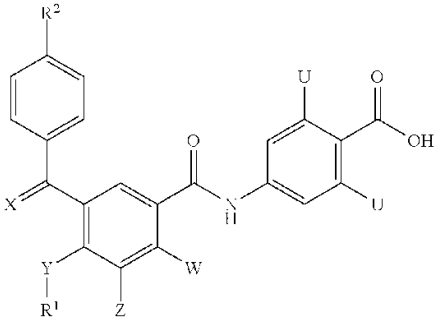
(I)



wherein R^1, R^2, R^3, and R^6 are independently H or C_{1-6} alkyl; R^4 and R^5 are independently H or F; Ar is phenyl, pyridyl, thienyl, furyl, or naphthyl; X is $C(CH_3)_2$, O, S, or NR^7, wherein R^7 is H or C_{1-6} alkyl; X^1 is H or halogen such as F, Cl or Br; and R^8 is H or OH; or

ii) a compound of general formula (II)

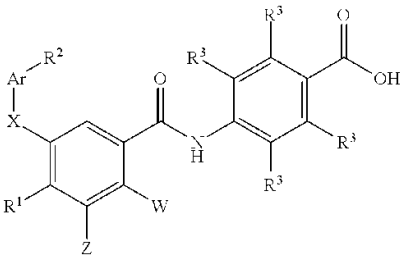
(II)



wherein R^1 and R^2 are independently C_{1-6} alkyl; X is O, S, or CH_2; Y is O, S, CH_2, or NR^3, wherein R^3 is C_{1-6}; Z is Cl or Br; W is H or OH; and U is independently H or F; or

iii) a compound of general formula (III):

(III)



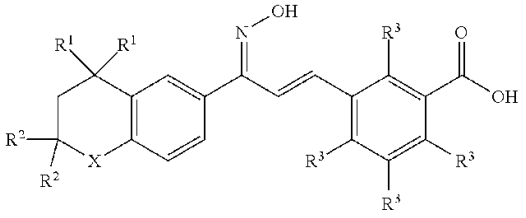
wherein R^1 and R^2 are independently H or C_{1-6} alkyl; R^3 is H or F; Ar is phenyl, pyridyl, thienyl, furyl, or naphthyl; X is O, S, N, or CH_2; W is H or OH; and Z is Cl or Br; or

iv) BMS185411, BMS614, Ro41-5253, Ro46-5471, or AGN 194777; or

b) a RARγ agonist, wherein the RARγ agonist is:

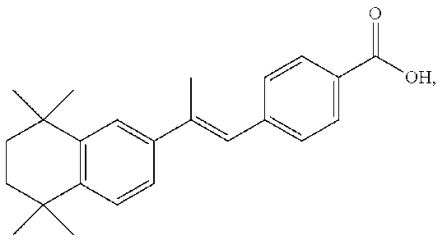
i) a compound of general formula (IV):

(IV)



wherein R^1 and R^2 are independently H or C_{1-6} alkyl; R^3 is H or F; and X is O, S, CH_2, $C(R^4)_2$, or NR^5, wherein R^4 and R^5 are independently H or C_{1-6} alkyl; or

ii)



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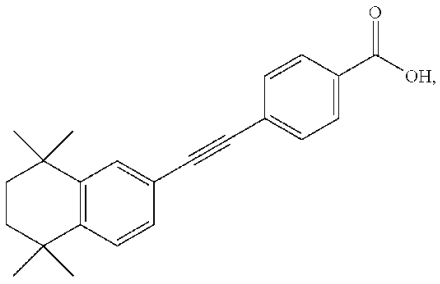

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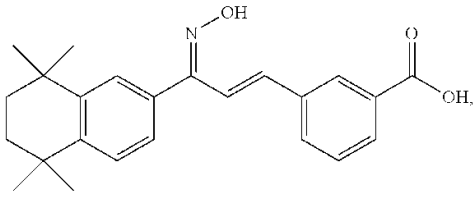
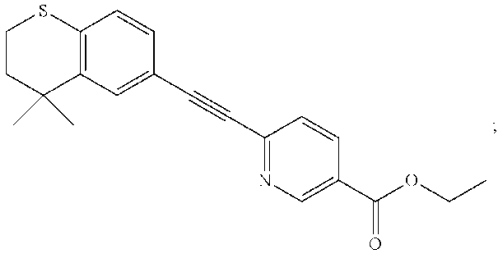


or



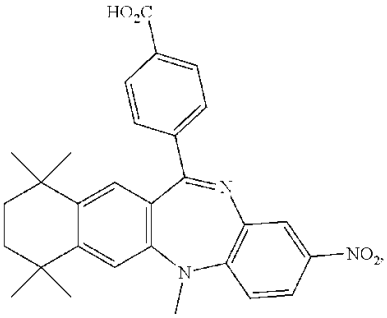
;

AGN 190168 (Tazarotene)

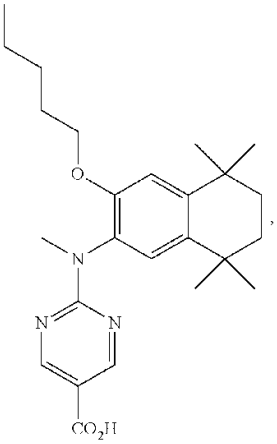
or

iii) CD437, CD2325, CD666, or BMS961; or

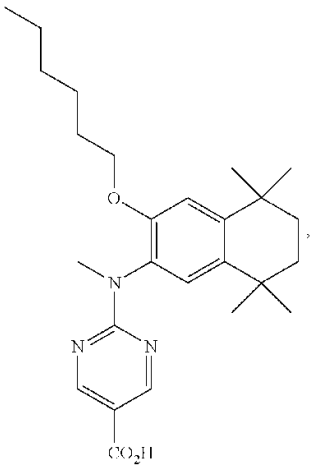
c) a RXR antagonist, wherein the RXR antagonist is: AGN195393, LGN100849,



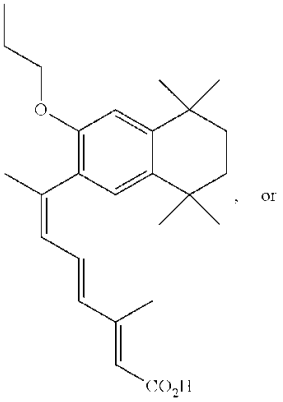
HX 531



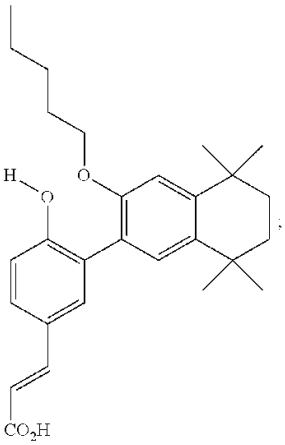
PA 451



PA 452



LG 100754



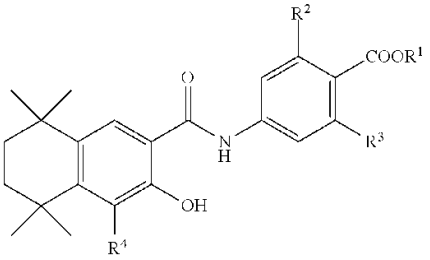
UVI 3003

or

d) a combination thereof; and

wherein the differentiating RAR active agent is a RARα agonist, wherein the RARα agonist is a compound of general formula (V):

(V)



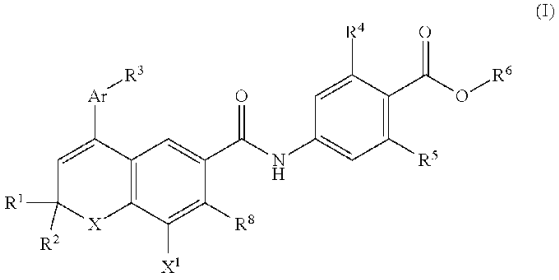
wherein R^1 is H or C_{1-6} alkyl, R^2 and R^3 are independently H or F, and R^4 is a halogen.

[0010b] In another aspect, provided herein is a use of an immunomodulatory retinoid active agent and/or rexinoid active agent (RAR/RXR active agent) in the manufacture of a medicament for potentiating chimeric antigen receptor-modified immune cells (CAR-MIC) cancer immunotherapy, wherein the RAR/RXR active agent is to be administered to a cancer patient who is receiving, has received, or is scheduled to receive, CAR-MIC, and wherein the RAR/RXR active agent is to be administered with a differentiating RAR active agent to , wherein the immunomodulatory RAR/RXR active agent is:

a) a RARα antagonist, wherein the RARα antagonist is:

i) a compound of general formula (I)

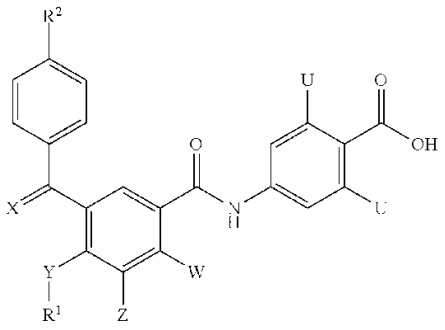
(I)



wherein R^1, R^2, R^3, and R^6 are independently H or C_{1-6} alkyl; R^4 and R^5 are independently H or F; Ar is phenyl, pyridyl, thienyl, furyl, or naphthyl; X is $C(CH_3)_2$, O, S, or NR^7, wherein R^7 is H or C_{1-6} alkyl; X^1 is H or halogen such as F, Cl or Br; and R^8 is H or OH; or

ii) a compound of general formula (II)

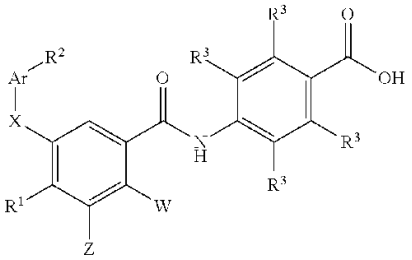
(II)



wherein R^1 and R^2 are independently C_{1-6} alkyl; X is O, S, or CH_2; Y is O, S, CH_2, or NR^3, wherein R^3 is C_{1-6} alkyl; Z is Cl or Br; W is H or OH; and U is independently H or F; or

iii) a compound of general formula (III):

(III)



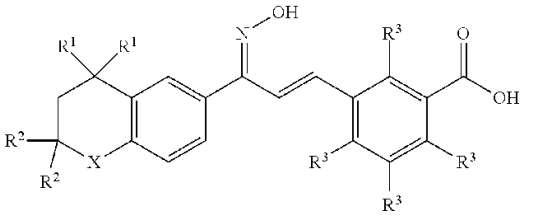
wherein R^1 and R^2 are independently H or C_{1-6} alkyl; R^3 is H or F; Ar is phenyl, pyridyl, thienyl, furyl, or naphthyl; X is O, S, N, or CH_2; W is H or OH; and Z is Cl or Br; or

iv) BMS185411, BMS614, Ro41-5253, Ro46-5471, or AGN 194777; or

b) a RARγ agonist, wherein the RARγ agonist is:

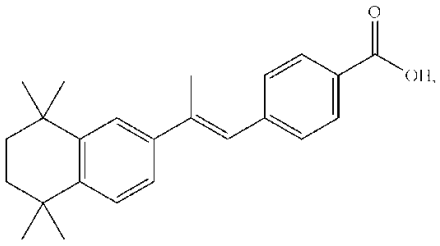
i) a compound of general formula (IV):

(IV)



wherein R^1 and R^2 are independently H or C_{1-6} alkyl; R^3 is H or F; and X is O, S, CH_2, $C(R^4)_2$, or NR^5, wherein R^4 and R^5 are independently H or C_{1-6} alkyl; or

ii)



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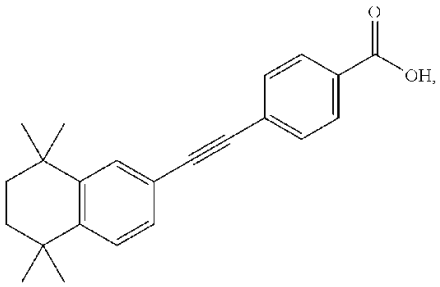
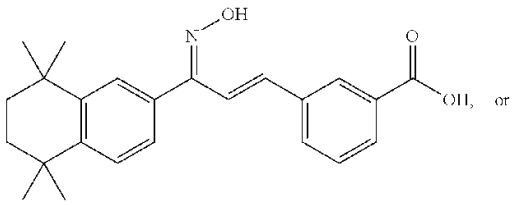
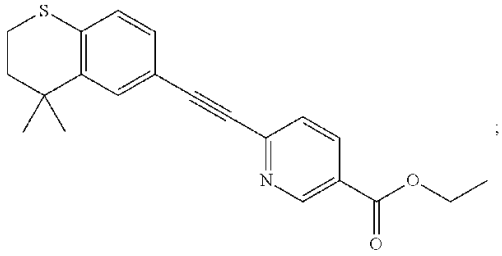


AGN 190205



or



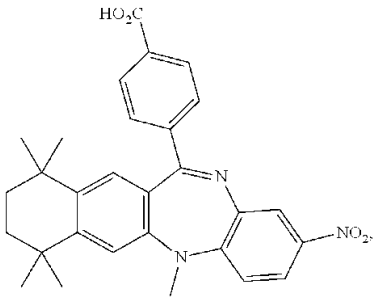
AGN 190168

(Tazarotene)

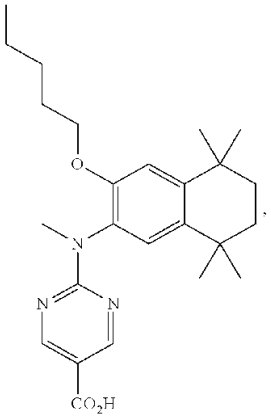
or

iii) CD437, CD2325, CD666, or BMS961; or

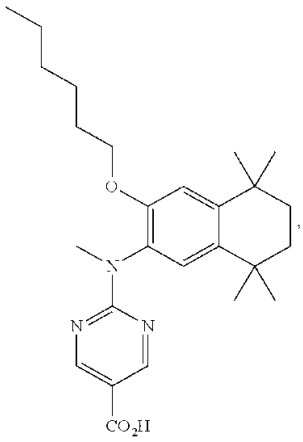
c) a RXR antagonist, wherein the RXR antagonist is: AGN195393, LGN100849,



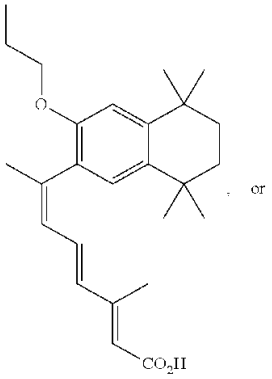
HX 531



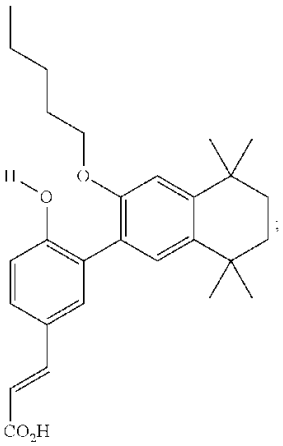
PA 451



PA 452



LG 100754



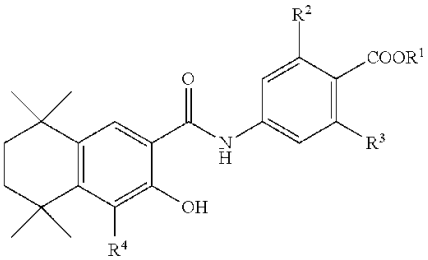
UVI 3003

or

d) a combination thereof; and

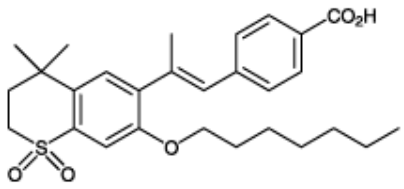
wherein the differentiating RAR active agent is a RARα agonist, wherein the RARα agonist is a compound of general formula (V):

(V)

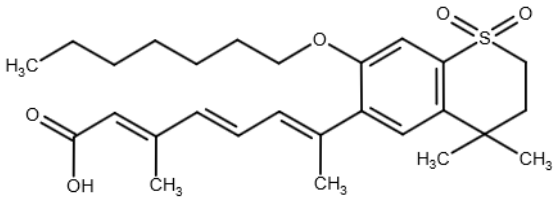


wherein R^1 is H or C_{1-6} alky, R^2 and R^3 are independently H or F, and R^4 is a halogen.

[0011] In some embodiments, the retinoid active agent is a RARα antagonist. In some embodiments, the RARα antagonist is a compound of general formula (I):

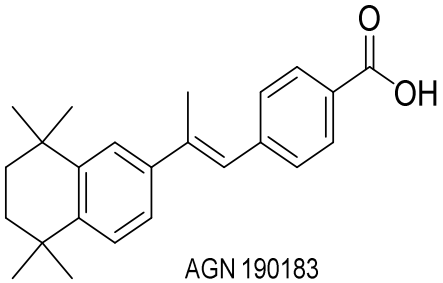


Ro41-5253, or



Ro46-5471.

[0017] In some embodiments, the retinoid active agent is a RARγ agonist. In some embodiments, the RARγ agonist is:



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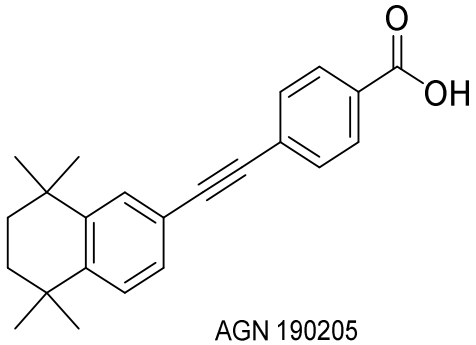

AGN 190205

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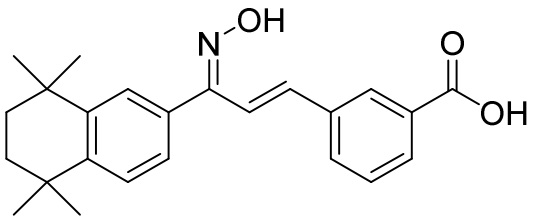
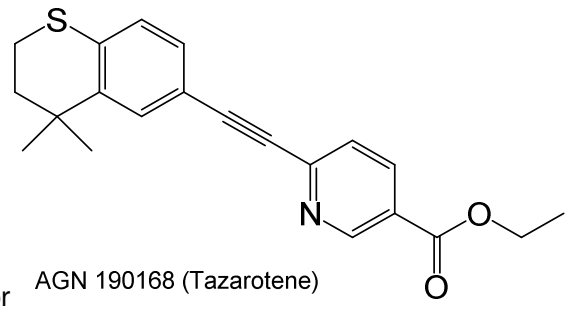


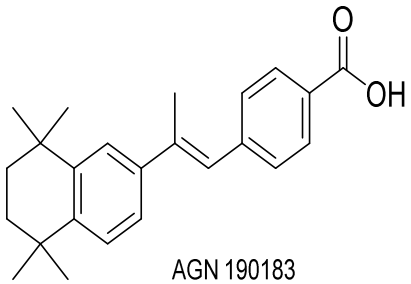
, or



AGN 190168 (Tazarotene)

.

[0018] In some embodiments, the RARγ agonist is a RARγ selective agonist of general formula (IV):



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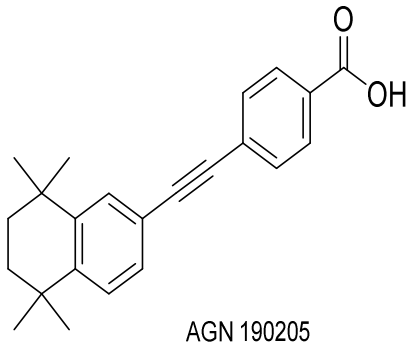

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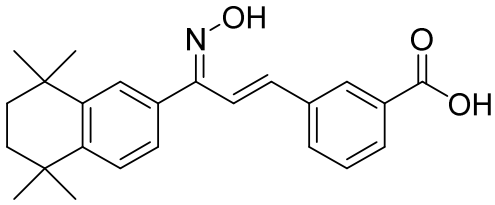
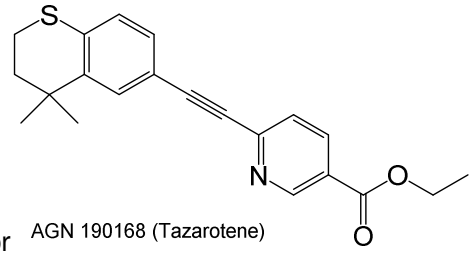
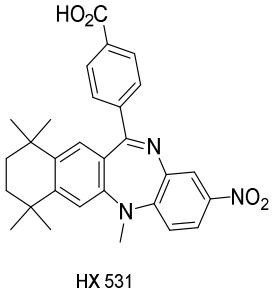




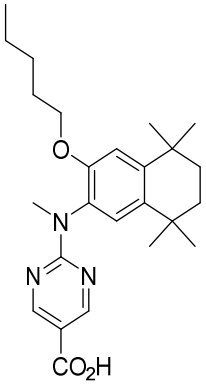
, or AGN 190168 (Tazarotene).

Embodiment 37. The method of any one of Embodiments 9, 18-19, or 26-28, wherein the RARɣ agonist is a selective RARɣ agonist selected from CD437, CD2325, CD666, and BMS961.

Embodiment 38. The method of any one of Embodiments 9 or 22-23, wherein the RXR antagonist is selected from



HX 531,



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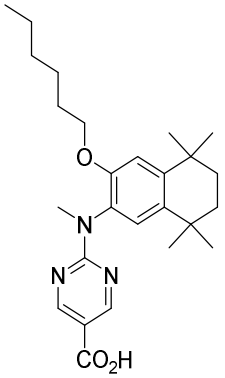


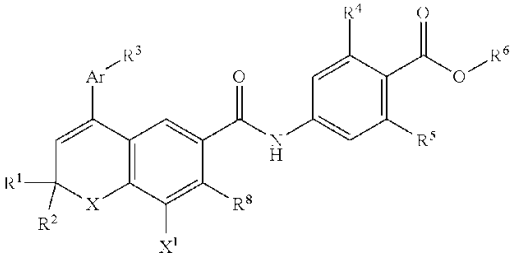
PA 452,

What is claimed is:

1. Use of an immunomodulatory retinoid active agent and/or rexinoid active agent (RAR/RXR active agent) in the manufacture of a medicament for cancer immunotherapy, wherein the RAR/RXR active agent is to be administered to a subject in need thereof, and wherein the RAR/RXR active agent is to be administered with chimeric antigen receptor-modified immune cells (CAR-MIC) and a differentiating RAR active agent,
wherein the immunomodulatory RAR/RXR active agent is:
a) a RARα antagonist, wherein the RARα antagonist is:

i) a compound of general formula (I)

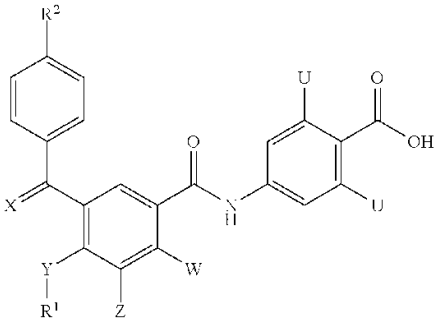
(I)



wherein R^1, R^2, R^3, and R^6 are independently H or $C_{1\text{-}6}$ alkyl; R^4 and R^5 are independently H or F; Ar is phenyl, pyridyl, thienyl, furyl, or naphthyl; X is $C(CH_3)_2$, O, S, or NR^7, wherein R^7 is H or $C_{1\text{-}6}$ alkyl; X^1 is H or halogen such as F, Cl or Br; and R^8 is H or OH; or

ii) a compound of general formula (II)

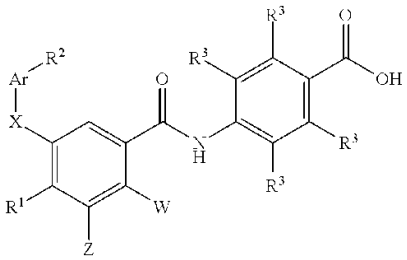
(II)



wherein R^1 and R^2 are independently $C_{1\text{-}6}$ alkyl; X is O, S, or CH_2; Y is O, S, CH_2, or NR^3, wherein R^3 is $C_{1\text{-}6}$; Z is Cl or Br; W is H or OH; and U is independently H or F; or

iii) a compound of general formula (III):

(III)



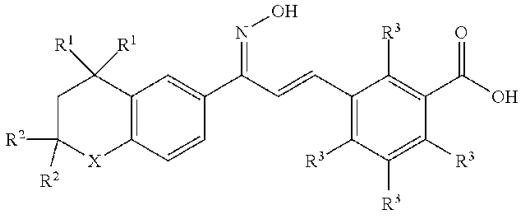
wherein R^1 and R^2 are independently H or C_{1-6} alkyl; R^3 is H or F; Ar is phenyl, pyridyl, thienyl, furyl, or naphthyl; X is O, S, N, or CH_2; W is H or OH; and Z is Cl or Br; or

iv) BMS185411, BMS614, Ro41-5253, Ro46-5471, or AGN 194777; or

b) a RARγ agonist, wherein the RARγ agonist is:

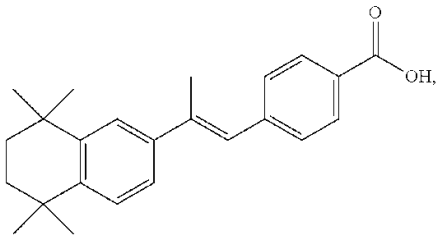
i) a compound of general formula (IV):

(IV)



wherein R^1 and R^2 are independently H or C_{1-6} alkyl; R^3 is H or F; and X is O, S, CH_2, $C(R^4)_2$, or NR^5, wherein R^4 and R^5 are independently H or C_{1-6} alkyl; or

ii)



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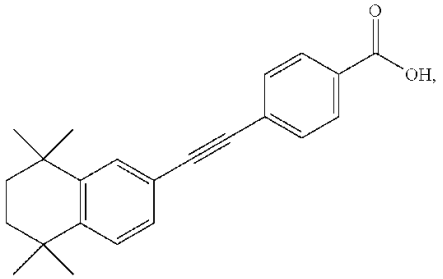

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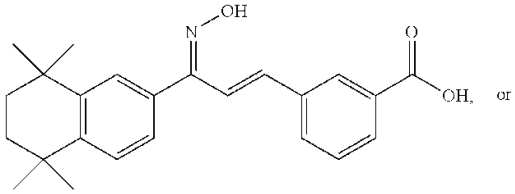
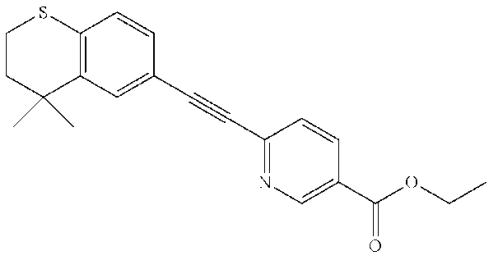


or



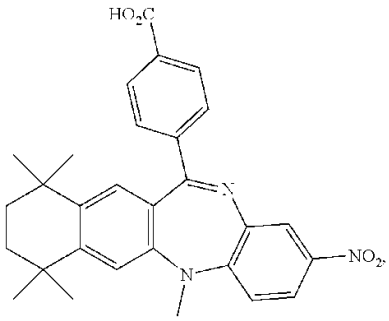
;

AGN 190168 (Tazarotene)

or

iii) CD437, CD2325, CD666, or BMS961; or

c) a RXR antagonist, wherein the RXR antagonist is: AGN195393, LGN100849,



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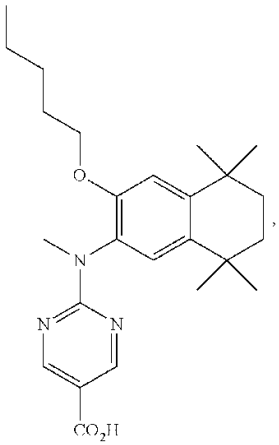

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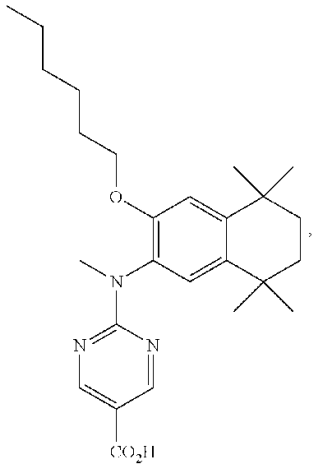

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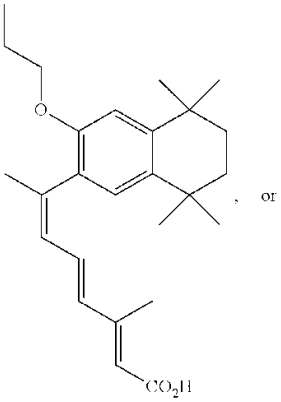

, or

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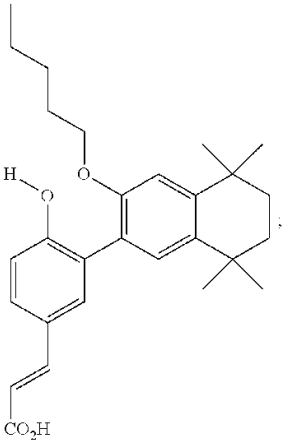

;

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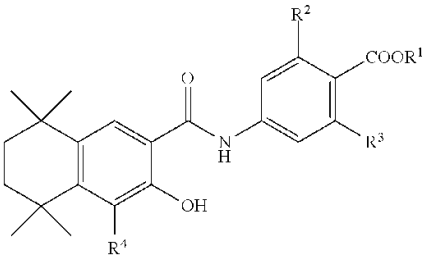
or

d) a combination thereof; and

wherein the differentiating RAR active agent is a RARα agonist, wherein the RARα agonist is a compound of general formula (V):

(V)



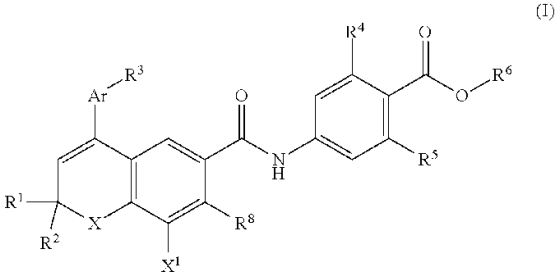
wherein R^1 is H or C_{1-6} alkyl, R^2 and R^3 are independently H or F, and R^4 is a halogen.

2. Use of an immunomodulatory retinoid active agent and/or rexinoid active agent (RAR/RXR active agent) in the manufacture of a medicament for potentiating chimeric antigen receptor-modified immune cells (CAR-MIC) cancer immunotherapy, wherein the RAR/RXR active agent is to be administered to a cancer patient who is receiving, has received, or is scheduled to receive, CAR-MIC, and wherein the RAR/RXR active agent is to be administered with a differentiating RAR active agent to , wherein the immunomodulatory RAR/RXR active agent is:

a) a RARα antagonist, wherein the RARα antagonist is:

i) a compound of general formula (I)

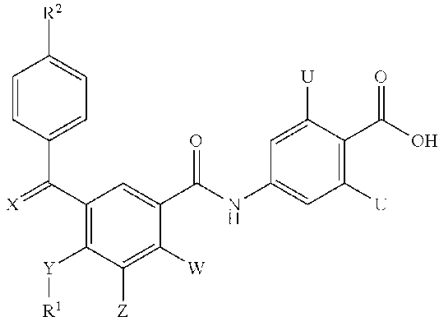
(I)



wherein R^1, R^2, R^3, and R^6 are independently H or C_{1-6} alkyl; R^4 and R^5 are independently H or F; Ar is phenyl, pyridyl, thienyl, furyl, or naphthyl; X is $C(CH_3)_2$, O, S, or NR^7, wherein R^7 is H or C_{1-6} alkyl; X^1 is H or halogen such as F, Cl or Br; and R^8 is H or OH; or

ii) a compound of general formula (II)

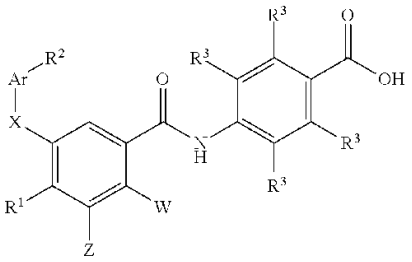
(II)



wherein R^1 and R^2 are independently C_{1-6} alkyl; X is O, S, or CH_2; Y is O, S, CH_2, or NR^3, wherein R^3 is C_{1-6} alkyl; Z is Cl or Br; W is H or OH; and U is independently H or F; or

iii) a compound of general formula (III):

(III)



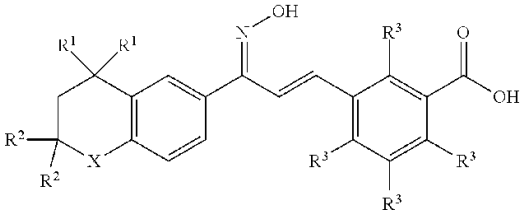
wherein R^1 and R^2 are independently H or C_{1-6} alkyl; R^3 is H or F; Ar is phenyl, pyridyl, thienyl, furyl, or naphthyl; X is O, S, N, or CH_2; W is H or OH; and Z is Cl or Br; or

iv) BMS185411, BMS614, Ro41-5253, Ro46-5471, or AGN 194777; or

b) a RARγ agonist, wherein the RARγ agonist is:

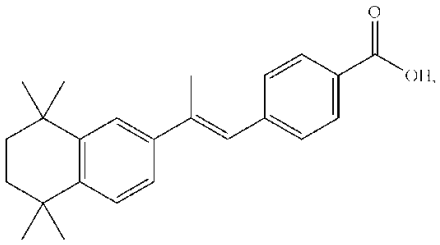
i) a compound of general formula (IV):

(IV)



wherein R^1 and R^2 are independently H or C_{1-6} alkyl; R^3 is H or F; and X is O, S, CH_2, $C(R^4)_2$, or NR^5, wherein R^4 and R^5 are independently H or C_{1-6} alkyl; or

ii)



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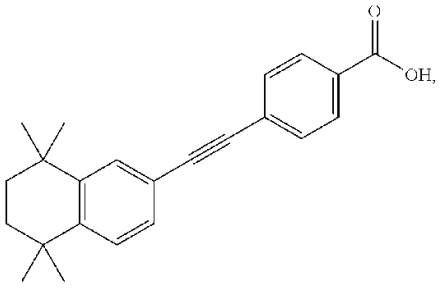

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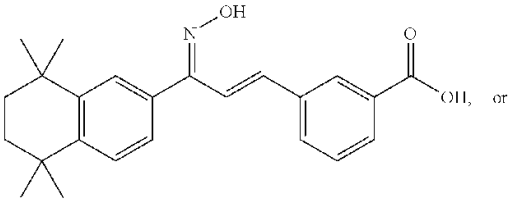
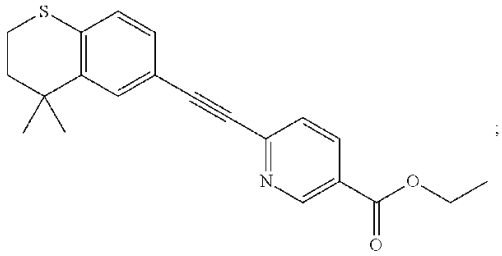


or



;

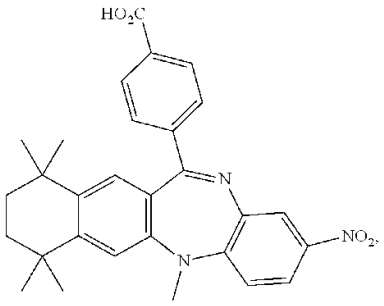
AGN 190168

(Tazarotene)

or

iii) CD437, CD2325, CD666, or BMS961; or

c) a RXR antagonist, wherein the RXR antagonist is: AGN195393, LGN100849,



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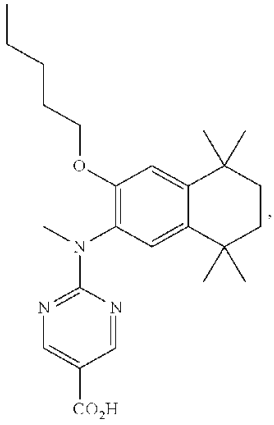

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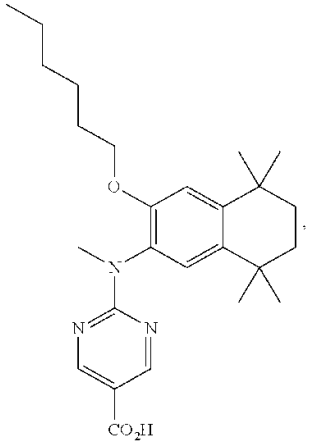

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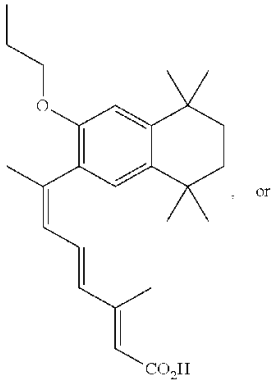

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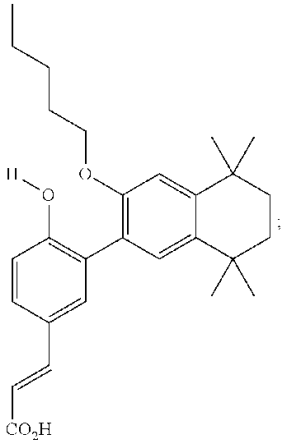

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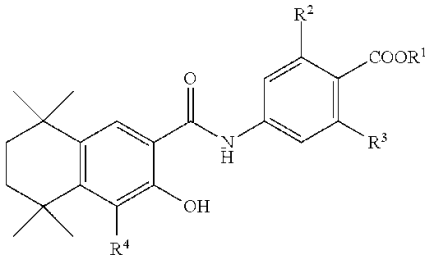
or

d) a combination thereof; and

wherein the differentiating RAR active agent is a RARα agonist, wherein the RARα agonist is a compound of general formula (V):

(V)



wherein R^1 is H or $C_{1\text{-}6}$ alky, R^2 and R^3 are independently H or F, and R^4 is a halogen.

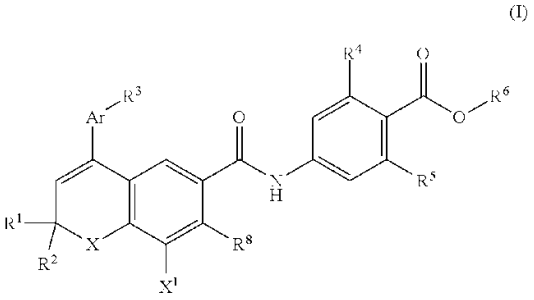
3. The use of claim 1 or 2, wherein the CAR-MIC are cultured in a culture medium comprising an immunomodulatory RAR/RXR active agent prior to administration to the subject or cancer patient.

4. The use of claim 1 or 2, wherein an immune checkpoint inhibitor that is an inhibitor of at least one of CTLA-4, PD-1, TIM-3, LAG-3, PD-L1 ligand, B7-H3, B7-H4, BTLA, or is an ICOS, or OX40 agonist is to be further administered, wherein the immune checkpoint inhibitor is an antibody.

5. The use of claim 1 or 2, wherein the immunomodulatory RAR/RXR active agent comprises at least two RAR active agents.

6. The use of claim 5, wherein a first RAR active agent is a RARα antagonist, and a second RAR active agent is a RARγ selective agonist, or wherein a first RAR active agent is a RARα selective antagonist, and a second RAR active agent is a RARγ agonist.

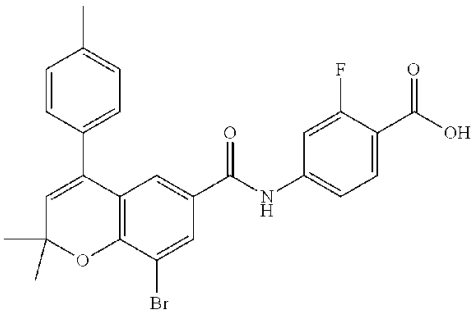
7. The use of claim 1 or 2, wherein the RARα antagonist is a compound of general formula (I)



(I)

wherein R^1, R^2, R^3, and R^6 are independently H or C_{1-6} alkyl; R^4 and R^5 are independently H or F; Ar is phenyl, pyridyl, thienyl, furyl, or naphthyl; X is $C(CH_3)_2$, O, S, or NR^7, wherein R^7 is H or C_{1-6} alkyl; X^1 is H or halogen such as F, Cl or Br; and R^8 is H or OH.

8. The method of claim 7, wherein the RARα antagonist is:



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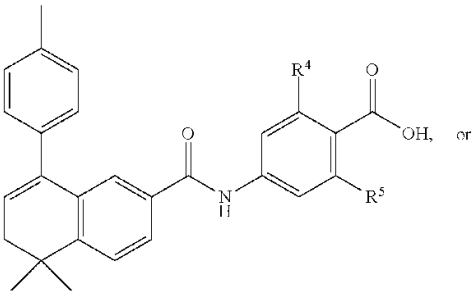
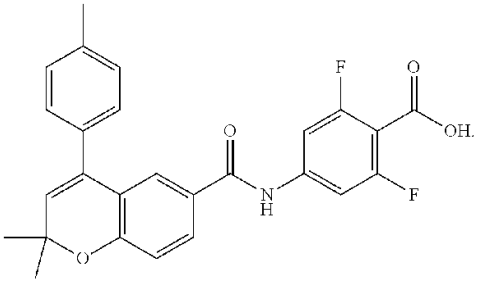


R^4 and R^5 both H; AGN193491
R^4 – F, R^5 – H; AGN193618
R^4 and R^5 both F; AGN194202



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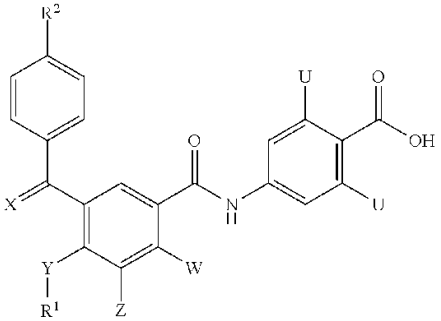
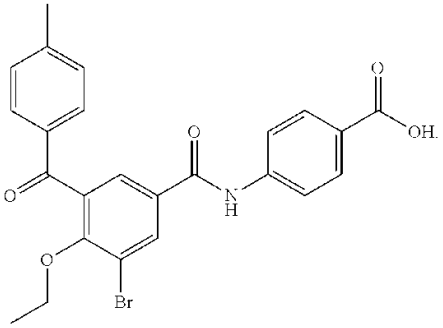
9. The use of claim 1 or 2, wherein the RARα antagonist is a compound of general formula (II)

(II)



wherein R^1 and R^2 are independently C_{1-6} alkyl; X is O, S, or CH_2; Y is O, S, CH_2, or NR^3, wherein R^3 is C_{1-6}; Z is Cl or Br; W is H or OH; and U is independently H or F.

10. The use of claim 9, wherein the RARα antagonist is:



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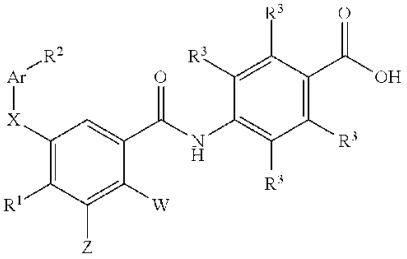
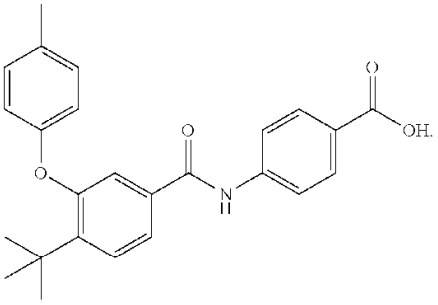
10. The use of claim 1, wherein the RARα antagonist is a compound of general formula (III):

(III)



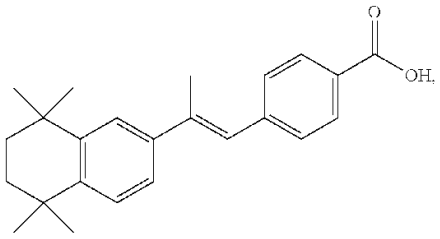
wherein R^1 and R^2 are independently H or C_{1-6} alkyl; R^3 is H or F; Ar is phenyl, pyridyl, thienyl, furyl, or naphthyl; X is O, S, N, or CH_2; W is H or OH; and Z is Cl or Br.

12. The use of claim 1 or 2, wherein the RARα antagonist is BMS185411, BMS614, Ro41-5253, Ro46-5471, or



AGN 194777

13. The use of claim 1 or 2, wherein the RARγ agonist is:



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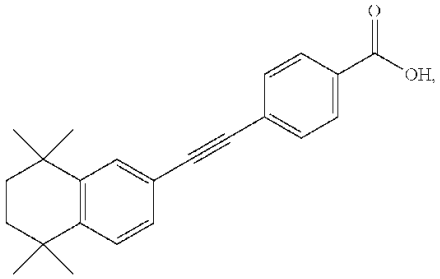

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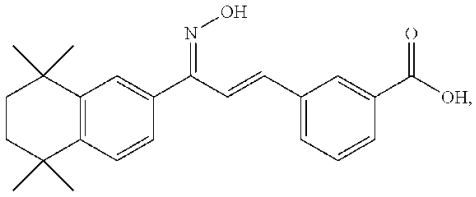
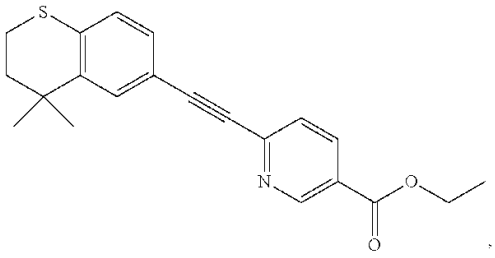


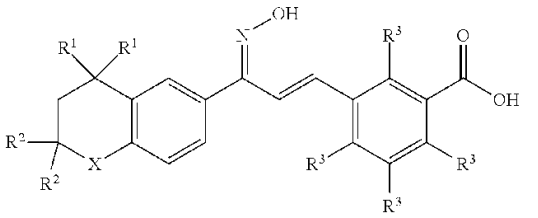


AGN 190168 (Tazarotene)

or is a RARγ selective agonist selected from CD437, CD2325, CD666, and BMS961.

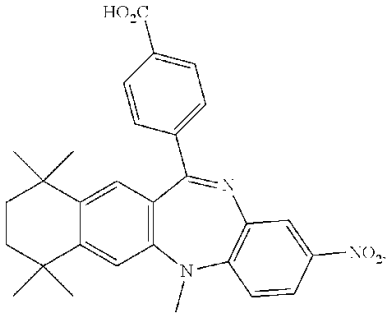
14. The use of claim 1 or 2, wherein the RARγ agonist is a RARγ agonist of general formula IV

(IV)



wherein R^1 and R^2 are independently H or C_{1-6} alkyl; R^3 is H or F; and X is O, S, CH_2, $C(R^4)_2$, or NR^5, wherein R^4 and R^5 are independently H or C_{1-6} alkyl.

15. The use of claim 1 or 2, wherein the RXR antagonist is selected from AGN195393, LGN100849,



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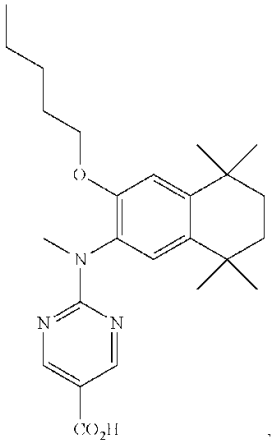

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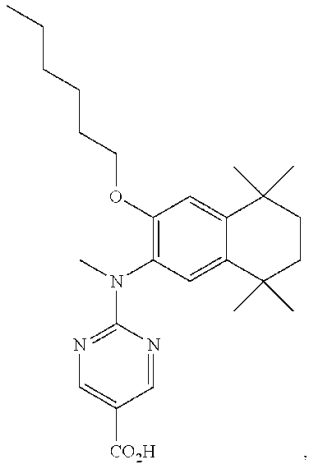

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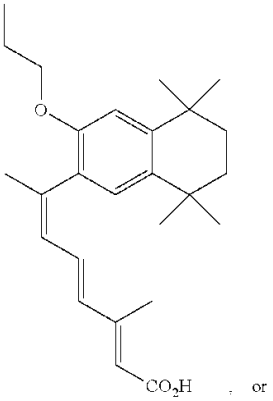

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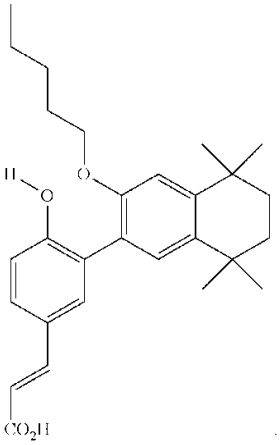
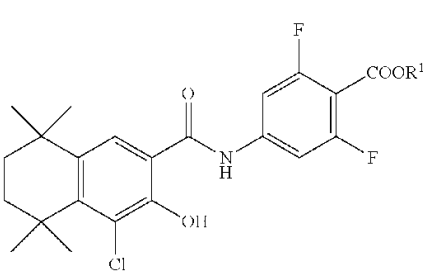


UVI 3003

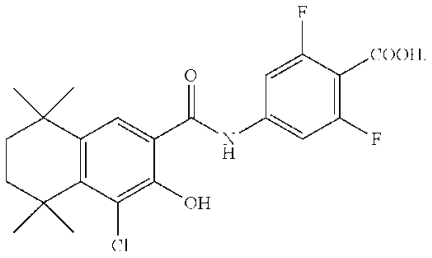
16. The use of claim 1 or 2, wherein the RARα agonist is a compound of general formula (VI):



(VI)

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

17. The use of claim 16 wherein the RARα agonist is a compound of formula (VII):



(VII; IRX5183)

18. The use of claim 1 or 2, wherein the CAR-MIC is a CAR-T cell.

19. The use of claim 1 or 2, wherein the differentiating RAR active agent is to be administered for a period of time of 1 to 4 weeks, and its administration is to be discontinued 2-10 days, before administration of CAR-MIC is scheduled to begin.

20. The use of claim 1 or 2, wherein the immunomodulatory RAR/RXR active agent is to be administered for at least 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 days before administration of CAR-MIC is scheduled to begin.

21. The use of claim 1 or 2, wherein the immunomodulatory RAR/RXR active agent is to be administered subsequent to administration of the CAR-MIC, wherein administration of the immunomodulatory RAR/RXR active agent is to be suspended for a period of 1 to 3 weeks during which time a differentiating RAR active agent is to be administered, and administration of the immunomodulatory RAR/RXR active agent is to be resumed thereafter.