# RECEPTOR SUBTYPE AND FUNCTION SELECTIVE RETINOID AND REXINOID COMPOUNDS IN COMBINATION WITH IMMUNE MODULATORS FOR CANCER IMMUNOTHERAPY

## BACKGROUND

**[0001]** The immune surveillance system provides a host with defense against foreign antigens, but also limits activity against self-antigens thereby preventing autoimmune disease. Cell surface immune checkpoint molecules are endogenous regulators of the immune response which limit autoimmunity by enabling co-inhibitory signaling pathways. Immune checkpoint pathways are important in tumor growth by leading to T-cell depletion and allowing tumors to escape from immune surveillance and enabling unchecked tumor growth. Molecules such as monoclonal antibodies (mAbs) can be designed to target immune checkpoints and such molecules can antagonize co-inhibitory immune pathways, restore immune surveillance, and produce an anti-tumor immune response.

**[0002]** Also, the full anti-tumor effects of immunotherapies can be derived only when they are used in combination with other compounds which can overcome resistance that develop to the immunotherapies by modulating immune pathways.

## SUMMARY

**[0003]** Disclosed herein are compounds for potentiation of immune checkpoint targeted therapies. Compounds which act on retinoic acid receptors (RAR) and retinoid X receptors (RXR) potentiate the activity of immune checkpoint targeted agents.

**[0004]** Thus, provided herein are methods of treating cancer, the methods comprising administering at least one immune checkpoint inhibitor and at least one retinoid active agent or rexinoid active agent (collectively RAR/RXR active agents).

**[0005]** Also provided is use of at least one RXR and/or RAR active agent and a least one immune checkpoint inhibitor for the treatment of disease.

**[0005a]** In one aspect, there is provided the use of at least one immune checkpoint inhibitor and at least one retinoid active agent or rexinoid active agent in the manufacture of a medicament for cancer immunotherapy; wherein the RAR/RXR active agent is to be administered to an individual in need thereof undergoing immune checkpoint inhibitor therapy; and wherein the RAR/RXR active agent potentiates activity of the immune checkpoint inhibitor to promote a T-cell mediated immune response.

**[0006]** 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

What is claimed is:

1. Use of at least one immune checkpoint inhibitor and at least one retinoid active agent or rexinoid active agent in the manufacture of a medicament for cancer immunotherapy; wherein the RAR/RXR active agent is to be administered to an individual in need thereof undergoing immune checkpoint inhibitor therapy; and wherein the RAR/RXR active agent potentiates activity of the immune checkpoint inhibitor to promote a T-cell mediated immune response.

2. The use of claim 1, wherein the retinoid active agent is a Retinoic Acid Receptor (RAR) active agent.

3. The use of claim 1, wherein the rexinoid active agent is a Retinoid X Receptor (RXR) active agent.

4. The use of claim 2, wherein the retinoid active agent is a RARα antagonist.

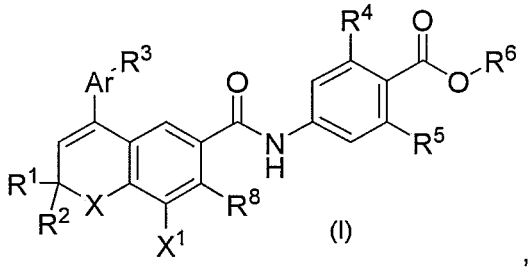
5. The use of claim 1, further comprising two RAR active agents to be administered.

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

7. The use of any one of claims 1-6, wherein the immune checkpoint inhibitor 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.

8. The use of any one of claims 1-6, wherein the immune checkpoint inhibitor is an antibody specific for at least one of CTLA-4, PD-1, TIM-3, LAG-3, PD-L1 ligand, B7-H3, B7-H4, BTLA, ICOS, or OX4.

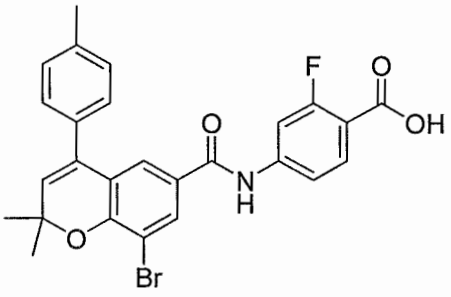
9. The use of any one of claims 4-7, wherein the RARα antagonist is a compound of general formula (I):



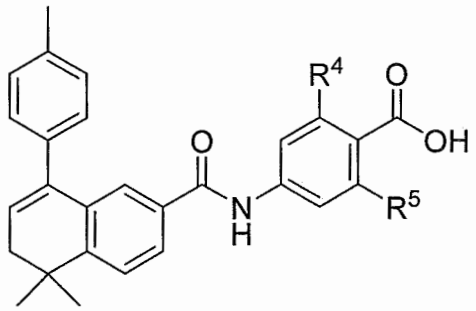

(I)

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.

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

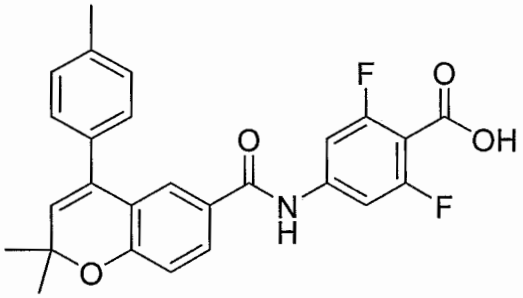


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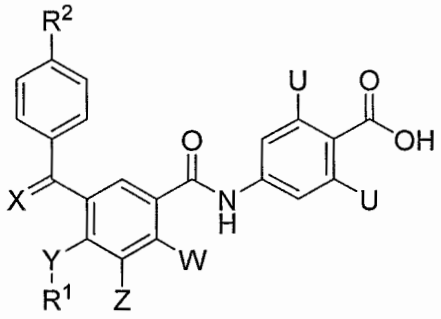
$R^4$ and $R^5$ both H; AGN193491
$R^4$ = F, $R^5$ = H; AGN193618
$R^4$ and $R^5$ both F; AGN194202

, or



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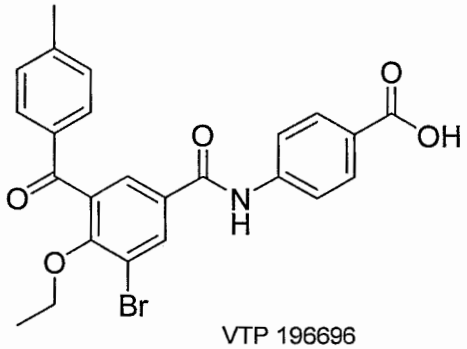
11. The use of any one of claims 4-7, wherein the RARα antagonist is a compound of general formula (II)



(II)

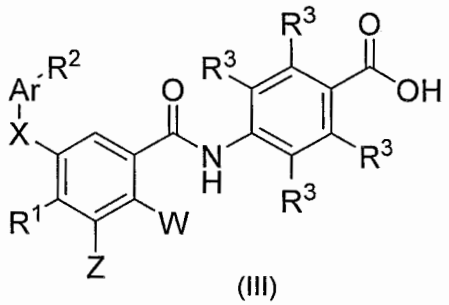
wherein $R^1$ and $R^2$ are independently $C_{1\text{-}6}$ alkyl; X is O, S, or $CH_2$; Y is O, S, $CH_2$, or $NR^3$, wherein $R^3$ is $C_{1\text{-}6}$ alkyl; Z is Cl or Br; W is H or OH; and U is independently H or F.

12. The use of claim 11, wherein the RARα antagonist is:




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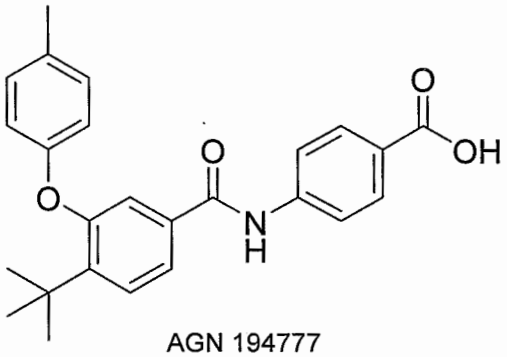
13. The use of any one of claims 4-7, wherein the RARα antagonist is a compound of general formula (III):




(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.

14. The use of any one of claims 4-7, wherein the RARα antagonist is:

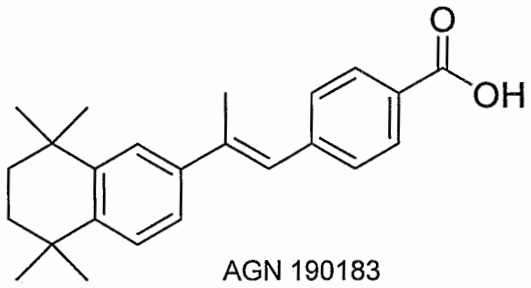



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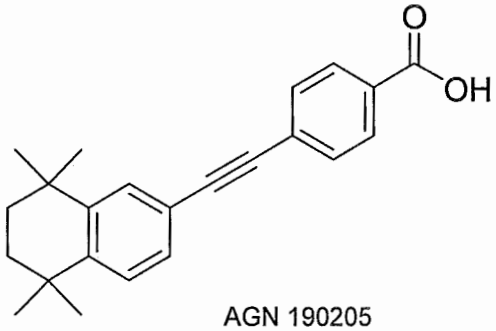
15. The use of any one of claims 4-7, wherein the RARα antagonist is BMS185411, BMS614, Ro41-5253, or Ro46-5471.

16. The use of any one of claims 1-2 or 6-8, wherein the retinoid active agent is a RAR agonist.

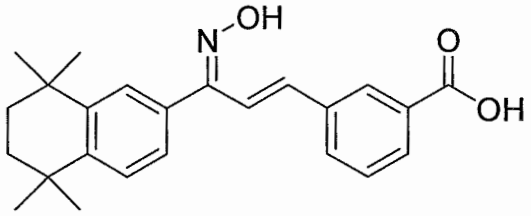
17. The use of claim 16, wherein the RAR agonist is:



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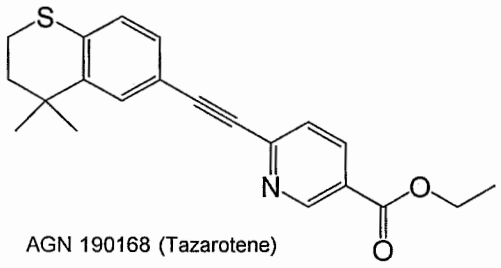


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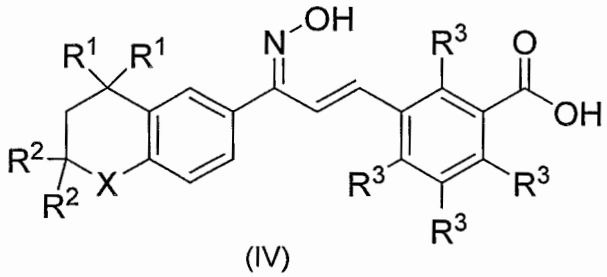
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, or



AGN 190168 (Tazarotene)

18. The use of claim 16, wherein the RAR agonist is a RARγ selective agonist of general formula IV



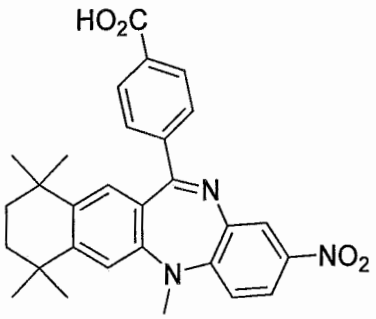
(IV)

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.

19. The use of claim 16, wherein the RAR agonist is a RARγ selective agonist selected from CD437, CD2325, CD666, LY2813631, and BMS961.

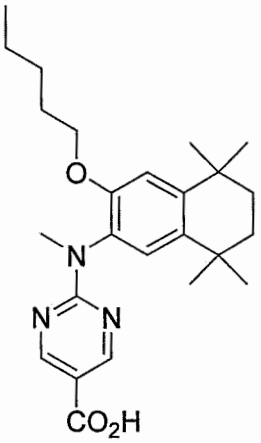
20. The use of claims 1or 3, wherein the rexinoid active agent is a RXR antagonist.

21. The use of claim 19, wherein the RXR antagonist is selected from



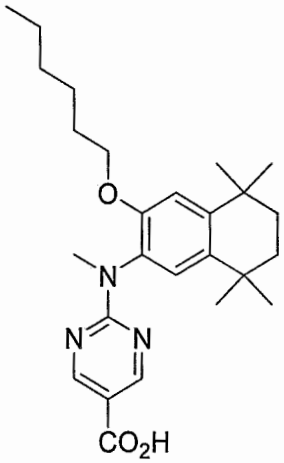
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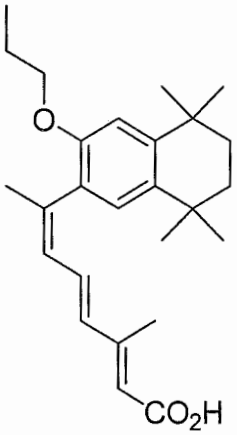
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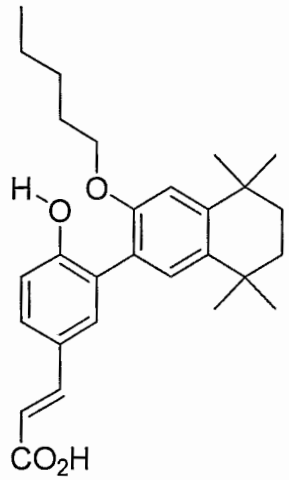
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LG 100754

, or



UVI 3003

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22. The use of claim 20, wherein the RXR antagonist is AGN195393, or LGN100849.

23. The use of any one of claims 1-22, further comprising at least one cancer chemotherapy agent to be administered.