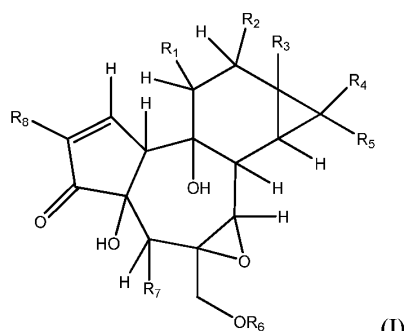


- 45 -

The Claims defining the Invention are as follows:

1. A method of treating a tumour comprising administering to a subject in need thereof, an epoxytiglane compound or a pharmaceutically acceptable salt thereof and an immune checkpoint inhibitor.
2. A method of treating or preventing one or more bystander tumours in a subject comprising administering to a subject in need thereof, an epoxytiglane compound or a pharmaceutically acceptable salt thereof and an immune checkpoint inhibitor; wherein the epoxytiglane compound is administered locally to a tumour other than the one or more bystander tumours.
3. The method according to claim 1 or claim 2 wherein the epoxytiglane compound is administered locally to the tumour.
4. The method according to any one of claims 1 to 3 wherein the epoxytiglane compound is administered by intra-tumoural injection.
5. The method according to any one of claims 1 to 4 wherein the immune checkpoint inhibitor is administered systemically.
6. The method according to claim 5 wherein the immune checkpoint inhibitor is administered by parenteral injection.
7. The method according to any one of claims 1 to 6 wherein the epoxytiglane compound is a compound of formula (I):



or a geometric isomer or stereoisomer or a pharmaceutically acceptable salt thereof;
wherein

- R₁ is hydrogen or C₁₋₆alkyl;
- R₂ is -OH or -OR₉;
- R₃ is -OH or -OR₉;

- 46 -

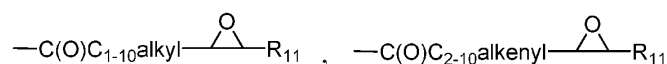
R₄ and R₅ are independently selected from hydrogen and C₁₋₆alkyl;

R₆ is hydrogen or -R₁₀;

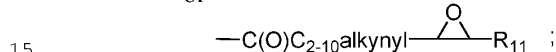
R₇ is hydroxy or OR₁₀;

R₈ is hydrogen or C₁₋₆alkyl;

5 R₉ is -C₁₋₂₀alkyl, -C₂₋₂₀alkenyl, -C₂₋₂₀alkynyl, -C(O)C₁₋₂₀alkyl, -C(O)C₂₋₂₀alkenyl, -C(O)C₂₋₂₀alkynyl, -C(O)cycloalkyl, -C(O)C₁₋₁₀alkylcycloalkyl, -C(O)C₂₋₁₀alkenylcycloalkyl, -C(O)C₂₋₁₀alkynylcycloalkyl, -C(O)aryl, -C(O)C₁₋₁₀alkylaryl, -C(O)C₂₋₁₀alkenylaryl, -C(O)C₂₋₁₀alkynylaryl, -C(O)C₁₋₁₀alkylC(O)R₁₁, -C(O)C₂₋₁₀alkenylC(O)R₁₁, -C(O)C₂₋₁₀alkynylC(O)R₁₁,
 10 -C(O)C₁₋₁₀alkylCH(OR₁₁)(OR₁₁), -C(O)C₂₋₁₀alkenylCH(OR₁₁)(OR₁₁), -C(O)C₂₋₁₀alkynylCH(OR₁₁)(OR₁₁), -C(O)C₁₋₁₀alkylSR₁₁, -C(O)C₂₋₁₀alkenylSR₁₁, -C(O)C₂₋₁₀alkynylSR₁₁, -C(O)C₁₋₁₀alkylC(O)OR₁₁, -C(O)C₂₋₁₀alkenylC(O)OR₁₁, -C(O)C₂₋₁₀alkynylC(O)OR₁₁, -C(O)C₁₋₁₀alkylC(O)SR₁₁, -C(O)C₂₋₁₀alkenylC(O)SR₁₁, -C(O)C₂₋₁₀alkynylC(O)SR₁₁,



or



R₁₀ is -C₁₋₆alkyl, -C₂₋₆alkenyl, -C₂₋₆alkynyl, -C(O)C₁₋₆alkyl, -C(O)C₂₋₆alkenyl, -C(O)C₂₋₆alkynyl, -C(O)aryl, -C(O)C₁₋₆alkylaryl, -C(O)C₂₋₆alkenylaryl, or -C(O)C₂₋₆alkynylaryl; and

R₁₁ is hydrogen, -C₁₋₁₀alkyl, -C₂₋₁₀alkenyl, -C₂₋₁₀alkynyl, cycloalkyl or aryl;

20 wherein each alkyl, alkenyl, alkynyl, cycloalkyl or aryl group is optionally substituted.

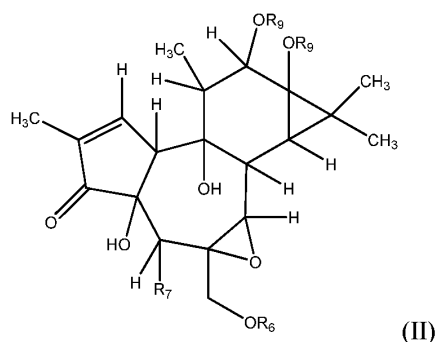
8. The method according to claim 7 wherein R₁ is -CH₃.

9. The method according to claim 7 or claim 8 wherein R₂ and R₃ are independently selected from -OC(O)C₁₋₂₀alkyl, -OC(O)C₂₋₂₀alkenyl, -OC(O)C₂₋₂₀alkynyl, -OC(O)cycloalkyl, -OC(O)C₁₋₁₀alkylcycloalkyl, -OC(O)C₂₋₁₀alkenylcycloalkyl, -OC(O)C₂₋₁₀alkynylcycloalkyl, -OC(O)aryl, -OC(O)C₁₋₁₀alkylaryl, -OC(O)C₂₋₁₀alkenylaryl, -OC(O)C₂₋₁₀alkynylaryl, -OC(O)C₁₋₁₀alkylC(O)R₁₁, -OC(O)C₂₋₁₀alkenylC(O)R₁₁, -OC(O)C₂₋₁₀alkynylC(O)R₁₁, -OC(O)C₁₋₁₀alkylCH(OR₁₁)(OR₁₁), -OC(O)C₂₋

- 47 -

$_{10}\text{alkenylCH(OR}_{11}\text{)(OR}_{11}\text{)}$, $-\text{OC(O)C}_{2-10}\text{alkynylCH(OR}_{11}\text{)(OR}_{11}\text{)}$, $-\text{OC(O)C}_{1-10}\text{alkylSR}_{11}$, $-\text{OC(O)C}_{2-10}\text{alkenylSR}_{11}$, $-\text{OC(O)C}_{2-10}\text{alkynylSR}_{11}$, $-\text{OC(O)C}_{1-10}\text{alkylC(O)OR}_{11}$, $-\text{OC(O)C}_{2-10}\text{alkenylC(O)OR}_{11}$, $-\text{OC(O)C}_{2-10}\text{alkynylC(O)OR}_{11}$, $-\text{OC(O)C}_{1-10}\text{alkylC(O)SR}_{11}$, $-\text{OC(O)C}_{2-10}\text{alkenylC(O)SR}_{11}$ and $-\text{OC(O)C}_{2-10}\text{alkynylC(O)SR}_{11}$.

10. The method according to claim 9 wherein R_2 and R_3 are independently selected from $-\text{OC(O)C}_{1-20}\text{alkyl}$, $-\text{OC(O)C}_{2-20}\text{alkenyl}$, $-\text{OC(O)C}_{2-20}\text{alkynyl}$, $-\text{OC(O)cycloalkyl}$, $-\text{OC(O)C}_{1-10}\text{alkylcycloalkyl}$, $-\text{OC(O)C}_{2-10}\text{alkenylcycloalkyl}$, $-\text{OC(O)C}_{2-10}\text{alkynylcycloalkyl}$ and $-\text{OC(O)aryl}$.
11. The method according to claim 9 or claim 10 wherein R_2 and R_3 are independently selected from $-\text{OC(O)C}_{1-20}\text{alkyl}$, $-\text{OC(O)C}_{2-20}\text{alkenyl}$ and $-\text{OC(O)C}_{2-20}\text{alkynyl}$.
12. The method according to any one of claims 7 to 11 wherein R_4 and R_5 are each independently selected from H and $-\text{CH}_3$.
13. The method according to any one of claims 7 to 12 wherein R_6 is hydrogen, $-\text{C(O)C}_{1-6}\text{alkyl}$, $-\text{C(O)C}_{2-6}\text{alkenyl}$, $-\text{C(O)C}_{2-6}\text{alkynyl}$ or $-\text{C(O)aryl}$.
14. The method according to any one of claims 7 to 13 wherein R_7 is hydroxyl, $-\text{OC(O)C}_{1-6}\text{alkyl}$, $-\text{OC(O)C}_{2-6}\text{alkenyl}$ or $-\text{OC(O)C}_{2-6}\text{alkynyl}$.
15. The method according to any one of claims 7 to 14 wherein R_8 is H or $-\text{CH}_3$.
16. The method according to claim 7 wherein the compound of formula (I) is a compound of formula (II):



or a geometric isomer or stereoisomer or a pharmaceutically acceptable salt thereof;

wherein R_6 , R_7 and R_9 are as defined in claim 7.

- 48 -

17. The method according to any one of claims 7 to 16 wherein the epoxytiglane compound of formula (II) is selected from the following compounds:
- 12-tigloyl-13-(2-methylbutanoyl)-6,7-epoxy-4,5,9,12,13,20-hexahydroxy-1-tiglien-3-one;
- 5 12,13-di-(2-methylbutanoyl)-6,7-epoxy-4,5,9,12,13,20-hexahydroxy-1-tiglien-3-one;
- 12-hexanoyl-13-(2-methylbutanoyl)-6,7-epoxy-4,5,9,12,13,20-hexahydroxy-1-tiglien-3-one;
- 12,13-dihexanoyl-6,7-epoxy-4,5,9,12,13,20-hexahydroxy-1-tiglien-3-one;
- 10 12-myristoyl-13-(2-methylbutanoyl)-6,7-epoxy-4,5,9,12,13,20-hexahydroxy-1-tiglien-3-one;
- 12-tigloyl-13-(2-methylbutanoyl)-6,7-epoxy-4,5,9,12,13-pentahydroxy-20-acetyloxy-1-tiglien-3-one;
- 12-myristoyl-13-acetyloxy-6,7-epoxy-4,5,9,12,13,20-hexahydroxy-1-tiglien-3-one;
- 15 12-propanoyl-13-(2-methylbutanoyl)-6,7-epoxy-4,5,9,12,13,20-hexahydroxy-1-tiglien-3-one; 12,13-ditigloyl-6,7-epoxy-4,5,9,12,13,20-hexahydroxy-1-tiglien-3-one; and
- 12-(2-methylbutanoyl)-13-tigloyl-6,7-epoxy-4,5,9,12,13,20-hexahydroxy-1-tiglien-3-one;
- 20 or a pharmaceutically acceptable salt thereof.
18. The method according to any one of claims 1 to 17 wherein the immune checkpoint inhibitor is an antagonist of Programmed Death 1 (PD-1) receptor, Cytotoxic T-Lymphocyte-Associated protein 4 (CTLA-4), Adenosine A2A
- 25 receptor, B7-H3, B7-H4, indoleamine 2,3-dioxygenase, Killer-cell Immunoglobulin-like receptor (KIR), Lymphocyte Activation Gene-3 (LAG3), T cell immunoreceptor with IG and ITIM domains (TIGIT), T-cell immunoglobulin and mucin-domain containing-3 (TIM-3), CD96 and V-domain Immunoglobulin Suppressor of T cell Activation (VISTA).
- 30 19. The method according to claim 18 wherein the immune checkpoint inhibitor is an antagonist of Programmed Death 1 (PD-1) receptor or Cytotoxic T-Lymphocyte-Associated protein 4 (CTLA-4).

- 49 -

20. The method according to any one of claims 1 to 19 wherein the immune checkpoint inhibitor is administered in multiple doses.
21. The method according to claim 20 wherein the multiple doses are administered prior to, simultaneously with and/or subsequent to the administration of the epoxytigliane compound.
- 5 22. The method according to claim 21 wherein the first dose of immune checkpoint inhibitor is administered prior to administration of the epoxytigliane compound.
23. The method according to claim 21 or 22 wherein a dose of immune checkpoint inhibitor is administered simultaneously with the epoxytigliane compound.
- 10 24. The method according to any one of claims 21 to 23 wherein one or more doses of immune checkpoint inhibitor are administered subsequently to the administration of the epoxytigliane compound.
25. A pharmaceutical composition comprising an epoxytigliane compound or a pharmaceutically acceptable salt thereof and an immune checkpoint inhibitor and optionally a pharmaceutically acceptable carrier.
- 15 26. A kit comprising a composition comprising an epoxytigliane compound and a composition comprising an immune checkpoint inhibitor.
27. The kit according to claim 26 comprising one or more doses of epoxytigliane compound and one or more doses of immune checkpoint inhibitor.
- 20 28. The kit according to claim 26 or 27 comprising one or more doses of epoxytigliane compound formulated for topical administration and one or more doses of immune checkpoint inhibitor formulated for administration by injection.
- 25 29. The kit according to claim 26 or 27 comprising one dose of epoxytigliane compound formulated for intra-tumoural injection and one or more doses of immune checkpoint inhibitor formulated for administration by injection.