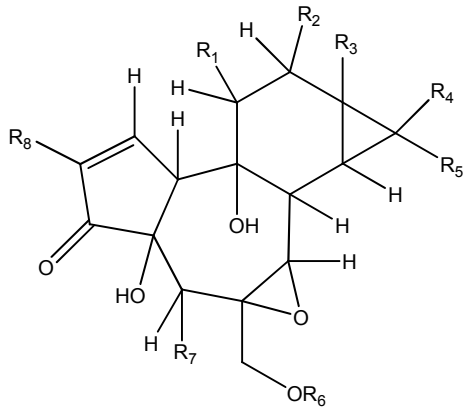
The Claims defining the Invention are as follows:

1. Use of an epoxytigliane compound or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating a tumour, wherein the medicament is to be administered in combination with an immune checkpoint inhibitor separately, simultaneously or sequentially; wherein the epoxytigliane compound is a compound of formula (I):



(I)

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

R_1 is hydrogen or C_{1-6}alkyl;

R_2 is -OH or $–OR_9$;

R_3 is -OH or $–OR_9$;

R_4 and R_5 are independently selected from hydrogen and C_{1-6}alkyl;

R_6 is hydrogen or $–R_{10}$;

R_7 is hydroxy or OR_{10};

R_8 is hydrogen or C_{1-6}alkyl;

R_9 is -C_{1-20}alkyl, -C_{2-20}alkenyl, -C_{2-20}alkynyl, -C(O)C_{1-20}alkyl, -C(O)C_{2-20}alkenyl, -C(O)C_{2-20}alkynyl, -C(O)cycloalkyl, -C(O)C_{1-10}alkylcycloalkyl; -C(O)C_{2-10}alkenylcycloalkyl, -C(O)C_{2-10}alkynylcycloalkyl, -C(O)aryl, -C(O)C_{1-10}alkylaryl, -C(O)C_{2-10}alkenylaryl, -C(O)C_{2-10}alkynylaryl, -C(O)C_{1-10}alkylC(O)R_{11}, -C(O)C_{2-10}alkenylC(O)R_{11}, -C(O)C_{2-10}alkynylC(O)R_{11}, -C(O)C_{1-10}alkylCH(OR_{11})(OR_{11}), -C(O)C_{2-10}alkenylCH(OR_{11})(OR_{11}), -C(O)C_{2-10}alkynylCH(OR_{11})(OR_{11}), -C(O)C_{1-10}alkylSR_{11}, -C(O)C_{2-10}alkenylSR_{11}, -C(O)C_{2-10}alkynylSR_{11}, -C(O)C_{1-10}alkylC(O)OR_{11}, -C(O)C_{2-10}alkenylC(O)OR_{11}, -C(O)C_{2-10}alkynylC(O)OR_{11}, -

$C(O)C_{1-10}alkylC(O)SR_{11}$, $-C(O)C_{2-10}alkenylC(O)SR_{11}$, $-C(O)C_{2-10}alkynylC(O)SR_{11}$,



,



or



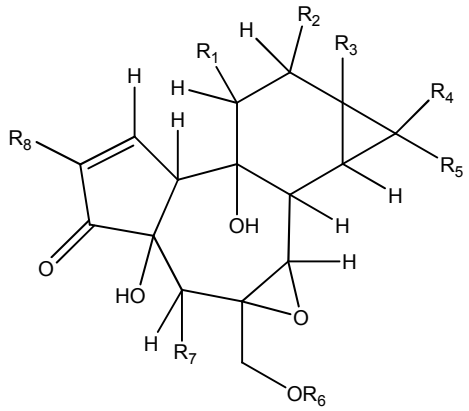
;

R_{10} is $-C_{1-6}alkyl$, $-C_{2-6}alkenyl$, $-C_{2-6}alkynyl$, $-C(O)C_{1-6}alkyl$, $-C(O)C_{2-6}alkenyl$, $-C(O)C_{2-6}alkynyl$, -C(O)aryl, $-C(O)C_{1-6}alkylaryl$, $-C(O)C_{2-6}alkenylaryl$, or $-C(O)C_{2-6}alkynylaryl$; and

R_{11} is hydrogen, $-C_{1-10}alkyl$, $-C_{2-10}alkenyl$, $-C_{2-10}alkynyl$, cycloalkyl or aryl;

wherein each alkyl, alkenyl, alkynyl, cycloalkyl or aryl group is optionally substituted; and wherein the immune checkpoint inhibitor is an antagonist of Programmed Death 1 (PD-1) receptor, Programmed Death Ligand 1 (PD-L1) or Cytotoxic T-Lymphocyte-Associated protein 4 (CTLA-4).

2. Use of an immune checkpoint inhibitor in the manufacture of a medicament for treating a tumour, wherein the medicament is to be administered in combination with an epoxytigliane compound or a pharmaceutically acceptable salt thereof separately, simultaneously or sequentially; wherein the epoxytigliane compound is a compound of formula (I):



(I)

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

R_1 is hydrogen or $C_{1-6}alkyl$;

R_2 is -OH or $–OR_9$;

R_3 is -OH or $–OR_9$;

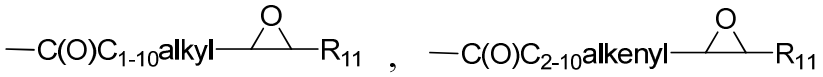
R_4 and R_5 are independently selected from hydrogen and C_{1-6}alkyl;

R_6 is hydrogen or $–R_{10}$;

R_7 is hydroxy or OR_{10};

R_8 is hydrogen or C_{1-6}alkyl;

R_9 is -C_{1-20}alkyl, -C_{2-20}alkenyl, -C_{2-20}alkynyl, -C(O)C_{1-20}alkyl, -C(O)C_{2-20}alkenyl, -C(O)C_{2-20}alkynyl, -C(O)cycloalkyl, -C(O)C_{1-10}alkylcycloalkyl; -C(O)C_{2-10}alkenylcycloalkyl, -C(O)C_{2-10}alkynylcycloalkyl, -C(O)aryl, -C(O)C_{1-10}alkylaryl, -C(O)C_{2-10}alkenylaryl, -C(O)C_{2-10}alkynylaryl, -C(O)C_{1-10}alkylC(O)R_{11}, -C(O)C_{2-10}alkenylC(O)R_{11}, -C(O)C_{2-10}alkynylC(O)R_{11}, -C(O)C_{1-10}alkylCH(OR_{11})(OR_{11}), -C(O)C_{2-10}alkenylCH(OR_{11})(OR_{11}), -C(O)C_{2-10}alkynylCH(OR_{11})(OR_{11}), -C(O)C_{1-10}alkylSR_{11}, -C(O)C_{2-10}alkenylSR_{11}, -C(O)C_{2-10}alkynylSR_{11}, -C(O)C_{1-10}alkylC(O)OR_{11}, -C(O)C_{2-10}alkenylC(O)OR_{11}, -C(O)C_{2-10}alkynylC(O)OR_{11}, -C(O)C_{1-10}alkylC(O)SR_{11}, -C(O)C_{2-10}alkenylC(O)SR_{11}, -C(O)C_{2-10}alkynylC(O)SR_{11},



or



;

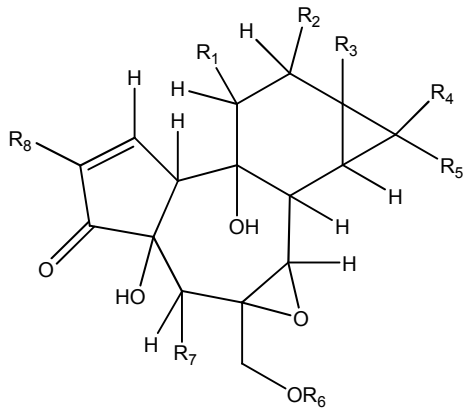
R_{10} is -C_{1-6}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C(O)C_{1-6}alkyl, -C(O)C_{2-6}alkenyl, -C(O)C_{2-6}alkynyl, -C(O)aryl, -C(O)C_{1-6}alkylaryl, -C(O)C_{2-6}alkenylaryl, or -C(O)C_{2-6}alkynylaryl; and

R_{11} is hydrogen, -C_{1-10}alkyl, -C_{2-10}alkenyl, -C_{2-10}alkynyl, cycloalkyl or aryl;

wherein each alkyl, alkenyl, alkynyl, cycloalkyl or aryl group is optionally substituted; and wherein the immune checkpoint inhibitor is an antagonist of Programmed Death 1 (PD-1) receptor, Programmed Death Ligand 1 (PD-L1) or Cytotoxic T-Lymphocyte-Associated protein 4 (CTLA-4).

3. Use of an epoxytigliane compound or a pharmaceutically acceptable salt thereof and an immune checkpoint inhibitor in the manufacture of a medicament for

treating a tumour; wherein the epoxytigliane compound is a compound of formula (I):



(I)

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

R_1 is hydrogen or C_{1-6}alkyl;

R_2 is -OH or $–OR_9$;

R_3 is -OH or $–OR_9$;

R_4 and R_5 are independently selected from hydrogen and C_{1-6}alkyl;

R_6 is hydrogen or $–R_{10}$;

R_7 is hydroxy or OR_{10};

R_8 is hydrogen or C_{1-6}alkyl;

R_9 is -C_{1-20}alkyl, -C_{2-20}alkenyl, -C_{2-20}alkynyl, -C(O)C_{1-20}alkyl, -C(O)C_{2-20}alkenyl, -C(O)C_{2-20}alkynyl, -C(O)cycloalkyl, -C(O)C_{1-10}alkylcycloalkyl; -C(O)C_{2-10}alkenylcycloalkyl, -C(O)C_{2-10}alkynylcycloalkyl, -C(O)aryl, -C(O)C_{1-10}alkylaryl, -C(O)C_{2-10}alkenylaryl, -C(O)C_{2-10}alkynylaryl, -C(O)C_{1-10}alkylC(O)R_{11}, -C(O)C_{2-10}alkenylC(O)R_{11}, -C(O)C_{2-10}alkynylC(O)R_{11}, -C(O)C_{1-10}alkylCH(OR_{11})(OR_{11}), -C(O)C_{2-10}alkenylCH(OR_{11})(OR_{11}), -C(O)C_{2-10}alkynylCH(OR_{11})(OR_{11}), -C(O)C_{1-10}alkylSR_{11}, -C(O)C_{2-10}alkenylSR_{11}, -C(O)C_{2-10}alkynylSR_{11}, -C(O)C_{1-10}alkylC(O)OR_{11}, -C(O)C_{2-10}alkenylC(O)OR_{11}, -C(O)C_{2-10}alkynylC(O)OR_{11}, -C(O)C_{1-10}alkylC(O)SR_{11}, -C(O)C_{2-10}alkenylC(O)SR_{11}, -C(O)C_{2-10}alkynylC(O)SR_{11},



,


or



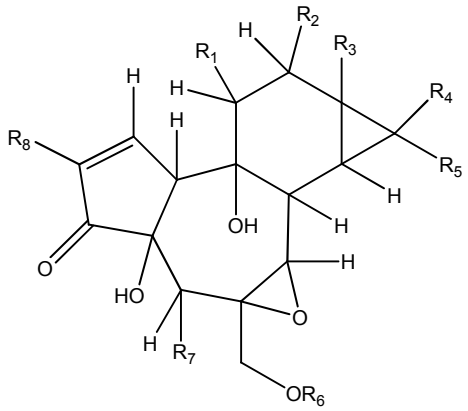
;

R_{10} is -C_{1-6}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C(O)C_{1-6}alkyl, -C(O)C_{2-6}alkenyl, -C(O)C_{2-6}alkynyl, -C(O)aryl, -C(O)C_{1-6}alkylaryl, -C(O)C_{2-6}alkenylaryl, or -C(O)C_{2-6}alkynylaryl; and

R_{11} is hydrogen, -C_{1-10}alkyl, -C_{2-10}alkenyl, -C_{2-10}alkynyl, cycloalkyl or aryl;

wherein each alkyl, alkenyl, alkynyl, cycloalkyl or aryl group is optionally substituted; and wherein the immune checkpoint inhibitor is an antagonist of Programmed Death 1 (PD-1) receptor, Programmed Death Ligand 1 (PD-L1) or Cytotoxic T-Lymphocyte-Associated protein 4 (CTLA-4).

4. Use of an epoxytigliane compound or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating one or more bystander tumours, wherein the medicament is to be administered in combination with an immune checkpoint inhibitor separately, simultaneously or sequentially; wherein the epoxytigliane compound is administered locally to a tumour other than the one or more bystander tumours; wherein the epoxytigliane compound is a compound of formula (I):



(I)

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

R_1 is hydrogen or C_{1-6}alkyl;

R_2 is -OH or –OR_9;

R_3 is -OH or $–OR_9$;

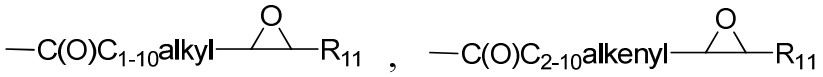
R_4 and R_5 are independently selected from hydrogen and C_{1-6}alkyl;

R_6 is hydrogen or $–R_{10}$;

R_7 is hydroxy or OR_{10};

R_8 is hydrogen or C_{1-6}alkyl;

R_9 is -C_{1-20}alkyl, -C_{2-20}alkenyl, -C_{2-20}alkynyl, -C(O)C_{1-20}alkyl, -C(O)C_{2-20}alkenyl, -C(O)C_{2-20}alkynyl, -C(O)cycloalkyl, -C(O)C_{1-10}alkylcycloalkyl; -C(O)C_{2-10}alkenylcycloalkyl, -C(O)C_{2-10}alkynylcycloalkyl, -C(O)aryl, -C(O)C_{1-10}alkylaryl, -C(O)C_{2-10}alkenylaryl, -C(O)C_{2-10}alkynylaryl, -C(O)C_{1-10}alkylC(O)R_{11}, -C(O)C_{2-10}alkenylC(O)R_{11}, -C(O)C_{2-10}alkynylC(O)R_{11}, -C(O)C_{1-10}alkylCH(OR_{11})(OR_{11}), -C(O)C_{2-10}alkenylCH(OR_{11})(OR_{11}), -C(O)C_{2-10}alkynylCH(OR_{11})(OR_{11}), -C(O)C_{1-10}alkylSR_{11}, -C(O)C_{2-10}alkenylSR_{11}, -C(O)C_{2-10}alkynylSR_{11}, -C(O)C_{1-10}alkylC(O)OR_{11}, -C(O)C_{2-10}alkenylC(O)OR_{11}, -C(O)C_{2-10}alkynylC(O)OR_{11}, -C(O)C_{1-10}alkylC(O)SR_{11}, -C(O)C_{2-10}alkenylC(O)SR_{11}, -C(O)C_{2-10}alkynylC(O)SR_{11},



or



;

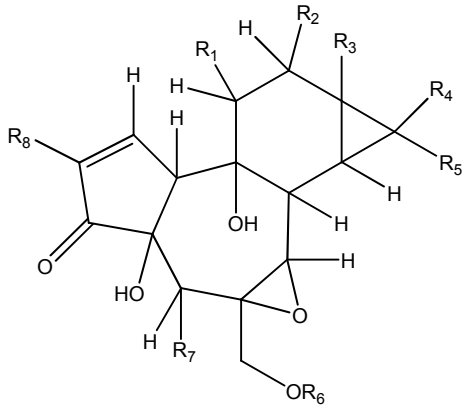
R_{10} is -C_{1-6}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C(O)C_{1-6}alkyl, -C(O)C_{2-6}alkenyl, -C(O)C_{2-6}alkynyl, -C(O)aryl, -C(O)C_{1-6}alkylaryl, -C(O)C_{2-6}alkenylaryl, or -C(O)C_{2-6}alkynylaryl; and

R_{11} is hydrogen, -C_{1-10}alkyl, -C_{2-10}alkenyl, -C_{2-10}alkynyl, cycloalkyl or aryl;

wherein each alkyl, alkenyl, alkynyl, cycloalkyl or aryl group is optionally substituted; and wherein the immune checkpoint inhibitor is an antagonist of Programmed Death 1 (PD-1) receptor, Programmed Death Ligand 1 (PD-L1) or Cytotoxic T-Lymphocyte-Associated protein 4 (CTLA-4).

5. Use of an immune checkpoint inhibitor in the manufacture of a medicament for treating one or more bystander tumours, wherein the medicament is to be administered in combination with an epoxytigliane compound or a

pharmaceutically acceptable salt thereof separately, simultaneously or sequentially; wherein the epoxytigliane compound is administered locally to a tumour other than the one or more bystander tumours; wherein the epoxytigliane compound is a compound of formula (I):



(I)

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

R_1 is hydrogen or C_{1-6}alkyl;

R_2 is -OH or $–OR_9$;

R_3 is -OH or $–OR_9$;

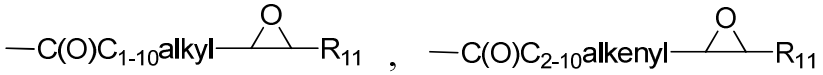
R_4 and R_5 are independently selected from hydrogen and C_{1-6}alkyl;

R_6 is hydrogen or $–R_{10}$;

R_7 is hydroxy or OR_{10};

R_8 is hydrogen or C_{1-6}alkyl;

R_9 is -C_{1-20}alkyl, -C_{2-20}alkenyl, -C_{2-20}alkynyl, -C(O)C_{1-20}alkyl, -C(O)C_{2-20}alkenyl, -C(O)C_{2-20}alkynyl, -C(O)cycloalkyl, -C(O)C_{1-10}alkylcycloalkyl; -C(O)C_{2-10}alkenylcycloalkyl, -C(O)C_{2-10}alkynylcycloalkyl, -C(O)aryl, -C(O)C_{1-10}alkylaryl, -C(O)C_{2-10}alkenylaryl, -C(O)C_{2-10}alkynylaryl, -C(O)C_{1-10}alkylC(O)R_{11}, -C(O)C_{2-10}alkenylC(O)R_{11}, -C(O)C_{2-10}alkynylC(O)R_{11}, -C(O)C_{1-10}alkylCH(OR_{11})(OR_{11}), -C(O)C_{2-10}alkenylCH(OR_{11})(OR_{11}), -C(O)C_{2-10}alkynylCH(OR_{11})(OR_{11}), -C(O)C_{1-10}alkylSR_{11}, -C(O)C_{2-10}alkenylSR_{11}, -C(O)C_{2-10}alkynylSR_{11}, -C(O)C_{1-10}alkylC(O)OR_{11}, -C(O)C_{2-10}alkenylC(O)OR_{11}, -C(O)C_{2-10}alkynylC(O)OR_{11}, -C(O)C_{1-10}alkylC(O)SR_{11}, -C(O)C_{2-10}alkenylC(O)SR_{11}, -C(O)C_{2-10}alkynylC(O)SR_{11},



or



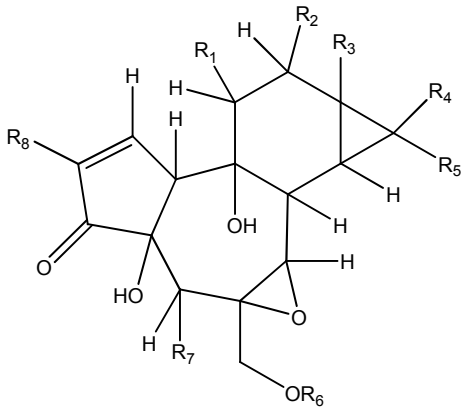
;

R_{10} is -C_{1-6}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C(O)C_{1-6}alkyl, -C(O)C_{2-6}alkenyl, -C(O)C_{2-6}alkynyl, -C(O)aryl, -C(O)C_{1-6}alkylaryl, -C(O)C_{2-6}alkenylaryl, or -C(O)C_{2-6}alkynylaryl; and

R_{11} is hydrogen, -C_{1-10}alkyl, -C_{2-10}alkenyl, -C_{2-10}alkynyl, cycloalkyl or aryl;

wherein each alkyl, alkenyl, alkynyl, cycloalkyl or aryl group is optionally substituted; and wherein the immune checkpoint inhibitor is an antagonist of Programmed Death 1 (PD-1) receptor, Programmed Death Ligand 1 (PD-L1) or Cytotoxic T-Lymphocyte-Associated protein 4 (CTLA-4).

6. Use of an epoxytigliane compound or a pharmaceutically acceptable salt thereof and an immune checkpoint inhibitor in the manufacture of a medicament for treating one or more bystander tumours; wherein the epoxytigliane compound is administered locally to a tumour other than the one or more bystander tumours**;** wherein the epoxytigliane compound is a compound of formula (I):



(I)

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

R_1 is hydrogen or C_{1-6}alkyl;

R_2 is -OH or –OR_9;

R_3 is -OH or –OR_9;

R_4 and R_5 are independently selected from hydrogen and C_{1-6}alkyl;

R_6 is hydrogen or $–R_{10}$;

R_7 is hydroxy or OR_{10};

R_8 is hydrogen or C_{1-6}alkyl;

R_9 is -C_{1-20}alkyl, -C_{2-20}alkenyl, -C_{2-20}alkynyl, -C(O)C_{1-20}alkyl, -C(O)C_{2-20}alkenyl, -C(O)C_{2-20}alkynyl, -C(O)cycloalkyl, -C(O)C_{1-10}alkylcycloalkyl; -C(O)C_{2-10}alkenylcycloalkyl, -C(O)C_{2-10}alkynylcycloalkyl, -C(O)aryl, -C(O)C_{1-10}alkylaryl, -C(O)C_{2-10}alkenylaryl, -C(O)C_{2-10}alkynylaryl, -C(O)C_{1-10}alkylC(O)R_{11}, -C(O)C_{2-10}alkenylC(O)R_{11}, -C(O)C_{2-10}alkynylC(O)R_{11}, -C(O)C_{1-10}alkylCH(OR_{11})(OR_{11}), -C(O)C_{2-10}alkenylCH(OR_{11})(OR_{11}), -C(O)C_{2-10}alkynylCH(OR_{11})(OR_{11}), -C(O)C_{1-10}alkylSR_{11}, -C(O)C_{2-10}alkenylSR_{11}, -C(O)C_{2-10}alkynylSR_{11}, -C(O)C_{1-10}alkylC(O)OR_{11}, -C(O)C_{2-10}alkenylC(O)OR_{11}, -C(O)C_{2-10}alkynylC(O)OR_{11}, -C(O)C_{1-10}alkylC(O)SR_{11}, -C(O)C_{2-10}alkenylC(O)SR_{11}, -C(O)C_{2-10}alkynylC(O)SR_{11},



,


or



;

R_{10} is -C_{1-6}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C(O)C_{1-6}alkyl, -C(O)C_{2-6}alkenyl, -C(O)C_{2-6}alkynyl, -C(O)aryl, -C(O)C_{1-6}alkylaryl, -C(O)C_{2-6}alkenylaryl, or -C(O)C_{2-6}alkynylaryl; and

R_{11} is hydrogen, -C_{1-10}alkyl, -C_{2-10}alkenyl, -C_{2-10}alkynyl, cycloalkyl or aryl;

wherein each alkyl, alkenyl, alkynyl, cycloalkyl or aryl group is optionally substituted; and wherein the immune checkpoint inhibitor is an antagonist of Programmed Death 1 (PD-1) receptor, Programmed Death Ligand 1 (PD-L1) or Cytotoxic T-Lymphocyte-Associated protein 4 (CTLA-4).

7. Use according to any one of claims 1 to 3 wherein the epoxytigliane compound is administered locally to the tumour.

8. Use according to any one of claims 1 to 7 wherein the epoxytigliane compound is administered by intra-tumoural injection.

9. Use according to any one of claims 1, 2, 4, 5, 7 and 8 wherein the immune

checkpoint inhibitor is administered systemically.

10. Use according to claim 9 wherein the immune checkpoint inhibitor is administered by parenteral injection.

11. Use according to any one of claims 1 to 10 wherein R_1 is $–CH_3$.

12. Use according to any one of claims 1 to 11 wherein R_2 and R_3 are independently selected from -OC(O)C_{1-20}alkyl, -OC(O)C_{2-20}alkenyl, -OC(O)C_{2-20}alkynyl, -OC(O)cycloalkyl, -OC(O)C_{1-10}alkylcycloalkyl; -OC(O)C_{2-10}alkenylcycloalkyl, -OC(O)C_{2-10}alkynylcycloalkyl, -OC(O)aryl, -OC(O)C_{1-10}alkylaryl, -OC(O)C_{2-10}alkenylaryl, -OC(O)C_{2-10}alkynylaryl, -OC(O)C_{1-10}alkylC(O)R_{11}, -OC(O)C_{2-10}alkenylC(O)R_{11}, -OC(O)C_{2-10}alkynylC(O)R_{11}, -OC(O)C_{1-10}alkylCH(OR_{11})(OR_{11}), -OC(O)C_{2-10}alkenylCH(OR_{11})(OR_{11}), -OC(O)C_{2-10}alkynylCH(OR_{11})(OR_{11}), -OC(O)C_{1-10}alkylSR_{11}, -OC(O)C_{2-10}alkenylSR_{11}, -OC(O)C_{2-10}alkynylSR_{11}, -OC(O)C_{1-10}alkylC(O)OR_{11}, -OC(O)C_{2-10}alkenylC(O)OR_{11}, -OC(O)C_{2-10}alkynylC(O)OR_{11}, -OC(O)C_{1-10}alkylC(O)SR_{11}, -OC(O)C_{2-10}alkenylC(O)SR_{11} and -OC(O)C_{2-10}alkynylC(O)SR_{11}.

13. Use according to claim 12 wherein R_2 and R_3 are independently selected from -OC(O)C_{1-20}alkyl, -OC(O)C_{2-20}alkenyl, -OC(O)C_{2-20}alkynyl, -OC(O)cycloalkyl, -OC(O)C_{1-10}alkylcycloalkyl; -OC(O)C_{2-10}alkenylcycloalkyl, -OC(O)C_{2-10}alkynylcycloalkyl and -OC(O)aryl.

14. Use according to claim 12 or claim 13 wherein R_2 and R_3 are independently selected from -OC(O)C_{1-20}alkyl, -OC(O)C_{2-20}alkenyl and -OC(O)C_{2-20}alkynyl.

15. Use according to any one of claims 1 to 14 wherein R_4 and R_5 are each independently selected from H and $–CH_3$.

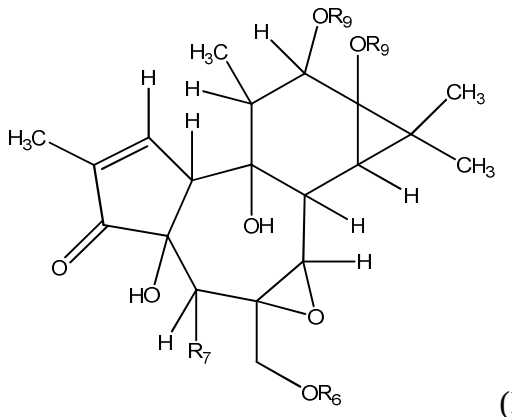
16. Use according to any one of claims 1 to 15 wherein R_6 is hydrogen, -C(O)C_{1-6}alkyl, -C(O)C_{2-6}alkenyl, –C(O)C_{2-6}alkynyl or -C(O)aryl.

17. Use according to any one of claims 1 to 16 wherein R_7 is hydroxyl, -OC(O)C_{1-6}alkyl, -OC(O)C_{2-6}alkenyl or –OC(O)C_{2-6}alkynyl.

18. Use according to any one of claims 1 to 17 wherein R_8 is H or $–CH_3$.

19. Use according to any one of claims 1 to 6 wherein the compound of formula (I)

is a compound of formula (II):



(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 1.

20. Use according to any one of claims 1 to 19 wherein the epoxytigliane 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;

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;

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;

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;

or a pharmaceutically acceptable salt thereof.

21. Use according to any one of claims 1 to 20 wherein the immune checkpoint inhibitor is an antagonist of Programmed Death 1 (PD-1) receptor or Cytotoxic

T-Lymphocyte-Associated protein 4 (CTLA-4).

22. Use according to any one of claims 1 to 21 wherein the immune checkpoint inhibitor is administered in multiple doses.

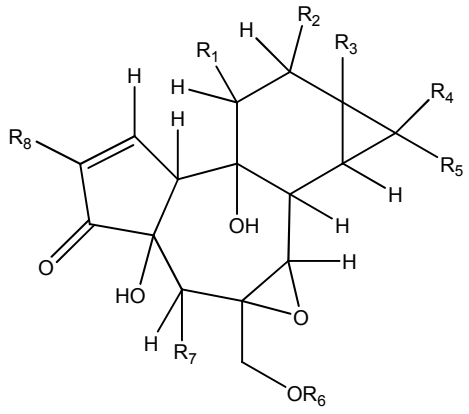
23. Use according to claim 22 wherein the multiple doses are administered prior to, simultaneously with and/or subsequent to the administration of the epoxytigliane compound.

24. Use according to claim 23 wherein the first dose of immune checkpoint inhibitor is administered prior to administration of the epoxytigliane compound.

25. Use according to claim 23 or claim 24 wherein a dose of immune checkpoint inhibitor is administered simultaneously with the epoxytigliane compound.

26. Use according to any one of claims 22 to 25 wherein one or more doses of immune checkpoint inhibitor are administered subsequently to the administration of the epoxytigliane compound.

27. A pharmaceutical composition comprising an epoxytigliane compound or a pharmaceutically acceptable salt thereof and an immune checkpoint inhibitor and optionally a pharmaceutically acceptable carrier; wherein the epoxytigliane compound is a compound of formula (I):



(I)

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

R_1 is hydrogen or $C_{1\text{-}6}$alkyl;

R_2 is -OH or $–OR_9$;

R_3 is -OH or $–OR_9$;

R_4 and R_5 are independently selected from hydrogen and $C_{1\text{-}6}$alkyl;

R_6 is hydrogen or $–R_{10}$;

R_7 is hydroxy or OR_{10};

R_8 is hydrogen or C_{1-6}alkyl;

R_9 is -C_{1-20}alkyl, -C_{2-20}alkenyl, -C_{2-20}alkynyl, -C(O)C_{1-20}alkyl, -C(O)C_{2-20}alkenyl, -C(O)C_{2-20}alkynyl, -C(O)cycloalkyl, -C(O)C_{1-10}alkylcycloalkyl; -C(O)C_{2-10}alkenylcycloalkyl, -C(O)C_{2-10}alkynylcycloalkyl, -C(O)aryl, -C(O)C_{1-10}alkylaryl, -C(O)C_{2-10}alkenylaryl, -C(O)C_{2-10}alkynylaryl, -C(O)C_{1-10}alkylC(O)R_{11}, -C(O)C_{2-10}alkenylC(O)R_{11}, -C(O)C_{2-10}alkynylC(O)R_{11}, -C(O)C_{1-10}alkylCH(OR_{11})(OR_{11}), -C(O)C_{2-10}alkenylCH(OR_{11})(OR_{11}), -C(O)C_{2-10}alkynylCH(OR_{11})(OR_{11}), -C(O)C_{1-10}alkylSR_{11}, -C(O)C_{2-10}alkenylSR_{11}, -C(O)C_{2-10}alkynylSR_{11}, -C(O)C_{1-10}alkylC(O)OR_{11}, -C(O)C_{2-10}alkenylC(O)OR_{11}, -C(O)C_{2-10}alkynylC(O)OR_{11}, -C(O)C_{1-10}alkylC(O)SR_{11}, -C(O)C_{2-10}alkenylC(O)SR_{11}, -C(O)C_{2-10}alkynylC(O)SR_{11},



,


or



;

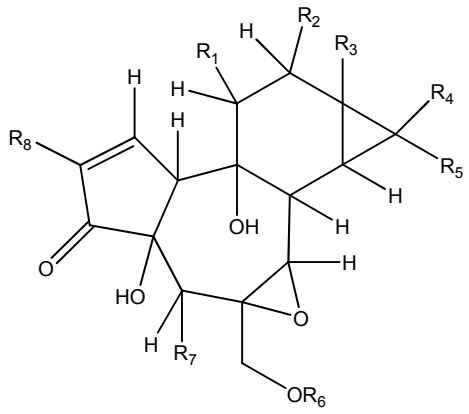
R_{10} is -C_{1-6}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C(O)C_{1-6}alkyl, -C(O)C_{2-6}alkenyl, -C(O)C_{2-6}alkynyl, -C(O)aryl, -C(O)C_{1-6}alkylaryl, -C(O)C_{2-6}alkenylaryl, or -C(O)C_{2-6}alkynylaryl; and

R_{11} is hydrogen, -C_{1-10}alkyl, -C_{2-10}alkenyl, -C_{2-10}alkynyl, cycloalkyl or aryl;

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

and wherein the immune checkpoint inhibitor is an antagonist of Programmed Death 1 (PD-1) receptor, Programmed Death Ligand 1 (PD-L1) or Cytotoxic T-Lymphocyte-Associated protein 4 (CTLA-4).

28. A kit comprising a composition comprising an epoxytigliane compound and a composition comprising an immune checkpoint inhibitor; wherein the epoxytigliane compound is a compound of formula (I):



(I)

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

R_1 is hydrogen or C_{1-6}alkyl;

R_2 is -OH or $–OR_9$;

R_3 is -OH or $–OR_9$;

R_4 and R_5 are independently selected from hydrogen and C_{1-6}alkyl;

R_6 is hydrogen or $–R_{10}$;

R_7 is hydroxy or OR_{10};

R_8 is hydrogen or C_{1-6}alkyl;

R_9 is -C_{1-20}alkyl, -C_{2-20}alkenyl, -C_{2-20}alkynyl, -C(O)C_{1-20}alkyl, -C(O)C_{2-20}alkenyl, -C(O)C_{2-20}alkynyl, -C(O)cycloalkyl, -C(O)C_{1-10}alkylcycloalkyl; -C(O)C_{2-10}alkenylcycloalkyl, -C(O)C_{2-10}alkynylcycloalkyl, -C(O)aryl, -C(O)C_{1-10}alkylaryl, -C(O)C_{2-10}alkenylaryl, -C(O)C_{2-10}alkynylaryl, -C(O)C_{1-10}alkylC(O)R_{11}, -C(O)C_{2-10}alkenylC(O)R_{11}, -C(O)C_{2-10}alkynylC(O)R_{11}, -C(O)C_{1-10}alkylCH(OR_{11})(OR_{11}), -C(O)C_{2-10}alkenylCH(OR_{11})(OR_{11}), -C(O)C_{2-10}alkynylCH(OR_{11})(OR_{11}), -C(O)C_{1-10}alkylSR_{11}, -C(O)C_{2-10}alkenylSR_{11}, -C(O)C_{2-10}alkynylSR_{11}, -C(O)C_{1-10}alkylC(O)OR_{11}, -C(O)C_{2-10}alkenylC(O)OR_{11}, -C(O)C_{2-10}alkynylC(O)OR_{11}, -C(O)C_{1-10}alkylC(O)SR_{11}, -C(O)C_{2-10}alkenylC(O)SR_{11}, -C(O)C_{2-10}alkynylC(O)SR_{11},



,



or



;

R_{10} is -C_{1-6}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C(O)C_{1-6}alkyl, -C(O)C_{2-6}alkenyl, -C(O)C_{2-6}alkynyl, -C(O)aryl, -C(O)C_{1-6}alkylaryl, -C(O)C_{2-6}alkenylaryl, or -C(O)C_{2-6}alkynylaryl; and

R_{11} is hydrogen, -C_{1-10}alkyl, -C_{2-10}alkenyl, -C_{2-10}alkynyl, cycloalkyl or aryl;

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

and wherein the immune checkpoint inhibitor is an antagonist of Programmed Death 1 (PD-1) receptor, Programmed Death Ligand 1 (PD-L1) or Cytotoxic T-Lymphocyte-Associated protein 4 (CTLA-4).

29. The kit according to claim 28 comprising one or more doses of epoxytigliane compound and one or more doses of immune checkpoint inhibitor.

30. The kit according to claim 28 or claim 29 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.

31. The kit according to claim 28 or claim 29 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.