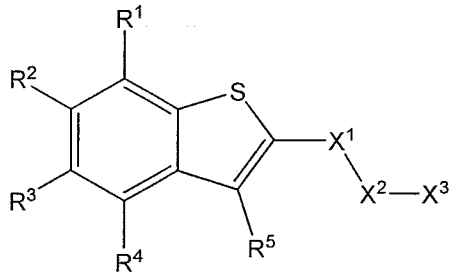
interferons, the development of STING activating agents is rapidly taking an important place in today's anti-tumor therapy landscape.

SUMMARY

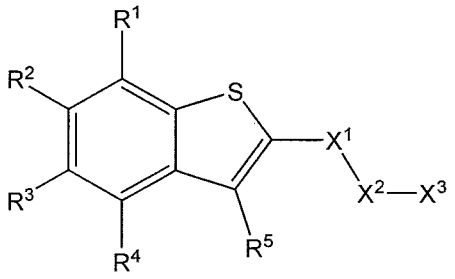
The present disclosure relates to novel compounds of general formula (Ia). In particular, the present disclosure relates to compounds having the general structural formula (Ia):



(Ia)

or pharmaceutically acceptable salts thereof, as described herein. Embodiments of the disclosure include compounds of general formula (Ia), and pharmaceutically acceptable salts thereof, as well as synthesis and isolation of compounds of general formula (Ia), and pharmaceutically acceptable salts thereof. Uses of compounds of general formula (Ia) are also disclosed.

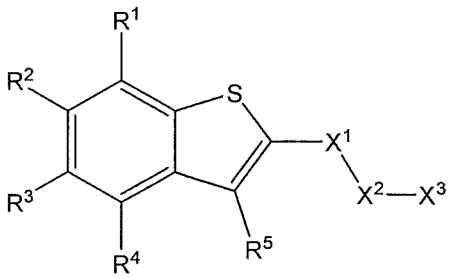
The present disclosure also relates to novel compounds of general formula (Ia'). In particular, the present disclosure relates to compounds having the general structural formula (Ia'):



(Ia')

or pharmaceutically acceptable salts thereof, as described herein.

In one aspect, there is provided a compound of formula (Ia'):



(Ia')

or a pharmaceutically acceptable salt thereof, wherein

R^1 is selected from the group consisting of H, F, C_1-C_6 alkyl, and C_1-C_6 haloalkyl;

R^2 is selected from the group consisting of halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, OC_1-C_3 alkyl, OC_1-C_3 haloalkyl, OH, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $N(C_1$-C_3 alkyl)$_2$, $NH(C_1$-C_3 alkyl), SC_1-C_3 alkyl;

R^3 is selected from the group consisting of halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, OC_1-C_3 alkyl, OC_1-C_3 haloalkyl, OH, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $N(C_1$-C_3 alkyl)$_2$, $NH(C_1$-C_3 alkyl), SC_1-C_3 alkyl;

R^4 is selected from the group consisting of H, F, C_1-C_6 alkyl, and C_1-C_6 haloalkyl;

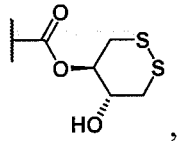
R^5 is selected from H, F, Cl, OR^6, C_1-C_6 alkyl and C_1-C_6 haloalkyl;

each R^6 is independently selected from the group consisting of H, C_1-C_4 alkyl, and C_1-C_4 haloalkyl;

X^1 is C(O);

X^2 is CHR^8CHR^8;

each R^8 is independently selected from the group consisting of H, C_1-C_4 alkyl, C_1-C_4 alkyl substituted by OH, C_1-C_4 alkyl substituted by OC_1-C_3 alkyl, and C_3-C_6 cycloalkyl, and where optionally 2 R^8 are taken together, along with the atoms to which they are attached, to form a 3- to 6-membered fused ring;

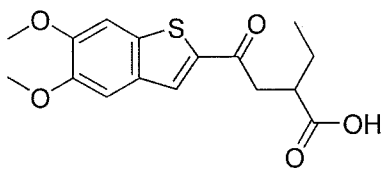
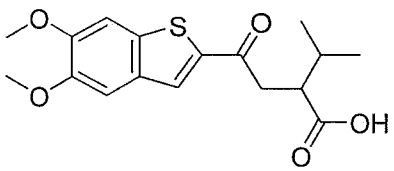
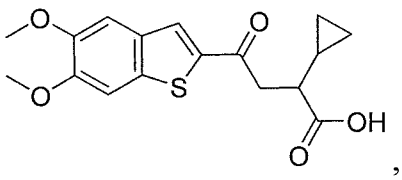
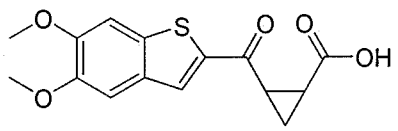
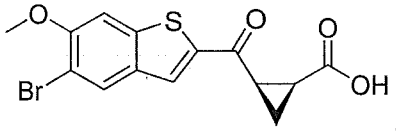
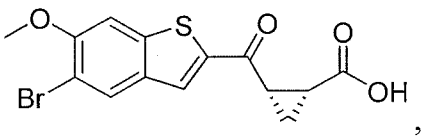
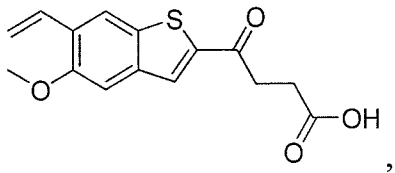
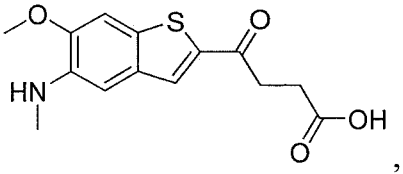
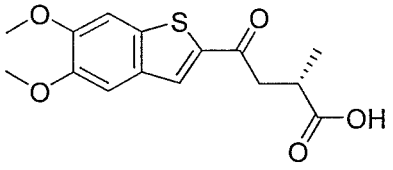
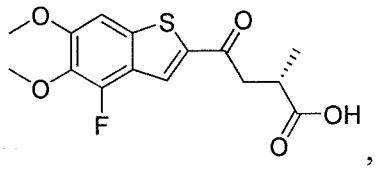
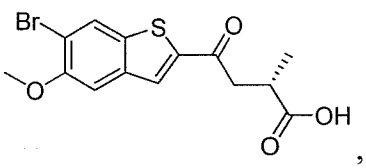
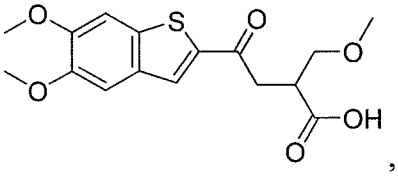
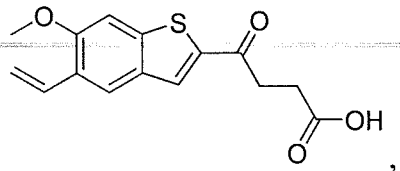
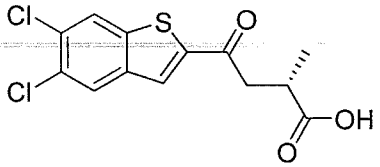
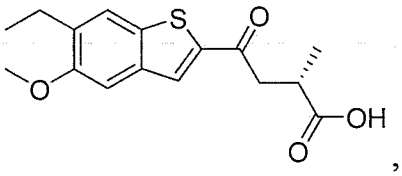
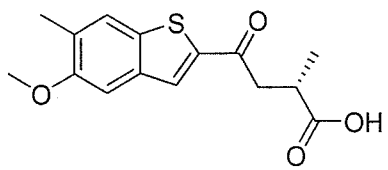
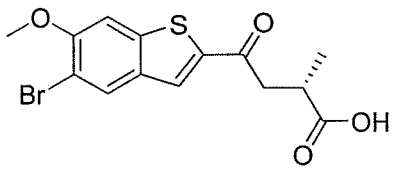
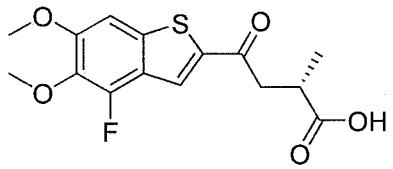
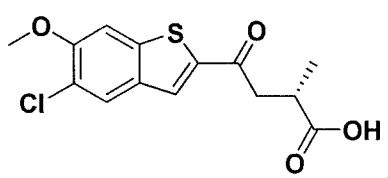
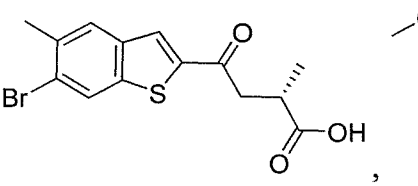
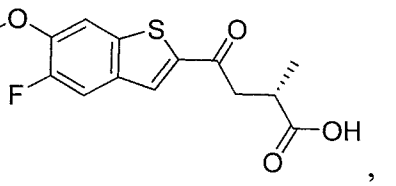
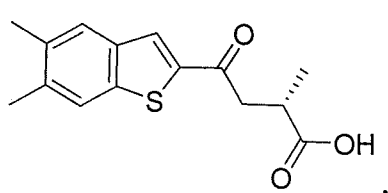
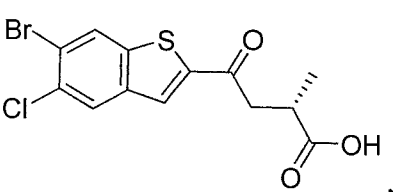
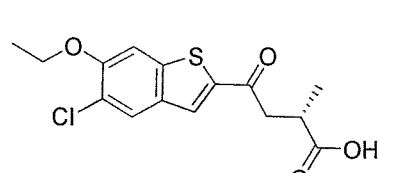
X^3 is selected from the group consisting of $COOR^6$, , $C(O)SR^6$, $C(S)OR^6$, SO_2R^6, and $C(O)N(R^9)_2$; and

each R^9 is independently selected from the group consisting of H, $COOR^6$, and SO_2R^6;

wherein when X^1-X^2-X^3 is X^1-CHR^8CH_2-X^3, at least one of R^2 and R^3 is not selected from the group consisting of halogen, OR^6, C_1-C_6 alkyl, and C_1-C_6 haloalkyl.

Embodiments of the disclosure include compounds of general formula (Ia'), and pharmaceutically acceptable salts thereof, as well as synthesis and isolation of compounds of general formula (Ia'), and pharmaceutically acceptable salts thereof. Uses of compounds of general formula (Ia') are also disclosed.

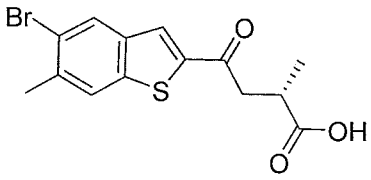
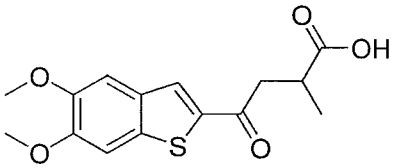
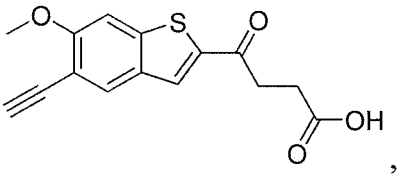
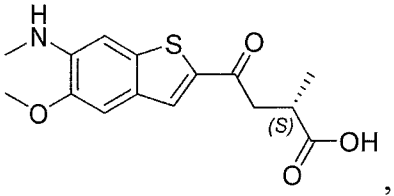
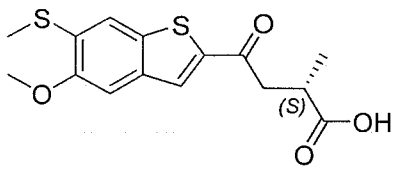
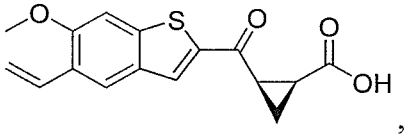
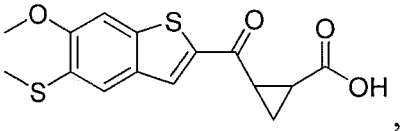
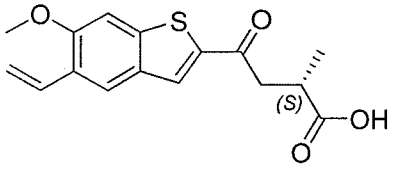
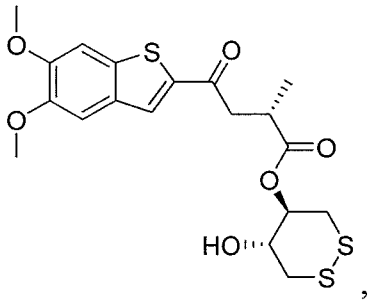
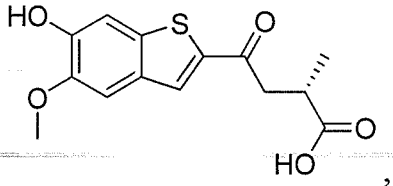
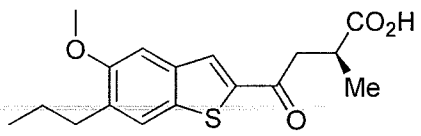
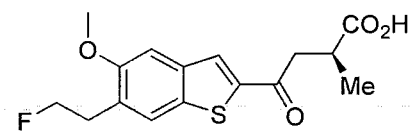
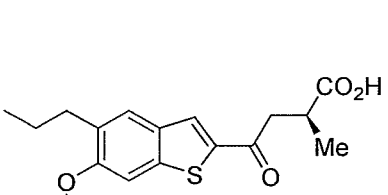
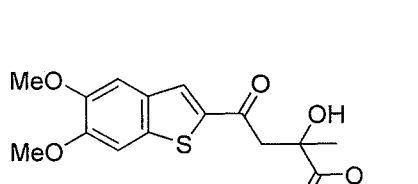
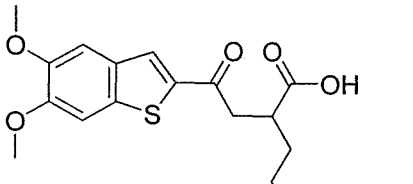
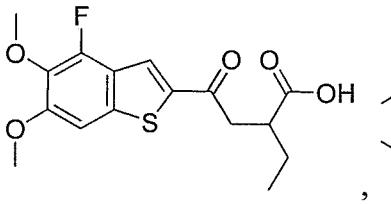
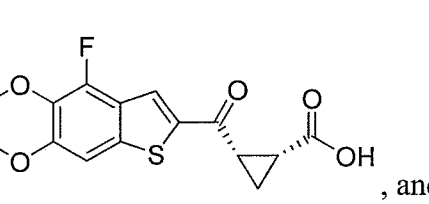
In another aspect, there is provided a compound selected from the group consisting of:

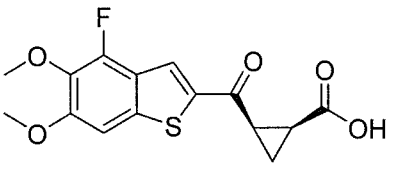

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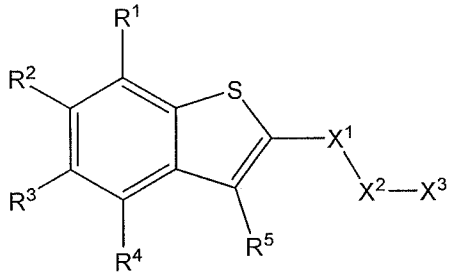
,



or a pharmaceutically acceptable salt thereof.

The present disclosure also relates to novel compounds of general formula (Ib). In particular, the present disclosure relates to compounds having the general structural formula (Ib):



(I')

or pharmaceutically acceptable salts thereof, as described herein.

In another aspect, there is provided a pharmaceutical composition, said pharmaceutical composition comprising a compound as defined herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

In another aspect, there is provided a compound as defined herein, or a pharmaceutically acceptable salt thereof, for use in treating a cell proliferation disorder in a subject.

In another aspect, there is provided a pharmaceutical composition as defined herein for use in treating a cell proliferation disorder in a subject.

In another aspect, there is provided a compound as defined herein, or a pharmaceutically acceptable salt thereof, for use in therapy.

In another aspect, there is provided a pharmaceutical combination that is (i) a compound of general formula (Ia') as defined herein, or a pharmaceutically acceptable salt thereof, and (ii) an active agent selected from the group consisting of STING agonist compounds, anti-viral compounds, antigens, adjuvants, CTLA-4 and PD-1 pathway antagonists and other immunomodulatory agents, lipids, liposomes, peptides, anti-cancer and chemotherapeutic agents; wherein the compound of general formula (Ia'), or pharmaceutically acceptable salt thereof, and the active agent are each employed in an amount that renders the combination effective for inducing an immune response in a patient.

In another aspect, there is provided use of a compound as defined herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a cell proliferation disorder.

Other embodiments, aspects and features of the present disclosure are either further described in or will be apparent from the ensuing description, examples and appended claims.

DETAILED DESCRIPTION OF THE INVENTION

The present disclosure includes compounds of general formula (Ia), and pharmaceutically acceptable salts thereof. These compounds and their pharmaceutically acceptable salts may be useful as agents to induce immune responses, to induce STING-dependent type I interferon production, and/or to treat a cell proliferation disorder.

The present disclosure includes compounds of general formula (Ia'), and pharmaceutically acceptable salts thereof. These compounds and their pharmaceutically acceptable salts may be useful as agents to induce immune responses, to induce STING-dependent type I interferon production, and/or to treat a cell proliferation disorder.

The present disclosure also includes compounds of general formula (Ib), and pharmaceutically acceptable salts thereof. These compounds and their pharmaceutically acceptable salts may be useful as agents to induce immune responses, to induce STING-dependent type I interferon production, and/or to treat a cell proliferation disorder.

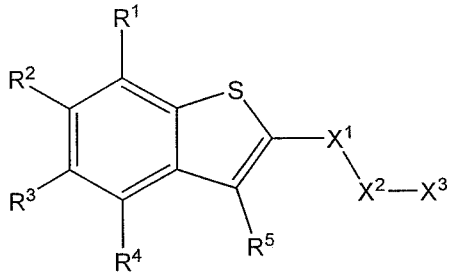
The present disclosure also includes compounds of general formula (Ib'), and pharmaceutically acceptable salts thereof. These compounds and their pharmaceutically acceptable salts may be useful as agents to induce immune responses, to induce STING-dependent type I interferon production, and/or to treat a cell proliferation disorder.

In addition, the present disclosure includes uses of compounds of general formula (I), and pharmaceutically acceptable salts thereof. The compounds of general formula (I) may be useful as agents to induce immune responses, to induce STING-dependent type I interferon production, and/or to treat a cell proliferation disorder.

In addition, the present disclosure includes uses of compounds of general formula (I'), and pharmaceutically acceptable salts thereof. The compounds of general formula (I') may

WHAT IS CLAIMED IS:

1. A compound of formula (Ia'):



(Ia')

or a pharmaceutically acceptable salt thereof, wherein

R^1 is selected from the group consisting of H, F, C_1-C_6 alkyl, and C_1-C_6 haloalkyl;

R^2 is selected from the group consisting of halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, OC_1-C_3 alkyl, OC_1-C_3 haloalkyl, OH, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $N(C_1$-C_3 alkyl$)_2$, $NH(C_1$-C_3 alkyl), SC_1-C_3 alkyl;

R^3 is selected from the group consisting of halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, OC_1-C_3 alkyl, OC_1-C_3 haloalkyl, OH, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $N(C_1$-C_3 alkyl$)_2$, $NH(C_1$-C_3 alkyl), SC_1-C_3 alkyl;

R^4 is selected from the group consisting of H, F, C_1-C_6 alkyl, and C_1-C_6 haloalkyl;

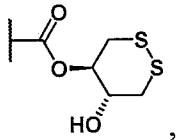
R^5 is selected from H, F, Cl, OR^6, C_1-C_6 alkyl and C_1-C_6 haloalkyl;

each R^6 is independently selected from the group consisting of H, C_1-C_4 alkyl, and C_1-C_4 haloalkyl;

X^1 is C(O);

X^2 is CHR^8CHR^8;

each R^8 is independently selected from the group consisting of H, C_1-C_4 alkyl, C_1-C_4 alkyl substituted by OH, C_1-C_4 alkyl substituted by OC_1-C_3 alkyl, and C_3-C_6 cycloalkyl, and where optionally 2 R^8 are taken together, along with the atoms to which they are attached, to form a 3- to 6-membered fused ring;

X^3 is selected from the group consisting of $COOR^6$, , $C(O)SR^6$, $C(S)OR^6$, SO_2R^6, and $C(O)N(R^9)_2$; and

each R^9 is independently selected from the group consisting of H, $COOR^6$, and SO_2R^6;

wherein when X^1-X^2-X^3 is X^1-CHR^8CH_2-X^3, at least one of R^2 and R^3 is not selected from the group consisting of halogen, OR^6, C_1-C_6 alkyl, and C_1-C_6 haloalkyl.

2. The compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein

R^1 is selected from the group consisting of H and F;

R^2 is selected from the group consisting of Br, Cl, F, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, CH_2CH_2F, $CH{=}CH_2$, $C{\equiv}CH$, OH, OCH_3, OCH_2CH_3, $OCHF_2$, SCH_3, and $NHCH_3$;

R^3 is selected from the group consisting of Br, Cl, F, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, CH_2CH_2F, $CH{=}CH_2$, $C{\equiv}CH$, OH, OCH_3, OCH_2CH_3, $OCHF_2$, SCH_3, and $NHCH_3$;

R^4 is selected from the group consisting of H and F;

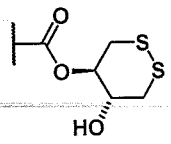
R^5 is selected from the group consisting of H and Cl;

each R^6 is independently selected from the group consisting of H, C_1-C_4 alkyl, and C_1-C_4 haloalkyl;

X^1 is C(O);

X^2 is CHR^8CHR^8;

X^3 is selected from the group consisting of COOH, $COOC(CH_3)_3$, and



; and

each R^8 is selected from the group consisting of H and C_1-C_4 alkyl.

3. The compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein

R^1 is selected from the group consisting of H and F;

R^2 is selected from the group consisting of Br, Cl, F, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, CH_2CH_2F, $CH{=}CH_2$, $C{\equiv}CH$, OH, OCH_3, OCH_2CH_3, $OCHF_2$, SCH_3, and $NHCH_3$;

R^3 is selected from the group consisting of Br, Cl, F, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, CH_2CH_2F, $CH{=}CH_2$, $C{\equiv}CH$, OH, OCH_3, OCH_2CH_3, $OCHF_2$, SCH_3, and $NHCH_3$;

R^4 is selected from the group consisting of H and F;

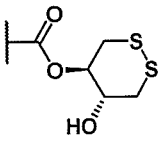
R^5 is selected from the group consisting of H and Cl;

each R^6 is independently selected from the group consisting of H, C_1-C_4 alkyl, and C_1-C_4 haloalkyl;

X^1 is C(O);

X^2 is CHR^8CHR^8;

X^3 is selected from the group consisting of COOH, $COOC(CH_3)_3$, and



; and

the 2 R^8 are taken together, along with the atoms to which they are attached, to form a 3- to 6-membered fused ring.

4. The compound according to claim 1 or a pharmaceutically acceptable salt thereof, wherein

R^1 is selected from the group consisting of H, F, C_1-C_3 alkyl, and C_1-C_3 haloalkyl;

R^2 is selected from the group consisting of halogen, C_1-C_3 alkyl, C_1-C_3 haloalkyl, OC_1-C_3 alkyl, OC_1-C_3 haloalkyl, OH, C_2-C_3 alkenyl, C_2-C_3 alkynyl, $N(C_1$-C_3 alkyl$)_2$, $NH(C_1$-C_3 alkyl), and SC_1-C_3 alkyl;

R^3 is selected from the group consisting of halogen, C_1-C_3 alkyl, C_1-C_3 haloalkyl, OC_1-C_3 alkyl, OC_1-C_3 haloalkyl, OH, C_2-C_3 alkenyl, C_2-C_3 alkynyl, $N(C_1$-C_3 alkyl$)_2$, $NH(C_1$-C_3 alkyl), and SC_1-C_3 alkyl;

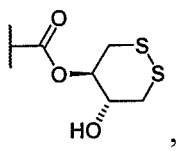
R^4 is selected from the group consisting of H, F, C_1-C_3 alkyl, and C_1-C_3 haloalkyl;

R^5 is selected from the group consisting of H, F, Cl, OR^6, C_1-C_3 alkyl, and C_1-C_3 haloalkyl;

each R^6 is independently selected from the group consisting of H, C_1-C_4 alkyl, and C_1-C_4 haloalkyl;

X^1 is C(O);

X^2 is $CH_2C(R^8)_2$;

X^3 is selected from the group consisting of $COOR^6$, , SO_2R^6, and $C(O)N(R^9)_2$, where each R^9 is independently selected from the group consisting of H, $COOR^6$, and SO_2R^6; and

each R^8 is selected from the group consisting of H, C_1-C_4 alkyl, C_1-C_4 alkyl substituted by OH, C_1-C_4 alkyl substituted by OC_1-C_4 alkyl, and C_3-C_6 cycloalkyl, and where optionally 2 R^8 are taken together, along with the atom to which they are attached, to form a 3- to 6-membered spirocycle.

5. The compound of claim 4 or a pharmaceutically acceptable salt thereof, wherein

R^1 is selected from the group consisting of H and F;

R^2 is selected from the group consisting of Br, Cl, F, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, CH_2CH_2F, $CH{=}CH_2$, $C{\equiv}CH$, OH, OCH_3, OCH_2CH_3, $OCHF_2$, SCH_3, and $NHCH_3$;

R^3 is selected from the group consisting of Br, Cl, F, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, CH_2CH_2F, $CH{=}CH_2$, $C{\equiv}CH$, OH, OCH_3, OCH_2CH_3, $OCHF_2$, SCH_3, and $NHCH_3$;

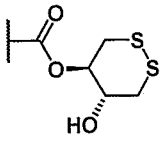
R^4 is selected from the group consisting of H and F;

R^5 is selected from the group consisting of H and Cl;

each R^6 is independently selected from the group consisting of H, C_1-C_4 alkyl, and C_1-C_3 haloalkyl;

X^1 is C(O);

X^2 is $CH_2C(R^8)_2$;

X^3 is selected from the group consisting of COOH, $COOC(CH_3)_3$, and ; and

each R^8 is selected from the group consisting of H, OH, and CH_3.

6. The compound of claim 4 or a pharmaceutically acceptable salt thereof, wherein

R^1 is selected from the group consisting of H and F;

R^2 is selected from the group consisting of Br, Cl, F, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, CH_2CH_2F, $CH{=}CH_2$, $C{\equiv}CH$, OH, OCH_3, OCH_2CH_3, $OCHF_2$, SCH_3, and $NHCH_3$;

R^3 is selected from the group consisting of Br, Cl, F, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, CH_2CH_2F, $CH{=}CH_2$, $C{\equiv}CH$, OH, OCH_3, OCH_2CH_3, $OCHF_2$, SCH_3, and $NHCH_3$;

R^4 is selected from the group consisting of H and F;

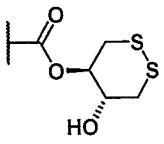
R^5 is selected from the group consisting of H and Cl;

each R^6 is independently selected from the group consisting of H, C_1-C_4 alkyl, and C_1-C_4 haloalkyl;

X^1 is C(O);

X^2 is $CH_2C(R^8)_2$;

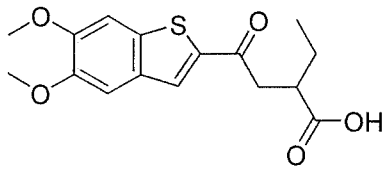
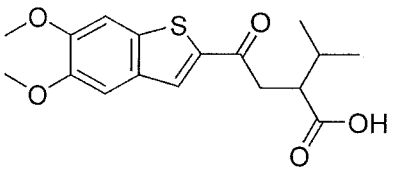
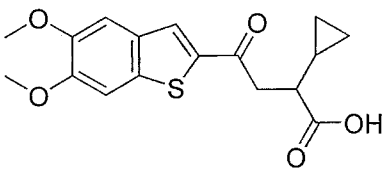
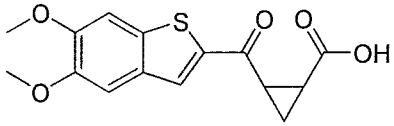
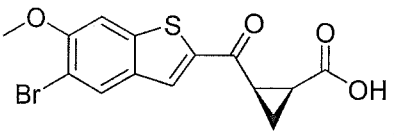
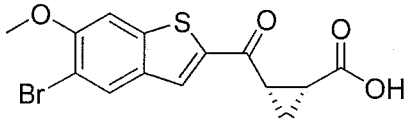
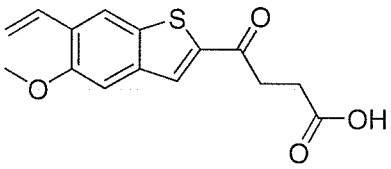
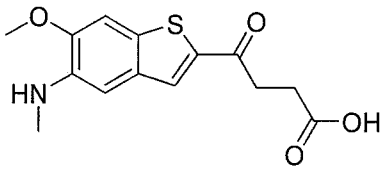
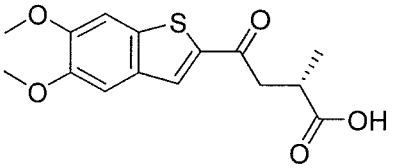
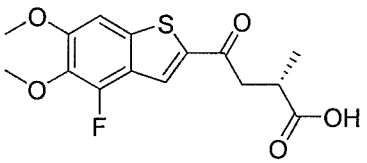
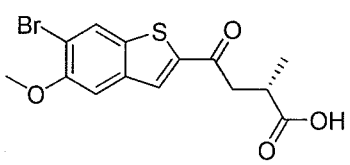
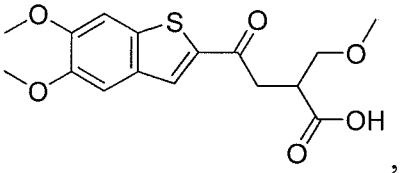
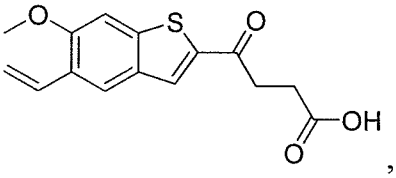
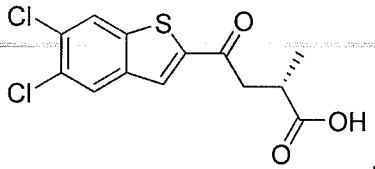
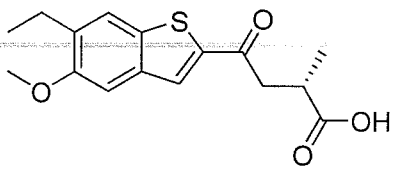
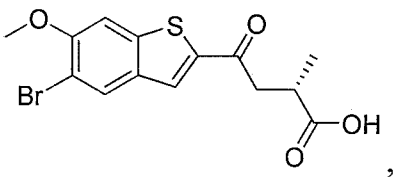
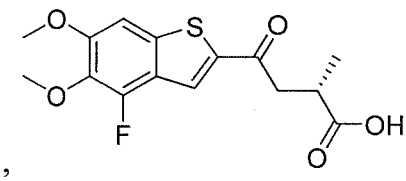
X^3 is selected from the group consisting of COOH, $COOC(CH_3)_3$, and



; and

the 2 R^8 are taken together, along with the atom to which they are attached, to form a 3- to 6-membered spirocycle.

7. A compound selected from the group consisting of:

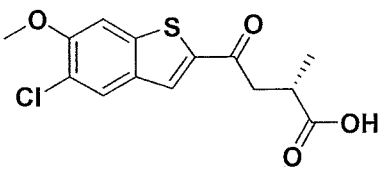
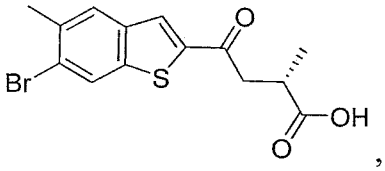
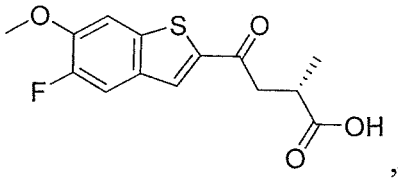

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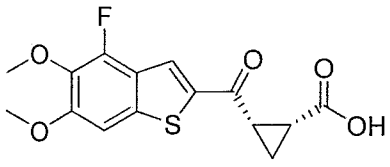
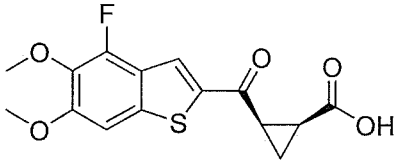
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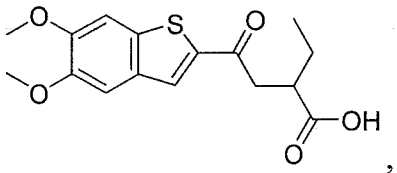
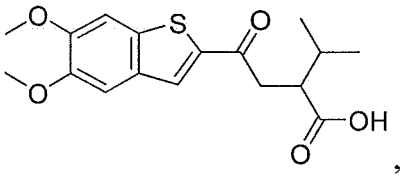
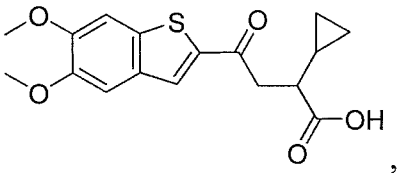
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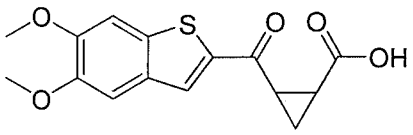
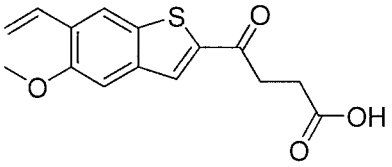
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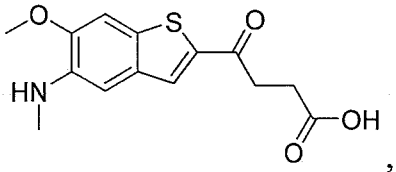
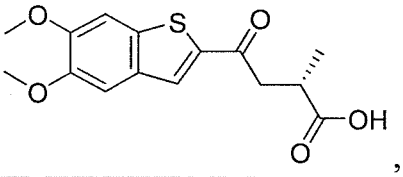
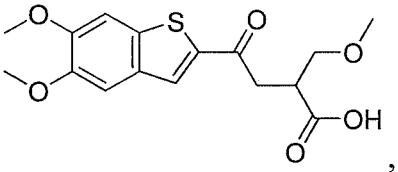

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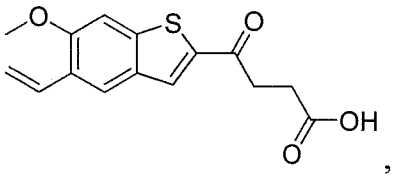
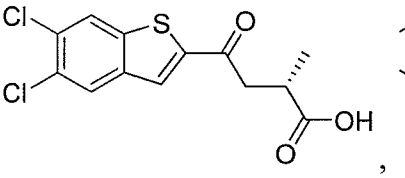
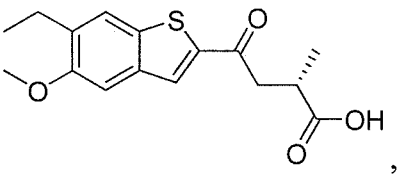

, and , or a pharmaceutically acceptable salt thereof.

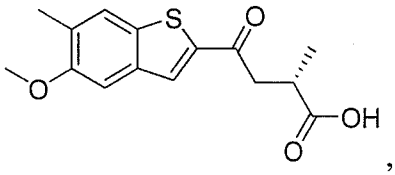
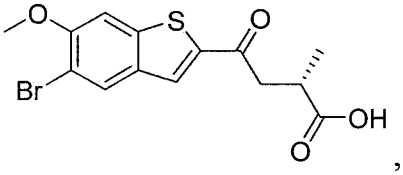
8. The compound according to claim 7, wherein the compound is selected from the group consisting of:

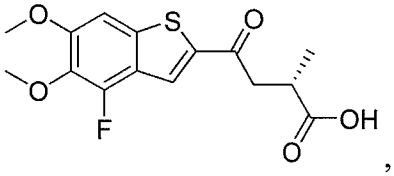
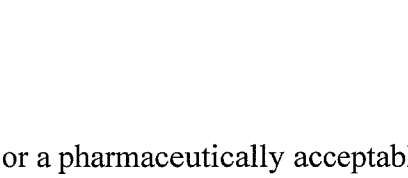

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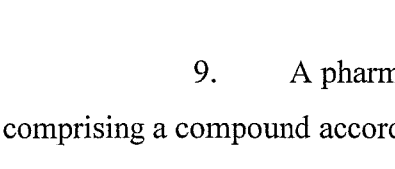

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, or a pharmaceutically acceptable salt thereof.

9. A pharmaceutical composition, said pharmaceutical composition comprising a compound according to any one of claims 1 to 8, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

10. A compound according to any one of claims 1 to 8, or a pharmaceutically acceptable salt thereof, for use in treating a cell proliferation disorder in a subject.

11. The compound for use according to claim 10, wherein the cell proliferation disorder is cancer.

12. A pharmaceutical composition according to claim 9 for use in treating a cell proliferation disorder in a subject.

13. The pharmaceutical composition for use according to claim 12, wherein the cell proliferation disorder is cancer.

14. A compound according to any one of claims 1 to 8, or a pharmaceutically acceptable salt thereof, for use in therapy.

15. A pharmaceutical combination that is (i) a compound of general formula (Ia') as defined in any one of claims 1 to 7, or a pharmaceutically acceptable salt thereof, and (ii) an active agent selected from the group consisting of STING agonist compounds, anti-viral compounds, antigens, adjuvants, CTLA-4 and PD-1 pathway antagonists and other immunomodulatory agents, lipids, liposomes, peptides, anti-cancer and chemotherapeutic agents; wherein the compound of general formula (Ia'), or pharmaceutically acceptable salt thereof, and the active agent are each employed in an amount that renders the combination effective for inducing an immune response in a patient.

16. Use of a compound according to any one of claims 1 to 8, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a cell proliferation disorder.

17. The use according to claim 16, wherein said cell proliferation disorder is cancer.