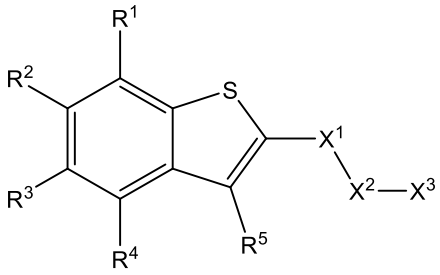
interferons, the development of STING activating agents is rapidly taking an important place in today's anti-tumor therapy landscape.

SUMMARY ~~OF THE INVENTION~~

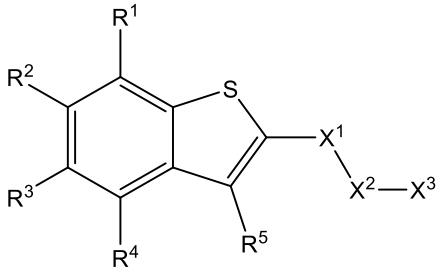
The present disclosure relates to novel compounds of general formula (Ia). In particular, the present disclosure relates to compounds having the general structural formula (Ia):



(Ia)

or pharmaceutically acceptable salts thereof, as described herein. ~~Embodiments~~ Examples 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 one aspect, the present disclosure provides for 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_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;

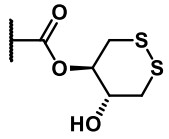
R^4 is selected from the group consisting of H, F, C_1-C_4 alkyl, and C_1-C_3 haloalkyl;

R^5 is selected from H, F, Cl, 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);

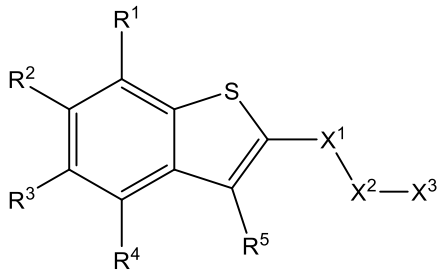
X^2 is CHR^8CHR^8;

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

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,

wherein when X^1-X^2-X^3 is X^1-CHR^8CH_2-X^3, at least one of R^2 and R3 is not selected from the group consisting of halogen, OC_1-C_3 alkyl, OC_1-C_3 haloalkyl, OH, C_1-C_3 alkyl, and C_1-C_3 haloalkyl.

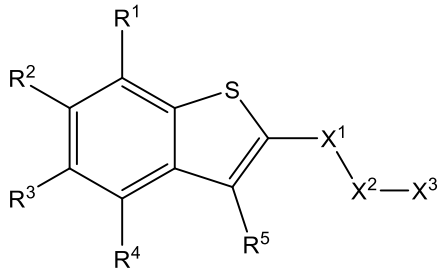
The present disclosure also relates to novel compounds of general formula (Ia'). In particular, the present disclosure relates to compounds having the general structural formula (Ia'):



(Ia')

or pharmaceutically acceptable salts thereof, as described herein. ~~Embodiments~~ Examples 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.

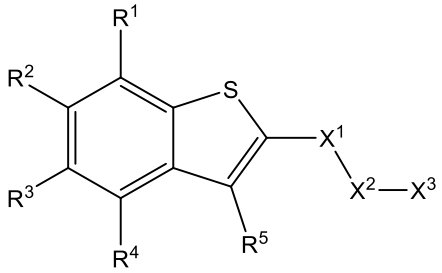
The present disclosure also relates to novel compounds of general formula (Ib). In particular, the present disclosure relates to compounds having the general structural formula (Ib):



(Ib)

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

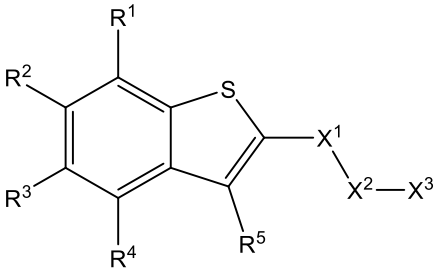
The present disclosure also relates to novel compounds of general formula (Ib'). In particular, the present disclosure relates to compounds having the general structural formula (Ib'):



(Ib')

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

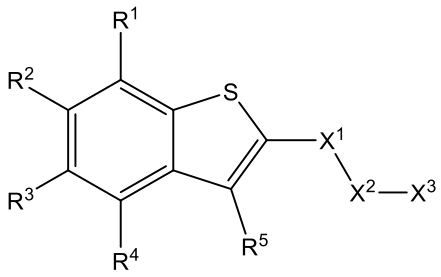
In addition, this disclosure relates to uses of compounds of general formula (I):



(I)

or pharmaceutically acceptable salts thereof, as described herein.

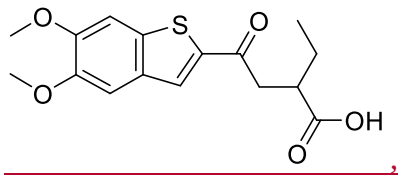
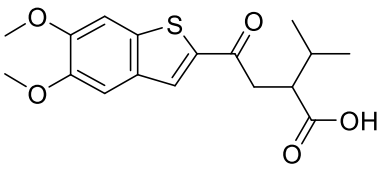
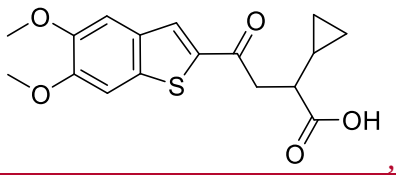
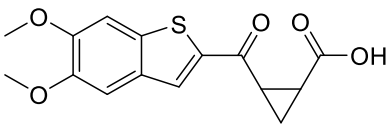
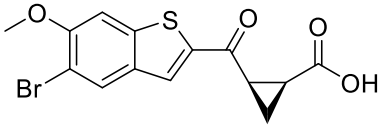
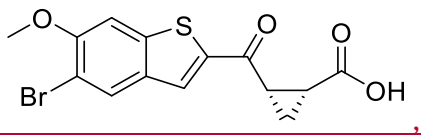
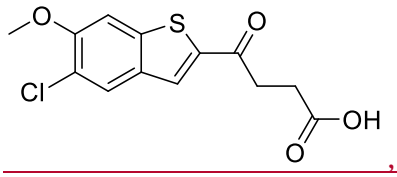
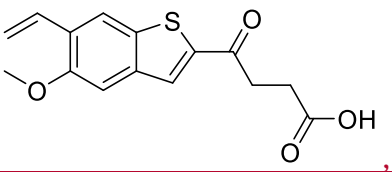
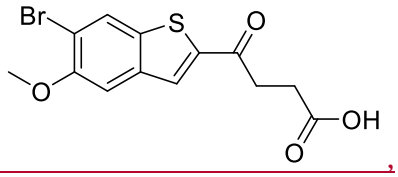
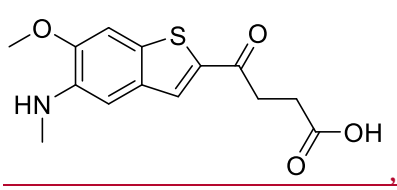
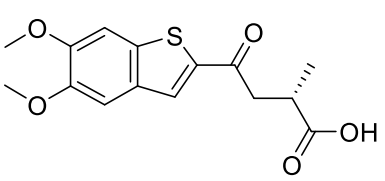
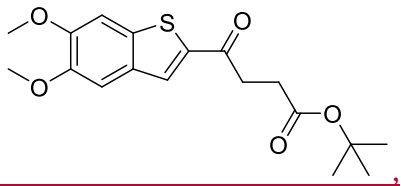
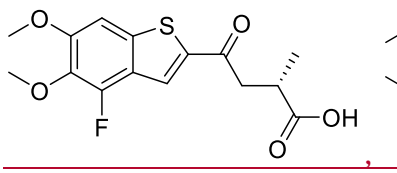
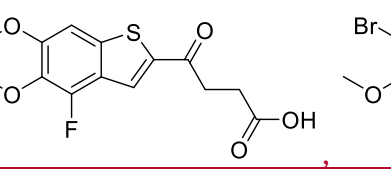
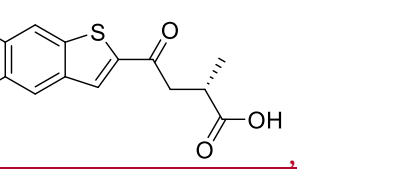
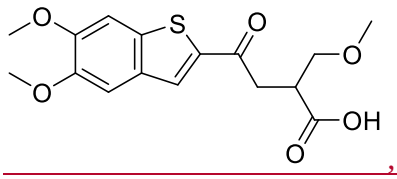
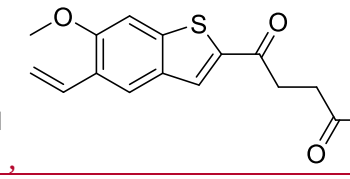
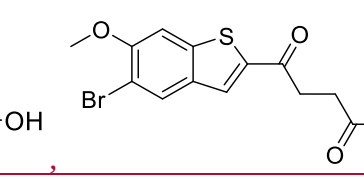
In addition, this disclosure relates to uses of compounds of general formula (I'):



(I')

or pharmaceutically acceptable salts thereof, as described herein.

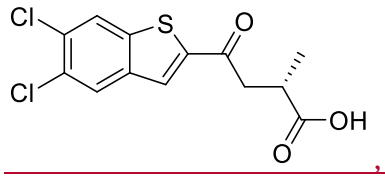
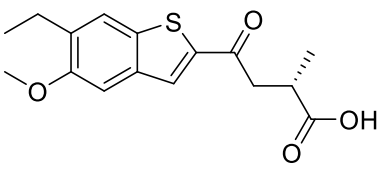
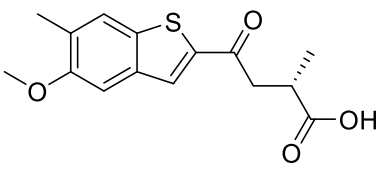
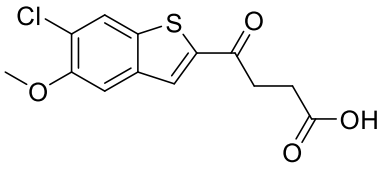
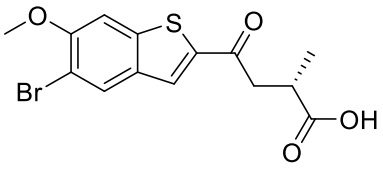
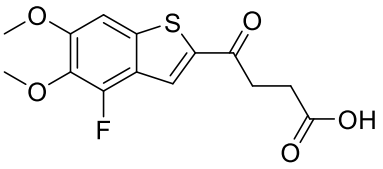
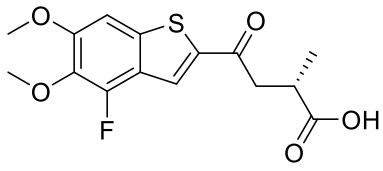
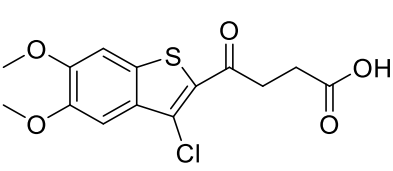
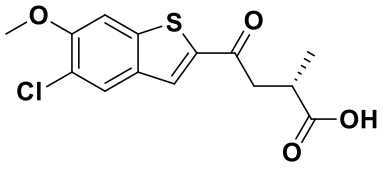
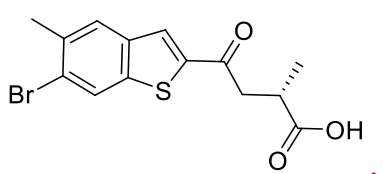
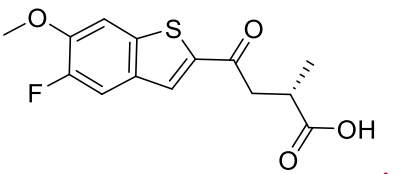
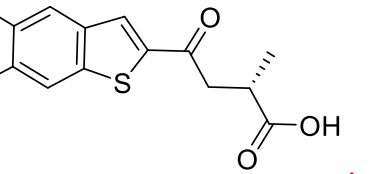
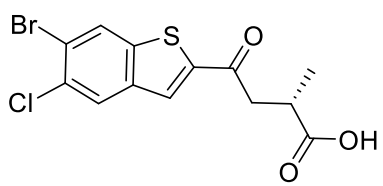
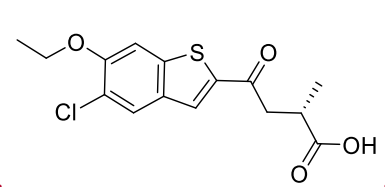
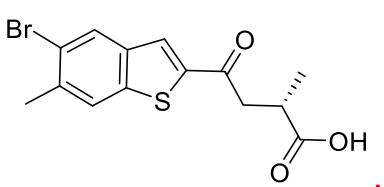
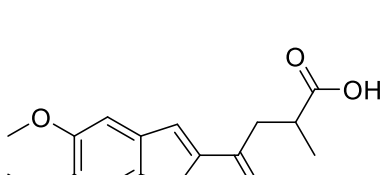
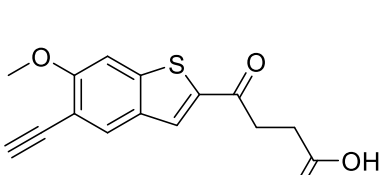
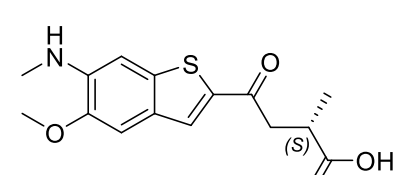
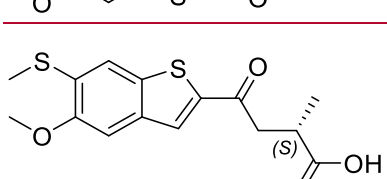
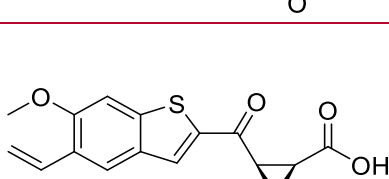
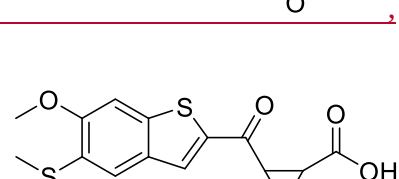
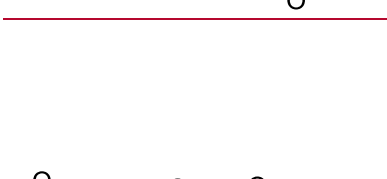
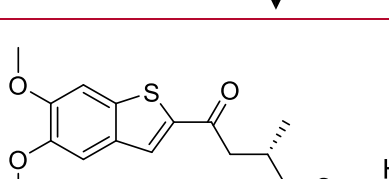
In another aspect, the present disclosure provides for a compound selected from the group consisting of:

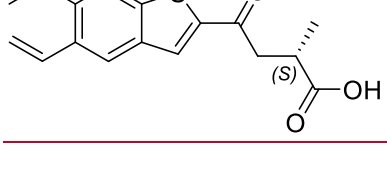

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

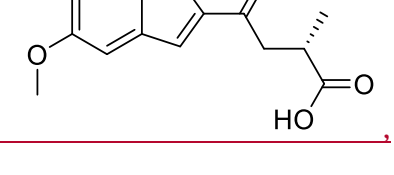
,

,

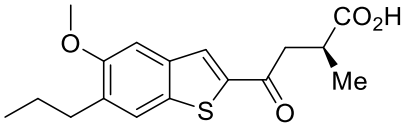
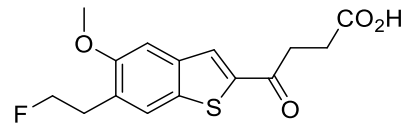
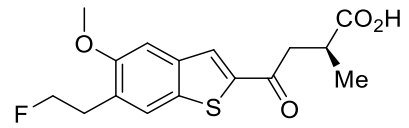
,

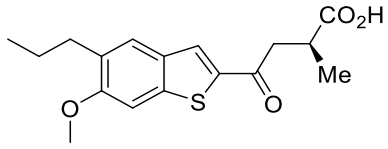
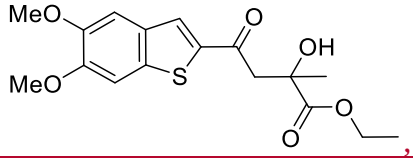
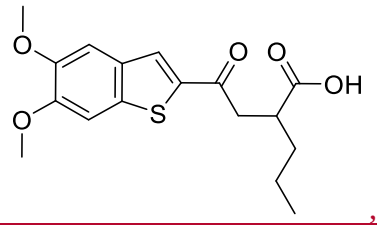
























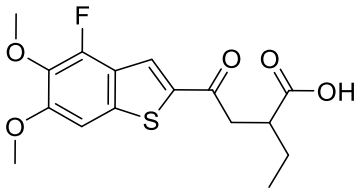
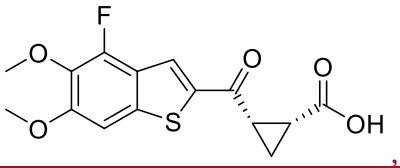
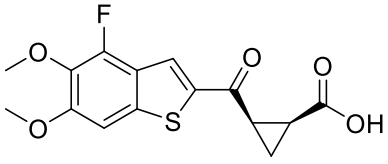


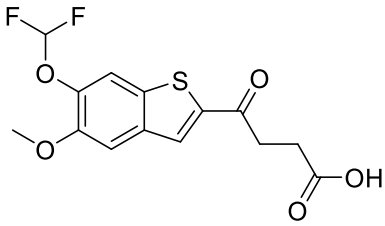


5

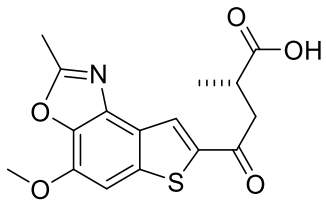






and

, or a pharmaceutically acceptable salt thereof.

In another aspect, the present disclosure provides for a compound which is;



, or a pharmaceutically acceptable salt thereof.

In another aspect, the present disclosure provides for a pharmaceutical composition, said pharmaceutical composition comprising a compound as described herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

In another aspect, the present disclosure provides for a compound as described herein, or a pharmaceutically acceptable salt thereof, for use in therapy.

In another aspect, the present disclosure provides for a compound as described herein, or a pharmaceutically acceptable salt thereof, for use in treating a cell proliferation disorder.

In another aspect, the present disclosure provides for a pharmaceutical composition as described herein for use in of treating a cell proliferation disorder.

In another aspect, the present disclosure provides for a combination comprising a compound as described herein, or a pharmaceutically acceptable salt thereof and one or more additional active agents.

Other ~~embodiments~~examples, 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.

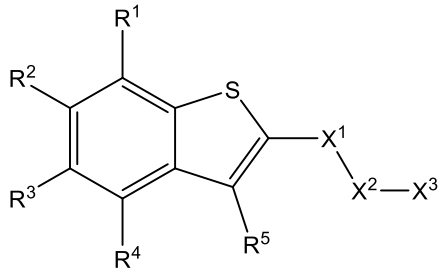
The present disclosure also includes compounds of general formula (Ib'), and pharmaceutically acceptable salts thereof. These compounds and their pharmaceutically acceptable salts may be useful as agents to induce immune responses, to induce STING-dependent type I interferon production, and/or to treat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

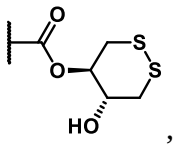
R^4 is selected from the group consisting of H, F, C_1-C_4 alkyl, and C_1-C_3 haloalkyl;

R^5 is selected from 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 CHR^8CHR^8;

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

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;

wherein when X^1-X^2-X^3 is X^1-CHR^8CH_2-X^3, at least one of R^2 and R3 is not selected from the group consisting of halogen, OC_1-C_3 alkyl, OC_1-C_3 haloalkyl, OH, C_1-C_3 alkyl, and C_1-C_3 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≡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≡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;

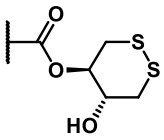
R^5 is selected from the group consisting of H and Cl;

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≡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≡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;

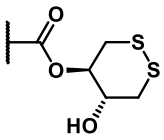
R^5 is selected from the group consisting of H and Cl;

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);

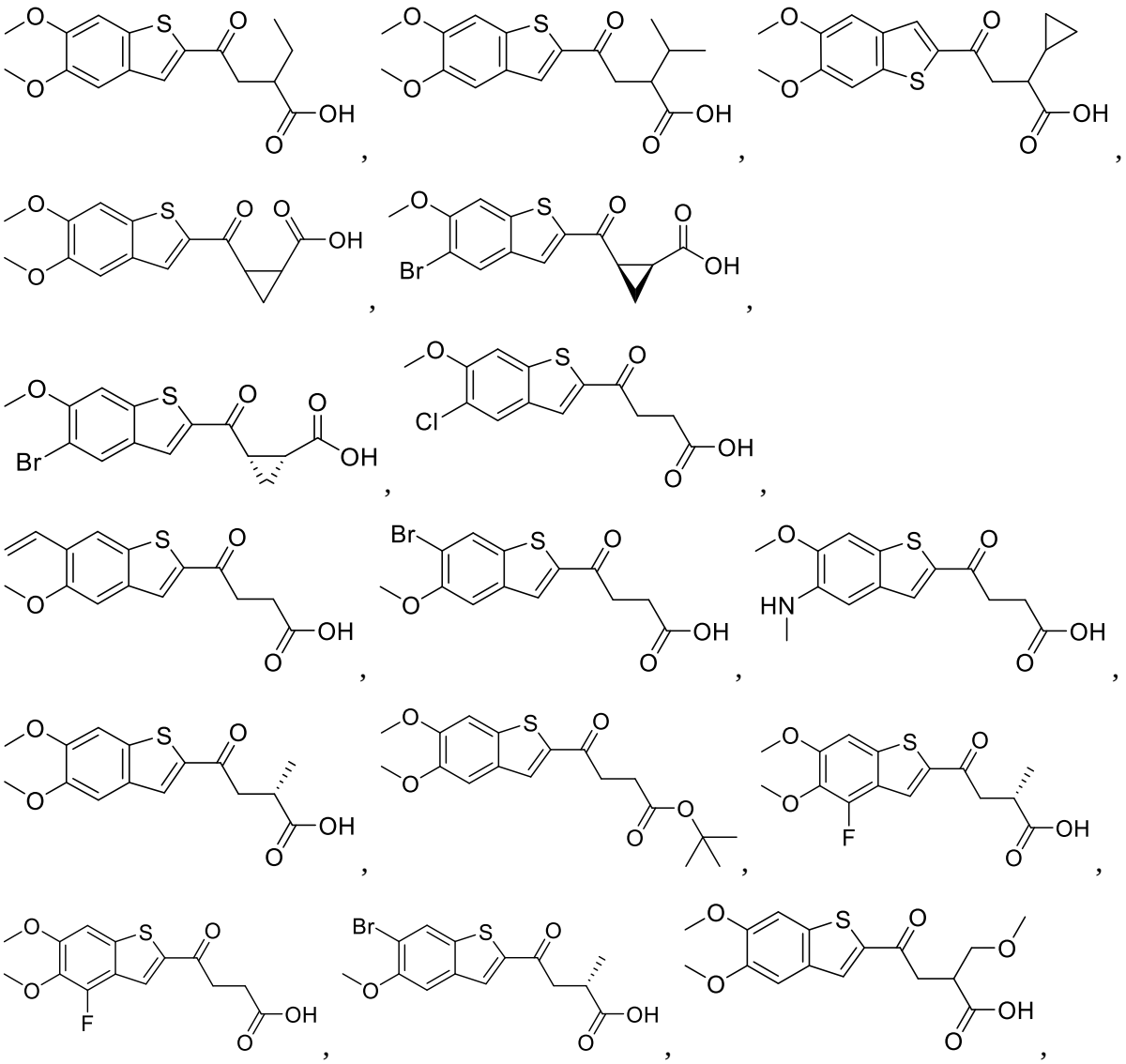
X^2 is CHR^8CHR^8;

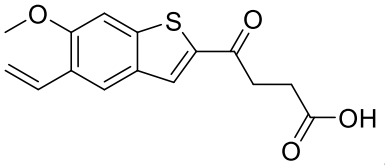
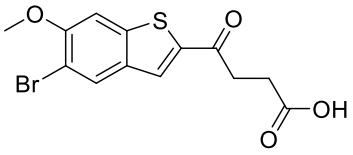
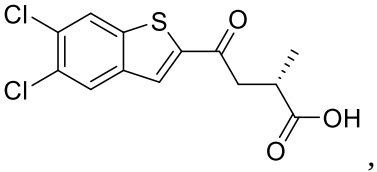
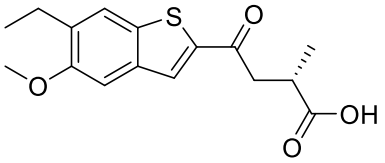
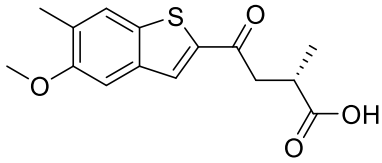
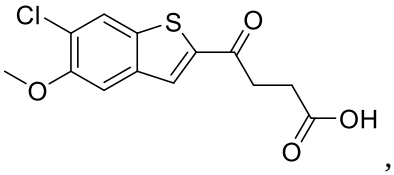
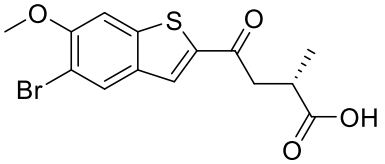
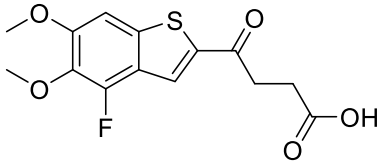
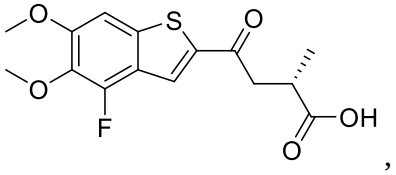
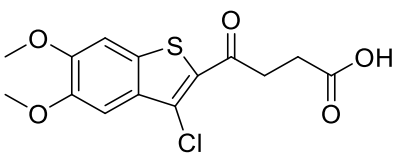
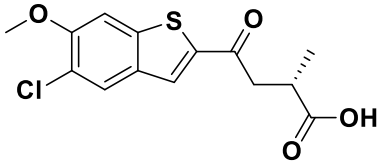
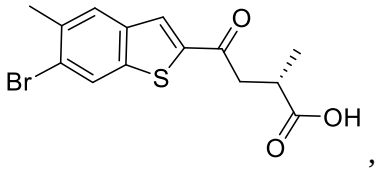
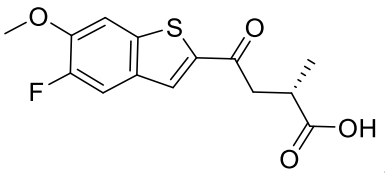
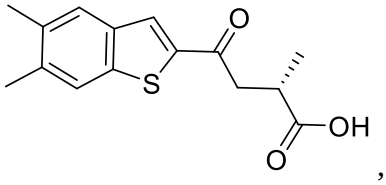
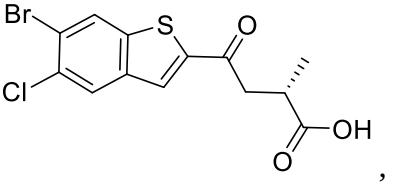
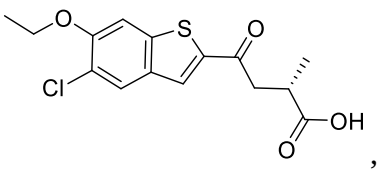
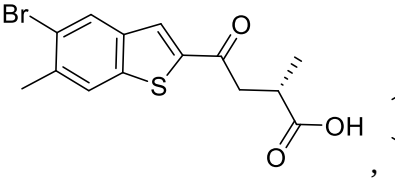
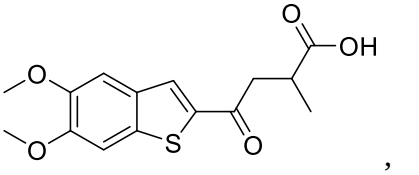
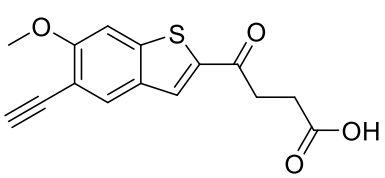
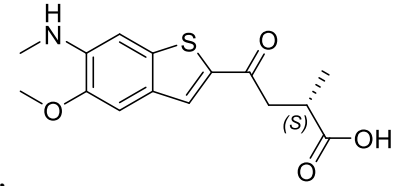
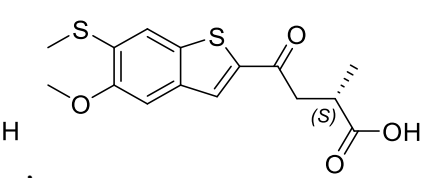
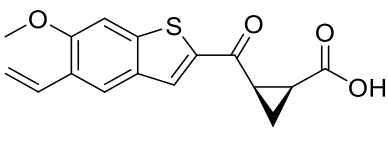
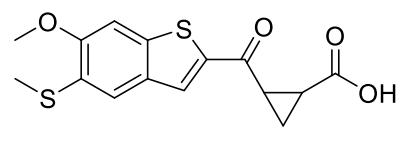
X^3 is selected from the group consisting of COOH, $COOC(CH_3)_3$, and

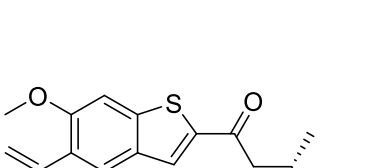
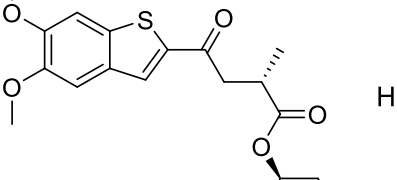
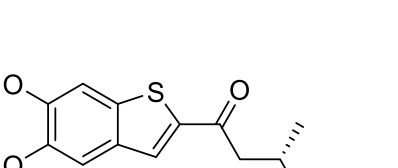

; and

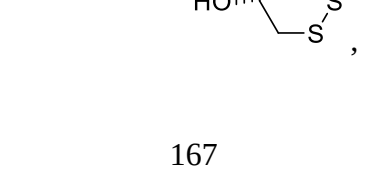
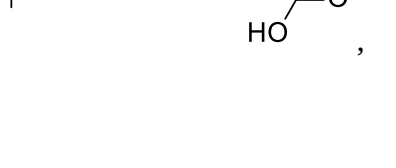
the 2 R^8 are taken together, along with the atoms to which they are attached, to form a 3- to 6-membered fused ring.

4. A compound selected from the group consisting of:

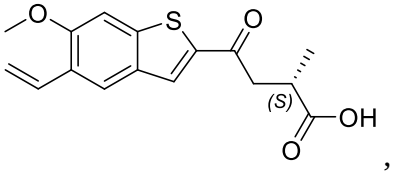



,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

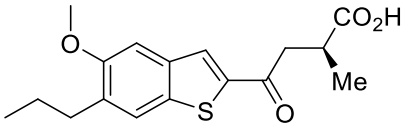
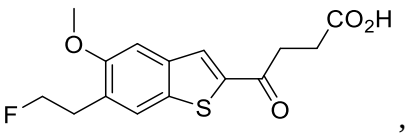
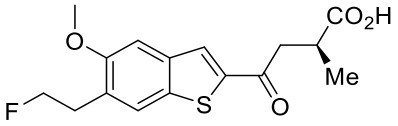
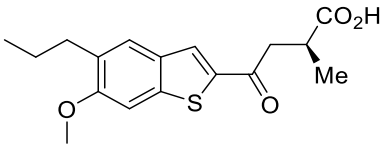
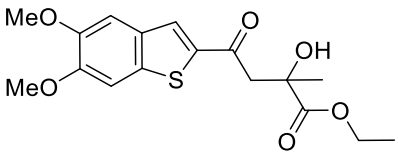
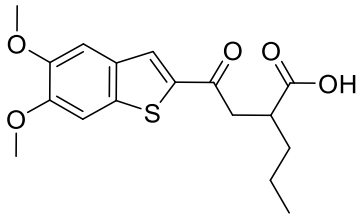
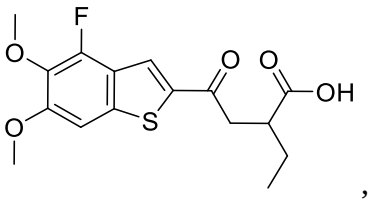
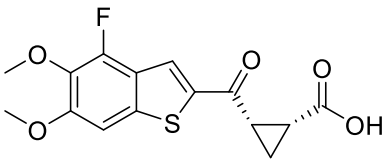
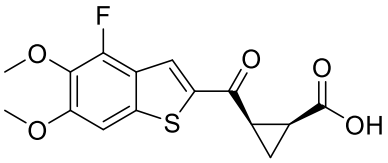
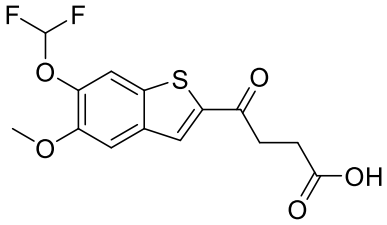
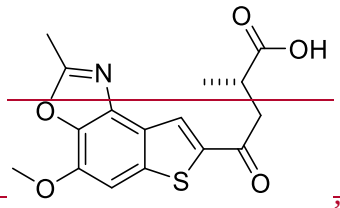
,

,

,

,

,

,

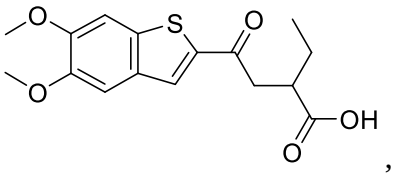
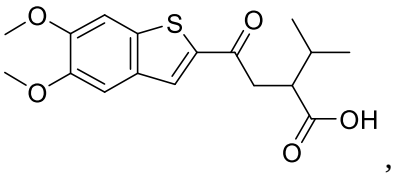
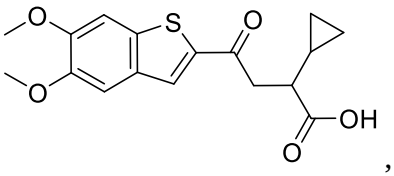
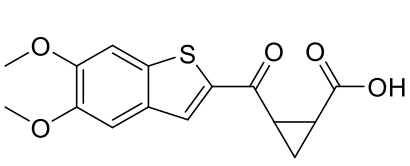
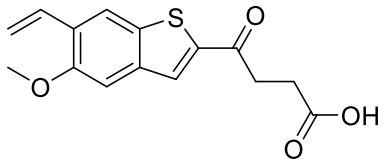
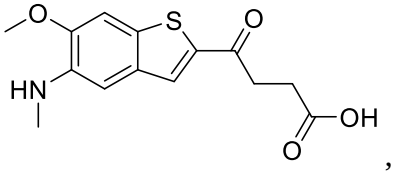
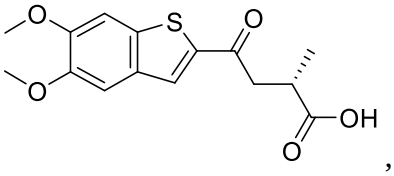
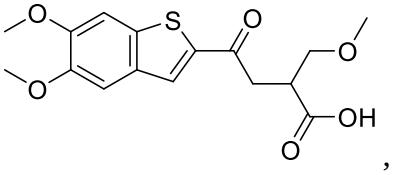
,

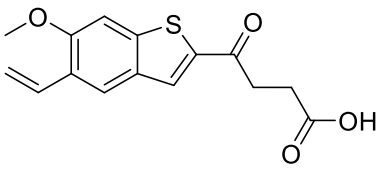
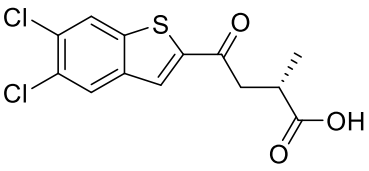
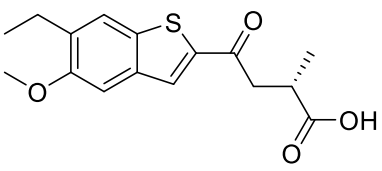
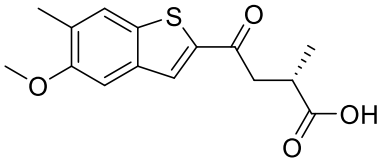
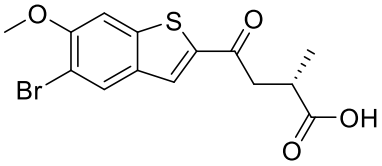
,

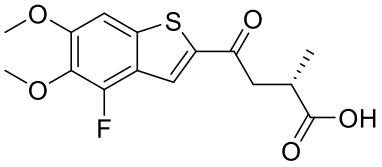











, and

, ~~and~~
~~,~~ or a pharmaceutically acceptable salt thereof.

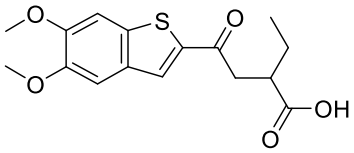
5. The compound according to claim 4, wherein the compound is selected from the group consisting of:






, and

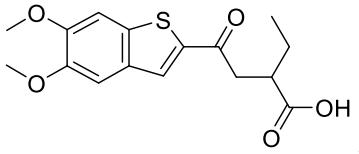

, or a pharmaceutically acceptable salt thereof.

6. The compound according to claim 5, wherein the compound is compound selected from the group consisting of

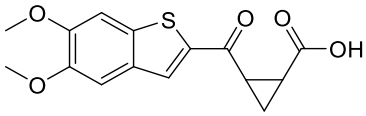


and pharmaceutically acceptable salts thereof.

7. The compound according to claim 6, wherein the compound is

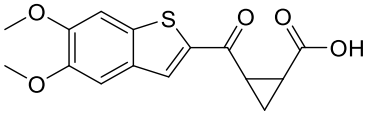

.

8. The compound according to claim 5, wherein the compound is compound selected from the group consisting of

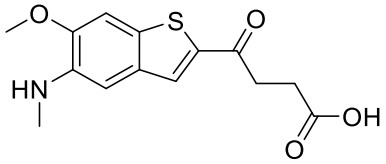


and pharmaceutically acceptable salts thereof.

9. The compound according to claim 8, wherein the compound is

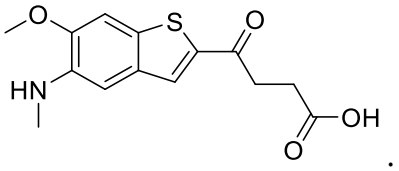

.

10. The compound according to claim 5, wherein the compound is compound selected from the group consisting of



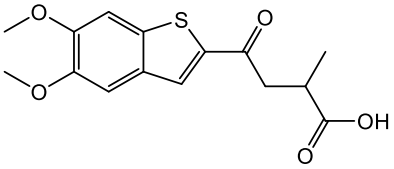
and pharmaceutically acceptable salts thereof.

11. The compound according to claim 10, wherein the compound is



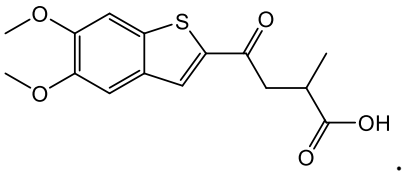
.

12. The compound according to claim 4, wherein the compound is compound selected from the group consisting of



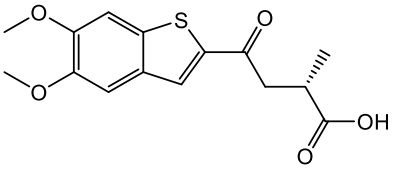
and pharmaceutically acceptable salts thereof.

13. The compound according to claim 12, wherein the compound is



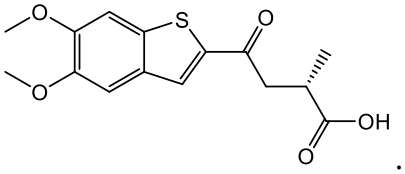
.

14. The compound according to claim 5, wherein the compound is compound selected from the group consisting of



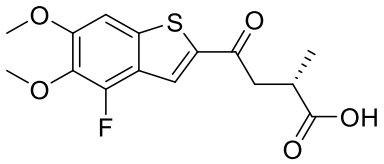
and pharmaceutically acceptable salts thereof.

15. The compound according to claim 14, wherein the compound is



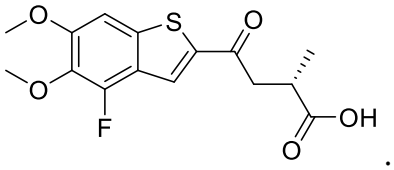
.

16. The compound according to claim 5, wherein the compound is compound selected from the group consisting of



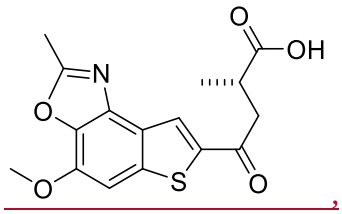
and pharmaceutically acceptable salts thereof.

17. The compound according to claim 16, wherein the compound is



.

18. A compound which is;



,

or a pharmaceutical acceptable salt thereof.

~~18~~19. A pharmaceutical composition, said pharmaceutical composition comprising a compound according to any one of claims 1 to ~~17~~18, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

~~19~~20. A compound according to any one of claims of 1 to ~~17~~18, or a pharmaceutically acceptable salt thereof, for use in therapy.

~~20~~21. A compound according to any one of claims of 1 to ~~17~~18, or a pharmaceutically acceptable salt thereof, for use in treating a cell proliferation disorder ~~in a subject~~.

~~21~~22. A compound, or a pharmaceutically acceptable salt thereof, for use according to claim ~~20~~21, wherein the cell proliferation disorder is cancer.

~~22~~23. A pharmaceutical composition according to claim ~~18~~ 19 for use in ~~of~~ treating a cell proliferation disorder ~~in a subject~~.

~~23~~24. A pharmaceutical composition for use according to claim ~~22~~23, wherein the cell proliferation disorder is cancer.

25. A combination comprising a compound according to any one of claims 1 to 18, or a pharmaceutically acceptable salt thereof and one or more additional active agents.

26. A combination according to claim 25, wherein said one or more additional active agents are selected from the group consisting of STING agonist compounds, anti-viral compounds, antigens, adjuvants, anti-cancer agents, CTLA-4, LAG-3 and PD-1 pathway antagonists, lipids, liposomes, peptides, cytotoxic agents, chemotherapeutic agents, immunomodulatory cell lines, checkpoint inhibitors, vascular endothelial growth factor (VEGF) receptor inhibitors, topoisomerase II inhibitors, smoothen inhibitors, alkylating agents, anti-tumor antibiotics, anti-metabolites, retinoids, and immunomodulatory agents including but not limited to anti-cancer vaccines.

27. A combination according to claim 25 or 26, wherein the additional active agent is pembrolizumab.

28. A combination according to any one of claims 25 to 27, wherein said compound or salt and said one or more additional active agent is to be administered separately.