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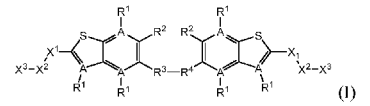
(54) Title: BENZOTHIOPHENES AND RELATED COMPOUNDS AS STING AGONISTS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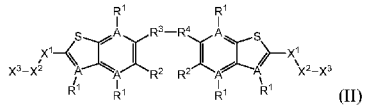
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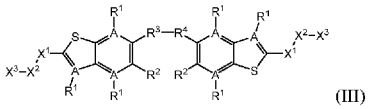
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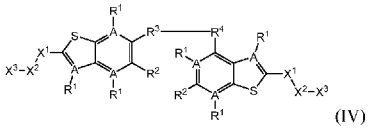
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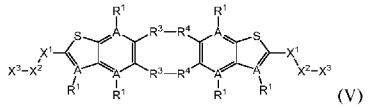
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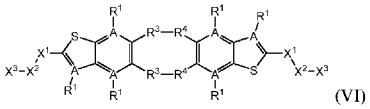
(VI)

(57) Abstract: Compounds of general formula (I), of general formula (II), of general formula (III), of general formula (IV), of general formula (V), of general formula (VI), and their pharmaceutically acceptable salts, wherein all variables are defined herein, that may be useful as inductors of type I interferon production, specifically as STING active agents, are provided. Also provided are compositions comprising such compounds, processes for the synthesis of such compounds, and to uses of such compounds, including administration of such compounds to induce immune response, to induce STING-dependent type I interferon production, and/or to treat a cell proliferation disorder, such as cancer.

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[Continued on next page]

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— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

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TITLE OF THE APPLICATION

BENZOTHIOPHENES AND RELATED COMPOUNDS AS STING AGONISTS

FIELD OF THE INVENTION

The present disclosure relates to compounds and derivatives thereof that may be useful as STING (Stimulator of Interferon Genes) agonists that activate the STING pathway. The present disclosure also relates to compositions comprising such compounds, processes for the synthesis of such compounds, and to uses of such compounds, including administration of such compounds to induce immune response, to induce STING-dependent type I interferon production, and/or to treat a cell proliferation disorder, such as cancer.

REFERENCE TO SEQUENCE LISTING SUBMITTED ELECTRONICALLY

The sequence listing of the present application is submitted electronically via EFS-Web as an ASCII-formatted sequence listing, with a file name of "24578_SEQLIST-FEB2019", a creation date of March 1, 2019, and a size of 25KB. This sequence listing submitted via EFS-Web is part of the specification and is herein incorporated by reference in its entirety.

BACKGROUND OF THE INVENTION

The immune system has evolved to recognize and neutralize different types of threats in order to maintain the homeostasis of the host, and it is generally broken down into two arms: adaptive and innate. The adaptive immune system is specialized to recognize as foreign those antigens not naturally expressed in the host and to mount an anti-antigen response through the coordinated actions of many leukocyte subsets. The hallmark of adaptive immune responses is the ability to provide "memory" or long-lasting immunity against the encountered antigen. While this specific and long-lasting effect is critical to host health and survival, the adaptive immune response requires time to generate a full-blown response.

The innate immune system compensates for this time delay and is specialized to act quickly against different insults or danger signals. It provides the first line of defense against bacteria, viruses, parasites and other infectious threats, but it also responds strongly to certain danger signals associated with cellular or tissue damage. The innate immune system has no antigen specificity but does respond to a variety of effector mechanisms. Opsonization, phagocytosis, activation of the complement system, and production of soluble bioactive

molecules such as cytokines or chemokines are all mechanisms by which the innate immune system mediates its response. By responding to these damage-associated molecular patterns (DAMPs) or pathogen-associated molecular patterns (PAMPs) described above, the innate immune system is able to provide broad protection against a wide range of threats to the host.

Free cytosolic DNA and RNA are among these PAMPs and DAMPs. It has recently been demonstrated that the main sensor for cytosolic DNA is cGAS (cyclic GMP-AMP synthase). Upon recognition of cytosolic DNA, cGAS catalyzes the generation of the cyclic-dinucleotide 2'3'-cGAMP, an atypical second messenger that strongly binds to the ER-transmembrane adaptor protein STING. A conformational change is undergone by cGAMP-bound STING, which translocates to a perinuclear compartment and induces the activation of critical transcription factors IRF-3 and NF-κB. This leads to a strong induction of type I interferons and production of pro-inflammatory cytokines such as IL-6, TNF-α and IFN-γ.

The importance of type I interferons and pro-inflammatory cytokines on various cells of the immune system has been very well established. In particular, these molecules strongly potentiate T-cell activation by enhancing the ability of dendritic cells and macrophages to uptake, process, present and cross-present antigens to T-cells. The T-cell stimulatory capacity of these antigen-presenting cells is augmented by the up-regulation of critical co-stimulatory molecules, such as CD80 or CD86. Finally, type I interferons can rapidly engage their cognate receptors and trigger the activation of interferon-responsive genes that can significantly contribute to adaptive immune cell activation.

From a therapeutic perspective, type I interferons are shown to have antiviral activities by directly inhibiting human hepatitis B virus and hepatitis C virus replication, and by stimulating immune responses to virally infected cells. Compounds that can induce type I interferon production are used in vaccines, where they act as adjuvants, enhancing specific immune responses to antigens and minimizing side effects by reducing dosage and broadening the immune response.

In addition, interferons, and compounds that can induce interferon production, have potential use in the treatment of human cancers. Such molecules are potentially useful as anti-cancer agents with multiple pathways of activity. Interferons can inhibit human tumor cell proliferation directly and may be synergistic with various approved chemotherapeutic agents. Type I interferons can significantly enhance anti-tumor immune responses by inducing activation

of both the adaptive and innate immune cells. Finally, tumor invasiveness may be inhibited by interferons by modulating enzyme expression related to tissue remodeling.

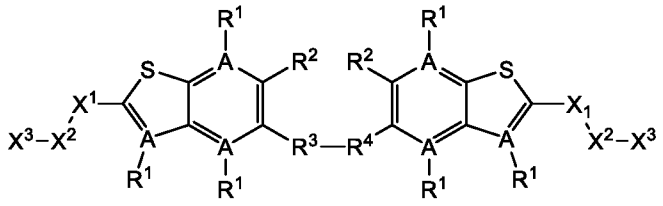
In view of the potential of type I interferons and type I interferon-inducing compounds as anti-viral and anti-cancer agents, there remains a need for new agents that can induce potent type I interferon production. With the growing body of data demonstrating that the cGAS-STING cytosolic DNA sensory pathway has a significant capacity to induce type I interferons, the development of STING activating agents is rapidly taking an important place in today's anti-tumor therapy landscape.

Any reference to or discussion of any document, act or item of knowledge in this specification is included solely for the purpose of providing a context for the present invention. It is not suggested or represented that any of these matters or any combination thereof formed at the priority date part of the common general knowledge, or was known to be relevant to an attempt to solve any problem with which this specification is concerned.

SUMMARY OF THE INVENTION

The present disclosure includes compounds of general formula (I), compounds of general formula (II), compounds of general formula (III), compounds of general formula (IV), compounds of general formula (V), compounds of general formula (VI), 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.

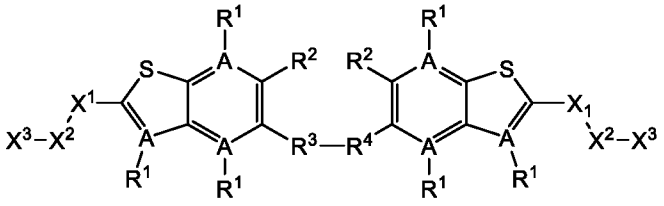
The present disclosure broadly relates to novel compounds of general formula (I). In particular, the present disclosure relates to compounds having the general structural formula (I):



(I)

or pharmaceutically acceptable salts thereof, as described herein. Uses of compounds of general formula (I) and processes for making compounds of general formula (I) are also disclosed.

According to one aspect, the present invention provides a compound according to general formula (I):



(I)

or a pharmaceutically acceptable salt thereof, wherein

each A-R^1 is independently selected from the group consisting of C-R^1 and N, wherein each R^1 is independently selected from the group consisting of H, halogen, OR^6, $N(R^6)_2$, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkyl substituted by OR^6, C_1-C_6 alkyl substituted by $N(R^6)_2$, $COOR^6$, and $C(O)N(R^6)_2$;

each R^2 is independently selected from the group consisting of H, halogen, CN, OR^6, $N(R^6)_2$, $COOR^6$, $C(O)N(R^6)_2$, SO_2R^6, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkyl substituted by OR^6, C_2-C_6 alkenyl, C_2-C_6 haloalkenyl, C_2-C_6 alkenyl substituted by OR^6, C_2-C_6 alkynyl, C_2-C_6 haloalkynyl, C_2-C_6 alkynyl substituted by OR^6, C_3-C_6 cycloalkyl, and a 3- to 6-membered heterocyclic ring including 1 to 2 ring members selected from the group consisting of O, S, and $N(R^6)$;

R^3 and R^4 are independently selected from the group consisting of O-(C_1-C_4 alkylene or haloalkylene), C_1-C_5 alkylene or haloalkylene, and $N(R_6)$-(C_1-C_4 alkylene or haloalkylene);

optionally R^4 may be taken together with an adjacent C-R^1 and the atom to which they are attached to form fused ring E, which is selected from phenyl or a 5- or 6-membered heterocyclic ring including 1 to 2 ring members selected from the group consisting of O, S, N, and $N(R^6)$ wherein the bond to R^3 from said ring E is from an atom on said ring E with an open valence for substitution and wherein said phenyl or heterocyclic ring is optionally substituted with one or more members of the group consisting of halogen, 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_6 alkyl, and C_1-C_6 haloalkyl;

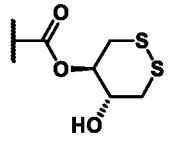
each X^1 is independently selected from the group consisting of C=O, -CH_2-, -CHF-, and -CF_2-;

each X^2 is independently selected from $(C(R^8)_2)_{(1\text{-}3)}$, wherein each R^8 is independently selected from the group consisting of H, halogen, C_1-C_6 alkyl, CN, OR^6, $N(R^6)_2$, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, C_1-C_6 alkyl substituted by OR^6, and C_1-C_6 alkyl substituted by $N(R^6)_2$;

optionally 2 R^8 on different carbon atoms may be taken together, along with the atoms to which they are attached, to form a 3- to 6-membered fused ring; and

optionally 2 R^8 on a single carbon atom may be taken together, along with the atom to which they are attached, to form a 3- to 6-membered spirocycle;

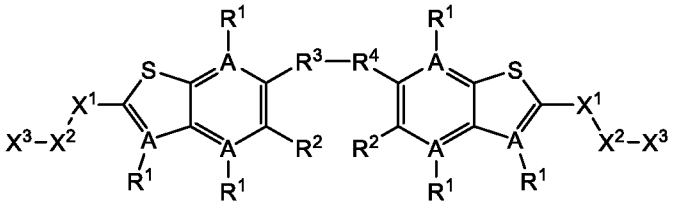
each X^3 is independently selected from the group consisting of $COOR^6$, $C(O)SR^6$,



$C(S)OR^6$, , SO_2R^6, $C(O)N(R^9)_2$, and CN; and

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

According to another aspect, the present invention provides a compound of general formula (II):



(II)

or a pharmaceutically acceptable salt thereof, wherein

each A-R^1 is independently selected from the group consisting of C-R^1 and N, wherein each R^1 is independently selected from the group consisting of H, halogen, OR^6, $N(R^6)_2$, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkyl substituted by OR^6, C_1-C_6 alkyl substituted by $N(R^6)_2$, $COOR^6$, and $C(O)N(R^6)_2$;

each R^2 is independently selected from the group consisting of H, halogen, CN, OR^6, $N(R^6)_2$, $COOR^6$, $C(O)N(R^6)_2$, SO_2R^6, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkyl substituted by OR^6, C_2-C_6 alkenyl, C_2-C_6 haloalkenyl, C_2-C_6 alkenyl substituted by OR^6, C_2-C_6 alkynyl, C_2-C_6 haloalkynyl, C_2-C_6 alkynyl substituted by OR^6, C_3-C_6 cycloalkyl, and a 3- to 6-membered heterocyclic ring including 1 to 2 ring members selected from the group consisting of O, S, and $N(R^6)$;

R^3 and R^4 are independently selected from the group consisting of O-(C_1-C_4 alkylene or haloalkylene), C_1-C_5 alkylene or haloalkylene, and $N(R_6)$-(C_1-C_4 alkylene or haloalkylene);

optionally R^4 may be taken together with an adjacent C-R^1 and the atom to which they are attached to form fused ring E, which is selected from phenyl or a 5- or 6-membered heterocyclic ring including 1 to 2 ring members selected from the group consisting of O, S, N, and $N(R^6)$ wherein the bond to R^3 from said ring E is from an atom on said ring E with an open valence for substitution and wherein said phenyl or heterocyclic ring is optionally substituted with one or more members of the group consisting of halogen, C_1-C_3 alkyl, and C_1-C_3 haloalkyl;

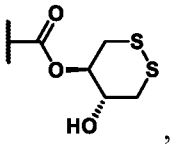
each R^6 is independently selected from the group consisting of H, C_1-C_6 alkyl, and C_1-C_6 haloalkyl;

each X^1 is independently selected from the group consisting of C=O, -CH_2-, -CHF-, and -CF_2-;

each X^2 is independently selected from $(C(R^8)_2)_{(1-3)}$, wherein each R^8 is independently selected from the group consisting of H, halogen, C_1-C_6 alkyl, CN, OR^6, $N(R^6)_2$, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, C_1-C_6 alkyl substituted by OR^6, and C_1-C_6 alkyl substituted by $N(R^6)_2$;

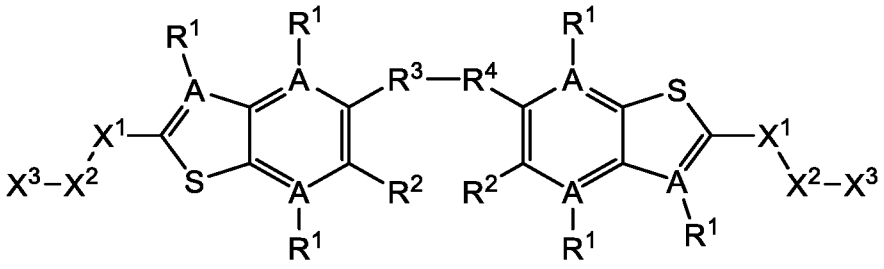
optionally 2 R^8 on different carbon atoms may be taken together, along with the atoms to which they are attached, to form a 3- to 6-membered fused ring; and

optionally 2 R^8 on a single carbon atom may be taken together, along with the atom to which they are attached, to form a 3- to 6-membered spirocycle;

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

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

According to another aspect, the present invention provides a compound of general formula (III):



(III)

or a pharmaceutically acceptable salt thereof, wherein

each A-R^1 is independently selected from the group consisting of C-R^1 and N, wherein each R^1 is independently selected from the group consisting of H, halogen, OR^6, $N(R^6)_2$, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkyl substituted by OR^6, C_1-C_6 alkyl substituted by $N(R^6)_2$, $COOR^6$, and $C(O)N(R^6)_2$;

each R^2 is independently selected from the group consisting of H, halogen, CN, OR^6, $N(R^6)_2$, $COOR^6$, $C(O)N(R^6)_2$, SO_2R^6, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkyl substituted by OR^6, C_2-C_6 alkenyl, C_2-C_6 haloalkenyl, C_2-C_6 alkenyl substituted by OR^6, C_2-C_6 alkynyl, C_2-C_6 haloalkynyl, C_2-C_6 alkynyl substituted by OR^6, C_3-C_6 cycloalkyl, and a 3- to 6-membered

heterocyclic ring including 1 to 2 ring members selected from the group consisting of O, S, and $N(R^6)$;

R^3 and R^4 are independently selected from the group consisting of O-(C_1-C_4 alkylene or haloalkylene), C_1-C_5 alkylene or haloalkylene, and $N(R_6)$-(C_1-C_4 alkylene or haloalkylene);

optionally R^3 may be taken together with an adjacent C-R^1 and the atom to which they are attached to form fused ring G, which is selected from phenyl or a 5- or 6-membered heterocyclic ring including 1 to 2 ring members selected from the group consisting of O, S, N, and $N(R^6)$ wherein the bond to R^3 from said ring G is from an atom on said ring G with an open valence for substitution and wherein said phenyl or heterocyclic ring is optionally substituted with one or more members of the group consisting of halogen, C_1-C_3 alkyl, and C_1-C_3 haloalkyl;

optionally R^4 may be taken together with an adjacent C-R^1 and the atom to which they are attached to form fused ring E, which is selected from phenyl or a 5- or 6-membered heterocyclic ring including 1 to 2 ring members selected from the group consisting of O, S, N, and $N(R^6)$ wherein the bond to R^4 from said ring E is from an atom on said ring E with an open valence for substitution and wherein said phenyl or heterocyclic ring is optionally substituted with one or more members of the group consisting of halogen, C_1-C_3 alkyl, and C_1-C_3 haloalkyl;

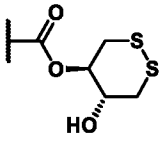
each R^6 is independently selected from the group consisting of H, C_1-C_6 alkyl, and C_1-C_6 haloalkyl;

each X^1 is independently selected from the group consisting of C=O, -CH_2-, -CHF-, and -CF_2-;

each X^2 is independently selected from $(C(R^8)_2)_{(1\text{-}3)}$, wherein each R^8 is independently selected from the group consisting of H, halogen, C_1-C_6 alkyl, CN, OR^6, $N(R^6)_2$, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, C_1-C_6 alkyl substituted by OR^6, and C_1-C_6 alkyl substituted by $N(R^6)_2$;

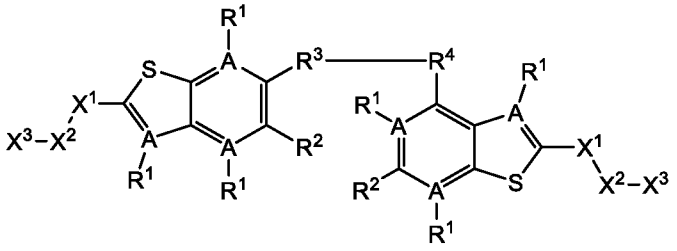
optionally 2 R^8 on different carbon atoms may be taken together, along with the atoms to which they are attached, to form a 3- to 6-membered fused ring; and

optionally 2 R^8 on a single carbon atom may be taken together, along with the atom to which they are attached, to form a 3- to 6-membered spirocycle;

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

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

According to another aspect, the present invention provides a compound of general formula (IV):



(IV)

or a pharmaceutically acceptable salt thereof, wherein

each A-R^1 is independently selected from the group consisting of C-R^1 and N, wherein each R^1 is independently selected from the group consisting of H, halogen, OR^6, $N(R^6)_2$, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkyl substituted by OR^6, C_1-C_6 alkyl substituted by $N(R^6)_2$, $COOR^6$, and $C(O)N(R^6)_2$;

each R^2 is independently selected from the group consisting of H, halogen, CN, OR^6, $N(R^6)_2$, $COOR^6$, $C(O)N(R^6)_2$, SO_2R^6, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkyl substituted by OR^6, C_2-C_6 alkenyl, C_2-C_6 haloalkenyl, C_2-C_6 alkenyl substituted by OR^6, C_2-C_6 alkynyl, C_2-C_6 haloalkynyl, C_2-C_6 alkynyl substituted by OR^6, C_3-C_6 cycloalkyl, and a 3- to 6-membered heterocyclic ring including 1 to 2 ring members selected from the group consisting of O, S, and $N(R^6)$;

R^3 and R^4 are independently selected from the group consisting of O-(C_1-C_4 alkylene or haloalkylene), C_1-C_5 alkylene or haloalkylene, and $N(R_6)$-(C_1-C_4 alkylene or haloalkylene);

each R^6 is independently selected from the group consisting of H, C_1-C_6 alkyl, and C_1-C_6 haloalkyl;

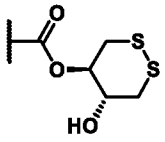
each X^1 is independently selected from the group consisting of C=O, -CH_2-, -CHF-, and -CF_2-;

each X^2 is independently selected from $(C(R^8)_2)_{(1\text{-}3)}$, wherein each R^8 is independently selected from the group consisting of H, halogen, C_1-C_6 alkyl, CN, OR^6, $N(R^6)_2$, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, C_1-C_6 alkyl substituted by OR^6, and C_1-C_6 alkyl substituted by $N(R^6)_2$;

optionally 2 R^8 on different carbon atoms may be taken together, along with the atoms to which they are attached, to form a 3- to 6-membered fused ring; and

optionally 2 R^8 on a single carbon atom may be taken together, along with the atom to which they are attached, to form a 3- to 6-membered spirocycle;

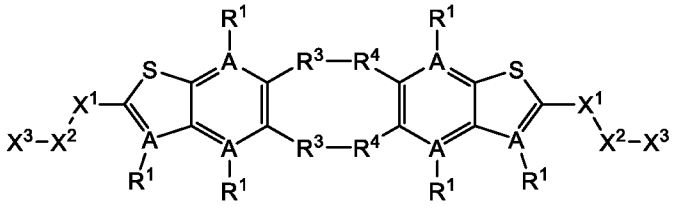
each X^3 is independently selected from the group consisting of $COOR^6$, $C(O)SR^6$,



$C(S)OR^6$, , SO_2R^6, $C(O)N(R^9)_2$, and CN; and

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

According to another aspect, the present invention provides a compound of general formula (V):



(V)

or a pharmaceutically acceptable salt thereof, wherein

each A-R^1 is independently selected from the group consisting of C-R^1 and N, wherein each R^1 is independently selected from the group consisting of H, halogen, OR^6, $N(R^6)_2$, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkyl substituted by OR^6, C_1-C_6 alkyl substituted by $N(R^6)_2$, $COOR^6$, and $C(O)N(R^6)_2$;

R^3 and R^4 are independently selected from the group consisting of O-(C_1-C_4 alkylene or haloalkylene), C_1-C_5 alkylene or haloalkylene, and $N(R_6)$-(C_1-C_4 alkylene or haloalkylene);

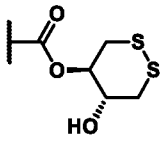
each X^1 is independently selected from the group consisting of C=O, $-CH_2-$, -CHF-, and $-CF_2-$;

each X^2 is independently selected from $(C(R^8)_2)_{(1-3)}$, wherein each R^8 is independently selected from the group consisting of H, halogen, C_1-C_6 alkyl, CN, OR^6, $N(R^6)_2$, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, C_1-C_6 alkyl substituted by OR^6, and C_1-C_6 alkyl substituted by $N(R^6)_2$;

optionally 2 R^8 on different carbon atoms may be taken together, along with the atoms to which they are attached, to form a 3- to 6-membered fused ring; and

optionally 2 R^8 on a single carbon atom may be taken together, along with the atom to which they are attached, to form a 3- to 6-membered spirocycle;

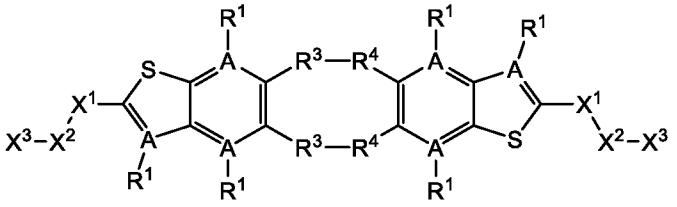
each X^3 is independently selected from the group consisting of $COOR^6$, $C(O)SR^6$,



$C(S)OR^6$, , SO_2R^6, $C(O)N(R^9)_2$, and CN; and

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

According to another aspect, the present invention provides a compound of general formula (VI):



(VI)

or a pharmaceutically acceptable salt thereof, wherein

each A-R^1 is independently selected from the group consisting of C-R^1 and N, wherein each R^1 is independently selected from the group consisting of H, halogen, OR^6, $N(R^6)_2$, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkyl substituted by OR^6, C_1-C_6 alkyl substituted by $N(R^6)_2$, $COOR^6$, and $C(O)N(R^6)_2$;

R^3 and R^4 are independently selected from the group consisting of O-(C_1-C_4 alkylene or haloalkylene), C_1-C_5 alkylene or haloalkylene, and $N(R_6)$-(C_1-C_4 alkylene or haloalkylene);

each R^6 is independently selected from the group consisting of H, C_1-C_6 alkyl, and C_1-C_6 haloalkyl;

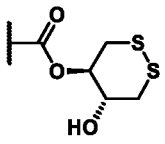
each X^1 is independently selected from the group consisting of C=O, -CH_2-, -CHF-, and -CF_2-;

each X^2 is independently selected from $(C(R^8)_2)_{(1-3)}$, wherein each R^8 is independently selected from the group consisting of H, halogen, C_1-C_6 alkyl, CN, OR^6, $N(R^6)_2$, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, C_1-C_6 alkyl substituted by OR^6, and C_1-C_6 alkyl substituted by $N(R^6)_2$;

optionally 2 R^8 on different carbon atoms may be taken together, along with the atoms to which they are attached, to form a 3- to 6-membered fused ring; and

optionally 2 R^8 on a single carbon atom may be taken together, along with the atom to which they are attached, to form a 3- to 6-membered spirocycle;

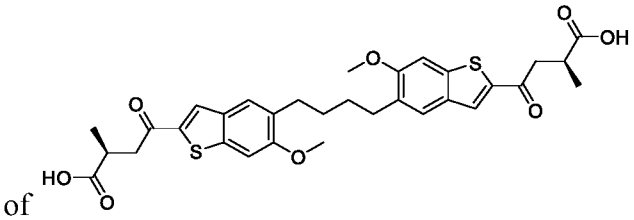
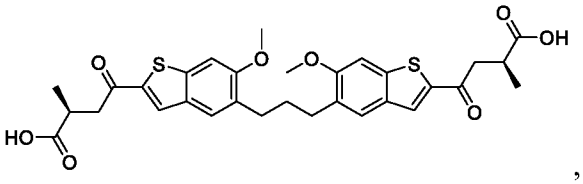
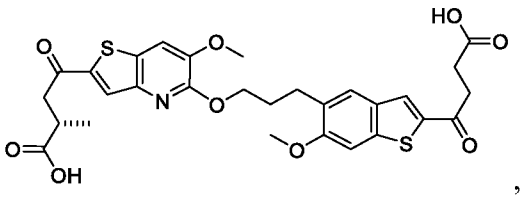
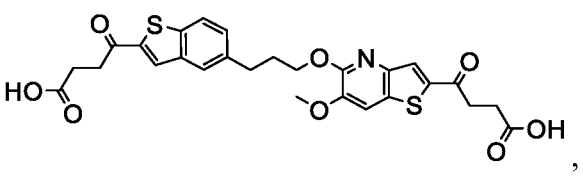
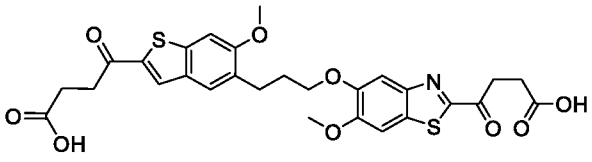
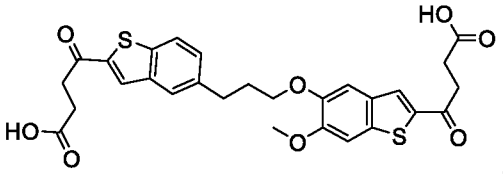
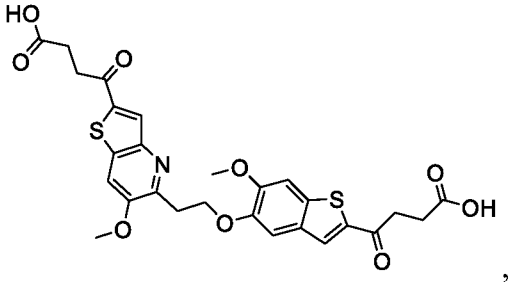
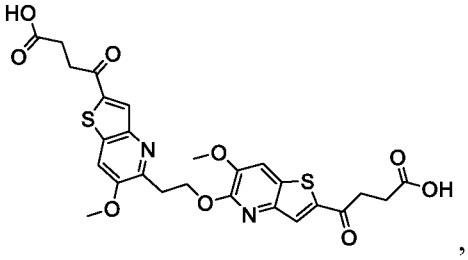
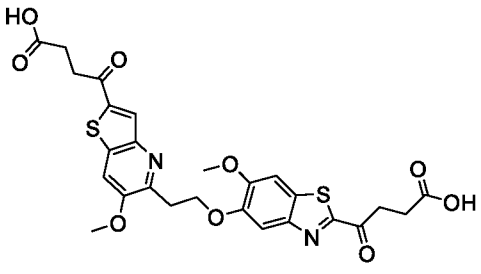
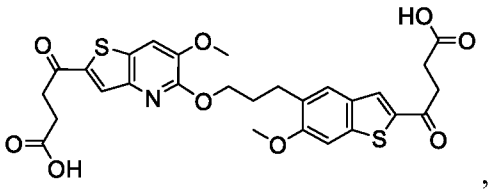
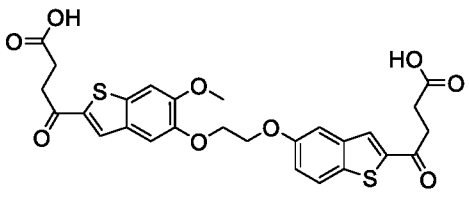
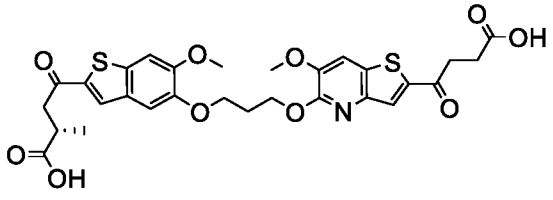
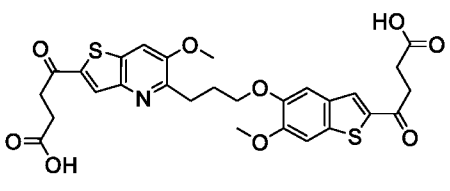
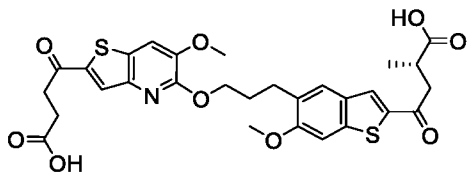
each X^3 is independently selected from the group consisting of $COOR^6$, $C(O)SR^6$,



$C(S)OR^6$, , SO_2R^6, $C(O)N(R^9)_2$, and CN; and

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

According to another aspect, the present invention provides a compound selected from the group consisting of

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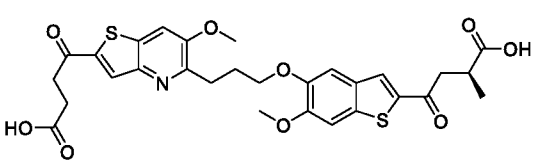
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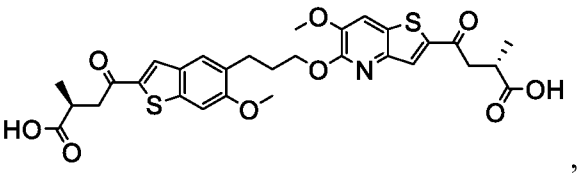
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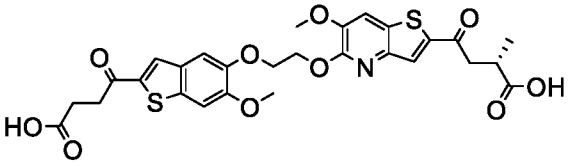
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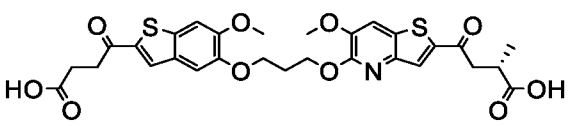
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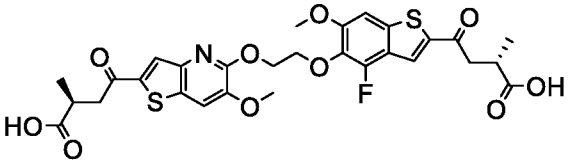
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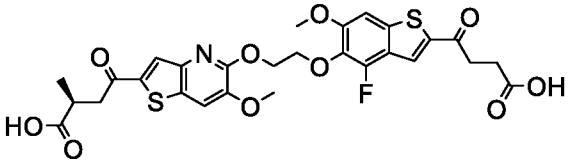
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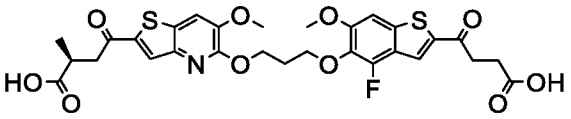
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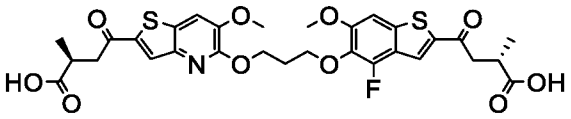
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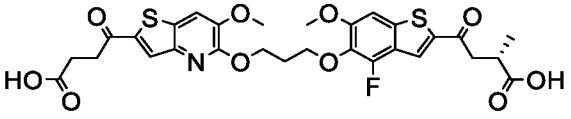
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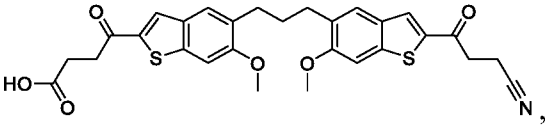
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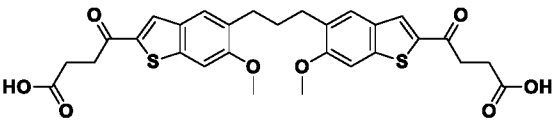
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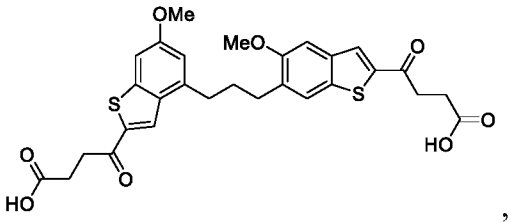
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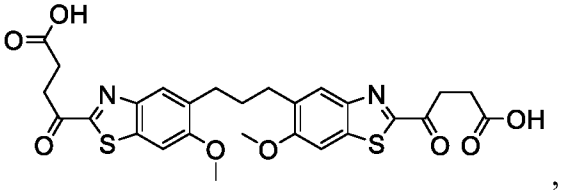
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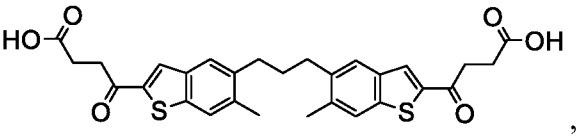
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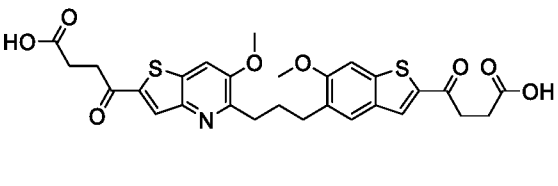
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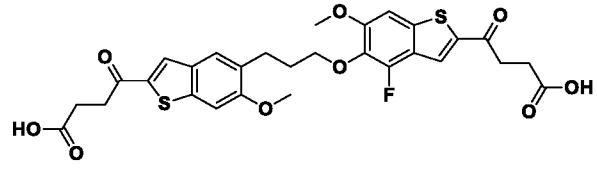
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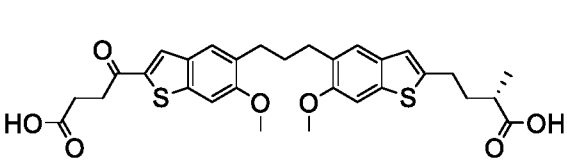
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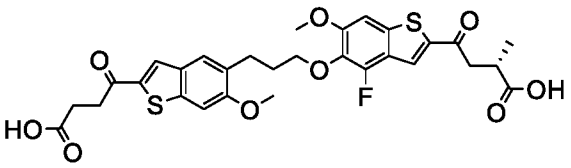
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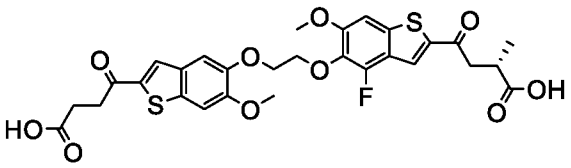
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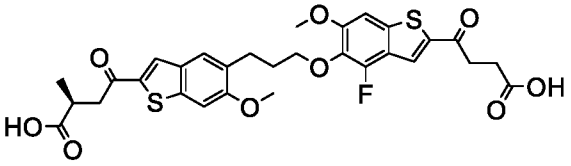
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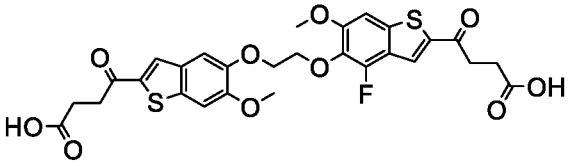
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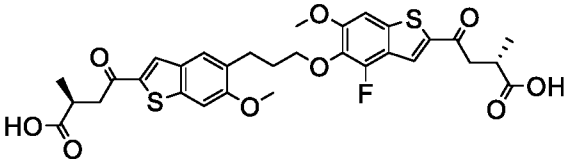
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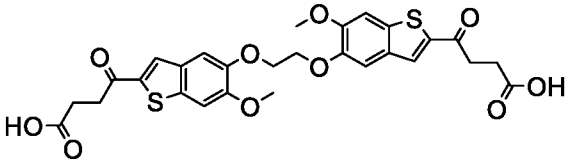
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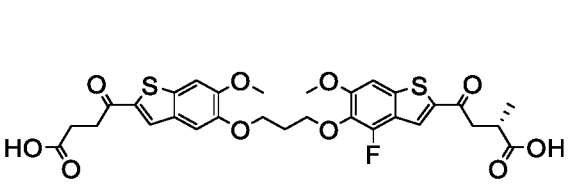
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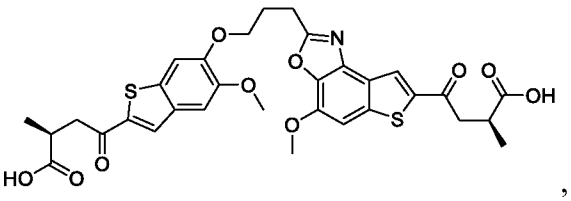
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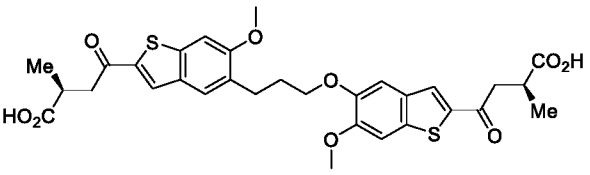
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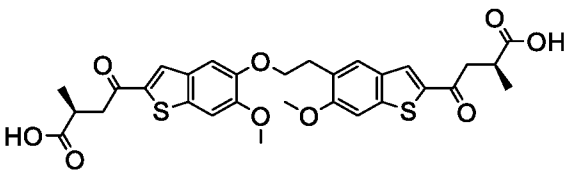
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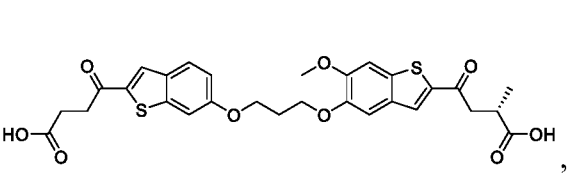
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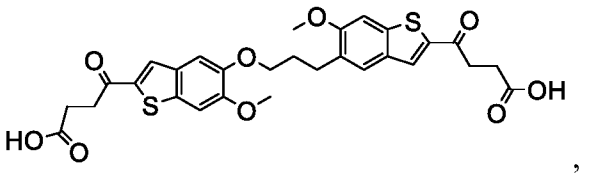
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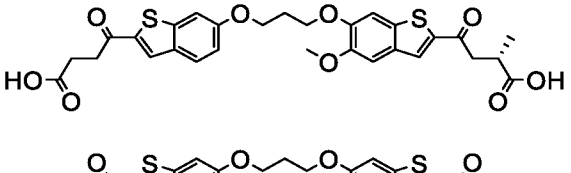
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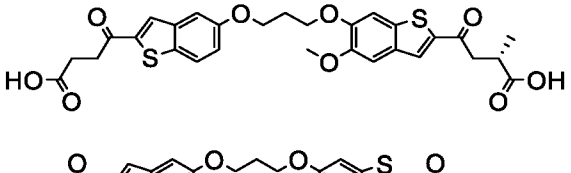
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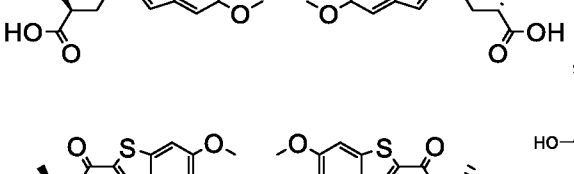
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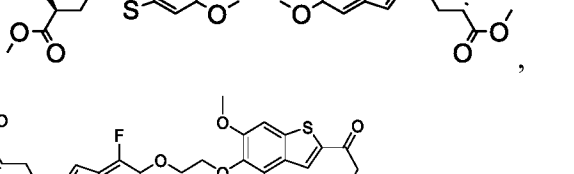
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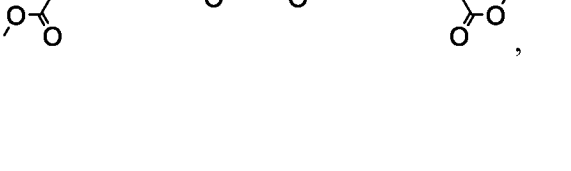
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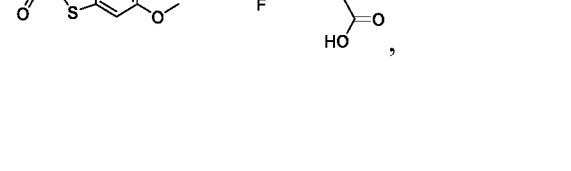
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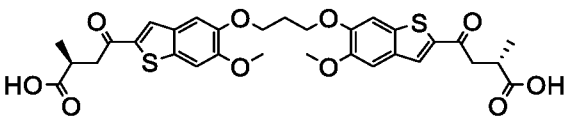
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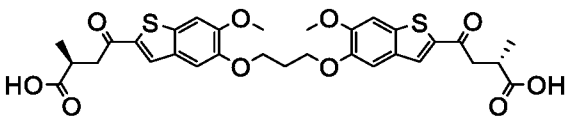
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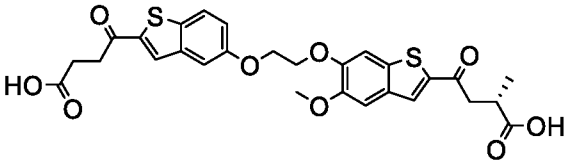
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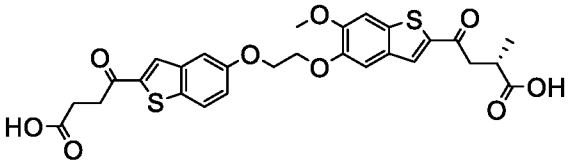
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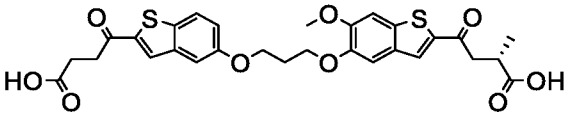
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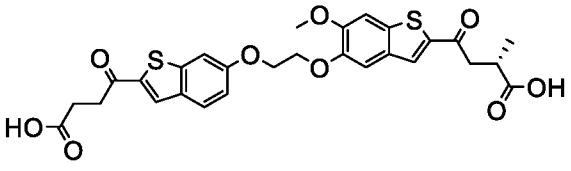
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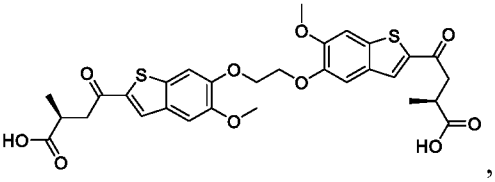
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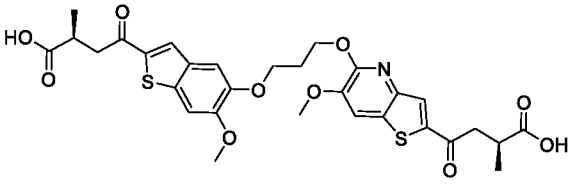
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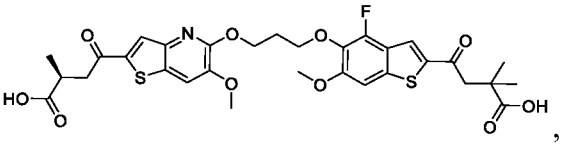
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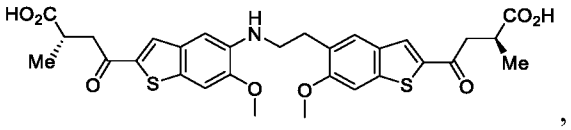
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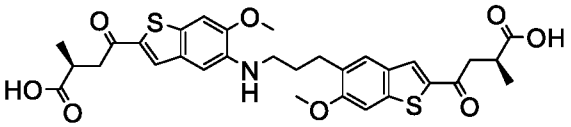
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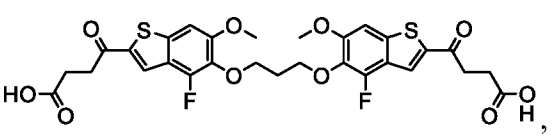
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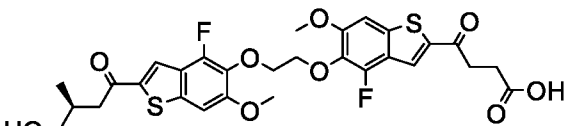
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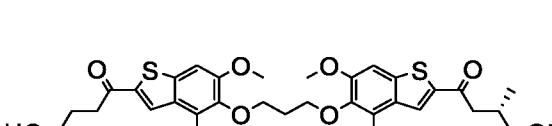
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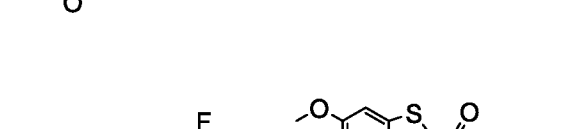
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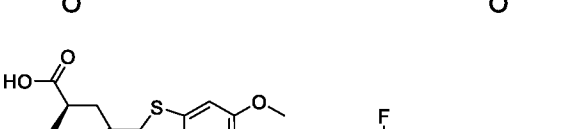
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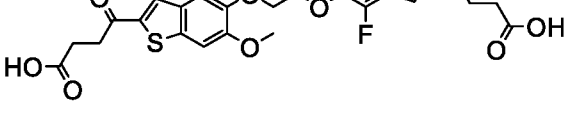
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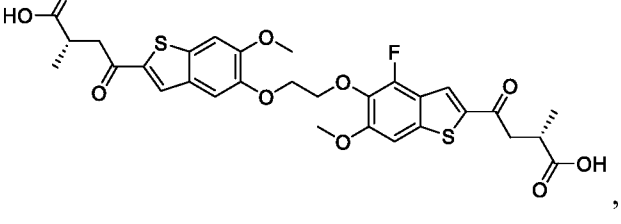
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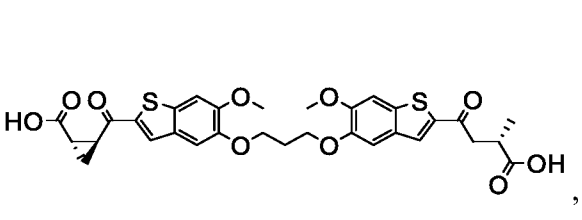
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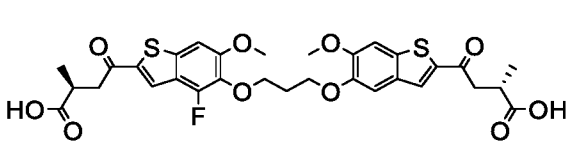
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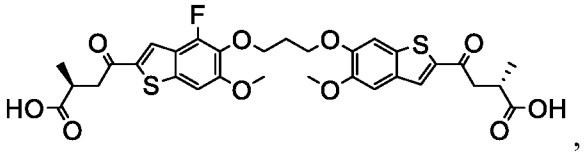
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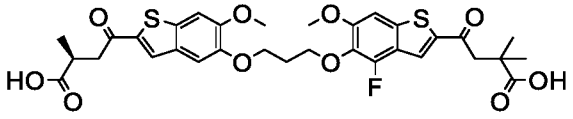
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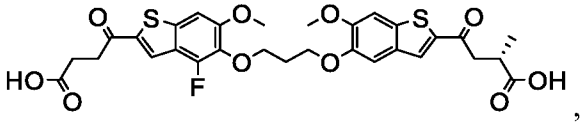
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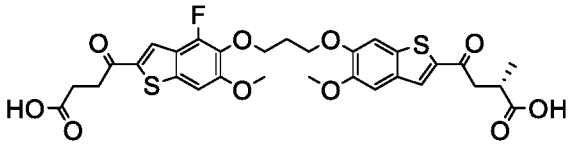
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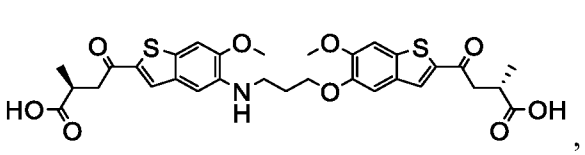
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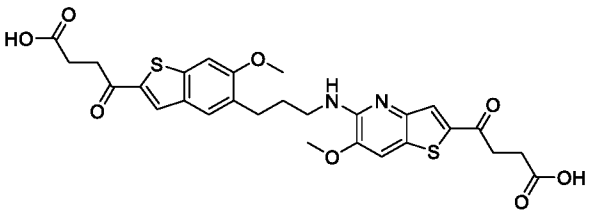
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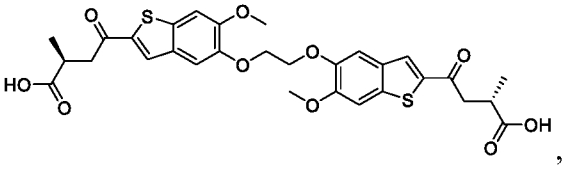
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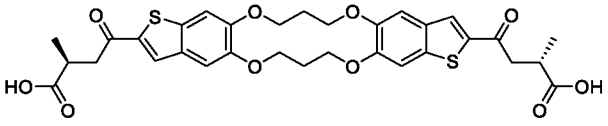
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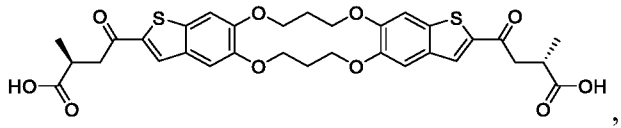
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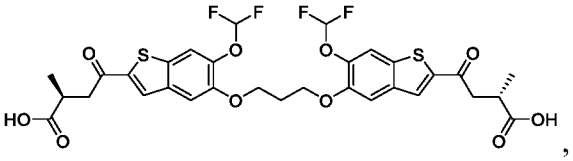
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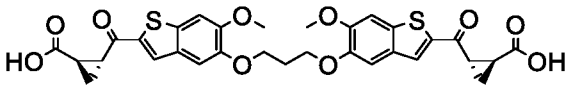
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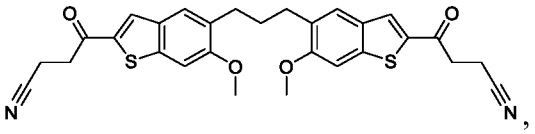
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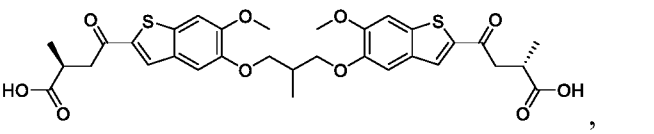
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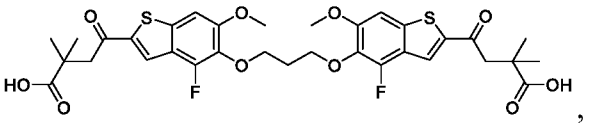
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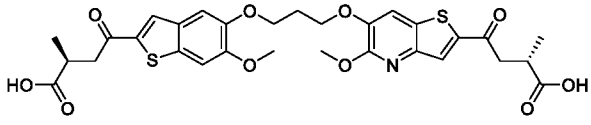
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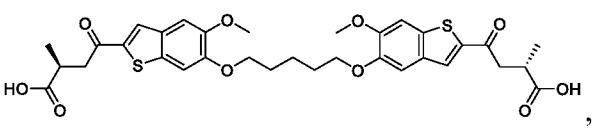
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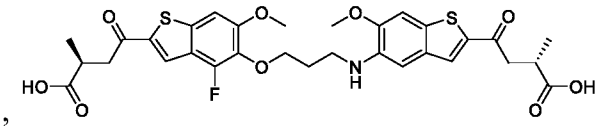
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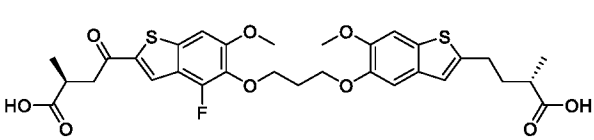
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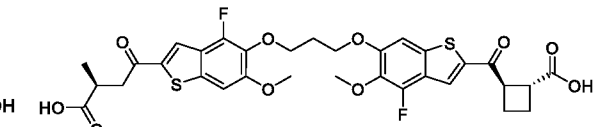
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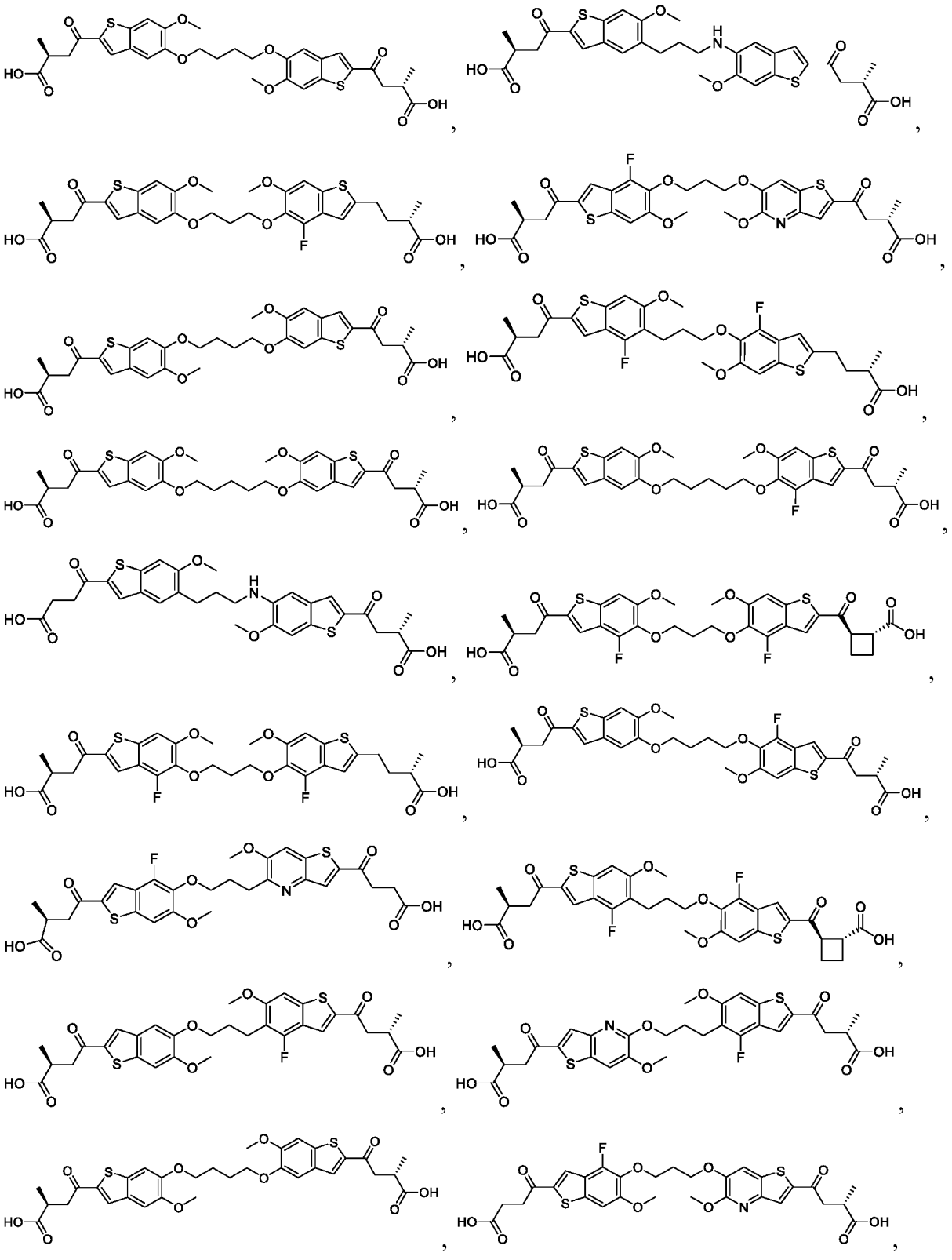

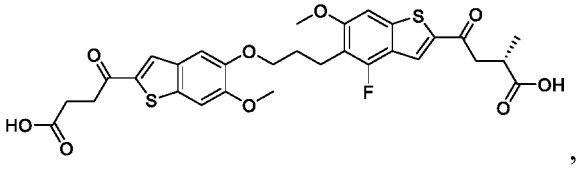
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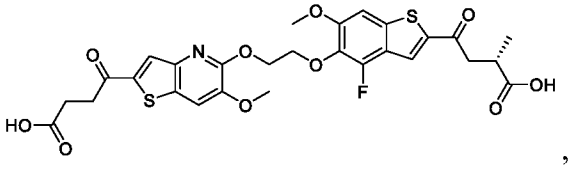
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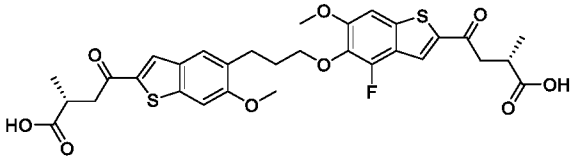
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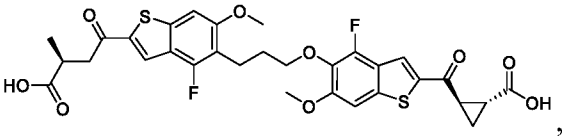
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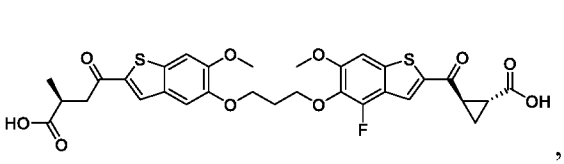
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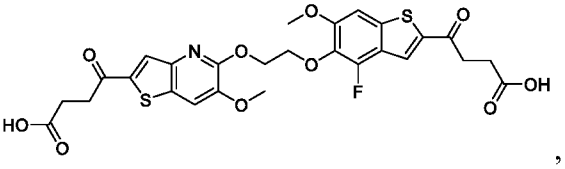
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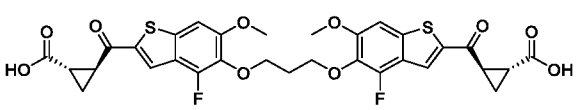
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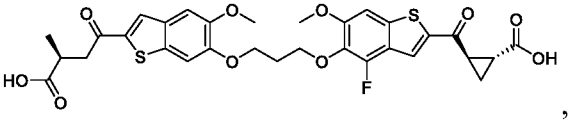
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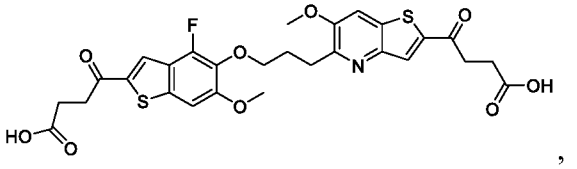
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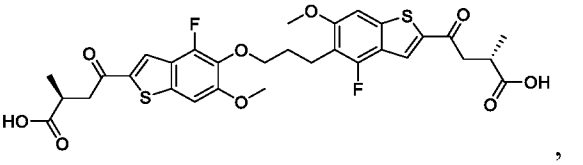
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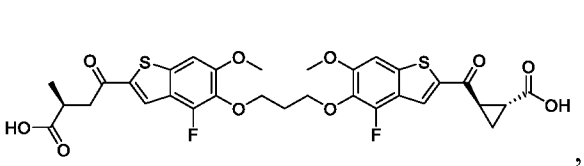
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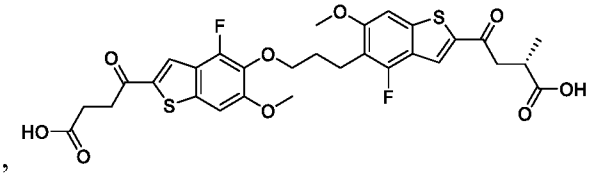
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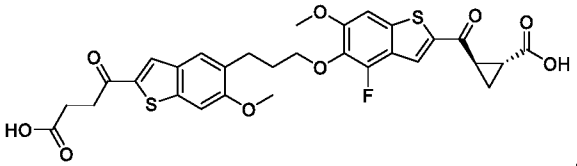
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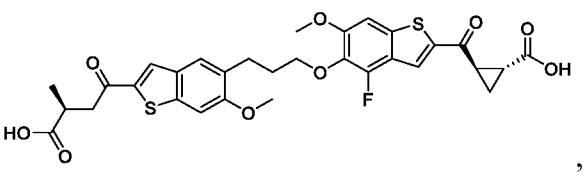
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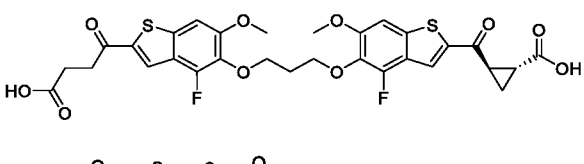
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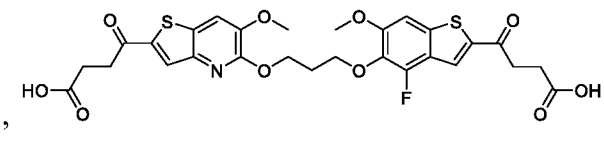
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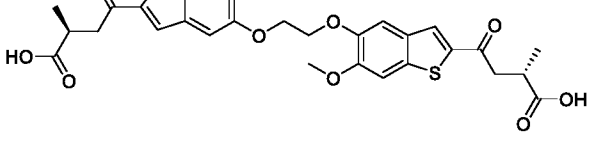
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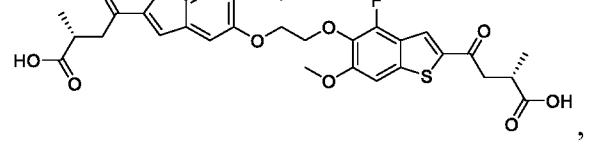
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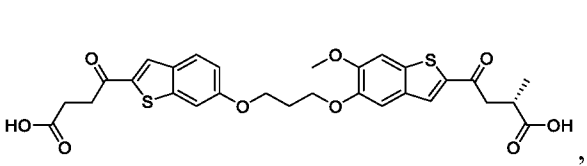
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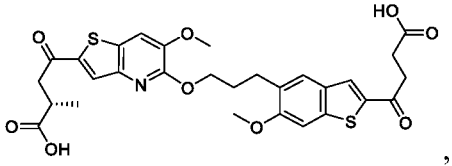
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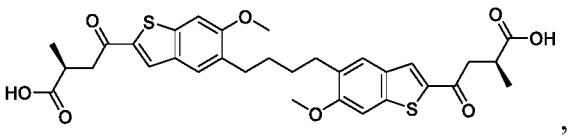
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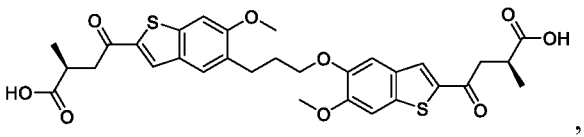
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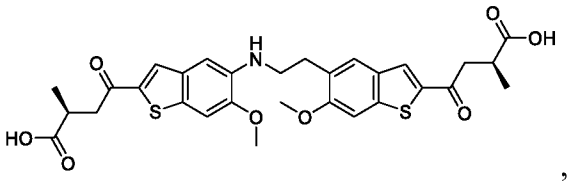
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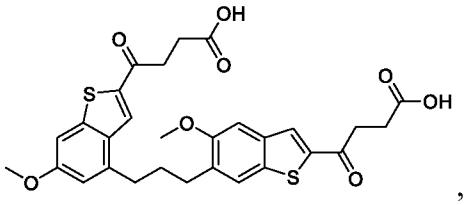
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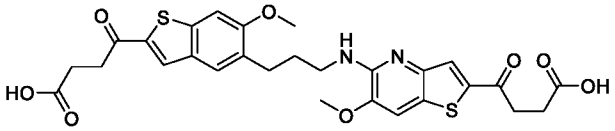
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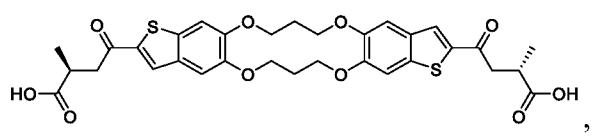
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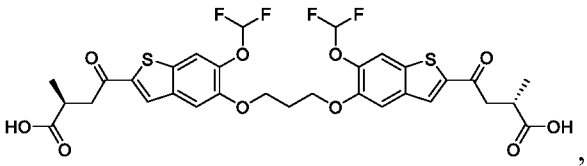
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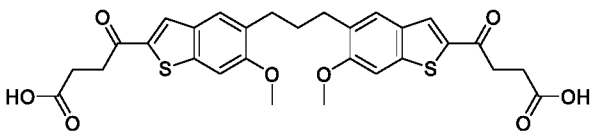
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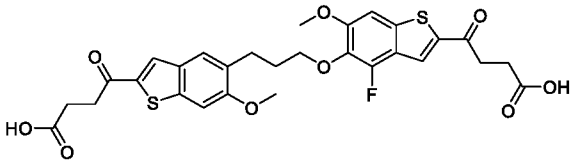
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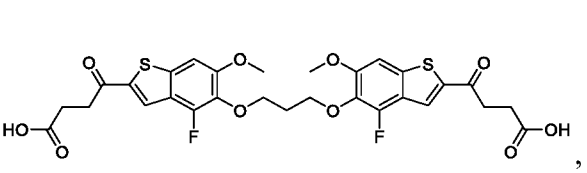
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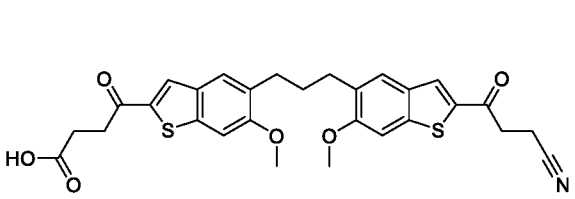
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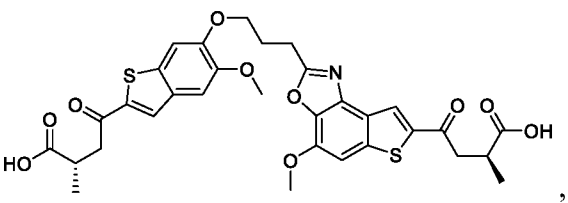
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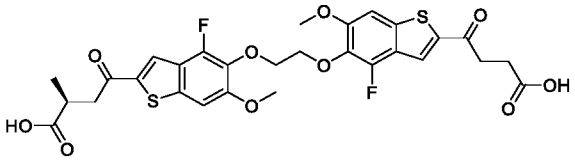
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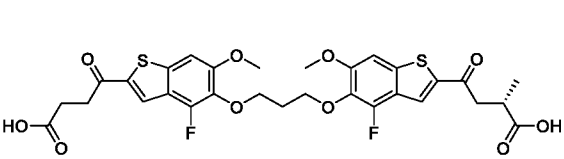
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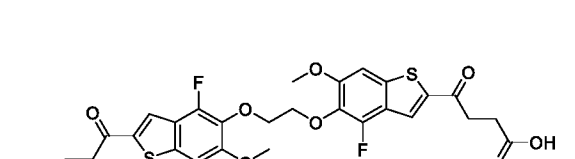
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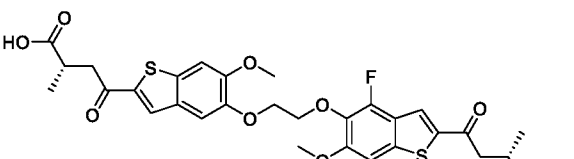
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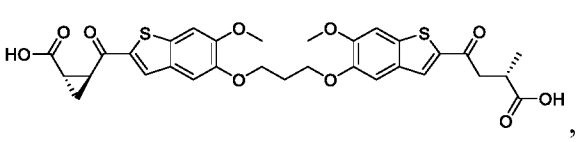
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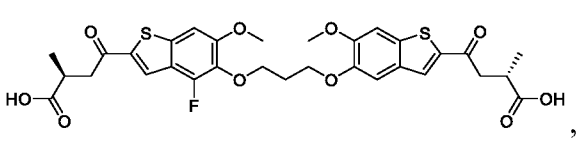
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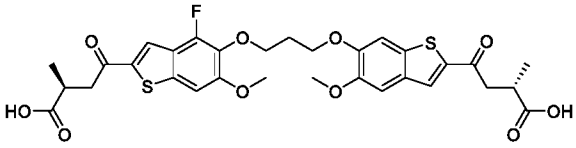
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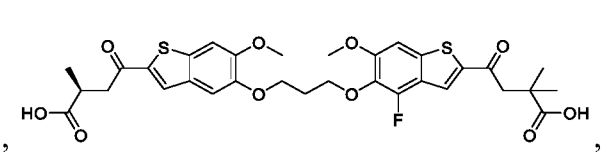
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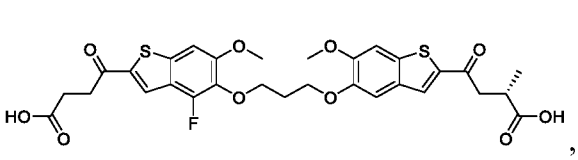
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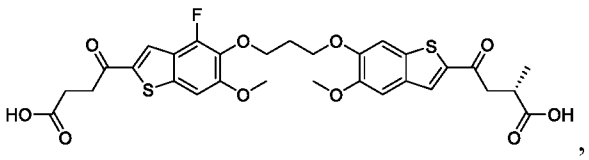
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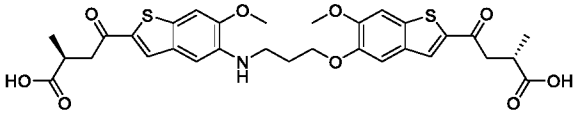
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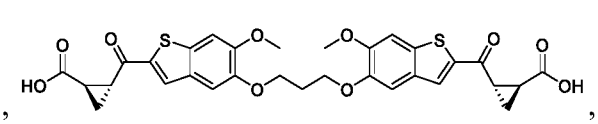
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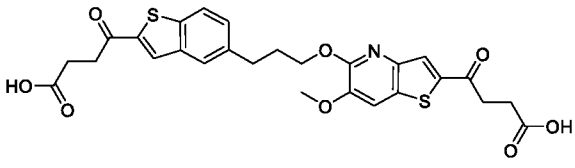
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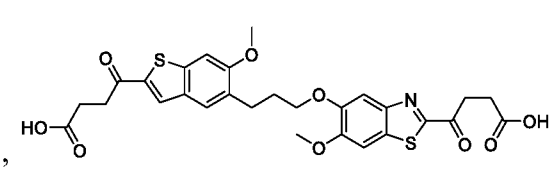
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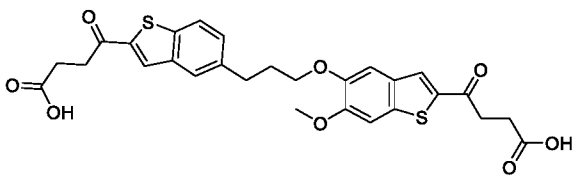
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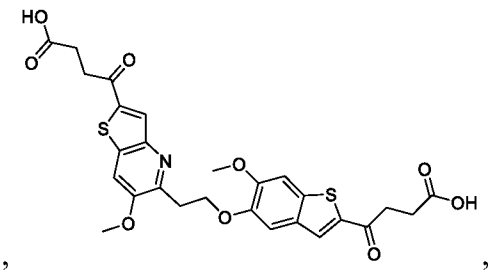
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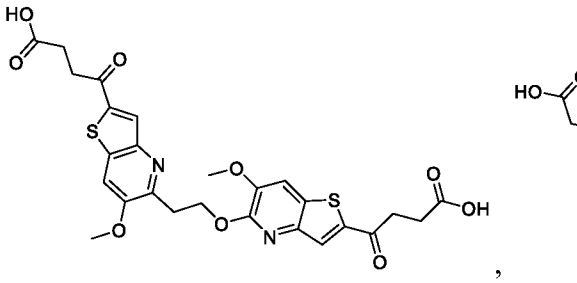
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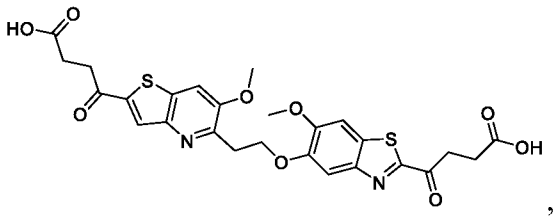
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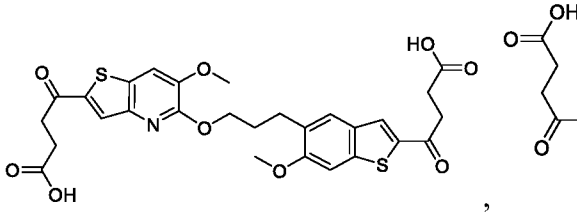
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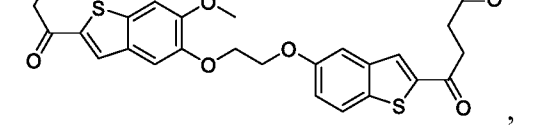
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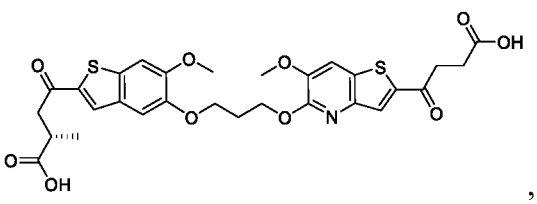
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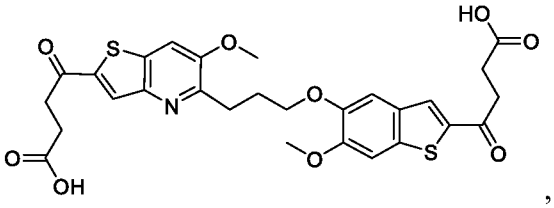
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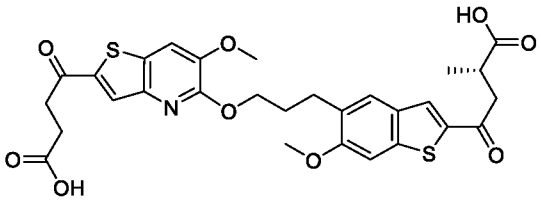
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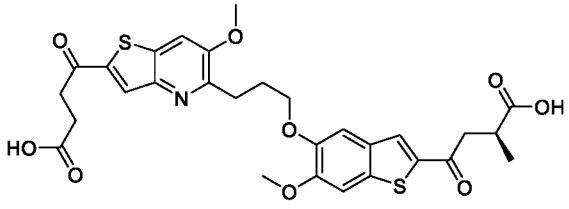
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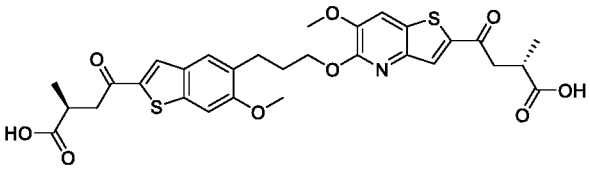
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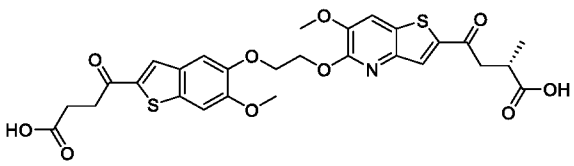
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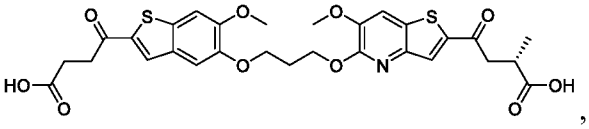
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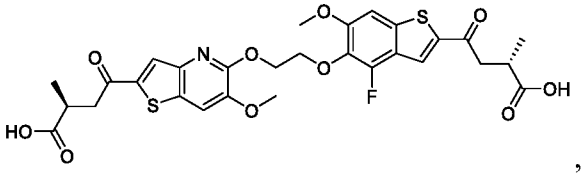
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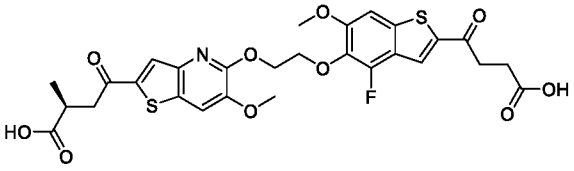
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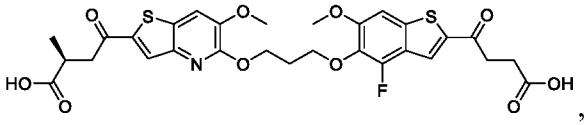
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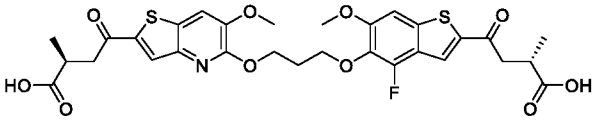
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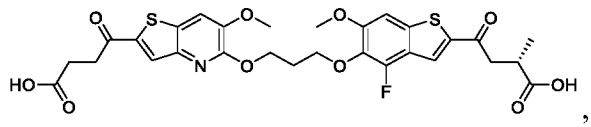
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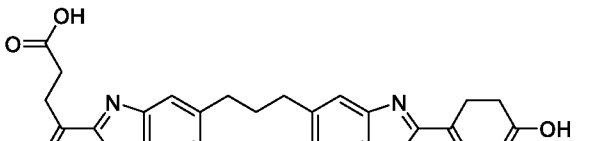
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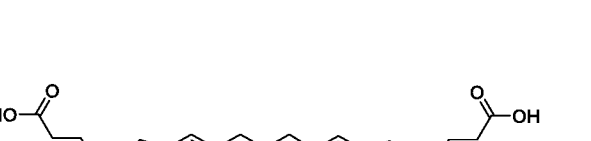
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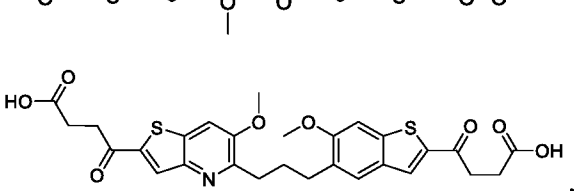
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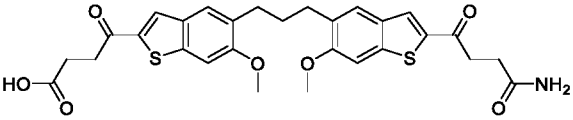
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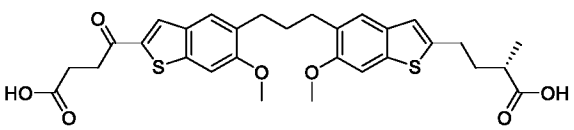
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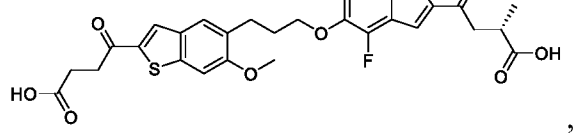
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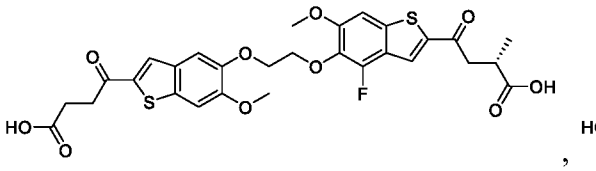
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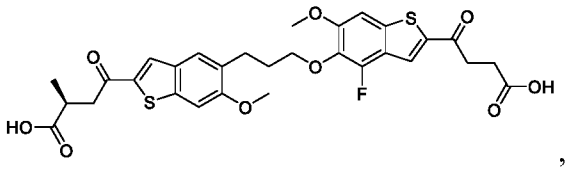
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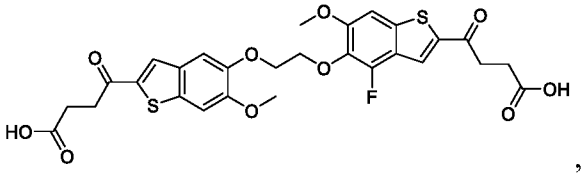
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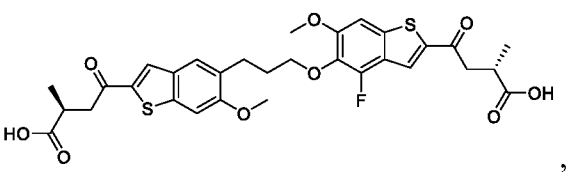
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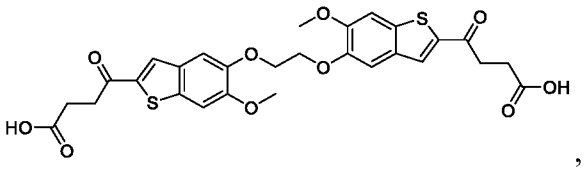
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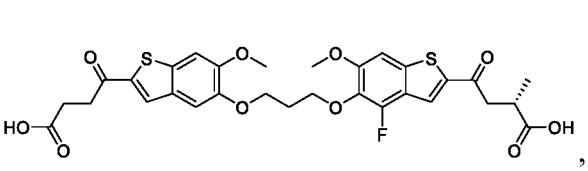
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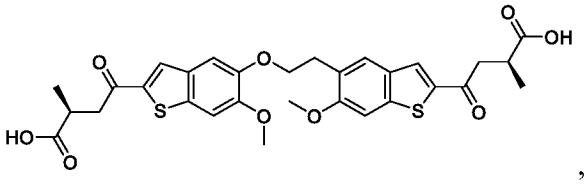
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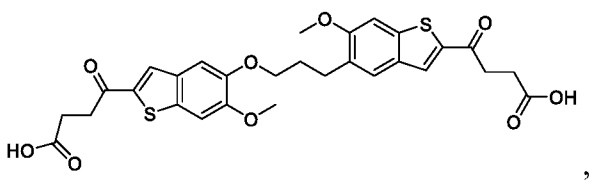
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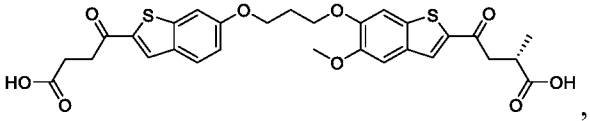
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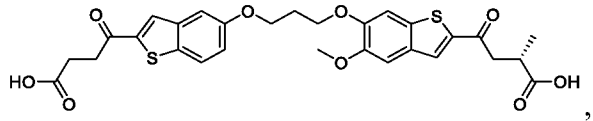
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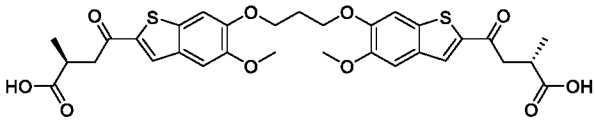
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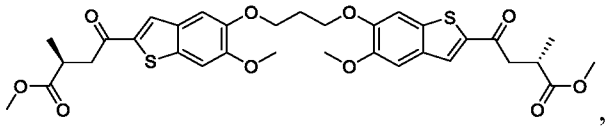
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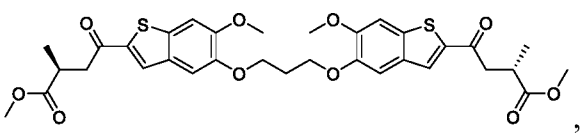
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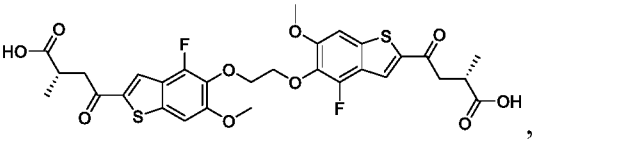
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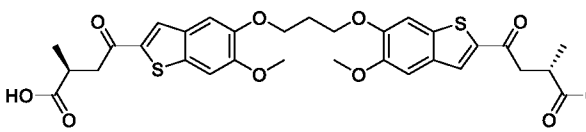
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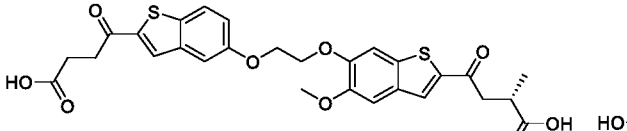
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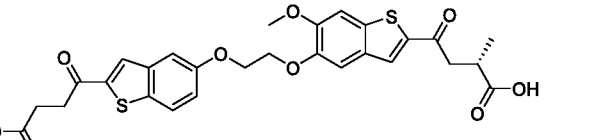
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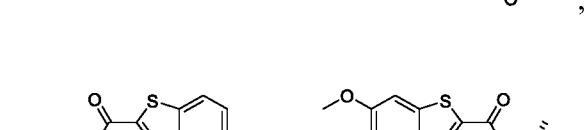
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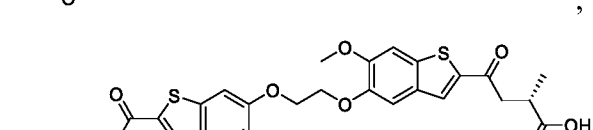
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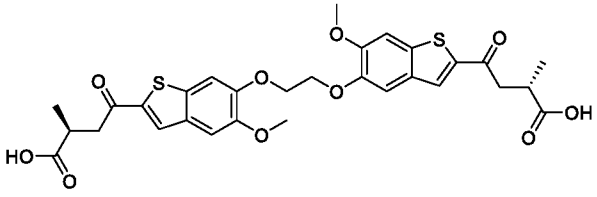
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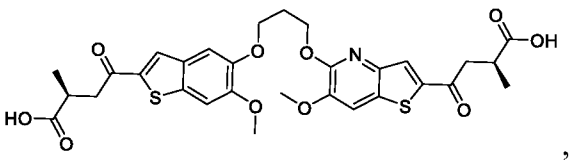
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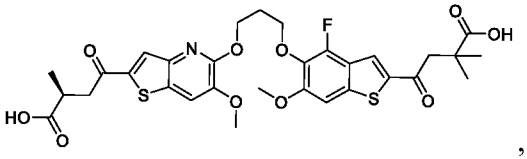
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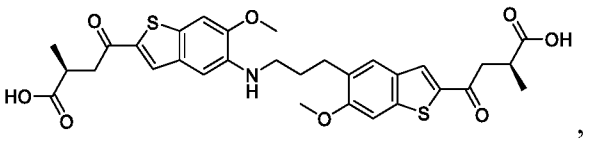
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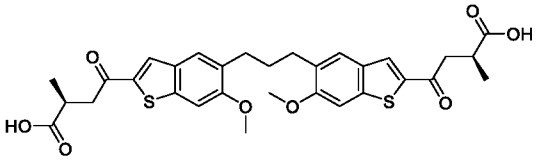
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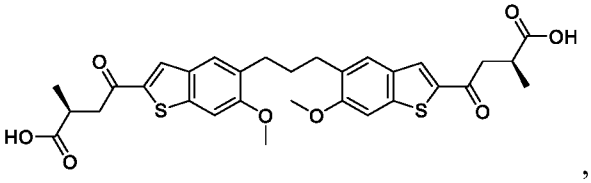
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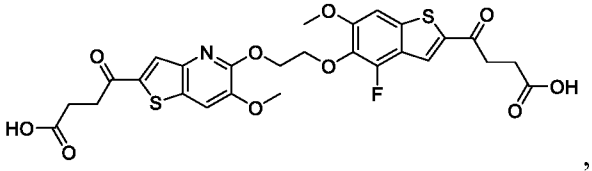
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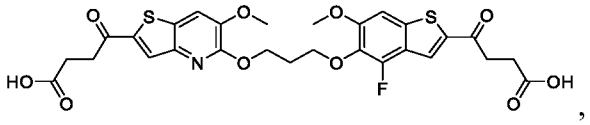
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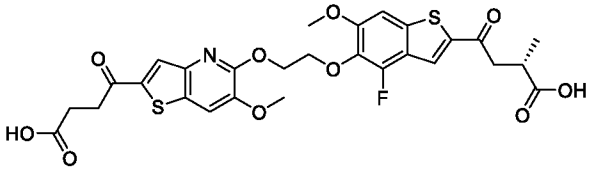
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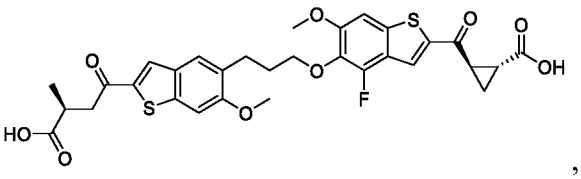
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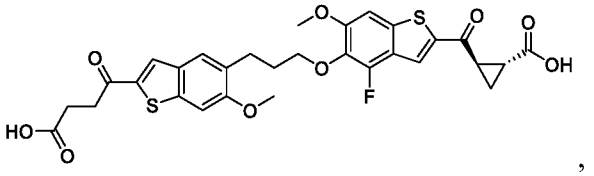
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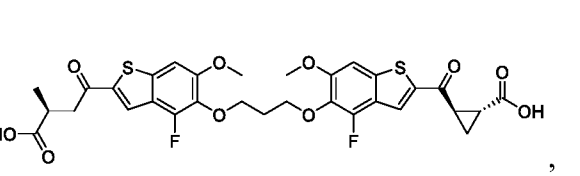
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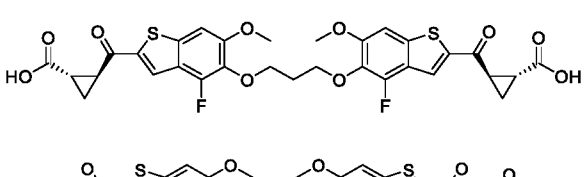
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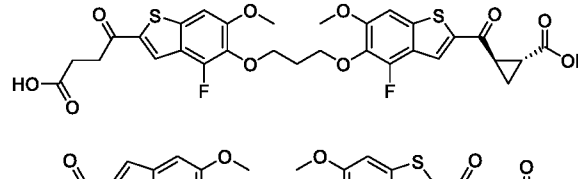
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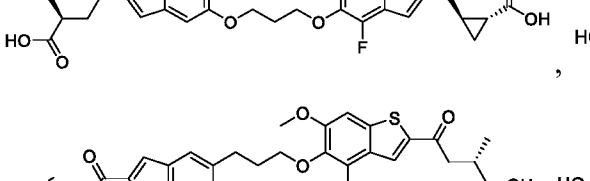
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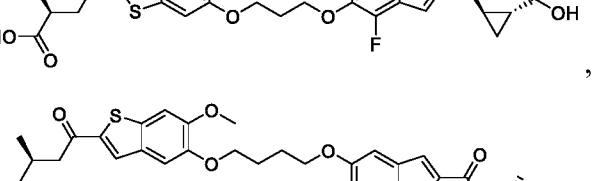
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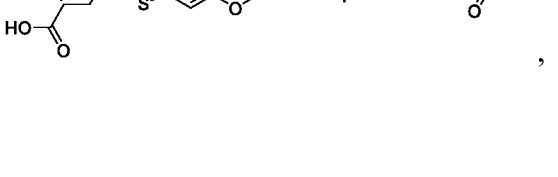
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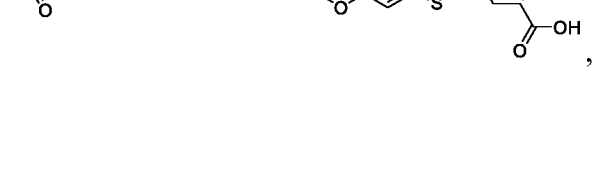
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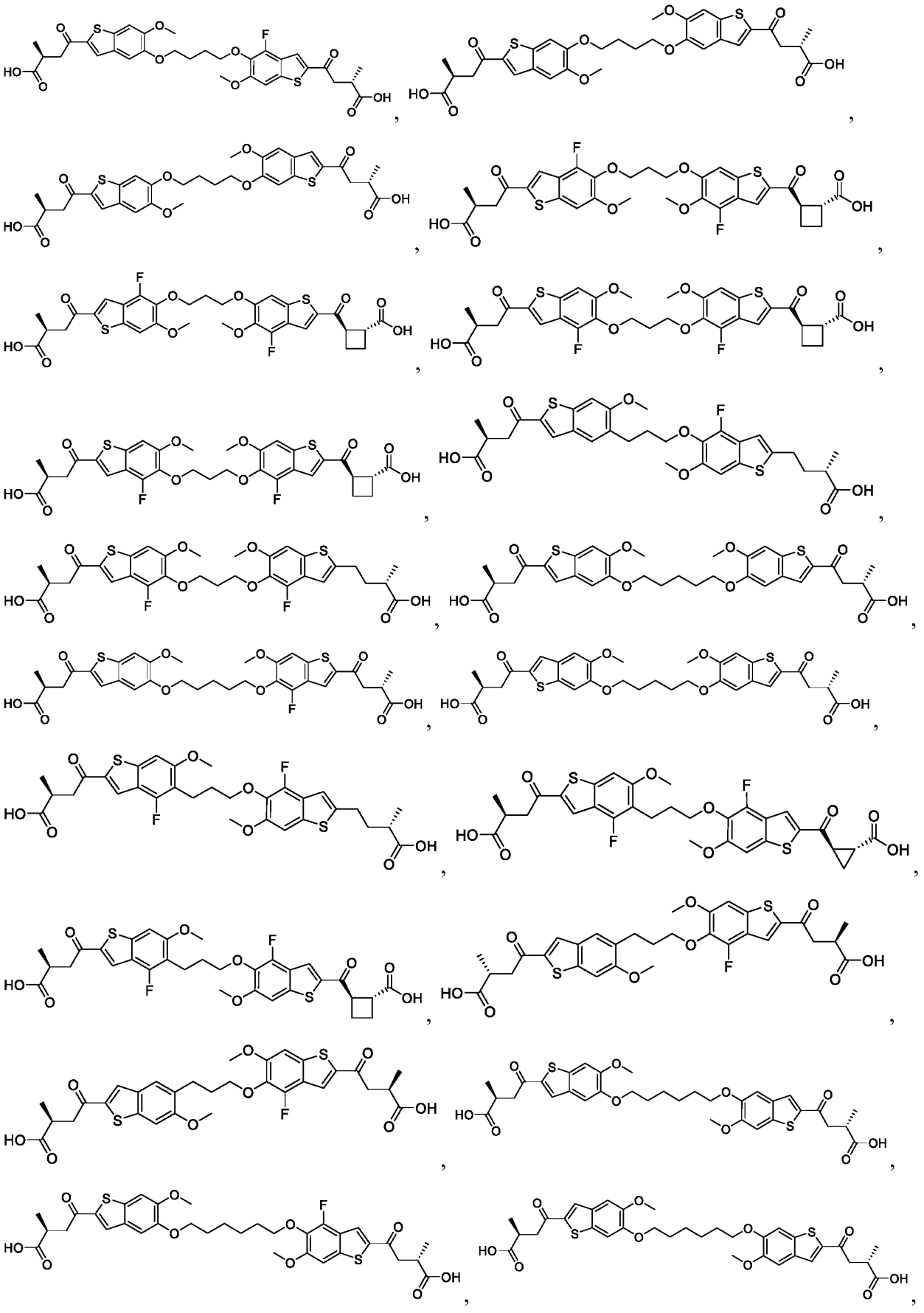

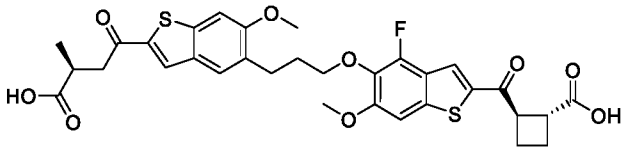
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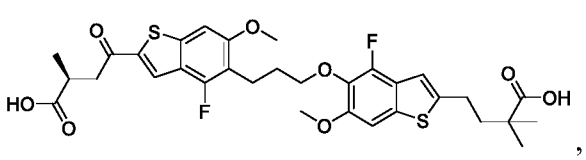
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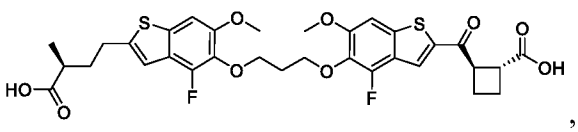
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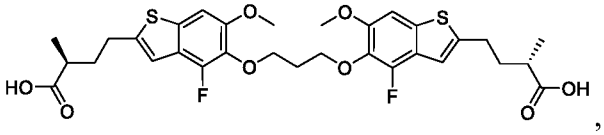
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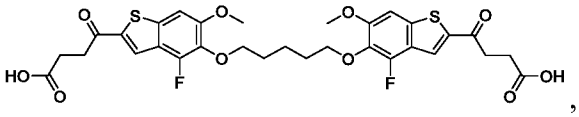
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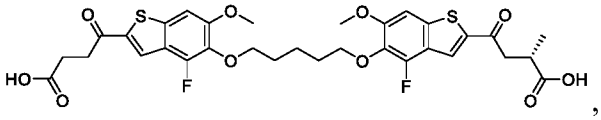
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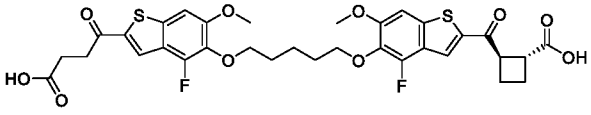
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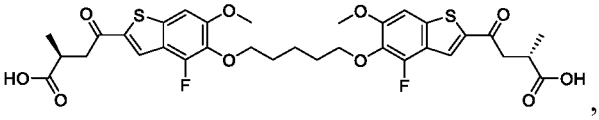
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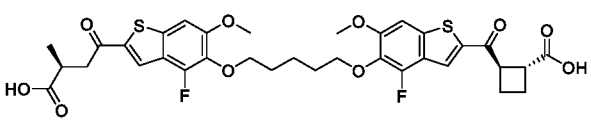
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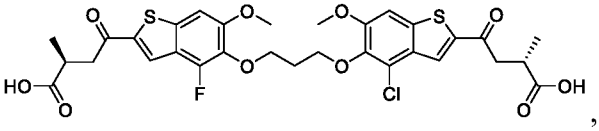
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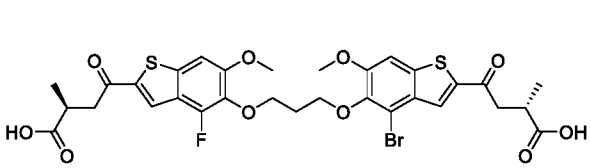
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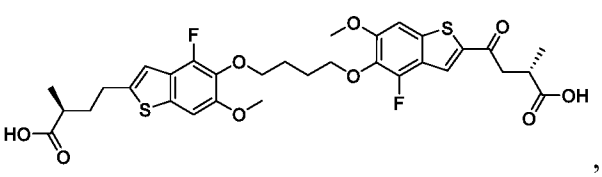
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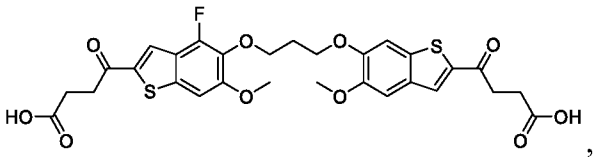
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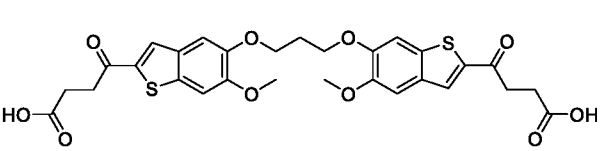
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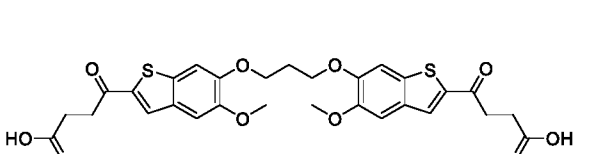
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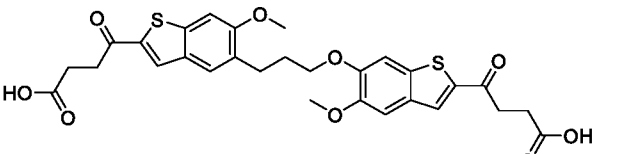
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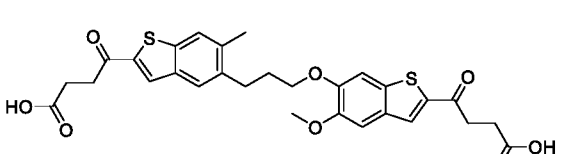
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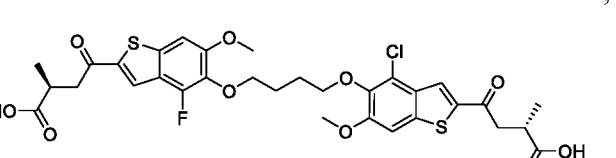
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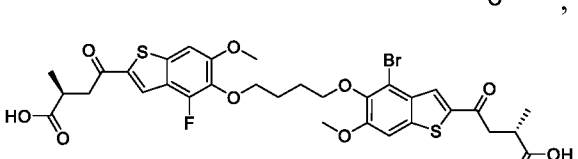
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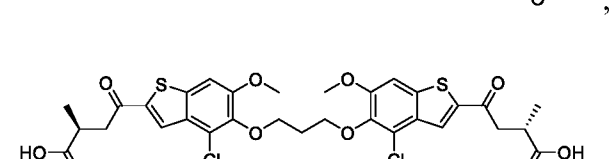
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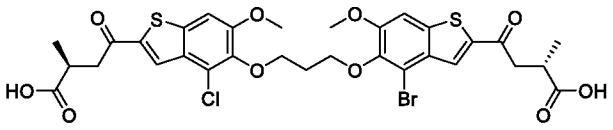
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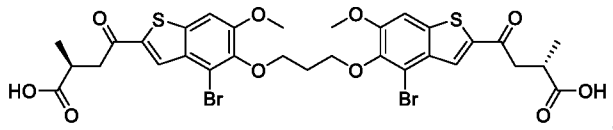
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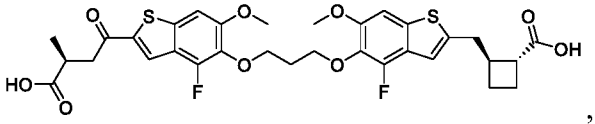
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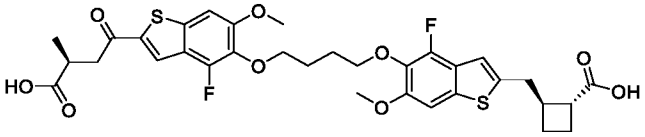
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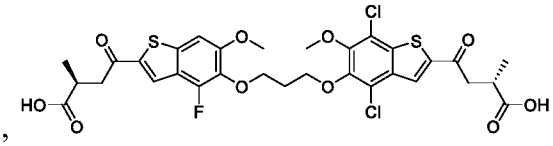
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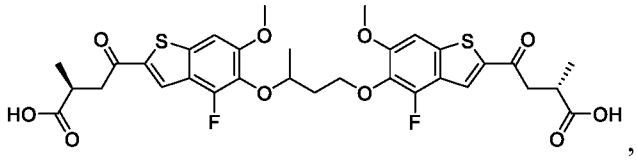
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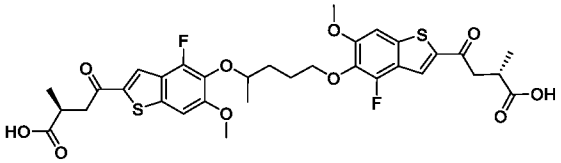
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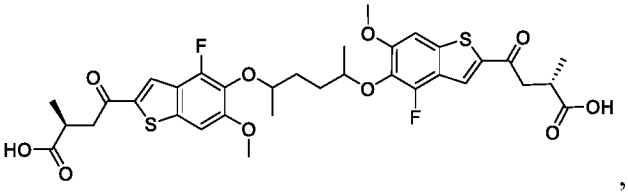
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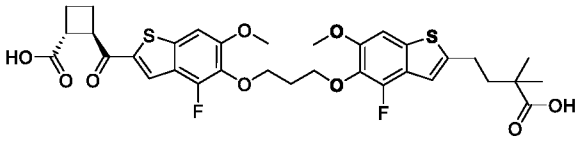
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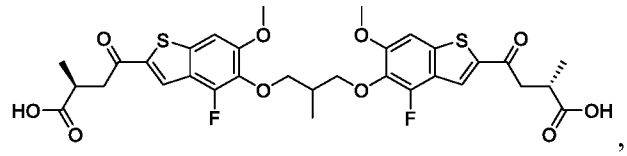
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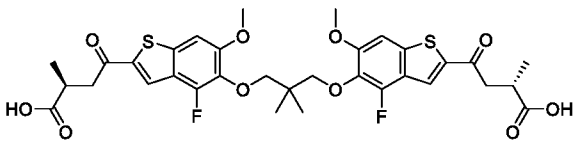
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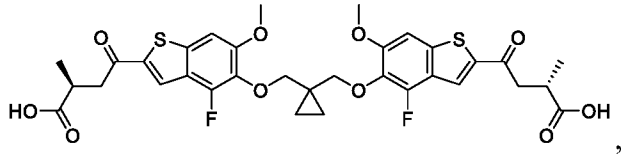
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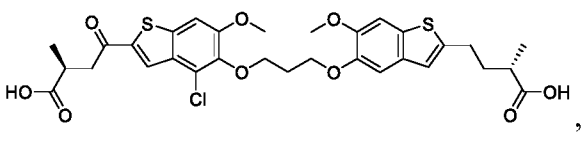
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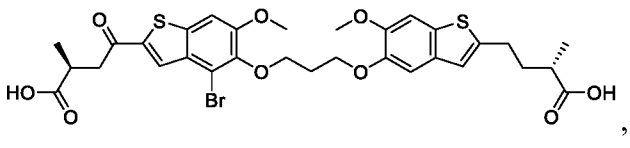
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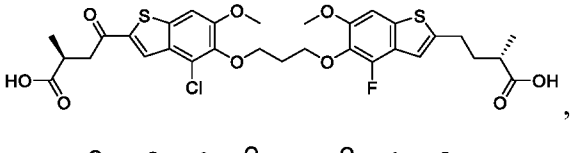
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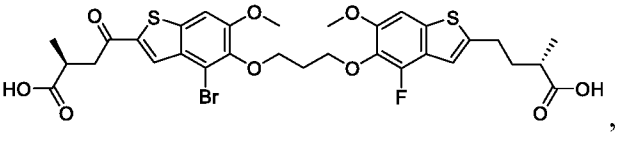
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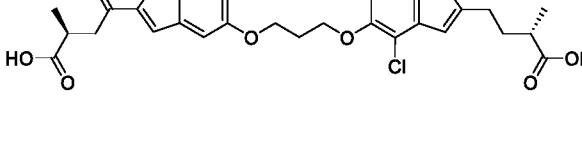
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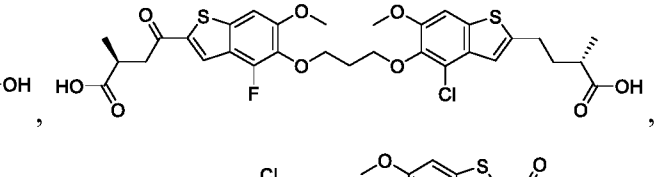
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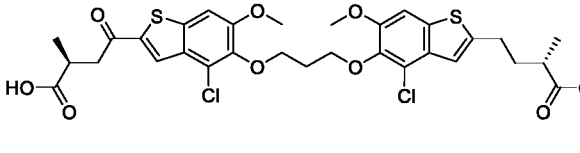
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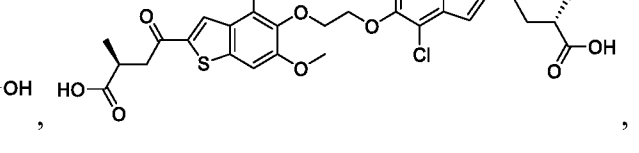
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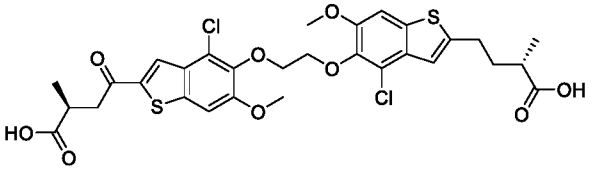
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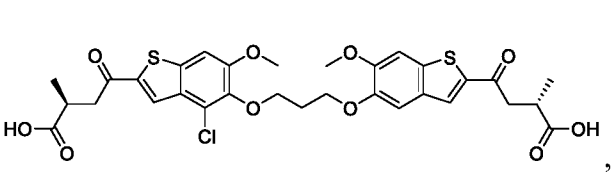
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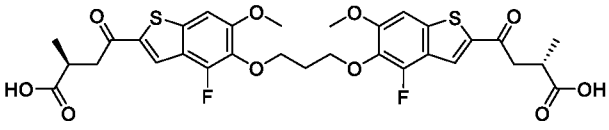
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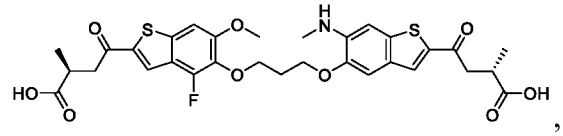
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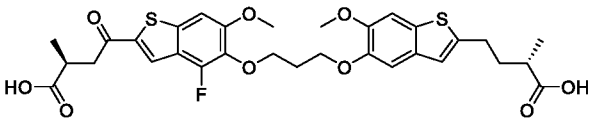
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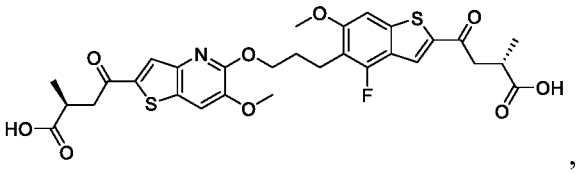
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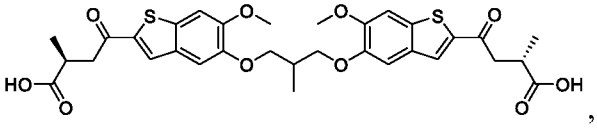
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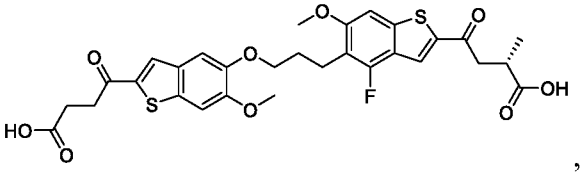
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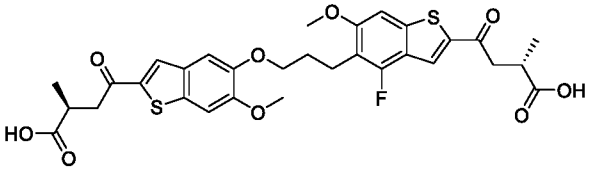
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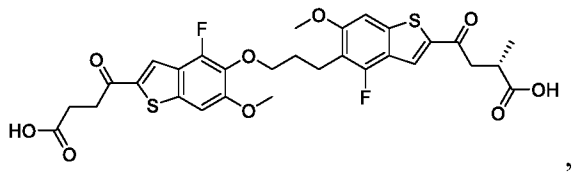
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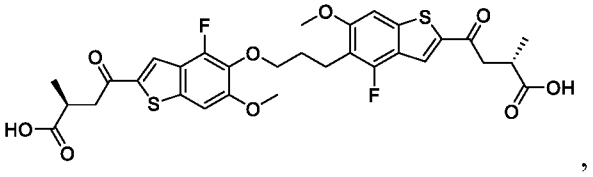
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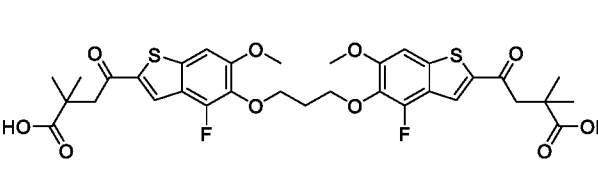
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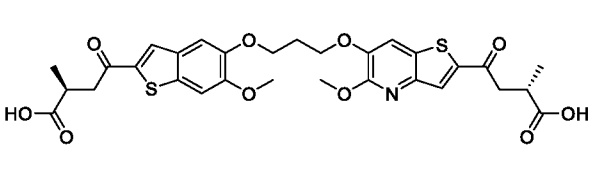
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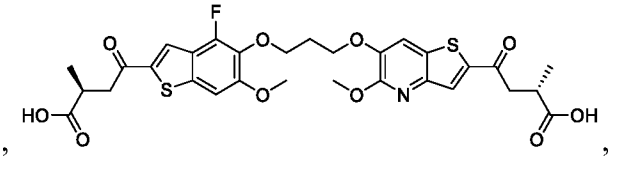
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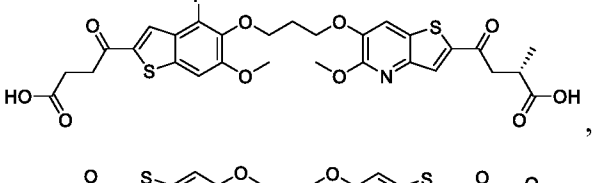
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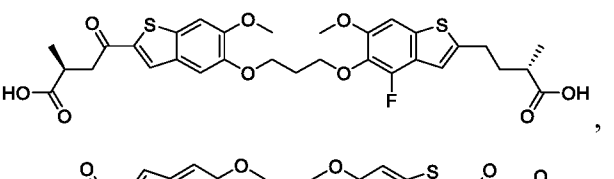
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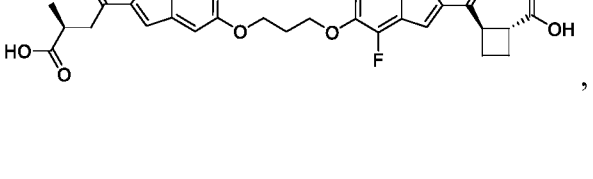
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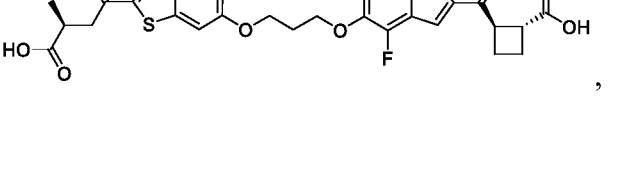
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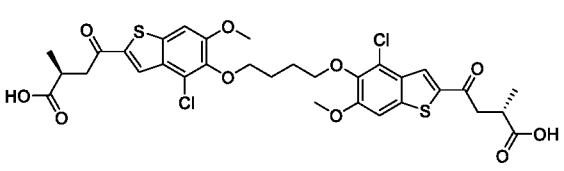
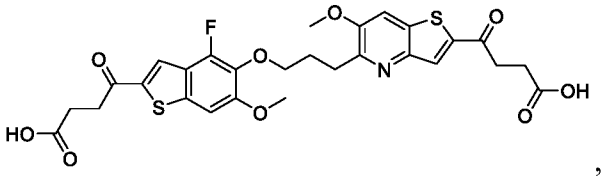
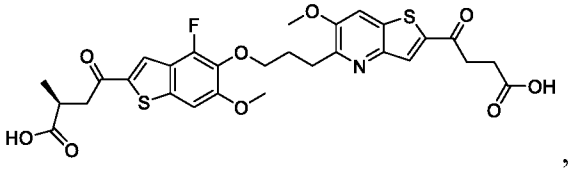
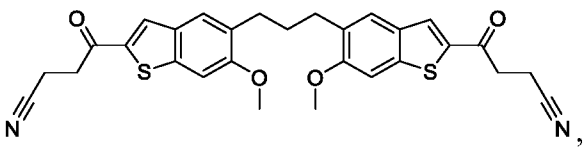
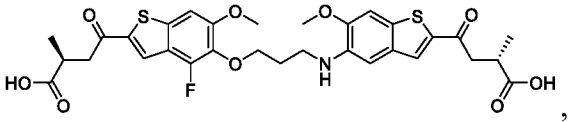
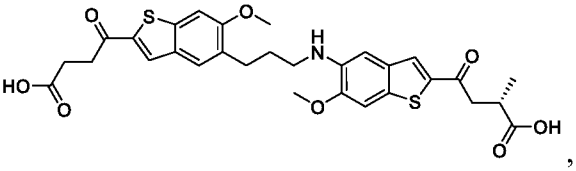
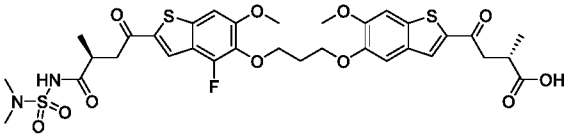
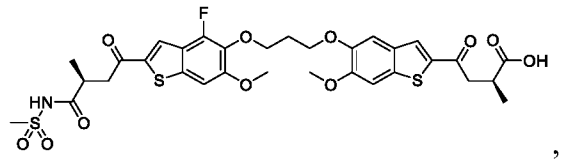
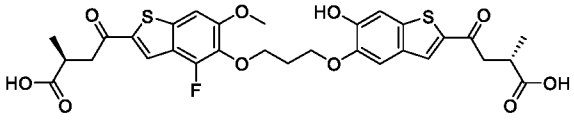
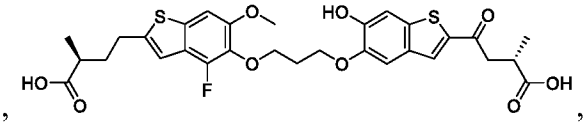
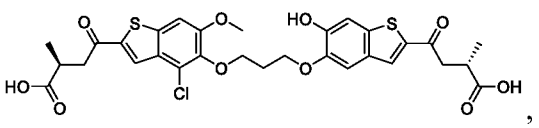
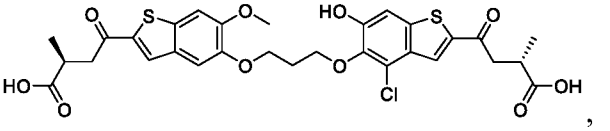
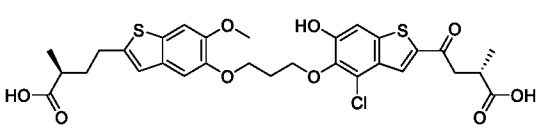
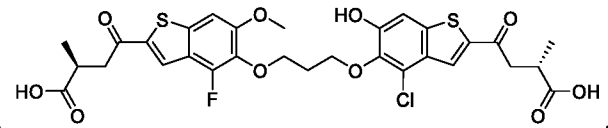
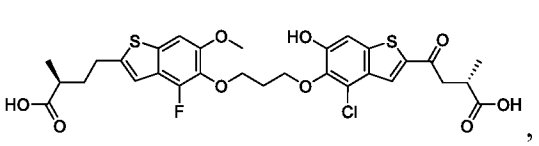
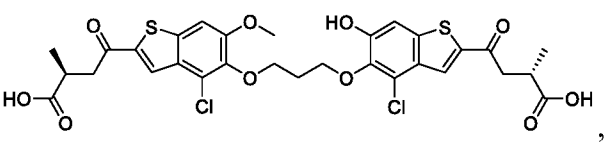
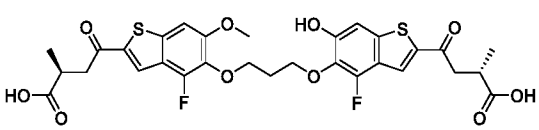
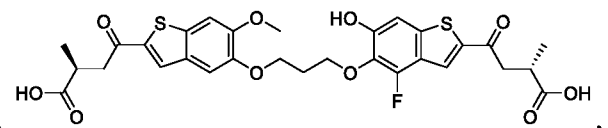
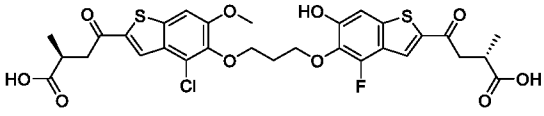
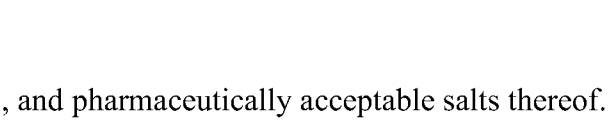
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 , and
, and pharmaceutically acceptable salts thereof.

According to another aspect, the present invention provides a pharmaceutical composition comprising a compound according to the invention, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

According to another aspect, the present invention provides a method of inducing an immune response in a subject, said method comprising:

administering a therapeutically effective amount of a compound according to the invention, or a pharmaceutically acceptable salt thereof, to the subject.

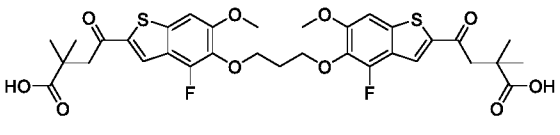
According to another aspect, the present invention provides a method of inducing an immune response in a subject, said method comprising:

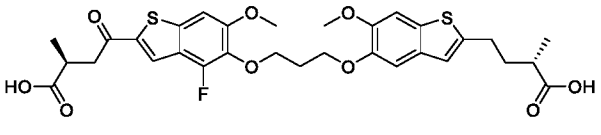
administering a therapeutically effective amount of a pharmaceutical composition according to the invention to the subject.

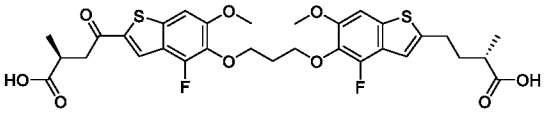
According to another aspect, the present invention provides a method of inducing STING-dependent type I interferon production in a subject, said method comprising administering a therapeutically effective amount of a compound according to the invention, or a pharmaceutically acceptable salt thereof, to the subject.

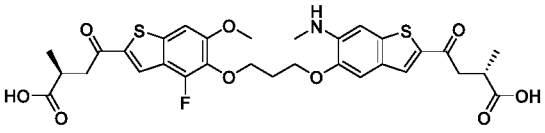
According to another aspect, the present invention provides a method of inducing STING-dependent type I interferon production in a subject, said method comprising administering a therapeutically effective amount of a pharmaceutical composition according to the invention to the subject.

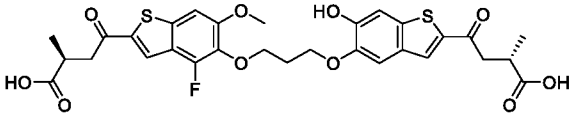
According to another aspect, the present invention provides a compound according to the invention, or a pharmaceutically acceptable salt thereof, for use in therapy.

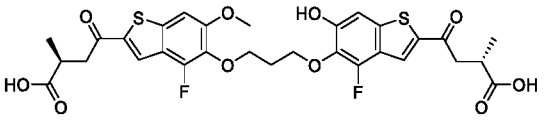
According to another aspect, the present invention provides a compound selected from the group consisting of  and pharmaceutically acceptable salts thereof.

According to another aspect, the present invention provides a compound selected from the group consisting of  and pharmaceutically acceptable salts thereof.

According to another aspect, the present invention provides a compound selected from the group consisting of  and pharmaceutically acceptable salts thereof.

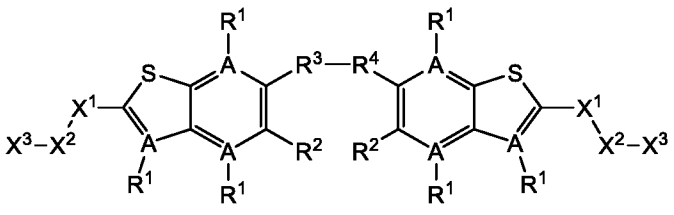
According to another aspect, the present invention provides a compound selected from the group consisting of  and pharmaceutically acceptable salts thereof.

According to another aspect, the present invention provides a compound selected from the group consisting of  and pharmaceutically acceptable salts thereof.

According to another aspect, the present invention provides a compound selected from the group consisting of  and pharmaceutically acceptable salts thereof.

For the avoidance of doubt, in this specification, the terms 'comprises', 'comprising', 'includes', 'including', or similar terms are intended to mean a non-exclusive inclusion, such that a method, system, composition or apparatus that comprises a list of elements does not include those elements solely, but may well include other elements not listed.

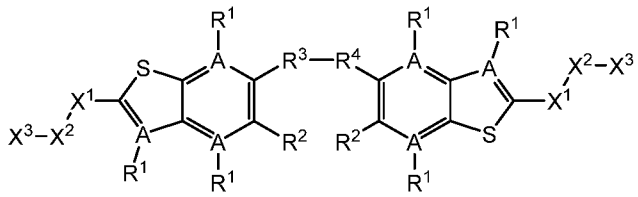
The present disclosure also relates to novel compounds of general formula (II). In particular, the present disclosure relates to compounds having the general structural formula (II):



(II)

or pharmaceutically acceptable salts thereof, as described herein. Uses of compounds of general formula (II) and processes for making compounds of general formula (II) are also disclosed.

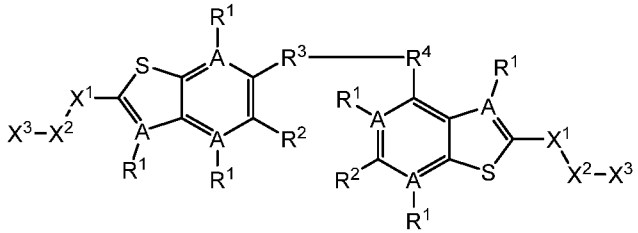
The present disclosure also relates to novel compounds of general formula (III). In particular, the present disclosure relates to compounds having the general structural formula (III):



(III)

or pharmaceutically acceptable salts thereof, as described herein. Uses of compounds of general formula (III) and processes for making compounds of general formula (III) are also disclosed.

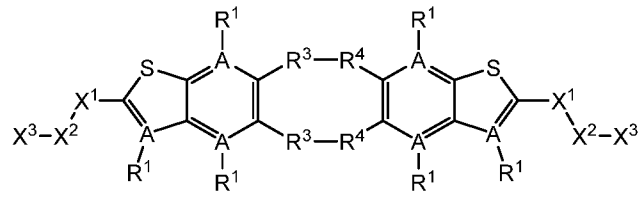
The present disclosure also relates to novel compounds of general formula (IV). In particular, the present disclosure relates to compounds having the general structural formula (IV):



(IV)

or pharmaceutically acceptable salts thereof, as described herein. Uses of compounds of general formula (IV) and processes for making compounds of general formula (IV) are also disclosed.

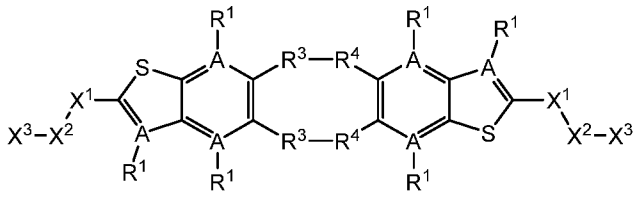
The present disclosure also relates to novel compounds of general formula (V). In particular, the present disclosure relates to compounds having the general structural formula (V):



(V)

or pharmaceutically acceptable salts thereof, as described herein. Uses of compounds of general formula (V) and processes for making compounds of general formula (V) are also disclosed.

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



(VI)

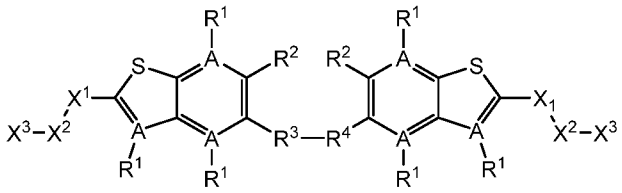
or pharmaceutically acceptable salts thereof, as described herein. Uses of compounds of general formula (VI) and processes for making compounds of general formula (VI) are also disclosed.

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

DETAILED DESCRIPTION OF THE INVENTION

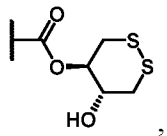
The present disclosure includes compounds of general formula (I), compounds of general formula (II), compounds of general formula (III), compounds of general formula (IV), compounds of general formula (V), compounds of general formula (VI), and pharmaceutically acceptable salts thereof. These compounds 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.

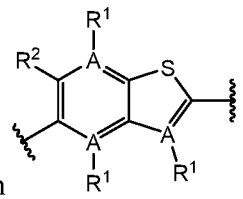
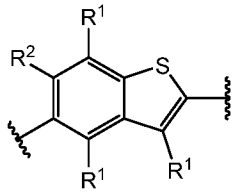
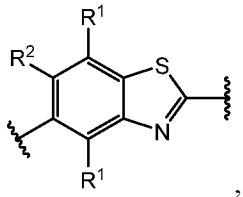
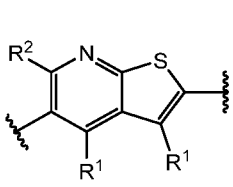
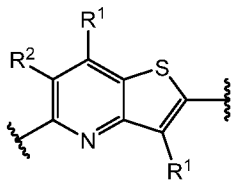
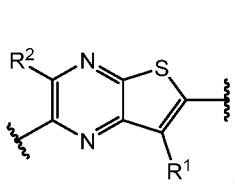
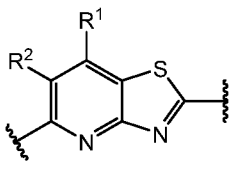
A first embodiment relates to compounds of general formula (I):

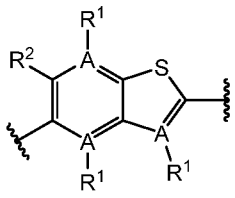
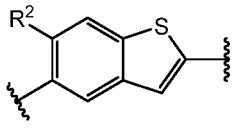
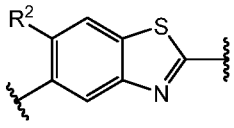
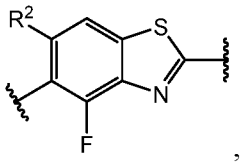
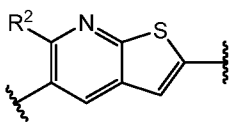
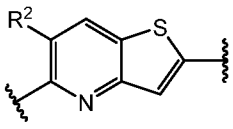
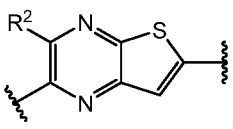
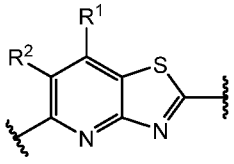


(I)

or a pharmaceutically acceptable salt thereof, wherein each A-R^1 is independently selected from the group consisting of C-R^1 and N; each R^1 is independently selected from the group consisting of H, halogen, OR^6, $N(R^6)_2$, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkyl substituted by OR^6, C_1-C_6 alkyl substituted by $N(R^6)_2$, $COOR^6$, and $C(O)N(R^6)_2$; each R^2 is independently selected from the group consisting of H, halogen, CN, OR^6, $N(R^6)_2$, $COOR^6$, $C(O)N(R^6)_2$, SO_2R^6, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkyl substituted by OR^6, C_2-C_6 alkenyl, C_2-C_6 haloalkenyl, C_2-C_6 alkenyl substituted by OR^6, C_2-C_6 alkynyl, C_2-C_6 haloalkynyl, C_2-C_6 alkynyl substituted by OR^6, C_3-C_6 cycloalkyl, and a 3- to 6-membered heterocyclic ring including 1 to 2 ring members selected from the group consisting of O, S, and $N(R^6)$; R^3 and R^4 are independently selected from the group consisting of O-(C_1-C_4 alkylene or haloalkylene), C_1-C_5 alkylene or haloalkylene, and $N(R_6)$-(C_1-C_4 alkylene or haloalkylene); optionally R^4 may be taken together with an adjacent

C-R^1 and the atom to which they are attached to form fused ring E, which is selected from phenyl or a 5- or 6-membered heterocyclic ring including 1 to 2 ring members selected from the group consisting of O, S, N, and N(R^6) wherein the bond to R^3 from said ring E is from an atom on said ring E with an open valence for substitution and wherein said phenyl or heterocyclic ring is optionally substituted with one or more members of the group consisting of halogen, 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_6 alkyl, and C_1-C_6 haloalkyl; each X^1 is independently selected from the group consisting of C=O, -CH_2-, -CHF-, and -CF_2-; each X^2 is independently selected from $(C(R^8)_2)_{(1-3)}$, wherein each R^8 is independently selected from the group consisting of H, halogen, C_1-C_6 alkyl, CN, OR^6, N(R^6)$_2$, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, C_1-C_6 alkyl substituted by OR^6, and C_1-C_6 alkyl substituted by N(R^6)$_2$; optionally 2 R^8 on different carbon atoms may be taken together, along with the atoms to which they are attached, to form a 3- to 6-membered fused ring; and optionally 2 R^8 on a single carbon atom may be taken together, along with the atom to which they are attached, to form a 3- to 6-membered spirocycle; each X^3 is independently selected from the group consisting of $COOR^6$, $C(O)SR^6$, $C(S)OR^6$,  , SO_2R^6, $C(O)N(R^9)_2$, and CN; and each R^9 is independently selected from the group consisting of H, $COOR^6$, and SO_2R^6.

In a first aspect of the first embodiment, each A-R^1 is independently selected from the group consisting of C-R^1 and N. In particular instances of this aspect, each  is independently selected from the group consisting of  ,  ,  ,  ,  , and  . In more

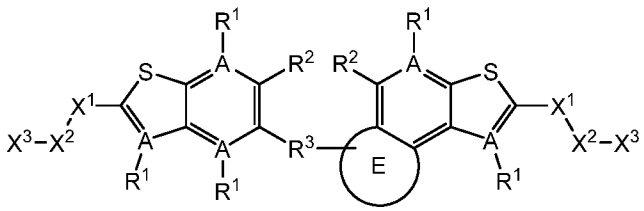
particular instances of this aspect, each  is independently selected from the group consisting of  ,  ,  ,  ,  ,  , and  . In this aspect, all other groups are as provided in the general formula (I) of the first embodiment above.

In a second aspect of the first embodiment, each R^1 is independently selected from the group consisting of H, halogen, OR^6, $N(R^6)_2$, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkyl substituted by OR^6, C_1-C_6 alkyl substituted by $N(R^6)_2$, $COOR^6$, and $C(O)N(R^6)_2$. In instances of this aspect, each R^1 is independently selected from the group consisting of H, halogen, C_1-C_3 alkyl, and C_1-C_3 haloalkyl. In particular instances of this aspect, each R^1 is independently selected from the group consisting of H and halogen. In more particular instances of this aspect, each R^1 is independently selected from the group consisting of H and F. In this aspect, all other groups are as provided in the general formula (I) of the first embodiment above or in the first aspect above.

In a third aspect of the first embodiment, each R^2 is independently selected from the group consisting of H, halogen, CN, OR^6, $N(R^6)_2$, $COOR^6$, $C(O)N(R^6)_2$, SO_2R^6, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkyl substituted by OR^6, C_2-C_6 alkenyl, C_2-C_6 haloalkenyl, C_2-C_6 alkenyl substituted by OR^6, C_2-C_6 alkynyl, C_2-C_6 haloalkynyl, C_2-C_6 alkynyl substituted by OR^6, C_3-C_6 cycloalkyl, and a 3- to 6-membered heterocyclic ring including 1 to 2 ring members selected from the group consisting of O, S, and $N(R^6)$. In instances of this aspect, each R^2 is independently selected from the group consisting of H, halogen, C_1-C_3 alkyl, C_1-C_3 haloalkyl, OC_1-C_3 alkyl, C_2-C_3 alkenyl, and $N(R^6)_2$. In particular instances of this aspect, each R^2 independently is selected from the group consisting of H, Br, Cl, CH_3, CH_2CH_3, $CH{=}CH_2$, OCH_3, $OCFH_2$, OCF_2H, OCF_3, and $N(R^6)_2$. In more particular instances of this aspect, each R^2 independently is selected from the group consisting of H, CH_3, OCH_3, and OCF_2H. In this

aspect, all other groups are as provided in the general formula (I) of the first embodiment or in the first or second aspects described above.

In a fourth aspect of the first embodiment, R^3 and R^4 are independently selected from the group consisting of O-(C_1-C_4 alkylene or haloalkylene), C_1-C_5 alkylene or haloalkylene, and $N(R_6)$-(C_1-C_4 alkylene or haloalkylene); optionally R^4 may be taken together with an adjacent C-R^1 and the atom to which they are attached to form fused ring E, which is selected from phenyl or a 5- or 6-membered heterocyclic ring including 1 to 2 ring members selected from the group consisting of O, S, N, and $N(R^6)$ wherein the bond to R^3 from said ring E is from an atom on said ring E with an open valence for substitution and wherein said phenyl or heterocyclic ring is optionally substituted with one or more members of the group consisting of halogen, C_1-C_3 alkyl, and C_1-C_3 haloalkyl. In instances of this fourth aspect, R^3-R^4 is selected from the group consisting of $-(CH_2)_{2\text{-}8}-$, $-O(CH_2)_{1\text{-}7}-$, $-O(CH_2)_{1\text{-}6}O-$, $-NH(CH_2)_{1\text{-}7}-$, and $-NH(CH_2)_{1\text{-}6}O-$. In particular instances of this fourth aspect, R^3-R^4 is selected from the group consisting of $-(CH_2)_2-$, $-(CH_2)_3-$, $-(CH_2)_4-$, $-O(CH_2)_2-$, $-O(CH_2)_3-$, $-O(CH_2)_4-$, $-O(CH_2)_2O-$, $-O(CH_2)_3O-$, $-OCH_2CH(CH_3)CH_2O-$, $-O(CH_2)_4O-$, $-O(CH_2)_5O-$, $-NH(CH_2)_2-$, $-NH(CH_2)_3-$, and $-NH(CH_2)_3O-$. In specific instances of this fourth aspect, R^4 may be taken together with an adjacent C-R^1 and the atom to which they are attached to form fused ring E, which is selected from phenyl or a 5- or 6-membered heterocyclic ring including 1 to 2 ring members selected from the group consisting of O, S, N, and $N(R^6)$ wherein the bond to R^3 from said ring E is from an atom on said ring E with an open valence for substitution and wherein said phenyl or heterocyclic ring is optionally substituted with one or more members of the group consisting of halogen, C_1-C_3 alkyl, and C_1-C_3 haloalkyl. In this instance, the structure of general formula (I) is formula (Ia):



(Ia)

wherein all groups are as provided in the general formula (I). In this aspect, all other groups are as provided in the general formula (I) of the first embodiment or in the first through third aspects described above.

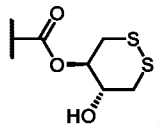
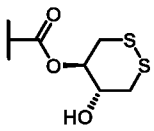
In a fifth aspect of the first embodiment, each R^6 is independently selected from the group consisting of H, C_1-C_6 alkyl, and C_1-C_6 haloalkyl. In instances of this aspect, each R^6 is

independently selected from the group consisting of H, C_1-C_3 alkyl, and C_1-C_3 haloalkyl. In particular instances of this aspect, each R^6 is independently selected from the group consisting of H, CH_3, and CHF_2. In this aspect, all other groups are as provided in the general formula (I) of the first embodiment or in the first through fourth aspects described above.

In a sixth aspect of the first embodiment, each X^1 is independently selected from the group consisting of C=O, -CH_2-, -CHF-, and -CF_2-. In instances of this aspect, X^1 is selected from the group consisting of C=O and -CH_2-. In particular instances of this aspect, X^1 is C=O. In this embodiment, all other groups are as provided in the general formula (I) of the first embodiment or in the first through fifth aspects described above.

In a seventh aspect of the first embodiment, each X^2 is independently selected from $(C(R^8)_2)_{(1-3)}$, wherein each R^8 is independently selected from the group consisting of H, halogen, C_1-C_6 alkyl, CN, OR^6, $N(R^6)_2$, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, C_1-C_6 alkyl substituted by OR^6, and C_1-C_6 alkyl substituted by $N(R^6)_2$; optionally 2 R^8 on different carbon atoms may be taken together, along with the atoms to which they are attached, to form a 3- to 6-membered fused ring; and optionally 2 R^8 on a single carbon atom may be taken together, along with the atom to which they are attached, to form a 3- to 6-membered spirocycle. In a first instance of this aspect, each X^2 is CH_2CHR^8, where R^8 is selected from the group consisting of H, C_1-C_3 alkyl, C_1-C_3 alkyl substituted by OH, C_1-C_3 alkyl substituted by OC_1-C_3 alkyl, and C_3-C_6 cycloalkyl. In particular occurrences of this first instance, each X^2 is CH_2CHR^8, wherein R^8 is selected from the group consisting of H, CH_3, CH_2OH, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, CH_2OCH_3, and cyclopropyl. In a second instance of this aspect, each X^2 is CHR^8CHR^8, where each R^8 is independently selected from the group consisting of H, C_1-C_3 alkyl, C_1-C_3 alkyl substituted by OH, C_1-C_3 alkyl substituted by OC_1-C_3 alkyl, and C_3-C_6 cycloalkyl, and optionally the 2 R^8 on different carbon atoms are taken together, along with the atoms to which they are attached, to form a 3- to 6-membered fused ring. In particular occurrences of this second instance, each X^2 is CHR^8CHR^8, where each R^8 is independently selected from the group consisting of H and C_1-C_3 alkyl, and optionally the 2 R^8 on different carbon atoms are taken together, along with the atoms to which they are attached, to form a 3- to 6-membered fused ring. In a third instance of this aspect, each X^2 is $CH_2C(R^8)_2$, where each R^8 is independently selected from the group consisting of H, C_1-C_3 alkyl, C_1-C_3 alkyl substituted by OH, C_1-C_3 alkyl substituted by OC_1-C_3 alkyl, and C_3-C_6 cycloalkyl, and optionally the 2 R^8 on a single carbon atom are taken together, along with the atoms to which they are attached, to form a 3- to 6-

membered spirocycle. In particular occurrences of this third instance, each X^2 is $CH_2C(R^8)_2$, where each R^8 is independently selected from the group consisting of H and C_1-C_3 alkyl, and optionally the 2 R^8 on a single carbon atom are taken together, along with the atoms to which they are attached, to form a 3- to 6-membered spirocycle. In this aspect, all other groups are as provided in the general formula (I) of the first embodiment or in the first through sixth aspects described above.

In an eighth aspect of the first embodiment, each X^3 is independently selected from the group consisting of $COOR^6$, $C(O)SR^6$, $C(S)OR^6$,  , SO_2R^6, $C(O)N(R^9)_2$, and CN. In instances of this aspect, each X^3 is independently selected from the group consisting of $COOR^6$,  , SO_2R^6, $C(O)N(R^9)_2$, and CN. In particular instances of this aspect, each X^3 is independently selected from the group consisting of $COOR^6$, $C(O)N(R^9)_2$, and CN. In even more particular instances of this aspect, each X^3 is independently selected from the group consisting of COOH, $COOCH_3$, $CONH_2$, and CN. In this aspect, all other groups are as provided in the general formula (I) of the first embodiment or in the first through seventh aspects described above.

In a ninth aspect of the first embodiment, each R^9 is independently selected from the group consisting of H, $COOR^6$, and SO_2R^6. In instances of this aspect, each R^9 is independently H. In this aspect, all other groups are as provided in the general formula (I) of the first embodiment or in the first through eighth aspects described above.

A tenth aspect of the first embodiment relates to a pharmaceutical composition, said pharmaceutical composition comprising (a) a compound according to general formula (I) above of the first embodiment or the first through ninth aspects described above or a pharmaceutically acceptable salt thereof; and (b) a pharmaceutically acceptable carrier.

An eleventh aspect of the first embodiment relates to methods of inducing an immune response in a patient in need of therapy, comprising administering a therapeutically effective amount of a compound according to general formula (I) above of the first embodiment or the first through ninth aspects described above described above or a pharmaceutically acceptable salt thereof to the patient.

A twelfth aspect of the first embodiment relates to methods of inducing an immune response in a patient in need of therapy, comprising administering a therapeutically effective amount of a composition according to the tenth aspect described above to the patient.

A thirteenth aspect of the first embodiment relates to methods of inducing a STING-dependent type I interferon production in a patient in need of therapy, comprising administering a therapeutically effective amount of a compound according to general formula (I) of the first embodiment above or the first through ninth aspects described above or a pharmaceutically acceptable salt thereof to the patient.

A fourteenth aspect of the first embodiment relates to methods of inducing STING-dependent type I interferon production in a patient in need of therapy, comprising administering a therapeutically effective amount of a composition according to the tenth aspect described above to the patient.

A fifteenth aspect of the first embodiment relates to methods of inducing STING-dependent cytokine production in a patient in need of therapy, comprising administering a therapeutically effective amount of a compound according to general formula (I) of the first embodiment above or the first through ninth aspects described above or a pharmaceutically acceptable salt thereof to the patient.

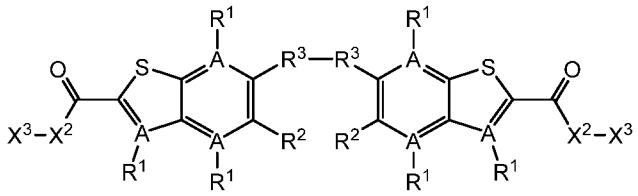
A sixteenth aspect of the first embodiment relates to methods of inducing a STING-dependent cytokine production in a patient in need of therapy, comprising administering a therapeutically effective amount of a composition according to the tenth aspect described above to the patient.

A seventeenth aspect of the first embodiment relates to methods of treating a cell proliferation disorder in a patient in need of therapy, comprising administering a therapeutically effective amount of a compound of general formula (I), or a pharmaceutically acceptable salt thereof to the patient. In instances of this seventeenth aspect of the first embodiment, the cell proliferation disorder is cancer.

An eighteenth aspect of the first embodiment relates to methods of treating a cell proliferation disorder in a patient in need of therapy, said method comprising administering a therapeutically effective amount of a composition according to the eleventh aspect described above to the patient. In instances of this eighteenth aspect of the first embodiment, the cell proliferation disorder is cancer.

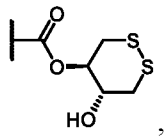
In each aspect of the first embodiment described herein, variables R^1, R^2, R^3, R^4, R^6, R^8, R^9, A, X^1, X^2, and X^3 of general formula (I) of the first embodiment, and the various aspects and instances thereof, are each independently selected from each other, with the proviso that at least one of R^1, R^2, R^3, R^4, R^6, R^8, and R^9 is not H.

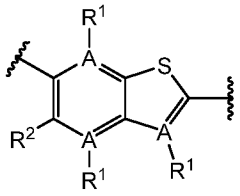
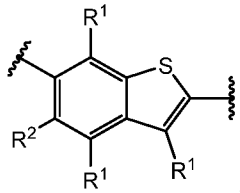
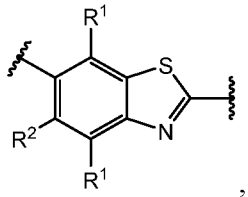
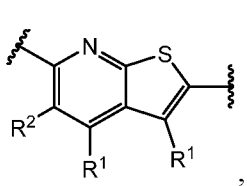
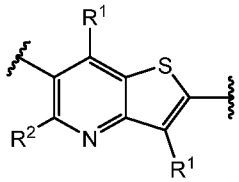
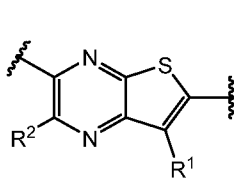
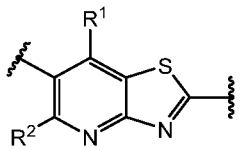
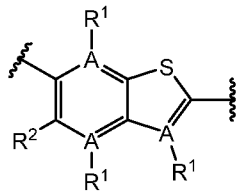
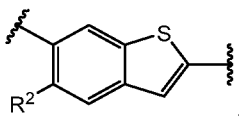
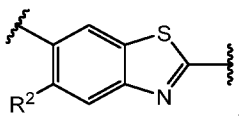
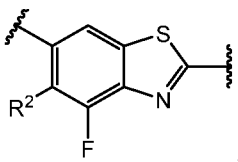
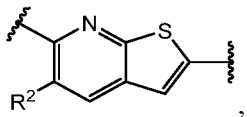
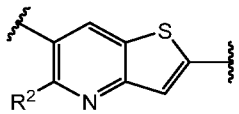
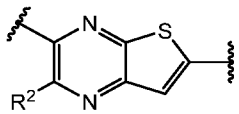
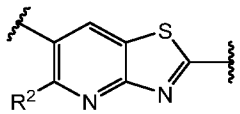
A second embodiment relates to compounds of general formula (II):



(II)

or a pharmaceutically acceptable salt thereof, wherein each A-R^1 is independently selected from the group consisting of C-R^1 and N; each R^1 is independently selected from the group consisting of H, halogen, OR^6, $N(R^6)_2$, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkyl substituted by OR^6, C_1-C_6 alkyl substituted by $N(R^6)_2$, $COOR^6$, and $C(O)N(R^6)_2$; each R^2 is independently selected from the group consisting of H, halogen, CN, OR^6, $N(R^6)_2$, $COOR^6$, $C(O)N(R^6)_2$, SO_2R^6, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkyl substituted by OR^6, C_2-C_6 alkenyl, C_2-C_6 haloalkenyl, C_2-C_6 alkenyl substituted by OR^6, C_2-C_6 alkynyl, C_2-C_6 haloalkynyl, C_2-C_6 alkynyl substituted by OR^6, C_3-C_6 cycloalkyl, and a 3- to 6-membered heterocyclic ring including 1 to 2 ring members selected from the group consisting of O, S, and $N(R^6)$; R^3 and R^4 are independently selected from the group consisting of O-(C_1-C_4 alkylene or haloalkylene), C_1-C_5 alkylene or haloalkylene, and $N(R_6)$-(C_1-C_4 alkylene or haloalkylene); optionally R^4 may be taken together with an adjacent C-R^1 and the atom to which they are attached to form fused ring E, which is selected from phenyl or a 5- or 6-membered heterocyclic ring including 1 to 2 ring members selected from the group consisting of O, S, N, and $N(R^6)$ wherein the bond to R^3 from said ring E is from an atom on said ring E with an open valence for substitution and wherein said phenyl or heterocyclic ring is optionally substituted with one or more members of the group consisting of halogen, 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_6 alkyl, and C_1-C_6 haloalkyl; each X^1 is independently selected from the group consisting of C=O, -CH_2-, -CHF-, and -CF_2-; each X^2 is independently selected from $(C(R^8)_2)_{(1\text{-}3)}$, wherein each R^8 is independently selected from the group consisting of H, halogen, C_1-C_6 alkyl, CN, OR^6, $N(R^6)_2$, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, C_1-C_6 alkyl substituted by OR^6, and C_1-C_6 alkyl substituted by $N(R^6)_2$; optionally 2 R^8 on different carbon atoms may be taken together, along with the atoms to which they are attached, to form a 3- to 6-membered fused ring; and optionally

2 R^8 on a single carbon atom may be taken together, along with the atom to which they are attached, to form a 3- to 6-membered spirocycle; each X^3 is independently selected from the group consisting of $COOR^6$, $C(O)SR^6$, $C(S)OR^6$,  , SO_2R^6, $C(O)N(R^9)_2$, and CN; and each R^9 is independently selected from the group consisting of H, $COOR^6$, and SO_2R^6.

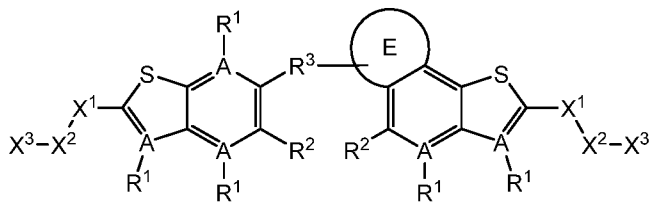
In a first aspect of the second embodiment, each A-R^1 is independently selected from the group consisting of C-R^1 and N. In particular instances of this aspect, each  is independently selected from the group consisting of  ,  ,  ,  ,  , and  . In more particular instances of this aspect, each  is independently selected from the group consisting of  ,  ,  ,  ,  ,  , and  . In this aspect, all other groups are as provided in the general formula (II) of the second embodiment above.

In a second aspect of the second embodiment, each R^1 is independently selected from the group consisting of H, halogen, OR^6, $N(R^6)_2$, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkyl substituted by OR^6, C_1-C_6 alkyl substituted by $N(R^6)_2$, $COOR^6$, and $C(O)N(R^6)_2$. In instances of this aspect, each R^1 is independently selected from the group consisting of H, halogen, C_1-C_3 alkyl, and C_1-C_3 haloalkyl. In particular instances of this aspect, each R^1 is independently selected from the group consisting of H and halogen. In more particular instances of this aspect, each R^1 is independently selected from the group consisting of H and F. In this aspect, all other groups are as provided in the general formula (II) of the second embodiment above or in the first aspect above.

In a third aspect of the second embodiment, each R^2 is independently selected from the group consisting of H, halogen, CN, OR^6, $N(R^6)_2$, $COOR^6$, $C(O)N(R^6)_2$, SO_2R^6, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkyl substituted by OR^6, C_2-C_6 alkenyl, C_2-C_6 haloalkenyl, C_2-C_6 alkenyl substituted by OR^6, C_2-C_6 alkynyl, C_2-C_6 haloalkynyl, C_2-C_6 alkynyl substituted by OR^6, C_3-C_6 cycloalkyl, and a 3- to 6-membered heterocyclic ring including 1 to 2 ring members selected from the group consisting of O, S, and $N(R^6)$. In instances of this aspect, each R^2 is independently selected from the group consisting of H, halogen, C_1-C_3 alkyl, C_1-C_3 haloalkyl, OC_1-C_3 alkyl, C_2-C_3 alkenyl, and $N(R^6)_2$. In particular instances of this aspect, each R^2 independently is selected from the group consisting of H, Br, Cl, CH_3, CH_2CH_3, $CH{=}CH_2$, OCH_3, $OCFH_2$, OCF_2H, OCF_3, and $N(R^6)_2$. In more particular instances of this aspect, each R^2 independently is selected from the group consisting of H, CH_3, OCH_3, and OCF_2H. In this aspect, all other groups are as provided in the general formula (II) of the second embodiment or in the first or second aspects described above.

In a fourth aspect of the second embodiment, R^3 and R^4 are independently selected from the group consisting of O-(C_1-C_4 alkylene or haloalkylene), C_1-C_5 alkylene or haloalkylene, and $N(R_6)$-(C_1-C_4 alkylene or haloalkylene); optionally R^4 may be taken together with an adjacent C-R^1 and the atom to which they are attached to form fused ring E, which is selected from phenyl or a 5- or 6-membered heterocyclic ring including 1 to 2 ring members selected from the group consisting of O, S, N, and $N(R^6)$ wherein the bond to R^3 from said ring E is from an atom on said ring E with an open valence for substitution and wherein said phenyl or heterocyclic ring is optionally substituted with one or more members of the group consisting of halogen, C_1-C_3 alkyl, and C_1-C_3 haloalkyl. In instances of this fourth aspect, R^3-R^4 is selected from the group consisting of -$(CH_2)_{2\text{-}8}$-, -$O(CH_2)_{1\text{-}7}$-, -$O(CH_2)_{1\text{-}6}O$-, -$NH(CH_2)_{1\text{-}7}$-, and

-$NH(CH_2)_{1-6}O$-. In particular instances of this fourth aspect, R^3-R^4 is selected from the group consisting of -$(CH_2)_2$-, -$(CH_2)_3$-, -$(CH_2)_4$-, -$O(CH_2)_2$-, -$O(CH_2)_3$-, -$O(CH_2)_4$-, -$O(CH_2)_2O$-, -$O(CH_2)_3O$-, -$OCH_2CH(CH_3)CH_2O$-, -$O(CH_2)_4O$-, -$O(CH_2)_5O$-, -$NH(CH_2)_2$-, -$NH(CH_2)_3$-, and -$NH(CH_2)_3O$-. In specific instances of this fourth aspect, R^4 may be taken together with an adjacent C-R^1 and the atom to which they are attached to form fused ring E, which is selected from phenyl or a 5- or 6-membered heterocyclic ring including 1 to 2 ring members selected from the group consisting of O, S, N, and N(R^6) wherein the bond to R^3 from said ring E is from an atom on said ring E with an open valence for substitution and wherein said phenyl or heterocyclic ring is optionally substituted with one or more members of the group consisting of halogen, C_1-C_3 alkyl, and C_1-C_3 haloalkyl. In this instance, the structure of general formula (II) is formula (IIa):



(IIa)

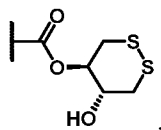
wherein all groups are as provided in the general formula (II). In this aspect, all other groups are as provided in the general formula (II) of the second embodiment or in the first through third aspects described above.

In a fifth aspect of the second embodiment, each R^6 is independently selected from the group consisting of H, C_1-C_6 alkyl, and C_1-C_6 haloalkyl. In instances of this aspect, each R^6 is independently selected from the group consisting of H, C_1-C_3 alkyl, and C_1-C_3 haloalkyl. In particular instances of this aspect, each R^6 is independently selected from the group consisting of H, CH_3, and CHF_2. In this aspect, all other groups are as provided in the general formula (II) of the second embodiment or in the first through fourth aspects described above.

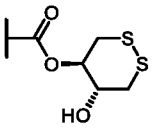
In a sixth aspect of the second embodiment, each X^1 is independently selected from the group consisting of C=O, -CH_2-, -CHF-, and -CF_2-. In instances of this aspect, X^1 is selected from the group consisting of C=O and -CH_2-. In particular instances of this aspect, X^1 is C=O. In this embodiment, all other groups are as provided in the general formula (II) of the second embodiment or in the first through fifth aspects described above

In a seventh aspect of the second embodiment, each X^2 is independently selected from $(C(R^8)_2)_{(1-3)}$, wherein each R^8 is independently selected from the group consisting of H, halogen, C_1-C_6 alkyl, CN, OR^6, $N(R^6)_2$, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, C_1-C_6 alkyl substituted by

OR^6, and C_1-C_6 alkyl substituted by $N(R^6)_2$; optionally 2 R^8 on different carbon atoms may be taken together, along with the atoms to which they are attached, to form a 3- to 6-membered fused ring; and optionally 2 R^8 on a single carbon atom may be taken together, along with the atom to which they are attached, to form a 3- to 6-membered spirocycle. In a first instance of this aspect, each X^2 is CH_2CHR^8, where R^8 is selected from the group consisting of H, C_1-C_3 alkyl, C_1-C_3 alkyl substituted by OH, C_1-C_3 alkyl substituted by OC_1-C_3 alkyl, and C_3-C_6 cycloalkyl. In particular occurrences of this first instance, each X^2 is CH_2CHR^8, wherein R^8 is selected from the group consisting of H, CH_3, CH_2OH, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, CH_2OCH_3, and cyclopropyl. In a second instance of this aspect, each X^2 is CHR^8CHR^8, where each R^8 is independently selected from the group consisting of H, C_1-C_3 alkyl, C_1-C_3 alkyl substituted by OH, C_1-C_3 alkyl substituted by OC_1-C_3 alkyl, and C_3-C_6 cycloalkyl, and optionally the 2 R^8 on different carbon atoms are taken together, along with the atoms to which they are attached, to form a 3- to 6-membered fused ring. In particular occurrences of this second instance, each X^2 is CHR^8CHR^8, where each R^8 is independently selected from the group consisting of H and C_1-C_3 alkyl, and optionally the 2 R^8 on different carbon atoms are taken together, along with the atoms to which they are attached, to form a 3- to 6-membered fused ring. In a third instance of this aspect, each X^2 is $CH_2C(R^8)_2$, where each R^8 is independently selected from the group consisting of H, C_1-C_3 alkyl, C_1-C_3 alkyl substituted by OH, C_1-C_3 alkyl substituted by OC_1-C_3 alkyl, and C_3-C_6 cycloalkyl, and optionally the 2 R^8 on a single carbon atom are taken together, along with the atoms to which they are attached, to form a 3- to 6-membered spirocycle. In particular occurrences of this third instance, each X^2 is $CH_2C(R^8)_2$, where each R^8 is independently selected from the group consisting of H and C_1-C_3 alkyl, and optionally the 2 R^8 on a single carbon atom are taken together, along with the atoms to which they are attached, to form a 3- to 6-membered spirocycle. In this aspect, all other groups are as provided in the general formula (II) of the second embodiment or in the first through sixth aspects described above.

In an eighth aspect of the second embodiment, each X^3 is independently selected from the group consisting of $COOR^6$, $C(O)SR^6$, $C(S)OR^6$, 

, SO_2R^6, $C(O)N(R^9)_2$, and CN. In instances of this aspect, each X^3 is independently selected from the group consisting of $COOR^6$,



, SO_2R^6, $C(O)N(R^9)_2$, and CN. In particular instances of this aspect, each X^3 is independently selected from the group consisting of $COOR^6$, $C(O)N(R^9)_2$, and CN. In even more particular instances of this aspect, each X^3 is independently selected from the group consisting of COOH, $COOCH_3$, $CONH_2$, and CN. In this aspect, all other groups are as provided in the general formula (II) of the second embodiment or in the first through seventh aspects described above.

In a ninth aspect of the second embodiment, each R^9 is independently selected from the group consisting of H, $COOR^6$, and SO_2R^6. In instances of this aspect, each R^9 is independently H. In this aspect, all other groups are as provided in the general formula (II) of the second embodiment or in the first through eighth aspects described above.

A tenth aspect of the second embodiment relates to a pharmaceutical composition, said pharmaceutical composition comprising (a) a compound according to general formula (II) above of the second embodiment or the first through ninth aspects described above or a pharmaceutically acceptable salt thereof; and (b) a pharmaceutically acceptable carrier.

An eleventh aspect of the second embodiment relates to methods of inducing an immune response in a patient in need of therapy, comprising administering a therapeutically effective amount of a compound according to general formula (II) above of the second embodiment or the first through ninth aspects described above described above or a pharmaceutically acceptable salt thereof to the patient.

A twelfth aspect of the second embodiment relates to methods of inducing an immune response in a patient in need of therapy, comprising administering a therapeutically effective amount of a composition according to the tenth aspect described above to the patient.

A thirteenth aspect of the second embodiment relates to methods of inducing a STING-dependent type I interferon production in a patient in need of therapy, comprising administering a therapeutically effective amount of a compound according to general formula (II) of the second embodiment above or the first through ninth aspects described above or a pharmaceutically acceptable salt thereof to the patient.

A fourteenth aspect of the second embodiment relates to methods of inducing STING-dependent type I interferon production in a patient in need of therapy, comprising administering

a therapeutically effective amount of a composition according to the tenth aspect described above to the patient.

A fifteenth aspect of the second embodiment relates to methods of inducing STING-dependent cytokine production in a patient in need of therapy, comprising administering a therapeutically effective amount of a compound according to general formula (II) of the second embodiment above or the first through ninth aspects described above or a pharmaceutically acceptable salt thereof to the patient.

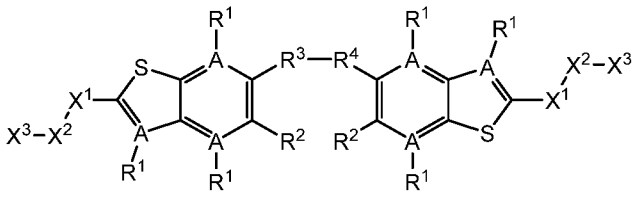
A sixteenth aspect of the second embodiment relates to methods of inducing a STING-dependent cytokine production in a patient in need of therapy, comprising administering a therapeutically effective amount of a composition according to the tenth aspect described above to the patient.

A seventeenth aspect of the second embodiment relates to methods of treating a cell proliferation disorder in a patient in need of therapy, comprising administering a therapeutically effective amount of a compound of general formula (II), or a pharmaceutically acceptable salt thereof to the patient. In instances of this seventeenth aspect of the second embodiment, the cell proliferation disorder is cancer.

An eighteenth aspect of the second embodiment relates to methods of treating a cell proliferation disorder in a patient in need of therapy, said method comprising administering a therapeutically effective amount of a composition according to the eleventh aspect described above to the patient. In instances of this eighteenth aspect of the second embodiment, the cell proliferation disorder is cancer.

In each aspect of the second embodiment described herein, variables R^1, R^2, R^3, R^4, R^6, R^8, R^9, A, X^1, X^2, and X^3 of general formula (II) of the second embodiment, and the various aspects and instances thereof, are each independently selected from each other, with the proviso that at least one of R^1, R^2, R^3, R^4, R^6, R^8, and R^9 is not H.

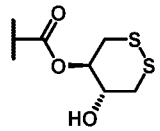
A third embodiment relates to compounds of general formula (III):



(III)

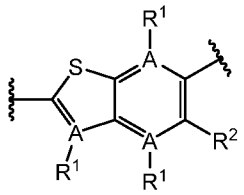
or a pharmaceutically acceptable salt thereof, wherein each A-R^1 is independently selected from the group consisting of C-R^1 and N; each R^1 is independently selected from the group consisting

of H, halogen, OR^6, $N(R^6)_2$, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkyl substituted by OR^6, C_1-C_6 alkyl substituted by $N(R^6)_2$, $COOR^6$, and $C(O)N(R^6)_2$; each R^2 is independently selected from the group consisting of H, halogen, CN, OR^6, $N(R^6)_2$, $COOR^6$, $C(O)N(R^6)_2$, SO_2R^6, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkyl substituted by OR^6, C_2-C_6 alkenyl, C_2-C_6 haloalkenyl, C_2-C_6 alkenyl substituted by OR^6, C_2-C_6 alkynyl, C_2-C_6 haloalkynyl, C_2-C_6 alkynyl substituted by OR^6, C_3-C_6 cycloalkyl, and a 3- to 6-membered heterocyclic ring including 1 to 2 ring members selected from the group consisting of O, S, and $N(R^6)$; R^3 and R^4 are independently selected from the group consisting of O-(C_1-C_4 alkylene or haloalkylene), C_1-C_5 alkylene or haloalkylene, and $N(R_6)$-(C_1-C_4 alkylene or haloalkylene); optionally R^3 may be taken together with an adjacent C-R^1 and the atom to which they are attached to form fused ring G, which is selected from phenyl or a 5- or 6-membered heterocyclic ring including 1 to 2 ring members selected from the group consisting of O, S, N, and $N(R^6)$ wherein the bond to R^3 from said ring G is from an atom on said ring G with an open valence for substitution and wherein said phenyl or heterocyclic ring is optionally substituted with one or more members of the group consisting of halogen, C_1-C_3 alkyl, and C_1-C_3 haloalkyl; optionally R^4 may be taken together with an adjacent C-R^1 and the atom to which they are attached to form fused ring E, which is selected from phenyl or a 5- or 6-membered heterocyclic ring including 1 to 2 ring members selected from the group consisting of O, S, N, and $N(R^6)$ wherein the bond to R^4 from said ring E is from an atom on said ring E with an open valence for substitution and wherein said phenyl or heterocyclic ring is optionally substituted with one or more members of the group consisting of halogen, 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_6 alkyl, and C_1-C_6 haloalkyl; each X^1 is independently selected from the group consisting of C=O, -CH_2-, -CHF-, and -CF_2-; each X^2 is independently selected from $(C(R^8)_2)_{(1\text{-}3)}$, wherein each R^8 is independently selected from the group consisting of H, halogen, C_1-C_6 alkyl, CN, OR^6, $N(R^6)_2$, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, C_1-C_6 alkyl substituted by OR^6, and C_1-C_6 alkyl substituted by $N(R^6)_2$; optionally 2 R^8 on different carbon atoms may be taken together, along with the atoms to which they are attached, to form a 3- to 6-membered fused ring; and optionally 2 R^8 on a single carbon atom may be taken together, along with the atom to which they are attached, to form a 3- to 6-membered spirocycle; each X^3 is independently selected from the group consisting

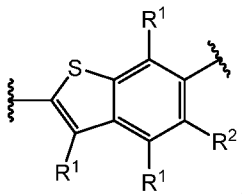


of $COOR^6$, $C(O)SR^6$, $C(S)OR^6$, , SO_2R^6, $C(O)N(R^9)_2$, and CN; and each R^9 is independently selected from the group consisting of H, $COOR^6$, and SO_2R^6.

In a first aspect of the third embodiment, each A-R^1 is independently selected from the group consisting of C-R^1 and N. In particular instances of this aspect, each



is independently selected from the group consisting of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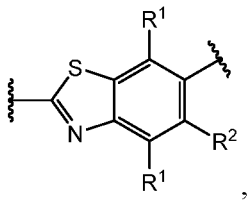
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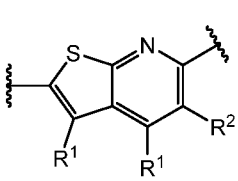
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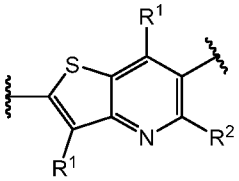
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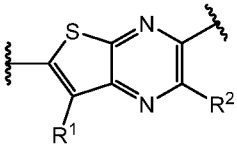
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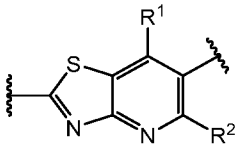
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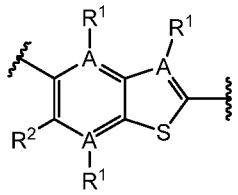
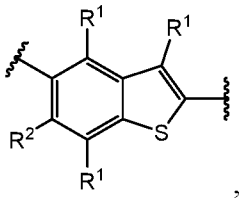

is selected from the group consisting of

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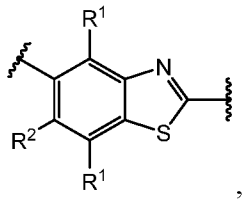
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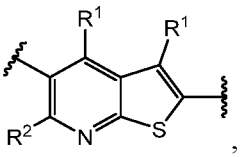
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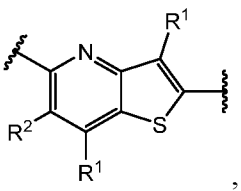
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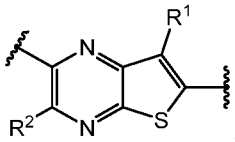
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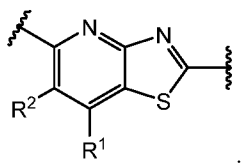
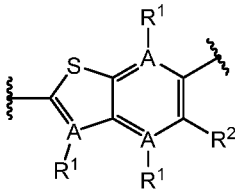

. In more particular instances of this aspect, each

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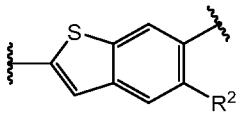
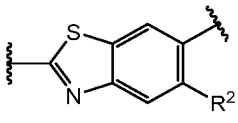
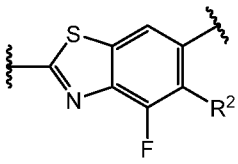
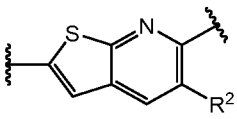
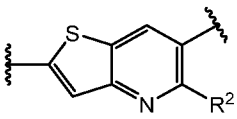
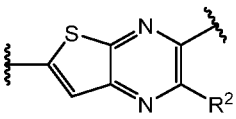
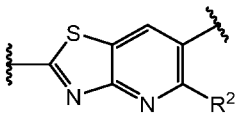
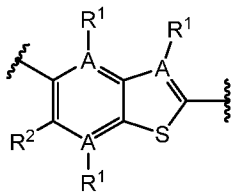
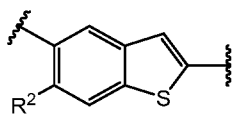
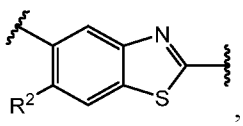
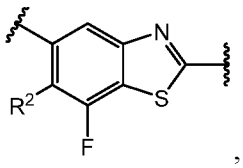
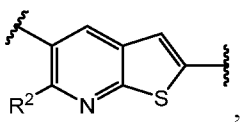
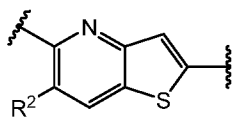
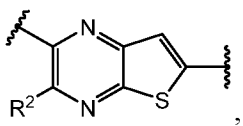
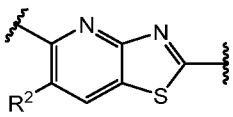
independently selected from the group consisting of  ,  ,  ,  ,  ,  , and  , and each  is selected from the group consisting of  ,  ,  ,  ,  ,  , and  . In this aspect, all other groups are as provided in the general formula (III) of the third embodiment above.

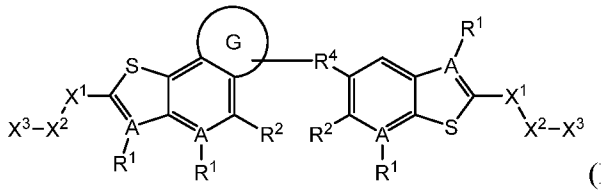
In a second aspect of the third embodiment, each R^1 is independently selected from the group consisting of H, halogen, OR^6, $N(R^6)_2$, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkyl substituted by OR^6, C_1-C_6 alkyl substituted by $N(R^6)_2$, $COOR^6$, and $C(O)N(R^6)_2$. In instances of this aspect, each R^1 is independently selected from the group consisting of H, halogen, C_1-C_3 alkyl, and C_1-C_3 haloalkyl. In particular instances of this aspect, each R^1 is independently selected from the group consisting of H and halogen. In more particular instances of this aspect, each R^1 is independently selected from the group consisting of H and F. In this aspect, all other groups are as provided in the general formula (III) of the third embodiment above or in the first aspect above.

In a third aspect of the third embodiment, each R^2 is independently selected from the group consisting of H, halogen, CN, OR^6, $N(R^6)_2$, $COOR^6$, $C(O)N(R^6)_2$, SO_2R^6, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkyl substituted by OR^6, C_2-C_6 alkenyl, C_2-C_6 haloalkenyl, C_2-C_6 alkenyl substituted by OR^6, C_2-C_6 alkynyl, C_2-C_6 haloalkynyl, C_2-C_6 alkynyl substituted by OR^6, C_3-C_6 cycloalkyl, and a 3- to 6-membered heterocyclic ring including 1 to 2 ring members selected

from the group consisting of O, S, and $N(R^6)$. In instances of this aspect, each R^2 is independently selected from the group consisting of H, halogen, C_1-C_3 alkyl, C_1-C_3 haloalkyl, OC_1-C_3 alkyl, C_2-C_3 alkenyl, and $N(R^6)_2$. In particular instances of this aspect, each R^2 independently is selected from the group consisting of H, Br, Cl, CH_3, CH_2CH_3, $CH=CH_2$, OCH_3, $OCFH_2$, OCF_2H, OCF_3, and $N(R^6)_2$. In more particular instances of this aspect, each R^2 independently is selected from the group consisting of H, CH_3, OCH_3, and OCF_2H. In this aspect, all other groups are as provided in the general formula (III) of the third embodiment or in the first or second aspects described above.

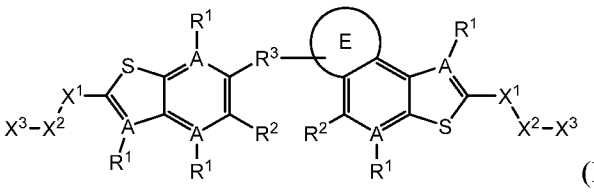
In a fourth aspect of the third embodiment, R^3 and R^4 are independently selected from the group consisting of O-(C_1-C_4 alkylene or haloalkylene), C_1-C_5 alkylene or haloalkylene, and $N(R_6)$-(C_1-C_4 alkylene or haloalkylene); optionally R^3 may be taken together with an adjacent C-R^1 and the atom to which they are attached to form fused ring G, which is selected from phenyl or a 5- or 6-membered heterocyclic ring including 1 to 2 ring members selected from the group consisting of O, S, N, and $N(R^6)$ wherein the bond to R^3 from said ring G is from an atom on said ring G with an open valence for substitution and wherein said phenyl or heterocyclic ring is optionally substituted with one or more members of the group consisting of halogen, C_1-C_3 alkyl, and C_1-C_3 haloalkyl; optionally R^4 may be taken together with an adjacent C-R^1 and the atom to which they are attached to form fused ring E, which is selected from phenyl or a 5- or 6-membered heterocyclic ring including 1 to 2 ring members selected from the group consisting of O, S, N, and $N(R^6)$ wherein the bond to R^4 from said ring E is from an atom on said ring E with an open valence for substitution and wherein said phenyl or heterocyclic ring is optionally substituted with one or more members of the group consisting of halogen, C_1-C_3 alkyl, and C_1-C_3 haloalkyl. In instances of this fourth aspect, R^3-R^4 is selected from the group consisting of -$(CH_2)_{2\text{-}8}$-, -$O(CH_2)_{1\text{-}7}$-, -$O(CH_2)_{1\text{-}6}O$-, -$NH(CH_2)_{1\text{-}7}$-, and -$NH(CH_2)_{1\text{-}6}O$-. In particular instances of this fourth aspect, R^3-R^4 is selected from the group consisting of -$(CH_2)_2$-, -$(CH_2)_3$-, -$(CH_2)_4$-, -$O(CH_2)_2$-, -$O(CH_2)_3$-, -$O(CH_2)_4$-, -$O(CH_2)_2O$-, -$O(CH_2)_3O$-, -$OCH_2CH(CH_3)CH_2O$-, -$O(CH_2)_4O$-, -$O(CH_2)_5O$-, -$NH(CH_2)_2$-, -$NH(CH_2)_3$-, and -$NH(CH_2)_3O$-. In specific instances of this fourth aspect, R^3 may be taken together with an adjacent C-R^1 and the atom to which they are attached to form fused ring G, which is selected from phenyl or a 5- or 6-membered heterocyclic ring including 1 to 2 ring members selected from the group consisting of O, S, N, and $N(R^6)$ wherein the bond to R^4 from said ring G is from an atom on said ring E with an open valence for substitution and wherein said phenyl or heterocyclic ring is

optionally substituted with one or more members of the group consisting of halogen, C_1-C_3 alkyl, and C_1-C_3 haloalkyl. In this instance, the structure of general formula (III) is formula (IIIa):



(IIIa)

wherein all groups are as provided in the general formula (III). In further specific instances of this fourth aspect, R^4 may be taken together with an adjacent C-R^1 and the atom to which they are attached to form fused ring E, which is selected from phenyl or a 5- or 6-membered heterocyclic ring including 1 to 2 ring members selected from the group consisting of O, S, N, and N(R^6) wherein the bond to R^3 from said ring E is from an atom on said ring E with an open valence for substitution and wherein said phenyl or heterocyclic ring is optionally substituted with one or more members of the group consisting of halogen, C_1-C_3 alkyl, and C_1-C_3 haloalkyl. In this instance, the structure of general formula (III) is formula (IIIb):



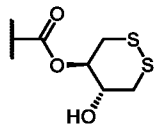
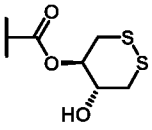
(IIIb);

wherein all groups are as provided in the general formula (III). In this aspect, all other groups are as provided in the general formula (III) of the first embodiment or in the first through third aspects described above.

In a fifth aspect of the third embodiment, each R^6 is independently selected from the group consisting of H, C_1-C_6 alkyl, and C_1-C_6 haloalkyl. In instances of this aspect, each R^6 is independently selected from the group consisting of H, C_1-C_3 alkyl, and C_1-C_3 haloalkyl. In particular instances of this aspect, each R^6 is independently selected from the group consisting of H, CH_3, and CHF_2. In this aspect, all other groups are as provided in the general formula (III) of the third embodiment or in the first through fourth aspects described above.

In a sixth aspect of the third embodiment, each X^1 is independently selected from the group consisting of C=O, -CH_2-, -CHF-, and -CF_2-. In instances of this aspect, X^1 is selected from the group consisting of C=O and -CH_2-. In particular instances of this aspect, X^1 is C=O. In this embodiment, all other groups are as provided in the general formula (III) of the third embodiment or in the first through fifth aspects described above.

In a seventh aspect of the third embodiment, each X^2 is independently selected from $(C(R^8)_2)_{(1-3)}$, wherein each R^8 is independently selected from the group consisting of H, halogen, C_1-C_6 alkyl, CN, OR^6, $N(R^6)_2$, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, C_1-C_6 alkyl substituted by OR^6, and C_1-C_6 alkyl substituted by $N(R^6)_2$; optionally 2 R^8 on different carbon atoms may be taken together, along with the atoms to which they are attached, to form a 3- to 6-membered fused ring; and optionally 2 R^8 on a single carbon atom may be taken together, along with the atom to which they are attached, to form a 3- to 6-membered spirocycle. In a first instance of this aspect, each X^2 is CH_2CHR^8, where R^8 is selected from the group consisting of H, C_1-C_3 alkyl, C_1-C_3 alkyl substituted by OH, C_1-C_3 alkyl substituted by OC_1-C_3 alkyl, and C_3-C_6 cycloalkyl. In particular occurrences of this first instance, each X^2 is CH_2CHR^8, wherein R^8 is selected from the group consisting of H, CH_3, CH_2OH, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, CH_2OCH_3, and cyclopropyl. In a second instance of this aspect, each X^2 is CHR^8CHR^8, where each R^8 is independently selected from the group consisting of H, C_1-C_3 alkyl, C_1-C_3 alkyl substituted by OH, C_1-C_3 alkyl substituted by OC_1-C_3 alkyl, and C_3-C_6 cycloalkyl, and optionally the 2 R^8 on different carbon atoms are taken together, along with the atoms to which they are attached, to form a 3- to 6-membered fused ring. In particular occurrences of this second instance, each X^2 is CHR^8CHR^8, where each R^8 is independently selected from the group consisting of H and C_1-C_3 alkyl, and optionally the 2 R^8 on different carbon atoms are taken together, along with the atoms to which they are attached, to form a 3- to 6-membered fused ring. In a third instance of this aspect, each X^2 is $CH_2C(R^8)_2$, where each R^8 is independently selected from the group consisting of H, C_1-C_3 alkyl, C_1-C_3 alkyl substituted by OH, C_1-C_3 alkyl substituted by OC_1-C_3 alkyl, and C_3-C_6 cycloalkyl, and optionally the 2 R^8 on a single carbon atom are taken together, along with the atoms to which they are attached, to form a 3- to 6-membered spirocycle. In particular occurrences of this third instance, each X^2 is $CH_2C(R^8)_2$, where each R^8 is independently selected from the group consisting of H and C_1-C_3 alkyl, and optionally the 2 R^8 on a single carbon atom are taken together, along with the atoms to which they are attached, to form a 3- to 6-membered spirocycle. In this aspect, all other groups are as provided in the general formula (III) of the third embodiment or in the first through sixth aspects described above.

In an eighth aspect of the third embodiment, each X^3 is independently selected from the group consisting of $COOR^6$, $C(O)SR^6$, $C(S)OR^6$,  , SO_2R^6, $C(O)N(R^9)_2$, and CN. In instances of this aspect, each X^3 is independently selected from the group consisting of $COOR^6$,  , SO_2R^6, $C(O)N(R^9)_2$, and CN. In particular instances of this aspect, each X^3 is independently selected from the group consisting of $COOR^6$, $C(O)N(R^9)_2$, and CN. In even more particular instances of this aspect, each X^3 is independently selected from the group consisting of COOH, $COOCH_3$, $CONH_2$, and CN. In this aspect, all other groups are as provided in the general formula (III) of the third embodiment or in the first through seventh aspects described above.

In a ninth aspect of the third embodiment, each R^9 is independently selected from the group consisting of H, $COOR^6$, and SO_2R^6. In instances of this aspect, each R^9 is independently H. In this aspect, all other groups are as provided in the general formula (III) of the third embodiment or in the first through sixth aspects described above.

A tenth aspect of the third embodiment relates to a pharmaceutical composition, said pharmaceutical composition comprising (a) a compound according to general formula (III) of the third embodiment or the first through ninth aspects described above or a pharmaceutically acceptable salt thereof; and (b) a pharmaceutically acceptable carrier.

An eleventh aspect of the third embodiment relates to methods of inducing an immune response in a patient in need of therapy, comprising administering a therapeutically effective amount of a compound according to general formula (III) of the third embodiment or the first through ninth aspects described above described above or a pharmaceutically acceptable salt thereof to the patient.

A twelfth aspect of the third embodiment relates to methods of inducing an immune response in a patient in need of therapy, comprising administering a therapeutically effective amount of a composition according to the tenth aspect described above to the patient.

A thirteenth aspect of the third embodiment relates to methods of inducing a STING-dependent type I interferon production in a patient in need of therapy, comprising administering a therapeutically effective amount of a compound according to general formula (III) of the third

embodiment above or the first through ninth aspects described above or a pharmaceutically acceptable salt thereof to the patient.

A fourteenth aspect of the third embodiment relates to methods of inducing STING-dependent type I interferon production in a patient in need of therapy, comprising administering a therapeutically effective amount of a composition according to the tenth aspect described above to the patient.

A fifteenth aspect of the third embodiment relates to methods of inducing STING-dependent cytokine production in a patient in need of therapy, comprising administering a therapeutically effective amount of a compound according to general formula (III) of the third embodiment above or the first through ninth aspects described above or a pharmaceutically acceptable salt thereof to the patient.

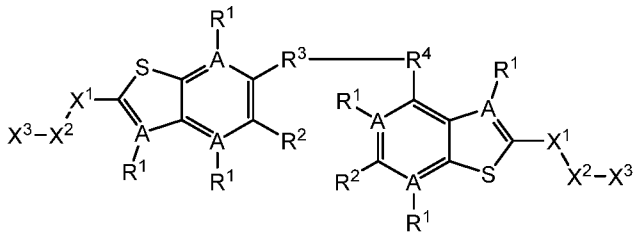
A sixteenth aspect of the third embodiment relates to methods of inducing a STING-dependent cytokine production in a patient in need of therapy, comprising administering a therapeutically effective amount of a composition according to the tenth aspect described above to the patient.

A seventeenth aspect of the third embodiment relates to methods of treating a cell proliferation disorder in a patient in need of therapy, comprising administering a therapeutically effective amount of a compound of general formula (III), or a pharmaceutically acceptable salt thereof to the patient. In instances of this seventeenth aspect of the third embodiment, the cell proliferation disorder is cancer.

An eighteenth aspect of the third embodiment relates to methods of treating a cell proliferation disorder in a patient in need of therapy, said method comprising administering a therapeutically effective amount of a composition according to the eleventh aspect described above to the patient. In instances of this eighteenth aspect of the third embodiment, the cell proliferation disorder is cancer.

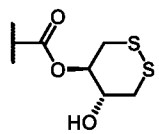
In each aspect of the third embodiment described herein, variables R^1, R^2, R^3, R^4, R^6, R^8, R^9, A, X^1, X^2, and X^3 of general formula (III) of the third embodiment, and the various aspects and instances thereof, are each independently selected from each other, with the proviso that at least one of R^1, R^2, R^3, R^4, R^6, R^8, and R^9 is not H.

A fourth embodiment relates to compounds of general formula (IV):

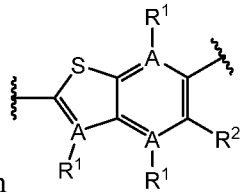
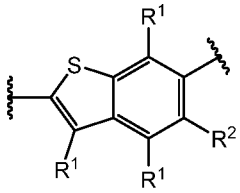
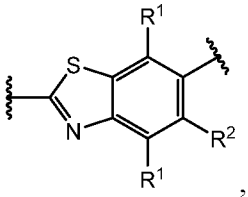
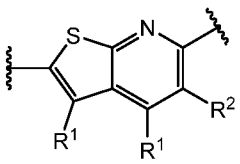
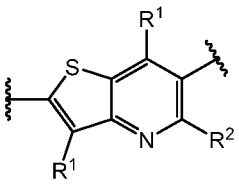
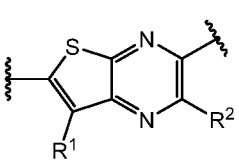
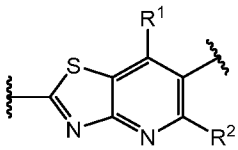
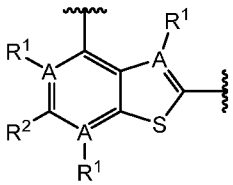
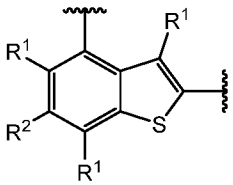
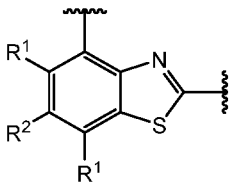
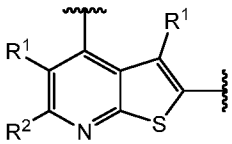
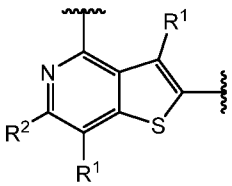
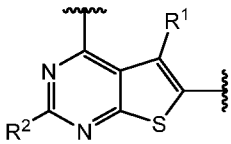
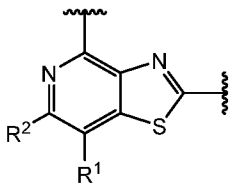
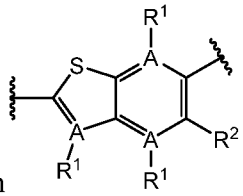
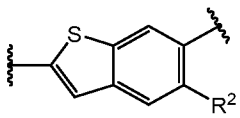
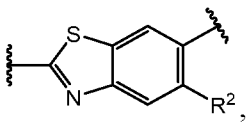
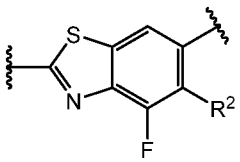
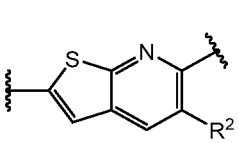
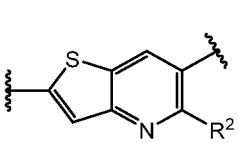
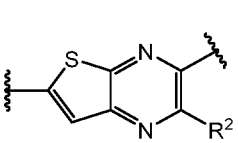


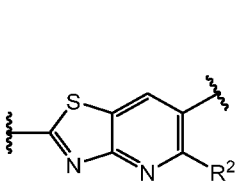
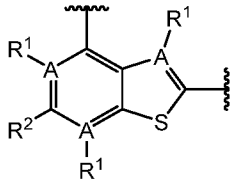
(IV)

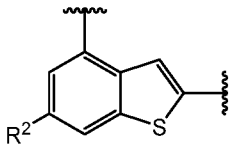
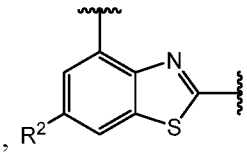
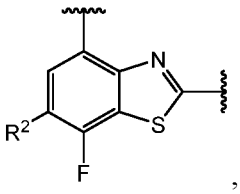
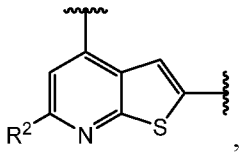
or a pharmaceutically acceptable salt thereof, wherein each A-R^1 is independently selected from the group consisting of C-R^1 and N; each R^1 is independently selected from the group consisting of H, halogen, OR^6, $N(R^6)_2$, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkyl substituted by OR^6, C_1-C_6 alkyl substituted by $N(R^6)_2$, $COOR^6$, and $C(O)N(R^6)_2$; each R^2 is independently selected from the group consisting of H, halogen, CN, OR^6, $N(R^6)_2$, $COOR^6$, $C(O)N(R^6)_2$, SO_2R^6, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkyl substituted by OR^6, C_2-C_6 alkenyl, C_2-C_6 haloalkenyl, C_2-C_6 alkenyl substituted by OR^6, C_2-C_6 alkynyl, C_2-C_6 haloalkynyl, C_2-C_6 alkynyl substituted by OR^6, C_3-C_6 cycloalkyl, and a 3- to 6-membered heterocyclic ring including 1 to 2 ring members selected from the group consisting of O, S, and $N(R^6)$; R^3 and R^4 are independently selected from the group consisting of O-(C_1-C_4 alkylene or haloalkylene), C_1-C_5 alkylene or haloalkylene, and $N(R_6)$-(C_1-C_4 alkylene or haloalkylene); each R^6 is independently selected from the group consisting of H, C_1-C_6 alkyl, and C_1-C_6 haloalkyl; each X^1 is independently selected from the group consisting of C=O, -CH_2-, -CHF-, and -CF_2-; each X^2 is independently selected from $(C(R^8)_2)_{(1\text{-}3)}$, wherein each R^8 is independently selected from the group consisting of H, halogen, C_1-C_6 alkyl, CN, OR^6, $N(R^6)_2$, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, C_1-C_6 alkyl substituted by OR^6, and C_1-C_6 alkyl substituted by $N(R^6)_2$; optionally 2 R^8 on different carbon atoms may be taken together, along with the atoms to which they are attached, to form a 3- to 6-membered fused ring; and optionally 2 R^8 on a single carbon atom may be taken together, along with the atom to which they are attached, to form a 3- to 6-membered spirocycle; each X^3 is

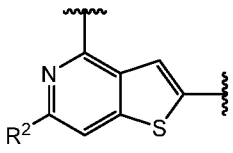
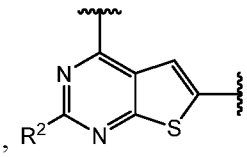
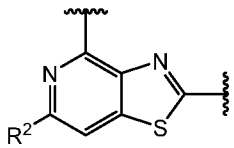


independently selected from the group consisting of $COOR^6$, $C(O)SR^6$, $C(S)OR^6$, , SO_2R^6, $C(O)N(R^9)_2$, and CN; and each R^9 is independently selected from the group consisting of H, $COOR^6$, and SO_2R^6.

In a first aspect of the fourth embodiment, each A-R^1 is independently selected from the group consisting of C-R^1 and N. In particular instances of this aspect, each  is independently selected from the group consisting of  ,  ,  ,  ,  , and  ; and  is selected from the group consisting of  ,  ,  ,  ,  , and  . In more particular instances of this aspect, each  is independently selected from the group consisting of  ,  ,  ,  ,  ,  , and

 ; and  is selected from the group consisting of

 ,  ,  ,  ,

 ,  , and  . In this aspect, all other groups are as provided in the general formula (IV) of the fourth embodiment above.

In a second aspect of the fourth embodiment, each R^1 is independently selected from the group consisting of H, halogen, OR^6, $N(R^6)_2$, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkyl substituted by OR^6, C_1-C_6 alkyl substituted by $N(R^6)_2$, $COOR^6$, and $C(O)N(R^6)_2$. In instances of this aspect, each R^1 is independently selected from the group consisting of H, halogen, C_1-C_3 alkyl, and C_1-C_3 haloalkyl. In particular instances of this aspect, each R^1 is independently selected from the group consisting of H and halogen. In more particular instances of this aspect, each R^1 is independently selected from the group consisting of H and F. In this aspect, all other groups are as provided in the general formula (IV) of the fourth embodiment above or in the first aspect above.

In a third aspect of the fourth embodiment, each R^2 is independently selected from the group consisting of H, halogen, CN, OR^6, $N(R^6)_2$, $COOR^6$, $C(O)N(R^6)_2$, SO_2R^6, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkyl substituted by OR^6, C_2-C_6 alkenyl, C_2-C_6 haloalkenyl, C_2-C_6 alkenyl substituted by OR^6, C_2-C_6 alkynyl, C_2-C_6 haloalkynyl, C_2-C_6 alkynyl substituted by OR^6, C_3-C_6 cycloalkyl, and a 3- to 6-membered heterocyclic ring including 1 to 2 ring members selected from the group consisting of O, S, and $N(R^6)$. In instances of this aspect, each R^2 is independently selected from the group consisting of H, halogen, C_1-C_3 alkyl, C_1-C_3 haloalkyl, OC_1-C_3 alkyl, C_2-C_3 alkenyl, and $N(R^6)_2$. In particular instances of this aspect, each R^2 independently is selected from the group consisting of H, Br, Cl, CH_3, CH_2CH_3, $CH{=}CH_2$, OCH_3, $OCFH_2$, OCF_2H, OCF_3, and $N(R^6)_2$. In more particular instances of this aspect, each R^2 independently is selected from the group consisting of H, CH_3, OCH_3, and OCF_2H. In this

aspect, all other groups are as provided in the general formula (IV) of the fourth embodiment or in the first or second aspects described above.

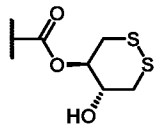
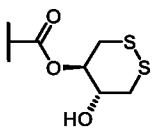
In a fourth aspect of the fourth embodiment, R^3 and R^4 are independently selected from the group consisting of O-(C_1-C_4 alkylene or haloalkylene), C_1-C_5 alkylene or haloalkylene, and $N(R_6)$-(C_1-C_4 alkylene or haloalkylene). In instances of this fourth aspect, R^3-R^4 is selected from the group consisting of -$(CH_2)_{2-8}$-, -$O(CH_2)_{1-7}$-, -$O(CH_2)_{1-6}O$-, -$NH(CH_2)_{1-7}$-, and -$NH(CH_2)_{1-6}O$-. In particular instances of this fourth aspect, R^3-R^4 is selected from the group consisting of -$(CH_2)_2$-, -$(CH_2)_3$-, -$(CH_2)_4$-, -$O(CH_2)_2$-, -$O(CH_2)_3$-, -$O(CH_2)_4$-, -$O(CH_2)_2O$-, -$O(CH_2)_3O$-, -$OCH_2CH(CH_3)CH_2O$-, -$O(CH_2)_4O$-, -$O(CH_2)_5O$-, -$NH(CH_2)_2$-, -$NH(CH_2)_3$-, and -$NH(CH_2)_3O$-. In this aspect, all other groups are as provided in the general formula (IV) of the fourth embodiment or in the first through third aspects described above.

In a fifth aspect of the fourth embodiment, each R^6 is independently selected from the group consisting of H, C_1-C_6 alkyl, and C_1-C_6 haloalkyl. In instances of this aspect, each R^6 is independently selected from the group consisting of H, C_1-C_3 alkyl, and C_1-C_3 haloalkyl. In particular instances of this aspect, each R^6 is independently selected from the group consisting of H, CH_3, and CHF_2. In this aspect, all other groups are as provided in the general formula (IV) of the fourth embodiment or in the first through fourth aspects described above.

In a sixth aspect of the fourth embodiment, each X^1 is independently selected from the group consisting of C=O, -CH_2-, -CHF-, and -CF_2-. In instances of this aspect, X^1 is selected from the group consisting of C=O and -CH_2-. In particular instances of this aspect, X^1 is C=O. In this embodiment, all other groups are as provided in the general formula (IV) of the fourth embodiment or in the first through fifth aspects described above.

In a seventh aspect of the fourth embodiment, each X^2 is independently selected from $(C(R^8)_2)_{(1-3)}$, wherein each R^8 is independently selected from the group consisting of H, halogen, C_1-C_6 alkyl, CN, OR^6, $N(R^6)_2$, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, C_1-C_6 alkyl substituted by OR^6, and C_1-C_6 alkyl substituted by $N(R^6)_2$; optionally 2 R^8 on different carbon atoms may be taken together, along with the atoms to which they are attached, to form a 3- to 6-membered fused ring; and optionally 2 R^8 on a single carbon atom may be taken together, along with the atom to which they are attached, to form a 3- to 6-membered spirocycle. In a first instance of this aspect, each X^2 is CH_2CHR^8, where R^8 is selected from the group consisting of H, C_1-C_3 alkyl, C_1-C_3 alkyl substituted by OH, C_1-C_3 alkyl substituted by OC_1-C_3 alkyl, and C_3-C_6 cycloalkyl. In particular occurrences of this first instance, each X^2 is CH_2CHR^8, wherein

R^8 is selected from the group consisting of H, CH_3, CH_2OH, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, CH_2OCH_3, and cyclopropyl. In a second instance of this aspect, each X^2 is CHR^8CHR^8, where each R^8 is independently selected from the group consisting of H, C_1-C_3 alkyl, C_1-C_3 alkyl substituted by OH, C_1-C_3 alkyl substituted by OC_1-C_3 alkyl, and C_3-C_6 cycloalkyl, and optionally the 2 R^8 on different carbon atoms are taken together, along with the atoms to which they are attached, to form a 3- to 6-membered fused ring. In particular occurrences of this second instance, each X^2 is CHR^8CHR^8, where each R^8 is independently selected from the group consisting of H and C_1-C_3 alkyl, and optionally the 2 R^8 on different carbon atoms are taken together, along with the atoms to which they are attached, to form a 3- to 6-membered fused ring. In a third instance of this aspect, each X^2 is $CH_2C(R^8)_2$, where each R^8 is independently selected from the group consisting of H, C_1-C_3 alkyl, C_1-C_3 alkyl substituted by OH, C_1-C_3 alkyl substituted by OC_1-C_3 alkyl, and C_3-C_6 cycloalkyl, and optionally the 2 R^8 on a single carbon atom are taken together, along with the atoms to which they are attached, to form a 3- to 6-membered spirocycle. In particular occurrences of this third instance, each X^2 is $CH_2C(R^8)_2$, where each R^8 is independently selected from the group consisting of H and C_1-C_3 alkyl, and optionally the 2 R^8 on a single carbon atom are taken together, along with the atoms to which they are attached, to form a 3- to 6-membered spirocycle. In this aspect, all other groups are as provided in the general formula (IV) of the fourth embodiment or in the first through sixth aspects described above.

In an eighth aspect of the fourth embodiment, each X^3 is independently selected from the group consisting of $COOR^6$, $C(O)SR^6$, $C(S)OR^6$,  , SO_2R^6, $C(O)N(R^9)_2$, and CN. In instances of this aspect, each X^3 is independently selected from the group consisting of $COOR^6$,  , SO_2R^6, $C(O)N(R^9)_2$, and CN. In particular instances of this aspect, each X^3 is independently selected from the group consisting of $COOR^6$, $C(O)N(R^9)_2$, and CN. In even more particular instances of this aspect, each X^3 is independently selected from the group consisting of COOH, $COOCH_3$, $CONH_2$, and CN. In this aspect, all other groups are as provided in the general formula (IV) of the fourth embodiment or in the first through seventh aspects described above.

In a ninth aspect of the fourth embodiment, each R^9 is independently selected from the group consisting of H, $COOR^6$, and SO_2R^6. In instances of this aspect, each R^9 is independently H. In this aspect, all other groups are as provided in the general formula (IV) of the fourth embodiment or in the first through eighth aspects described above.

A tenth aspect of the fourth embodiment relates to a pharmaceutical composition, said pharmaceutical composition comprising (a) a compound according to general formula (IV) of the fourth embodiment or the first through ninth aspects described above or a pharmaceutically acceptable salt thereof; and (b) a pharmaceutically acceptable carrier.

An eleventh aspect of the fourth embodiment relates to methods of inducing an immune response in a patient in need of therapy, comprising administering a therapeutically effective amount of a compound according to general formula (IV) of the fourth embodiment or the first through ninth aspects described above described above or a pharmaceutically acceptable salt thereof to the patient.

A twelfth aspect of the fourth embodiment relates to methods of inducing an immune response in a patient in need of therapy, comprising administering a therapeutically effective amount of a composition according to the tenth aspect described above to the patient.

A thirteenth aspect of the fourth embodiment relates to methods of inducing a STING-dependent type I interferon production in a patient in need of therapy, comprising administering a therapeutically effective amount of a compound according to general formula (IV) of the fourth embodiment above or the first through ninth aspects described above or a pharmaceutically acceptable salt thereof to the patient.

A fourteenth aspect of the fourth embodiment relates to methods of inducing STING-dependent type I interferon production in a patient in need of therapy, comprising administering a therapeutically effective amount of a composition according to the tenth aspect described above to the patient.

A fifteenth aspect of the fourth embodiment relates to methods of inducing STING-dependent cytokine production in a patient in need of therapy, comprising administering a therapeutically effective amount of a compound according to general formula (IV) of the fourth embodiment above or the first through ninth aspects described above or a pharmaceutically acceptable salt thereof to the patient.

A sixteenth aspect of the fourth embodiment relates to methods of inducing a STING-dependent cytokine production in a patient in need of therapy, comprising administering a

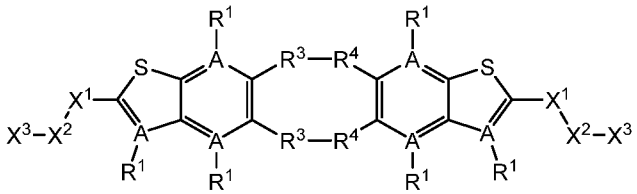
therapeutically effective amount of a composition according to the tenth aspect described above to the patient.

A seventeenth aspect of the fourth embodiment relates to methods of treating a cell proliferation disorder in a patient in need of therapy, comprising administering a therapeutically effective amount of a compound of general formula (IV), or a pharmaceutically acceptable salt thereof to the patient. In instances of this seventeenth aspect of the fourth embodiment, the cell proliferation disorder is cancer.

An eighteenth aspect of the fourth embodiment relates to methods of treating a cell proliferation disorder in a patient in need of therapy, said method comprising administering a therapeutically effective amount of a composition according to the eleventh aspect described above to the patient. In instances of this eighteenth aspect of the fourth embodiment, the cell proliferation disorder is cancer.

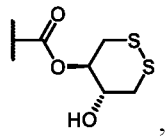
In each aspect of the fourth embodiment described herein, variables R^1, R^2, R^3, R^4, R^6, R^8, R^9, A, X^1, X^2, and X^3 of general formula (IV) of the fourth embodiment, and the various aspects and instances thereof, are each independently selected from each other, with the proviso that at least one of R^1, R^2, R^3, R^4, R^6, R^8, and R^9 is not H.

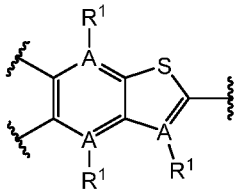
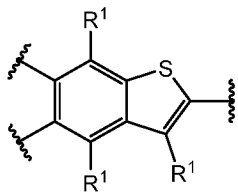
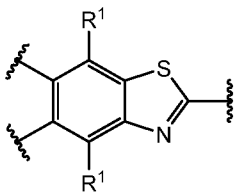
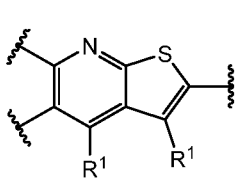
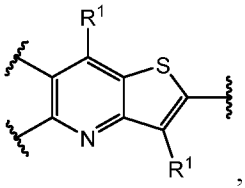
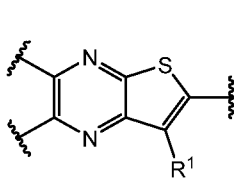
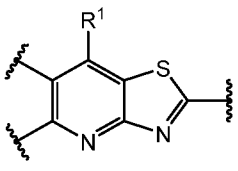
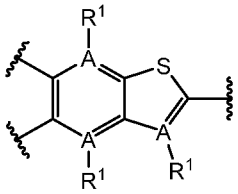
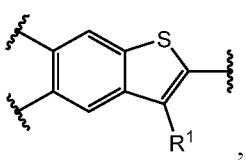
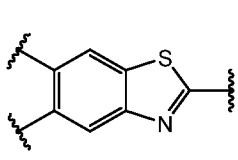
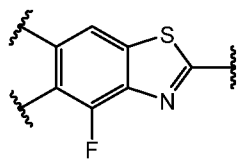
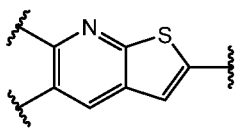
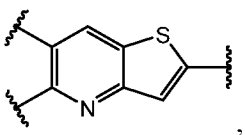
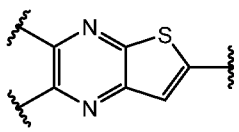
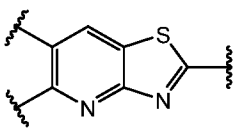
A fifth embodiment relates to compounds of general formula (V):



(V)

or a pharmaceutically acceptable salt thereof, wherein each A-R^1 is independently selected from the group consisting of C-R^1 and N; each R^1 is independently selected from the group consisting of H, halogen, OR^6, $N(R^6)_2$, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkyl substituted by OR^6, C_1-C_6 alkyl substituted by $N(R^6)_2$, $COOR^6$, and $C(O)N(R^6)_2$; R^3 and R^4 are independently selected from the group consisting of O-(C_1-C_4 alkylene or haloalkylene), C_1-C_5 alkylene or haloalkylene, and $N(R_6)$-(C_1-C_4 alkylene or haloalkylene); each X^1 is independently selected from the group consisting of C=O, -CH_2-, -CHF-, and -CF_2-; each X^2 is independently selected from $(C(R^8)_2)_{(1\text{-}3)}$, wherein each R^8 is independently selected from the group consisting of H, halogen, C_1-C_6 alkyl, CN, OR^6, $N(R^6)_2$, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, C_1-C_6 alkyl substituted by OR^6, and C_1-C_6 alkyl substituted by $N(R^6)_2$; optionally 2 R^8 on different carbon atoms may be taken together, along with the atoms to which they are attached, to form a 3- to 6-membered

fused ring; and optionally 2 R^8 on a single carbon atom may be taken together, along with the atom to which they are attached, to form a 3- to 6-membered spirocycle; each X^3 is independently selected from the group consisting of $COOR^6$, $C(O)SR^6$, $C(S)OR^6$,  , SO_2R^6, $C(O)N(R^9)_2$, and CN; and each R^9 is independently selected from the group consisting of H, $COOR^6$, and SO_2R^6.

In a first aspect of the fifth embodiment, each A-R^1 is independently selected from the group consisting of C-R^1 and N. In particular instances of this aspect, each  is independently selected from the group consisting of  ,  ,  ,  ,  , and  . In more particular instances of this aspect, each  is independently selected from the group consisting of  ,  ,  ,  ,  ,  , and  . In this

aspect, all other groups are as provided in the general formula (V) of the fifth embodiment above.

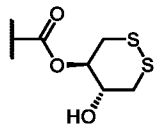
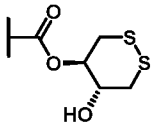
In a second aspect of the fifth embodiment, each R^1 is independently selected from the group consisting of H, halogen, OR^6, $N(R^6)_2$, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkyl substituted by OR^6, C_1-C_6 alkyl substituted by $N(R^6)_2$, $COOR^6$, and $C(O)N(R^6)_2$. In instances of this aspect, each R^1 is independently selected from the group consisting of H, halogen, C_1-C_3 alkyl, and C_1-C_3 haloalkyl. In particular instances of this aspect, each R^1 is independently selected from the group consisting of H and halogen. In more particular instances of this aspect, each R^1 is independently selected from the group consisting of H and F. In this aspect, all other groups are as provided in the general formula (V) of the fifth embodiment above or in the first aspect above.

In a third aspect of the fifth embodiment, R^3 and R^4 are independently selected from the group consisting of O-(C_1-C_4 alkylene or haloalkylene), C_1-C_5 alkylene or haloalkylene, and $N(R_6)$-(C_1-C_4 alkylene or haloalkylene). In instances of this fourth aspect, R^3-R^4 is selected from the group consisting of $-(CH_2)_{2\text{-}8}$-, $-O(CH_2)_{1\text{-}7}$-, $-O(CH_2)_{1\text{-}6}O$-, $-NH(CH_2)_{1\text{-}7}$-, and $-NH(CH_2)_{1\text{-}6}O$-. In particular instances of this fourth aspect, R^3-R^4 is selected from the group consisting of $-(CH_2)_2$-, $-(CH_2)_3$-, $-(CH_2)_4$-, $-O(CH_2)_2$-, $-O(CH_2)_3$-, $-O(CH_2)_4$-, $-O(CH_2)_2O$-, $-O(CH_2)_3O$-, $-OCH_2CH(CH_3)CH_2O$-, $-O(CH_2)_4O$-, $-O(CH_2)_5O$-, $-NH(CH_2)_2$-, $-NH(CH_2)_3$-, and $-NH(CH_2)_3O$-. In this aspect, all other groups are as provided in the general formula (V) of the fifth embodiment or in the first and second aspects described above.

In a fourth aspect of the fifth embodiment, each R^6 is independently selected from the group consisting of H, C_1-C_6 alkyl, and C_1-C_6 haloalkyl. In instances of this aspect, each R^6 is independently selected from the group consisting of H, C_1-C_3 alkyl, and C_1-C_3 haloalkyl. In particular instances of this aspect, each R^6 is independently selected from the group consisting of H, CH_3, and CHF_2. In this aspect, all other groups are as provided in the general formula (V) of the fifth embodiment or in the first through third aspects described above.

In a fifth aspect of the fifth embodiment, each X^1 is independently selected from the group consisting of C=O, $-CH_2$-, -CHF-, and $-CF_2$-. In instances of this aspect, X^1 is selected from the group consisting of C=O and $-CH_2$-. In particular instances of this aspect, X^1 is C=O. In this embodiment, all other groups are as provided in the general formula (V) of the fifth embodiment or in the first through fourth aspects described above.

In a sixth aspect of the fifth embodiment, each X^2 is independently selected from $(C(R^8)_2)_{(1-3)}$, wherein each R^8 is independently selected from the group consisting of H, halogen, C_1-C_6 alkyl, CN, OR^6, $N(R^6)_2$, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, C_1-C_6 alkyl substituted by OR^6, and C_1-C_6 alkyl substituted by $N(R^6)_2$; optionally 2 R^8 on different carbon atoms may be taken together, along with the atoms to which they are attached, to form a 3- to 6-membered fused ring; and optionally 2 R^8 on a single carbon atom may be taken together, along with the atom to which they are attached, to form a 3- to 6-membered spirocycle. In a first instance of this aspect, each X^2 is CH_2CHR^8, where R^8 is selected from the group consisting of H, C_1-C_3 alkyl, C_1-C_3 alkyl substituted by OH, C_1-C_3 alkyl substituted by OC_1-C_3 alkyl, and C_3-C_6 cycloalkyl. In particular occurrences of this first instance, each X^2 is CH_2CHR^8, wherein R^8 is selected from the group consisting of H, CH_3, CH_2OH, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, CH_2OCH_3, and cyclopropyl. In a second instance of this aspect, each X^2 is CHR^8CHR^8, where each R^8 is independently selected from the group consisting of H, C_1-C_3 alkyl, C_1-C_3 alkyl substituted by OH, C_1-C_3 alkyl substituted by OC_1-C_3 alkyl, and C_3-C_6 cycloalkyl, and optionally the 2 R^8 on different carbon atoms are taken together, along with the atoms to which they are attached, to form a 3- to 6-membered fused ring. In particular occurrences of this second instance, each X^2 is CHR^8CHR^8, where each R^8 is independently selected from the group consisting of H and C_1-C_3 alkyl, and optionally the 2 R^8 on different carbon atoms are taken together, along with the atoms to which they are attached, to form a 3- to 6-membered fused ring. In a third instance of this aspect, each X^2 is $CH_2C(R^8)_2$, where each R^8 is independently selected from the group consisting of H, C_1-C_3 alkyl, C_1-C_3 alkyl substituted by OH, C_1-C_3 alkyl substituted by OC_1-C_3 alkyl, and C_3-C_6 cycloalkyl, and optionally the 2 R^8 on a single carbon atom are taken together, along with the atoms to which they are attached, to form a 3- to 6-membered spirocycle. In particular occurrences of this third instance, each X^2 is $CH_2C(R^8)_2$, where each R^8 is independently selected from the group consisting of H and C_1-C_3 alkyl, and optionally the 2 R^8 on a single carbon atom are taken together, along with the atoms to which they are attached, to form a 3- to 6-membered spirocycle. In this aspect, all other groups are as provided in the general formula (V) of the fifth embodiment or in the first through fifth aspects described above.

In a seventh aspect of the fifth embodiment, each X^3 is independently selected from the group consisting of $COOR^6$, $C(O)SR^6$, $C(S)OR^6$,  , SO_2R^6, $C(O)N(R^9)_2$, and CN. In instances of this aspect, each X^3 is independently selected from the group consisting of $COOR^6$,  , SO_2R^6, $C(O)N(R^9)_2$, and CN. In particular instances of this aspect, each X^3 is independently selected from the group consisting of $COOR^6$, $C(O)N(R^9)_2$, and CN. In even more particular instances of this aspect, each X^3 is independently selected from the group consisting of COOH, $COOCH_3$, $CONH_2$, and CN. In this aspect, all other groups are as provided in the general formula (V) of the fifth embodiment or in the first through sixth aspects described above.

In an eighth aspect of the fifth embodiment, each R^9 is independently selected from the group consisting of H, $COOR^6$, and SO_2R^6. In instances of this aspect, each R^9 is independently H. In this aspect, all other groups are as provided in the general formula (V) of the fifth embodiment or in the first through seventh aspects described above.

A ninth aspect of the fifth embodiment relates to a pharmaceutical composition, said pharmaceutical composition comprising (a) a compound according to general formula (V) of the fifth embodiment or the first through eighth aspects described above or a pharmaceutically acceptable salt thereof; and (b) a pharmaceutically acceptable carrier.

A tenth aspect of the fifth embodiment relates to methods of inducing an immune response in a patient in need of therapy, comprising administering a therapeutically effective amount of a compound according to general formula (V) of the fifth embodiment or the first through eighth aspects described above described above or a pharmaceutically acceptable salt thereof to the patient.

An eleventh aspect of the fifth embodiment relates to methods of inducing an immune response in a patient in need of therapy, comprising administering a therapeutically effective amount of a composition according to the ninth aspect described above to the patient.

A twelfth aspect of the fifth embodiment relates to methods of inducing a STING-dependent type I interferon production in a patient in need of therapy, comprising administering a therapeutically effective amount of a compound according to general formula (V) of the fifth

embodiment above or the first through eighth aspects described above or a pharmaceutically acceptable salt thereof to the patient.

A thirteenth aspect of the fifth embodiment relates to methods of inducing STING-dependent type I interferon production in a patient in need of therapy, comprising administering a therapeutically effective amount of a composition according to the ninth aspect described above to the patient.

A fourteenth aspect of the fifth embodiment relates to methods of inducing STING-dependent cytokine production in a patient in need of therapy, comprising administering a therapeutically effective amount of a compound according to general formula (V) of the fifth embodiment above or the first through eighth aspects described above or a pharmaceutically acceptable salt thereof to the patient.

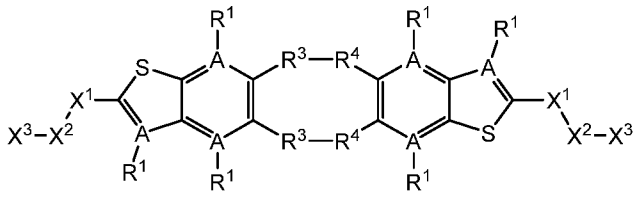
A fifteenth aspect of the fifth embodiment relates to methods of inducing a STING-dependent cytokine production in a patient in need of therapy, comprising administering a therapeutically effective amount of a composition according to the ninth aspect described above to the patient.

A sixteenth aspect of the fifth embodiment relates to methods of treating a cell proliferation disorder in a patient in need of therapy, comprising administering a therapeutically effective amount of a compound according to general formula (V) of the fifth embodiment above or the first through eighth aspects described above or a pharmaceutically acceptable salt thereof to the patient. In instances of this sixteenth aspect of the fifth embodiment, the cell proliferation disorder is cancer.

A seventeenth aspect of the fifth embodiment relates to methods of treating a cell proliferation disorder in a patient in need of therapy, said method comprising administering a therapeutically effective amount of a composition according to the ninth aspect described above to the patient. In instances of this seventeenth aspect of the fifth embodiment, the cell proliferation disorder is cancer.

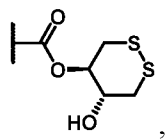
In each aspect of the fifth embodiment described herein, variables R^1, R^2, R^3, R^4, R^6, R^8, R^9, A, X^1, X^2, and X^3 of general formula (V) of the fifth embodiment, and the various aspects and instances thereof, are each independently selected from each other, with the proviso that at least one of R^1, R^2, R^3, R^4, R^6, R^8, and R^9 is not H.

A sixth embodiment relates to compounds of general formula (VI):



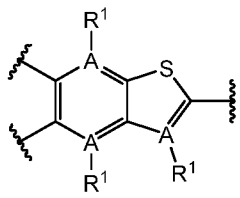
(VI)

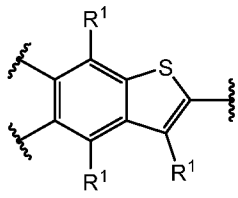
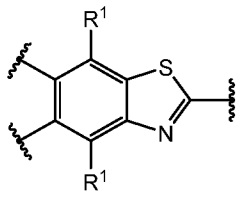
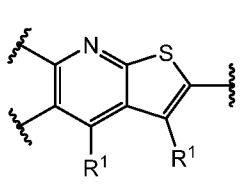
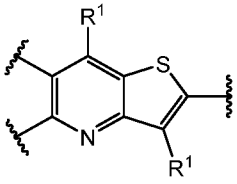
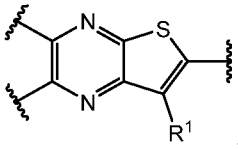
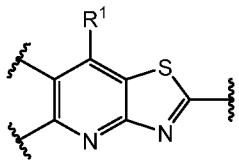
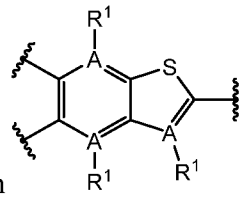
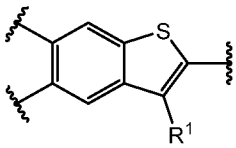
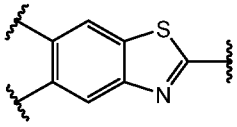
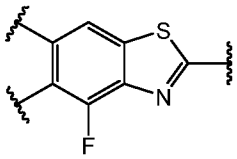
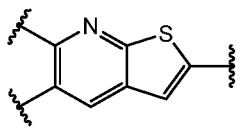
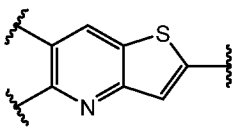
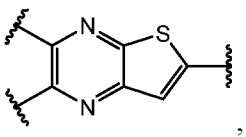
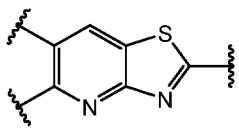
or a pharmaceutically acceptable salt thereof, wherein each A-R^1 is independently selected from the group consisting of C-R^1 and N; each R^1 is independently selected from the group consisting of H, halogen, OR^6, $N(R^6)_2$, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkyl substituted by OR^6, C_1-C_6 alkyl substituted by $N(R^6)_2$, $COOR^6$, and $C(O)N(R^6)_2$; R^3 and R^4 are independently selected from the group consisting of O-(C_1-C_4 alkylene or haloalkylene), C_1-C_5 alkylene or haloalkylene, and $N(R_6)$-(C_1-C_4 alkylene or haloalkylene); each R^6 is independently selected from the group consisting of H, C_1-C_6 alkyl, and C_1-C_6 haloalkyl; each X^1 is independently selected from the group consisting of C=O, -CH_2-, -CHF-, and -CF_2-; each X^2 is independently selected from $(C(R^8)_2)_{(1\text{-}3)}$, wherein each R^8 is independently selected from the group consisting of H, halogen, C_1-C_6 alkyl, CN, OR^6, $N(R^6)_2$, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, C_1-C_6 alkyl substituted by OR^6, and C_1-C_6 alkyl substituted by $N(R^6)_2$; optionally 2 R^8 on different carbon atoms may be taken together, along with the atoms to which they are attached, to form a 3- to 6-membered fused ring; and optionally 2 R^8 on a single carbon atom may be taken together, along with the atom to which they are attached, to form a 3- to 6-membered spirocycle; each X^3 is



independently selected from the group consisting of $COOR^6$, $C(O)SR^6$, $C(S)OR^6$, SO_2R^6, $C(O)N(R^9)_2$, and CN; and each R^9 is independently selected from the group consisting of H, $COOR^6$, and SO_2R^6.

In a first aspect of the sixth embodiment, each A-R^1 is independently selected from the group consisting of C-R^1 and N. In particular instances of this aspect, each



is independently selected from the group consisting of  ,  ,  ,  ,  , and  . In more particular instances of this aspect, each each  is independently selected from the group consisting of  ,  ,  ,  ,  ,  , and  . In this aspect, all other groups are as provided in the general formula (VI) of the sixth embodiment above.

In a second aspect of the sixth embodiment, each R^1 is independently selected from the group consisting of H, halogen, OR^6, $N(R^6)_2$, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkyl substituted by OR^6, C_1-C_6 alkyl substituted by $N(R^6)_2$, $COOR^6$, and $C(O)N(R^6)_2$. In instances of this aspect, each R^1 is independently selected from the group consisting of H, halogen, C_1-C_3 alkyl, and C_1-C_3 haloalkyl. In particular instances of this aspect, each R^1 is independently selected from the group consisting of H and halogen. In more particular instances of this aspect, each R^1 is independently selected from the group consisting of H and F. In this aspect, all other groups are as provided in the general formula (VI) of the sixth embodiment above or in the first aspect above.

In a third aspect of the sixth embodiment, R^3 and R^4 are independently selected from the group consisting of O-(C_1-C_4 alkylene or haloalkylene), C_1-C_5 alkylene or haloalkylene, and

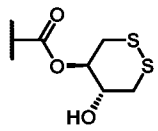
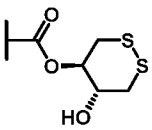
$N(R_6)$-(C_1-C_4 alkylene or haloalkylene). In instances of this fourth aspect, R^3-R^4 is selected from the group consisting of -$(CH_2)_{2-8}$-, -$O(CH_2)_{1-7}$-, -$O(CH_2)_{1-6}O$-, -$NH(CH_2)_{1-7}$-, and -$NH(CH_2)_{1-6}O$-. In particular instances of this fourth aspect, R^3-R^4 is selected from the group consisting of -$(CH_2)_2$-, -$(CH_2)_3$-, -$(CH_2)_4$-, -$O(CH_2)_2$-, -$O(CH_2)_3$-, -$O(CH_2)_4$-, -$O(CH_2)_2O$-, -$O(CH_2)_3O$-, -$OCH_2CH(CH_3)CH_2O$-, -$O(CH_2)_4O$-, -$O(CH_2)_5O$-, -$NH(CH_2)_2$-, -$NH(CH_2)_3$-, and -$NH(CH_2)_3O$-. In this aspect, all other groups are as provided in the general formula (VI) of the sixth embodiment or in the first and second aspects described above.

In a fourth aspect of the sixth embodiment, each R^6 is independently selected from the group consisting of H, C_1-C_6 alkyl, and C_1-C_6 haloalkyl. In instances of this aspect, each R^6 is independently selected from the group consisting of H, C_1-C_3 alkyl, and C_1-C_3 haloalkyl. In particular instances of this aspect, each R^6 is independently selected from the group consisting of H, CH_3, and CHF_2. In this aspect, all other groups are as provided in the general formula (VI) of the sixth embodiment or in the first through third aspects described above.

In a fifth aspect of the sixth embodiment, each X^1 is independently selected from the group consisting of C=O, -CH_2-, -CHF-, and -CF_2-. In instances of this aspect, X^1 is selected from the group consisting of C=O and -CH_2-. In particular instances of this aspect, X^1 is C=O. In this embodiment, all other groups are as provided in the general formula (VI) of the sixth embodiment or in the first through fourth aspects described above

In a sixth aspect of the sixth embodiment, each X^2 is independently selected from $(C(R^8)_2)_{(1-3)}$, wherein each R^8 is independently selected from the group consisting of H, halogen, C_1-C_6 alkyl, CN, OR^6, $N(R^6)_2$, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, C_1-C_6 alkyl substituted by OR^6, and C_1-C_6 alkyl substituted by $N(R^6)_2$; optionally 2 R^8 on different carbon atoms may be taken together, along with the atoms to which they are attached, to form a 3- to 6-membered fused ring; and optionally 2 R^8 on a single carbon atom may be taken together, along with the atom to which they are attached, to form a 3- to 6-membered spirocycle. In a first instance of this aspect, each X^2 is CH_2CHR^8, where R^8 is selected from the group consisting of H, C_1-C_3 alkyl, C_1-C_3 alkyl substituted by OH, C_1-C_3 alkyl substituted by OC_1-C_3 alkyl, and C_3-C_6 cycloalkyl. In particular occurrences of this first instance, each X^2 is CH_2CHR^8, wherein R^8 is selected from the group consisting of H, CH_3, CH_2OH, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, CH_2OCH_3, and cyclopropyl. In a second instance of this aspect, each X^2 is CHR^8CHR^8, where each R^8 is independently selected from the group consisting of H, C_1-C_3 alkyl, C_1-C_3 alkyl substituted by OH, C_1-C_3 alkyl substituted by OC_1-C_3 alkyl, and C_3-C_6 cycloalkyl, and optionally

the 2 R^8 on different carbon atoms are taken together, along with the atoms to which they are attached, to form a 3- to 6-membered fused ring. In particular occurrences of this second instance, each X^2 is CHR^8CHR^8, where each R^8 is independently selected from the group consisting of H and C_1-C_3 alkyl, and optionally the 2 R^8 on different carbon atoms are taken together, along with the atoms to which they are attached, to form a 3- to 6-membered fused ring. In a third instance of this aspect, each X^2 is $CH_2C(R^8)_2$, where each R^8 is independently selected from the group consisting of H, C_1-C_3 alkyl, C_1-C_3 alkyl substituted by OH, C_1-C_3 alkyl substituted by OC_1-C_3 alkyl, and C_3-C_6 cycloalkyl, and optionally the 2 R^8 on a single carbon atom are taken together, along with the atoms to which they are attached, to form a 3- to 6-membered spirocycle. In particular occurrences of this third instance, each X^2 is $CH_2C(R^8)_2$, where each R^8 is independently selected from the group consisting of H and C_1-C_3 alkyl, and optionally the 2 R^8 on a single carbon atom are taken together, along with the atoms to which they are attached, to form a 3- to 6-membered spirocycle. In this aspect, all other groups are as provided in the general formula (VI) of the sixth embodiment or in the first through fifth aspects described above.

In a seventh aspect of the sixth embodiment, each X^3 is independently selected from the group consisting of $COOR^6$, $C(O)SR^6$, $C(S)OR^6$,  , SO_2R^6, $C(O)N(R^9)_2$, and CN. In instances of this aspect, each X^3 is independently selected from the group consisting of $COOR^6$,  , SO_2R^6, $C(O)N(R^9)_2$, and CN. In particular instances of this aspect, each X^3 is independently selected from the group consisting of $COOR^6$, $C(O)N(R^9)_2$, and CN. In even more particular instances of this aspect, each X^3 is independently selected from the group consisting of COOH, $COOCH_3$, $CONH_2$, and CN. In this aspect, all other groups are as provided in the general formula (VI) of the sixth embodiment or in the first through sixth aspects described above.

In an eighth aspect of the sixth embodiment, each R^9 is independently selected from the group consisting of H, $COOR^6$, and SO_2R^6. In instances of this aspect, each R^9 is independently H. In this aspect, all other groups are as provided in the general formula (V) of the fifth embodiment or in the first through seventh aspects described above.

A ninth aspect of the sixth embodiment relates to a pharmaceutical composition, said pharmaceutical composition comprising (a) a compound according to general formula (VI) of the sixth embodiment or the first through eighth aspects described above or a pharmaceutically acceptable salt thereof; and (b) a pharmaceutically acceptable carrier.

A tenth aspect of the sixth embodiment relates to methods of inducing an immune response in a patient in need of therapy, comprising administering a therapeutically effective amount of a compound according to general formula (VI) of the sixth embodiment or the first through eighth aspects described above described above or a pharmaceutically acceptable salt thereof to the patient.

An eleventh aspect of the sixth embodiment relates to methods of inducing an immune response in a patient in need of therapy, comprising administering a therapeutically effective amount of a composition according to the ninth aspect described above to the patient.

A twelfth aspect of the sixth embodiment relates to methods of inducing a STING-dependent type I interferon production in a patient in need of therapy, comprising administering a therapeutically effective amount of a compound according to general formula (VI) of the sixth embodiment above or the first through eighth aspects described above or a pharmaceutically acceptable salt thereof to the patient.

A thirteenth aspect of the sixth embodiment relates to methods of inducing STING-dependent type I interferon production in a patient in need of therapy, comprising administering a therapeutically effective amount of a composition according to the ninth aspect described above to the patient.

A fourteenth aspect of the sixth embodiment relates to methods of inducing STING-dependent cytokine production in a patient in need of therapy, comprising administering a therapeutically effective amount of a compound according to general formula (VI) of the sixth embodiment above or the first through eighth aspects described above or a pharmaceutically acceptable salt thereof to the patient.

A fifteenth aspect of the sixth embodiment relates to methods of inducing a STING-dependent cytokine production in a patient in need of therapy, comprising administering a therapeutically effective amount of a composition according to the ninth aspect described above to the patient.

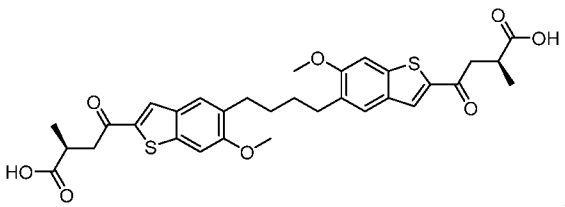
A sixteenth aspect of the sixth embodiment relates to methods of treating a cell proliferation disorder in a patient in need of therapy, comprising administering a therapeutically

effective amount of a compound according to general formula (VI) of the sixth embodiment above or the first through eighth aspects described above or a pharmaceutically acceptable salt thereof to the patient. In instances of this sixteenth aspect of the sixth embodiment, the cell proliferation disorder is cancer.

A seventeenth aspect of the sixth embodiment relates to methods of treating a cell proliferation disorder in a patient in need of therapy, said method comprising administering a therapeutically effective amount of a composition according to the ninth aspect described above to the patient. In instances of this seventeenth aspect of the sixth embodiment, the cell proliferation disorder is cancer.

In each aspect of the sixth embodiment described herein, variables R^1, R^2, R^3, R^4, R^6, R^8, R^9, A, X^1, X^2, and X^3 of general formula (VI) of the sixth embodiment, and the various aspects and instances thereof, are each independently selected from each other, with the proviso that at least one of R^1, R^2, R^3, R^4, R^6, R^8, and R^9 is not H.

A seventh embodiment relates to a compound selected from the group consisting of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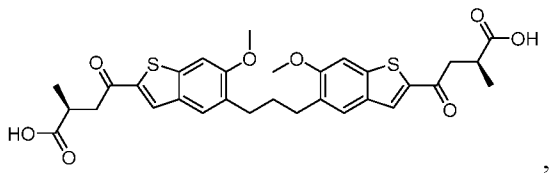
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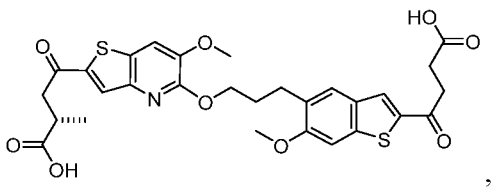
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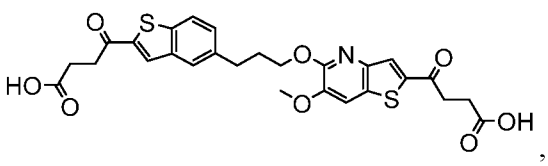
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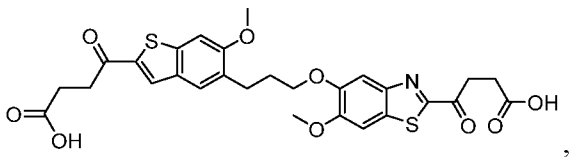
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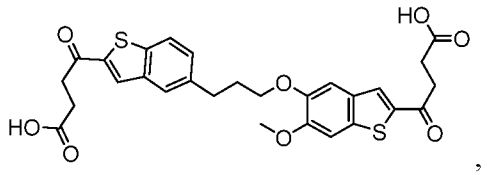
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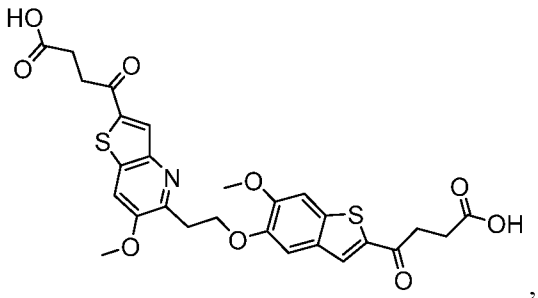
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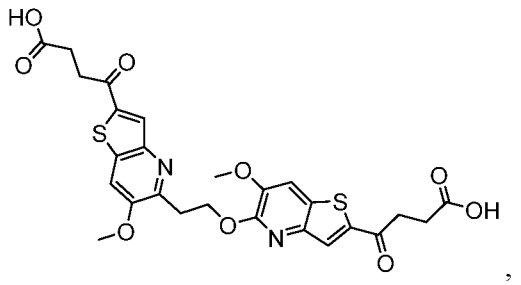
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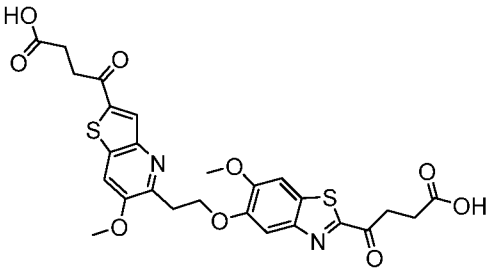
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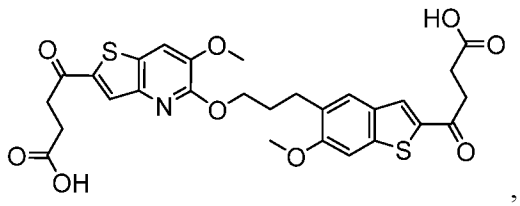
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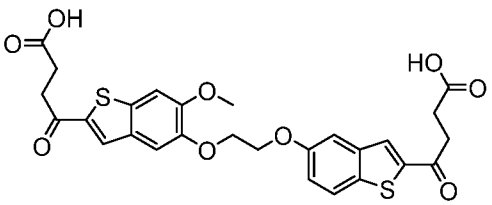
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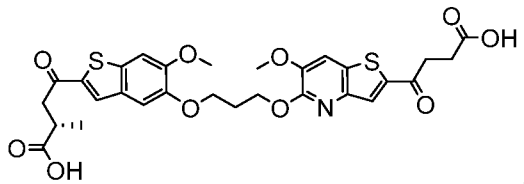
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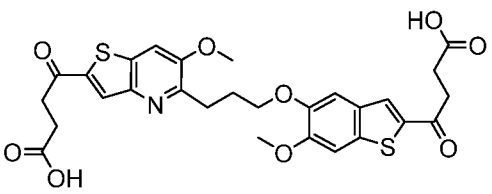
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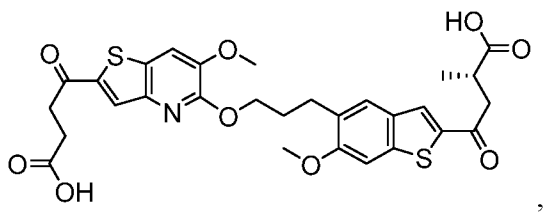
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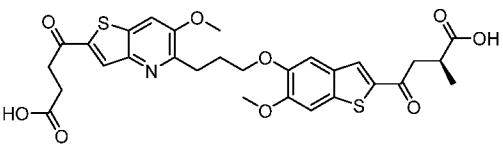
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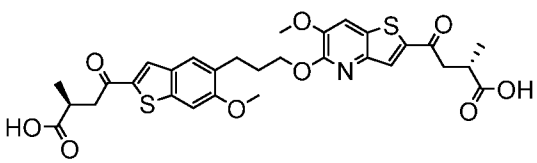
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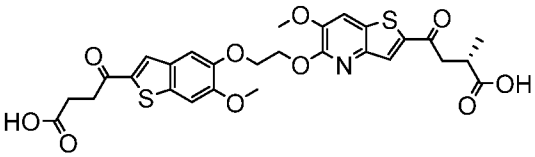
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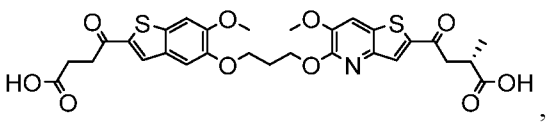
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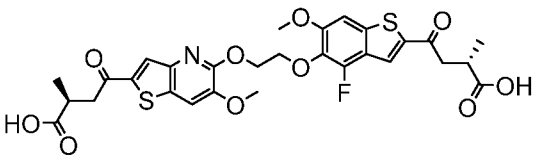
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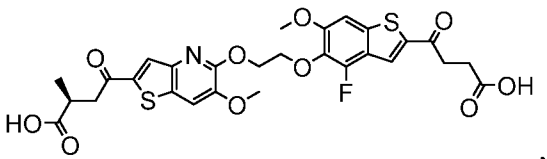
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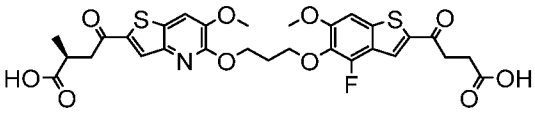
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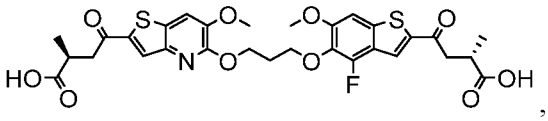
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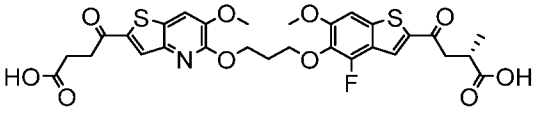
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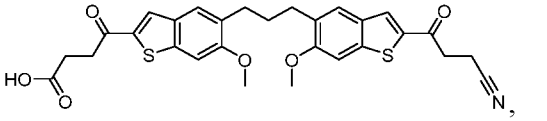
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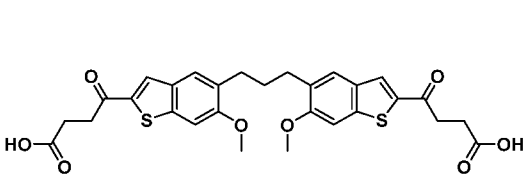
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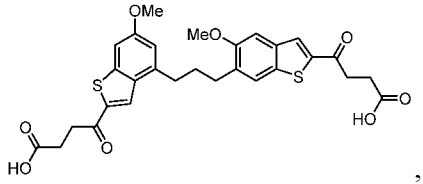
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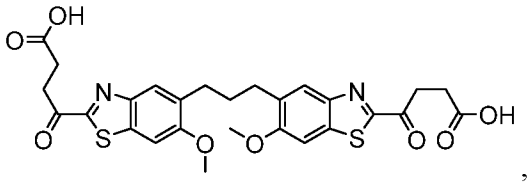
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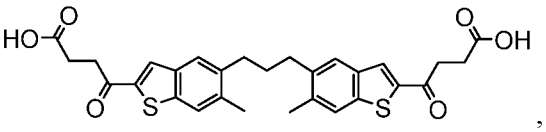
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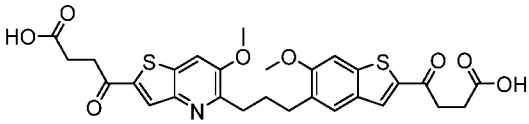
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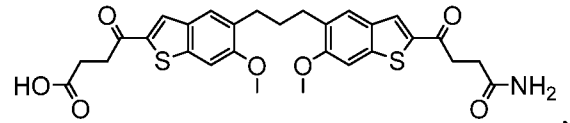
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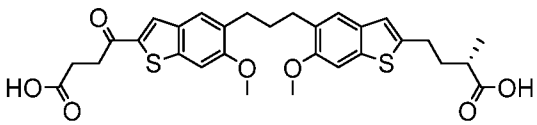
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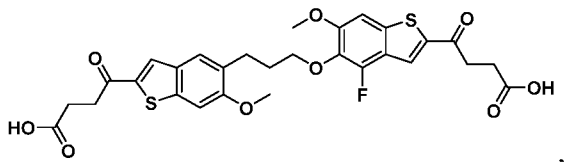
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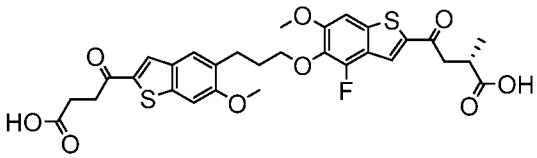
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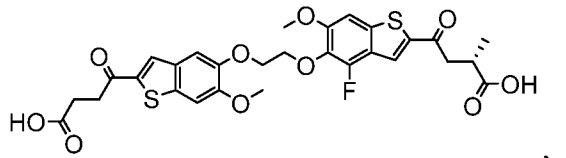
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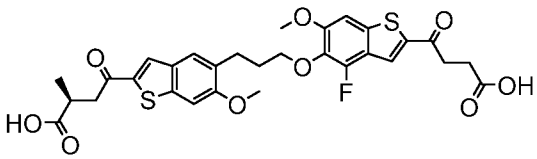
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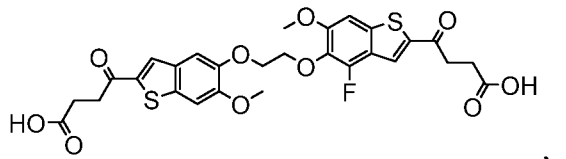
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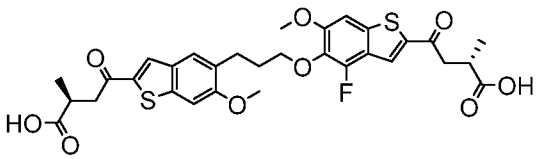
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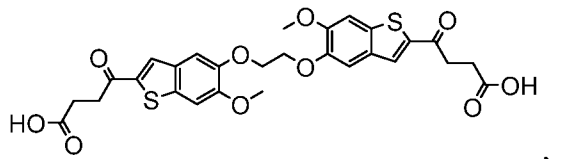
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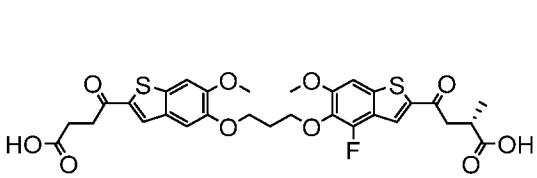
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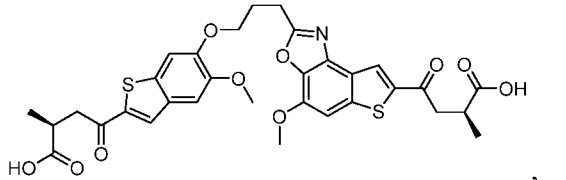
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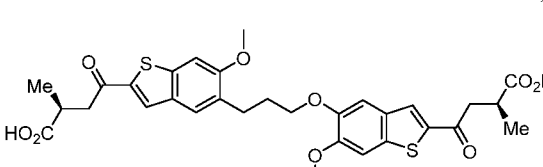
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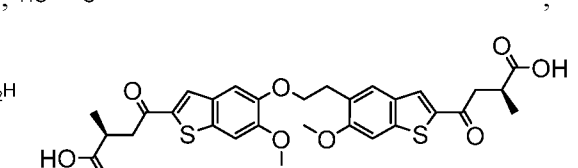
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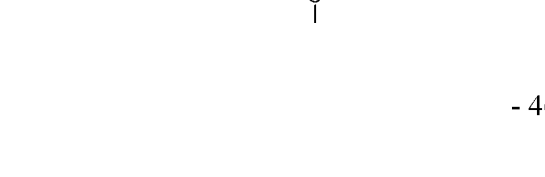
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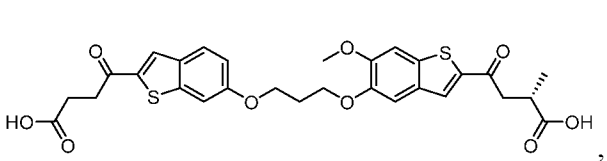
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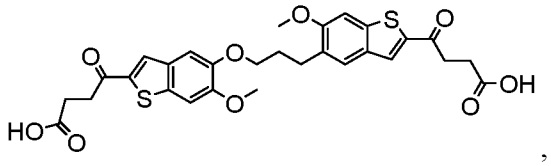
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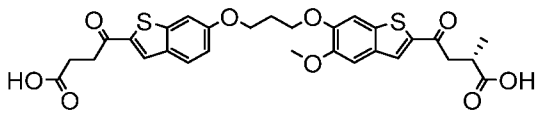
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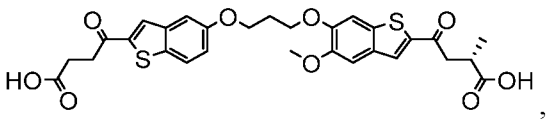
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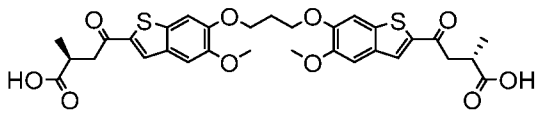
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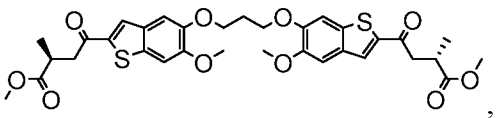
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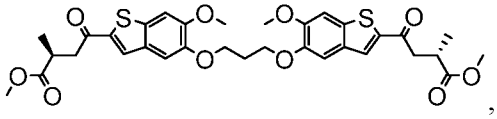
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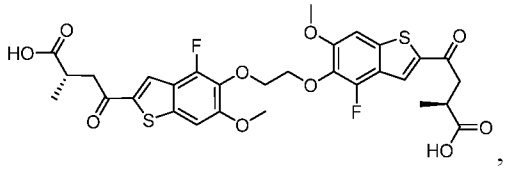
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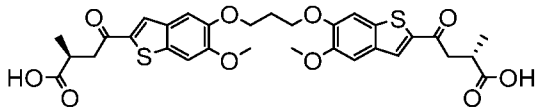
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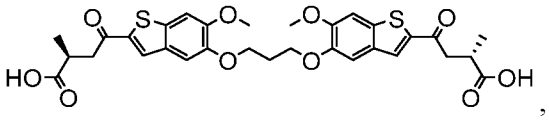
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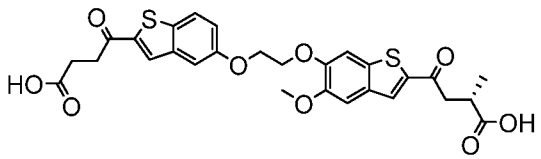
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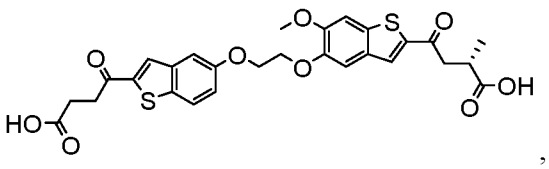
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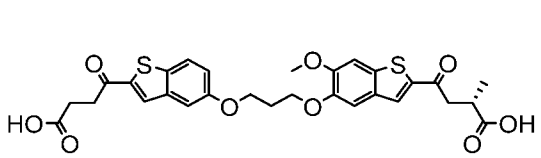
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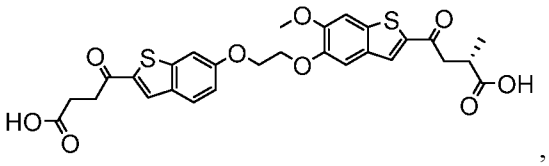
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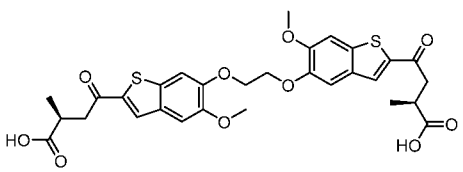
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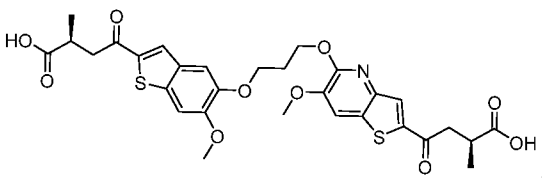
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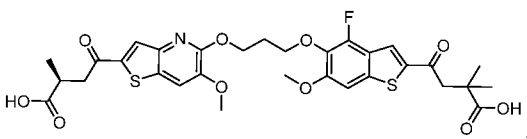
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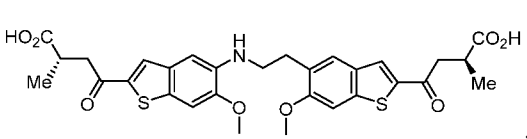
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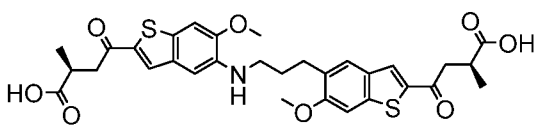
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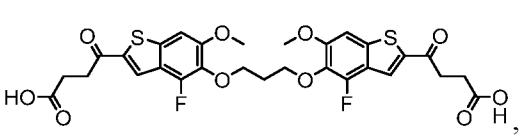
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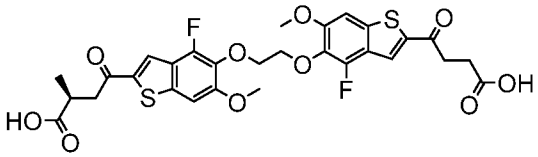
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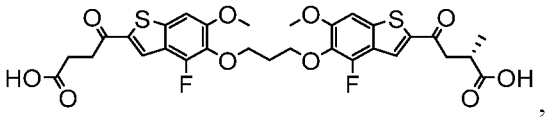
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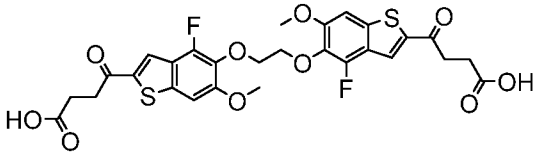
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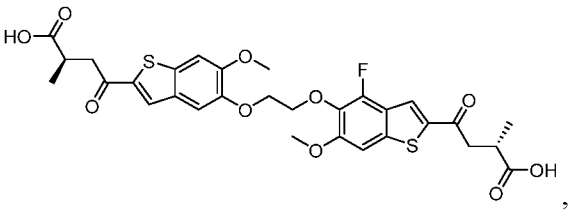
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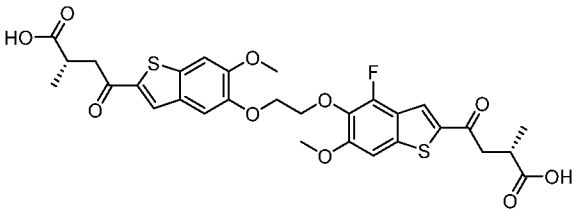
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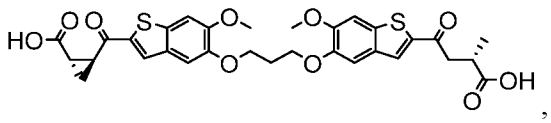
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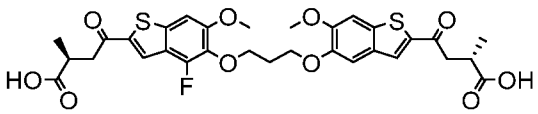
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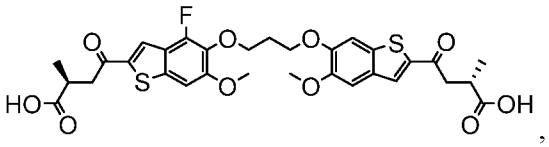
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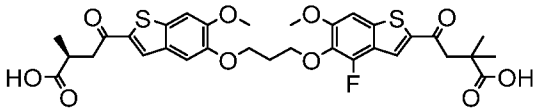
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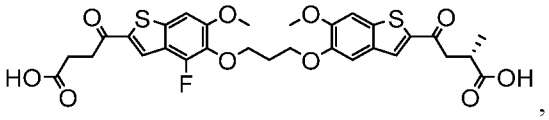
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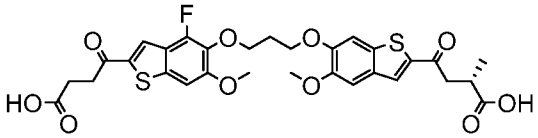
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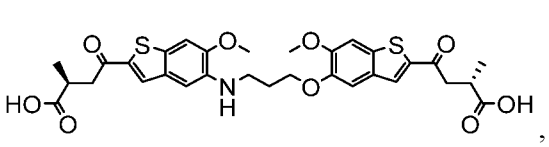
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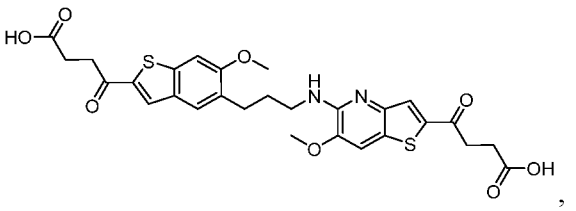
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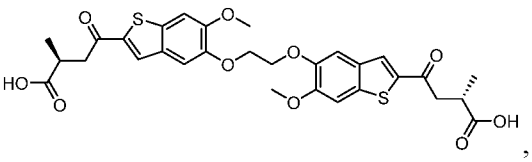
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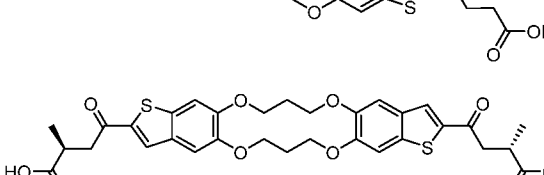
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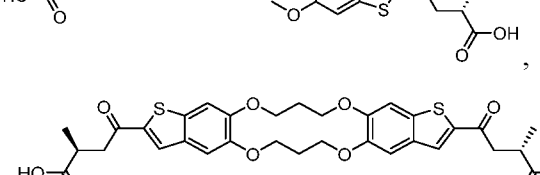
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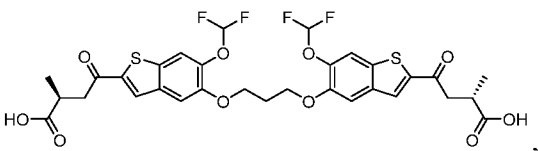
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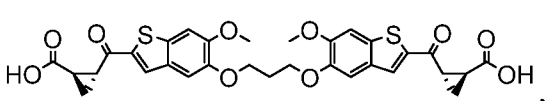
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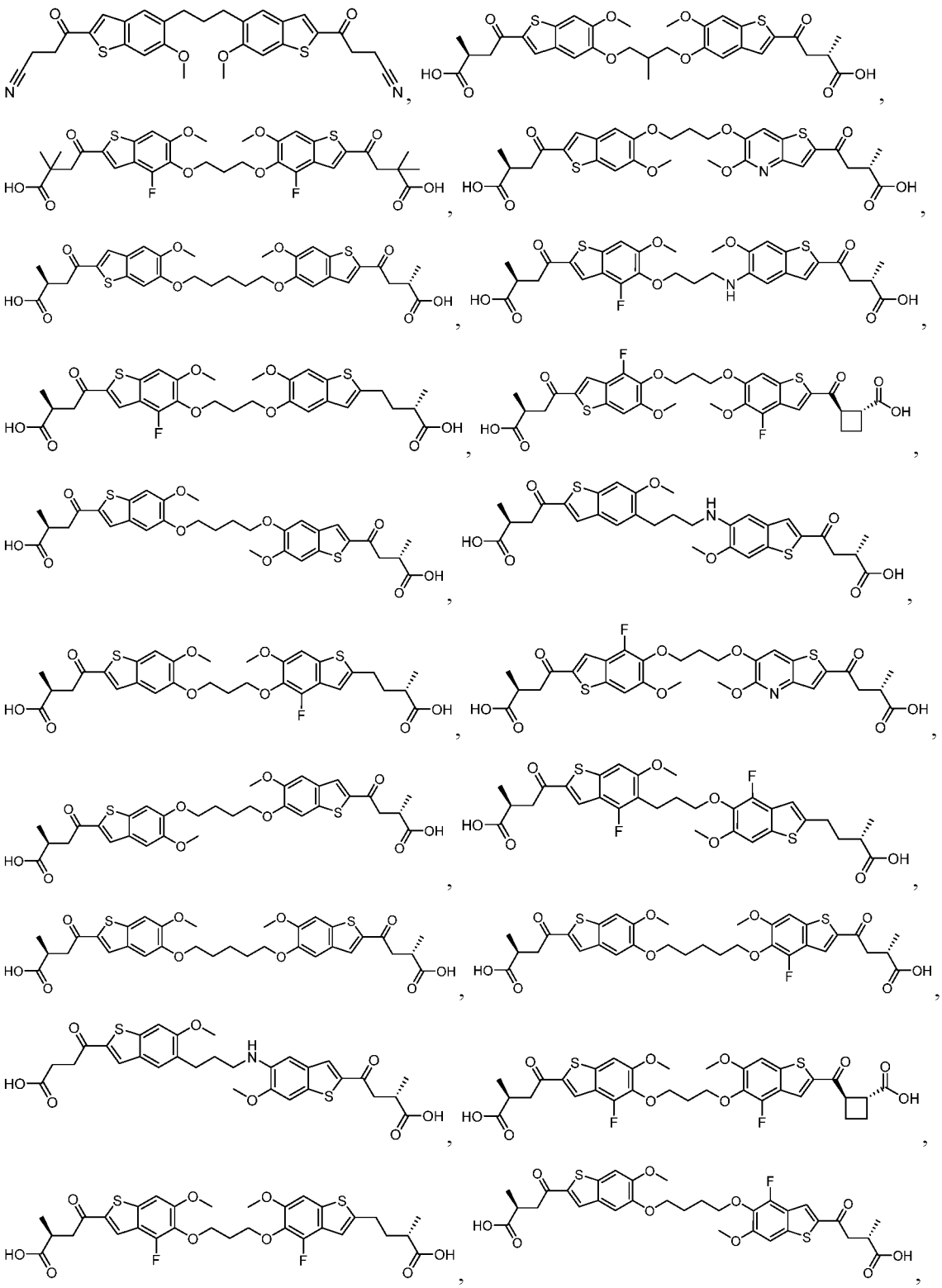

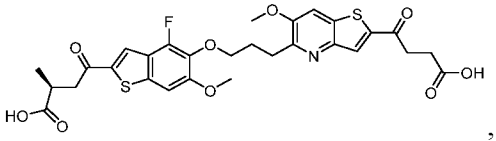
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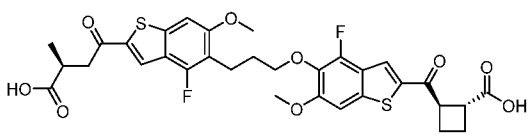
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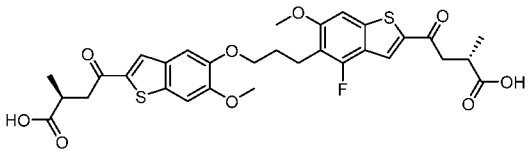
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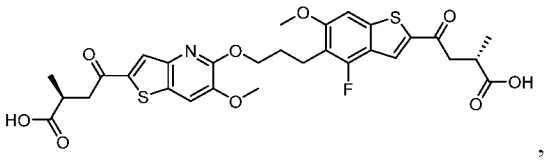
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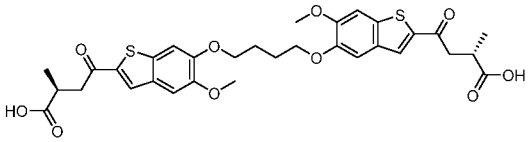
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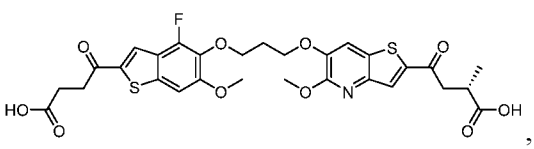
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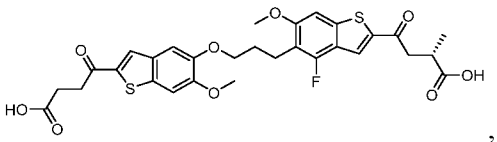
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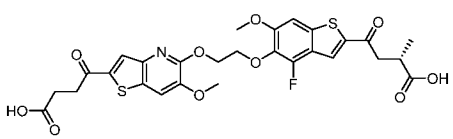
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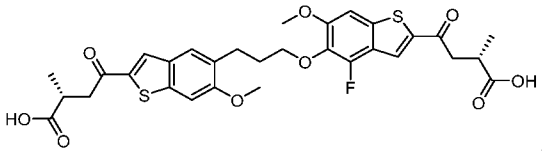
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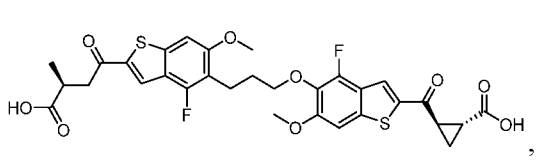
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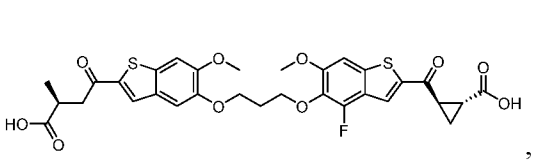
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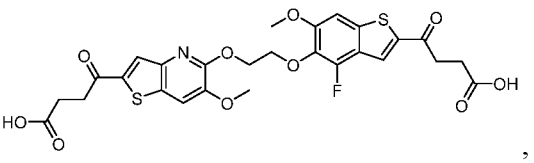
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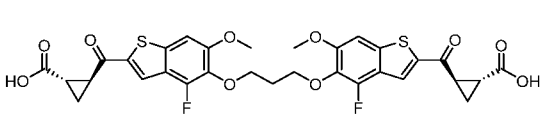
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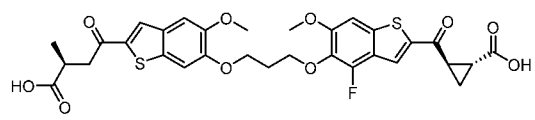
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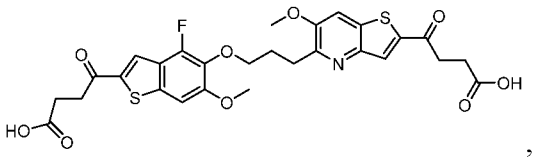
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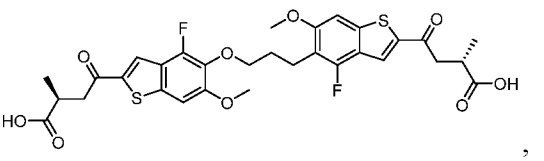
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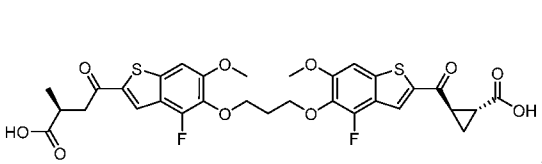
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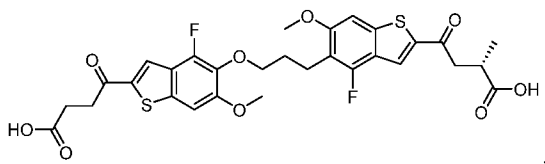
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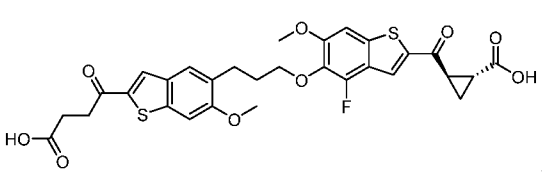
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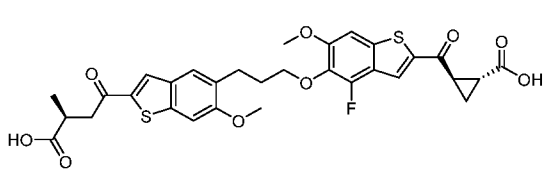
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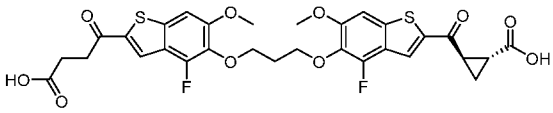
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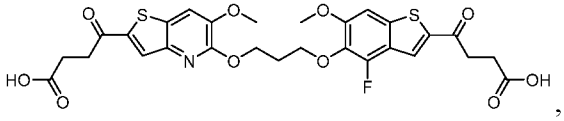
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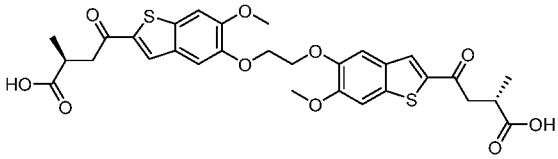
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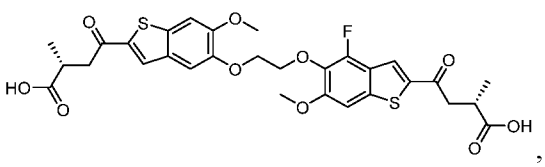
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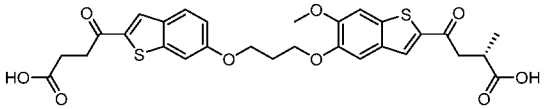
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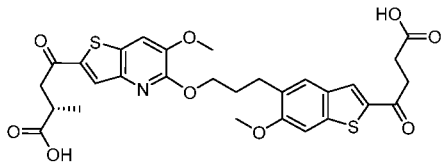
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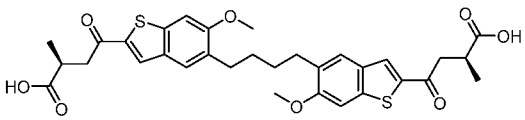
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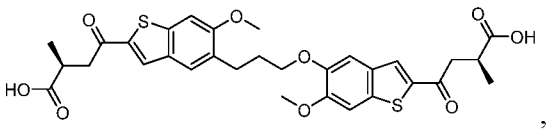
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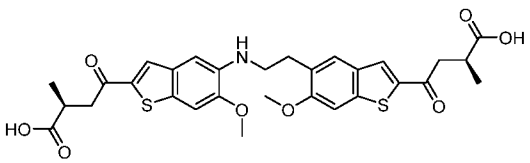
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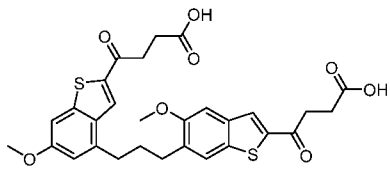
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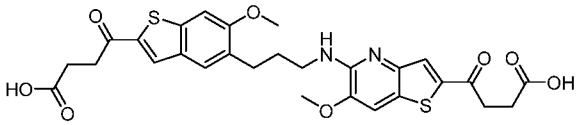
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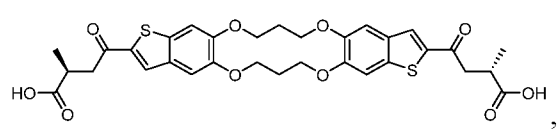
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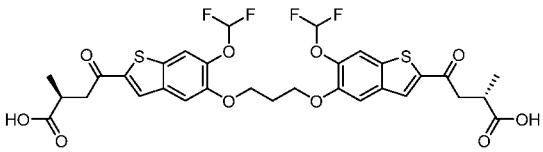
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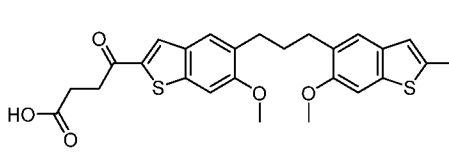
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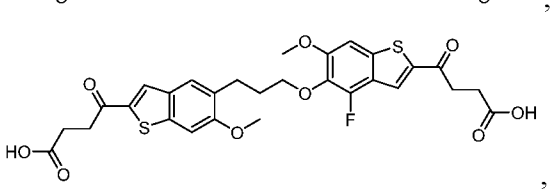
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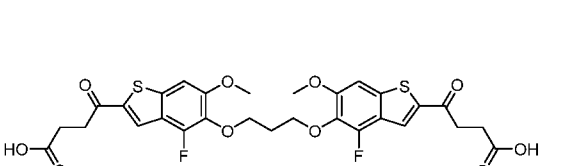
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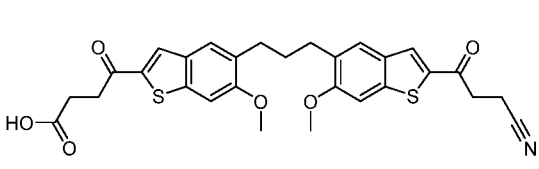
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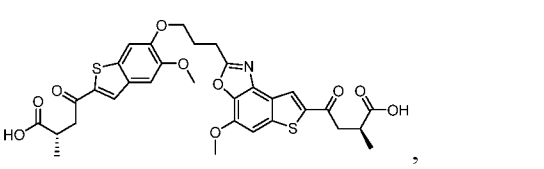
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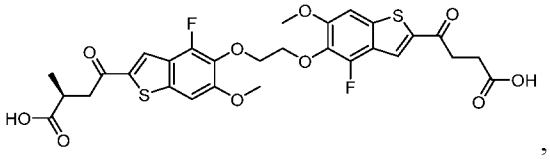
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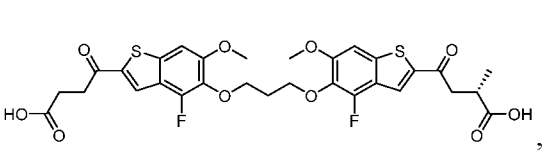
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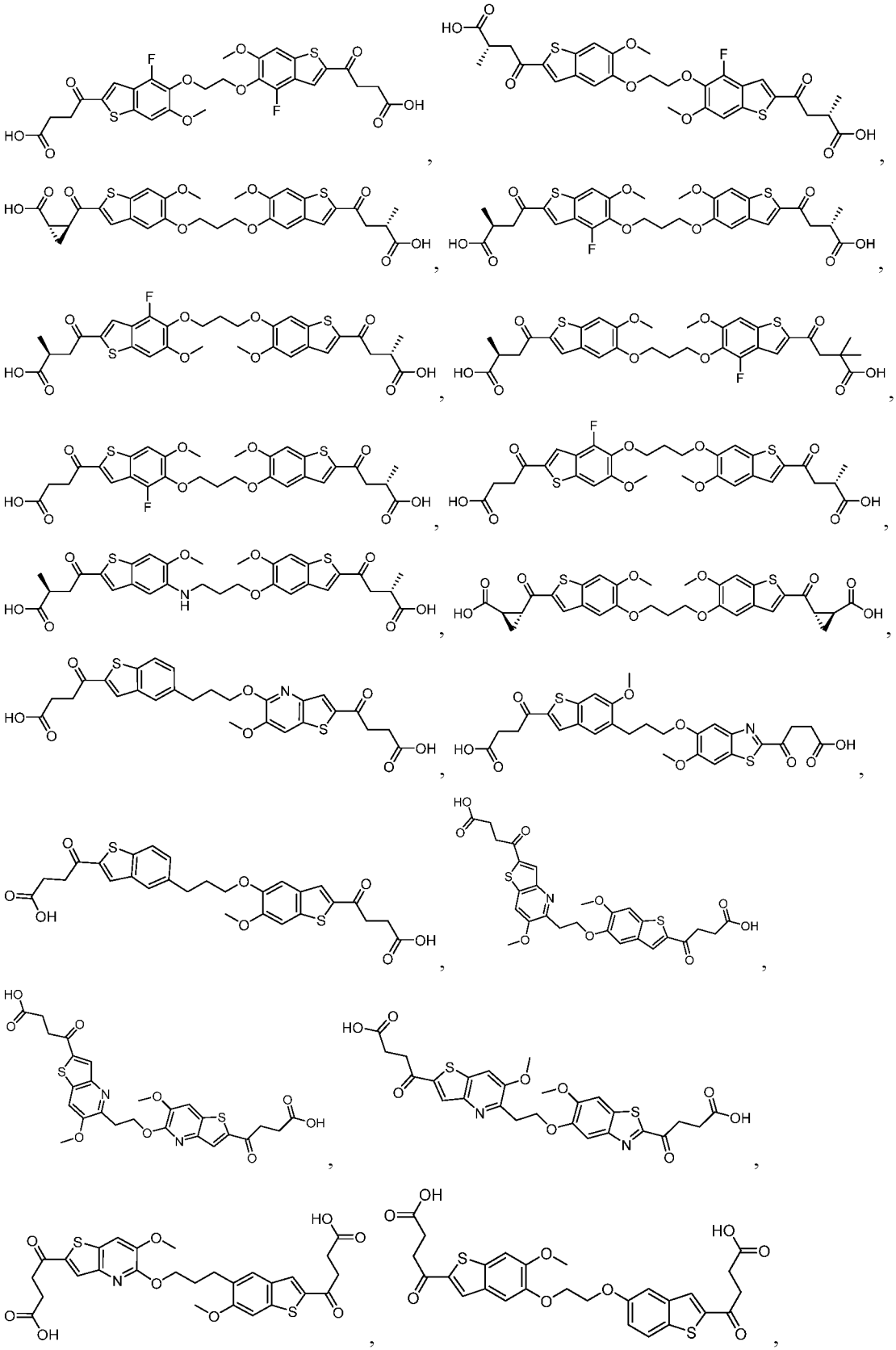

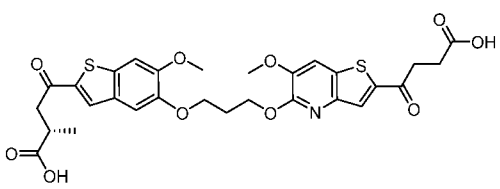
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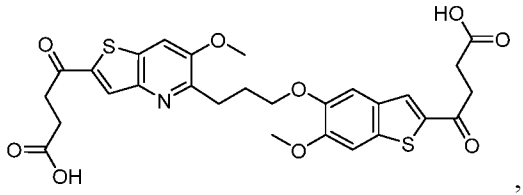
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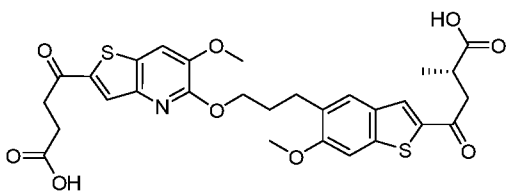
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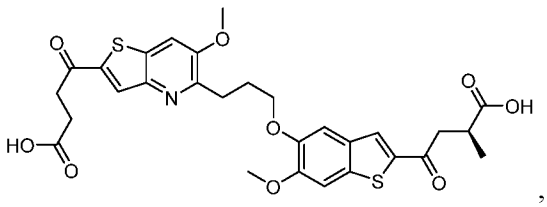
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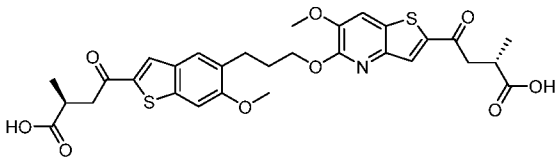
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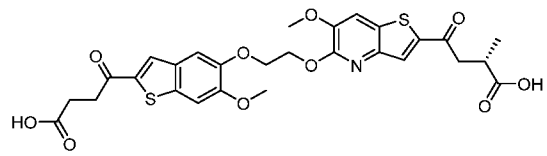
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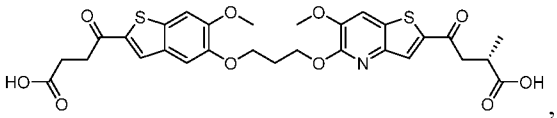
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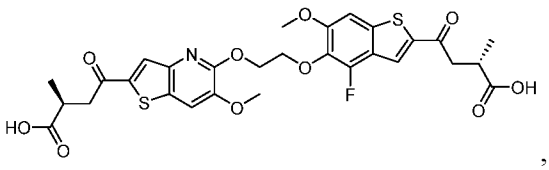
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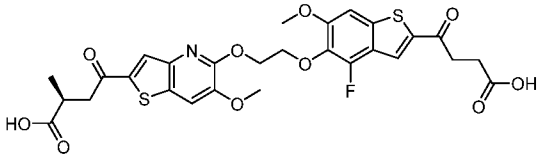
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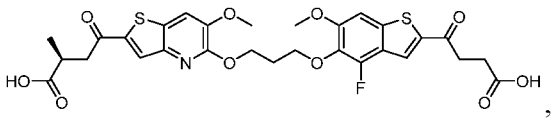
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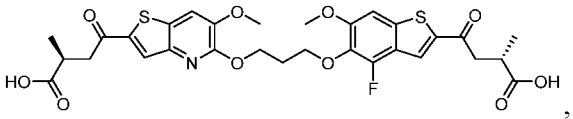
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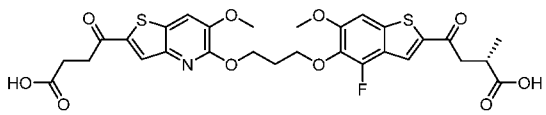
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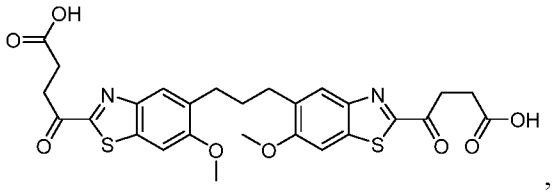
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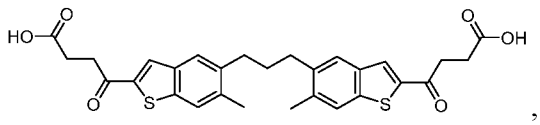
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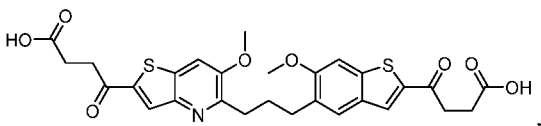
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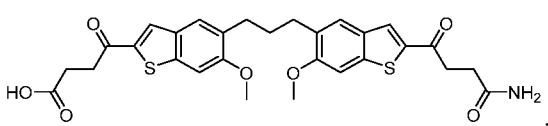
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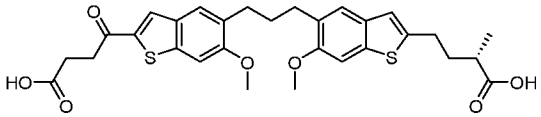
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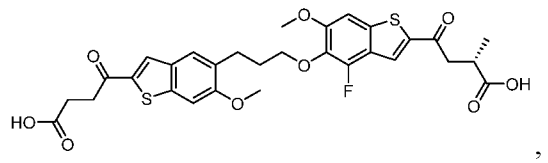
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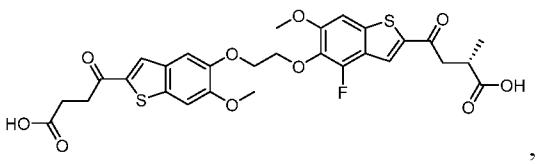
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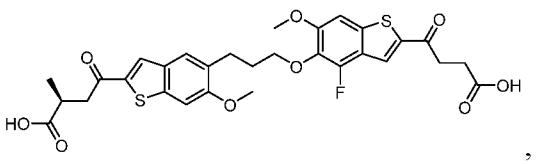
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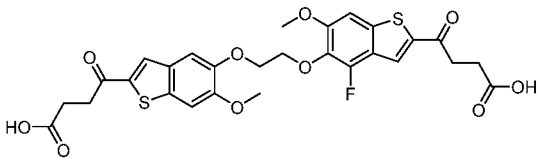
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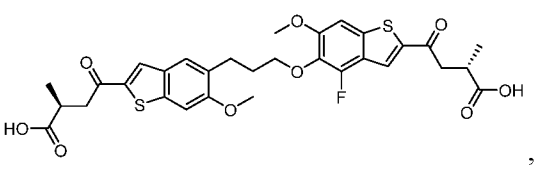
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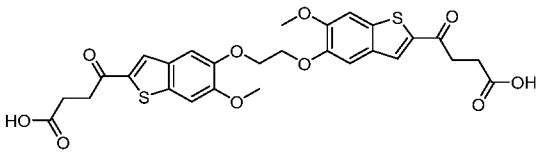
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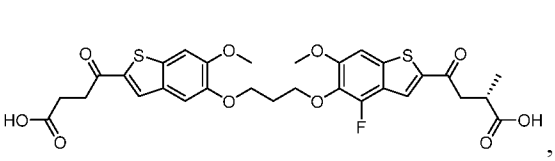
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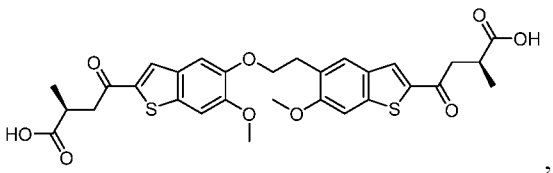
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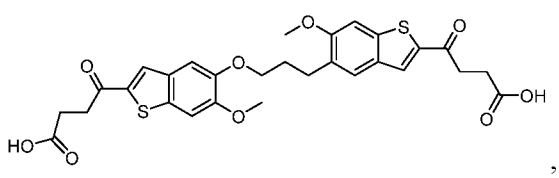
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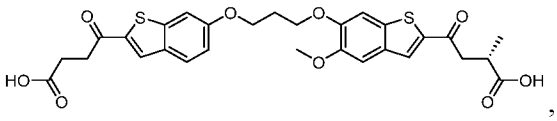
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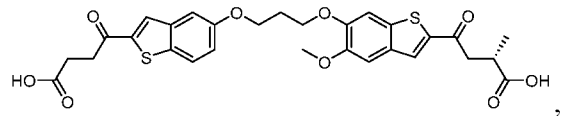
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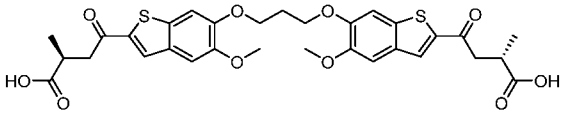
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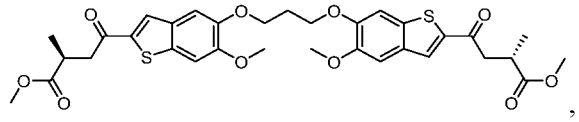
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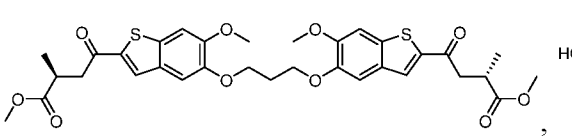
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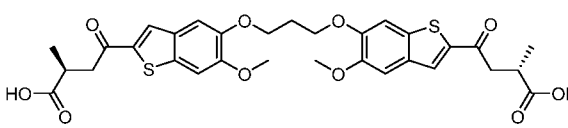
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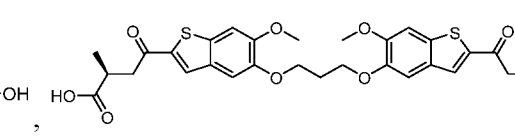
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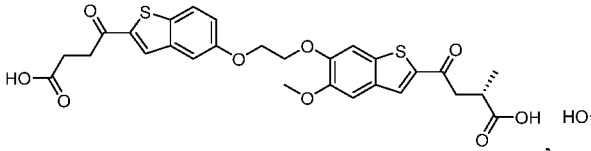
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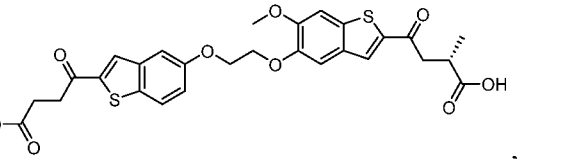
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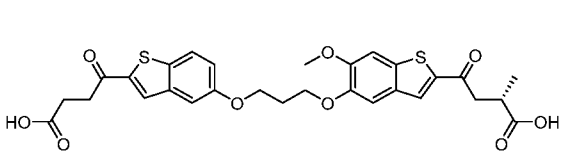
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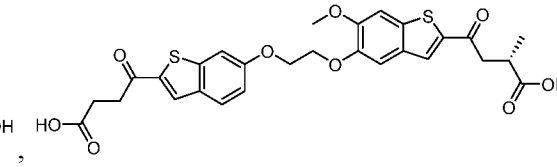
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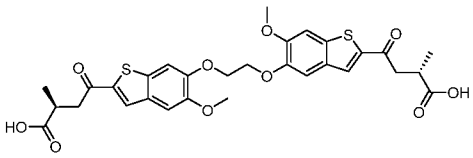
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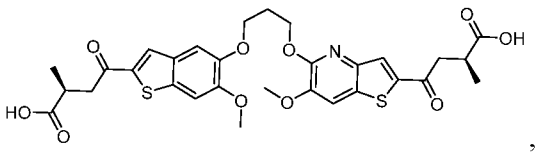
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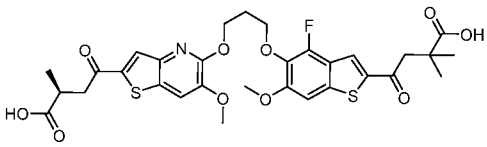
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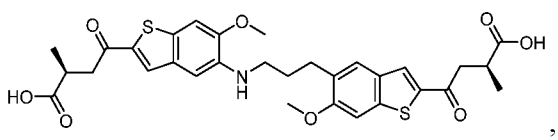
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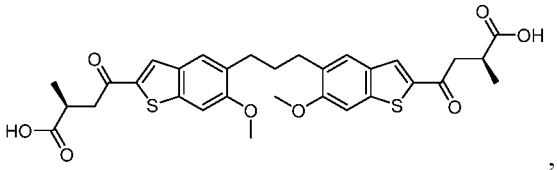
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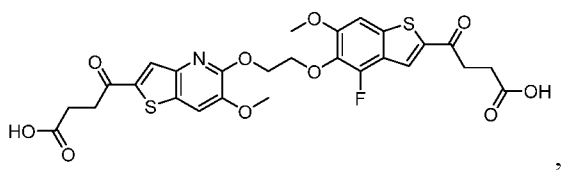
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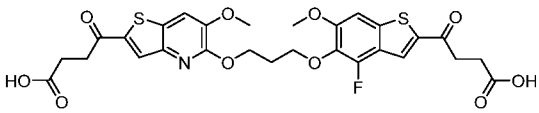
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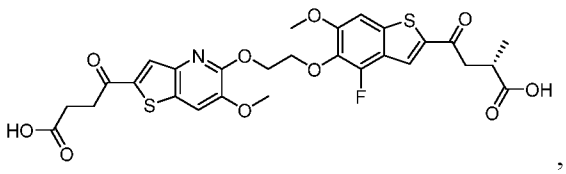
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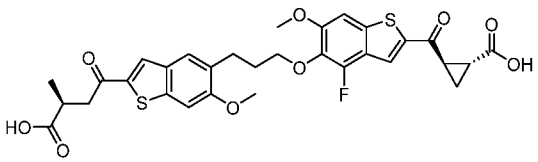
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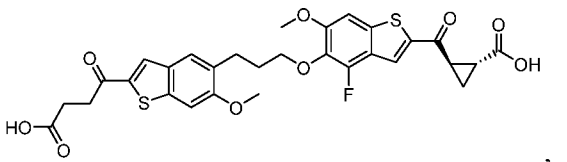
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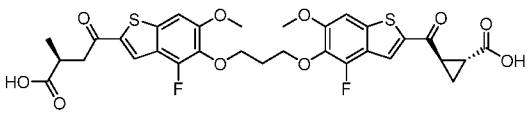
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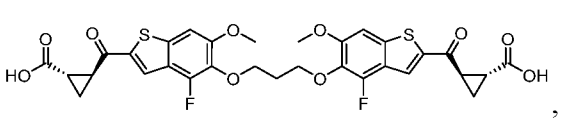
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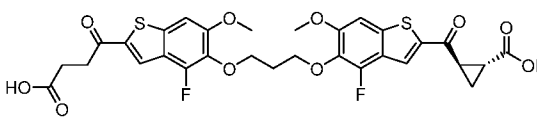
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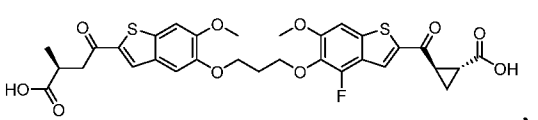
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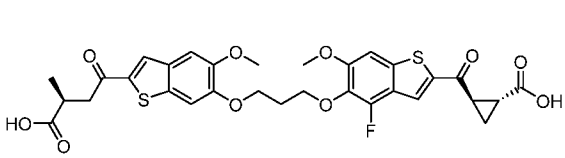
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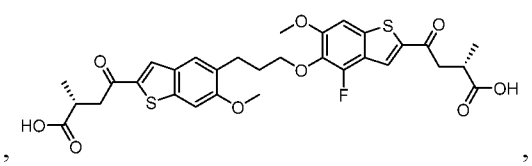
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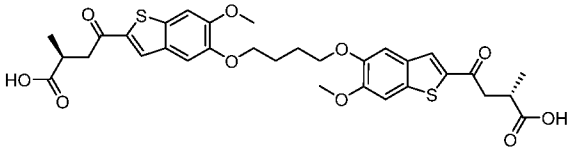
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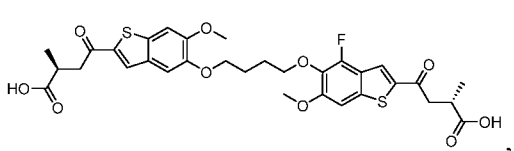
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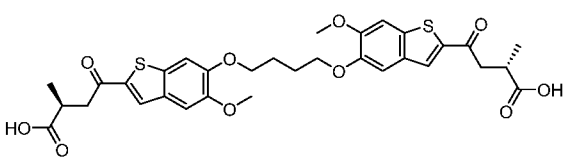
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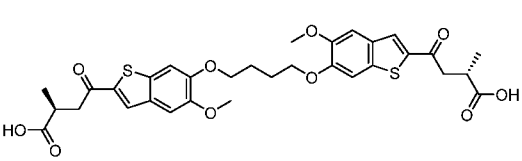
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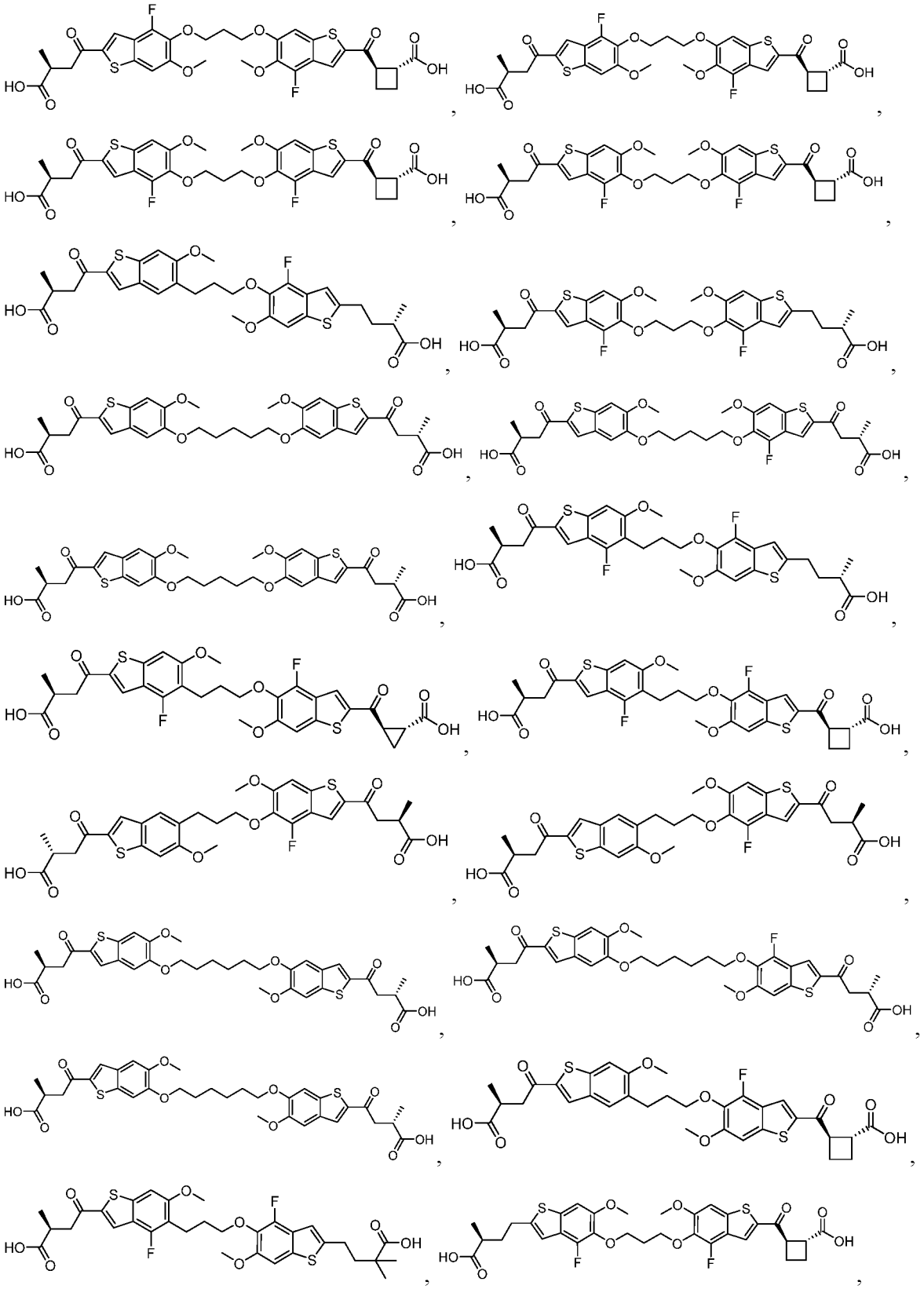

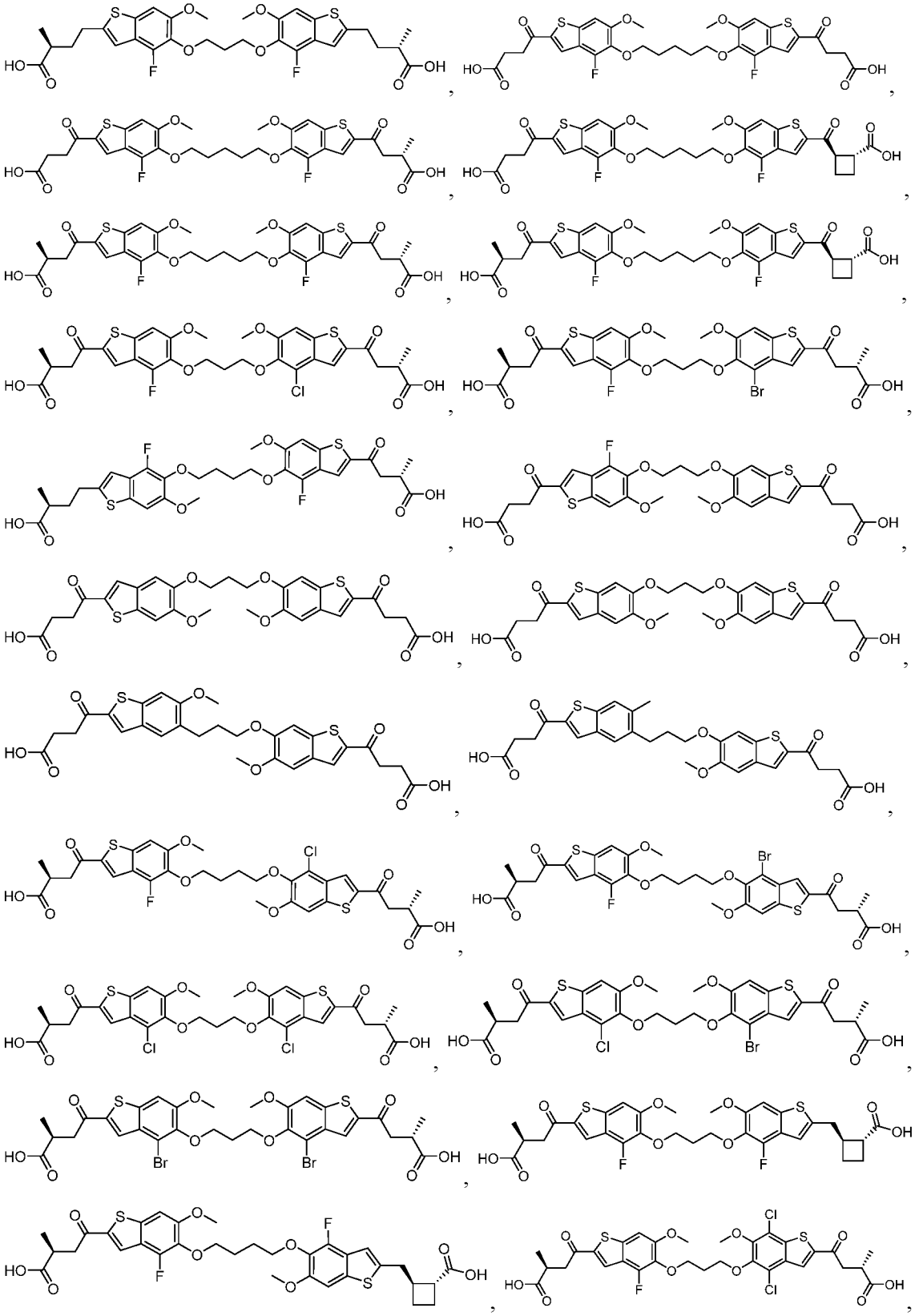

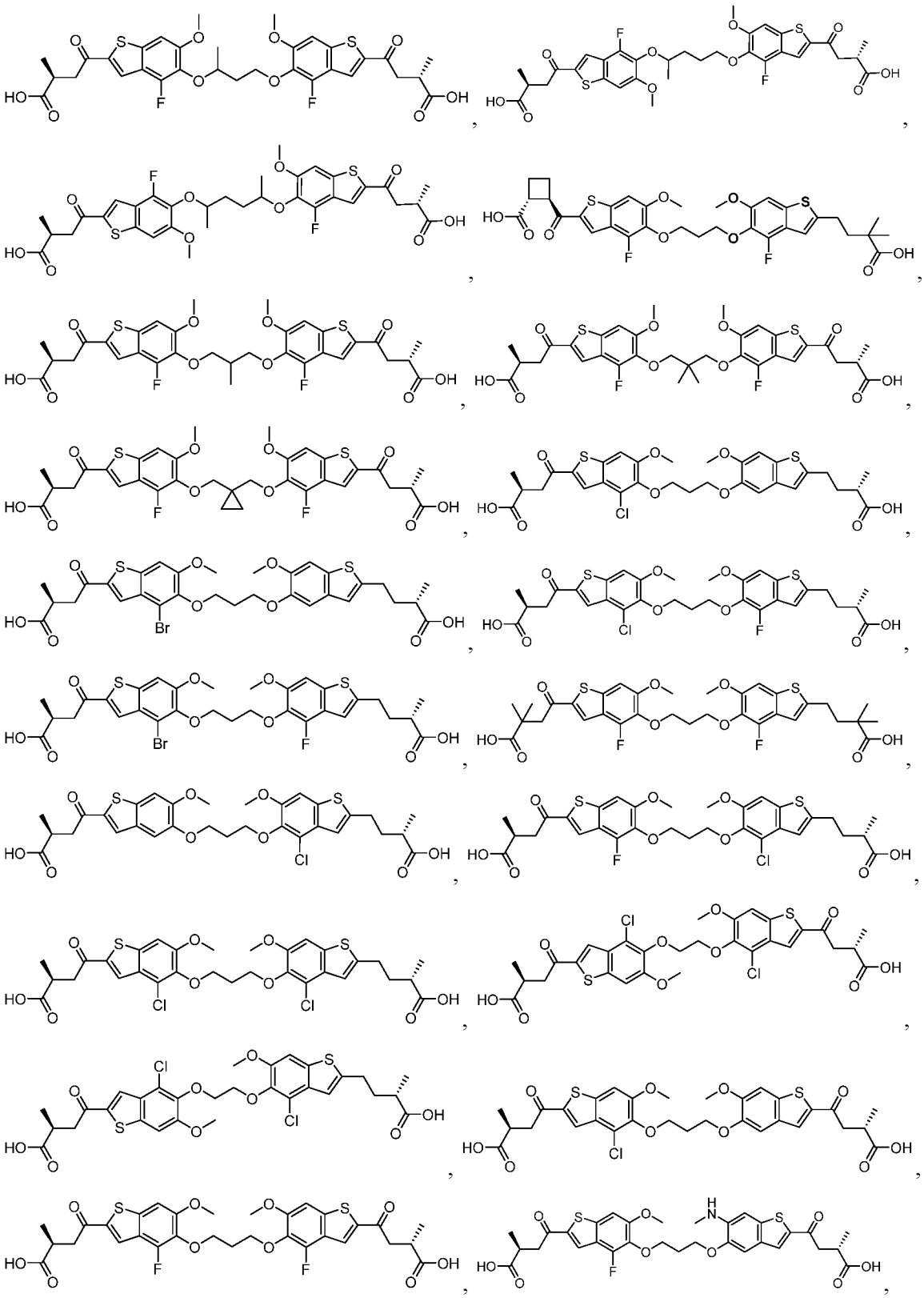

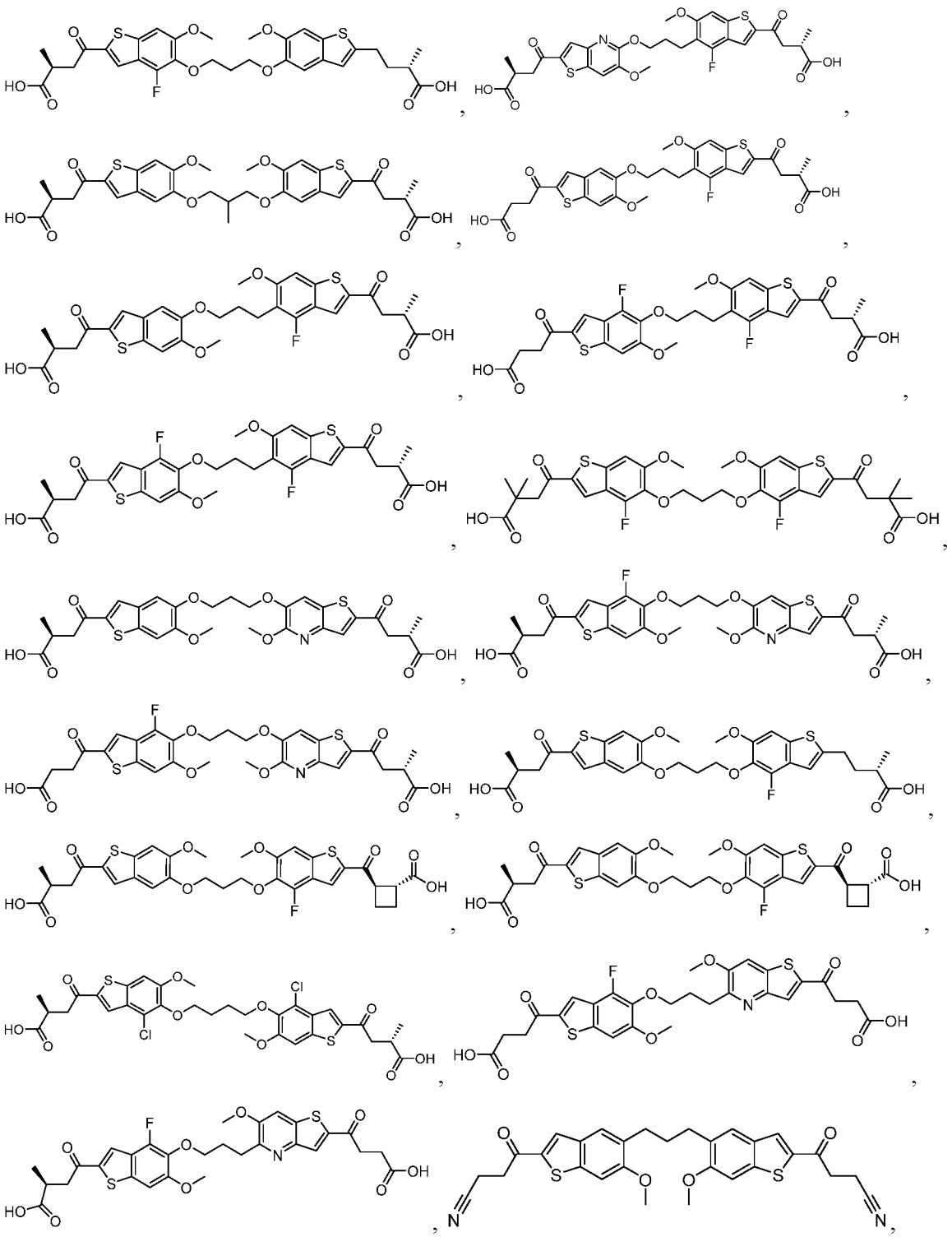

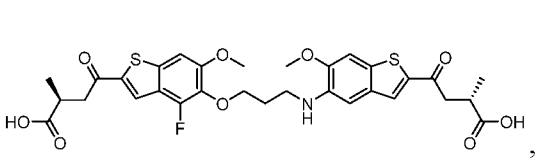
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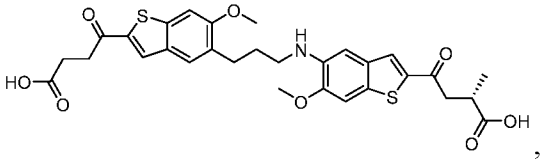
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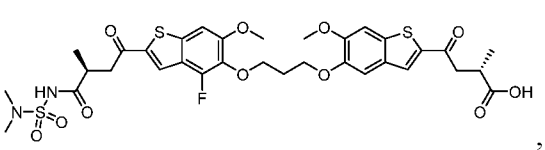
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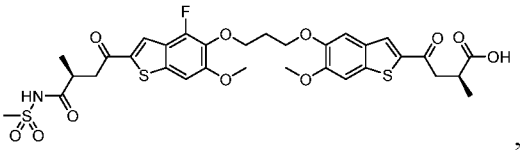
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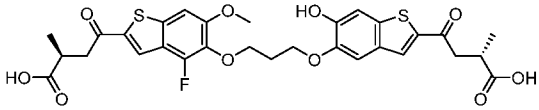
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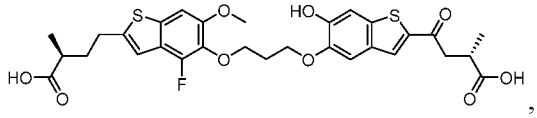
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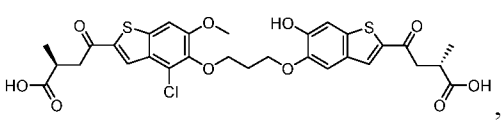
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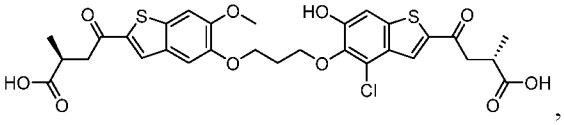
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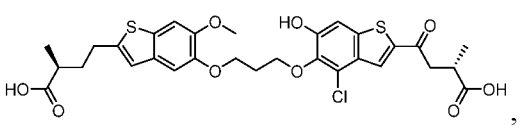
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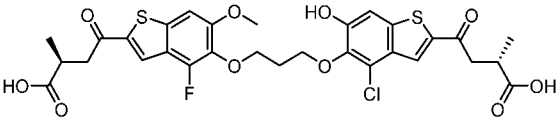
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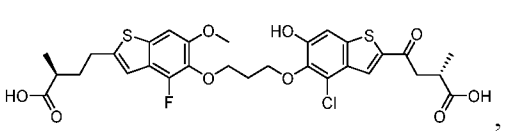
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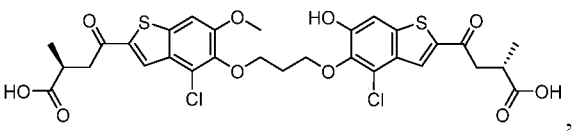
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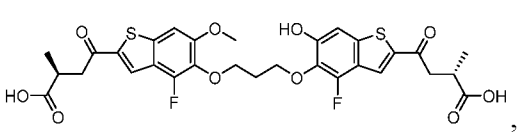
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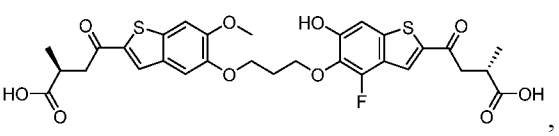
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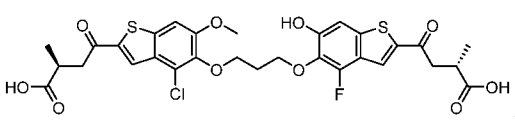
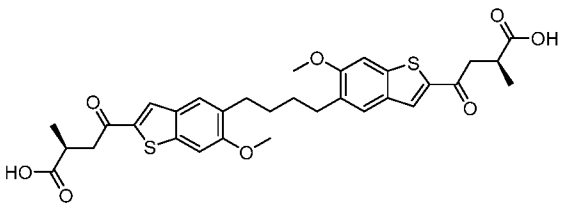

, and pharmaceutically acceptable salts thereof.

Particular aspects of this seventh embodiment relate to a compound selected from the group consisting of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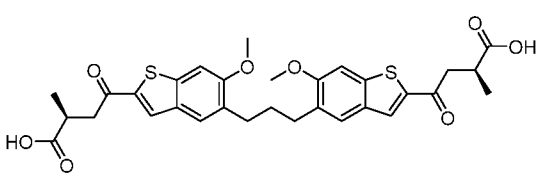
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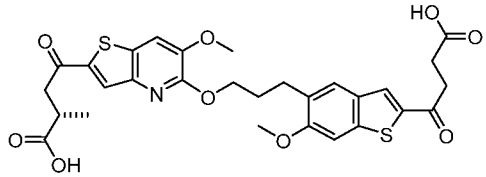
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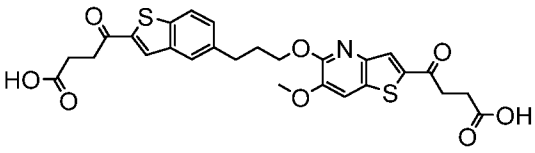
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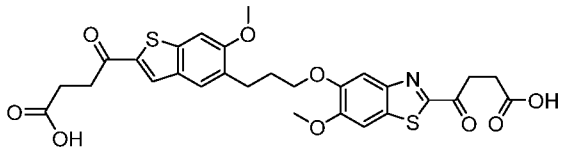
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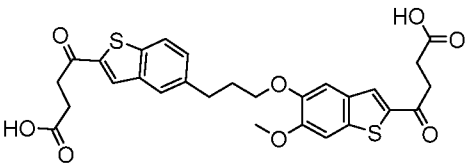
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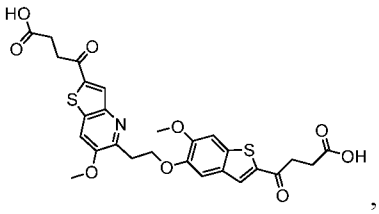
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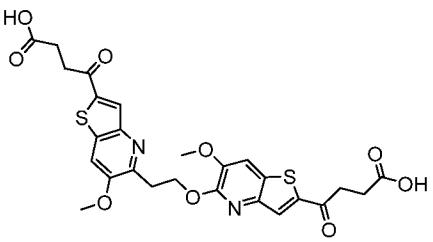
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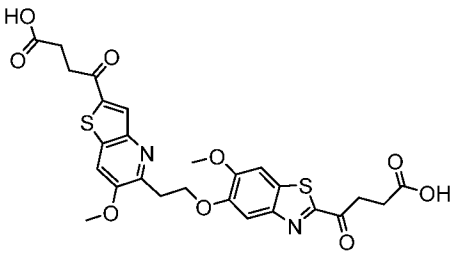
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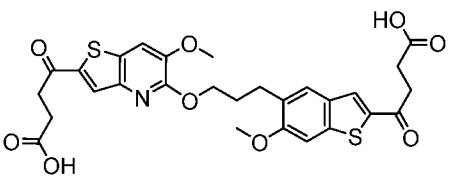
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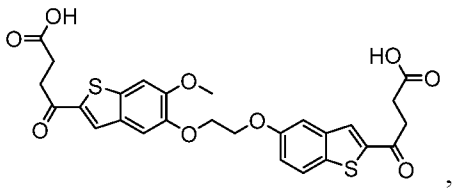
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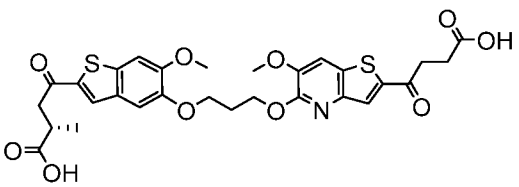
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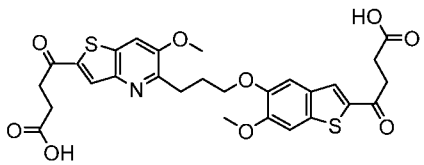
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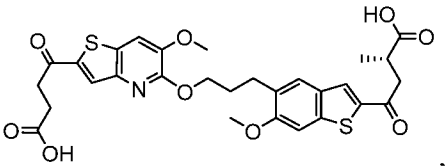
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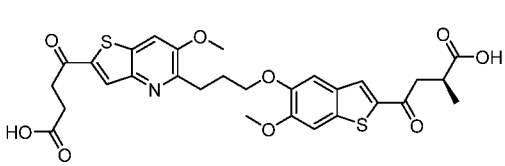
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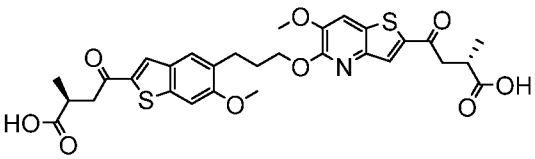
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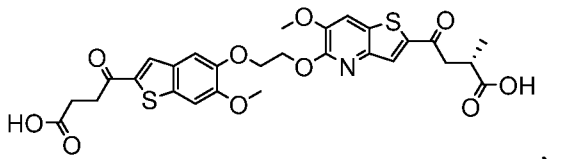
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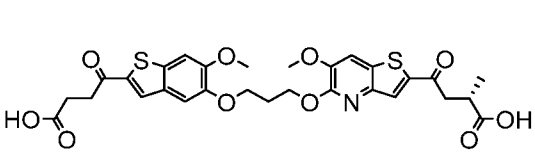
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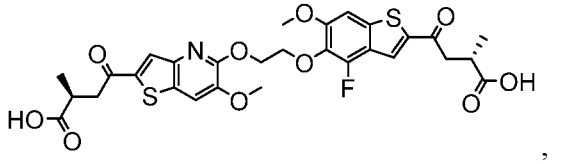
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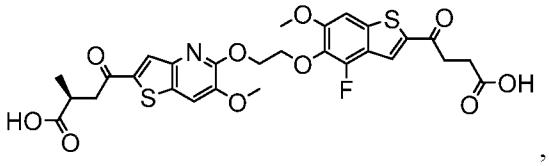
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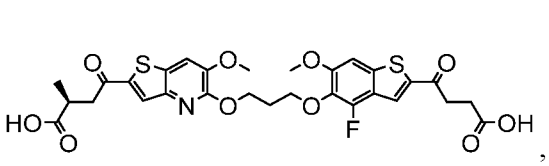
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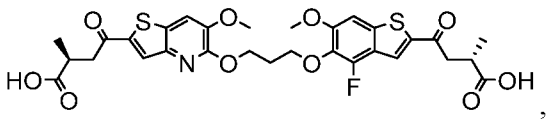
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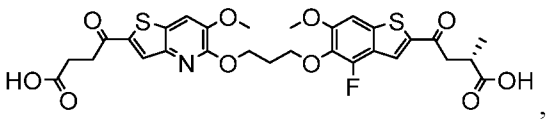
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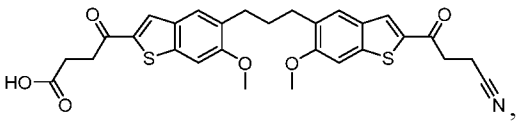
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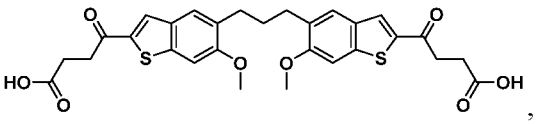
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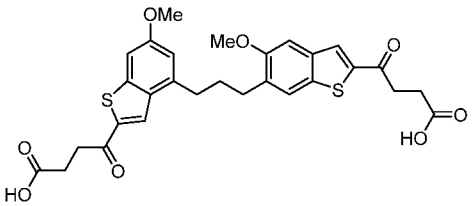
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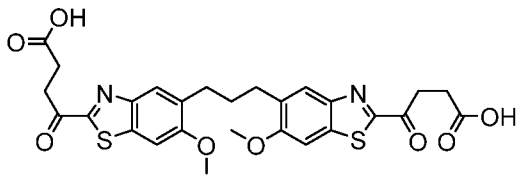
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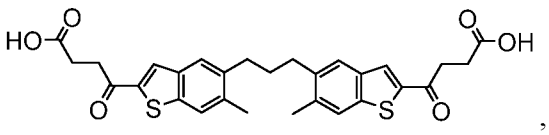
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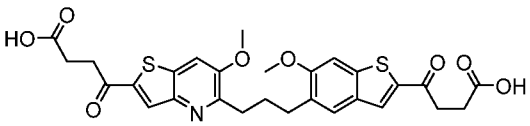
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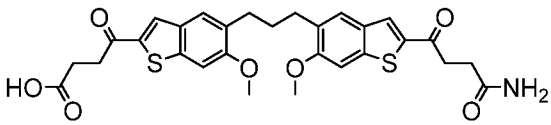
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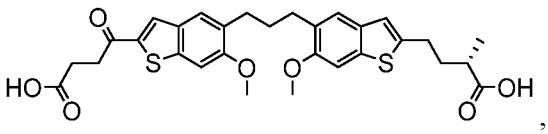
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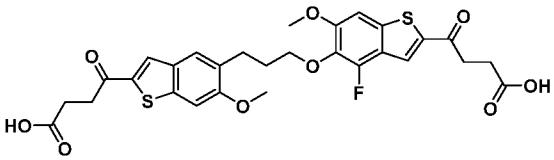
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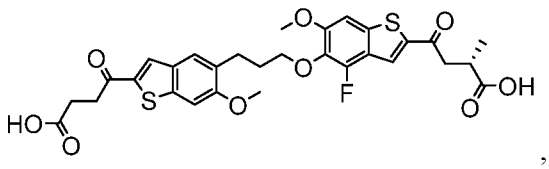
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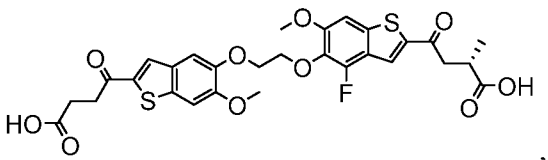
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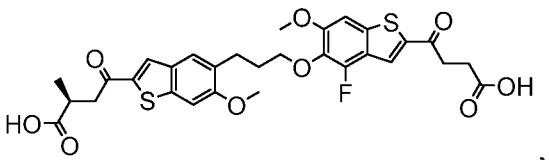
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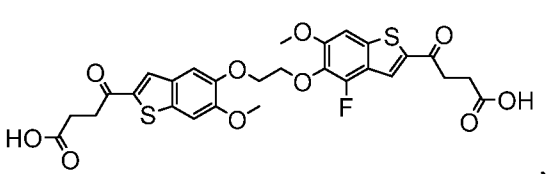
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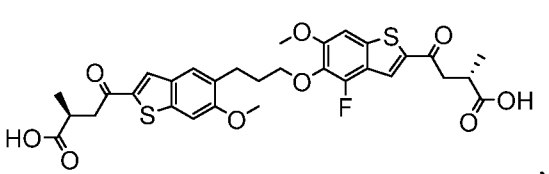
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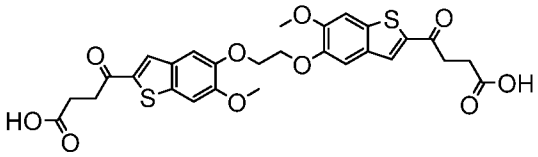
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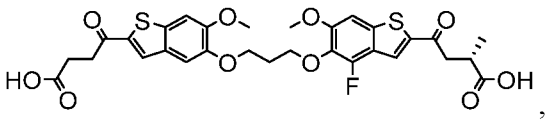
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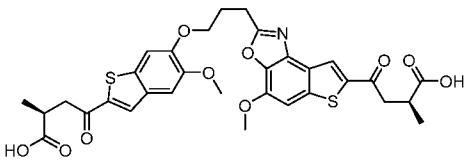
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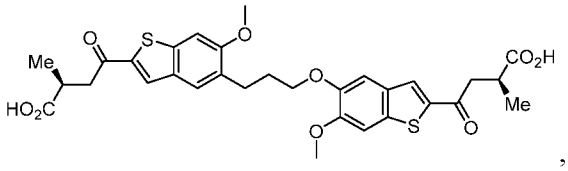
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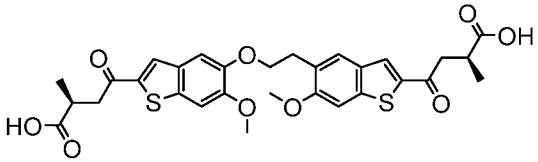
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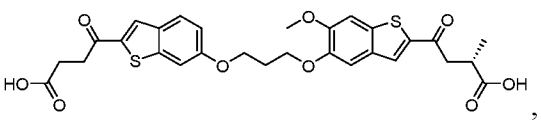
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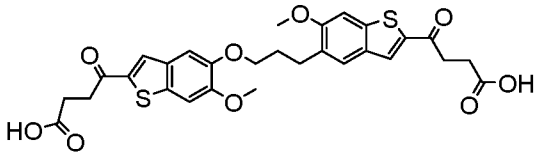
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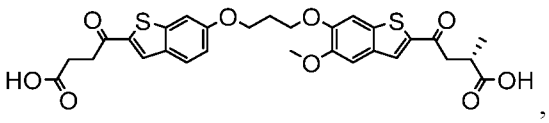
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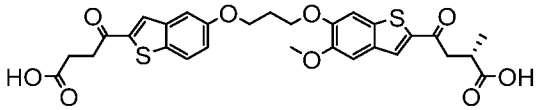
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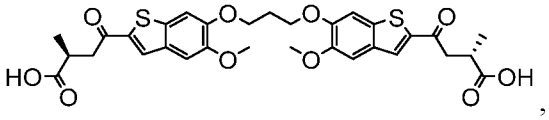
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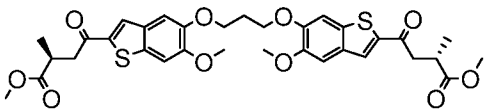
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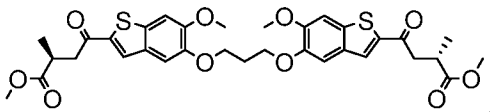
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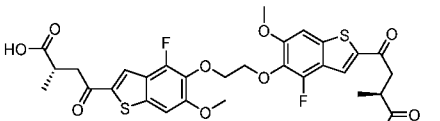
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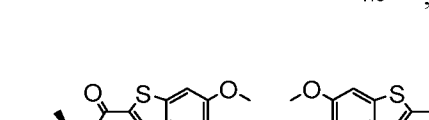
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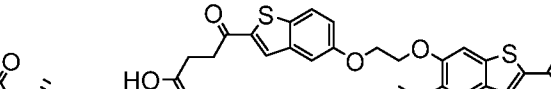
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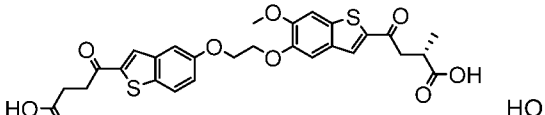
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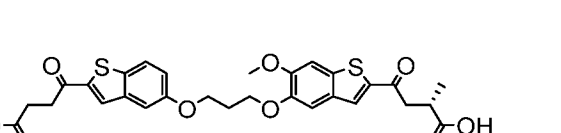
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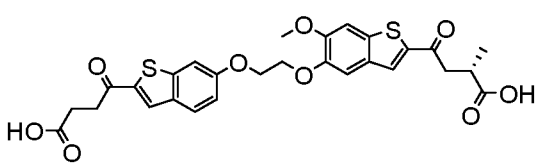
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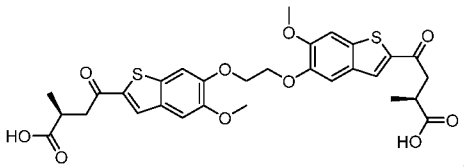
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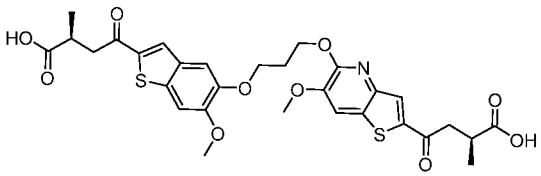
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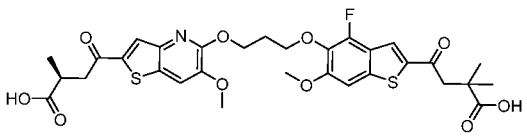
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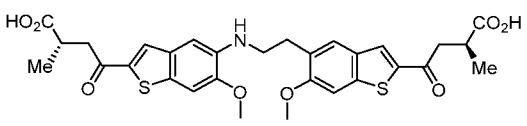
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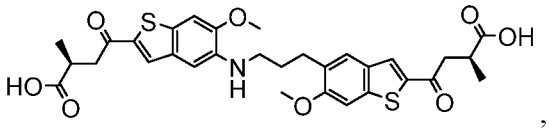
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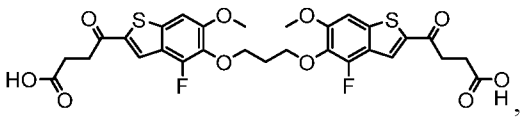
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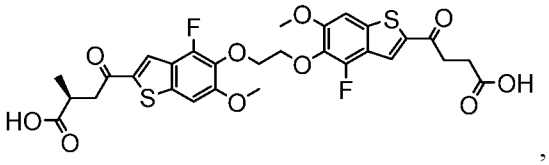
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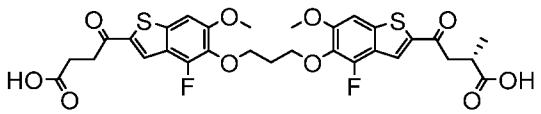
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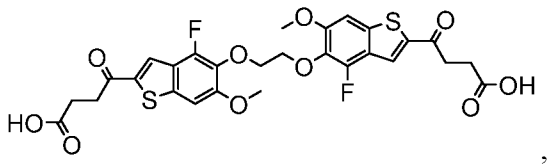
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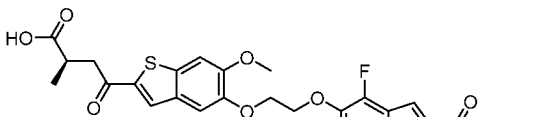
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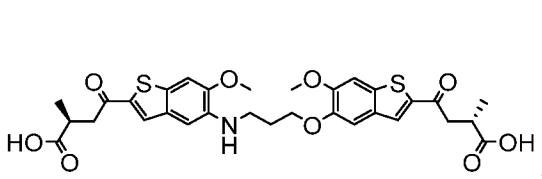
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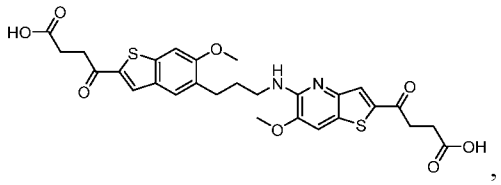
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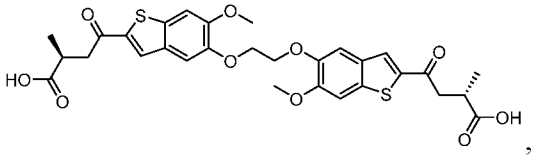
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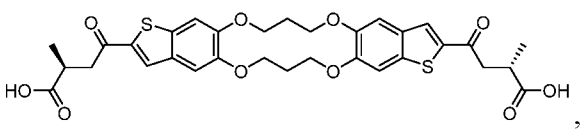
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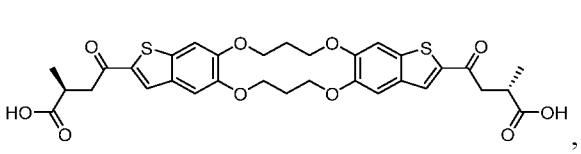
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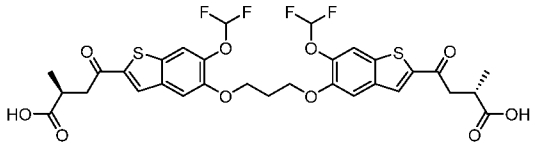
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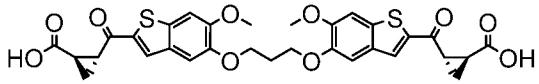

, and pharmaceutically acceptable salts thereof.

A first aspect of the seventh embodiment relates to methods of inducing an immune response in a patient in need of therapy, comprising administering a therapeutically effective amount of a compound according to the seventh embodiment above or a pharmaceutically acceptable salt thereof to the patient.

A second aspect of the seventh embodiment relates to methods of inducing an immune response in a patient in need of therapy, comprising administering a therapeutically effective amount of a composition comprising a compound according to the seventh embodiment above or a pharmaceutically acceptable salt thereof to the patient.

A third aspect of the seventh embodiment relates to methods of inducing STING-dependent type I interferon production in a patient in need of therapy, comprising administering a therapeutically effective amount of a compound according to the seventh embodiment above or a pharmaceutically acceptable salt thereof to the patient.

A fourth aspect of the seventh embodiment relates to methods of inducing STING-dependent type I interferon production in a patient in need of therapy, comprising administering a therapeutically effective amount of a composition comprising a compound according to the seventh embodiment above or a pharmaceutically acceptable salt thereof to the patient.

A fifth aspect of the seventh embodiment relates to methods of inducing STING-dependent cytokine production in a patient in need of therapy, comprising administering a therapeutically effective amount of a compound according to the seventh embodiment above or a pharmaceutically acceptable salt thereof to the patient.

A sixth aspect of the seventh embodiment relates to methods of inducing a STING-dependent cytokine production in a patient in need of therapy, comprising administering a therapeutically effective amount of a composition comprising a compound according to the seventh embodiment above or a pharmaceutically acceptable salt thereof to the patient.

A seventh aspect of the seventh embodiment relates to methods of treating a cell proliferation disorder in a patient in need of therapy, comprising administering a therapeutically effective amount of a compound according to the seventh embodiment above or a pharmaceutically acceptable salt thereof to the patient. In instances of the seventh aspect of the seventh embodiment, the cell proliferation disorder is cancer.

An eighth aspect of the seventh embodiment relates to methods of treating a cell proliferation disorder in a patient in need of therapy, said method comprising administering a therapeutically effective amount of a composition comprising a compound according to the seventh embodiment above to the patient. In instances of this eighth aspect of the seventh embodiment, the cell proliferation disorder is cancer.

An eighth embodiment relates to a compound selected from the exemplary species depicted in Examples 1 through 190 shown below.

A first aspect of the eighth embodiment relates to methods of inducing an immune response in a patient in need of therapy, comprising administering a therapeutically effective amount of a compound according to the eighth embodiment above or a pharmaceutically acceptable salt thereof to the patient.

A second aspect of the eighth embodiment relates to methods of inducing an immune response in a patient in need of therapy, comprising administering a therapeutically effective amount of a composition comprising a compound according to the eighth embodiment above or a pharmaceutically acceptable salt thereof to the patient.

A third aspect of the eighth embodiment relates to methods of inducing STING-dependent type I interferon production in a patient in need of therapy, comprising administering a therapeutically effective amount of a compound according to the eighth embodiment above or a pharmaceutically acceptable salt thereof to the patient.

A fourth aspect of the eighth embodiment relates to methods of inducing STING-dependent type I interferon production in a patient in need of therapy, comprising administering a therapeutically effective amount of a composition comprising a compound according to the eighth embodiment above or a pharmaceutically acceptable salt thereof to the patient.

A fifth aspect of the eighth embodiment relates to methods of inducing STING-dependent cytokine production in a patient in need of therapy, comprising administering a therapeutically effective amount of a compound according to the eighth embodiment above or a pharmaceutically acceptable salt thereof to the patient.

A sixth aspect of the eighth embodiment relates to methods of inducing STING-dependent cytokine production in a patient in need of therapy, comprising administering a therapeutically effective amount of a composition comprising a compound according to the eighth embodiment above or a pharmaceutically acceptable salt thereof to the patient.

A seventh aspect of the eighth embodiment relates to methods of treating a cell proliferation disorder in a patient in need of therapy, comprising administering a therapeutically effective amount of a compound according to the eighth embodiment above or a pharmaceutically acceptable salt thereof to the patient. In instances of the seventh aspect of the eighth embodiment, the cell proliferation disorder is cancer.

An eighth aspect of the eighth embodiment relates to methods of treating a cell proliferation disorder in a patient in need of therapy, said method comprising administering a therapeutically effective amount of a composition comprising a compound according to the eighth embodiment above to the patient. In instances of this eighth aspect of the eighth embodiment, the cell proliferation disorder is cancer.

Other embodiments of the present disclosure include the following:

(a) A pharmaceutical composition comprising an effective amount of a compound of general formula (I), compound of general formula (II), compound of general formula (III), compound of general formula (IV), compound of general formula (V), compound of general formula (VI), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

(b) The pharmaceutical composition of (a), further comprising 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.

(c) A pharmaceutical combination that is (i) a compound of general formula (I), compound of general formula (II), compound of general formula (III), compound of general formula (IV), compound of general formula (V), compound of general formula (VI), 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 (I), compound of general formula (II), compound of general formula (III), compound of general formula (IV), compound of general formula (V), compound of general formula (VI), 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.

(d) A method of inducing an immune response in a patient, which comprises administering to the patient in need of therapy a therapeutically effective amount of a compound of general formula (I), compound of general formula (II), compound of general formula (III), compound of general formula (IV), compound of general formula (V), compound of general formula (VI), or a pharmaceutically acceptable salt thereof.

(e) A method of inducing an immune response in a patient, which comprises administering to the patient in need of therapy a therapeutically effective amount of a composition of (a), a composition of (b), or a combination of (c).

(f) A method of inducing STING-dependent type I interferon production in a patient, which comprises administering to the patient in need of therapy a therapeutically effective amount of a compound of general formula (I), compound of general formula (II), compound of general formula (III), compound of general formula (IV), compound of general formula (V), compound of general formula (VI), or a pharmaceutically acceptable salt thereof.

A method of inducing STING-dependent type I interferon production in a patient, which comprises administering to the patient in need of therapy a therapeutically effective amount of a composition of (a), a composition of (b), or a combination of (c).

(h) A method of inducing STING-dependent cytokine production in a patient, which comprises administering to the patient in need of therapy a therapeutically effective amount of a compound of general formula (I), compound of general formula (II), compound of general formula (III), compound of general formula (IV), compound of general formula (V), compound of general formula (VI), or a pharmaceutically acceptable salt thereof.

(i) A method of inducing STING-dependent cytokine production in a patient, which comprises administering to the patient in need of therapy a therapeutically effective amount of a composition of (a), a composition of (b), or a combination of (c).

(j) A method of treating a cell proliferation disorder in a patient in need of therapy, said method comprising administering a therapeutically effective amount of a compound of general formula (I), compound of general formula (II), compound of general formula (III), compound of general formula (IV), compound of general formula (V), compound of general formula (VI), or a pharmaceutically acceptable salt thereof to the patient;

(k) The method of (j), wherein the cell proliferation disorder is cancer.

(l) A method of treating a cell proliferation disorder in a patient in need of therapy, said method comprising administering a therapeutically effective amount of a composition of (a), a composition of (b), or a combination of (c) to the patient.

(m) The method of (l), wherein the cell proliferation disorder is cancer.

The present disclosure also includes a compound of the present disclosure for use (i) in, (ii) as a medicament for, or (iii) in the preparation of a medicament for: (a) inducing an immune response in a patient, or (b) inducing STING-dependent cytokine production in a patient. In these uses, the compounds of the present disclosure can optionally be employed in combination with one or more active agents selected from STING agonist compounds, anti-viral compounds, antigens, adjuvants, CTLA-4 and PD-1 pathway antagonists and other immunomodulatory agents, lipids, liposomes, peptides, anti-cancer agents, and chemotherapeutic agents.

Additional embodiments of the disclosure include the pharmaceutical compositions, combinations, and methods set forth in (a) through (m) above, and the uses set forth in the preceding paragraph, wherein the compound of the present disclosure employed therein is a compound of one of the embodiments, aspects, instances, occurrences, or features of the compounds described above. In all of these embodiments, the compound may optionally be used in the form of a pharmaceutically acceptable salt, as appropriate.

In the embodiments of the compound provided above, it is to be understood that each embodiment may be combined with one or more other embodiments, to the extent that such a combination provides a stable compound and is consistent with the description of the embodiments. It is further to be understood that the embodiments of compositions and methods provided as (a) through (m) above are understood to include all embodiments of the compounds, including such embodiments as result from combinations of embodiments.

The term "subject" (alternatively "patient") as used herein refers to a mammal that has been the object of treatment, observation, or experiment. The mammal may be male or female. The mammal may be one or more selected from the group consisting of humans, bovine (*e.g.*,

cows), porcine (*e.g.*, pigs), ovine (*e.g.*, sheep), capra (*e.g.*, goats), equine (*e.g.*, horses), canine (*e.g.*, domestic dogs), feline (*e.g.*, house cats), Lagomorpha (rabbits), rodents (*e.g.*, rats or mice), Procyon lotor (*e.g.*, raccoons). In particular embodiments, the subject is human.

As used herein, the term "immune response" relates to any one or more of the following: specific immune response, non-specific immune response, both specific and non-specific response, innate response, primary immune response, adaptive immunity, secondary immune response, memory immune response, immune cell activation, immune cell proliferation, immune cell differentiation, and cytokine expression. In certain embodiments, a compound of general formula (I), compound of general formula (II), compound of general formula (III), compound of general formula (IV), compound of general formula (V), compound of general formula (VI), or a pharmaceutically acceptable salt of the foregoing, is administered in conjunction with one or more additional therapeutic agents including anti-viral compounds, vaccines intended to stimulate an immune response to one or more predetermined antigens, adjuvants, CTLA-4 and PD-1 pathway antagonists and other immunomodulatory agents, lipids, liposomes, peptides, anti-cancer agents, and chemotherapeutic agents, etc. In certain embodiments, a compound of general formula (I), compound of general formula (II), compound of general formula (III), compound of general formula (IV), compound of general formula (V), compound of general formula (VI), or a pharmaceutically acceptable salt of the foregoing, is administered in conjunction with one or more additional compositions including anti-viral compounds, vaccines intended to stimulate an immune response to one or more predetermined antigens, adjuvants, CTLA-4 and PD-1 pathway antagonists and other immunomodulatory agents, lipids, liposomes, peptides, anti-cancer agents, and chemotherapeutic agents, etc.

Compounds

As used herein, the term "alkyl" refers to a monovalent straight or branched chain, saturated aliphatic hydrocarbon radical having a number of carbon atoms in the specified range. Thus, for example, "C_{1-6} alkyl" (or "C_1-C_6 alkyl") refers to any of the hexyl alkyl and pentyl alkyl isomers as well as n-, iso-, sec- and *tert*-butyl, n- and iso-propyl, ethyl, and methyl. As another example, "C_{1-4} alkyl" refers to n-, iso-, sec- and *tert*-butyl, n- and isopropyl, ethyl, and methyl.

As used herein, the term "alkylene" refers to a bivalent straight chain, saturated aliphatic hydrocarbon radical having a number of carbon atoms in the specified range.

As used herein, the term "alkenyl" refers to a monovalent straight or branched chain, unsaturated aliphatic hydrocarbon radical having a number of carbon atoms in the specified range and including one or more double bonds.

As used herein, the term "alkenylene" refers to a bivalent straight chain, unsaturated aliphatic hydrocarbon radical having a number of carbon atoms in the specified range and including one or more double bonds.

As used herein, the term "alkynyl" refers to a monovalent straight or branched chain, unsaturated aliphatic hydrocarbon radical having a number of carbon atoms in the specified range and including one or more triple bonds.

As used herein, the term "alkynylene" refers to a bivalent straight chain, unsaturated aliphatic hydrocarbon radical having a number of carbon atoms in the specified range and including one or more triple bonds.

As used herein, the term "halogen" (or "halo") refers to fluorine, chlorine, bromine, and iodine (alternatively fluoro, chloro, bromo, and iodo or F, Cl, Br, and I).

As used herein, the term "haloalkyl" refers to an alkyl group as defined above in which one or more of the hydrogen atoms have been replaced with a halogen. Thus, for example, "$C_{1\text{-}6}$ haloalkyl" (or "C_1-C_6 haloalkyl") refers to a C_1 to C_6 linear or branched alkyl group as defined above with one or more halogen substituents. The term "fluoroalkyl" has an analogous meaning except the halogen substituents are restricted to fluoro. Suitable fluoroalkyls include the series $(CH_2)_{0\text{-}4}CF_3$ (*i.e.*, trifluoromethyl, 2,2,2-trifluoroethyl, 3,3,3-trifluoro-n-propyl, etc.).

As used herein, the term "haloalkylene" refers to an alkylene group as defined above in which one or more of the hydrogen atoms have been replaced by a halogen, as in the haloalkyl group defined above.

As used herein, the term "haloalkenyl" refers to an alkenyl group as defined above in which one or more of the hydrogen atoms have been replaced with a halogen.

As used herein, the term "haloalkenylene" refers to an alkenylene group as defined above in which one or more of the hydrogen atoms have been replaced by a halogen.

As used herein, the term "haloalkynyl" refers to an alkynyl group as defined above in which one or more of the hydrogen atoms have been replaced with a halogen.

As used herein, the term "haloalkynylene" refers to an alkynylene group as defined above in which one or more of the hydrogen atoms have been replaced by a halogen.

As used herein, the term "alkoxy" as used herein, alone or in combination, includes an alkyl group connected to the oxy connecting atom. The term "alkoxy" also includes alkyl ether groups, where the term "alkyl" is defined above, and "ether" means two alkyl groups with an oxygen atom between them. Examples of suitable alkoxy groups include methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, s-butoxy, t-butoxy, methoxymethane (also referred to as "dimethyl ether"), and methoxyethane (also referred to as "ethyl methyl ether").

As used herein, the term "cycloalkyl" refers to a saturated hydrocarbon containing one ring having a specified number of carbon atoms. Examples of cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

As used herein, the term "heterocycle", "heterocyclyl", or "heterocyclic", as used herein, represents a stable 3- to 6-membered monocyclic that is either saturated or unsaturated, and that consists of carbon atoms and from one to two heteroatoms selected from the group consisting of N, O, and S. The heterocyclic ring may be attached at any heteroatom or carbon atom which results in the creation of a stable structure. The term includes heteroaryl moieties. Examples of such heterocyclic elements include, but are not limited to, azepinyl, benzimidazolyl, benzisoxazolyl, benzofurazanyl, benzopyranyl, benzothiopyranyl, benzofuryl, benzothiazolyl, benzothienyl, benzoxazolyl, chromanyl, cinnolinyl, dihydrobenzofuryl, dihydrobenzothienyl, dihydrobenzothiopyranyl, dihydrobenzothiopyranyl sulfone, 1,3-dioxolanyl, furyl, imidazolidinyl, imidazolinyl, imidazolyl, indolinyl, indolyl, isochromanyl, isoindolinyl, isoquinolinyl, isothiazolidinyl, isothiazolyl, isothiazolidinyl, morpholinyl, naphthyridinyl, oxadiazolyl, 2-oxoazepinyl, oxazolyl, 2-oxopiperazinyl, 2-oxopiperdinyl, 2-oxopyrrolidinyl, piperidyl, piperazinyl, pyridyl, pyrazinyl, pyrazolidinyl, pyrazolyl, pyridazinyl, pyrimidinyl, pyrrolidinyl, pyrrolyl, quinazolinyl, quinolinyl, quinoxalinyl, tetrahydrofuryl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiazolyl, thiazolinyl, thienofuryl, thienothienyl, triazolyl and thienyl.

As used herein, the term "fused ring" refers to a cyclic group formed by substituents on separate atoms in a straight or branched alkane, or to a cyclic group formed by substituents on separate atoms in another ring.

As used herein, the term "spirocycle" or "spirocyclic ring" refers to a pendant cyclic group formed by substituents on a single atom.

Unless expressly stated to the contrary, all ranges cited herein are inclusive; *i.e.*, the range includes the values for the upper and lower limits of the range as well as all values in between.

As an example, temperature ranges, percentages, ranges of equivalents, and the like described herein include the upper and lower limits of the range and any value in the continuum there between. Numerical values provided herein, and the use of the term "about", may include variations of ± 1%, ± 2%, ±3%, ± 4%, ± 5%, ± 10%, ± 15%, and ± 20% and their numerical equivalents.

As used herein, the term "one or more" item includes a single item selected from the list as well as mixtures of two or more items selected from the list.

In the compounds of general formula (I), compounds of general formula (II), compounds of general formula (III), compounds of general formula (IV), compounds of general formula (V), compounds of general formula (VI), and pharmaceutically acceptable salts of the foregoing, the atoms may exhibit their natural isotopic abundances, or one or more of the atoms may be artificially enriched in a particular isotope having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number predominantly found in nature. The present disclosure is meant to include all suitable isotopic variations of the compounds of general formula (I), compounds of general formula (II), compounds of general formula (III), compounds of general formula (IV), compounds of general formula (V), compounds of general formula (VI), and pharmaceutically acceptable salts of the foregoing. For example, different isotopic forms of hydrogen (H) include protium (^{1}H), deuterium (^{2}H), and tritium (^{3}H). Protium is the predominant hydrogen isotope found in nature. Enriching for deuterium may afford certain therapeutic advantages, such as increasing *in vivo* half-life or reducing dosage requirements, or may provide a compound useful as a standard for characterization of biological samples. Isotopically-enriched the compounds of general formula (I), compounds of general formula (II), compounds of general formula (III), compounds of general formula (IV), compounds of general formula (V), compounds of general formula (VI), and pharmaceutically acceptable salts of the foregoing, can be prepared without undue experimentation by conventional techniques well known to those skilled in the art or by processes analogous to those described in the Schemes and Examples herein using appropriate isotopically-enriched reagents and/or intermediates.

In particular embodiments of the compounds of general formula (I), compounds of general formula (II), compounds of general formula (III), compounds of general formula (IV), compounds of general formula (V), compounds of general formula (VI), and pharmaceutically

acceptable salts of the foregoing, the compounds are isotopically enriched with deuterium. In aspects of these embodiments, one or more of R^1, R^2, R^3, R^6, R^8, and R^9 may include deuterium.

As shown in the general structural formulas and the structures of specific compounds as provided herein, a straight line at a chiral center includes both (R) and (S) stereoisomers and mixtures thereof. Also, unless otherwise specified (*e.g.*, 100% purified compound), reference to a particular stereochemistry at a position provides a compound having the indicated stereochemistry but does not exclude the presence of stereoisomers having different stereochemistry at the indicated position.

Recitation or depiction of a specific compound in the claims (*i.e.*, a species) without a specific stereoconfiguration designation, or with such a designation for less than all chiral centers, is intended to encompass, for such undesignated chiral centers, the racemate, racemic mixtures, each individual enantiomer, a diastereoisomeric mixture and each individual diastereomer of the compound where such forms are possible due to the presence of one or more asymmetric centers. The separation of a mixture of stereoisomers can be carried out at an intermediate step during the synthesis of a compound of general formula (I), compound of general formula (II), compound of general formula (III), compound of general formula (IV), compound of general formula (V), compound of general formula (VI), or a pharmaceutically acceptable salt of the foregoing, or it can be done on a final racemic product. Absolute stereochemistry may be determined by X-ray crystallography of crystalline products or crystalline intermediates, which are derivatized, if necessary, with a reagent containing a stereogenic center of known configuration. Alternatively, absolute stereochemistry may be determined by Vibrational Circular Dichroism (VCD) spectroscopy analysis. The present invention includes all such isomers, as well as salts, solvates (including hydrates), and solvated salts of such racemates, enantiomers, diastereomers, tautomers, and mixtures thereof.

The invention includes all possible enantiomers and diastereomers and mixtures of two or more stereoisomers, for example mixtures of enantiomers and/or diastereomers, in all ratios. Thus, enantiomers are a subject of the invention in enantiomerically pure form, both as levorotatory and as dextrorotatory antipodes, in the form of racemates and in the form of mixtures of the two enantiomers in all ratios. In the case of a cis/trans isomerism, the invention includes both the cis form and the trans form, as well as mixtures of these forms in all ratios. The preparation of individual stereoisomers can be carried out, if desired, by separation of a mixture by customary methods, for example by chromatography or crystallization, by the use of

stereochemically uniform starting materials for the synthesis or by stereoselective synthesis. Optionally a derivatization can be carried out before a separation of stereoisomers. The separation of a mixture of stereoisomers can be carried out at an intermediate step during the synthesis of a compound of general formula (I), compound of general formula (II), compound of general formula (III), compound of general formula (IV), compound of general formula (V), compound of general formula (VI), or a pharmaceutically acceptable salt of the foregoing, or it can be done on a final racemic product. Absolute stereochemistry may be determined by X-ray crystallography of crystalline products or crystalline intermediates that are derivatized, if necessary, with a reagent containing a stereogenic center of known configuration. Unless a particular isomer, salt, solvate (including hydrates) or solvated salt of such racemate, enantiomer, or diastereomer is indicated, the present invention includes all such isomers, as well as salts, solvates (including hydrates), and solvated salts of such racemates, enantiomers, diastereomers, and mixtures thereof.

The term "compound" refers to the compound and, in certain embodiments, to the extent they are stable, any hydrate or solvate thereof. A hydrate is the compound complexed with water, and a solvate is the compound complexed with a solvent, which may be an organic solvent or an inorganic solvent.

A "stable" compound is a compound that can be prepared and isolated and whose structure and properties remain or can be caused to remain essentially unchanged for a period of time sufficient to allow use of the compound for the purposes described herein (*e.g.*, therapeutic administration to a patient). The compounds of the present invention are limited to stable compounds embraced by general formula (I), general formula (II), general formula (III), general formula (IV), general formula (V), general formula (VI), or pharmaceutically acceptable salts thereof.

Salts

As indicated above, the compounds of the present invention can be employed in the form of pharmaceutically acceptable salts. Those skilled in the art will recognize those instances in which the compounds of the invention may form salts. Examples of such compounds are described herein by reference to possible salts. Such reference is for illustration only. Pharmaceutically acceptable salts can be used with compounds for treating patients. Non-pharmaceutical salts may, however, be useful in the preparation of intermediate compounds.

The term "pharmaceutically acceptable salt" refers to a salt (including an inner salt such as a zwitterion) that possesses effectiveness similar to the parent compound and that is not biologically or otherwise undesirable (*e.g.*, is neither toxic nor otherwise deleterious to the recipient thereof). Thus, an embodiment of the invention provides pharmaceutically acceptable salts of the compounds of the invention. The term "salt(s)", as employed herein, denotes any of the following: acidic salts formed with inorganic and/or organic acids, as well as basic salts formed with inorganic and/or organic bases. Salts of compounds of the invention may be formed by methods known to those of ordinary skill in the art, for example, by reacting a compound of the invention with an amount of acid or base, such as an equivalent amount, in a medium such as one in which the salt precipitates or in aqueous medium followed by lyophilization.

Exemplary acid addition salts include acetates, ascorbates, benzoates, benzenesulfonates, bisulfates, borates, butyrates, citrates, camphorates, camphorsulfonates, fumarates, hydrochlorides, hydrobromides, hydroiodides, lactates, maleates, methanesulfonates ("mesylates"), naphthalenesulfonates, nitrates, oxalates, phosphates, propionates, salicylates, succinates, sulfates, tartarates, thiocyanates, toluenesulfonates ("tosylates") and the like. Suitable salts include acid addition salts that may, for example, be formed by mixing a solution of a compound with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, sulfuric acid, acetic acid, trifluoroacetic acid, or benzoic acid. Additionally, acids that are generally considered suitable for the formation of pharmaceutically useful salts from basic pharmaceutical compounds are discussed, for example, by P. Stahl *et al*, Camille G. (eds.), *Handbook of Pharmaceutical Salts. Properties, Selection and Use.* (2002) Zurich: Wiley-VCH; S. Berge *et al*, *Journal of Pharmaceutical Sciences* (1977) 66(1) 1-19; P. Gould, *International J. of Pharmaceutics* (1986) 33 201-217; Anderson *et al*, *The Practice of Medicinal Chemistry* (1996), Academic Press, New York; and in *The Orange Book* (Food & Drug Administration, Washington, D.C. on their website). These disclosures are incorporated herein by reference thereto.

Exemplary basic salts include ammonium salts, alkali metal salts such as sodium, lithium, and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, salts with organic bases (for example, organic amines) such as dicyclohexylamine, *t*-butyl amine, choline, and salts with amino acids such as arginine, lysine and the like. Basic nitrogen-containing groups may be quarternized with agents such as lower alkyl halides (*e.g.*, methyl, ethyl, and butyl chlorides, bromides and iodides), dialkyl sulfates (*e.g.*, dimethyl, diethyl, and dibutyl

sulfates), long chain halides (*e.g.*, decyl, lauryl, and stearyl chlorides, bromides and iodides), aralkyl halides (*e.g.*, benzyl and phenethyl bromides), and others. Compounds carrying an acidic moiety can be mixed with suitable pharmaceutically acceptable salts to provide, for example, alkali metal salts (*e.g.*, sodium or potassium salts), alkaline earth metal salts (*e.g.*, calcium or magnesium salts), and salts formed with suitable organic ligands such as quaternary ammonium salts. Also, in the case of an acid (-COOH) or alcohol group being present, pharmaceutically acceptable esters can be employed to modify the solubility or hydrolysis characteristics of the compound.

All such acid salts and base salts are intended to be pharmaceutically acceptable salts within the scope of the invention and all acid and base salts are considered equivalent to the free forms of the corresponding compounds for purposes of the invention.

In addition, when a compound of the invention contains both a basic moiety, such as, but not limited to an aliphatic primary, secondary, tertiary or cyclic amine, an aromatic or heteroaryl amine, pyridine or imidazole, and an acidic moiety, such as, but not limited to tetrazole or carboxylic acid, zwitterions ("inner salts") may be formed and are included within the terms "salt(s)" as used herein. It is understood that certain compounds of the invention may exist in zwitterionic form, having both anionic and cationic centers within the same compound and a net neutral charge. Such zwitterions are included within the invention.

Methods of Preparing Compounds

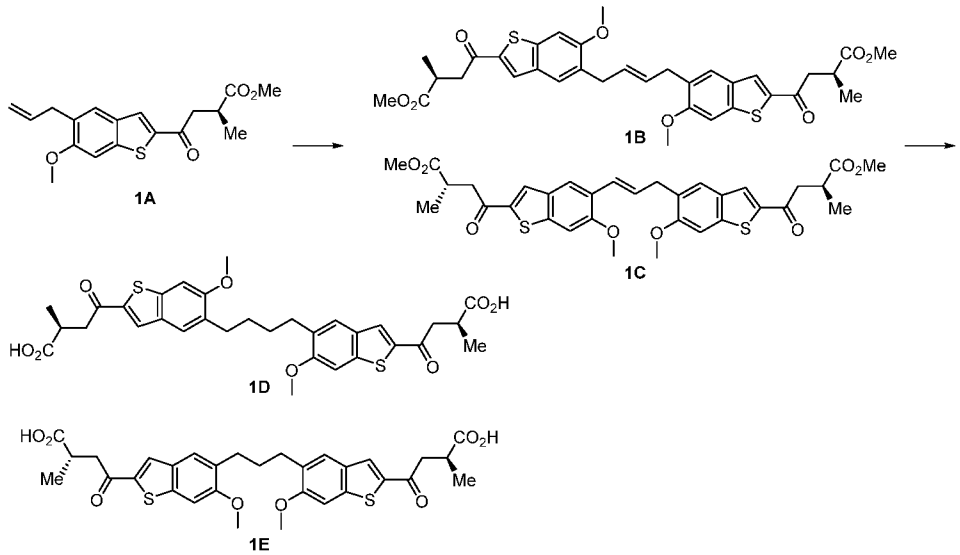
Several methods for preparing the compounds of general formula (I), compounds of general formula (II), compounds of general formula (III), compounds of general formula (IV), compounds of general formula (V), compounds of general formula (VI), and pharmaceutically acceptable salts of the foregoing, are described in the following Schemes and Examples. Starting materials and intermediates are purchased from commercial sources, made from known procedures, or are otherwise illustrated. In some cases the order of carrying out the steps of the reaction schemes may be varied to facilitate the reaction or to avoid unwanted reaction products.

In the following Methods and Schemes, LG represents a leaving group, which may be a halide or triflate group. The variables included in the Methods and Schemes have the meanings provided; exemplary catalysts are defined in the Abbreviations (below).

Method 1

Benzothiophene dimers **1D** and **1E**, and pharmaceutically acceptable salts thereof, can be prepared in multiple ways. One way is shown in Scheme 1. The sequence begins with allyl-benzothiophene **1A**. Cross-metathesis with Grubbs catalyst 2G affords the olefinic dimers **1B** and **1C**. Hydrogenation and then hydrolysis affords the dimers **1D** and **1E** with different tether lengths.

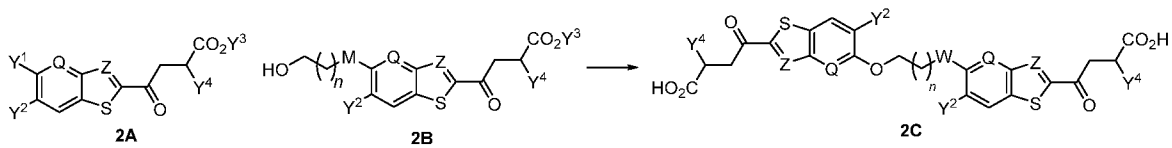
Scheme 1



Method 2

Another method for the preparation of benzothiophene dimers, and pharmaceutically salts thereof, is detailed in Scheme 2. The sequence starts with an appropriately substituted aryl halide, **2A**. Cross-coupling with a primary alcohol containing benzothiophene (**2B**) using RockPhos Pd G3 followed by hydrolysis affords the dimer **2C**.

Scheme 2



M = CH_2, O Q = C-H, N, C-F Z = C-H, N

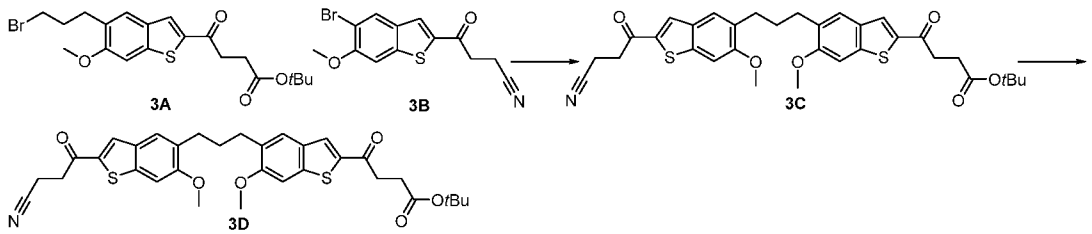
Y^1 = Br, Cl Y^2 = H, OCH_3 Y^3 = CH_3, *t*-Bu Y^4 = H, CH_3

Method 3

Another method for the preparation of benzothiophene dimers, and pharmaceutically acceptable salts thereof, is detailed in Scheme 3. The cross-coupling of alkyl bromide

benzothiophene **3A** and an aryl bromide **3B** affords the ester nitrile dimer **3C**. Hydrolysis with aqueous sodium hydroxide affords the dimer **3D**.

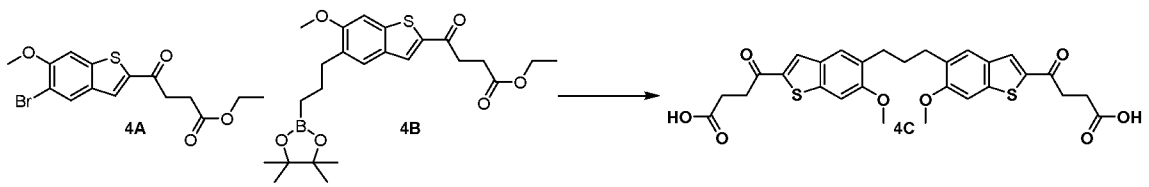
Scheme 3



Method 4

Another method for the preparation of benzothiphene dimers, and pharmaceutically acceptable salts thereof, is detailed in Scheme 4. Alkyl Suzuki reaction between aryl bromide **4a** and alkyl boronate ester **4B** in the presence of a palladium catalyst followed by hydrolysis of the ester affords the dimer **4C**.

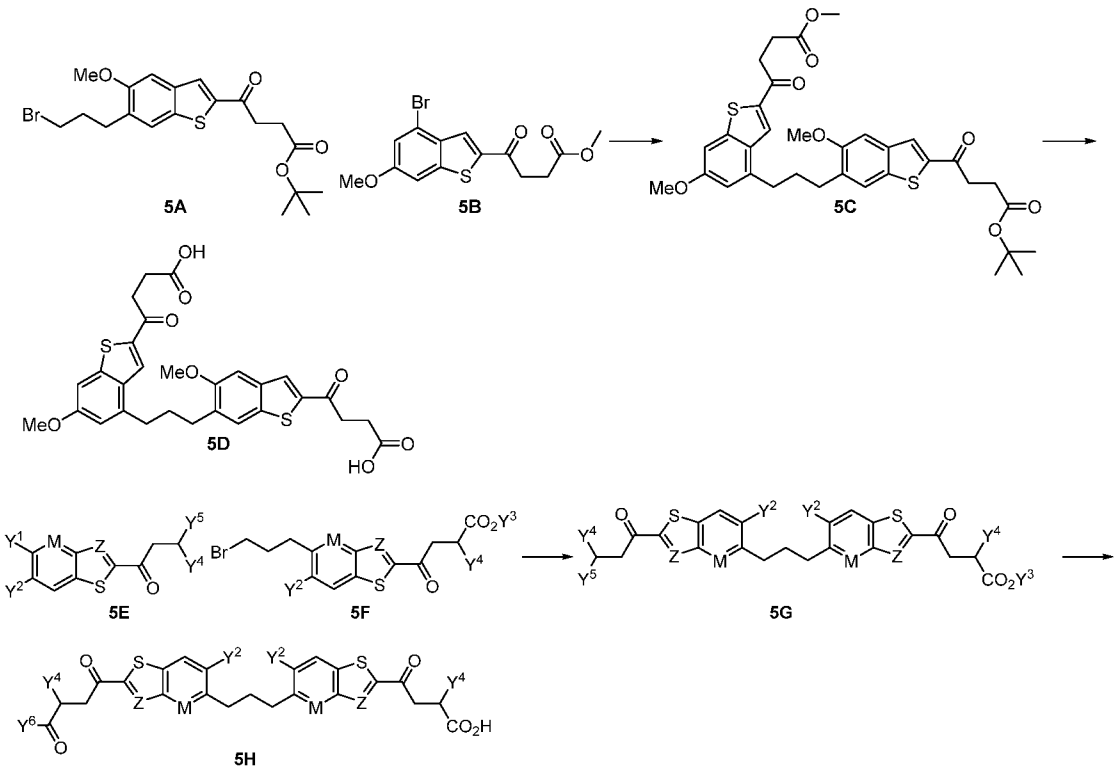
Scheme 4



Method 5

Another method for the preparation of benzothiophene dimers, and pharmaceutically acceptable salts thereof, is detailed in Scheme 5. The cross-coupling of alkyl bromide benzothiophene **5A** and an aryl bromide **5B** affords the dimer **5C**. Hydrolysis affords the dimer **5D**. Similarly, aryl halide **5E** can be coupled with alkyl bromide **5F** to create intermediate **5G**. Hydrolysis affords the acid affords **5H**.

Scheme 5

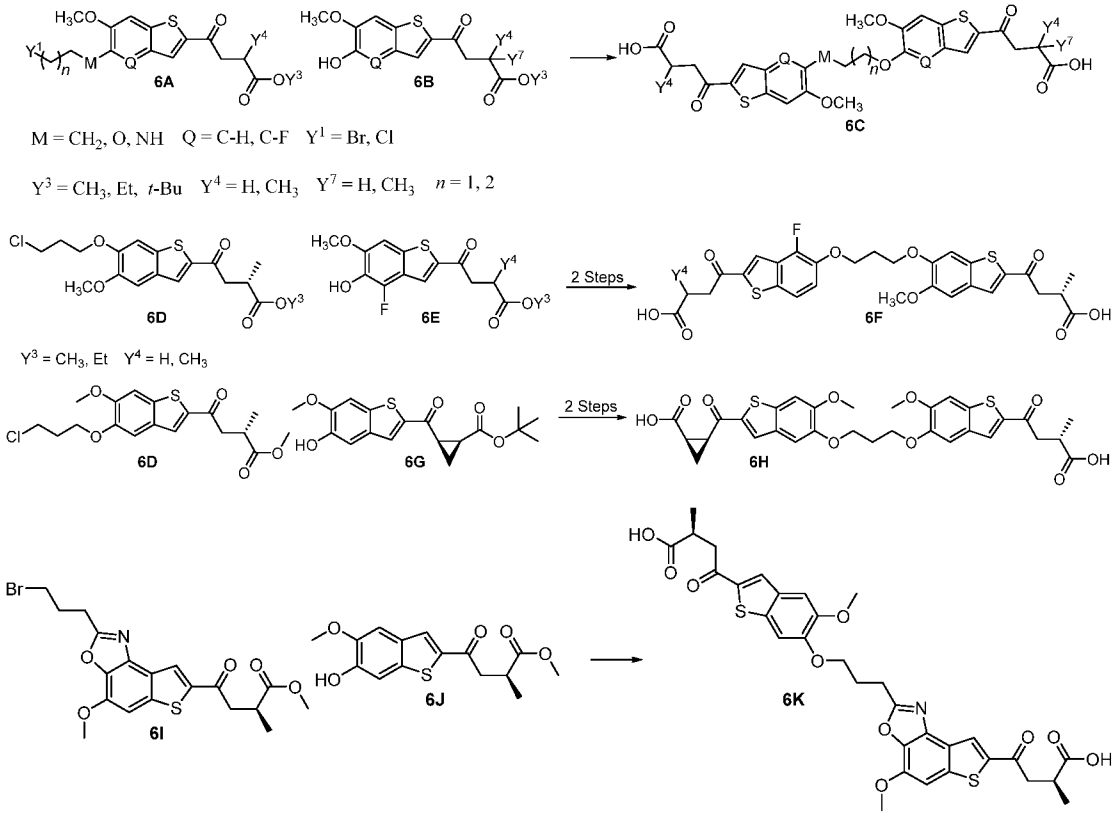


M = C-H, N Z = C-H, N Y^1 = Br, Cl Y^2 = CH_3, OCH_3
Y^3 = CH_3, *t*-Bu Y^4 = H, CH_3 Y^5 = CO_2CH_3, CO_2*t*-Bu, CN Y^6 = NH_2, OH

Method 6

Another method for the preparation of benzothiophene dimers, and pharmaceutically acceptable salts thereof, is detailed in Scheme 6. The sequence begins with alkyl halide **6A**. Displacement of the halide with an appropriately substituted phenol, **6B**, under basic conditions followed by hydrolysis affords dimer **6C**. Similarly, alkyl chloride **6D** can be displaced by phenol **6E** under basic conditions to afford **6F** after conversion to the diacid. Phenol **6G** can also be used to displace alkyl chloride **6D** to afford the desired **6H** after conversion to the diacid. Finally, alkyl bromide **6I** can be displaced by the phenol **6J** to afford **6K** after conversion to the diacid.

Scheme 6

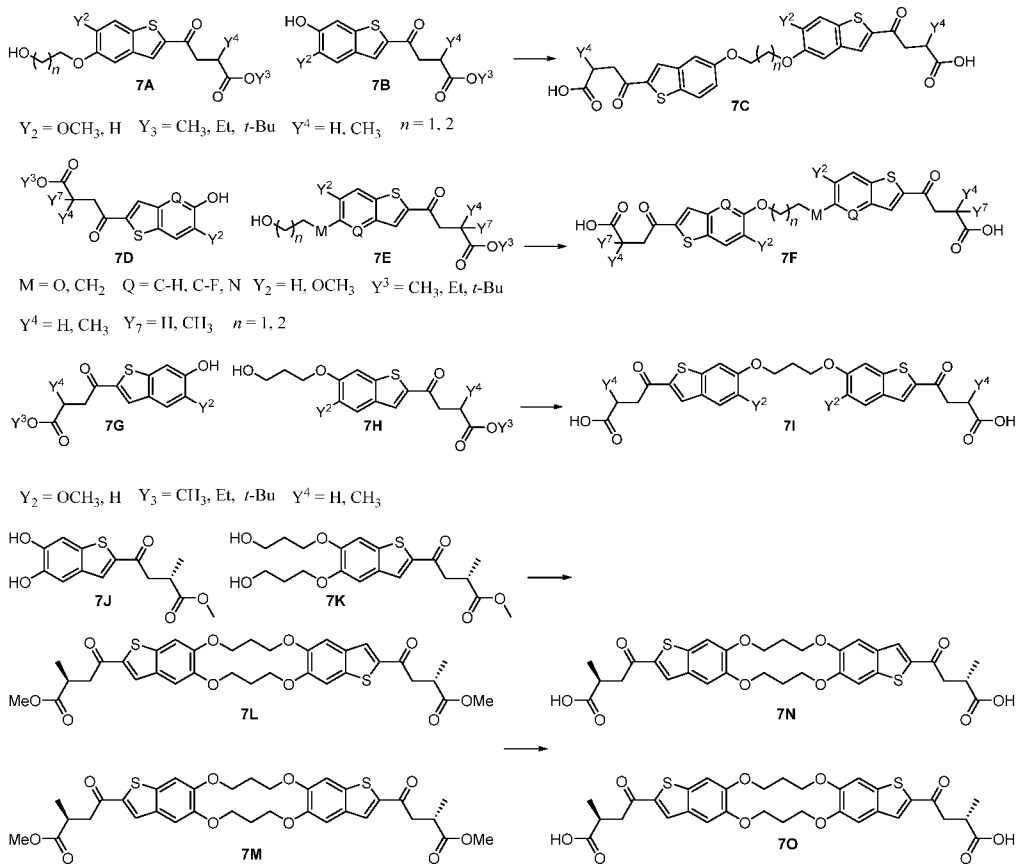


Method 7

Another method for the preparation of benzothiophene dimers, and pharmaceutically acceptable salts thereof, is detailed in Scheme 7. The sequence begins with a Mitsunobu reaction between a primary alcohol **7A** and a phenol **7B** to afford **7C** after hydrolysis of the diester. Alternatively, phenol **7D** can be reacted with alcohol **7E** under Mitsunobu conditions. Subsequent saponification affords the diacid **7F**. Phenol **7G** can also be used in a Mitsunobu reaction with **7H** to afford **7I** after conversion of the diester to the diacid.

Similarly, a bis-phenol benzothiophene **7J** and an appropriately substituted diol (**7K**) can be subjected to Mitsnobu conditions to afford a mixture of **7L** and **7M**. Hydrolysis affords a mixture of the diacids **7N** and **7O**.

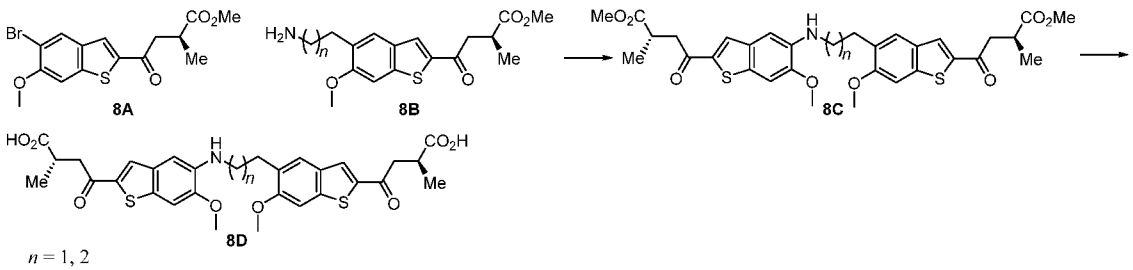
Scheme 7



Method 8

Another method for the preparation of benzothiophene dimers, and pharmaceutically acceptable salts thereof, is detailed in Scheme 8. The sequence begins with an appropriately substituted aryl bromide, **8A**. Reaction with an alkyl amine **8B** in the presence of a palladium catalyst affords the alkyl amino dimer diester **8C**. Hydrolysis affords the desired diacid **8D**.

Scheme 8

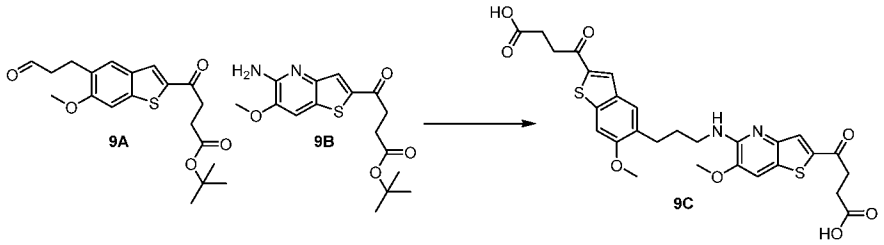


Method 9

Another method for the preparation of benzothiophene dimers, and pharmaceutically acceptable salts thereof, is detailed in Scheme 9. The sequence begins with a reductive

amination between aldehyde **9A** and amino azabenzothiphene **9B** in the presence of sodium triacetoxyborohydride. Addition of TFA to the crude mixture affords the desired diacid **9C**.

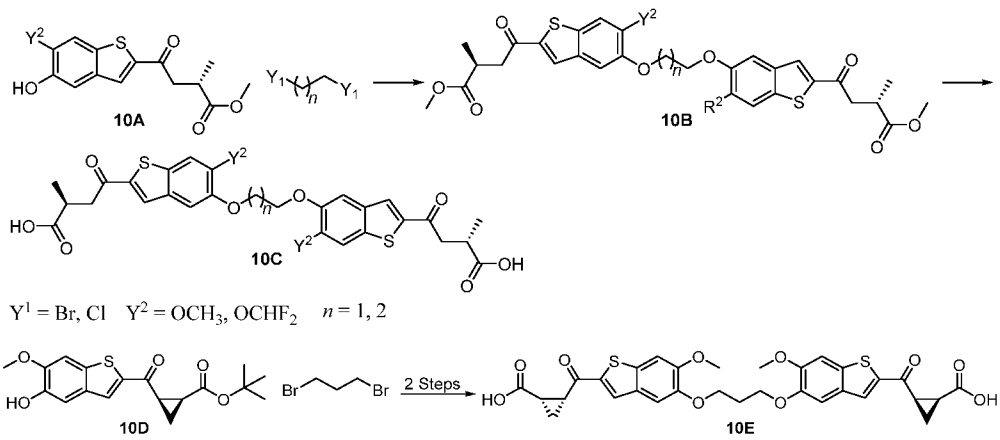
Scheme 9



Method 10

Another method for the preparation of benzothiophene dimers, and pharmaceutically acceptable salts thereof, is detailed in Scheme 10. The sequence begins with the bis-alkylation of an alkyl dihalide with an appropriately substituted phenolic benzothiophene **10A** to afford the dimer diester **10B**. Hyrolysis affords the desired diacid, **10C**. Similarly, a dihalide can be bis-alkylated with **10D** to afford the diacid **10E** after conversion of the diester to the diacid.

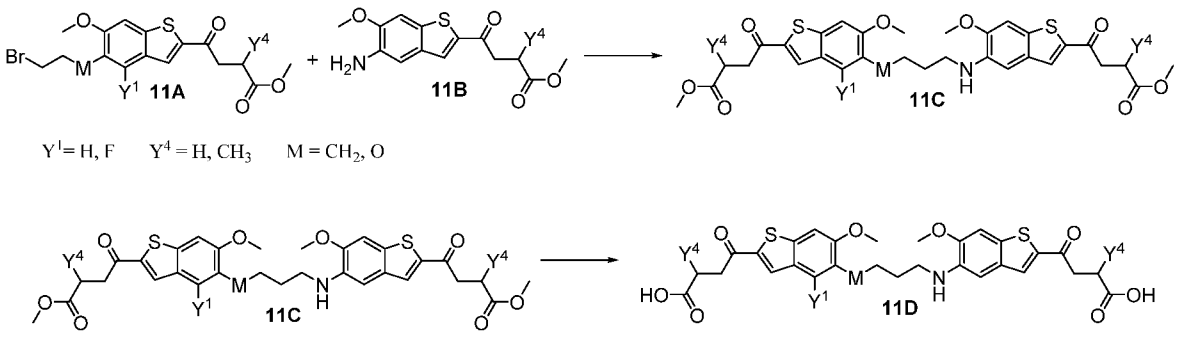
Scheme 10



Method 11

Another method for the preparation of benzothiophene dimers, and pharmaceutically acceptable salts thereof, is detailed in Scheme 11. The sequence begins with the alkylation of aniline 11B with the alkyl bromide 11A to afford 11C. Hydrolysis of the diester affords 11D.

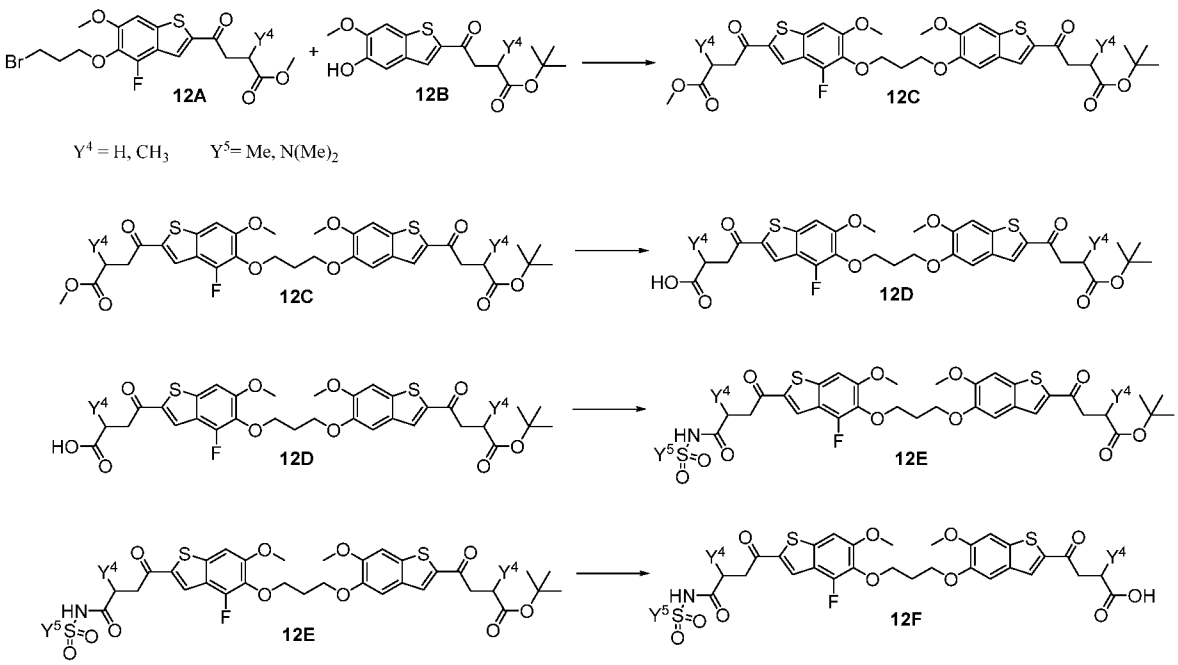
Scheme 11



Method 12

Another method for the preparation of benzothiophene dimers, and pharmaceutically acceptable salts thereof, is detailed in Scheme 12. The sequence begins with the alkylation of phenol 12B with the alkyl bromide 12A to afford 12C. Selective base-mediated hydrolysis affords the mono-acid 12D. Coupling of 12D with either a sulfonamide or a sulfamide affords 12E. Acid-mediated hydrolysis affords 12F.

Scheme 12

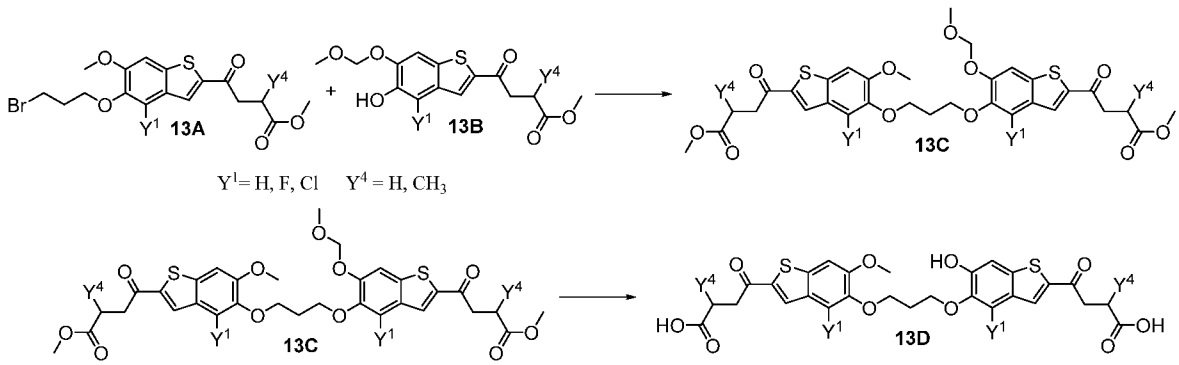


Method 13

Another method for the preparation of benzothiophene dimers, and pharmaceutically acceptable salts thereof, is detailed in Scheme 13. The sequence begins with the alkylation of

phenol 13B with the alkyl bromide 13A to afford 13C. Hydrolysis of the diester followed by acid-mediated deprotection of the methoxymethyl acetal (MOM)-protected phenol affords 13D.

Scheme 13



Methods of Use

Compounds described herein having therapeutic applications, such as the compounds of general formula (I), compounds of general formula (II), compounds of general formula (III), compounds of general formula (IV), compounds of general formula (V), compounds of general formula (VI), the compounds of the Examples 1 through 190, and pharmaceutically acceptable salts of the foregoing, may be administered to a patient for the purpose of inducing an immune response, inducing STING-dependent cytokine production and/or inducing anti-tumor activity. The term "administration" and variants thereof (*e.g.*, "administering" a compound) means providing the compound to the individual in need of treatment. When a compound is provided in combination with one or more additional active agents (*e.g.*, antiviral agents useful for treating HCV infection or anti-tumor agents for treating cancers), "administration" and its variants are each understood to include concurrent and sequential provision of the compound or salt and other agents.

The compounds disclosed herein may be STING agonists. These compounds are potentially useful in treating diseases or disorders including, but not limited to, cell proliferation disorders. Cell-proliferation disorders include, but are not limited to, cancers, benign papillomatosis, gestational trophoblastic diseases, and benign neoplastic diseases, such as skin papilloma (warts) and genital papilloma.

In specific embodiments, the disease or disorder to be treated is a cell proliferation disorder. In certain embodiments, the cell proliferation disorder is cancer. In particular embodiments, the cancer is selected from brain and spinal cancers, cancers of the head and neck,

leukemia and cancers of the blood, skin cancers, cancers of the reproductive system, cancers of the gastrointestinal system, liver and bile duct cancers, kidney and bladder cancers, bone cancers, lung cancers, malignant mesothelioma, sarcomas, lymphomas, glandular cancers, thyroid cancers, heart tumors, germ cell tumors, malignant neuroendocrine (carcinoid) tumors, midline tract cancers, and cancers of unknown primary (*i.e.*, cancers in which a metastasized cancer is found but the original cancer site is not known). In particular embodiments, the cancer is present in an adult patient; in additional embodiments, the cancer is present in a pediatric patient. In particular embodiments, the cancer is AIDS-related.

In specific embodiments, the cancer is selected from brain and spinal cancers. In particular embodiments, the cancer is selected from the group consisting of anaplastic astrocytomas, glioblastomas, astrocytomas, and estheosioneuroblastomas (also known as olfactory blastomas). In particular embodiments, the brain cancer is selected from the group consisting of astrocytic tumor (*e.g.*, pilocytic astrocytoma, subependymal giant-cell astrocytoma, diffuse astrocytoma, pleomorphic xanthoastrocytoma, anaplastic astrocytoma, astrocytoma, giant cell glioblastoma, glioblastoma, secondary glioblastoma, primary adult glioblastoma, and primary pediatric glioblastoma), oligodendroglial tumor (*e.g.*, oligodendroglioma, and anaplastic oligodendroglioma), oligoastrocytic tumor (*e.g.*, oligoastrocytoma, and anaplastic oligoastrocytoma), ependymoma (*e.g.*, myxopapillary ependymoma, and anaplastic ependymoma); medulloblastoma, primitive neuroectodermal tumor, schwannoma, meningioma, atypical meningioma, anaplastic meningioma, pituitary adenoma, brain stem glioma, cerebellar astrocytoma, cerebral astorcytoma/malignant glioma, visual pathway and hypothalmic glioma, and primary central nervous system lymphoma. In specific instances of these embodiments, the brain cancer is selected from the group consisting of glioma, glioblastoma multiforme, paraganglioma, and suprantentorial primordial neuroectodermal tumors (sPNET).

In specific embodiments, the cancer is selected from cancers of the head and neck, including nasopharyngeal cancers, nasal cavity and paranasal sinus cancers, hypopharyngeal cancers, oral cavity cancers (*e.g.*, squamous cell carcinomas, lymphomas, and sarcomas), lip cancers, oropharyngeal cancers, salivary gland tumors, cancers of the larynx (*e.g.*, laryngeal squamous cell carcinomas, rhabdomyosarcomas), and cancers of the eye or ocular cancers. In particular embodiments, the ocular cancer is selected from the group consisting of intraocular melanoma and retinoblastoma.

In specific embodiments, the cancer is selected from leukemia and cancers of the blood. In particular embodiments, the cancer is selected from the group consisting of myeloproliferative neoplasms, myelodysplastic syndromes, myelodysplastic/myeloproliferative neoplasms, acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), chronic myelogenous leukemia (CML), myeloproliferative neoplasm (MPN), post-MPN AML, post-MDS AML, del(5q)-associated high risk MDS or AML, blast-phase chronic myelogenous leukemia, angioimmunoblastic lymphoma, acute lymphoblastic leukemia, Langerans cell histiocytosis, hairy cell leukemia, and plasma cell neoplasms including plasmacytomas and multiple myelomas. Leukemias referenced herein may be acute or chronic.

In specific embodiments, the cancer is selected from skin cancers. In particular embodiments, the skin cancer is selected from the group consisting of melanoma, squamous cell cancers, and basal cell cancers.

In specific embodiments, the cancer is selected from cancers of the reproductive system. In particular embodiments, the cancer is selected from the group consisting of breast cancers, cervical cancers, vaginal cancers, ovarian cancers, prostate cancers, penile cancers, and testicular cancers. In specific instances of these embodiments, the cancer is a breast cancer selected from the group consisting of ductal carcinomas and phyllodes tumors. In specific instances of these embodiments, the breast cancer may be male breast cancer or female breast cancer. In specific instances of these embodiments, the cancer is a cervical cancer selected from the group consisting of squamous cell carcinomas and adenocarcinomas. In specific instances of these embodiments, the cancer is an ovarian cancer selected from the group consisting of epithelial cancers.

In specific embodiments, the cancer is selected from cancers of the gastro-intestinal system. In particular embodiments, the cancer is selected from the group consisting of esophageal cancers, gastric cancers (also known as stomach cancers), gastrointestinal carcinoid tumors, pancreatic cancers, gallbladder cancers, colorectal cancers, and anal cancer. In instances of these embodiments, the cancer is selected from the group consisting of esophageal squamous cell carcinomas, esophageal adenocarcinomas, gastric adenocarcinomas, gastrointestinal carcinoid tumors, gastrointestinal stromal tumors, gastric lymphomas, gastrointestinal lymphomas, solid pseudopapillary tumors of the pancreas, pancreatoblastoma, islet cell tumors, pancreatic carcinomas including acinar cell carcinomas and ductal adenocarcinomas, gallbladder adenocarcinomas, colorectal adenocarcinomas, and anal squamous cell carcinomas.

In specific embodiments, the cancer is selected from liver and bile duct cancers. In particular embodiments, the cancer is liver cancer (also known as hepatocellular carcinoma). In particular embodiments, the cancer is bile duct cancer (also known as cholangiocarcinoma); in instances of these embodiments, the bile duct cancer is selected from the group consisting of intrahepatic cholangiocarcinoma and extrahepatic cholangiocarcinoma.

In specific embodiments, the cancer is selected from kidney and bladder cancers. In particular embodiments, the cancer is a kidney cancer selected from the group consisting of renal cell cancer, Wilms tumors, and transitional cell cancers. In particular embodiments, the cancer is a bladder cancer selected from the group consisting of urethelial carcinoma (a transitional cell carcinoma), squamous cell carcinomas, and adenocarcinomas.

In specific embodiments, the cancer is selected from bone cancers. In particular embodiments, the bone cancer is selected from the group consisting of osteosarcoma, malignant fibrous histiocytoma of bone, Ewing sarcoma, chordoma (cancer of the bone along the spine).

In specific embodiments, the cancer is selected from lung cancers. In particular embodiments, the lung cancer is selected from the group consisting of non-small cell lung cancer, small cell lung cancers, bronchial tumors, and pleuropulmonary blastomas.

In specific embodiments, the cancer is selected from malignant mesothelioma. In particular embodiments, the cancer is selected from the group consisting of epithelial mesothelioma and sarcomatoids.

In specific embodiments, the cancer is selected from sarcomas. In particular embodiments, the sarcoma is selected from the group consisting of central chondrosarcoma, central and periosteal chondroma, fibrosarcoma, clear cell sarcoma of tendon sheaths, and Kaposi's sarcoma.

In specific embodiments, the cancer is selected from lymphomas. In particular embodiments, the cancer is selected from the group consisting of Hodgkin lymphoma (*e.g.*, Reed-Sternberg cells), non-Hodgkin lymphoma (*e.g.*, diffuse large B-cell lymphoma, follicular lymphoma, mycosis fungoides, Sezary syndrome, primary central nervous system lymphoma), cutaneous T-cell lymphomas, primary central nervous system lymphomas.

In specific embodiments, the cancer is selected from glandular cancers. In particular embodiments, the cancer is selected from the group consisting of adrenocortical cancer (also known as adrenocortical carcinoma or adrenal cortical carcinoma), pheochromocytomas, paragangliomas, pituitary tumors, thymoma, and thymic carcinomas.

In specific embodiments, the cancer is selected from thyroid cancers. In particular embodiments, the thyroid cancer is selected from the group consisting of medullary thyroid carcinomas, papillary thyroid carcinomas, and follicular thyroid carcinomas.

In specific embodiments, the cancer is selected from germ cell tumors. In particular embodiments, the cancer is selected from the group consisting of malignant extracranial germ cell tumors and malignant extragonadal germ cell tumors. In specific instances of these embodiments, the malignant extragonadal germ cell tumors are selected from the group consisting of nonseminomas and seminomas.

In specific embodiments, the cancer is selected from heart tumors. In particular embodiments, the heart tumor is selected from the group consisting of malignant teratoma, lymphoma, rhabdomyosacroma, angiosarcoma, chondrosarcoma, infantile fibrosarcoma, and synovial sarcoma.

In specific embodiments, the cell-proliferation disorder is selected from benign papillomatosis, benign neoplastic diseases and gestational trophoblastic diseases. In particular embodiments, the benign neoplastic disease is selected from skin papilloma (warts) and genital papilloma. In particular embodiments, the gestational trophoblastic disease is selected from the group consisting of hydatidiform moles, and gestational trophoblastic neoplasia (*e.g.*, invasive moles, choriocarcinomas, placental-site trophoblastic tumors, and epithelioid trophoblastic tumors).

As used herein, the terms "treatment" and "treating" refer to all processes in which there may be a slowing, interrupting, arresting, controlling, or stopping of the progression of a disease or disorder described herein. The terms do not necessarily indicate a total elimination of all disease or disorder symptoms.

The terms "administration of" and or "administering" a compound should be understood to include providing a compound described herein, or a pharmaceutically acceptable salt thereof, and compositions of the foregoing to a patient.

The amount of a compound administered to a patient is an amount sufficient to induce an immune response and/or to induce STING-dependent type I interferon production in the patient. In an embodiment, the amount of a compound can be an "effective amount" or "therapeutically effective amount," such that the subject compound is administered in an amount that will elicit, respectively, a biological or medical (*i.e.,* intended to treat) response of a tissue, system, animal, or human that is being sought by a researcher, veterinarian, medical doctor, or other clinician.

An effective amount does not necessarily include considerations of toxicity and safety related to the administration of a compound.

An effective amount of a compound will vary with the particular compound chosen (*e.g.*, considering the potency, efficacy, and/or half-life of the compound); the route of administration chosen; the condition being treated; the severity of the condition being treated; the age, size, weight, and physical condition of the patient being treated; the medical history of the patient being treated; the duration of the treatment; the nature of a concurrent therapy; the desired therapeutic effect; and like factors and can be routinely determined by the skilled artisan.

The compounds disclosed herein may be administered by any suitable route including oral and parenteral administration. Parenteral administration is typically by injection or infusion and includes intravenous, intramuscular, and subcutaneous injection or infusion.

The compounds disclosed herein may be administered once or according to a dosing regimen where a number of doses are administered at varying intervals of time for a given period of time. For example, doses may be administered one, two, three, or four times per day. Doses may be administered until the desired therapeutic effect is achieved or indefinitely to maintain the desired therapeutic effect. Suitable dosing regimens for a compound disclosed herein depend on the pharmacokinetic properties of that compound, such as absorption, distribution and half-life, which can be determined by a skilled artisan. In addition, suitable dosing regimens, including the duration such regimens are administered, for a compound disclosed herein depend on the disease or condition being treated, the severity of the disease or condition, the age and physical condition of the patient being treated, the medical history of the patient being treated, the nature of concurrent therapy, the desired therapeutic effect, and like factors within the knowledge and expertise of the skilled artisan. It will be further understood by such skilled artisans that suitable dosing regimens may require adjustment given an individual patient's response to the dosing regimen or over time as the individual patient needs change. Typical daily dosages may vary depending upon the particular route of administration chosen.

One embodiment of the present disclosure provides for a method of treating a cell proliferation disorder comprising administration of a therapeutically effective amount of a compound of general formula (I), compound of general formula (II), compound of general formula (III), compound of general formula (IV), compound of general formula (V), compound of general formula (VI), and pharmaceutically acceptable salts of the foregoing, to a patient in need of treatment thereof. In embodiments, the disease or disorder to be treated is a cell

proliferation disorder. In aspects of these embodiments, the cell proliferation disorder is cancer. In further aspects of these embodiments, the cancer is selected from brain and spinal cancers, cancers of the head and neck, leukemia and cancers of the blood, skin cancers, cancers of the reproductive system, cancers of the gastrointestinal system, liver and bile duct cancers, kidney and bladder cancers, bone cancers, lung cancers, malignant mesothelioma, sarcomas, lymphomas, glandular cancers, thyroid cancers, heart tumors, germ cell tumors, malignant neuroendocrine (carcinoid) tumors, midline tract cancers, and cancers of unknown primary.

In one embodiment, disclosed herein is the use of a compound of general formula (I), compound of general formula (II), compound of general formula (III), compound of general formula (IV), compound of general formula (V), compound of general formula (VI), or a pharmaceutically acceptable salt of the foregoing, in a therapy. The compound may be useful in a method of inducing an immune response and/or inducing STING-dependent type I interferon production in a patient, such as a mammal in need of such inhibition, comprising administering an effective amount of the compound to the patient.

In one embodiment, disclosed herein is a pharmaceutical composition comprising at least one compound of general formula (I), at least one compound of general formula (II), at least one compound of general formula (III), at least one compound of general formula (IV), at least one compound of general formula (V), at least one compound of general formula (VI), or at least one pharmaceutically acceptable salt of the foregoing, for use in potential treatment to induce an immune response and/or to induce STING-dependent type I interferon production.

One embodiment disclosed herein is the use of a compound of general formula (I), a compound of general formula (II), a compound of general formula (III), a compound of general formula (IV), a compound of general formula (V), a compound of general formula (VI), or a pharmaceutically acceptable salt of the foregoing, in the manufacture of a medicament to induce an immune response and/or to induce STING-dependent type I interferon production. In embodiments, the disease or disorder to be treated is a cell proliferation disorder. In aspects of these embodiments, the cell proliferation disorder is cancer. In further aspects of these embodiments, the cancer is selected from brain and spinal cancers, cancers of the head and neck, leukemia and cancers of the blood, skin cancers, cancers of the reproductive system, cancers of the gastrointestinal system, liver and bile duct cancers, kidney and bladder cancers, bone cancers, lung cancers, malignant mesothelioma, sarcomas, lymphomas, glandular cancers, thyroid

cancers, heart tumors, germ cell tumors, malignant neuroendocrine (carcinoid) tumors, midline tract cancers, and cancers of unknown primary.

Compositions

The term "composition" as used herein is intended to encompass a dosage form comprising a specified compound in a specified amount, as well as any dosage form that results, directly or indirectly, from combination of a specified compound in a specified amount. Such term is intended to encompass a dosage form comprising a compound of general formula (I), a compound of general formula (II), a compound of general formula (III), a compound of general formula (IV), a compound of general formula (V), a compound of general formula (VI), or a pharmaceutically acceptable salt of the foregoing, and one or more pharmaceutically acceptable carriers or excipients. Accordingly, the compositions of the present disclosure encompass any composition made by admixing a compound of the present disclosure and one or more pharmaceutically acceptable carrier or excipients. By "pharmaceutically acceptable", it is meant the carriers or excipients are compatible with the compound disclosed herein and with other ingredients of the composition.

For the purpose of inducing an immune response and/or inducing STING-dependent type I interferon production, the compounds of general formula (I), compounds of general formula (II), compounds of general formula (III), compounds of general formula (IV), compounds of general formula (V), compounds of general formula (VI), or pharmaceutically acceptable salts of the foregoing, can be administered by means that produces contact of the active agent with the agent's site of action. The compounds can be administered by conventional means available for use in conjunction with pharmaceuticals, either as individual therapeutic agents or in a combination of therapeutic agents. The compounds can be administered alone, but typically are administered with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice.

In one embodiment, disclosed herein is a composition comprising a compound of general formula (I), a compound of general formula (II), a compound of general formula (III), a compound of general formula (IV), a compound of general formula (V), a compound of general formula (VI), or a pharmaceutically acceptable salt of the foregoing, and one or more pharmaceutically acceptable carriers or excipients. The composition may be prepared and packaged in bulk form in which a therapeutically effective amount of a compound of the

disclosure can be extracted and then given to a patient, such as with powders or syrups. Alternatively, the composition may be prepared and packaged in unit dosage form in which each physically discrete unit contains a therapeutically effective amount of a compound of general formula (I), a compound of general formula (II), a compound of general formula (III), a compound of general formula (IV), a compound of general formula (V), a compound of general formula (VI), or a pharmaceutically acceptable salt of the foregoing.

The compounds disclosed herein and a pharmaceutically acceptable carrier or excipient(s) will typically be formulated into a dosage form adapted for administration to a patient by a desired route of administration. For example, dosage forms include those adapted for (1) oral administration, such as tablets, capsules, caplets, pills, troches, powders, syrups, elixirs, suspensions, solutions, emulsions, sachets, and cachets; and (2) parenteral administration, such as sterile solutions, suspensions, and powders for reconstitution. Suitable pharmaceutically acceptable carriers or excipients will vary depending upon the particular dosage form chosen. In addition, suitable pharmaceutically acceptable carriers or excipients may be chosen for a particular function that they may serve in the composition. For example, certain pharmaceutically acceptable carriers or excipients may be chosen for their ability to facilitate the production of uniform dosage forms. Certain pharmaceutically acceptable carriers or excipients may be chosen for their ability to facilitate the production of stable dosage forms. Certain pharmaceutically acceptable carriers or excipients may be chosen for their ability to facilitate the carrying or transporting of a compound disclosed herein, once administered to the patient, from one organ or portion of the body to another organ or another portion of the body. Certain pharmaceutically acceptable carriers or excipients may be chosen for their ability to enhance patient compliance.

Suitable pharmaceutically acceptable excipients include the following types of excipients: diluents, lubricants, binders, disintegrants, fillers, glidants, granulating agents, coating agents, wetting agents, solvents, co-solvents, suspending agents, emulsifiers, sweeteners, flavoring agents, flavor masking agents, coloring agents, anti-caking agents, hemectants, chelating agents, plasticizers, viscosity increasing agents, antioxidants, preservatives, stabilizers, surfactants, and buffering agents.

A skilled artisan possesses the knowledge and skill in the art to select suitable pharmaceutically acceptable carriers and excipients in appropriate amounts for the use in the compositions of the disclosure. In addition, there are a number of resources available to the

skilled artisan, which describe pharmaceutically acceptable carriers and excipients and may be useful in selecting suitable pharmaceutically acceptable carriers and excipients. Examples include REMINGTON'S PHARMACEUTICAL SCIENCES (Mack Publishing Company), THE HANDBOOK OF PHARMACEUTICAL ADDITIVES (Gower Publishing Limited), and THE HANDBOOK OF PHARMACEUTICAL EXCIPIENTS (the American Pharmaceutical Association and the Pharmaceutical Press).

The compositions of the disclosure are prepared using techniques and methods known to those skilled in the art. Some methods commonly used in the art are described in REMINGTON'S PHARMACEUTICAL SCIENCES (Mack Publishing Company).

In one embodiment, the disclosure is directed to a solid oral dosage form such as a tablet or capsule comprising a therapeutically effective amount of a compound of general formula (I), a compound of general formula (II), a compound of general formula (III), a compound of general formula (IV), a compound of general formula (V), a compound of general formula (VI), or a pharmaceutically acceptable salt of the foregoing, and a diluent or filler. Suitable diluents and fillers include lactose, sucrose, dextrose, mannitol, sorbitol, starch (*e.g.*, corn starch, potato starch, and pre-gelatinized starch), cellulose and its derivatives, (*e.g.*, microcrystalline cellulose), calcium sulfate, and dibasic calcium phosphate. The solid oral dosage form may further comprise a binder. Suitable binders include starch (*e.g.*, corn starch, potato starch, and pre-gelatinized starch) gelatin, acacia, sodium alginate, alginic acid, tragacanth, guar gum, povidone, and cellulose and its derivatives (*e.g.*, microcrystalline cellulose). The solid oral dosage form may further comprise a disintegrant. Suitable disintegrants include crospovidone, sodium starch glycolate, croscarmelose, alginic acid, and sodium carboxymethyl cellulose. The solid oral dosage form may further comprise a lubricant. Suitable lubricants include stearic acid, magnesium stearate, calcium stearate, and talc.

Where appropriate, dosage unit formulations for oral administration can be microencapsulated. The composition can also be prepared to prolong or sustain the release as, for example, by coating or embedding particulate material in polymers, wax, or the like.

The compounds disclosed herein may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyrancopolymer, polyhydroxypropylmethacrylamidephenol, polyhydroxyethylaspartamidephenol, or polyethyleneoxidepolylysine substituted with palmitoyl residues. Furthermore, the compounds of the disclosure may be coupled to a class of biodegradable polymers useful in achieving

controlled release of a drug, for example polylactic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanacrylates, and cross-linked or amphipathic block copolymers of hydrogels.

In one embodiment, the disclosure is directed to a liquid oral dosage form. Oral liquids such as solutions, syrups, and elixirs can be prepared in dosage unit form so that a given quantity contains a predetermined amount of a compound or a pharmaceutically acceptable salt thereof disclosed herein. Syrups can be prepared by dissolving the compound of the disclosure in a suitably flavored aqueous solution; elixirs are prepared through the use of a non-toxic alcoholic vehicle. Suspensions can be formulated by dispersing a compound disclosed herein in a non-toxic vehicle. Solubilizers and emulsifiers such as ethoxylated isostearyl alcohols and polyoxy ethylene sorbitol ethers, preservatives, flavor additives such as peppermint oil, or other natural sweeteners or saccharin or other artificial sweeteners and the like can also be added.

In one embodiment, the disclosure is directed to compositions for parenteral administration. Compositions adapted for parenteral administration include aqueous and non-aqueous sterile injection solutions that may contain anti-oxidants, buffers, bacteriostats, and solutes that render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions that may include suspending agents and thickening agents. The compositions may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition, requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules, and tablets.

Combinations

The compounds of general formula (I), compounds of general formula (II), compounds of general formula (III), compounds of general formula (IV), compounds of general formula (V), compounds of general formula (VI), and/or pharmaceutically acceptable salts of the foregoing, may be administered in combination with one or more additional active agents. In embodiments, one or more compounds of general formula (I), compounds of general formula (II), compounds of general formula (III), compounds of general formula (IV), compounds of general formula (V), compounds of general formula (VI), or one or more pharmaceutically acceptable salts of the foregoing, and the one or more additional active agents may be co-administered. The additional

active agent(s) may be administered in a single dosage form with the compound of general formula (I), compound of general formula (II), compound of general formula (III), compound of general formula (IV), compound of general formula (V), compound of general formula (VI), or pharmaceutically acceptable salt of the foregoing, or the additional active agent(s) may be administered in separate dosage form(s) from the dosage form containing the compound of general formula (I), compound of general formula (II), compound of general formula (III), compound of general formula (IV), compound of general formula (V), compound of general formula (VI), or pharmaceutically acceptable salt of the foregoing.

The additional active agent(s) may be provided as a pharmaceutically acceptable salt, where appropriate.

The additional active agent(s) may be one or more agents 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. It will be understood that such additional active agent(s) may be provided as a pharmaceutically acceptable salt. It will be understood the descriptions of the above additional active agents may be overlapping. It will also be understood that the treatment combinations are subject to optimization, and it is understood that the best combination to use of the compounds of general formula (I), compounds of general formula (II), compounds of general formula (III), compounds of general formula (IV), compounds of general formula (V), compounds of general formula (VI), or pharmaceutically acceptable salts of the foregoing, and one or more additional active agents will be determined based on the individual patient needs.

A compound disclosed herein may be used in combination with one or more other active agents, including but not limited to, other anti-cancer agents that are used in the prevention, treatment, control, amelioration, or reduction of risk of a particular disease or condition (*e.g.*, cell proliferation disorders). In one embodiment, a compound disclosed herein is combined with one or more other anti-cancer agents for use in the prevention, treatment, control amelioration, or reduction of risk of a particular disease or condition for which the compounds disclosed herein are useful. Such other active agents may be administered, by a route and in an amount

commonly used therefor, contemporaneously or sequentially with a compound of the present disclosure.

When a compound disclosed herein is used contemporaneously with one or more other active agents, a composition containing such other active agents in addition to the compound disclosed herein is contemplated. Accordingly, the compositions of the present disclosure include those that also contain one or more other active ingredients, in addition to a compound disclosed herein. A compound disclosed herein may be administered either simultaneously with, or before or after, one or more other active agent(s). A compound disclosed herein may be administered separately, by the same or different route of administration, or together in the same pharmaceutical composition as the other agent(s).

Products provided as combinations may include a composition comprising a compound of general formula (I), compound of general formula (II), compound of general formula (III), compound of general formula (IV), compound of general formula (V), compound of general formula (VI), or a pharmaceutically acceptable salt of the foregoing, and one or more other active agent(s) together in the same pharmaceutical composition, or may include a composition comprising a compound of general formula (I), compound of general formula (II), compound of general formula (III), compound of general formula (IV), compound of general formula (V), compound of general formula (VI), or a pharmaceutically acceptable salt of the foregoing, and a composition comprising one or more other active agent(s) in separate form, *e.g.* in the form of a kit or in any form designed to enable separate administration either concurrently or on separate dosing schedules.

The weight ratio of a compound of general formula (I), compound of general formula (II), compound of general formula (III), compound of general formula (IV), compound of general formula (V), compound of general formula (VI), or a pharmaceutically acceptable salt of the foregoing, to a second active agent may be varied and will depend upon the therapeutically effective dose of each agent. Generally, a therapeutically effective dose of each will be used. Combinations of a compound disclosed herein and other active agents will generally also be within the aforementioned range, but in each case, a therapeutically effective dose of each active agent should be used. In such combinations, the compound disclosed herein and other active agents may be administered separately or in conjunction. In addition, the administration of one element may be prior to, concurrent to, or subsequent to the administration of other agent(s).

In one embodiment, this disclosure provides a composition comprising a compound of general formula (I), compound of general formula (II), compound of general formula (III), compound of general formula (IV), compound of general formula (V), compound of general formula (VI), or a pharmaceutically acceptable salt of the foregoing, and at least one other active agent as a combined preparation for simultaneous, separate, or sequential use in therapy. In one embodiment, the therapy is the treatment of a cell proliferation disorder, such as cancer.

In one embodiment, the disclosure provides a kit comprising two or more separate pharmaceutical compositions, at least one of which contains a compound of general formula (I), compound of general formula (II), compound of general formula (III), compound of general formula (IV), compound of general formula (V), compound of general formula (VI), or a pharmaceutically acceptable salt of the foregoing. In one embodiment, the kit comprises means for separately retaining said compositions, such as a container, divided bottle, or divided foil packet. An example of such a kit is a blister pack, as typically used for the packaging of tablets, capsules, and the like.

A kit of this disclosure may be used for administration of different dosage forms, for example, oral and parenteral, for administration of the separate compositions at different dosage intervals, or for titration of the separate compositions against one another. To assist with compliance, a kit of the disclosure typically comprises directions for administration.

Disclosed herein is a use of a compound of general formula (I), compound of general formula (II), compound of general formula (III), compound of general formula (IV), compound of general formula (V), compound of general formula (VI), or a pharmaceutically acceptable salt of the foregoing, for treating a cell proliferation disorder, where the medicament is prepared for administration with another active agent. The disclosure also provides the use of another active agent for treating a cell proliferation disorder, where the medicament is administered with a compound of general formula (I), compound of general formula (II), compound of general formula (III), compound of general formula (IV), compound of general formula (V), compound of general formula (VI), or a pharmaceutically acceptable salt of the foregoing.

The disclosure also provides the use of a compound of general formula (I), compound of general formula (II), compound of general formula (III), compound of general formula (IV), compound of general formula (V), compound of general formula (VI), or a pharmaceutically acceptable salt of the foregoing, for treating a cell proliferation disorder, where the patient has previously (*e.g.*, within 24 h) been treated with another active agent. The disclosure also

provides the use of another active agent for treating a cell proliferation disorder, where the patient has previously (*e.g.*, within 24 h) been treated with a compound of general formula (I), compound of general formula (II), compound of general formula (III), compound of general formula (IV), compound of general formula (V), compound of general formula (VI), or a pharmaceutically acceptable salt of the foregoing. The second agent may be administered a week, several weeks, a month, or several months after the administration of a compound disclosed herein.

STING agonist compounds that may be used in combination with the compounds of general formula (I), compounds of general formula (II), compounds of general formula (III), compounds of general formula (IV), compounds of general formula (V), compounds of general formula (VI), or pharmaceutically acceptable salts of the foregoing, disclosed herein include but are not limited to cyclic di-nucleotide compounds, such as those disclosed, for example, in International Patent Application Publication Nos. WO2014093936, WO2014189805, WO2014189806, WO2015185565, WO2016120305, WO2016096174, WO2016096577, WO2017027645, WO2017027646, WO2017075477, WO2017093933, and WO2018009466.

Anti-viral compounds that may be used in combination with the compounds of general formula (I), compounds of general formula (II), compounds of general formula (III), compounds of general formula (IV), compounds of general formula (V), compounds of general formula (VI), or pharmaceutically acceptable salts of the foregoing, disclosed herein include hepatitis B virus (HBV) inhibitors, hepatitis C virus (HCV) protease inhibitors, HCV polymerase inhibitors, HCV NS4A inhibitors, HCV NS5A inhibitors, HCV NS5b inhibitors, and human immunodeficiency virus (HIV) inhibitors. Such anti-viral compounds may be provided as a pharmaceutically acceptable salt, where appropriate.

Antigens and adjuvants that may be used in combination with the compounds of general formula (I), compounds of general formula (II), compounds of general formula (III), compounds of general formula (IV), compounds of general formula (V), compounds of general formula (VI), or the pharmaceutically acceptable salts of the foregoing, include B7 costimulatory molecule, interleukin-2, interferon-y, GM-CSF, CTLA-4 antagonists, OX-40/0X-40 ligand, CD40/CD40 ligand, sargramostim, levamisol, vaccinia virus, Bacille Calmette-Guerin (BCG), liposomes, alum, Freund's complete or incomplete adjuvant, detoxified endotoxins, mineral oils, surface active substances such as lipolecithin, pluronic polyols, polyanions, peptides, and oil or hydrocarbon emulsions. Adjuvants, such as aluminum hydroxide or aluminum phosphate, can

be added to increase the ability of the vaccine to trigger, enhance, or prolong an immune response. Additional materials, such as cytokines, chemokines, and bacterial nucleic acid sequences, like CpG, a toll-like receptor (TLR) 9 agonist as well as additional agonists for TLR 2, TLR 4, TLR 5, TLR 7, TLR 8, TLR9, including lipoprotein, LPS, monophosphoryllipid A, lipoteichoic acid, imiquimod, resiquimod, and in addition retinoic acid-inducible gene I (RIG-I) agonists such as poly I:C, used separately or in combination with the described compositions are also potential adjuvants. Such antigens and anjuvants may be provided as a pharmaceutically acceptable salt, where appropriate.

CLTA-4 and PD-1 pathways are important negative regulators of immune response. Activated T-cells up-regulate CTLA-4, which binds on antigen-presenting cells and inhibits T-cell stimulation, IL-2 gene expression, and T-cell proliferation; these anti-tumor effects have been observed in mouse models of colon carcinoma, metastatic prostate cancer, and metastatic melanoma. PD-1 binds to active T-cells and suppresses T-cell activation; PD-1 antagonists have demonstrated anti-tumor effects as well. CTLA-4 and PD-1 pathway antagonists that may be used in combination with the compounds of general formula (I), compounds of general formula (II), compounds of general formula (III), compounds of general formula (IV), compounds of general formula (V), compounds of general formula (VI), or the pharmaceutically acceptable salts of the foregoing, disclosed herein, include ipilimumab, tremelimumab, nivolumab, pembrolizumab, CT-011, AMP-224, and MDX-1106.

"PD-1 antagonist" or "PD-1 pathway antagonist" means any chemical compound or biological molecule that blocks binding of PD-L1 expressed on a cancer cell to PD-1 expressed on an immune cell (T-cell, B-cell, or NKT-cell) and preferably also blocks binding of PD-L2 expressed on a cancer cell to the immune-cell expressed PD-1. Alternative names or synonyms for PD-1 and its ligands include: PDCD1, PD1, CD279, and SLEB2 for PD-1; PDCD1L1, PDL1, B7H1, B7-4, CD274, and B7-H for PD-L1; and PDCD1L2, PDL2, B7-DC, Btdc, and CD273 for PD-L2. In any of the treatment method, medicaments and uses of the present disclosure in which a human individual is being treated, the PD-1 antagonist blocks binding of human PD-L1 to human PD-1, and preferably blocks binding of both human PD-L1 and PD-L2 to human PD-1. Human PD-1 amino acid sequences can be found in NCBI Locus No.: NP_005009. Human PD-L1 and PD-L2 amino acid sequences can be found in NCBI Locus No.: NP_054862 and NP_079515, respectively.

PD-1 antagonists useful in any of the treatment method, medicaments and uses of the present disclosure include a monoclonal antibody (mAb), or antigen binding fragment thereof, which specifically binds to PD-1 or PD-L1, and preferably specifically binds to human PD-1 or human PD-L1. The mAb may be a human antibody, a humanized antibody, or a chimeric antibody and may include a human constant region. In some embodiments, the human constant region is selected from the group consisting of IgG1, IgG2, IgG3, and IgG4 constant regions, and in preferred embodiments, the human constant region is an IgG1 or IgG4 constant region. In some embodiments, the antigen binding fragment is selected from the group consisting of Fab, Fab'-SH, $F(ab')_2$, scFv, and Fv fragments.

Examples of mAbs that bind to human PD-1, and useful in the treatment method, medicaments and uses of the present disclosure, are described in U.S. Patent Nos. US7488802, US7521051, US8008449, US8354509, and US8168757, PCT International Patent Application Publication Nos. WO2004/004771, WO2004/072286, and WO2004/056875, and U.S. Patent Application Publication No. US2011/0271358.

Examples of mAbs that bind to human PD-L1, and useful in the treatment method, medicaments and uses of the present disclosure, are described in PCT International Patent Application Nos. WO2013/019906 and WO2010/077634 A1 and in U.S. Patent No. US8383796. Specific anti-human PD-L1 mAbs useful as the PD-1 antagonist in the treatment method, medicaments and uses of the present disclosure include MPDL3280A, BMS-936559, MEDI4736, MSB0010718C, and an antibody that comprises the heavy chain and light chain variable regions of SEQ ID NO:24 and SEQ ID NO:21, respectively, of WO2013/019906.

Other PD-1 antagonists useful in any of the treatment method, medicaments, and uses of the present disclosure include an immune-adhesion that specifically binds to PD-1 or PD-L1, and preferably specifically binds to human PD-1 or human PD-L1, *e.g.*, a fusion protein containing the extracellular or PD-1 binding portion of PD-L1 or PD-L2 fused to a constant region such as an Fc region of an immunoglobulin molecule. Examples of immune-adhesion molecules that specifically bind to PD-1 are described in PCT International Patent Application Publication Nos. WO2010/027827 and WO2011/066342. Specific fusion proteins useful as the PD-1 antagonist in the treatment method, medicaments, and uses of the present disclosure include AMP-224 (also known as B7-DCIg), which is a PD-L2-FC fusion protein and binds to human PD-1.

The disclosure further relates to a method of treating cancer in a human patient comprising administration of a compound disclosed herein (i.e., a compound of general formula

(I), a compound of general formula (II), a compound of general formula (III), a compound of general formula (IV), a compound of general formula (V), a compound of general formula (VI), or a pharmaceutically acceptable salt of the foregoing) and a PD-1 antagonist to the patient. The compound of the disclosure and the PD-1 antagonist may be administered concurrently or sequentially.

In particular embodiments, the PD-1 antagonist is an anti-PD-1 antibody, or antigen binding fragment thereof. In alternative embodiments, the PD-1 antagonist is an anti-PD-L1 antibody, or antigen binding fragment thereof. In some embodiments, the PD-1 antagonist is pembrolizumab (KEYTRUDA™, Merck & Co., Inc., Kenilworth, NJ, USA), nivolumab (OPDIVO™, Bristol-Myers Squibb Company, Princeton, NJ, USA), cemiplimab (LIBTAYO™, Regeneron Pharmaceuticals, Inc., Tarrytown , NY, USA), atezolizumab (TECENTRIQ™, Genentech, San Francisco, CA, USA), durvalumab (IMFINZI™, AstraZeneca Pharmaceuticals LP, Wilmington, DE), or avelumab (BAVENCIO™, Merck KGaA, Darmstadt, Germany).

In some embodiments, the PD-1 antagonist is pembrolizumab. In particular sub-embodiments, the method comprises administering 200 mg of pembrolizumab to the patient about every three weeks. In other sub-embodiments, the method comprises administering 400 mg of pembrolizumab to the patient about every six weeks.

In further sub-embodiments, the method comprises administering 2 mg/kg of pembrolizumab to the patient about every three weeks. In particular sub-embodiments, the patient is a pediatric patient.

In some embodiments, the PD-1 antagonist is nivolumab. In particular sub-embodiments, the method comprises administering 240 mg of nivolumab to the patient about every two weeks. In other sub-embodiments, the method comprises administering 480 mg of nivolumab to the patient about every four weeks.

In some embodiments, the PD-1 antagonist is cemiplimab. In particular embodiments, the method comprises administering 350 mg of cemiplimab to the patient about every 3 weeks.

In some embodiments, the PD-1 antagonist is atezolizumab. In particular sub-embodiments, the method comprises administering 1200 mg of atezolizumab to the patient about every three weeks.

In some embodiments, the PD-1 antagonist is durvalumab. In particular sub-embodiments, the method comprises administering 10 mg/kg of durvalumab to the patient about every two weeks.

In some embodiments, the PD-1 antagonist is avelumab. In particular sub-embodiments, the method comprises administering 800 mg of avelumab to the patient about every two weeks.

Examples of cytotoxic agents that may be used in combination with the compounds of general formula (I), compounds of general formula (II), compounds of general formula (III), compounds of general formula (IV), compounds of general formula (V), compounds of general formula (VI), or pharmaceutically acceptable salts of the foregoing, include, but are not limited to, arsenic trioxide (sold under the tradename TRISENOX®), asparaginase (also known as L-asparaginase, and Erwinia L-asparaginase, sold under the tradenames ELSPAR® and KIDROLASE®).

Chemotherapeutic agents that may be used in combination with the compounds of general formula (I), compounds of general formula (II), compounds of general formula (III), compounds of general formula (IV), compounds of general formula (V), compounds of general formula (VI), or pharmaceutically acceptable salts of the foregoing, disclosed herein include abiraterone acetate, altretamine, anhydrovinblastine, auristatin, bexarotene, bicalutamide, BMS 184476, 2,3,4,5,6-pentafluoro-N-(3-fluoro-4-methoxyphenyl) benzene sulfonamide, bleomycin, N,N-dimethyl-L-valyl-L-valyl-N-methyl-L-valyl-L-prolyl- 1-Lproline-t-butylamide, cachectin, cemadotin, chlorambucil, cyclophosphamide, 3',4'-didehydro-4'deoxy-8'-norvin-caleukoblastine, docetaxol, doxetaxel, cyclophosphamide, carboplatin, carmustine, cisplatin, cryptophycin, cyclophosphamide, cytarabine, dacarbazine (DTIC), dactinomycin, daunorubicin, decitabine dolastatin, doxorubicin (adriamycin), etoposide, 5-fluorouracil, finasteride, flutamide, hydroxyurea and hydroxyurea andtaxanes, ifosfamide, liarozole, lonidamine, lomustine (CCNU), MDV3100, mechlorethamine (nitrogen mustard), melphalan, mivobulin isethionate, rhizoxin, sertenef, streptozocin, mitomycin, methotrexate, taxanes, nilutamide, nivolumab, onapristone, paclitaxel, pembrolizumab, prednimustine, procarbazine, RPR109881, stramustine phosphate, tamoxifen, tasonermin, taxol, tretinoin, vinblastine, vincristine, vindesine sulfate, and vinflunine. Such chemotherapeutic agents may be provided as a pharmaceutically acceptable salt, where appropriate.

Examples of vascular endothelial growth factor (VEGF) receptor inhibitors include, but are not limited to, bevacizumab (sold under the trademark AVASTIN), axitinib (described in PCT International Patent Publication No. WO01/002369), Brivanib Alaninate ((S)-((R)-1-(4-(4-Fluoro-2-methyl-1H-indol-5-yloxy)-5-methylpyrrolo[2,1-f][1,2,4]triazin-6-yloxy) propan-2-yl)2-aminopropanoate, also known as BMS-582664), motesanib (N-(2,3-dihydro-3,3-dimethyl-1H-

indol-6-yl)-2-[(4-pyridinylmethyl)amino]-3-pyridinecarboxamide. and described in PCT International Patent Application Publication No. WO02/068470), pasireotide (also known as SO 230, and described in PCT International Patent Publication No. WO02/010192), and sorafenib (sold under the tradename NEXAVAR). Such inhibitors may be provided as a pharmaceutically acceptable salt, where appropriate.

Examples of topoisomerase II inhibitors, include but are not limited to, etoposide (also known as VP-16 and Etoposide phosphate, sold under the tradenames TOPOSAR, VEPESID, and ETOPOPHOS), and teniposide (also known as VM-26, sold under the tradename VUMON). Such inhibitors may be provided as a pharmaceutically acceptable salt, where appropriate.

Examples of alkylating agents, include but are not limited to, 5-azacytidine (sold under the trade name VIDAZA), decitabine (sold under the trade name of DECOGEN), temozolomide (sold under the trade names TEMCAD, TEMODAR, and TEMODAL), dactinomycin (also known as actinomycin-D and sold under the tradename COSMEGEN), melphalan (also known as L-PAM, L-sarcolysin, and phenylalanine mustard, sold under the tradename ALKERAN), altretamine (also known as hexamethylmelamine (HMM), sold under the tradename HEXALEN), carmustine (sold under the tradename BCNU), bendamustine (sold under the tradename TREANDA), busulfan (sold under the tradenames BUSULFEX® and MYLERAN®), carboplatin (sold under the tradename PARAPLATIN®), lomustine (also known as CCNU, sold under the tradename CEENU®), cisplatin (also known as CDDP, sold under the tradenames PLATINOL® and PLATINOL®-AQ), chlorambucil (sold under the tradename LEUKERAN®), cyclophosphamide (sold under the tradenames CYTOXAN® and NEOSAR®), dacarbazine (also known as DTIC, DIC and imidazole carboxamide, sold under the tradename DTIC-DOME®), altretamine (also known as hexamethylmelamine (HMM) sold under the tradename HEXALEN®), ifosfamide (sold under the tradename IFEX®), procarbazine (sold under the tradename MATULANE®), mechlorethamine (also known as nitrogen mustard, mustine and mechloroethamine hydrochloride, sold under the tradename MUSTARGEN®), streptozocin (sold under the tradename ZANOSAR®), thiotepa (also known as thiophosphoamide, TESPA and TSPA, and sold under the tradename THIOPLEX®. Such alkylating agents may be provided as a pharmaceutically acceptable salt, where appropriate.

Examples of anti-tumor antibiotics include, but are not limited to, doxorubicin (sold under the tradenames ADRIAMYCIN® and RUBEX®), bleomycin (sold under the tradename LENOXANE®), daunorubicin (also known as dauorubicin hydrochloride, daunomycin, and

rubidomycin hydrochloride, sold under the tradename CERUBIDINE®), daunorubicin liposomal (daunorubicin citrate liposome, sold under the tradename DAUNOXOME®), mitoxantrone (also known as DHAD, sold under the tradename NOVANTRONE®), epirubicin (sold under the tradename ELLENCE™), idarubicin (sold under the tradenames IDAMYCIN®, IDAMYCIN PFS®), and mitomycin C (sold under the tradename MUTAMYCIN®). Such anti-tumor antibiotics may be provided as a pharmaceutically acceptable salt, where appropriate.

Examples of anti-metabolites include, but are not limited to, claribine (2-chlorodeoxyadenosine, sold under the tradename LEUSTATIN®), 5-fluorouracil (sold under the tradename ADRUCIL®), 6-thioguanine (sold under the tradename PURINETHOL®), pemetrexed (sold under the tradename ALIMTA®), cytarabine (also known as arabinosylcytosine (Ara-C), sold under the tradename CYTOSAR-U®), cytarabine liposomal (also known as Liposomal Ara-C, sold under the tradename DEPOCYT™), decitabine (sold under the tradename DACOGEN®), hydroxyurea and (sold under the tradenames HYDREA®, DROXIA™ and MYLOCEL™), fludarabine (sold under the tradename FLUDARA®), floxuridine (sold under the tradename FUDR®), cladribine (also known as 2-chlorodeoxyadenosine (2-CdA) sold under the tradename LEUSTATIN™), methotrexate (also known as amethopterin, methotrexate sodium (MTX), sold under the tradenames RHEUMATREX® and TREXALL™), and pentostatin (sold under the tradename NIPENT®). Such anti-metabolites may be provided as a pharmaceutically acceptable salt, where appropriate.

Examples of retinoids include, but are not limited to, alitretinoin (sold under the tradename PANRETIN®), tretinoin (all-trans retinoic acid, also known as ATRA, sold under the tradename VESANOID®), Isotretinoin (13-c/s-retinoic acid, sold under the tradenames ACCUTANE®, AMNESTEEM®, CLARAVIS®, CLARUS®, DECUTAN®, ISOTANE®, IZOTECH®, ORATANE®, ISOTRET®, and SOTRET®), and bexarotene (sold under the tradename TARGRETIN®). Such compounds may be provided as a pharmaceutically acceptable salt, where appropriate.

Activity: STING Biochemical [3H]cGAMP Competition Assay

The individual compounds described in the Examples herein are defined as STING agonists by (i) binding to the STING protein as evidenced by a reduction in binding of tritiated cGAMP ligand to the STING protein by at least 20% at 20uM (concentration of compound being tested) in a STING Biochemical [3H]cGAMP Competition Assay and/or (ii) demonstrating

interferon production with a 6% or greater induction of IFN-β secretion at 30uM in the THP1 cell assay (where induction caused by cGAMP at 30uM was set at 100%).

The ability of compounds to bind STING is quantified by the ability to compete with tritiated cGAMP ligand for human STING receptor membrane using a radioactive filter-binding assay. The binding assay employs STING receptor obtained from Hi-Five cell membranes overexpressing full-length HAQ STING prepared in-house and tritiated cGAMP ligand also purified in-house.

The following experimental procedures detail the preparation of specific examples of the instant disclosure. The compounds of the examples are drawn in their neutral forms in the procedures and tables below. In some cases, the compounds were isolated as salts depending on the method used for their final purification and/or intrinsic molecular properties. The examples are for illustrative purposes only and are not intended to limit the scope of the instant disclosure in any way.

EXAMPLES

ABBREVIATIONS

2',3'cGAMP, cGAMP	2',3'-cyclic guanosine monophosphate-adenosine monophosphate
18-Crown-6	1,4,7,10,13,16-hexaoxacyclooctadecane
Ac	Acetyl
ACN, MeCN	Acetonitrile
AcOH, HOAc	Acetic acid
AMP	Adenosine monophosphate
aq	Aqueous
ATP	Adenosine 5'-triphosphate
BIIC	Baculovirus Infected Insect Cell
br	Broad
Bu	Butyl, C_4H_9
cat	Catalog number
CBZ	Benzyl chlorocarbonate
CD_3OD	Deuterium-enriched methyl alcohol, deuterium-enriched methanol
$CDCl_3$	Deuterated trichloromethane, deuterated chloroform

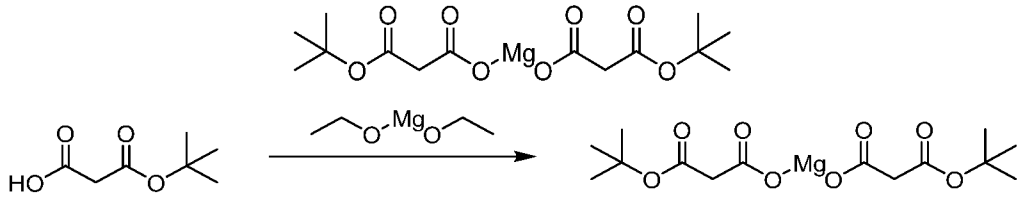
CDI	Carbonyl diimidazole
cGAMP	Cyclic GMP-AMP synthase
Ci	Curie, a non-standard unit of radioactivity; $1Ci=3.7\times10^{10}Bq$, where Bq is Becquerel, the SI unit of radioactivity, equivalent to 1 disintegration per second (dps)
C-Phos Pd G3	[(2-Dicyclohexylphosphino-2′,6′-bis(N,N-dimethylamino) -1,1′-biphenyl)-2-(2′-amino-1,1′-biphenyl)] palladium(II) methanesulfonate
C-Phos Pd G4	2-Aminobiphenylpalladium methanesulfonate palladium CPhos precatalyst (4^{th} generation precatalyst); [(2-Dicyclohexylphosphino-2′,6′-bis(N,N-dimethylamino) -1,1′-biphenyl)-2-(2′-methylamino-1,1′-biphenyl)] palladium(II) methanesulfonate
Cy	Cyclohexyl
d	Doublet
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-Dichloroethane
DCM, CH_2Cl_2	Dichloromethane
ddd	Doublet of doublet of doublet
ddt	Doublet of doublet of triplet
DIAD	Diisopropyl azodicarboxylate
DIPEA	N,N-Diisopropylethylamine
DMA	Dimethylacetamide
DMAP	4-dimethylaminopyridine
DME	Dimethylether
DMEA	N,N-dimethyl ethyl amine
DMF	N,N-dimethylformamide
DMPU	1,3-Dimethyl-3,4,5,6-tetrahydro-2-pyrimidinone
DMSO	Dimethylsulfoxide
DMTr	4,4'-dimethoxytrityl
DMTrCl	4,4'-dimethoxytrityl chloride
dq	Doublet of quartet

EC_{50}	half maximal effective concentration; concentration of a drug, antibody, or toxicant that induces a response halfway between the baseline and maximum after a specified exposure time
EDC	Ethylene dichloride
eq	Equivalents
ES	Electron spray
Et	Ethyl, C_2H_5
GMP	Guanosine 5'-monophosphate
Grubbs catalyst 2G	(1,3-Bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene)dichloro (phenylmethylene)(tricyclohexylphosphine)ruthenium; Benzylidene[1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene] dichloro(tricyclohexylphosphine)ruthenium; Dichloro[1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene](benzylidene) (tricyclohexylphosphine)ruthenium(II)
GTP	Guanosine 5'-triphosphate
h	Hour
HAQ STING	Common STING variant containing the three mutations R71H-G230A-R293Q (DNA construct used herein: STING(1-379)R71H, G230A,H232R,R293Q-GG-AviTag-GS-HRV3C-HIS8/pBAC1)
HEPES	2-[4-(2-hydroxyethyl)piperazin-1-yl]ethanesulfonic acid, a zwitterionic organic chemical buffering agent
hept	Heptet
Hex	Hexanes
HPLC	High performance liquid chromatography
IC_{50}	half maximal inhibitory concentration; concentration of a drug, antibody, or toxicant required for 50% inhibition of response or binding
Inh	Inhibition
IPA	Isopropyl alcohol, $CH_3CHOHCH_3$
LAH	Lithium aluminum hydride
Lawesson's reagent	2,4-Bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane-2,4-dithione
LCMS	Liquid chromatography-mass spectroscopy

LDA	Lithium di-isopropyl amide
m	Multiplet
M	Molar, moles per liter
m/z	Mass-to-charge ratio
M+H	Protonated mass, mass measurement produced by mass spectrometry
Me	Methyl, CH_3
min	Minute(s)
MOI	Multiplicity of infection
MOM-Cl	Cloromethyl methyl ether
MP-TsOH	*para*-Tolune sulfonated macroporous polystyrene resin
n-BuLi	n-Butyl lithium
NBS	N-Bromosuccinamide
NCS	N-Chlorosuccinamide
NMP	N-methyl-2-pyrrolidone
OXONE®	Potassium peroxymonosulfate, specifically $2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$
Pd/C	Palladium on carbon
$PdCl_2(dppf)\text{-}CH_2Cl_2$	[1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane
$Pd(Ph_3P)_4$	Tetrakis(triphenyl phosphine) palladium(0)
$Pd_2(dba)_3$	Tris(dibenzylidene acetone) dipalladium(0)
PE	Petroleum ether
pfu	Plaque-forming unit
Ph_3P	Triphenyl phosphine
prep-HPLC	Preparative high performance liquid chromatography
prep-TLC	Preparative thin layer liquid chromatography
PS-TPP	Polymer-supported triphenylphospine
PSI	Pounds per square inch
pTsOH	*para*-Tolunesulfonic acid
Py, py	Pyridine
q	Quartet
Rac, rac	Racemic

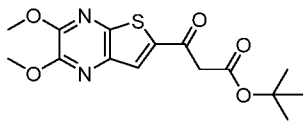
Rac BINAP Pd G3	2-(2-aminophenyl)benzen-1-ide methanesulfonic acid {1-[2-(diphenyl-phosphanyl)naphthalen-1-yl]naphthalen-2-yl}diphenylphosphane palladium
RockPhos Pd G3	[(2-Di-*tert*-butylphosphino-3-methoxy-6-methyl-2′,4′,6′-triisopropyl-1,1′-biphenyl)-2-(2-aminobiphenyl)]palladium(II) methanesulfonate
RP-HPLC	Reverse-phase high performance liquid chromatography
RPM, rpm	Revolutions per minute
RT, rt	Room temperature, approximately 25°C
s	Singlet
sat	Saturated
SFC	Supercritical fluid chromatography
t	Triplet
TBAF, nBu_4NF	Tetra-n-Butylammonium fluoride
TBS, TBDMS	*tert*-Butyldimethylsilyl
TBTU	2-(1H-Benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate
TEA	Triethylamine
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Trimethylsilyl
T_R	Retention time
TrisCl	Tris(hydroxymethyl)aminomethane hydrochloride
v/v	Volume/volume
WT STING	Wild type (most abundant) variant of STING in humans (DNA construct used herein: STING(1-379)H232R-gg-AviTag-gs-HRV3C-HIS8/pBAC1)
X-Phos	2-Dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl
Xantphos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene
λ_{em}	Emission wavelength
λ_{ex}	Excitation wavelength

Preparation 1: Magnesium 3-(*tert*-butoxy)-3-oxopropanoate

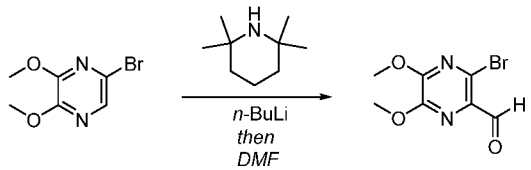


Magnesium ethanolate (3.57g, 31.2mmol) was added to a mixture of 3-(*tert*-butoxy)-3-oxopropanoic acid (10.0g, 62.4mmol) in THF (100mL) at 20°C. The reaction mixture was stirred at 20°C for 18h under Ar. The reaction mixture was then concentrated under reduced pressure. The residue was dried under reduced pressure to afford magnesium 3-(*tert*-butoxy)-3-oxopropanoate. ^{1}H NMR (499MHz, DMSO-d_6) δ 2.96 (s, 4H), 1.39 (s, 18H).

Preparation 2: *tert*-Butyl 3-(2,3-dimethoxythieno[2,3-b]pyrazin-6-yl)-3-oxopropanoate

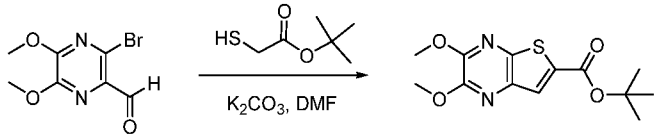


Step 1: 3-Bromo-5,6-dimethoxypyrazine-2-carbaldehyde



To a solution of 2,2,6,6-tetramethylpiperidine (5.12mL, 30.1mmol) in THF (40mL) at -78°C was added dropwise a solution of *n*-BuLi (2.5M in Hex, 11.5mL, 28.8mmol). The reaction mixture was stirred for 10min at -78°C and then warmed to 0°C and stirred for 20min. The reaction mixture was then cooled back to -78°C, and a solution of 5-bromo-2,3-dimethoxypyrazine (3.00g, 13.7mmol) in THF (10mL) was added over 5min. The reaction mixture was stirred at -78°C for 1h and then quenched with DMF (1.06mL, 13.7mmol). The reaction mixture was warmed to 0°C and stirred for an additional 20min. AcOH (3.0mL) was added at 0°C, and the reaction mixture was warmed to RT and stirred overnight. The mixture was diluted with EtOAc (300mL) and then washed with H_2O (2x150mL) and sat aq NaCl. The organic layer was separated, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting EtOAc in Hex) to afford 3-bromo-5,6-dimethoxypyrazine-2-carbaldehyde. LCMS ($C_7H_8BrN_2O_3$) (ES, m/z): 247, 249 $[M+H]^+$. ^{1}H NMR (500MHz, $CDCl_3$) δ 10.19 (s, 1H), 4.17 (s, 3H), 4.14 (s, 3H).

Step 2: tert-*Butyl 2,3-dimethoxythieno[2,3-b]pyrazine-6-carboxylate*

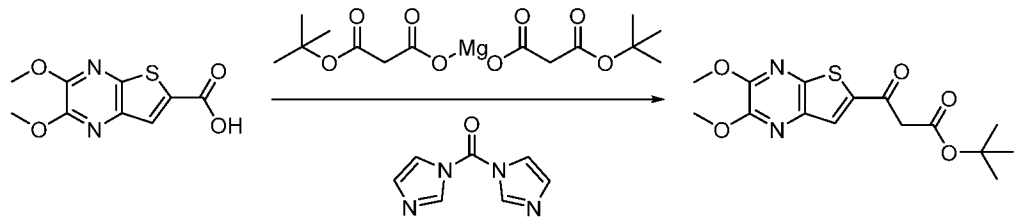


tert-Butyl 2-sulfanylacetate (424µL, 2.92mmol) and DMF (2.9mL) were added to 3-bromo-5,6-dimethoxypyrazine-2-carbaldehyde (650mg, 2.63mmol) at RT. K_2CO_3 (1090mg, 7.89mmol) was then added portion-wise to the reaction mixture at RT. The reaction mixture was heated to 80°C and stirred overnight. The reaction mixture was then cooled to RT, diluted with Et_2O, and quenched with H_2O. The reaction mixture was extracted with Et_2O, and the combined organics were washed with sat aq NaCl, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting EtOAc in Hex) to yield *tert*-butyl 2,3-dimethoxythieno[2,3-b]pyrazine-6-carboxylate. LCMS ($C_{13}H_{17}N_2O_4S$) (ES, m/z): 297 $[M+H]^+$. ^1H NMR (500MHz, DMSO-d_6) δ 7.89 (s, 1H), 4.02 (s, 3H), 3.99 (s, 3H), 1.55 (s, 9H).

Step 3: 2,3-Dimethoxythieno[2,3-b]pyrazine-6-carboxylic acid

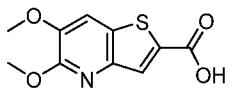
To a stirred solution of *tert*-butyl 2,3-dimethoxythieno[2,3-b]pyrazine-6-carboxylate (400mg, 1.35mmol) in DCM (6.0mL) was added HCl (4.0M in dioxane, 1.7mL, 6.8mmol) at RT. The reaction mixture was stirred overnight at RT, and then diluted by the dropwise addition of Hex (50mL) and stirred for 1h at RT. The reaction mixture was filtered, and the collected materials were washed with Hex (2x10mL) and dried under reduced pressure to afford 2,3-dimethoxythieno[2,3-b]pyrazine-6-carboxylic acid. LCMS ($C_9H_9N_2O_4S$) (ES, m/z): 241 $[M+H]^+$. ^1H NMR (500MHz, DMSO-d_6) δ 12.71 (br s, 1H), 7.90 (s, 1H), 4.03 (s, 3H), 3.99 (s, 3H).

Step 4: <u>tert-*Butyl 3-(2,3-dimethoxythieno[2,3-b]pyrazin-6-yl)-3-oxopropanoate*</u>

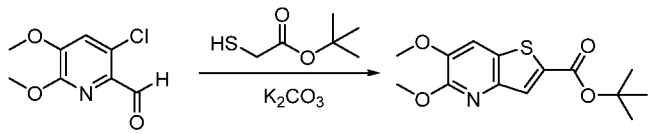


A mixture of 2,3-dimethoxythieno[2,3-b]pyrazine-6-carboxylic acid (80mg, 0.33mmol) and CDI (324mg, 2.00mmol) in THF (5.5mL) was stirred at RT for 3 h. Magnesium bis(3-*tert*-butoxy-3-oxopropanoate) (628mg, 1.83mmol) was added to the mixture, and the resulting mixture was stirred overnight at RT. The reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting (25% EtOH in EtOAc) in Hex) to afford *tert*-butyl 3-(2,3-dimethoxythieno[2,3-b]pyrazin-6-yl)-3-oxopropanoate. LCMS ($C_{15}H_{19}N_2O_5S$) (ES, m/z): 339 $[M+H]^+$. ^1H NMR (500MHz, DMSO-d_6) δ 8.32 (s, 1H), 4.13 (s, 2H), 4.04 (s, 3H), 4.00 (s, 3H), 1.41 (s, 9H).

Preparation 3: 5,6-Dimethoxythieno[3,2-b]pyridine-2-carboxylic acid

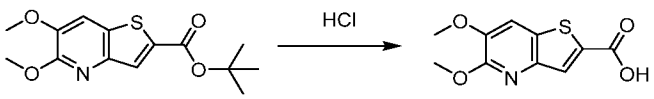


Step 1: tert-*Butyl 5,6-dimethoxythieno[3,2-b]pyridine-2-carboxylate*



K_2CO_3 (1180mg, 8.56mmol) was added to a mixture of 3-chloro-5,6-dimethoxypicolinaldehyde (575mg, 2.86mmol) and *tert*-butyl 2-sulfanylacetate (0.456mL, 3.14mmol) in DMF (8.3mL) at RT. The reaction mixture was stirred and heated to 60°C for 3 days. The reaction mixture was cooled to RT, and then diluted with Et_2O and H_2O. The organic layer was separated, washed with sat aq NaCl, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting EtOAc in Hex) to afford *tert*-butyl 5,6-dimethoxythieno[3,2-b]pyridine-2-carboxylate. ^1H NMR (499MHz, DMSO-d_6) δ 7.95 (s, 1H), 7.84 (s, 1H), 3.93 (s, 3H), 3.87 (s, 3H), 1.54 (s, 9H).

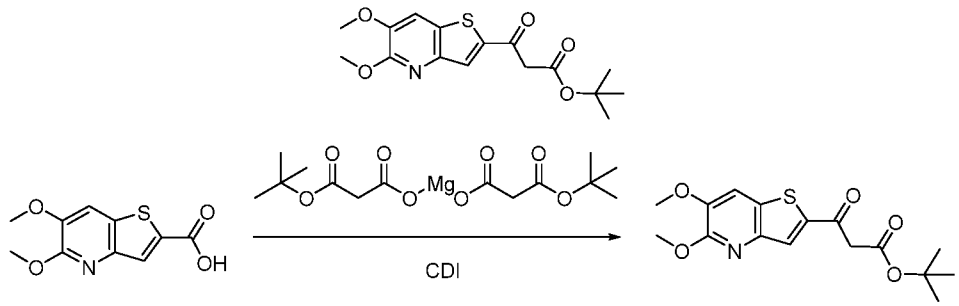
Step 2: 5,6-dimethoxythieno[3,2-b]pyridine-2-carboxylic acid



HCl (4.0M in H_2O, 2.1mL, 8.4mmol) was added to a solution of *tert*-butyl 5,6-dimethoxythieno[3,2-b]pyridine-2-carboxylate (493mg, 1.67mmol) in DCM (7.4mL) at RT. The reaction mixture was stirred overnight at RT, and then diluted by the dropwise addition of Hex (50mL). The mixture was stirred for 1 h and then filtered. The collected materials were washed with Hex (2x10mL) and then dried under reduced pressure to afford 5,6-dimethoxythieno[3,2-

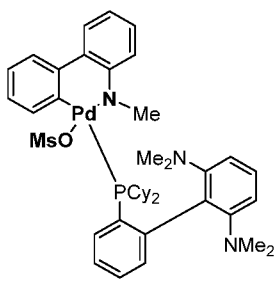
b]pyridine-2-carboxylic acid. LCMS ($C_{10}H_{10}NO_4S$) (ES, m/z): 240 $[M+H]^+$. ^1H NMR (499MHz, DMSO-d_6) δ 7.97 (s, 1H), 7.85 (s, 1H), 3.95 (s, 3H), 3.88 (s, 3H).

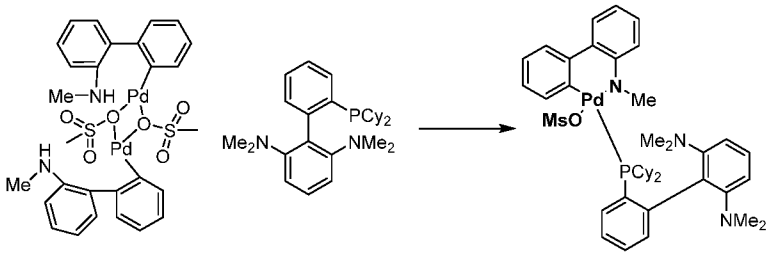
Preparation 4: *tert*-Butyl 3-(5,6-dimethoxythieno[3,2-b]pyridin-2-yl)-3-oxopropanoate



CDI (508mg, 3.13mmol) was added to a mixture of 5,6-dimethoxythieno[3,2-b]pyridine-2-carboxylic acid (500mg, 2.09mmol) in THF (5mL). The reaction mixture was stirred at RT for 3 h. The reaction mixture was added to a separate flask containing magnesium 3-(*tert*-butoxy)-3-oxopropanoate (1220mg, 3.55mmol). The reaction mixture was diluted with additional THF (4mL) and was stirred overnight at RT. The reaction mixture was then heated to 50°C for 1 h. The reaction mixture was cooled to RT and diluted with H_2O (20mL). Sodium citrate tribasic dihydrate (2g) and EtOAc (50mL) were added. The organic layer was separated, and the aqueous layer was extracted with EtOAc. The organic layers were combined, washed with sat aq NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified via silica gel chromatography (eluting EtOAc in Hex) to afford *tert*-butyl 3-(5,6-dimethoxythieno[3,2-b]pyridin-2-yl)-3-oxopropanoate. LCMS ($C_{16}H_{20}NO_5S$) (ES, m/z): 338 $[M+H]^+$. ^1H NMR (500MHz, $CDCl_3$) δ 7.97 (s, 1H), 7.44 (s, 1H), 4.13 (s, 3H), 3.99 (s, 3H), 3.92 (s, 2H), 1.48 (s, 9H).

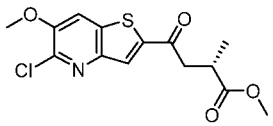
Preparation 5: C-Phos Pd G4



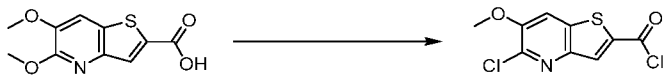


A mixture of (2'-methylamino-1,1'-biphenyl-2-yl)methanesulfonatopalladium (II) dimer (439mg, 0.573mmol) and 2'-(dicyclohexylphosphino)-*N*2,*N*2,*N*6,*N*6-tetramethyl-[1,1'-biphenyl]-2,6-diamine (500mg, 1.15mmol) in DCM (6mL) was stirred at RT for 2h. The solution was then diluted with Et_2O (30mL). The solution was filtered and concentrated under reduced pressure. The residue was then slurried in pentanes and again concentrated under reduced pressure to afford C-Phos Pd G4. *See* Bruno, N. C.; Niljianskul, N.; Buchwald, S. L. *J. Org. Chem.* **2014**, *79*, 4161.

Intermediate 1: methyl (S)-4-(5-chloro-6-methoxythieno[3,2-b]pyridin-2-yl)-2-methyl-4-oxobutanoate

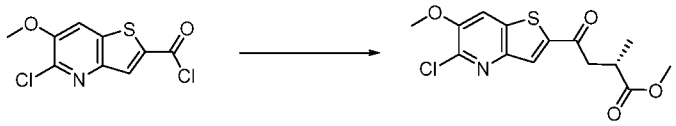


Step 1: 5-Chloro-6-methoxythieno[3,2-b]pyridine-2-carbonyl chloride



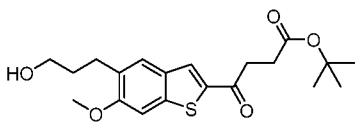
$POCl_3$ (1.17mL, 12.5mmol) was added dropwise to a stirred mixture of 5,6-dimethoxythieno[3,2-b]pyridine-2-carboxylic acid (1.00g, 4.1 mmol) in DMF (10.45 ml) at 0°C under N_2. After 10min, the reaction mixture was allowed to warm to RT. The reaction mixture was then heated to 100°C and stirred for 45min. The reaction mixture was added ice water (100mL) and stirred. The mixture was filtered, and the collected materials were washed with water (2x30mL) and Hex (50 mL). The collected materials were diluted with Et_2O (50mL) and filtered. The collected materials were dissolved in CH_2Cl_2 (60mL), and the mixture was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford 5-chloro-6-methoxythieno[3,2-b]pyridine-2-carbonyl chloride. ^1H NMR (500MHz, $CDCl_3$) δ 8.32 (s, 1H), 7.60 (s, 1H), 4.06 (s, 3H).

Step 2: Methyl (S)-4-(5-chloro-6-methoxythieno[3,2-b]pyridin-2-yl)-2-methyl-4-oxobutanoate

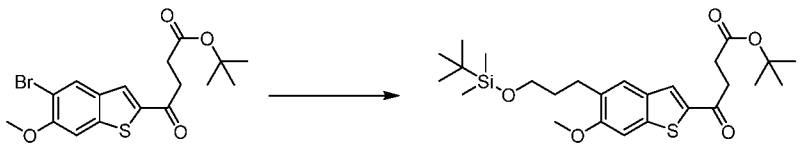


CuI (0.073g, 0.38mmol) was placed under vacuum and heated for 1min with a heat gun. The flask was allowed to cool to RT and was then opened to N_2. Twice more the flask was evacuated then backfilled with N_2. The flask was kept under positive N_2 pressure with a rubber septum and N_2 inlet attached. THF (2 mL) was added to the flask, and the reaction mixture was cooled in an ice water bath. A solution of (*R*)-(3-methoxy-2-methyl-3-oxopropyl) zinc(II) bromide in THF (0.50M, 1.68 mL, 0.84mmol) was added dropwise to the reaction mixture over a period of 5min. The reaction mixture was stirred for 105min at 0°C. A mixture of 5-chloro-6-methoxythieno[3,2-b]pyridine-2-carbonyl chloride (0.200g, 0.763mmol) in NMP (3 mL) was then added dropwise over 5min. The reaction mixture was then stirred for 3 h at 0°C. The reaction mixture was then added to a stirred mixture of isopropyl acetate (50mL) and sodium citrate (20% w/v in water, 50mL). After stirring for 20min, the layers were separated, and the aqueous layer was extracted with isopropyl acetate (30mL). The organic layers were combined, washed with sat aq NaCl (2x50mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting EtOAc in Hex) to afford (S)-methyl 4-(5-chloro-6-methoxythieno[3,2-b]pyridin-2-yl)-2-methyl-4-oxobutanoate. LCMS ($C_{14}H_{15}ClNO_4S$) (ES, m/z): 328 $[M+H]^+$. ^1H NMR (500MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.60 (s, 1H), 4.03 (s, 3H), 3.72 (s, 3H), 3.51 (dd, *J*=17.2, 7.9Hz, 1H), 3.21-3.12 (m, 1H), 3.06 (dd, *J*=17.2, 5.2Hz, 1H), 1.32 (d, *J*=7.1Hz, 3H).

Intermediate 2:* tert-*Butyl 4-(5-(3-hydroxypropyl)-6-methoxybenzo[b]thiophen-2-yl)-4-oxobutanoate

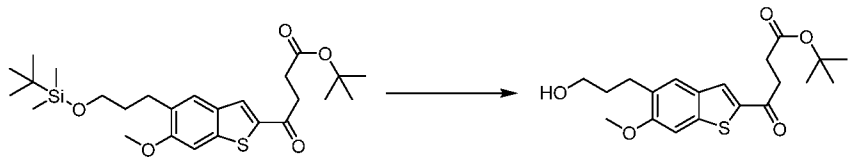


Step 1: tert-*butyl 4-(5-(3-((*tert-*butyldimethylsilyl)oxy)propyl)-6-methoxybenzo[b]thiophen-2-yl)-4-oxobutanoate*



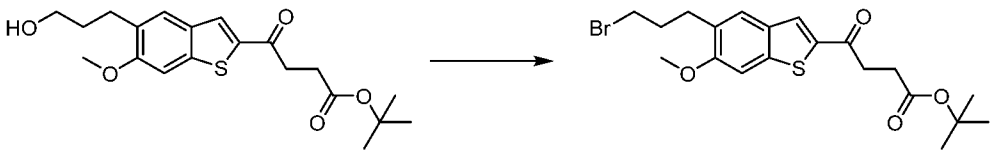
tert-Butyl 4-(5-bromo-6-methoxybenzo[b]thiophen-2-yl)-4-oxobutanoate (1.75g, 4.38mmol; 81% pure) and C-Phos Pd G3 (0.177g, 0.219mmol) were added to a 40mL vial with a septum-containing screw cap. The vial was evacuated and backfilled with N_2 three times. THF (15.7mL) was added to the vial under N_2 with stirring. While stirring the resulting suspension at RT, (3-((*tert*-butyldimethylsilyl)oxy)propyl)zinc(II) bromide (0.50M in THF, 17.5mL, 8.75mmol) was added dropwise with stirring. The mixture was stirred at RT for 18h. The reaction was then partitioned between EtOAc (75mL) and 10% aq sodium citrate (75mL) and stirred vigorously for 5min. The layers were separated, and the aqueous layer was extracted with EtOAc (20mL). The organic layers were combined, washed with sat aq NaCl (50mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (0→40% EtOAc gradient in Hex) to afford *tert*-butyl 4-(5-(3-((*tert*-butyldimethylsilyl)oxy)propyl)-6-methoxybenzo[b]thiophen-2-yl)-4-oxobutanoate. LCMS ($C_{26}H_{40}NaO_5SSi$) (ES, m/z): 515 $[M+Na]^+$. ^1H NMR (500MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.62 (s, 1H), 7.24 (s, 1H), 3.92 (s, 3H), 3.67 (t, *J*=6.3Hz, 2H), 3.28 (t, *J*=6.8Hz, 2H), 2.76 (t, *J*=7.2Hz, 2H), 2.72 (t, *J*=7.2Hz, 2H), 1.85 (p, *J*=6.5Hz, 2H), 1.46 (s, 9H), 0.94 (s, 9H), 0.08 (s, 6H).

Step 2: tert-*butyl 4-(5-(3-hydroxypropyl)-6-methoxybenzo[b]thiophen-2-yl)-4-oxobutanoate*



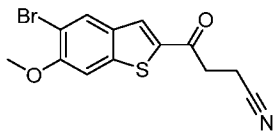
To a mixture of *tert*-butyl 4-(5-(3-((*tert*-butyldimethylsilyl)oxy)propyl)-6-methoxybenzo[b]thiophen-2-yl)-4-oxobutanoate (1.45g, 2.94mmol) in MeOH (5.0mL) was added water (5.0mL) and HOAc (5.0mL). The resulting suspension was stirred at RT for 18h. The reaction was partitioned between EtOAc and aq NaCl. The layers were separated, and the aqueous layer was extracted with EtOAc. The organic layers were combined, washed with sat aq NaCl twice, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford a crude residue. The resulting residue was purified by silica gel chromatography (0→100% EtOAc gradient in Hex) to afford *tert*-butyl 4-(5-(3-hydroxypropyl)-6-methoxybenzo[b]thiophen-2-yl)-4-oxobutanoate. LCMS ($C_{20}H_{26}NaO_5S$) (ES, m/z): 401 $[M+Na]^+$. ^1H NMR (500MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.64 (s, 1H), 7.26 (s, 1H), 3.94 (s, 3H), 3.68 (t, *J*=5.5Hz, 2H), 3.28 (t, *J*=6.6Hz, 2H), 2.82 (t, *J*=7.3Hz, 2H), 2.72 (t, *J*=6.6Hz, 2H), 1.96-1.83 (m, 2H), 1.46 (s, 9H).

Intermediate 3:* tert-*butyl 4-(5-(3-bromopropyl)-6-methoxybenzo[b]thiophen-2-yl)-4-oxobutanoate

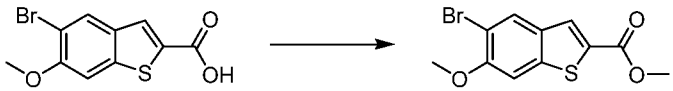


Triphenylphosphine (0.24g, 0.91mmol) was added to a mixture of *tert*-butyl 4-(5-(3-hydroxypropyl)-6-methoxybenzo[b]thiophen-2-yl)-4-oxobutanoate (0.22g, 0.57mmol) in THF (2.8mL). The resulting mixture was cooled to 0°C, and NBS (0.15g, 0.85mmol) was added in a single portion. After stirring for 30min at 0°C, the reaction was diluted with sat aq $AlCl_3$ and EtOAc. The organic layer was separated, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting product was then purified by silica gel chromatography to afford *tert*-butyl 4-(5-(3-bromopropyl)-6-methoxybenzo[b]thiophen-2-yl)-4-oxobutanoate. LCMS ($C_{16}H_{18}BrO_4S$) (ES, m/z): 385, 387 $[M-C_4H_8]^+$. ^1H NMR (500MHz, DMSO-d_6) δ 8.27 (s, 1H), 7.78 (s, 1H), 7.62 (s, 1H), 3.90 (s, 3H), 3.60-3.49 (m, 2H), 3.30-3.21 (m, 2H), 2.88-2.75 (m, 2H), 2.67-2.56 (m, 2H), 2.18-2.06 (m, 2H), 1.38 (s, 9H).

Intermediate 4: 4-(5-bromo-6-methoxybenzo[b]thiophen-2-yl)-4-oxobutanenitrile

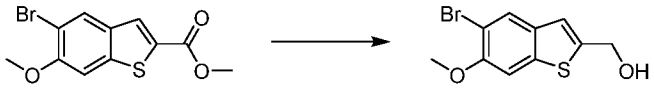


Step 1: methyl 5-bromo-6-methoxybenzo[b]thiophene-2-carboxylate



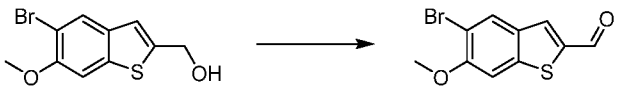
Concentrated H_2SO_4 (3.0mL, 56mmol) was added to a suspension of 5-bromo-6-methoxybenzo[b]thiophene-2-carboxylic acid (5.0g, 17mmol) in MeOH (60mL). The reaction mixture was heated to 70°C for 4.5 days. The mixture was then cooled to RT and diluted with water. To the mixture was added 30% IPA in $CHCl_3$. The organic layer was separated, dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford methyl 5-bromo-6-methoxybenzo[b]thiophene-2-carboxylate. ^1H NMR (500MHz, DMSO-d_6) δ 8.30 (s, 1H), 8.09 (s, 1H), 7.83 (s, 1H), 3.95 (s, 3H), 3.88 (s, 3H).

Step 2: (5-bromo-6-methoxybenzo[b]thiophen-2-yl)methanol



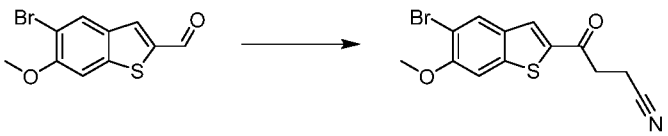
LAH (1.0M in THF, 2.8mL, 2.8mmol) was slowly added to a mixture of methyl 5-bromo-6-methoxybenzo[b]thiophene-2-carboxylate (0.78g, 2.3mmol) in THF (9.0mL) at 0°C. After 40min, the reaction mixture was diluted with sat aq $AlCl_3$. EtOAc was added, and the organic layer was separated, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting material was purified by silica gel chromatography to afford (5-bromo-6-methoxybenzo[b]thiophen-2-yl)methanol. LCMS ($C_{10}H_8BrOS$) (ES, m/z): 255, 257 $[M-OH]^+$. ^1H NMR (500MHz, DMSO-d_6) δ 8.01 (s, 1H), 7.69 (s, 1H), 7.14 (s, 1H), 5.69-5.59 (m, 1H), 4.73-4.64 (m, 2H), 3.89 (s, 3H).

Step 3: 5-bromo-6-methoxybenzo[b]thiophene-2-carbaldehyde



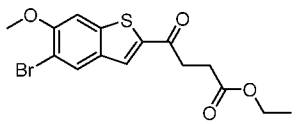
Manganese dioxide (6.3g, 73mmol) was added to a mixture of (5-bromo-6-methoxybenzo[b]thiophen-2-yl)methanol (4.0g, 15mmol) in DCM (97mL). The reaction mixture was stirred at RT for 20 h then filtered through a plug of CELITE. The filtrate was concentrated under reduced pressure. The resulting product was triturated in MeOH and the mixture was passed through a glass frit to collect 5-bromo-6-methoxybenzo[b]thiophene-2-carbaldehyde. LCMS ($C_{10}H_8BrO_2S$) (ES, m/z): 271, 273 $[M+H]^+$. ^1H NMR (500MHz, DMSO-d_6) δ 10.07 (s, 1H), 8.40 (s, 1H), 8.29 (s, 1H), 7.87 (s, 1H), 3.97 (s, 3H).

Step 4: 4-(5-bromo-6-methoxybenzo[b]thiophen-2-yl)-4-oxobutanenitrile

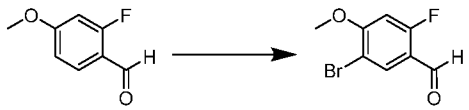


ACN (0.15mL, 2.2mmol) was added to a suspension of 5-bromo-6-methoxybenzo[b]thiophene-2-carbaldehyde (0.30g, 1.1mmol), 2-mesityl-2,5,6,7-tetrahydropyrrolo[2,1-c][1,2,4]triazol-4-ium chloride (0.029g, 0.11mmol) and K_3PO_4 (0.24g, 1.1mmol) in toluene (2.2mL). The reaction mixture was placed under Ar and stirred at RT for 18 h. The reaction mixture was then concentrated under reduced pressure, and the resulting residue was purified by silica gel chromatography to afford 4-(5-bromo-6-methoxybenzo[b] thiophen-2-yl)-4-oxobutanenitrile. LCMS ($C_{13}H_{11}BrNO_2S$) (ES, m/z): 324, 326 $[M+H]^+$. ^1H NMR (500MHz, DMSO-d_6) δ 8.33-8.22 (m, 2H), 7.84 (s, 1H), 3.96 (s, 3H), 3.59-3.44 (m, 2H), 2.88-2.73 (m, 2H).

Intermediate 5: ethyl 4-(5-bromo-6-methoxybenzo[b]thiophen-2-yl)-4-oxobutanoate

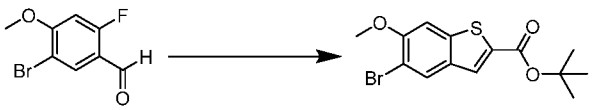


Step 1: 5-Bromo-2-fluoro-4-methoxybenzaldehyde



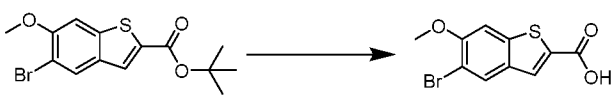
2-Fluoro-4-methoxybenzaldehyde (9.0g, 58mmol) was added slowly (portion-wise) to a solution of Br_2 (6.0mL, 120mmol) in MeOH (40mL) at 0°C. The reaction mixture was stirred at 0°C for 2h. A solution of $NaHSO_3$ (24.3g, 234mmol) in H_2O (300mL) was added slowly to the reaction mixture at 0°C. The resulting suspension was then stirred for 30min at 0°C. The reaction mixture was filtered, and the filtrate was washed with additional H_2O (3x25mL). The filtrate was then dried under reduced pressure to afford 5-bromo-2-fluoro-4-methoxybenzaldehyde. The product was used without purification. ^{1}H NMR (500MHz, DMSO-d_6): δ 10.02 (s, 1H), 7.98 (d, *J*=7.5Hz, 1H), 7.26 (d, *J*=13.0Hz, 1H), 3.97 (s, 3H).

Step 2: tert-Butyl 5-bromo-6-mehoxybenzo[b]thiophene-2-carboxylate



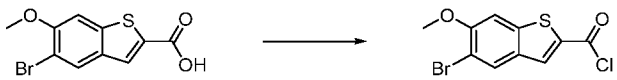
K_2CO_3 (19.0g, 137mmol) was added slowly (portion-wise) to a solution of 5-bromo-2-fluoro-4-methoxybenzaldehyde (10.7g, 45.8mmol) and *tert*-butyl 2-mercaptoacetate (6.65mL, 45.8mmol) in DMF (50mL) at 20°C under Ar. The reaction mixture was stirred and heated to 100°C for 16h. The reaction mixture was then cooled to RT and diluted with Et_2O (1000mL). The mixture was then washed with H_2O (500mL, then 2x250mL), and the combined aq layers were extracted with Et_2O (2x200mL). The organic layers were then combined and washed with sat aq NaCl (50mL). The organic layer was separated, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford *tert*-butyl 5-bromo-6-methoxybenzo [*b*]thiophene-2-carboxylate. The product was used without purification. ^{1}H NMR (500MHz, DMSO-d_6): δ 8.26 (s, 1H), 7.96 (s, 1H), 7.78 (s, 1H), 3.92 (s, 3H), 1.55 (s, 9H).

Step 3: 5-Bromo-6-methoxybenzo[b]thiophene-2-carboxylic acid



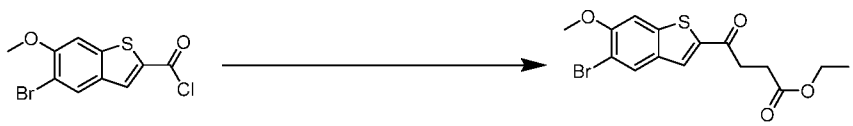
HCl (56mL, 4.0M in 1,4-dioxane, 230mmol) was added to a solution of *tert*-butyl 5-bromo-6-methoxybenzo[*b*]thiophene-2-carboxylate (15.5g, 45.0mmol) in DCM (200mL) at 20°C. The reaction mixture was stirred at 20°C for 3days. The reaction mixture was then diluted by the dropwise addition of Hex (500mL). The resulting suspension was stirred for an additional 2h post-addition at RT. The reaction mixture was filtered, and the collected material was washed with Hex (2x50mL) and dried under reduced pressure to afford 5-bromo-6-methoxybenzo[*b*] thiophene-2-carboxylic acid, which was used without purification. ^{1}H NMR (500MHz, DMSO-d_6): δ 13.42 (s, 1H), 8.26 (s, 1H), 7.98 (s, 1H), 7.80 (s, 1H), 3.93 (s, 3H).

Step 4: 5-Bromo-6-methoxybenzo[b]thiophene-2-carbonyl chloride



DMF (0.049mL, 0.63mmol) was added slowly (dropwise) to a solution of 5-bromo-6-methoxybenzo[*b*]thiophene-2-carboxylic acid (6.0g, 21mmol) and $(COCl)_2$ (5.5mL, 63mmol) in THF (100mL) at 0°C under Ar. The reaction mixture was stirred at 0°C for 2h and then allowed to warm to RT. The reaction mixture was stirred for 18h at RT. The reaction mixture was then concentrated under reduced pressure to afford 5-bromo-6-methoxybenzo[*b*] thiophene-2-carbonyl chloride. The product was used without purification.

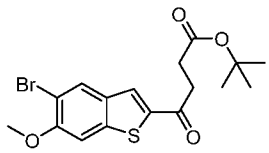
Step 5: Ethyl 4-(5-bromo-6-methoxybenzo[b]thiophen-2-yl)-4-oxobutanoate



A solution of (3-ethoxy-3-oxopropyl)zinc(II) bromide (13.8mL, 0.50M in THF, 6.9mmol) was added to an oven-dried flask containing ((thiophene-2-carbonyl)oxy)copper (1.31g, 6.87mmol) under Ar at 0°C. The reaction mixture was stirred for 20min at 0°C under Ar. An Ar-degassed solution of 5-bromo-6-methoxybenzo[*b*]thiophene-2-carbonyl chloride (1.52g, 4.98mmol) in THF (25.0mL) was then added via cannula to the reaction mixture at 0°C; the resulting suspension was allowed to warm to RT and was stirred for 3h. The reaction mixture was cooled to 0°C and quenched with sat aq NH_4Cl (50mL). The mixture was allowed to warm to RT and stirred for 10min. The mixture was filtered, and the filtrate was diluted with EtOAc (500mL) and sat aq NaCl (50mL). The organic layer was separated, washed with sat aq NaCl (25mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc in DCM) to afford ethyl 4-(5-bromo-6-methoxybenzo[*b*]thiophen-2-yl)-4-oxobutanoate. LCMS ($C_{15}H_{16}BrO_4S$) (ES, m/z): 371, 373

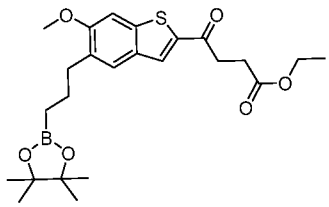
$[M+H]^+$. ^1H NMR (500MHz, DMSO-d_6): δ 8.27 (s, 1H), 8.26 (s, 1H), 7.81 (s, 1H), 4.07-4.02 (m, 2H), 3.94 (s, 3H), 3.35-3.25 (m, 2H), 2.68-2.64 (m, 2H), 1.20-1.14 (m, 3H).

Intermediate 6:* tert-*butyl 4-(5-bromo-6-methoxybenzo[b]thiophen-2-yl)-4-oxobutanoate

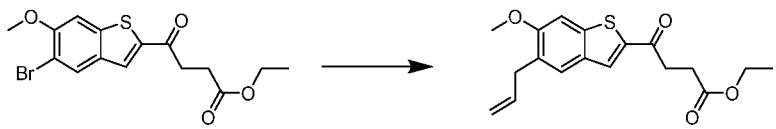


Intermediate 6 may be prepared according to procedures analogous to those outlined for Intermediate 5 above using the appropriate starting materials, described as Preparations or as obtained from commercially available sources.

Intermediate 7: Ethyl 4-(6-methoxy-5-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propyl)benzo[b]thiophen-2-yl)-4-oxobutanoate

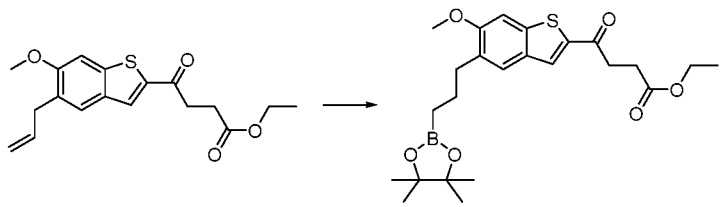


Step 1: Ethyl 4-(5-allyl-6-methoxybenzo[b]thiophen-2-yl)-4-oxobutanoate



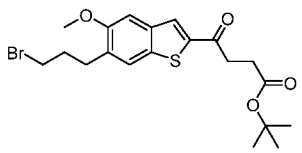
To a vial containing ethyl 4-(5-bromo-6-methoxybenzo[b]thiophen-2-yl)-4-oxobutanoate (5.0g, 13mmol), $Pd(Ph_3P)_4$ (1.6g, 1.3mmol), and dioxane (15mL), was added allyltri-n-butyltin (5.4mL, 18mmol). The reaction was heated to 90°C for 18h. Upon cooling to RT, the mixture was diluted with DCM, filtered through CELITE and added to flask containing aq KF (0.5M, 200mL). The mixture stirred, and the organic layer was then separated, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (0→30% EtOAc gradient in Hex) to afford ethyl 4-(5-allyl-6-methoxybenzo[b]thiophen-2-yl)-4-oxobutanoate. LCMS ($C_{18}H_{21}O_4S$) (ES, m/z): 333 $[M+H]^+$. ^1H NMR (600MHz, DMSO-d_6) δ 8.23 (s, 1H), 7.69 (s, 1H), 7.58 (s, 1H), 5.96 (dq, *J*=15.9, 6.6Hz, 1H), 5.04 (d, *J*=4.5Hz, 1H), 5.02 (s, 1H), 4.01 (q, *J*=7.0Hz, 2H), 3.85 (s, 3H), 3.37 (d, *J*=6.3Hz, 2H), 3.27 (dd, *J*=11.0, 4.3Hz, 2H), 2.62 (t, *J*=6.1Hz, 2H), 1.13 (t, *J*=7.1Hz, 3H).

Step 2: Ethyl 4-(6-methoxy-5-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propyl)benzo[b] thiophen-2-yl)-4-oxobutanoate

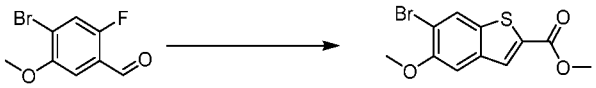


To a mixture of 1,4-bis(diphenylphosphino)butane (0.45g, 1.1mmol), chloro(1,5-cyclooctadiene)iridium(i) dimer (0.35g, 0.53mmol), ethyl 4-(5-allyl-6-methoxybenzo[b] thiophen-2-yl)-4-oxobutanoate (3.5g, 11mmol), and THF (20 mL) was added pinacolborane (1.0M in THF, 15.8mL, 15.8mmol). The reaction was stirred at RT for 4 h. The solvent was then removed under reduced pressure, and the residue was purified by silica gel column chromatography (0→20% EtOAc gradient in Hex) to afford ethyl 4-(6-methoxy-5-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propyl)benzo[b]thiophen-2-yl)-4-oxobutanoate. ^{1}H NMR (600MHz, DMSO-d_6) δ 8.21 (s, 1H), 7.66 (s, 1H), 7.53 (s, 1H), 4.02 (q, *J*=7.0Hz, 2H), 3.84 (s, 3H), 3.27 (t, *J*=6.2Hz, 2H), 2.62 (t, *J*=6.1Hz, 2H), 2.58 (t, J=7.4Hz, 2H), 1.58 (p, *J*=7.4Hz, 2H), 1.16-1.11 (m, 15H), 0.67 (t, *J*=7.6Hz, 2H).

Intermediate 8:* tert-*Butyl 4-(6-(3-bromopropyl)-5-methoxybenzo[b]thiophen-2-yl)-4-oxobutanoate



Step 1: Methyl 6-bromo-5-methoxybenzo[b]thiophene-2-carboxylate



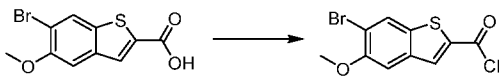
To a stirred solution of 4-bromo-2-fluoro-5-methoxybenzaldehyde (5.00g, 21.5mmol) in DMF (100mL) was added methyl 2-mercaptoacetate (2.51g, 23.6mmol) and K_2CO_3 (8.90g, 64.4mmol). The reaction mixture was degassed with N_2 3 times. The resulting mixture was then stirred at RT for 15h. EtOAc (500mL) and H_2O (1200mL) were added to the reaction mixture. The organic layer was separated and washed with sat aq NaCl (2x200mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc in PE) to give methyl 6-bromo-5-methoxybenzo

[*b*]thiophene-2-carboxylate. LCMS ($C_{11}H_{10}BrO_3S$) (ES, m/z): 301, 303 $[M+H]^+$. ^1H NMR (400MHz, $CDCl_3$): δ=8.01 (s, 1H), 7.93 (s, 1H), 7.26 (s, 1H), 3.96 (s, 3H), 3.94 (s, 3H).

Step 2: 6-Bromo-5-methoxybenzo[b]thiophene-2-carboxylic acid

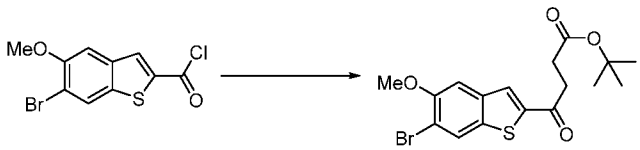
To a suspension of methyl 6-bromo-5-methoxybenzo[*b*]thiophene-2-carboxylate (1.45g, 4.81mmol) in MeOH (20mL), THF (20mL), and H_2O (20mL) was added NaOH (1.93g, 48.1mmol). The resulting suspension was heated to 50°C for 0.5h. The reaction mixture was concentrated under reduced pressure to remove the solvent. H_2O (200mL) was added to the residue, and citric acid was added to adjust the solution to pH=6. The remaining aq suspension was extracted with EtOAc (3x50mL). The combined organic layers were washed with sat aq NaCl (100mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give 6-bromo-5-methoxybenzo[*b*]thiophene-2-carboxylic acid, which was used without further purification. ^1H NMR (400MHz, DMSO-d_6): δ=13.52 (br s, 1H), 8.35 (s, 1H), 8.01 (s, 1H), 7.65 (s, 1H), 3.90 (s, 3H).

Step 3: 6-Bromo-5-methoxybenzo[b]thiophene-2-carbonyl chloride



To a stirred solution of 6-bromo-5-methoxybenzo[*b*]thiophene-2-carboxylic acid (800mg, 2.79mmol) in anhydrous THF (6mL) was added $(COCl)_2$ (1.06g, 8.36mmol) dropwise at 0°C. The mixture was then heated at 75°C for 15h and then cooled to RT. The solvent was removed under reduced pressure to give the crude 6-bromo-5-methoxybenzo[*b*]thiophene-2-carbonyl chloride, which was used without further purification.

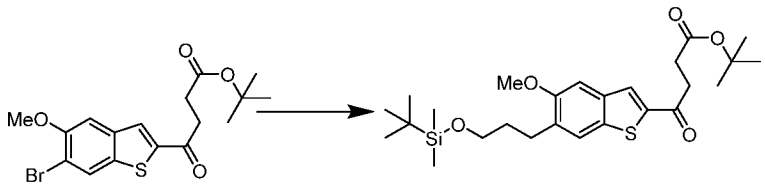
Step 4: tert-Butyl 4-(6-bromo-5-methoxybenzo[b]thiophen-2-yl)-4-oxobutanoate



To a round bottom flask was added CuI (0.24g, 2.4 mmol). The flask was evacuated and then opened to N_2. This was repeated three times. THF (4.0mL) was added and the mixture was cooled to 0°C. A mixture of (3-(*tert*-butoxy)-3-oxopropyl)zinc(II) bromide (0.50M in THF, 9.6mL, 4.8mmol) was added dropwise at 0°C over 10min. The resulting mixture was allowed to stir for 30min. 6-bromo-5-methoxybenzo[b]thiophene-2-carbonyl chloride (0.73 g, 2.4mmol)

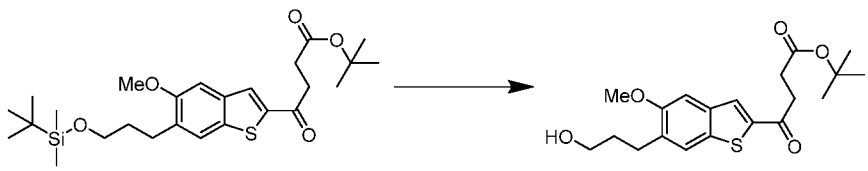
was added. The mixture was removed from the ice bath and allowed to warm to RT. The mixture was stirred for 2 h. The mixture was then cooled to 0°C, and concentrated NH_4OH (4.5mL) was added. To the resulting suspension was added water (240mL) and MeOH (60mL). The mixture was stirred for 5min and sonicated in a bath sonicator. The mixture was then diluted with EtOAc, and the organic layer was separated, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product residue was purified by silica gel chromatography to afford *tert*-butyl 4-(6-bromo-5-methoxybenzo[b] thiophen-2-yl)-4-oxobutanoate. LCMS ($C_{17}H_{19}BrO_4S$) (ES, m/z): 421, 423 $[M+Na]^+$.

Step 5: tert-*Butyl 4-(6-(3-((*tert*-butyldimethylsilyl)oxy)propyl)-5-methoxybenzo[b]thiophen-2-yl)-4-oxobutanoate*



To a flask containing *tert*-butyl 4-(6-bromo-5-methoxybenzo[b]thiophen-2-yl)-4-oxobutanoate (0.16g, 0.40mmol) and THF (2.0mL) was added [(2-dicyclohexylphosphino-2′,6′-bis(*N,N*-dimethylamino) -1,1′-biphenyl)-2-(2′-amino-1,1′-biphenyl)] palladium(II) methane sulfonate (C-Phos Pd G3, 16mg, 0.020mmol). The flask was evacuated and backfilled 3 times with N_2. (3-((*tert*-butyldimethylsilyl)oxy)propyl)zinc(II) bromide (0.50M in THF, 2.4mL, 1.2mmol) was added, and the mixture was allowed to stir at RT for 2.5h. The mixture was then quenched with a mixture of EtOAc and 10% aqueous sodium citrate. The organic layer was separated, washed with sat aq NaCl, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography to afford *tert*-butyl 4-(6-(3-((*tert*-butyldimethylsilyl)oxy)propyl)-5-methoxybenzo[b]thiophen-2-yl)-4-oxobutanoate. LCMS ($C_{26}H_{41}O_5SSi$-C_4H_8) (ES, m/z): 437 $[M-C_4H_8]^+$.

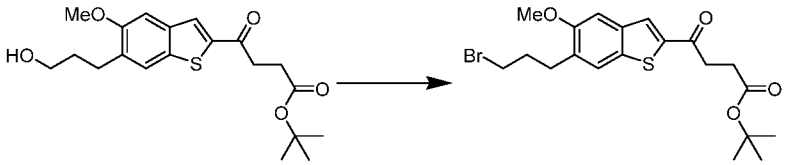
Step 6: tert-*Butyl 4-(6-(3-hydroxypropyl)-5-methoxybenzo[b]thiophen-2-yl)-4-oxobutanoate*



To a flask containing *tert*-butyl 4-(6-(3-((*tert*-butyldimethylsilyl)oxy)propyl)-5-methoxybenzo[b]thiophen-2-yl)-4-oxobutanoate (0.11g, 0.23 mmol) was added MeOH (1.5mL), water (1.5mL) and HOAc (1.5mL). The mixture was allowed to stir for 4 h. The mixture was

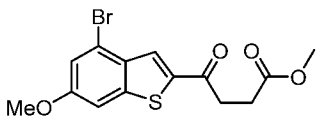
diluted with EtOAc and then washed with water (3x50mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography to afford *tert*-butyl 4-(6-(3-hydroxypropyl)-5-methoxy-benzo[b]thiophen-2-yl)-4-oxobutanoate. LCMS ($C_{20}H_{27}O_5S$-C_4H_8) (ES, m/z): 323 $[M-C_4H_8]^+$.

Step 7: tert-*Butyl 4-(6-(3-bromopropyl)-5-methoxybenzo[b]thiophen-2-yl)-4-oxobutanoate*

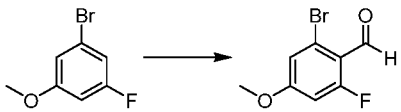


To a mixture of *tert*-butyl 4-(6-(3-hydroxypropyl)-5-methoxybenzo[b]thiophen-2-yl)-4-oxobutanoate (74mg, 0.20mmol) and triphenylphosphine (82mg, 0.31mmol) in THF (1.0mL) at 0°C was added NBS (52mg, 0.29mmol). After 15min at 0°C, the mixture was quenched with sat aq NH_4Cl and diluted with EtOAc. The organic layer was separated, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography to afford *tert*-butyl 4-(6-(3-bromopropyl)-5-methoxybenzo [b]thiophen-2-yl)-4-oxobutanoate. LCMS ($C_{20}H_{26}BrO_4S$-C_4H_8) (ES, m/z): 385, 387 $[M-C_4H_8]$.

Intermediate 9: Methyl 4-(4-bromo-6-methoxybenzo[b]thiophen-2-yl)-4-oxobutanoate

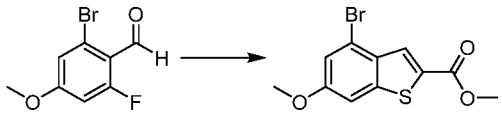


Step 1: 2-Bromo-6-fluoro-4-methoxybenzaldehyde



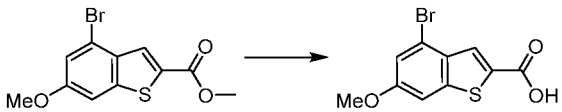
To a mixture of 1-bromo-3-fluoro-5-methoxybenzene (7.5g, 37mmol) in THF (120mL) at -78°C was added LDA (2.0M in THF, 22mL, 44mmol), and the mixture was allowed to stir for 30min at -78°C. After 30min, DMF (3.4mL, 44mmol) was added dropwise, and the mixture was then allowed to stir for 30min. The mixture was then quenched with water, warmed to RT, and then EtOAc was added. The layers were separated, and the water layer was extracted with EtOAc two more times. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product residue was purified by silica gel chromatography to afford 2-bromo-6-fluoro-4-methoxybenzaldehyde. LCMS ($C_8H_7BrFO_2$) (ES, m/z): 233, 235 $[M+H]^+$.

Step 2: Methyl 4-bromo-6-methoxybenzo[b]thiophene-2-carboxylate



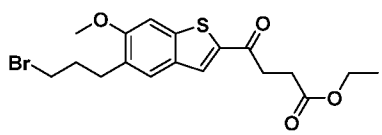
To a mixture of 2-bromo-6-fluoro-4-methoxybenzaldehyde (2.5g, 11mmol) in DMSO (54mL) was added TEA (3.0mL, 21mmol). After 10min, methyl thioglycolate (3.1mL, 32mmol) was added, and the mixture was allowed to stir for 30min at RT. After 30min, the mixture was heated to 60°C for 1 h. Upon cooling to RT, the mixture was diluted with sat aq $NaHCO_3$ and EtOAc. The organic layer was separated, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product residue was purified by silica gel chromatography (0→15% EtOAc gradient in Hex) to afford methyl 4-bromo-6-methoxybenzo[b] thiophene-2-carboxylate. LCMS ($C_{11}H_{10}BrO_3S$) (ES, m/z): 301, 303 $[M+H]^+$. ^1H NMR (500MHz, DMSO-d_6) δ 7.93 (s, 1H), 7.73 (s, 1H), 7.44–7.37 (m, 1H), 3.89 (s, 3H), 3.87 (s, 3H).

Step 3: 4-Bromo-6-methoxybenzo[b]thiophene-2-carboxylic acid

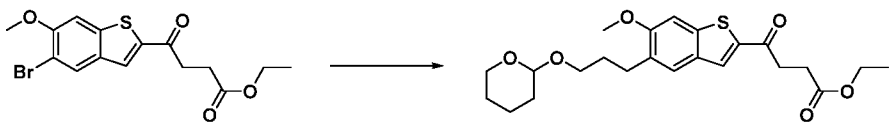


To a mixture of methyl 4-bromo-6-methoxybenzo[b]thiophene-2-carboxylate (1.7g, 5.5mmol) in THF (14mL), MeOH (7.0mL), and water (7.0mL) was added LiOH (0.66g, 28mmol), and the mixture was heated to 40°C for 2 h. After 2 h, the mixture was allowed to cool to RT. The mixture was quenched with aq HCl (2.0M in water, 14mL, 28mmol). The mixture was filtered, and the residue was washed with EtOAc. The residue was then dried under vacuum and used without further purification. LCMS ($C_{10}H_8BrO_3S$) (ES, m/z): 287, 289 $[M+H]^+$. ^1H NMR (500MHz, DMSO-d_6) δ 13.57 (s, 1H), 7.86 (s, 1H), 7.71 (s, 1H), 7.38 (d, *J*=1.7Hz, 1H), 3.86 (s, 3H).

Intermediate 10: Ethyl 4-(5-(3-bromopropyl)-6-methoxybenzo[b]thiophen-2-yl)-4-oxobutanoate

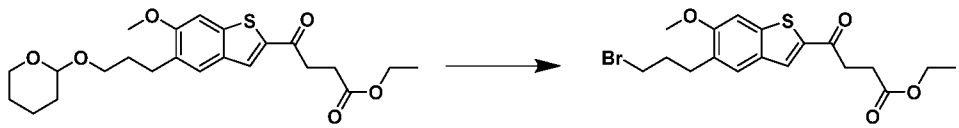


Step 1: Ethyl 4-(6-methoxy-5-(3-((tetrahydro-2H-pyran-2-yl)oxy)propyl)benzo[b]thiophen-2-yl)-4-oxobutanoate



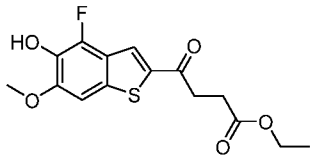
To a mixture of ethyl 4-(5-bromo-6-methoxybenzo[b]thiophen-2-yl)-4-oxobutanoate (13g, 35mmol), and C-Phos Pd G4 (1.4g, 1.7mmol) was added (3-((tetrahydro-2H-pyran-2-yl)oxy)propyl)zinc(II) bromide (0.50M in THF, 100 mL, 50mmol) at once. The reaction was heated to 40°C for 2 h. The mixture was then allowed to cool to RT and filtered through CELITE. The filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (0→30% EtOAc gradient in Hex) to afford ethyl 4-(6-methoxy-5-(3-((tetrahydro-2H-pyran-2-yl)oxy)propyl)benzo[b]thiophen-2-yl)-4-oxobutanoate. LCMS ($C_{23}H_{31}O_6S$) (ES, m/z): 435 $[M+H]^+$. ^1H NMR (600MHz, DMSO-d_6) δ 8.21 (s, 1H), 7.71 (s, 1H), 7.55 (s, 1H), 4.50 (s, 1H), 4.02 (q, *J*=7.0Hz, 2H), 3.85 (s, 3H), 3.70 (t, *J*=8.1Hz, 1H), 3.65-3.58 (m, 1H), 3.40-3.34 (m, 1H), 3.33-3.29 (m, 3H), 2.73-2.59 (m, 4H), 1.79 (p, *J*=6.7Hz, 2H), 1.69 (d, *J*=8.7Hz, 1H), 1.58 (t, *J*=7.9Hz, 1H), 1.48-1.34 (m, 4H), 1.14 (t, *J*=7.1Hz, 3H).

Step 2: Ethyl 4-(5-(3-bromopropyl)-6-methoxybenzo[b]thiophen-2-yl)-4-oxobutanoate

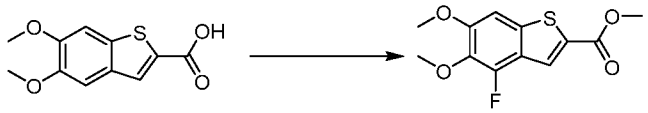


To a mixture of 4-(6-methoxy-5-(3-((tetrahydro-2H-pyran-2-yl)oxy)propyl)benzo[b]thiophen-2-yl)-4-oxobutanoate (6.2g, 14mmol) and DCM (100 mL) at 0°C was added triphenylphosphine dibromide (9.03 g, 21.4mmol) portion-wise. The mixture was allowed to warm to RT and then stirred for 1 h. The mixture was then quenched with water and diluted with DCM. The organic layer was separated, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (0→30% EtOAc gradient in Hex) to afford ethyl 4-(5-(3-bromopropyl)-6-methoxybenzo[b]thiophen-2-yl)-4-oxobutanoate LCMS ($C_{18}H_{22}BrO_4S$) (ES, m/z): 413, 415 $[M+H]^+$. ^1H NMR (600MHz, DMSO-d_6) δ 8.23 (s, 1H), 7.73 (s, 1H), 7.58 (s, 1H), 4.02 (q, *J*=7.0Hz, 2H), 3.86 (s, 3H), 3.50 (t, *J*=6.5Hz, 2H), 3.27 (d, *J*=6.4Hz, 2H), 2.75 (t, *J*=7.3Hz, 2H), 2.63 (t, *J*=6.2Hz, 2H), 2.07 (p, *J*=6.7Hz, 2H), 1.14 (t, *J*=7.1Hz, 3H).

Intermediate 11: Ethyl 4-(4-fluoro-5-hydroxy-6-methoxybenzo[b]thiophen-2-yl)-4-oxobutanoate

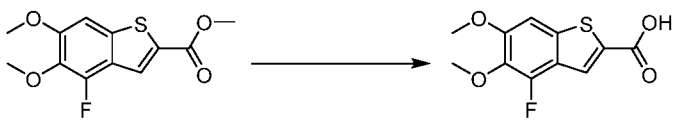


Step 1: Methyl 4-fluoro-5,6-dimethoxybenzo[b]thiophene-2-carboxylate



1-Chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (SELECTFLUOR™, 77mg, 0.22mmol) was added to a mixture of methyl 5,6-dimethoxybenzo[*b*] thiophene-2-carboxylate (50mg, 0.20mmol) in ACN (1ml) at RT. The resulting mixture was stirred at 45°C for 15h. The mixture was cooled to RT, diluted with sat aq $NaHCO_3$ (10mL), and extracted with EtOAc (3x10mL). The combined organic layers were washed with sat aq NaCl (10mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by prep-TLC (SiO_2, EtOAc in PE) to give methyl 4-fluoro-5,6-dimethoxybenzo[*b*] thiophene-2-carboxylate. LCMS ($C_{12}H_{12}FO_4S$) (ES, m/z): 293 $[M+H]^+$. ^1H NMR (400MHz, $CDCl_3$): δ 8.05 (s, 1H), 7.08 (s, 1H), 3.99 (s, 3H), 3.97 (s, 3H), 3.94 (s, 3H).

Step 2: 4-Fluoro-5,6-dimethoxybenzo[b]thiophene-2-carboxylic acid

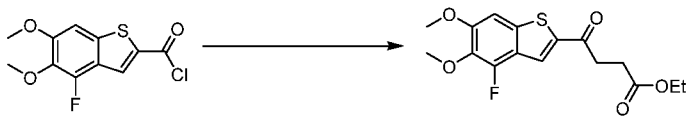


$LiOH·H_2O$ (71.4 mg, 1.70mmol) was added portion-wise to a mixture of methyl 4-fluoro-5, 6-dimethoxybenzo[*b*]thiophene-2-carboxylate (46mg, 0.170mmol) in THF (3ml), MeOH (1ml), and H_2O (1ml) at RT. Then, the mixture was stirred for 15h. The mixture was adjusted to pH=5 with 1N HCl and extracted with EtOAc (3x10ml). The combined organic layers were washed with sat aq NaCl (10mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by prep-HPLC (ACN/H_2O with 0.1% TFA) to give 4-fluoro-5,6-dimethoxybenzo[*b*]thiophene-2-carboxylic acid. LCMS ($C_{11}H_9FO_4S$) (ES, m/z): 257 $[M+H]^+$. ^1H NMR (400MHz, $CDCl_3$): δ 8.12 (s, 1H), 7.09 (s, 1H), 3.99 (s, 3H), 3.97 (s, 3H).

Step 3: 4-Fluoro-5,6-dimethoxybenzo[b]thiophene-2-carbonyl chloride

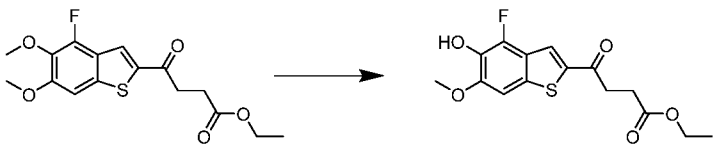
To a stirred solution of 4-fluoro-5,6-dimethoxybenzo[*b*]thiophene-2-carboxylic acid (153mg, 0.60mmol) in anhydrous THF (5mL) was added $(COCl)_2$ (0.21mL, 2.40mmol) dropwise at 0°C. The mixture was stirred at 0°C for 1h and then at RT for 1h. The solvent was removed under reduced pressure to give 4-fluoro-5,6-dimethoxybenzo[*b*]thiophene-2-carbonyl chloride, which was used without further purification.

Step 4: Ethyl 4-(4-fluoro-5,6-dimethoxybenzo[b]thiophen-2-yl)-4-oxobutanoate



A suspension of copper(I) thiophene-2-carboxylate (125mg, 0.65mmol) was sparged with N_2 for 5min and then cooled to 0°C. A solution of (3-ethoxy-3-oxopropyl)zinc(II) bromide (17.7mL, 0.5M in THF, 8.83mmol) was added under N_2 at 0°C, and the reaction mixture was stirred for 20min at 0°C. A N_2-sparged solution of 4-fluoro-5,6-dimethoxybenzo [*b*]thiophene-2-carbonyl chloride (130mg, 0.47mmol) in THF (3mL) was then added at 0°C. The resulting suspension was allowed to warm to RT and was stirred for 8h. The mixture was poured into sat aq NH_4Cl (20mL) with stirring. The mixture was extracted with EtOAc (2x20mL). The combined organic layers were washed with H_2O and sat aq NaCl, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc in Hex) to give ethyl 4-(4-fluoro-5,6-dimethoxybenzo[*b*] thiophen-2-yl)-4-oxobutanoate. LCMS ($C_{16}H_{18}FO_5S$) (ES, m/z): 341 $[M+H]^+$. ^1H NMR (500MHz, $CDCl_3$) δ 8.02 (d, *J*=0.7Hz, 1H), 7.10 (t, *J*=1.0Hz, 1H), 4.19 (q, *J*=7.2Hz, 2H), 4.05-3.97 (m, 6H), 3.36 (t, *J*=6.7Hz, 2H), 2.81 (t, *J*=6.7Hz, 2H), 1.29 (t, *J*=7.2Hz, 3H).

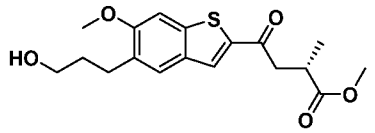
Step 5: Ethyl 4-(4-fluoro-5-hydroxy-6-methoxybenzo[b]thiophen-2-yl)-4-oxobutanoate



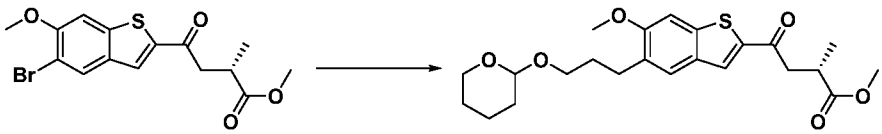
To a mixture of ethyl 4-(4-fluoro-5,6-dimethoxybenzo[b]thiophen-2-yl)-4-oxobutanoate (3.6g, 11mmol) and DCM (50mL) was added $AlCl_3$ (5.64g, 42.3mmol). The reaction mixture was allowed to stir at RT for 18h. An addition funnel was then connected to the reaction vessel, and water (50 mL) was added slowly to the mixture with vigorous stirring followed by aq HCl (1N, 50mL). The mixture was then diluted with 20% IPA/DCM. The organic layer was separated, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting

residue was purified by silica gel column chromatography (100% DCM) to afford ethyl 4-(4-fluoro-5-hydroxy-6-methoxybenzo[b]thiophen-2-yl)-4-oxobutanoate. LCMS ($C_{15}H_{16}FO_5S$) (ES, m/z): 327 $[M+H]^+$. ^1H NMR (600MHz, DMSO-d_6) δ 9.53 (s, 1H), 8.25 (s, 1H), 7.47 (s, 1H), 4.06 (q, *J*=7.1Hz, 2H), 3.92 (s, 3H), 3.39-3.34 (m, 2H), 2.68-2.63 (m, 2H), 1.18 (t, *J*=7.1Hz, 3H).

Intermediate 12: (S)-methyl 4-(5-(3-hydroxypropyl)-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate

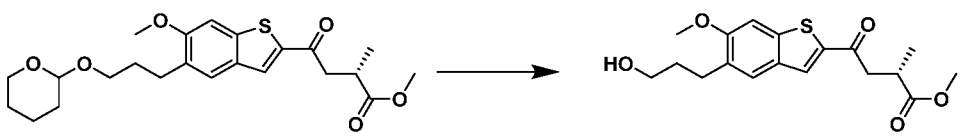


Step 1: (2S)-methyl-4-(6-methoxy-5-(3-((tetrahydro-2H-pyran-2-yl)oxy)propyl) benzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate



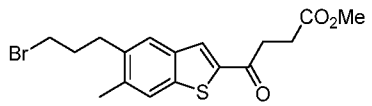
To a mixture of (S)-methyl-4-(5-bromo-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate (7.0g, 19mmol), and C-Phos Pd G4 (0.76g, 0.94mmol) was added (3-((tetrahydro-2H-pyran-2-yl)oxy)propyl)zinc(II) bromide (0.50M in THF, 100 mL, 50mmol). The mixture was heated to 40°C for 2h. The mixture was then allowed to cool to RT and filtered through CELITE. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0→30% EtOAc gradient in Hex) to afford ethyl (2S)-methyl-4-(6-methoxy-5-(3-((tetrahydro-2H-pyran-2-yl)oxy)propyl)benzo[b] thiophen-2-yl)-2-methyl-4-oxobutanoate. LCMS ($C_{23}H_{31}O_6S$) (ES, m/z): 435 $[M+H]^+$. ^1H NMR (600MHz, DMSO-d_6) δ 8.21 (s, 1H), 7.70 (s, 1H), 7.55 (s, 1H), 4.50 (s, 1H), 3.85 (s, 3H), 3.70 (dd, *J*=13.2, 5.3Hz, 1H), 3.64-3.58 (m, 1H), 3.56 (s, 3H), 3.42-3.35 (m, 2H), 3.35-3.29 (m, 1H), 3.15 (dd, *J*=17.4, 4.9Hz, 1H), 2.94 (dt, *J*=12.9, 7.1Hz, 1H), 2.67 (hept, *J*=7.6, 7.1Hz, 2H), 1.79 (p, *J*= 6.7Hz, 2H), 1.69 (d, *J*=8.7Hz, 1H), 1.58 (t, *J*=7.9Hz, 1H), 1.48-1.35 (m, 4H), 1.18-1.11 (m, 3H).

Step 2: (S)-methyl 4-(5-(3-hydroxypropyl)-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate

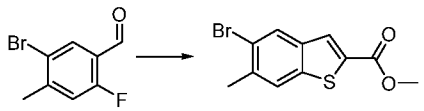


To a mixture of (2S)-methyl-4-(6-methoxy-5-(3-((tetrahydro-2H-pyran-2-yl)oxy) propyl)benzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate (2.62g, 6.03mmol) and MeOH (50mL) was added pTsOH (1.72g, 9.04mmol). The mixture was allowed to stir at RT for 1h. The mixture was then quenched with water and diluted with DCM. The organic layer was separated and then washed with aq sat $NaHCO_3$. The organic layer was then dried over Na_2SO_4, filtered and concentrated under reduced pressure afford (S)-methyl 4-(5-(3-hydroxypropyl)-6-methoxybenzo[b]thiophen-2-yl)-2methyl-4-oxobutanoate. LCMS ($C_{18}H_{23}O_5S$) (ES, m/z): 351 $[M+H]^+$. ^1H NMR (600MHz, DMSO-d_6) δ 8.21 (s, 1H), 7.69 (s, 1H), 7.54 (s, 1H), 4.44 (t, J=5.0Hz, 1H), 3.85 (s, 3H), 3.56 (s, 3H), 3.42-3.35 (m, 3H), 3.15 (dd, J=17.4, 4.9Hz, 1H), 2.93 (h, J=7.0Hz, 1H), 2.64 (t, J=7.6Hz, 2H), 1.68 (p, J=6.6Hz, 2H), 1.15 (d, J=7.1Hz, 3H).

Intermediate 13: Methyl 4-(5-(3-bromopropyl)-6-methylbenzo[b]thiophen-2-yl)-4-oxobutanoate

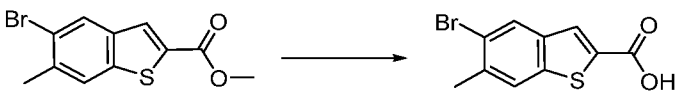


Step 1: Methyl 5-bromo-6-methylbenzo[b]thiophene-2-carboxylate



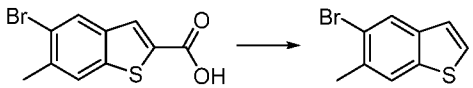
To a mixture of 5-bromo-2-fluoro-4-methylbenzaldehyde (5.0g, 23mmol) in DMSO (120mL) was added TEA (6.4mL, 46mmol). After 10min, methyl thioglycolate (6.7mL, 69mmol) was added, and the mixture was then heated to 60°C for 18 h. After 18h, the mixture was cooled to RT, and the mixture was diluted with EtOAc and water. The organic layer was separated, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The mixture was diluted with DCM. The mixture was filtered, and the residue was dried under vacuum. To the mother liquor was added silica gel (50g), and the mixture was concentrated. The mixture was then purified by silica gel chromatography to afford methyl 5-bromo-6-methylbenzo[b] thiophene-2-carboxylate. ^1H NMR (500MHz, DMSO-d_6) δ 8.31 (s, 1H), 8.13 (s, 1H), 8.08 (s, 1H), 3.89 (s, 3H), 2.48 (s, 3H).

Step 2: 5-Bromo-6-methylbenzo[b]thiophene-2-carboxylic acid



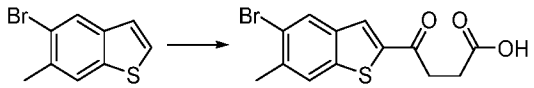
To a mixture of methyl 5-bromo-6-methylbenzo[b]thiophene-2-carboxylate (2.76g, 9.68mmol) in THF (24ml), water (12ml), and MeOH (12ml) was added LiOH (1.16g, 48.4mmol), and the mixture was stirred for 30min at RT. The mixture was then acidified to near neutral with HCl (1.0M in water, 48ml, 48mmol). The mixture was then diluted with EtOAc and water. The organic layer was separated, dried over $MgSO_4$, filtered, and concentrated to afford 5-bromo-6-methylbenzo[b]thiophene-2-carboxylic acid. The product was used without purification. LCMS ($C_{10}H_8BrO_2S$) (ES, m/z): 271, 273 $[M+H]^+$. ^1H NMR (499MHz, DMSO-d_6) δ 13.56 (s, 1H), 8.29 (s, 1H), 8.05 (s, 1H), 8.04 (s, 1H), 2.47 (s, 3H).

Step 3: 5-Bromo-6-methylbenzo[b]thiophene



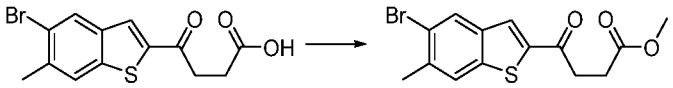
To 5-bromo-6-methylbenzo[b]thiophene-2-carboxylic acid (5.7g, 21mmol) was added DMA (100mL). The mixture was then split evenly among 5 vials. DBU (1.6mL) was added to each vial, and each vial was then irradiated in the microwave to 200°C for 2h. Upon completion, the five vials were combined and then diluted with EtOAc and sat aq $NaHCO_3$. The organic layer was separated, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography to afford 5-bromo-6-methylbenzo[b]thiophene. ^1H NMR (500MHz, DMSO-d_6) δ 8.15 (s, 1H), 8.00 (s, 1H), 7.75 (d, J=5.4Hz, 1H), 7.39 (d, J=5.3Hz, 1H), 2.45 (s, 3H).

Step 4: 4-(5-Bromo-6-methylbenzo[b]thiophen-2-yl)-4-oxobutanoic acid



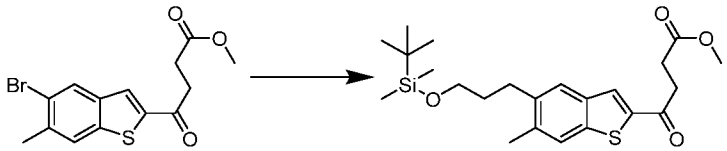
To a mixture of 5-bromo-6-methylbenzo[b]thiophene (2.0g, 8.8mmol) in DCM (88mL) at 0°C was added succinic anhydride (1.1g, 11mmol) and then $AlCl_3$ (2.3g, 18mmol). The mixture was warmed to RT and stirred for 18 h. The mixture was then diluted with EtOAc and HCl (1.0N in water). The organic layer was separated, dried over $MgSO_4$ and filtered. To the filtrate was added silica gel (10g), and the mixture was concentrated under reduced pressure. The mixture was put under vacuum for 18 h and then was purified by silica gel chromatography (0→50% EtOAc gradient in Hex) to afford 4-(5-bromo-6-methylbenzo[b]thiophen-2-yl)-4-oxobutanoic acid. LCMS ($C_{13}H_{12}BrO_3S$) (ES, m/z): 327, 329 $[M+H]^+$.

Step 5: Methyl 4-(5-bromo-6-methylbenzo[b]thiophen-2-yl)-4-oxobutanoate



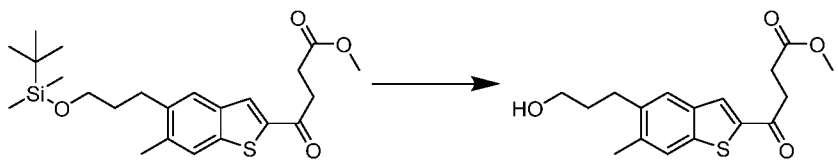
To a mixture of 4-(5-bromo-6-methylbenzo[b]thiophen-2-yl)-4-oxobutanoic acid (0.99g, 3.0mmol) in DMF (20mL) was added K_2CO_3 (1.0g, 7.6mmol). After 10min, CH_3I (0.95mL, 15mmol) was added, and the mixture was allowed to stir until complete by LCMS. The mixture was then diluted with EtOAc and water. The organic layer was separated, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography to afford methyl 4-(5-bromo-6-methylbenzo[b]thiophen-2-yl)-4-oxobutanoate. LCMS ($C_{14}H_{14}BrO_3S$) (ES, m/z): 341, 343 $[M+H]^+$. ^1H NMR (500MHz, DMSO-d_6) δ 8.32 (s, 1H), 8.30 (s, 1H), 8.07 (s, 1H), 3.61 (s, 3H), 3.37 (t, J=6.3Hz, 2H), 2.70 (t, J=6.3Hz, 2H), 2.48 (s, 3H).

*Step 6: Methyl 4-(5-(3-((*tert*-butyldimethylsilyl)oxy)propyl)-6-methylbenzo[b]thiophen-2-yl)-4-oxobutanoate*



To a flask containing methyl 4-(5-bromo-6-methylbenzo[b]thiophen-2-yl)-4-oxobutanoate (0.40g, 1.2mmol) and THF (5.9mL) was added C-Phos Pd G3 (47mg, 0.059mmol), and the mixture was evacuated and backfilled with N_2 three times. (3-((*tert*-butyldimethylsilyl) oxy)propyl)zinc(II) bromide (0.50M in THF, 7.0mL, 3.5 mmol) was added, and the mixture was allowed to stir at RT for 2.5h. The mixture was then quenched with a mixture of EtOAc and 10% aq sodium citrate. The organic layer was separated, washed with sat aq NaCl, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography to afford methyl 4-(5-(3-((*tert*-butyldimethylsilyl)oxy) propyl)-6-methylbenzo[b]thiophen-2-yl)-4-oxobutanoate. LCMS ($C_{23}H_{35}O_4SSi$) (ES, m/z): 435 $[M+H]^+$.

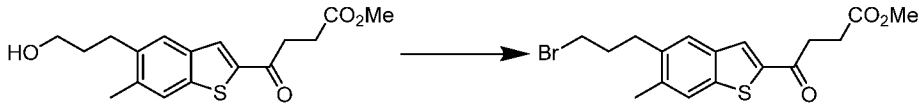
Step 7: Methyl 4-(5-(3-hydroxypropyl)-6-methylbenzo[b]thiophen-2-yl)-4-oxobutanoate



To a mixture of methyl 4-(5-(3-((*tert*-butyldimethylsilyl)oxy)propyl)-6-methyl-benzo[b]thiophen-2-yl)-4-oxobutanoate (0.23g, 0.54mmol) in THF (2.7mL) was added TBAF

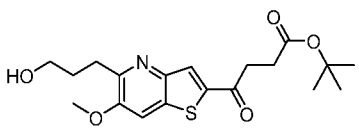
(1.0M in THF, 1.0mL, 1.0mmol). After 1.5 h, the mixture was diluted with EtOAc and sat aq NH_4Cl. The organic layer was separated, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (0→70% EtOAc gradient in Hex) to afford methyl 4-(5-(3-hydroxypropyl)-6-methylbenzo[b]thiophen-2-yl)-4-oxobutanoate. LCMS ($C_{17}H_{21}O_4S$) (ES, m/z): 321 $[M+H]^+$. ^1H NMR (499MHz, DMSO-d_6) δ 8.30 (s, 1H), 7.81 (s, 1H), 7.78 (s, 1H), 4.55 (t, *J*=5.1Hz, 1H), 3.61 (s, 3H), 3.51-3.46 (m, 2H), 3.38-3.34 (m, 2H), 2.77-2.66 (m, 4H), 2.41 (s, 3H), 1.79-1.67 (m, 2H).

Step 8: Methyl 4-(5-(3-bromopropyl)-6-methylbenzo[b]thiophen-2-yl)-4-oxobutanoate

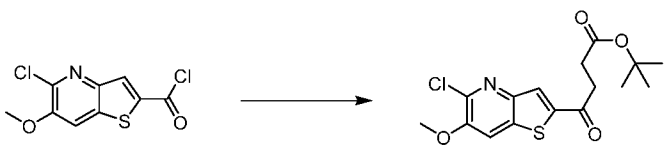


To a stirred mixture of methyl 4-(5-(3-hydroxypropyl)-6-methylbenzo[b] thiophen-2-yl)-4-oxobutanoate (97mg, 0.30mmol) and Ph_3P (130mg, 0.48mmol) in THF (1.5mL) at 0°C was added NBS (81mg, 0.45mmol) in one portion. After 30min, the reaction was quenched with sat aq NH_4Cl and EtOAc. The organic layer was separated, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (0→25% EtOAc gradient in Hex) to afford methyl 4-(5-(3-bromopropyl)-6-methylbenzo[b]thiophen-2-yl)-4-oxobutanoate. LCMS ($C_{17}H_{20}BrO_3S$) (ES, m/z): 383, 385 $[M+H]^+$.

Intermediate 14:* tert-*butyl 4-(5-(3-hydroxypropyl)-6-methoxythieno[3,2-b]pyridin-2-yl)-4-oxobutanoate



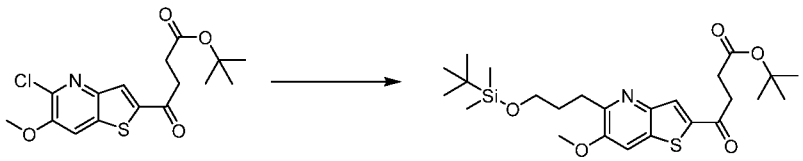
Step 1: tert-*butyl 4-(5-chloro-6-methoxythieno[3,2-b]pyridin-2-yl)-4-oxobutanoate*



CuCl (0.721g, 7.29mmol) was added to a 250mL round bottom flask with a stir bar. The flask was evacuated and then purged with N_2 three times. THF (14.6mL) was added to the flask, which was then stirred and cooled to 0°C with an ice water bath. (3-(*tert*-butoxy)-3-oxopropyl)zinc(II) (0.50M THF, 30mL, 15mmol) was then added dropwise over 10min while

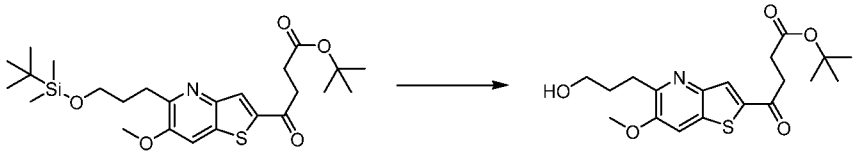
stirring at 0°C. The resulting mixture was stirred at 0°C for 35min. 5-chloro-6-methoxy thieno[3,2-b]pyridine-2-carbonyl chloride (1.91g, 7.29mmol) was added, followed by NMP (14.6mL). The resulting mixture was stirred for 7h at 0°C. Concentrated NH_4OH (4mL) was added to the reaction with rapid stirring at 0°C. To this suspension was added water:MeOH (4:1 140mL) along with ~20g sodium citrate tribasic dihydrate. The mixture was stirred for 20min. The resulting suspension was filtered, and the filter cake was washed with water. The cake was then slurried in Hex and filtered twice. Vacuum was pulled through the cake with N_2 sweep over 72h to afford *tert*-butyl 4-(5-chloro-6-methoxythieno[3,2-b]pyridin-2-yl)-4-oxobutanoate. LCMS ($C_{16}H_{19}ClNO_4S$) (ES, m/z): 356 $[M+H]^+$. ^1H NMR (500MHz, $CDCl_3$) δ 8.03 (s, 1H), 7.61 (s, 1H), 4.03 (s, 3H), 3.30 (t, *J*=6.5Hz, 2H), 2.87-2.59 (m, 2H), 1.46 (s, 9H).

Step 2: tert-*butyl 4-(5-(3-((*tert*-butyldimethylsilyl)oxy)propyl)-6-methoxythieno[3,2-b]pyridin-2-yl)-4-oxobutanoate*



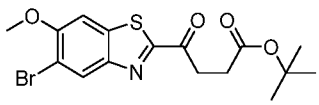
tert-Butyl 4-(5-chloro-6-methoxythieno[3,2-b]pyridin-2-yl)-4-oxobutanoate (1.00g, 2.81mmol) and CPhos Pd G3 (0.113g, 0.141mmol) were added to a 40mL vial with a septum-containing screw cap. The vial was evacuated and backfilled with N_2 three times. THF (10.0mL) was added to the vial under N_2 with stirring. While stirring the resulting suspension at RT, (3-((*tert*-butyldimethylsilyl)oxy)propyl)zinc(II) bromide (0.50M in THF, 11.2mL, 5.60mmol) was added dropwise. The resulting mixture was stirred for 3h at RT. The mixture was partitioned between EtOAc (75mL) and 10% aqueous sodium citrate (75mL) and stirred vigorously for 5min. The layers were separated, and the aqueous layer was extracted with EtOAc (20mL). The organic layers were combined, washed with sat aq NaCl (50mL), dried over anhydrous Na_2SO_4, concentrated under reduced pressure to afford a crude residue. The resulting residue was purified by silica gel chromatography (0→40% EtOAc gradient in Hex) to afford *tert*-butyl 4-(5-(3-((*tert*-butyldimethylsilyl)oxy)propyl)-6-methoxythieno[3,2-b]pyridin-2-yl)-4-oxobutanoate. LCMS ($C_{25}H_{40}NO_5SSi$) (ES, m/z): 494 $[M+H]^+$. ^1H NMR (500MHz, $CDCl_3$) δ 8.08 (s, 1H), 7.48 (s, 1H), 3.94 (s, 3H), 3.75 (t, *J*=6.5Hz, 2H), 3.30 (t, *J*=6.6Hz, 2H), 3.02-2.95 (m, 2H), 2.73 (t, *J*=6.6Hz, 2H), 2.03-1.96 (m, 2H), 1.46 (s, 9H), 0.92 (s, 9H), 0.07 (s, 6H).

Step 3: tert-*butyl 4-(5-(3-hydroxypropyl)-6-methoxythieno[3,2-b]pyridin-2-yl)-4-oxobutanoate*

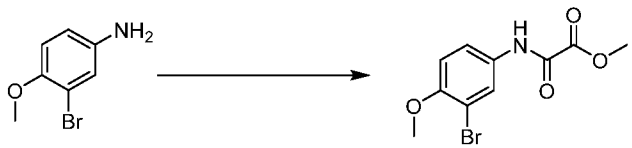


To a mixture of *tert*-butyl 4-(5-(3-((*tert*-butyldimethylsilyl)oxy)propyl)-6-methoxythieno[3,2-b]pyridin-2-yl)-4-oxobutanoate (0.735g, 1.49mmol) in MeOH (3.0mL) was added water (3.0mL) and then HOAc (3.0mL). The resulting mixture was stirred at RT for 18h. The mixture was then partitioned between EtOAc (50mL), water (25mL) and sat aq NaCl (25mL). The layers were separated, and the aqueous layer was extracted with EtOAc (50mL). The organic layers were combined, washed with sat aq NaCl (50mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (0→100% EtOAc gradient in Hex then isocratic at 100% EtOAc) to afford *tert*-butyl 4-(5-(3-hydroxypropyl)-6-methoxythieno[3,2-b]pyridin-2-yl)-4-oxobutanoate. LCMS ($C_{19}H_{26}NO_5S$) (ES, m/z): 380 $[M+H]^+$. ^1H NMR (500MHz, $CDCl_3$) δ 8.06 (s, 1H), 7.51 (s, 1H), 3.95 (s, 3H), 3.73 (t, *J*=5.8Hz, 2H), 3.28 (t, *J*=6.6Hz, 2H), 3.10 (t, *J*=6.9Hz, 2H), 2.72 (t, *J*=6.6Hz, 2H), 2.06 (p, *J*=6.5Hz, 2H), 1.45 (s, 9H).

Intermediate 15:* tert-*Butyl 4-(5-bromo-6-methoxybenzo[d]thiazol-2-yl)-4-oxobutanoate

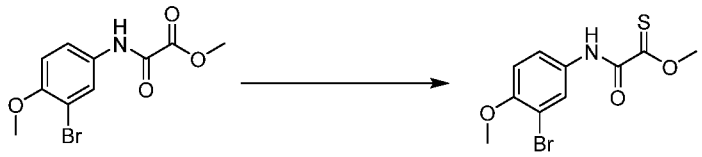


Step 1: Methyl 2-((3-bromo-4-methoxyphenyl)amino)-2-oxoacetate



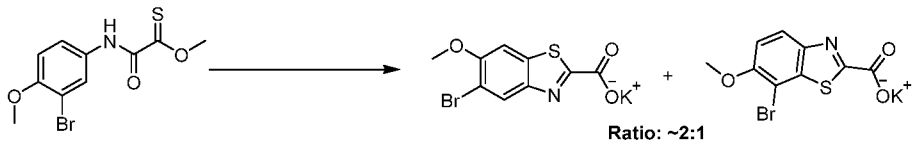
Into a 5-L 4-necked round-bottom flask that was purged and maintained with an inert atmosphere of N_2 was placed a mixture of 3-bromo-4-methoxyaniline (232g, 1.15mol) in DCM (3.0L), DIPEA (171g, 1.32mol), and methyl 2-chloro-2-oxoacetate (148g, 1.21mol). The resulting mixture was stirred for 1 h at RT. The mixture was then quenched by the addition of water/ice (2L). The resulting mixture was extracted with DCM (3x1L). The organic layers were combined and concentrated under reduced pressure to afford methyl 2-((3-bromo-4-methoxyphenyl)amino)-2-oxoacetate, which was used without purification or characterization.

Step 2: O-Methyl 2-((3-bromo-4-methoxyphenyl)amino)-2-oxoethanethioate



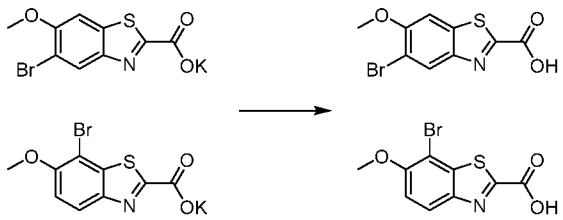
Into a 3-L 4-necked round-bottom flask that was purged and maintained with an inert atmosphere of N_2 was placed a mixture of methyl 2-((3-bromo-4-methoxyphenyl)amino)-2-oxoacetate (111g, 386mmol) in toluene (1.5L) and Lawesson's reagent (86.4 g, 214 mmol). The resulting mixture was heated to 85°C for 16h. The reaction mixture was then cooled to RT. The resulting materials were removed by filtration and washed with DCM (3x500mL). The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel chromatography (EtOAc/PE (1:20)) to afford O-methyl 2-((3-bromo-4-methoxyphenyl)amino)-2-oxoethanethioate, which was used without characterization.

Step 3: 5-Bromo-6-methoxybenzo[d]thiazole-2-carboxylic acid, potassium salt and 7-bromo-6-methoxybenzo[d]thiazole-2-carboxylic acid, potassium salt (2:1 mixture of isomers)



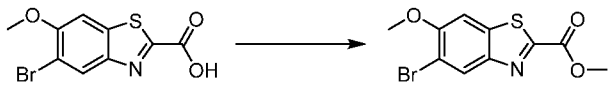
Into a 2-L 4-necked round-bottom flask that was purged and maintained with an inert atmosphere of N_2, was placed methyl O-methyl 2-((3-bromo-4-methoxyphenyl)amino)-2-oxoethanethioate (84.5g, 278mmol). A mixture of KOH (50g, 90mmol) in H_2O (500mL) was added to the reaction mixture over a period of 10min. A mixture of potassium ferricyanide (III) hydrate (242g, 735mmol) in H_2O (2L) was then added to the reaction mixture over a period of 10min. The pH of the resulting mixture was adjusted to 2 with aq HCl (2.0M). Water (500mL) was then added. The resulting mixture was allowed to stir for 1h at RT. The resulting product was then collected by filtration and washed with DCM (1L). The cake was slurried in aq KOH (2.0M, 500mL, 1mol) for 0.5 h. The resulting product was then collected by filtration and washed with H_2O (2x500mL) to afford a 2:1 a mixture of 5-bromo-6-methoxybenzo[d]thiazole-2-carboxylic acid, potassium salt and 7-bromo-6-methoxybenzo[d] thiazole-2-carboxylic acid, potassium salt. Characterization data for 5-bromo-6-methoxybenzo [d]thiazole-2-carboxylic acid, potassium salt (major isomer): ^{1}H NMR (400MHz, DMSO-d_6, ppm) δ 8.13 (s, 1H), 7.70 (s, 1H), 3.80 (s, 3H). Characterization data 7-bromo-6-methoxybenzo [d]thiazole-2-carboxylic acid, potassium salt (minor isomer): ^{1}H NMR (400MHz, DMSO-d_6, ppm) 7.90 (d, J=8.9Hz, 1H), 7.26 (d, J=8.9Hz, 1H), 3.91 (s, 3H).

Step 4: 5-Bromo-6-methoxybenzo[d]thiazole-2-carboxylic acid and 7-bromo-6-methoxybenzo[d]thiazole-2-carboxylic acid (2:1 mixture of isomers)



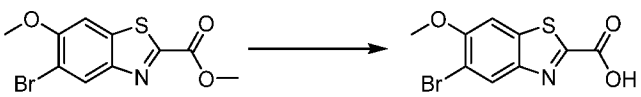
To a 1 L flask were added 5-bromo-6-methoxybenzo[d]thiazole-2-carboxylic acid, potassium salt and 7-bromo-6-methoxybenzo[d]thiazole-2-carboxylic acid, potassium salt (2:1 mixture of isomers) (22.4g, 49.4mmol), water (300mL), ACN (180mL), MeOH (120mL), and TFA (11.4mL, 148mmol). The mixture was stirred vigorously for 15min at RT. The resulting product were collected by filtration and washed with water (2x20mL), MeOH (2x5mL), and Et_2O (2x10mL) to afford a 2:1 mixture of 5-bromo-6-methoxybenzo[d] thiazole-2-carboxylic acid and 7-bromo-6-methoxybenzo[d]thiazole-2-carboxylic acid. Characterization data for 5-bromo-6-methoxybenzo[d]thiazole-2-carboxylic acid (major isomer): ^{1}H NMR (500MHz, DMSO-d_6) δ 8.45 (s, 1H), 7.97 (s, 1H), 3.96 (s, 3H). Characterization data for 7-bromo-6-methoxybenzo[d]thiazole-2-carboxylic acid (minor isomer): ^{1}H NMR (500MHz, DMSO-d_6) δ 8.21 (d, *J*=9.0Hz, 1H), 7.51 (d, *J*=9.0Hz, 1H), 4.00 (s, 3H).

Step 5: Methyl 5-bromo-6-methoxybenzo[d]thiazole-2-carboxylate



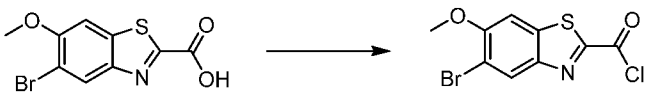
To a 250 mL flask was added 5-bromo-6-methoxybenzo[d]thiazole-2-carboxylic acid and 7-bromo-6-methoxybenzo[d]thiazole-2-carboxylic acid (2:1 mixture of isomers) (17.2g, 41.8mmol) and MeOH (150mL). The mixture was stirred vigorously and cooled to 0°C. To the stirring mixture was added $SOCl_2$ (6.1mL, 84mmol) dropwise over a period of 10min. The mixture was then heated to reflux for 18 h. Upon cooling to RT, the resulting product was collected by filtration and washed with MeOH (2x20mL). The product was purified by silica gel chromatography (0→30% EtOAc gradient in DCM) to afford methyl 5-bromo-6-methoxybenzo [d]thiazole-2-carboxylate as a single isomer. LCMS ($C_{10}H_9BrNO_3S$) (ES, m/z): 302, 304 $(M+H)^+$. ^{1}H NMR (500MHz, $CDCl_3$) δ 8.42 (s, 1H), 7.40 (s, 1H), 4.09 (s, 3H), 4.02 (s, 3H).

Step 6: 5-Bromo-6-methoxybenzo[d]thiazole-2-carboxylic acid



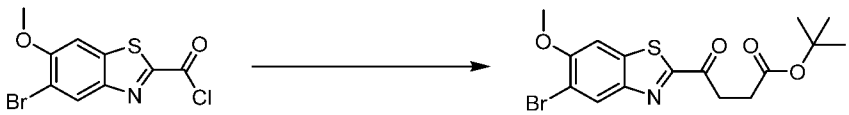
To a 500 mL round bottom flask was added methyl 5-bromo-6-methoxybenzo[d] thiazole-2-carboxylate (7.3g, 24mmol) and MeOH (150mL). To the vigorously stirring mixture was added aq NaOH (2.0M, 37mL, 74mmol). The mixture was heated to reflux for 30min. Upon cooling to RT, aq HCl (2.0M, 37mL, 74mmol) was added dropwise. The mixture was stirred vigorously at RT for 18 h. The resulting product was collected by filtration and washed with water (2x50mL) and MeOH (2x20mL) to afford 5-bromo-6-methoxybenzo[d] thiazole-2-carboxylic acid. LCMS ($C_9H_7BrNO_3S$) (ES, m/z): 288, 290 (M+H). ^{1}H NMR (500MHz, DMSO-d_6) δ 8.45 (s, 1H), 7.97 (s, 1H), 3.96 (s, 3H).

Step 7: 5-Bromo-6-methoxybenzo[d]thiazole-2-carbonyl chloride



To a 100 mL round bottom flask was added 5-bromo-6-methoxybenzo[d]thiazole-2-carboxylic acid (1.46g, 5.07mmol), DCM (25mL), and DMF (0.080mL, 1.0mmol). To the mixture was added $(COCl)_2$ (5.32mL, 10.6mmol) dropwise over 1min, and the mixture was vigorously stirred at RT for 15min. The mixture was then filtered through CELITE. The filtrate was concentrated under reduced pressure to afford 5-bromo-6-methoxybenzo[d]thiazole-2-carbonyl chloride used without further purification or characterization.

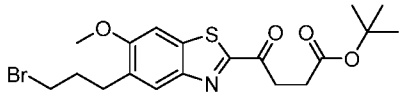
Step 8: tert-*Butyl 4-(5-bromo-6-methoxybenzo[d]thiazol-2-yl)-4-oxobutanoate*



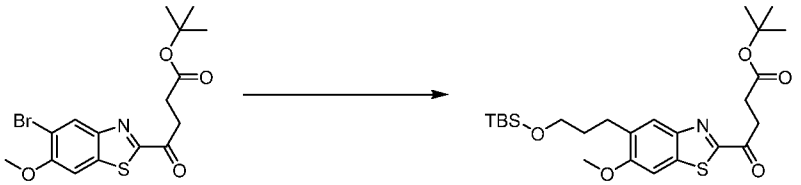
To a 250 mL round bottom flask was added CuCl (0.45g, 4.6mmol). The flask was evacuated and refilled with N_2 three times. THF (10 mL) was added, and the mixture was stirred and cooled to 0°C. To the mixture was added (3-(*tert*-butoxy)-3-oxopropyl)zinc(II) bromide (0.50M in THF, 18mL, 9.0mmol). After 10min, a mixture of 5-bromo-6-methoxy-benzo[d]thiazole-2-carbonyl chloride (1.4g, 4.6mmol) in NMP (30mL) was added dropwise over a period of 5min. After 5min, the mixture was allowed to warm to RT and was then stirred for 1 h. To the mixture was added water (30mL) and concentrated aq NH_4OH (15mL). The mixture was extracted with EtOAc (125mL), and the organic layer was washed with water (2x75mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (0→75% EtOAc gradient in Hex) to afford *tert*-butyl 4-(5-bromo-6-methoxybenzo[d]thiazol-2-yl)-4-oxobutanoate. LCMS

($C_{16}H_{18}BrNO_4S$ + Na) (ES, m/z): 422, 424 $[M+Na]^+$. ^1H NMR (500MHz, $CDCl_3$) δ 8.38 (s, 1H), 7.40 (s, 1H), 4.02 (s, 3H), 3.51 (t, *J*=6.6Hz, 2H), 2.75 (t, *J*=6.6Hz, 2H), 1.46 (s, 9H).

Intermediate 16: **tert-*butyl 4-(5-(3-bromopropyl)-6-methoxybenzo[d]thiazol-2-yl)-4-oxobutanoate***

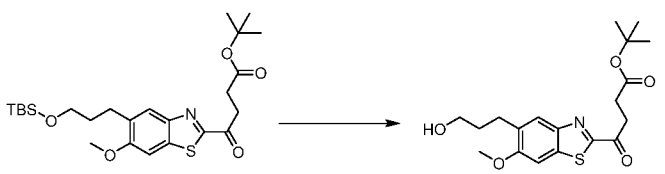


Step 1: tert-*butyl 4-(5-(3-((*tert-*butyldimethylsilyl)oxy)propyl)-6-methoxybenzo[d]thiazol-2-yl)-4-oxobutanoate*



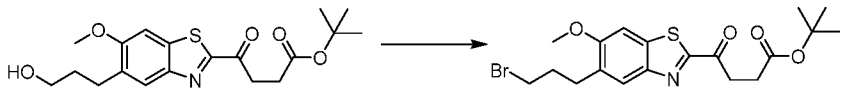
To a 4 mL vial was added *tert*-butyl 4-(5-bromo-6-methoxybenzo[d]thiazol-2-yl)-4-oxobutanoate (233mg, 0.581mmol) and C-Phos Pd G3 (14mg, 0.018mmol). The vial was evacuated and refilled with N_2 three times. To the vial was added THF (0.60mL) followed by (3-((*tert*-butyldimethylsilyl)oxy)propyl)zinc(II) bromide (0.50M in THF, 2.90 mL, 1.45mmol). The mixture was stirred at RT for 20min. To the mixture was added additional (3-((*tert*-butyl dimethylsilyl)oxy)-propyl)zinc(II) bromide (0.50M in THF, 1.4mL, 0.73mmol). After 30min, the mixture was diluted in EtOAc (30mL) and washed with 10% aq tribasic sodium citrate (30mL). The organic layer was separated, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (0→40% EtOAc gradient in Hex) to afford *tert*-butyl 4-(5-(3-((*tert*-butyldimethylsilyl)oxy) propyl)-6-methoxybenzo[d]thiazol-2-yl)-4-oxobutanoate. LCMS ($C_{25}H_{40}NO_5SSi$) (ES, m/z): 494 $[M+H]^+$. ^1H NMR (500MHz, $CDCl_3$) δ 7.93 (s, 1H), 7.31 (s, 1H), 3.94 (s, 3H), 3.70 (t, J=6.3Hz, 2H), 3.53 (t, J=6.6Hz, 2H), 2.86-2.78 (m, 2H), 2.74 (t, J=6.6Hz, 2H), 1.94-1.84 (m, 2H), 1.45 (s, 9H), 0.93 (s, 9H).

Step 2: tert-*butyl 4-(5-(3-hydroxypropyl)-6-methoxybenzo[d]thiazol-2-yl)-4-oxobutanoate*



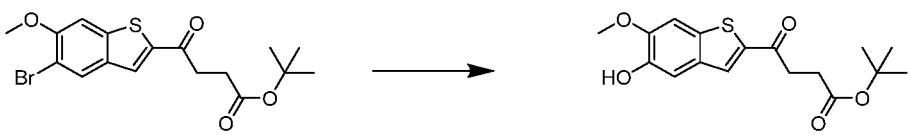
To a 100 mL flask was added *tert*-butyl 4-(5-(3-((*tert*-butyldimethylsilyl)oxy) propyl)-6-methoxybenzo[d]thiazol-2-yl)-4-oxobutanoate (229 mg, 0.464 mmol), MeOH (5.0mL), water (5.0mL), and AcOH (5.0mL). The mixture was allowed to stir at RT for 4h. The mixture was then diluted with EtOAc (50mL) and washed with water (3x50mL). The organic layer was separated, dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford *tert*-butyl 4-(5-(3-hydroxypropyl)-6-methoxybenzo[d]thiazol-2-yl)-4-oxobutanoate. LCMS ($C_{19}H_{26}NO_5S$) (ES, m/z): 380 $[M+H]^+$. ^1H NMR (500MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.34 (s, 1H), 3.96 (s, 3H), 3.70 (t, *J*=6.3Hz, 2H), 3.52 (t, *J*=6.7Hz, 2H), 2.87 (t, *J*=7.5Hz, 2H), 2.75 (t, *J*=6.6Hz, 2H), 2.00-1.90 (m, 2H), 1.46 (s, 9H).

Step 3: tert-*butyl 4-(5-(3-bromopropyl)-6-methoxybenzo[d]thiazol-2-yl)-4-oxobutanoate*



To a 4 mL vial was added CBr_4 (72mg, 0.22mmol), triphenylphosphine (62mg, 0.24mmol), and *tert*-butyl 4-(5-(3-hydroxypropyl)-6-methoxybenzo[d]thiazol-2-yl)-4-oxobutanoate (69mg, 0.18mmol). The vial was cooled to 0°C, and the DCM (1.0mL) was added. The mixture was allowed to warm to RT for 90min. The mixture was then directly purified by silica gel chromatography (0→30% EtOAc gradient in Hex) to afford *tert*-butyl 4-(5-(3-bromopropyl)-6-methoxybenzo[d]thiazol-2-yl)-4-oxobutanoate. LCMS ($C_{19}H_{25}BrNO_4S$) (ES, m/z): 442, 444 $[M+H]^+$. ^1H NMR (499MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.33 (s, 1H), 3.52 (t, *J*=6.6Hz, 2H), 3.95 (s, 3H), 3.45 (t, *J*=6.6Hz, 2H), 2.93 (t, *J*=7.2Hz, 2H), 2.75 (t, *J*=6.6Hz, 2H), 2.30-2.19 (m, 2H), 1.46 (s, 9H).

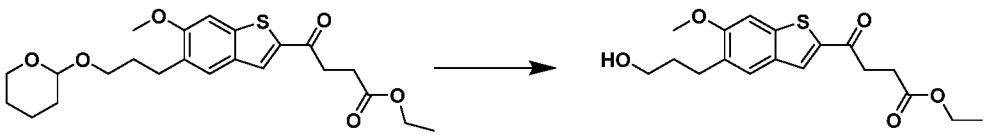
Intermediate 17:* tert-*butyl 4-(5-hydroxy-6-methoxybenzo[b]thiophen-2-yl)-4-oxobutanoate



To a mixture of RockPhos Pd G3 (0.105g, 0.125mmol), benzaldoxime (3.03g, 25.0mmol), *tert*-butyl 4-(5-bromo-6-methoxybenzo[b]thiophen-2-yl)-4-oxobutanoate (5.0g, 13mmol), and Cs_2CO_3 (12.2g, 37.6mmol) was added DMF (40 mL). The reaction was heated to 80°C for 18h. The reaction mixture was then allowed to cool to RT and poured into a flask containing aq HCl (0.5M, 100mL). The resulting mixture was extracted with DCM. The organic layer was then dried over Na_2SO_4, filtered, and concentrated under reduced pressure.

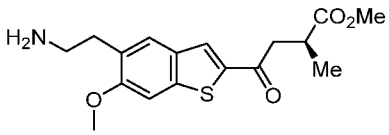
The resulting residue was purified by silica gel column chromatography (0→50% EtOAc gradient in Hex) to afford *tert*-butyl 4-(5-hydroxy-6-methoxybenzo[b]thiophen-2-yl)-4-oxobutanoate. LCMS ($C_{17}H_{20}O_5SNa$) (ES, m/z): 359 $[M+Na]^+$. ^1H NMR (600MHz, DMSO-d_6) δ 9.35 (s, 1H), 8.12 (s, 1H), 7.49 (s, 1H), 7.27 (s, 1H), 3.83 (s, 3H), 3.18 (t, *J*=6.2Hz, 2H), 2.52 (t, *J*=6.2Hz, 2H), 1.33 (s, 9H).

Intermediate 18: Ethyl 4-(5-(3-hydroxypropyl)-6-methoxybenzo[b]thiophen-2-yl)-4-oxobutanoate

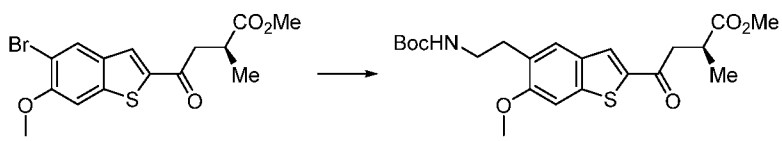


To a mixture ethyl 4-(6-methoxy-5-(3-((tetrahydro-2H-pyran-2-yl)oxy)propyl) benzo[b]thiophen-2-yl)-4-oxobutanoate (5.0g, 12mmol) and EtOH (100mL) was added pTsOH (4.4g, 23mmol). The reaction was allowed to stir at RT for 1 h. The reaction was then quenched with water and diluted with DCM. The organic layer was separated and then washed with aq sat $NaHCO_3$. The organic layer was then dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford ethyl 4-(5-(3-hydroxypropyl)-6-methoxybenzo[b]thiophen-2-yl)-4-oxobutanoate. LCMS ($C_{18}H_{23}O_5S$) (ES, m/z): 351 $[M+H]^+$. ^1H NMR (600MHz, DMSO-d_6) δ 8.21 (s, 1H), 7.70 (s, 1H), 7.55 (s, 1H), 4.44 (t, *J*=5.0Hz, 1H), 4.02 (q, *J*=7.0Hz, 2H), 3.85 (s, 3H), 3.40 (q, *J*=6.0Hz, 2H), 3.27 (d, *J*=6.4Hz, 2H), 2.63 (q, *J*=7.0, 5.9Hz, 4H), 1.68 (p, *J*=6.6Hz, 2H), 1.14 (t, *J*=7.1Hz, 3H).

Intermediate 19: methyl (2S)-4-[5-(2-aminoethyl)-6-methoxy-1-benzothiophen-2-yl]-2-methyl-4-oxobutanoate

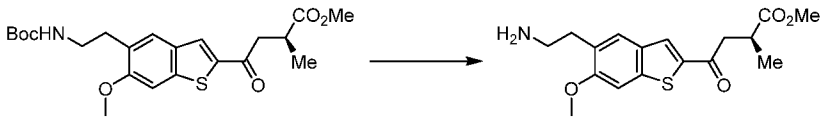


Step 1: methyl (2S)-4-(5-{2-[(tert-butoxycarbonyl)amino]ethyl}-6-methoxy-1-benzothiophen-2-yl)-2-methyl-4-oxobutanoate



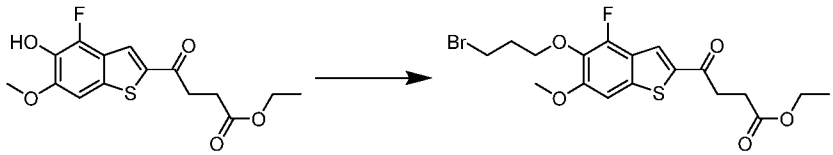
To the stirred mixture of methyl (2S)-4-(5-bromo-6-methoxy-1-benzothiophen-2-yl)-2-methyl-4-oxobutanoate (124mg, 0.334mmol), tris(trimethylsilyl)silane (103µL, 0.334 mmol), and anhydrous Na_2CO_3 (71mg, 0.67mmol) in degassed DME (1.7mL) under N_2, was added a mixture of Ir(2-(2,4-difluorophenyl)-5-(trifluoromethyl) pyridine)$_2$ (4,4'-di-*tert*-butyl-2,2'-bipyridine)PF_6 (3.8mg, 3.3µmol) in degassed DME (1.2mL). A suspension of Nickel(II) chloride ethylene glycol dimethyl ether complex (0.37mg, 1.7µmol) and 4,4'-di-*tert*-butyl-2,2'-bipyridine (0.45mg, 1.7µmol) in degassed DME (445 µL) was added, and the resulting mixture was stirred under N_2 for 15min at RT. *tert*-butyl N-(2-bromoethyl)carbamate (150mg, 0.67mmol) was added in one portion under N_2, and the reaction mixture was stirred and irradiated with two 34 W blue LED lamps (7 cm away on each side) for 18h at RT. The mixture was then directly purified by silica gel flash column chromatography (EtOAc in Hex) to afford methyl (2S)-4-(5-{2-[(*tert*-butoxycarbonyl)amino] ethyl}-6-methoxy-1-benzothiophen-2-yl)-2-methyl-4-oxobutanoate. LCMS ($C_{22}H_{30}NO_6S$) (ES, m/z): 436 $[M+H]^+$. ^{1}H NMR (500MHz, DMSO-d_6): δ 8.25 (s, 1H), 7.70 (s, 1H), 7.60 (s, 1H), 6.86 (br, 1H), 3.88 (s, 3H), 3.59 (s, 3H), 3.43 (dd, *J*=17.5, 8.6Hz, 1H), 3.19 (dd, *J*=17.5, 5.0Hz, 1H), 3.15 (t, *J*=7.0Hz, 2H), 3.01-2.93 (m, 1H), 2.77 (t, *J*=7.0Hz, 2H), 1.34 (s, 9H), 1.19 (d, *J*=7.1Hz, 3H).

Step 2: methyl (2S)-4-[5-(2-aminoethyl)-6-methoxy-1-benzothiophen-2-yl]-2-methyl-4-oxobutanoate



To the stirred solution of methyl (2S)-4-(5-{2-[(*tert*-butoxycarbonyl)amino] ethyl}-6-methoxy-1-benzothiophen-2-yl)-2-methyl-4-oxobutanoate (54mg, 0.12mmol) in CH_2Cl_2 (2.8mL) was added TFA (476µL, 6.18mmol) in one portion at RT, and the reaction mixture was stirred at RT for 2h. The mixture was concentrated, and the residue was dissolved in CH_3CN and water and lyophilized overnight to afford methyl (2S)-4-[5-(2-aminoethyl)-6-methoxy-1-benzothiophen-2-yl]-2-methyl-4-oxobutanoate. LCMS ($C_{17}H_{22}NO_4S$) (ES, m/z): 336 $[M+H]^+$. ^{1}H NMR (500MHz, DMSO-d_6): δ 8.29 (s, 1H), 7.80 (br, 2H), 7.79 (s, 1H), 7.68 (s, 1H), 3.91 (s, 3H), 3.60 (s, 3H), 3.45-3.39 (m, 1H), 3.20 (dd, *J*=17.5, 5.0Hz, 1H), 3.10-3.01 (m, 2H), 3.01-2.93 (m, 1H), 2.95 (t, *J*=7.0Hz, 2H), 1.20 (d, *J*=7.1Hz, 3H).

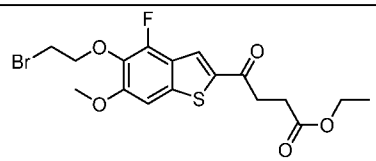
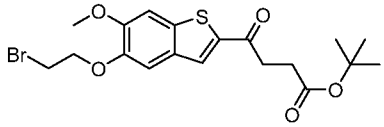
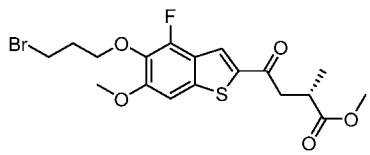
Intermediate 20: Ethyl 4-(5-(3-bromopropyl)-6-methoxybenzo[b]thiophen-2-yl)-4-oxobutanoate

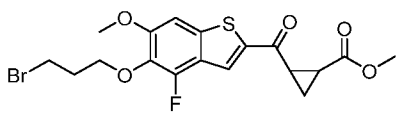
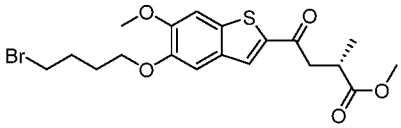
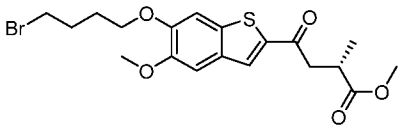
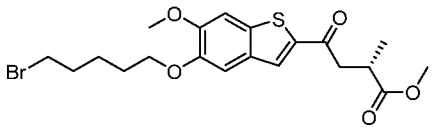
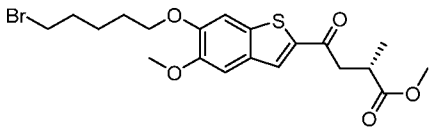
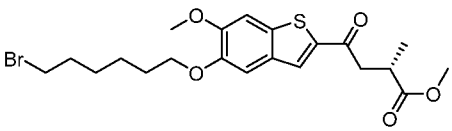
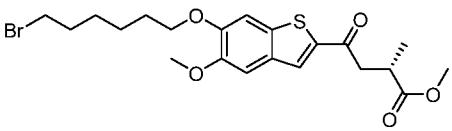


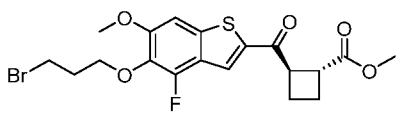
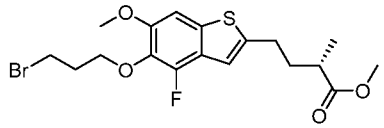
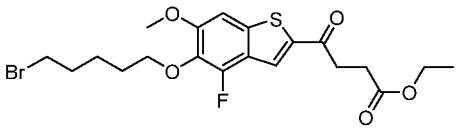
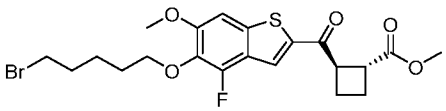
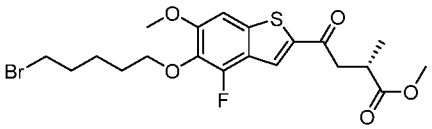
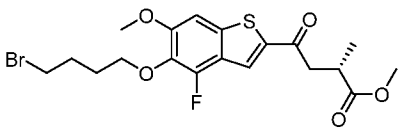
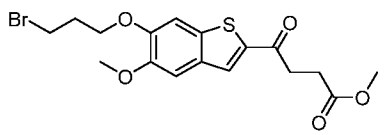
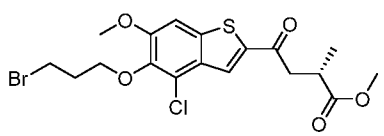
To a mixture of ethyl 4-(4-fluoro-5-hydroxy-6-methoxybenzo[b]thiophen-2-yl)-4-oxobutanoate(0.065g, 0.2mmol), Cs_2CO_3 (0.326g, 1.00mmol), and ACN (2mL) was added 1,3-dibromopropane (1.0mL, 9.9mmol). The mixture was heated to 65°C for 2 h. Upon cooling to RT, the mixture was filtered, and the filtered material was washed with THF. The filtrate was diluted with Hex, and the mixture was then concentrated under reduced pressure to afford ethyl 4-(6-methoxy-5-(3-((tetrahydro-2H-pyran-2-yl)oxy)propyl)benzo[b]thiophen-2-yl)-4-oxobutanoate. LCMS ($C_{18}H_{21}BrFO_5S$) (ES, m/z): 447, 449 $[M+H]^+$.

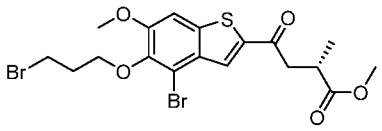
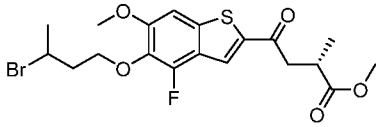
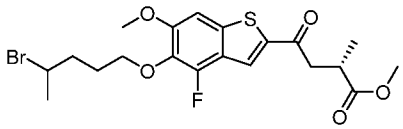
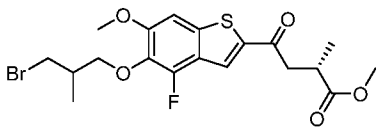
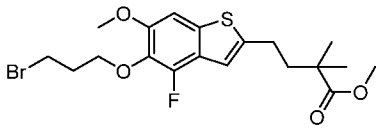
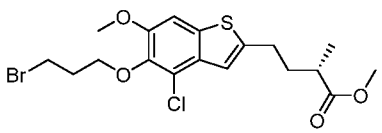
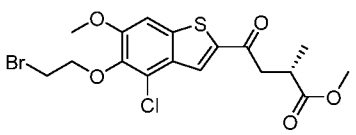
Intermediates 21 through 23 and 62 through 86, as shown in Table 1 below, were or may be prepared according to procedures analogous to those outlined in Intermediate 20 above using the appropriate starting materials, described as Preparations or as obtained from commercial sources.

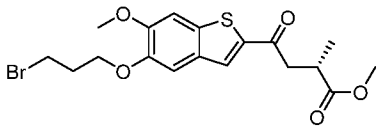
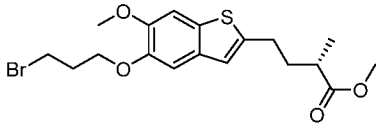
Table 1

Intermediate	Structure	Name	Mass $[M+H]^+$
21		ethyl 4-(5-(2-bromoethoxy)-4-fluoro-6-methoxybenzo[b]thiophen-2-yl)-4-oxobutanoate	433, 435
22		*tert*-butyl 4-(5-(2-bromoethoxy)-6-methoxybenzo[b]thiophen-2-yl)-4-oxobutanoate	387, 389 $[M-C_4H_8]^+$
23		methyl (S)-4-(5-(3-bromopropoxy)-4-fluoro-6-methoxybenzo[b] thiophen-2-yl)-2-methyl-4-oxobutanoate	447, 449

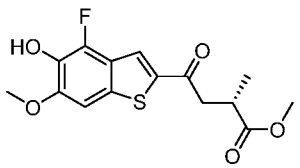
Intermediate	Structure	Name	Mass $[M+H]^+$
62		methyl 2-(5-(3-bromopropoxy)-4-fluoro-6-methoxybenzo[b]thiophene-2-carbonyl)cyclopropane-1-carboxylate	445, 447
63		methyl (S)-4-(5-(4-bromobutoxy)-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate	443, 445
64		methyl (S)-4-(6-(4-bromobutoxy)-5-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate	443, 445
65		(S)-methyl 4-(5-((5-bromopentyl)oxy)-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate	457, 459
66		(S)-methyl 4-(6-((5-bromopentyl)oxy)-5-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate	457, 459
67		methyl (S)-4-(5-((6-bromohexyl)oxy)-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate	471,473
68		methyl (S)-4-(6-((6-bromohexyl)oxy)-5-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate	471, 473

Intermediate	Structure	Name	Mass $[M+H]^+$
69		trans-methyl 2-(5-(3-bromopropoxy)-4-fluoro-6-methoxybenzo[b]thiophene-2-carbonyl)cyclobutane-carboxylate	459, 461
70		(S)-methyl 4-(5-(3-bromopropoxy)-4-fluoro-6-methoxybenzo[b]thiophen-2-yl)-2-methylbutanoate	450, 452 ($M+H_2O$)
71		ethyl 4-(5-((5-bromopentyl)oxy)-4-fluoro-6-methoxybenzo[b] thiophen-2-yl)-4-oxobutanoate	475, 477
72		trans-methyl 2-(5-((5-bromopentyl)oxy)-4-fluoro-6-methoxybenzo[b] thiophene-2-carbonyl) cyclobutane-carboxylate	487, 489
73		(S)-methyl 4-(5-((5-bromopentyl)oxy)-4-fluoro-6-methoxybenzo[b] thiophen-2-yl)-2-methyl-4-oxobutanoate	475, 477
74		(S)-methyl 4-(5-(4-bromobutoxy)-4-fluoro-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate	461, 463
75		methyl 4-(6-(3-bromopropoxy)-5-methoxybenzo[b]thiophen-2-yl)-4-oxobutanoate	415, 417
76		methyl (S)-4-(5-(3-bromopropoxy)-4-chloro-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate	463, 465

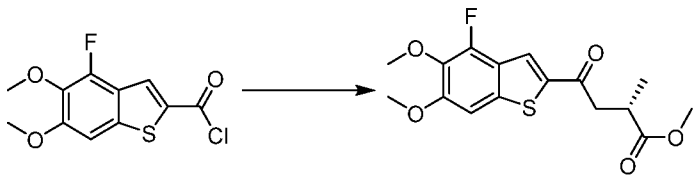
Intermediate	Structure	Name	Mass $[M+H]^+$
77		methyl (S)-4-(4-bromo-5-(3-bromopropoxy)-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate	507, 509, 511
78		methyl (2S)-4-(5-(3-bromobutoxy)-4-fluoro-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate	461, 463
79		methyl (2S)-4-(5-((4-bromopentyl)oxy)-4-fluoro-6-methoxybenzo[b] thiophen-2-yl)-2-methyl-4-oxobutanoate	475, 477
80		methyl (2S)-4-(5-((5-bromohexan-2-yl)oxy)-4-fluoro-6-methoxybenzo [b]thiophen-2-yl)-2-methyl-4-oxobutanoate	489, 491
81		methyl (2S)-4-(5-(3-bromo-2-methylpropoxy)-4-fluoro-6-methoxybenzo[b] thiophen-2-yl)-2-methyl-4-oxobutanoate	461, 463
82		methyl 4-(5-(3-bromopropoxy)-4-fluoro-6-methoxybenzo[b]thiophen-2-yl)-2,2-dimethylbutanoate	464, 466 ($M+H_2O$)
83		methyl (S)-4-(5-(3-bromopropoxy)-4-chloro-6-methoxybenzo[b]thiophen-2-yl)-2-methylbutanoate	466, 468 ($M+H_2O$)
84		methyl (S)-4-(5-(2-bromoethoxy)-4-chloro-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate	449, 451

Intermediate	Structure	Name	Mass $[M+H]^+$
85		methyl (S)-4-(5-(3-bromopropoxy)-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate	429, 431
86		methyl (S)-4-(5-(3-bromopropoxy)-6-methoxybenzo[b]thiophen-2-yl)-2-methylbutanoate	415, 417

Intermediate 24: (S)-methyl 4-(4-fluoro-5-hydroxy-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate

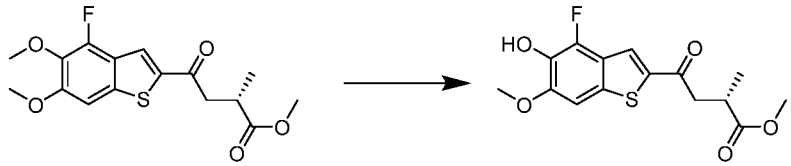


Step 1: (S)-methyl 4-(4-fluoro-5,6-dimethoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate



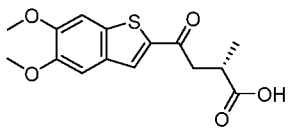
To a mixture of 4-fluoro-5,6-dimethoxybenzo[b]thiophene-2-carbonyl chloride (4.3g, 16mmol), C-Phos Pd G4 (0.26g, 0.31mmol), and THF (25mL) was added (R)-(3-methoxy-2-methyl-3-oxopropyl)zinc(II) bromide (0.50M in THF, 25.0mL, 12.5mmol). The reaction was allowed to stir for 2h at RT. The reaction was then quenched with aq sat NH_4Cl and diluted with DCM. The organic layer was separated, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (0→50% EtOAc gradient in Hex) to afford (S)-methyl 4-(4-fluoro-5,6-dimethoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate. LCMS ($C_{16}H_{18}FO_5S$) (ES, m/z): 341 $[M+H]^+$. ^1H NMR (600MHz, DMSO-d_6) δ 8.33 (s, 1H), 7.58 (s, 1H), 3.92 (s, 3H), 3.86 (s, 3H), 3.60 (s, 3H), 3.50 (dd, *J*=17.7, 8.7Hz, 1H), 3.25 (dd, *J*=17.7, 5.0Hz, 1H), 3.00-2.92 (m, 1H), 1.20 (d, *J*=7.3Hz, 3H).

Step 2: (S)-methyl 4-(4-fluoro-5-hydroxy-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate

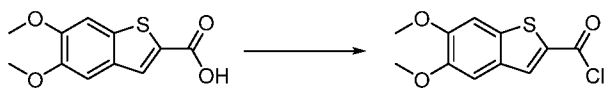


To a mixture of (S)-methyl 4-(4-fluoro-5,6-dimethoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate (4.0g, 12mmol), and DCM (50mL), was added $AlCl_3$ (6.27g, 47.0mmol). The reaction mixture was allowed to stir at RT for 18h. An addition funnel was then added to the reaction, and water (50 mL) was added slowly to the mixture with vigorous stirring followed by aq HCl (1N, 50 mL). The mixture was then poured into a separatory funnel, and 20% IPA/DCM was added. The organic layer was separated, dried over Na_2SO_4, filtered, and the filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (100% DCM) to afford (S)-methyl 4-(4-fluoro-5-hydroxy-6-methoxy benzo[b] thiophen-2-yl)-2-methyl-4-oxobutanoate. LCMS ($C_{15}H_{16}FO_5S$) (ES, m/z): 327 $[M+H]^+$. ^1H NMR (600MHz, DMSO-d_6) δ 9.53 (s, 1H), 8.25 (s, 1H), 7.47 (s, 1H), 3.92 (s, 3H), 3.60 (s, 3H), 3.48 (dd, *J*=17.7, 8.7Hz, 1H), 3.24 (dd, *J*=17.7, 5.0Hz, 1H), 3.01-2.89 (m, 1H), 1.19 (d, *J*=7.2Hz, 3H).

Intermediate 25: methyl (R)-4-(5-hydroxy-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate

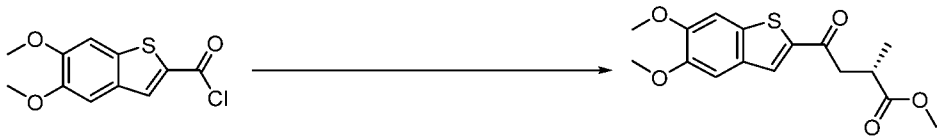


Step 1: 5,6-Dimethoxybenzo[b]thiophene-2-carbonyl chloride



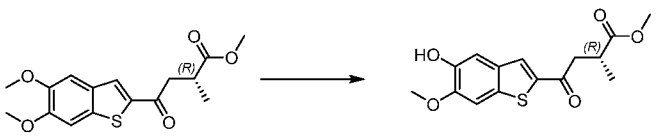
To a stirring solution of 5,6-dimethoxybenzo[*b*]thiophene-2-carboxylic acid (5.0g, 21mmol) in THF (200mL) at 0°C under Ar was added $(COCl)_2$ (5.5ml, 63mmol) followed by DMF (0.1ml, 1.3mmol). The reaction mixture was stirred at 0°C for 1h and then allowed to warm to RT and stirred overnight. The reaction mixture was concentrated under reduced pressure, and the resulting 5,6-dimethoxybenzo[*b*]thiophene-2-carbonyl chloride was used without purification. ^1H NMR (600MHz, CH_3CN-d_3): δ 8.25 (s, 1H), 7.46 (s, 1H), 7.45 (s, 1H), 3.92 (s, 3H), 3.88 (s, 3H).

Step 2: Methyl (S)-4-(5,6-dimethoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate



To an oven-dried, Ar-purged, round-bottomed flask containing copper (I) thiophene-2-carboxylate (797mg, 4.2mmol) at 0°C was added (*R*)-(3-methoxy-2-methyl-3-oxopropyl)zinc(II) bromide (7.8mL, 0.5M in THF, 3.9mmol) dropwise. The reaction mixture was stirred at 0°C for 20min. A suspension of 5,6-dimethoxybenzo[*b*]thiophene-2-carbonyl chloride (777mg, 3.0mmol) in THF (15mL) was added dropwise to the reaction mixture. The reaction mixture was allowed to warm to RT and stirred for 6h. The reaction mixture was diluted with sat aq NH_4Cl solution (15mL), followed by DCM (30mL). Precipitates were removed by filtration prior to extraction. The layers were separated, and the aq layer was extracted with DCM (3x30mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by silica gel column chromatography ((25% EtOH in EtOAc) in Hex) to afford methyl (*S*)-4-(5,6-dimethoxybenzo[*b*] thiophen-2-yl)-2-methyl-4-oxobutanoate. LCMS ($C_{16}H_{19}O_5S$) (ES, m/z): 323 $[M+H]^+$. ^1H NMR (500MHz, $CDCl_3$): δ 7.89 (s, 1H), 7.26 (s, 2H), 4.00 (s, 3H), 3.97 (s, 3H), 3.72 (s, 3H), 3.48 (dd, *J*=16.9, 7.6Hz, 1H), 3.22-3.16 (m, 1H), 3.05 (dd, *J*=16.9, 6.0Hz, 1H), 1.31 (d, *J*=7.2Hz, 3H).

Step 3: methyl (R)-4-(5-hydroxy-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate

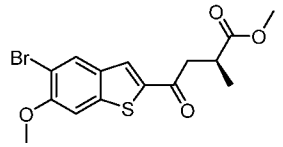
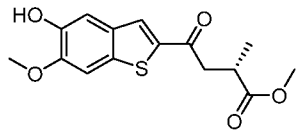


$AlCl_3$ (1.0g, 7.5mmol) was added to (R)-methyl 4-(5,6-dimethoxybenzo[b] thiophen-2-yl)-2-methyl-4-oxobutanoate (1.0g, 3.0mmol) in CH_2Cl_2 (40mL) at 0°C. The reaction mixture was allowed to warm to RT for 18h. The reaction mixture was then cooled to 0°C, and MeOH (85mL) was added. The mixture was allowed to stir at 0°C for 30min. The mixture was then allowed to warm to RT and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (EtOAc gradient in Hex) to afford impure methyl (R)-4-(5-hydroxy-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate. The mixture was then purified by chiral-SFC (Column AD-H (21x250mm), 30% MeOH with 0.25% DMEA in CO_2) to afford methyl (R)-4-(5-hydroxy-6-methoxybenzo[b] thiophen-2-yl)-2-methyl-4-oxobutanoate with a retention time of 4.7min. LCMS ($C_{15}H_{17}O_5S$) (ES, m/z): 309 $[M+H]^+$. ^1H NMR (DMSO-d_6) δ: 9.41 (s, 1H), 8.17 (s, 1H), 7.54 (s, 1H), 7.31 (s, 1H), 3.87 (s, 3H), 3.60 (s,

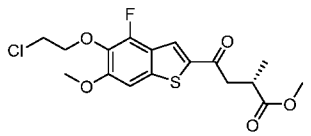
3H), 3.40 (dd, J=17.4, 8.6Hz, 1H), 3.17 (dd, J=17.5, 5.1Hz, 1H), 3.02-2.91 (m, 1H), 1.19 (d, J=7.1Hz, 3H).

Intermediates 26 through 27, as shown in Table 2 below, were or may be prepared according to procedures analogous to those outlined in Intermediate 25 above using the appropriate starting materials, described as Preparations or as obtained from commercial sources.

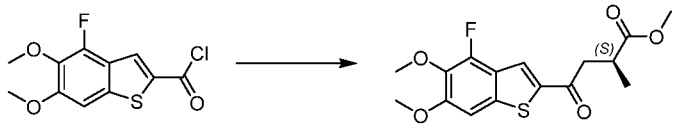
Table 2

Intermediate	Structure	Name	Mass $[M+H]^+$
26		methyl (S)-4-(5-bromo-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate	371, 373
27		methyl (S)-4-(5-hydroxy-6-methoxybenzo[b] thiophen-2-yl)-2-methyl-4-oxobutanoate	309

Intermediate 28: methyl (S)-4-(5-(2-chloroethoxy)-4-fluoro-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate



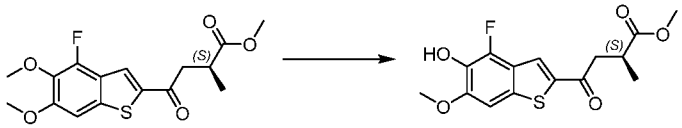
Step 1: methyl (S)-4-(4-fluoro-5,6-dimethoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate



A flask containing CuCl (2.5g, 25mmol) was sparged with Ar and then cooled to 0°C. 3-Methoxy-(2R)-(+)-methyl-3-oxopropylzinc bromide (0.50M in THF, 50 mL, 25 mmol) was added dropwise. A mixture of 4-fluoro-5,6-dimethoxybenzo[b]thiophene-2-carbonyl chloride (5.0g, 20mmol) in THF (25mL) and NMP (25mL) was added dropwise to the stirring reaction mixture. The reaction mixture was then allowed to warm to RT for 18h. The reaction mixture was then quenched with sat aq NH_4Cl (100 mL) and extracted with EtOAc (3x100mL). The combined organics were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was purified by normal phase silica column chromatography (EtOAc in

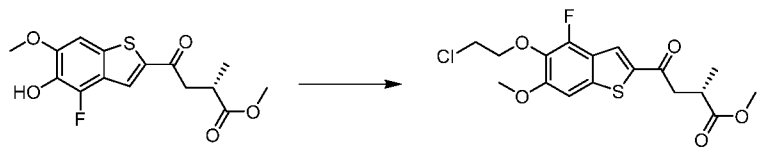
Hex) to afford (S)-methyl 4-(4-fluoro-5,6-dimethoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate. LCMS ($C_{16}H_{18}FO_5S$) (ES, m/z): 341 $[M+H]^+$. ^1H NMR ($CDCl_3$) δ: 7.99 (s, 1H), 7.09 (s, 1H), 4.00 (s, 3H), 3.98 (s, 3H), 3.73 (s, 3H), 3.51 (dd, J=17.0, 7.9Hz, 1H), 3.24-3.12 (m, 1H), 3.06 (dd, J=17.0, 5.6Hz, 1H), 1.32 (d, J=7.1Hz, 3H).

Step 2: (S)-methyl 4-(4-fluoro-5-hydroxy-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate



To a mixture of methyl (S)-4-(4-fluoro-5,6-dimethoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate (1.0g, 2.9mmol) and $CH{=}CCl_2$ (40mL) was added $AlCl_3$ (1.0g, 7.5mmol). The reaction mixture was allowed to stir at RT for 18h. The reaction mixture was then cooled to 0°C and diluted with MeOH (40 mL). The mixture was then allowed to warm to RT and then concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (EtOAc in Hex) to afford (S)-methyl 4-(4-fluoro-5-hydroxy-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate. LCMS ($C_{15}H_{16}FO_5S$) (ES, m/z): 327 $[M+H]^+$. ^1H NMR (methanol-d_4) δ: 8.11 (s, 1H), 7.29 (s, 1H), 3.98 (s, 3H), 3.69 (s, 3H), 3.50 (dd, J=17.5, 8.6Hz, 1H), 3.23-3.16 (m, 1H), 3.11-3.02 (m, 1H), 1.28 (d, J=7.2Hz, 3H).

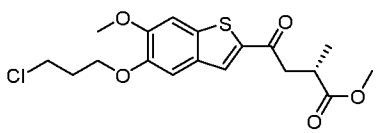
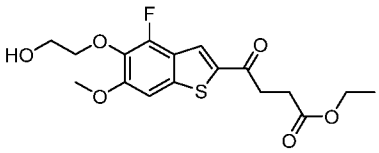
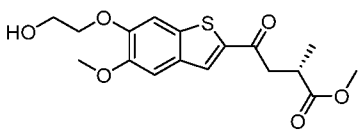
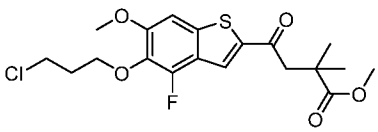
Step 3: methyl (S)-4-(5-(2-chloroethoxy)-4-fluoro-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate



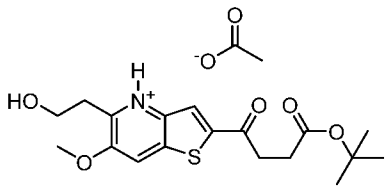
K_2CO_3 (170mg, 1.2mmol) was added to a stirring mixture of (S)-methyl 4-(4-fluoro-5-hydroxy-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate (200mg, 0.61mmol) and DMF (2.7 mL). 1-Bromo-2-chloroethane (50μL, 0.6 mmol) was added to the stirring reaction mixture, and the reaction mixture was then heated to 80°C for 18h. Upon cooling to RT, the reaction mixture was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (EtOAc in Hex) to afford methyl (S)-4-(5-(2-chloroethoxy)-4-fluoro-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate. LCMS ($C_{17}H_{19}ClFO_5S$) (ES, m/z): 389 $[M+H]^+$.

Intermediates 29 through 31 and 87, as shown in Table 3 below, were or may be prepared according to procedures analogous to those outlined in Intermediate 28 above using the appropriate starting materials, described as Preparations or as obtained from commercial sources.

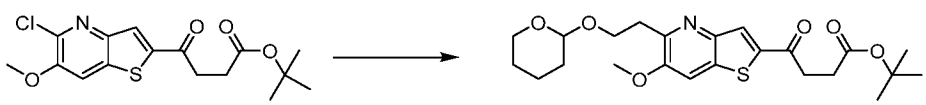
Table 3

Intermediate	Structure	Name	Mass $[M+H]^+$
29		methyl (S)-4-(5-(3-chloropropoxy)-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate	385
30		ethyl 4-(4-fluoro-5-(2-hydroxyethoxy)-6-methoxybenzo[b]thiophen-2-yl)-4-oxobutanoate	371
31		methyl (S)-4-(6-(2-hydroxyethoxy)-5-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate	353
87		methyl 4-(5-(3-chloro propoxy)-4-fluoro-6-methoxybenzo[b]thiophen-2-yl)-2,2-dimethyl-4-oxobutanoate	417

Intermediate 32: **tert-*butyl 4-(5-(2-hydroxyethyl)-6-methoxythieno[3,2-b]pyridin-2-yl)-4-oxobutanoate, acetate salt***

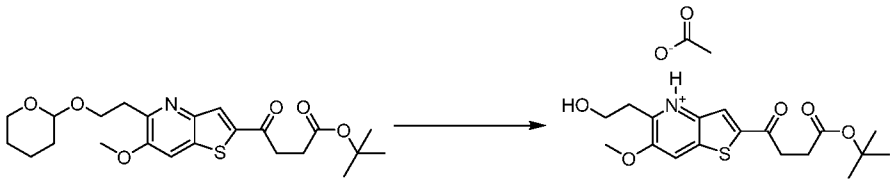


Step 1: tert-*butyl 4-(6-methoxy-5-(2-((tetrahydro-2H-pyran-2-yl)oxy)ethyl)thieno[3,2-b]pyridin-2-yl)-4-oxobutanoate*



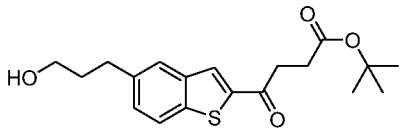
To a 4 mL vial was added bis(di-*tert*-butyl(4-dimethylaminophenyl)phosphine) dichloro-palladium(II) (5.0mg, 7.0μmol), Cs_2CO_3 (137mg, 0.422mmol), *tert*-butyl 4-(5-chloro-6-methoxythieno[3,2-b]pyridin-2-yl)-4-oxobutanoate (50.0mg, 0.141mmol), and potassium trifluoro(2-((tetrahydro-2H-pyran-2-yl)oxy)ethyl)borate (39.8mg, 0.169mmol). To the vial was added toluene (0.50mL) and water (0.10mL). The vial was degassed with N_2 for 5min. The mixture was heated to 100°C for 18h. Upon cooling to RT, the mixture was filtered through CELITE, and the CELITE was washed with EtOAc. The filtrate was concentrated under reduced pressure, and the resulting residue was purified by silica gel chromatography (0→75% EtOAc gradient in Hex) to afford *tert*-butyl 4-(6-methoxy-5-(2-((tetrahydro-2H-pyran-2-yl)oxy) ethyl)thieno[3,2-b]pyridin-2-yl)-4-oxobutanoate. LCMS ($C_{23}H_{32}NO_6S$) (ES, m/z): 450 $[M+H]^+$. ^1H NMR (500MHz, $CDCl_3$) δ 8.45 (s, 1H), 7.80 (s, 1H), 4.71 (s, 1H), 4.26-4.15 (m, 1H), 4.04 (s, 3H), 3.78 (t, *J*=8.3Hz, 1H), 3.65-3.42 (m, 4H), 3.33 (t, *J*=6.3Hz, 2H), 2.73 (t, *J*=6.3Hz, 2H), 1.64-1.48 (m, 6H), 1.46 (s, 9H).

Step 2: tert-*butyl 4-(5-(2-hydroxyethyl)-6-methoxythieno[3,2-b]pyridin-2-yl)-4-oxobutanoate, acetate salt*

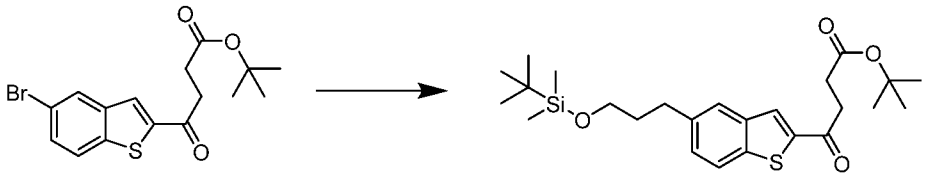


To a 4 mL vial was added *tert*-butyl 4-(6-methoxy-5-(2-((tetrahydro-2H-pyran-2-yl)oxy)ethyl)-thieno[3,2-b]pyridin-2-yl)-4-oxobutanoate (28mg, 0.062mmol), HOAc (0.50mL), MeOH (0.50mL), and water (0.5mL). The mixture was heated to 50°C for 75min. Upon cooling to RT, the mixture was diluted with EtOAc (30mL) and washed with water (2x30mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford *tert*-butyl 4-(5-(2-hydroxyethyl)-6-methoxythieno[3,2-b]pyridin-2-yl)-4-oxobutanoate, acetate salt. LCMS ($C_{18}H_{24}NO_5S$) (ES, m/z): 366 $[M+H]^+$. ^1H NMR (500MHz, $CDCl_3$) δ 8.22 (s, 1H), 7.68 (s, 1H), 4.13 (t, *J*=5.4Hz, 2H), 4.01 (s, 3H), 3.39-3.22 (m, 4H), 2.74 (t, *J*=6.5Hz, 2H), 1.46 (s, 9H).

Intermediate 33:* tert-*butyl 4-(5-(3-hydroxypropyl)benzo[b]thiophen-2-yl)-4-oxobutanoate

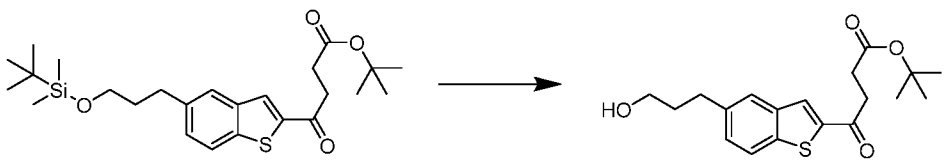


Step 1: tert-*butyl 4-(5-(3-((*tert*-butyldimethylsilyl)oxy)propyl)benzo[b]thiophen-2-yl)-4-oxobutanoate*



tert-Butyl 4-(5-bromobenzo[b]thiophen-2-yl)-4-oxobutanoate (0.207g, 0.561 mmol) and chloro(2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II) (0.022g, 0.028mmol) were placed in a 20mL screw cap vial with a magnetic stir bar. The vial was evacuated and backfilled with N_2 3 times. The vial was capped with a N_2 inlet and then THF (2.0mL) was added. (3-((*tert*-butyldimethylsilyl)oxy)propyl) zinc(II) bromide (0.50M in THF, 3.4mL, 1.7mmol) was added dropwise with stirring. After the addition was complete, the reaction was stirred at RT under N_2 for 1.5h. The reaction was then partitioned between EtOAc (50mL) and 10% aqueous sodium citrate (10mL) and stirred for 30min. The layers were then separated, and the organic layer was washed with sat aq NaCl, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (0→55% EtOAc gradient in Hex) to afford *tert*-butyl 4-(5-(3-((*tert*-butyldimethylsilyl)oxy)propyl)benzo[b]thiophen-2-yl)-4-oxobutanoate. LCMS ($C_{25}H_{38}NaO_4SSi$) (ES, m/z): 485 $[M+Na]^+$. ^1H NMR (500MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.78 (d, J=8.2Hz, 1H), 7.70 (s, 1H), 7.33 (d, J=8.2Hz, 1H), 3.66 (t, J=5.8Hz, 2H), 3.31 (t, J=6.5Hz, 2H), 2.82 (t, J=7.5Hz, 2H), 2.73 (t, J=6.5Hz, 2H), 1.93-1.86 (m, 2H), 1.47 (s, 9H), 0.94 (s, 9H), 0.08 (s, 6H).

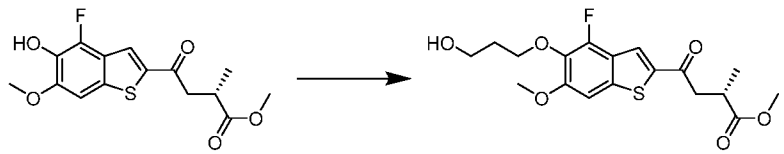
Step 2: tert-*butyl 4-(5-(3-hydroxypropyl)benzo[b]thiophen-2-yl)-4-oxobutanoate*



TBAF (1.0M in THF, 0.44mL, 0.44mmol) was added to a stirred mixture of *tert*-butyl 4-(5-(3-((tert-butyldimethylsilyl)oxy)propyl)benzo[b]thiophen-2-yl)-4-oxobutanoate (102mg, 0.220mmol) in THF (1.3mL) at RT under N_2. The resulting mixture was stirred at RT for 4.5h.

The reaction was then partitioned between Et_2O and sat aq NH_4Cl and stirred at RT for 1h. The layers were separated, and the organic layer was washed with sat aq NaCl, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to afford a crude residue. The resulting residue was purified by silica gel chromatography (0→60% EtOAc gradient in Hex) to afford *tert*-butyl 4-(5-(3-hydroxypropyl)benzo[b]thiophen-2-yl)-4-oxobutanoate. LCMS ($C_{19}H_{24}NaO_4S$) (ES, m/z): 371 $[M+Na]^+$. ^1H NMR (500MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.77 (d, *J*=8.3Hz, 1H), 7.70 (s, 1H), 7.33 (d, *J*=8.3Hz, 1H), 3.71 (t, *J*=6.3Hz, 2H), 3.30 (t, *J*=6.7Hz, 2H), 2.84 (t, *J*=7.7Hz, 2H), 2.72 (t, *J*=6.7Hz, 2H), 1.98-1.91 (m, 2H), 1.46 (s, 9H).

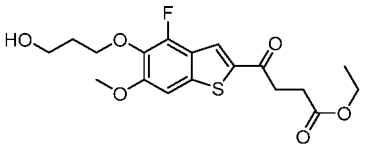
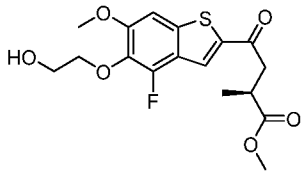
Intermediate 34: (S)-methyl 4-(4-fluoro-5-(3-hydroxypropoxy)-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate



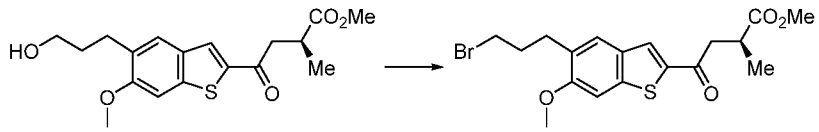
To a mixture of (S)-methyl 4-(4-fluoro-5-hydroxy-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate (0.065g, 0.2mmol) and Cs_2CO_3 (0.33g, 1.0mmol) in ACN (2.0mL) was added (3-bromopropoxy)(*tert*-butyl)dimethylsilane (0.10mL, 0.20mmol). The reaction was then heated to 65°C for 2h. Upon cooling to RT, the mixture was then filtered and washed with THF (5mL). Water (2mL) was added to the resulting filtrate followed by MP-TsOH (4.38mmol/g loading, 1.00g, 4.38mmol). The mixture was then heated to 60°C for 30min. Upon cooling to RT, the mixture was filtered and washed with THF. The filtrate was concentrated under reduced pressure to afford (S)-methyl 4-(4-fluoro-5-(3-hydroxypropoxy)-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate that was used without further purification. LCMS ($C_{18}H_{22}FO_6S$) (ES, m/z): 385 $[M+H]^+$.

Intermediates 35 through 36, as shown in Table 4 below, were or may be prepared according to procedures analogous to those outlined in Intermediate 34 above using the appropriate starting materials, described as Preparations or as obtained from commercial sources.

Table 4

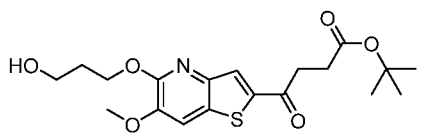
Intermediate	Structure	Name	Mass $[M+H]^+$
35		ethyl 4-(4-fluoro-5-(3-hydroxypropoxy)-6-methoxybenzo[b]thiophen-2-yl)-4-oxobutanoate	385
36		methyl (S)-4-(4-fluoro-5-(2-hydroxyethoxy)-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate	371

Intermediate 37: methyl (2S)-4-[5-(3-bromopropyl)-6-methoxy-1-benzothiophen-2-yl]-2-methyl-4-oxobutanoate

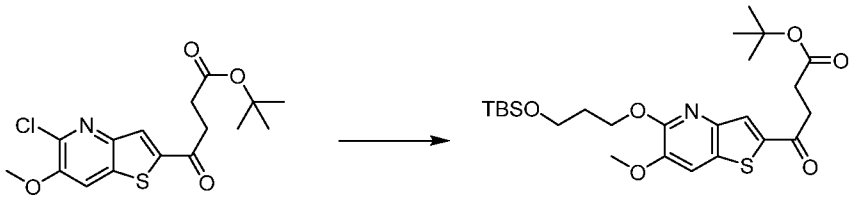


To the stirred mixture of methyl (2S)-4-[5-(3-hydroxypropyl)-6-methoxy-1-benzothiophen-2-yl]-2-methyl-4-oxobutanoate (187mg, 0.534mmol) and Ph_3P (224mg, 0.854 mmol) in THF (2.7 mL) at 0°C was added NBS (142mg, 0.800mmol) in one portion under N_2. The reaction mixture was stirred for 20min at 0°C. The mixture was directly purified by silica gel flash column chromatography (EtOAc in Hex) to afford methyl (2S)-4-[5-(3-bromopropyl)-6-methoxy-1-benzothiophen-2-yl]-2-methyl-4-oxobutanoate. LCMS ($C_{18}H_{22}BrO_4S$) (ES, m/z): 413, 415 $[M+H]^+$. ^1H NMR (500MHz, DMSO-d_6): δ 8.27 (s, 1H), 7.76 (s, 1H), 7.62 (s, 1H), 3.89 (s, 3H), 3.59 (s, 3H), 3.54 (t, *J*=6.8Hz, 2H), 3.43 (dd, *J*=17.5, 8.6Hz, 1H), 3.19 (dd, *J*=17.5, 5.0Hz, 1H), 3.02-2.92 (m, 1H), 2.79 (t, *J*=7.0Hz, 2H), 2.10 (pentet, *J*=6.9Hz, 2H), 1.19 (d, *J*=7.1Hz, 3H).

Intermediate 38:* tert-*butyl 4-(5-(3-hydroxypropoxy)-6-methoxythieno[3,2-b]pyridin-2-yl)-4-oxobutanoate

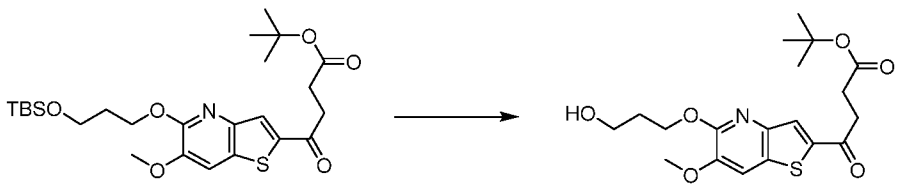


Step 1: tert-*butyl 4-(5-(3-((*tert*-butyldimethylsilyl)oxy)propoxy)-6-methoxythieno[3,2-b]pyridin-2-yl)-4-oxobutanoate*



tert-Butyl 4-(5-chloro-6-methoxythieno[3,2-b]pyridin-2-yl)-4-oxobutanoate (265mg, 0.745mmol), 3-((*tert*-butyldimethylsilyl)oxy)propan-1-ol (156mg, 0.819mmol), RockPhos Pd G3 (31mg, 0.037mmol) and Cs_2CO_3 (364mg, 1.12mmol) were added to a 20mL screw-cap vial with a magnetic stir bar. The vial was capped, and a N_2 inlet needle was inserted. Via this needle, the vial was evacuated and backfilled with N_2 three times. Under N_2, toluene (2.5mL) was added, the N_2 inlet was removed, and the sealed vial was heated to 110°C for 18h. The reaction was allowed to cool to RT, and MeOH (3.0mL), water (3.0mL) and HOAc (3.0mL) were added. The reaction mixture was stirred for 7h at RT, then partitioned between EtOAc and sat aq NaCl. The layers were separated, and the aqueous layer was extracted with EtOAc. The organic layers were combined, washed with aq NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure afford a crude residue. The residue was purified by silica gel chromatography (0→100% 3:1 EtOAc:EtOH gradient in Hex) to afford *tert*-butyl 4-(5-(3-((*tert*-butyldimethylsilyl)oxy) propoxy)-6-methoxythieno [3,2-b]pyridin-2-yl)-4-oxobutanoate. LCMS ($C_{25}H_{40}NO_6SSi$) (ES, m/z): 510 $[M+H]^+$. ^1H NMR (500MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.39 (s, 1H), 4.56 (t, *J*=6.5Hz, 2H), 3.94 (s, 3H), 3.83 (t, *J*=6.0Hz, 2H), 3.26 (t, *J*=6.7Hz, 2H), 2.70 (t, *J*=6.7Hz, 2H), 2.12-2.05 (m, 2H), 1.44 (s, 9H), 0.89 (s, 9H), 0.07 (s, 6H).

Step 2: tert-*butyl 4-(5-(3-hydroxypropoxy)-6-methoxythieno[3,2-b]pyridin-2-yl)-4-oxobutanoate*

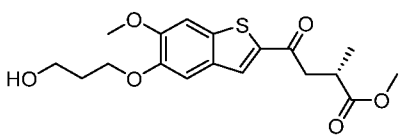


To a vial containing *tert*-Butyl 4-(5-(3-((*tert*-butyldimethylsilyl)oxy)propoxy)-6-methoxythieno[3,2-b]pyridin-2-yl)-4-oxobutanoate (83mg, 0.16mmol) was added MeOH (1.0mL), water (1.0mL) and then HOAc (1.0mL). The resulting mixture was stirred for 30min at RT. MeOH (1.0mL) was added and stirring was continued. After 30min, THF (1.0mL) was added, and the mixture was allowed to stir for 18h at RT. The mixture was partitioned between

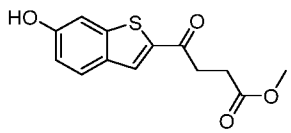
EtOAc (25mL) and aq NaCl (25mL) and stirred. The layers were separated, and the aqueous layer was extracted with EtOAc. The organic layers were combined, washed with sat aq NaCl twice, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford a crude residue. The resulting residue was purified by silica gel chromatography (0→100% EtOAc gradient in Hex, then isocratic at 100% EtOAc) to afford *tert*-butyl 4-(5-(3-hydroxypropoxy)-6-methoxythieno[3,2-b]pyridin-2-yl)-4-oxobutanoate. LCMS ($C_{19}H_{26}NO_6S$) (ES, m/z): 396 $[M+H]^+$. ^1H NMR (500MHz, $CDCl_3$) δ 7.93 (s, 1H), 7.44 (s, 1H), 4.69 (t, *J*=5.6Hz, 2H), 3.97 (s, 3H), 3.80-3.76 (m, 2H), 3.31-3.20 (m, 2H), 2.71 (t, J=6.5Hz, 2H), 2.14-2.07 (m, 2H), 1.46 (s, 9H).

Intermediate 39, as shown in Table 5 below, was or may be prepared according to procedures analogous to those outlined in Intermediate 38 above using the appropriate starting materials, described as Preparations or as obtained from commercial sources.

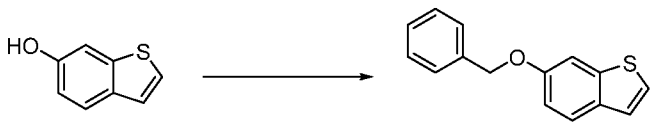
Table 5

Intermediate	Structure	Name	Mass $[M+H]^+$
39		methyl (S)-4-(5-(3-hydroxypropoxy)-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate	367

Intermediate 40: Methyl 4-(6-hydroxybenzo[b]thiophen-2-yl)-4-oxobutanoate



Step 1: 6-(Benzyloxy)benzo[b]thiophene



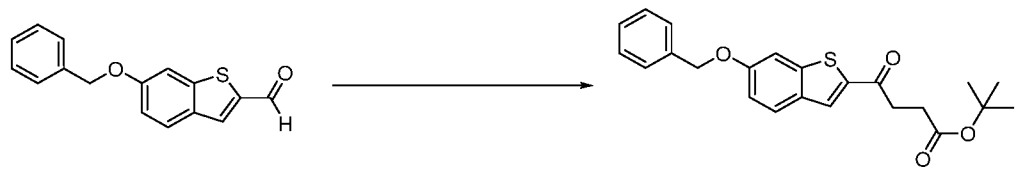
K_2CO_3 (2.62g, 19.0mmol) was added to a mixture of benzo[b]thiophen-6-ol (1.9g, 13mmol) and benzyl bromide (1.51mL, 12.7mmol) in DMF (10.0mL) at 20°C under Ar. The reaction mixture was stirred and heated to 50°C for 18 h. Upon cooling to RT, the reaction mixture was then diluted with EtOAc (500mL) and water (100mL). The organic layer was separated, washed with water (50mL) and then sat aq NaCl (50mL), dried over $MgSO_4$, filtered,

and concentrated under reduced pressure to afford the crude product residue. The crude product residue was purified by silica gel chromatography (0→100% EtOAc gradient in Hex) to afford 6-(benzyloxy)benzo[b]thiophene. LCMS ($C_{15}H_{13}OS$) (ES, m/z): 241 $[M+H]^+$. ^1H NMR (500MHz, DMSO-d_6) δ 7.77 (d, J=8.6Hz, 1H), 7.67 (s, 1H), 7.54 (d, J=5.2Hz, 1H), 7.49 (d, J=7.2Hz, 2H), 7.44-7.38 (m,2H), 7.37-7.32 (m, 2H), 7.08 (d, J=8.5Hz, 1H), 5.17 (s, 2H).

Step 2: 6-(Benzyloxy)benzo[b]thiophene-2-carbaldehyde

LDA (2.0M in THF, 7.3mL, 15mmol) was added to a mixture of 6-(benzyloxy) benzo[b]thiophene (2.92g, 12.2mmol) in THF (10.0mL) at -78°C under Ar. The reaction mixture was stirred at -78°C for 20min. DMF (2.4mL, 30mmol) was added to the reaction mixture at -78°C, and the reaction mixture was then allowed to warm slowly to RT. The reaction mixture was stirred for 15min at RT. The reaction mixture was quenched with citric acid (1.0M in water, 24mL, 24mmol) at 0°C and then diluted with EtOAc (200mL). The suspension was stirred for 15min. The organic layer was separated, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford the crude residue. The crude residue was purified by silica gel chromatography (0→100% EtOAc gradient in Hex) to afford 6-(benzyloxy)benzo [b]thiophene-2-carbaldehyde. LCMS ($C_{16}H_{13}O_2S$) (ES, m/z): 269 $[M+H]^+$. ^1H NMR (500MHz, DMSO-d_6) δ 10.05 (s, 1H), 8.34 (s, 1H), 8.01 (d, J=8.8Hz, 1H), 7.78 (s, 1H), 7.50 (d, J=7.3Hz, 2H), 7.42 (t, J=7.3Hz, 2H), 7.40-7.33 (m, 1H), 7.20 (d, J=8.4Hz, 1H), 5.23 (s, 2H).

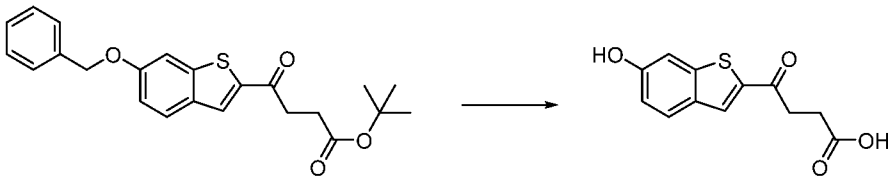
Step 3: tert-*Butyl 4-(6-(benzyloxy)benzo[b]thiophen-2-yl)-4-oxobutanoate*



A mixture of 6-(benzyloxy)benzo[b]thiophene-2-carbaldehyde (2.02g, 7.53mmol), 2-mesityl-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-2-ium chloride (0.099g, 0.38mmol), and potassium phosphate tribasic (1.6g, 7.5mmol) was flushed with Ar for 5min at 20°C. Toluene (15mL) and *tert*-butyl acrylate (2.2mL, 15mmol) were then added at 20°C. The reaction mixture was allowed to stir for 18h at 20°C. The reaction mixture was then diluted with EtOAc (200mL) and filtered to remove inorganic salts. The filtrate was concentrated under reduced pressure to afford the crude product residue. The crude product residue was purified by silica gel

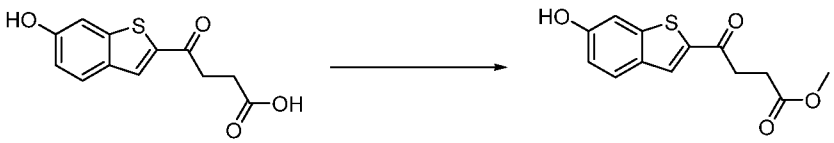
chromatography (0→100% EtOAc gradient in Hex) to afford *tert*-butyl 4-(6-(benzyl oxy)benzo[b]thiophen-2-yl)-4-oxobutanoate. LCMS ($C_{23}H_{25}O_4S$) (ES, m/z): 397 $[M+H]^+$. ^1H NMR (500MHz, DMSO-d_6) δ 8.35 (s, 1H), 7.96 (d, *J*=7.0Hz, 1H), 7.75 (s, 1H), 7.56-7.39 (m, 2H), 7.47-7.33 (m, 3H), 7.25-7.15 (m, 1H), 5.24 (s, 2H), 3.34-3.23 (m, 2H), 2.65-2.55 (m, 2H), 1.40 (s, 9H).

Step 4: 4-(6-Hydroxybenzo[b]thiophen-2-yl)-4-oxobutanoic acid



HCl (37% in water, 19.6mL, 238mmol) was added to a mixture of *tert*-butyl 4-(6-(benzyloxy)benzo[b]thiophen-2-yl)-4-oxobutanoate (2.36g, 5.96mmol) in dioxane (100mL). The reaction mixture heated to 90°C for 2 days. The reaction mixture was cooled to RT and diluted with EtOAc (500mL). The organic layer was separated, washed with water (3x100mL) and then sat aq NaCl (50mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford 4-(6-hydroxybenzo[b]thiophen-2-yl)-4-oxobutanoic acid, which was used without further purification. LCMS ($C_{12}H_{11}O_4S$) (ES, m/z): 251 $[M+H]^+$.

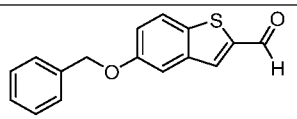
Step 5: Methyl 4-(6-hydroxybenzo[b]thiophen-2-yl)-4-oxobutanoate



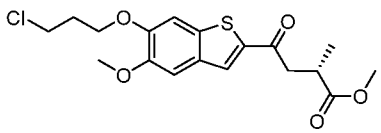
TMS-diazomethane (2.0M in Hex, 3.0mL, 6.0mmol) was added to a mixture of 4-(6-hydroxybenzo[b]thiophen-2-yl)-4-oxobutanoic acid (1.5g, 6.0mmol) in DCM (25mL) and MeOH (25mL) at 0°C. The reaction mixture was stirred at 0°C for 15min (until gas evolution ceased). HOAc (several drops) was added to quench any remaining TMS-diazomethane. The reaction mixture was then concentrated under reduced pressure to afford the crude product residue. The crude product residue was purified by silica gel chromatography (0→100% EtOAc gradient in Hex) to afford methyl 4-(6-hydroxybenzo[b]thiophen-2-yl)-4-oxobutanoate. LCMS ($C_{13}H_{13}O_4S$) (ES, m/z): 265 $[M+H]^+$. ^1H NMR (500MHz, DMSO-d_6) δ 10.17 (s, 1H), 8.26 (s, 1H), 7.84 (d, *J*=8.7Hz, 1H), 7.30 (s, 1H), 6.97 (d, *J*=8.2Hz, 1H), 3.76-3.65 (m, 1H), 3.60 (s, 3H), 3.54-3.44 (m, 1H), 2.72-2.67 (m, 2H).

Intermediate 41, as shown in Table 6 below, was or may be prepared according to procedures analogous to those outlined in Intermediate 40 above using the appropriate starting materials, described as Preparations or as obtained from commercial sources.

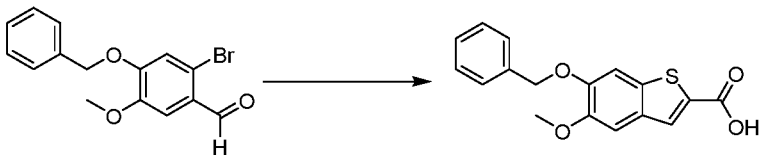
Table 6

Intermediate	Structure	Name	Mass $[M+H]^+$
41		5-(benzyloxy)benzo[b] thiophene-2-carbaldehyde	269

Intermediate 42: Methyl (S)-4-(6-(3-chloropropoxy)-5-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate



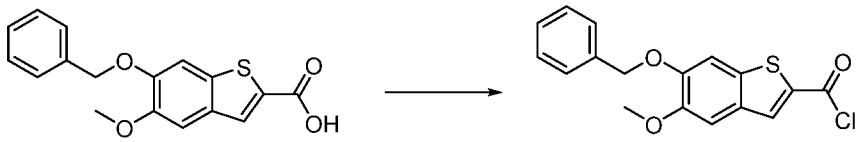
Step 1: 6-(Benzyloxy)-5-methoxybenzo[b]thiophene-2-carboxylic acid



A mixture of 4-(benzyloxy)-2-bromo-5-methoxybenzaldehyde (13g, 41mmol), K_2CO_3 (11g, 81mmol), 18-Crown-6 (2.1g, 8.1mmol) and methyl 2-mercaptoacetate (6.0mL, 67mmol) in DMF (150 mL) was heated to 90°C under Ar for 14 h. Upon cooling to RT, the reaction mixture was quenched with water (400mL), acidified with 1N HCl to pH~ 5, and extracted with EtOAc (3x250mL). The combined organic layers were washed with 10% aq LiCl (3x50mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced. The residue was diluted with EtOAc/MeOH (50mL/50mL) and treated with aq LiOH (2.0M, 80mL, 160mmol) at 20°C. The reaction mixture was heated to 60°C for 2 h. Upon cooling to RT, the mixture was concentrated under reduced pressure. The residue was diluted with aq NaOH (1.0M, 50mL, 50mmol), water (300mL), and EtOAc (300mL). The layers were separated, and the aqueous layer was washed with EtOAc (3x200mL). The aqueous layer was then acidified with 6N HCl to pH ~5, and extracted with EtOAc (3x300mL). The organics were combined, washed with sat aq NaCl (50mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was triturated with 1:1 EtOAc/PE (3x30mL) and 1:1 DCM/PE (3x30mL) to afford 6-

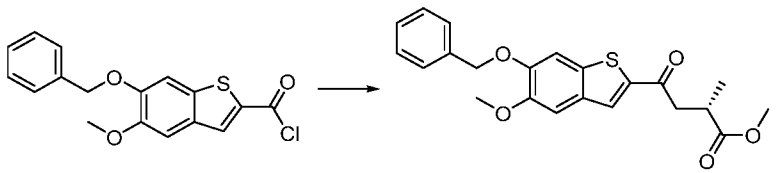
(benzyloxy)-5-methoxybenzo[b] thiophene-2-carboxylic acid. LCMS ($C_{17}H_{15}O_4S$) (ES, m/z): 315 $[M+H]^+$. ^1H NMR (400MHz, DMSO-d_6) δ 13.16 (br s, 1H), 7.95 (s, 1H), 7.69 (s, 1H), 7.51 (s, 1H), 7.50-7.46 (m, 2H), 7.44-7.32 (m, 3H), 5.17 (s, 2H), 3.83 (s, 3H).

Step 2: 6-(Benzyloxy)-5-methoxybenzo[b]thiophene-2-carbonyl chloride



DMF (0.023mL, 0.29mmol) was added to a mixture of 6-(benzyloxy)-5-methoxybenzo[b]thiophene-2-carboxylic acid (3.05g, 9.70mmol) and $(COCl)_2$ (2.55mL, 29.1 mmol) in THF (50 mL) at 0°C under Ar. The mixture was stirred at 0°C for 30min and then warmed to RT. The reaction mixture was then stirred for 2 h at RT. The reaction mixture was concentrated under reduced pressure to afford 6-(benzyloxy)-5-methoxybenzo[b] thiophene-2-carbonyl chloride, which was used without purification.

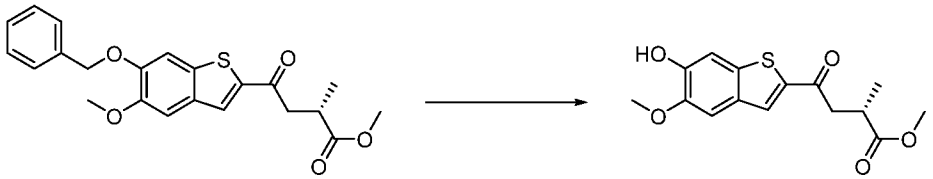
Step 3: Methyl (S)-4-(6-(benzyloxy)-5-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate



A mixture of (R)-(3-methoxy-2-methyl-3-oxopropyl)zinc(II) bromide (0.50M in THF, 25mL, 13mmol) was added slowly to a flask containing ((thiophene-2-carbonyl)oxy) copper (2.38g, 12.5mmol) under Ar at 0°C. The reaction mixture was stirred for 20min at 0°C under Ar. An Ar-degassed mixture of 6-(benzyloxy)-5-methoxybenzo[b]thiophene-2-carbonyl chloride (3.2g, 9.6mmol) in THF (50mL) was then added slowly via cannula to the mixture at 0°C. The mixture was allowed to warm to RT, and then stirred for 16 h at RT. The reaction mixture was cooled to 0°C and quenched by adding sat aq NH_4Cl (50mL), water (100mL), and EtOAc (500mL). The resulting biphasic mixture was warmed to RT and stirred for 1h at RT. The mixture was then filtered through a CELITE frit, and the filtrate was partitioned in a separatory funnel. The organic layer was separated, washed with sat aq NaCl (50mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (0→50% EtOAc gradient in Hex) to afford the desired product, which was repurified by silica gel chromatography (eluting 0-50% EtOAc in DCM) to afford (S)-methyl 4-(6-(benzyloxy)-5-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate. LCMS

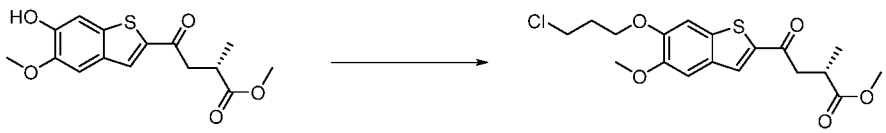
($C_{22}H_{23}O_5S$) (ES, m/z): 399 $[M+H]^+$. ^1H NMR (499MHz, DMSO-d_6) δ 8.22 (s, 1H), 7.72 (s, 1H), 7.52-7.47 (m, 3H), 7.42 (t, *J*=7.3Hz, 2H), 7.38-7.34 (m, 1H), 5.19 (s, 2H), 3.85 (s, 3H), 3.60 (s, 3H), 3.42 (dd, *J*=17.5, 8.6Hz, 1H), 3.19 (dd, *J*=17.4, 4.9Hz, 1H), 3.04-2.91 (m, 1H), 1.20 (d, *J*=7.1Hz, 3H).

Step 4: Methyl (S)-4-(6-hydroxy-5-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate



A mixture of (S)-methyl 4-(6-(benzyloxy)-5-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate (1.60g, 4.02mmol) and Pd/C (1.07g, 1.00mmol) was degassed with Ar. EtOAc (50mL), MeOH (50mL), and HCl (37% in water, 0.66mL, 8.0mmol) were added slowly to the mixture under Ar stream. The headspace above the reaction mixture was degassed via vacuum and backfilled with H_2. The reaction mixture was stirred under H_2 for 3h. The reaction mixture was filtered through CELITE, washing with EtOAc. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting 0-100% EtOAc in Hex) to afford (S)-methyl 4-(6-hydroxy-5-methoxybenzo[b] thiophen-2-yl)-2-methyl-4-oxobutanoate. LCMS ($C_{15}H_{17}O_5S$) (ES, m/z): 309 $[M+H]^+$. ^1H NMR (499MHz, DMSO-d_6) δ 9.93 (s, 1H), 8.17 (s, 1H), 7.44 (s, 1H), 7.30 (s, 1H), 3.85 (s, 3H), 3.60 (s, 3H), 3.44-3.38 (m, 1H), 3.16 (dd, *J*=17.3, 4.7Hz, 1H), 3.01-2.92 (m, 1H), 1.19 (d, *J*=7.0Hz, 3H).

Step 5: Methyl (S)-4-(6-(3-chloropropoxy)-5-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate

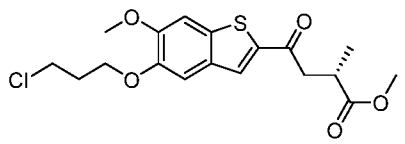


A mixture of (S)-methyl 4-(6-hydroxy-5-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate (141mg, 0.457mmol), 1-bromo-3-chloropropane (360mg, 2.3mmol), and K_2CO_3 (379mg, 2.74mmol) was degassed with Ar. ACN (4.0mL) was added to the mixture, and the reaction mixture was heated to 50°C for 18h. Upon cooling to RT, the reaction mixture was then diluted with DCM (25mL) and filtered. The filtrate was concentrated under reduced pressure and then purified by silica gel chromatography (0→100% EtOAc gradient in DCM) to afford

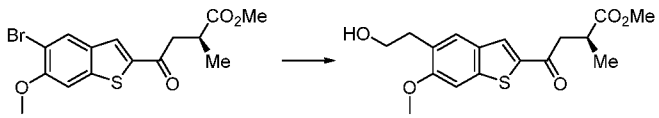
(S)-methyl 4-(6-(3-chloropropoxy)-5-methoxybenzo [b]thiophen-2-yl)-2-methyl-4-oxobutanoate. LCMS ($C_{18}H_{22}ClO_5S$) (ES, m/z): 385 $[M+H]^+$.

Intermediate 43, as shown in Table 7 below, was or may be prepared according to procedures analogous to those outlined in Intermediate 42 above using the appropriate starting materials, described as Preparations or as obtained from commercial sources.

Table 7

Intermediate	Structure	Name	Mass $[M+H]^+$
43		methyl (S)-4-(5-(3-chloropropoxy)-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate	385

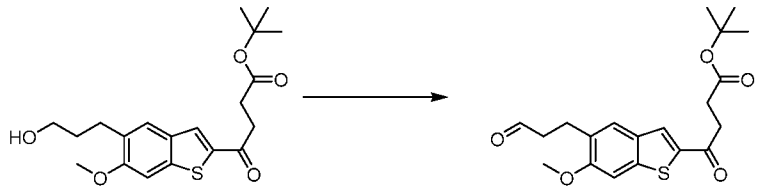
Intermediate 44: methyl (2S)-4-[5-(2-hydroxyethyl)-6-methoxy-1-benzothiophen-2-yl]-2-methyl-4-oxobutanoate



To the stirred mixture of methyl (2S)-4-(5-bromo-6-methoxy-1-benzothiophen-2-yl)-2-methyl-4-oxobutanoate (1.24g, 3.34mmol), tris(trimethylsilyl)silane (1.0mL, 3.3mmol), and anhydrous Na_2CO_3 (708mg, 6.68mmol) in degassed DME (16.5mL) under N_2, was added a mixture of Ir(2-(2,4-difluorophenyl)-5-(trifluoromethyl)pyridine)$_2$ (4,4'-di-*tert*-butyl-2,2'-bipyridine)PF_6 (38mg, 33µmol) in degassed DME (12mL). A suspension of Nickel(II) chloride ethylene glycol dimethyl ether complex (3.7mg, 17µmol) and 4,4'-di-*tert*-butyl-2,2'-bipyridine (4.5mg, 17µmol) in degassed DME (4.5mL) was added, and the resulting mixture was stirred under N_2 for 15min at RT. 2-Bromoethanol (835 mg, 6.68 mmol) was added in one portion under N_2, and the reaction mixture was stirred and irridiated in a photo-reactor with 20% light intensity for 24h at RT. The mixture was then filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (EtOAc in Hex) to afford methyl (2S)-4-[5-(2-hydroxyethyl)-6-methoxy-1-benzothiophen-2-yl]-2-methyl-4-oxobutanoate. LCMS ($C_{17}H_{21}O_5S$) (ES, m/z): 337 $[M+H]^+$. ^1H NMR (500MHz, DMSO-d_6): δ 8.26 (s, 1H), 7.76 (s, 1H), 7.58 (s, 1H), 4.64 (t, *J*=5.2Hz, 1H), 3.88 (s, 3H), 3.64-

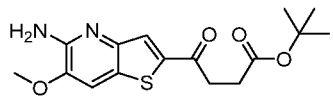
3.55 (m, 2H), 3.59 (s, 3H), 3.42 (dd, *J*=17.5, 8.6Hz, 1H), 3.19 (dd, *J*=17.5, 5.0Hz, 1H), 3.01-2.92 (m, 1H), 2.81 (t, *J*=6.9Hz, 2H), 1.19 (d, *J*=7.1Hz, 3H).

Intermediate 45: **tert-*butyl 4-(6-methoxy-5-(3-oxopropyl)benzo[b]thiophen-2-yl)-4-oxobutanoate***



To a 4 mL vial was added *tert*-butyl 4-(5-(3-hydroxypropyl)-6-methoxybenzo[b] thiophen-2-yl)-4-oxobutanoate (30mg, 0.079mmol), Dess-Martin periodinane (1,1,1-Triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one ; 50mg, 0.1mmol), and DCM (1.0mL). The mixture was stirred at RT for 1h. The mixture was purified by silica gel chromatography (0→55% EtOAc gradient in Hex) to afford *tert*-butyl 4-(6-methoxy-5-(3-oxopropyl)benzo[b]thiophen-2-yl)-4-oxobutanoate. LCMS ($C_{20}H_{24}O_5SNa$) (ES, m/z): 399 $[M+Na]^+$. ^1H NMR (500MHz, $CDCl_3$) δ 9.85 (s, 1H), 7.89 (s, 1H), 7.64 (s, 1H), 3.27 (t, *J*=6.8Hz, 2H), 3.05 (t, *J*=7.4Hz, 2H), 2.80 (t, *J*=7.2Hz, 2H), 2.72 (t, *J*=6.7Hz, 2H), 1.46 (s, 9H).

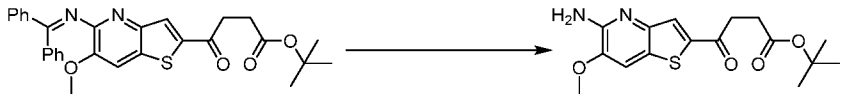
Intermediate 46: **tert-*butyl 4-(5-amino-6-methoxythieno[3,2-b]pyridin-2-yl)-4-oxobutanoate***



Step 1: tert-*butyl 4-(5-((diphenylmethylene)amino)-6-methoxythieno[3,2-b]pyridin-2-yl)-4-oxobutanoate*

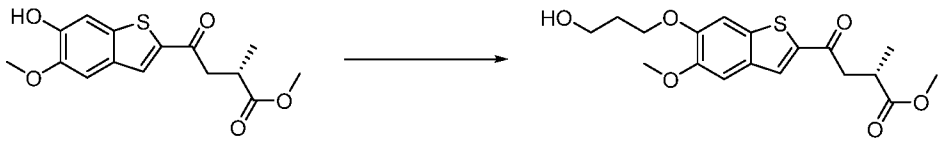
To a 4 mL vial was added Cs_2CO_3 (252mg, 0.773mmol), diphenylmethanimine (129μL, 0.773mmol), *tert*-butyl 4-(5-chloro-6-methoxythieno[3,2-b]pyridin-2-yl)-4-oxobutanoate (138mg, 0.387mmol), Rac BINAP Pd G3 (19mg, 0.019mmol), and toluene (2.0mL). The mixture was heated to 120°C for 3.5h. Upon cooling to RT, the mixture was directly purified by silica gel chromatography (0→50% EtOAc gradient in Hex) to afford *tert*-butyl 4-(5-((diphenylmethylene) amino)-6-methoxythieno[3,2-b]pyridin-2-yl)-4-oxobutanoate. LCMS ($C_{29}H_{29}N_2O_4S$) (ES, m/z): 501 $[M+H]^+$.

Step 2: tert-*butyl 4-(5-amino-6-methoxythieno[3,2-b]pyridin-2-yl)-4-oxobutanoate*



To a 20 mL vial was added *tert*-butyl 4-(5-((diphenylmethylene)amino)-6-methoxythieno[3,2-b]pyridin-2-yl)-4-oxobutanoate (146mg, 0.291mmol), AcOH (2.0mL), MeOH (2.0mL), water (2.0mL), and THF (6.0mL). The mixture was heated to 50°C for 1h. Upon cooling to RT, the mixture was then allowed to stir at RT for 24h. The mixture was then diluted with EtOAc (50mL) and washed with aq sat $NaHCO_3$ (50mL) and water (50mL). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (0→50% EtOAc gradient in Hex) to afford *tert*-butyl 4-(5-amino-6-methoxythieno[3,2-b]pyridin-2-yl)-4-oxobutanoate. LCMS ($C_{16}H_{21}N_2O_4S$) (ES, m/z): 337 $[M+H]^+$. ^1H NMR (500MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.53 (s, 1H), 4.11 (s, 3H), 3.24 (t, *J*=6.4Hz, 2H), 2.74-2.70 (m, 2H), 1.46 (s, 9H).

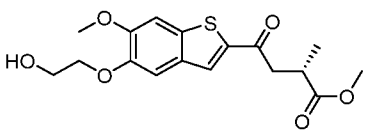
Intermediate 47: Methyl (S)-4-(6-(3-hydroxypropoxy)-5-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate



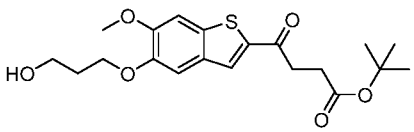
A mixture of (S)-methyl 4-(6-hydroxy-5-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate (25mg, 0.081mmol), 3-chloropropan-1-ol (10mg, 0.1mmol), and K_2CO_3 (22mg, 0.16mmol) was degassed with Ar. DMF (0.50mL) was added to the mixture, and the reaction mixture was irradiated in a microwave to 100°C for 1h. The reaction mixture was allowed to cool to RT and then diluted with EtOAc (25mL) and water (5mL). The organic layer was separated, washed with additional water (5 mL) and then sat aq NaCl (5 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford the crude product residue. The crude product residue was purified by silica gel chromatography (eluting 0-100% [5% MeOH in EtOAc] in DCM) to afford (S)-methyl 4-(6-(3-hydroxypropoxy)-5-methoxybenzo [b]thiophen-2-yl)-2-methyl-4-oxobutanoate. LCMS ($C_{18}H_{23}O_6S$) (ES, m/z): 367 $[M+H]^+$.

Intermediate 48, as shown in Table 8 below, was or may be prepared according to procedures analogous to those outlined in Intermediate 47 above using the appropriate starting materials, described as Preparations or as obtained from commercial sources.

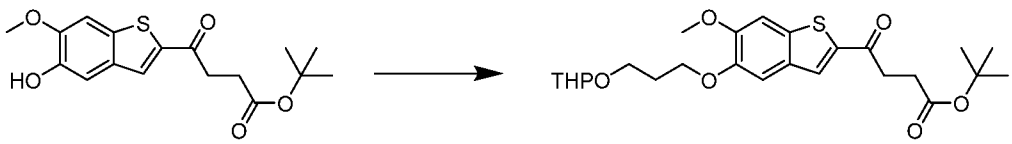
Table 8

Intermediate	Structure	Name	Mass $[M+H]^+$
48		methyl (S)-4-(5-(2-hydroxy ethoxy)-6-methoxybenzo[b] thiophen-2-yl)-2-methyl-4-oxobutanoate	453

Intermediate 49:* tert-*butyl 4-(5-hydroxy-6-methoxybenzo[b]thiophen-2-yl)-4-oxobutanoate

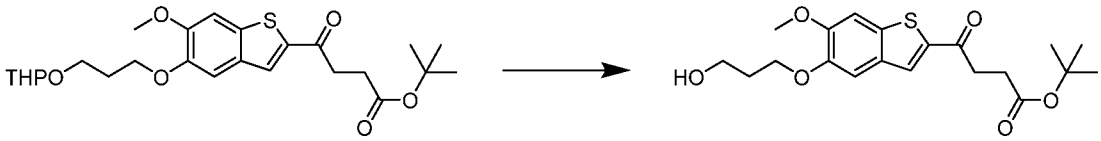


Step 1: tert-*butyl 4-(6-methoxy-5-(3-((tetrahydro-2H-pyran-2-yl)oxy)propoxy)benzo[b] thiophen-2-yl)-4-oxobutanoate*



To a mixture of *tert*-butyl 4-(5-hydroxy-6-methoxybenzo[b]thiophen-2-yl)-4-oxobutanoate (3.0g, 8.9mmol), K_2CO_3 (7.4g, 54mmol) and ACN (20mL) was added 2-(3-bromopropoxy)tetrahydro-2H-pyran (3.8mL, 22mmol). The reaction was heated to 65°C for 4h. Upon cooling to RT, the mixture was filtered, washed with ACN, and then the solvent was removed under reduced pressure. The resulting residue was dissolved in DCM (10mL), and Hex (100mL) was slowly added. The resulting precipitate was filtered, washed with Hex, and air dried to afford *tert*-butyl 4-(6-methoxy-5-(3-((tetrahydro-2H-pyran-2-yl)oxy)propoxy)benzo[b] thiophen-2-yl)-4-oxobutanoate. LCMS ($C_{25}H_{34}O_7SNa$) (ES, m/z): 501 $[M+Na]^+$. ^1H NMR (600MHz, DMSO-d_6) δ 8.16 (s, 1H), 7.56 (s, 1H), 7.46 (s, 1H), 4.54 (s, 1H), 4.06 (t, *J*=6.2Hz, 2H), 3.83 (s, 3H), 3.78 (dt, *J*=9.6, 6.4Hz, 1H), 3.69 (dd, *J*=13.5, 5.5Hz, 1H), 3.52-3.45 (m, 1H), 3.41-3.35 (m, 1H), 3.20 (t, *J*=6.2Hz, 2H), 2.54 (t, *J*=6.2Hz, 2H), 2.02-1.95 (m, 2H), 1.71-1.62 (m, 1H), 1.58 (t, *J*=7.8Hz, 1H), 1.47-1.39 (m, 3H), 1.36 –1.33 (m, 10H).

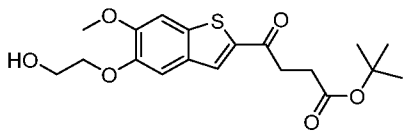
Step 2: tert-*butyl 4-(5-hydroxy-6-methoxybenzo[b]thiophen-2-yl)-4-oxobutanoate*



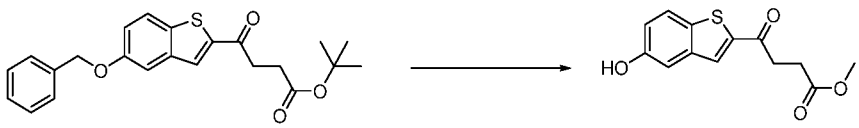
To a mixture of *tert*-butyl 4-(6-methoxy-5-(3-((tetrahydro-2H-pyran-2-yl)oxy) propoxy)benzo[b]thiophen-2-yl)-4-oxobutanoate (3.78g, 7.90mmol) and EtOH (50mL) was added pTsOH (2.2g, 12mmol), and the mixture was allowed to stir at RT for 2h. The mixture was then diluted with DCM and quenched with aq sat $NaHCO_3$. The organic layer was then separated, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford *tert*-butyl 4-(5-hydroxy-6-methoxybenzo[b]thiophen-2-yl)-4-oxobutanoate. LCMS ($C_{20}H_{26}O_6SNa$) (ES, m/z): 417 $[M+Na]^+$. ^1H NMR (600MHz, DMSO-d_6) δ 8.15 (s, 1H), 7.55 (s, 1H), 7.44 (s, 1H), 4.53 (t, *J*=4.7Hz, 1H), 4.05 (t, *J*=6.2Hz, 2H), 3.83 (s, 3H), 3.55 (q, *J*=5.4Hz, 2H), 3.20 (t, *J*=6.1Hz, 2H), 2.54 (t, *J*=6.1Hz, 2H), 1.88 (p, *J*=5.8Hz, 2H), 1.33 (s, 9H).

Intermediate 50, as shown in Table 9 below, was or may be prepared according to procedures analogous to those outlined in Intermediate 49 above using the appropriate starting materials, described as Preparations or as obtained from commercial sources.

Table 9

Intermediate	Structure	Name	Mass $[M+H]^+$
50		*tert*-butyl 4-(5-(2-hydroxyethoxy)-6-methoxybenzo[b]thiophen-2-yl)-4-oxobutanoate	403 $[M+Na]^+$

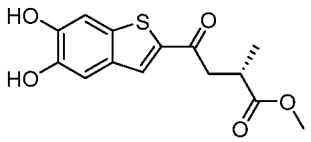
Intermediate 51: Methyl 4-(5-hydroxybenzo[b]thiophen-2-yl)-4-oxobutanoate



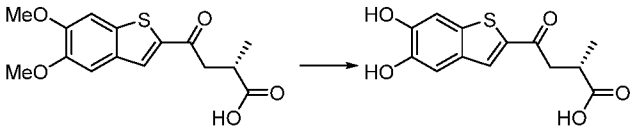
A mixture of *tert*-butyl 4-(5-(benzyloxy)benzo[b]thiophen-2-yl)-4-oxobutanoate (1.43g, 3.60mmol) and Pd/C (10% w/w, 1.5g, 1.4mmol) was degassed with Ar. MeOH (25mL), EtOAc (25mL), and HCl (37% in water, 0.59mL, 7.2mmol) were added slowly to the mixture under Ar stream. The headspace above the reaction mixture was degassed via vacuum and backfilled with H_2. The resulting mixture was stirred under H_2 for 24h. The reaction mixture was then filtered through CELITE, and the CELITE was washed with EtOAc. The filtrate was concentrated under

reduced pressure to afford the crude product residue. The crude product residue was purified by silica gel chromatography (0→100% EtOAc gradient in Hex) to afford methyl 4-(5-hydroxybenzo[b]thiophen-2-yl)-4-oxobutanoate. LCMS ($C_{13}H_{13}O_4S$) (ES, m/z): 265 $[M+H]^+$. ^1H NMR (500MHz, DMSO-d_6) δ 9.74 (s, 1H), 8.28 (s, 1H), 7.85 (d, *J*=8.5Hz, 1H), 7.36 (s, 1H), 7.07 (d, *J*=8.0Hz, 1H), 3.63 (s, 3H), 2.75-2.67 (m, 2H); 2 aliphatic protons buried under solvent peak and not apparent.

Intermediate 52: methyl (2S)-4-(5,6-dihydroxy-1-benzothiophen-2-yl)-2-methyl-4-oxobutanoate



Step 1: (2S)-4-(5,6-dihydroxy-1-benzothiophen-2-yl)-2-methyl-4-oxobutanoic acid



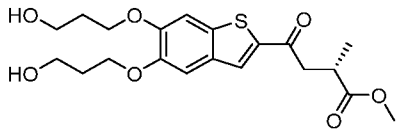
To a stirred solution of (2*S*)-4-(5,6-dimethoxy-1-benzothiophen-2-yl)-2-methyl-4-oxobutanoic acid (2.0g, 6.5mmol) in DCM (65mL) was added BBr_3 (1M in DCM, 19.5mL, 19.5mmol) at 0°C. The reaction mixture was allowed to warm to RT for 2.5h. The mixture was then cooled to 0°C, treated with water, and concentrated under reduced pressure. The residue was filtered, washed with water, and dried under high vacuum to afford (2*S*)-4-(5,6-dihydroxy-1-benzothiophen-2-yl)-2-methyl-4-oxobutanoic acid, which was used without further purification. LCMS ($C_{13}H_{13}O_5S$) ES, m/z): 281 $[M+H]^+$. ^1H NMR (500MHz, DMSO-d_6) δ 12.18 (s, 1H), 9.78 (brs, 1H), 9.49 (brs, 1H), 8.12 (s, 1H), 7.28 (s, 1H), 7.24 (s, 1H), 3.39-3.33 (m, 1H), 3.03 (dd, *J*=17.2, 5.2Hz, 1H), 2.91-2.84 (m, 1H), 1.16 (d, *J*=7.1Hz, 3H).

Step 2: methyl (2S)-4-(5,6-dihydroxy-1-benzothiophen-2-yl)-2-methyl-4-oxobutanoate

To a stirred solution of (2*S*)-4-(5,6-dihydroxy-1-benzothiophen-2-yl)-2-methyl-4-oxobutanoic acid (1.35g, 4.82mmol) in DCM (24mL) and MeOH (24mL) was added TMS-diazomethane (2M in Hex, 3.6 mL, 7.2mmol). The mixture was left to stir for 30min, treated

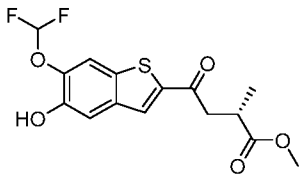
with HOAc (0.28mL, 4.8mmol) and concentrated under reduced pressure. The residue was purified by silica gel chromatography (0→10% MeOH gradient in DCM) to afford methyl (2*S*)-4-(5,6-dihydroxy-1-benzothiophen-2-yl)-2-methyl-4-oxobutanoate. LCMS ($C_{14}H_{15}O_5S$) (ES, m/z): 295 $[M+H]^+$. ^1H NMR (500MHz, DMSO-d_6) δ 9.85 (s, 1H), 9.45 (s, 1H), 8.13 (s, 1H), 7.28 (s, 1H), 7.25 (s, 1H), 3.59 (s, 3H), 3.41-3.34 (m, 1H), 3.17-3.11 (m, 1H), 2.98-2.91 (m, 1H), 1.17 (d, *J*=7.1Hz, 3H).

Intermediate 53: Methyl (2S)-4-[5,6-bis(3-hydroxypropoxy)-1-benzothiophen-2-yl]-2-methyl-4-oxobutanoate



A mixture of methyl (2*S*)-4-(5,6-dihydroxy-1-benzothiophen-2-yl)-2-methyl-4-oxobutanoate (230mg, 0.78mmol), 3-chloro-1-propanol (196µL, 2.34mmol), and K_2CO_3 (432mg, 3.13mmol) in DMF (7.8mL) was irradiated in a microwave to 100°C for 1h. Upon cooling to RT, the mixture was diluted with EtOAc and sat aq NaCl. The organic layer was separated, dried over Na_2SO_4, filtered and then concentrated under reduced pressure. The resulting residue was purified by flash chromatography (0→10% MeOH gradient in DCM) to afford methyl (2*S*)-4-[5,6-bis(3-hydroxypropoxy)-1-benzothiophen-2-yl]-2-methyl-4-oxobutanoate. LCMS ($C_{20}H_{27}O_7S$) (ES, m/z): 411 $[M+H]^+$

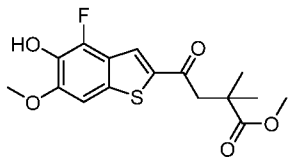
Intermediate 54: methyl (2S)-4-[6-(difluoromethoxy)-5-hydroxy-1-benzothiophen-2-yl]-2-methyl-4-oxobutanoate



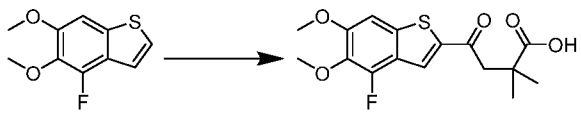
To a frozen mixture of methyl (2*S*)-4-(5,6-dihydroxy-1-benzothiophen-2-yl)-2-methyl-4-oxobutanoate (177mg, 0.601mmol) and KOH (1.0M in water, 120µL, 1.2mmol) in ACN (5.5mL) and water (0.55mL) at -78°C was added diethyl (bromodifluoromethyl) phosphonate (170µL, 0.96mmol). The cooling bath was removed, and the reaction mixture was left to stir for 4h. The mixture was diluted with EtOAc and water. The layers were separated, and the water

layer was re-extracted EtOAc (x3). The combined organics were dried over Na_2SO_4, filtered, and then concentrated under reduced pressure. The resulting mixture was purified by flash chromatography (0-50% EtOAc in DCM) to afford crude methyl (2*S*)-4-[6-(difluoromethoxy)-5-hydroxy-1-benzothiophen-2-yl]-2-methyl-4-oxobutanoate. The desired fractions were purified by SFC (15% MeOH (+0.25% DMEA) in CO_2) to afford methyl (2*S*)-4-[6-(difluoromethoxy)-5-hydroxy-1-benzothiophen-2-yl]-2-methyl-4-oxobutanoate with a retention time of 4.4min. LCMS ($C_{15}H_{15}F_2O_5S$) (ES, m/z): 345 $[M+H]^+$. ^1H NMR (500MHz, DMSO-d_6) δ 10.25 (s, 1H), 8.28 (s, 1H), 7.83 (s, 1H), 7.50 (s, 1H), 7.18 (t, *J*=74.4Hz, 1H), 3.59 (s, 3H), 3.44 (dd, *J*=17.6, 8.7Hz, 1H), 3.20 (dd, *J*=17.6, 4.9Hz, 1H), 3.01-2.94 (m, 1H), 1.19 (d, *J*=7.1Hz, 3H).

Intermediate 55: Methyl 4-(4-fluoro-5-hydroxy-6-methoxybenzo[b]thiophen-2-yl)-2,2-dimethyl-4-oxobutanoate

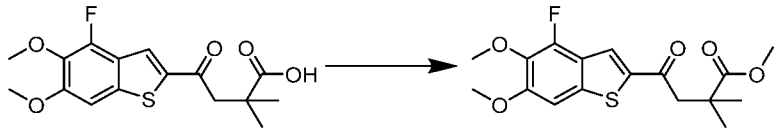


Step 1: 4-(4-Fluoro-5,6-dimethoxybenzo[b]thiophen-2-yl)-2,2-dimethyl-4-oxobutanoic acid



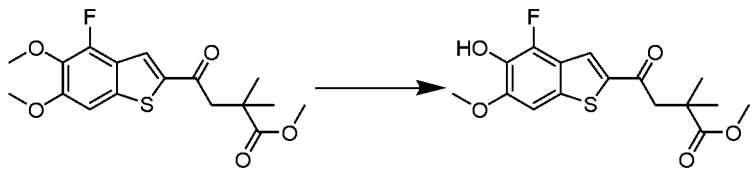
3,3-dimethyldihydrofuran-2,5-dione (4.6g, 36mmol) was added to a mixture of 4-fluoro-5,6-dimethoxybenzo[b]thiophene (3.8g, 18mmol) and $AlCl_3$ (3.1g, 23mmol) in DCM (100mL) at 0°C under Ar. The reaction mixture was stirred at 0°C for 2 h and then warmed to RT and stirred for 16 h. The reaction mixture was then quenched by slowly adding the reaction mixture to a mixture of water (200mL) and EtOAc (500mL) at 0°C. The resulting mixture was stirred for 1h at 20°C and then diluted with HCl (2.0M in water, 36mL, 72mmol). The organic layer was separated, washed with sat aq NaCl (50mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The mixture was then purified by silica gel chromatography to afford 4-(4-fluoro-5,6-dimethoxybenzo[b]thiophen-2-yl)-2,2-dimethyl-4-oxobutanoic acid. LCMS ($C_{16}H_{18}FO_5S$) (ES, m/z): 341 $[M+H]^+$.

Step 2: Methyl 4-(4-fluoro-5,6-dimethoxybenzo[b]thiophen-2-yl)-2,2-dimethyl-4-oxobutanoate



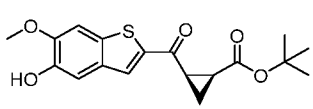
To a mixture of 4-(4-fluoro-5,6-dimethoxybenzo[b]thiophen-2-yl)-2,2-dimethyl-4-oxobutanoic acid (2.3g, 6.8mmol) in DMF (45mL) was added K_2CO_3 (2.3g, 17mmol). After 10min, CH_3I (2.1mL, 34mmol) was added, and the mixture was stirred for 18h at RT. The mixture was then diluted with water and Et_2O. The organic layer was separated, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The mixture was then purified by silica gel chromatography to afford methyl 4-(4-fluoro-5,6-dimethoxybenzo[b] thiophen-2-yl)-2,2-dimethyl-4-oxobutanoate. LCMS ($C_{17}H_{20}FO_5S$) (ES, m/z): 355 $[M+H]^+$. ^1H NMR (500MHz, DMSO-d_6) δ 8.32 (s, 1H), 7.59 (s, 1H), 3.92 (s, 3H), 3.85 (s, 3H), 3.57 (s, 3H), 3.44 (s, 2H), 1.23 (s, 6H).

Step 3: Methyl 4-(4-fluoro-5-hydroxy-6-methoxybenzo[b]thiophen-2-yl)-2,2-dimethyl-4-oxobutanoate

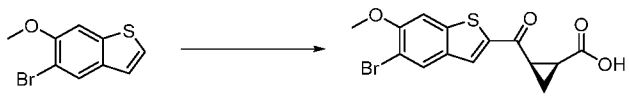


To a mixture of methyl 4-(4-fluoro-5,6-dimethoxybenzo[b]thiophen-2-yl)-2,2-dimethyl-4-oxobutanoate (1.1g, 3.1mmol) and DCM (20mL) was added $AlCl_3$ (1.7g, 12mmol). The reaction mixture was stirred at RT for 18h. The reaction mixture was poured into a flask containing ice and 1N HCl and stirred for 5min. EtOAc was then added. The organic layer was separated, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The mixture was then purified by silica gel chromatography to afford methyl 4-(4-fluoro-5-hydroxy-6-methoxybenzo[b]thiophen-2-yl)-2,2-dimethyl-4-oxobutanoate. LCMS ($C_{16}H_{18}FO_5S$) (ES, m/z): 341 $[M+H]^+$. 1H NMR (500MHz, DMSO-d_6) δ 9.55 (s, 1H), 8.24 (s, 1H), 7.47 (s, 1H), 3.91 (s, 3H), 3.57 (s, 3H), 3.43 (s, 2H), 1.23 (s, 6H).

Intermediate 56:* tert-*Butyl (1S,2R and 1R,2S)-2-(5-hydroxy-6-methoxybenzo[b]thiophene-2-carbonyl)cyclopropane-1-carboxylate

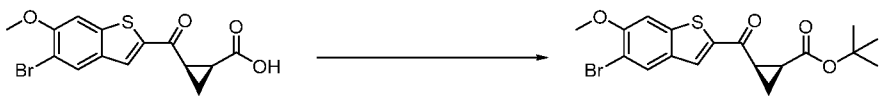


Step 1: (1S,2R and 1R,2S)-2-(5-Bromo-6-methoxybenzo[b]thiophene-2-carbonyl)cyclopropane-1-carboxylic acid



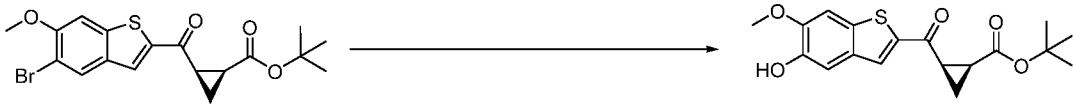
3-Oxabicyclo[3.1.0]hexane-2,4-dione (3.78g, 33.7mmol) was added to a mixture of 5-bromo-6-methoxybenzo[b]thiophene (4.1g, 17mmol) and $AlCl_3$ (2.92g, 21.9mmol) in DCM (100mL) at 0°C under Ar. The reaction mixture was stirred at 0°C for 2h and then allowed to warm to RT. The reaction mixture was stirred at RT for 16h. The reaction mixture was then quenched by slowly adding the reaction mixture to a mixture of water (200mL) and EtOAc (500mL) at 0°C. The resulting mixture was allowed to warm to RT and stirred for 1h. The mixture was then diluted with HCl (2.0M in water, 34mL, 68mmol). The organic layer was separated, washed with sat aq NaCl (50mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford the crude product residue. The crude product residue was purified by silica gel chromatography (eluting 0-100% [5% MeOH in EtOAc] in DCM) to afford (1S,2R and 1R,2S)-2-(5-bromo-6-methoxybenzo[b]thiophene-2-carbonyl)cyclopropane carboxylic acid. LCMS ($C_{14}H_{12}BrO_4S$) (ES, m/z): 355, 357 $[M+H]^+$.

Step 2: tert-*Butyl (1S,2R and 1R,2S)-2-(5-bromo-6-methoxybenzo[b]thiophene-2-carbonyl)cyclopropane-1-carboxylate*



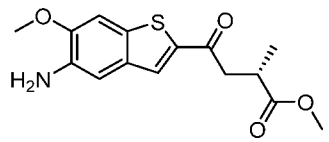
tert-Butanol (25.8 mL, 270 mmol) was added to a mixture of BOC-anhydride (6.3mL, 27mmol), DMAP (0.33g, 2.7mmol), and (1S,2R and 1R,2S)-2-(5-bromo-6-methoxy benzo[b]thiophene-2-carbonyl)cyclopropanecarboxylic acid (4.8g, 14mmol) in DCE (30mL) at RT under Ar. The reaction mixture was stirred and heated to 50°C for 2h. The reaction mixture was then cooled to RT and concentrated under reduced pressure to afford the crude product residue. The crude product residue was purified by silica gel chromatography (0→100% EtOAc gradient in Hex) to afford (1S,2R and 1R,2S)-*tert*-butyl 2-(5-bromo-6-methoxybenzo[b]thio phene-2-carbonyl)cyclopropanecarboxylate. LCMS ($C_{18}H_{20}BrO_4S$-C_4H_8) (ES, m/z): 355, 357 $[M+H\text{-}tBu]^+$. ^1H NMR (500MHz, DMSO-d_6) δ 8.33 (s, 1H), 8.26 (s, 1H), 7.81 (s, 1H), 3.95 (s, 3H), 3.10-3.03 (m, 1H), 2.32-2.25 (m, 1H), 1.57-1.52 (m, 1H), 1.32-1.28 (m, 1H), 1.14 (s, 9H).

Step 3: tert-*Butyl (1S,2R and 1R,2S)-2-(5-hydroxy-6-methoxybenzo[b]thiophene-2-carbonyl) cyclopropane-1-carboxylate*



A mixture of (1S,2R and 1R,2S)-*tert*-butyl 2-(5-bromo-6-methoxybenzo[b] thiophene-2-carbonyl)cyclopropanecarboxylate (1.64g, 3.99mmol), RockPhos Pd G3 (0.100g, 0.120mmol), Cs_2CO_3 (3.90g, 12.0mmol), and (*E*)-benzaldehyde oxime (0.725g, 5.98mmol) was degassed with Ar for 5min. DMF (10.0mL) was added under Ar, and the mixture was then degassed with Ar for 5min. The reaction mixture was stirred and heated to 80°C for 18h. The reaction mixture was cooled to RT and diluted with water (100mL) and EtOAc (250mL). The organic layer was separated, washed with water (50mL) and then sat aq NaCl (50mL). The organic layer was separated, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford the crude product residue. The crude product residue was purified by silica gel chromatography (0→75% EtOAc gradient in Hex) to afford (1S,2R and 1R,2S)-*tert*-butyl 2-(5-hydroxy-6-methoxybenzo[b]thiophene-2-carbonyl) cyclopropanecarboxylate. LCMS ($C_{18}H_{20}O_5SNa$) (ES, m/z): 371 $[M+Na]^+$.

Intermediate 57: (S)-Methyl-4-(5-amino-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoatexylate



Step 1: Methyl (S)-4-(5-((diphenylmethylene)amino)-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate

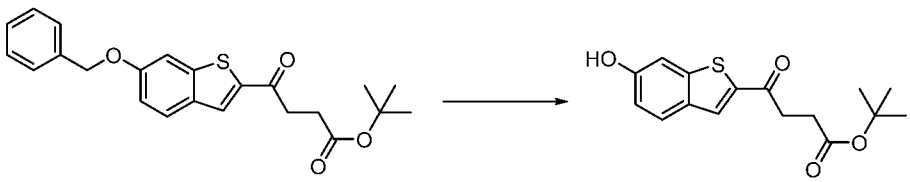
A mixture of (S)-methyl 4-(5-bromo-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate (0.50g, 1.4mmol), benzophenone imine (0.45mL, 2.7mmol), Rac BINAP Pd G3 (0.067g, 0.067mmol), and Cs_2CO_3 (0.878g, 2.69mmol) was degassed with Ar for 5min. Toluene (10.0mL) was added at 20°C under Ar, and the mixture was then degassed with Ar for 5min. The reaction mixture was stirred and heated to 110°C for 18h under Ar. The reaction mixture was then cooled to RT and diluted with DCM (25mL). The mixture was filtered, and the filtrate

was concentrated under reduced pressure to afford methyl (S)-4-(5-((diphenylmethylene) amino)-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate, which was used without purification. LCMS ($C_{28}H_{26}NO_4S$) (ES, m/z): 472 $[M+H]^+$.

Step 2: (S)-Methyl 4-(5-amino-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate

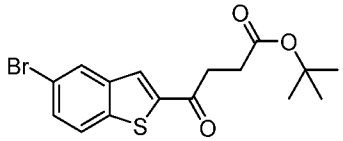
TFA (2.1mL, 27mmol) was added to a mixture of (S)-methyl 4-(5-((diphenyl methylene)amino)-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate (635mg, 1.35mmol) in DCM (5.0mL) at 20°C. The resulting mixture was stirred at 20°C for 30min. The reaction mixture was then concentrated under reduced pressure to afford the crude product residue. The crude product residue was purified by silica gel chromatography (0→100% EtOAc gradient in DCM) to afford (S)-methyl 4-(5-amino-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate. LCMS ($C_{15}H_{18}NO_4S$) (ES, m/z): 308 $[M+H]^+$.

Intermediate 58:* tert-*Butyl 4-(6-hydroxybenzo[b]thiophen-2-yl)-4-oxobutanoate

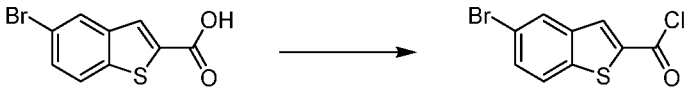


A mixture of *tert*-butyl 4-(6-(benzyloxy)benzo[b]thiophen-2-yl)-4-oxobutanoate (256mg, 0.646mmol) and Pd/C (172mg, 0.161mmol) was degassed with Ar. EtOAc (5.0mL), MeOH (5.0mL), and HCl (37% in water, 0.053mL, 0.65mmol) were added slowly to the mixture under Ar. The headspace above the reaction mixture was degassed via vacuum and backfilled with H_2. The resulting mixture was stirred under H_2 for 24h. The reaction mixture was then filtered through CELITE, washing with EtOAc. The filtrate was concentrated under reduced pressure to afford the crude product residue. The crude product residue was purified by silica gel chromatography (eluting 0-100% EtOAc in Hex) to afford *tert*-butyl 4-(6-hydroxybenzo[b] thiophen-2-yl)-4-oxobutanoate. LCMS ($C_{16}H_{19}O_4S$-C_4H_8) (ES, m/z): 251 $[M+H-tBu]^+$.

Intermediate 59:* tert-*butyl 4-(5-bromobenzo[b]thiophen-2-yl)-4-oxobutanoate

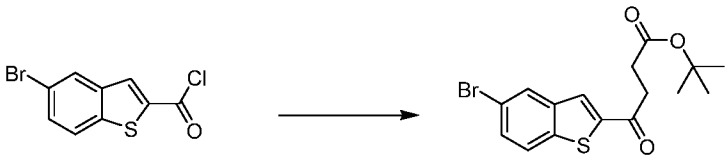


Step 1: 5-bromobenzo[b]thiophene-2-carbonyl chloride



$(COCl)_2$ (0.30mL, 3.4mmol) was added dropwise with stirring to a 0°C mixture of 5-bromobenzo[b]thiophene-2-carboxylic acid (0.750g, 2.92mmol) in CH_2Cl_2 (15mL) over 3min. To the reaction was added DMF (0.023mL, 0.29mmol) followed by additional $(COCl)_2$ (0.20mL, 2.3mmol). The reaction mixture was then stirred at 0°C for 1h. The reaction flask was removed from the ice water bath, and stirring was continued at RT for 1.5h. The reaction was concentrated to afford 5-bromobenzo[b]thiophene-2-carbonyl chloride, which was used without further purification or characterization.

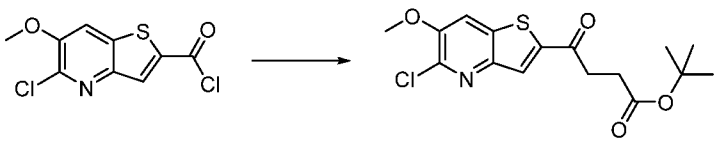
Step 2: tert-*butyl 4-(5-bromobenzo[b]thiophen-2-yl)-4-oxobutanoate*



CuCl (0.269 g, 2.72 mmol) was added to a 100mL round bottom flask with a stir bar. The flask was evacuated and then backfilled with N_2 three times. THF (6.0mL) was added to the flask, which was then stirred and cooled to 0°C with an ice water bath. (3-(*tert*-butoxy)-3-oxopropyl)zinc(II) bromide (0.50M in THF, 11mL, 5.5mmol) was added dropwise with stirring at 0°C over a period of 3min to the CuCl mixture. The resulting mixture was stirred at 0°C for 30min. A mixture of 5-bromobenzo[b]thiophene-2-carbonyl chloride (0.75g, 2.7mmol) in NMP (24mL) was added dropwise to the mixture over a period of 7min at 0°C with stirring. The resulting mixture was stirred at 0°C for 2h. The reaction mixture was then partitioned between isopropyl acetate (300mL) and 10% aq. sodium citrate (300mL). The resulting mixture was stirred for 20min. The layers were separated, and the aqueous layer was extracted with isopropyl acetate (150mL). The organic layers were combined, washed with aq NaCl, then sat aq NaCl, dried over anhydrous $MgSO_4$, and filtered, and the filtrate was allowed to stand overnight. The filtrate was then filtered, and the filtrate concentrated to afford a crude residue. The crude

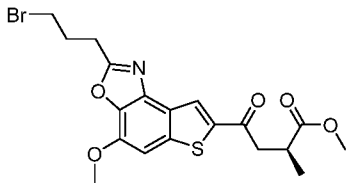
residue was loaded onto a silica gel column with acetone. The column was dried by blowing pressurized N_2 through it. The dried column was then subjected to a 0→30% EtOAc gradient with Hex. All product-containing fractions were collected, concentrated, and purified by silica gel chromatography (0→25% EtOAc gradient in Hex). The product-containing fractions were concentrated and purified by achiral SFC (Phenomenex biphenyl, 21mmx250mm column, 90:10 CO_2:MeOH w/ 0.25% DMEA, 70 mL/min, 100 bar outlet pressure, 18.5 mg/mL in MeOH/MeCN loading concentration, 1.6 mL injection volume, 215 nm detection) to afford *tert*-butyl 4-(5-bromobenzo[b]thiophen-2-yl)-4-oxobutanoate. LCMS ($C_{16}H_{17}BrNaO_3S$) (ES, m/z): 391, 393 $[M+Na]^+$. ^1H NMR (500MHz, $CDCl_3$) δ 8.05 (s, 1H), 7.94 (s, 1H), 7.75 (d, *J*=8.6Hz, 1H), 7.57 (d, *J*=8.6Hz, 1H), 3.31 (t, *J*=6.6Hz, 2H), 2.74 (t, *J*=6.6Hz, 2H), 1.46 (s, 9H).

Intermediate 60: tert-***Butyl 4-(5-chloro-6-methoxythieno[3,2-b]pyridin-2-yl)-4-oxobutanoate***



A flask containing CuCl (0.76g, 7.6mmol) was evacuated and then purged three times with N_2. THF (15mL) was added, and the mixture was cooled to 0°C. (3-(*tert*-butoxy)-3-oxopropyl)zinc(II) bromide (0.50M in THF, 31mL, 16mmol) was added dropwise over 10 min. After 30min, 5-chloro-6-methoxythieno[3,2-b]pyridine-2-carbonyl chloride (2.0g, 7.6mmol) was added followed by NMP (15mL). The mixture was then allowed to warm to RT. After 1h, the mixture was cooled to 0°C, and concentrated aq NH_4OH (4.5mL) was added. To this mixture was added water (240mL) and MeOH (60mL). The mixture was stirred for 5min and sonicated in a water bath sonicator. The resulting mixture was filtered, and the precipitates were washed with water and then Hex. The precipitates were isolated and dried under vacuum. The precipitates were then partitioned between EtOAc and 10% aqueous sodium citrate. The layers were separated, and the aqueous layer was washed with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. During the concentration, precipitation occurred, and the precipitates were collected via filtration, washed with EtOAc, and dried under vacuum to afford *tert*-butyl 4-(5-chloro-6-methoxythieno[3,2-b]pyridin-2-yl)-4-oxobutanoate. LCMS ($C_{16}H_{19}ClNO_4S$) (ES, m/z): 356 $[M+H]^+$. ^1H NMR (500MHz, $CDCl_3$) δ 8.03 (s, 1H), 7.62 (s, 1H), 4.04 (s, 3H), 3.30 (t, *J*=6.4Hz, 2H), 2.74 (t, *J*=6.4Hz, 2H), 1.46 (s, 9H).

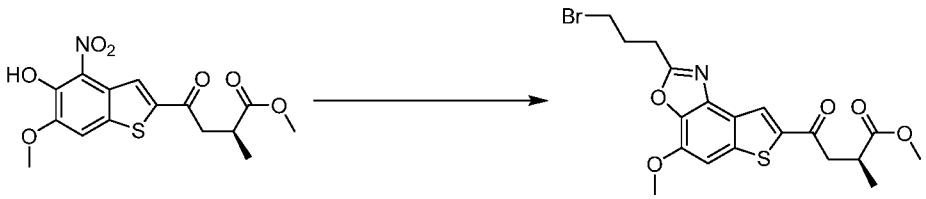
Intermediate 61: methyl (S)-4-(2-(3-bromopropyl)-4-methoxythieno[2',3':5,6]benzo[1,2-d]oxazol-7-yl)-2-methyl-4-oxobutanoate



Step 1: methyl (S)-4-(5-hydroxy-6-methoxy-4-nitrobenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate

To a 20mL vial was added (S)-methyl 4-(5-hydroxy-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate (100mg, 0.21mmol) and EtOAc (3.0mL). HNO_3 (0.017mL, 0.27mmol) was added, and the mixture was allowed to stir for 1h. After 1h, the mixture was concentrated under reduced pressure and then triturated with Et_2O (3.0mL). The resulting materials were collected by filtration to afford (S)-methyl 4-(5-hydroxy-6-methoxy-4-nitrobenzo [b]thiophen-2-yl)-2-methyl-4-oxobutanoate. ^1H NMR (500MHz, $CDCl_3$) δ 12.08 (s, 1H), 8.75 (s, 1H), 7.53 (s, 1H), 4.07 (s, 3H), 3.74 (s, 3H), 3.59 (dd, *J*=17.1, 7.9Hz, 1H), 3.23-3.16 (m, 1H), 3.16-3.09 (m, 1H), 1.35 (d, *J*=7.1Hz, 3H).

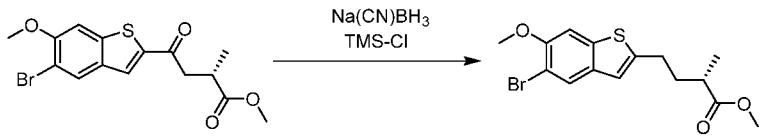
Step 2: methyl (S)-4-(2-(3-bromopropyl)-4-methoxythieno[2',3':5,6]benzo[1,2-d]oxazol-7-yl)-2-methyl-4-oxobutanoate



To a 4mL vial was added (S)-methyl 4-(5-hydroxy-6-methoxy-4-nitrobenzo[b] thiophen-2-yl)-2-methyl-4-oxobutanoate (45mg, 0.13mmol), Pd (0.040g, 0.038mmol), and MeOH (0.60mL). To the mixture was added 4-bromo-1,1,1-trimethoxybutane (0.61mL, 3.8mmol). The mixture was stirred under H_2 for 1h. The mixture was then filtered, and the filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (0→70% EtOAc gradient in Hex) to afford (S)-methyl 4-(2-(3-bromopropyl)-4-

methoxythieno[2',3':5,6]benzo[1,2-d]oxazol-7-yl)-2-methyl-4-oxobutanoate. LCMS ($C_{19}H_{21}BrNO_5S$) (ES, m/z): 454, 456 $[M+H]^+$. 1H NMR (500MHz, $CDCl_3$) δ 8.36 (s, 1H), 7.25 (s, 1H), 4.11 (s, 3H), 3.73 (s, 3H), 3.62 (t, *J*=6.4Hz, 2H), 3.55 (dd, *J*=16.7, 7.5Hz, 1H), 3.24 (t, *J*=7.3Hz, 2H), 3.18 (dd, *J*=13.5, 6.8Hz, 1H), 3.12 (dd, *J*=16.7, 5.8Hz, 1H), 2.53 (p, *J*=6.8Hz, 2H), 1.32 (d, *J*=7.0Hz, 3H).

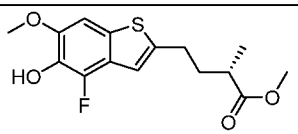
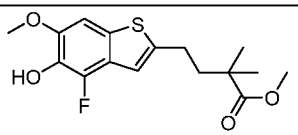
Intermediate 88: Methyl (S)-4-(5-bromo-6-methoxybenzo[b]thiophen-2-yl)-2-methylbutanoate

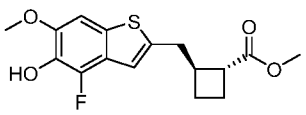
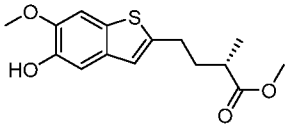
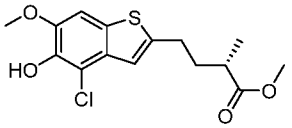


To a cooled solution of methyl (S)-4-(5-bromo-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate (0.637g, 1.72mmol) in ACN (15mL) was added TMS-Cl (1.32mL, 10.3mmol). Sodium cyanoborohydride (0.65g, 10mmol) was added, and the reaction mixture was stirred at 0°C for 2h. The reaction mixture was quenched with sat. aq. NH_4Cl and extracted with DCM. The organic layer was separated, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (EtOAc/hexanes) to afford methyl (S)-4-(5-bromo-6-methoxybenzo[b]thiophen-2-yl)-2-methylbutanoate. ^1H NMR (600MHz, DMSO-δ_6) δ 7.96 (s, 1H), 7.66 (s, 1H), 7.04 (s, 1H), 3.88 (s, 3H), 3.61 (s, 3H), 2.87-2.83 (m, 2H), 2.57-2.52 (m, 1H), 2.00-1.94 (m, 1H), 1.82-1.73 (m, 1H), 1.14 (d, J=7.0Hz, 3H).

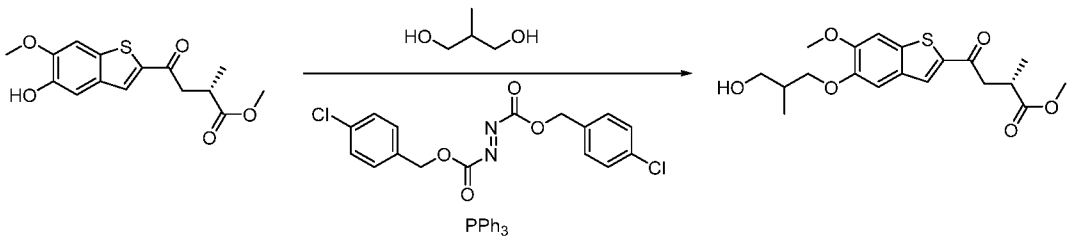
Intermediates 89 through 93, as shown in Table 10 below, was or may be prepared according to procedures analogous to those outlined in Intermediate 88 above using the appropriate starting materials, described as Preparations or as obtained from commercial sources.

Table 10

Intermediate	Structure	Name	Mass $[M+H]^+$
89		(S)-methyl 4-(4-fluoro-5-hydroxy-6-methoxybenzo[b]thiophen-2-yl)-2-methylbutanoate	330 ($M+H_2O$)
90		methyl 4-(4-fluoro-5-hydroxy-6-methoxybenzo[b]thiophen-2-yl)-2,2-dimethylbutanoate	344 ($M+H_2O$)

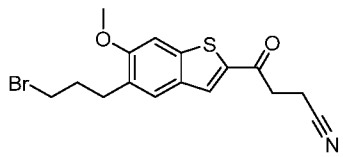
91		methyl (1R,2S)-2-((4-fluoro-5-hydroxy-6-methoxybenzo[b] thiophen-2-yl)methyl)cyclobutane-1-carboxylate	342 ($M+H_2O$)
92		methyl (S)-4-(5-hydroxy-6-methoxybenzo[b]thiophen-2-yl)-2-methylbutanoate	295
93		methyl (S)-4-(4-chloro-5-hydroxy-6-methoxybenzo[b]thiophen-2-yl)-2-methylbutanoate	346 ($M+H_2O$)

Intermediate 94: Methyl (2S)-4-(5-(3-hydroxy-2-methylpropoxy)-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate

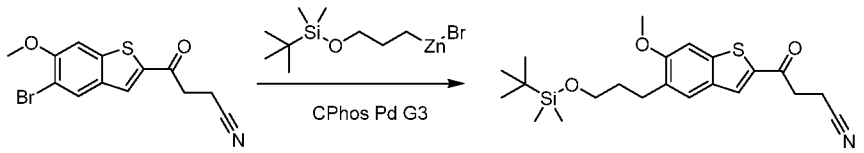


A mixture of 2-methylpropane-1,3-diol (146mg, 1.62mmol), (S)-methyl 4-(5-hydroxy-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate (50mg, 0.16mmol), (E)-bis(4-chlorobenzyl) diazene-1,2-dicarboxylate (60mg, 0.16mmol), and triphenylphosphine (43mg, 0.16mmol) in NMP (0.30mL) was degassed with Ar and then stirred and heated to 100°C for 3h. The reaction mixture was cooled to RT and purified directly by reverse phase HPLC (ACN/water with 0.1% TFA) to afford (2S)-methyl 4-(5-(3-hydroxy-2-methylpropoxy)-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate. LCMS ($C_{19}H_{25}O_6S$) (ES, m/z): 381 $[M+H]^+$.

Intermediate 95: 4-(5-(3-Bromopropyl)-6-methoxybenzo[b]thiophen-2-yl)-4-oxobutanenitrile

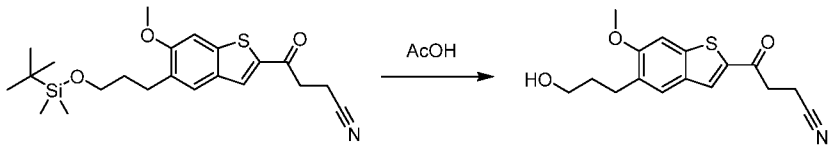


Step 1: 4-(5-(3-((tert-Butyldimethylsilyl)oxy)propyl)-6-methoxybenzo[b]thiophen-2-yl)-4-oxobutanenitrile



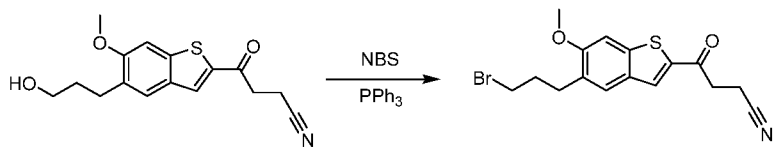
4-(5-Bromo-6-methoxybenzo[b]thiophen-2-yl)-4-oxobutanenitrile (161mg, 0.496mmol) and CPhos Pd G3 (20mg, 0.025mmol) were added to THF (2.5mL). The reaction mixture was sealed, and the headspace above the reaction mixture was evacuated and backfilled with nitrogen (3x). 3-(*tert*-Butyldimethylsiloxy)propylzinc bromide (0.50M in THF, 3.0mL, 1.5mmol) was added to the reaction mixture, and the reaction mixture was stirred at RT for 96h. The reaction mixture was diluted with EtOAc and then extracted with aq $NaHCO_3$. The aqueous layer was separated and extracted with EtOAc (3x). The organic layers were combined, washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford 4-(5-(3-((tert-butyldimethylsilyl)oxy)propyl)-6-methoxy-benzo[b]thiophen-2-yl)-4-oxobutanenitrile. LCMS ($C_{22}H_{32}NO_3SSi$) (ES, m/z): 418 $[M+H]^+$.

Step 2: 4-(5-(3-Hydroxypropyl)-6-methoxybenzo[b]thiophen-2-yl)-4-oxobutanenitrile



4-(5-(3-((*tert*-Butyldimethylsilyl)oxy)propyl)-6-methoxybenzo[b]thiophen-2-yl)-4-oxobutanenitrile (165mg, 0.395mmol) was suspended in a mixture of MeOH (2.0mL), water (2.0mL), and HOAc (2.0mL). The resulting suspension was stirred at RT for 19h. The reaction mixture was diluted with aq $NaHCO_3$ and then extracted with EtOAc (3x). The organic layers were combined, washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford 4-(5-(3-hydroxypropyl)-6-methoxybenzo[b]thiophen-2-yl)-4-oxobutanenitrile. LCMS ($C_{16}H_{18}NO_3S$) (ES, m/z): 304 $[M+H]^+$. ^1H NMR (499MHz, DMSO-d_6) δ 8.27 (s, 1H), 7.75 (s, 1H), 7.61 (s, 1H), 4.50-4.47 (m, 1H), 3.90 (s, 3H), 3.53-3.40 (m, 4H), 2.79 (t, *J*=6.5Hz, 2H), 2.68 (t, *J*=7.4Hz, 2H), 1.79-1.66 (m, 2H).

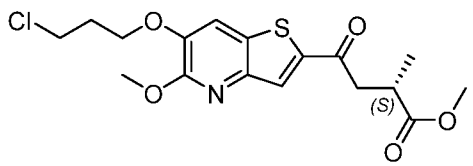
Step 3: 4-(5-(3-Bromopropyl)-6-methoxybenzo[b]thiophen-2-yl)-4-oxobutanenitrile



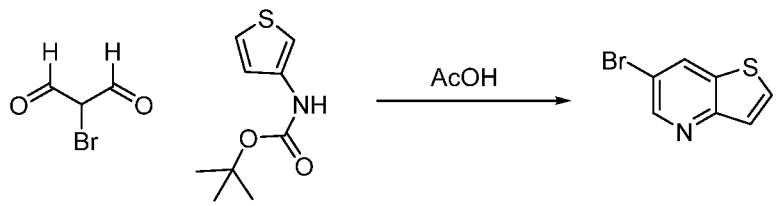
Triphenylphosphine (39mg, 0.15mmol) was added to a solution of 4-(5-(3-hydroxypropyl)-6-methoxybenzo[b]thiophen-2-yl)-4-oxobutanenitrile (45mg, 0.15mmol) in THF

(1.0mL). The mixture was cooled to 0°C, and then NBS (26mg, 0.15mmol) was added. After 1h additional triphenylphosphine (23mg, 0.089mmol) and NBS (13mg, 0.074mmol) were added to the reaction mixture. The mixture was stirred for an additional 10min at 0°C. The reaction mixture was quenched with aq sat NH_4Cl and then diluted with EtOAc. The organic layer was separated, washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (EtOAc/Hex) to afford 4-(5-(3-bromopropyl)-6-methoxy-benzo[b]thiophen-2-yl)-4-oxobutanenitrile. LCMS ($C_{16}H_{17}BrNO_2SNa$) (ES, m/z): 388, 390 $[M+Na]^+$.

Intermediate 96: Methyl (S)-4-(6-(3-chloropropoxy)-5-methoxythieno[3,2-b]pyridin-2-yl)-2-methyl-4-oxobutanoate

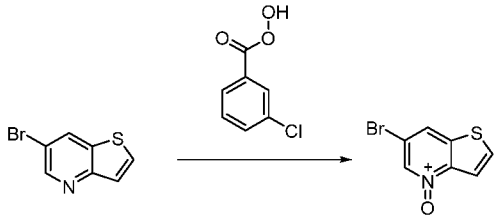


Step 1: 6-Bromothieno[3,2-b]pyridine



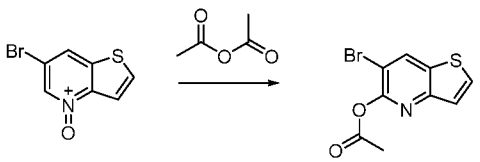
AcOH (50mL) was added to a mixture of 2-bromomalonaldehyde (3.56g, 23.6mmol) and *tert*-butyl thiophen-3-ylcarbamate (4.70g, 23.6mmol) at RT under air atmosphere. The reaction mixture was stirred and heated to 100°C for 24h. The reaction mixture was then cooled to RT and diluted with EtOAc (300mL). Sat aq $NaHCO_3$ was added until gas evolution ceased. The organic layer was separated, washed with brine (50mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting EtOAc in Hex) to afford 6-bromothieno[3,2-b]pyridine. LCMS (C_7H_5BrNS) (ES, m/z): 214, 216 $[M+H]^+$. ^1H NMR (499MHz, DMSO-d_6) δ 8.86 (s, 1H), 8.74 (s, 1H), 8.18 (d, *J*=5.4Hz, 1H), 7.58 (d, *J*=5.4Hz, 1H).

Step 2: 6-Bromothieno[3,2-b]pyridine 4-oxide



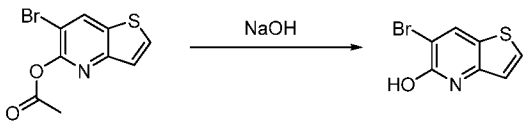
mCPBA (1.49g, 6.63mmol) was added to a mixture of 6-bromothieno[3,2-b]pyridine (1.42g, 6.63mmol) in DCM (50mL) at 0°C under Ar. The reaction mixture was then allowed to warm to RT and stirred for an additional 24h. The reaction mixture was then concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting [5% MeOH in EtOAc] in DCM) to afford 6-bromothieno[3,2-b]pyridine 4-oxide. LCMS (C_7H_5BrNOS) (ES, m/z): 230, 232 $[M+H]^+$.

Step 3: 6-Bromothieno[3,2-b]pyridin-5-yl acetate



Acetic anhydride (20mL, 210mmol) was added to 6-bromothieno[3,2-b]pyridine 4-oxide (1.38g, 6.00mmol) at RT under $N_{2(g)}$. The reaction mixture was then heated to 140°C and stirred for 4h. The reaction mixture was then cooled to RT and diluted with EtOAc (200mL) and H_2O (200mL). $NaHCO_3$ was slowly added portionwise to the reaction mixture until all gas evolution ceased. The organic layer was separated, washed with brine (25mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting [5% MeOH in EtOAc] in DCM) to afford 6-bromothieno[3,2-b] pyridin-5-yl acetate. LCMS ($C_9H_7BrNO_2S$-C_2H_2O) (ES, m/z): 230, 232 $[M+H\text{-acetate}]^+$. ^1H NMR (499MHz, DMSO-d_6) δ 9.04 (s, 1H), 8.29 (d, J=5.2Hz, 1H), 7.54 (d, J=5.4Hz, 1H), 2.41 (s, 3H).

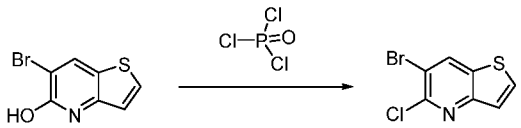
Step 4: 6-Bromothieno[3,2-b]pyridin-5-ol



NaOH (2.0M in H_2O, 4.0mL, 8.0mmol) was added to a solution of 6-bromothieno [3,2-b]pyridin-5-yl acetate (431mg, 1.58mmol) in MeOH (5.0mL) at 20°C under $N_{2(g)}$. The reaction mixture was then stirred for 1h at 20°C. The reaction mixture was quenched with HCl (1.0M in H_2O, 8.0mL, 8.0mmol) and then diluted by the addition of H_2O (10mL). The reaction mixture

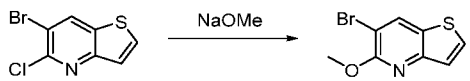
was stirred for 30min and then filtered. The collected material was washed with additional H_2O (10mL) and then dried under reduced pressure to afford 6-bromothieno[3,2-b]pyridin-5-ol. LCMS (C_7H_5BrNOS) (ES, m/z): 230, 232 $[M+H]^+$. ^1H NMR (499MHz, DMSO-d_6) δ 12.65 (s, 1H), 8.59 (s, 1H), 7.91 (d, J=5.3Hz, 1H), 6.99 (d, J=5.1Hz, 1H).

Step 5: 6-Bromo-5-chlorothieno[3,2-b]pyridine



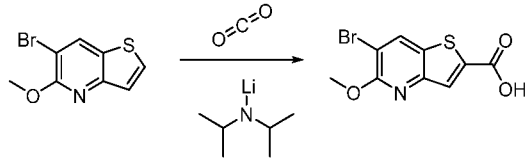
Phosphorus oxychloride (15.2mL, 163mmol) was added to 6-bromothieno[3,2-b]pyridin-5-ol (375mg, 1.63mmol) at 20°C under $N_{2(g)}$. The reaction mixture was then stirred and heated to 100°C for 2 days. The reaction mixture was cooled to RT and quenched by the dropwise addition of the reaction mixture to a solution of aq sat $NaHCO_3$ solution. The reaction mixture was further diluted with EtOAc (250mL) and stirred. The organic layer was separated, washed with brine (25mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford 6-bromo-5-chlorothieno[3,2-b]pyridine which was used without purification. LCMS ($C_7H_4BrClNS$) (ES, m/z): 248, 250 $[M+H]^+$.

Step 6: 6-Bromo-5-methoxythieno[3,2-b]pyridine



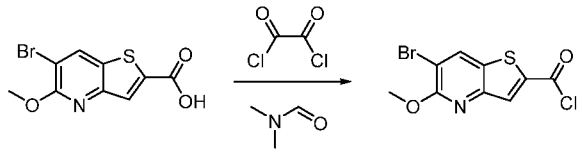
NaOMe (25% in MeOH, 3.24mL, 14mmol) was added to a mixture of 6-bromo-5-chlorothieno[3,2-b]pyridine (352mg, 1.42mmol) in MeOH (10mL) at 20°C under $N_{2(g)}$. The reaction mixture was stirred and heated to 100°C for 1h in a microwave reactor. The reaction mixture was quenched with citric acid (1.0M in H_2O, 28mL, 28mmol) and diluted with EtOAc (250mL). The organic layer was separated, washed with brine (25mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting [5% MeOH in EtOAc] in DCM) to afford 6-bromo-5-methoxythieno [3,2-b]pyridine. LCMS (C_8H_7BrNOS) (ES, m/z): 244, 246 $[M+H]^+$. ^1H NMR (499MHz, DMSO-d_6) δ 8.78 (s, 1H), 8.09 (d, J=5.3Hz, 1H), 7.44 (d, J=5.2Hz, 1H), 3.99 (s, 3H).

Step 7: 6-Bromo-5-methoxythieno[3,2-b]pyridine-2-carboxylic acid



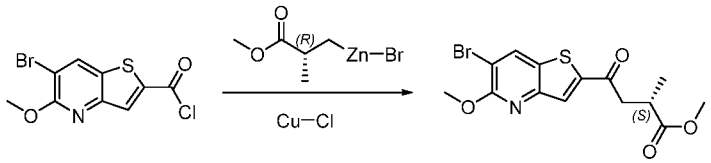
LDA (2.0M in THF, 12.3mL, 24.6mmol) was added to a solution of 6-bromo-5-methoxythieno[3,2-b]pyridine (5.0g, 20mmol) in THF (100mL) at -78°C. The mixture was aged for 15min, and was then quenched by the addition of $CO_{2(g)}$ at -78°C. The reaction mixture was then warmed to 0°C over 10min. The reaction mixture was quenched with HCl (2.0M in water, 12.3mL, 24.6mmol) at 0°C and then diluted with EtOAc (500mL). The organic layer was separated, washed with brine (50 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was suspended in DCM (90 mL) and stirred for 1h. Hex (250mL) were then added dropwise via an addition funnel over a period of ~ 4h at RT. The resulting suspension was then stirred for an additional 16h at RT. The suspension was then filtered, and the residue was washed with a 4:1 mixture of Hex/DCM (50mL). The residue was dried under vacuum to afford 6-bromo-5-methoxythieno[3,2-b]pyridine-2-carboxylic acid. LCMS ($C_9H_7BrNO_3S$) (ES, m/z): 288, 290 $[M+H]^+$. ^1H NMR (499MHz, DMSO-d_6) δ 13.79 (s, 1H), 8.87 (s, 1H), 7.93 (s, 1H), 4.01 (s, 3H).

Step 8: 6-Bromo-5-methoxythieno[3,2-b]pyridine-2-carbonyl chloride



DMF (8µl, 0.1mmol) was added to a solution of 6-bromo-5-methoxythieno[3,2-b]pyridine-2-carboxylic acid (1.05 g, 3.64 mmol) and oxalyl chloride (0.64mL, 7.3mmol) in THF (40 mL) at 0°C under Ar. The reaction mixture was stirred at 0°C for 1h. The reaction mixture was concentrated under reduced pressure to afford 6-bromo-5-methoxythieno[3,2-b]pyridine-2-carbonyl chloride, which was used directly in the subsequent step.

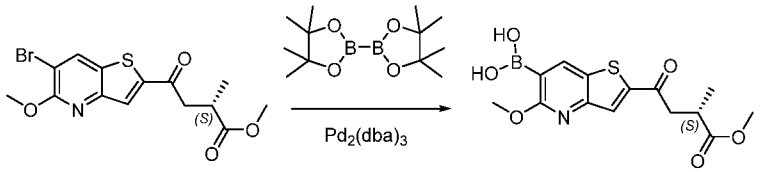
Step 9: Methyl (S)-4-(6-bromo-5-methoxythieno[3,2-b]pyridin-2-yl)-2-methyl-4-oxobutanoate



A solution of (R)-(3-methoxy-2-methyl-3-oxopropyl)zinc(II) bromide (0.5M in THF, 14.6mL, 7.29mmol) was added slowly to an oven-dried flask containing copper(I) chloride (0.361g, 3.64mmol) under Ar at 0°C. The reaction mixture was stirred for 20min at 0°C under Ar. An Ar-degassed solution of 6-bromo-5-methoxythieno[3,2-b]pyridine-2-carbonyl chloride (1.12g, 3.64mmol) in THF (10mL) and NMP (5.0mL) was then added slowly via cannula to the

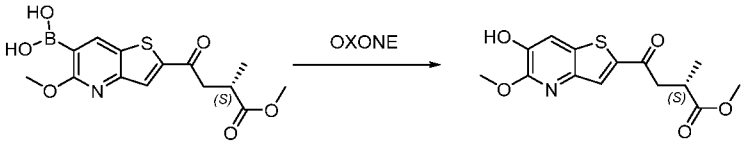
reaction mixture at 0°C; the resulting solution was warmed to RT and was stirred for an additional 18h at RT. The reaction mixture was cooled to 0°C and quenched by the addition of a solution of sat aq NH_4Cl (50 mL) and EtOAc (100 mL). The resulting biphasic mixture was warmed to RT and stirred for an additional 1h. The mixture was then filtered, and the filtrate was diluted with additional EtOAc (250mL) and brine (50mL). The organic layer was separated, washed with additional brine (50mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (EtOAc/Hex) to afford (S)-methyl 4-(6-bromo-5-methoxythieno[3,2-b]pyridin-2-yl)-2-methyl-4-oxobutanoate. LCMS ($C_{14}H_{15}BrNO_4S$) (ES, m/z): 372, 374 $[M+H]^+$. ^1H NMR (499MHz, DMSO-d_6) δ 8.87 (s, 1H), 8.37 (s, 1H), 4.02 (s, 3H), 3.59 (s, 3H), 3.52 (dd, *J*=17.9, 8.7Hz, 1H), 3.27 (dd, *J*=18.0, 4.5Hz, 1H), 3.03-2.91 (m, 1H), 1.20 (d, *J*=7.1Hz, 3H).

Step 10: (S)-(5-Methoxy-2-(4-methoxy-3-methyl-4-oxobutanoyl)thieno[3,2-b]pyridin-6-yl)boronic acid



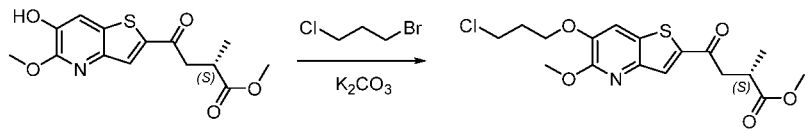
A mixture of (S)-methyl 4-(6-bromo-5-methoxythieno[3,2-b]pyridin-2-yl)-2-methyl-4-oxobutanoate (700mg, 1.88mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (597mg, 2.351mmol), $Pd_2(dba)_3$ (43mg, 0.047mmol), tricyclohexylphosphine (53mg, 0.19mmol), and potassium acetate (oven dried) (295mg, 3.01mmol) was degassed with Ar for 5min. Dioxane (15mL) was added at RT, and the resulting mixture was degassed with Ar for 5min. The reaction mixture was then heated to 80°C and stirred for 18h under Ar. The reaction mixture was cooled to RT and then diluted with EtOAc (20mL). The suspension was stirred at RT for 10min, and then filtered through CELITE, washing with EtOAc (20mL). The filtrate was concentrated under reduced pressure to afford (S)-(5-methoxy-2-(4-methoxy-3-methyl-4-oxobutanoyl)thieno[3,2-b]pyridin-6-yl)boronic acid, which was used without purification in the subsequent step. LCMS ($C_{14}H_{17}BNO_6S$) (ES, m/z): 338 $[M+H]^+$.

Step 11: Methyl (S)-4-(6-hydroxy-5-methoxythieno[3,2-b]pyridin-2-yl)-2-methyl-4-oxobutanoate



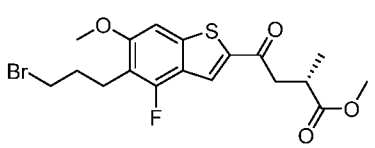
A solution of OXONE® ($KHSO_5$•½$KHSO_4$•½K_2SO_4; 0.2M in water, 14.10mL, 2.82mmol) was added to a mixture of (S)-(5-methoxy-2-(4-methoxy-3-methyl-4-oxobutanoyl) thieno[3,2-b]pyridin-6-yl)boronic acid (634mg, 1.88mmol) in acetone (20mL) at RT. The reaction mixture was stirred at RT for 30m. The reaction mixture was quenched by the addition of a solution of sodium bisulfite (587mg, 5.64mmol) in water (5mL) and then stirred for 5min. The reaction mixture was diluted with DCM (200mL). The organic layer was separated, and the aqueous layer was washed with additional DCM (2x50mL). The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (EtOAc/DCM) to afford (S)-methyl 4-(6-hydroxy-5-methoxythieno [3,2-b]pyridin-2-yl)-2-methyl-4-oxobutanoate. LCMS ($C_{14}H_{16}NO_5S$) (ES, m/z): 310 $[M+H]^+$. ^1H NMR (600MHz, DMSO-d_6) δ 10.46 (s, 1H), 8.23 (s, 1H), 7.66 (s, 1H), 3.97 (s, 3H), 3.60 (s, 3H), 3.44 (dd, *J*=17.5, 8.6Hz, 1H), 3.20 (dd, *J*=17.5, 5.0Hz, 1H), 3.00-2.92 (m, 1H), 1.19 (d, *J*=7.2Hz, 3H).

Step 12: Methyl (S)-4-(6-(3-chloropropoxy)-5-methoxythieno[3,2-b]pyridin-2-yl)-2-methyl-4-oxobutanoate

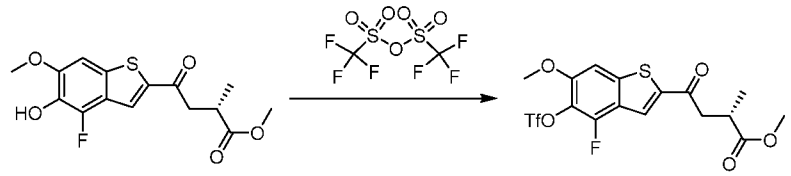


1-Bromo-3-chloropropane (244mg, 1.55mmol) was added to a mixture of (S)-methyl 4-(6-hydroxy-5-methoxythieno[3,2-b]pyridin-2-yl)-2-methyl-4-oxobutanoate (96mg, 0.31mmol) and potassium carbonate (257mg, 1.86mmol) in DMF (1.0mL) at RT. The reaction mixture was stirred and heated to 50°C for 4h. The reaction mixture was cooled to RT and filtered, and then the solvate was purified directly by silica gel chromatography (EtOAc/DCM) to afford (S)-methyl 4-(6-(3-chloropropoxy)-5-methoxythieno[3,2-b]pyridin-2-yl)-2-methyl-4-oxobutanoate. LCMS ($C_{17}H_{21}ClNO_5S$) (ES, m/z): 386 $[M+H]^+$.

Intermediate 97: Methyl (S)-4-(5-(3-bromopropyl)-4-fluoro-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate

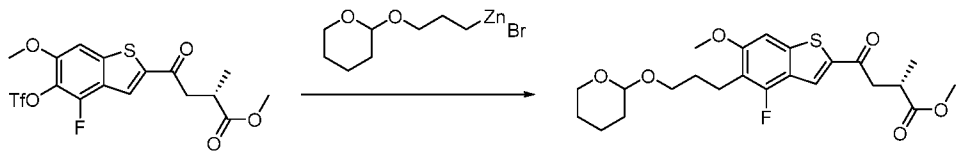


Step 1: Methyl (S)-4-(4-fluoro-6-methoxy-5-(((trifluoromethyl)sulfonyl)oxy)benzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate



Methyl (S)-4-(4-fluoro-5-hydroxy-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate (750mg, 2.30mmol), DCM (10mL), Hunig's base (2.0mL, 11mmol), and trifluoromethanesulfonic anhydride (1.0M in DCM, 3.5mL, 3.5mmol) were combined. The reaction mixture was stirred at RT for 20min. The reaction mixture was then quenched with water and diluted with DCM. The organic layer was separated, washed with sat $NaHCO_3$, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (EtOAc/Hex) to afford (S)-methyl 4-(4-fluoro-6-methoxy-5-(((trifluoromethyl)sulfonyl)oxy)benzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate. LCMS ($C_{16}H_{15}F_4O_7S_2$) (ES, m/z): 459 $[M+H]^+$. ^1H NMR (600MHz, DMSO-d_6) δ 8.52 (s, 1H), 7.93 (s, 1H), 4.03 (s, 3H), 3.61 (s, 3H), 3.53 (dd, *J*=17.8, 8.7Hz, 1H), 3.27 (dd, *J*=17.8, 5.0Hz, 1H), 3.05-2.92 (m, 1H), 1.21 (d, *J*=7.2Hz, 3H).

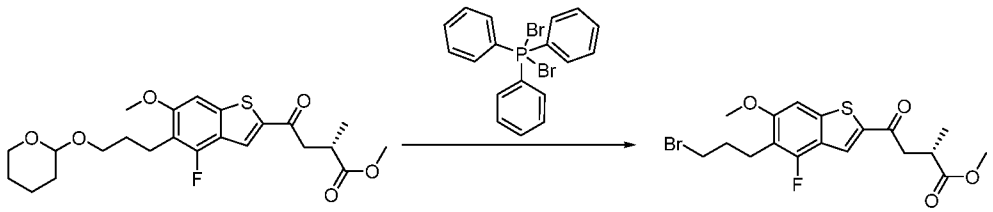
Step 2: Methyl (2S)-4-(4-fluoro-6-methoxy-5-(3-((tetrahydro-2H-pyran-2-yl)oxy)propyl)benzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate



(S)-Methyl 4-(4-fluoro-6-methoxy-5-(((trifluoromethyl)sulfonyl)oxy)benzo-[b]thiophen-2-yl)-2-methyl-4-oxobutanoate (1.00g, 2.18mmol), CPhos Pd G4 (0.088g, 0.11mmol), and (3-((tetrahydro-2H-pyran-2-yl)oxy)propyl)zinc(II) bromide (0.50M in THF, 8.7mL, 4.4mmol) were combined in a vial. The reaction mixture was heated at 40°C for 2h. The reaction mixture was filtered through CELITE and then concentrated under reduced pressure. The residue was purified by silica gel chromatography (EtOAc/Hex) to afford methyl (2S)-4-(4-fluoro-6-methoxy-5-(3-((tetrahydro-2H-pyran-2-yl)oxy)propyl)benzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate. LCMS ($C_{23}H_{30}FO_6S$) (ES, m/z): 453 $[M+H]^+$. ^1H NMR (600MHz, DMSO-d_6) δ 8.31 (s, 1H), 7.52 (s, 1H), 4.54 (t, *J*=3.4Hz, 1H), 3.92 (s, 3H), 3.75-3.70 (m, 1H), 3.69-3.62 (m, 1H), 3.60 (s, 3H), 3.49 (dd, *J*=17.7, 8.7Hz, 1H), 3.44-3.39 (m, 1H), 3.38-3.28 (m, 1H), 3.25 (dd, *J*=17.6,

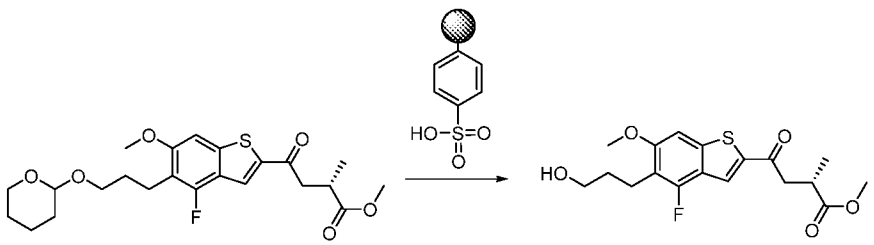
5.0Hz, 1H), 3.02-2.92 (m, 1H), 2.80-2.70 (m, 2H), 1.84-1.76 (m, 2H), 1.76-1.67 (m, 1H), 1.63-1.57 (m, 1H), 1.50-1.40 (m, 4H), 1.20-1.17 (m, 3H).

Step 3: Methyl (S)-4-(5-(3-bromopropyl)-4-fluoro-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate



Methyl (2S)-4-(4-fluoro-6-methoxy-5-(3-((tetrahydro-2H-pyran-2-yl)oxy) propyl)benzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate (350mg, 0.773mmol) and DCM (5mL) were combined in a vial. Triphenylphosphine dibromide (653mg, 1.55mmol) was to the reaction mixture and stirred for 30min. The reaction mixture was quenched with water. The organic layer was separated, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (EtOAc/Hex) to afford methyl (S)-4-(5-(3-bromopropyl)-4-fluoro-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate. LCMS ($C_{18}H_{21}BrFO_4S$) (ES, m/z): 431, 433 $[M+H]^+$.

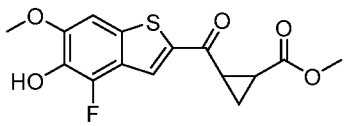
Intermediate 98: Methyl (S)-4-(4-fluoro-5-(3-hydroxypropyl)-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate



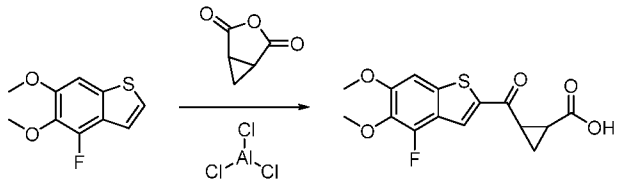
Methyl (2S)-4-(4-fluoro-6-methoxy-5-(3-((tetrahydro-2H-pyran-2-yl)oxy)propyl) benzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate (350mg, 0.773mmol), MeOH (5mL) and Mp-TsOH (1.00g, 4.33mmol) were combined in a vial. The reaction mixture was shaken for 2h. The reaction mixture was then filtered, washed with MeOH, and concentrated under reduced pressure to afford methyl (S)-4-(4-fluoro-5-(3-hydroxypropyl)-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate. LCMS ($C_{18}H_{22}FO_5S$) (ES, m/z): 369 $[M+H]^+$. ^1H NMR (600MHz, DMSO-d_6) δ 8.31 (s, 1H), 7.51 (s, 1H), 3.92 (s, 3H), 3.60 (s, 3H), 3.50 (dd, J=17.7, 8.7Hz, 1H),

3.44 (t, *J*=6.5Hz, 2H), 3.25 (dd, *J*=17.4, 4.7Hz, 1H), 3.02-2.93 (m, 1H), 2.71 (t, *J*=7.4Hz, 2H), 1.69-1.63 (m, 2H), 1.20 (d, *J*=7.0Hz, 3H).

Intermediate 99: Methyl 2-(4-fluoro-5-hydroxy-6-methoxybenzo[b]thiophene-2-carbonyl)cyclopropane-1-carboxylate

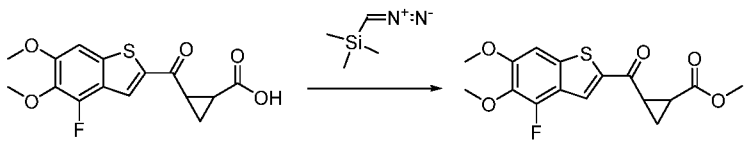


Step 1: 2-(4-Fluoro-5,6-dimethoxybenzo[b]thiophene-2-carbonyl)cyclopropane-1-carboxylic acid



Aluminum chloride (0.923g, 6.92mmol) was added to a mixture of 4-fluoro-5,6-dimethoxybenzo[b]thiophene (1.13g, 5.32mmol) and 3-oxabicyclo[3.1.0]hexane-2,4-dione (1.19g, 10.7mmol) in DCM (20.0mL) at 0°C. The reaction mixture was warmed to RT and then stirred for 18h. The reaction mixture was cooled to 0°C and quenched with water (50mL). The mixture was then diluted with EtOAc (500mL). The organic layer was separated, washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford 2-(4-fluoro-5,6-dimethoxybenzo[b]thiophene-2-carbonyl)cyclopropane-1-carboxylic acid, which was used without purification in the subsequent step. LCMS ($C_{15}H_{14}FO_5S$) (ES, m/z): 325 $[M+H]^+$.

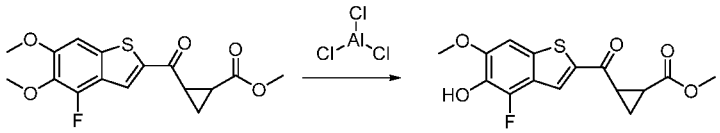
Step 2: Methyl 2-(4-fluoro-5,6-dimethoxybenzo[b]thiophene-2-carbonyl)cyclopropane-1-carboxylate



TMS-diazomethane (2.0M in diethyl ether, 4.3mL, 8.6mmol) was added dropwise to a mixture of 2-(4-fluoro-5,6-dimethoxybenzo[b]thiophene-2-carbonyl)cyclopropanecarboxylic acid (1.40g, 4.32mmol) in DCM (20mL) and MeOH (20mL) at 0°C. The reaction mixture was stirred at 0°C for 15min. The reaction mixture was quenched with HOAc. The reaction mixture was then concentrated under reduced pressure. The residue was purified by silica gel

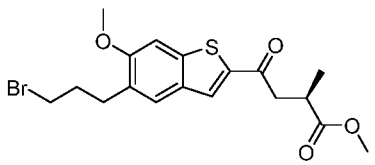
chromatography (EtOAc/DCM) to afford methyl 2-(4-fluoro-5,6-dimethoxybenzo[b]thiophene-2-carbonyl)cyclopropanecarboxylate. LCMS ($C_{16}H_{16}FO_5S$) (ES, m/z): 339 $[M+H]^+$. ^1H NMR (499MHz, DMSO-d_6) δ 8.37 (s, 1H), 7.59 (s, 1H), 3.93 (s, 3H), 3.87 (s, 3H), 3.48 (s, 3H), 3.31-3.25 (m, 1H), 2.47-2.41 (m, 1H), 1.62-1.58 (m, 1H), 1.44-1.40 (m, 1H).

Step 3: Methyl 2-(4-fluoro-5-hydroxy-6-methoxybenzo[b]thiophene-2-carbonyl)cyclopropane-1-carboxylate

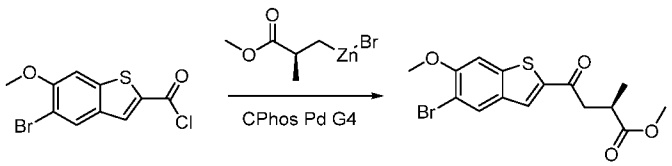


Aluminum chloride (2.66g, 20.0mmol) was added portionwise to a mixture of methyl 2-(4-fluoro-5,6-dimethoxybenzo[b]thiophene-2-carbonyl)cyclopropanecarboxylate (1.50g, 4.43mmol) in DCM (40mL) at RT. The reaction mixture was stirred at RT for 6h under Ar. The reaction mixture was cooled to 0°C and then quenched slowly with water (50mL). The reaction mixture was diluted with additional DCM (250mL). The organic layer was separated, washed with brine (25mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (EtOAc/DCM) to afford methyl 2-(4-fluoro-5-hydroxy-6-methoxybenzo[b]thiophene-2-carbonyl)cyclopropanecarboxylate. LCMS ($C_{15}H_{14}FO_5S$) (ES, m/z): 325 $[M+H]^+$. ^1H NMR (499MHz, DMSO-d_6) δ 9.55 (s, 1H), 8.29 (s, 1H), 7.48 (s, 1H), 3.92 (s, 3H), 3.48 (s, 3H), 3.30-3.23 (m, 1H), 2.45-2.39 (m, 1H), 1.61-1.57 (m, 1H), 1.43-1.38 (m, 1H).

Intermediate 100: Methyl (R)-4-(5-(3-bromopropyl)-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate

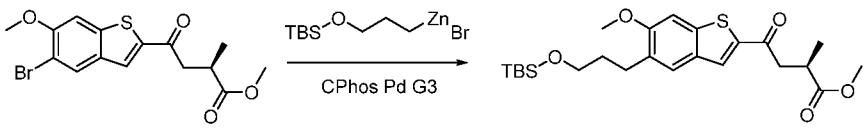


Step 1: Methyl (R)-4-(5-bromo-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate



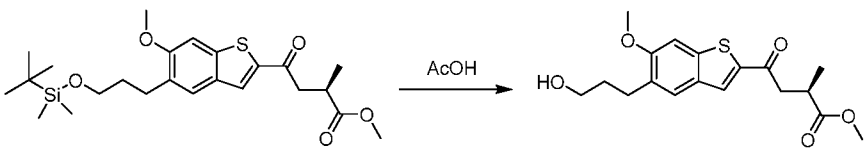
5-Bromo-6-methoxybenzo[b]thiophene-2-carbonyl chloride (3.00g, 9.82mmol) and THF (98ml) were combined. The reaction mixture was then degassed with Ar for 10min. CPhos Pd G4 (0.081g, 0.098mmol) was added to the reaction mixture, and the mixture was cooled to 0°C. (S)-(3-methoxy-2-methyl-3-oxopropyl)zinc(II) bromide (0.50M in THF, 21mL, 11mmol) was then added to the reaction mixture via addition funnel. The mixture was stirred at 0°C for 1h. The reaction mixture was quenched with sat aq NH_4Cl and diluted with EtOAc. The organic layer was separated, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (EtOAc/hex) to afford methyl (R)-4-(5-bromo-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate. LCMS ($C_{15}H_{16}BrO_4S$) (ES, m/z): 371, 373 $[M+H]^+$. ^1H NMR (499MHz, DMSO-d_6) δ 8.28-8.26 (m, 2H), 7.82 (s, 1H), 3.95 (s, 3H), 3.60 (s, 3H), 3.44 (dd, *J*=17.6, 8.6Hz, 1H), 3.21 (dd, *J*=17.6, 5.1Hz, 1H), 3.03-2.93 (m, 1H), 1.20 (d, *J*=7.2Hz, 3H).

Step 2: Methyl (R)-4-(5-(3-((tert-butyldimethylsilyl)oxy)propyl)-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate



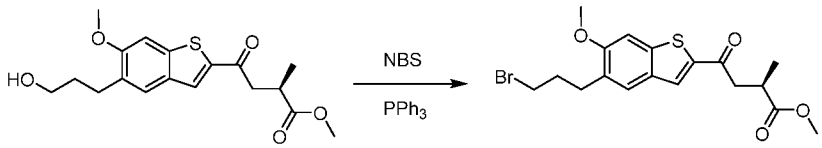
CPhos Pd G3 (174mg, 0.215mmol) and then (3-((tert-butyldimethylsilyl)oxy) propyl)zinc(II) bromide (0.50M in THF, 9.7mL, 4.9mmol) were added to a mixture of (R)-methyl 4-(5-bromo-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate (1.00g, 2.69mmol) in THF (13.5mL). The reaction mixture was heated at 40°C for 3h. The reaction mixture was cooled to RT, quenched with water, and diluted with EtOAc. The organic layer was separated, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (EtOAc/Hex) to afford methyl (R)-4-(5-(3-((tert-butyldimethylsilyl)oxy)propyl)-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate. LCMS ($C_{24}H_{37}O_5SSi$) (ES, m/z): 465 $[M+H]^+$.

Step 3: Methyl (R)-4-(5-(3-hydroxypropyl)-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate



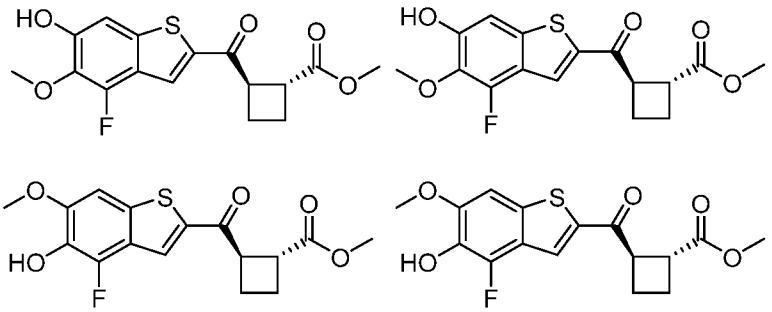
(R)-Methyl 4-(5-(3-((tert-butyldimethylsilyl)oxy)propyl)-6-methoxybenzo[b] thiophen-2-yl)-2-methyl-4-oxobutanoate (1.04g, 2.24mmol) was suspended in a mixture of MeOH (4mL), water (4mL) and HOAc (4mL). The reaction mixture was stirred at RT for 3.5h. The reaction mixture was diluted with EtOAc and water. The aqueous layer was separated and extracted with additional EtOAc (3x). The organic layers were combined, washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was was purified by silica gel chromatography (EtOAc/Hex) to afford methyl (R)-4-(5-(3-hydroxypropyl)-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate. LCMS ($C_{18}H_{23}O_5S$) (ES, m/z): 351 $[M+H]^+$.

Step 4: Methyl (R)-4-(5-(3-bromopropyl)-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate

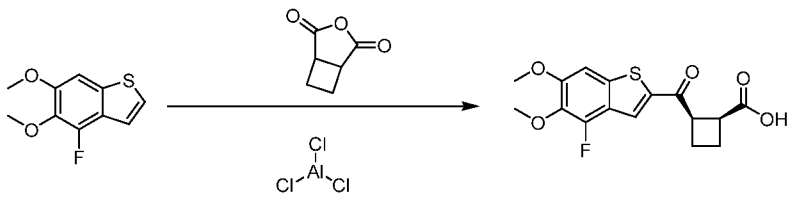


NBS (518mg, 2.91mmol) was added to a mixture of (R)-methyl 4-(5-(3-hydroxypropyl)-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate (680mg, 1.94mmol) and triphenylphosphine (814mg, 3.10mmol) in THF (9.7mL) at 0°C. After 1.5h, the reaction mixture was quenched with sat aq NH_4Cl and then diluted with EtOAc. The organic layer was separated, washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was was purified by silica gel chromatography (EtOAc/Hex) to afford methyl (R)-4-(5-(3-bromopropyl)-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate. LCMS ($C_{18}H_{22}BrO_4S$) (ES, m/z): 413, 415 $[M+H]^+$. ^1H NMR (499MHz, DMSO-d_6) δ 8.27 (s, 1H), 7.77 (s, 1H), 7.62 (s, 1H), 3.90 (s, 3H), 3.60 (s, 3H), 3.55 (t, *J*=6.6Hz, 2H), 3.43 (dd, *J*=17.5, 8.6Hz, 1H), 3.20 (dd, *J*=17.5, 5.1Hz, 1H), 3.04-2.94 (m, 1H), 2.83-2.77 (m, 2H), 2.14-2.08 (m, 2H), 1.20 (d, *J*=7.2Hz, 3H).

Intermediates 101, 102, 103, and 104: Methyl (1R,2R or 1S,2S)-2-(4-fluoro-6-hydroxy-5-methoxybenzo[b]thiophene-2-carbonyl)cyclobutane-1-carboxylate, methyl (1R,2R or 1S,2S)-2-(4-fluoro-6-hydroxy-5-methoxybenzo[b]thiophene-2-carbonyl)cyclobutane-1-carboxylate, methyl (1R,2R or 1S, 2S)-2-(4-fluoro-5-hydroxy-6-methoxybenzo[b]thiophene-2-carbonyl)cyclobutane-1-carboxylate, methyl (1R,2R or 1S, 2S)-2-(4-fluoro-5-hydroxy-6-methoxybenzo[b]thiophene-2-carbonyl)cyclobutane-1-carboxylate

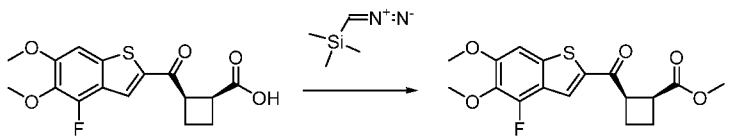


Step 1: (cis)-2-(4-Fluoro-5,6-dimethoxybenzo[b]thiophene-2-carbonyl)cyclobutane-1-carboxylic acid



Aluminum chloride (776mg, 5.82mmol) was added to a mixture of 4-fluoro-5,6-dimethoxybenzo[b]thiophene (950mg, 4.48mmol) and 3-oxabicyclo[3.2.0]heptane-2,4-dione (1130mg, 8.95mmol) in DCM (20.0mL) at 0°C. The reaction mixture was warmed to RT and then stirred for 18h. The reaction mixture was cooled to 0°C and then quenched by the dropwise addition of water (50mL). The mixture was then diluted with additional DCM (200mL). The organic layer was separated, washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford (cis)-2-(4-fluoro-5,6-dimethoxybenzo[b]thiophene-2-carbonyl)cyclobutane-1-carboxylic acid, which was used without purification in the next step. LCMS ($C_{16}H_{16}FO_5S$) (ES, m/z): 339 $[M+H]^+$.

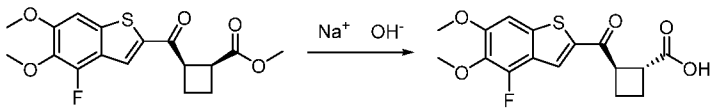
Step 2: Methyl (cis)-2-(4-fluoro-5,6-dimethoxybenzo[b]thiophene-2-carbonyl)cyclobutane-1-carboxylate



TMS-diazomethane (2.0M in diethyl ether, 4.0mL, 8.0mmol) was added dropwise to a mixture of (cis)-2-(4-fluoro-5,6-dimethoxybenzo[b]thiophene-2-carbonyl)cyclobutane carboxylic acid (1.35g, 3.99mmol) in DCM (20mL) and MeOH (20mL) at 0°C. The reaction mixture was stirred at 0°C for 15min. The reaction mixture was quenched with HOAc. The reaction mixture was then concentrated under reduced pressure. The residue was purified by silica gel chromatography (EtOAc/DCM) to afford (cis)-methyl 2-(4-fluoro-5,6-dimethoxybenzo

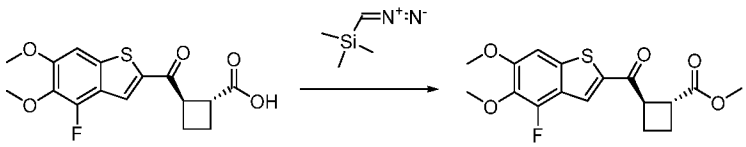
[b]thiophene-2-carbonyl)cyclobutanecarboxylate. LCMS ($C_{17}H_{18}FO_5S$) (ES, m/z): 353 $[M+H]^+$. ^1H NMR (499MHz, DMSO-d_6) δ 8.15 (s, 1H), 7.58 (s, 1H), 4.59-4.50 (m, 1H), 3.93 (s, 3H), 3.86 (s, 3H), 3.68 (q, *J*=8.9, 8.5Hz, 1H), 3.41 (s, 3H), 2.34-2.10 (m, 4H).

Step 3: (trans)-2-(4-Fluoro-5,6-dimethoxybenzo[b]thiophene-2-carbonyl)cyclobutane-1-carboxylic acid



NaOH (5.0M, 1.8mL, 9.0mmol) was added to a mixture of (cis)-methyl 2-(4-fluoro-5,6-dimethoxybenzo[b]thiophene-2-carbonyl)cyclobutanecarboxylate (650mg, 1.85mmol) in MeOH (25mL) at RT. The reaction mixture was stirred at RT for 4h. The reaction mixture was quenched with TFA (0.85mL, 11mmol) and then diluted with DCM (250mL). The organic layer was separated, washed with brine (50mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (MeOH/DCM) to afford (trans)-2-(4-fluoro-5,6-dimethoxybenzo[b]thiophene-2-carbonyl)cyclobutanecarboxylic acid. LCMS ($C_{16}H_{16}FO_5S$) (ES, m/z): 339 $[M+H]^+$.

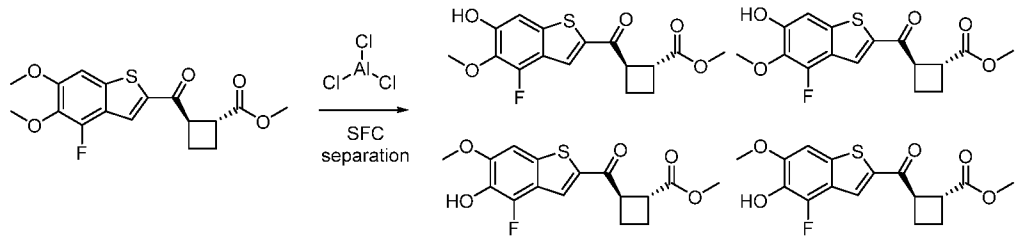
Step 4: Methyl (trans)-2-(4-fluoro-5,6-dimethoxybenzo[b]thiophene-2-carbonyl)cyclobutane-1-carboxylate



TMS-diazomethane (2.0M in diethyl ether, 1.7mL, 3.4mmol) was added dropwise to a mixture of (trans)-2-(4-fluoro-5,6-dimethoxybenzo[b]thiophene-2-carbonyl)cyclobutane carboxylic acid (570mg, 1.69mmol) in DCM (20mL) and MeOH (20mL) at 0°C. The reaction mixture was stirred at 0°C for 15min. The reaction mixture was quenched with HOAc. The reaction mixture was then concentrated under reduced pressure. The residue was purified by silica gel chromatography (EtOAc/DCM) to afford (trans)-methyl 2-(4-fluoro-5,6-dimethoxy benzo[b]thiophene-2-carbonyl)cyclobutanecarboxylate. LCMS ($C_{17}H_{18}FO_5S$) (ES, m/z): 353 $[M+H]^+$. ^1H NMR (499MHz, DMSO-d_6) δ 8.22 (s, 1H), 7.60 (s, 1H), 4.42 (q, *J*=9.0Hz, 1H), 3.93 (s, 3H), 3.86 (s, 3H), 3.63 (s, 3H), 3.58-3.48 (m, 1H), 2.38-2.30 (m, 1H), 2.26-2.18 (m, 1H), 2.17 -2.10 (m, 2H).

Step 5: Methyl (1R,2R or 1S,2S)-2-(4-fluoro-6-hydroxy-5-methoxybenzo[b]thiophene-2-carbonyl)cyclobutane-1-carboxylate, methyl (1R,2R or 1S,2S)-2-(4-fluoro-6-hydroxy-5-

methoxybenzo[b]thiophene-2-carbonyl)cyclobutane-1-carboxylate, methyl (1R,2R or 1S, 2S)-2-(4-fluoro-5-hydroxy-6-methoxybenzo[b]thiophene-2-carbonyl)cyclobutane-1-carboxylate, methyl (1R,2R or 1S, 2S)-2-(4-fluoro-5-hydroxy-6-methoxybenzo[b]thiophene-2-carbonyl)cyclobutane-1-carboxylate



$AlCl_3$ (1.10g, 8.27mmol) was added to a mixture of (trans)-methyl 2-(4-fluoro-5,6-dimethoxybenzo[b]thiophene-2-carbonyl)cyclobutanecarboxylate (530mg, 1.50mmol) in DCM (40mL) at RT. The reaction mixture was stirred at RT for 6h under Ar. The reaction mixture was cooled to 0°C and then quenched slowly with water (50mL). The reaction mixture was then diluted with additional DCM (250mL). The organic layer was separated, washed with brine (25mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (EtOAc/DCM) to afford a mixture of (+/- trans)-methyl-2-(4-fluoro-5-hydroxy-6-methoxybenzo[b]thiophene-2-carbonyl)cyclobutane-1-carboxylate and (+/- trans)-methyl-2-(4-fluoro-6-hydroxy-5-methoxybenzo[b]thiophene-2-carbonyl)cyclobutane-1-carboxylate. The mixture of racemic regioisomers was purified by chiral SFC (CCA column, 20% [MeOH with 0.25% DMEA] in CO_2) to afford:

Peak 1 (3.0min): methyl (1R,2R or 1S,2S)-2-(4-fluoro-6-hydroxy-5-methoxybenzo[b]thiophene-2-carbonyl)cyclobutane-1-carboxylate. LCMS ($C_{16}H_{16}FO_5S$) (ES, m/z): 339 $[M+H]^+$. ^1H NMR (499MHz, DMSO-d_6) δ 10.58 (br s, 1H), 8.15 (s, 1H), 7.24 (s, 1H), 4.45-4.34 (m, 1H), 3.86 (s, 3H), 3.62 (s, 3H), 3.56-3.47 (m, 1H), 2.36-2.24 (m, 1H), 2.25-2.16 (m, 1H), 2.16-2.07 (m, 2H).

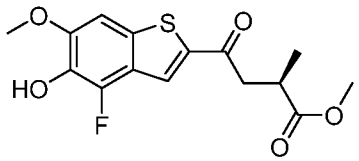
Peak 2 (3.5min): methyl (1R,2R or 1S,2S)-2-(4-fluoro-6-hydroxy-5-methoxybenzo[b]thiophene-2-carbonyl)cyclobutane-1-carboxylate. LCMS ($C_{16}H_{16}FO_5S$) (ES, m/z): 339 $[M+H]^+$.

Peak 3 (3.9min): methyl (1R,2R or 1S, 2S)-2-(4-fluoro-5-hydroxy-6-methoxybenzo[b]thiophene-2-carbonyl)cyclobutane-1-carboxylate. LCMS ($C_{16}H_{16}FO_5S$) (ES, m/z): 339 $[M+H]^+$. ^1H NMR (499MHz, DMSO-d_6) δ 9.55 (s, 1H), 8.14 (s, 1H), 7.48 (s, 1H),

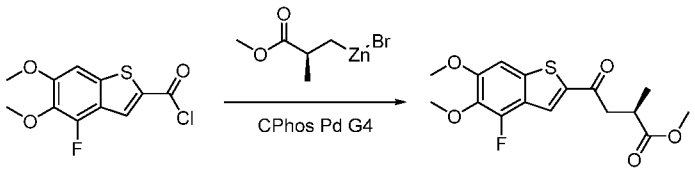
4.45-4.38 (m, 1H), 3.92 (s, 3H), 3.62 (s, 3H), 3.58-3.49 (m, 1H), 2.38-2.27 (m, 1H), 2.25-2.19 (m, 1H), 2.17-2.09 (m, 2H).

Peak 4 (5.0min): methyl (1R,2R or 1S, 2S)-2-(4-fluoro-5-hydroxy-6-methoxybenzo[b]thiophene-2-carbonyl)cyclobutane-1-carboxylate. LCMS ($C_{16}H_{16}FO_5S$) (ES, m/z): 339 $[M+H]^+$. ^1H NMR (499MHz, DMSO-d_6) δ 9.54 (s, 1H), 8.14 (s, 1H), 7.48 (s, 1H), 4.44-4.38 (m, 1H), 3.92 (s, 3H), 3.62 (s, 3H), 3.55-3.49 (m, 1H), 2.38-2.26 (m, 1H), 2.26-2.17 (m, 1H), 2.17-2.10 (m, 2H).

Intermediate 105: Methyl (R)-4-(4-fluoro-5-hydroxy-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate

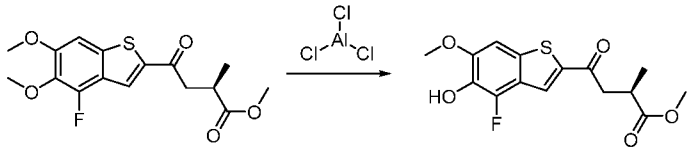


Step 1: Methyl (R)-4-(4-fluoro-5,6-dimethoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate



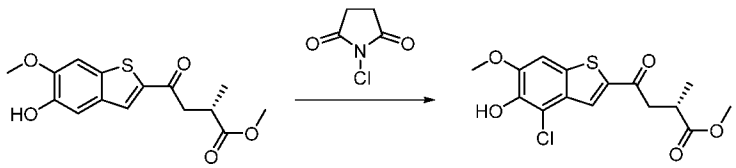
A mixture of 4-fluoro-5,6-dimethoxybenzo[b]thiophene-2-carbonyl chloride (1.00g, 3.64mmol) and THF (36.4mL) was degassed with Ar for 10min. CPhos Pd G4 (0.030g, 0.036mmol) was added to the mixture, and the reaction mixture was cooled to 0°C. (S)-(3-methoxy-2-methyl-3-oxopropyl)zinc(II) bromide (0.50M in THF, 8.0mL, 4.0mmol) was then added to the reaction mixture via an addition funnel. The mixture was stirred at 0°C for 1h. The reaction mixture was quenched with sat aq NH_4Cl and then diluted with EtOAc. The organic layer was separated, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (EtOAc /Hex) to afford methyl (R)-4-(4-fluoro-5,6-dimethoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate. LCMS ($C_{16}H_{18}FO_5S$) (ES, m/z): 341 $[M+H]^+$.

Step 2: Methyl (R)-4-(4-fluoro-5-hydroxy-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate



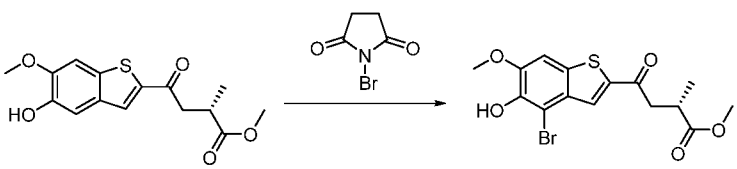
$AlCl_3$ (1.16g, 8.72mmol) was added to a mixture of (R)-methyl 4-(4-fluoro-5,6-dimethoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate (0.742g, 2.18mmol) in DCM (22mL) at RT. The reaction mixture was stirred for 18h. The reaction mixture was then cooled to 0°C and quenched by the addition of water (50mL) and HCl (1.0M in water, 50mL, 50mmol). The reaction mixture was then diluted with EtOAc. The organic layer was separated, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford methyl (R)-4-(4-fluoro-5-hydroxy-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate which was used without purification. LCMS ($C_{15}H_{16}FO_5S$) (ES, m/z): 327 $[M+H]^+$.

Intermediate 106: Methyl (S)-4-(4-chloro-5-hydroxy-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate



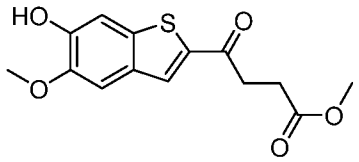
NCS (11mg, 0.081mmol) was added to a mixture of (S)-methyl 4-(5-hydroxy-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate (25mg, 0.081mmol) in DMF (0.25mL) at RT. The reaction mixture was then heated to 40°C and stirred for 2h. The reaction mixture was cooled to RT and purified directly by silica gel chromatography (EtOAC/Hex) to afford (S)-methyl 4-(4-chloro-5-hydroxy-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate. LCMS ($C_{15}H_{16}ClO_5S$) (ES, m/z): 343 $[M+H]^+$. ^1H NMR (499MHz, DMSO-d_6) δ 9.78 (s, 1H), 8.16 (s, 1H), 7.63 (s, 1H), 3.94 (s, 3H), 3.60 (s, 3H), 3.50 (dd, *J*=17.8, 8.7Hz, 1H), 3.31-3.23 (m, 1H), 3.02-2.92 (m, 1H), 1.20 (d, *J*=7.2Hz, 3H).

Intermediate 107: Methyl (S)-4-(4-bromo-5-hydroxy-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate

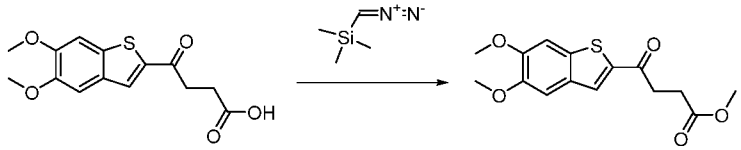


NBS (14mg, 0.081mmol) was added to a mixture of (S)-methyl 4-(5-hydroxy-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate (25mg, 0.081mmol) in DMF (0.25mL) at RT. The reaction mixture was then heated to 40°C and stirred for 2h. The reaction mixture was cooled to RT and purified directly by silica gel chromatography (EtOAc/DCM) to afford (S)-methyl 4-(4-bromo-5-hydroxy-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate. LCMS ($C_{15}H_{16}BrO_5S$) (ES, m/z): 387, 389 $[M+H]^+$. ^1H NMR (499MHz, DMSO-d_6) δ 9.82 (s, 1H), 8.08 (s, 1H), 7.66 (s, 1H), 3.94 (s, 3H), 3.60 (s, 3H), 3.50 (dd, J=17.8, 8.7Hz, 1H), 3.31-3.24 (m, 1H), 3.03-2.92 (m, 1H), 1.21 (d, J=7.2Hz, 3H).

Intermediate 108: Methyl 4-(6-hydroxy-5-methoxybenzo[b]thiophen-2-yl)-4-oxobutanoate

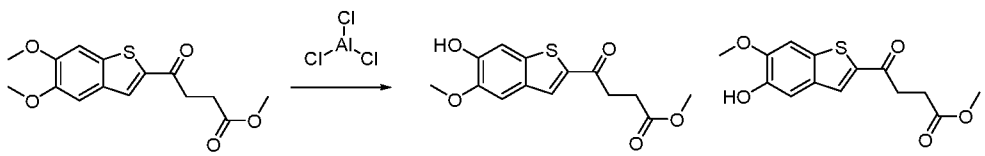


Step 1: Methyl 4-(5,6-dimethoxybenzo[b]thiophen-2-yl)-4-oxobutanoate



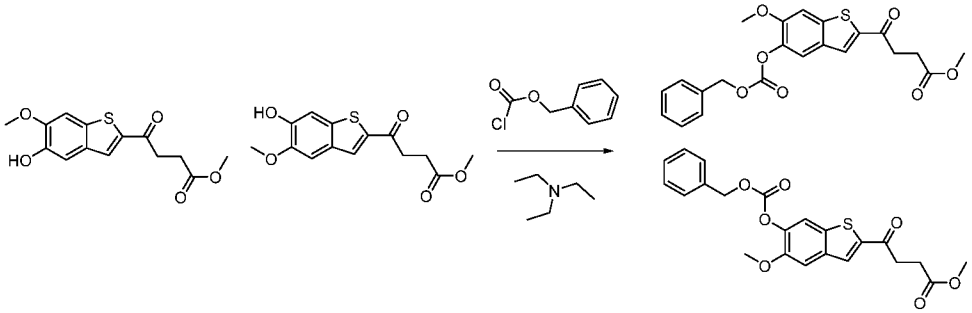
TMS-diazomethane (2.0M in diethyl ether, 5.5mL, 11mmol) was added dropwise to a mixture of 4-(5,6-dimethoxybenzo[b]thiophen-2-yl)-4-oxobutanoic acid (2.15g, 7.30mmol) in DCM (50mL) and MeOH (50mL) at 0°C. The reaction mixture was stirred at 0°C for 1h. The reaction mixture was quenched with HOAc. The reaction mixture was concentrated under reduced pressure to afford methyl 4-(5,6-dimethoxybenzo[b]thiophen-2-yl)-4-oxobutanoate, which was used without purification in the next step. LCMS ($C_{15}H_{17}O_5S$) (ES, m/z): 309 $[M+H]^+$. ^1H NMR (499MHz, DMSO-d_6) δ 8.22 (s, 1H), 7.61 (s, 1H), 7.49 (s, 1H), 3.87 (s, 3H), 3.84 (s, 3H), 3.61 (s, 3H), 3.35-3.30 (m, 2H), 2.71-2.66 (m, 2H).

Step 2: Methyl 4-(6-hydroxy-5-methoxybenzo[b]thiophen-2-yl)-4-oxobutanoate and methyl 4-(5-hydroxy-6-methoxybenzo[b]thiophen-2-yl)-4-oxobutanoate



$AlCl_3$ (5.71g, 42.8mmol) was added to a mixture of methyl 4-(5,6-dimethoxy benzo[b]thiophen-2-yl)-4-oxobutanoate (2.20g, 7.13mmol) in DCM (250mL) at RT. The reaction mixture was stirred at RT for 24h. The reaction mixture was cooled to 0°C and quenched with water (50mL, added dropwise via addition funnel). The reaction mixture was then warmed to RT and diluted with additional DCM (250mL). The organic layer was separated, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (EtOAc/DCM) to afford an inseparable mixture of methyl 4-(6-hydroxy-5-methoxybenzo[b]thiophen-2-yl)-4-oxobutanoate (77%) and methyl 4-(5-hydroxy-6-methoxybenzo[b]thiophen-2-yl)-4-oxobutanoate (23%). LCMS ($C_{14}H_{15}O_5S$) (ES, m/z): 295 $[M+H]^+$.

Step 3: Methyl 4-(5-(((benzyloxy)carbonyl)oxy)-6-methoxybenzo[b]thiophen-2-yl)-4-oxobutanoate and methyl 4-(6-(((benzyloxy)carbonyl)oxy)-5-methoxybenzo[b]thiophen-2-yl)-4-oxobutanoate



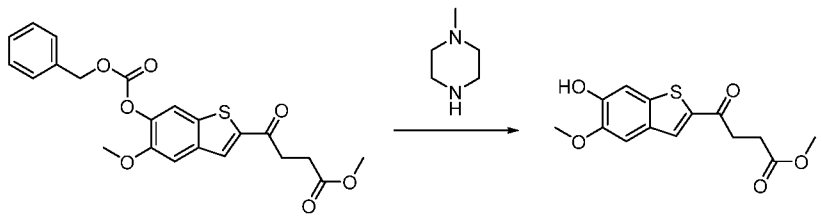
CBZ-Cl (1.06mL, 7.42mmol) was added to a mixture of methyl 4-(6-hydroxy-5-methoxybenzo[b]thiophen-2-yl)-4-oxobutanoate (77%) and methyl 4-(5-hydroxy-6-methoxy benzo[b]thiophen-2-yl)-4-oxobutanoate (23%) (1.82g, 6.18mmol) and TEA (1.29mL, 9.28mmol) in DCM (30 mL) at 0°C. The reaction mixture was then warmed to RT and stirred for an additional 2h. The reaction mixture was concentrated under reduced pressure and the residue was purified by silica gel chromatography (EtOAc/Hex) to afford:

Peak 1: methyl 4-(5-(((benzyloxy)carbonyl)oxy)-6-methoxybenzo[b]thiophen-2-yl)-4-oxobutanoate. LCMS ($C_{22}H_{21}O_7S$) (ES, m/z): 429 $[M+H]^+$. ^1H NMR (499MHz, DMSO-d_6) δ 8.30 (s, 1H), 7.89 (s, 1H), 7.84 (s, 1H), 7.48-7.38 (m, 5H), 5.30 (s, 2H), 3.87 (s, 3H), 3.61 (s, 3H), 3.40-3.33 (m, 2H), 2.69 (t, *J*=6.4Hz, 2H).

Peak 2: methyl 4-(6-(((benzyloxy)carbonyl)oxy)-5-methoxybenzo[b]thiophen-2-yl)-4-oxobutanoate. LCMS ($C_{22}H_{21}O_7S$) (ES, m/z): 429 $[M+H]^+$. ^1H NMR (499MHz, DMSO-d_6) δ

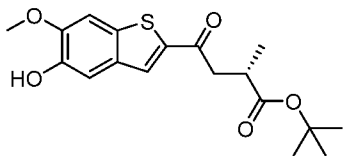
8.32 (s, 1H), 8.01 (s, 1H), 7.71 (s, 1H), 7.47-7.37 (m, 5H), 5.31 (s, 2H), 3.85 (s, 3H), 3.62 (s, 3H), 3.41-3.36 (m, 2H), 2.74-2.68 (m, 2H).

Step 4: Methyl 4-(6-hydroxy-5-methoxybenzo[b]thiophen-2-yl)-4-oxobutanoate

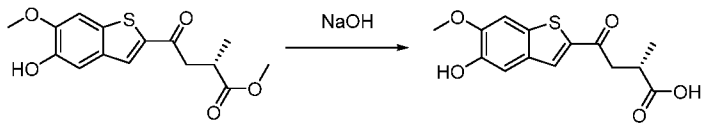


1-Methylpiperazine (1.4 mL, 13 mmol) was added to a mixture of methyl 4-(6-(((benzyloxy)carbonyl)oxy)-5-methoxybenzo[b]thiophen-2-yl)-4-oxobutanoate (1.84g, 4.29mmol) in DMF (5mL) and MeOH (5mL) at RT. The reaction mixture was then heated to 50°C and stirred for an additional 30min. The reaction mixture was cooled to RT and partially concentrated under reduced pressure. The crude mixture was purified by silica gel chromatography (EtOAc/DCM) to afford methyl 4-(6-hydroxy-5-methoxybenzo[b]thiophen-2-yl)-4-oxobutanoate. LCMS ($C_{14}H_{15}O_5S$) (ES, m/z): 295 $[M+H]^+$. ^1H NMR (499MHz, DMSO-d_6) δ 9.88 (s, 1H), 8.18 (s, 1H), 7.47 (s, 1H), 7.32 (s, 1H), 3.86 (s, 3H), 3.61 (s, 3H), 3.33-3.29 (m, 2H), 2.71-2.66 (m, 2H).

Intermediate 109:* tert-*Butyl (S)-4-(5-hydroxy-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate



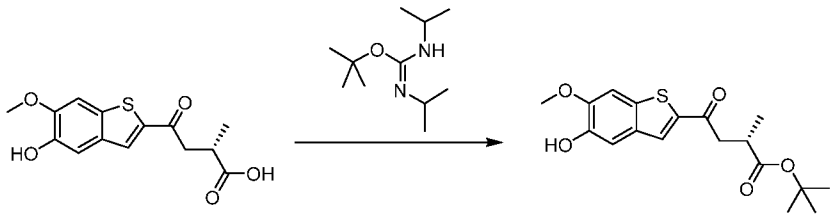
Step 1: (S)-4-(5-Hydroxy-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoic acid



To a mixture of (S)-methyl 4-(5-hydroxy-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate (3.00g, 9.73mmol) in MeOH (97mL) and THF (97mL) was added NaOH (5.0M in water, 39mL, 200mmol). The mixture was heated to 50°C for 1.5h. The reaction mixture was cooled to RT and acidified to a pH~3 with HCl (2.0M in water, 100ml, 200mmol). The mixture was diluted with EtOAc and water. The organic layer was separated, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford (S)-4-(5-hydroxy-6-

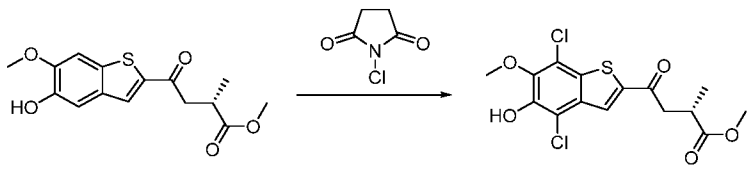
methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoic acid. LCMS ($C_{14}H_{15}O_5S$) (ES, m/z): 295 $[M+H]^+$. ^1H NMR (499MHz, DMSO-d_6) δ 12.18 (s, 1H), 9.39 (s, 1H), 8.17 (s, 1H), 7.54 (s, 1H), 7.32 (s, 1H), 3.88 (s, 3H), 3.38 (dd, *J*=17.3, 8.5Hz, 1H), 3.07 (dd, *J*=17.3, 5.3Hz, 1H), 2.94-2.83 (m, 1H), 1.18 (d, *J*=7.2Hz, 3H).

Step 2: tert-*Butyl (S)-4-(5-hydroxy-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate*



2-*tert*-Butyl-1,3-diisopropylisourea (2.3 mL, 10 mmol) was added to a mixture of (S)-4-(5-hydroxy-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoic acid (1.00g, 3.40mmol) in DMF (6.8mL) at RT. The reaction mixture was stirred at RT for 2h. The mixture was diluted with EtOAc and water. The organic layer was separated, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (EtOAc/Hex) to afford *tert*-butyl (S)-4-(5-hydroxy-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate. LCMS ($C_{18}H_{23}O_5S$ + Na) (ES, m/z): 373 $[M+Na]^+$. ^1H NMR (499MHz, DMSO-d_6) δ 9.40 (s, 1H), 8.17 (s, 1H), 7.54 (s, 1H), 7.31 (s, 1H), 3.88 (s, 3H), 3.36-3.30 (m, 1H), 3.05 (dd, *J*=17.1, 5.0Hz, 1H), 2.90-2.79 (m, 1H), 1.35 (s, 9H), 1.16 (d, *J*=7.2Hz, 3H).

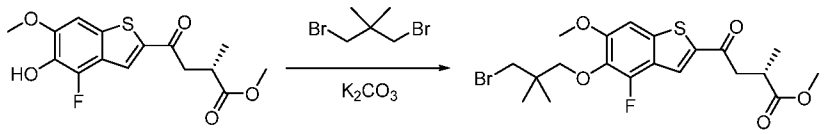
Intermediate 110: Methyl (S)-4-(4,7-dichloro-5-hydroxy-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate



NCS (433 mg, 3.24 mmol) was added to a mixture of (S)-methyl 4-(5-hydroxy-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate (500mg, 1.62mmol) in DMF (4.0mL) at 20°C. The reaction mixture was then heated to 40°C and stirred for 2h. The reaction mixture was cooled to RT and diluted with EtOAc (100mL). The mixture was washed with water (3x25mL) and brine (1x25mL). The organic layer was separated, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (EtOAc/Hex) followed by additional purification by silica gel chromatography (EtOAc/DCM) to

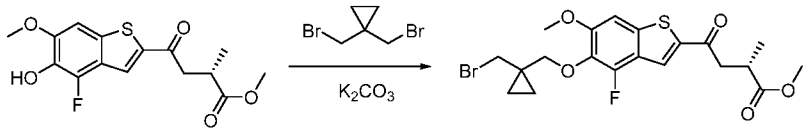
afford methyl (S)-4-(4,7-dichloro-5-hydroxy-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate. LCMS ($C_{15}H_{15}Cl_2O_5S$) (ES, m/z): 377, 379 $[M+H]^+$.

Intermediate 111: Methyl (S)-4-(5-(3-bromo-2,2-dimethylpropoxy)-4-fluoro-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate



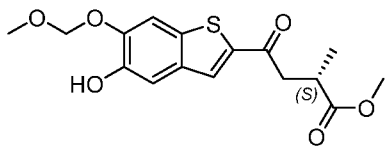
1,3-Dibromo-2,2-dimethylpropane (176 mg, 0.766 mmol) was added to a mixture of (S)-methyl 4-(4-fluoro-5-hydroxy-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate (25mg, 0.077mmol) and potassium carbonate (42mg, 0.31mmol) in DMF (0.5mL) at RT. The reaction mixture was then stirred and heated to 100°C for 24h. The reaction mixture was cooled to RT, diluted with DCM (2mL), and filtered. The filtrate was directly purified by silica gel chromatography (EtOAc/Hex) to afford methyl (S)-4-(5-(3-bromo-2,2-dimethylpropoxy)-4-fluoro-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate. LCMS ($C_{20}H_{25}BrFO_5S$) (ES, m/z): 475, 477 $[M+H]^+$.

Intermediate 112: Methyl (S)-4-(5-((1-(bromomethyl)cyclopropyl)methoxy)-4-fluoro-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate

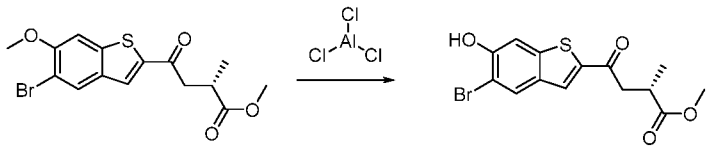


1,1-Bis(bromomethyl)cyclopropane (175mg, 0.766mmol) was added to a mixture of (S)-methyl 4-(4-fluoro-5-hydroxy-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate (25mg, 0.077mmol) and potassium carbonate (42mg, 0.31mmol) in DMF (0.5mL) at RT. The reaction mixture was then stirred and heated to 40°C for 4h. The reaction mixture was cooled to RT, diluted with DCM (2 mL), and filtered. The filtrate was directly purified by silica gel chromatography (EtOAc/Hex) to afford methyl (S)-4-(5-((1-(bromomethyl) cyclopropyl)methoxy)-4-fluoro-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate. LCMS ($C_{20}H_{23}BrFO_5S$) (ES, m/z): 473, 475 $[M+H]^+$.

Intermediate 113: Methyl (S)-4-(5-hydroxy-6-(methoxymethoxy)benzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate

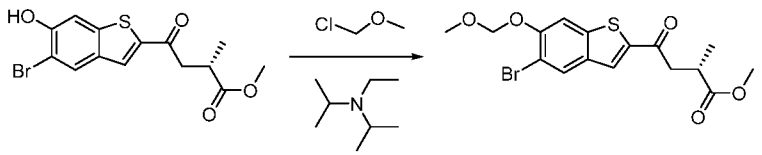


Step 1: Methyl (S)-4-(5-bromo-6-hydroxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate



$AlCl_3$ (3.23g, 24.2mmol) was added to a mixture of methyl (S)-4-(5-bromo-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate (1.50g, 4.04mmol) in DCM (35mL) at RT. The reaction mixture was stirred and heated to 35°C for 24h. The reaction mixture was cooled to 0°C and then quenched by the slow addition of water (10mL). The mixture was then warmed to RT and stirred for an additional 15min. The reaction mixture was diluted with DCM (250mL), and the organic layer was separated. The organic layer was washed with brine (50mL). The organic layer was separated, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (EtOAc/Hex) to afford methyl (S)-4-(5-bromo-6-hydroxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate. LCMS ($C_{14}H_{14}BrO_4S$) (ES, m/z): 357, 359 $[M+H]^+$.

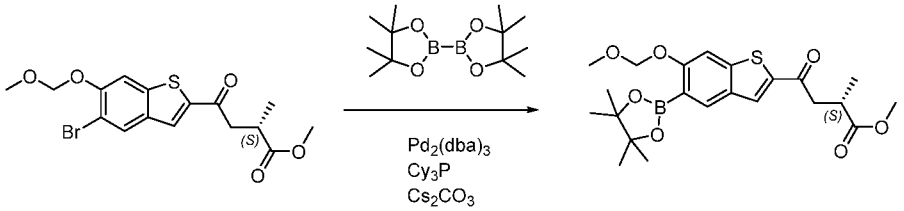
Step 2: Methyl (S)-4-(5-bromo-6-(methoxymethoxy)benzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate



MOM-Cl (0.91mL, 12mmol) was added to a mixture of methyl (S)-4-(5-bromo-6-hydroxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate (1.42g, 3.98mmol) and Hunig's base (4.2mL, 24mmol) in DCM (25mL) at 0°C. The reaction mixture was stirred at 0°C for 1h and then warmed to RT and stirred for an additional 24h. The reaction mixture was quenched by the addition of sat aq $NaHCO_3$ (10mL) and then diluted with EtOAc (250mL) and water (50mL). The organic layer was separated, washed with brine (25mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography

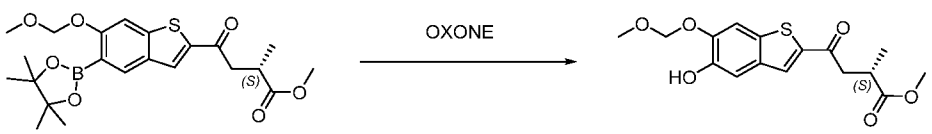
(EtOAc/Hex) to afford methyl (S)-4-(5-bromo-6-(methoxymethoxy)benzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate. LCMS ($C_{16}H_{18}BrO_5S$) (ES, m/z): 401, 403 $[M+H]^+$. ^1H NMR (499MHz, DMSO-d_6) δ 8.30 (s, 1H), 8.28 (s, 1H), 7.87 (s, 1H), 5.41 (s, 2H), 3.60 (s, 3H), 3.48-3.42 (m, 1H), 3.45 (s, 3H), 3.22 (dd, *J*=17.6, 5.1Hz, 1H), 3.04-2.93 (m, 1H), 1.20 (d, *J*=7.4Hz, 3H).

Step 3: Methyl (S)-4-(6-(methoxymethoxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate



A mixture of methyl (S)-4-(5-bromo-6-(methoxymethoxy)benzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate (1.57g, 3.91mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (1.19g, 4.70mmol), $Pd_2(dba)_3$ (0.179g, 0.196mmol), tricyclohexylphosphine (0.219g, 0.783mmol), and potassium acetate (0.614g, 6.26mmol) was degassed with Ar for 5min. Dioxane (20mL) was added at RT, and the resulting mixture was degassed with Ar for 5min. The reaction mixture was then heated to 90°C and stirred for 6h under Ar. The reaction mixture was cooled to RT and then diluted with EtOAc (50mL). The suspension was stirred at RT for 10min, and then filtered through CELITE, washing with EtOAc (50mL). The filtrate was concentrated under reduced pressure to afford methyl (S)-4-(6-(methoxymethoxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate, which was used without purification in the subsequent step. LCMS ($C_{22}H_{30}BO_7S$) (ES, m/z): 449 $[M+H]^+$.

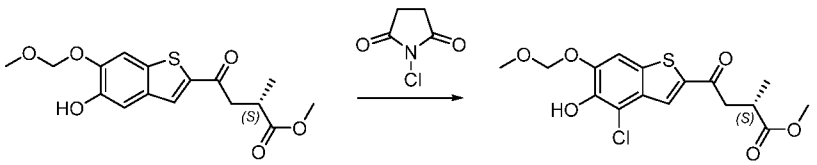
Step 4: Methyl (S)-4-(5-hydroxy-6-(methoxymethoxy)benzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate



A solution of OXONE® (0.20M in water, 21mL, 4.3mmol) was added to a solution of methyl (S)-4-(6-(methoxymethoxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate (1.75g, 3.90mmol) in acetone (50mL) at RT. The reaction mixture was stirred at RT for 60min. The reaction mixture was quenched by the

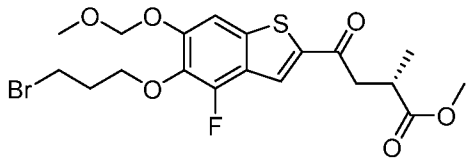
addition of a solution of sodium bisulfite (0.81g, 7.8mmol) in water (5mL) and then stirred for 5min. The reaction mixture was diluted with EtOAc (250mL). The organic layer was separated, and the aqueous layer was washed with additional EtOAc e (2x100mL). The organic layers were combined, washed with brine (25mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (EtOAc/Hex) to afford methyl (S)-4-(5-hydroxy-6-(methoxymethoxy)benzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate contaminated with pinacol byproduct. The isolated material was repurified by silica gel chromatography (EtOAc/DCM) to afford methyl (S)-4-(5-hydroxy-6-(methoxymethoxy)-benzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate. LCMS ($C_{16}H_{19}O_6S$) (ES, m/z): 339 $[M+H]^+$. ^1H NMR (499MHz, DMSO-d_6) δ 9.52 (s, 1H), 8.20 (s, 1H), 7.61 (s, 1H), 7.37 (s, 1H), 5.29 (s, 2H), 3.60 (s, 3H), 3.44 (s, 3H), 3.43-3.38 (m, 1H), 3.18 (dd, *J*=17.5, 5.1Hz, 1H), 3.03-2.91 (m, 1H), 1.19 (d, *J*=7.2Hz, 3H).

Intermediate 114: Methyl (S)-4-(4-chloro-5-hydroxy-6-(methoxymethoxy)benzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate

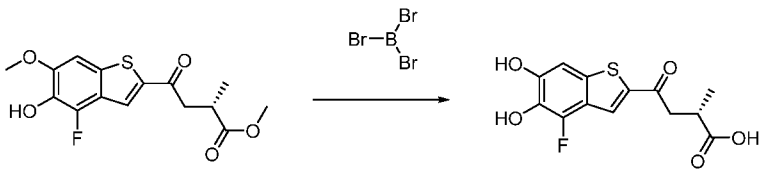


NCS (99mg, 0.74mmol) was added to a mixture of methyl (S)-4-(5-hydroxy-6-(methoxymethoxy)benzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate (250mg, 0.74mmol) in DMF (2.0mL) at RT. The reaction mixture was stirred and heated to 40°C for 2h. The reaction mixture was cooled to RT and then directly purified by silica gel chromatography (EtOAc/Hex) to afford methyl (S)-4-(4-chloro-5-hydroxy-6-(methoxymethoxy)benzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate. LCMS ($C_{16}H_{18}ClO_6S$) (ES, m/z): 373 $[M+H]^+$. ^1H NMR (499MHz, DMSO-d_6) δ 9.83 (s, 1H), 8.17 (s, 1H), 7.67 (s, 1H), 5.35 (s, 2H), 3.60 (s, 3H), 3.51 (dd, *J*=17.8, 8.7Hz, 1H), 3.46 (s, 3H), 3.27 (dd, *J*=17.8, 5.0Hz, 1H), 3.02-2.91 (m, 1H), 1.20 (d, *J*=7.2Hz, 3H).

Intermediate 115: Methyl (S)-4-(5-(3-bromopropoxy)-4-fluoro-6-(methoxymethoxy)benzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate

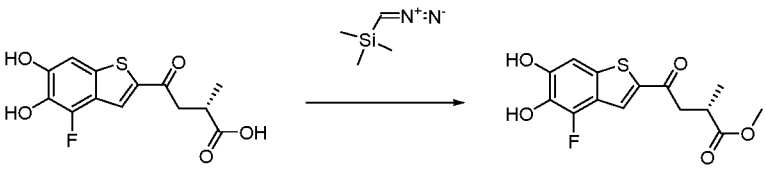


Step 1: (S)-4-(4-Fluoro-5,6-dihydroxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoic acid



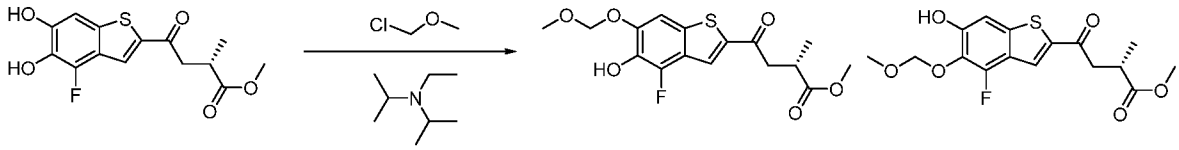
Boron tribromide (1.0M in DCM, 31ml, 31mmol) was added to a mixture of methyl (S)-4-(4-fluoro-5-hydroxy-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate (2.0g, 6.1mmol) in DCM (100ml) at 0°C. The reaction mixture was stirred and heated to 30°C for 2h. The reaction mixture was cooled to 0°C and then quenched by the dropwise addition of MeOH (10ml). The reaction mixture was stirred for an additional 15min. The reaction mixture was then diluted with water (100ml) and additional DCM (500ml). The organic layer was separated, washed with brine (50ml), dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford (S)-4-(4-fluoro-5,6-dihydroxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoic acid, which was used without purification in the subsequent step. LCMS ($C_{13}H_{12}FO_5S$) (ES, m/z): 299 $[M+H]^+$.

Step 2: Methyl (S)-4-(4-fluoro-5,6-dihydroxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate



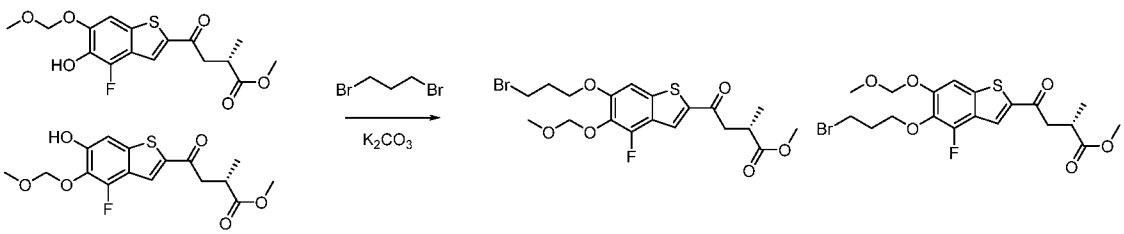
TMS-diazomethane (2.0 M in diethyl ether, 3.1ml, 6.2mmol) was added to a mixture of (S)-4-(4-fluoro-5,6-dihydroxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoic acid (1.83 g, 6.14mmol) in DCM (10ml) and MeOH (10ml) at 0°C. The reaction mixture was then stirred at 0°C for 15min. The reaction mixture was quenched with HOAc and then concentrated under reduced pressure. The residue was purified by silica gel chromatography (EtOAc/Hex) to afford the desired product. The isolated material was purified by silica gel chromatography ([25% EtOH in EtOAc]/Hex) to afford methyl (S)-4-(4-fluoro-5,6-dihydroxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate. LCMS ($C_{14}H_{14}FO_5S$) (ES, m/z): 313 $[M+H]^+$.

Step 3: Methyl (S)-4-(4-fluoro-5-hydroxy-6-(methoxymethoxy)benzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate and methyl (S)-4-(4-fluoro-6-hydroxy-5-(methoxymethoxy)benzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate



MOM-Cl (0.12ml, 1.6mmol) was added to a mixture of methyl (S)-4-(4-fluoro-5,6-dihydroxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate (460mg, 1.47mmol) and Hunig's base (0.52ml, 3.0mmol) in DCM (25ml) at 0°C. The reaction mixture was stirred at 0°C for 1h and then warmed to RT and stirred for an additional 24h. The reaction mixture was quenched by the addition of sat aq $NaHCO_3$ (10ml) and then diluted with EtOAc (250ml) and water (50ml). The organic layer was separated, washed with brine (25ml), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (EtOAc/Hex) to afford an inseparable mixture of methyl (S)-4-(4-fluoro-5-hydroxy-6-(methoxy methoxy)benzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate and methyl (S)-4-(4-fluoro-6-hydroxy-5-(methoxymethoxy)benzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate. The mixture was used in the subsequent reaction without further purification. LCMS ($C_{18}H_{18}FO_6S$) (ES, m/z): 357 $[M+H]^+$.

Step 4: Methyl (S)-4-(6-(3-bromopropoxy)-4-fluoro-5-(methoxymethoxy)benzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate and methyl (S)-4-(5-(3-bromopropoxy)-4-fluoro-6-(methoxymethoxy) benzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate



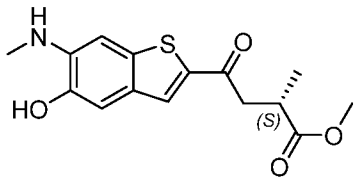
1,3-dibromopropane (0.58ml, 5.6mmol) was added to a mixture of methyl (S)-4-(4-fluoro-5-hydroxy-6-(methoxymethoxy)benzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate and methyl (S)-4-(4-fluoro-6-hydroxy-5-(methoxymethoxy)benzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate (270mg, 0.75mmol) and potassium carbonate (260mg, 1.9mmol) in DMF (2.0ml) at RT. The mixture was stirred at RT for 18h. The reaction mixture was diluted with EtOAc (250ml) and water (50ml). The organic layer was separated, washed with brine (50ml), dried

over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (EtOAc/hexanes) to afford a mixture of the regioisomers. The mixture of regioisomers was purified by reverse phase HPLC (ACN/water with 0.1% TFA) to afford:

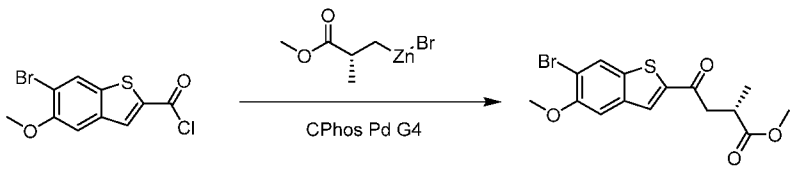
First eluting peak on HPLC: methyl (S)-4-(6-(3-bromopropoxy)-4-fluoro-5-(methoxymethoxy)benzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate. LCMS ($C_{19}H_{23}BrFO_6S$) (ES, m/z): 477, 479 $[M+H]^+$.

Second eluting peak on HPLC: methyl (S)-4-(5-(3-bromopropoxy)-4-fluoro-6-(methoxymethoxy)benzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate. LCMS ($C_{19}H_{23}BrFO_6S$) (ES, m/z): 477, 479 $[M+H]^+$.

Intermediate 116: Methyl (S)-4-(5-hydroxy-6-(methylamino)benzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate



Step 1: Methyl (S)-4-(6-bromo-5-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoateoate

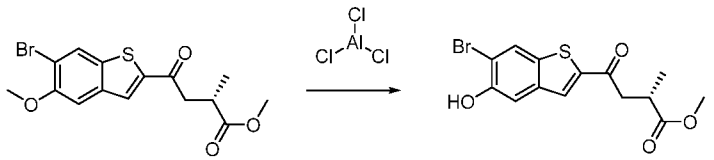


6-bromo-5-methoxybenzo[b]thiophene-2-carbonyl chloride (5.96 g, 19.5mmol) and CPhos Pd G4 (0.160 g, 0.195mmol) were combined in a flask and degassed with Ar for 5min. THF (75ml) was added under Ar stream, and the mixture was cooled to 0°C. (R)-(3-methoxy-2-methyl-3-oxopropyl)zinc(II) bromide (0.50 M in THF, 40ml, 20mmol) was then added dropwise, and the resulting mixture was stirred at 0°C for 2h and then warmed to RT. The mixture was stirred at RT for 3 days.

The reaction mixture was quenched with sat aq NH_4Cl (25ml) and then diluted with EtOAc (500ml). The organic layer was separated, washed with brine (50ml), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (EtOAc/hexanes) to afford methyl (S)-4-(6-bromo-5-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate. LCMS ($C_{15}H_{16}BrO_4S$) (ES, m/z): 371, 373 $[M+H]^+$. ^1H NMR

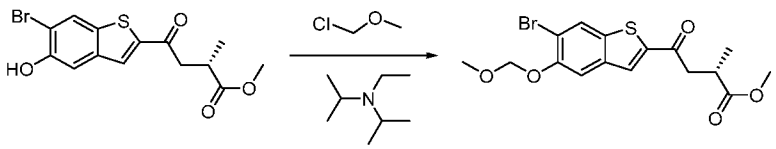
(499MHz, DMSO-d_6) δ 8.39 (s, 1H), 8.30 (s, 1H), 7.65 (s, 1H), 3.94 (s, 3H), 3.61 (s, 3H), 3.52-3.43 (m, 1H), 3.28-3.18 (m, 1H), 3.05-2.95 (m, 1H), 1.23-1.18 (m, 3H).

Step 2: Methyl (S)-4-(6-bromo-5-hydroxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate



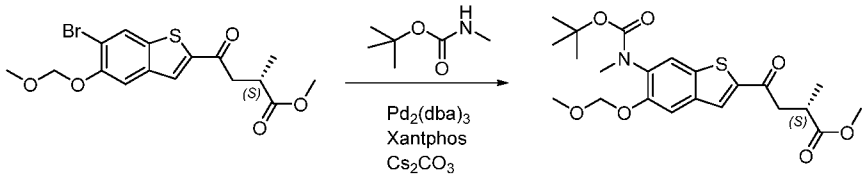
$AlCl_3$ (366mg, 2.75mmol) was added to a mixture of methyl (S)-4-(6-bromo-5-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate (170mg, 0.458mmol) in DCM (35ml) at RT. The reaction mixture was stirred and heated to 45°C for 3 days. The reaction mixture was cooled to 0°C and then quenched by the slow addition of water (10ml). The mixture was then warmed to RT and stirred for an additional 15min. The reaction mixture was diluted with DCM (250ml), and the organic layer was separated. The organic layer was washed with brine (50ml). The organic layer was separated, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (EtOAc/Hex) to afford methyl (S)-4-(6-bromo-5-hydroxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate. LCMS ($C_{14}H_{14}BrO_4S$) (ES, m/z): 357, 359 $[M+H]^+$.

Step 3: Methyl (S)-4-(6-bromo-5-(methoxymethoxy)benzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate



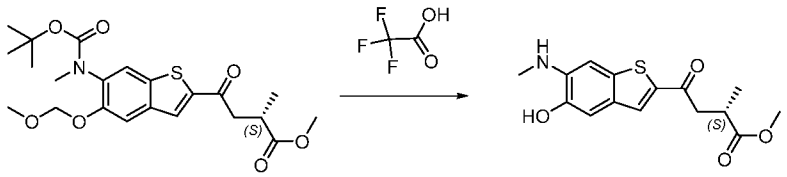
Hunig's base (0.44ml, 2.5mmol) was added to a mixture of methyl (S)-4-(6-bromo-5-hydroxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate (150mg, 0.42mmol) and MOM-Cl (0.096ml, 1.3mmol) in DCM (5.0ml) at 0°C. The reaction mixture was stirred at 0°C for 1h. The reaction mixture was directly purified by silica gel chromatography (EtOAc/Hex) to afford methyl (S)-4-(6-bromo-5-(methoxymethoxy)benzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate. LCMS ($C_{16}H_{18}BrO_5S$) (ES, m/z): 401, 403 $[M+H]^+$. ^1H NMR (499MHz, DMSO-d_6) δ 8.42 (s, 1H), 8.33 (s, 1H), 7.77 (s, 1H), 5.38 (s, 2H), 3.61 (s, 3H), 3.53-3.42 (m, 4H), 3.23 (dd, J=17.7, 3.0Hz, 1H), 3.07-2.95 (m, 1H), 1.21 (d, J=5.0Hz, 3H).

Step 4: Methyl (S)-4-(6-((tert-butoxycarbonyl)(methyl)amino)-5-(methoxymethoxy)benzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate



To an Ar-degassed mixture of methyl (S)-4-(6-bromo-5-(methoxymethoxy)benzo [b]thiophen-2-yl)-2-methyl-4-oxobutanoate (144mg, 0.359mmol), tert-butyl methylcarbamate (71mg, 0.54mmol), $Pd_2(dba)_3$ (16mg, 0.018mmol), XANTPHOS (31mg, 0.054mmol), and cesium carbonate (234mg, 0.718mmol) was added dioxane (4.0ml) at RT while degassing with Ar. The mixture was stirred for 5min while degassing with Ar, after which the mixture was heated to 90°C and stirred under Ar for 18h. The reaction mixture was cooled to RT and diluted with EtOAc (20ml). The resulting suspension was filtered through CELITE. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography (EtOAc/Hex) to afford the product. LCMS ($C_{22}H_{30}NO_7S$) (ES, m/z): 452 $[M+H]^+$.

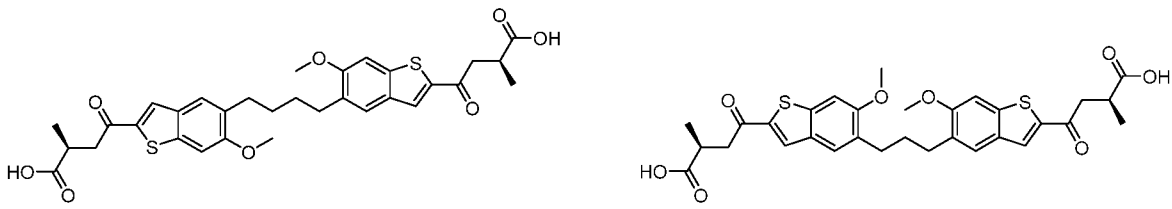
Step 5: Methyl (S)-4-(5-hydroxy-6-(methylamino)benzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate



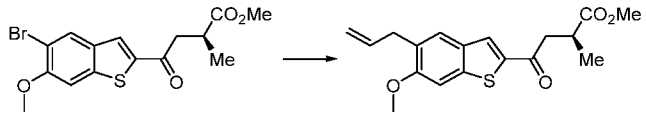
TFA (1.0ml, 13mmol) was added to a mixture of methyl (S)-4-(6-((tert-butoxycarbonyl)(methyl)amino)-5-(methoxymethoxy)benzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate (18mg, 0.040mmol) in DCM (2.0ml) at RT. The reaction mixture was stirred at RT for 2h. The reaction mixture was diluted with EtOAc (10ml) and quenched slowly by the addition of sat aq $NaHCO_3$ solution (10ml). The resulting mixture was stirred for 10min. The organic layer was separated, washed with brine (5ml), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (EtOAc/Hex) to afford methyl (S)-4-(5-hydroxy-6-(methylamino)benzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate. LCMS ($C_{15}H_{18}NO_4S$) (ES, m/z): 308 $[M+H]^+$.

Example 1 (2S,2'S)-4,4'-[butane-1,4-diylbis(6-methoxy-1-benzothiene-5,2-diyl)]bis(2-methyl-4-oxobutanoic acid) and

Example 2: (2S,2'S)-4,4'-[propane-1,3-diylbis(6-methoxy-1-benzothiene-5,2-diyl)]bis(2-methyl-4-oxobutanoic acid)

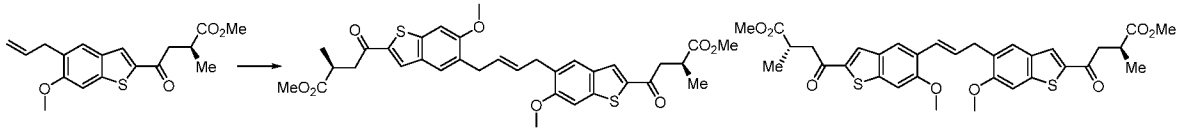


Step 1: methyl (2S)-4-[6-methoxy-5-(prop-2-en-1-yl)-1-benzothiophen-2-yl]-2-methyl-4-oxobutanoate



To the stirred mixture of methyl (2S)-4-(5-bromo-6-methoxy-1-benzothiophen-2-yl)-2-methyl-4-oxobutanoate (120mg, 0.32mmol), bis(dibenzylideneacetone)palladium (7.1mg, 12μmol), and allyltributylstannane (120μL, 0.39mmol) in toluene (0.49mL) was added tri-*tert*-butylphosphine (1.0M in toluene, 26μL, 26μmol) under N_2. The reaction mixture was heated to 65°C for 18h. Upon cooling to RT, the mixture was diluted with Et_2O, and then CsF was added. The crude mixture was stirred for 5min at RT. The mixture was then filtered, and the filtrate was directly purified by silica gel column chromatography (EtOAc in Hex) to afford methyl (2S)-4-[6-methoxy-5-(prop-2-en-1-yl)-1-benzothiophen-2-yl]-2-methyl-4-oxobutanoate. LCMS ($C_{18}H_{21}O_4S$) (ES, m/z): 333 $[M+H]^+$. ^1H NMR (500MHz, DMSO-*d6*): δ 8.27 (s, 1H), 7.72 (s, 1H), 7.62 (s, 1H), 6.06-5.94 (m, 1H), 5.07 (d, *J*=12.5Hz, 2H), 3.89 (s, 3H), 3.59 (s, 3H), 3.46-3.38 (m, 3H), 3.19 (dd, *J*=17.5, 5.0Hz, 1H), 3.02-2.92 (m, 1H), 1.19 (d, *J*=7.1Hz, 3H).

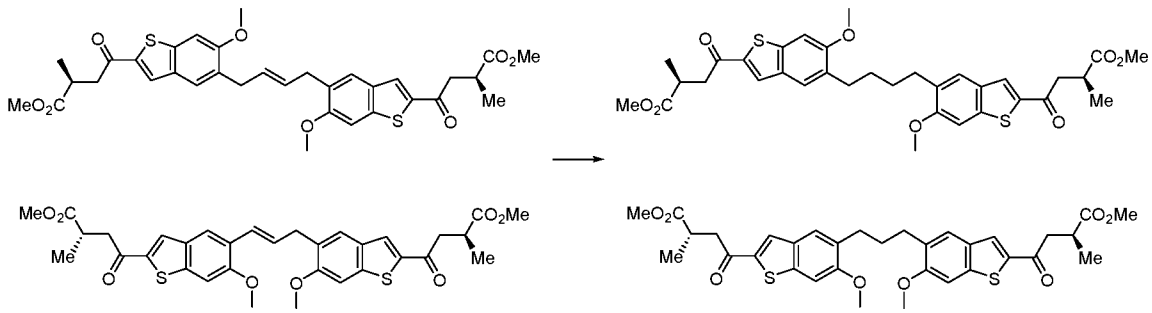
Step 2: dimethyl (2S,2'S)-4,4'-[but-2-ene-1,4-diylbis(6-methoxy-1-benzothiene-5,2-diyl)]bis(2-methyl-4-oxobutanoate) and dimethyl (2S,2'S)-4,4'-[prop-1-ene-1,3-diylbis(6-methoxy-1-benzothiene-5,2-diyl)]bis(2-methyl-4-oxobutanoate)



To a mixture of methyl (2S)-4-[6-methoxy-5-(prop-2-en-1-yl)-1-benzothiophen-2-yl]-2-methyl-4-oxobutanoate (44mg, 0.13mmol) in CH_2Cl_2 (1.3 mL) was added Grubbs catalyst 2G (11mg, 0.013mmol) in CH_2Cl_2 (1.3 mL) in one portion under N_2. The reaction mixture was heated to 65°C for 18h. Upon cooling to RT, the mixture was directly purified by silica gel

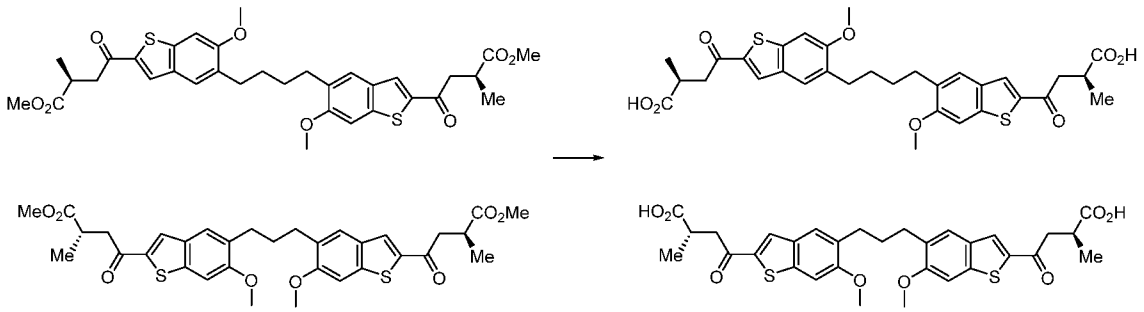
column chromatography (EtOAc in Hex) to afford a mixture of dimethyl (2S,2'S)-4,4'-[but-2-ene-1,4-diylbis(6-methoxy-1-benzothiene-5,2-diyl)]bis(2-methyl-4-oxobutanoate) and dimethyl (2S,2'S)-4,4'-[prop-1-ene-1,3-diylbis(6-methoxy-1-benzothiene-5,2-diyl)]bis(2-methyl-4-oxobutanoate). Characterization of dimethyl (2S,2'S)-4,4'-[but-2-ene-1,4-diylbis(6-methoxy-1-benzothiene-5,2-diyl)]bis(2-methyl-4-oxobutanoate): LCMS ($C_{34}H_{37}O_8S_2$) (ES, m/z): 637 $[M+H]^+$. Characterization of dimethyl (2S,2'S)-4,4'-[prop-1-ene-1,3-diylbis(6-methoxy-1-benzothiene-5,2-diyl)]bis(2-methyl-4-oxobutanoate): LCMS ($C_{33}H_{35}O_8S_2$) (ES, m/z): 623 $[M+H]^+$.

Step 3: dimethyl (2S,2'S)-4,4'-[butane-1,4-diylbis(6-methoxy-1-benzothiene-5,2-diyl)]bis(2-methyl-4-oxobutanoate) and dimethyl (2S,2'S)-4,4'-[propane-1,3-diylbis(6-methoxy-1-benzothiene-5,2-diyl)]bis(2-methyl-4-oxobutanoate)



To a mixture of dimethyl (2S,2'S)-4,4'-[but-2-ene-1,4-diylbis(6-methoxy-1-benzothiene-5,2-diyl)]bis(2-methyl-4-oxobutanoate) and dimethyl (2S,2'S)-4,4'-[prop-1-ene-1,3-diylbis(6-methoxy-1-benzothiene-5,2-diyl)]bis(2-methyl-4-oxobutanoate) (57.0 mg, ~ 3/2 mixture by ^{1}H-NMR) in EtOAc (0.5mL) under N_2 was added 10% Pd/C (6.0mg, 5.4μmol) in one portion at RT. The reaction mixture was degassed and backfilled with H_2 (three times), and stirred under H_2 (balloon) for 18h at RT. The mixture was then concentrated under reduced pressure to afford a crude mixture of dimethyl (2S,2'S)-4,4'-[butane-1,4-diylbis(6-methoxy-1-benzothiene-5,2-diyl)]bis (2-methyl-4-oxobutanoate) and dimethyl (2S,2'S)-4,4'-[propane-1,3-diylbis(6-methoxy-1-benzothiene-5,2-diyl)]bis(2-methyl-4-oxobutanoate). The mixture was used without further purification or characterization.

Step 4: (2S,2'S)-4,4'-[butane-1,4-diylbis(6-methoxy-1-benzothiene-5,2-diyl)]bis(2-methyl-4-oxobutanoic acid) and (2S,2'S)-4,4'-[propane-1,3-diylbis(6-methoxy-1-benzothiene-5,2-diyl)]bis(2-methyl-4-oxobutanoic acid)

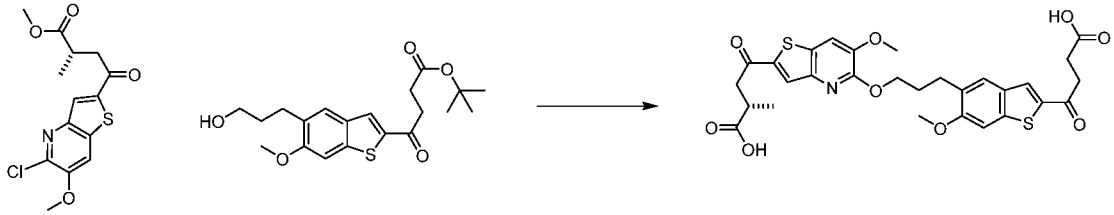


To a mixture of dimethyl (2S,2'S)-4,4'-[butane-1,4-diylbis(6-methoxy-1-benzothiene-5,2-diyl)]bis(2-methyl-4-oxobutanoate) and dimethyl (2S,2'S)-4,4'-[propane-1,3-diylbis(6-methoxy-1-benzothiene-5,2-diyl)]bis(2-methyl-4-oxobutanoate) (57mg) in THF (1.0mL), MeOH (1.0mL) and water (0.20mL) was added LiOH (26mg, 1.1mmol) in one portion at RT. The reaction mixture was stirred at RT for 1h and then quenched with aq HCl (2N, 0.52mL). The mixture was diluted with DMSO, and the resulting mixture was filtered. The filtrate was purified by RP-HPLC [C18 column, water (0.1% TFA)-CH_3CN] to afford (2S,2'S)-4,4'-[butane-1,4-diylbis(6-methoxy-1-benzothiene-5,2-diyl)]bis(2-methyl-4-oxobutanoic acid) and (2S,2'S)-4,4'-[propane-1,3-diylbis(6-methoxy-1-benzothiene-5,2-diyl)]bis(2-methyl-4-oxobutanoic acid).

Characterization data for (2S,2'S)-4,4'-[butane-1,4-diylbis(6-methoxy-1-benzothiene-5,2-diyl)]bis(2-methyl-4-oxobutanoic acid): LCMS ($C_{32}H_{34}O_8S_2Na$) (ES, m/z): 633 $[M+Na]^+$. ^1H NMR (500MHz, DMSO-d_6): δ 12.20 (br, 2H), 8.21 (s, 2H), 7.72 (s, 2H), 7.57 (s, 2H), 3.87 (s, 6H), 3.39 (dd, J=17.5, 8.6Hz, 2H), 3.07 (dd, J=17.5, 5.0Hz, 2H), 2.94-2.84 (m, 2H), 2.69 (br, 4H), 1.62 (br, 4H), 1.18 (d, J=7.1Hz, 6H).

Characterization data for (2S,2'S)-4,4'-[propane-1,3-diylbis(6-methoxy-1-benzothiene-5,2-diyl)]bis(2-methyl-4-oxobutanoic acid): LCMS ($C_{31}H_{32}O_8S_2Na$) (ES, m/z): 619 $[M+Na]^+$. ^1H NMR (500MHz, DMSO-d_6): δ 12.21 (br, 2H), 8.23 (s, 2H), 7.76 (s, 2H), 7.59 (s, 2H), 3.88 (s, 6H), 3.40 (dd, J=17.5, 8.6Hz, 2H), 3.08 (dd, J=17.5, 5.0Hz, 2H), 2.94-2.85 (m, 2H), 2.71 (t, J=7.1Hz, 4H), 1.91 (pentet, J=7.1Hz, 2H), 1.18 (d, J=7.1Hz, 6H).

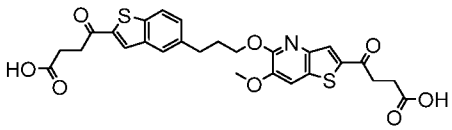
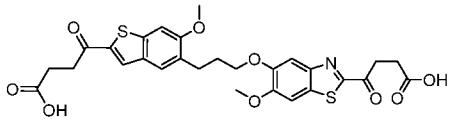
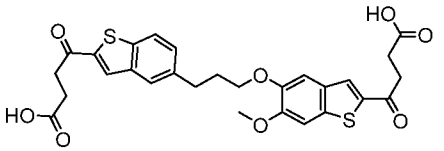
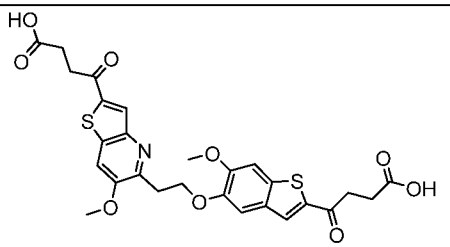
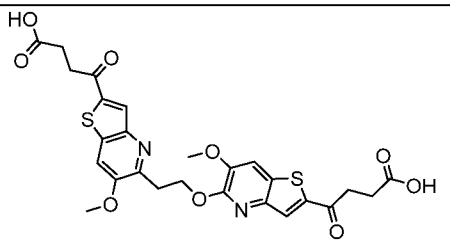
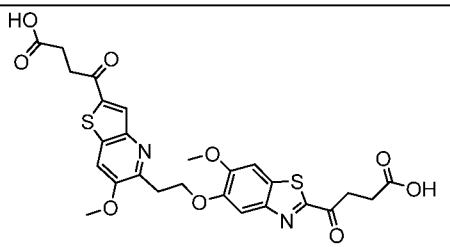
Example 3: (S)-4-(5-(3-(2-(3-carboxypropanoyl)-6-methoxybenzo[b]thiophen-5-yl)propoxy)-6-methoxythieno[3,2-b]pyridin-2-yl)-2-methyl-4-oxobutanoic acid

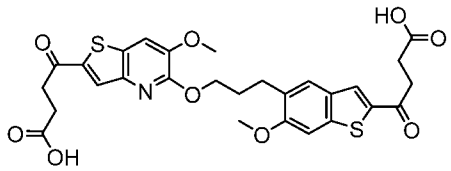
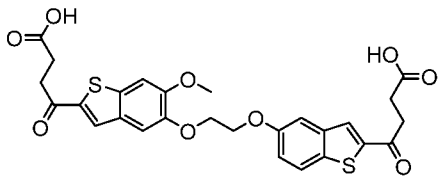
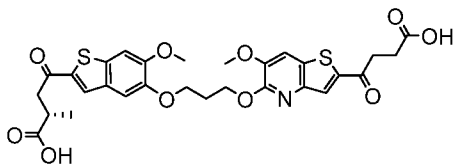
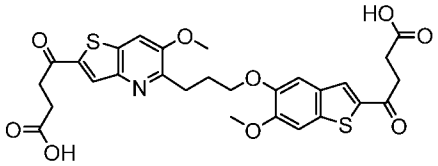
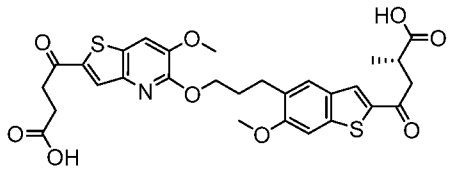
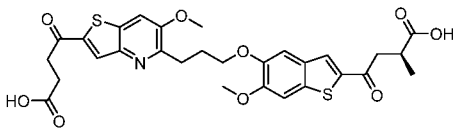


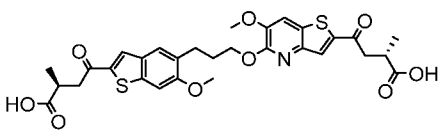
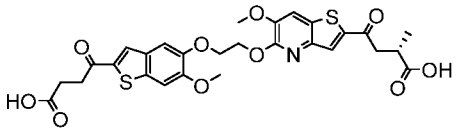
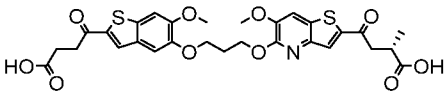
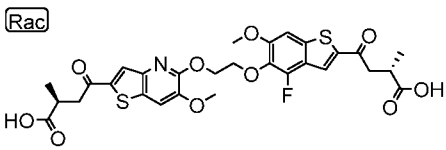
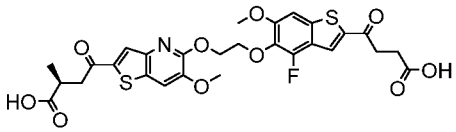
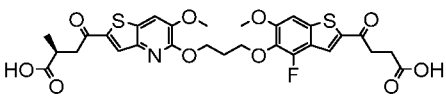
A 1 dram screw cap vial with a magnetic stir bar was charged with (S)-methyl 4-(5-chloro-6-methoxythieno[3,2-b]pyridin-2-yl)-2-methyl-4-oxobutanoate (60mg, 0.18mmol), *tert*-butyl 4-(5-(3-hydroxypropyl)-6-methoxybenzo[b]thiophen-2-yl)-4-oxobutanoate (76mg, 0.20mmol), RockPhos Pd G3 (7.7mg, 9.2μmol) and Cs_2CO_3 (89mg, 0.28mmol) was sealed with a septum-containing cap. The vial was evacuated and backfilled with N_2 3 times. Toluene (0.61mL) was added, and the suspension was vortexed, sonicated, and then heated to 110°C with stirring for 2.25h. The reaction was then allowed to cool to RT. TFA (0.60mL, 7.8mmol) was added, and the mixture was stirred at RT for 1.5h. The mixture was then concentrated under reduced pressure. To the resulting residue was added THF (1.0mL) and MeOH (0.50mL). Aq NaOH (2.0M, 0.50mL, 1.0mmol) was added, and the resulting mixture was heated to 40°C for 5h. Upon cooling to RT, additional aq NaOH (2.0M, 0.50mL, 1.0mmol) was added, and the mixture was heated to 40°C for an additional 2.5h. The reaction was then allowed to cool to RT and concentrated under reduced pressure. DMSO (1.0mL) was added, and the resulting mixture was filtered through a syringe filter. The filtrate was then purified by RP-HPLC (C18, MeCN/water gradient, NH_4OH modifier). The product-containing fraction was concentrated under reduced pressure and then purified further by RP-HPLC (C18, MeCN/water gradient, TFA modifier) to afford (S)-4-(5-(3-(2-(3-carboxypropanoyl)-6-methoxybenzo[b] thiophen-5-yl)propoxy)-6-methoxythieno[3,2-b]pyridin-2-yl)-2-methyl-4-oxobutanoic acid. LCMS ($C_{29}H_{30}NO_9S_2$) (ES, m/z): 600 $[M+H]^+$. ^1H NMR (500MHz, DMSO-d_6) δ 12.18 (s, 2H), 8.22 (s, 1H), 8.20 (s, 1H), 7.97 (s, 1H), 7.78 (s, 1H), 7.60 (s, 1H), 4.39 (t, *J*=6.3Hz, 2H), 3.90 (s, 3H), 3.87 (s, 3H), 3.43 (dd, *J*=17.5, 8.6Hz, 1H), 3.29-3.22 (m, 2H), 3.15-3.06 (m, 1H), 2.91-2.80 (m, 3H), 2.63-2.56 (m, 2H), 2.18-2.06 (m, 2H), 1.17 (d, *J*=7.2Hz, 3H).

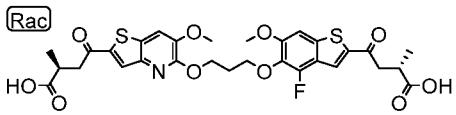
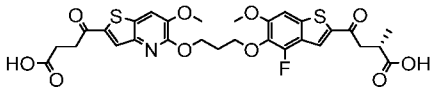
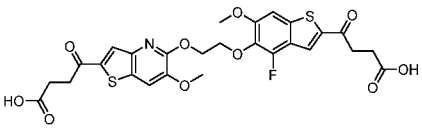
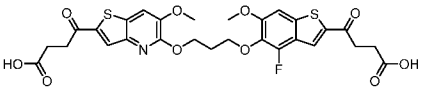
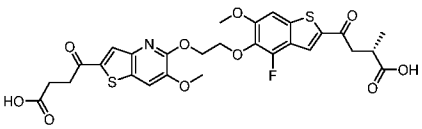
Examples 4 through 23 and 81-83, as shown in Table 11 below, were or may be prepared according to procedures analogous to those outlined in Example 3 above using the appropriate starting materials, described in the Preparations or Intermediates above, or as obtained from commercial sources.

Table 11

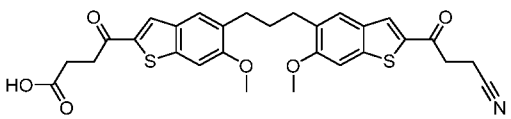
Example	Structure	Name	Mass $[M+H]^+$
4		4-(5-(3-((2-(3-carboxy propanoyl)-6-methoxythieno [3,2-b] pyridin-5-yl)oxy) propyl)benzo[b]thiophen-2-yl)-4-oxobutanoic acid	556
5		4-(5-(3-(2-(3-carboxy propanoyl)-6-methoxybenzo [b]thiophen-5-yl)propoxy)-6-methoxybenzo[d]thiazol-2-yl)-4-oxobutanoic acid	586
6		4-(5-(3-((2-(3-carboxy propanoyl)-6-methoxybenzo [b]thiophen-5-yl)oxy)propyl) benzo[b]thiophen-2-yl)-4-oxobutanoic acid	555
7		4-(5-(2-((2-(3-carboxy propanoyl)-6-methoxybenzo [b]thiophen-5-yl)oxy)ethyl)-6-methoxythieno[3,2-b] pyridin-2-yl)-4-oxobutanoic acid	572
8		4-(5-(2-(2-(3-carboxypropanoyl)-6-methoxythieno[3,2-b] pyridin-5-yl)ethoxy)-6-methoxythieno[3,2-b]pyridin-2-yl)-4-oxobutanoic acid	573
9		4-(5-(2-((2-(3-carboxypropanoyl)-6-methoxybenzo[d]thiazol-5-yl)oxy)ethyl)-6-methoxythieno[3,2-b]pyridin-2-yl)-4-oxobutanoic acid	573

Example	Structure	Name	Mass $[M+H]^+$
10		4-(5-(3-(2-(3-carboxy propanoyl)-6-methoxybenzo [b]thiophen-5-yl)propoxy)-6-methoxythieno[3,2-b]pyridin-2-yl)-4-oxobutanoic acid	586
11		4-(5-(2-((2-(3-carboxy propanoyl)-6-methoxybenzo [b]thiophen-5-yl)oxy)ethoxy) benzo[b]thiophen-2-yl)-4-oxobutanoic acid	557
12		(S)-4-(5-(3-((2-(3-carboxy propanoyl)-6-methoxythieno [3,2-b] pyridin-5-yl)oxy) propoxy)-6-methoxybenzo[b] thiophen-2-yl)-2-methyl-4-oxobutanoic acid	616
13		4-(5-(3-((2-(3-carboxypropanoyl)-6-methoxybenzo[b]thiophen-5-yl)oxy)propyl)-6-methoxythieno[3,2-b]pyridin-2-yl)-4-oxobutanoic acid	586
14		(S)-4-(5-(3-((2-(3-carboxypropanoyl)-6-methoxythieno[3,2-b]pyridin-5-yl)oxy)propyl)-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoic acid	600
15		(S)-4-(5-(3-(2-(3-carboxy propanoyl)-6-methoxythieno [3,2-b]pyridin-5-yl)propoxy)-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoic acid	600

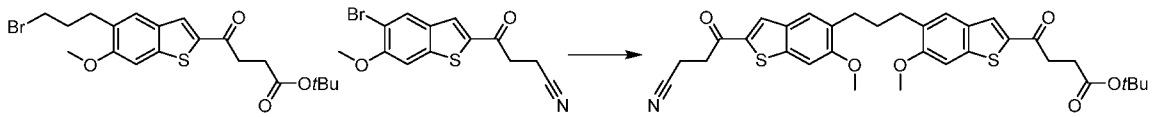
Example	Structure	Name	Mass $[M+H]^+$
16		(S)-4-(5-(3-(2-((S)-3-carboxybutanoyl)-6-methoxybenzo[b]thiophen-5-yl)propoxy)-6-methoxythieno[3,2-b]pyridin-2-yl)-2-methyl-4-oxobutanoic acid	614
17		(S)-4-(5-(2-((2-(3-carboxypropanoyl)-6-methoxybenzo[b]thiophen-5-yl)oxy)ethoxy)-6-methoxythieno[3,2-b]pyridin-2-yl)-2-methyl-4-oxobutanoic acid	602
18		(S)-4-(5-(3-((2-(3-carboxypropanoyl)-6-methoxybenzo[b]thiophen-5-yl)oxy)propoxy)-6-methoxythieno[3,2-b]pyridin-2-yl)-2-methyl-4-oxobutanoic acid	616
19		rac-(R)-4-(5-(2-((2-((R)-3-carboxybutanoyl)-4-fluoro-6-methoxybenzo[b]thiophen-5-yl)oxy)ethoxy)-6-methoxythieno[3,2-b]pyridin-2-yl)-2-methyl-4-oxobutanoic acid	634
20		(S)-4-(5-(2-((2-(3-carboxypropanoyl)-4-fluoro-6-methoxybenzo[b]thiophen-5-yl)oxy)ethoxy)-6-methoxythieno[3,2-b]pyridin-2-yl)-2-methyl-4-oxobutanoic acid	620
21		(S)-4-(5-(3-((2-(3-carboxypropanoyl)-4-fluoro-6-methoxybenzo[b]thiophen-5-yl)oxy)propoxy)-6-methoxythieno[3,2-b]pyridin-2-yl)-2-methyl-4-oxobutanoic acid	634

Example	Structure	Name	Mass $[M+H]^+$
22		rac-(R)-4-(5-(3-((2-((R)-3-carboxybutanoyl)-4-fluoro-6-methoxybenzo[b] thiophen-5-yl)oxy)propoxy)-6-methoxy thieno[3,2-b]pyridin-2-yl)-2-methyl-4-oxobutanoic acid	648
23		(S)-4-(5-(3-((2-(3-carboxy propanoyl)-6-methoxythieno [3,2-b]pyridin-5-yl)oxy) propoxy)-4-fluoro-6-methoxy benzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoic acid	634
81		4-(5-(2-((2-(3-carboxypropanoyl)-4-fluoro-6-methoxybenzo[b]thiophen-5-yl)oxy)ethoxy)-6-methoxythieno[3,2-b]pyridin-2-yl)-4-oxobutanoic acid	606
82		4-(5-(3-((2-(3-carboxypropanoyl)-4-fluoro-6-methoxybenzo[b]thiophen-5-yl)oxy)propoxy)-6-methoxythieno[3,2-b]pyridin-2-yl)-4-oxobutanoic acid	620
83		(S)-4-(5-(2-((2-(3-carboxypropanoyl)-6-methoxythieno[3,2-b]pyridin-5-yl)oxy)ethoxy)-4-fluoro-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoic acid	620

Example 24: 4-(5-(3-(2-(3-cyanopropanoyl)-6-methoxybenzo[b]thiophen-5-yl)propyl)-6-methoxybenzo[b]thiophen-2-yl)-4-oxobutanoic acid

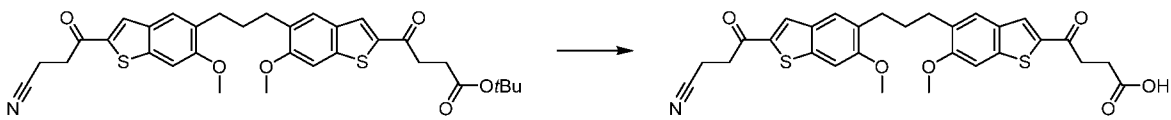


Step 1: tert-*butyl 4-(5-(3-(2-(3-cyanopropanoyl)-6-methoxybenzo[b]thiophen-5-yl)propyl)-6-methoxybenzo[b]thiophen-2-yl)-4-oxobutanoate*



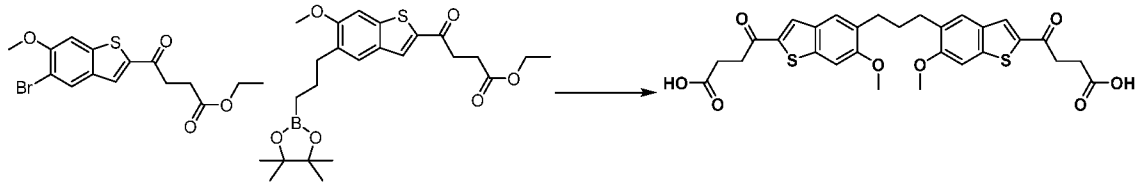
To a vial was added *tert*-butyl 4-(5-(3-bromopropyl)-6-methoxybenzo[b]thio phen-2-yl)-4-oxobutanoate (45mg, 0.10mmol), 4-(5-bromo-6-methoxybenzo[b]thiophen-2-yl)-4-oxobutanenitrile (33mg, 0.10mmol), NaI (7.6mg, 0.051mmol), nickel(II) bromide ethylene glycol dimethyl ether complex (9.4mg, 0.031mmol), Mn (22mg, 0.41mmol) and 4,4'-dimethoxy-2,2'-bipyridine (6.6mg, 0.031mmol). To the vial was added DMPU (1.0mL) followed by the addition of 5% v/v solutions in DMPU of Py (82µl, 0.051mmol) and TMS-Cl (78µl, 0.031mmol). The vial was degassed with Ar for 5min. The mixture was heated to 90°C for 2h. After 2h, the mixture was allowed to cool to RT and directly purified by prep-HPLC (ACN/H_2O with 0.1% TFA) to afford *tert*-butyl 4-(5-(3-(2-(3-cyanopropanoyl)-6-methoxybenzo[b]thiophen-5-yl)propyl)-6-methoxybenzo[b]thiophen-2-yl)-4-oxobutanoate. LCMS ($C_{33}H_{35}NO_6S_2Na$) (ES, m/z): 628 $[M+Na]^+$.

Step 2: 4-(5-(3-(2-(3-cyanopropanoyl)-6-methoxybenzo[b]thiophen-5-yl)propyl)-6-methoxybenzo[b]thiophen-2-yl)-4-oxobutanoic acid



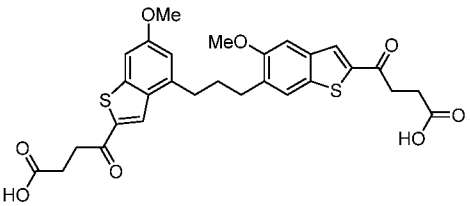
To a mixture of *tert*-butyl 4-(5-(3-(2-(3-cyanopropanoyl)-6-methoxybenzo[b] thiophen-5-yl)propyl)-6-methoxybenzo[b]thiophen-2-yl)-4-oxobutanoate (8.5mg, 0.014mmol), MeOH (500µL) and ACN (500µL) was added NaOH (5.0M in water, 0.56µL, 0.28mmol). The mixture was heated to 40°C for 4h. Upon cooling to RT, the mixture was purified by prep-HPLC (ACN/H_2O with 0.1% TFA) to afford 4-(5-(3-(2-(3-cyanopropanoyl)-6-methoxybenzo [b]thiophen-5-yl)propyl)-6-methoxybenzo[b]thiophen-2-yl)-4-oxobutanoic acid. LCMS ($C_{29}H_{28}NO_6S_2$) (ES, m/z): 550 $[M+H]^+$. ^1H NMR (500MHz, DMSO-d_6) δ 12.20 (s, 1H), 8.30-8.20 (m, 2H), 7.82-7.75 (m, 2H), 7.65-7.56 (m, 2H), 3.89 (s, 6H), 3.54-3.46 (m, 2H), 2.82-2.76 (m, 2H), 2.76-2.58 (m, 8H), 1.99-1.86 (m, 2H).

Example 25: 4,4'-(5,5'-(propane-1,3-diyl)bis(6-methoxybenzo[b]thiophene-5,2-diyl))bis(4-oxobutanoic acid)

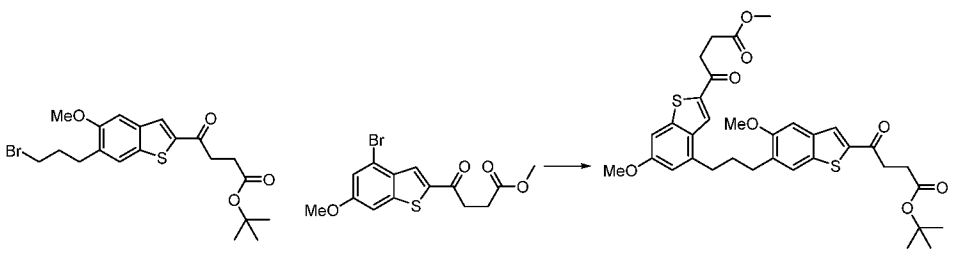


To a mixture of ethyl 4-(6-methoxy-5-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propyl)benzo[b]thiophen-2-yl)-4-oxobutanoate (69mg, 0.15mmol), ethyl 4-(5-bromo-6-methoxybenzo[b]thiophen-2-yl)-4-oxobutanoate (84mg, 0.23mmol), $PdCl_2(dppf)$-CH_2Cl_2 (25mg, 0.030mmol) and Cs_2CO_3 (195mg, 0.600mmol) was added dioxane (0.80mL) and water (0.2 mL). The reaction was heated to 100°C for 18h. Upon cooling to RT, the mixture was then filtered, and the residual materials were washed with dioxane. The filtrate was concentrated under reduced pressure. The resulting residue was then purified via prep-HPLC (ACN/H_2O with 0.1% NH_4OH) to afford 4,4'-(5,5'-(propane-1,3-diyl)bis(6-methoxybenzo[b]thiophene-5,2-diyl))bis(4-oxobutanoic acid). LCMS ($C_{29}H_{27}O_8S_2$) (ES, m/z): 566 $[M-H]^-$. ^1H NMR (600MHz, DMSO-d_6) δ 8.11 (s, 2H), 7.68 (s, 2H), 7.50 (s, 2H), 3.82 (s, 6H), 3.16-3.09 (m, 4H), 2.66 (t, *J*=6.6Hz, 4H), 2.40 (s, 4H), 1.93-1.83 (m, 2H).

Example 26: 4-(4-(3-(2-(3-carboxypropanoyl)-5-methoxybenzo[b]thiophen-6-yl)propyl)-6-methoxybenzo[b]thiophen-2-yl)-4-oxobutanoic acid



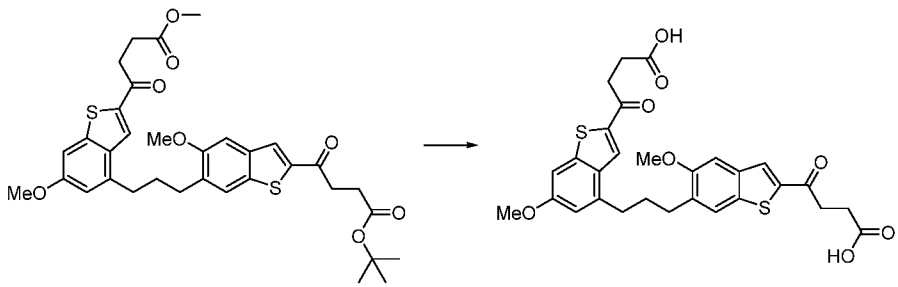
Step 1: tert-*butyl 4-(5-methoxy-6-(3-(6-methoxy-2-(4-methoxy-4-oxobutanoyl)benzo[b]thiophen-4-yl)propyl)benzo[b]thiophen-2-yl)-4-oxobutanoate*



To a vial was added *tert*-butyl 4-(6-(3-bromopropyl)-5-methoxybenzo[b] thiophen-2-yl)-4-oxobutanoate (72mg, 0.16mmol), methyl 4-(4-bromo-6-methoxybenzo[b] thiophen-2-yl)-4-oxobutanoate (58mg, 0.16mmol), NaI (12mg, 0.082mmol), nickel(II) bromide ethylene glycol

dimethyl ether complex (15mg, 0.049mmol), Mn (36mg, 0.65mmol) and 4,4'-dimethoxy-2,2'-bipyridine (11mg, 0.049mmol). To the vial was added DMPU (1.6mL) followed by the addition of 5% v/v solutions in DMPU of Py (130µl, 0.082mmol) and TMS-Cl (130µl, 0.049mmol). The vial was degassed with Ar for 5min. The mixture was heated to 90°C for 1h. After 1h, the mixture was allowed to cool to RT and then diluted with EtOAc and water. The organic layer was separated, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting mixture was used without further purification or characterization.

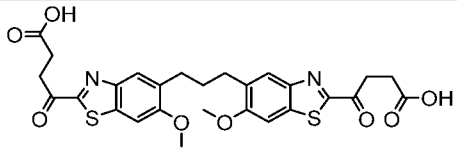
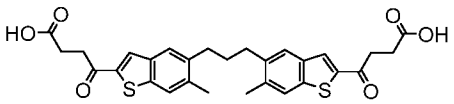
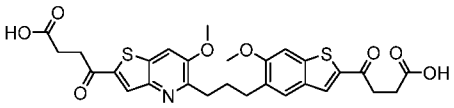
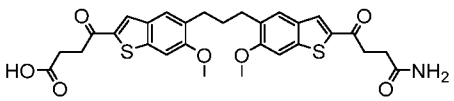
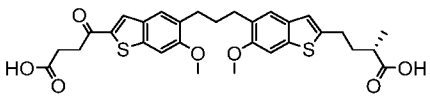
Step 2: 4-(4-(3-(2-(3-carboxypropanoyl)-5-methoxybenzo[b]thiophen-6-yl)propyl)-6-methoxybenzo[b]thiophen-2-yl)-4-oxobutanoic acid



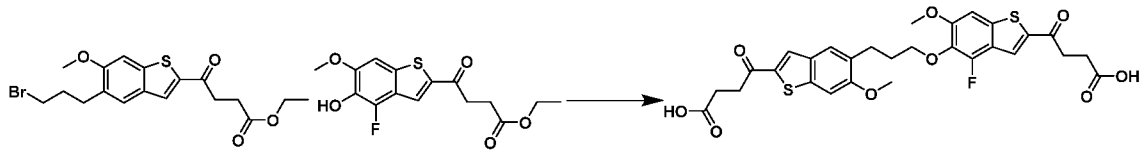
To a mixture of *tert*-butyl 4-(5-methoxy-6-(3-(6-methoxy-2-(4-methoxy-4-oxobutanoyl)benzo[b]thiophen-4-yl)propyl)benzo[b]thiophen-2-yl)-4-oxobutanoate (100mg, 0.16mmol) and MeOH (1.6mL) was added NaOH (5M in water, 0.65mL, 3.3mmol), and the mixture was heated to 50°C for 1h. Upon cooling to RT, the mixture was purified by prep-HPLC (ACN/H_2O with 0.1% TFA) to afford 4-(4-(3-(2-(3-carboxypropanoyl)-5-methoxybenzo[b]thiophen-6-yl)propyl)-6-methoxybenzo[b]thiophen-2-yl)-4-oxobutanoic acid. LCMS ($C_{29}H_{29}O_8S_2$) (ES, m/z): 569 $[M+H]^+$. ^1H NMR (500MHz, DMSO-d_6) δ 12.23 (s, 2H), 8.27 (s, 1H), 8.25 (s, 1H), 7.82 (s, 1H), 7.50 (s, 1H), 7.44 (s, 1H), 6.93 (s, 1H), 3.89-3.79 (m, 6H), 3.34-3.19 (m, 4H), 3.03 (t, *J*=7.3Hz, 2H), 2.82-2.74 (m, 2H), 2.66-2.55 (m, 4H), 2.06-1.96 (m, 2H).

Examples 27 through 31, as shown in Table 12 below, were or may be prepared according to procedures analogous to those outlined in Example 26 above using the appropriate starting materials, described in the Preparations or Intermediates above, or as obtained from commercial sources.

Table 12

Example	Structure	Name	Mass $[M+H]^+$
27		4,4'-(propane-1,3-diylbis(6-methoxybenzo[d]thiazole-5,2-diyl))bis(4-oxobutanoic acid)	571
28		4,4'-(propane-1,3-diylbis(6-methylbenzo[b]thiophene-5,2-diyl))bis(4-oxobutanoic acid)	537
29		4-(5-(3-(2-(3-carboxy propanoyl)-6-methoxybenzo [b]thiophen-5-yl)propyl)-6-methoxythieno[3,2-b]pyridin-2-yl)-4-oxobutanoic acid	570
30		4-(5-(3-(2-(4-amino-4-oxobutanoyl)-6-methoxy benzo[b]thiophen-5-yl) propyl)-6-methoxybenzo [b]thiophen-2-yl)-4-oxobutanoic acid	568
31		(S)-4-(5-(3-(2-(3-carboxy butyl)-6-methoxybenzo[b] thiophen-5-yl)propyl)-6-methoxybenzo[b]thiophen-2-yl)-4-oxobutanoic acid	569

Example 32: 4-(5-(3-((2-(3-carboxypropanoyl)-4-fluoro-6-methoxybenzo[b]thiophen-5-yl)oxy)propyl)-6-methoxybenzo[b]thiophen-2-yl)-4-oxobutanoic acid

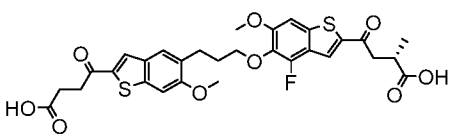
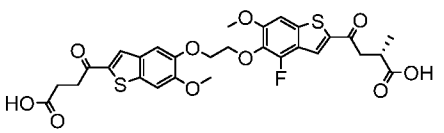
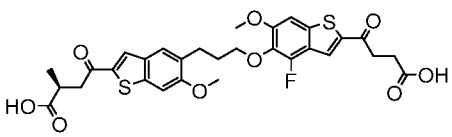


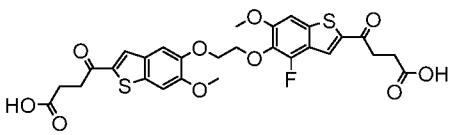
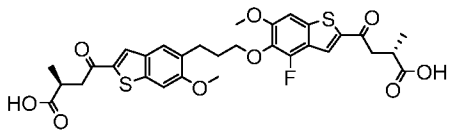
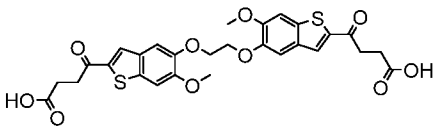
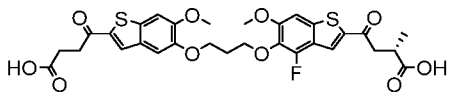
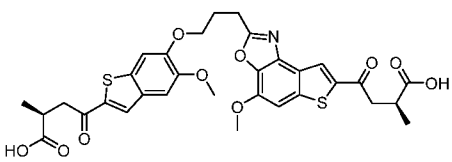
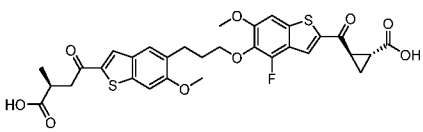
To a mixture of ethyl 4-(5-(3-bromopropyl)-6-methoxybenzo[b]thiophen-2-yl)-4-oxobutanoate (83mg, 0.20mmol), ethyl 4-(4-fluoro-5-hydroxy-6-methoxybenzo[b]thiophen-2-yl)-4-oxobutanoate (78mg, 0.24mmol), and K_2CO_3 (28mg, 0.20mmol) was added ACN (1mL). The reaction was heated to 65°C for 18h. Upon cooling to RT, the mixture was diluted with ACN (4mL) and filtered. The filtrate was then concentrated under reduced pressure. THF (2.0mL), MeOH (0.50mL), water (1.0mL) and LiOH (48mg, 2.0mmol) were then added, and the

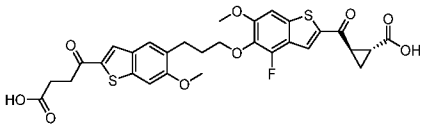
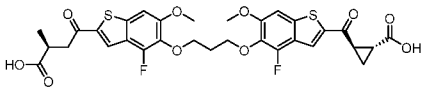
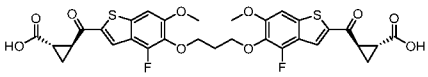
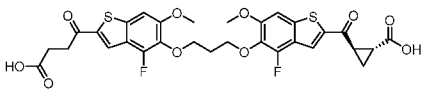
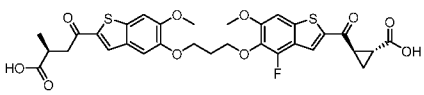
mixture was allowed to stir at RT for 2h. The mixture was then quenched with AcOH (0.40mL), and the mixture was concentrated under reduced pressure. The resulting residue was then purified via prep-HPLC (ACN/H_2O with 0.1% TFA) to afford 4-(5-(3-((2-(3-carboxypropanoyl)-4-fluoro-6-methoxybenzo[b]thiophen-5-yl)oxy)propyl)-6-methoxybenzo[b] thiophen-2-yl)-4-oxobutanoic acid. LCMS ($C_{29}H_{28}FO_9S_2$) (ES, m/z): 603 $[M+H]^+$. ^1H NMR (600MHz, DMSO-d_6) δ 8.28 (s, 1H), 8.20 (s, 1H), 7.73 (d, *J*=13.7Hz, 1H), 7.55 (d, *J*=11.4Hz, 2H), 4.06-4.00 (m, 2H), 3.90-3.81 (m, 6H), 3.28 (t, *J*=6.1Hz, 2H), 3.23 (t, *J*=6.2Hz, 2H), 2.82 (s, 2H), 2.58-2.56 (m, 4H), 1.95-193 (m, 2H).

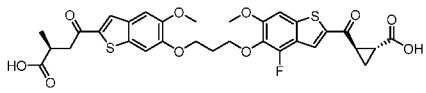
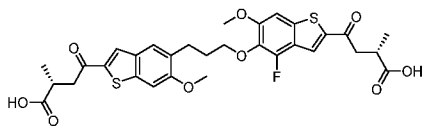
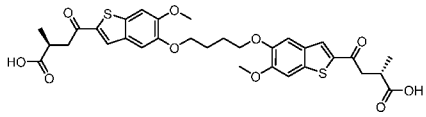
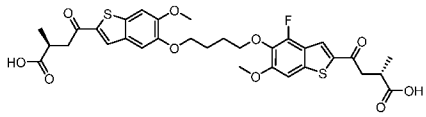
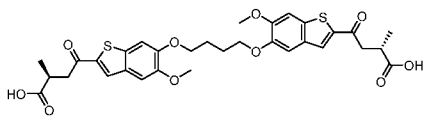
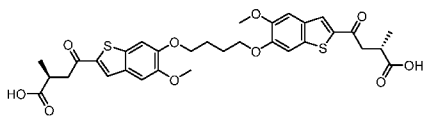
Examples 33 through 40 and 84 through 157, as shown in Table 13 below, were or may be prepared according to procedures analogous to those outlined in Example 32 above using the appropriate starting materials, described in the Preparations or Intermediates above, or as obtained from commercial sources.

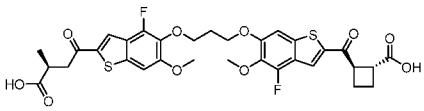
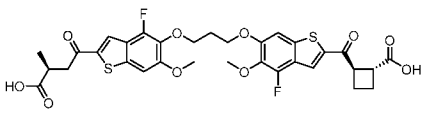
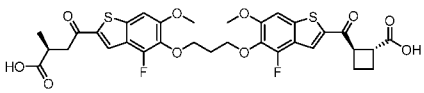
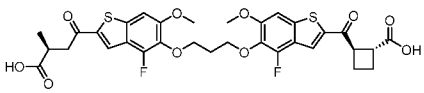
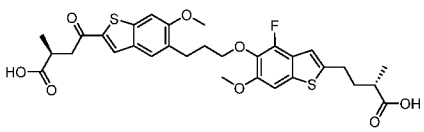
Table 13

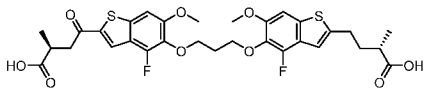
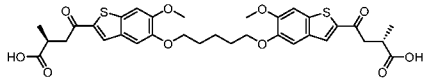
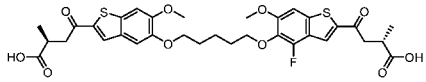
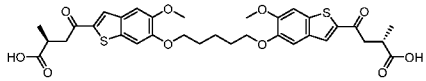
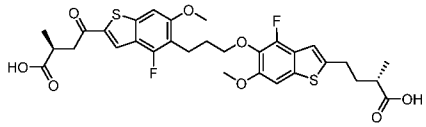
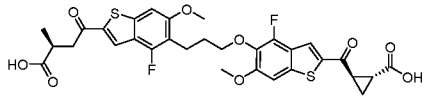
Example	Structure	Name	Mass $[M+H]^+$
33		(S)-4-(5-(3-(2-(3-carboxy propanoyl)-6-methoxybenzo [b]thiophen-5-yl)propoxy)-4-fluoro-6-methoxybenzo[b] thiophen-2-yl)-2-methyl-4-oxobutanoic acid	617
34		(S)-4-(5-(2-((2-(3-carboxy propanoyl)-6-methoxybenzo [b]thiophen-5-yl)oxy)ethoxy)-4-fluoro-6-methoxybenzo[b] thiophen-2-yl)-2-methyl-4-oxobutanoic acid	619
35		(S)-4-(5-(3-((2-(3-carboxy propanoyl)-4-fluoro-6-methoxybenzo[b]thiophen-5-yl)oxy)propyl)-6-methoxy benzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoic acid	617

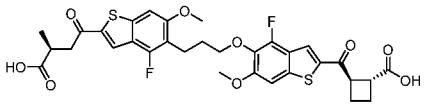
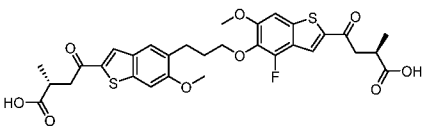
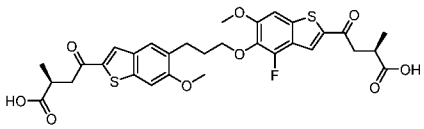
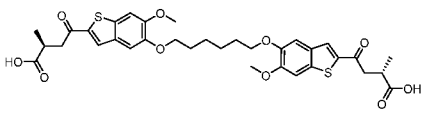
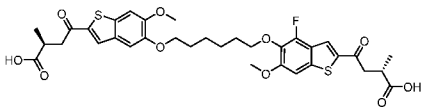
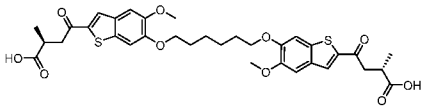
Example	Structure	Name	Mass $[M+H]^+$
36		4-(5-(2-((2-(3-carboxy propanoyl)-4-fluoro-6-methoxybenzo[b]thiophen-5-yl)oxy)ethoxy)-6-methoxy benzo[b]thiophen-2-yl)-4-oxobutanoic acid	605
37		(S)-4-(5-(3-((2-((S)-3-carboxybutanoyl)-4-fluoro-6-methoxybenzo[b]thiophen-5-yl)oxy)propyl)-6-methoxy benzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoic acid	613
38		4,4'-((ethane-1,2-diylbis (oxy))bis(6-methoxybenzo [b]thiophene-5,2-diyl))bis(4-oxobutanoic acid)	587
39		(S)-4-(5-(3-((2-(3-carboxy propanoyl)-6-methoxybenzo [b]thiophen-5-yl)oxy) propoxy)-4-fluoro-6-methoxy benzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoic acid	633
40		(S)-4-(6-(3-(7-((S)-3-carboxybutanoyl)-4-methoxythieno[2',3':5,6] benzo[1,2-d]oxazol-2-yl) propoxy)-5-methoxybenzo [b]thiophen-2-yl)-2-methyl-4-oxobutanoic acid	654
84		trans-2-(5-(3-(2-((S)-3-carboxybutanoyl)-6-methoxybenzo[b]thiophen-5-yl)propoxy)-4-fluoro-6-methoxybenzo[b]thiophene-2-carbonyl)-cyclopropanecarboxylic acid	629

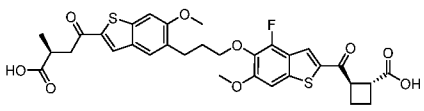
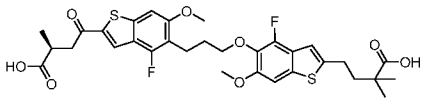
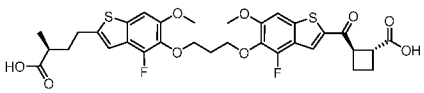
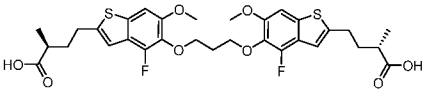
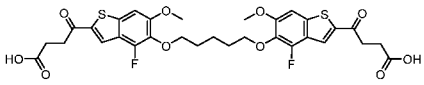
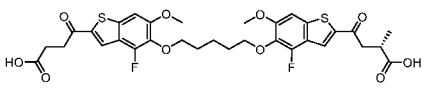
Example	Structure	Name	Mass $[M+H]^+$
85		trans-2-(5-(3-(2-(3-carboxypropanoyl)-6-methoxybenzo[b]thiophen-5-yl)propoxy)-4-fluoro-6-methoxybenzo[b]thiophene-2-carbonyl)cyclopropane carboxylic acid	615
86		trans-2-(5-(3-((2-((S)-3-carboxybutanoyl)-4-fluoro-6-methoxybenzo[b]thiophen-5-yl)oxy)propoxy)-4-fluoro-6-methoxybenzo[b]thiophene-2-carbonyl)cyclopropane carboxylic acid	663
87		trans-2-(5-(3-((2-((1R,2R)-2-carboxycyclopropane carbony)-4-fluoro-6-methoxybenzo[b]thiophen-5-yl)oxy)propoxy)-4-fluoro-6-methoxybenzo[b]thiophene-2-carbonyl)cyclopropane carboxylic acid	661
88		trans-2-(5-(3-((2-(3-carboxypropanoyl)-4-fluoro-6-methoxybenzo[b]thiophen-5-yl)oxy)propoxy)-4-fluoro-6-methoxybenzo[b]thiophene-2-carbonyl)cyclopropane carboxylic acid	649
89		trans-2-(5-(3-((2-((S)-3-carboxybutanoyl)-6-methoxybenzo[b]thiophen-5-yl)oxy)propoxy)-4-fluoro-6-methoxybenzo[b]thiophene-2-carbonyl)cyclopropane carboxylic acid	645

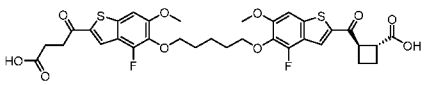
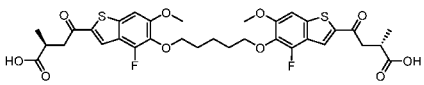
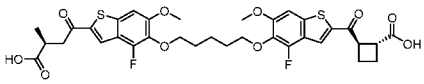
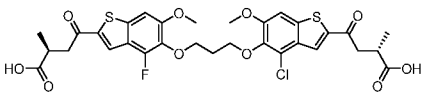
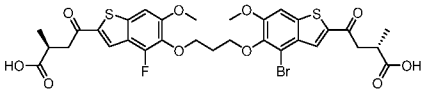
Example	Structure	Name	Mass $[M+H]^+$
90		trans-2-(5-(3-((2-((S)-3-carboxybutanoyl)-5-methoxybenzo[b]thiophen-6-yl)oxy)propoxy)-4-fluoro-6-methoxybenzo[b]thiophene-2-carbonyl)cyclopropane carboxylic acid	645
91		(R)-4-(5-(3-((2-((S)-3-carboxybutanoyl)-4-fluoro-6-methoxybenzo[b]thiophen-5-yl)oxy)propyl)-6-methoxy benzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoic acid	631
92		(2S,2'S)-4,4'-(5,5'-(butane-1,4-diylbis(oxy))bis(6-methoxybenzo[b]thiophene-5,2-diyl))bis(2-methyl-4-oxobutanoic acid)	643
93		(S)-4-(5-(4-((2-((S)-3-carboxybutanoyl)-4-fluoro-6-methoxybenzo[b]thiophen-5-yl)oxy)butoxy)-6-methoxy benzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoic acid	661
94		(S)-4-(5-(4-((2-((S)-3-carboxybutanoyl)-5-methoxybenzo[b]thiophen-6-yl)oxy)butoxy)-6-methoxy benzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoic acid	643
95		(2S,2'S)-4,4'-(6,6'-(butane-1,4-diylbis(oxy))bis(5-methoxybenzo[b]thiophene-6,2-diyl))bis(2-methyl-4-oxobutanoic acid)	643

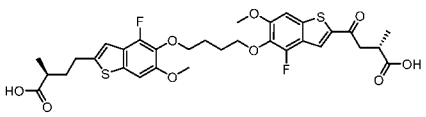
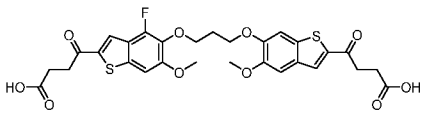
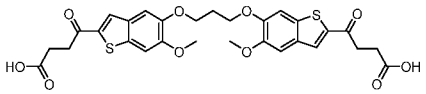
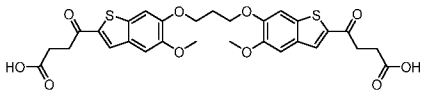
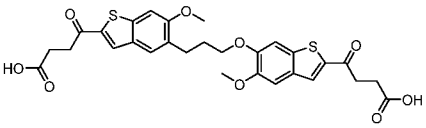
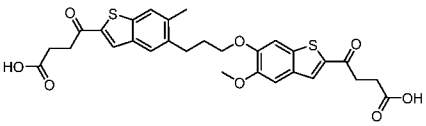
Example	Structure	Name	Mass $[M+H]^+$
96		trans-2-(6-(3-((2-((S)-3-carboxybutanoyl)-4-fluoro-6-methoxybenzo[b]thiophen-5-yl)oxy)propoxy)-4-fluoro-5-methoxybenzo[b]thiophene-2-carbonyl)cyclobutane carboxylic acid	677
97		trans-2-(6-(3-((2-((S)-3-carboxybutanoyl)-4-fluoro-6-methoxybenzo[b]thiophen-5-yl)oxy)propoxy)-4-fluoro-5-methoxybenzo[b]thiophene-2-carbonyl)cyclobutane carboxylic acid	677
98		trans-2-(5-(3-((2-((S)-3-carboxybutanoyl)-4-fluoro-6-methoxybenzo[b]thiophen-5-yl)oxy)propoxy)-4-fluoro-6-methoxybenzo[b]thiophene-2-carbonyl)cyclobutane carboxylic acid	677
99		trans-2-(5-(3-((2-((S)-3-carboxybutanoyl)-4-fluoro-6-methoxybenzo[b]thiophen-5-yl)oxy)propoxy)-4-fluoro-6-methoxybenzo[b]thiophene-2-carbonyl)cyclobutane carboxylic acid	677
100		(S)-4-(5-(3-((2-((S)-3-carboxybutyl)-4-fluoro-6-methoxybenzo[b]thiophen-5-yl)oxy)propyl)-6-methoxy benzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoic acid	617

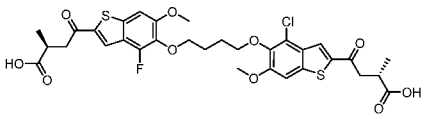
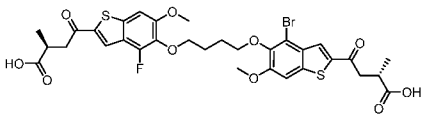
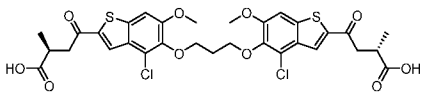
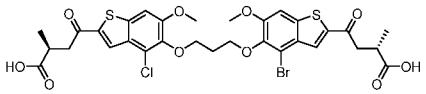
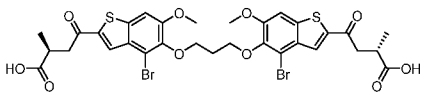
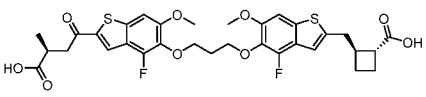
Example	Structure	Name	Mass $[M+H]^+$
101		(S)-4-(5-(3-((2-((S)-3-carboxybutyl)-4-fluoro-6-methoxybenzo[b]thiophen-5-yl)oxy)propoxy)-4-fluoro-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoic acid	651
102		(2S,2'S)-4,4'-(5,5'-(pentane-1,5-diylbis(oxy))bis(6-methoxybenzo[b]thiophene-5,2-diyl))bis(2-methyl-4-oxobutanoic acid)	657
103		(S)-4-(5-((5-((2-((S)-3-carboxybutanoyl)-4-fluoro-6-methoxybenzo[b]thiophen-5-yl)oxy)pentyl)oxy)-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoic acid	675
104		(S)-4-(5-((5-((2-((S)-3-carboxybutanoyl)-5-methoxybenzo[b]thiophen-6-yl)oxy)pentyl)oxy)-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoic acid	657
105		(S)-4-(5-(3-((2-((S)-3-carboxybutyl)-4-fluoro-6-methoxybenzo[b]thiophen-5-yl)oxy)propyl)-4-fluoro-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoic acid	635
106		trans-2-(5-(3-(2-((S)-3-carboxybutanoyl)-4-fluoro-6-methoxybenzo[b]thiophen-5-yl)propoxy)-4-fluoro-6-methoxybenzo[b]thiophene-2-carbonyl)cyclopropane carboxylic acid	647

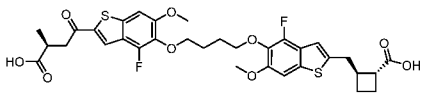
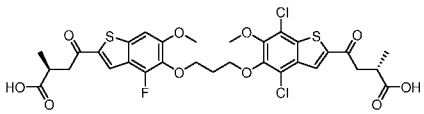
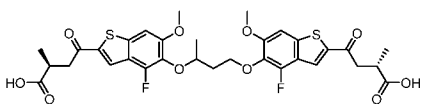
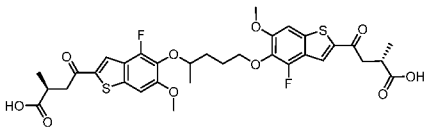
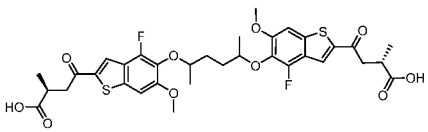
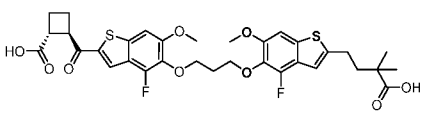
Example	Structure	Name	Mass $[M+H]^+$
107		trans-2-(5-(3-(2-((S)-3-carboxybutanoyl)-4-fluoro-6-methoxybenzo[b]thiophen-5-yl)propoxy)-4-fluoro-6-methoxybenzo[b]thiophene-2-carbonyl)cyclobutane carboxylic acid	661
108		(R)-4-(5-(3-((2-((R)-3-carboxybutanoyl)-4-fluoro-6-methoxybenzo[b]thiophen-5-yl)oxy)propyl)-6-methoxy benzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoic acid	631
109		(S)-4-(5-(3-((2-((R)-3-carboxybutanoyl)-4-fluoro-6-methoxybenzo[b]thiophen-5-yl)oxy)propyl)-6-methoxy benzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoic acid	631
110		(2S,2'S)-4,4'-(5,5'-(hexane-1,6-diylbis(oxy))bis(6-methoxybenzo[b]thiophene-5,2-diyl))bis(2-methyl-4-oxobutanoic acid)	671
111		(S)-4-(5-((6-((2-((S)-3-carboxybutanoyl)-4-fluoro-6-methoxybenzo[b]thiophen-5-yl)oxy)hexyl)oxy)-6-methoxy benzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoic acid	689
112		(2S,2'S)-4,4'-(6,6'-(hexane-1,6-diylbis(oxy))bis(5-methoxybenzo[b]thiophene-6,2-diyl))bis(2-methyl-4-oxobutanoic acid)	671

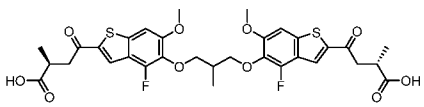
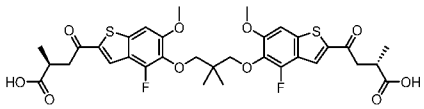
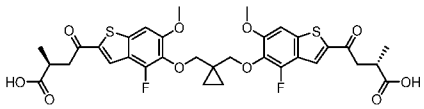
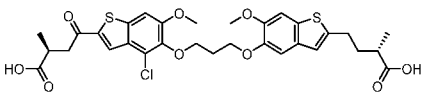
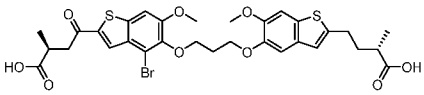
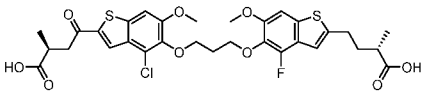
Example	Structure	Name	Mass $[M+H]^+$
113		trans-2-(5-(3-(2-((S)-3-carboxybutanoyl)-6-methoxybenzo[b]thiophen-5-yl)propoxy)-4-fluoro-6-methoxybenzo[b]thiophene-2-carbonyl)cyclobutane carboxylic acid	643
114		(S)-4-(5-(3-((2-(3-carboxy-3-methylbutyl)-4-fluoro-6-methoxybenzo[b]thiophen-5-yl)oxy)propyl)-4-fluoro-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoic acid	649
115		trans-2-(5-(3-((2-((S)-3-carboxybutyl)-4-fluoro-6-methoxybenzo[b]thiophen-5-yl)oxy)propoxy)-4-fluoro-6-methoxybenzo[b]thiophene-2-carbonyl)cyclo-butanecarboxylic acid	663
116		(2S,2'S)-4,4'-(5,5'-(propane-1,3-diylbis(oxy))bis(4-fluoro-6-methoxybenzo[b]thiophene-5,2-diyl))bis(2-methylbutanoic acid)	654 (M+ H_2O)
117		4,4'-(5,5'-(pentane-1,5-diylbis(oxy))bis(4-fluoro-6-methoxybenzo[b]thiophene-5,2-diyl))bis(4-oxobutanoic acid)	665
118		(S)-4-(5-((5-((2-(3-carboxypropanoyl)-4-fluoro-6-methoxybenzo[b]thiophen-5-yl)oxy)pentyl)oxy)-4-fluoro-6-methoxy benzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoic acid	679

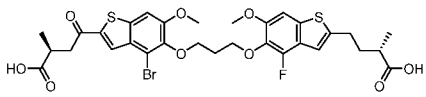
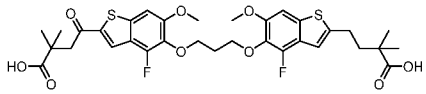
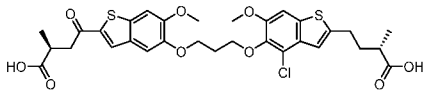
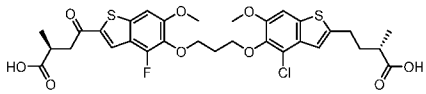
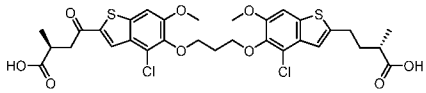
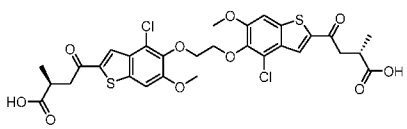
Example	Structure	Name	Mass $[M+H]^+$
119		2-(5-((5-((2-(3-carboxypropanoyl)-4-fluoro-6-methoxybenzo[b]thiophen-5-yl)oxy)pentyl)oxy)-4-fluoro-6-methoxybenzo[b]thiophene-2-carbonyl)cyclobutanecarboxylic acid	691
120		(2S,2'S)-4,4'-(5,5'-(pentane-1,5-diylbis(oxy))bis(4-fluoro-6-methoxybenzo[b]thiophene-5,2-diyl))bis(2-methyl-4-oxobutanoic acid)	693
121		trans-2-(5-((5-((2-((S)-3-carboxybutanoyl)-4-fluoro-6-methoxybenzo[b]thiophen-5-yl)oxy)pentyl)oxy)-4-fluoro-6-methoxybenzo[b]thiophene-2-carbonyl)cyclobutane carboxylic acid	705
122		(S)-4-(5-(3-((2-((S)-3-carboxybutanoyl)-4-chloro-6-methoxybenzo[b]thiophen-5-yl)oxy)propoxy)-4-fluoro-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoic acid	663 (M-H_2O+H^+)
123		(S)-4-(5-(3-((4-bromo-2-((S)-3-carboxybutanoyl)-6-methoxybenzo[b]thiophen-5-yl)oxy)propoxy)-4-fluoro-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoic acid	707, 709 (M-H_2O+H^+)

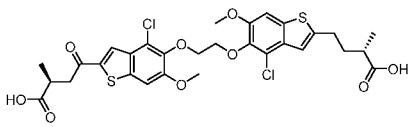
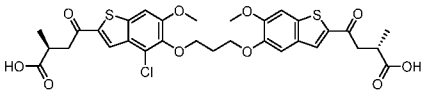
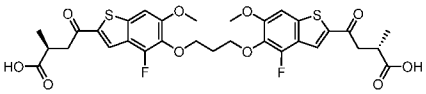
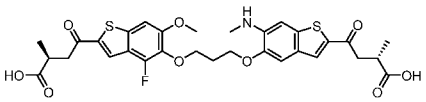
Example	Structure	Name	Mass $[M+H]^+$
124		(S)-4-(5-(4-((2-((S)-3-carboxybutyl)-4-fluoro-6-methoxybenzo[b]thiophen-5-yl)oxy)butoxy)-4-fluoro-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoic acid	665
125		4-(6-(3-((2-(3-carboxypropanoyl)-4-fluoro-6-methoxybenzo[b]thiophen-5-yl)oxy)propoxy)-5-methoxybenzo[b]thiophen-2-yl)-4-oxobutanoic acid	619
126		4-(5-(3-((2-(3-carboxypropanoyl)-5-methoxybenzo[b]thiophen-6-yl)oxy)propoxy)-6-methoxybenzo[b]thiophen-2-yl)-4-oxobutanoic acid	601
127		4,4'-(6,6'-(propane-1,3-diylbis(oxy))bis(5-methoxybenzo[b]thiophene-6,2-diyl))bis(4-oxobutanoic acid)	601
128		4-(5-(3-((2-(3-carboxypropanoyl)-5-methoxybenzo[b]thiophen-6-yl)oxy)propyl)-6-methoxybenzo[b]thiophen-2-yl)-4-oxobutanoic acid	585
129		4-(5-(3-((2-(3-carboxypropanoyl)-5-methoxybenzo[b]thiophen-6-yl)oxy)propyl)-6-methylbenzo[b]thiophen-2-yl)-4-oxobutanoic acid	569

Example	Structure	Name	Mass $[M+H]^+$
130		(S)-4-(5-(4-((2-((S)-3-carboxybutanoyl)-4-chloro-6-methoxybenzo[b]thiophen-5-yl)oxy)butoxy)-4-fluoro-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoic acid	695
131		(S)-4-(5-(4-((4-bromo-2-((S)-3-carboxybutanoyl)-6-methoxybenzo[b]thiophen-5-yl)oxy)butoxy)-4-fluoro-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoic acid	739, 741
132		(2S,2'S)-4,4'-(5,5'-(propane-1,3-diylbis(oxy))bis(4-chloro-6-methoxybenzo[b]thiophene-5,2-diyl))bis(2-methyl-4-oxobutanoic acid)	697, 699
133		(S)-4-(5-(3-((4-bromo-2-((S)-3-carboxybutanoyl)-6-methoxybenzo[b]thiophen-5-yl)oxy)propoxy)-4-chloro-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoic acid	723, 725 (M-H_2O+ H^+)
134		(2S,2'S)-4,4'-(5,5'-(propane-1,3-diylbis(oxy))bis(4-bromo-6-methoxybenzo[b]thiophene-5,2-diyl))bis(2-methyl-4-oxobutanoic acid)	767, 769, 771 (M-H_2O+ H^+)
135		2-((5-(3-((2-((S)-3-carboxybutanoyl)-4-fluoro-6-methoxybenzo[b]thiophen-5-yl)oxy)propoxy)-4-fluoro-6-methoxybenzo[b]thiophen-2-yl)methyl)cyclobutanecarboxylic acid	663

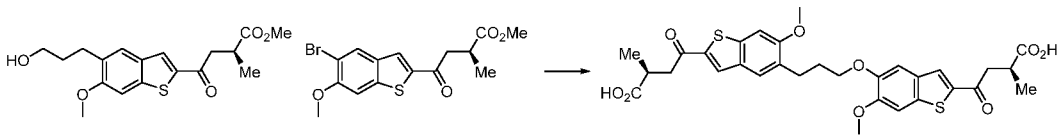
Example	Structure	Name	Mass $[M+H]^+$
136		2-((5-(4-((2-((S)-3-carboxybutanoyl)-4-fluoro-6-methoxybenzo[b]thiophen-5-yl)oxy)butoxy)-4-fluoro-6-methoxybenzo[b]thiophen-2-yl)methyl)cyclo-butanecarboxylic acid	677
137		(S)-4-(5-(3-((2-((S)-3-carboxybutanoyl)-4,7-dichloro-6-methoxybenzo[b] thiophen-5-yl)oxy)propoxy)-4-fluoro-6-methoxybenzo[b] thiophen-2-yl)-2-methyl-4-oxobutanoic acid	715, 717
138		(2S,2'S)-4,4'-((butane-1,3-diylbis(oxy))bis(4-fluoro-6-methoxybenzo[b]thiophene-5,2-diyl))bis(2-methyl-4-oxobutanoic acid)	679
139		(2S,2'S)-4,4'-((pentane-1,4-diylbis(oxy))bis(4-fluoro-6-methoxybenzo[b]thiophene-5,2-diyl))bis(2-methyl-4-oxobutanoic acid)	693
140		(2S,2'S)-4,4'-((hexane-2,5-diylbis(oxy))bis(4-fluoro-6-methoxybenzo[b]thiophene-5,2-diyl))bis(2-methyl-4-oxobutanoic acid)	707
141		trans-2-(5-(3-((2-(3-carboxy-3-methylbutyl)-4-fluoro-6-methoxybenzo[b]thiophen-5-yl)oxy)propoxy)-4-fluoro-6-methoxybenzo[b]thiophene-2-carbonyl)cyclobutane-1-carboxylic acid	705

Example	Structure	Name	Mass $[M+H]^+$
142		(2S,2'S)-4,4'-(((2-methylpropane-1,3-diyl)bis(oxy))bis(4-fluoro-6-methoxybenzo[b]thiophene-5,2-diyl))bis(2-methyl-4-oxobutanoic acid)	661 ($M-H_2O+H^+$)
143		(2S,2'S)-4,4'-(((2,2-dimethylpropane-1,3-diyl)bis(oxy))bis(4-fluoro-6-methoxybenzo[b]thiophene-5,2-diyl))bis(2-methyl-4-oxobutanoic acid)	675 ($M-H_2O+H^+$)
144		(2S,2'S)-4,4'-(((cyclopropane-1,1-diylbis-(methylene))bis(oxy))bis(4-fluoro-6-methoxybenzo[b]thiophene-5,2-diyl))bis(2-methyl-4-oxobutanoic acid)	691
145		(S)-4-(5-(3-((2-((S)-3-carboxybutyl)-6-methoxy benzo[b]thiophen-5-yl)oxy) propoxy)-4-chloro-6-methoxy benzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoic acid	649
146		(S)-4-(4-bromo-5-(3-((2-((S)-3-carboxybutyl)-6-methoxy benzo[b]thiophen-5-yl)oxy) propoxy)-6-methoxy benzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoic acid	693, 695
147		(S)-4-(5-(3-((2-((S)-3-carboxybutyl)-4-fluoro-6-methoxybenzo[b]thiophen-5-yl)oxy)propoxy)-4-chloro-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoic acid	667

Example	Structure	Name	Mass $[M+H]^+$
148		(S)-4-(4-bromo-5-(3-((2-((S)-3-carboxybutyl)-4-fluoro-6-methoxybenzo[b]thiophen-5-yl)oxy)propoxy)-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoic acid	711, 713
149		4-(5-(3-((2-(3-carboxy-3-methylbutyl)-4-fluoro-6-methoxybenzo[b]thiophen-5-yl)oxy)propoxy)-4-fluoro-6-methoxybenzo[b]thiophen-2-yl)-2,2-dimethyl-4-oxobutanoic acid	679
150		(S)-4-(5-(3-((2-((S)-3-carboxybutyl)-4-chloro-6-methoxybenzo[b]thiophen-5-yl)oxy)propoxy)-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoic acid	649
151		(S)-4-(5-(3-((2-((S)-3-carboxybutyl)-4-chloro-6-methoxybenzo[b]thiophen-5-yl)oxy)propoxy)-4-fluoro-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoic acid	667
152		(S)-4-(5-(3-((2-((S)-3-carboxybutyl)-4-chloro-6-methoxybenzo[b]thiophen-5-yl)oxy)propoxy)-4-chloro-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoic acid	683, 685
153		(2S,2'S)-4,4'-((ethane-1,2-diylbis(oxy))bis(4-chloro-6-methoxybenzo[b]thiophene-5,2-diyl))bis(2-methyl-4-oxobutanoic acid)	683, 685

Example	Structure	Name	Mass $[M+H]^+$
154		(S)-4-(5-(2-((2-((S)-3-carboxybutyl)-4-chloro-6-methoxybenzo[b]thiophen-5-yl)oxy)ethoxy)-4-chloro-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoic acid	669, 671
155		(S)-4-(5-(3-((2-((S)-3-carboxybutanoyl)-4-chloro-6-methoxybenzo[b]thiophen-5-yl)oxy)propoxy)-6-methoxy benzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoic acid	663
156		(2S,2'S)-4,4'-((propane-1,3-diylbis(oxy))bis(4-fluoro-6-methoxybenzo[b]thiophene-5,2-diyl))bis(2-methyl-4-oxobutanoic acid)	647 (M-H_2O+ H^+)
157		(S)-4-(5-(3-((2-((S)-3-carboxybutanoyl)-4-fluoro-6-methoxybenzo[b]thiophen-5-yl)oxy)propoxy)-6-(methylamino)benzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoic acid	646

Example 41: (2S)-4-{5-[3-({2-[(3S)-3-carboxybutanoyl]-6-methoxy-1-benzothiophen-5-yl}oxy)propyl]-6-methoxy-1-benzothiophen-2-yl}-2-methyl-4-oxobutanoic acid

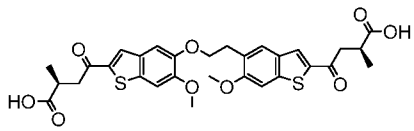
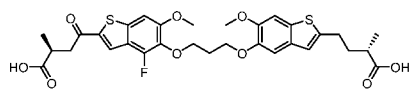
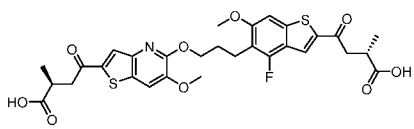


To a mixture of methyl (2S)-4-(5-bromo-6-methoxy-1-benzothiophen-2-yl)-2-methyl-4-oxobutanoate (107mg, 0.287mmol), RockPhos Pd G3 (11mg, 0.013mmol), and Cs_2CO_3 (128mg, 0.392mmol) under N_2 was added a mixture of methyl (2S)-4-[5-(3-hydroxy-propyl)-6-methoxy-1-benzothiophen-2-yl]-2-methyl-4-oxobutanoate (92mg, 0.26mmol) in toluene (870µL). The reaction mixture was sparged with N_2 for 5min and then heated to 110°C for 2h. Upon cooling

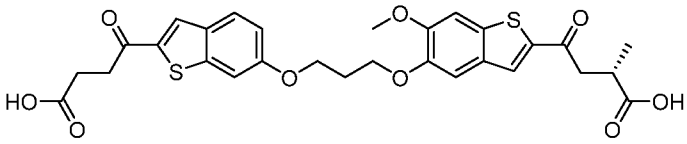
to RT, THF (1.0mL), MeOH (1.0mL) and water (0.25mL) were added followed by $LiOH \cdot H_2O$ (157 mg, 3.75 mmol) in one portion at RT. The reaction mixture was stirred at RT for 4h, then quenched with aq HCl (2.0N, 1.35mL). DMSO was added, and the resulting mixture was filtered. The filtrate was purified by RP-HPLC [C18 column, water (0.1% TFA)-CH_3CN] to afford (2S)-4-{5-[3-({2-[(3S)-3-carboxybutanoyl]-6-methoxy-1-benzothiophen-5-yl}oxy)propyl]-6-methoxy-1-benzothiophen-2-yl}-2-methyl-4-oxobutanoic acid. LCMS ($C_{31}H_{32}O_9S_2Na$) (ES, m/z): 635 $[M+Na]^+$. ^1H NMR (500MHz, DMSO-d_6): δ 12.19 (br, 2H), 8.23 (s, 1H), 8.16 (s, 1H), 7.77 (s, 1H), 7.61 (s, 1H), 7.60 (s, 1H), 7.44 (s, 1H), 4.05 (d, J=6.2Hz, 2H), 3.88 (s, 3H), 3.88 (s, 3H), 3.06 (dt, J=17.5, 4.3Hz, 2H), 2.94-2.80 (m, 4H), 2.10 (pentet, J=6.9Hz, 2H), 1.17 (d, J=7.1Hz, 6H).

Examples 42, 158 and 159, as shown in Table 14 below, were or may be prepared according to procedures analogous to those outlined in Example 41 above using the appropriate starting materials, described in the Preparations or Intermediates above, or as obtained from commercial sources.

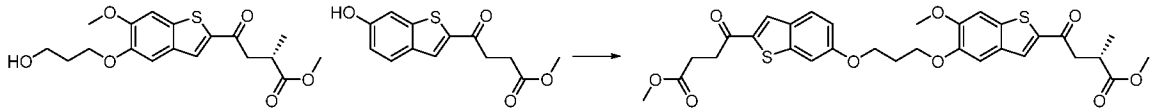
Table 14

Example	Structure	Name	Mass $[M+H]^+$
42		(S)-4-(5-(2-(2-((S)-3-carboxybutanoyl)-6-methoxybenzo[b]thiophen-5-yl)ethoxy)-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoic acid	599
158		(S)-4-(5-(3-((2-((S)-3-carboxybutyl)-6-methoxybenzo[b]thiophen-5-yl)oxy)propoxy)-4-fluoro-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoic acid	633
159		(S)-4-(5-(3-(2-((S)-3-carboxybutanoyl)-4-fluoro-6-methoxybenzo[b]thiophen-5-yl)propoxy)-6-methoxythieno[3,2-b]pyridin-2-yl)-2-methyl-4-oxobutanoic acid	632

Example 43: (S)-4-(5-(3-((2-(3-carboxypropanoyl)benzo[b]thiophen-6-yl)oxy)propoxy)-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoic acid

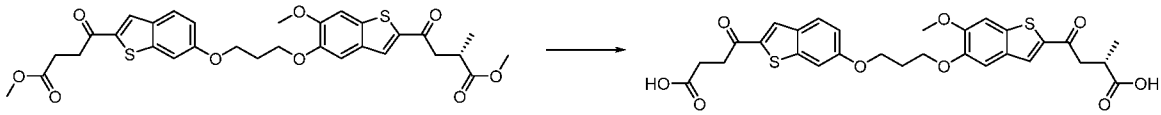


Step 1: Methyl (S)-4-(6-methoxy-5-(3-((2-(4-methoxy-4-oxobutanoyl)benzo[b]thiophen-6-yl)oxy)propoxy)benzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate



A mixture of (S)-methyl 4-(5-(3-hydroxypropoxy)-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate (16mg, 0.044mmol), methyl 4-(6-hydroxybenzo[b]thiophen-2-yl)-4-oxobutanoate (14mg, 0.052mmol), (E)-diazene-1,2-diylbis(piperidin-1-ylmethanone) (28mg, 0.11mmol), and Ph_3P (29mg, 0.11mmol) in THF (1.0mL) was degassed with Ar and was then stirred at 20°C for 18h. The reaction mixture was then diluted with DMSO (1.0mL) and filtered. The mixture was then directly purified by reverse phase HPLC (ACN in water, 0.1% TFA modifier, C-18 stationary phase) to afford methyl (S)- 4-(6-methoxy-5-(3-((2-(4-methoxy-4-oxobutanoyl)benzo[b]thiophen-6-yl)oxy)propoxy)benzo[b] thiophen-2-yl)-2-methyl-4-oxobutanoate. LCMS ($C_{31}H_{33}O_9S_2$) (ES, m/z): 613 $[M+H]^+$.

Step 2: (S)-4-(5-(3-((2-(3-carboxypropanoyl)benzo[b]thiophen-6-yl)oxy)propoxy)-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoic acid

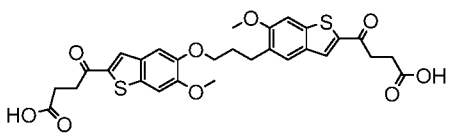
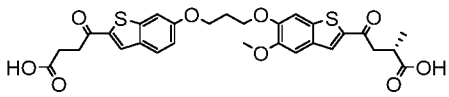
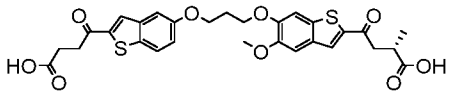
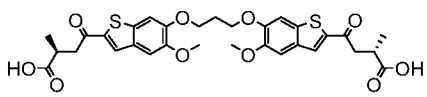
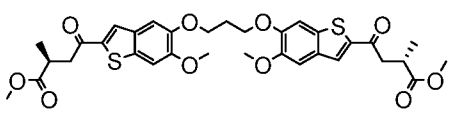


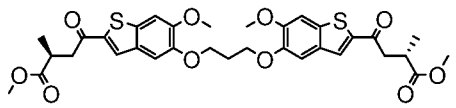
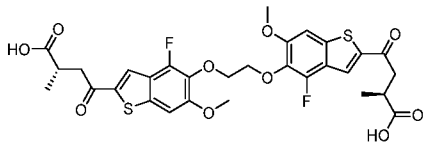
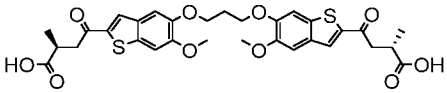
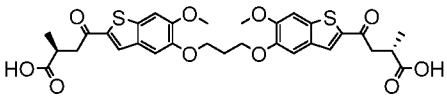
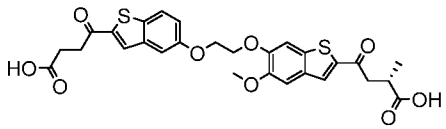
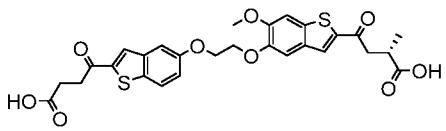
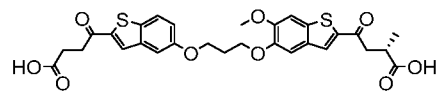
NaOH (5.0M in water, 21μL, 0.11mmol) was added to a mixture of methyl (S)-4-(6-methoxy-5-(3-((2-(4-methoxy-4-oxobutanoyl)benzo[b]thiophen-6-yl)oxy)propoxy)benzo[b] thiophen-2-yl)-2-methyl-4-oxobutanoate (6.3mg, 10μmol) in MeOH (1.0mL) at RT. The reaction mixture was stirred and heated to 50°C for 2h. The crude reaction mixture was cooled to RT, quenched with TFA (16μL, 0.21mmol), diluted with DMSO (1.0mL), and then filtered. The filtrate was then purified directly by reverse phase HPLC (ACN in water, 0.1% TFA modifier, C-18 stationary phase) to afford (S)-4-(5-(3-((2-(3-carboxypropanoyl)benzo[b] thiophen-6-yl)oxy) propoxy)-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoic acid. LCMS ($C_{29}H_{29}O_9S_2$) (ES, m/z): 585 $[M+H]^+$. ^1H NMR (500MHz, DMSO-d_6) δ 12.22 (s, 2H),

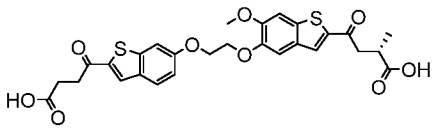
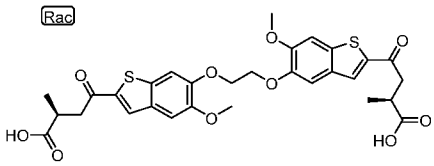
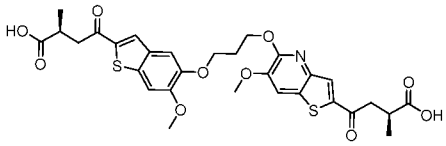
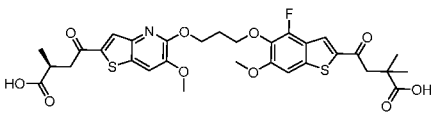
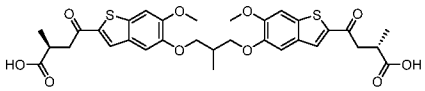
8.33 (s, 1H), 8.19 (s, 1H), 7.94 (d, *J*=7.8Hz, 1H), 7.69 (s, 1H), 7.63 (s, 1H), 7.55 (s, 1H), 7.15 (d, *J*=7.6Hz, 1H), 4.34-4.18 (m, 4H), 3.89 (s, 3H), 3.44-3.25 (m, 3H), 3.13-3.05 (m, 1H), 2.95-2.87 (m, 1H), 2.66-2.60 (m, 2H), 2.34-2.27 (m, 2H), 1.25-1.14 (m, 3H).

Examples 44 through 59, and 160, as shown in Table 15 below, were or may be prepared according to procedures analogous to those outlined in Example 43 above using the appropriate starting materials, described in the Preparations or Intermediates above, or as obtained from commercial sources.

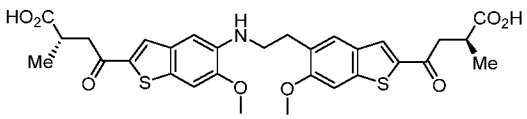
Table 15

Example	Structure	Name	Mass $[M+H]^+$
44		4-(5-(3-((2-(3-carboxy propanoyl)-6-methoxybenzo [b]thiophen-5-yl)oxy)propyl)-6-methoxybenzo[b]thiophen-2-yl)-4-oxobutanoic acid	585
45		(S)-4-(6-(3-((2-(3-carboxy propanoyl)benzo[b]thiophen-6-yl)oxy)propoxy)-5-methoxy benzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoic acid	585
46		(S)-4-(6-(3-((2-(3-carboxy propanoyl)benzo[b]thiophen-5-yl)oxy)propoxy)-5-methoxy benzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoic acid	585
47		(2S,2'S)-4,4'-((propane-1,3-diylbis(oxy))bis(5-methoxybenzo[b]thiophene-6,2-diyl))bis(2-methyl-4-oxobutanoic acid)	629
48		methyl (S)-4-(6-methoxy-5-(3-((5-methoxy-2-((S)-4-methoxy-3-methyl-4-oxobutanoyl)benzo[b] thiophen-6-yl)oxy)propoxy) benzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate	657

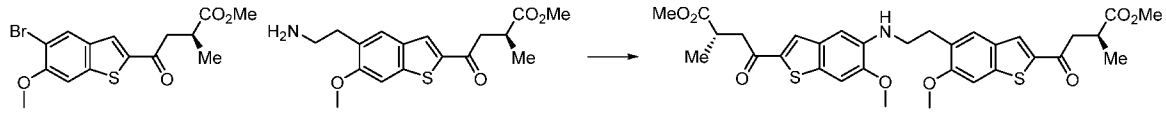
Example	Structure	Name	Mass $[M+H]^+$
49		dimethyl 4,4'-((propane-1,3-diylbis(oxy))bis(6-methoxybenzo[b]thiophene-5,2-diyl))(2S,2'S)-bis(2-methyl-4-oxobutanoate)	657
50		(2S,2'S)-4,4'-((ethane-1,2-diylbis(oxy))bis(4-fluoro-6-methoxybenzo[b]thiophene-5,2-diyl))bis(2-methyl-4-oxobutanoic acid)	673 [M+Na]
51		(S)-4-(5-(3-((2-((S)-3-carboxybutanoyl)-5-methoxybenzo[b]thiophen-6-yl)oxypropoxy)-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoic acid	629
52		(2S,2'S)-4,4'-((propane-1,3-diylbis(oxy))bis(6-methoxybenzo[b]thiophene-5,2-diyl))bis(2-methyl-4-oxobutanoic acid)	629
53		(S)-4-(6-(2-((2-(3-carboxypropanoyl)benzo[b]thiophen-5-yl)oxy)ethoxy)-5-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoic acid	571
54		(S)-4-(5-(2-((2-(3-carboxypropanoyl)benzo[b]thiophen-5-yl)oxy)ethoxy)-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoic acid	571
55		(S)-4-(5-(3-((2-(3-carboxypropanoyl)benzo[b]thiophen-5-yl)oxy)propoxy)-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoic acid	585

Example	Structure	Name	Mass $[M+H]^+$
56		(S)-4-(5-(2-((2-(3-carboxy propanoyl)benzo[b]thiophen-6-yl)oxy)ethoxy)-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoic acid	571
57		rac-(R)-4-(5-(2-((2-((R)-3-carboxybutanoyl)-5-methoxybenzo[b]thiophen-6-yl)oxy)ethoxy)-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoic acid	637 [M+Na]
58		(S)-4-(5-(3-((2-((S)-3-carboxybutanoyl)-6-methoxybenzo[b]thiophen-5-yl)oxy)propoxy)-6-methoxythieno[3,2-b]pyridin-2-yl)-2-methyl-4-oxobutanoic acid	630
59		(S)-4-(5-(3-((2-(3-carboxybutanoyl)-6-methoxythieno[3,2-b]pyridin-5-yl)oxy)propoxy)-4-fluoro-6-methoxybenzo[b]thiophen-2-yl)-2,2-dimethyl-4-oxobutanoic acid	662
160		(2S,2'S)-4,4'-(((2-methylpropane-1,3-diyl)bis(oxy))bis(6-methoxybenzo[b]thiophene-5,2-diyl))bis(2-methyl-4-oxobutanoic acid)	643

Example 60: (2S)-4-{5-[2-({2-[(3S)-3-carboxybutanoyl]-6-methoxy-1-benzothiophen-5-yl}amino)ethyl]-6-methoxy-1-benzothiophen-2-yl}-2-methyl-4-oxobutanoic acid

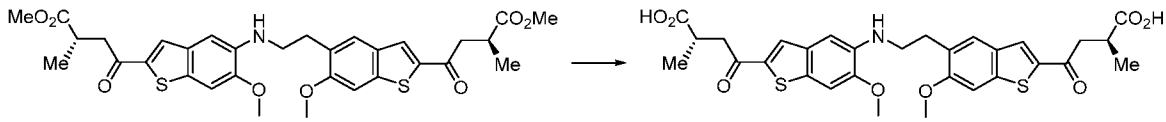


Step 1: methyl (2S)-4-{6-methoxy-5-[2-({6-methoxy-2-[(3S)-4-methoxy-3-methyl-4-oxobutanoyl]-1-benzothiophen-5-yl}amino)ethyl]-1-benzothiophen-2-yl}-2-methyl-4-oxobutanoate



To a mixture of methyl (2S)-4-(5-bromo-6-methoxy-1-benzothiophen-2-yl)-2-methyl-4-oxobutanoate (54mg, 0.14mmol), Rac BINAP Pd G3 (12mg, 0.012mmol), and Cs_2CO_3 (117mg, 0.360mmol) under N_2 was added a suspension of methyl (2S)-4-[5-(2-aminoethyl)-6-methoxy-1-benzothiophen-2-yl]-2-methyl-4-oxobutanoate (54mg, 0.120 mmol) in toluene (1.6mL). The reaction mixture was sparged with N_2 for 45min, then heated to 110°C for 12h. Upon cooling to RT, the mixture was purified by silica gel column chromatography (EtOAc in Hex) to afford methyl (2S)-4-{6-methoxy-5-[2-({6-methoxy-2-[(3S)-4-methoxy-3-methyl-4-oxobutanoyl]-1-benzothiophen-5-yl}amino)ethyl]-1-benzothio-phen-2-yl}-2-methyl-4-oxobutanoate. LCMS ($C_{32}H_{35}NO_8S_2Na$) (ES, m/z): 648 $[M+Na]^+$.

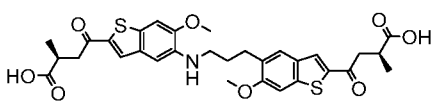
Step 2: (2S)-4-{5-[2-({2-[(3S)-3-carboxybutanoyl]-6-methoxy-1-benzothiophen-5-yl}amino)ethyl]-6-methoxy-1-benzothiophen-2-yl}-2-methyl-4-oxobutanoic acid



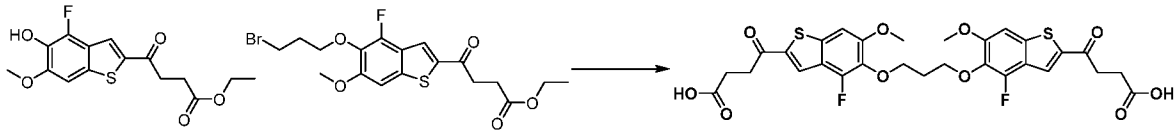
To a mixture of methyl (2S)-4-{6-methoxy-5-[2-({6-methoxy-2-[(3S)-4-methoxy-3-methyl-4-oxobutanoyl]-1-benzothiophen-5-yl}amino)ethyl]-1-benzothiophen-2-yl}-2-methyl-4-oxobutanoate (20mg, 0.03mmol) in THF (280µL), MeOH (280µL) and water (70µL) was added $LiOH \cdot H_2O$ (13mg, 0.32 mmol) in one portion at RT. The reaction mixture was stirred at RT for 2h, then quenched with aq HCl (2N, 170uL). The mixture was diluted with DMSO, and the resulting mixture was filtered. The filtrate was purified by RP-HPLC [C18 column, water (0.1% TFA)-CH_3CN] to afford (2S)-4-{5-[2-({2-[(3S)-3-carboxybutanoyl]-6-methoxy-1-benzothiophen-5-yl}amino)ethyl]-6-methoxy-1-benzothiophen-2-yl}-2-methyl-4-oxobutanoic acid. LCMS ($C_{30}H_{32}NO_8S_2$) (ES, m/z): 598 $[M+H]^+$. ^1H NMR (500MHz, DMSO-*d6*): δ 12.12 (br, 2H), 8.27 (s, 1H), 8.11 (s, 1H), 7.82 (s, 1H), 7.66 (s, 1H), 7.44 (s, 1H), 7.07 (s, 1H), 3.98 (s, 3H), 3.90 (s, 3H), 3.41 (dd, *J*=17.5, 8.6Hz, 2H), 3.36 (t, *J*=6.5Hz, 2H), 3.14-2.96 (m, 4H), 2.94-2.84 (m, 2H), 1.18 (d, *J*=7.1Hz, 6H).

Example 61, as shown in Table 16 below, was or may be prepared according to procedures analogous to those outlined in Example 60 above using the appropriate starting materials, described in the Preparations or Intermediates above, or as obtained from commercial sources.

Table 16

Example	Structure	Name	Mass $[M+H]^+$
61		(S)-4-(5-(3-((2-((S)-3-carboxy butanoyl)-6-methoxybenzo[b] thiophen-5-yl)amino)propyl)-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoic acid	612

Example 62: 4,4'-((propane-1,3-diylbis(oxy))bis(4-fluoro-6-methoxybenzo[b]thiophene-5,2-diyl))bis(4-oxobutanoic acid)

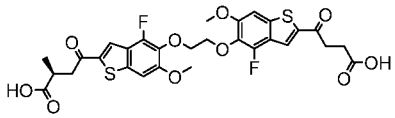
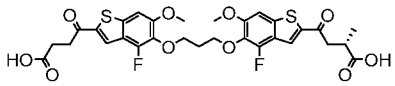
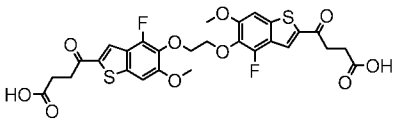
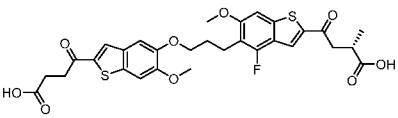
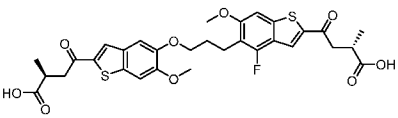
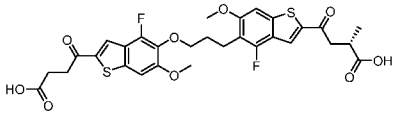


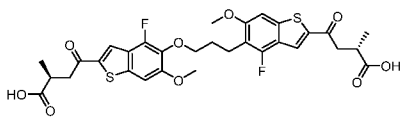
To a mixture of ethyl 4-(4-fluoro-5-hydroxy-6-methoxybenzo[b]thiophen-2-yl)-4-oxobutanoate (0.024g, 0.073mmol), ethyl 4-(5-(3-bromopropoxy)-4-fluoro-6-methoxybenzo[b] thiophen-2-yl)-4-oxobutanoate (0.025g, 0.056mmol) and Cs_2CO_3 (0.091g, 0.28mmol) was added ACN (1.0mL). The reaction mixture was then heated to 65°C for 1h. Upon cooling to RT, the mixture was diluted with THF, filtered, and the filtrate was concentrated under reduced pressure. To the resulting residue was added THF (1.0mL), MeOH (0.20mL), water (0.5mL), and LiOH (0.013g, 0.56mmol). The mixture was allowed to stir at RT for 2h. The mixture was then quenched with AcOH, and the mixture was concentrated under reduced pressure. The resulting residue was purified via prep-HPLC (ACN/H_2O with 0.1% TFA) to afford 4,4'-((propane-1,3-diylbis(oxy))bis(4-fluoro-6-methoxybenzo[b]thiophene-5,2-diyl))bis(4-oxobutanoic acid). LCMS ($C_{29}H_{27}F_2O_{10}S_2$) (ES, m/z): 637 $[M+H]^+$. ^1H NMR (600MHz, DMSO-d_6) δ 8.26 (s, 2H), 7.55 (s, 2H), 4.31-4.24 (m, 4H), 3.99-3.80 (m, 6H), 3.34-3.32 (m, 4H), 2.60 (q, J=6.4Hz, 4H), 2.09 (dt, J=11.5, 5.8Hz, 2H).

Examples 63 through 65 and 161 through 164, as shown in Table 17 below, were or may be prepared according to procedures analogous to those outlined in Example 62 above using the

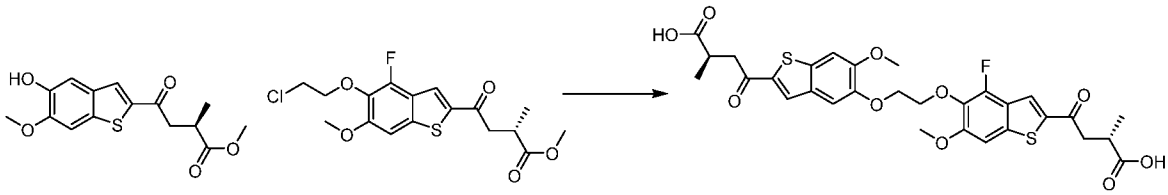
appropriate starting materials, described in the Preparations or Intermediates above, or as obtained from commercial sources.

Table 17

Example	Structure	Name	Mass $[M+H]^+$
63		(S)-4-(5-(2-((2-(3-carboxy propanoyl)-4-fluoro-6-methoxy benzo[b]thiophen-5-yl)oxy) ethoxy)-4-fluoro-6-methoxybenzo [b]thiophen-2-yl)-2-methyl-4-oxobutanoic acid	637
64		(S)-4-(5-(3-((2-(3-carboxy propanoyl)-4-fluoro-6-methoxybenzo[b]thiophen-5-yl)oxy) propoxy)-4-fluoro-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoic acid	650
65		4,4'-((ethane-1,2-diylbis(oxy)) bis(4-fluoro-6-methoxybenzo [b]thiophene-5,2-diyl))bis(4-oxobutanoic acid)	623
161		(S)-4-(5-(3-((2-(3-carboxypropanoyl)-6-methoxybenzo[b]thiophen-5-yl)oxy)propyl)-4-fluoro-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoic acid	617
162		(S)-4-(5-(3-(2-((S)-3-carboxybutanoyl)-4-fluoro-6-methoxybenzo[b]thiophen-5-yl)propoxy)-6-methoxybenzo [b]thiophen-2-yl)-2-methyl-4-oxobutanoic acid	631
163		(S)-4-(5-(3-((2-(3-carboxy propanoyl)-4-fluoro-6-methoxy benzo[b]thiophen-5-yl)oxy) propyl)-4-fluoro-6-methoxybenzo [b]thiophen-2-yl)-2-methyl-4-oxobutanoic acid	635

Example	Structure	Name	Mass $[M+H]^+$
164		(S)-4-(5-(3-((2-((S)-3-carboxybutanoyl)-4-fluoro-6-methoxybenzo[b]thiophen-5-yl)oxy)propyl)-4-fluoro-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoic acid	649

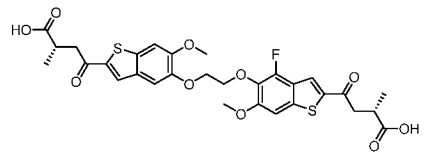
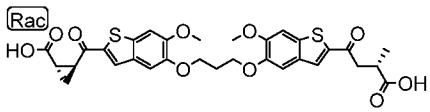
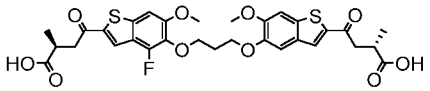
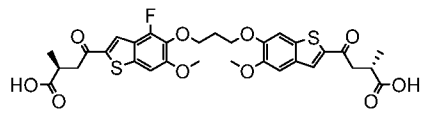
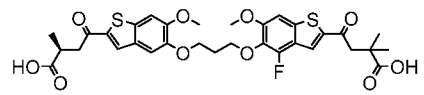
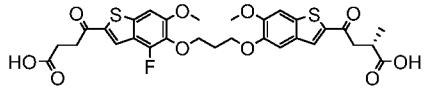
Example 66: (R)-4-(5-(2-((2-((S)-3-carboxybutanoyl)-4-fluoro-6-methoxybenzo[b]thiophen-5-yl)oxy)ethoxy)-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoic acid

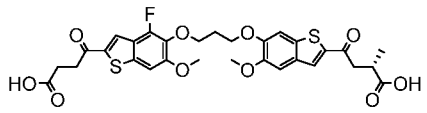
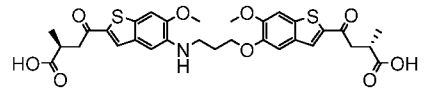
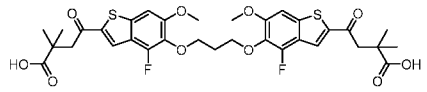
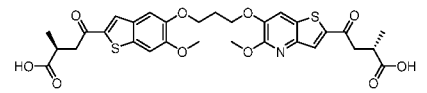
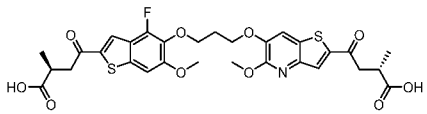
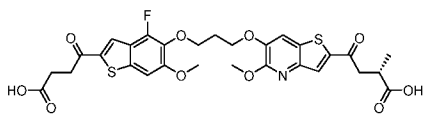
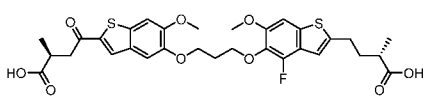


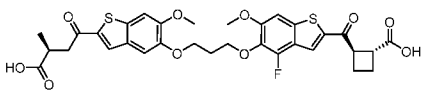
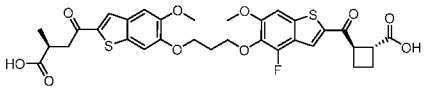
(R)-methyl 4-(5-hydroxy-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate (0.20M in DMF, 500µL, 0.11mmol) was added to a stirring suspension of methyl (S)-4-(5-(2-chloroethoxy)-4-fluoro-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate (0.20M in DMF, 500µL, 0.11mmol) and K_2CO_3 (30mg, 0.2mmol). The reaction mixture was heated to 100°C for 18h. Upon cooling to RT, DMSO (500µL) was added, and the reaction mixture was filtered. Water (500µL) was added followed by $LiOH \cdot H_2O$ (30 mg, 0.7 mmol), and the reaction mixture was stirred at RT for 18h. The mixture was filtered, and the product was purified mass-directed reverse phase C-18 column chromatography (ACN/water + 0.1% TFA) to afford (R)-4-(5-(2-((2-((S)-3-carboxybutanoyl)-4-fluoro-6-methoxybenzo[b]thiophen-5-yl)oxy)ethoxy)-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoic acid. LCMS ($C_{30}H_{29}FO_{10}S_2Na$) (ES, m/z): 655 $[M+Na]^+$. ^1H NMR (DMSO-d_6) δ: 12.18 (s, 2H), 8.31 (s, 1H), 8.18 (s, 1H), 7.58 (s, 2H), 7.50 (s, 1H), 4.50-4.41 (m, 2H), 4.36-4.30 (m, 2H), 3.88 (s, 3H), 3.75 (s, 3H), 3.46 (dd, J=18, 9Hz, 1H), 3.40 (dd, J=17, 9Hz, 1H), 3.10 (ddd, J=22, 18, 5Hz, 2H), 2.95-2.81 (m, 2H), 1.24-1.14 (m, 6H).

Examples 67 through 74 and 165 throught 171, as shown in Table 18 below, were or may be prepared according to procedures analogous to those outlined in Example 66 above using the appropriate starting materials, described in the Preparations or Intermediates above, or as obtained from commercial sources.

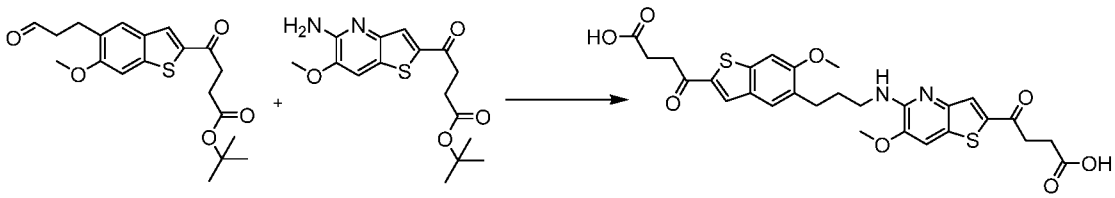
Table 18

Example	Structure	Name	Mass $[M+H]^+$
67		(S)-4-(5-(2-((2-((S)-3-carboxybutanoyl)-4-fluoro-6-methoxybenzo[b]thiophen-5-yl)oxy)ethoxy)-6-methoxy benzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoic acid	633
68		rac-(1R,2R)-2-(5-(3-((2-((R)-3-carboxybutanoyl)-6-methoxy benzo[b]thiophen-5-yl)oxy) propoxy)-6-methoxybenzo [b]thiophene-2-carbonyl) cyclopropane-1-carboxylic acid	627
69		(S)-4-(5-(3-((2-((S)-3-carboxybutanoyl)-4-fluoro-6-methoxybenzo[b]thiophen-5-yl)oxy)propoxy)-6-methoxy benzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoic acid	647
70		(S)-4-(6-(3-((2-((S)-3-carboxybutanoyl)-4-fluoro-6-methoxybenzo[b]thiophen-5-yl)oxy)propoxy)-5-methoxy benzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoic acid	647
71		(S)-4-(5-(3-((2-(3-carboxy butanoyl)-6-methoxybenzo[b] thiophen-5-yl)oxy)propoxy)-4-fluoro-6-methoxybenzo[b] thiophen-2-yl)-2,2-dimethyl-4-oxobutanoic acid	683 $[M+Na]^+$
72		(S)-4-(5-(3-((2-(3-carboxypropanoyl)-4-fluoro-6-methoxybenzo[b]thiophen-5-yl)oxy)propoxy)-6-methoxy benzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoic acid	633

Example	Structure	Name	Mass $[M+H]^+$
73		(S)-4-(6-(3-((2-(3-carboxy propanoyl)-4-fluoro-6-methoxy benzo[b]thiophen-5-yl)oxy) propoxy)-5-methoxybenzo[b] thiophen-2-yl)-2-methyl-4-oxobutanoic acid	633
74		(S)-4-(5-(3-((2-((S)-3-carboxy butanoyl)-6-methoxybenzo[b] thiophen-5-yl)amino)propoxy)-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoic acid	628
165		4,4'-((propane-1,3-diylbis(oxy))bis(4-fluoro-6-methoxybenzo[b]thiophene-5,2-diyl))bis(2,2-dimethyl-4-oxobutanoic acid)	693
166		(S)-4-(5-(3-((2-((S)-3-carboxy butanoyl)-5-methoxythieno[3,2-b]pyridin-6-yl)oxy)propoxy)-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoic acid	630
167		(S)-4-(6-(3-((2-((S)-3-carboxy butanoyl)-4-fluoro-6-methoxy benzo[b]thiophen-5-yl)oxy) propoxy)-5-methoxythieno[3,2-b]pyridin-2-yl)-2-methyl-4-oxobutanoic acid	648
168		(S)-4-(6-(3-((2-(3-carboxy propanoyl)-4-fluoro-6-methoxy benzo[b]thiophen-5-yl)oxy) propoxy)-5-methoxythieno[3,2-b]pyridin-2-yl)-2-methyl-4-oxobutanoic acid	634
169		(S)-4-(5-(3-((2-((S)-3-carboxy butyl)-4-fluoro-6-methoxy benzo[b]thiophen-5-yl)oxy) propoxy)-6-methoxybenzo[b] thiophen-2-yl)-2-methyl-4-oxobutanoic acid	633

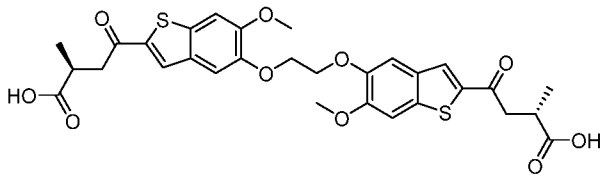
Example	Structure	Name	Mass $[M+H]^+$
170		trans-2-(5-(3-((2-((S)-3-carboxy butanoyl)-6-methoxybenzo[b] thiophen-5-yl)oxy)propoxy)-4-fluoro-6-methoxybenzo[b] thiophene-2-carbonyl) cyclobutanecarboxylic acid	659
171		trans-2-(5-(3-((2-((S)-3-carboxy butanoyl)-5-methoxy benzo[b]thiophen-6-yl)oxy) propoxy)-4-fluoro-6-methoxy benzo[b]thiophene-2-carbonyl) cyclobutanecarboxylic acid	659

Example 75: 4-(5-((3-(2-(3-carboxypropanoyl)-6-methoxybenzo[b]thiophen-5-yl)propyl)amino)-6-methoxythieno[3,2-b]pyridin-2-yl)-4-oxobutanoic acid

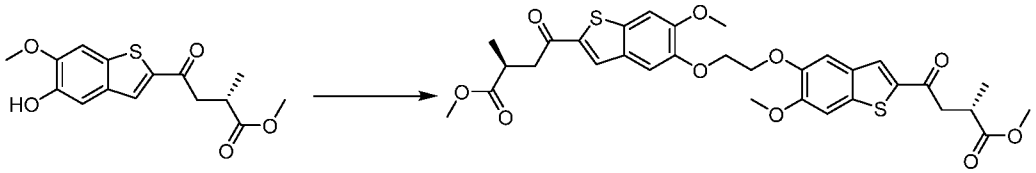


To a 4 mL vial was added *tert*-butyl 4-(6-methoxy-5-(3-oxopropyl)benzo[b] thiophen-2-yl)-4-oxobutanoate (10mg, 0.03mmol), *tert*-butyl 4-(5-amino-6-methoxythieno[3,2-b]pyridin-2-yl)-4-oxobutanoate (8.9mg, 0.027mmol), and THF (0.50mL). To the slurry was added AcOH (0.015mL, 0.27mmol). The mixture was heated to 55°C for 10min. Upon cooling to RT, sodium triacetoxyborohydride (17mg, 0.080mmol) was added. The mixture was then heated to 55°C for 3h. Upon cooling to RT, TFA (1mL) was added, and the mixture was allowed to stir at RT for 1h. The mixture was then concentrated under reduced pressure and then diluted with DMSO (1mL). The mixture was purified by prep-HPLC (ACN/H_2O w/ 0.1% TFA) to afford 4-(5-((3-(2-(3-carboxypropanoyl)-6-methoxybenzo[b]thiophen-5-yl)propyl) amino)-6-methoxythieno [3,2-b]pyridin-2-yl)-4-oxobutanoic acid. LCMS ($C_{28}H_{29}N_2O_8S_2$) (ES, m/z): 585 $[M+H]^+$. ^{1}H NMR (500MHz, DMSO-d_6) δ 12.18 (br, 2H), 8.22 (s, 1H), 8.03 (s, 1H), 7.79 (s, 1H), 7.63 (s, 1H), 7.59 (s, 1H), 6.55 (br s, 1H), 3.90 (s, 3H), 3.88 (s, 3H), 3.48-3.43 (m, 2H), 3.27-3.24 (m, 4H), 2.73 (t, *J*=7.3Hz, 2H), 2.61-2.56 (m, 4H), 1.98-1.91 (m, 2H).

Example 76: (2S,2'S)-4,4'-((ethane-1,2-diylbis(oxy))bis(6-methoxybenzo[b]thiophene-5,2-diyl))bis(2-methyl-4-oxobutanoic acid)

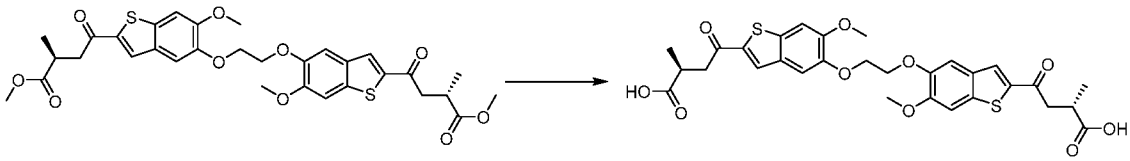


Step 1: dimethyl 4,4'-((ethane-1,2-diylbis(oxy))bis(6-methoxybenzo[b]thiophene-5,2-diyl))(2S,2'S)-bis(2-methyl-4-oxobutanoate)



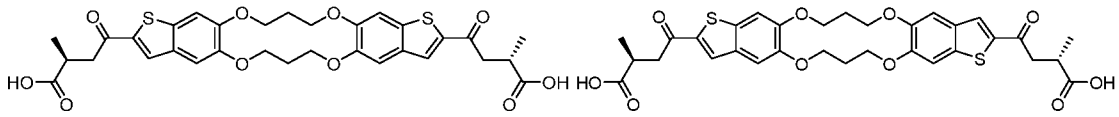
A mixture of methyl (S)-4-(5-hydroxy-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate (50mg, 0.17mmol) and K_2CO_3 (47mg, 0.34mmol) was diluted with DMF (750µL). 1-Bromo-2-chloroethane (18µL, 0.22mmol) was added, and the reaction mixture was heated to 100°C for 18h. The reaction mixture was concentrated under reduced pressure and used without further purification or characterization.

Step 2: (2S,2'S)-4,4'-((ethane-1,2-diylbis(oxy))bis(6-methoxybenzo[b]thiophene-5,2-diyl))bis(2-methyl-4-oxobutanoic acid)

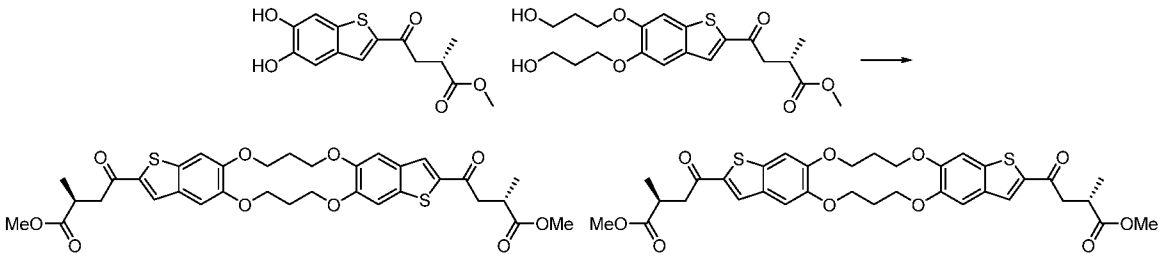


LiOH (16mg, 0.67mmol) was added to a stirring solution of dimethyl 4,4'-((ethane-1,2-diylbis(oxy))bis(6-methoxybenzo[b]thiophene-5,2-diyl))(2S,2'S)-bis(2-methyl-4-oxobutanoate) (50 mg, 0.08 mmol) in THF (340µl)/Water (80µl). The reaction mixture was allowed to stir at RT for 4h. The reaction mixture was filtered and concentrated under reduced pressure. The residue was dissolved in DMSO (4mL) and filtered. The product was purified by mass directed reversed-phase C18 column chromatography (ACN/water with 0.1% TFA) to afford (2S,2'S)-4,4'-(5,5'-(ethane-1,2-diylbis(oxy))bis(6-methoxybenzo[b]thiophene-5,2-diyl))bis(2-methyl-4-oxobutanoic acid). LCMS ($C_{30}H_{30}O_{10}S_2Na$) (ES, m/z): 637 $[M+Na]^+$. ^1H NMR (500MHz, DMSO-d_6) δ: 12.21 (br s, 2H), 8.20 (s, 2H), 7.64 (s, 2H), 7.59 (s, 2H), 4.44 (s, 4H), 3.87 (s, 6H), 3.41 (dd, J=17, 9Hz, 2H), 3.09 (dd, J=17, 5Hz, 2H), 3.05-2.58 (m, 2H), 1.19 (d, J=7Hz, 6H).

Example 77: (2*S*,2'*S*)-4,4'-(7,8,17,18-tetrahydro-6*H*,16*H*-bis[1]benzothieno[5,6-*b*:6',5'-*i*][1,4,8,11] tetraoxacyclotetradecine-2,12-diyl)bis(2-methyl-4-oxobutanoic acid) and Example 78: (2*S*,2'*S*)-4,4'-(7,8,17,18-tetrahydro-6*H*,16*H*-bis[1]benzothieno[5,6-*b*:5',6'-*i*][1,4,8,11]tetraoxacyclotetradecine-2,12-diyl)bis(2-methyl-4-oxobutanoic acid)

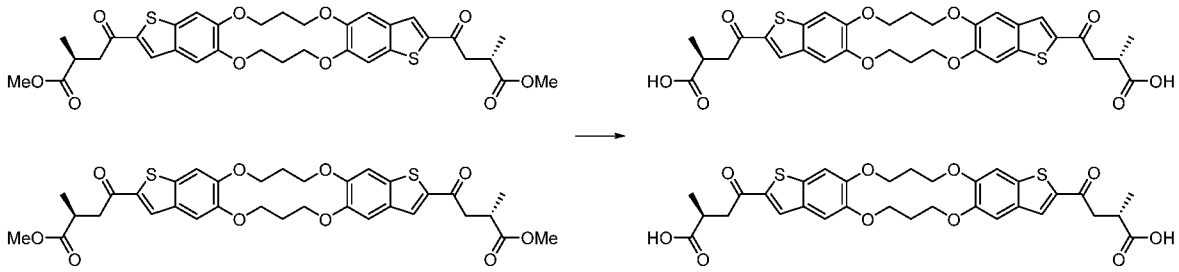


Step 1: dimethyl (2S,2'S)-4,4'-(7,8,17,18-tetrahydro-6H,16H-bis[1]benzothieno[5,6-b:5',6'-i][1,4,8,11]tetraoxacyclotetradecine-2,12-diyl)bis(2-methyl-4-oxobutanoate) and dimethyl (2S,2'S)-4,4'-(7,8,17,18-tetrahydro-6H,16H-bis[1]benzothieno[5,6-b:6',5'-i][1,4,8,11] tetraoxacyclotetradecine-2,12-diyl)bis(2-methyl-4-oxobutanoate)



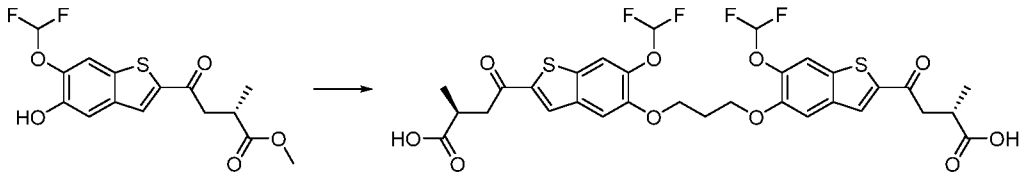
A mixture of methyl (2*S*)-4-(5,6-dihydroxy-1-benzothiophen-2-yl)-2-methyl-4-oxobutanoate (60mg, 0.20mmol), methyl (2*S*)-4-[5,6-bis(3-hydroxypropoxy)-1-benzothiophen-2-yl]-2-methyl-4-oxobutanoate (120mg, 0.20mmol), Ph_3P (193mg, 0.737mmol), and 1,1'-(azodicarbonyl)dipiperidine (186mg, 0.737mmol) in THF (2.0mL) was allowed to stir at RT for 18h. The mixture was then filtered and purified by reverse phase HPLC (gradient of MeCN/water with 0.1% TFA) to afford a 1:1 mixture of dimethyl (2*S*,2'*S*)-4,4'-(7,8,17,18-tetrahydro-6*H*,16*H*-bis[1]benzothieno[5,6-*b*:5',6'-*i*][1,4,8,11]tetraoxacyclotetradecine-2,12-diyl)bis(2-methyl-4-oxobutanoate) and dimethyl (2*S*,2'*S*)-4,4'-(7,8,17,18-tetrahydro-6*H*,16*H*-bis[1]benzothieno[5,6-*b*:6',5'-*i*][1,4,8,11]tetraoxacyclotetradecine-2,12-diyl)bis(2-methyl-4-oxobutanoate). LCMS ($C_{34}H_{36}O_{10}S_2Na$) (ES, m/z): 691 $[M+Na]^+$.

Step 2: (2S,2'S)-4,4'-(7,8,17,18-tetrahydro-6H,16H-bis[1]benzothieno[5,6-b:5',6'-i][1,4,8,11] tetraoxacyclotetradecine-2,12-diyl)bis(2-methyl-4-oxobutanoic acid) and (2S,2'S)-4,4'-(7,8,17,18-tetrahydro-6H,16H-bis[1]benzothieno[5,6-b:6',5'-i][1,4,8,11] tetraoxacyclotetradecine-2,12-diyl)bis(2-methyl-4-oxobutanoic acid)



To a stirred solution of a 1:1 mixture of dimethyl (2*S*,2'*S*)-4,4'-(7,8,17,18-tetrahydro-6*H*,16*H*-bis[1]benzothieno[5,6-*b*:5',6'-*i*][1,4,8,11]tetraoxacyclotetradecine-2,12-diyl) bis(2-methyl-4-oxobutanoate) and dimethyl (2*S*,2'*S*)-4,4'-(7,8,17,18-tetrahydro-6*H*,16*H*-bis[1] benzothieno[5,6-*b*:6',5'-*i*][1,4,8,11]tetraoxacyclotetradecine-2,12-diyl)bis(2-methyl-4-oxobutanoate) (67mg, 0.10mmol) in MeOH (1.0mL), THF (1.0mL), and water (0.2mL) was added LiOH (24mg, 1.0mmol). The reaction mixture was allowed to stir for 4h and then purified by reverse phase HPLC (gradient of MeCN/water with 0.1% TFA) to afford a 1:1 mixture of (2*S*, 2'*S*)-4,4'-(7,8,17,18-tetrahydro-6*H*,16*H*-bis[1]benzothieno[5,6-*b*:5',6'-*i*][1,4,8,11] tetraoxacyclo tetradecine-2,12-diyl)bis(2-methyl-4-oxobutanoic acid) and (2*S*,2'*S*)-4,4'-(7,8,17,18-tetrahydro-6*H*,16*H*-bis[1]benzothieno[5,6-*b*:6',5'-*i*][1,4,8,11]tetraoxacyclo-tetradecine-2,12-diyl)bis(2-methyl-4-oxobutanoic acid). LCMS ($C_{32}H_{33}O_{10}S_2$) (ES, m/z): 641 $[M+H]^+$. ^{1}H NMR (500MHz, DMSO-d_6) δ 12.20 (brs, 2H), 8.18 (s, 2H), 7.52 (s, 2H), 7.40 (s, 2H), 4.27-4.18 (m, 8H), 3.42-3.34 (m, 2H), 3.10-3.03 (m, 2H), 2.92-2.85 (m, 2H), 2.29 (brs, 4H), 1.17 (d, *J*=6.8Hz, 6H).

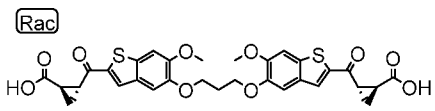
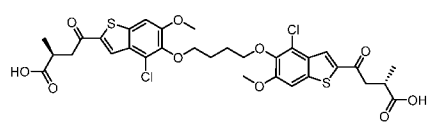
Example 79: (2*S*,2'*S*)-4,4'-(1,3-propanediylbis{oxy[6-(difluoromethoxy)-1-benzothiene-5,2-diyl]})bis(2-methyl-4-oxobutanoic acid)



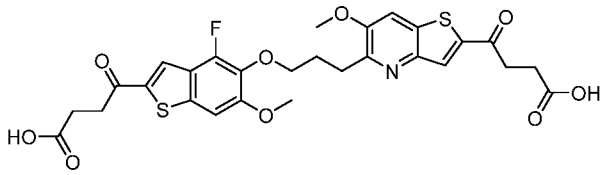
To a stirred solution of methyl (2*S*)-4-[6-(difluoromethoxy)-5-hydroxy-1-benzo thiophen-2-yl]-2-methyl-4-oxobutanoate (54mg, 0.16mmol) and K_2CO_3 (109mg, 0.788mmol) in DMF (0.8mL) was added 1,3-dibromopropane (8µL, 0.08mmol). The mixture was heated to 50°C for 4h. Upon cooling to RT, the mixture was treated with LiOH (2M in water, 790µL, 1.58mmol) and allowed to stir at RT for 4h. The mixture was then concentrated under reduced pressure and purified by RP-HPLC (gradient of MeCN/water with 0.1% TFA) to afford (2*S*,2'*S*)-4,4'-(1,3-propanediylbis{oxy[6-(difluoromethoxy)-1-benzothiene-5,2-diyl]})bis(2-methyl-4-oxobutanoic acid). LCMS ($C_{31}H_{28}F_4O_{10}S_2Na$) (ES, m/z): 723 $[M+23]^+$. ^{1}H NMR (500MHz, DMSO-d_6) δ 12.25 (s, 2H), 8.27 (s, 2H), 7.94 (s, 2H), 7.73 (s, 2H), 7.20 (t, *J*=74.0Hz, 2H), 4.33-4.29 (m, 4H), 3.46-3.40 (m, 2H), 3.12 (dd, *J*=17.5, 4.9Hz, 2H), 2.94-2.87 (m, 2H), 2.37-2.32 (m, 2H), 1.19 (d, *J*=7.1Hz, 6H).

Examples 80 and 172, as shown in Table 19 below, were or may be prepared according to procedures analogous to those outlined in Example 79 above using the appropriate starting materials, described in the Preparations or Intermediates above, or as obtained from commercial sources.

Table 19

Example	Structure	Name	Mass $[M+H]^+$
80		rac-(1S,2S)-2-(5-(3-((2-((1R, 2R)-2-carboxy-cyclopropane-1-carbonyl)-6-methoxybenzo[b] thiophen-5-yl)oxy) propoxy)-6-methoxybenzo [b]thiophene-2-carbonyl) cyclopropane-1-carboxylic acid	625
172		(2S,2'S)-4,4'-(5,5'-(butane-1,4-diylbis(oxy))bis(4-chloro-6-methoxybenzo[b]thiophene-5,2-diyl))bis(2-methyl-4-oxobutanoic acid)	711, 713

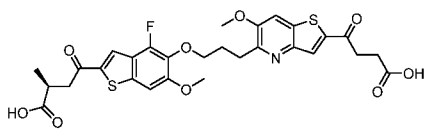
Example 173: (4-(5-(3-((2-(3-Carboxypropanoyl)-4-fluoro-6-methoxybenzo[b]thiophen-5-yl)oxy)propyl)-6-methoxythieno[3,2-b]pyridin-2-yl)-4-oxobutanoic acid



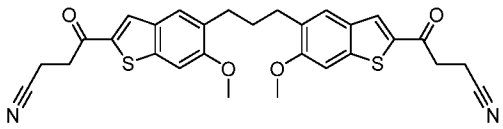
tert-Butyl 4-(5-(3-hydroxypropyl)-6-methoxythieno[3,2-b]pyridin-2-yl)-4-oxobutanoate (76mg, 0.20mmol) was added to a vial containing ethyl 4-(4-fluoro-5-hydroxy-6-methoxybenzo[b]thiophen-2-yl)-4-oxobutanoate (250mg, 0.77mmol), PS-TPP (319mg, 0.600mmol), DIAD (0.117ml, 0.600mmol), and THF (3ml). The reaction mixture was stirred for 3h at RT. The reaction mixture was filtered, washed with THF (5ml). MeOH (2ml), water (3ml), and LiOH (48mg, 2.0mmol) were added, and the reaction mixture was stirred for an additional 2h. The reaction mixture was then quenched with HOAc and concentrated under reduced pressure. The residue was suspended in DCM (5ml), and TFA (1ml) was added. The reaction mixture was stirred for 1h. The reaction mixture was then concentrated under reduced pressure, and the residue was purified by reverse phase HPLC (acetonitrile/water gradient with 0.1% TFA) to afford (4-(5-(3-((2-(3-carboxypropanoyl)-4-fluoro-6-methoxybenzo[b]thiophen-5-yl)oxy)propyl)-6-methoxythieno[3,2-b]pyridin-2-yl)-4-oxobutanoic acid. LCMS ($C_{28}H_{27}FNO_9S_2$) (ES, m/z): 604 $[M+H]^+$. ^1H NMR (600MHz, DMSO-d_6) δ 8.34 (s, 1H), 8.31 (s, 1H), 8.07 (s, 1H), 7.57 (s, 1H), 4.17 (t, J=6.3Hz, 2H), 3.93 (s, 3H), 3.90 (s, 3H), 3.35-3.29 (m, 4H), 3.10-3.04 (m, 2H), 2.63-2.58 (m, 4H), 2.18-2.13 (m, 2H).

Example 174, as shown in Table 20 below, was or may be prepared according to procedures analogous to those outlined in Example 173 above using the appropriate starting materials, described in the Preparations or Intermediates above, or as obtained from commercial sources.

Table 20

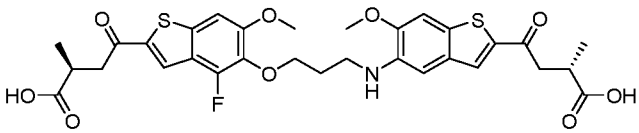
Example	Structure	Name	Mass $[M+H]^+$
174		(S)-4-(5-(3-(2-(3-carboxypropanoyl)-6-methoxythieno[3,2-b]pyridin-5-yl)propoxy)-4-fluoro-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoic acid	618

Example 175: 4,4'-(Propane-1,3-diylbis(6-methoxybenzo[b]thiophene-5,2-diyl))bis(4-oxobutanenitrile)



4-(5-Bromo-6-methoxybenzo[b]thiophen-2-yl)-4-oxobutanenitrile (35mg, 0.11mmol), nickel(II) bromide ethylene glycol dimethyl ether complex (10mg, 0.033mmol), manganese (24mg, 0.44mmol), NaI (8mg, 0.06mmol) and 4,4'-dimethoxy-2,2'-bipyridine (7mg, 0.03mmol) were combined in a vial. A solution of 4-(5-(3-bromopropyl)-6-methoxybenzo[b] thiophen-2-yl)-4-oxobutanenitrile (40mg, 0.11mmol) in DMPU (1.1ml) was added to the vial. 5% v/v solutions in DMPU of Py (88µl, 0.055mmol) and TMS-Cl (84µl, 0.033mmol) were added to the reaction mixture. The reaction mixture was degassed with Ar for 5min, and then stirred and heated at 90°C for 2h. The reaction mixture was cooled to RT, diluted with DMSO (2ml), and filtered. The filtrate was purified by reverse phase HPLC (ACN/water with TFA modifier) to afford 4,4'-(propane-1,3-diylbis(6-methoxybenzo[b]thiophene-5,2-diyl))bis(4-oxobutanenitrile). LCMS ($C_{29}H_{27}N_2O_4S_2$) (ES, m/z): 531 $[M+H]^+$. ^{1}H NMR (499MHz, DMSO-d_6) δ 8.26 (s, 2H), 7.78 (s, 2H), 7.61 (s, 2H), 3.89 (s, 6H), 3.55-3.45 (m, 4H), 2.81-2.76 (m, 4H), 2.74-2.69 (m, 4H), 1.95-1.90 (m, 2H).

Example 176: (S)-4-(5-((3-((2-((S)-3-Carboxybutanoyl)-4-fluoro-6-methoxybenzo[b]thiophen-5-yl)oxy)propyl)amino)-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoic acid

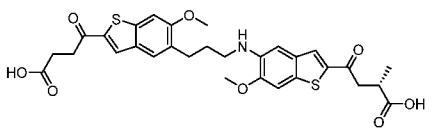


A mixture of (S)-methyl 4-(5-amino-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate (37mg, 0.12mmol), (S)-methyl 4-(5-(3-bromopropoxy)-4-fluoro-6-methoxy benzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate (54mg, 0.12mmol), and potassium carbonate (67mg, 0.48mmol) was degassed with Ar. DMF (1.0ml) was added to the mixture, and the reaction mixture was stirred and heated at 60°C for 2 days. The reaction mixture was cooled to RT and then NaOH (1.0 M in water, 0.48ml, 0.48mmol) was added to the reaction mixture. The

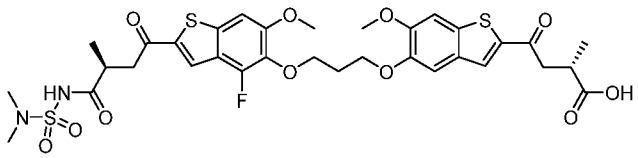
mixture was further diluted with DMSO (1.5ml) and then stirred at RT for 1h. The reaction mixture was quenched with TFA (0.056ml, 0.72mmol) and filtered. The filtrate was purified by reverse phase HPLC (ACN/water with 0.1% TFA) to afford (S)-4-(5-((3-((2-((S)-3-carboxy butanoyl)-4-fluoro-6-methoxybenzo[b]thiophen-5-yl)oxy)propyl)amino)-6-methoxybenzo[b] thiophen-2-yl)-2-methyl-4-oxobutanoic acid. LCMS ($C_{31}H_{33}FNO_9S_2$) (ES, m/z): 646 $[M+H]^+$. ^1H NMR (499MHz, DMSO-d_6) δ 8.32 (s, 1H), 8.11 (s, 1H), 7.60 (s, 1H), 7.45 (s, 1H), 7.04 (s, 1H), 4.17 (t, *J*=5.9Hz, 2H), 3.92 (s, 3H), 3.90 (s, 3H), 3.47 (dd, *J*=17.6, 8.6Hz, 1H), 3.43-3.34 (m, 3H), 3.17-3.05 (m, 2H), 2.94-2.95 (m, 2H), 2.09-2.02 (m, 2H), 1.20-1.15 (m, 6H).

Example 177, as shown in Table 21 below, was or may be prepared according to procedures analogous to those outlined in Example 176 above using the appropriate starting materials, described in the Preparations or Intermediates above, or as obtained from commercial sources.

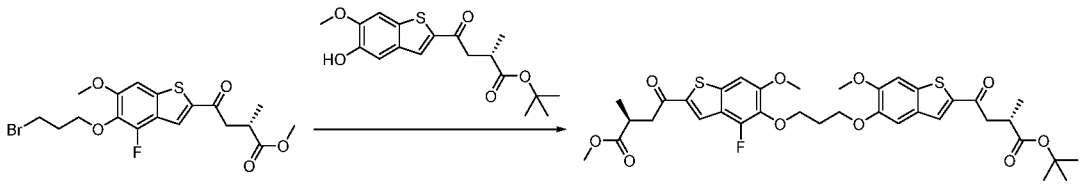
Table 21

Example	Structure	Name	Mass $[M+H]^+$
177		(S)-4-(5-((3-(2-(3-carboxy propanoyl)-6-methoxybenzo[b] thiophen-5-yl)propyl)amino)-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoic acid	598

Example 178: (S)-4-(5-(3-((2-((S)-4-((N,N-Dimethylsulfamoyl)amino)-3-methyl-4-oxobutanoyl)-4-fluoro-6-methoxybenzo[b]thiophen-5-yl)oxy)propoxy)-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoic acid

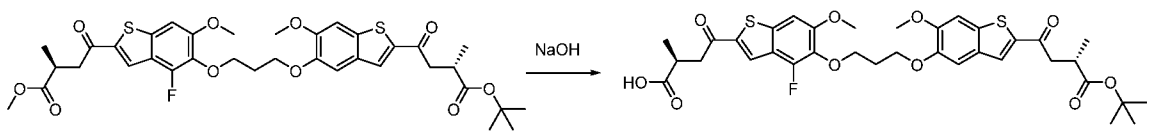


Step 1: tert-*Butyl (S)-4-(5-(3-((4-fluoro-6-methoxy-2-((S)-4-methoxy-3-methyl-4-oxobutanoyl) benzo[b]thiophen-5-yl)oxy)propoxy)-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate*



A mixture of (S)-methyl 4-(5-(3-bromopropoxy)-4-fluoro-6-methoxybenzo[b] thiophen-2-yl)-2-methyl-4-oxobutanoate (111mg, 0.248mmol), (S)-*tert*-butyl 4-(5-hydroxy-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate (87mg, 0.25mmol), and potassium carbonate (137mg, 0.993mmol) was degassed with Ar. DMF (1.Ar) was added to the mixture, and the reaction mixture was stirred and heated at 40°C for 18h. The reaction mixture was cooled to RT and then diluted with EtOAc and water. The organic layer was separated, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (EtOAc/Hex) to afford *tert*-butyl (S)-4-(5-(3-((4-fluoro-6-methoxy-2-((S)-4-methoxy-3-methyl-4-oxobutanoyl)benzo[b]thiophen-5-yl)oxy)propoxy)-6-methoxybenzo [b]thiophen-2-yl)-2-methyl-4-oxobutanoate. LCMS ($C_{36}H_{42}FO_{10}S_2$) (ES, m/z): 739 $[M+Na]^+$. ^1H NMR (499MHz, DMSO-d_6) δ 8.30 (s, 1H), 8.21 (s, 1H), 7.59 (s, 1H), 7.57 (s, 1H), 7.51 (s, 1H), 4.26 (q, *J*=5.9Hz, 4H), 3.86 (s, 3H), 3.85 (s, 3H), 3.60 (s, 3H), 3.48 (dd, *J*=17.7, 8.7Hz, 1H), 3.39-3.33 (m, 1H), 3.23 (dd, *J*=17.7, 5.0Hz, 1H), 3.07 (dd, *J*=17.1, 5.0Hz, 1H), 3.02-2.93 (m, 1H), 2.91-2.81 (m, 1H), 2.23-2.18 (m, 2H), 1.35 (s, 9H), 1.20-1.15 (m, 6H).

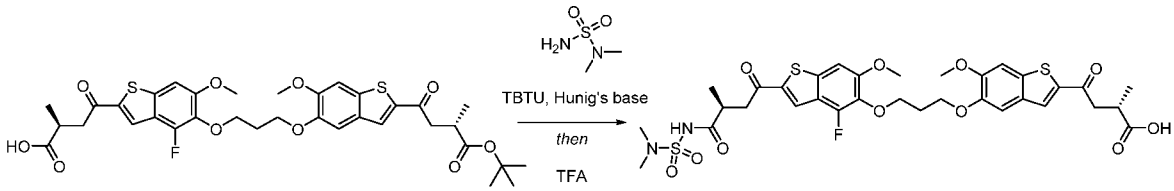
*Step 2: (S)-4-(5-(3-((2-((S)-4-(*tert-*Butoxy)-3-methyl-4-oxobutanoyl)-6-methoxybenzo[b]thiophen-5-yl)oxy)propoxy)-4-fluoro-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoic acid*



NaOH (1.0M in water, 0.94ml, 0.94mmol) was added to a mixture of (S)-*tert*-butyl 4-(5-(3-((4-fluoro-6-methoxy-2-((S)-4-methoxy-3-methyl-4-oxobutanoyl)-benzo[b] thiophen-5-yl)oxy)propoxy)-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate (135mg, 0.188mmol) in THF (0.94ml) and MeOH (0.94ml). The mixture was stirred at RT for oneh. The reaction mixture was quenched with HCl (2.0 M in water, 0.47ml, 0.94mmol) and diluted with EtOAc and water. The organic layer was separated, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford (S)-4-(5-(3-((2-((S)-4-(*tert*-butoxy)-3-methyl-4-

oxobutanoyl)-6-methoxybenzo[b]thiophen-5-yl)oxy)propoxy)-4-fluoro-6-methoxybenzo[b] thiophen-2-yl)-2-methyl-4-oxobutanoic acid. LCMS ($C_{35}H_{40}FO_{10}S_2$) (ES, m/z): 725 $[M+Na]^+$.

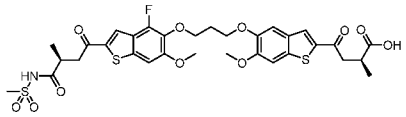
Step 3: (S)-4-(5-(3-((2-((S)-4-((N,N-Dimethylsulfamoyl)amino)-3-methyl-4-oxobutanoyl)-4-fluoro-6-methoxybenzo[b]thiophen-5-yl)oxy)propoxy)-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoic acid



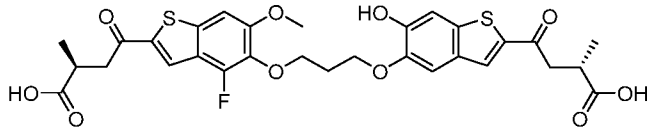
Hunig's base (0.062ml, 0.36mmol) and TBTU (23mg, 0.071mmol) were added to a mixture of (S)-4-(5-(3-((2-((S)-4-(*tert*-butoxy)-3-methyl-4-oxobutanoyl)-6-methoxy-benzo[b] thiophen-5-yl)oxy)propoxy)-4-fluoro-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoic acid (50mg, 0.071mmol) in DCM (0.7ml). The mixture was stirred at RT for 30min. N,N-dimethylsulfamide (11mg, 0.085mmol) was added and the mixture was stirred for an additional 4h. TFA (0.055ml, 0.71mmol) was then added and the mixture was stirred and heated to 45°C for 2h. The mixture was cooled to RT and was concentrated under reduced pressure. The residue was purified by reverse phase HPLC (ACN/water with 0.1% TFA) to afford (S)-4-(5-(3-((2-((S)-4-((N,N-dimethylsulfamoyl)amino)-3-methyl-4-oxobutanoyl)-4-fluoro-6-methoxy benzo[b]thiophen-5-yl)oxy)propoxy)-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoic acid. LCMS ($C_{33}H_{38}FN_2O_{11}S_3$) (ES, m/z): 775 $[M+Na]^+$. ^{1}H NMR (499MHz, DMSO-d_6) δ 11.50 (s, 1H), 8.30 (s, 1H), 8.22 (s, 1H), 7.59 (s, 1H), 7.56 (s, 1H), 7.52 (s, 1H), 4.26 (q, *J*=5.9Hz, 4H), 3.87 (s, 3H), 3.85 (s, 3H), 3.48 (dd, *J*=17.8, 9.8Hz, 1H), 3.40 (dd, *J*=17.3, 8.4Hz, 1H), 3.16 (dd, *J*=17.8, 4.4Hz, 1H), 3.09 (dd, *J*=17.3, 5.3Hz, 1H), 3.00-2.94 (m, 1H), 2.94-2.87 (m, 1H), 2.79 (s, 6H), 2.23-2.17 (m, 2H), 1.21-1.15 (m, 6H).

Example 179, as shown in Table 22 below, was or may be prepared according to procedures analogous to those outlined in Example 178 above using the appropriate starting materials, described in the Preparations or Intermediates above, or as obtained from commercial sources.

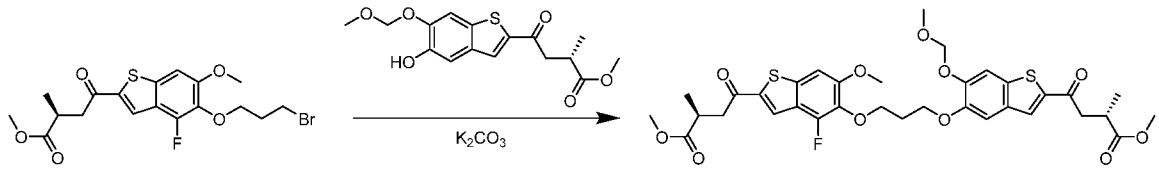
Table 22

Example	Structure	Name	Mass $[M+H]^+$
179		(S)-4-(5-(3-((4-fluoro-6-methoxy-2-((S)-3-methyl-4-(methylsulfonamido)-4-oxobutanoyl)-benzo[b]thiophen-5-yl)oxy)propoxy)-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoic acid	724

Example 180: (S)-4-(5-(3-((2-((S)-3-Carboxybutanoyl)-4-fluoro-6-methoxybenzo[b]thiophen-5-yl)oxy)propoxy)-6-hydroxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoic acid

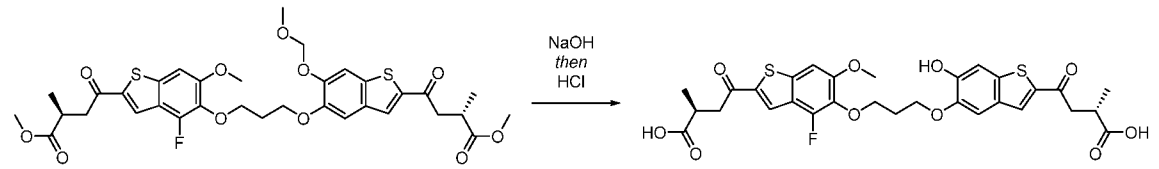


Step 1: Methyl (S)-4-(5-(3-((4-fluoro-6-methoxy-2-((S)-4-methoxy-3-methyl-4-oxobutanoyl)benzo[b]thiophen-5-yl)oxy)propoxy)-6-(methoxymethoxy)benzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate



A mixture of methyl (S)-4-(5-(3-bromopropoxy)-4-fluoro-6-methoxybenzo[b] thiophen-2-yl)-2-methyl-4-oxobutanoate (30mg, 0.068mmol), methyl (S)-4-(5-hydroxy-6-(methoxymethoxy)benzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate (23mg, 0.068mmol), and potassium carbonate (38mg, 0.27mmol) was degassed with Ar. DMF (0.5ml) was added to the mixture, and the reaction mixture was stirred and heated at 40°C for 24h. The reaction mixture was cooled to RT and then used without workup or purification in the subsequent reaction. LCMS ($C_{34}H_{38}FO_{11}S_2$) (ES, m/z): 705 $[M+H]^+$.

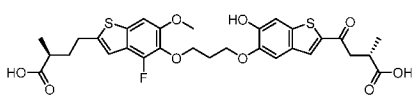
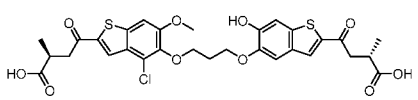
Step 2: (S)-4-(5-(3-((2-((S)-3-carboxybutanoyl)-4-fluoro-6-methoxybenzo[b]thiophen-5-yl)oxy)propoxy)-6-hydroxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoic acid

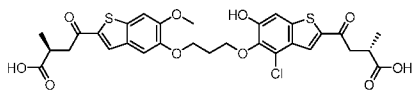
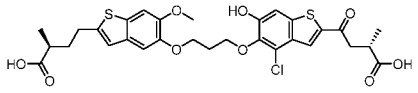
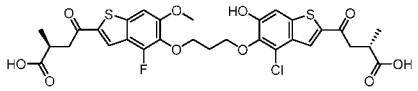
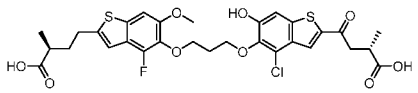
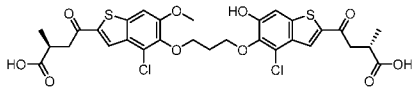
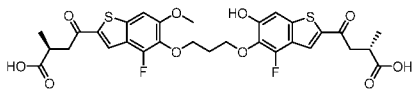


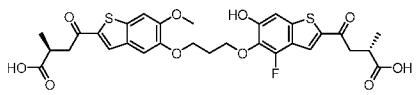
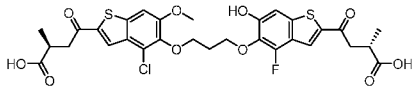
NaOH (0.55ml, 1.0M in water, 0.55mmol) was added to a solution of methyl (S)-4-(5-(3-((4-fluoro-6-methoxy-2-((S)-4-methoxy-3-methyl-4-oxobutanoyl)benzo[b]thiophen-5-yl)oxy)propoxy)-6-(methoxymethoxy)benzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoate (48mg, 0.068mmol) in DMSO (2.5ml) at 20°C. The reaction mixture was then stirred at 20°C for 15min. The reaction mixture was quenched with HCl (0.280ml, 37% in water, 3.41mmol). The reaction mixture was stirred at 20°C for 20h. The reaction mixture was filtered. The residue was purified by reverse phase HPLC (ACN/water with 0.1% TFA) to afford (S)-4-(5-(3-((2-((S)-3-carboxybutanoyl)-4-fluoro-6-methoxybenzo[b]thiophen-5-yl)oxy)propoxy)-6-hydroxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoic acid. LCMS ($C_{30}H_{30}FO_{10}S_2$) (ES, m/z): 633 $[M+H]^+$. ^1H NMR (499MHz, DMSO-d_6) δ 12.17 (s, 2H), 9.70 (s, 1H), 8.30 (s, 1H), 8.17 (s, 1H), 7.57 (s, 1H), 7.48 (s, 1H), 7.33 (s, 1H), 4.31-4.26 (m, 4H), 3.87 (s, 3H), 3.46 (dd, *J*=17.6, 8.6Hz, 1H), 3.38 (dd, *J*=17.2, 8.4Hz, 1H), 3.13 (dd, *J*=17.6, 5.1Hz, 1H), 3.06 (dd, *J*=17.2, 5.3Hz, 1H), 2.91-2.85 (m, 2H), 2.24-2.18 (m, 2H), 1.19 (d, *J*=7.2Hz, 6H).

Examples 181 through 190, as shown in Table 23 below, were or may be prepared according to procedures analogous to those outlined in Example 180 above using the appropriate starting materials, described in the Preparations or Intermediates above, or as obtained from commercial sources.

Table 23

Example	Structure	Name	Mass $[M+H]^+$
181		(S)-4-(5-(3-((2-((S)-3-carboxybutyl)-4-fluoro-6-methoxybenzo[b]thiophen-5-yl)oxy)propoxy)-6-hydroxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoic acid	619
182		(S)-4-(5-(3-((2-((S)-3-carboxybutanoyl)-4-chloro-6-methoxybenzo[b]thiophen-5-yl)oxy)propoxy)-6-hydroxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoic acid	649

Example	Structure	Name	Mass $[M+H]^+$
183		(S)-4-(5-(3-((2-((S)-3-carboxybutanoyl)-4-chloro-6-hydroxybenzo[b]thiophen-5-yl)oxy)propoxy)-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoic acid	649
184		(S)-4-(5-(3-((2-((S)-3-carboxybutyl)-6-methoxybenzo[b]thiophen-5-yl)oxy)propoxy)-4-chloro-6-hydroxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoic acid	635
185		(S)-4-(5-(3-((2-((S)-3-carboxybutanoyl)-4-chloro-6-hydroxybenzo[b]thiophen-5-yl)oxy)propoxy)-4-fluoro-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoic acid	649 (M-H_2O+ H^+)
186		(S)-4-(5-(3-((2-((S)-3-carboxybutyl)-4-fluoro-6-methoxybenzo[b]thiophen-5-yl)oxy)propoxy)-4-chloro-6-hydroxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoic acid	653
187		(S)-4-(5-(3-((2-((S)-3-carboxybutanoyl)-4-chloro-6-hydroxybenzo[b]thiophen-5-yl)oxy)propoxy)-4-chloro-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoic acid	683, 685
188		(S)-4-(5-(3-((2-((S)-3-carboxybutanoyl)-4-fluoro-6-hydroxybenzo[b]thiophen-5-yl)oxy)propoxy)-4-fluoro-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoic acid	651

Example	Structure	Name	Mass $[M+H]^+$
189		(S)-4-(5-(3-((2-((S)-3-carboxybutanoyl)-4-fluoro-6-hydroxybenzo[b]thiophen-5-yl)oxy)propoxy)-6-methoxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoic acid	633
190		(S)-4-(5-(3-((2-((S)-3-carboxybutanoyl)-4-chloro-6-methoxybenzo[b]thiophen-5-yl)oxy)propoxy)-4-fluoro-6-hydroxybenzo[b]thiophen-2-yl)-2-methyl-4-oxobutanoic acid	667

BIOLOGICAL EVALUATION

The individual compounds described in the Examples herein are defined as STING agonists by (i) binding to the STING protein as evidenced by a reduction in binding of tritiated cGAMP ligand to the STING protein by at least 20% at 20uM (concentration of compound being tested) in a STING Biochemical [3H]cGAMP Competition Assay and (ii) demonstrating interferon production with a 6% or greater induction of IFN-β secretion at 30uM in the THP1 cell assay (where induction caused by cGAMP at 30uM was set at 100%).

[^{3}H]-cGAMP Synthesis

2.3mL of buffer solution containing 80mM TrisCl, 200mM $MgCl_2$, and 20mM NaCl followed by 0.32mL of a 10mM aq solution of GTP was added to a plastic 50mL AMICON tube. A solution of [^{3}H]ATP (21Ci/mmol, 45mCi) in 0.5mL H_2O was then added followed by 1mL of a 1mg/mL solution of DNA (Herring testes activator DNA, Sigma, #D6898) and 53uL of a 47mM solution of cGAS enzyme. Additional H_2O was added to bring the total volume to 10mL.

The reaction was stirred for 2h at 37°C and then added directly to an Amicon Ultra-15 10K centrifuge tube and spun for 1h at 4,000g. The collected solution was then purified on a semi-prep Mono Q column using the following mobile phases:

A: 0.05M TrisCl pH 8.5 adjusted with 1M NaOH

B: 0.05M TrisCl, 0.5M NaCl pH 8.5 adjusted with 1M NaOH

Gradient: 100% A for 5min followed by a linear gradient to 50:50 (A:B) over 25min, 3mL/min, 254nm.

The collected product fractions were pooled and adjusted to a total volume of 30mL with buffer A. A total yield of 15.5mCi of [^{3}H]cGAMP was isolated at a radiochemical purity of 98.0% at a specific activity of 21.5Ci/mmol.

cGAS Enzyme

A recombinant DNA vector was chemically synthesized to express the truncated human cGAS enzyme (residues 161-522). To aid in expression and purification, the amino terminus contains a hexahistidine tag, SUMO tag and TEV cleavage site. The recombinant enzyme was overexpressed in ROSETTA™ 2(DE3) Single Competent Cells (Novagen). Affinity purification was carried out using HIS-Select HF Nickel Affinity Gel (Sigma) followed by size exclusion chromatography using a Hi-Load 26/60 SUPERDEX200 prep grade column (GE Healthcare). Fractions were pooled, concentrated, flash-frozen in liquid nitrogen and stored at -80°C until needed.

^{3}H-cGAMP filtration binding assay (HAQ STING)

The ability of compounds to bind STING is quantified by their ability to compete with tritiated cGAMP ligand for human STING receptor membrane using a radioactive filter-binding assay. The binding assay employs STING receptor obtained from *Trichoplusia ni* cell membranes (*T.ni*; Expression Systems, cat # 94-002F, www.expressionsystems.com) overexpressing full-length HAQ STING and tritiated cGAMP ligand.

The basic HAQ STING filtration assay protocol is as follows:

The compounds were serially titrated by the Hamilton STARPlus CORE in a 96-well plate (Greiner, # 651201) using a 1:3 ten-point dose response format. After compound preparation, a 2.2ug/ml working concentration of STING membrane (SEQ. ID. No. 1) was prepared by diluting concentrated membrane into assay buffer (1x PBS; Invitrogen # SH30028.02) and douncing 7x using a manual tissue homogenizer (Wheaton, # 357546). 148uL of prepared membrane was then manually added to each well of a 96-well deep-well polypropylene plate (Fisher Scientific, # 12-566-121). Following membrane addition, 2uL of either titrated test compound, DMSO control (Sigma # 276855), or cold cGAMP control was added to the appropriate wells using a BIOMEK FX. Compound and membrane then preincubated

for 60min at RT to allow compound binding to equilibrate. Following equilibration, 8nM of [^{3}H] c-GAMP ligand was prepared by diluting into assay buffer, and 50uL of this working stock was then manually added to each well of the assay plate. Plates were then incubated at RT for 60min, and the contents of each assay plate were then filtered through a 96-well GF/B filter plate (PerkinElmer, # 6005250) using a TOMTEC MACH III Cell Harvester equipped with 20mM HEPES buffer (Fisher Scientific, # BP299500). The filter plates were then dried at 55°C for 30min using a pressurized oven before 30uL of ULTIMA GOLD F scintillate was added to each well. Tritium levels for each reaction well were then measured using a PerkinElmer TopCount plate reader.

After normalization to controls, the percent activity for each compound concentration was calculated by measuring the amount of remaining radioactivity. The plot of percent activity versus the log of compound concentration was fit with a 4-parameter dose response equation to calculate EC_{50} values.

The final reaction conditions were:

Component	**Volume (uL)**	**Final Concentration**
STING membrane	148	1.5ug/ml
^{3}H-cGAMP	50	2.0nM
Low Control (cold cGAMP)	2	10uM
Test compound/DMSO	2	10uM

Compound concentrations tested were 20.000, 637.00, 2.200, 0.740, 0.247, 0.082, 0.027, 0.009, 0.003, and 0.001μM with 1.0% residual DMSO.

Full-Length STING (HAQ) Virus Generation

STING virus was generated using an insect cell baculovirus system. *Spodoptera frugiperda Sf21* cells (Kempbio, Inc.) were diluted to 5e5 cells/ml in Sf-900II SFM media (LifeTechnologies # 10902088) without antibiotics. The cell suspension was added to each well of a treated 6-well plate (2mL per well, 1e6 cells total), and the cells were allowed to adhere for at least 30min. Meanwhile, a 1mL co-transfection mix was assembled by combining 500ng of HAQ STING [STING(1-379)R71H,G230A,H232R,R293Q-GG-AviTag-GS-HRV3C-HIS8/pBAC1] DNA (Genewiz custom synthesis) with 1mL Sf-900II SFM media containing 10μL Cellfectin® II Reagent (Invitrogen # 10362100) and 100ng viral backbone BestBac 2.0, v-cath/chiA Deleted Linearized Baculovirus DNA (Expression Systems # 91-002). The

transfection mixtures were allowed to incubate for 30min. After incubation, media was gently removed from the adhered cells in the 6-well plate, the 1mL transfection mixtures were added (1mL per well), and the plate was placed in a humidified incubator at 27°C. The following day, 1mL Sf-900II SFM media (no antibiotics) was added to each well of the 6-well plate. After media addition, the cells were allowed to incubate with DNA (SEQ. ID. No. 2) at 27°C for 5-7 days to generate the P0 viral stock. To generate P1 viral stocks, 0.5mL of P0 viral supernatant was added to 50mL uninfected *Sf21* cells (seeded the day prior to infection at a density of $5x10^5$ cells/mL to allow for one overnight doubling) in Sf-900II SFM media containing 5µg/mL gentamicin (Invitrogen #15710072). The infected cells were then incubated at 27°C for 3days while shaking at 110rpm (ATR Biotech Multitron Infors HT #AJ118). On day 3, P1 cultures were counted using a ViCell XR (Beckman Coulter Life Sciences # 383556) to confirm infection had occurred (cell size ≥3µm larger than uninfected cells and viability approximately 85-95%). Cultures were harvested in 50mL conical tubes and centrifuged at 2000xg for 10min at 4°C. The P1 viral supernatants were poured off into clean 50ml centrifuge tubes, and the remaining P1 cell pellets were used to generate Baculovirus Infected Insect Cells (BIICs). Cryopreservation media containing Sf-900II SFM media with 10% heat inactivated FBS, 10% DMSO (Sigma #D2650), and 5µg/ml gentamicin was prepared and sterilized through 0.22µM filter immediately prior to use. P1 cell pellets were resuspended to a density of 2e7 cells/ml and aliquoted into cryovials (1mL per vial). Cryovials were placed in MR. FROSTY™ cell freezers O/N at -80°C and transferred to liquid nitrogen for long term storage the following day. To generate P2 viral stock, 0.5mL of the P1 viral supernatant was added to 50mL uninfected *Sf21* cells (seeded the day prior to infection at a density of $5x10^5$ cells/mL to allow for one overnight doubling) in Sf-900II SFM media containing 5µg/mL gentamicin. These cells were incubated at 27°C for 3days while shaking at 110rpm before harvesting P2 stock with centrifugation at 2000xg for 10min at 4°C. The P2 viral supernatants were poured off and discarded, while the P2 cell pellets were used to generate P2 BIICs following the same protocol described above. The baculovirus generation protocol has been validated to consistently produce P1/P2 BIICs with titers of 2e9 pfu/mL (2e7 cells/mLx100 pfu/cell).

Full-Length STING (HAQ) Expression

To generate STING membranes, P1/P2 BIICs were amplified overnight by adding thawed BIICs to *Sf21* cells seeded at a density of $1.0x10^6$cells/mL. The volume of BIIC used to

infect the culture was calculated using an assumed BIIC titer of 2e9 pfu/ml to achieve an MOI of 10 in the overnight amplification. After culturing overnight, the cells were counted on a ViCell XR to confirm infection had occurred (cell size ≥3µm larger than uninfected cells and viability approximately 80-90%). The volume of infected *Sf21* cells from the overnight amplification used to infect the large-scale expression of *Trichoplusia ni* (*T.ni*; Expression Systems, cat # 94-002F, www.expressionsystems.com) seeded at a density of $1.0x10^6$ in cell media (ESF921 SFM containing 5µg/mL gentamicin) at MOI=2.0 was calculated based on (100 pfu/infected *Sf21* cell). The cells were allowed to express for 48h at 27°C before harvesting the cell pellet, by centrifugation at 3,400xg for 10min at 4°C. *T. ni* cells were counted on a ViCell XR to confirm infection had occurred (cell size ≥3µm larger than uninfected cells and viability approximately 80-90%) prior to harvest.

Full-Length STING (HAQ) Membrane Generation

Buffer stock reagents:

1) 1M HEPES pH 7.5, Teknova, Cat#H1035
2) 5M NaCl, Sigma Aldrich, Cat#S5150-1L
3) KCl, Sigma Aldrich, Cat#319309-500ML
4) Complete EDTA-free protease inhibitor tablets, Roche Diagnostics, Cat#11873580001
5) Benzonase, Universal Nuclease, Pierce, Cat#88702

Lysis buffer [25mM HEPES pH 7.5, 10mM $MgCl_2$, 20mM KCl, (Benzonase 1:5000, Complete Protease Inhibitor tab/50mL)] was added to the pellet of cells expressing full-length STING (HAQ) prepared above at 5mL Lysis buffer per g of cell pellet. The pellet was resuspended and dounced twenty times using a Wheaton Dounce Homogenizer to disrupt the cell membrane. Homogenized lysate was then passed through the EMULSIFLEX-C5 microfluidizer at a pressure close to 5000PSI. The resuspended pellet was centrifuged at 36,000rpm (100,000xg) in a 45Ti rotor ultra-high speed centrifuge for 45min, 4°C. The supernatant was removed. The pellet then was resuspended in wash buffer [(25mM HEPES pH7.5, 1mM $MgCl_2$, 20mM KCl, 1M NaCl (Complete Protease Inhibitor tab/50mL)] at a volume of 50mL pellet/centrifuge tube. The pellet/wash buffer mixture was then homogenized, using a glass homogenizer on ice (20 strokes), followed by centrifugation at 36,000rpm for 45min at 4°C. The supernatant was removed. The wash step was repeated once more. The resulting membrane was resuspended in

20mM HEPES pH 7.5, 500mM NaCl, 10% glycerol, EDTA-free Protease Inhibitors (1tablet/50mL). The protein concentration was measured by Bradford assay (Bio-Rad Protein Assay, Cat# 500-0006), and protein enrichment was determined by SDS-PAGE and confirmed by Western blot. The resuspended membranes were stored at -80°C.

Full-Length HAQ STING [STING(1-379)R71H,G230A,H232R,R293Q-GG-AviTag-GS-HRV3C-HIS8]Amino Acid Sequence:

MPHSSLHPSIPCPRGHGAQKAALVLLSACLVTLWGLGEPPEHTLRYLVLHLASLQLGLL
LNGVCSLAEELHHIHSRYRGSYWRTVRACLGCPLRRGALLLLSIYFYYSLPNAVGPPFT
WMLALLGLSQALNILLGLKGLAPAEISAVCEKGNFNVAHGLAWSYYIGYLRLILPELQA
RIRTYNQHYNNLLRGAVSQRLYILLPLDCGVPDNLSMADPNIRFLDKLPQQTADRAGIK
DRVYSNSIYELLENGQRAGTCVLEYATPLQTLFAMSQYSQAGFSREDRLEQAKLFCQTL
EDILADAPESQNNCRLIAYQEPADDSSFSLSQEVLRHLRQEEKEEVTVGSLKTSAVPSTST
MSQEPELLISGMEKPLPLRTDFSGGGLNDIFEAQKIEWHEGSLEVLFQGPHHHHHHHH
(SEQ. ID. No. 1)

Full-length HAQ [STING(1-379)R71H,G230A,H232R,R293Q-GG-AviTag-GS-HRV3C-HIS8/pBAC1] Plasmid DNA Sequence:

GGAACGGCTCCGCCCACTATTAATGAAATTAAAAATTCCAATTTTAAAAAACGCAG
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GCAACTGTTGGGAAGGGCGATCGGTGCGGGCCTCTTCGCTATTACGCCA
(SEQ. ID. No. 2)

Certain compounds of the disclosure were evaluated in HAQ STING *in vitro* binding assay as described above. The following table tabulates the biological data for these compounds as EC_{50} values.

Table 24: ^{3}H-cGAMP filtration binding assay for HAQ STING

Example	EC_{50} (nM)	Example	EC_{50} (nM)	Example	EC_{50} (nM)
1	6	64	2	128	1082
2	7	65	1	129	3496
3	114	66	4	130	3
4	6	67	40	131	25
5	84	68	50	132	3
6	53	69	1	133	15
7	17	70	1	134	22
8	12	71	3	135	1
9	116	72	1	136	314
10	123	73	1	137	40
11	1762	74	4	138	2
12	2	75	139	139	3
13	158	76	22	140	2146
14	3	77/78 (mixture)	44	141	24
15	107	79	5	142	1
16	22	80	1305	143	75
17	52	81	2	144	15
18	2	82	1	145	143
19	2	83	2	146	55% inhibition at 2,000nM
20	7	84	50	147	18
21	1	85	360	148	395
22	1	86	1	149	4
23	1	87	167	150	213
24	17760	88	3	151	77

Example	EC_{50} (nM)	Example	EC_{50} (nM)	Example	EC_{50} (nM)
25	6	89	2	152	35% inhibition at 2,000nM
26	9	90	58	153	3
27	89	91	7	154	694
28	46	92	3	155	3
29	8	93	1	156	1
30	1001	94	6	157	1
31	3319	95	237	158	2
32	4	96	18	159	3
33	1	97	20	160	1
34	3	98	1	161	1
35	2	99	1	162	1
36	4	100	277	163	1
37	1	101	1	164	1
38	695	102	15	165	2
39	1	103	22	166	8
40	86	104	467	167	4
41	16	105	39	168	13
42	6	106	10	169	1
43	49	107	1	170	1
44	14	108	35	171	9
45	4328	109	10	172	454
46	133	110	18580	173	1
47	14	111	861	174	1
48	12790	112	15540	175	4016
49	44% inhibition at 20,000nM	113	2	176	1
50	1	114	21	177	68
51	3	115	20	178	4
52	2	116	623	179	1
53	146	117	340	180	1
54	804	118	60	181	5
55	14	119	1796	182	1
56	1068	120	38	183	1
57	92	121	1551	184	353
58	1	122	1	185	1
59	1	123	1	186	133
60	19	124	263	187	4

Example	EC_{50} (nM)	Example	EC_{50} (nM)	Example	EC_{50} (nM)
61	33	125	1	188	1
62	2	126	2	189	1
63	1	127	16	190	1

^{3}H-cGAMP filtration binding assay (WT STING)

The ability of compounds to bind STING is quantified by their ability to compete with tritiated cGAMP ligand for human STING receptor membrane using a radioactive filter-binding assay. The binding assay employs STING receptor obtained from *Trichoplusia ni* cell membranes (*T.ni*; Expression Systems, cat # 94-002F, www.expressionsystems.com) overexpressing full-length WT STING and tritiated cGAMP ligand.

The basic WT STING filtration assay protocol is as follows:

16nM of [^{3}H] c-GAMP ligand was prepared by diluting into assay buffer, and 50uL of this working stock was manually added to each well of the assay plate. After ligand addition, 2uL of either titrated test compound, DMSO control (Sigma # 276855), or cold cGAMP control was added to the appropriate wells using a BIOMEK FX. The serially titrated compound was prepared on a Hamilton STARPlus CORE in a 96-well plate (Greiner, # 651201) using a 1:3 ten-point dose response format. Following compound addition, a 2.2ug/ml working concentration of STING membrane (SEQ. ID. No. 3) was prepared by diluting concentrated membrane into assay buffer (1x PBS; Invitrogen # SH30028.02) and douncing 7x using a manual tissue homogenizer (Wheaton, # 357546). 148uL of this prepared membrane was then manually added to each well of a 96-well deep-well polypropylene plate (Fisher Scientific, # 12-566-121). Compound, ligand, and membrane then incubated for 60min at RT before the contents of each assay plate were filtered through a 96-well GF/B filter plate (PerkinElmer, # 6005250) using a TOMTEC MACH III Cell Harvester equipped with 20mM HEPES buffer (Fisher Scientific, # BP299500). The filter plates were then dried at 55°C for 30min using a pressurized VWR oven before 30uL of ULTIMA GOLD F scintillate was added to each well. Tritium levels for each reaction well were then measured using a PerkinElmer TopCount plate reader.

After normalization to controls, the percent activity for each compound concentration was calculated by measuring the amount of remaining radioactivity. The plot of percent activity versus the log of compound concentration was fit with a 4-parameter dose response equation to calculate EC_{50} values.

The final reaction conditions were:

Component	Volume (uL)	Final Concentration
STING membrane	148	1.5ug/ml
^{3}H-cGAMP	50	4.0nM
Low Control (cold cGAMP)	2	10uM
Test compound/DMSO	2	10uM

Compound concentrations tested were 20.000, 637.00, 2.200, 0.740, 0.247, 0.082, 0.027, 0.009, 0.003, and 0.001μM with 1.0% residual DMSO.

Full-Length STING (WT) Virus Generation

STING virus was generated using an insect cell baculovirus system. *Spodoptera frugiperda Sf21* cells (Kempbio, Inc.) were diluted to 5e5 cells/ml in Sf-900II SFM media (LifeTechnologies # 10902088) without antibiotics. The cell suspension was added to each well of a treated 6-well plate (2mL per well, 1e6 cells total), and the cells were allowed to adhere for at least 30min. Meanwhile, a 1mL co-transfection mix was assembled by combining 500ng of WT STING[STING(1-379)H232R-gg-AviTag-gs-HRV3C-HIS8/pBAC1] (Genewiz custom synthesis) with 1mL Sf-900II SFM media containing 10μL CELLFECTIN® II Reagent (Invitrogen # 10362100) and 100ng viral backbone BestBac 2.0, v-cath/chiA Deleted Linearized Baculovirus DNA (Expression Systems # 91-002). The transfection mixtures were allowed to incubate for 30min. After incubation, media was gently removed from the adhered cells in the 6-well plate, the 1mL transfection mixtures were added (1mL per well), and the plate was placed in a humidified incubator at 27°C. The following day, 1mL Sf-900II SFM media (no antibiotics) was added to each well of the 6-well plate. After media addition, the cells were allowed to incubate with DNA [(SEQ. ID. No. 4) and linearized viral backbone BestBac 2.0] at 27°C for 5-7 days to generate the P0 viral stock. To generate P1 viral stocks, 0.5mL of P0 viral supernatant was added to 50mL uninfected *Sf21* cells (seeded the day prior to infection at a density of $5x10^{5}$ cells/mL to allow for one overnight doubling) in Sf-900II SFM media containing 5μg/mL gentamicin (Invitrogen #15710072). The infected cells were then incubated at 27°C for 3days while shaking at 110rpm (ATR Biotech Multitron Infors HT #AJ118). On day 3, P1 cultures were counted using a ViCell XR (Beckman Coulter Life Sciences # 383556) to confirm infection had occurred (cell size ≥3μm larger than uninfected cells and viability approximately 85-95%). Cultures were harvested in 50mL conical tubes and centrifuged at 2000xg for 10min at 4°C. The P1 viral supernatants were poured off into clean 50ml centrifuge tubes, and the remaining P1 cell

pellets were used to generate Baculovirus Infected Insect Cells (BIICs). Cryopreservation media containing Sf-900II SFM media with 10% heat inactivated FBS, 10% DMSO (Sigma #D2650), and 5µg/ml gentamicin was prepared and sterilized through 0.22µM filter immediately prior to use. P1 cell pellets were resuspended to a density of 2e7 cells/ml and aliquoted into cryovials (1mL per vial). Cryovials were placed in MR. FROSTY™ cell freezers O/N at -80°C and transferred to liquid nitrogen for long term storage the following day. To generate P2 viral stock, 0.5mL of the P1 viral supernatant was added to 50mL uninfected *Sf21* cells (seeded the day prior to infection at a density of $5x10^5$ cells/mL to allow for one overnight doubling) in Sf-900II SFM media containing 5µg/mL gentamicin. These cells were incubated at 27°C for 3days while shaking at 110rpm before harvesting P2 stock with centrifugation at 2000xg for 10min at 4°C. The P2 viral supernatants were poured off and discarded, while the P2 cell pellets were used to generate P2 BIICs following the same protocol described above. The baculovirus generation protocol has been validated to consistently produce P1/P2 BIICs with titers of 2e9 pfu/mL (2e7 cells/mLx100pfu/cell).

Full-Length STING (WT) Expression

To generate STING membranes, P1/P2 BIICs were amplified overnight by adding thawed BIICs to *Sf21* cells seeded at a density of $1.0x10^6$ cells/mL. The volume of BIIC used to infect the culture was calculated using an assumed BIIC titer of 2e9 pfu/ml to achieve an MOI of 10 in the overnight amplification. After culturing overnight, the cells were counted on a ViCell XR to confirm infection had occurred (cell size ≥3µm larger than uninfected cells and viability approximately 80-90%). The volume of infected *Sf21* cells from the overnight amplification used to infect the large-scale expression of *Trichoplusia ni* (*T.ni*; Expression Systems, cat # 94-002F, www.expressionsystems.com) seeded at a density of $1.0x10^6$ in cell media (ESF921 SFM containing 5µg/mL gentamicin) at MOI=2.0 was calculated based on (100pfu/infected *Sf21* cell). The cells were allowed to express for 48h at 27°C before harvesting the cell pellet, by centrifugation at 3,400xg for 10min at 4°C. *T. ni* cells were counted on a ViCell XR to confirm infection had occurred (cell size ≥3µm larger than uninfected cells and viability approximately 80-90%) prior to harvest.

Full-Length STING (WT) Membrane Generation

Buffer stock reagents:

1) 1 M HEPES pH 7.5, Teknova, Cat#H1035
2) 5 M NaCl, Sigma Aldrich, Cat#S5150-1L
3) KCl, Sigma Aldrich, Cat#319309-500ML
4) Complete EDTA-free protease inhibitor tablets, Roche Diagnostics, Cat#11873580001
5) Benzonase, Universal Nuclease, Pierce, Cat#88702

Lysis buffer [25mM HEPES pH 7.5, 10mM $MgCl_2$, 20mM KCl, (Benzonase 1:5000, Complete Protease Inhibitor tab/50mL)] was added to the pellet of cells expressing full-length STING (WT) prepared above at 5mL Lysis buffer per g of cell pellet. The pellet was resuspended and dounced twenty times using a Wheaton Dounce Homogenizer to disrupt the cell membrane. Homogenized lysate was then passed through the emulsiflex-C5 microfluidizer at a pressure close to 5000PSI. The resuspended pellet was centrifuged at 36,000rpm (100,000xg) in a 45Ti rotor ultra-high speed centrifuge for 45min, 4°C. The supernatant was removed. The pellet then was resuspended in wash buffer [(25mM HEPES pH 7.5, 1mM $MgCl_2$, 20mM KCl, 1M NaCl (Complete Protease Inhibitor tab/50mL)] at a volume of 50mL/pellet/centrifuge tube. The pellet/wash buffer mixture was then homogenized, using a glass homogenizer on ice (20 strokes), followed by centrifugation at 36,000rpm for 45min at 4°C. The supernatant was removed. The wash step was repeated once more. The resulting membrane was resuspended in 20mM HEPES pH 7.5, 500mM NaCl, 10% glycerol, EDTA-free Protease Inhibitors (1tablet/50mL). The protein concentration was measured by Bradford assay (Bio-Rad Protein Assay, Cat# 500-0006), and protein enrichment was determined by SDS-PAGE and confirmed by Western blot. The resuspended membranes were stored at -80°C.

Full-Length STING WT [STING(1-379)H232R-gg-AviTag-gs-HRV3C-HIS8] Amino Acid Sequence:

MPHSSLHPSIPCPRGHGAQKAALVLLSACLVTLWGLGEPPEHTLRYLVLHLASLQLGLL
LNGVCSLAEELRHIHSRYRGSYWRTVRACLGCPLRRGALLLLSIYFYYSLPNAVGPPFT
WMLALLGLSQALNILLGLKGLAPAEISAVCEKGNFNVAHGLAWSYYIGYLRLILPELQA
RIRTYNQHYNNLLRGAVSQRLYILLPLDCGVPDNLSMADPNIRFLDKLPQQTGDRAGIK
DRVYSNSIYELLENGQRAGTCVLEYATPLQTLFAMSQYSQAGFSREDRLEQAKLFCRTL
EDILADAPESQNNCRLIAYQEPADDSSFSLSQEVLRHLRQEEKEEVTVGSLKTSAVPSTST
MSQEPELLISGMEKPLPLRTDFSGGGLNDIFEAQKIEWHEGSLEVLFQGPHHHHHHHH

(SEQ. ID. No. 3)

Full-length WT STING [STING(1-379)H232R-gg-AviTag-gs-HRV3C-HIS8/pBAC1] plasmid sequence:

GGAACGGCTCCGCCCACTATTAATGAAATTAAAAATTCCAATTTTAAAAAACGCAG
CAAGAGAAACATTTGTATGAAAGAATGCGTAGAAGGAAAGAAAAATGTCGTCGAC
ATGCTGAACAACAAGATTAATATGCCTCCGTGTATAAAAAAAATATTGAACGATTTG
AAAGAAAACAATGTACCGCGCGGCGGTATGTACAGGAAGAGGTTTATACTAAACTG
TTACATTGCAAACGTGGTTTCGTGTGCCAAGTGTGAAAACCGATGTTTAATCAAGGC
TCTGACGCATTTCTACAACCACGACTCCAAGTGTGTGGGTGAAGTCATGCATCTTTT
AATCAAATCCCAAGATGTGTATAAACCACCAAACTGCCAAAAAATGAAAACTGTCG
ACAAGCTCTGTCCGTTTGCTGGCAACTGCAAGGGTCTCAATCCTATTTGTAATTATTG
AATAATAAAACAATTATAAATGTCAAATTTGTTTTTTATTAACGATACAAACCAAAC
GCAACAAGAACATTTGTAGTATTATCTATAATTGAAAACGCGTAGTTATAATCGCTG
AGGTAATATTTAAAATCATTTTCAAATGATTCACAGTTAATTTGCGACAATATAATT
TTATTTTCACATAAACTAGACGCCTTGTCGTCTTCTTCTTCGTATTCCTTCTCTTTTTC
ATTTTTCTCTTCATAAAAATTAACATAGTTATTATCGTATCCATATATGTATCTATCG
TATAGAGTAAATTTTTTGTTGTCATAAATATATATGTCTTTTTTAATGGGGTGTATAG
TACCGCTGCGCATAGTTTTTCTGTAATTTACAACAGTGCTATTTTCTGGTAGTTCTTC
GGAGTGTGTTGCTTTAATTATTAAATTTATATAATCAATGAATTTGGGATCGTCGGTT
TTGTACAATATGTTGCCGGCATAGTACGCAGCTTCTTCTAGTTCAATTACACCATTTT
TTAGCAGCACCGGATTAACATAACTTTCCAAAATGTTGTACGAACCGTTAAACAAAA
ACAGTTCACCTCCCTTTTCTATACTATTGTCTGCGAGCAGTTGTTTGTTGTTAAAAAT
AACAGCCATTGTAATGAGACGCACAAACTAATATCACAAACTGGAAATGTCTATCA
ATATATAGTTGCTGATCAGATCTGATCATGGAGATAATTAAAATGATAACCATCTCG
CAAATAAATAAGTATTTTACTGTTTTCGTAACAGTTTTGTAATAAAAAAACCTATAA
ATATAGGATCCATGCCCCACTCCAGCCTGCATCCATCCATCCCGTGTCCCAGGGGTC
ACGGGGCCCAGAAGGCAGCCTTGGTTCTGCTGAGTGCCTGCCTGGTGACCCTTTGGG
GGCTAGGAGAGCCACCAGAGCACACTCTCCGGTACCTGGTGCTCCACCTAGCCTCCC
TGCAGCTGGGACTGCTGTTAAACGGGGTCTGCAGCCTGGCTGAGGAGCTGCGCCAC
ATCCACTCCAGGTACCGGGGCAGCTACTGGAGGACTGTGCGGGCCTGCCTGGGCTG
CCCCCTCCGCCGTGGGGCCCTGTTGCTGCTGTCCATCTATTTCTACTACTCCCTCCCA

AATGCGGTCGGCCCGCCCTTCACTTGGATGCTTGCCCTCCTGGGCCTCTCGCAGGCA
CTGAACATCCTCCTGGGCCTCAAGGGCCTGGCCCCAGCTGAGATCTCTGCAGTGTGT
GAAAAAGGGAATTTCAACGTGGCCCATGGGCTGGCATGGTCATATTACATCGGATA
TCTGCGGCTGATCCTGCCAGAGCTCCAGGCCCGGATTCGAACTTACAATCAGCATTA
CAACAACCTGCTACGGGGTGCAGTGAGCCAGCGGCTGTATATTCTCCTCCCATTGGA
CTGTGGGGTGCCTGATAACCTGAGTATGGCTGACCCCAACATTCGCTTCCTGGATAA
ACTGCCCCAGCAGACCGGTGACCGTGCTGGCATCAAGGATCGGGTTTACAGCAACA
GCATCTATGAGCTTCTGGAGAACGGGCAGCGGGCGGGCACCTGTGTCCTGGAGTAC
GCCACCCCCTTGCAGACTTTGTTTGCCATGTCACAATACAGTCAAGCTGGCTTTAGC
CGGGAGGATAGGCTTGAGCAGGCCAAACTCTTCTGCCGGACACTTGAGGACATCCT
GGCAGATGCCCCTGAGTCTCAGAACAACTGCCGCCTCATTGCCTACCAGGAACCTGC
AGATGACAGCAGCTTCTCGCTGTCCCAGGAGGTTCTCCGGCACCTGCGGCAGGAGG
AAAAGGAAGAGGTTACTGTGGGCAGCTTGAAGACCTCAGCGGTGCCCAGTACCTCC
ACGATGTCCCAAGAGCCTGAGCTCCTCATCAGTGGAATGGAAAAGCCCCTCCCTCTC
CGCACGGATTTCTCTGGCGGTGGCCTGAACGACATCTTCGAAGCCCAGAAAATCGA
ATGGCATGAAGGCAGCCTGGAAGTGCTGTTCCAGGGCCCACACCACCATCATCACC
ATCACCATTAATGAGCGGCCGCACTCGAGCACCACCACCACCACCACTAACCTAGG
TAGCTGAGCGCATGCAAGCTGATCCGGGTTATTAGTACATTTATTAAGCGCTAGATT
CTGTGCGTTGTTGATTTACAGACAATTGTTGTACGTATTTTAATAATTCATTAAATTT
ATAATCTTTAGGGTGGTATGTTAGAGCGAAAATCAAATGATTTTCAGCGTCTTTATA
TCTGAATTTAAATATTAAATCCTCAATAGATTTGTAAAATAGGTTTCGATTAGTTTCA
AACAAGGGTTGTTTTTCCGAACCGATGGCTGGACTATCTAATGGATTTTCGCTCAAC
GCCACAAAACTTGCCAAATCTTGTAGCAGCAATCTAGCTTTGTCGATATTCGTTTGT
GTTTTGTTTTGTAATAAAGGTTCGACGTCGTTCAAAATATTATGCGCTTTTGTATTTC
TTTCATCACTGTCGTTAGTGTACAATTGACTCGACGTAAACACGTTAAATAGAGCTT
GGACATATTTAACATCGGGCGTGTTAGCTTTATTAGGCCGATTATCGTCGTCGTCCC
AACCCTCGTCGTTAGAAGTTGCTTCCGAAGACGATTTTGCCATAGCCACACGACGCC
TATTAATTGTGTCGGCTAACACGTCCGCGATCAAATTTGTAGTTGAGCTTTTTGGAAT
TATTTCTGATTGCGGGCGTTTTTGGGCGGGTTTCAATCTAACTGTGCCCGATTTTAAT
TCAGACAACACGTTAGAAAGCGATGGTGCAGGCGGTGGTAACATTTCAGACGGCAA
ATCTACTAATGGCGGCGGTGGTGGAGCTGATGATAAATCTACCATCGGTGGAGGCG
CAGGCGGGGCTGGCGGCGGAGGCGGAGGCGGAGGTGGTGGCGGTGATGCAGACGG

CGGTTTAGGCTCAAATGTCTCTTTAGGCAACACAGTCGGCACCTCAACTATTGTACT
GGTTTCGGGCGCCGTTTTTGGTTTGACCGGTCTGAGACGAGTGCGATTTTTTTCGTTT
CTAATAGCTTCCAACAATTGTTGTCTGTCGTCTAAAGGTGCAGCGGGTTGAGGTTCC
GTCGGCATTGGTGGAGCGGGCGGCAATTCAGACATCGATGGTGGTGGTGGTGGTGG
AGGCGCTGGAATGTTAGGCACGGGAGAAGGTGGTGGCGGCGGTGCCGCCGGTATAA
TTTGTTCTGGTTTAGTTTGTTCGCGCACGATTGTGGGCACCGGCGCAGGCGCCGCTG
GCTGCACAACGGAAGGTCGTCTGCTTCGAGGCAGCGCTTGGGGTGGTGGCAATTCA
ATATTATAATTGGAATACAAATCGTAAAAATCTGCTATAAGCATTGTAATTTCGCTA
TCGTTTACCGTGCCGATATTTAACAACCGCTCAATGTAAGCAATTGTATTGTAAAGA
GATTGTCTCAAGCTCGGATCGATCCCGCACGCCGATAACAAGCCTTTTCATTTTTACT
ACAGCATTGTAGTGGCGAGACACTTCGCTGTCGTCGAGGTTTAAACGCTTCCTCGCT
CACTGACTCGCTGCGCTCGGTCGTTCGGCTGCGGCGAGCGGTATCAGCTCACTCAAA
GGCGGTAATACGGTTATCCACAGAATCAGGGGATAACGCAGGAAAGAACATGTGAG
CAAAAGGCCAGCAAAAGGCCAGGAACCGTAAAAAGGCCGCGTTGCTGGCGTTTTTC
CATAGGCTCCGCCCCCCTGACGAGCATCACAAAAATCGACGCTCAAGTCAGAGGTG
GCGAAACCCGACAGGACTATAAAGATACCAGGCGTTTCCCCCTGGAAGCTCCCTCG
TGCGCTCTCCTGTTCCGACCCTGCCGCTTACCGGATACCTGTCCGCCTTTCTCCCTTC
GGGAAGCGTGGCGCTTTCTCATAGCTCACGCTGTAGGTATCTCAGTTCGGTGTAGGT
CGTTCGCTCCAAGCTGGGCTGTGTGCACGAACCCCCCGTTCAGCCCGACCGCTGCGC
CTTATCCGGTAACTATCGTCTTGAGTCCAACCCGGTAAGACACGACTTATCGCCACT
GGCAGCAGCCACTGGTAACAGGATTAGCAGAGCGAGGTATGTAGGCGGTGCTACAG
AGTTCTTGAAGTGGTGGCCTAACTACGGCTACACTAGAAGGACAGTATTTGGTATCT
GCGCTCTGCTGAAGCCAGTTACCTTCGGAAAAAGAGTTGGTAGCTCTTGATCCGGCA
AACAAACCACCGCTGGTAGCGGTGGTTTTTTTGTTTGCAAGCAGCAGATTACGCGCA
GAAAAAAAGGATCTCAAGAAGATCCTTTGATCTTTTCTACGGGGTCTGACGCTCAGT
GGAACGAAAACTCACGTTAAGGGATTTTGGTCATGAGATTATCAAAAAGGATCTTC
ACCTAGATCCTTTTAAATTAAAAATGAAGTTTTAAATCAATCTAAAGTATATATGAG
TAAACTTGGTCTGACAGTTACCAATGCTTAATCAGTGAGGCACCTATCTCAGCGATC
TGTCTATTTCGTTCATCCATAGTTGCCTGACTCCCCGTCGTGTAGATAACTACGATAC
GGGAGGGCTTACCATCTGGCCCCAGTGCTGCAATGATACCGCGAGACCCACGCTCA
CCGGCTCCAGATTTATCAGCAATAAACCAGCCAGCCGGAAGGGCCGAGCGCAGAAG
TGGTCCTGCAACTTTATCCGCCTCCATCCAGTCTATTAATTGTTGCCGGGAAGCTAG

AGTAAGTAGTTCGCCAGTTAATAGTTTGCGCAACGTTGTTGCCATTGCTACAGGCAT
CGTGGTGTCACGCTCGTCGTTTGGTATGGCTTCATTCAGCTCCGGTTCCCAACGATCA
AGGCGAGTTACATGATCCCCCATGTTGTGCAAAAAAGCGGTTAGCTCCTTCGGTCCT
CCGATCGTTGTCAGAAGTAAGTTGGCCGCAGTGTTATCACTCATGGTTATGGCAGCA
CTGCATAATTCTCTTACTGTCATGCCATCCGTAAGATGCTTTTCTGTGACTGGTGAGT
ACTCAACCAAGTCATTCTGAGAATAGTGTATGCGGCGACCGAGTTGCTCTTGCCCGG
CGTCAATACGGGATAATACCGCGCCACATAGCAGAACTTTAAAAGTGCTCATCATTG
GAAAACGTTCTTCGGGGCGAAAACTCTCAAGGATCTTACCGCTGTTGAGATCCAGTT
CGATGTAACCCACTCGTGCACCCAACTGATCTTCAGCATCTTTTACTTTCACCAGCGT
TTCTGGGTGAGCAAAAACAGGAAGGCAAAATGCCGCAAAAAAGGGAATAAGGGCG
ACACGGAAATGTTGAATACTCATACTCTTCCTTTTTCAATATTATTGAAGCATTTATC
AGGGTTATTGTCTCATGAGCGGATACATATTTGAATGTATTTAGAAAAATAAACAAA
TAGGGGTTCCGCGCACATTTCCCCGAAAAGTGCCACCTGACGCGCCCTGTAGCGGCG
CATTAAGCGCGGCGGGTGTGGTGGTTACGCGCAGCGTGACCGCTACACTTGCCAGC
GCCCTAGCGCCCGCTCCTTTCGCTTTCTTCCCTTCCTTTCTCGCCACGTTCGCCGGCTT
TCCCCGTCAAGCTCTAAATCGGGGGCTCCCTTTAGGGTTCCGATTTAGTGCTTTACG
GCACCTCGACCCCAAAAAACTTGATTAGGGTGATGGTTCACGTAGTGGGCCATCGCC
CTGATAGACGGTTTTTCGCCCTTTGACGTTGGAGTCCACGTTCTTTAATAGTGGACTC
TTGTTCCAAACTGGAACAACACTCAACCCTATCTCGGTCTATTCTTTTGATTTATAAG
GGATTTTGCCGATTTCGGCCTATTGGTTAAAAAATGAGCTGATTTAACAAAAATTTA
ACGCGAATTTTAACAAAATATTAACGTTTACAATTTCCCATTCGCCATTCAGGCTGC
GCAACTGTTGGGAAGGGCGATCGGTGCGGGCCTCTTCGCTATTACGCCA
(SEQ. ID. No. 4)

Certain compounds of the disclosure were evaluated in WT STING *in vitro* binding assay as described above. The following table tabulates the biological data for these compounds as EC_{50} values.

Table 25: ^{3}H-cGAMP filtration binding assay for WT STING

Example	EC_{50} (nM)	Example	EC_{50} (nM)	Example	EC_{50} (nM)
1	117	64	4	128	6314
2	14	65	1	129	17080
3	273	66	20	130	25
4	33	67	45	131	242

Example	EC_{50} (nM)	Example	EC_{50} (nM)	Example	EC_{50} (nM)
5	381	68	443	132	10
6	206	69	2	133	147
7	71	70	1	134	233
8	76	71	2	135	5
9	322	72	2	136	10310
10	421	73	4	137	319
11	4560	74	6	138	2
12	3	75	691	139	12
13	625	76	56	140	28% inhibition at 7,000nM
14	21	77/78 (mixture)	224	141	219
15	615	79	12	142	1
16	51	80	12650	143	1452
17	299	81	23	144	93
18	8	82	2	145	47% inhibition at 2,000nM
19	9	83	9	146	18% inhibition at 2,000nM
20	24	84	1058	147	207
21	5	85	9008	148	411
22	1	86	9	149	46
23	2	87	1921	150	1035
24	39% inhibition at 20,000nM	88	109	151	1039
25	23	89	94	152	3% inhibition at 2,000nM
26	19	90	978	153	10
27	362	91	30	154	30% inhibition at 2,000nM
28	112	92	7	155	5
29	44	93	3	156	1
30	7520	94	131	157	1
31	9482	95	813	158	32
32	9	96	628	159	3
33	4	97	69	160	6

Example	EC_{50} (nM)	Example	EC_{50} (nM)	Example	EC_{50} (nM)
34	4	98	1	161	4
35	4	99	3	162	4
36	10	100	2240	163	1
37	2	101	2	164	1
38	1039	102	213	165	3
39	2	103	371	166	117
40	1365	104	8900	167	19
41	50	105	311	168	199
42	12	106	251	169	18
43	151	107	2	170	3
44	64	108	244	171	59
45	14760	109	39	172	15060
46	394	110	15% inhibition at 20,000nM	173	3
47	81	111	50% inhibition at 20,000nM	174	1
48	43% inhibition at 20,000nM	112	11% inhibition at 20,000nM	175	46% inhibition at 20,000nM
49	34% inhibition at 20,000nM	113	23	176	2
50	1	114	264	177	720
51	8	115	295	178	31
52	4	116	4241	179	1
53	713	117	2640	180	1
54	3084	118	4996	181	177
55	48	119	32% inhibition at 20,000nM	182	2
56	3127	120	698	183	3
57	398	121	43% inhibition at 20,000nM	184	29% inhibition at 2,000nM
58	1	122	1	185	1
59	2	123	2	186	756
60	67	124	3060	187	46
61	327	125	5	188	1
62	2	126	19	189	2

Example	EC_{50} (nM)	Example	EC_{50} (nM)	Example	EC_{50} (nM)
63	4	127	270	190	2

IFN-β secretion in THP1 cell culture (5h)

The ability of compounds to stimulate the secretion of interferon-beta from THP1 cells was measured using a human IFN-β AlphaLISA kit (Perkin Elmer, Cat. No. AL265F). The basic protocol is as follows:

A Labcyte Echo 550 acoustic dispenser was used to transfer 120nL of compound dissolved in DMSO into the wells of an empty, sterile 384-well microplate, (Corning, Cat. No. 3712). THP1 cells (American Type Culture Collection, Cat. No. TIB202) previously frozen in Recovery Medium (Life Technologies, Cat. No. 12648-010) were thawed and immediately diluted 10-fold into 37°C assay medium (RPMI 1640 + L-Glutamine & phenol red, Life Technologies, Cat. No. 11875-085; 0.5% heat inactivated fetal bovine serum, Sigma Aldrich, Cat. No. F4135; 1mM Sodium Pyruvate, Life Technologies, Cat. No. 11360-070; 1x non-essential amino acids; Life Technologies, Cat. No. 11140-050). The cell viability and count was ascertained using a Beckman Coulter V-Cell XR cell counter. The cells suspension was centrifuged at 200xg for 5min at RT. Cells were resuspended to a density of $0.8x10^6$/mL in 37°C assay medium. Subsequent liquid transfers were performed using either a Matrix electronic multichannel pipette or an Agilent Bravo Automated Liquid Handling Platform.

The assay was started by dispensing 40µL of the previously prepared cell suspension into the wells of the plate containing compounds. After 5h incubation at 37°C, 5% CO_2 in a humidified atmosphere, the plate of cells and compounds was centrifuged at 200xg for 5min at RT. From each well, 5µL of supernatant was transferred into corresponding wells of a white 384-well plate (Perkin Elmer, Cat. No. 6005620). To these supernatant-containing wells was added 10µL of 5x Anti-Analyte Acceptor beads (50µg/mL of AlphaLISA HiBlock Buffer) and incubated for 30min at RT while shaking on an orbital plate shaker. To each well was added 10µL of 5x Biotinylated Antibody Anti-analyte (5nM in AlphaLISA HiBlock Buffer) and incubated on an orbital plate shaker for 60min at RT or overnight at 4°C. To each well was added 25µL of 2x SA-Donor beads (80µg/mL in AlphaLISA HiBlock Buffer) and incubated for 30-45min at RT in the dark while shaking on an orbital plate shaker. The plate was then read on a Perkin Elmer Envision (λ_{ex}=680nm, λ_{em}=570nm). The percent effect of the AlphaLISA signal at each compound concentration was calculated based on 30uM cGAMP positive controls and

0.3% DMSO negative controls. The plot of percent effect versus the log of compound concentration was fit with a 4-parameter concentration response equation to calculate EC_{50} values. The test compounds were tested at concentrations 30000, 10000, 3333, 1111, 370.4, 123.4, 41.2, 13.7, 4.6, and 1.5nM with 0.3% residual DMSO. The control compound, cGAMP was tested at concentrations 100000, 33333, 11111, 3704, 1235, 412, 137, 46, and 15nM with 0.3% residual DMSO.

Compounds of the disclosure were evaluated for IFN-β secretion in THP1 cell culture as described above. The following table tabulates the biological data for these compounds as percent activation relative to 2'3'-cGAMP at the 30μM concentration.

Table 26: IFN-β secretion in THP1 cell culture (5h)

Example	% Effect at 30μM relative to 2'3'-cGAMP	Example	% Effect at 30μM relative to 2'3'-cGAMP	Example	% Effect at 30μM relative to 2'3'-cGAMP
1	26	64	58	128	83
2	192	65	105	129	50
3	151	66	103	130	61
4	93	67	92	131	38 (@ 3uM)
5	96	68	24	132	131
6	106	69	46	133	80
7	97	70	47	134	89
8	99	71	15	135	100
9	48	72	77	136	37
10	134	73	67	137	155
11	7	74	16	138	89
12	74	75	63	139	57
13	67	76	44	140	31 (@ 3uM)
14	77	77/78 mixture	43	141	143
15	114	79	49	142	81
16	70	80	12	143	26 (@ 3uM)
17	38	81	120	144	8
18	62	82	158	145	59 (@ 3uM)
19	30	83	107	146	27 (@ 3uM)
20	63	84	148	147	71 (@ 3uM)
21	59	85	145	148	41 (@ 3uM)
22	48	86	131	149	70 (@ 3uM)
23	83	87	120	150	52 (@ 3uM)
24	150	88	152	151	63 (@ 3uM)

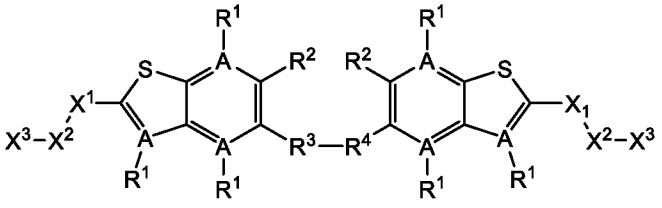
Example	% Effect at 30μM relative to 2'3'-cGAMP	Example	% Effect at 30μM relative to 2'3'-cGAMP	Example	% Effect at 30μM relative to 2'3'-cGAMP
25	136	89	112	152	7 (@ 3uM)
26	129	90	125	153	137 (@ 3uM)
27	113	91	109	154	76 (@ 3uM)
28	116	92	62	155	129 (@ 3uM)
29	107	93	87	156	118 (@ 3uM)
30	103	94	100	157	63% @ 3uM
31	117	95	72	158	43
32	117	96	43	159	99
33	104	97	54	160	18
34	72	98	92	161	106
35	80	99	82	162	98
36	102	100	33 (@ 3uM)	163	135
37	76	101	85	164	131
38	17	102	69	165	21
39	75	103	79	166	34
40	27	104	35	167	66
41	117	105	130	168	102
42	67	106	74	169	64
43	69	107	108	170	86
44	108	108	86	171	97
45	8	109	96	172	16 (@ 3uM)
46	60	110	6	173	127
47	62	111	45 (@ 3uM)	174	88
48	22	112	23	175	13
49	17	113	93	176	44
50	44	114	57	177	80
51	43	115	110	178	107
52	53	116	8	179	79
53	23	117	123	180	121 (@ 3uM)
54	9	118	117	181	104 (@ 3uM)
55	53	119	13	182	147 (@ 3uM)
56	30	120	45 (@ 3uM)	183	127 (@ 3uM)
57	15	121	26	184	10 (@ 3uM)
58	46	122	79	185	122 (@ 3uM)
59	18	123	105	186	56 (@ 3uM)
60	106	124	45 (@ 3uM)	187	128 (@ 3uM)

Example	% Effect at 30μM relative to 2'3'-cGAMP	Example	% Effect at 30μM relative to 2'3'-cGAMP	Example	% Effect at 30μM relative to 2'3'-cGAMP
61	62	125	156	188	104 (@ 3uM)
62	106	126	91	189	111 (@ 3uM)
63	62	127	120	190	126 (@ 3uM)

It will be appreciated that various of the above-discussed and other features and functions, or alternatives thereof, may be desirably combined into many other different systems or applications. It also will be appreciated that various presently unforeseen or unanticipated alternatives, modifications, variations or improvements therein may be subsequently made by those skilled in the art and are also intended to be encompassed by the following claims.

The claims defining the invention are as follows:

1. A compound according to general formula (I):



(I)

or a pharmaceutically acceptable salt thereof, wherein

each A-R^1 is independently selected from the group consisting of C-R^1 and N, wherein each R^1 is independently selected from the group consisting of H, halogen, OR^6, $N(R^6)_2$, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkyl substituted by OR^6, C_1-C_6 alkyl substituted by $N(R^6)_2$, $COOR^6$, and $C(O)N(R^6)_2$;

each R^2 is independently selected from the group consisting of H, halogen, CN, OR^6, $N(R^6)_2$, $COOR^6$, $C(O)N(R^6)_2$, SO_2R^6, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkyl substituted by OR^6, C_2-C_6 alkenyl, C_2-C_6 haloalkenyl, C_2-C_6 alkenyl substituted by OR^6, C_2-C_6 alkynyl, C_2-C_6 haloalkynyl, C_2-C_6 alkynyl substituted by OR^6, C_3-C_6 cycloalkyl, and a 3- to 6-membered heterocyclic ring including 1 to 2 ring members selected from the group consisting of O, S, and $N(R^6)$;

R^3 and R^4 are independently selected from the group consisting of O-(C_1-C_4 alkylene or haloalkylene), C_1-C_5 alkylene or haloalkylene, and $N(R_6)$-(C_1-C_4 alkylene or haloalkylene);

optionally R^4 may be taken together with an adjacent C-R^1 and the atom to which they are attached to form fused ring E, which is selected from phenyl or a 5- or 6-membered heterocyclic ring including 1 to 2 ring members selected from the group consisting of O, S, N, and $N(R^6)$ wherein the bond to R^3 from said ring E is from an atom on said ring E with an open valence for substitution and wherein said phenyl or heterocyclic ring is optionally substituted with one or more members of the group consisting of halogen, C_1-C_3 alkyl, and C_1-C_3 haloalkyl;

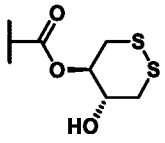
each R^6 is independently selected from the group consisting of H, C_1-C_6 alkyl, and C_1-C_6 haloalkyl;

each X^1 is independently selected from the group consisting of C=O, -CH_2-, -CHF-, and -CF_2-;

each X^2 is independently selected from $(C(R^8)_2)_{(1-3)}$, wherein each R^8 is independently selected from the group consisting of H, halogen, C_1-C_6 alkyl, CN, OR^6, $N(R^6)_2$, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, C_1-C_6 alkyl substituted by OR^6, and C_1-C_6 alkyl substituted by $N(R^6)_2$;

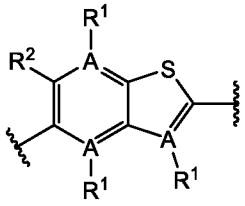
optionally 2 R^8 on different carbon atoms may be taken together, along with the atoms to which they are attached, to form a 3- to 6-membered fused ring; and

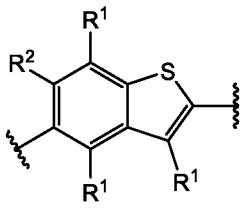
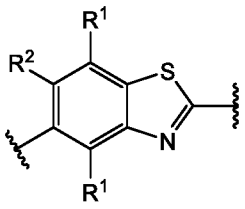
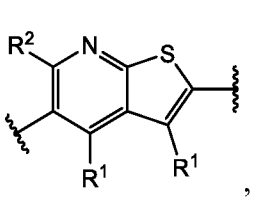
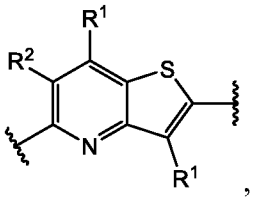
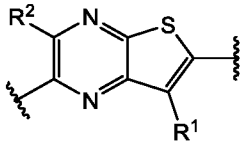
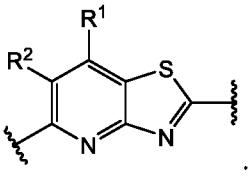
optionally 2 R^8 on a single carbon atom may be taken together, along with the atom to which they are attached, to form a 3- to 6-membered spirocycle;

each X^3 is independently selected from the group consisting of $COOR^6$, $C(O)SR^6$, 

$C(S)OR^6$, , SO_2R^6, $C(O)N(R^9)_2$, and CN; and

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

2. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein each  is independently selected from the group consisting of






, and 
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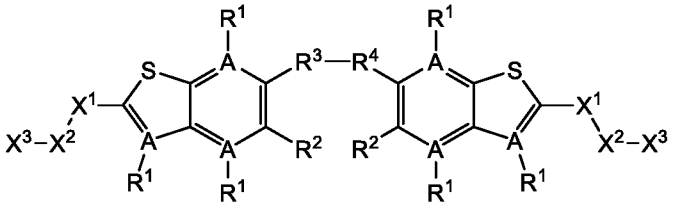
3. A compound of general formula (II):


(II)

or a pharmaceutically acceptable salt thereof, wherein

each A-R^1 is independently selected from the group consisting of C-R^1 and N, wherein each R^1 is independently selected from the group consisting of H, halogen, OR^6, $N(R^6)_2$, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkyl substituted by OR^6, C_1-C_6 alkyl substituted by $N(R^6)_2$, $COOR^6$, and $C(O)N(R^6)_2$;

each R^2 is independently selected from the group consisting of H, halogen, CN, OR^6, $N(R^6)_2$, $COOR^6$, $C(O)N(R^6)_2$, SO_2R^6, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkyl substituted by OR^6, C_2-C_6 alkenyl, C_2-C_6 haloalkenyl, C_2-C_6 alkenyl substituted by OR^6, C_2-C_6 alkynyl, C_2-C_6 haloalkynyl, C_2-C_6 alkynyl substituted by OR^6, C_3-C_6 cycloalkyl, and a 3- to 6-membered heterocyclic ring including 1 to 2 ring members selected from the group consisting of O, S, and $N(R^6)$;

R^3 and R^4 are independently selected from the group consisting of O-(C_1-C_4 alkylene or haloalkylene), C_1-C_5 alkylene or haloalkylene, and $N(R_6)$-(C_1-C_4 alkylene or haloalkylene);

optionally R^4 may be taken together with an adjacent C-R^1 and the atom to which they are attached to form fused ring E, which is selected from phenyl or a 5- or 6-membered heterocyclic ring including 1 to 2 ring members selected from the group consisting of O, S, N, and $N(R^6)$ wherein the bond to R^3 from said ring E is from an atom on said ring E with an open valence for substitution and wherein said phenyl or heterocyclic ring is optionally substituted with one or more members of the group consisting of halogen, C_1-C_3 alkyl, and C_1-C_3 haloalkyl;

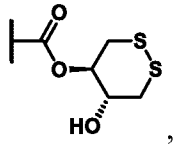
each R^6 is independently selected from the group consisting of H, C_1-C_6 alkyl, and C_1-C_6 haloalkyl;

each X^1 is independently selected from the group consisting of C=O, -CH_2-, -CHF-, and -CF_2-;

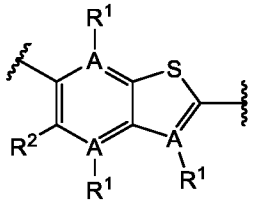
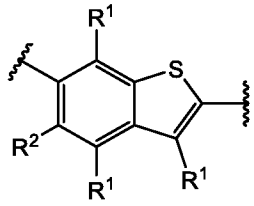
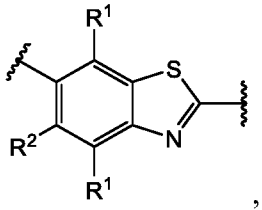
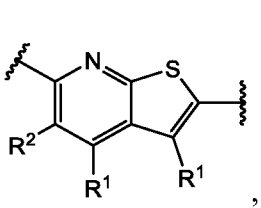
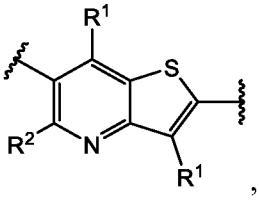
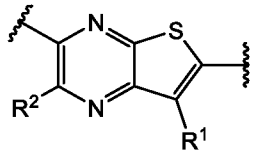
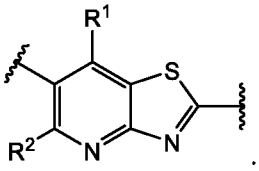
each X^2 is independently selected from $(C(R^8)_2)_{(1\text{-}3)}$, wherein each R^8 is independently selected from the group consisting of H, halogen, C_1-C_6 alkyl, CN, OR^6, $N(R^6)_2$, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, C_1-C_6 alkyl substituted by OR^6, and C_1-C_6 alkyl substituted by $N(R^6)_2$;

optionally 2 R^8 on different carbon atoms may be taken together, along with the atoms to which they are attached, to form a 3- to 6-membered fused ring; and

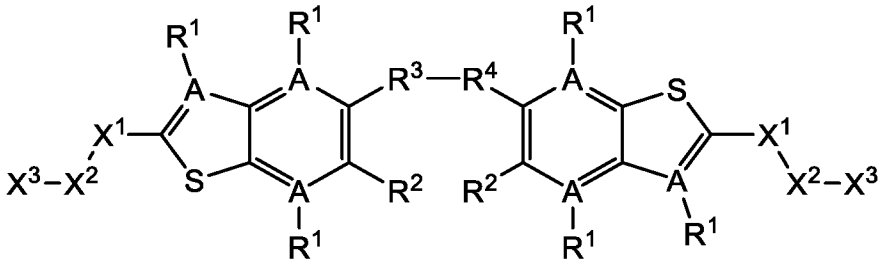
optionally 2 R^8 on a single carbon atom may be taken together, along with the atom to which they are attached, to form a 3- to 6-membered spirocycle;

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

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

4. The compound according to claim 3, or a pharmaceutically acceptable salt thereof, wherein each  is independently selected from the group consisting of  ,  ,  ,  ,  , and  .

5. A compound of general formula (III):



(III)

or a pharmaceutically acceptable salt thereof, wherein

each A-R^1 is independently selected from the group consisting of C-R^1 and N, wherein each R^1 is independently selected from the group consisting of H, halogen, OR^6, $N(R^6)_2$, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkyl substituted by OR^6, C_1-C_6 alkyl substituted by $N(R^6)_2$, $COOR^6$, and $C(O)N(R^6)_2$;

each R^2 is independently selected from the group consisting of H, halogen, CN, OR^6, $N(R^6)_2$, $COOR^6$, $C(O)N(R^6)_2$, SO_2R^6, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkyl substituted by OR^6, C_2-C_6 alkenyl, C_2-C_6 haloalkenyl, C_2-C_6 alkenyl substituted by OR^6, C_2-C_6 alkynyl, C_2-C_6 haloalkynyl, C_2-C_6 alkynyl substituted by OR^6, C_3-C_6 cycloalkyl, and a 3- to 6-membered heterocyclic ring including 1 to 2 ring members selected from the group consisting of O, S, and $N(R^6)$;

R^3 and R^4 are independently selected from the group consisting of O-(C_1-C_4 alkylene or haloalkylene), C_1-C_5 alkylene or haloalkylene, and $N(R_6)$-(C_1-C_4 alkylene or haloalkylene);

optionally R^3 may be taken together with an adjacent C-R^1 and the atom to which they are attached to form fused ring G, which is selected from phenyl or a 5- or 6-membered heterocyclic ring including 1 to 2 ring members selected from the group consisting of O, S, N, and $N(R^6)$ wherein the bond to R^3 from said ring G is from an atom on said ring G with an open valence for substitution and wherein said phenyl or heterocyclic ring is optionally substituted with one or more members of the group consisting of halogen, C_1-C_3 alkyl, and C_1-C_3 haloalkyl;

optionally R^4 may be taken together with an adjacent C-R^1 and the atom to which they are attached to form fused ring E, which is selected from phenyl or a 5- or 6-membered heterocyclic ring including 1 to 2 ring members selected from the group consisting of O, S, N, and $N(R^6)$ wherein the bond to R^4 from said ring E is from an atom on said ring E with an open valence for substitution and wherein said phenyl or heterocyclic ring is optionally substituted with one or more members of the group consisting of halogen, C_1-C_3 alkyl, and C_1-C_3 haloalkyl;

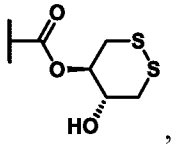
each R^6 is independently selected from the group consisting of H, C_1-C_6 alkyl, and C_1-C_6 haloalkyl;

each X^1 is independently selected from the group consisting of C=O, -CH_2-, -CHF-, and -CF_2-;

each X^2 is independently selected from $(C(R^8)_2)_{(1\text{-}3)}$, wherein each R^8 is independently selected from the group consisting of H, halogen, C_1-C_6 alkyl, CN, OR^6, $N(R^6)_2$, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, C_1-C_6 alkyl substituted by OR^6, and C_1-C_6 alkyl substituted by $N(R^6)_2$;

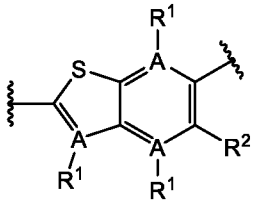
optionally 2 R^8 on different carbon atoms may be taken together, along with the atoms to which they are attached, to form a 3- to 6-membered fused ring; and

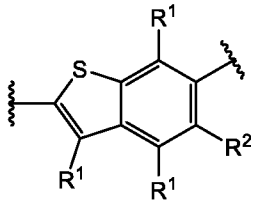
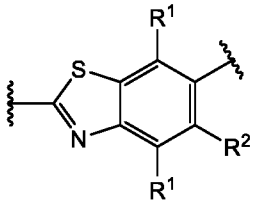
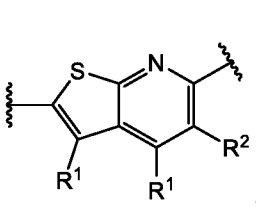
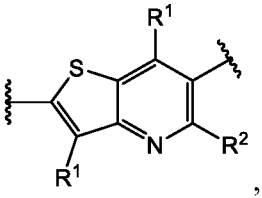
optionally 2 R^8 on a single carbon atom may be taken together, along with the atom to which they are attached, to form a 3- to 6-membered spirocycle;

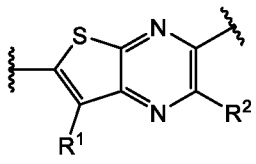
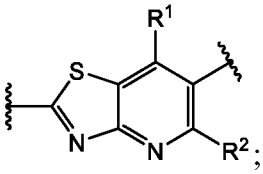
each X^3 is independently selected from the group consisting of $COOR^6$, $C(O)SR^6$, $C(S)OR^6$,  , SO_2R^6, $C(O)N(R^9)_2$, and CN; and

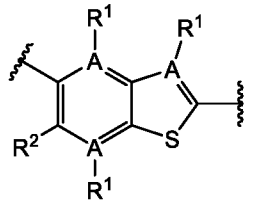
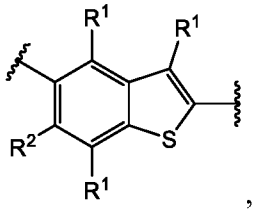
each R^9 is independently selected from the group consisting of H, $COOR^6$, and SO_2R^6.

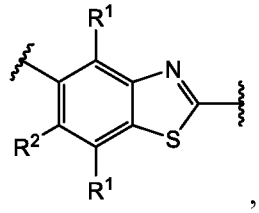
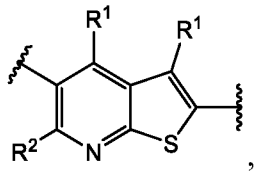
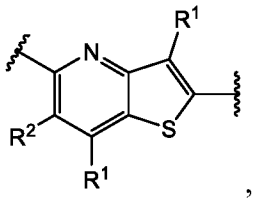
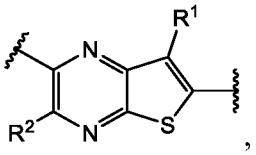
6. The compound according to claim 5, or a pharmaceutically acceptable salt thereof, wherein

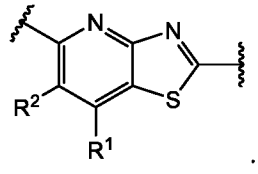
 is independently selected from the group consisting of

 ,  ,  ,  ,

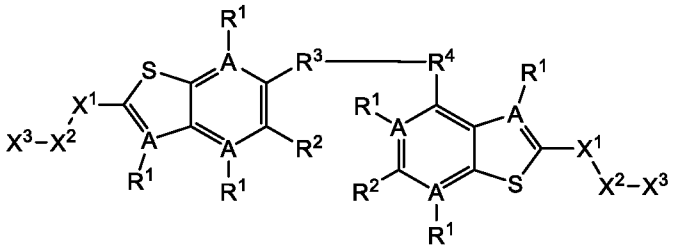
 , and  ; and

 is selected from the group consisting of  ,

 ,  ,  ,  , and

 .

7. A compound of general formula (IV):



(IV)

or a pharmaceutically acceptable salt thereof, wherein

each A-R^1 is independently selected from the group consisting of C-R^1 and N, wherein each R^1 is independently selected from the group consisting of H, halogen, OR^6, $N(R^6)_2$, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkyl substituted by OR^6, C_1-C_6 alkyl substituted by $N(R^6)_2$, $COOR^6$, and $C(O)N(R^6)_2$;

each R^2 is independently selected from the group consisting of H, halogen, CN, OR^6, $N(R^6)_2$, $COOR^6$, $C(O)N(R^6)_2$, SO_2R^6, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkyl substituted by OR^6, C_2-C_6 alkenyl, C_2-C_6 haloalkenyl, C_2-C_6 alkenyl substituted by OR^6, C_2-C_6 alkynyl, C_2-C_6 haloalkynyl, C_2-C_6 alkynyl substituted by OR^6, C_3-C_6 cycloalkyl, and a 3- to 6-membered heterocyclic ring including 1 to 2 ring members selected from the group consisting of O, S, and $N(R^6)$;

R^3 and R^4 are independently selected from the group consisting of O-(C_1-C_4 alkylene or haloalkylene), C_1-C_5 alkylene or haloalkylene, and $N(R_6)$-(C_1-C_4 alkylene or haloalkylene);

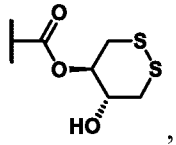
each R^6 is independently selected from the group consisting of H, C_1-C_6 alkyl, and C_1-C_6 haloalkyl;

each X^1 is independently selected from the group consisting of C=O, -CH_2-, -CHF-, and -CF_2-;

each X^2 is independently selected from $(C(R^8)_2)_{(1\text{-}3)}$, wherein each R^8 is independently selected from the group consisting of H, halogen, C_1-C_6 alkyl, CN, OR^6, $N(R^6)_2$, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, C_1-C_6 alkyl substituted by OR^6, and C_1-C_6 alkyl substituted by $N(R^6)_2$;

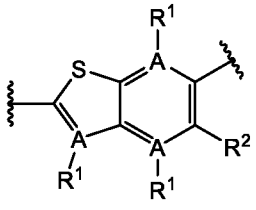
optionally 2 R^8 on different carbon atoms may be taken together, along with the atoms to which they are attached, to form a 3- to 6-membered fused ring; and

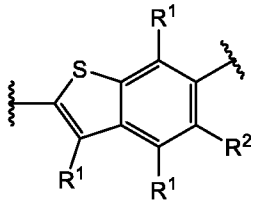
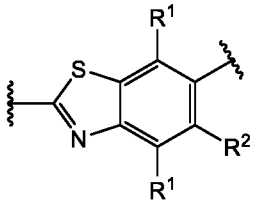
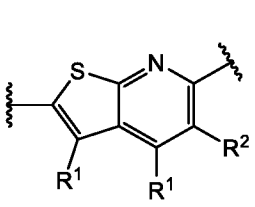
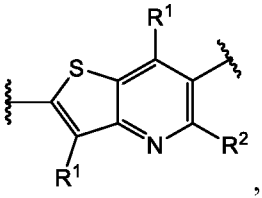
optionally 2 R^8 on a single carbon atom may be taken together, along with the atom to which they are attached, to form a 3- to 6-membered spirocycle;

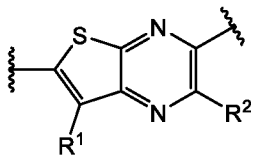
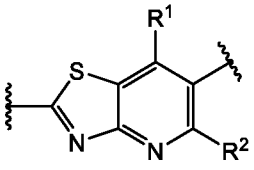
each X^3 is independently selected from the group consisting of $COOR^6$, $C(O)SR^6$, $C(S)OR^6$,  , SO_2R^6, $C(O)N(R^9)_2$, and CN; and

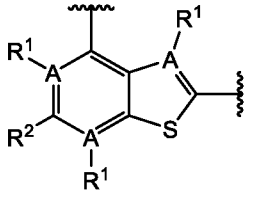
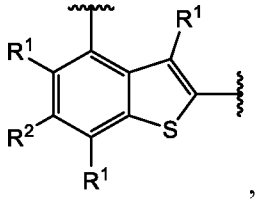
each R^9 is independently selected from the group consisting of H, $COOR^6$, and SO_2R^6.

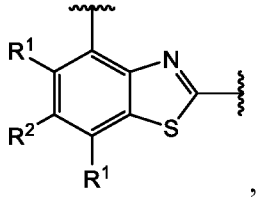
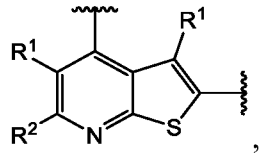
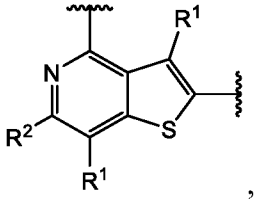
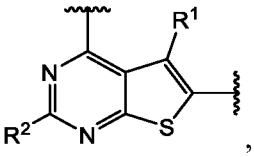
8. The compound according to claim 7, or a pharmaceutically acceptable salt thereof, wherein

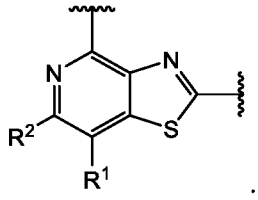
 is independently selected from the group consisting of

 ,  ,  ,  ,

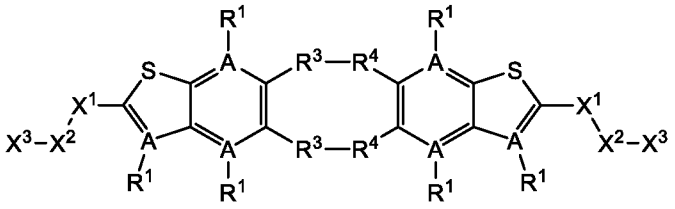
 , and  ; and

 is selected from the group consisting of  ,

 ,  ,  ,  , and

 .

9. A compound of general formula (V):



(V)

or a pharmaceutically acceptable salt thereof, wherein

each A-R^1 is independently selected from the group consisting of C-R^1 and N, wherein each R^1 is independently selected from the group consisting of H, halogen, OR^6, $N(R^6)_2$, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkyl substituted by OR^6, C_1-C_6 alkyl substituted by $N(R^6)_2$, $COOR^6$, and $C(O)N(R^6)_2$;

R^3 and R^4 are independently selected from the group consisting of O-(C_1-C_4 alkylene or haloalkylene), C_1-C_5 alkylene or haloalkylene, and $N(R_6)$-(C_1-C_4 alkylene or haloalkylene);

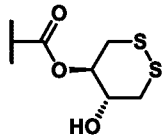
each X^1 is independently selected from the group consisting of C=O, $-CH_2-$, -CHF-, and $-CF_2-$;

each X^2 is independently selected from $(C(R^8)_2)_{(1-3)}$, wherein each R^8 is independently selected from the group consisting of H, halogen, C_1-C_6 alkyl, CN, OR^6, $N(R^6)_2$, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, C_1-C_6 alkyl substituted by OR^6, and C_1-C_6 alkyl substituted by $N(R^6)_2$;

optionally 2 R^8 on different carbon atoms may be taken together, along with the atoms to which they are attached, to form a 3- to 6-membered fused ring; and

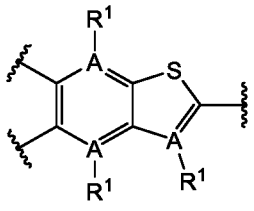
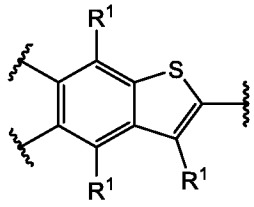
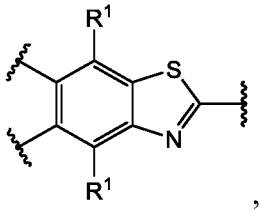
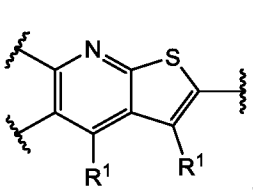
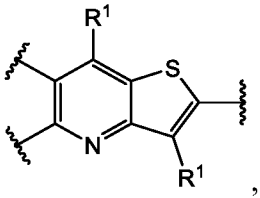
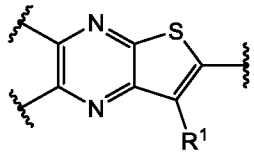
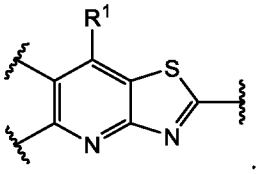
optionally 2 R^8 on a single carbon atom may be taken together, along with the atom to which they are attached, to form a 3- to 6-membered spirocycle;

each X^3 is independently selected from the group consisting of $COOR^6$, $C(O)SR^6$,

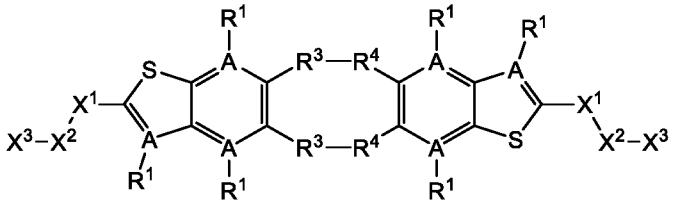


$C(S)OR^6$, , SO_2R^6, $C(O)N(R^9)_2$, and CN; and

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

10. The compound according to claim 9, or a pharmaceutically acceptable salt thereof, wherein each  is independently selected from the group consisting of  ,  ,  ,  ,  , and  .

11. A compound of general formula (VI):



(VI)

or a pharmaceutically acceptable salt thereof, wherein

each A-R^1 is independently selected from the group consisting of C-R^1 and N, wherein each R^1 is independently selected from the group consisting of H, halogen, OR^6, $N(R^6)_2$, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkyl substituted by OR^6, C_1-C_6 alkyl substituted by $N(R^6)_2$, $COOR^6$, and $C(O)N(R^6)_2$;

R^3 and R^4 are independently selected from the group consisting of O-(C_1-C_4 alkylene or haloalkylene), C_1-C_5 alkylene or haloalkylene, and $N(R_6)$-(C_1-C_4 alkylene or haloalkylene);

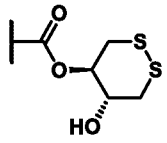
each R^6 is independently selected from the group consisting of H, C_1-C_6 alkyl, and C_1-C_6 haloalkyl;

each X^1 is independently selected from the group consisting of C=O, -CH_2-, -CHF-, and -CF_2-;

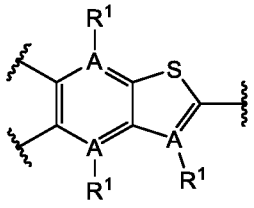
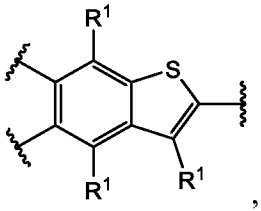
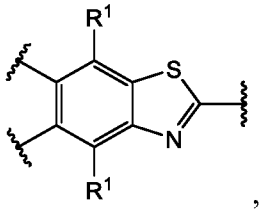
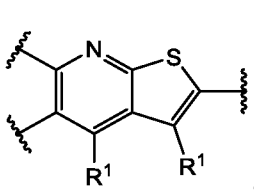
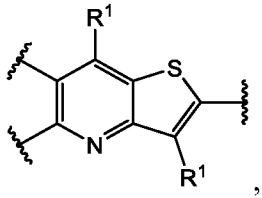
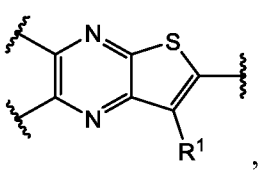
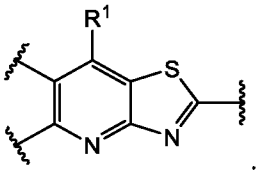
each X^2 is independently selected from $(C(R^8)_2)_{(1-3)}$, wherein each R^8 is independently selected from the group consisting of H, halogen, C_1-C_6 alkyl, CN, OR^6, $N(R^6)_2$, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, C_1-C_6 alkyl substituted by OR^6, and C_1-C_6 alkyl substituted by $N(R^6)_2$;

optionally 2 R^8 on different carbon atoms may be taken together, along with the atoms to which they are attached, to form a 3- to 6-membered fused ring; and

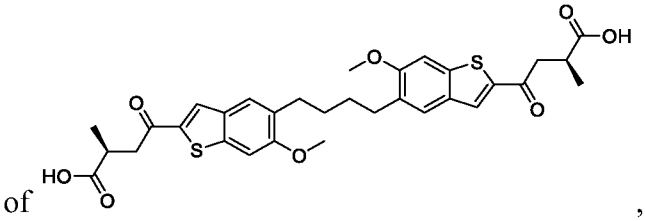
optionally 2 R^8 on a single carbon atom may be taken together, along with the atom to which they are attached, to form a 3- to 6-membered spirocycle;

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

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

12. The compound according to claim 11, or a pharmaceutically acceptable salt thereof, wherein each  is independently selected from the group consisting of  ,  ,  ,  ,  , and  .

13. A compound selected from the group consisting of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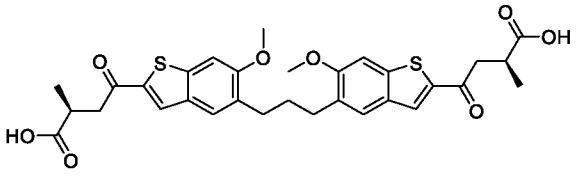
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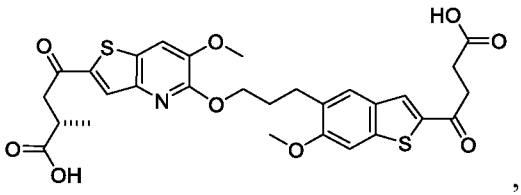
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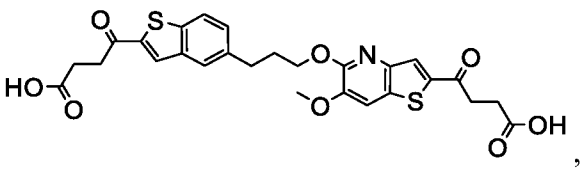
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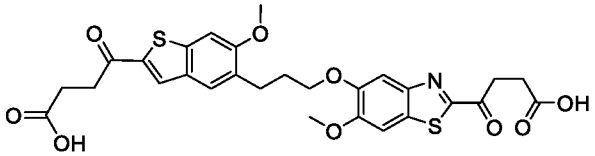
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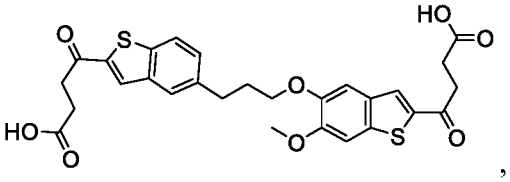
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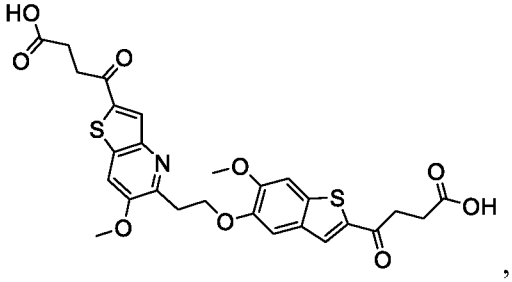
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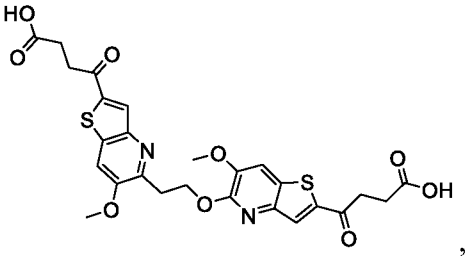
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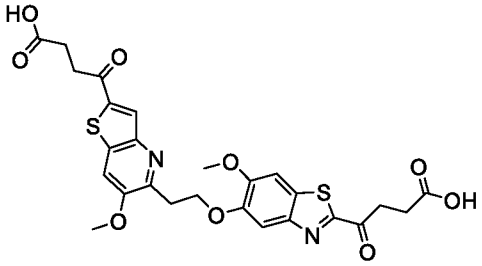
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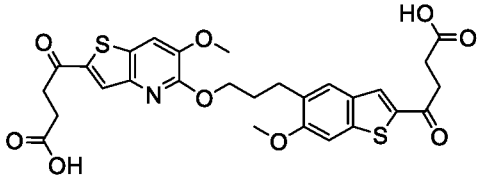
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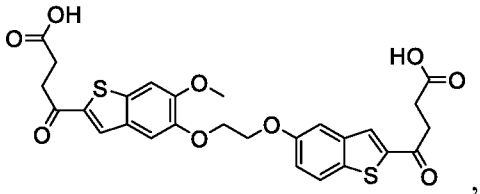
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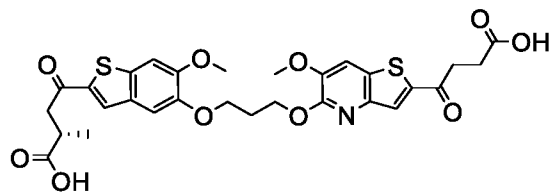
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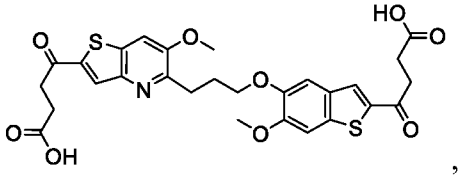
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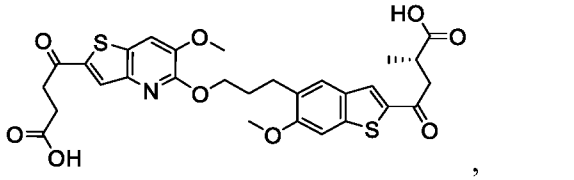
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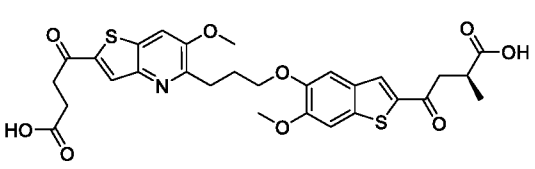
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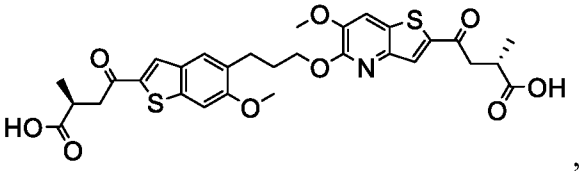
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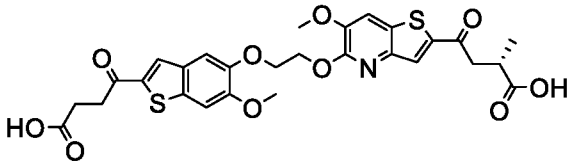
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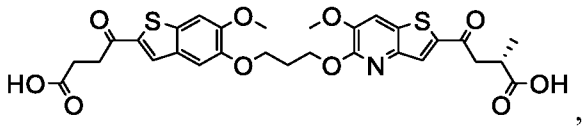
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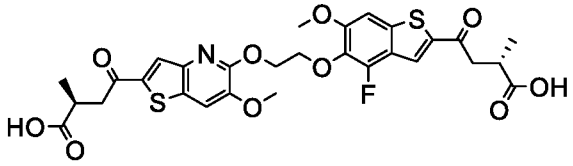
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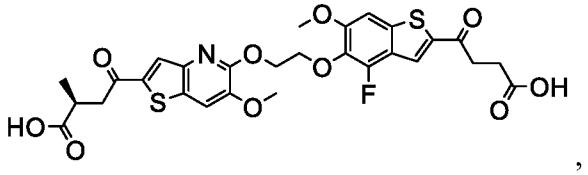
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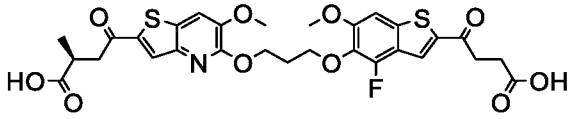
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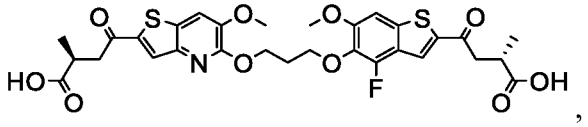
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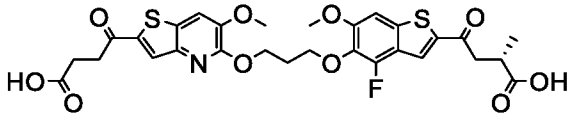
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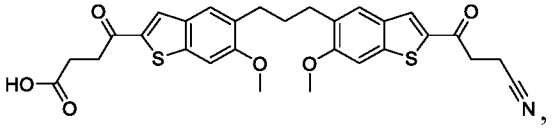
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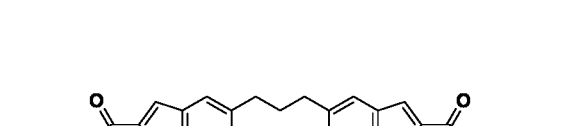
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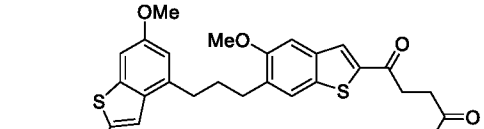
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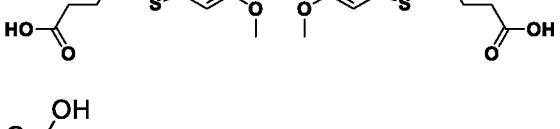
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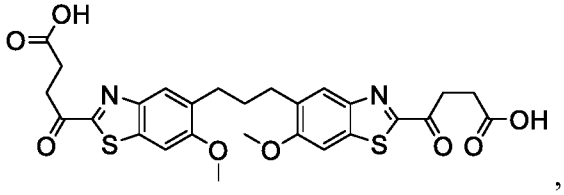
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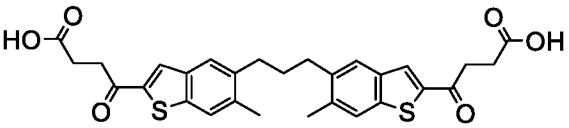
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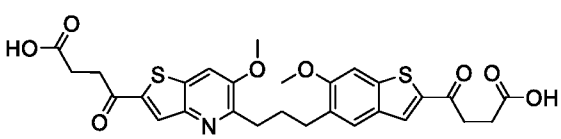
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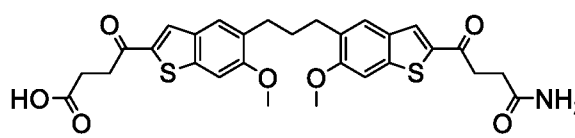
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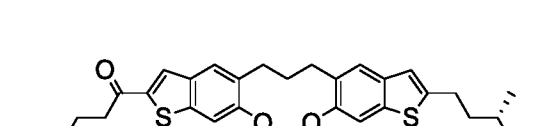
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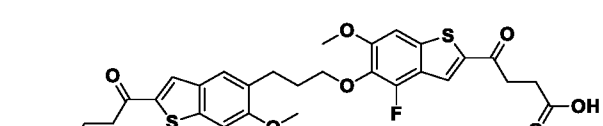
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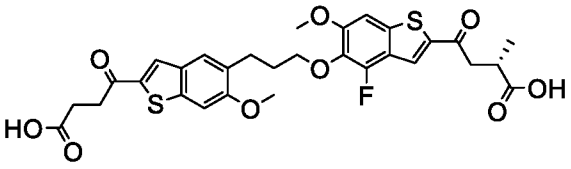
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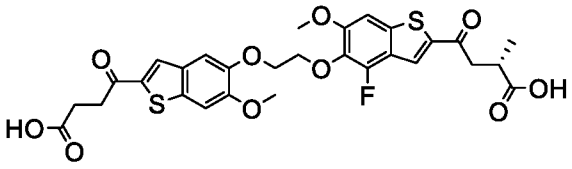
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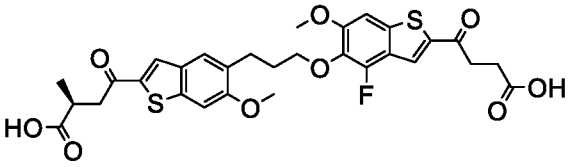
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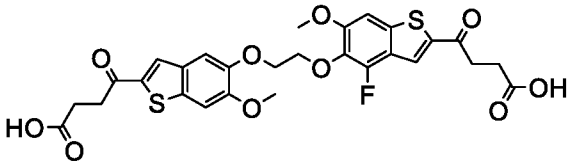
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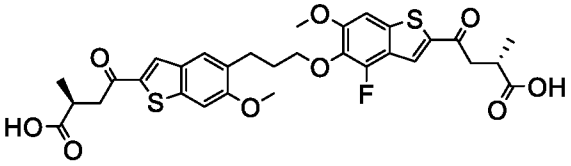
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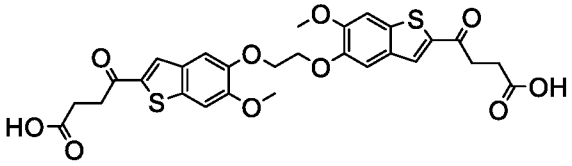
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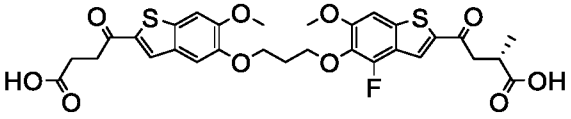
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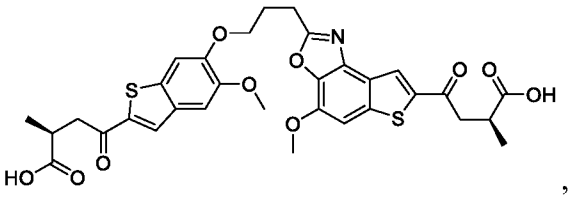
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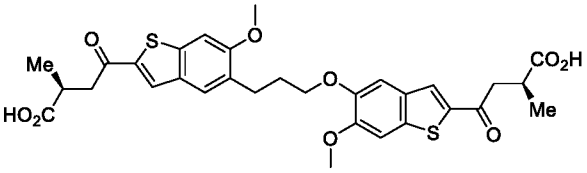
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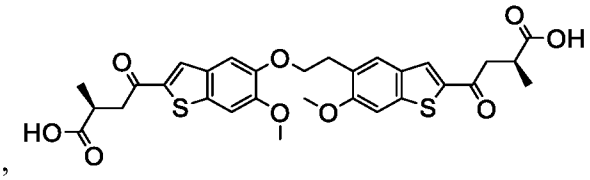
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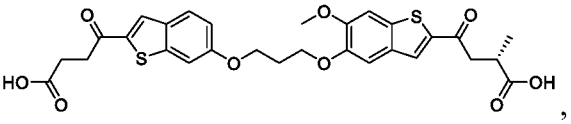
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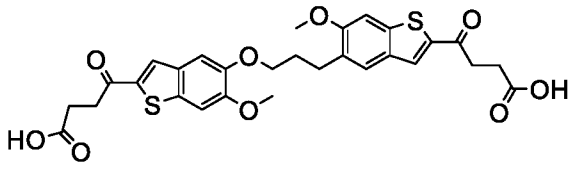
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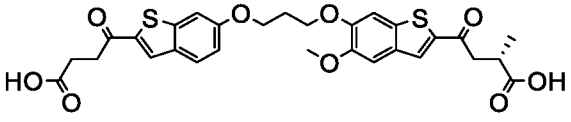
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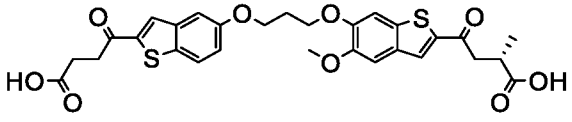
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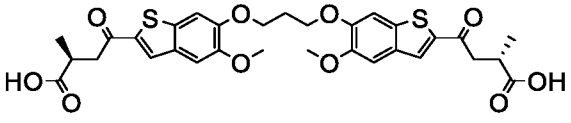
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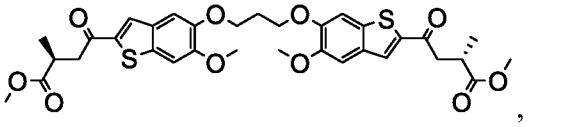
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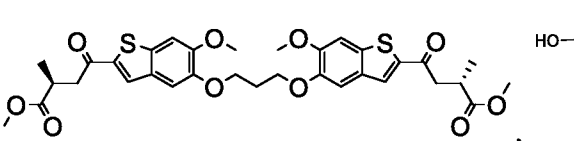
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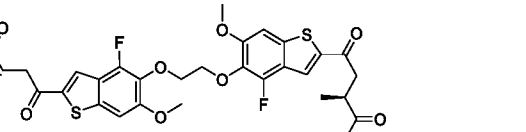
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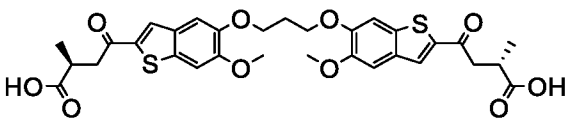
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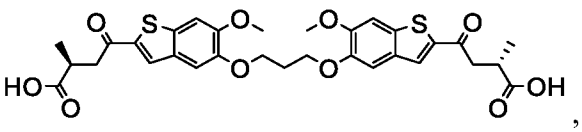
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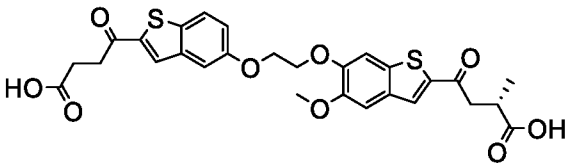
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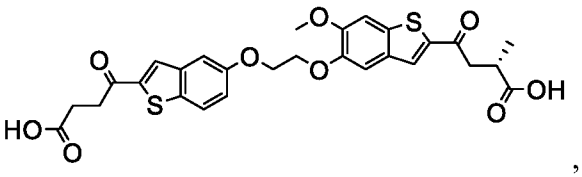
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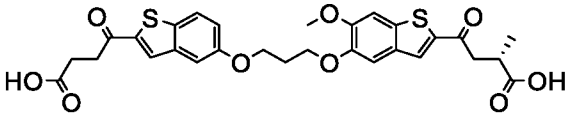
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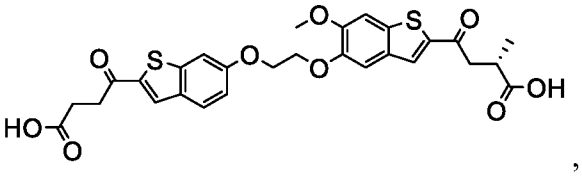
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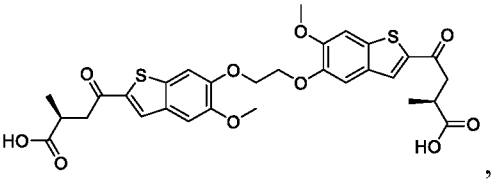
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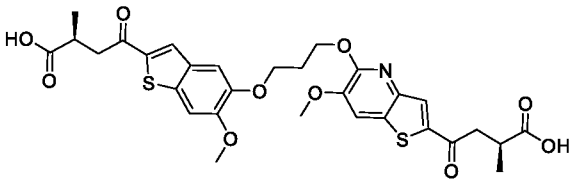
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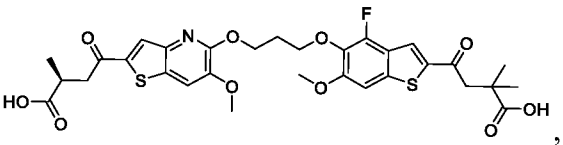
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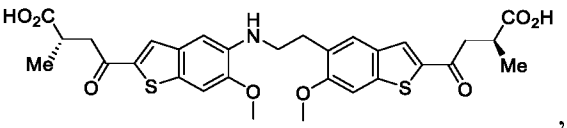
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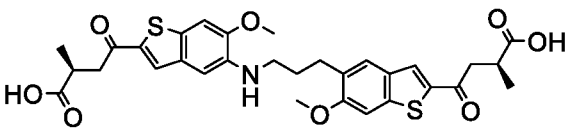
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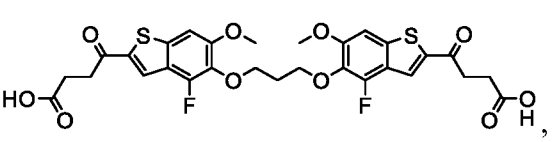
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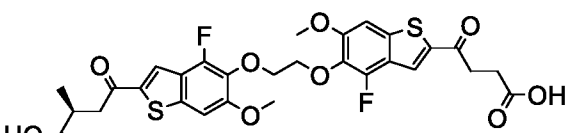
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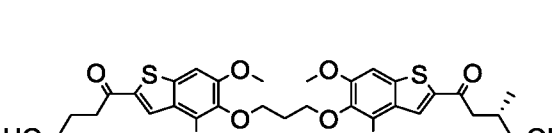
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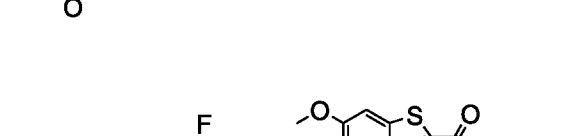
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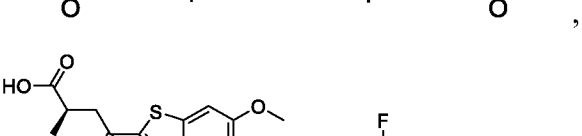
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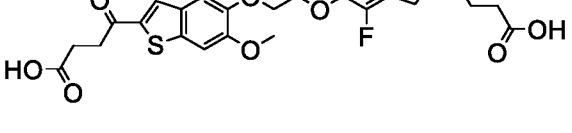
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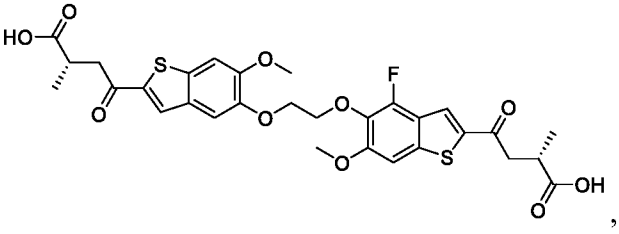
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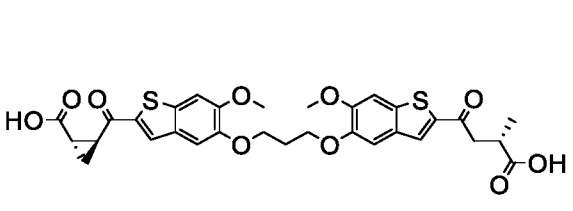
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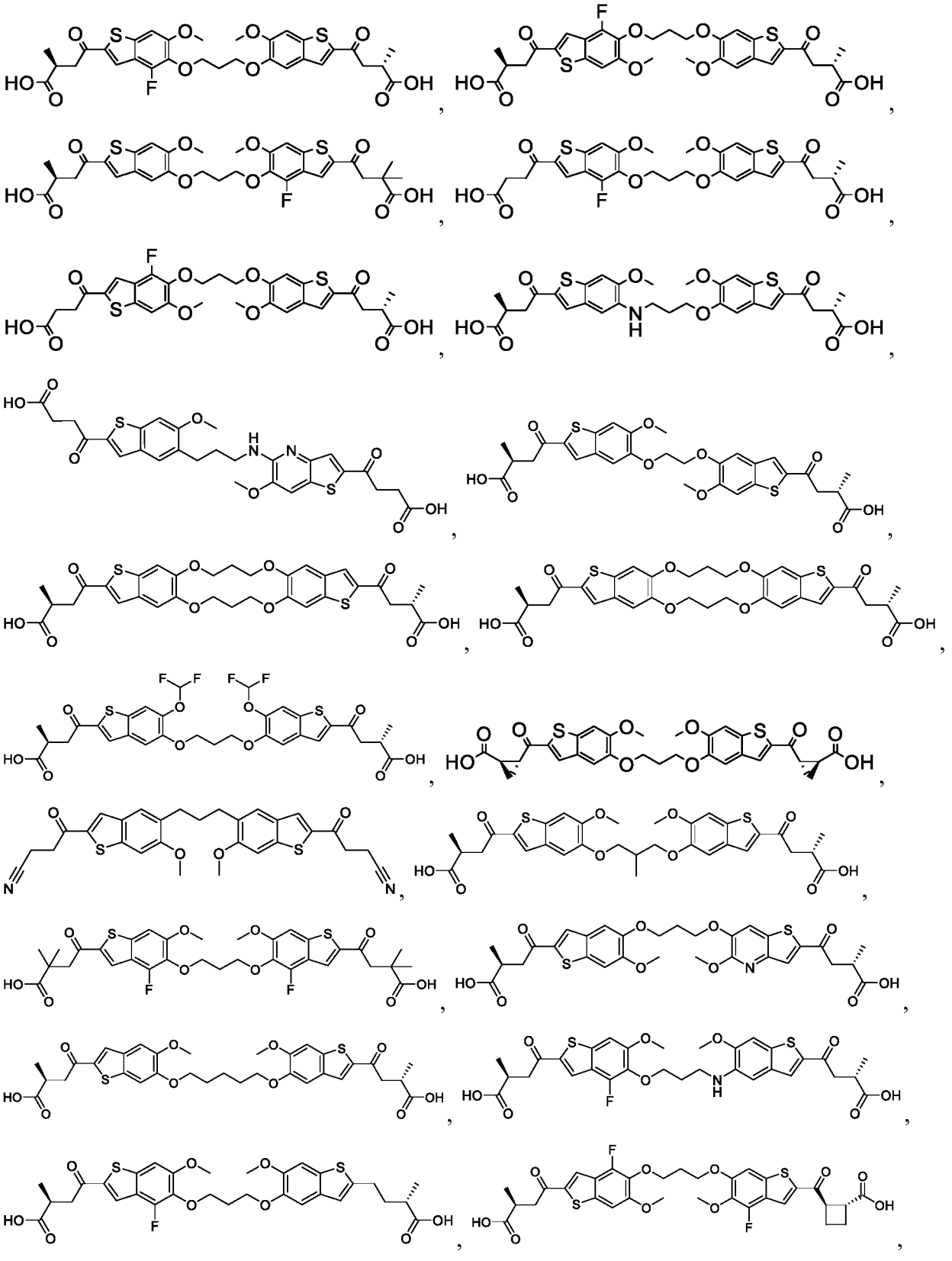

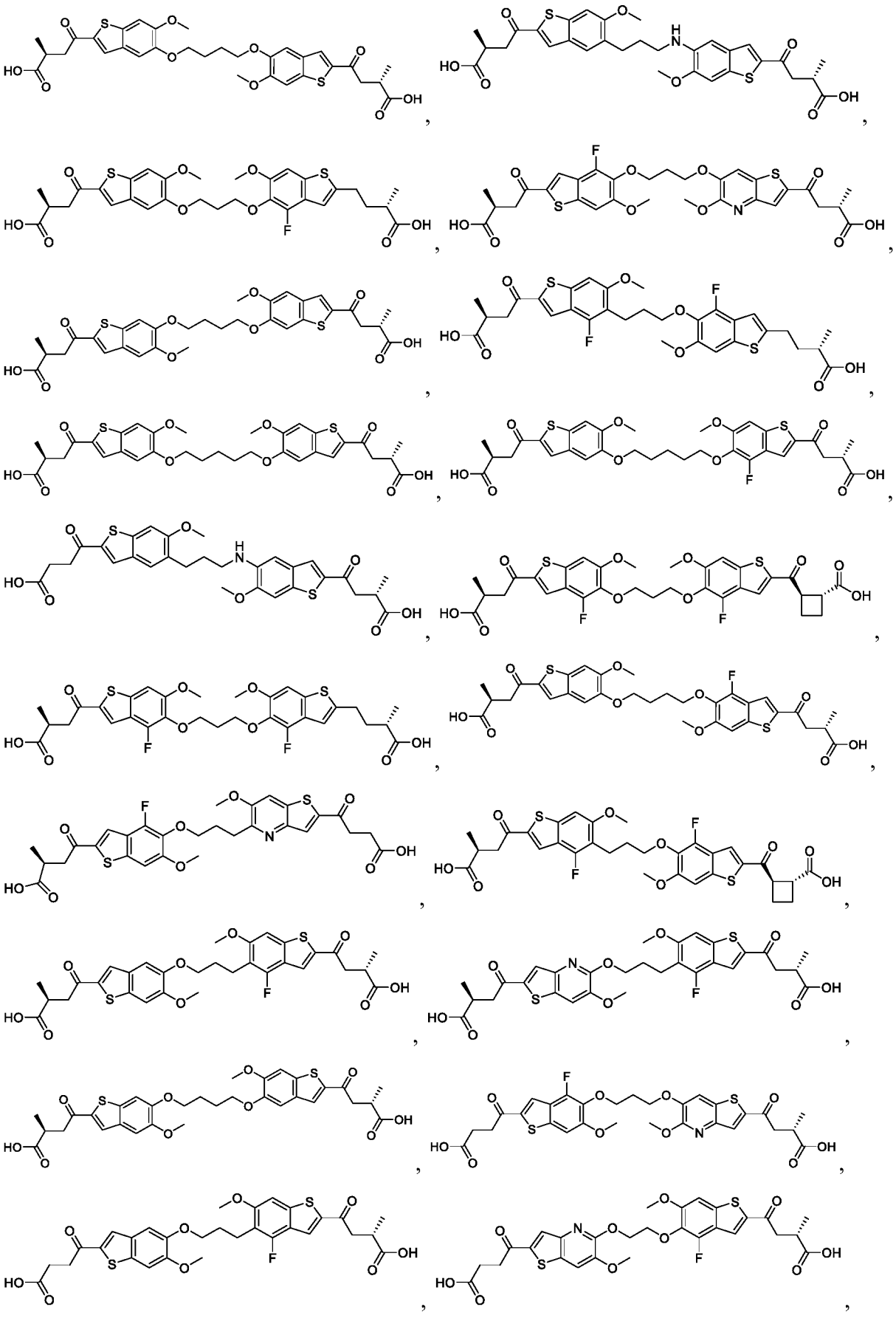

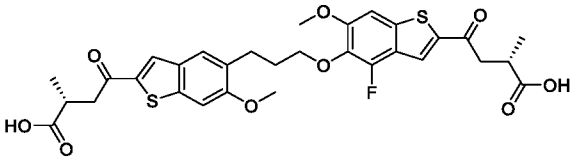
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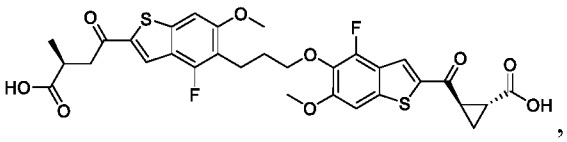
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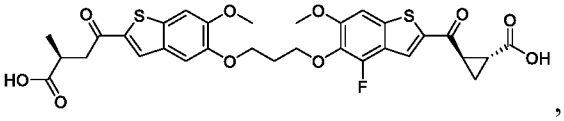
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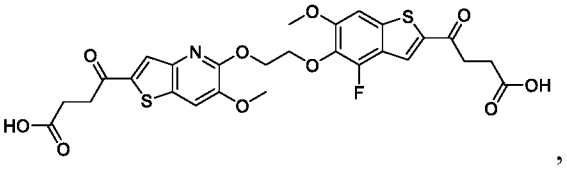
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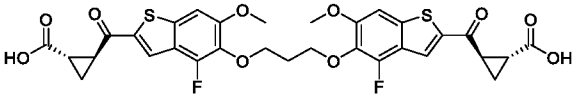
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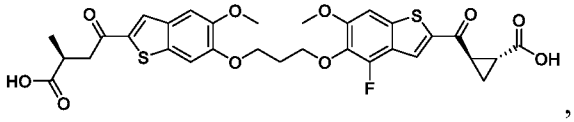
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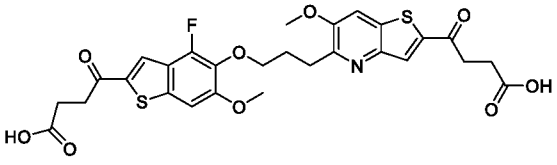
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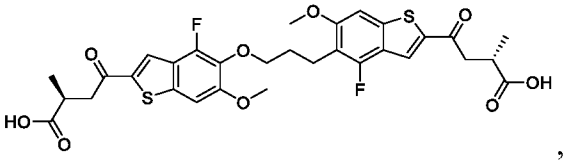
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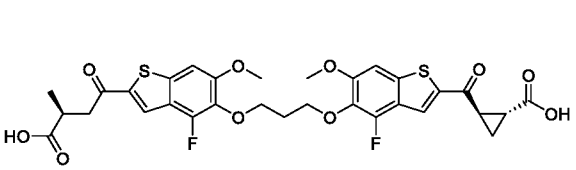
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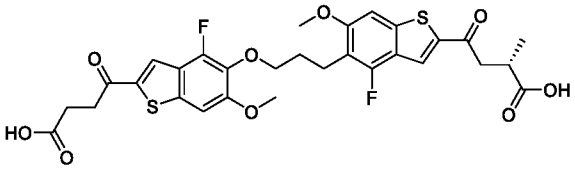
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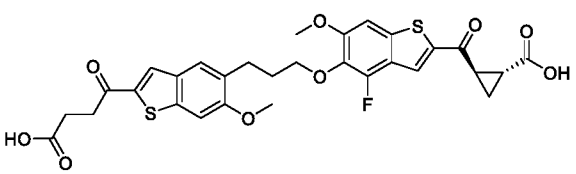
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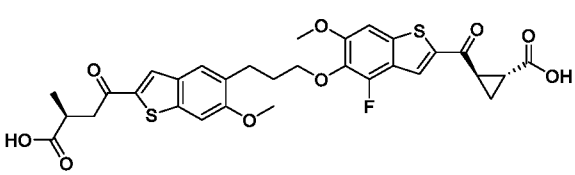
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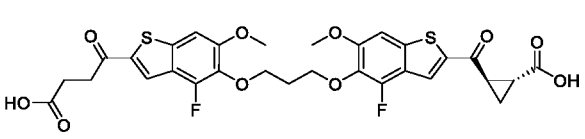
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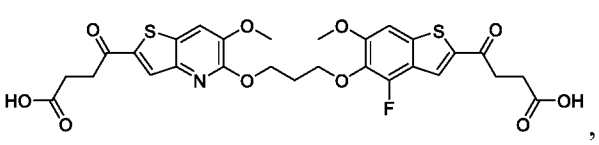
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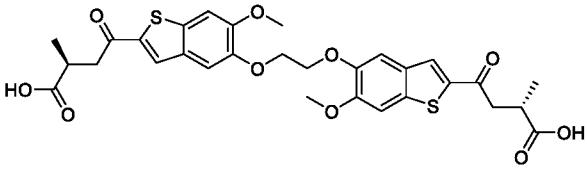
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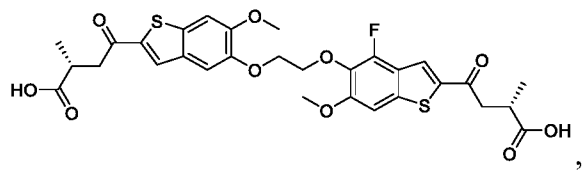
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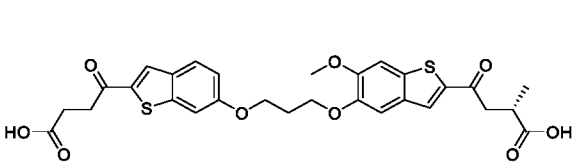
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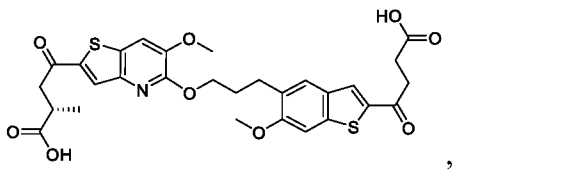
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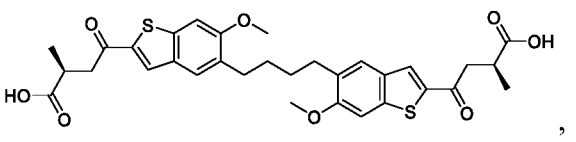
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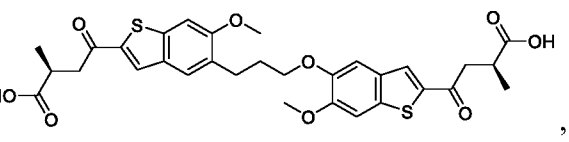
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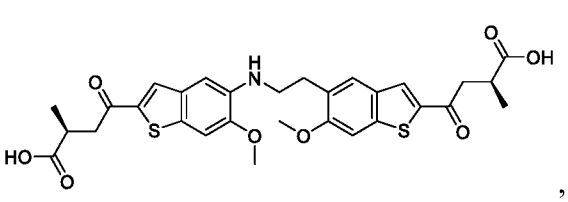
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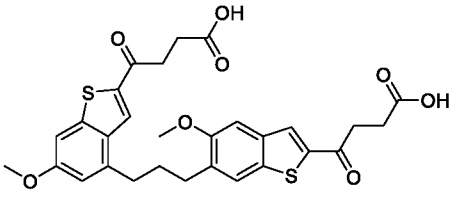
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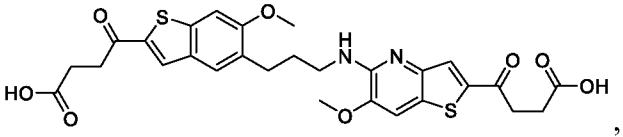
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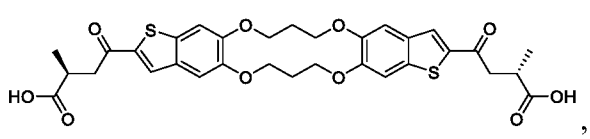
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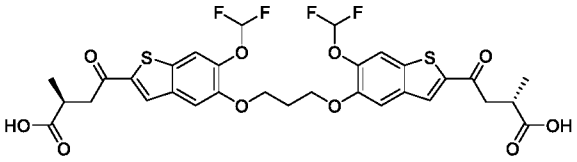
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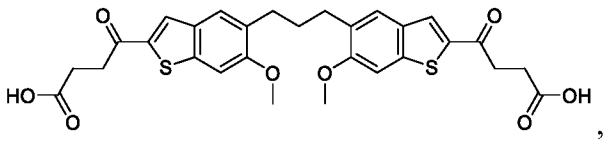
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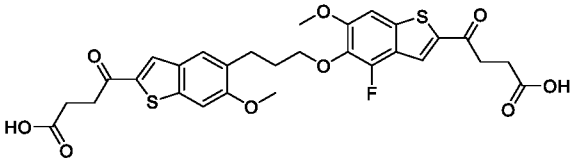
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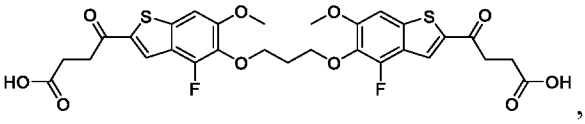
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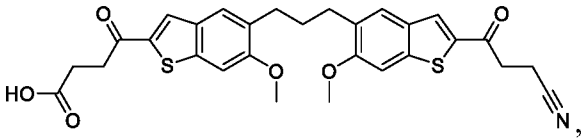
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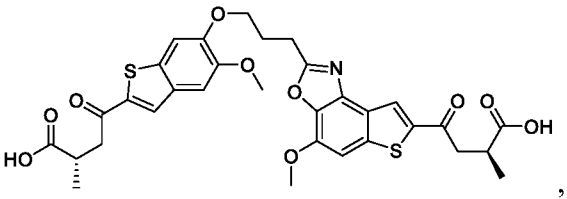
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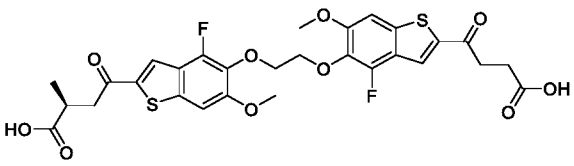
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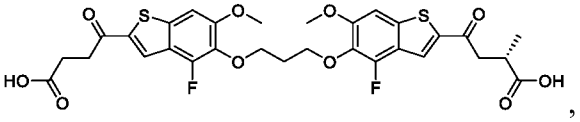
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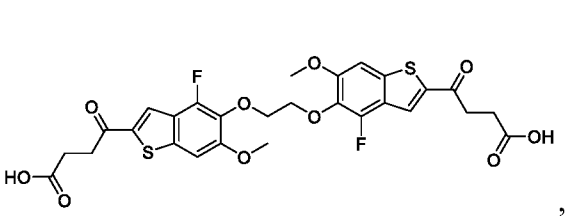
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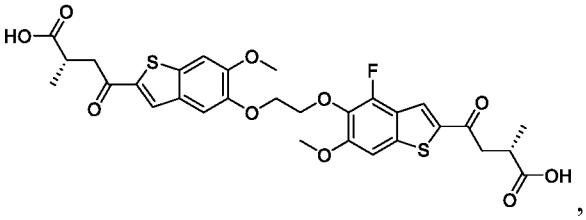
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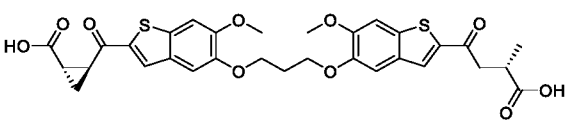
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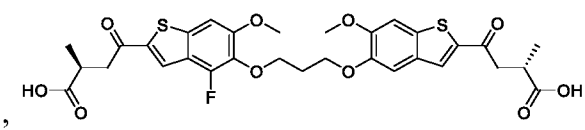
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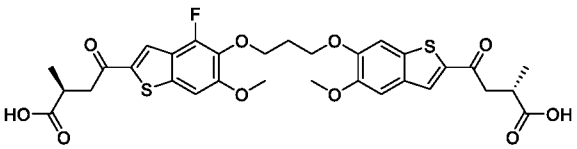
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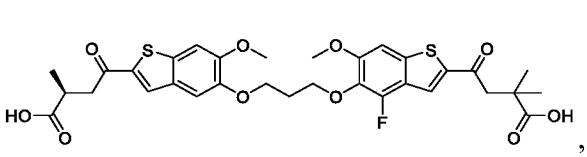
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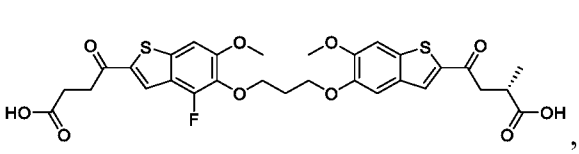
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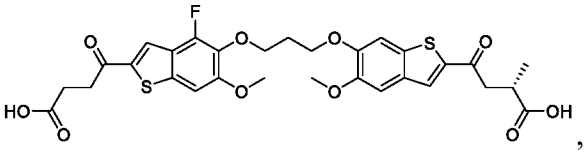
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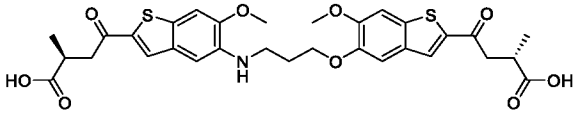
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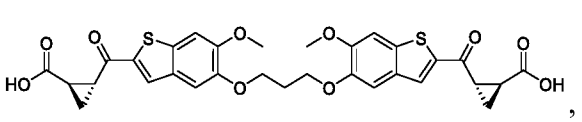
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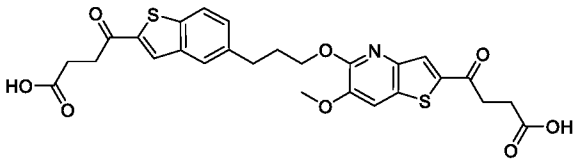
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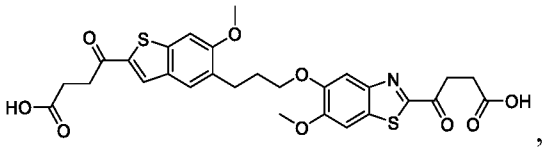
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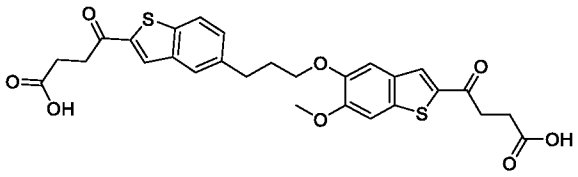
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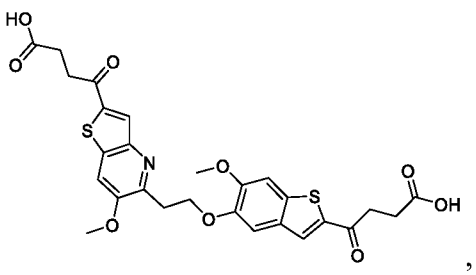
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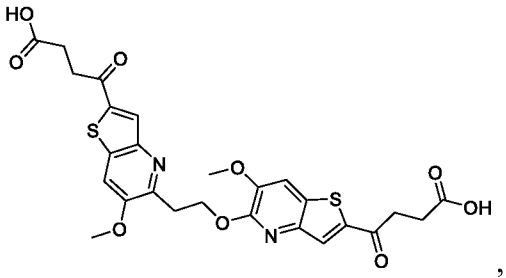
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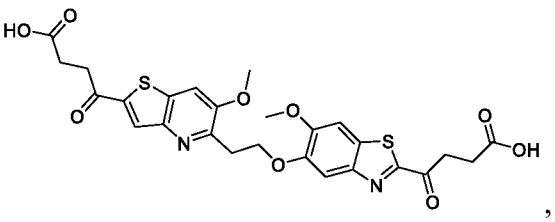
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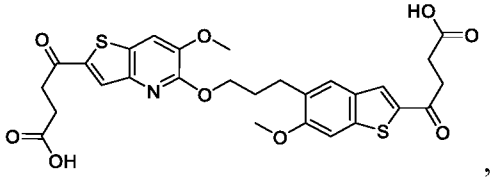
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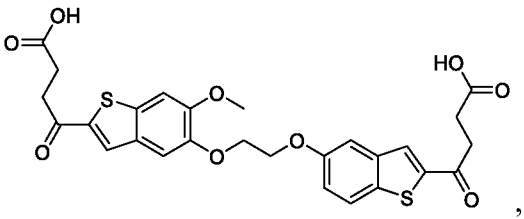
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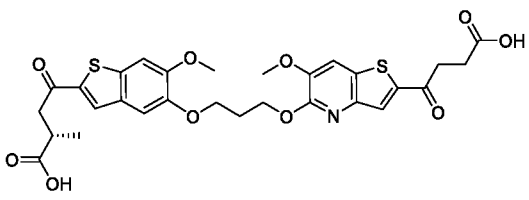
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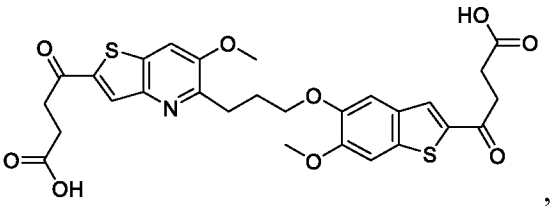
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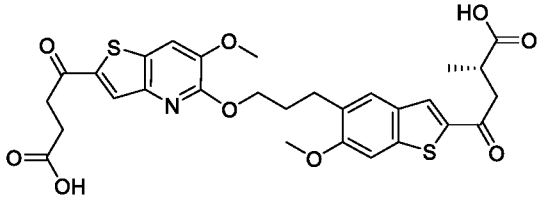
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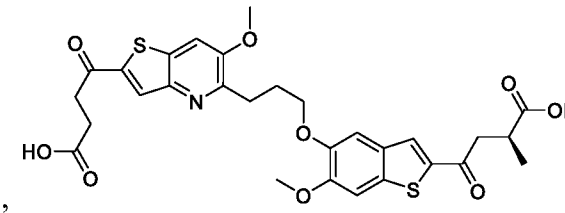
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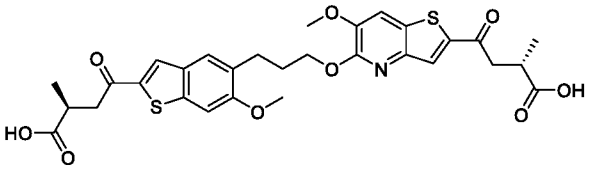
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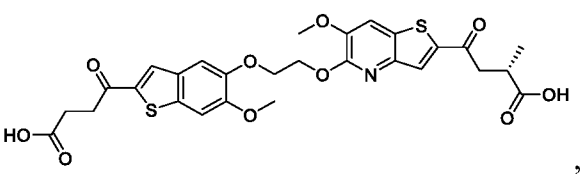
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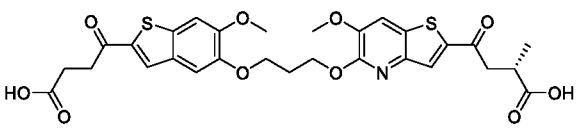
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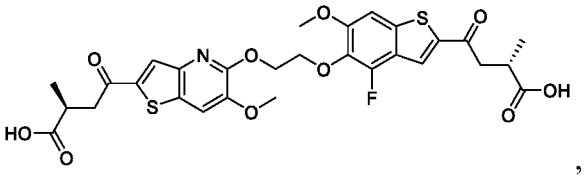
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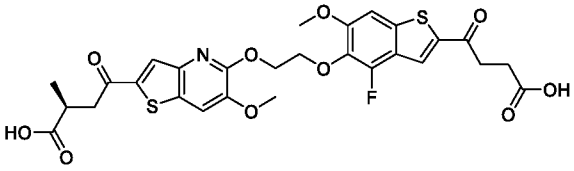
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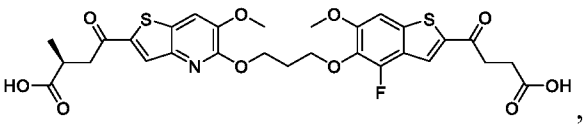
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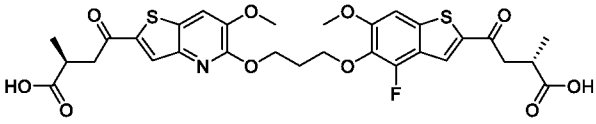
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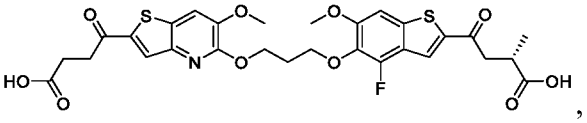
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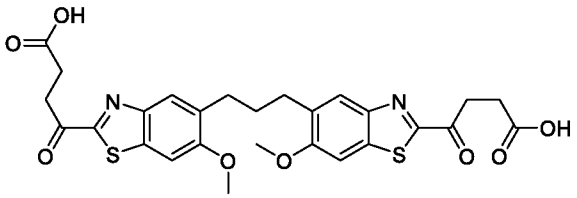
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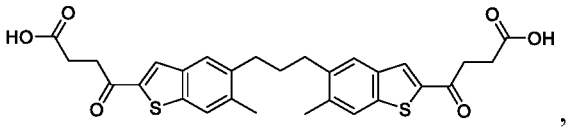
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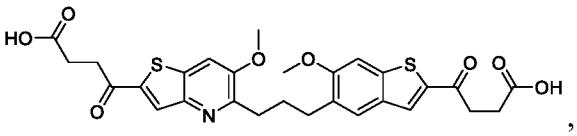
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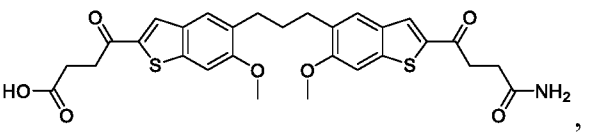
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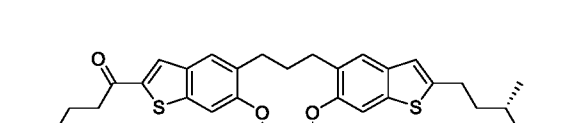
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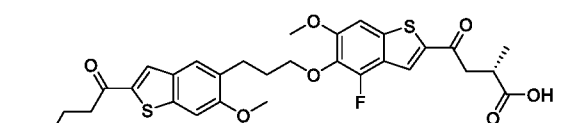
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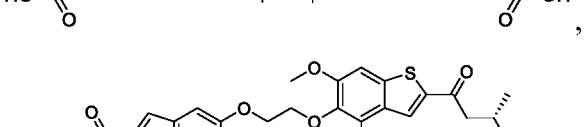
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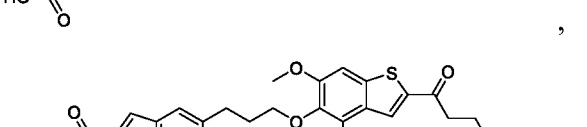
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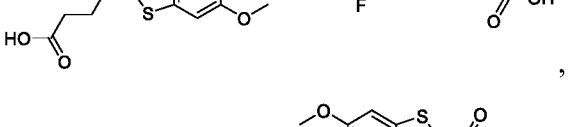
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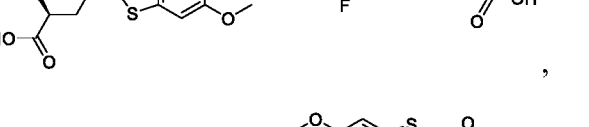
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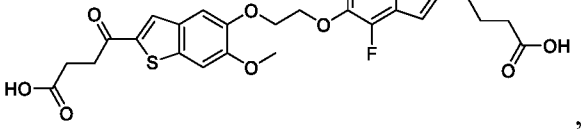
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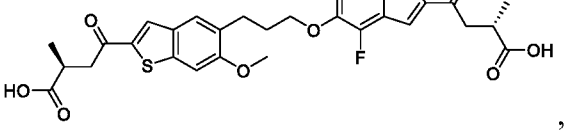
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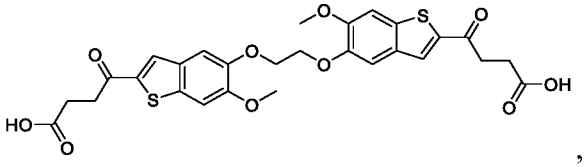
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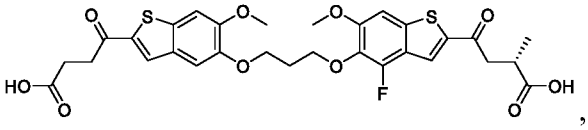
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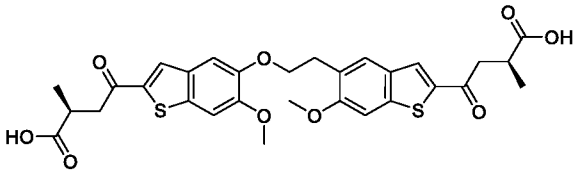
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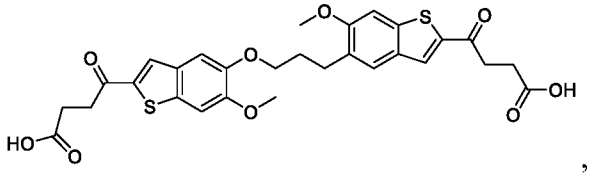
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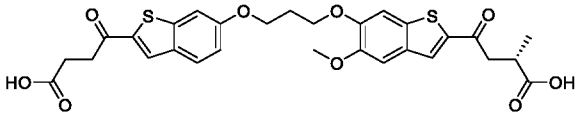
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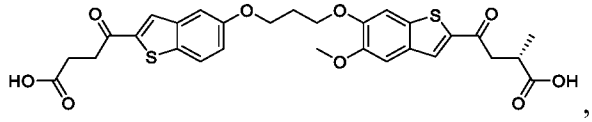
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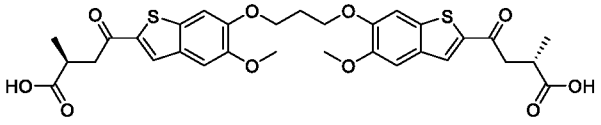
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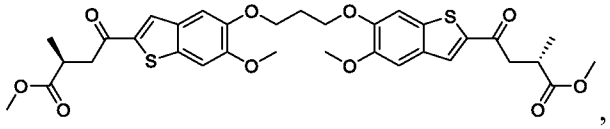
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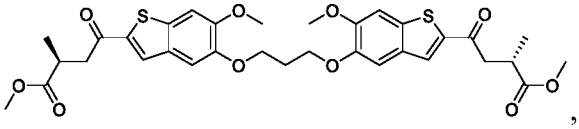
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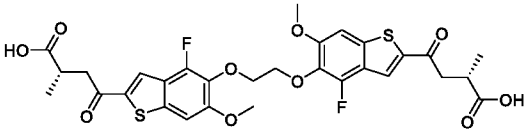
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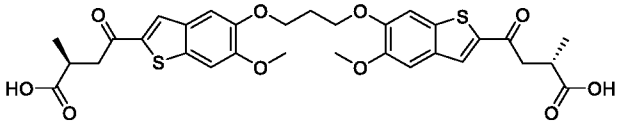
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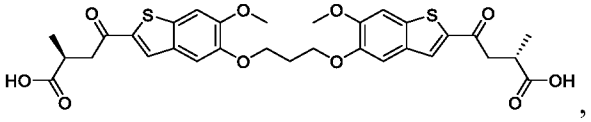
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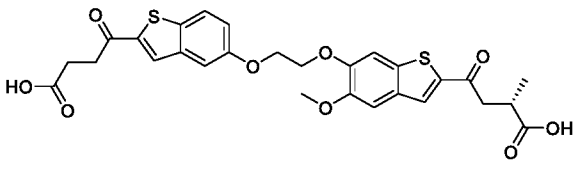
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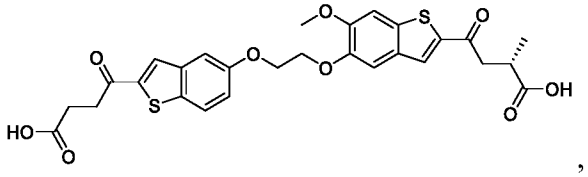
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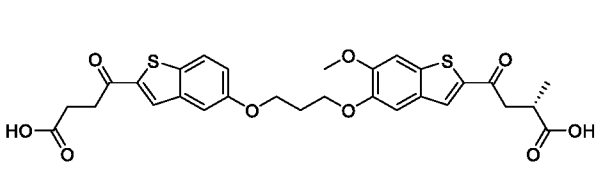
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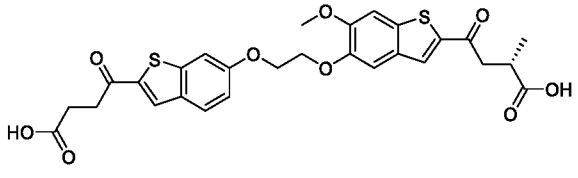
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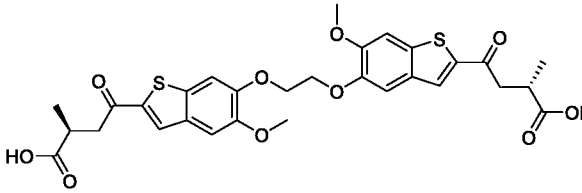
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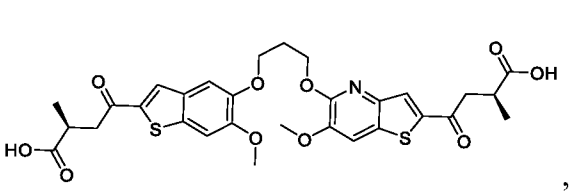
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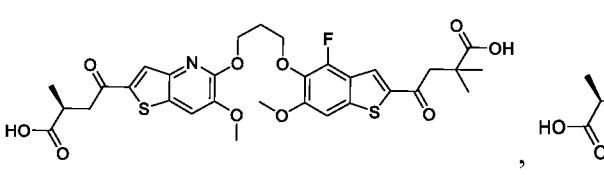
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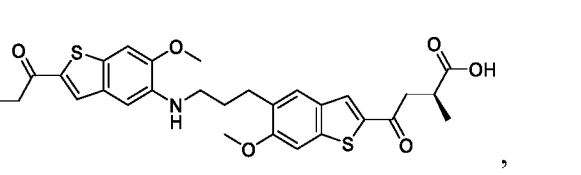
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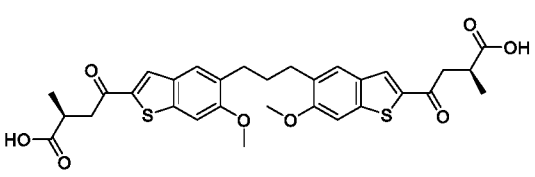
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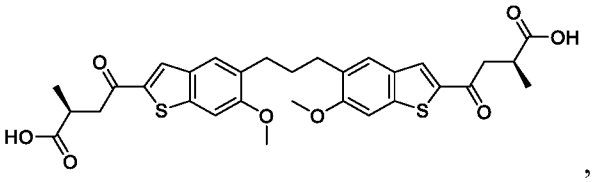
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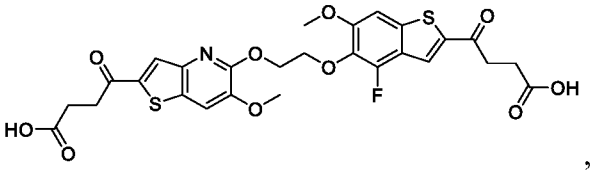
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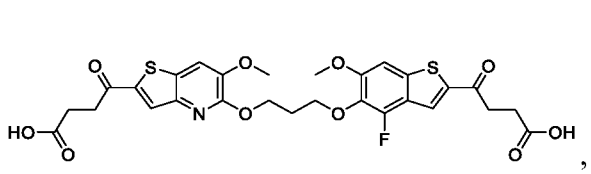
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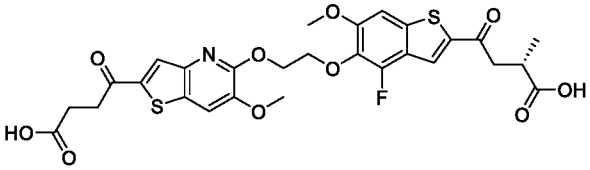
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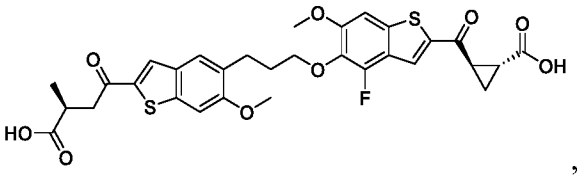
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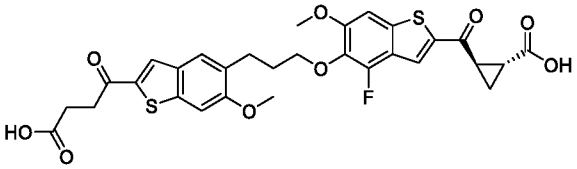
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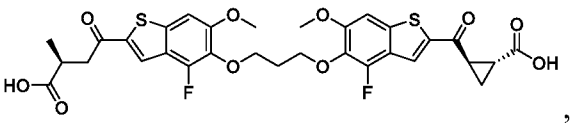
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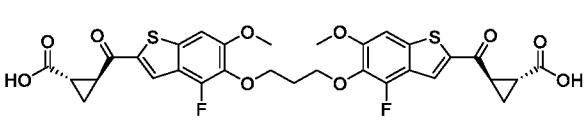
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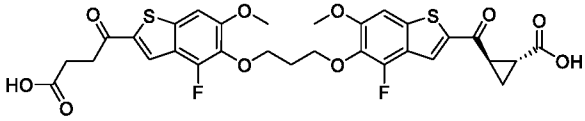
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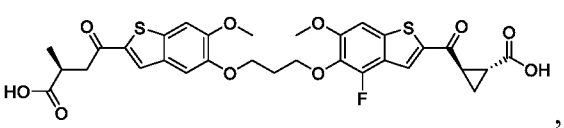
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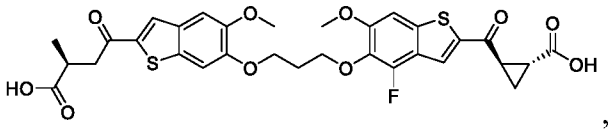
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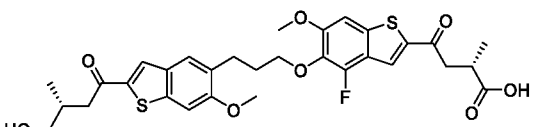
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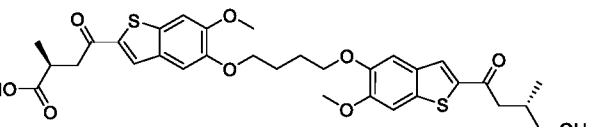
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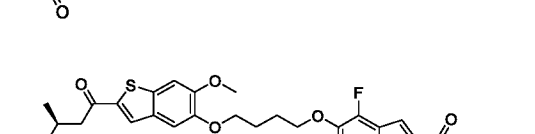
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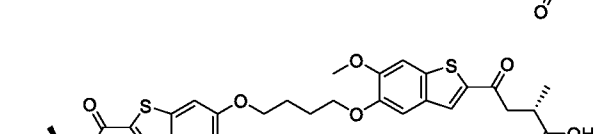
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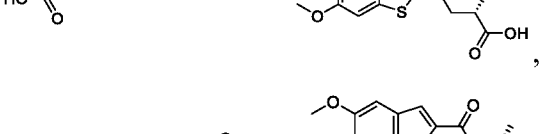
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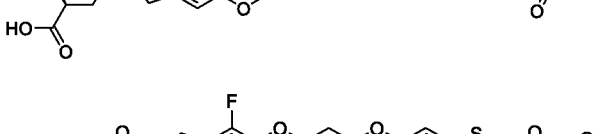
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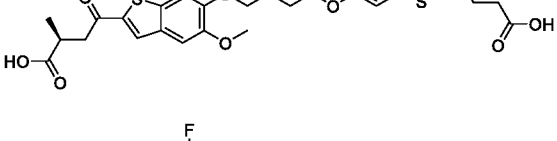
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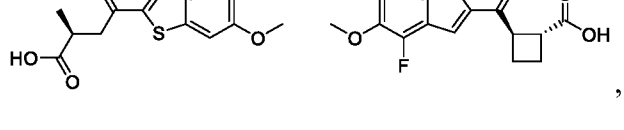
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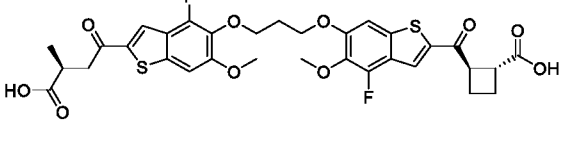
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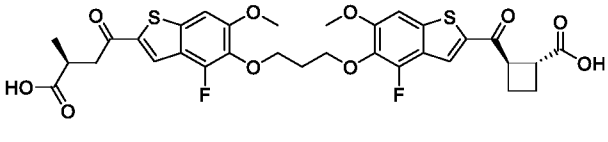
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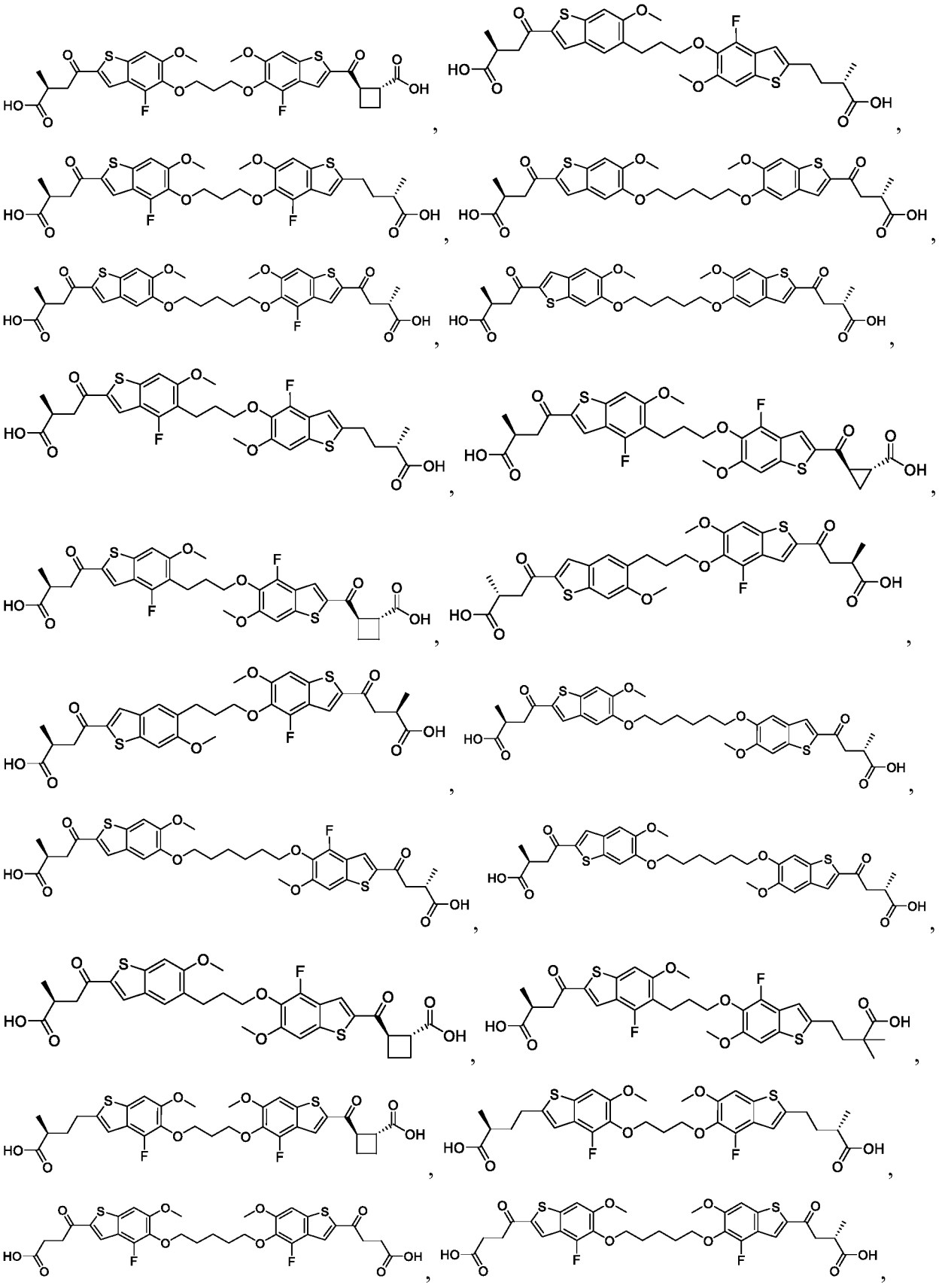

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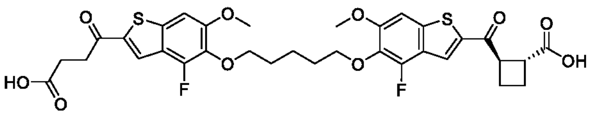
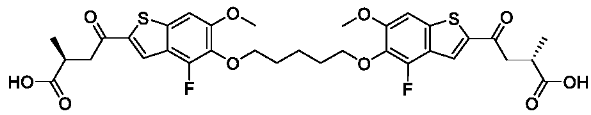
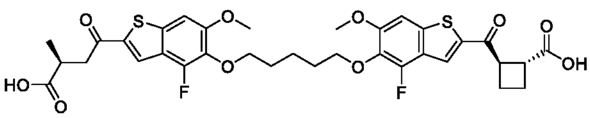
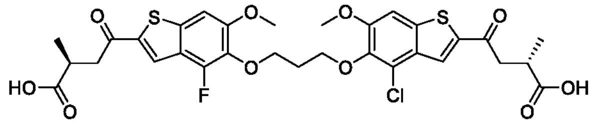
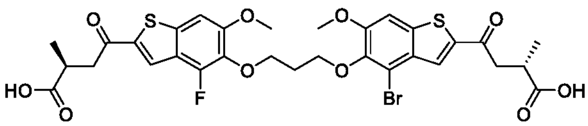
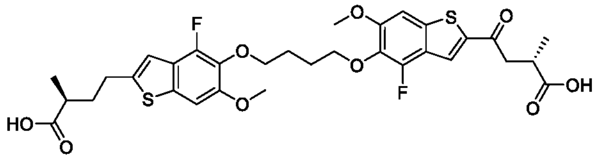
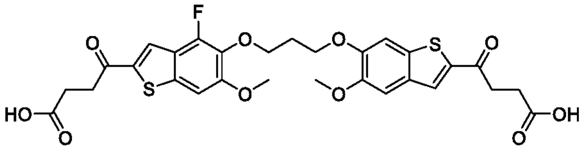
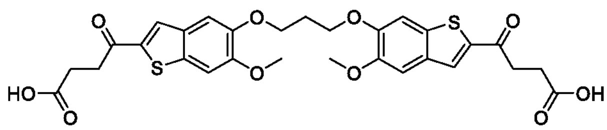
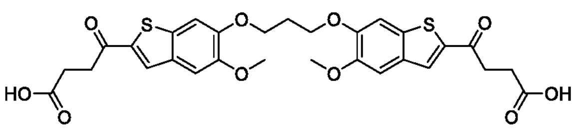
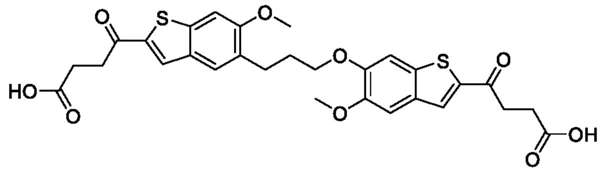
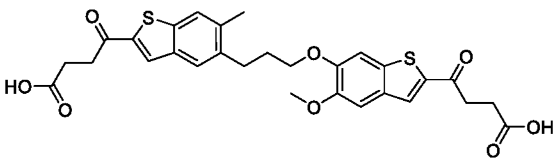
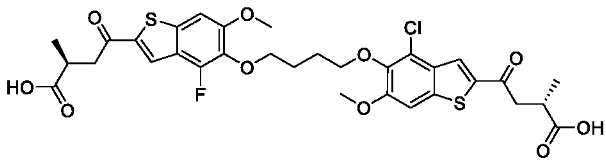
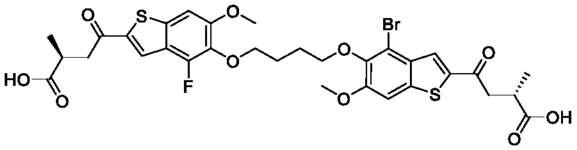
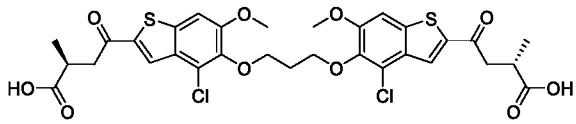
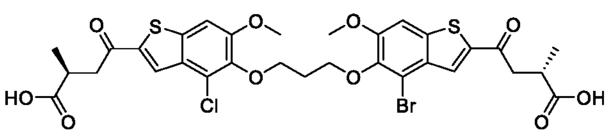
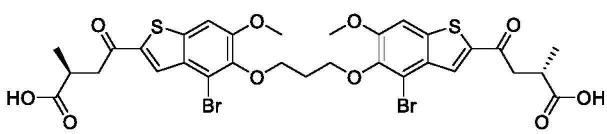
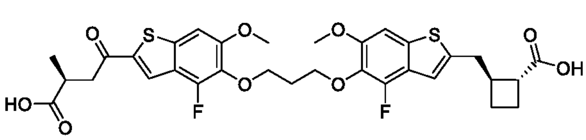
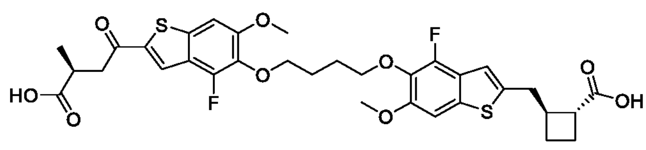
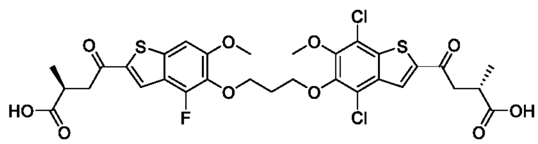
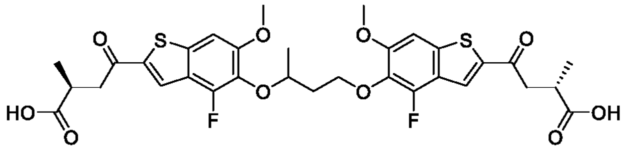
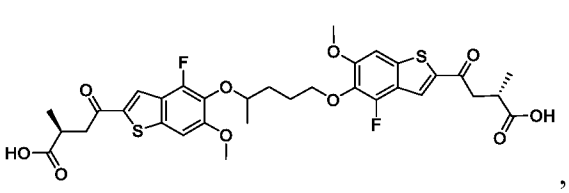
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
,  ,
 ,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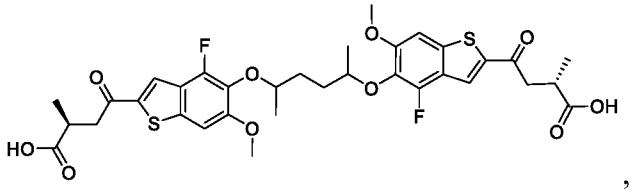
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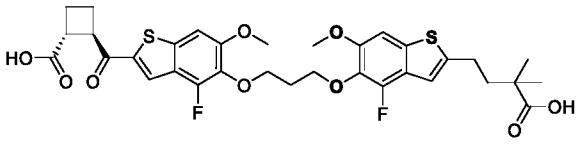
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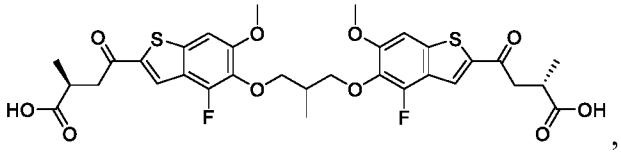
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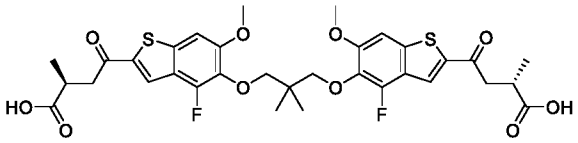
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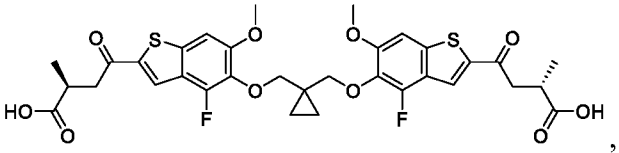
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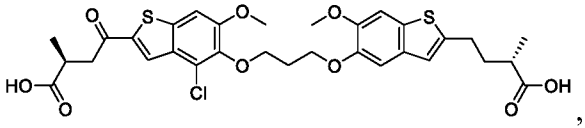
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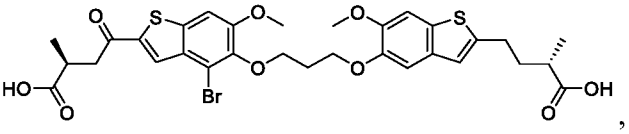
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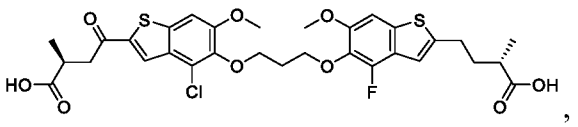
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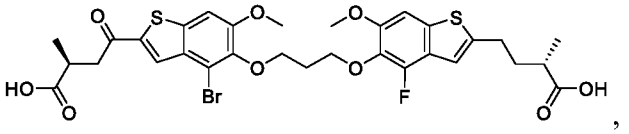
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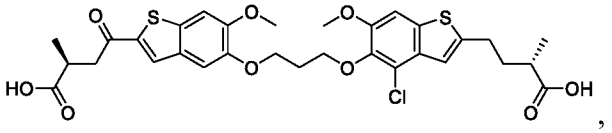
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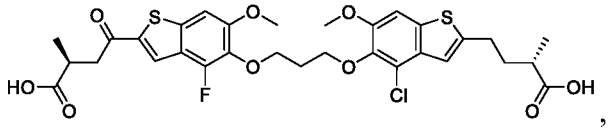
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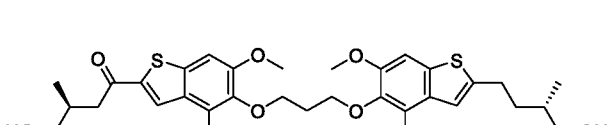
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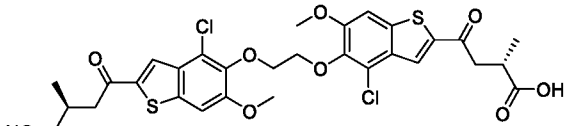
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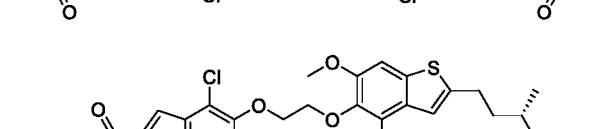
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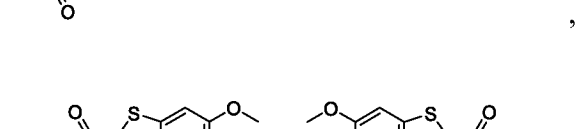
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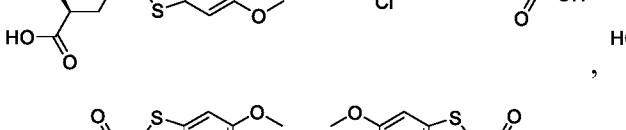
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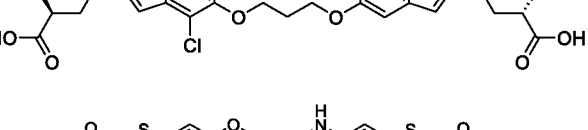
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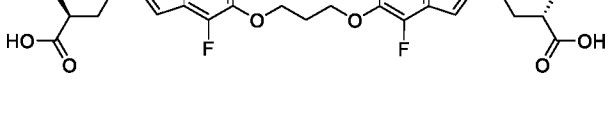
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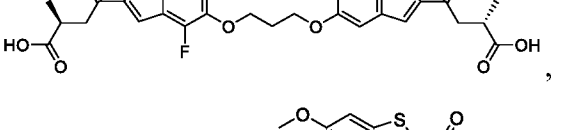
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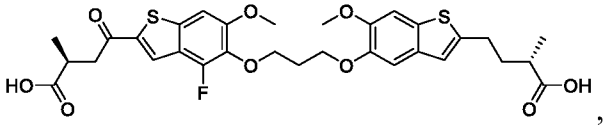
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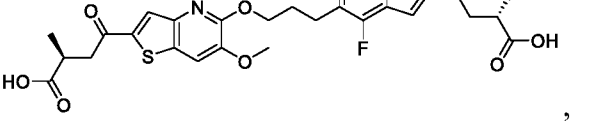
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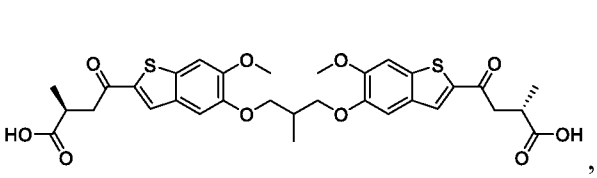
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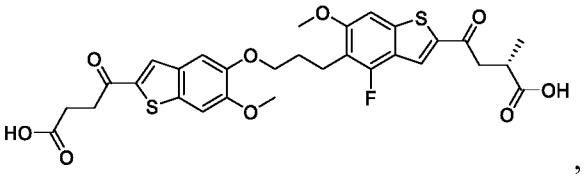
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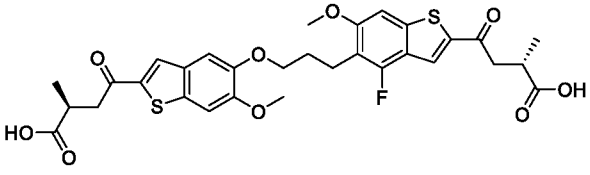
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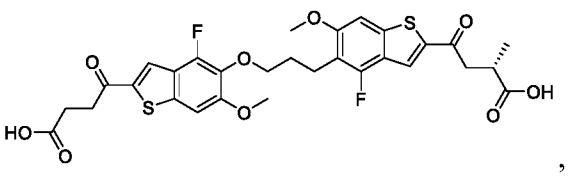
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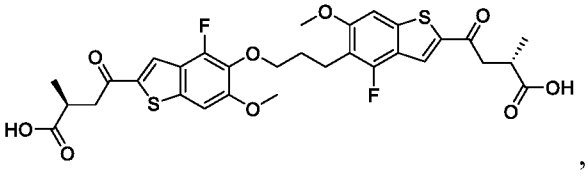
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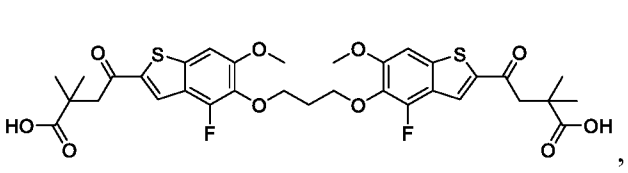
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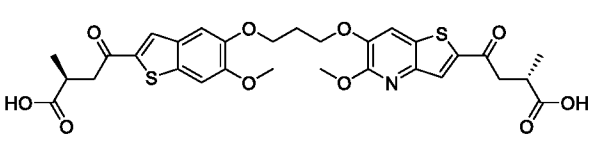
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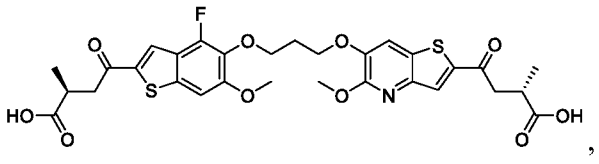
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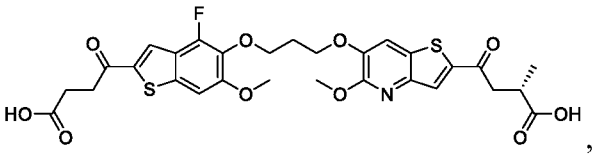
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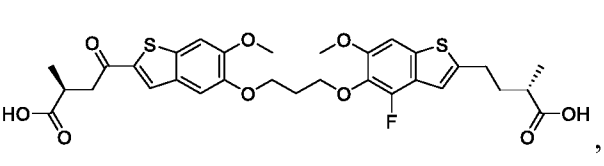
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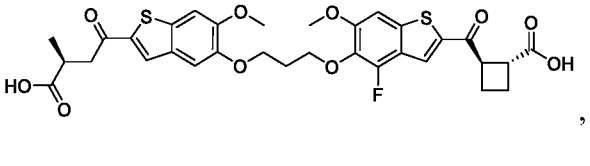
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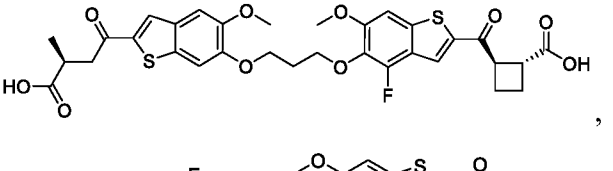
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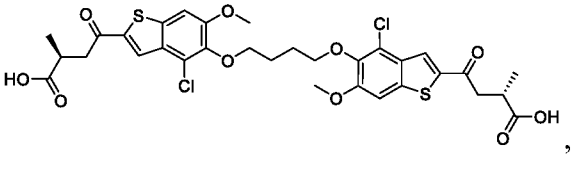
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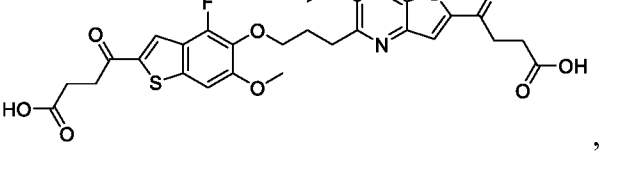
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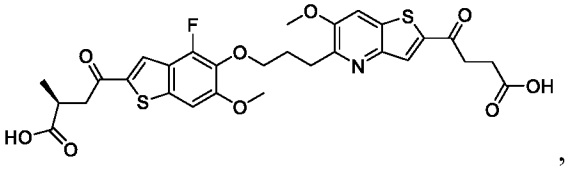
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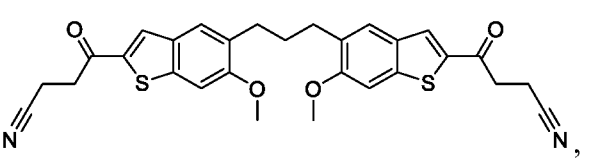
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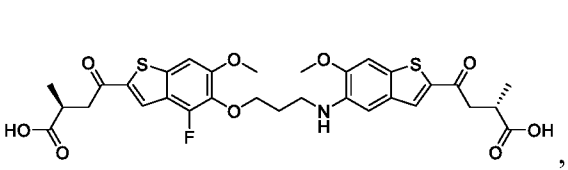
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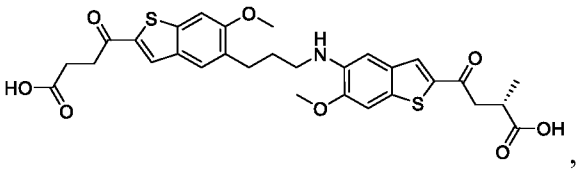
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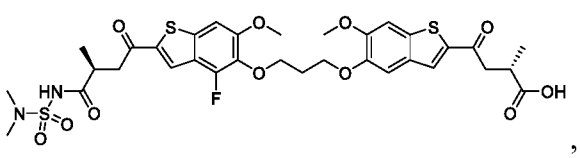
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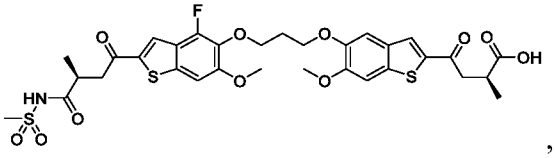
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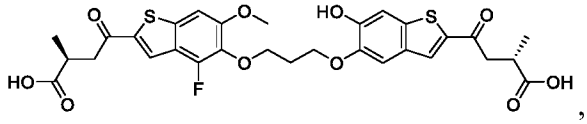
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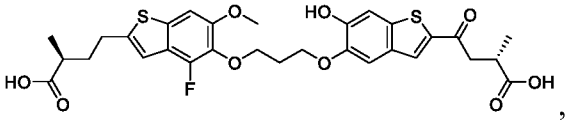
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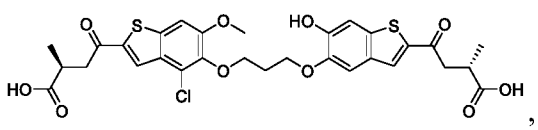
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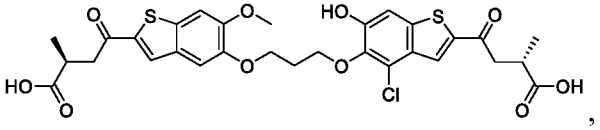
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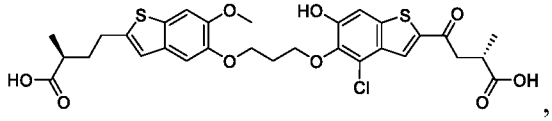
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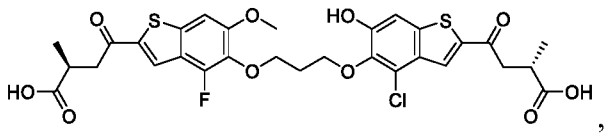
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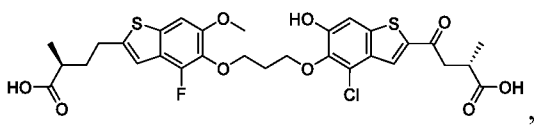
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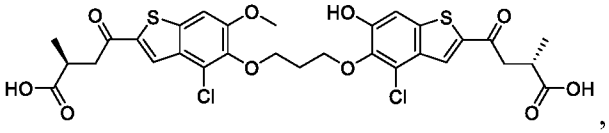
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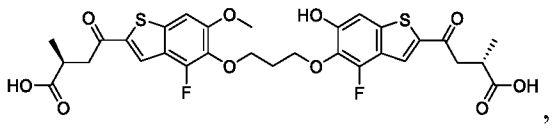
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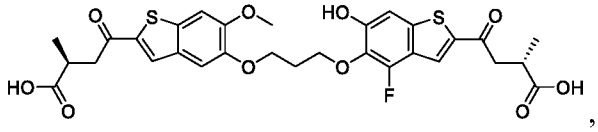
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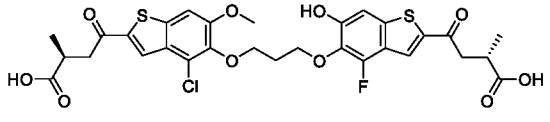
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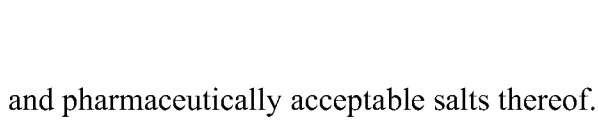
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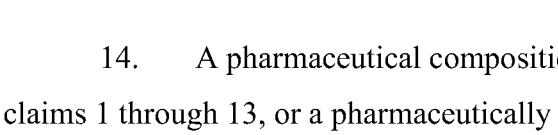

, and pharmaceutically acceptable salts thereof.

14. A pharmaceutical composition comprising a compound according to any one of claims 1 through 13, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

15. A method of inducing an immune response in a subject, said method comprising:

administering a therapeutically effective amount of a compound according to any one of claims 1 through 13, or a pharmaceutically acceptable salt thereof, to the subject.

16. A method of inducing an immune response in a subject, said method comprising:

administering a therapeutically effective amount of a pharmaceutical composition according to claim 14 to the subject.

17. A method of inducing STING-dependent type I interferon production in a subject, said method comprising administering a therapeutically effective amount of a compound according to any one of claims 1 through 13, or a pharmaceutically acceptable salt thereof, to the subject.

18. A method of inducing STING-dependent type I interferon production in a subject, said method comprising administering a therapeutically effective amount of a pharmaceutical composition according to claim 14 to the subject.

19. A compound according to any one of claims 1 through 13, or a pharmaceutically acceptable salt thereof, for use in therapy.

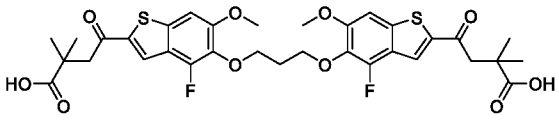
20. Use of a compound according to any one of claims 1 through 13, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a cell proliferation disorder in a subject.

21. The use according to claim 20, wherein the cell proliferation disorder is cancer.

22. Use of a pharmaceutical composition according to claim 14 in the manufacture of a medicament for treating a cell proliferation disorder in a subject.

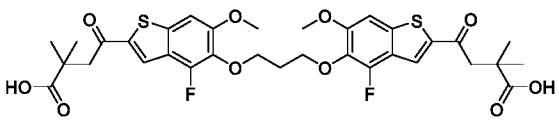
23. The use according to claim 22, wherein the cell proliferation disorder is cancer.

24. A compound selected from the group consisting of



and pharmaceutically acceptable salts thereof.

25. The compound according to claim 24, wherein the compound is



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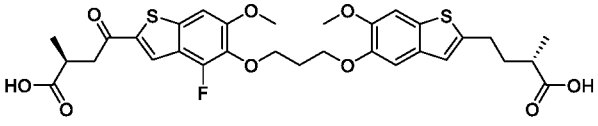
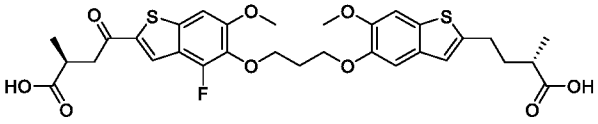


and pharmaceutically acceptable salts thereof.

27. The compound according to claim 26, wherein the compound is



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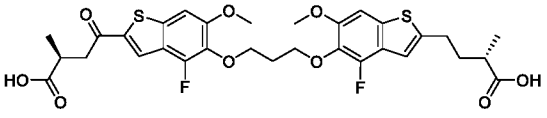
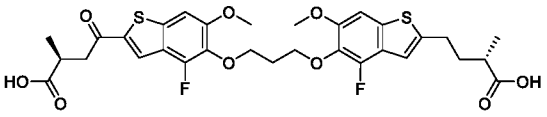


and pharmaceutically acceptable salts thereof.

29. The compound according to claim 28, wherein the compound is



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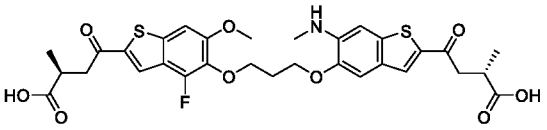
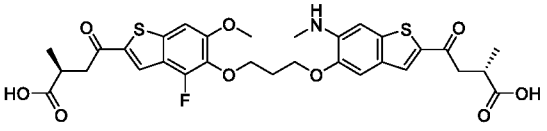


and pharmaceutically acceptable salts thereof.

31. The compound according to claim 30, wherein the compound is



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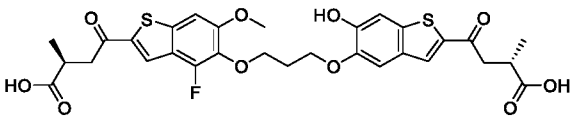
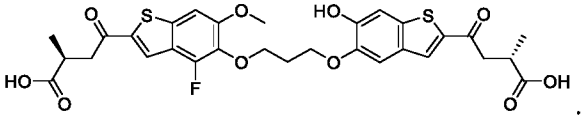


and pharmaceutically acceptable salts thereof.

33. The compound according to claim 328, wherein the compound is



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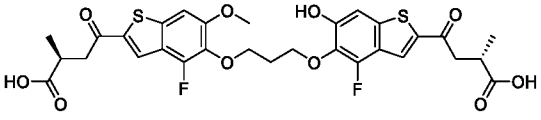
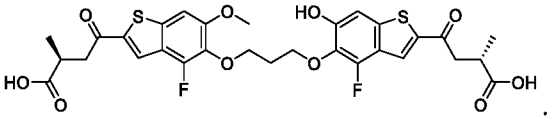


and pharmaceutically acceptable salts thereof.

35. The compound according to claim 34, wherein the compound is



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HAIDLE, ANDREW MARC
HENDERSON, TIMOTHY J.
JEWELL, JAMES P.
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Ala Arg Ile Arg Thr Tyr Asn Gln His Tyr Asn Asn Leu Leu Arg Gly
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