(12) STANDARD PATENT (11) Application No. **AU 2016366680 B2**
(19) AUSTRALIAN PATENT OFFICE

(54) Title
Benzothiophene-based selective estrogen receptor downregulators

(51) International Patent Classification(s)
C07D 409/04 (2006.01) ***C07D 409/12*** (2006.01)
A61K 31/381 (2006.01)

(21) Application No: **2016366680** (22) Date of Filing: **2016.12.09**

(87) WIPO No: **WO17/100712**

(30) Priority Data

(31) Number	(32) Date	(33) Country
62/322,878	**2016.04.15**	**US**
62/264,971	**2015.12.09**	**US**

(43) Publication Date: **2017.06.15**
(44) Accepted Journal Date: **2021.06.24**

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(56) Related Art
WO 2014130310 A1
WO 2014066695 A1

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
15 June 2017 (15.06.2017)

WIPO | PCT

(10) International Publication Number
WO 2017/100712 A1

(51) International Patent Classification:
A61K 31/381 (2006.01) *C07D 409/12* (2006.01)
C07D 409/04 (2006.01)

(21) International Application Number:
PCT/US2016/066023

(22) International Filing Date:
9 December 2016 (09.12.2016)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/264,971 9 December 2015 (09.12.2015) US
62/322,878 15 April 2016 (15.04.2016) US

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

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

Published:

— *with international search report (Art. 21(3))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

(54) Title: BENZOTHIOPHENE-BASED SELECTIVE ESTROGEN RECEPTOR DOWNREGULATORS

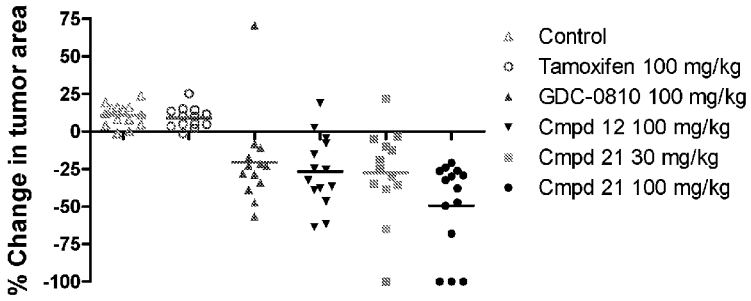


FIG. 7B

(57) Abstract: This invention is benzothiophene-based estrogen receptor downregulators and their compositions and uses to treat estrogen-related medical disorders.

WO 2017/100712 A1

BENZOTHIOPHENE-BASED SELECTIVE ESTROGEN RECEPTOR DOWNREGULATORS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application 62/264,971 filed December 9, 2015, and U.S. Provisional Application 62/322,878 filed April 15, 2016. The entirety of these applications is hereby incorporated by reference for all purposes.

TECHNICAL FIELD

This invention provides compounds and compositions that include benzothiophene-based estrogen receptor ligands and uses of these compounds to treat estrogen-related medical disorders.

STATEMENT OF GOVERNMENTAL INTEREST

This invention was made with government support under contract no. 1R01CA188017-01A1 awarded by the National Institutes of Health. The government has certain rights in this invention.

BACKGROUND OF THE INVENTION

Estrogens are the primary female hormones responsible for the development and regulation of the female reproductive system and secondary female sex characteristics. Estrogens also have pleotropic roles in protein synthesis, coagulation, lipid balance, fluid balance, melanin, gastrointestinal track function, lung function, cognition, immune response and heart disease, among others.

The estrogen receptor ("ER") is a ligand-activated transcriptional regulatory protein that mediates induction of the variety of biological effects through its interaction with endogenous estrogens, including 17β-estradiol and estrones. ER has been found to have two isoforms, ER-α and ER-β, and both receptors are involved in the regulation and development of the female reproductive tract.

ERs and estrogens regulate biological processes through several distinct pathways. The classical pathway involves the binding of a ligand-activated ER to a specific DNA sequence motif called an estrogen response element (ERE). ERs can also participate in non-classical pathways such as ERE-independent gene transcription via protein-protein interactions with other transcription factors, non-genomic pathways with rapid effects, and ligand-independent pathways that involve activation through other signaling pathways. This ER signaling is not only crucial for the development and maintenance of female reproductive organs, but also for bone metabolism and mass, lipid metabolism, cardiovascular protection, and central nervous system signaling.

Research in this area has confirmed the enormous complexity of estrogen and ER activities. A goal of drug development has been to create new compounds that modulate estrogen activity, either by acting as an antagonist or an agonist, or a partial antagonist or partial agonist.

One goal has been to identify complete anti-estrogens (complete antagonists) that have the effect of shutting down all estrogenic activity in the body. Fulvestrant is an example of a complete estrogen receptor antagonist with no agonist activity. It is a selective estrogen receptor downregulator (SERD). Fulvestrant was disclosed by Imperial Chemical Industries (ICI) in U.S. Patent No. 4,659,516 and is sold by AstraZeneca under the name Faslodex. It is indicated for the treatment of hormone receptor positive metastatic breast cancer in post-menopausal women with disease progression following anti-estrogen therapy. Fulvestrant has limited water solubility and requires monthly intramuscular (IM) injections. Fulvestrant's aqueous insolubility creates a challenge to achieve and maintain efficacious serum concentrations.

Another class of anti-estrogens are selective estrogen receptor modulators (SERMs) which act as antagonists or agonists in a gene-specific and tissue-specific fashion. A goal of SERM therapy is to identify drugs with mixed profiles that afford beneficial target anti-estrogenic activity and either avoid adverse off-target effects or exhibit incidental beneficial estrogenic side effects. An example of a SERM is tamoxifen, initially sold by AstraZeneca under the name Nolvadex. Tamoxifen was also disclosed by ICI in U.S. Patent No. 4,659,516, (see also U.S. Patent Nos. 6,774,122 and 7,456,160). Tamoxifen is a prodrug that is metabolized to 4-hydroxytamoxifen and N-desmethyl-4-hydroxytamoxifen which have high binding affinity to the estrogen receptor. Tamoxifen is indicated to prevent further breast cancer after breast cancer treatment and to treat node-positive breast cancer in women following mastectomy and radiation. Tamoxifen can affect bone health. In pre-menopausal women, tamoxifen can cause bone thinning, while it can be

beneficial for bone health in post-menopausal woman. Serious side effects have been noted, including increased risk of uterine cancer in post-menopausal women and "tumor flares" in women with breast cancer that has spread to the bone. In addition to these side effects, some women who initially respond to tamoxifen experience acquired resistance over time, and in some cases ER positive breast cancer not only becomes resistant to tamoxifen, but tamoxifen becomes an agonist which induces tumor proliferation.

A third line of treatment for breast cancer includes steroidal and non-steroidal aromatase inhibitors that block the production of estrogen and therefore block ER-dependent growth. These drugs, which include letrozole, anastrozole, and exemestane, have the risk of removing all estrogens from women after menopause, increasing the risk of bone thinning, osteoporosis, and fractures.

A number of SERDs, SERMs, and aromatase inhibitors have been disclosed. The SERM raloxifene was disclosed by Eli Lilly in 1981 (U.S. Patent Nos. 4,418,068; 5,478,847; 5,393,763; and 5,457,117) for prevention of breast cancer and treatment of osteoporosis. In June 2011, Aragon Pharmaceuticals disclosed benzopyran derivatives and acolbifene analogs for treatment of tamoxifen-resistant breast cancer (see WO2011/156518, US Patent Nos. 8,455,534 and 8,299,112). Aragon became Seragon in 2013, and was purchased by Genentech in 2014. See also U.S. Patent Nos. 9,078,871; 8,853,423; 8,703,810; US 2015/0005286; and WO 2014/205138. Genentech is now developing Brilanstrant (GDC-0810, formerly ARN-810) for the treatment of locally advanced or metastatic estrogenic receptor positive breast cancer.

Genentech disclosed a series of tetrahydro-pyrido[3,4-b]indol-1-yl compounds with estrogen receptor modulation activity in US2016/0175289 and a combination therapy of three compounds, one of which was GDN-0810, for estrogen receptor modulation in US2015/0258080.

AstraZeneca is currently developing AZD9496, a novel, oral selective estrogen receptor downregulator in patients with estrogen receptor positive breast cancer (WO 2014/191726).

Additional anti-estrogenic compounds are disclosed in WO 2012/084711; WO 2002/013802; WO 2002/004418; WO 2002/003992; WO 2002/003991; WO 2002/003990; WO 2002/003989; WO 2002/003988; WO 2002/003986; WO 2002/003977; WO 2002/003976; WO 2002/003975; WO 2006/078834; US 6821989; US 2002/0128276; US 6777424; US 2002/0016340; US 6326392; US 6756401; US 2002/0013327; US 6512002; US 6632834; US

2001/0056099; US 6583170; US 6479535; WO 1999/024027; US 6005102; EP 0802184; US 5998402; US 5780497 and US 5880137.

J-Pharma is currently developing benzothiophene compounds for the treatment of disorders related to urate transportation. See for example WO 2012/048058.

Bionomics LTD is developing benzofurans, benzothiophenes, benzoselenophenes, and indoles for treatment of tubulin polymerization related disorders. See for example WO 2007/087684.

Additional benzothiophene compounds are disclosed in WO 2010/127452, WO 2010/093578, WO 2009/013195, EP1947085, JP 2005-129430, US 2007/0112009, WO 2005/016929, EP0752421, EP0622673, EP0551849, EP0545478, US 5,491,123, and WO 2006/084338.

Given the often devastating effects of estrogen-modulated disorders, including cancer, tumors, and in particular breast cancer, there remains a strong need to create new drugs that have significant anti-estrogenic efficacy without unacceptable side effects.

SUMMARY OF THE INVENTION

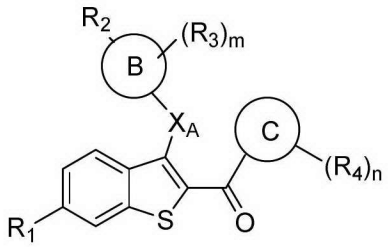
Benzothiophene compounds and their pharmaceutically acceptable salts are provided that have advantageous selective estrogen receptor modulating activity, and in particular, anti-estrogenic activity. The compounds can be used for the treatment of a patient, typically a human, with an estrogen-related medical disorder, including but not limited to a cancer or a tumor by administering an effective amount to the patient in need thereof, optionally in a pharmaceutically acceptable carrier. In certain embodiments, the cancer is selected from breast, ovarian, endometrial, kidney, and uterine. In another embodiment the cancer is metastatic endocrine therapy resistant breast cancer. Alternatively, a compound or its pharmaceutically acceptable salt can be used to prevent an estrogen-mediated disorder, including but not limited to a cancer or a tumor, including breast, ovarian, endometrial, kidney, and uterine cancer. In some embodiments, the compound is used following chemotherapy or radiation treatment to avoid recurrence, or instead of chemotherapy or radiation as a primary treatment.

In one embodiment, a compound of the present invention is a selective estrogen downregulator (SERD). In another embodiment, a compound of the present invention can be a

selective mixed estrogen receptor downregulator (SMERD). In one embodiment the compound antagonizes E_2 in breast epithelial cells and causes significant degradation of ERα.

In one aspect, a compound of the present invention or its pharmaceutically acceptable salt or prodrug, can be used to treat a hormone-related cancer or tumor that has metastasized to the brain, bone or other organ. In one embodiment of this aspect, the hormone-related cancer is estrogen mediated. In another embodiment, the estrogen mediated cancer is selected from breast, uterine, ovarian and endometrial. In other embodiments, a compound of the present invention or its pharmaceutically acceptable salt or prodrug, can be used to prevent a hormone-related cancer or tumor from metastasizing to the brain, bone or other organ, including a hormone-related cancer that is estrogen mediated, for example, breast, uterine, ovarian or endometrial.

In one aspect, this invention is a compound of Formula A, or a pharmaceutically acceptable salt thereof:



Formula A

wherein:

m is 0, 1, 2, 3, or 4;

n is 0, 1, 2, 3, or 4;

X_A is selected from -O-, -CH_2-, -S-, -NH-, -NMe-, -CF_2-, and C_3cycloalkyl;

Ring B is phenyl, naphthyl, quinolinyl, 5- or 6- membered monocyclic heteroaryl or 7-, 8-, 9- or 10 membered bicyclic heterocyclyl;

Ring C is phenyl, thiophenyl, 5- or 6- membered monocyclic heteroaryl or 7-, 8-, 9- or 10-membered bicyclic heterocyclyl;

R_1 is selected from hydroxyl, hydrogen, halogen, –O(C_1-C_6 alkyl), –OC(O)(C_1-C_6 alkyl), –OC(O)C_6H_5, –OC(O)O(C_1-C_6 alkyl), –OC(O)OC_6H_5 and –OSO_2(C_2-C_6 alkyl);

R_2 is selected from –CH=CHCOOH, –NH(CO)COOH, –COOH, -C_2-C_6alkenylene-COOH and -C_2-C_6alkynylene-COOH;

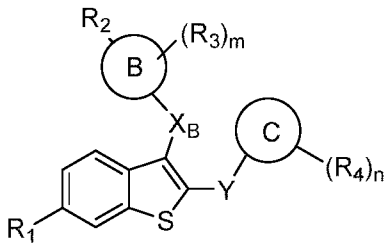
R_3 is independently selected at each occurrence from hydrogen, halogen, –CN, –NO_2, -C_1-C_6alkyl and -C_1-C_6fluoroalkyl; and

R_4 is independently selected at each occurrence from hydrogen, halogen, hydroxyl, -C_1-C_6alkyl, -C_1-C_6fluoroalkyl, –CN, –O(C_1-C_6 alkyl), and –O(C_1-C_6fluoroalkyl).

In another aspect, this invention includes a pharmaceutical composition that includes a compound of Formula A and a pharmaceutically acceptable carrier or excipient.

In another aspect, this invention is a method to treat or prevent a tumor or cancer that includes administering to a subject, typically a human, in need of such treatment, a therapeutically effective amount of a compound of Formula A or a pharmaceutically acceptable salt thereof.

In another aspect, this invention is a compound of Formula B, or a pharmaceutically acceptable salt thereof:



Formula B

wherein:

m is 0, 1, 2, 3, or 4;

n is 0, 1, 2, 3, or 4;

X_B is selected from -O-, -CH_2-, -S-, -NH-, -NMe-, -CF_2-, and -C_3cycloalkyl-;

Y is selected from -C(O)-, -O-, -CF_2-, or -C_3cycloalkyl-, -CH_2-, -S-, -NH-, and -N(Me)-;

Ring B is phenyl, naphthyl, quinolinyl, 5- or 6- membered monocyclic heteroaryl or 7-, 8-, 9- or 10 membered bicyclic heterocyclyl;

Ring C is phenyl, thiophenyl (i.e., thienyl), 5- or 6- membered monocyclic heteroaryl or 7-, 8-, 9- or 10- membered bicyclic heterocyclyl;

R_1 is selected from hydroxyl, hydrogen, halogen, –O(C_1-C_6 alkyl), –OC(O)(C_1-C_6 alkyl),

–OC(O)C_6H_5, –OC(O)O(C_1-C_6 alkyl), –OC(O)OC_6H_5 and –OSO_2(C_2-C_6 alkyl);

R_2 is selected from –CH=CHCOOH, –NH(CO)COOH, –COOH, -C_2-C_6alkenylene-COOH and -C_2-C_6alkynylene-COOH;

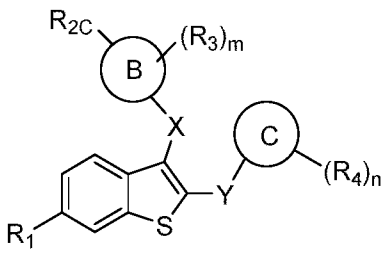
R_3 is independently selected at each occurrence from hydrogen, halogen, –CN, –NO_2, -C_1-C_6alkyl and -C_1-C_6fluoroalkyl; and

R_4 is independently selected at each occurrence from hydrogen, halogen, hydroxyl, -C_1-C_6alkyl, -C_1-C_6fluoroalkyl, –CN, –O(C_1-C_6 alkyl), and –O(C_1-C_6fluoroalkyl).

In another aspect, this invention includes a pharmaceutical composition that includes a compound of Formula B and a pharmaceutically acceptable carrier or excipient.

In another aspect, this invention is a method to treat or prevent a tumor or cancer that includes administering to a subject such as a human in need of such treatment a therapeutically effective amount of a compound of Formula B or a pharmaceutically acceptable salt thereof.

In another aspect, this invention provides a compound of Formula C:



Formula C

wherein:

m is 0, 1, 2, 3, or 4;

n is 0, 1, 2, 3, or 4;

X is selected from -O-, -C(O)-, -CH_2-, -S-, -NH-, -NMe-, -CF_2-, and -C_3cycloalkyl-;

Y is selected from -C(O)-, -O-, -CF_2-, or -C_3cycloalkyl-, -CH_2-, -S-, -NH-, and -N(Me)-;

Ring B is phenyl, naphthyl, quinolinyl, 5- or 6- membered monocyclic heteroaryl, cycloalkyl, or 7-, 8-, 9- or 10 membered bicyclic heterocyclyl;

Ring C is phenyl, thiophenyl (i.e., thienyl), 5- or 6- membered monocyclic heteroaryl, cycloalkyl or 7-, 8-, 9- or 10- membered bicyclic heterocyclyl;

R_1 is selected from hydroxyl, hydrogen, halogen, –O(C_1-C_6 alkyl), –OC(O)(C_1-C_6 alkyl),

–OC(O)C_6H_5, –OC(O)O(C_1-C_6 alkyl), –OC(O)OC_6H_5 and –OSO_2(C_2-C_6 alkyl);

R_{2C} is selected from –CH=CHCOOH, –NH(CO)COOH, -cycloalkyl(COOH), -C_2-C_6alkenylene-COOH, and -C_2-C_6alkynylene-COOH.

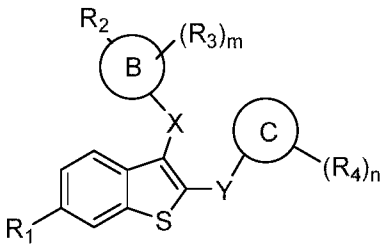
R_3 is independently selected at each occurrence from hydrogen, halogen, –CN, –NO_2, -C_1-C_6alkyl and -C_1-C_6fluoroalkyl; and

R_4 is independently selected at each occurrence from hydrogen, halogen, hydroxyl, -C_1-C_6alkyl, -C_1-C_6fluoroalkyl, –CN, –O(C_1-C_6 alkyl), and –O(C_1-C_6fluoroalkyl).

In another aspect, this invention includes a pharmaceutical composition that includes one or more compounds of Formula C and a pharmaceutically acceptable carrier or excipient.

In another aspect, this invention is a method to treat or prevent a tumor or cancer that includes administering to a subject such as a human in need of such treatment a therapeutically effective amount of a compound of Formula C or a pharmaceutically acceptable salt thereof.

In one aspect, this invention is a compound of Formula D, or a pharmaceutically acceptable salt thereof:



Formula D

wherein:

m is 0, 1, 2, 3, or 4;

n is 0, 1, 2, 3, or 4;

X is selected from -O-, -C(O)-, -CH_2-, -S-, -NH-, -NMe-, -CF_2-, and -C_3cycloalkyl-;

Y is selected from -C(O)-, -O-, -CF_2-, or -C_3cycloalkyl-, -CH_2-, -S-, -NH-, and -NMe-;

Ring B is phenyl, naphthyl, quinolinyl, 5- or 6- membered monocyclic heteroaryl or 7-, 8-, 9- or 10 membered bicyclic heterocyclyl;

Ring C is phenyl, thiophenyl (i.e., thienyl), 5- or 6- membered monocyclic heteroaryl or 7-, 8-, 9- or 10- membered bicyclic heterocyclyl;

R_1 is selected from hydroxyl, hydrogen, halogen, –O(C_1-C_6 alkyl), –OC(O)(C_1-C_6 alkyl), –OC(O)C_6H_5, –OC(O)O(C_1-C_6 alkyl), –OC(O)OC_6H_5 and –OSO_2(C_2-C_6 alkyl);

R_2 is selected from –CH=CHCOOH, –NH(CO)COOH, –COOH, C_2-C_6alkenylene-COOH and C_2-C_6alkynylene-COOH;

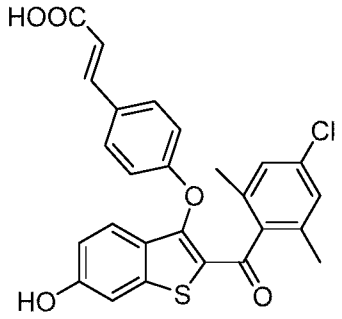
R_3 is independently selected at each occurrence from hydrogen, halogen, –CN, –NO_2, C_1-C_6alkyl and -C_1-C_6fluoroalkyl; and

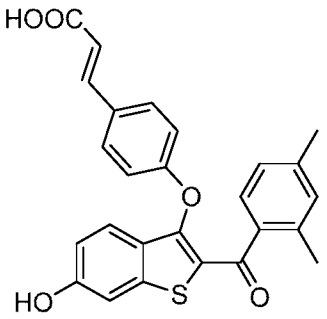
R_4 is independently selected at each occurrence from hydrogen, halogen, hydroxyl, -C_1-C_6alkyl, -C_1-C_6fluoroalkyl, –CN, –O(C_1-C_6 alkyl), and –O(C_1-C_6fluoroalkyl).

In another aspect, this invention includes a pharmaceutical composition that includes one or more compounds of Formula D and a pharmaceutically acceptable carrier or excipient.

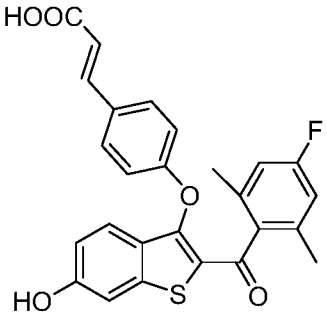
In another aspect, this invention is a method to treat or prevent cancer or a tumor that includes administering to a subject such as a human in need of such treatment a therapeutically effective amount of a compound of Formula D or a pharmaceutically acceptable salt thereof.

In certain embodiments, the compound has the structure selected from, or is a pharmaceutically acceptable salt thereof:





and



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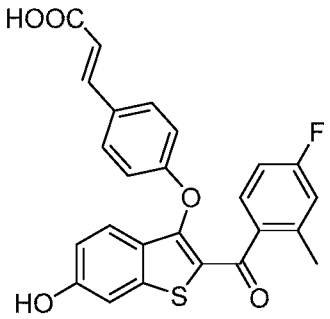
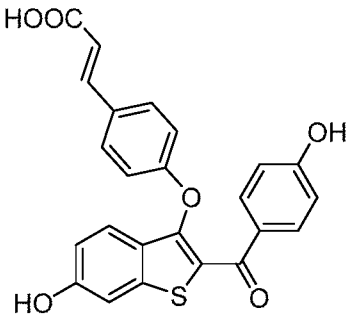
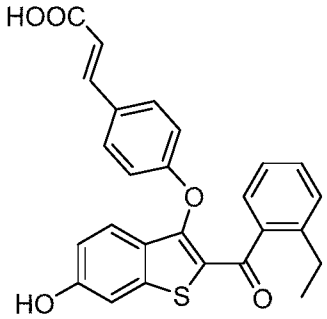
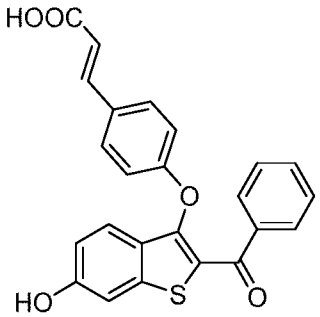
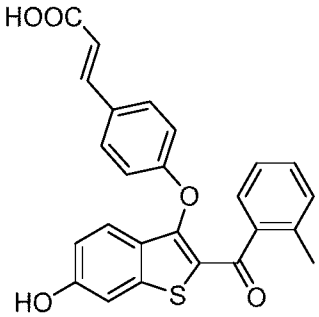
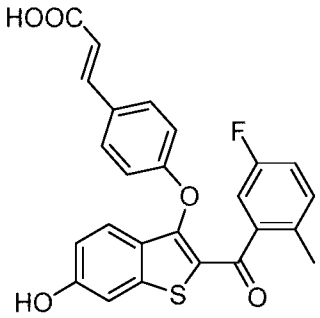
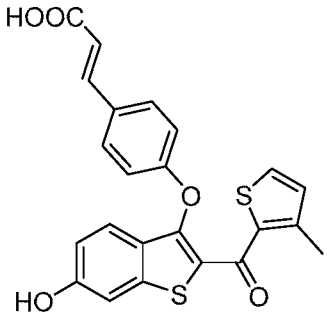
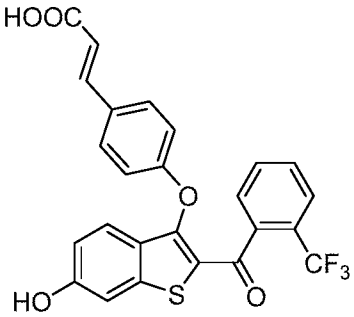
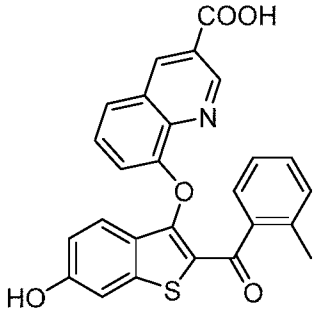
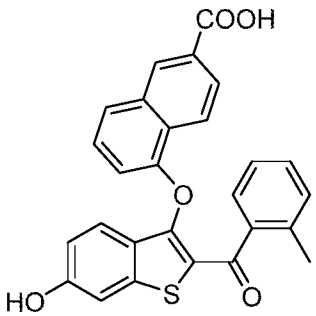
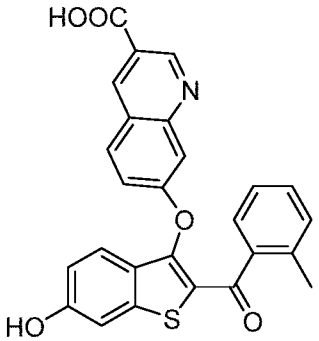
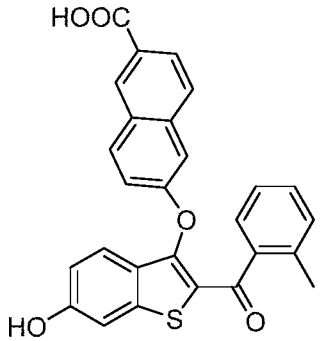
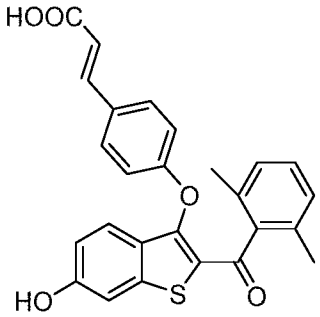
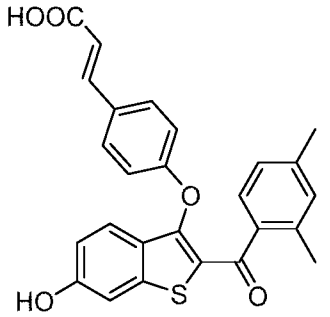
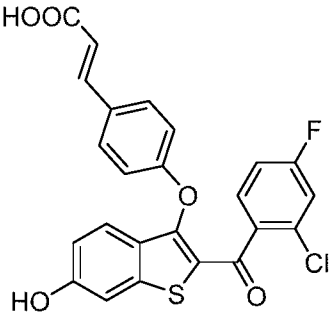
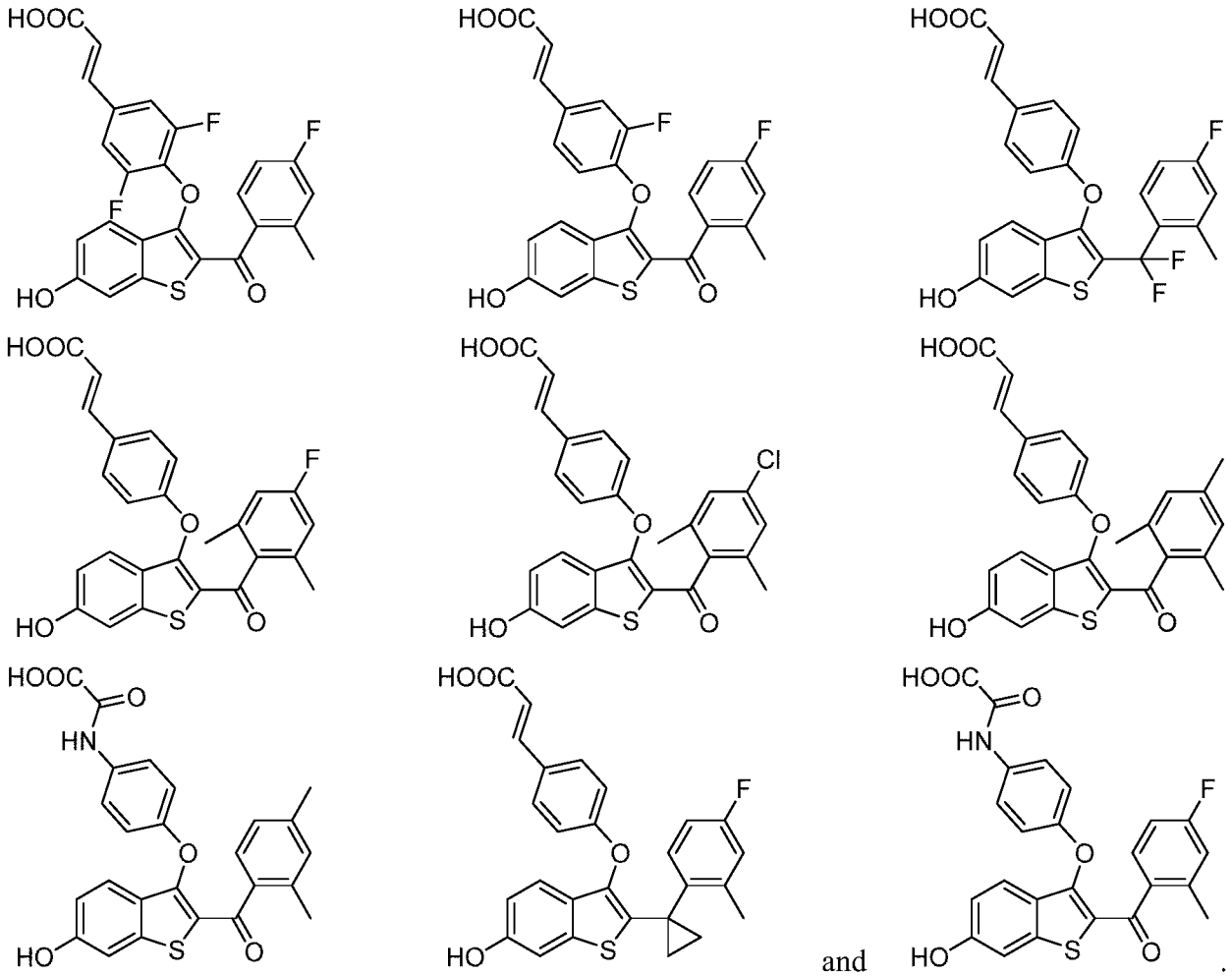
In other embodiments, the compound is selected from the following, or is a pharmaceutically acceptable salt thereof:



and .

In certain embodiments of the above structures that have a $-CO_2H$, the compound can be presented, for example, as an ester, amide, or ether prodrug. The ester may be, for example, $-CO_2R$, wherein R is alkyl (including cycloalkyl), heteroalkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclic, or any other moiety that is metabolized in vivo to provide the parent drug.

The present invention includes at least the following features:

(a) a compound as described herein, or a pharmaceutically acceptable salt or prodrug thereof;

(b) a compound as described herein, or a pharmaceutically acceptable salt or prodrug thereof that is useful in the treatment or prevention of an estrogen-related disorder, including without limitation a tumor or cancer;

(c) use of a compound as described herein, or a pharmaceutically acceptable salt or prodrug thereof in the manufacture of a medicament for the treatment or prevention of an estrogen-related disorder, including but not limited to a tumor or cancer;

(d) a method for manufacturing a medicament for the therapeutic use to treat or prevent a disorder of abnormal cellular proliferation including but not limited to a tumor or cancer, characterized in that a compound of the present invention or its salt or prodrug as described herein is used in the manufacture;

(e) a compound as described herein or its pharmaceutically acceptable salt or prodrug for use in the treatment or prevention of breast, kidney, uterine, ovarian or endometrial cancer;

(f) use of a compound as described herein or a pharmaceutically acceptable salt or prodrug thereof in the manufacture of a medicament for the treatment or prevention of breast, kidney, uterine, ovarian or endometrial cancer;

(g) a method for manufacturing a medicament for the therapeutic use in treating or preventing breast, kidney, uterine, ovarian or endometrial cancer, characterized in that a compound as described herein or its pharmaceutically acceptable salt or prodrug is used in the manufacture;

(h) a compound as described herein or a pharmaceutically acceptable salt or prodrug thereof for use in the treatment or prevention of hormone receptor positive metastatic breast cancer;

(i) use of a compound as described herein or a pharmaceutically acceptable salt or prodrug thereof in the manufacture of a medicament for the treatment or prevention of a hormone receptor positive metastatic breast cancer tumor;

(j) a method for manufacturing a medicament for treatment or prevention of a hormone receptor positive metastatic breast cancer, characterized in that a compound as described herein or its pharmaceutically acceptable salt or prodrug is used in the manufacture;

(k) a compound as described herein or a pharmaceutically acceptable salt or prodrug thereof for use to treat or prevent bone loss, including osteoporosis;

(l) use of a compound as described herein or a pharmaceutically acceptable salt or prodrug thereof in the manufacture of a medicament for the treatment or prevention of bone loss, including osteoporosis;

(m) a method for manufacturing a medicament for use to treat or prevent bone loss, including osteoporosis, characterized in that a compound as described herein is used in the manufacture;

(n) a pharmaceutical formulation comprising an effective treatment or prevention amount of a compound of a compound as described herein or a pharmaceutically acceptable salt or prodrug thereof together with a pharmaceutically acceptable carrier or diluent;

(o) a compound as described herein, or its pharmaceutically acceptable salt or prodrug as a mixture of enantiomers or diastereomers (as relevant), including as a racemate;

(p) a compound of the present invention as described herein in enantiomerically or diastereomerically (as relevant) enriched form, including as an isolated enantiomer or disastereomer (i.e., greater than 85, 90, 95, 97 or 99% pure); and,

(q) a process for the preparation of a therapeutic product that contain an effective amount of a compound as described herein, or its pharmaceutically acceptable salt or prodrug.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1A, FIG. 1B, FIG. 1C, FIG. 1D, and FIG. 1E are graphs of the efficacy of Compounds **1**, **5**, **11**, and **12** compared to known compound GDN-0810 against tamoxifen-resistant MCF-7:5C cells. The y-axis is normalized DNA content in percent and the x-axis is the concentration of compound measured in log(molar) units. The graph shows that representative compounds have sub-nanomolar efficacy in tamoxifen-resistant MCF-7:5C cells using DNA content assay.

FIG. 2A, FIG. 2B, FIG. 2C, and FIG. 2D are graphs of the efficacy of Compounds **11**, **12**, and **13** compared to known compound GDN-0810 against tamoxifen-resistant MCF-7:WS8 cells. The y-axis is normalized DNA content in percent and the x-axis is the concentration of compound measured in log(molar) units. The graph shows that representative compounds have sub-nanomolar efficacy in tamoxifen-resistant MCF-7:WS8 cells using DNA content assay.

FIG. 3 is a graph of the efficacy of Compounds **11** and **12** compared to known compound GDN-0810 GDN-0810 GDN-0810 GDN-0810 and prostaglandin E2 against MCF-7:ws8, T47D:A18, and T47D:A18-TAM1 tamoxifen resistant spheroid cells. The y-axis is normalized spheroid cell population where 1 is the population exposed to 100 nM DMSO (the control) and the x-axis is compound dosed at 100 nM concentrations. The graph shows that representative compounds of the invention have efficacy at 100 nM in multiple tamoxifen resistant and sensitive 3D cells.

FIG. 4 is a western blot analysis that shows the estrogen receptor downregulation at 10 nM concentrations of Compounds **1**, **3**, **4**, **5**, **6**, and **7** compared to the known compounds GDN-0810

and Raloxifene. The western blot shows that Compound **1**, **3**, **4**, **5**, **6**, and **7** all downregulate the estrogen receptor at 10 nM concentrations.

FIG. 5A is a graph demonstrating the cell viability of treatment resistance MCF-7:5C breast cancer cells. The y-axis is cell survival measured in percent and normalized to baseline measurements and the x-axis is concentration of GDN-0810 or Compound **21** measured in log(molar) units. The measurements were taken 4 days after treatment and normalized to 100% vehicle dosing.

FIG. 5B is a graph demonstrating the cell viability of treatment sensitive MCF-7:WS8 breast cancer cells. The y-axis is cell survival measured in percent and normalized to baseline measurements and the x-axis is concentration of GDN-0810 or Compound **21** measured in log(molar) units. The measurements were taken 4 days after treatment and normalized to 100% vehicle dosing.

FIG. 5C is a graph demonstrating the level of estrogen receptor downregulation measured in western blot experiments. The y-axis is estrogen receptor expression level measured in percent and normalized to baseline measurements and the x-axis is concentration of GDN-0810 or Compound **21** measured in log(molar) units. Data was normalized to 1 μM GDN-0810 as 0% and DMSO control as 100%.

FIG. 5D is a graph demonstrating the level of estrogen receptor antagonism measured in an ERE luciferase assay in MCF-7:WS8 cells. The y-axis is ERE luciferase level measured in percent and normalized to baseline measurements and the-x axis is concentration of GDN-0810 or Compound **21** measured in log(molar) units. Data was normalized to 1 uM GDN-0810 as 0% and 0.1 nM E_2 as 100%. Data show mean and s.e.m. from at least 3 cell passages.

FIG. 6 is cell microscopy images showing that SERDs inhibit growth of MCF-7:TAM1 spheroids after 10 days of treatment. Image A is spheroids in DMSO. Image B is spheroids in the presence of 1 nM concentration of GDN-0810. Image C is spheroids in the presence of 1 nM concentration of Compound **21**. Image D is spheroids in the presence of 10 nM concentration of Compound **21**.

FIG. 7A is a graph of tumor area using MCF7:TAM1 tumors that were grown to an average section area of 0.32 cm^2. The y-axis is tumor area measured in cm^2 and the x-axis is time measured in weeks. For the study, mice were randomized into six treatment groups: control, tamoxifen (100

mg/kg), GDN-0810 (100 mg/kg), Compound **12** (10 mg/kg), and two doses of Compound **21** (30 mg/kg and 100 mg/kg). Compounds were administrated by oral gavage daily.

FIG. 7B is a graph of tumor area using MCF7:TAM1 tumors that were grown to an average section area of 0.32 cm^2. The y-axis is change in tumor area measured as percent change at day 23 and the x-axis is compound identity. For the study, mice were randomized into six treatment groups: control, tamoxifen (100 mg/kg), GDN-0810 (100 mg/kg), Compound **12** (10 mg/kg), and two doses of Compound **21** (30 mg/kg and 100 mg/kg). Compounds were administrated by oral gavage daily.

FIG. 8A, FIG. 8B, and FIG. C are docketing images of Compounds **4**, **5**, and **21**. Compound **4** (A), **5** (B), and **21** (C) were docked to ER LBD (pdb ID: 5ak2). Compound **4** has minimum contacts with hydrophobic pockets (close to Phe 425 and Leu 384), while compound **5** and **21** have methyl groups that tightly fit into the hydrophobic cavity and correspond to better potency in cell viability assays.

FIG. 9 is the docked pose of Compound **4** docked to ERα LBD (pdb ID: 1R5K), showing similar global topology compared to the GW5638-ER complex. The acrylate side chain interaction with helix 12 is a key structural feature of SERD-ER complexes.

FIG. 10 is the docked pose of Compound **4** docked to ERα LBD (pdb ID: 1R5K). Residues within 5 Å of Compound **12** are highlighted and two hydrophobic cavities in the vicinity of Leu384 and Phe 425 are circled.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

The following terms and expressions used herein have the indicated meanings.

Terms used herein may be preceded and/or followed by a single dash, "-", or a double dash, "=", to indicate the bond order of the bond between the named substituent and its parent moiety; a single dash indicates a single bond and a double dash indicates a double bond. In the absence of a single or double dash it is understood that a single bond is formed between the substituent and its parent moiety; further, substituents are intended to be read "left to right" unless a dash indicates otherwise. For example, C_1-C_6alkoxycarbonyloxy and -OC(O)C_1-C_6 alkyl indicate the same functionality; similarly arylalkyl and –alkylaryl indicate the same functionality.

"Alkenyl" means a straight or branched chain hydrocarbon containing from 2 to 10 carbons, unless otherwise specified, and containing at least one carbon-carbon double bond. Representative examples of alkenyl include, but are not limited to, ethenyl, 2-propenyl, 2-methyl-2-propenyl, 3-butenyl, 4-pentenyl, 5-hexenyl, 2-heptenyl, 2-methyl-1-heptenyl, 3-decenyl, and 3,7-dimethylocta-2,6-dienyl.

"Alkoxy" means an alkyl group, as defined herein, appended to the parent molecular moiety through an oxygen atom. Representative examples of alkoxy include, but are not limited to, methoxy, ethoxy, propoxy, 2-propoxy, butoxy, *tert*-butoxy, pentyloxy, and hexyloxy.

"Alkyl" means a straight or branched chain hydrocarbon containing from 1 to 10 carbon atoms unless otherwise specified. Representative examples of alkyl include, but are not limited to, methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *sec*-butyl, *iso*-butyl, *tert*-butyl, *n*-pentyl, isopentyl, neopentyl, *n*-hexyl, 3-methylhexyl, 2,2-dimethylpentyl, 2,3-dimethylpentyl, *n*-heptyl, *n*-octyl, *n*-nonyl, and *n*-decyl. When an "alkyl" group is a linking group between two other moieties, then it may also be a straight or branched chain; examples include, but are not limited to $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CHC(CH_3)-$, and $-CH_2CH(CH_2CH_3)CH_2-$.

"Alkynyl" means a straight or branched chain hydrocarbon group containing from 2 to 10 carbon atoms and containing at least one carbon-carbon triple bond. Representative examples of alkynyl include, but are not limited, to acetylenyl, 1-propynyl, 2-propynyl, 3-butynyl, 2-pentynyl, and 1-butynyl.

"Aryl" means a phenyl (*i.e.*, monocyclic aryl), or a bicyclic ring system containing at least one phenyl ring or an aromatic bicyclic ring containing only carbon atoms in the aromatic bicyclic ring system. The bicyclic aryl can be azulenyl, naphthyl, or a phenyl fused to a monocyclic cycloalkyl, a monocyclic cycloalkenyl, or a monocyclic heterocyclyl. The bicyclic aryl is attached to the parent molecular moiety through any carbon atom contained within the phenyl portion of the bicyclic system, or any carbon atom with the napthyl or azulenyl ring. The fused monocyclic cycloalkyl or monocyclic heterocyclyl portions of the bicyclic aryl are optionally substituted with one or two oxo and/or thia groups. Representative examples of the bicyclic aryls include, but are not limited to, azulenyl, naphthyl, dihydroinden-1-yl, dihydroinden-2-yl, dihydroinden-3-yl, dihydroinden-4-yl, 2,3-dihydroindol-4-yl, 2,3-dihydroindol-5-yl, 2,3-dihydroindol-6-yl, 2,3-dihydroindol-7-yl, inden-1-yl, inden-2-yl, inden-3-yl, inden-4-yl, dihydronaphthalen-2-yl, dihydronaphthalen-3-yl, dihydronaphthalen-4-yl, dihydronaphthalen-1-yl, 5,6,7,8-

tetrahydronaphthalen-1-yl, 5,6,7,8-tetrahydronaphthalen-2-yl, 2,3-dihydrobenzofuran-4-yl, 2,3-dihydrobenzofuran-5-yl, 2,3-dihydrobenzofuran-6-yl, 2,3-dihydrobenzofuran-7-yl, benzo[d][1,3]dioxol-4-yl, benzo[d][1,3]dioxol-5-yl, 2H-chromen-2-on-5-yl, 2*H*-chromen-2-on-6-yl, 2*H*-chromen-2-on-7-yl, 2*H*-chromen-2-on-8-yl, isoindoline-1,3-dion-4-yl, isoindoline-1,3-dion-5-yl, inden-1-on-4-yl, inden-1-on-5-yl, inden-1-on-6-yl, inden-1-on-7-yl, 2,3-dihydrobenzo[b][1,4]dioxan-5-yl, 2,3-dihydrobenzo[b][1,4]dioxan-6-yl, 2*H*-benzo[b][1,4]oxazin3(4*H*)-on-5-yl, 2H-benzo[b][1,4]oxazin3(4*H*)-on-6-yl, 2*H*-benzo[b][1,4]oxazin3(4*H*)-on-7-yl, 2*H*-benzo[b][1,4]oxazin3(4*H*)-on-8-yl, benzo[d]oxazin-2(3H)-on-5-yl, benzo[d]oxazin-2(3*H*)-on-6-yl, benzo[d]oxazin-2(3*H*)-on-7-yl, benzo[d]oxazin-2(3H)-on-8-yl, quinazolin-4(3*H*)-on-5-yl, quinazolin-4(3*H*)-on-6-yl, quinazolin-4(3*H*)-on-7-yl, quinazolin-4(3*H*)-on-8-yl, quinoxalin-2(1*H*)-on-5-yl, quinoxalin-2(1*H*)-on-6-yl, quinoxalin-2(1*H*)-on-7-yl, quinoxalin-2(1*H*)-on-8-yl, benzo[d]thiazol-2(3*H*)-on-4-yl, benzo[d]thiazol-2(3*H*)-on-5-yl, benzo[d]thiazol-2(3*H*)-on-6-yl, and, benzo[d]thiazol-2(3*H*)-on-7-yl. In certain embodiments, the bicyclic aryl is (i) naphthyl or (ii) a phenyl ring fused to either a 5 or 6 membered monocyclic cycloalkyl, a 5 or 6 membered monocyclic cycloalkenyl, or a 5 or 6 membered monocyclic heterocyclyl, wherein the fused cycloalkyl, cycloalkenyl, and heterocyclyl groups are optionally substituted with one or two groups which are independently oxo or thia. In certain embodiments of the disclosure, the aryl group is phenyl or naphthyl. In certain other embodiments, the aryl group is phenyl.

"Cyano" and "nitrile" mean a -CN group.

"Halo" or "halogen" means -Cl, -Br, -I or -F. In certain embodiments, "halo" or "halogen" refers to -Cl or -F.

"Haloalkyl" means at least one halogen, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein. Representative examples of haloalkyl include, but are not limited to, chloromethyl, 2-fluoroethyl, trifluoromethyl, pentafluoroethyl, and 2-chloro-3-fluoropentyl. In certain embodiments, each "haloalkyl" is a fluoroalkyl, for example, a polyfluoroalkyl such as a substantially perfluorinated alkyl.

"Heteroaryl" means a monocyclic heteroaryl or a bicyclic ring system containing at least one heteroaromatic ring. The monocyclic heteroaryl can be a 5 or 6 membered ring. The 5 membered ring consists of two double bonds and one, two, three or four nitrogen atoms and optionally one oxygen or sulfur atom. The 6 membered ring consists of three double bonds and

one, two, three or four nitrogen atoms. The 5 or 6 membered heteroaryl is connected to the parent molecular moiety through any carbon atom or any nitrogen atom contained within the heteroaryl. Representative examples of monocyclic heteroaryl include, but are not limited to, furyl, imidazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, oxazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, pyrazolyl, pyrrolyl, tetrazolyl, thiadiazolyl, thiazolyl, thienyl, triazolyl, and triazinyl. The bicyclic heteroaryl consists of a monocyclic heteroaryl fused to a phenyl, a monocyclic cycloalkyl, a monocyclic cycloalkenyl, a monocyclic heterocyclyl, or a monocyclic heteroaryl. The fused cycloalkyl or heterocyclyl portion of the bicyclic heteroaryl group is optionally substituted with one or two groups which are independently oxo or thia. When the bicyclic heteroaryl contains a fused cycloalkyl, cycloalkenyl, or heterocyclyl ring, then the bicyclic heteroaryl group is connected to the parent molecular moiety through any carbon or nitrogen atom contained within the monocyclic heteroaryl portion of the bicyclic ring system. When the bicyclic heteroaryl is a monocyclic heteroaryl fused to a phenyl ring, then the bicyclic heteroaryl group is connected to the parent molecular moiety through any carbon atom or nitrogen atom within the bicyclic ring system. Representative examples of bicyclic heteroaryl include, but are not limited to, benzimidazolyl, benzofuranyl, benzothienyl, benzoxadiazolyl, benzoxathiadiazolyl, benzothiazolyl, cinnolinyl, 5,6-dihydroquinolin-2-yl, 5,6-dihydroisoquinolin-1-yl, furopyridinyl, indazolyl, indolyl, isoquinolinyl, naphthyridinyl, quinolinyl, purinyl, 5,6,7,8-tetrahydroquinolin-2-yl, 5,6,7,8-tetrahydroquinolin-3-yl, 5,6,7,8-tetrahydroquinolin-4-yl, 5,6,7,8-tetrahydroisoquinolin-1-yl, thienopyridinyl, 4,5,6,7-tetrahydrobenzo[c][1,2,5]oxadiazolyl, and 6,7-dihydrobenzo[c][1,2,5]oxadiazol-4(5*H*)-onyl. In certain embodiments, the fused bicyclic heteroaryl is a 5 or 6 membered monocyclic heteroaryl ring fused to either a phenyl ring, a 5 or 6 membered monocyclic cycloalkyl, a 5 or 6 membered monocyclic cycloalkenyl, a 5 or 6 membered monocyclic heterocyclyl, or a 5 or 6 membered monocyclic heteroaryl, wherein the fused cycloalkyl, cycloalkenyl, and heterocyclyl groups are optionally substituted with one or two groups which are independently oxo or thia. In certain embodiments of the disclosure, the heteroaryl group is furyl, imidazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyrazolyl, pyrrolyl, thiazolyl, thienyl, triazolyl, benzimidazolyl, benzofuranyl, indazolyl, indolyl, or quinolinyl.

"Heterocyclyl" means a monocyclic heterocycle or a bicyclic heterocycle. The monocyclic heterocycle is a 3, 4, 5, 6 or 7 membered ring containing at least one heteroatom independently selected from the group consisting of O, N, and S where the ring is saturated or unsaturated, but

not aromatic. The 3 or 4 membered ring contains 1 heteroatom selected from the group consisting of O, N and S. The 5 membered ring can contain zero or one double bond and one, two or three heteroatoms selected from the group consisting of O, N and S. The 6 or 7 membered ring contains zero, one or two double bonds and one, two or three heteroatoms selected from the group consisting of O, N and S. The monocyclic heterocycle is connected to the parent molecular moiety through any carbon atom or any nitrogen atom contained within the monocyclic heterocycle. Representative examples of monocyclic heterocycle include, but are not limited to, azetidinyl, azepanyl, aziridinyl, diazepanyl, 1,3-dioxanyl, 1,3-dioxolanyl, 1,3-dithiolanyl, 1,3-dithianyl, imidazolinyl, imidazolidinyl, isothiazolinyl, isothiazolidinyl, isoxazolinyl, isoxazolidinyl, morpholinyl, oxadiazolinyl, oxadiazolidinyl, oxazolinyl, oxazolidinyl, piperazinyl, piperidinyl, pyranyl, pyrazolinyl, pyrazolidinyl, pyrrolinyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydrothienyl, thiadiazolinyl, thiadiazolidinyl, thiazolinyl, thiazolidinyl, thiomorpholinyl,1,1-dioxidothiomorpholinyl (thiomorpholine sulfone), thiopyranyl, and trithianyl. The bicyclic heterocycle is a monocyclic heterocycle fused to either a phenyl, a monocyclic cycloalkyl, a monocyclic cycloalkenyl, a monocyclic heterocycle, or a monocyclic heteroaryl. The bicyclic heterocycle is connected to the parent molecular moiety through any carbon atom or any nitrogen atom contained within the monocyclic heterocycle portion of the bicyclic ring system. Representative examples of bicyclic heterocyclyls include, but are not limited to, 2,3-dihydrobenzofuran-2-yl, 2,3-dihydrobenzofuran-3-yl, indolin-1-yl, indolin-2-yl, indolin-3-yl, 2,3-dihydrobenzothien-2-yl, decahydroquinolinyl, decahydroisoquinolinyl, octahydro-1H-indolyl, and octahydrobenzofuranyl. Heterocyclyl groups are optionally substituted with one or two groups which are independently oxo or thia. In certain embodiments, the bicyclic heterocyclyl is a 5 or 6 membered monocyclic heterocyclyl ring fused to phenyl ring, a 5 or 6 membered monocyclic cycloalkyl, a 5 or 6 membered monocyclic cycloalkenyl, a 5 or 6 membered monocyclic heterocyclyl, or a 5 or 6 membered monocyclic heteroaryl, wherein the bicyclic heterocyclyl is optionally substituted by one or two groups which are independently oxo or thia. In certain embodiments of the disclosure, the heterocyclyl is pyrrolidinyl, piperidinyl, piperazinyl, or morpholinyl.

"Saturated" means the referenced chemical structure does not contain any multiple carbon-carbon bonds. For example, a saturated cycloalkyl group as defined herein includes cyclohexyl, cyclopropyl, and the like.

"Unsaturated" means the referenced chemical structure contains at least one multiple carbon-carbon bond, but is not aromatic. For example, a unsaturated cycloalkyl group as defined herein includes cyclohexenyl, cyclopentenyl, cyclohexadienyl, and the like.

"Pharmaceutically acceptable salt" refers to both acid and base addition salts.

"Modulating" or "modulate" refers to the treating, prevention, suppression, enhancement or induction of a function, condition or disorder.

"Treating" or "treatment" refer to the treatment of a disease or disorder described herein, in a subject, preferably a human, and includes:

i. inhibiting a disease or disorder, *i.e.*, arresting its development;

ii. relieving a disease or disorder, *i.e.*, causing regression of the disorder;

iii. slowing progression of the disorder; and/or

iv. inhibiting, relieving, or slowing progression of one or more symptoms of the disease or disorder.

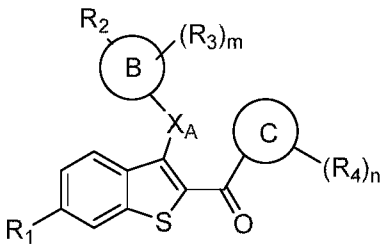
"Subject" refers to a warm blooded animal such as a mammal, preferably a human, or a human child, which is afflicted with, or has the potential to be afflicted with one or more diseases and disorders described herein.

A "prodrug" as used herein, means a compound which when administered to a host *in vivo* is converted into a parent drug. As used herein, the term "parent drug" means any of the presently described chemical compounds described herein. Prodrugs can be used to achieve any desired effect, including to enhance properties of the parent drug or to improve the pharmaceutic or pharmacokinetic properties of the parent. Nonlimiting examples of prodrugs include those ith covalent attachment of removable groups, or removable portions of groups, for example, but not limited to acylation, phosphorylation, phosphonylation, phosphoramidate derivatives, amidation, reduction, oxidation, esterification, alkylation, other carboxy derivatives, sulfoxy or sulfone derivatives, carbonylation or anhydride, among others.

The materials, compounds, compositions, articles, and methods described herein may be understood more readily by reference to the following detailed description of specific aspects of the disclosed subject matter and the Examples and Figures. It is to be understood that the aspects described below are not limited to specific embodiments which may, of course, vary, as known to those skilled in the art. It is also to be understood that the terminology used herein is for the purpose of describing particular aspects only and is not intended to be limiting.

Compounds

Benzothiophene based estrogen receptor ligands of the invention includes compounds of Formula A, or a pharmaceutically acceptable salt thereof:



Formula A

wherein:

m is 0, 1, 2, 3, or 4;

n is 0, 1, 2, 3, or 4;

X_A is selected from -O-, -CH_2-, -S-, -NH-, -NMe-, -CF_2-, and -C_3cycloalkyl-;

Ring B is phenyl, naphthyl, quinolinyl, 5- or 6- membered monocyclic heteroaryl or 7-, 8-, 9- or 10 membered bicyclic heterocyclyl;

Ring C is phenyl, thiophenyl (i.e., thienyl), 5- or 6- membered monocyclic heteroaryl or 7-, 8-, 9- or 10- membered bicyclic heterocyclyl;

R_1 is selected from hydroxyl, hydrogen, halogen, –O(C_1-C_6 alkyl), –OC(O)(C_1-C_6 alkyl), –OC(O)C_6H_5, –OC(O)O(C_1-C_6 alkyl), –OC(O)OC_6H_5 and –OSO_2(C_2-C_6 alkyl);

R_2 is selected from –CH=CHCOOH, –NH(CO)COOH, –COOH, -C_2-C_6alkenylene-COOH and -C_2-C_6alkynylene-COOH;

R_3 is independently selected at each occurrence from hydrogen, halogen, –CN, –NO_2, -C_1-C_6alkyl and -C_1-C_6fluoroalkyl; and

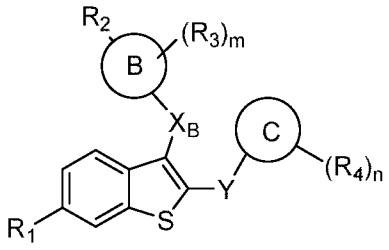
R_4 is independently selected at each occurrence from hydrogen, halogen, hydroxyl, -C_1-C_6alkyl, C_1-C_6fluoroalkyl, –CN, –O(C_1-C_6 alkyl), and –O(C_1-C_6fluoroalkyl).

In another aspect, this invention includes a pharmaceutical composition comprising one or more compounds of Formula A and a pharmaceutically acceptable carrier or excipient.

In another aspect, this invention is a method of treating or preventing cancer (including breast, ovarian, uterine, kidney, or endometrial) or a tumor that includes administering to a subject

such as a human in need of such treatment a therapeutically effective amount of a compound of Formula A or a pharmaceutically acceptable salt thereof.

In another aspect, this invention is a compound of Formula B, or a pharmaceutically acceptable salt thereof:



Formula B

wherein:

m is 0, 1, 2, 3, or 4;

n is 0, 1, 2, 3, or 4;

X_B is selected from -O-, -CH_2-, -S-, -NH-, -NMe-, -CF_2-, and -C_3cycloalkyl-;

Y is selected from -C(O)-, -O-, -CF_2-, or -C_3cycloalkyl-, -CH_2-, -S-, -NH-, and -N(Me)-;

Ring B is phenyl, naphthyl, quinolinyl, 5- or 6- membered monocyclic heteroaryl or 7-, 8-, 9- or 10 membered bicyclic heterocyclyl;

Ring C is phenyl, thiophenyl (i.e., thienyl), 5- or 6- membered monocyclic heteroaryl or 7-, 8-, 9- or 10- membered bicyclic heterocyclyl;

R_1 is selected from hydroxyl, hydrogen, halogen, –O(C_1-C_6 alkyl), –OC(O)(C_1-C_6 alkyl), –OC(O)C_6H_5, –OC(O)O(C_1-C_6 alkyl), –OC(O)OC_6H_5 and –OSO_2(C_2-C_6 alkyl);

R_2 is selected from –CH=CHCOOH, –NH(CO)COOH, –COOH, -C_2-C_6alkenylene-COOH and -C_2-C_6alkynylene-COOH;

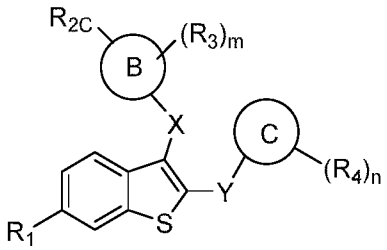
R_3 is independently selected at each occurrence from hydrogen, halogen, –CN, –NO_2, -C_1-C_6alkyl and -C_1-C_6fluoroalkyl; and

R_4 is independently selected at each occurrence from hydrogen, halogen, hydroxyl, -C_1-C_6alkyl, -C_1-C_6fluoroalkyl, –CN, –O(C_1-C_6 alkyl), and –O(C_1-C_6fluoroalkyl).

In another aspect, this invention includes a pharmaceutical composition comprising one or more compounds of Formula B and a pharmaceutically acceptable carrier or excipient.

In another aspect, this invention is a method of treating or preventing cancer (including breast, ovarian, uterine, kidney, or endometrial) or a tumor comprising administering to a subject such as a human in need of such treatment a therapeutically effective amount of a compound of Formula B or a pharmaceutically acceptable salt or prodrug thereof.

In another aspect, this invention provides a compound of Formula C:



Formula C

wherein:

m is 0, 1, 2, 3, or 4;

n is 0, 1, 2, 3, or 4;

X is selected from -O-, -C(O)-, -CH_2-, -S-, -NH-, -NMe-, -CF_2-, and -C_3cycloalkyl-;

Y is selected from -C(O)-, -O-, -CF_2-, or C_3cycloalkyl, -CH_2-, -S-, -NH-, and -NMe-;

Ring B is phenyl, naphthyl, quinolinyl, 5- or 6- membered monocyclic heteroaryl, cycloalkyl, or 7-, 8-, 9- or 10 membered bicyclic heterocyclyl;

Ring C is phenyl, thiophenyl (i.e., thienyl), 5- or 6- membered monocyclic heteroaryl, cycloalkyl or 7-, 8-, 9- or 10- membered bicyclic heterocyclyl;

R_1 is selected from hydroxyl, hydrogen, halogen, –O(C_1-C_6 alkyl), –OC(O)(C_1-C_6 alkyl), –OC(O)C_6H_5, –OC(O)O(C_1-C_6 alkyl), –OC(O)OC_6H_5 and –OSO_2(C_2-C_6 alkyl);

R_{2C} is selected from –CH=CHCOOH, –NH(CO)COOH, -C_2-C_6alkenylene-COOH and -C_2-C_6alkynylene-COOH;

R_3 is independently selected at each occurrence from hydrogen, halogen, –CN, –NO_2, -C_1-C_6alkyl and -C_1-C_6fluoroalkyl; and

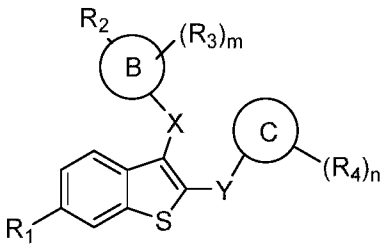
R_4 is independently selected at each occurrence from hydrogen, halogen, hydroxyl,

-C_1-C_6alkyl, -C_1-C_6fluoroalkyl, –CN, –O(C_1-C_6 alkyl), and –O(C_1-C_6fluoroalkyl).

In another aspect, this invention includes a pharmaceutical composition that includes one or more compounds of Formula C and a pharmaceutically acceptable carrier or excipient.

In another aspect, this invention is a method of treating or preventing a cancer (including breast, ovarian, uterine, kidney, or endometrial) or tumor that includes administering to a subject such as a human in need of such treatment a therapeutically effective amount of a compound of Formula C or a pharmaceutically acceptable salt or prodrug thereof.

In one aspect, this invention is a compound of Formula D, or a pharmaceutically acceptable salt thereof:



Formula D

wherein:

m is 0, 1, 2, 3, or 4;

n is 0, 1, 2, 3, or 4;

X is selected from -O-, -C(O)-, -CH_2-, -S-, -NH-, -NMe-, -CF_2-, and -C_3cycloalkyl-;

Y is selected from -C(O)-, -O-, -CF_2-, or -C_3cycloalkyl, -CH_2-, -S-, -NH-, and -NMe-;

Ring B is phenyl, naphthyl, quinolinyl, 5- or 6- membered monocyclic heteroaryl or 7-, 8-, 9- or 10 membered bicyclic heterocyclyl;

Ring C is phenyl, thiophenyl (i.e., thienyl), 5- or 6- membered monocyclic heteroaryl or 7-, 8-, 9- or 10- membered bicyclic heterocyclyl;

R_1 is selected from hydroxyl, hydrogen, halogen, –O(C_1-C_6 alkyl), –OC(O)(C_1-C_6 alkyl), –OC(O)C_6H_5, –OC(O)O(C_1-C_6 alkyl), –OC(O)OC_6H_5 and –OSO_2(C_2-C_6 alkyl);

R_2 is selected from –CH=CHCOOH, –NH(CO)COOH, –COOH, -C_2-C_6alkenylene-COOH and -C_2-C_6alkynylene-COOH;

R_3 is independently selected at each occurrence from hydrogen, halogen, –CN,

–NO_2, -C_1-C_6alkyl and -C_1-C_6fluoroalkyl; and

R_4 is independently selected at each occurrence from hydrogen, halogen, hydroxyl, -C_1-C_6alkyl, -C_1-C_6fluoroalkyl, –CN, –O(C_1-C_6 alkyl), and –O(C_1-C_6fluoroalkyl).

In another aspect, this invention includes a pharmaceutical composition that includes one or more compounds of Formula D or its pharmaceutically acceptable salt or prodrug and a pharmaceutically acceptable carrier or excipient.

In another aspect, this invention is a method of treating or preventing cancer (including breast, ovarian, uterine, kidney, or endometrial) that includes administering to a subject in need of such treatment a therapeutically effective amount of a compound of Formula D or a pharmaceutically acceptable salt or prodrug thereof.

In one embodiment of the present invention, X is –O–.

In another embodiment, Y is -C(O)-.

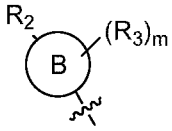
In a further embodiment X is –O– and Y is -C(O)-.

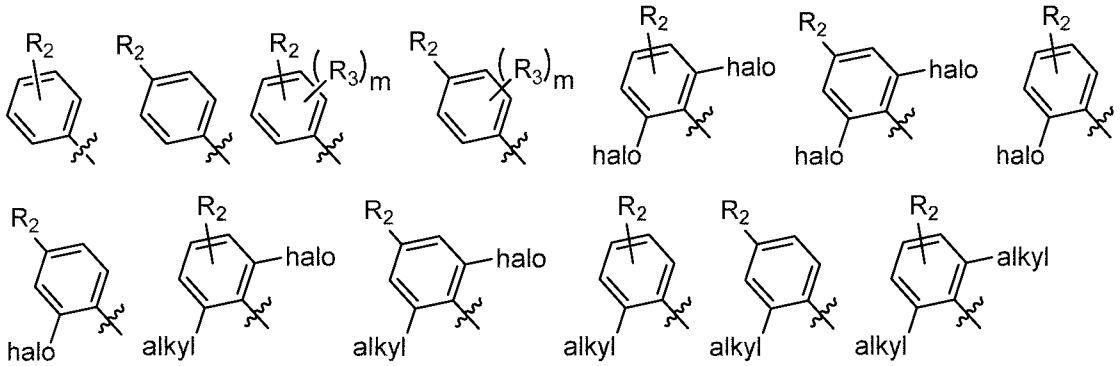
In one embodiment, R_1 is selected from hydroxyl and -O(C_1-C_6 alkyl).

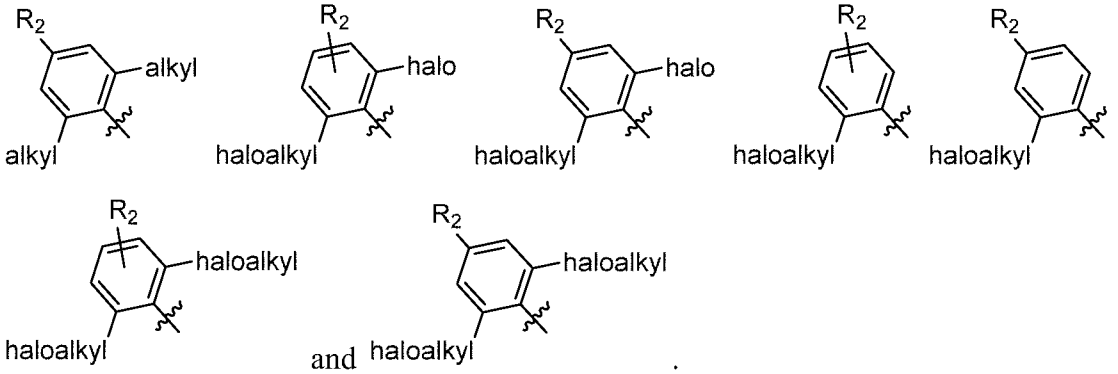
In one embodiment, R_2 is selected from –COOH, –NH(CO)COOH and –CH=CHCOOH.

In one embodiment, Ring B is phenyl, naphthyl or quinolinyl and Ring C is phenyl or thienyl.

In one embodiment, Ring C is phenyl.

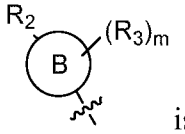
In one embodiment,  is selected from:





.

In one embodiment of the above B-ring embodiments, alkyl is methyl. In another embodiment of the above B-ring embodiments, alkyl is independently, methyl, ethyl, propyl or cyclopropyl. In one embodiment of the above B-ring embodiments, halo is fluoro. In another embodiment of the above B-rings, halo is independently fluoro or chloro, including wherein one halo is fluoro and the other is chloro. In one embodiment of the above B-ring embodiments, haloalkyl is independently mono-, di- or trifluoro-methyl.

In another embodiment, 

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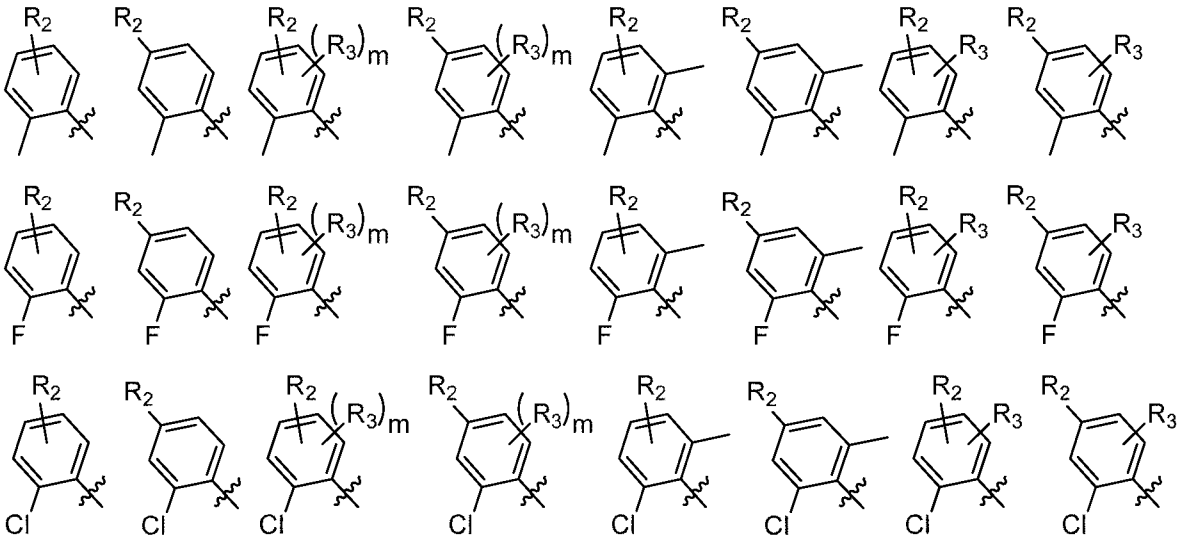
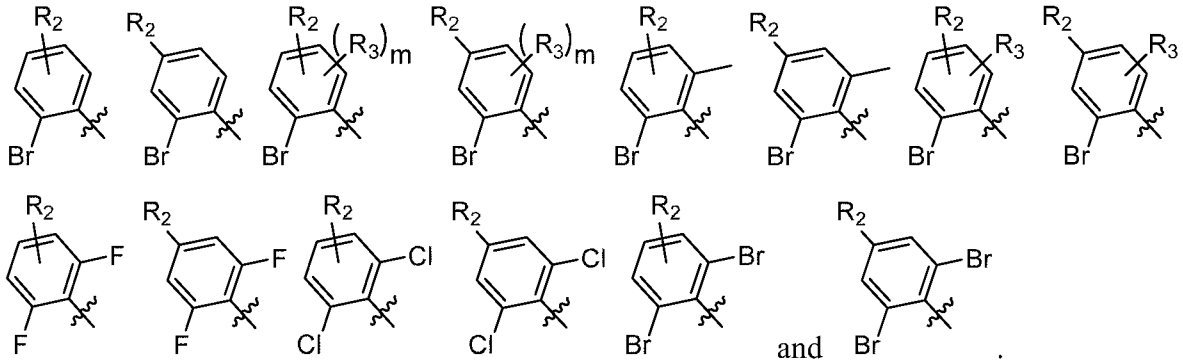
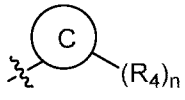
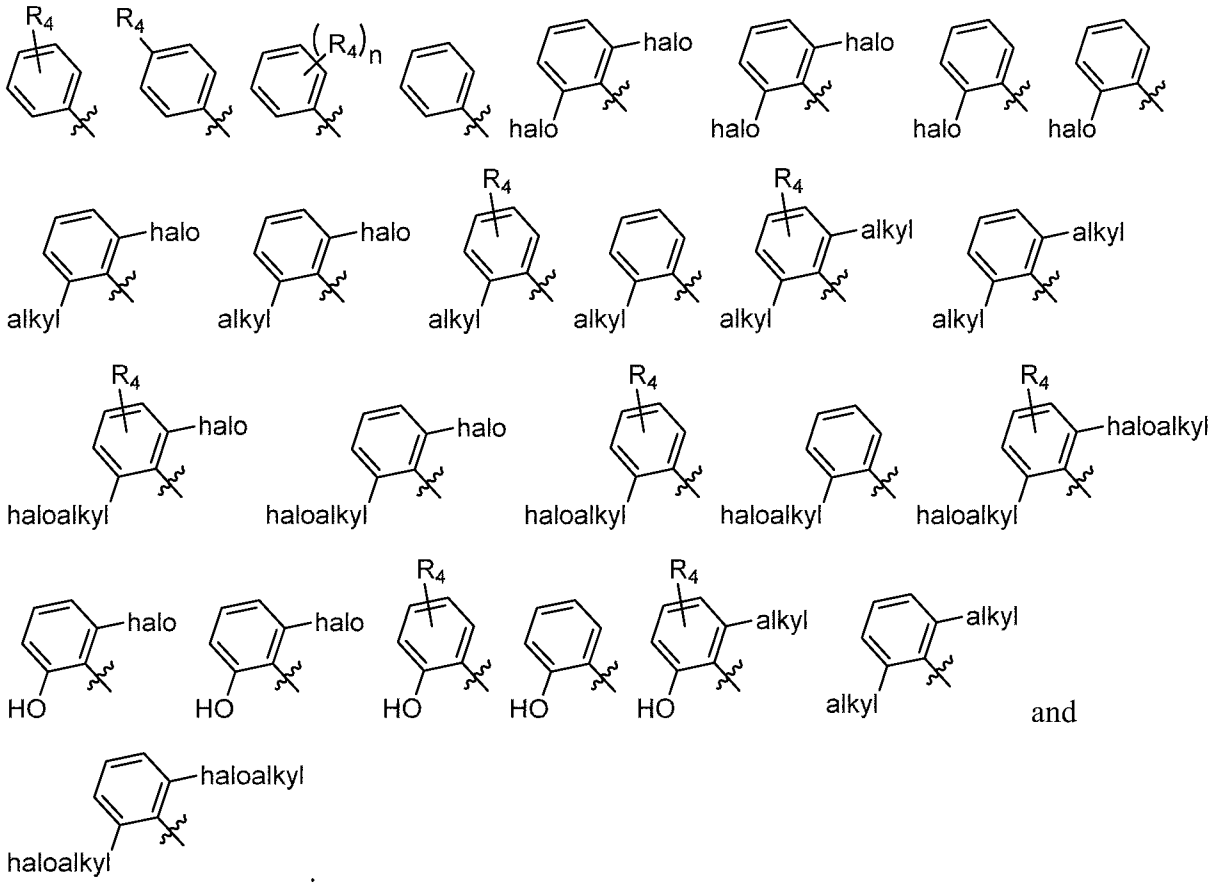


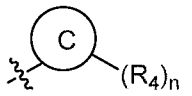


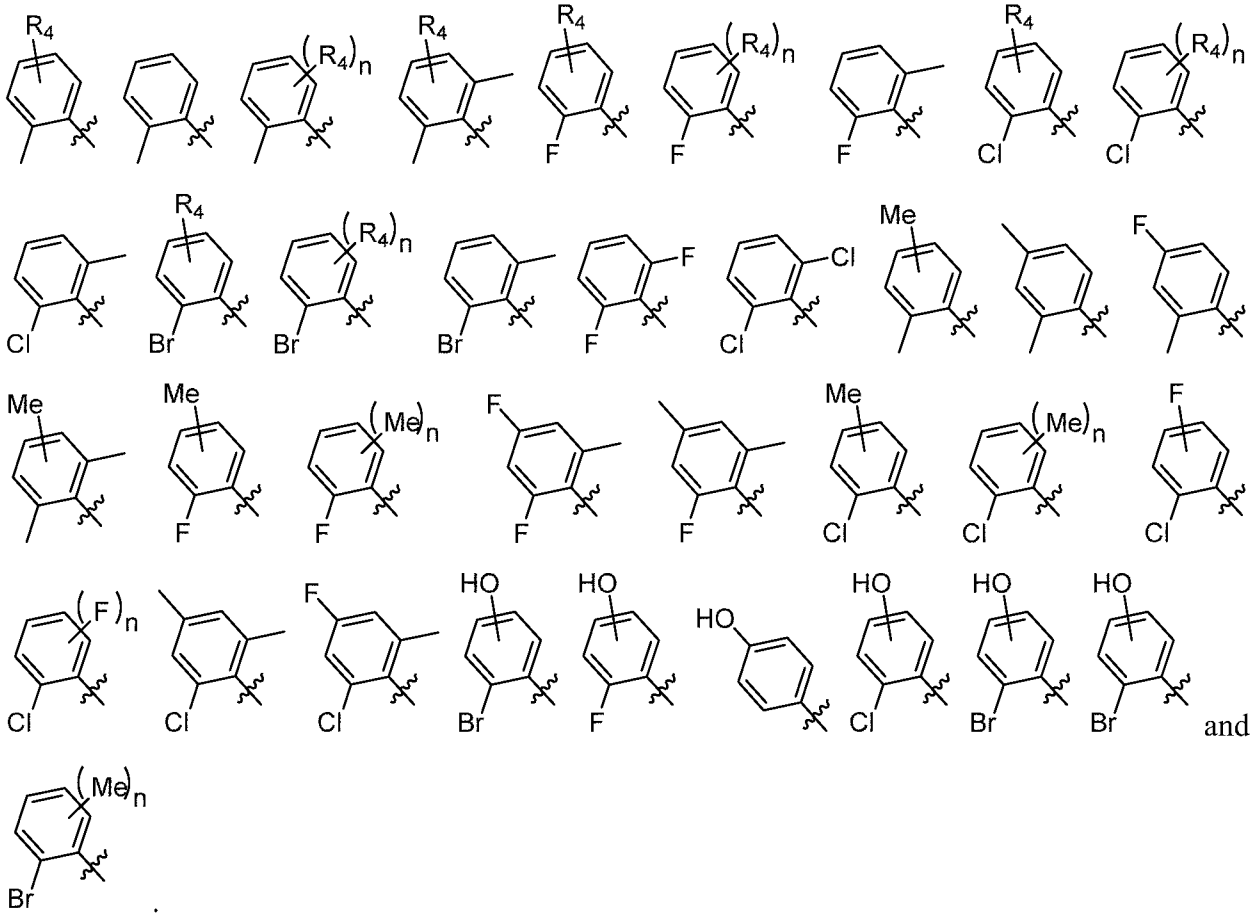
In one embodiment,  is selected from:



In one embodiment of the above C-ring embodiments, alkyl is methyl. In another embodiment of the above C-ring embodiments, alkyl is independently, methyl, ethyl, propyl or

cyclopropyl. In one embodiment of the above C-ring embodiments, halo is fluoro. In another embodiment of the above C-rings, halo is independently fluoro or chloro, including wherein one halo is fluoro and the other is chloro. In one embodiment of the above B-ring embodiments, haloalkyl is independently mono-, di- or trifluoro-methyl.

In another embodiment,  is selected from:

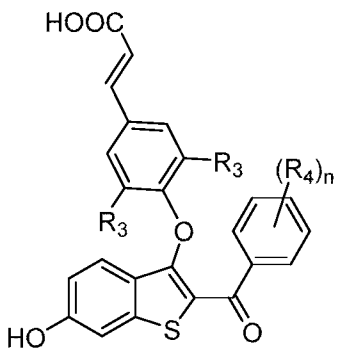


and

.

In one embodiment of the above C-ring embodiments, R_4 is hydrogen. In another embodiment, R_4 is -C_1-C_6alkyl, such as methyl, ethyl, or propyl. In yet another embodiment, R_4 is -C_1-C_6fluoroalkyl, including trifluoromethyl, difluoromethyl, fluoromethyl, fluoroethyl, and difluoroethyl. In other embodiments, R_4 is selected from –CN, –O(C_1-C_6 alkyl), and –O(C_1-C_6fluoroalkyl).

In another embodiment, the compound is Formula E:



Formula E

wherein:

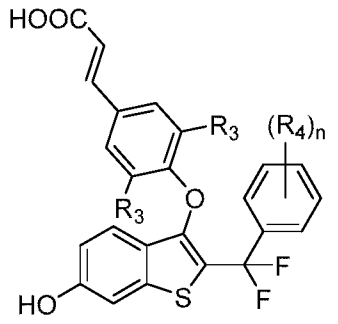
n is 0, 1, 2, 3, or 4;

R_3 is independently selected at each occurrence from hydrogen, halogen, -CN, $-NO_2$, C_1-C_6alkyl and C_1-C_6fluoroalkyl; and

R_4 is independently selected at each occurrence from hydrogen, halogen, hydroxyl, C_1-C_6alkyl, C_1-C_6fluoroalkyl, -CN, -O(C_1-C_6 alkyl), and -O(C_1-C_6fluoroalkyl).

In one embodiment R_3 is independently selected at each occurrence from hydrogen, halogen, methyl and –CN.

In another embodiment, the compound is Formula F:



Formula F

wherein

n is 0, 1, 2, 3, or 4;

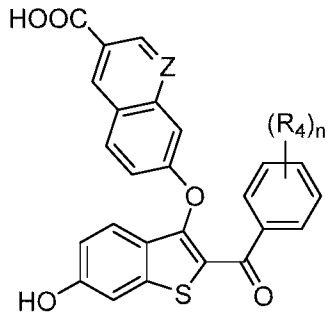
R_3 is independently selected at each occurrence from hydrogen, halogen, –CN, $–NO_2$, -C_1-C_6alkyl and -C_1-C_6fluoroalkyl; and

R_4 is independently selected at each occurrence from hydrogen, halogen, hydroxyl,

C_1-C_6alkyl, C_1-C_6fluoroalkyl, –CN, –O(C_1-C_6 alkyl), and –O(C_1-C_6fluoroalkyl).

In one embodiment R_3 is independently selected at each occurrence from hydrogen, halogen, methyl and –CN; and

In another embodiment, the compound is Formula G:



Formula G

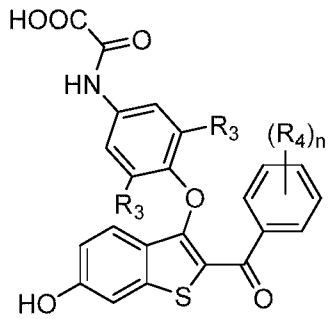
wherein:

Z is CH or N;

n is 0, 1, 2, 3, or 4; and

R_4 is independently selected at each occurrence from hydrogen, halogen, hydroxyl, -C_1-C_6alkyl, -C_1-C_6fluoroalkyl, –CN, –O(C_1-C_6 alkyl) and –O(C_1-C_6fluoroalkyl).

In another embodiment, the compound is Formula H:



Formula H

wherein:

n is 0, 1, 2, 3, or 4;

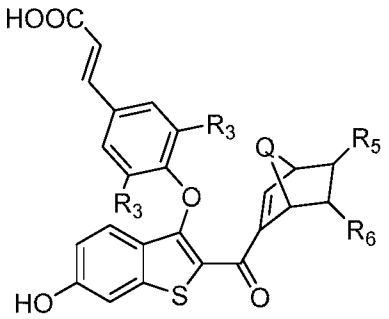
R_3 is independently selected at each occurrence from hydrogen, halogen, –CN, –NO_2, -C_1-C_6alkyl and -C_1-C_6fluoroalkyl; and

R_4 is independently selected at each occurrence from hydrogen, halogen, hydroxyl,

-C_1-C_6alkyl, -C_1-C_6fluoroalkyl, –CN, –O(C_1-C_6 alkyl), and –O(C_1-C_6fluoroalkyl).

In one embodiment R_3 is independently selected at each occurrence from hydrogen, halogen, methyl and –CN.

In another embodiment, a compound of Formula I is provided:



Formula I

wherein:

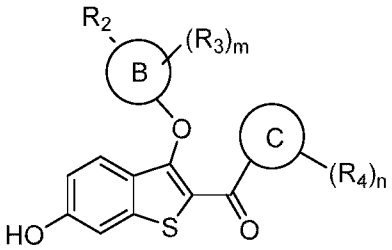
Q is selected from O, S, CH_2, NH and S(O);

R_5 and R_6 are independently selected from –CN, halogen and –$COOR_7$;

R_3 is independently selected at each occurrence from hydrogen, halogen, methyl and –CN; and

R_7 is selected from haloalkyl, alkyl, cycloalkyl, aryl and heteroaryl.

In an additional embodiment, a compound of Formula J is provided:



Formula J

wherein:

m is 0, 1, 2, 3, or 4;

n is 0, 1, 2, 3, or 4;

Ring B is phenyl, naphthyl, quinolinyl, 5- or 6-membered monocyclic heteroaryl or 7-, 8-, 9- or 10 membered bicyclic heterocyclyl;

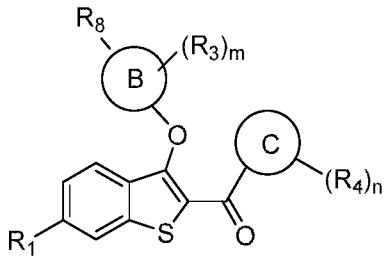
Ring C is phenyl, thiophenyl (i.e., thienyl), 5- or 6-membered monocyclic heteroaryl or 7-, 8-, 9- or 10-membered bicyclic heterocyclyl;

R_2 is selected from –CH=CHCOOH, –NH(CO)COOH, –COOH, -C_2-C_6alkenylene-COOH and -C_2-C_6alkynylene-COOH;

R_3 is independently selected at each occurrence from hydrogen, halogen, –CN, –NO_2, -C_1-C_6alkyl and -C_1-C_6fluoroalkyl; and

R_4 is independently selected at each occurrence from hydrogen, halogen, hydroxyl, -C_1-C_6alkyl, -C_1-C_6fluoroalkyl, –CN, –O(C_1-C_6 alkyl), and –O(C_1-C_6fluoroalkyl).

In an additional embodiment, a compound of Formula K is provided:



Formula K

wherein:

m is 0, 1, 2, 3, or 4;

n is 0, 1, 2, 3, or 4;

Ring B is phenyl, naphthyl, quinolinyl, 5- or 6-membered monocyclic heteroaryl or 7-, 8-, 9- or 10 membered bicyclic heterocyclyl;

Ring C is phenyl, thiophenyl (i.e., thienyl), 5- or 6-membered monocyclic heteroaryl or 7-, 8-, 9- or 10-membered bicyclic heterocyclyl;

R_1 is selected from hydroxyl, hydrogen, halogen, –O(C_1-C_6 alkyl), –OC(O)(C_1-C_6 alkyl), –OC(O)C_6H_5, –OC(O)O(C_1-C_6 alkyl), –OC(O)OC_6H_5 and –OSO_2(C_2-C_6 alkyl);

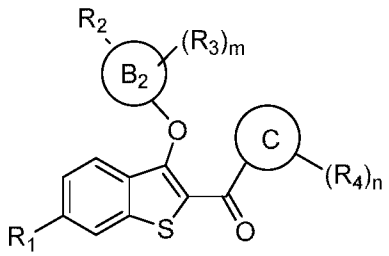
R_8 is selected from –CH=CHCOOH, –NH(CO)COOH, -C_2-C_6alkenylene-COOH and -C_2-C_6alkynylene-COOH;

R_3 is independently selected at each occurrence from hydrogen, halogen, –CN, –NO_2, -C_1-C_6alkyl and -C_1-C_6fluoroalkyl; and

R_4 is independently selected at each occurrence from hydrogen, halogen, hydroxyl,

-C_1-C_6alkyl, -C_1-C_6fluoroalkyl, –CN, –O(C_1-C_6 alkyl), and –O(C_1-C_6fluoroalkyl).

In an additional embodiment, a compound of Formula L is provided:



Formula L

wherein:

m is 0, 1, 2, 3, or 4;

n is 0, 1, 2, 3, or 4;

Ring B_2 is naphthyl, quinolinyl, or 10 membered bicyclic heterocyclyl;

Ring C is phenyl, thiophenyl (i.e., thienyl), 5- or 6-membered monocyclic heteroaryl or 7-, 8-, 9- or 10-membered bicyclic heterocyclyl;

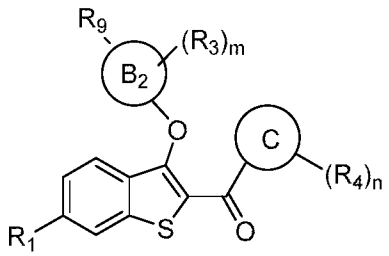
R_1 is selected from hydroxyl, hydrogen, halogen, –O(C_1-C_6 alkyl), –OC(O)(C_1-C_6 alkyl), –OC(O)C_6H_5, –OC(O)O(C_1-C_6 alkyl), –OC(O)OC_6H_5 and –OSO_2(C_2-C_6 alkyl);

R_2 is selected from –CH=CHCOOH, –NH(CO)COOH, –COOH, -C_2-C_6alkenylene-COOH and -C_2-C_6alkynylene-COOH;

R_3 is independently selected at each occurrence from hydrogen, halogen, –CN, –NO_2, C_1-C_6alkyl and C_1-C_6fluoroalkyl; and

R_4 is independently selected at each occurrence from hydrogen, halogen, hydroxyl, C_1-C_6alkyl, C_1-C_6fluoroalkyl, –CN, –O(C_1-C_6 alkyl), and –O(C_1-C_6fluoroalkyl).

In an additional embodiment, a compound of Formula M is provided:



Formula M

wherein:

m is 0, 1, 2, 3, or 4;

n is 0, 1, 2, 3, or 4;

Ring B_2 is naphthyl, quinolinyl, or 10 membered bicyclic heterocyclyl;

Ring C is phenyl, thiophenyl (i.e., thienyl), 5- or 6-membered monocyclic heteroaryl or 7-, 8-, 9- or 10-membered bicyclic heterocyclyl;

R_1 is selected from hydroxyl, hydrogen, halogen, –O(C_1-C_6 alkyl), –OC(O)(C_1-C_6 alkyl), –OC(O)C_6H_5, –OC(O)O(C_1-C_6 alkyl), –OC(O)OC_6H_5 and –OSO_2(C_2-C_6 alkyl);

R_9 is –COOH;

R_3 is independently selected at each occurrence from hydrogen, halogen, –CN, –NO_2, -C_1-C_6alkyl and -C_1-C_6fluoroalkyl; and

R_4 is independently selected at each occurrence from hydrogen, halogen, hydroxyl, -C_1-C_6alkyl, -C_1-C_6fluoroalkyl, –CN, –O(C_1-C_6 alkyl), and –O(C_1-C_6fluoroalkyl).

In one embodiment R_1 is hydroxyl.

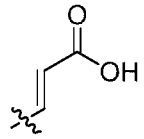
In one embodiment the compound is selected from Formula A and R_1 is hydroxyl, halogen, or –O(C_1-C_6 alkyl).

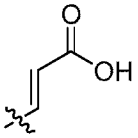
In one embodiment the compound is selected from Formula B and R_1 is hydroxyl, halogen, or –O(C_1-C_6 alkyl).

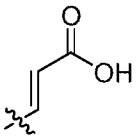
In one embodiment the compound is selected from Formula C and R_1 is hydroxyl, halogen, or –O(C_1-C_6 alkyl).

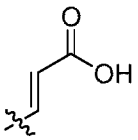
In one embodiment the compound is selected from Formula D and R_1 is hydroxyl, halogen, or –O(C_1-C_6 alkyl).

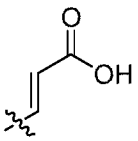
In one embodiment R_2 is –COOH.

In one embodiment R_2 is  .

In one embodiment the compound is selected from Formula A and R_2 is –COOH or  .

In one embodiment the compound is selected from Formula B and R_2 is –COOH or  .

In one embodiment the compound is selected from Formula C and R_2 is –COOH or  .

In one embodiment the compound is selected from Formula D and R_2 is –COOH or  .

In one embodiment, R_3 is fluorine.

In one embodiment, R_3 is chlorine.

In one embodiment, R_3 is methyl.

In one embodiment the compound is selected from Formula A and R_3 is halogen or -C_1-C_6alkyl, including methyl, ethyl, propyl, and isopropyl.

In one embodiment the compound is selected from Formula B and R_3 is halogen or -C_1-C_6alkyl, including methyl, ethyl, propyl, and isopropyl.

In one embodiment the compound is selected from Formula C and R_3 is halogen or

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-C_1-C_6alkyl, including methyl, ethyl, propyl, and isopropyl.

In one embodiment the compound is selected from Formula D and R_3 is halogen or -C_1-C_6alkyl, including methyl, ethyl, propyl, and isopropyl.

In one embodiment R_4 is halogen.

In one embodiment R_4 is -C_1-C_6alkyl.

In one embodiment R_4 is hydroxyl.

In one embodiment the compound is selected from Formula A and R_4 is halogen, -C_1-C_6alkyl, or hydroxyl.

In one embodiment the compound is selected from Formula B and R_4 is halogen, -C_1-C_6alkyl, or hydroxyl.

In one embodiment the compound is selected from Formula C and R_4 is halogen, -C_1-C_6alkyl, or hydroxyl.

In one embodiment the compound is selected from Formula D and R_4 is halogen, -C_1-C_6alkyl, or hydroxyl.

In one embodiment m is 0.

In one embodiment m is 1.

In one embodiment m is 2

In one embodiment the compound is selected from Formula A and m is 0, 1, or 2.

In one embodiment the compound is selected from Formula B and m is 0, 1, or 2.

In one embodiment the compound is selected from Formula C and m is 0, 1, or 2.

In one embodiment the compound is selected from Formula D and m is 0, 1, or 2.

In one embodiment n is 0.

In one embodiment n is 1.

In one embodiment n is 2

In one embodiment the compound is selected from Formula A and n is 0, 1, or 2.

In one embodiment the compound is selected from Formula B and n is 0, 1, or 2.

In one embodiment the compound is selected from Formula C and n is 0, 1, or 2.

In one embodiment the compound is selected from Formula D and n is 0, 1, or 2.

In one embodiment X is –O-.

In one embodiment the compound is selected from Formula B and X is –O-.

In one embodiment the compound is selected from Formula C and X is –O-.

In one embodiment the compound is selected from Formula D and X is –O-.

In one embodiment Y is –CO-.

In one embodiment the compound is selected from Formula B and Y is –CO-.

In one embodiment the compound is selected from Formula C and Y is –CO-.

In one embodiment the compound is selected from Formula D and Y is –CO-.

In one embodiment Ring B is phenyl.

In one embodiment Ring B is napthyl.

In one embodiment Ring B is quinolinyl.

In one embodiment the compound is selected from Formula A and Ring B is phenyl, napthyl, or quinolinyl.

In one embodiment the compound is selected from Formula B and Ring B is phenyl, napthyl, or quinolinyl.

In one embodiment the compound is selected from Formula C and Ring B is phenyl, napthyl, or quinolinyl.

In one embodiment the compound is selected from Formula D and Ring B is phenyl, napthyl, or quinolinyl.

In one embodiment Ring C is phenyl.

In one embodiment the compound is selected from Formula A and Ring C is phenyl.

In one embodiment the compound is selected from Formula B and Ring C is phenyl.

In one embodiment the compound is selected from Formula C and Ring C is phenyl.

In one embodiment m and n are 0.

In one embodiment m is 0 and n is 1.

In one embodiment m is 0 and n is 2.

In one embodiment m is 1 and n is 0.

In one embodiment m is 1 and n is 1.

In one embodiment m is 1 and n is 2.

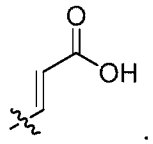
In one embodiment m is 2 and n is 0.

In one embodiment m is 2 and n is 1.

In one embodiment m is 2 and n is 2.

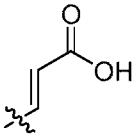
In one embodiment X is –O- and Y is –C(O)-.

In one embodiment R_1 is hydroxyl, X is –O-, and Y is –C(O).

In one embodiment R_1 is hydroxyl, X is –O-, Y is –C(O), and R_2 is  .

In one embodiment R_1 is hydroxyl, X is –O-, Y is –C(O), and n is 0.

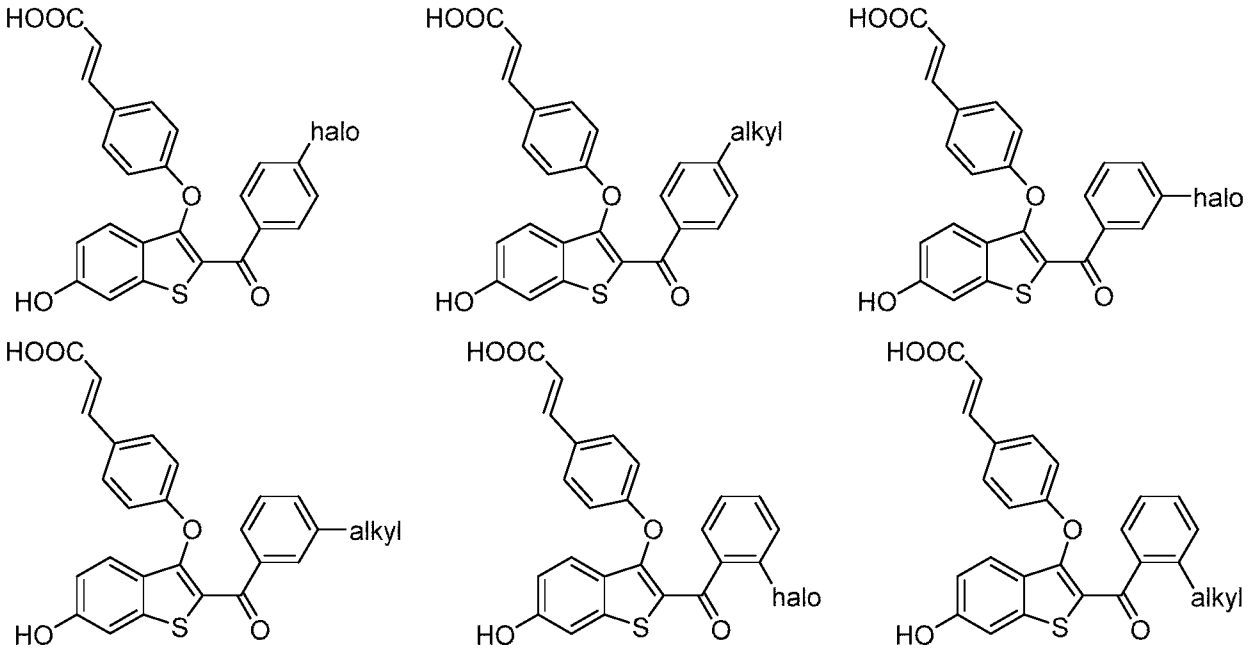
In one embodiment R_1 is hydroxyl, X is –O-, Y is –C(O), and m is 0.

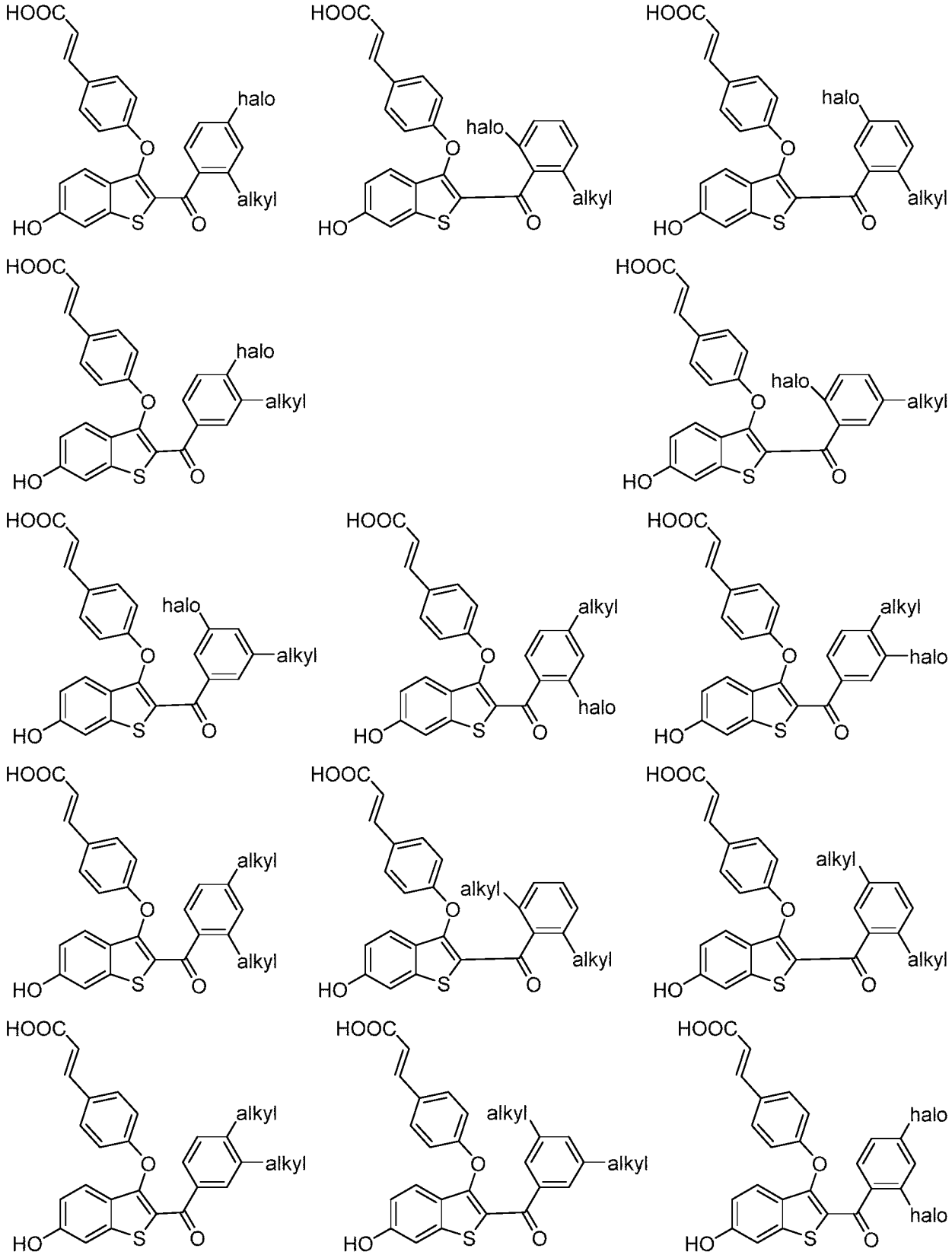
In one embodiment R_1 is hydroxyl, X is –O-, Y is –C(O), Ring B is phenyl and R_2 is  .

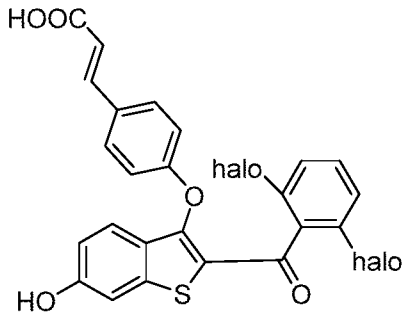
In one embodiment R_1 is hydroxyl, X is –O-, Y is –C(O), and Ring B is napthyl, and R_2 is -COOH.

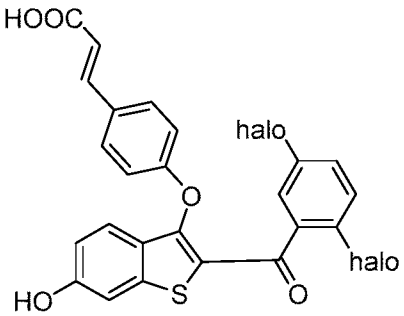
In one embodiment R_1 is hydroxyl, X is –O-, Y is –C(O), and Ring B is quinolinyl, and R_2 is -COOH.

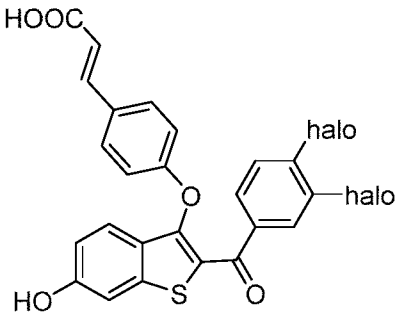
Non-limiting examples of compounds of the present invention include:

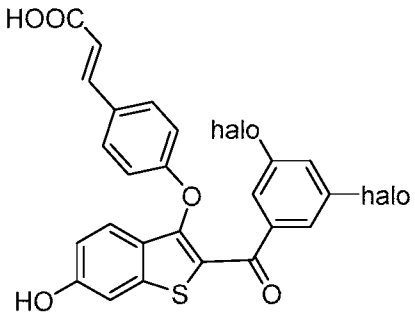



HOOC
halo
alkyl
O
S
HO





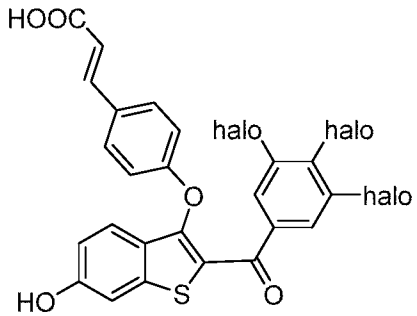


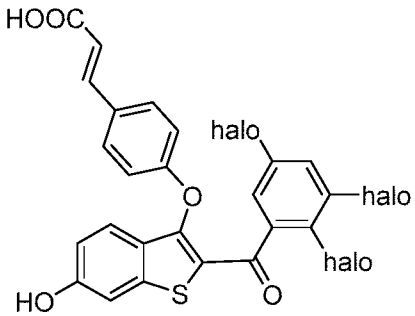


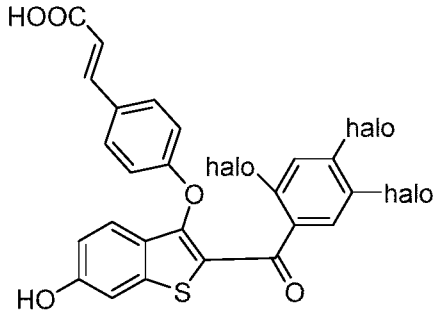
and .

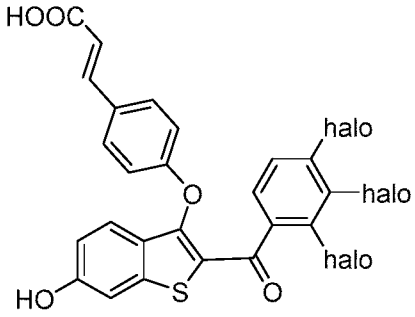
In certain embodiments of the above structures, alkyl is methyl. In other embodiments of the above structures embodiments, alkyl is independently methyl, ethyl, propyl or cyclopropyl. In some embodiments of the above embodiments, halo is fluoro. In some embodiments, haloalkyl is independently mono-, di- or trifluoro-methyl. In certain embodiments where the benzene ring has two halos, the halos can be one fluoro one chloro, two fluoros, or two chloros. In certain embodiments where the benzene ring has three halos, the halos can be one fluoro two chloros, two fluoros one chloro, three fluoros, or three chloros.

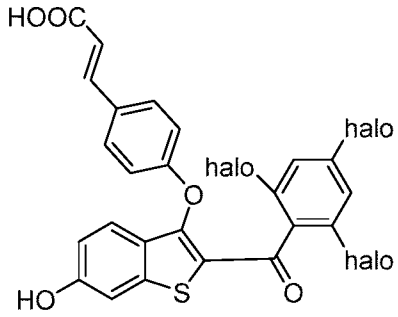
Additional non-limiting examples of compounds of the present invention include:

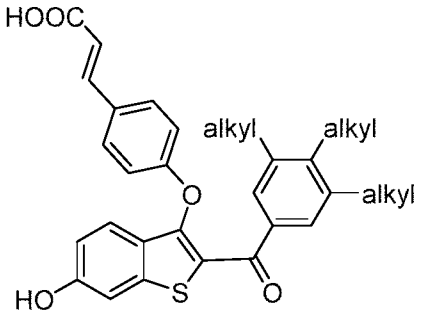


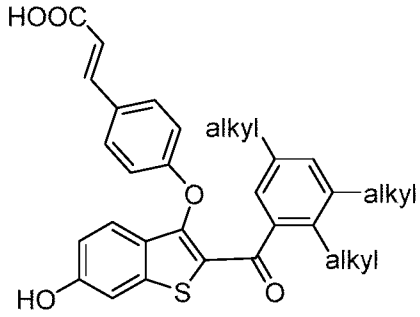


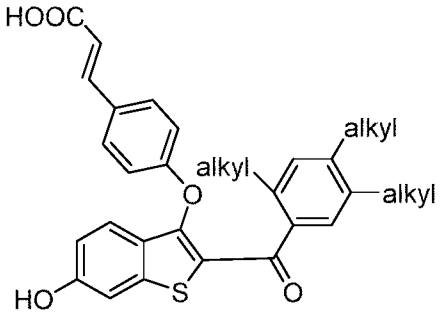

HOOC
halo
halo
halo
O
HO
S
O

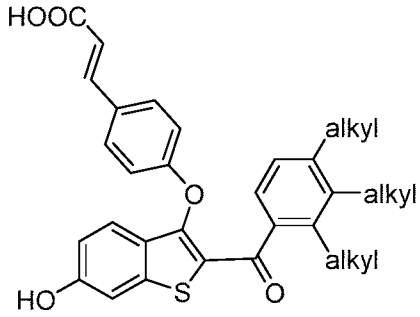

HOOC
halo
halo
halo
O
HO
S
O


HOOC
halo
halo
halo
O
HO
S
O

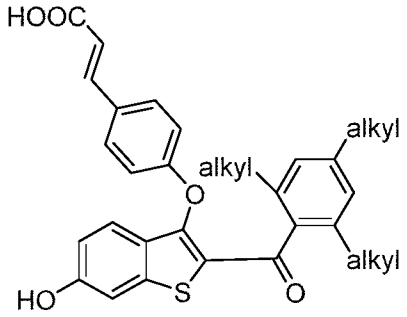

HOOC
alkyl
alkyl
alkyl
O
HO
S
O


HOOC
alkyl
alkyl
alkyl
O
HO
S
O


HOOC
alkyl
alkyl
alkyl
O
HO
S
O

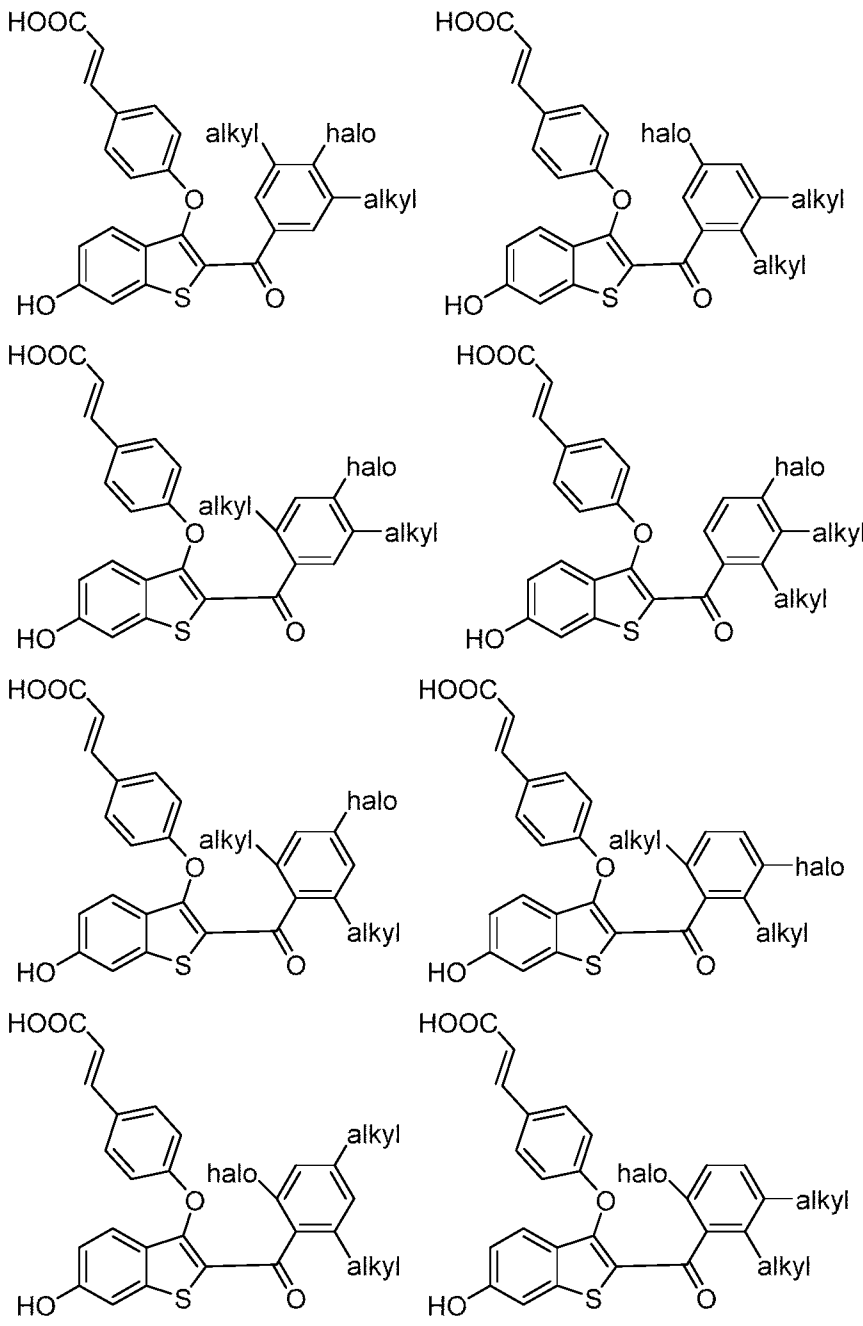

HOOC
alkyl
alkyl
alkyl
O
HO
S
O

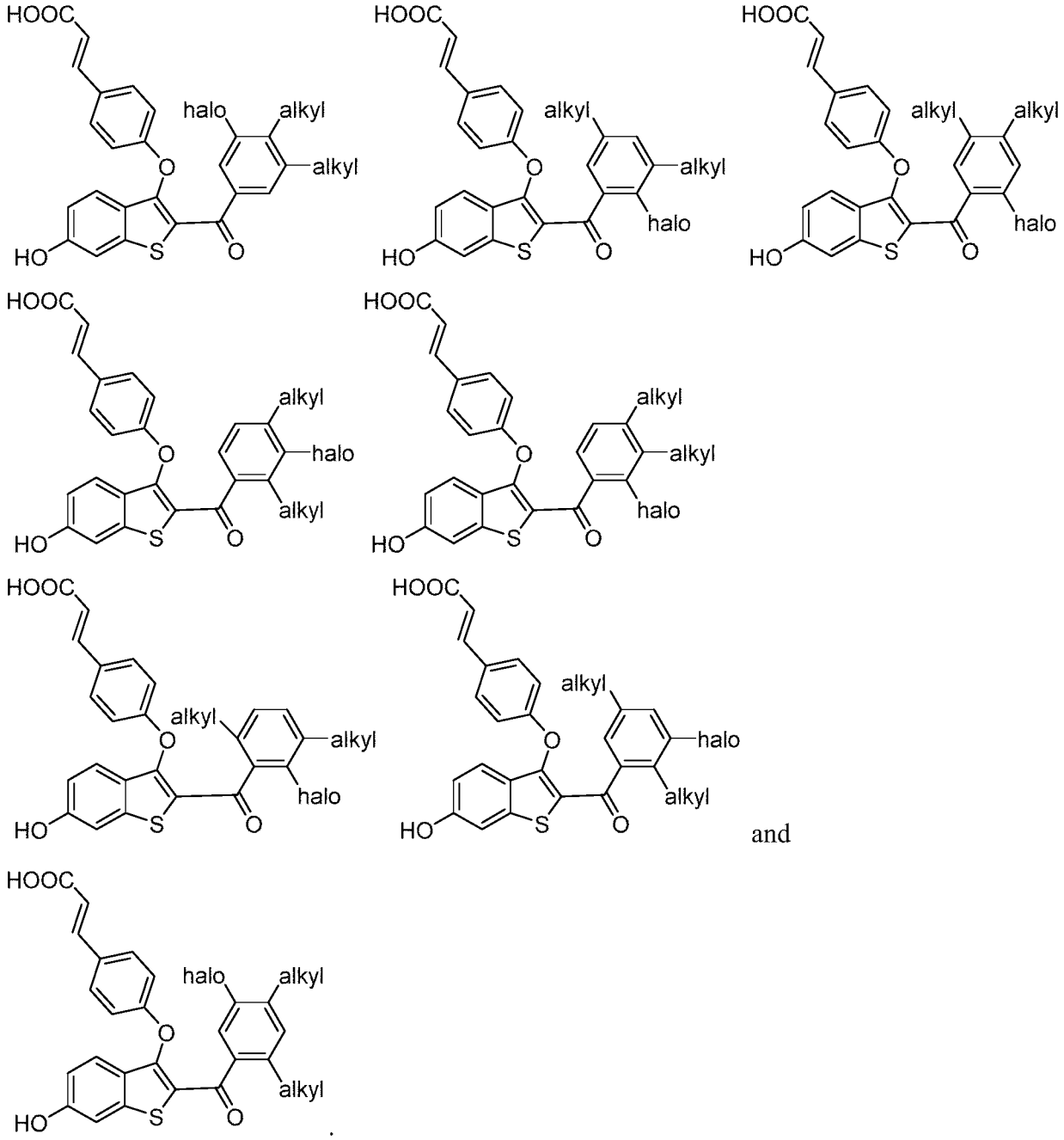
and


HOOC
alkyl
alkyl
alkyl
O
HO
S
O

5

Additional non-limiting examples of compounds of the present invention include:



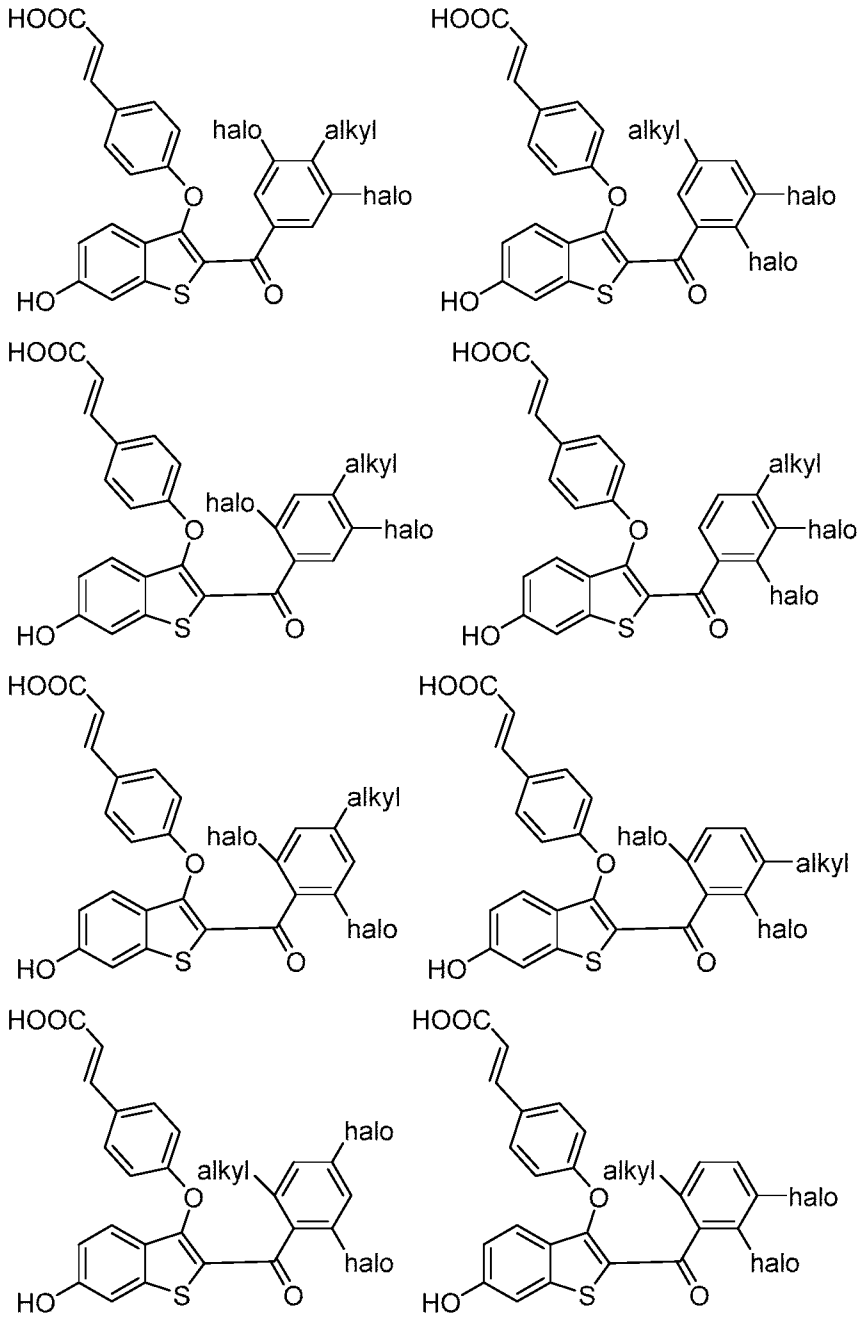


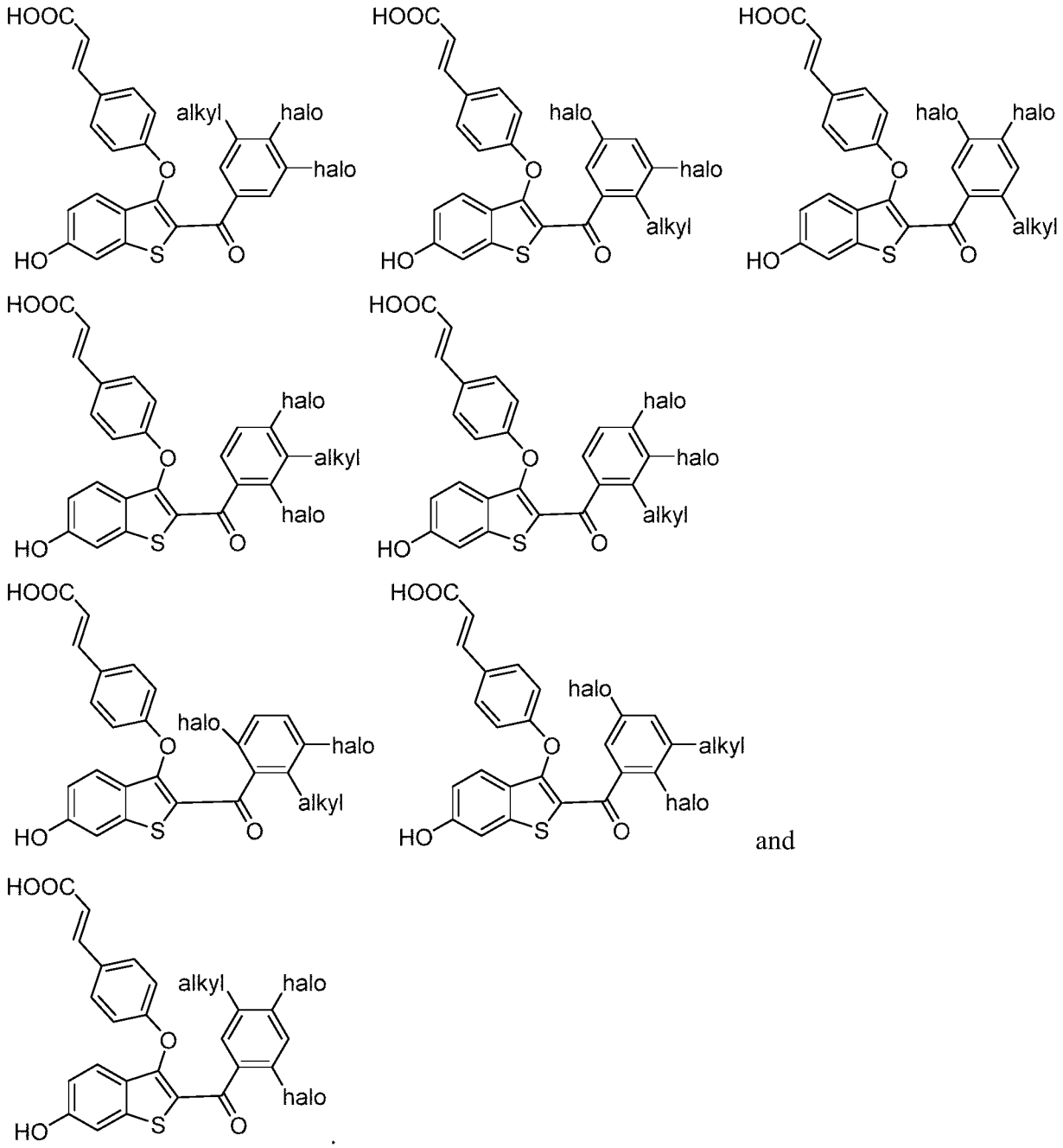
.

In certain embodiments of the above structures, alkyl is methyl. In other embodiments of the above structures embodiments, alkyl is independently methyl, ethyl, propyl or cyclopropyl. In some embodiments of the above embodiments, halo is fluoro. In some embodiments, haloalkyl is independently mono-, di- or trifluoro-methyl. In certain embodiments where the benzene ring has two halos, the halos can be one fluoro one chloro, two fluoros, or two chloros. In certain

embodiments where the benzene ring has three halos, the halos can be one fluoro two chloros, two fluoros one chloro, three fluoros, or three chloros.

Additional non-limiting examples of compounds of the present invention include:





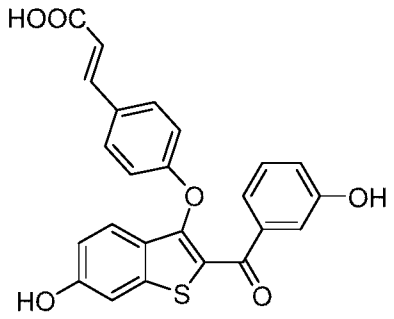
and

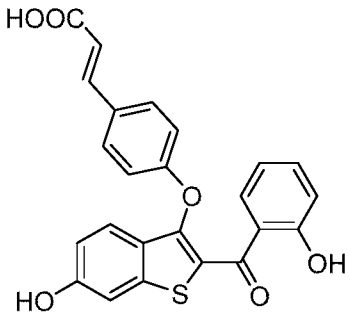
.

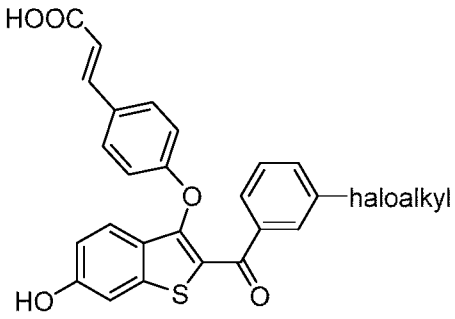
In certain embodiments of the above structures, alkyl is methyl. In other embodiments of the above structures embodiments, alkyl is independently methyl, ethyl, propyl or cyclopropyl. In some embodiments of the above embodiments, halo is fluoro. In some embodiments, haloalkyl is independently mono-, di- or trifluoro-methyl. In certain embodiments where the benzene ring has two halos, the halos can be one fluoro one chloro, two fluoros, or two chloros. In certain

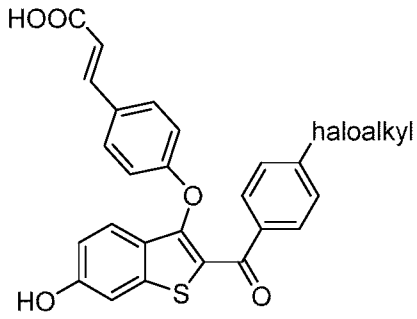
embodiments where the benzene ring has three halos, the halos can be one fluoro two chloros, two fluoros one chloro, three fluoros, or three chloros.

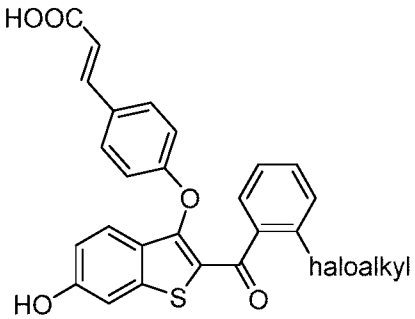
Additional non-limiting examples of compounds of the present invention include:

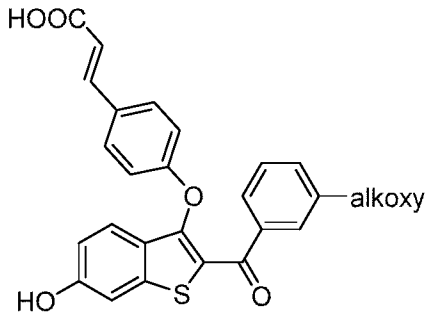


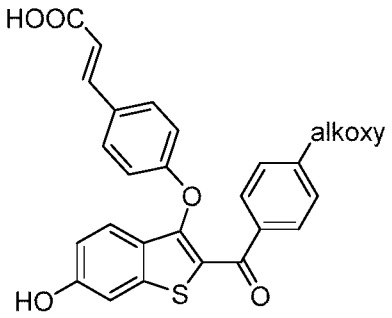




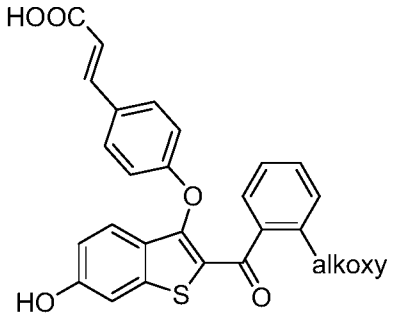






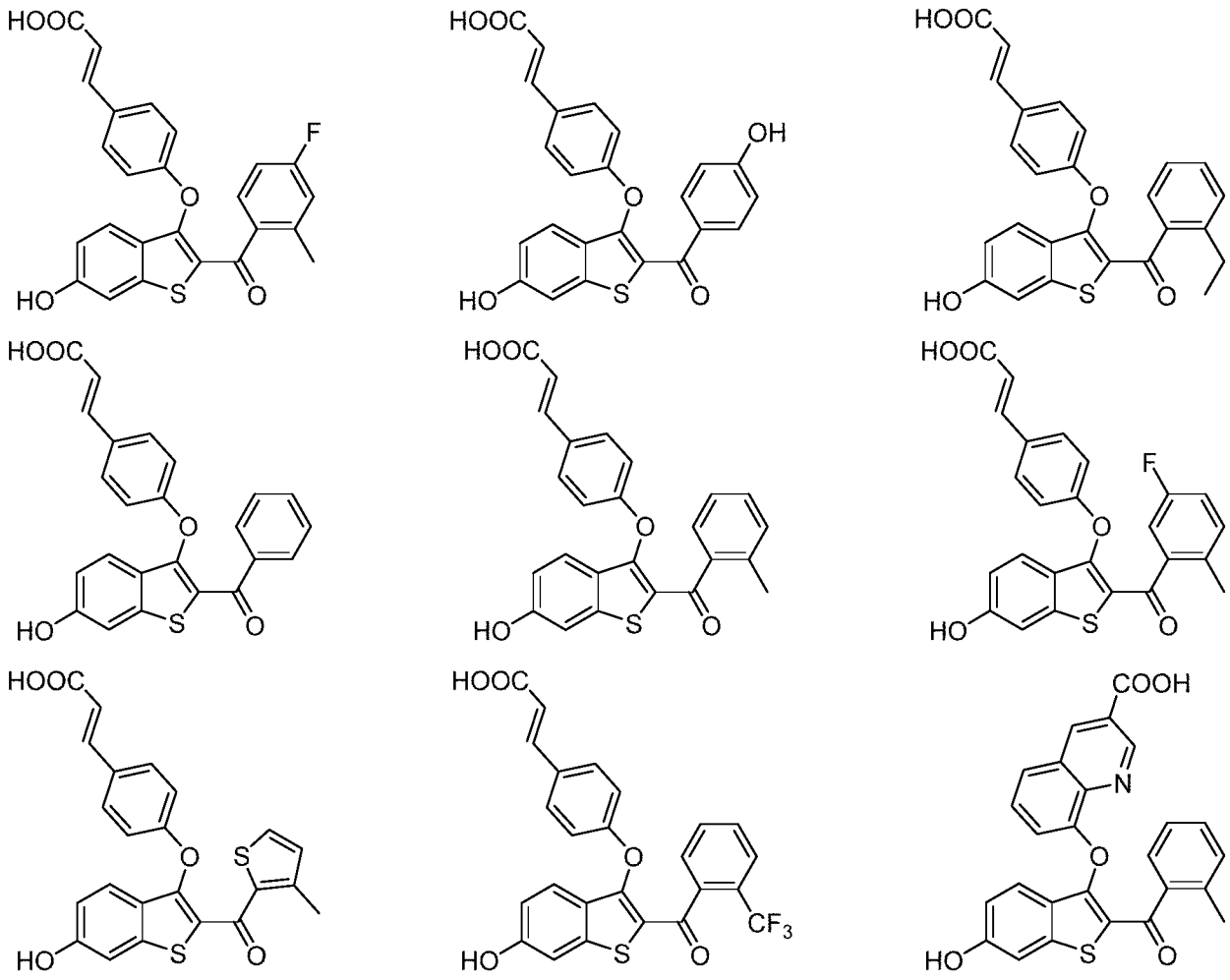


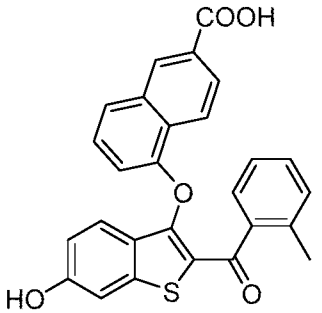
and

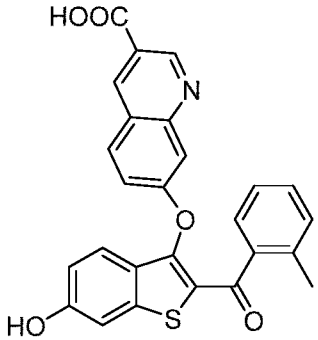


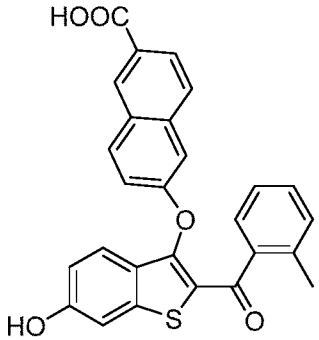
In certain embodiment of the above structures, alkoxy is methoxy. In other embodiments of the above structures embodiments, alkoxy is ethoxy, propoxy or cyclopropyloxy. In some embodiments, haloalkyl is mono-, di- or trifluoro-methyl.

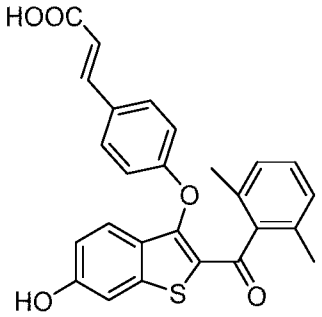
Representative compounds of the invention include, but are not limited to compounds of formula:




COOH
O
HO
S
O


HOOC
N
O
HO
S
O


HOOC
O
HO
S
O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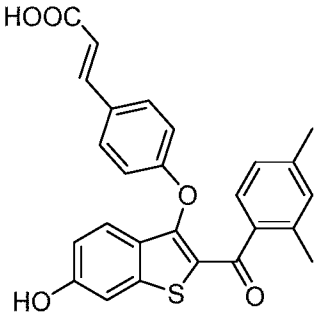
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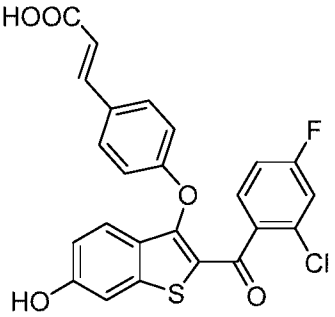
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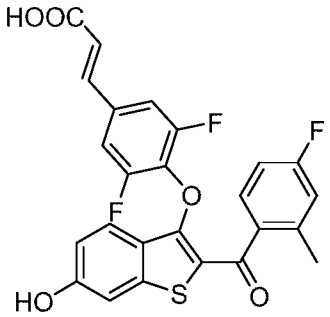
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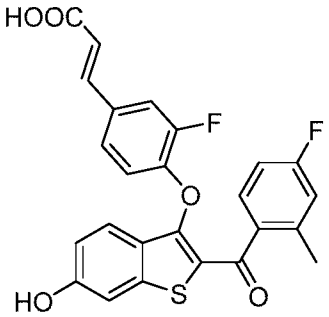
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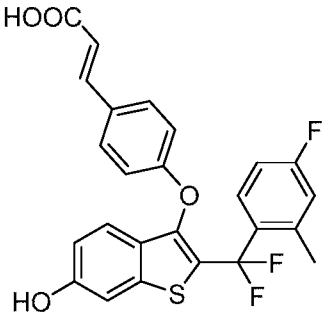
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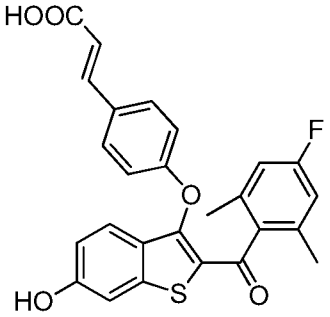
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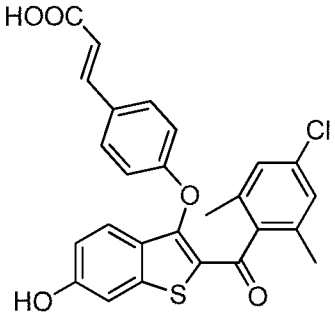
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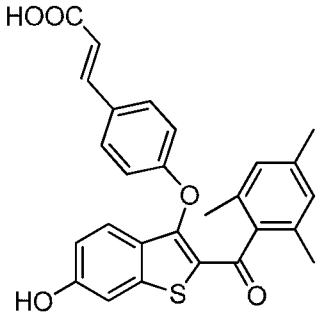
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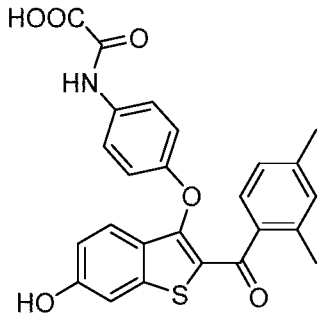
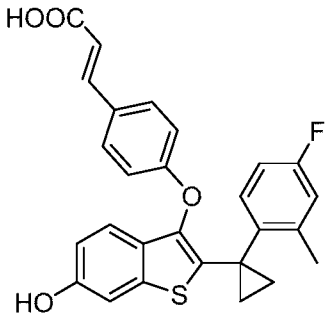
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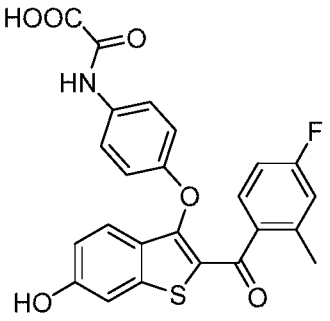
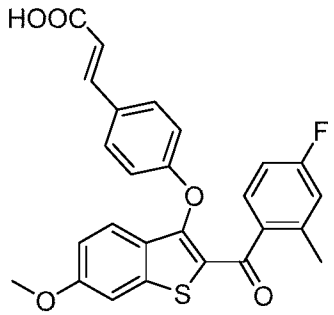
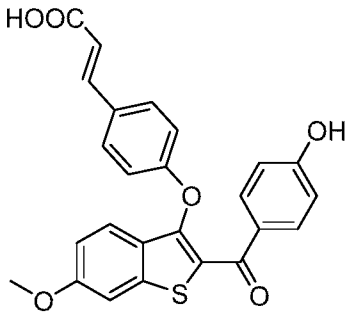
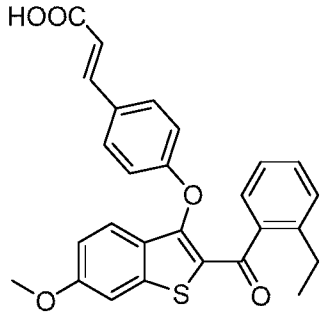
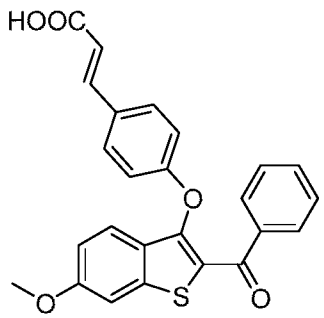
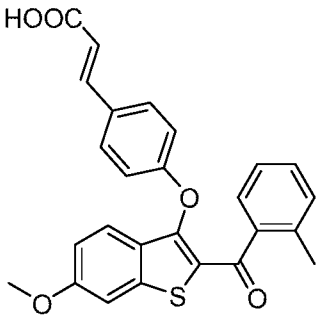
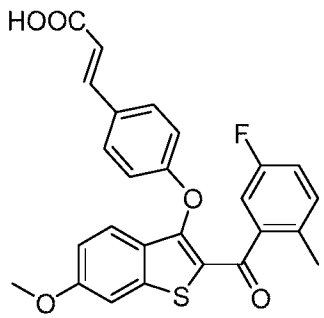
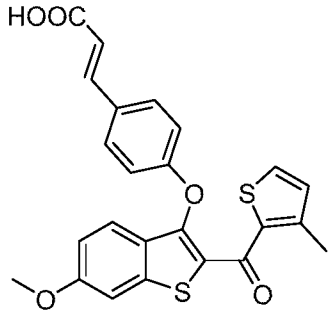
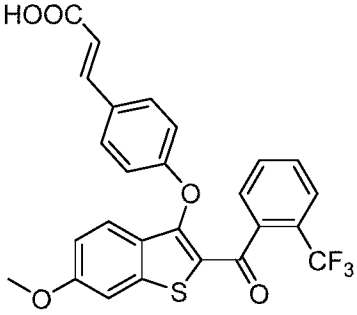
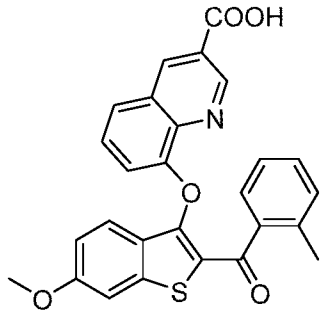
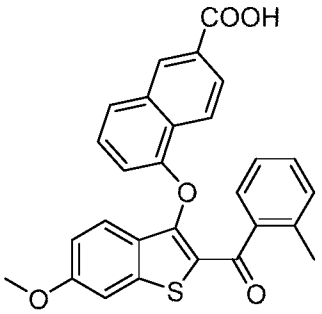

, or a pharmaceutically acceptable salt or prodrug thereof.

Additional representative compounds of the invention include, but are not limited to compounds of formula: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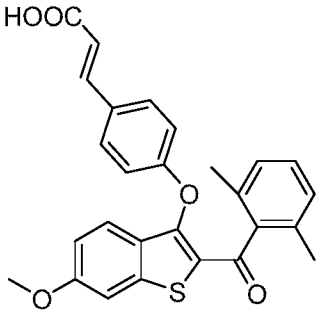
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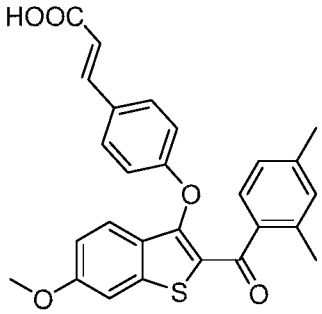
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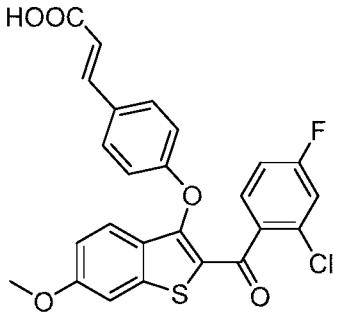
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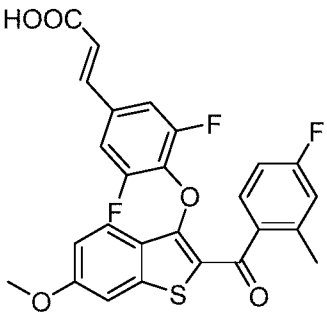
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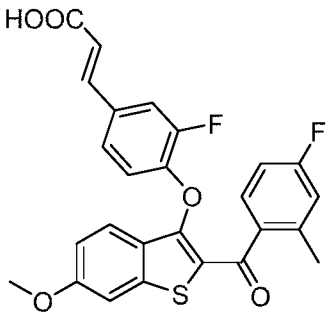
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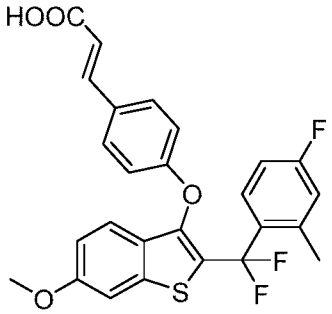
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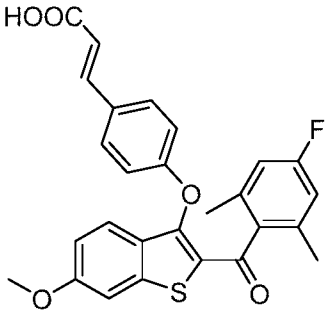
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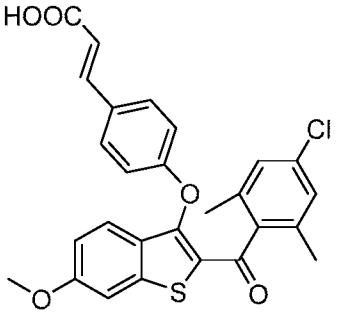
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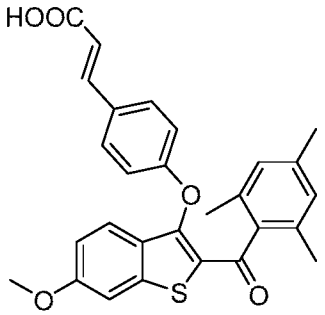
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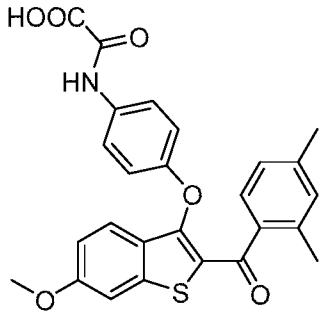
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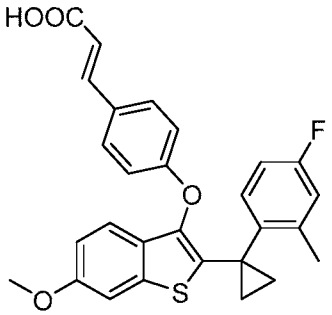
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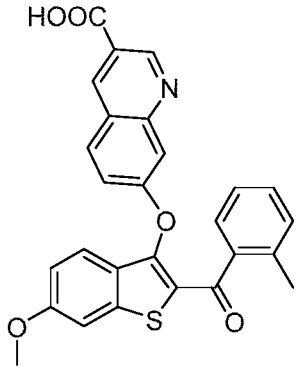
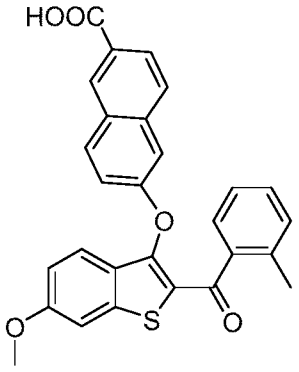
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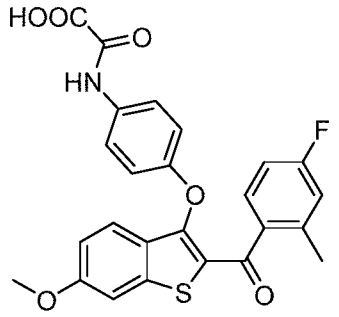
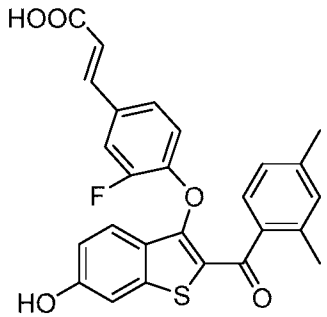
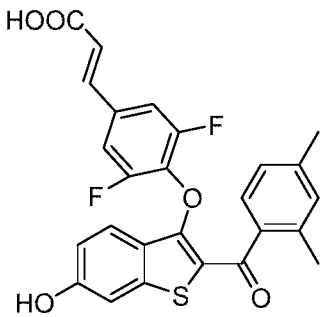
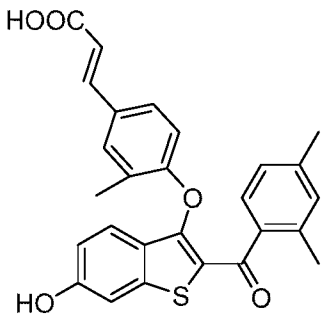
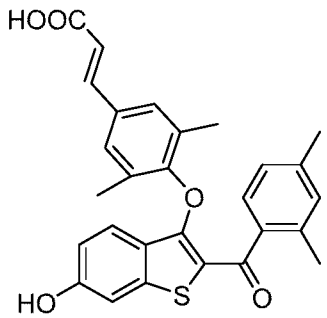
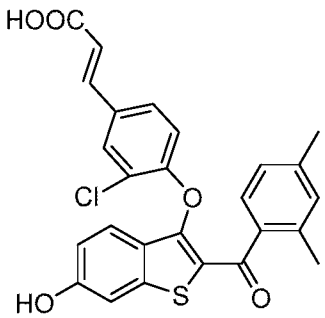
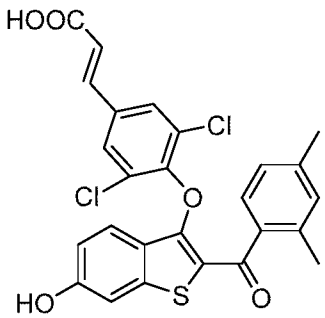
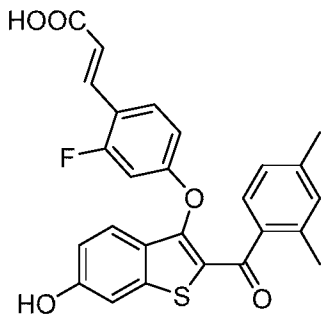
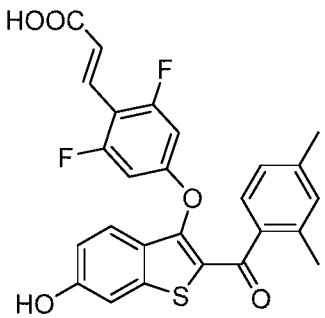
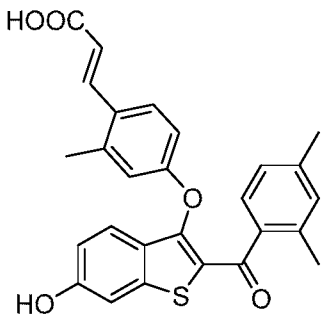
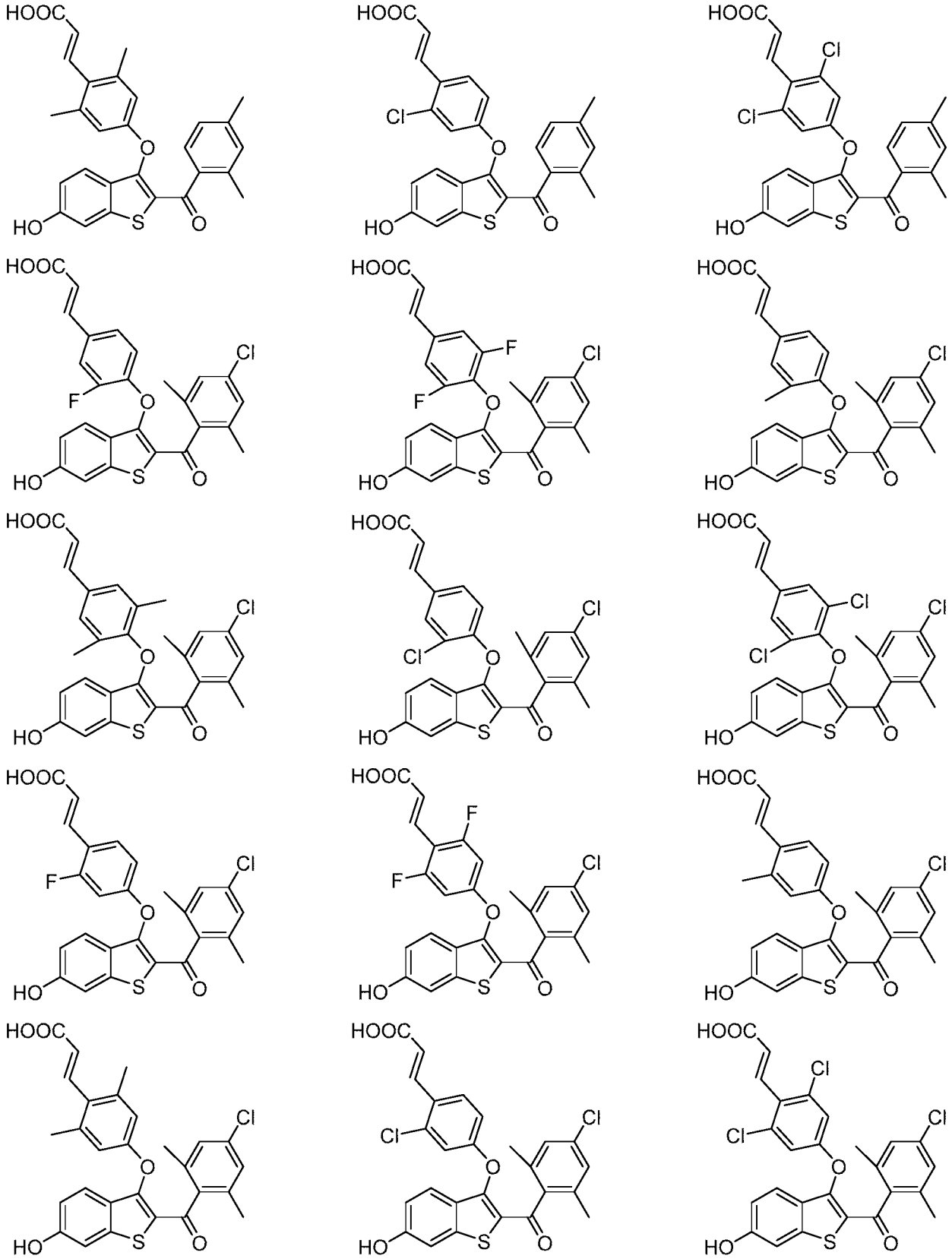
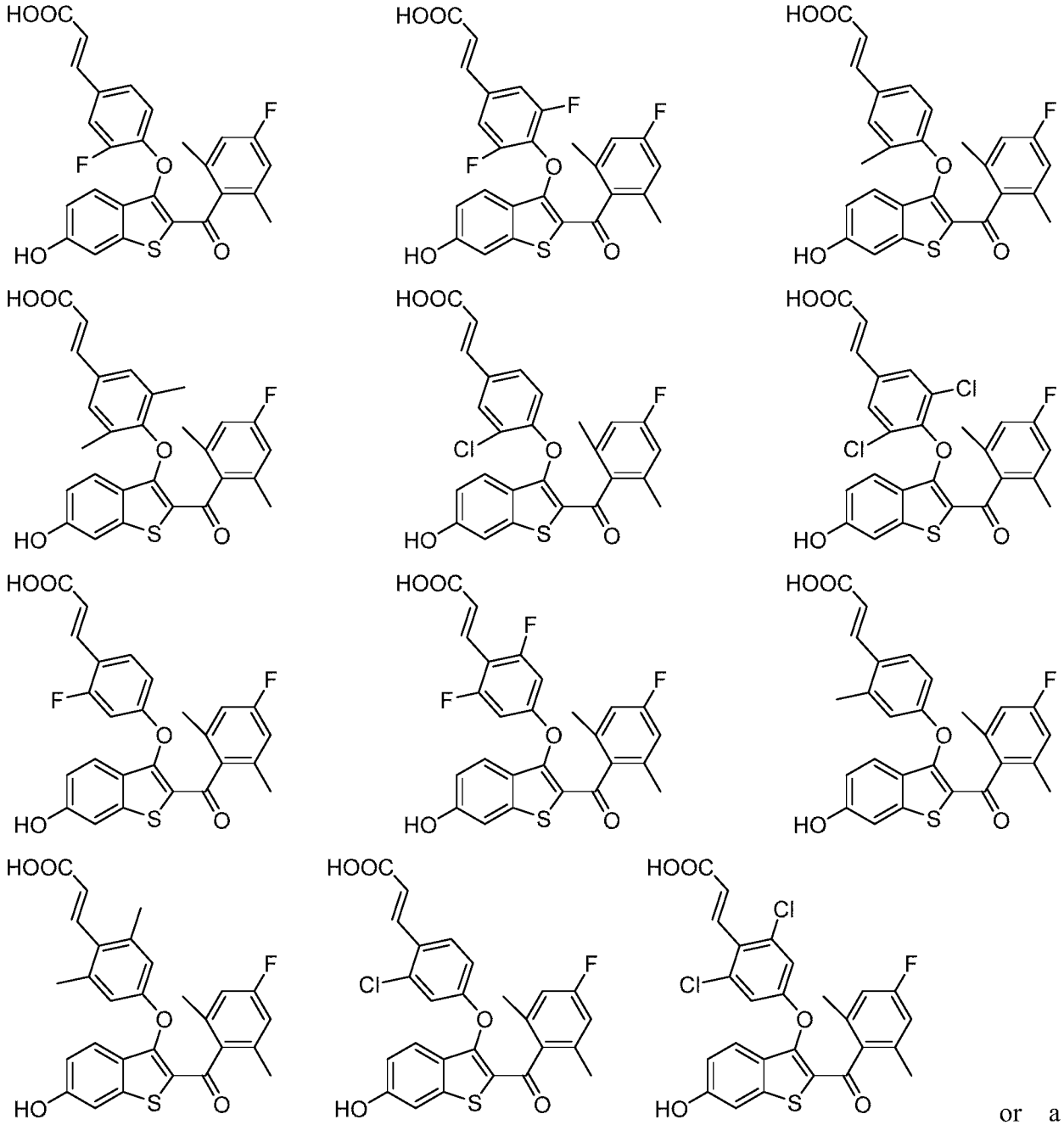

, or a pharmaceutically acceptable salt thereof.

Additional representative compounds of the invention include, but are not limited to compounds of formula:

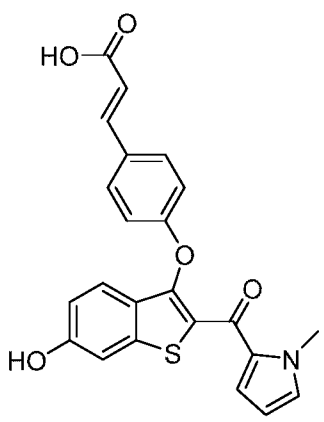










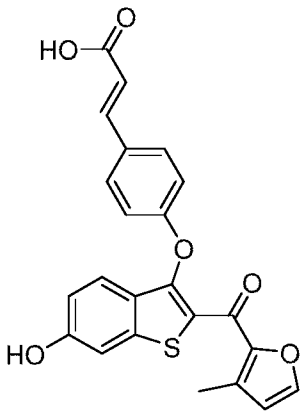


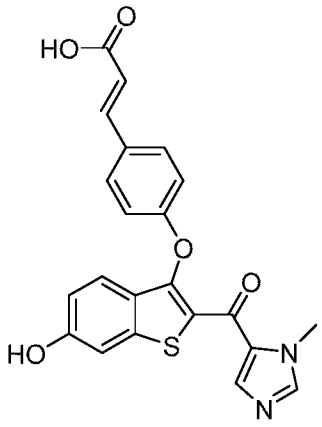


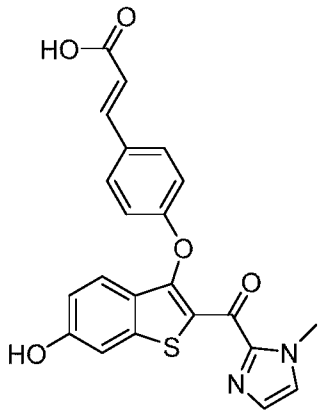
or a pharmaceutically acceptable salt thereof.

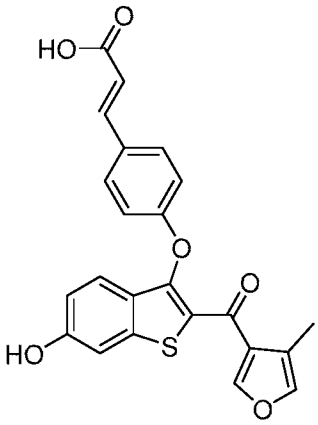
Additional representative compounds of the invention include, but are not limited to compounds of formula:

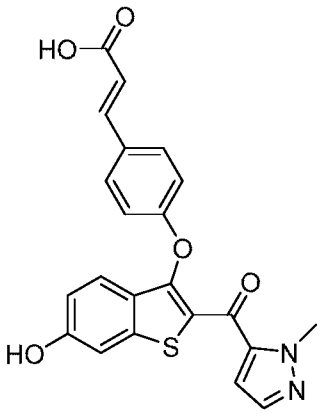


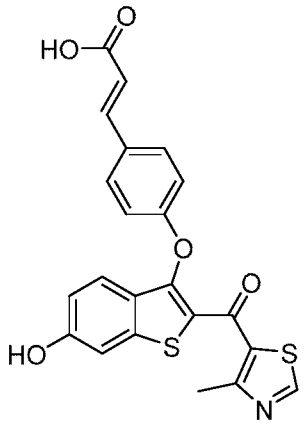


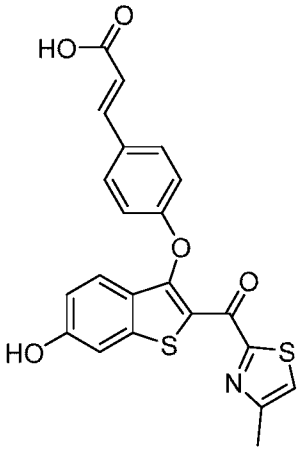


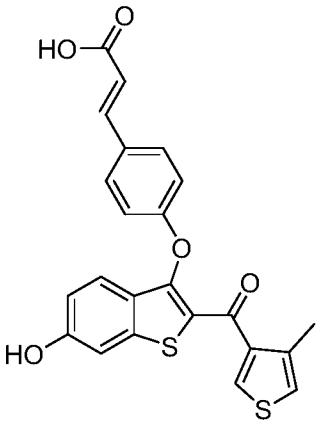




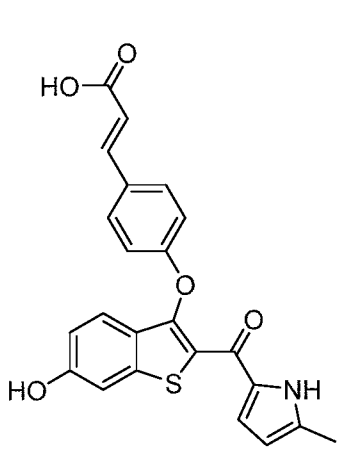
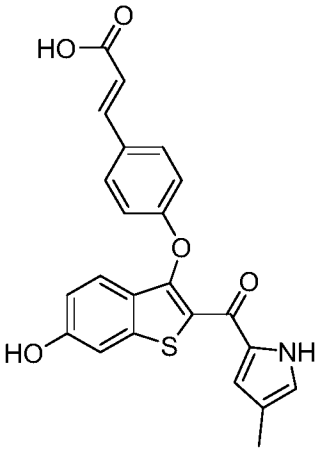
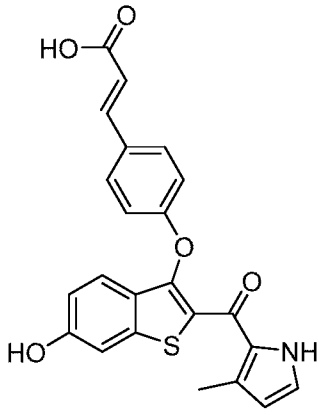
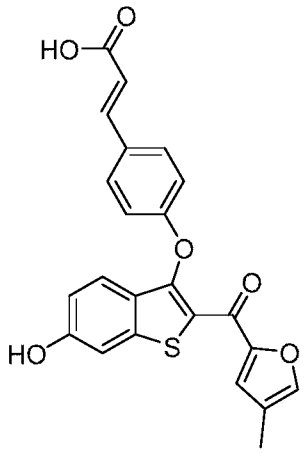
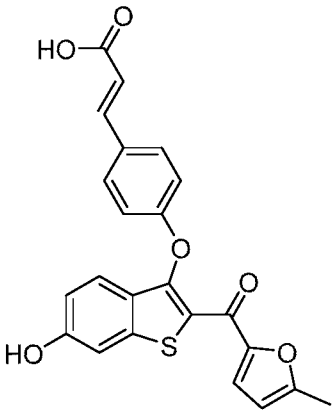
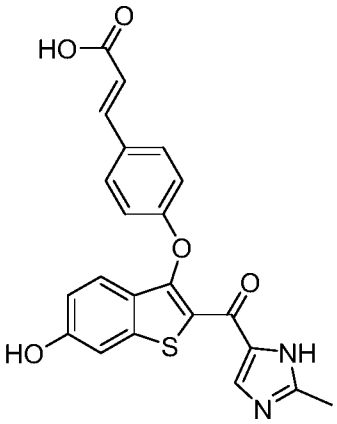
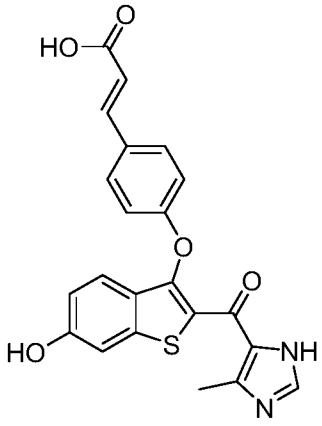
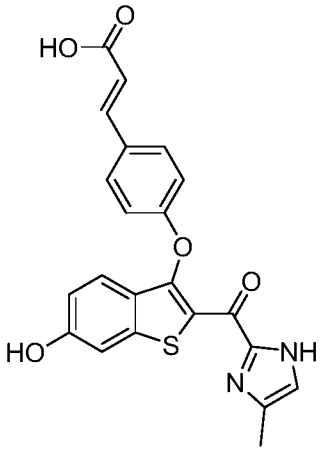
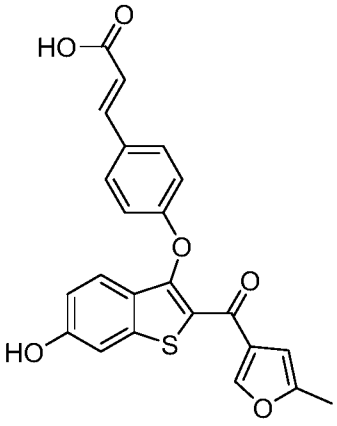


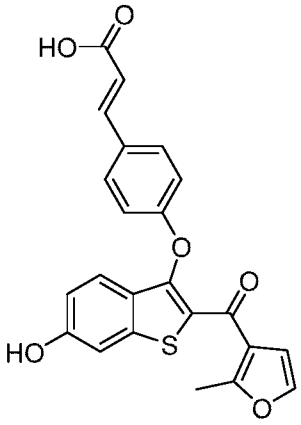


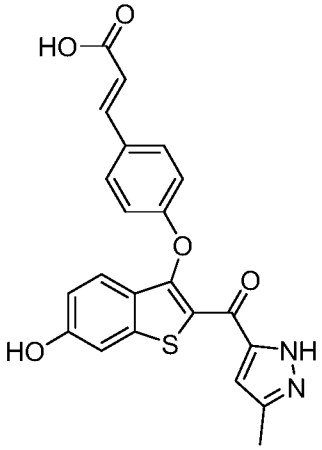


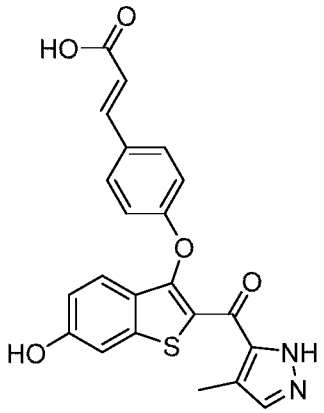


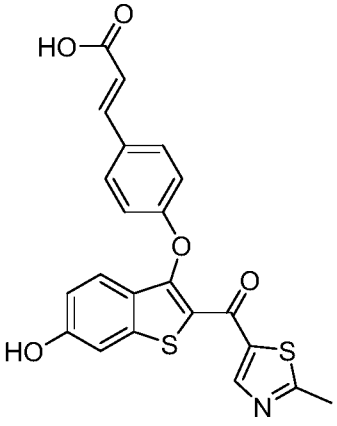
Additional representative compounds of the invention include, but are not limited to compounds of formula:

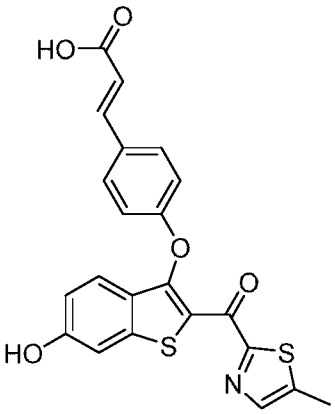










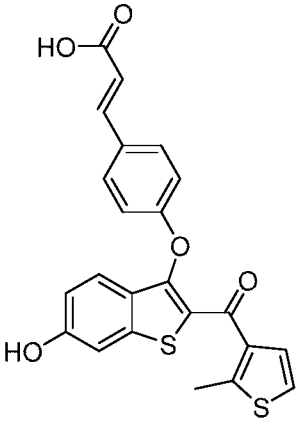












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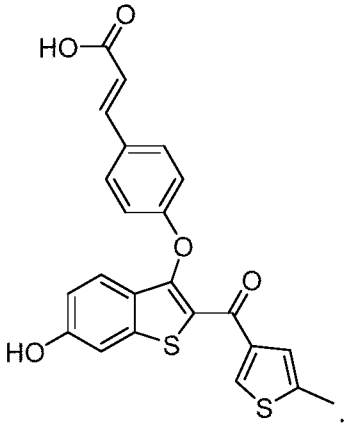

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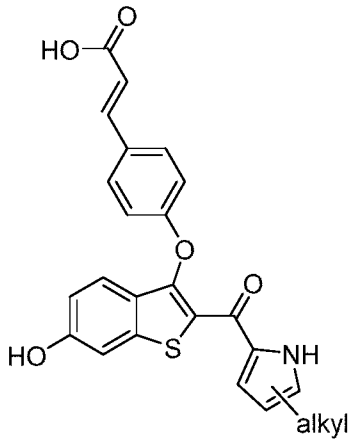
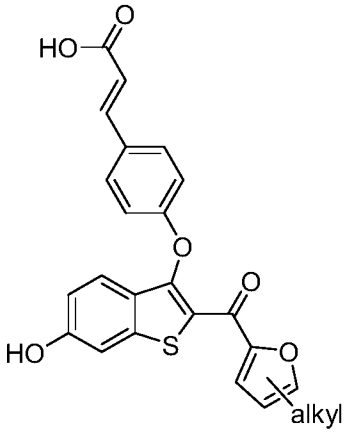
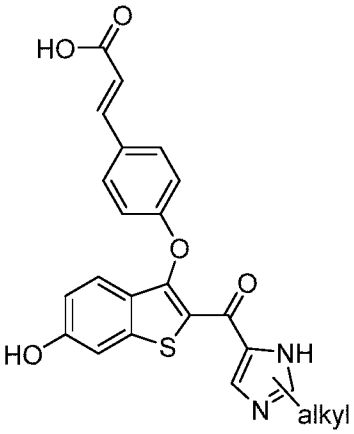
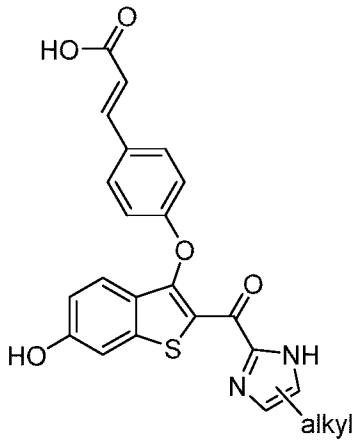
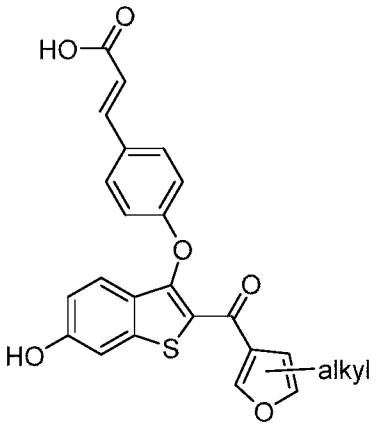
Additional representative compounds of the invention include, but are not limited to compounds of formula:

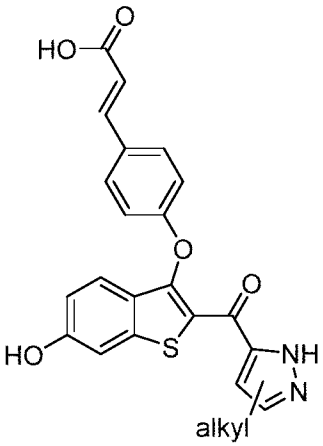


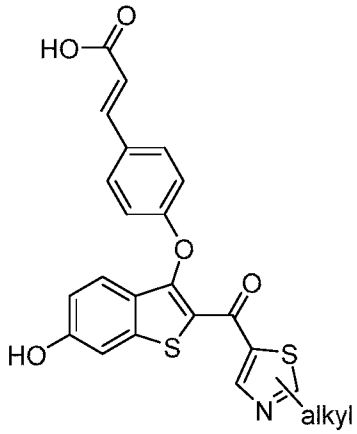


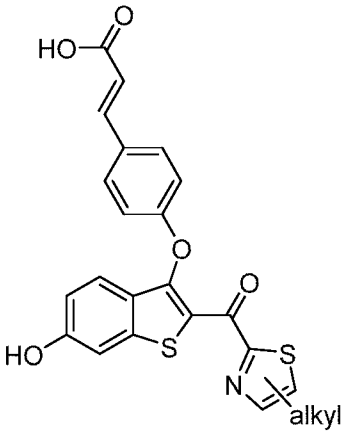


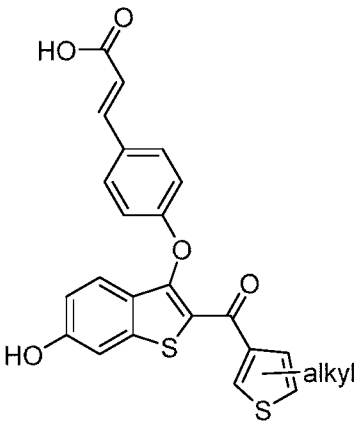












In one embodiment of any of the above structures that have a $-CO_2H$, the compound can be presented, for example, as an ester, amide, or ether prodrug. The ester may be, for example, $-CO_2R$, wherein R is alkyl (including cycloalkyl), heteroalkyl, alkenyl, alkynyl, aryl, heteoraryl, heterocyclic, or any other moiety that is metabolized in vivo to provide the parent drug.

Pharmaceutical Compositions and Methods of Treatment

This invention includes pharmaceutical compositions that include a therapeutically effective amount of a compound as described herein or its pharmaceutically acceptable salt or prodrug, and one or more of a pharmaceutically acceptable vehicle such as a diluent, preservative, solubilizer, emulsifier, adjuvant, excipient, or carrier. Excipients include, but are not limited to, liquids such as water, saline, glycerol, polyethylene glycol, hyaluronic acid, ethanol, and the like.

The term "pharmaceutically acceptable carrier" refers to a diluent, adjuvant, excipient or carrier with which a compound of the disclosure is administered. The terms "effective amount" or "pharmaceutically effective amount" refer to a nontoxic but sufficient amount of the agent to provide the desired biological result. That result can be reduction and/or alleviation of the signs, symptoms, or causes of a disease, or any other desired alteration of a biological system. An appropriate "effective" amount in any individual case can be determined by one of ordinary skill in the art using routine experimentation. "Pharmaceutically acceptable carriers" for therapeutic use are well known in the pharmaceutical art, and are described, for example, in Remington's Pharmaceutical Sciences, 18th Edition (Easton, Pennsylvania: Mack Publishing Company, 1990). For example, sterile saline and phosphate-buffered saline at physiological pH can be used. Preservatives, stabilizers, dyes and even flavoring agents can be provided in the pharmaceutical composition. For example, sodium benzoate, sorbic acid and esters of p-hydroxybenzoic acid can be added as preservatives. *Id.* at 1449. In addition, antioxidants and suspending agents can be used. *Id.*

Suitable excipients for non-liquid formulations are also known to those of skill in the art. A thorough discussion of pharmaceutically acceptable excipients and salts is available in Remington's Pharmaceutical Sciences, 18th Edition (Easton, Pennsylvania: Mack Publishing Company, 1990).

Additionally, auxiliary substances, such as wetting or emulsifying agents, biological buffering substances, surfactants, and the like, can be present in such vehicles. A biological buffer

can be any solution which is pharmacologically acceptable and which provides the formulation with the desired pH, i.e., a pH in the physiologically acceptable range. Examples of buffer solutions include saline, phosphate buffered saline, Tris buffered saline, Hank's buffered saline, and the like.

Depending on the intended mode of administration, the pharmaceutical compositions can be in the form of solid, semi-solid or liquid dosage forms, such as, for example, tablets, suppositories, pills, capsules, powders, liquids, suspensions, creams, ointments, lotions or the like, preferably in unit dosage form suitable for single administration of a precise dosage. The compositions will include an effective amount of the selected drug in combination with a pharmaceutically acceptable carrier and, in addition, can include other pharmaceutical agents, adjuvants, diluents, buffers, and the like.

In general, the compositions of the disclosure will be administered in a therapeutically effective amount by any of the accepted modes of administration. Suitable dosage ranges depend upon numerous factors such as the severity of the disease to be treated, the age and relative health of the subject, the potency of the compound used, the route and form of administration, the indication towards which the administration is directed, and the preferences and experience of the medical practitioner involved. One of ordinary skill in the art of treating such diseases will be able, without undue experimentation and in reliance upon personal knowledge and the disclosure of this application, to ascertain a therapeutically effective amount of the compositions of the disclosure for a given disease.

Compositions for administration of the active compound include but are not limited to those suitable for oral (including but not limited to a tablet, capsule, liquid, gel formulation), topical, rectal, nasal, pulmonary, parenteral (including intramuscular, intra-arterial, intrathecal, subcutaneous and intravenous), intramuscular, intravenous, sub-cutaneous, transdermal (which may include a penetration enhancement agent), vaginal and suppository administration. Enteric coated oral tablets may also be used to enhance bioavailability of the compounds for an oral route of administration. The most effective dosage form will depend upon the bioavailability/pharmacokinetics of the particular compound chosen as well as the severity of disease in the patient. Oral dosage forms are particularly typical, because of ease of administration and prospective favorable patient compliance.

For solid compositions, conventional nontoxic solid carriers include, for example, pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharin, talc,

cellulose, glucose, sucrose, magnesium carbonate, and the like. Liquid pharmaceutically administrable compositions can, for example, be prepared by dissolving, dispersing, and the like, an active compound as described herein and optional pharmaceutical adjuvants in an excipient, such as, for example, water, saline, aqueous dextrose, glycerol, ethanol, and the like, to thereby form a solution or suspension. If desired, the pharmaceutical composition to be administered can also contain minor amounts of nontoxic auxiliary substances such as wetting or emulsifying agents, pH buffering agents and the like, for example, sodium acetate, sorbitan monolaurate, triethanolamine sodium acetate, triethanolamine oleate, and the like. Actual methods of preparing such dosage forms are known, or will be apparent, to those skilled in this art; for example, see Remington's Pharmaceutical Sciences, referenced above.

Yet another embodiment is the use of permeation enhancer excipients including polymers such as: polycations (chitosan and its quaternary ammonium derivatives, poly-L-arginine, aminated gelatin); polyanions (N-carboxymethyl chitosan, poly-acrylic acid); and, thiolated polymers (carboxymethyl cellulose-cysteine, polycarbophil-cysteine, chitosan-thiobutylamidine, chitosan-thioglycolic acid, chitosan-glutathione conjugates).

For oral administration, the composition will generally take the form of a tablet, capsule, a softgel capsule or can be an aqueous or nonaqueous solution, suspension or syrup. Tablets and capsules are typical oral administration forms. Tablets and capsules for oral use can include one or more commonly used carriers such as lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. Typically, the compositions of the disclosure can be combined with an oral, non-toxic, pharmaceutically acceptable, inert carrier such as lactose, starch, sucrose, glucose, methyl cellulose, magnesium stearate, dicalcium phosphate, calcium sulfate, mannitol, sorbitol and the like. Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents, and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth, or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes, and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride, and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum, and the like.

When liquid suspensions are used, the active agent can be combined with any oral, non-toxic, pharmaceutically acceptable inert carrier such as ethanol, glycerol, water, and the like and with emulsifying and suspending agents. If desired, flavoring, coloring and/or sweetening agents can be added as well. Other optional components for incorporation into an oral formulation herein include, but are not limited to, preservatives, suspending agents, thickening agents, and the like.

Parenteral formulations can be prepared in conventional forms, either as liquid solutions or suspensions, solid forms suitable for solubilization or suspension in liquid prior to injection, or as emulsions. Preferably, sterile injectable suspensions are formulated according to techniques known in the art using suitable carriers, dispersing or wetting agents and suspending agents. The sterile injectable formulation can also be a sterile injectable solution or a suspension in a acceptable nontoxic parenterally acceptable diluent or solvent. Among the acceptable vehicles and solvents that can be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils, fatty esters or polyols are conventionally employed as solvents or suspending media. In addition, parenteral administration can involve the use of a slow release or sustained release system such that a constant level of dosage is maintained.

Parenteral administration includes intraarticular, intravenous, intramuscular, intradermal, intraperitoneal, and subcutaneous routes, and include aqueous and non-aqueous, isotonic sterile injection solutions, which can contain antioxidants, buffers, bacteriostats, and solutes that render the formulation isotonic with the blood of the intended recipient, and aqueous and non-aqueous sterile suspensions that can include suspending agents, solubilizers, thickening agents, stabilizers, and preservatives. Administration via certain parenteral routes can involve introducing the formulations of the disclosure into the body of a patient through a needle or a catheter, propelled by a sterile syringe or some other mechanical device such as an continuous infusion system. A formulation provided by the disclosure can be administered using a syringe, injector, pump, or any other device recognized in the art for parenteral administration.

Preferably, sterile injectable suspensions are formulated according to techniques known in the art using suitable carriers, dispersing or wetting agents and suspending agents. The sterile injectable formulation can also be a sterile injectable solution or a suspension in a nontoxic parenterally acceptable diluent or solvent. Among the acceptable vehicles and solvents that can be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils, fatty esters or polyols are conventionally employed as solvents or suspending media. In

addition, parenteral administration can involve the use of a slow release or sustained release system such that a constant level of dosage is maintained.

Preparations according to the disclosure for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions, or emulsions. Examples of non-aqueous solvents or vehicles are propylene glycol, polyethylene glycol, vegetable oils, such as olive oil and corn oil, gelatin, and injectable organic esters such as ethyl oleate. Such dosage forms can also contain adjuvants such as preserving, wetting, emulsifying, and dispersing agents. They can be sterilized by, for example, filtration through a bacteria retaining filter, by incorporating sterilizing agents into the compositions, by irradiating the compositions, or by heating the compositions. They can also be manufactured using sterile water, or some other sterile injectable medium, immediately before use.

Sterile injectable solutions are prepared by incorporating one or more of the compounds of the disclosure in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the various sterilized active ingredients into a sterile vehicle which contains the basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum-drying and freeze-drying techniques which yield a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof. Thus, for example, a parenteral composition suitable for administration by injection is prepared by stirring 1.5% by weight of active ingredient in 10% by volume propylene glycol and water. The solution is made isotonic with sodium chloride and sterilized.

Alternatively, the pharmaceutical compositions of the disclosure can be administered in the form of suppositories for rectal administration. These can be prepared by mixing the agent with a suitable nonirritating excipient which is solid at room temperature but liquid at the rectal temperature and therefore will melt in the rectum to release the drug. Such materials include cocoa butter, beeswax and polyethylene glycols.

The pharmaceutical compositions of the disclosure can also be administered by nasal aerosol or inhalation. Such compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and can be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability,

propellants such as fluorocarbons or nitrogen, and/or other conventional solubilizing or dispersing agents.

Preferred formulations for topical drug delivery are ointments and creams. Ointments are semisolid preparations which are typically based on petrolatum or other petroleum derivatives. Creams containing the selected active agent, are, as known in the art, viscous liquid or semisolid emulsions, either oil-in-water or water-in-oil. Cream bases are water-washable, and contain an oil phase, an emulsifier and an aqueous phase. The oil phase, also sometimes called the "internal" phase, is generally comprised of petrolatum and a fatty alcohol such as cetyl or stearyl alcohol. The aqueous phase usually, although not necessarily, exceeds the oil phase in volume, and generally contains a humectant. The emulsifier in a cream formulation is generally a nonionic, anionic, cationic or amphoteric surfactant. The specific ointment or cream base to be used, as will be appreciated by those skilled in the art, is one that will provide for optimum drug delivery. As with other carriers or vehicles, an ointment base should be inert, stable, nonirritating and nonsensitizing.

Formulations for buccal administration include tablets, lozenges, gels and the like. Alternatively, buccal administration can be effected using a transmucosal delivery system as known to those skilled in the art. The compounds of the disclosure can also be delivered through the skin or muscosal tissue using conventional transdermal drug delivery systems, i.e., transdermal "patches" wherein the agent is typically contained within a laminated structure that serves as a drug delivery device to be affixed to the body surface. In such a structure, the drug composition is typically contained in a layer, or "reservoir," underlying an upper backing layer. The laminated device can contain a single reservoir, or it can contain multiple reservoirs. In one embodiment, the reservoir comprises a polymeric matrix of a pharmaceutically acceptable contact adhesive material that serves to affix the system to the skin during drug delivery. Examples of suitable skin contact adhesive materials include, but are not limited to, polyethylenes, polysiloxanes, polyisobutylenes, polyacrylates, polyurethanes, and the like. Alternatively, the drug-containing reservoir and skin contact adhesive are present as separate and distinct layers, with the adhesive underlying the reservoir which, in this case, can be either a polymeric matrix as described above, or it can be a liquid or gel reservoir, or can take some other form. The backing layer in these laminates, which serves as the upper surface of the device, functions as the primary structural element of the laminated structure and provides the device with much of its flexibility. The material selected for

the backing layer should be substantially impermeable to the active agent and any other materials that are present.

The compositions of the disclosure can be formulated for aerosol administration, particularly to the respiratory tract and including intranasal administration. The compound may, for example generally have a small particle size, for example of the order of 5 microns or less. Such a particle size can be obtained by means known in the art, for example by micronization. The active ingredient is provided in a pressurized pack with a suitable propellant such as a chlorofluorocarbon (CFC) for example dichlorodifluoromethane, trichlorofluoromethane, or dichlorotetrafluoroethane, carbon dioxide or other suitable gas. The aerosol can conveniently also contain a surfactant such as lecithin. The dose of drug can be controlled by a metered valve. Alternatively the active ingredients can be provided in a form of a dry powder, for example a powder mix of the compound in a suitable powder base such as lactose, starch, starch derivatives such as hydroxypropylmethyl cellulose and polyvinylpyrrolidine (PVP). The powder carrier will form a gel in the nasal cavity. The powder composition can be presented in unit dose form for example in capsules or cartridges of e.g., gelatin or blister packs from which the powder can be administered by means of an inhaler.

A pharmaceutically or therapeutically effective amount of the composition should be delivered to the subject. The precise effective amount will vary from subject to subject and will depend upon the species, age, the subject's size and health, the nature and extent of the condition being treated, recommendations of the treating physician, and the therapeutics or combination of therapeutics selected for administration. The effective amount for a given situation can be determined by routine experimentation. For purposes of the disclosure, a therapeutic amount may for example be in the range of about 0.01 mg/kg to about 250 mg/kg body weight, more preferably about 0.1 mg/kg to about 10 mg/kg, in at least one dose. In some non-limiting embodiments, the daily dosage may be from about 1 mg to 300 mg, one or more times per day, more preferably in the range of about 10 mg to 200 mg. The subject can be administered in as many doses as is required to reduce and/or alleviate the signs, symptoms, or causes of the disorder in question, or bring about any other desired alteration of a biological system. When desired, formulations can be prepared with enteric coatings adapted for sustained or controlled release administration of the active ingredient.

In some embodiments, for example, the dosage may be the amount of compound needed to provide a serum concentration of the active compound of up to about 10 nM, 50 nM, 100 nM, 200 nM, 300 nM, 400 nM, 500 nM, 600 nM, 700 nM, 800 nM, 900 nM, 1 μM, 5 μM, 10 μM, 20 μM, 30 μM, or 40 μM.

In certain embodiments the pharmaceutical composition is in a dosage form that contains from about 0.1 mg to about 2000 mg, from about 10 mg to about 1000 mg, from about 100 mg to about 800 mg, or from about 200 mg to about 600 mg of the active compound and optionally from about 0.1 mg to about 2000 mg, from about 10 mg to about 1000 mg, from about 100 mg to about 800 mg, or from about 200 mg to about 600 mg of an additional active agent in a unit dosage form. Examples of dosage forms are those with at least, or no greater than, 1, 2, 5, 10, 15, 20, 25, 50, 75, 100, 150, 200, 250, 300, 350, 400, 450, 500, 550, 600, 650, 700, or 750 mg of active compound, or its salt or prodrug. The pharmaceutical composition may also include a molar ratio of the active compound and an additional active agent, in a ratio that achieves the desired results.

The unit dosage form can be for example, a packaged preparation containing discrete quantities of preparation, such as packeted tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

The compounds and compositions of the invention may be used in methods for treatment or prevention of estrogen-related medical disorders, for example, cancer. The cancer may be for example a breast cancer, a uterine cancer, an ovarian cancer, endometrial, a prostate cancer, and a lung cancer. Particularly, the breast cancer may be a tamoxifen resistant breast cancer or a triple negative breast cancer.

The method of treatment may prevent or reduce the risk of cancer or a tumor. The method of treatment may cause partial or complete regression of cancer or a tumor in a subject.

The method of treatment may cause partial or complete regression of a tamoxifen resistant cancer or tumor. The method of treatment may cause partial or complete regression of a triple negative breast cancer.

In other embodiments, the compound or its pharmaceutically acceptable salt or prodrug or a pharmaceutical composition thereof can be used to prevent recurrence of a cancer or tumor after treatment, as adjunctive therapy. In one example, the compound or its pharmaceutically acceptable salt or prodrug or a pharmaceutical composition thereof can be used to prevent further breast

cancer after breast cancer treatment or to treat node-positive breast cancer in women following mastectomy and/or radiation.

If desired, multiple doses of a compound described herein can be administered to the subject. Alternatively, the subject can be given a single dose of a compound described herein.

In one aspect of the invention, a compound disclosed herein can be beneficially administered in combination with any therapeutic regimen entailing radiotherapy, chemotherapy, or other therapeutic agents. In additional embodiments the compounds disclosed herein can be beneficially administered in combination with therapeutic agents targeting auto-immune disorders.

The compound or its pharmaceutically acceptable salt or prodrug or a pharmaceutical composition thereof may also be used to promote bone health or to prevent or treat osteopenia or osteoporosis.

The foregoing may be better understood by reference to the following Examples, which are presented for purposes of illustration and are not intended to limit the scope of the invention.

In one embodiment "cancer" refers to an abnormal growth of cells which tend to proliferate in an uncontrolled way and, in some cases, to metastasize (spread). The types of cancer include, but is not limited to, solid tumors (such as those of the bladder, bowel, brain, breast, endometrium, heart, kidney, lung, uterus, lymphatic tissue (lymphoma), ovary, pancreas or other endocrine organ (thyroid), prostate, skin (melanoma or basal cell cancer) or hematological tumors (such as the leukemias and lymphomas) at any stage of the disease with or without metastases.

In one embodiment, the cancer or tumor is estrogen-mediated. In an alternative embodiment, the cancer or tumor is not estrogen-mediated. In variable embodiments, the cancer or tumor is not hormone-mediated. Non-limiting examples of cancers include, acute lymphoblastic leukemia, acute myeloid leukemia, adrenocortical carcinoma, anal cancer, appendix cancer, astrocytomas, atypical teratoid/rhabdoid tumor, basal cell carcinoma, bile duct cancer, bladder cancer, bone cancer (osteosarcoma and malignant fibrous histiocytoma), brain stem glioma, brain tumors, brain and spinal cord tumors, breast cancer, bronchial tumors, Burkitt lymphoma, cervical cancer, chronic lymphocytic leukemia, chronic myelogenous leukemia, colon cancer, colorectal cancer, craniopharyngioma, cutaneous T-Cell lymphoma, embryonal tumors, endometrial cancer, ependymoblastoma, ependymoma, esophageal cancer, ewing sarcoma family of tumors, eye cancer, retinoblastoma, gallbladder cancer, gastric (stomach) cancer, gastrointestinal carcinoid tumor, gastrointestinal stromal tumor (GIST), gastrointestinal stromal

cell tumor, germ cell tumor, glioma, hairy cell leukemia, head and neck cancer, hepatocellular (liver) cancer, hodgkin lymphoma, hypopharyngeal cancer, intraocular melanoma, islet cell tumors (endocrine pancreas), Kaposi sarcoma, kidney cancer, Langerhans cell histiocytosis, laryngeal cancer, leukemia, Acute lymphoblastic leukemia, acute myeloid leukemia, chronic lymphocytic leukemia, chronic myelogenous leukemia, hairy cell leukemia, liver cancer, lung cancer, non-small cell lung cancer, small cell lung cancer, Burkitt lymphoma, cutaneous T-cell lymphoma, Hodgkin lymphoma, non-Hodgkin lymphoma, lymphoma, Waldenström macroglobulinemia, medulloblastoma, medulloepithelioma, melanoma, mesothelioma, mouth cancer, chronic myelogenous leukemia, myeloid leukemia, multiple myeloma, nasopharyngeal cancer, neuroblastoma, non-Hodgkin lymphoma, non-small cell lung cancer, oral cancer, oropharyngeal cancer, osteosarcoma, malignant fibrous histiocytoma of bone, ovarian cancer, ovarian epithelial cancer, ovarian germ cell tumor, ovarian low malignant potential tumor, pancreatic cancer, papillomatosis, parathyroid cancer, penile cancer, pharyngeal cancer, pineal parenchymal tumors of intermediate differentiation, pineoblastoma and supratentorial primitive neuroectodermal tumors, pituitary tumor, plasma cell neoplasm/multiple myeloma, pleuropulmonary blastoma, primary central nervous system lymphoma, prostate cancer, rectal cancer, renal cell (kidney) cancer, retinoblastoma, rhabdomyosarcoma, salivary gland cancer, sarcoma, Ewing sarcoma family of tumors, sarcoma, kaposi, Sézary syndrome, skin cancer, small cell Lung cancer, small intestine cancer, soft tissue sarcoma, squamous cell carcinoma, stomach (gastric) cancer, supratentorial primitive neuroectodermal tumors, T-cell lymphoma, testicular cancer, throat cancer, thymoma and thymic carcinoma, thyroid cancer, urethral cancer, uterine cancer, uterine sarcoma, vaginal cancer, vulvar cancer, Waldenström macroglobulinemia, Wilms tumor.

The method of treatment may prevent or reduce the risk of cancer. The method of treatment may cause partial or complete regression of cancer in a subject.

The method of treatment may cause partial or complete regression of a tamoxifen resistant cancer or tumor. The method of treatment may cause partial or complete regression of a triple negative breast cancer.

In some embodiments, compounds disclosed herein are used to treat or prevent cancer or a tumor in a mammal such as a human. In some embodiments, the cancer is breast cancer, ovarian cancer, endometrial cancer, prostate cancer, or uterine cancer. In some embodiments, the cancer is breast cancer, lung cancer, ovarian cancer, endometrial cancer, prostate cancer, or uterine cancer.

In some embodiments, the cancer is breast cancer. In some embodiments, the cancer is a hormone dependent cancer. In some embodiments, the cancer is an estrogen receptor dependent cancer. In some embodiments, the cancer is an estrogen-sensitive cancer. In some embodiments, the cancer is resistant to anti-hormonal treatment. In some embodiments, the cancer is an estrogen-sensitive cancer or an estrogen receptor dependent cancer that is resistant to anti-hormonal treatment. In some embodiments, the cancer is a hormone-sensitive cancer or a hormone receptor dependent cancer that is resistant to anti-hormonal treatment. In some embodiments, anti-hormonal treatment includes treatment with at least one agent selected from tamoxifen, fulvestrant, steroidal aromatase inhibitors, and non-steroidal aromatase inhibitors.

In some embodiments, compounds disclosed herein are used to treat hormone receptor positive metastatic breast cancer in a postmenopausal woman with disease progression following anti-estrogen therapy.

In some embodiments, compounds disclosed herein are used to treat a hormonal dependent benign or malignant disease of the breast or reproductive tract in a mammal. In some embodiments, the benign or malignant disease is breast cancer.

In one embodiment a compound of the present invention is used for hormone therapy.

The foregoing may be better understood by reference to the following Examples, which are presented for purposes of illustration and are not intended to limit the scope of the invention.

In one aspect, a compound of the present invention or its pharmaceutically acceptable salt or prodrug, can be used to treat a hormone-related cancer or tumor that has metastasized to the brain, bone or other organ. In one embodiment of this aspect, the hormone-related cancer is estrogen mediated. In another embodiment, the estrogen mediated cancer is selected from breast, uterine, ovarian and endometrial. In other embodiments, a compound of the present invention or its pharmaceutically acceptable salt or prodrug, can be used to prevent a hormone-related cancer or tumor from metastasizing to the brain, bone or other organ, including a hormone-related cancer that is estrogen mediated, for example, breast, uterine, ovarian or endometrial.

Combination Therapy

In one aspect, a method for the treatment of a disorder of abnormal cellular proliferation in a host such as a human is provided that includes administering an effective amount of a

combination of one or more of the active compounds described herein in combination or alternation with another active compound.

In one aspect of this embodiment, the second active compound is an immune modulator, including but not limited to a checkpoint inhibitor. Checkpoint inhibitors for use in the methods described herein include, but are not limited to PD-1 inhibitors, PD-L1 inhibitors, PD-L2 inhibitors, CTLA-4 inhibitors, LAG-3 inhibitors, TIM-3 inhibitors, and V-domain Ig suppressor of T-cell activation (VISTA) inhibitors, or combination thereof.

In one embodiment, the checkpoint inhibitor is a PD-1 inhibitor that blocks the interaction of PD-1 and PD-L1 by binding to the PD-1 receptor, and in turn inhibits immune suppression. In one embodiment, the checkpoint inhibitor is a PD-1 checkpoint inhibitor selected from nivolumab, pembrolizumab, pidilizumab, AMP-224 (AstraZeneca and MedImmune), PF-06801591 (Pfizer), MEDI0680 (AstraZeneca), PDR001 (Novartis), REGN2810 (Regeneron), SHR-12-1 (Jiangsu Hengrui Medicine Company and Incyte Corporation), TSR-042 (Tesaro), and the PD-L1/VISTA inhibitor CA-170 (Curis Inc.).

In one embodiment, the checkpoint inhibitor is a PD-L1 inhibitor that blocks the interaction of PD-1 and PD-L1 by binding to the PD-L1 receptor, and in turn inhibits immune suppression. PD-L1 inhibitors include, but are not limited to, avelumab, atezolizumab, durvalumab, KN035, and BMS-936559 (Bristol-Myers Squibb).

In one aspect of this embodiment, the checkpoint inhibitor is a CTLA-4 checkpoint inhibitor that binds to CTLA-4 and inhibits immune suppression. CTLA-4 inhibitors include, but are not limited to, ipilimumab, tremelimumab (AstraZeneca and MedImmune), AGEN1884 and AGEN2041 (Agenus).

In another embodiment, the checkpoint inhibitor is a LAG-3 checkpoint inhibitor. Examples of LAG-3 checkpoint inhibitors include, but are not limited to, BMS-986016 (Bristol-Myers Squibb), GSK2831781 (GlaxoSmithKline), IMP321 (Prima BioMed), LAG525 (Novartis), and the dual PD-1 and LAG-3 inhibitor MGD013 (MacroGenics). In yet another aspect of this embodiment, the checkpoint inhibitor is a TIM-3 checkpoint inhibitor. A specific TIM-3 inhibitor includes, but is not limited to, TSR-022 (Tesaro).

In yet another embodiment, one of the active compounds described herein is administered in an effective amount for the treatment of abnormal tissue of the female reproductive system such as breast, ovarian, kidney, endometrial, or uterine cancer, in combination or alternation with an

effective amount of an estrogen inhibitor including but not limited to a SERM (selective estrogen receptor modulator), a SERD (selective estrogen receptor downregulator), a complete estrogen receptor downregulator, or another form of partial or complete estrogen antagonist. Partial anti-estrogens like raloxifene and tamoxifen retain some estrogen-like effects, including an estrogen-like stimulation of uterine growth, and also, in some cases, an estrogen-like action during breast cancer progression which actually stimulates tumor growth. In contrast, fulvestrant, a complete anti-estrogen, is free of estrogen-like action on the uterus and is effective in tamoxifen-resistant tumors. Non-limiting examples of anti-estrogen compounds are provided in WO 2014/19176 assigned to AstraZeneca. Additional non-limiting examples of anti-estrogen compounds include: SERMS such as anordrin, bazedoxifene, broparestriol, chlorotrianisene, clomiphene citrate, cyclofenil, lasofoxifene, ormeloxifene, raloxifene, tamoxifen, toremifene, and fulvestrant; aromatase inhibitors such as aminoglutethimide, testolactone, anastrozole, exemestane, fadrozole, formestane, and letrozole; and antigonadotropins such as leuprorelin, cetrorelix, allylestrenol, chloromadinone acetate, cyproterone acetate, delmadinone acetate, dydrogesterone, medroxyprogesterone acetate, megestrol acetate, nomegestrol acetate, norethisterone acetate, progesterone, and spironolactone.

In another embodiment, one of the active compounds described herein is administered in an effective amount for the treatment of abnormal tissue of the male reproductive system such as prostate or testicular cancer, in combination or alternation with an effective amount of an androgen (such as testosterone) inhibitor including but not limited to a selective androgen receptor modulator, a selective androgen receptor downregulator and/or degrader, a complete androgen receptor degrader, or another form of partial or complete androgen antagonist. In one embodiment, the prostate or testicular cancer is androgen-resistant. Non-limiting examples of anti-androgen compounds are provided in WO 2011/156518 and US Patent Nos. 8,455,534 and 8,299,112. Additional non-limiting examples of anti-androgen compounds include: enzalutamide, apalutamide, cyproterone acetate, chlormadinone acetate, spironolactone, canrenone, drospirenone, ketoconazole, topilutamide, abiraterone acetate, and cimetidine.

In one aspect, a treatment regimen is provided comprising the administration of a compound of the present invention in combination with at least one additional chemotherapeutic agent. The combinations disclosed herein can be administered for beneficial, additive, or synergistic effect in the treatment of abnormal cellular proliferative disorders.

In specific embodiments, the treatment regimen includes the administration of a compound of the present invention in combination with at least one kinase inhibitor. In one embodiment, the at least one kinase inhibitor is selected from a phosphoinositide 3-kinase (PI3K) inhibitor, a Bruton's tyrosine kinase (BTK) inhibitor, or a spleen tyrosine kinase (Syk) inhibitor, or a combination thereof.

PI3k inhibitors that may be used in the present invention are well known. Examples of PI3 kinase inhibitors include but are not limited to Wortmannin, demethoxyviridin, perifosine, idelalisib, pictilisib, Palomid 529, ZSTK474, PWT33597, CUDC-907, and AEZS-136, duvelisib, GS-9820, GDC-0032 (2-[4-[2-(2-Isopropyl-5-methyl-1,2,4-triazol-3-yl)-5,6-dihydroimidazo[1,2-d][1,4]benzoxazepin-9-yl]pyrazol-1-yl]-2-methylpropanamide), MLN-1117 ((2*R*)-1-Phenoxy-2-butanyl hydrogen (*S*)-methylphosphonate; or Methyl(oxo) {[(2*R*)-l-phenoxy-2-butanyl]oxy}phosphonium)), BYL-719 ((2*S*)-*N*1-[4-Methyl-5-[2-(2,2,2-trifluoro-1,1-dimethylethyl)-4-pyridinyl]-2-thiazolyl]-1,2-pyrrolidinedicarboxamide), GSK2126458 (2,4-Difluoro-*N*-{2-(methyloxy)-5-[4-(4-pyridazinyl)-6-quinolinyl]-3-pyridinyl}benzenesulfonamide), TGX-221 ((±)-7-Methyl-2-(morpholin-4-yl)-9-(l-phenylaminoethyl)-pyrido[l,2-a]-pyrimidin-4-one), GSK2636771 (2-Methyl-1-(2-methyl-3-(trifluoromethyl)benzyl)-6-morpholino-lH-benzo[d]imidazole-4-carboxylic acid dihydrochloride), KIN-193 ((R)-2-((l-(7-methyl-2-morpholino-4-oxo-4*H*-pyrido[1,2-a]pyrimidin-9-yl)ethyl)amino)benzoic acid), TGR-1202/RP5264, GS-9820 ((*S*)- l-(4-((2-(2-aminopyrimidin-5-yl)-7-methyl-4-mohydroxypropan- 1 -one), GS-1101 (5-fluoro-3-phenyl-2-([*S*)]-1-[9*H*-purin-6-ylamino]-propyl)-3H-quinazolin-4-one), AMG-319, GSK-2269557, SAR245409 (*N*-(4-(*N*-(3-((3,5-dimethoxyphenyl)amino)quinoxalin-2-yl)sulfamoyl)phenyl)-3-methoxy-4 methylbenzamide), BAY80-6946 (2-amino-*N*-(7-methoxy-8-(3-morpholinopropoxy)-2,3-dihydroimidazo[l,2-c]quinaz), AS 252424 (5-[l-[5-(4-Fluoro-2-hydroxy-phenyl)-furan-2-yl]-meth-(*Z*)-ylidene]-thiazolidine-2,4-dione), CZ 24832 (5-(2-amino-8-fluoro-[l,2,4]triazolo[l,5-a]pyridin-6-yl)-*N*-*tert*-butylpyridine-3-sulfonamide), buparlisib (5-[2,6-Di(4-morpholinyl)-4-pyrimidinyl]-4-(trifluoromethyl)-2-pyridinamine), GDC-0941 (2-(l*H*-Indazol-4-yl)-6-[[4-(methylsulfonyl)-l-piperazinyl]methyl]-4-(4-morpholinyl)thieno[3,2-d]pyrimidine), GDC-0980 ((*S*)-1-(4-((2-(2-aminopyrimidin-5-yl)-7-methyl-4-morpholinothieno[3,2-d]pyrimidin-6 yl)methyl)piperazin-l-yl)-2-hydroxypropan-l-one (also known as RG7422)), SF1126 ((8S,14S,17S)-14-(carboxymethyl)-8-(3-guanidinopropyl)-17-(hydroxymethyl)-3,6,9,12,15-

pentaoxo-1-(4-(4-oxo-8-phenyl-4H-chromen-2-yl)morpholino-4-ium)-2-oxa-7,10,13,16-tetraazaoctadecan-18-oate), PF-05212384 (*N*-[4-[[4-(Dimethylamino)-1-piperidinyl]carbonyl]phenyl]-*N*'-[4-(4,6-di-4-morpholinyl-l,3,5-triazin-2-yl)phenyl]urea), LY3023414, BEZ235 (2-Methyl-2-{4-[3-methyl-2-oxo-8-(quinolin-3-yl)-2,3-dihydro-l*H*-imidazo[4,5-c]quinolin-l-yl]phenyl}propanenitrile), XL-765 (*N*-(3-(*N*-(3-(3,5-dimethoxyphenylamino)quinoxalin-2-yl)sulfamoyl)phenyl)-3-methoxy-4-methylbenzamide), and GSK1059615 (5-[[4-(4-Pyridinyl)-6-quinolinyl]methylene]-2,4-thiazolidenedione), PX886 ([(3a*R*,6*E*,9*S*,9a*R*,10*R*,11a*S*)-6-[[bis(prop-2-enyl)amino]methylidene]-5-hydroxy-9-(methoxymethyl)-9a,11a-dimethyl-l,4,7-trioxo-2,3,3a,9,10,ll-hexahydroindeno[4,5h]isochromen-10-yl] acetate (also known as sonolisib)).

In one embodiment, the compound of the present invention is combined in a single dosage form with the PIk3 inhibitor.

BTK inhibitors for use in the present invention are well known. Examples of BTK inhibitors include ibrutinib (also known as PCI-32765)(Imbruvica™)(1-[(3R)-3-[4-amino-3-(4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidin-1-yl]prop-2-en-1-one), dianilinopyrimidine-based inhibitors such as AVL-101 and AVL-291/292 (*N*-(3-((5-fluoro-2-((4-(2-methoxyethoxy)phenyl)amino)pyrimidin-4-yl)amino)phenyl)acrylamide) (Avila Therapeutics) (*see* US Patent Publication No 2011/0117073, incorporated herein in its entirety), dasatinib ([*N*-(2-chloro-6-methylphenyl)-2-(6-(4-(2-hydroxyethyl)piperazin-1-yl)-2-methylpyrimidin-4-ylamino)thiazole-5-carboxamide], LFM-A13 (alpha-cyano-beta-hydroxy-beta-methyl-*N*-(2,5-ibromophenyl) propenamide), GDC-0834 ([*R*-*N*-(3-(6-(4-(1,4-dimethyl-3-oxopiperazin-2-yl)phenylamino)-4-methyl-5-oxo-4,5-dihydropyrazin-2-yl)-2-methylphenyl)-4,5,6,7-tetrahydrobenzo[b]thiophene-2-carboxamide], CGI-560 4-(*tert*-butyl)-*N*-(3-(8-(phenylamino)imidazo[1,2-a]pyrazin-6-yl)phenyl)benzamide, CGI-1746 (4-(*tert*-butyl)-*N*-(2-methyl-3-(4-methyl-6-((4-(morpholine-4-carbonyl)phenyl)amino)-5-oxo-4,5-dihydropyrazin-2-yl)phenyl)benzamide), CNX-774 (4-(4-((4-((3-acrylamidophenyl)amino)-5-fluoropyrimidin-2-yl)amino)phenoxy)-*N*-methylpicolinamide), CTA056 (7-benzyl-1-(3-(piperidin-1-yl)propyl)-2-(4-(pyridin-4-yl)phenyl)-1*H*-imidazo[4,5-g]quinoxalin-6(5*H*)-one), GDC-0834 ((*R*)-*N*-(3-(6-((4-(1,4-dimethyl-3-oxopiperazin-2-yl)phenyl)amino)-4-methyl-5-oxo-4,5-dihydropyrazin-2-yl)-2-methylphenyl)-4,5,6,7-tetrahydrobenzo[b]thiophene-2-carboxamide), GDC-0837 ((*R*)-*N*-(3-(6-((4-(1,4-dimethyl-3-oxopiperazin-2-yl)phenyl)amino)-4-methyl-5-oxo-4,5-dihydropyrazin-2-yl)-

2-methylphenyl)-4,5,6,7-tetrahydrobenzo[b]thiophene-2-carboxamide), HM-71224, ACP-196, ONO-4059 (Ono Pharmaceuticals), PRT062607 (4-((3-(2*H*-1,2,3-triazol-2-yl)phenyl)amino)-2-(((1*R*,2*S*)-2-aminocyclohexyl)amino)pyrimidine-5-carboxamide hydrochloride), QL-47 (1-(1-acryloylindolin-6-yl)-9-(1-methyl-1*H*-pyrazol-4-yl)benzo[h][1,6]naphthyridin-2(1*H*)-one), and RN486 (6-cyclopropyl-8-fluoro-2-(2-hydroxymethyl-3-{1-methyl-5-[5-(4-methyl-piperazin-1-yl)-pyridin-2-ylamino]-6-oxo-1,6-dihydro-pyridin-3-yl}-phenyl)-2*H*-isoquinolin-1-one), and other molecules capable of inhibiting BTK activity, for example those BTK inhibitors disclosed in Akinleye et ah, *Journal of Hematology & Oncology*, 2013, 6:59, the entirety of which is incorporated herein by reference. In one embodiment, the compound of the present invention is combined in a single dosage form with the BTK inhibitor.

Syk inhibitors for use in the present invention are well known, and include, for example, Cerdulatinib (4-(cyclopropylamino)-2-((4-(4-(ethylsulfonyl)piperazin-1-yl)phenyl)amino)pyrimidine-5-carboxamide), entospletinib (6-(1*H*-indazol-6-yl)-*N*-(4-morpholinophenyl)imidazo[1,2-a]pyrazin-8-amine), fostamatinib ([6-({5-Fluoro-2-[(3,4,5-trimethoxyphenyl)amino]-4-pyrimidinyl}amino)-2,2-dimethyl-3-oxo-2,3-dihydro-4*H*-pyrido[3,2-b][1,4]oxazin-4-yl]methyl dihydrogen phosphate), fostamatinib disodium salt (sodium (6-((5-fluoro-2-((3,4,5-trimethoxyphenyl)amino)pyrimidin-4-yl)amino)-2,2-dimethyl-3-oxo-2H-pyrido[3,2-b][1,4]oxazin-4(3*H*)-yl)methyl phosphate), BAY 61-3606 (2-(7-(3,4-Dimethoxyphenyl)-imidazo[1,2-c]pyrimidin-5-ylamino)-nicotinamide HCl), RO9021 (6-[(1*R*,2*S*)-2-Amino-cyclohexylamino]-4-(5,6-dimethyl-pyridin-2-ylamino)-pyridazine-3-carboxylic acid amide), imatinib (Gleevec; 4-[(4-methylpiperazin-1-yl)methyl]-*N*-(4-methyl-3-{[4-(pyridin-3-yl)pyrimidin-2-yl]amino}phenyl)benzamide), staurosporine, GSK143 (2-(((3*R*,4*R*)-3-aminotetrahydro-2*H*-pyran-4-yl)amino)-4-(p-tolylamino)pyrimidine-5-carboxamide), PP2 (1-(*tert*-butyl)-3-(4-chlorophenyl)-1*H*-pyrazolo[3,4-d]pyrimidin-4-amine), PRT-060318 (2-(((1*R*,2*S*)-2-aminocyclohexyl)amino)-4-(m-tolylamino)pyrimidine-5-carboxamide), PRT-062607 (4-((3-(2*H*-1,2,3-triazol-2-yl)phenyl)amino)-2-(((1*R*,2*S*)-2-aminocyclohexyl)amino)pyrimidine-5-carboxamide hydrochloride), R112 (3,3'-((5-fluoropyrimidine-2,4-diyl)bis(azanediyl))diphenol), R348 (3-Ethyl-4-methylpyridine), R406 (6-((5-fluoro-2-((3,4,5-trimethoxyphenyl)amino)pyrimidin-4-yl)amino)-2,2-dimethyl-2*H*-pyrido[3,2-b][1,4]oxazin-3(4*H*)-one), YM193306(see Singh et al. Discovery and Development of Spleen Tyrosine Kinase (SYK) Inhibitors, *J. Med. Chem.* 2012, 55, 3614-3643), 7-azaindole,

piceatannol, ER-27319 (see Singh et al. Discovery and Development of Spleen Tyrosine Kinase (SYK) Inhibitors, *J. Med. Chem.* 2012, 55, 3614-3643 incorporated in its entirety herein), Compound D (see Singh et al. Discovery and Development of Spleen Tyrosine Kinase (SYK) Inhibitors, *J. Med. Chem.* 2012, 55, 3614-3643 incorporated in its entirety herein), PRT060318 (see Singh et al. Discovery and Development of Spleen Tyrosine Kinase (SYK) Inhibitors, *J. Med. Chem.* 2012, 55, 3614-3643 incorporated in its entirety herein), luteolin (see Singh et al. Discovery and Development of Spleen Tyrosine Kinase (SYK) Inhibitors, *J. Med. Chem.* 2012, 55, 3614-3643 incorporated in its entirety herein), apigenin (see Singh et al. Discovery and Development of Spleen Tyrosine Kinase (SYK) Inhibitors, *J. Med. Chem.* 2012, 55, 3614-3643 incorporated in its entirety herein), quercetin (see Singh et al. Discovery and Development of Spleen Tyrosine Kinase (SYK) Inhibitors, *J. Med. Chem.* 2012, 55, 3614-3643 incorporated in its entirety herein), fisetin (see Singh et al. Discovery and Development of Spleen Tyrosine Kinase (SYK) Inhibitors, *J. Med. Chem.* 2012, 55, 3614-3643 incorporated in its entirety herein), myricetin (see Singh et al. Discovery and Development of Spleen Tyrosine Kinase (SYK) Inhibitors, *J. Med. Chem.* 2012, 55, 3614-3643 incorporated in its entirety herein), morin (see Singh et al. Discovery and Development of Spleen Tyrosine Kinase (SYK) Inhibitors, *J. Med. Chem.* 2012, 55, 3614-3643 incorporated in its entirety herein). In one embodiment, the compound of the present invention is combined in a single dosage form with the Syk inhibitor.

In one embodiment, the at least one additional chemotherapeutic agent is a B-cell lymphoma 2 (Bcl-2) protein inhibitor. BCL-2 inhibitors are known in the art, and include, for example, ABT-199 (4-[4-[[2-(4-Chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-l-yl]-*N*-[[3-nitro-4-[[(tetrahydro-2*H*-pyran-4-yl)methyl]amino]phenyl]sulfonyl]-2-[(l*H*- pyrrolo[2,3-b]pyridin-5-yl)oxy]benzamide), ABT-737 (4-[4-[[2-(4-chlorophenyl)phenyl]methyl]piperazin-1-yl]-*N*-[4- [[(2*R*)-4-(dimethylamino)-1-phenylsulfanylbutan-2-yl] amino]-3- nitrophenyl]sulfonylbenzamide), ABT-263 ((*R*)-4-(4-((4'-chloro-4,4-dimethyl-3,4,5,6-tetrahydro-[l, l'-biphenyl]-2-yl)methyl)piperazin-1-yl)-*N*-((4-((4-morpholino-1-(phenylthio)butan-2-yl)amino)-3((trifluoromethyl)sulfonyl)phenyl)sulfonyl)benzamide), GX15-070 (obatoclax mesylate, (2*Z*)-2-[(5*Z*)-5-[(3,5- dimethyl-l*H*-pyrrol-2-yl)methylidene]-4-methoxypyrrol-2-ylidene]indole; methanesulfonic acid))), 2-methoxy-antimycin A3, YC137 (4-(4,9-dioxo-4,9-dihydronaphtho[2,3-d]thiazol-2-ylamino)-phenyl ester), pogosin, ethyl 2-amino-6-bromo-4-(1-

cyano-2-ethoxy-2-oxoethyl)-4*H*-chromene-3-carboxylate, Nilotinib-d3, TW-37 (*N*-[4-[[2-(1,1-Dimethylethyl)phenyl]sulfonyl]phenyl]-2,3,4-trihydroxy-5-[[2-(1-methylethyl)phenyl]methyl]benzamide), Apogossypolone (ApoG2), or G3139 (Oblimersen). In one embodiment, the compound of the present invention is combined in a single dosage form with the at least one BCL-2 inhibitor.

The compound of the present invention or its pharmaceutically active salt can be combined with an immunotherapy. As discussed in more detail below, the compound of the present invention can be conjugated to an antibody, radioactive agent, or other targeting agent that directs the compound to the diseased or abnormally proliferating cell.

In one embodiment, the additional therapy is a monoclonal antibody (MAb). Some MAbs stimulate an immune response that destroys cancer cells. Similar to the antibodies produced naturally by B cells, these MAbs "coat" the cancer cell surface, triggering its destruction by the immune system. For example, bevacizumab targets vascular endothelial growth factor (VEGF), a protein secreted by tumor cells and other cells in the tumor's microenvironment that promotes the development of tumor blood vessels. When bound to bevacizumab, VEGF cannot interact with its cellular receptor, preventing the signaling that leads to the growth of new blood vessels. Similarly, cetuximab and panitumumab target the epidermal growth factor receptor (EGFR), and trastuzumab targets the human epidermal growth factor receptor 2 (HER-2). MAbs, which bind to cell surface growth factor receptors, prevent the targeted receptors from sending their normal growth-promoting signals. They may also trigger apoptosis and activate the immune system to destroy tumor cells.

In some embodiments, the combination can be administered to the subject in further combination with other chemotherapeutic agents. If convenient, the combination described herein can be administered at the same time as another chemotherapeutic agent in order to simplify the treatment regimen. In some embodiments, the combination and the other chemotherapeutic can be provided in a single formulation. In one embodiment, the use of the compounds described herein is combined in a therapeutic regime with other agents. Such agents may include, but are not limited to, tamoxifen, midazolam, letrozole, bortezomib, anastrozole, goserelin, an mTOR inhibitor, a PI3 kinase inhibitors, dual mTOR-PI3K inhibitors, MEK inhibitors, RAS inhibitors, ALK inhibitors, HSP inhibitors (for example, HSP70 and HSP 90 inhibitors, or a combination thereof), BCL-2 inhibitors, apoptotic compounds, AKT inhibitors, including but not limited to,

MK-2206, GSK690693, Perifosine, (KRX-0401), GDC-0068, Triciribine, AZD5363, Honokiol, PF-04691502, and Miltefosine, PD-1 inhibitors including but not limited to, Nivolumab, CT-011, MK-3475, BMS936558, and AMP-514 or FLT-3 inhibitors, including but not limited to, P406, Dovitinib, Quizartinib (AC220), Amuvatinib (MP-470), Tandutinib (MLN518), ENMD-2076, and KW-2449, or combinations thereof. Examples of mTOR inhibitors include but are not limited to rapamycin and its analogs, everolimus (Afinitor), temsirolimus, ridaforolimus (Deforolimus), and sirolimus. Examples of MEK inhibitors include but are not limited to trametinib /GSKl120212 (*N*-(3-{3-cyclopropyl-5-[(2-fluoro-4-iodophenyl)amino]-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydropyrido[4,3-d]pyrimidin-l(2H-yl}phenyl)acetamide), selumetinib (6-(4-bromo-2-chloroanilino)-7-fluoro-*N*-(2-hydroxyethoxy)-3-methylbenzimidazole-5-carboxamide), pimasertib/AS703026/MSC1935369 ((*S*)-*N*-(2,3-dihydroxypropyl)-3-((2-fluoro-4-iodophenyl)amino)isonicotinamide), XL-518/GDC-0973 (l-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[(2S)-piperidin-2-yl]azetidin-3-ol), refametinib/BAY869766/RDEAl19 (*N*-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide), PD-0325901 (*N*-[(2*R*)-2,3-dihydroxypropoxy]-3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]-benzamide), TAK733 ((*R*)-3-(2,3-dihydroxypropyl)-6-fluoro-5-(2-fluoro-4-iodophenylamino)-8-methylpyrido[2,3d]pyrimidine-4,7(3H,8H)-dione), MEK162/ARRY438162 (5-[(4-Bromo-2-fluorophenyl)amino]-4-fluoro-*N*-(2-hydroxyethoxy)-1-methyl-1*H*-benzimidazole-6 carboxamide), R05126766 (3-[[3-fluoro-2-(methylsulfamoylamino)-4-pyridyl]methyl]-4-methyl-7-pyrimidin-2-yloxychromen-2-one), WX-554, R04987655/CH4987655 (3,4-difluoro-2-((2-fluoro-4-iodophenyl)amino)-*N*-(2-hydroxyethoxy)-5-((3-oxo-l,2-oxazinan-2 yl)methyl)benzamide), or AZD8330 (2-((2-fluoro-4-iodophenyl)amino)-*N*-(2-hydroxyethoxy)-1,5-dimethyl-6-oxo-l,6-dihydropyridine-3-carboxamide). Examples of RAS inhibitors include but are not limited to Reolysin and siG12D LODER. Examples of ALK inhibitors include but are not limited to Crizotinib, AP26113, and LDK378. HSP inhibitors include but are not limited to Geldanamycin or 17-*N*-Allylamino-17-demethoxygeldanamycin (17AAG), and Radicicol. In a particular embodiment, a compound described herein is administered in combination with letrozole and/or tamoxifen. Other chemotherapeutic agents that can be used in combination with the compounds described herein include, but are not limited to, chemotherapeutic agents that do not require cell cycle activity for their anti-neoplastic effect.

In one embodiment, a compound of the present invention described herein can be combined with a chemotherapeutic selected from, but are not limited to, Imatinib mesylate (Gleevec®), Dasatinib (Sprycel®), Nilotinib (Tasigna®), Bosutinib (Bosulif®), Trastuzumab (Herceptin®), Pertuzumab (Perjeta TM), Lapatinib (Tykerb®), Gefitinib (Iressa®), Erlotinib (Tarceva®), Cetuximab (Erbitux®), Panitumumab (Vectibix®), Vandetanib (Caprelsa®), Vemurafenib (Zelboraf®), Vorinostat (Zolinza®), Romidepsin (Istodax®), Bexarotene (Targretin®), Alitretinoin (Panretin®), Tretinoin (Vesanoid®), Carfilzomib (Kyprolis TM), Pralatrexate (Folotyn®), Bevacizumab (Avastin®), Ziv-aflibercept (Zaltrap®), Sorafenib (Nexavar®), Sunitinib (Sutent®), Pazopanib (Votrient®), Regorafenib (Stivarga®), and Cabozantinib (Cometriq TM).

In certain aspects, the additional therapeutic agent is an anti-inflammatory agent, a chemotherapeutic agent, a radiotherapeutic, additional therapeutic agents, or immunosuppressive agents.

Suitable chemotherapeutic agents include, but are not limited to, radioactive molecules, toxins, also referred to as cytotoxins or cytotoxic agents, which includes any agent that is detrimental to the viability of cells, agents, and liposomes or other vesicles containing chemotherapeutic compounds. General anticancer pharmaceutical agents include: Vincristine (Oncovin®) or liposomal vincristine (Marqibo®), Daunorubicin (daunomycin or Cerubidine®) or doxorubicin (Adriamycin®), Cytarabine (cytosine arabinoside, ara-C, or Cytosar®), L-asparaginase (Elspar®) or PEG-L-asparaginase (pegaspargase or Oncaspar®), Etoposide (VP-16), Teniposide (Vumon®), 6-mercaptopurine (6-MP or Purinethol®), Methotrexate, Cyclophosphamide (Cytoxan®), Prednisone, Dexamethasone (Decadron), imatinib (Gleevec®), dasatinib (Sprycel®), nilotinib (Tasigna®), bosutinib (Bosulif®), and ponatinib (Iclusig™). Examples of additional suitable chemotherapeutic agents include but are not limited to 1-dehydrotestosterone, 5-fluorouracil, dacarbazine, 6-mercaptopurine, 6-thioguanine, actinomycin D, adriamycin, alkylating agents, allopurinol sodium, altretamine, amifostine, anastrozole, anthramycin (AMC)), anti-mitotic agents, cis-dichlorodiamine platinum (II) (DDP) cisplatin), diamino dichloro platinum, anthracyclines, antibiotics, antimetabolites, asparaginase, BCG live (intravesical), betamethasone sodium phosphate and betamethasone acetate, bicalutamide, bleomycin sulfate, busulfan, calcium leucovorin, calicheamicin, capecitabine, carboplatin, lomustine (CCNU), carmustine (BSNU), Chlorambucil, Cisplatin, Cladribine, Colchicine,

conjugated estrogens, Cyclophosphamide, Cyclothosphamide, Cytarabine, Cytarabine, cytochalasin B, Cytoxan, Dacarbazine, Dactinomycin, dactinomycin (formerly actinomycin), daunorubicin HCl, daunorubicin citrate, denileukin diftitox, Dexrazoxane, Dibromomannitol, dihydroxy anthracin dione, Docetaxel, dolasetron mesylate, doxorubicin HCl, dronabinol, *E. coli* L-asparaginase, emetine, epoetin-α, *Erwinia* L-asparaginase, esterified estrogens, estradiol, estramustine phosphate sodium, ethidium bromide, ethinyl estradiol, etidronate, etoposide citrovorum factor, etoposide phosphate, filgrastim, floxuridine, fluconazole, fludarabine phosphate, fluorouracil, flutamide, folinic acid, gemcitabine HCl, glucocorticoids, goserelin acetate, gramicidin D, granisetron HCl, hydroxyurea, idarubicin HCl, ifosfamide, interferon α-2b, irinotecan HCl, letrozole, leucovorin calcium, leuprolide acetate, levamisole HCl, lidocaine, lomustine, maytansinoid, mechlorethamine HCl, medroxyprogesterone acetate, megestrol acetate, melphalan HCl, mercaptopurine, Mesna, methotrexate, methyltestosterone, mithramycin, mitomycin C, mitotane, mitoxantrone, nilutamide, octreotide acetate, ondansetron HCl, paclitaxel, pamidronate disodium, pentostatin, pilocarpine HCl, plicamycin, polifeprosan 20 with carmustine implant, porfimer sodium, procaine, procarbazine HCl, propranolol, sargramostim, streptozotocin, tamoxifen, taxol, teniposide, teniposide, testolactone, tetracaine, thioepa chlorambucil, thioguanine, thiotepa, topotecan HCl, toremifene citrate, trastuzumab, tretinoin, valrubicin, vinblastine sulfate, vincristine sulfate, and vinorelbine tartrate.

Additional therapeutic agents that can be administered in combination with a compound disclosed herein can include 2-methoxyestradiol or 2ME2, finasunate, vatalanib, volociximab, etaracizumab (MEDI-522), cilengitide, dovitinib, figitumumab, atacicept, rituximab, alemtuzumab, aldesleukin, atlizumab, tocilizumab, lucatumumab, dacetuzumab, HLL1, huN901-DM1, atiprimod, natalizumab, bortezomib, marizomib, tanespimycin, saquinavir mesylate, ritonavir, nelfinavir mesylate, indinavir sulfate, belinostat, panobinostat, mapatumumab, lexatumumab, dulanermin, plitidepsin, talmapimod, P276-00, enzastaurin, tipifarnib, lenalidomide, thalidomide, pomalidomide, simvastatin, and celecoxib.

In one aspect of the present invention, a compound described herein can be combined with at least one immunosuppressive agent. The immunosuppressive agent in one embodiment is selected from the group consisting of a calcineurin inhibitor, e.g. a cyclosporin or an ascomycin, e.g. Cyclosporin A (Neoral®), FK506 (tacrolimus), pimecrolimus, a mTOR inhibitor, e.g. rapamycin or a derivative thereof, e.g. Sirolimus (Rapamune®), Everolimus (Certican®),

temsirolimus, zotarolimus, biolimus-7, biolimus-9, a rapalog, e.g. ridaforolimus, azathioprine, campath 1H, a S1P receptor modulator, e.g. fingolimod or an analogue thereof, an anti IL-8 antibody, mycophenolic acid or a salt thereof, e.g. sodium salt, or a prodrug thereof, e.g. Mycophenolate Mofetil (CellCept®), OKT3 (Orthoclone OKT3®), Prednisone, ATGAM®, Thymoglobulin®, Brequinar Sodium, OKT4, T10B9.A-3A, 33B3.1, 15-deoxyspergualin, tresperimus, Leflunomide Arava®, anti-CD25, anti-IL2R, Basiliximab (Simulect®), Daclizumab (Zenapax®), mizoribine, methotrexate, dexamethasone, ISAtx-247, SDZ ASM 981 (pimecrolimus, Elidel®), CTLA4lg, Abatacept, belatacept, LFA3lg, etanercept (sold as Enbrel® by ImmuneXcite), adalimumab (Humira®), infliximab (Remicade®), an anti-LFA-1 antibody, natalizumab (Antegren®), Enlimomab, gavilimomab, Golimumab, antithymocyte immunoglobulin, siplizumab, Alefacept, efalizumab, Pentasa, mesalazine, asacol, codeine phosphate, benorylate, fenbufen, naprosyn, diclofenac, etodolac, indomethacin, aspirin, and ibuprofen.

In certain embodiments, a compound described herein is administered to the subject prior to treatment with another chemotherapeutic agent, during treatment with another chemotherapeutic agent, after administration of another chemotherapeutic agent, or a combination thereof.

Synthetic Methods

The compounds described herein can be prepared by methods known by those skilled in the art. In one non-limiting example the disclosed compounds can be prepared using the schemes.

As used herein alkenylene can encompass both *cis* and *trans* isomers of alkenes, unless indicated otherwise. In one embodiment the isomer is *cis*. In a preferred embodiment the isomer is *trans*. In one embodiment R_2 is -C_2-C_6alkenylene-$COOR_{17}$ and the alkene group is *cis*. In a preferred embodiment R_2 is -C_2-C_6alkenylene-$COOR_{17}$ and the alkene group is *trans*.

Some of the compounds described herein can have a chiral center, and the compound can exist in isomeric or diastereomeric form. When multiple chiral variables are present on formulas of the present invention, the formula further encompasses every possible diastereomer unless indicated otherwise. For example (R,R), (S,R), (S,S), and (R,S) for a molecule with two chiral centers. One skilled in the art will recognize that pure enantiomers, diastereomers, and *cis*/*trans*

isomers can be prepared by methods known in the art. Examples of methods to obtain optically active materials include at least the following.

i) Physical separation of crystals—a technique whereby macroscopic crystals of the individual enantiomers are manually separated. This technique can be used if crystals of the separate enantiomers exist, i.e., the material is a conglomerate, and the crystals are visually distinct;

ii) Simultaneous crystallization—a technique whereby the individual enantiomers are separately crystallized from a solution of the racemate, possible only if the latter is a conglomerate in the solid state;

iii) Enzymatic resolutions—a technique whereby partial or complete separation of a racemate by virtue of differing rates of reaction for the enantiomers with an enzyme;

iv) Enzymatic asymmetric synthesis—a synthetic technique whereby at least one step of the synthesis uses an enzymatic reaction to obtain an enantiomerically pure or enriched synthetic precursor of the desired enantiomer;

v) Chemical asymmetric synthesis—a synthetic technique whereby the desired enantiomer is synthesized from an achiral precursor under conditions that produce asymmetry (i.e., chirality) in the product, which may be achieved using chiral catalysts or chiral auxiliaries;

vi) Diastereomer separations—a technique whereby a racemic compound is reacted with an enantiomerically pure reagent (the chiral auxiliary) that converts the individual enantiomers to diastereomers. The resulting diastereomers are then separated by chromatography or crystallization by virtue of their now more distinct structural differences and the chiral auxiliary later removed to obtain the desired enantiomer;

vii) First- and second-order asymmetric transformations—a technique whereby diastereomers from the racemate equilibrate to yield a preponderance in solution of the diastereomer from the desired enantiomer or where preferential crystallization of the diastereomer from the desired enantiomer perturbs the equilibrium such that eventually in

principle all the material is converted to the crystalline diastereomer from the desired enantiomer. The desired enantiomer is then released from the diastereomer;

viii) Kinetic resolutions—this technique refers to the achievement of partial or complete resolution of a racemate (or of a further resolution of a partially resolved compound) by virtue of unequal reaction rates of the enantiomers with a chiral, non-racemic reagent or catalyst under kinetic conditions;

ix) Enantiospecific synthesis from non-racemic precursors—a synthetic technique whereby the desired enantiomer is obtained from non-chiral starting materials and where the stereochemical integrity is not or is only minimally compromised over the course of the synthesis;

x) Chiral liquid chromatography—a technique whereby the enantiomers of a racemate are separated in a liquid mobile phase by virtue of their differing interactions with a stationary phase (including via chiral HPLC). The stationary phase can be made of chiral material or the mobile phase can contain an additional chiral material to provoke the differing interactions;

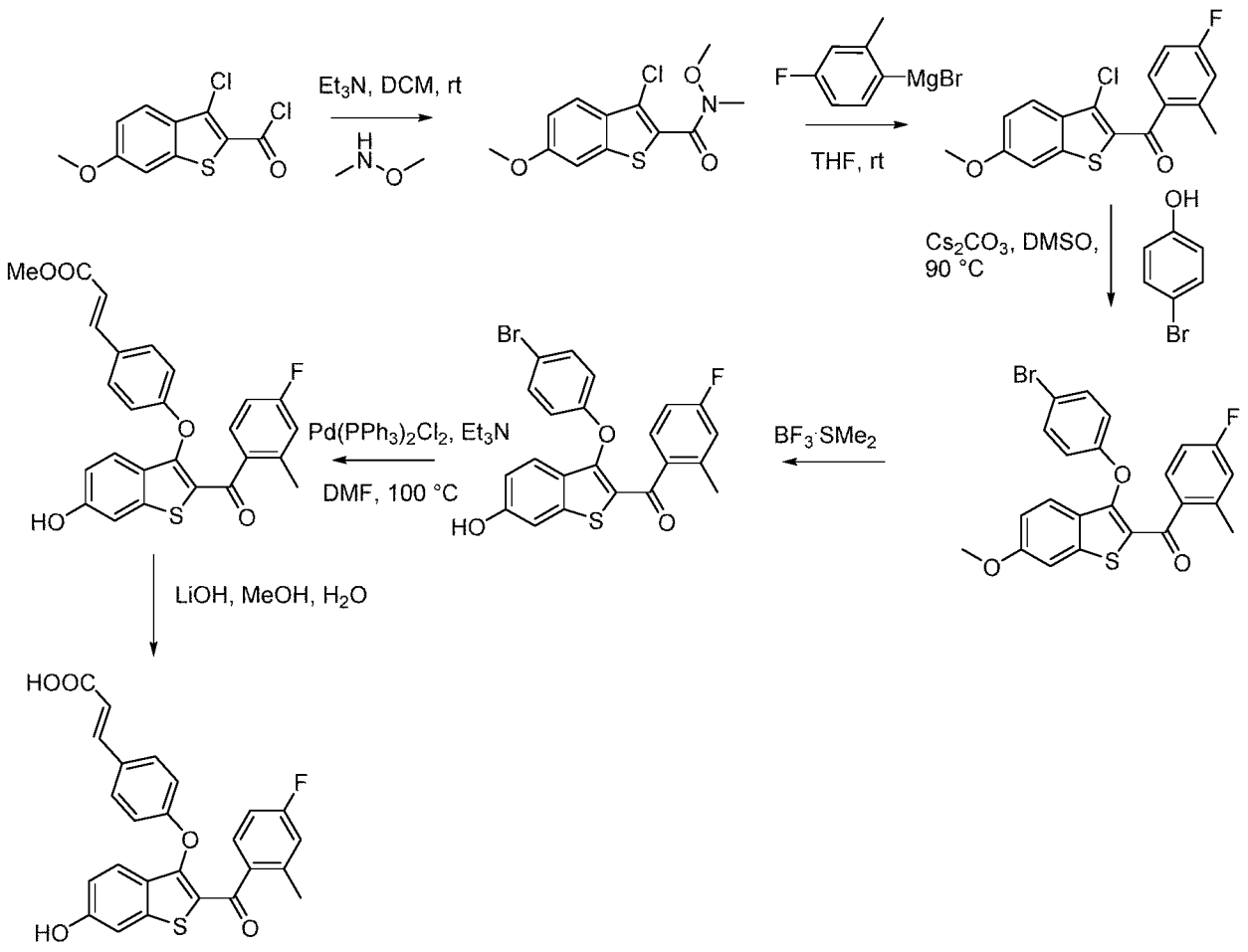
xi) Chiral gas chromatography—a technique whereby the racemate is volatilized and enantiomers are separated by virtue of their differing interactions in the gaseous mobile phase with a column containing a fixed non-racemic chiral adsorbent phase;

xii) Extraction with chiral solvents—a technique whereby the enantiomers are separated by virtue of preferential dissolution of one enantiomer into a particular chiral solvent;

xiii) Transport across chiral membranes—a technique whereby a racemate is placed in contact with a thin membrane barrier. The barrier typically separates two miscible fluids, one containing the racemate, and a driving force such as concentration or pressure differential causes preferential transport across the membrane barrier. Separation occurs as a result of the non-racemic chiral nature of the membrane that allows only one enantiomer of the racemate to pass through.

xiv) Simulated moving bed chromatography, is used in one embodiment. A wide variety of chiral stationary phases are commercially available.

General Synthetic Route 1:



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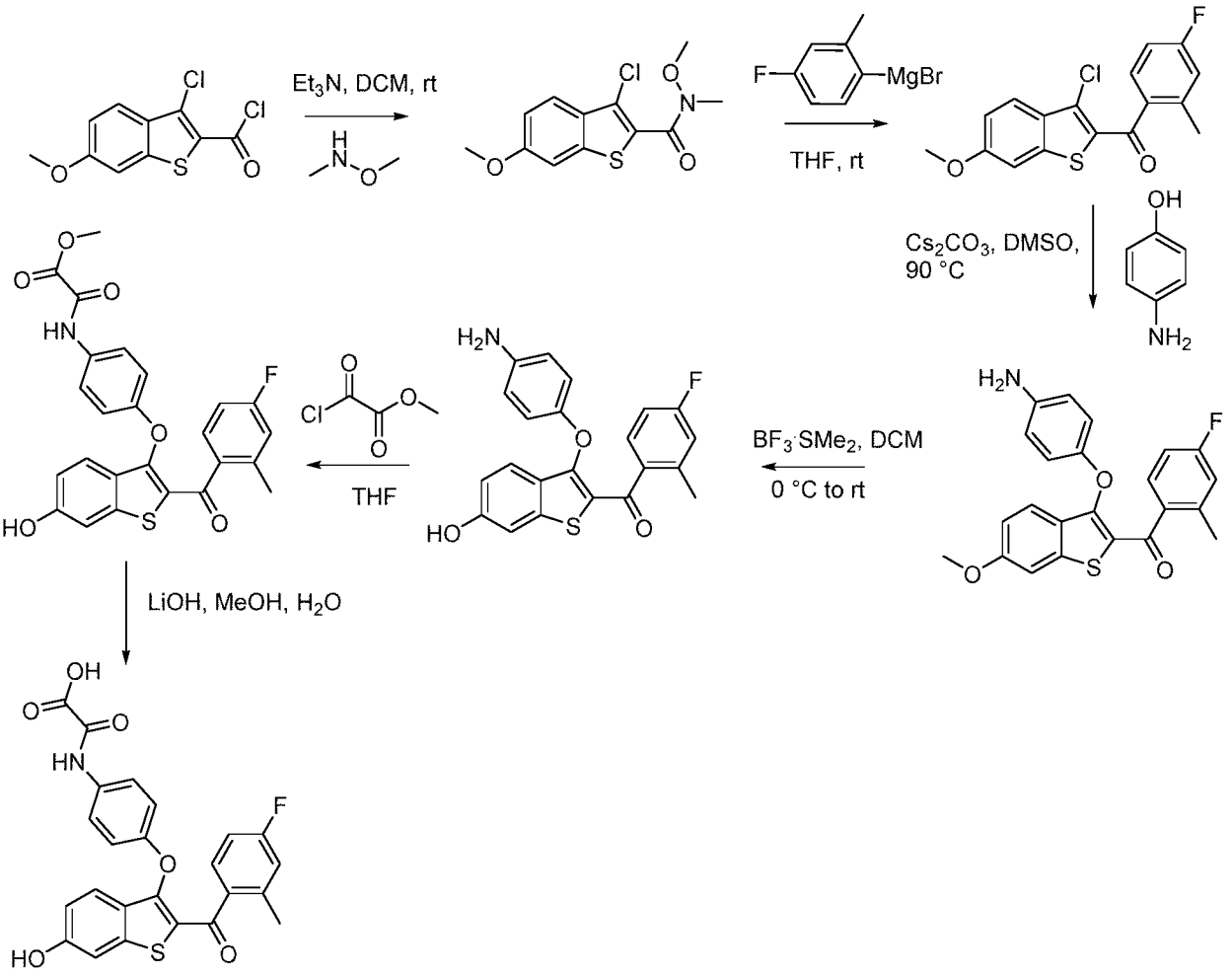
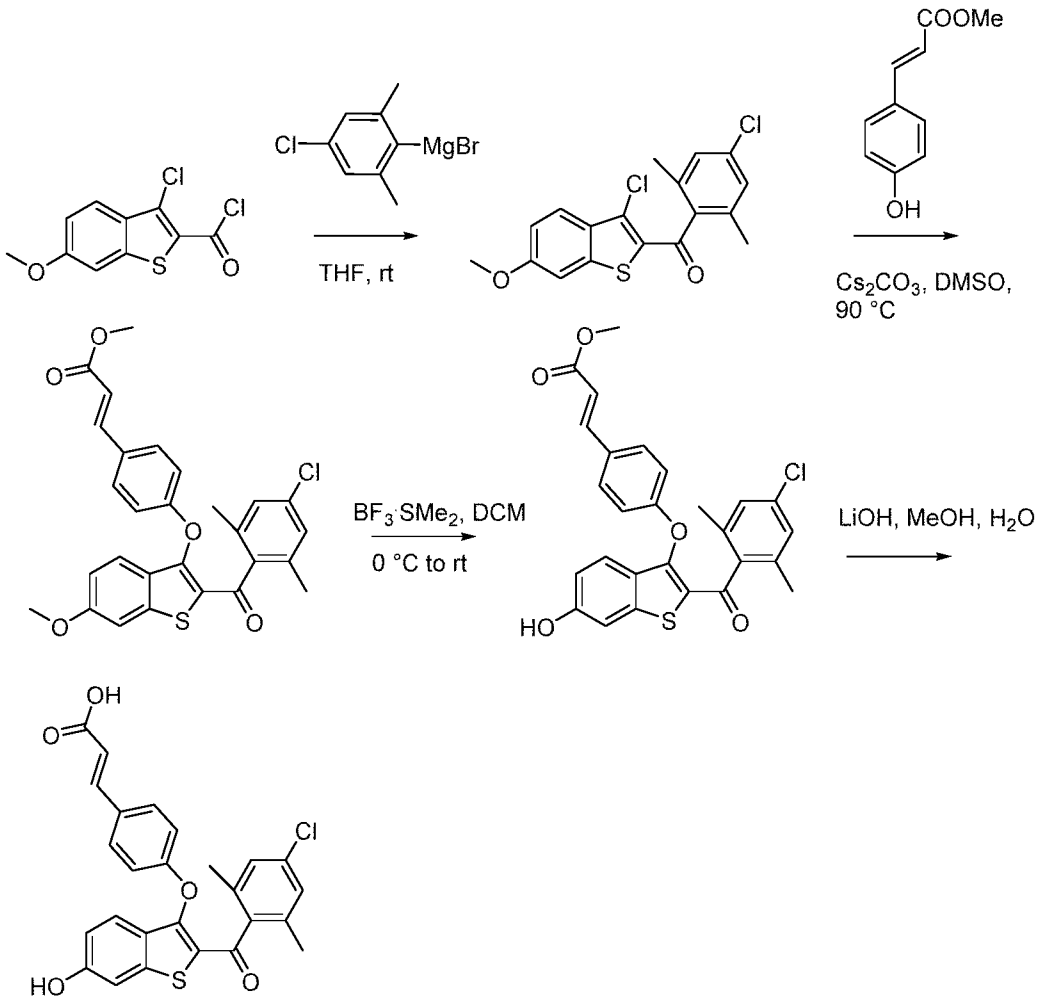
General Synthetic Route 2:



General Synthetic Route 3:



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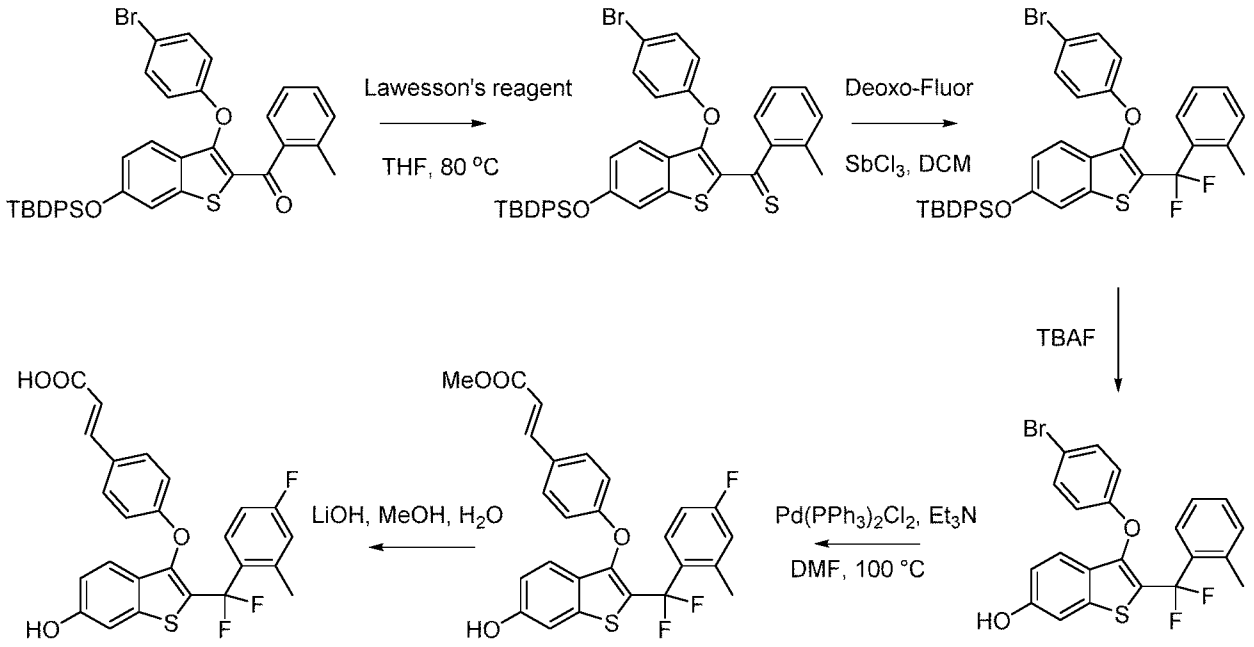
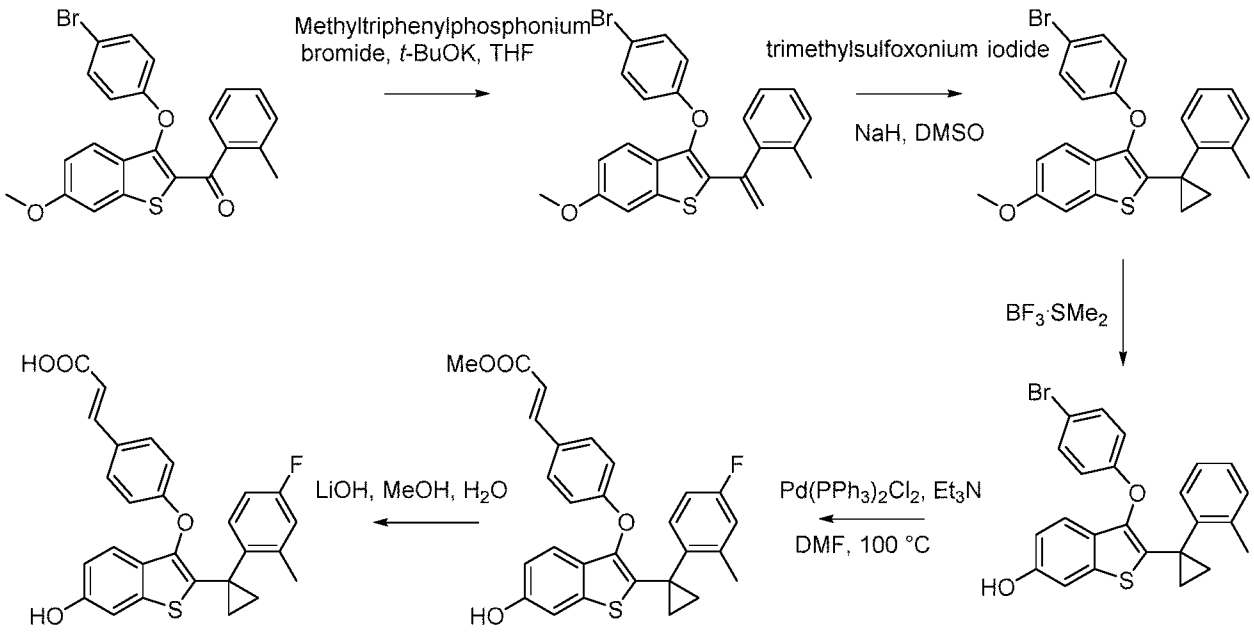
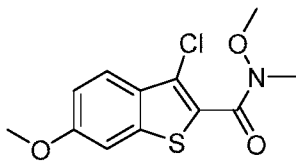


General Synthetic Route 5:

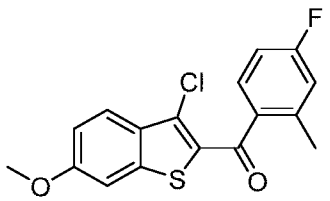


Intermediate 1: 3-Chloro-*N*,6-dimethoxy-*N*-methylbenzo[b]thiophene-2-carboxamide



In an oven-dried round-bottom flask, 3-chloro-6-methoxybenzo[b]thiophene-2-carbonyl chloride (8.9 g, 34.9 mmol) was dissolved in 50 mL of anhydrous dichloromethane under argon atmosphere and *N*,*O*-dimethylhydroxylamine hydrochloride (3.75g, 38.4 mmol) was added in one portion. After stirring for 10 minutes, Et_3N (17.6g, 174.5 mmol) was added dropwise. The reaction mixture was stirred overnight until TLC indicated consumption of all starting materials. The reaction was quenched by ice water, the solution was extracted with ethyl acetate, and washed with brine. The organic extracts were combined, dried over anhydrous Na_2SO_4, concentrated in vacuum, and purified by flash chromatography (5% - 50% ethyl acetate in hexane) to afford 7.6 g as a white solid (76%).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, J = 8.9 Hz, 1H), 7.23 (s, 1H), 7.10 (dd, J = 8.9, 2.3 Hz, 1H), 3.90 (s, 3H), 3.73 (s, 3H), 3.39 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.04, 159.88, 140.35, 130.23, 124.19, 116.09, 104.29, 62.04, 55.87, 33.75.

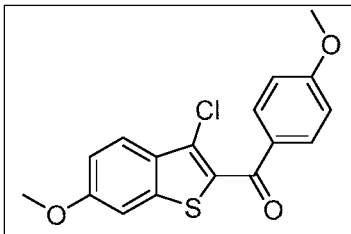
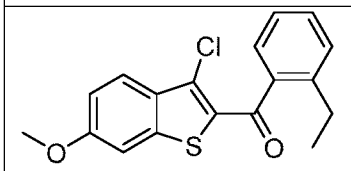
Intermediate 2: (3-Chloro-6-methoxybenzo[b]thiophen-2-yl)(4-fluoro-2-methylphenyl)methanone

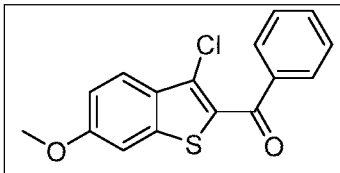
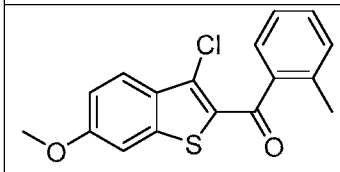
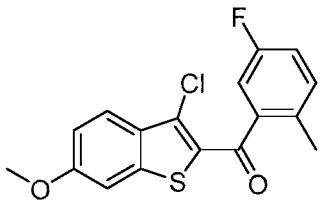


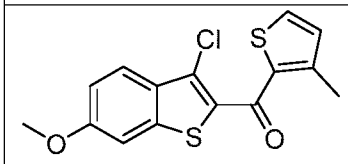
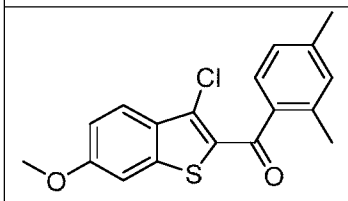
To a solution of intermediate (**1**) (500 mg, 1.75 mmol) in THF under argon atmosphere was added a 0.5 M solution of (4-fluoro-2-methylphenyl)magnesium bromide (4 mL, 2 mmol) dropwise. The reaction mixture was stirred overnight and quenched by 1 N HCl/ice water. The solution was extracted with ethyl acetate and washed with brine. The organic extracts were

combined, dried over anhydrous Na_2SO_4, concentrated in vacuum, and purified by flash chromatography (1% - 15% ethyl acetate in hexane) to afford 550 mg of a white solid (94%).

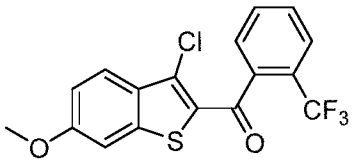
The following intermediates were made by an analogous procedure utilizing the appropriate Grignard reagent:

	(3-Chloro-6-methoxybenzo[b]thiophen-2-yl)(4-methoxyphenyl)methanone	^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 – 7.86 (m, 2H), 7.81 (d, *J* = 8.9 Hz, 1H), 7.25 (d, *J* = 1.5 Hz, 1H), 7.11 (dd, *J* = 8.9, 2.2 Hz, 1H), 7.00 – 6.88 (m, 2H), 3.90 (s, 3H), 3.89 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.57, 163.95, 160.22, 140.70, 132.50, 132.12, 131.07, 130.63, 124.64, 123.70, 116.54, 113.83, 104.54, 55.91, 55.67.
	(3-Chloro-6-methoxybenzo[b]thiophen-2-yl)(2-ethylphenyl)methanone	^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 9.0 Hz, 1H), 7.45 (td, *J* = 7.6, 1.3 Hz, 1H), 7.40 – 7.32 (m, 2H), 7.30 – 7.26 (m, 1H), 7.24 (d, *J* = 2.2 Hz, 1H), 7.09 (dd, *J* = 9.0, 2.3 Hz, 1H), 3.91 (s, 3H), 2.74 (q, *J* = 7.5 Hz, 2H), 1.21 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.07, 160.96, 142.52, 141.85, 139.10, 134.02, 131.67, 130.80, 129.48, 127.86, 125.73, 125.36, 116.86, 104.50, 55.92, 26.38, 15.81.

	(3-Chloro-6-methoxybenzo[b]thiophen-2-yl)(phenyl)methanone	^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 – 7.78 (m, 3H), 7.61 (t, *J* = 7.4 Hz, 1H), 7.49 (t, *J* = 7.6 Hz, 2H), 7.26 (d, *J* = 2.3 Hz, 1H), 7.12 (dd, *J* = 9.0, 2.3 Hz, 1H), 3.92 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.94, 160.37, 140.96, 138.08, 132.88, 131.76, 131.05, 129.56, 128.34, 124.86, 124.77, 116.59, 104.31, 55.76.
	(3-Chloro-6-methoxybenzo[b]thiophen-2-yl)(*o*-tolyl)methanone	^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 9.0 Hz, 1H), 7.45 – 7.35 (m, 2H), 7.34 – 7.19 (m, 3H), 7.09 (dd, *J* = 9.0, 2.3 Hz, 1H), 3.91 (s, 3H), 2.39 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.06, 160.90, 141.81, 139.41, 136.21, 133.86, 131.59, 131.03, 130.72, 127.93, 126.44, 125.77, 125.32, 116.86, 104.45, 55.91, 19.70.
	(3-chloro-6-methoxybenzo[b]thiophen-2-yl)(5-fluoro-2-methylphenyl)methanone	^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 9.0 Hz, 1H), 7.26-7.23 (m, 2H), 7.13-7.08 (m, 3H), 3.92 (s, 3H), 2.32 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.59, 161.17, 160.92 (d, *J* = 245.5 Hz), 142.07, 140.77 (d, *J* = 6.3 Hz), 133.30, 132.55 (d, *J* = 7.4 Hz), 131.64 (d, *J* = 3.5 Hz), 131.58,

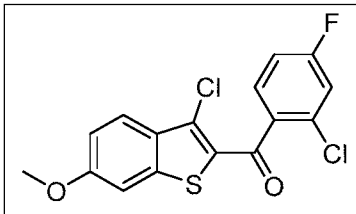
		127.03, 125.48, 117.45 (d, J = 21.0 Hz), 117.06, 114.61 (d, J = 23.0 Hz), 104.52, 55.95, 18.84.
	(3-chloro-6-methoxybenzo[b]thiophen-2-yl)(3-methylthiophen-2-yl)methanone	^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, J = 8.9 Hz, 1H), 7.54 (d, J = 4.9 Hz, 1H), 7.26 (d, J = 2.2 Hz, 1H), 7.12 (dd, J = 8.9, 2.2 Hz, 1H), 6.99 (d, J = 4.9 Hz, 1H), 3.91 (s, 3H), 2.50 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.18, 160.26, 146.19, 140.41, 135.96, 132.23, 132.15, 131.81, 130.83, 124.63, 124.02, 116.64, 104.52, 55.89, 16.40.
	(3-chloro-6-methoxybenzo[b]thiophen-2-yl)(2,4-dimethylphenyl)methanone	^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, J = 9.0 Hz, 1H), 7.33 (d, J = 7.7 Hz, 1H), 7.20 (d, J = 2.0 Hz, 1H), 7.10 – 7.00 (m, 3H), 3.87 (s, 3H), 2.37 (s, 6H).

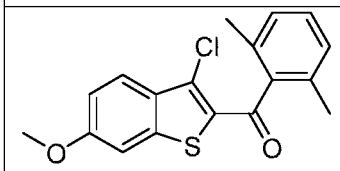
Intermediate 3: (3-Chloro-6-methoxybenzo[b]thiophen-2-yl)(2-(trifluoromethyl)phenyl)methanone



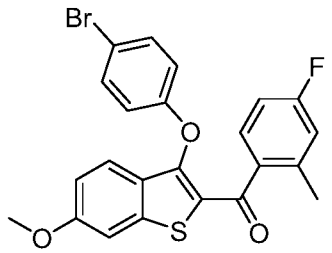
To a solution of 3-chloro-6-methoxybenzo[b]thiophene-2-carbonyl chloride (1.04 g, 4 mmol) in THF under argon atmosphere was added a freshly prepared solution of (2-(trifluoromethyl)phenyl)magnesium bromide (5 mmol) dropwise. The reaction mixture was stirred overnight and quenched by 1 N HCl/ice water. The solution was extracted with ethyl acetate and washed with brine. The organic extracts were combined, dried over anhydrous Na_2SO_4, concentrated in vacuum, and purified by flash chromatography (1% - 15% ethyl acetate in hexane) to afford 350 mg of a white solid (19%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (t, J = 8.3 Hz, 2H), 7.70 – 7.57 (m, 2H), 7.47 (d, J = 6.4 Hz, 1H), 7.24 (s, 1H), 7.07 (dd, J = 9.0, 1.9 Hz, 1H), 3.90 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.86, 161.27, 142.29, 138.58 (q, J = 2.1 Hz), 133.23, 131.99, 131.49, 130.20, 127.88, 127.75, 127.69 (q, J = 32.3 Hz), 126.89 (q, J = 4.5 Hz), 125.49, 123.70 (q, J = 274.0 Hz), 117.07, 104.41, 55.91. ^{19}F NMR (400 MHz, $CDCl_3$) δ -58.46.

The following intermediates were made by an analogous procedure utilizing the appropriate Grignard reagent:

	(2-Chloro-4-fluorophenyl)(3-chloro-6-methoxybenzo[b]thiophen-2-yl)methanone	^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, J = 9.0 Hz, 1H), 7.43 (dd, J = 8.5, 5.9 Hz, 1H), 7.24 – 7.16 (m, 2H), 7.13 – 7.02 (m, 2H), 3.90 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.58, 163.57 (d, J = 253.9 Hz), 161.19, 142.19, 135.45 (d, J = 3.7 Hz), 133.24, 132.81 (d, J = 10.6

		Hz), 131.39, 130.35 (d, J = 9.4 Hz), 127.28, 125.42, 117.63 (d, J = 24.9 Hz), 117.03, 114.63 (d, J = 21.6 Hz), 104.40, 55.87.
	(3-Chloro-6-methoxybenzo[b]thiophen-2-yl)(2,6-dimethylphenyl)methanone	^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 9.0 Hz, 1H), 7.26 – 7.18 (m, 2H), 7.12 – 7.02 (m, 3H), 3.90 (s, 3H), 2.22 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.58, 161.14, 142.18, 140.22, 134.18, 131.75, 129.31, 127.84, 126.81, 125.55, 116.91, 104.53, 55.91, 19.31.

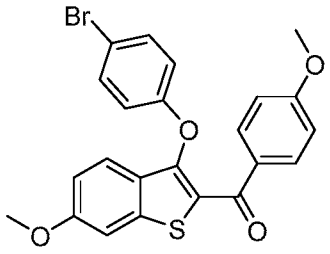
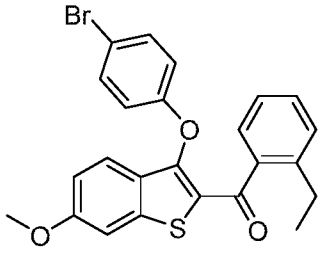
Compound I-4: (3-(4-Bromophenoxy)-6-methoxybenzo[b]thiophen-2-yl)(4-fluoro-2-methylphenyl)methanone

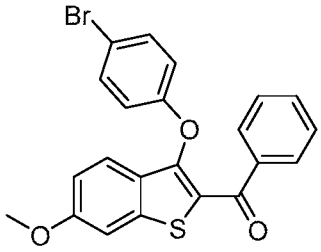
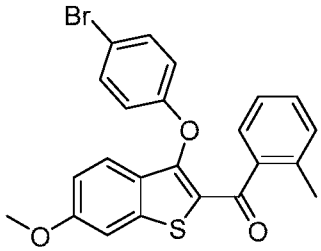
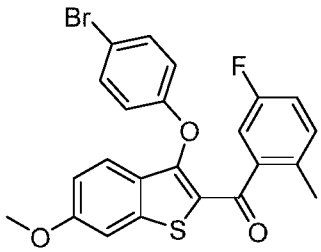


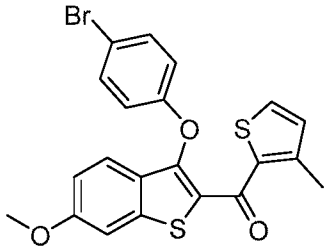
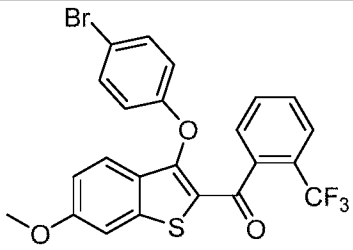
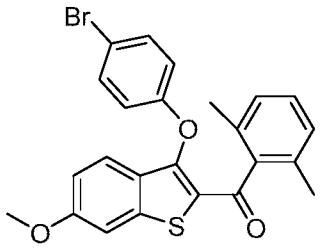
Cs_2CO_3 (1.52g, 4.67 mmol) was added in one portion to a solution of intermediate **2** (520 mg, 1.56 mmol) and 4-bromophenol in 5 mL DMF. The reaction mixture was raised to 50 °C and after stirring overnight, the reaction mixture was quenched with ice water, extracted with ethyl acetate, and washed with brine. The organic extracts were combined, dried over anhydrous Na_2SO_4, concentrated in vacuum, and purified by flash chromatography (1% - 15% ethyl acetate in hexane) to afford 490 mg white solid (67%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, J = 8.9 Hz, 1H), 7.34 – 7.27 (m, 2H), 7.22 – 7.17 (m, 2H), 6.96 (dd, J = 8.9, 2.2 Hz, 1H), 6.80-6.76 (m, 2H), 6.40 – 6.33

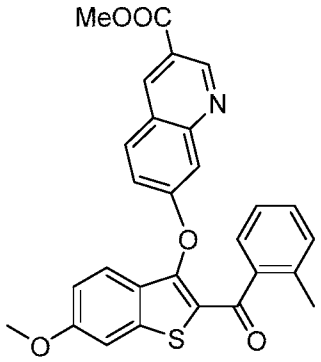
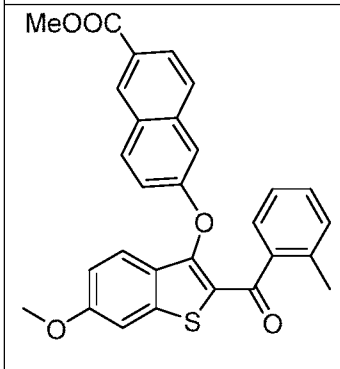
(m, 2H), 3.91 (s, 3H), 2.16 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.34, 163.72 (d, J = 250.2 Hz), 161.07, 157.45, 148.25, 142.21, 139.63 (d, J = 8.6 Hz), 135.29 (d, J = 3.1 Hz), 132.38, 130.24 (d, J = 9.2 Hz), 126.82, 127.48, 124.57, 117.45 (d, J = 21.4 Hz), 116.74, 116.55, 115.09, 112.19 (d, J = 21.7 Hz), 105.19, 55.89, 19.53 (d, J = 1.3 Hz).

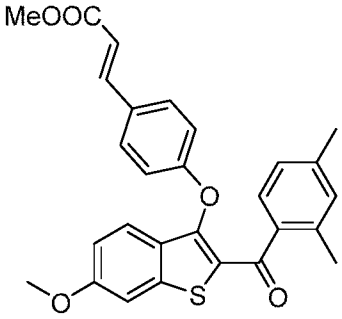
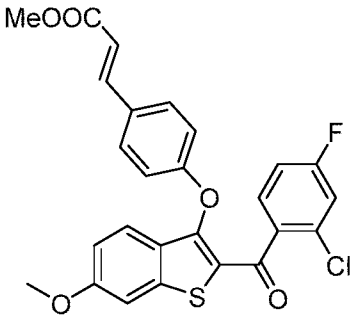
The following Compounds were made by an analogous procedure utilizing the appropriate starting materials:

	(3-(4-Bromophenoxy)-6-methoxybenzo[b]thiophen-2-yl)(4-methoxyphenyl)methanone	^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, J = 8.9 Hz, 2H), 7.47 (d, J = 8.9 Hz, 1H), 7.28 (d, J = 2.1 Hz, 1H), 7.21 (d, J = 9.0 Hz, 2H), 6.98 (dd, J = 8.9, 2.2 Hz, 1H), 6.86 (d, J = 8.9 Hz, 2H), 6.54 (d, J = 9.0 Hz, 2H), 3.91 (s, 3H), 3.86 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.33, 163.49, 160.43, 157.45, 146.58, 141.29, 132.47, 131.84, 130.92, 126.71, 125.99, 124.18, 117.46, 116.23, 115.05, 113.43, 105.08, 55.87, 55.64.
	(3-(4-Bromophenoxy)-6-methoxybenzo[b]thiophen-2-yl)(2-ethylphenyl)methanone	^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, J = 8.9 Hz, 1H), 7.29 – 7.24 (m, 3H), 7.17-7.13 (m, 3H), 7.07 (t, J = 7.5 Hz, 1H), 6.94 (dd, J = 8.9, 2.2 Hz, 1H), 6.35 – 6.29 (m, 2H), 3.91 (s, 3H), 2.50 (q, J = 7.5 Hz, 2H), 1.06 (t, J = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.68, 160.98, 157.30, 148.30, 142.19, 142.15, 138.95, 132.27, 130.35, 128.91, 128.06, 127.55, 126.90, 125.21, 124.66, 116.93, 116.46, 114.91, 105.22, 55.89, 26.21, 15.62.

	(3-(4-Bromophenoxy)-6-methoxybenzo[b]thiophen-2-yl)(phenyl)methanone	^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 – 7.65 (m, 2H), 7.52 – 7.44 (m, 2H), 7.34 (t, *J* = 7.7 Hz, 2H), 7.28 (d, *J* = 2.1 Hz, 1H), 7.21 – 7.15 (m, 2H), 6.97 (dd, *J* = 8.9, 2.2 Hz, 1H), 6.49 – 6.43 (m, 2H), 3.92 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.95, 160.72, 157.40, 147.59, 141.76, 138.49, 132.47, 132.40, 129.02, 128.09, 126.72, 125.92, 124.44, 117.33, 116.40, 115.07, 105.10, 55.88.
	(3-(4-Bromophenoxy)-6-methoxybenzo[b]thiophen-2-yl)(*o*-tolyl)methanone	^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, *J* = 8.9 Hz, 1H), 7.29 – 7.20 (m, 3H), 7.18 – 7.12 (m, 2H), 7.11 – 7.04 (m, 2H), 6.95 (dd, *J* = 8.9, 2.2 Hz, 1H), 6.37 – 6.26 (m, 2H), 3.91 (s, 3H), 2.16 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.66, 160.99, 157.45, 148.38, 142.20, 139.30, 135.92, 132.27, 130.63, 130.28, 127.74, 127.63, 126.92, 125.25, 124.60, 116.86, 116.48, 114.92, 105.20, 55.89, 19.36.
	(3-(4-Bromophenoxy)-6-methoxybenzo[b]thiophen-2-yl)(5-fluoro-2-methylphenyl)methanone	^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8.9 Hz, 1H), 7.28 (d, *J* = 2.1 Hz, 1H), 7.19 (d, *J* = 9.0 Hz, 2H), 7.04-6.91 (m, 4H), 6.38 (d, *J* = 9.0 Hz, 2H), 3.91 (s, 3H), 2.11 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.11, 161.19, 160.60 (d, *J* = 245.3 Hz), 157.28, 148.76, 142.47, 140.60 (d, *J* = 6.3 Hz), 132.42, 132.06

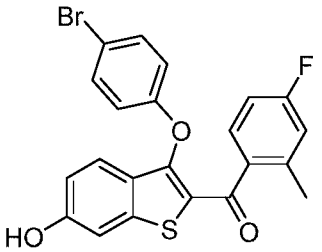
		(d, *J* = 7.4 Hz), 131.36 (d, *J* = 3.5 Hz), 127.15, 126.70, 124.75, 116.90 (d, *J* = 20.9 Hz), 116.76, 116.64, 115.15, 114.34 (d, *J* = 23.0 Hz), 105.22, 55.90, 18.56.
	(3-(4-Bromophenoxy)-6-methoxybenzo[b]thiophen-2-yl)(3-methylthiophen-2-yl)methanone	^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, *J* = 8.9 Hz, 1H), 7.42 (d, *J* = 4.9 Hz, 1H), 7.28-7.23 (m, 3H), 6.99 (dd, *J* = 8.9, 2.2 Hz, 1H), 6.87 (d, *J* = 4.9 Hz, 1H), 6.67 – 6.59 (m, 2H), 3.91 (s, 3H), 2.34 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 181.10, 160.50, 157.62, 147.31, 145.02, 140.99, 135.76, 132.50, 131.63, 130.84, 126.58, 125.44, 124.19, 117.62, 116.31, 115.25, 104.96, 55.87, 15.94.
	(3-(4-Bromophenoxy)-6-methoxybenzo[b]thiophen-2-yl)(2-(trifluoromethyl)phenyl)methanone	^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 7.7 Hz, 1H), 7.43 (t, *J* = 7.5 Hz, 1H), 7.37 (t, *J* = 7.3 Hz, 1H), 7.33 – 7.28 (m, 1H), 7.27 – 7.21 (m, 2H), 7.18 (d, *J* = 8.9 Hz, 2H), 6.89 (dd, *J* = 8.9, 2.2 Hz, 1H), 6.33 (d, *J* = 8.9 Hz, 2H), 3.89 (s, 3H).
	(3-(4-Bromophenoxy)-6-methoxybenzo[b]thiophen-2-yl)(2,6-dimethylphenyl)methanone	^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, *J* = 8.9 Hz, 1H), 7.28 (d, *J* = 2.1 Hz, 1H), 7.17 (d, *J* = 8.9 Hz, 2H), 7.04 (t, *J* = 7.6 Hz, 1H), 6.92 (dd, *J* = 8.9, 2.2 Hz, 1H), 6.86 (d, *J* = 7.7 Hz, 2H), 6.34 (d, *J* = 8.9 Hz, 2H), 3.88 (s, 3H), 2.11 (s, 6H). ^{13}C

		NMR (100 MHz, $CDCl_3$) δ 192.08, 160.94, 156.72, 148.28, 142.22, 140.16, 133.71, 131.95, 128.73, 128.49, 127.35, 126.59, 124.67, 116.52, 116.40, 114.74, 105.22, 55.75, 19.18.
	Methyl 7-((6-methoxy-2-(2-methylbenzoyl)benzo[b]thiophen-3-yl)oxy)quinoline-3-carboxylate	^{1}H NMR (400 MHz, $CDCl_3$) δ 9.29 (d, *J* = 1.7 Hz, 1H), 8.71 (s, 1H), 7.64 (d, *J* = 9.0 Hz, 1H), 7.45 (d, *J* = 8.9 Hz, 1H), 7.30 (d, *J* = 1.8 Hz, 1H), 7.25 (d, *J* = 7.3 Hz, 1H), 7.16 (t, *J* = 7.3 Hz, 1H), 7.08 (d, *J* = 1.9 Hz, 1H), 6.99 – 6.88 (m, 3H), 6.83 (dd, *J* = 8.9, 2.3 Hz, 1H), 3.98 (s, 3H), 3.91 (s, 3H), 2.04 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.40, 165.93, 161.07, 160.98, 150.88, 150.81, 147.66, 142.34, 139.30, 138.37, 135.65, 130.48, 130.41, 130.14, 128.07, 127.33, 126.64, 125.14, 124.40, 122.83, 121.83, 118.87, 116.73, 111.31, 105.15, 55.89, 52.53, 19.22.
	Methyl 6-((6-methoxy-2-(2-methylbenzoyl)benzo[b]thiophen-3-yl)oxy)-2-naphthoate	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (s, 1H), 7.96 (dd, *J* = 8.6, 1.5 Hz, 1H), 7.64 (d, *J* = 9.0 Hz, 1H), 7.50 (d, *J* = 8.7 Hz, 1H), 7.47 (d, *J* = 8.9 Hz, 1H), 7.32 – 7.27 (m, 2H), 7.16 (t, *J* = 7.5 Hz, 1H), 6.98 (t, *J* = 7.5 Hz, 1H), 6.95 – 6.86 (m, 2H), 6.77 (d, *J* = 2.2 Hz, 1H), 6.73 (dd, *J* = 8.9, 2.5 Hz, 1H), 3.93 (s, 3H), 3.86 (s, 3H), 1.99 (s, 3H). ^{13}C NMR (100

		MHz, $CDCl_3$) δ 190.43, 167.05, 160.88, 158.00, 148.20, 142.08, 139.06, 136.21, 135.72, 131.02, 130.70, 130.36, 130.05, 128.52, 127.67, 127.47, 127.05, 126.85, 126.09, 126.02, 125.04, 124.43, 117.70, 116.38, 109.49, 105.09, 55.69, 52.11, 19.06.
	Methyl (*E*)-3-(4-((2-(2,4-dimethylbenzoyl)-6-methoxybenzo[b]thiophen-3-yl)oxy)phenyl)acrylate	^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, *J* = 16.0 Hz, 1H), 7.46 (d, *J* = 8.9 Hz, 1H), 7.28 (d, *J* = 2.1 Hz, 1H), 7.23 (t, *J* = 8.9 Hz, 3H), 6.96 (dd, *J* = 8.9, 2.2 Hz, 1H), 6.85 (d, *J* = 11.2 Hz, 2H), 6.47 (d, *J* = 8.8 Hz, 2H), 6.27 (d, *J* = 16.0 Hz, 1H), 3.91 (s, 3H), 3.79 (s, 3H), 2.29 (s, 3H), 2.09 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.48, 167.65, 160.87, 160.01, 147.81, 144.09, 141.92, 140.64, 136.30, 136.22, 131.40, 129.33, 128.91, 128.29, 127.79, 127.05, 125.79, 124.43, 116.48, 116.43, 115.58, 105.11, 55.87, 51.79, 21.47, 19.38.
	Methyl (*E*)-3-(4-((2-(2-chloro-4-fluorobenzoyl)-6-methoxybenzo[b]thiophen-3-yl)oxy)phenyl)acrylate	^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 16.0 Hz, 1H), 7.37 (d, *J* = 9.0 Hz, 1H), 7.28 (t, *J* = 8.8 Hz, 3H), 7.20 (dd, *J* = 8.5, 5.9 Hz, 1H), 7.00 (dd, *J* = 8.6, 2.3 Hz, 1H), 6.93 (dd, *J* = 9.0, 2.2 Hz, 1H), 6.81 (td, *J* = 8.3, 2.4 Hz, 1H), 6.55 (d, *J* = 8.7 Hz, 2H), 6.29 (d, *J* = 16.0 Hz, 1H), 3.91 (s, 3H), 3.79 (s, 3H). ^{13}C NMR

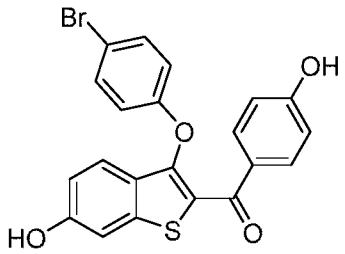
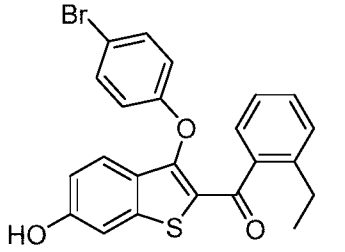
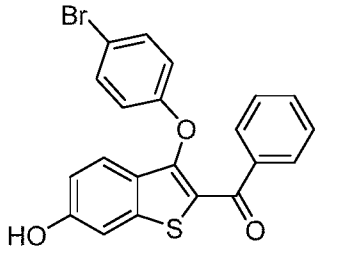
		(100 MHz, $CDCl_3$) δ 186.10, 167.53, 163.16 (d, J = 253.1 Hz), 161.27, 159.30, 148.85, 143.81, 142.73, 135.48 (d, J = 3.7 Hz), 132.49 (d, J = 10.6 Hz), 129.79 (d, J = 9.3 Hz), 129.56, 129.36, 127.18, 126.36, 124.83, 117.18 (d, J = 24.9 Hz), 116.91, 116.72, 115.45, 113.83 (d, J = 21.6 Hz), 105.22, 55.91, 51.82.

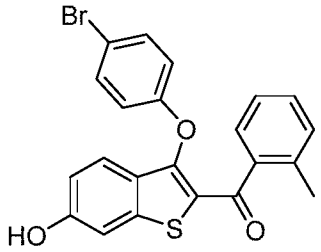
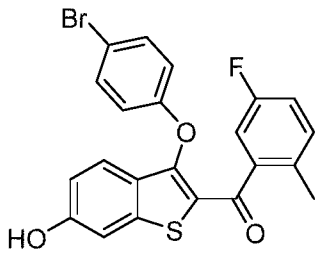
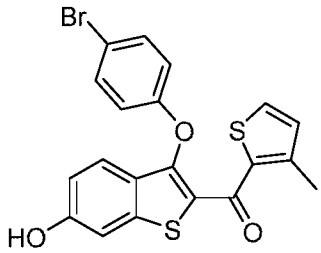
Compound I-5: (3-(4-Bromophenoxy)-6-hydroxybenzo[b]thiophen-2-yl)(4-fluoro-2-methylphenyl)methanone

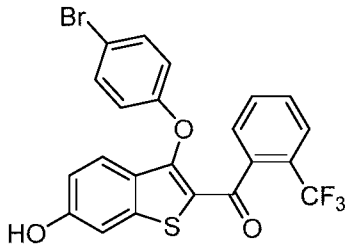
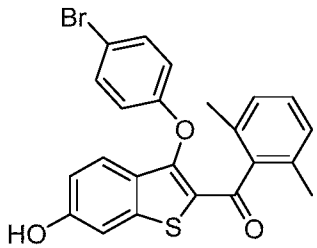


Compound I-**4** (480 mg, 1 mmol) was dissolved in 10 mL of anhydrous dichloromethane at room temperature and BF_3•SMe_2 (1.2 ml, 5 mmol) was added dropwise to this solution. The reaction mixture was stirred until starting material, as monitored by TLC, was consumed. The reaction was then quenched with saturated $NaHCO_3$/ice water, extracted with ethyl acetate, and washed with brine. The organic extracts were combined, dried over anhydrous Na_2SO_4, concentrated in vacumn, and purified by flash chromatography (5%-60% ethyl acetate in hexane) to afford 390 mg as a white powder (85%). ^{1}H NMR (400 MHz, MeOD) δ 7.38 (d, J = 8.8 Hz, 1H), 7.35 – 7.28 (m, 1H), 7.28 – 7.20 (m, 3H), 6.90 (dd, J = 8.8, 2.1 Hz, 1H), 6.87-6.80 (m, 2H), 6.46 – 6.38 (m, 2H), 2.13 (s, 3H).

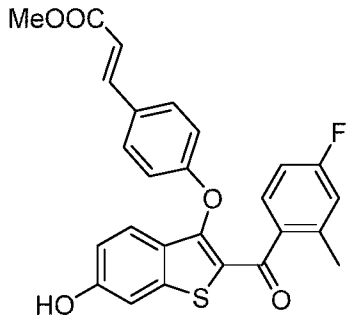
The following compounds were made by an analogous procedure utilizing appropriate starting materials:

	(3-(4-Bromophenoxy)-6-hydroxybenzo[b]thiophen-2-yl) (4-hydroxyphenyl)methanone	^{1}H NMR (400 MHz, Acetone) δ 7.71 (d, *J* = 8.7 Hz, 2H), 7.47 (d, *J* = 8.7 Hz, 1H), 7.41 (d, *J* = 2.0 Hz, 1H), 7.35 (d, *J* = 9.0 Hz, 2H), 7.02 (dd, *J* = 8.8, 2.1 Hz, 1H), 6.86 (d, *J* = 8.7 Hz, 2H), 6.68 (d, *J* = 9.0 Hz, 2H).
	(3-(4-Bromophenoxy)-6-hydroxybenzo[b]thiophen-2-yl) (2-ethylphenyl)methanone	^{1}H NMR (400 MHz, Acetone) δ 9.25 (s, 1H), 7.44-7.38 (m, 2H), 7.35 – 7.26 (m, 4H), 7.19 (d, *J* = 7.5 Hz, 1H), 7.12 (t, *J* = 7.5 Hz, 1H), 6.99 (dd, *J* = 8.8, 2.2 Hz, 1H), 6.52 – 6.44 (m, 2H), 2.49 (q, *J* = 7.5 Hz, 2H), 1.04 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.58, 159.88, 158.26, 149.03, 142.77, 142.50, 140.15, 133.10, 130.97, 129.63, 128.13, 128.05, 126.79, 126.01, 125.59, 118.04, 117.20, 115.18, 108.98, 26.72, 15.95.
	(3-(4-Bromophenoxy)-6-hydroxybenzo[b]thiophen-2-yl)(phenyl)methanone	^{1}H NMR (400 MHz, MeOD) δ 7.62 (d, *J* = 7.2 Hz, 2H), 7.51 (t, *J* = 7.5 Hz, 1H), 7.44 – 7.32 (m, 3H), 7.25-7.21 (m, 3H), 6.91 (dd, *J* = 8.8, 2.1 Hz, 1H), 6.49 (d, *J* = 9.0 Hz, 2H). ^{13}C NMR (101 MHz, MeOD) δ 190.76, 160.50, 158.77, 149.54, 143.24, 139.95, 133.47, 133.38, 129.69, 129.14, 126.80, 125.81, 125.53, 118.42, 117.39, 115.88, 108.74.

	(3-(4-Bromophenoxy)-6-hydroxybenzo[b]thiophen-2-yl) (*o*-tolyl)methanone	^{1}H NMR (400 MHz, MeOD) δ 7.36 (d, *J* = 8.8 Hz, 1H), 7.30 – 7.17 (m, 5H), 7.09 (t, *J* = 7.4 Hz, 2H), 6.89 (dd, *J* = 8.8, 2.1 Hz, 1H), 6.41 – 6.32 (m, 2H), 2.11 (s, 3H). ^{13}C NMR (100 MHz, MeOD) δ 192.45, 160.86, 158.79, 150.45, 143.73, 140.77, 136.58, 133.33, 131.53, 131.27, 128.38, 127.60, 126.95, 126.34, 125.74, 117.99, 117.49, 115.77, 108.88, 19.29.
	(3-(4-Bromophenoxy)-6-hydroxybenzo[b]thiophen-2-yl) (5-fluoro-2-methylphenyl)methanone	^{1}H NMR (400 MHz, Acetone) δ 7.44-7.41 (m, 2H), 7.33 (d, *J* = 9.0 Hz, 2H), 7.18-7.13 (m, 1H), 7.09 (dd, *J* = 8.9, 2.7 Hz, 1H), 7.05-6.99 (m, 2H), 6.54 (d, *J* = 9.0 Hz, 2H), 2.11 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 189.08, 161.39 (d, *J* = 243.4 Hz), 160.11, 158.23, 149.48, 143.09, 142.07 (d, *J* = 6.4 Hz), 133.24, 132.96 (d, *J* = 7.6 Hz), 131.83 (d, *J* = 3.4 Hz), 127.43, 126.60, 125.72, 117.91, 117.34, 117.29 (d, *J* = 21.3 Hz), 115.39, 114.60 (d, *J* = 23.2 Hz), 109.04, 18.45.
	(3-(4-Bromophenoxy)-6-hydroxybenzo[b]thiophen-2-yl) (3-methylthiophen-2-yl) methanone	^{1}H NMR (400 MHz, Acetone-d6) δ 9.19 (s, 1H), 7.65 (d, *J* = 4.9 Hz, 1H), 7.54 (d, *J* = 8.8 Hz, 1H), 7.42 (d, *J* = 2.1 Hz, 1H), 7.39 – 7.32 (m, 2H), 7.04 (dd, *J* = 8.8, 2.1 Hz, 1H), 6.97 (d, *J* = 4.9 Hz, 1H), 6.74 – 6.65 (m, 2H), 2.29 (s, 3H). ^{13}C NMR (100 MHz, Acetone-d6) δ 181.07,

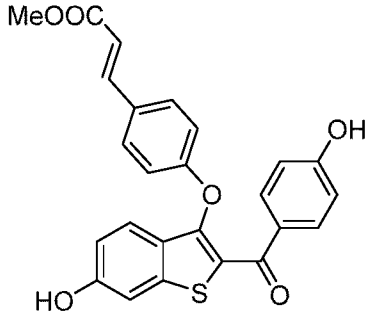
		159.40, 158.68, 147.89, 144.79, 141.57, 136.57, 133.26, 132.38, 131.63, 126.53, 125.63, 124.95, 118.55, 117.13, 115.47, 108.74, 15.70.
	(3-(4-Bromophenoxy)-6-hydroxybenzo[b]thiophen-2-yl) (2-(trifluoromethyl)phenyl) methanone	^{1}H NMR (400 MHz, MeOD) δ 7.58 (d, *J* = 7.8 Hz, 1H), 7.43 (t, *J* = 7.5 Hz, 1H), 7.36 (t, *J* = 7.3 Hz, 1H), 7.31 (d, *J* = 7.2 Hz, 1H), 7.23 (d, *J* = 2.0 Hz, 1H), 7.19 – 7.09 (m, 3H), 6.80 (dd, *J* = 8.9, 2.1 Hz, 1H), 6.31 (d, *J* = 9.0 Hz, 2H).
	(3-(4-Bromophenoxy)-6-hydroxybenzo[b]thiophen-2-yl)(2,6-dimethylphenyl) methanone	^{1}H NMR (400 MHz, Acetone) δ 9.29 (s, 1H), 7.43 (d, *J* = 2.1 Hz, 1H), 7.35 (d, *J* = 8.8 Hz, 1H), 7.29 (d, *J* = 9.0 Hz, 2H), 7.06 (t, *J* = 7.6 Hz, 1H), 6.98 (dd, *J* = 8.8, 2.1 Hz, 1H), 6.90 (d, *J* = 7.5 Hz, 2H), 6.46 (d, *J* = 8.9 Hz, 2H), 2.08 (s, 6H). ^{13}C NMR (100 MHz, Acetone) δ 191.96, 159.98, 157.87, 149.06, 142.90, 141.45, 134.37, 132.90, 129.46, 128.64, 128.13, 126.65, 125.75, 117.72, 117.26, 115.12, 109.12, 19.29.

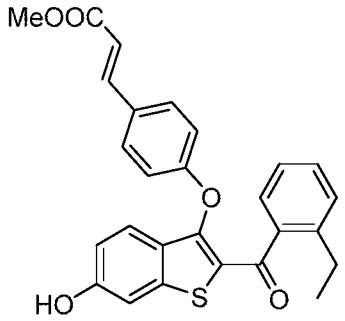
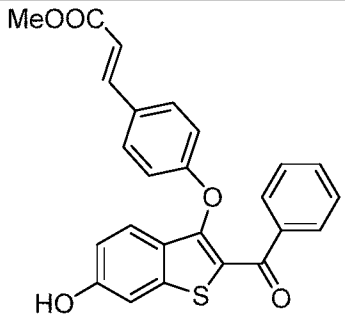
Compound I-6: Methyl (*E*)-3-(4-((2-(4-fluoro-2-methylbenzoyl)-6-hydroxybenzo[b]thiophen-3-yl)oxy)phenyl)acrylate

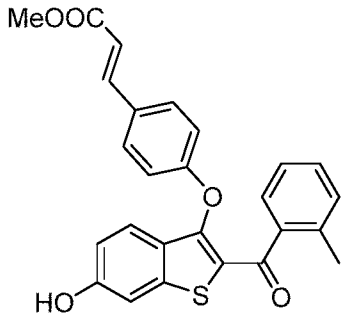
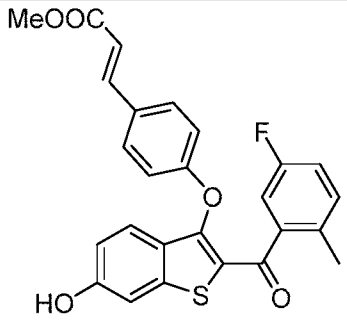


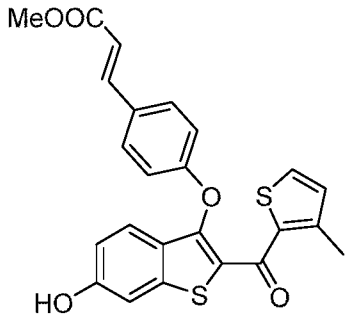
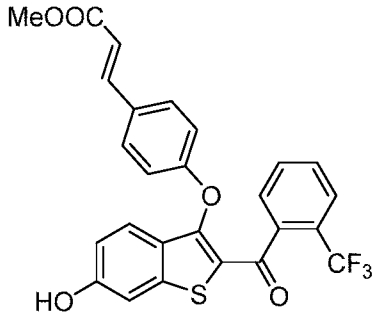
In a sealed tube, compound I-**5** (200 mg, 0.46 mmol), methyl acrylate (240mg, 2.76 mmol), and $Pd(PPh_3)_2Cl_2$ were suspended in DMF (2 ml) and triethylamine (235 mg, 2.3 mmol). The reaction was heated at 110 °C for 6 hours. The reaction mixture was quenched by water and extracted with ethyl acetate. The organic layers was collected and purified by flash chromatography (5%-60% ethyl acetate in hexane) to afford 170 mg as a white powder (85%). ^{1}H NMR (400 MHz, MeOD) δ 7.57 (d, *J* = 16.0 Hz, 1H), 7.40-7.36 (m, 3H), 7.32 (dd, *J* = 8.8, 6.0 Hz, 1H), 7.27 (d, *J* = 1.8 Hz, 1H), 6.89 (m *J* = 8.9, 1.9 Hz, 1H), 6.83-6.78 (m, 2H), 6.52 (d, *J* = 8.7 Hz, 2H), 6.37 (d, *J* = 16.0 Hz, 1H), 3.76 (s, 3H), 2.10 (s, 3H). ^{13}C NMR (100 MHz, MeOD) δ 191.09, 169.17, 164.95 (d, *J* = 248.7 Hz), 161.19, 160.91, 150.13, 145.22, 143.71, 140.41 (d, *J* = 8.6 Hz), 136.86 (d, *J* = 3.0 Hz), 131.11 (d, *J* = 9.2 Hz), 130.77, 130.47, 127.59, 126.92, 125.70, 118.13 (d, *J* = 21.8 Hz), 117.55, 117.48, 116.47, 113.11 (d, *J* = 21.9 Hz), 108.89, 52.09, 19.41.

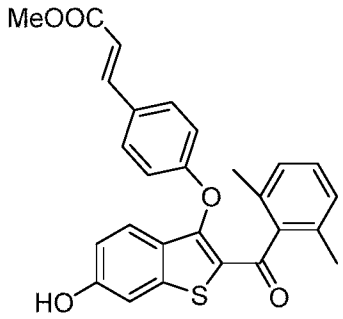
The following compounds were made by an analogous procedure utilizing appropriate starting materials:

	Methyl (*E*)-3-(4-((6-hydroxy-2-(4-hydroxybenzoyl)benzo[b]thiophen-3-yl)oxy)phenyl)acrylate	^{1}H NMR (400 MHz, MeOD) δ 7.61 (d, *J* = 8.7 Hz, 2H), 7.55 (d, *J* = 16.0 Hz, 1H), 7.42 (d, *J* = 8.8 Hz, 1H), 7.39 (d, *J* = 8.8 Hz, 2H), 7.26 (d, *J* = 2.0 Hz, 1H), 6.91 (dd, *J* = 8.8, 2.1 Hz, 1H), 6.74 (d, *J* = 8.7 Hz, 2H), 6.66 (d, *J* = 8.8 Hz,

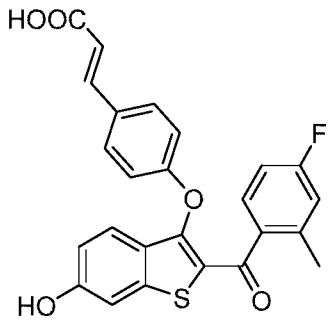
		2H), 6.35 (d, *J* = 16.0 Hz, 1H), 3.74 (s, 3H).
	Methyl (*E*)-3-(4-((2-(2-ethylbenzoyl)-6-hydroxybenzo[b]thiophen-3-yl)oxy)phenyl)acrylate	^{1}H NMR (400 MHz, MeOD) δ 7.57 (d, *J* = 16.0 Hz, 1H), 7.40 – 7.20 (m, 6H), 7.14 (d, *J* = 7.7 Hz, 1H), 7.06 (t, *J* = 7.5 Hz, 1H), 6.88 (dd, *J* = 8.8, 2.1 Hz, 1H), 6.47 (d, *J* = 8.8 Hz, 2H), 6.36 (d, *J* = 16.0 Hz, 1H), 3.76 (s, 3H), 2.46 (q, *J* = 7.5 Hz, 2H), 1.02 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.46, 169.17, 161.00, 160.81, 150.20, 145.31, 143.66, 142.87, 140.35, 131.30, 130.70, 130.29, 129.89, 128.29, 127.97, 126.89, 126.30, 125.79, 117.47, 117.31, 116.67, 108.90, 52.09, 27.10, 15.96.
	Methyl (*E*)-3-(4-((2-benzoyl-6-hydroxybenzo[b]thiophen-3-yl)oxy)phenyl)acrylate	^{1}H NMR (400 MHz, DMSO) δ 10.39 (s, 1H), 7.65 (d, *J* = 7.9 Hz, 2H), 7.56-7.52 (m, 4H), 7.39-7.34 (m, 4H), 6.93 (d, *J* = 8.8 Hz, 1H), 6.66 (d, *J* = 8.5 Hz, 2H), 6.47 (d, *J* = 16.1 Hz, 1H), 3.69 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 187.95, 166.69, 159.08, 158.90, 147.19, 143.62, 141.00, 138.11, 132.27, 130.10, 128.67, 128.32, 128.03, 124.63, 124.32, 124.29, 116.55, 116.51, 115.66, 108.03, 51.37.

	Methyl (*E*)-3-(4-((6-hydroxy-2-(2-methylbenzoyl)benzo[b]thiophen-3-yl)oxy)phenyl)acrylate	^{1}H NMR (400 MHz, MeOD) δ 7.56 (d, *J* = 16.0 Hz, 1H), 7.35 (d, *J* = 8.6 Hz, 3H), 7.28-7.21 (m, 3H), 7.10 – 7.01 (m, 2H), 6.88 (dd, *J* = 8.8, 2.1 Hz, 1H), 6.46 (d, *J* = 8.7 Hz, 2H), 6.35 (d, *J* = 16.0 Hz, 1H), 3.76 (s, 3H), 2.09 (s, 3H). ^{13}C NMR (100 MHz, MeOD) δ 192.43, 169.18, 161.17, 160.84, 150.28, 145.31, 143.69, 140.72, 136.56, 131.51, 131.25, 130.70, 130.31, 128.36, 127.69, 126.95, 126.32, 125.73, 117.49, 117.33, 116.58, 108.90, 52.09, 19.31.
	Methyl (*E*)-3-(4-((2-(5-fluoro-2-methylbenzoyl)-6-hydroxybenzo[b]thiophen-3-yl)oxy)phenyl)acrylate	^{1}H NMR (400 MHz, MeOD) δ 7.55 (d, *J* = 16.0 Hz, 1H), 7.38-7.31 (m, 3H), 7.26 (d, *J* = 2.1 Hz, 1H), 7.09 – 7.00 (m, 1H), 6.99-6.92 (m, 2H), 6.87 (dd, *J* = 8.9, 2.1 Hz, 1H), 6.50 (d, *J* = 8.7 Hz, 2H), 6.35 (d, *J* = 16.0 Hz, 1H), 3.75 (s, 3H), 2.06 (s, 3H). ^{13}C NMR (100 MHz, MeOD) δ 190.64, 169.15, 161.89 (d, *J* = 244.5 Hz), 161.01, 160.96, 150.54, 145.21, 143.94, 142.19 (d, *J* = 6.4 Hz), 133.17 (d, *J* = 7.5 Hz), 132.14 (d, *J* = 3.4 Hz), 130.80, 130.47, 127.31, 126.75, 125.87, 117.62 (d, *J* = 21.3 Hz), 117.60, 117.45, 116.49, 114.83 (d, *J* = 23.3 Hz), 108.94, 52.09, 18.49.

	Methyl (*E*)-3-(4-((6-hydroxy-2-(3-methylthiophene-2-carbonyl)benzo[b]thiophen-3-yl)oxy)phenyl)acrylate	^{1}H NMR (400 MHz, MeOD) δ 7.61-7.55 (m, 2H), 7.50 (d, *J* = 8.8 Hz, 1H), 7.42 (d, *J* = 8.7 Hz, 2H), 7.28 (d, *J* = 2.1 Hz, 1H), 6.98 – 6.87 (m, 2H), 6.71 (d, *J* = 8.7 Hz, 2H), 6.38 (d, *J* = 16.0 Hz, 1H), 3.77 (s, 3H), 2.24 (s, 3H). ^{13}C NMR (100 MHz, MeOD) δ 182.78, 169.15, 161.50, 160.27, 148.90, 145.52, 145.28, 142.40, 136.89, 132.55, 132.19, 130.85, 130.50, 126.82, 125.53, 125.13, 117.39, 117.09, 108.64, 52.09, 15.67.
	Methyl (*E*)-3-(4-((6-hydroxy-2-(2-(trifluoromethyl)benzoyl)benzo[b]thiophen-3-yl)oxy)phenyl)acrylate	^{1}H NMR (400 MHz, MeOD) δ 7.58 (d, *J* = 7.8 Hz, 1H), 7.52 (d, *J* = 16.0 Hz, 1H), 7.43 (t, *J* = 7.3 Hz, 1H), 7.38 – 7.21 (m, 5H), 7.17 (d, *J* = 8.8 Hz, 1H), 6.80 (dd, *J* = 8.8, 2.0 Hz, 1H), 6.42 (d, *J* = 8.7 Hz, 2H), 6.30 (d, *J* = 16.0 Hz, 1H), 3.71 (s, 3H). ^{13}C NMR (100 MHz, MeOD) δ 188.88, 169.00, 160.87, 160.11, 150.85, 145.06, 143.97, 139.62 (q, *J* = 1.9 Hz), 132.62, 130.84, 130.65, 130.39, 128.51, 127.81 (q, *J* = 32.0 Hz), 127.29, 127.26 (q, *J* = 4.5 Hz), 126.13, 126.02, 125.02 (q, *J* = 273.4 Hz), 117.48, 117.42, 116.64, 109.01, 52.10. ^{19}F NMR (400 MHz, MeOD) δ -57.84.

	Methyl (*E*)-3-(4-((2-(2,6-dimethylbenzoyl)-6-hydroxybenzo[b]thiophen-3-yl)oxy)phenyl)acrylate	^{1}H NMR (400 MHz, MeOD) δ 7.57 (d, *J* = 16.0 Hz, 1H), 7.35 (d, *J* = 8.7 Hz, 2H), 7.30 – 7.24 (m, 2H), 7.03 (t, *J* = 7.6 Hz, 1H), 6.88 – 6.80 (m, 3H), 6.45 (d, *J* = 8.7 Hz, 2H), 6.36 (d, *J* = 16.0 Hz, 1H), 3.75 (s, 3H), 2.06 (s, 6H). ^{13}C NMR (100 MHz, MeOD) δ 194.05, 169.17, 160.99, 160.62, 150.45, 145.33, 143.89, 141.52, 134.80, 130.57, 130.30, 129.92, 128.47, 126.75, 125.99, 117.57, 117.27, 116.42, 109.04, 52.10, 19.34.

Example 1: Synthetic Procedures for Representative Compounds (*E*)-3-(4-((2-(4-Fluoro-2-methylbenzoyl)-6-hydroxybenzo[b]thiophen-3-yl)oxy)phenyl)acrylic acid (Compound 1)



To a solution of Compound I-**6** (75 mg, 0.16 mmol) in methanol (2 ml) was added 10% LiOH solution (2 ml) dropwise. The reaction was monitored by TLC and once TLC indicated consumption of starting materials, the reaction was quenched by 1 N HCl/ice water. After stirring for 10 minutes, the mixture was extracted with ethyl acetate. The organic layers were collected and purified by C18 chromatography (5%-60% ethyl methanol in water) to afford 71 mg as a white powder (99%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 16.0 Hz, 1H), 7.37 (d, *J* = 9.0 Hz, 1H),

7.28 (t, J = 8.8 Hz, 3H), 7.20 (dd, J = 8.5, 5.9 Hz, 1H), 7.00 (dd, J = 8.6, 2.3 Hz, 1H), 6.93 (dd, J = 9.0, 2.2 Hz, 1H), 6.81 (td, J = 8.3, 2.4 Hz, 1H), 6.55 (d, J = 8.7 Hz, 2H), 6.29 (d, J = 16.0 Hz, 1H), 3.91 (s, 3H), 3.79 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.10, 167.53, 163.16 (d, J = 253.1 Hz), 161.27, 159.30, 148.85, 143.81, 142.73, 135.48 (d, J = 3.7 Hz), 132.49 (d, J = 10.6 Hz), 129.79 (d, J = 9.3 Hz), 129.56, 129.36, 127.18, 126.36, 124.83, 117.18 (d, J = 24.9 Hz), 116.91, 116.72, 115.45, 113.83 (d, J = 21.6 Hz), 105.22, 55.91, 51.82.

Compounds **2-8 and 11-22** were made via an analogous procedure for the synthesis of Compound **1** utilizing appropriate starting materials. Characterization for these compounds is shown below in Table 1.

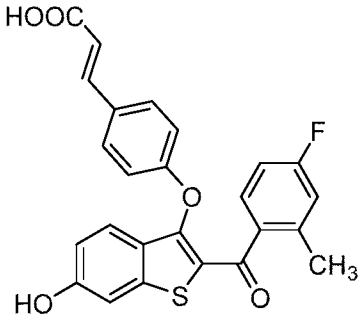
Compound 9: 5-((6-Hydroxy-2-(2-methylbenzoyl)benzo[*b*]thiophen-3-yl)oxy)-2-naphthoic acid

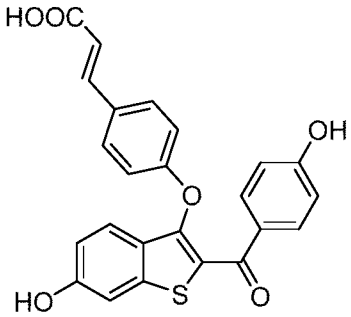
Compound **4** (100 mg, 0.21 mmol) was dissolved in 3 mL of anhydrous dichloromethane at room temperature under argon atomosphere. The solution was cooled using an ice water bath and BF_3•SMe_2 (1 ml, 4.2 mmol) was added dropwise. After stirring for 30 minutes, the solution was allowed to warm to 35 °C. The reaction mixture was stirred until starting material was consumed, as monitored by TLC, and then quenched by saturated $NaHCO_3$/ice water. The reaction mixture was extracted with ethyl acetate and washed with brine. The organic extracts were combined, dried over anhydrous Na_2SO_4, concentrated in vacumn, and purified by flash chromatography (5%-60% ethyl acetate in hexane) to afford 37 mg white powder (38%). ^{1}H NMR (400 MHz, MeOD) δ 8.47 (s, 1H), 7.93 (d, J = 8.4 Hz, 1H), 7.72 (d, J = 8.9 Hz, 1H), 7.56 (d, J = 8.4 Hz, 1H), 7.40 (d, J = 8.8 Hz, 1H), 7.30 (d, J = 1.9 Hz, 1H), 7.28 – 7.08 (m, 2H), 7.01 (t, J = 7.4 Hz, 1H), 6.94 (d, J = 7.6 Hz, 1H), 6.88 (dd, J = 8.8, 2.1 Hz, 1H), 6.79 (s, 1H), 6.74 (dd, J = 8.9, 2.4 Hz, 1H), 1.95 (s, 3H). ^{13}C NMR (100 MHz, MeOD) δ 192.50, 169.84, 160.87, 159.24, 150.50, 143.78, 140.65, 137.54, 136.54, 132.21, 131.70, 131.42, 131.18, 130.09, 128.34, 128.08, 127.69, 127.38, 127.05, 126.27, 125.78, 118.69, 117.51, 110.58, 108.92, 19.19. ESI-HRMS (m/z): $[M + H]^+$ calcd. for $C_{27}H_{18}O_5S$: 455.0953; observed, 455.0939.

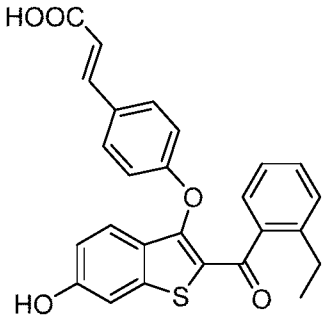
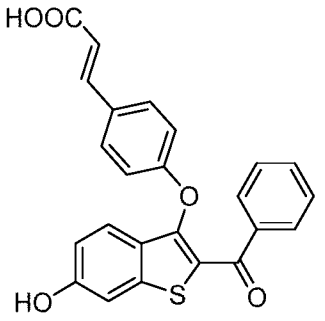
Compound 10: 8-((6-Hydroxy-2-(2-methylbenzoyl)benzo[b]thiophen-3-yl)oxy)quinoline-3-carboxylic acid

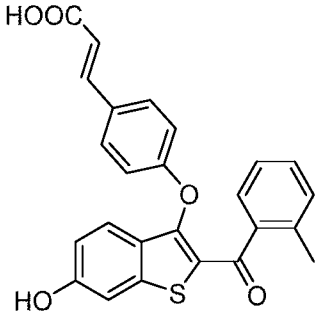
Compound **24** was prepared following the procedure for the synthesis of Compound **9** to afford 33 mg (57%).^{1}H NMR (400 MHz, MeOD) δ 9.20 (s, 1H), 8.85 (s, 1H), 7.83 (d, J = 9.0 Hz, 1H), 7.44 (d, J = 8.8 Hz, 1H), 7.31 (s, 1H), 7.27 – 7.13 (m, 2H), 7.04 – 6.81 (m, 5H), 1.97 (s, 3H). ^{13}C NMR (100 MHz, MeOD with TFA vapor) δ 192.08, 165.75, 162.47, 161.00, 151.79, 151.11, 149.43, 143.78, 140.53, 140.32, 136.47, 132.26, 131.43, 131.32, 128.29, 127.90, 126.64, 126.32, 125.56, 124.53, 119.98, 117.75, 110.96, 108.96, 19.21. ESI-HRMS (m/z): $[M + H]^+$ calcd. for $C_{26}H_{17}NO_5S$: 456.0906; observed, 456.0893.

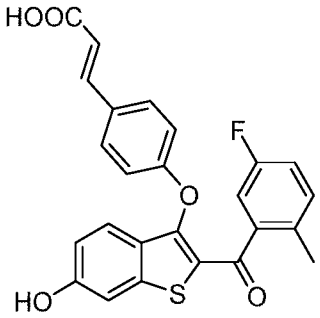
Table 1. Characterization and Biological Data of Compounds 1 – 24

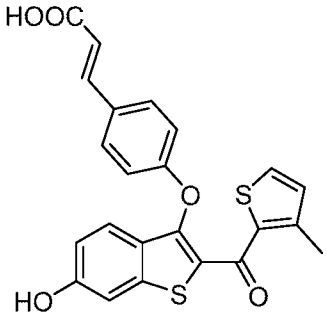
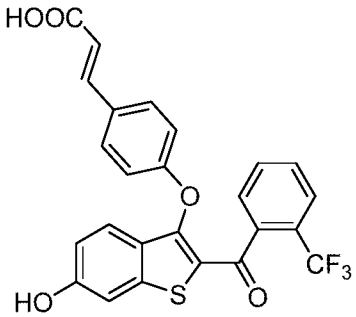
Cmpd #	Structure	Name/Physical Data	MCF-7:5C IC_{50} (nM)	MCF-7WS8 IC_{50} (nM)
1		^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, J = 16.0 Hz, 1H), 7.37 (d, J = 9.0 Hz, 1H), 7.28 (t, J = 8.8 Hz, 3H), 7.20 (dd, J = 8.5, 5.9 Hz, 1H), 7.00 (dd, J = 8.6, 2.3 Hz, 1H), 6.93 (dd, J = 9.0, 2.2 Hz, 1H), 6.81 (td, J = 8.3, 2.4 Hz, 1H), 6.55 (d, J = 8.7 Hz, 2H), 6.29 (d, J = 16.0 Hz, 1H), 3.91 (s, 3H), 3.79 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.10, 167.53, 163.16 (d, J = 253.1 Hz), 161.27, 159.30, 148.85, 143.81, 142.73, 135.48 (d, J = 3.7 Hz), 132.49 (d, J = 10.6 Hz), 129.79 (d, J = 9.3 Hz), 129.56, 129.36, 127.18, 126.36, 124.83, 117.18 (d,	1.0 +/- 0.05	0.4 +/- 0.07

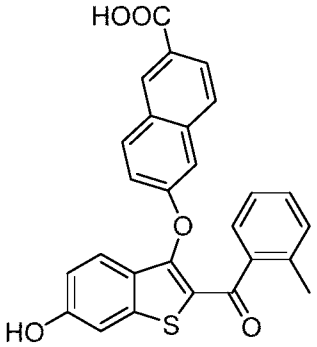
Cmpd #	Structure	Name/Physical Data	MCF-7:5C IC_{50} (nM)	MCF-7WS8 IC_{50} (nM)
		J = 24.9 Hz), 116.91, 116.72, 115.45, 113.83 (d, *J* = 21.6 Hz), 105.22, 55.91, 51.82.		
2		(*E*)-3-(4-((6-Hydroxy-2-(4-hydroxybenzoyl) benzo[b]thiophen-3-yl)oxy)phenyl) acrylic acid ^{1}H NMR (400 MHz, MeOD) δ 7.61 (d, *J* = 8.7 Hz, 2H), 7.55 (d, *J* = 16.0 Hz, 1H), 7.43 (d, *J* = 8.8 Hz, 1H), 7.39 (d, *J* = 8.7 Hz, 2H), 7.26 (d, *J* = 2.1 Hz, 1H), 6.92 (dd, *J* = 8.8, 2.1 Hz, 1H), 6.74 (d, *J* = 8.7 Hz, 2H), 6.67 (d, *J* = 8.7 Hz, 2H), 6.31 (d, *J* = 16.0 Hz, 1H). ^{13}C NMR (100 MHz, MeOD) δ 189.36, 170.39, 163.61, 161.20, 160.04, 148.16, 145.39, 142.57, 132.95, 130.77, 130.74, 130.42, 126.91, 125.84, 125.15, 118.03, 117.20, 117.05, 115.87, 108.68. 24	3.9 +/- 0.06 (54% Emax)	No Inhiibition

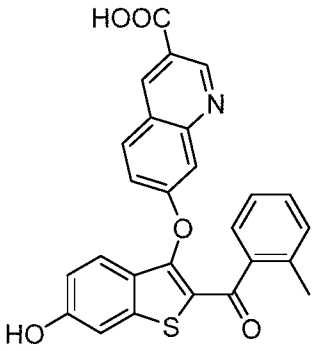
Cmpd #	Structure	Name/Physical Data	MCF-7:5C IC_{50} (nM)	MCF-7WS8 IC_{50} (nM)
3		(*E*)-3-(4-((2-(2-Ethylbenzoyl)-6-hydroxybenzo[b]thiophen-3-yl)oxy)phenyl) acrylic acid ^{1}H NMR (400 MHz, MeOD) δ 7.55 (d, *J* = 16.0 Hz, 1H), 7.42 – 7.26 (m, 5H), 7.24 (d, *J* = 7.6 Hz, 1H), 7.15 (d, *J* = 7.7 Hz, 1H), 7.07 (t, *J* = 7.5 Hz, 1H), 6.88 (dd, *J* = 8.8, 2.1 Hz, 1H), 6.47 (d, *J* = 8.7 Hz, 2H), 6.32 (d, *J* = 16.0 Hz, 1H), 2.47 (q, *J* = 7.6 Hz, 2H), 1.02 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (101 MHz, MeOD) δ 192.52, 170.42, 160.94, 160.82, 150.26, 145.35, 143.68, 142.88, 140.37, 131.31, 130.64, 130.43, 129.91, 128.29, 127.98, 126.92, 126.31, 125.81, 118.08, 117.47, 116.67, 108.91, 27.10, 15.95.	1.2 +/- 0.04	0.9 +/- 0.04
4		(*E*)-3-(4-((2-Benzoyl-6-hydroxybenzo[b]thiophen-3-yl)oxy)phenyl) acrylic acid ^{1}H NMR (400 MHz, MeOD) δ 7.66 – 7.58 (m, 2H), 7.55 (d, *J* = 16.0 Hz, 1H), 7.50 (d, *J* = 7.4 Hz, 1H), 7.43-7.34 (m, 5H), 7.28 (d, *J* = 2.0 Hz, 1H), 6.92 (dd, *J* = 8.8, 2.1 Hz,	13 +/- 0.08	2.2 +/- 0.1

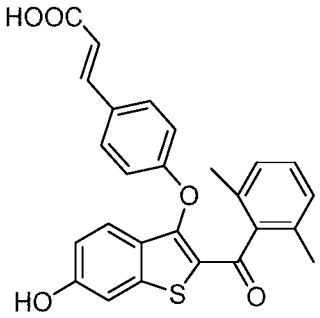
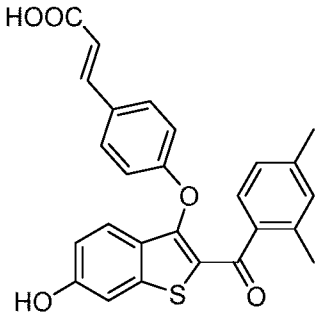
Cmpd #	Structure	Name/Physical Data	MCF-7:5C IC_{50} (nM)	MCF-7WS8 IC_{50} (nM)
		1H), 6.61 (d, *J* = 8.8 Hz, 2H), 6.32 (d, *J* = 16.0 Hz, 1H). ^{13}C NMR (100 MHz, MeOD) δ 190.76, 170.39, 161.08, 160.51, 149.38, 145.33, 143.23, 139.90, 133.38, 130.77, 130.47, 129.70, 129.13, 126.82, 125.95, 125.55, 118.13, 117.38, 116.96, 108.75		
5		(*E*)-3-(4-((6-Hydroxy-2-(2-methylbenzoyl)benzo[b]thiophen-3-yl)oxy)phenyl) acrylic acid ^{1}H NMR (400 MHz, MeOD) δ 7.54 (d, *J* = 16.0 Hz, 1H), 7.32 (dd, *J* = 8.7, 6.0 Hz, 3H), 7.28 – 7.2 (m, 3H), 7.06 – 7.03 (m, 2H), 6.87 (dd, *J* = 8.8, 2.0 Hz, 1H), 6.44 (d, *J* = 8.7 Hz, 2H), 6.30 (d, *J* = 16.0 Hz, 1H), 2.07 (s, 3H). ^{13}C NMR (100 MHz, MeOD) δ 192.43, 170.39, 161.05, 160.78, 150.29, 145.35, 143.66, 140.66, 136.53, 131.49, 131.22, 130.61, 130.37, 128.35, 127.64, 126.93, 126.29, 125.73, 118.02, 117.47, 116.54, 108.90, 19.32.	1.3 +/- .06	0.9 +/- .09

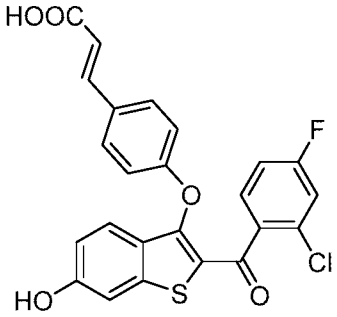
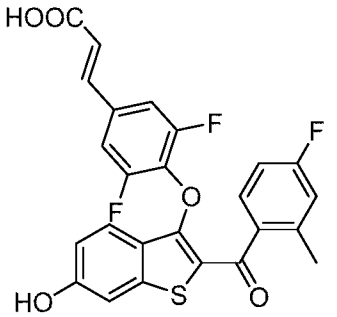
Cmpd #	Structure	Name/Physical Data	MCF-7:5C IC_{50} (nM)	MCF-7WS8 IC_{50} (nM)
6		(*E*)-3-(4-((2-(5-Fluoro-2-methylbenzoyl)-6-hydroxybenzo[b]thiophen-3-yl)oxy)phenyl) acrylic acid ^{1}H NMR (400 MHz, MeOD) δ 7.56 (d, *J* = 16.0 Hz, 1H), 7.41-7.34 (m, 3H), 7.27 (d, *J* = 2.0 Hz, 1H), 7.10-7.06 (m, 1H), 7.02 – 6.93 (m, 2H), 6.89 (dd, *J* = 8.9, 2.1 Hz, 1H), 6.53 (d, *J* = 8.8 Hz, 2H), 6.33 (d, *J* = 16.0 Hz, 1H), 2.08 (s, 3H). ^{13}C NMR (100 MHz, MeOD) δ 190.69, 170.37, 161.92 (d, *J* = 244.8 Hz), 161.03, 160.90, 150.60, 145.27, 143.95, 142.21 (d, *J* = 6.5 Hz), 133.18 (d, *J* = 7.5 Hz), 132.15 (d, *J* = 3.4 Hz), 130.74, 130.62, 127.31, 126.78, 125.88, 118.21, 117.63 (d, *J* = 21.3Hz), 117.59, 116.48, 114.82 (d, *J* = 23.3 Hz), 108.93, 18.48.	4.7 +/- 0.04	0.7 +/- 0.3

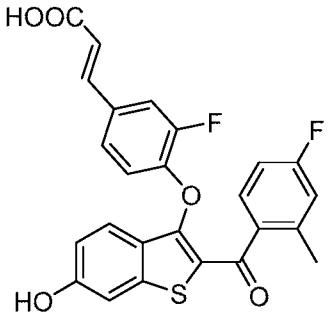
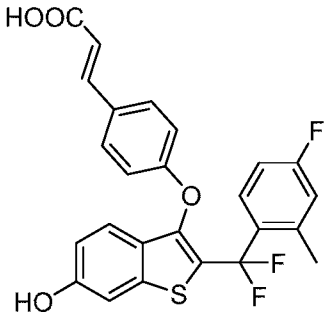
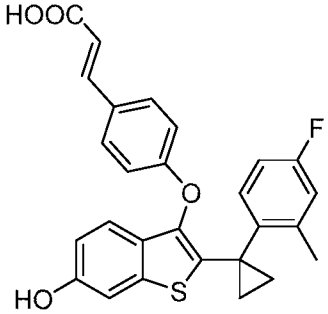
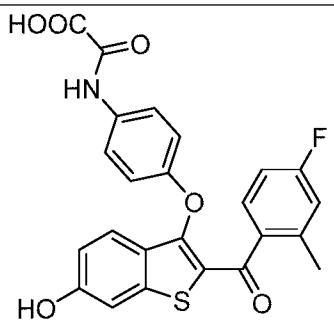
Cmpd #	Structure	Name/Physical Data	MCF-7:5C IC_{50} (nM)	MCF-7WS8 IC_{50} (nM)
7		(*E*)-3-(4-((6-Hydroxy-2-(3-methylthiophene-2-carbonyl)benzo[b]thiophen-3-yl)oxy)phenyl) acrylic acid ^{1}H NMR (400 MHz, MeOD) δ 7.59 – 7.51 (m, 2H), 7.49 (d, *J* = 8.8 Hz, 1H), 7.40 (d, *J* = 8.7 Hz, 2H), 7.26 (d, *J* = 2.1 Hz, 1H), 6.93 (dd, *J* = 8.8, 2.1 Hz, 1H), 6.90 (d, *J* = 4.9 Hz, 1H), 6.70 (d, *J* = 8.7 Hz, 2H), 6.32 (d, *J* = 16.0 Hz, 1H), 2.23 (s, 3H). ^{13}C NMR (100 MHz, MeOD) δ 182.84, 170.46, 161.42, 160.27, 148.95, 145.51, 145.27, 142.41, 136.91, 132.55, 132.20, 130.78, 130.65, 126.84, 125.52, 125.14, 118.24, 117.38, 117.08, 108.63, 15.66.	12.5 +/- 0.01	2.8 +/- 0.16
8		(*E*)-3-(4-((6-Hydroxy-2-(2-(trifluoromethyl)benzoyl)benzo[b]thiophen-3-yl)oxy)phenyl) acrylic acid ^{1}H NMR (400 MHz, Acetone) δ 7.69 (d, *J* = 7.9 Hz, 1H), 7.62 – 7.53 (m, 2H), 7.53 – 7.46 (m, 4H), 7.45 (d, *J* = 1.9 Hz, 1H), 7.31 (d, *J*	2.7 +/- 0.11 (61% Emax)	1.2 +/- 0.08 (65% Emax)

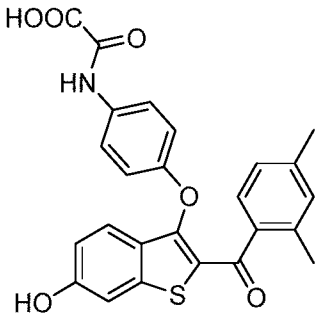
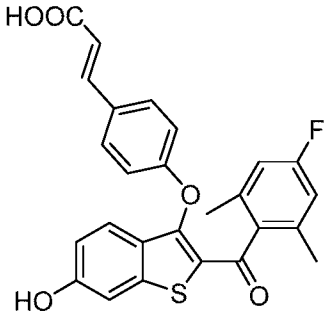
Cmpd #	Structure	Name/Physical Data	MCF-7:5C IC_{50} (nM)	MCF-7WS8 IC_{50} (nM)
		= 8.8 Hz, 1H), 6.97 (dd, *J* = 8.9, 2.1 Hz, 1H), 6.57 (d, *J* = 8.8 Hz, 2H), 6.39 (d, *J* = 16.0 Hz, 1H). ^{13}C NMR (100 MHz, Acetone) ^{13}C NMR (101 MHz, $CDCl_3$) δ 187.60, 167.78, 160.17, 159.68, 149.95, 144.51, 143.23, 139.58, 132.63, 130.73, 130.49, 130.33, 128.38, 127.45, 127.24 (q, *J* = 31.9 Hz), 127.11 (q, *J* = 4.6 Hz), 126.14, 125.91, 124.85 (q, *J* = 273.3 Hz), 118.10, 117.32, 116.51, 109.12.		
9		^{1}H NMR (400 MHz, MeOD) δ 8.47 (s, 1H), 7.93 (d, *J* = 8.4 Hz, 1H), 7.72 (d, *J* = 8.9 Hz, 1H), 7.56 (d, *J* = 8.4 Hz, 1H), 7.40 (d, *J* = 8.8 Hz, 1H), 7.30 (d, *J* = 1.9 Hz, 1H), 7.28 – 7.08 (m, 2H), 7.01 (t, *J* = 7.4 Hz, 1H), 6.94 (d, *J* = 7.6 Hz, 1H), 6.88 (dd, *J* = 8.8, 2.1 Hz, 1H), 6.79 (s, 1H), 6.74 (dd, *J* = 8.9, 2.4 Hz, 1H), 1.95 (s, 3H). ^{13}C NMR (100 MHz, MeOD) δ 192.50, 169.84, 160.87, 159.24, 150.50, 143.78, 140.65, 137.54, 136.54, 132.21, 131.70, 131.42, 131.18, 130.09, 128.34,	4.8 +/- 0.06	2.4 +/- 0.12

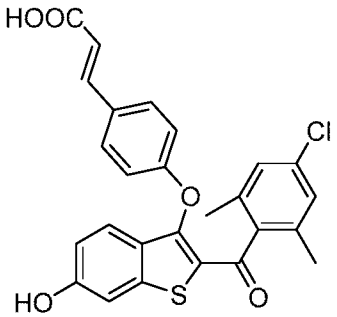
Cmpd #	Structure	Name/Physical Data	MCF-7:5C IC_{50} (nM)	MCF-7WS8 IC_{50} (nM)
		128.08, 127.69, 127.38, 127.05, 126.27, 125.78, 118.69, 117.51, 110.58, 108.92, 19.19. ESI-HRMS (m/z): $[M + H]^+$ calcd. for $C_{27}H_{18}O_5S$: 455.0953; observed, 455.0939.		
10		^{1}H NMR (400 MHz, MeOD) δ 9.20 (s, 1H), 8.85 (s, 1H), 7.83 (d, *J* = 9.0 Hz, 1H), 7.44 (d, *J* = 8.8 Hz, 1H), 7.31 (s, 1H), 7.27 – 7.13 (m, 2H), 7.04 – 6.81 (m, 5H), 1.97 (s, 3H). ^{13}C NMR (100 MHz, MeOD with TFA vapor) δ 192.08, 165.75, 162.47, 161.00, 151.79, 151.11, 149.43, 143.78, 140.53, 140.32, 136.47, 132.26, 131.43, 131.32, 128.29, 127.90, 126.64, 126.32, 125.56, 124.53, 119.98, 117.75, 110.96, 108.96, 19.21. ESI-HRMS (m/z): $[M + H]^+$ calcd. for $C_{26}H_{17}NO_5S$: 456.0906; observed, 456.0893	32.3 +/- 0.19 (52% Emax)	No Inhibition

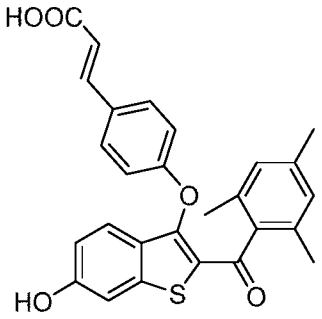
Cmpd #	Structure	Name/Physical Data	MCF-7:5C IC_{50} (nM)	MCF-7WS8 IC_{50} (nM)
11		(*E*)-3-(4-((2-(2,6-Dimethylbenzoyl)-6-hydroxybenzo[b]thiophen-3-yl)oxy)phenyl) acrylic acid ^{1}H NMR (400 MHz, MeOD) δ 7.55 (d, *J* = 16.0 Hz, 1H), 7.32 (d, *J* = 8.7 Hz, 2H), 7.27 – 7.19 (m, 2H), 7.01 (t, *J* = 7.6 Hz, 1H), 6.87 – 6.77 (m, 3H), 6.43 (d, *J* = 8.6 Hz, 2H), 6.31 (d, *J* = 16.0 Hz, 1H), 2.04 (s, 6H). ^{13}C NMR (100 MHz, MeOD) δ 194.06, 170.40, 160.93, 160.50, 150.47, 145.38, 143.86, 141.47, 134.76, 130.48, 130.35, 129.90, 128.44, 126.74, 125.99, 117.97, 117.55, 116.38, 109.04, 19.35.	0.5 +/- 0.04	0.1 +/- 0.07
12		(*E*)-3-(4-((2-(2,4-Dimethylbenzoyl)-6-hydroxybenzo[b]thiophen-3-yl)oxy)phenyl) acrylic acid ^{1}H NMR (400 MHz, Acetone) δ 7.58 (d, *J* = 16.0 Hz, 1H), 7.50 – 7.38 (m, 4H), 7.25 (d, *J* = 7.7 Hz, 1H), 7.01 (dd, *J* = 8.8, 2.1 Hz, 1H)), 6.96 – 6.86 (m, 2H), 6.57 (d, *J* = 8.7 Hz, 2H), 6.38 (d, *J* = 16.0 Hz,	0.4 +/- 0.04	0.1 +/- 0.08

Cmpd #	Structure	Name/Physical Data	MCF-7:5C IC_{50} (nM)	MCF-7WS8 IC_{50} (nM)
		1H), 2.29 (s, 3H), 2.07 (s, 3H). ^{13}C NMR (100 MHz, Acetone) δ 190.44, 167.80, 160.72, 159.80, 148.66, 144.67, 142.52, 141.14, 137.47, 136.47, 131.96, 130.35, 130.01, 128.72, 127.86, 126.99, 126.55, 125.39, 117.81, 117.15, 116.34, 108.90, 21.31, 19.33.		
13		(*E*)-3-(4-((2-(2-Chloro-4-fluorobenzoyl)-6-hydroxybenzo[b]thiophen-3-yl)oxy)phenyl) acrylic acid LC-MS M/Z $(M-H)^-$: 467.9	2.2 +/- 0.12	0.4 +/- 0.13
14		(*E*)-3-(3,5-Difluoro-4-((2-(4-fluoro-2-methylbenzoyl)-6-hydroxybenzo[b]thiophen-3-yl)oxy)phenyl) acrylic acid LC-MS M/Z $(M-H)^-$: 483.4	>10	>10

Cmpd #	Structure	Name/Physical Data	MCF-7:5C IC_{50} (nM)	MCF-7WS8 IC_{50} (nM)
15		(*E*)-3-(3-Fluoro-4-((2-(4-fluoro-2-methylbenzoyl)-6-hydroxybenzo[b]thiophen-3-yl)oxy)phenyl) acrylic acid LC-MS M/Z $(M-H)^-$: 465.4	<10	<10
16		(*E*)-3-(4-((2-(Difluoro(4-fluoro-2-methylphenyl)methyl)-6-hydroxybenzo[b]thiophen-3-yl)oxy)phenyl)acrylic acid LC-MS M/Z $(M-H)^-$: 469.5	<100	<100
17		(*E*)-3-(4-((2-(1-(4-Fluoro-2-methylphenyl)cyclopropyl)-6-hydroxybenzo[b]thiophen-3-yl)oxy)phenyl) acrylic acid LC-MS M/Z $(M-H)^-$: 459.5	<100	<100
18		2-((4-((2-(4-Fluoro-2-methylbenzoyl)-6-hydroxybenzo[b]thiophen-3-yl)oxy)phenyl) amino)-2-oxoacetic acid ^{1}H NMR (400 MHz, MeOD) δ 7.46 (d, *J* = 8.3 Hz, 2H), 7.38 – 7.27 (m,	1.7 +/- 0.07 (64% Emax)	No Inhibition

Cmpd #	Structure	Name/Physical Data	MCF-7:5C IC_{50} (nM)	MCF-7WS8 IC_{50} (nM)
		2H), 7.24 (s, 1H), 6.90 – 6.77 (m, 3H), 6.46 (d, *J* = 8.2 Hz, 2H), 2.11 (s, 3H). ^{13}C NMR (100 MHz, MeOD) δ 191.26, 164.87 (d, *J* = 248.6 Hz), 160.76, 156.78, 150.82, 143.70, 140.40 (d, *J* = 8.6 Hz), 136.90, 136.87, 133.35, 131.10 (d, *J* = 9.1 Hz), 127.30, 127.03, 125.84, 123.09, 118.11 (d, *J* = 21.7 Hz), 117.38, 116.16, 113.05 (d, *J* = 21.9 Hz), 108.85, 19.46.		
19		2-((4-((2-(2,4-Dimethylbenzoyl)-6-hydroxybenzo[b]thiophen-3-yl)oxy)phenyl) amino)-2-oxoacetic acid LC-MS M/Z $(M-H)^-$: 460.1	>10	No inhibition
20		(*E*)-3-(4-((2-(4-Fluoro-2,6-dimethylbenzoyl)-6-hydroxybenzo[b]thiophen-3-yl)oxy)phenyl) acrylic acid ^{1}H NMR (400 MHz, Acetone-*d6*) δ 7.60 (d, *J* = 16.0 Hz, 1H), 7.51 (d, *J* = 8.7 Hz, 2H), 7.44 (d, *J* = 1.7 Hz, 1H), 7.37 (d, *J* = 8.8 Hz, 1H), 6.99	0.4 +/- 0.03	<0.1

Cmpd #	Structure	Name/Physical Data	MCF-7:5C IC_{50} (nM)	MCF-7WS8 IC_{50} (nM)
		(dd, *J* = 8.8, 1.9 Hz, 1H), 6.66 (d, *J* = 9.8 Hz, 2H), 6.60 (d, *J* = 8.6 Hz, 2H), 6.40 (d, *J* = 16.0 Hz, 1H), 2.10 (s, 6H). ^{13}C NMR (100 MHz, Acetone-*d6*) δ 191.13, 167.89, 163.21 (d, *J* = 244.9 Hz), 160.08, 149.15, 144.65, 142.99, 137.66, 137.58 (d, *J* = 8.8 Hz), 130.34, 130.13, 128.63, 126.65, 125.79, 117.89, 117.34, 115.99, 114.64 (d, *J* = 21.5 Hz), 109.12, 19.34, 19.32.		
21		(*E*)-3-(4-((2-(4-Chloro-2,6-dimethylbenzoyl)-6-hydroxybenzo[b]thiophen-3-yl)oxy)phenyl) acrylic acid ^{1}H NMR (400 MHz, Acetone-*d6*) δ 7.60 (d, *J* = 16.0 Hz, 1H), 7.51 (d, *J* = 8.6 Hz, 2H), 7.45 (d, *J* = 1.7 Hz, 1H), 7.39 (d, *J* = 8.8 Hz, 1H), 7.00 (dd, *J* = 8.8, 1.9 Hz, 1H), 6.91 (s, 2H), 6.58 (d, *J* = 8.6 Hz, 2H), 6.40 (d, *J* = 16.0 Hz, 1H), 2.09 (s, 6H). ^{13}C NMR (100 MHz, Acetone-*d6*) δ 190.91, 167.77, 160.17, 160.00, 149.30, 144.62, 143.07, 139.99, 136.85, 134.53, 130.26, 130.17,	0.3 +/- 0.04	<0.1

Cmpd #	Structure	Name/Physical Data	MCF-7:5C IC_{50} (nM)	MCF-7WS8 IC_{50} (nM)
		128.40, 127.88, 126.67, 125.82, 117.94, 117.38, 115.91, 109.13, 19.12.		
22		(*E*)-3-(4-((6-Hydroxy-2-(2,4,6-trimethylbenzoyl)benzo[b]thiophen-3-yl)oxy)phenyl) acrylic acid ^{1}H NMR (400 MHz, MeOD) δ 7.55 (d, *J* = 15.9 Hz, 1H), 7.34 (d, *J* = 8.7 Hz, 2H), 7.29 (d, *J* = 8.9 Hz, 1H), 7.26 (d, *J* = 1.9 Hz, 1H), 6.86 (dd, *J* = 8.8, 2.1 Hz, 1H), 6.63 (s, 2H), 6.44 (d, *J* = 8.6 Hz, 2H), 6.32 (d, *J* = 15.9 Hz, 1H), 2.18 (s, 3H), 2.01 (s, 6H). ^{13}C NMR (100 MHz, MeOD) δ 194.48, 160.95, 160.62, 150.30, 145.28, 143.76, 139.89, 138.64, 134.74, 130.39, 130.27, 129.13, 128.72, 126.95, 125.91, 118.20, 117.55, 116.26, 109.00, 21.13, 19.30.	0.5 +/- 0.03	<0.1

Assays:

Cell viability of MCF7:WS8 and cell viability of MCF7:5C (tamoxifen resistant)

The DNA content of the cells was determined as previously described using a Fluorescent DNA Quantitation kit (cat. No. 170-2480; Bio-Rad Laboratories, Hercules, CA). Briefly, five thousand

cells were plated per well in 96-well plates, and treatment with indicated concentrations of compounds was started at the same time in each well. On day 4 or 6, for MCF7:WS8 or MCF7:5C respectively, the cells in the plates were lysed and frozen at -80 °C. To measure the total DNA in each well, the plates were allowed to warm to room temperature, incubated with Hoechst dye, and mixed well. The fluorescence was measured using a Synergy H4 Hybrid Multi-Mode Microplate Reader. For each analysis, six replicate wells were used and at least three independent experiments were performed.

Cell Viability of 3D spheroids

Spheroids were plated at a concentration of 1000 cells per well in Corning® 96-well clear black round-bottom ultra-low attachment spheroid microplate and allowed to grow in the absence of treatment for 48 hours. 100 µL media was removed from each well and 100 µL 2X concentration of the treatment was added. This procedure was repeated every 2-3 days for 12 days. Analysis occured on day 15 after plating. CellTiter-Glo® 3D Cell Viability Assay protocol was used to determine growth inhibition of the spheroids. The plates and reagent were allowed to warm to room temperature for 30 minutes. During this time, the spheroids were washed with PBS 2 times by removing 100 µL media and replacing with PBS. 100 µL from each well was then removed and replaced with 100 µL CellTiter-Glo® 3D reagent and spheroids were disrupted by pipetting. The plates were placed on a shaker for 5 minutes before allowing to equilibrate in the dark for 25 minutes. 125 µL from each well was then transferred to a white 96-well plate before recording luminescence.

Western blot:

Whole-cell extracts of cultured cells were prepared in lysis buffer (200 mmol/L Tris, 1% Triton X-100, 5 mmol/L EDTA) with protease and phosphatase inhibitor cocktails (1:50, both from Sigma-Aldrich) after scraping from the culture plates. Protein concentration was measured using the Bradford method (Bio-Rad). Proteins were separated under denaturing conditions and blotted onto nitrocellulose membrane (Bio-Rad) using a wet transfer system (Bio-Rad). Images of blots were acquired on a Bio-Rad ChemiDoc System following incubation with SuperSignal West Dura luminol solution (Thermo Fisher Scientific).

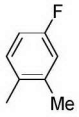
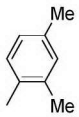
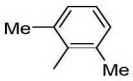
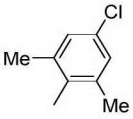
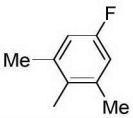
The results of the foregoing are shown in Figs. 1-4 and Table 2.

Table 2. IC_{50} of ER downregulation from in-cell western blot experiments

Compound	IC_{50} (nM)
1	0.7
3	1.2
4	5.0
5	1.1
6	1.1
7	4.6

A selection of compounds of the current invention were further characterized by their estrogen receptor degradation, estrogen receptor binding efficacy, and inhibition of 3D spheroid growth.

Table 3. ERα degradation, antagonism of E_2 signaling, ERα relative binding affinity, and inhibition of growth of ER+ cells cultured in 3D spheroids

Compounds	R_1	ERα ICW EC_{50} (nM)[a]	ERE luciferase IC_{50} (nM)[b]	% growth of MCF-7:ws8 3D spheroids (rel. to vehicle)[c]	ERα binding *Ki* (nM)[d]	RBA % (relative to E_2)[e]
GDN-0810		0.8 ± 0.07	11.1 ± 0.14	15 ± 3.00	0.37 ± 0.1	53.4 ± 15.0
5		1.1 ± 0.05	16.7 ± 0.07	12 ± 0.02	1.29 ± 0.4	15.5 ± 4.2
1		0.71 ± 0.05	8.8 ± 0.11	3.3 ± 0.01	0.65 ± 0.2	30.6 ± 8.7
12		0.92 ± 0.05	4.5 ± 0.07	12 ± 0.01	0.50 ± 0.1	40.3 ± 4.8
11		0.65 ± 0.06	4.2 ± 0.05	14 ± 1.00	2.0 ± 0.2	9.8 ± 0.7
21		0.07 ± 0.13	2.4 ± 0.10	1.3 ± 0.01	0.57 ± 0.1	34.8 ± 6.2
20		0.24 ± 0.16	3.1 ± 0.07	2.1 ± 0.01	0.73 ± 0.2	27.5 ± 7.0

[a]Potency for induction of ER degradation measured at 10 concentrations using in-cell westerns (ICW). [b]Potency of antagonism of ERE-luciferase reporter. [c]Spheroid growth inhibition after SERD treatment (100 nM) expressed as % of growth of DMSO vehicle control. Data show mean and s.e.m. [d]Binding affinities calculated by the formula: *Ki* = (*Kd*[estradiol]/RBA)*100, where the *Kd* for estradiol is 0.2 nM. [e]Relative binding affinity (RBA) values, determined by radioligand displacement assays expressed as IC_{50} estradiol/IC_{50} compound × 100 (RBA, estradiol = 100%).

Mouse PK and animal data

The plasma concentrations of Compounds **1**, **5**, **11**, **12**, **20**, and **21**, at 0.5 hours and 4 hours (100 mg/kg in a 0.5% CMC suspension p.o.) were measured to select a BT-SERD for study in an

ectopic xenograft mouse model of endocrine-resistant ER+ breast cancer (Table 4). The oral bioavailability of Compounds **20** and **21** were further studied by measuring plasma concentrations at multiple time points. The MCF-7:TAM1 xenograft model was allowed to proceed for 5.5 weeks prior to treatment and was randomized to six treatment groups with an average tumor area of 0.325 cm^2. Tamoxifen (100 mg/kg) was entirely without effect, demonstrating the anticipated resistance of this tumorigenic TR breast cancer cell line to tamoxifen. GDN-0810 at a dose of 100 mg/kg, used previously in the literature, caused regression of tumor size by 21% at day 23 after treatment. Compound **12** (100 mg/kg) also caused tumor regression similar to GDN-0810 (26.7% in tumor area reduction at day 20), whereas Compound **21** showed the best efficacy in tumor regression (49% reduction) at a dose of 100 mg/kg. Regression was dose-dependent for Compound **21**: at 30 mg/kg average tumor area was reduced 27%. Injection of tumorigenic cells into mammary fat pads of nude mice produces distinct mammary tumors allowing assessment of individual tumor response, again demonstrating the efficacy of SERD Compound **21**. No weight loss was observed during the course of the animal study.

Table 4. **Plasma concentration of benzothiophene analogs after oral administration**

Compound/Time	**1** (nM)	**11** (nM)	**12** (nM)	**5** (nM)	**21** (nM)	**20** (nM)
0.5 h	1238	1006	3874	5575	10183	9723
4 h	145	0.5	432	47	858	164

[a]All compounds administered by oral gavage at 100 mg/kg in PEG400/PVP/TW80/CMC in water, 9:0.5:0.5:90. Data was the average plasma concentration of three mice at 0.5 h and 4 h.

Animal Experiments

MCF-7:Tam1 tumors were grown in 4–6 week old ovariectomized athymic nude mice (Harlan Laboratories) and E2 was administered via silastic capsules (1.0 cm) implanted subcutaneously between the scapulae as previously described. The compound was administered at a dose of 100 mg/kg or 30 mg/kg daily for 3.5 weeks in a formulation of 0.5% CMC: PEG-400: Tween-80: PVP (90: 9: 05: 0.5) solution. Tumor cross-sectional area was determined weekly using Vernier calipers and calculated using the formula (length/2) × (width/2) × π. Mean tumor area was plotted against time (in weeks) to monitor tumor growth.

Cell Lines and Culture Conditions

MCF-7:WS8 is hormone-dependent human breast cancer cell clones maintained in phenol red containing RPMI-1640 medium supplemented with 10% FBS at 37 °C, 5% CO_2 that have been previously described. MCF-7:5C cells were maintained in phenol-red free RPMI 1640 medium supplemented with 10% charcoal-dextran treated fetal bovine serum at 37 °C, 5% CO_2 as previously described. The MCF-7:5C cells served as AI resistant cells and were generated from MCF-7:WS8 cells by long-term estrogen deprivation.

Cell Growth Assay

Cells were grown in phenol red-free media for 2 days prior to each experiment. On the day of the experiment, cells were seeded in 96-well plate at a density of 5000 cells/well and treated with either 0.1% (v/v) DMSO, 1nM E_2, or compounds prepared in phenol red free media. All compounds were dissolved in DMSO and added to the medium at a final 1:1000 dilution. DNA content was determined on Day 5 (WS8) or Day 6 (5C) by Hoechst 33258 dye. Fluorescence signals were read by the Synergy H4 (BioTek).

In-cell Western Analysis

MCF-7:WS8 cells were kept in stripped medium 2 days, and 2.0 x 104/well of the cells were plated in clear bottom 96-well black plates for 48 hours prior to addition of compounds for 24 hours. Fixation, detection of ESR1 (sc-8002) and analysis were performed per LI-COR manufacturer's protocol using the In-Cell Western™ Assay Kits and LI-COR ODYSSEY infra-red imaging system. Data was normalized to CellTag 700 stain.

3D-spheroid growth assay

Spheroids were plated at 1000 cells/well in Corning® 96-well black clear round-bottom, ultra-low attachment spheroid microplates and grown in the absence of treatment for 24 hours. Spheroids were then treated with 2X treatment media following the removal of 100 µL media from each well. Treatment was repeated every 2-3 days for 14 days. CellTiter-Glo® 3D Cell Viability Assay protocol was used to determine growth inhibition of the spheroids. On day 15, spheroid

plates and reagent (CellTiter-Glo® 3D Reagent) were allowed to come to room temperature for 30 minutes. During this time, the spheroids were washed with PBS by removing 100 µL media and replacing with PBS. 100 µL from each well was then removed and replaced with 100 µL of the reagent and spheroids were disrupted by pipetting. The plates were then placed on a shaker for 5 minutes before equilibrating in dark for 25 minutes. 125 µL from each well was then transferred to a white 96-well plate before recording luminescence using an empty well for the background reading.

Binding affinity studies

Binding affinities were also determined by a competitive radiometric binding assay using 2 nM [^{3}H]estradiol as tracer (PerkinElmer, Waltham, MA) and full-length purified human ERα (Pan Vera/Invitrogen, Carlsbad, CA), as reported previously. The RBA values were calculated using the following equation: IC_{50} estradiol/IC_{50} compound × 100.

Estrogen Response Elements (ERE) Luciferase Assay in MCF-7 Cells.

MCF-7:WS8 cells were kept in stripped medium 3 days prior to treatment. Cells were plated at a density of 2×10^4 cells/well in 96-well plates and were co-transfected with 5 µg of the pERE-luciferase plasmid per plate, which contained three copies of the *Xenopus laevis* vitellogenin A2 ERE upstream of firefly luciferase and 0.5 µg of pRL-TK plasmid (Promega, Madison, WI) containing a cDNA encoding Renilla luciferase. Transfection was performed for 6 hours using the Lipofectamine 2000 transfection reagent (Invitrogen) in Opti-MEM medium according to the manufacturer's instructions. Cells were treated with test compounds after 6 hours, and the luciferase activity was measured after 18 hours of treatment using the dual luciferase assay system (Promega) with Synergy H4 (Bio Tek).

This specification has been described with reference to embodiments of the invention. However, one of ordinary skill in the art will appreciate that various modifications and changes can be made without departing from the scope of the invention as set forth in the claims below. While only certain representative materials, methods, and aspects of these materials and methods are specifically described, other materials and methods and combinations of various features of the materials and methods are intended to fall within the scope of the appended claims, as if specifically recited. Accordingly, the specification is to be regarded in an illustrative rather than a

restrictive sense, and all such modifications are intended to be included within the scope of invention.

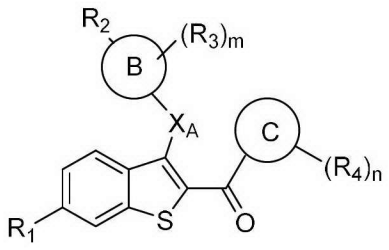
The reference in this specification to any prior publication (or information derived from it), or to any matter which is known, is not, and should not be taken as an acknowledgment or admission or any form of suggestion that that prior publication (or information derived from it) or known matter forms part of the common general knowledge in the field of endeavour to which this specification relates.

Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" and "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

2016366680 19 May 2021

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A compound or a pharmaceutically acceptable salt thereof of formula:



wherein:

m is 0, 1, 2, 3, or 4;

n is 0, 1, 2, 3, or 4;

X_A is -O--;

Ring B is phenyl, naphthyl, quinolinyl, 5- or 6- membered monocyclic heteroaryl or 7-, 8-, 9- or 10 membered bicyclic heterocyclyl;

Ring C is phenyl, thiophenyl, 5- or 6- membered monocyclic heteroaryl or 7-, 8-, 9- or 10-membered bicyclic heterocyclyl;

R_1 is selected from hydroxyl, hydrogen, halogen, –O(C_1-C_6 alkyl), –OC(O)(C_1-C_6 alkyl), –OC(O)C_6H_5, –OC(O)O(C_1-C_6 alkyl), –OC(O)OC_6H_5 and –OSO_2(C_2-C_6 alkyl);

R_2 is selected from –CH=CHCOOH, –NH(CO)COOH, –COOH, C_2-C_6alkenylene-COOH and C_2-C_6alkynylene-COOH;

R_3 is independently selected at each occurrence from hydrogen, halogen, –CN, –NO_2, C_1-C_6alkyl and C_1-C_6fluoroalkyl; and

R_4 is independently selected at each occurrence from hydrogen, halogen, hydroxyl, C_1-C_6alkyl, C_1-C_6fluoroalkyl, –CN, –O(C_1-C_6 alkyl), and –O(C_1-C_6fluoroalkyl).

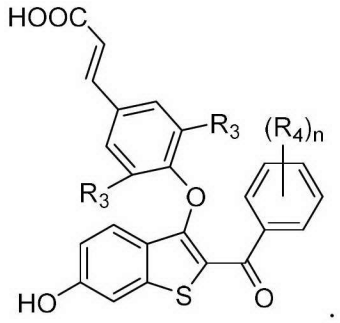
2. The compound of any one of claims 1wherein R_1 is selected from hydroxyl and -O(C_1-C_6 alkyl).

3. The compound of any one of claim 2, wherein R_2 is selected from –COOH, -NH(CO)COOH and –CH=CHCOOH.

4. The compound of claim 3, wherein Ring B is phenyl, naphthyl or quinolinyl and Ring C is phenyl or a 5- or 6-membered monocyclic heteroaryl wherein the 5- or 6-membered monocyclic heteroaryl is thienyl.

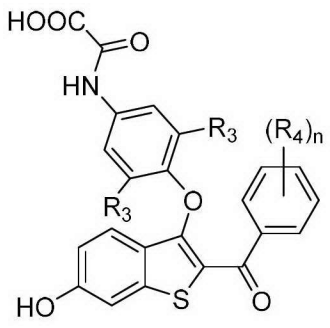
5. The compound of any one of claims 1 to 4, wherein m is 0.

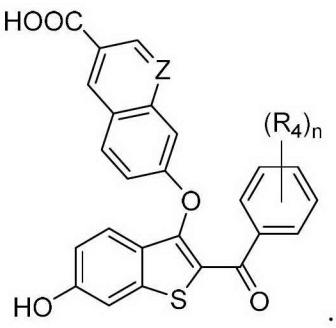
6. The compound of claim 1, or a pharmaceutically acceptable salt thereof, of Formula:



.

7. The compound of claim 1, or a pharmaceutically acceptable salt thereof, of Formula:



or


.

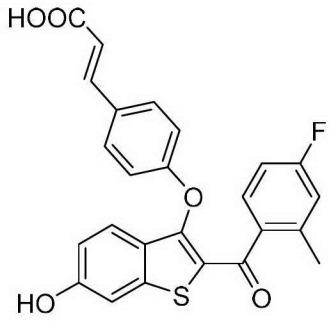
8. The compound of any one of claims 1 to 7, wherein R_3 is independently selected at each occurrence from hydrogen, halogen, and C_1-C_6alkyl.

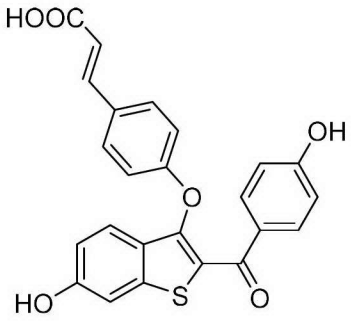
9. The compound of any one of claims 1 to 8, wherein C_1-C_6alkyl is methyl.

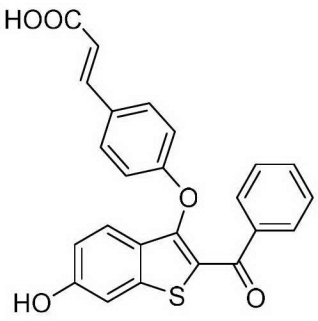
10. The compound of any one of claims 1 to 9, wherein halogen is fluoro.

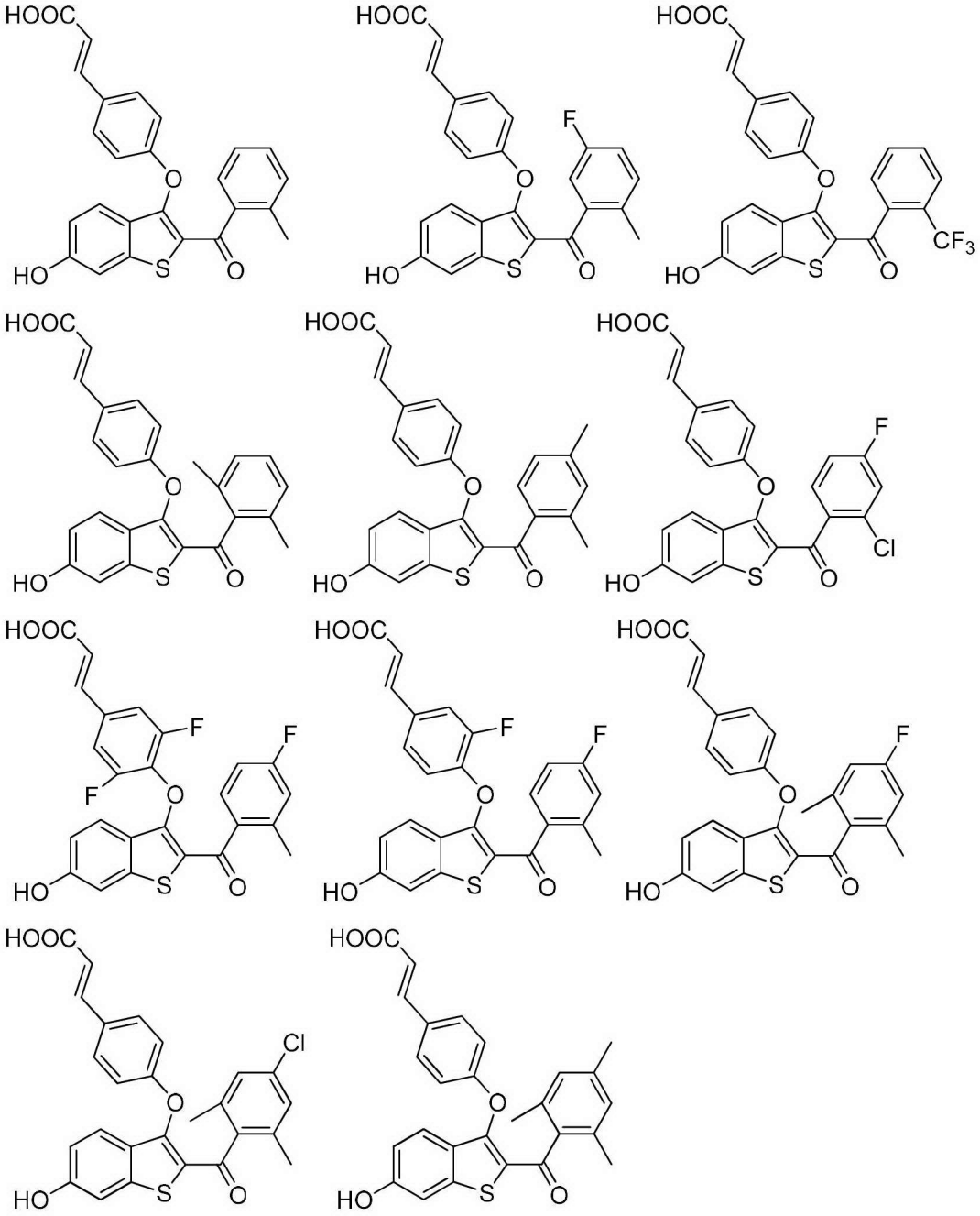
11. The compound of any one of claims 1 to 10, wherein n is 1, 2, or 3.

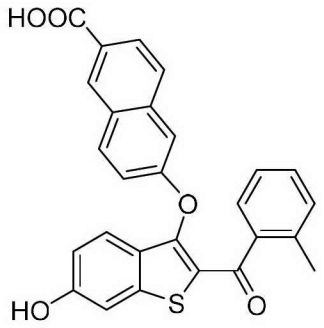
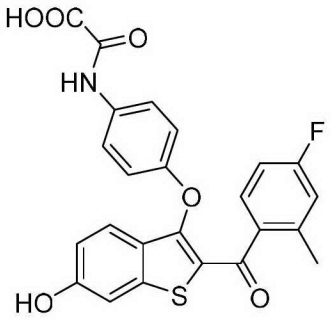
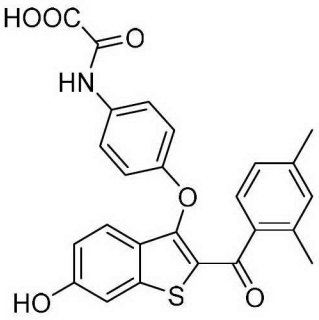
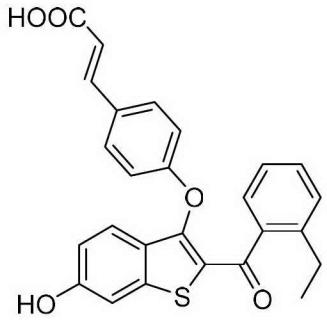
12. The compound according to claim 1 selected from





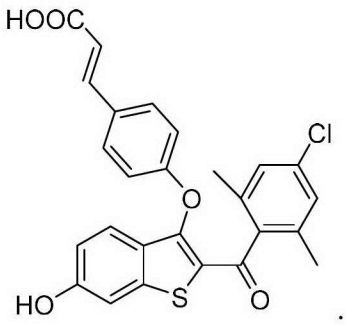




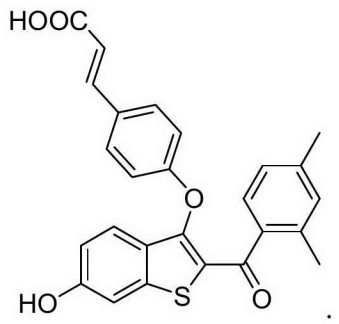



and


or a pharmaceutically acceptable salt thereof.

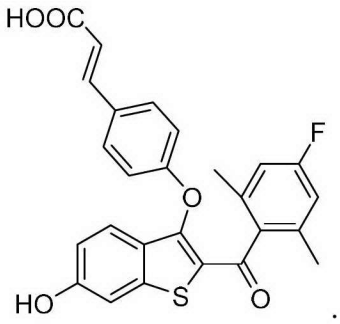
13. The compound of claim 1, or its pharmaceutically acceptable salt thereof, of structure:



14. The compound of claim 1, or its pharmaceutically acceptable salt thereof, of structure:

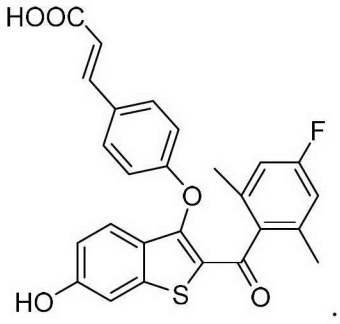


15. The compound of claim 1, or its pharmaceutically acceptable salt thereof, of structure:



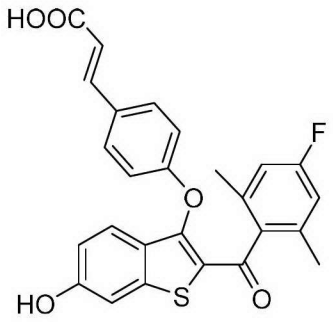
16. A pharmaceutical composition comprising a compound according to any one of claims 1 to 15 and a pharmaceutically acceptable carrier or excipient.

17. The pharmaceutical composition of claim 16, wherein the compound is of structure:



18. A method of treating an estrogen-related disorder comprising administering to a subject in need thereof a therapeutically effective amount of a compound or pharmaceutical composition according to any one of claims 1 to 17 or a pharmaceutically acceptable salt thereof.

19. The method of claim 18, wherein the compound is of structure:



or a pharmaceutically acceptable salt thereof.

20. The method of any one of claims 18 to 19, wherein the estrogen-related disorder is a cancer.

21. The method of claim 20, wherein the cancer is selected from the group consisting of prostate, kidney, and lung cancer.

22. The method of claim 20, wherein the cancer is selected from the group consisting of breast cancer, ovarian cancer, and endometrial cancer.

23. The method of claim 20, wherein the cancer is breast cancer.

24. The method of claim 23, wherein the breast cancer is hormone receptor positive metastatic breast cancer.

25. The method of claim 23, wherein the breast cancer is a tamoxifen resistant breast cancer.

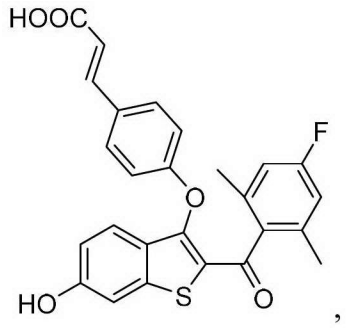
26. The method of claim 23, wherein the breast cancer is a triple negative breast cancer.

27. The method of any one of claims 18 to 19, wherein the estrogen-related disorder is bone loss.

28. The method of claim 27, wherein the bone loss is caused by osteoporosis.

29. Use of a compound or pharmaceutical composition according to any one of claims 1 to 17 in the manufacture of a medicament for the treatment of an estrogen-related disorder.

30. The use of claim 29, wherein the compound is of structure:



,

or a pharmaceutically acceptable salt thereof.

31. The use of any one of claims 29 to 30, wherein the estrogen-related disorder is a cancer.

32. The use of claim 31, wherein the cancer is selected from the group consisting of prostate, kidney, and lung cancer.

33. The use of claim 31, wherein the cancer is selected from the group consisting of breast cancer, ovarian cancer, and endometrial cancer.

34. The use of claim 31, wherein the cancer is breast cancer.

35. The use of claim 34, wherein the breast cancer is hormone receptor positive metastatic breast cancer.

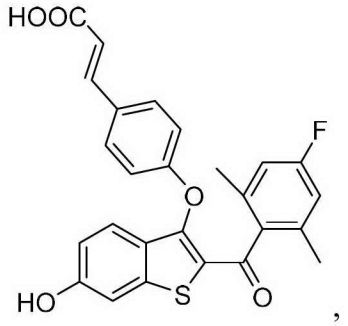
36. The use of claim 34, wherein the breast cancer is a tamoxifen resistant breast cancer.

37. The use of any one of claims 29 to 30, wherein the estrogen-related disorder is bone loss.

38. The use of claim 37, wherein the bone loss is caused by osteoporosis.

39. A method of preventing an estrogen-related disorder comprising administering to a subject in need thereof a therapeutically effective amount of a compound or pharmaceutical composition according to any one of claims 1 to 17 or a pharmaceutically acceptable salt thereof.

40. The method of claim 39, wherein the compound is of structure:



,

or a pharmaceutically acceptable salt thereof.

41. A method of treating an estrogen-related disorder that has metathesized to the brain comprising administering to a subject in need thereof a therapeutically effective amount of a compound or pharmaceutical composition according to any one of claims 1 to 17 or a pharmaceutically acceptable salt thereof.

42. A method of treating an estrogen-related disorder that has metathesized to the bone comprising administering to a subject in need thereof a therapeutically effective amount

of a compound or pharmaceutical composition according to any one of claims 1 to 17 or a pharmaceutically acceptable salt thereof.

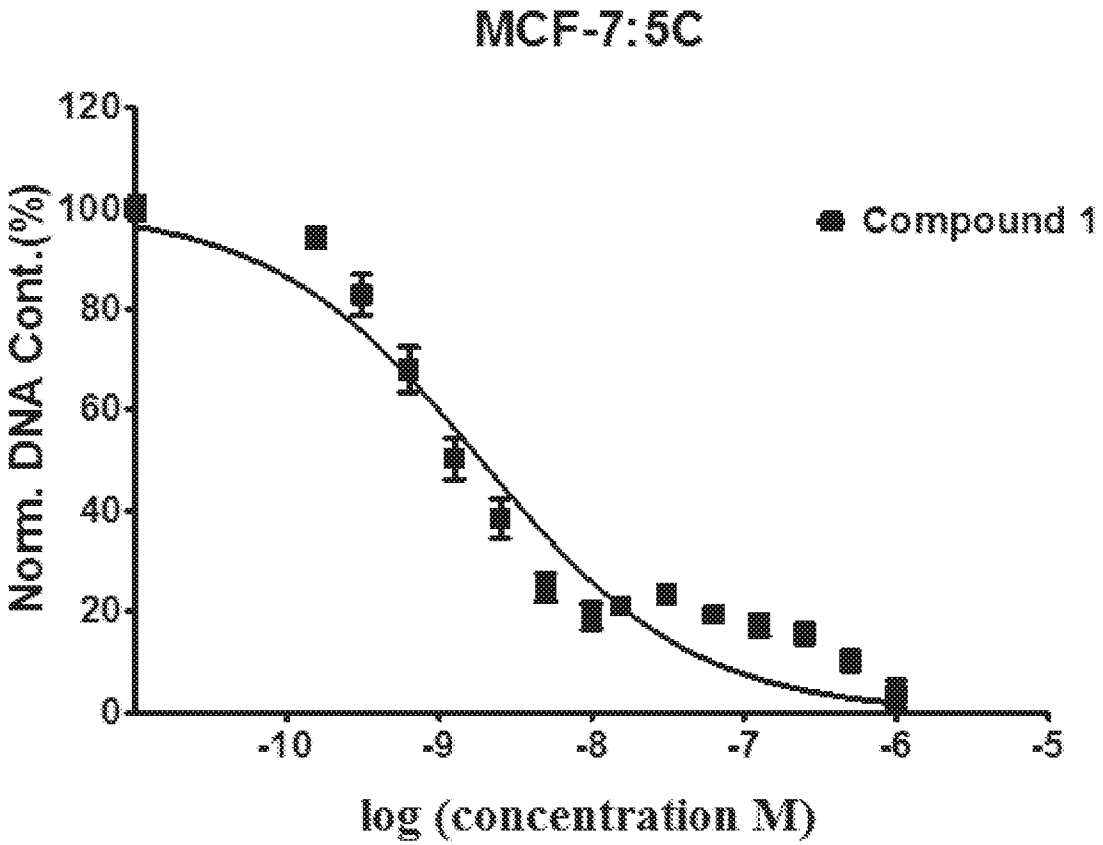

MCF-7:5C
Compound 1
Norm. DNA Cont.(%)
120
100
80
60
40
20
0
-10
-9
-8
-7
-6
-5
log (concentration M)

FIG. 1A

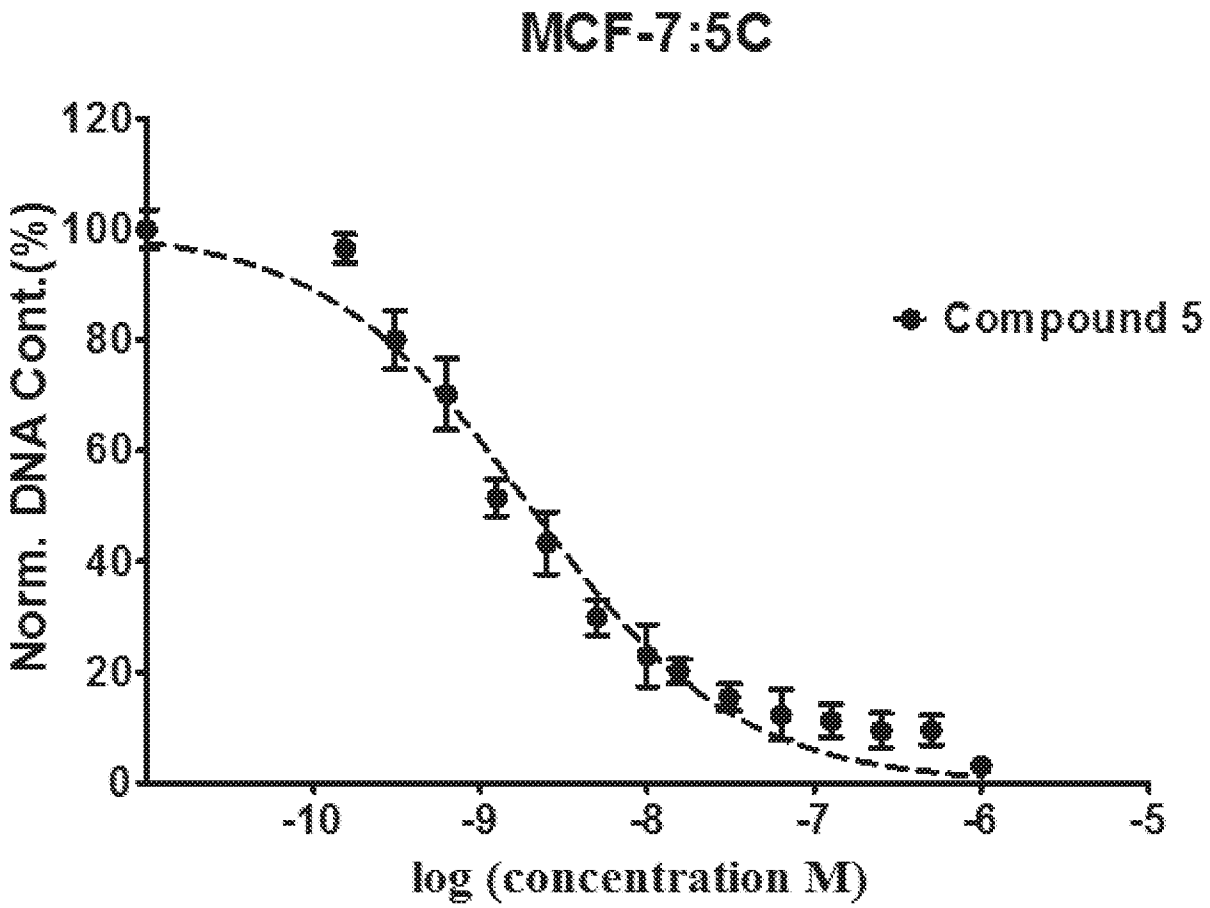

MCF-7:5C
Norm. DNA Cont.(%)
120
100
80
60
40
20
0
-10
-9
-8
-7
-6
-5
log (concentration M)
Compound 5

FIG. 1B

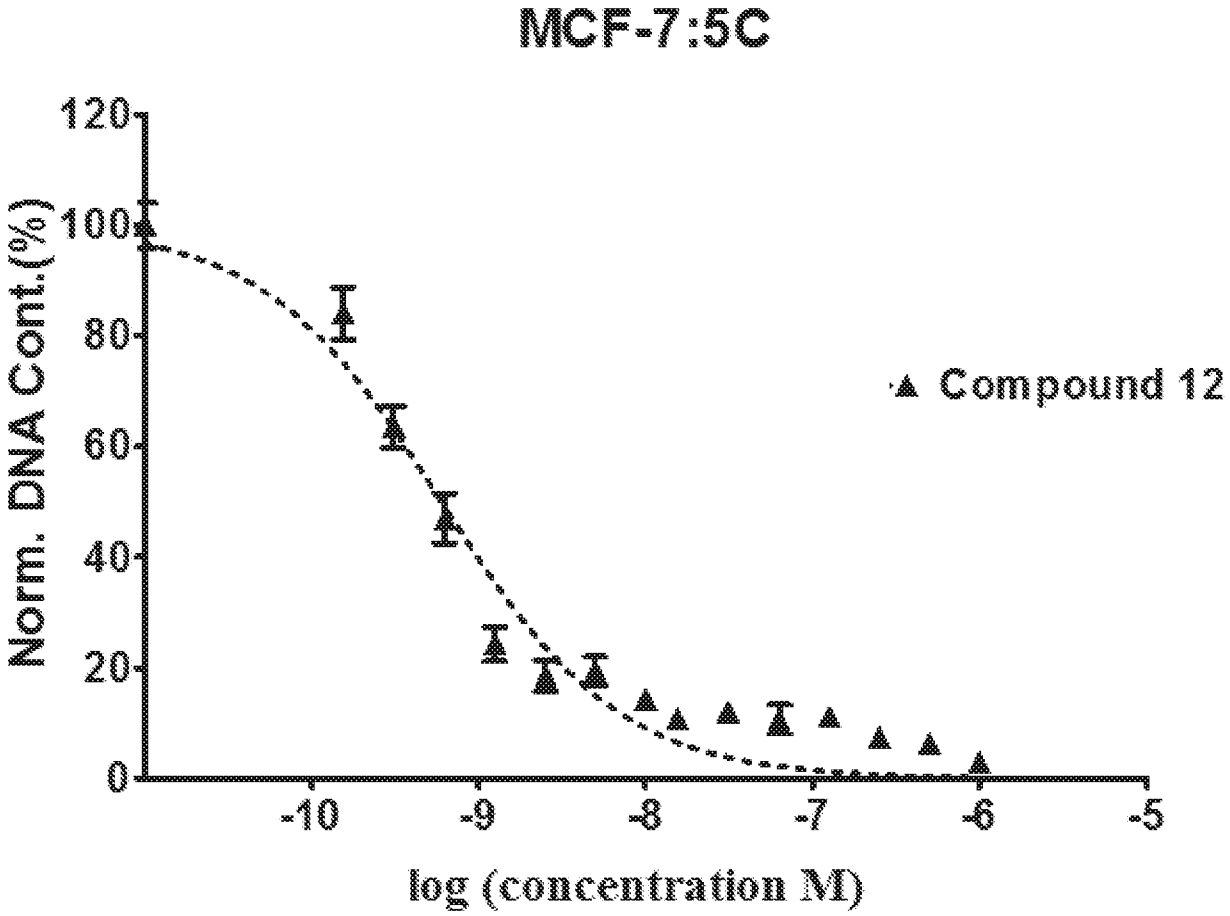

MCF-7:5C
Norm. DNA Cont.(%)
120
100
80
60
40
20
0
-10
-9
-8
-7
-6
-5
log (concentration M)
Compound 12

FIG. 1C

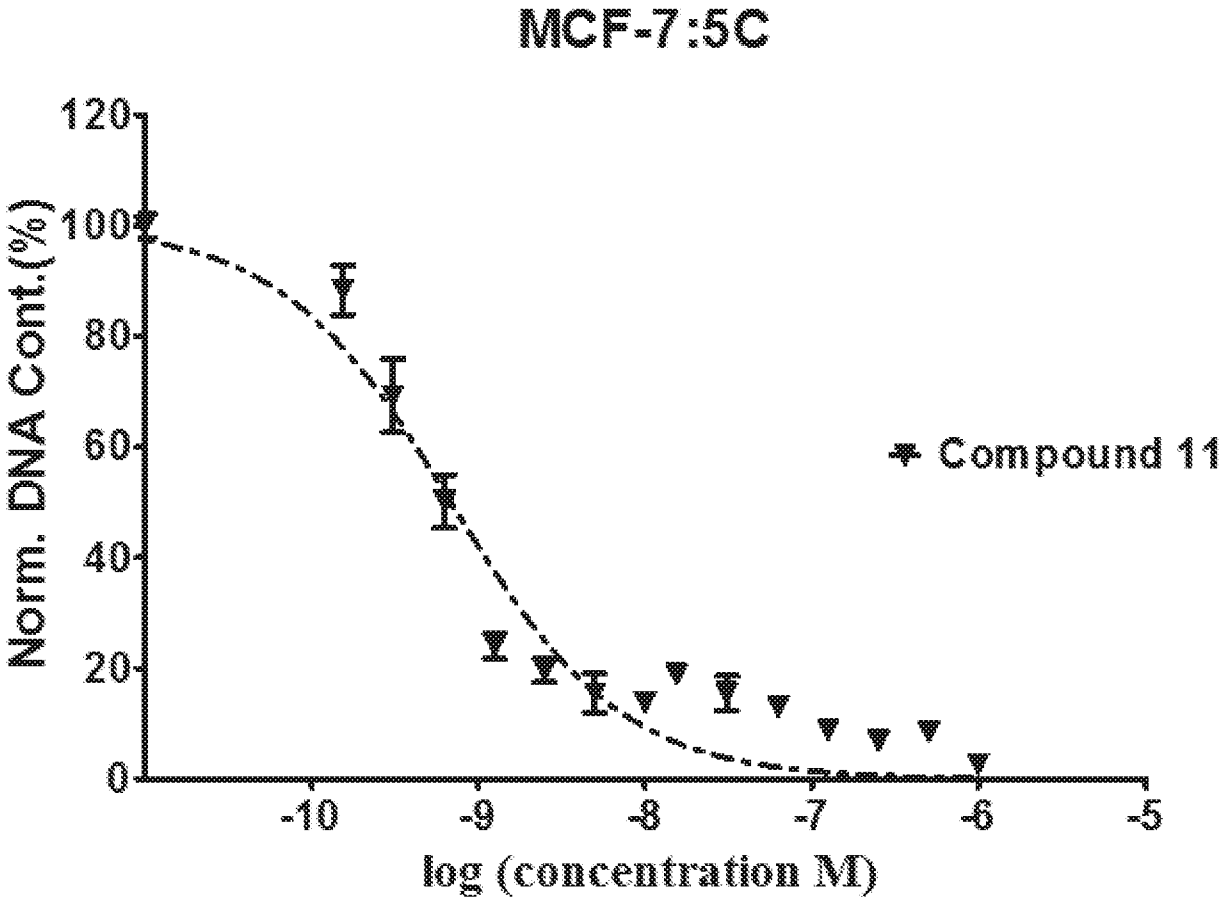

MCF-7:5C
Norm. DNA Cont.(%)
120
100
80
60
40
20
0
-10
-9
-8
-7
-6
-5
log (concentration M)
Compound 11

FIG. 1D

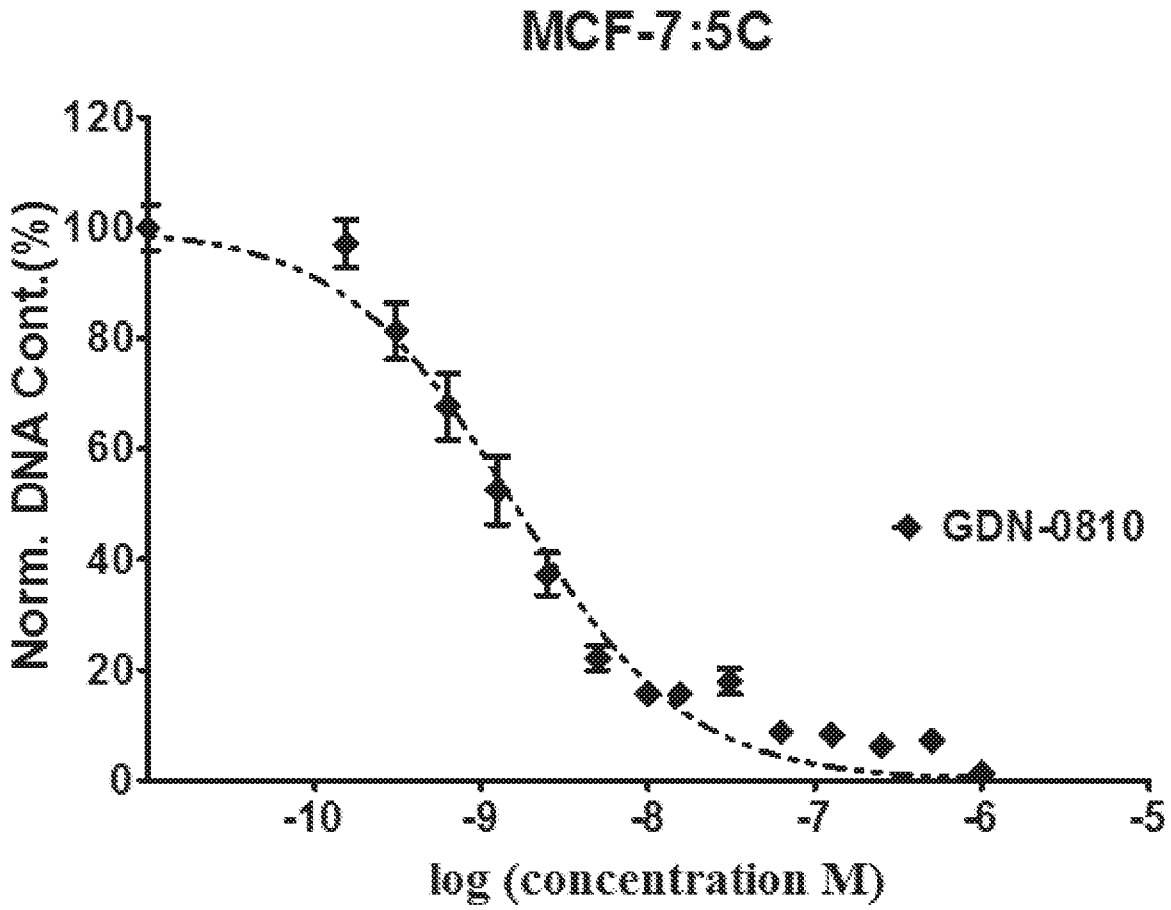

MCF-7:5C
Norm. DNA Cont.(%)
120
100
80
60
40
20
0
-10
-9
-8
-7
-6
-5
log (concentration M)
GDN-0810

FIG. 1E

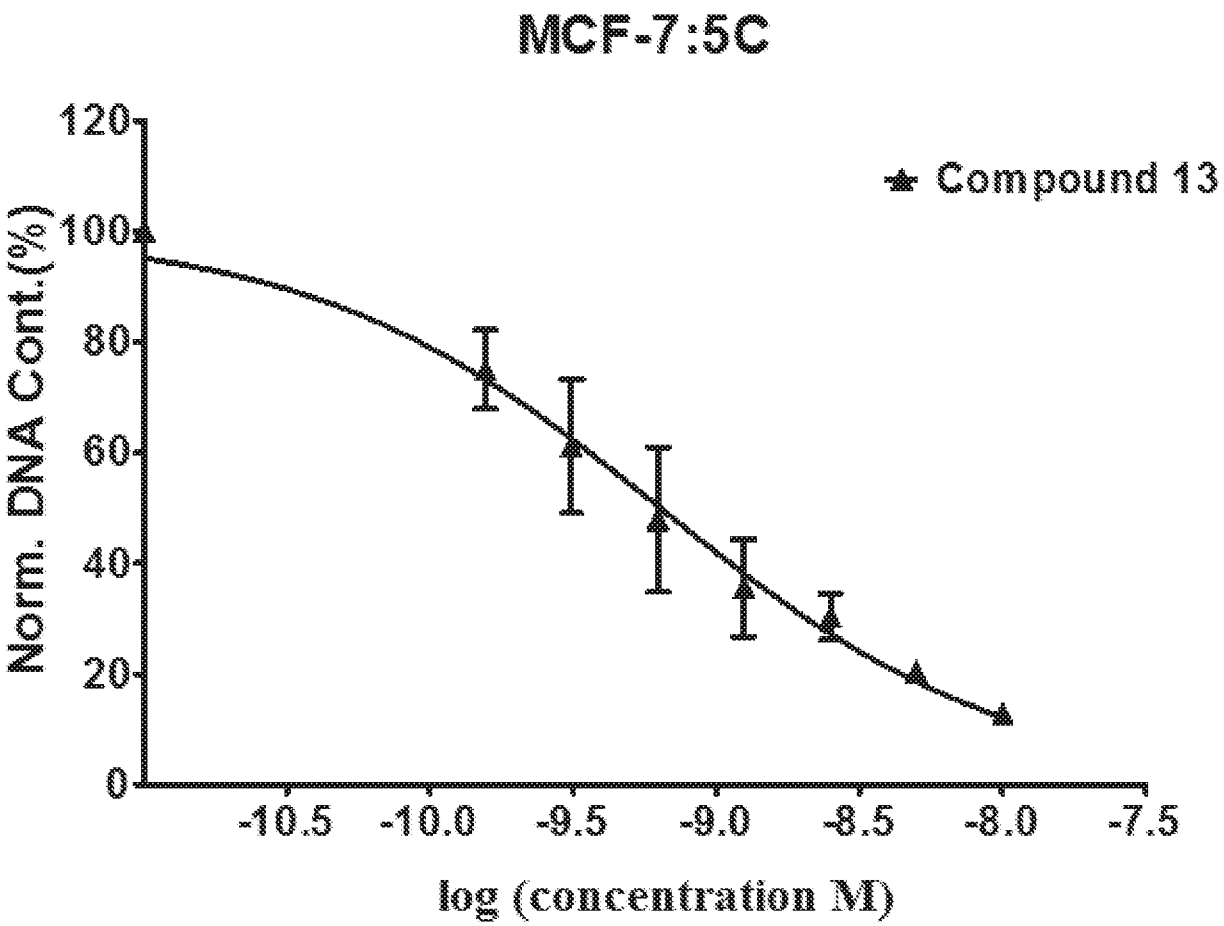

MCF-7:5C
Compound 13
Norm. DNA Cont.(%)
120
100
80
60
40
20
0
-10.5
-10.0
-9.5
-9.0
-8.5
-8.0
-7.5
log (concentration M)

FIG. 2A

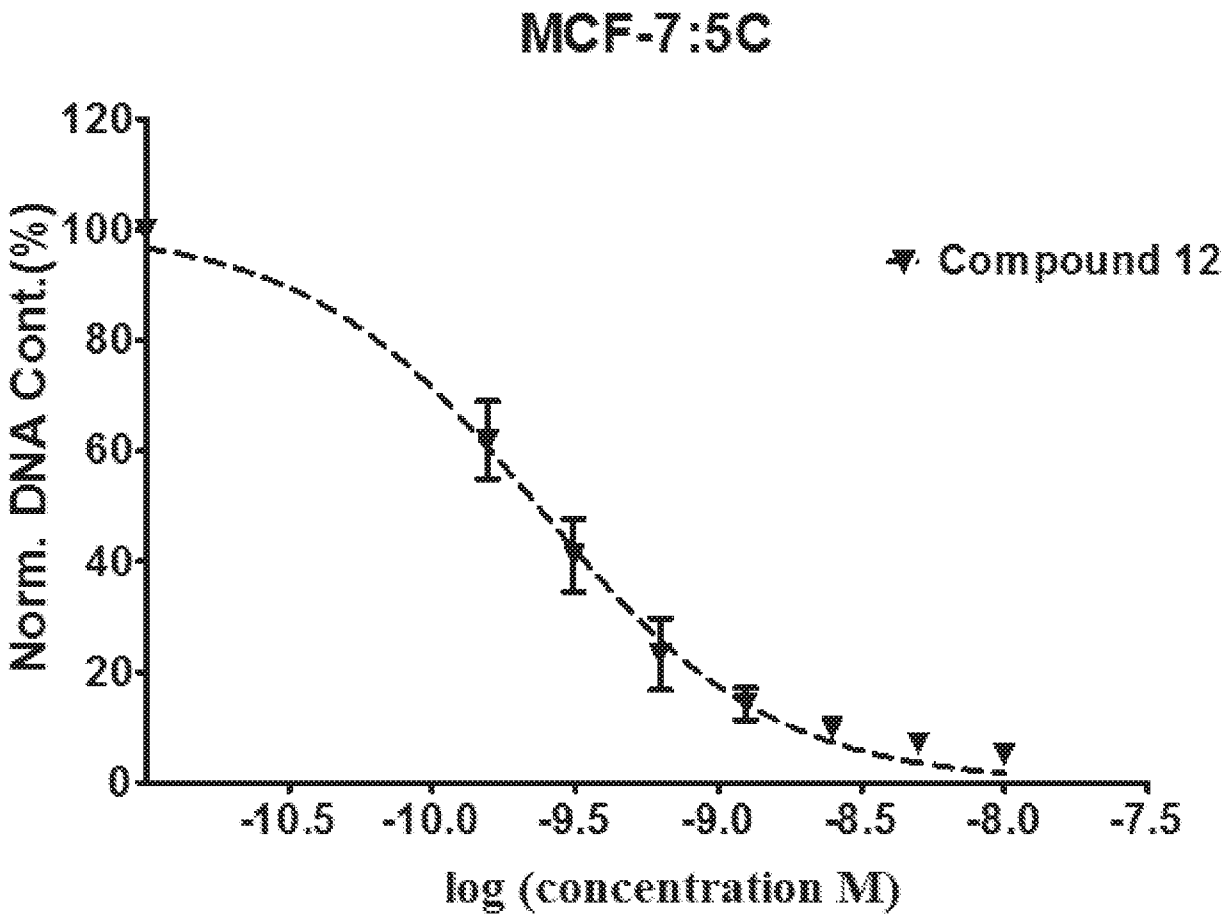

MCF-7:5C
Norm. DNA Cont.(%)
120
100
80
60
40
20
0
-10.5
-10.0
-9.5
-9.0
-8.5
-8.0
-7.5
log (concentration M)
Compound 12

FIG. 2B

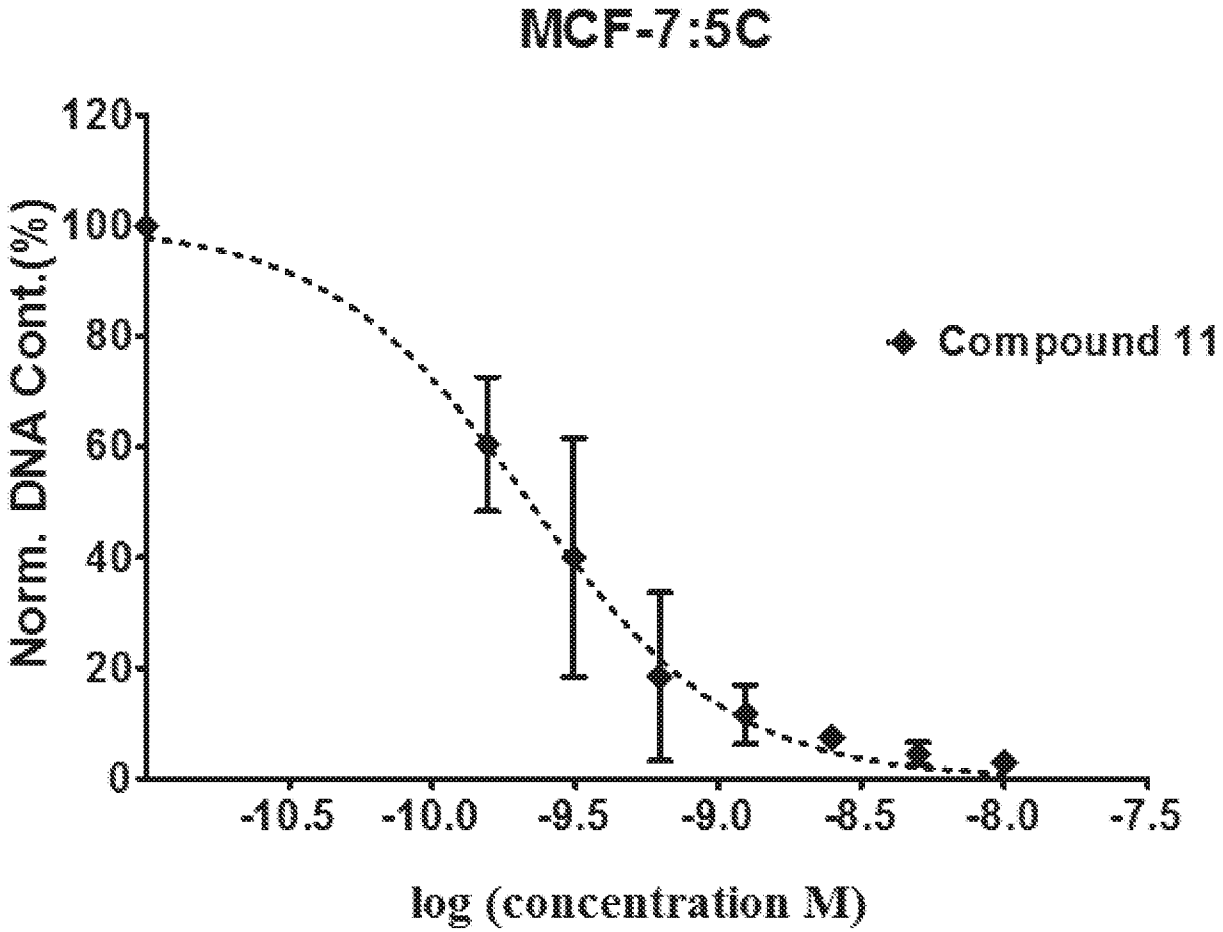

MCF-7:5C
Norm. DNA Cont.(%)
120
100
80
60
40
20
0
-10.5
-10.0
-9.5
-9.0
-8.5
-8.0
-7.5
log (concentration M)
Compound 11

FIG. 2C

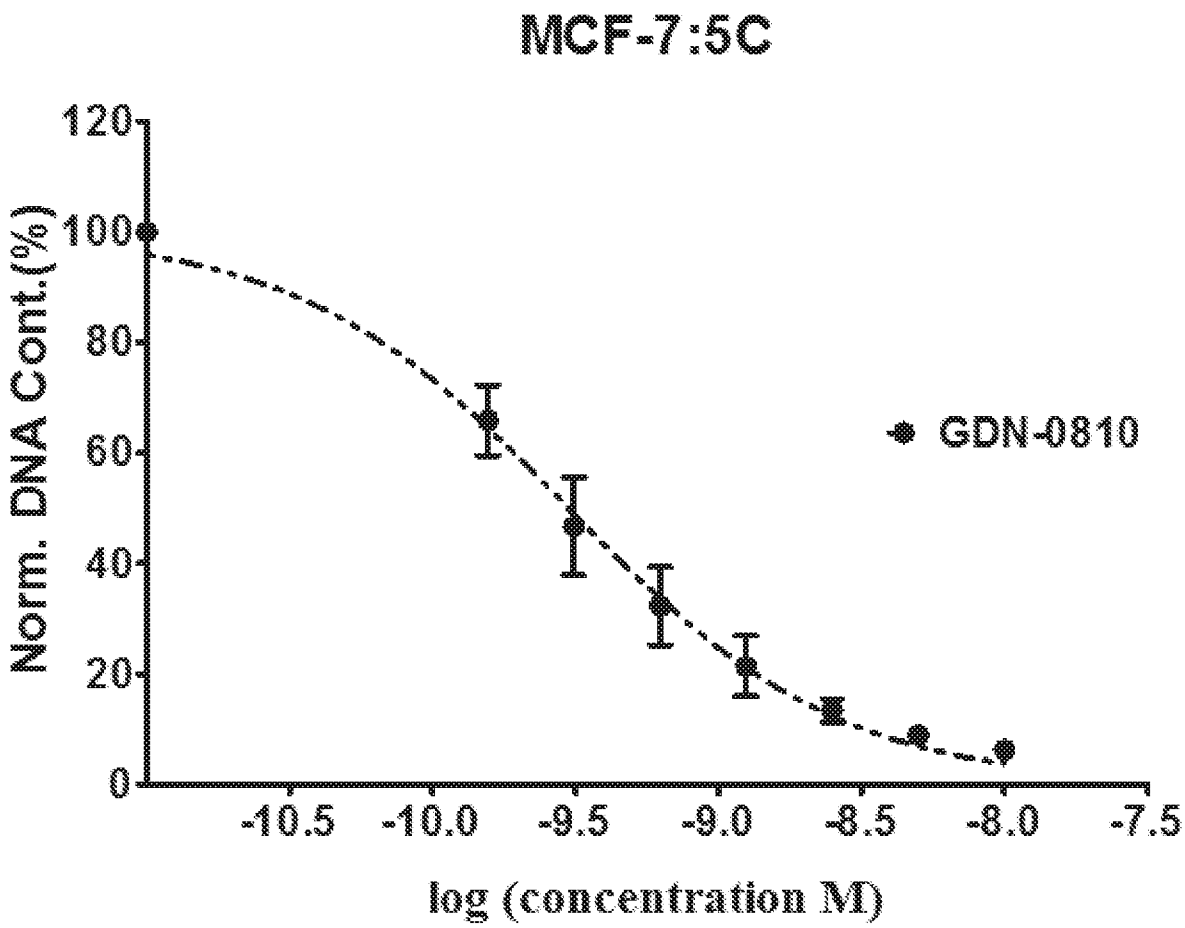

MCF-7:5C
Norm. DNA Cont.(%)
120
100
80
60
40
20
0
-10.5
-10.0
-9.5
-9.0
-8.5
-8.0
-7.5
log (concentration M)
GDN-0810

FIG. 2D

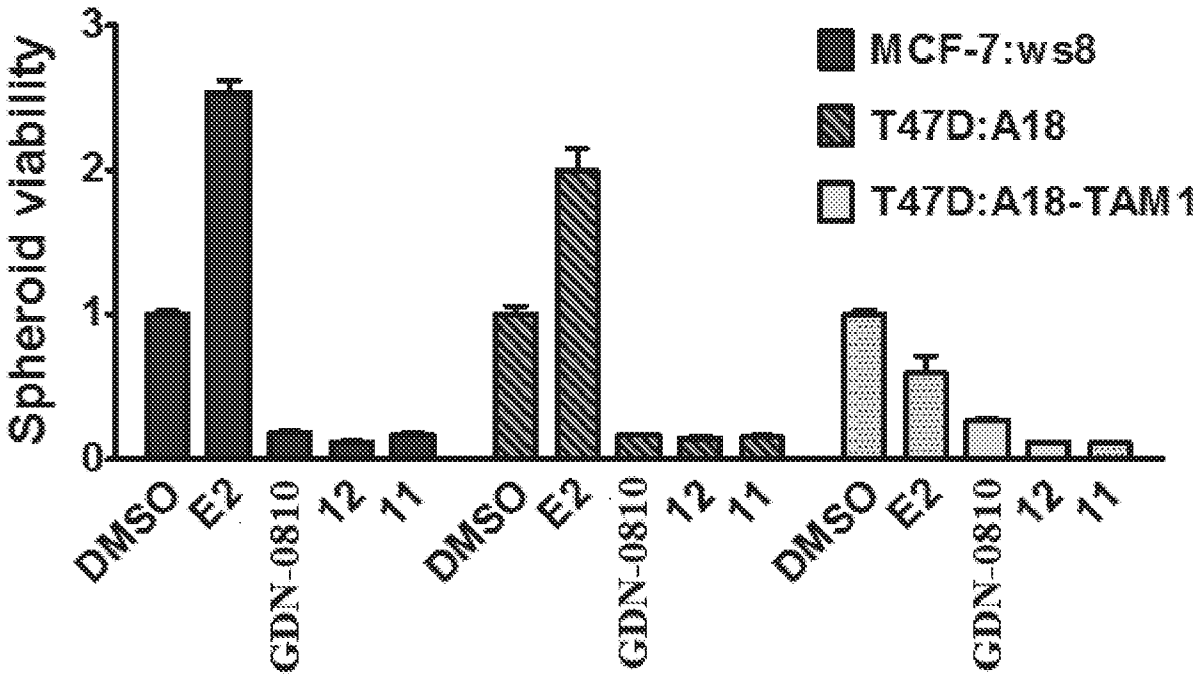

Spheroid viability
0
1
2
3
MCF-7:ws8
T47D:A18
T47D:A18-TAM1
DMSO
E2
GDN-0810
12
11
DMSO
E2
GDN-0810
12
11
DMSO
E2
GDN-0810
12
11

FIG. 3

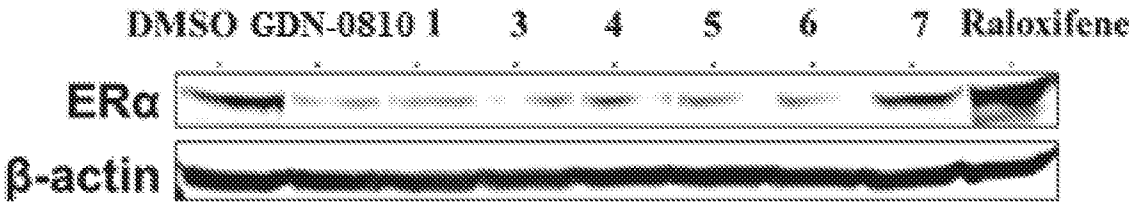


FIG. 4

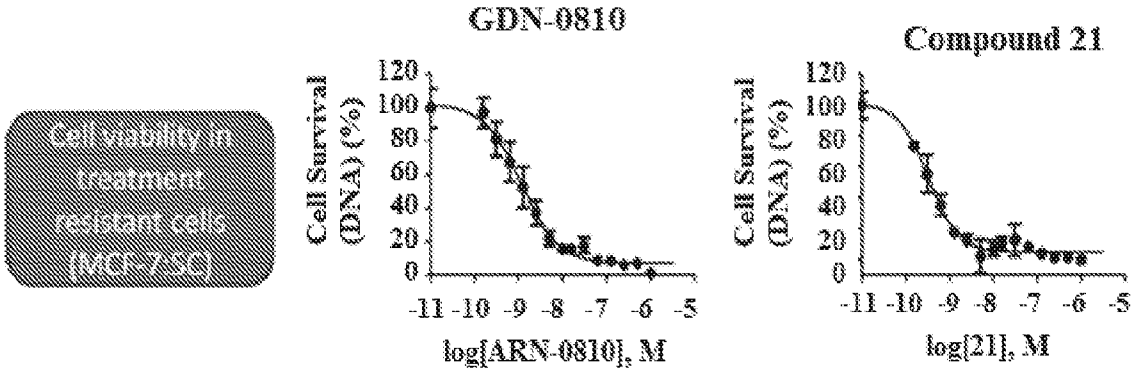


FIG. 5A

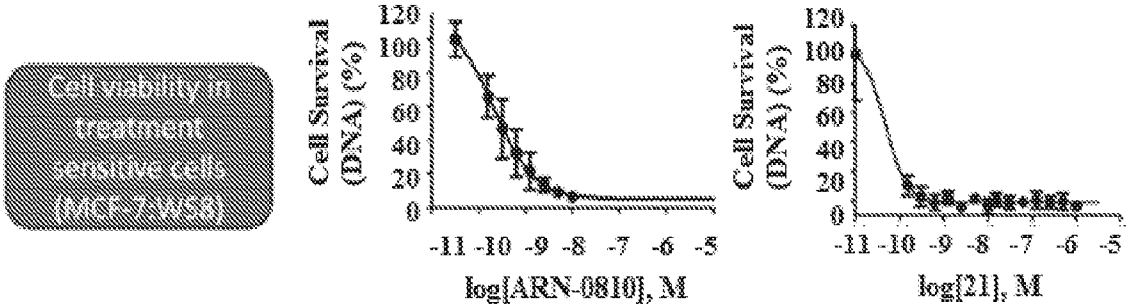


FIG. 5B

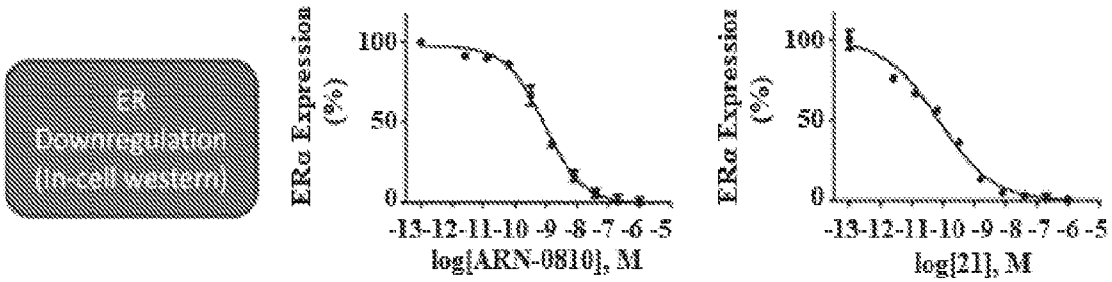


FIG. 5C

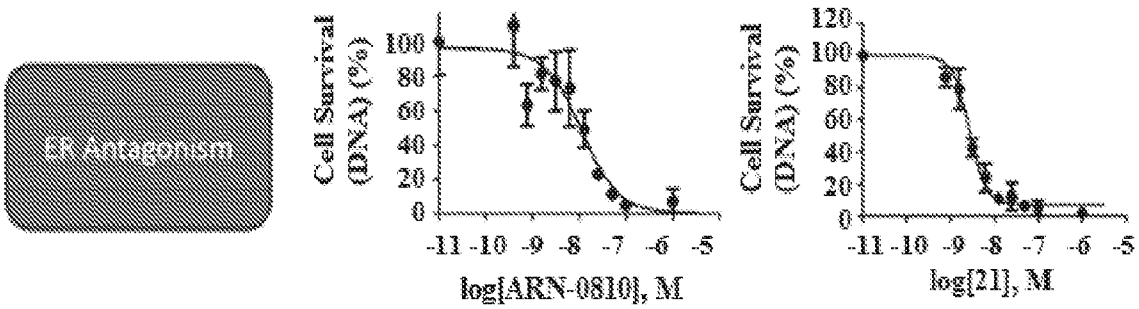


FIG. 5D

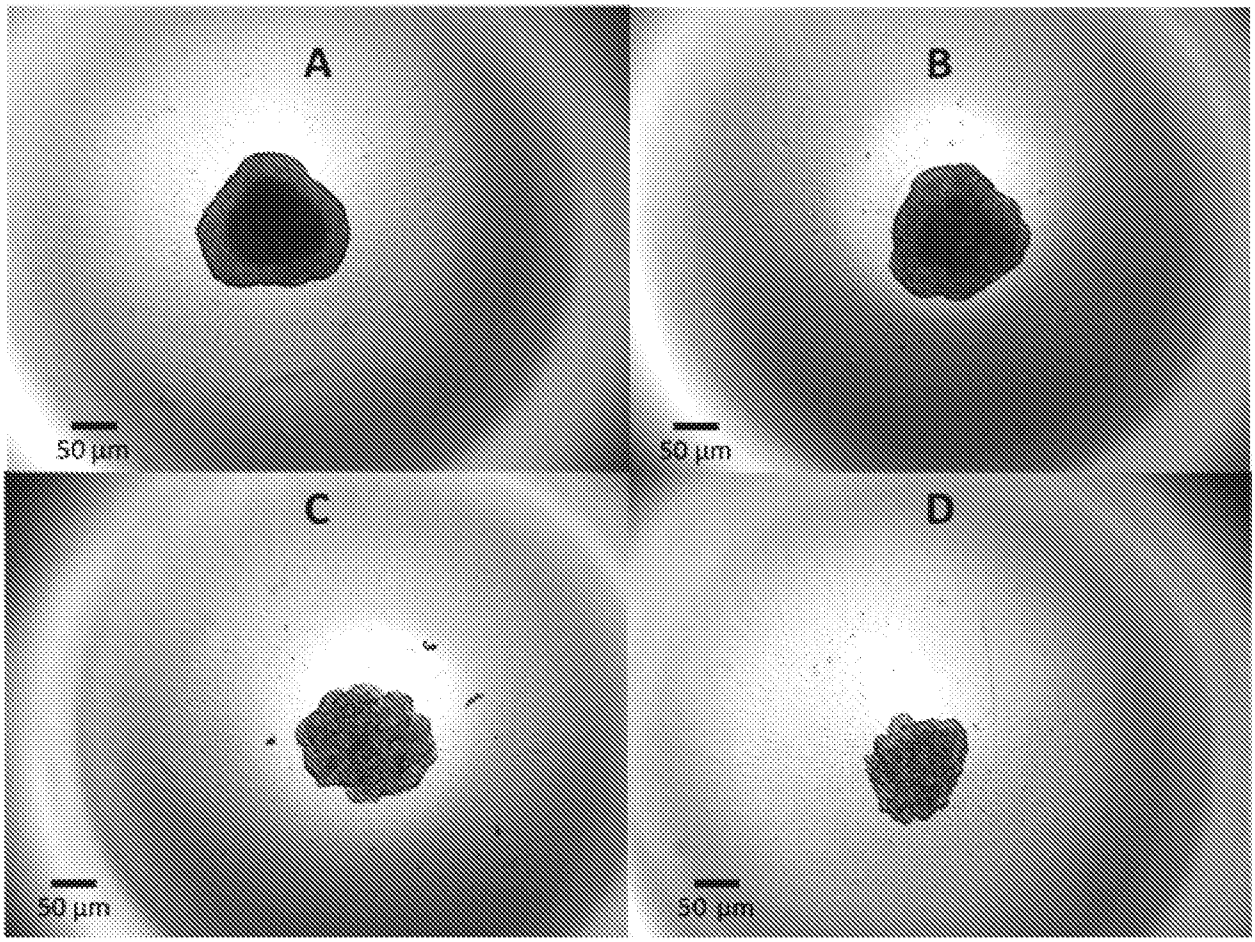


FIG. 6

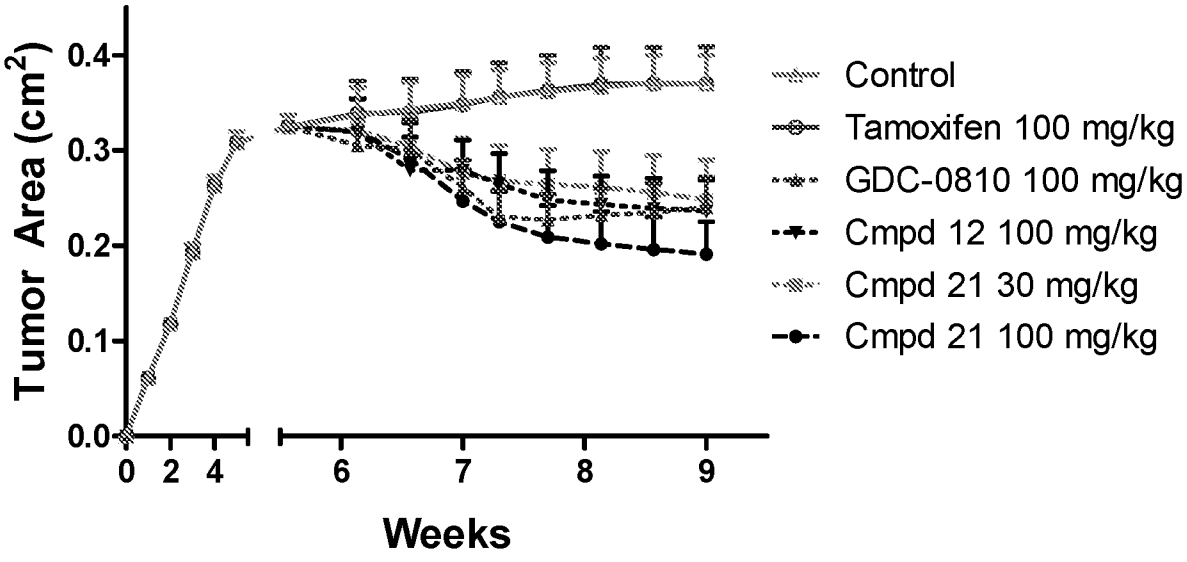

Tumor Area (cm2)
0.4
0.3
0.2
0.1
0.0
0 2 4 6 7 8 9
Weeks
Control
Tamoxifen 100 mg/kg
GDC-0810 100 mg/kg
Cmpd 12 100 mg/kg
Cmpd 21 30 mg/kg
Cmpd 21 100 mg/kg

FIG. 7A

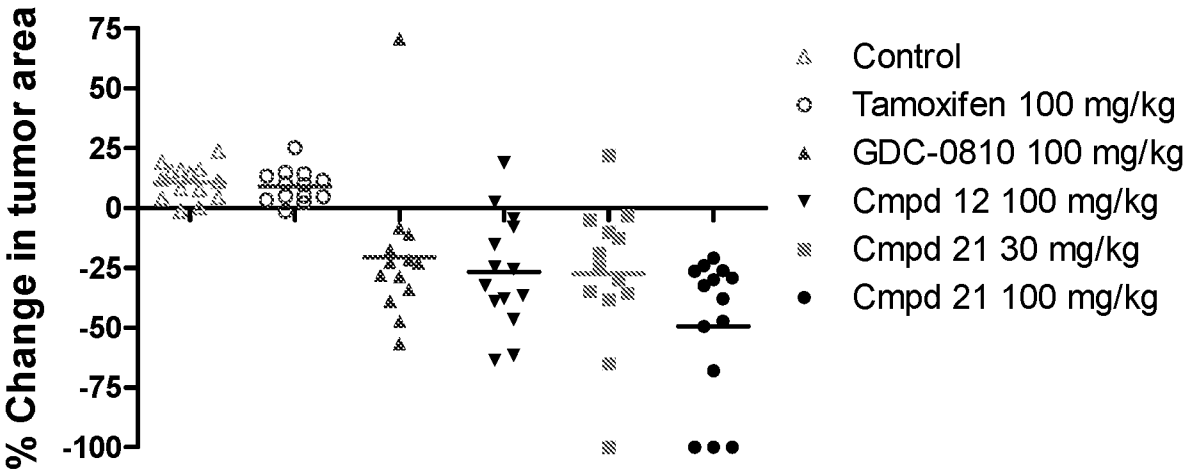
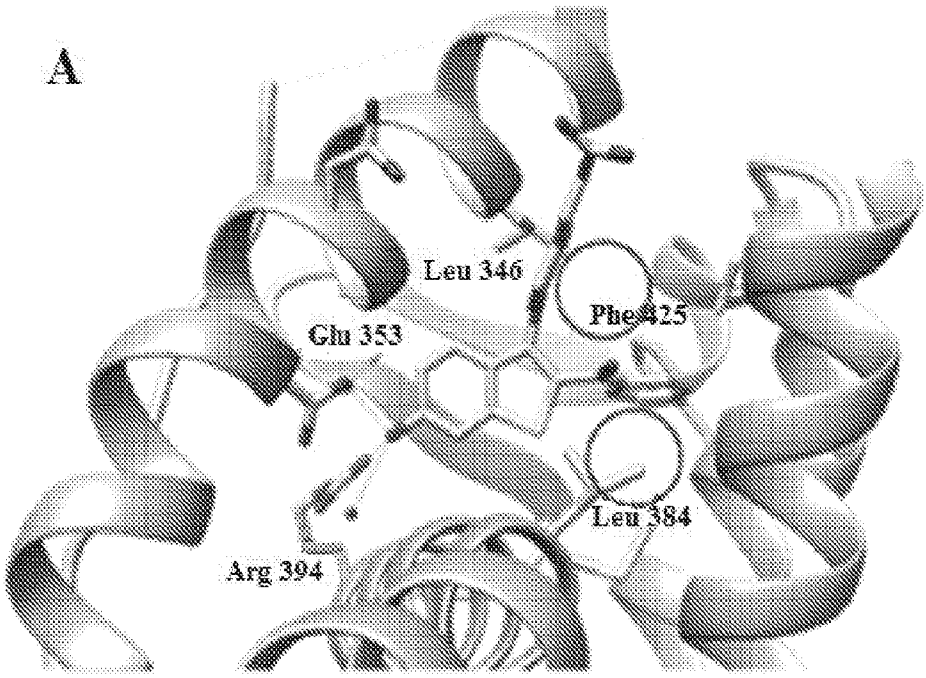
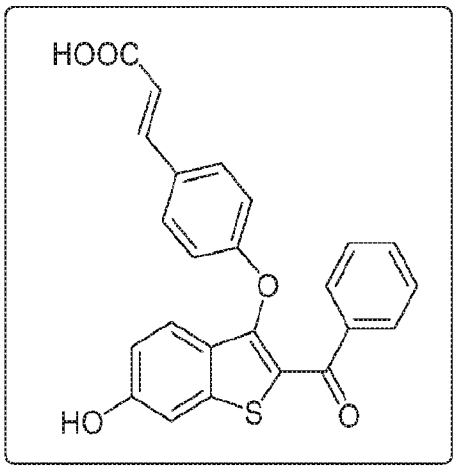

% Change in tumor area
75
50
25
0
-25
-50
-75
-100
Control
Tamoxifen 100 mg/kg
GDC-0810 100 mg/kg
Cmpd 12 100 mg/kg
Cmpd 21 30 mg/kg
Cmpd 21 100 mg/kg

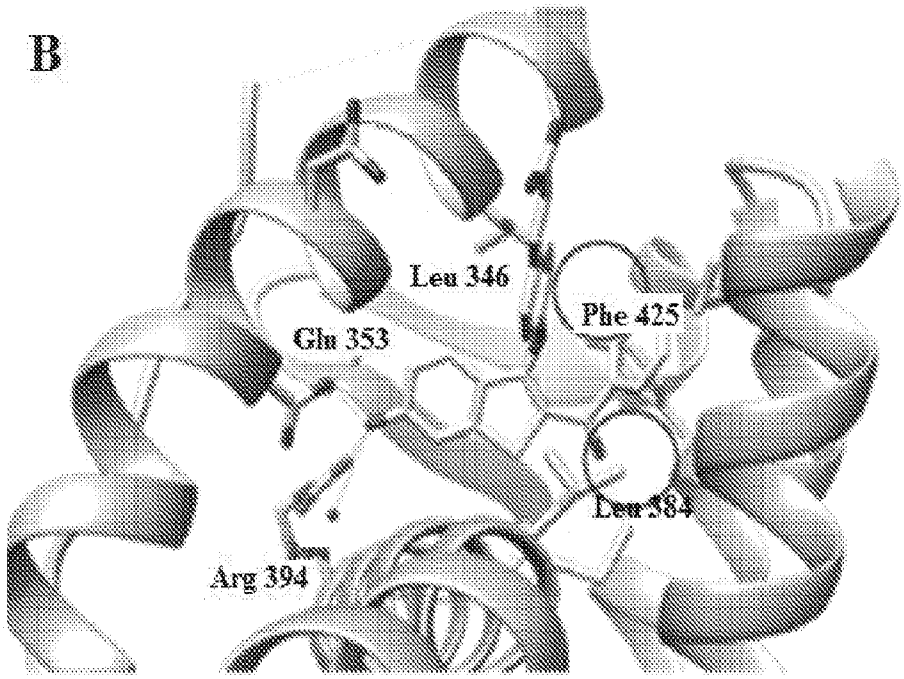
FIG. 7B

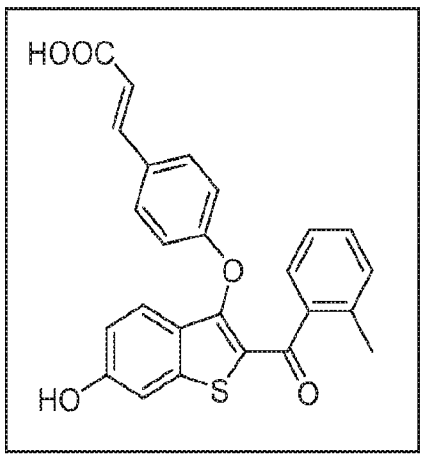




4

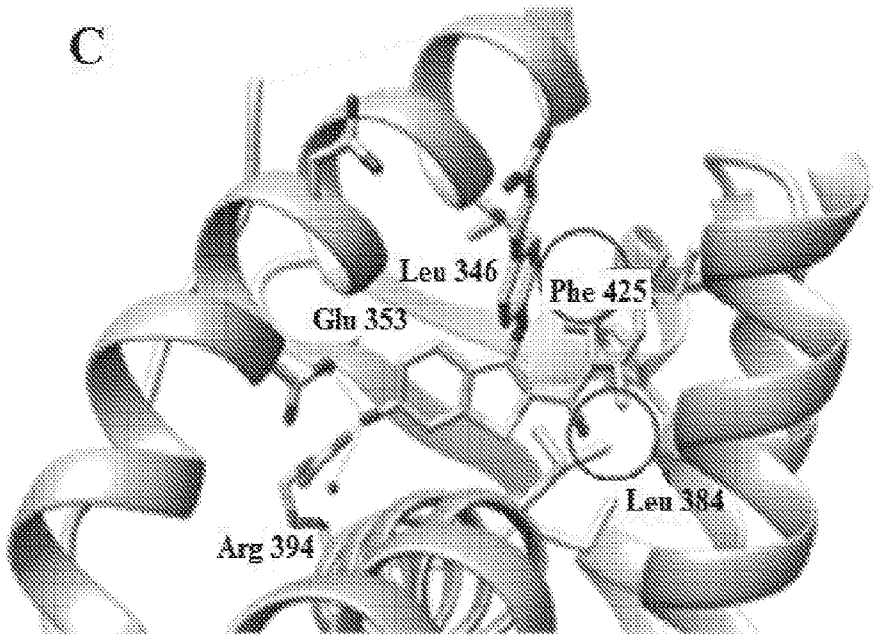
FIG. 8A





5

FIG. 8B



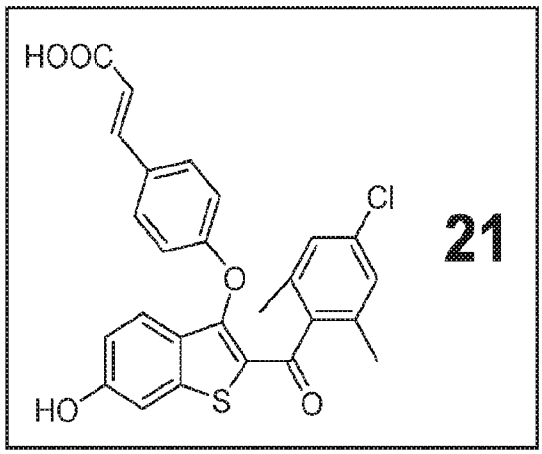


FIG. 8C

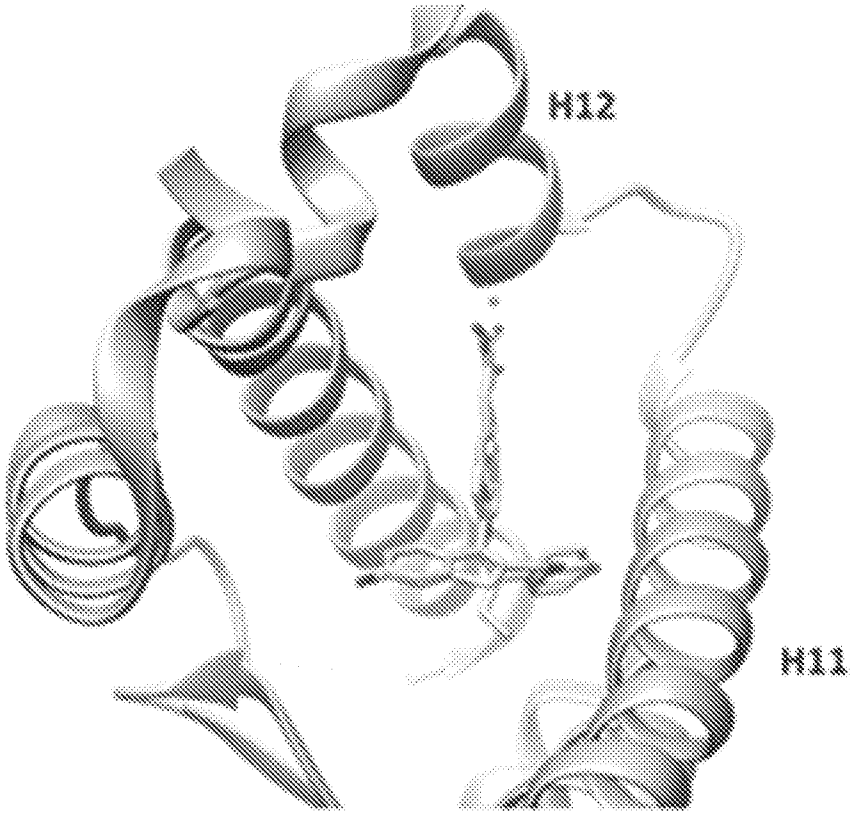


FIG. 9

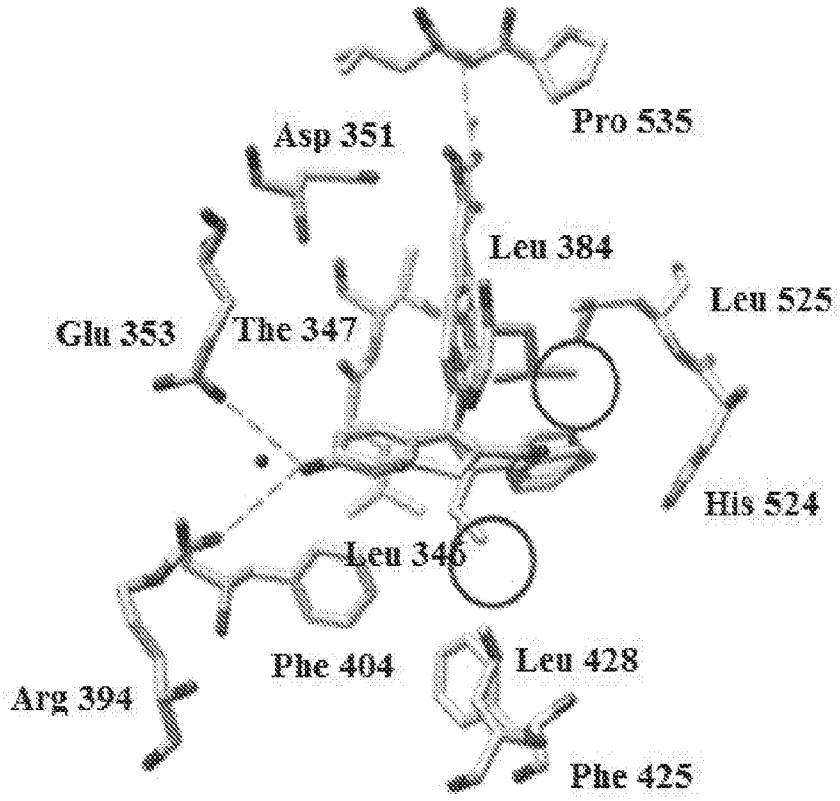

Pro 535
Asp 351
Leu 384
Leu 525
Glu 353
The 347
His 524
Leu 346
Phe 404
Leu 428
Arg 394
Phe 425

FIG. 10