prediction of clinical stage synergy of anti-cancer pharmaceutical therapeutic combinations such as capecitabine and taxanes for the treatment of breast cancer (Sawada et al (1998) Clin. Cancer Res. 4:1013-1019). Certain doses and schedules of combination therapy can improve safety without compromising efficacy (O'Shaughnessy et al (2006) Clin. Breast Cancer Apr 7(1):42-50). Synergistic effects in vitro have been correlated with clinical stage synergy (Steinbach et al (2003) Clin. Inf. Dis. Oct 1:37 Suppl 3:S188-224).

SUMMARY ~~OF THE INVENTION~~

~~In one aspect, p~~Presented herein are compounds of Formula (A), (B), and (C) that diminish the effects of estrogens with estrogen receptors and/or lower the concentrations of estrogen receptors, and therefore, are useful as agents for the treatment or prevention of diseases or conditions in which the actions of estrogens and/or estrogen receptors are involved in the etiology or pathology of the disease or condition or contribute to at least one symptom of the disease or condition and wherein such actions of estrogens and/or estrogen receptors are undesirable. In some embodiments, compounds disclosed herein are estrogen receptor degrader compounds.

~~In one aspect, c~~Compounds of Formula (A), (B), and (C) are useful for the treatment of ER-related diseases or conditions including, but not limited to, ER-α dysfunction associated with cancer (bone cancer, breast cancer, lung cancer, colorectal cancer, endometrial cancer, prostate cancer, ovarian and uterine cancer), central nervous system (CNS) defects (alcoholism, migraine), cardiovascular system defects (aortic aneurysm, susceptibility to myocardial infarction, aortic valve sclerosis, cardiovascular disease, coronary artery disease, hypertension), hematological system defects (deep vein thrombosis), immune and inflammation diseases (Graves' Disease, arthritis, multiple sclerosis, cirrhosis), susceptibility to infection (hepatitis B, chronic liver disease), metabolic defects (bone density, cholestasis, hypospadias, obesity, osteoarthritis, osteopenia, osteoporosis), neurological defects (Alzheimer's disease, Parkinson's disease, migraine, vertigo), psychiatric defects (anorexia nervosa, attention deficit hyperactivity disorder (ADHD), dementia, major depressive disorder, psychosis), uterine diseases (e.g. leiomyoma, uterine leiomyoma, endometrial hyperplasia, endometriosis), and reproductive defects (age of menarche, endometriosis, infertility).

~~In one aspect, d~~Described herein are compounds of Formula (A), (B), and (C), pharmaceutically acceptable salts, solvates, metabolites and prodrugs thereof. Compounds described herein are estrogen receptor modulators. In some embodiments, the compound of

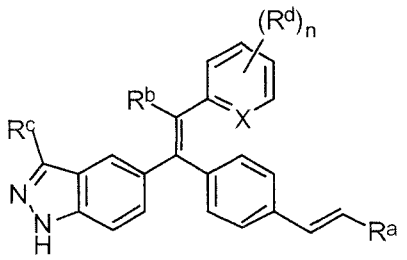
Formula (A), (B), or (C) is an estrogen receptor antagonist. In some embodiments, the compound of Formula (A), (B), or (C) is an estrogen receptor degrader. In some embodiments, the compound of Formula (A), (B), or (C) is an estrogen receptor antagonist as well as an estrogen receptor degrader. In some embodiments, the compound of Formula (A), (B), or (C) displays minimal or no estrogen receptor agonist activity. In some embodiments, in the context of treating cancers, the compound of Formula (A), (B), or (C) may offer improved therapeutic activity characterized by complete or longer-lasting tumor regression, a lower incidence or rate of development of resistance to treatment, and/or a reduction in tumor invasiveness.

In some embodiments, compounds disclosed herein have high specificity for the estrogen receptor and have desirable, tissue-selective pharmacological activities. Desirable, tissue-selective pharmacological activities include, but are not limited to, ER antagonist activity in breast cells and no ER agonist activity in uterine cells. In some embodiments, compounds disclosed herein are estrogen receptor degraders that display full estrogen receptor antagonist activity with negligible or minimal estrogen receptor agonist activity.

In some embodiments, compounds disclosed herein are estrogen receptor degraders. In some embodiments, compounds disclosed herein are estrogen receptor antagonists. In some embodiments, compounds disclosed herein have minimal or negligible estrogen receptor agonist activity.

In some embodiments, presented herein are compounds selected from active metabolites, tautomers, pharmaceutically acceptable solvates, pharmaceutically acceptable salts or prodrugs of a compound of Formula (A), (B), or (C).

~~In one aspect, d~~Described herein is a method for treating an ER-related disease or condition in a patient comprising administering to the patient an estrogen receptor modulator compound of Formula (A) in combination with a second therapeutic agent, wherein the compound of Formula (A) has the structure:

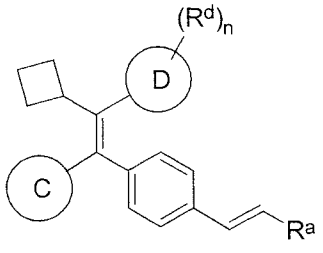


Formula (A)

wherein,

R^a is $-CO_2H$ or a 5-membered heterocycle selected from the group consisting of

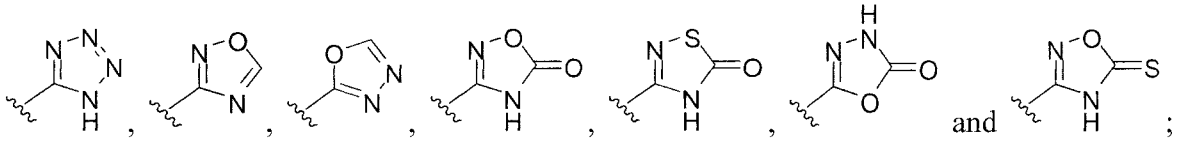
~~In one aspect, d~~Described herein is a method for treating an ER-related disease or condition in a patient comprising administering to the patient an estrogen receptor modulator compound of Formula (B) in combination with a second therapeutic agent, wherein the compound of Formula (B) has the structure:



Formula (B)

wherein,

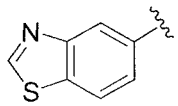
R^a is $-CO_2H$ or a 5-membered heterocycle selected from the group consisting of



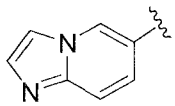
and

;

ring C is



or



;

ring D is phenyl or thienyl;

each R^d is independently selected from H, halogen, -CN, $-OR^e$, $-NHR^e$, $-NR^eR^f$, $-SR^e$, $-S(=O)R^f$, $-S(=O)_2R^f$, C_1-C_6 alkyl, and C_1-C_6 fluoroalkyl;

each R^e is independently selected from H, $-C(=O)R^f$, $-C(=O)OR^f$, $-C(=O)NHR^f$, C_1-C_6 alkyl, C_1-C_6 fluoroalkyl, C_3-C_6cycloalkyl, substituted or unsubstituted monocyclic C_2-C_6 heterocycloalkyl, substituted or unsubstituted phenyl, and substituted or unsubstituted monocyclic heteroaryl;

each R^f is independently selected from C_1-C_6 alkyl, C_1-C_6 fluoroalkyl, C_3-C_6 cycloalkyl, substituted or unsubstituted monocyclic C_2-C_6 heterocycloalkyl, substituted or unsubstituted phenyl, and substituted or unsubstituted monocyclic heteroaryl;

n is 0, 1, or 2; or a pharmaceutically acceptable salt, or solvate thereof.

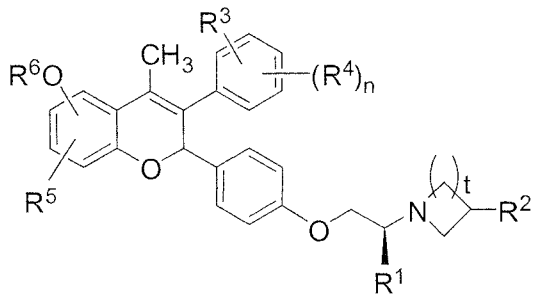
In some embodiments, the estrogen receptor modulator is compound 2-1, 2-2, 2-3, 2-4, or 2-5, or a pharmaceutically acceptable salt, or solvate thereof.

In some embodiments, the ER-related disease or condition is cancer. In some embodiments, the cancer is a breast cancer. In some embodiments, the breast cancer is a metastatic breast cancer. In some embodiments, the breast cancer is a hormone resistant breast cancer. In some embodiments, the breast cancer is an estrogen receptor positive breast cancer. In

some embodiments, the breast cancer is a HER2 positive breast cancer. In some embodiments, the breast cancer is a HER2 negative breast cancer. In some embodiments, the breast cancer is resistant to treatment with an aromatase inhibitor. In some embodiments, the aromatase inhibitor is anastrozole, letrozole, or exemestane. In some embodiments, the patient has a tumor. In some embodiments, the patient is a female patient and is pre-menopausal or post-menopausal. In some embodiments, the patient has failed one or more anti-cancer therapies. In some embodiments, the patient has received a chemotherapeutic agent, a biological therapy, a cancer vaccine, an angiogenesis inhibitor, hormone therapy, radiation therapy, surgery, or any combination thereof. In some embodiments, the biological therapy is a peptide, a cytokine, an antibody, a therapeutic virus, a therapeutic bacterium, gene therapy, siRNA, adoptive T-cell transfer, or any combination thereof. In some embodiments, the patient has received an aromatase inhibitor, a selective estrogen receptor modulator (SERM), a selective estrogen degrader (SERD), a phosphoinositide 3-kinase (PI3K)/mTOR pathway inhibitor, a CDK 4/6 inhibitor, a HER-2 inhibitor, an EGFR inhibitor, a PD-1 inhibitor, poly ADP-ribose polymerase (PARP) inhibitor, a histone deacetylase (HDAC) inhibitor, an HSP90 inhibitor, or any combination thereof. In some embodiments, the patient has received fulvestrant, tamoxifen, anastrozole, letrozole, exemestane, goserelin, leuprolide, raloxifene, toremifene, megestrol acetate, bazedoxifene, or any combination thereof. In some embodiments, the patient has received an anthracyclcine, a taxane, a platinum agent, an epothilone, or a nucleoside analog. In some embodiments, the patient has received cisplatin, carboplatin, capecitabine, cyclophosphamide, docetaxel, doxorubicin, epirubicin, eribulin, fluorouracil, gemcitabine, ixabepilone, mitoxantrone, methotrexate, paclitaxel, pamidronate, vinorelbine, or any combination thereof. In some embodiments, the patient has received pertuzumab, trastuzumab, lapatinib, everolimus, bevacizumab, or temsirolimus, or any combination thereof. In some embodiments, the second therapeutic agent is an anti-cancer agent. In some embodiments, the anti-cancer agent is doxorubicin, cyclophosphamide, capecitabine, vinorelbine, paclitaxel, doxetaxel, or cisplatin. In some embodiments, the second therapeutic agent is an aromatase inhibitor, a phosphoinositide 3-kinase (PI3K)/mTOR pathway inhibitor, a CDK 4/6 inhibitor, a HER-2 inhibitor, an EGFR inhibitor, a PD-1 inhibitor, poly ADP-ribose polymerase (PARP) inhibitor, a histone deacetylase (HDAC) inhibitor, an HSP90 inhibitor, a VEGFR inhibitor, an AKT inhibitor, chemotherapy, or any combination thereof.

~~In one aspect, d~~Described herein is a method for treating an ER-related disease or condition in a patient comprising administering to the patient an estrogen receptor modulator compound of

Formula (C) in combination with a second therapeutic agent, wherein the compound of Formula (C) has the structure:



Formula (C)

wherein, R^1 is H, C_1-C_4alkyl, or C_1-C_4fluoroalkyl;

R^2 is H, F, C_1-C_4alkyl or C_1-C_4fluoroalkyl;

R^3 is H, halogen, -CN, -OR^6, -NHR^6, -NR^6R^7, -SR^6, -$S(=O)R^7$, -$S(=O)_2R^7$, C_1-C_4alkyl, or C_1-C_4fluoroalkyl;

each R^4 is independently selected from H, halogen, -CN, -OH, C_1-C_6alkyl, C_1-C_4fluoroalkyl, C_1-C_4fluoroalkoxy, and C_1-C_4alkoxy;

each R^5 is H, F, Cl, -OH, -CH_3, -CF_3, or –OCH_3;

each R^6 is independently selected from H, -$C(=O)R^7$, -$C(=O)OR^7$, -$C(=O)NHR^7$, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_3-C_6cycloalkyl, substituted or unsubstituted C_2-C_6heterocycloalkyl, substituted or unsubstituted phenyl, and substituted or unsubstituted monocyclic heteroaryl; each R^7 is independently selected from C_1-C_6alkyl, C_1-C_6fluoroalkyl, substituted or unsubstituted C_3-C_6cycloalkyl, substituted or unsubstituted monocyclic C_2-C_6heterocycloalkyl, substituted or unsubstituted phenyl, and substituted or unsubstituted monocyclic heteroaryl;

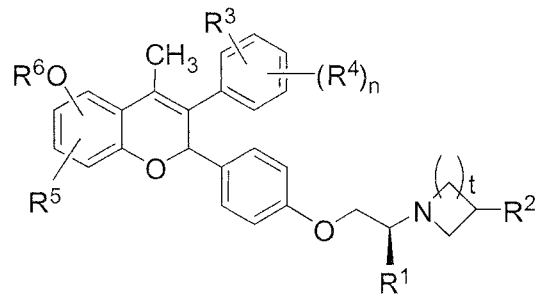
n is 0, 1, or 2;

t is 1 or 2;

or a pharmaceutically acceptable salt, or solvate thereof.

In one aspect, there is provided a therapeutic combination comprising a therapeutically effective amount of an estrogen receptor modulator compound of Formula (C) and a therapeutically effective amount of a second therapeutic agent;

wherein the compound of Formula (C) has the structure:



Formula (C)

where,

R^1 is H, C_1-C_4 alkyl, or C_1-C_4 fluoroalkyl;

R^2 is H, F, C_1-C_4 alkyl or C_1-C_4 fluoroalkyl;

R^3 is H, halogen, -CN, $-OR^6$, $-NHR^6$, $-NR^6R^7$, $-SR^6$, $-S(=O)R^7$, $-S(=O)_2R^7$, C_1-C_4 alkyl, or C_1-C_4 fluoroalkyl;

each R^4 is independently selected from H, halogen, -CN, -OH, C_1-C_6 alkyl, C_1-C_4 fluoroalkyl, C_1-C_4 fluoroalkoxy, and C_1-C_4 alkoxy;

each R^5 is H, F, Cl, -OH, $-CH_3$, $-CF_3$, or $-OCH_3$;

each R^6 is independently selected from H, $-C(=O)R^7$, $-C(=O)OR^7$, $-C(=O)NHR^7$, C_1-C_6 alkyl, C_1-C_6 fluoroalkyl, C_3-C_6 cycloalkyl, substituted or unsubstituted C_2-C_6 heterocycloalkyl, substituted or unsubstituted phenyl, and substituted or unsubstituted monocyclic heteroaryl; each R^7 is independently selected from C_1-C_6 alkyl, C_1-C_6 fluoroalkyl, substituted or unsubstituted C_3-C_6 cycloalkyl, substituted or unsubstituted monocyclic C_2-C_6 heterocycloalkyl, substituted or unsubstituted phenyl, and substituted or unsubstituted monocyclic heteroaryl;

n is 0, 1, or 2;

t is 1 or 2;

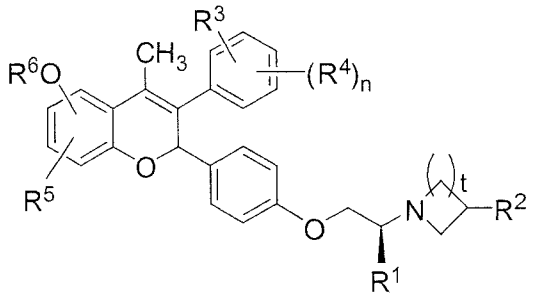
or a pharmaceutically acceptable salt, or solvate thereof;

wherein the second therapeutic agent is an aromatase inhibitor, a phosphoinositide 3-kinase (PI3K)/mTOR pathway inhibitor, a CDK 4/6 inhibitor, a HER-2 inhibitor, an EGFR inhibitor, a PD-1 inhibitor, poly ADP-ribose polymerase (PARP) inhibitor, a histone deacetylase (HDAC) inhibitor, an HSP90 inhibitor, a VEGFR inhibitor, an AKT inhibitor, chemotherapy, or any combination thereof.

In another aspect, there is provided a therapeutic combination comprising a therapeutically effective amount of an estrogen receptor modulator compound of Formula (C) and a therapeutically effective amount of a second therapeutic agent for use in the treatment of an ER-related disease or condition;

wherein the combination is administered to the patient as a combined formulation or by alternation;

wherein the compound of Formula (C) has the structure:



Formula (C)

where,

R^1 is H, C_1-C_4 alkyl, or C_1-C_4 fluoroalkyl;

R^2 is H, F, C_1-C_4 alkyl or C_1-C_4 fluoroalkyl;

R^3 is H, halogen, -CN, $-OR^6$, $-NHR^6$, $-NR^6R^7$, $-SR^6$, $-S(=O)R^7$, $-S(=O)_2R^7$, C_1-C_4 alkyl, or C_1-C_4 fluoroalkyl;

each R^4 is independently selected from H, halogen, -CN, -OH, C_1-C_6 alkyl, C_1-C_4 fluoroalkyl, C_1-C_4 fluoroalkoxy, and C_1-C_4 alkoxy;

each R^5 is H, F, Cl, -OH, $-CH_3$, $-CF_3$, or $-OCH_3$;

each R^6 is independently selected from H, $-C(=O)R^7$, $-C(=O)OR^7$, $-C(=O)NHR^7$, C_1-C_6 alkyl, C_1-C_6 fluoroalkyl, C_3-C_6 cycloalkyl, substituted or unsubstituted C_2-C_6 heterocycloalkyl, substituted or unsubstituted phenyl, and substituted or unsubstituted monocyclic heteroaryl; each R^7 is independently selected from C_1-C_6 alkyl, C_1-C_6 fluoroalkyl, substituted or unsubstituted C_3-C_6 cycloalkyl, substituted or unsubstituted monocyclic C_2-C_6 heterocycloalkyl, substituted or unsubstituted phenyl, and substituted or unsubstituted monocyclic heteroaryl;

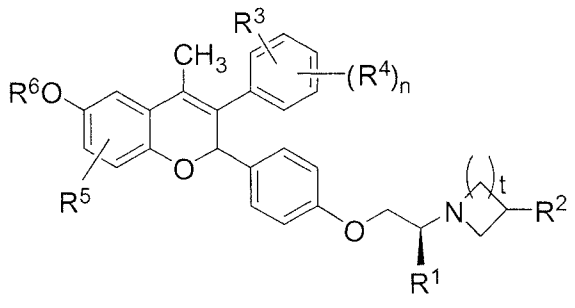
n is 0, 1, or 2;

t is 1 or 2;

or a pharmaceutically acceptable salt, or solvate thereof;

wherein the second therapeutic agent is an aromatase inhibitor, a phosphoinositide 3-kinase (PI3K)/mTOR pathway inhibitor, a CDK 4/6 inhibitor, a HER-2 inhibitor, an EGFR inhibitor, a PD-1 inhibitor, poly ADP-ribose polymerase (PARP) inhibitor, a histone deacetylase (HDAC) inhibitor, an HSP90 inhibitor, a VEGFR inhibitor, an AKT inhibitor, chemotherapy, or any combination thereof.

In some embodiments, the estrogen receptor modulator of Formula (C) is selected from Formulas (C-1), (C-2), (C-3), (C-4), (C-5), and (C-6), having the structures:



Formula (C-1)

carboplatin, capecitabine, cyclophosphamide, docetaxel, doxorubicin, epirubicin, eribulin, fluorouracil, gemcitabine, ixabepilone, mitoxantrone, methotrexate, paclitaxel, pamidronate, vinorelbine, or any combination thereof. In some embodiments, the patient has received pertuzumab, trastuzumab, lapatinib, everolimus, bevacizumab, or temsirolimus, or any combination thereof. In some embodiments, the second therapeutic agent is an anti-cancer agent. In some embodiments, the anti-cancer agent is doxorubicin, cyclophosphamide, capecitabine, vinorelbine, paclitaxel, docetaxel, or cisplatin. In some embodiments, the second therapeutic agent is an aromatase inhibitor, a phosphoinositide 3-kinase (PI3K)/mTOR pathway inhibitor, a CDK 4/6 inhibitor, a HER-2 inhibitor, an EGFR inhibitor, a PD-1 inhibitor, poly ADP-ribose polymerase (PARP) inhibitor, a histone deacetylase (HDAC) inhibitor, an HSP90 inhibitor, a VEGFR inhibitor, an AKT inhibitor, chemotherapy, or any combination thereof.

In another aspect, there is provided a pharmaceutical composition comprising a therapeutic combination for use in the treatment of an ER-related disease or condition as defined herein and one or more pharmaceutically acceptable excipients. In some embodiments, the compound of Formula (A), (B) or (C), or a pharmaceutically acceptable salt, or solvate thereof is administered as a pharmaceutical composition, wherein the pharmaceutical composition is formulated for intravenous injection, subcutaneous injection, oral administration, or topical administration. In some embodiments, the pharmaceutical composition is a tablet, a pill, a capsule, a liquid, a suspension, a gel, a dispersion, a solution, an emulsion, an ointment, or a lotion.

In some embodiments, the pharmaceutical composition described herein further comprises, in addition to the compound of Formula (A), (B), or (C), one or more additional therapeutically active agents. In some embodiments, one or more additional therapeutically active agents are selected from: corticosteroids, anti-emetic agents, analgesics, anti-cancer agents, anti-inflammatories, kinase inhibitors, antibodies, HSP90 inhibitors, histone deacetylase (HDAC) inhibitors, poly ADP-ribose polymerase (PARP) inhibitors, and aromatase inhibitors.

Embodiments include a method comprising administering a compound of Formula (A), (B), or (C), or a pharmaceutically acceptable salt or prodrug thereof, to a human with a diseases or condition that is estrogen sensitive, estrogen receptor meditated or estrogen receptor dependent. In some embodiments, the human is already being administered one or more additional therapeutically active agents other than a compound of Formula (A), (B), or (C), or a pharmaceutically acceptable salt or prodrug thereof. In some embodiments, the method further comprises administering one or more additional therapeutically active agents other than a compound of Formula (A), (B), or (C), or a pharmaceutically acceptable salt or prodrug thereof.

In some embodiments, the one or more additional therapeutically active agents other than a compound of Formula (A), (B), or (C), or a pharmaceutically acceptable salt or prodrug

thereof, are selected from: corticosteroids, anti-emetic agents, analgesics, anti-cancer agents, anti-inflammatories, kinase inhibitors, antibodies, HSP90 inhibitors, histone deacetylase (HDAC) inhibitors, and aromatase inhibitors.

Pharmaceutical formulations described herein are administered to a mammal in a variety of ways, including but not limited to, oral, parenteral (e.g., intravenous, subcutaneous, intramuscular), buccal, topical or transdermal administration routes. The pharmaceutical formulations described herein include, but are not limited to, aqueous liquid dispersions, self-emulsifying dispersions, solid solutions, liposomal dispersions, solid dosage forms, powders, immediate release formulations, controlled release formulations, fast melt formulations, tablets, capsules, pills, delayed release formulations, extended release formulations, pulsatile release formulations, multiparticulate formulations, and mixed immediate and controlled release formulations.

In some embodiments, the compound of Formula (A), (B), or (C), or a pharmaceutically acceptable salt or prodrug thereof, is administered orally, systemically, intravenously, subcutaneously or topically. In such embodiments, the compound of Formula (A), (B), or (C), or a pharmaceutically acceptable salt or prodrug thereof, is formulated into a variety of topically administrable compositions, such as solutions, suspensions, lotions, gels, pastes, shampoos, scrubs, rubs, smears, medicated sticks, medicated bandages, balms, creams or ointments. In some embodiments, the compound of Formula (A), (B), or (C), or a pharmaceutically acceptable salt or prodrug thereof, is administered topically to the skin of mammal.

In another aspect is use of a therapeutic combination as defined herein for the preparation of medicaments for the treatment of an ER-related disease or condition. There is provided the use of a compound of Formula (A), (B), or (C), or a pharmaceutically acceptable salt or prodrug thereof, in the manufacture of a medicament for treating a disease, disorder or conditions in which the activity of estrogen receptors contributes to the pathology and/or symptoms of the disease or condition. In one ~~aspect~~embodiment, the disease or condition is any of the diseases or conditions specified herein.

In any of the aforementioned aspects are further embodiments in which the effective amount of the compound of Formula (A), (B), or (C), or a pharmaceutically acceptable salt thereof, is: (a) systemically administered to the mammal; and/or (b) administered orally to the mammal; and/or (c) intravenously administered to the mammal; and/or (d) administered by injection to the mammal; and/or (e) administered topically to the mammal; and/or (f) adminstered non-systemically or locally to the mammal.

In any of the aforementioned aspects are further embodiments in which the effective amount of the additional therapeutic agent (other than the compound of Formula (A), (B), or (C),

or a pharmaceutically acceptable salt thereof), is: (a) systemically administered to the mammal; and/or (b) administered orally to the mammal; and/or (c) intravenously administered to the mammal; and/or (d) administered by injection to the mammal; and/or (e) administered topically to the mammal; and/or (f) adminstered non-systemically or locally to the mammal.

In any of the aforementioned aspects are further embodiments comprising single administrations of the effective amount of the compound, including further embodiments in which (i) the compound is administered once; (ii) the compound is administered to the mammal multiple times over the span of one day; (iii) continually; or (iv) continuously.

In any of the aforementioned aspects are further embodiments comprising multiple administrations of the effective amount of the compound, including further embodiments in which (i) the compound is administered continuously or intermittently: as in a a single dose; (ii) the time between multiple administrations is every 6 hours; (iii) the compound is administered to the mammal every 8 hours; (iv) the compound is administered to the mammal every 12 hours; (v) the compound is administered to the mammal every 24 hours. In further or alternative embodiments, the method comprises a drug holiday, wherein the administration of the compound is temporarily suspended or the dose of the compound being administered is temporarily reduced; at the end of the drug holiday, dosing of the compound is resumed. In one embodiment, the length of the drug holiday varies from 2 days to 1 year.

Also provided is a method of reducing ER activation in a mammal comprising administering to the mammal at least one compound having the structure of Formula (A), (B), or (C), or a pharmaceutically acceptable salt thereof. In some embodiments, the method comprises reducing ER activation in breast cells, lung cells, ovarian cells, colon cells, prostate cells, endometrial cellls, or uterine cells in the mammal. In some embodiments, the method comprises reducing ER activation in breast cells, ovarian cells, colon cells, prostate cells, endometrial cellls, or uterine cells in the mammal. In some embodiments, the method of reducing ER activation in the mammal comprises reducing the binding of estrogens to estrogen receptors in the mammal. In some embodiments, the method of reducing ER activation in the mammal comprises reducing ER concentrations in the mammal.

There is provided ~~In one aspect is~~ the use of a compound of Formula (A), (B), or (C), or a pharmaceutically acceptable salt thereof, in the treatment or prevention of diseases or conditions of the uterus in a mammal. In some embodiments, the disease or condition of the uterus is leiomyoma, uterine leiomyoma, endometrial hyperplasia, or endometriosis. In some

embodiments, the disease or condition of the uterus is a cancerous disease or condition of the uterus. In some other embodiments, the disease or condition of the uterus is a non-cancerous disease or condition of the uterus.

There is provided ~~In one aspect is~~ the use of a compound of Formula (A), (B), or (C), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of diseases or conditions that are estrogen sentitive, estrogen receptor dependent or estrogen receptor mediated. In some embodiments, the disease or condition is breast cancer, lung cancer, ovarian cancer, colon cancer, prostate cancer, endometrial cancer, or uterine cancer. In some embodiments, the disease or condition is described herein.

In some cases disclosed herein is the use of a compound of Formula (A), (B), or (C), or a pharmaceutically acceptable salt thereof, in the treatment or prevention of diseases or conditions that are estrogen sensitive, estrogen receptor dependent or estrogen receptor mediated. In some embodiments, the disease or condition is described herein.

In any of the embodiments disclosed herein, the mammal is a human.

In any of the embodiments disclosed herein, the patient is a human.

In some embodiments, compounds provided herein are used to diminish, reduce, or eliminate the activity of estrogen receptors.

Articles of manufacture, which include: packaging material; a compound of Formula (A), (B), or (C), or a pharmaceutically acceptable salt, active metabolite, prodrug, or pharmaceutically acceptable solvate thereof, or composition thereof, within the packaging material; and a label that indicates that the compound or pharmaceutically acceptable salt, active metabolite, prodrug, or pharmaceutically acceptable solvate thereof, or composition thereof, or composition thereof, is used for reducing, diminishing or eliminating the effects of estrogen receptors, or for the treatment, prevention or amelioration of one or more symptoms of a disease or condition that would benefit from a reduction or elimination of estrogen receptor activity, are provided.

Other objects, features and advantages of the compounds, methods and compositions described herein will become apparent from the following detailed description. It should be understood, however, that the detailed description and the specific examples, while indicating specific embodiments, are given by way of illustration only, since various changes and modifications within the spirit and scope of the instant disclosure will become apparent to those skilled in the art from this detailed description.

In one embodiment, the ~~invention~~ disclosure relates to a therapeutic combination comprising a therapeutically effective amount of an estrogen receptor modulator compound as described herein, and a therapeutically effective amount of a second therapeutic agent.

In one embodiment, the disclosure ~~invention~~ relates to a therapeutic combination for use in the treatment of an ER-related disease or condition, wherein the therapeutic combination comprises a therapeutically effective amount of an estrogen receptor modulator compound as described herein, and a therapeutically effective amount of a second therapeutic agent.

In one embodiment, the disclosure ~~invention~~ relates to a pharmaceutical composition comprising a therapeutic combination for use in the treatment of an ER-related disease or condition as described herein and one or more pharmaceutically acceptable excipients.

In one embodiment, the disclosure ~~invention~~ relates to the use of a therapeutic combination as described herein for the preparation of medicaments for use in the treatment of an ER-related disease or condition.

In one embodiment, the disclosure ~~invention~~ relates to the use of a therapeutic combination according as described herein for the treatment of an ER-related disease or condition.

In one embodiment, the disclosure ~~invention~~ relates to a method for treating an ER-related disease or condition in a patient comprising administering a therapeutic combination as described herein.

BRIEF DESCRIPTION OF THE DRAWINGS

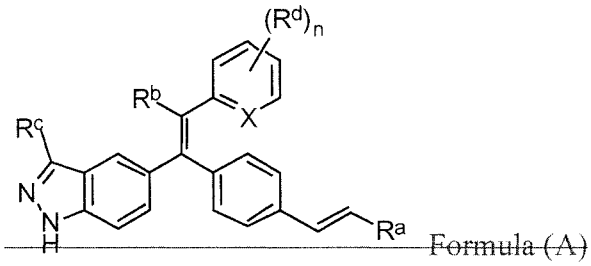
Figure 1 shows the fitted tumor volume change over 42 days in cohorts of 8 immunocompromised mice bearing HCI-003 breast tumor (BC PDX model) xenografts harboring ESR1 WT (wild type) and PIK3CA H1047R (PI3Kα) mutation, dosed daily by 100 microliter (μl) PO (oral) administration with Vehicle (+), Vehicle (-), PI3K inhibitor GDC-0032 at 2 mg/kg and 5 mg/kg, estrogen receptor modulator (ERM) 1-3 from Table 1 at 10 mg/kg, and the combination of ERM 1-3 and GDC-0032. Vehicle (+) is solvent/buffer with ethynyl estradiol (0.1 mg/kg). Vehicle (-) is solvent/buffer without ethynyl estradiol.

Figure 2 shows the fitted tumor volume change over 38 days in cohorts of 8 immunocompromised mice bearing HCI-005 breast tumor (BC PDX model) xenografts harboring ESR1 L536P mutant, HER2+, dosed daily by 100 microliter (μl) PO (oral) administration with Vehicle (+), Vehicle (-), PI3K inhibitor GDC-0032 at 2 mg/kg and 5 mg/kg, estrogen receptor modulator (ERM) 1-3 from Table 1 at 100 mg/kg, and the combination of ERM 1-3 and GDC-0032.

WHAT IS CLAIMED IS:

1. A therapeutic combination comprising a therapeutically effective amount of an estrogen receptor modulator compound ~~selected from~~of Formulae ~~(A), (B), or~~ (C) and a therapeutically effective amount of a second therapeutic agent;

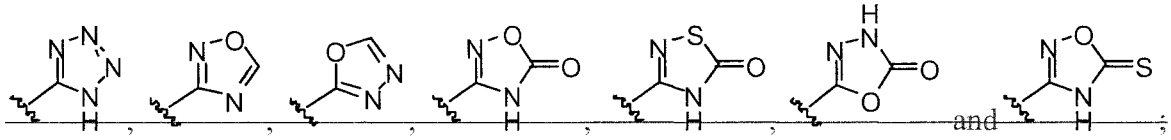
~~wherein the compound of Formula (A) has the structure:~~



~~Formula (A)~~

~~where,~~

~~R^a is $-CO_2H$ or a 5-membered heterocycle selected from the group consisting of~~



and ~~;~~

~~R^b is C_1-C_6 alkyl or C_3-C_6 cycloalkyl;~~

~~R^c is H or F;~~

~~each R^d is independently selected from H, halogen, $-CN$, $-OR^e$, $-NHR^e$, $-NR^eR^f$, $-SR^e$, $-S(=O)R^f$, $-S(=O)_2R^f$, C_1-C_6alkyl, and C_1-C_6fluoroalkyl;~~

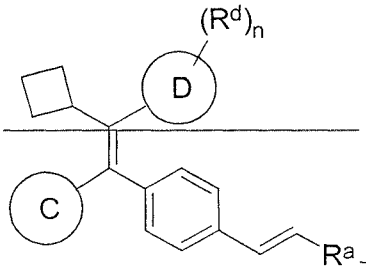
~~each R^e is independently selected from H, $-C(=O)R^f$, $-C(=O)OR^f$, $-C(=O)NHR^f$, C_1-C_6 alkyl, C_1-C_6 fluoroalkyl, C_3-C_6 cycloalkyl, substituted or unsubstituted monocyclic C_2-C_6 heterocycloalkyl, substituted or unsubstituted phenyl, and substituted or unsubstituted monocyclic heteroaryl;~~

~~each R^f is independently selected from C_1-C_6 alkyl, C_1-C_6 fluoroalkyl, C_3-C_6 cycloalkyl, substituted or unsubstituted monocyclic C_2-C_6 heterocycloalkyl, substituted or unsubstituted phenyl, and substituted or unsubstituted monocyclic heteroaryl;~~

~~X is CH or N; and~~

~~n is 0, 1, or 2, or a pharmaceutically acceptable salt, or solvate thereof;~~

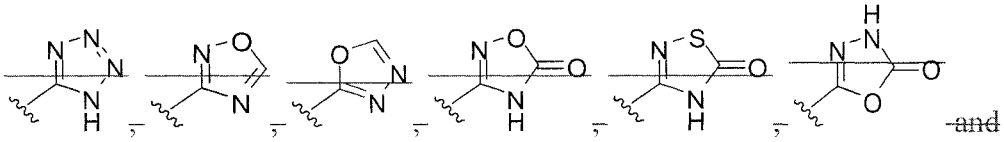
~~wherein the compound of Formula (B) has the structure:~~



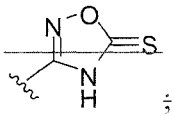
~~Formula (B)~~

~~where,~~

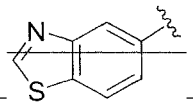
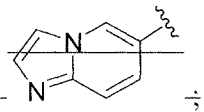
~~R^a is $-CO_2H$ or a 5-membered heterocycle selected from the group consisting of~~



~~and~~



~~;~~

~~ring C is~~  ~~or~~  ~~;~~

~~ring D is phenyl or thienyl;~~

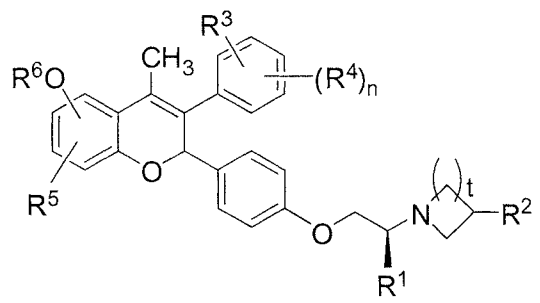
~~each R^d is independently selected from H, halogen, $-CN$, $-OR^e$, $-NHR^e$, $-NR^eR^f$, $-SR^e$, $-S(=O)R^f$, $-S(=O)_2R^f$, C_1-C_6 alkyl, and C_1-C_6 fluoroalkyl;~~

~~each R^e is independently selected from H, $-C(=O)R^f$, $-C(=O)OR^f$, $-C(=O)NHR^f$, C_1-C_6 alkyl, C_1-C_6 fluoroalkyl, C_3-C_6 cycloalkyl, substituted or unsubstituted monocyclic C_2-C_6 heterocycloalkyl, substituted or unsubstituted phenyl, and substituted or unsubstituted monocyclic heteroaryl;~~

~~each R^f is independently selected from C_1-C_6 alkyl, C_1-C_6 fluoroalkyl, C_3-C_6 cycloalkyl, substituted or unsubstituted monocyclic C_2-C_6 heterocycloalkyl, substituted or unsubstituted phenyl, and substituted or unsubstituted monocyclic heteroaryl;~~

~~n is 0, 1, or 2; or a pharmaceutically acceptable salt, or solvate thereof;~~

wherein the compound of Formula (C) has the structure:



Formula (C)

where,

R^1 is H, C_1-C_4 alkyl, or C_1-C_4 fluoroalkyl;

R^2 is H, F, C_1-C_4 alkyl or C_1-C_4 fluoroalkyl;

R^3 is H, halogen, -CN, -OR^6, -NHR^6, -NR^6R^7, -SR^6, -S(=O)R^7, -$S(=O)_2R^7$, C_1-C_4 alkyl, or C_1-C_4 fluoroalkyl;

each R^4 is independently selected from H, halogen, -CN, -OH, C_1-C_6 alkyl, C_1-C_4 fluoroalkyl, C_1-C_4 fluoroalkoxy, and C_1-C_4 alkoxy;

each R^5 is H, F, Cl, -OH, $-CH_3$, $-CF_3$, or $-OCH_3$;

each R^6 is independently selected from H, -C(=O)R^7, -C(=O)OR^7, -C(=O)NHR^7, C_1-C_6 alkyl, C_1-C_6 fluoroalkyl, C_3-C_6 cycloalkyl, substituted or unsubstituted C_2-C_6 heterocycloalkyl, substituted or unsubstituted phenyl, and substituted or unsubstituted monocyclic heteroaryl; each R^7 is independently selected from C_1-C_6 alkyl, C_1-C_6 fluoroalkyl, substituted or unsubstituted C_3-C_6 cycloalkyl, substituted or unsubstituted monocyclic C_2-C_6 heterocycloalkyl, substituted or unsubstituted phenyl, and substituted or unsubstituted monocyclic heteroaryl;

n is 0, 1, or 2;

t is 1 or 2;

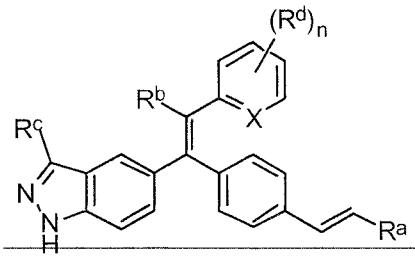
or a pharmaceutically acceptable salt, or solvate thereof;

wherein the second therapeutic agent is an aromatase inhibitor, a phosphoinositide 3-kinase (PI3K)/mTOR pathway inhibitor, a CDK 4/6 inhibitor, a HER-2 inhibitor, an EGFR inhibitor, a PD-1 inhibitor, poly ADP-ribose polymerase (PARP) inhibitor, a histone deacetylase (HDAC) inhibitor, an HSP90 inhibitor, a VEGFR inhibitor, an AKT inhibitor, chemotherapy, or any combination thereof.

2. A therapeutic combination comprising a therapeutically effective amount of an estrogen receptor modulator compound of ~~selected from~~ Formula~~e (A), (B), or~~ (C) and a therapeutically effective amount of a second therapeutic agent for use in the treatment of an ER-related disease or condition;

wherein the combination is administered to the patient as a combined formulation or by alternation;

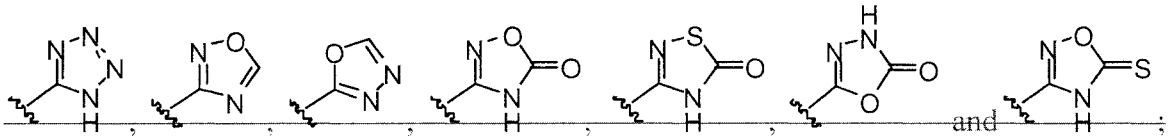
~~wherein the compound of Formula (A) has the structure:~~



~~Formula (A)~~

~~where,~~

R^a is $-CO_2H$ or a 5-membered heterocycle selected from the group consisting of



;

R^b is C_1-C_6 alkyl or C_3-C_6 cycloalkyl;

R^c is H or F;

each R^d is independently selected from H, halogen, $-CN$, $-OR^e$, $-NHR^e$, $-NR^eR^f$, $-SR^e$, $-S(=O)R^f$, $-S(=O)_2R^f$, C_1-C_6alkyl, and C_1-C_6fluoroalkyl;

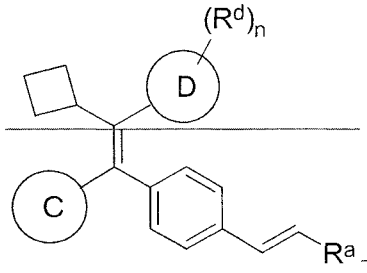
each R^e is independently selected from H, $-C(=O)R^f$, $-C(=O)OR^f$, $-C(=O)NHR^f$, C_1-C_6 alkyl, C_1-C_6 fluoroalkyl, C_3-C_6 cycloalkyl, substituted or unsubstituted monocyclic C_2-C_6 heterocycloalkyl, substituted or unsubstituted phenyl, and substituted or unsubstituted monocyclic heteroaryl;

each R^f is independently selected from C_1-C_6 alkyl, C_1-C_6 fluoroalkyl, C_3-C_6 cycloalkyl, substituted or unsubstituted monocyclic C_2-C_6 heterocycloalkyl, substituted or unsubstituted phenyl, and substituted or unsubstituted monocyclic heteroaryl;

X is CH or N; and

n is 0, 1, or 2, or a pharmaceutically acceptable salt, or solvate thereof;

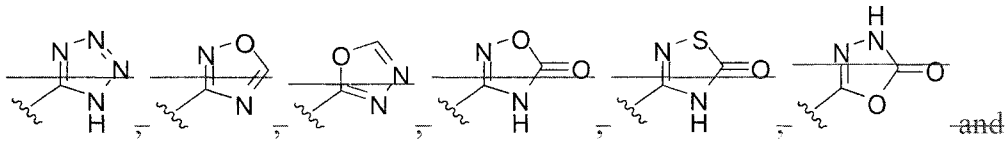
wherein the compound of Formula (B) has the structure:



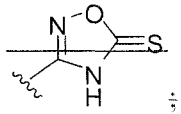
Formula (B)

where,

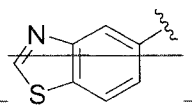
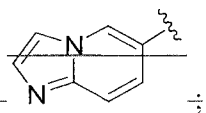
R^a is $-CO_2H$ or a 5-membered heterocycle selected from the group consisting of



and



;

ring C is  or  ;

ring D is phenyl or thienyl;

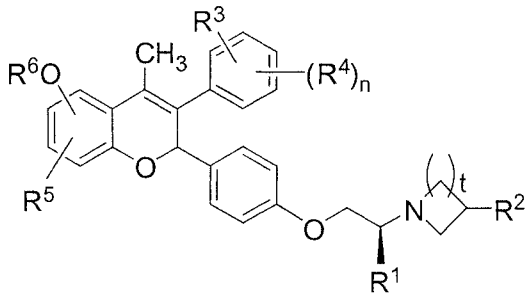
each R^d is independently selected from H, halogen, $-CN$, $-OR^e$, $-NHR^e$, $-NR^eR^f$, $-SR^e$, $-S(=O)R^f$, $-S(=O)_2R^f$, C_1-C_6 alkyl, and C_1-C_6 fluoroalkyl;

~~each R^e is independently selected from H, $-C(=O)R^f$, $-C(=O)OR^f$, $-C(=O)NHR^f$, C_1-C_6 alkyl, C_1-C_6 fluoroalkyl, C_3-C_6 cycloalkyl, substituted or unsubstituted monocyclic C_2-C_6 heterocycloalkyl, substituted or unsubstituted phenyl, and substituted or unsubstituted monocyclic heteroaryl;~~

~~each R^f is independently selected from C_1-C_6 alkyl, C_1-C_6 fluoroalkyl, C_3-C_6 cycloalkyl, substituted or unsubstituted monocyclic C_2-C_6 heterocycloalkyl, substituted or unsubstituted phenyl, and substituted or unsubstituted monocyclic heteroaryl;~~

~~n is 0, 1, or 2; or a pharmaceutically acceptable salt, or solvate thereof;~~

wherein the compound of Formula (C) has the structure:



Formula (C)

where,

R^1 is H, C_1-C_4 alkyl, or C_1-C_4 fluoroalkyl;

R^2 is H, F, C_1-C_4 alkyl or C_1-C_4 fluoroalkyl;

R^3 is H, halogen, -CN, $-OR^6$, $-NHR^6$, $-NR^6R^7$, $-SR^6$, $-S(=O)R^7$, $-S(=O)_2R^7$, C_1-C_4 alkyl, or C_1-C_4 fluoroalkyl;

each R^4 is independently selected from H, halogen, -CN, -OH, C_1-C_6 alkyl, C_1-C_4 fluoroalkyl, C_1-C_4 fluoroalkoxy, and C_1-C_4 alkoxy;

each R^5 is H, F, Cl, -OH, $-CH_3$, $-CF_3$, or $-OCH_3$;

each R^6 is independently selected from H, $-C(=O)R^7$, $-C(=O)OR^7$, $-C(=O)NHR^7$, C_1-C_6 alkyl, C_1-C_6 fluoroalkyl, C_3-C_6 cycloalkyl, substituted or unsubstituted C_2-C_6 heterocycloalkyl, substituted or unsubstituted phenyl, and substituted or unsubstituted monocyclic heteroaryl; each R^7 is independently selected from C_1-C_6 alkyl, C_1-C_6 fluoroalkyl, substituted or unsubstituted C_3-C_6 cycloalkyl, substituted or unsubstituted monocyclic C_2-C_6 heterocycloalkyl, substituted or unsubstituted phenyl, and substituted or unsubstituted monocyclic heteroaryl;

n is 0, 1, or 2;

t is 1 or 2;

or a pharmaceutically acceptable salt, or solvate thereof;

wherein the second therapeutic agent is an aromatase inhibitor, a phosphoinositide 3-kinase (PI3K)/mTOR pathway inhibitor, a CDK 4/6 inhibitor, a HER-2 inhibitor, an EGFR inhibitor, a PD-1 inhibitor, poly ADP-ribose polymerase (PARP) inhibitor, a histone deacetylase (HDAC) inhibitor, an HSP90 inhibitor, a VEGFR inhibitor, an AKT inhibitor, chemotherapy, or any combination thereof.

3. The therapeutic combination for use in the treatment of an ER-related disease or condition according to claim 2 wherein the therapeutically effective amounts of the estrogen receptor modulator compound and the second therapeutic agent are administered as a combined formulation.

4. The therapeutic combination for use in the treatment of an ER-related disease or condition according to claim 2 wherein the therapeutically effective amounts of the estrogen receptor modulator compound and the second therapeutic agent are administered by alternation.

5. The therapeutic combination for use in the treatment of an ER-related disease or condition according to claim 2 wherein the patient is administered with the estrogen receptor modulator compound and subsequently administered with the second therapeutic agent.

6. The therapeutic combination for use in the treatment of an ER-related disease or condition according to claim 2 wherein the therapeutic combination is administered by a dosing regimen where the therapeutically effective amount of the estrogen receptor modulator compound is administered in a range from twice daily to once every three weeks, and the therapeutically effective amount of the second therapeutic agent is administered in a range from twice daily to once every three weeks.

7. The therapeutic combination for use in the treatment of an ER-related disease or condition according to claim 6 wherein the dosing regimen is repeated one or more times.

8. The therapeutic combination for use in the treatment of an ER-related disease or condition according to claim 2 wherein the estrogen receptor modulator compound and the second therapeutic agent are each administered in an amount from about 1 mg to about 1000 mg per unit dosage form.

9. The therapeutic combination for use in the treatment of an ER-related disease or condition according to claim 2 wherein the estrogen receptor modulator compound and the second therapeutic agent are administered in a ratio of about 1:50 to about 50:1 by weight.

10. The therapeutic combination for use in the treatment of an ER-related disease or condition according to claim 2 wherein administration of the therapeutic combination results in a synergistic effect.

11. The therapeutic combination for use in the treatment of an ER-related disease or condition according to claim 2 wherein the ER-related disease or condition is cancer.

12. The therapeutic combination for use in the treatment of an ER-related disease or condition according to claim 11 wherein the cancer is selected from breast, cervical, colon, endometrial, glioma, lung, melanoma, ovarian, pancreatic, and prostate.

13. The therapeutic combination for use in the treatment of an ER-related disease or condition according to claim 12 wherein the cancer expresses a PIK3CA mutant selected from E542K, E545K, Q546R, H1047L and H1047R, a K-ras mutant, or a PTEN mutant.

14. The therapeutic combination for use in the treatment of an ER-related disease or condition according to claim 12 wherein the cancer is breast cancer.

15. The therapeutic combination for use in the treatment of an ER-related disease or condition according to claim 14 wherein the breast cancer is metastatic, hormone resistant, estrogen receptor positive, estrogen receptor negative, progesterone receptor negative, HER2 positive, or HER2 negative breast cancer.

16. The therapeutic combination for use in the treatment of an ER-related disease or condition according to claim 14 wherein the breast cancer is resistant to treatment with an aromatase inhibitor.

17. The therapeutic combination for use in the treatment of an ER-related disease or condition according to claim 16 wherein the aromatase inhibitor is anastrozole, letrozole, or exemestane.

18. The therapeutic combination for use in the treatment of an ER-related disease or condition according to claim 15 wherein the breast cancer is Basal or Luminal subtype.

19. The therapeutic combination for use in the treatment of an ER-related disease or condition according to claim 2 wherein the patient is a pre-menopausal or post-menopausal female patient.

20. The therapeutic combination for use in the treatment of an ER-related disease or condition according to claim 2 wherein the patient has failed one or more anti-cancer therapies.

21. The therapeutic combination for use in the treatment of an ER-related disease or condition according to claim 2 wherein the second therapeutic agent is a phosphoinositide 3-kinase (PI3K)/mTOR pathway inhibitor.

22. The therapeutic combination for use in the treatment of an ER-related disease or condition according to claim 21 wherein the phosphoinositide 3-kinase (PI3K)/mTOR pathway inhibitor is GDC-0032 or GDC-0941.

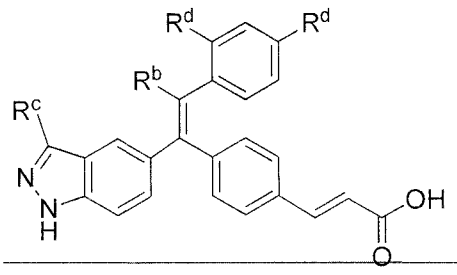
23. The therapeutic combination for use in the treatment of an ER-related disease or condition according to claim 21 wherein a biological sample obtained from the patient, prior to administration of the therapeutic combination to the patient, has been tested for PIK3CA or PTEN mutation status, and wherein PIK3CA or PTEN mutation status is indicative of therapeutic responsiveness by the patient to the therapeutic combination.

24. The therapeutic combination for use in the treatment of an ER-related disease or condition according to claim 21 wherein a biological sample has been tested by measuring functional PI3K protein level after administration of the therapeutic combination, wherein a change in the level of functional PI3K protein indicates that the patient will be resistant or responsive to the therapeutic combination.

25. The therapeutic combination for use in the treatment of an ER-related disease or condition according to claim 2 wherein the second therapeutic agent is an AKT inhibitor.

26. The therapeutic combination for use in the treatment of an ER-related disease or condition according to claim 25 wherein the AKT inhibitor is GDC-0068.

~~27. The therapeutic combination for use in the treatment of an ER-related disease or condition according to claim 2 wherein the estrogen receptor modulator is a compound of Formula (A-1) having the structure:~~



~~Formula (A-1)~~

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

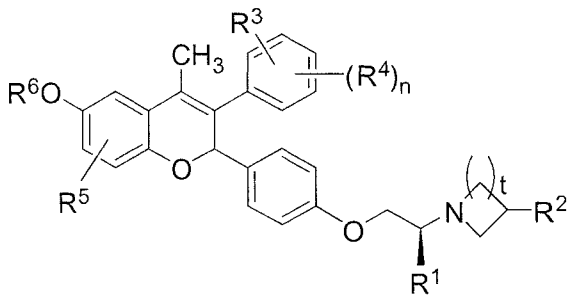
~~28. The therapeutic combination for use in the treatment of an ER-related disease or condition according to claim 27 wherein the estrogen receptor modulator is a Formula (A) compound~~

~~selected from 1-1, 1-2, 1-3, 1-4, 1-5, 1-6, 1-7, 1-8, 1-9, 1-10, 1-11, or 1-12, or a pharmaceutically acceptable salt, or solvate thereof.~~

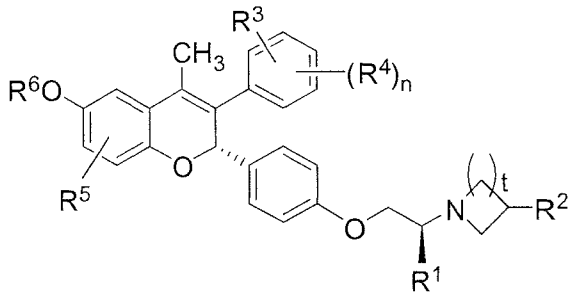
~~29. The therapeutic combination for use in the treatment of an ER-related disease or condition according to claim 28 wherein the estrogen receptor modulator is 1-3.~~

~~30. The therapeutic combination for use in the treatment of an ER-related disease or condition according to claim 2 wherein estrogen receptor modulator is a Formula (B) compound selected from 2-1, 2-2, 2-3, 2-4, or 2-5, or a pharmaceutically acceptable salt, or solvate thereof.~~

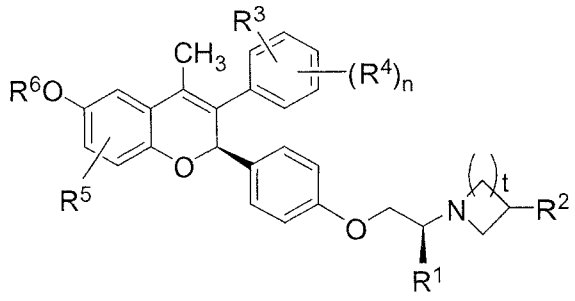
~~31~~27. The therapeutic combination for use in the treatment of an ER-related disease or condition according to claim 2 wherein estrogen receptor modulator of Formula (C) is selected from Formulas (C-1), (C-2), (C-3), (C-4), (C-5), and (C-6), having the structures:



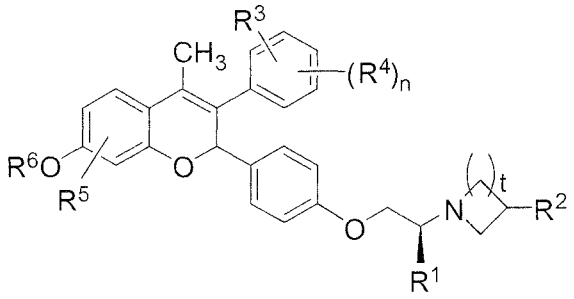
Formula (C-1)



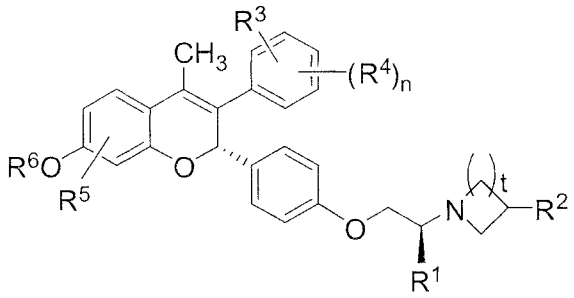
Formula (C-2)



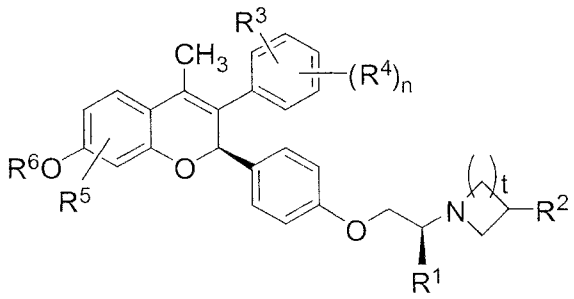
Formula (C-3)



Formula (C-4)



Formula (C-5)



Formula (C-6),

or a pharmaceutically acceptable salt, or solvate thereof.

~~32~~28. The therapeutic combination for use in the treatment of an ER-related disease or condition according to claim ~~31~~27, wherein estrogen receptor modulator is a Formula (C) compound selected from 4-1, 4-2, 4-3, 4-4, 4-5, 4-6, 4-7, 4-8, 4-9, 4-10, 4-11, 4-12, 4-13, 4-14, 4-15, 4-16, 4-17, 4-18, 4-19, 4-20, 4-21, 4-22, 4-23, 4-24, 4-25, 4-26, 4-27, 4-28, 4-29, 4-30, 4-31, 4-32, 4-33, 4-34, 4-35; or a pharmaceutically acceptable salt, or solvate thereof.

~~33~~29. The therapeutic combination for use in the treatment of an ER-related disease or condition according to claim ~~32~~28, wherein estrogen receptor modulator is 4-34.

~~34~~30. The therapeutic combination for use in the treatment of an ER-related disease or condition according to claim ~~32~~28, wherein estrogen receptor modulator is 4-35.

~~35~~31. A pharmaceutical composition comprising a therapeutic combination for use in the treatment of an ER-related disease or condition according to any of claims 1 to ~~34~~30 and one or more pharmaceutically acceptable excipients.

~~36~~32. The use of a therapeutic combination according to any of claims 1 to ~~34~~30 for the preparation of medicaments for use in the treatment of an ER-related disease or condition.

~~37. The use of a therapeutic combination according to any of claims 1 to 34 for the treatment of an ER-related disease or condition.~~

~~38. A method for treating an ER-related disease or condition in a patient comprising administering a therapeutic combination according to any of claims 1 to 34 to a patient.~~