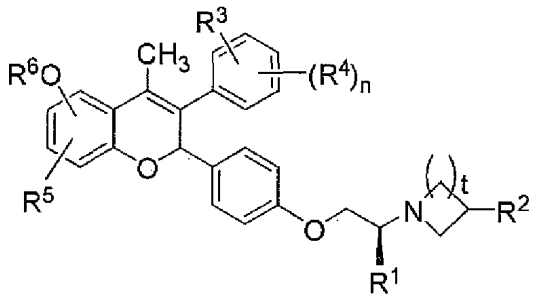
Formula (C) in combination with a second therapeutic agent, wherein the compound of Formula (C) has the structure:



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;

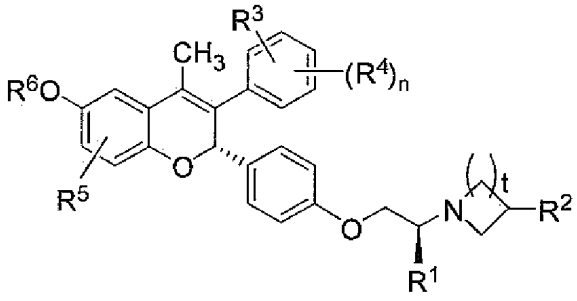
n is 0, 1, or 2;

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-2) and a therapeutically effective amount of a second therapeutic agent;

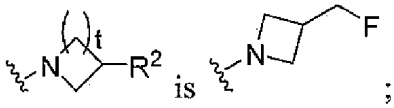
wherein the compound of Formula (C-2) has the structure:



Formula (C-2)

where,

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

 is ;

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;

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

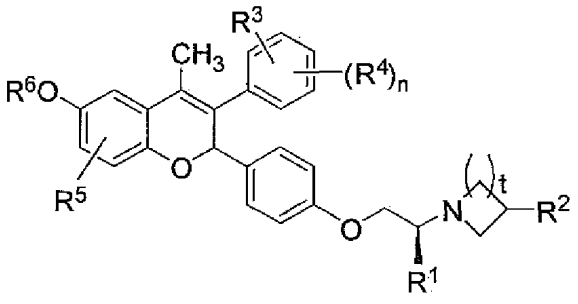
R^6 is independently selected from H, -C(=O)R^7, -C(=O)OR^7, -C(=O)NHR^7, C_1-C_6 alkyl, C_1-C_6 fluoroalkyl, C_3-C_6 cycloalkyl, substituted or unsubstituted C_2-C_6 heterocycloalkyl, substituted or unsubstituted phenyl, and substituted or unsubstituted monocyclic heteroaryl; each R^7 is independently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

or a pharmaceutically acceptable salt, or solvate thereof;

wherein the second therapeutic agent is aa phosphoinositide 3-kinase (PI3K) inhibitor.

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)

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.

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 embodiment, the disease or condition is any of the diseases or conditions specified herein.

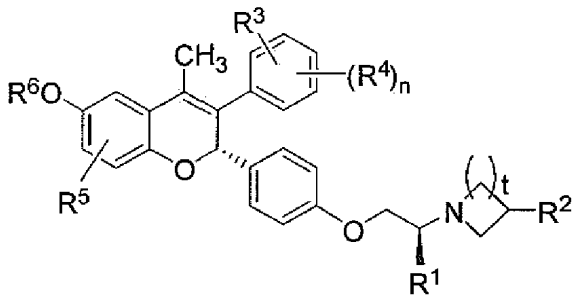
In any of the aforementioned aspects are further embodiments in which the effective amount of the compound of Formula (A), (B), or (C), or a pharmaceutically acceptable salt thereof, is: (a) systemically administered to the mammal; and/or (b) administered orally to the mammal; and/or (c) intravenously 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),

WHAT IS CLAIMED IS:

1. A therapeutic combination comprising a therapeutically effective amount of an estrogen receptor modulator compound of Formula (C-2) and a therapeutically effective amount of a second therapeutic agent;

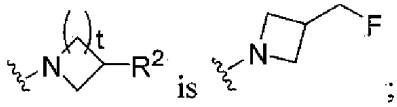
wherein the compound of Formula (C-2) has the structure:



Formula (C-2)

where,

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

 is ;

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;

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

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;

or a pharmaceutically acceptable salt, or solvate thereof;

wherein the second therapeutic agent is a phosphoinositide 3-kinase (PI3K) pathway inhibitor.

2. The therapeutic combination according to claim 1 for use in the treatment of an ER-related disease or condition; wherein the combination is to be administered to the patient as a combined formulation or by alternation; and wherein the ER-related disease or condition is breast cancer.

3. The therapeutic combination for use in the treatment of an ER-related disease or condition according to claim 2 wherein the breast cancer is metastatic, hormone resistant, estrogen receptor positive, estrogen receptor negative, progesterone receptor negative, HER2 positive, or HER2 negative breast cancer.

4. The therapeutic combination for use in the treatment of an ER-related disease or condition according to claim 2 wherein the breast cancer is resistant to treatment with an aromatase inhibitor.

5. The therapeutic combination for use in the treatment of an ER-related disease or condition according to claim 4 wherein the aromatase inhibitor is anastrozole, letrozole, or exemestane.

6. The therapeutic combination for use in the treatment of an ER-related disease or condition according to claim 3 wherein the breast cancer is Basal or Luminal subtype.

7. The therapeutic combination for use in the treatment of an ER-related disease or condition according to claim 2 wherein the phosphoinositide 3-kinase (PI3K) pathway inhibitor is GDC-0032 or GDC-0941.

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

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

10. A pharmaceutical composition comprising a therapeutic combination for use in the treatment of an ER-related disease or condition according to any of claims 2 to 9 and one or more pharmaceutically acceptable excipients.