Abstract:

This invention relates to a method of treating a disorder modulated, mediated or affected by the estrogen receptor in a subject comprising administering to the subject a specific benzopyran (in the form of a mixture of S-C2 and R-C2 diastereomers or its pure S-diastereomer) in combination with an agent selected from the group consisting of a mTOR inhibitor, a CDK 4/6 inhibit - or, a PI3 Kinase inhibitor, a taxane, an antimitabolite, and an antitumor antibiotic.
— as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(H))

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

Published:

— with international search report (Art. 21(3))
COMBINATIONS OF BENZOPYRAN COMPOUNDS,
COMPOSITIONS AND USES THEREOF

FIELD

[0001] This invention is in the field of pharmaceuticals, and in particular, this invention is related to the treatment of cancers mediated by the estrogen receptor by administering a specific benzopyran (in the form of a mixture of S-C2 and R-C2 diastereomers or its pure S-diastereomer) as described in US 2013/0178445 and WO 2013/090921 in combination with particular agents, active agents, anti-cancer agents or chemotherapeutic agents.

BACKGROUND

[0002] Estrogen receptor modulators are a class of compounds that act on the estrogen receptor. These compounds can be pure agonists (mimicking estrogen), pure antagonists, or mixed agonist-antagonists (sometimes referred to as Selective Estrogen Receptor Modulators (SERMs)). For example, estradiol (A) is a pure agonist, fulvestrant (B) is a complete antagonist, and tamoxifen (C) and raloxifene (D) are SERMs.

[0003] Most breast cancers express estrogen receptors (ER), and their growth is driven by the action of estrogen at its receptors, primarily at ER alpha. This type of cancer is treated with an estrogen antagonist, which competes with estrogen for binding to the receptor, but does not activate it, preventing estrogen-driven growth. 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. A recent study also suggests that fulvestrant is substantially superior to the aromatase inhibitor anastrozole in treating metastatic breast cancer (Robertson et al. J Clin Oncol (2009) 27(27):4530-5).

[0004] Estradiol is a naturally-occurring female estrogenic hormone.Raloxifene was disclosed by Eli Lilly in 1981 (U.S. Patent No. 4,418,068; 5,478,847; 5,393,763; and 5,457,117) for prevention of breast cancer and treatment of osteoporosis. Fulvestrant was disclosed by Imperial Chemical Industries (ICI) in 1983 (U.S. Patent No. 4,659,516, expired in 2007 with a patent term extension; U.S. Patent Nos. 6,774,122 and 7,456,160). Tamoxifen was also disclosed
by ICI in the ’516 patent. Tamoxifen was developed for the treatment of breast cancer on the basis of strong antagonism of estrogen action in mammary tissue (Jordan, J. Cell. Biochem. 51 (1995)).

Tamoxifen and other partial anti-estrogens stimulate uterine weight gain in the agonist mode and only partly block estrogen-driven uterine weight gain in the antagonist mode. Fulvestrant and other complete anti-estrogens do not stimulate uterine weight gain in the agonist mode and completely block estrogen-driven weight gain in the antagonist mode. The induction of estrogen-regulated alkaline phosphatase expression in human uterine cancer cell growth in culture can be used to distinguish partial and complete anti-estrogenicity and correlates well with the rodent weight gain assay.
Tamoxifen and fulvestrant both inhibit cultured human breast cancer cell proliferation provoked by estrogen. However, fulvestrant more fully inhibits the proliferation when provoked with growth factors, especially of the insulin/insulin-like growth factor family. Thus the inhibition of growth-factor driven breast cancer cell proliferation and the effect on uterine weight provide two assays which can distinguish between complete and partial anti-estrogens.

Tamoxifen binding stabilizes the estrogen receptor whereas fulvestrant and chemically related antiestrogens, such as ICI-164384 and RU-58668, cause degradation of the estrogen receptor. (Dodge et al, J. Bone Miner. Res., 8 (Suppl 1, S278 (1993); Wakeling, Breast Cancer Res. Treat. 25, 1 (1993); Baer et al, Calcified Tissue Int., 55, 338 (1994). However, some compounds, like GW-5638 (Wu et al, Mol Cell.,18,413 (2005), and OP1075, described below, degrade the receptor but are partial estrogens- that is, not complete anti-estrogens. Thus the ability to degrade the estrogen receptor does not ensure complete antiestrogenicity. The ability to induce degradation of the receptor is nonetheless a factor that differentiates the behavior of tamoxifen and fulvestrant and may be desirable in a drug to treat breast cancer.

Fulvestrant, which degrades the estrogen receptor, incorporates a core of 17-beta estradiol. It has a long flexible aliphatic side chain that blocks oral absorption. The estradiol core blocks oral absorption and the long flexible aliphatic side chain makes the drug very insoluble which worsens the problem. Fulvestrant must be injected because of the poor oral bioavailability. Two 5 ml intramuscular depot injections, one into each buttock, must be administered monthly by a health professional. Furthermore, it is unclear whether these two injections provide sufficient drug exposure for optimal action. The drug does not seem to work in pre-menopausal women.

In 1990, an important step in oral anti-estrogen development came with the discovery of a family of high-affinity benzopyran anti-estrogens by Kapil and coworkers. (Sharma et al. (1990) J Med Chem, 33(12):3222-9; Sharma et al. (1990) J Med Chem, 33(12):3216-22). The numbering scheme of benzopyrans is typically:
Sharma et al. showed that the combination of 7-hydroxyl and 4'-hydroxyl groups conferred high-affinity binding of the benzopyran core to the estrogen receptor (Compound G; see Compound 25 of Sharma et al. (1990) J Med Chem, 33(12):3222-9 where R¹ and R² are OH).

Further, Sharma et al. reported that the presence of a methyl group at the 4 position of the benzopyran core enhanced receptor binding affinity, without a hydroxyl group at the 4'-position.

In 1991, Labrie and coworkers filed a patent application which issued as U.S. Patent No. 5,395,842 (see claim 29) which taught that EM-343 (H), showed superior binding to the estrogen receptor with no loss of anti-estrogen action. EM-343 differed from the Saeed compounds by including the hydroxyl at the 4'-position of a 4-methyl, 7-hydroxyl benzopyran.

In 1995, Labrie et al. filed a continuation-in-part patent application, which issued in 2000 as U.S. Patent No. 6,060,503, disclosing prodrugs and optically active species of EM-343. Particularly, Labrie et al. disclosed a pure isomer of EM-343, EM-652, referred to as acolbifene (I), which is (S)-3-(4-hydroxyphenyl)-4-methyl-2-(4-(2-(piperidin-1-yl)ethoxy)phenyl)-2H-chromen-7-ol.
Labrie et al. in WO 01/54699 (see Figure 4a and 4b) also presented several broad generic Markush formulae of benzopyran-containing compounds, including acolbifene analogs, in which the side chain terminates in various substituted ring systems including pyrrolidinyl, piperidinyl, and methyl-1-pyrrolidinyl and dimethyl-1-pyrrolidinyl.

U.S. Patent Nos. 7,005,428 and 6,465,445 to Labrie, which claim priority to a June 1998 application describe the following generic formulas for use as anti-estrogenic compounds:

\[
\text{EM-652, acolbifene}
\]

\[
\text{I}
\]

[0013] wherein \( D \) is \(-\text{OCH}_2\text{CH}_2\text{N}(R_3)R_4\) (\(R_3\) and \(R_4\) either being independently selected from the group consisting of \(\text{C}_1-\text{C}_4\) alkyl, or \(R_3, R_4\) and the nitrogen atom to which they are bound together being a ring structure selected from the group consisting of pyrrolidino, dimethyl-1-pyrrolidinyl, methyl-1-purrolidinyl, piperidino, hexamethyleneimino and morpholino); and

[0014] wherein \(R_1\) and \(R_2\) are independently selected from the group consisting of hydrogen, hydroxyl and a moiety converted in vivo in to hydroxyl, and
wherein $R_1$ and $R_2$ are independently selected from the group consisting of hydroxyl and a moiety converted in vivo into hydroxyl;

wherein $R_3$ is a species selected from the group consisting of saturated, unsaturated or substituted pyrrolidinyl, saturated, unsaturated or substituted piperidino, saturated, unsaturated or substituted piperidinyl, saturated, unsaturated or substituted morpholino, nitrogen-containing cyclic moiety, nitrogen-containing polycyclic moiety, and NRaRb (Ra and Rb being independently hydrogen, straight or branched C$_i$-C$_6$ alkyl, straight or branched C$_2$-C$_6$ alkenyl, and straight of branched C$_2$-C$_6$ alkynyl.

[0015] Acolbifene binds to the estrogen receptor alpha with three times the affinity of 17-beta estradiol, the native ligand (Katzenellenbogen (2011) J Med Chem 54(15):5271-82). Since anti-estrogens must compete with estradiol for binding to the estrogen receptor, high affinity binding is an important drug virtue. Both the Labrie '842 and the Labrie '503 patents disclosed benzopyran compounds that can contain an unsubstituted pyrrolidine in the "tail" or $R^3$ position as depicted in Compound F. EM-800, a pivalate prodrug of EM-652, and HCl salts of EM-652 were also described in the '503 patent.

[0016] Acolbifene was initially thought to be a complete anti-estrogen. However, careful studies with the rodent uterine assay and human uterine cell alkaline phosphatase assays revealed that it retained some estrogen-like action, about 12% that of estradiol (Labrie et al. "The combination of a novel selective estrogen receptor modulator with an estrogen protects the mammary gland and uterus in a rodent model: the future of postmenopausal women's health?" Endocrinology. 2003 144(11):4700-6). This contrasts with fulvestrant where the residual estrogen-like action is almost unmeasurable. Furthermore, fulvestrant binding induces dramatic degradation of the estrogen receptor, while acolbifene induces either no or modest receptor degradation. Raloxifene and bazedoxifene don't degrade the receptor, but stabilize the receptor to a much lesser degree than tamoxifen.
Acolbifene is orally bioavailable and is currently being positioned for Phase III clinical trials for the treatment of breast cancer by the Canadian company Endoceutics (Founded by Dr. Labrie). A daily oral dose of 40 mg of acolbifene or EM800 in women produces mean drug exposures of 8.3 and 15 ng/ml of circulating acolbifene, respectively. In preclinical studies both forms of the drug are effective against tamoxifen-resistant human breast cancer xenografts growing on immunocompromised mice. In clinical studies the 40mg dose of EM800 was numerically as effective as anastrozole in preventing progression of metastatic estrogen receptor positive breast cancer.


The group tried to maximize the estrogen receptor α/β selectivity ratio and minimize uterine activity (e.g., maximize antagonism of uterine activity). They reported that the unbranched linker with 3-methyl pyrrolidinyl and 3,4-methyl pyrrolidinyl as well as the a-methyl (i.e., a methyl on the a-position of the ethylene) linker with an unsubstituted pyrrolidinyl side chains were noteworthy. Blizzard et al. concluded that minor modifications in the side chain or linker resulted in significant effects on biological activity, especially in uterine tissue.

Blizzard et al. also studied a chromane core (Blizzard et al. (2005) Bioorg Med Chem Lett. 15(6): 1675-81) (Compound K).
The Merck chromane core differs from the acolbifene core by the absence of a double bond in the oxane ring. These structures also had a hydroxyl at position 6 (not 7) of the fused benzene ring. A chromane core with a 2-methyl pyrrolidine (but not a 3-methyl) with a methyl on the linker created a nearly complete anti-estrogen, (see compound 12 of the Blizzard et al. paper). Blizzard et al. commented on the differences among anti-estrogenic activities of variously substituted cores, and noted that the size and stereogenic placement of substituents is crucial for receptor potency and selectivity.

In the third publication of this series (Blizzard et al. (2005) Bioorg Med Chem Lett. 15(17):3912-6); Blizzard et al. again studied the dihydrobenzoxathiin core and reported that their studies have resulted in the discovery that addition of a methyl group to the side chain at the appropriate position and with the right stereochemistry, either on the pyrrolidine ring or on the linker substantially increased estrogen antagonist activity in uterine tissue. Blizzard et al. also reported that the best estrogen antagonist activity in this dihydrobenzoxathiin series was determined to have a methyl group on the pyrrolidine and a methyl group on the linker, with the hydroxyl in the 6-position of the fused benzene ring. Blizzard et al. also noted that to their knowledge, their optimized side chain with two methyl groups represented the first example where a relatively small structural modification of an existing SERM resulted in a conversion of a SERM to a SERAM/SERD (Selective Estrogen Receptor alpha Modulator and Down-regulator).

The Merck team then investigated whether the optimized side chain modification reported for the dihydrobenzoxathiin core was "portable" and could confer strong anti-estrogenicity when appended to different cores (Blizzard et al. (2005) Bioorg Med Chem Lett. 15(23):5214-8). Merck demonstrated that none of the three cores tested (raloxifene, bazedoxifene, or lasofoxifene) became more anti-estrogenic with either the 3-methyl pyrrolidine or the chiral side chain modifications. Blizzard et al. concluded that "The lack of a dramatic
effect on the uterine profile upon incorporation of side chains A and B clearly indicates that the side chain Structure Activity Relationship of the dihydrobenzoxathiin SERAMs is not transferable to other platforms."

[0024] In yet another 2005 research publication, Gauthier, Labrie and colleagues reported the synthesis and structure-activity relationships of analogs of acolbifene (Gauthier et al. (2005) J Enzyme Inhib Med Chem, 20(2): 165-77). They attempted to improve on the anti-estrogenicity of acolbifene by creating analogs in which the terminal piperidine was either replaced by pyrrolidine or substituted in various ways. All of these analogs proved to be more estrogenic than acolbifene as revealed by the rodent uterus assay. This experience suggests that improvement of the anti-estrogenicity of acolbifene will be a challenge and modifications provide unpredictable results.

[0025] Blizzard reviewed the Merck research on anti-estrogens in 2008 (Curr Top Med Chem. 8(9):792-812). He noted that:

"Selective Estrogen Receptor Modulators (SERMs) have been the subject of extensive medicinal chemistry efforts at several pharmaceutical companies, including Merck…..The Merck SERM project involved a large number of talented and dedicated chemists and biologists who worked for several years to discover novel classes of SERMs with a range of selectivities. …no drugs have yet reached the market as a result of this effort."

[0026] Indeed, the Merck effort began in the early 1990's and continued well into the 2000's, reflecting impressive science but no commercial products. Their most promising compounds, which included side chains in which the piperidine ring was replaced with a mono- or di-substituted pyrrolidine ring appended to a benzoxathiin core, especially with a 3-R methyl pyrrolidine terminus, showed anti-estrogenicity, although not as complete as fulvestrant in the rodent uterus assay. A chiral methyl on atom 2 of the flexible linker also conferred improved anti-estrogenicity. The two features together in a doubly substituted side chain conferred anti-estrogenicity that was similar to fulvestrant. Unfortunately the Merck core had problematic reactive metabolites when investigated in primates, which halted clinical development.

[0027] Aragon Pharmaceuticals filed PCT/US201 1/039669 (published December 15, 2011 as WO201 1/156518), which claimed priority to U.S. Provisional Application 61/353,531 titled "Estrogen Receptor Modulators and Uses Thereof” filed in June 2010. Aragon disclosed large genuses of benzopyran derivatives and at least 71 acolbifene analogs intended for treatment of tamoxifen resistant breast cancer. Aragon appears to have taken the prior art teachings of
Merck regarding how to optimize the dihydrobenzoxathiin core, and applied the teachings to the acolbifene benzopyran core. Aragon is considering advancing a drug to the clinic for late stage progressive metastatic disease.

[0028] Kushner et al. (US 2013/0178445 and WO 2013/090921, both filed Dec. 17, 2012 and both assigned to Olema Pharmaceuticals) describe OP-1038 (3-(4-hydroxyphenyl)-4-methyl-2-(4-{2-[(3R)-3-methylpyrrolidin-1-yl]ethoxy}phenyl)-2H-chromen-7-ol) and OP-1074 ((2S)-3-(4-hydroxyphenyl)-4-methyl-2-(4-{2-[(3R)-3-methylpyrrolidin-1-yl]ethoxy}phenyl)-2H-chromen-7-ol), as well as pharmaceutical compositions and methods of use.


[0035] Thus, there is a need for new combinations and pharmaceutical compositions for the treatment of medical disorders that are mediated or affected by an estrogen receptor.

**SUMMARY OF THE INVENTION**

[0036] Each of the embodiments described below can be combined with any other embodiment described herein not inconsistent with the embodiment with which it is combined. The phrase "or a pharmaceutically acceptable salt thereof" is implicit in the description of all compounds described herein; however, in one aspect of any of the embodiments herein, the compound is in the form of a free base.

[0037] Embodiments described herein relate to a method of treating a disorder modulated, mediated or affected by the estrogen receptor in a subject comprising administering to the subject a compound, which is
wherein \( R_1 \) and \( R_2 \) are independently either:

(i) \( \text{OH or OR}^9 \),

(ii) wherein \( R^9 \) is independently selected from H, halogen (Cl, Br, I or F), natural or non-naturally occurring amino acid (bound through either the OC(O)- or C(0)O- (an ester) or the amino (through either -C(0)-N- or -N-C(O)- (an amide linkage)), \( R^{10} \), -OR\(^{10} \), or -SR\(^{11} \)

where \( R^{10} \) is \(-\text{C}(=0)\text{R}^{\text{Cl}}\), \(-\text{C}(=0)\text{OR}^{\text{Cl}}\), \(-\text{C}(=0)\text{SR}^{\text{Cl}}\), \(-\text{N}(\text{R}^{\text{Cl}})^2\); or polyethylene glycol, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or
unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;
-\(-S(=0)\)\(_2\)R\(^{C1}\), -\(S(=0)\)OR\(^{C1}\), -\(S(=0)R\)\(^{C1}\), -\(S(=0)OR\)\(^{C1}\), -\(P(=0)\)\(_2\)R\(^{C1}\),
-\(P(=0)\)OR\(^{C1}\), -\(P(=0)(OR)^{C1}\)_2, -\(P(=0)(R)^{C1}\)_2, or -\(P(R)^{C1}(OR)^{C1}\); or oxygen attached to an oxygen protecting group (to produce OH on administration), sulfur attached to a sulfur protecting group (to produce SH or a disulfide on administration), or nitrogen attached to a nitrogen protecting group (to produce -NH- on administration);
and R\(^{C1}\) can be independently selected from hydrogen, polyethylene glycol, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, or two R\(^{C1}\) groups are joined to form an substituted or unsubstituted heterocyclic ring;
or a pharmaceutically acceptable salt, solvate, hydrate, prodrug, stereoisomer, tautomer, or N-oxide thereof,
in combination with an agent selected from the group consisting of an mTOR inhibitor, a CDK 4/6 inhibitor, a PI3 Kinase inhibitor, a taxane, an antimetabolite, and an antitumor antibiotic.

[0038] In embodiments of the method of the invention, the compound is in the form of a pharmaceutically acceptable salt.

[0039] In embodiments of the method of the invention, either or both of R1 or R2 is an ester, amide, carbonate or phosphate.

[0040] In embodiments of the method of the invention, compound is in the form of a prodrug, further wherein the prodrug is

\[
\text{OP-1 088}
\]
In embodiments of the method of the invention, the compound is (2S)-3-(4-hydroxyphenyl)-4-methyl-2-(4-{2-[(3R)-3-methylpyrrolidin-1-yl]ethoxy}phenyl)-2H-chromen-7-ol, which has the chemical structure:

![Chemical Structure](image)

OP-1074 or a pharmaceutically acceptable salt, solvate, hydrate, or N-oxide thereof.

Embodiments described herein relate to a method of treating a disorder modulated, mediated or affected by the estrogen receptor in a subject comprising administering to the subject a compound, which is (2S)-3-(4-hydroxyphenyl)-4-methyl-2-(4-{2-[(3R)-3-methylpyrrolidin-1-yl]ethoxy}phenyl)-2H-chromen-7-ol, which has the chemical structure:

![Chemical Structure](image)

OP-1074 or a pharmaceutically acceptable salt thereof, in combination with an agent selected from the group consisting of an mTOR inhibitor, a CDK 4/6 inhibitor, a PI3 Kinase inhibitor, a taxane, an antimetabolite, and an antitumor antibiotic.
In embodiments of the method of the invention, the compound is administered in alternation with an agent selected from the group consisting of an mTOR inhibitor, a CDK 4/6 inhibitor, a PI3 Kinase inhibitor, a taxane, an antimetabolite, and an antitumor antibiotic.

Embodiments described herein relate to a combination of a compound, which is

wherein R₁ and R₂ are independently either:

(i) OH or OR⁹,

(ii) wherein R⁹ is independently selected from H, halogen (Cl, Br, I or F), natural or non-naturally occurring amino acid (bound through either the OC(O)- or C(0)0- (an ester) or the amino (through either -C(0)-N- or -N-C(O)- (an amide linkage)), R¹⁰, -OR¹⁰, or -SR¹⁰
where \( R^{10} \) is \(-\text{C}(=\text{O})\text{R}^{\text{Cl}}, -\text{C}(=\text{O})\text{OR}^{\text{Cl}}, -\text{C}(=\text{O})\text{SR}^{\text{Cl}}, -\text{C}(=\text{O})\text{N}((\text{R}^{\text{Cl}}))_2; \) or polyethylene glycol, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

\(-\text{S}(=\text{O})_2\text{R}^{\text{Cl}}, -\text{S}(=\text{O})_2\text{OR}^{\text{Cl}}, -\text{S}(=\text{O})\text{R}^{\text{Cl}}, -\text{S}(=\text{O})\text{OR}^{\text{Cl}}, -\text{P}(=\text{O})_2\text{R}^{\text{Cl}}, -\text{P}(=\text{O})_2\text{OR}^{\text{Cl}}, -\text{P}(=\text{O})(\text{OR}^{\text{Cl}})_2, -\text{P}(=\text{O})(\text{R}^{\text{Cl}})_2, \) or \(-\text{P}((\text{R}^{\text{Cl}}))(\text{OR}^{\text{Cl}}); \) or oxygen attached to an oxygen protecting group (to produce OH on administration), sulfur attached to a sulfur protecting group (to produce SH or a disulfide on administration), or nitrogen attached to a nitrogen protecting group (to produce -NH- on administration),

and \( \text{R}^{\text{Cl}} \) can be independently selected from hydrogen, polyethylene glycol, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, or two \( \text{R}^{\text{Cl}} \) groups are joined to form an substituted or unsubstituted heterocyclic ring;

or a pharmaceutically acceptable salt, solvate, hydrate, prodrug, stereoisomer, tautomer, or N-oxide thereof,

and an agent selected from the group consisting of an mTOR inhibitor, a CDK 4/6 inhibitor, a PI3 Kinase inhibitor, a taxane, an antimetabolite, and an antitumor antibiotic, for the treatment of a disorder modulated, mediated or affected by the estrogen receptor.

[0045] In embodiments of the combination of the invention, the compound is in the form of a pharmaceutically acceptable salt.

[0046] In embodiments of the combination of the invention, the compound is \((2\text{S})-3-(4\text{-hydroxyphenyl})-4\text{-methyl}-2-(4\{-2\{-(3\text{R})-\text{3}-\text{methylpyrrolidin-1-yl}\text{ethoxy}\}\text{phenyl})-2\text{H}-\text{chromen}-7\text{-ol}, which has the chemical structure:

\[
\text{OP-1074}
\]

or a pharmaceutically acceptable salt, solvate, hydrate, or N-oxide thereof.
[0047] Embodiments described herein relate to a combination of (2S)-3-(4-hydroxyphenyl)-4-methyl-2-(4-{2-[(3R)-3-methylpyrrolidin-1-yl]ethoxy}phenyl)-2H-chromen-7-ol, which has the chemical structure:

```
OP-1074
```

or a pharmaceutically acceptable salt thereof, and an agent selected from the group consisting of an mTOR inhibitor, a CDK 4/6 inhibitor, a PI3 Kinase inhibitor, a taxane, an antimetabolite, and an antitumor antibiotic for the treatment of a disorder modulated, mediated or affected by the estrogen receptor.

[0048] In embodiments of the method and combination of the invention, the disorder is mediated by the estrogen receptor.

[0049] In embodiments of the method and combination of the invention, the disorder is breast cancer.

[0050] In embodiments of the method and combination of the invention, the breast cancer is local, advanced or metastatic estrogen or progesterone receptor positive advanced breast cancer.

[0051] In embodiments of the method and combination of the invention, the breast cancer is estrogen or progesterone receptor positive advanced breast cancer.

[0052] In embodiments of the method and combination of the invention, the breast cancer is estrogen or progesterone receptor negative breast cancer.

[0053] In embodiments of the method and combination of the invention, the disorder is selected from the group consisting of ovarian cancer, endometrial cancer, vaginal cancer, endometriosis, lung cancer, and bronchial cancer.

[0054] In embodiments of the method and combination of the invention, the disorder is selected from the group consisting of ovarian, endometrial, and vaginal cancer and endometriosis.

[0055] In embodiments of the method and combination of the invention, the disorder is retinoblastoma positive breast cancer.
In embodiments of the method and combination of the invention, the disorder is selected from the group consisting of retinoblastoma positive endometrial, vaginal and ovarian cancers and lung and bronchial cancers.

In embodiments of the method and combination of the invention, the disorder is lung cancer or bronchial cancer.

In embodiments of the method and combination of the invention, the subject is a patient.

In embodiments of the method and combination of the invention, the agent is a CDK 4/6 inhibitor.

In embodiments of the method and combination of the invention, the CDK 4/6 inhibitor is PD-0332991, LY2835219, or LEE011.

In embodiments of the method and combination of the invention, the CDK 4/6 inhibitor is PD-0332991, or a pharmaceutically acceptable salt thereof.

In embodiments of the method and combination of the invention, the CDK 4/6 inhibitor is PD-0332991.

In embodiments of the method and combination of the invention, the agent is an mTOR inhibitor.

In embodiments of the method and combination of the invention, the mTOR inhibitor is rapamycin, everolimus, temsirolimus, AP23573, AZD8055, WYE-354, WYE-600, WYE-687, or Ppl21.

In embodiments of the method and combination of the invention, the mTOR inhibitor is everolimus.

In embodiments of the method and combination of the invention, the agent is a PI3 Kinase inhibitor.

In embodiments of the method and combination of the invention, the PI3 Kinase inhibitor is BKM-120, XL-147, RG-7321, CH-5132799 and BAY-80-6946.

In embodiments of the method and combination of the invention, the PI3 Kinase inhibitor is BKM-120.

In embodiments of the method and combination of the invention, the agent is a taxane.

In embodiments of the method and combination of the invention, the taxane is paclitaxel or docetaxel.
[0071] In embodiments of the method and combination of the invention, the agent is an antimetabolite.

[0072] In embodiments of the method of the invention, the antimetabolite is 5-fluorouracil.

[0073] In embodiments of the method and combination of the invention, the agent is an antitumor antibiotic.

[0074] In embodiments of the method and combination of the invention, the antitumor antibiotic is doxorubicin.

[0075] Embodiments described herein relate to a pharmaceutical composition comprising a pharmaceutically effective amount of a compound, which is

![OP-1038](image1)

![OP-1074](image2)

, or
wherein R_i and R_2 are independently either:

(i) OH or OR^9,

(ii) wherein R^9 is independently selected from H, halogen (Cl, Br, I or F), natural or non-naturally occurring amino acid (bound through either the OC(0)- or C(0)0- (an ester) or the amino (through either -C(0)-N- or -N-C(0)- (an amide linkage)), R^10, -OR^10, or -SR^10 where R^10 is -C(=0)R^C_1, -C(=0)OR^C_1, -C(=0)SR^C_1, -C(=0)N(R^C_1)_2; or polyethylene glycol, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; -S(=0)R^C_1, -S(=0)OR^C_1, -S(=0)SR^C_1, -S(=0)N(R^C_1)_2; or -P(=0)R^C_1, -P(=0)OR^C_1, -P(=0)SR^C_1, -P(=0)N(R^C_1)_2; or oxygen attached to an oxygen protecting group (to produce OH on administration), sulfur attached to a sulfur protecting group (to produce SH or a disulfide on administration), or nitrogen attached to a nitrogen protecting group (to produce -NH- on administration); and R^C_1 can be independently selected from hydrogen, polyethylene glycol, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, or two R^C_1 groups are joined to form an substituted or unsubstituted heterocyclic ring; or a pharmaceutically acceptable salt, solvate, hydrate, prodrug, stereoisomer, tautomer, or N-oxide thereof,

in combination with an agent selected from the group consisting of an mTOR inhibitor, a CDK 4/6 inhibitor, a PI3 Kinase inhibitor, a taxane, an antimetabolite, and an antitumor antibiotic, and a pharmaceutically acceptable carrier.

[0076] In embodiments of the pharmaceutical composition of the invention, the compound is in the form of a pharmaceutically acceptable salt.
In embodiments of the pharmaceutical composition of the invention, \( R_1 \) or \( R_2 \) is an ester, amide, carbonate or phosphate.

In embodiments of the pharmaceutical composition of the invention, the compound is in the form of a prodrug, further wherein the prodrug is

\[
\text{OP-1088,}
\]  
\[
\text{OP-1074\textsuperscript{+}HCl,}
\]  
\[
\text{OP-1086,}
\]  
\[
\text{OP-1084.}
\]
In embodiments of the pharmaceutical composition of the invention, the compound is (2S)-3-(4-hydroxyphenyl)-4-methyl-2-(4-{2-[(3R)-3-methylpyrrolidin-1-yl]ethoxy}phenyl)-2H-chromen-7-ol, which has the chemical structure:

Or a pharmaceutically acceptable salt, solvate, hydrate, or N-oxide thereof.

Embodiments described herein relate to a pharmaceutical composition of the invention relates to a compound, which is (2S)-3-(4-hydroxyphenyl)-4-methyl-2-(4-{2-[(3R)-3-methylpyrrolidin-1-yl]ethoxy}phenyl)-2H-chromen-7-ol, which has the chemical structure:
or a pharmaceutically acceptable salt thereof,
in combination with an agent selected from the group consisting of an mTOR inhibitor, a CDK 4/6 inhibitor, a PI3 Kinase inhibitor, a taxane, an antimetabolite, and an antitumor antibiotic, and a pharmaceutically acceptable carrier.

[0081] In embodiments of the pharmaceutical composition of the invention, the agent is a CDK 4/6 inhibitor.

[0082] In embodiments of the pharmaceutical composition of the invention, the CDK 4/6 inhibitor is PD-0332991, LY2835219, or LEE011.

[0083] In embodiments of the pharmaceutical composition of the invention, the CDK 4/6 inhibitor is PD-0332991, or a pharmaceutically acceptable salt thereof.

[0084] In embodiments of the pharmaceutical composition of the invention, the CDK 4/6 inhibitor is PD-0332991.

[0085] In embodiments of the pharmaceutical composition of the invention, the agent is an mTOR inhibitor.

[0086] In embodiments of the pharmaceutical composition of the invention, the mTOR inhibitor is rapamycin, everolimus, temsirolimus, AP23573, AZD8055, WYE-354, WYE-600, WYE-687, or Ppl21.

[0087] In embodiments of the pharmaceutical composition of the invention, the mTOR inhibitor is everolimus.

[0088] In embodiments of the pharmaceutical composition of the invention, the agent is a PI3 Kinase inhibitor.

[0089] In embodiments of the pharmaceutical composition of the invention, the PI3 Kinase inhibitor is BKM-120, XL-147, RG-7321, CH-5132799 and BAY-80-6946.

[0090] In embodiments of the pharmaceutical composition of the invention, the PI3 Kinase inhibitor is BKM-120.

[0091] In embodiments of the pharmaceutical composition of the invention, the agent is a taxane.
In embodiments of the pharmaceutical composition of the invention, the taxane is paclitaxel or docetaxel.

In embodiments of the pharmaceutical composition of the invention, the agent is an antimetabolite.

In embodiments of the pharmaceutical composition of the invention, the antimetabolite is 5-fluorouracil.

In embodiments of the pharmaceutical composition of the invention, the agent is an antitumor antibiotic.

In embodiments of the pharmaceutical composition of the invention, the antitumor antibiotic is doxorubicin.

The present invention relates to the treatment of tumors, including cancers, mediated by the estrogen receptor with the combination of a specific benzopyran (in the form of a mixture of S-C2 and R-C2 diastereomers and also its pure S-diastereomer) as described in US 2013/0178445 and WO 2013/090921 in combination or alternation with specific agents, active agents, anti-cancer agents or chemotherapeutic agents, and in some embodiments, in certain improved dosages or formulations. Benefits that can result include increased efficacy and/or lower doses when the specified combinations are used. Tumors, including cancers which benefit from such combinations or alternations are those that are mediated by the estrogen receptor and will also respond to the second agent. Specific examples of agents, active agents, anti-cancer agents or chemotherapeutic agents that can be combined with compounds described in US 2013/0178445 and WO 2013/090921 include an mTOR inhibitor such as everolimus, or a CDK 4/6 inhibitor such as PD-0332991, or a PI3 Kinase Inhibitor such as BKM-120, or a taxane, or an antimetabolite such as 5-fluorouracil, or an antitumor antibiotic such as doxorubicin. In one embodiment, the combination therapy includes the described anti-estrogenic compounds combined with PD-0332991 for treatment of retinoblastoma positive breast cancer as well as retinoblastoma positive endometrial, vaginal and ovarian cancers and lung and bronchial cancers.

The term "combinations of the invention" or the like (such as "combined with") as used herein refers to the concerted use of one or more of the compounds described in US 2013/0178445 and WO 2013/090921 with an agent, active agent, anti-cancer agent or chemotherapeutic agent, wherein the concerted use can be either (i) a pharmaceutically acceptable formulation that includes both active agents; or (ii) separate pharmaceutical formulations that independently provide each active and are either administered at the same time or at different times but in a concerted synchronized fashion in a manner that optimizes the
benefit of the combination therapy (i.e., alternation therapy). For example, certain actives will normally be administered orally, such as in a tablet, pill or liquid, and others might be normally administered via intravenous injection or other systemic, topical, parenteral, transdermal or other route.

[0099] The compounds that can be combined or alternated with agents, active agents, anti-cancer agents or chemotherapeutic agents are described in US 2013/0178445 and WO 2013/090921 and depicted below as OP-1038 and OP-1074. The chemical name for OP-1038 is 3-(4-hydroxyphenyl)-4-methyl-2-(4- {2-[(3R)-3-methylpyrrolidin-1-yl]ethoxy} phenyl)-2H-chromen-7-ol. The chemical name for OP-1074 is (2S)-3-(4-hydroxyphenyl)-4-methyl-2-(4-{2-[(3R)-3-methylpyrrolidin-1-yl]ethoxy}phenyl)-2H-chromen-7-ol.

[00100] The active compound to be combined or alternated with an agent, active agent, anti-cancer agent or chemotherapeutic agent, can be provided if desired as a pharmaceutically acceptable salt, solvate, hydrate, prodrug, stereoisomer, tautomer, N-oxide or R¹ and/or R²-substituted derivative optionally in a pharmaceutically acceptable composition to treat a tumor that is modulated or affected by an estrogen receptor, including those treatable with an anti-estrogenic compound optimally with virtually no estrogenic effect.

![Chemical Structure of OP-1038](image)

OP-1038
[00101] OP-1038 and OP-1074 have two chiral carbons and thus there are four possible diastereomers. The chiral carbon at the C2 position is in the S-configuration in OP-1074 (the same configuration in EM-652, acolbifene) and is a mixture of R and S in OP-1038.

[00102] OP-1038, OP-1074 and their prodrugs (including esters, carbonates and phosphates), derivatives and their salts when combined with specific agents, active agents, anti-cancer agents or chemotherapeutic agents, are especially useful to treat locally advanced or metastatic breast cancer that is positive for expression of estrogen receptors, progesterone receptors or both (receptor positive advanced breast cancer) and are also responsive to the specific agent, active agent, anti-cancer agent or chemotherapeutic agent. In an alternative embodiment, the combinations are used to treat estrogen or progesterone receptor negative breast cancer. The combinations can be used as the initial treatment of advanced breast cancer in patients who have never received previous hormonal therapy for advanced breast cancer. Specific examples of active agents that can be combined with compounds described in US 2013/0178445 and WO 2013/090921 include an mTOR inhibitor such as everolimus, or a CDK 4/6 inhibitor such as PD-0332991, or a PI3 Kinase Inhibitor such as BKM-120, or a taxane, or an antimetabolite such as 5-fluorouracil, or an antitumor antibiotic such as doxorubicin. In one embodiment, the combination therapy includes the compounds described in US 2013/0178445 and WO 2013/090921 combined with PD-0332991 for treatment of retinoblastoma positive breast cancer as well as retinoblastoma positive endometrial, vaginal and ovarian cancers and lung and bronchial cancers.
The combinations described in the present invention are also useful as adjuvant therapy after surgery to prevent recurrence. Such adjuvant use is often administered for several years, for instance 5 years, or even up to 10 years after surgery and associated chemotherapy and radiotherapy have been concluded. In one embodiment, the adjuvant combination therapy includes the compounds described in US 2013/0178445 and WO 2013/090921 combined with PD-0332991 for treatment of retinoblastoma positive breast cancer as well as retinoblastoma positive endometrial, vaginal and ovarian cancers and lung and bronchial cancers.

The combinations described in the present invention are also useful for the prevention of breast cancer in women at high risk for breast cancer and can be taken for any desired time period, including indefinitely. For example, a patient, typically a woman, with a family history of breast cancer, or who has been determined to carry a mutation in the BRCA1 or BRCA2 gene or other genes that predispose a patient to breast cancer may choose to use such preventative treatment instead of a mastectomy or other intervention. The combinations described herein are also useful as neoadjuvants to shrink large tumors prior to surgical removal, both to enable breast conservative surgery and to reduce the risk of recurrence. In addition to breast cancer these combinations are also useful to treat other cancers and other overgrowth diseases of the female reproductive tract including ovarian, endometrial, and vaginal cancer and endometriosis. Besides these reproductive tissues the combinations are useful in treating lung cancers that are positive for estrogen or progesterone receptors. When such cancers are retinoblastoma positive, the combination of the compound described in US 2013/0178445 and WO 2013/090921 with PD-0332991 is beneficial.

Other objects and advantages will become apparent to those skilled in the art from a consideration of the ensuing detailed description. All variations and modifications of the disclosed invention are considered within the scope of this invention.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1. OP-1074 increases the potency and efficacy of the CDK 4/6 inhibitor PD-0332991 in inhibiting E2-stimulated MCF-7 breast cell proliferation. The antiestrogen OP-1074 enhances the efficacy and potency of PD-0332991 in inhibiting E2-stimulated breast cell proliferation in vitro. MCF-7 cells were treated with the indicated amount of antiestrogen and PD-0332991 in hormone-depleted medium for 6-7 days in the presence of 100 pM 17P-estradiol (E2). Fig. 1A plots the effects on MCF-7 cell proliferation of vehicle, 1, 10 or 100nM OP-1074.
in combination with increasing amounts of PD-0332991. Fig. 1B plots the effects on MCF-7 cell proliferation of vehicle or 100nM PD-0332991 in combination with increasing amounts of OP-1074. Fig. 1C plots the effects on MCF-7 cell proliferation of vehicle or 3nM OP-1074, tamoxifen, or fulvestrant in combination with increasing amounts of PD-0332991. Proliferation was measured using Cyquant fluorescent DNA-binding dye (Invitrogen, Grand Island, NY).

Results were from a single representative experiment and reported as the mean percent induction relative to E2 from triplicate treatments, with error bars representing SEM.

[00107] Figure 2. OP-1074 increases the potency of the mTOR inhibitor everolimus in inhibiting E2-stimulated MCF-7 breast cell proliferation. The antiestrogen OP-1074 enhances the efficacy and potency of the mTOR inhibitor everolimus in inhibiting E2-stimulated breast cell proliferation in vitro. MCF-7 cells were treated with the indicated amount of OP-1074 and everolimus in hormone-depleted medium for 6 days in the presence of 100 pM 17P-estradiol (E2). Fig. 2A plots the effects on MCF-7 cell proliferation of vehicle, 1, 10 or 100nM OP-1074 in combination with increasing amounts of everolimus. Fig. 2B plots the effects on MCF-7 cell proliferation of vehicle, InM or 10nM everolimus in combination with increasing amounts of OP-1074. Fig. 2C plots the effects on MCF-7 cell proliferation of vehicle or 3nM OP-1074, tamoxifen, or fulvestrant in combination with increasing amounts of everolimus. Proliferation was measured as in Figure 1 and results were from a single representative experiment and reported as the mean percent induction relative to E2 from triplicate treatments, with error bars representing SEM.

[00108] Figure 3. OP-1074 increases the potency of the pan PI3K inhibitor BKM-120 in inhibiting E2-stimulated MCF-7 breast cell proliferation. The antiestrogen OP-1074 enhances the efficacy and potency of the PI3K inhibitor BKM-120 in inhibiting E2-stimulated breast cell proliferation in vitro. MCF-7 cells were treated with the indicated amount of OP-1074 and BKM-120 in hormone-depleted medium for 7 days in the presence of 100 pM 17P-estradiol (E2). Fig. 3A plots the effects on MCF-7 cell proliferation of vehicle, 1, 10 or 100nM OP-1074 in combination with increasing amounts of BKM-120. Fig. 3B plots the effects on MCF-7 cell proliferation of vehicle, 32nM or 100nM BKM-120 in combination with increasing amounts of OP-1074. Proliferation was measured as in Figure 1 and results were from a single representative experiment and reported as the mean percent induction relative to E2 from triplicate treatments, with error bars representing SEM.

[00109] Figure 4. OP-1074 increases the potency of 5-Fluorouracil in inhibiting E2-stimulated MCF-7 breast cell proliferation. The antiestrogen OP-1074 enhances the efficacy and
potency of the thymidylate synthase inhibitor 5-Fluorouracil in inhibiting E2-stimulated breast cell proliferation in vitro. MCF-7 cells were treated with the indicated amount of OP-1074 and 5-fluorouracil in hormone-depleted medium for 6 days in the presence of 100 pM 17P-estradiol (E2). The effects on MCF-7 cell proliferation of vehicle, 1, 10 or 100nM OP-1074 in combination with increasing amounts of 5-fluorouracil are plotted. Proliferation was measured as in Figure 1 and results were from a single representative experiment and reported as the mean percent induction relative to E2 from triplicate treatments, with error bars representing SEM.

Figure 5. OP-1074 increases the potency of taxanes in inhibiting E2-stimulated MCF-7 breast cell proliferation. The antiestrogen OP-1074 enhances the efficacy and potency of paclitaxel and docetaxel in inhibiting E2-stimulated breast cell proliferation in vitro. MCF-7 cells were treated with the indicated amount of OP-1074 and taxane in hormone-depleted medium for 6 days in the presence of 100 pM 17P-estradiol (E2). Fig. 5A plots the effects on MCF-7 cell proliferation of vehicle, 1, 10 or 100nM OP-1074 in combination with increasing amounts of paclitaxel. Fig. 5B plots the effects on MCF-7 cell proliferation of vehicle, 1, 10 or 100nM OP-1074 in combination with increasing amounts of docetaxel. Proliferation was measured as in Figure 1 and results were from a single representative experiment and reported as the mean percent induction relative to E2 from triplicate treatments, with error bars representing SEM.

Figure 6. OP-1074 increases the potency of the anthracycline doxorubicin in inhibiting E2-stimulated MCF-7 breast cell proliferation. The antiestrogen OP-1074 enhances the efficacy and potency of the anthracycline doxorubicin in inhibiting E2-stimulated breast cell proliferation in vitro. MCF-7 cells were treated with the indicated amount of OP-1074 and doxorubicin in hormone-depleted medium for 7 days in the presence of 100 pM 17P-estradiol (E2). The effects on MCF-7 cell proliferation of vehicle, 1, 10 or 100nM OP-1074 in combination with increasing amounts of doxorubicin are plotted. Proliferation was measured as in Figure 1 and results were from a single representative experiment and reported as the mean percent induction relative to E2 from triplicate treatments, with error bars representing SEM.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to the treatment of tumors, including cancers, mediated by the estrogen receptor with the combination of a specific benzopyran (in the form of a mixture of S-C2 and R-C2 diastereomers and also its pure S-diastereomer) as described in US 2013/0178445 and WO 2013/090921 in combination or alternation with specific agents, active
agents, anti-cancer agents or chemotherapeutic agents, and in some embodiments, in certain improved dosages or formulations. Benefits that can result include increased efficacy and/or lower doses when the specified combinations are used. Cancers which benefit from such combinations or alternations are those that are mediated by the estrogen receptor and will also respond to the second agent. Specific examples of agents, active agents, anti-cancer agents or chemotherapeutic agents that can be combined with compounds described in US 2013/0178445 and WO 2013/090921 include an mTOR inhibitor such as everolimus, or a CDK 4/6 inhibitor such as PD-0332991, or a PI3 Kinase Inhibitor such as BKM-120, or a taxane, or an antimetabolite such as 5-fluorouracil, or an antitumor antibiotic such as doxorubicin. In one embodiment, the combination therapy includes the described anti-estrogenic compounds combined with PD-0332991 for treatment of retinoblastoma positive breast cancer as well as retinoblastoma positive endometrial, vaginal and ovarian cancers and lung and bronchial cancers.

[00113] The compound to be provided in combination or alternation with particular agents, active agents, anti-cancer agents or chemotherapeutic agents, can be provided if desired as a pharmaceutically acceptable salt, solvate, hydrate, prodrug, stereoisomer, tautomer, N-oxide or R₁ and/or R₂-substituted derivative or a pharmaceutically acceptable composition thereof to treat a disorder that is mediated, modulated or affected by an estrogen receptor, including those treatable with an anti-estrogenic compound with virtually no estrogenic effect.
wherein $R_i$ and $R_2$ are independently either:

(i) OH or OR$^9$,

(ii) wherein $R^9$ is independently selected from H, halogen (Cl, Br, I or F), natural or non-naturally occurring amino acid (bound through either the OC(O)- or C(0)O- (an ester) or the amino (through either -C(0)-N- or -N-C(0)- (an amide linkage)), R$^{10}$, -OR$^{10}$, or -SR$^{10}$ where R$^{10}$ is -C(=0)R$^1$, -C(=0)0R$^1$, -C(=0)SR$^1$, -C(=0)N(R$^1$)$_2$; or polyethylene glycol, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; -S(=0)$_2$R$^1$, -S(=0)$_2$OR$^1$, -S(=0)OR$^1$, -S(=0)0R$^1$, -P(=0)$_2$R$^1$, -P(=0)$_2$OR$^1$, -P(=0)(OR$^1$)$_2$, -P(=0)(R$^1$)$_2$, or -P(R$^1$)(0R$^1$)$_2$; or oxygen attached to an oxygen protecting group (to produce OH on administration), sulfur attached to a sulfur protecting group (to produce SH or a disulfide on administration), or nitrogen attached to a nitrogen protecting group (to produce -NH- on administration);

and R$^1$ can be independently selected from hydrogen, polyethylene glycol, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or
unsubstituted heteroaryl, or two $\text{R}^1$ groups are joined to form an substituted or unsubstituted heterocyclic ring.

[00114] In certain embodiments either or both of $\text{R}_1$ or $\text{R}_2$ is an ester, amide, carbonate or phosphate.

[00115] Specific examples of prodrugs of the described compounds that can be combined or alternated with the particular agents, active agents, anti-cancer agents or chemotherapeutic agents are:

- [OP-1088](#)
- [OP-1074·HCl](#)
- [OP-1086](#)
- [OP-1084](#)
Examples of useful metabolically cleavable prodrug groups include acetyl, methoxycarbonyl, benzoyl, methoxymethyl and trimethylsilyl groups.

Combinations of OP-1038, OP-1074 and their prodrugs (including esters, carbonates and phosphates), derivatives and their salts as described in US 2013/0178445 and WO 2013/090921 when combined with particular agents, active agents, anti-cancer agents or chemotherapeutic agents, are especially useful to treat locally advanced or metastatic breast cancer that is positive for expression of estrogen receptors, progesterone receptors or both (receptor positive advanced breast cancer). In an alternative embodiment, the combinations are used to treat estrogen or progesterone receptor negative breast cancer. Specific examples of active agents that can be combined with compounds of the present invention include an mTOR inhibitor such as everolimus, or a CDK 4/6 inhibitor such as PD-0332991, or a PI3 Kinase Inhibitor such as BKM-120, or a taxane, or an antimetabolite such as 5-fluorouracil, or an antitumor antibiotic such as doxorubicin.
In one embodiment, the compounds as described in US 2013/0178445 and WO 2013/090921 can be combined with a CDK 4/6 inhibitor, for example PD-0332991. In another embodiment, OP-1074 is combined with PD-0332991.

In one embodiment, the compounds as described in US 2013/0178445 and WO 2013/090921 can be combined with an mTOR inhibitor, for example everolimus. In another embodiment, OP-1074 is combined with everolimus.

In one embodiment, the compounds as described in US 2013/0178445 and WO 2013/090921 can be combined with a PI3 Kinase Inhibitor, for example BKM-120. In another embodiment, OP-1074 is combined with BKM-120.

In one embodiment, the compounds as described in US 2013/0178445 and WO 2013/090921 can be combined with a taxane, for example paclitaxel or docetaxel. In another embodiment, OP-1074 is combined with paclitaxel or docetaxel.

In one embodiment, the compounds as described in US 2013/0178445 and WO 2013/090921 can be combined with antimetabolites, for example 5-fluorouracil. In another embodiment, OP-1074 is combined with 5-fluorouracil.

In one embodiment, the compounds as described in US 2013/0178445 and WO 2013/090921 can be combined with antitumor antibiotics, for example doxorubicin. In another embodiment, OP-1074 is combined with doxorubicin.

Compositions are described of combinations of the compounds as described in US 2013/0178445 and WO 2013/090921 combined or alternated with particular agents, active agents, anti-cancer agents or chemotherapeutic agents. The compositions can be administered in a pharmaceutical composition suitable for oral delivery to the patient, typically a human. Alternatively, the compounds can be delivered in a carrier suitable for topical, transdermal (including by patch), intravenous, parenteral, intraoral, subcutaneous or other desired delivery route, including any method of controlled delivery, for example, using degradable polymers, or with nano or microparticles, liposomes, layered tablets or other structural frameworks which slow delivery.

The compositions can be in the form of salts of the actives. They can be administered as a pharmaceutically acceptable salt, for example, a pharmaceutically acceptable acid addition salt, including a hydrochloride, hydroiodide, hydrobromide, nitrate, sulfate, bisulfate, phosphate, acetate, lactate, citrate, tartrate, succinate, maleate, fumarate, benzoate, para-toluenesulfonate and the like.
The compositions are used to treat or prevent a disorder modulated by the estrogen receptor in an animal, typically a mammal, and most typically a human.

The combinations can also be used as adjunctive therapy. For example, a therapeutically effective amount of the compound can be used in combination with another anti-cancer agent, especially for estrogen receptor positive breast cancer, but in some embodiments, for estrogen receptor negative breast cancer.

In another aspect of an embodiment of the present invention, a method of treating a patient with combinations of a once-a-day, orally administered, treatment regimen is provided, including selecting one of the plurality of treatment regimens and titrating the dosages supplied to the patient after weekly, monthly or quarterly periods of time. Some embodiments of the present invention facilitate the selection of a combination treatment regimen and/or the change in dosages or titration of dosages of a treatment regimen over time. The combination of the compounds of the present invention with other actives, in particular other agents, active agents, anti-cancer agents or chemotherapeutic actives, can be done in a single fixed dose combination pill such as a multi-pill, combopill or polypill. A polypill is a medication that is a drug product in pill form (i.e., tablet or capsule) that combines multiple active pharmaceutical ingredients. In one embodiment it is manufactured as a fixed-dose combination (FDC) drug product targeting treatment or prevention of a disease. Polypills can reduce the number of tablets or capsules (generally orally administered) that need to be taken, which in turn may facilitate handling and administration of pharmaceuticals as well as alleviate patient pill-burden. Sometimes the multiple drugs in a given polypill might all be aimed at a single underlying condition (or, group of related conditions), for whom a given combination of drugs/dosages might be appropriate (particularly in the case of mass-produced polypills, i.e. FDCs). In addition to the noted fixed-dose types of polypills, polypills can also be custom-made for specific patients through a process called pharmacy compounding.

In alternative embodiments, rather than combining the customized combination of medications into a single treatment regimen, the present invention also relates to protocols enabling the physician or other healthcare provider to deliver the medications in a plurality of treatment regimens in a combination or alternation dose packaging (once-a-day, more than once a day, alternate days, every third day, twice a week, once a week, once every other week, once a month and so on) to increase compliance with medical therapy.

The present invention provides protocols for a plurality of pills into a combination dose packaging or polypill corresponding to the combination treatments mentioned above used in
treating a patient for cancer, and in particular breast cancer, as well as other estrogen mediated diseases that would benefit from the compounds of the present invention, and related health issues over a weekly, monthly, quarterly, or longer period of time.

[00131] The present invention can further greatly improve patient compliance by providing the combination doses over a period of time (e.g. week, month, quarter, or longer) and having the physician titrate the dosages (adjust the dosages of each effective therapeutic ingredient) over the period of time based upon the condition of the patient. If necessary, the combination treatment pack may provide alternative dosages for treatment at more than one time per day.

[00132] Additional embodiments within the scope provided herein are set forth in non-limiting fashion elsewhere herein and in the examples. It should be understood that these examples are for illustrative purposes only and are not to be construed as limiting in any manner.

**PHARMACEUTICAL COMPOSITIONS**

[00133] The term "combinations of the invention" or the like as used herein refers to the concerted use of one or more of the compounds described in US 2013/0178445 and WO 2013/090921 with an agent, active agent, anti-cancer agent or chemotherapeutic agent, wherein the concerted use can be either (i) a pharmaceutically acceptable formulation that includes both active agents; or (ii) separate pharmaceutical formulations that independently provide each active and are either administered at the same time or at different times but in a concerted synchronized fashion in a manner that optimizes the benefit of the combination therapy (i.e., alternation therapy). For example, certain actives will normally be administered orally, such as in a tablet, pill or liquid, and others might be normally administered via intravenous injection or other systemic, topical, parenteral, transdermal or other route. A "pharmaceutical composition" can thus contain either one of the active agents or a combination of agents, based on how the active agents are best administered according to compatibility with the carrier, dosage, dosage scheduling, possibility of drug holidays and other general differences in physical properties, convenience, efficacy, toxicity and dosage regimes.

[00134] In one aspect, the invention provides a pharmaceutical composition comprising a pharmaceutically effective amount of a compound as described in US 2013/0178445 and WO 2013/090921 in combination with a particular agent, active agent, anti-cancer agent or chemotherapeutic agent, and a pharmaceutically acceptable carrier. The amount of the
composition administered will typically be determined by a physician, in the light of the relevant circumstances, including the condition to be treated, the chosen route of administration, the age, weight, and response of the individual patient, the severity of the patient's symptoms, and the like.

[00135] The pharmaceutical compositions provided herein can be administered by a variety of routes including oral, topical, parenteral, rectal, transdermal, subcutaneous, intravenous, intramuscular, and intranasal with a pharmaceutical carrier suitable for such administration. In one embodiment, the compound is administered in a controlled release formulation.

[00136] The compositions for oral administration can take the form of bulk liquid solutions or suspensions, or bulk powders. Typically, the compositions are presented in unit dosage forms to facilitate accurate dosing. The term "unit dosage forms" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient. Typical unit dosage forms include prefilled, premeasured ampules or syringes of the liquid compositions or pills, tablets, capsules or the like in the case of solid compositions. In such compositions, the compound is usually a minor component (as a nonlimiting example, from about 0.1 to about 50% by weight or preferably from about 1 to about 40% by weight) with the remainder being various vehicles or carriers and processing aids helpful for forming the desired dosing form.

[00137] The compositions can be used for treating a patient with combinations of a once-a-day, orally administered, treatment regimen, including selecting one of the plurality of treatment regimens and titrating the dosages supplied to the patient after weekly, monthly or quarterly periods of time. Some embodiments of the present invention facilitate the selection of a combination treatment regimen and/or the change in dosages or titration of dosages of a treatment regimen over time. The combination of the compounds of the present invention with other actives, in particular other chemotherapeutic actives, can be done in a single fixed dose combination pill such as a multi-pill, combopill or polypill. A polypill is a medication that is a drug product in pill form (i.e., tablet or capsule) that combines multiple active pharmaceutical ingredients. In one embodiment it is manufactured as a fixed-dose combination (FDC) drug product targeting treatment or prevention of a disease. Polypills can reduce the number of tablets or capsules (generally orally administered) that need to be taken, which in turn may facilitate handling and administration of pharmaceuticals as well as alleviate patient pill-burden.
Sometimes the multiple drugs in a given polypill might all be aimed at a single underlying condition (or, group of related conditions), for whom a given combination of drugs/dosages might be appropriate (particularly in the case of mass-produced polypills, i.e. FDCs). In addition to the noted fixed-dose types of polypills, polypills can also be custom-made for specific patients through a process called pharmacy compounding.

[00138] In addition, rather than combining the customized combination of medications into a single treatment regimen, the present invention also relates to protocols enabling the physician or other healthcare provider to deliver the medications in a plurality of treatment regimens in a combination protocol (once-a-day, more than once a day, alternate days, every third day, twice a week, once a week, once every other week, once a month and so on) to increase compliance with medical therapy.

[00139] The present invention provides protocols for a plurality of pills into a combination protocol or polypill corresponding to the combination treatments mentioned above used in treating a patient for cancer, and in particular breast cancer, as well as other estrogen mediated diseases that would benefit from the compounds of the present invention, over a weekly, monthly, quarterly, or longer period of time.

[00140] The present invention can further greatly improve patient compliance by providing the combination doses over a period of time (e.g. week, month, quarter, or longer) and having the physician titrate the dosages (adjust the dosages of each effective therapeutic ingredient) over the period of time based upon the condition of the patient. If necessary, the combination treatment may provide alternative dosages for treatment at more than one time per day.

[00141] Liquid forms suitable for oral administration may include a suitable aqueous or nonaqueous vehicle with buffers, suspending and dispensing agents, colorants, flavors and the like. Solid forms may include, for example, any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring.

[00142] Injectable compositions are typically based upon injectable sterile saline or phosphate-buffered saline or other injectable carriers known in the art.
[00143] Transdermal compositions are typically formulated as a topical ointment or cream containing the active ingredient(s), for example in an amount ranging from about 0.01 to about 20% by weight, preferably from about 0.1 to about 20% by weight, preferably from about 0.1 to about 10%, by weight, and more preferably from about 0.5 to about 15%> by weight. When formulated as an ointment, the active ingredients will typically be combined with either a suitable delivery polymeric composition, or a paraffinic or a water-miscible ointment base. Alternatively, the active ingredients may be formulated in a cream with, for example an oil-in-water cream base. Such transdermal formulations are well-known in the art and generally include additional ingredients to enhance the dermal penetration of stability of the active ingredients or the formulation. All such known transdermal formulations and ingredients are included within the scope provided herein.

[00144] The compositions provided herein can be administered by a transdermal device. Transdermal administration can be accomplished using a patch either of the reservoir or porous membrane type, or of a solid matrix variety.


[00146] The compositions of this invention can also be administered in sustained release forms or from sustained release drug delivery systems. A description of representative sustained release materials can be found in Remington’s Pharmaceutical Sciences.

[00147] In certain embodiments, the formulation comprises water. In another embodiment, the formulation comprises a cyclodextrin derivative. In certain embodiments, the formulation comprises hexapropyl -P-cyclodextrin. In a more particular embodiment, the formulation comprises hexapropyl -P-cyclodextrin (10-50%, in water).

[00148] The present invention also includes pharmaceutically acceptable acid addition salts of compounds of the compositions of the invention. The acids which are used to prepare the pharmaceutically acceptable salts are those which form non-toxic acid addition salts, i.e. salts containing pharmacologically acceptable anions such as the hydrochloride, hydroiodide, hydrobromide, nitrate, sulfate, bisulfate, phosphate, acetate, lactate, citrate, tartrate, succinate, maleate, fumarate, benzoate, para-toluenesulfonate, and the like.
USE OF COMPOUNDS IN MEDICAL THERAPY

[00149] Combinations of OP-1038, OP-1074 and their prodrugs (including esters, carbonates and phosphates), derivatives and their salts as described in US 2013/0178445 and WO 2013/090921 with particular agent, active agent, anti-cancer agent or chemotherapeutic agents are useful to treat disorders modulated, mediated or affected by the estrogen receptor.

[00150] In one embodiment, the combinations of the present invention can be used to treat local, advanced or metastatic breast cancer that is positive for expression of estrogen receptors, progesterone receptors or both (receptor positive advanced breast cancer). In an alternative embodiment, the combinations are used to treat estrogen or progesterone receptor negative breast cancer. The combinations can be used as the initial treatment of advanced breast cancer in patients who have never received previous hormonal therapy for advanced breast cancer, in combination with one or more other anti-cancer agents described below or otherwise known to those skilled in the art. They are also useful for second line therapy for treatment after a previous hormonal therapy has failed, either by itself or in combination with another anti-cancer agent, for example, a targeted therapy such as an mTOR inhibitor such as everolimus or a CDK 4/6 inhibitor such as PD-0332991.

[00151] The combinations of the invention are also useful as adjunctive therapy after or instead of chemotherapy, radiation or surgery. Such adjuvant use is often used for several years, perhaps 5 years, after chemotherapy or other therapies have been concluded, but may optimally be continued for additional years.

[00152] The combinations of the invention are also useful for the prevention of breast cancer in women at high risk and can be taken for any desired time period, including indefinitely. For example, a patient, typically a woman, with a family history of breast cancer, or who has been determined to carry a mutation in the BRCA1 or BRCA2 gene or other genes that predispose a patient to breast cancer may choose to use such preventative treatment instead of a mastectomy or other intervention. The combinations described herein are also useful as neoadjuvants to shrink large tumors prior to surgical removal, both to enable breast conservative surgery and to reduce the risk of recurrence. In addition to breast cancer these combinations also are useful in treating other cancers and other overgrowth diseases of the female reproductive tract including ovarian, endometrial, and vaginal cancer and endometriosis. Besides these reproductive tissues the combinations are useful in treating lung cancers that are positive for estrogen or progesterone receptors.
The present combinations are used as therapeutic or prophylactic agents for the treatment of conditions in mammals, particularly humans whose conditions are modulated by estrogen receptors.

Combinations described herein are useful for treating locally advanced or metastatic breast cancer, preventing recurrence or early breast cancer after surgery, and preventing breast cancer in women at high risk. Such combinations are useful for treating all estrogen-dependent cancers of the reproductive tract including endometrial and ovarian cancers. Such combinations have potential uses in the treatment of lung and bronchial cancers that express estrogen receptors.

Specific examples of active agents that can be combined with compounds as described in US 2013/0178445 and WO 2013/090921 include an mTOR inhibitor such as everolimus, or a CDK 4/6 inhibitor such as palbociclib (PD-0332991), or a PI3 Kinase Inhibitor such as BKM-120, or taxanes, or antimetabolites such as 5-fluorouracil, or antitumor antibiotics such as doxorubicin. Such combinations are described in more detail below.

**CDK 4/6 Combination Therapy**

CDK 4/6 inhibitors for the treatment of cancer are presently in the clinic. Examples include PD-0332991 (palbociclib, Pfizer), LY2835219 (Lilly), and LEEO11 (Novartis). CDK 4/6 normal function in cell cycle regulation is through phosphorylation of retinoblastoma protein at Serine 780 and 795. Cancers which are Retinoblastoma positive are targets for CDK 4/6 inhibitors.


PD-0332991 is currently being evaluated in numerous tumor types including late-line metastatic breast cancer, liposarcoma, non-small cell lung cancer, liver cancer, ovarian cancer, glioblastoma, refractory solid tumors, multiple myeloma and mantle cell lymphoma. Such cancers are generally categorized as retinoblastoma positive as CDK 4/6 normal function in cell cycle regulation is through phosphorylation of retinoblastoma protein at Serine 780 and 795.
Currently PD-0332991 is dosed at 125 mg, orally once daily on Day 1 to Day 21 of every 28-day cycle followed by 7 days off treatment.

PD-0332991 is being evaluated in combination with the aromatase inhibitor letrozole in a comparison trial with letrozole plus placebo for 1st line metastatic breast cancer. Preliminary results reported in December 2012 suggest the combination is substantially superior to letrozole alone in progression-free survival.

Cancers that would benefit from the combination of compounds of the present invention, including OP-1038 and OP-1074 include include advanced or metastatic breast cancer, preventing recurrence or early breast cancer after surgery, and preventing breast cancer in women at high risk. Other cancers include retinoblastoma positive estrogen-dependent cancers of the reproductive tract including endometrial and ovarian cancers as well as retinoblastoma positive lung and bronchial cancers that express estrogen receptors.

Suitably, the amount of PD-0332991 administered as part of the combination according to the present invention will be an amount selected from about 1.25 mg to about 250 mg; suitably, the amount will be selected from about 2 mg to about 150 mg; suitably, the amount will be selected from about 2.5 mg to about 125 mg. Accordingly, the amount of PD-0332991 administered as part of the combination according to the present invention will be an amount selected from about 1.25 mg to about 250 mg. For example, the amount of PD-0332991 administered as part of the combination according to the present invention can be a lower dose than that currently administered alone, such as 1.25 mg, 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg, 35 mg, 40 mg, 45 mg, 50 mg, 55 mg, 60 mg, 65 mg, 70 mg, 75 mg, 80 mg, 85 mg, 90 mg, 95 mg, 100 mg, 105 mg, 110 mg, 115 mg, 120 mg, or 125 mg. Suitably, the selected amount of PD-0332991 is administered once a day. Suitably, the selected amount of PD-0332991 is administered twice a day.

PD-0332991 administered as part of the combination according to the present invention orally once daily on Day 1 to Day 21 of every 28-day cycle followed by 7 days off treatment. Alternatively, PD-0332991 may be administered with less days off treatment as part of every 28 day cycle, for instance daily on Day 1 to Day 22 of every 28-day cycle followed by 6 days off treatment, daily on Day 1 to Day 23 of every 28-day cycle followed by 5 days off treatment, daily on Day 1 to Day 24 of every 28-day cycle followed by 4 days off treatment, daily on Day 1 to Day 25 of every 28-day cycle followed by 3 days off treatment, daily on Day 1 to Day 26 of every 28-day cycle followed by 2 days off treatment, daily on Day 1 to Day 27 of
every 28-day cycle followed by 1 days off treatment, or daily for the entire 28-day cycle with no
days of off treatment.

M-Tor Inhibitor Combination Therapy

For use herein, the term mTOR inhibitor, mTOR and derivatives thereof, unless
otherwise defined, include but are not limited to rapamycin and its analogs, RAD001 or
everolimus (Afinitor), CCI-779 or temsirolimus, AP23573, AZD8055, WYE-354, WYE-600,
WYE-687 and Ppl21. Suitably, the mTOR inhibitor is selected from rapamycin, everolimus
(Afinitor) and temsirolimus. Suitably, the mTOR inhibitor is selected from rapamycin and
everolimus (Afinitor). Suitably the mTOR inhibitor is everolimus.

Suitably, the amount of everolimus administered as part of the combination
according to the present invention will be an amount selected from about 1.25 mg to about 20
mg; suitably, the amount will be selected from about 2 mg to about 15 mg; suitably, the amount
will be selected from about 2.5 mg to about 10 mg. Accordingly, the amount of everolimus
administered as part of the combination according to the present invention will be an amount
selected from about 1.25 mg to about 20 mg. For example, the amount of everolimus
administered as part of the combination according to the present invention can be 1.25 mg, 1.5
mg, 2 mg, 2.5 mg, 3 mg, 3.5 mg, 4 mg, 4.5 mg, 5 mg, 5.5 mg, 6 mg, 6.5 mg, 7 mg, 7.5 mg, 8 mg,
8.5 mg, 9 mg, 9.5 mg, 10 mg, 11 mg, 12 mg, 13 mg, 14 mg, 15 mg, 16 mg, 17 mg, 18 mg, 19 mg,
20 mg. Suitably, the selected amount of everolimus is administered twice a day. Suitably, the
selected amount of everolimus is administered once a day. Suitably, the administration of
everolimus will begin as a loading dose. Suitably, the loading dose will be an amount from 2 to
100 times the maintenance dose; suitably from 2 to 10 times; suitably from 2 to 5 times; suitably
2 times; suitably 3 times; suitably 4 times; suitably 5 times. Suitably, the loading does will be
administered from 1 to 7 days; suitably from 1 to 5 days; suitably from 1 to 3 days; suitably for 1
day; suitably for 2 days; suitably for 3 days, followed by a maintenance dosing protocol.

Suitably, the amount of temsirolimus administered as part of the combination
according to the present invention will be an amount infused over a 30 to 60 minute period,
where the amount is selected from about 5 mg to about 50 mg; suitably, the amount will be
selected from about 10 mg to about 40 mg; suitably, the amount will be selected from about 15
mg to about 35 mg. Accordingly, the amount of temsirolimus administered as part of the
combination according to the present invention will be an amount selected from about 5 mg to
about 50 mg. For example, the amount of temsiroli
according to the present invention can be 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg, 35 mg, 40 mg, 45 mg, 50 mg. Suitably, the selected amount of temsirolimus is administered twice a day. Suitably, the selected amount of temsirolimus is administered once a day. Suitably, the administration of temsirolimus will begin as a loading dose. Suitably, the loading dose will be an amount from 2 to 100 times the maintenance dose; suitably from 2 to 10 times; suitably from 2 to 5 times; suitably 2 times; suitably 3 times; suitably 4 times; suitably 5 times. Suitably, the loading does will be administered from 1 to 7 days; suitably from 1 to 5 days; suitably from 1 to 3 days; suitably for 1 day; suitably for 2 days; suitably for 3 days, followed by a maintenance dosing protocol.

**PI3 Kinase Inhibitors Combination Therapy**

[00166] PI3K inhibitors may include, without being limited to, BKM-120, XL-147, RG-7321 (GDC-0941), CH-5132799 and BAY-80-6946.

[00167] Phosphoinositides (Pis), which are phosphorylated derivatives of phosphatidylinositol, are essential in eukaryotic cells, regulating nuclear processes, cytoskeletal dynamics, signaling and membrane trafficking. Among the enzymes involved in PI metabolism, PI3-kinases (PI3K) have attracted special attention because of their oncogenic properties and potential as drug targets. PI3-kinases phosphorylate phosphatidylinositols or Pis at the 3-position of the inositol ring. (Lindmo et. al. Journal of Cell Science 119, 605-614, 2006). The 3-phosphorylated phospholipids generated by PI3K activity bind to the pleckstrin homology (PH) domain of protein kinase B (PKB or AKT), causing translocation of PKB to the cell membrane and subsequent phosphorylation of PKB. Phosphorylated PKB inhibits apoptosis-inducing proteins such as FKHR, Bad, and caspases, and is thought to play an important role in cancer progression. The PDKs are divided into classes I-III, and class I is further subclassified into classes 1a and 1b. Among these isoforms, class 1a enzymes are thought to play the most important role in cell proliferation in response to growth factor-tyrosine kinase pathway activation (Hayakawa et al., Bioorganic & Medicinal Chemistry 14 6847-6858, 2006). Three frequent mutations in cancer constitutively activate PI3K. alpha, and, when expressed in cells, they drive the oncogenic transformation and chronic activation of downstream signaling by molecules such as PKB, S6K and 4E bpl that is commonly seen in cancer cells. (Stephens et. al., Current Opinion in Pharmacology, 5(4) 357-365, 2005). As such, PI3-kinases are attractive targets for the treatment of proliferative diseases.
[00168] There are several known PI3-kinase inhibitors including wortmannin and LY294002. Although wortmannin is a potent PI3K inhibitor with a low nanomolar IC₅₀ value, it has low in vivo anti-tumor activity. (Hayakawa et al, Bioorg Med Chem 14(20), 6847-6858 (2006)). Recently, a group of morpholine substituted quinazoline, pyridopyrimidine and thienopyrimidine compounds have been reported to be effective in inhibiting PI3 kinase p110alpha.. (Hayakawa, 6847-6858). Oral dosage of a morpholine substituted thienopyrimidine compound (GDC-0941) has shown tumor suppression in glioblastoma xenografts in vivo. (Folkes et al., Journal of Medicinal Chemistry, 51, 5522-5532, 2008). The following publications disclose a series of thienopyrimidine, pyridopyrimidine and quinazoline based PI3-Kinase inhibitors: WO 2008/073785; WO 2008/070740; WO 2007/127183; U.S. Patent Publication 20080242665.

[00169] Examples of Phosphatidylinositol-3-kinase (PI3-kinase) inhibitors include, but are not limited to, e.g., celecoxib and analogs thereof, such as OSU-03012 and OSU-03013 (e.g., Zhu et al, Cancer Res., 64(12): 4309-18, 2004); 3-deoxy-D-myo-inositol analogs (e.g., U.S. Application No. 20040192770; Meuillet et al., Oncol. Res., 14:513-27, 2004), such as PX-316; 2'-substituted 3'-deoxy-phosphatidyl-myo-inositol analogs (e.g., Tabellini et al., Br. J. Haematol., 126(4): 574-82, 2004); fused heteroaryl derivatives (U.S. Pat. No. 6,608,056); 3-(imidazo[1,2-a]pyridin-3-yl) derivatives (e.g., U.S. Pat. Nos. 6,403,588 and 6,653,320); Ly294002 (e.g., Vlahos, et al., J. Biol., Chem., 269(7) 5241-5248, 1994); quinazoline-4-one derivatives, such as IC486068 (e.g., U.S. Application No. 20020161014; Geng et al., Cancer Res., 64:4893-99, 2004); 3-(hetero)aryloxy substituted benzo(b)thiophene derivatives (e.g., WO 04 108715; also WO 04 108713); viridins, including semi-synthetic viridins such as such as PX-866 (acetic acid (1S,4E,10R,11R,13S,14R)-[4-diallylaminomethylene-6-hydroxy-1-methoxymethyl-1-10,13-dimethyl-3,7,17-trioxo-1,3,4,7,10,l 1,12,13,14,15,16,17-dodecahydro-2-oxa-cyclopenta[al]phenanthren-1-yl ester) (e.g., Ihle et al., Mol Cancer Ther., 3(7):763-72, 2004; U.S. Application No. 20020037276; U.S. Pat. No. 5,726,167); and wortmannin and derivatives thereof (e.g., U.S. Pat. Nos. 5,504,103; 5,480,906, 5,468,773; 5,441,947; 5,378,725; 3,668,222). In a certain embodiment the PI3K inhibitor is 5-[2,6-di(4-morpholiny1)-4-pyrimidinyl]-4-(trifluoromethyl)-2-pyridinamine (BKM-120).

[00170] BKM-120 is currently being tested in Phase III clinical trials at a daily dose of 100 mg via oral capsules. Suitably, the amount of BKM-120 administered as part of the combination according to the present invention will be an amount selected from about 1.25 mg to about 250 mg; suitably, the amount will be selected from about 2 mg to about 150 mg; suitably, the amount
will be selected from about 2.5 mg to about 100 mg. Accordingly, the amount of BKM-120 administered as part of the combination according to the present invention will be an amount selected from about 1.25 mg to about 250 mg. For example, the amount of BKM-120 administered as part of the combination according to the present invention can be a lower dose than that currently administered alone, such as 1.25 mg, 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg, 35 mg, 40 mg, 45 mg, 50 mg, 55 mg, 60 mg, 65 mg, 70 mg, 75 mg, 80 mg, 85 mg, 90 mg, or 95 mg. Suitably, the selected amount of BKM-120 is administered once a day. Suitably, the selected amount of BKM-120 is administered twice a day.

5-Flourouracil Combination Therapy

[00171] Fluorouracil or 5-FU (5-fluoro-lH,3H-pyrimidine-2,4-dione, trademarked as Efudex) is a drug that is a pyrimidine analog which is used in the treatment of cancer. It is a suicide inhibitor and works through irreversible inhibition of thymidylate synthase. 5-FU is an intravenously (IV) administered fluorinated pyrimidine cytotoxic agent that inhibits the function of thymidylate synthase, an enzyme necessary for the production of the thymidine nucleotides required for DNA synthesis. 5-FU has activity in the therapy of a number of tumor types but is most commonly given in the treatment of colorectal cancer, upper gastrointestinal malignancies, and breast cancer.

[00172] 5-FU is currently administered in various protocols such as 500 mg/m² IV on Days 1-5, or 450-600 mg/m² IV weekly, or 200-400 mg/m² IV continuous infusion every day; generally not to exceed 800 mg/day.

[00173] A method that has been used to overcome the poor oral bioavailability of 5-FU involves the administration of a prodrug that has good bioavailability and is ultimately converted to 5-FU. Capecitabine (pentyl [1-(3,4-dihydroxy-5-methyltetrahydrofuran-2-yl)-5-fluoro-2-oxo-lH-pyrimidin-4-yl]carbamate, Xeloda) is such a novel oral fluoropyrimidine carbamate. It is readily absorbed from the gastrointestinal tract and is preferentially converted to 5-FU in tumor tissue. After oral administration, capecitabine passes intact from the gastrointestinal tract to the liver, where it is converted by carboxylesterases to 5'-deoxy-5-flourouridine (5'-DFUR), then by cytidine deaminase in liver and tumor tissue to 5'-deoxy-5-flourouridine (5'-DFUR), and finally by thymidine phosphorylase (dThdPase) in tumor tissue to 5-FU. The usual starting dose is 2,500 mg/m²/day in two divided doses, 12 hours apart. One cycle includes two weeks of treatment followed by one week without treatment. Cycles can be repeated every three weeks.
More specifically, when the compound of the invention is combined with 5-FU, the dosage of 5-FU may be, for example, 10-1000 mg/ m²/day, preferably 50-1000 mg/ m²/day and more preferably 100-600 mg/ m²/day.

More specifically, when the compound of the invention is combined with Capecitabine, the dosage Capecitabine may be, for example, 100-10000 mg/ m²/day, preferably 500-5000 mg/ m²/day and more preferably 1000-5000 mg/ m²/day.

**Doxorubicin Combination Therapy**

Doxorubicin, also known as Adriamycin, is one of the more common cytotoxic agents used for the treatment of breast cancer. The term doxorubicin includes doxorubicin as well as the pharmaceutically acceptable salts of doxorubicin. Doxorubicin or hydroxydaunorubicin is an antineoplastic drug widely used in chemotherapy (Hortobagyi, Drugs, 54 (Supplement 4): 1-7 (1997)). It is an anthracycline antibiotic and structurally closely related to daunomycin (Minotti et al., Pharmacology. Rev., 56; 185-229 (2004). Doxorubicin (DOX) is commonly used in the treatment of a wide range of cancers, including cancers of the blood, lymph system, bladder, breast, stomach, lung, ovaries, thyroid, nerves, kidneys, bones, soft tissues, including muscles and tendons, multiple myeloma, and others. The hydrochloride salt of doxorubicin is one of the most common forms. It is referred to by various names, such as doxorubicin hydrochloride; 14-hydroxydaunorubicin hydrochloride; 3-hydroxyacetyl daunorubicin hydrochloride; and 5,12-naphthacenedione, 10-[(3-amino-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,1 1-tri hydroxy-8-(hydroxyacet)yl-l-methoxy- , hydrochloride, (8S-cis)-(9Cl).

Doxorubicin hydrochloride has the molecular formula C_{27}H_{49}NClO_{11}.HCl, a molecular weight (MW) of 580.0, and CAS number 253 16-40-9.

The dosage amount of doxorubicin is preferably in the range from 30 to 100 mg/m²/day, more preferably 40 to 80 mg/m²/day, more preferably a dose of about 50 mg/m²/day or about 60 mg/m²/day. Infusion times for doxorubicin are generally up to 6 hours, more preferable 1-3 hours, with 1 hour most preferred.

More specifically, when the compound of the present invention is combined with doxorubicin, the dosage may be, for example, 10-100 mg/ m²/day, preferably 30-100 mg/ m²/day and more preferably 30-60 mg/ m²/day.

**Taxane Combination Therapy**
Examples of taxane include paclitaxel (trade name: Taxol) and docetaxel (trade name: Taxotere). Poliglumex paclitaxel (trade name: Opaxio) is also included in taxanes. Such taxanes have been approved and developed for application to breast cancer, non-small-cell lung cancer, gastric cancer, head and neck cancer, ovarian cancer, esophageal cancer, gastric cancer, uterine body cancer or the like. In addition, combination therapy for various cancers has also been approved or developed by combining taxane with various drugs, for example, with bevacizumab for breast cancer and with carboplatin for ovarian cancer and non-small-cell lung cancer.

Taxane may be administered according to known clinical practice. The dosage and dosing schedule may be altered according to a specific symptom or all symptoms of the patient's disease. The dosage may appropriately be reduced according to age, symptoms or incidence of side effects. Upon use of the pharmaceutical composition and/or the kit of the invention, taxane may usually, but without limitation, be administered for 0.01-10000 mg/m²/day, preferably 0.1-1000 mg/m²/day and more preferably 1-500 mg/m²/day for an adult, which may be administered usually once to three times a day. The dosage needs to be reduced if undue toxicity occurs in the patient. The dosage and dosing schedule may be altered when one or more additional agents, active agents, anti-cancer agents or chemotherapeutic agents are used in addition to the combination therapy of the invention. The dosing schedule may be determined by the physician in charge of the treatment of the specific patient.

More specifically, when the compound of the invention is combined with paclitaxel, the dosage paclitaxel may be 0.01-10000 mg/m²/day, preferably 0.1-1000 mg/m²/day and more preferably 1-500 mg/m²/day.

Furthermore, when the compound of the invention is combined with docetaxel, the dosage of docetaxel may be 0.01-10000 mg/m²/day, preferably 0.1-1000 mg/m²/day and more preferably 1-500 mg/m²/day.

In addition, when the compound of the invention is combined with poliglumex paclitaxel, the dosage of poliglumex paclitaxel may be 0.01-10000 mg/m²/day, preferably 0.1-1000 mg/m²/day and more preferably 1-500 mg/m²/day.

In another embodiment, the combinations of the present invention are provided for use in medical therapy, including for any of the conditions described herein. The use of the present compositions in the manufacture of a medicament for the treatment or prevention of one of the aforementioned conditions and diseases is also provided.
Injection dose levels range are provided in any desired dosage of the active agents, for example, from about 0.1 mg/kg/hour to at least 10 mg/kg/hour, all for from about 1 to about 120 hours and especially 24 to 96 hours. In one embodiment, a preloading bolus of from about 0.1 mg/kg to about 10 mg/kg or more may also be administered to achieve adequate steady state levels. The maximum total dose is not expected to exceed about 2 g/day for a 40 to 80 kg human patient.

For oral dosing, any dose of the active agents, as combined, is appropriate that achieved the desired goals. In one example, suitable daily dosages of active agents of the present invention are between about 0.1-4000 mg, more typically between 5 mg and 1 gram, more typically between 10 mg and 500 mg, and administered orally once-daily, twice-daily or three times-daily, continuous (every day) or intermittently (e.g., 3-5 days a week). For example, when used to treat any disorder described herein, the dose of the compounds of this invention usually ranges between about 0.1 mg, more usually 10, 50, 100, 200, 250, 1000 or up to about 2000 mg per day.

**GENERAL SYNTHETIC PROCEDURES**

The compounds provided herein can be prepared from readily available starting materials using the following general methods and procedures. See, e.g., Synthetic Schemes below. It will be appreciated that where typical or preferred process conditions (i.e., reaction temperatures, times, mole ratios of reactants, solvents, pressures, etc.) are given, other process conditions can also be used unless otherwise stated. Optimum reaction conditions may vary with the particular reactants or solvent used, but such conditions can be determined by one skilled in the art by routine optimization procedures.

Additionally, as will be apparent to those skilled in the art, conventional protecting groups may be necessary to prevent certain functional groups from undergoing undesired reactions. The choice of a suitable protecting group for a particular functional group as well as suitable conditions for protection and deprotection are well known in the art. For example, numerous protecting groups, and their introduction and removal, are described in T. W. Greene and P. G. M. Wuts, *Protecting Groups in Organic Synthesis*, Second Edition, Wiley, New York, 1991, and references cited therein.

The compounds provided herein may be isolated and purified by known standard procedures. Such procedures include (but are not limited to) recrystallization, column
chromatography or HPLC. The following schemes are presented with details as to the preparation of representative substituted benzopyrans that have been listed herein. The compounds provided herein may be prepared from known or commercially available starting materials and reagents by one skilled in the art of organic synthesis.


[00191] In certain embodiments, a diastereomerically pure compound may be obtained by reaction of the racemate or mix of diastereomers with a suitable optically active acid or base. Suitable acids or bases include those described in Bighley et al., 1995, Salt Forms of Drugs and Adsorption, in Encyclopedia of Pharmaceutical Technology, vol. 13, Swarbrick & Boylan, eds., Marcel Dekker, New York; ten Hoeve & H. Wynberg, 1985, Journal of Organic Chemistry 50:4508-4514; Dale & Mosher, 1973, J. Am. Chem. Soc. 95:512; and CRC Handbook of Optical Resolution via Diastereomeric Salt Formation, the contents of which are hereby incorporated by reference in their entireties.

[00192] Enantiomerically or diastereomerically pure compounds can also be recovered either from the crystallized diastereomer or from the mother liquor, depending on the solubility properties of the particular acid resolving agent employed and the particular acid enantiomer or diastereomer used. The identity and optical purity of the particular compound so recovered can be determined by polarimetry or other analytical methods known in the art. The diastereoisomers can then be separated, for example, by chromatography or fractional crystallization, and the desired enantiomer or diastereomer regenerated by treatment with an appropriate base or acid.
The other enantiomer or diasteromer may be obtained from the racemate or mix of diastereomers in a similar manner or worked up from the liquors of the first separation.

[00193] In certain embodiments, enantiomerically or diastereomerically pure compound can be separated from racemic compound or a mixture of diastereomers by chiral chromatography. Various chiral columns and eluents for use in the separation of the enantiomers or diastereomers are available and suitable conditions for the separation can be empirically determined by methods known to one of skill in the art. Exemplary chiral columns available for use in the separation of the enantiomers provided herein include, but are not limited to CHIRALPACK® IC, CHIRALCEL® OB, CHIRALCEL® OB-H, CHIRALCEL® OD, CHIRALCEL® OD-H, CHIRALCEL® OF, CHIRALCEL® OG, CHIRALCEL® OJ and CHIRALCEL® OK.

[00194] General processes for preparing compounds of the instant invention are provided as further embodiments of the invention and are illustrated in the following Schemes.

Synthesis of 3-(4-hydroxyphenyl)-4-methyl-2-(4-{2-[(3R)-3-methylpyrrolidin-1-yl]ethoxy}phenyl)-2H-chromen-7-ol (OP-1038) and Separation and Purification of Stereoisomers (OP-1074 and OP-1075)

Step 1:
Reaction to produce l-(2,4-Dihydroxyphenyl)-2-(4-hydroxyphenyl)ethanone

[00195]  Resorcinol (1,3-dihydroxybenzene) (62.000 g, 563.1 mmol, 1.0 equiv.) and 4-Hydroxyphenyl acetic acid (94.237 g, 619.4 mmol, 1.1 equiv.) were added to a 3 neck 2 L round bottomed flask fitted with a paddle, a pressure equalizing addition funnel and a thermometer and a heating mantle. Toluene (350 mL) was added to the flask to give a suspension. The reaction purged with nitrogen and the addition funnel filled with Boron trifluoride etherate (198.201 ml, 1578.0 mmol, 2.8 equiv.) via canula. The reaction was stirred at 150 rpm and boron trifluoride etherate was added in portions of 3-4 mL and the reaction heated. During addition the internal temperature rose to 100 °C. The reaction went through various changes in color from yellow to dark red. After complete addition of boron trifluoride etherate the addition funnel was removed and replaced with a condenser. The reaction was stirred for 1.5 h at an internal temperature of 108 °C. A sample was taken and HPLC analysis indicated the reaction was complete. The reaction was cooled and stirring stopped to give a biphasic solution. A 12 % aqueous solution of sodium acetate (41 g, 336 mL) was slowly added to the reaction with stirring. The reaction was stirred for 16 hours. A precipitate formed overnight and was collected in a sintered glass funnel. The solid was dried on a vacuum oven for 16 h to give the product as a white powder (119.67 g, 87.0 %).

Step 2:

Reaction to produce l-(2-hydroxy-4-((tetrahydro-2H-pyran-2-yl)oxy)phenyl)-2-(4-((tetrahydro-2H-pyran-2-yl)oxy)phenyl)ethanone

[00196]  l-(2,4-Dihydroxyphenyl)-2-(4-hydroxyphenyl)ethanone (119.000 g, 487.2 mmol, 1.0 equiv.) and ethyl acetate (400 mL) was added to a 2 L 3 neck round bottomed flask equipped with a stir bar a thermometer, a condenser and a nitrogen inlet. The flask was flushed with nitrogen for 2 minutes and 3,4-dihydro-2H-pyran (222.252 ml, 2436.1 mmol, 5.0 equiv.) was added from a graduated cylinder. The suspension was flushed with nitrogen for 2 minutes and p-toluenesulfonic acid (0.378 g, 2.2 mmol, 0.0 equiv.) was added to the reaction. An exothermic reaction took place and the temperature rose from 20 to 33 °C over 5 minutes. The yellow suspension became a red solution within 1 minute of PTSA addition. The reaction was stirred for 66 h at room temperature. The reaction was monitored by HPLC at 4, 5 and 6 hours. The chromatograms indicated the reaction was 74 %, 90 % and 100 % complete at the time indicated respectively. TEA (5 mL) was added to the cream colored slurry to stop the reaction. The slurry
was transferred to a round bottomed flask (2 L) and the three neck flask rinsed with ethyl acetate. The slurry was concentrated on a rotovap to give a cream colored powdery solid. The solid was transferred to a 2 L Erlenmeyer flask. Isopropyl alcohol (IPA) was used to rinse the flask. The solid was recrystallized from IPA (1.4 L). The suspension was cooled in an ice bath for 30 minutes and the solid collected by vacuum filtration. The solid was rinsed with ice cold IPA until the filtrate was colorless and dried in a vacuum oven to give a white powder (162.24 g). The mother liquor and washes were combined and concentrated to orange oil (38.09 g).

**Step 3:**

**Reaction to produce** 2-(4-iodophenyl)-7-((tetrahydro-2H-pyran-2-yl)oxy)-3-(4-((tetrahydro-2H-pyran-2-yl)oxy)phenyl)chroman-4-one

[00197] 1-(2-hydroxy-4-((tetrahydro-2H-pyran-2-yl)oxy)phenyl)-2-(4-((tetrahydro-2H-pyran-2-yl)oxy)phenyl)ethanone (16.228 g, 39.34 mmol) was added to a 3 neck 1 L RB flask. 2-Butanol (380 mL, 0.197 M) and 4-iodobenzaldehyde (51.700 g, 222.8 mmol, 1.0 equiv.) was added to the flask to give a suspension. Piperidine (7.300 ml, 73.9 mmol, 0.3 equiv.) and 1,8-Diazabicyclo[5.4.0]undec-7-ene (11.300 ml, 75.6 mmol, 0.3 equiv.) was added to the suspension. The flask was fitted with a Dean-Stark apparatus and condenser, a thermometer, a stirrer shaft and heated in an oil bath at 130 °C to give an orange solution (became a solution when the internal temperature was 80 °C). Half the solvent (190 mL) was collected over 1.5 hours. The Dean-Stark trap was removed and the condenser was placed on the flask the reaction heated for a further 1 hour. The solution gradually darkens to an orange color. The oil bath was cooled to 90 °C and 380 mL of isopropyl alcohol was added in one portion. The reaction mixture became a cloudy white suspension and redissolved to give a solution in less than a minute at 90 °C. The heating to the bath was set to 50 °C and the flask was allowed to gradually cool to 50 °C. A precipitate started to form at 60 °C and gave a suspension at 50 °C. A thick oily mass falls out of solution ~ 55-53 °C. Vigorous agitation with overhead stirrer (300 rpm) was required to prevent the oily mass from solidifying into one solid as seen with small scale reactions equipped with stir bar. The reaction was left to stir until the mixture cooled to room temperature. The oily mass solidified into a cake even with vigorous agitation. The mother liquor was decanted and fresh isopropanol (100 mL) was added to the flask to rinse the solid. The liquid was decanted and combined with the mother liquor. The mother liquor was concentrated to a dark red oil (27.13 g) and DCM (150 mL) was added to the flask to give a red solution. Silica gel (55 g) was added to solution and concentrated to dryness. The silica gel mixture was poured into a 600 mL sintered
glass funnel filled with silica gel (50 g). The solids were washed with ethyl acetate (1.2 L) and the filtrate concentrated to an orange oil (137.61 g crude). The oil was dissolved into boiling 80 \% IPA/water (1.2 L) and the solution allowed to cool to room temperature and stand overnight to give a cake. The cake was filtered and washed with cold IPA (100 mL). The mother liquor was partially concentrated on a rotovap to give a tan powder. This process was repeated until an oil could not be washed away from the powder. The product was pooled and dried in a vacuum oven to give an impure tan powder (118.25 g, 85.6 \%).

**Step 4a:**

Reaction to produce 2-(4-iodophenyl)-4-methyl-7-((tetrahydro-2H-pyran-2-yl)oxy)-3-(4-((tetrahydro-2H-pyran-2-yl)oxy)phenyl)chroman-4-ol

[00198] To a solution of 90.0\% 2-(4-iodophenyl)-7-((tetrahydro-2H-pyran-2-yl)oxy)-3-(4-((tetrahydro-2H-pyran-2-yl)oxy)phenyl)chroman-4-one (104.891 g, 150.7 mmol, 1.0 equiv.) in THF (1.2 L) at 5°C, was added Methylmagnesium chloride 3.0 M solution in THF (160.000 ml, 480.0 mmol, 3.2 equiv.) by addition funnel over 30 minutes. The temperature did not rise about 8 °C during the addition. The reaction was removed from the ice bath and stirred at room temperature and stirred for another hour. TLC (20\% ethyl acetate in hexanes) showed the reaction had no starting material. The solution was cooled in an ice bath, and carefully quenched with saturated ammonium chloride (35 mL). Ethyl acetate (1.2 L) and water (1.2 L) were added to the reaction mixture, and the layers were separated. The aqueous layer was extracted with EA (1 L). The combined organic layer was washed with brine (1 L), dried over anhydrous Na$_2$SO$_4$, filtered and concentrated in vacuo to yield a pale yellow foam (111.26 g crude). This material was used without further purification.

**Step 4b:**

Reaction to produce 3-(4-hydroxyphenyl)-2-(4-iodophenyl)-4-methyl-2H-chromen-7-ol

[00199] 2-(4-iodophenyl)-4-methyl-7-((tetrahydro-2H-pyran-2-yl)oxy)-3-(4-((tetrahydro-2H-pyran-2-yl)oxy)phenyl)chroman-4-ol (96.820 g, 150.7 mmol, 1.0 equiv.) and 80\% acetic acid in H$_2$O (686 mL) was added to a 2 L RB flask. The suspension was degassed, flushed with nitrogen and heated at 90 °C for 1.5 hours. TLC analysis (1:2 EA/Hex) of the reaction showed no starting material was present. The solvent was removed to give a red oil. The red oil was
dissolved into ethyl acetate (500 mL) and washed with saturated sodium bicarbonate solution (3 x 1 L). The organic layers was washed with brine (1 L), filtered and concentrated to give a red oil (109.32 g, crude). The oil was loaded onto 100 g of silica gel and chromatographed in 40 g portions on silica gel (100 g cartridge, 5-30 % EA/Hex). Fractions containing spots with Rf 0.55 (33 % EA/Hex) were pooled and concentrated to a light red glass (53.37 g). The glass was mixed with DCM (200 mL) and sonicated to give a pink suspension. The solid was filtered through a sintered glass funnel washed with a 20 % DCM in Hexanes solution (250 mL) and dried in a vacuum oven overnight (32.41 g). The mother liquor was concentrated to a glass and the process repeated a second time to give a pink solid (4.2784 g). The impure mixed fractions were pooled and concentrated to a glass (16.71 g). The glass was dissolved into DCM (75 mL) and pink crystals formed on standing (7.0862 g). This process was repeated to give a second crop of pink crystals (2.3643). The mother liquors from both the pure and impure fractions were combined and chromatographed with the same method (2 x 100 g cartridges). The fractions with Rf 0.55 were pooled and concentrated to give a red oil (17.388 g) which did not solidify. The oil was not combined with previous batches but reprotected in a separate reaction.

Gradient method: (5-30 % EA/Hex) 5 % EA hold for 2 minutes, gradient to 15 % over 3 minutes and hold at 15 % EA/Hex for 7 minutes, gradient to 30 % over 7 minutes and hold at 30 % EA/Hex for 17 minutes. Fractions with Rf 0.55 (33 % EA/Hex) were pooled and concentrated to a light pink oil which was triturated with DCM.

**Step 5:**

**Reaction to produce 2-(4-iodophenyl)-4-methyl-7-((tetrahydro-2H-pyran-2-yl)oxy)-3-(4-((tetrahydro-2H-pyran-2-yl)oxy)phenyl)-2H-chromene**

To a solution of 3-(4-hydroxyphenyl)-2-(4-iodophenyl)-4-methyl-2H-chromen-7-ol (41.860 g, 91.7 mmol, 1.0 equiv.) and pyridinium para-toluene sulfonate (4.822 g, 19.3 mmol, 0.2 equiv.) in DCM (200 mL) was added 3,4-dihydro-2H-pyran (49.226 ml, 539.6 mmol, 5.9 equiv.). The reaction was stirred at room temperature overnight (17 h). TLC showed major desired product. The reaction was diluted with DCM (200 mL), washed with saturated NaHCO3 (200 mL), water (200 mL), brine (200 mL), dried over Na2SO4, filtered and concentrated to give a red viscous residue. The residue adsorbed onto silica gel (75 g) was purified on a silica gel column (4 x 100 g, 0 - 20 % EA/Hex) to give a white solid which was triturated with methanol.
and dried in a vacuum oven at 40° C for 16 h to afford the titled compound as a white powder (51.67 g 90.2 %).

[00202] 

1H NMR (300 MHz, CDCl3): δ 7.53 (d, J = 5.4 Hz, 2H), 7.18 (d, J = 8.7 Hz, 1H), 7.06 (parent t, J = 7.8 Hz, 4H), 6.71 (s, 1H), 6.59 (d, J = 2.4 Hz, 1H), 6.45 (d, J = 2.4 Hz, 1H), 5.15 (s, 2H), 4.59 (s, 2H), 4.63 (d, J = 5.7 Hz, 2H), 3.98 (s, 3H), 3.84 (s, 3H).

Step 6:

Reaction to produce -(3R)-3-methyl-l-(2-(4-(4-methyl-7-((tetrahydro-2H-pyran-2-yl)oxy)-3-(4-((tetrahydro-2H-pyran-2-yl)oxy)phenyl)-2H-chromen-2-yl)phenoxy)ethyl)pyrrolidine

[00203] 

A mixture of 2-(4-iodophenyl)-4-methyl-7-((tetrahydro-2H-pyran-2-yl)oxy)-3-(4-((tetrahydro-2H-pyran-2-yl)oxy)phenyl)-2H-chromene (16.800 g, 26.9 mmol, 1.0 equiv.), (R)-2-(3-methylpyrrolidin-1-yl)ethanol (10.416 g, 80.6 mmol, 3.0 equiv.), 1,10-Phenanthroline (0.970 g, 5.4 mmol, 0.2 equiv.), and Cesium carbonate (17.530 g, 53.8 mmol, 2.0 equiv.) in butyronitrile (84 mL) was charged into a 250 mL round bottom flask which was evacuated and backfilled with argon (3 x), Copper(I) iodide (5.123 g, 26.9 mmol, 1.0 equiv.) was added to the suspension and evacuated and backfilled with argon (3 x). The reaction mixture was heated in an oil bath at 120 °C. After 9.1 h of heating the reaction was cooled to room temperature and the mixture filtered through a pad of Celite (3 cm) which was successively washed with DCM (200 mL), EA (200 mL) and MeOH (200 mL). The filtrate was collected and concentrated. The residue was adsorbed onto silica gel (25 g) purified with silica gel (100 g cartridge, 0 - 30% MeOH/DCM) [TLC: 5 % MeOH/DCM, 4 major spots, Rf(SM:0.95), 0.9, 0.83, (prod. 0.43)]. The fractions containing product were pooled and concentrated to give a brown foam (13.64 g, 81.0 %).

[00204] 

Gradient method 0 % MeOH 4 minutes, gradient to 1 % MeOH/DCM over 3 minutes, hold at 1 % MeOH/DCM for 10 minutes, gradient to 5 % MeOH/DCM over 3 minutes, hold at 5 % MeOH/DCM for 12 minutes, gradient to 25 % MeOH/DCM over zero minutes, hold at 25 % MeOH/DCM for 15 minutes. Many fractions contained a mixture of the starting material and product all fractions were pooled, concentrated, and rechromatographed on silica gel (loaded onto 15 g and 100 g cartridge) and gradient eluted with this gradient method (0 % MeOH 4 minutes, gradient to 1 % MeOH/DCM over 3 minutes, hold at 1 % MeOH/DCM for 20 minutes, gradient to 5 % MeOH/DCM over 5 minutes, hold at 5 % MeOH/DCM for 20 minutes). Fractions 74 to 126 were pooled and concentrated to a brown oil which solidified to foam (13.64
g, 81 %) (Late eluting fractions from the first column contained a spot which corresponded to the amino alcohol. These fractions were pooled and concentrated to give a red black liquid (6.38 g).

**Step 7:**

**Reaction to produce 3-(4-hydroxyphenyl)-4-methyl-2-(4-{2-[(3R)-3-methylpyrrolidin-1-yl]ethoxy}phenyl)-2H-chromen-7-ol (OP-1038)**

(3R)-3-methyl-1-[(2-(4-((tetrahydro-2H-pyran-2-yl)oxy)-3H-chromen-2-yl)phenoxy)ethyl]pyrrolidine (15.130 g, 24.2 mmol, 1.0 equiv.) was dissolved into 80% acetic acid/water (150 mL). The solution was heated in an oil bath at 90 °C for 1 hour. HPLC analysis of the reaction mixture indicated the reaction was complete. The dark red solution was concentrated to a dark red oil. The oil was suspended into ethyl acetate (600 mL) and washed with saturated NaHCO3 (3 x 300 mL). The combined aqueous layer was extracted with ethyl acetate (2 x 100 mL). The combined organic layer was washed with brine (2 x 200 mL), dried over anhydrous magnesium sulfate, filtered and concentrated to give a red oil (14.03 g, crude). The oil was adsorbed onto silica gel (30 g) and chromatographed on silica gel (2 x 100 g cartridge) with 0-10 % MeOH in DCM. Fractions containing the product were pooled and concentrated to give a red colored foam (6.68 g). Impure fractions were concentrated and repurified with the same conditions to give an additional 0.9496 g of red foam which was combined with the previous foam. Total yield 7.6296 g, 69.0 %.

**Step 8:**

OP-1038 was separated into its diastereomers (2S)-3-(4-hydroxyphenyl)-4-methyl-2-(4-[(3R)-3-methylpyrrolidin-1-yl]ethoxy)phenyl)-2H-chromen-7-ol (OP-1074) and (2R)-3-(4-hydroxyphenyl)-4-methyl-2-(4-[(3R)-3-methylpyrrolidin-1-yl]ethoxy)phenyl)-2H-chromen-7-ol (OP-1075) using a Diacel, Chiralpak IC column at room temperature in isocratic mode with 80 % hexanes, 20 % 2-propanol with 0.1 % dimethylethylamine or 0.1% diethyl amine as a modifier. This method was used at analytical and preparative scale.
Step 9:
Reaction to produce (R)-2-(benzyloxy)-l-(3-methylpyrrolidin-l-yl)ethanone

(R)-3-methylpyrrolidine hydrochloride (20.000 g, 164.5 mmol, 1.0 equiv.) was added to a round bottom flask and dissolved into anhydrous DCM (45 mL). Freshly distilled Diisopropylethylamine (60.157 ml, 345.4 mmol, 2.1 equiv.) and freshly activated 4Å molecular sieves (∼21 g) was added to the solution and stirred for 10 minutes. 2-(Benzyloxy)acetyl chloride (31.881 g, 172.7 mmol, 1.1 equiv.) dissolved into DCM (50 mL) was added to the reaction at room temperature dropwise via syringe over 20 minutes with a room temperature water bath for cooling. After complete addition the reaction was stirred for 17 hours. TLC analysis (1:1, EA/Hex, Rf: 0.83, 0.33, 0.05) showed no presence of acid chloride. The reaction poured into a separatory funnel and the organic layer washed successively with 1 M HCl (2 x 200 mL), saturated sodium bicarbonate (200 mL) and brine (200 mL). The organic layer was dried over anhydrous MgSO₄, filtered and concentrated to an orange oil (42.40 g). The oil was loaded onto silica gel (30 g) and the mixture split into 18 g portions and chromatographed on silica gel (4 x 100 g cartridges) with a gradient method 10-80% EA/Hex. Fraction with Rf 0.33 spot were pooled and concentrated to give a yellow oil (34.02 g, 88.7%).

Gradient method: 10% EA/Hex hold 5 minutes, gradient to 80% EA/Hex over 15 minutes, hold at 80% EA/Hex for 10 minutes. Fractions with Rf 0.33 were pooled and concentrated.

Step 10:
Reaction to produce (R)-l-(2-(benzyloxy)ethyl)-3-methylpyrrolidine

Aluminum trichloride (54.513 g, 408.8 mmol, 3.0 equiv.) was dissolved into anhydrous THF (750 mL) and cooled in an ice bath. Lithium aluminum hydride (35.688 g, 940.3 mmol, 6.9 equiv.) was added in small portions via a powder addition funnel to the above suspension over 35 minutes and stirred for an additional 10 minutes. The suspension was cooled to -78 °C for 15 minutes and a solution of (R)-2-(Benzyloxy)-l-(3-methylpyrrolidin-l-yl)ethanone (33.980 g, 136.3 mmol, 1.0 equiv.) in anhydrous THF (150 mL) was added dropwise to the cold suspension via a pressure equalizing addition funnel over 20 minutes. The reaction was kept at -78 °C for 1 hour and stirred at room temperature for 1 hours. The reaction was
carefully quenched with 6 N HCl solution (100 mL) and stirred for 17 h to give grey suspension. A solution 6 N NaOH (216 mL) was added to the mixture to give a white suspension after stirring for 30 minutes. The mixture was filtered through a pad of Celite (4 cm). The solids were washed with DCM (5 x 500 mL). The filtrate was poured into a separatory funnel and the layers separated (-200 mL aqueous layer recovered). The aqueous layer was extracted with DCM (3 x 100 mL). The organic layers were combined and washed with brine (500 mL), dried over anhydrous sodium sulfate, filtered and concentrated to a yellow liquid (33.43 g). This liquid was loaded onto silica gel (25 g) and chromatographed through silica gel (2 x 100 g cartridge) with 50-100 % ethyl acetate in hexanes followed by 10-40 % methanol in dichloromethane to give a yellow oil (29.17 g, quant).

Gradient method: 50 % EA/Hex 4 minutes, gradient to 100 % EA over 6 minutes, hold at 100 % EA for 5 minutes, Solvent change to 10 % MeOH in DCM hold for 0 minutes, gradient to 40 % MeOH in DCM over 1 minute, hold at 40 % MeOH in DCM for 8 minutes. The fractions were pooled and concentrated to a yellow oil (29.17 g, quant).

**Step 11:**

(R)-1-(2-(benzyloxy)ethyl)-3-methylpyrrolidinone (10.000 g, 45.6 mmol, 1.0 equiv.) (0.4822 g; 0.7137 g) was added to a 400 mL Parr flask, methanol (60 mL) was added and the solution cooled in an ice bath for 10 minutes. 20% Pd(OH)2 on Carbon, 50 % H2O (6.403 g, 45.6 mmol, 1.0 equiv.) was added to the cooled solution and flushed with nitrogen. Hydrochloric acid (6 M, 7.6 mL) was added to mixture. The flask was pressurized with hydrogen to 30 psi shaken for 1 minute and the hydrogen released. This was repeated twice more and pressurized to 100 psi with hydrogen. This suspension was shaken for 16 hours. A sample was taken and the TLC (10 % MeOH in DCM) indicated the reaction was incomplete and additional catalyst (2.0 g) was added to the mixture. The reaction was treated in a similar manner described above and shaken on the hydrogenator for an additional 30 hours. Celite (5 g) was added to the Parr flask and the mixture filtered through a pad of Celite (2 cm). The solid was washed with methanol (2 x 250 mL). The filtrate was concentrated on a rotovap to dryness to give a red oil (7.81 g). The oil was taken up in methanol (50 mL) and 25 % sodium methoxide in methanol (9.9 mL, 45.5 mmol, 1 equiv) was added to the methanolic solution to give a white suspension. The mixture was concentrated to dryness and taken up into anhydrous DCM (35 mL). The suspension was centrifuged at 3K rpm for 5 minutes. The clear solution was collected and the solid resuspended
into DCM (35 mL). This process was repeated a total of 4 times. The combined solution was concentrated to a yellow liquid (5.6341 g, 95.6 %).

[00213] Following the general method above and using the appropriate reagents and starting materials, OP-1046 and OP-1047 were synthesized.

Synthesis of HCl Salts of OP-1038 and OP-1074

[00214] 3-(4-hydroxyphenyl)-4-methyl-2-(4-{2-[(3R)-3-methylpyrrolidin-1-yl]ethoxy}phenyl)-2H-chromen-7-ol (OP-1038; 0.020 g, 0.0 mmol, 1.0 equiv.) or (2S)-3-(4-hydroxyphenyl)-4-methyl-2-(4-{2-[(3R)-3-methylpyrrolidin-1-yl]ethoxy}phenyl)-2H-chromen-7-ol (OP-1074; 0.020 g, 0.0 mmol, 1.0 equiv.) (Compound 33) was placed into a 1 dram vial and dissolved into methanol (0.2 mL). 4 M HCl in methanol (200 µL) was added to the solution and stirred for 15 minutes. The yellow solution was concentrated a yellow orange solid (0.022 g and 0.0206 respectively).

Synthesis of OP-1083

[00215] OP-1083 was prepared by air oxidation on OP-1074, followed by chromatographic separation of OP-1083 and OP-1074. The mixture of OP-1074 and OP-1083 (560 mg) was dissolved in methanol (15 mL) and mixed with silica gel (3 g). The mixture was dried to give a dark red powder. This powder was loaded into a cartridge and chromatographed on silica gel (4 g cartridge) with 0-25 % methanol in dichloromethane to give OP-1074 as an orange solid (0.261 g, 46.6 %) and OP-1083 as an orange solid (41.1 mg, 15 %)

[00216] Method: 0 % MeOH for 4 min, gradient to 5 % MeOH/DCM over 5 minutes, hold at 5 % for 6 minutes, gradient to 10 % MeOH/DCM over 2 minutes, hold at 10 % MeOH/DCM for 8 minutes, gradient to 25 % MeOH/DCM over 0 minutes, hold at 25 % for 5 minutes.

Synthesis of OP-1084

[00217] (2S)-3-(4-hydroxyphenyl)-4-methyl-2-(4-{2-[(3R)-3-methylpyrrolidin-1-yl]ethoxy}phenyl)-2H-chromen-7-ol (0.020 g, 0.0 mmol, 1.0 equiv.) was added to a 30 mL vial and suspended into anhydrous ethyl acetate (20 mL). Diisopropylethylamine (19 ul, 0.1 mmol, 2.5 equiv.) was added to the suspension and the solution was cooled in an ice bath for 5 minutes.
Ethyl chloroformate (10 μl, 0.1 mmol, 2.3 equiv.) was added to the reaction via a gas tight syringe. The reaction immediately became a cloudy white suspension. The reaction was removed from the ice bath and stirred at room temperature for 16 h. The reaction was concentrated to dryness and dissolved into a minimum of DCM to load onto a 4 g silica gel cartridge. The crude material was eluted with 0-15 % MeOH/DCM to give the desired product as a pale yellow film (0.006.8 g, 27 %).

[TLC] (5 % MeOH/DCM): 4 spots, 0.84, 0.42, 0.26 (Product), 0.16 (Mono carbonate). Gradient method: 0 % MeOH/DCM hold for 2 minutes, gradient to 5 % MeOH/DCM over 5 minutes, hold at 5 % MeOH/DCM for 3 minutes, gradient to 15 % MeOH/DCM over 3 minutes, hold at 15 % MeOH/DCM for 2 minutes. Fractions 16-19 pooled: 6.8 mg LCMS (m/z): 602; HPLC (254 nm): 95.65 %.

**Synthesis of OP-1085**

(2S)-3-(4-hydroxyphenyl)-4-methyl-2-(4-{2-[(3R)-3-methylpyrrolidin-1-yl]ethoxy}phenyl)-2H-chromen-7-ol (0.035 g, 0.1 mmol, 1.0 equiv.) was added to a dry 1 dram vial equipped with a stir bar under a stream of N2. The vial was sealed with a septum and freshly distilled Pyridine (400 μl, 5.0 mmol, 113.6 equiv.) was added to the vial via syringe to give pink red solution. The vial was cooled in a 0 °C ice/water bath for 10 minutes and Trimethylacetyl Chloride (100 μl, 0.8 mmol, 10.6 equiv.) was added via a GC syringe in one portion to the solution. The solution immediately became a light yellow color and was stirred for 30 minutes at 0 °C. The reaction was allowed to reach room temperature over 30 min and stirred at room temperature for 1 h. A sample was analyzed by LCMS to show the presence of a mixture of mono ester and diester. The reaction mixture was concentrated to dryness and dissolved into a minimum amount of DCM and chromatographed on silica gel (4 g cartridge) with 0-25 MeOH/DCM. The fractions containing product were pooled and concentrated to give a pale yellow film (9.2 mg, 33 %).

Gradient: 0 % MeOH/DCM for 2 minutes, gradient to 2.5 % MeOH/DCM over 4 minutes, hold at 2.5 % MeOH/DCM for 5 minutes, gradient to 10 % MeOH/DCM over 1 minute, hold at 10 % MeOH/DCM for 4 minutes, gradient to 25 % MeOH/DCM over 2 minutes, hold at 25 % for 7 minutes. Fractions 11-17 and 19-28 pooled. LCMS (m/z): M+1, 626; HPLC (254 nm): 98.0 %.
Synthesis of OP-1086 and OP-1088

Pyridine (2000 ul, 24.8 mmol, 113.6 equiv.) was added to a dry 1 dram vial with a stir bar. The vial was cooled in a -15 °C dry ice methanol/water bath. Phosphorus oxychloride (71 ul, 0.8 mmol, 3.5 equiv.) was added via a GC syringe in one portion to the solution. The solution was stirred for 5 minutes then the solid 3-(4-hydroxyphenyl)-4-methyl-2-(4-{2-[(3R)-3-methylpyrrolidin-1-yl]ethoxy}phenyl)-2H-chromen-7-ol (OP-1038; 0.100 g, 0.2 mmol, 1.0 equiv.) or (2S)-3-(4-hydroxyphenyl)-4-methyl-2-(4-{2-[(3R)-3-methylpyrrolidin-1-yl]ethoxy}phenyl)-2H-chromen-7-ol (OP-1074; 0.100 g, 0.2 mmol, 1.0 equiv.) was added in one portion under a stream of N2. The reaction stirred at this temperature for 1.5 h. The solution became slurry after -45 minutes. The reaction was allowed to reach room temperature over 45 min and stirred at room temperature for 2 h. A sample was quenched with water and analysis showed the mass of the desired product. The reaction mixture was concentrated to dryness. The crude mixture was suspended into 2 N HCl (5 mL). The suspension was sonicated and centrifuged at 5000 rpm for 6 minutes. The supernatant was decanted and the solid resuspended into 5 mL of 2 N HCl and the process was repeated. The solid was dried under vacuum to give 129 mg of the crude product. The solid was suspended into water (2 mL) and 6 N sodium hydroxide solution (174 μL, 1 mmol, 5 equiv) was added to give an orange solution. This was purified by Preparative LC with acetonitrile and water to give the product as a tan solid.

Synthesis of OP-1087

(2S)-3-(4-hydroxyphenyl)-4-methyl-2-(4-{2-[(3R)-3-methylpyrrolidin-1-yl]ethoxy}phenyl)-2H-chromen-7-ol (0.020 g, 0.0 mmol, 1.0 equiv.) was added to a 30 mL vial and suspended into anhydrous ethyl acetate (20 mL). Diisopropylethylamine (19 ul, 0.1 mmol, 2.5 equiv.) was added to the suspension and the solution was cooled in an ice bath for 5 minutes. Methyl chloroformate (7 ul, 0.1 mmol, 2.2 equiv.) was added to the reaction via a gas tight syringe. The reaction immediately became a cloudy white suspension. The reaction was removed from the ice bath and stirred at room temperature for 16 h. The reaction was concentrated to dryness and dissolved into a minimum of DCM to load onto a 4 g silica gel cartridge. The crude material was eluted with 0-15 % MeOH/DCM to give the desired product as a pale yellow film (0.0096 g, 40 %).
[00223] TLC (5% MeOH/DCM): 4 spots, 0.95, 0.55, 0.38 (Product), 0.25 (Mono carbonate).

[00224] Gradient method: 0% MeOH/DCM hold for 2 minutes, gradient to 5% MeOH/DCM over 5 minutes, hold at 5% MeOH/DCM for 3 minutes, gradient to 15% MeOH/DCM over 3 minutes, hold at 15% MeOH/DCM for 2 minutes. Fractions 11-15 pooled: 9.6 mg. LCMS (m/z): 574; HPLC (254 nm): 95.08 %.

**ASSAYS**

[00225] Compounds provided herein can be evaluated using various in vitro and in vivo assays; examples of which are described below.

[00226] The following biological examples are offered to illustrate the compounds, pharmaceutical compositions and methods provided herein and are not to be construed in any way as limiting the scope thereof.

**Demonstration of the Superiority of OP-1074 Combined With Chemotherapeutics Using Sensitive In vitro Proliferation Assays**

[00227] Proliferation in MCF-7 was measured using a fluorescent DNA binding dye 6-8 days after treatment in triplicate with anti-estrogens in the presence of 100 pM E2. Specifically, MCF-7 cells were treated with anti-estrogens alone or in combination with other chemotherapeutics in hormone-depleted medium for 6-8 days in the presence of 100 pM E2. Proliferation was measured using Cyquant fluorescent DNA-binding dye (Invitrogen, Grand Island, NY). Results were from a single representative experiment and reported as the mean percent induction relative to E2 from triplicate treatments, with error bars representing SEM.

[00228] As shown in Figure 1, OP-1074 increases the potency and efficacy of the CDK 4/6 inhibitor PD-0332991 in inhibiting E2-stimulated MCF-7 breast cell proliferation. The antiestrogen OP-1074 enhances the efficacy and potency of PD-0332991 in inhibiting E2-stimulated breast cell proliferation in vitro. MCF-7 cells were treated with the indicated amount of antiestrogen and PD-0332991 in hormone-depleted medium for 6-7 days in the presence of 100 pM 17p-estradiol (E2). Fig. 1A plots the effects on MCF-7 cell proliferation of vehicle, 1, 10 or 100µM OP-1074 in combination with increasing amounts of PD-0332991. Fig. IB plots the effects on MCF-7 cell proliferation of vehicle or 100µM PD-0332991 in combination with increasing amounts of OP-1074. Fig. 1C plots the effects on MCF-7 cell proliferation of vehicle
or 3nM OP-1074, tamoxifen, or fulvestrant in combination with increasing amounts of PD-0332991. As can be seen from these experiments, the combination of OP-1074 with PD-0332991 at several concentrations leads to a lower percentage of proliferation of MCF-7 breast cells than either agent by themselves.

[00229] As shown in Figure 2, OP-1074 increases the potency of the mTOR inhibitor everolimus in inhibiting E2-stimulated MCF-7 breast cell proliferation. The antiestrogen OP-1074 enhances the efficacy and potency of the mTOR inhibitor everolimus in inhibiting E2-stimulated breast cell proliferation in vitro. MCF-7 cells were treated with the indicated amount of OP-1074 and everolimus in hormone-depleted medium for 6 days in the presence of 100 nM 17P-estradiol (E2). Fig. 2A plots the effects on MCF-7 cell proliferation of vehicle, 1, 10 or 100μM OP-1074 in combination with increasing amounts of everolimus. Fig. 2B plots the effects on MCF-7 cell proliferation of vehicle, InM or 10nM everolimus in combination with increasing amounts of OP-1074. Fig. 2C plots the effects on MCF-7 cell proliferation of vehicle or 3nM OP-1074, tamoxifen, or fulvestrant in combination with increasing amounts of everolimus. As can be seen from these experiments, the combination of OP-1074 with everolimus at several concentrations leads to a lower percentage of proliferation of MCF-7 breast cells than either agent by themselves.

[00230] As shown in Figure 3, OP-1074 increases the potency of the pan PI3K inhibitor BKM-120 in inhibiting E2-stimulated MCF-7 breast cell proliferation. The antiestrogen OP-1074 enhances the efficacy and potency of the PI3K inhibitor BKM-120 in inhibiting E2-stimulated breast cell proliferation in vitro. MCF-7 cells were treated with the indicated amount of OP-1074 and BKM-120 in hormone-depleted medium for 7 days in the presence of 100 pM 17P-estradiol (E2). Fig. 3A plots the effects on MCF-7 cell proliferation of vehicle, 1, 10 or 100μM OP-1074 in combination with increasing amounts of BKM-120. Fig. 3B plots the effects on MCF-7 cell proliferation of vehicle, 32nM or 100nM BKM-120 in combination with increasing amounts of OP-1074. As can be seen from these experiments, the combination of OP-1074 with BKM-120 at several concentrations leads to a lower percentage of proliferation of MCF-7 breast cells than either agent by themselves.

[00231] As shown in Figure 4, OP-1074 increases the potency of 5-fluorouracil in inhibiting E2-stimulated MCF-7 breast cell proliferation. The antiestrogen OP-1074 enhances the efficacy and potency of the thymidylate synthase inhibitor 5-fluorouracil in inhibiting E2-stimulated breast cell proliferation in vitro. MCF-7 cells were treated with the indicated amount of OP-1074 and 5-fluorouracil in hormone-depleted medium for 6 days in the presence of 100
pM 17p-estradiol (E2). The effects on MCF-7 cell proliferation of vehicle, 1, 10 or 100 nM OP-1074 in combination with increasing amounts of 5-fluorouracil are plotted. As can be seen from these experiments, the combination of OP-1074 with 5-fluorouracil at several concentrations leads to a lower percentage of proliferation of MCF-7 breast cells than either agent by themselves.

[00232] As shown in Figure 5, OP-1074 increases the potency of taxanes in inhibiting Estradiol-stimulated MCF-7 breast cell proliferation. The antiestrogen OP-1074 enhances the efficacy and potency of paclitaxel and docetaxel in inhibiting E2-stimulated breast cell proliferation in vitro. MCF-7 cells were treated with the indicated amount of OP-1074 and taxane in hormone-depleted medium for 6 days in the presence of 100 pM 17p-estradiol (E2). Fig. 5A plots the effects on MCF-7 cell proliferation of vehicle, 1, 10 or 100 nM OP-1074 in combination with increasing amounts of paclitaxel. Fig. 5B plots the effects on MCF-7 cell proliferation of vehicle, 1, 10 or 100 nM OP-1074 in combination with increasing amounts of docetaxel. As can be seen from these experiments, the combination of OP-1074 with paclitaxel or docetaxel at several concentrations leads to a lower percentage of proliferation of MCF-7 breast cells than either agent by themselves.

[00233] As shown in Figure 6, OP-1074 increases the potency of the anthracycline doxorubicin in inhibiting E2-stimulated MCF-7 breast cell proliferation. The antiestrogen OP-1074 enhances the efficacy and potency of the anthracycline doxorubicin in inhibiting Estradiol-stimulated breast cell proliferation in vitro. MCF-7 cells were treated with the indicated amount of OP-1074 and Doxorubicin in hormone-depleted medium for 7 days in the presence of 100 pM 17p-estradiol (E2). The effects on MCF-7 cell proliferation of vehicle, 1, 10 or 100 nM OP-1074 in combination with increasing amounts of doxorubicin are plotted. As can be seen from these experiments, the combination of OP-1074 with doxorubicin at several concentrations leads to a lower percentage of proliferation of MCF-7 breast cells than either agent by themselves.

DEFINITIONS

[00234] Compounds described herein can comprise one or more asymmetric centers, and thus can exist in various isomeric forms, e.g., enantiomers and/or diastereomers. For example, the compounds described herein can be in the form of an individual enantiomer, diastereomer or geometric isomer, or can be in the form of a mixture of stereoisomers, including racemic mixtures and mixtures enriched in one or more stereoisomer. Isomers can be isolated from
mixtures by methods known to those skilled in the art, including chiral high pressure liquid chromatography (HPLC) and the formation and crystallization of chiral salts; or preferred isomers can be prepared by asymmetric syntheses. See, for example, Jacques et al., *Enantiomers, Racemates and Resolutions* (Wiley Interscience, New York, 1981); Wilen et al., *Tetrahedron* 33:2725 (1977); Eliel, *Stereochemistry of Carbon Compounds* (McGraw-Hill, NY, 1962); and Wilen, *Tables of Resolving Agents and Optical Resolutions* p. 268 (E.L. Eliel, Ed., Univ. of Notre Dame Press, Notre Dame, IN 1972). Unless otherwise stated, the invention encompasses compounds described herein as individual isomers substantially free of other isomers, and alternatively, as mixtures of various isomers.

[00235] The articles "a" and "an" may be used herein to refer to one or to more than one (i.e. at least one) of the grammatical objects of the article. By way of example "an analogue" means one analogue or more than one analogue.

[00236] "Pharmacologically acceptable salt" refers to a salt of a compound of the invention that is pharmacologically acceptable and that possesses the desired pharmacological activity of the parent compound. In particular, such salts are non-toxic may be inorganic or organic acid addition salts and base addition salts. Specifically, such salts include: (1) acid addition salts, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or formed with organic acids such as acetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, 3-(4-hydroxybenzoyl) benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethane-disulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, 4-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, 4-toluenesulfonic acid, camphorsulfonic acid, 4-methylbicyclo[2.2.2]-oct-2-ene-l-carboxylic acid, glucoheptonic acid, 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid, and the like; or (2) salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, e.g., an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base such as ethanolamine, diethanolamine, triethanolamine, N-methylglucamine and the like. Salts further include, by way of example only, sodium, potassium, calcium, magnesium, ammonium, tetraalkylammonium, and the like; and when the compound contains a basic functionality, salts of non toxic organic or inorganic acids, such as hydrochloride, hydrobromide, tartrate, mesylate, acetate, maleate, oxalate and the like. The term
"pharmaceutically acceptable cation" refers to an acceptable cationic counter-ion of an acidic functional group. Such cations are exemplified by sodium, potassium, calcium, magnesium, ammonium, tetraalkyl ammonium cations, and the like (see, e.g., Berge, et al., J. Pharm. Sci. 66(1): 1-79 (Jan.'77).

[00237] "Pharmaceutically acceptable vehicle" refers to a diluent, adjuvant, excipient or carrier with which a compound of the invention is administered.

"Pharmaceutically acceptable metabolically cleavable group" refers to a group which is cleaved in vivo to yield the parent molecule indicated herein.

[00238] "Prodrugs" refers to compounds, including derivatives of the compounds of the invention, which have cleavable groups and become by solvolysis or under physiological conditions a compound of the invention that are pharmaceutically active in vivo.

[00239] "Solvate" refers to forms of the compound that are associated with a solvent or water (also referred to as "hydrate"), usually by a solvolysis reaction. This physical association includes hydrogen bonding. Conventional solvents include water, ethanol, acetic acid and the like. The compounds of the invention may be prepared e.g. in crystalline or liquid form and may be solvated or hydrated. Suitable solvates include pharmaceutically acceptable solvates, such as hydrates, and further include both stoichiometric solvates and non-stoichiometric solvates. In certain instances the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. "Solvate" encompasses both solution-phase and isolable solvates. Representative solvates include hydrates, ethanolates and methanolates.

[00240] A "subject" to which administration is contemplated includes, but is not limited to, humans (i.e., a male or female of any age group, e.g., a pediatric subject (e.g. infant, child, adolescent) or adult subject (e.g., young adult, middle-aged adult or senior adult)) and/or a non-human animal, e.g., a mammal such as primates (e.g., cynomolgus monkeys, rhesus monkeys), cattle, pigs, horses, sheep, goats, rodents, cats, and/or dogs. In certain embodiments, the subject is a human. In certain embodiments, the subject is a non-human animal. The terms "human", "patient" and "subject" are used interchangeably herein.

[00241] As used herein the term "enantiomerically pure" or "pure enantiomer" denotes that the compound comprises more than 95% by weight. In alternative embodiments, when specified, the term may refer to more than 96% by weight, more than 97% by weight, more than 98% by weight, more than 98.5% by weight, more than 99% by weight, more than 99.2% by weight, more than 99.5% by weight, more than 99.6% by weight, more than 99.7% by weight,
more than 99.8% by weight or more than 99.9% by weight, of the enantiomer. The weights are based upon total weight of all enantiomers or stereoisomers of the compound.

As used herein and unless otherwise indicated, the term "enantiomerically pure R-compound" refers to at least 95% by weight R-compound and at most about 5% by weight S-compound. In alternative embodiments, when specified, the term can refer to at least about 99% by weight R-compound and at most about 1% by weight S-compound or at least about 99.9% by weight R-compound or at most about 0.1% by weight S-compound. In certain embodiments, the weights are based upon total weight of compound.

As used herein and unless otherwise indicated, the term "enantiomerically pure S-compound" or "S-compound" refers to at least about 95% by weight S-compound and at most about 5% by weight R-compound. In alternative embodiments, when specified, the term can refer to at least about 99% by weight S-compound and at most about 1% by weight R-compound or at least about 99.9% by weight S-compound and at most about 0.1% by weight R-compound. In certain embodiments, the weights are based upon total weight of compound.

These and other exemplary substituents are described in more detail in the Detailed Description, Examples, and claims. The invention is not intended to be limited in any manner by the above exemplary listing of substituents.
What is claimed is:

1. A method of treating a disorder modulated, mediated or affected by the estrogen receptor in a subject comprising administering to the subject a compound, which is

\[
\text{OP-1038}
\]

\[
\text{OP-1074}
\]

wherein \( R_1 \) and \( R_2 \) are independently either:

(i) \( \text{OH or OR}^9 \),
(ii) wherein R⁹ is independently selected from H, halogen (Cl, Br, I or F), natural or non-naturally occurring amino acid (bound through either the OC(O)- or C(0)0- (an ester) or the amino (through either -C(0)-N- or -N-C(O)- (an amide linkage)), R¹⁰, -OR¹⁰, or -SR¹⁰ where R¹⁰ is -C(=0)R Cl, -C(=0)0R Cl, -C(=0)SR Cl, -C(=0)N(R Cl)₂; or polyethylene glycol, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; -S(=0)₂R Cl, -S(=0)₂OR Cl, -S(=0)R Cl, -S(=0)OR Cl, -P(=0)₂R Cl, -P(=0)₂OR Cl, -P(=0)(OR Cl)₂, -P(=0)(R Cl)₂, or -P(R Cl)(0R Cl); or oxygen attached to an oxygen protecting group (to produce OH on administration), sulfur attached to a sulfur protecting group (to produce SH or a disulfide on administration), or nitrogen attached to a nitrogen protecting group (to produce -NH- on administration);

and R Cl can be independently selected from hydrogen, polyethylene glycol, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, or two R Cl groups are joined to form an substituted or unsubstituted heterocyclic ring;

or a pharmaceutically acceptable salt, solvate, hydrate, prodrug, stereoisomer, tautomer, or N-oxide thereof,

in combination with an agent selected from the group consisting of an mTOR inhibitor, a CDK 4/6 inhibitor, a PI3 Kinase inhibitor, a taxane, an antimetabolite, and an antitumor antibiotic.

2. The method of claim 1, wherein the compound is in the form of a pharmaceutically acceptable salt.

3. The method of claim 1, wherein the compound is (2S)-3-(4-hydroxyphenyl)-4-methyl-2-(4-{2-[(3R)-3-methylpyrrolidin-1-yl]ethoxy}phenyl)-2H-chromen-7-ol, which has the chemical structure:
or a pharmaceutically acceptable salt, solvate, hydrate, or N-oxide thereof.

4. A method of treating a disorder modulated, mediated or affected by the estrogen receptor in a subject comprising administering to the subject a compound, which is (2S)-3-(4-hydroxyphenyl)-4-methyl-2-(4-{2-[(3R)-3-methylpyrrolidin-1-yl]ethoxy}phenyl)-2H-chromen-7-ol, which has the chemical structure:

![Chemical Structure of OP-1074](image)

or a pharmaceutically acceptable salt thereof,
in combination with an agent selected from the group consisting of an mTOR inhibitor, a CDK 4/6 inhibitor, a PI3 Kinase inhibitor, a taxane, an antimetabolite, and an antitumor antibiotic.

5. The method of claim 1 or 4, wherein the disorder is mediated by the estrogen receptor.

6. The method of claim 1 or 4, wherein the disorder is breast cancer.

7. The method of claim 6, wherein the breast cancer is local, advanced or metastatic estrogen or progesterone receptor positive advanced breast cancer.

8. The method of claim 6, wherein the breast cancer is estrogen or progesterone receptor positive advanced breast cancer.

9. The method of claim 6, wherein the breast cancer is estrogen or progesterone receptor negative breast cancer.
10. The method of claim 1 or 4, wherein the disorder is selected from the group consisting of ovarian, endometrial, and vaginal cancer and endometriosis.

11. The method of claim 1 or 4, wherein the disorder is retinoblastoma positive breast cancer.

12. The method of claim 1 or 4, wherein the disorder is selected from the group consisting of retinoblastoma positive endometrial, vaginal and ovarian cancers and lung and bronchial cancers.

13. The method of claim 1 or 4, wherein the disorder is lung cancer or bronchial cancer.

14. The method of claim 1 or 4, wherein the agent is a CDK 4/6 inhibitor.

15. The method of claim 14, wherein the CDK 4/6 inhibitor is PD-0332991, LY2835219, or LEE011.

16. The method of claim 14, wherein the CDK 4/6 inhibitor is PD-0332991, or a pharmaceutically acceptable salt thereof.

17. The method of claim 14, wherein the CDK 4/6 inhibitor is PD-0332991.

18. The method of claim 1 or 4, wherein the agent is an mTOR inhibitor.

19. The method of claim 18, wherein the mTOR inhibitor is everolimus.

20. The method of claim 18, wherein the mTOR inhibitor is rapamycin, everolimus, temsirolimus, AP23573, AZD8055, WYE-354, WYE-600, WYE-687, or Ppl21.

21. The method of claim 1 or 4, wherein the agent is a PI3 Kinase inhibitor.

22. The method of claim 21, wherein the PI3 Kinase inhibitor is BKM-120, XL-147, RG-7321, CH-5 132799 and BAY-80-6946.

23. The method of claim 21, wherein the PI3 Kinase inhibitor is BKM-120.

24. The method of claim 1 or 4, wherein the agent is a taxane.

25. The method of claim 24, wherein the taxane is paclitaxel or docetaxel.

26. The method of claim 1 or 4, wherein the agent is an antimetabolite.
27. The method of claim 26, wherein the antimetabolite is 5-fluorouracil.

28. The method of claim 1 or 4, wherein the agent is an antitumor antibiotic.

29. The method of claim 28, wherein the antitumor antibiotic is doxorubicin.

30. A pharmaceutical composition comprising a pharmaceutically effective amount of a compound, which is

\[
\text{OP-1038}
\]

\[
\text{OP-1074}
\]

wherein \( R_1 \) and \( R_2 \) are independently either:

(i) \( \text{OH} \) or \( \text{OR}^9 \),
(ii) wherein \( R^9 \) is independently selected from \( H \), halogen (Cl, Br, I or F), natural or non-naturally occurring amino acid (bound through either the \(\mathrm{OC(O)}-\) or \(\mathrm{C(0)O}-\) (an ester) or the amino (through either \(-\mathrm{C(0)}-\mathrm{N}\)- or \(-\mathrm{N-C(O)}-\) (an amide linkage)), \( R^{10} \), \(-\mathrm{OR}^{10}\), or \(-\mathrm{SR}^{10}\) where \( R^{10} \) is \(-\mathrm{C(=0)}\mathrm{R}^{\mathrm{Cl}}\), \(-\mathrm{C(=0)OR}^{\mathrm{Cl}}\), \(-\mathrm{C(=0)SR}^{\mathrm{Cl}}\), \(-\mathrm{C(=0)N(R^{\mathrm{Cl}})_2}\); or polyethylene glycol, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; \(-\mathrm{S(=0)}_2\mathrm{R}^{\mathrm{Cl}}\), \(-\mathrm{S(=0)}_2\mathrm{OR}^{\mathrm{Cl}}\), \(-\mathrm{S(=0)}\mathrm{OR}^{\mathrm{Cl}}\), \(-\mathrm{P(=0)}_2\mathrm{R}^{\mathrm{Cl}}\), \(-\mathrm{P(=0)}_2\mathrm{OR}^{\mathrm{Cl}}\), \(-\mathrm{P(=0)}_2\mathrm{OR}^{\mathrm{Cl}}\), or \(-\mathrm{P(=0)}(\mathrm{OR}^{\mathrm{Cl}})_2\); or oxygen attached to an oxygen protecting group (to produce \(\mathrm{OH}\) on administration), sulfur attached to a sulfur protecting group (to produce \(\mathrm{SH}\) or a disulfide on administration), or nitrogen attached to a nitrogen protecting group (to produce \(-\mathrm{NH}\)- on administration);

and \( R^{\mathrm{Cl}} \) can be independently selected from hydrogen, polyethylene glycol, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; or two \( R^{\mathrm{Cl}} \) groups are joined to form an substituted or unsubstituted heterocyclic ring;

or a pharmaceutically acceptable salt, solvate, hydrate, prodrug, stereoisomer, tautomer, or \( N\)-oxide thereof,

in combination with an agent selected from the group consisting of an mTOR inhibitor, a CDK 4/6 inhibitor, a PI3 Kinase inhibitor, a taxane, an antimetabolite, and an antitumor antibiotic, and a pharmaceutically acceptable carrier.

31. The pharmaceutical composition of claim 30, wherein the compound is in the form of a pharmaceutically acceptable salt.

32. The pharmaceutical composition of claim 31, wherein the compound is \((2S)-3-(4-hydroxyphenyl)-4-methyl-2-(4-{2-[(3R)-3-methylpyrrolidin-1-yl]ethoxy}phenyl)-2H-chromen-7-ol\), which has the chemical structure:
or a pharmaceutically acceptable salt, solvate, hydrate, or N-oxide thereof.

33. A pharmaceutical composition comprising a pharmaceutically effective amount of a compound, which is \((2S)-3-(4\text{-hydroxyphenyl})-4\text{-methyl}-2-(4\{-2\{-[(3R)-3\text{methylpyrrolidin-1-yl}]ethoxy\}phenyl\}-2\text{H-chromen-7-ol})\), which has the chemical structure:

\[
\text{OP-1074}
\]

or a pharmaceutically acceptable salt thereof,
in combination with an agent selected from the group consisting of an mTOR inhibitor, a CDK 4/6 inhibitor, a PI3 Kinase inhibitor, a taxane, an antimetabolite, and an antitumor antibiotic, and a pharmaceutically acceptable carrier.

34. A combination of a compound, which is

\[
\text{OP-1038}
\]
wherein $R_i$ and $R_2$ are independently either:

(i) OH or OR$^9$,

(ii) wherein $R^9$ is independently selected from H, halogen (Cl, Br, I or F), natural or non-naturally occurring amino acid (bound through either the OC(O)- or C(0)O- (an ester) or the amino (through either -C(0)-N- or -N-C(O)- (an amide linkage)), R$^{10}$, -OR$^{10}$, or -SR$^{10}$ where R$^{10}$ is -C(=0)R$^1$, -C(=0)0R$^1$, -C(=0)SR$^1$, -C(=0)N(R$^1$)$_2$; or polyethylene glycol, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

-S(=0)$_2$R$^1$, -S(=0)$_2$OR$^1$, -S(=0)R$^1$, -S(=0)OR$^1$, -P(=0)$_2$R$^1$, -P(=0)$_2$OR$^1$, -P(=0)(OR$^1$)$_2$, -P(=0)(R$^1$)$_2$, or -P(R$^1$)(OR$^1$)$_2$; or oxygen attached to an oxygen protecting group (to produce OH on administration), sulfur attached to a sulfur protecting group (to produce SH or a disulfide on administration), or nitrogen attached to a nitrogen protecting group (to produce -NH- on administration);
and \( R_C \) can be independently selected from hydrogen, polyethylene glycol, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclic, substituted or unsubstituted heterocyclic, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, or two \( R_C \) groups are joined to form an substituted or unsubstituted heterocyclic ring;

or a pharmaceutically acceptable salt, solvate, hydrate, prodrug, stereoisomer, tautomer, or N-oxide thereof,

and an agent selected from the group consisting of an mTOR inhibitor, a CDK 4/6 inhibitor, a PI3 Kinase inhibitor, a taxane, an antimetabolite, and an antitumor antibiotic, for the treatment of a disorder modulated, mediated or affected by the estrogen receptor.

35. The combination of claim 34, wherein the compound is in the form of a pharmaceutically acceptable salt.

36. The combination of claim 34, wherein the compound is \((2S)-3-(4-hydroxyphenyl)-4-methyl-2-(4-{2-[(3R)-3-methylpyrrolidin-1-yl]ethoxy}phenyl)-2H-chromen-7-ol, \) which has the chemical structure:

![OP-1074](image)

or a pharmaceutically acceptable salt, solvate, hydrate, or N-oxide thereof.

37. A combination of \((2S)-3-(4-hydroxyphenyl)-4-methyl-2-(4-{2-[(3R)-3-methylpyrrolidin-1-yl]ethoxy}phenyl)-2H-chromen-7-ol, \) which has the chemical structure:

![OP-1074](image)
or a pharmaceutically acceptable salt thereof,
and an agent selected from the group consisting of an mTOR inhibitor, a CDK 4/6 inhibitor, a
PI3 Kinase inhibitor, a taxane, an antimetabolite, and an antitumor antibiotic for the treatment of
a disorder modulated, mediated or affected by the estrogen receptor.
FIG. 1A
FIG. 1B
PD-0332991 + antiestrogens

- Veh
- +3nM OP-1074
- +3nM Fulv
- +3nM OH-Tam

Proliferation (% E2) vs nM PD-0332991

FIG. 1C
FIG. 2B

OP-1074 + Everolimus

- Veh
- +1 nM Everolimus
- +10 nM Everolimus

Proliferation (% E2)

OP-1074

no E2
Everolimus + antiestrogens

Proliferation (% E2) vs. nM Everolimus

- Veh
- +3nM OP-1074
- +3nM OH-Tam
- +3nM Fulv

no E2

FIG. 2C
FIG. 3B
FIG. 4

OP-1074 + 5-Fluorouracil

- Veh
- 1 nM OP-1074
- +10 nM OP-1074
- +100 nM OP-1074

Proliferation (% E2)

nM 5-Fluorouracil
FIG. 5A
OP-1074 + Docetaxel

Proliferation (% E2)

Veh
+1nM OP-1074
+10nM OP-1074
+100nM OP-1074

nM Docetaxel

FIG. 5B
FIG. 6

OP-1074 + Doxorubicin

Proliferation (% E2)

nM Doxorubicin

Veh
+1nM OP-1074
+10nM OP-1074
+100nM OP-1074

no E2
A. CLASSIFICATION OF SUBJECT MATTER

A61K31/519 A61K31/5377 A61K31/704 A61P35/00

ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic database consulted during the international search (name of database and, where practicable, search terms used)

EPO-Internal, WPI Data, BIOSIS, CHEM ABS Data, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Y</td>
<td>wo 2010/145010 AI (ENDORECH INC [CA]; LABRI E FERNAND [CA]) 23 December 2010 (2010-12-23) cited in the application</td>
<td>1-37</td>
</tr>
<tr>
<td></td>
<td>paragraph [0144] example 8</td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>US 2013/116232 AI (KAHRAMAN MEHMET [US] ET AL) 9 May 2013 (2013-05-09) paragraph [0157] - paragraph [0158]; claims 1-31; examples 77,78; compounds 8, 26, 28</td>
<td>1-37</td>
</tr>
</tbody>
</table>

Further documents are listed in the continuation of Box C. See patent family annex.

* Special categories of cited documents:
  *A* document defining the general state of the art which is not considered to be of particular relevance
  *E* earlier application or patent but published on or after the international filing date
  *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
  *O* document referring to an oral disclosure, use, exhibition or other means
  *P* document published prior to the international filing date but later than the priority date claimed
  *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
  *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
  *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
  *A* document member of the same patent family

Date of the actual completion of the international search 18 September 2014

Date of mailing of the international search report 29/09/2014

Name and mailing address of the ISA/Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040,
Fax. (+31-70) 340-3016

Ganschow, S i l ke
<table>
<thead>
<tr>
<th>Patent document</th>
<th>Publication date</th>
<th>Patent family member(s)</th>
<th>Publication date</th>
</tr>
</thead>
<tbody>
<tr>
<td>wo 2010145010</td>
<td>23-12-2010</td>
<td>AR 077119 Al</td>
<td>03-08-2011</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AU 2010262722 Al</td>
<td>19-01-2012</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CA 2765446 Al</td>
<td>23-12-2010</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CN 102458404 A</td>
<td>16-05-2012</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EA 201200016 Al</td>
<td>30-08-2012</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EP 2442807 Al</td>
<td>25-04-2012</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JP 2012530074 A</td>
<td>29-11-2012</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JP 2014088442 A</td>
<td>15-05-2014</td>
</tr>
<tr>
<td></td>
<td></td>
<td>KR 20120097470 A</td>
<td>04-09-2012</td>
</tr>
<tr>
<td></td>
<td></td>
<td>KR 20140070650 A</td>
<td>10-06-2014</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MA 33434 Bl</td>
<td>03-07-2012</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SG 177497 Al</td>
<td>28-02-2012</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TW 201100403 A</td>
<td>01-01-2011</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 2010317635 Al</td>
<td>16-12-2010</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 2013244989 Al</td>
<td>19-09-2013</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Wo 2010145010 Al</td>
<td>23-12-2010</td>
</tr>
<tr>
<td>us 2013116232</td>
<td>09-05-2013</td>
<td>AR 077119 Al</td>
<td>03-08-2011</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CA 2800673 Al</td>
<td>15-12-2011</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CN 102939287 A</td>
<td>20-02-2013</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EA 201270815 Al</td>
<td>28-06-2013</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EP 2580210 A2</td>
<td>17-04-2013</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JP 2013528223 A</td>
<td>08-07-2013</td>
</tr>
<tr>
<td></td>
<td></td>
<td>KR 20130082496 A</td>
<td>19-07-2013</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SG 185637 Al</td>
<td>28-12-2012</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 2013116232 Al</td>
<td>09-05-2013</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 2014107095 Al</td>
<td>17-04-2014</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Wo 2011156518 A2</td>
<td>15-12-2011</td>
</tr>
<tr>
<td>wo 2013090921</td>
<td>20-06-2013</td>
<td>AR 077119 Al</td>
<td>03-08-2011</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CA 2800673 Al</td>
<td>15-12-2011</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CN 102939287 A</td>
<td>20-02-2013</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EA 201270815 Al</td>
<td>28-06-2013</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EP 2580210 A2</td>
<td>17-04-2013</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JP 2013528223 A</td>
<td>08-07-2013</td>
</tr>
<tr>
<td></td>
<td></td>
<td>KR 20130082496 A</td>
<td>19-07-2013</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SG 185637 Al</td>
<td>28-12-2012</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 2013116232 Al</td>
<td>09-05-2013</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 2014107095 Al</td>
<td>17-04-2014</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Wo 2011156518 A2</td>
<td>15-12-2011</td>
</tr>
</tbody>
</table>