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(54) Titre : METHODES DIAGNOSTIQUES ET THERAPEUTIQUES POUR LE TRAITEMENT DU CANCER DU SEIN
(54) Title: DIAGNOSTIC AND THERAPEUTIC METHODS FOR THE TREATMENT OF BREAST CANCER

(57) **Abrégé/Abstract:**

Provided herein, inter alia, are predictive diagnostic, pharmacodynamic, and therapeutic methods for the treatment of breast cancer. In embodiments, the methods and compositions are based, at least in part, on the discovery that the estradiol (E2)-induced score or estrogen receptor (ER) pathway activity score determined from a sample (e.g., a tissue sample, e.g., a tumor tissue sample, e.g., a FFPE, a FF, an archival, a fresh, or a frozen tumor tissue sample) from an individual can be used in methods of determining whether the individual having breast cancer is likely to respond to a treatment including an endocrine therapy, selecting a therapy for an individual having breast cancer; treating an individual having breast cancer; and monitoring therapeutic efficacy of an endocrine therapy, as well as related kits.

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(54) Title: DIAGNOSTIC AND THERAPEUTIC METHODS FOR THE TREATMENT OF BREAST CANCER

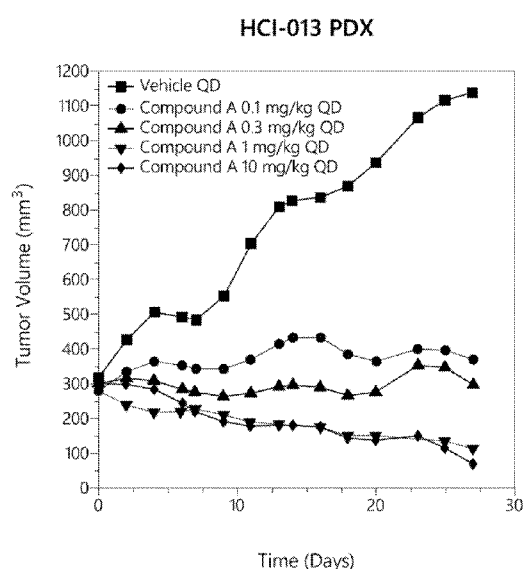


FIG. 2A

(57) Abstract: Provided herein, inter alia, are predictive diagnostic, pharmacodynamic, and therapeutic methods for the treatment of breast cancer. In embodiments, the methods and compositions are based, at least in part, on the discovery that the estradiol (E2)-induced score or estrogen receptor (ER) pathway activity score determined from a sample (e.g., a tissue sample, e.g., a tumor tissue sample, e.g., a FFPE, a FF, an archival, a fresh, or a frozen tumor tissue sample) from an individual can be used in methods of determining whether the individual having breast cancer is likely to respond to a treatment including an endocrine therapy, selecting a therapy for an individual having breast cancer; treating an individual having breast cancer; and monitoring therapeutic efficacy of an endocrine therapy, as well as related kits.

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DIAGNOSTIC AND THERAPEUTIC METHODS FOR THE TREATMENT OF BREAST CANCER

CROSS-REFERENCE TO RELATED APPLICATION

[0001] This application claims priority to US Provisional Application No. 62/719,545, filed August 17, 2018, the disclosure of which is incorporated herein in its entirety and for all purposes.

REFERENCES TO A “SEQUENCE LISTING”

[0002] The Sequence Listing written in file 048893-517001WO_SEQUENCE_LISTING_ST25.txt, 560,154 bytes, created on August 13, 2019, machine format IBM-PC, MS-Windows operating system, is hereby incorporated by reference in its entirety for all purposes.

FIELD

[0003] Provided herein, *inter alia*, are diagnostic and therapeutic methods for the treatment of breast cancer. For example, provided are methods of predicting therapeutic responsiveness, methods of monitoring responsiveness to treatment, methods of selecting a treatment, methods of treatment, and diagnostic kits.

BACKGROUND

[0004] Cancer remains one of the most deadly threats to human health. In the U.S., cancer affects nearly 1.3 million new patients each year and is the second leading cause of death after heart disease, accounting for approximately 1 in 4 deaths. Solid tumors are responsible for most of those deaths. Although there have been significant advances in the medical treatment of certain cancers, the overall 5-year survival rate for all cancers has improved only by about 10% in the past 20 years.

[0005] The estrogen receptor (“ER”) is a ligand-activated transcriptional regulatory protein that mediates induction of a variety of biological effects through its interaction with endogenous estrogens. Estrogens and estrogen receptors are implicated in cancers, such as breast cancer, lung cancer, ovarian cancer, colon cancer, prostate cancer, endometrial cancer, uterine cancer, as well as other diseases or conditions. Estrogen receptor degradation as measured by immunohistochemistry (IHC) however, is insufficient as a predictor of ER pathway activity or as a pharmacodynamics (PD) biomarker for endocrine therapy; levels of ER protein do not always correlate with ER pathway status. For example, activators of ER signaling, such as the ER ligand estradiol (E2), promote degradation of ER. Furthermore, the progesterone receptor (PR), a well-established ER target gene, is often measured as a read-out of ER pathway activity; however, PR is not always present in ER+ breast tumors, and, even if present, PR suppression may not fully capture ER pathway status.

[0006] Thus, there exists an unmet need for biomarkers (e.g., transcriptional signatures), which comprehensively reflect ER pathway activity and can be useful in both diagnostic and therapeutic methods.

SUMMARY

[0007] Provided herein, *inter alia*, are diagnostic methods, therapeutic methods, kits for informing the treating an individual having a breast cancer and kits for predicting of responsiveness of an individual to a treatment for breast cancer.

[0008] In an aspect is provided a method of identifying an individual having a breast cancer who may benefit from a treatment including an endocrine therapy, the method including determining an estrogen receptor (ER) pathway activity score from a sample from the individual, where an ER pathway activity score from the sample that is at or above a reference ER pathway activity score identifies the individual as one who may benefit from a treatment including an endocrine therapy.

[0009] In an aspect is provided a method for selecting a therapy for an individual having a breast cancer, the method including determining an ER pathway activity score from a sample from the individual, where an ER pathway activity score from the sample that is at or above a reference ER pathway activity score identifies the individual as one who may benefit from a treatment including an endocrine therapy.

[0010] In an aspect is provided a method of treating an individual having a breast cancer, the method including administering an effective amount of an endocrine therapy to the individual, where the individual has been identified as one who is more likely to benefit from a treatment including an endocrine therapy as described herein.

[0011] In an aspect is provided a method of treating an individual having a breast cancer, the individual being identified as having an ER pathway activity score that is at or above a reference ER pathway activity score, the method including administering to the individual an effective amount of an endocrine therapy.

[0012] In an aspect is provided a method of treating an individual having a breast cancer, the method including: (a) determining an ER pathway activity score from a sample from the individual, where the ER pathway activity score from the sample is determined to be at or above a reference ER pathway activity score; and (b) administering to the individual an effective amount of an endocrine therapy.

[0013] In an aspect is provided a method for monitoring the response of an individual having a breast cancer to treatment with an endocrine therapy, the method including: (a) determining a first ER pathway activity score from a sample from the individual at a first time point; (b) following step (a), determining a second ER pathway activity score from a sample from the individual at a second time point following administration of an endocrine therapy; and (c) comparing the first ER pathway activity score with the second ER pathway activity score, where a decrease in the second ER pathway activity score relative to the first ER pathway activity score is predictive of an individual who is likely to respond to treatment with an endocrine therapy.

[0014] In an aspect is provided a method of identifying an individual having a breast cancer who may benefit from a treatment including an endocrine therapy, the method including determining an estradiol (E2)-induced score from a sample from the individual, where an E2-induced score from the sample that is at or above a reference E2-induced score identifies the individual as one who may benefit from a treatment including an endocrine therapy.

[0015] In an aspect is provided a method for selecting a therapy for an individual having a breast cancer, the method including determining an E2-induced score from a sample from the individual, where an E2-induced score from the sample that is at or above a reference E2-

induced score identifies the individual as one who may benefit from a treatment including an endocrine therapy.

[0016] In an aspect is provided a method of treating an individual having a breast cancer, the method including administering an effective amount of an endocrine therapy to the individual, where the individual has been identified as one who is more likely to benefit from a treatment including an endocrine therapy as described herein.

[0017] In an aspect is provided a method of treating an individual having a breast cancer, the individual being identified as having an E2-induced score that is at or above a reference E2-induced score, the method including administering to the individual an effective amount of an endocrine therapy.

[0018] In an aspect is provided a method of treating an individual having a breast cancer, the method including: (a) determining an E2-induced score from a sample from the individual, where the E2-induced score from the sample is determined to be at or above a reference E2-induced score; and (b) administering to the individual an effective amount of an endocrine therapy.

[0019] In an aspect is provided a method for monitoring the response of an individual having a breast cancer to treatment with an endocrine therapy, the method including: (a) determining a first E2-induced score from a sample from the individual at a first time point; (b) following step (a), determining a second E2-induced score from a sample from the individual at a second time point following administration of an endocrine therapy; and (c) comparing the first E2-induced score with the second E2-induced score, where a decrease in the second E2-induced score relative to the first E2-induced score is predictive of an individual who is likely to respond to treatment with an endocrine therapy.

[0020] In an aspect is provided a method of detecting estrogen receptor (ER) pathway activity in a subject that has breast cancer, the method including detecting an expression level of at least five genes set forth in Table 1 and at least five genes set forth in Table 4; at least five genes set forth in Table 2 and at least five genes set forth in Table 5; or at least five genes set forth in Table 3 and at least five genes set forth in Table 6.

[0021] In an aspect is provided a method, including: detecting, by one or more processors, a first expression level of at least five genes set forth in Table 1, at least five genes set forth in Table 2, or at least five genes set forth in Table 3; detecting, by the one or more processors, a second expression level of at least five genes set forth in Table 4, at least five genes set forth in Table 5 or at least five genes set forth in Table 6; and detecting, based at least on the first expression level and/or the second expression level, estrogen receptor (ER) pathway activity in a subject that has cancer.

[0022] In an aspect is provided a kit including a plurality of nucleic acids, where the plurality of nucleic acids are at least 5 nucleotides in length and are at least 95% identical to a 5 nucleotide continuous sequence within at least five genes set forth in Table 1 and at least five genes set forth in Table 4; at least five genes set forth in Table 2 and at least five genes set forth in Table 4; or at least five genes set forth in Table 3 and at least five genes set forth in Table 6, or 95% identical to a sequence complementary to the 5 nucleotide continuous sequence.

BRIEF DESCRIPTION OF THE DRAWINGS

[0023] The application file contains at least one drawing executed in color. Copies of this patent or patent application with color drawings will be provided by the Office upon request and payment of the necessary fee.

[0024] **FIG. 1A** is an overview of estradiol (E2)-induced genes shown in red (columns) in seven breast cancer cell lines (rows). E2 induction is defined as ≥ 2 -fold change in expression following E2 treatment compared to treatment with DMSO (p-value ≤ 0.05).

[0025] **FIG. 1B** is an overview of E2-repressed genes shown in blue (columns) in seven breast cancer cell lines (rows). E2 repression is defined as $\leq 1/2$ -fold change in expression following E2 treatment compared to treatment with DMSO (p-value ≤ 0.05).

[0026] **FIG. 1C** is a heat map with z-scored expression of 23 E2-induced and 18 E2-repressed genes in 989 breast tumors from The Cancer Genome Atlas (TCGA), annotated by estrogen receptor (ER) immunohistochemistry (IHC) status and PAM50 subtype.

[0027] **FIG. 1D** is a graph showing overlaid reference density curves of the E2-induced score (defined as the average z-scored expression of the 23 E2-induced genes shown in FIG. 1C) for 726 ER IHC+ and 213 ER IHC- breast tumors from the TCGA RNA-seq data.

[0028] FIG. 1E is a graph showing overlaid reference density curves of the E2-repressed score (defined as average z-scored expression of 18 E2-repressed genes shown in FIG. 1C) in 726 ER IHC+ and 213 ER IHC- breast tumors from the TCGA RNA-seq data.

[0029] FIG. 1F is a graph showing overlaid reference density curves of the ER pathway activity score (defined as the difference between the E2-induced score and the E2-repressed score) in 726 ER IHC+ and 213 ER IHC- breast tumors from the TCGA RNA-seq data.

[0030] FIG. 2A is a graph showing the *in vivo* efficacy of treatment with Compound A, a selective estrogen receptor degrader (SERD), in a HCI-013 patient-derived xenograft (PDX) mouse model of hormone receptor (HR)-positive breast cancer, as assessed by tumor volume over time at the indicated Compound A concentrations.

[0031] FIG. 2B is a heat map showing the relative change in z-scored expression, for the indicated 20 E2-induced and 14 E2-repressed genes in HCI-013 tumors following treatment with Compound A. Treatment regimens are annotated above.

[0032] FIG. 2C is a set of bar plots of the E2-induced score, E2-repressed score, and ER pathway activity score expressed as the average log₁₀-fold change, in HCI-013 tumors after Compound A exposure relative to vehicle-treated animals. Bar plots show average relative score and standard error, with n=4. One-sided t-test: *, p<0.05; **, p<0.01; ***, p<0.001; comparison 1 mg/kg vs. 0.1 mg/kg in black; 10 mg/kg vs. 1 mg/kg in red.

[0033] FIG. 2D is a graph showing the *in vivo* efficacy of treatment with vehicle, or Compound B (a SERD), Compound C (a SERD/SERM hybrid), or Compound F (a SERD) in a HCI-013 PDX mouse model of HR-positive breast cancer, as assessed by tumor volume over time at the indicated concentrations.

[0034] FIG. 2E is a heat map showing the relative change in z-scored expression, for the indicated 20 E2-induced and 14 E2-repressed genes in HCI-013 tumors following treatment with the indicated therapy. Treatment regimens are annotated above.

[0035] FIG. 2F is a set of bar plots of the E2-induced score, E2-repressed score, and ER pathway activity score expressed as the average log₁₀-fold change, in HCI-013 tumors after exposure to the indicated compounds relative to vehicle-treated animals. Bar plots show average

relative score and standard error, with n=4. One-sided t-test: *, p<0.1; **, p<0.05; ***, p<0.01; ****, p<0.001; comparison Compound E vs. Vehicle, Compound C vs. Compound E, Compound D vs. Compound C, and Compound B vs. Compound D.

[0036] FIG. 2G is a graph showing the *in vivo* efficacy of treatment with vehicle, Compound B, Compound C, or Compound F in a HCI-011 PDX mouse model of HR-positive breast cancer, as assessed by tumor volume over time at the indicated endocrine therapy concentrations.

[0037] FIG. 2H is a heat map showing the relative change in z-scored expression, for the indicated 20 E2-induced and 14 E2-repressed genes in HCI-011 tumors following treatment with the indicated therapy. Treatment regimens are annotated above.

[0038] FIG. 2I is a set of bar plots of the E2-induced score, E2-repressed score, and ER pathway activity score expressed as the average log₁₀-fold change, in HCI-011 tumors after exposure to the indicated compounds relative to vehicle-treated animals. Bar plots show average relative score and standard error, with n=4. One-sided t-test: *, p<0.1; **, p<0.05; ***, p<0.01; ****, p<0.001; comparison Compound E vs. Vehicle, Compound C vs. Compound E, Compound B vs. Compound C, and Compound A vs. Compound B.

[0039] FIG. 3A is a heat map showing the relative change in z-scored expression of the 21 indicated E2-induced and 17 indicated E2-repressed genes from a collection of 139 hormone receptor-positive/human epidermal growth factor receptor 2-negative (HR+/HER2-) breast tumors.

[0040] FIGS. 3B-3D are a series of reference density curves for the E2-induced score (FIG. 3B), E2-repressed score (FIG. 3C), and ER pathway activity score (FIG. 3D) in the collection of 139 HR+/HER2- breast tumors. Pre- and post-treatment with Compound B expression data for six patients are overlaid: pre-treatment scores are indicated as a diamond; post-treatment scores as a circle. Arrows show the magnitude and direction of change in ER pathway activity score per patient.

[0041] FIG. 3E is a scatter plot of pre-treatment ER pathway activity score versus pre-treatment ESR1 expression levels for six patients treated with Compound B.

[0042] **FIG. 3F** is a scatter plot of the treatment-induced difference in ER pathway activity pre-treatment to post-treatment versus pre-treatment ER pathway activity levels for six patients treated with Compound B.

[0043] **FIG. 3G** is a scatter plot of the treatment-induced difference in E2-induced score pre-treatment to post-treatment versus pre-treatment E2-induced scores for six patients treated with Compound B.

[0044] **FIGS. 3H-3J** are a series of reference density curves for the E2-induced score (FIG. 3H), E2-repressed score (FIG. 3I), and ER pathway activity score (FIG. 3J) in the collection of 139 HR+/HER2- breast tumors. Pre- and post-treatment with Compound A expression data for seven patients are overlaid: pre-treatment scores are indicated as a diamond; post-treatment scores as a circle. Arrows show the magnitude and direction of change in ER pathway activity score per patient.

[0045] **FIG. 3K** is a scatter plot of pre-treatment ER pathway activity score versus pre-treatment ESR1 expression levels for seven patients treated with Compound A.

[0046] **FIG. 3L** is a scatter plot of the treatment-induced difference in ER pathway activity pre-treatment to post-treatment versus pre-treatment ER pathway activity levels for seven patients treated with Compound A.

[0047] **FIG. 3M** is a scatter plot of the treatment-induced difference in E2-induced score pre-treatment to post-treatment versus pre-treatment E2-induced scores for seven patients treated with Compound A.

[0048] **FIGS. 4A-4C** are a series of bar plots of the E2-induced score, E2-repressed score, and ER pathway suppression expressed as the average log₁₀-fold change, based on the complete 41-gene signature (FIG. 4A), 19-gene signature (FIG. 4B), or 14-gene signature (FIG. 4C), in HCI-013 PDX breast tumors after exposure to Compound A relative to vehicle-treated animals. Bar plots show average relative score and standard error, with n=4. One-sided t-test: *, p<0.05; **, p<0.01; ***, p<0.001; comparison 1mg/kg vs. 0.1mg/kg in black; 10mg/kg vs. 1mg/kg in red.

[0049] **FIGS. 4D-4F** are a series of reference density curves for the ER pathway activity score based on the 41-gene signature (FIG. 4D), 19-gene signature (FIG. 4E), or 14-gene signature

(FIG. 4F) in the collection of 139 HR+/HER2- breast tumors. Pre- and post-treatment expression data for six patients are overlaid: pre-treatment scores are indicated as a diamond; post-treatment scores as a circle. Arrows show the magnitude and direction of change in ER pathway activity score per patient.

[0050] FIGS. 4G-4I are a series of reference density curves for the E2-induced score based on the 41-gene signature (FIG. 4G), 19-gene signature (FIG. 4H), or 14-gene signature (FIG. 4I) in the collection of 139 HR+/HER2- breast tumors. Pre- and post- treatment expression data for six patients are overlaid: pre-treatment scores are indicated as a diamond; post-treatment scores as a circle. Arrows show the magnitude and direction of change in E2-induced score per patient.

[0051] FIG. 4J is a table showing the 41-gene signature (23 E2-induced and 18 E2-repressed genes).

[0052] FIG. 4K is a table showing the 19-gene signature (11 E2-induced and 8 E2-repressed genes).

[0053] FIG. 4L is a table showing the 14-gene signature (8 E2-induced and 6 E2-repressed genes).

[0054] FIG. 5 is a scatterplot of ER pathway activity score in 60 tissue samples, with expression data prepared with RIBO-ZERO TRUSEQ® OR RNA ACCESS®. Formalin-fixed and paraffin-embedded (FFPE) samples are shown as triangles; fresh frozen samples are shown as circles. Breast tumors are shown in pink; other tissues are shown in black.

[0055] FIG. 6 is a plot of E2-induced scores of ER+/HER2- breast cancer cell lines.

[0056] FIG. 7 is a plot of E2-induced score versus impact of fulvestrant on cellular growth rate.

DETAILED DESCRIPTION

I. GENERAL TECHNIQUES

[0057] The techniques and procedures described or referenced herein are generally well understood and commonly employed using conventional methodology by those skilled in the art, such as, for example, the widely utilized methodologies described in Sambrook et al., *Molecular Cloning: A Laboratory Manual* 3d edition (2001) Cold Spring Harbor Laboratory Press, Cold

Spring Harbor, N.Y.; *Current Protocols in Molecular Biology* (F.M. Ausubel, et al. eds., (2003)); the series *Methods in Enzymology* (Academic Press, Inc.): *PCR 2: A Practical Approach* (M.J. MacPherson, B.D. Hames and G.R. Taylor eds. (1995)), Harlow and Lane, eds. (1988) *Antibodies, A Laboratory Manual*, and *Animal Cell Culture* (R.I. Freshney, ed. (1987)); *Oligonucleotide Synthesis* (M.J. Gait, ed., 1984); *Methods in Molecular Biology*, Humana Press; *Cell Biology: A Laboratory Notebook* (J.E. Cellis, ed., 1998) Academic Press; *Animal Cell Culture* (R.I. Freshney), ed., 1987); *Introduction to Cell and Tissue Culture* (J.P. Mather and P.E. Roberts, 1998) Plenum Press; *Cell and Tissue Culture: Laboratory Procedures* (A. Doyle, J.B. Griffiths, and D.G. Newell, eds., 1993-8) J. Wiley and Sons; *Handbook of Experimental Immunology* (D.M. Weir and C.C. Blackwell, eds.); *Gene Transfer Vectors for Mammalian Cells* (J.M. Miller and M.P. Calos, eds., 1987); *PCR: The Polymerase Chain Reaction*, (Mullis et al., eds., 1994); *Current Protocols in Immunology* (J.E. Coligan et al., eds., 1991); *Short Protocols in Molecular Biology* (Wiley and Sons, 1999); *Immunobiology* (C.A. Janeway and P. Travers, 1997); *Antibodies* (P. Finch, 1997); *Antibodies: A Practical Approach* (D. Catty., ed., IRL Press, 1988-1989); *Monoclonal Antibodies: A Practical Approach* (P. Shepherd and C. Dean, eds., Oxford University Press, 2000); *Using Antibodies: A Laboratory Manual* (E. Harlow and D. Lane (Cold Spring Harbor Laboratory Press, 1999); *The Antibodies* (M. Zanetti and J. D. Capra, eds., Harwood Academic Publishers, 1995); and *Cancer: Principles and Practice of Oncology* (V.T. DeVita et al., eds., J.B. Lippincott Company, 1993).

II. DEFINITIONS

[0058] It is to be understood that aspects and embodiments described herein include “comprising,” “consisting,” and “consisting essentially of” aspects and embodiments. As used herein, the singular form “a,” “an,” and “the” includes plural references unless indicated otherwise.

[0059] The term “about” as used herein refers to the usual error range for the respective value readily known to the skilled person in this technical field. Reference to “about” a value or parameter herein includes (and describes) embodiments that are directed to that value or parameter per se. For example, description referring to “about X” includes description of “X.”

[0060] As used herein, “administering” is meant a method of giving a dosage of a compound (e.g., an endocrine therapy as described herein or a composition (e.g., a pharmaceutical

composition, e.g., a pharmaceutical composition including an endocrine therapy (e.g., a selective estrogen receptor modulator (SERM) (e.g., a selective estrogen receptor degrader (SERD)), a gonadotropin-releasing hormone (GnRH) agonist, and/or an aromatase inhibitor (AI)) to a subject. The compounds and/or compositions utilized in the methods described herein can be administered, for example, orally, intramuscularly, intravenously (e.g., by intravenous infusion), subcutaneously, intradermally, percutaneously, intraarterially, intraperitoneally, intralesionally, intracranially, intraarticularly, intraprostatically, intrapleurally, intratracheally, intranasally, intravitreally, intravaginally, intrarectally, topically, intratumorally, peritoneally, subconjunctivally, intravesicularly, mucosally, intrapericardially, intraumbilically, intraocularly, topically, locally, by inhalation, by injection, by infusion, by continuous infusion, by localized perfusion bathing target cells directly, by catheter, by lavage, in creams, or in lipid compositions. The method of administration can vary depending on various factors (e.g., the compound or composition being administered and the severity of the condition, disease, or disorder being treated).

[0061] The term “anti-cancer therapy” refers to a therapy useful for treating a cancer (e.g., a breast cancer, e.g., an HR+ breast cancer (e.g., an ER+ breast cancer (e.g., a luminal A breast cancer or a luminal B breast cancer)) and/or a metastatic or a locally advanced breast cancer). Examples of anti-cancer therapeutic agents include, but are not limited to, endocrine therapies as described herein, growth inhibitory agents, cytotoxic agents, agents used in radiation therapy, anti-angiogenesis agents, apoptotic agents, anti-tubulin agents, and other agents to treat cancer, for example, anti-CD20 antibodies, platelet derived growth factor inhibitors (e.g., GLEEVEC™ (imatinib mesylate)), a COX-2 inhibitor (e.g., celecoxib), interferons, cytokines, antagonists (e.g., neutralizing antibodies), other bioactive and organic chemical agents, and the like. Combinations thereof are also included herein. An anti-cancer therapy as used herein can also be referred to a “non-endocrine therapy” which in turn refers to any anti-cancer therapy excluding endocrine therapies as defined herein.

[0062] The term “endocrine therapy” refers to a therapy or treatment useful for modulating (e.g. regulating, reducing, blocking, or inhibiting) the effects of the expression, a level, or an amount of one or more hormones found to cause or otherwise cause progression of a breast cancer as described herein. Endocrine therapy as described herein includes non-hormone and

hormone therapies such as, for example, a selective estrogen receptor modulator (SERM) as described herein and understood in the art, a selective estrogen receptor degrader (SERD) as described herein and understood in the art, a gonadotropin-releasing hormone (GnRH) agonist as described herein and understood in the art, a Selective Estrogen Receptor Covalent Antagonist (SERCA) as described herein and understood in the art, a Selective Human Estrogen Receptor Partial Agonist (ShERPA) as described herein and understood in the art; an aromatase inhibitor (AI) as described herein, or a combination thereof. In one embodiment, an endocrine therapy comprises one or more compounds from Section IV-A herein.

[0063] Additional exemplary endocrine therapies for use in the methods described herein include, but are not limited to: anti-estrogens, for example, tamoxifen (including NOLVADEX® tamoxifen), raloxifene, droloxifene, 4-hydroxytamoxifen, trioxifene, keoxifene, LY117018, onapristone, FARESTON® (toremifene citrate), nafoxidine, clomifene, anordrin, bazedoxifene, broparestrol, cyclofenil, lasofoxifene, ormeloxifene, acolbifene, elacestrant (RAD1901), clomifenoxide, etacstil, ospemifene, fulvestrant (FASLODEX®), EM800, brilanestrant (GDC-0810), LX-039, AZ9496, GDC-0927 (SRN-0927); GDC-9545, G1T48 (G1 Therapeutics), H3B 6545 (H3 Biomedicine), SAR439859 (Sanofi), aromatase inhibitors that inhibit the enzyme aromatase, which regulates estrogen production in the adrenal glands, such as, for example, 4(5)-imidazoles, aminoglutethimide, MEGASE® megestrol acetate, AROMASIN® (exemestane), formestanie, fadrozole, RIVISOR® (vorozole), FEMARA® (letrozole), and ARIMIDEX® (anastrozole); anti-androgens such as flutamide, nilutamide, bicalutamide, leuprolide, and goserelin; as well as troxacitabine (a 1,3-dioxolane nucleoside cytosine analog); and antisense oligonucleotides, particularly those which inhibit expression of genes in signaling pathways implicated in aberrant cell proliferation, as well as combinations of two or more of the above.

[0064] Examples of chemotherapeutic agents (and as applicable non-endocrine therapies) include, but are not limited to, mammalian target of rapamycin (mTOR) inhibitors such as sirolimus (also known as rapamycin), temsirolimus (also known as CCI-779 or TORISEL®), everolimus (also known as RAD001 or AFINITOR®), ridaforolimus (also known as AP-23573, MK-8669, or deforolimus), OSI-027, AZD8055, and INK128; phosphatidylinositol 3-kinase (PI3K) inhibitors such as idelalisib (also known as GS-1101 or CAL-101), BKM120, and perifosine (also known as KRX-0401); dual phosphatidylinositol 3-kinase (PI3K)/mTOR

inhibitors such as XL765, GDC-0980, BEZ235 (also known as NVP-BEZ235), BGT226, GSK2126458, PF-04691502, and PF-05212384 (also known as PKI-587); and cyclin-dependent kinase (CDK)4/6 inhibitors such as abemaciclib (VERZENIO®), palbociclib (IBRANCE®), ribociclib (KISQALI®), trilaciclib (G1T28); anthracyclines such as daunorubicin, doxorubicin, epirubicin, idarubicin, mitoxantrone, valrubicin; taxanes, including paclitaxel and docetaxel; podophyllotoxin; gemcitabine (GEMZAR®); 5-fluorouracil (5-FU); cyclophosphamide (CYTOXAN®); platinum analogs such as cisplatin and carboplatin; vinorelbine (NAVELBINE®); capecitabine (XELODA®); ixabepilone (IXEMPRA®); and eribulin (HALAVEN®); ribozymes such as a VEGF expression inhibitor (e.g., ANGIOZYME® ribozyme) and a HER2 expression inhibitor; vaccines such as gene therapy vaccines, for example, ALLOVECTIN® vaccine, LEUVECTIN® vaccine, and VAXID® vaccine; PROLEUKIN® rIL-2; LURTOTECAN® topoisomerase 1 inhibitor; ABARELIX® rmRH; Vinorelbine and Esperamicins (see U.S. Pat. No. 4,675,187), any of the compounds described in Section IV-A, below, and pharmaceutically acceptable salts, acids or derivatives of any of the above; as well as combinations of two or more of the above.

[0065] Further exemplary chemotherapeutic agents (and non-endocrine therapies) include alkylating agents such as thiotepa and cyclophosphamide (CYTOXAN®); alkyl sulfonates such as busulfan, improsulfan and piposulfan; aziridines such as benzodopa, carboquone, meturedopa, and uredopa; ethylenimines and methylamelamines including altretamine, triethylenemelamine, triethylenephosphoramidate, triethylenethiophosphoramidate and trimethylmelamine; acetogenins (especially bullatacin and bullatacinone); delta-9-tetrahydrocannabinol (dronabinol, MARINOL®); beta-lapachone; lapachol; colchicines; betulinic acid; a camptothecin (including the synthetic analogue topotecan (HYCAMTIN®), CPT-11 (irinotecan, CAMPTOSAR®), acetylcamptothecin, scoplectin, and 9-aminocamptothecin); bryostatin; callystatin; CC-1065 (including its adozelesin, carzelesin and bizelesin synthetic analogues); podophyllotoxin; podophyllinic acid; teniposide; cryptophycins (particularly cryptophycin 1 and cryptophycin 8); dolastatin; duocarmycin (including the synthetic analogues, KW-2189 and CB1-TM1); eleutherobin; pancratistatin; a sarcodictyin; spongistatin; nitrogen mustards such as chlorambucil, chlornaphazine, chlorophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard; nitrosoureas such as carmustine, chlorozotocin, fotemustine,

lomustine, nimustine, and ranimustine; antibiotics such as the enediyne antibiotics (e.g., calicheamicin, especially calicheamicin γ_1^I and calicheamicin omegaII (see, e.g., Nicolaou et al., *Angew. Chem Intl. Ed. Engl.*, 33: 183-186 (1994)); CDP323, an oral alpha-4 integrin inhibitor; dynemicin, including dynemicin A; an esperamicin; as well as neocarzinostatin chromophore and related chromoprotein enediyne antibiotic chromophores), aclacinomysins, actinomycin, authramycin, azaserine, bleomycins, cactinomycin, carabycin, caminomycin, carzinophilin, chromomycins, dactinomycin, daunorubicin, detorubicin, 6-diazo-5-oxo-L-norleucine, doxorubicin (including ADRIAMYCIN®, morpholino-doxorubicin, cyanomorpholino-doxorubicin, 2-pyrrolino-doxorubicin, doxorubicin HCl liposome injection (DOXIL®), liposomal doxorubicin TLC D-99 (MYOCET®), pegylated liposomal doxorubicin (CAELYX®), and deoxydoxorubicin), epirubicin, esorubicin, idarubicin, marcellomycin, mitomycins such as mitomycin C, mycophenolic acid, nogalamycin, olivomycins, peplomycin, porfiromycin, puromycin, quelamycin, rodorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, zorubicin; anti-metabolites such as methotrexate, gemcitabine (GEMZAR®), tegafur (UFTORAL®), capecitabine (XELODA®), an epothilone, and 5-fluorouracil (5-FU); combretastatin; folic acid analogues such as denopterin, methotrexate, pteropterin, trimetrexate; purine analogs such as fludarabine, 6-mercaptopurine, thiamiprine, thioguanine; pyrimidine analogs such as ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, floxuridine; androgens such as calusterone, dromostanolone propionate, epitio stanol, mepitio stanane, testolactone; anti-adrenals such as aminoglutethimide, mitotane, trilostane; folic acid replenisher such as frolinic acid; aceglatone; aldophosphamide glycoside; aminolevulinic acid; eniluracil; amsacrine; bestrabucil; bisantrene; edatraxate; defofamine; demecolcine; diaziquone; elformithine; elliptinium acetate; an epothilone; etoglucid; gallium nitrate; hydroxyurea; lentinan; lonidainine; maytansinoids such as maytansine and ansamitocins; mitoguazone; mitoxantrone; mopidanmol; nitraerine; pentostatin; phenamet; pirarubicin; losoxantrone; 2-ethylhydrazide; procarbazine; PSK® polysaccharide complex (JHS Natural Products, Eugene, Oreg.); razoxane; rhizoxin; sizofuran; spirogermanium; tenuazonic acid; triaziquone; 2,2',2'-trichlorotriethylamine; trichothecenes (especially T-2 toxin, verracurin A, roridin A and anguidine); urethan; vindesine (ELDISINE®, FILDESIN®); dacarbazine; mannomustine; mitobronitol; mitolactol; pipobroman; gacytosine; arabinoside ("Ara-C"); thiotepa; taxoid, e.g., paclitaxel (TAXOL®, Bristol-Myers Squibb

Oncology, Princeton, N.J.), albumin-engineered nanoparticle formulation of paclitaxel (ABRAXANETM), and docetaxel (TAXOTERE®, Rhone-Poulenc Rorer, Antony, France); chloranbucil; 6-thioguanine; mercaptopurine; methotrexate; platinum agents such as cisplatin, oxaliplatin (e.g., ELOXATIN®), and carboplatin; vincas, which prevent tubulin polymerization from forming microtubules, including vinblastine (VELBAN®), vincristine (ONCOVIN®), vindesine (ELDISINE®, FILDESIN®), and vinorelbine (NAVELBINE®); etoposide (VP-16); ifosfamide; mitoxantrone; leucovorin; novantrone; edatrexate; daunomycin; aminopterin; ibandronate; topoisomerase inhibitor RFS 2000; difluoromethylornithine (DMFO); retinoids such as retinoic acid, including bexarotene (TARGRETIN®); bisphosphonates such as clodronate (for example, BONEFOS® or OSTAC®), etidronate (DIDROCAL®), NE-58095, zoledronic acid/zoledronate (ZOMETA®), alendronate (FOSAMAX®), pamidronate (AREDIA®), tiludronate (SKELID®), or risedronate (ACTONEL®); troxacitabine (a 1,3-dioxolane nucleoside cytosine analog); antisense oligonucleotides, particularly those that inhibit expression of genes in signaling pathways implicated in aberrant cell proliferation, such as, for example, PKC- α , Raf, H-Ras, and epidermal growth factor receptor (EGF-R) (e.g., erlotinib (TARCEVATM)); and VEGF-A that reduce cell proliferation; vaccines such as THERATOPE® vaccine and gene therapy vaccines, for example, ALLOVECTIN® vaccine, LEUVECTIN® vaccine, and VAXID® vaccine; topoisomerase 1 inhibitor (e.g., LURTOTECAN®); rmRH (e.g., ABARELIX®); BAY439006 (sorafenib; Bayer); SU-11248 (sunitinib, SUTENT®, Pfizer); perifosine, COX-2 inhibitor (e.g., celecoxib or etoricoxib), proteasome inhibitor (e.g., PS341); bortezomib (VELCADE®); CCI-779; tipifarnib (R11577); orafenib, ABT510; Bcl-2 inhibitor such as oblimersen sodium (GENASENSE®); pixantrone; EGFR inhibitors; tyrosine kinase inhibitors; serine-threonine kinase inhibitors such as rapamycin (sirolimus, RAPAMUNE®); farnesyltransferase inhibitors such as lonafarnib (SCH 6636, SARASARTM); and pharmaceutically acceptable salts, acids or derivatives of any of the above; as well as combinations of two or more of the above such as CHOP, an abbreviation for a combined therapy of cyclophosphamide, doxorubicin, vincristine, and prednisolone; and FOLFOX, an abbreviation for a treatment regimen with oxaliplatin (ELOXATINTM) combined with 5-FU and leucovorin, and pharmaceutically acceptable salts, acids or derivatives of any of the above; as well as combinations of two or more of the above.

[0066] The term “cytotoxic agent” as used herein refers to a substance that inhibits or prevents a cellular function and/or causes cell death or destruction. Cytotoxic agents include, but are not limited to, radioactive isotopes (e.g., At²¹¹, I¹³¹, I¹²⁵, Y⁹⁰, Re¹⁸⁶, Re¹⁸⁸, Sm¹⁵³, Bi²¹², P³², Pb²¹² and radioactive isotopes of Lu); chemotherapeutic agents or drugs (e.g., methotrexate, adriamycin, vinca alkaloids (vincristine, vinblastine, etoposide), doxorubicin, melphalan, mitomycin C, chlorambucil, daunorubicin or other intercalating agents); growth inhibitory agents; enzymes and fragments thereof such as nucleolytic enzymes; antibiotics; toxins such as small molecule toxins or enzymatically active toxins of bacterial, fungal, plant or animal origin, including fragments and/or variants thereof; and the various antitumor or anticancer agents disclosed below. A cytotoxic agent can be a non-endocrine agent.

[0067] An “article of manufacture” is any manufacture (e.g., a package or container) or kit comprising at least one reagent, e.g., a medicament for treatment of a disease or disorder (e.g., a cancer, e.g., a breast cancer, e.g., an HR+ breast cancer (e.g., an ER+ breast cancer (e.g., luminal A breast cancer or luminal B breast cancer))), DCIS, and/or a metastatic or a locally advanced breast cancer), and/or a probe for specifically detecting a biomarker described herein. In certain embodiments, the manufacture or kit is promoted, distributed, or sold as a unit for performing the methods described herein.

[0068] The term “biomarker” as used herein refers to an indicator, e.g., a predictive, prognostic, and/or a pharmacodynamic indicator which can be detected in a sample (e.g., a tissue sample, e.g., a tumor tissue sample, e.g., a formalin-fixed and paraffin-embedded (FFPE), a fresh frozen (FF), an archival, a fresh, or a frozen tumor tissue sample). The biomarker may serve as an indicator of a particular subtype of a disease or disorder (e.g., a breast cancer, an HR+ breast cancer (e.g., an ER+ breast cancer (e.g., luminal A breast cancer or luminal B breast cancer))), DCIS, and/or a metastatic or a locally advanced breast cancer) characterized by certain molecular, pathological, histological, and/or clinical features. In some embodiments, a biomarker is a gene or a set of genes. Biomarkers include, but are not limited to, polynucleotides (e.g., DNA, and/or RNA), polynucleotide copy number alterations (e.g., DNA copy numbers), polypeptides, polypeptide and polynucleotide modifications (e.g., posttranslational modifications), carbohydrates, and/or glycolipid-based molecular markers. Exemplary sets of biomarkers are found in Tables 1-6.

[0069] The term “biomarker signature,” “signature,” “biomarker expression signature,” or “expression signature” are used interchangeably herein and refer to a combination of biomarkers whose expression is an indicator, e.g., predictive, prognostic, and/or pharmacodynamic (e.g., the 41-gene signature (e.g., the combination of genes set forth in Tables 3 and 6), the 19-gene signature (e.g., the combination of genes set forth in Tables 2 and 5), or the 14-gene signature (e.g., the combination of genes set forth in Tables 1 and 4)). The biomarker signature may serve as an indicator of a particular subtype of a disease or disorder (e.g., cancer, e.g., breast cancer, e.g., an HR⁺ breast cancer (e.g., an ER⁺ breast cancer (e.g., luminal A breast cancer or luminal B breast cancer)), DCIS, and/or a metastatic or a locally advanced breast cancer) characterized by certain molecular, pathological, histological, and/or clinical features. In some embodiments, the biomarker signature is a “gene signature.” The term “gene signature” is used interchangeably with “gene expression signature” and refers to a combination of polynucleotides whose expression is an indicator, e.g., predictive, diagnostic, and/or prognostic. In some embodiments, the biomarker signature is a “protein signature.” The term “protein signature” is used interchangeably with “protein expression signature” and refers to a combination of polypeptides whose expression is an indicator, e.g., predictive, prognostic, and/or pharmacodynamic.

[0070] The term “AGR3” refers to any native Anterior Gradient 3, Protein Disulphide Isomerase Family Member from any vertebrate source, including mammals such as primates (e.g., humans) and rodents (e.g., mice and rats), unless otherwise indicated. The term encompasses “full-length,” unprocessed AGR3 as well as any form of AGR3 that results from processing in the cell. The term also encompasses naturally occurring variants of AGR3, e.g., splice variants or allelic variants. AGR3 is also referred to in the art as Protein Disulfide Isomerase Family A Member 18, Breast Cancer Membrane Protein 11, BCMP11, PDIA18, HAG-3, HAG3, AG-3, AG3, and Anterior Gradient Protein 3 Homolog. The nucleic acid sequence of an exemplary human AGR3 is shown under NCBI Reference Sequence: NM_176813.4 or in SEQ ID NO: 1. The amino acid sequence of an exemplary protein encoded by human *AGR3* is shown under UniProt Accession No. Q8TD06 or in SEQ ID NO: 2.

[0071] The term “AMZ1” refers to any native Archaelysin Family Metallopeptidase 1 from any vertebrate source, including mammals such as primates (e.g., humans) and rodents (e.g., mice and rats), unless otherwise indicated. The term encompasses “full-length,” unprocessed

AMZ1 as well as any form of AMZ1 that results from processing in the cell. The term also encompasses naturally occurring variants of AMZ1, e.g., splice variants or allelic variants. AMZ1 is also referred to in the art as Archeobacterial Metalloproteinase-Like Protein 1, Archametzincin-1, Metalloproteinase-Like Protein, and KIAA1950. The nucleic acid sequence of an exemplary human AMZ1 is shown under NCBI Reference Sequence: NM_133463.3 or in SEQ ID NO: 3. The amino acid sequence of an exemplary protein encoded by human *AMZ1* is shown under UniProt Accession No. Q400G9 or in SEQ ID NO: 4.

[0072] The term “AREG” refers to any native Amphiregulin from any vertebrate source, including mammals such as primates (e.g., humans) and rodents (e.g., mice and rats), unless otherwise indicated. The term encompasses “full-length,” unprocessed AREG as well as any form of AREG that results from processing in the cell. The term also encompasses naturally occurring variants of AREG, e.g., splice variants or allelic variants. AREG is also referred to in the art as Colorectum Cell-Derived Growth Factor, Schwannoma-Derived Growth Factor, Amphiregulin B, AREGB, CRDGF, and SDGF. The nucleic acid sequence of an exemplary human AREG is shown under NCBI Reference Sequence: NM_001657.3 or in SEQ ID NO: 5. The amino acid sequence of an exemplary protein encoded by human *AREG* is shown under UniProt Accession No. P15514 or in SEQ ID NO: 6.

[0073] The term “C5AR2” refers to any native Complement Component 5a Receptor 2 from any vertebrate source, including mammals such as primates (e.g., humans) and rodents (e.g., mice and rats), unless otherwise indicated. The term encompasses “full-length,” unprocessed C5AR2 as well as any form of C5AR2 that results from processing in the cell. The term also encompasses naturally occurring variants of C5AR2, e.g., splice variants or allelic variants. C5AR2 is also referred to in the art as Complement Component 5a Receptor 2, G Protein-Coupled Receptor 77, GPR77, C5L2, C5a Anaphylatoxin Chemotactic Receptor C5L2, and GPF77. The nucleic acid sequence of an exemplary human C5AR2 is shown under NCBI Reference Sequence: NM_001271749.1 or in SEQ ID NO: 7. The amino acid sequence of an exemplary protein encoded by human *C5AR2* is shown under UniProt Accession No. Q9P296 or in SEQ ID NO: 8.

[0074] The term “CELSR2” refers to any native Cadherin EGF LAG Seven-Pass G-Type Receptor 2 from any vertebrate source, including mammals such as primates (e.g., humans) and

rodents (e.g., mice and rats), unless otherwise indicated. The term encompasses “full-length,” unprocessed CELSR2 as well as any form of CELSR2 that results from processing in the cell. The term also encompasses naturally occurring variants of CELSR2, e.g., splice variants or allelic variants. CELSR2 is also referred to in the art as Multiple Epidermal Growth Factor-Like Domains Protein 3, Multiple Epidermal Growth Factor-Like Domains Protein 3, Adhesion G Protein-Coupled Receptor C2, Epidermal Growth Factor-Like Protein 2, Multiple EGF-Like Domains Protein 3, Cadherin Family Member 10, Flamingo Homolog 3, EGF-Like Protein 2, CDHF10, EGFL2, MEGF3, Flamingo1, KIAA0279, and ADGRC2. The nucleic acid sequence of an exemplary human CELSR2 is shown under NCBI Reference Sequence: NM_001408.2 or in SEQ ID NO: 9. The amino acid sequence of an exemplary protein encoded by human *CELSR2* is shown under UniProt Accession No. Q9HCU4 or in SEQ ID NO: 10.

[0075] The term “CT62” refers to any native Cancer/Testis Antigen 62 from any vertebrate source, including mammals such as primates (e.g., humans) and rodents (e.g., mice and rats), unless otherwise indicated. The term encompasses “full-length,” unprocessed CT62 as well as any form of CT62 that results from processing in the cell. The term also encompasses naturally occurring variants of CT62, e.g., splice variants or allelic variants. The nucleic acid sequence of an exemplary human CT62 is shown under NCBI Reference Sequence: XM_006720429 or in SEQ ID NO: 11. The amino acid sequence of an exemplary protein encoded by human *CT62* is shown under UniProt Accession No. P0C5K7 or in SEQ ID NO: 12.

[0076] The term “FKBP4” refers to any native FK506 Binding Protein 4 from any vertebrate source, including mammals such as primates (e.g., humans) and rodents (e.g., mice and rats), unless otherwise indicated. The term encompasses “full-length,” unprocessed FKBP4 as well as any form of FKBP4 that results from processing in the cell. The term also encompasses naturally occurring variants of FKBP4, e.g., splice variants or allelic variants. FKBP4 is also referred to in the art as Rotamase, FKBP51, FKBP52, FKBP59, HBI, Peptidyl-Prolyl Cis-Trans Isomerase FKBP4, T-Cell FK506-Binding Protein (59kD), HSP Binding Immunophilin, Immunophilin FKBP52, PPIase FKBP4, PPIASE, Hsp56, P52, and P59. The nucleic acid sequence of an exemplary human FKBP4 is shown under NCBI Reference Sequence: NM_002014.3 or in SEQ ID NO: 13. The amino acid sequence of an exemplary protein encoded by human *FKBP4* is shown under UniProt Accession No. Q02790 or in SEQ ID NO: 14.

[0077] The term “FMN1” refers to any native Formin 1 from any vertebrate source, including mammals such as primates (e.g., humans) and rodents (e.g., mice and rats), unless otherwise indicated. The term encompasses “full-length,” unprocessed FMN1 as well as any form of FMN1 that results from processing in the cell. The term also encompasses naturally occurring variants of FMN1, e.g., splice variants or allelic variants. FMN1 is also referred to in the art as Limb Deformity Protein Homolog, FMN, and LD. The nucleic acid sequence of an exemplary human FMN1 is shown under NCBI Reference Sequence: NM_001277313.1 or in SEQ ID NO: 15. The amino acid sequence of an exemplary protein encoded by human *FMN1* is shown under UniProt Accession No. Q68DA7 or in SEQ ID NO: 16.

[0078] The term “GREB1” refers to any native Growth Regulation By Estrogen in Breast Cancer 1 from any vertebrate source, including mammals such as primates (e.g., humans) and rodents (e.g., mice and rats), unless otherwise indicated. The term encompasses “full-length,” unprocessed GREB1 as well as any form of GREB1 that results from processing in the cell. The term also encompasses naturally occurring variants of GREB1, e.g., splice variants or allelic variants. GREB1 is also referred to in the art as Gene Regulated in Breast Cancer 1 Protein and KIAA0575. The nucleic acid sequence of an exemplary human GREB1 is shown under NCBI Reference Sequence: NM_014668.3 or in SEQ ID NO: 17. The amino acid sequence of an exemplary protein encoded by human *GREB1* is shown under UniProt Accession No. Q4ZG55 or in SEQ ID NO: 18.

[0079] The term “IGFBP4” refers to any native Insulin Like Growth Factor Binding Protein 4 from any vertebrate source, including mammals such as primates (e.g., humans) and rodents (e.g., mice and rats), unless otherwise indicated. The term encompasses “full-length,” unprocessed IGFBP4 as well as any form of IGFBP4 that results from processing in the cell. The term also encompasses naturally occurring variants of IGFBP4, e.g., splice variants or allelic variants. IGFBP4 is also referred to in the art as IGF-Binding Protein 4, IBP-4, HT29-IGFBP, and BP-4. The nucleic acid sequence of an exemplary human IGFBP4 is shown under NCBI Reference Sequence: NM_001552.2 or in SEQ ID NO: 19. The amino acid sequence of an exemplary protein encoded by human *IGFBP4* is shown under UniProt Accession No. P22692 or in SEQ ID NO: 20.

[0080] The term “NOS1AP” refers to any native Nitric Oxide Synthase 1 Adaptor Protein from any vertebrate source, including mammals such as primates (e.g., humans) and rodents (e.g., mice and rats), unless otherwise indicated. The term encompasses “full-length,” unprocessed NOS1AP as well as any form of NOS1AP that results from processing in the cell. The term also encompasses naturally occurring variants of NOS1AP, e.g., splice variants or allelic variants. NOS1AP is also referred to in the art as C-Terminal PDZ Ligand of Neuronal Nitric Oxide Synthase Protein, Nitric Oxide Synthase 1 (Neuronal) Adaptor Protein, CAPON, Ligand of Neuronal Nitric Oxide Synthase with Carboxyl-Terminal PDZ Domain, 6330408P19Rik, and KIAA0464. The nucleic acid sequence of an exemplary human NOS1AP is shown under NCBI Reference Sequence: NM_014697.2 or in SEQ ID NO: 21. The amino acid sequence of an exemplary protein encoded by human *NOS1AP* is shown under UniProt Accession No. O75052 or in SEQ ID NO: 22.

[0081] The term “NXPH3” refers to any native Neurexophilin 3 from any vertebrate source, including mammals such as primates (e.g., humans) and rodents (e.g., mice and rats), unless otherwise indicated. The term encompasses “full-length,” unprocessed NXPH3 as well as any form of NXPH3 that results from processing in the cell. The term also encompasses naturally occurring variants of NXPH3, e.g., splice variants or allelic variants. NXPH3 is also referred to in the art as NPH3 and KIAA1159. The nucleic acid sequence of an exemplary human NXPH3 is shown under NCBI Reference Sequence: NM_007225.2 or in SEQ ID NO: 23. The amino acid sequence of an exemplary protein encoded by human *NXPH3* is shown under UniProt Accession No. O95157 or in SEQ ID NO: 24.

[0082] The term “OLFM1” refers to any native Olfactomedin 1 from any vertebrate source, including mammals such as primates (e.g., humans) and rodents (e.g., mice and rats), unless otherwise indicated. The term encompasses “full-length,” unprocessed OLFM1 as well as any form of OLFM1 that results from processing in the cell. The term also encompasses naturally occurring variants of OLFM1, e.g., splice variants or allelic variants. OLFM1 is also referred to in the art as Neuronal Olfactomedin-Related ER Localized Protein, Noelin, NOE1, Olfactomedin Related ER Localized Protein, Neuroblastoma Protein, Pancortin 1, Pancortin, NOELIN1, NOEL1, OlfA, and AMY. The nucleic acid sequence of an exemplary human OLFM1 is shown under NCBI Reference Sequence: NM_014279.4 or in SEQ ID NO: 25. The amino acid

sequence of an exemplary protein encoded by human *OLFM1* is shown under UniProt Accession No. Q99784 or in SEQ ID NO: 26.

[0083] The term “PGR” refers to any native Progesterone Receptor from any vertebrate source, including mammals such as primates (e.g., humans) and rodents (e.g., mice and rats), unless otherwise indicated. The term encompasses “full-length,” unprocessed PGR as well as any form of PGR that results from processing in the cell. The term also encompasses naturally occurring variants of PGR, e.g., splice variants or allelic variants. PGR is also referred to in the art as Nuclear Receptor Subfamily 3 Group C Member 3, NR3C3, and PR. The nucleic acid sequence of an exemplary human PGR is shown under NCBI Reference Sequence: NM_000926.4 or in SEQ ID NO: 27. The amino acid sequence of an exemplary protein encoded by human *PGR* is shown under UniProt Accession No. P06401 or in SEQ ID NO: 28.

[0084] The term “PPM1J” refers to any native Protein Phosphatase, Mg²⁺/Mn²⁺ Dependent 1J from any vertebrate source, including mammals such as primates (e.g., humans) and rodents (e.g., mice and rats), unless otherwise indicated. The term encompasses “full-length,” unprocessed PPM1J as well as any form of PPM1J that results from processing in the cell. The term also encompasses naturally occurring variants of PPM1J, e.g., splice variants or allelic variants. PPM1J is also referred to in the art as Protein Phosphatase 1J (PP2C Domain Containing), Protein Phosphatase 2C Zeta, EC 3.1.3.16, PP2C-Zeta, Protein Phosphatase 2a, Catalytic Subunit, Zeta Isoform, Protein Phosphatase 1J, PP2Czeta, and PP2CZ. The nucleic acid sequence of an exemplary human PPM1J is shown under NCBI Reference Sequence: NM_005167.5 or in SEQ ID NO: 29. The amino acid sequence of an exemplary protein encoded by human *PPM1J* is shown under UniProt Accession No. Q5JR12 or in SEQ ID NO: 30.

[0085] The term “RAPGEFL1” refers to any native Rap Guanine Nucleotide Exchange Factor Like 1 from any vertebrate source, including mammals such as primates (e.g., humans) and rodents (e.g., mice and rats), unless otherwise indicated. The term encompasses “full-length,” unprocessed RAPGEFL1 as well as any form of RAPGEFL1 that results from processing in the cell. The term also encompasses naturally occurring variants RAPGEFL1, e.g., splice variants or allelic variants. RAPGEFL1 is also referred to in the art as Link Guanine Nucleotide Exchange Factor II, Rap Guanine Nucleotide Exchange Factor (GEF)-Like 1, and Link GEFII. The nucleic acid sequence of an exemplary human RAPGEFL1 is shown under NCBI Reference Sequence:

NM_001303533.1 or in SEQ ID NO: 31. The amino acid sequence of an exemplary protein encoded by human *RAPGEFL1* is shown under UniProt Accession No. Q9UHV5 or in SEQ ID NO: 32.

[0086] The term “RBM24” refers to any native RNA Binding Motif Protein 24 from any vertebrate source, including mammals such as primates (e.g., humans) and rodents (e.g., mice and rats), unless otherwise indicated. The term encompasses “full-length,” unprocessed RBM24 as well as any form of RBM24 that results from processing in the cell. The term also encompasses naturally occurring variants of RBM24, e.g., splice variants or allelic variants. RBM24 is also referred to in the art as RNA-Binding Region (RNP1, RRM) Containing 6, RNPC6, RNA-Binding Protein 24, and DJ259A10.1. The nucleic acid sequence of an exemplary human RBM24 is shown under NCBI Reference Sequence: NM_001143942.1 or in SEQ ID NO: 33. The amino acid sequence of an exemplary protein encoded by human *RBM24* is shown under UniProt Accession No. Q9BX46 or in SEQ ID NO: 34.

[0087] The term “RERG” refers to any native RAS Like Estrogen Regulated Growth Inhibitor from any vertebrate source, including mammals such as primates (e.g., humans) and rodents (e.g., mice and rats), unless otherwise indicated. The term encompasses “full-length,” unprocessed RERG as well as any form of RERG that results from processing in the cell. The term also encompasses naturally occurring variants of RERG, e.g., splice variants or allelic variants. The nucleic acid sequence of an exemplary human RERG is shown under NCBI Reference Sequence: NM_032918.2 or in SEQ ID NO: 35. The amino acid sequence of an exemplary protein encoded by human *RERG* is shown under UniProt Accession No. Q96A58 or in SEQ ID NO: 36.

[0088] The term “RET” refers to any native Ret Proto-Oncogene from any vertebrate source, including mammals such as primates (e.g., humans) and rodents (e.g., mice and rats), unless otherwise indicated. The term encompasses “full-length,” unprocessed RET as well as any form of RET that results from processing in the cell. The term also encompasses naturally occurring variants of RET, e.g., splice variants or allelic variants. RET is also referred to in the art as Cadherin-Related Family Member 16, Rearranged During Transfection, RET Receptor Tyrosine Kinase, Cadherin Family Member 12, Proto-Oncogene C-Ret, EC 2.7.10.1, CDHF12, CDHR16, PTC, Multiple Endocrine Neoplasia And Medullary Thyroid Carcinoma 1, EC 2.7.10, RET-

ELE1, HSCR1, MEN2A, MEN2B, RET51, and MTC1. The nucleic acid sequence of an exemplary human RET is shown under NCBI Reference Sequence: NM_020975.5 or in SEQ ID NO: 37. The amino acid sequence of an exemplary protein encoded by human *RET* is shown under UniProt Accession No. P07949 or in SEQ ID NO: 38.

[0089] The term “SGK3” refers to any native Serum/Glucocorticoid Regulated Kinase Family Member 3 from any vertebrate source, including mammals such as primates (e.g., humans) and rodents (e.g., mice and rats), unless otherwise indicated. The term encompasses “full-length,” unprocessed SGK3 as well as any form of SGK3 that results from processing in the cell. The term also encompasses naturally occurring variants of SGK3, e.g., splice variants or allelic variants. SGK3 is also referred to in the art as Cytokine-Independent Survival Kinase, EC 2.7.11.1, SGK1, CISK, EC 2.7.11, Serine/Threonine-Protein Kinase Sgk3, and SGK2. The nucleic acid sequence of an exemplary human SGK3 is shown under NCBI Reference Sequence: NM_001033578.2 or in SEQ ID NO: 39. The amino acid sequence of an exemplary protein encoded by human *SGK3* is shown under UniProt Accession No. Q96BR1 or in SEQ ID NO: 40.

[0090] The term “SLC9A3R1” refers to any native SLC9A3 Regulator 1 from any vertebrate source, including mammals such as primates (e.g., humans) and rodents (e.g., mice and rats), unless otherwise indicated. The term encompasses “full-length,” unprocessed SLC9A3R1 as well as any form of SLC9A3R1 that results from processing in the cell. The term also encompasses naturally occurring variants of SLC9A3R1, e.g., splice variants or allelic variants. SLC9A3R1 is also referred to in the art as Solute Carrier Family 9, Subfamily A (NHE3, Cation Proton Antiporter 3), Member 3 Regulator 1, Regulatory Cofactor Of Na(+)/H(+) Exchanger, NHERF-1, EBP50, NHERF, Ezrin-Radixin-Moesin Binding Phosphoprotein-50, Sodium-Hydrogen Exchanger Regulatory Factor 1, and NPHLOP2. The nucleic acid sequence of an exemplary human SLC9A3R1 is shown under NCBI Reference Sequence: NM_004252.4 or in SEQ ID NO: 41. The amino acid sequence of an exemplary protein encoded by human *SLC9A3R1* is shown under UniProt Accession No. O14745 or in SEQ ID NO: 42.

[0091] The term “TFF1” refers to any native Trefoil Factor 1 from any vertebrate source, including mammals such as primates (e.g., humans) and rodents (e.g., mice and rats), unless otherwise indicated. The term encompasses “full-length,” unprocessed TFF1 as well as any form of TFF1 that results from processing in the cell. The term also encompasses naturally occurring

variants of TFF1, e.g., splice variants or allelic variants. TFF1 is also referred to in the art as Breast Cancer Estrogen-Inducible Protein, Polypeptide P1.A, Protein PS2, HP1.A, PNR-2, BCEI, PS2, Gastrointestinal Trefoil Protein PS2, D21S21, and HPS2. The nucleic acid sequence of an exemplary human TFF1 is shown under NCBI Reference Sequence: NM_003225.2 or in SEQ ID NO: 43. The amino acid sequence of an exemplary protein encoded by human *TFF1* is shown under UniProt Accession No. P04155 or in SEQ ID NO: 44.

[0092] The term “ZNF703” refers to any native Zinc Finger Protein 703 from any vertebrate source, including mammals such as primates (e.g., humans) and rodents (e.g., mice and rats), unless otherwise indicated. The term encompasses “full-length,” unprocessed ZNF703 as well as any form of ZNF703 that results from processing in the cell. The term also encompasses naturally occurring variants of ZNF703, e.g., splice variants or allelic variants. ZNF703 is also referred to in the art as Zinc Finger Elbow-Related Proline Domain Protein 1, ZEPP01, ZPO1, ZNF503L, and NLZ1. The nucleic acid sequence of an exemplary human ZNF703 is shown under NCBI Reference Sequence: NM_025069.2 or in SEQ ID NO: 45. The amino acid sequence of an exemplary protein encoded by human *ZNF703* is shown under UniProt Accession No. Q9H7S9 or in SEQ ID NO: 46.

[0093] The term “BAMBI” refers to any native BMP and Activin Membrane Bound Inhibitor from any vertebrate source, including mammals such as primates (e.g., humans) and rodents (e.g., mice and rats), unless otherwise indicated. The term encompasses “full-length,” unprocessed BAMBI as well as any form of BAMBI that results from processing in the cell. The term also encompasses naturally occurring variants of BAMBI, e.g., splice variants or allelic variants. BAMBI is also referred to in the art as Putative Transmembrane Protein NMA, Non-Metastatic Gene A Protein, NMA, and BMP And Activin Membrane-Bound Inhibitor Homolog. The nucleic acid sequence of an exemplary human BAMBI is shown under NCBI Reference Sequence: NM_012342.2 or in SEQ ID NO: 47. The amino acid sequence of an exemplary protein encoded by human *BAMBI* is shown under UniProt Accession No. Q13145 or in SEQ ID NO: 48.

[0094] The term “BCAS1” refers to any native Breast Carcinoma Amplified Sequence 1 from any vertebrate source, including mammals such as primates (e.g., humans) and rodents (e.g., mice and rats), unless otherwise indicated. The term encompasses “full-length,” unprocessed

BCAS1 as well as any form of BCAS1 that results from processing in the cell. The term also encompasses naturally occurring variants of BCAS1, e.g., splice variants or allelic variants. BCAS1 is also referred to in the art as Amplified and Overexpressed in Breast Cancer, Novel Amplified in Breast Cancer 1, AIBC1, and NABC1. The nucleic acid sequence of an exemplary human BCAS1 is shown under NCBI Reference Sequence: NM_003657.3 or in SEQ ID NO: 49. The amino acid sequence of an exemplary protein encoded by human *BCAS1* is shown under UniProt Accession No. O75363 or in SEQ ID NO: 50.

[0095] The term “CCNG2” refers to any native Cyclin G2 from any vertebrate source, including mammals such as primates (e.g., humans) and rodents (e.g., mice and rats), unless otherwise indicated. The term encompasses “full-length,” unprocessed CCNG2 as well as any form of CCNG2 that results from processing in the cell. The term also encompasses naturally occurring variants of CCNG2, e.g., splice variants or allelic variants. The nucleic acid sequence of an exemplary human CCNG2 is shown under NCBI Reference Sequence: XM_011532399.2 or in SEQ ID NO: 51. The amino acid sequence of an exemplary protein encoded by human *CCNG2* is shown under UniProt Accession No. Q16589 or in SEQ ID NO: 52.

[0096] The term “DDIT4” refers to any native DNA Damage Inducible Transcript 4 from any vertebrate source, including mammals such as primates (e.g., humans) and rodents (e.g., mice and rats), unless otherwise indicated. The term encompasses “full-length,” unprocessed DDIT4 as well as any form of DDIT4 that results from processing in the cell. The term also encompasses naturally occurring variants of DDIT4, e.g., splice variants or allelic variants. DDIT4 is also referred to in the art as Protein Regulated in Development and DNA Damage Response 1, HIF-1 Responsive Protein RTP801, REDD1, RTP801, and Dig2. The nucleic acid sequence of an exemplary human *DDIT4* is shown under NCBI Reference Sequence: NM_019058.3 or in SEQ ID NO: 53. The amino acid sequence of an exemplary protein encoded by human DDIT4 is shown under UniProt Accession No. Q9NX09 or in SEQ ID NO: 54.

[0097] The term “EGLN3” refers to any native Egl-9 Family Hypoxia Inducible Factor 3 from any vertebrate source, including mammals such as primates (e.g., humans) and rodents (e.g., mice and rats), unless otherwise indicated. The term encompasses “full-length,” unprocessed EGLN3 as well as any form of EGLN3 that results from processing in the cell. The term also encompasses naturally occurring variants of EGLN3, e.g., splice variants or allelic variants.

EGLN3 is also referred to in the art as Prolyl Hydroxylase Domain-Containing Protein 3, Hypoxia-Inducible Factor Prolyl Hydroxylase 3, HIF-Prolyl Hydroxylase 3, HPH-1, HPH-3, PHD3, Egl Nine-Like Protein 3 Isoform, Egl Nine Homolog 3, EC 1.14.11.29, EC 1.14.11, HIFP4H3, and HIFPH3. The nucleic acid sequence of an exemplary human EGLN3 is shown under NCBI Reference Sequence: NM_022073.3 or in SEQ ID NO: 55. The amino acid sequence of an exemplary protein encoded by human *EGLN3* is shown under UniProt Accession No. Q9H6Z9 or in SEQ ID NO: 56.

[0098] The term “FAM171B” refers to any native Family With Sequence Similarity 171 Member B from any vertebrate source, including mammals such as primates (e.g., humans) and rodents (e.g., mice and rats), unless otherwise indicated. The term encompasses “full-length,” unprocessed FAM171B as well as any form of FAM171B that results from processing in the cell. The term also encompasses naturally occurring variants of FAM171B, e.g., splice variants or allelic variants. FAM171B is also referred to in the art as KIAA1946 and Protein FAM171B. The nucleic acid sequence of an exemplary human FAM171B is shown under NCBI Reference Sequence: NM_177454.3 or in SEQ ID NO: 57. The amino acid sequence of an exemplary protein encoded by human *FAM171B* is shown under UniProt Accession No. Q6P995 or in SEQ ID NO: 58.

[0099] The term “GRM4” refers to any native Glutamate Metabotropic Receptor 4 from any vertebrate source, including mammals such as primates (e.g., humans) and rodents (e.g., mice and rats), unless otherwise indicated. The term encompasses “full-length,” unprocessed GRM4 as well as any form of GRM4 that results from processing in the cell. The term also encompasses naturally occurring variants of GRM4, e.g., splice variants or allelic variants. GRM4 is also referred to in the art as GPRC1D, MGLUR4, and MGlu4. The nucleic acid sequence of an exemplary human GRM4 is shown under NCBI Reference Sequence: NM_000841.4 or in SEQ ID NO: 59. The amino acid sequence of an exemplary protein encoded by human *GRM4* is shown under UniProt Accession No. Q14833 or in SEQ ID NO: 60.

[0100] The term “IL1R1” refers to any native Interleukin 1 Receptor Type 1 from any vertebrate source, including mammals such as primates (e.g., humans) and rodents (e.g., mice and rats), unless otherwise indicated. The term encompasses “full-length,” unprocessed IL1R1 as well as any form of IL1R1 that results from processing in the cell. The term also encompasses

naturally occurring variants of IL1R1, e.g., splice variants or allelic variants. IL1R1 is also referred to in the art as CD121 Antigen-Like Family Member A, Interleukin-1 Receptor Alpha, IL-1R-Alpha, IL1RA, IL1R, P80, CD121a Antigen, D2S1473, CD121A, and IL1RT1. The nucleic acid sequence of an exemplary human IL1R1 is shown under NCBI Reference Sequence: NM_001288706.1 or in SEQ ID NO: 61. The amino acid sequence of an exemplary protein encoded by human *IL1R1* is shown under UniProt Accession No. P14778 or in SEQ ID NO: 62.

[0101] The term “LIPH” refers to any native Lipase H from any vertebrate source, including mammals such as primates (e.g., humans) and rodents (e.g., mice and rats), unless otherwise indicated. The term encompasses “full-length,” unprocessed LIPH as well as any form of LIPH that results from processing in the cell. The term also encompasses naturally occurring variants of LIPH, e.g., splice variants or allelic variants. LIPH is also referred to in the art as Membrane-Associated Phosphatidic Acid-Selective Phospholipase A1-Alpha, PD Lipase-Related Protein, Phospholipase A1 Member B, MPA-PLA1 Alpha, LPDLR, Membrane-Bound Phosphatidic Acid-Selective Phospholipase A1, Lipase Member H, EC 3.1.1.3, C 3.1., ARWH2, HYPT7, LAH2, and AH. The nucleic acid sequence of an exemplary human LIPH is shown under NCBI Reference Sequence: XM_006713529.4 or in SEQ ID NO: 63. The amino acid sequence of an exemplary protein encoded by human *LIPH* is shown under UniProt Accession No. Q8WWY8 or in SEQ ID NO: 64.

[0102] The term “NBEA” refers to any native Neurobeachin from any vertebrate source, including mammals such as primates (e.g., humans) and rodents (e.g., mice and rats), unless otherwise indicated. The term encompasses “full-length,” unprocessed NBEA as well as any form of NBEA that results from processing in the cell. The term also encompasses naturally occurring variants of NBEA, e.g., splice variants or allelic variants. NBEA is also referred to in the art as Lysosomal-Trafficking Regulator 2, BCL8B, LYST2, Protein BCL8B, EC 1.14.14.5, EC 6.1.1.11, and KIAA1544. The nucleic acid sequence of an exemplary human NBEA is shown under NCBI Reference Sequence: NM_015678.4 or in SEQ ID NO: 65. The amino acid sequence of an exemplary protein encoded by human *NBEA* is shown under UniProt Accession No. Q8NFP9 or in SEQ ID NO: 66.

[0103] The term “PNPLA7” refers to any native Patatin Like Phospholipase Domain Containing 7 from any vertebrate source, including mammals such as primates (e.g., humans)

and rodents (e.g., mice and rats), unless otherwise indicated. The term encompasses “full-length,” unprocessed PNPLA7 as well as any form of PNPLA7 that results from processing in the cell. The term also encompasses naturally occurring variants of PNPLA7, e.g., splice variants or allelic variants. PNPLA7 is also referred to in the art as C9orf111, Patatin-Like Phospholipase Domain-Containing Protein 7, Chromosome 9 Open Reading Frame 111, EC 3.1.1.5, NTE-R1, and NTEL1. The nucleic acid sequence of an exemplary human PNPLA7 is shown under NCBI Reference Sequence: NM_001098537.2 or in SEQ ID NO: 67. The amino acid sequence of an exemplary protein encoded by human *PNPLA7* is shown under UniProt Accession No. Q6ZV29 or in SEQ ID NO: 68.

[0104] The term “PSCA” refers to any native Prostate Stem Cell Antigen from any vertebrate source, including mammals such as primates (e.g., humans) and rodents (e.g., mice and rats), unless otherwise indicated. The term encompasses “full-length,” unprocessed PSCA as well as any form of PSCA that results from processing in the cell. The term also encompasses naturally occurring variants of PSCA, e.g., splice variants or allelic variants. PSCA is also referred to in the art as PRO232. The nucleic acid sequence of an exemplary human PSCA is shown under NCBI Reference Sequence: NM_005672.4 or in SEQ ID NO: 69. The amino acid sequence of an exemplary protein encoded by human *PSCA* is shown under UniProt Accession No. O43653 or in SEQ ID NO: 70.

[0105] The term “SEMA3E” refers to any native Semaphorin 3E from any vertebrate source, including mammals such as primates (e.g., humans) and rodents (e.g., mice and rats), unless otherwise indicated. The term encompasses “full-length,” unprocessed SEMA3E as well as any form of SEMA3E that results from processing in the cell. The term also encompasses naturally occurring variants of SEMA3E, e.g., splice variants or allelic variants. SEMA3E is also referred to in the art as Sema Domain, Immunoglobulin Domain (Ig), Short Basic Domain, Secreted, (Semaphorin) 3E, SEMAH, Semaphorin-3E, M-Sema H, KIAA0331, M-SemaK, and Coll-5. The nucleic acid sequence of an exemplary human SEMA3E is shown under NCBI Reference Sequence: NM_012431.2 or in SEQ ID NO: 71. The amino acid sequence of an exemplary protein encoded by human *SEMA3E* is shown under UniProt Accession No. O15041 or in SEQ ID NO: 72.

[0106] The term “SSPO” refers to any native SCO-Spondin from any vertebrate source, including mammals such as primates (e.g., humans) and rodents (e.g., mice and rats), unless otherwise indicated. The term encompasses “full-length,” unprocessed SSPO as well as any form of SSPO that results from processing in the cell. The term also encompasses naturally occurring variants of SSPO, e.g., splice variants or allelic variants. SSPO is also referred to in the art as SCO Protein, Thrombospondin Domain Containing, Subcommissural Organ Spondin, EC 3.4.24.82, EC 3.4.21.9, and KIAA2036. The nucleic acid sequence of an exemplary human SSPO is shown under NCBI Reference Sequence: BN000852.1 or in SEQ ID NO: 73. The amino acid sequence of an exemplary protein encoded by human *SSPO* is shown under UniProt Accession No. A2VEC9 or in SEQ ID NO: 74.

[0107] The term “STON1” refers to any native Stonin 1 from any vertebrate source, including mammals such as primates (e.g., humans) and rodents (e.g., mice and rats), unless otherwise indicated. The term encompasses “full-length,” unprocessed STON1 as well as any form of STON1 that results from processing in the cell. The term also encompasses naturally occurring variants of STON1, e.g., splice variants or allelic variants. STON1 is also referred to in the art as Stoned B-Like Factor, SALF, SBLF, STN1, Stoned B Homolog 1, and STNB1. The nucleic acid sequence of an exemplary human STON1 is shown under NCBI Reference Sequence: NM_001198595.1 or in SEQ ID NO: 75. The amino acid sequence of an exemplary protein encoded by human *STON1* is shown under UniProt Accession No. Q9Y6Q2 or in SEQ ID NO: 76.

[0108] The term “TGFB3” refers to any native Transforming Growth Factor Beta 3 from any vertebrate source, including mammals such as primates (e.g., humans) and rodents (e.g., mice and rats), unless otherwise indicated. The term encompasses “full-length,” unprocessed TGFB3 as well as any form of TGFB3 that results from processing in the cell. The term also encompasses naturally occurring variants of TGFB3, e.g., splice variants or allelic variants. TGFB3 is also referred to in the art as Prepro-Transforming Growth Factor Beta-3, Arrhythmogenic Right Ventricular Dysplasia 1, TGF-Beta-3, ARVD1, LDS5, RNHF, and ARVD. The nucleic acid sequence of an exemplary human TGFB3 is shown under NCBI Reference Sequence: NM_003239.4 or in SEQ ID NO: 77. The amino acid sequence of an

exemplary protein encoded by human *TGFB3* is shown under UniProt Accession No. P10600 or in SEQ ID NO: 78.

[0109] The term “TP53INP1” refers to any native Tumor Protein P53 Inducible Nuclear Protein 1 from any vertebrate source, including mammals such as primates (e.g., humans) and rodents (e.g., mice and rats), unless otherwise indicated. The term encompasses “full-length,” unprocessed TP53INP1 as well as any form of TP53INP1 that results from processing in the cell. The term also encompasses naturally occurring variants of TP53INP1, e.g., splice variants or allelic variants. TP53INP1 is also referred to in the art as P53-Dependent Damage-Inducible Nuclear Protein 1, Stress-Induced Protein, P53DINP1, SIP, P53-Inducible P53DINP1, TP53DINP1, TP53INP1A, TP53INP1B, and Teap. The nucleic acid sequence of an exemplary human *TGFB3* is shown under NCBI Reference Sequence: NM_033285.3 or in SEQ ID NO: 79. The amino acid sequence of an exemplary protein encoded by human *TP53INP1* is shown under UniProt Accession No. Q96A56 or in SEQ ID NO: 80.

[0110] The term “TP53INP2” refers to any native Tumor Protein P53 Inducible Nuclear Protein 2 from any vertebrate source, including mammals such as primates (e.g., humans) and rodents (e.g., mice and rats), unless otherwise indicated. The term encompasses “full-length,” unprocessed TP53INP2 as well as any form of TP53INP2 that results from processing in the cell. The term also encompasses naturally occurring variants of TP53INP2, e.g., splice variants or allelic variants. TP53INP2 is also referred to in the art as P53-Inducible Protein U, C20orf110, PIG-U, PINH, DOR, Chromosome 20 Open Reading Frame 110, Diabetes And Obesity-Regulated Gene, and DJ1181N3.1. The nucleic acid sequence of an exemplary human TP53INP2 is shown under NCBI Reference Sequence: NM_021202.2 or in SEQ ID NO: 81. The amino acid sequence of an exemplary protein encoded by human *TP53INP2* is shown under UniProt Accession No. Q8IXH6 or in SEQ ID NO: 82.

[0111] The term “GUSB” refers to any native Glucuronidase Beta from any vertebrate source, including mammals such as primates (e.g., humans) and rodents (e.g., mice and rats), unless otherwise indicated. The term encompasses “full-length,” unprocessed GUSB as well as any form of GUSB that results from processing in the cell. The term also encompasses naturally occurring variants of GUSB, e.g., splice variants or allelic variants. GUSB is also referred to in the art as EC 3.2.1.31, Beta-G1, Beta-D-Glucuronidase, MPS7, and BG. The nucleic acid

sequence of an exemplary human *GUSB* is shown under NCBI Reference Sequence: NM_000181.3 or in SEQ ID NO: 83. The amino acid sequence of an exemplary protein encoded by human *GUSB* is shown under UniProt Accession No. P08236 or in SEQ ID NO: 84.

[0112] The term “PPIA” refers to any native Peptidylprolyl Isomerase A from any vertebrate source, including mammals such as primates (e.g., humans) and rodents (e.g., mice and rats), unless otherwise indicated. The term encompasses “full-length,” unprocessed PPIA as well as any form of PPIA that results from processing in the cell. The term also encompasses naturally occurring variants of PPIA, e.g., splice variants or allelic variants. PPIA is also referred to in the art as Cyclosporin A-Binding Protein, Cyclophilin A, Rotamase A, EC 5.2.1.8, PPIase A, CYPA, Epididymis Secretory Sperm Binding Protein Li 69p, Peptidyl-Prolyl Cis-Trans Isomerase A, T Cell Cyclophilin, HEL-S-69p, and CYPH. The nucleic acid sequence of an exemplary human PPIA is shown under NCBI Reference Sequence: NM_021130.4 or in SEQ ID NO: 85. The amino acid sequence of an exemplary protein encoded by human *PPIA* is shown under UniProt Accession No. P62937 or in SEQ ID NO: 86.

[0113] The term “UBC” refers to any native Ubiquitin C from any vertebrate source, including mammals such as primates (e.g., humans) and rodents (e.g., mice and rats), unless otherwise indicated. The term encompasses “full-length,” unprocessed UBC as well as any form of UBC that results from processing in the cell. The term also encompasses naturally occurring variants of UBC, e.g., splice variants or allelic variants. UBC is also referred to in the art as Polyubiquitin-C and HMG20. The nucleic acid sequence of an exemplary human UBC is shown under NCBI Reference Sequence: NM_021009.6 or in SEQ ID NO: 87. The amino acid sequence of an exemplary protein encoded by human *UBC* is shown under UniProt Accession No. P0CG48 or in SEQ ID NO: 88.

[0114] The term “SDHA” refers to Succinate Dehydrogenase Complex Flavoprotein Subunit A from any vertebrate source, including mammals such as primates (e.g., humans) and rodents (e.g., mice and rats), unless otherwise indicated. The term encompasses “full-length,” unprocessed SDHA as well as any form of SDHA that results from processing in the cell. The term also encompasses naturally occurring variants of SDHA, e.g., splice variants or allelic variants. The nucleic acid sequence of an exemplary human SDHA is shown under NCBI Reference Sequence: NM_001330758 or in SEQ ID NO: 89. The amino acid sequence of an

exemplary protein encoded by human *SDHA* is shown under UniProt Accession No. P31040 or in SEQ ID NO: 90.

[0115] The terms “cancer” and “cancerous” refer to or describe the physiological condition in mammals that is typically characterized by unregulated cell growth. Examples of cancer include but are not limited to, carcinoma, lymphoma, blastoma, sarcoma, and leukemia or lymphoid malignancies. More particular examples of such cancers include, but are not limited to, breast cancer (e.g., an HR+ breast cancer (e.g., an ER+ breast cancer (e.g., luminal A breast cancer or luminal B breast cancer)), DCIS, and/or a metastatic or a locally advanced breast cancer)); lung cancer, including small-cell lung cancer, non-small cell lung cancer, adenocarcinoma of the lung, and squamous carcinoma of the lung; bladder cancer (e.g., urothelial bladder cancer (UBC), muscle invasive bladder cancer (MIBC), and BCG-refractory non-muscle invasive bladder cancer (NMIBC)); kidney or renal cancer (e.g., renal cell carcinoma (RCC)); cancer of the urinary tract; prostate cancer, such as castration-resistant prostate cancer (CRPC); cancer of the peritoneum; hepatocellular cancer; gastric or stomach cancer, including gastrointestinal cancer and gastrointestinal stromal cancer; pancreatic cancer; glioblastoma; cervical cancer; ovarian cancer; liver cancer; hepatoma; colon cancer; rectal cancer; colorectal cancer; endometrial or uterine carcinoma; salivary gland carcinoma; prostate cancer; vulval cancer; thyroid cancer; hepatic carcinoma; anal carcinoma; penile carcinoma; melanoma, including superficial spreading melanoma, lentigo maligna melanoma, acral lentiginous melanomas, and nodular melanomas; multiple myeloma and B-cell lymphoma (including low grade/follicular non-Hodgkin’s lymphoma (NHL); small lymphocytic (SL) NHL; intermediate grade/follicular NHL; intermediate grade diffuse NHL; high grade immunoblastic NHL; high grade lymphoblastic NHL; high grade small non-cleaved cell NHL; bulky disease NHL; mantle cell lymphoma; AIDS-related lymphoma; and Waldenstrom’s Macroglobulinemia); chronic lymphocytic leukemia (CLL); acute lymphoblastic leukemia (ALL); acute myelogenous leukemia (AML); hairy cell leukemia; chronic myeloblastic leukemia (CML); post-transplant lymphoproliferative disorder (PTLD); and myelodysplastic syndromes (MDS), as well as abnormal vascular proliferation associated with phakomatoses, edema (such as that associated with brain tumors), Meigs’ syndrome, brain cancer, head and neck cancer, and associated metastases.

[0116] The term “breast cancer” as used herein, refers to histologically or cytologically confirmed cancer of the breast. In some embodiments, the breast cancer is a carcinoma. In some embodiments, the breast cancer is an adenocarcinoma. In some embodiments, the breast cancer is a sarcoma. In some embodiments, the breast cancer is an HR+ breast cancer. In some embodiments, the HR+ breast cancer is an ER+ breast cancer. In some embodiments, the ER+ breast cancer is luminal A breast cancer. In some embodiments, the ER+ breast cancer is luminal B breast cancer. In some embodiments, the breast cancer is a metastatic or a locally advanced breast cancer.

[0117] The term “locally advanced breast cancer” refers to cancer that has spread from where it started in the breast to nearby tissue or lymph nodes, but not to other parts of the body.

[0118] The term “metastatic breast cancer” refers to cancer that has spread from the breast to other parts of the body, such as the bones, liver, lungs, or brain. Metastatic breast cancer may also be referred to as stage IV breast cancer.

[0119] The term “ductal carcinoma in situ breast cancer” or (DCIS cancer) refers breast cancers characterized as being intraductal, non-invasive, and pre-invasive primary tumors as understood in the art.

[0120] The terms “cell proliferative disorder” and “proliferative disorder” refer to disorders that are associated with some degree of abnormal cell proliferation. In one embodiment, the cell proliferative disorder is a breast cancer (e.g., an HR+ breast cancer (e.g., an ER+ breast cancer (e.g., luminal A breast cancer or luminal B breast cancer)), DCIS, and/or a metastatic or a locally advanced breast cancer). In another embodiment, the cell proliferative disorder is a tumor.

[0121] The term “concurrently” is used herein to refer to administration of two or more therapeutic agents, where at least part of the administration overlaps in time. Accordingly, concurrent administration includes a dosing regimen when the administration of one or more agent(s) continues after discontinuing the administration of one or more other agent(s).

[0122] As used herein, “delaying progression” of a disorder or disease means to defer, hinder, slow, retard, stabilize, and/or postpone development of the disease or disorder (e.g., a breast cancer, e.g., an HR+ breast cancer (e.g., an ER+ breast cancer (e.g., luminal A breast cancer or luminal B breast cancer)), DCIS, and/or a metastatic or a locally advanced breast cancer). This

delay can be of varying lengths of time, depending on the history of the disease and/or subject being treated. As is evident to one skilled in the art, a sufficient or significant delay can, in effect, encompass prevention, in that the subject does not develop the disease.

[0123] The terms “determination,” “determining,” “detection,” “detecting,” and grammatical variations thereof include any means of determining or detecting, including direct and indirect determination or detection.

[0124] A “disorder” or “disease” is any condition that would benefit from treatment including, but not limited to, chronic and acute disorders or diseases including those pathological conditions which predispose the mammal to the disorder in question (e.g., a cancer, e.g., a breast cancer, e.g., an HR+ breast cancer (e.g., an ER+ breast cancer (e.g., luminal A breast cancer or luminal B breast cancer))), DCIS, and/or a metastatic or a locally advanced breast cancer).

[0125] The term “diagnosis” is used herein to refer to the identification or classification of a molecular or pathological state, disease, or condition (e.g., a cancer, e.g., a breast cancer, e.g., an HR+ breast cancer (e.g., an ER+ breast cancer (e.g., luminal A breast cancer or luminal B breast cancer))), DCIS, and/or a metastatic or a locally advanced breast cancer). For example, “diagnosis” may refer to identification of a particular type of breast cancer. “Diagnosis” may also refer to the classification of a particular subtype of breast cancer, e.g., by histopathological criteria, or by molecular features (e.g., a subtype characterized by expression of a combination of biomarkers (e.g., particular genes or proteins encoded by said genes)).

[0126] An “effective amount” of a compound, for example, an endocrine therapy as described herein, or a composition (e.g., pharmaceutical composition) thereof, is at least the minimum amount required to achieve the desired therapeutic or prophylactic result, such as a measurable increase in overall survival (OS) or progression-free survival (PFS) of a particular disease or disorder (e.g., a breast cancer, e.g., an HR+ breast cancer (e.g., an ER+ breast cancer (e.g., luminal A breast cancer or luminal B breast cancer))), DCIS, and/or a metastatic or a locally advanced breast cancer). An effective amount herein may vary according to factors such as the disease state, age, sex, and weight of the individual, and the ability of the antibody to elicit a desired response in the subject. An effective amount is also one in which any toxic or detrimental effects of the treatment are outweighed by the therapeutically beneficial effects. For prophylactic use, beneficial or desired results include results such as eliminating or reducing the risk,

lessening the severity, or delaying the onset of the disease, including biochemical, histological and/or behavioral symptoms of the disease, its complications, and intermediate pathological phenotypes presenting during development of the disease. An effective amount can be administered in one or more administrations. For purposes provided herein, an effective amount of drug, compound, or pharmaceutical composition is an amount sufficient to accomplish prophylactic or therapeutic treatment either directly or indirectly. As is understood in the clinical context, an effective amount of a drug, compound, or pharmaceutical composition may or may not be achieved in conjunction with another drug, compound, or pharmaceutical composition. Thus, an “effective amount” may be considered in the context of administering one or more therapeutic agents, and a single agent may be considered to be given in an effective amount if, in conjunction with one or more other agents, a desirable result may be or is achieved. For example, an effective amount of an endocrine therapy as described herein as a cancer treatment may reduce the number of cancer cells; reduce the primary tumor size; inhibit (i.e., slow to some extent and preferably stop) cancer cell infiltration into peripheral organs; inhibit (i.e., slow to some extent and preferably stop) tumor metastasis; inhibit, to some extent, tumor growth; and/or relieve to some extent one or more of the symptoms associated with the disorder. To the extent the drug may prevent growth and/or kill existing cancer cells, it may be cytostatic and/or cytotoxic. For cancer therapy, efficacy in vivo can, for example, be measured by assessing the duration of survival, time to disease progression (TTP), the response rates (RR), duration of response, and/or quality of life.

[0127] The “expression level,” “amount,” or “level,” or used herein interchangeably, of a biomarker is a detectable level in a biological sample. “Expression” generally refers to the process by which information (e.g., gene-encoded and/or epigenetic) is converted into the structures present and operating in the cell. Therefore, as used herein, “expression” may refer to transcription into a polynucleotide, translation into a polypeptide, or even polynucleotide and/or polypeptide modifications (e.g., posttranslational modification of a polypeptide). Fragments of the transcribed polynucleotide, the translated polypeptide, or polynucleotide and/or polypeptide modifications (e.g., posttranslational modification of a polypeptide) shall also be regarded as expressed whether they originate from a transcript generated by alternative splicing or a degraded transcript, or from a post-translational processing of the polypeptide, e.g., by proteolysis. “Expressed genes” include those that are transcribed into a polynucleotide as mRNA

and then translated into a polypeptide, and also those that are transcribed into RNA but not translated into a polypeptide (for example, transfer and ribosomal RNAs). Expression levels can be measured by methods known to one skilled in the art and also disclosed herein. The expression level or amount of a biomarker can be used to identify/characterize a subject having a breast cancer (e.g., an HR+ breast cancer (e.g., an ER+ breast cancer (e.g., luminal A breast cancer or luminal B breast cancer)), DCIS, and/or a metastatic or a locally advanced breast cancer) who may be likely to respond to, or benefit from, a particular therapy (e.g., a therapy comprising an endocrine therapy, e.g., a SERM (e.g., a SERD), a GnRH agonist, and/or an AI). The expression level or amount of a biomarker provided herein in a subject having a breast cancer described herein can also be used to determine and/or track the benefit of an administered endocrine therapy over time.

[0128] Expression levels can be measured using assays and techniques suitable for measuring RNA levels. For example, a RNA-Seq kit can be used to measure expression levels and is suitable for kits as described herein. Exemplary technologies useful in measuring expression levels herein include, but are not limited to, RNA ACCESS® protocol or TRUSEQ® RIBO-ZERO® protocol (ILLUMINA®), RT-qPCR, qPCR, multiplex qPCR (e.g. fluidigm), nanostring technologies, RT-qPCR, microarray analysis, SAGE, or MassARRAY.

[0129] The term “E2-induced score” as used herein, refers to a numerical value that reflects an aggregated expression level of a predetermined set of genes whose induction is reflective of estrogen receptor (ER) pathway activity. For example, an E2-induced score may reflect an aggregated expression level of at least five, six, seven, or eight of the genes set forth in Table 1 (i.e., AMZ1, C5AR2, CELSR2, FKBP4, GREB1, OLFM1, SLC9A3R1, and TFF1), at least the 5, 6, 7, 8, 9, 10, or 11 of the genes set forth in Table 2 (i.e., AMZ1, AREG, C5AR2, CELSR2, FKBP4, FMN1, GREB1, OLFM1, RBM24, SLC9A3R1, and TFF1), or at least the 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, or 23 of the genes set forth in Table 3 (i.e., AGR3, AMZ1, AREG, C5AR2, CELSR2, CT62, FKBP4, FMN1, GREB1, IGFBP4, NOS1AP, NXPH3, OLFM1, PGR, PPM1J, RAPGEFL1, RBM24, RERG, RET, SGK3, SLC9A3R1, TFF1, and ZNF703), whose induction is reflective of estrogen receptor (ER) pathway activity. The aggregated expression level of the predetermined set of genes may determine, for example as an average z-scored expression of the predetermined set of genes detected in a sample (e.g., a tissue

sample, e.g., a tumor tissue sample, e.g., a FFPE, a FF, an archival, a fresh, or a frozen tumor tissue sample) obtained from an individual (e.g., an individual having a cancer, e.g., a breast cancer (e.g., an HR⁺ breast cancer (e.g., an ER⁺ breast cancer (e.g., luminal A breast cancer or luminal B breast cancer))), DCIS, and/or a metastatic or a locally advanced breast cancer). However, it should be understood that the aggregated expression levels can be determined using methods and known in the art such as, for example, an average expression of genes portrayed onto the space of a reference population or, for example, as an average expression of genes relative to an untreated or vehicle-treated tumor, optionally expressed as a fold change.

[0130] The “E2-repressed score” as used herein, refers to a numerical value that reflects an aggregated expression level of a predetermined set of genes whose repression is reflective of estrogen receptor (ER) pathway activity. For example, an E2-repressed score may reflect an aggregated expression level of at least the three, four, five, or six of the genes set forth in Table 4 (i.e., BCAS1, CCNG2, IL1R1, PNPLA7, SEMA3E, and STON1), at least the four, five, six, seven, or eight of the genes set forth in Table 5 (i.e., BCAS1, CCNG2, IL1R1, NBEA, PNPLA7, SEMA3E, STON1, and TP53INP1), or at least the 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, or 18 of the genes set forth in Table 6 (i.e., BAMBI, BCAS1, CCNG2, DDIT4, EGLN3, FAM171B, GRM4, IL1R1, LIPH, NBEA, PNPLA7, PSCA, SEMA3E, SSPO, STON1, TGFB3, TP53INP1, and TP53INP2), whose repression is reflective of estrogen receptor (ER) pathway activity. The aggregated expression level of the predetermined set of genes can be calculated as described above for the E2-induced score. an HR⁺ breast cancer (e.g., an ER⁺ breast cancer (e.g., luminal A breast cancer or luminal B breast cancer))), DCIS, and/or a metastatic or a locally advanced breast cancer.

[0131] The terms “estrogen receptor pathway activity score,” “ER pathway activity score,” and “composite score for ER pathway activity,” as used herein, refer to a numerical value that reflects mathematical difference between the E2-induced score and the E2-repressed score. The ER pathway activity score can be used as a predictive, prognostic, and/or pharmacodynamic biomarker (e.g., to identify an individual having a breast cancer as one who is likely to benefit from a therapy comprising an endocrine therapy or to monitor responsiveness of an individual having a breast cancer to a treatment comprising an endocrine therapy).

[0132] The terms “reference estrogen receptor pathway activity score” and “reference ER pathway activity score” refer to an ER pathway activity score against which another ER pathway activity score is compared, e.g., to make a predictive, prognostic, and/or therapeutic determination. For example, the reference ER pathway activity score may be an ER pathway activity score in a reference sample, an ER pathway activity score in a reference population (e.g., a population of patients with HR+ breast cancer), and/or a pre-determined value. In some instances, the reference ER pathway activity score is a cut-off value that significantly separates individuals having a breast cancer with ER pathway activity from individuals having a breast cancer with low or no ER pathway activity (e.g., a reference ER pathway activity score that is at or above -1.0 (e.g., -1.0, -0.9, -0.8, -0.7, -0.6, -0.5, -0.4, -0.3, -0.2, or higher). In some instances, the reference ER pathway activity score is a cut-off value that significantly separates individuals having a breast cancer that are likely to respond to a therapy including an endocrine therapy as described herein from those who are not likely to respond to a therapy including an endocrine therapy (e.g., a reference ER pathway activity score that is at or above -1.0 (e.g., -1.0, -0.9, -0.8, -0.7, -0.6, -0.5, -0.4, -0.3, -0.2, or higher). It will be appreciated by one skilled in the art that the numerical value for the reference ER pathway activity score may vary depending on the type of breast cancer (e.g., an HR+ breast cancer (e.g., an ER+ breast cancer (e.g., luminal A breast cancer or luminal B breast cancer)), DCIS, and/or a metastatic or a locally advanced breast cancer), the methodology used to measure an ER pathway activity score, the specific gene signatures examined (e.g., the combination of genes set forth in Tables 1-6), and/or the statistical methods used to generate an ER pathway activity score. For example, the activity score described herein can be calculated by calculating a z-score for a reference population and using the formula below to re-scale the expression of each gene across the samples to a mean of 0 and a standard deviation of 1. The expression data for a given patient can then be overlayed onto the z-scored reference space as described herein.

[0133] The z score may be described by the formula: $z = (x - \mu) / \sigma$, where z is the rescaled score, x is gene expression level measured, μ is the mean gene expression calculated from a reference population; and σ is the standard deviation for gene expression calculated from a reference population.

[0134] In some embodiments, the reference estrogen receptor pathway activity score is calculated in reference to a standard control as defined herein.

[0135] The term “reference E2-induced activity score” refers to an E2-induced activity score against which another E2-induced activity score is compared, e.g., to make a predictive, prognostic, and/or therapeutic determination. For example, the reference E2-induced activity score may be a reference E2-induced activity score in a reference sample, a reference E2-induced activity score in a reference population (e.g., a population of patients with HR+ breast cancer), and/or a pre-determined value. In some instances, the reference E2-induced activity score is a cut-off value that significantly separates individuals having a breast cancer with E2-induced activity from individuals having a breast cancer with low or no E2-induced activity (e.g., a reference E2-induced activity score that is at or above -2.0 (e.g., -2.0, -1.9, -1.8, -1.7, -1.6, -1.5, -1.4, -1.3, -1.2, -1.1, 1.0, -0.9, -0.8, -0.7, -0.6, -0.5, -0.4, -0.3, -0.2, or higher). In some instances, the reference E2-induced activity score is a cut-off value that significantly separates individuals having a breast cancer that are likely to respond to a therapy including an endocrine therapy as described herein from those who are not likely to respond to a therapy including an endocrine therapy (e.g., a reference E2-induced activity score that is at or above -2.0 (e.g., -2.0, -1.9, -1.8, -1.7, -1.6, -1.5, -1.4, -1.3, -1.2, -1.1, 1.0, -0.9, -0.8, -0.7, -0.6, -0.5, -0.4, -0.3, -0.2, or higher). It will be appreciated by one skilled in the art that the numerical value for the reference E2-induced activity score may vary depending on the type of breast cancer (e.g., an HR+ breast cancer (e.g., an ER+ breast cancer (e.g., luminal A breast cancer or luminal B breast cancer)), DCIS, and/or a metastatic or a locally advanced breast cancer), the methodology used to measure an E2-induced activity score, the specific gene signatures examined (e.g., the combination of genes set forth herein and in, for example, in Tables 1-6), and/or the statistical methods used to generate an E2-induced activity score. A E2-induced activity score can be calculated as described herein for an estrogen receptor pathway activity score. In some embodiments, the E2-induced activity score is calculated in reference to a standard control as defined herein.

[0136] The ability to discriminate (e.g. calculate an activity score as defined herein) is relative to the identification/characterization/quantification of expression of the genes described herein and not by the form of the assay used to determine the level of expression of the genes.

[0137] A “reference gene” as used herein, refers to a gene or group of genes (e.g., one, two, three, or more genes) that is used for comparison purposes, such as a housekeeping gene. A “housekeeping gene” refers herein to a gene or group of genes (e.g., one, two, three, or more genes) which encode proteins whose activities are essential for the maintenance of cell function and which are typically similarly present in all cell types. Exemplary housekeeping genes include SDHA, GUSB, PPIA, and UBC.

[0138] As used herein, the terms “individual,” “patient,” and “subject” are used interchangeably and refer to any single animal, more preferably a mammal (including such non-human animals as, for example, dogs, cats, horses, rabbits, zoo animals, cows, pigs, sheep, and non-human primates) for which treatment is desired. In certain embodiments, the individual, patient, or subject is a human.

[0139] An “isolated” nucleic acid refers to a nucleic acid molecule that has been separated from a component of its natural environment. An isolated nucleic acid includes a nucleic acid molecule contained in cells that ordinarily contain the nucleic acid molecule, but the nucleic acid molecule is present extrachromosomally or at a chromosomal location that is different from its natural chromosomal location.

[0140] The word “label” when used herein refers to a detectable compound or composition. The label is typically conjugated or fused directly or indirectly to a reagent, such as a polynucleotide probe or an antibody, and facilitates detection of the reagent to which it is conjugated or fused. The label may itself be detectable (e.g., radioisotope labels or fluorescent labels) or, in the case of an enzymatic label, may catalyze chemical alteration of a substrate compound or composition which results in a detectable product.

[0141] The term “modulator” as used herein, refers to an agent that interacts with a target either directly or indirectly. The interactions include, but are not limited to, the interactions of an agonist, partial agonist, an inverse agonist, antagonist, degrader, or combinations thereof. In some embodiments, a modulator is an antagonist. In some embodiments, a modulator is a degrader.

[0142] The term “degrader” as used herein, refers to an agent that binds to a nuclear hormone receptor and subsequently lowers the steady state protein levels of said receptor. In some

embodiments, a degrader as described herein lowers steady state estrogen receptor levels by at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%. In some embodiments, a degrader as described herein lowers steady state estrogen receptor levels by at least 65%. In some embodiments, a degrader as described herein lowers steady state estrogen receptor levels by at least 85%.

[0143] The term "nucleic acid" refers to deoxyribonucleotides or ribonucleotides and polymers thereof in either single- or double-stranded form, and complements thereof. The term "polynucleotide" refers to a linear sequence of nucleotides. The term "nucleotide" typically refers to a single unit of a polynucleotide, i.e., a monomer. Nucleotides can be ribonucleotides, deoxyribonucleotides, or modified versions thereof. Examples of polynucleotides contemplated herein include single and double stranded DNA, single and double stranded RNA (including siRNA), and hybrid molecules having mixtures of single and double stranded DNA and RNA. Nucleic acid as used herein also refers to nucleic acids that have the same basic chemical structure as a naturally occurring nucleic acid. Such analogues have modified sugars and/or modified ring substituents, but retain the same basic chemical structure as the naturally occurring nucleic acid. A nucleic acid mimetic refers to chemical compounds that have a structure that is different the general chemical structure of a nucleic acid, but that functions in a manner similar to a naturally occurring nucleic acid. Examples of such analogues include, without limitation, phosphorothioates, phosphoramidates, methyl phosphonates, chiral-methyl phosphonates, 2-O-methyl ribonucleotides, and peptide-nucleic acids (PNAs). The term "oligonucleotide" refers to a relatively short polynucleotide (e.g., less than about 250 nucleotides in length), including, without limitation, single-stranded deoxyribonucleotides, single- or double-stranded ribonucleotides, RNA:DNA hybrids and double-stranded DNAs. Oligonucleotides, such as single-stranded DNA probe oligonucleotides, are often synthesized by chemical methods, for example using automated oligonucleotide synthesizers that are commercially available. However, oligonucleotides can be made by a variety of other methods, including in vitro recombinant DNA-mediated techniques and by expression of DNAs in cells and organisms.

[0144] The term "package insert" is used to refer to instructions customarily included in commercial packages of therapeutic products, that contain information about the indications,

usage, dosage, administration, combination therapy, contraindications and/or warnings concerning the use of such therapeutic products.

[0145] The term “pharmaceutical formulation” refers to a preparation which is in such form as to permit the biological activity of an active ingredient contained therein to be effective, and which contains no additional components which are unacceptably toxic to a subject to which the formulation would be administered.

[0146] A “pharmaceutically acceptable carrier” refers to an ingredient in a pharmaceutical formulation, other than an active ingredient, which is nontoxic to a subject. A pharmaceutically acceptable carrier includes, but is not limited to, a buffer, excipient, stabilizer, or preservative.

[0147] The term “protein,” as used herein, refers to any native protein from any vertebrate source, including mammals such as primates (e.g., humans) and rodents (e.g., mice and rats), unless otherwise indicated. The term encompasses “full-length,” unprocessed protein as well as any form of the protein that results from processing in the cell. The term also encompasses naturally occurring variants of the protein, e.g., splice variants or allelic variants.

[0148] “Percent (%) sequence identity” with respect to a reference polynucleotide or polypeptide sequence is defined as the percentage of nucleic acids or amino acid residues in a candidate sequence that are identical with the nucleic acids or amino acid residues in the reference polynucleotide or polypeptide sequence, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity, and not considering any conservative substitutions as part of the sequence identity. Alignment for purposes of determining percent nucleic acid or amino acid sequence identity can be achieved in various ways that are within the skill in the art, for instance, using publicly available computer software such as BLAST, BLAST-2, ALIGN, or Megalign (DNASTAR) software. Those skilled in the art can determine appropriate parameters for aligning sequences, including any algorithms needed to achieve maximal alignment over the full length of the sequences being compared. For purposes herein, however, % sequence identity values are generated using the sequence comparison computer program ALIGN-2. The ALIGN-2 sequence comparison computer program was authored by Genentech, Inc., and the source code has been filed with user documentation in the U.S. Copyright Office, Washington D.C., 20559, where it is registered under U.S. Copyright Registration No. TXU510087. The ALIGN-2 program is publicly available from Genentech,

Inc., South San Francisco, California, or may be compiled from the source code. The ALIGN-2 program should be compiled for use on a UNIX operating system, including digital UNIX V4.0D. All sequence comparison parameters are set by the ALIGN-2 program and do not vary.

[0149] In situations where ALIGN-2 is employed for nucleic acid or amino acid sequence comparisons, the % sequence identity of a given nucleic acid or amino acid sequence A to, with, or against a given nucleic acid or amino acid sequence B (which can alternatively be phrased as a given nucleic acid or amino acid sequence A that has or comprises a certain % sequence identity to, with, or against a given nucleic acid or amino acid sequence B) is calculated as follows:

$$100 \text{ times the fraction } X/Y,$$

where X is the number of nucleic acid or amino acid residues scored as identical matches by the sequence alignment program ALIGN-2 in that program's alignment of A and B, and where Y is the total number of nucleic acid or amino acid residues in B. It will be appreciated that where the length of nucleic acid or amino acid sequence A is not equal to the length of nucleic acid or amino acid sequence B, the % sequence identity of A to B will not equal the % sequence identity of B to A. Unless specifically stated otherwise, all % sequence identity values used herein are obtained as described in the immediately preceding paragraph using the ALIGN-2 computer program.

[0150] By “correlate” or “correlating” is meant comparing, in any way, the performance and/or results of a first analysis or protocol with the performance and/or results of a second analysis or protocol. For example, one may use the results of a first analysis or protocol in carrying out a second protocols and/or one may use the results of a first analysis or protocol to determine whether a second analysis or protocol should be performed. With respect to the embodiment of polypeptide analysis or protocol, one may use the results of the polypeptide expression analysis or protocol to determine whether a specific therapeutic regimen should be performed. With respect to the embodiment of polynucleotide analysis or protocol, one may use the results of the polynucleotide expression analysis or protocol to determine whether a specific therapeutic regimen should be performed.

[0151] “Polynucleotide” or “nucleic acid,” as used interchangeably herein, refers to polymers of nucleotides of any length, and includes DNA and RNA. The nucleotides can be deoxyribonucleotides, ribonucleotides, modified nucleotides or bases, and/or their analogs, or

any substrate that can be incorporated into a polymer by DNA or RNA polymerase, or by a synthetic reaction.

[0152] A polynucleotide may comprise modified nucleotides, such as methylated nucleotides and their analogs. If present, modification to the nucleotide structure may be imparted before or after assembly of the polymer. The sequence of nucleotides may be interrupted by non-nucleotide components. A polynucleotide may be further modified after synthesis, such as by conjugation with a label. Other types of modifications include, for example, “caps,” substitution of one or more of the naturally occurring nucleotides with an analog, internucleotide modifications such as, for example, those with uncharged linkages (e.g., methyl phosphonates, phosphotriesters, phosphoramidates, carbamates, etc.) and with charged linkages (e.g., phosphorothioates, phosphorodithioates, etc.), those containing pendant moieties, such as, for example, proteins (e.g., nucleases, toxins, antibodies, signal peptides, poly-L-lysine, etc.), those with intercalators (e.g., acridine, psoralen, etc.), those containing chelators (e.g., metals, radioactive metals, boron, oxidative metals, etc.), those containing alkylators, those with modified linkages (e.g., alpha anomeric nucleic acids, etc.), as well as unmodified forms of the polynucleotide(s). Further, any of the hydroxyl groups ordinarily present in the sugars may be replaced, for example, by phosphonate groups, phosphate groups, protected by standard protecting groups, or activated to prepare additional linkages to additional nucleotides, or may be conjugated to solid or semi-solid supports. The 5' and 3' terminal OH can be phosphorylated or substituted with amines or organic capping group moieties of from 1 to 20 carbon atoms. Other hydroxyls may also be derivatized to standard protecting groups. Polynucleotides can also contain analogous forms of ribose or deoxyribose sugars that are generally known in the art, including, for example, 2'-O-methyl-, 2'-O-allyl, 2'-fluoro- or 2'-azido-ribose, carbocyclic sugar analogs, α -anomeric sugars, epimeric sugars such as arabinose, xyloses or lyxoses, pyranose sugars, furanose sugars, sedoheptuloses, acyclic analogs and abasic nucleoside analogs such as methyl riboside. One or more phosphodiester linkages may be replaced by alternative linking groups. These alternative linking groups include, but are not limited to, embodiments wherein phosphate is replaced by P(O)S(“thioate”), P(S)S (“dithioate”), “(O)NR₂ (“amidate”), P(O)R, P(O)OR', CO or CH₂ (“formacetal”), in which each R or R' is independently H or substituted or unsubstituted alkyl (1-20 C) optionally containing an ether (-O-) linkage, aryl, alkenyl,

cycloalkyl, cycloalkenyl or araldyl. Not all linkages in a polynucleotide need be identical. The preceding description applies to all polynucleotides referred to herein, including RNA and DNA.

[0153] The technique of “polymerase chain reaction” or “PCR” as used herein generally refers to a procedure wherein minute amounts of a specific piece of nucleic acid, RNA and/or DNA, are amplified as described in U.S. Pat. No. 4,683,195 issued 28 July 1987. Generally, sequence information from the ends of the region of interest or beyond needs to be available, such that oligonucleotide primers can be designed; these primers will be identical or similar in sequence to opposite strands of the template to be amplified. The 5' terminal nucleotides of the two primers may coincide with the ends of the amplified material. PCR can be used to amplify specific RNA sequences, specific DNA sequences from total genomic DNA, and cDNA transcribed from total cellular RNA, bacteriophage or plasmid sequences, etc. See generally Mullis et al., *Cold Spring Harbor Symp. Quant. Biol.*, 51: 263 (1987); Erlich, ed., *PCR Technology*, (Stockton Press, NY, 1989). As used herein, PCR is considered to be one, but not the only, example of a nucleic acid polymerase reaction method for amplifying a nucleic acid test sample, comprising the use of a known nucleic acid (DNA or RNA) as a primer and utilizes a nucleic acid polymerase to amplify or generate a specific piece of nucleic acid or to amplify or generate a specific piece of nucleic acid which is complementary to a particular nucleic acid.

[0154] As used herein, the term “reverse transcriptase polymerase chain reaction” or “RT-PCR” refers to the replication and amplification of RNA sequences. In this method, reverse transcription is coupled to PCR, e.g., as described in U.S. Patent No. 5,322,770, herein incorporated by reference in its entirety. In RT-PCR, the RNA template is converted to cDNA due to the reverse transcriptase activity of an enzyme, and then amplified using the polymerizing activity of the same or a different enzyme. Both thermostable and thermolabile reverse transcriptase and polymerase can be used. The “reverse transcriptase” (RT) may include reverse transcriptases from retroviruses, other viruses, as well as a DNA polymerase exhibiting reverse transcriptase activity.

[0155] As used herein, the term “reverse transcriptase quantitative polymerase chain reaction” or “RT-qPCR” is a form of PCR wherein the nucleic acid to be amplified is RNA that is first reverse transcribed into cDNA and the amount of PCR product is measured at each step in a PCR reaction.

[0156] “Quantitative real time polymerase chain reaction” or “qRT-PCR” refers to a form of PCR wherein the amount of PCR product is measured at each step in a PCR reaction. This technique has been described in various publications including Cronin et al., *Am. J. Pathol.* 164(1):35-42 (2004); and Ma et al., *Cancer Cell* 5:607-616 (2004).

[0157] The term “multiplex-PCR” refers to a single PCR reaction carried out on nucleic acid obtained from a single source (e.g., an individual) using more than one primer set for the purpose of amplifying two or more DNA sequences in a single reaction.

[0158] The term “RNA-seq,” also called “Whole Transcriptome Shotgun Sequencing (WTSS),” refers to the use of high-throughput sequencing technologies to sequence and/or quantify cDNA to obtain information about a sample’s RNA content. Publications describing RNA-seq include: Wang et al. “RNA-Seq: a revolutionary tool for transcriptomics” *Nature Reviews Genetics* 10 (1): 57-63 (January 2009); Ryan et al. *BioTechniques* 45 (1): 81-94 (2008); and Maher et al. “Transcriptome sequencing to detect gene fusions in cancer”. *Nature* 458 (7234): 97-101 (January 2009). Exemplary RNA-seq protocols include the use of RNA ACCESS® protocol or TRUSEQ® RIBO-ZERO® protocol (ILLUMINA®).

[0159] “Response to a treatment,” “responsiveness to treatment,” or “benefit from a treatment” can be assessed using any endpoint indicating a benefit to the individual, including, without limitation, (1) inhibition, to some extent, of disease progression (e.g., breast cancer progression), including slowing down and complete arrest; (2) a reduction in tumor size; (3) inhibition (i.e., reduction, slowing down or complete stopping) of cancer cell infiltration into adjacent peripheral organs and/or tissues; (4) inhibition (i.e. reduction, slowing down or complete stopping) of metastasis; (5) relief, to some extent, of one or more symptoms associated with the disease or disorder (e.g., cancer); (6) increase or extend in the length of survival, including recurrence free survival (RFS), disease free survival (DFS), overall survival (OS HR < 1) and progression free survival (PFS HR<1); and/or (9) decreased mortality at a given point of time following treatment (e.g., a treatment including an endocrine therapy, a SERM (e.g., a SERD), a GnRH agonist, and/or an AI). Response to a treatment can also refer to a pharmacodynamic response or the response of a pathway (e.g. the ER pathway) and can be assessed using methods known in the art.

[0160] As used herein, “progression-free survival” or “PFS” refers to the length of time during and after treatment during which the disease being treated (e.g., breast cancer, e.g., HR+ breast cancer, e.g., ER+ breast cancer, e.g., luminal A or luminal B breast cancer, e.g., advanced or metastatic breast cancer) does not progress or get worse. Progression-free survival may include the amount of time individuals have experienced a complete response or a partial response, as well as the amount of time individuals have experienced stable disease.

[0161] As used herein, “overall survival” or “OS” refers to the percentage of subjects in a group who are likely to be alive after a particular duration of time (e.g., 6 months, 1 year, 2 years, 3 years, 4 years, 5 years, 10 years, 15 years, 20 years, or more than 20 years from the time of diagnosis or treatment).

[0162] As used herein “recurrence free survival” or “RFS” refers to the length of time after primary treatment ends that the patient survives without any signs, symptoms, or relapses of the tumor in the same local or regional area.

[0163] As used herein “disease free survival” or “DFS” refers to the length of time after primary treatment ends that the patient survives without any signs, symptoms, or relapses of the tumor in any area, including development of distant metastases.

[0164] As used herein, “complete response” or “CR” refers to disappearance of all signs of cancer in response to treatment. This does not necessarily mean the cancer has been cured.

[0165] As used herein, “partial response” or “PR” refers to a decrease in the size of one or more tumors or lesions, or in the extent of cancer in the body, in response to treatment.

[0166] As used herein, “hazard ratio” or “HR” is a statistical definition for rates of events. For purposes provided herein, hazard ratio is defined as representing the probability of an event (e.g., PFS or OS) in the experimental (e.g., treatment) group/arm divided by the probability of an event in the control group/arm at any specific point in time. An HR with a value of 1 indicates that the relative risk of an endpoint (e.g., death) is equal in both the “treatment” and “control” groups; a value greater than 1 indicates that the risk is greater in the treatment group relative to the control group; and a value less than 1 indicates that the risk is greater in the control group relative to the treatment group. “Hazard ratio” in progression-free survival analysis (i.e., PFS HR) is a summary of the difference between two progression-free survival curves, representing the

reduction in the risk of death on treatment compared to control, over a period of follow-up. “Hazard ratio” in overall survival analysis (i.e., OS HR) is a summary of the difference between two overall survival curves, representing the reduction in the risk of death on treatment compared to control, over a period of follow-up.

[0167] By “extending survival” is meant increasing overall survival or progression free survival in a treated individual relative to an untreated individual (i.e. relative to an individual not treated with the medicament), or relative to an individual who does not express a biomarker at the designated level, and/or relative to an individual treated with an approved anti-cancer therapy. An objective response refers to a measurable response, including complete response (CR) or partial response (PR).

[0168] By “reduce or inhibit” is meant the ability to cause an overall decrease of 20%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 85%, 90%, 95%, or greater. Reduce or inhibit can refer to the symptoms of the disorder being treated (e.g., a breast cancer, e.g., an HR+ breast cancer (e.g., an ER+ breast cancer (e.g., luminal A breast cancer or luminal B breast cancer)), DCIS, and/or a metastatic or a locally advanced breast cancer), the presence or size of metastases, or the size of the primary tumor. Reduce or inhibit, when referring to a tumor pathway, refers to the reduction of expression or activity of any component of the pathway (e.g. reduction of the expression ER, reduced activity of ER, or degradation of ER).

[0169] A “reference sample,” “reference cell,” “reference tissue,” “control sample,” “control cell,” or “control tissue,” as used herein, refers to a sample, cell, tissue, standard, or level that is used for comparison purposes. In one embodiment, a reference sample, reference cell, reference tissue, control sample, control cell, or control tissue is obtained from the same subject or individual. In another embodiment, a reference sample is obtained from one or more individuals who are not the subject or individual. In either of the preceding embodiments, the one or more individuals from which the reference sample, reference cell, reference tissue, control sample, control cell, or control tissue is obtained has a breast cancer (e.g., e.g., an HR+ breast cancer (e.g., an ER+ breast cancer (e.g., luminal A breast cancer or luminal B breast cancer)), DCIS, and/or a metastatic or a locally advanced breast cancer). In certain embodiments, the one or more individuals from which the reference sample, reference cell, reference tissue, control sample, control cell, or control tissue is obtained has a breast cancer and has been previously treated with

an anti-cancer therapy (e.g., one or more doses of an endocrine therapy, e.g., a SERM (e.g., a SERD), a GnRH agonist, and/or an AI). In other embodiments, the one or more individuals from which the reference sample, reference cell, reference tissue, control sample, control cell, or control tissue is obtained has a breast cancer and is treatment naïve. In any of the preceding embodiments, the subject/individual and the one or more individuals who are not the subject or individual have the same breast cancer.

[0170] A “standard control” as used herein in reference to the expression level of one or more genes refers to the expression level measured in a control subject (e.g. in a sample from the control subject) or population of control subjects. In embodiments, the control subject is a healthy control subject relative to the subject being tested, wherein the healthy control subject does not have breast cancer. In embodiments, the control subject is the test subject prior to treatment of the test subject, wherein the test subject and control subject have breast cancer. For example, in embodiments, the test subject has been treated for breast cancer with an anticancer agent and the control subject is the test subject prior to treatment. In embodiments, the population of control subjects is a diverse collection of healthy subjects and diseased subjects, wherein the expression level of the test subject is compared to the expression levels of the population of control subjects (e.g. an average of expression levels of the population of control subjects). In embodiments, the population of control subjects is a collection of healthy subjects that do not have breast cancer, wherein the expression level of the test subject is compared to the expression levels of the population of control subjects (e.g. an average of expression levels of the population of control subjects). In embodiments, the population of control subjects is a collection of subjects that have been treated for breast cancer, wherein the expression level of the test subject is compared to the expression levels of the population of control subjects (e.g. an average of expression levels of the population of control subjects).

[0171] The term “sample,” as used herein, refers to a composition that is obtained or derived from a subject and/or individual of interest that contains a cellular and/or other molecular entity that is to be characterized and/or identified, for example based on physical, biochemical, chemical and/or physiological characteristics. For example, the phrase “disease sample” and variations thereof refers to any sample obtained from a subject of interest that would be expected or is known to contain the cellular and/or molecular entity that is to be characterized. Samples

include, but are not limited to, tissue extracts such as homogenized tissue, tumor tissue, cellular extracts, primary or cultured cells or cell lines, cell supernatants, cell lysates, platelets, serum, plasma, vitreous fluid, lymph fluid, synovial fluid, follicular fluid, seminal fluid, amniotic fluid, milk, whole blood, blood-derived cells, urine, cerebro-spinal fluid, saliva, sputum, tears, perspiration, mucus, tumor lysates, and tissue culture medium, and combinations thereof.

[0172] By “tissue sample” or “cell sample” is meant a collection of similar cells obtained from a tissue of a subject or individual. The source of the tissue or cell sample may be solid tissue as from a FFPE, FF, fresh, frozen, and/or preserved organ, tissue sample, biopsy, and/or aspirate; blood or any blood constituents such as plasma; bodily fluids such as cerebral spinal fluid, amniotic fluid, peritoneal fluid, or interstitial fluid; cells from any time in gestation or development of the subject. The tissue sample may also be primary or cultured cells or cell lines. Optionally, the tissue or cell sample is obtained from a disease (e.g., breast cancer, e.g., e.g., an HR+ breast cancer (e.g., an ER+ breast cancer (e.g., luminal A breast cancer or luminal B breast cancer))), DCIS, and/or a metastatic or a locally advanced breast cancer) tissue/organ. The tissue sample may contain compounds which are not naturally intermixed with the tissue in nature such as preservatives, anticoagulants, buffers, fixatives, nutrients, antibiotics, or the like.

[0173] For the purposes herein a “section” of a tissue sample is meant a single part or piece of a tissue sample, e.g. a thin slice of tissue or cells cut from a tissue sample. It is understood that multiple sections of tissue samples may be taken and subjected to analysis, provided that it is understood that the same section of tissue sample may be analyzed at both morphological and molecular levels, or analyzed with respect to both polypeptides and polynucleotides.

[0174] As used herein, “treatment” (and grammatical variations thereof, such as “treat” or “treating”) refers to clinical intervention in an attempt to alter the natural course of the subject being treated, and can be performed either for prophylaxis or during the course of clinical pathology. Desirable effects of treatment include, but are not limited to, preventing occurrence or recurrence of a disease (e.g., a breast cancer, e.g., e.g., an HR+ breast cancer (e.g., an ER+ breast cancer (e.g., luminal A breast cancer or luminal B breast cancer))), DCIS, and/or a metastatic or a locally advanced breast cancer), alleviation of symptoms, diminishment of any direct or indirect pathological consequences of the disease, preventing metastasis, decreasing the rate of disease progression, amelioration or palliation of the disease state, and remission or improved prognosis.

In some embodiments, the treatments described herein are used to delay development of a disease or to slow the progression of a disease (e.g., a breast cancer, e.g., an HR+ breast cancer (e.g., an ER+ breast cancer (e.g., luminal A breast cancer or luminal B breast cancer)), DCIS, and/or a metastatic or a locally advanced breast cancer). In some instances, the treatment may increase overall survival (OS) (e.g., by about 20% or greater, about 25% or greater, about 30% or greater, about 35% or greater, about 40% or greater, about 45% or greater, about 50% or greater, about 55% or greater, about 60% or greater, about 65% or greater, about 70% or greater, about 75% or greater, about 80% or greater, about 85% or greater, about 90% or greater, about 95% or greater, about 96% or greater, about 97% or greater, about 98% or greater, or about 99% or greater). In some instances, the treatment may increase OS, e.g., by about 5% to about 500%, e.g., from about 10% to about 450%, e.g., from about 20% to about 400%, e.g., from about 25% to about 350%, e.g., from about 30% to about 400%, e.g., from about 35% to about 350%, e.g., from about 40% to about 300%, e.g., from about 45% to about 250%, e.g., from about 50% to about 200%, e.g., from about 55% to about 150%, e.g., from about 60% to about 100%, e.g., from about 65% to about 100%, e.g., from about 70% to about 100%, e.g., from about 75% to about 100%, e.g., from about 80% to about 100%, e.g., from about 85% to about 100%, e.g., from about 90% to about 100%, e.g., from about 95% to about 100%, e.g., from about 98% to about 100%. In some instances, the treatment may increase the progression-free survival (PFS) (e.g., by about 20% or greater, about 25% or greater, about 30% or greater, about 35% or greater, about 40% or greater, about 45% or greater, about 50% or greater, about 55% or greater, about 60% or greater, about 65% or greater, about 70% or greater, about 75% or greater, about 80% or greater, about 85% or greater, about 90% or greater, about 95% or greater, about 96% or greater, about 97% or greater, about 98% or greater, or about 99% or greater). In some instances, the treatment may increase PFS, e.g., by about 5% to about 500%, e.g., from about 10% to about 450%, e.g., from about 20% to about 400%, e.g., from about 25% to about 350%, e.g., from about 30% to about 400%, e.g., from about 35% to about 350%, e.g., from about 40% to about 300%, e.g., from about 45% to about 250%, e.g., from about 50% to about 200%, e.g., from about 55% to about 150%, e.g., from about 60% to about 100%, e.g., from about 65% to about 100%, e.g., from about 70% to about 100%, e.g., from about 75% to about 100%, e.g., from about 80% to about 100%, e.g., from about 85% to about 100%, e.g., from about 90% to about 100%, e.g., from about 95% to about 100%, e.g., from about 98% to about 100%.

[0175] “Tumor,” as used herein, refers to all neoplastic cell growth and proliferation, whether malignant or benign, and all pre-cancerous and cancerous cells and tissues. The terms “cancer,” “cancerous,” “cell proliferative disorder,” “proliferative disorder,” and “tumor” are not mutually exclusive as referred to herein.

III. METHODS

[0176] Provided herein are methods and assays for identifying an individual having a breast cancer (e.g., an HR+ breast cancer (e.g., an ER+ breast cancer (e.g., luminal A breast cancer or luminal B breast cancer)), DCIS, and/or a metastatic or a locally advanced breast cancer, an ER+ breast cancer (e.g., luminal A breast cancer or luminal B breast cancer)), DCIS, and/or a metastatic or a locally advanced breast cancer who may benefit from a treatment including an endocrine therapy as described herein; selecting a therapy for an individual having breast cancer; treating an individual having breast cancer based on a diagnostic method provided herein; and monitoring therapeutic efficacy of an endocrine therapy. In one embodiment, the endocrine therapy is a compound as set forth herein. In another embodiment, the endocrine therapy is a SERM, a SERD, an AI, or a combination thereof.

[0177] The methods and assays described herein are based on the finding that the estradiol (E2)-induced score or estrogen receptor (ER) pathway activity score determined from a sample (e.g., a tissue sample, e.g., a tumor tissue sample, e.g., a FFPE, a FF, an archival, a fresh, or a frozen tumor tissue sample) from an individual may be used to predict the therapeutic efficacy of an endocrine therapy described herein. Any of the methods may further include administering an endocrine therapy (e.g., as described in Section IV-A, below) to the individual.

[0178] Accordingly, provided herein are also methods and assays of determining an E2-induced score and/or an ER pathway activity score from a sample from the individual. Any of the methods provided herein may include administering an anti-cancer therapy other than an endocrine therapy (e.g., as described in Section IV-A, below) to the individual. Any of the methods may further include administering an effective amount of an additional therapeutic agent, as described herein, to the individual.

A. Diagnostic Methods and Assays

[0179] Predictive Diagnostic Methods and Assays

[0180] In particular instances, the methods and assays provided herein may be used to identify an individual having a breast cancer (e.g., an HR+ breast cancer (e.g., an ER+ breast cancer (e.g., luminal A breast cancer or luminal B breast cancer)), DCIS, and/or a metastatic or a locally advanced breast cancer) who may benefit from a treatment including an endocrine therapy as described herein, the method including determining an ER pathway activity score from a sample (e.g., a tissue sample, e.g., a tumor tissue sample, e.g., a formalin-fixed paraffin-embedded (FFPE), a fresh frozen (FF), an archival, a fresh, or a frozen tumor tissue sample) from the individual, wherein an ER pathway activity score that is at or above a reference ER pathway activity score identifies the individual as one who may benefit from a treatment including an endocrine therapy as described herein.

[0181] In particular instances, the methods and assays provided herein may be used to identify an individual having a breast cancer (e.g., an HR+ breast cancer (e.g., an ER+ breast cancer (e.g., luminal A breast cancer or luminal B breast cancer)), DCIS, and/or a metastatic or a locally advanced breast cancer) who may benefit from a treatment including an endocrine therapy as described herein, the method including determining an E2-induced score from a sample (e.g., a tissue sample, e.g., a tumor tissue sample, e.g., a FFPE, a FF, an archival, a fresh, or a frozen tumor tissue sample) from the individual, wherein an E2-induced score that is at or above a reference E2-induced score identifies the individual as one who may benefit from a treatment including an endocrine therapy as described herein.

[0182] In particular instances, the methods and assays provided herein may be used to select a therapy for an individual having a breast cancer (e.g., an HR+ breast cancer (e.g., an ER+ breast cancer (e.g., luminal A breast cancer or luminal B breast cancer)), DCIS, and/or a metastatic or a locally advanced breast cancer), the method including determining an ER pathway activity score from a sample (e.g., a tissue sample, e.g., a tumor tissue sample, e.g., a FFPE, a FF, an archival, a fresh, or a frozen tumor tissue sample) from the individual, wherein an ER pathway activity score that is at or above a reference ER pathway activity score identifies the individual as one who may benefit from a treatment including an endocrine therapy as described herein.

[0183] In particular instances, the methods and assays provided herein may be used to select a therapy for an individual having a breast cancer (e.g., an HR+ breast cancer (e.g., an ER+ breast cancer (e.g., luminal A breast cancer or luminal B breast cancer)), DCIS, and/or a metastatic or a

locally advanced breast cancer), the method including determining an E2-induced score from a sample (e.g., a tissue sample, e.g., a tumor tissue sample, e.g., a FFPE, a FF, an archival, a fresh, or a frozen tumor tissue sample) from the individual, wherein an E2-induced score that is at or above a reference E2-induced score identifies the individual as one who may benefit from a treatment including an endocrine therapy as described herein.

[0184] In particular instances, the methods and assays provided herein may be used to identify an individual having a breast cancer (e.g., an HR+ breast cancer (e.g., an ER+ breast cancer (e.g., luminal A breast cancer or luminal B breast cancer)), DCIS, and/or a metastatic or a locally advanced breast cancer) who may benefit from a treatment including an endocrine therapy as described herein, the method including determining an ER pathway activity score from a sample (e.g., a tissue sample, e.g., a tumor tissue sample, e.g., a FFPE, a FF, an archival, a fresh, or a frozen tumor tissue sample) from the individual, wherein an ER pathway activity score that is below a reference ER pathway activity score identifies the individual as one who is less likely to benefit from a treatment including an endocrine therapy as described herein.

[0185] In particular instances, the methods and assays provided herein may be used to identify an individual having a breast cancer who may benefit from a treatment including an endocrine therapy as described herein, the method including determining an E2-induced score from a sample (e.g., a tissue sample, e.g., a tumor tissue sample, e.g., a FFPE, a FF, an archival, a fresh, or a frozen tumor tissue sample) from the individual, wherein an E2-induced score that is below a reference E2-induced score identifies the individual as one who is less likely to benefit from a treatment including an endocrine therapy as described herein.

[0186] In particular instances, the methods and assays provided herein may be used to select a therapy for an individual having a breast cancer (e.g., an HR+ breast cancer (e.g., an ER+ breast cancer (e.g., luminal A breast cancer or luminal B breast cancer)), DCIS, and/or a metastatic or a locally advanced breast cancer), the method including determining an ER pathway activity score from a sample (e.g., a tissue sample, e.g., a tumor tissue sample, e.g., a FFPE, a FF, an archival, a fresh, or a frozen tumor tissue sample) from the individual, wherein an ER pathway activity score that is below a reference ER pathway activity score identifies the individual as one who is less likely to benefit from a treatment including an endocrine therapy as described herein. For

example, the method involves selecting an anti-cancer therapy for the individual other than an endocrine therapy.

[0187] In particular instances, the methods and assays provided herein may be used to select a therapy for an individual having a breast cancer (e.g., an HR+ breast cancer (e.g., an ER+ breast cancer (e.g., luminal A breast cancer or luminal B breast cancer)), DCIS, and/or a metastatic or a locally advanced breast cancer), the method including determining an E2-induced score from a sample (e.g., a tissue sample, e.g., a tumor tissue sample, e.g., a FFPE, a FF, an archival, a fresh, or a frozen tumor tissue sample) from the individual, wherein an E2-induced score that is below a reference E2-induced score identifies the individual as one who is less likely to benefit from a treatment including an endocrine therapy as described herein. For example, the method involves selecting an anti-cancer therapy for the individual other than an endocrine therapy.

[0188] In particular instances, the methods and assays provided herein may be used to identify an individual having a breast cancer (e.g., an HR+ breast cancer (e.g., an ER+ breast cancer (e.g., luminal A breast cancer or luminal B breast cancer)), DCIS, and/or a metastatic or a locally advanced breast cancer) who may benefit from a treatment including an anti-cancer therapy other than an endocrine therapy, the method including determining an ER pathway activity score from a sample (e.g., a tissue sample, e.g., a tumor tissue sample, e.g., a FFPE, a FF, an archival, a fresh, or a frozen tumor tissue sample) from the individual, wherein an ER pathway activity score that is below a reference ER pathway activity score identifies the individual as one who may benefit from a treatment including an anti-cancer therapy other than an endocrine therapy.

[0189] In particular instances, the methods and assays provided herein may be used to identify an individual having a breast cancer who may benefit from a treatment including an anti-cancer therapy other than an endocrine therapy, the method including determining an E2-induced score from a sample (e.g., a tissue sample, e.g., a tumor tissue sample, e.g., a FFPE, a FF, an archival, a fresh, or a frozen tumor tissue sample) from the individual, wherein an E2-induced score that is below a reference E2-induced score identifies the individual as one who may benefit from a treatment including an anti-cancer therapy other than an endocrine therapy.

[0190] In particular instances, the methods and assays provided herein may be used to select a therapy for an individual having a breast cancer (e.g., an HR+ breast cancer (e.g., an ER+ breast cancer (e.g., luminal A breast cancer or luminal B breast cancer)), DCIS, and/or a metastatic or a

locally advanced breast cancer), the method including determining an ER pathway activity score from a sample (e.g., a tissue sample, e.g., a tumor tissue sample, e.g., a FFPE, a FF, an archival, a fresh, or a frozen tumor tissue sample) from the individual, wherein an ER pathway activity score that is below a reference ER pathway activity score identifies the individual as one who may benefit from a treatment including an anti-cancer therapy other than an endocrine therapy.

[0191] In particular instances, the methods and assays provided herein may be used to select a therapy for an individual having a breast cancer (e.g., an HR+ breast cancer (e.g., an ER+ breast cancer (e.g., luminal A breast cancer or luminal B breast cancer)), DCIS, and/or a metastatic or a locally advanced breast cancer), the method including determining an E2-induced score from a sample (e.g., a tissue sample, e.g., a tumor tissue sample, e.g., a FFPE, a FF, an archival, a fresh, or a frozen tumor tissue sample) from the individual, wherein an E2-induced score that is below a reference E2-induced score identifies the individual as one who may benefit from a treatment including an anti-cancer therapy other than an endocrine therapy.

[0192] In any of the preceding instances, the reference ER pathway activity score may be an ER pathway activity score in a reference population of individuals having an HR+ breast cancer (e.g., an ER+ breast cancer (e.g., luminal A breast cancer or luminal B breast cancer)), DCIS, and/or a metastatic or a locally advanced breast cancer). In some instances, the reference population is a population of individuals who have not received a treatment including an endocrine therapy as described herein. In some instances, the reference population is a population of individuals who have not received a prior endocrine therapy as described herein. In some instances, the reference population is a population of individuals who are not currently receiving an anti-cancer treatment, including an endocrine therapy as described herein. In some instances, the reference ER pathway activity score may be a pre-assigned reference ER pathway activity score. In some instances, the reference ER pathway activity score may be at or above -1.0 (e.g., -1.0, -0.9, -0.8, -0.7, -0.6, -0.5, -0.4, -0.3, -0.2, or higher). For example, in some instances, the reference ER pathway activity score may be at or above -0.9. In some instances, the reference ER pathway activity score may be at or above -0.8. In some instances, the reference ER pathway activity score may be at or above -0.7. In some instances, the reference ER pathway activity score may be at or above -0.6. In some instances, the reference ER pathway activity score may be at or above -0.5. In some instances, the reference ER pathway activity score may

be at or above -0.4. In some instances, the reference ER pathway activity score may be at or above -0.3. In some instances, the reference ER pathway activity score may be at or above -0.2. In some instances, the reference ER pathway activity score may be between about -1.0 to about -0.2 (e.g., between about -0.9 to about -0.2, e.g., between about -0.8 to about -0.2, e.g., between about -0.7 to about -0.2, e.g., between about -0.6 to about -0.2, e.g., between about -0.5 to about -0.2, e.g., between about -0.4 to about -0.2, or e.g., between about -0.3 to about -0.2).

[0193] In any of the preceding instances, the ER pathway activity score from the sample (e.g., a tissue sample, e.g., a tumor tissue sample, e.g., a FFPE, a FF, an archival, a fresh, or a frozen tumor tissue sample) from the individual may be at or above -1.0 (e.g., -1.0, -0.9, -0.8, -0.7, -0.6, -0.5, -0.4, -0.3, -0.2 or higher). For example, in some instances, the ER pathway activity score may be at or above -0.9. In some instances, the ER pathway activity score may be at or above -0.8. In some instances, the ER pathway activity score may be at or above -0.7. In some instances, the ER pathway activity score may be at or above -0.6. In some instances, the ER pathway activity score may be at or above -0.5. In some instances, the ER pathway activity score may be at or above -0.4. In some instances, the ER pathway activity score may be at or above -0.3. In some instances, the ER pathway activity score may be at or above -0.2. In some instances, the ER pathway activity score may be between about -1.0 to about -0.2 (e.g., between about -0.9 to about -0.2, e.g., between about -0.8 to about -0.2, e.g., between about -0.7 to about -0.2, e.g., between about -0.6 to about -0.2, e.g., between about -0.5 to about -0.2, e.g., between about -0.4 to about -0.2, or e.g., between about -0.3 to about -0.2). In some instances, the ER activity score from the sample may be less than -1.0.

[0194] In any of the preceding instances, the reference E2-induced score may be an E2-induced score in a reference population of individuals having a hormone receptor (HR)+ breast cancer (e.g., an ER+ breast cancer (e.g., luminal A breast cancer or luminal B breast cancer) and/or a metastatic or a locally advanced breast cancer). In some instances, the reference population is a population of individuals who have not received a treatment including an endocrine therapy as described herein. In some instances, the reference E2-induced score may be a pre-assigned reference E2-induced score. In some instances, the reference E2-induced score may be at or above -2.0 (e.g., -2.0, -1.0, -0.9, -0.8, -0.7, -0.6, -0.5, -0.4, -0.3, -0.2, or higher). For example, in some instances, the reference E2-induced score may be at or above -1.0. In some

instances, the reference E2-induced score may be at or above -0.9. In some instances, the reference E2-induced score may be at or above -0.8. In some instances, the reference E2-induced score may be at or above -0.7. In some instances, the reference E2-induced score may be at or above -0.6. In some instances, the reference E2-induced score may be at or above -0.5. In some instances, the reference E2-induced score may be at or above -0.4. In some instances, the reference E2-induced score may be at or above -0.3. In some instances, the reference E2-induced score may be at or above -0.2. In some instances, the reference E2-induced score may be at or above -0.1. In some instances, the reference E2-induced score may be between about -2.0 to about -0.1 (e.g., between about -1.0 to about -0.1, e.g., between about -0.7 to about -0.1, e.g., between about -0.6 to about -0.1, e.g., between about -0.5 to about -0.1, e.g., between about -0.4 to about -0.1, e.g., between about -0.3 to about -0.1, or e.g., between about -0.2 to about -0.1).

[0195] In any of the preceding instances, the E2-induced score from the sample (e.g., a tissue sample, e.g., a tumor tissue sample, e.g., a FFPE, a FF, an archival, a fresh, or a frozen tumor tissue sample) from the individual may be at or above -2.0 (e.g., -2.0, -1.0, -0.9, -0.8, -0.7, -0.6, -0.5, -0.4, -0.3, -0.2, -0.1 or higher). For example, in some instances, the E2-induced score may be at or above -1.0. In some instances, the E2-induced score may be at or above -0.9. In some instances, the E2-induced score may be at or above -0.8. In some instances, the E2-induced score may be at or above -0.7. In some instances, the E2-induced score may be at or above -0.6. In some instances, the E2-induced score may be at or above -0.5. In some instances, the E2-induced score may be at or above -0.4. In some instances, the E2-induced score may be at or above -0.3. In some instances, the E2-induced score may be at or above -0.2. In some instances, the E2-induced score may be at or above -0.1. In some instances, the E2-induced score may be between about -2.0 to about -0.1 (e.g., between about -1.0 to about -0.1, e.g., between about -0.7 to about -0.1, e.g., between about -0.6 to about -0.1, e.g., between about -0.5 to about -0.1, e.g., between about -0.4 to about -0.1, e.g., between about -0.3 to about -0.1, or e.g., between about -0.2 to about -0.1). In some instances, the E2-induced score from the sample may be less than -2.0.

[0196] In any of the predictive methods and assays described above, the methods and assays may further include administering to the individual an endocrine therapy (e.g., as described in Section IV-A, below). In particular instances, when the ER pathway activity score from a sample (e.g., a tissue sample, e.g., a tumor tissue sample, e.g., a FFPE, a FF, an archival, a fresh, or a

frozen tumor tissue sample) from an individual is at or above a reference ER pathway activity score, the method further includes administering to the individual an endocrine therapy. In particular instances, when the E2-induced score from a sample (e.g., a tissue sample, e.g., a tumor tissue sample, e.g., a FFPE, a FF, an archival, a fresh, or a frozen tumor tissue sample) from an individual is at or above a reference E2-induced score, the method further includes administering to the individual an endocrine therapy.

[0197] In any of the predictive methods and assays described above, the methods and assays may further include administering to the individual an anti-cancer therapy other than an endocrine therapy (e.g., as described in Section IV-A, below). In particular instances, when the ER pathway activity score from a sample (e.g., a tissue sample, e.g., a tumor tissue sample, e.g., a FFPE, a FF, an archival, a fresh, or a frozen tumor tissue sample) from an individual is below a reference ER pathway activity score, the method further includes administering to the individual an anti-cancer therapy other than an endocrine therapy. In particular instances, when the E2-induced score from a sample (e.g., a tissue sample, e.g., a tumor tissue sample, e.g., a FFPE, a FF, an archival, a fresh, or a frozen tumor tissue sample) from an individual is below a reference E2-induced score, the method further includes administering to the individual an anti-cancer therapy other than an endocrine therapy.

[0198] The methods provided herein may include determining an ER pathway activity score from a sample (e.g., a tissue sample, e.g., a tumor tissue sample, e.g., a FFPE, a FF, an archival, a fresh, or a frozen tumor tissue sample) from an individual. The methods provided herein may include determining an E2-induced score from a sample (e.g., a tissue sample, e.g., a tumor tissue sample, e.g., a FFPE, a FF, an archival, a fresh, or a frozen tumor tissue sample) from an individual. In some instances, the sample may be a FFPE tumor tissue sample. In some instances, the sample may be a FF tumor tissue sample.

[0199] In any of the preceding instances, the individual may have an HR+ breast cancer. In some instances, the HR+ cancer may be an ER+ breast cancer. In some instances, the individual may have an ER+ breast cancer selected from, for example, a luminal A breast cancer or a luminal B breast cancer. In some instances, the breast cancer may be an advanced or a metastatic breast cancer.

[0200] In some instances of any of the preceding methods or assays involving determining an ER pathway activity score and/or E2-induced score from a sample (e.g., a tissue sample, e.g., a tumor tissue sample, e.g., a FFPE, a FF, an archival, a fresh, or a frozen tumor tissue sample) from an individual, the individual has been previously treated with an endocrine therapy as described herein. In other instances, the individual has not been previously treated with an endocrine therapy. In another embodiment, the individual has received one or more prior therapies prior to performing the methods and assays described herein where such therapy may be an endocrine therapy or a non-endocrine therapy as described herein.

[0201] In some instances, the methods further comprise generating a report, e.g., an electronic, web-based, or paper report, to the individual or to another person or entity, a caregiver, a physician, an oncologist, a hospital, clinic, third-party payor, insurance company, a pharmaceutical or biotechnology company, or government office. In some embodiments, the report comprises output from the method which comprises evaluation of the ER pathway activity and/or E2-induced score.

[0202] Pharmacodynamic Diagnostic Methods

[0203] Also provided herein are pharmacodynamics methods. In some instances, the methods may involve monitoring a response of an individual to treatment with an endocrine therapy as described herein.

[0204] In some instances, the method includes: (a) determining an ER pathway activity score from a sample (e.g., a tissue sample, e.g., a tumor tissue sample, e.g., a FFPE, a FF, an archival, a fresh, or a frozen tumor tissue sample) from the individual at a first time point; (b) following step (a), determining a second ER pathway activity score from a sample from the individual at a second time point following administration of an endocrine therapy as described herein; and (c) comparing the first ER pathway activity score with the second ER pathway activity score, wherein a decrease (e.g., a decrease in the ER pathway activity score of about 0.1, 0.2, 0.3, or greater) in the second ER pathway activity score relative to the first ER pathway activity score is predictive of an individual who is likely to respond to treatment with an endocrine therapy e.g., a SERM (e.g., a SERD), a GnRH agonist, and/or an AI. In some instances, a decrease in the ER pathway activity score refers to an overall decrease of the ER pathway activity score of at least 0.1. In some instances, a decrease in the ER pathway activity score refers to an overall decrease

of the ER pathway activity score of at least 0.2. In some instances, a decrease in the ER pathway activity score refers to an overall decrease of the ER pathway activity score of at least 0.3.

[0205] In some instances, the method further comprises administering one or more additional doses of the endocrine therapy if the second ER pathway activity score in the sample (e.g., a tissue sample, e.g., a tumor tissue sample, e.g., a formalin-fixed paraffin-embedded (FFPE), a fresh frozen (FF), an archival, a fresh, or a frozen tumor tissue sample) from the individual is decreased relative to the first ER pathway activity score. In some instances, a decreased ER pathway activity score refers to an overall decrease of the ER pathway activity score of at least 0.1 (e.g., a decrease of 0.1, 0.2, 0.3, or greater). In some instances, a decreased ER pathway activity score refers to an overall decrease of the ER pathway activity score of at least 0.2. In some instances, a decreased ER pathway activity refers to an overall decrease of ER pathway activity score of at least 0.3.

[0206] In some instances of any of the preceding methods, the first ER pathway activity score is an ER pathway activity score determined from a sample (e.g., a tissue sample, e.g., a tumor tissue sample, e.g., a FFPE, a FF, an archival, a fresh, or a frozen tumor tissue sample) from the individual obtained prior to administration of a first dose of an endocrine therapy as described herein. In other words, the sample may be a baseline sample. In other instances, the first ER pathway activity score is an ER pathway activity score determined from a sample from the individual obtained at a previous time point, wherein the previous time point is following administration of a first dose of an endocrine therapy as described herein. In other instances, the first ER pathway activity score is an ER pathway activity score determined from a sample from the individual obtained at a previous time point, wherein the previous time point is following administration of a first dose of a non-endocrine therapy as described herein. In other instances, the first ER pathway activity score is a pre-determined ER pathway activity score.

[0207] In some instances, the method includes: (a) determining an E2-induced score from a sample (e.g., a tissue sample, e.g., a tumor tissue sample, e.g., a FFPE, a FF, an archival, a fresh, or a frozen tumor tissue sample) from the individual at a first time point; (b) following step (a), determining a second E2-induced score from a sample from the individual at a second time point following administration of an endocrine therapy as described herein; and (c) comparing the first E2-induced score with the second E2-induced score, wherein a decrease (e.g., a decrease in the

E2-induced score of at least 0.1, 0.2, 0.3, or greater) in the second E2-induced score relative to the first E2-induced score is predictive of an individual who is likely to respond to treatment with an endocrine therapy as described herein. In some instances, a decrease in the E2-induced score refers to an overall decrease of at least 0.1. In some instances, a decrease in the E2-induced score refers to an overall decrease of at least 0.2. In some instances, a decrease in the E2-induced score refers to an overall decrease of at least 0.3.

[0208] In some instances, the method further comprises administering one or more additional doses of the endocrine therapy as described herein if the second E2-induced in the sample (e.g., a tissue sample, e.g., a tumor tissue sample, e.g., a FFPE, a FF, an archival, a fresh, or a frozen tumor tissue sample) is decreased relative to the first E2-induced score. In some instances, a decreased E2-induced score refers to an overall decrease of the E2-induced score of at least 0.1 (e.g., a decrease of 0.1, 0.2, 0.3, or greater). In some instances, a decreased E2-induced score refers to an overall decrease of the E2-induced score of at least 0.2. In some instances, a decreased E2-induced score refers to an overall decrease of the E2-induced score of at least 0.3.

[0209] In some instances of any of the preceding methods, the first E2-induced score is E2-induced score determined from a sample (e.g., a tissue sample, e.g., a tumor tissue sample, e.g., a FFPE, a FF, an archival, a fresh, or a frozen tumor tissue sample) from the individual obtained prior to administration of a first dose of an anti-cancer therapy (e.g., an endocrine therapy as described herein. In other words, the sample may be a baseline sample. In other instances, the first E2-induced score is an E2-induced score determined from a sample from the individual obtained at a previous time point, wherein the previous time point is following administration of a first dose of an endocrine therapy as described herein. In other instances, the first E2-induced score is a pre-determined E2-induced score.

[0210] In some instances, the second ER pathway activity score from the sample (e.g., a tissue sample, e.g., a tumor tissue sample, e.g., a FFPE, a FF, an archival, a fresh, or a frozen tumor tissue sample) from the individual is decreased relative to the first ER pathway activity score, and the method or assay further involves administering an additional dose of an endocrine therapy as described herein to the individual. In some instances, the second E2-induced score from the sample (e.g., a tissue sample, e.g., a tumor tissue sample, e.g., a FFPE, a FF, an archival, a fresh, or a frozen tumor tissue sample) from the individual is decreased relative to the

first E2-induced score, and the method or assay further involves administering an additional dose of an endocrine therapy as described herein to the individual.

[0211] The methods provided herein may include determining an ER pathway activity score from a sample (e.g., a tissue sample, e.g., a tumor tissue sample, e.g., a FFPE, a FF, an archival, a fresh, or a frozen tumor tissue sample) from an individual. The methods provided herein may include determining an E2-induced score from a sample (e.g., a tissue sample, e.g., a tumor tissue sample, e.g., a FFPE, a FF, an archival, a fresh, or a frozen tumor tissue sample) from an individual. In some instances, the sample may be a FFPE tumor tissue sample. In some instances, the sample may be a FF tumor tissue sample.

[0212] In any of the preceding instances, the individual may have an HR+ breast cancer. In some instances, the HR+ cancer may be an ER+ breast cancer. In some instances, the individual may have an ER+ breast cancer selected from, for example, a luminal A breast cancer or a luminal B breast cancer. In some instances, the breast cancer may be an advanced or a metastatic breast cancer.

[0213] In some instances of any of the preceding methods or assays involving determining an ER pathway activity score and/or E2-induced score from a sample (e.g., a tissue sample, e.g., a tumor tissue sample, e.g., a FFPE, a FF, an archival, a fresh, or a frozen tumor tissue sample) from the individual, the individual has been previously treated with an endocrine therapy as described herein. In other instances, the individual has not been previously treated with an endocrine therapy. In some instances of any of the methods and assays, the sample (e.g., a tissue sample, e.g., a tumor tissue sample, e.g., a FFPE, a FF, an archival, a fresh, or a frozen tumor tissue sample) is obtained from the individual prior to (e.g., minutes, hours, days, weeks, months, or years prior to) administration of an endocrine therapy as described herein. In other words, the sample may be a baseline sample. In some instances of any of the preceding methods, the sample is obtained from the individual following (e.g., minutes, hours, or days following) administration of an endocrine therapy. In some instances, the sample from the individual is obtained within thirty hours following administration of an endocrine therapy. In some instances, multiple samples are obtained from the same individual at different time points (e.g., prior to and following administration of an endocrine therapy).

[0214] In some instances, the methods further comprise generating a report, e.g., an electronic, web-based, or paper report, to the individual or to another person or entity, a caregiver, a physician, an oncologist, a hospital, clinic, third-party payor, insurance company, a pharmaceutical or biotechnology company, or government office. In some instances, the report comprises output from the method which comprises evaluation of the ER pathway activity and/or E2-induced score.

[0215] In one aspect, a method of detecting estrogen receptor (ER) pathway activity in a subject that has breast cancer is provided. The method includes detecting an expression level of at least five genes set forth in Table 1 and at least five genes set forth in Table 4; at least five genes set forth in Table 2 and at least five genes set forth in Table 5; or at least five genes set forth in Table 3 and at least five genes set forth in Table 6.

[0216] Controls used for the methods provided herein are valuable for determining the significance of data. For example, if values for a given parameter are widely variant in controls, variation in test samples will not be considered as significant. In some examples of the disclosed methods, when the expression level of any of the genes provided in Table 1-6 is assessed, the expression level is compared with a control expression level of the gene. By control expression level is meant the expression level of a gene from a sample or subject lacking breast cancer, a sample or subject at a selected stage of breast cancer or cancer state, or in the absence of a particular variable such as a therapeutic agent. Alternatively, the control level comprises a known amount of the gene. Such a known amount correlates with an average level of subjects lacking breast cancer, at a selected stage of breast cancer or cancer state, or in the absence of a particular variable such as a therapeutic agent. A control level also includes the expression level of the gene from one or more selected samples or subjects as described herein. For example, a control level includes an assessment of the expression level of the gene in a sample from a subject that does not have breast cancer, is at a selected stage of breast cancer or cancer state, or have breast cancer but have not yet received treatment for breast cancer. Another exemplary control level includes an assessment of the expression level of the gene in samples taken from multiple subjects that do not have breast cancer, are at a selected stage of cancer, or have cancer but have not yet received treatment for breast cancer. In embodiments, a threshold for elevated

gene expression levels is above the median expression level of a group of control sample, where the control sample is optionally a group of subjects who have breast cancer.

[0217] In embodiments, the method includes detecting an expression level of at least five (e.g., 5, 6, 7, 8, etc.) genes set forth in Table 1 and at least five genes set forth in Table 4. In embodiments, the method includes detecting an expression level of at least five genes set forth in Table 2 and at least five genes set forth in Table 5. In embodiments, the method includes detecting an expression level of at least five genes set forth in Table 3 and at least five genes set forth in Table 6.

[0218] In embodiments, the expression level of the at least five genes set forth in Table 1, at least five genes set forth in Table 2 or at least five genes set forth in Table 3 are greater than a standard control. In embodiments, the expression level of all the genes set forth in Table 1, all of the genes set forth in Table 2 or all of the genes set forth in Table 3 are greater than a standard control. In embodiments, the expression level of the at least five genes set forth in Table 1 are greater than a standard control. In embodiments, the expression level of all genes set forth in Table 1 are greater than a standard control. In embodiments, the expression level of the at least five genes set forth in Table 2 are greater than a standard control. In embodiments, the expression level of all genes set forth in Table 2 are greater than a standard control. In embodiments, the expression level of the at least five genes set forth in Table 3 are greater than a standard control. In embodiments, the expression level of all genes set forth in Table 3 are greater than a standard control.

[0219] In embodiments, a threshold for elevated gene expression levels (e.g., expression of any one gene set forth in Table 1-6) is above the median expression level of a group of control samples, where the control sample is optionally a group of subjects who have breast cancer. In embodiments, it is above the first quartile of gene expression in a group of control samples, where the control sample is optionally a group of subjects who have breast cancer. In embodiments, it is above the third quartile of gene expression in a group of control samples, where the control sample is optionally a group of subjects who have breast cancer. In embodiments, it is above the 5th percentile of gene expression in a group of control samples, where the control sample is optionally a group of subjects who have breast cancer. In embodiments, it is above the 10th percentile of gene expression in a group of control samples,

where the control sample is optionally a group of subjects who have breast cancer. In embodiments, it is above the 20th percentile of gene expression in a group of control samples, where the control sample is optionally a group of subjects who have breast cancer. In embodiments, it is above the 30th percentile of gene expression in a group of control samples, where the control sample is optionally a group of subjects who have breast cancer. In embodiments, it is above the 40th percentile of gene expression in a group of control samples, where the control sample is optionally a group of subjects who have breast cancer. In embodiments, it is above the 45th percentile of gene expression in a group of control samples, where the control sample is optionally a group of subjects who have breast cancer. In embodiments, it is above the 50th percentile of gene expression in a group of control samples, where the control sample is optionally a group of subjects who have breast cancer. In embodiments, it is above the 60th percentile of gene expression in a group of control samples, where the control sample is optionally a group of subjects who have breast cancer. In embodiments, it is above the 70th percentile of gene expression in a group of control samples, where the control sample is optionally a group of subjects who have breast cancer. In embodiments, it is above the 80th percentile of gene expression in a group of control samples, where the control sample is optionally a group of subjects who have breast cancer. In embodiments, it is above the 90th percentile of gene expression in a group of control samples, where the control sample is optionally a group of subjects who have breast cancer.

[0220] In embodiments, the expression level of the at least five genes set forth in Table 4, at least five genes set forth in Table 5 or at least five genes set forth in Table 6 are less than a standard control. In embodiments, the expression level of all genes set forth in Table 4, of all genes set forth in Table 5 or of all genes set forth in Table 6 are less than a standard control. In embodiments, the expression level of the at least five genes set forth in Table 4 are less than a standard control. In embodiments, the expression level of all genes set forth in Table 4 are less than a standard control. In embodiments, the expression level of the at least five genes set forth in Table 5 are less than a standard control. In embodiments, the expression level of all genes set forth in Table 5 are less than a standard control. In embodiments, the expression level of the at least five genes set forth in Table 6 are less than a standard control. In embodiments, the expression level of all genes set forth in Table 6 are less than a standard control.

[0221] In embodiments, a threshold for decreased gene expression levels (e.g., expression of any one gene set forth in Table 1-6) is below the median expression level of a group of control samples, where the control sample is optionally a group of subjects who have breast cancer. In embodiments, it is below the first quartile of gene expression in a group of control samples, where the control sample is optionally a group of subjects who have breast cancer. In embodiments, it is below the third quartile of gene expression in a group of control samples, where the control sample is optionally a group of subjects who have breast cancer. In embodiments, it is below the 5th percentile of gene expression in a group of control samples, where the control sample is optionally a group of subjects who have breast cancer. In embodiments, it is below the 10th percentile of gene expression in a group of control samples, where the control sample is optionally a group of subjects who have breast cancer. In embodiments, it is below the 20th percentile of gene expression in a group of control samples, where the control sample is optionally a group of subjects who have breast cancer. In embodiments, it is below the 30th percentile of gene expression in a group of control samples, where the control sample is optionally a group of subjects who have breast cancer. In embodiments, it is below the 40th percentile of gene expression in a group of control samples, where the control sample is optionally a group of subjects who have breast cancer. In embodiments, it is below the 45th percentile of gene expression in a group of control samples, where the control sample is optionally a group of subjects who have breast cancer. In embodiments, it is below the 50th percentile of gene expression in a group of control samples, where the control sample is optionally a group of subjects who have breast cancer. In embodiments, it is below the 60th percentile of gene expression in a group of control samples, where the control sample is optionally a group of subjects who have breast cancer. In embodiments, it is below the 70th percentile of gene expression in a group of control samples, where the control sample is optionally a group of subjects who have breast cancer. In embodiments, it is below the 80th percentile of gene expression in a group of control samples, where the control sample is optionally a group of subjects who have breast cancer. In embodiments, it is below the 90th percentile of gene expression in a group of control samples, where the control sample is optionally a group of subjects who have breast cancer.

[0222] In embodiments, the subject has been treated with an endocrine therapy prior to the detecting. In embodiments, the subject is treated with an endocrine therapy subsequent to the detecting.

[0223] In embodiments, the method includes detecting an expression level of all genes set forth in Table 1 and all genes set forth in Table 4. In embodiments, the method includes detecting an expression level of all genes set forth in Table 2 and all genes set forth in Table 5. In embodiments, the method includes detecting an expression level of all genes set forth in Table 3 and all genes set forth in Table 6. In embodiments, the method includes detecting an expression level of all genes set forth in Table 1 and all genes set forth in Table 4 and not detecting an expression level of any other genes in the subject. In embodiments, the method includes detecting an expression level of all genes set forth in Table 2 and all genes set forth in Table 5 and not detecting an expression level of any other genes in the subject. In embodiments, the method includes detecting an expression level of all genes set forth in Table 3 and all genes set forth in Table 6 and not detecting an expression level of any other genes in the subject.

[0224] In embodiments, the subject is treated with an endocrine therapy where the endocrine therapy is a selective estrogen receptor degrader.

[0225] In embodiments, the method includes determining an estrogen receptor (ER) pathway activity score from a sample from the subject. In embodiments, an ER pathway activity score from the sample that is at or above a reference ER pathway activity score identifies the individual as one who may benefit from a treatment including an endocrine therapy. In embodiments, the method includes comparing an ER pathway activity score from the sample that is at or above a reference ER pathway activity score identifies the individual as one who may benefit from a treatment including an endocrine therapy.

[0226] In one aspect a method is provided, the method includes detecting, by one or more processors, a first expression level of at least five genes set forth in Table 1, at least five genes set forth in Table 2, or at least five genes set forth in Table 3; detecting, by the one or more processors, a second expression level of at least five genes set forth in Table 4, at least five genes set forth in Table 5 or at least five genes set forth in Table 6; and detecting, based at least on the first expression level and/or the second expression level, estrogen receptor (ER) pathway activity in a subject that has cancer. In embodiments, the first expression is elevated relative to the

second expression level. In embodiments, the first expression is decreased relative to the second expression level.

[0227] In embodiments, a threshold for an elevated first gene expression level (e.g., a first expression level of any one gene set forth in Table 1-6) is above the second expression level. In embodiments, it is above the first quartile of the second gene expression level. In embodiments, it is above the third quartile of the second gene expression level. In embodiments, it is above the 5th percentile of the second gene expression level. In embodiments, it is above the 10th percentile of the second gene expression level. In embodiments, it is above the 20th percentile of the second gene expression level. In embodiments, it is above the 30th percentile of the second gene expression level. In embodiments, it is above the 40th percentile of the second gene expression level. In embodiments, it is above the 45th percentile of the second gene expression level. In embodiments, it is above the 50th percentile of the second gene expression level. In embodiments, it is above the 60th percentile of the second gene expression level. In embodiments, it is above the 70th percentile of the second gene expression level. In embodiments, it is above the 80th percentile of the second gene expression level. In embodiments, it is above the 90th percentile of the second gene expression level.

[0228] In embodiments, a threshold for a decreased first gene expression level (e.g., a first expression level of any one gene set forth in Table 1-6) is below the second expression level. In embodiments, it is below the first quartile of the second gene expression level. In embodiments, it is below the third quartile of the second gene expression level. In embodiments, it is below the 5th percentile of the second gene expression level. In embodiments, it is below the 10th percentile of the second gene expression level. In embodiments, it is below the 20th percentile of the second gene expression level. In embodiments, it is below the 30th percentile of the second gene expression level. In embodiments, it is below the 40th percentile of the second gene expression level. In embodiments, it is below the 45th percentile of the second gene expression level. In embodiments, it is below the 50th percentile of the second gene expression level. In embodiments, it is below the 60th percentile of the second gene expression level. In embodiments, it is below the 70th percentile of the second gene expression level. In embodiments, it is below the 80th percentile of the second gene expression level. In embodiments, it is below the 90th percentile of the second gene expression level.

[0229] In embodiments, the expression level of the at least five genes set forth in Table 1, at least five genes set forth in Table 2 or at least five genes set forth in Table 3 are greater than a standard control. In embodiments, the expression level of the at least five genes set forth in Table 4, at least five genes set forth in Table 5 or at least five genes set forth in Table 6 are less than a standard control.

[0230] In embodiments, the method includes treating the subject with an endocrine therapy prior to the detecting. In embodiments, the method includes treating, based at least on the estrogen receptor (ER) pathway activity detected in the subject, the subject with an endocrine therapy.

B. Therapeutic Methods

[0231] Also provided herein are methods for treating an individual having a breast cancer (e.g., an HR+ breast cancer (e.g., an ER+ breast cancer (e.g., luminal A breast cancer or luminal B breast cancer)), DCIS, and/or a metastatic or a locally advanced breast cancer). Accordingly, in some instances, the methods provided herein include administering to the individual an endocrine therapy as described herein. In other instances, the methods provided herein include administering to the individual an anti-cancer agent other than an endocrine therapy. Any of the anti-cancer agents described herein (e.g., in Section IV, below), or known in the art may be used in connection with the methods.

[0232] Provided herein is a method of treating an individual having a breast cancer (e.g., an HR+ breast cancer (e.g., an ER+ breast cancer (e.g., luminal A breast cancer or luminal B breast cancer)), DCIS, and/or a metastatic or a locally advanced breast cancer) that includes (i) determining an ER pathway activity score from a sample (e.g., a tissue sample, e.g., a tumor tissue sample, e.g., a FFPE, a FF, an archival, a fresh, or a frozen tumor tissue sample) from the individual, wherein the ER pathway activity score is determined to be at or above a reference ER pathway activity score (e.g., a reference ER pathway activity score in a reference population, e.g., a reference ER pathway activity score at or above -1.0); and (ii) administering to the individual an effective amount of an endocrine therapy as described herein.

[0233] Provided herein is a method of treating an individual having a breast cancer (e.g., an HR+ breast cancer (e.g., an ER+ breast cancer (e.g., luminal A breast cancer or luminal B breast cancer)), DCIS, and/or a metastatic or a locally advanced breast cancer), that includes

administering to the individual an endocrine therapy as described herein, wherein the individual has been identified to be more likely to benefit from a treatment comprising an endocrine therapy by one or more of the predictive diagnostic methods described in Section III-A, above.

[0234] Provided herein is a method of treating an individual having a breast cancer (e.g., an HR+ breast cancer (e.g., an ER+ breast cancer (e.g., luminal A breast cancer or luminal B breast cancer)), DCIS, and/or a metastatic or a locally advanced breast cancer), that includes administering to the individual an endocrine therapy as described herein, wherein the individual has been identified as having an ER pathway activity score that is at or above a reference ER pathway activity score by any of the predictive diagnostic methods described in Section III-A, above.

[0235] Provided herein is a method of treating an individual having a breast cancer (e.g., an HR+ breast cancer (e.g., an ER+ breast cancer (e.g., luminal A breast cancer or luminal B breast cancer)), DCIS, and/or a metastatic or a locally advanced breast cancer) that includes (i) determining an E2-induced score from a sample (e.g., a tissue sample, e.g., a tumor tissue sample, e.g., a FFPE, a FF, an archival, a fresh, or a frozen tumor tissue sample) from the individual, wherein the E2-induced score is determined to be at or above a reference E2-induced score (e.g., a reference E2-induced score in a reference population, e.g., a reference E2-induced score at or above -2.0); and (ii) administering to the individual an effective amount of an endocrine therapy as described herein.

[0236] Provided herein is a method of treating an individual having a breast cancer (e.g., an HR+ breast cancer (e.g., an ER+ breast cancer (e.g., luminal A breast cancer or luminal B breast cancer)), DCIS, and/or a metastatic or a locally advanced breast cancer), that includes administering to the individual an endocrine therapy as described herein, wherein the individual has been identified as having an E2-induced score that is at or above a reference E2-induced score by any of the predictive diagnostic methods described in Section III-A, above.

[0237] Also provided herein is a method of treating an individual having a breast cancer (e.g., an HR+ breast cancer (e.g., an ER+ breast cancer (e.g., luminal A breast cancer or luminal B breast cancer)), DCIS, and/or a metastatic or a locally advanced breast cancer) that includes (i) determining an ER pathway activity score from a sample (e.g., a tissue sample, e.g., a tumor tissue sample, e.g., a FFPE, a FF, an archival, a fresh, or a frozen tumor tissue sample) from the

individual, wherein the ER pathway activity score is determined to be below a reference ER pathway activity score (e.g., a reference ER pathway activity score in a reference population, e.g., a reference ER pathway activity score below -1.0); and (ii) administering to the individual an effective amount of an anti-cancer therapy other than endocrine therapy.

[0238] Provided herein is a method of treating an individual having a breast cancer (e.g., an HR+ breast cancer (e.g., an ER+ breast cancer (e.g., luminal A breast cancer or luminal B breast cancer))), DCIS, and/or a metastatic or a locally advanced breast cancer), that includes administering to the individual an effective amount of an anti-cancer therapy other than endocrine therapy, wherein the individual has been identified to be less likely to benefit from a treatment comprising an endocrine therapy by one or more of the predictive diagnostic methods described in Section III-A, above.

[0239] Provided herein is a method of treating an individual having a breast cancer (e.g., an HR+ breast cancer (e.g., an ER+ breast cancer (e.g., luminal A breast cancer or luminal B breast cancer))), DCIS, and/or a metastatic or a locally advanced breast cancer), that includes administering to the individual an anti-cancer therapy other than an endocrine therapy, wherein the individual has been identified to be more likely to benefit from a treatment comprising an anti-cancer therapy other than an endocrine therapy by one or more of the predictive diagnostic methods described in Section III-A, above.

[0240] Provided herein is a method of treating an individual having a breast cancer (e.g., an HR+ breast cancer (e.g., an ER+ breast cancer (e.g., luminal A breast cancer or luminal B breast cancer))), DCIS, and/or a metastatic or a locally advanced breast cancer), that includes administering to the individual an effective amount of an anti-cancer therapy other than endocrine therapy, wherein the individual has been identified as having an ER pathway activity score that is below a reference ER pathway activity score by any of the predictive diagnostic methods described in Section III-A, above.

[0241] Provided herein is a method of treating an individual having a breast cancer (e.g., an HR+ breast cancer (e.g., an ER+ breast cancer (e.g., luminal A breast cancer or luminal B breast cancer))), DCIS, and/or a metastatic or a locally advanced breast cancer) that includes (i) determining an E2-induced score from a sample (e.g., a tissue sample, e.g., a tumor tissue sample, e.g., a FFPE, a FF, an archival, a fresh, or a frozen tumor tissue sample) from the

individual, wherein the E2-induced score is determined to be below a reference E2-induced score (e.g., a reference E2-induced score in a reference population, e.g., a reference E2-induced score below -2.0); and (ii) administering to the individual an effective amount of an effective amount of an anti-cancer therapy other than endocrine therapy.

[0242] Provided herein is a method of treating an individual having a breast cancer (e.g., an HR+ breast cancer (e.g., an ER+ breast cancer (e.g., luminal A breast cancer or luminal B breast cancer)), DCIS, and/or a metastatic or a locally advanced breast cancer), that includes administering to the individual an effective amount of an anti-cancer therapy other than endocrine therapy, wherein the individual has been identified as having an E2-induced score that is below a reference E2-induced score by any of the predictive diagnostic methods described in Section III-A, above.

[0243] In any of the preceding instances, the reference ER pathway activity score may be an ER pathway activity score in a reference population of individuals having an HR+ breast cancer (e.g., an ER+ breast cancer (e.g., luminal A breast cancer or luminal B breast cancer)), DCIS, and/or a metastatic or a locally advanced breast cancer). In some instances, the reference population is a population of individuals who have not received a treatment including an endocrine therapy, including those described herein. In some instances, the reference ER pathway activity score may be a pre-assigned reference ER pathway activity score. In some instances, the reference ER pathway activity score may be at or above -1.0 (e.g., -1.0, -0.9, -0.8, -0.7, -0.6, -0.5, -0.4, -0.3, and -0.2, or higher). For example, in some instances, the reference ER pathway activity score may be at or above -0.9. In some instances, the reference ER pathway activity score may be at or above -0.8. In some instances, the reference ER pathway activity score may be at or above -0.7. In some instances, the reference ER pathway activity score may be at or above -0.6. In some instances, the reference ER pathway activity score may be at or above -0.5. In some instances, the reference ER pathway activity score may be at or above -0.4. In some instances, the reference ER pathway activity score may be at or above -0.3. In some instances, the reference ER pathway activity score may be at or above -0.2. In some instances, the reference ER pathway activity score may be between about -1.0 to about -0.2 (e.g., between about -0.9 to about -0.2, e.g., between about -0.8 to about -0.2, e.g., between about -0.7 to about -

0.2, e.g., between about -0.6 to about -0.2, e.g., between about -0.5 to about -0.2, e.g., between about -0.4 to about -0.2, or e.g., between about -0.3 to about -0.2).

[0244] In any of the preceding instances, the ER pathway activity score from the sample (e.g., a tissue sample, e.g., a tumor tissue sample, e.g., a formalin-fixed paraffin-embedded (FFPE), a fresh frozen (FF), an archival, a fresh, or a frozen tumor tissue sample) from the individual may be at, or above -1.0 (e.g., -1.0, -0.9, -0.8, -0.7, -0.6, -0.5, -0.4, -0.3, -0.2 or higher). For example, in some instances, the ER pathway activity score may be at or above -0.9. In some instances, the ER pathway activity score may be at or above -0.8. In some instances, the ER pathway activity score may be at or above -0.7. In some instances, the ER pathway activity score may be at or above -0.6. In some instances, the ER pathway activity score may be at or above -0.5. In some instances, the ER pathway activity score may be at or above -0.4. In some instances, the ER pathway activity score may be at or above -0.3. In some instances, the ER pathway activity score may be at or above -0.2. In some instances, the ER pathway activity score may be between about -1.0 to about -0.2 (e.g., between about -0.9 to about -0.2, e.g., between about -0.8 to about -0.2, e.g., between about -0.7 to about -0.2, e.g., between about -0.6 to about -0.2, e.g., between about -0.5 to about -0.2, e.g., between about -0.4 to about -0.2, or e.g., between about -0.3 to about -0.2). In some instances, the ER activity score from the sample may be less than -1.0.

[0245] In any of the preceding instances, the reference E2-induced score may be an E2-induced score in a reference population of individuals having an HR+ breast cancer (e.g., an ER+ breast cancer (e.g., luminal A breast cancer or luminal B breast cancer)), DCIS, and/or a metastatic or a locally advanced breast cancer). In some instances, the reference population is a population of individuals who have not received a treatment including an endocrine therapy as described herein. In some instances, the reference E2-induced score may be a pre-assigned reference E2-induced score. In some instances, the reference E2-induced score may be at or above -2.0 (e.g., -2.0, -1.0, -0.9, -0.8, -0.7, -0.6, -0.5, -0.4, -0.3, -0.2, or higher). For example, in some instances, the reference E2-induced score may be at or above -1.0. In some instances, the reference E2-induced score may be at or above -0.9. In some instances, the reference E2-induced score may be at or above -0.8. In some instances, the reference E2-induced score may be at or above -0.7. In some instances, the reference E2-induced score may be at or above -0.6. In some instances, the reference E2-induced score may be at or above -0.5. In some instances, the

reference E2-induced score may be at or above -0.4. In some instances, the reference E2-induced score may be at or above -0.3. In some instances, the reference E2-induced score may be at or above -0.2. In some instances, the reference E2-induced score may be at or above -0.1. In some instances, the reference E2-induced score may be between about -2.0 to about -0.1 (e.g., between about -1.0 to about -0.1, e.g., between about -0.7 to about -0.1, e.g., between about -0.6 to about -0.1, e.g., between about -0.5 to about -0.1, e.g., between about -0.4 to about -0.1, e.g., between about -0.3 to about -0.1, or e.g., between about -0.2 to about -0.1).

[0246] In any of the preceding instances, the E2-induced score from the sample (e.g., a tissue sample, e.g., a tumor tissue sample, e.g., a formalin-fixed paraffin-embedded (FFPE), a fresh frozen (FF), an archival, a fresh, or a frozen tumor tissue sample) from the individual may be at, or above -2.0 (e.g., -2.0, -1.0, -0.9, -0.8, -0.7, -0.6, -0.5, -0.4, -0.3, -0.2, -0.1 or higher). In some instances, the E2-induced score may be at or above -1.0. In some instances, the E2-induced score may be at or above -0.9. In some instances, the E2-induced score may be at or above -0.8. For example, in some instances, the E2-induced score may be at or above -0.7. In some instances, the E2-induced score may be at or above -0.6. In some instances, the E2-induced score may be at or above -0.5. In some instances, the E2-induced score may be at or above -0.4. In some instances, the E2-induced score may be at or above -0.3. In some instances, the E2-induced score may be at or above -0.2. In some instances, the E2-induced score may be at or above -0.1. In some instances, the E2-induced score may be between about -2.0 to about -0.1 (e.g., between about -1.0 to about -0.1, e.g., between about -0.7 to about -0.1, e.g., between about -0.6 to about -0.1, e.g., between about -0.5 to about -0.1, e.g., between about -0.4 to about -0.1, e.g., between about -0.3 to about -0.1, or e.g., between about -0.2 to about -0.1). In some instances, the E2-induced score from the sample may be less than -2.0.

[0247] The methods provided herein may include determining an ER pathway activity score from a sample (e.g., a tissue sample, e.g., a tumor tissue sample, e.g., a FFPE, a FF, an archival, a fresh, or a frozen tumor tissue sample) from an individual. The methods provided herein may include determining an E2-induced score from a sample (e.g., a tissue sample, e.g., a tumor tissue sample, e.g., a FFPE, a FF, an archival, a fresh, or a frozen tumor tissue sample) from an individual. In some instances, the sample may be a FFPE tumor tissue sample. In some instances, the sample may be a FF tumor tissue sample.

[0248] In any of the preceding instances, the individual may have an HR+ breast cancer. In some instances, the HR+ cancer may be an ER+ breast cancer. In some instances, the individual may have an ER+ breast cancer selected from, for example, a luminal A breast cancer or a luminal B breast cancer. In some instances, the breast cancer may be an advanced or a metastatic breast cancer.

[0249] In some instances of any of the preceding methods or assays involving determining an ER pathway activity score and/or E2-induced score in a sample (e.g., a tissue sample, e.g., a tumor tissue sample, e.g., a formalin-fixed paraffin-embedded (FFPE), a fresh frozen (FF), an archival, a fresh, or a frozen tumor tissue sample) from the individual, the individual has been previously treated with an endocrine therapy as described herein. In other instances, the individual has not been previously treated with an endocrine therapy.

[0250] In some instances, the methods further comprise generating a report, e.g., an electronic, web-based, or paper report, to the individual or to another person or entity, a caregiver, a physician, an oncologist, a hospital, clinic, third-party payor, insurance company, a pharmaceutical or biotechnology company, or government office. In some instances, the report comprises output from the method which comprises evaluation of the ER pathway activity and/or E2-induced score.

C. Exemplary Methods for Determination of an E2-Induced, E2-Repressed, and ER Pathway Activity Scores

[0251] The methods and assays provided herein may include determining an E2-induced, an E2-repressed, and/or an ER pathway activity score based on an expression level of a predetermined set of genes (e.g., a biomarker) in a sample (e.g., a tissue sample, e.g., a tumor tissue sample, e.g., a FFPE, a FF, an archival, a fresh, or a frozen tumor tissue sample) from an individual (e.g., an individual having a breast cancer (e.g., an HR+ breast cancer (e.g., an ER+ breast cancer (e.g., luminal A breast cancer or luminal B breast cancer)), DCIS, and/or a metastatic or a locally advanced breast cancer)). In some instances, the predetermined set of genes is the set of genes listed in any one of Tables 1-3. In some instances, the pre-determined set of genes are the sets of genes listed in Table 1 and Table 4 (e.g., the 14-gene signature). In some instances, the pre-determined set of genes are the sets of genes listed in Table 2 and Table 5 (e.g., the 19-gene signature). In some instances, the pre-determined set of genes are the sets of

genes listed in Table 3 and Table 6 (e.g., the 41-gene signature). In some instances, the pre-determined set of genes are the sets of genes listed in Table 1 and Table 4 (e.g., the 14-gene signature) and no other genes. In some instances, the pre-determined set of genes are the sets of genes listed in Table 2 and Table 5 (e.g., the 19-gene signature) and no other genes. In some instances, the pre-determined set of genes are the sets of genes listed in Table 3 and Table 6 (e.g., the 41-gene signature) and no other genes.

[0252] In some embodiments, the ER pathway activity score is calculated using an 8-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of three of the E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of five of the E2-induced genes set forth in Table 3.

[0253] In some embodiments, the ER pathway activity score is calculated using a 9-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of four of the E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of five of the E2-induced genes set forth in Table 3. In some embodiments, the ER pathway activity score is calculated using a 9-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of three of the E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of six of the E2-induced genes set forth in Table 3.

[0254] In some embodiments, the ER pathway activity score is calculated using a 10-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of three of the E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of seven of the E2-induced genes set forth in Table 3. In some embodiments, the ER pathway activity score is calculated using a 10-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of four of the E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of six of the E2-induced genes set forth in Table 3. In some embodiments, the ER pathway activity score is calculated using a 10-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of five of the E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of five of the E2-induced genes set forth in Table 3.

[0255] In some embodiments, the ER pathway activity score is calculated using an 11-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of three of the E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of eight of the E2-induced genes set forth in Table 3. In some embodiments, the ER pathway activity score is calculated using an 11-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of four of the E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of seven of the E2-induced genes set forth in Table 3. In some embodiments, the ER pathway activity score is calculated using an 11-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of five of the E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of six of the E2-induced genes set forth in Table 3.

[0256] In some embodiments, the ER pathway activity score is calculated using a 12-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of three of the E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of nine of the E2-induced genes set forth in Table 3. In some embodiments, the ER pathway activity score is calculated using a 12-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of four of the E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of eight of the E2-induced genes set forth in Table 3. In some embodiments, the ER pathway activity score is calculated using a 12-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of five of the E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of seven of the E2-induced genes set forth in Table 3. In some embodiments, the ER pathway activity score is calculated using a 12-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of six of the E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of six of the E2-induced genes set forth in Table 3.

[0257] In some embodiments, the ER pathway activity score is calculated using a 13-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression

of three of the E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of ten of the E2-induced genes set forth in Table 3. In some embodiments, the ER pathway activity score is calculated using a 13-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of four of the E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of nine of the E2-induced genes set forth in Table 3. In some embodiments, the ER pathway activity score is calculated using a 13-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of five of the E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of eight of the E2-induced genes set forth in Table 3. In some embodiments, the ER pathway activity score is calculated using a 13-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of six of the E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of seven of the E2-induced genes set forth in Table 3.

[0258] In some embodiments, the ER pathway activity score is calculated using a 14-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of 3 E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of 11 E2-induced genes set forth in Table 3. In some embodiments, the ER pathway activity score is calculated using a 14-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of 4 E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of 10 E2-induced genes set forth in Table 3. In some embodiments, the ER pathway activity score is calculated using a 14-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of 5 E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of 9 E2-induced genes set forth in Table 3. In some embodiments, the ER pathway activity score is calculated using a 14-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of 6 E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of the 8 E2-induced genes set forth in Table 3. In some embodiments, the ER pathway activity score is calculated using a 14-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of the 6 E2-repressed genes set forth in

Table 4, from an E2-induced score, determined from the average z-scored expression of the 8 E2-induced genes set forth in Table 1. In some embodiments, the ER pathway activity score is calculated using a 14-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of 7 E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of 7 E2-induced genes set forth in Table 3.

[0259] In some embodiments, the ER pathway activity score is calculated using a 15-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of 3 of the E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of 12 of the E2-induced genes set forth in Table 3. In some embodiments, the ER pathway activity score is calculated using a 15-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of 4 of the E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of 11 of the E2-induced genes set forth in Table 3. In some embodiments, the ER pathway activity score is calculated using a 15-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of 5 of the E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of 10 of the E2-induced genes set forth in Table 3. In some embodiments, the ER pathway activity score is calculated using a 15-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of 6 of the E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of 9 of the E2-induced genes set forth in Table 3. In some embodiments, the ER pathway activity score is calculated using a 15-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of 7 of the E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of 8 of the E2-induced genes set forth in Table 3.

[0260] In some embodiments, the ER pathway activity score is calculated using a 16-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of 3 of the E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of 13 of the E2-induced genes set forth in Table 3. In some

embodiments, the ER pathway activity score is calculated using a 16-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of 4 of the E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of 12 of the E2-induced genes set forth in Table 3. In some embodiments, the ER pathway activity score is calculated using a 16-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of 5 of the E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of 11 of the E2-induced genes set forth in Table 3. In some embodiments, the ER pathway activity score is calculated using a 16-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of 6 of the E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of 10 of the E2-induced genes set forth in Table 3. In some embodiments, the ER pathway activity score is calculated using a 16-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of 7 of the E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of 9 of the E2-induced genes set forth in Table 3. In some embodiments, the ER pathway activity score is calculated using a 16-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of 8 of the E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of 8 of the E2-induced genes set forth in Table 3.

[0261] In some embodiments, the ER pathway activity score is calculated using a 17-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of 3 of the E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of 14 of the E2-induced genes set forth in Table 3. In some embodiments, the ER pathway activity score is calculated using a 17-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of 4 of the E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of 13 of the E2-induced genes set forth in Table 3. In some embodiments, the ER pathway activity score is calculated using a 17-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of 5 of the E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression

of 12 of the E2-induced genes set forth in Table 3. In some embodiments, the ER pathway activity score is calculated using a 17-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of 6 of the E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of 11 of the E2-induced genes set forth in Table 3. In some embodiments, the ER pathway activity score is calculated using a 17-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of 7 of the E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of 10 of the E2-induced genes set forth in Table 3. In some embodiments, the ER pathway activity score is calculated using a 17-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of 8 of the E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of 9 of the E2-induced genes set forth in Table 3.

[0262] In some embodiments, the ER pathway activity score is calculated using an 18-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of 3 of the E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of 15 of the E2-induced genes set forth in Table 3. In some embodiments, the ER pathway activity score is calculated using an 18-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of 4 of the E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of 14 of the E2-induced genes set forth in Table 3. In some embodiments, the ER pathway activity score is calculated using an 18-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of 5 of the E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of 13 of the E2-induced genes set forth in Table 3. In some embodiments, the ER pathway activity score is calculated using an 18-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of 6 of the E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of 12 of the E2-induced genes set forth in Table 3. In some embodiments, the ER pathway activity score is calculated using an 18-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of 7 of the E2-repressed genes set forth in Table 6, from an E2-

induced score, determined from the average z-scored expression of 11 of the E2-induced genes set forth in Table 3. In some embodiments, the ER pathway activity score is calculated using an 18-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of 8 of the E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of 10 of the E2-induced genes set forth in Table 3. In some embodiments, the ER pathway activity score is calculated using an 18-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of 9 of the E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of 9 of the E2-induced genes set forth in Table 3.

[0263] In some embodiments, the ER pathway activity score is calculated using a 19-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of 3 of the E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of 16 of the E2-induced genes set forth in Table 3. In some embodiments, the ER pathway activity score is calculated using a 19-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of 4 of the E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of 15 of the E2-induced genes set forth in Table 3. In some embodiments, the ER pathway activity score is calculated using a 19-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of 5 of the E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of 14 of the E2-induced genes set forth in Table 3. In some embodiments, the ER pathway activity score is calculated using a 19-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of 6 of the E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of 13 of the E2-induced genes set forth in Table 3. In some embodiments, the ER pathway activity score is calculated using a 19-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of 7 of the E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of 12 of the E2-induced genes set forth in Table 3. In some embodiments, the ER pathway activity score is calculated using a 19-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of 8 of the E2-repressed genes set forth in Table 6, from an E2-induced score,

determined from the average z-scored expression of 11 of the E2-induced genes set forth in Table 3. In some embodiments, the ER pathway activity score is calculated using a 19-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of the 8 E2-repressed genes set forth in Table 5, from an E2-induced score, determined from the average z-scored expression of the 11 E2-induced genes set forth in Table 2. In some embodiments, the ER pathway activity score is calculated using a 19-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of 9 of the E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of 10 of the E2-induced genes set forth in Table 3.

[0264] In some embodiments, the ER pathway activity score is calculated using a 20-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of 3 of the E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of 17 of the E2-induced genes set forth in Table 3. In some embodiments, the ER pathway activity score is calculated using a 20-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of 4 of the E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of 16 of the E2-induced genes set forth in Table 3. In some embodiments, the ER pathway activity score is calculated using a 20-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of 5 of the E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of 15 of the E2-induced genes set forth in Table 3. In some embodiments, the ER pathway activity score is calculated using a 20-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of 6 of the E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of 14 of the E2-induced genes set forth in Table 3. In some embodiments, the ER pathway activity score is calculated using a 20-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of 7 of the E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of 13 of the E2-induced genes set forth in Table 3. In some embodiments, the ER pathway activity score is calculated using a 20-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of 8 of the E2-repressed genes set forth in Table 6, from an E2-induced score,

determined from the average z-scored expression of 12 of the E2-induced genes set forth in Table 3. In some embodiments, the ER pathway activity score is calculated using a 20-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of 9 of the E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of 11 of the E2-induced genes set forth in Table 3. In some embodiments, the ER pathway activity score is calculated using a 20-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of 10 of the E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of 10 of the E2-induced genes set forth in Table 3.

[0265] In some embodiments, the ER pathway activity score is calculated using a 21-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of 3 of the E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of 18 of the E2-induced genes set forth in Table 3. In some embodiments, the ER pathway activity score is calculated using a 21-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of 4 of the E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of 17 of the E2-induced genes set forth in Table 3. In some embodiments, the ER pathway activity score is calculated using a 21-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of 5 of the E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of 16 of the E2-induced genes set forth in Table 3. In some embodiments, the ER pathway activity score is calculated using a 21-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of 6 of the E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of 15 of the E2-induced genes set forth in Table 3. In some embodiments, the ER pathway activity score is calculated using a 21-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of 7 of the E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of 14 of the E2-induced genes set forth in Table 3. In some embodiments, the ER pathway activity score is calculated using a 21-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of 8 of the E2-repressed genes set forth in Table 6, from an E2-induced score,

determined from the average z-scored expression of 13 of the E2-induced genes set forth in Table 3. In some embodiments, the ER pathway activity score is calculated using a 21-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of 9 of the E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of 12 of the E2-induced genes set forth in Table 3. In some embodiments, the ER pathway activity score is calculated using a 21-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of 10 of the E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of 11 of the E2-induced genes set forth in Table 3.

[0266] In some embodiments, the ER pathway activity score is calculated using a 22-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of 3 of the E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of 19 of the E2-induced genes set forth in Table 3. In some embodiments, the ER pathway activity score is calculated using a 22-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of 4 of the E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of 18 of the E2-induced genes set forth in Table 3. In some embodiments, the ER pathway activity score is calculated using a 22-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of 5 of the E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of 17 of the E2-induced genes set forth in Table 3. In some embodiments, the ER pathway activity score is calculated using a 22-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of 6 of the E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of 16 of the E2-induced genes set forth in Table 3. In some embodiments, the ER pathway activity score is calculated using a 22-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of 7 of the E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of 15 of the E2-induced genes set forth in Table 3. In some embodiments, the ER pathway activity score is calculated using a 22-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of 8 of the E2-repressed genes set forth in Table 6, from an E2-induced score,

determined from the average z-scored expression of 14 of the E2-induced genes set forth in Table 3. In some embodiments, the ER pathway activity score is calculated using a 22-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of 9 of the E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of 13 of the E2-induced genes set forth in Table 3. In some embodiments, the ER pathway activity score is calculated using a 22-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of 10 of the E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of 12 of the E2-induced genes set forth in Table 3. In some embodiments, the ER pathway activity score is calculated using a 22-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of 11 of the E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of 11 of the E2-induced genes set forth in Table 3.

[0267] In some embodiments, the ER pathway activity score is calculated using a 23-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of 3 of the E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of 20 of the E2-induced genes set forth in Table 3. In some embodiments, the ER pathway activity score is calculated using a 23-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of 4 of the E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of 19 of the E2-induced genes set forth in Table 3. In some embodiments, the ER pathway activity score is calculated using a 23-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of 5 of the E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of 18 of the E2-induced genes set forth in Table 3. In some embodiments, the ER pathway activity score is calculated using a 23-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of 6 of the E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of 17 of the E2-induced genes set forth in Table 3. In some embodiments, the ER pathway activity score is calculated using a 23-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of 7 of the E2-repressed genes set forth in Table 6, from an E2-

induced score, determined from the average z-scored expression of 16 of the E2-induced genes set forth in Table 3. In some embodiments, the ER pathway activity score is calculated using a 23-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of 8 of the E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of 15 of the E2-induced genes set forth in Table 3. In some embodiments, the ER pathway activity score is calculated using a 23-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of 9 of the E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of 14 of the E2-induced genes set forth in Table 3. In some embodiments, the ER pathway activity score is calculated using a 23-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of 10 of the E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of 13 of the E2-induced genes set forth in Table 3. In some embodiments, the ER pathway activity score is calculated using a 23-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of 11 of the E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of 12 of the E2-induced genes set forth in Table 3.

[0268] In some embodiments, the ER pathway activity score is calculated using a 24-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of 3 of the E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of 21 of the E2-induced genes set forth in Table 3. In some embodiments, the ER pathway activity score is calculated using a 24-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of 4 of the E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of 20 of the E2-induced genes set forth in Table 3. In some embodiments, the ER pathway activity score is calculated using a 24-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of 5 of the E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of 19 of the E2-induced genes set forth in Table 3. In some embodiments, the ER pathway activity score is calculated using a 24-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of 6 of the E2-repressed genes set forth in

Table 6, from an E2-induced score, determined from the average z-scored expression of 18 of the E2-induced genes set forth in Table 3. In some embodiments, the ER pathway activity score is calculated using a 24-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of 7 of the E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of 17 of the E2-induced genes set forth in Table 3. In some embodiments, the ER pathway activity score is calculated using a 24-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of 8 of the E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of 16 of the E2-induced genes set forth in Table 3. In some embodiments, the ER pathway activity score is calculated using a 24-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of 9 of the E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of 15 of the E2-induced genes set forth in Table 3. In some embodiments, the ER pathway activity score is calculated using a 24-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of 10 of the E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of 14 of the E2-induced genes set forth in Table 3. In some embodiments, the ER pathway activity score is calculated using a 24-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of 11 of the E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of 13 of the E2-induced genes set forth in Table 3. In some embodiments, the ER pathway activity score is calculated using a 24-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of 12 of the E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of 12 of the E2-induced genes set forth in Table 3.

[0269] In some embodiments, the ER pathway activity score is calculated using a 25-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of 3 of the E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of 22 of the E2-induced genes set forth in Table 3. In some embodiments, the ER pathway activity score is calculated using a 25-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of 4 of the

E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of 21 of the E2-induced genes set forth in Table 3. In some embodiments, the ER pathway activity score is calculated using a 25-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of 5 of the E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of 20 of the E2-induced genes set forth in Table 3. In some embodiments, the ER pathway activity score is calculated using a 25-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of 6 of the E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of 19 of the E2-induced genes set forth in Table 3. In some embodiments, the ER pathway activity score is calculated using a 25-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of 7 of the E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of 18 of the E2-induced genes set forth in Table 3. In some embodiments, the ER pathway activity score is calculated using a 25-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of 8 of the E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of 17 of the E2-induced genes set forth in Table 3. In some embodiments, the ER pathway activity score is calculated using a 25-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of 9 of the E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of 16 of the E2-induced genes set forth in Table 3. In some embodiments, the ER pathway activity score is calculated using a 25-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of 10 of the E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of 15 of the E2-induced genes set forth in Table 3. In some embodiments, the ER pathway activity score is calculated using a 25-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of 11 of the E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of 14 of the E2-induced genes set forth in Table 3. In some embodiments, the ER pathway activity score is calculated using a 25-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of 12 of the E2-repressed genes set forth

in Table 6, from an E2-induced score, determined from the average z-scored expression of 13 of the E2-induced genes set forth in Table 3.

[0270] In some embodiments, the ER pathway activity score is calculated using a 26-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of 3 of the E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of 23 of the E2-induced genes set forth in Table 3. In some embodiments, the ER pathway activity score is calculated using a 26-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of 4 of the E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of 22 of the E2-induced genes set forth in Table 3. In some embodiments, the ER pathway activity score is calculated using a 26-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of 5 of the E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of 21 of the E2-induced genes set forth in Table 3. In some embodiments, the ER pathway activity score is calculated using a 26-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of 6 of the E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of 20 of the E2-induced genes set forth in Table 3. In some embodiments, the ER pathway activity score is calculated using a 26-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of 7 of the E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of 19 of the E2-induced genes set forth in Table 3. In some embodiments, the ER pathway activity score is calculated using a 26-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of 8 of the E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of 18 of the E2-induced genes set forth in Table 3. In some embodiments, the ER pathway activity score is calculated using a 26-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of 9 of the E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of 17 of the E2-induced genes set forth in Table 3. In some embodiments, the ER pathway activity score is calculated using a 26-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of 10 of the

E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of 16 of the E2-induced genes set forth in Table 3. In some embodiments, the ER pathway activity score is calculated using a 26-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of 11 of the E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of 15 of the E2-induced genes set forth in Table 3. In some embodiments, the ER pathway activity score is calculated using a 26-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of 12 of the E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of 14 of the E2-induced genes set forth in Table 3. In some embodiments, the ER pathway activity score is calculated using a 26-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of 13 of the E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of 13 of the E2-induced genes set forth in Table 3.

[0271] In some embodiments, the ER pathway activity score is calculated using a 27-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of 4 of the E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of 23 of the E2-induced genes set forth in Table 3.

[0272] In some embodiments, the ER pathway activity score is calculated using a 28-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of 5 of the E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of 23 of the E2-induced genes set forth in Table 3.

[0273] In some embodiments, the ER pathway activity score is calculated using a 29-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of 6 of the E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of 23 of the E2-induced genes set forth in Table 3.

[0274] In some embodiments, the ER pathway activity score is calculated using a 30-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of 7 of the E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of 23 of the E2-induced genes set forth in Table 3.

[0275] In some embodiments, the ER pathway activity score is calculated using a 31-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of 8 of the E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of 23 of the E2-induced genes set forth in Table 3.

[0276] In some embodiments, the ER pathway activity score is calculated using a 32-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of 9 of the E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of 23 of the E2-induced genes set forth in Table 3.

[0277] In some embodiments, the ER pathway activity score is calculated using a 33-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of 10 of the E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of 23 of the E2-induced genes set forth in Table 3.

[0278] In some embodiments, the ER pathway activity score is calculated using a 34-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of 11 of the E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of 23 of the E2-induced genes set forth in Table 3.

[0279] In some embodiments, the ER pathway activity score is calculated using a 35-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of 12 of the E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of 23 of the E2-induced genes set forth in Table 3.

[0280] In some embodiments, the ER pathway activity score is calculated using a 36-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of 13 of the E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of 23 of the E2-induced genes set forth in Table 3.

[0281] In some embodiments, the ER pathway activity score is calculated using a 37-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of 14 of the E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of 23 of the E2-induced genes set forth in Table 3.

[0282] In some embodiments, the ER pathway activity score is calculated using a 38-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of 15 of the E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of 23 of the E2-induced genes set forth in Table 3.

[0283] In some embodiments, the ER pathway activity score is calculated using a 39-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of 16 of the E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of 23 of the E2-induced genes set forth in Table 3.

[0284] In some embodiments, the ER pathway activity score is calculated using a 40-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of 17 of the E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of 23 of the E2-induced genes set forth in Table 3.

[0285] In some embodiments, the ER pathway activity score is calculated using a 41-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of the 18 E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of the 23 E2-induced genes set forth in Table 3.

[0286] In some embodiments, the ER pathway activity score is calculated using a 14-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of the six E2-repressed genes set forth in Table 4, from an E2-induced score, determined from the average z-scored expression of the eight E2-induced genes set forth in Table 1. In some embodiments, the ER pathway activity score is calculated using a 19-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of the eight E2-repressed genes set forth in Table 5, from an E2-induced score, determined from the average z-scored expression of the 11 E2-induced genes set forth in Table 2. In some embodiments, the ER pathway activity score is calculated using a 41-gene signature by subtracting an E2-repressed score, determined from the average z-scored expression of the 18 E2-repressed genes set forth in Table 6, from an E2-induced score, determined from the average z-scored expression of the 23 E2-induced genes set forth in Table 3. The ER pathway activity score can serve as a surrogate biomarker of ER pathway activity in a tumor in an individual.

[0287] In any of the methods or assays provided herein in which the expression level of a predetermined set of genes is determined in a sample (e.g., a tissue sample, e.g., a tumor tissue sample, e.g., a formalin-fixed paraffin-embedded (FFPE), a fresh frozen (FF), an archival, a fresh, or a frozen tumor tissue sample) from an individual, it is to be understood that the expression level of the predetermined set of genes may be normalized, e.g., to a reference gene, e.g., a housekeeping gene. In some instances, the reference gene is SDHA, GUSB, PPIA, and/or UBC. In some instances, an expression level for more than one gene of interest (e.g., the predetermined set of genes listed in any one of Tables 1-6) may be determined by aggregation methods known to one skilled in the art and also disclosed herein, including, for example, by calculating the median or mean of all the expression levels of the genes of interest. Before aggregation, the expression level of each gene of interest may be normalized by using statistical methods known to one skilled in the art and also disclosed herein, including, for example, normalized to the expression level of one or more housekeeping genes, to the median or mean expression level value for each gene as measured across a reference population, normalized to a total library size, or normalized to the median or mean expression level value across all genes measured. In some instances, before aggregation across multiple genes of interest, the normalized expression level of each gene of interest may be standardized by using statistical methods known to one skilled in the art and also disclosed herein, including, for example, by calculating the Z-score of the normalized expression level of each gene of interest or by, for example, scaling the normalized expression level of each gene to the respective scaling of those expression levels in a reference population.

[0288] The sample from the individual may be a FFPE sample, a FF sample, a fresh sample, frozen sample, or an archival sample. In some instances, the sample is a FFPE sample. In some instances, the sample is a FF sample. The expression level of the predetermined set of genes can be determined quantitatively based on any suitable criterion known in the art, including, but not limited to, the measurement of mRNA, DNA, cDNA, and/or gene copy number levels in an individual.

[0289] Table 1: Eight E2-induced genes of the 14-gene signature

E2- Induced
AMZ1

C5AR2
CELSR2
FKBP4
GREB1
OLFM1
SLC9A3R1
TFF1

[0290] Table 2: Eleven E2-induced genes of the 19-gene signature

E2-Induced
AMZ1
AREG
C5AR2
CELSR2
FKBP4
FMN1
GREB1
OLFM1
RBM24
SLC9A3R1
TFF1

[0291] Table 3: Twenty-three E2-induced genes of the 41 gene signature

E2-Induced
AGR3
AMZ1
AREG
C5AR2
CELSR2
CT62
FKBP4
FMN1
GREB1
IGFBP4
NOS1AP
NXPH3
OLFM1
PGR
PPM1J
RAPGEFL1
RBM24

RERG
RET
SGK3
SLC9A3R1
TFF1
ZNF703

[0292] Table 4: Six E2-repressed genes of the 14-gene signature

E2-repressed
BCAS1
CCNG2
IL1R1
PNPLA7
SEMA3E
STON1

[0293] Table 5: Eight E2-repressed genes of the 19-gene signature

E2-repressed
BCAS1
CCNG2
IL1R1
NBEA
PNPLA7
SEMA3E
STON1
TP53INP1

[0294] Table 6: Eighteen E2-repressed genes of the 41-gene signature

E2-repressed
BAMBI
BCAS1
CCNG2
DDIT4
EGLN3
FAM171B
GRM4
IL1R1

LIPH
NBEA
PNPLA7
PSCA
SEMA3E
SSPO
STON1
TGFB3
TP53INP1
TP53INP2

[0295] In some instances of any of the preceding methods and assays, the expression level of a gene may be a nucleic acid expression level (e.g., an RNA expression level (e.g., an mRNA expression level) or a DNA expression level). Any suitable method of determining a nucleic acid expression level may be used, for example, as described in Section VII, below. In some instances, the nucleic acid expression level is determined using RNA-seq (e.g., using an RNA ACCESS® protocol or TRUSEQ® RIBO-ZERO® protocol (ILLUMINA®)), RT-qPCR, qPCR, multiplex qPCR or RT-qPCR, microarray analysis, SAGE, MassARRAY techniques, or a combination thereof.

[0296] Methods for the evaluation of mRNAs in cells are well known and include, for example, RNA sequencing (RNA-seq), whole genome sequencing (WGS), serial analysis of gene expression (SAGE), and various nucleic acid amplification assays (such as RT-PCR (e.g., qRT-PCR) using complementary primers specific for the predetermined set of genes. In addition, such methods can include one or more steps that allow one to determine the levels of target mRNA in a biological sample (e.g., by simultaneously examining the levels of a comparative control mRNA sequence of a “housekeeping” gene such as an actin family member). Optionally, the sequence of the amplified target cDNA can be determined. Optional methods include protocols which examine or detect mRNAs, such as target mRNAs, in a tissue or cell sample by microarray technologies. Using nucleic acid microarrays, test and control mRNA samples from test and control tissue samples are reverse transcribed and labeled to generate cDNA probes. The probes are then hybridized to an array of nucleic acids immobilized on a solid support. The array is configured such that the sequence and position of each member of the array is known. For example, a selection of genes whose expression correlates with increased or reduced clinical benefit of treatment comprising an immunotherapy and a suppressive stromal antagonist may be

arrayed on a solid support. Hybridization of a labeled probe with a particular array member indicates that the sample from which the probe was derived expresses that gene.

[0297] In some instances of any of the methods and assays, the sample (e.g., a tissue sample, e.g., a tumor tissue sample, e.g., a FFPE, a FF, an archival, a fresh, or a frozen tumor tissue sample) is obtained from the individual prior to (e.g., minutes, hours, days, weeks, months, or years prior to) administration of an endocrine therapy as described herein. In other words, the sample may be a baseline sample. In some instances of any of the preceding methods, the sample is obtained from the individual following (e.g., minutes, hours, or days following) administration of an endocrine therapy. In some instances, the sample from the individual is obtained within thirty hours following administration of an endocrine therapy. In some instances, multiple samples are obtained from the same individual at different time points (e.g., prior to and following administration of an endocrine therapy).

[0298] In any of the preceding instances, the individual may have an HR+ breast cancer. In some instances, the HR+ cancer may be an ER+ breast cancer. In some instances, the individual may have an ER+ breast cancer selected from, for example, a luminal A breast cancer or a luminal B breast cancer. In some instances, the breast cancer may be an advanced or a metastatic breast cancer.

[0299] In some instances of any of the preceding methods or assays involving determining an ER pathway activity score and/or E2-induced score from a sample (e.g., a tissue sample, e.g., a tumor tissue sample, e.g., a formalin-fixed paraffin-embedded (FFPE), a fresh frozen (FF), an archival, a fresh, or a frozen tumor tissue sample) from an individual, the individual has been previously treated with an endocrine therapy as described herein. In other instances, the individual has not been previously treated with an endocrine therapy.

[0300] In some instances, the methods further comprise generating a report, e.g., an electronic, web-based, or paper report, to the individual or to another person or entity, a caregiver, a physician, an oncologist, a hospital, clinic, third-party payor, insurance company, a pharmaceutical or biotechnology company, or government office. In some instances, the report comprises output from the method which comprises evaluation of the ER pathway activity and/or E2-induced score.

IV. ANTI-CANCER AGENTS

[0301] Provided herein are methods for treating an individual having a breast cancer (e.g., an HR+ breast cancer (e.g., an ER+ breast cancer (e.g., luminal A cancer breast or luminal B breast cancer)) and/or a metastatic or a locally advanced breast cancer). Any of the preceding methods may be based on the determination of an E2-induced score and/or an ER pathway activity score from a sample (e.g., a tissue sample, e.g., a tumor tissue sample, e.g., a FFPE, a FF, an archival, a fresh, or a frozen tumor tissue sample) from the individual.

[0302] In some instances of any of the preceding methods, the anti-cancer therapeutic agents utilized in the methods described herein can be administered, for example, orally, intramuscularly, subcutaneously, intravenously, intradermally, percutaneously, intraarterially, intraperitoneally, intralesionally, intracranially, intraarticularly, intraprostatically, intrapleurally, intratracheally, intrathecally, intranasally, intravaginally, intrarectally, topically, intratumorally, peritoneally, subconjunctivally, intravesicularly, mucosally, intrapericardially, intraumbilically, intraocularly, intraorbitally, intravitreally (e.g., by intravitreal injection), by eye drop, topically, transdermally, parenterally, by inhalation, by injection, by implantation, by infusion, by continuous infusion, by localized perfusion bathing target cells directly, by catheter, by lavage, in creams, or in lipid compositions. In some instances of any of the preceding methods, the anti-cancer therapeutic agents utilized in the methods described herein can be administered orally. For example, in some instances, an endocrine therapy as described herein may be administered orally or intramuscularly. In some instances, a SERM may be administered orally or intramuscularly. In some instances, a SERD may be administered orally or intramuscularly. In some instances of any of the preceding methods, the anti-cancer therapeutic agents utilized in the methods described herein can be administered intramuscularly. For example, in some instances, an endocrine therapy as described herein may be administered orally. In some instances, a SERM may be administered orally. In some instances, a SERD may be administered orally. The anti-cancer therapeutic agents utilized in the methods described herein can also be administered systemically or locally. The method of administration can vary depending on various factors (e.g., the anti-cancer therapeutic agents being administered and the severity of the condition, disease, or disorder (e.g., breast cancer) being treated).

[0303] Anti-cancer agents, including endocrine agents as described herein (and any additional therapeutic agent) may be formulated, dosed, and administered in a fashion consistent with good medical practice. Factors for consideration in this context include the particular disorder being treated, the particular mammal being treated, the clinical condition of the individual patient, the cause of the disorder, the site of delivery of the agent, the method of administration, the scheduling of administration, and other factors known to medical practitioners. The anti-cancer agent need not be, but is optionally formulated with and/or administered concurrently with one or more agents currently used to prevent or treat the disorder in question. The effective amount of such other agents depends on the amount of the anti-cancer present in the formulation, the type of disorder or treatment, and other factors discussed above. These are generally used in the same dosages and with administration routes as described herein, or about from 1 to 99% of the dosages described herein, or in any dosage and by any route that is empirically/clinically determined to be appropriate.

[0304] For the prevention or treatment of a breast cancer e.g., an HR+ breast cancer (e.g., an ER+ breast cancer (e.g., luminal A breast cancer or luminal B breast cancer)), DCIS, and/or a metastatic or a locally advanced breast cancer), the appropriate dosage of an anti-cancer agent (e.g., an endocrine therapy) described herein (when used alone or in combination with one or more other additional therapeutic agents) will depend on the type of disease to be treated, the severity and course of the disease, whether the anti-cancer agent is administered for preventive or therapeutic purposes, previous therapy, the individual's clinical history and response to the anti-cancer agent, and the discretion of the attending physician. The anti-cancer agent is suitably administered to the individual at one time or over a series of treatments. For repeated administrations over several days or longer, depending on the condition, the treatment would generally be sustained until a desired suppression of disease symptoms occurs. An initial higher loading dose, followed by one or more lower doses may be administered. However, other dosage regimens may be useful. The progress of this therapy is easily monitored by conventional techniques and assays. In some instances, an endocrine therapy as provided herein is dosed at an amount of about 1 mg/kg to about 100 mg/kg. In another instance, an endocrine therapy provided herein is dosed at an amount of about 100 mg/kg to about 1000 mg/kg. In still another instance, an endocrine therapy described herein is dosed at an amount of about 1000 mg/kg to about 2000 mg/kg. Certain endocrine therapies described herein can be administered in cyclic administration

routines as understood in the art - for example for 20, 21, 22, 23, 24, 25, 26, 27, or 28, or more continual days followed by a rest period of 1, 2, 3, 4, 5, 6, 7, or more days. In yet another instance, an endocrine therapy described herein is administered in accordance with a package insert.

A. Endocrine Therapies

[0305] In some instances of any of the preceding methods, an endocrine therapy may be administered to the individual.

[0306] Exemplary endocrine therapies for use in the methods described herein include compounds that modulate the activity of the estrogen receptor. In certain instances, the compounds herein include Selective Estrogen Receptor Modulators (SERMs), Selective Estrogen Receptor Degradors (SERDs), aromatase inhibitors (AIs), or combinations thereof.

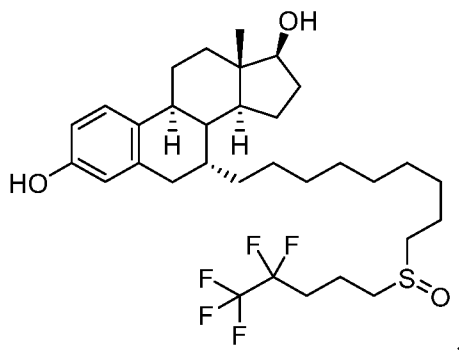
[0307] In some instances, the endocrine therapy comprises an aromatase inhibitor. The aromatase inhibitor can be an agent known in the art. For example, in one instance, the aromatase inhibitor is letrozole, anastrozole, exemestane, or testolactone, or a pharmaceutically acceptable salt thereof, or a combination thereof.

[0308] In another instance, the endocrine therapy comprises a SERM.

[0309] The endocrine therapy can comprise a compound that can be a tetra-substituted olefin compound known to have antagonist activity against ER. For example, the endocrine therapy can be tamoxifen, including derivatives thereof such as hydroxytamoxifen. In one instance, the endocrine therapy comprises nafoxidine. In another instance, the endocrine therapy comprises clomifene, toremifene, raloxifene, anordrin, bazedoxifene, broparestrol, cyclofenil, lasofoxifene, ormeloxifene, acolbifene, elacestrant, brilanestrant, clomifenoxide, droloxifene, etacstil, or ospemifene, or a pharmaceutically acceptable salt thereof, or a combination thereof. In another instance, the endocrine therapy comprises G1T48, or a pharmaceutically acceptable salt thereof.

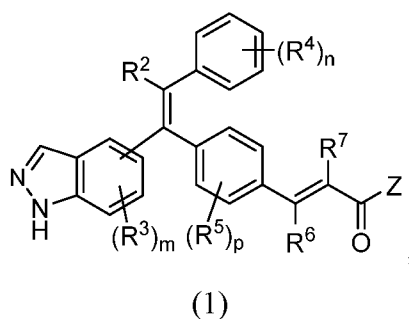
[0310] In still another instance, the endocrine therapy comprises a SERD.

[0311] In one instance, the endocrine therapy comprises fulvestrant.



or a pharmaceutically acceptable salt thereof.

[0312] In one aspect, the endocrine therapy comprises a compound has formula (1):



wherein;

Z is -OH or -OR¹⁰;

R² is C₁₋₄ alkyl, C₁₋₄ fluoroalkyl, C₁₋₄ deuterioalkyl, C₃₋₆ cycloalkyl, or C₁₋₄ alkylene-W;

W is hydroxy, halogen, CN, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ alkoxy, C₁₋₄ haloalkoxy, or C₃₋₆ cycloalkyl;

each R³ is independently halogen, C₁₋₄ alkyl, or C₁₋₄ fluoroalkyl;

each R⁴ is independently halogen, -CN, -OR⁹, -S(O)₂R¹⁰, C₁₋₄ alkyl, C₁₋₄ fluoroalkyl, or C₁₋₄ heteroalkyl;

each R⁵ is independently halogen, -CN, -OR⁹, -S(O)₂R¹⁰, C₁₋₄ alkyl, C₁₋₄ fluoroalkyl, or C₁₋₄ heteroalkyl;

R⁶ is H, C₁₋₄ alkyl, or halogen;

R⁷ is H, C₁₋₄ alkyl, or halogen;

R⁹ is H, C₁₋₆ alkyl, C₁₋₆ fluoroalkyl, or C₃₋₆ cycloalkyl;

R¹⁰ is C₁₋₆ alkyl;

m is 0, 1, or 2;

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

p is 0, 1, or 2.

[0313] In another instance of the compound of formula (1), Z is -OH or -OR¹⁰; R² is C₁₋₄ alkyl, C₁₋₄ fluoroalkyl, C₁₋₄ deuterioalkyl, C₃₋₆ cycloalkyl, or C₁₋₄ alkylene-W, where W is hydroxy, halogen, CN, or C₁₋₄ alkyl; each R³ is independently halogen, C₁₋₄ alkyl, or C₁₋₄ fluoroalkyl; each R⁴ is independently halogen, -CN, -OR⁹, -S(O)₂R¹⁰, C₁₋₄ alkyl, C₁₋₄ fluoroalkyl, or C₁₋₄ heteroalkyl; each R⁵ is independently halogen, -CN, -OR⁹, -S(O)₂R¹⁰, C₁₋₄ alkyl, C₁₋₄ fluoroalkyl, or C₁₋₄ heteroalkyl; R⁶ is H, C₁₋₄ alkyl, or halogen; R⁷ is H, C₁₋₄ alkyl, or halogen; R⁹ is H, C₁₋₆ alkyl, C₁₋₆ fluoroalkyl, or C₃₋₆ cycloalkyl; R¹⁰ is C₁₋₆ alkyl; m is 0, 1, or 2; n is 0, 1, 2, 3, or 4; and p is 0, 1, or 2.

[0314] In another instance of the compound of formula (1), Z is -OH. In another instance of the compound of formula (1), Z is -OR¹⁰. In another instance of the compound of formula (1), Z is -OH, -OCH₃, or -OCH₂CH₃.

[0315] In another instance of the compound of formula (1), R⁶ is H, -CH₃, F, or Cl. In another instance of the compound of formula (1), R⁶ is H. In another instance of the compound of formula (1), R⁷ is H, -CH₃, F, or Cl. In another instance of the compound of formula (1), R⁷ is H.

[0316] In another instance of the compound of formula (1), R³ is independently halogen, C₁₋₄ alkyl, or C₁₋₄ fluoroalkyl. In another instance of the compound of formula (1), each R³ is independently F, Cl, or -CH₃. In another instance of the compound of formula (1), each R⁴ is independently halogen, -CN, -OH, -OR⁹, -S(O)₂R¹⁰, C₁₋₄ alkyl, C₁₋₄ fluoroalkyl, or C₁₋₄ heteroalkyl. In another instance of the compound of formula (1), each R⁴ is independently halogen, -CN, -OH, -S(O)₂CH₃, -S(O)₂CH₂CH₃, -CH₃, -CH₂CH₃, -CF₃, -CH₂OH, -OCF₃, -OCH₃, or -OCH₂CH₃. In another instance of the compound of formula (1), each R⁴ is independently F, Cl, -CN, -OH, -CH₃, -CH₂CH₃, -CF₃, -CH₂OH, -OCF₃, -OCH₃, or -OCH₂CH₃. In another instance of the compound of formula (1), each R⁴ is independently F or Cl. In another instance of the compound of formula (1), each R⁵ is independently halogen, C₁₋₄ alkyl, or C₁₋₄ fluoroalkyl. In another instance of the compound of formula (1), each R⁵ is independently F, Cl, or -CH₃.

[0317] In another instance of the compound of formula (1), m is 0 or 1. In another instance of the compound of formula (1), m is 0. In another instance of the compound of formula (1), m is 1. In another instance of the compound of formula (1), n is 0, 1, or 2. In another instance of the compound of formula (1), n is 0. In another instance of the compound of formula (1), n is 1. In

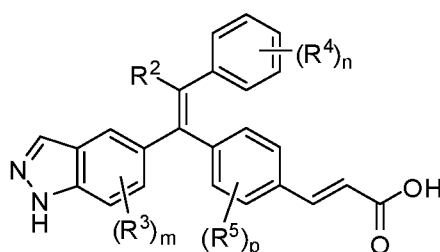
another instance of the compound of formula (1), n is 2. In another instance of the compound of formula (1), p is 0 or 1. In another instance of the compound of formula (1), p is 0. In another instance of the compound of formula (1), p is 1.

[0318] In another instance of the compound of formula (1), Z is -OH; R⁶ is H, -CH₃, F, or Cl; R⁷ is H, -CH₃, F, or Cl; each R³ is independently halogen, C₁₋₄ alkyl, or C₁₋₄ fluoroalkyl; each R⁴ is independently halogen, -CN, -OR⁹, -S(O)₂R¹⁰, C₁₋₄ alkyl, C₁₋₄ fluoroalkyl, or C₁₋₄ heteroalkyl; each R⁵ is independently halogen, C₁₋₄alkyl, or C₁₋₄fluoroalkyl; m is 0 or 1; n is 0, 1, or 2; and p is 0 or 1.

[0319] In another instance of the compound of formula (1), R² is C₁₋₄ alkyl, C₁₋₄ fluoroalkyl, C₁₋₄ deuterioalkyl, C₃₋₆ cycloalkyl, or C₁₋₄ alkylene-W; W is hydroxy, halogen, CN, C₁₋₄ alkoxy, or C₃₋₆ cycloalkyl. In another instance of the compound of formula (1), R² is C₁₋₄ alkyl, C₁₋₄ fluoroalkyl, or C₁₋₄ deuterioalkyl. In another instance of the compound of formula (1), R² is C₁₋₄ alkyl. In another instance of the compound of formula (1), R² is -CH₃, -CH₂CH₃, -CH₂CH₂CH₃, -CH(CH₃)₂, -CH₂CH₂CH₂CH₃, -CH₂CH(CH₃)₂, -CH₂F, -CHF₂, -CF₃, -CH₂CF₃, -CD₃, -CH₂CD₃, -CD₂CD₃, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, -CH₂-W, or -CH₂CH₂-W; W is hydroxy, F, Cl, -CN, -OCH₃, -OCH₂CH₃, -OCH₂CH₂CH₃, -OCH(CH₃)₂, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl. In another instance of the compound of formula (1), W is hydroxy, F, Cl, -CN, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl. In another instance of the compound of formula (1), R² is -CH₃, -CH₂CH₃, -CH₂CH₂CH₃, -CH(CH₃)₂, -CH₂CH₂CH₂CH₃, -CH₂CH(CH₃)₂, -CH₂F, -CHF₂, -CF₃, -CH₂CF₃, -CD₃, -CH₂CD₃, -CD₂CD₃, -CH₂-W, or -CH₂CH₂-W. In another instance of the compound of formula (1), R² is -CH₃, -CH₂CH₃, -CH₂F, -CHF₂, -CF₃, -CH₂CF₃, -CD₃, -CD₂CD₃, -CH₂CD₃, or cyclopropyl.

[0320] In another instance of the compound of formula (1), Z is -OH; R⁶ is H; R⁷ is H; m is 0; n is 0, 1, or 2; and p is 0.

[0321] In another instance of the compound of formula (1), the compound of Formula (1) has the structure of Formula (1a), or a pharmaceutically acceptable salt, or N-oxide thereof:



Formula (1a).

[0322] In another aspect, the endocrine therapy comprises a compound set forth in U.S. Patent No. 8,299,112, for example in Table 1 therein, which is incorporated herein by reference in its entirety and for all purposes.

[0323] In another aspect, the endocrine therapy comprises a compound having the formula: (E)-Ethyl 3-(4-((E)-1-(1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenyl)acrylate; (E)-3-(4-((E)-1-(1H-Indazol-5-yl)-2-phenylbut-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-1-(1H-Benzo[d][1,2,3]triazol-5-yl)-2-phenylbut-1-en-1-yl)phenyl) acrylic acid; (E)-3-(4-((E)-2-(4-Fluorophenyl)-1-(1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-2-(4-Chlorophenyl)-1-(1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-1-(1H-Indazol-5-yl)-2-(3-methoxyphenyl)but-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-2-(3-(Hydroxymethyl)phenyl)-1-(1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-2-(4-(Hydroxymethyl)phenyl)-1-(1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-2-2-(2-(Hydroxymethyl)phenyl)-1-(1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-1-(1H-Indazol-5-yl)-2-(o-tolyl)but-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-1-(1H-Indazol-5-yl)-2-(m-tolyl)but-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-1-(1H-Indazol-5-yl)-2-(p-tolyl)but-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-1-(1H-Indazol-5-yl)-2-(2-methoxyphenyl)but-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-1-(1H-Indazol-5-yl)-2-(4-methoxyphenyl)but-1-en-1-yl)phenyl)acrylic acid; ((E)-3-(4-((E)-2-(2-Chlorophenyl)-1-(1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-2-(3-Chlorophenyl)-1-(1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-2-(2-Fluorophenyl)-1-(1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-2-(3-Fluorophenyl)-1-(1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-2-(2-Ethylphenyl)-1-(1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-1-(1H-Indazol-5-yl)-2-(2-(trifluoromethyl)phenyl)but-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-4-Chloro-1-(1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-2-(2-Fluorophenyl)-1-(1H-indazol-4-yl)but-1-en-1-

yl)phenyl)acrylic acid; (E)-3-(4-((E)-2-(2-Cyanophenyl)-1-(1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-2-(2,4-Difluorophenyl)-1-(1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-2-(2-Chloro-3-fluorophenyl)-1-(1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-2-Cyclopropyl-1-(1H-indazol-5-yl)-2-phenylvinyl)phenyl)acrylic acid; (E)-3-(4-((E)-2-(4-Fluoro-2-methylphenyl)-1-(1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-2-(2,6-Difluorophenyl)-1-(1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-2-(2,6-Dichlorophenyl)-1-(1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-4,4,4-Trideutero-1-(1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-2-(4-Fluoro-3-methylphenyl)-1-(1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-2-(5-Fluoro-2-methylphenyl)-1-(1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-2-(2,3-Difluorophenyl)-1-(1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-2-(2,5-Difluorophenyl)-1-(1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-2-(2-Chloro-5-fluorophenyl)-1-(1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-2-(2-Chloro-6-methylphenyl)-1-(1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-1-(7-Chloro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-1-(4-Methyl-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-1-(7-Methyl-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-1-(6-Methyl-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-1-(3-Methyl-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-1-(3-Chloro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-2-(4-Chloro-2-methylphenyl)-1-(1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-1-(1H-Indazol-5-yl)-2-phenylprop-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-1-(1H-Indazol-5-yl)-2-phenylpent-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-2-(3-Cyanophenyl)-1-(1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-2-(4-Cyanophenyl)-1-(1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-4-Hydroxy-1-(1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-1-(1H-Indazol-5-yl)-4-methoxy-2-phenylbut-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((Z)-1-(1H-Indazol-5-yl)-3-methoxy-2-phenylprop-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-1-(4-Fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-1-(1H-Indol-5-yl)-2-phenylbut-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-1-(6-Chloro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenyl)acrylic acid;

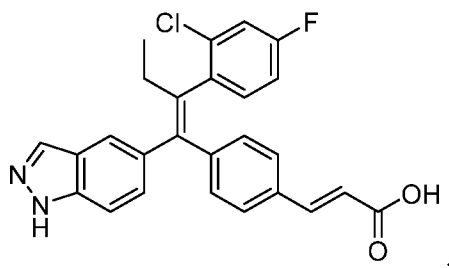
(E)-3-(4-((E)-1-(1H-Indazol-5-yl)-4-methyl-2-phenylpent-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-1-(1H-Benzo[d][1,2,3]triazol-5-yl)-2-(2-chloro-4-fluorophenyl)but-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-1-(4-Chloro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-2-Cyclopentyl-1-(1H-indazol-5-yl)-2-phenylvinyl)phenyl)acrylic acid; (E)-3-(4-((E)-2-Cyclohexyl-1-(1H-indazol-5-yl)-2-phenylvinyl)phenyl)acrylic acid; (E)-3-(4-((E)-1-(1H-Indazol-5-yl)-3-methyl-2-phenylbut-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-3-Cyclopropyl-1-(1H-indazol-5-yl)-2-phenylprop-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-2-(2-Chlorophenyl)-2-cyclopropyl-1-(1H-indazol-5-yl)vinyl)phenyl)acrylic acid; (E)-3-(4-((E)-1-(6-Fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-1-(1H-Benzo[d]imidazol-5-yl)-2-phenylbut-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-1-(1H-Indazol-5-yl)-2-phenylhex-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-3-Cyclopentyl-1-(1H-indazol-5-yl)-2-phenylprop-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-2-(2-Chloro-4-fluorophenyl)-1-(4-fluoro-1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-1-(7-Fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-1-(7-Fluoro-1H-indol-5-yl)-2-phenylbut-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-2-(2-Chloro-4-fluorophenyl)-1-(1H-indazol-5-yl)-4-methylpent-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((Z)-3,3-Difluoro-1-(1H-indazol-5-yl)-2-phenylprop-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-2-(2-Chloro-4-fluorophenyl)-1-(7-fluoro-1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-4-Fluoro-1-(1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-4-Chloro-2-(2-chloro-4-fluorophenyl)-1-(1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((Z)-3,3,3-Trifluoro-1-(1H-indazol-5-yl)-2-phenylprop-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-1-(4-Fluoro-1H-indazol-5-yl)-2-(4-fluoro-2-methylphenyl)but-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-2-(4-Chloro-2-methylphenyl)-1-(4-fluoro-1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-2-Cyclopropyl-1-(4-fluoro-1H-indazol-5-yl)-2-(4-fluoro-2-methylphenyl)vinyl)phenyl)acrylic acid; (E)-3-(4-((E)-2-(4-Chloro-2-methylphenyl)-2-cyclopropyl-1-(4-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid; (E)-3-(4-((E)-1-(4-Chloro-1H-indazol-5-yl)-2-(2-chloro-4-fluorophenyl)but-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((Z)-2-(2-Chloro-4-fluorophenyl)-3,3-difluoro-1-(1H-indazol-5-yl)prop-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-2-Cyclopropyl-1-(4-fluoro-1H-indazol-5-yl)-2-phenylvinyl)phenyl)acrylic acid; (E)-3-(4-((E)-4-Chloro-1-(4-fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenyl)acrylic acid;

(E)-3-(4-((E)-4-Chloro-2-(2-chloro-4-fluorophenyl)-1-(4-fluoro-1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-4-Fluoro-2-(4-fluorophenyl)-1-(1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-4-Fluoro-1-(4-fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-1-(1H-Indazol-5-yl)-5-methoxy-2-phenylpent-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-1-(1H-Indazol-5-yl)-6-methoxy-2-phenylhex-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-2-(2-Chloro-4-fluorophenyl)-1-(1H-indazol-5-yl)-3-methylbut-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-1-(1H-Indazol-5-yl)-2-(3-(trifluoromethoxy)phenyl)but-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-2-Cyclobutyl-1-(1H-indazol-5-yl)-2-phenylvinyl)phenyl)acrylic acid; (E)-3-(4-((E)-2-(2-Chloro-4-fluorophenyl)-2-cyclobutyl-1-(1H-indazol-5-yl)vinyl)phenyl)acrylic acid; (E)-3-(4-((E)-1-(3-Fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-2-Cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)-2-phenylvinyl)phenyl)acrylic acid; (E)-3-(4-((E)-2-(2-Chloro-4-fluorophenyl)-1-(3-fluoro-1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-2-(2-Chloro-4-fluorophenyl)-2-cyclobutyl-1-(3-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid; (E)-Ethyl 3-(4-((E)-2-(4-fluorophenyl)-1-(1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylate; (E)-Ethyl 3-(4-((E)-1-(1H-Indazol-5-yl)-2-(2-methoxyphenyl)but-1-en-1-yl)phenyl)acrylate; (E)-Ethyl 3-(4-((E)-1-(1H-Indazol-5-yl)-2-(4-methoxyphenyl)but-1-en-1-yl)phenyl)acrylate; (E)-3-(4-((E)-1-(1H-Indazol-5-yl)-2-phenylbut-1-en-1-yl)phenyl)-2-methylacrylic acid; (E)-3-(4-((Z)-1-(1H-Indazol-5-yl)-2-phenylbut-1-en-1-yl)-3-methylphenyl)acrylic acid; (E)-3-(4-((E)-1-(1H-Indazol-5-yl)-2-phenylbut-1-en-1-yl)-2-methylphenyl)acrylic acid; (E)-3-(4-((Z)-1-(1H-Indazol-5-yl)-2-phenylbut-1-en-1-yl)-2-chlorophenyl)acrylic acid; (Z)-3-(4-((E)-1-(1H-Indazol-5-yl)-2-phenylbut-1-en-1-yl)phenyl)-2-fluoroacrylic acid; (Z)-3-(4-((E)-1-(1H-Indazol-5-yl)-2-phenylbut-1-en-1-yl)phenyl)-2-chloroacrylic acid; (E)-3-(4-((Z)-1-(1H-Indazol-5-yl)-2-phenylbut-1-en-1-yl)-3-fluorophenyl)acrylic acid; (E)-3-(4-((Z)-1-(1H-Indazol-5-yl)-2-phenylbut-1-en-1-yl)-2-fluorophenyl)acrylic acid; (E)-3-(4-((Z)-1-(1H-Indazol-5-yl)-2-phenylbut-1-en-1-yl)-2-(trifluoromethyl)phenyl)acrylic acid; (E)-3-(4-((Z)-1-(1H-Indazol-5-yl)-2-phenylbut-1-en-1-yl)-3-methoxyphenyl)acrylic acid; (E)-3-(4-((Z)-1-(1H-Indazol-5-yl)-2-phenylbut-1-en-1-yl)-2-methoxyphenyl)acrylic acid; (E)-Ethyl 3-(4-((E)-2-(2-chloro-4-fluorophenyl)-1-(1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylate hydrochloride; (E)-3-(4-((E)-2-(2-Chloro-4-fluorophenyl)-1-(1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid; (E)-Ethyl 3-(4-((E)-2-(2,4-dichlorophenyl)-1-(1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylate; (E)-3-(4-((E)-2-

(2,4-Dichlorophenyl)-1-(1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-2-(4-Chloro-2-(trifluoromethyl)phenyl)-1-(1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-2-(2-Chloro-4-fluorophenyl)-2-cyclopropyl-1-(1H-indazol-5-yl)vinyl)phenyl)acrylic acid; (E)-3-(4-((E)-2-(4-Fluoro-2-(trifluoromethyl)phenyl)-1-(1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-(1-(4-Fluoro-1H-indazol-5-yl)-2-(4-fluoro-2-(trifluoromethyl)phenyl)butyl)phenyl)acrylic acid; (E)-3-(4-((E)-2-(2,4-Dichlorophenyl)-1-(4-fluoro-1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-2-(4-Chloro-2-(trifluoromethyl)phenyl)-1-(4-fluoro-1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-2-(2-Chloro-4-fluorophenyl)-4-fluoro-1-(1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-2-(2-Chloro-4-methoxyphenyl)-1-(1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-2-(2,4-Dichlorophenyl)-4-fluoro-1-(4-fluoro-1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-2-Cyclopropyl-2-(2,4-dichlorophenyl)-1-(4-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid; (E)-3-(4-((E)-2-(2-Chloro-4-fluorophenyl)-2-cyclopropyl-1-(4-fluoro-1H-indazol-5-yl)vinyl)phenyl)acrylic acid; (E)-3-(4-((E)-2-Cyclopropyl-2-(2,4-dichlorophenyl)-1-(1H-indazol-5-yl)vinyl)phenyl)acrylic acid; (E)-3-(4-((E)-2-(4-Chloro-2-methylphenyl)-2-cyclopropyl-1-(1H-indazol-5-yl)vinyl)phenyl)acrylic acid; (E)-3-(4-((E)-1-(1H-Indazol-5-yl)-2-(2-methyl-5-(methylsulfonyl)phenyl)but-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-1-(1H-Indazol-5-yl)-2-(4-methoxy-2-methylphenyl)but-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-2-(2-Fluoro-4-methoxyphenyl)-1-(1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-2-(2-Chloro-5-methoxyphenyl)-1-(1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-2-(2-Fluoro-4-(methylsulfonyl)phenyl)-1-(1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-2-(2,4-Dichlorophenyl)-3,3,4,4,4-pentadeutero-1-(1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-1-(1H-Indazol-5-yl)-2-(3-(methylsulfonyl)phenyl)but-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-2-(2,4-Dichlorophenyl)-1-(7-fluoro-1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-2-(2-Chloro-3-methoxyphenyl)-1-(1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-2-(2,4-Dichlorophenyl)-1-(7-fluoro-1H-indol-5-yl)but-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-2-(2-Chloro-4-fluorophenyl)-1-(7-fluoro-1H-indol-5-yl)but-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-2-(2-Chloro-4-fluorophenyl)-3,3,4,4,4-pentadeutero-1-(1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-2-(4-Chloro-2-cyanophenyl)-1-(1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-2-(2-Cyano-4-fluorophenyl)-1-(1H-indazol-5-yl)but-1-en-

1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-2-(2-Cyano-4-(trifluoromethyl)phenyl)-1-(1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-2-(2-Chloro-4-cyanophenyl)-1-(1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-2-(3-Cyano-2-methylphenyl)-1-(1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-2-(4-Cyano-2-methylphenyl)-1-(1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-2-(5-Cyano-2-methylphenyl)-1-(1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-2-(2-Cyano-4-methoxyphenyl)-1-(1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-2-(3-Hydroxyphenyl)-1-(1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-2-(2-Hydroxyphenyl)-1-(1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-2-(4-Hydroxyphenyl)-1-(1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-(1-(1H-Indazol-5-yl)-2-phenylbut-1-en-1-yl)phenyl)propanoic acid; (E)-3-(4-((E)-1-(1H-Indazol-5-yl)-2-(4-(2-methoxyethoxy)phenyl)but-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-1-(1H-Indazol-5-yl)-2-(4-(3-methoxypropoxy)phenyl)but-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-1-(1H-Indazol-5-yl)-2-(3-(2-methoxyethoxy)phenyl)but-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-1-(1H-Indazol-5-yl)-2-(3-(3-methoxypropoxy)phenyl)but-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-2-(3-(Cyclohexyloxy)phenyl)-1-(4-fluoro-1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-2-(3-Butoxyphenyl)-1-(1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-1-(1H-Indazol-5-yl)-2-(3-(pentyloxy)phenyl)but-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-2-(3-(Hexyloxy)phenyl)-1-(1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-2-(4-Butoxyphenyl)-1-(1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-1-(1H-Indazol-5-yl)-2-(4-(pentyloxy)phenyl)but-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-2-(4-(Hexyloxy)phenyl)-1-(1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-2-(4-(2-Hydroxyethoxy)phenyl)-1-(1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-1-(1H-Indazol-5-yl)-2-(2-(methylsulfonyl)phenyl)but-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-2-(2-Chlorophenyl)-1-(1-methyl-1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-2-Cyclobutyl-1-(1-methyl-1H-indazol-5-yl)-2-phenylvinyl)phenyl)acrylic acid; (E)-3-(4-((E)-2-(2-Chloro-4-fluorophenyl)-1-(1-methyl-1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid; (E)-3-(4-((E)-2-(2-Chloro-4-fluorophenyl)-1-(1-(difluoromethyl)-1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid; or a pharmaceutically acceptable salt, or N-oxide thereof, or a combination thereof.

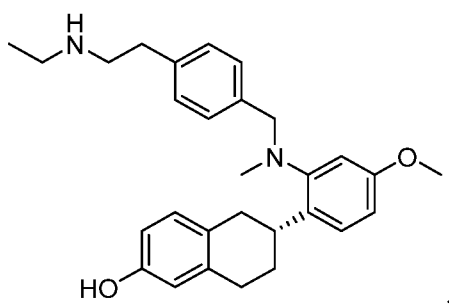
[0324] In one instance, the endocrine therapy comprises brilanestrant (GDC-0810) having the structure:



or a pharmaceutically acceptable salt thereof.

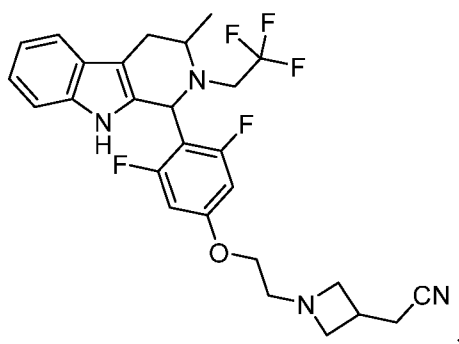
[0325] In another aspect, the endocrine therapy comprises a compound set forth in USPN 9,499,538 or 9,586,952, each of which is incorporated herein by reference in its entirety and for all purposes.

[0326] In another aspect, the endocrine therapy comprises a compound set forth in USPN 7,612,114 or 8,399,520, each of which is incorporated herein by reference in its entirety and for all purposes. In one instance, the endocrine therapy comprises elacestrant (RAD1901):



or a pharmaceutically acceptable salt thereof.

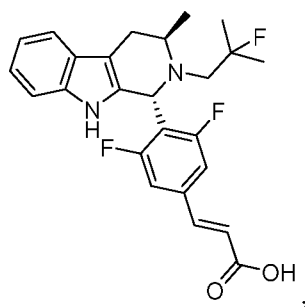
[0327] In another aspect, the endocrine therapy comprises a compound set forth in International Patent Application No. WO2018077260, for example in Table 2 therein, which is incorporated herein by reference in its entirety and for all purposes. In one instance, the endocrine therapy comprises a LX-039. In another instance, the endocrine therapy comprises a compound having the structure:



or a pharmaceutically acceptable salt thereof.

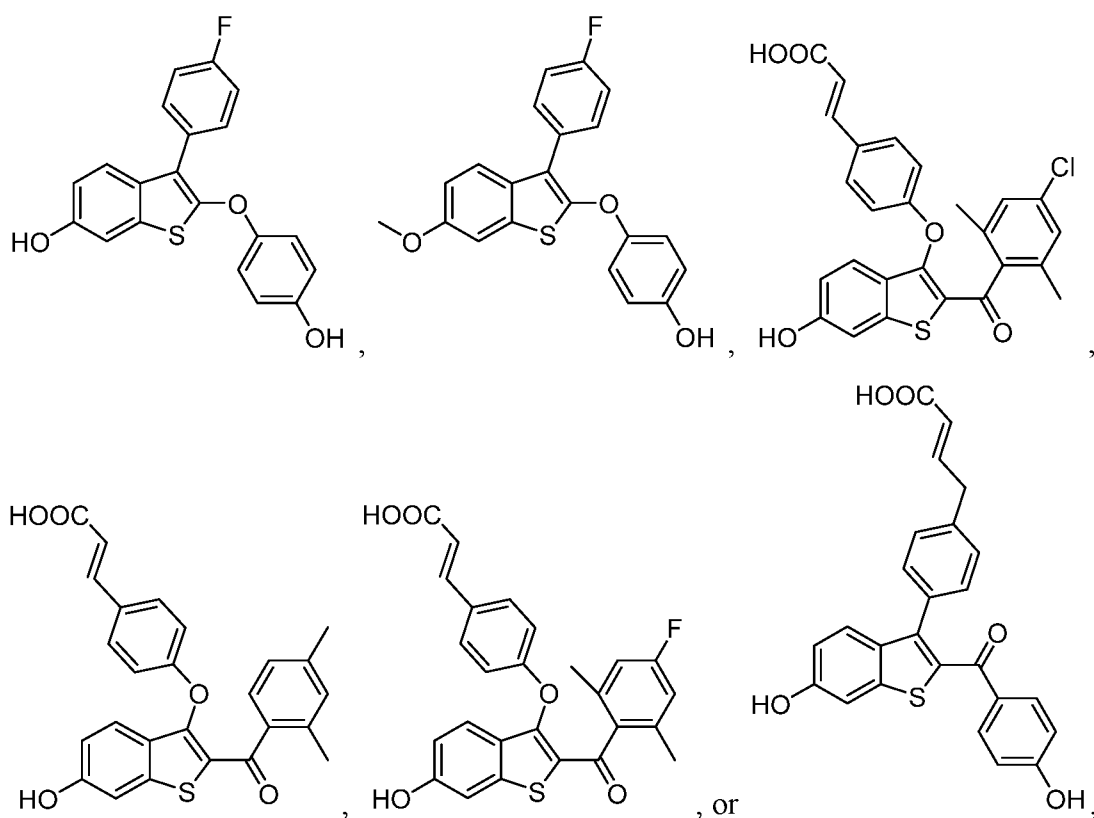
[0328] In another aspect, the endocrine therapy comprises a compound set forth in International Patent Application No. WO2017136688, WO2017162206, WO2017140669, WO2017216280, WO2017216279, WO2018091153, WO2018019793, WO2018077630, each of which is incorporated herein by reference in its entirety and for all purposes.

[0329] In another instance, the endocrine therapy comprises AZ9496 having the structure:



or a pharmaceutically acceptable salt thereof.

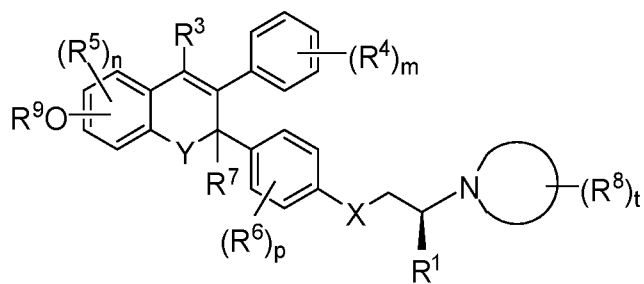
[0330] In another aspect, the endocrine therapy comprises a compound as set forth in U.S. Patent Application No. 20150284357, which is incorporated herein by reference in its entirety and for all purposes. In another aspect, the endocrine therapy comprises a compound as set forth in USPN 9,475,791 which is incorporated herein by reference in its entirety and for all purposes. In still another aspect, the endocrine therapy comprises a compound as set forth in international patent application no WO2018081168 or WO2018129387, each of which is incorporated herein by reference in its entirety and for all purposes. In one aspect, the endocrine therapy comprises a compound having formula:



or a stereoisomer or and pharmaceutically acceptable salt thereof.

[0331] In another aspect, the endocrine therapy comprises a compound set forth in USPN 8,703,810, for example in table of compounds provided therein, which is incorporated herein by reference in its entirety and for all purposes.

[0332] In one aspect, the endocrine therapy comprises a compound having formula (2):



Formula (2)

or a pharmaceutically acceptable salt thereof, wherein:

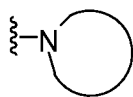
R^1 is H, F, C_1 - C_4 alkyl, or C_1 - C_4 fluoroalkyl;

R^3 is H, halogen, C_1 - C_4 alkyl, C_3 - C_6 cycloalkyl, or C_1 - C_4 fluoroalkyl;

each R^4 is independently selected from H, halogen, -CN, -OH, -OR⁹, -SR⁹, -S(O)R¹⁰, -S(O)₂R¹⁰, -C(O)R¹⁰, -C(O)OH, -C(O)OR¹⁰, -C(O)NHR¹⁰, -C(O)N(R¹⁰)₂, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆fluoroalkyl, substituted or unsubstituted C₁-C₆fluoroalkoxy, substituted or unsubstituted C₁-C₆alkoxy, and substituted or unsubstituted C₁-C₆heteroalkyl;

each R^5 is independently selected from H, halogen, -CN, -OH, -OR⁹, -SR⁹, -S(O)R¹⁰, -S(O)₂R¹⁰, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆fluoroalkyl, substituted or unsubstituted C₁-C₆fluoroalkoxy, substituted or unsubstituted C₁-C₆alkoxy, and substituted or unsubstituted C₁-C₆heteroalkyl;

each R^6 is independently selected from H, halogen, -CN, -OH, -OR⁹, -SR⁹, -S(O)R¹⁰, -S(O)₂R¹⁰, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆fluoroalkyl, substituted or unsubstituted C₁-C₆fluoroalkoxy, substituted or unsubstituted C₁-C₆alkoxy, and substituted or unsubstituted C₁-C₆heteroalkyl;



is pyrrolidinyl or azetidiny;

R^7 is H or C₁-C₄alkyl;

each R^8 is independently selected from F, Cl, -CN, -OH, -OR⁹, -SR⁹, -S(O)R¹⁰, -S(O)₂R¹⁰, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆fluoroalkyl, substituted or unsubstituted C₁-C₆fluoroalkoxy, substituted or unsubstituted C₁-C₆alkoxy, and substituted or unsubstituted C₁-C₆heteroalkyl;

or 1 R^8 is taken together with R^1 along with the intervening atoms joining R^8 to R^1 to form a 5-, 6-, or 7 -membered ring;

each R^9 is independently selected from H, -C(O)R¹⁰, -C(O)OR¹⁰, -C(O)NHR¹⁰, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆heteroalkyl, substituted or unsubstituted C₁-C₆fluoroalkyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, -C₁-C₂alkylene-(substituted or unsubstituted C₃-C₁₀cycloalkyl), -C₁-C₂alkylene-(substituted or unsubstituted C₂-C₁₀heterocycloalkyl), -C₁-C₂alkylene-(substituted or unsubstituted aryl), and -C₁-C₂alkylene-(substituted or unsubstituted heteroaryl); or

each R^{10} is independently selected from substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆heteroalkyl, substituted or unsubstituted C₁-C₆fluoroalkyl,

substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, -C₁-C₂alkylene-(substituted or unsubstituted C₃-C₁₀cycloalkyl), -C₁-C₂alkylene-(substituted or unsubstituted C₂-C₁₀heterocycloalkyl), -C₁-C₂alkylene-(substituted or unsubstituted aryl), and -C₁-C₂alkylene-(substituted or unsubstituted heteroaryl);

Y is -O-, -S-, or -NR¹¹-; R¹¹ is H, -C(O)R¹⁰, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆fluoroalkyl, or substituted or unsubstituted C₁-C₆heteroalkyl;

X is -O-, -S-, -CH₂-, -NH- or -N(C₁-C₆alkyl)-;

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

n is 0, 1, 2, or 3;

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

t is 1, 2, 3 or 4.

[0333] In one instance, the compound of formula (2) is a compound wherein R¹ is H or C₁-C₄alkyl; R³ is C₁-C₄alkyl or C₁-C₄fluoroalkyl; each R⁴ is independently selected from H, halogen, -CN, -OH, -OR⁹, -SR⁹, -S(=O)R¹⁰, -S(=O)₂R¹⁰, C₁-C₄alkyl, C₁-C₄fluoroalkyl, C₁-C₄fluoroalkoxy, C₁-C₄alkoxy, and C₁-C₄heteroalkyl; each R⁵ is independently selected from H, F, Cl, -OH, -CH₃, -CF₃, -OCF₃, and -OCH₃; each R⁶ is independently selected from H, F, Cl, -OH, -CH₃, -CF₃, -OCF₃, and -OCH₃; R⁷ is H; each R⁸ is independently selected from H, F, Cl, -OH, C₁-C₄alkyl, C₁-C₄fluoroalkyl, C₁-C₄fluoroalkoxy, C₁-C₄alkoxy, and C₁-C₄heteroalkyl; Y is -O- or -S-; X is -O-, -S-, -CH₂-, -NH- or -N(CH₃)-; and p is 0, 1, or 2.

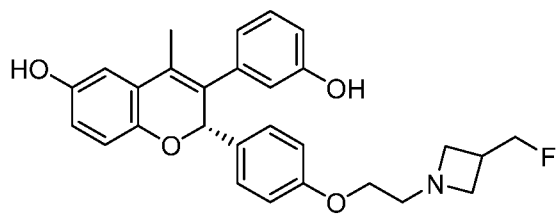
[0334] In another aspect, the endocrine therapy comprises a compound having formula:

3-(3-Hydroxyphenyl)-4-methyl-2-(4-((S)-2-((R)-3-methylpyrrolidin-1-yl)propoxy)phenyl)-2H-chromen-6-ol; (S)-3-(3-Hydroxyphenyl)-4-methyl-2-(4-((S)-2-((R)-3-methylpyrrolidin-1-yl)propoxy)phenyl)-2H-chromen-6-ol; (R)-3-(3-Hydroxyphenyl)-4-methyl-2-(4-((S)-2-((R)-3-methylpyrrolidin-1-yl)propoxy)phenyl)-2H-chromen-6-ol; 3-(3-Hydroxyphenyl)-4-methyl-2-(4-(2-((R)-3-methylpyrrolidin-1-yl)ethoxy)phenyl)-2H-chromen-6-ol; 3-(3-Hydroxyphenyl)-4-methyl-2-(4-((R)-2-((R)-3-methylpyrrolidin-1-yl)propoxy)phenyl)-2H-chromen-6-ol; 3-(3-Hydroxyphenyl)-4-methyl-2-(4-(2-((S)-3-methylpyrrolidin-1-yl)ethoxy)phenyl)-2H-chromen-6-ol; 3-(3-hydroxyphenyl)-4-methyl-2-(4-((S)-2-((S)-3-methylpyrrolidin-1-yl)propoxy)phenyl)-2H-chromen-6-ol; 3-(3-hydroxyphenyl)-4-methyl-2-(4-((R)-2-((S)-3-methylpyrrolidin-1-

yl)propoxy)phenyl)-2H-chromen-6-ol; 2-(4-((S)-2-(3,3-Dimethylpyrrolidin-1-yl)propoxy)phenyl)-3-(3-hydroxyphenyl)-4-methyl-2H-chromen-6-ol; 2-(4-(2-(3,3-Dimethylpyrrolidin-1-yl)ethoxy)phenyl)-3-(3-hydroxyphenyl)-4-methyl-2H-chromen-6-ol; 3-(3-Hydroxyphenyl)-4-methyl-2-(4-(2-((R)-2-methylpyrrolidin-1-yl)ethoxy)phenyl)-2H-chromen-6-ol; 3-(3-Hydroxyphenyl)-4-methyl-2-(4-((S)-2-((R)-2-methylpyrrolidin-1-yl)propoxy)phenyl)-2H-chromen-6-ol; 3-(3-Hydroxyphenyl)-4-methyl-2-(4-((S)-2-((S)-2-methylpyrrolidin-1-yl)propoxy)phenyl)-2H-chromen-6-ol; 3-(3-Hydroxyphenyl)-4-methyl-2-(4-((S)-2-((R)-3-methylpyrrolidin-1-yl)propoxy)phenyl)-2H-chromen-7-ol; 3-(4-Hydroxyphenyl)-4-methyl-2-(4-((S)-2-((R)-3-methylpyrrolidin-1-yl)propoxy)phenyl)-2H-chromen-7-ol; 4-Methyl-2-(4-((S)-2-((R)-3-methylpyrrolidin-1-yl)propoxy)phenyl)-3-phenyl-2H-chromen-6-ol; 3-(4-Fluorophenyl)-4-methyl-2-(4-((S)-2-((R)-3-methylpyrrolidin-1-yl)propoxy)phenyl)-2H-chromen-6-ol; (S)-3-(4-Fluorophenyl)-4-methyl-2-(4-((S)-2-((R)-3-methylpyrrolidin-1-yl)propoxy)phenyl)-2H-chromen-6-ol; (R)-3-(4-Fluorophenyl)-4-methyl-2-(4-((S)-2-((R)-3-methylpyrrolidin-1-yl)propoxy)phenyl)-2H-chromen-6-ol; 3-(4-Hydroxyphenyl)-4-methyl-2-(4-((S)-2-((R)-3-methylpyrrolidin-1-yl)propoxy)phenyl)-2H-chromen-6-ol; 3-(3-Fluorophenyl)-4-methyl-2-(4-((S)-2-((R)-3-methylpyrrolidin-1-yl)propoxy)phenyl)-2H-chromen-6-ol; 3-(3-Fluoro-4-hydroxyphenyl)-4-methyl-2-(4-((S)-2-((R)-3-methylpyrrolidin-1-yl)propoxy)phenyl)-2H-chromen-6-ol; 2-(2-Fluoro-4-((S)-2-((R)-3-methylpyrrolidin-1-yl)propoxy)phenyl)-3-(3-hydroxyphenyl)-4-methyl-2H-chromen-6-ol; 3-(3-Hydroxy-4-methylphenyl)-4-methyl-2-(4-((S)-2-((R)-3-methylpyrrolidin-1-yl)propoxy)phenyl)-2H-chromen-6-ol; 3-(3-Hydroxy-2-methylphenyl)-4-methyl-2-(4-((S)-2-((R)-3-methylpyrrolidin-1-yl)propoxy)phenyl)-2H-chromen-6-ol; 3-(4-Hydroxy-2-methylphenyl)-4-methyl-2-(4-((S)-2-((R)-3-methylpyrrolidin-1-yl)propoxy)phenyl)-2H-chromen-6-ol; 3-(4-Hydroxy-3-methylphenyl)-4-methyl-2-(4-((S)-2-((R)-3-methylpyrrolidin-1-yl)propoxy)phenyl)-2H-chromen-6-ol; 3-(3-Fluoro-5-hydroxyphenyl)-4-methyl-2-(4-((S)-2-((R)-3-methylpyrrolidin-1-yl)propoxy)phenyl)-2H-chromen-6-ol; 3-(4-Chlorophenyl)-4-methyl-2-(4-((S)-2-((R)-3-methylpyrrolidin-1-yl)propoxy)phenyl)-2H-chromen-6-ol; 3-(2-Fluoro-4-hydroxyphenyl)-4-methyl-2-(4-((S)-2-((R)-3-methylpyrrolidin-1-yl)propoxy)phenyl)-2H-chromen-6-ol; 3-(3,4-Difluorophenyl)-4-methyl-2-(4-((S)-2-((R)-3-methylpyrrolidin-1-yl)propoxy)phenyl)-2H-chromen-6-ol; 3-(3,5-Difluoro-4-hydroxyphenyl)-4-methyl-2-(4-((S)-2-((R)-3-methylpyrrolidin-1-yl)propoxy)phenyl)-2H-chromen-6-ol; 3-(2,4-Difluoro-3-hydroxyphenyl)-4-methyl-2-(4-((S)-2-((R)-3-methylpyrrolidin-

1-yl)propoxy)phenyl)-2H-chromen-6-ol; 3-(3,4-Difluoro-5-hydroxyphenyl)-4-methyl-2-(4-((S)-2-((R)-3-methylpyrrolidin-1-yl)propoxy)phenyl)-2H-chromen-6-ol; 3-(2-Chloro-4-fluorophenyl)-4-methyl-2-(4-((S)-2-((R)-3-methylpyrrolidin-1-yl)propoxy)phenyl)-2H-chromen-6-ol; 3-(2,4-Difluorophenyl)-4-methyl-2-(4-((S)-2-((R)-3-methylpyrrolidin-1-yl)propoxy)phenyl)-2H-chromen-6-ol; 3-(4-Bromophenyl)-4-methyl-2-(4-((S)-2-((R)-3-methylpyrrolidin-1-yl)propoxy)phenyl)-2H-chromen-6-ol; 4-Methyl-2-(4-((S)-2-((R)-3-methylpyrrolidin-1-yl)propoxy)phenyl)-3-(o-tolyl)-2H-chromen-6-ol; 3-(4-Fluoro-3-hydroxyphenyl)-4-methyl-2-(4-((S)-2-((R)-3-methylpyrrolidin-1-yl)propoxy)phenyl)-2H-chromen-6-ol; 3-(4-Ethynylphenyl)-4-methyl-2-(4-((S)-2-((R)-3-methylpyrrolidin-1-yl)propoxy)phenyl)-2H-chromen-6-ol; 4-Methyl-2-(4-((S)-2-((R)-3-methylpyrrolidin-1-yl)propoxy)phenyl)-3-(4-(methylsulfonyl)phenyl)-2H-chromen-6-ol; 3-(2-Fluoro-3-hydroxyphenyl)-4-methyl-2-(4-((S)-2-((R)-3-methylpyrrolidin-1-yl)propoxy)phenyl)-2H-chromen-6-ol; 5-Fluoro-3-(3-hydroxyphenyl)-4-methyl-2-(4-((S)-2-((R)-3-methylpyrrolidin-1-yl)propoxy)phenyl)-2H-chromen-6-ol; 3-(2-Fluoro-5-hydroxyphenyl)-4-methyl-2-(4-((S)-2-((R)-3-methylpyrrolidin-1-yl)propoxy)phenyl)-2H-chromen-6-ol; 3-(4-Fluorophenyl)-4-methyl-2-(4-((S)-2-((R)-2-methylpyrrolidin-1-yl)propoxy)phenyl)-2H-chromen-6-ol; 2-(4-((S)-2-((R)-3-Fluoropyrrolidin-1-yl)propoxy)phenyl)-3-(3-hydroxyphenyl)-4-methyl-2H-chromen-6-ol; 3-(4-Hydroxyphenyl)-2-(4-((S)-2-((R)-3-methylpyrrolidin-1-yl)propoxy)phenyl)-4-(trifluoromethyl)-2H-chromen-6-ol; 3-(3-Hydroxyphenyl)-2-(4-((S)-2-((R)-3-methylpyrrolidin-1-yl)propoxy)phenyl)-4-(trifluoromethyl)-2H-chromen-6-ol; 3-(3-Hydroxy-4-(trifluoromethyl)phenyl)-4-methyl-2-(4-((S)-2-((R)-3-methylpyrrolidin-1-yl)propoxy)phenyl)-2H-chromen-6-ol; 3-(4-Hydroxy-3-(trifluoromethyl)phenyl)-4-methyl-2-(4-((S)-2-((R)-3-methylpyrrolidin-1-yl)propoxy)phenyl)-2H-chromen-6-ol; or a pharmaceutically acceptable salt thereof, or a combination thereof.

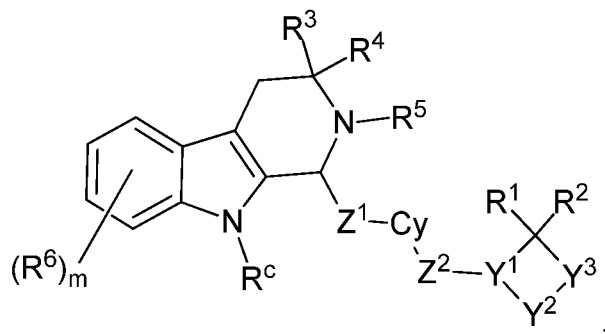
[0335] In one instance, the endocrine therapy comprises a GDC-0927 (SRN-0927) having the structure:



or a pharmaceutically acceptable salt thereof.

[0336] In another aspect, the endocrine therapy comprises a compound set forth in USPN 9,980,947, for example in Table 1 therein, which is incorporated herein by reference in its entirety and for all purposes.

[0337] In one aspect, the endocrine therapy comprises a compound of formula (3):



(3)

or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein:

Y^1 is CR^b or N;

Y^2 is $-(CH_2)-$, $-(CH_2CH_2)-$, or NR^a ;

Y^3 is NR^a or $C(R^b)_2$;

where one of Y^1 , Y^2 and Y^3 is N or NR^a ;

R^a is H, C_1 - C_6 alkyl, C_2 - C_8 alkenyl, propargyl, C_3 - C_6 cycloalkyl, or C_3 - C_6 heterocyclyl, optionally substituted with one or more groups independently selected from the group consisting of F, Cl, Br, I, CN, OH, OCH_3 , and SO_2CH_3 ;

R^b is H, $-O(C_1$ - C_3 alkyl), C_1 - C_6 alkyl, C_2 - C_8 alkenyl, propargyl, $-(C_1$ - C_6 alkylidyl)-(C_3 - C_6 cycloalkyl), C_3 - C_6 cycloalkyl, or C_3 - C_6 heterocyclyl, optionally substituted with one or more groups independently selected from the group consisting of F, Cl, Br, I, CN, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CH_2CF_3$, $-CH_2CHF_2$, $-CH_2CH_2F$, OH, OCH_3 , and SO_2CH_3 ;

R^c is H, C_1 - C_6 alkyl, allyl, or propargyl, optionally substituted with one or more groups independently selected from the group consisting of F, Cl, Br, I, CN, OH, OCH_3 , and SO_2CH_3 ;

Z^1 is CR^aR^b , $C(O)$, or a bond;

Cy is C_6 - C_{20} arylidyl, C_3 - C_{12} carbocyclyldiyl, C_2 - C_{20} heterocyclyldiyl, or C_1 - C_{20} heteroaryldiyl;

Z² is O, S, NR^a, C₁–C₆ alkylidyl, C₁–C₆ fluoroalkylidyl, O–(C₁–C₆ alkylidyl), O–(C₁–C₆ fluoroalkylidyl), C(O), or a bond;

R¹, R², R³ and R⁴ are independently H, F, Cl, Br, I, –CN, –CH₃, –CH₂CH₃, –CH(CH₃)₂, –CH₂CH(CH₃)₂, –CH₂OH, –CH₂OCH₃, –CH₂CH₂OH, –C(CH₃)₂OH, –CH(OH)CH(CH₃)₂, –C(CH₃)₂CH₂OH, –CH₂CH₂SO₂CH₃, –CH₂OP(O)(OH)₂, –CH₂F, –CHF₂, –CH₂NH₂, –CH₂NHSO₂CH₃, –CH₂NHCH₃, –CH₂N(CH₃)₂, –CF₃, –CH₂CF₃, –CH₂CHF₂, –CH(CH₃)CN, –C(CH₃)₂CN, –CH₂CN, –CO₂H, –COCH₃, –CO₂CH₃, –CO₂C(CH₃)₃, –COCH(OH)CH₃, –CONH₂, –CONHCH₃, –CONHCH₂CH₃, –CONHCH(CH₃)₂, –CON(CH₃)₂, –C(CH₃)₂CONH₂, –NH₂, –NHCH₃, –N(CH₃)₂, –NHCOCH₃, –N(CH₃)COCH₃, –NHS(O)₂CH₃, –N(CH₃)C(CH₃)₂CONH₂, –N(CH₃)CH₂CH₂S(O)₂CH₃, –NO₂, =O, –OH, –OCH₃, –OCH₂CH₃, –OCH₂CH₂OCH₃, –OCH₂CH₂OH, –OCH₂CH₂N(CH₃)₂, –OP(O)(OH)₂, –S(O)₂N(CH₃)₂, –SCH₃, –S(O)₂CH₃, –S(O)₃H, cyclopropyl, cyclopropylamide, cyclobutyl, oxetanyl, azetidiny, 1-methylazetidin-3-yl)oxy, N-methyl-N-oxetan-3-ylamino, azetidin-1-ylmethyl, benzyloxyphenyl, pyrrolidin-1-yl, pyrrolidin-1-yl-methanone, piperazin-1-yl, morpholinomethyl, morpholino-methanone, or morpholino;

R⁵ is H, C₁–C₉ alkyl, C₃–C₉ cycloalkyl, C₃–C₉ heterocycle, C₆–C₉ aryl, C₆–C₉ heteroaryl, –(C₁–C₆ alkylidyl)–(C₃–C₉ cycloalkyl), –(C₁–C₆ alkylidyl)–(C₃–C₉ heterocycle), C(O)R^b, C(O)NR^a, SO₂R^a, or SO₂NR^a, optionally substituted with one or more of halogen, CN, OR^a, N(R^a)₂, C₁–C₉ alkyl, C₃–C₉ cycloalkyl, C₃–C₉ heterocycle, C₆–C₉ aryl, C₆–C₉ heteroaryl, C(O)R^b, C(O)NR^a, SO₂R^a, or SO₂NR^a;

R⁶ is F, Cl, Br, I, –CN, –CH₃, –CH₂CH₃, –CH(CH₃)₂, –CH₂CH(CH₃)₂, –CH₂OH, –CH₂OCH₃, –CH₂CH₂OH, –C(CH₃)₂OH, –CH(OH)CH(CH₃)₂, –C(CH₃)₂CH₂OH, –CH₂CH₂SO₂CH₃, –CH₂OP(O)(OH)₂, –CH₂F, –CHF₂, –CH₂NH₂, –CH₂NHSO₂CH₃, –CH₂NHCH₃, –CH₂N(CH₃)₂, –CF₃, –CH₂CF₃, –CH₂CHF₂, –CH(CH₃)CN, –C(CH₃)₂CN, –CH₂CN, –CO₂H, –COCH₃, –CO₂CH₃, –CO₂C(CH₃)₃, –COCH(OH)CH₃, –CONH₂, –CONHCH₃, –CONHCH₂CH₃, –CONHCH(CH₃)₂, –CON(CH₃)₂, –C(CH₃)₂CONH₂, –NH₂, –NHCH₃, –N(CH₃)₂, –NHCOCH₃, –N(CH₃)COCH₃, –NHS(O)₂CH₃, –N(CH₃)C(CH₃)₂CONH₂, –N(CH₃)CH₂CH₂S(O)₂CH₃, –NO₂, =O, –OH, –OCH₃, –OCH₂CH₃, –OCH₂CH₂OCH₃, –OCH₂CH₂OH, –OCH₂CH₂N(CH₃)₂, –OP(O)(OH)₂, –S(O)₂N(CH₃)₂, –SCH₃, –S(O)₂CH₃, –S(O)₃H, cyclopropyl, cyclopropylamide, cyclobutyl, oxetanyl, azetidiny, 1-methylazetidin-3-

yl)oxy, N-methyl-N-oxetan-3-ylamino, azetidin-1-ylmethyl, benzyloxyphenyl, pyrrolidin-1-yl, pyrrolidin-1-yl-methanone, piperazin-1-yl, morpholinomethyl, morpholino-methanone, or morpholino; and

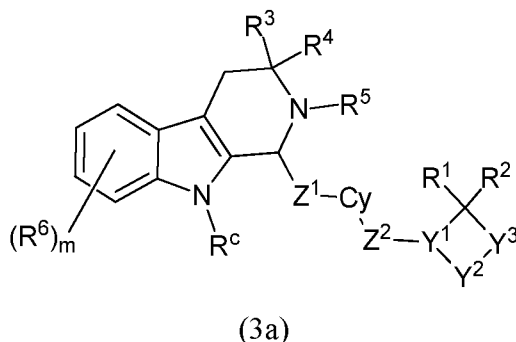
m is 0, 1, 2, 3, or 4;

where alkylidiyl, fluoroalkylidiyl, arylidiyl, carbocyclyldiyl, heterocyclyldiyl, and heteroarylidiyl are optionally substituted with one or more groups independently selected from the group consisting of F, Cl, Br, I, -CN, -CH₃, -CH₂CH₃, -CH(CH₃)₂, -CH₂CH(CH₃)₂, -CH₂OH, -CH₂OCH₃, -CH₂CH₂OH, -C(CH₃)₂OH, -CH(OH)CH(CH₃)₂, -C(CH₃)₂CH₂OH, -CH₂CH₂SO₂CH₃, -CH₂OP(O)(OH)₂, -CH₂F, -CHF₂, -CF₃, -CH₂CF₃, -CH₂CHF₂, -CH₂CH₂F, -CH(CH₃)CN, -C(CH₃)₂CN, -CH₂CN, -CH₂NH₂, -CH₂NHSO₂CH₃, -CH₂NHCH₃, -CH₂N(CH₃)₂, -CO₂H, -COCH₃, -CO₂CH₃, -CO₂C(CH₃)₃, -COCH(OH)CH₃, -CONH₂, -CONHCH₃, -CON(CH₃)₂, -C(CH₃)₂CONH₂, -NH₂, -NHCH₃, -N(CH₃)₂, -NHCOCH₃, -N(CH₃)COCH₃, -NHS(O)₂CH₃, -N(CH₃)C(CH₃)₂CONH₂, -N(CH₃)CH₂CH₂S(O)₂CH₃, -NO₂, =O, -OH, -OCH₃, -OCH₂CH₃, -OCH₂CH₂OCH₃, -OCH₂CH₂OH, -OCH₂CH₂N(CH₃)₂, -OP(O)(OH)₂, -S(O)₂N(CH₃)₂, -SCH₃, -S(O)₂CH₃, -S(O)₃H, cyclopropyl, cyclopropylamide, cyclobutyl, oxetanyl, azetidiny, 1-methylazetidin-3-yl)oxy, N-methyl-N-oxetan-3-ylamino, azetidin-1-ylmethyl, benzyloxyphenyl, pyrrolidin-1-yl, pyrrolidin-1-yl-methanone, piperazin-1-yl, morpholinomethyl, morpholino-methanone, and morpholino.

[0338] In one instance of the compounds of formula (3), Y¹ is CR^b and Y³ is NR^a. In another instance of the compounds of formula (3), Y¹ is N and Y³ is C(R^b)₂. In another instance of the compounds of formula (3), Y² is -(CH₂)-. In another instance of the compounds of formula (3), Y² is -(CH₂CH₂)-.

[0339] In another instance of the compounds of formula (3), R^c is H. In another instance of the compounds of formula (3), Cy is C₆-C₂₀ arylidiyl, C₆-C₂₀ arylidiyl is phenylidiyl, and phenylidiyl is substituted with one or more F. In another instance of the compounds of formula (3), R¹ and R² are H. In another instance of the compounds of formula (3), R³ is H, and R⁴ is -CH₃. In another instance of the compounds of formula (3), R⁵ is C₁-C₆ fluoroalkyl. In another instance of the compounds of formula (3), m is 0.

[0340] In another instance, the endocrine therapy comprises a compound of formula (3) having formula (3a):



or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein:

Y^1 is CR^b or N;

Y^2 is $-(CH_2)-$, $-(CH_2CH_2)-$, or NR^a ;

Y^3 is NR^a or $C(R^b)_2$;

where one of Y^1 , Y^2 and Y^3 is N or NR^a ;

R^a is independently H, C_1-C_6 alkyl, C_2-C_8 alkenyl, propargyl, C_3-C_6 cycloalkyl, and C_3-C_6 heterocyclyl, optionally substituted with one or more groups independently selected from F, Cl, Br, I, CN, OH, OCH₃, or SO₂CH₃;

R^b is independently H, $-O(C_1-C_3 \text{ alkyl})$, C_1-C_6 alkyl, C_2-C_8 alkenyl, propargyl, $-(C_1-C_6 \text{ alkylidyl})-(C_3-C_6 \text{ cycloalkyl})$, C_3-C_6 cycloalkyl, and C_3-C_6 heterocyclyl, optionally substituted with one or more groups independently selected from F, Cl, Br, I, CN, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CH_2CF_3$, $-CH_2CHF_2$, $-CH_2CH_2F$, OH, OCH₃, or SO₂CH₃;

R^c is independently H, C_1-C_6 alkyl, allyl, propargyl, optionally substituted with one or more groups independently selected from F, Cl, Br, I, CN, OH, OCH₃, or SO₂CH₃;

Z^1 is CR^aR^b , C(O), or a bond;

Cy is C_6-C_{20} arylidyl, C_3-C_{12} carbocyclyldiyl, C_2-C_{20} heterocyclyldiyl, or C_1-C_{20} heteroarylidyl;

Z^2 is O;

R^1 , R^2 , R^3 and R^4 are each independently H, F, Cl, Br, I, $-CN$, $-CH_3$, $-CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2CH(CH_3)_2$, $-CH_2OH$, $-CH_2OCH_3$, $-CH_2CH_2OH$, $-C(CH_3)_2OH$, $-CH(OH)CH(CH_3)_2$, $-C(CH_3)_2CH_2OH$, $-CH_2CH_2SO_2CH_3$, $-CH_2OP(O)(OH)_2$, $-CH_2F$, $-CHF_2$, $-CH_2NH_2$, $-CH_2NHSO_2CH_3$, $-CH_2NHCH_3$, $-CH_2N(CH_3)_2$, $-CF_3$, $-CH_2CF_3$, $-CH_2CHF_2$,

$-\text{CH}(\text{CH}_3)\text{CN}$, $-\text{C}(\text{CH}_3)_2\text{CN}$, $-\text{CH}_2\text{CN}$, $-\text{CO}_2\text{H}$, $-\text{COCH}_3$, $-\text{CO}_2\text{CH}_3$, $-\text{CO}_2\text{C}(\text{CH}_3)_3$,
 $-\text{COCH}(\text{OH})\text{CH}_3$, $-\text{CONH}_2$, $-\text{CONHCH}_3$, $-\text{CONHCH}_2\text{CH}_3$, $-\text{CONHCH}(\text{CH}_3)_2$, $-\text{CON}(\text{CH}_3)_2$,
 $-\text{C}(\text{CH}_3)_2\text{CONH}_2$, $-\text{NH}_2$, $-\text{NHCH}_3$, $-\text{N}(\text{CH}_3)_2$, $-\text{NHCOCH}_3$, $-\text{N}(\text{CH}_3)\text{COCH}_3$, $-\text{NHS}(\text{O})_2\text{CH}_3$,
 $-\text{N}(\text{CH}_3)\text{C}(\text{CH}_3)_2\text{CONH}_2$, $-\text{N}(\text{CH}_3)\text{CH}_2\text{CH}_2\text{S}(\text{O})_2\text{CH}_3$, $-\text{NO}_2$, $=\text{O}$, $-\text{OH}$, $-\text{OCH}_3$, $-\text{OCH}_2\text{CH}_3$,
 $-\text{OCH}_2\text{CH}_2\text{OCH}_3$, $-\text{OCH}_2\text{CH}_2\text{OH}$, $-\text{OCH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$, $-\text{OP}(\text{O})(\text{OH})_2$, $-\text{S}(\text{O})_2\text{N}(\text{CH}_3)_2$, $-\text{SCH}_3$,
 $-\text{S}(\text{O})_2\text{CH}_3$, $-\text{S}(\text{O})_3\text{H}$, cyclopropyl, cyclopropylamide, cyclobutyl, oxetanyl, azetidiny, 1-
methylazetidin-3-yl)oxy, N-methyl-N-oxetan-3-ylamino, azetidin-1-ylmethyl, benzyloxyphenyl,
pyrrolidin-1-yl, pyrrolidin-1-yl-methanone, piperazin-1-yl, morpholinomethyl, morpholino-
methanone, or morpholino;

R^5 is H, $\text{C}_1\text{--C}_9$ alkyl, $\text{C}_3\text{--C}_9$ cycloalkyl, $\text{C}_3\text{--C}_9$ heterocycle, $\text{C}_6\text{--C}_9$ aryl, $\text{C}_6\text{--C}_9$ heteroaryl,
 $-(\text{C}_1\text{--C}_6 \text{ alkylidyl})-(\text{C}_3\text{--C}_9 \text{ cycloalkyl})$, $-(\text{C}_1\text{--C}_6 \text{ alkylidyl})-(\text{C}_3\text{--C}_9 \text{ heterocycle})$, $\text{C}(\text{O})\text{R}^b$,
 $\text{C}(\text{O})\text{NR}^a$, SO_2R^a , and SO_2NR^a , optionally substituted with one or more of halogen, CN, OR^a ,
 $\text{N}(\text{R}^a)_2$, $\text{C}_1\text{--C}_9$ alkyl, $\text{C}_3\text{--C}_9$ cycloalkyl, $\text{C}_3\text{--C}_9$ heterocycle, $\text{C}_6\text{--C}_9$ aryl, $\text{C}_6\text{--C}_9$ heteroaryl, $\text{C}(\text{O})\text{R}^b$,
 $\text{C}(\text{O})\text{NR}^a$, SO_2R^a , or SO_2NR^a ;

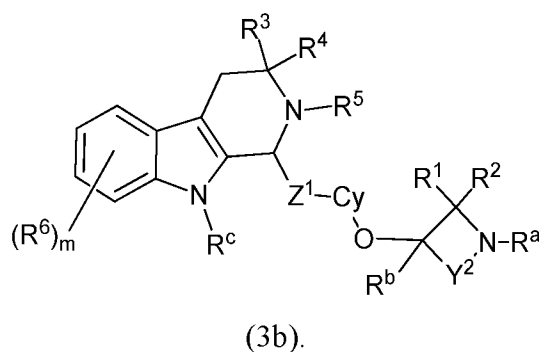
R^6 is F, Cl, Br, I, $-\text{CN}$, $-\text{CH}_3$, $-\text{CH}_2\text{CH}_3$, $-\text{CH}(\text{CH}_3)_2$, $-\text{CH}_2\text{CH}(\text{CH}_3)_2$, $-\text{CH}_2\text{OH}$,
 $-\text{CH}_2\text{OCH}_3$, $-\text{CH}_2\text{CH}_2\text{OH}$, $-\text{C}(\text{CH}_3)_2\text{OH}$, $-\text{CH}(\text{OH})\text{CH}(\text{CH}_3)_2$, $-\text{C}(\text{CH}_3)_2\text{CH}_2\text{OH}$,
 $-\text{CH}_2\text{CH}_2\text{SO}_2\text{CH}_3$, $-\text{CH}_2\text{OP}(\text{O})(\text{OH})_2$, $-\text{CH}_2\text{F}$, $-\text{CHF}_2$, $-\text{CH}_2\text{NH}_2$, $-\text{CH}_2\text{NHSO}_2\text{CH}_3$,
 $-\text{CH}_2\text{NHCH}_3$, $-\text{CH}_2\text{N}(\text{CH}_3)_2$, $-\text{CF}_3$, $-\text{CH}_2\text{CF}_3$, $-\text{CH}_2\text{CHF}_2$, $-\text{CH}_2\text{CH}_2\text{F}$, $-\text{CH}(\text{CH}_3)\text{CN}$,
 $-\text{C}(\text{CH}_3)_2\text{CN}$, $-\text{CH}_2\text{CN}$, $-\text{CO}_2\text{H}$, $-\text{COCH}_3$, $-\text{CO}_2\text{CH}_3$, $-\text{CO}_2\text{C}(\text{CH}_3)_3$, $-\text{COCH}(\text{OH})\text{CH}_3$,
 $-\text{CONH}_2$, $-\text{CONHCH}_3$, $-\text{CONHCH}_2\text{CH}_3$, $-\text{CONHCH}(\text{CH}_3)_2$, $-\text{CON}(\text{CH}_3)_2$, $-\text{C}(\text{CH}_3)_2\text{CONH}_2$,
 $-\text{NH}_2$, $-\text{NHCH}_3$, $-\text{N}(\text{CH}_3)_2$, $-\text{NHCOCH}_3$, $-\text{N}(\text{CH}_3)\text{COCH}_3$, $-\text{NHS}(\text{O})_2\text{CH}_3$,
 $-\text{N}(\text{CH}_3)\text{C}(\text{CH}_3)_2\text{CONH}_2$, $-\text{N}(\text{CH}_3)\text{CH}_2\text{CH}_2\text{S}(\text{O})_2\text{CH}_3$, $-\text{NO}_2$, $=\text{O}$, $-\text{OH}$, $-\text{OCH}_3$, $-\text{OCH}_2\text{CH}_3$,
 $-\text{OCH}_2\text{CH}_2\text{OCH}_3$, $-\text{OCH}_2\text{CH}_2\text{OH}$, $-\text{OCH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$, $-\text{OP}(\text{O})(\text{OH})_2$, $-\text{S}(\text{O})_2\text{N}(\text{CH}_3)_2$, $-\text{SCH}_3$,
 $-\text{S}(\text{O})_2\text{CH}_3$, $-\text{S}(\text{O})_3\text{H}$, cyclopropyl, cyclopropylamide, cyclobutyl, oxetanyl, azetidiny, 1-
methylazetidin-3-yl)oxy, N-methyl-N-oxetan-3-ylamino, azetidin-1-ylmethyl, benzyloxyphenyl,
pyrrolidin-1-yl, pyrrolidin-1-yl-methanone, piperazin-1-yl, morpholinomethyl, morpholino-
methanone, or morpholino; and

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

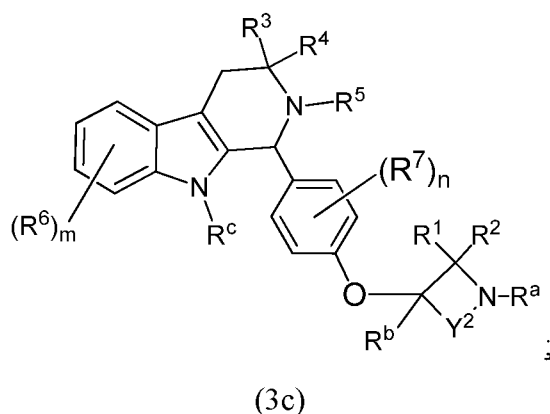
where alkylidyl, fluoroalkylidyl, arylidyl, carbocyclyldyl, heterocyclyldyl, and
heteroaryldyl are optionally substituted with one or more groups independently selected from

the group consisting of F, Cl, Br, I, $-\text{CN}$, $-\text{CH}_3$, $-\text{CH}_2\text{CH}_3$, $-\text{CH}(\text{CH}_3)_2$, $-\text{CH}_2\text{CH}(\text{CH}_3)_2$, $-\text{CH}_2\text{OH}$, $-\text{CH}_2\text{OCH}_3$, $-\text{CH}_2\text{CH}_2\text{OH}$, $-\text{C}(\text{CH}_3)_2\text{OH}$, $-\text{CH}(\text{OH})\text{CH}(\text{CH}_3)_2$, $-\text{C}(\text{CH}_3)_2\text{CH}_2\text{OH}$, $-\text{CH}_2\text{CH}_2\text{SO}_2\text{CH}_3$, $-\text{CH}_2\text{OP}(\text{O})(\text{OH})_2$, $-\text{CH}_2\text{F}$, $-\text{CHF}_2$, $-\text{CF}_3$, $-\text{CH}_2\text{CF}_3$, $-\text{CH}_2\text{CHF}_2$, $-\text{CH}_2\text{CH}_2\text{F}$, $-\text{CH}(\text{CH}_3)\text{CN}$, $-\text{C}(\text{CH}_3)_2\text{CN}$, $-\text{CH}_2\text{CN}$, $-\text{CH}_2\text{NH}_2$, $-\text{CH}_2\text{NHSO}_2\text{CH}_3$, $-\text{CH}_2\text{NHCH}_3$, $-\text{CH}_2\text{N}(\text{CH}_3)_2$, $-\text{CO}_2\text{H}$, $-\text{COCH}_3$, $-\text{CO}_2\text{CH}_3$, $-\text{CO}_2\text{C}(\text{CH}_3)_3$, $-\text{COCH}(\text{OH})\text{CH}_3$, $-\text{CONH}_2$, $-\text{CONHCH}_3$, $-\text{CON}(\text{CH}_3)_2$, $-\text{C}(\text{CH}_3)_2\text{CONH}_2$, $-\text{NH}_2$, $-\text{NHCH}_3$, $-\text{N}(\text{CH}_3)_2$, $-\text{NHCOCH}_3$, $-\text{N}(\text{CH}_3)\text{COCH}_3$, $-\text{NHS}(\text{O})_2\text{CH}_3$, $-\text{N}(\text{CH}_3)\text{C}(\text{CH}_3)_2\text{CONH}_2$, $-\text{N}(\text{CH}_3)\text{CH}_2\text{CH}_2\text{S}(\text{O})_2\text{CH}_3$, $-\text{NO}_2$, $=\text{O}$, $-\text{OH}$, $-\text{OCH}_3$, $-\text{OCH}_2\text{CH}_3$, $-\text{OCH}_2\text{CH}_2\text{OCH}_3$, $-\text{OCH}_2\text{CH}_2\text{OH}$, $-\text{OCH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$, $-\text{OP}(\text{O})(\text{OH})_2$, $-\text{S}(\text{O})_2\text{N}(\text{CH}_3)_2$, $-\text{SCH}_3$, $-\text{S}(\text{O})_2\text{CH}_3$, $-\text{S}(\text{O})_3\text{H}$, cyclopropyl, cyclopropylamide, cyclobutyl, oxetanyl, azetidynyl, 1-methylazetidin-3-yl)oxy, N-methyl-N-oxetan-3-ylamino, azetidin-1-ylmethyl, benzyloxyphenyl, pyrrolidin-1-yl, pyrrolidin-1-yl-methanone, piperazin-1-yl, morpholinomethyl, morpholino-methanone, and morpholino.

[0341] In one instance, the compound of formula (3a) comprises formula (3b):



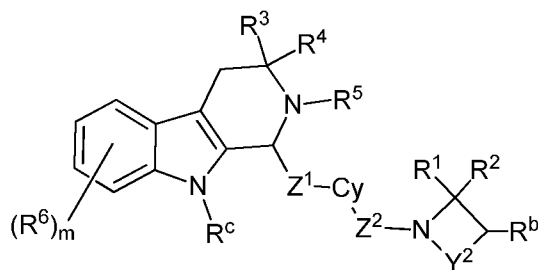
[0342] In another instance, the compound of formula (3a) comprises formula (3c):



wherein R^7 is F, Cl, Br, I, $-\text{CN}$, $-\text{CH}_3$, $-\text{CH}_2\text{CH}_3$, $-\text{CH}(\text{CH}_3)_2$, $-\text{CH}_2\text{CH}(\text{CH}_3)_2$, $-\text{CH}_2\text{OH}$, $-\text{CH}_2\text{OCH}_3$, $-\text{CH}_2\text{CH}_2\text{OH}$, $-\text{C}(\text{CH}_3)_2\text{OH}$, $-\text{CH}(\text{OH})\text{CH}(\text{CH}_3)_2$, $-\text{C}(\text{CH}_3)_2\text{CH}_2\text{OH}$, $-\text{CH}_2\text{CH}_2\text{SO}_2\text{CH}_3$, $-\text{CH}_2\text{OP}(\text{O})(\text{OH})_2$, $-\text{CH}_2\text{F}$, $-\text{CHF}_2$, $-\text{CH}_2\text{NH}_2$, $-\text{CH}_2\text{NHSO}_2\text{CH}_3$, $-\text{CH}_2\text{NHCH}_3$, $-\text{CH}_2\text{N}(\text{CH}_3)_2$, $-\text{CF}_3$, $-\text{CH}_2\text{CF}_3$, $-\text{CH}_2\text{CHF}_2$, $-\text{CH}(\text{CH}_3)\text{CN}$, $-\text{C}(\text{CH}_3)_2\text{CN}$, $-\text{CH}_2\text{CN}$, $-\text{CO}_2\text{H}$, $-\text{COCH}_3$, $-\text{CO}_2\text{CH}_3$, $-\text{CO}_2\text{C}(\text{CH}_3)_3$, $-\text{COCH}(\text{OH})\text{CH}_3$, $-\text{CONH}_2$, $-\text{CONHCH}_3$, $-\text{CONHCH}_2\text{CH}_3$, $-\text{CONHCH}(\text{CH}_3)_2$, $-\text{CON}(\text{CH}_3)_2$, $-\text{C}(\text{CH}_3)_2\text{CONH}_2$, $-\text{NH}_2$, $-\text{NHCH}_3$, $-\text{N}(\text{CH}_3)_2$, $-\text{NHCOCH}_3$, $-\text{N}(\text{CH}_3)\text{COCH}_3$, $-\text{NHS}(\text{O})_2\text{CH}_3$, $-\text{N}(\text{CH}_3)\text{C}(\text{CH}_3)_2\text{CONH}_2$, $-\text{N}(\text{CH}_3)\text{CH}_2\text{CH}_2\text{S}(\text{O})_2\text{CH}_3$, $-\text{NO}_2$, $=\text{O}$, $-\text{OH}$, $-\text{OCH}_3$, $-\text{OCH}_2\text{CH}_3$, $-\text{OCH}_2\text{CH}_2\text{OCH}_3$, $-\text{OCH}_2\text{CH}_2\text{OH}$, $-\text{OCH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$, $-\text{OP}(\text{O})(\text{OH})_2$, $-\text{S}(\text{O})_2\text{N}(\text{CH}_3)_2$, $-\text{SCH}_3$, $-\text{S}(\text{O})_2\text{CH}_3$, $-\text{S}(\text{O})_3\text{H}$, cyclopropyl, cyclopropylamide, oxetanyl, azetidiny, 1-methylazetidin-3-yl)oxy, N-methyl-N-oxetan-3-ylamino, azetidin-1-ylmethyl, benzyloxyphenyl, pyrrolidin-1-yl, pyrrolidin-1-yl-methanone, piperazin-1-yl, morpholinomethyl, morpholino-methanone, or morpholino; and

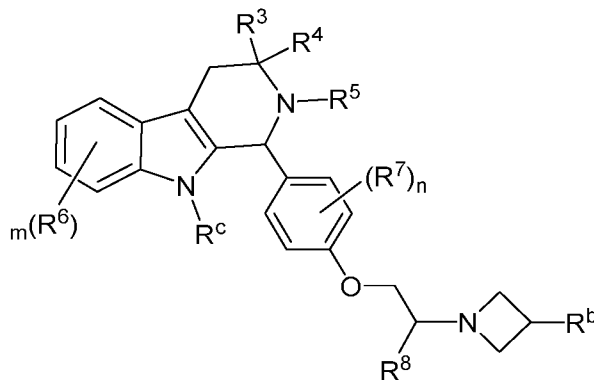
n is 0, 1, 2, 3, or 4.

[0343] In another instance, the compound of formula (3a) comprises formula (3d):



(3d)

[0344] In still another instance, the compound of formula (3a) comprises formula (3e):



(3e)

wherein R⁸ is H or -CH₃.

[0345] In another instance of the compounds of formula (3a)-(3e), Y¹ is CR^b and Y³ is NR^a. In another instance of the compounds of formula (3a)-(3e), Y¹ is N and Y³ is C(R^b)₂. In another instance of the compounds of formula (3a)-(3e), Y² is -(CH₂)- or -(CH₂CH₂)-. In another instance of the compounds of formula (3a)-(3e), R^c is H. In another instance of the compounds of formula (3a)-(3e), Cy is phenyldiyl. In one instance of the compounds of formula (3a)-(3e), phenyldiyl is substituted with one or more F.

[0346] In another instance of the compounds of formula (3a)-(3e), R¹ and R² are H. In another instance of the compounds of formula (3a)-(3e), R³ is H, and R⁴ is -CH₃. In another instance of the compounds of formula (3a)-(3e), R⁵ is C₁-C₆ fluoroalkyl. In another instance of the compounds of formula (3a)-(3e), m is 0.

[0347] In another aspect, the endocrine therapy comprises a compound having formula:

(1R,3R)-1-(2,6-difluoro-4-((1-(3-fluoropropyl)azetidin-3-yl)oxy)phenyl)-2-(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole; (1R,3R)-1-(2,6-difluoro-4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-2-(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole; 1-((1R,3R)-1-(2,6-difluoro-4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-3-methyl-3,4-dihydro-1H-pyrido[3,4-b]indol-2(9H)-yl)-2-methylpropan-1-one; 1-((1R,3R)-1-(2,6-difluoro-4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-3-methyl-3,4-dihydro-1H-pyrido[3,4-b]indol-2(9H)-yl)-2-fluoro-2-methylpropan-1-one; (1R,3R)-1-(4-(2-(3-(difluoromethyl)azetidin-1-yl)ethoxy)-2,6-difluorophenyl)-2-(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole; (1R,3R)-1-(4-((1-(3-chloropropyl)azetidin-3-yl)oxy)-2,6-difluorophenyl)-2-(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole; (1R,3R)-1-(2,6-difluoro-4-((1-propylazetidin-3-yl)oxy)phenyl)-2-(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole; (1R,3R)-1-(2,6-difluoro-4-((S)-2-((R)-3-(fluoromethyl)pyrrolidin-1-yl)propoxy)phenyl)-2-(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole; (1R,3R)-1-(2,6-difluoro-4-(2-((R)-3-(fluoromethyl)pyrrolidin-1-yl)ethoxy)phenyl)-2-(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole; (1R,3R)-2-(2-fluoro-2-methylpropyl)-1-(6-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)pyridin-3-yl)-3-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole; (1S,3R)-2-(2-fluoro-2-methylpropyl)-1-(3-fluoro-5-(2-(3-(fluoromethyl)azetidin-1-

yl)ethoxy)pyridin-2-yl)-3-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole; (1R,3R)-2-(cyclobutylmethyl)-1-(2,6-difluoro-4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-3-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole; (1R,3R)-1-(2,6-difluoro-4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-3-methyl-2-((3-methyloxetan-3-yl)methyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole; (1R,3R)-1-(2,6-difluoro-4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-3-methyl-2-(oxetan-3-ylmethyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole; (1R,3R)-1-(2,6-difluoro-4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-3-methyl-2-(oxetan-3-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole; (1R,3R)-1-(2,6-difluoro-4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)-2-(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole; (1R,3R)-1-(2,6-difluoro-4-(2-(piperidin-1-yl)ethoxy)phenyl)-2-(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole; (1-(2-(3,5-difluoro-4-((1R,3R)-2-(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)phenoxy)ethyl)azetidin-3-yl)methanol; (1R,3R)-2-(2-fluoro-2-methylpropyl)-1-(2-fluoro-4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-3-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole; 1-((1R,3R)-1-(2,6-difluoro-4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-3-methyl-3,4-dihydro-1H-pyrido[3,4-b]indol-2(9H)-yl)ethanone; 1-((1R,3R)-1-(2,6-difluoro-4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-3-methyl-3,4-dihydro-1H-pyrido[3,4-b]indol-2(9H)-yl)-2-hydroxy-2-methylpropan-1-one; (R)-3-((1R,3R)-1-(2,6-difluoro-4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-3-methyl-3,4-dihydro-1H-pyrido[3,4-b]indol-2(9H)-yl)-2-methylpropan-1-ol; ((1R,3R)-1-(2,6-difluoro-4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-3-methyl-3,4-dihydro-1H-pyrido[3,4-b]indol-2(9H)-yl)((1S,3S)-3-hydroxycyclobutyl)methanone; 1-(1-(2,6-difluoro-4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-3,3-dimethyl-3,4-dihydro-1H-pyrido[3,4-b]indol-2(9H)-yl)-2-methylpropan-1-one; (1R,3R)-1-(2,6-difluoro-4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-3-methyl-2-(methylsulfonyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole; 1-[(1R,3R)-1-[2,6-difluoro-4-[2-[3-(fluoromethyl)azetidin-1-yl]ethoxy]phenyl]-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indol-2-yl]-2-methylpropan-2-ol; (1R,3R)-1-[4-[2-[3-(difluoromethyl)azetidin-1-yl]ethoxy]-2,6-difluorophenyl]-2-(2-fluoro-2-methylpropyl)-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indole; (1R,3R)-1-[4-[1-(3-chloropropyl)azetidin-3-yl]oxy-2,6-difluoro-phenyl]-2-(2-fluoro-2-methylpropyl)-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indole; (1R,3R)-1-[2,6-difluoro-4-(1-propylazetidin-3-yl)oxy-phenyl]-2-(2-fluoro-2-methylpropyl)-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indole;

((1S,3R)-1-(2,6-difluoro-4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-2-(2-fluoro-2-methylpropyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-3-yl)methanol; (1R,3R)-1-[4-(azetidin-3-yloxy)-2,6-difluoro-phenyl]-2-(2-fluoro-2-methyl-propyl)-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indole; (1R,3R)-2-(2-fluoro-2-methylpropyl)-1-(2-fluoro-4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-3-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole; (1R,3R)-2-cyclobutyl-1-[2,6-difluoro-4-[2-[3-(fluoromethyl)azetidin-1-yl]ethoxy]phenyl]-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indole; (1R,3S)-1-[2,6-difluoro-4-[2-[3-(fluoromethyl)azetidin-1-yl]ethoxy]phenyl]-3-(fluoromethyl)-2-(2-fluoro-2-methyl-propyl)-1,3,4,9-tetrahydropyrido[3,4-b]indole; (1R,3R)-1-[2,6-difluoro-4-[2-[3-(fluoromethyl)azetidin-1-yl]ethoxy]phenyl]-2-[(3-fluorooxetan-3-yl)methyl]-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indole; cyclohexyl((1R,3R)-1-(2,6-difluoro-4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-3-methyl-3,4-dihydro-1H-pyrido[3,4-b]indol-2(9H)-yl)methanone; 1-[(1R,3R)-1-[2,6-difluoro-4-[2-[3-(fluoromethyl)azetidin-1-yl]ethoxy]phenyl]-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indol-2-yl]-2,2-dimethyl-propan-1-one; cyclopropyl((1R,3R)-1-(2,6-difluoro-4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-3-methyl-3,4-dihydro-1H-pyrido[3,4-b]indol-2(9H)-yl)methanone; (1R,3R)-1-[2,6-difluoro-4-[2-(3-methylazetidin-1-yl)ethoxy]phenyl]-2-(2-fluoro-2-methyl-propyl)-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indole; (1R,3R)-1-(2,6-difluoro-4-(2-((R)-3-methylpyrrolidin-1-yl)ethoxy)phenyl)-2-(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole; (1R,3R)-1-[2,6-difluoro-4-[(2S)-2-pyrrolidin-1-ylpropoxy]phenyl]-2-(2-fluoro-2-methyl-propyl)-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indole; (1R,3R)-1-[2,6-difluoro-4-[3-[3-(fluoromethyl)azetidin-1-yl]propoxy]phenyl]-2-(2-fluoro-2-methyl-propyl)-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indole; (1R,3R)-1-[2,6-difluoro-4-[(E)-3-[3-(fluoromethyl)azetidin-1-yl]prop-1-enyl]phenyl]-2-(2-fluoro-2-methyl-propyl)-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indole; (1R,3R)-2-[(3,3-difluorocyclobutyl)methyl]-1-[2,6-difluoro-4-[2-[3-(fluoromethyl)azetidin-1-yl]ethoxy]phenyl]-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indole; (1R,3R)-1-[2,6-difluoro-4-[2-[3-(fluoromethyl)azetidin-1-yl]ethoxy]phenyl]-2-(2,2-dimethylpropyl)-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indole; cyclobutyl-[(1R,3R)-1-[2,6-difluoro-4-[2-[3-(fluoromethyl)azetidin-1-yl]ethoxy]phenyl]-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indol-2-yl]methanone; cyclopentyl-[(1R,3R)-1-[2,6-difluoro-4-[2-[3-(fluoromethyl)azetidin-1-yl]ethoxy]phenyl]-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indol-2-yl]methanone; (1R,3R)-1-

[2,6-difluoro-4-[2-[(3S)-3-methylpyrrolidin-1-yl]ethoxy]phenyl]-2-(2-fluoro-2-methyl-propyl)-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indole; (1R,3R)-1-[2,6-difluoro-4-[(2R)-2-pyrrolidin-1-ylpropoxy]phenyl]-2-(2-fluoro-2-methyl-propyl)-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indole; (1R,3R)-1-[2,6-difluoro-4-[(1-propylazetidin-3-yl)methoxy]phenyl]-2-(2-fluoro-2-methyl-propyl)-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indole; (1R,3R)-1-[2,6-difluoro-4-[2-[3-(fluoromethyl)azetidin-1-yl]ethoxy]phenyl]-2-[(1-fluorocyclobutyl)methyl]-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indole; (S)-3-((1R,3R)-1-(2,6-difluoro-4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-3-methyl-3,4-dihydro-1H-pyrido[3,4-b]indol-2(9H)-yl)-2-fluoro-2-methylpropan-1-ol; (2R)-3-[(1R,3R)-1-[2,6-difluoro-4-[2-[3-(fluoromethyl)azetidin-1-yl]ethoxy]phenyl]-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indol-2-yl]-2-fluoro-2-methylpropan-1-ol; (1R,3R)-1-[4-[2-[3-(fluoromethyl)azetidin-1-yl]ethoxy]phenyl]-2-(2-fluoro-2-methyl-propyl)-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indole; 2-cyclopropyl-1-[(1R,3R)-1-[2,6-difluoro-4-[2-[3-(fluoromethyl)azetidin-1-yl]ethoxy]phenyl]-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indol-2-yl]ethanone; 2-cyclobutyl-1-[(1R,3R)-1-[2,6-difluoro-4-[2-[3-(fluoromethyl)azetidin-1-yl]ethoxy]phenyl]-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indol-2-yl]ethanone; 1-[(1R,3R)-1-[2,6-difluoro-4-[2-[3-(fluoromethyl)azetidin-1-yl]ethoxy]phenyl]-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indol-2-yl]-2,2-difluoro-propan-1-one; (1R,3R)-1-[2,6-difluoro-4-[2-[3-(fluoromethyl)-3-methyl-azetidin-1-yl]ethoxy]phenyl]-2-(2-fluoro-2-methyl-propyl)-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indole; (1R,3R)-1-[2,6-difluoro-4-(1-methylazetidin-3-yl)oxy-phenyl]-2-(2-fluoro-2-methyl-propyl)-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indole; (1R,3R)-1-[4-(1-ethylazetidin-3-yl)oxy-2,6-difluoro-phenyl]-2-(2-fluoro-2-methyl-propyl)-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indole; (1R,3R)-1-[2,6-difluoro-4-(1-pentylazetidin-3-yl)oxy-phenyl]-2-(2-fluoro-2-methyl-propyl)-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indole; (1R,3R)-1-[4-[1-(cyclopropylmethyl)azetidin-3-yl]oxy-2,6-difluoro-phenyl]-2-(2-fluoro-2-methyl-propyl)-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indole; (1R,3R)-1-[4-[1-(cyclopentylmethyl)azetidin-3-yl]oxy-2,6-difluoro-phenyl]-2-(2-fluoro-2-methyl-propyl)-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indole; (1R,3R)-1-[2,6-difluoro-4-[1-(2-fluoroethyl)azetidin-3-yl]oxy-phenyl]-2-(2-fluoro-2-methyl-propyl)-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indole; (1R,3R)-1-[2,6-difluoro-4-(1-prop-2-ynylazetidin-3-yl)oxy-phenyl]-2-(2-fluoro-2-methyl-propyl)-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indole; (1R,3R)-1-[2,6-difluoro-4-(1-isopropylazetidin-3-yl)oxy-phenyl]-2-(2-fluoro-2-methyl-propyl)-3-methyl-

1,3,4,9-tetrahydropyrido[3,4-b]indole; (1R,3R)-1-[2,6-difluoro-4-(1-isobutylazetidin-3-yl)oxy-phenyl]-2-(2-fluoro-2-methyl-propyl)-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indole; tert-butyl 3-[3,5-difluoro-4-[(1R,3R)-2-(2-fluoro-2-methyl-propyl)-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indol-1-yl]phenoxy]azetidine-1-carboxylate; (1R,3R)-1-(2,6-difluoro-4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-3-ethyl-2-(2-fluoro-2-methylpropyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole; (1R,3S)-1-(2,6-difluoro-4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-3-ethyl-2-(2-fluoro-2-methylpropyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole; (1R,3R)-1-[2,6-difluoro-4-[2-[3-(fluoromethyl)azetidin-1-yl]ethoxy]phenyl]-3-methyl-2-[(1-methylcyclobutyl)methyl]-1,3,4,9-tetrahydropyrido[3,4-b]indole; (1R,3R)-1-[2,6-difluoro-4-[2-[3-(fluoromethyl)azetidin-1-yl]ethoxy]phenyl]-3-methyl-2-(2,2,2-trifluoroethyl)-1,3,4,9-tetrahydropyrido[3,4-b]indole; (1S,3R)-1-[2,6-difluoro-4-[2-[3-(fluoromethyl)azetidin-1-yl]ethoxy]phenyl]-3-methyl-2-(2,2,2-trifluoroethyl)-1,3,4,9-tetrahydropyrido[3,4-b]indole; (1R,3R)-1-[4-[1-(3,3-dimethoxypropyl)azetidin-3-yl]oxy-2,6-difluoro-phenyl]-2-(2-fluoro-2-methyl-propyl)-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indole; (1R,3R)-1-[2-fluoro-4-[1-(3-fluoropropyl)azetidin-3-yl]oxy-phenyl]-2-(2-fluoro-2-methyl-propyl)-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indole; 1-[2,6-difluoro-4-[2-[3-(fluoromethyl)azetidin-1-yl]ethoxy]phenyl]-2-(2-fluoro-2-methyl-propyl)-1,3,4,9-tetrahydropyrido[3,4-b]indole; (1S,3R)-1-[4-[2-[3-(fluoromethyl)azetidin-1-yl]ethoxy]phenyl]-3-methyl-2-methylsulfonyl-1,3,4,9-tetrahydropyrido[3,4-b]indole; (1R,3R)-1-(4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-3-methyl-2-(methylsulfonyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole; 1-((1R,3R)-1-(2,6-difluoro-4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-3-methyl-3,4-dihydro-1H-pyrido[3,4-b]indol-2(9H)-yl)-3-hydroxy-2-methylpropan-1-one; azetidin-3-yl-[(1R,3R)-1-[2,6-difluoro-4-[2-[3-(fluoromethyl)azetidin-1-yl]ethoxy]phenyl]-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indol-2-yl]methanone; ((1R,3R)-1-(2,6-difluoro-4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-3-methyl-3,4-dihydro-1H-pyrido[3,4-b]indol-2(9H)-yl)(2-fluorocyclopropyl)methanone; (1R,3R)-1-[2,6-difluoro-4-[(2S)-2-[(3R)-3-methylpyrrolidin-1-yl]propoxy]phenyl]-2-(2-fluoro-2-methyl-propyl)-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indole; [(1R,3R)-1-[2,6-difluoro-4-[2-[3-(fluoromethyl)azetidin-1-yl]ethoxy]phenyl]-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indol-2-yl]-phenyl-methanone; (1R,3R)-2-(cyclopropylmethyl)-1-[2,6-difluoro-4-[2-[3-(fluoromethyl)azetidin-1-yl]ethoxy]phenyl]-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indole; (1R,3R)-1-[4-[1-(2-

cyclopropylethyl)azetidin-3-yl]oxy-2,6-difluoro-phenyl]-2-(2-fluoro-2-methyl-propyl)-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indole; (1R,3R)-1-[4-(1-allylazetidin-3-yl)oxy-2,6-difluoro-phenyl]-2-(2-fluoro-2-methyl-propyl)-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indole; (1R,3R)-1-[4-[1-(cyclobutylmethyl)azetidin-3-yl]oxy-2,6-difluoro-phenyl]-2-(2-fluoro-2-methyl-propyl)-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indole; (1R,3R)-1-[2,6-difluoro-4-(1-isopentylazetidin-3-yl)oxy-phenyl]-2-(2-fluoro-2-methyl-propyl)-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indole; (1R,3R)-1-(2,6-difluoro-4-((1-(2-methylbutyl)azetidin-3-yl)oxy)phenyl)-2-(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole; (1R,3R)-1-(2,6-difluoro-4-((1-(pentan-2-yl)azetidin-3-yl)oxy)phenyl)-2-(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole; (1R,3R)-1-[4-(1-cyclobutylazetidin-3-yl)oxy-2,6-difluoro-phenyl]-2-(2-fluoro-2-methyl-propyl)-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indole; (1R,3R)-1-[2,6-difluoro-4-[1-(oxetan-3-yl)azetidin-3-yl]oxy-phenyl]-2-(2-fluoro-2-methyl-propyl)-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indole; (1R,3R)-1-[4-(1-cyclopropylazetidin-3-yl)oxy-2,6-difluoro-phenyl]-2-(2-fluoro-2-methyl-propyl)-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indole; (1R,3R)-1-[2,6-difluoro-4-[1-(3-fluoropropyl)azetidin-3-yl]sulfonyl-phenyl]-2-(2-fluoro-2-methyl-propyl)-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indole; (1R,3R)-1-[2,6-difluoro-4-[2-[3-(fluoromethyl)azetidin-1-yl]ethoxy]phenyl]-2-isobutyl-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indole; (1R,3R)-1-(2,6-difluoro-4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-3-methyl-2-((R)-2-phenylpropyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole; (1R,3R)-1-(2,6-difluoro-4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-3-methyl-2-((S)-2-phenylpropyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole; (1R,3R)-1-[2,6-difluoro-4-(1-propylazetidin-3-yl)oxy-phenyl]-2-isobutyl-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indole; (1R,3R)-2-(2-fluoro-2-methyl-propyl)-1-[4-[1-(3-fluoropropyl)azetidin-3-yl]oxyphenyl]-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indole; (1R,3R)-1-[2,6-difluoro-4-[1-(3-fluoropropyl)azetidin-3-yl]oxy-phenyl]-3-methyl-2-methylsulfonyl-1,3,4,9-tetrahydropyrido[3,4-b]indole; [1-[2,6-difluoro-4-[2-[3-(fluoromethyl)azetidin-1-yl]ethoxy]phenyl]-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indol-2-yl]-(3-fluorocyclobutyl)methanone; (1R,3R)-1-[4-[(2S)-2-[3-(difluoromethyl)azetidin-1-yl]propoxy]-2,6-difluoro-phenyl]-2-(2-fluoro-2-methyl-propyl)-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indole; (1R,3R)-1-[2,6-difluoro-4-[2-[3-fluoro-3-(fluoromethyl)azetidin-1-yl]ethoxy]phenyl]-2-(2-fluoro-2-methyl-propyl)-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indole; 4-[(1R,3R)-1-[2,6-difluoro-4-[2-[3-(fluoromethyl)azetidin-1-

yl]ethoxy]phenyl]-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indol-2-yl]-4-oxo-butanenitrile; (1R,3R)-2-(cyclohexylmethyl)-1-[2,6-difluoro-4-[2-[3-(fluoromethyl)azetidin-1-yl]ethoxy]phenyl]-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indole; (1R,3R)-1-[2,6-difluoro-4-[1-[2-(oxetan-3-yl)ethyl]azetidin-3-yl]oxy-phenyl]-2-(2-fluoro-2-methyl-propyl)-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indole; (1R,3R)-1-[4-[1-(cyclohexylmethyl)azetidin-3-yl]oxy-2,6-difluoro-phenyl]-2-(2-fluoro-2-methyl-propyl)-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indole; (1R,3R)-1-[2-chloro-4-[2-[3-(fluoromethyl)azetidin-1-yl]ethoxy]phenyl]-2-(2-fluoro-2-methyl-propyl)-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indole; (1R,3R)-1-[2-chloro-4-[1-(3-fluoropropyl)azetidin-3-yl]oxy-phenyl]-2-(2-fluoro-2-methyl-propyl)-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indole; 1-((1R,3R)-1-(2,6-difluoro-4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-3-methyl-3,4-dihydro-1H-pyrido[3,4-b]indol-2(9H)-yl)-3-hydroxybutan-1-one; [(1R,3R)-1-[2,6-difluoro-4-[2-[3-(fluoromethyl)azetidin-1-yl]ethoxy]phenyl]-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indol-2-yl]-(oxetan-3-yl)methanone; [(1R,3R)-1-[2,6-difluoro-4-[2-[3-(fluoromethyl)azetidin-1-yl]ethoxy]phenyl]-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indol-2-yl]-(thietan-3-yl)methanone; (R)-1-((1R,3R)-1-(2,6-difluoro-4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-3-methyl-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indol-2-yl)-3-fluoro-2-methylpropan-1-one; (1R,3R)-2-(cyclopentylmethyl)-1-[2,6-difluoro-4-[2-[3-(fluoromethyl)azetidin-1-yl]ethoxy]phenyl]-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indole; (1R,3R)-1-[4-[1-[(4,4-difluorocyclohexyl)methyl]azetidin-3-yl]oxy-2,6-difluoro-phenyl]-2-(2-fluoro-2-methyl-propyl)-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indole; (S)-1-((1R,3R)-1-(2,6-difluoro-4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-3-methyl-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indol-2-yl)-3-fluoro-2-methylpropan-1-one; ((1R,3R)-1-(2,6-difluoro-4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-3-methyl-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indol-2-yl)(oxetan-2-yl)methanone; (1R,3R)-1-[2,6-difluoro-4-[2-[3-(fluoromethyl)azetidin-1-yl]ethoxy]phenyl]-3-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole; 2-fluoro-1-[(1R,3R)-1-[4-[2-[3-(fluoromethyl)azetidin-1-yl]ethoxy]phenyl]-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indol-2-yl]-2-methyl-propan-1-one; 1-[(1R,3R)-1-[2,6-difluoro-4-[1-(3-fluoropropyl)azetidin-3-yl]oxy-phenyl]-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indol-2-yl]-2-fluoro-2-methyl-propan-1-one; 1-[(1R,3R)-1-[2,6-difluoro-4-[2-[3-(fluoromethyl)azetidin-1-yl]ethoxy]phenyl]-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indol-2-yl]-2-(dimethylamino)ethanone; (1R,3R)-1-[2,6-difluoro-4-[1-[(1-fluorocyclopropyl)methyl]azetidin-3-yl]oxy-phenyl]-2-(2-fluoro-2-methyl-propyl)-3-

methyl-1,3,4,9-tetrahydropyrido[3,4-b]indole; [(1R,3R)-1-[2,6-difluoro-4-[1-(3-fluoropropyl)azetidin-3-yl]oxy-phenyl]-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indol-2-yl]-(1-fluorocyclobutyl)methanone; [(1R,3R)-1-[2,6-difluoro-4-[1-(3-fluoropropyl)azetidin-3-yl]oxy-phenyl]-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indol-2-yl]-(1-methylcyclopropyl)methanone; (1R,3R)-1-[2,6-difluoro-4-[1-(3-fluoropropyl)azetidin-3-yl]oxy-phenyl]-2-[[1-(fluoromethyl)cyclopropyl]methyl]-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indole; ; [1-[[[(1R,3R)-1-[2,6-difluoro-4-[1-(3-fluoropropyl)azetidin-3-yl]oxy-phenyl]-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indol-2-yl]methyl]cyclopropyl]methanol; 2-fluoro-1-[(1S,3R)-1-[2-fluoro-4-[2-[3-(fluoromethyl)azetidin-1-yl]ethoxy]phenyl]-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indol-2-yl]-2-methyl-propan-1-one; 2-fluoro-1-[(1R,3R)-1-[2-fluoro-4-[2-[3-(fluoromethyl)azetidin-1-yl]ethoxy]phenyl]-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indol-2-yl]-2-methyl-propan-1-one; (1S,3R)-1-[2-fluoro-4-[2-[3-(fluoromethyl)azetidin-1-yl]ethoxy]phenyl]-3-methyl-2-methylsulfonyl-1,3,4,9-tetrahydropyrido[3,4-b]indole; (1R,3R)-1-[2-fluoro-4-[2-[3-(fluoromethyl)azetidin-1-yl]ethoxy]phenyl]-3-methyl-2-methylsulfonyl-1,3,4,9-tetrahydropyrido[3,4-b]indole; 3-((1R,3R)-1-(2,6-difluoro-4-((1-(3-fluoropropyl)azetidin-3-yl)oxy)phenyl)-3-methyl-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indol-2-yl)-2-fluoro-2-methylpropan-1-ol; 3-((1R,3R)-1-(2,6-difluoro-4-((1-(3-fluoropropyl)azetidin-3-yl)oxy)phenyl)-3-methyl-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indol-2-yl)-2-fluoro-2-methylpropan-1-ol; 2-fluoro-1-[(1S,3R)-1-[4-[2-[3-(fluoromethyl)azetidin-1-yl]ethoxy]phenyl]-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indol-2-yl]-2-methyl-propan-1-one; (1R)-1-[2,6-difluoro-4-[2-[3-(fluoromethyl)azetidin-1-yl]ethoxy]phenyl]-2-(2-fluoro-2-methyl-propyl)-1,3,4,9-tetrahydropyrido[3,4-b]indole; (1S)-1-[2,6-difluoro-4-[2-[3-(fluoromethyl)azetidin-1-yl]ethoxy]phenyl]-2-(2-fluoro-2-methyl-propyl)-1,3,4,9-tetrahydropyrido[3,4-b]indole; [(1R,3R)-1-[2,6-difluoro-4-[1-(3-fluoropropyl)azetidin-3-yl]oxy-phenyl]-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indol-2-yl]-(1-fluorocyclopropyl)methanone; (1R,3R)-6-chloro-1-(2,6-difluoro-4-((1-(3-fluoropropyl)azetidin-3-yl)oxy)phenyl)-2-(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole; (1R,3R)-1-(2,6-difluoro-4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-7-fluoro-2-(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole; (1R,3R)-1-(2,6-difluoro-4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-6-fluoro-2-(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole; (1R,3R)-1-(2,6-difluoro-4-((1-(3-

fluoropropyl)azetidin-3-yl)oxy)phenyl)-6-fluoro-2-(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole; (1-(((1R,3R)-1-(2,6-difluoro-4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-3-methyl-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indol-2-yl)methyl)cyclopropyl)methanol; (1S,3S)-6-chloro-1-(2,6-difluoro-4-((1-(3-fluoropropyl)azetidin-3-yl)oxy)phenyl)-2-(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole; (1S,3S)-1-(2,6-difluoro-4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-6-fluoro-2-(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole; (1R,3R)-1-[2,6-difluoro-4-[1-(3-fluoropropyl)azetidin-3-yl]oxy-phenyl]-3-methyl-2-[(3-methyloxetan-3-yl)methyl]-1,3,4,9-tetrahydropyrido[3,4-b]indole; (1R,3R)-1-(2,6-difluoro-4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-5-fluoro-2-(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole; (1R,3R)-1-(2,6-difluoro-4-((1-(3-fluoropropyl)azetidin-3-yl)oxy)phenyl)-7-fluoro-2-(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole; (1R,3R)-1-(2,6-difluoro-4-((1-(3-fluoropropyl)azetidin-3-yl)oxy)phenyl)-5-fluoro-2-(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole; (1R,3R)-2-(2-fluoro-2-methyl-propyl)-1-[4-[2-[(3R)-3-(fluoromethyl)pyrrolidin-1-yl]ethoxy]phenyl]-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indole; (1S,3S)-1-(2,6-difluoro-4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-5-fluoro-2-(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole; (1S,3S)-1-(2,6-difluoro-4-((1-(3-fluoropropyl)azetidin-3-yl)oxy)phenyl)-7-fluoro-2-(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole; (1S,3S)-1-(2,6-difluoro-4-((1-(3-fluoropropyl)azetidin-3-yl)oxy)phenyl)-5-fluoro-2-(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole; 2-[(1R,3R)-1-[2,6-difluoro-4-[2-[3-(fluoromethyl)azetidin-1-yl]ethoxy]phenyl]-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indol-2-yl]-N,N-dimethyl-acetamide; 3-((1R,3R)-1-(2,6-difluoro-4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-3-methyl-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indol-2-yl)-2-fluoro-2-methylpropan-1-ol; (1R,3R)-2-(2-fluoro-2-methyl-propyl)-1-[4-[1-(3-fluoropropyl)azetidin-3-yl]oxy-2-methyl-phenyl]-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indole; (1R)-1-[2,6-difluoro-4-[2-[3-(fluoromethyl)azetidin-1-yl]ethoxy]phenyl]-2-(2-fluoro-2-methyl-propyl)-3,3-dimethyl-4,9-dihydro-1H-pyrido[3,4-b]indole; (S)-1-(2,6-difluoro-4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-2-(2-fluoro-2-methylpropyl)-3,3-dimethyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole; (1R,3R)-1-[4-[1-[(3,3-difluorocyclobutyl)methyl]azetidin-3-yl]oxy-2,6-difluoro-phenyl]-2-(2-fluoro-2-methyl-propyl)-

3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indole; (1R,3R)-1-(2,6-difluoro-4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-8-fluoro-2-(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole; (1R,3R)-1-(2,6-difluoro-4-((1-(3-fluoropropyl)azetidin-3-yl)oxy)phenyl)-8-fluoro-2-(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole; (1S,3S)-1-(2,6-difluoro-4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-8-fluoro-2-(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole; (S)-1-((1R,3R)-1-(2,6-difluoro-4-((1-(3-fluoropropyl)azetidin-3-yl)oxy)phenyl)-3-methyl-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indol-2-yl)propan-2-ol; (R)-1-((1R,3R)-1-(2,6-difluoro-4-((1-(3-fluoropropyl)azetidin-3-yl)oxy)phenyl)-3-methyl-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indol-2-yl)propan-2-ol; (1R,3R)-1-[4-[2-[3-(chloromethyl)azetidin-1-yl]ethoxy]-2,6-difluoro-phenyl]-2-(2-fluoro-2-methyl-propyl)-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indole; (1R,3R)-1-[3-chloro-4-[1-(3-fluoropropyl)azetidin-3-yl]oxy-phenyl]-2-(2-fluoro-2-methyl-propyl)-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indole; (1R,3R)-1-[3-fluoro-4-[1-(3-fluoropropyl)azetidin-3-yl]oxy-phenyl]-2-(2-fluoro-2-methyl-propyl)-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indole; (2R)-3-[(1R,3R)-1-[2,6-difluoro-4-[2-[3-(fluoromethyl)azetidin-1-yl]ethoxy]phenyl]-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indol-2-yl]propane-1,2-diol; (1R,3R)-1-[2,6-difluoro-4-[1-[(1S,2R)-2-fluorocyclopropyl]methyl]azetidin-3-yl]oxy-phenyl]-2-(2-fluoro-2-methyl-propyl)-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indole; (1R,3R)-1-(2,6-difluoro-4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-2-((S)-3-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole; (S)-3-((1R,3R)-1-(2,6-difluoro-4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-3-methyl-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indol-2-yl)-2-methylpropane-1,2-diol; (1R,3R)-1-[2,6-difluoro-4-[1-(3-fluoropropyl)azetidin-3-yl]oxy-phenyl]-2-(3-fluoro-2,2-dimethyl-propyl)-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indole; (R)-2-fluoro-3-((1R,3R)-1-(2-fluoro-4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-3-methyl-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indol-2-yl)-2-methylpropan-1-ol; (S)-2-fluoro-3-((1R,3R)-1-(2-fluoro-4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-3-methyl-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indol-2-yl)-2-methylpropan-1-ol; (R)-2-fluoro-3-((1R,3R)-1-(4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-3-methyl-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indol-2-yl)-2-methylpropan-1-ol; (S)-2-fluoro-3-((1R,3R)-1-(4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-3-methyl-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indol-2-yl)-2-methylpropan-1-ol; (1R,3R)-1-[2,6-difluoro-4-[1-(3-fluoropropyl)azetidin-3-

yl]oxy-phenyl]-3-methyl-2-(2,2,2-trifluoroethyl)-1,3,4,9-tetrahydropyrido[3,4-b]indole; (2R)-3-[(1R,3R)-1-[2,6-difluoro-4-[2-[3-(fluoromethyl)azetidin-1-yl]ethoxy]phenyl]-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indol-2-yl]-2-methyl-propane-1,2-diol; (1R,3R)-2-(2-fluoro-2-methylpropyl)-1-(3-fluoro-4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-3-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole; (1S,3R)-2-(2-fluoro-2-methylpropyl)-1-(3-fluoro-4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-3-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole; (1R,3R)-1-(2,3-difluoro-4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-2-(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole; (1R,3R)-1-(2,6-difluoro-4-((1-(((1S,2S)-2-fluorocyclopropyl)methyl)azetidin-3-yl)oxy)phenyl)-2-(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole; 1-[(1R,3R)-1-[2,6-difluoro-4-[1-(3-fluoropropyl)azetidin-3-yl]oxy-phenyl]-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indol-2-yl]propan-2-one; 3-[(1R,3R)-1-[2,6-difluoro-4-[1-(3-fluoropropyl)azetidin-3-yl]oxy-phenyl]-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indol-2-yl]-2,2-dimethyl-propan-1-ol; (1R,3R)-1-[2,6-difluoro-4-[1-(3-fluoropropyl)azetidin-3-yl]oxy-phenyl]-2-ethylsulfonyl-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indole; 3-[(1R,3R)-1-[2,6-difluoro-4-[2-[3-(fluoromethyl)azetidin-1-yl]ethoxy]phenyl]-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indol-2-yl]-2,2-difluoro-propan-1-ol; 3-[(1R,3R)-1-[2,6-difluoro-4-[2-[3-(fluoromethyl)azetidin-1-yl]ethoxy]phenyl]-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indol-2-yl]-2,2-dimethyl-propan-1-ol; 3-((1R,3R)-1-(2,6-difluoro-4-((1-(3-fluoropropyl)azetidin-3-yl)oxy)phenyl)-3-methyl-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indol-2-yl)-2-fluoro-2-methylpropan-1-ol; 1-((1S,3R)-1-(2,6-difluoro-4-((1-(3-fluoropropyl)azetidin-3-yl)oxy)phenyl)-3-methyl-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indol-2-yl)propan-2-one; (S)-3-((1R,3R)-1-(2,6-difluoro-4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-3-methyl-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indol-2-yl)-N,N,2-trimethylpropanamide; (R)-3-((1R,3R)-1-(2,6-difluoro-4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-3-methyl-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indol-2-yl)-N,N,2-trimethylpropanamide; (S)-3-((1R,3R)-1-(2,6-difluoro-4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-3-methyl-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indol-2-yl)-2-methylpropanoic acid; (R)-3-((1R,3R)-1-(2,6-difluoro-4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-3-methyl-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indol-2-yl)-2-methylpropanoic acid; (1R,3S)-1-(2,6-difluoro-4-((1-(3-fluoropropyl)azetidin-3-yl)oxy)phenyl)-2-(2-fluoro-2-methylpropyl)-3-(fluoromethyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole; 3-((1R,3R)-1-(2,6-difluoro-4-((1-(3-

fluoropropyl)azetidin-3-yl)oxy)phenyl)-3-methyl-3,4-dihydro-1H-pyrido[3,4-b]indol-2(9H)-yl)-2,2-difluoropropan-1-ol; (1R,3R)-2-(2,2-difluoroethyl)-1-[2,6-difluoro-4-[1-(3-fluoropropyl)azetidin-3-yl]oxy-phenyl]-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indole; (1R,3R)-2-(2,2-difluoroethyl)-1-[2,6-difluoro-4-[2-[3-(fluoromethyl)azetidin-1-yl]ethoxy]phenyl]-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indole; (1S,3R)-2-(2,2-difluoroethyl)-1-[2,6-difluoro-4-[2-[3-(fluoromethyl)azetidin-1-yl]ethoxy]phenyl]-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indole; (1R,3R)-1-[4-[1-(3,3-difluorocyclobutyl)azetidin-3-yl]oxy-2,6-difluoro-phenyl]-2-(2-fluoro-2-methyl-propyl)-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indole; (1R,3R)-1-[2,6-difluoro-4-[1-[(E)-3-fluoroallyl]azetidin-3-yl]oxy-phenyl]-2-(2-fluoro-2-methyl-propyl)-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indole; (1R,3R)-1-(2,6-difluoro-4-((1-(3-fluoropropyl)azetidin-3-yl)oxy)phenyl)-3-methyl-2-(2-(methylsulfonyl)propyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole; (1R,3R)-1-[4-[2-[3-(fluoromethyl)azetidin-1-yl]ethoxy]phenyl]-3-methyl-2-vinylsulfonyl-1,3,4,9-tetrahydropyrido[3,4-b]indole; (1R,3R)-1-[4-[2-[3-(fluoromethyl)azetidin-1-yl]ethoxy]phenyl]-N,3-dimethyl-1,3,4,9-tetrahydropyrido[3,4-b]indole-2-sulfonamide; 3-[(1R,3R)-1-[2,6-difluoro-4-[1-(3-fluoropropyl)azetidin-3-yl]oxy-phenyl]-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indol-2-yl]-2,2-dimethyl-propanenitrile; (1R,3R)-1-[4-[1-(3,3-difluoroallyl)azetidin-3-yl]oxy-2,6-difluoro-phenyl]-2-(2-fluoro-2-methyl-propyl)-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indole; (S)-2-(((1R,3R)-1-(2,6-difluoro-4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-3-methyl-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indol-2-yl)methyl)-3,3,3-trifluoropropan-1-ol; (R)-2-(((1R,3R)-1-(2,6-difluoro-4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-3-methyl-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indol-2-yl)methyl)-3,3,3-trifluoropropan-1-ol; (1R,3R)-2-ethylsulfonyl-1-[4-[2-[3-(fluoromethyl)azetidin-1-yl]ethoxy]phenyl]-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indole; (1R,3R)-1-[4-[2-[3-(fluoromethyl)azetidin-1-yl]ethoxy]phenyl]-N,N,3-trimethyl-1,3,4,9-tetrahydropyrido[3,4-b]indole-2-sulfonamide; (1R,3R)-1-[4-[1-(3-fluoropropyl)azetidin-3-yl]oxyphenyl]-3-methyl-2-methylsulfonyl-1,3,4,9-tetrahydropyrido[3,4-b]indole; 3-[3-[3,5-difluoro-4-[(1R,3R)-2-(2-fluoro-2-methyl-propyl)-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indol-1-yl]phenoxy]azetidin-1-yl]cyclobutanol; (1R,3R)-1-(4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-2-((S)-isopropylsulfinyl)-3-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole; (1R,3R)-1-(4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-2-((R)-isopropylsulfinyl)-3-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-

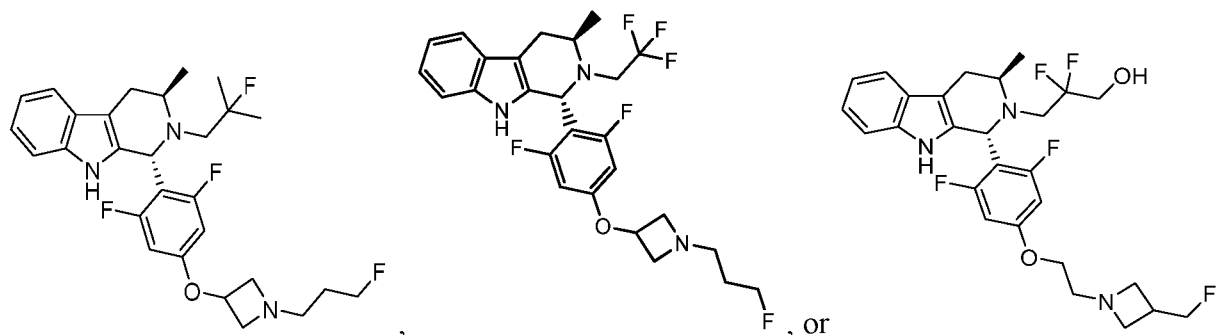
b]indole; (1S,3s)-3-(3-(3,5-difluoro-4-((1R,3R)-2-(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)phenoxy)azetidin-1-yl)cyclobutanol; (1R,3R)-1-[2,6-difluoro-4-[1-(5-fluoropentyl)azetidin-3-yl]oxy-phenyl]-2-(2-fluoro-2-methyl-propyl)-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indole; (1R,3R)-1-[3,5-difluoro-4-[1-(3-fluoropropyl)azetidin-3-yl]oxy-phenyl]-2-(2-fluoro-2-methyl-propyl)-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indole; (1R,3R)-1-[2,6-difluoro-4-[1-(4-fluorobutyl)azetidin-3-yl]oxy-phenyl]-2-(2-fluoro-2-methyl-propyl)-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indole; (1R,3R)-1-[3,5-difluoro-4-[1-(5-fluoropentyl)azetidin-3-yl]oxy-phenyl]-2-(2-fluoro-2-methyl-propyl)-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indole; (1R,3R)-1-[2,5-difluoro-4-[1-(3-fluoropropyl)azetidin-3-yl]oxy-phenyl]-2-(2-fluoro-2-methyl-propyl)-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indole; 3-[(1R,3R)-1-[2,6-difluoro-4-[2-[3-(fluoromethyl)azetidin-1-yl]ethylamino]phenyl]-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indol-2-yl]-2,2-difluoro-propan-1-ol; (1S,3R)-2-(2-fluoro-2-methylpropyl)-1-(5-((1-(3-fluoropropyl)azetidin-3-yl)oxy)pyrazin-2-yl)-3-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole; (1R,3R)-1-(2,6-difluoro-4-((1-(3-fluoropropyl)-3-methylazetidin-3-yl)oxy)phenyl)-2-(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole; 2-[(1R,3R)-2-(2-fluoro-2-methyl-propyl)-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indol-1-yl]-5-[1-(3-fluoropropyl)azetidin-3-yl]oxy-benzonitrile; 4-((1R,3R)-2-(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)-1-(3-(3-(fluoromethyl)azetidin-1-yl)propyl)pyridin-2(1H)-one; [4-[(1R,3R)-2-(2-fluoro-2-methyl-propyl)-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indol-1-yl]phenyl]-[1-(3-fluoropropyl)azetidin-3-yl]methanone; (R)-3-((1R,3R)-1-(2,6-difluoro-4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-3-methyl-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indol-2-yl)-2-methylpropanamide; (R)-3-((1R,3R)-1-(2,6-difluoro-4-((1-(3-fluoropropyl)azetidin-3-yl)oxy)phenyl)-3-methyl-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indol-2-yl)-2-methylpropanoic acid; (S)-3-((1R,3R)-1-(2,6-difluoro-4-((1-(3-fluoropropyl)azetidin-3-yl)oxy)phenyl)-3-methyl-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indol-2-yl)-2-methylpropanoic acid; 3-[1-[2,6-difluoro-4-[1-(3-fluoropropyl)azetidin-3-yl]oxy-phenyl]-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indol-2-yl]-2-methyl-propanoic acid; 3-[1-[2,6-difluoro-4-[1-(3-fluoropropyl)azetidin-3-yl]oxy-phenyl]-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indol-2-yl]-2-methyl-propanoic acid; (1S,3S)-1-(2,6-difluoro-4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-6-fluoro-3-methyl-2-(2,2,2-trifluoroethyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole; (1R,3R)-1-(2,6-difluoro-4-(2-(3-

(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-6-fluoro-3-methyl-2-(2,2,2-trifluoroethyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole; (1S,3S)-1-(2,6-difluoro-4-((1-(3-fluoropropyl)azetidin-3-yl)oxy)phenyl)-6-fluoro-3-methyl-2-(2,2,2-trifluoroethyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole; (1R,3R)-1-(2,6-difluoro-4-((1-(3-fluoropropyl)azetidin-3-yl)oxy)phenyl)-6-fluoro-3-methyl-2-(2,2,2-trifluoroethyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole; 3-((1R,3R)-1-(2,6-difluoro-4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-6-fluoro-3-methyl-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indol-2-yl)-2,2-difluoropropan-1-ol; 3-((1S,3S)-1-(2,6-difluoro-4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-6-fluoro-3-methyl-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indol-2-yl)-2,2-difluoropropan-1-ol; (1R,3R)-1-[2,6-difluoro-4-[2-[3-(fluoromethyl)azetidin-1-yl]ethoxy]phenyl]-3-methyl-2-(3,3,3-trifluoropropyl)-1,3,4,9-tetrahydropyrido[3,4-b]indole; (1S,3R)-1-[2,6-difluoro-4-[2-[3-(fluoromethyl)azetidin-1-yl]ethoxy]phenyl]-3-methyl-2-(3,3,3-trifluoropropyl)-1,3,4,9-tetrahydropyrido[3,4-b]indole; 3-((1R,3R)-1-(2,6-difluoro-4-((1-(3-fluoropropyl)azetidin-3-yl)oxy)phenyl)-6-fluoro-3-methyl-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indol-2-yl)-2,2-difluoropropan-1-ol; 3-((1S,3S)-1-(2,6-difluoro-4-((1-(3-fluoropropyl)azetidin-3-yl)oxy)phenyl)-6-fluoro-3-methyl-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indol-2-yl)-2,2-difluoropropan-1-ol; 3-((1R,3R)-1-(2,6-difluoro-4-((1-(3-fluoropropyl)azetidin-3-yl)oxy)phenyl)-6-fluoro-3-methyl-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indol-2-yl)-2-fluoro-2-methylpropan-1-ol; 3-((1S,3S)-1-(2,6-difluoro-4-((1-(3-fluoropropyl)azetidin-3-yl)oxy)phenyl)-6-fluoro-3-methyl-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indol-2-yl)-2-fluoro-2-methylpropan-1-ol; 3-((1R,3R)-1-(2,6-difluoro-4-((1-(3-fluoropropyl)azetidin-3-yl)oxy)phenyl)-6-fluoro-3-methyl-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indol-2-yl)-2-fluoro-2-methylpropan-1-ol; 3-((1S,3S)-1-(2,6-difluoro-4-((1-(3-fluoropropyl)azetidin-3-yl)oxy)phenyl)-6-fluoro-3-methyl-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indol-2-yl)-2-fluoro-2-methylpropan-1-ol; 3-((1R,3R)-1-(2,6-difluoro-4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-3-methyl-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indol-2-yl)-2,2-dimethylpropanoic acid; (R)-2-(((1R,3R)-1-(2,6-difluoro-4-((1-(3-fluoropropyl)azetidin-3-yl)oxy)phenyl)-3-methyl-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indol-2-yl)methyl)-3,3,3-trifluoropropan-1-ol; (S)-2-(((1R,3R)-1-(2,6-difluoro-4-((1-(3-fluoropropyl)azetidin-3-yl)oxy)phenyl)-3-methyl-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indol-2-yl)methyl)-3,3,3-trifluoropropan-1-ol; (1R,3R)-2-(2-fluoro-2-methylpropyl)-1-(2-((1-(3-fluoropropyl)azetidin-3-yl)oxy)pyrimidin-5-yl)-3-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-

b]indole; 3-[(1S,3R)-1-[2,6-difluoro-4-[2-[3-(fluoromethyl)azetidin-1-yl]ethoxy]phenyl]-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indol-2-yl]-2,2-dimethyl-propanoic acid; (1R,3R)-1-(2,6-difluoro-4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-2-(2,2-difluoropropyl)-3-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole; (S)-(4-((1R,3R)-2-(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)phenyl)(1-(3-fluoropropyl)azetidin-3-yl)methanol; (R)-(4-((1R,3R)-2-(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)phenyl)(1-(3-fluoropropyl)azetidin-3-yl)methanol; (1R,3R)-1-(2,6-difluoro-4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-2-(2,2-difluoroethyl)-6-fluoro-3-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole; (1S,3S)-1-(2,6-difluoro-4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-2-(2,2-difluoroethyl)-6-fluoro-3-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole; (1R,3R)-1-(2,6-difluoro-4-((1-(3-fluoropropyl)azetidin-3-yl)oxy)phenyl)-2-(2,2-difluoroethyl)-6-fluoro-3-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole; (1S,3S)-1-(2,6-difluoro-4-((1-(3-fluoropropyl)azetidin-3-yl)oxy)phenyl)-2-(2,2-difluoroethyl)-6-fluoro-3-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole; (1R,3R)-1-(2,6-difluoro-4-((1-cis-(3-(fluoromethyl)cyclobutyl)azetidin-3-yl)oxy)phenyl)-2-(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole; (1R,3R)-1-(2,6-difluoro-4-((1-trans-(3-(fluoromethyl)cyclobutyl)azetidin-3-yl)oxy)phenyl)-2-(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole; (1R,3R)-1-(2,6-difluoro-4-((1-(3-fluoropropyl)azetidin-3-yl)oxy)phenyl)-2-((1-fluorocyclobutyl)methyl)-3-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole;; (S)-3-((1R,3R)-1-(2,6-difluoro-4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-3-methyl-3,4-dihydro-1H-pyrido[3,4-b]indol-2(9H)-yl)-2-fluoropropan-1-ol;; (R)-3-((1R,3R)-1-(2,6-difluoro-4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-3-methyl-3,4-dihydro-1H-pyrido[3,4-b]indol-2(9H)-yl)-2-fluoropropan-1-ol;; (R)-3-((1R,3R)-1-(2,6-difluoro-4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-3-methyl-3,4-dihydro-1H-pyrido[3,4-b]indol-2(9H)-yl)-2-(fluoromethyl)propan-1-ol;; (S)-3-((1R,3R)-1-(2,6-difluoro-4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-3-methyl-3,4-dihydro-1H-pyrido[3,4-b]indol-2(9H)-yl)-2-(fluoromethyl)propan-1-ol;; (1R,3R)-1-(2,6-difluoro-4-(1-(3-fluoropropyl)azetidin-3-yloxy)phenyl)-2-((3-fluorooxetan-3-yl)methyl)-3-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole;; (1R,3R)-1-(2,6-difluoro-4-(1-(3-fluoropropyl)azetidin-3-yloxy)phenyl)-6,8-difluoro-2-(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole;; (1R,3R)-1-(2,6-difluoro-4-((1-((1-

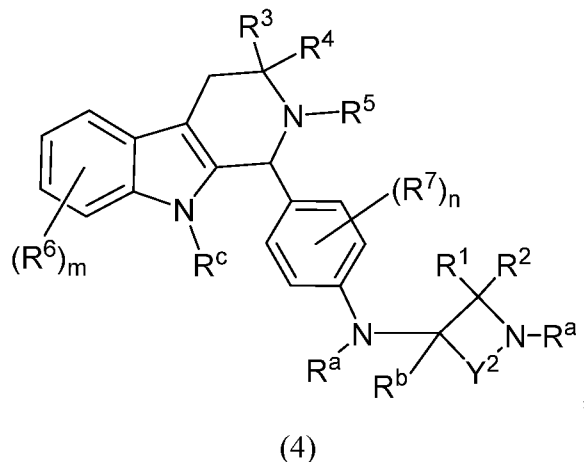
(fluoromethyl)cyclopropyl)methyl)azetidin-3-yl)oxy)phenyl)-2-(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole;; (1R,3R)-1-(2,6-difluoro-4-(1-(3-fluoropropyl)azetidin-3-yloxy)phenyl)-6,7-difluoro-2-(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole; or (1R,3R)-2-(2-fluoro-2-methylpropyl)-1-(1-((1-(3-fluoropropyl)azetidin-3-yl)methyl)-1H-pyrazol-4-yl)-3-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole, or a pharmaceutically acceptable salt thereof or combination thereof.

[0348] In another aspect, the endocrine therapy comprises a compound having formula:



or a pharmaceutically acceptable salt thereof.

[0349] In another aspect, the endocrine therapy comprises a compound having formula (4):



or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein:

Y^2 is $-(CH_2)$;

R^a is independently selected from the group consisting of H, C_1 - C_6 alkyl, C_2 - C_8 alkenyl, propargyl, C_3 - C_6 cycloalkyl, and C_3 - C_6 heterocyclyl, each optionally substituted with one or more groups independently selected from the group consisting of F, Cl, Br, I, CN, OH, OCH_3 , and SO_2CH_3 ;

R^b is independently selected from the group consisting of H, $-O(C_1-C_3 \text{ alkyl})$, C_1-C_6 alkyl, C_2-C_8 alkenyl, and propargyl, each optionally substituted with one or more groups independently selected from the group consisting of F, Cl, Br, I, CN, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CH_2CF_3$, $-CH_2CHF_2$, $-CH_2CH_2F$, OH, OCH_3 , and SO_2CH_3 ;

R^c is H;

R^1 , R^2 , R^3 and R^4 are independently selected from the group consisting of H, $-CH_3$, $-CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2CH(CH_3)_2$, $-CH_2OH$, $-CH_2OCH_3$, $-CH_2CH_2OH$, $-C(CH_3)_2OH$, $-CH(OH)CH(CH_3)_2$, $-C(CH_3)_2CH_2OH$, $-CH_2CH_2SO_2CH_3$, $-CH_2OP(O)(OH)_2$, $-CH_2F$, $-CHF_2$, $-CH_2NH_2$, $-CH_2NHSO_2CH_3$, $-CH_2NHCH_3$, $-CH_2N(CH_3)_2$, $-CF_3$, $-CH_2CF_3$, $-CH_2CHF_2$, $-CH(CH_3)CN$, $-C(CH_3)_2CN$, and $-CH_2CN$;

R^5 is selected from the group consisting of C_1-C_9 alkyl, C_3-C_9 cycloalkyl, C_3-C_9 heterocycle, C_6-C_9 aryl, C_6-C_9 heteroaryl, $-(C_1-C_6 \text{ alkylidyl})-(C_3-C_9 \text{ cycloalkyl})$, $-(C_1-C_6 \text{ alkylidyl})-(C_3-C_9 \text{ heterocycle})$, $C(O)NR^a$, SO_2R^a , and SO_2NR^a , each optionally substituted with one or more of halogen, CN, OR^a , $N(R^a)_2$, C_1-C_9 alkyl, C_3-C_9 cycloalkyl, C_3-C_9 heterocycle, C_6-C_9 aryl, C_6-C_9 heteroaryl, $C(O)R^b$, $C(O)NR^a$, SO_2R^a , and SO_2NR^a ;

R^6 is independently F or Cl;

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

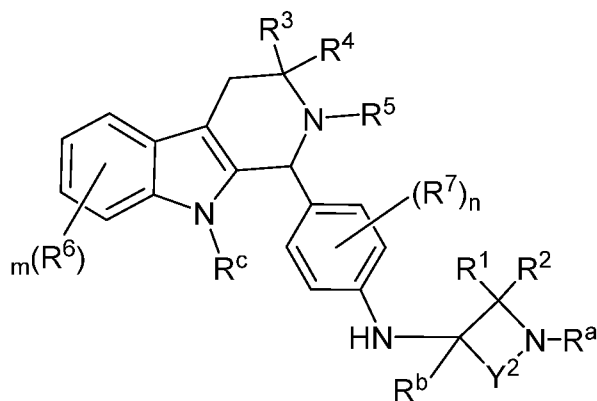
wherein R^7 is F, Cl, Br, I, $-CN$, $-CH_3$, $-CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2CH(CH_3)_2$, $-CH_2OH$, $-CH_2OCH_3$, $-CH_2CH_2OH$, $-C(CH_3)_2OH$, $-CH(OH)CH(CH_3)_2$, $-C(CH_3)_2CH_2OH$, $-CH_2CH_2SO_2CH_3$, $-CH_2OP(O)(OH)_2$, $-CH_2F$, $-CHF_2$, $-CH_2NH_2$, $-CH_2NHSO_2CH_3$, $-CH_2NHCH_3$, $-CH_2N(CH_3)_2$, $-CF_3$, $-CH_2CF_3$, $-CH_2CHF_2$, $-CH(CH_3)CN$, $-C(CH_3)_2CN$, $-CH_2CN$, $-CO_2H$, $-COCH_3$, $-CO_2CH_3$, $-CO_2C(CH_3)_3$, $-COCH(OH)CH_3$, $-CONH_2$, $-CONHCH_3$, $-CONHCH_2CH_3$, $-CONHCH(CH_3)_2$, $-CON(CH_3)_2$, $-C(CH_3)_2CONH_2$, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-NHCOCH_3$, $-N(CH_3)COCH_3$, $-NHS(O)_2CH_3$, $-N(CH_3)C(CH_3)_2CONH_2$, $-N(CH_3)CH_2CH_2S(O)_2CH_3$, $-NO_2$, $=O$, $-OH$, $-OCH_3$, $-OCH_2CH_3$, $-OCH_2CH_2OCH_3$, $-OCH_2CH_2OH$, $-OCH_2CH_2N(CH_3)_2$, $-OP(O)(OH)_2$, $-S(O)_2N(CH_3)_2$, $-SCH_3$, $-S(O)_2CH_3$, $-S(O)_3H$, cyclopropyl, cyclopropylamide, oxetanyl, azetidiny, 1-methylazetidin-3-yl)oxy, N-methyl-N-oxetan-3-ylamino, azetidin-1-ylmethyl, benzyloxyphenyl, pyrrolidin-1-yl, pyrrolidin-1-yl-methanone, piperazin-1-yl, morpholinomethyl, morpholino-methanone, or morpholino;

n is 0, 1 or 2; and

R^7 is independently halogen.

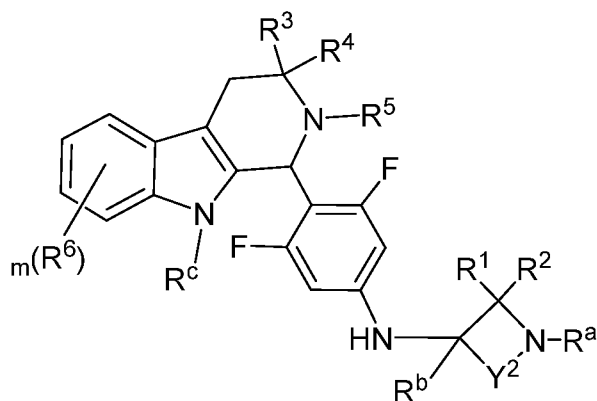
[0350] Variables R^1 , R^2 , R^3 , R^4 , R^5 , R^a , R^b , R^c , m , n , and Y^2 are as defined herein for compounds of formula (3).

[0351] In one instance, the compound of formula (4) comprises formula (4a):



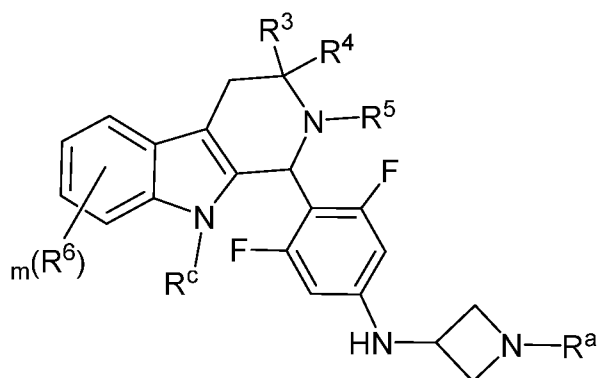
(4a)

[0352] In another instance, the compound of formula (4) comprises formula (4b):



(4b)

[0353] In still another instance, the compound of formula (4) comprises formula (4c):



(4c)

[0354] In one instance of the compounds of formula (4a)-(4c), R^7 is F. In one instance of the compounds of formula (4a)-(4c), R^1 and R^2 are H. In one instance of the compounds of formula (4a)-(4c), R^3 is H, and R^4 is $-\text{CH}_3$. In one instance of the compounds of formula (4a)-(4c), R^5 is $\text{C}_1\text{--C}_6$ fluoroalkyl. In one instance of the compounds of formula (4a)-(4c), m is 0.

[0355] In another aspect, the endocrine therapy comprises a compound having formula: N-(3,5-difluoro-4-((1R,3R)-2-(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)phenyl)-1-(3-fluoropropyl)azetidin-3-amine; (R)-3-((1R,3R)-1-(2,6-difluoro-4-((1-(3-fluoropropyl)azetidin-3-yl)amino)phenyl)-3-methyl-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indol-2-yl)-2-fluoro-2-methylpropan-1-ol; (S)-3-((1R,3R)-1-(2,6-difluoro-4-((1-(3-fluoropropyl)azetidin-3-yl)amino)phenyl)-3-methyl-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indol-2-yl)-2-fluoro-2-methylpropan-1-ol; (R)-2-fluoro-3-((1R,3R)-1-(2-fluoro-4-((1-(3-fluoropropyl)azetidin-3-yl)amino)phenyl)-3-methyl-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indol-2-yl)-2-methylpropan-1-ol; (S)-2-fluoro-3-((1R,3R)-1-(2-fluoro-4-((1-(3-fluoropropyl)azetidin-3-yl)amino)phenyl)-3-methyl-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indol-2-yl)-2-methylpropan-1-ol; (R)-2-fluoro-3-((1R,3R)-1-(4-((1-(3-fluoropropyl)azetidin-3-yl)amino)phenyl)-3-methyl-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indol-2-yl)-2-methylpropan-1-ol; (S)-2-fluoro-3-((1R,3R)-1-(4-((1-(3-fluoropropyl)azetidin-3-yl)amino)phenyl)-3-methyl-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indol-2-yl)-2-methylpropan-1-ol; 3,5-difluoro-N-(2-(3-(fluoromethyl)azetidin-1-yl)ethyl)-4-((1R,3R)-3-methyl-2-(2,2,2-trifluoroethyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)aniline; N-(3,5-difluoro-4-((1R,3R)-3-methyl-2-(2,2,2-trifluoroethyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)phenyl)-1-(3-fluoropropyl)azetidin-3-amine; 1-(3-fluoropropyl)-N-[4-[(1R,3R)-3-methyl-2-methylsulfonyl-1,3,4,9-tetrahydropyrido[3,4-b]indol-1-yl]phenyl]azetidin-3-amine; N-[3,5-

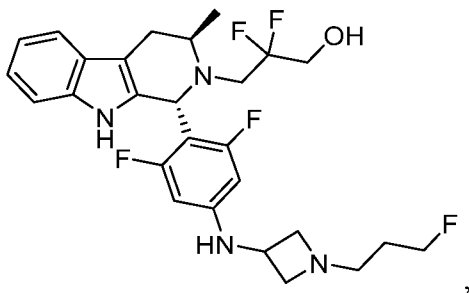
difluoro-4-[(1R,3R)-3-methyl-2-methylsulfonyl-1,3,4,9-tetrahydropyrido[3,4-b]indol-1-yl]phenyl]-1-(3-fluoropropyl)azetidin-3-amine; 1-(3-fluoropropyl)-N-[4-[(1S,3R)-3-methyl-2-methylsulfonyl-1,3,4,9-tetrahydropyrido[3,4-b]indol-1-yl]phenyl]azetidin-3-amine; N-[3,5-difluoro-4-[(1S,3R)-3-methyl-2-methylsulfonyl-1,3,4,9-tetrahydropyrido[3,4-b]indol-1-yl]phenyl]-1-(3-fluoropropyl)azetidin-3-amine; 3-((1R,3R)-1-(2,6-difluoro-4-((2-(3-(fluoromethyl)azetidin-1-yl)ethyl)amino)phenyl)-3-methyl-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indol-2-yl)-2-fluoro-2-methylpropan-1-ol; 3,5-difluoro-N-[2-[3-(fluoromethyl)azetidin-1-yl]ethyl]-4-[(1R,3R)-2-(2-fluoro-2-methyl-propyl)-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indol-1-yl]aniline; 3-fluoro-N-[2-[3-(fluoromethyl)azetidin-1-yl]ethyl]-4-[(1R,3R)-2-(2-fluoro-2-methyl-propyl)-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indol-1-yl]aniline; N-[2-[3-(fluoromethyl)azetidin-1-yl]ethyl]-4-[(1R,3R)-2-(2-fluoro-2-methyl-propyl)-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indol-1-yl]aniline; N-[2-[3-(fluoromethyl)azetidin-1-yl]ethyl]-4-[(1R,3R)-3-methyl-2-methylsulfonyl-1,3,4,9-tetrahydropyrido[3,4-b]indol-1-yl]aniline; 3,5-difluoro-N-[2-[3-(fluoromethyl)azetidin-1-yl]ethyl]-4-[(1R,3R)-3-methyl-2-methylsulfonyl-1,3,4,9-tetrahydropyrido[3,4-b]indol-1-yl]aniline; 2-fluoro-3-((1R,3R)-1-(2-fluoro-4-((2-(3-(fluoromethyl)azetidin-1-yl)ethyl)amino)phenyl)-3-methyl-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indol-2-yl)-2-methylpropan-1-ol; 2-fluoro-3-((1R,3R)-1-(4-((2-(3-(fluoromethyl)azetidin-1-yl)ethyl)amino)phenyl)-3-methyl-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indol-2-yl)-2-methylpropan-1-ol; 3-[(1R,3R)-1-[2,6-difluoro-4-[[1-(3-fluoropropyl)azetidin-3-yl]amino]phenyl]-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indol-2-yl]-2,2-difluoro-propan-1-ol; (R)-3-((1R,3R)-1-(2,6-difluoro-4-((2-(3-(fluoromethyl)azetidin-1-yl)ethyl)amino)phenyl)-3-methyl-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indol-2-yl)-2-fluoro-2-methylpropan-1-ol; (S)-3-((1R,3R)-1-(2,6-difluoro-4-((2-(3-(fluoromethyl)azetidin-1-yl)ethyl)amino)phenyl)-3-methyl-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indol-2-yl)-2-fluoro-2-methylpropan-1-ol; (2R)-3-[(1R,3R)-1-[2,6-difluoro-4-[[1-(3-fluoropropyl)azetidin-3-yl]amino]phenyl]-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indol-2-yl]-2-methyl-propanoic acid; 3-((1R,3R)-1-(2,6-difluoro-4-((1-(3-fluoropropyl)azetidin-3-yl)amino)phenyl)-6-fluoro-3-methyl-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indol-2-yl)-2,2-difluoropropan-1-ol; 3-((1S,3S)-1-(2,6-difluoro-4-((1-(3-fluoropropyl)azetidin-3-yl)amino)phenyl)-6-fluoro-3-methyl-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indol-2-yl)-2,2-difluoropropan-1-ol; (2S)-3-[(1R,3R)-1-[2,6-difluoro-4-[[1-(3-fluoropropyl)azetidin-3-yl]amino]phenyl]-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indol-2-yl]-

2-methyl-propanoic acid; N-(3,5-difluoro-4-((1R,3R)-6-fluoro-3-methyl-2-(2,2,2-trifluoroethyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)phenyl)-1-(3-fluoropropyl)azetidin-3-amine; N-(3,5-difluoro-4-((1S,3S)-6-fluoro-3-methyl-2-(2,2,2-trifluoroethyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)phenyl)-1-(3-fluoropropyl)azetidin-3-amine; 3-((1R,3R)-1-(2,6-difluoro-4-((1-(3-fluoropropyl)azetidin-3-yl)amino)phenyl)-3-methyl-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indol-2-yl)-2,2-dimethylpropanoic acid; N-(3,5-difluoro-4-((1R,3R)-6-fluoro-3-methyl-2-(methylsulfonyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)phenyl)-1-(3-fluoropropyl)azetidin-3-amine; N-(3,5-difluoro-4-((1S,3S)-6-fluoro-3-methyl-2-(methylsulfonyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)phenyl)-1-(3-fluoropropyl)azetidin-3-amine; N-(4-((1R,3R)-2-(2,2-difluoroethyl)-6-fluoro-3-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)-3,5-difluorophenyl)-1-(3-fluoropropyl)azetidin-3-amine; N-(4-((1S,3S)-2-(2,2-difluoroethyl)-6-fluoro-3-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)-3,5-difluorophenyl)-1-(3-fluoropropyl)azetidin-3-amine; N-(3,5-difluoro-4-((1R,3R)-7-fluoro-3-methyl-2-(2,2,2-trifluoroethyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)phenyl)-1-(3-fluoropropyl)azetidin-3-amine; N-(3,5-difluoro-4-((1S,3S)-7-fluoro-3-methyl-2-(2,2,2-trifluoroethyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)phenyl)-1-(3-fluoropropyl)azetidin-3-amine; (S)-3-((1R,3R)-1-(2,6-difluoro-4-((1-(3-fluoropropyl)azetidin-3-yl)amino)phenyl)-5-fluoro-3-methyl-3,4-dihydro-1H-pyrido[3,4-b]indol-2(9H)-yl)-2-fluoro-2-methylpropan-1-ol; (R)-3-((1S,3S)-1-(2,6-difluoro-4-((1-(3-fluoropropyl)azetidin-3-yl)amino)phenyl)-5-fluoro-3-methyl-3,4-dihydro-1H-pyrido[3,4-b]indol-2(9H)-yl)-2-fluoro-2-methylpropan-1-ol; (R)-3-((1R,3R)-1-(2,6-difluoro-4-((1-(3-fluoropropyl)azetidin-3-yl)amino)phenyl)-5-fluoro-3-methyl-3,4-dihydro-1H-pyrido[3,4-b]indol-2(9H)-yl)-2-fluoro-2-methylpropan-1-ol; (S)-3-((1S,3S)-1-(2,6-difluoro-4-((1-(3-fluoropropyl)azetidin-3-yl)amino)phenyl)-5-fluoro-3-methyl-3,4-dihydro-1H-pyrido[3,4-b]indol-2(9H)-yl)-2-fluoro-2-methylpropan-1-ol; N-(3,5-difluoro-4-((1R,3R)-2-(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)phenyl)-1-(3-fluoropropyl)-N-methylazetidin-3-amine; (R)-N-(4-(2-(2,2-difluoroethyl)-3,3-dimethyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)-3,5-difluorophenyl)-1-(3-fluoropropyl)azetidin-3-amine; (S)-N-(4-(2-(2,2-difluoroethyl)-3,3-dimethyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)-3,5-difluorophenyl)-1-(3-fluoropropyl)azetidin-3-amine; N-(3,5-difluoro-4-((1R,3R)-5-fluoro-3-methyl-2-(2,2,2-trifluoroethyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)phenyl)-1-(3-

fluoropropyl)azetidin-3-amine; N-(3,5-difluoro-4-((1S,3S)-5-fluoro-3-methyl-2-(2,2,2-trifluoroethyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)phenyl)-1-(3-fluoropropyl)azetidin-3-amine; N-(3,5-difluoro-4-((1S,3S)-8-fluoro-3-methyl-2-(2,2,2-trifluoroethyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)phenyl)-1-(3-fluoropropyl)azetidin-3-amine; N-(3,5-difluoro-4-((1R,3R)-8-fluoro-3-methyl-2-(2,2,2-trifluoroethyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)phenyl)-1-(3-fluoropropyl)azetidin-3-amine; (S)-3-((1S,3S)-1-(2,6-difluoro-4-((1-(3-fluoropropyl)azetidin-3-yl)amino)phenyl)-7-fluoro-3-methyl-3,4-dihydro-1H-pyrido[3,4-b]indol-2(9H)-yl)-2-fluoro-2-methylpropan-1-ol; (R)-3-((1R,3R)-1-(2,6-difluoro-4-((1-(3-fluoropropyl)azetidin-3-yl)amino)phenyl)-7-fluoro-3-methyl-3,4-dihydro-1H-pyrido[3,4-b]indol-2(9H)-yl)-2-fluoro-2-methylpropan-1-ol; (S)-3-((1R,3R)-1-(2,6-difluoro-4-((1-(3-fluoropropyl)azetidin-3-yl)amino)phenyl)-7-fluoro-3-methyl-3,4-dihydro-1H-pyrido[3,4-b]indol-2(9H)-yl)-2-fluoro-2-methylpropan-1-ol; (R)-3-((1S,3S)-1-(2,6-difluoro-4-((1-(3-fluoropropyl)azetidin-3-yl)amino)phenyl)-7-fluoro-3-methyl-3,4-dihydro-1H-pyrido[3,4-b]indol-2(9H)-yl)-2-fluoro-2-methylpropan-1-ol; 3-((1R,3R)-1-(2,6-difluoro-4-((1-(3-fluoropropyl)azetidin-3-yl)amino)phenyl)-5-fluoro-3-methyl-3,4-dihydro-1H-pyrido[3,4-b]indol-2(9H)-yl)-2,2-difluoropropan-1-ol; 3-((1S,3S)-1-(2,6-difluoro-4-((1-(3-fluoropropyl)azetidin-3-yl)amino)phenyl)-5-fluoro-3-methyl-3,4-dihydro-1H-pyrido[3,4-b]indol-2(9H)-yl)-2,2-difluoropropan-1-ol; (R)-3-((1R,3R)-1-(2,6-difluoro-4-((1-(3-fluoropropyl)azetidin-3-yl)amino)phenyl)-3-methyl-3,4-dihydro-1H-pyrido[3,4-b]indol-2(9H)-yl)-2-fluoro-2-(hydroxymethyl)propanenitrile; (S)-3-((1R,3R)-1-(2,6-difluoro-4-((1-(3-fluoropropyl)azetidin-3-yl)amino)phenyl)-3-methyl-3,4-dihydro-1H-pyrido[3,4-b]indol-2(9H)-yl)-2-fluoro-2-(hydroxymethyl)propanenitrile; (R)-3-((1-(2,6-difluoro-4-((1-(3-fluoropropyl)azetidin-3-yl)amino)phenyl)-3,3-dimethyl-3,4-dihydro-1H-pyrido[3,4-b]indol-2(9H)-yl)-2,2-difluoropropan-1-ol; (S)-3-((1-(2,6-difluoro-4-((1-(3-fluoropropyl)azetidin-3-yl)amino)phenyl)-3,3-dimethyl-3,4-dihydro-1H-pyrido[3,4-b]indol-2(9H)-yl)-2,2-difluoropropan-1-ol; 3-((1S,3S)-1-(2,6-difluoro-4-((1-(3-fluoropropyl)azetidin-3-yl)amino)phenyl)-8-fluoro-3-methyl-3,4-dihydro-1H-pyrido[3,4-b]indol-2(9H)-yl)-2,2-difluoropropan-1-ol; 3-((1R,3R)-1-(2,6-difluoro-4-((1-(3-fluoropropyl)azetidin-3-yl)amino)phenyl)-8-fluoro-3-methyl-3,4-dihydro-1H-pyrido[3,4-b]indol-2(9H)-yl)-2,2-difluoropropan-1-ol; 3-((1R,3R)-1-(2,6-difluoro-4-((1-(3-fluoropropyl)azetidin-3-yl)amino)phenyl)-7-fluoro-3-methyl-3,4-dihydro-1H-pyrido[3,4-b]indol-

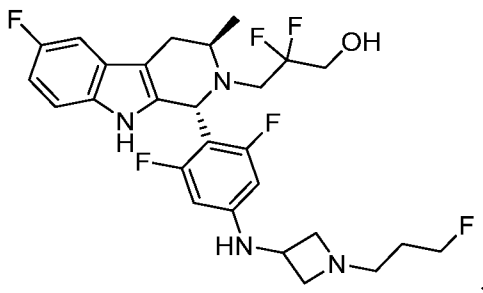
2(9H)-yl)-2,2-difluoropropan-1-ol; 3-((1S,3S)-1-(2,6-difluoro-4-((1-(3-fluoropropyl)azetidin-3-yl)amino)phenyl)-7-fluoro-3-methyl-3,4-dihydro-1H-pyrido[3,4-b]indol-2(9H)-yl)-2,2-difluoropropan-1-ol; N-[4-[(1R,3R)-2-(2,2-difluoroethyl)-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indol-1-yl]-3,5-difluoro-phenyl]-1-(3-fluoropropyl)azetidin-3-amine; (R)-3-((1R,3R)-1-(2,6-difluoro-4-((1-(3-fluoropropyl)azetidin-3-yl)amino)phenyl)-6-fluoro-3-methyl-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indol-2-yl)-2-fluoro-2-methylpropan-1-ol; (S)-3-((1S,3S)-1-(2,6-difluoro-4-((1-(3-fluoropropyl)azetidin-3-yl)amino)phenyl)-6-fluoro-3-methyl-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indol-2-yl)-2-fluoro-2-methylpropan-1-ol; (S)-3-((1R,3R)-1-(2,6-difluoro-4-((1-(3-fluoropropyl)azetidin-3-yl)amino)phenyl)-6-fluoro-3-methyl-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indol-2-yl)-2-fluoro-2-methylpropan-1-ol; or (R)-3-((1R,3S)-1-(2,6-difluoro-4-((1-(3-fluoropropyl)azetidin-3-yl)amino)phenyl)-6-fluoro-3-methyl-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indol-2-yl)-2-fluoro-2-methylpropan-1-ol, or a pharmaceutically acceptable salt thereof or a combination thereof.

[0356] In another aspect, the endocrine therapy comprises a compound having formula:



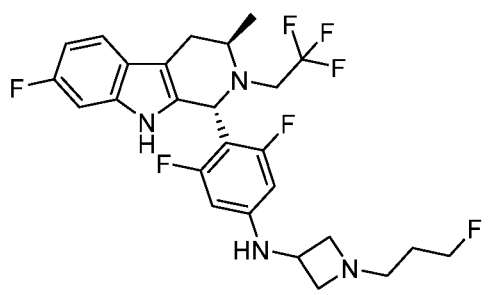
or a pharmaceutically acceptable salt thereof.

[0357] In another aspect, the endocrine therapy comprises a compound having formula:



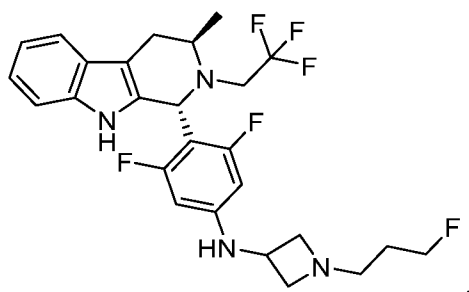
or a pharmaceutically acceptable salt thereof.

[0358] In another aspect, the endocrine therapy comprises a compound having formula:



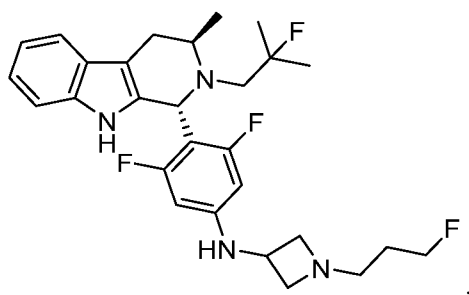
or a pharmaceutically acceptable salt thereof.

[0359] In another aspect, the endocrine therapy comprises a compound having formula:



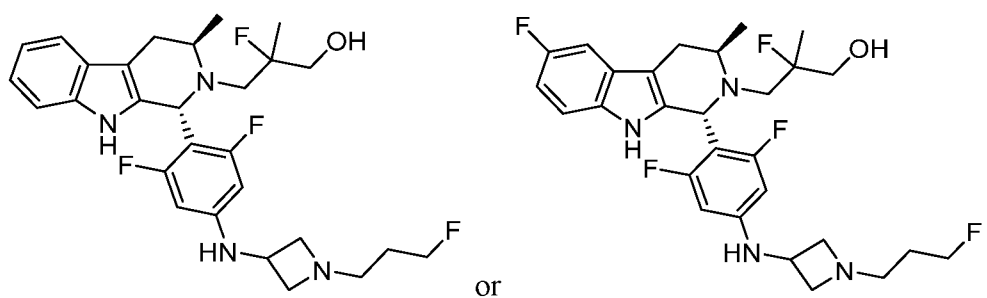
or a pharmaceutically acceptable salt thereof.

[0360] In another aspect, the endocrine therapy comprises a compound having formula:



or a pharmaceutically acceptable salt thereof.

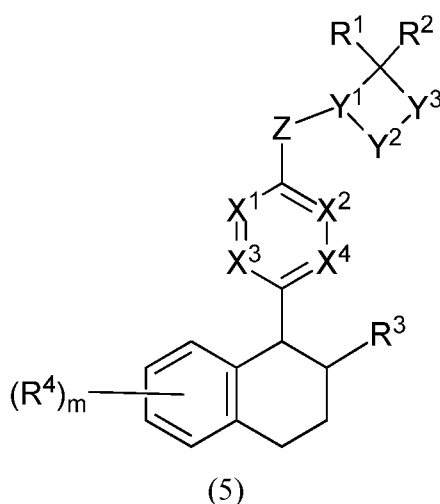
[0361] In another aspect, the endocrine therapy comprises a compound having formula:



including stereoisomers thereof, or a pharmaceutically acceptable salt thereof.

[0362] In another aspect, the endocrine therapy comprises a compound set forth in U.S. Patent Application No. 20170129855, for example in Table 1 therein, which is incorporated herein by reference in its entirety and for all purposes.

[0363] In one aspect, the endocrine therapy comprises a compound of formula (5):



or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein:

Y^1 is CR^b or N;

Y^2 is $-(CH_2)-$, $-(CH_2CH_2)-$, or NR^a ;

Y^3 is NR^a or $C(R^b)_2$;

where one of Y^1 , Y^2 and Y^3 is N or NR^a ;

R^a and R^c are independently selected from H, C_1 - C_6 alkyl, C_1 - C_6 fluoroalkyl, allyl, propargyl, C_3 - C_6 cycloalkyl, and C_3 - C_6 heterocyclyl, optionally substituted with one or more groups independently selected from F, Cl, Br, I, CN, OH, OCH_3 , and SO_2CH_3 ;

R^b is independently selected from H, $-O(C_1$ - C_3 alkyl), C_1 - C_6 alkyl, C_1 - C_6 fluoroalkyl, allyl, propargyl, C_3 - C_6 cycloalkyl, and C_3 - C_6 heterocyclyl, optionally substituted with one or more groups independently selected from F, Cl, Br, I, CN, OH, OCH_3 , and SO_2CH_3 ;

where at least one of R^a and R^b is $-CH_2Cl$, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CH_2CH_2F$, $-CH_2CHF_2$, $-CH_2CF_3$, CH_2CH_2Cl , $CH_2CH_2CH_2F$, $CH_2CH_2CHF_2$, $CH_2CH_2CF_3$, or $CH_2CH_2CH_2Cl$;

X^1 , X^2 , X^3 , and X^4 are independently selected from CH, CR^5 and N; where none, one, or two of X^1 , X^2 , X^3 , and X^4 is N;

Z is selected from O, S, S(O), S(O)₂, C(=O), CH(OH), C₁-C₆ alkylidiyl, CH(OH)-(C₁-C₆ alkylidiyl), C₁-C₆ fluoroalkylidiyl, NR^c, NR^c-(C₁-C₆ alkylidiyl), NR^c-(C₁-C₆ fluoroalkylidiyl), O-(C₁-C₆ alkylidiyl), and O-(C₁-C₆ fluoroalkylidiyl) ;

R¹ and R² are independently selected from H, F, Cl, Br, I, -CN, -CH₃, -CH₂CH₃, -CH(CH₃)₂, -CH₂CH(CH₃)₂, -CH₂OH, -CH₂OCH₃, -CH₂CH₂OH, -C(CH₃)₂OH, -CH(OH)CH(CH₃)₂, -C(CH₃)₂CH₂OH, -CH₂CH₂SO₂CH₃, -CH₂OP(O)(OH)₂, -CH₂Cl, -CH₂F, -CHF₂, -CH₂NH₂, -CH₂NHSO₂CH₃, -CH₂NHCH₃, -CH₂N(CH₃)₂, -CF₃, -CH₂CF₃, -CH₂CHF₂, -CH(CH₃)CN, -C(CH₃)₂CN, -CH₂CN, -CO₂H, -COCH₃, -CO₂CH₃, -CO₂C(CH₃)₃, -COCH(OH)CH₃, -CONH₂, -CONHCH₃, -CONHCH₂CH₃, -CONHCH(CH₃)₂, -CON(CH₃)₂, -C(CH₃)₂CONH₂, -NH₂, -NHCH₃, -N(CH₃)₂, -NHCOCH₃, -N(CH₃)COCH₃, -NHS(O)₂CH₃, -N(CH₃)C(CH₃)₂CONH₂, -N(CH₃)CH₂CH₂S(O)₂CH₃, -NO₂, =O, -OH, -OCH₃, -OCH₂CH₃, -OCH₂CH₂OCH₃, -OCH₂CH₂OH, -OCH₂CH₂N(CH₃)₂, -OP(O)(OH)₂, -S(O)₂N(CH₃)₂, -SCH₃, -S(O)₂CH₃, -S(O)₃H, cyclopropyl, cyclopropylamide, cyclobutyl, oxetanyl, azetidiny, 1-methylazetidin-3-yl)oxy, N-methyl-N-oxetan-3-ylamino, azetidin-1-ylmethyl, benzyloxyphenyl, pyrrolidin-1-yl, pyrrolidin-1-yl-methanone, piperazin-1-yl, morpholinomethyl, morpholino-methanone, and morpholino;

R³ is selected from C₃-C₂₀ cycloalkyl, C₂-C₂₀ heterocyclyl, C₆-C₂₀ aryl, C₁-C₂₀ heteroaryl, -(C₁-C₆ alkylidiyl)-(C₃-C₂₀ cycloalkyl), -(C₁-C₆ alkylidiyl)-(C₂-C₂₀ heterocyclyl), -(C₁-C₆ alkylidiyl)-(C₆-C₂₀ aryl), and -(C₁-C₆ alkylidiyl)-(C₁-C₂₀ heteroaryl);

or R³ forms a 3-6-membered spiro carbocyclic or heterocyclic group;

R⁴ and R⁵ are independently selected from F, Cl, Br, I, -CN, -CH₃, -CH₂CH₃, -CH(CH₃)₂, -CH₂CH(CH₃)₂, -CH₂OH, -CH₂OCH₃, -CH₂CH₂OH, -C(CH₃)₂OH, -CH(OH)CH(CH₃)₂, -C(CH₃)₂CH₂OH, -CH₂CH₂SO₂CH₃, -CH₂OP(O)(OH)₂, -CH₂F, -CHF₂, -CH₂NH₂, -CH₂NHSO₂CH₃, -CH₂NHCH₃, -CH₂N(CH₃)₂, -CF₃, -CH₂CF₃, -CH₂CHF₂, -CH(CH₃)CN, -C(CH₃)₂CN, -CH₂CN, -CO₂H, -COCH₃, -CO₂CH₃, -CO₂C(CH₃)₃, -COCH(OH)CH₃, -CONH₂, -CONHCH₃, -CONHCH₂CH₃, -CONHCH(CH₃)₂, -CON(CH₃)₂, -C(CH₃)₂CONH₂, -NH₂, -NHCH₃, -N(CH₃)₂, -NHCOCH₃, -N(CH₃)COCH₃, -NHS(O)₂CH₃, -N(CH₃)C(CH₃)₂CONH₂, -N(CH₃)CH₂CH₂S(O)₂CH₃, -NO₂, =O, -OH, -OCH₃, -OCH₂CH₃, -OCH₂CH₂OCH₃, -OCH₂CH₂OH, -OCH₂CH₂N(CH₃)₂, -OP(O)(OH)₂, -S(O)₂N(CH₃)₂, -SCH₃, -S(O)₂CH₃, -S(O)₃H, cyclopropyl, cyclopropylamide, cyclobutyl, oxetanyl, azetidiny, 1-

methylazetidin-3-yl)oxy, N-methyl-N-oxetan-3-ylamino, azetidin-1-ylmethyl, benzyloxyphenyl, pyrrolidin-1-yl, pyrrolidin-1-yl-methanone, piperazin-1-yl, morpholinomethyl, morpholino-methanone, and morpholino; and

m is selected from 0, 1, 2, 3, and 4;

where alkylidiyl, fluoroalkylidiyl, aryl, carbocyclyl, heterocyclyl, and heteroaryl are optionally substituted with one or more groups independently selected from F, Cl, Br, I, -CN, -CH₃, -CH₂CH₃, -CH(CH₃)₂, -CH₂CH(CH₃)₂, -CH₂OH, -CH₂OCH₃, -CH₂CH₂OH, -C(CH₃)₂OH, -CH(OH)CH(CH₃)₂, -C(CH₃)₂CH₂OH, -CH₂CH₂SO₂CH₃, -CH₂OP(O)(OH)₂, -CH₂F, -CHF₂, -CF₃, -CH₂CF₃, -CH₂CHF₂, -CH(CH₃)CN, -C(CH₃)₂CN, -CH₂CN, -CH₂NH₂, -CH₂NHSO₂CH₃, -CH₂NHCH₃, -CH₂N(CH₃)₂, -CO₂H, -COCH₃, -CO₂CH₃, -CO₂C(CH₃)₃, -COCH(OH)CH₃, -CONH₂, -CONHCH₃, -CON(CH₃)₂, -C(CH₃)₂CONH₂, -NH₂, -NHCH₃, -N(CH₃)₂, -NHCOCH₃, -N(CH₃)COCH₃, -NHS(O)₂CH₃, -N(CH₃)C(CH₃)₂CONH₂, -N(CH₃)CH₂CH₂S(O)₂CH₃, -NO₂, =O, -OH, -OCH₃, -OCH₂CH₃, -OCH₂CH₂OCH₃, -OCH₂CH₂OH, -OCH₂CH₂N(CH₃)₂, -OP(O)(OH)₂, -S(O)₂N(CH₃)₂, -SCH₃, -S(O)₂CH₃, -S(O)₃H, cyclopropyl, cyclopropylamide, cyclobutyl, oxetanyl, azetidiny, 1-methylazetidin-3-yl)oxy, N-methyl-N-oxetan-3-ylamino, azetidin-1-ylmethyl, benzyloxyphenyl, pyrrolidin-1-yl, pyrrolidin-1-yl-methanone, piperazin-1-yl, morpholinomethyl, morpholino-methanone, and morpholino.

[0364] In one instance of the compounds of formula (5), Y¹ is N and Y³ is C(R^b)₂. In one instance of the compounds of formula (5), Y² is -(CH₂)-. In one instance of the compounds of formula (5), Y² is -(CH₂CH₂)-. In one instance of the compounds of formula (5), Y³ is NR^a and R^a is -CH₂Cl, -CH₂F, -CHF₂, -CF₃, -CH₂CH₂F, -CH₂CHF₂, or -CH₂CF₃. In one instance of the compounds of formula (5), X¹, X², X³, and X⁴ are independently selected from CH and CR⁵. In one instance of the compounds of formula (5), one of X¹, X², X³, and X⁴ is N. In one instance of the compounds of formula (5), Z is O or O-(C₁-C₆ alkylidiyl). In one instance of the compounds of formula (5), R¹ and R² are H. In one instance of the compounds of formula (5), R³ is C₆-C₂₀ aryl. In one instance of the compounds of formula (5), C₆-C₂₀ aryl is phenyl. In one instance of the compounds of formula (5), phenyl is substituted with one or more F. In one instance of the compounds of formula (5). In one instance of the compounds of formula (5), R⁴ is OH, and m is 1. In one instance of the compounds of formula (5), R⁵ is F and n is 2. In one

instance of the compounds of formula (5), R^5 is H. In one instance of the compounds of formula (5), n is 0.

[0365] In one aspect, the endocrine therapy comprises a compound having formula: (1R,2S)-1-[4-[2-[3-(fluoromethyl)azetidin-1-yl]ethoxy]phenyl]-2-phenyl-tetralin-6-ol; (1S,2R)-1-[4-[2-[3-(fluoromethyl)azetidin-1-yl]ethoxy]phenyl]-2-phenyl-tetralin-6-ol; (1S,2R)-1-[4-[2-[3-(fluoromethyl)azetidin-1-yl]ethoxy]phenyl]-2-(4-fluorophenyl)tetralin-6-ol; (1R,2R)-1-[2,6-difluoro-4-[2-[3-(fluoromethyl)azetidin-1-yl]ethoxy]phenyl]-2-phenyl-tetralin-6-ol; (1S,2S)-1-[2,6-difluoro-4-[2-[3-(fluoromethyl)azetidin-1-yl]ethoxy]phenyl]-2-phenyl-tetralin-6-ol; (1R,2S)-1-[4-[2-[3-(fluoromethyl)azetidin-1-yl]ethoxy]phenyl]-2-(4-fluorophenyl)tetralin-6-ol; (5R,6R)-5-(4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-6-(tetrahydro-2H-pyran-4-yl)-5,6,7,8-tetrahydronaphthalen-2-ol; (5S,6S)-6-(4,4-difluorocyclohexyl)-5-(4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-5,6,7,8-tetrahydronaphthalen-2-ol; (5S,6S)-5-(4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-6-(tetrahydro-2H-pyran-4-yl)-5,6,7,8-tetrahydronaphthalen-2-ol; (5R,6R)-6-(4,4-difluorocyclohexyl)-5-(4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-5,6,7,8-tetrahydronaphthalen-2-ol; (5R,6S)-5-(4-(2-(3-(fluoromethyl)pyrrolidin-1-yl)ethoxy)phenyl)-6-phenyl-5,6,7,8-tetrahydronaphthalen-2-ol; (5R,6S)-5-(4-(2-(3-(chloromethyl)azetidin-1-yl)ethoxy)phenyl)-6-phenyl-5,6,7,8-tetrahydronaphthalen-2-ol; (5S,6R)-5-(4-(2-(3-(chloromethyl)azetidin-1-yl)ethoxy)phenyl)-6-phenyl-5,6,7,8-tetrahydronaphthalen-2-ol; (5S,6R)-5-(4-(2-(3-(fluoromethyl)pyrrolidin-1-yl)ethoxy)phenyl)-6-phenyl-5,6,7,8-tetrahydronaphthalen-2-ol; (5S,6R)-5-(4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-6-(4-(methylsulfonyl)phenyl)-5,6,7,8-tetrahydronaphthalen-2-ol; (5S,6R)-5-(4-(2-(3-(difluoromethyl)azetidin-1-yl)ethoxy)phenyl)-6-phenyl-5,6,7,8-tetrahydronaphthalen-2-ol; (5R,6S)-5-(4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-6-(4-(methylsulfonyl)phenyl)-5,6,7,8-tetrahydronaphthalen-2-ol; (5R,6S)-5-(4-(2-(3-(difluoromethyl)azetidin-1-yl)ethoxy)phenyl)-6-phenyl-5,6,7,8-tetrahydronaphthalen-2-ol; (5R,6R)-5-(2-fluoro-4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-6-phenyl-5,6,7,8-tetrahydronaphthalen-2-ol; (5S,6S)-5-(2-fluoro-4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-6-phenyl-5,6,7,8-tetrahydronaphthalen-2-ol; (S)-1'-(4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-3',4'-dihydro-1'H-spiro[cyclopentane-1,2'-naphthalen]-6'-ol; (R)-1'-(4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-3',4'-dihydro-1'H-spiro[cyclopentane-1,2'-naphthalen]-6'-ol; (5R,6S)-5-(4-((S)-2-((R)-3-(fluoromethyl)pyrrolidin-

1-yl)propoxy)phenyl)-6-phenyl-5,6,7,8-tetrahydronaphthalen-2-ol; (5S,6R)-5-(4-((S)-2-((R)-3-(fluoromethyl)pyrrolidin-1-yl)propoxy)phenyl)-6-phenyl-5,6,7,8-tetrahydronaphthalen-2-ol; (5R,6S)-5-(4-(((R)-1-((R)-3-(fluoromethyl)pyrrolidin-1-yl)propan-2-yl)oxy)phenyl)-6-phenyl-5,6,7,8-tetrahydronaphthalen-2-ol; (5S,6R)-5-(4-(((R)-1-((R)-3-(fluoromethyl)pyrrolidin-1-yl)propan-2-yl)oxy)phenyl)-6-phenyl-5,6,7,8-tetrahydronaphthalen-2-ol; (5S,6S)-5-(6-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)pyridin-3-yl)-6-phenyl-5,6,7,8-tetrahydronaphthalen-2-ol; (5R,6R)-5-(6-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)pyridin-3-yl)-6-phenyl-5,6,7,8-tetrahydronaphthalen-2-ol; (5S,6R)-5-(4-((1-(3-fluoropropyl)azetidin-3-yl)oxy)phenyl)-6-phenyl-5,6,7,8-tetrahydronaphthalen-2-ol; (5R,6S)-5-(4-((1-(3-fluoropropyl)azetidin-3-yl)oxy)phenyl)-6-phenyl-5,6,7,8-tetrahydronaphthalen-2-ol; (5S,6R)-5-(4-((1-(3-fluoropropyl)azetidin-3-yl)amino)phenyl)-6-phenyl-5,6,7,8-tetrahydronaphthalen-2-ol; or (5R,6S)-5-(4-((1-(3-fluoropropyl)azetidin-3-yl)amino)phenyl)-6-phenyl-5,6,7,8-tetrahydronaphthalen-2-ol, or a pharmaceutically acceptable salt thereof or combination.

B. Non-Endocrine Anti-Cancer Therapies

[0366] In some instances of any of the preceding methods, an anti-cancer therapy other than an endocrine therapy may be administered to the individual. Exemplary anti-cancer therapies other than endocrine therapies include, but are not limited to, mammalian target of rapamycin (mTOR) inhibitors such as sirolimus (also known as rapamycin), temsirolimus (also known as CCI-779 or TORISEL®), everolimus (also known as RAD001 or AFINITOR®), ridaforolimus (also known as AP-23573, MK-8669, or deforolimus), OSI-027, AZD8055, and INK128; phosphatidylinositol 3-kinase (PI3K) inhibitors such as idelalisib (also known as GS-1101 or CAL-101), BKM120, and perifosine (also known as KRX-0401); dual phosphatidylinositol 3-kinase (PI3K)/mTOR inhibitors such as XL765, GDC-0980, BEZ235 (also known as NVP-BEZ235), BGT226, GSK2126458, PF-04691502, and PF-05212384 (also known as PKI-587); and cyclin-dependent kinase (CDK)4/6 inhibitors such as abemaciclib (VERZENIO®), palbociclib (IBRANCE®), ribociclib (KISQALI®), trilaciclib (G1T28); anthracyclines such as daunorubicin, doxorubicin, epirubicin, idarubicin, mitoxantrone, valrubicin; taxanes, including paclitaxel and docetaxel; podophyllotoxin; gemcitabine (GEMZAR®); 5-fluorouracil (5-FU); cyclophosphamide (CYTOXAN®); platinum analogs such as cisplatin and carboplatin; vinorelbine (NAVELBINE®); capecitabine (XELODA®); ixabepilone (IXEMPRA®); eribulin (HALAVEN®); and pharmaceutically acceptable salts acids or derivatives thereof; as well as

combinations thereof. In certain instances, an anti-cancer agent described herein can be used in combination with an endocrine therapy as described herein in the methods provided herein. For example, in one embodiment, a CDK4/6 inhibitor such as palbociclib can be administered in combination with an endocrine therapy described herein (e.g. a SERD as set forth herein). For example, in some instances, the anti-cancer therapy other than an endocrine therapy comprises a chemotherapeutic and a PI3K inhibitor.

[0367] The non-endocrine therapy can comprise administration of, for example, AKT inhibitors (e.g. Ipatasertib), angiogenic agents (e.g. Avastin), BCL-2 inhibitors (e.g. Venetoclax), HDAC inhibitors, AURK inhibitors, or cancer immunotherapy agents (e.g. anti-PD1/PDL1 agents, including for example, atezoluzimab, pembrolizumab, nivolumab, avelumab, durvalumab, and pidilizumab).

C. Combination Therapies

[0368] It is to be understood that the methods described herein can be used with all compounds described herein whether administered as monotherapies or in combination including, for example, double, triple, or quadruple therapy combinations. In one instance, the compounds described herein have been administered before a tested patient has had surgery. In another instance, the compounds described herein have been administered after a tested patient has had surgery. In still another instance, the compounds described herein have been administered as either a 1L, 2L, 3L or more therapy. In particular instance, patients described herein may have received prior treatment with a CDK4/6 inhibitor such as, for example, palbociclib, ribociclib, or abemaciclib before, during, or after treatment with a compound described herein.

[0369] In some instances of any of the preceding methods, a combination therapy including an endocrine therapy and one or more additional anti-cancer agents may be administered to the individual. Such combination therapies noted above encompass combined administration (where two or more therapeutic agents are included in the same or separate formulations), and separate administration, in which case, administration of an endocrine therapy as described herein can occur prior to, simultaneously, and/or following, administration of the additional therapeutic agent or agents.

V. COMPOSITIONS AND PHARMACEUTICAL FORMULATIONS

[0370] Therapeutic formulations of the therapeutic agents, including an anti-cancer agent as provided herein or an endocrine therapy as provided herein, used in accordance with the methods and compositions provided herein are prepared for storage by mixing the therapeutic agent having the desired degree of purity with optional pharmaceutically acceptable carriers, excipients, or stabilizers in the form of lyophilized formulations or aqueous solutions. For general information concerning formulations, see, e.g., Gilman et al. (eds.) *The Pharmacological Bases of Therapeutics*, 8th Ed., Pergamon Press, 1990; A. Gennaro (ed.), *Remington's Pharmaceutical Sciences*, 22nd Edition, Mack Publishing Co., Pennsylvania, 2012; Avis et al. (eds.) *Pharmaceutical Dosage Forms: Parenteral Medications* Dekker, New York, 1993; Lieberman et al. (eds.) *Pharmaceutical Dosage Forms: Tablets* Dekker, New York, 1990; Lieberman et al. (eds.), *Pharmaceutical Dosage Forms: Disperse Systems* Dekker, New York, 1990; and Walters (ed.) *Dermatological and Transdermal Formulations* (Drugs and the Pharmaceutical Sciences), Vol 119, Marcel Dekker, 2002.

[0371] Acceptable carriers, excipients, or stabilizers are non-toxic to recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate, and other organic acids; antioxidants including ascorbic acid and methionine; preservatives (such as octadecyldimethylbenzyl ammonium chloride; hexamethonium chloride; benzalkonium chloride, benzethonium chloride; phenol, butyl or benzyl alcohol; alkyl parabens such as methyl or propyl paraben; catechol; resorcinol; cyclohexanol; 3-pentanol; and m-cresol); low molecular weight (less than about 10 residues) polypeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine, histidine, arginine, or lysine; monosaccharides, disaccharides, and other carbohydrates including glucose, mannose, or dextrans; chelating agents such as EDTA; sugars such as sucrose, mannitol, trehalose or sorbitol; salt-forming counter-ions such as sodium; metal complexes (e.g., Zn-protein complexes); and/or non-ionic surfactants such as TWEEN™, PLURONICS™, or polyethylene glycol (PEG).

[0372] The formulation herein may also contain more than one active compound, preferably those with complementary activities that do not adversely affect each other. The type and effective amounts of such medicaments depend, for example, on the amount and type of

therapeutic agent described herein present in the formulation, and clinical parameters of the individuals.

[0373] The active ingredients may also be entrapped in microcapsules prepared, for example, by coacervation techniques or by interfacial polymerization, for example, hydroxymethylcellulose or gelatin-microcapsules and poly-(methylmethacrylate) microcapsules, respectively, in colloidal drug delivery systems (for example, liposomes, albumin microspheres, microemulsions, nanoparticles and nanocapsules) or in macroemulsions. Such techniques are disclosed in *Remington's Pharmaceutical Sciences* 16th edition, Osol, A. Ed., 1980.

[0374] Sustained-release preparations may be prepared. Suitable examples of sustained-release preparations include semi-permeable matrices of solid hydrophobic polymers containing the therapeutic agent, which matrices are in the form of shaped articles, e.g., films, or microcapsules. Examples of sustained-release matrices include polyesters, hydrogels (for example, poly(2-hydroxyethyl-methacrylate), or poly(vinylalcohol)), polylactides (U.S. Patent No. 3,773,919), copolymers of L-glutamic acid and γ ethyl-L-glutamate, non-degradable ethylene-vinyl acetate, degradable lactic acid-glycolic acid copolymers such as the LUPRON DEPOT™ (injectable microspheres composed of lactic acid-glycolic acid copolymer and leuprolide acetate), and poly-D-(-)-3-hydroxybutyric acid.

[0375] The formulations to be used for *in vivo* administration must be sterile. This is readily accomplished by filtration through sterile filtration membranes.

VI. ARTICLES OF MANUFACTURE AND KITS

[0376] In another aspect, provided herein is a kit or an article of manufacture containing materials useful for the treatment, diagnosis, and/or monitoring of individuals is provided.

[0377] In some instances, such diagnostic kits including one or more reagents for identifying an individual having a breast cancer (e.g., an HR+ breast cancer (e.g., an ER+ breast cancer (e.g., luminal A breast cancer or luminal B breast cancer)), DCIS, and/or a metastatic or a locally advanced breast cancer) who may benefit from a treatment including an endocrine therapy as described herein, by determining an ER pathway activity score or an E2-induced score, as described herein, from a sample (e.g., a tissue sample, e.g., a tumor tissue sample, e.g., a FFPE, a FF, an archival, a fresh, or a frozen tumor tissue sample) from the individual. In some instances,

the kit further includes one or more reagents for determining an ER pathway activity score or an E2-induced score from a sample.

[0378] Optionally, the kit may further include instructions to use the kit to select a therapy such as an endocrine therapy provided herein for treating a breast cancer if the ER pathway activity score or E2-induced score determined from the sample (e.g., a tissue sample, e.g., a tumor tissue sample, e.g., a FFPE, a FF, an archival, a fresh, or a frozen tumor tissue sample) from the individual is at or above a reference ER pathway activity score or a reference E2-induced score. In another instance, the instructions are to use the kit to select an anti-cancer therapy other than an endocrine therapy, if the ER pathway activity score or E2-induced score determined from the sample (e.g., a tissue sample, e.g., a tumor tissue sample, e.g., a FFPE, a FF, an archival, a fresh, or a frozen tumor tissue sample) from the individual is below a reference ER pathway activity score or a reference E2-induced score.

[0379] In other instances, the articles of manufacture or kits may include instructions to use the kit to monitor and/or assess the response of an individual having a breast cancer to treatment with an endocrine therapy as described herein.

[0380] In one aspect a kit including a plurality of nucleic acids is provided. The plurality of nucleic acids are at least 5 nucleotides in length and are at least 95, 98, 99, or 100% identical to a 5 nucleotide continuous sequence within at least five genes set forth in Table 1 and at least five genes set forth in Table 4; at least five genes set forth in Table 2 and at least five genes set forth in Table 4; or at least five genes set forth in Table 3 and at least five genes set forth in Table 6, or 95, 98, 99, or 100% identical to a sequence complementary to the 5 nucleotide continuous sequence.

[0381] In embodiments, the plurality of nucleic acids are attached to a solid support. In embodiments, the plurality of nucleic acids comprise a detectable label. In embodiments, the plurality of nucleic acids are at least 95, 98, 99, or 100% identical to a 5 nucleotide continuous sequence within at least five genes set forth in Table 1, at least five genes set forth in Table 2 or at least five genes set forth in Table 3 are greater than a standard control. In embodiments, the plurality of nucleic acids are at least 95, 98, 99, or 100% identical to a 5 nucleotide continuous sequence within at least five genes set forth in Table 4, at least five genes set forth in Table 5 or at least five genes set forth in Table 6 are less than a standard control. In embodiments, the

plurality of nucleic acids are at least 95, 98, 99, or 100% identical to a 5 nucleotide continuous sequence within all genes set forth in Table 1 and all genes set forth in Table 4. In embodiments, the plurality of nucleic acids are at least 95, 98, 99, or 100% identical to a 5 nucleotide continuous sequence within all genes set forth in Table 2 and all genes set forth in Table 5. In embodiments, the plurality of nucleic acids are at least 95, 98, 99, or 100% identical to a 5 nucleotide continuous sequence within all genes set forth in Table 3 and all genes set forth in Table 6. In embodiments, the plurality of nucleic acids are at least 95, 98, 99, or 100% identical to a 5 nucleotide continuous sequence within all genes set forth in Table 1 and all genes set forth in Table 4 and no other genes. In embodiments, the plurality of nucleic acids are at least 95, 98, 99, or 100% identical to a 5 nucleotide continuous sequence within all genes set forth in Table 2 and all genes set forth in Table 5 and no other genes. In embodiments, the plurality of nucleic acids are at least 95, 98, 99, or 100% identical to a 5 nucleotide continuous sequence within all genes set forth in Table 3 and all genes set forth in Table 6 and no other genes in the subject.

[0382] In a further embodiment, the plurality of nucleic acids are at least 95, 98, 99, or 100% identical to a continuous nucleotide sequence comprising at least 10, 20, 25, 50, 75, 100, 150, or 200 nucleotides.

[0383] Provided herein are also articles of manufacture including, packaged together an endocrine therapy as described herein in a pharmaceutically acceptable carrier and a package insert indicating that the endocrine therapy is for treating an individual with a breast cancer as described herein based on an ER pathway activity score or an E2-induced score determined from a sample (e.g., a tissue sample, e.g., a tumor tissue sample, e.g., a FFPE, a FF, an archival, a fresh, or a frozen tumor tissue sample) from the individual.

[0384] The article of manufacture may include, for example, a container and a label or package insert on or associated with the container. Suitable containers include, for example, bottles, vials, syringes, and the like. The container may be formed from a variety of materials such as glass or plastic. The container holds or contains a composition comprising the cancer medicament as the active agent and may have a sterile access port (e.g., the container may be an intravenous solution bag or a vial having a stopper pierceable by a hypodermic injection needle).

[0385] The article of manufacture may further include a second container comprising a pharmaceutically-acceptable diluent buffer, such as bacteriostatic water for injection (BWFI),

phosphate-buffered saline, Ringer's solution, and/or dextrose solution. The article of manufacture may further include other materials desirable from a commercial and user standpoint, including other buffers, diluents, filters, needles, and syringes.

[0386] The kits or articles of manufacture described herein may have a number of instances. In one instance, the kits or articles of manufacture includes a container, a label on said container, and a composition contained within said container, wherein the composition includes one or more polynucleotides that hybridize to a complement of a gene listed herein (e.g., a set of genes set forth in any one of Tables 1-6) under stringent conditions, and the label on said container indicates that the composition can be used to evaluate the presence a set of genes listed herein (e.g., a set of genes set forth in any one of Tables 1-6) in a sample, and wherein the kit includes instructions for using the polynucleotide(s) for evaluating the presence of the genes' RNA or DNA in a particular sample type.

[0387] For oligonucleotide-based articles of manufacture or kits, the article of manufacture or kit can include, for example: (1) an oligonucleotide, e.g., a detectably labeled oligonucleotide, which hybridizes to a nucleic acid sequence encoding a protein or (2) a pair of primers useful for amplifying a nucleic acid molecule. The article of manufacture or kit can also include, e.g., a buffering agent, a preservative, or a protein stabilizing agent. The article of manufacture or kit can further include components necessary for detecting the detectable label (e.g., an enzyme or a substrate). The article of manufacture or kit can also contain a control sample or a series of control samples that can be assayed and compared to the test sample. Each component of the article of manufacture or kit can be enclosed within an individual container and all of the various containers can be within a single package, along with instructions for interpreting the results of the assays performed using the kit.

[0388] The article of manufacture provided herein also includes information, for example in the form of a package insert, indicating that the composition is used for treating a breast cancer (e.g., an HR+ breast cancer (e.g., an ER+ breast cancer (e.g., luminal A breast cancer or luminal B breast cancer)), DCIS, and/or a metastatic or a locally advanced breast cancer) based on an ER pathway activity score or an E2-induced score from determined from a sample (e.g., a tissue sample, e.g., a tumor tissue sample, e.g., a FFPE, a FF, an archival, a fresh, or a frozen tumor tissue sample) from an individual as described herein. The insert or label may take any form,

such as paper or on electronic media such as a magnetically recorded medium (e.g., floppy disk), a CD-ROM, a Universal Serial Bus (USB) flash drive, and the like. The label or insert may also include other information concerning the pharmaceutical compositions and dosage forms in the kit or article of manufacture.

VII. EXAMPLES

[0389] The following are examples of the methods and compositions provided herein. It is understood that various other embodiments may be practiced, given the general description provided above.

Example 1. Identification of an ER pathway activity signature

[0390] Gene expression levels in breast cancer cell lines and a breast cancer xenograft mouse model were evaluated for their association with estrogen receptor (ER) pathway activity to identify potential biomarkers for predictive purposes.

[0391] *In vitro derived ER pathway activity signature.* To derive a transcriptional signature of ER pathway activity, RNA sequencing was performed on seven breast cancer cell lines following treatment with either DMSO or 1 μ M estradiol (E2) for 24 hours. Briefly, RNA libraries for cell lines were made with TRUSEQ® RNA sample preparation kit (ILLUMINA®) according to the manufacturer's protocol. The libraries were sequenced on an ILLUMINA® HiSeq 2000, using 1-4 lanes per cell line. RNA sequencing (RNA-seq) data were analyzed with HTSeqGenie (R package version 3.14.0) in BioConductor (Huber et al. *Nature Methods*. 112:115-21, 2015) as follows: reads were trimmed to 75 base pairs (bp), filtered for quality and rRNA/adaptor contamination, and aligned to the reference genome GRCh38 using GSNAP (Wu et al. *Bioinforma Oxf Engl*. 26:873-81, 2010). Gene expression was quantified as Reads per Kilobase of exon model per Million mapped reads normalized by size factor (nRPKM), defined as number of reads aligning to a gene in a sample/(total number of uniquely mapped reads for that sample x gene length x size factor). Genes without gene symbol and genes of uncertain function (LOC and Corf symbols) were excluded.

[0392] 233 to 1,390 genes were significantly induced by E2 relative to DMSO in individual cell lines (fold change ≥ 2 , and p-value ≤ 0.05) (Fig. 1A), and 365 to 1,251 genes were significantly suppressed by E2 in individual cell lines (fold change ≤ 0.5 , and p-value ≤ 0.05) (Fig. 1B). In order to capture a core set of ER-responsive genes that are most reflective of ER pathway

activity across heterogeneous tumors, and would thus likely be widely sensitive to ER perturbation, selected genes were those that were significantly and consistently induced or repressed by E2 in at least 6 out of 7 cell lines. E2-induced genes were additionally required to be higher expressed in 12 ER IHC+ breast cell lines compared to 25 ER IHC- breast cell lines (one-sided t-test $p < 0.05$). To compare the genes in a broader panel of ER+ vs. ER- breast cell lines, RNA-sequencing data from 37 breast cell lines was performed as described in Klijn et al, Nat Biotech 2015 and deposited on the European Genome-phenome Archive (<http://www.ebi.ac.uk/ega/>) under accession number EGAS00001000610. These data were processed in the same way as the RNAseq data for the 7 breast lines (previous paragraph). Together, this resulted in the identification of 28 E2-induced and 19 E2-repressed genes.

[0393] In order to generalize this core set of E2-induced and E2-repressed genes to patient data, RNA-seq data from 939 breast tumors from The Cancer Genome Atlas (TCGA), which included 726 ER+ (by IHC) breast tumors and 213 ER- breast tumors were examined. Briefly, RNA-seq data were downloaded from the National Cancer Institute Genomic Data Commons (<https://gdc.cancer.gov>) and were analyzed with HTSeqGenie in BioConductor as follows: first, reads with low nucleotide qualities (70% of bases with quality < 23) or rRNA and adapter contamination were removed. The reads that passed were then aligned to the reference genome GRCh38 using GSNAP. Alignments of the reads that were reported by GSNAP as “uniquely mapping” were used for subsequent analysis. Raw counts were converted to counts per million (cpm), filtered for lowly expressed genes (e.g., $\text{cpm} < 0.25$ in over 90% of samples), normalized using TMM normalization in the edgeR package, and finally voom transformed using the limma package in R. ER IHC was available for 84% of tumors, and RNA-seq-derived PAM50 subtype labels were assigned as previously described (Daemen et al. *Breast Cancer Research*. 20:8, 2018). Genes that were on average low expressed across the 726 ER+ (by IHC) breast tumors were discarded (average expression in bottom 15th percentile).

[0394] Signature genes were required to be expressed in ER+ TCGA tumors, and E2-induced genes were required to be higher expressed in ER+ compared to ER- tumors (one-sided t-test $p < 0.05$). This resulted in a further refinement of the signature to a 41-gene signature composed of 23 E2-induced and 18 E2-repressed genes of which are shown in Table 7 below. (See Fig. 1C).

[0395] Table 7: ER Repressed Genes

Gene symbol	Entrez gene ID	MDA-MB-320	HCC1500	MCF7	EFM19	T47D	BT474	CAMA1
		Log2 FC E2 vs no E2	Log2 FC E2 vs no E2	Log2 FC E2 vs no E2	Log2 FC E2 vs no E2	Log2 FC E2 vs no E2	Log2 FC E2 vs no E2	Log2 FC E2 vs no E2
BAMBI	25805	-1.352	-1.438	-0.571	-1.554	-1.394	-1.153	-1.072
BCAS1	8537	-1.772	-2.105	-0.981	-2.169	-2.536	-1.110	-2.311
CCNG2	901	-1.009	-1.525	-1.267	-1.442	-1.310	-0.935	-2.094
DDIT4	54541	-1.321	-1.865	-1.080	-1.101	-1.878	-0.862	-2.737
EGLN3	112399	-2.785	-2.504	-1.090	-1.008	-2.052	-0.118	-1.533
FAM171B	165215	-2.790	-0.683	-1.287	-1.910	-1.158	-1.279	-2.271
GRM4	2914	-2.281	-1.071	-1.106	-1.141	-1.340	-1.883	-2.021
IL1R1	3554	-0.941	-1.943	-2.169	-2.327	-2.433	-1.490	-1.666
LIPH	200879	-1.737	-1.384	-1.170	-1.844	-1.330	-0.804	-1.583
NBEA	26960	-1.044	-1.190	-1.132	-1.105	-1.368	-0.346	-1.550
PNPLA7	375775	-1.084	-1.376	-1.046	-0.901	-1.211	-1.427	-2.068
PSCA	8000	-2.529	-1.726	-2.199	-1.593	-1.253	-1.956	-3.517
SEMA3E	9723	-2.427	-1.058	-1.034	-1.100	-0.741	-1.101	-1.374
SSPO	23145	-1.383	-1.304	-1.338	-0.605	-1.181	-1.739	-2.298
STON1	11037	-1.081	-1.279	-2.067	-1.506	-2.304	-0.656	-2.609
TGFB3	7043	-1.111	-1.214	-1.707	-1.350	-1.263	-0.304	-1.444
TP53INP1	94241	-1.304	-1.777	-1.816	-1.461	-1.363	-1.496	-3.177
TP53INP2	58476	-1.210	-1.073	-1.207	-1.373	-0.959	-2.069	-2.068

[0396] To assess the spectrum of ER activity across a large patient population, density curves of three scores were derived using TCGA RNA-seq data from 939 treatment-naïve, primary breast tumors. The E2-induced score was defined as the average z-scored expression of 23 E2-induced genes (Fig. 1D); the E2-repressed score was defined as the average z-scored expression of 18 E2-repressed genes (Fig. 1E); and the ER pathway activity score was defined as the difference between the E2-induced and E2-repressed score (Fig. 1F). Genes identified as being modulated by ER as contained within the signature, irrespective of whether they are induced by, or repressed by E2, were expressed at low levels in ER-/basal tumors; E2 repressed genes are thus not necessarily anticipated to be more highly expressed in ER- tumors versus ER+ tumors.

[0397] *In vivo validation of ER pathway activity signature.* The HCI-013 PDX breast model was treated with vehicle or with different doses of Compound A, a selective estrogen receptor degrader (SERD), (0.1 mg/kg, 1 mg/kg, or 10 mg/kg), with four animals per treatment group (Fig. 2A). Samples were collected 8hrs after the last dose, and expression of the 23 E2-induced genes, 18 E2-repressed genes, and housekeeping genes were measured using FLUIDIGM®, and the data processed using SPOTFIRE® software. Expression data were normalized to housekeeping genes *GUSB*, *PPIA*, and *UBC*. Three genes that did not meet quality control standards were excluded (*GRM4*, *FMN1*, and *TP53INP2*). Two E2-induced genes, *AMZ1* and *CT62*, and two E2-repressed genes, *EGLN3* and *SEMA3A*, that were lowly expressed across the tumors in this study (average housekeeping-normalized expression in bottom 10th percentile of expressed genes) (Fig. 2B) were also excluded.

[0398] The effect of treatment with Compound A on ER pathway activity in the HCI-013 PDX model was assessed based on 20 E2-induced and 14 E2-repressed genes. The fold change in expression of each gene after Compound A exposure was calculated relative to the average expression of that gene in four vehicle treated animals. The E2-induced score was calculated as the average $\log_{10}$ fold change in expression of 20 E2-induced genes. The E2-repressed score was calculated as the average $\log_{10}$ fold change in expression of 14 E2-repressed genes. A composite score for ER pathway activity was calculated as the difference between the E2-induced score and the E2-repressed score (Fig. 2C). The three scores show a dose-response effect, with increased suppression of the ER pathway with increased dose (0.1 to 1 to 10 mg/kg).

[0399] The HCI-013 and HCI-011 PDX breast models were treated with various endocrine agents including Compound A, Compound B, Compound D, or Compound F at various doses, with four animals per treatment group. Tumor samples were collected 8hrs after the last dose, and the expression of the 23 E2-induced genes, 18 E2-repressed genes, housekeeping genes were measured using a FLUIDIGM® assay, and genes with low expression or that did not meet quality control standards were removed from the analysis, as described above. For data shown in FIGs. 2D-2F, expression data were normalized to housekeeping genes GUSB, SDHA, and UBC. One gene that did not meet quality control standards was excluded (FMN1). One E2-induced gene, AMZ1, and four E2-repressed genes, EGLN3, GRM4, SEMA3A, and TP53INP2, that were lowly expressed across the tumors in this study (average housekeeping-normalized expression in bottom 10th percentile of expressed genes) (Fig. 2E) were also excluded. For FIGs. 2G-2I, expression data were normalized to housekeeping genes GUSB, PPIA, and UBC. Two genes that did not meet quality control standards were excluded (CXCL12 and TP52INP2). Two E2-induced genes, FMN1 and CT62, and three E2-repressed genes, GRM4, IL1R1 and SSPO, that were lowly expressed across the tumors in this study (average housekeeping-normalized expression in bottom 10th percentile of expressed genes) (Fig. 2B) were also excluded. Gene expression analysis of HCI-013 and HCI-011 tumors revealed that modulation of ER target gene expression: 21 E2-induced genes were robustly decreased by treatment with the compounds, and the 14 E2-repressed genes were significantly up-regulated by the compounds (Figs. 2E and 2H). The degree of ER pathway suppression, as capture by the signature, associates with anti-tumor activity (Figs. 2F and 2I).

Example 2. ER pathway activity signature captures suppression of ER pathway activity in response to SERD treatment in patients.

[0400] In clinical practice, transcriptional profiling is routinely generated from formalin-fixed paraffin-embedded (FFPE) tissue, using the RNA ACCESS® protocol.

[0401] In order to use the ER pathway activity signature as PD biomarker for SERD activity or as predictive biomarker of potential ER pathway dependency in patients, a reference distribution of ER activity was derived from RNA ACCESS® data. RNA ACCESS® data were generated from FFPE tissue of a procured collection of 139 HR+/HER2- breast tumors. Raw counts for the 139 breast tumors were converted to counts per million (cpm), filtered for lowly expressed genes (i.e. cpm < 0.25 in over 90% of samples), normalized using TMM normalization in the edgeR package, and voom-transformed using the limma package in R. ER pathway signature genes with average voom-normalized expression across all 139 tumors in the bottom 5th percentile of all genes were removed from downstream analyses.

[0402] Two E2-induced genes, *SGK3* and *CT62*, were not or low expressed, and E2-repressed gene *PSCA* was low expressed in this reference collection. The expression of the signature genes, excluding these 3 genes, was next evaluated (Fig. 3A). RNA ACCESS® reference densities were defined for the E2-induced score, E2-repressed score, and ER pathway activity on the basis of 21 E2-induced and 17 E2-repressed genes, for the collection of 139 HR+/HER2- breast tumors (Figs. 3B-3D, 3H-3J).

[0403] Six patients with HR+/HER2- breast cancer were treated with a SERD (Compound B), and seven patients with HR+/HER2- breast cancer were treated with another SERD (Compound A). RNA ACCESS® data were generated (as described above) from FFPE tissue collected at time of screening (pre-treatment), and during the second or third cycle of SERD treatment (post-treatment). Genes were re-centered and re-scaled, using the mean and standard deviation from the reference collection.

[0404] Signature scores for the pre- and post-treated tumors were calculated and displayed on top of the reference densities, for the six patients treated with Compound B (Figs. 3B-3D) and for the seven patients treated with Compound A (Figs. 3H-3J). In the first cohort of six patients treated with Compound B, ER pathway activity was suppressed by SERD treatment in 4 out of 6 patients. There was no change in ER pathway activity for the two patients with low pre-treatment

ER pathway activity (patients Pb and Pf); ER pathway suppression in response to SERD-treatment is thus captured only in tumors which exhibit evidence of ER pathway activity prior to treatment (Fig. 3F). Two patients were considered PR+ (expression >4) and four patients PR-. Pre-treatment ESR1 expression levels are also an insufficient biomarker for ER pathway activity (Fig. 3E). These results were confirmed in the second cohort of seven patients treated with Compound A (Figs. 3H-M), among which four patients with PR+ and three patients with PR- breast cancer, with an observed suppression of ER pathway activity by SERD treatment in 6 out of 7 patients. Taken together, these results show that the signature can be used as a measure of pre-treatment ER pathway activity and as a PD biomarker in both PR+ and PR- breast tumors.

Example 3: Identification of core signature genes

[0405] To identify a set of core genes for inclusion in the ER pathway activity score, pre-and post-treatment expression data from the 4 out of 6 patients treated with Compound B for whom Compound B was effective in suppressing the ER pathway (excluding patients Pb and Pf) were analyzed. A subset of genes among the 41 *in vitro* derived genes that were impacted most and most consistently by endocrine therapy treatment in those four patients was selected to create a 19-gene signature with 11 E2-induced and 8 E2-repressed genes (one-sided t-test, $p < 0.1$) and a 14-gene signature with 8 E2-induced and 6 E2-repressed genes (one-sided t-test, $p < 0.05$). Both reduced gene sets performed equally well in the HCI-013 PDX model treated with different doses of compound A compared to the 41-gene signature (Figs. 4A-4C). Inclusion of both E2-induced and E2-repressed genes provided the largest dynamic range in ER pathway suppression in this *in vivo* model by dose. The reduced gene sets also resulted in a similar ER pathway suppression by treatment with Compound B in patients Pa through Pf as obtained with the 41-gene signature (Figs. 4D-4F). Similar results were also observed when assessing changes in ER pathway activity based on only E2-induced genes (Figs. 4G-4I). Signature genes are provided herein in Tables 1-6.

Example 4. ER pathway activity signature levels are agnostic to the sequencing platform employed, and to the tissue preparation method

[0406] The ER pathway activity scores in 30 FFPE samples, including five breast tumor samples, and in 30 FF (fresh frozen) samples, including five breast tumor samples, were determined. All breast samples were primary ER+ breast tissues, stage II or III, ductal

carcinoma. RNA-sequencing data were generated for all samples using two different library kits: RNA ACCESS®, and RIBO-ZERO® TRUSEQ®. In the 60 tissue samples, ER pathway activity levels obtained with either sequencing method were highly similar (Fig. 5; Pearson correlation 0.97). Furthermore, ER pathway activity scores in breast FFPE (pink triangles) vs. breast FF samples (pink circles) were in the same range (Fig. 5). These results suggest that the signature can be used in a platform-agnostic way (RNA ACCESS®, TRUSEQ®) and in a tissue preparation-agnostic way (FFPE, FF).

Example 5. ER inhibition and ER transcriptional activity

[0407] The relationship between ER pathway activity and the anti-proliferative effect of the ER antagonist fulvestrant was explored in a panel of 14 ER+/HER2- breast cancer cell lines. RNA-sequencing data was leveraged to determine the E2-induced score, determined by expression of a set of E2-induced genes (as described above), of a series of ER+/HER2- breast cancer cell lines grown under standard culture conditions, in the presence of estrogen. The effect of ER inhibition by 300 nM fulvestrant on cellular proliferation was determined in an 8-day in vitro viability assay using the GR (Growth Rate) method described by Hafner et al. (Nat Methods 13:6, 2016). The E2-induced score was then plotted against the effect of fulvestrant on cellular growth rate.

[0408] ER+/HER2- breast cancer cell lines displayed E2-induced scores ranging from 1.73 to -0.57, with a median of 0.63 (Figure 6). Fulvestrant had little impact on the growth rate of cell lines with E2-induced scores in the lowest 25th percentile for the panel of 14 cell lines (ZR-75-1, MDA-MB-415, MDA-MB-175-VII, KPL-1), while having a considerably greater impact on cell lines exhibiting higher E2-induced scores (Figure 7). These in vitro data support the hypothesis that ER inhibition is likely to be most impactful in contexts in which gene expression profiles reflect ER transcriptional activity.

VIII. OTHER EMBODIMENTS

[0409] Although the foregoing methods and compositions have been described in some detail by way of illustration and example for purposes of clarity and understanding, the descriptions and examples should not be construed as limiting the scope of the methods and compositions provided herein. The disclosures of all patent and scientific literature cited herein are expressly incorporated in their entirety by reference.

EMBODIMENTS

[0410] Embodiment 1. A method of identifying an individual having a breast cancer who may benefit from a treatment comprising an endocrine therapy, the method comprising determining an estrogen receptor (ER) pathway activity score from a sample from the individual, wherein an ER pathway activity score from the sample that is at or above a reference ER pathway activity score identifies the individual as one who may benefit from a treatment comprising an endocrine therapy.

[0411] Embodiment 2. A method for selecting a therapy for an individual having a breast cancer, the method comprising determining an ER pathway activity score from a sample from the individual, wherein an ER pathway activity score from the sample that is at or above a reference ER pathway activity score identifies the individual as one who may benefit from a treatment comprising an endocrine therapy.

[0412] Embodiment 3. The method of embodiment 1 or 2, wherein the ER pathway activity score determined from the sample is at or above the reference ER pathway activity score, and the method further comprises administering to the individual an effective amount of an endocrine therapy.

[0413] Embodiment 4. The method of embodiment 1 or 2, wherein an ER pathway activity score from the sample that is below a reference ER pathway activity score identifies the individual as one who is less likely to benefit from a treatment comprising an endocrine therapy.

[0414] Embodiment 5. The method of embodiment 4, wherein the ER pathway activity score determined from the sample is below the reference ER pathway activity score, and the method further comprises administering to the individual an effective amount of an anti-cancer therapy other than an endocrine therapy.

[0415] Embodiment 6. A method of treating an individual having a breast cancer, the method comprising administering an effective amount of an endocrine therapy to the individual, wherein the individual has been identified as one who is more likely to benefit from a treatment comprising an endocrine therapy by the method of embodiment 1.

[0416] Embodiment 7. A method of treating an individual having a breast cancer, the individual being identified as having an ER pathway activity score that is at or above a reference

ER pathway activity score, the method comprising administering to the individual an effective amount of an endocrine therapy.

[0417] Embodiment 8. A method of treating an individual having a breast cancer, the method comprising:

(a) determining an ER pathway activity score from a sample from the individual, wherein the ER pathway activity score from the sample is determined to be at or above a reference ER pathway activity score; and

(b) administering to the individual an effective amount of an endocrine therapy.

[0418] Embodiment 9. The method of any one of embodiments 1-8, wherein the reference ER pathway activity score is an ER pathway activity score in a reference population.

[0419] Embodiment 10. The method of any one of embodiments 1-3 and 6-9, wherein the ER pathway activity score in the sample is at or above -1.0.

[0420] Embodiment 11. The method of embodiment 10, wherein the ER pathway activity score in the sample is at or above -0.2.

[0421] Embodiment 12. The method of embodiment 4 or 5, wherein the ER pathway activity score in the sample is below -0.2.

[0422] Embodiment 13. The method of embodiment 4 or 5, wherein the ER pathway activity score in the sample is below -1.0.

[0423] Embodiment 14. The method of any one of embodiments 9-13, wherein the reference population is a population of individuals having hormone receptor-positive (HR+) breast cancer.

[0424] Embodiment 15. A method for monitoring the response of an individual having a breast cancer to treatment with an endocrine therapy, the method comprising:

(a) determining a first ER pathway activity score from a sample from the individual at a first time point;

(b) following step (a), determining a second ER pathway activity score from a sample from the individual at a second time point following administration of an endocrine therapy; and

(c) comparing the first ER pathway activity score with the second ER pathway activity score, wherein a decrease in the second ER pathway activity score relative to the first ER pathway activity score is predictive of an individual who is likely to respond to treatment with an endocrine therapy.

[0425] Embodiment 16. The method of embodiment 15, wherein the second ER pathway activity score is decreased relative to the first ER pathway activity score, and the method further comprises administering an additional dose of the endocrine therapy to the individual.

[0426] Embodiment 17. The method of embodiment 15 or 16, wherein the decrease in the second ER pathway activity score relative to the first ER pathway activity score is a decrease of at least 0.1.

[0427] Embodiment 18. The method of any one of embodiments 15-17, wherein the first ER pathway activity score is:

(a) an ER pathway activity score determined from a sample from the individual obtained prior to administration of a first dose of an endocrine therapy;

(b) an ER pathway activity score determined from a sample from the individual at a previous time point, wherein the previous time point is following administration of a first dose of an endocrine therapy; or

(c) a pre-assigned ER pathway activity score.

[0428] Embodiment 19. A method of identifying an individual having a breast cancer who may benefit from a treatment comprising an endocrine therapy, the method comprising determining an estradiol (E2)-induced score from a sample from the individual, wherein an E2-induced score from the sample that is at or above a reference E2-induced score identifies the individual as one who may benefit from a treatment comprising an endocrine therapy.

[0429] Embodiment 20. A method for selecting a therapy for an individual having a breast cancer, the method comprising determining an E2-induced score from a sample from the individual, wherein an E2-induced score from the sample that is at or above a reference E2-induced score identifies the individual as one who may benefit from a treatment comprising an endocrine therapy.

[0430] Embodiment 21. The method of embodiment 19 or 20, wherein the E2-induced score determined from the sample is at or above the reference E2-induced score, and the method further comprises administering to the individual an effective amount of an endocrine therapy.

[0431] Embodiment 22. The method of embodiment 19 or 20, wherein an E2-induced score from the sample that is below a reference E2-induced score identifies the individual as one who is less likely to benefit from a treatment comprising an endocrine therapy.

[0432] Embodiment 23. The method of embodiment 22, wherein the E2-induced score determined from the sample is below the reference E2-induced score, and the method further comprises administering to the individual an effective amount of an anti-cancer therapy other than an endocrine therapy.

[0433] Embodiment 24. A method of treating an individual having a breast cancer, the method comprising administering an effective amount of an endocrine therapy to the individual, wherein the individual has been identified as one who is more likely to benefit from a treatment comprising an endocrine therapy by the method of embodiment 19.

[0434] Embodiment 25. A method of treating an individual having a breast cancer, the individual being identified as having an E2-induced score that is at or above a reference E2-induced score, the method comprising administering to the individual an effective amount of an endocrine therapy.

[0435] Embodiment 26. A method of treating an individual having a breast cancer, the method comprising:

(a) determining an E2-induced score from a sample from the individual, wherein the E2-induced score from the sample is determined to be at or above a reference E2-induced score; and

(b) administering to the individual an effective amount of an endocrine therapy.

[0436] Embodiment 27. The method of any one of embodiments 19-26, wherein the reference E2-induced score is an E2-induced score in a reference population.

[0437] Embodiment 28. The method of any one of embodiments 19-21 and 24-27, wherein the E2-induced score in the sample is at or above -2.0.

[0438] Embodiment 29. The method of embodiment 28, wherein the E2-induced score in the sample is at or above -0.1.

[0439] Embodiment 30. The method of embodiment 22 or 23, wherein the E2-induced score in the sample is below -0.1.

[0440] Embodiment 31. The method of embodiment 30, wherein the E2-induced score in the sample is below -2.0.

[0441] Embodiment 32. The method of any one of embodiments 27-31, wherein the reference population is a population of individuals having HR+ breast tumors.

[0442] Embodiment 33. A method for monitoring the response of an individual having a breast cancer to treatment with an endocrine therapy, the method comprising:

(a) determining a first E2-induced score from a sample from the individual at a first time point;

(b) following step (a), determining a second E2-induced score from a sample from the individual at a second time point following administration of an endocrine therapy; and

(c) comparing the first E2-induced score with the second E2-induced score, wherein a decrease in the second E2-induced score relative to the first E2-induced score is predictive of an individual who is likely to respond to treatment with an endocrine therapy.

[0443] Embodiment 34. The method of embodiment 33, wherein the second E2-induced score is decreased relative to the first E2-induced score, and the method further comprises administering an additional dose of the endocrine therapy to the individual.

[0444] Embodiment 35. The method of embodiment 33 or 34, wherein the decrease in the second E2-induced score relative to the first E2-induced score is a decrease of at least 0.1.

[0445] Embodiment 36. The method of any one of embodiments 33-35, wherein the first E2-induced score is:

(a) an E2-induced score determined from a sample from the individual obtained prior to administration of a first dose of an endocrine therapy;

(b) an E2-induced score determined from a sample from the individual at a previous time point, wherein the previous time point is following administration of a first dose of an endocrine therapy; or

(c) a pre-assigned E2-induced score.

[0446] Embodiment 37. The method of any one of embodiments 1-6, 8-24, and 26-36, wherein the sample is a tissue sample.

[0447] Embodiment 38. The method of embodiment 37, wherein the tissue sample is a tumor tissue sample.

[0448] Embodiment 39. The method of embodiment 38, wherein the tumor tissue sample is a formalin-fixed and paraffin-embedded (FFPE) sample, a fresh frozen (FF) sample, an archival sample, a fresh sample, or a frozen sample.

[0449] Embodiment 40. The method of embodiment 39, wherein the tumor tissue sample is a FFPE sample.

[0450] Embodiment 41. The method of embodiment 39, wherein the tumor tissue sample is a FF sample.

[0451] Embodiment 42. The method of any one of embodiments 1-41, wherein the breast cancer is an ER+ breast cancer.

[0452] Embodiment 43. The method of embodiment 42, wherein the ER+ breast cancer is a luminal A breast cancer.

[0453] Embodiment 44. The method of embodiment 42, wherein the ER+ breast cancer is a luminal B breast cancer.

[0454] Embodiment 45. The method of any one of embodiments 1-44, wherein the breast cancer is an advanced or a metastatic breast cancer.

[0455] Embodiment 46. The method of any one of embodiments 3, 5-18, 21, and 23-45, wherein the endocrine therapy is administered orally, intravenously, intratumorally, intramuscularly, subcutaneously, topically, or intranasally.

[0456] Embodiment 47. The method of embodiment 46, wherein the endocrine therapy is administered orally.

[0457] Embodiment 48. The method of embodiment 46, wherein the endocrine therapy is administered intramuscularly.

[0458] Embodiment 49. A method of detecting estrogen receptor (ER) pathway activity in a subject that has breast cancer, the method comprising detecting an expression level of at least five genes set forth in Table 1 and at least five genes set forth in Table 4; at least five genes set forth in Table 2 and at least five genes set forth in Table 5; or at least five genes set forth in Table 3 and at least five genes set forth in Table 6.

[0459] Embodiment 50. The method of embodiment 49, wherein the expression level of said at least five genes set forth in Table 1, at least five genes set forth in Table 2 or at least five genes set forth in Table 3 are greater than a standard control.

[0460] Embodiment 51. The method of embodiment 49, wherein the expression level of said at least five genes set forth in Table 4, at least five genes set forth in Table 5 or at least five genes set forth in Table 6 are less than a standard control.

[0461] Embodiment 52. The method of one of embodiments 49 to 51, wherein the subject has been treated with an endocrine therapy prior to said detecting.

[0462] Embodiment 53. The method of one of embodiments 49 to 52, wherein the subject is treated with an endocrine therapy subsequent to said detecting.

[0463] Embodiment 54. The method of one of embodiments 49 to 53 comprising detecting an expression level of all genes set forth in Table 1 and all genes set forth in Table 4.

[0464] Embodiment 55. The method of one of embodiments 49 to 53 comprising detecting an expression level of all genes set forth in Table 2 and all genes set forth in Table 5.

[0465] Embodiment 56. The method of one of embodiments 49 to 53 comprising detecting an expression level of all genes set forth in Table 3 and all genes set forth in Table 6.

[0466] Embodiment 57. The method of one of embodiments 49 to 53 comprising detecting an expression level of all genes set forth in Table 1 and all genes set forth in Table 4 and not detecting an expression level of any other genes in said subject.

[0467] Embodiment 58. The method of one of embodiments 49 to 53 comprising detecting an expression level of all genes set forth in Table 2 and all genes set forth in Table 5 and not detecting an expression level of any other genes in said subject.

[0468] Embodiment 59. The method of one of embodiments 49 to 53 comprising detecting an expression level of all genes set forth in Table 3 and all genes set forth in Table 6 and not detecting an expression level of any other genes in said subject.

[0469] Embodiment 60. The method of one of embodiments 49 to 59, wherein the subject is treated with an endocrine therapy comprising a selective estrogen receptor degrader.

[0470] Embodiment 61. The method of one of embodiments 49 to 60, further comprising determining an estrogen receptor (ER) pathway activity score from a sample from the subject.

[0471] Embodiment 62. The method of embodiment 61, wherein an ER pathway activity score from the sample that is at or above a reference ER pathway activity score identifies the individual as one who may benefit from a treatment comprising an endocrine therapy.

[0472] Embodiment 63. The method of embodiment 61, further comprising comparing an ER pathway activity score from the sample that is at or above a reference ER pathway activity score identifies the individual as one who may benefit from a treatment comprising an endocrine therapy.

[0473] Embodiment 64. A method, comprising:

detecting, by one or more processors, a first expression level of at least five genes set forth in Table 1, at least five genes set forth in Table 2, or at least five genes set forth in Table 3;

detecting, by the one or more processors, a second expression level of at least five genes set forth in Table 4, at least five genes set forth in Table 5 or at least five genes set forth in Table 6; and

detecting, based at least on the first expression level and/or the second expression level, estrogen receptor (ER) pathway activity in a subject that has cancer.

[0474] Embodiment 65. The method of embodiment 64, wherein the expression level of said at least five genes set forth in Table 1, at least five genes set forth in Table 2 or at least five genes set forth in Table 3 are greater than a standard control.

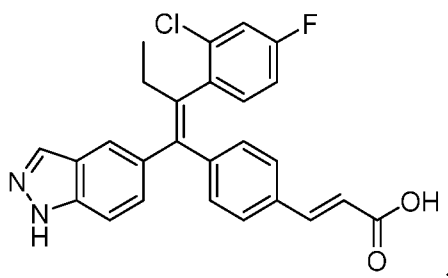
[0475] Embodiment 66. The method of embodiment 64, wherein the expression level of said at least five genes set forth in Table 4, at least five genes set forth in Table 5 or at least five genes set forth in Table 6 are less than a standard control.

[0476] Embodiment 67. The method of one of embodiments 64 to 66, further comprising: treating the subject with an endocrine therapy prior to said detecting.

[0477] Embodiment 68. The method of one of embodiments 64 to 67, further comprising: treating, based at least on the estrogen receptor (ER) pathway activity detected in the subject, the subject with an endocrine therapy.

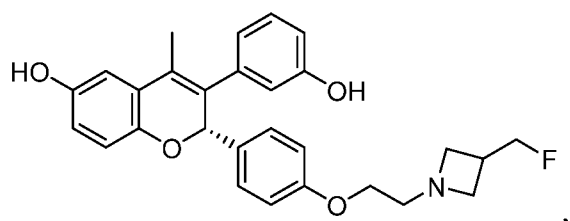
[0478] Embodiment 69. The method of any one of embodiments 1-68, wherein the endocrine therapy comprises a selective estrogen receptor degrader (SERD), a selective estrogen receptor modulator (SERM), a selective estrogen receptor covalent antagonist (SERCA), a selective human estrogen receptor agonist (ShERPA), an aromatase inhibitor (AI), or a combination thereof.

[0479] Embodiment 70. The method of embodiment 69, wherein the SERD comprises brilanestrant (GDC-0810) having the structure:



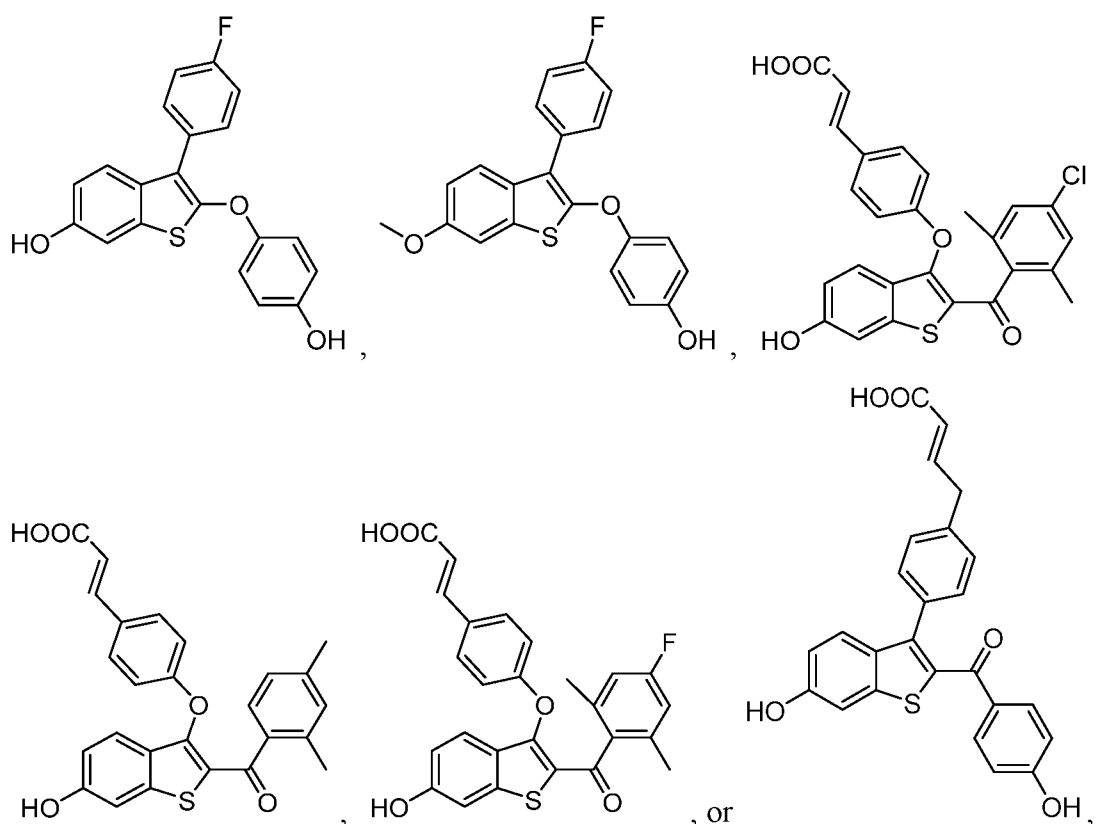
or a pharmaceutically acceptable salt thereof.

[0480] Embodiment 71. The method of embodiment 69, wherein the SERD comprises GDC-0927 (SRN-0927) having the structure:



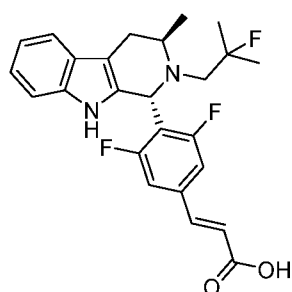
or a pharmaceutically acceptable salt thereof.

[0481] Embodiment 72. The method of any one of embodiments 1-68, wherein the endocrine therapy comprises a compound having formula:

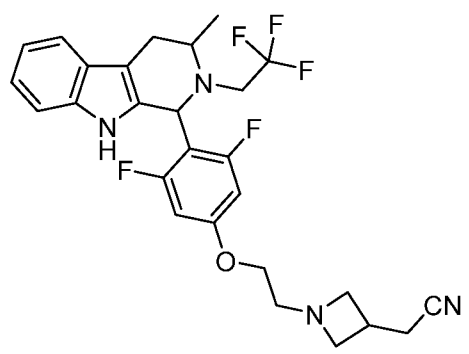


or a pharmaceutically acceptable salt thereof.

[0482] Embodiment 73. The method of any one of embodiments 1-68, wherein the endocrine therapy comprises a compound having formula:

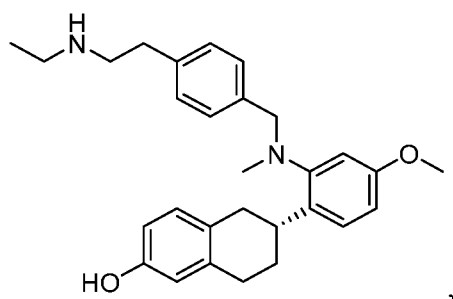


[0483] Embodiment 74. The method of any one of embodiments 1-68, wherein the endocrine therapy comprises a compound having formula:



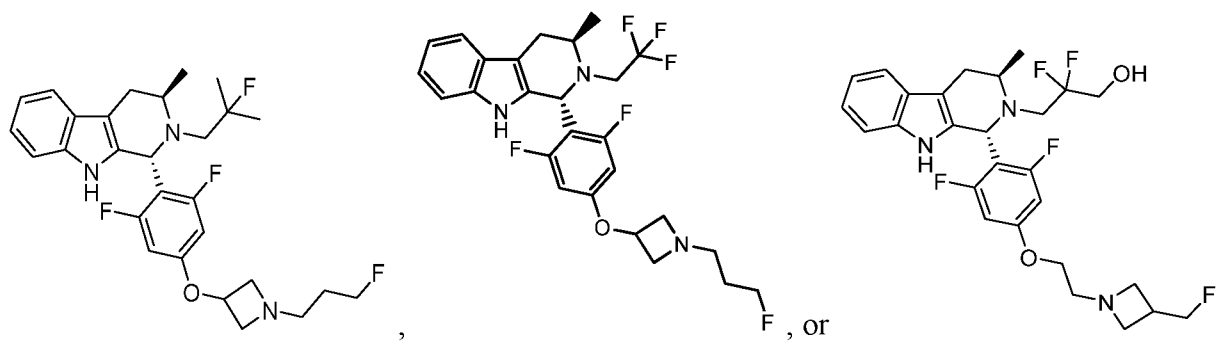
or a pharmaceutically acceptable salt thereof.

[0484] Embodiment 75. The method of any one of embodiments 1-68, wherein the endocrine therapy comprises a compound having formula:



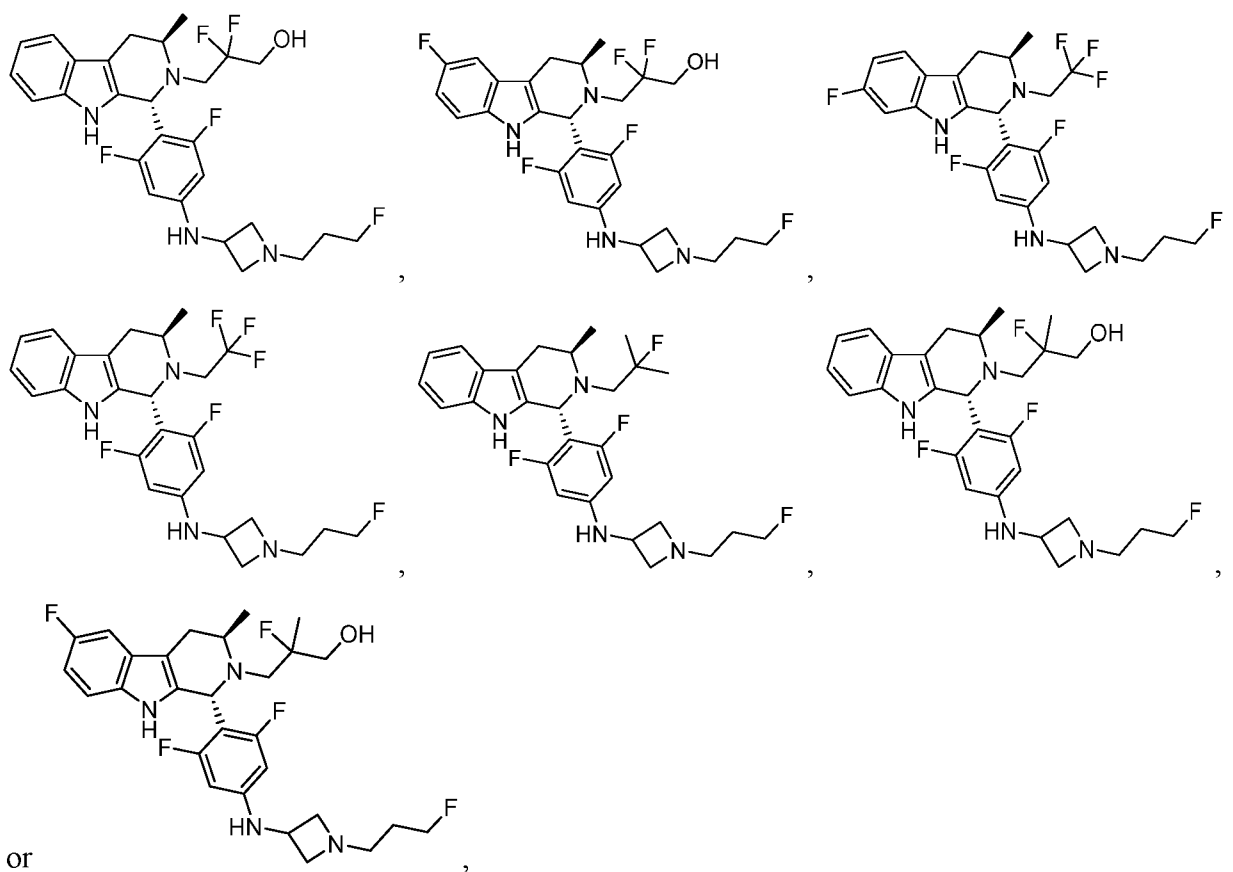
or a pharmaceutically acceptable salt thereof.

[0485] Embodiment 76. The method of any one of embodiments 1-68, wherein the endocrine therapy comprises a compound having formula:



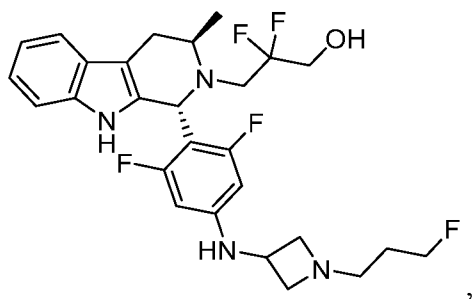
or a pharmaceutically acceptable salt thereof.

[0486] Embodiment 77. The method of any one of embodiments 1-68, wherein the endocrine therapy comprises a compound having formula:



or a pharmaceutically acceptable salt thereof.

[0487] Embodiment 78. The method of any one of embodiments 1-68, wherein the endocrine therapy comprises a compound having formula:



or a pharmaceutically acceptable salt thereof.

[0488] Embodiment 79. The method of embodiment 5 or 23, wherein the anti-cancer therapy other than an endocrine therapy comprises a chemotherapy.

[0489] Embodiment 80. The method of embodiment 79, wherein the chemotherapy comprises an anthracycline, a taxane, 5-fluorouracil, cyclophosphamide, a platinum agent, vinorelbine, capecitabine, gemcitabine, ixabepilone, eribulin, or a combination thereof.

[0490] Embodiment 81. The method of embodiment 79, wherein the anti-cancer therapy other than an endocrine therapy comprises a PI3K inhibitor, an mTOR inhibitor, a CDK4/6 inhibitor, or a combination thereof.

[0491] Embodiment 82. The method of any one of embodiments 1-81, wherein the individual is a human.

[0492] Embodiment 83. A kit comprising a plurality of nucleic acids, wherein said plurality of nucleic acids are at least 5 nucleotides in length and are at least 95% identical to a 5 nucleotide continuous sequence within at least five genes set forth in Table 1 and at least five genes set forth in Table 4; at least five genes set forth in Table 2 and at least five genes set forth in Table 4; or at least five genes set forth in Table 3 and at least five genes set forth in Table 6, or 95% identical to a sequence complementary to said 5 nucleotide continuous sequence.

[0493] Embodiment 84. The kit of embodiment 83, wherein said plurality of nucleic acids are attached to a solid support.

[0494] Embodiment 85. The kit of embodiment 84, wherein said plurality of nucleic acids comprise a detectable label.

[0495] Embodiment 86. The kit of embodiment 83, wherein said plurality of nucleic acids are at least 95% identical to a 5 nucleotide continuous sequence within at least five genes set forth in Table 1, at least five genes set forth in Table 2 or at least five genes set forth in Table 3 are greater than a standard control.

[0496] Embodiment 87. The kit of embodiment 83, wherein said plurality of nucleic acids are at least 95% identical to a 5 nucleotide continuous sequence within at least five genes set forth in Table 4, at least five genes set forth in Table 5 or at least five genes set forth in Table 6 are less than a standard control.

[0497] Embodiment 88. The kit of one of embodiments 83-87, wherein said plurality of nucleic acids are at least 95% identical to a 5 nucleotide continuous sequence within all genes set forth in Table 1 and all genes set forth in Table 4.

[0498] Embodiment 89. The kit of one of embodiments 83-87, wherein said plurality of nucleic acids are at least 95% identical to a 5 nucleotide continuous sequence within all genes set forth in Table 2 and all genes set forth in Table 5.

[0499] Embodiment 90. The kit of one of embodiments 83-87, wherein said plurality of nucleic acids are at least 95% identical to a 5 nucleotide continuous sequence within all genes set forth in Table 3 and all genes set forth in Table 6.

[0500] Embodiment 91. The kit of one of embodiments 83-87, wherein said plurality of nucleic acids are at least 95% identical to a 5 nucleotide continuous sequence within all genes set forth in Table 1 and all genes set forth in Table 4 and no other genes.

[0501] Embodiment 92. The kit of one of embodiments 83-87, wherein said plurality of nucleic acids are at least 95% identical to a 5 nucleotide continuous sequence within all genes set forth in Table 2 and all genes set forth in Table 5 and no other genes.

[0502] Embodiment 93. The kit of one of embodiments 83-87, wherein said plurality of nucleic acids are at least 95% identical to a 5 nucleotide continuous sequence within all genes set forth in Table 3 and all genes set forth in Table 6 and no other genes in said subject.

[0503] Embodiment 94. The kit of one of embodiments 83-93, wherein the plurality of nucleic acids are identical to a 5 nucleotide continuous sequence within said genes.

[0504] Embodiment 95. The kit of one of embodiments 83-94, wherein the plurality of nucleic acids are identical to a continuous nucleotide sequence comprising at least 10, 20, 25, 50, 75, 100, 150, or 200 nucleotides.

WHAT IS CLAIMED IS:

1. A method of identifying an individual having a breast cancer who may benefit from a treatment comprising an endocrine therapy, the method comprising determining an estrogen receptor (ER) pathway activity score from a sample from the individual, wherein an ER pathway activity score from the sample that is at or above a reference ER pathway activity score identifies the individual as one who may benefit from a treatment comprising an endocrine therapy.

2. A method for selecting a therapy for an individual having a breast cancer, the method comprising determining an ER pathway activity score from a sample from the individual, wherein an ER pathway activity score from the sample that is at or above a reference ER pathway activity score identifies the individual as one who may benefit from a treatment comprising an endocrine therapy.

3. The method of claim 1, wherein the ER pathway activity score determined from the sample is at or above the reference ER pathway activity score, and the method further comprises administering to the individual an effective amount of an endocrine therapy.

4. The method of claim 1, wherein an ER pathway activity score from the sample that is below a reference ER pathway activity score identifies the individual as one who is less likely to benefit from a treatment comprising an endocrine therapy.

5. The method of claim 4, wherein the ER pathway activity score determined from the sample is below the reference ER pathway activity score, and the method further comprises administering to the individual an effective amount of an anti-cancer therapy other than an endocrine therapy.

6. A method of treating an individual having a breast cancer, the method comprising administering an effective amount of an endocrine therapy to the individual, wherein the individual has been identified as one who is more likely to benefit from a treatment comprising an endocrine therapy by the method of claim 1.

7. A method of treating an individual having a breast cancer, the individual being identified as having an ER pathway activity score that is at or above a reference ER pathway activity score, the method comprising administering to the individual an effective amount of an endocrine therapy.

8. A method of treating an individual having a breast cancer, the method comprising:
(a) determining an ER pathway activity score from a sample from the individual, wherein the ER pathway activity score from the sample is determined to be at or above a reference ER pathway activity score; and
(b) administering to the individual an effective amount of an endocrine therapy.

9. The method of claim 1, wherein the reference ER pathway activity score is an ER pathway activity score in a reference population.

10. The method of claim 1, wherein the ER pathway activity score in the sample is at or above -1.0.

11. The method of claim 10, wherein the ER pathway activity score in the sample is at or above -0.2.

12. The method of claim 4, wherein the ER pathway activity score in the sample is below -0.2.

13. The method of claim 4, wherein the ER pathway activity score in the sample is below -1.0.

14. The method of claim 9, wherein the reference population is a population of individuals having hormone receptor-positive (HR+) breast cancer.

15. A method for monitoring the response of an individual having a breast cancer to treatment with an endocrine therapy, the method comprising:

- (a) determining a first ER pathway activity score from a sample from the individual at a first time point;
- (b) following step (a), determining a second ER pathway activity score from a sample from the individual at a second time point following administration of an endocrine therapy; and
- (c) comparing the first ER pathway activity score with the second ER pathway activity score, wherein a decrease in the second ER pathway activity score relative to the first ER pathway activity score is predictive of an individual who is likely to respond to treatment with an endocrine therapy.

16. The method of claim 15, wherein the second ER pathway activity score is decreased relative to the first ER pathway activity score, and the method further comprises administering an additional dose of the endocrine therapy to the individual.

17. The method of claim 15, wherein the decrease in the second ER pathway activity score relative to the first ER pathway activity score is a decrease of at least 0.1.

18. The method of claim 15, wherein the first ER pathway activity score is:

- (a) an ER pathway activity score determined from a sample from the individual obtained prior to administration of a first dose of an endocrine therapy;
- (b) an ER pathway activity score determined from a sample from the individual at a previous time point, wherein the previous time point is following administration of a first dose of an endocrine therapy; or
- (c) a pre-assigned ER pathway activity score.

19. A method of identifying an individual having a breast cancer who may benefit from a treatment comprising an endocrine therapy, the method comprising determining an estradiol (E2)-induced score from a sample from the individual, wherein an E2-induced score from the sample that is at or above a reference E2-induced score identifies the individual as one who may benefit from a treatment comprising an endocrine therapy.

20. A method for selecting a therapy for an individual having a breast cancer, the method comprising determining an E2-induced score from a sample from the individual, wherein an E2-induced score from the sample that is at or above a reference E2-induced score identifies the individual as one who may benefit from a treatment comprising an endocrine therapy.

21. The method of claim 19, wherein the E2-induced score determined from the sample is at or above the reference E2-induced score, and the method further comprises administering to the individual an effective amount of an endocrine therapy.

22. The method of claim 19, wherein an E2-induced score from the sample that is below a reference E2-induced score identifies the individual as one who is less likely to benefit from a treatment comprising an endocrine therapy.

23. The method of claim 22, wherein the E2-induced score determined from the sample is below the reference E2-induced score, and the method further comprises administering to the individual an effective amount of an anti-cancer therapy other than an endocrine therapy.

24. A method of treating an individual having a breast cancer, the method comprising administering an effective amount of an endocrine therapy to the individual, wherein the individual has been identified as one who is more likely to benefit from a treatment comprising an endocrine therapy by the method of claim 19.

25. A method of treating an individual having a breast cancer, the individual being identified as having an E2-induced score that is at or above a reference E2-induced score, the method comprising administering to the individual an effective amount of an endocrine therapy.

26. A method of treating an individual having a breast cancer, the method comprising:
(a) determining an E2-induced score from a sample from the individual, wherein the E2-induced score from the sample is determined to be at or above a reference E2-induced score; and
(b) administering to the individual an effective amount of an endocrine therapy.

27. The method of claim 19, wherein the reference E2-induced score is an E2-induced score in a reference population.

28. The method of claim 19, wherein the E2-induced score in the sample is at or above -2.0.

29. The method of claim 28, wherein the E2-induced score in the sample is at or above -0.1.

30. The method of claim 22, wherein the E2-induced score in the sample is below -0.1.

31. The method of claim 30, wherein the E2-induced score in the sample is below -2.0.

32. The method of claim 27, wherein the reference population is a population of individuals having HR+ breast tumors.

33. A method for monitoring the response of an individual having a breast cancer to treatment with an endocrine therapy, the method comprising:

- (a) determining a first E2-induced score from a sample from the individual at a first time point;
- (b) following step (a), determining a second E2-induced score from a sample from the individual at a second time point following administration of an endocrine therapy; and
- (c) comparing the first E2-induced score with the second E2-induced score, wherein a decrease in the second E2-induced score relative to the first E2-induced score is predictive of an individual who is likely to respond to treatment with an endocrine therapy.

34. The method of claim 33, wherein the second E2-induced score is decreased relative to the first E2-induced score, and the method further comprises administering an additional dose of the endocrine therapy to the individual.

35. The method of claim 33, wherein the decrease in the second E2-induced score relative to the first E2-induced score is a decrease of at least 0.1.

36. The method of claim 33, wherein the first E2-induced score is:

(a) an E2-induced score determined from a sample from the individual obtained prior to administration of a first dose of an endocrine therapy;

(b) an E2-induced score determined from a sample from the individual at a previous time point, wherein the previous time point is following administration of a first dose of an endocrine therapy; or

(c) a pre-assigned E2-induced score.

37. The method of claim 36, wherein the sample is a tissue sample.

38. The method of claim 37, wherein the tissue sample is a tumor tissue sample.

39. The method of claim 38, wherein the tumor tissue sample is a formalin-fixed and paraffin-embedded (FFPE) sample, a fresh frozen (FF) sample, an archival sample, a fresh sample, or a frozen sample.

40. The method of claim 39, wherein the tumor tissue sample is a FFPE sample.

41. The method of claim 39, wherein the tumor tissue sample is a FF sample.

42. The method of claim 41, wherein the breast cancer is an ER⁺ breast cancer.

43. The method of claim 42, wherein the ER⁺ breast cancer is a luminal A breast cancer.

44. The method of claim 42, wherein the ER⁺ breast cancer is a luminal B breast cancer.

45. The method of claim 44, wherein the breast cancer is an advanced or a metastatic breast cancer.

46. The method of claim 45, wherein the endocrine therapy is administered orally, intravenously, intratumorally, intramuscularly, subcutaneously, topically, or intranasally.

47. The method of claim 46, wherein the endocrine therapy is administered orally.

48. The method of claim 46, wherein the endocrine therapy is administered intramuscularly.

49. A method of detecting estrogen receptor (ER) pathway activity in a subject that has breast cancer, the method comprising detecting an expression level of at least five genes set forth in Table 1 and at least five genes set forth in Table 4; at least five genes set forth in Table 2 and at least five genes set forth in Table 5; or at least five genes set forth in Table 3 and at least five genes set forth in Table 6.

50. The method of claim 49, wherein the expression level of said at least five genes set forth in Table 1, at least five genes set forth in Table 2 or at least five genes set forth in Table 3 are greater than a standard control.

51. The method of claim 49, wherein the expression level of said at least five genes set forth in Table 4, at least five genes set forth in Table 5 or at least five genes set forth in Table 6 are less than a standard control.

52. The method of claim 49, wherein the subject has been treated with an endocrine therapy prior to said detecting.

53. The method of claim 49, wherein the subject is treated with an endocrine therapy subsequent to said detecting.

54. The method claim 49, comprising detecting an expression level of all genes set forth in Table 1 and all genes set forth in Table 4.

55. The method of claim 49, comprising detecting an expression level of all genes set forth in Table 2 and all genes set forth in Table 5.

56. The method of claim 49, comprising detecting an expression level of all genes set forth in Table 3 and all genes set forth in Table 6.

57. The method of claim 49, comprising detecting an expression level of all genes set forth in Table 1 and all genes set forth in Table 4 and not detecting an expression level of any other genes in said subject.

58. The method of claim 49, comprising detecting an expression level of all genes set forth in Table 2 and all genes set forth in Table 5 and not detecting an expression level of any other genes in said subject.

59. The method of claim 49, comprising detecting an expression level of all genes set forth in Table 3 and all genes set forth in Table 6 and not detecting an expression level of any other genes in said subject.

60. The method of claim 49, wherein the subject is treated with an endocrine therapy comprising a selective estrogen receptor degrader.

61. The method of claim 49, further comprising determining an estrogen receptor (ER) pathway activity score from a sample from the subject.

62. The method of claim 61, wherein an ER pathway activity score from the sample that is at or above a reference ER pathway activity score identifies the individual as one who may benefit from a treatment comprising an endocrine therapy.

63. The method of claim 61, further comprising comparing an ER pathway activity score from the sample that is at or above a reference ER pathway activity score identifies the individual as one who may benefit from a treatment comprising an endocrine therapy.

64. A method, comprising:

detecting, by one or more processors, a first expression level of at least five genes set forth in Table 1, at least five genes set forth in Table 2, or at least five genes set forth in Table 3;

detecting, by the one or more processors, a second expression level of at least five genes set forth in Table 4, at least five genes set forth in Table 5 or at least five genes set forth in Table 6; and

detecting, based at least on the first expression level and/or the second expression level, estrogen receptor (ER) pathway activity in a subject that has cancer.

65. The method of claim 64, wherein the expression level of said at least five genes set forth in Table 1, at least five genes set forth in Table 2 or at least five genes set forth in Table 3 are greater than a standard control.

66. The method of claim 64, wherein the expression level of said at least five genes set forth in Table 4, at least five genes set forth in Table 5 or at least five genes set forth in Table 6 are less than a standard control.

67. The method of claim 64, further comprising:

treating the subject with an endocrine therapy prior to said detecting.

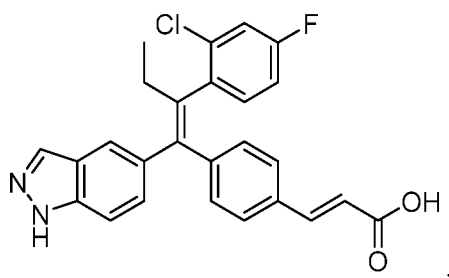
68. The method of claim 64, further comprising:

treating, based at least on the estrogen receptor (ER) pathway activity detected in the subject, the subject with an endocrine therapy.

69. The method claim 1, wherein the endocrine therapy comprises a selective estrogen receptor degrader (SERD), a selective estrogen receptor modulator (SERM), a selective estrogen

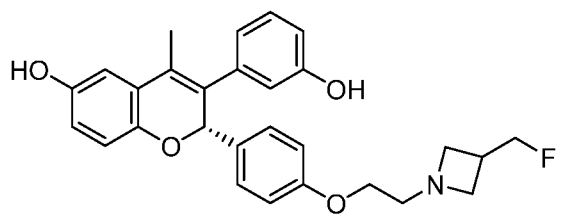
receptor covalent antagonist (SERCA), a selective human estrogen receptor agonist (ShERPA), an aromatase inhibitor (AI), or a combination thereof.

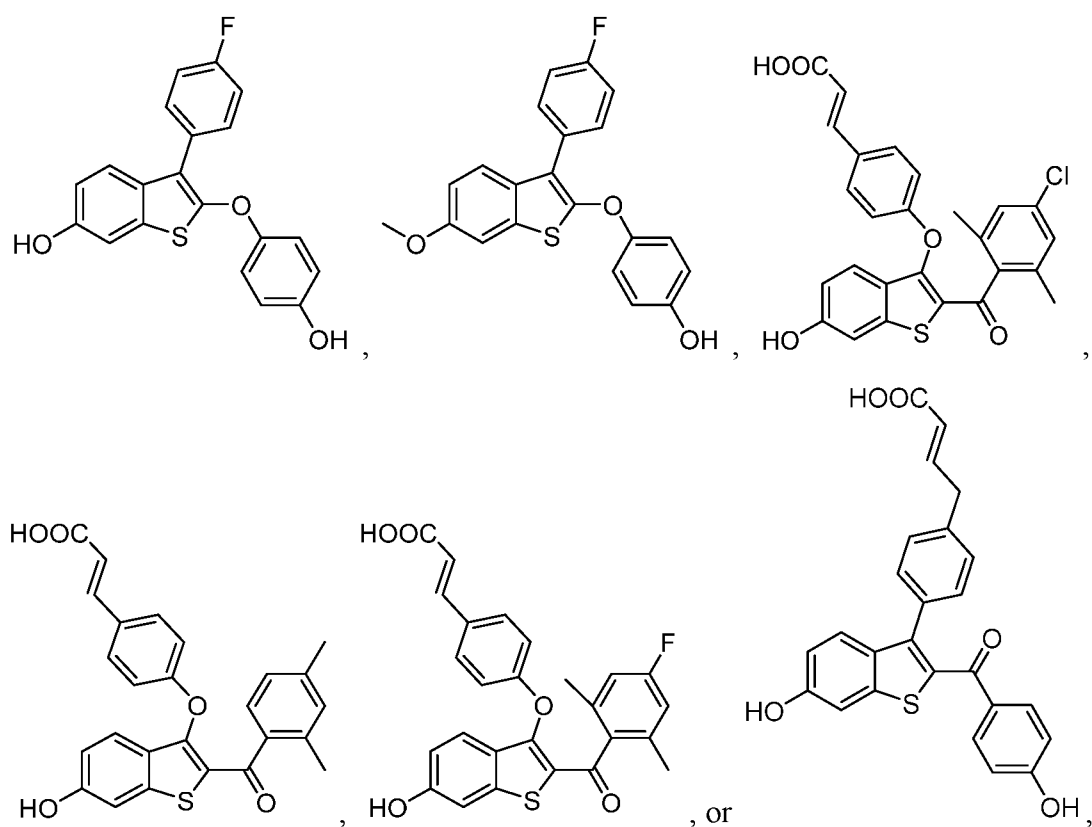
70. The method of claim 69, wherein the SERD comprises brilanestrant (GDC-0810) having the structure:



or a pharmaceutically acceptable salt thereof.

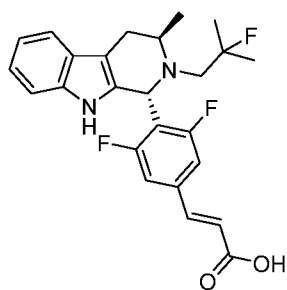
71. The method of claim 69, wherein the SERD comprises GDC-0927 (SRN-0927) having the structure:



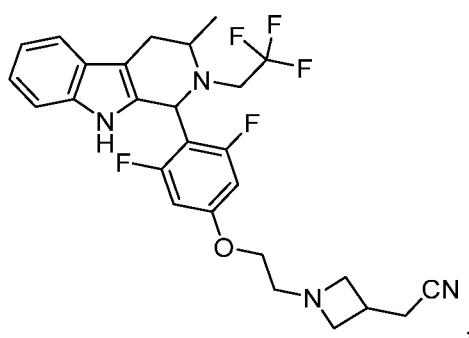


or a pharmaceutically acceptable salt thereof.

73. The method of claim 1, wherein the endocrine therapy comprises a compound having formula:

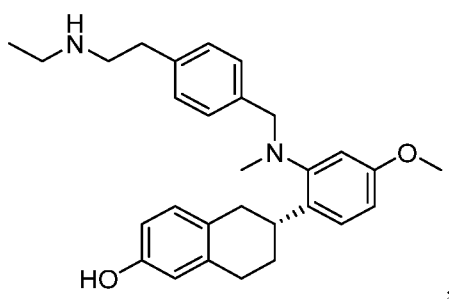


74. The method of claim 1, wherein the endocrine therapy comprises a compound having formula:



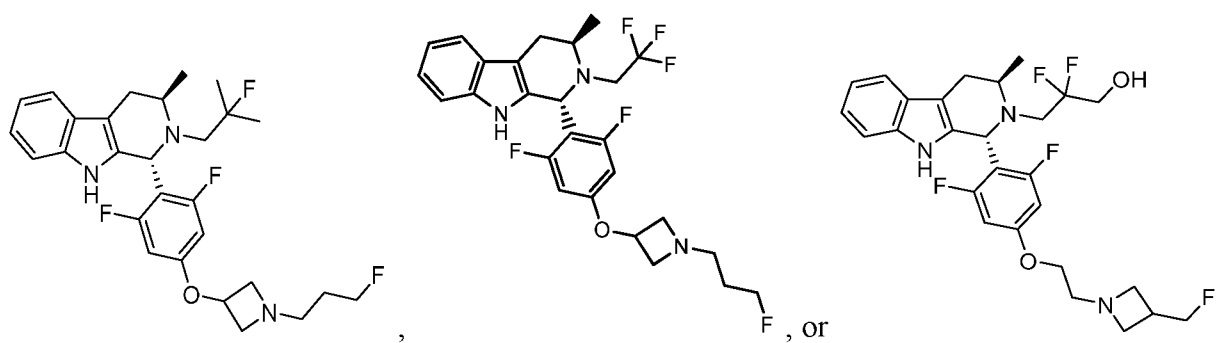
or a pharmaceutically acceptable salt thereof.

75. The method of claim 1, wherein the endocrine therapy comprises a compound having formula:



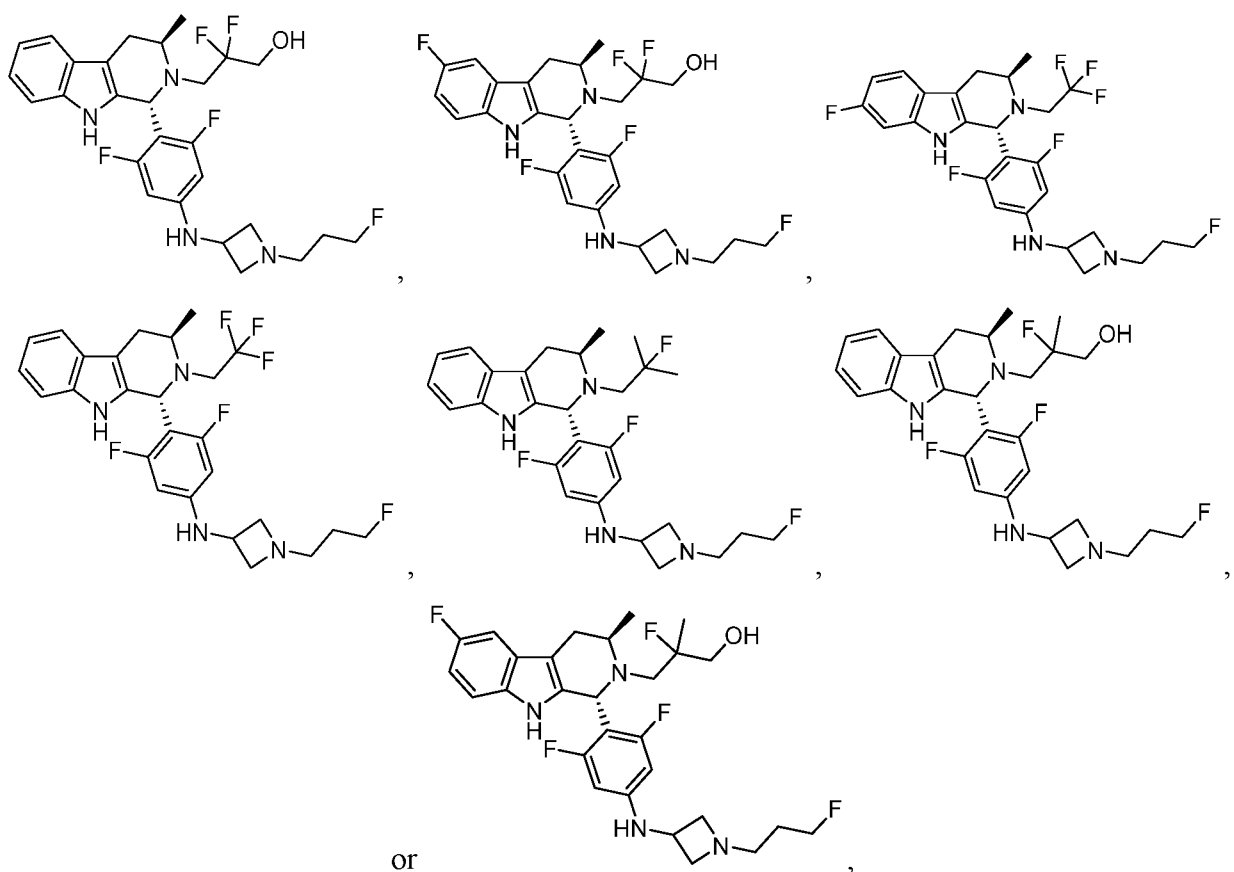
or a pharmaceutically acceptable salt thereof.

76. The method of claim 1, wherein the endocrine therapy comprises a compound having formula:



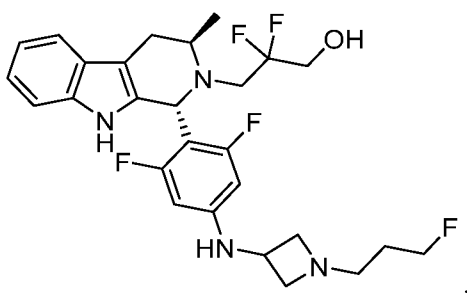
or a pharmaceutically acceptable salt thereof.

77. The method of claim 1, wherein the endocrine therapy comprises a compound having formula:



or a pharmaceutically acceptable salt thereof.

78. The method of claim 1, wherein the endocrine therapy comprises a compound having formula:



or a pharmaceutically acceptable salt thereof.

79. The method of claim 5, wherein the anti-cancer therapy other than an endocrine therapy comprises a chemotherapy.

80. The method of claim 79, wherein the chemotherapy comprises an anthracycline, a taxane, 5-fluorouracil, cyclophosphamide, a platinum agent, vinorelbine, capecitabine, gemcitabine, ixabepilone, eribulin, or a combination thereof.

81. The method of claim 79, wherein the anti-cancer therapy other than an endocrine therapy comprises a PI3K inhibitor, an mTOR inhibitor, a CDK4/6 inhibitor, or a combination thereof.

82. The method of claim 1, wherein the individual is a human.

83. A kit comprising a plurality of nucleic acids, wherein said plurality of nucleic acids are at least 5 nucleotides in length and are at least 95% identical to a 5 nucleotide continuous sequence within at least five genes set forth in Table 1 and at least five genes set forth in Table 4; at least five genes set forth in Table 2 and at least five genes set forth in Table 4; or at least five genes set forth in Table 3 and at least five genes set forth in Table 6, or 95% identical to a sequence complementary to said 5 nucleotide continuous sequence.

84. The kit of claim 83, wherein said plurality of nucleic acids are attached to a solid support.

85. The kit of claim 84, wherein said plurality of nucleic acids comprise a detectable label.

86. The kit of claim 83, wherein said plurality of nucleic acids are at least 95% identical to a 5 nucleotide continuous sequence within at least five genes set forth in Table 1, at least five genes set forth in Table 2 or at least five genes set forth in Table 3 are greater than a standard control.

87. The kit of claim 83, wherein said plurality of nucleic acids are at least 95% identical to a 5 nucleotide continuous sequence within at least five genes set forth in Table 4, at least five

genes set forth in Table 5 or at least five genes set forth in Table 6 are less than a standard control.

88. The kit of claim 83, wherein said plurality of nucleic acids are at least 95% identical to a 5 nucleotide continuous sequence within all genes set forth in Table 1 and all genes set forth in Table 4.

89. The kit of claim 83, wherein said plurality of nucleic acids are at least 95% identical to a 5 nucleotide continuous sequence within all genes set forth in Table 2 and all genes set forth in Table 5.

90. The kit of claim 83, wherein said plurality of nucleic acids are at least 95% identical to a 5 nucleotide continuous sequence within all genes set forth in Table 3 and all genes set forth in Table 6.

91. The kit of claim 83, wherein said plurality of nucleic acids are at least 95% identical to a 5 nucleotide continuous sequence within all genes set forth in Table 1 and all genes set forth in Table 4 and no other genes.

92. The kit of claim 83, wherein said plurality of nucleic acids are at least 95% identical to a 5 nucleotide continuous sequence within all genes set forth in Table 2 and all genes set forth in Table 5 and no other genes.

93. The kit of claim 83, wherein said plurality of nucleic acids are at least 95% identical to a 5 nucleotide continuous sequence within all genes set forth in Table 3 and all genes set forth in Table 6 and no other genes in said subject.

94. The kit of claim 83, wherein the plurality of nucleic acids are identical to a 5 nucleotide continuous sequence within said genes.

95. The kit of claim 83, wherein the plurality of nucleic acids are identical to a continuous nucleotide sequence comprising at least 10, 20, 25, 50, 75, 100, 150, or 200 nucleotides.

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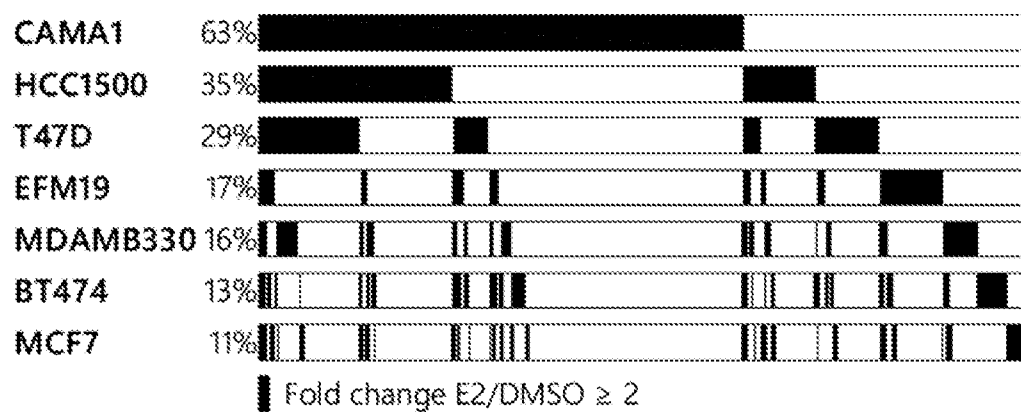


FIG. 1A

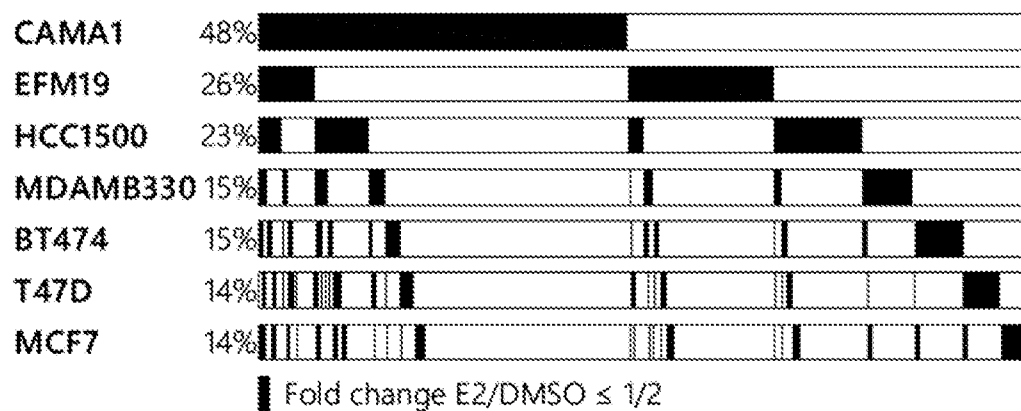


FIG. 1B

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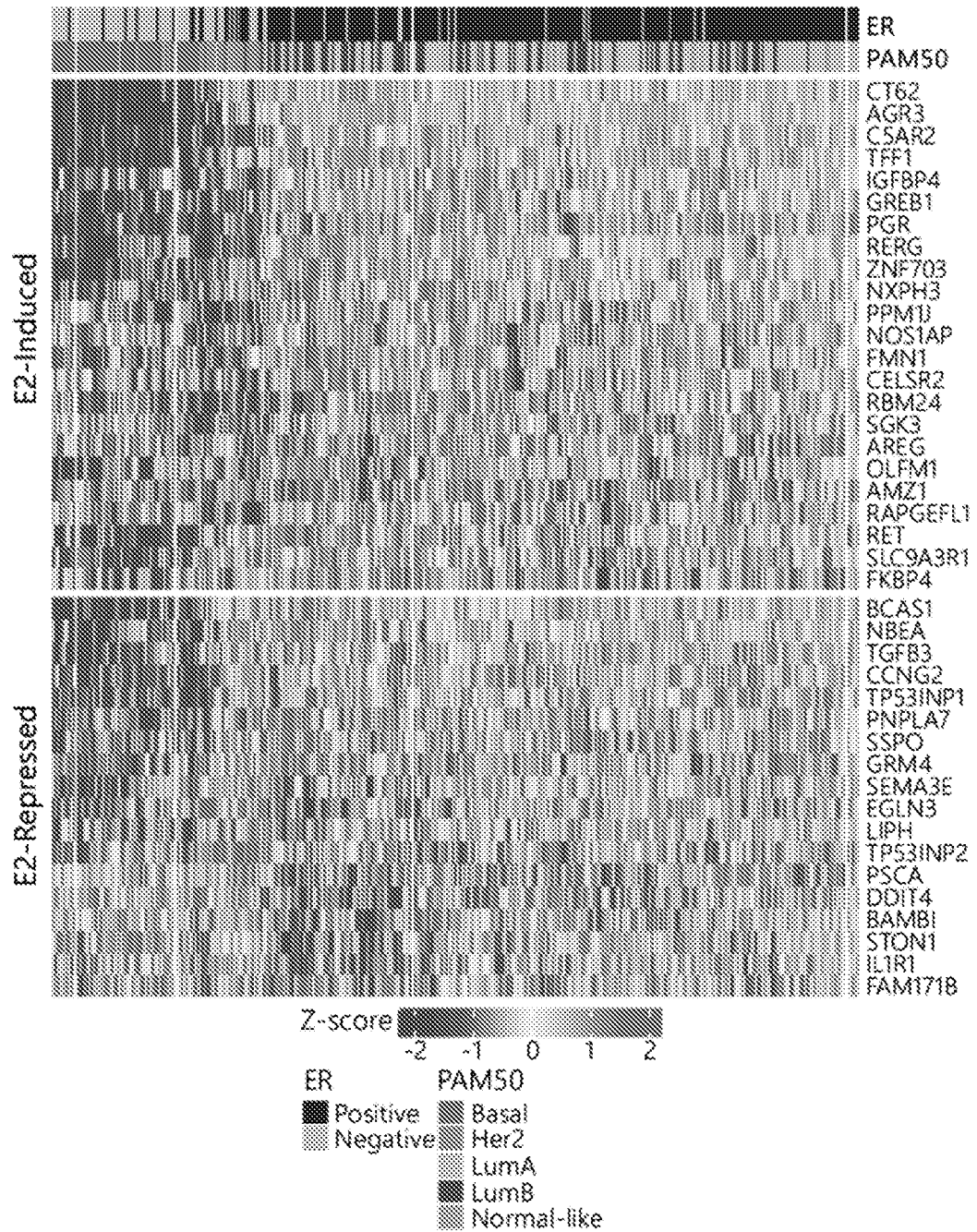


FIG. 1C

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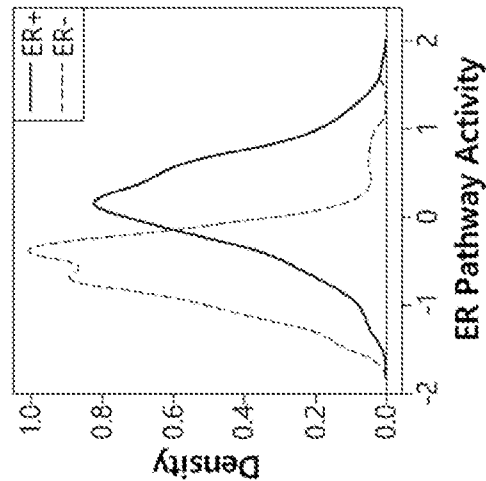


FIG. 1F

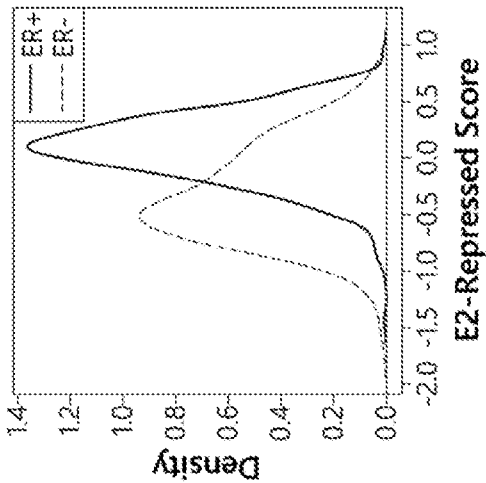


FIG. 1E

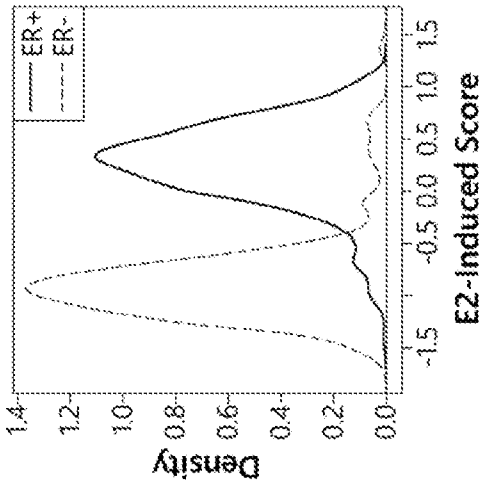


FIG. 1D

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HCI-013 PDX

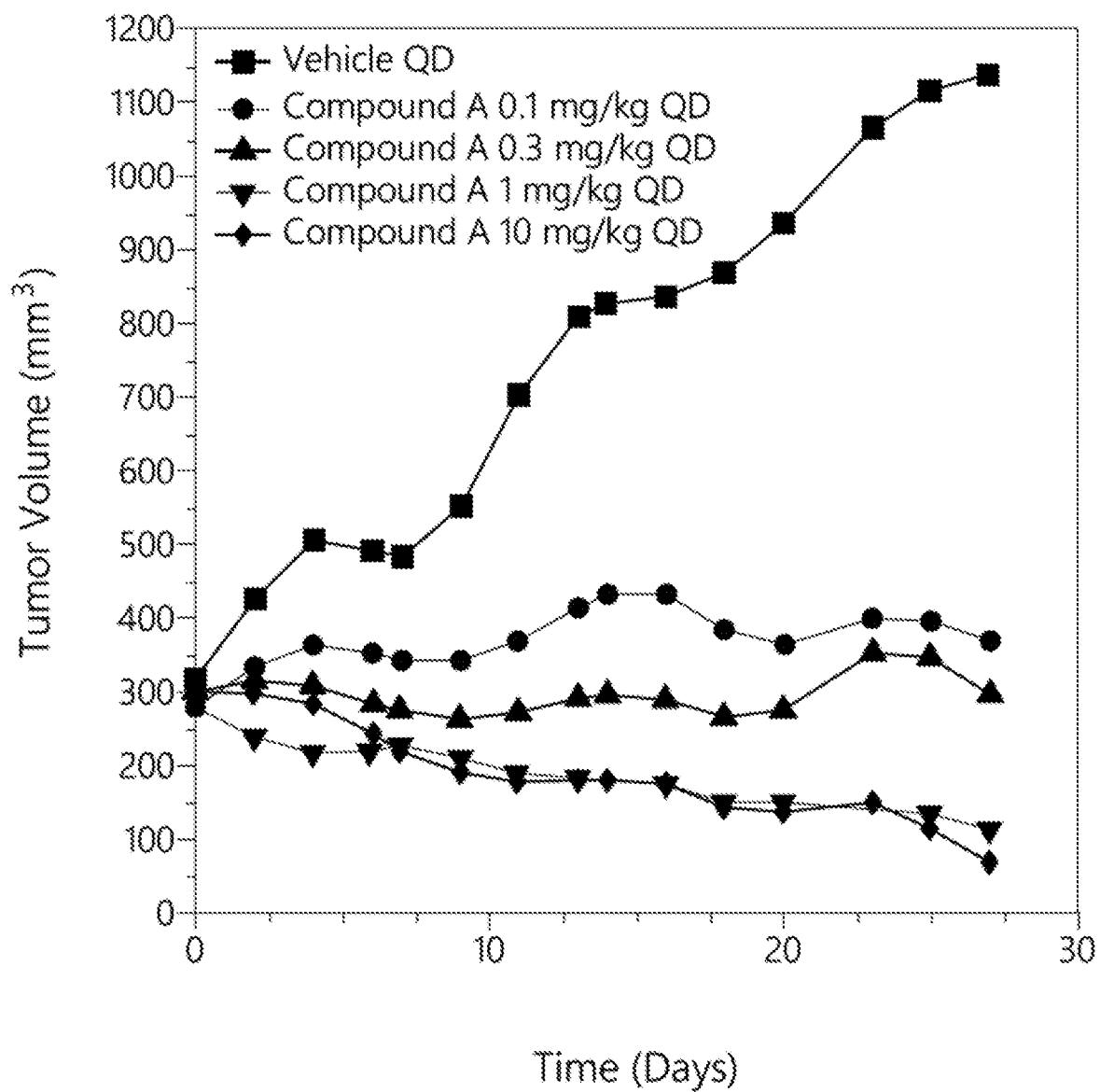


FIG. 2A

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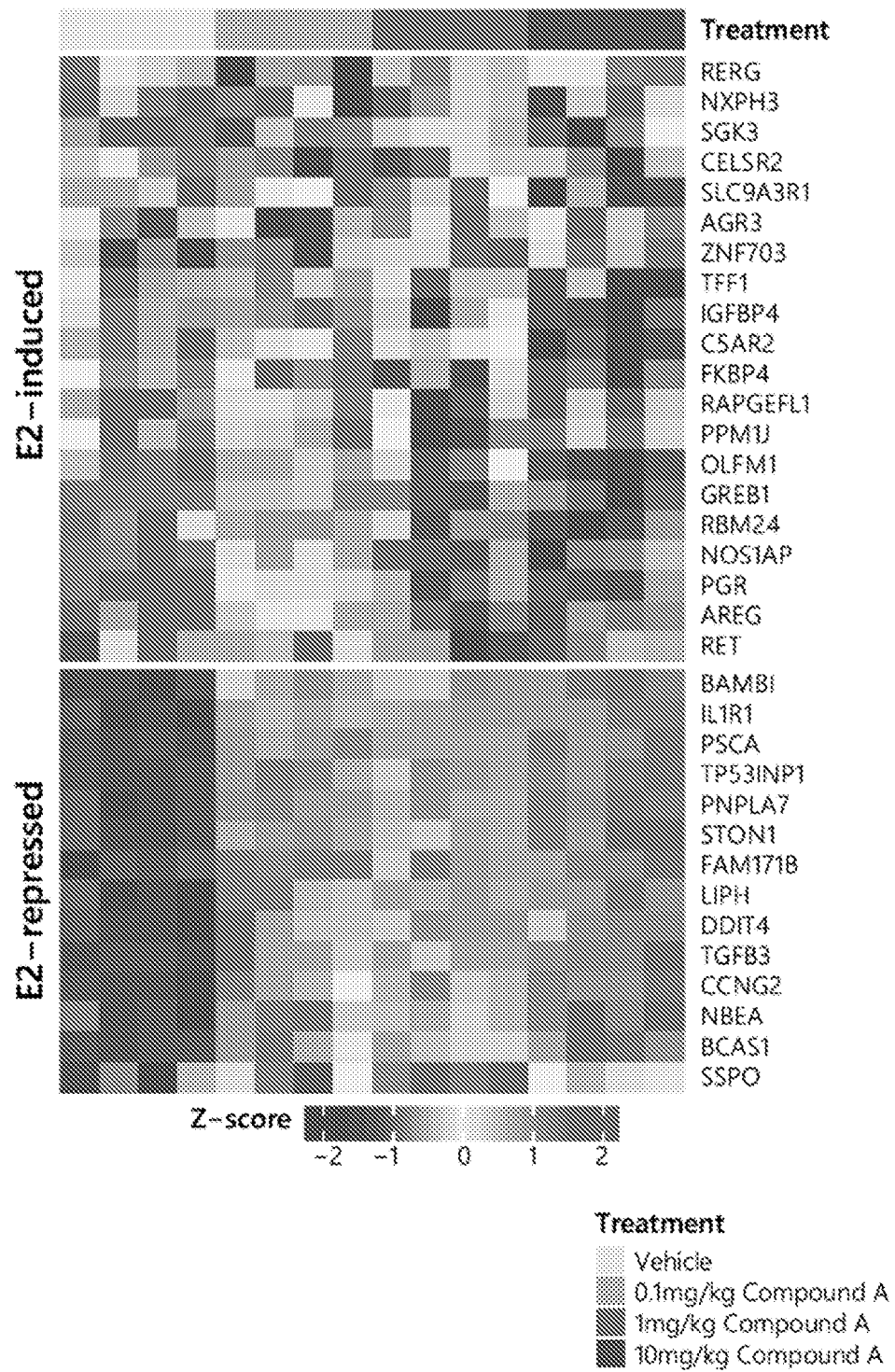


FIG. 2B

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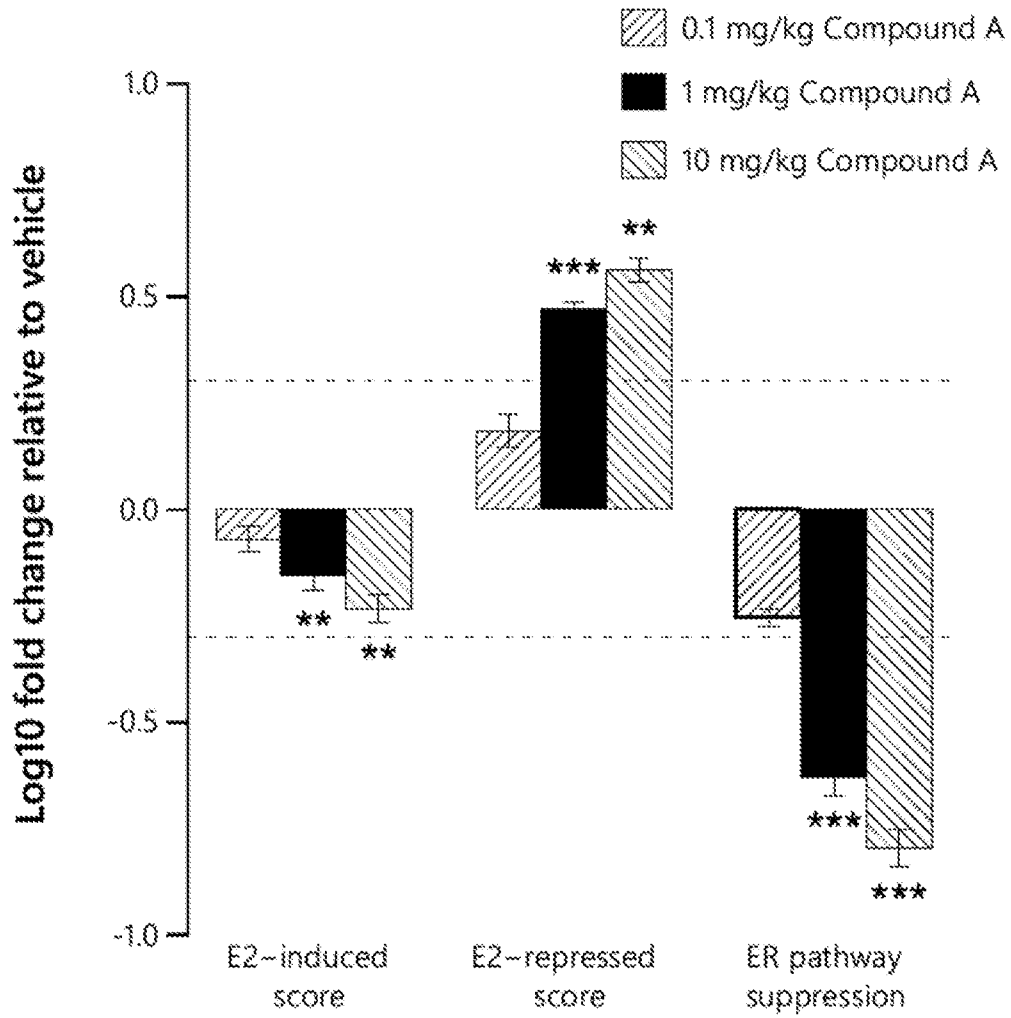


FIG. 2C

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HCI-013 PDX

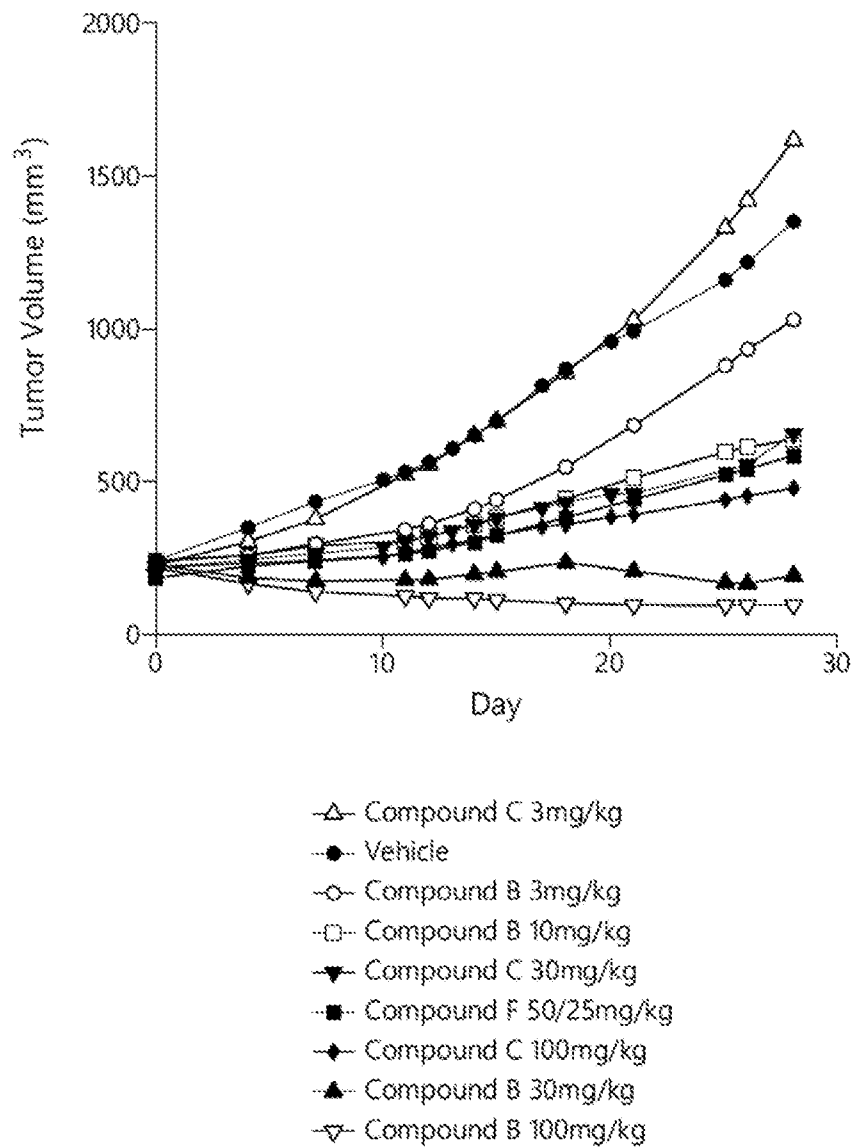


FIG. 2D

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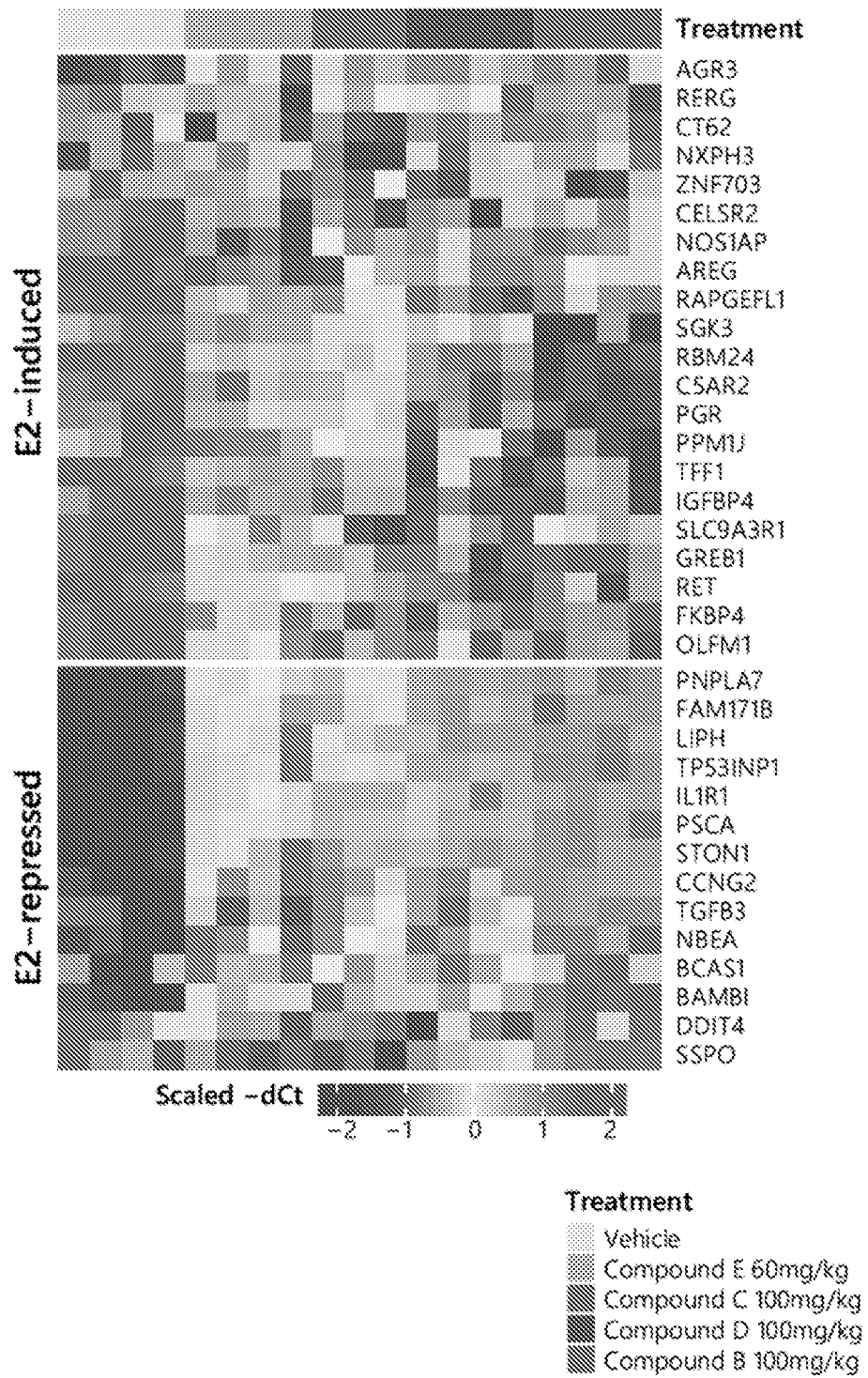


FIG. 2E

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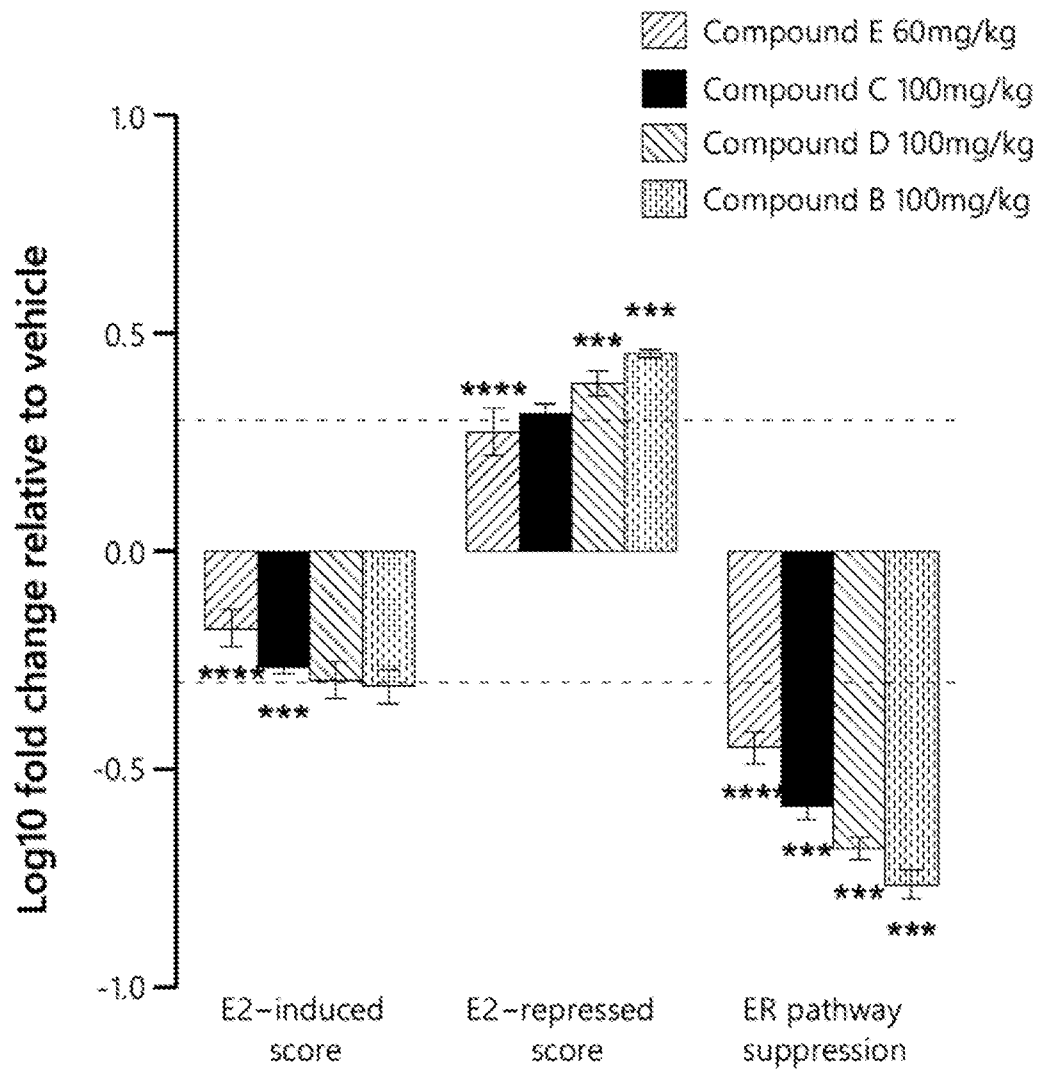


FIG. 2F

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HCI-011 PDX

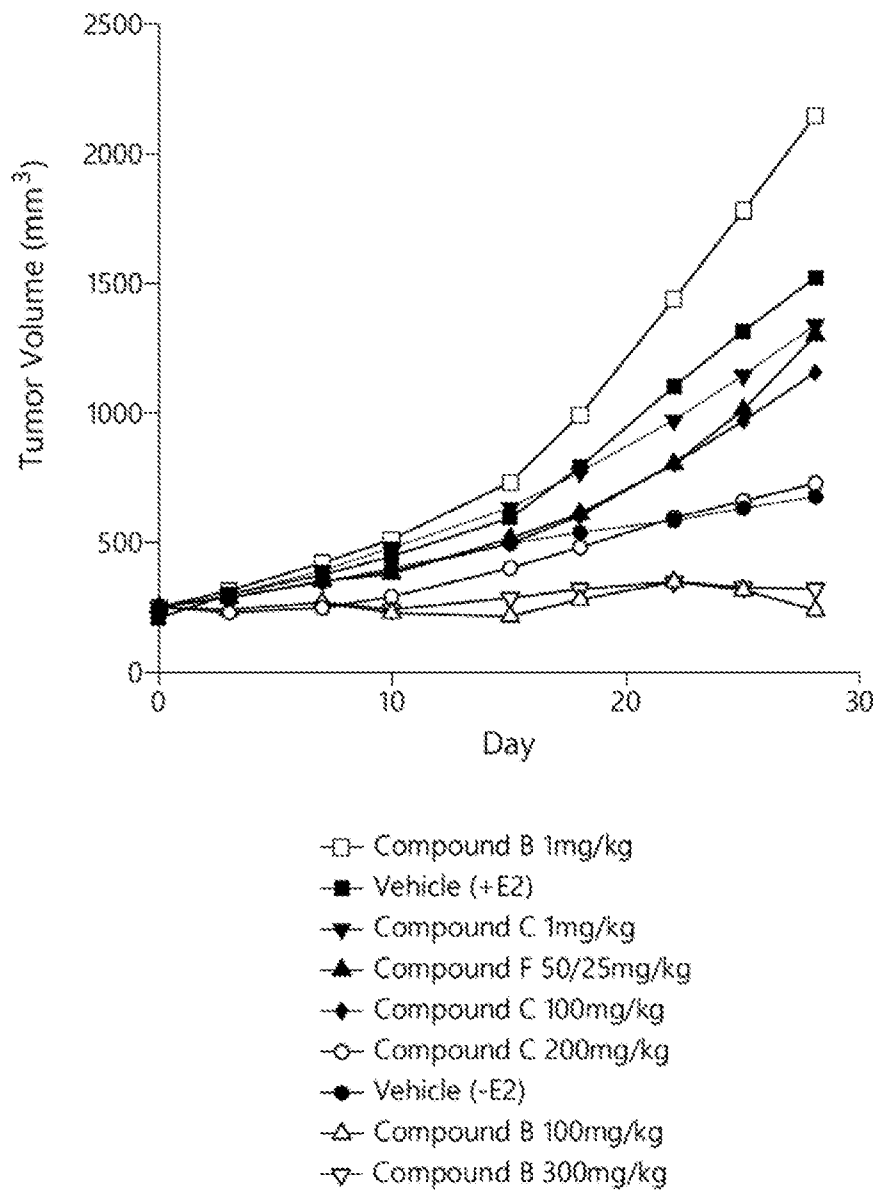


FIG. 2G

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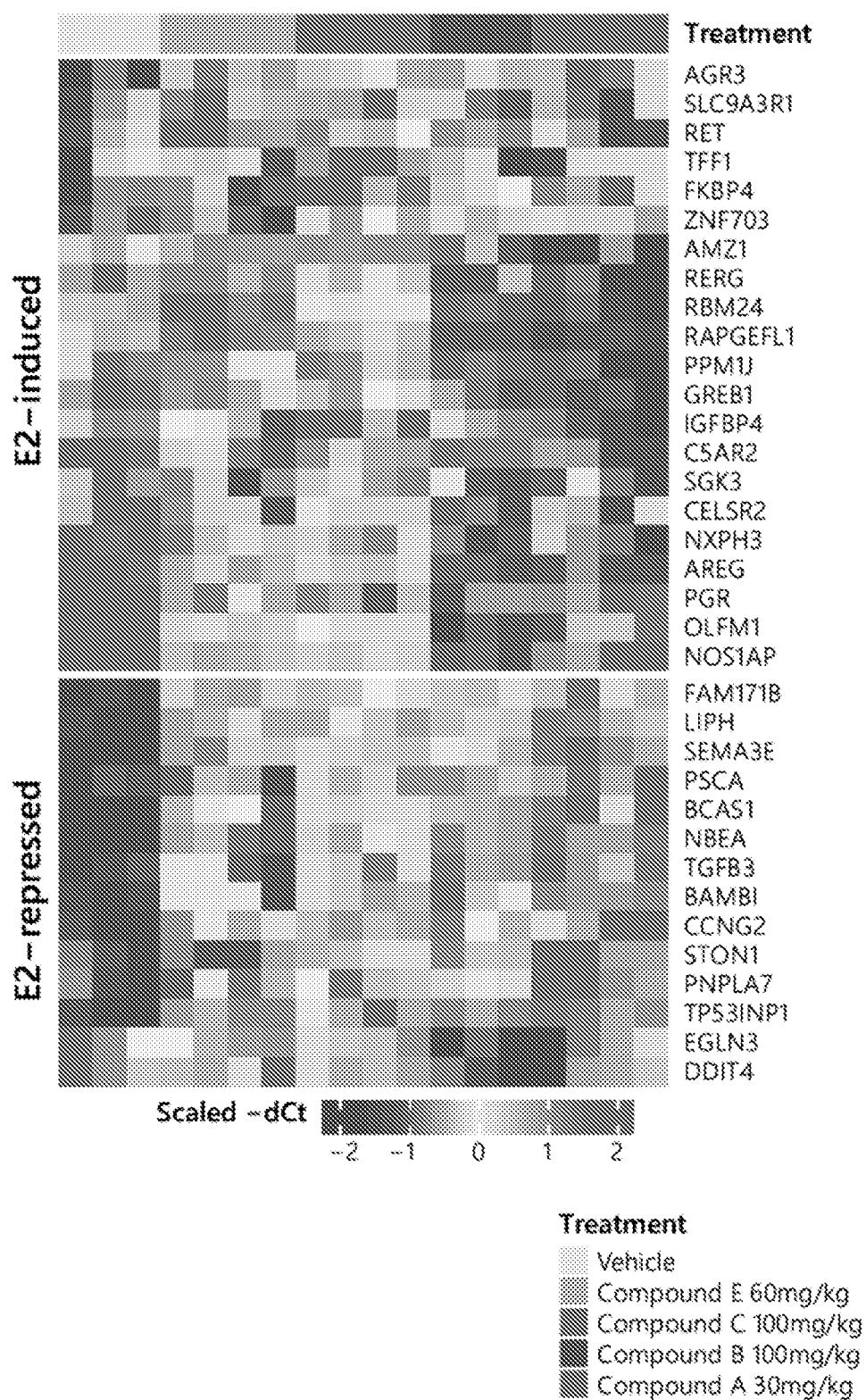


FIG. 2H

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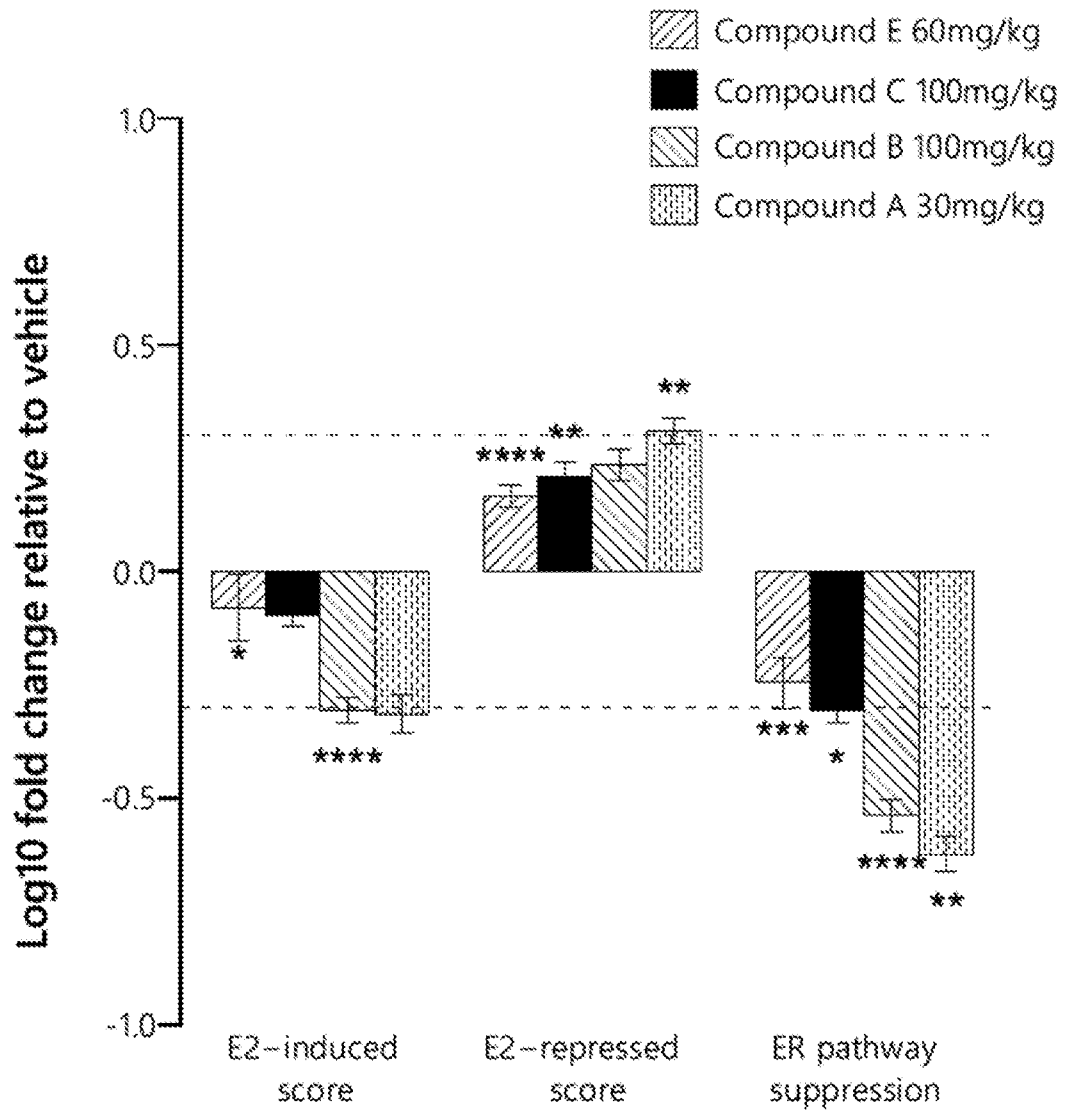


FIG. 2I

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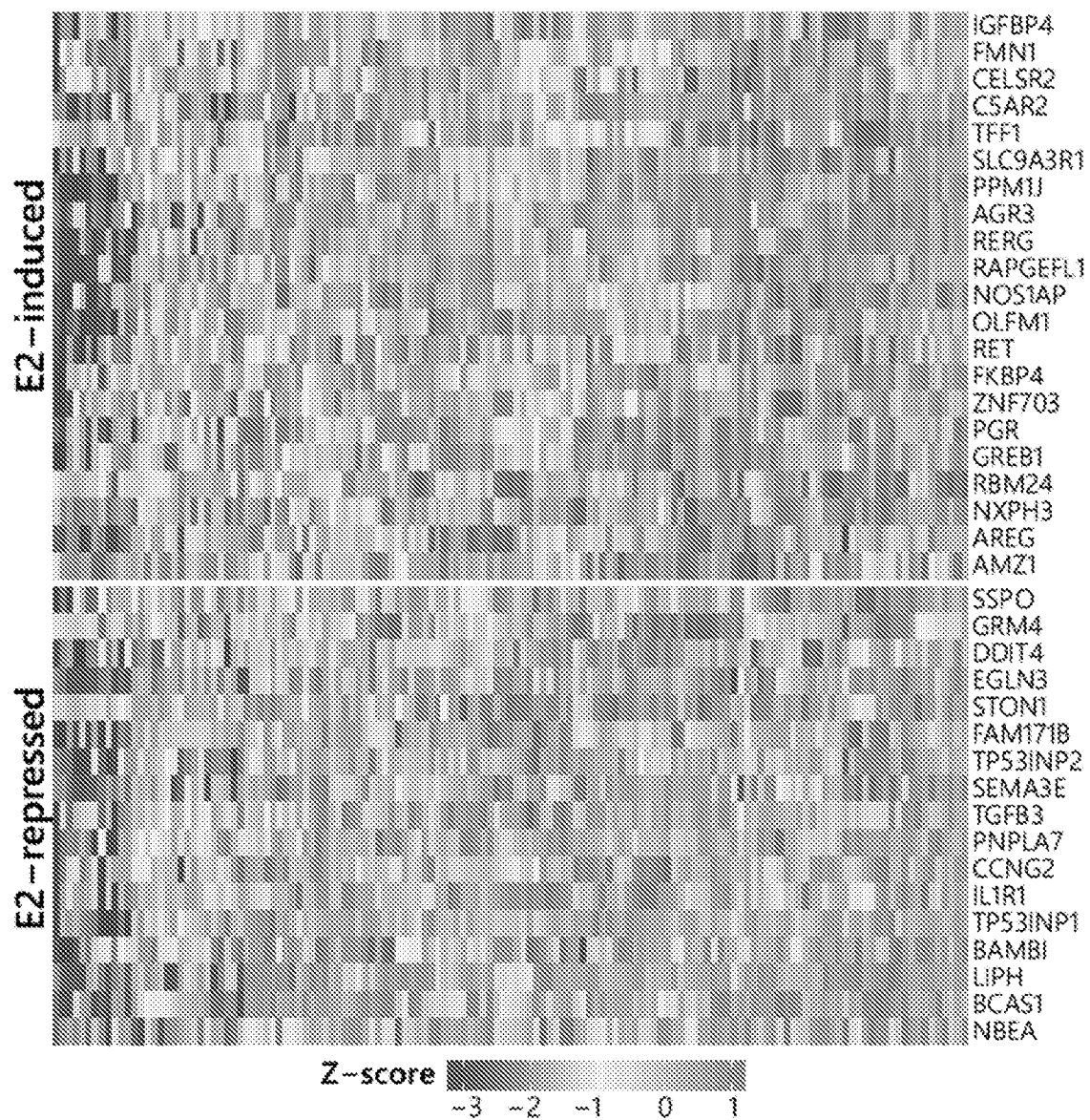


FIG. 3A

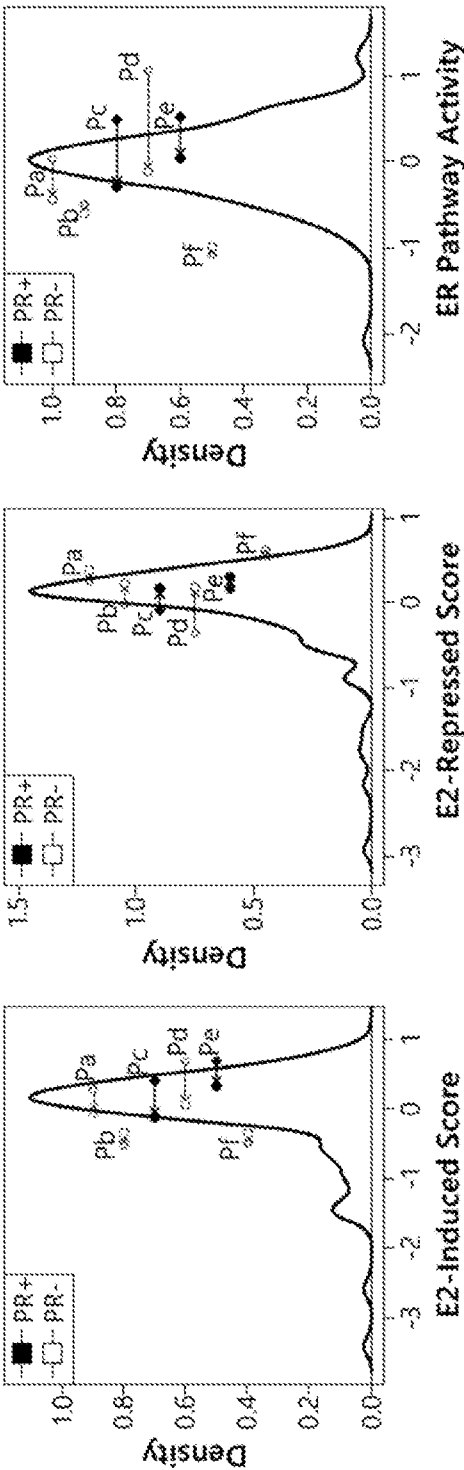


FIG. 3B

FIG. 3C

FIG. 3D

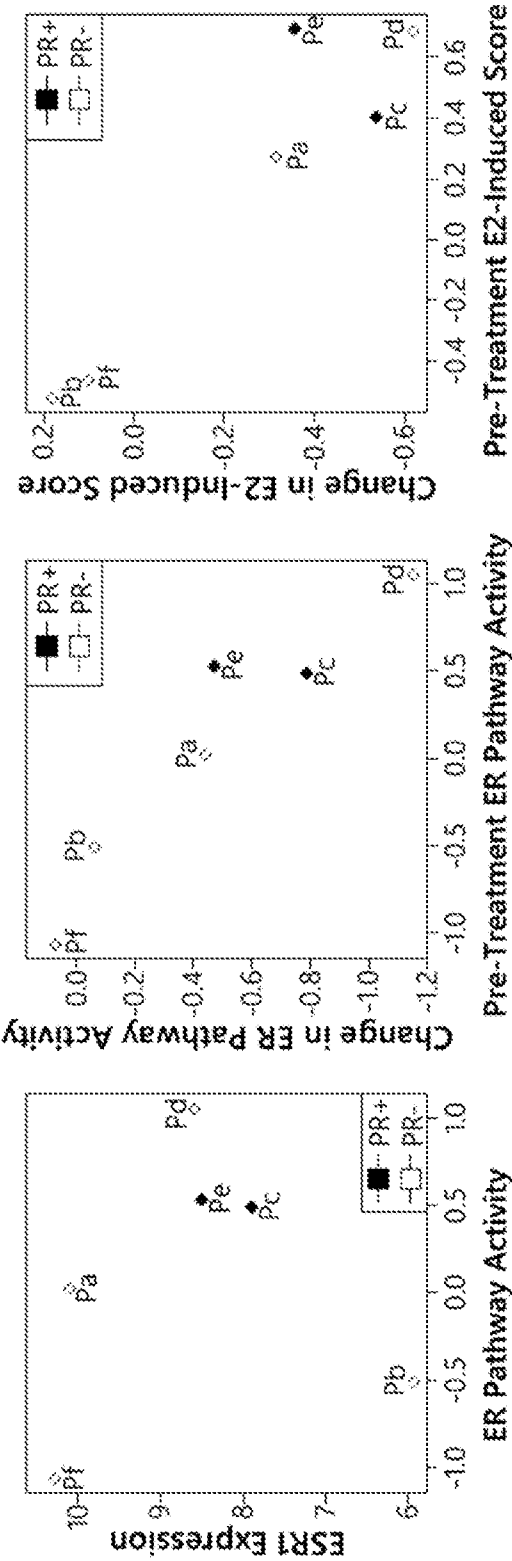


FIG. 3G

FIG. 3F

FIG. 3E

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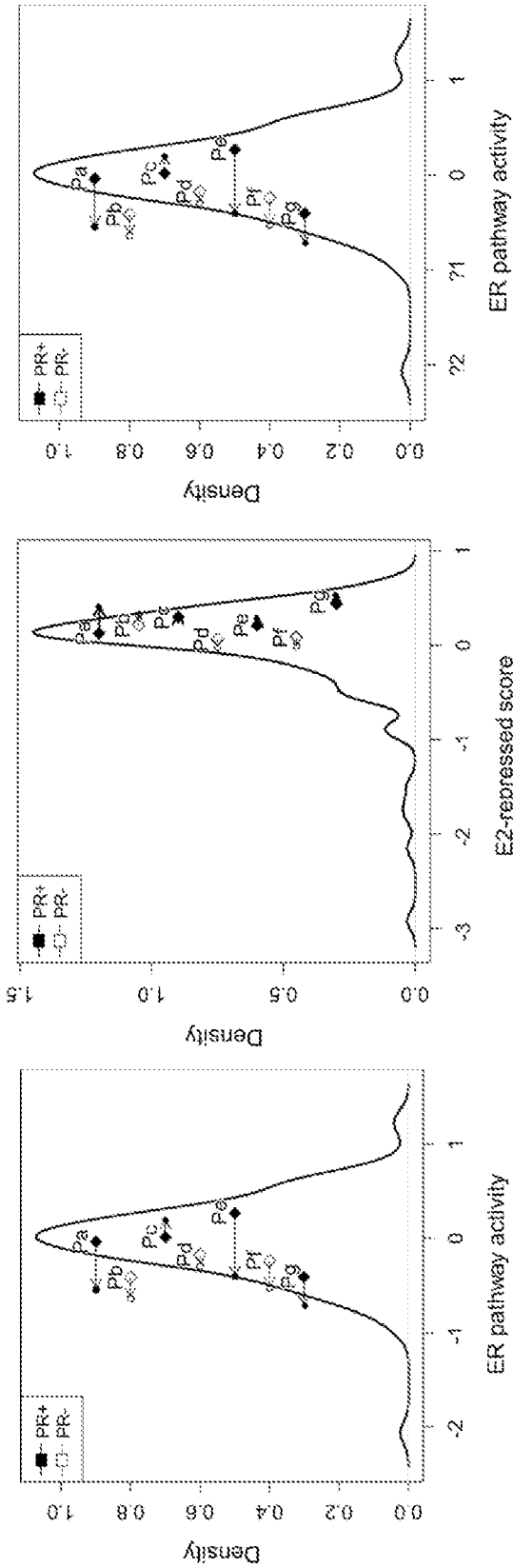


FIG. 3J

FIG. 3I

FIG. 3H

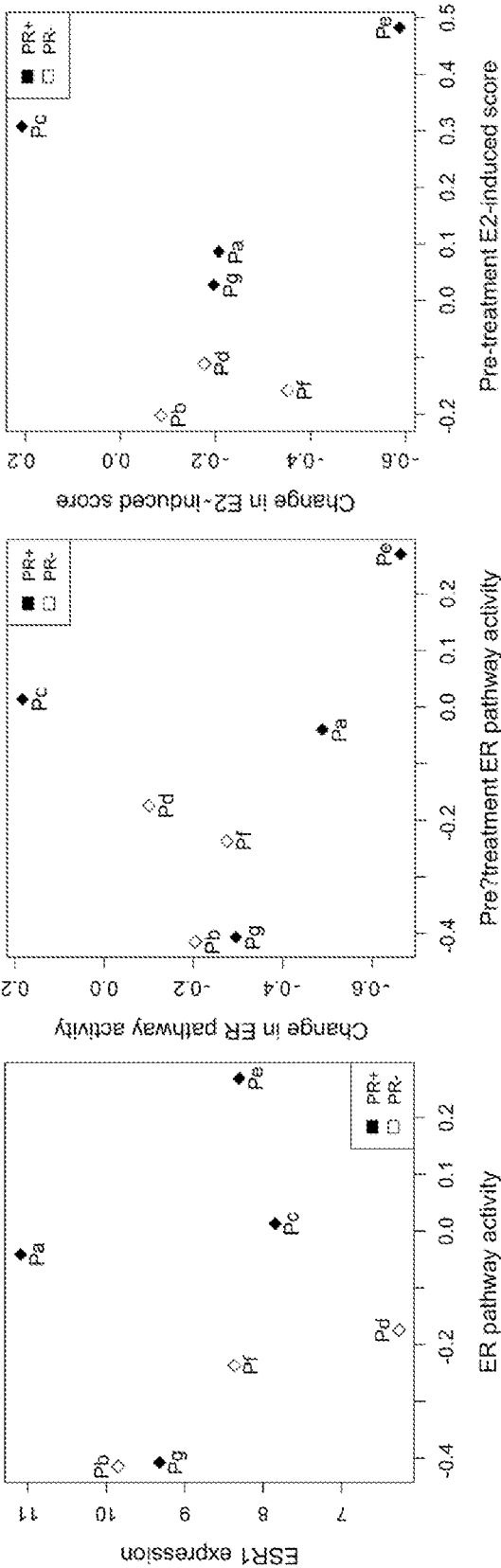


FIG. 3M

FIG. 3L

FIG. 3K

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41-gene signature

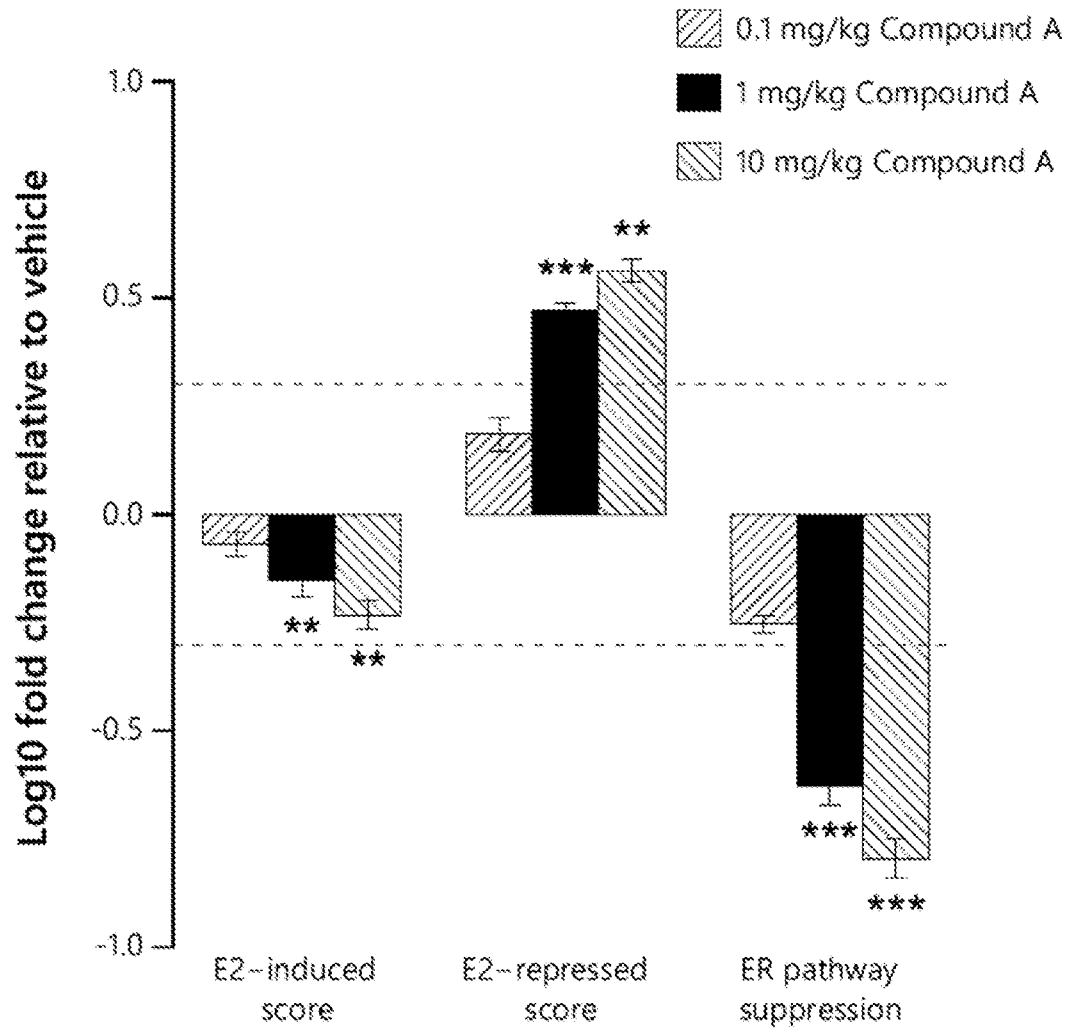


FIG. 4A

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19-gene signature

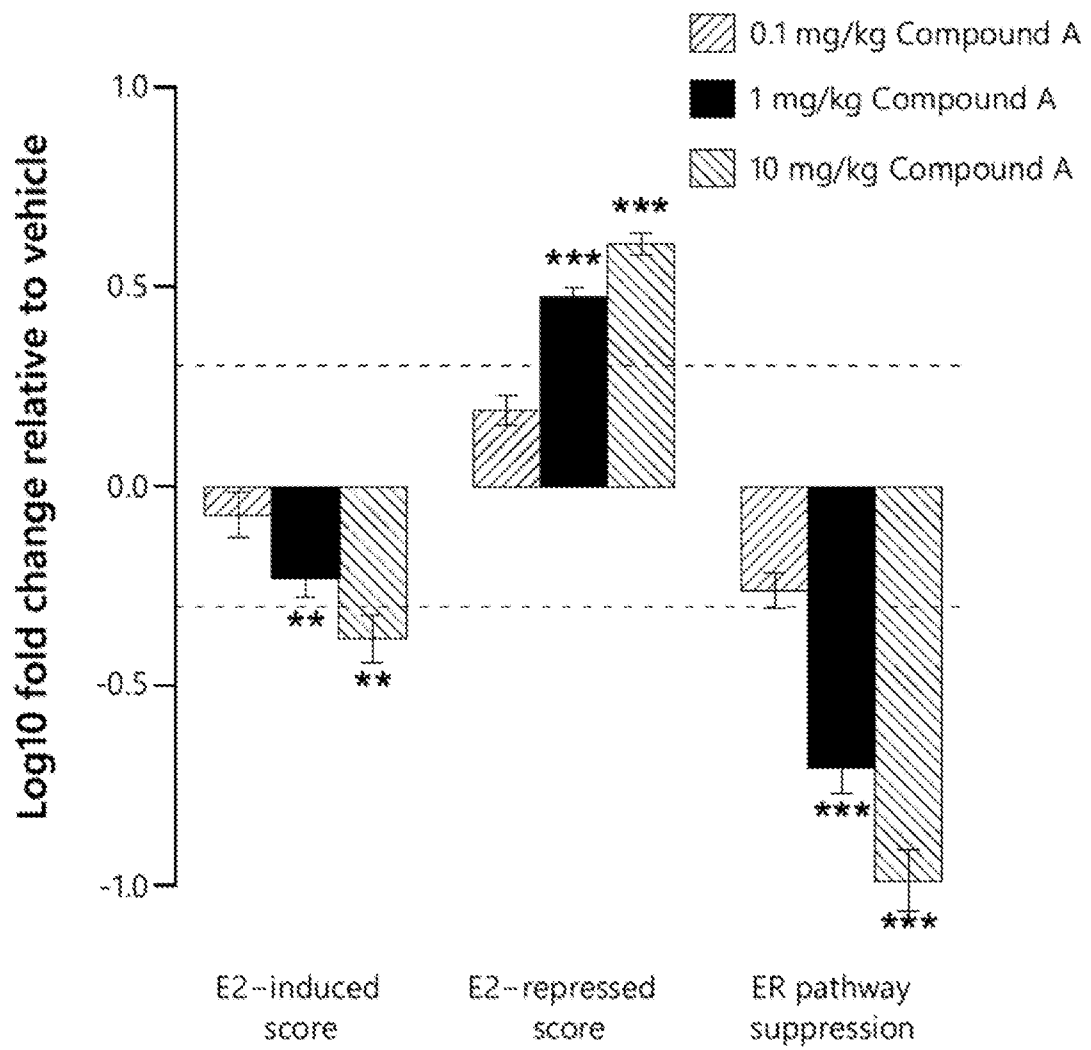


FIG. 4B

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14-gene signature

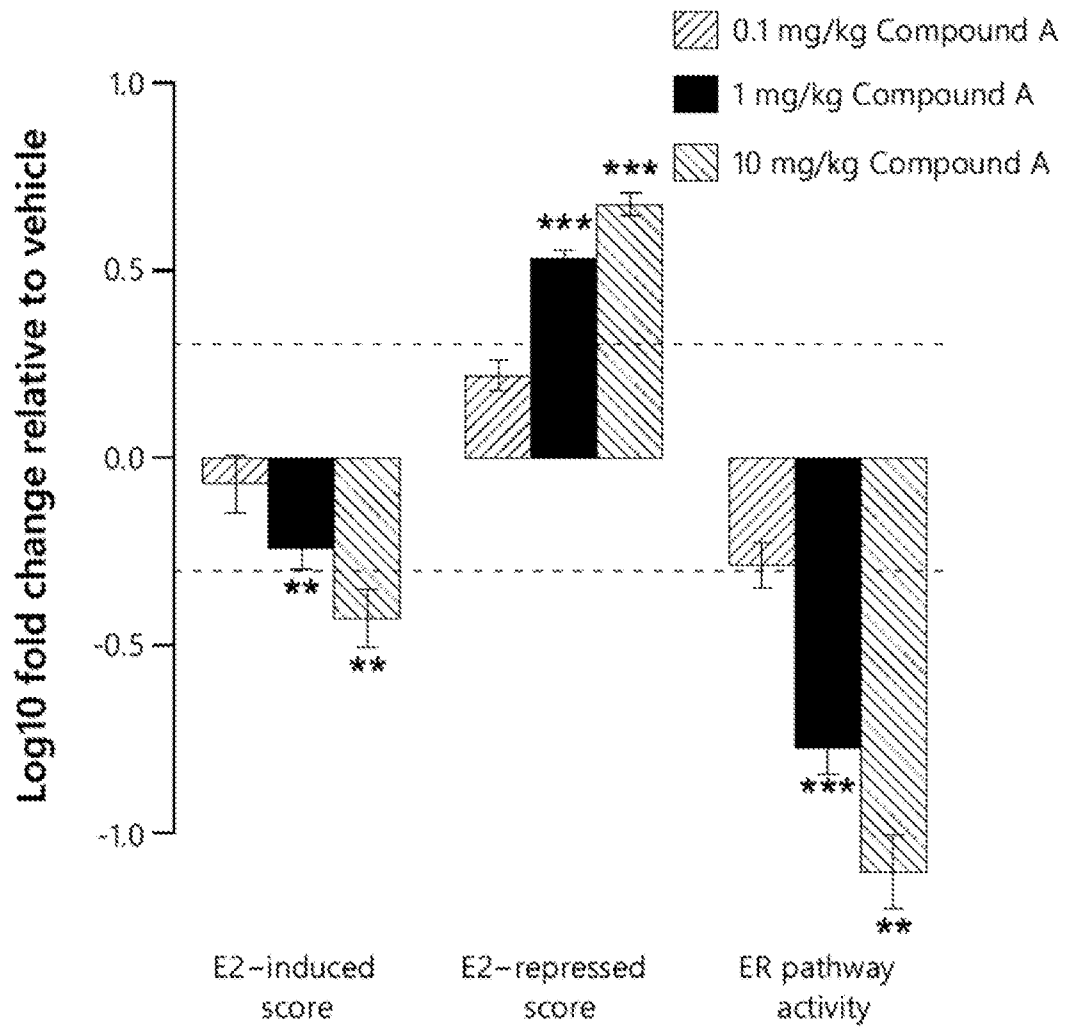


FIG. 4C

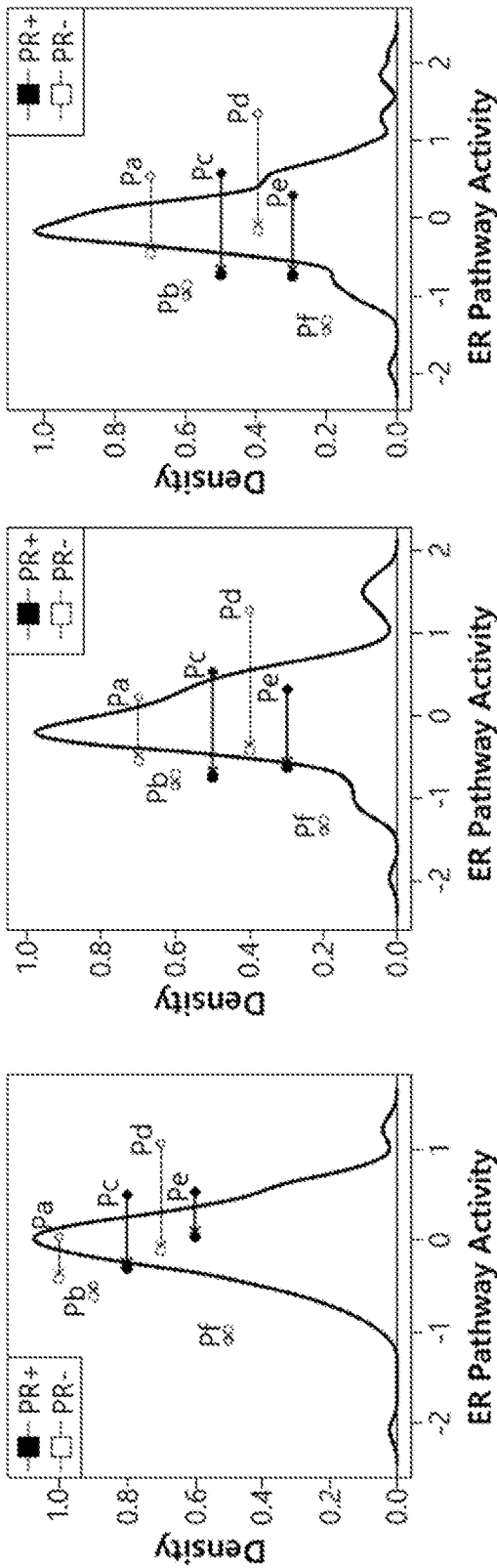


FIG. 4F

FIG. 4E

FIG. 4D

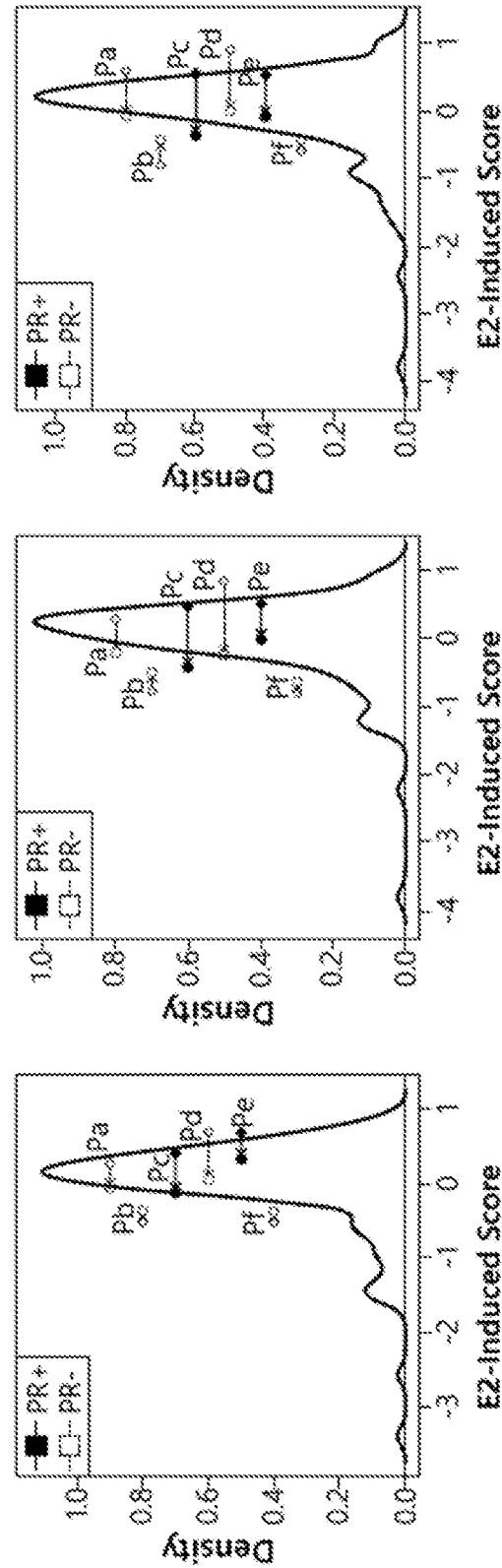


FIG. 4G

FIG. 4H

FIG. 4I

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E2-Induced	E2-repressed
AGR3	BAMBI
AMZ1	BCAS1
AREG	CCNG2
C5AR2	DDIT4
CELSR2	EGLN3
CT62	FAM171B
FKBP4	GRM4
FMN1	IL1R1
GREB1	LIPH
IGFBP4	NBEA
NOS1AP	PNPLA7
NXPH3	PSCA
OLFM1	SEMA3E
PGR	SSPO
PPM1J	STON1
RAPGEFL1	TGFB3
RBM24	TP53INP1
RERG	TP53INP2
RET	
SGK3	
SLC9A3R1	
TFF1	
ZNF703	

FIG. 4J

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E2-Induced	E2-Repressed
AMZ1	BCAS1
AREG	CCNG2
C5AR2	IL1R1
CELSR2	NBEA
FKBP4	PNPLA7
FMN1	SEMA3E
GREB1	STON1
OLFM1	TP53INP1
RBM24	
SLC9A3R1	
TFF1	

FIG. 4K

E2-Induced	E2-Repressed
AMZ1	BCAS1
C5AR2	CCNG2
CELSR2	IL1R1
FKBP4	PNPLA7
GREB1	SEMA3E
OLFM1	STON1
SLC9A3R1	
TFF1	

FIG. 4L

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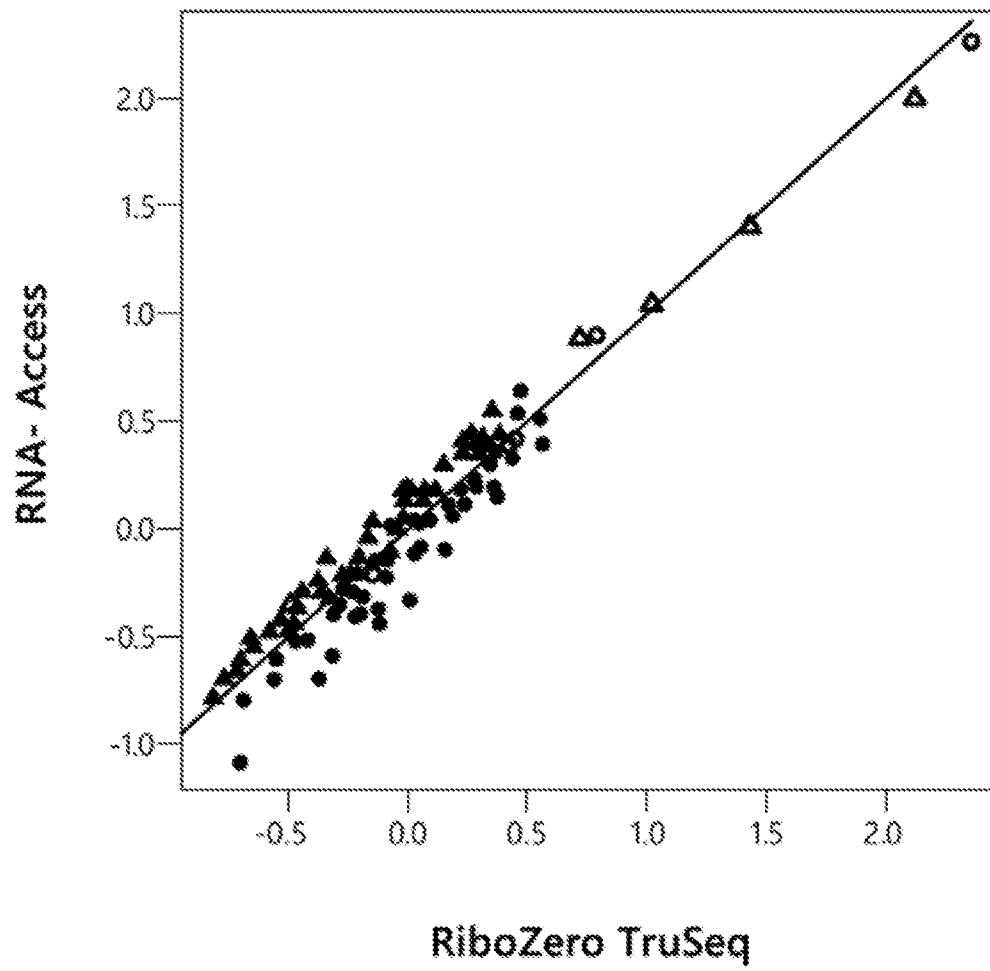


FIG. 5

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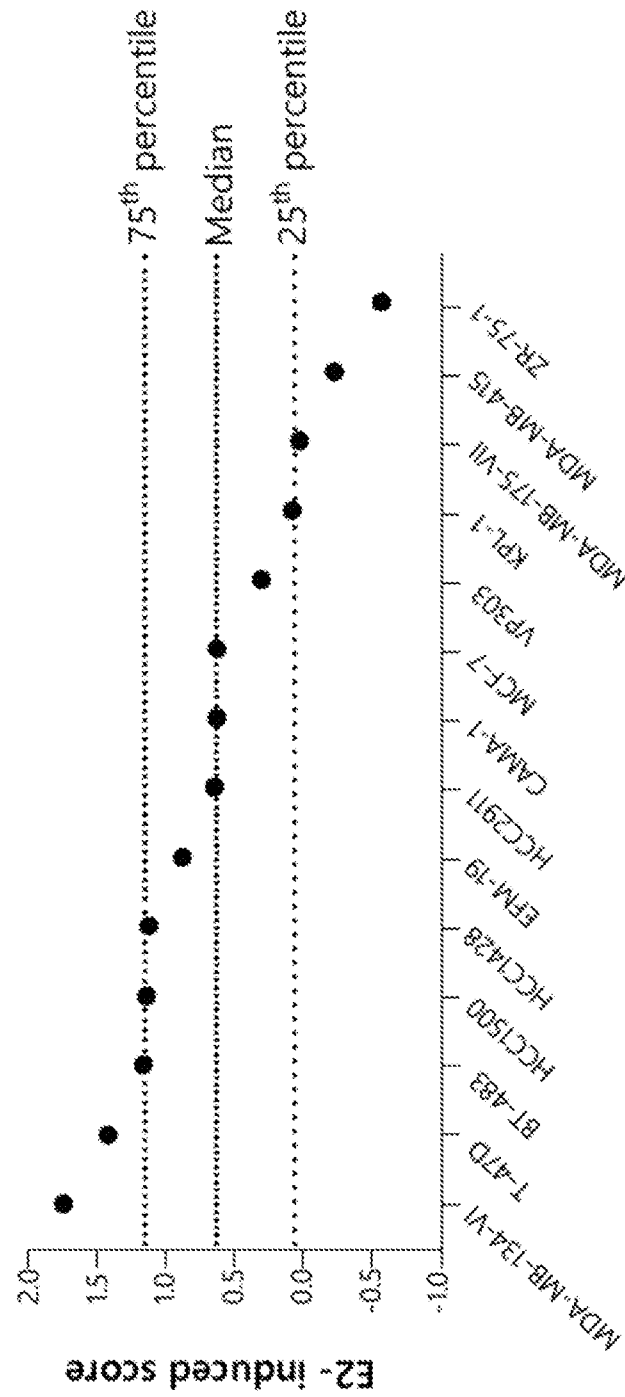


FIG 6

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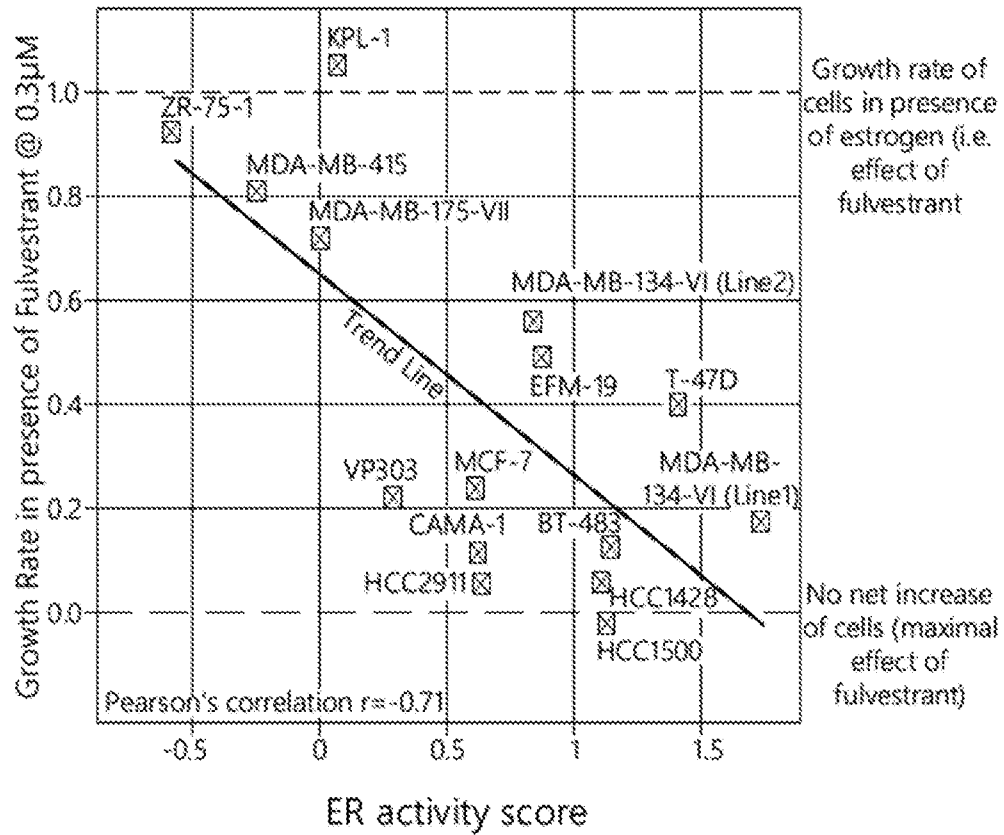


FIG. 7