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(54) Title: ANTIESTROGENS FOR CANCER THERAPY

(57) Abstract: 1, 1-Diarylmethylcycloalkanylidene are antiestrogens having utility in the treatment of cancer, including recurrent breast cancer and estrogen receptor-positive, endocrine therapy-sensitive tumors or endocrine therapy resistant tumors.



WO 2018/175965 A1

ANTIESTROGENS FOR CANCER THERAPY

CROSS-REFERENCE TO RELATED APPLICATION

[0001] This application claims the benefit of and priority to U.S. Provisional Application No. 62/475,912, filed on March 24, 2017, the content of which is incorporated by reference herein in its entirety, and priority to which is hereby claimed.

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT

[0002] This invention was made with government support under DK015556 awarded by the National Institutes of Health. The government has certain rights in the invention.

BACKGROUND

[0003] Recent clinical observations that many patients with estrogen receptor alpha (ER α) positive breast cancers effectively treated with tamoxifen or aromatase inhibitors may later experience a recurrence of their breast cancer that is now resistant to these treatments, has clearly highlighted the need for developing new antiestrogens that retain their effectiveness on this form of endocrine therapy-resistant cancer (1, 2). About one third of these recurrent breast cancers harbor activating mutations that convey constitutive activity and relative resistance to antiestrogens (3-9). A clearer understanding of the molecular mechanisms by which antiestrogens are able to suppress the agonist activity of ER α is needed so that better compounds can be developed, and it is likely that new agents that are more potent and efficacious inhibitors of wild type ER α (WT-ER α) will also show greater effectiveness in inhibiting the growth of breast cancers driven by ER α with activating mutations and displaying resistance to current standard of care treatments.

[0004] Conceptually, antiestrogens can be thought to consist of a ligand core element that is accommodated within the ligand-binding pocket (LBP) and provides robust binding affinity, onto which is appended a side chain that extends outward from the ligand binding domain (LBD) and whose function is to disrupt the agonist activity of the receptor by mispositioning helix-12

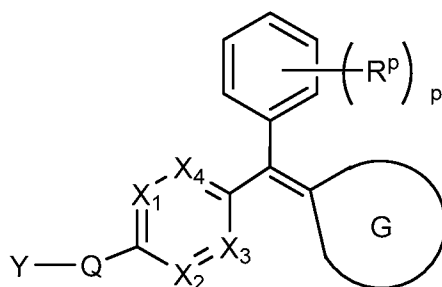
(h12) of the LBD in various ways (10). Historically, remarkably few side chains have been studied thoroughly.

[0005] Antiestrogens of the selective ER modulator (SERM) class, like tamoxifen, raloxifene, lasofoxifene, and bazedoxifene, have structurally distinct aromatic-rich, non-steroidal cores but very similar positively charged basic side chains (FIG. 1). By forming strong charge-charge interactions with D351, these basic side chains displace h12, causing it to be repositioned into the hydrophobic groove into which coactivators bind in ER-agonist complexes. An alternative antiestrogen design, first exemplified in 1994 on the tamoxifen core structure in compounds from Glaxo-SmithKline (GSK), GW-5638 and GW-7604, has an acrylic acid as a functional side chain (FIG. 1) (11, 12). This side chain, which also moves h12 to block the coactivator binding groove, has been replicated without any change in two orally active antiestrogens currently in clinical development, AZD-9496 and GDC-0810 (FIG. 1) (13, 14).

[0006] Additionally, some antiestrogens regulate ER α levels. Those that downregulate ER α , termed SERDs (for selective ER downregulators), were initially exemplified by fulvestrant, a steroid onto which is appended a long, largely hydrophobic side chain at the 7 α position. SERD activity is also found with the GSK, AZD, and GDC compounds mentioned above. Because of its very poor oral bioavailability, fulvestrant needs to be administered by painful intramuscular injection, and even this does not provide sufficiently high blood levels of drug to fully occupy ER in tumors. These pharmaceutical problems are avoided by the AZD and GDC compounds because they are orally active and can be dosed at higher levels, providing high internal exposure to the drug. Despite this promise, concerns with toxicities associated with both of these new antiestrogens are proving to be impediments to their clinical implementation, which suggests the need for developing other new antiestrogens.

SUMMARY

[0007] The present invention provides compounds or a pharmaceutically acceptable salt thereof and the methods and compositions disclosed herein for treating breast cancer. In one aspect, the invention provides compounds or compositions of formula (I), or a pharmaceutically acceptable salt thereof,



(I)

wherein

G is an optionally substituted polycycloalkylidene;

X_1 , X_2 , X_3 , and X_4 are each independently N, CH, or CR^m , wherein at most two of X_1 , X_2 , X_3 , and X_4 are N, and wherein at most one of X_1 and X_4 is N;

Y is alkyl, $-OR^A$, $-COOR^B$, $-N(R^C)(R^D)$, $-CON(R^C)(R^D)$, $-N(R^C)-OH$, $-NH-N(R^C)(R^D)$, or $-CR^Y=CR^X-CN$;

Q is a bond, $-C(Q^1)-CR^Y=CR^X-$, $-C(Q^2)-NH-N=CR^X-$, $-C(O)-NH-$, $-C(O)-Q^3-$, or $-SO_2-CR^Y=CR^Z-$, wherein the $C(Q^1)$, $C(Q^2)$, $C(O)$, or SO_2 group is attached to Y;

R^p and R^m at each occurrence are independently alkyl, alkoxy, halogen, $-OH$, $-CN$, haloalkyl, or hydroxyalkyl;

p is 0, 1, 2, 3, 4, or 5;

Q^1 and Q^2 are O, NH, or S;

Q^3 is an optionally substituted cycloalkylene;

R^A , R^B , R^C , and R^D at each occurrence are independently hydrogen, alkyl, cycloalkyl, aryl, heterocycle, heteroaryl, or alkyl substituted by one or more substituents selected from the group consisting of $-OH$, $-NH_2$, $-NH(C_{1-4}alkyl)$, $-N(C_{1-4}alkyl)_2$, halogen, phenyl, and $-NHCO-R^Z$, wherein the cycloalkyl, aryl, heterocycle, and heteroaryl are each optionally substituted;

R^X and R^Y at each occurrence are independently hydrogen, alkyl, halogen, haloalkyl, or $-CN$; and

R^Z is $-OC_{1-4}alkyl$, cycloalkyl or $-C_{1-4}alkylene-cycloalkyl$.

[0008] Another aspect of the present invention provides pharmaceutical compositions comprising a therapeutically effective amounts of a compound of formula (I), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

[0009] Another aspect of the present invention provides a compound or composition of formula (I), or a pharmaceutically acceptable salt thereof, for use in treating or preventing breast cancer. Also provided is a compound or composition of formula (I), or a pharmaceutically acceptable salt thereof, for use in inhibiting or slowing the growth of estrogen receptor-positive, endocrine therapy-sensitive tumors or endocrine therapy resistant tumors driven by active estrogen receptors. Also provided is use of a compound or composition of formula (I), or a pharmaceutically acceptable salt thereof, for manufacturing a medicament for treating or preventing breast cancer. Also provided is use of a compound or composition of formula (I), or a pharmaceutically acceptable salt thereof, for manufacturing a medicament for inhibiting or slowing the growth of estrogen receptor-positive, endocrine therapy-sensitive tumors or endocrine therapy resistant tumors driven by active estrogen receptors.

[0010] Another aspect of the invention provides a method of treating breast cancer comprising administering to a subject in need thereof, a therapeutically effective amount of a compound or composition of formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition or medicament thereof.

[0011] Another aspect of the invention provides a method for inhibiting or slowing the growth of estrogen receptor-positive, endocrine therapy-sensitive tumors or endocrine therapy resistant tumors driven by active estrogen receptors comprising administering to a subject, in need thereof, a therapeutically effective amount of a compound or composition of formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition or medicament thereof.

[0012] Other aspects will become apparent by consideration of the detailed description and accompanying drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

[0013] The features, objects and advantages other than those set forth above will become more readily apparent when consideration is given to the detailed description below. Such detailed description makes reference to the following drawings.

[0014] FIG. 1. Evolutionary Design of Antiestrogen Cores and Side Chains. The direction upward from the GW-7604 structure is taken in the present disclosure; the direction downward is that taken by Genentech and AstraZeneca.

[0015] FIG. 2. Detail of Crystal Structure of GW-5638-ER α LBD Complex. This structure shows that one of the interactions between the carboxylate in GW-5638 and the N-terminus of h12 is mediated through a water molecule. (PDB code: 1R5K).

[0016] FIG. 3. Binding affinities of isostructural esters and amines terminated either with a methyl, hydroxyl or amino group.

[0017] FIG. 4A. Star plots of the antiproliferative efficacy (solid line) and ER α Downregulating Efficacies (dashed line) of Fulvestrant (Fulv), GW-7604, and Compounds **5-15**. All compounds tested at 3 μ M and values plotted at percent of vehicle control.

[0018] FIG. 4B. Star plots of the antiproliferative efficacy (solid line) and ER α Downregulating Efficacies (dashed line) of Fulvestrant (Fulv), GW-7604, and Compounds **16-28**. All compounds tested at 3 μ M and values plotted at percent of vehicle control.

[0019] FIG. 4C. Star plots of the antiproliferative efficacy (solid line) and ER α Downregulating Efficacies (dashed line) of Fulvestrant (Fulv), GW-7604, and Compounds **5, 18, 20, 24, and 27-31**. All compounds tested at 3 μ M and values plotted at percent of vehicle control.

[0020] FIG. 5. Dose Response Curves for Antiproliferative Activities of Selected Compounds. Compounds with high efficacy are compounds **5, 20, and 21**, and those with low efficacy are compounds **29 and 30**. IC₅₀ values are extracted from this experiment.

[0021] FIG. 6A. Dose-response curves from in-cell Western blots of ER α downregulating activities of selected compounds. IC₅₀ values are extracted from this experiment.

[0022] FIG. 6B. In-cell Western blots used for dose-response measurements of FIG. 6A.

[0023] FIG. 7A. Dose-response suppression of E2-stimulated expression of GREB1 by antiestrogen ligands.

[0024] FIG. 7B. Dose-response suppression of E2-stimulated expression of PgR by antiestrogen ligands.

[0025] FIG. 7C. Dose-response suppression of E2-stimulated expression of pS2 by antiestrogen ligands.

[0026] FIG. 8. Correlation between Suppression of Cellular Proliferation and ER α Downregulation.

[0027] FIG. 9. Conformational Preferences of Esters, and Secondary and Tertiary Amides. Both esters and secondary amides prefer an extended conformation due to n- σ^* or σ - σ^* π -overlap, respectively. The tertiary amides have no such electronic preference.

[0028] FIG. 10A. Structures of three Antiestrogens (AE), compounds **5**(K-07), **21**(K-09), and **32**(K-62).

[0029] FIG. 10B. Cell viability of T47D cells with WT-ER α , Y537S-ER α or D538G-ER α cultured in E2-deprived conditions and compounds **5**, **21**, and **32** at 3×10^{-6} M for 6 days. Values are the mean $\pm$ SD of 3 determinations from 3 separate experiments.

[0030] FIG. 10C. Cell viability of T47D cells with WT-ER α , Y537S-ER α or D538G-ER α cultured with E2 (3×10^{-9} M) and compounds **5**, **21**, and **32** at 3×10^{-6} M for 6 days. Values are the mean $\pm$ SD of 3 determinations from 3 separate experiments.

[0031] FIG. 11. Dose-dependent inhibition of T47D cell proliferation by AEs: D538G-ER α is more effectively suppressed by AEs vs. Y537S-ER α . T47D cells with WT- ER α , Y537S- ER α or D538G-ER α were cultured under estrogen-deprived conditions (in phenol red-free medium with 5% charcoal dextran-treated serum). They were treated with ligands at the concentrations indicated (3×10^{-11} to 3×10^{-6} M) and cell proliferation was monitored after 6 days. Values are mean $\pm$ SD of 3 determinations from 3 separate experiments.

[0032] FIG. 12A. Effects of E2 ligands of the expression of the ER target gene GREB1 after T47D cell treatments with Veh, E2 and ligands for 24 h followed by RNA extraction and qPCR analysis. Solid line (set at 1) indicates mRNA expression in Veh-treated WT T47D cells, and dashed line indicates mRNA expression level in E2-treated cells. Values are the mean $\pm$ SD of 3 determinations from 2 separate experiments.

[0033] FIG. 12 B. Effects of E2 ligands of the expression of the ER target gene PGR monitored after T47D cell treatments with Veh, E2 and ligands for 24 h followed by RNA extraction and qPCR analysis. Solid line (set at 1) indicates mRNA expression in Veh-treated WT T47D cells, and dashed line indicates mRNA expression level in E2-treated cells. Values are the mean $\pm$ SD of 3 determinations from 2 separate experiments.

[0034] FIG. 13. Differences in the ability of compounds to induce the degradation of WT or mutant ER α protein in T47D cells. T47D cells were treated with Control Vehicle, E2 or compounds alone for 24 h at the concentrations indicated, and cells were subjected to in cell Western (ICW) blot analysis for evaluation of ER α protein levels.

[0035] FIG. 14A. New AEs show good growth suppression of MCF7 xenograft tumors and inhibition of estrogen target gene expression. NSG mice were supplemented with E2 (0.36mg, 60-day release) pellets, injected with WT MCF7 cells to generate xenograft tumors, and dosed with 80mg/kg of Fulv, K-07, K-09 or K-62 by daily sc injection. Tumor progression was monitored and compared by tumor volume measurements with calipers (2-way ANOVA, Bonferroni post-test, ****, $P < 0.0001$, $n = 8-9$ per group).

[0036] FIG. 14B. NSG mice were supplemented with E2 (0.36mg, 60-day release) pellets, injected with WT MCF7 cells to generate xenograft tumors, and dosed with 80mg/kg of Fulv, K-07, K-09 or K-62 by daily sc injection. On the final day of treatment, tumor volumes were compared.

[0037] FIG. 14C. NSG mice were supplemented with E2 (0.36mg, 60-day release) pellets, injected with WT MCF7 cells to generate xenograft tumors, and dosed with 80mg/kg of Fulv, K-07, K-09 or K-62 by daily sc injections. Harvested tumors were analyzed by qPCR for GREB1 and PGR RNA levels (1-way ANOVA, Tukey post-test, $n = 8-9$ /group).

[0038] FIG. 15. Pharmacokinetics (PK) of K-07 after single dose administration via sc injection (20mg/kg) or oral gavage (20mg/kg). PK of K-09 after single dose sc injection at 20 mg/kg or oral gavage at 40 mg/kg. PK of K-62 after single dose sc injection at 40 mg/kg and oral gavage at 20 mg/kg. Multiple plasma samples were collected from each mouse (n=4 for each experiment) over the course of 48 h after compounds were administered. Compounds were quantified using LC-MS/MS. The data were fitted to a non-compartment PK model.

[0039] FIG. 16A. Antitumor efficacy of orally administered K-07 and suppression of estrogen target gene expression in tumors. E2-supplemented mice bearing MCF7 tumors were dosed daily with 80mg/kg of K-07 by oral gavage. Volumes of Veh and K-07 treated tumors were monitored (2-way ANOVA, Bonferroni post-test, ****, $P < 0.0001$, n=8 per group).

[0040] FIG. 16B. Antitumor efficacy of orally administered K-07 and suppression of estrogen target gene expression in tumors. E2-supplemented mice bearing MCF7 tumors were dosed daily with 80mg/kg of K-07 by oral gavage. After 28 days, tumors were compared in size. (T-test, ****, $P < 0.0001$, n=8 per group).

[0041] FIG. 16C. Antitumor efficacy of orally administered K-07 and suppression of estrogen target gene expression in tumors. E2-supplemented mice bearing MCF7 tumors were dosed daily with 80mg/kg of K-07 by oral gavage. After 28 days, tumors were harvested for gene expression analysis. (T-test, ****, $P < 0.0001$, n=8 per group).

[0042] FIG. 17A. Y537S- and D538G-containing tumors grow in the absence of estrogen and are arrested by K-07 treatment. NSG mice were ovariectomized and 3 weeks later received MCF7 cells containing only wild type (WT) ER or MCF7 cells containing half Y537S ER or D538G ER and half wild type ER. Mice were then given daily sc injection with Vehicle or 80mg/kg of K-07 or Fulv. Volumes of Veh, Fulv, and K-07 treated tumors were monitored over time (2-way ANOVA, Bonferroni post-test, ****, $P < 0.0001$, n=8 per group).

[0043] FIG. 17B. Y537S- and D538G-containing tumors grow in the absence of estrogen and are arrested by K-07 treatment. NSG mice were ovariectomized and 3 weeks later received MCF7 cells containing only wild type (WT) ER or MCF7 cells containing half Y537S ER or

D538G ER and half wild type ER. Mice were then given daily sc injection with Vehicle or 80mg/kg of K-07 or Fulv. After 28 days, tumors were compared in size.

[0044] FIG. 17C. Y537S- and D538G-containing tumors grow in the absence of estrogen and are arrested by K-07 treatment. NSG mice were ovariectomized and 3 weeks later received MCF7 cells containing only wild type (WT) ER or MCF7 cells containing half Y537S ER or D538G ER and half wild type ER. Mice were then given daily sc injection with Vehicle or 80mg/kg of K-07 or Fulv. Animal body weights were monitored.

[0045] FIG. 17D. Y537S- and D538G-containing tumors grow in the absence of estrogen and are arrested by K-07 treatment. NSG mice were ovariectomized and 3 weeks later received MCF7 cells containing only wild type (WT) ER or MCF7 cells containing half Y537S ER or D538G ER and half wild type ER. Mice were then given daily sc injection with Vehicle or 80mg/kg of K-07 or Fulv. Tumors were harvested and analyzed for expression of estrogen target genes. (T-test, ****, $P < 0.0001$, $n = 8$ per group).

[0046] FIG. 18. Dose-dependent inhibition of the growth of T47D cells by antiestrogen compounds with WT or mutant-ER α in tissue culture medium with 5% fetal bovine serum and 3×10^{-10} M E2. T47D cells with WT, Y537S- or D538G-ER α were cultured in E2-containing media, and were treated with E2 (3×10^{-9} M) or compounds at the concentrations indicated (3×10^{-11} to 3×10^{-6} M) for 6 days. Cell viability values are mean $\pm$ SD of 3 determinations from 3 separate experiments.

[0047] FIG. 19A. Compounds suppress proliferation of breast cancer cells with heterozygous levels of mutant Y537S ER α . MCF-7 or T47D cells containing 50% mutant ER α and 50% wild type ER α were treated with E2 or compounds alone for 6 days at the concentrations indicated and cell viability was measured. Values are mean $\pm$ SD from 3 determinations from 3 separate experiments.

[0048] FIG. 19B Compounds suppress proliferation of breast cancer cells with heterozygous levels of mutant D538G ER α . MCF-7 or T47D cells containing 50% mutant ER α and 50% wild type ER α were treated with E2 or compounds alone for 6 days at the concentrations indicated

and cell viability was measured. Values are mean $\pm$ SD from 3 determinations from 3 separate experiments.

[0049] FIG. 20. Compounds induce degradation of ER α in MCF-7 and T47D breast cancer cells containing half mutant and half wild type ER α . ICW assay of ER α was performed in breast cancer cells treated for 24 h with Control Vehicle, E2 or compounds alone at the concentrations indicated.

[0050] FIG. 21. Suppression of ER α -regulated gene expressions in MCF-7 and T47D breast cancer cells containing half mutant and half wild type ER α . After 24 h of Control Vehicle, E2 or compound treatment, cells were harvested and processed for qPCR analysis of the ER α -regulated genes GREB1 and PGR. Fold change of mRNA level was calculated relative to the vehicle treated cell samples, set at 1.

[0051] FIG. 22. Treatment with antiestrogen compounds *in vivo* does not affect animal body weights. Mice received daily 80mg/kg of the compounds indicated or Vehicle by sc injection or oral gavage, and body weights of the mice bearing wild type MCF-7 xenograft tumors were monitored over the 28 days of dosing (2-way ANOVA, Bonferroni post-test, $P > 0.05$, $n = 8-9$ per group).

[0052] FIG. 23. Effect of certain disclosed compounds on MCF-7 cell proliferation at 3 μ M. The activity in suppressing cell proliferation was calculated as a percent of vehicle control; maximum suppression is ca. 0% (corresponding to essentially no increase in cell number after 6 days). All assays were performed in triplicates, the values are the average of two to three independent experiments.

[0053] FIG. 24. In-cell western blotting for certain disclosed compounds at 3 μ M. The value of 0% represents the ER α level after 24 h with 3 μ M fulvestrant treatment, the value of 100% represents the ER α level in vehicle control cells. The values are the average from at least three independent experiments.

[0054] FIG. 25. Crystal structure of GW-5638-ER α LBD complex. The left-side panel shows an overlay of the ER α LBD complex with hydroxytamoxifen (OHT; blue color for h12, OHT, and arrow) and with GW-5638 (yellow color for h12, GW, and arrow). The differing orientation

of h12 is evident in the two structures. The right-side panel shows the interaction of the carboxylate in GW-5638 with the N-terminus of h12. One of the interactions between these two units is mediated through a structural water molecule. (PDB code 1R5K).

[0055] FIG. 26. Fluorescence Resonance Energy Transfer (FRET) analysis of antiestrogen compounds **5**(K-07), **21**(K-09), and **32**(K-62) and trans-hydroxy-tamoxifen (TOT) show dose dependent suppression of the binding of SRC3 to wild type ER, Y537S-ER, and D538G-ER. Site-specific labeled biotin-streptavidin/terbium ER-ligand binding domain constructs (donor) were primed to ~50% activity with estradiol and were then incubated with a fluorescein labeled SRC3 (acceptor); the priming concentration required for each receptor is given in square brackets in each panel.

[0056] FIG. 27A. Western blot examination of GREB1 and ER α protein in individual tumors. β -actin served as the loading control.

[0057] FIG. 27B. Quantitation of ER α and GREB1 protein in vehicle and K-07-treated tumors (t test, $P < 0.0005$; $n \frac{1}{4} 5$ vehicle and $n \frac{1}{4} 6$ K-07 tumors).

[0058] FIG. 28A. Tumor volumes of ovariectomized NSG mice. Three weeks after ovariectomy, mice received MCF7 cells containing half D538G ER and half WT ER and daily subcutaneous injections with vehicle or 80 mg/kg of K-07 or fulvestrant. Two-way ANOVA, Bonferroni posttest, $P < 0.0001$; $n \frac{1}{4} 8$ per group.

[0059] FIG. 28B. Tumor volumes of ovariectomized NSG mice. Three weeks after ovariectomy mice received MCF7 cells containing half Y537S ER or D538G ER and half WT ER and daily treatments with oral vehicle or oral K-07 at 80 mg/kg. Two-way ANOVA, Bonferroni post-test, $P < 0.0001$; $n \frac{1}{4} 8$ per group.

[0060] FIG. 28C. Expression of the estrogen target genes GREB1 and PGR in tumor harvested at day 26 from NSG mice ovariectomized 3 weeks prior to receiving MCF7 cells containing half D538G ER and half WT ER and daily subcutaneous injection with vehicle or 80 mg/kg of K-07 or fulvestrant. One-way ANOVA, Tukey posttest; $n \frac{1}{4} 8$ per group.

[0061] FIG. 28D. Expression of the estrogen target genes GREB1 and PGR in tumors harvested at day 26 from NSG mice ovariectomized 3 weeks prior to receiving MCF7 cells containing half Y537S ER or half D538G ER and half WT ER and daily subcutaneous injection with vehicle or 80 mg/kg of K-07 or fulvestrant. T-test, $P < 0.0001$; $n = 8$ per group.

[0062] FIG. 28E. Expression of ER α protein by Western blot analysis of tumor lysates from the harvested tumors in FIGS. 28C-28D.

[0063] FIG. 28F. Expression of ER α protein by IHC for ER α in tumor tissue sections from the harvested tumors in FIGS. 28C-28D.

[0064] FIG. 29A. Metastasis growth after intracardiac injection into NOD-SCID-gamma (NSG) female mice with 0.5×10^6 MCF-7 breast cancer cells expressing luciferase and D538G ER (ca. 50% mutant ER and 50% wild type ER). Animals were treated 6-times per week with vehicle or K-07 (80 mg/kg orally for 30 days and then 40 mg/kg). Tumor metastasis growth was monitored at by bioluminescence (IVIS) imaging 19 days after injection. $p=0.08$ unpaired t-test, two tailed.

[0065] FIG. 29B. Metastasis growth after intracardiac injection into NOD-SCID-gamma (NSG) female mice with 0.5×10^6 MCF-7 breast cancer cells expressing luciferase and D538G ER (ca. 50% mutant ER and 50% wild type ER). Animals were treated 6-times per week with vehicle or K-07 (80 mg/kg orally for 30 days and then 40 mg/kg). Tumor metastasis growth was monitored at by bioluminescence (IVIS) imaging 25 days after injection. $p=0.02$ unpaired t-test, two tailed.

[0066] FIG. 29C. Animal survival after intracardiac injection into NOD-SCID-gamma (NSG) female mice with 0.5×10^6 MCF-7 breast cancer cells expressing luciferase and D538G ER (ca. 50% mutant ER and 50% wild type ER). Animals were treated 6-times per week with vehicle or K-07 (80 mg/kg orally for 30 days and then 40 mg/kg). Animal survival was followed to 70 days. Hazard Ratio (Mantel-Haenszel) = 4.7, CI: 1.616 to 13.91.

[0067] FIG. 30A. Metastasis growth after tail vein injection of NOD-SCID-gamma (NSG) female mice with 0.5×10^6 MCF-7 breast cancer cells expressing luciferase and Y537S ER (ca. 50% mutant ER and 50% wild type ER). Animals were treated 6-times per week with vehicle or

K-07 (80 mg/kg orally for 30 days and then 40 mg/kg). Tumor metastasis growth was monitored with time by bioluminescence (IVIS) imaging. $p=0.1$, 2way ANOVA.

[0068] FIG. 30B. Metastasis growth after tail vein injection of NOD-SCID-gamma (NSG) female mice with 0.5×10^6 MCF-7 breast cancer cells expressing luciferase and Y537S ER (ca. 50% mutant ER and 50% wild type ER). Animals were treated 6-times per week with vehicle or K-07 (80 mg/kg orally for 30 days and then 40 mg/kg). Tumor metastasis growth was monitored after 57 days by bioluminescence (IVIS) imaging.

[0069] FIG. 30C. Animal survival after tail vein injection of NOD-SCID-gamma (NSG) female mice with 0.5×10^6 MCF-7 breast cancer cells expressing luciferase and Y537S ER (ca. 50% mutant ER and 50% wild type ER). Animals were treated 6-times per week with vehicle or K-07 (80 mg/kg orally for 30 days and then 40 mg/kg). Animal survival was followed to 100 days. Hazard Ratio (Mantel-Haenszel) = 10.2, CI: 1.396 to 74.28.

[0070] FIG. 31A. Metastasis growth after tail vein injection into NOD-SCID-gamma (NSG) female mice with 0.5×10^6 MCF-7 breast cancer cells expressing luciferase and D538G ER (ca. 50% mutant ER and 50% wild type ER). Animals were treated 6-times per week with vehicle or K-07 (80 mg/kg orally for 30 days and then 40 mg/kg). Tumor metastasis growth was monitored with time by bioluminescence (IVIS) imaging.

[0071] FIG. 31B. Animal survival after tail vein injection into NOD-SCID-gamma (NSG) female mice with 0.5×10^6 MCF-7 breast cancer cells expressing luciferase and D538G ER (ca. 50% mutant ER and 50% wild type ER). Animals were treated 6-times per week with vehicle or K-07 (80 mg/kg orally for 30 days and then 40 mg/kg). Animal survival was followed to 90 days. Hazard Ratio (Mantel-Haenszel) = 12.2, CI: 2.011 to 73.90.

[0072] FIG. 32. Reversal of coactivator SRC3/AIB1 binding to WT and mutant ERs.

[0073] While the present invention is susceptible to various modifications and alternative forms, exemplary embodiments thereof are shown by way of example in the drawings and are herein described in detail. It should be understood, however, that the description of exemplary embodiments is not intended to limit the invention to the particular forms disclosed, but on the contrary, the intention is to cover all modifications, equivalents and alternatives falling within

the spirit and scope of the invention as defined by the embodiments above and the claims below. Reference should therefore be made to the embodiments above and claims below for interpreting the scope of the invention.

[0074] The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawing(s) will be provided by the Office upon request and payment of the necessary fee.

DETAILED DESCRIPTION

1. Definitions

[0075] As described herein, compounds of the invention can optionally be substituted with one or more substituents, such as are illustrated generally above, or as exemplified by particular classes, subclasses, and species of the invention. As described herein, the variables in formula I encompass specific groups, such as, for example, alkyl and cycloalkyl. As one of ordinary skill in the art will recognize, combinations of substituents envisioned by this invention are those combinations that result in the formation of stable or chemically feasible compounds. The term "stable," as used herein, refers to compounds that are not substantially altered when subjected to conditions to allow for their production, detection, and preferably their recovery, purification, and use for one or more of the purposes disclosed herein. In some embodiments, a stable compound or chemically feasible compound is one that is not substantially altered when kept at a temperature of 40°C or less, in the absence of moisture or other chemically reactive conditions, for at least a week.

[0076] Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art. All publications, patent applications, patents and other references mentioned herein are incorporated by reference in their entirety. The materials, methods, and examples disclosed herein are illustrative only and not intended to be limiting.

[0077] The terms "comprise(s)," "include(s)," "having," "has," "can," "contain(s)," and variants thereof, as used herein, are intended to be open-ended transitional phrases, terms, or words that do not preclude the possibility of additional acts or structures. The singular forms

“a,” “an” and “the” include plural references unless the context clearly dictates otherwise. The present disclosure also contemplates other embodiments “comprising,” “consisting of” and “consisting essentially of,” the embodiments or elements presented herein, whether explicitly set forth or not.

[0078] The modifier “about” used in connection with a quantity is inclusive of the stated value and has the meaning dictated by the context (for example, it includes at least the degree of error associated with the measurement of the particular quantity). The modifier “about” should also be considered as disclosing the range defined by the absolute values of the two endpoints. For example, the expression “from about 2 to about 4” also discloses the range “from 2 to 4.” The term “about” may refer to plus or minus 10% of the indicated number. For example, “about 10%” may indicate a range of 9% to 11%, and “about 1” may mean from 0.9-1.1. Other meanings of “about” may be apparent from the context, such as rounding off, so, for example “about 1” may also mean from 0.5 to 1.4.

[0079] Definitions of specific functional groups and chemical terms are described in more detail below. For purposes of this disclosure, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 75th Ed., inside cover, and specific functional groups are generally defined as described therein. Additionally, general principles of organic chemistry, as well as specific functional moieties and reactivity, are described in *Organic Chemistry*, Thomas Sorrell, University Science Books, Sausalito, 1999; Smith and March *March's Advanced Organic Chemistry*, 5th Edition, John Wiley & Sons, Inc., New York, 2001; Larock, *Comprehensive Organic Transformations*, VCH Publishers, Inc., New York, 1989; Carruthers, *Some Modern Methods of Organic Synthesis*, 3rd Edition, Cambridge University Press, Cambridge, 1987; the entire contents of each of which are incorporated herein by reference.

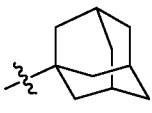
[0080] The term “alkoxy” as used herein, refers to an alkyl group, as defined herein, appended to the parent molecular moiety through an oxygen atom. Representative examples of alkoxy include, but are not limited to, methoxy, ethoxy, propoxy, 2-propoxy, butoxy and tert-butoxy.

[0081] The term “alkyl” as used herein, means a straight or branched chain saturated hydrocarbon. Representative examples of alkyl include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, isopentyl, neopentyl, n-hexyl, 3-methylhexyl, 2,2-dimethylpentyl, 2,3-dimethylpentyl, n-heptyl, n-octyl, n-nonyl, and n-decyl.

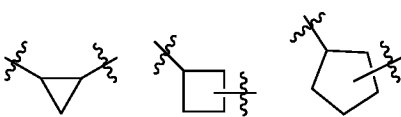
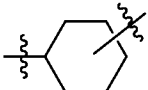
[0082] The term “alkylene,” as used herein, means a divalent group derived from a straight or branched chain saturated hydrocarbon. Representative examples of alkylene include, but are not limited to, $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{CH}_2\text{CH}_2\text{CH}_2-$, $-\text{CH}_2\text{CH}(\text{CH}_3)\text{CH}_2-$, and $\text{CH}_2\text{CH}(\text{CH}_3)\text{CH}(\text{CH}_3)\text{CH}_2-$.

[0083] The term “aryl,” as used herein, means phenyl or a bicyclic aryl. The bicyclic aryl is naphthyl, dihydronaphthalenyl, tetrahydronaphthalenyl, indanyl, or indenyl. The phenyl and bicyclic aryls are attached to the parent molecular moiety through any carbon atom contained within the phenyl or bicyclic aryl.

[0084] The term “cycloalkyl” as used herein, means a monovalent group derived from an all-carbon ring system containing zero heteroatoms as ring atoms, and zero double bonds. The all-carbon ring system can be a monocyclic, bicyclic, or tricyclic ring system, and can be a fused ring system, a bridged ring system, or a spiro ring system, or combinations thereof. Examples of cycloalkyls include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl,

cycloheptyl, cyclooctyl, and . The cycloalkyl groups described herein can be appended to the parent molecular moiety through any substitutable carbon atom.

[0085] The term “cycloalkylene” as used herein, means a divalent group derived from an all-carbon ring system containing zero heteroatoms as ring atoms and zero double bonds, which attaches to the parent molecule at two different ring carbons atoms. The all-carbon ring system can be a monocyclic, bicyclic, or tricyclic ring system, and can be a fused ring system, a bridged ring system, or a spiro ring system. Representative examples of cycloalkylene include, but are

not limited to those derived from C₃₋₁₀ rings, such as , and .

[0086] The term “halogen” means a chlorine, bromine, iodine, or fluorine atom.

[0087] The term “haloalkyl,” as used herein, means an alkyl, as defined herein, in which one, two, three, four, five, six, or seven hydrogen atoms are replaced by halogen. For example, representative examples of haloalkyl include, but are not limited to, 2-fluoroethyl, difluoromethyl, trifluoromethyl, 2,2,2-trifluoroethyl, 2,2,2-trifluoro-1, 1-dimethylethyl, and the like.

[0088] The term “heteroaryl,” as used herein, means an aromatic heterocycle, i.e., an aromatic ring that contains at least one heteroatom selected from O, N, or S. A heteroaryl may contain from 5 to 12 ring atoms. A heteroaryl may be a 5- to 6-membered monocyclic heteroaryl or an 8- to 12-membered bicyclic heteroaryl. A 5-membered monocyclic heteroaryl ring contains two double bonds, and one, two, three, or four heteroatoms as ring atoms. Representative examples of 5-membered monocyclic heteroaryls include, but are not limited to, furanyl, imidazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, oxazolyl, pyrazolyl, pyrrolyl, tetrazolyl, thiadiazolyl, thiazolyl, thienyl, and triazolyl. A 6-membered heteroaryl ring contains three double bonds, and one, two, three or four heteroatoms as ring atoms. Representative examples of 6-membered monocyclic heteroaryls include, but are not limited to, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, and triazinyl. The bicyclic heteroaryl is an 8- to 12-membered ring system having a monocyclic heteroaryl fused to an aromatic, saturated, or partially saturated carbocyclic ring, or fused to a second monocyclic heteroaryl ring. Representative examples of bicyclic heteroaryl include, but are not limited to, benzofuranyl, benzoxadiazolyl, 1,3-benzothiazolyl, benzimidazolyl, benzothienyl, indolyl, indazolyl, isoquinolinyl, naphthyridinyl, oxazolopyridine, quinolinyl, thienopyridinyl, 5,6,7,8-tetrahydroquinolinyl, and 6,7-dihydro-5H-cyclopenta[b]pyridinyl. The heteroaryl groups are connected to the parent molecular moiety through any substitutable carbon atom or any substitutable nitrogen atom contained within the groups.

[0089] The terms “heterocycle” or “heterocyclic” refer generally to ring systems containing at least one heteroatom as a ring atom where the heteroatom is selected from oxygen, nitrogen, and sulfur. In some embodiments, a nitrogen or sulfur atom of the heterocycle is optionally substituted with oxo. Heterocycles may be a monocyclic heterocycle, a fused bicyclic heterocycle, or a spiro heterocycle. The monocyclic heterocycle is generally a 4, 5, 6, 7, or 8-membered non-aromatic ring containing at least one heteroatom selected from O, N, or S. The 4-membered ring contains one heteroatom and optionally one double bond. The 5-membered ring contains zero or one double bond and one, two or three heteroatoms. The 6, 7, or 8-membered ring contains zero, one, or two double bonds, and one, two, or three heteroatoms. Representative examples of monocyclic heterocycle include, but are not limited to, azetidiny, azepanyl, diazepanyl, 1,3-dioxanyl, 1,4-dioxanyl, 1,3-dioxolanyl, 4,5-dihydroisoxazol-5-yl, 3,4-dihydropyranyl, 1,3-dithiolanyl, 1,3-dithianyl, imidazoliny, imidazolidiny, isothiazoliny, isothiazolidiny, isoxazoliny, isoxazolidiny, morpholiny, oxadiazoliny, oxadiazolidiny, oxazoliny, oxazolidiny, oxetanyl, piperaziny, piperidiny, pyranyl, pyrazoliny, pyrazolidiny, pyrroliny, pyrrolidiny, tetrahydrofuranyl, tetrahydropyranyl, tetrahydrothienyl, thiadiazoliny, thiadiazolidiny, thiazoliny, thiazolidiny, thiomorpholiny, 1,1-dioxidothiomorpholiny, thiopyranyl, and trithianyl. The fused bicyclic heterocycle is a 7-12-membered ring system having a monocyclic heterocycle fused to a phenyl, to a saturated or partially saturated carbocyclic ring, or to another monocyclic heterocyclic ring, or to a monocyclic heteroaryl ring. Representative examples of fused bicyclic heterocycle include, but are not limited to, 1,3-benzodioxol-4-yl, 1,3-benzodithiolyl, 3-azabicyclo[3.1.0]hexanyl, hexahydro-1H-furo[3,4-c]pyrrolyl, 2,3-dihydro-1,4-benzodioxiny, 2,3-dihydro-1-benzofuranyl, 2,3-dihydro-1-benzothienyl, 2,3-dihydro-1H-indolyl, 5,6,7,8-tetrahydroimidazo[1,2-a]pyraziny, and 1,2,3,4-tetrahydroquinoliny. Spiro heterocycle means a 4-, 5-, 6-, 7-, or 8-membered monocyclic heterocycle ring wherein two of the substituents on the same carbon atom form a second ring having 3, 4, 5, 6, 7, or 8 members. Examples of a spiro heterocycle include, but are not limited to, 1,4-dioxa-8-azaspiro[4.5]decanyl, 2-oxa-7-azaspiro[3.5]nonanyl, 2-oxa-6-azaspiro[3.3]heptanyl, and 8-azaspiro[4.5]decane. The monocyclic heterocycle groups of the present invention may contain an alkylene bridge of 1, 2, or 3 carbon atoms, linking two nonadjacent atoms of the group. Examples of such a bridged heterocycle include, but are not limited to, 2,5-diazabicyclo[2.2.1]heptanyl, 2-azabicyclo[2.2.1]heptanyl, 2-

azabicyclo[2.2.2]octanyl, and oxabicyclo[2.2.1]heptanyl. The monocyclic, fused bicyclic, and spiro heterocycle groups are connected to the parent molecular moiety through any substitutable carbon atom or any substitutable nitrogen atom contained within the group.

[0090] The term “hydroxy” as used herein, means an –OH group.

[0091] The term hydroxyalkyl as used herein means an alkyl, as defined herein, in which a hydrogen atom is replaced by –OH. For example, representative examples of hydroxyalkyl include, but are not limited to those derived from C₁₋₆ alkyls, such as –CH₂OH, –CH₂CH₂OH, –CH₂CH₂CH₂OH, and the like.

[0092] The term “oxo” as used herein refers to an oxygen atom bonded to the parent molecular moiety. An oxo may be attached to a carbon atom or a sulfur atom by a double bond. Alternatively, an oxo may be attached to a nitrogen atom by a single bond, i.e., an N-oxide.

[0093] The term “polycycloalkylidene” as used herein refers to an all-carbon ring system having a divalent ring carbon atom that bonds to the parent molecular moiety through a carbon-carbon double bond. The divalent ring carbon atom is formed by removal of two hydrogen atoms from the same ring carbon atom of a corresponding polycycloalkane. A polycycloalkane refers to an all-carbon ring system having at least one alkylene bridge (i.e., an alkylene that connects two non-adjacent carbon atoms) and optionally having a fused ring (i.e., an alkylene connecting two adjacent carbon atoms) and/or a spirocyclic ring (i.e., an alkylene connected at either end to the same carbon atom). Representative structures of the polycycloalkane include, but are not limited to adamantane, noradamantane, norbornane, (3aR,4R,7S,7aS)-octahydro-1H-4,7-methanoindene, bicyclo[2.2.2]octane, and (2R,3S,4S,5R)-pentacyclo[4.3.0.0^{2,5}.0^{3,8}.0^{4,7}]nonane (alternatively named homocubane).

[0094] Terms such as “alkyl,” “cycloalkyl,” “alkylene,” “cycloalkylene,” “polycycloalkylidene” etc. may be preceded by a designation indicating the number of atoms present in the group in a particular instance (e.g., “C₁₋₄alkyl,” “C₁₋₄alkyl,” “C₃₋₆cycloalkyl,” “C₁₋₄alkylene”). These designations are used as generally understood by those skilled in the art. For example, the representation “C” followed by a subscripted number indicates the number of carbon atoms present in the group that follows. Thus, “C₃alkyl” is an alkyl group with three

carbon atoms (i.e., n-propyl, isopropyl). Where a range is given, as in “C₁-C₄” or “C₁₋₄,” the members of the group that follows may have any number of carbon atoms falling within the recited range. A “C₁-C₄alkyl” or “C₁₋₄alkyl,” for example, is an alkyl group having from 1 to 4 carbon atoms, however arranged (i.e., straight chain or branched).

[0095] If a group is described as being “substituted”, a non-hydrogen substituent group is in the place of hydrogen radical on a carbon or nitrogen of that group. Thus, for example, a substituted alkyl is an alkyl in which at least one non-hydrogen radical is in the place of a hydrogen radical on the alkyl. To illustrate, monofluoroalkyl is alkyl substituted with a fluoro radical, and difluoroalkyl is alkyl substituted with two fluoro radicals. It should be recognized that if there is more than one substitution on a substituent, each non-hydrogen radical may be identical or different (unless otherwise stated). Substituent groups include, but are not limited to, halogen, =O, =S, cyano, nitro, fluoroalkyl, alkoxyfluoroalkyl, fluoroalkoxy, alkyl, alkenyl, alkynyl, haloalkyl, haloalkoxy, heteroalkyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocycle, cycloalkylalkyl, heteroarylalkyl, arylalkyl, hydroxy, hydroxyalkyl, alkoxy, alkoxyalkyl, alkylene, aryloxy, phenoxy, benzyloxy, amino, alkylamino, acylamino, aminoalkyl, arylamino, sulfonylamino, sulfinylamino, sulfonyl, alkylsulfonyl, arylsulfonyl, aminosulfonyl, sulfinyl, -COOH, ketone, amide, carbamate, and acyl.

[0096] When a group is referred to as “unsubstituted” or not referred to as “substituted” or “optionally substituted”, it means that the group does not have any substituents. If a group is described as being “optionally substituted”, the group may be either (1) not substituted or (2) substituted. If a group is described as being optionally substituted with up to a particular number of non-hydrogen radicals, that group may be either (1) not substituted; or (2) substituted by up to that particular number of substituent groups or by up to the maximum number of substitutable positions on that group, whichever is less.

[0097] If substituents are described as being independently selected from a group, each substituent is selected independent of the other. Each substituent, therefore, may be identical to or different from the other substituent(s).

[0098] Unless otherwise stated, structures depicted herein are also meant to include all isomeric (e.g., enantiomeric, diastereomeric, and geometric (or conformational)) forms of the

structure; for example, the R and S configurations for each asymmetric center, (Z) and (E) double bond isomers, and (Z) and (E) conformational isomers. Therefore, single stereochemical isomers as well as enantiomeric, diastereomeric, and geometric (or conformational) mixtures of the present compounds are within the scope of the invention. Unless otherwise stated, all tautomeric forms of the compounds of the invention are within the scope of the invention. Thus, included within the scope of the invention are tautomers of compounds of formula I. The structures also include zwitterionic forms of the compounds or salts of formula I where appropriate.

[0099] As used herein, the term "E2" refers to estradiol.

[00100] The terms "effective amount" or "therapeutically effective amount," as used herein, refer to a sufficient amount of an agent or a composition or combination of compositions being administered which will relieve to some extent one or more of the symptoms of the disease or condition being treated. The result can be reduction and/or alleviation of the signs, symptoms, or causes of a disease, or any other desired alteration of a biological system. For example, an "effective amount" for therapeutic uses is the amount of the composition comprising a compound as disclosed herein required to provide a clinically significant decrease in disease symptoms. An appropriate "effective" amount in any individual case may be determined using techniques, such as a dose escalation study. The dose could be administered in one or more administrations. However, the precise determination of what would be considered an effective dose may be based on factors individual to each patient, including, but not limited to, the patient's age, size, type or extent of disease, stage of the disease, route of administration of the regenerative cells, the type or extent of supplemental therapy used, ongoing disease process and type of treatment desired (e.g., aggressive vs. conventional treatment).

[00101] As used herein, "treat," "treating" and the like means a slowing, stopping or reversing of progression of cancer when provided a composition described herein to an appropriate control subject. The term also means a reversing of the progression of such a disease or disorder to a point of eliminating or greatly reducing the cell proliferation. As such, "treating" means an application or administration of the compositions described herein to a subject, where the subject

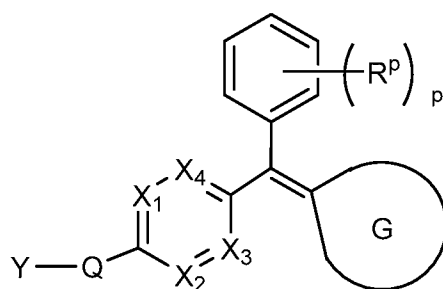
has a disease or a symptom of a disease, where the purpose is to cure, heal, alleviate, relieve, alter, remedy, ameliorate, improve or affect the disease or symptoms of the disease.

[00102] As used herein, "subject" or "patient" means an individual having symptoms of, or at risk for, cancer or other malignancy. A patient may be human or non-human and may include, for example, animal strains or species used as "model systems" for research purposes, such as a mouse model as described herein. Likewise, patient may include either adults or juveniles (*e.g.*, children). Moreover, patient may mean any living organism, preferably a mammal (*e.g.*, human or non-human) that may benefit from the administration of compositions contemplated herein. Examples of mammals include, but are not limited to, any member of the Mammalian class: humans, non-human primates such as chimpanzees, and other apes and monkey species; farm animals such as cattle, horses, sheep, goats, swine; domestic animals such as rabbits, dogs, and cats; laboratory animals including rodents, such as rats, mice and guinea pigs, and the like. Examples of non-mammals include, but are not limited to, birds, fish and the like. In one embodiment of the methods and compositions provided herein, the mammal is a human.

[00103] As used herein, the terms "providing", "administering," "introducing," are used interchangeably herein and refer to the placement of the compositions of the disclosure into a subject by a method or route which results in at least partial localization of the composition to a desired site. The compositions can be administered by any appropriate route which results in delivery to a desired location in the subject.

2. Compounds

[00104] A first aspect of the invention provides compounds or compositions of formula (I), or a pharmaceutically acceptable salt thereof,



(I)

wherein

G is an optionally substituted polycycloalkylidene;

X₁, X₂, X₃, and X₄ are each independently N, CH, or CR^m, wherein at most two of X₁, X₂, X₃, and X₄ are N, and wherein at most one of X₁ and X₄ is N;

Y is alkyl, -OR^A, -COOR^B, -N(R^C)(R^D), -CON(R^C)(R^D), -N(R^C)-OH, -NH-N(R^C)(R^D), or -CR^y=CR^x-CN;

Q is a bond, -C(Q¹)-CR^y=CR^x-, -C(Q²)-NH-N=CR^x-, -C(O)-NH-, -C(O)-Q³-, or -SO₂-CR^y=CR^z-, wherein the C(Q¹), C(Q²), C(O), or SO₂ group is attached to Y;

R^p and R^m at each occurrence are independently alkyl, alkoxy, halogen, -OH, -CN, haloalkyl, or hydroxyalkyl;

p is 0, 1, 2, 3, 4, or 5;

Q¹ and Q² are O, NH, or S;

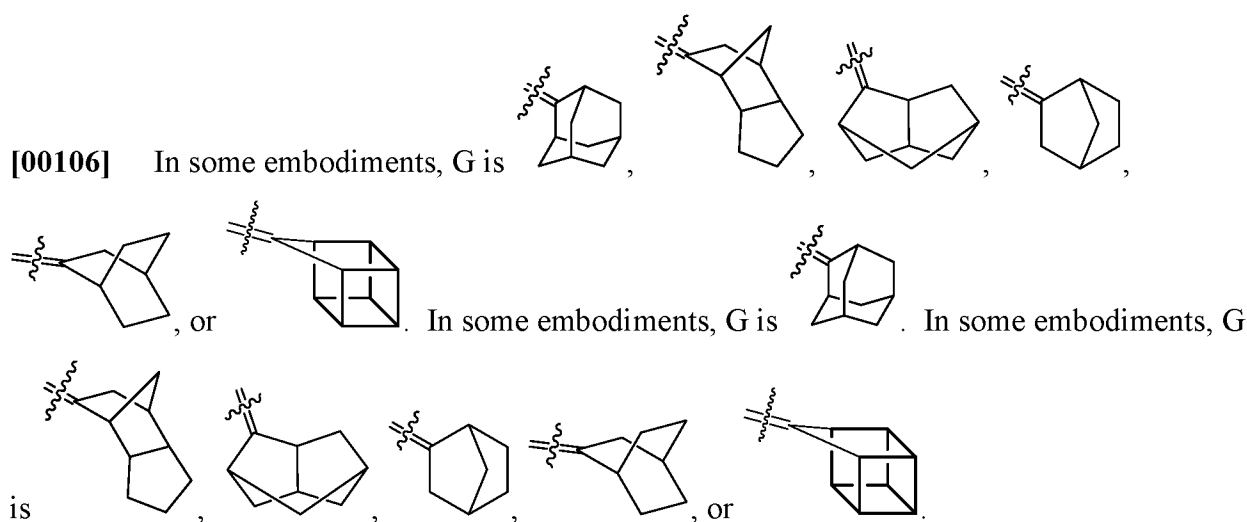
Q³ is an optionally substituted cycloalkylene;

R^A, R^B, R^C, and R^D at each occurrence are independently hydrogen, alkyl, cycloalkyl, aryl, heterocycle, heteroaryl, or alkyl substituted by one or more substituents selected from the group consisting of -OH, -NH₂, -NH(C₁₋₄alkyl), -N(C₁₋₄alkyl)₂, halogen, phenyl, and -NHCO-R^Z, wherein the cycloalkyl, aryl, heterocycle, and heteroaryl are each optionally substituted;

R^x and R^y at each occurrence are independently hydrogen, alkyl, halogen, haloalkyl, or -CN; and

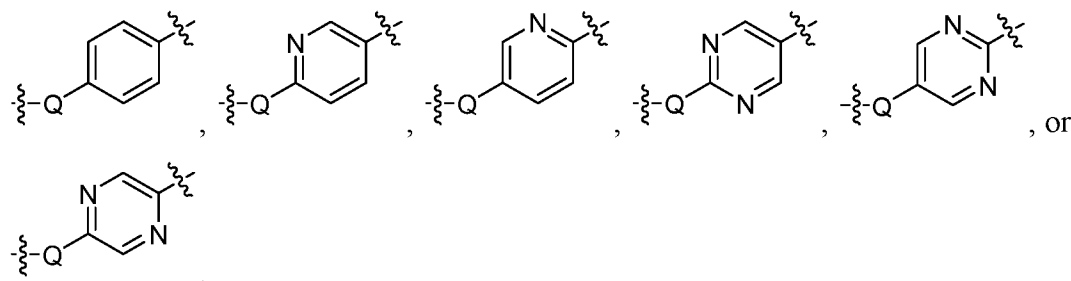
R^Z is -OC₁₋₄alkyl, cycloalkyl or -C₁₋₄ alkylene-cycloalkyl.

[00105] G is a polycycloalkylidene group as defined herein. In some embodiments, G is a C₆₋₃₀ bicyclic or tricyclic ring system, or a ring system with an even higher number of rings. In some embodiments, G is fused ring system, a bridged ring system, or a spiro ring systems. In some embodiments, G is a C₆₋₂₅, a C₆₋₂₀, a C₈₋₂₀, or a C₁₀₋₂₀ ring system. In some embodiments, G is a C₆, C₇, C₈, C₉, C₁₀, C₁₁, C₁₂, C₁₃, C₁₄, C₁₅, or C₁₆ polycycloalkylidene group as disclosed herein. G may be substituted or unsubstituted. In some embodiments, G is substituted with C₁₋₁₀alkyl, halogen, C₁₋₁₀haloalkyl, C₁₋₁₀hydroxyalkyl, cyano, nitro, amino, or other substituent groups as disclosed herein. In some embodiments, G is unsubstituted.

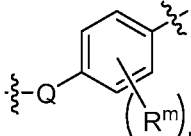


[00107] In some embodiments, X_1 , X_2 , X_3 , and X_4 are each independently CH or CR^m. In some embodiments, only one of X_1 , X_2 , X_3 , and X_4 is N, with the others being independently CH or CR^m. In some embodiments, X_1 and X_2 are N, and X_3 and X_4 are independently CH or CR^m. In some embodiments, X_1 and X_3 are N, and X_2 and X_4 are independently CH or CR^m.

[00108] In some embodiments, the ring containing X_1 , X_2 , X_3 , and X_4 together with Q is

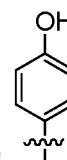


[00109] In some embodiments, one or two or three or four of X_1 , X_2 , X_3 , and X_4 are independently CR^m. In some embodiments, the ring containing X_1 , X_2 , X_3 , and X_4 together with

Q is , in which R^m at each occurrence is independently alkyl (such as C₁₋₄alkyl), alkoxy (such as C₁₋₄alkoxy), halogen, -OH, -CN, haloalkyl (such as C₁₋₄haloalkyl), or hydroxyalkyl (such as C₁₋₄hydroxyalkyl), and m is 0, 1, 2, 3, or 4. In some embodiments, R^m at each occurrence is independently halogen, -OH, -CN, C₁₋₄haloalkyl, or C₁₋₄hydroxyalkyl. In some embodiments, R^m at each occurrence is independently halogen, such as fluoro.

[00110] In some embodiments, R^p at each occurrence is independently alkyl (such as C_{1-4} alkyl), alkoxy (such as C_{1-4} alkoxy), halogen, $-OH$, $-CN$, haloalkyl (such as C_{1-4} haloalkyl), or hydroxyalkyl (such as C_{1-4} hydroxyalkyl). In some embodiments, R^p at each occurrence is independently halogen, $-OH$, $-CN$, or C_{1-4} hydroxyalkyl. In some embodiments, R^p at each occurrence is independently halogen (such as fluoro) or $-OH$. In some embodiments, R^p is $-OH$.

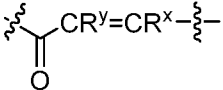
[00111] In some embodiments, p is 0, 1, 2, 3, 4, or 5. In some embodiments, p is 0, 1, or 2. In some embodiments, p is 1, and R^p is halogen, $-OH$, $-CN$, or C_{1-4} hydroxyalkyl. In some

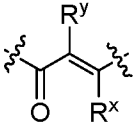


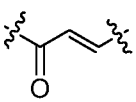
embodiments, p is 1, and R^p is $-OH$. In some embodiments, the ring containing R^p is

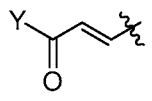
[00112] Q is a linker between Y and the ring moieties of formula (I). In some embodiments, Q is a bond. In some embodiments, Q is $-C(Q^1)-CR^y=CR^x-$, $-C(Q^2)-NH-N=CR^x-$, $-C(O)-NH-$, $-C(O)-Q^3-$, or $-SO_2-CR^y=CR^z-$, wherein the $C(Q^1)$, $C(Q^2)$, $C(O)$, or SO_2 group is attached to Y .

[00113] In some embodiments, Q is $-C(Q^1)-CR^y=CR^x-$. Q^1 is O, NH, or S, corresponding to a $C=O$, $C=NH$, or $C=S$ group, respectively, through which Q is attached to Y . In some

embodiments, Q is , wherein the $C(O)$ group is attached to Y . In some

embodiments, Q is , wherein in the $C(O)$ group is attached to Y . In some

embodiments, Q is , wherein in the $C(O)$ group is attached to Y . For example, in some

embodiments, the Y - Q group is .

[00114] In some embodiments, Q is $-C(Q^2)-NH-N=CR^x-$. Q^2 is O, NH, or S, corresponding to a $C=O$, $C=NH$, or $C=S$ group, respectively, through which Q is attached to Y . In some

embodiments, Q is , , , or ,

wherein the C=O, C=NH, or C=S group is attached to Y. In some embodiments, Q is

$$\begin{array}{c} \text{H} \\ | \\ \text{---} \text{N} - \text{N} = \text{CH} - \text{---} \\ || \\ \text{O} \end{array}, \quad \begin{array}{c} \text{H} \\ | \\ \text{---} \text{N} - \text{N} = \text{CH} - \text{---} \\ || \\ \text{NH} \end{array}, \text{ or } \begin{array}{c} \text{H} \\ | \\ \text{---} \text{N} - \text{N} = \text{CH} - \text{---} \\ || \\ \text{S} \end{array}, \text{ wherein the C=O, C=NH, or C=S}$$

group is attached to Y. For example, in some embodiments, the Y-Q group is



The chemical structure shows a group 'Y' connected to a carbonyl group (C=O). The carbonyl carbon is also bonded to an NH group. This NH group is part of a hydrazine-like chain: -NH-N=CH-CH₂-. The terminal CH₂ group is connected to a wavy line, indicating the point of attachment to the rest of the molecule.

$$\begin{array}{c} \text{NH} \\ \parallel \\ \text{Y}-\text{C} \\ | \\ \text{NH} \\ | \\ \text{N} \\ | \\ \text{C} \\ \diagup \quad \diagdown \\ \text{---} \quad \text{---} \end{array}, \text{ or } \begin{array}{c} \text{S} \\ \parallel \\ \text{Y}-\text{C} \\ | \\ \text{NH} \\ | \\ \text{N} \\ | \\ \text{C} \\ \diagup \quad \diagdown \\ \text{---} \quad \text{---} \end{array}$$

[00115] In some embodiments, the Y-Q group is Y-C(O)-NH-.

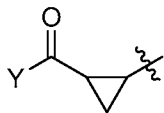
[00116] In some embodiments, Q is $-\text{SO}_2-\text{CR}^y=\text{CR}^z-$, wherein the SO_2 group is attached to Y. In some embodiments, Q is $-\text{SO}_2-\text{CH}=\text{CH}-$, wherein the SO_2 group is attached to Y. For example, in some embodiments, the Y-Q group is $\text{Y}-\text{SO}_2-\text{CH}=\text{CH}-$.

[00117] In some embodiments, Q is $-\text{C}(\text{O})-\text{Q}^3-$, wherein the $\text{C}(\text{O})$ group is attached to Y. In some embodiments, Q^3 is an optionally substituted cycloalkylene derived from a C_{3-10} ring system as disclosed herein. In some embodiments, Q^3 is an optionally substituted cycloalkylene which is monocyclic. In some embodiments, Q^3 is an optionally substituted cycloalkylene

derived from a C₃₋₁₀ monocyclic ring, such as , , , and .

In some embodiments, Q³ is unsubstituted. In some embodiments, Q³ is substituted with one or more substituent groups disclosed herein. In some embodiments, Q³ is substituted with one or more substituents selected from the group consisting of -OH, -NH₂, -NH(C₁₋₄alkyl), -N(C₁₋

alkyl)₂, halogen, C₁₋₄haloalkyl, and -CN. For example, in some embodiments, the Y-Q group is



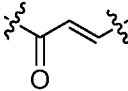
[00118] In some embodiments, R^x and R^y at each occurrence are independently hydrogen, alkyl (such as C₁₋₄alkyl), halogen, haloalkyl (such as C₁₋₄haloalkyl), or -CN. In some embodiments, R^x and R^y are independently hydrogen, C₁₋₄alkyl, halogen, C₁₋₄haloalkyl, or -CN. In some embodiments, at least one of R^x and R^y is C₁₋₄alkyl, halogen, C₁₋₄haloalkyl, or -CN. For example, in some embodiments, R^y is C₁₋₄alkyl, -CN, or halogen, and R^x is hydrogen. In some embodiments, R^x is C₁₋₄alkyl, -CN, or halogen, and R^y is hydrogen. In some embodiments, R^x and R^y are both hydrogen.

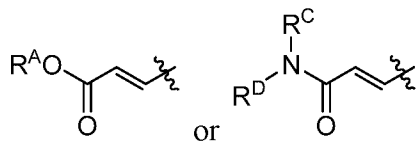
[00119] In some embodiments, Y is alkyl (such as C₁₋₁₀alkyl), -OR^A, -COOR^B, -N(R^C)(R^D), -CON(R^C)(R^D), -N(R^C)-OH, -NH-N(R^C)(R^D), or -CR^y=CR^x-CN.

[00120] In some embodiments, Q is bond and Y is -OR^A or CR^y=CR^x-CN. In some embodiment, Q is bond and Y is -OR^A.

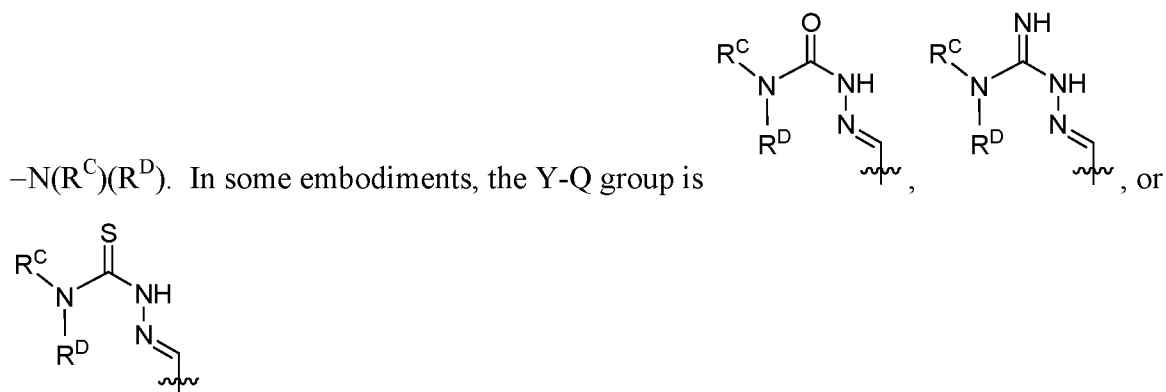
[00121] In some embodiment, Q is -C(Q¹)-CR^y=CR^x-, -C(Q²)-NH-N=CR^x-, -C(O)-NH-, -C(O)-Q³-, or -SO₂-CR^y=CR^z- as defined herein, and Y is alkyl (such as C₁₋₁₀alkyl), -OR^A, -COOR^B, -N(R^C)(R^D), -CON(R^C)(R^D), -N(R^C)-OH, or -NH-N(R^C)(R^D).

[00122] In some embodiments, Q is -C(Q¹)-CR^y=CR^x as defined herein, and Y is -OR^A, -N(R^C)(R^D), -CON(R^C)(R^D), -N(R^C)-OH, or -NH-N(R^C)(R^D). For example, in some

embodiments, Q is , the C(O) group being attached to Y, and Y is -OR^A, -N(R^C)(R^D), or -N(R^C)-OH, or -NH-N(R^C)(R^D). In some embodiments, the Y-Q group is

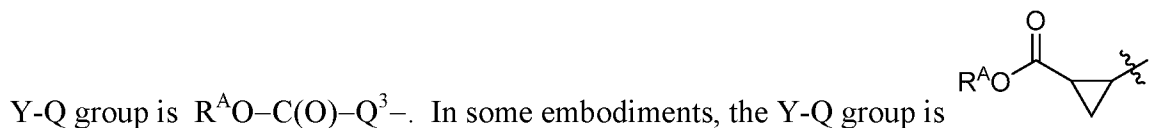


[00123] In some embodiments, Q is $-\text{C}(\text{Q}^2)-\text{NH}-\text{N}=\text{CR}^x-$ as defined herein, and Y is



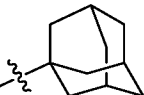
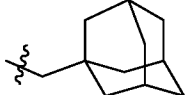
[00124] In some embodiments, Q is $-\text{C}(\text{O})-\text{NH}-$ as defined herein. In some embodiments, the Y-Q group is $\text{R}^{\text{B}}\text{OOC}-\text{C}(\text{O})-\text{NH}-$ or $(\text{R}^{\text{C}})(\text{R}^{\text{D}})\text{NC}(\text{O})-\text{C}(\text{O})-\text{NH}-$, wherein R^{B} , R^{C} , and R^{D} are as defined herein. In some embodiments, Q is $-\text{C}(\text{O})-\text{NH}-$ as defined herein, and Y is $-\text{COOR}^{\text{B}}$. In some embodiments, the Y-Q group is $\text{R}^{\text{B}}\text{OOC}-\text{C}(\text{O})-\text{NH}-$, wherein R^{B} is hydrogen or C_{1-10} alkyl. In some embodiments, the Y-Q group is $\text{HOOC}-\text{C}(\text{O})-\text{NH}-$.

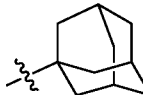
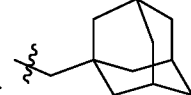
[00125] In some embodiments, Q is $-\text{C}(\text{O})-\text{Q}^3-$ as defined herein. In some embodiments, the



[00126] R^{A} , R^{B} , R^{C} , and R^{D} at each occurrence are independently selected from hydrogen, alkyl (such as C_{1-10} alkyl), cycloalkyl (such as C_{3-10} cycloalkyl), aryl (such as C_{6-12} aryl), heterocycle (such as C_{5-12} heterocycle), and heteroaryl (such as C_{5-12} heteroaryl), wherein the alkyl, cycloalkyl, aryl, heterocycle, and heteroaryl are each optionally substituted. In some embodiments, R^{A} , R^{B} , R^{C} , and R^{D} are unsubstituted. In some embodiments, each of R^{A} , R^{B} , R^{C} , and R^{D} are independently substituted with one or more substituents disclosed herein.

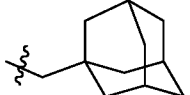
[00127] In some embodiments, R^{A} is an alkyl optionally substituted with one or more substituents selected from the group consisting of $-\text{OH}$, $-\text{NH}_2$, $-\text{NH}(\text{C}_{1-4}\text{alkyl})$, $-\text{N}(\text{C}_{1-4}\text{alkyl})_2$, halogen, haloalkyl, phenyl, and $-\text{NHCO}-\text{R}^{\text{Z}}$, wherein R^{Z} is $-\text{OC}_{1-4}\text{alkyl}$, cycloalkyl (such as C_{3-10} cycloalkyl), or $-\text{C}_{1-4}$ alkylene-cycloalkyl (such as $-\text{C}_{1-4}$ alkylene- C_{3-10} cycloalkyl). In some

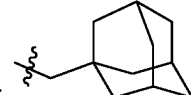
embodiments, R^Z is  or . In some embodiments, R^A is an alkyl

substituted with $-NHCO-R^Z$, and R^Z is R^Z is  or . In some embodiments, R^A is hydrogen, C_{1-10} alkyl, C_{1-10} alkylene-OH, C_{1-10} alkylene-NH₂, C_{1-10} alkylene-NH(C_{1-4} alkyl), C_{1-10} alkylene-N(C_{1-4} alkyl)₂, C_{1-10} alkyl substituted with 1, 2, 3, or 4 halogen, C_{1-10} alkyl substituted with a phenyl, C_{1-10} alkyl substituted with $-NHCO-R^Z$, or C_{1-10} alkyl substituted with -OH and at least one halogen, wherein R^Z is a $-OC_{1-4}$ alkyl, C_{3-10} cycloalkyl, or $-C_{1-4}$ alkylene- C_{3-10} cycloalkyl.

[00128] In some embodiments, Q is a bond, Y is $-OR^A$, and R^A is an alkyl (such as C_{1-10} alkyl) substituted with $-NHCO-R^Z$. In some embodiments, Q is a bond, Y is $-OR^A$, and R^A is C_{1-10} alkyl substituted with $-NHCO-R^Z$, wherein R^Z is C_{3-10} cycloalkyl or $-C_{1-4}$ alkylene- C_{3-10} cycloalkyl

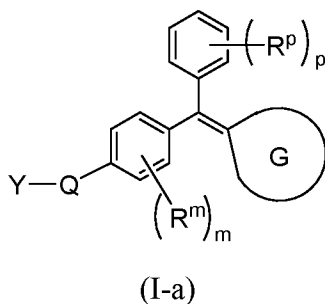
[00129] In some embodiments, R^C is an alkyl optionally substituted with one or more substituents selected from the group consisting of -OH, -NH₂, -NH(C_{1-4} alkyl), -N(C_{1-4} alkyl)₂, halogen, haloalkyl, phenyl, and $-NHCO-R^Z$, wherein R^Z is $-OC_{1-4}$ alkyl, cycloalkyl (such as C_{3-10} cycloalkyl), or $-C_{1-4}$ alkylene-cycloalkyl (such as $-C_{1-4}$ alkylene- C_{3-10} cycloalkyl). In some

embodiments, R^Z is  or . In some embodiments, R^C is an alkyl

substituted with $-NHCO-R^Z$, and R^Z is R^Z is  or . In some embodiments, R^C is hydrogen, C_{1-10} alkyl, C_{1-10} alkylene-OH, C_{1-10} alkylene-NH₂, C_{1-10} alkylene-NH(C_{1-4} alkyl), C_{1-10} alkylene-N(C_{1-4} alkyl)₂, C_{1-10} alkyl substituted with 1, 2, 3, or 4 halogen, C_{1-10} alkyl substituted with a phenyl, C_{1-10} alkyl substituted with $-NHCO-R^Z$, or C_{1-10} alkyl substituted with -OH and at least one halogen, wherein R^Z is a $-OC_{1-4}$ alkyl, C_{3-10} cycloalkyl, or $-C_{1-4}$ alkylene- C_{3-10} cycloalkyl.

[00130] In some embodiments, R^D is hydrogen, C_{1-4} alkyl, or C_{1-4} hydroxyalkyl.

[00131] In some embodiments, formula (I) is formula (I-a)

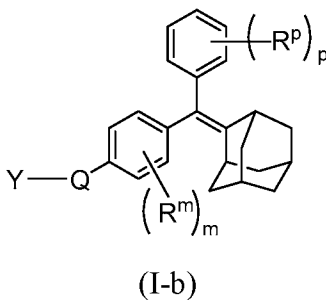


wherein

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

G, Q, Y, R^p, R^m, and p are as defined herein.

[00132] In some embodiments, formula (I) is formula (I-b)

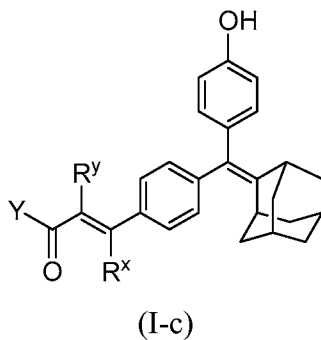


wherein

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

Q, Y, R^p, R^m, and p are as defined herein.

[00133] In some embodiments, formula (I) is formula (I-c)



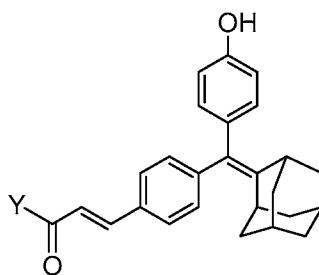
wherein

Y is alkyl, $-OR^A$, or $-N(R^C)(R^D)$; and

R^x , R^y , R^A , R^C , and R^D are as defined herein.

[00134] In some embodiments, formula (I) is formula (I-c), wherein R^x and R^y are independently hydrogen, C_{1-4} alkyl, halogen, or $-CN$. In some embodiments, formula (I) is formula (I-c), wherein R^y is C_{1-4} alkyl, $-CN$, or halogen, and R^x is hydrogen. In some embodiments, R^x is C_{1-4} alkyl, $-CN$, or halogen, and R^y is hydrogen. In some embodiments, R^x and R^y are both hydrogen.

[00135] In some embodiments, formula (I-c) is formula (I-c-1),



(I-c-1)

wherein

Y is alkyl, $-OR^A$, or $-N(R^C)(R^D)$; and

R^A , R^C , and R^D are as defined herein.

[00136] In some embodiments, formula (I-c) is formula (I-c-1), wherein Y is $-OR^A$, R^A is hydrogen, C_{1-10} alkyl optionally substituted with one or more substituents selected from the group consisting of $-OH$, $-NH_2$, $-NH(C_1-C_4 \text{ alkyl})$, $-N(C_1-C_4 \text{ alkyl})_2$, halogen, phenyl, and $-NHCO-R^Z$, wherein R^Z is C_{3-10} cycloalkyl or $-C_{1-4}$ alkylene- C_{3-10} cycloalkyl.

[00137] In some embodiments, formula (I-c) is formula (I-c-1), wherein Y is $-N(R^C)(R^D)$, R^C is hydrogen, C_{1-10} alkyl optionally substituted with one or more substituents selected from the group consisting of $-OH$, $-NH_2$, $-NH(C_1-C_4 \text{ alkyl})$, $-N(C_1-C_4 \text{ alkyl})_2$, halogen, phenyl, and

$-\text{NHCO}-\text{R}^Z$, wherein R^Z is C_{3-10} cycloalkyl or $-\text{C}_{1-4}$ alkylene- C_{3-10} cycloalkyl, and R^D is hydrogen, C_{1-4} alkyl, or C_{1-4} hydroxyalkyl

[00138] In some embodiments, formula (I-c) is formula (I-c-1), wherein

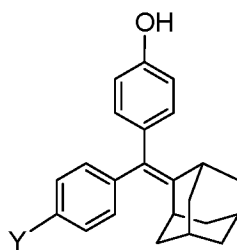
Y is $-\text{OR}^A$ or $-\text{N}(\text{R}^C)(\text{R}^D)$;

R^A and R^C are hydrogen, C_{1-10} alkyl, C_{1-10} alkylene- OH , C_{1-10} alkylene- NH_2 , C_{1-10} alkylene- $\text{NH}(\text{C}_{1-4}$ alkyl), C_{1-10} alkylene- $\text{N}(\text{C}_{1-4}$ alkyl) $_2$, C_{1-10} alkyl substituted with 1, 2, 3, or 4 halogen, C_{1-10} alkyl substituted with a phenyl, C_{1-10} alkyl substituted with $-\text{NHCO}-\text{R}^Z$, or C_{1-10} alkyl substituted with $-\text{OH}$ and at least one halogen;

R^D is hydrogen, C_{1-4} alkyl, or C_{1-4} hydroxyalkyl; and

R^Z is a $-\text{OC}_{1-4}$ alkyl, C_{3-10} cycloalkyl, or $-\text{C}_{1-4}$ alkylene- C_{3-10} cycloalkyl.

[00139] In some embodiments, formula (I) is formula (I-d)



(I-d)

wherein

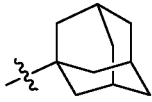
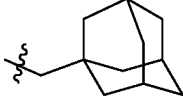
Y is $-\text{OR}^A$ or $-\text{CR}^y=\text{CR}^x-\text{CN}$; and

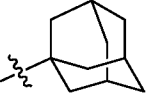
R^A , R^x , and R^y are as defined herein.

[00140] In some embodiments, formula (I) is formula (I-d), wherein Y is $-\text{OR}^A$ or $-\text{CR}^y=\text{CR}^x-\text{CN}$; R^A is C_{1-10} alkyl substituted with $-\text{NHCO}-\text{R}^Z$; R^x and R^y is each independently hydrogen, C_{1-4} alkyl, halogen, C_{1-4} haloalkyl, or $-\text{CN}$; and R^Z is C_{3-10} cycloalkyl or $-\text{C}_{1-4}$ alkylene- C_{3-10} cycloalkyl.

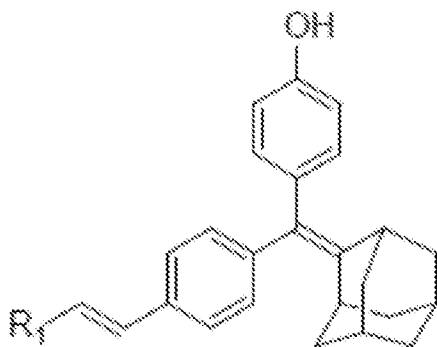
[00141] In some embodiments, formula (I) is formula (I-d), wherein Y is $-\text{OR}^A$, and R^A is C_{1-10} alkyl substituted with $-\text{NHCO}-\text{R}^Z$, wherein R^Z is C_{3-10} cycloalkyl or $-\text{C}_{1-4}$ alkylene- C_{3-10} cycloalkyl.

cycloalkyl. In some embodiments, formula (I) is formula (I-d), wherein Y is $-\text{OR}^A$, and R^A is

C_{1-10} alkyl substituted with $-\text{NHCO}-\text{R}^Z$, wherein R^Z is  or . In some embodiments, formula (I) is formula (I-d), wherein Y is $-\text{OR}^A$, and R^A is an C_{1-10} alkyl

substituted with $-\text{NHCO}-\text{R}^Z$, wherein R^Z is .

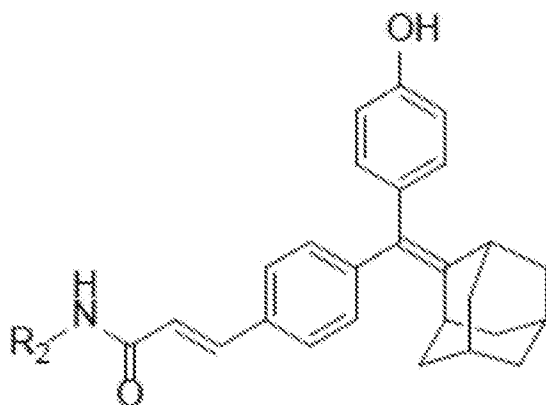
[00142] In some embodiments, provided is a compound of structure (i) or a composition comprising structure (i):



(i),

[00143] wherein R_1 is selected from $-\text{CO}(\text{CH}_2)_4\text{CH}_3$, $-\text{COOCH}_3$, $-\text{COOCH}_2\text{CH}_3$, $\text{COO}(\text{CH}_2)_3\text{CH}_3$, $-\text{COO}(\text{CH}_2)_5\text{CH}(\text{CH}_3)_2$, $-\text{COO}(\text{CH}_2)_2\text{OH}$, $-\text{COO}(\text{CH}_2)_4\text{OH}$, $-\text{CN}$, $-\text{SO}_2\text{NH}(\text{CH}_2)_2\text{CH}_3$, $-\text{COO}(\text{CH}_2)_3\text{OH}$, $-\text{CO}_2\text{H}$ and $-\text{CONH}_2$.

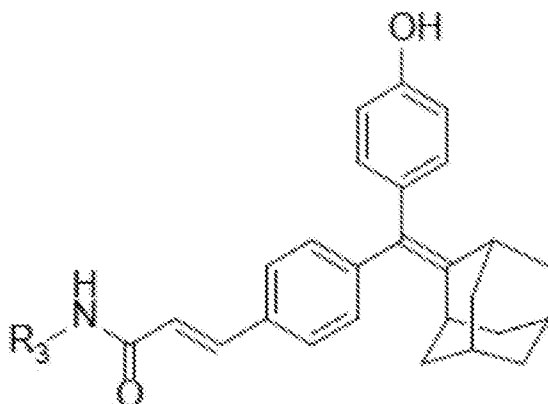
[00144] In some embodiments, provided is a compound of structure (ii) or a composition comprising structure (ii):



(ii),

[00145] wherein R_2 is selected from $-(CH_2)_2CH_3$, $-(CH_2)_3CH_3$, $-(CH_2)_4CH_3$, $-(CH_2)_2OH$, $-(CH_2)_3OH$, $-(CH_2)_4OH$, $-(CH_2)_5OH$, $-(CH_2)CF_3$, $-(CH_2)_2N(CH_3)_2$, $-(CH_2)_2NHBoc$, $-(CH_2)_3NHBoc$, and $-(CH_2)_4NHBoc$.

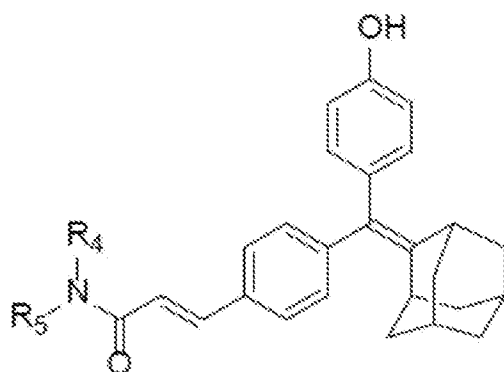
[00146] In some embodiments, provided is a compound of structure (iii) or a composition comprising structure (iii):



(iii),

[00147] wherein R_3 is selected from $-(CH_2)_2NH_2$, $-(CH_2)_3NH_2$, and $-(CH_2)_4NH_2$.

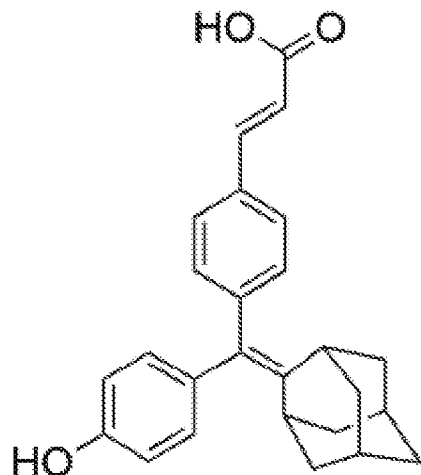
[00148] In some embodiments, provided is a compound of structure (iv) or a composition comprising structure (iv):



(iv),

[00149] wherein R_4 is selected from $-CH_3$ and $-(CH_2)_2OH$, and R_5 is selected from $-(CH_2)_2OH$ and $-(CH_2)_3CH_3$.

[00150] In some embodiments, provided is a compound of structure (v) or a the composition comprising structure (v):



(v).

[00151] In some embodiments, disclosed is a compound selected from the group consisting of:

(E)-3-(4-(((1r,3r,5R,7S)-Adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)acrylic acid;

(E)-1-(4-(((1r,3r,5R,7S)-Adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)oct-1-en-3-one;

Methyl (E)-3-(4-(((1r,3r,5R,7S)-Adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)acrylate;

Ethyl(E)-3-(4-(((1r,3r,5R,7S)-Adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)acrylate;

Butyl (E)-3-(4-(((1r,3r,5R,7S)-Adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)acrylate;

6-Methylheptyl (E)-3-(4-(((1r,3r,5R,7S)-Adamantan-2-ylidene)(4-hydroxyphenyl)methyl) phenyl)acrylate;

2-Hydroxyethyl (E)-3-(4-(((1r,3r,5R,7S)-Adamantan-2-ylidene)(4-hydroxyphenyl)methyl) phenyl)acrylate;

3-Hydroxypropyl (E)-3-(4-(((1r,3r,5R,7S)-Adamantan-2-ylidene)(4-hydroxyphenyl)methyl) phenyl)acrylate;

4-Hydroxybutyl (E)-3-(4-(((1r,3r,5R,7S)-Adamantan-2-ylidene)(4-hydroxyphenyl)methyl) phenyl)acrylate;

(E)-3-(4-(((1r,3r,5R,7S)-Adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)acrylonitrile;

(E)-2-(4-(((1r,3r,5R,7S)-Adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)-N-propylethene-1-sulfonamide;

(E)-3-(4-(((1r,3r,5R,7S)-Adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)acrylamide;

(E)-3-(4-(((1r,3r,5R,7S)-Adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)-N-propylacrylamide;

(E)-3-(4-(((1r,3r,5R,7S)-Adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)-N-butylacrylamide;

(E)-3-(4-(((1r,3r,5R,7S)-Adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)-N-pentylacrylamide;

(E)-3-(4-(((1r,3r,5R,7S)-Adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)-N-(2-hydroxyethyl)acrylamide;

(E)-3-(4-(((1r,3r,5R,7S)-Adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)-N-(3-hydroxypropyl)acrylamide

(E)-3-(4-(((1r,3r,5R,7S)-Adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)-N-(4-hydroxybutyl)acrylamide

(E)-3-(4-(((1r,3r,5R,7S)-Adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)-N-(5-hydroxypentyl)acrylamide

(E)-3-(4-(((1r,3r,5R,7S)-Adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)-N-(2-aminoethyl)acrylamide

(E)-3-(4-(((1r,3r,5R,7S)-Adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)-N-(3-aminopropyl)acrylamide

(E)-3-(4-(((1r,3r,5R,7S)-Adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)-N-(4-aminobutyl)acrylamide

(E)-3-(4-(((1r,3r,5R,7S)-Adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)-N-(2,2,2-trifluoroethyl)acrylamide

(E)-3-(4-(((1r,3r,5R,7S)-Adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)-N-butyl-N-methylacrylamide

(E)-3-(4-(((1r,3r,5R,7S)-Adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)-N-(2-hydroxyethyl)-N-methylacrylamide

(E)-3-(4-(((1r,3r,5R,7S)-Adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)-N,N-bis(2-hydroxyethyl)acrylamide

(E)-3-(4-(((1r,3r,5R,7S)-Adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)-N-(2-(dimethylamino)ethyl)acrylamide

(3r,5r,7r)-N-(3-(4-(((1r,3r,5R,7S)-adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenoxy)propyl)adamantane-1-carboxamide

(E)-3-(4-(((1r,3r,5R,7S)-adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)-2-methylacrylic acid

(E)-3-(4-(((1r,3r,5R,7S)-adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)-2-cyanoacrylic acid

(Z)-3-(4-(((1r,3r,5R,7S)-adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)-2-chloroacrylic acid

(Z)-3-(4-(((1r,3r,5R,7S)-adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)-2-fluoroacrylic acid

(E)-3-(4-(((1r,3r,5R,7S)-adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)but-2-enoic acid

(E)-3-(4-(((1r,3r,5R,7S)-adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)-N-hydroxyacrylamide

(E)-3-(4-(((1r,3r,5R,7S)-adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)-N-hydroxy-N-methylacrylamide

(E)-3-(4-(((1r,3r,5R,7S)-adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)-N-hydroxy-N-isopropylacrylamide

(E)-3-(4-(((1r,3r,5R,7S)-adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)acrylohydrazide

(E)-3-(4-(((1r,3r,5R,7S)-adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)-N-(2,2-difluoro-3-hydroxypropyl)acrylamide

(E)-N-((3s,5s,7s)-adamantan-1-yl)-3-(4-(((1r,3r,5R,7S)-adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)acrylamide

(E)-N-((3r,5r,7r)-adamantan-1-yl)methyl-3-(4-(((1r,3r,5R,7S)-adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)acrylamide

(E)-3-(4-(((1r,3r,5R,7S)-adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)-N-benzylacrylamide

(E)-N-(4-(2-((3r,5r,7r)-adamantan-1-yl)acetamido)butyl)-3-(4-(((1r,3r,5R,7S)-adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)acrylamide

(E)-3-(4-(((1r,3r,5R,7S)-adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)-N-butylprop-2-enethioamide

2-((E)-4-(((1r,3r,5R,7S)-adamantan-2-ylidene)(4-hydroxyphenyl)methyl)benzylidene)hydrazine-1-carboxamide

2-((E)-4-(((1r,3r,5R,7S)-adamantan-2-ylidene)(4-hydroxyphenyl)methyl)benzylidene)hydrazine-1-carbothioamide

N'-((E)-4-(((1r,3r,5R,7S)-adamantan-2-ylidene)(4-hydroxyphenyl)methyl)benzylidene)hydrazinecarbohydrazide

2-((E)-4-(((1r,3r,5R,7S)-adamantan-2-ylidene)(4-hydroxyphenyl)methyl)benzylidene)hydrazine-1-carboximidamide

N'-((E)-4-(((1r,3r,5R,7S)-adamantan-2-ylidene)(4-hydroxyphenyl)methyl)benzylidene)hydrazinecarbothiohydrazide

(E)-3-(4-(((1r,3r,5R,7S)-adamantan-2-ylidene)(4-hydroxyphenyl)methyl)-3-fluorophenyl) acrylic acid

(E)-3-(4-(((1r,3r,5R,7S)-adamantan-2-ylidene)(4-hydroxyphenyl)methyl)-3,5-difluorophenyl) acrylic acid

(E)-3-(4-(((1r,3r,5R,7S)-adamantan-2-ylidene)(4-hydroxyphenyl)methyl)-2-fluorophenyl) acrylic acid

(E)-3-(4-(((1r,3r,5R,7S)-adamantan-2-ylidene)(4-hydroxyphenyl)methyl)-2-(trifluoromethyl) phenyl)acrylic acid

(Z)-3-(4-(((1r,3r,5R,7S)-adamantan-2-ylidene)(4-hydroxyphenyl)methyl)-3-fluorophenyl)-2-fluoroacrylic acid

(E)-3-(5-(((1r,3r,5R,7S)-adamantan-2-ylidene)(4-hydroxyphenyl)methyl)pyridin-2-yl)acrylic acid

(E)-3-(4-(((1r,3r,5R,7S)-adamantan-2-ylidene)(phenyl)methyl)phenyl)acrylic acid

(E)-3-(4-(((1r,3r,5R,7S)-adamantan-2-ylidene)(phenyl)methyl)phenyl)-N-(3-hydroxypropyl)acrylamide

(E)-3-(4-(((1r,3r,5R,7S)-adamantan-2-ylidene)(4-fluorophenyl)methyl)phenyl)acrylic acid

(E)-3-(4-(((1r,3r,5R,7S)-adamantan-2-ylidene)(4-fluorophenyl)methyl)phenyl)-N-(3-hydroxypropyl)acrylamide

(E)-3-(4-((Z)-(4-hydroxyphenyl)((3aS,4R,7R,7aS)-octahydro-5H-4,7-methanoinden-5-ylidene)methyl)phenyl)acrylic acid;

(E)-3-(4-((4-hydroxyphenyl)(4-methylcyclohexylidene)methyl)phenyl)acrylic acid;

2-((4-(((1r,3r,5R,7S)-adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)amino)-2-oxoacetic acid;

trans 2-(4-((Z)-((5S,7S)-adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)cyclopropane-1-carboxylic acid; and

cis 2-(4-((Z)-((5S,7S)-adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)cyclopropane-1-carboxylic acid,
or a pharmaceutically acceptable salt thereof.

[00152] In another embodiment, the compounds include isotope-labelled forms. An isotope-labelled form of a compound is identical to the compound apart from the fact that one or more atoms of the compound have been replaced by an atom or atoms having an atomic mass or mass number which differs from the atomic mass or mass number of the atom which usually occurs in greater natural abundance. Examples of isotopes which are readily commercially available and which can be incorporated into a compound by well-known methods include isotopes of hydrogen, carbon, nitrogen, oxygen, fluorine and chlorine, for example ^2H , ^3H , ^{13}C , ^{14}C , ^{15}N , ^{18}O , ^{17}O , ^{18}F and ^{36}Cl .

3. Methods of Use

[00153] Overview

[00154] Because overcoming the development of resistance to endocrine therapies in breast cancers is a large unmet clinical need, a broad range of side chain structures in antiestrogens in a search for new compounds were explored that might have high potency and efficacy as antiproliferative agents and possibly as ER α downregulators. A structurally and stereochemically simple, rigid core unit, derived from the cyclofenil class of ER ligands, but having the bridged tricyclic adamantane system in place of the cyclohexane ring of cyclofenil (19) was used to expedite the synthesis. This adamantane-based ligand core and its evolution are shown in FIG. 1, together with other compounds for comparison. In place of the acrylic acid side chain, a considerable number and variety of carboxylate analogs (ketones, esters, and amides) were explored. The side chain design was influenced in part by a crystal structure of GW-5638 bound to the ER LBD showing that the acidic side chain interaction with the N-terminus of h12 was assisted by a structural water molecule (FIG. 2) (20). In other systems, inhibitors designed to include a polar atom that replaced a structural water had particularly high affinity (21-23). Thus, to explore this potential opportunity, oxygen or nitrogen atoms were included in the side chain of in some of the compounds.

[00155] For each new compound ER α binding affinity, and efficacy in suppressing proliferation of ER-positive breast cancer cells and in downregulating ER α levels were evaluated. The potency of the most efficacious compounds in these assays was explored in ER target gene regulation. In the process, some rather striking structure-activity relationships (SARs) were uncovered whereby small structural changes resulted in large changes in activity, and in a number of cases, the inclusion on a polar atom at the terminus of the side chain gave a substantial boost to binding affinity. With this set of compounds, comparisons of the degree to which antiproliferative activity is related to ER α -downregulating activity were made. The best members of this series are as efficacious as fulvestrant in suppressing cell proliferation and nearly as complete in downregulating ER α levels, and they have low nanomolar potencies for both activities.

[00156] In this disclosure, structure-activity relationships in adamantyl antiestrogens having variations on the acrylic acid side chain were explored. This side chain, which is clearly an important functional element in conveying the effectiveness of ER antagonism, has survived over several decades in structurally unaltered form in antiestrogens from GSK (11, 12), Genentech (13), AstraZeneca (14, 31), and other pharma companies (32). In contrast, while many variations have been made in the structures of their core elements (FIG. 1), only limited alterations have been made in the acrylate side chain and none have been explored in a systematic fashion (11, 33, 34). Starting with a structurally simple biaryl adamantyl core structure, which provides very high ER α binding affinity and stereochemical simplicity for ease of synthesis, a considerable number of compounds having systematic acrylic acid side chain variants were surveyed. These were evaluated for their ER α binding affinities, and nearly all proved to have K_i values in the single-digit nanomolar range or below. All compounds were then assayed for their antiproliferative and ER α downregulating (SERD) *efficacies*, and in several cases, relatively small structural changes resulted in marked alterations in efficacies and potencies. In particular, extension of the acrylic acid side chain as secondary amides provided a favorable combination of high affinity, high efficacy and high potency in suppressing E2-driven proliferation of MCF-7 cells and in downregulating ER α levels. Closely related tertiary amides, however, were much less efficacious. Several of those compounds having promising antiproliferative efficacies were evaluated further in terms of their *potencies* and gene-regulating activities.

[00157] *Relationship Between Suppression of MCF-7 Proliferation and ER α Downregulation.*

There has been considerable discussion of how antagonism of breast cancer proliferation may be related to or indeed dependent upon the downregulation of the level of ER α (i.e., SERD activity) (35). ER α downregulation does not predict antagonism of proliferation because agonists such as E2, and herein the acrylonitrile compound **14**, are strong ER α downregulators and are either stimulatory or essentially neutral on proliferation. It is notable as well that some SERMs, such as tamoxifen and raloxifene, are effective in suppressing proliferation yet have no effect on ER α level or can even stabilize the receptor and upregulate cellular ER α levels, as observed in FIG. 7B for tamoxifen and as observed by others.

[00158] When ER α is occupied by a SERM or a SERD, its overall effect on gene expression is not only a suppression of pro-proliferative and anti-apoptotic activity but also an upregulation of anti-proliferative and pro-apoptotic factors (36-38). The potential benefits of such effects would be lost in the complete absence of ER α (39, 40) and might, in fact, engender the development of more aggressive forms of breast cancer that are independent of ER α or fully resistant to ER α -targeted endocrine therapy agents (1). Hence, while the importance of ER downregulation for effective antiestrogenic activity is far from being settled, it would appear illogical to discard interest in a particularly potent and complete antiproliferative antiestrogen just because it may not be fully efficacious in reducing cellular ER α levels.

[00159] *Partitioning the Functional Characteristics of Antiestrogens: The Core-Side Chain Paradigm and Structural Features of the Acrylate Side Chain.* The approach taken in this disclosure was predicated on the concept that an antiestrogen can be thought of as a core-side chain construct, each part of which operates rather independently: the core provides the binding energy and the side chain the functional regulation, with side chains being essentially interchangeable among various cores (10). The interchangeability of antiestrogen side chains onto different core elements is certainly well illustrated in the literature, and while it may not apply strictly in all cases (41) (particularly with compounds having more bulky cores and altogether lacking side chains, which are considered indirect antagonists, 42-45), it supports the selection of a simplified adamantyl core element (19). This core facilitated an expeditious search for side chains that might afford more effective and potent antiproliferative and ER α downregulating activities, the expectation being that once found, these side chains would be

transferrable to other, possibly more complex ligand cores. The core element, of course, contributes to the drug-like attributes of the overall molecule that defines its pharmacokinetic behavior, such as oral bioavailability.

[00160] The choice of the acrylic acid side chain as the starting point for side chain exploration was first based on the recognition that the rigidity of the double bond is important in its ER α antagonizing function. In an earlier study, a variety of other acid side chains on a different core element were explored, and although many of them bound to ER α with excellent affinity, only those bearing the rigid acrylic acid unit attached directly to the phenyl proved to be effective antagonists and ER downregulators (46). Some X-ray structures of these compounds showed that those having more flexible side chains were able to bend the side chain around h12 in the LBD without ejecting it from the agonist conformation, whereas the rigid acrylate ejected h12 from the agonist conformation and furthermore by interaction with its N-terminus seemed to stabilize it in a position where it blocked access to the coactivator binding groove. This study was limited to groups that maintained side chain rigidity through direct attachment of the double bond to the ring.

[00161] *Possible Role of a Structural Water Molecule and Conformational Preferences of Amides.* A crystal structure of GW-5638 bound to the ER α LBD showed a structural water molecule linking the carboxylic acid group to the N-terminus of h12 when it was positioned to obstruct coactivator binding (FIG. 2) (20), and within some the compounds of this disclosure a terminal polar atoms in the side chains was included to explore they might replace this water molecule. In other systems, replacement of a structural water has resulted in a large jump in ligand potency or binding affinity, presumed to be due to the gain in entropy in releasing the water from the bound state (21-23). While no direct structural evidence shows such a replacement, in a number of amides and esters, substitution of a terminal CH₃ group with an OH or NH₂ group caused a systematic two to five-fold increase in binding affinity (FIG. 3). It was not apparent, however, that this increase in affinity translated into greater antiproliferative or ER α -downregulating efficacies or potencies, nor did binding affinity in general translate into measures of efficacy or potency.

[00162] A striking feature of members of the amide class is that the secondary amides are much more efficacious than the tertiary amides, particularly in terms of their antiproliferative activity. While it is possible that adding a second alkyl group on the nitrogen might cause steric hindrance that diminishes affinity and efficacy, there is certainly no consistent effect of the second substituent on binding affinity ($2^\circ 18 \sim 3^\circ 28$; but $2^\circ 20 < 3^\circ (29 \ll 30)$). Both esters and secondary amides are notable in having an extended (*Z* or *s-cis*) conformation, which is energetically favored due to $n-\sigma^*$ or $\sigma-\sigma^*$ π overlap, respectively (47, 48), that would project the single substituent directly outward, away from the ring and presumably in a functional direction, toward h12 (FIG. 9). The two possible geometries of tertiary amides, on the other hand, are of essentially equal energy, so the smaller group could be extended.

[00163] Studies included in this disclosure provide new insights about mutant ERs that drive hormone-independent constitutive activity. Of note, the nature of the mutant ER (D538G or Y537S), the cell background (T47D or MCF-7), and the chemical structure of the antiestrogens (K-07 vs. K-09 vs. K-62 vs. Fulv) all affected response to AE ligands. Thus, these mutant ERs showed differential responsiveness to chemically distinct AEs with the mutant Y537S-ER being more resistant to the AEs compared to the mutant D538G receptor and requiring higher compound concentrations for growth suppression. For other key regulators in breast cancer, such as EZH2, resistance to EZH2 inhibitors is associated with various mutations in EZH2 that also differ in their sensitivities to different inhibitors. In these studies, the cell background was also important. Thus, in T47D cells, Y537S elicited a more endocrine-resistant phenotype, whereas the Y537S and D538G mutant ERs were more similar to each other in their response to antiestrogens in the MCF-7 cell background. This suggests that cell context, including alterations in genomic and cell signaling pathways, may work with ERs to confer different cell behaviors and responsiveness or resistance to treatment with different endocrine agents. This is not surprising, since it is known for example, that among other differences, MCF-7 and T47D cells carry different mutant forms of PI3K. Also, GATA3, an important factor for ER activity, is often mutated in breast cancers and could influence responsiveness of WT and mutant ERs to antiestrogens.

[00164] The studies herein also document that the mutant ER allele fraction is crucial in the extent of endocrine treatment resistance observed. In fact, T47D cells with both alleles

homozygous for the mutant ER showed greater resistance to antiestrogens than did cells with 50% mutant and 50% wild type ER. Notably however, even 50% mutant ER conferred a dominant antiestrogen resistant phenotype. This is of importance because metastatic breast cancers usually contain a mixture of both mutant and wild type ERs.

[00165] It is now recognized that approximately 40% of ER-positive breast cancers that become resistant to endocrine treatment and recur contain ER mutations. Most of these mutations are found in the C-terminal transactivation domain in the ligand binding domain of the ER and result in changes at amino acids Y537, D538, L536, P535, or V534 and also at E380. Several large analyses have shown that the two most common mutations are at Y537 (changing Y to S, but also less commonly to N or C) and at D538 (always changed to G). There are single nucleotide changes in the codons for these amino acids resulting in the one amino acid alteration. X-ray crystallography and molecular modeling have shown that Y537 and D538 are present at key locations in the activation function-2 region of the ligand binding domain that determines the three-dimensional structure of helix 12 of the ER that is key in interactions with co-activators. These changes in ER structure result in ligand-independent interaction with co-activators that is normally seen in wild type receptor only in the presence of estrogenic hormones. Notably, this disclosure shows that these changes in ER also reduce the receptor's affinity for binding of antiestrogen ligands. This reduced binding affinity likely contributes to the relative resistance of these ER mutant cells to antiestrogens. However, other factors are also involved since Y537S-ER was always more resistant to suppressive effects of ligands compared to D538G-ER.

[00166] When breast cancer patients become resistant to treatment with tamoxifen or aromatase inhibitors, second line treatment with Fulvestrant is often used. However, Fulvestrant is not orally available so that large volumes of Fulvestrant are administered intramuscularly, which can be painful and is not liked by many patients. Therefore, there has been considerable effort directed toward the development of new orally active antiestrogens for treatment of these recurrent, usually metastatic, breast cancers. Recently, two orally available antiestrogens have been reported, AZD9496 from Astra Zeneca and GDC-0810 from Genentech/Seragon. While effective, each is not fully optimal, and has some troubling side effects that may limit their clinical utility. AZD9496 has shown some liver toxicity and GDC-0810 causes gastrointestinal problems including diarrhea in about one- third of patients. RAD-0910 shows promise but

clinical trials are at an earlier stage. Thus, there is an unmet need for orally active antiestrogens with an improved clinical profile and reduced side effects.

[00167] Because clinical studies have shown that patients with recurrent ER-positive breast cancer can respond to second and often third-line endocrine treatments, having a toolkit of new antiestrogens of different chemical classes should increase the beneficial options for such patients. It could bring therapeutic advances and result in inhibitors better matched for effectiveness in subsets of patients with breast tumors carrying differing ER mutations. Of interest, different inhibitors of the histone methyl transferase EZH2 show differential effectiveness in cells and non-small cell lung cancers carrying different activating EZH2 mutations.

[00168] Methods

[00169] In one aspect, one or more compounds of the present invention, or pharmaceutically acceptable salts thereof, or a pharmaceutical composition as described herein, can be used to inhibit the growth of a cell. In an embodiment, the cell is identified as having an estrogen receptor that mediates a growth characteristic of the cell. Growth of a cell can be inhibited by contacting the cell with an effective amount of at least one of the compounds described herein, or pharmaceutically acceptable salts thereof, or a pharmaceutical composition as described elsewhere herein. Such contacting of the one or more compounds, or pharmaceutically acceptable salts thereof, can take place in various ways and locations, including without limitation away from a living subject (e.g., in a laboratory, diagnostic and/or analytical setting) or in proximity to a living subject (e.g., within or on an exterior portion of an animal, e.g., a human).

[00170] Also disclosed are methods of using the disclosed compounds and compositions to treat a disease or condition that is estrogen receptor dependent and/or estrogen receptor mediated and administering to said subject an effective amount of one or more compounds of the present invention, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition, as described elsewhere herein. Another embodiment provides a use of one or more compounds of the present invention, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition (as described elsewhere herein), in the manufacture of a medicament for the

treatment of a disease or condition that is estrogen receptor alpha dependent and/or estrogen receptor alpha mediated.

[00171] In some embodiments, a method of treating or preventing breast cancer in a subject is provided, the method comprising administering to a subject a therapeutically effective amount of a compound or composition of formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as described herein. In some embodiments, the breast cancer is primary, metastatic, or recurrent breast cancer.

[00172] In some embodiments, provided is a method of preventing breast cancer recurrence in a subject with prior breast cancer, the method comprising administering to a subject a therapeutically effective amount of a compound or composition of formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as described herein.

[00173] In some embodiments, provided is a method of inhibiting or slowing the growth of estrogen receptor-positive, endocrine therapy-sensitive tumors or endocrine therapy resistant tumors driven by active estrogen receptors in a subject, the method comprising administering to a subject a therapeutically effective amount of a compound or composition of formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as described herein.

[00174] In some embodiments, the compounds and pharmaceutical compositions as disclosed herein may be used for treating or preventing breast cancer or inhibiting the growth of tumors as disclosed herein, wherein the tumor is driven by wild type, constitutively active estrogen receptors, and combinations thereof.

[00175] The compounds of the present invention have several potential benefits as therapeutic drugs for treating or ameliorating diseases or conditions that are estrogen receptor alpha dependent and/or estrogen receptor alpha mediated. Compounds of the invention show ability to downregulate ER α with robust correlation with suppression of cell proliferation. Among most of the compounds disclosed herein, there was reasonable overall correlation between the maximum level of proliferation suppression and ER α downregulation; this is evident from the similar shape and level of the cell proliferation and ER α level lines in the star plots (FIG. 4B& 4C). There are, however, some compounds more efficacious ER α downregulators than antiproliferative

compounds, such as the esters **7** and **10** (FIG. 4A) and the primary amide **16** (FIG. 4B). This is indicated by the line for cell proliferation (solid) being substantially outside of the line for ER α level (dashed). In fact, if only the three least antiproliferative compounds (**7**, **10**, and **14**) are eliminated, there is a statistically robust correlation between suppression of cell proliferation and ER α downregulation (FIG. 8).

[00176] The compounds of the present invention have antiproliferative and ER α downregulating efficacies comparable to that of fulvestrant. However, unlike fulvestrant the compounds show good pharmacokinetic properties by either subcutaneous or oral routes. The compounds are orally effective antiestrogens, and preliminary studies had no impact on overall animal health suggesting the compounds are generally safe and effective. The pharmacokinetic properties of the antiestrogens proved to be very important in their tumor suppressive efficacies *in vivo*. K-07 displayed the best pharmacokinetic properties by either subcutaneous or oral routes. It was also the most effective growth inhibitor in breast tumor xenografts *in vivo*, despite the fact that other antiestrogens showed good anti-proliferative and target gene inhibitory activities in cells in culture. K-07 appears to be a potential alternative orally effective antiestrogen. Although in the initial studies no impact on overall animal health was observed with this compound, or with K-09 or K-62, further investigations and ultimate safety and effectiveness studies will be needed with K-07 or related antiestrogens.

[00177] Compounds of the invention also have efficacy in suppressing growth of breast cancer cells and tumors containing WT ERs and that, at higher concentrations, these compounds can also inhibit ER-regulated gene expression and proliferation of breast cancer cells containing constitutively active mutant ERs. Compounds of the present invention are effective growth inhibitors in breast tumor xenografts *in vivo*, and show good anti-proliferative and target gene inhibitory activities in cells in culture. Three antiestrogen compounds with novel chemical structures of the present disclosure were shown to have efficacy in suppressing growth of breast cancer cells and tumors containing WT ERs and that, at higher concentrations, these compounds can also inhibit ER-regulated gene expression and proliferation of breast cancer cells containing constitutively active mutant ERs. K-07 had the most optimal PK profile in mice, and it was the most effective in suppression of WT and Y537S and D538G mutant tumor growth *in vivo*.

[00178] Non-limiting examples of diseases or conditions that are estrogen receptor alpha dependent and/or estrogen alpha receptor mediated and thus suitable for treatment using the compounds, compositions and methods described herein include breast cancers, gynecological cancers and pituitary cancers. For example, such diseases or conditions may include one or more of the following: breast cancer, endometrial cancer, ovarian cancer and cervical cancer. An embodiment provides a use of one or more compounds of the present invention, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition (as described elsewhere herein), in the manufacture of a medicament for the treatment of breast cancers and gynecological cancers, including for example one or more of the following: breast cancer, endometrial cancer, ovarian cancer and cervical cancer.

[00179] An embodiment provides the use of the compounds herein for the treatment of primary, metastatic, or recurrent breast cancer. Primary breast cancer is breast cancer that hasn't spread beyond the breast or the lymph nodes under the arm. Metastatic breast cancer (also called stage IV or advanced breast cancer) is not a specific type of breast cancer, but rather the most advanced stage of breast cancer. Metastatic breast cancer is breast cancer that has spread beyond the breast to other organs in the body (most often the bones, lungs, liver or brain). Although metastatic breast cancer has spread to another part of the body, it's considered and treated as breast cancer. When breast cancer comes back, it's called recurrence. Breast cancer can recur at any time or not at all, but most recurrences happen in the first 5 years after breast cancer treatment. Breast cancer can come back as a local recurrence (meaning in the treated breast or near the mastectomy scar) or somewhere else in the body. Some of the most common sites of recurrence outside the breast are the lymph nodes, bones, liver, lungs, and brain.

[00180] In one embodiment, compounds of the invention are used to inhibit or slow the growth of estrogen receptor-positive, endocrine therapy-sensitive tumors or endocrine therapy resistant tumors driven by active estrogen receptors. In some embodiments, the cancer cell or tumor growth may be driven by wild type, constitutively active estrogen receptors, and combinations thereof.

[00181] Another aspect of the present invention provides a compound or composition of formula (I), or a pharmaceutically acceptable salt thereof, for use in treating or preventing breast

cancer. In some embodiments, disclosed are compounds or compositions of formula (I), or pharmaceutically acceptable salts thereof, for use in treating or preventing primary, metastatic, or recurrent breast cancer.

[00182] Also provided are compounds or compositions of formula (I), or pharmaceutically acceptable salts thereof, for use in inhibiting or slowing the growth of estrogen receptor-positive, endocrine therapy-sensitive tumors or endocrine therapy resistant tumors driven by active estrogen receptors. In some embodiments, such tumors are driven by wild type, constitutively active estrogen receptors, and combinations thereof.

[00183] Also provided is use of a compound or composition of formula (I), or a pharmaceutically acceptable salt thereof, for manufacturing a medicament for treating or preventing breast cancer. In some embodiments, the breast cancer is primary, metastatic, or recurrent breast cancer.

[00184] Also provided is use of a compound or composition of formula (I), or a pharmaceutically acceptable salt thereof, for manufacturing a medicament for inhibiting or slowing the growth of estrogen receptor-positive, endocrine therapy-sensitive tumors or endocrine therapy resistant tumors driven by active estrogen receptors.

[00185] Administration

[00186] As described herein, compounds of the present invention, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as described elsewhere herein, can be administered to such subjects by a variety of methods. In any of the uses or methods described herein, administration can be by various routes known to those skilled in the art, including without limitation oral, inhalation, intravenous, intramuscular, topical, subcutaneous, systemic, and/or intraperitoneal administration to a subject in need thereof.

[00187] The amount of the compound of the present invention, or a pharmaceutically acceptable salt thereof, required for use in treatment will vary not only with the particular compound or salt selected but also with the route of administration, the nature and/or symptoms of the estrogen receptor dependent and/or estrogen receptor mediated disease or condition being treated and the age and condition of the patient and will be ultimately at the discretion of the

attendant physician or clinician. In cases of administration of a pharmaceutically acceptable salt, dosages may be calculated as the free base. As will be understood by those of skill in the art, in certain situations it may be necessary to administer the compounds disclosed herein in amounts that exceed, or even far exceed, the dosage ranges described herein in order to effectively and aggressively treat particularly aggressive estrogen receptor dependent and/or estrogen receptor mediated diseases or conditions.

[00188] In some embodiments, the compounds, or pharmaceutically acceptable salts thereof, or pharmaceutical compositions as disclosed herein may be administered by inhalation, oral administration, or intravenous administration. In general, however, a suitable dose will often be in the range of from about 0.01 mg/kg to about 100 mg/kg, such as from about 0.05 mg/kg to about 10 mg/kg. For example, a suitable dose may be in the range from about 0.10 mg/kg to about 7.5 mg/kg of body weight per day, such as about 0.10 mg/kg to about 0.50 mg/kg of body weight of the recipient per day, about 0.10 mg/kg to about 1.0 mg/kg of body weight of the recipient per day, about 0.15 mg/kg to about 5.0 mg/kg of body weight of the recipient per day, about 0.2 mg/kg to 4.0 mg/kg of body weight of the recipient per day. The compound may be administered in unit dosage form; for example, containing 1 to 100 mg, 10 to 100 mg or 5 to 50 mg of active ingredient per unit dosage form.

[00189] The desired dose may conveniently be presented in a single dose or as divided doses administered at appropriate intervals, for example, as two, three, four or more sub-doses per day. The sub-dose itself may be further divided, e.g., into a number of discrete loosely spaced administrations.

[00190] As will be readily apparent to one skilled in the art, the useful *in vivo* dosage to be administered and the particular mode of administration will vary depending upon the age, weight, the severity of the affliction, and mammalian species treated, the particular compounds employed, and the specific use for which these compounds are employed. The determination of effective dosage levels, that is the dosage levels necessary to achieve the desired result, can be accomplished by one skilled in the art using routine methods, for example, human clinical trials, *in vivo* studies and *in vitro* studies. For example, useful dosages of a compound of the present invention, or pharmaceutically acceptable salts thereof, can be determined by comparing their *in*

vitro activity, and *in vivo* activity in animal models. Such comparison can be done by comparison against an established drug, such as fulvestrant.

[00191] Dosage amount and interval may be adjusted individually to provide plasma levels of the active moiety which are sufficient to maintain the modulating effects, or minimal effective concentration (MEC). The MEC will vary for each compound but can be estimated from *in vivo* and/or *in vitro* data. Dosages necessary to achieve the MEC will depend on individual characteristics and route of administration. However, FIPLC assays or bioassays can be used to determine plasma concentrations. Dosage intervals can also be determined using MEC value. Compositions should be administered using a regimen which maintains plasma levels above the MEC for 10-90% of the time, preferably between 30-90% and most preferably between 50-90%. In cases of local administration or selective uptake, the effective local concentration of the drug may not be related to plasma concentration.

[00192] It should be noted that the attending physician would know how to and when to terminate, interrupt, or adjust administration due to toxicity or organ dysfunctions. Conversely, the attending physician would also know to adjust treatment to higher levels if the clinical response were not adequate (precluding toxicity). The magnitude of an administered dose in the management of the disorder of interest will vary with the severity of the estrogen receptor dependent and/or estrogen receptor mediated disease or condition to be treated and to the route of administration. The severity of the estrogen receptor dependent and/or estrogen receptor mediated disease or condition may, for example, be evaluated, in part, by standard prognostic evaluation methods. Further, the dose, and perhaps dose frequency, will also vary according to the age, body weight, and response of the individual patient. A program comparable to that discussed above may be used in veterinary medicine.

[00193] Compounds, salts and compositions disclosed herein can be evaluated for efficacy and toxicity using known methods. For example, the toxicology of a particular compound, or of a subset of the compounds, sharing certain chemical moieties, may be established by determining *in vitro* toxicity towards a cell line, such as a mammalian, and preferably human, cell line. The results of such studies are often predictive of toxicity in animals, such as mammals, or more specifically, humans. Alternatively, the toxicity of particular compounds in an animal model,

such as mice, rats, rabbits, dogs or monkeys, may be determined using known methods. The efficacy of a particular compound may be established using several recognized methods, such as *in vitro* methods, animal models, or human clinical trials. When selecting a model to determine efficacy, the skilled artisan can be guided by the state of the art to choose an appropriate model, dose, route of administration and/or regime.

[00194] A therapeutically effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as disclosed herein may be administered alone or in combination with a therapeutically effective amount of at least one additional anti-cancer therapeutic agents. In some embodiments, the compounds or pharmaceutical compositions as disclosed herein are administered in combination with at least one additional anti-cancer therapeutic agents. In some embodiments, the at least one additional anti-cancer therapeutic is administered prior to or following administration of the compounds or pharmaceutical compositions as disclosed herein.

4. Pharmaceutical Compositions

[00195] In another aspect of the invention, pharmaceutically acceptable compositions are provided, wherein these compositions comprise any of the compounds as described herein, and optionally comprise a pharmaceutically acceptable carrier, adjuvant or vehicle. In certain embodiments, these compositions optionally further comprise one or more additional therapeutic agents. In one embodiment, the pharmaceutical composition comprises a therapeutically effective amount of a compound of the present invention or a pharmaceutically acceptable salt thereof and one or more pharmaceutically acceptable carriers or vehicles.

[00196] Pharmaceutical compositions of the present invention may be manufactured by processes well known in the art, e.g., by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or lyophilizing processes.

[00197] As used herein, the term "pharmaceutically acceptable salt" refers to those salts which are, within the scope of sound medical judgement, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, S. M. Berge, et al. describe pharmaceutically acceptable salts in

detail in J Pharmaceutical Sciences, 1977, 66, 1-19, incorporated herein by reference.

Pharmaceutically acceptable salts of the compounds of this invention include those derived from suitable inorganic and organic acids and bases. Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid or by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p-toluenesulfonate, undecanoate, valerate salts, and the like. Salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium and N(C1-4alkyl)4 salts. This invention also envisions the quaternization of any basic nitrogen-containing groups of the compounds disclosed herein. Water or oil-soluble or dispersable products may be obtained by such quaternization. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, lower alkyl sulfonate and aryl (e.g., phenyl/substituted phenyl) sulfonate.

[00198] As described herein, the pharmaceutically acceptable compositions of the invention additionally comprise a pharmaceutically acceptable carrier, adjuvant, or vehicle, which, as used herein, includes any and all solvents, diluents, or other liquid vehicle, dispersion or suspension aids, surface active agents, isotonic agents, thickening or emulsifying agents, preservatives, solid binders, lubricants and the like, as suited to the particular dosage form desired. Remington's Pharmaceutical Sciences, Sixteenth Edition, E.W. Martin (Mack Publishing Co., Easton, Pa., 1980) discloses various carriers used in formulating pharmaceutically acceptable compositions

and known techniques for the preparation thereof. Except insofar as any conventional carrier medium is incompatible with the compounds of the invention, such as by producing any undesirable biological effect or otherwise interacting in a deleterious manner with any other component(s) of the pharmaceutically acceptable composition, its use is contemplated to be within the scope of this invention. Some examples of materials which can serve as pharmaceutically acceptable carriers include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, or potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, polyacrylates, waxes, polyethylenepolyoxypropylene-block polymers, wool fat, sugars such as lactose, glucose and sucrose; starches such as corn starch and potato starch; cellulose and its derivatives such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients such as cocoa butter and suppository waxes; oils such as peanut oil, cottonseed oil; safflower oil; sesame oil; olive oil; corn oil and soybean oil; glycols; such as propylene glycol or polyethylene glycol; esters such as ethyl oleate and ethyl laurate; agar; buffering agents such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol, and phosphate buffer solutions, as well as other non-toxic compatible lubricants such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, releasing agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the composition, according to the judgment of the formulator.

[00199] The pharmaceutically acceptable compositions of this invention can be administered to humans and other animals orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, or drops), buccally, as an oral or nasal spray, or the like, depending on the severity of the disease being treated.

[00200] Pharmaceutical compositions for parenteral injection comprise pharmaceutically acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions as well as sterile powders for reconstitution into sterile injectable solutions or dispersions just prior

to use. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents or vehicles include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol and the like), vegetable oils (such as olive oil), injectable organic esters (such as ethyl oleate) and suitable mixtures thereof. Proper fluidity can be maintained, for example, by the use of coating materials such as lecithin, by the maintenance of the required particle size in the case of dispersions and by the use of surfactants.

[00201] These compositions can also contain adjuvants such as preservatives, wetting agents, emulsifying agents and dispersing agents. Prevention of the action of microorganisms can be ensured by the inclusion of various antibacterial and antifungal agents, for example, paraben, chlorobutanol, phenol sorbic acid and the like. It can also be desirable to include isotonic agents such as sugars, sodium chloride and the like. Prolonged absorption of the injectable pharmaceutical form can be brought about by the inclusion of agents which delay absorption such as aluminum monostearate and gelatin.

[00202] In some cases, in order to prolong the effect of the drug, it is desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This can be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution which, in turn, can depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle.

[00203] Liquid dosage forms for oral administration include, but are not limited to, pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

[00204] Solid dosage forms for oral administration include capsules, tablets, pills, powders, cement, putty, and granules. In such solid dosage forms, the active compound can be mixed with at least one inert, pharmaceutically acceptable excipient or carrier, such as sodium citrate or dicalcium phosphate and/or a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol and silicic acid; b) binders such as carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidone, sucrose and acacia; c) humectants such as glycerol; d) disintegrating agents such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates and sodium carbonate; e) solution retarding agents such as paraffin; f) absorption accelerators such as quaternary ammonium compounds; g) wetting agents such as cetyl alcohol and glycerol monostearate; h) absorbents such as kaolin and bentonite clay and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate and mixtures thereof. In the case of capsules, tablets and pills, the dosage form can also comprise buffering agents.

[00205] Solid compositions of a similar type may also be employed as fillers in soft and hardfilled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

[00206] The active compounds can also be in microencapsulated form with one or more excipients as noted above. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings, release controlling coatings and other coatings well known in the pharmaceutical formulating art. In such solid dosage forms the active compound may be admixed with at least one inert diluent such as sucrose, lactose or starch. Such dosage forms may also comprise, as is normal practice,

additional substances other than inert diluents, e.g., tableting lubricants and other tableting aids such a magnesium stearate and microcrystalline cellulose. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes.

[00207] Compositions for rectal or vaginal administration are preferably suppositories which can be prepared by mixing the compounds of this invention with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

[00208] Dosage forms for topical or trans dermal administration of a compound of this invention include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants or patches. The active component is admixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives or buffers as may be required. Ophthalmic formulation, eardrops, and eye drops are also contemplated as being within the scope of this invention. Additionally, the invention contemplates the use of transdermal patches, which have the added advantage of providing controlled delivery of a compound to the body. Such dosage forms are prepared by dissolving or dispensing the compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate can be controlled by either providing a rate controlling membrane or by dispersing the compound in a polymer matrix or gel.

[00209] Compounds described herein can be administered as a pharmaceutical composition comprising the compounds of interest in combination with one or more pharmaceutically acceptable carriers. It is understood, however, that the total daily dosage of the compounds and compositions can be decided by the attending physician within the scope of sound medical judgment. The specific therapeutically effective dose level for any particular patient can depend upon a variety of factors including the disorder being treated and the severity of the disorder; activity of the specific compound employed; the specific composition employed; the age, body

weight, general health and prior medical history, sex and diet of the patient; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed; and like factors well-known in the medical arts. For example, it is well within the skill of the art to start doses of the compound at levels lower than required to achieve the desired therapeutic effect and to gradually increase the dosage until the desired effect is achieved. Actual dosage levels of active ingredients in the pharmaceutical compositions can be varied so as to obtain an amount of the active compound(s) that is effective to achieve the desired therapeutic response for a particular patient and a particular mode of administration. In the treatment of certain medical conditions, repeated or chronic administration of compounds can be required to achieve the desired therapeutic response. "Repeated or chronic administration" refers to the administration of compounds daily (i.e., every day) or intermittently (i.e., not every day) over a period of days, weeks, months, or longer.

[00210] The compositions described herein may be administered with additional compositions to prolong stability, delivery, and/or activity of the compositions, or combined with additional therapeutic agents, or provided before or after the administration of additional therapeutic agents.

[00211] Combination therapy includes administration of a single pharmaceutical dosage formulation containing one or more of the compounds described herein and one or more additional pharmaceutical agents, as well as administration of the compounds and each additional pharmaceutical agent, in its own separate pharmaceutical dosage formulation. For example, a compound described herein and one or more additional pharmaceutical agents, can be administered to the patient together, in a single oral dosage composition having a fixed ratio of each active ingredient, such as a tablet or capsule; or each agent can be administered in separate oral dosage formulations. Where separate dosage formulations are used, the present compounds and one or more additional pharmaceutical agents can be administered at essentially the same time (e.g., concurrently) or at separately staggered times (e.g., sequentially).

[00212] For adults, the doses are generally from about 0.01 to about 100 mg/kg, desirably about 0.1 to about 1 mg/kg body weight per day by inhalation, from about 0.01 to about 100 mg/kg, desirably 0.1 to 70 mg/kg, more desirably 0.5 to 10 mg/kg body weight per day by oral

administration, and from about 0.01 to about 50 mg/kg, desirably 0.1 to 1 mg/kg body weight per day by intravenous administration.

[00213] The compositions and methods will be described more fully hereinafter with reference to the accompanying drawings, in which some, but not all embodiments of the invention are shown. Indeed, the invention may be embodied in many different forms and should not be construed as limited to the embodiments set forth herein.

[00214] Likewise, many modifications and other embodiments of the compositions and methods described herein will come to mind to one of skill in the art to which the invention pertains having the benefit of the teachings presented in the foregoing descriptions and the associated drawings. Therefore, it is to be understood that the invention is not to be limited to the specific embodiments disclosed and that modifications and other embodiments are intended to be included within the scope of the appended claims. Although specific terms are employed herein, they are used in a generic and descriptive sense only and not for purposes of limitation.

[00215] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of skill in the art to which the invention pertains. Although any methods and materials similar to or equivalent to those described herein can be used in the practice or testing of the present invention, the preferred methods and materials are described herein.

5. Examples

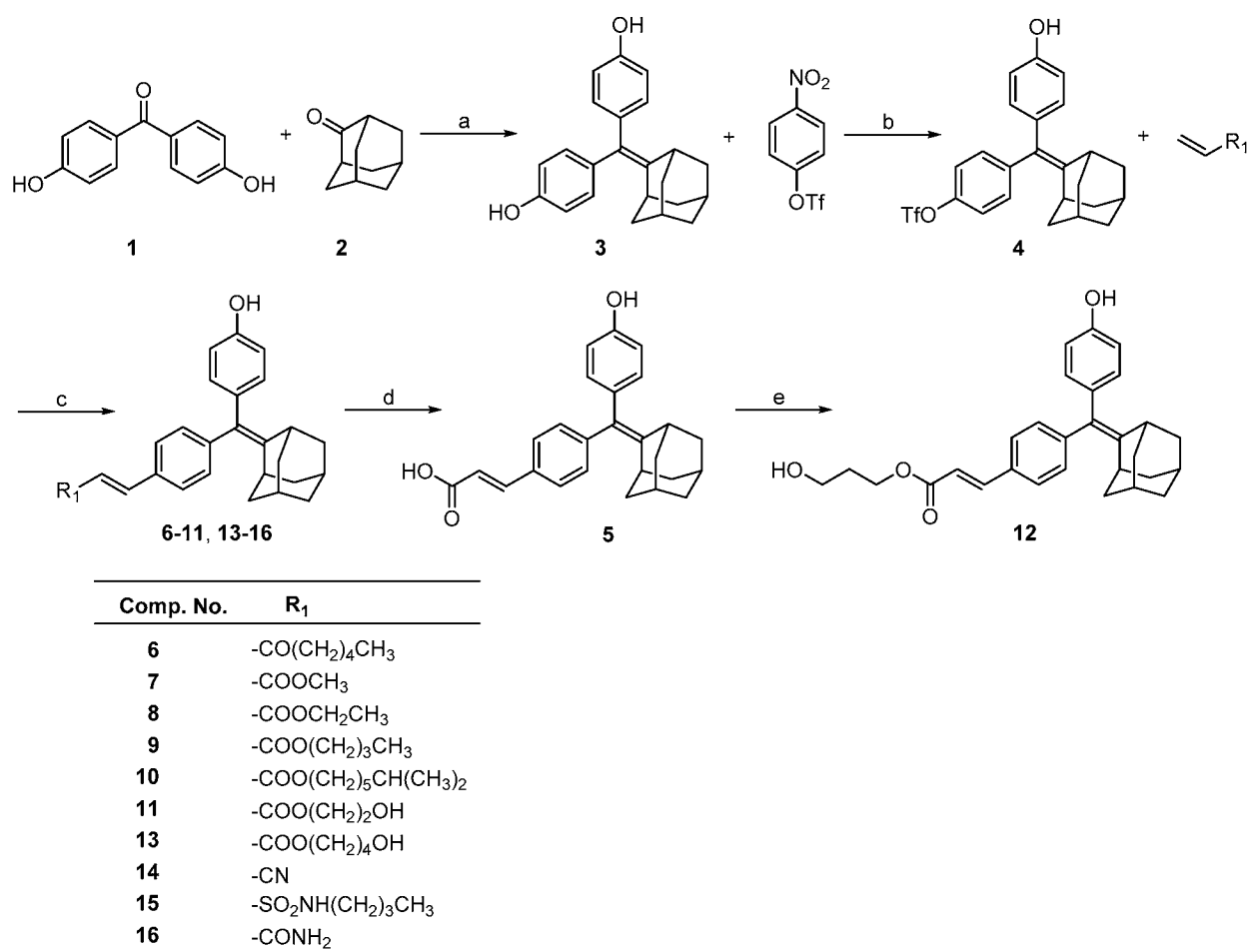
[00216] Example 1. Compound Selection and Synthesis

[00217] The ligand core was selected based on the well-known SERM cyclofenil, in which the monocyclic cyclohexane was replaced with the much bulkier tricyclic adamantane, generating a series of ER ligands that we term “adamantyls” (FIG. 1). This adamantane-based core was identified from an earlier exploration of substitutions for the cyclohexane ring of cyclofenil (19). Major advantages of this structurally simple adamantane-based core are its planar symmetry, which avoids problems with geometric isomerism (present in the antiestrogens GW-5638/7604 and in GCD-0810), and its lack of chirality and stereoisomers, which avoids stereochemical issues (present in AZD-9496). In addition, ligands having the 4,4'-dihydroxybenzhydrylidine

substructure (two phenols attached para to one end of a double bond) almost universally have very high binding affinities for ER α (19, 24); the parent bisphenolic adamantyl-core, in fact, demonstrated an affinity ca. 3 fold higher than that of estradiol (E2), which corresponds to a K_i value of 70 pM (19).

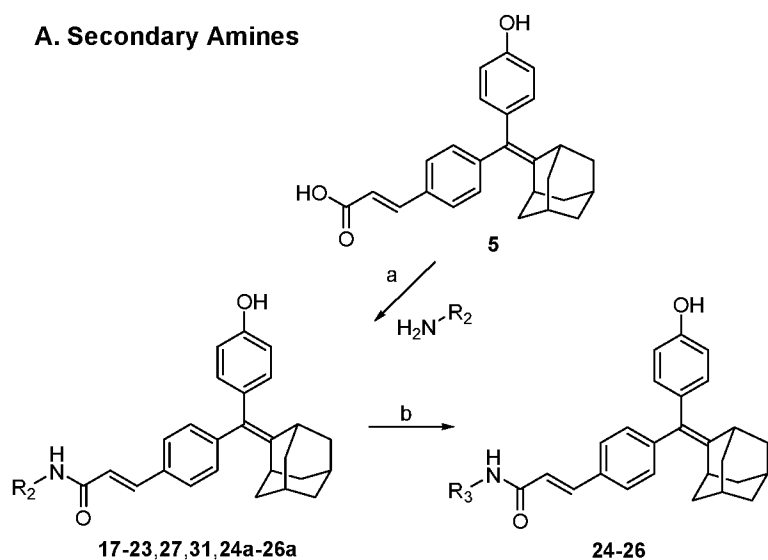
[00218] The adamantyl core system **3** was easily prepared by a McMurray coupling between 4,4'-dihydroxybenzophenone (compound **1**) and 2-adamantanone (compound **2**) (Scheme 1) (25). The monotriflate **4** could be obtained efficiently by treatment with *p*-nitrophenyl trifluoromethanesulfonate (26), and then various acryloyl groups were appended by a Heck reaction (25). The ketone **6**, the various esters **7-13**, as well as the nitrile **14**, sulfonamide **15**, and simple carboxamide **16**, were prepared in one step by a Heck reaction with the corresponding acrylate derivative (Scheme 1). The acrylic acid **5** was obtained by hydrolysis of the ethyl ester **8**, and then the secondary amides **17-27**, **31** and tertiary amides **28-30** were prepared by HATU-mediated coupling (27) of the primary and secondary amines (Scheme 2A) (28), respectively, with the acrylic acid core structure **5**, the couplings with secondary amines requiring somewhat elevated temperatures (50 °C) (Scheme 2B). To explore the possible role of a water molecule in mediating the side chain-h12 interaction, a few isostructural esters and amides were prepared in which the side chains had the same number of non-hydrogen atoms but were terminated either with a methyl group or an OH or NH₂ group.

[00219] Scheme 1. Synthesis of compound 5-16



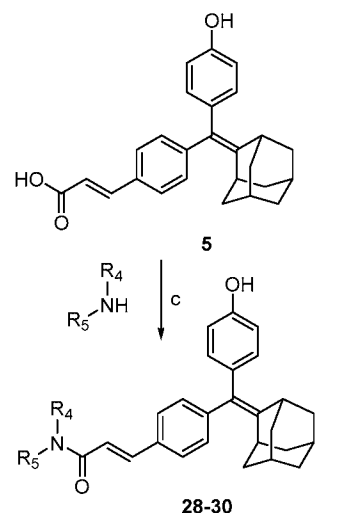
[00220] Reaction conditions and reagents: a) TiCl_4/Zn , THF, reflux; b) K_2CO_3 , DMF, r.t.; c) $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$, TEA, DMF, 120°C ; d) KOH , CH_3OH ; e) i) Isobutyl chloroformate, DMAP, Et_3N , DCM, propane-1,3-diol, -15°C to 0°C , 3 h; and ii) piperidine, 1 h, r.t.

[00221] Scheme 2. Synthesis of amides 17-31.

A. Secondary Amines

Comp. No.	R ₂
17	-(CH ₂) ₂ CH ₃
18	-(CH ₂) ₃ CH ₃
19	-(CH ₂) ₄ CH ₃
20	-(CH ₂) ₂ OH
21	-(CH ₂) ₃ OH
22	-(CH ₂) ₄ OH
23	-(CH ₂) ₅ OH
27	-CH ₂ CF ₃
31	-(CH ₂) ₂ N(CH ₃) ₂
24a	-(CH ₂) ₂ NHBoc
25a	-(CH ₂) ₃ NHBoc
26a	-(CH ₂) ₄ NHBoc

Comp. No.	R ₃
24	-(CH ₂) ₂ NH ₂
25	-(CH ₂) ₃ NH ₂
26	-(CH ₂) ₄ NH ₂

B. Tertiary Amines

Comp. No.	R ₄	R ₅
28	-CH ₃	-(CH ₂) ₃ CH ₃
29	-CH ₃	-(CH ₂) ₂ OH
30	-(CH ₂) ₂ OH	-(CH ₂) ₂ OH

[00222] Reaction conditions and reagents: a) HATU, DMF, r.t.; b) TFA/DCM, 0°C; c) HATU, DMF, 50 °C.

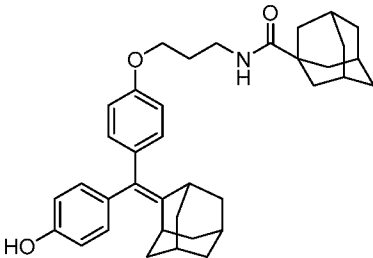
[00223] Example 2. ER α Binding Affinities

[00224] The affinities of all compounds for purified, full-length, human ER α were determined using a competitive radiometric binding assay, with [³H]estradiol as tracer (29). The affinities were given as relative binding affinity (RBA) values (E₂ = 100), as presented in Table 1. By selecting the high affinity adamantyl core as the building block for these new antiestrogens, it was observed that essentially all of these compounds demonstrated with high binding affinities; most of the RBA values being in the range of 10-60, with some compounds showing affinities that were comparable (for example, compound 26 (RBA = 62) and compound 16 (RBA = 71)) or

even exceeding (for example, compound **20** (RBA = 109) and compound **30** (RBA = 115)) the affinity of E2 (RBA = 100). Considering that the K_d of E2 for ER α is 0.2 nM, almost all of these compounds bind to ER α with affinities in the single digit nanomolar range or below (Table 1).

[00225] Table 1. Relative Binding Affinities of Adamantyl Compounds and GW-7604 for full-length human estrogen receptor alpha (ER α).

K designation	Compd #	Structure/Moiety	RBA ER α (%) ^a	K _i (nM) ^a
		Reference compounds		
		Estradiol	(100)	0.2 (K _d value)
53		GW-7604	20 ± 6	1.0 ± 0.3
		Adamantyl Compounds		
		Acid		
07	5	-COOH	51 ± 12	0.40 ± 0.09
		Ketone		
37	6	-CO(CH ₂) ₄ CH ₃	12 ± 2	1.7 ± 0.3
		Esters		
28	7	-COOCH ₃	46 ± 14	0.43 ± 0.13
27	8	-COOCH ₂ CH ₃	13 ± 1	3.3 ± 0.3
35	9	-COO(CH ₂) ₃ CH ₃	11 ± 2	1.8 ± 0.3
36	10	-COO(CH ₂) ₅ CH(CH ₃) ₂	2.8 ± 0.4	7.1 ± 1.0
24	11	-COO(CH ₂) ₂ OH	54 ± 11	0.37 ± 0.08
25	12	-COO(CH ₂) ₃ OH	28 ± 2	0.71 ± 0.05
26	13	-COO(CH ₂) ₄ OH	44 ± 9	0.45 ± 0.09
		Other groups		
78	14	-CN	14 ± 4	1.4 ± 0.4
79	15	-SO ₂ NH(CH ₂) ₂ CH ₃	52 ± 1	0.38 ± 0.01
		Amides		
91	16	-CONH ₂	71 ± 18	0.27 ± 0.07
48	17	-CONH(CH ₂) ₂ CH ₃	18 ± 0.1	1.1 ± 0.0
49	18	-CONH(CH ₂) ₃ CH ₃	28 ± 3	0.71 ± 0.08
50	19	-CONH(CH ₂) ₄ CH ₃	27 ± 7	0.74 ± 0.18
08	20	-CONH(CH ₂) ₂ OH	109 ± 17	0.18 ± 0.03
09	21	-CONH(CH ₂) ₃ OH	47 ± 8	0.43 ± 0.07
10	22	-CONH(CH ₂) ₄ OH	56 ± 12	0.36 ± 0.08

43	23	-CONH(CH ₂) ₅ OH	31 ± 7	0.65 ± 0.15
44	24	-CONH(CH ₂) ₂ NH ₂	35 ± 9	0.57 ± 0.15
45	25	-CONH(CH ₂) ₃ NH ₂	54 ± 7	0.35 ± 0.09
46	26	-CONH(CH ₂) ₄ NH ₂	62 ± 1	0.32 ± 0.0
11	27	-CONHCH ₂ CF ₃	15 ± 3	1.33 ± 0.27
74	28	-CON(CH ₃)(CH ₂ CH ₂ CH ₂ CH ₃)	28 ± 8	0.71 ± 0.2
76	29	-CON(CH ₃)(CH ₂ CH ₂ OH)	54 ± 12	0.37 ± 0.08
47	30	-CON(CH ₂ CH ₂ OH) ₂	115 ± 33	0.13 ± 0.04
77	31	-CONH(CH ₂) ₂ N(CH ₃) ₂	57 ± 14	0.35 ± 0.09
62	32		30	0.65

^a. Relative binding affinity values were determined by a competitive radiometric binding assay with [³H]estradiol and purified, full-length human ER α . Values are reported as percent relative to E₂ = 100%, and expressed as the mean $\pm$ range or SD of 2 or more independent experiments. The K_d for estradiol is 0.2nM. K_i values can be calculated from the formula: K_i = (K_d[estradiol]/RBA) $\times$ 100.

[00226] One structure-affinity trend examined herein related to potential replacement of the structural water linking the side chain to the N-terminus of h12, noted crystal structures with GW-5638 (FIGS. 2 & 25). In the amide and ester series where direct comparisons can be made between isostructural alkyl vs. hydroxyl- or amino-alkyl side chains, the replacement of a terminal methyl group with an OH or NH₂ polar atom provides a substantial and consistent (2 to 5-fold) increment in affinity, at least in the 2-4 methylene group range (FIG. 3).

[00227] Example 3. Initial Screen of Antiproliferative and ER α Downregulating Activities

[00228] Because of the large number of compounds evaluated, they were initially screened in ER-positive MCF-7 breast cancer cells for their suppression of cell proliferation (CP) and for their effects on ER α levels, using a single high, saturating concentration of 3 μ M. Relationships between the results of these initial screening assays and compound structures are displayed graphically in a series of star plots (FIGS. 4A-4C) (30). On these plots, the levels of suppression

of proliferation and downregulation of ER α , plotted on percent scales, are displayed in a radial manner, each spoke of which is associated with the structure of a compound. The antiestrogen and SERD, fulvestrant (Fulv) is included for comparison in each star plot. The activity in suppressing cell proliferation is given as percent of vehicle control (CP, shown in blue); maximum suppression is ca. 20% (corresponding essentially to no increase in cell number after 6 days). For ER α levels (ER α , shown in red), 20% is the ER α level after 3 μ M fulvestrant treatment, with 100% being the ER α level in vehicle control cells. Representative compounds were also screened in ER α -negative MDA-MB-231 breast cancer cells, and they had no effect on proliferation of cells lacking ER α (not shown).

[00229] Example 4. Comparison of the Antiproliferative and ER α Downregulating Efficacies of Core Structures and of Ketone, Ester, and Other Variant Side Chains.

[00230] A comparison between the parent adamantyl acrylic acid analog **5** and the GSK antiestrogen GW-7604 (FIG. 4A) indicates that the parent compound has somewhat better ER downregulating and antiproliferative efficacies.

[00231] Among the compound with various side chains, the ketone compound **6** prepared herein showed reduced efficacy in terms of antiproliferative and ER downregulating activities; hence, further ketone analogs were not explored. The series of acrylate esters **7-10** and ω -hydroxyl esters **11-13** showed a broad span in both dimensions of efficacy. The best in terms of antiproliferative activity was **9** at 40%, but none were better than **5**. The ER α downregulating activity of this series varies a great deal, with the butyl **9**, iso-octyl **10**, and hydroxybutyl **13** esters being good to very good, but the methyl and ethyl esters **7** and **8**, and the ω -hydroxy esters **11** and **12** being very non-efficacious in reducing cell ER levels.

[00232] The two other variant side chains shown in this star plot again reveal marked differences in both antiproliferative and ER downregulating efficacies. The acrylonitrile **14** was neither anti- or pro-proliferative, with proliferation matching that of vehicle control; nevertheless, it was very effective in reducing the cellular ER α level. The propyl sulfonamide **15** was only modest as an ER downregulator and an antiproliferative agent.

[00233] Example 5. Comparison of the Antiproliferative and ER α Downregulating Activities of Various Carboxamide Analogs

[00234] The activities of a significant number of adamantyl carboxamides are displayed in two separate star plots (FIGS. 4B-4C). The amides presented in FIG. 4B are all secondary amides except for the primary amide **16**. The alkyl amides **17-19** and ω -hydroxyalkyl amides **20-23** all showed relatively comparable antiproliferative efficacies, with the best two (**21** and **23**) being equivalent to that of the parent acid **5**; the ER downregulating activities of these two were also good and similar to that of the parent **5**. Further distinction among some of these compounds based on their potencies in dose-response assays is shown in FIGS. 6 and 7. Much more variable were the activities of the primary amide **16**, the ω -aminoalkyl amides **24-26**, and the trifluoroethyl amide **27**. Of these, only the 3-aminopropyl amide **25** rivaled the antiproliferative efficacies of the amides discussed above; both **25** and the butyl homolog **26** showed good ER α downregulatory activity. Least good were the primary amide **16** and the trifluoroethyl amide **27**. The compounds shown in FIG. 4B showed overall quite a detailed concordance between antiproliferative and ER α -downregulating efficacies, more so than those in FIG. 4A.

[00235] In evaluating the amides, a marked difference in both antiproliferative and ER α downregulating efficacies of secondary vs. tertiary amides was noted. Rather striking comparisons between sets of related compounds in these two structural series are illustrated in FIG. 4C. The good efficacies of the N-butyl secondary amide **18** can be contrasted with the very poor efficacies of the N-methyl tertiary amide analog **28**. Similarly, the impressive efficacies of the hydroxyethyl secondary amide **20** are markedly better than those of the N-methyl analog **29** and the bis-hydroxyethyl analog **30**. The symmetrically substituted tertiary amide **30** showed the highest ER binding affinity of the compounds we have studied, yet it was relatively unimpressive in both antiproliferative and ER downregulating activities. Similar comparisons can be made between the 2-aminoethyl secondary amide **24** and the trimethyl tertiary amide analog **31**. Similar to FIG. 4B, the compounds in FIG. 4C showed a good concordance between antiproliferative and ER α downregulating activities.

[00236] Example 6. Antiproliferative and ER α Downregulating Potencies, and Suppression of Estrogen Target Gene Expression, of the Most Efficacious Adamantyl Compounds.

[00237] The initial examination of compounds in the adamantyl series was based on their efficacies at a single, high concentration of 3 μ M. Therefore, to identify from among the best compounds those that would also be most potent in terms of their antiproliferative and ER α downrelating activities, dose-response assays were conducted on a number of compounds that had excellent anti-proliferative efficacies as well as a few others for comparison.

[00238] As shown in FIG. 5, the hydroxypropyl **21** (IC_{50} = 1.9 nM) and hydroxyethyl **20** (IC_{50} = 2.4 nM) amides were clearly more potent than the parent carboxylic acid **5** (IC_{50} = 31 nM), with the hydroxypropyl analog **21** having a slight edge over the hydroxyethyl analog **20** both in terms of potency and in maximum efficacy (24% vs 30%, see also FIG. 4B). Consistent with the markedly greater antiproliferative efficacy of the secondary vs. tertiary amides observed in other experiments, the dose-response curves of FIG. 5 show that the two tertiary amide compounds (analogs of **20**), the N-methyl compound **29** and the bis-hydroxyethyl compound **30**, demonstrated very limited antiproliferative efficacy (46% and 54%, respectively) despite having good potencies (IC_{50} = 5.4 nM and 2.1 nM, respectively).

[00239] Dose-response curves for ER α downregulation by **5**, **20**, and **21**, as well as fulvestrant, derived from in-cell western immunoassays for ER α , are shown in FIG. 6A. Of the three new compounds, the hydroxypropyl amide **21** was clearly the most potent (IC_{50} = 0.53 nM), with the hydroxyethyl amide **20** and carboxylic acid **5** being considerably less potent (IC_{50} = 5.6 nM and 17 nM, respectively). These ER downregulating activities were confirmed by direct Western blot assays (FIG. 6B). The maximum level of ER α downregulation from both the ICW dose-response assays and the western blots were equivalent to those from single-dose assays, previously shown in FIG. 4, and were close to that of fulvestrant in efficacy.

[00240] We selected the most efficacious antiproliferative adamantyl compounds **5** and **21** to assay for their suppression of E2-stimulated gene expression (FIG. 7). Expression of the ER-target genes, GREB1, progesterone receptor (PgR), and pS2, was monitored in cells grown in full media (with 5% fetal bovine serum) and with added estradiol (E2). The dose-response studies revealed that **21** was more potent than **5** in inhibiting these estrogen-stimulated genes (IC_{50} of 50 nM for **21** and 500 nM for **5**) and that fulvestrant was 10 to 20-fold more potent than **21**.

[00241] Example 7. Synthesis and Spectroscopic Characterization.

[00242] Materials and Methods

[00243] All reagents and solvents were obtained from Sigma-Aldrich, Acros, TCI and Matrix Scientific. Tetrahydrofuran, dimethylformamide, trimethylamine and dichloromethane were obtained from a solvent dispensing system (SDS) (Pangborn et. al. *Organometallics* **1996**, 15, 1518-1520). Glassware was oven-dried, assembled while hot, and cooled under an inert atmosphere. Unless otherwise noted, all reactions were conducted in an inert atmosphere. Reaction progress was monitored using analytical thin-layer chromatography (TLC) on 0.25 mm Merck F-254 silica gel glass plates. Visualization was achieved by either UV light (254 nm) or potassium permanganate indicator spray. Flash chromatography was performed with Woelm silica gel (0.040-0.063 mm) packing.

[00244] ^1H NMR and ^{13}C NMR spectra were obtained on a 400 or 500 MHz instrument. The chemical shifts are reported in ppm and are referenced to either tetramethylsilane or the solvent. Mass spectra were recorded under electron impact conditions at 70 eV. Melting points are uncorrected.

[00245] General procedure for McMurry coupling (**3**)

[00246] Zinc powder (8.0 eq.) was suspended in dry THF at 0 °C in a three-neck round bottom flask under a nitrogen atmosphere. Titanium tetrachloride (4.0 eq.) was added dropwise via a syringe while stirring. The reaction mixture was then refluxed for 2 h. After cooling to r. t., a THF solution containing 4,4'-dihydroxy benzophenone (**1**, 1.0 eq.) and 2-Adamantanone (**2**, 1.0 eq.) was added dropwise to the slurry. The mixture was refluxed for an additional two hours and then was cooled, poured into NaHCO_3 solution, and kept stirring until the dark color disappeared. After filtration through Celite, the filtrate was extracted with ethyl acetate, dried with anhydrous Na_2SO_4 and concentrated *in vacuo*. The resulting residue (**3**) was used for the next step without any purification.

[00247] General procedure for Mono-triflate synthesis (**4**)

[00248] At room temperature, potassium carbonate (K_2CO_3 , 2 eq.) was added to the DMF solution of compound **3** (1.0 eq.) 4-Nitrophenyl trifluoromethanesulfonate (1.2 eq.) was then slowly added to the suspension (Zhu et. al. *Tetrahedron Letters* **1997**, 38, 1181-1182). The reaction mixture was stirred at r.t. overnight and extracted with ethyl acetate, washed with water and brine. The organic layer was dried with anhydrous Na_2SO_4 and concentrated *in vacuo*. The resulting residue was purified by flash chromatography on silica gel to give the desired product (**4**).

[00249] General procedure for Heck reaction

[00250] A mixture of triflate derivative **4** (1.0 eq.), corresponding alkene (1.2 eq.), $Pd(PPh_3)_2Cl_2$ (10 mol%), Et_3N (3 equivalent) in DMF was heated under N_2 at 120 °C for 12 h. The reaction mixture was cooled and extracted with ethyl acetate, washed with water and brine. The organic layer was dried with anhydrous Na_2SO_4 and concentrated *in vacuo*. The resulting residue was purified by flash chromatography (10-80% Ethyl acetate/Hexane gradient) on silica gel to give the desired products **6-16**.

[00251] General Procedure for Hydrolysis of Ester to Acid Product (**5**)

[00252] To the solution of the ester **8** (1.0 equiv) in CH_3OH was added 2N KOH (2.0 mL). The mixture was stirred at room temperature and monitored by TLC. After complete consumption of starting material, the reaction mixture was poured into 1 N HCl (4.0 mL) and extracted from the aqueous phase with ethyl acetate. The organic layer was dried with anhydrous Na_2SO_4 and concentrated *in vacuo*. Flash column chromatography (10% CH_3OH/CH_2Cl_2) gave the acid product **5**.

[00253] General procedure for Amide Synthesis using HATU

[00254] O-(7-Azabenzotriazole-1-yl)-N,N,N,N'-tetramethyluronium hexafluorophosphate (HATU, 1.5 eq.) was added to the DMF solution of the carboxylic acid (1.0 eq.). The mixture was stirred at r.t. for 10 min the corresponding amine (3.0 eq.) was injected dropwise. The resulting yellow solution was stirred for 20 min before diisopropylethylamine (DIPEA, 3.0 eq.) was added by syringe. For primary amine, the mixture was stirred at r.t. while for secondary amine, temperature was elevated to 50 °C. The reaction was monitored by TLC. After complete

consumption of starting material, ethyl acetate was added, and the resulting solution was washed with brine. The organic layer was dried with anhydrous Na₂SO₄ and concentrated *in vacuo*. The resulting residue was purified by flash chromatography on silica gel to give the desired products **17-23**, **24a-26a**, **27-31**.

[00255] General Procedure for the deprotection of Boc-group

[00256] The corresponding compounds (**24a-26a**) were dissolved in dry DCM and cooled to 0 °C. TFA (equal amount as the solvent) was added dropwise and the solution was stirred at r.t. After complete consumption of starting material (as monitored by TLC), the solution was concentrated *in vacuo*. The residue was extracted with ethyl acetate, washed with water and sat. NaHCO₃ solution. The combined organic layers were dried with anhydrous Na₂SO₄ evaporated *in vacuo*. The resulting residue was purified by flash chromatography on silica gel to give the desired products (**24-26**).

[00257] (E)-3-(4-(((1r,3r,5R,7S)-Adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)acrylic acid (**5**). Following the general procedure for hydrolysis of ester **8**, compound **5** was obtained as white solid (Yield 92%, mp 228°C). ¹H NMR (500 MHz, Acetone-*d*₆) δ 7.66 (d, *J* = 16.0 Hz, 1H), 7.61 (d, *J* = 8.2 Hz, 2H), 7.20 (d, *J* = 8.2 Hz, 2H), 6.98 (d, *J* = 8.5 Hz, 2H), 6.78 (d, *J* = 8.5 Hz, 2H), 6.50 (d, *J* = 16.0 Hz, 1H), 2.81 (s, 1H), 2.76 (s, 1H), 1.99 (s, 2H), 1.88 (d, *J* = 13.1 Hz, 10H). ¹³C NMR (126 MHz, Acetone-*d*₆) δ 167.14, 156.17, 146.59, 145.87, 144.65, 133.78, 132.56, 130.71, 130.46, 130.16, 128.09, 117.82, 115.10, 39.44, 39.42, 37.04, 34.75, 34.62, 28.37. HRMS (ESI) calcd for C₂₆H₂₇O₃ (M+H⁺) 387.1960, found 387.1971.

[00258] (E)-1-(4-(((1r,3r,5R,7S)-Adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)oct-1-en-3-one (**6**). Following the general procedure for Heck reaction using corresponding triflate and 1-Octen-3-one, compound **6** was obtained as yellow solid (Yield 47%, mp 158°C). ¹H NMR (500 MHz, CDCl₃) δ 7.51 (d, *J* = 16.2 Hz), 7.44 – 7.39 (m, 2H), 7.15 – 7.10 (m, 2H), 6.98 – 6.90 (m, 2H), 6.83 – 6.75 (m, 2H), 6.68 (d, *J* = 16.2 Hz, 1H), 2.77 (m, 1H), 2.66 – 2.60 (m, 2H), 1.98 (m, 2H), 1.83 (m, 10H), 1.66 (m, 2H), 1.31 (m, 4H), 0.93 – 0.83 (m, 3H). ¹³C NMR (125 MHz, CDCl₃) δ 201.6, 154.7, 147.6, 146.2, 142.9, 134.7, 132.2, 131.0, 130.9, 130.4, 129.8, 128.2, 128.0, 125.6, 115.2, 115.1, 41.0, 39.8, 39.8, 37.3, 36.7, 34.8, 34.7, 34.7, 31.7, 31.2, 28.4, 28.3,

24.5, 24.2, 22.7, 19.9, 14.2, 13.8. HRMS-ESI: m/z $[M+H]^+$ for $C_{31}H_{37}O_2$, calculated 441.2794; observed 441.2801.

[00259] Methyl (E)-3-(4-(((1*r*,3*r*,5*R*,7*S*)-Adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl) acrylate (**7**). Following the general procedure for Heck reaction using corresponding triflate and methyl acrylate, compound **7** was obtained as white solid (Yield 68%, mp 209°C). 1H NMR (500 MHz, $CDCl_3$) δ 7.68 (d, $J = 16.0$ Hz, 1H), 7.44 (d, $J = 8.2$ Hz, 2H), 7.15 (d, $J = 8.2$ Hz, 2H), 7.00 (d, $J = 6.5$ Hz, 2H), 6.77 (d, $J = 8.6$ Hz, 2H), 6.41 (d, $J = 16.0$ Hz, 1H), 3.82 (s, 3H), 2.80 (d, $J = 10.4$ Hz, 2H), 2.02 (s, 2H), 1.87 (d, $J = 12.4$ Hz, 11H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.92, 154.20, 147.82, 145.90, 145.11, 135.32, 132.24, 131.12, 130.38, 129.64, 128.05, 117.10, 115.16, 51.95, 39.85, 39.82, 37.31, 34.81, 34.75, 28.36. HRMS (ESI) calcd for $C_{27}H_{29}O_3$ ($M+H^+$) 401.2117, found 401.2129.

[00260] Ethyl(E)-3-(4-(((1*r*,3*r*,5*R*,7*S*)-Adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl) acrylate (**8**). Following the general procedure for Heck reaction using corresponding triflate and ethyl acrylate, compound **8** was obtained as white solid (Yield 65%, mp 135-137°C). 1H NMR (500 MHz, $CDCl_3$) δ 7.67 (d, $J = 16.0$ Hz, 1H), 7.44 (d, $J = 8.2$ Hz, 2H), 7.15 (d, $J = 8.2$ Hz, 2H), 7.00 (d, $J = 8.6$ Hz, 2H), 6.77 (d, $J = 8.6$ Hz, 2H), 6.40 (d, $J = 16.0$ Hz, 1H), 4.28 (q, $J = 7.1$ Hz, 2H), 2.80 (d, $J = 9.8$ Hz, 2H), 2.02 (s, 2H), 1.87 (d, $J = 12.4$ Hz, 11H), 1.35 (t, $J = 7.1$ Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.55, 154.29, 147.76, 145.83, 144.86, 135.25, 132.30, 131.11, 130.36, 128.02, 117.55, 115.17, 60.74, 39.85, 39.82, 37.31, 34.81, 34.76, 28.36, 14.58. HRMS (ESI) calcd for $C_{28}H_{31}O_3$ ($M+H^+$) 415.2273, found 415.2264.

[00261] Butyl (E)-3-(4-(((1*r*,3*r*,5*R*,7*S*)-Adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl) acrylate (**9**). Following the general procedure for Heck reaction using corresponding triflate and butyl acrylate, compound **9** was obtained as yellow solid (Yield 54%, mp 140°C). 1H NMR (500 MHz, $CDCl_3$) δ 7.64 (d, $J = 15.9$ Hz, 1H), 7.43 – 7.35 (m, 2H), 7.12 (m, 2H), 6.98 – 6.94 (m, 2H), 6.76 (m, 2H), 6.38 (d, $J = 15.9$ Hz, 1H), 4.19 (t, $J = 6.3$ Hz, 2H), 2.77 (d, $J = 19.4$ Hz, 2H), 1.98 (m, 2H), 1.83 (d, $J = 13.2$ Hz, 10H), 1.68 (m, 2H), 1.41 (m, 2H), 0.95 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.9, 154.5, 147.6, 145.9, 145.1, 134.9, 133.0, 132.1, 131.0, 130.3, 129.7, 128.0, 117.3, 115.2, 77.5, 77.2, 64.8, 39.8, 39.8, 37.3, 34.8,

34.7, 30.9, 28.3, 28.3, 19.4, 14.0. HRMS-ESI: m/z $[M-H]^+$ for $C_{30}H_{33}O_3$, calculated 441.2430; observed 441.2420.

[00262] 6-Methylheptyl (E)-3-(4-(((1r,3r,5R,7S)-Adamantan-2-ylidene)(4-hydroxyphenyl)methyl) phenyl)acrylate (**10**). Following the general procedure for Heck reaction using corresponding triflate and 6-methylheptyl acrylate, compound **10** was obtained as yellow solid (Yield 45%, sticky semisolid, no mp determined). 1H NMR (499 MHz, $CDCl_3$) δ 7.68 (d, J = 16.0 Hz, 1H), 7.45 (d, J = 7.5 Hz, 2H), 7.16 (d, J = 8.1 Hz, 2H), 7.01 (d, J = 8.5 Hz, 2H), 6.78 (d, J = 8.5 Hz, 2H), 6.41 (d, J = 15.9 Hz, 1H), 4.27 (m, 2H), 2.81 (d, J = 10.7 Hz, 2H), 2.04 (m, 2H), 1.88 (m, 10H), 1.68 (m, 5H), 1.46 – 1.25 (m, 5H), 0.90 (m, Hz, 7H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.7, 154.3, 147.8, 145.8, 144.8, 135.3, 132.3, 131.1, 130.4, 129.7, 128.0, 117.6, 115.2, 77.5, 65.3, 65.0, 39.8, 39.8, 37.3, 34.8, 34.7, 28.4. HRMS-ESI: m/z $[M-H]^+$ for $C_{34}H_{41}O_3$, calculated 497.3056; observed 497.3052.

[00263] 2-Hydroxyethyl (E)-3-(4-(((1r,3r,5R,7S)-Adamantan-2-ylidene)(4-hydroxyphenyl)methyl) phenyl)acrylate (**11**). Following the general procedure for Heck reaction using corresponding triflate and 2-hydroxyethyl acrylate, compound **11** was obtained as white solid (Yield 46%, mp 158°C). 1H NMR (500 MHz, $CDCl_3$) δ 7.67 (d, J = 16.0 Hz, 1H), 7.39 (d, J = 8.0 Hz, 2H), 7.11 (d, J = 7.9 Hz, 2H), 6.95 (d, J = 8.4 Hz, 2H), 6.73 (d, J = 8.5 Hz, 2H), 6.40 (d, J = 16.0 Hz, 1H), 4.36 – 4.31 (m, 2H), 3.92 – 3.87 (m, 2H), 2.76 (d, J = 11.6 Hz, 2H), 1.98 (m, 2H), 1.83 (m, Hz, 10H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.8, 154.5, 147.7, 145.9, 145.0, 135.0, 133.3, 132.2, 131.0, 130.3, 129.9, 129.7, 128.5, 128.0, 117.4, 115.2, 77.5, 69.4, 64.2, 60.8, 39.8, 39.8, 37.3, 34.8, 34.7, 28.3, 14.5. HRMS-ESI: m/z $[M-H]^+$ for $C_{28}H_{29}O_4$, calculated 429.2066; observed 429.2057.

[00264] 3-Hydroxypropyl (E)-3-(4-(((1r,3r,5R,7S)-Adamantan-2-ylidene)(4-hydroxyphenyl)methyl) phenyl)acrylate (**12**). To a solution of cinnamic acid (1, 1 equivalent) and DMAP (2 mol%) in DCM at -15 °C, Et_3N (1 equivalent) and isobutyl chloroformate (2.2 equivalent) were added sequentially and the reaction mixture was allowed to reach room temperature (22 °C) over 3 h. Thereafter, piperidine (15 equivalent) was added and the resulting mixture further stirred for 1 h at room temperature. The reaction mixture was evaporated under vacuum and ethyl acetate was added followed by washing with $KHSO_4$ (10%). The organic

component was dried with Na_2SO_4 and vacuum evaporated. The resulting residue was purified by flash chromatography (10-80% Ethyl acetate/Hexane gradient) on silica gel to give the desired product **12** as white solid (Yield 49%, mp 165-168°C). ^1H NMR (500 MHz, CDCl_3) δ 7.65 (d, $J = 16.0$ Hz, 1H), 7.42 – 7.37 (m, 2H), 7.14 – 7.09 (m, 2H), 6.98 – 6.93 (m, 2H), 6.76 – 6.71 (m, 2H), 6.37 (d, $J = 16.0$ Hz, 1H), 4.36 (t, $J = 6.1$ Hz, 2H), 3.72 (t, $J = 6.0$ Hz, 2H), 2.76 (d, $J = 16.2$ Hz, 2H), 2.02 – 1.96 (m, 2H), 1.93 (p, $J = 6.0$ Hz, 2H), 1.89 – 1.78 (m, 10H). ^{13}C NMR (125 MHz, CDCl_3) δ 168.0, 154.4, 147.8, 146.1, 145.5, 135.1, 132.1, 131.1, 130.4, 129.7, 128.1, 117.0, 115.2, 77.5, 61.6, 59.4, 39.8, 39.8, 37.3, 34.8, 34.7, 32.1, 28.3. HRMS-ESI: m/z $[\text{M-H}]^-$ for $\text{C}_{29}\text{H}_{31}\text{O}_4$, calculated 443.2222; observed 443.2215.

[00265] 4-Hydroxybutyl (E)-3-(4-(((1r,3r,5R,7S)-Adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)acrylate (**13**). Following the general procedure for Heck reaction using corresponding triflate and 4-hydroxybutyl acrylate, compound **13** was obtained as yellow solid (Yield 57%, mp 180-181°C). ^1H NMR (500 MHz, CDCl_3) δ 7.63 (d, $J = 15.9$ Hz, 1H), 7.41 – 7.34 (m, 2H), 7.10 (m, $J = 2.1$, 8.4 Hz, 2H), 6.96 – 6.91 (m, 2H), 6.76 – 6.70 (m, 2H), 6.36 (d, $J = 15.9$ Hz, 1H), 4.22 (t, $J = 6.5$ Hz, 2H), 3.70 (t, $J = 6.4$ Hz, 2H), 2.76 (d, $J = 18$ Hz, 2H), 2.00 – 1.95 (m, 2H), 1.89 – 1.74 (m, 12H), 1.67 (m, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 167.7, 154.5, 147.7, 146.0, 145.2, 134.9, 132.1, 131.0, 130.3, 129.7, 128.0, 117.2, 115.2, 77.0, 64.6, 62.7, 39.8, 39.8, 37.3, 34.8, 34.7, 29.3, 28.3, 25.4. HRMS-ESI: m/z $[\text{M-H}]^-$ for $\text{C}_{30}\text{H}_{33}\text{O}_4$, calculated 457.2379; observed 457.2377.

[00266] (E)-3-(4-(((1r,3r,5R,7S)-Adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)acrylonitrile (**14**). Following the general procedure for Heck reaction using corresponding triflate and acrylonitrile, compound **14** was obtained as yellow solid (Yield 55%, mp 156°C). ^1H NMR (500 MHz, CDCl_3) δ 7.42 – 7.35 (m, 3H), 7.17 (d, $J = 8.2$ Hz, 2H), 6.99 (d, $J = 8.5$ Hz, 2H), 6.77 (d, $J = 8.5$ Hz, 2H), 5.84 (d, $J = 16.6$ Hz, 1H), 2.81 (s, 1H), 2.76 (s, 1H), 2.03 (s, 2H), 1.93 – 1.83 (m, 10H). ^{13}C NMR (126 MHz, CDCl_3) δ 154.29, 150.71, 148.29, 146.89, 135.06, 131.43, 131.12, 130.58, 129.40, 127.33, 118.70, 115.22, 95.46, 39.84, 39.80, 37.26, 34.87, 34.77, 28.31. HRMS (ESI) calcd for $\text{C}_{30}\text{H}_{37}\text{N}_2\text{O}_2$ ($\text{M}+\text{H}^+$) 457.2855, found 457.2864.

[00267] (E)-2-(4-(((1r,3r,5R,7S)-Adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)-N-propylethene-1-sulfonamide (**15**). Following the general procedure for Heck reaction using

corresponding triflate and N-propylethene sulfonamide, compound **15** was obtained as yellow solid (Yield 46%, mp 205-207°C). ¹H NMR (500 MHz, CDCl₃) δ 7.46 (d, *J* = 15.4 Hz, 1H), 7.40 (d, *J* = 8.2 Hz, 2H), 7.17 (d, *J* = 8.2 Hz, 2H), 6.99 (d, *J* = 8.6 Hz, 2H), 6.78 (d, *J* = 8.6 Hz, 2H), 6.70 (d, *J* = 15.4 Hz, 1H), 3.03 (q, *J* = 6.9 Hz, 2H), 2.82 (s, 1H), 2.77 (d, *J* = 3.8 Hz, 1H), 2.03 (s, 2H), 1.87 (d, *J* = 11.5 Hz, 10H), 1.64 – 1.57 (m, 2H), 0.95 (t, *J* = 7.4 Hz, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 154.41, 148.04, 146.46, 141.88, 135.02, 131.09, 130.55, 130.40, 129.51, 128.18, 124.28, 115.22, 45.04, 39.85, 39.81, 37.28, 34.85, 34.75, 28.33, 23.52, 11.43. HRMS (ESI) calcd for C₃₀H₃₇N₂O₂ (M+H⁺) 457.2855, found 457.2864.

[00268] (E)-3-(4-(((1r,3r,5R,7S)-Adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)acrylamide (**16**). Following the general procedure for Heck reaction using corresponding triflate and acrylamide, compound **16** was obtained as white solid (Yield 56%, mp 221°C). ¹H NMR (500 MHz, DMSO-*d*₆) δ 9.32 (s, 1H), 7.45 (d, *J* = 8.1 Hz, 2H), 7.35 (d, *J* = 15.8 Hz, 1H), 7.07 (d, *J* = 7.9 Hz, 2H), 6.86 (d, *J* = 8.4 Hz, 2H), 6.67 (d, *J* = 8.4 Hz, 2H), 6.53 (d, *J* = 15.8 Hz, 1H), 2.70 (s, 1H), 2.64 (s, 1H), 1.94 (s, 2H), 1.80 (s, 10H). ¹³C NMR (126 MHz, DMSO-*d*₆) δ 167.37, 156.48, 146.21, 144.85, 139.58, 133.29, 130.89, 130.32, 128.00, 122.35, 115.59, 37.19, 34.69, 34.53, 28.17. HRMS (ESI) calcd for C₂₆H₂₈NO₂ (M+H⁺) 386.2120, found 386.2110.

[00269] (E)-3-(4-(((1r,3r,5R,7S)-Adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)-N-propylacrylamide (**17**). Following the general procedure for amide synthesis between **5** and propylamine, compound **17** was obtained as white solid (Yield 82%, mp 250°C). ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.07 (t, *J* = 5.4 Hz, 1H), 7.44 (d, *J* = 7.7 Hz, 2H), 7.34 (d, *J* = 15.8 Hz, 1H), 7.06 (d, *J* = 7.6 Hz, 2H), 6.85 (d, *J* = 7.8 Hz, 2H), 6.67 (d, *J* = 7.7 Hz, 2H), 6.57 (s, 1H), 3.10 (q, *J* = 6.5 Hz, 2H), 2.69 (s, 1H), 2.64 (s, 1H), 1.94 (s, 2H), 1.79 (s, 11H), 1.44 (q, *J* = 7.2 Hz, 2H), 0.85 (t, *J* = 7.4 Hz, 3H). ¹³C NMR (126 MHz, DMSO-*d*₆) δ 165.54, 156.48, 146.19, 144.74, 138.77, 133.38, 133.30, 130.87, 130.34, 130.30, 127.90, 122.41, 115.59, 37.19, 34.67, 34.54, 28.18, 23.09, 12.17. HRMS (ESI) calcd for C₂₉H₃₄NO₂ (M+H⁺) 428.2590, found 428.2581.

[00270] (E)-3-(4-(((1r,3r,5R,7S)-Adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)-N-butylacrylamide (**18**). Following the general procedure for amide synthesis between **5** and butylamine, compound **18** was obtained as white solid (Yield 86%, mp 304°C). ¹H NMR (500

MHz, DMSO- d_6) δ 8.04 (t, J = 5.6 Hz, 1H), 7.44 (d, J = 8.2 Hz, 2H), 7.34 (d, J = 15.7 Hz, 1H), 7.06 (d, J = 8.1 Hz, 2H), 6.85 (d, J = 8.5 Hz, 2H), 6.66 (d, J = 8.5 Hz, 2H), 6.54 (d, J = 15.8 Hz, 1H), 3.14 (q, J = 6.8 Hz, 2H), 2.69 (s, 1H), 2.64 (s, 1H), 1.94 (s, 2H), 1.79 (s, 11H), 1.41 (p, J = 7.1 Hz, 2H), 1.32 – 1.25 (m, 2H), 0.86 (t, J = 7.3 Hz, 3H). ^{13}C NMR (126 MHz, DMSO- d_6) δ 165.50, 156.48, 146.19, 144.74, 138.76, 133.39, 133.31, 130.88, 130.34, 130.31, 127.90, 122.40, 115.59, 37.19, 34.54, 31.93, 28.18, 20.32, 14.36. HRMS (ESI) calcd for $\text{C}_{30}\text{H}_{36}\text{NO}_2$ ($\text{M}+\text{H}^+$) 442.2746, found 442.2739.

[00271] (E)-3-(4-(((1r,3r,5R,7S)-Adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)-N-pentylacrylamide (**19**). Following the general procedure for amide synthesis between **5** and pentylamine, compound **19** was obtained as white solid (Yield 82%, mp 301-303°C). ^1H NMR (500 MHz, DMSO- d_6) δ 8.05 (t, J = 5.7 Hz, 1H), 7.44 (d, J = 8.2 Hz, 2H), 7.34 (d, J = 15.7 Hz, 1H), 7.06 (d, J = 8.2 Hz, 2H), 6.85 (d, J = 8.5 Hz, 2H), 6.67 (d, J = 8.5 Hz, 2H), 6.54 (d, J = 15.8 Hz, 1H), 3.13 (q, J = 6.8 Hz, 2H), 2.69 (s, 1H), 2.64 (s, 1H), 1.94 (s, 2H), 1.79 (s, 11H), 1.42 (p, J = 7.2 Hz, 2H), 1.33 – 1.13 (m, 6H), 0.85 (t, J = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, DMSO- d_6) δ 165.49, 156.49, 146.18, 144.74, 138.74, 133.39, 133.30, 130.87, 130.34, 130.30, 127.90, 122.42, 115.59, 37.19, 34.68, 34.54, 29.51, 29.37, 28.18, 22.55, 14.61. HRMS (ESI) calcd for $\text{C}_{31}\text{H}_{38}\text{NO}_2$ ($\text{M}+\text{H}^+$) 456.2903, found 456.2897.

[00272] (E)-3-(4-(((1r,3r,5R,7S)-Adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)-N-(2-hydroxyethyl)acrylamide (**20**). Following the general procedure for amide synthesis between **5** and ethanolamine, compound **20** was obtained as white solid (Yield 76%, mp 259°C). ^1H NMR (500 MHz, DMSO- d_6) δ 9.32 (s, 1H), 8.11 (t, J = 5.6 Hz, 1H), 7.44 (d, J = 8.0 Hz, 2H), 7.36 (d, J = 15.7 Hz, 1H), 7.07 (d, J = 7.9 Hz, 2H), 6.86 (d, J = 8.2 Hz, 2H), 6.67 (d, J = 8.4 Hz, 2H), 6.60 (d, J = 15.8 Hz, 1H), 4.73 (t, J = 5.4 Hz, 1H), 3.45 (d, J = 5.9 Hz, 2H), 3.22 (q, J = 5.8 Hz, 2H), 2.70 (s, 1H), 2.64 (s, 1H), 1.94 (s, 2H), 1.79 (s, 10H). ^{13}C NMR (126 MHz, DMSO- d_6) δ 165.79, 156.49, 146.19, 144.77, 138.88, 133.38, 133.31, 130.87, 130.34, 130.31, 127.92, 122.39, 115.59, 60.58, 42.35, 37.19, 34.67, 34.54, 28.18. HRMS (ESI) calcd for $\text{C}_{28}\text{H}_{32}\text{NO}_3$ ($\text{M}+\text{H}^+$) 430.2382, found 430.2374.

[00273] (E)-3-(4-(((1r,3r,5R,7S)-Adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)-N-(3-hydroxypropyl)acrylamide (**21**). Following the general procedure for amide synthesis between

5 and 3-amino-1-propanol, compound **21** was obtained as white solid (Yield 74%, mp 155°C). ¹H NMR (500 MHz, DMSO-*d*₆) δ 7.44 (d, *J* = 8.1 Hz, 2H), 7.35 (d, *J* = 15.7 Hz, 1H), 7.07 (d, *J* = 8.1 Hz, 2H), 6.85 (d, *J* = 8.4 Hz, 2H), 6.66 (d, *J* = 8.5 Hz, 2H), 6.54 (d, *J* = 15.8 Hz, 1H), 4.46 (t, *J* = 5.1 Hz, 1H), 3.41 (q, *J* = 6.0 Hz, 2H), 3.19 (q, *J* = 6.7 Hz, 2H), 2.69 (s, 1H), 2.64 (s, 1H), 1.94 (s, 2H), 1.79 (s, 10H), 1.58 (p, *J* = 6.5 Hz, 2H). ¹³C NMR (126 MHz, DMSO-*d*₆) δ 165.67, 156.48, 146.19, 144.76, 138.80, 133.37, 133.30, 130.87, 130.34, 130.30, 127.91, 122.33, 115.59, 59.09, 37.19, 36.59, 34.67, 34.54, 33.11, 28.18. HRMS (ESI) calcd for C₂₉H₃₄NO₃ (M+H⁺) 444.2540, found 444.2533.

[00274] (E)-3-(4-(((1*r*,3*r*,5*R*,7*S*)-Adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)-N-(4-hydroxybutyl)acrylamide (**22**). Following the general procedure for amide synthesis between **5** and 4-amino-1-butanol, compound **22** was obtained as white solid (Yield 72%, mp 250°C). ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.06 (t, *J* = 5.6 Hz, 1H), 7.44 (d, *J* = 8.2 Hz, 2H), 7.35 (d, *J* = 15.7 Hz, 1H), 7.07 (d, *J* = 8.2 Hz, 2H), 6.85 (d, *J* = 8.5 Hz, 2H), 6.67 (d, *J* = 8.5 Hz, 2H), 6.55 (d, *J* = 15.8 Hz, 1H), 3.38 (q, *J* = 5.6 Hz, 2H), 3.14 (q, *J* = 6.4 Hz, 2H), 2.69 (s, 1H), 2.64 (s, 1H), 1.94 (s, 2H), 1.79 (s, 11H), 1.52 – 1.35 (m, 4H). ¹³C NMR (126 MHz, DMSO-*d*₆) δ 165.50, 146.19, 144.74, 138.77, 133.38, 133.31, 130.87, 130.34, 130.31, 127.90, 122.41, 115.57, 61.09, 39.28, 37.19, 34.67, 34.54, 30.66, 28.18, 26.53. HRMS (ESI) calcd for C₂₉H₃₄NO₃ (M+H⁺) 458.2699, found 458.2690.

[00275] (E)-3-(4-(((1*r*,3*r*,5*R*,7*S*)-Adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)-N-(5-hydroxypentyl)acrylamide (**23**). Following the general procedure for amide synthesis between **5** and 5-amino-1-pentanol, compound **23** was obtained as white solid (Yield 78%, mp 180°C). ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.05 (t, *J* = 5.6 Hz, 1H), 7.44 (d, *J* = 8.2 Hz, 2H), 7.34 (d, *J* = 15.7 Hz, 1H), 7.07 (d, *J* = 8.2 Hz, 2H), 6.85 (d, *J* = 8.5 Hz, 2H), 6.66 (d, *J* = 8.5 Hz, 2H), 6.54 (d, *J* = 15.8 Hz, 1H), 4.35 (t, *J* = 5.1 Hz, 1H), 3.40 – 3.35 (m, 2H), 3.13 (q, *J* = 6.7 Hz, 2H), 2.69 (s, 1H), 2.64 (s, 1H), 1.94 (s, 2H), 1.79 (s, 11H), 1.41 (dq, *J* = 14.7, 7.0, 6.6 Hz, 5H), 1.29 (q, *J* = 8.4 Hz, 2H). ¹³C NMR (126 MHz, DMSO-*d*₆) δ 165.49, 156.48, 146.19, 144.74, 138.76, 133.38, 133.31, 130.88, 130.33, 130.31, 127.91, 122.41, 115.59, 61.29, 39.41, 37.19, 34.67, 34.54, 32.91, 29.74, 28.17, 23.74. HRMS (ESI) calcd for C₃₁H₃₈NO₃ (M+H⁺) 472.2852, found 472.2848.

[00276] (E)-3-(4-(((1r,3r,5R,7S)-Adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)-N-(2-aminoethyl)acrylamide (**24**). Following the general procedure for amide synthesis between **5** and N-Boc-ethylenediamine, then following the general procedure for Boc deprotection, compound **24** was obtained as brown solid (Yield 46%, mp 163°C). ¹H NMR (500 MHz, Acetone-*d*₆) δ 7.53 (d, *J* = 15.7 Hz, 1H), 7.48 (d, *J* = 8.1 Hz, 3H), 7.15 (d, *J* = 8.2 Hz, 2H), 6.96 (d, *J* = 11.3 Hz, 2H), 6.77 (d, *J* = 9.3 Hz, 2H), 6.64 (d, *J* = 15.7 Hz, 1H), 3.40 – 3.33 (m, 2H), 3.12 (s, 2H), 2.80 (s, 1H), 2.74 (s, 1H), 1.98 (s, 2H), 1.85 (s, 11H). ¹³C NMR (126 MHz, Acetone-*d*₆) δ 146.46, 141.15, 133.83, 132.90, 130.69, 130.12, 127.72, 120.03, 115.06, 39.45, 39.42, 37.04, 34.73, 34.61, 28.37. HRMS (ESI) calcd for C₂₈H₃₃N₂O₂ (M+H⁺) 429.2542, found 429.2531.

[00277] (E)-3-(4-(((1r,3r,5R,7S)-Adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)-N-(3-aminopropyl)acrylamide (**25**). Following the general procedure for amide synthesis between **5** and N-Boc-1,3-propane-diamine, then following the general procedure for Boc deprotection, compound **25** was obtained as yellow solid (Yield 42%, mp 187°C). ¹H NMR (500 MHz, DMSO-*d*₆) δ 7.45 (dd, *J* = 8.1, 5.3 Hz, 2H), 7.36 (dd, *J* = 15.7, 13.1 Hz, 1H), 7.07 (dd, *J* = 8.2, 3.8 Hz, 2H), 6.85 (d, *J* = 11.1 Hz, 2H), 6.67 (d, *J* = 8.5 Hz, 2H), 6.55 (dd, *J* = 15.8, 2.3 Hz, 1H), 3.25 – 3.17 (m, 2H), 3.12 (s, 1H), 2.72 (s, 2H), 2.64 (s, 1H), 1.94 (s, 2H), 1.79 (s, 11H), 1.72 – 1.62 (m, 2H). ¹³C NMR (126 MHz, DMSO-*d*₆) δ 165.98, 165.57, 156.48, 146.19, 144.75, 138.74, 133.38, 133.29, 130.86, 130.31, 127.98, 127.91, 122.41, 122.03, 115.59, 48.91, 37.18, 34.67, 34.54, 31.38, 31.06, 28.17. HRMS (ESI) calcd for C₂₉H₃₅N₂O₂ (M+H⁺) 443.2699, found 443.2689.

[00278] (E)-3-(4-(((1r,3r,5R,7S)-Adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)-N-(4-aminobutyl)acrylamide (**26**). Following the general procedure for amide synthesis between **5** and N-Boc-1,4-butane- diamine, then following the general procedure for Boc deprotection, compound **26** was obtained as yellow solid (Yield 45%, mp 191°C). ¹H NMR (500 MHz, DMSO-*d*₆) δ 7.44 (t, *J* = 7.5 Hz, 2H), 7.36 (d, *J* = 15.7 Hz, 1H), 7.08 (d, *J* = 8.2 Hz, 2H), 6.86 (d, *J* = 8.4 Hz, 2H), 6.67 (d, *J* = 8.2 Hz, 2H), 6.56 (d, *J* = 15.8 Hz, 1H), 3.56 (t, *J* = 7.0 Hz, 1H), 3.19 (t, *J* = 6.7 Hz, 2H), 2.70 (s, 1H), 2.64 (s, 1H), 2.35 – 2.24 (m, 2H), 1.94 (s, 2H), 1.80 (s, 10H), 1.63 (d, *J* = 7.3 Hz, 2H), 1.51 (t, *J* = 10.8 Hz, 2H). ¹³C NMR (126 MHz, DMSO-*d*₆) δ 164.78, 156.52, 146.14, 144.56, 138.10, 133.56, 133.30, 130.83, 130.37, 130.27, 127.80, 123.86, 115.61,

110.00, 51.53, 41.69, 36.73, 35.80, 34.55, 29.49, 28.98, 28.18. HRMS (ESI) calcd for $C_{30}H_{37}N_2O_2 (M+H^+)$ 457.2855, found 457.2847.

[00279] (E)-3-(4-(((1r,3r,5R,7S)-Adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)-N-(2,2,2-trifluoroethyl)acrylamide (**27**). Following the general procedure for amide synthesis between **5** and 2,2,2-trifluoroethylamine, compound **27** was obtained as yellow solid (Yield 65%, mp 217°C). 1H NMR (500 MHz, DMSO- d_6) δ 9.32 (s, 1H), 8.72 (t, J = 6.4 Hz, 1H), 7.51 – 7.44 (m, 3H), 7.09 (d, J = 8.2 Hz, 2H), 6.86 (d, J = 8.5 Hz, 2H), 6.72 – 6.58 (m, 3H), 4.08 – 3.95 (m, 2H), 2.70 (s, 1H), 2.64 (s, 1H), 1.95 (s, 2H), 1.80 (s, 10H). ^{13}C NMR (126 MHz, DMSO- d_6) δ 146.46, 141.15, 133.83, 132.90, 130.69, 130.12, 127.72, 120.03, 115.06, 39.45, 39.42, 37.04, 34.73, 34.61, 28.37. HRMS (ESI) calcd for $C_{29}H_{34}NO_2F_3 (M+H^+)$ 468.2150, found 468.2144.

[00280] (E)-3-(4-(((1r,3r,5R,7S)-Adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)-N-butyl-N-methylacrylamide (**28**). Following the general procedure for amide synthesis between **5** and N-methylbutylamine, compound **28** was obtained as white solid (Yield 66%, mp 207-209°C). 1H NMR (500 MHz, DMSO- d_6) δ 9.32 (s, 1H), 7.65 – 7.51 (m, 2H), 7.41 (dd, J = 15.3, 11.9 Hz, 1H), 7.11 – 7.02 (m, 3H), 6.85 (d, J = 11.0 Hz, 2H), 6.67 (d, J = 8.5 Hz, 2H), 3.47 (t, J = 7.3 Hz, 1H), 3.34 (d, J = 7.8 Hz, 1H), 3.09 (s, 1H), 2.88 (s, 2H), 2.71 (s, 1H), 2.64 (s, 1H), 1.94 (s, 2H), 1.79 (s, 10H), 1.54 – 1.40 (m, 2H), 1.25 (dq, J = 14.6, 7.5 Hz, 2H), 0.87 (t, J = 7.3 Hz, 3H). ^{13}C NMR (126 MHz, DMSO- d_6) δ 166.05, 165.87, 156.48, 146.15, 144.88, 141.34, 133.68, 133.63, 133.26, 130.88, 130.38, 130.15, 128.38, 119.00, 118.45, 115.57, 49.38, 47.53, 37.20, 35.61, 34.71, 34.52, 34.36, 31.51, 29.61, 28.18, 20.26, 19.96, 14.47. HRMS (ESI) calcd for $C_{31}H_{38}NO_2 (M+H^+)$ 456.2903, found 456.2904.

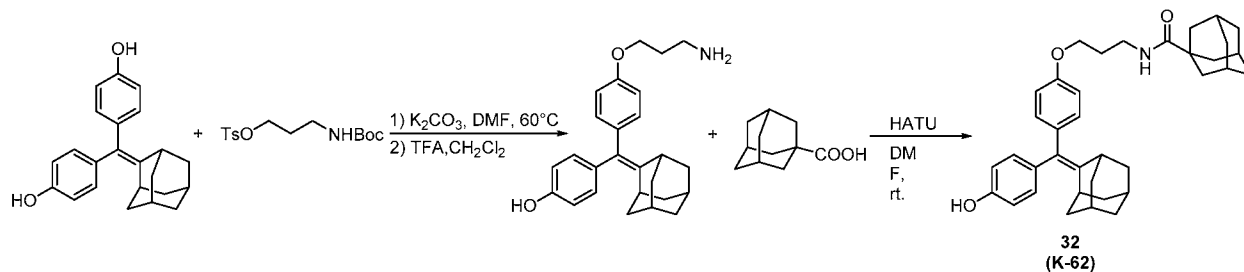
[00281] (E)-3-(4-(((1r,3r,5R,7S)-Adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)-N-(2-hydroxyethyl)-N-methylacrylamide (**29**). Following the general procedure for amide synthesis between **5** and 2-(methylamino)ethanol, compound **29** was obtained as white solid (Yield 71%, mp 225-228°C). 1H NMR (500 MHz, DMSO- d_6) δ 9.33 (s, 1H), 7.57 (dd, J = 15.0, 8.1 Hz, 2H), 7.40 (dd, J = 15.3, 9.1 Hz, 1H), 7.15 – 7.02 (m, 3H), 6.86 (d, J = 8.4 Hz, 2H), 6.67 (d, J = 8.4 Hz, 2H), 3.53 (s, 3H), 3.41 (t, J = 5.9 Hz, 1H), 3.16 (s, 1H), 2.92 (s, 2H), 2.71 (s, 1H), 2.64 (s, 1H), 1.94 (s, 2H), 1.79 (s, 10H). ^{13}C NMR (126 MHz, DMSO- d_6) δ 166.47, 166.17, 156.47, 146.13, 144.91, 144.80, 140.81, 133.77, 133.25, 130.89, 130.38, 130.14, 128.40, 128.29, 119.24,

118.91, 115.57, 59.92, 59.40, 52.09, 37.20, 34.85, 34.73, 34.51, 28.18. HRMS (ESI) calcd for $C_{29}H_{34}NO_3$ ($M+H^+$) 444.2539, found 444.2519.

[00282] (E)-3-(4-(((1r,3r,5R,7S)-Adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)-N,N-bis(2-hydroxyethyl)acrylamide (**30**). Following the general procedure for amide synthesis between **5** and diethanolamine, compound **30** was obtained as yellow solid (Yield 78%, mp 219°C). 1H NMR (499 MHz, $DMSO-d_6$) δ 7.57 (d, J = 8.1 Hz, 2H), 7.42 (d, J = 15.4 Hz, 1H), 7.14 – 7.03 (m, 3H), 6.87 (d, J = 8.2 Hz, 2H), 6.68 (d, J = 8.2 Hz, 2H), 4.84 (t, J = 5.3 Hz, 1H), 4.72 (t, J = 5.3 Hz, 1H), 3.64 – 3.48 (m, 6H), 3.44 (t, J = 6.0 Hz, 2H), 2.72 (s, 1H), 2.65 (s, 1H), 1.96 (s, 2H), 1.81 (s, 10H). ^{13}C NMR (126 MHz, $DMSO-d_6$) δ 171.55, 166.46, 156.47, 153.20, 146.16, 144.84, 141.07, 134.92, 133.75, 133.26, 130.87, 130.37, 130.14, 128.31, 119.32, 115.58, 114.33, 60.52, 59.65, 54.22, 51.34, 50.01, 37.20, 34.72, 34.51, 28.18. HRMS (ESI) calcd for $C_{30}H_{36}NO_4$ ($M+H^+$) 474.2644, found 474.2648.

[00283] (E)-3-(4-(((1r,3r,5R,7S)-Adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)-N-(2-(dimethylamino)ethyl)acrylamide (**31**). Following the general procedure for amide synthesis between **5** and N,N-dimethyl-ethylenediamine, compound **31** was obtained as white solid (Yield 75%, mp 283°C). 1H NMR (500 MHz, $DMSO-d_6$) δ 8.00 (t, J = 5.6 Hz, 1H), 7.45 (d, J = 8.1 Hz, 2H), 7.35 (d, J = 15.7 Hz, 1H), 7.07 (d, J = 7.9 Hz, 2H), 6.85 (d, J = 8.2 Hz, 2H), 6.67 (d, J = 8.4 Hz, 2H), 6.63 – 6.55 (m, 1H), 3.25 (q, J = 6.3 Hz, 2H), 2.70 (s, 1H), 2.64 (s, 1H), 2.32 (t, J = 6.5 Hz, 2H), 2.14 (s, 6H), 1.93 (s, 2H), 1.79 (s, 10H). ^{13}C NMR (126 MHz, $DMSO-d_6$) δ 165.61, 156.50, 146.19, 144.78, 138.90, 133.40, 133.31, 130.87, 130.36, 130.30, 127.94, 122.37, 115.60, 58.92, 45.83, 37.50, 37.20, 34.57, 28.20. HRMS (ESI) calcd for $C_{30}H_{37}N_2O_2$ ($M+H^+$) 457.2855, found 457.2864.

[00284] (3r,5r,7r)-N-(3-(4-(((1r,3r,5R,7S)-adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenoxy)propyl)adamantane-1-carboxamide (**32**, code K-62).



[00285] To a DMF solution of 4,4'-(((1r,3r,5r,7r)-adamantan-2-ylidene)methylene)diphenol (1.0 eq.), K₂CO₃ (1.5 eq.) and 3-((tert-butoxycarbonyl)amino)propyl 4-methylbenzenesulfonate (1.2 eq.) were added subsequently. The reaction mixture was kept stirring at 60 °C overnight. The mixture then was cooled to r.t. and extracted with ethyl acetate. The organic layer was dried with anhydrous Na₂SO₄ and concentrated under vacuum. The resulting residue was dissolved in CH₂Cl₂. TFA was added dropwise at 0 °C. The reaction was monitored by TLC. After complete consumption of starting material, ethyl acetate was added, and the resulting solution was washed with brine. The organic layer was dried with anhydrous Na₂SO₄ and concentrated under vacuum. The resulting residue was dissolved in DMF and reacted with 1-adamantanecarboxylic acid following the general procedure for amide synthesis. Further purification by flash chromatography (10–80% ethyl acetate/hexane gradient) on silica gave compound **32** as white powder. ¹H NMR (500 MHz, CDCl₃) δ 7.10 – 7.02 (m, 2H), 7.02 – 6.94 (m, 2H), 6.87 – 6.79 (m, 2H), 6.79 – 6.72 (m, 2H), 6.23 (s, 1H), 4.05 (t, *J* = 5.6 Hz, 2H), 3.47 (q, *J* = 5.9 Hz, 2H), 2.81 (s, 1H), 2.78 (s, 1H), 2.09 – 1.96 (m, 7H), 1.86 (q, *J* = 5.0, 4.5 Hz, 16H), 1.79 – 1.65 (m, 6H). ¹³C NMR (126 MHz, CDCl₃) δ 133.03, 130.97, 125.23, 115.03, 113.87, 77.52, 77.26, 77.01, 67.23, 62.57, 39.85, 39.49, 38.20, 36.77, 34.64, 29.03, 28.44, 28.36. HRMS-ESI: *m/z* [M+H]⁺ for C₃₇H₄₆NO₃, calculated 552.3478; observed 552.3472.

[00286] Biological Methods

[00287] Cell cultures, reagents and ligands

[00288] 17β-Estradiol (E2), 4-hydroxytamoxifen (4-OHT) and fulvestrant (ICI 182,780, Fulv) were from Sigma-Aldrich. Tritiated estradiol was obtained from Perkin Elmer and purified, full-length human estrogen receptor α from Invitrogen. MCF7 cells from the ATCC were maintained and cultured as described (Sengupta et. al. *Breast Cancer Res Treat* 2009, 117, 243-51). Cells were cultured in phenol-red free media supplemented with 5% charcoal stripped FBS for 5 days to be in an E2-deprived condition for some western blot and gene regulation studies. All cells were tested for mycoplasma using Real-Time PCR Mycoplasma Detection Kit (Akron Biotech, Boca Raton, FL).

[00289] Binding Assays

[00290] Competitive radiometric binding assays were performed on 96-well microtiter filter plates (Millipore), using full length human estrogen receptor α , with tritiated estradiol as tracer, as previously described (Carlson et. al. *Biochemistry* 1997, 36, 14897-905). After incubation on ice for 18-24 h, ER α -bound tracer was absorbed onto hydroxyapatite (BioRad), washed with buffer, and measured by scintillation counting. RBA values are the average $\pm$ SD of 2-3 determinations.

[00291] Cell proliferation assay

[00292] WST-1 assay (Roche, Basel, Switzerland) was used to quantify cell viability after a 6-day exposure to compounds, as described (Gong et. al. *Molecular and cellular endocrinology* **2016**, 437, 190-200). Absorbance was measured at 450 nm using a VICTOR X5 PerkinElmer 2030 Multilabel Plate Reader, and cell proliferation values represent signal from compound-treated samples relative to vehicle-treated controls. All assays were performed in triplicate, and the values shown in FIGS. 4A-4C are the average of 2-3 independent experiments.

[00293] In-cell western assay

[00294] Cells were cultured in 96-well plates at 3000 cells/well, and treated with compound for 24 h. Cells were washed twice in PBS, fixed with 4% formaldehyde (Fisher Scientific) solution in PBS, permeabilized in 0.1% Triton X-100 in PBS, blocked with Odyssey Blocking Buffer (LI-COR), and incubated with rabbit HC-20 ER α antibody (Santa Cruz, Cat# SC-543) at 4 °C overnight. Both IRDye 800 CW goat anti-rabbit secondary antibody (LI-COR, Cat# 926-32211) and Cell Tag 700 (LI-COR, Cat# 926-41090) were diluted (1:600) for incubation with cells. Plates were washed and ER α staining signals were quantified and normalized with Cell Tag signals using LI-COR Odyssey infrared imaging system. The ER α protein levels were calculated relative to the vehicle-treated samples. The values shown in FIGS. 4A-4C are the average from at least three independent experiments.

[00295] Western blot analysis

[00296] Western blot was performed as described (Jiang et. al. *FASEB journal: official publication of the Federation of American Societies for Experimental Biology* 2013, 27, 4406-18). Briefly, whole-cell protein extracts were prepared using 1 $\times$ complete protease inhibitor and

phosphatase inhibitor (Roche). Proteins were separated on 10% SDS-PAGE gels, transferred to nitrocellulose membranes and incubated with primary ER α antibody (F10, Santa Cruz Cat# 8002) and β -actin antibody (Sigma-Aldrich).

[00297] RNA isolation and real-time PCR

[00298] Total RNA was isolated using TRIzol (Invitrogen) and reverse transcribed using MMTV reverse transcriptase (New England BioLabs). Real-time PCR was performed using SYBRgreen PCR Master Mix (Roche) as described (Zhao et. al. *Endocrinology* 2016, 157, 900-12). Relative mRNA levels of genes were normalized to the housekeeping gene 36B4, and fold change calculated relative to the vehicle-treated samples. Results are the average $\pm$ SD from at least two independent experiments carried out in triplicate.

[00299] Example 8. Structurally Novel Antiestrogens Suppress Growth of Breast Cancer Cells with Constitutively Active Mutant ER α

[00300] Three new antiestrogens disclosed herein were first examined for their effects in T47D cells containing all wild type ER or all mutant ER (Y537S or D538G) (FIG. 10A). The mutant ERs were introduced by knockin using CRISPR-Cas9 technology (Mao et. al. *Scientific reports* 2016, 6:34753). The mutants examined are two of the most commonly occurring mutant ER α 's in humans with breast cancer, namely Y537S and D538G.

[00301] As shown in FIG. 10B, the mutants showed high constitutive activity in the absence of estrogen, having 11-times and four-times higher proliferative activity than that of cells containing wild type (WT) ER. Treatments with the known antiestrogens fulvestrant (Fulv) or AZD9496 resulted in marked suppression of this constitutive activity in both mutants. All three of the new compounds disclosed herein fully suppressed proliferative activity of the D538G cells, whereas in Y537S cells, good suppression was brought about by K-62 but to only a more limited extent by the K-07 and K-09 compounds. In the presence of E2 (FIG. 10C), proliferation of wild type and D538G cells was increased, whereas cells with Y537S ER proliferated rapidly in the absence of added E2 and showed no further increase with E2. Again, all five compounds suppressed proliferation of the mutant ER-containing cell lines, with proliferation of the D538G cells being more effectively suppressed by the antiestrogens versus the Y537S cells. In cells with

wild type and Y537S ER, K-62 was as inhibitory as Fulv and AZD, with K-07 and K-09 being less effective anti-proliferative agents.

[00302] In addition to the studies in FIG. 10 conducted at only one high concentration of each compound (3 μ M), dose-response studies with each of these compounds were carried out in the three cell types, i.e. containing WT or mutant ERs. As shown in FIG. 11, the mutants again showed constitutive ER activity that was not further increased by E2, whereas E2 increased WT cell proliferation to that of the constitutively active mutant ER cells in the absence of E2. With all five compounds, dose-dependent inhibition of cell proliferation revealed that mutant Y537S-ER and D538G-ER cells were more resistant to suppression by all of the antiestrogens, with Y537S cells requiring the highest concentrations of antiestrogens to bring about growth inhibition. Approximately 10-100 times higher concentrations of compounds were needed for equal suppression of growth in Y537S cells compared to D538G cells. Comparisons of cell proliferation conducted in WT and mutant ER α -expressing T47D cells in estrogen-replete conditions (i.e., full medium with 5% fetal bovine serum) again showed high resistance of Y537S ER containing cells to growth suppression by all antiestrogens (FIG. 18).

[00303] This difference in resistance between Y537S- and D538G-containing cells is not due to differences in the affinity of binding of these ligands to these two mutant ERs (Table 2). Of note, AEs bound about 10 to 40 times less well to these mutant ERs versus WT ERs. E2 was also found to bind 7 times less well to the mutants. These differences in ligand binding to the mutant ERs could in part explain their relative resistance to inhibition of proliferation by the AE compounds, but not the greater resistance of the Y537S mutant compared with the D538G mutant. In assays monitoring the reversal of coactivator SRC3/AIB1 binding to WT and mutant ERs, we again found that 10 to 50 times higher concentrations of AE ligands were required with mutant ERs than with WT ERs, but in this assay, the interaction of SRC3 with the Y537S mutant was more difficult to reverse than with the D538G mutant (FIG. 32), better reflecting the results from the proliferation inhibition assays.

[00304] Fluorescence Resonance Energy Transfer (FRET) analysis indicated that antiestrogen compounds K-07, K-09, K-62 and trans-hydroxy-tamoxifen (TOT) suppress the binding of SRC3 to wild type ER, Y537S-ER, and D538G-ER, in a dose dependent fashion (FIG. 26). Site-

specific labeled biotin-streptavidin/terbium ER-ligand binding domain constructs (donor) were primed to ~50% activity with estradiol and were then incubated with a fluorescein labeled SRC3 (acceptor). Increasing concentrations of E2 increased the interaction of ER and SRC3, and show increased FRET, whereas increasing concentrations of K-07, K-09, K-62 and TOT reduced the interaction of E2-ER and SRC3 and, as such, show reduced FRET. WT and mutant ERs required different E2 concentrations to be primed to ca. 50% activity (shown in brackets), reflecting their differing levels of constitutive activities and differing affinities for E2.

[00305] Table 2. Ligand Binding to Wild Type (WT) and Mutant ERs.

Ligand	K _i (nM) [Fold Increase Over WT]		
	WT	Y537S	D538G
E ₂ (Kd)	0.22 ± 0.11	1.40 ± 0.54 [6.4x]	1.77 ± 0.66 [8.0x]
Trans hydroxytamoxifen	0.12 ± 0.01	2.64 ± 0.4 [22.0x]	3.28 ± 0.7 [27.3x]
Fulvestrant	0.13 ± 0.03	3.68 ± 0.77 [28.3x]	5.06 ± 1.16 [38.9x]
AZD 9496	0.19 ± 0.05	5.20 ± 1.16 [26.9x]	7.52 ± 1.9 [39.0x]
K-07	0.30 ± 0.01	3.94 ± 1.10 [13.1x]	4.60 ± 1.28 [15.3x]
K-09	0.45 ± 0.07	2.88 ± 0.37 [6.4x]	7.00 ± 1.36 [15.6x]
K-62	0.47 ± 0.02	5.35 ± 1.37 [11.4x]	10.31 ± 2.93 [21.9x]

[00306] Example 9. Reduced Binding Affinities of AE Ligands for Mutant vs. WT ERs

[00307] Table 2 summarizes the binding affinity of these ligands to WT, Y537S and D538G ERs. Of note, antiestrogens bound about 10-40x less well to these mutant ERs vs. WT ER. E2 was also found to bind 7x less well to the mutants. Hence, higher concentrations of Antiestrogens (AEs) will be needed to reverse the constitutive activity of the mutants, as we have observed in our cell studies. These differences in ligand binding to the mutant ERs might in part explain their relative resistance to inhibition by the antiestrogen compounds.

[00308] Example 10. The Constitutive ER α Gene Expression Activity of Mutant ERs Is Suppressed by Novel Antiestrogen Compound

[00309] Constitutive expression of the ER target genes GREB1 and PGR in cells with mutant ER was observed, and consistent with the findings of anti-proliferative activities of Fulv and the three new compounds disclosed herein, it was found that Fulv, K-07, K-09 and K-62 effectively suppressed the expression of these genes in a dose-dependent manner (FIG. 12). Stimulation was most effectively turned off in the WT cells, with both GREB1 and PGR gene expression also being suppressed in both mutants by all compounds; however, higher concentrations of AEs were needed for suppression of gene expression in mutant ER versus WT ER-containing cells.

[00310] Example 11. Antiestrogenic Compounds Differentially Downregulate WT and Mutant ER α Proteins in Cells

[00311] Further experiments were conducted to compare the abilities of the compounds to elicit downregulation of WT ER α and mutant ER α proteins in the T47D cells. Levels of WT- and D538G-ER α were markedly reduced by Fulv and by our three antiestrogens, whereas the Y537S-ER α protein was very resistant to downregulation by all ligands (FIG. 13). Of note, 4-OHT did not downregulate mutant or WT-ER α (FIG. 13), although it reduced proliferation of WT and mutant ER-expressing cells (FIG. 11). In fact, 4-OHT reproducibly and dose-dependently upregulated Y537S ER α , implying a possible change in the dynamics of turnover of this particular mutant ER protein.

[00312] Example 12. Comparison of Ligand Effects in T47D and MCF-7 Cells Containing Both WT and Mutant ERs

[00313] Comparison studies were also carried out using MCF7 cells and T47D cells containing 50% mutant ER and 50% WT ER (FIG. 11). In these cells, it was found that high concentrations of Fulv, OHT, and K-07, K-09, and K-62 were also needed to obtain suppression of cell proliferation, similar to that observed in the T47D cells containing only mutant ER (FIG. 18). This suggests that the mutant ER α is dominant in determining cell phenotypic behavior when both receptors are present, as seems to be the case in human metastatic breast tumors with these mutant ERs. Of interest, some differences were seen in ligand potency and efficacy when

monitored in MCF7 or T47D cells. Hence, K-07 and K-09 worked more effectively as growth suppressors in MCF7 cells with mutant ERs, whereas Fulv was somewhat more potent in T47D cells with mutant ERs (FIG. 19). Likewise, the present compounds and Fulv could reduce the ER protein level in these MCF-7 and T47D cells, with Fulv generally eliciting a somewhat greater magnitude of down-regulation (FIG. 20).

[00314] When expression of estrogen target genes GREB1 and PGR was assessed in MCF-7 and T47D cells with 50% mutant and 50% WT ER, gene expression was constitutively high (FIG. 21) and only little increased with added E2. Gene expression was generally more fully suppressed by compounds in MCF7 cells versus T47D cells. Of note, the D538G ER was more fully inhibited than Y537S-ER, regardless of the cell background. These findings suggest that beyond the status of ER itself (WT or mutant), other genomic and cellular alterations in the different cell backgrounds may well contribute to differences in responsiveness to treatment with different antiestrogens. Hence, cell response to ligand depends on the cell type, the particular mutant ER, and the nature of the AE chemical compound.

[00315] Example 13. Structurally Novel Compounds Inhibit Tumor Growth of Wild Type and Mutant ER-containing Breast Cancer Cells *In Vivo*

[00316] As the new compounds disclosed herein suppress cell proliferation and ER target gene expression, the ability of K-07, K-09 and K-62 to suppress growth of ER-positive breast cancer xenografts in NSG mice was investigated. Studies were first conducted in MCF-7 xenografts containing wild type ER α . T47D xenografts containing wild type ER α was not studied because it was found that wild type T47D cells with E2 supplementation and mutant ER T47D cells without E2 pellets formed only very small tumors, whereas MCF-7 cells formed much larger and faster growing tumors. Mice were injected with cells sc into the mammary fat pad and compounds or Fulv were then administered daily sc at 80 mg/kg per day (FIG. 14). All compounds reduced tumor growth, with K-09 and K-62 being as effective as Fulv, and K-07 being the most effective in growth suppression (FIGS. 14A-14B). All compounds greatly reduced expression of the GREB1 and PGR genes monitored in tumors harvested at day 26 (FIG. 14C).

[00317] Example 14. Pharmacokinetic Properties of Antiestrogens K-07, K-09 and K-62

[00318] The pharmacokinetic properties of the antiestrogens, K-07, K-09 and K-62 after sc and oral administration in mice was monitored (FIG. 15). Overall, K-07 showed the most optimal PK properties by both sc and oral routes, having the highest blood levels and a long half-life in blood ($t_{1/2}$ = 14.0 h after sc injection or $t_{1/2}$ = 97.2 h after oral administration). This favorable PK profile underlies the observation that K-07 evoked the greatest tumor growth inhibition. Although K-09 and K-62 had long half-lives after sc injection, their blood levels were much lower compared with those of compound K-07. Because of its especially high blood levels and long half-life (97.2 h) after oral administration, K-07 was used by oral gavage in subsequent tumor growth experiments.

[00319] Example 15. K-07 is a Potent Oral Inhibitor of Tumor Progression *In Vivo*

[00320] Delivered (oral) K-07 very effectively reduced tumor growth within a few days of the start of treatment (FIGS. 16A-16B). ER target gene expression was also fully suppressed in tumors taken from these animals (FIG. 16C). Analysis of GREB1 and ER α protein showed almost complete loss of GREB1 protein expression and a 51% reduction of ER α in the tumors of K-07-treated animals (FIGS. 27A-27B). Although K-07, K-09 and K-62 by sc and K-07 by oral administration suppressed tumor growth substantially, there was no effect on animal body weight over the time course of the treatments (FIG. 22).

[00321] Example 16. Y537S-ER and D538G-ER-containing Cells Form Tumors in the Absence of Estrogen that are Arrested by K-07 Treatment

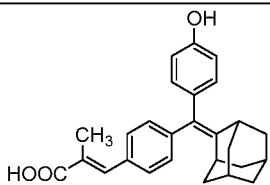
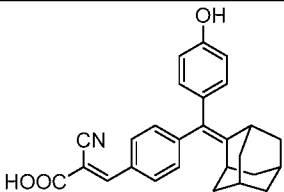
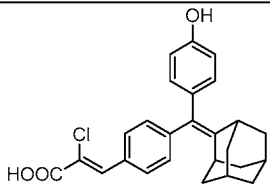
[00322] Y537S-ER and D538G-ER-containing cells form tumors in the absence of estrogen and are arrested by K-07 treatment to mirror the low estrogen environment in postmenopausal women, tumor xenograft studies with Y537S and D538G-containing MCF7 cells were conducted in ovariectomized NSG mice in the absence of any added E2. Y537S and D538G tumors grew well under these conditions, and growth of these constitutively active tumors was acutely arrested by subcutaneous treatment with K-07, as effectively as by fulvestrant (FIGS. 17A, 17B and 28A). Notably, oral K-07 was also very effective in arresting growth of the mutant ER tumors (FIG. 28B), and D538G tumors were more fully suppressed by K-07 treatment compared with Y537S tumors, consistent with the greater resistance of Y537S cells to antiproliferative effects of AEs that we found in cell cultures *in vitro*. Expression of estrogen-regulated genes,

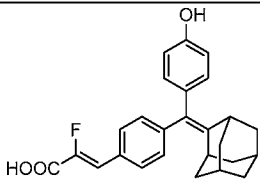
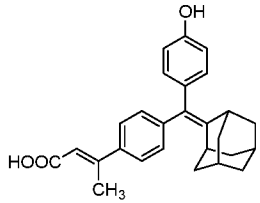
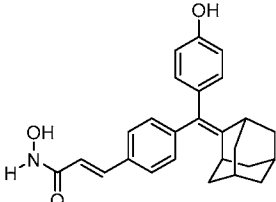
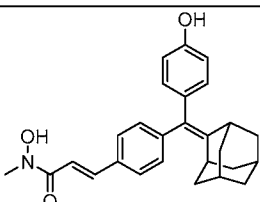
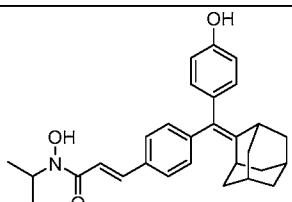
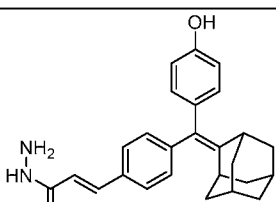
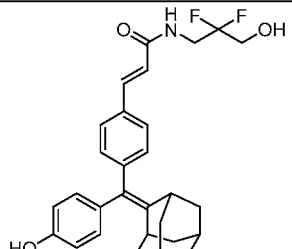
monitored in the small mutant ER-containing tumors at the end of the study, was almost fully suppressed by K-07 in both Y537S and D538G tumors (FIGS. 17D, 28C and 28D). Analysis of ER α protein by Western immunoblot in the small tumors harvested at the end of the study revealed a 60% and 75% decrease in ER α in Y537S and D538G tumors, respectively (FIG. 28E). This substantial decrease in ER α in Y537S and D538G tumors receiving K-07 versus vehicle treatment was also seen by IHC of tumors as a marked decrease in nuclear ER α staining (FIG. 28F).

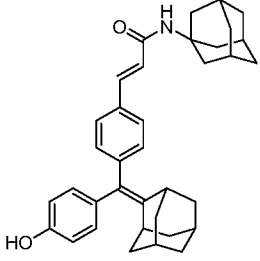
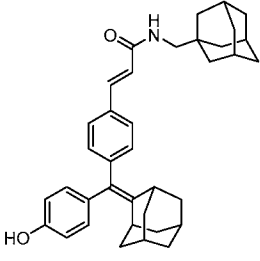
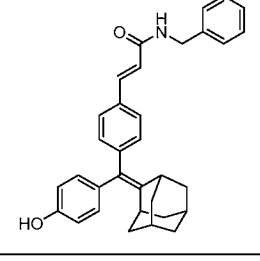
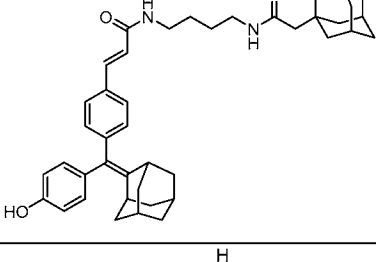
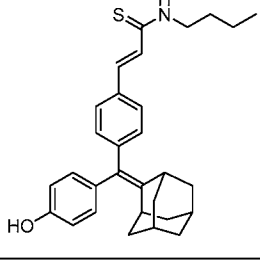
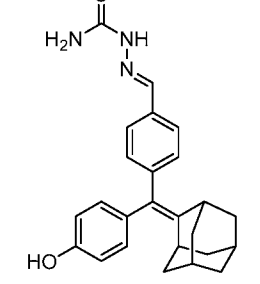
[00323] Example 17. Additional Compounds and Their Biological Activities

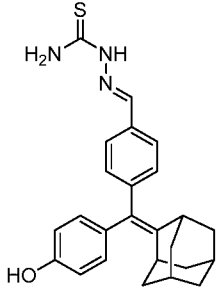
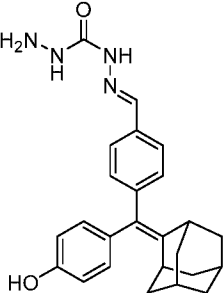
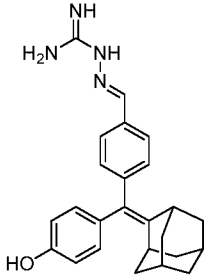
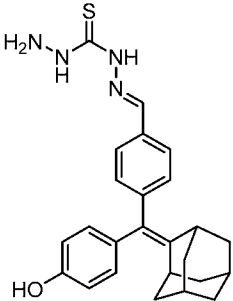
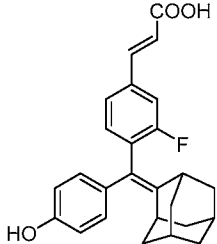
[00324] Additional compounds **33-67** were synthesized. The affinities of these compounds for purified, full-length, human ER α were determined using a competitive radiometric binding assay, with [3 H]estradiol as tracer. The affinity data are given as relative binding affinity (RBA) values (estradiol = 100), as presented in Table 3.

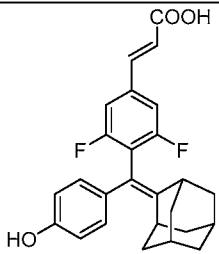
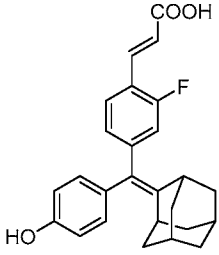
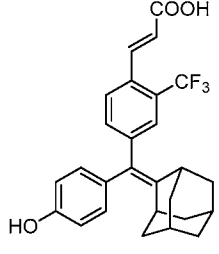
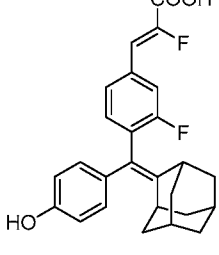
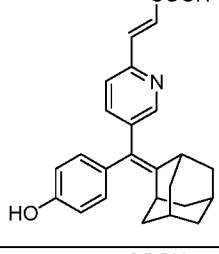
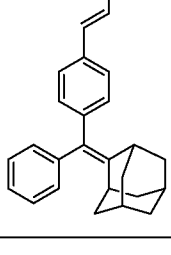
[00325] Table 3. Relative Binding Affinities for Additional Compounds for Full-Length Human Estrogen Receptor Alpha (ER α).

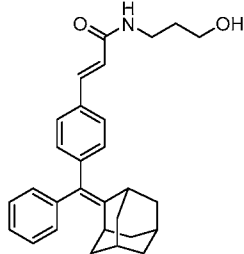
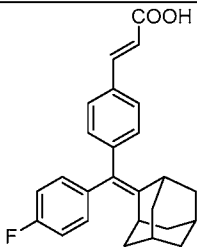
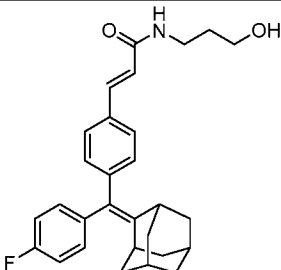
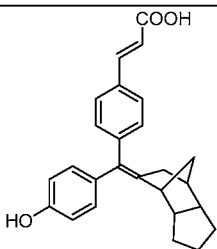
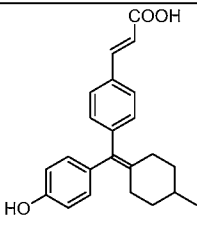
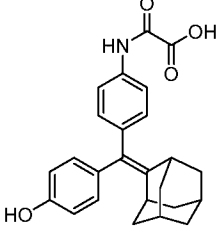
No.	Compound	RBA ER α (%) ^a	K_i (nM) ^b
33		32.44	0.616
34		5.52	3.62
35		21.69	0.92

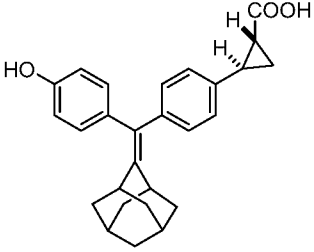
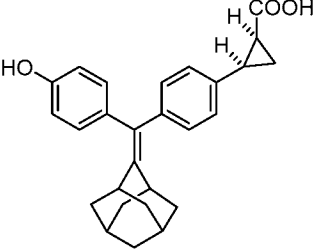
36		61.6	0.32
37		31.9	0.63
38		65.56	0.31
39		35.1	0.57
40		26.4	0.76
41		0.213	93.9
42			

43		7.31	2.74
44		8.67	2.31
45		31.9	0.63
46		8.4	2.38
47		11.32	1.77
48		93.04	0.21

49		25.39	0.79
50		28.96	0.69
51		9.19	2.18
52		12.28	1.63
53		102.00	0.20

54		13.1	1.53
55			
56			
57			
58		0.27	74.07
59		0.125	160

60		0.419	47.73
61		0.052	384.60
62		0.007	2857.14
63			
64			
65		98.06	0.20

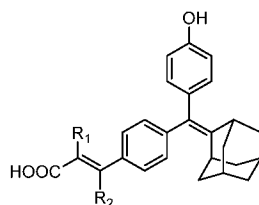
66		58.07	0.34
67		1.442	13.87

^a Relative binding affinity values, determined by a competitive radiometric binding assay with [³H]estradiol and purified, full-length human ER α , are reported as percent relative to E2 = 100% and expressed as the mean $\pm$ SD of two or more independent experiments.

^b K_i values were calculated from the following formula: $K_i = (K_d[\text{estradiol}]/\text{RBA}) \times 100$. K_d for estradiol is 0.2 nM.

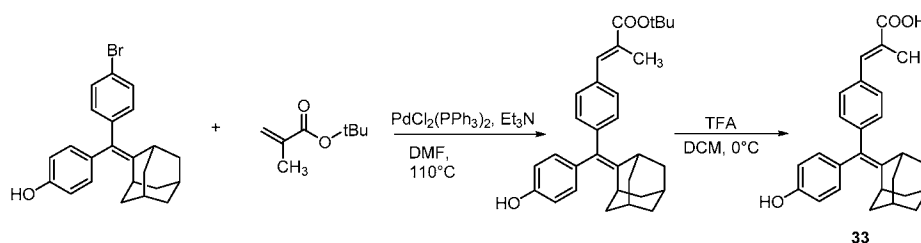
[00326] Compound Synthesis and experimental data

[00327] I. Substituted Acrylates



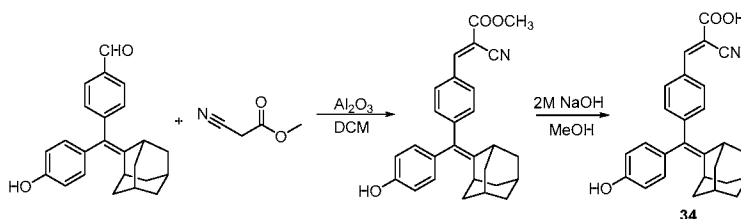
[00328] where R1 is selected from -Me, -CN, -Cl and -F when R2 = H. R2 is -CH3 when R1 = H.

[00329] Compound **33**: (E)-3-(4-(((1r,3r,5R,7S)-adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)-2-methylacrylic acid



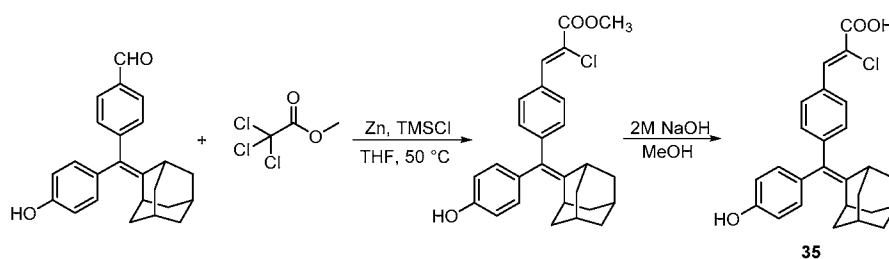
[00330] 4-(((1r,3r,5R,7S)-adamantan-2-ylidene)(4-bromophenyl)methyl)phenol was reacted with tert-butyl methacrylate following the general Heck reaction. The reaction mixture was extracted with ethyl acetate and washed with brine. The organic extracts were combined, dried over anhydrous Na₂SO₄, and concentrated *in vacuo*. The crude product was dissolved in CH₂Cl₂ at 0 °C. TFA solution was added dropwise. The reaction was monitored by TLC and quenched by ice water. After stirring for 10 min, the mixture was extracted with ethyl acetate. The organic layers were collected and purified by flash column chromatography to give compound **33** as a white powder. ¹H NMR (500 MHz, DMSO-*d*₆) δ 7.54 (q, *J* = 1.1 Hz, 1H), 7.44 – 7.37 (m, 2H), 7.29 – 7.23 (m, 2H), 7.05 – 6.99 (m, 2H), 6.90 – 6.84 (m, 2H), 2.90 (p, *J* = 7.3 Hz, 2H), 2.07 (d, *J* = 1.1 Hz, 3H), 1.91 – 1.78 (m, 2H), 1.79 – 1.64 (m, 10H).

[00331] Compound **34**: (E)-3-(4-(((1r,3r,5R,7S)-adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)-2-cyanoacrylic acid



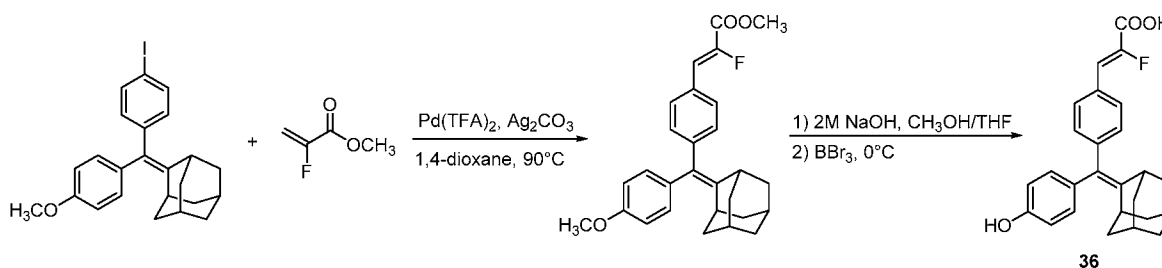
[00332] Al₂O₃ was added to the CH₂Cl₂ solution of methyl 2-cyanoacetate and benzaldehyde. The reaction mixture was kept stirring at 65 °C until dry. Purified by silica column. Then add 1M NaOH and MeOH, until TLC analysis indicated the end of the reaction, neutralized with HCl (10% aq.), washed with water and dried, providing the cyanoacrylic acid **34**. ¹H NMR (500 MHz, Acetone-*d*₆) δ 8.31 (s, 1H), 8.05 (d, *J* = 8.3 Hz, 2H), 7.36 (d, *J* = 8.4 Hz, 2H), 7.01 (d, *J* = 8.6 Hz, 2H), 6.80 (d, *J* = 8.6 Hz, 2H), 2.80 (d, *J* = 23.2 Hz, 2H), 2.03 – 1.98 (m, 2H), 1.90 (dd, *J* = 16.1, 3.3 Hz, 10H). LRMS (ESI for C₂₇H₂₄NO₃ (M-H⁺), found 410.3.

[00333] Compound **35**: (Z)-3-(4-(((1r,3r,5R,7S)-adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)-2-chloroacrylic acid



[00334] A THF suspension of Zn metal and TMSCl was stirred under a nitrogen atmosphere for about 15 min at 50°C. A mixture of trichloroacetate and benzaldehyde was dissolved in THF and then was slowly added to the suspended solution. The reaction mixture was then stirred for about 3h. The mixture was poured into saturated aqueous ammonium chloride solution, then purified by silica column. Then add 1M NaOH and MeOH, until TLC analysis indicated the end of the reaction, neutralized with HCl (10% aq.), washed with water and dried, providing the chloroacrylic acid product **35**. ^1H NMR (499 MHz, DMSO- d_6) δ 7.64 (d, J = 8.2 Hz, 2H), 7.55 (s, 1H), 7.06 (d, J = 8.3 Hz, 3H), 6.87 (d, J = 8.5 Hz, 2H), 6.68 (d, J = 8.5 Hz, 2H), 2.69 (d, J = 15.8 Hz, 3H), 1.96 (s, 3H), 1.83 – 1.79 (m, 10H). LRMS (ESI) for $\text{C}_{26}\text{H}_{24}\text{ClO}_3$ ($\text{M}-\text{H}^+$), found 419.3.

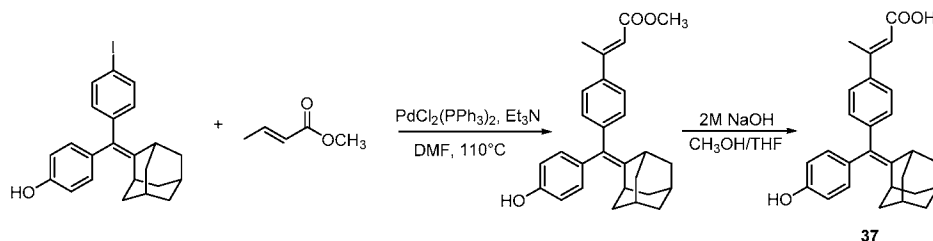
[00335] Compound **36**: (Z)-3-(4-(((1r,3r,5R,7S)-adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)-2-fluoroacrylic acid



[00336] (1r,3r,5R,7S)-2-((4-iodophenyl)(4-methoxyphenyl)methylene)adamantane was reacted with methyl 2-fluoroacrylate following the general Heck reaction using $\text{Pd}(\text{TFA})_2$ as catalyst and Ag_2CO_3 as base. The reaction mixture was extracted with ethyl acetate and washed with brine. The organic extracts were combined, dried over anhydrous Na_2SO_4 , and concentrated *in vacuo*. The crude product was dissolved in methanol. A 2M NaOH solution (2 mL) was added dropwise. After stirring for 10 min, the mixture was extracted with ethyl acetate. The organic layers were collected and concentrated *in vacuo*. Demethylation with BBr_3 and further purification by flash column chromatography gave compound **36** as a white powder. ^1H NMR

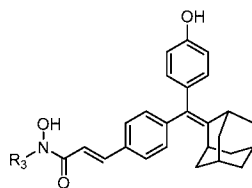
(500 MHz, acetone- d_6) δ 7.61 (d, J = 8.2 Hz, 2H), 7.20 (d, J = 8.2 Hz, 2H), 6.98 (d, J = 8.5 Hz, 2H), 6.78 (d, J = 8.5 Hz, 2H), 6.50 (d, J = 16.0 Hz, 1H), 2.81 (s, 1H), 2.76 (s, 1H), 1.99 (s, 2H), 1.88 (d, J = 13.1 Hz, 10H). LRMS (ESI) for $C_{26}H_{24}FO_3$ ($M-H^+$), found 403.3.

[00337] Compound **37**: (E)-3-(4-(((1*r*,3*r*,5*R*,7*S*)-adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)but-2-enoic acid



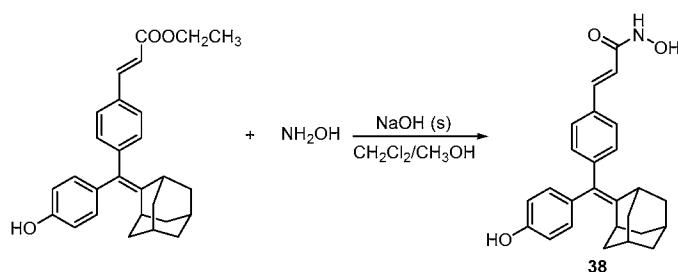
[00338] 4-(((1*r*,3*r*,5*R*,7*S*)-adamantan-2-ylidene)(4-iodophenyl)methyl)phenol was reacted with methyl (E)-but-2-enoate following the general Heck reaction. The reaction mixture was extracted with ethyl acetate and washed with brine. The organic extracts were combined, dried over anhydrous Na_2SO_4 , and concentrated *in vacuo*. The crude product was dissolved in methanol. A 2M NaOH solution (2 mL) was added dropwise. The reaction was monitored by TLC and quenched by 1 N HCl/ice water. After stirring for 10 min, the mixture was extracted with ethyl acetate. The organic layers were collected and purified by flash column chromatography to give compound **37** as a yellow powder. 1H NMR (500 MHz, $DMSO-d_6$) 7.30 (s, 3H), 7.05 – 6.99 (m, 2H), 6.90 – 6.84 (m, 2H), 6.00 (q, J = 1.3 Hz, 1H), 2.90 (p, J = 7.4 Hz, 2H), 2.58 (d, J = 1.1 Hz, 3H), 1.84 (dt, J = 14.1, 7.0 Hz, 2H), 1.77 – 1.61 (m, 10H).

[00339] II. Hydroxyacrylamide Derivatives



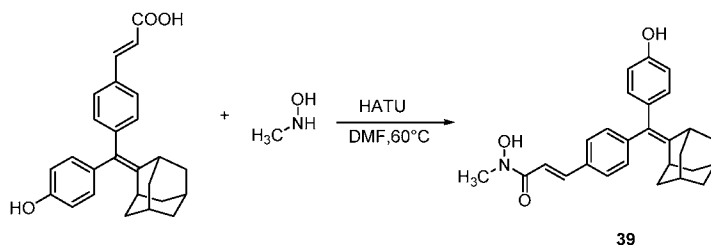
[00340] Where R_3 is selected from -H, -Me, and -isopropyl.

[00341] Compound **38**: (E)-3-(4-(((1*r*,3*r*,5*R*,7*S*)-adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)-N-hydroxyacrylamide



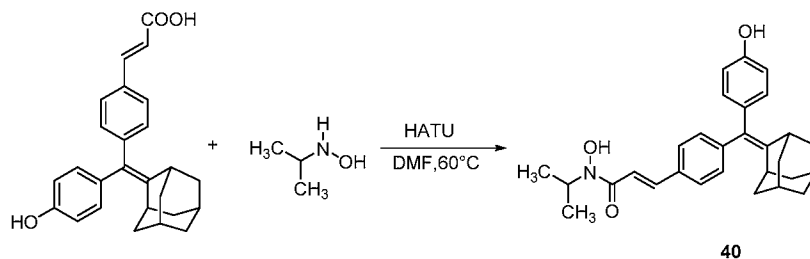
[00342] Ethyl (E)-3-(4-(((1r,3r,5R,7S)-adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)acrylate was dissolved in CH_2Cl_2 and methanol (1:2). The resulting solution was cooled to 0°C , and hydroxylamine (30 equiv) was added, followed by sodium hydroxide (10.0 equiv). The reaction was warmed to room temperature and kept stirring for 12 h. After complete consumption of starting material, ethyl acetate was added, and the resulting solution was washed with brine. The organic layer was dried with anhydrous Na_2SO_4 and concentrated under vacuum. The resulting residue was purified by flash chromatography (10–80% ethyl acetate/hexane gradient) on silica gel to give **38**. ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 7.45 (d, $J = 7.9$ Hz, 2H), 7.39 (d, $J = 15.7$ Hz, 1H), 7.07 (d, $J = 7.9$ Hz, 2H), 6.89 – 6.83 (m, 2H), 6.71 – 6.64 (m, 2H), 6.39 (d, $J = 15.8$ Hz, 1H), 2.67 (d, $J = 32.8$ Hz, 2H), 1.94 (s, 2H), 1.82 – 1.76 (m, 10H). HRMS (ESI) calcd for $\text{C}_{26}\text{H}_{28}\text{NO}_3$ ($\text{M}+\text{H}^+$) 402.2069, found 402.2070.

[00343] Compound **39**: (E)-3-(4-(((1r,3r,5R,7S)-adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)-N-hydroxy-N-methylacrylamide



[00344] Following the general procedure for amide synthesis between (E)-3-(4-(((1r,3r,5R,7S)-adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)acrylic acid and N-methylhydroxylamine, compound **39** was obtained as white solid. ^1H NMR (500 MHz, $\text{acetone}-d_6$) δ 7.66 (d, $J = 16.0$ Hz, 1H), 7.61 (d, $J = 8.2$ Hz, 2H), 7.20 (d, $J = 8.2$ Hz, 2H), 6.98 (d, $J = 8.5$ Hz, 2H), 6.78 (d, $J = 8.5$ Hz, 2H), 6.50 (d, $J = 16.0$ Hz, 1H), 2.81 (s, 1H), 2.76 (s, 1H), 1.99 (s, 2H), 1.88 (d, $J = 13.1$ Hz, 10H). LRMS (ESI) for $\text{C}_{27}\text{H}_{30}\text{NO}_3$ ($\text{M}+\text{H}^+$), found 416.2.

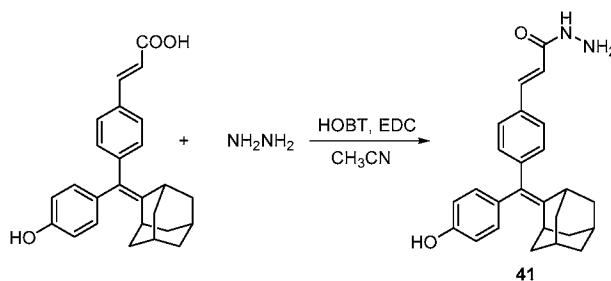
[00345] Compound **40**: (E)-3-(4-(((1r,3r,5R,7S)-adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)-N-isopropylacrylamide



[00346] Following the general procedure for amide synthesis between (E)-3-(4-(((1r,3r,5R,7S)-adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)acrylic acid and N-isopropylhydroxylamine, compound **40** was obtained as white solid. ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.07 (t, J = 5.4 Hz, 1H), 7.44 (d, J = 7.7 Hz, 2H), 7.34 (d, J = 15.8 Hz, 1H), 7.06 (d, J = 7.6 Hz, 2H), 6.85 (d, J = 7.8 Hz, 2H), 6.67 (d, J = 7.7 Hz, 2H), 6.57 (s, 1H), 3.10 (q, J = 6.5 Hz, 2H), 2.69 (s, 1H), 2.64 (s, 1H), 1.94 (s, 2H), 1.79 (s, 11H), 1.44 (q, J = 7.2 Hz, 2H), 0.85 (t, J = 7.4 Hz, 3H). LRMS (ESI) for C₂₉H₃₄NO₃ (M+H⁺), found 444.2.

[00347] III. New Acrylamide derivatives

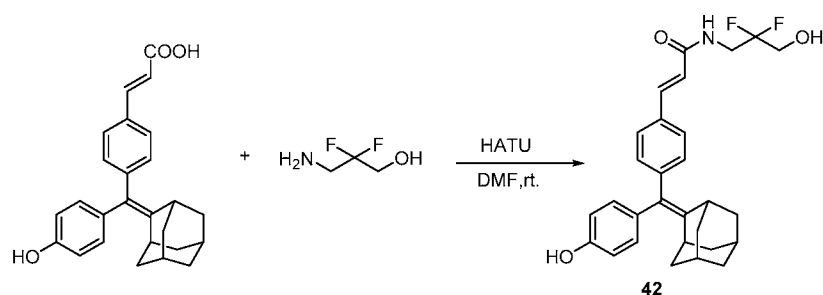
[00348] Compound **41**: (E)-3-(4-(((1r,3r,5R,7S)-adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl) acrylohydrazide



[00349] To the solution of cinnamic acid in CH₃CN at room temperature, HOBT (1.2 equiv) was added in a single portion, followed by EDC (1.2 equiv). The reaction was stirred at room temperature for 2 h, the time required for the complete consumption of cinnamic acid. The resulting mixture was then slowly added to a solution of hydrazine hydrate (2.0 equiv) in 15 mL of CH₃CN kept between 0 and 10°C. The reaction was usually completed upon the end of addition. After complete consumption of starting material, ethyl acetate was added, and the

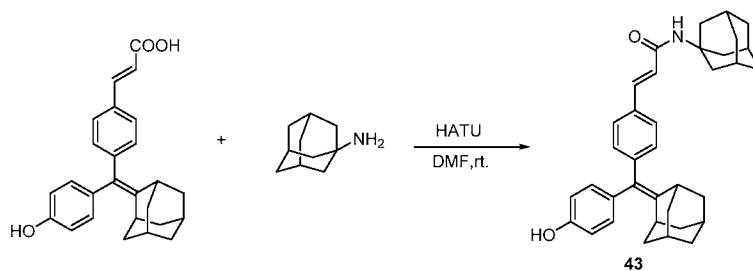
resulting solution was washed with brine. The organic layer was dried with anhydrous Na_2SO_4 and concentrated under vacuum. The resulting residue was purified by flash chromatography (10–80% ethyl acetate/hexane gradient) on silica gel to give **41**. ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 7.52 – 7.46 (m, 3H), 7.10 (d, $J = 7.9$ Hz, 2H), 6.89 – 6.85 (m, 2H), 6.72 – 6.65 (m, 3H), 2.68 (d, $J = 26.0$ Hz, 2H), 1.95 (s, 2H), 1.80 (d, $J = 11.1$ Hz, 10H). LRMS (ESI) calcd for $\text{C}_{26}\text{H}_{29}\text{N}_2\text{O}_2$ ($\text{M}+\text{H}^+$) 401.2, found 401.2.

[00350] Compound **42**: (E)-3-(4-(((1r,3r,5R,7S)-adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)-N-(2,2-difluoro-3-hydroxypropyl)acrylamide



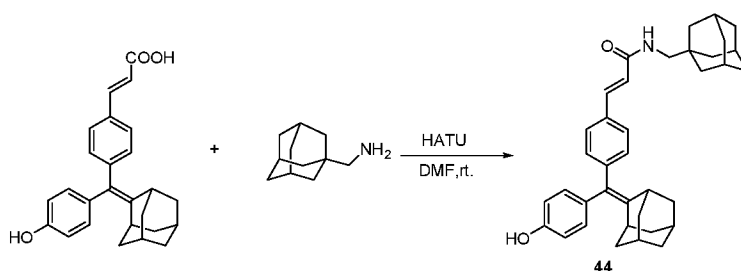
[00351] Following the general procedure for amide synthesis between (E)-3-(4-(((1r,3r,5R,7S)-adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)acrylic acid and 3-amino-2,2-difluoropropan-1-ol, compound **42** was obtained as white solid. ^1H NMR (500 MHz, Acetone- d_6) δ 7.63 (d, $J = 15.7$ Hz, 1H), 7.54 (d, $J = 8.1$ Hz, 2H), 7.18 (d, $J = 8.1$ Hz, 2H), 6.97 (d, $J = 8.4$ Hz, 2H), 6.80 – 6.72 (m, 3H), 3.81 (td, $J = 13.4, 6.4$ Hz, 2H), 3.64 (td, $J = 12.7, 7.1$ Hz, 3H), 2.81 (s, 1H), 2.75 (s, 1H), 1.99 (s, 2H), 1.88 (d, $J = 12.3$ Hz, 1H). LRMS (ESI) for $\text{C}_{30}\text{H}_{35}\text{NO}_3$ ($\text{M}+\text{H}^+$), found 480.2344.

[00352] Compound **43**: (E)-N-((3s,5s,7s)-adamantan-1-yl)-3-(4-(((1r,3r,5R,7S)-adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)acrylamide



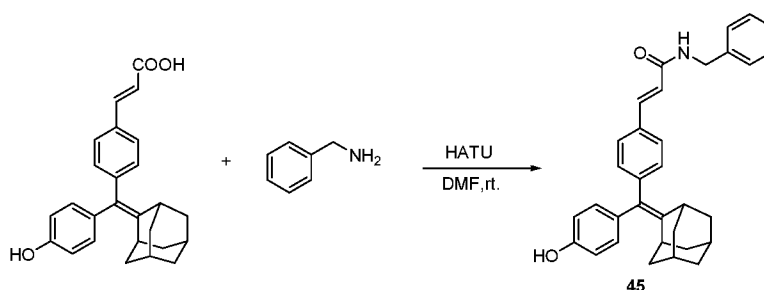
[00353] Following the general procedure for amide synthesis between (E)-3-(4-(((1r,3r,5R,7S)-adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)acrylic acid and 1-Adamantanamine, compound **43** was obtained as white solid. ^1H NMR (500 MHz, DMSO- d_6) δ 7.58 (s, 1H), 7.40 (d, $J = 8.2$ Hz, 2H), 7.25 (d, $J = 15.7$ Hz, 1H), 7.06 (d, $J = 8.2$ Hz, 2H), 6.85 (d, $J = 8.5$ Hz, 2H), 6.67 (d, $J = 8.6$ Hz, 2H), 6.62 (d, $J = 15.7$ Hz, 1H), 2.69 (s, 1H), 2.64 (s, 1H), 2.00 (s, 3H), 1.96 (s, 9H), 1.78 (d, $J = 8.0$ Hz, 12H), 1.61 (s, 7H). ^{13}C NMR (126 MHz, DMSO- d_6) δ 208.68, 164.78, 156.52, 146.15, 144.56, 138.10, 133.56, 133.30, 130.83, 130.37, 130.27, 127.80, 123.86, 115.61, 51.53, 41.69, 37.19, 36.73, 35.80, 34.55, 29.49, 28.99, 28.18. HRMS (ESI) calcd for $\text{C}_{36}\text{H}_{42}\text{NO}_2$ ($\text{M}+\text{H}^+$) 520.3216, found 520.3202.

[00354] Compound **44**: (E)-N-(((3r,5r,7r)-adamantan-1-yl)methyl)-3-(4-(((1r,3r,5R,7S)-adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)acrylamide



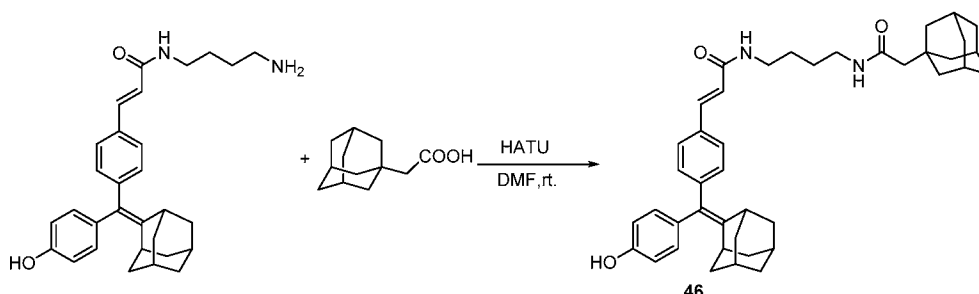
[00355] Following the general procedure for amide synthesis between (E)-3-(4-(((1r,3r,5R,7S)-adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)acrylic acid and ((3r,5r,7r)-adamantan-1-yl)methanamine, compound **44** was obtained as white solid. ^1H NMR (500 MHz, DMSO- d_6) δ 7.58 (s, 1H), 7.40 (d, $J = 8.2$ Hz, 2H), 7.25 (d, $J = 15.7$ Hz, 1H), 7.06 (d, $J = 8.2$ Hz, 2H), 6.85 (d, $J = 8.5$ Hz, 2H), 6.67 (d, $J = 8.6$ Hz, 2H), 6.62 (d, $J = 15.7$ Hz, 1H), 2.69 (s, 1H), 2.64 (s, 1H), 2.00 (s, 3H), 1.96 (s, 9H), 1.78 (d, $J = 8.0$ Hz, 12H), 1.61 (s, 7H). HRMS (ESI) calcd for $\text{C}_{37}\text{H}_{44}\text{NO}_2$ ($\text{M}+\text{H}^+$) 534.3372, found 534.3358.

[00356] Compound **45**: (E)-3-(4-(((1r,3r,5R,7S)-adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)-N-benzylacrylamide



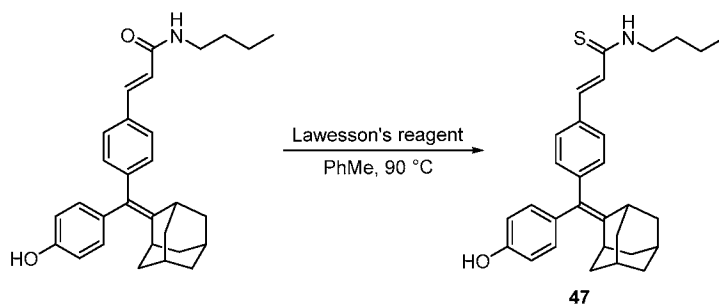
[00357] Following the general procedure for amide synthesis between (E)-3-(4-(((1r,3r,5R,7S)-adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)acrylic acid and phenylmethanamine, compound **45** was obtained as white solid. ^1H NMR (500 MHz, Acetone- d_6) δ 7.57 (d, J = 15.7 Hz, 1H), 7.50 (d, J = 8.1 Hz, 2H), 7.36 – 7.28 (m, 6H), 7.28 – 7.18 (m, 2H), 7.16 (d, J = 8.2 Hz, 2H), 7.00 – 6.94 (m, 2H), 6.72 (d, J = 15.7 Hz, 1H), 4.52 (d, J = 6.0 Hz, 2H), 4.36 (d, J = 6.0 Hz, 1H), 2.81 (s, 1H), 2.75 (s, 1H), 1.99 (s, 2H), 1.87 (d, J = 11.3 Hz, 11H). ^{13}C NMR (126 MHz, Acetone- d_6) δ 165.39, 156.20, 146.33, 144.97, 139.90, 139.65, 133.85, 133.32, 130.68, 130.55, 130.07, 128.56, 128.54, 128.48, 127.80, 127.67, 127.52, 127.09, 126.97, 121.43, 115.10, 43.01, 39.45, 39.44, 37.06, 34.72, 34.60, 28.38. HRMS (ESI) calcd for $\text{C}_{33}\text{H}_{34}\text{NO}_2$ ($\text{M}+\text{H}^+$) 476.2590, found 476.2581.

[00358] Compound **46**: (E)-N-(4-(2-((3r,5r,7r)-adamantan-1-yl)acetamido)butyl)-3-(4-(((1r,3r,5R,7S)-adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)acrylamide



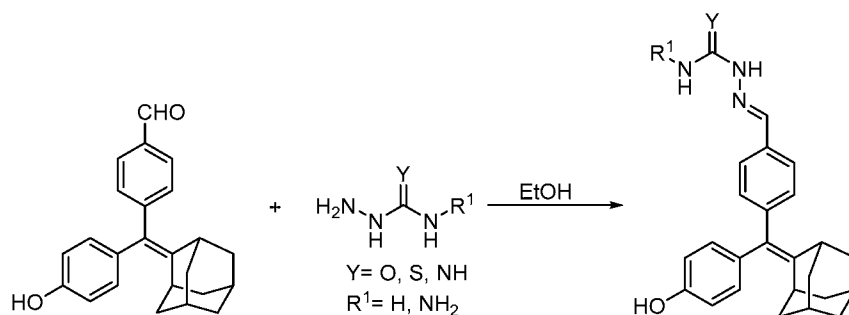
[00359] Following the general procedure for amide synthesis between (E)-3-(4-(((1r,3r,5R,7S)-adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)-N-(4-aminobutyl)acrylamide and 2-((3r, 5r, 7r)-adamantan-1-yl)acetic acid, compound **46** was obtained as white solid. ^1H NMR (500 MHz, CDCl_3) δ 7.83 (s, 1H), 7.59 – 7.49 (m, 3H), 7.34 – 7.28 (m, 2H), 6.99 – 6.93 (m, 2H), 6.85 – 6.79 (m, 2H), 6.64 (t, J = 4.3 Hz, 1H), 6.55 (d, J = 15.7 Hz, 1H), 6.30 (t, J = 4.3 Hz, 1H), 3.24 (dtd, J = 24.0, 6.1, 4.3 Hz, 4H), 2.93 (p, J = 7.3 Hz, 2H), 2.03 – 1.90 (m, 4H), 1.94 – 1.80 (m, 9H), 1.84 – 1.65 (m, 13H), 1.63 – 1.43 (m, 7H).

[00360] Compound **47**: (E)-3-(4-(((1r,3r,5R,7S)-adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)-N-butylprop-2-enethioamide



[00361] Lawesson's reagent (3.0 equiv) was added to a toluene solution of (E)-3-(4-(((1r,3r,5R,7S)-adamantan-2-ylidene)(4-hydroxyphenyl)methyl) phenyl)-N-butylacrylamide (1.0 equiv). The reaction mixture was kept stirring at 90 °C overnight. The resulting residue was purified by flash chromatography (10–80% ethyl acetate/hexane gradient) on silica gel to give **47** as brown solid. ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 8.04 (t, J = 5.6 Hz, 1H), 7.44 (d, J = 8.2 Hz, 2H), 7.34 (d, J = 15.7 Hz, 1H), 7.06 (d, J = 8.1 Hz, 2H), 6.85 (d, J = 8.5 Hz, 2H), 6.66 (d, J = 8.5 Hz, 2H), 6.54 (d, J = 15.8 Hz, 1H), 3.14 (q, J = 6.8 Hz, 2H), 2.69 (s, 1H), 2.64 (s, 1H), 1.94 (s, 2H), 1.79 (s, 11H), 1.41 (p, J = 7.1 Hz, 2H), 1.32–1.25 (m, 2H), 0.86 (t, J = 7.3 Hz, 3H). LRMS (ESI) for $\text{C}_{30}\text{H}_{35}\text{NOS}$ ($\text{M}+\text{H}^+$), found 458.6.

[00362] IV. Hydrazine derivatives

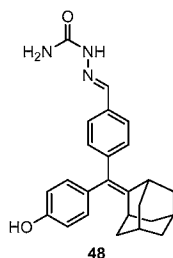


[00363] General synthesis route of hydrazine derivatives:

[00364] Dissolve the corresponding amide/ hydrazide in water, then 4-(((1r,3r,5R,7S)-adamantan-2-ylidene)(4-hydroxyphenyl)methyl)benzaldehyde was dissolved in anhydrous ethanol. The ethanol solution was added to the aqueous solution of the corresponding

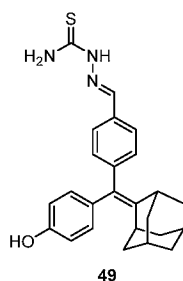
amide/hydrazide drop by drop. The mixture was kept stirring at room temperature for 3 h. The organic layer was dried with anhydrous Na_2SO_4 and concentrated under vacuum. The resulting residue was purified by flash chromatography (10–80% ethyl acetate/hexane gradient) on silica gel to give the desired products **48–52**.

[00365] Compound **48**: 2-((E)-4-(((1r,3r,5R,7S)-adamantan-2-ylidene)(4-hydroxyphenyl)methyl)benzylidene) hydrazine-1-carboxamide



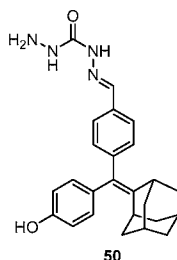
[00366] ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 7.78 (s, 1H), 7.59 (d, $J = 7.9$ Hz, 2H), 7.03 (d, $J = 8.2$ Hz, 2H), 6.85 (d, $J = 8.4$ Hz, 2H), 6.67 (d, $J = 8.4$ Hz, 2H), 2.67 (d, $J = 35.8$ Hz, 2H), 1.94 (s, 2H), 1.79 (q, $J = 4.0$ Hz, 10H). LRMS (ESI) for $\text{C}_{25}\text{H}_{28}\text{N}_3\text{O}_2$ ($\text{M}+\text{H}^+$), found 402.2.

[00367] Compound **49**: 2-((E)-4-(((1r,3r,5R,7S)-adamantan-2-ylidene)(4-hydroxyphenyl)methyl)benzylidene) hydrazine-1-carbothioamide



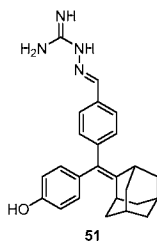
[00368] ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 7.98 (s, 1H), 7.68 (d, $J = 7.9$ Hz, 2H), 7.05 (d, $J = 8.0$ Hz, 2H), 6.86 (d, $J = 8.1$ Hz, 2H), 6.66 (d, $J = 8.2$ Hz, 2H), 2.66 (d, $J = 40.9$ Hz, 2H), 1.94 (s, 2H), 1.79 (t, $J = 6.0$ Hz, 10H). LRMS (ESI) for $\text{C}_{25}\text{H}_{28}\text{N}_3\text{OS}$ ($\text{M}+\text{H}^+$), found 418.1.

[00369] Compound **50**: N'-((E)-4-(((1r,3r,5R,7S)-adamantan-2-ylidene)(4-hydroxyphenyl)methyl)benzylidene) hydrazinecarbohydrazide



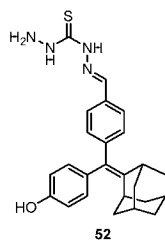
[00370] ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 8.11 (s, 1H), 7.63 (s, 2H), 7.09 (d, $J = 7.8$ Hz, 2H), 6.87 (d, $J = 7.9$ Hz, 2H), 6.67 (d, $J = 8.2$ Hz, 2H), 2.68 (d, $J = 29.5$ Hz, 2H), 1.95 (s, 2H), 1.79 (d, $J = 11.4$ Hz, 10H). LRMS (ESI) for $\text{C}_{25}\text{H}_{29}\text{N}_4\text{O}_2$ ($\text{M}+\text{H}^+$), found 417.2

[00371] Compound **51**: 2-((E)-4-(((1r,3r,5R,7S)-adamantan-2-ylidene)(4-hydroxyphenyl)methyl)benzylidene) hydrazine-1-carboximidamide



[00372] ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 7.94 (s, 1H), 7.58 (d, $J = 8.0$ Hz, 2H), 7.00 (d, $J = 8.0$ Hz, 2H), 6.85 (d, $J = 8.5$ Hz, 2H), 6.67 (d, $J = 8.5$ Hz, 2H), 2.68 (d, $J = 26.1$ Hz, 2H), 1.94 (s, 2H), 1.79 (d, $J = 5.0$ Hz, 10H). LRMS (ESI) for $\text{C}_{25}\text{H}_{29}\text{N}_4\text{O}$ ($\text{M}+\text{H}^+$), found 401.1

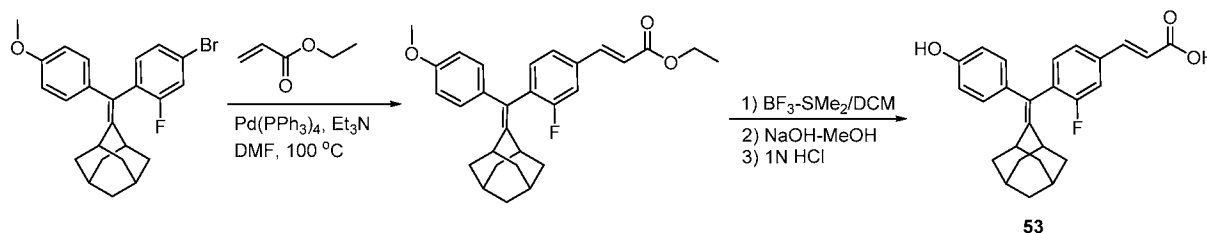
[00373] Compound **52**: N'-((E)-4-(((1r,3r,5R,7S)-adamantan-2-ylidene)(4-hydroxyphenyl)methyl)benzylidene) hydrazinecarbothiohydrazide



[00374] ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 7.99 (s, 1H), 7.68 (d, $J = 7.9$ Hz, 2H), 7.05 (d, $J = 7.8$ Hz, 2H), 6.86 (d, $J = 8.1$ Hz, 2H), 6.67 (d, $J = 8.0$ Hz, 2H), 2.67 (d, $J = 41.0$ Hz, 2H), 1.94 (s, 2H), 1.80 (s, 10H). LRMS (ESI) for $\text{C}_{25}\text{H}_{29}\text{N}_4\text{OS}$ ($\text{M}+\text{H}^+$), found 433.1

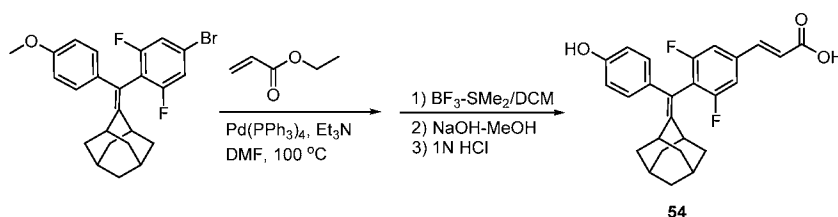
[00375] V. Substituted cinnamic ring

[00376] Compound **53**: (E)-3-(4-(((1*r*,3*r*,5*R*,7*S*)-adamantan-2-ylidene)(4-hydroxyphenyl)methyl)-3-fluorophenyl) acrylic acid



[00377] The mixture of the bromo compound (43 mg, 0.1 mmol), ethyl acrylate (150 μ L), Et_3N (150 μ L) in DMF (300 μ L) was purged with argon for 5 min before adding cat. amount of $\text{Pd}(\text{PPh}_3)_4$ (2 mg) and heated up at 100 $^\circ\text{C}$ overnight in a sealed vial. The solvent was concentrated with stream of nitrogen to load a SiO_2 TLC plate (0.25 mm, 20 x 20 cm). Development with 10% EA/n-Hexane (v/v) and collection of R_f 6.5 and that is a fluorescent by visualizing at 256 nm uv lamp provides ethyl acrylate (18 mg). Subsequently successive treatment of ethyl acrylate with 1) $\text{BF}_3\cdot\text{SMe}_2$ (100 μ L), 2) 25% NaOH solution (100 μ L), 3) and 1N HCl for acidification afforded the title acrylic acid **11** (11 mg). ^1H NMR (500 MHz, $\text{CDCl}_3 + \text{CD}_3\text{OD}$) δ 1.73~1.93 (m, 10H), 1.93 (s, 2H), 2.41 (s, 1H), 2.84 (s, 1H), 6.35 (d, $J = 16.0$ Hz, 1H), 6.72 (d, $J = 8.5$ Hz, 2H), 6.99 (d, $J = 8.5$ Hz, 2H), 7.12 (d, $J = 8.0$ Hz, 1H), 7.16 (dd, $J = 10.0, 1.5$ Hz, 1H), 7.20 (dd, $J = 8.0, 1.5$ Hz, 1H), 7.59 (d, $J = 16.0$ Hz, 1H). HRMS (ESI, (M-1) $^{+1}$) $\text{C}_{26}\text{H}_{24}\text{FO}_3$ Calcd 403.17, found 403.17.

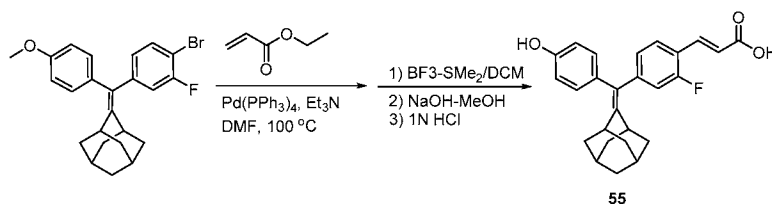
[00378] Compound **54**: (E)-3-(4-(((1*r*,3*r*,5*R*,7*S*)-adamantan-2-ylidene)(4-hydroxyphenyl)methyl)-3,5-difluorophenyl) acrylic acid



[00379] The compound **54** was obtained from the (5*R*,7*R*,*E*)-2-((4-bromo-2,6-difluorophenyl)(4-methoxyphenyl)methylene)adamantine and ethyl acrylate and subsequently deprotecting reaction as described to make compound **53**. ^1H NMR (500 MHz, $\text{CDCl}_3 + \text{CD}_3\text{OD}$) δ 1.76~1.86 (m, 10H), 1.92 (s, 2H), 2.25 (s, 1H), 2.82 (s, 1H), 6.31 (d, $J = 16.0$ Hz, 1H), 6.73 (d, $J = 9.0$ Hz, 2H), 7.00 (d, $J = 7.0$ Hz, 2H), 7.05 (d, $J = 9.0$ Hz, 2H), 7.49 (d, $J = 16.0$

Hz, 1H). ^{19}F NMR (470 MHz, CDCl_3) δ -114.15 (d, J = 7.5 Hz). HRMS (ESI, $(\text{M}-1)^{+1}$) $\text{C}_{26}\text{H}_{23}\text{F}_2\text{O}_3$ Calcd 421.16, found 421.16.

[00380] Compound **55**: (E)-3-(4-(((1*r*,3*r*,5*R*,7*S*)-adamantan-2-ylidene)(4-hydroxyphenyl)methyl)-2-fluorophenyl) acrylic acid

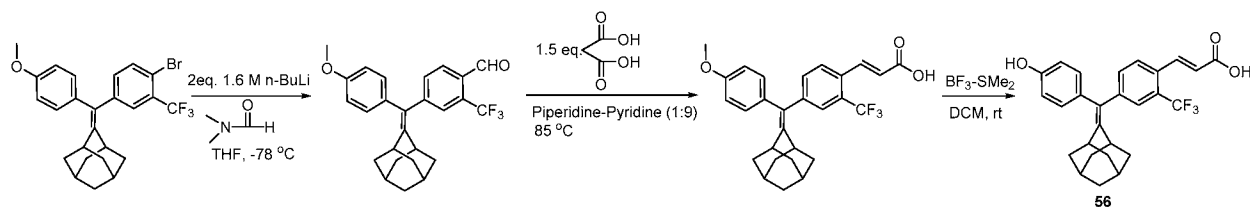


[00381] The *o*-fluorophenyl acrylic acid derivative **55** was obtained from the Heck coupling reaction using (5*R*,7*R*,*E*)-2-((4-bromo-3-fluorophenyl)(4-methoxyphenyl)methylene)adamantane and ethyl acrylate and subsequently deprotecting reaction as described to make compound **53**.

^1H NMR (500 MHz, $\text{CDCl}_3 + \text{CD}_3\text{OD}$) δ 1.74~1.86 (m, 10H), 1.94 (s, 2H), 2.71 (s, 1H), 2.73 (s, 1H), 6.40 (d, J = 16.0 Hz, 1H), 6.69 (d, J = 8.5 Hz, 2H), 6.79 (dd, J = 11.7, 1.3 Hz, 1H), 6.88 (d, J = 7.0 Hz, 1H), 6.89 (d, J = 8.5 Hz, 2H), 7.36 (t, J = 7.5 Hz, 1H), 7.70 (d, J = 16.0 Hz, 1H).

HRMS (ESI, $\text{M}^{+1}+1$) $\text{C}_{26}\text{H}_{25}\text{FO}_3$ Calcd 405.1866, found 405.1849.

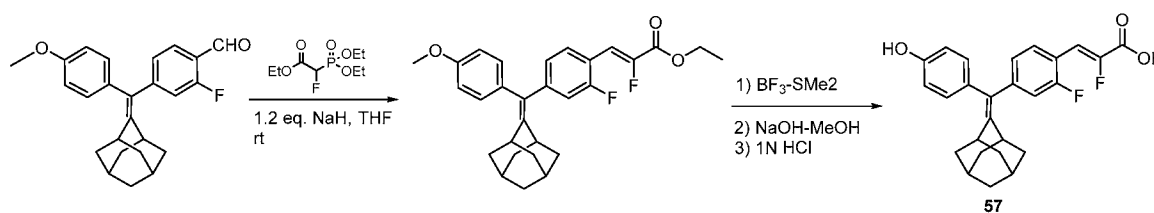
[00382] Compound **56**: (E)-3-(4-(((1*r*,3*r*,5*R*,7*S*)-adamantan-2-ylidene)(4-hydroxyphenyl)methyl)-2-(trifluoromethyl) phenyl)acrylic acid



[00383] The *o*-trifluoromethylphenyl aldehyde derivative was prepared from the reaction of (5*R*,7*R*,*E*)-2-((4-bromo-3-(trifluoromethyl)phenyl)(4-methoxyphenyl)methylene)adamantine (60 mg, 0.13 mmol), *n*-BuLi (157 μL , 1.6 M *n*-hexane), and DMF (20 mg, .28 mmol) as described to prepare for 4-((*E*)-((5*R*,7*R*)-adamantan-2-ylidene)(4-methoxyphenyl)methyl)-3-fluorobenzaldehyde. The aldehyde (43 mg, 01 mmol) in a mixture of piperidine-pyridine (1:9, v/v, 20 μL) was treated with a malonic acid (12.5 mg, 0.12 mmol) and heated up overnight at 85 °C. After cooling down to rt, 1N HCl (100 μL) was added to the reaction mixture and extracted with ethyl acetate (500 μL x 3), washed with DI water (100 μL x 5), dried over Na_2SO_4 ,

concentrated under vacuum to load onto a TLC (SiO₂, 0.25 mm, 25 x 25 cm). Development with 50% EA/n-Hexane (v/v) afforded the (*E*)-3-(4-((*E*)-((5*R*,7*R*)-adamantan-2-ylidene)(4-methoxyphenyl)methyl)-2-(trifluoromethyl)phenyl)acrylic acid (38 mg). Subsequently treatment of acrylic acid with BF₃-SMe₂ (300 μL) at rt provided the phenolic acrylic acid **56** (28 mg) as a colorless powder. ¹H NMR (500 MHz, CDCl₃) δ 1.80~1.92 (m, 10H), 1.99 (s, 2H), 2.67 (s, 1H), 2.80 (s, 1H), 6.34 (d, *J* = 15.5 Hz, 1H), 6.73 (d, *J* = 8.5 Hz, 2H), 6.91 (d, *J* = 8.5 Hz, 2H), 7.27 (d, *J* = 7.0 Hz, 1H), 7.413 (s, 1H), 7.60 (d, *J* = 8.0 Hz, 1H), 8.00 (d, *J* = 15.5 Hz, 1H). ¹⁹F (470 MHz, CDCl₃) δ -59.21. HRMS (ESI, M⁺+1) C₂₇H₂₆F₃O₃ Calcd. 455.1834, found 455.1819.

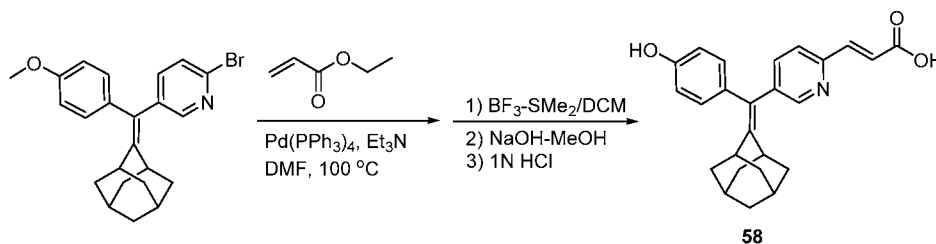
[00384] Compound **57**: (Z)-3-(4-(((1*r*,3*r*,5*R*,7*S*)-adamantan-2-ylidene)(4-hydroxyphenyl)methyl)-3-fluorophenyl)-2-fluoroacrylic acid



[00385] To the mixture of aldehyde (60 mg, 0.16 mmol) and triethyl 2-fluoro-2-phosphonoacetate (58 mg, 0.24 mmol) in THF (500 μL) was added NaH (10 mg, 65 wt% in mineral oil) at rt and stirred for 1 hr. The reaction was quenched with few drop of DI water, loaded directly onto a SiO₂ TLC plate (Merck, 0.25 mm, 20 x 20 cm), and developed with 15% EA/n-Hexane to collect a ethyl (Z)-3-(4-((*E*)-((5*R*,7*R*)-adamantan-2-ylidene)(4-methoxyphenyl)methyl)-2-fluorophenyl)-2-fluoroacrylate (51 mg). This acrylate (25 mg, 53.8 μmol) was treated successively with BF₃-SMe₂ (200 μL), 25% NaOH solution, and 1N HCl for acidification to collect the α-F-acrylic acid (13 mg). ¹H NMR (500 MHz, CDCl₃) δ 1.75~1.90 (m, 10H), 1.94 (s, 2H), 2.39 (s, 1H), 2.84 (s, 1H), 6.69 (d, *J*_{H-αF} = 44.5 Hz, 1H), 6.96 (d, *J* = 8.5 Hz, 2H), 7.10 (t, *J* = 8.0 Hz, 1H), 7.24 (d, *J* = 8.0 Hz, 1H), 7.30 (d, *J* = 8.0 Hz, 1H). ¹⁹F (470 MHz, CDCl₃) δ -114.27 (t, *J* = 9.4 Hz), -124.27 (d, *J* = 33.37 Hz). HRMS (ESI, (M-1)⁺) C₂₆H₂₃F₂O₃ Calcd 421.1615, found 421.1610.

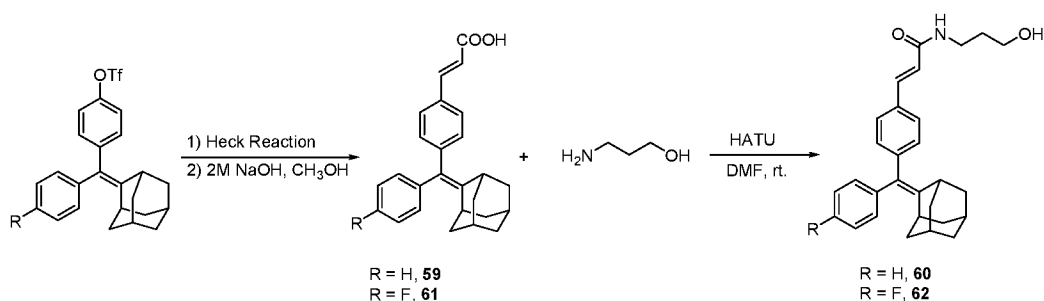
[00386] VI. Hetero cinnamyl ring

[00387] Compound **58**: (E)-3-(5-(((1*r*,3*r*,5*R*,7*S*)-adamantan-2-ylidene)(4-hydroxyphenyl)methyl)pyridin-2-yl)acrylic acid



[00388] The picolinic acid derivative **58** was obtained from the Heck coupling reaction using 5-((E)-((5*R*,7*R*)-adamantan-2-ylidene)(4-methoxyphenyl)methyl)-2-bromopyridine and ethyl acrylate and subsequently deprotecting reaction as described to make compound **53**. ^1H NMR (500 MHz, $\text{CDCl}_3 + \text{CD}_3\text{OD}$) δ 1.80~1.96 (m, 10H), 1.99 (s, 2H), 2.62 (s, 1H), 2.87 (s, 1H), 6.46 (d, $J = 16.0$ Hz, 1H), 6.73 (d, $J = 8.5$ Hz, 2H), 6.97 (d, $J = 8.5$ Hz, 2H), 7.25 (d, $J = 8.0$ Hz, 1H), 7.63 (d, $J = 16.0$ Hz, 1H), 7.85 (dd, $J = 8.0, 3.0$ Hz, 1H), 8.62 (d, $J = 3.0$ Hz, 1H). ^{13}C NMR (126 MHz, $\text{CDCl}_3 + \text{CD}_3\text{OD}$) δ 28.21, 34.40, 34.98, 37.13, 39.51, 39.55, 109.98, 115.19, 125.19, 128.14, 129.45, 130.82, 132.31, 134.65, 140.56, 145.30, 149.00, 150.25, 155.61, 162.95. HRMS (ESI, $\text{M}+\text{H}^+$) $\text{C}_{25}\text{H}_{26}\text{NO}_3$ Calcd 388.1913, found 388.1906.

[00389] VII. Altered Phenol



[00390] Compound **59**: (E)-3-(4-(((1*r*,3*r*,5*R*,7*S*)-adamantan-2-ylidene)(phenyl)methyl)phenyl)acrylic acid

[00391] Step 1. The corresponding triflate was reacted with ethyl acrylate following the general Heck reaction procedure. The reaction mixture was cooled and extracted with ethyl acetate and washed with water and brine. The organic layer was dried with anhydrous Na_2SO_4 and concentrated under vacuum.

[00392] Step 2. The crude product was dissolved in methanol. A 2M NaOH solution (2 mL) was added dropwise. The reaction was monitored by TLC and quenched by 1 N HCl/ice water. After stirring for 10 min, the mixture was extracted with ethyl acetate. The organic layers were collected and purified by flash column chromatography to give compound **59** as a yellow powder. ^1H NMR (500 MHz, DMSO- d_6) δ 7.59 (d, J = 7.9 Hz, 2H), 7.53 (d, J = 16.0 Hz, 1H), 7.29 (t, J = 7.5 Hz, 2H), 7.19 (t, J = 7.4 Hz, 1H), 7.09 (dd, J = 10.0, 7.8 Hz, 4H), 6.45 (d, J = 16.0 Hz, 1H), 2.66 (s, 1H), 2.62 (s, 1H), 1.95 (s, 2H), 1.80 (dd, J = 10.4, 6.9 Hz, 10H). HRMS (ESI) calcd for $\text{C}_{26}\text{H}_{25}\text{O}_2$ ($\text{M}-\text{H}^+$) 369.1855, found 369.1852

[00393] Compound **60**: (E)-3-(4-(((1r,3r,5R,7S)-adamantan-2-ylidene)(phenyl)methyl)phenyl)-N-(3-hydroxypropyl)acrylamide

[00394] Following the general procedure for amide synthesis using HATU between **59** and 3-aminopropan-1-ol, compound **60** was obtained as white solid. ^1H NMR (500 MHz, DMSO- d_6) δ 7.46 (d, J = 8.0 Hz, 2H), 7.35 (d, J = 15.7 Hz, 1H), 7.29 (t, J = 7.5 Hz, 2H), 7.19 (t, J = 7.4 Hz, 1H), 7.10 (td, J = 8.2, 1.4 Hz, 4H), 6.55 (d, J = 15.8 Hz, 1H), 4.45 (t, J = 5.2 Hz, 1H), 3.41 (q, J = 6.0 Hz, 2H), 3.19 (q, J = 6.6 Hz, 2H), 2.67 (s, 1H), 2.63 (s, 1H), 1.96 (s, 2H), 1.81 (dd, J = 11.0, 7.2 Hz, 10H), 1.58 (p, J = 6.5 Hz, 2H). HRMS (ESI) calcd for $\text{C}_{29}\text{H}_{34}\text{NO}_2$ ($\text{M}+\text{H}^+$) 428.2590, found 428.2580

[00395] Compound **61**: (E)-3-(4-(((1r,3r,5R,7S)-adamantan-2-ylidene)(4-fluorophenyl)methyl)phenyl)acrylic acid

[00396] Following the synthesis of compound **59**, Compound **61** was obtained as white solid. ^1H NMR (500 MHz, DMSO- d_6) δ 7.60 (d, J = 7.8 Hz, 2H), 7.53 (d, J = 16.0 Hz, 1H), 7.11 (dq, J = 5.0, 3.5, 2.7 Hz, 6H), 6.46 (d, J = 16.0 Hz, 1H), 2.65 (s, 1H), 2.60 (s, 1H), 1.94 (s, 2H), 1.79 (d, J = 13.9 Hz, 10H). HRMS (ESI) calcd for $\text{C}_{26}\text{H}_{24}\text{O}_2\text{F}$ ($\text{M}-\text{H}^+$) 387.1760, found 387.1754

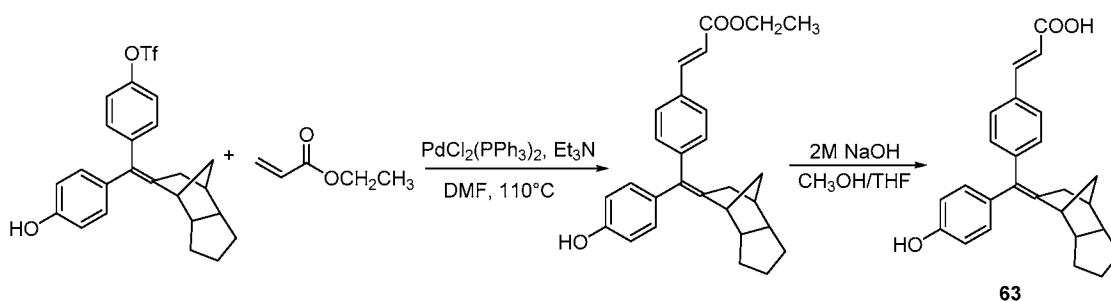
[00397] Compound **62**: (E)-3-(4-(((1r,3r,5R,7S)-adamantan-2-ylidene)(4-fluorophenyl)methyl)phenyl)-N-(3-hydroxypropyl)acrylamide

[00398] Following the synthesis of compound **60**, Compound **62** was obtained as white solid. ^1H NMR (500 MHz, DMSO- d_6) δ 8.07 (dd, J = 7.2, 3.9 Hz, 1H), 7.47 (d, J = 8.0 Hz, 2H), 7.11 (t, J = 5.5 Hz, 6H), 6.55 (d, J = 15.8 Hz, 1H), 3.41 (q, J = 5.6 Hz, 2H), 3.20 (q, J = 6.5 Hz, 2H), 2.60

(s, 1H), 1.95 (s, 2H), 1.80 (d, $J = 13.7$ Hz, 10H), 1.58 (p, $J = 6.4$ Hz, 2H). HRMS (ESI) calcd for $C_{29}H_{33}NO_2F$ ($M+H^+$) 446.2495, found 446.2491

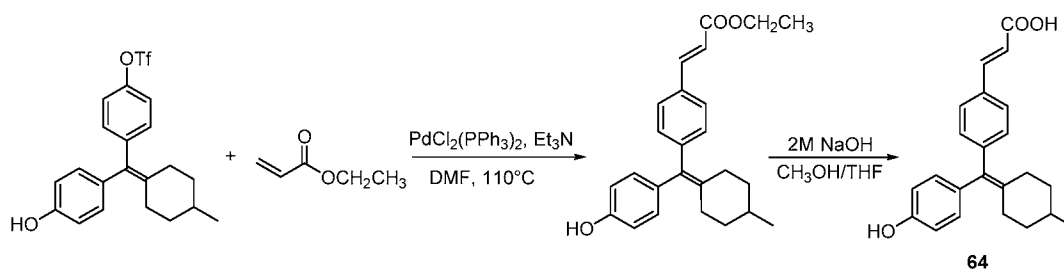
[00399] VIII. Altered Aliphatic Cyclic

[00400] Compound **63**: (E)-3-(4-((Z)-(4-hydroxyphenyl)((3aS,4R,7R,7aS)-octahydro-5H-4,7-methanoinden-5-ylidene)methyl)phenyl)acrylic acid



[00401] Following the general procedure of Heck reaction and hydrolysis of ester, compound **31** was obtained as light yellow solid. 1H NMR (500 MHz, $CDCl_3$) δ 7.79 (dd, $J = 15.9, 7.8$ Hz, 1H), 7.48 (t, $J = 8.8$ Hz, 2H), 7.23 (t, $J = 8.3$ Hz, 2H), 7.05 (dd, $J = 14.5, 8.5$ Hz, 2H), 6.79 (t, $J = 8.1$ Hz, 2H), 6.43 (dd, $J = 15.9, 6.7$ Hz, 1H), 2.71 (d, $J = 11.0$ Hz, 1H), 2.43 (td, $J = 16.0, 4.4$ Hz, 1H), 2.19 (ddd, $J = 26.6, 13.6, 7.0$ Hz, 2H), 1.95 (dtt, $J = 21.9, 14.2, 7.9$ Hz, 4H), 1.87 – 1.77 (m, 1H), 1.71 (dt, $J = 12.1, 6.0$ Hz, 1H), 1.51 (t, $J = 7.8$ Hz, 1H), 1.24 (d, $J = 9.0$ Hz, 2H), 1.07 – 0.92 (m, 2H). HRMS (ESI) calcd for $C_{26}H_{25}O_3$ ($M-H^+$) 385.1804, found 385.1797.

[00402] Compound **64**: (E)-3-(4-((4-hydroxyphenyl)(4-methylcyclohexylidene)methyl)phenyl)acrylic acid



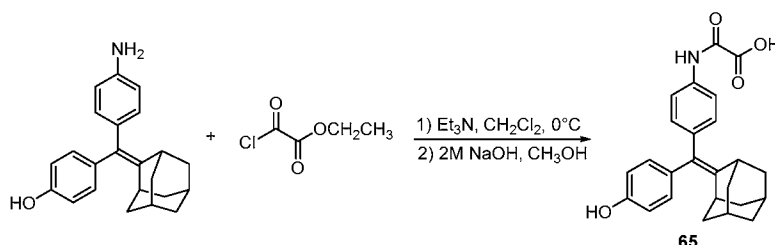
[00403] Compound **64** was obtained through same procedure as described in **31**, starting from 4,4'-((4-methylcyclohexylidene)methylene)diphenol. 1H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, $J = 15.9$ Hz, 1H), 7.47 (d, $J = 8.0$ Hz, 2H), 7.16 (d, $J = 8.0$ Hz, 2H), 6.99 (d, $J = 8.3$ Hz, 2H), 6.77 (d,

$J = 8.3$ Hz, 2H), 6.42 (d, $J = 15.9$ Hz, 1H), 2.65 – 2.52 (m, 2H), 2.04 – 1.91 (m, 3H), 1.79 (d, $J = 11.6$ Hz, 3H), 1.72 – 1.59 (m, 2H), 1.10 (q, $J = 12.8, 11.8$ Hz, 3H), 0.95 (d, $J = 6.4$ Hz, 4H).

HRMS (ESI) calcd for $C_{23}H_{23}O_3$ ($M-H^+$) 347.1647, found 347.1640.

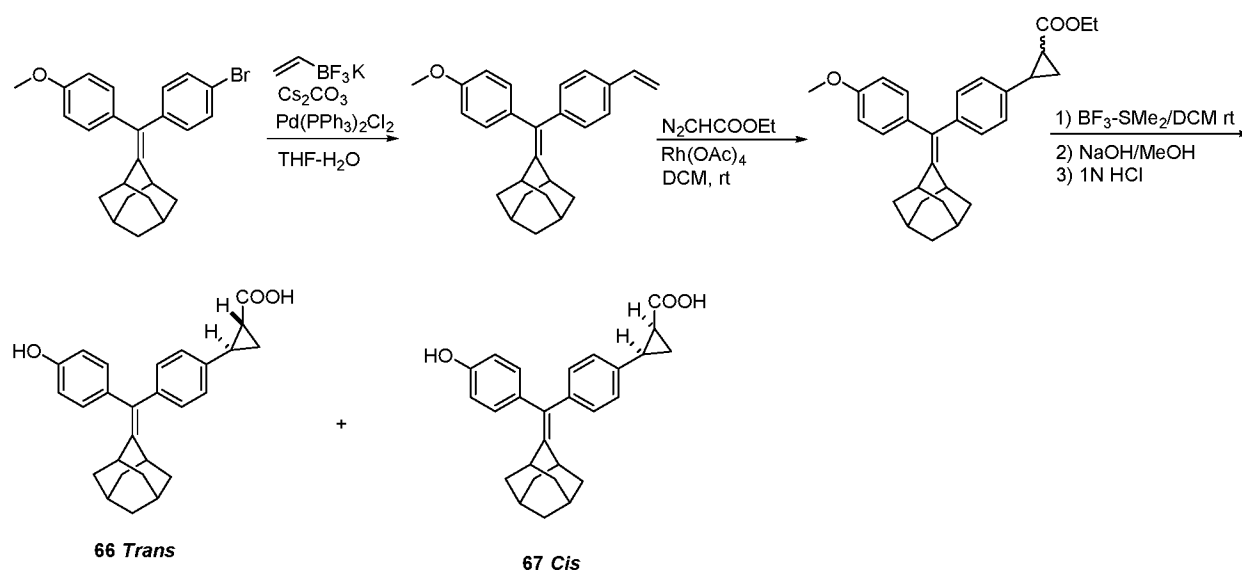
[00404] IX. Oxoacetic acid analog

[00405] Compound **65**: 2-((4-(((1r,3r,5R,7S)-adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)amino)-2-oxoacetic acid



[00406] To an dry flask charged with 4-(((1r,3r,5R,7S)-adamantan-2-ylidene)(4-aminophenyl)methyl)phenol was added methyl 2-chloro-2-oxoacetate (1.2 equiv) with anhydrous THF at room temperature under an argon atmosphere. Triethylamine (1.2 equiv) was added dropwise to this solution in an ice/water bath. The reaction mixture was stirred until the starting material was consumed, as monitored by TLC, and then quenched by saturated $NaHCO_3$ /ice water. The reaction mixture was extracted with ethyl acetate and washed with brine. The organic extracts were combined, dried over anhydrous Na_2SO_4 , and concentrated *in vacuo*. The crude product was dissolved in methanol. A 2M NaOH solution (2 mL) was added dropwise. The reaction was monitored by TLC and quenched by 1 N HCl/ice water. After stirring for 10 min, the mixture was extracted with ethyl acetate. The organic layers were collected and purified by flash column chromatography to give compound **65** as a yellow powder. 1H NMR (500 MHz, Acetone- d_6) δ 7.48 (d, $J = 7.7$ Hz, 2H), 7.16 (d, $J = 7.8$ Hz, 2H), 6.95 (d, $J = 8.3$ Hz, 2H), 6.78 (d, $J = 8.4$ Hz, 2H), 2.79 (s, 1H), 2.70 (s, 1H), 1.97 (s, 2H), 1.87 (s, 10H). ^{13}C NMR (126 MHz, Acetone- d_6) δ 156.33, 146.89, 133.47, 132.51, 130.70, 130.28, 129.94, 119.89, 115.21, 39.43, 37.01, 34.73, 34.63, 31.64, 25.15, 22.63. HRMS (ESI) calcd for $C_{25}H_{24}NO_4$ ($M-H^+$) 402.1705, found 402.1706.

[00407] X. Trans and Cis cyclopropane acid



[00408] Step 1. The mixture of bromo compound (111 mg, 0.27 mmol), potassium vinyltrifluoroborate (40 mg, 0.3 mmol), Pd(PPh₃)₂Cl₂ (5 mg, 7.1 μmol), Cs₂CO₃ (100 mg, 0.31 mmol) in THF (2 mL) and H₂O (100 μL) under argon was heated up in a 5 mL sealed vial at 80 °C for 8 hr. The reaction mixture was loaded SiO₂ column directly. Eluent with 10% EtOAc in n-Hexane (v/v) afforded the styrene compound (75 mg) of which TLC spot monitored as blue fluorescence and slightly lower R_f than a starting material.

[00409] Step 2. To the mixture of styrene (71 mg, 0.20 mmol) and catalytic amount of Rhodium(II) acetate dimer in DCM (500 μL) was add dropwise an ethyl diazoacetate (13 wt.% DCM, 300 μg) at 0 °C. Once bubbling was stopped from solution, the reaction mixture was loaded on the SiO₂ preparative TLC (Analtech, 1000 micron) and developed with 10% ethyl acetate/n-Hexane to separate cis (30 mg) and trans (30 mg) isomer.

[00410] Step 3. Each isomer (20 mg, 0.05 mmol) was dissolved into DCM (500 μL) and treated with BF₃-SMe₂ (200 μL) at rt. After stirring the reaction mixture for 3 h, the solvent was evaporated, followed by addition of 25 wt.% aqueous NaOH (100 μL), sonication for 20 min, and an adjustment of pH to ~3 with 6N HCl to collect each **66** (15 mg) and **67** (13 mg).

[00411] Compound **66**: trans 2-(4-((Z)-((5S,7S)-adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)cyclopropane-1-carboxylic acid

[00412] ^1H NMR (500 MHz, $\text{CDCl}_3 + \text{CD}_3\text{OD}$) δ 1.23~1.28 (m, 1H), 1.48~1.54 (m, 2H), 1.75~1.83 (m, 10H), 1.93 (s, 2H), 2.40~2.46 (m, 1H), 2.67 (s, 1H), 2.74 (s, 1H), 6.66 (d, $J = 8.5$ Hz, 2H), 6.88 (d, $J = 8.5$ Hz, 2H), 6.93 (d, $J = 8.5$ Hz, 2H), 6.97 (d, $J = 8.5$ Hz, 2H). ^{13}C NMR (126 MHz, $\text{CDCl}_3 + \text{CD}_3\text{OD}$) δ 17.29, 24.20, 26.50, 28.36, 34.51, 34.61, 37.31, 39.71, 48.93, 114.87, 125.79, 129.80, 130.02, 130.81, 134.71, 137.61, 141.95, 146.22, 155.01, 176.31. HRMS (ESI, $\text{M}^+ + 1$) $\text{C}_{25}\text{H}_{29}\text{O}_3$ Calcd. 401.2093 found. 401.2090

[00413] Compound 67: cis 2-(4-((Z)-((5S,7S)-adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)cyclopropane-1-carboxylic acid

[00414] ^1H NMR (500 MHz, $\text{CDCl}_3 + \text{CD}_3\text{OD}$) δ 1.35~1.40 (m, 1H), 1.36~1.40 (m, 1H), 1.64~1.09 (m, 1H), 1.82~1.93 (m, 10H), 2.01 (s, 2H), 2.03~2.09 (m, 1H), 2.63 (q, $J = 8.5$ Hz, 1H), 2.75 (s, 1H), 2.81 (s, 1H), 6.68 (d, $J = 8.5$ Hz, 2H), 6.91 (d, $J = 8.5$ Hz, 2H), 6.99 (d, $J = 8.5$ Hz, 2H), 7.16 (d, $J = 8.5$ Hz, 2H). ^{13}C NMR (126 MHz, $\text{CDCl}_3 + \text{CD}_3\text{OD}$) δ 11.81, 14.37, 21.84, 25.96, 28.40, 34.55, 37.38, 39.76, 114.88, 128.99, 129.25, 130.23, 130.82, 134.12, 141.91, 146.13, 154.84, 173.97.

[00415] *In vitro* Results

[00416] The compounds were initially screened in ER α -positive MCF-7 breast cancer cells for their suppression of cell proliferation (CP) and for their effects on ER α levels, using a single, saturating concentration of 3 μM , as shown in FIGS. 23 and 24. The antiestrogen and SERD, fulvestrant (Fulv), was included for comparison. The levels of suppression of proliferation and downregulation of ER α were plotted on percent scales. The activity in suppressing cell proliferation (CP, FIG. 23) was calculated as a percent of vehicle control; maximum suppression is ca. 0% (corresponding to essentially no increase in cell number after 6 days). For ER α levels (ER α , FIG. 24), 0% is the ER α level after 24 h with 3 μM fulvestrant treatment, with 100% being the ER α level in vehicle control cells.

[00417] Cell Proliferation Assay. WST-1 assay (Roche, Basel, Switzerland) was used to quantify cell viability after a 6 day exposure to compounds, as described. Absorbance was measured at 450 nm using a VICTOR X5 PerkinElmer 2030 Multilabel Plate Reader, and cell

proliferation values represent signal from compound-treated samples relative to vehicle-treated controls.

[00418] In-Cell Western Assay. Cells were cultured in 96-well plates at 3000 cells/well and treated with compound for 24 h. Cells were washed twice in PBS, fixed with 4% formaldehyde (Fisher Scientific) solution in PBS, permeabilized in 0.1% Triton X-100 in PBS, blocked with Odyssey Blocking Buffer (LI-COR), and incubated with rabbit HC-20 ER α antibody (Santa Cruz, Cat. No. SC-543) at 4 °C overnight. Both IRDye 800 CW goat anti-rabbit secondary antibody (LI-COR, Cat. No. 926-32211) and Cell Tag 700 (LI-COR, Cat. No. 926-41090) were diluted (1:600) for incubation with cells. Plates were washed, and ER α staining signals were quantified and normalized with Cell Tag signals using LI-COR Odyssey infrared imaging system. The ER α protein levels were calculated relative to the vehicle-treated samples.

[00419] The results in FIG 23 show that certain compounds (38, 39, and 44) are very effective in suppressing proliferation, whereas others (36, 40, 45, 46, 51, 53, 54, and 58) show more moderate proliferation suppression; some (37, 42, 43, 48, 49, 50, 52, 60, 61, and 62) are only minimally suppressive. The results in FIG 24 show that compounds 53, 54, and 58 are most effective in downregulating ER α levels, and compounds 36, 37, 38, 39-46, and 59-62 are moderately effective in ER α downregulation.

[00420] Example 18 Suppression of breast cancer metastasis and extension of host animal survival by K-07 in a pre-clinical breast cancer metastasis model driven by constitutively active mutant estrogen receptors

[00421] Over one-third of human breast tumors that become resistant to endocrine therapies have acquired mutations in the estrogen receptor (ER α) that result in constitutive receptor activity in the absence of estrogen, and these tumors are much less sensitive to suppression by current standard-of-care antiestrogens such as tamoxifen and fulvestrant. Because mutant ERs are usually enriched in recurrent, metastatic breast cancers compared to the primary breast cancer, the effectiveness of compound K-07 in preventing the growth of breast cancer metastases and in extending survival in a metastatic tumor model was examined.

[00422] Metastasis growth was monitored by bioluminescence (IVIS) imaging 19 days (FIG. 29A) and 25 days (FIG. 29B) after intracardiac injection into NOD-SCID-gamma (NSG) female mice with 0.5×10^6 MCF-7 breast cancer cells expressing luciferase and D538G ER (ca. 50% mutant ER and 50% wild type ER). Following injection mice were treated 6-times per week with vehicle or K-07 (80 mg/kg orally for 30 days and then 40 mg/kg). The reduced tumor burden in K-07 treated animals is evident from the reduced bioluminescence signal observed at Day 25 (FIG. 29B). As shown in FIG. 29C, shows animal survival increased with K-07 treatment.

[00423] MCF-7 breast cancer cells expressing luciferase and Y537S ER or D538G ER (ca. 50% mutant ER and 50% wild type ER) were also injected i.v. by the tail vein into NOD-SCID-gamma (NSG) female mice. The constitutively active ER-containing breast cancer cells established metastases in liver, bone and brain that increased in number and size over time (day zero – 80 days) as monitored by IVIS imaging and immunohistochemical (IHC) analysis (FIGS. 30A, 30B and 31A). Daily oral treatment with K-07 (80 mg/kg orally for 30 days and then 40 mg/kg) versus oral vehicle greatly reduced the metastasis burden of mutant ER-containing breast cancer cells as noted by the reduced bioluminescence signal in the K-07 treated animals (FIG. 30A and 31A). Notably, mice with mutant ER-containing metastases treated with K-07 survived much longer than mice given daily control vehicle. In fact, by day 60, only 25% of vehicle treated mice with mutant ER breast cancers were alive whereas all K-07 treated D538G mice and 80% of Y537S mice were alive (FIGS. 30C and 31B).

[00424] Hence, the results indicated that the antiestrogen reduced the *in vivo* metastasis of breast cancers driven by constitutively active mutant ERs and extend host survival. The findings suggested that the antiestrogen K-07 may be suitable for further translational and clinical examination of its efficacy in suppression of metastasis in patients with breast cancers containing constitutively active mutant ERs.

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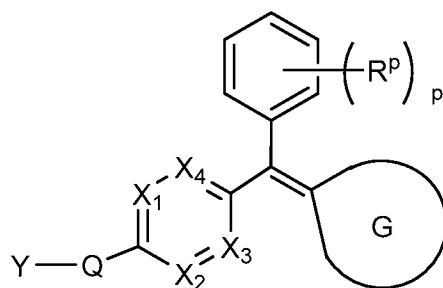
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Claims

The invention claimed is:

1. A compound of formula (I), or a pharmaceutically acceptable salt thereof,



(I)

wherein

G is an optionally substituted polycycloalkylidene;

X_1 , X_2 , X_3 , and X_4 are each independently N, CH, or CR^m , wherein at most two of X_1 , X_2 , X_3 , and X_4 are N, and wherein at most one of X_1 and X_4 is N;

Y is alkyl, $-OR^A$, $-COOR^B$, $-N(R^C)(R^D)$, $-CON(R^C)(R^D)$, $-N(R^C)-OH$, $-NH-N(R^C)(R^D)$, or $-CR^y=CR^x-CN$;

Q is a bond, $-C(Q^1)-CR^y=CR^x-$, $-C(Q^2)-NH-N=CR^x-$, $-C(O)-NH-$, $-C(O)-Q^3-$, or $-SO_2-CR^y=CR^z-$, wherein the $C(Q^1)$, $C(Q^2)$, $C(O)$, or SO_2 group is attached to Y;

R^p and R^m at each occurrence are independently alkyl, alkoxy, halogen, $-OH$, $-CN$, haloalkyl, or hydroxyalkyl;

p is 0, 1, 2, 3, 4, or 5;

Q^1 and Q^2 are O, NH, or S;

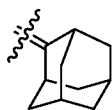
Q^3 is an optionally substituted cycloalkylene;

R^A , R^B , R^C , and R^D at each occurrence are independently hydrogen, alkyl, cycloalkyl, aryl, heterocycle, heteroaryl, or alkyl substituted by one or more substituents selected from the group consisting of $-OH$, $-NH_2$, $-NH(C_{1-4}alkyl)$, $-N(C_{1-4}alkyl)_2$, halogen, phenyl, and $-NHCO-R^Z$, wherein the cycloalkyl, aryl, heterocycle, and heteroaryl are each optionally substituted;

R^x and R^y at each occurrence are independently hydrogen, alkyl, halogen, haloalkyl, or $-\text{CN}$; and

R^Z is $-\text{OC}_{1-4}\text{alkyl}$, cycloalkyl or $-\text{C}_{1-4}\text{ alkylene-cycloalkyl}$.

2. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein G is

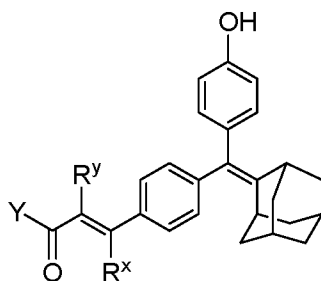


3. The compound of any one of claims 1-2, or a pharmaceutically acceptable salt thereof, wherein Q is $-\text{C}(\text{Q}^1)-\text{CR}^y=\text{CR}^x-$.

4. The compound of any one of claims 1-3, or a pharmaceutically acceptable salt thereof, wherein Q^1 is O.

5. The compound of any one of claims 1-4, or a pharmaceutically acceptable salt thereof, wherein R^p is $-\text{OH}$, and p is 1.

6. The compound of any one of claims 1-5, or a pharmaceutically acceptable salt thereof, having a structure of formula (I-c):

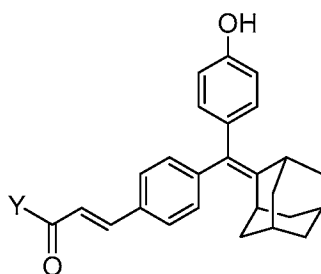


(I-c)

wherein Y is alkyl, $-\text{OR}^A$, or $-\text{N}(\text{R}^C)(\text{R}^D)$; and

R^x , R^y , R^A , R^C , and R^D are as defined in claim 1.

7. The compound of claim 6, or a pharmaceutically acceptable salt thereof, having a structure of formula (I-c-1):



(I-c-1).

8. The compound of any one of claims 1-7, wherein

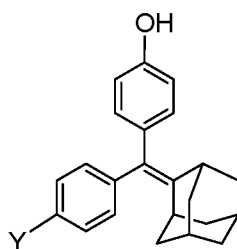
Y is $-\text{OR}^{\text{A}}$ or $-\text{N}(\text{R}^{\text{C}})(\text{R}^{\text{D}})$;

R^{A} and R^{C} are hydrogen, C_{1-10} alkyl, C_{1-10} alkylene-OH, C_{1-10} alkylene-NH₂, C_{1-10} alkylene-NH(C_{1-4} alkyl), C_{1-10} alkylene-N(C_{1-4} alkyl)₂, C_{1-10} alkyl substituted with 1, 2, 3, or 4 halogen, C_{1-10} alkyl substituted with a phenyl, C_{1-10} alkyl substituted with $-\text{NHCO}-\text{R}^{\text{Z}}$, or C_{1-10} alkyl substituted with -OH and at least one halogen;

R^{D} is hydrogen, C_{1-4} alkyl, or C_{1-4} hydroxyalkyl; and

R^{Z} is a $-\text{OC}_{1-4}$ alkyl, C_{3-10} cycloalkyl, or $-\text{C}_{1-4}$ alkylene- C_{3-10} cycloalkyl.

9. The compound of any one of claims 1-2, or a pharmaceutically acceptable salt thereof, having a structure of formula (I-d):



(I-d)

wherein

Y is $-\text{OR}^{\text{A}}$ or $-\text{CR}^{\text{y}}=\text{CR}^{\text{x}}-\text{CN}$;

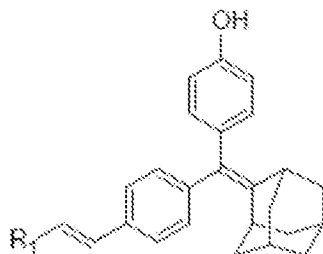
R^{A} is C_{1-10} alkyl substituted with $-\text{NHCO}-\text{R}^{\text{Z}}$;

R^{x} and R^{y} is each independently hydrogen, C_{1-4} alkyl, halogen, C_{1-4} haloalkyl, or -CN; and

R^{Z} is C_{3-10} cycloalkyl or $-\text{C}_{1-4}$ alkylene- C_{3-10} cycloalkyl.

10. The compound of claim 9, or a pharmaceutically acceptable salt thereof, wherein Y is $-OR^A$.

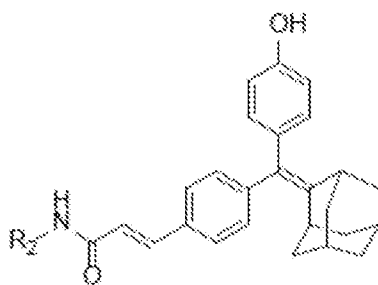
11. The compound of claim 1, or a pharmaceutically acceptable salt thereof, having a structure of (i):



(i)

wherein R_1 is selected from $-\text{CO}(\text{CH}_2)_4\text{CH}_3$, $-\text{COOCH}_3$, $-\text{COOCH}_2\text{CH}_3$, $\text{COO}(\text{CH}_2)_3\text{CH}_3$, $-\text{COO}(\text{CH}_2)_5\text{CH}(\text{CH}_3)_2$, $-\text{COO}(\text{CH}_2)_2\text{OH}$, $-\text{COO}(\text{CH}_2)_4\text{OH}$, $-\text{CN}$, $-\text{SO}_2\text{NH}(\text{CH}_2)_2\text{CH}_3$, $-\text{COO}(\text{CH}_2)_3\text{OH}$, $-\text{CO}_2\text{H}$ and $-\text{CONH}_2$.

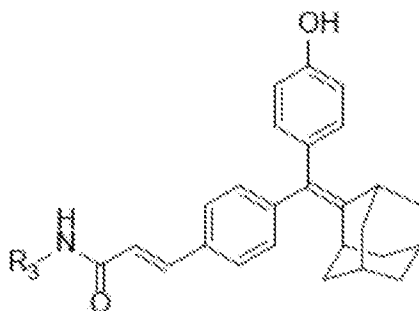
12. The compound of claim 1, or a pharmaceutically acceptable salt thereof, having a structure of (ii):



(ii)

wherein R_2 is selected from $-(CH_2)_2CH_3$, $-(CH_2)_3CH_3$, $-(CH_2)_4CH_3$, $-(CH_2)_2OH$, $-(CH_2)_3OH$, $-(CH_2)_4OH$, $-(CH_2)_5OH$, $-(CH_2)CF_3$, $-(CH_2)_2N(CH_3)_2$, $-(CH_2)_2NHBoc$, $-(CH_2)_3NHBoc$, and $-(CH_2)_4NHBoc$.

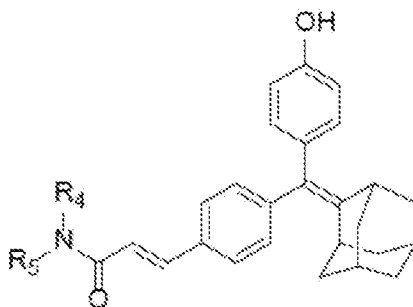
13. The compound of claim 1, or a pharmaceutically acceptable salt thereof, having a structure of (iii):



(iii)

wherein R_3 is selected from $-(CH_2)_2NH_2$, $-(CH_2)_3NH_2$, and $-(CH_2)_4NH_2$.

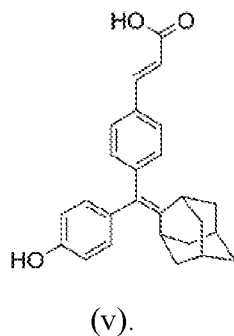
14. The compound of claim 1, or a pharmaceutically acceptable salt thereof, having a structure of (iv):



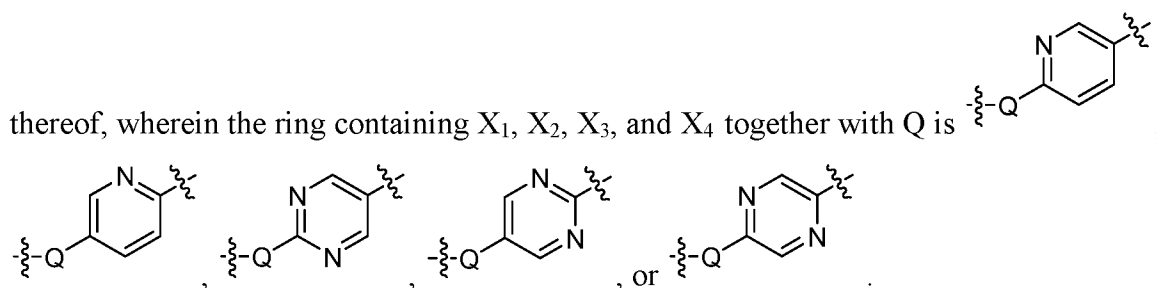
(iv)

wherein R_4 is selected from $-CH_3$ and $-(CH_2)_2OH$, and wherein R_5 is selected from $-(CH_2)_2OH$ and $-(CH_2)_3CH_3$.

15. The compound of claim 1, or a pharmaceutically acceptable salt thereof, having a structure of (v):

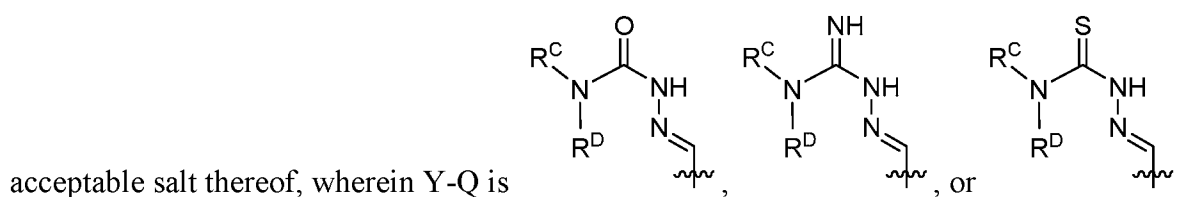


16. The compound of any one of claims 1-5 and 8, or a pharmaceutically acceptable salt



17. The compound of any one of claims 1, 2, 5, 8, and 16, or a pharmaceutically acceptable salt thereof, wherein Q is $-\text{C}(\text{Q}^2)-\text{NH}-\text{N}=\text{CR}^x-$, $-\text{C}(\text{O})-\text{NH}-$, $-\text{C}(\text{O})-\text{Q}^3-$, or $-\text{SO}_2-\text{CR}^y=\text{CR}^z-$, wherein the $\text{C}(\text{Q}^2)$, $\text{C}(\text{O})$, or SO_2 group is attached to Y.

18. The compound of any one of claims 1, 2, 5, 8, 16, and 17, or a pharmaceutically

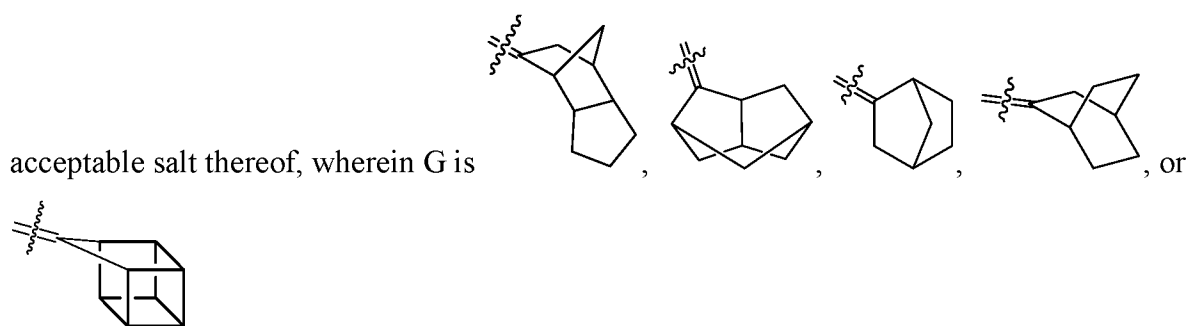


19. The compound of any one of claims 1, 2, 5, 8, 16, and 17, or a pharmaceutically acceptable salt thereof, wherein the Y-Q group is $\text{R}^{\text{B}}\text{OOC}-\text{C}(\text{O})-\text{NH}-$ or $(\text{R}^{\text{C}})(\text{R}^{\text{D}})\text{NCO}-\text{C}(\text{O})-\text{NH}-$.

20. The compound of any one of claims 1, 2, 5, 8, 16, and 17, or a pharmaceutically acceptable salt thereof, wherein the Y-Q group is $R^A O-C(O)-Q^3-$.

21. The compound of any one of claims 1-6, 8, 16, and 17, or a pharmaceutically acceptable salt thereof, wherein at least one of R^x and R^y is C_{1-4} alkyl, halogen, C_{1-4} haloalkyl, or $-CN$.

22. The compound of any one of claims 1, 3-5, 8, and 16-21, or a pharmaceutically



23. The compound of claim 1, selected from the group consisting of:

(E)-3-(4-(((1r,3r,5R,7S)-Adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)acrylic acid;

(E)-1-(4-(((1r,3r,5R,7S)-Adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)oct-1-en-3-one;

Methyl (E)-3-(4-(((1r,3r,5R,7S)-Adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)acrylate;

Ethyl(E)-3-(4-(((1r,3r,5R,7S)-Adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)acrylate;

Butyl (E)-3-(4-(((1r,3r,5R,7S)-Adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)acrylate;

6-Methylheptyl (E)-3-(4-(((1r,3r,5R,7S)-Adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)acrylate;

2-Hydroxyethyl (E)-3-(4-(((1r,3r,5R,7S)-Adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)acrylate;

3-Hydroxypropyl (E)-3-(4-(((1r,3r,5R,7S)-Adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)acrylate;

4-Hydroxybutyl (E)-3-(4-(((1r,3r,5R,7S)-Adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)acrylate;

(E)-3-(4-(((1r,3r,5R,7S)-Adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)acrylonitrile;

(E)-2-(4-(((1r,3r,5R,7S)-Adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)-N-propylethene-1-sulfonamide;

(E)-3-(4-(((1r,3r,5R,7S)-Adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)acrylamide;

(E)-3-(4-(((1r,3r,5R,7S)-Adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)-N-propylacrylamide;

(E)-3-(4-(((1r,3r,5R,7S)-Adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)-N-butylacrylamide;

(E)-3-(4-(((1r,3r,5R,7S)-Adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)-N-pentylacrylamide;

(E)-3-(4-(((1r,3r,5R,7S)-Adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)-N-(2-hydroxyethyl)acrylamide;

(E)-3-(4-(((1r,3r,5R,7S)-Adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)-N-(3-hydroxypropyl)acrylamide

(E)-3-(4-(((1r,3r,5R,7S)-Adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)-N-(4-hydroxybutyl)acrylamide

(E)-3-(4-(((1r,3r,5R,7S)-Adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)-N-(5-hydroxypentyl)acrylamide

(E)-3-(4-(((1r,3r,5R,7S)-Adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)-N-(2-aminoethyl)acrylamide

(E)-3-(4-(((1r,3r,5R,7S)-Adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)-N-(3-aminopropyl)acrylamide

(E)-3-(4-(((1r,3r,5R,7S)-Adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)-N-(4-aminobutyl)acrylamide

(E)-3-(4-(((1r,3r,5R,7S)-Adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)-N-(2,2,2-trifluoroethyl)acrylamide

(E)-3-(4-(((1r,3r,5R,7S)-Adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)-N-butyl-N-methylacrylamide

(E)-3-(4-(((1r,3r,5R,7S)-Adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)-N-(2-hydroxyethyl)-N-methylacrylamide

(E)-3-(4-(((1r,3r,5R,7S)-Adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)-N,N-bis(2-hydroxyethyl)acrylamide

(E)-3-(4-(((1r,3r,5R,7S)-Adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)-N-(2-(dimethylamino)ethyl)acrylamide

(3r,5r,7r)-N-(3-(4-(((1r,3r,5R,7S)-adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenoxy)propyl)adamantane-1-carboxamide

(E)-3-(4-(((1r,3r,5R,7S)-adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)-2-methylacrylic acid

(E)-3-(4-(((1r,3r,5R,7S)-adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)-2-cyanoacrylic acid

(Z)-3-(4-(((1r,3r,5R,7S)-adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)-2-chloroacrylic acid

(Z)-3-(4-(((1r,3r,5R,7S)-adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)-2-fluoroacrylic acid

(E)-3-(4-(((1r,3r,5R,7S)-adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)but-2-enoic acid

(E)-3-(4-(((1r,3r,5R,7S)-adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)-N-hydroxyacrylamide

(E)-3-(4-(((1r,3r,5R,7S)-adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)-N-hydroxy-N-methylacrylamide

(E)-3-(4-(((1r,3r,5R,7S)-adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)-N-hydroxy-N-isopropylacrylamide

(E)-3-(4-(((1r,3r,5R,7S)-adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)acrylohydrazide

(E)-3-(4-(((1r,3r,5R,7S)-adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)-N-(2,2-difluoro-3-hydroxypropyl)acrylamide

(E)-N-((3s,5s,7s)-adamantan-1-yl)-3-(4-(((1r,3r,5R,7S)-adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)acrylamide

(E)-N-(((3r,5r,7r)-adamantan-1-yl)methyl)-3-(4-(((1r,3r,5R,7S)-adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)acrylamide

(E)-3-(4-(((1r,3r,5R,7S)-adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)-N-benzylacrylamide

(E)-N-(4-(2-((3r,5r,7r)-adamantan-1-yl)acetamido)butyl)-3-(4-(((1r,3r,5R,7S)-adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)acrylamide

(E)-3-(4-(((1r,3r,5R,7S)-adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)-N-butylprop-2-enethioamide

2-((E)-4-(((1r,3r,5R,7S)-adamantan-2-ylidene)(4-hydroxyphenyl)methyl)benzylidene)hydrazine-1-carboxamide

2-((E)-4-(((1r,3r,5R,7S)-adamantan-2-ylidene)(4-hydroxyphenyl)methyl)benzylidene)hydrazine-1-carbothioamide

N'-((E)-4-(((1r,3r,5R,7S)-adamantan-2-ylidene)(4-hydroxyphenyl)methyl)benzylidene)hydrazinecarbohydrazide

2-((E)-4-(((1r,3r,5R,7S)-adamantan-2-ylidene)(4-hydroxyphenyl)methyl)benzylidene)hydrazine-1-carboximidamide

N'-((E)-4-(((1r,3r,5R,7S)-adamantan-2-ylidene)(4-hydroxyphenyl)methyl)benzylidene)hydrazinecarbothiohydrazide

(E)-3-(4-(((1r,3r,5R,7S)-adamantan-2-ylidene)(4-hydroxyphenyl)methyl)-3-fluorophenyl) acrylic acid

(E)-3-(4-(((1r,3r,5R,7S)-adamantan-2-ylidene)(4-hydroxyphenyl)methyl)-3,5-difluorophenyl) acrylic acid

(E)-3-(4-(((1r,3r,5R,7S)-adamantan-2-ylidene)(4-hydroxyphenyl)methyl)-2-fluorophenyl) acrylic acid

(E)-3-(4-(((1r,3r,5R,7S)-adamantan-2-ylidene)(4-hydroxyphenyl)methyl)-2-(trifluoromethyl) phenyl)acrylic acid

(Z)-3-(4-(((1r,3r,5R,7S)-adamantan-2-ylidene)(4-hydroxyphenyl)methyl)-3-fluorophenyl)-2-fluoroacrylic acid

(E)-3-(5-(((1r,3r,5R,7S)-adamantan-2-ylidene)(4-hydroxyphenyl)methyl)pyridin-2-yl)acrylic acid

(E)-3-(4-(((1r,3r,5R,7S)-adamantan-2-ylidene)(phenyl)methyl)phenyl)acrylic acid

(E)-3-(4-(((1r,3r,5R,7S)-adamantan-2-ylidene)(phenyl)methyl)phenyl)-N-(3-hydroxypropyl)acrylamide

(E)-3-(4-(((1r,3r,5R,7S)-adamantan-2-ylidene)(4-fluorophenyl)methyl)phenyl)acrylic acid

(E)-3-(4-(((1r,3r,5R,7S)-adamantan-2-ylidene)(4-fluorophenyl)methyl)phenyl)-N-(3-hydroxypropyl)acrylamide

(E)-3-(4-((Z)-(4-hydroxyphenyl)((3aS,4R,7R,7aS)-octahydro-5H-4,7-methanoinden-5-ylidene)methyl)phenyl)acrylic acid;

2-((4-(((1r,3r,5R,7S)-adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)amino)-2-oxoacetic acid;

trans 2-(4-((Z)-((5S,7S)-adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)cyclopropane-1-carboxylic acid; and

cis 2-(4-((Z)-((5S,7S)-adamantan-2-ylidene)(4-hydroxyphenyl)methyl)phenyl)cyclopropane-1-carboxylic acid,

or a pharmaceutically acceptable salt thereof.

24. A pharmaceutical composition comprising a therapeutically effective amount of a compound of any one of claims 1-23, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

25. The pharmaceutical composition of claim 24, further comprising a therapeutically effective amount of at least one additional anti-cancer therapeutic agent.

26. The compound of any one of claims 1-23, or a pharmaceutically acceptable salt thereof, for use in treating or preventing breast cancer.

27. The compound of claim 26, wherein the breast cancer is primary, metastatic, or recurrent breast cancer.

28. The compound of any one of claims 1-23, or a pharmaceutically acceptable salt thereof, for use in inhibiting or slowing the growth of estrogen receptor-positive, endocrine therapy-sensitive tumors or endocrine therapy resistant tumors driven by active estrogen receptors.

29. The compound of claim 28, wherein the tumor is driven by wild type, constitutively active estrogen receptors, and combinations thereof.

30. Use of a compound of any one of claims 1-23, or a pharmaceutically acceptable salt thereof, for manufacturing a medicament for treating or preventing breast cancer.

31. Use of a compound of any one of claims 1-23, or a pharmaceutically acceptable salt thereof, for manufacturing a medicament for inhibiting or slowing the growth of estrogen receptor-positive, endocrine therapy-sensitive tumors or endocrine therapy resistant tumors driven by active estrogen receptors.

32. A method of treating or preventing breast cancer comprising administering to a subject in need thereof a therapeutically effective amount of the compound of any one of claims 1-23, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 24.

33. A method of treating primary, metastatic, or recurrent breast cancer comprising administering to a subject in need thereof, a therapeutically effective amount of a compound of any one of claims 1-23, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 24.

34. A method of preventing breast cancer recurrence in a subject with prior breast cancer comprising administering to the subject a therapeutically effective amount of a compound of any one of claims 1-23, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 24.

35. A method of inhibiting or slowing the growth of estrogen receptor-positive, endocrine therapy-sensitive tumors or endocrine therapy resistant tumors driven by active estrogen receptors comprising administering to a subject a therapeutically effective amount of a compound of any one of claims 1-23, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 24.

36. The method of any one of claims 32-35, wherein the tumor is driven by wild type, constitutively active estrogen receptors, and combinations thereof.

37. The method of any one of claims 32-35, further comprising administering a therapeutically effective amount of at least one additional anti-cancer therapeutic agents.

38. The method of claim 37, wherein the at least one additional anti-cancer therapeutic agents are administered prior to or following administration of the compound of any one of claims 1-23, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 24.

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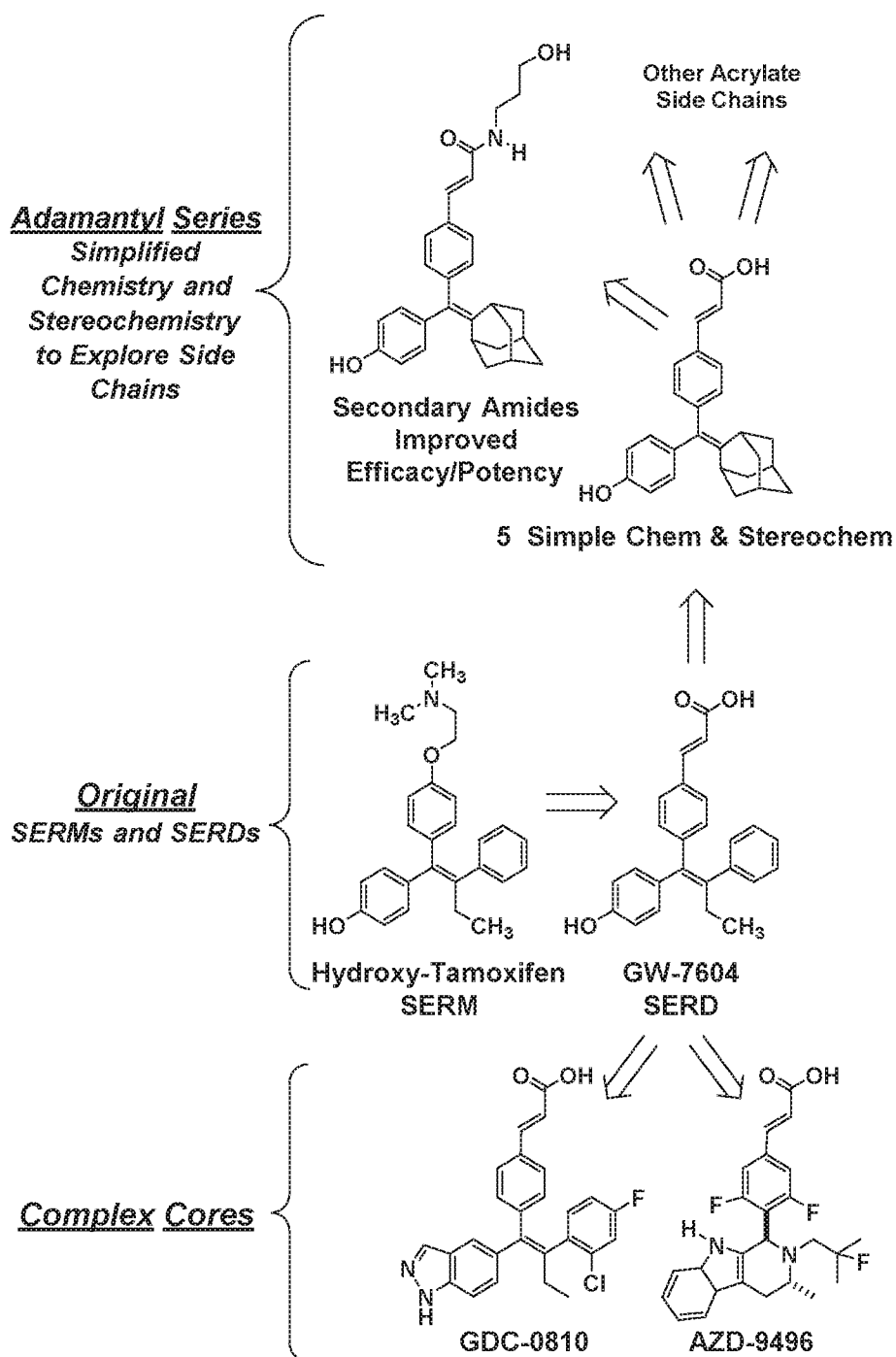


FIG. 1

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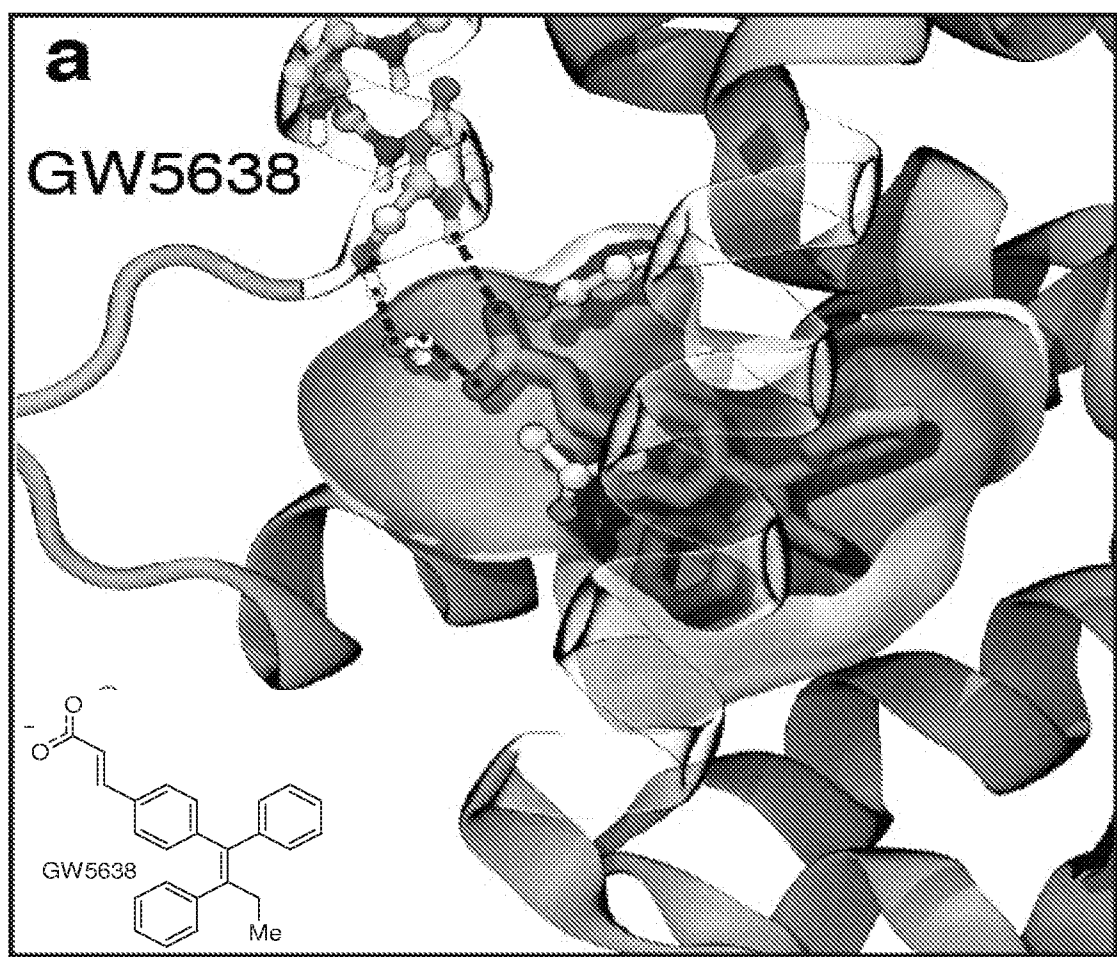


FIG. 2

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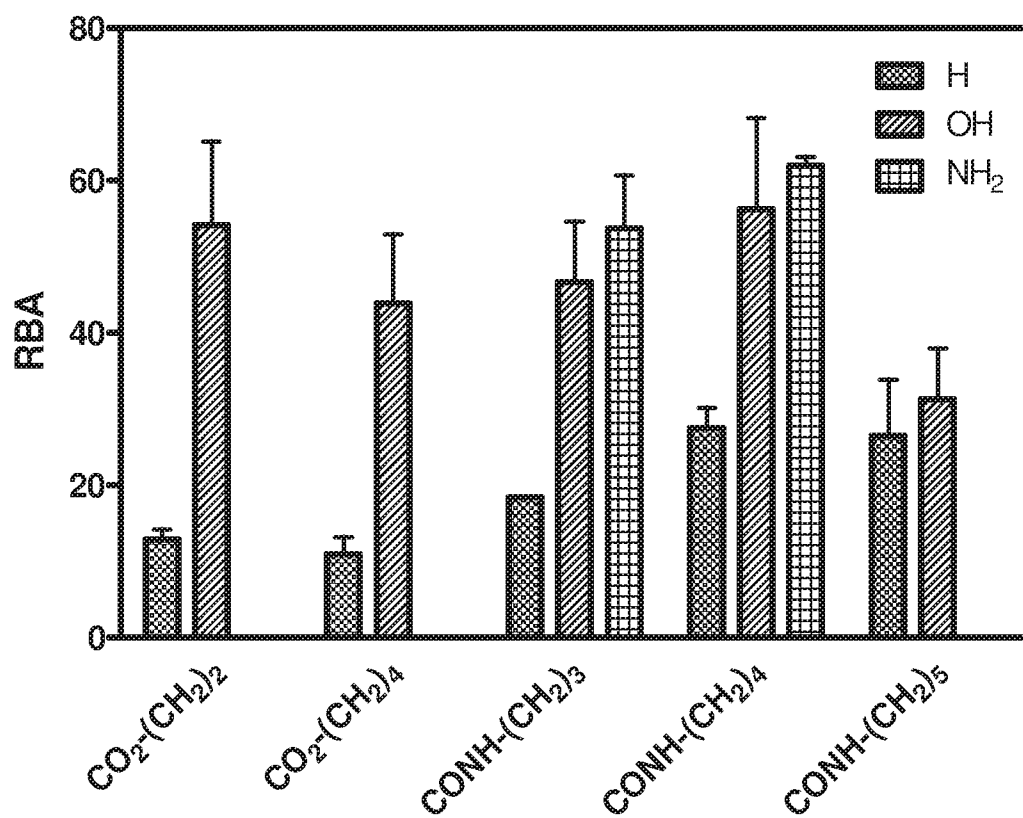


FIG. 3

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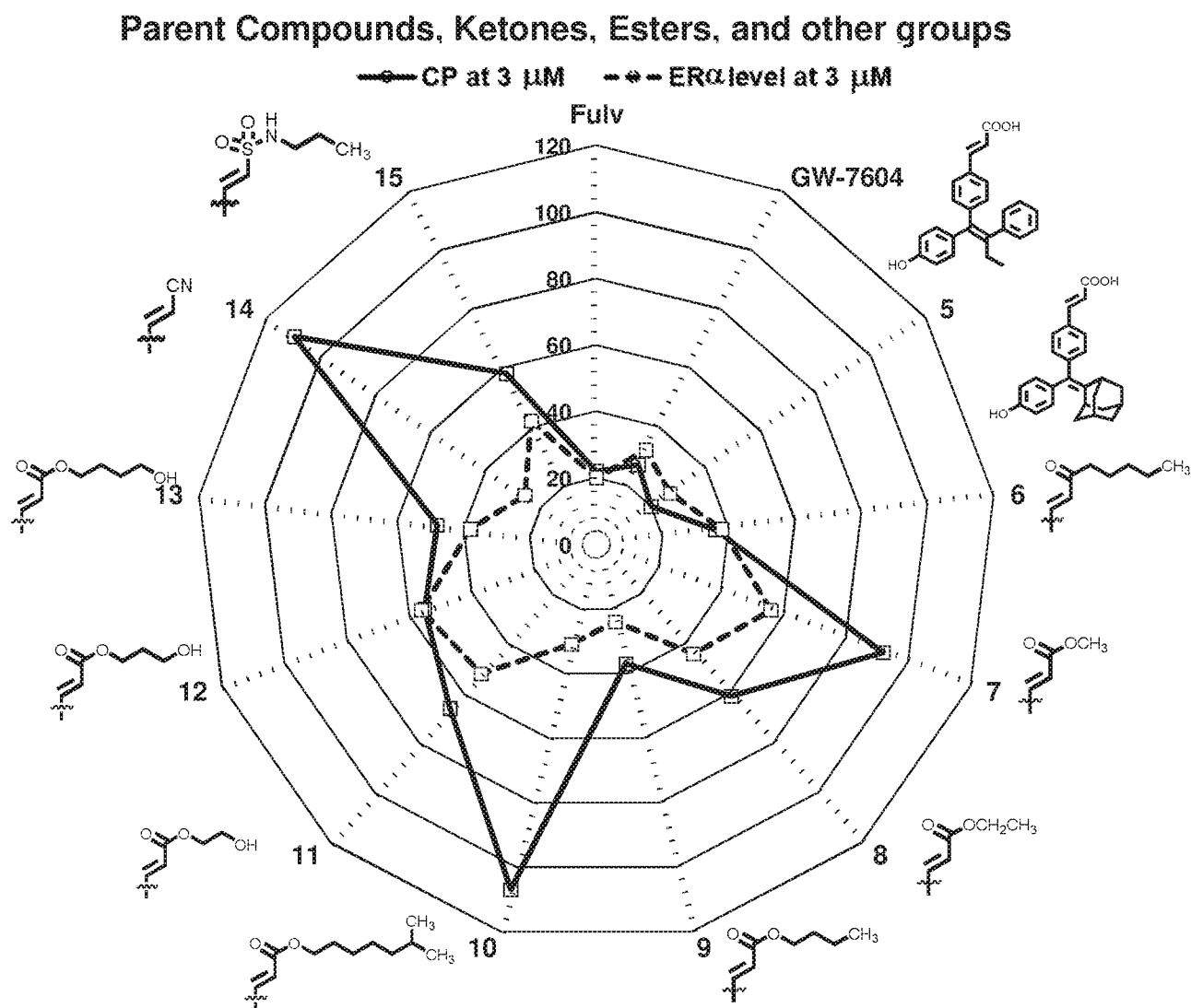


FIG. 4A

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Primary and Secondary Amides

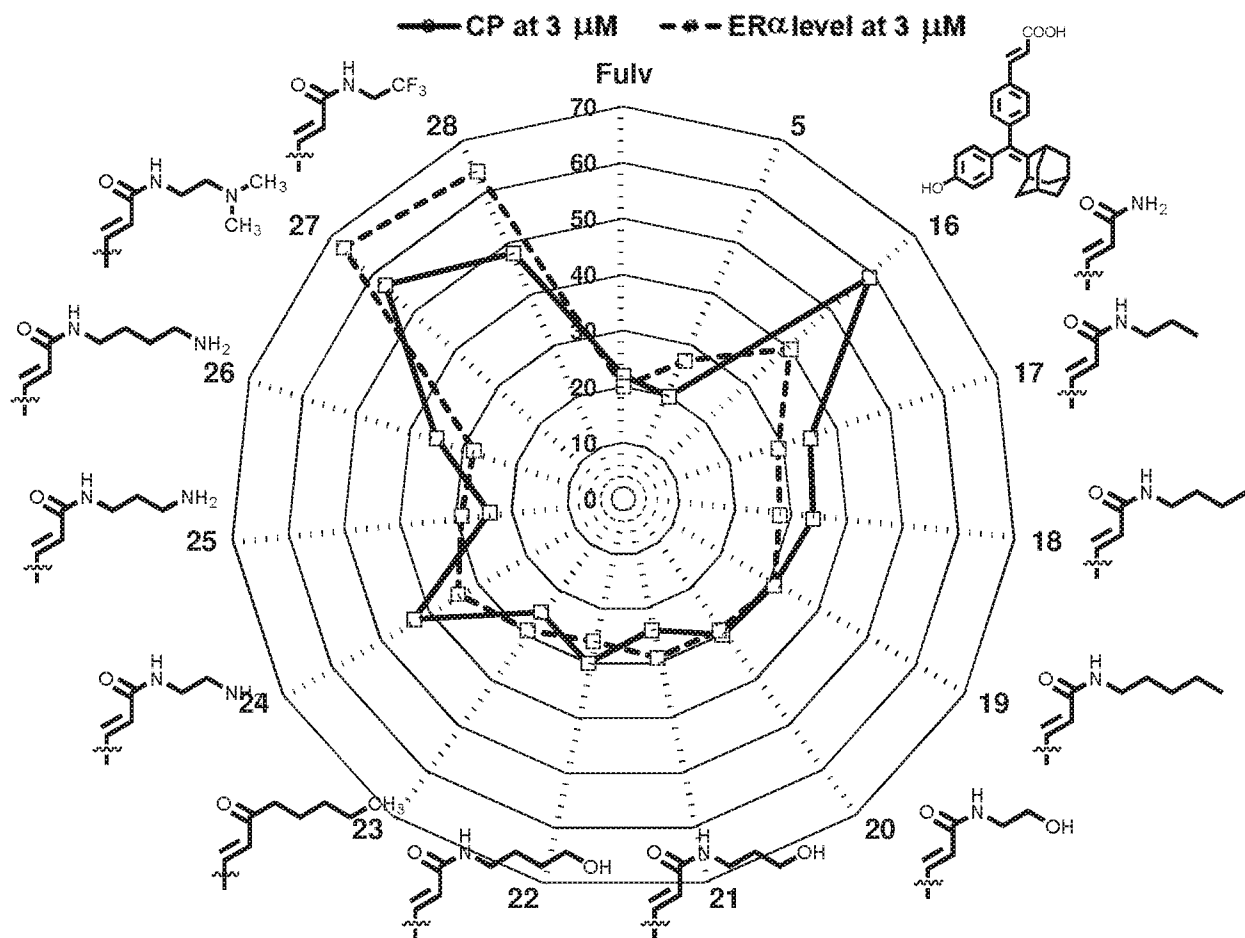


FIG. 4B

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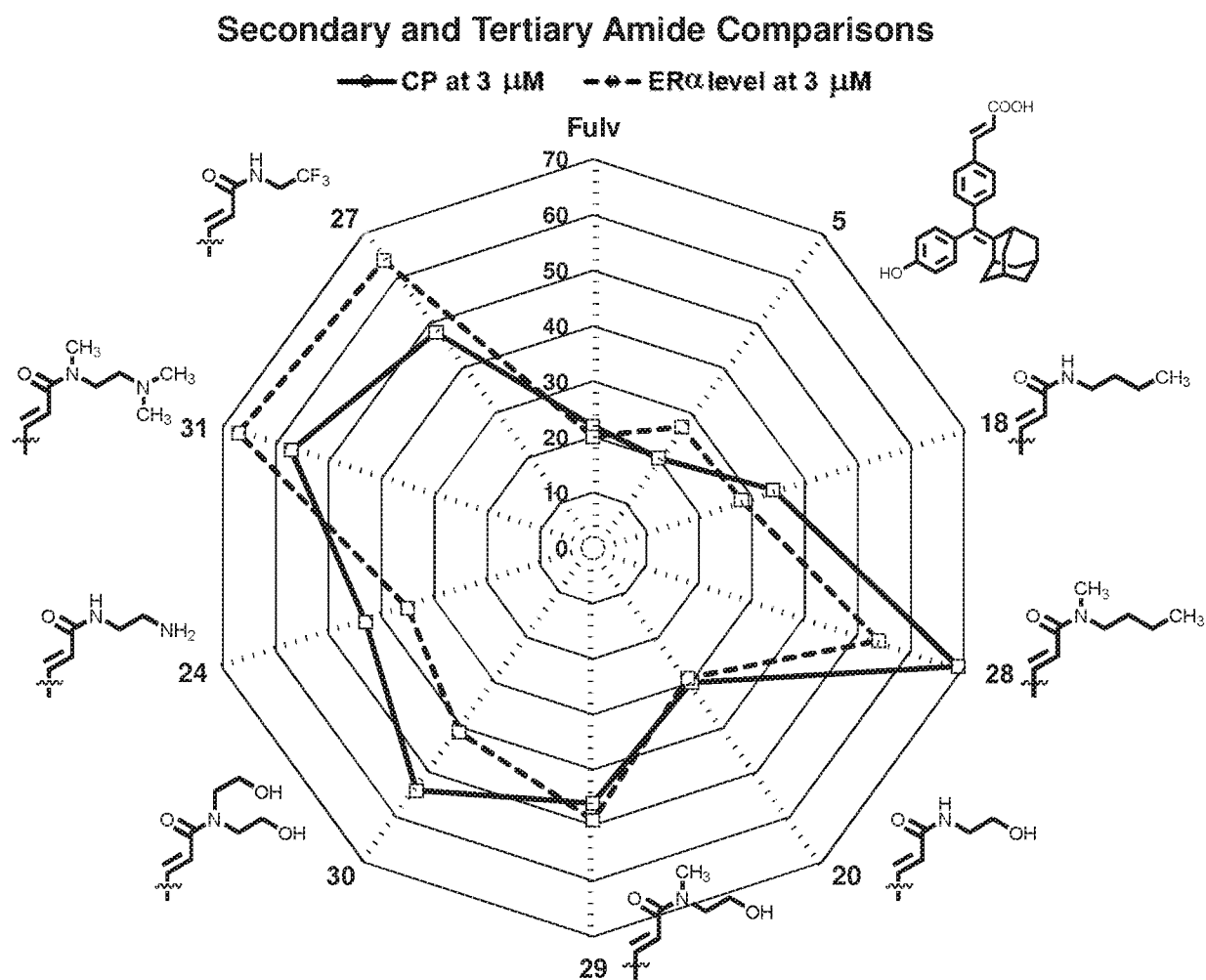


FIG. 4C

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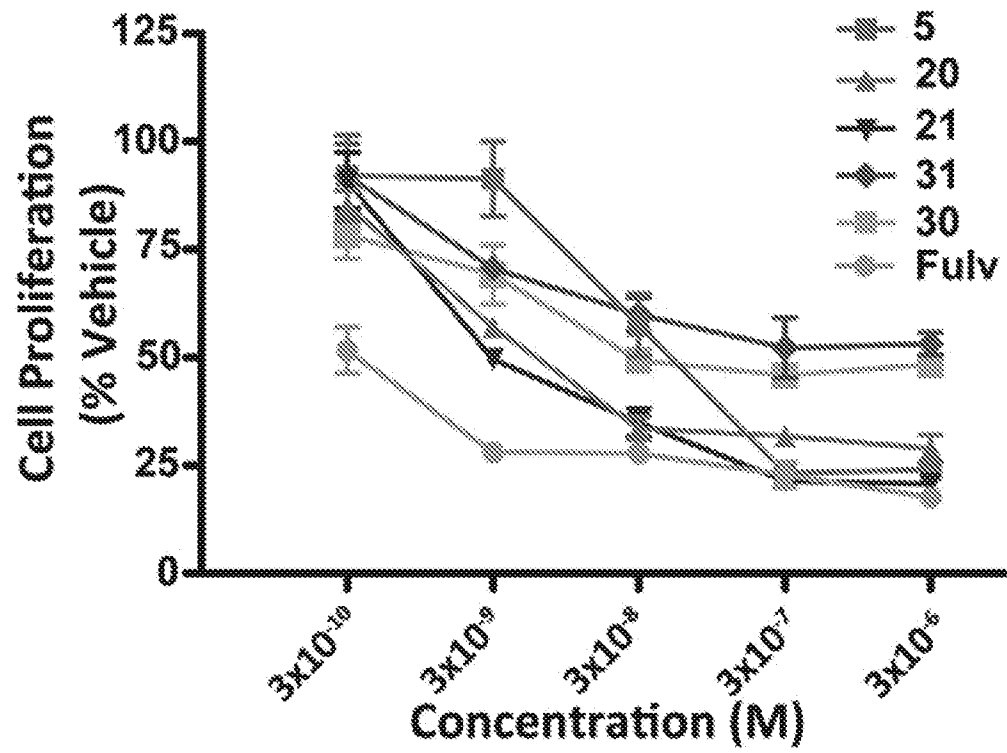


FIG. 5

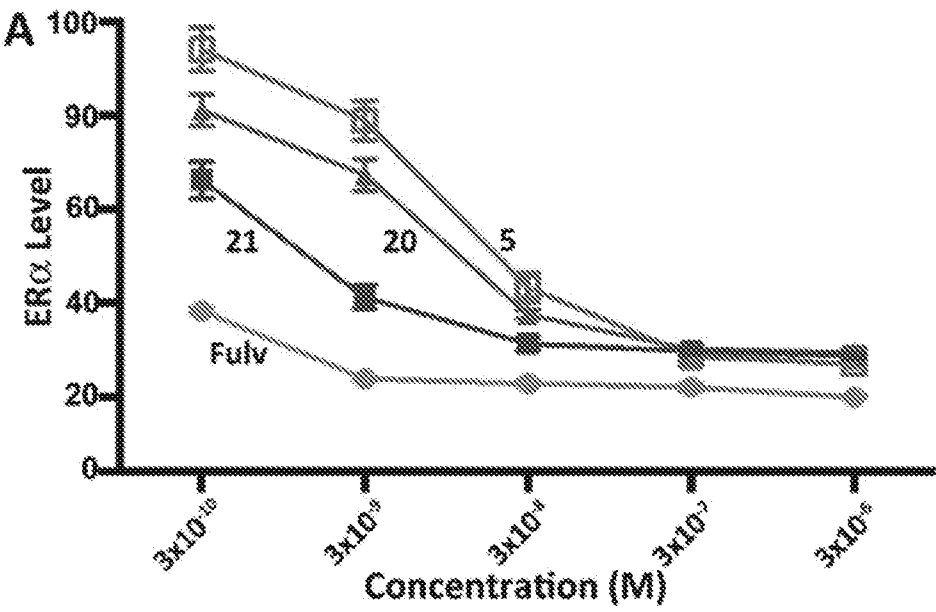


FIG. 6A

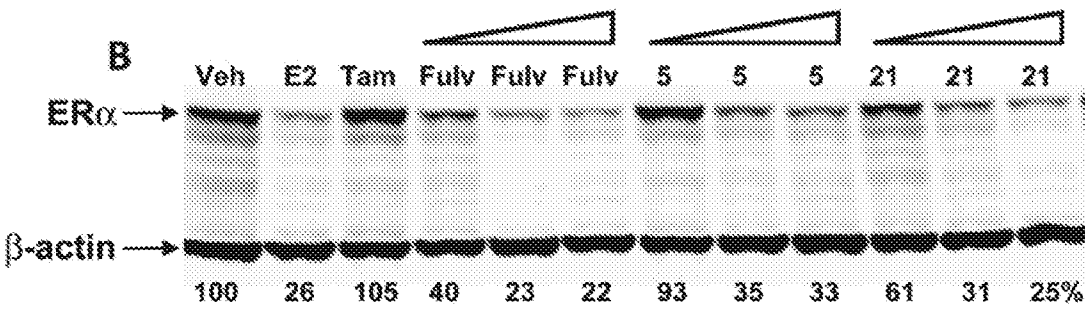


FIG. 6B

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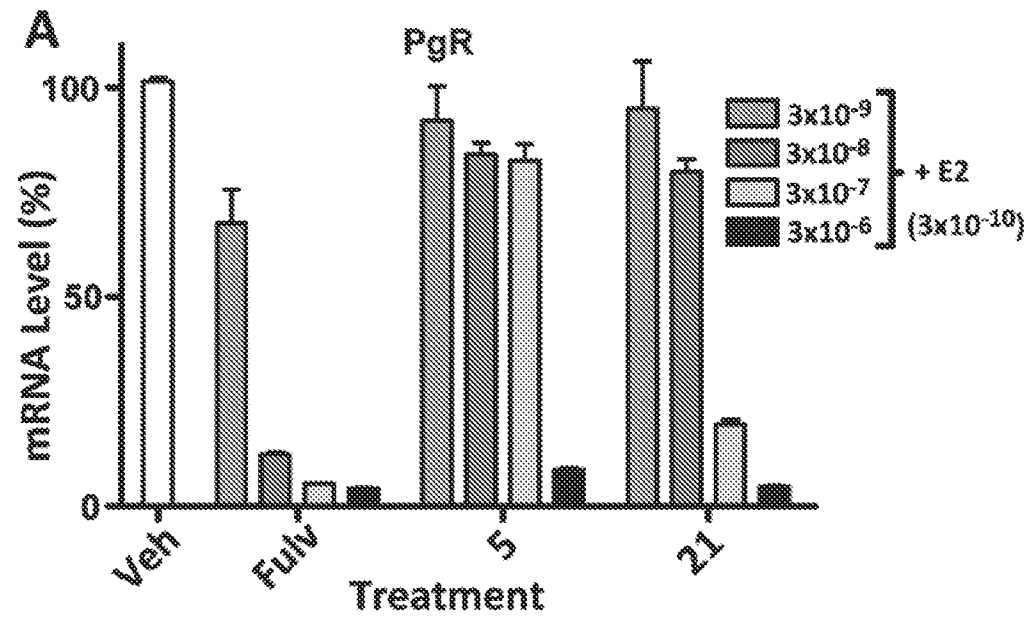


FIG. 7A

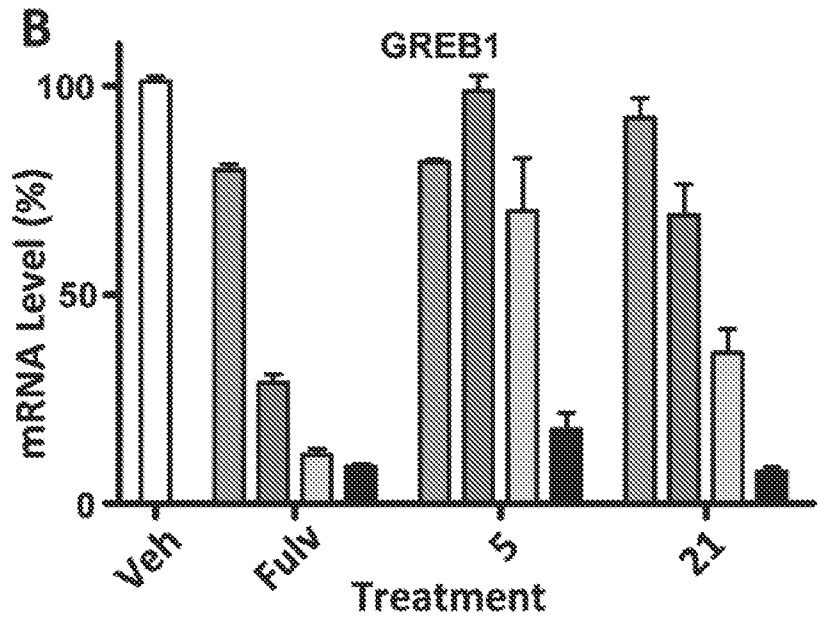


FIG. 7B

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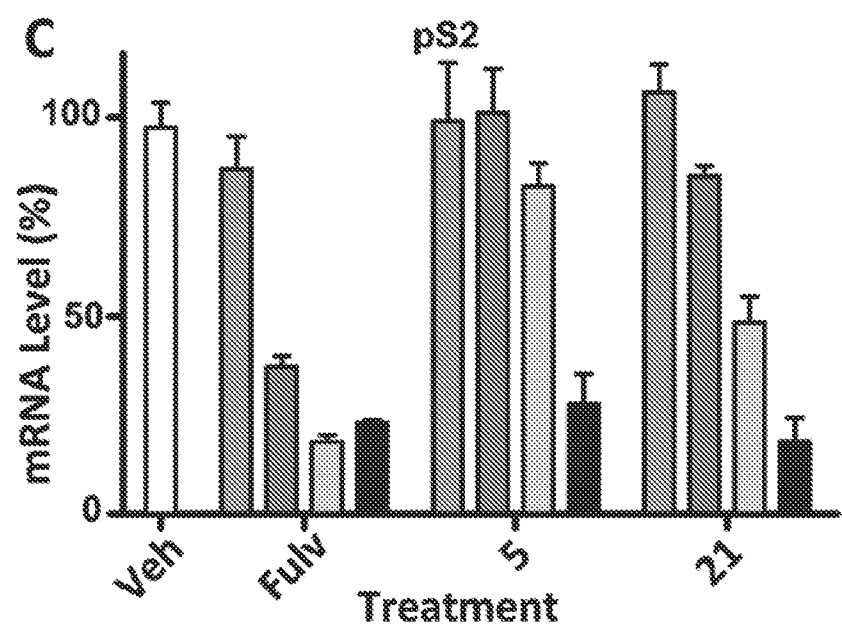


FIG. 7C

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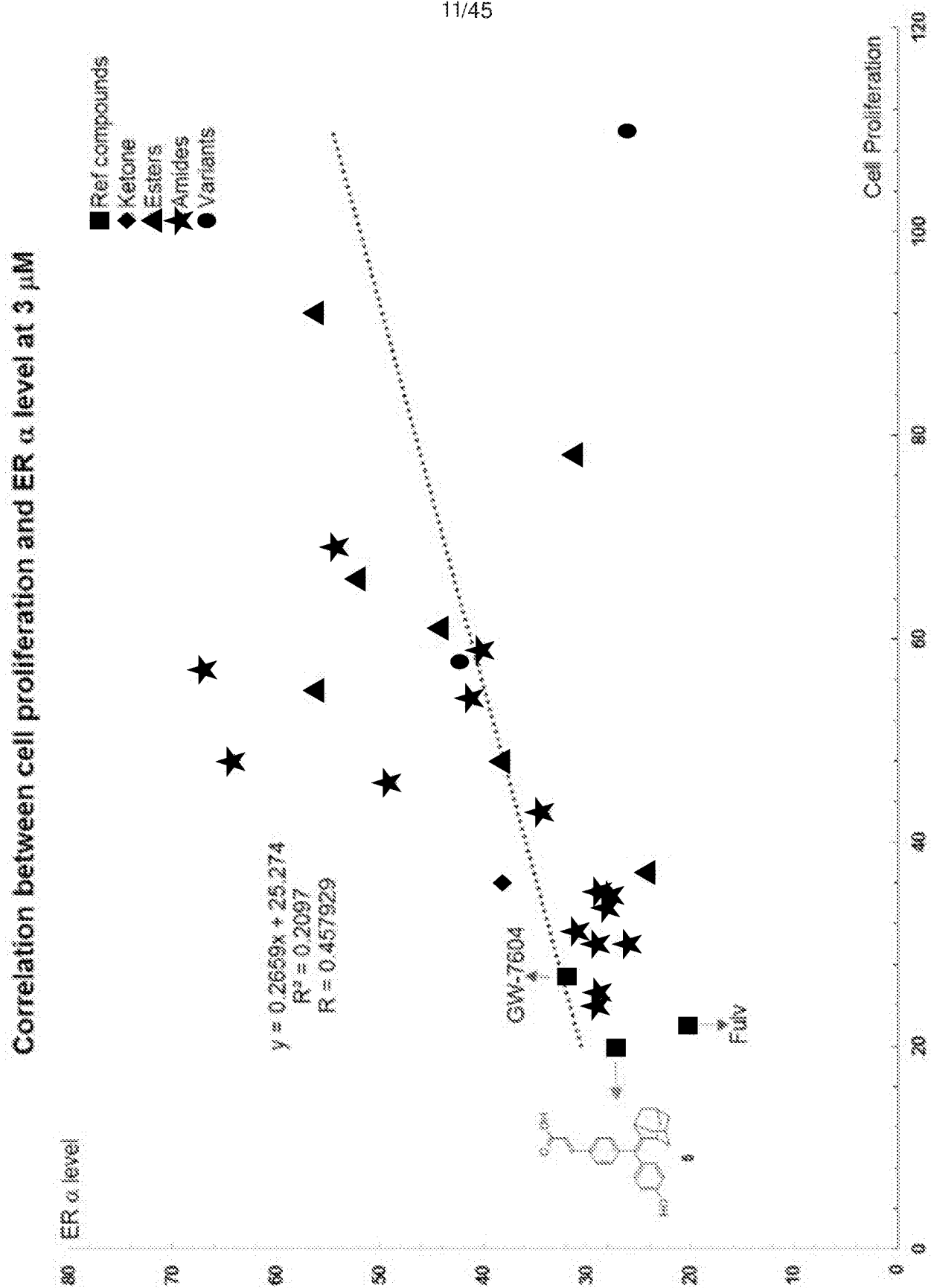


FIG. 8

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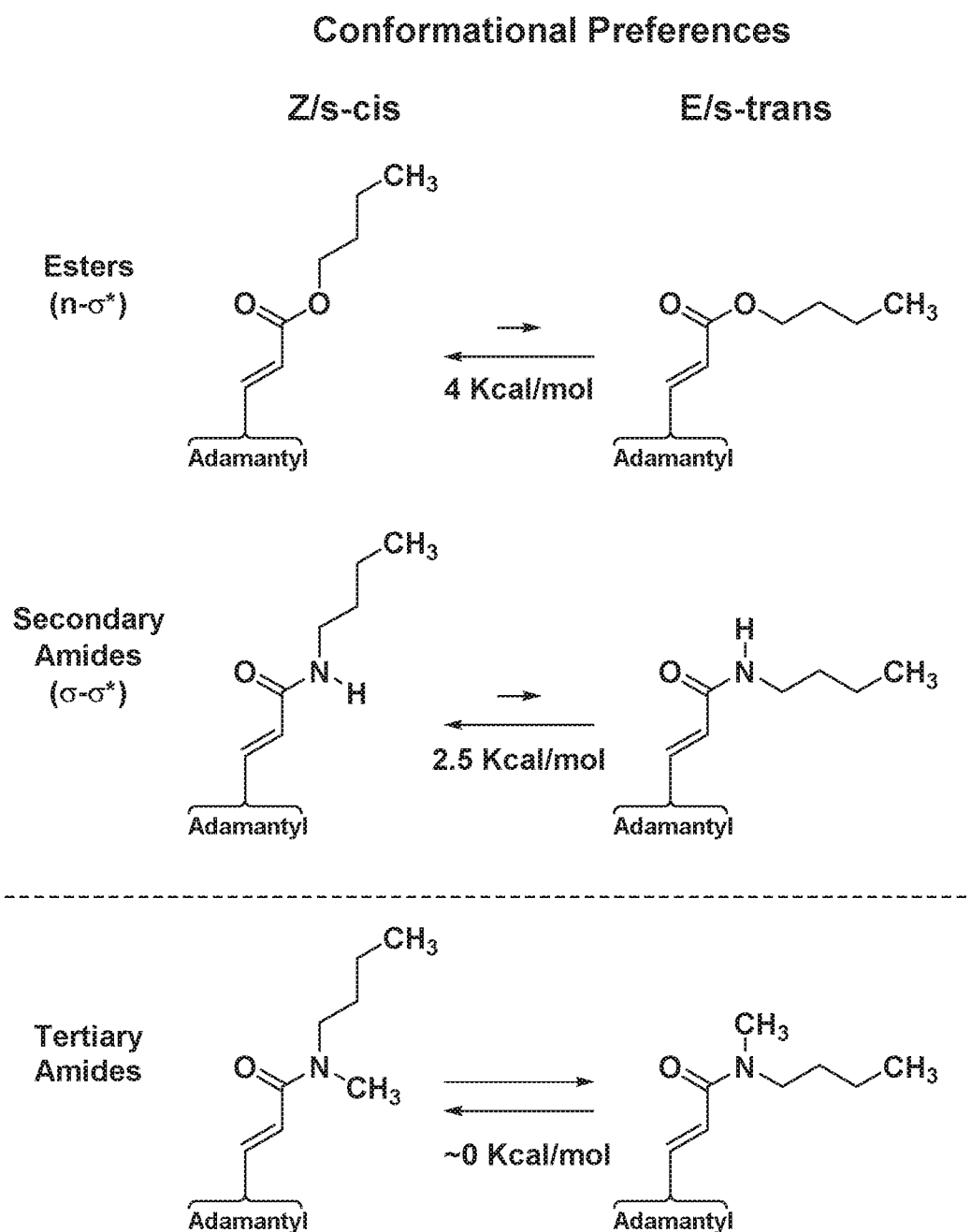


FIG. 9

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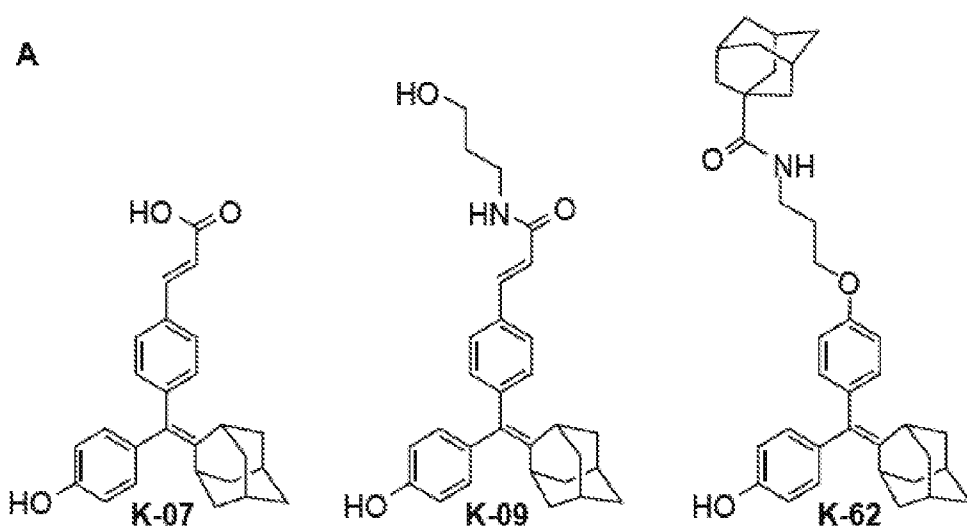


FIG. 10A

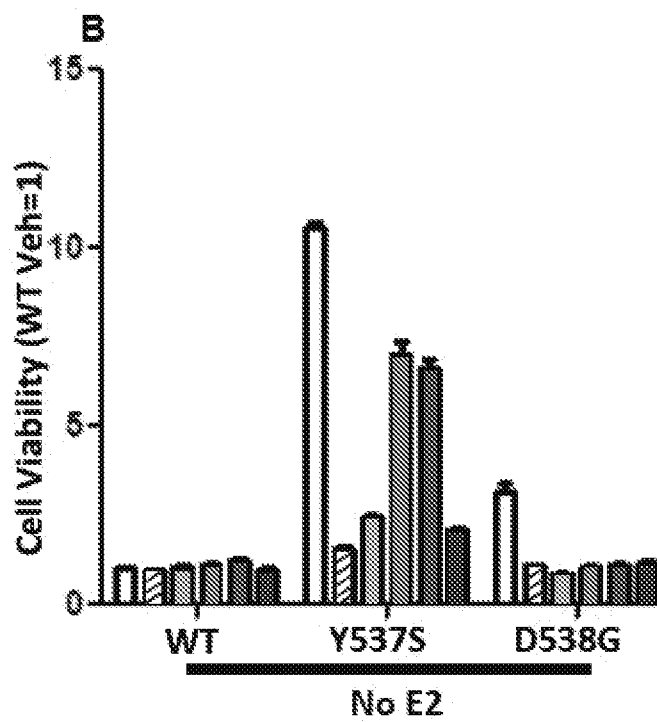


FIG. 10B

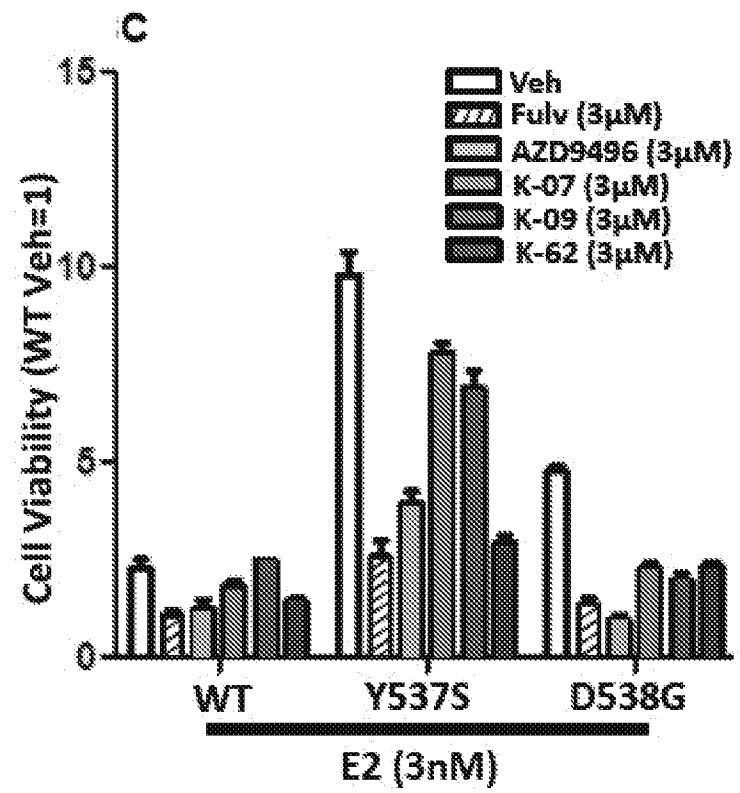


FIG. 10C

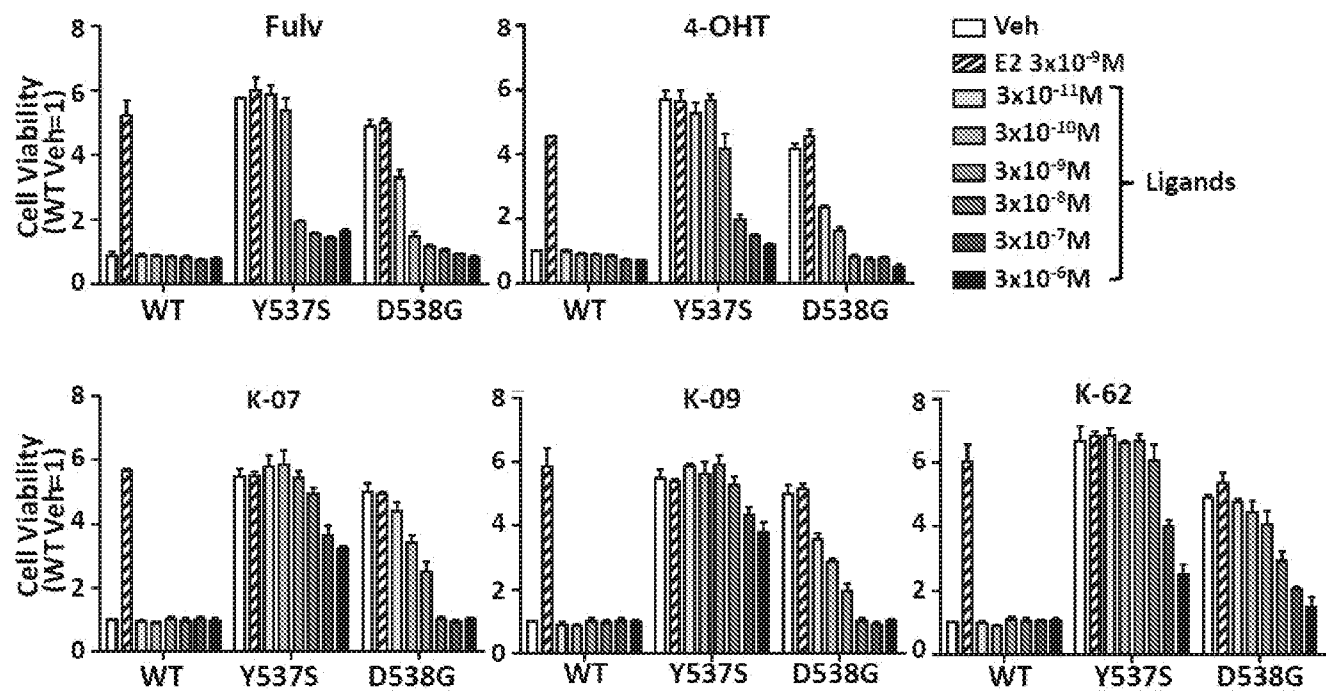


FIG. 11

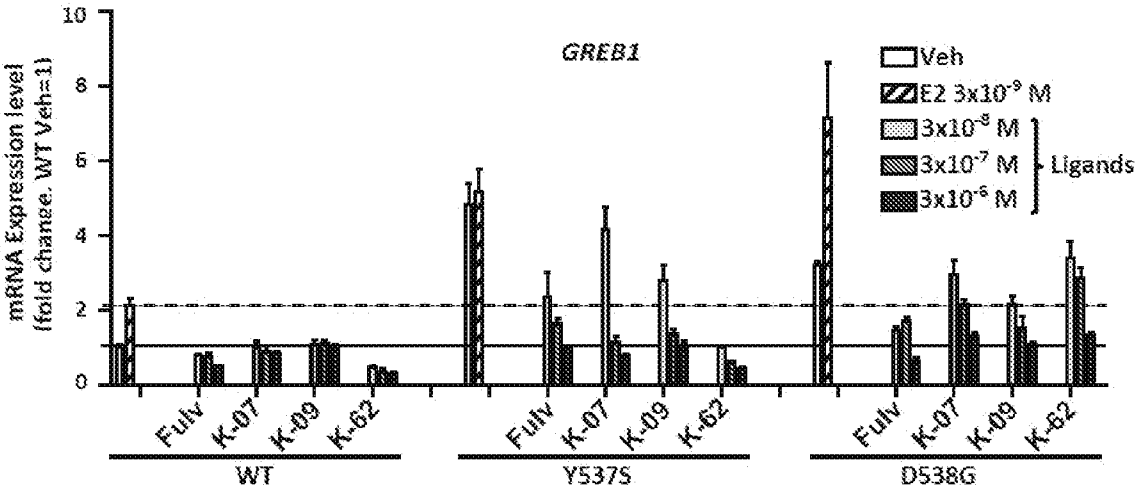


FIG. 12A

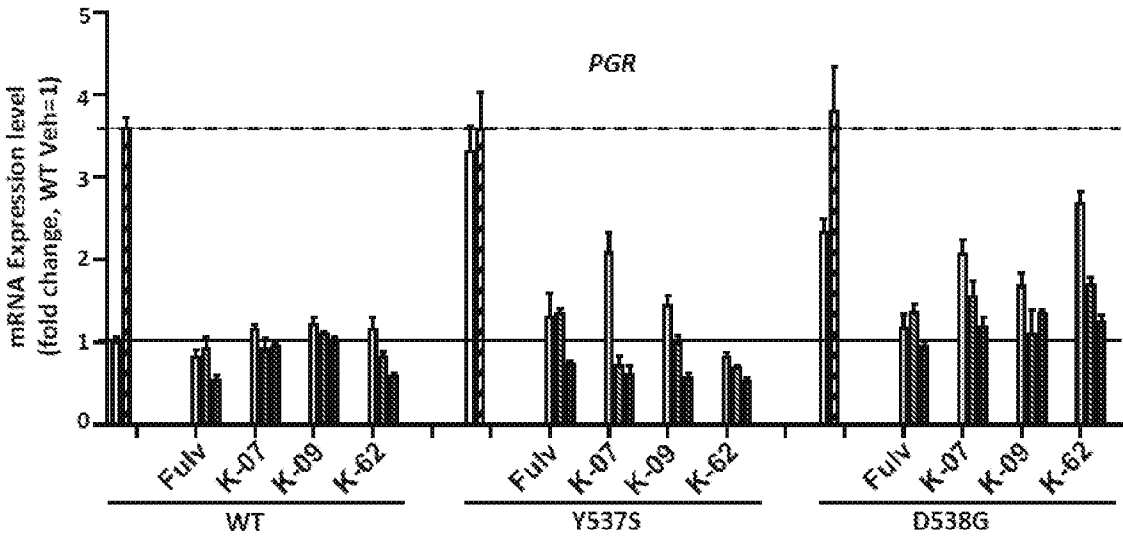


FIG. 12B

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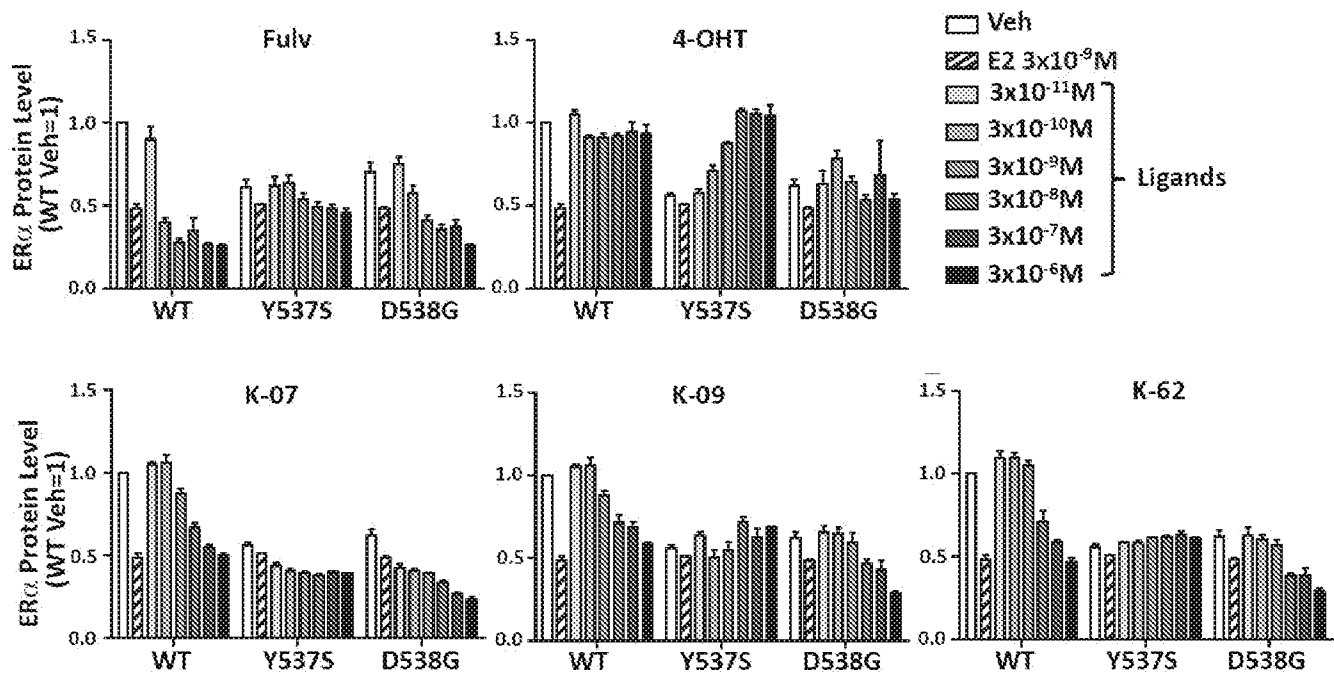


FIG. 13

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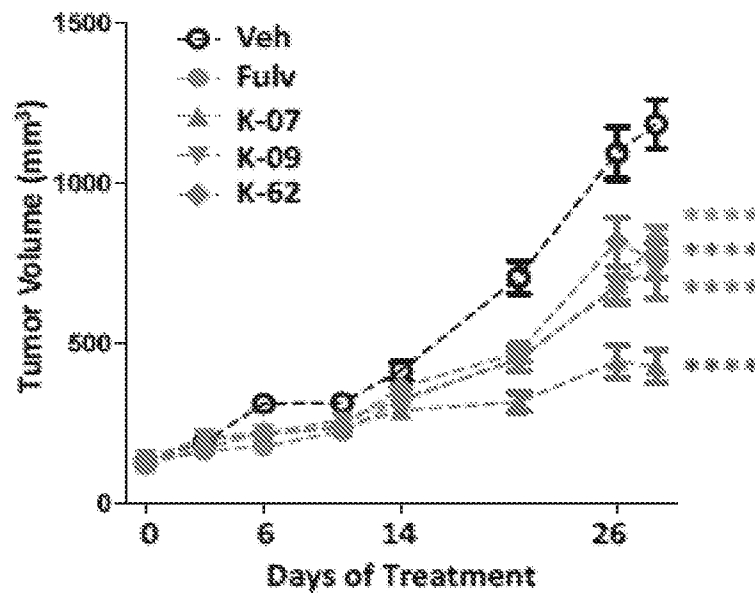


FIG. 14A

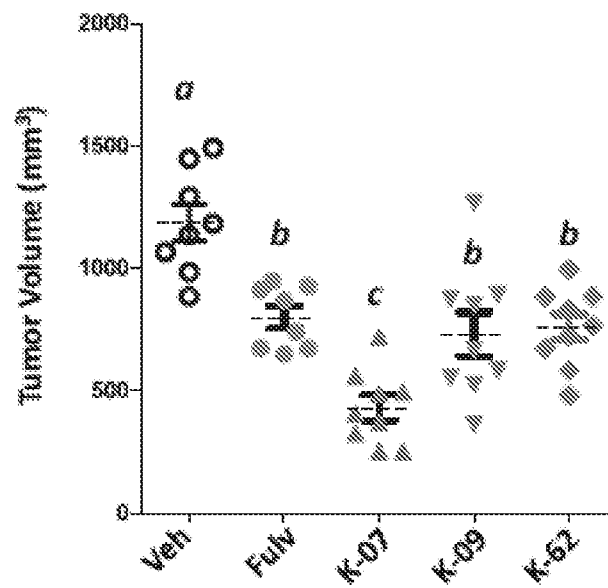


FIG. 14B

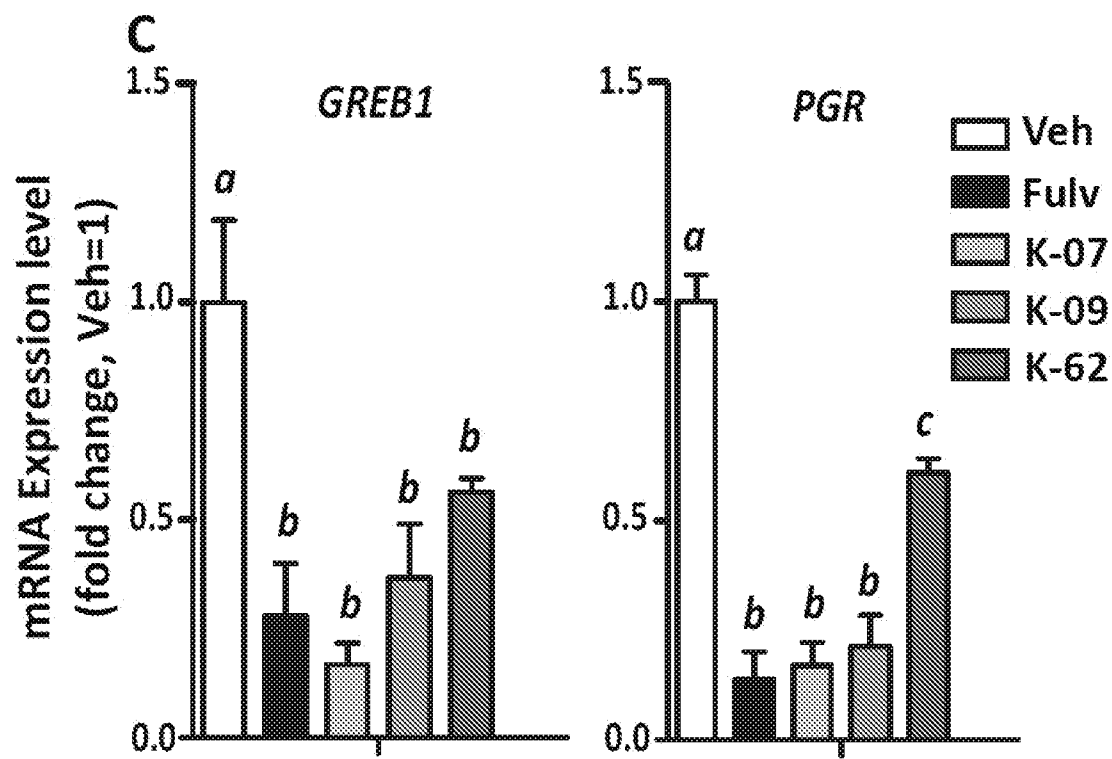


FIG. 14C

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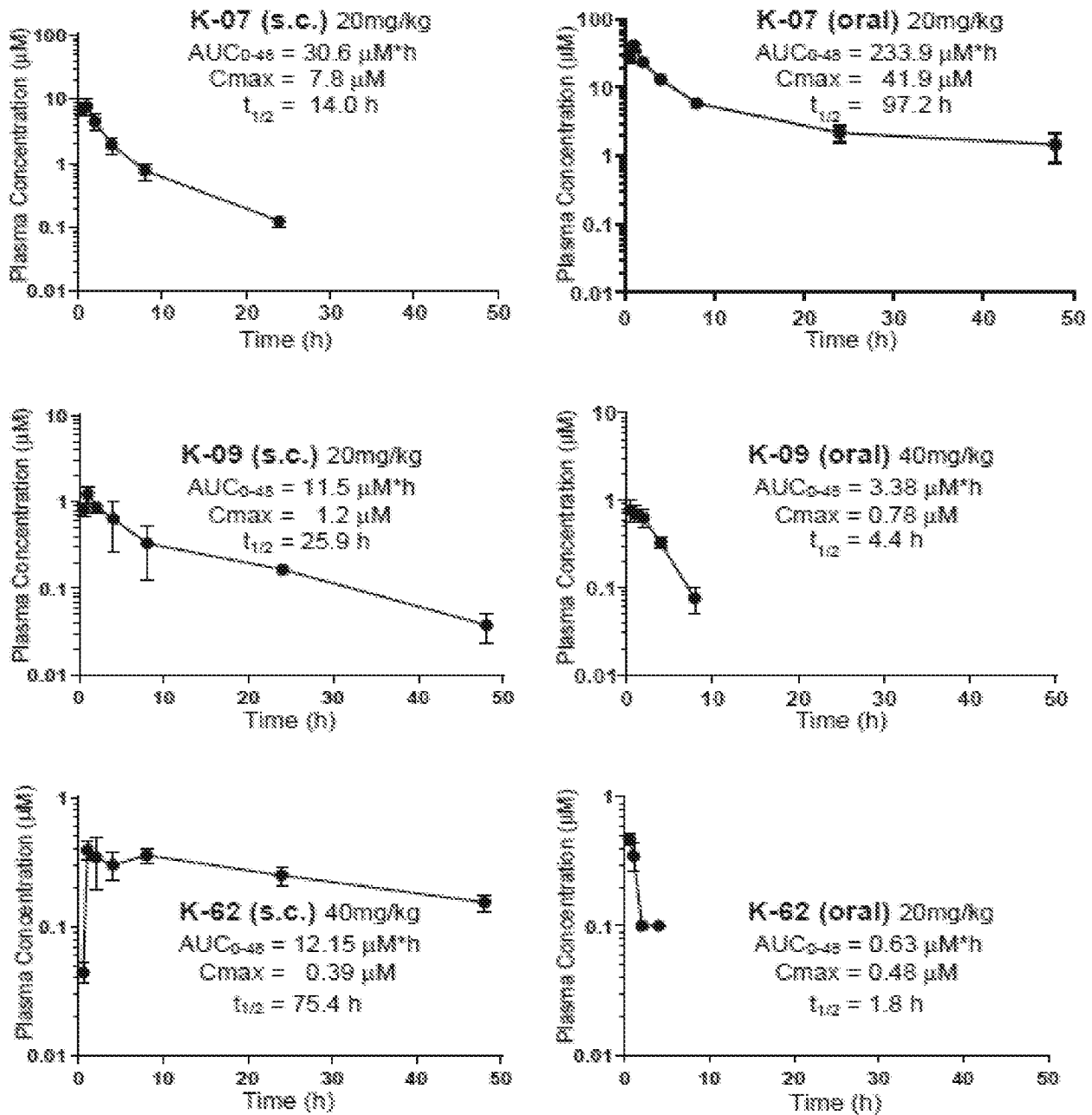


FIG. 15

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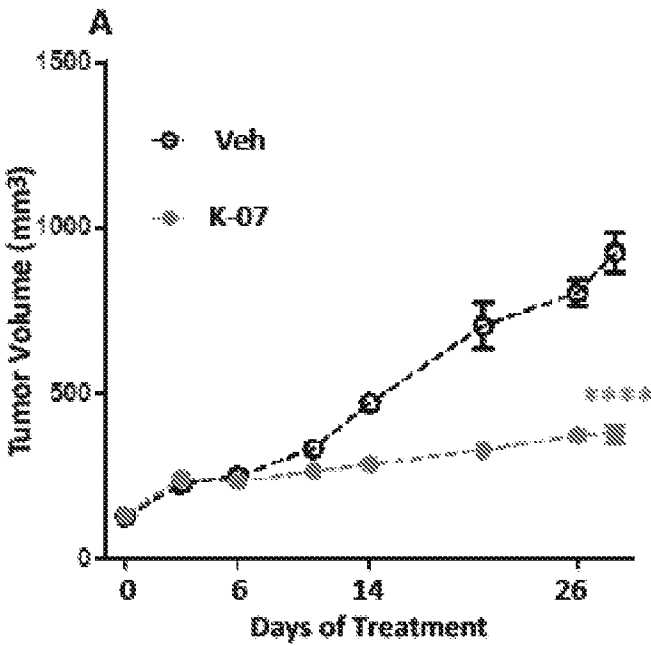


FIG. 16A

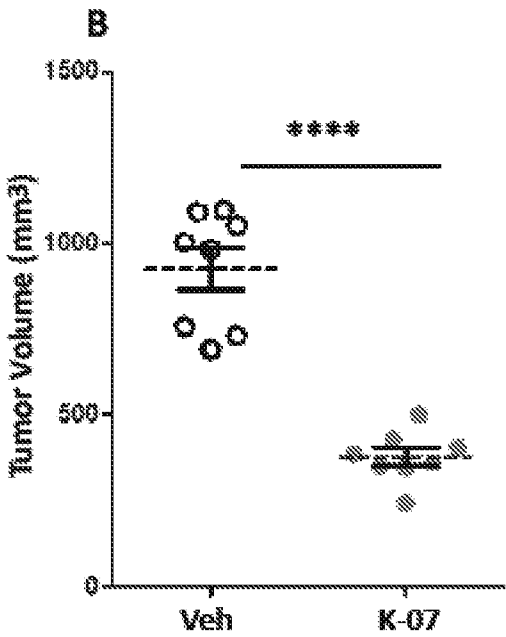


FIG. 16B

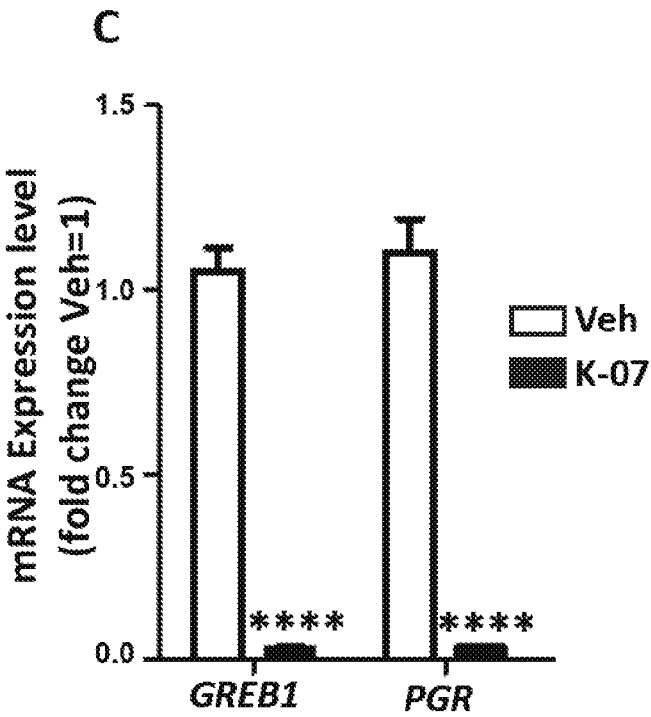


FIG. 16C

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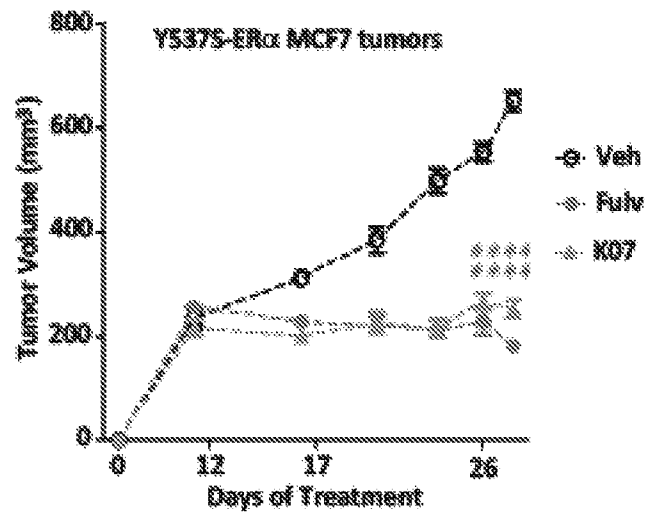


FIG. 17A

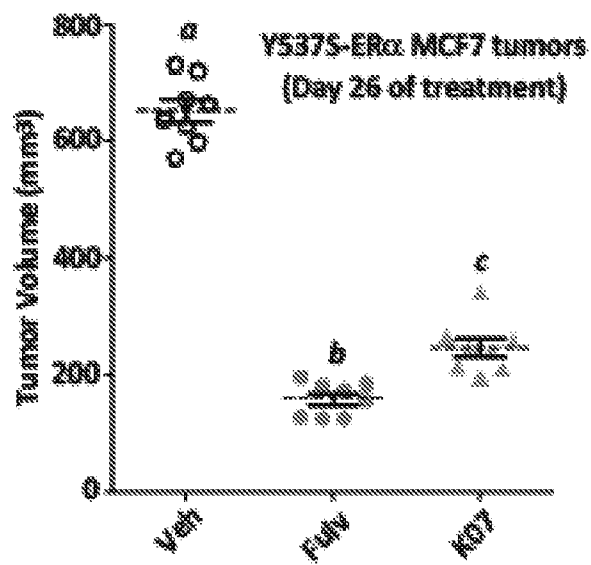


FIG. 17B

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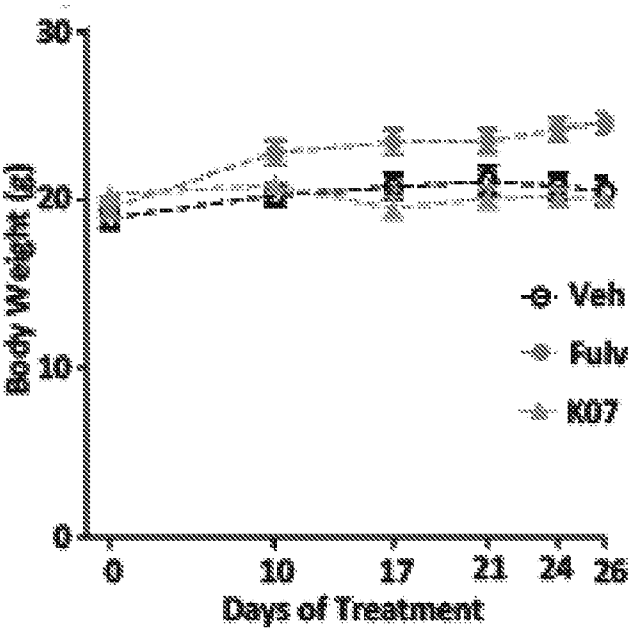


FIG. 17C

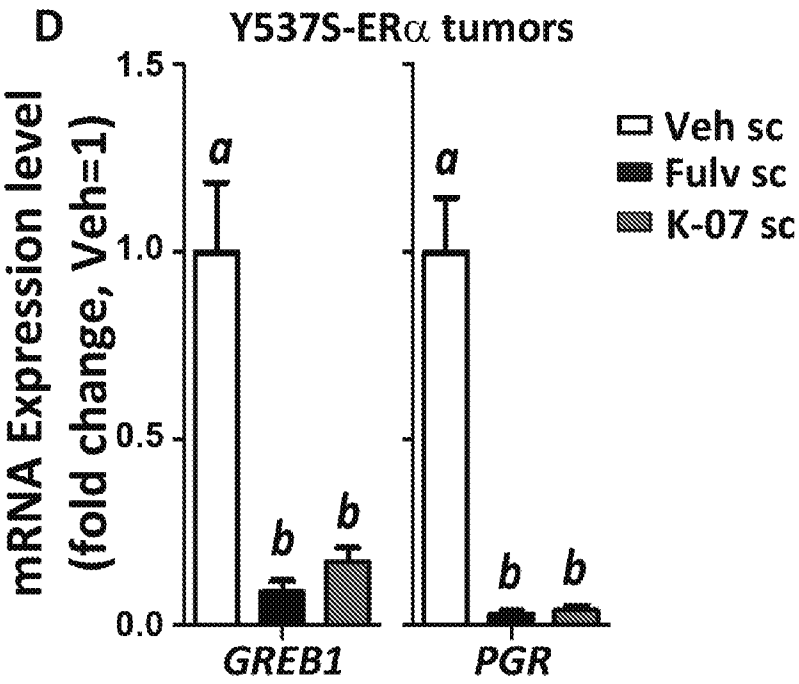


FIG. 17D

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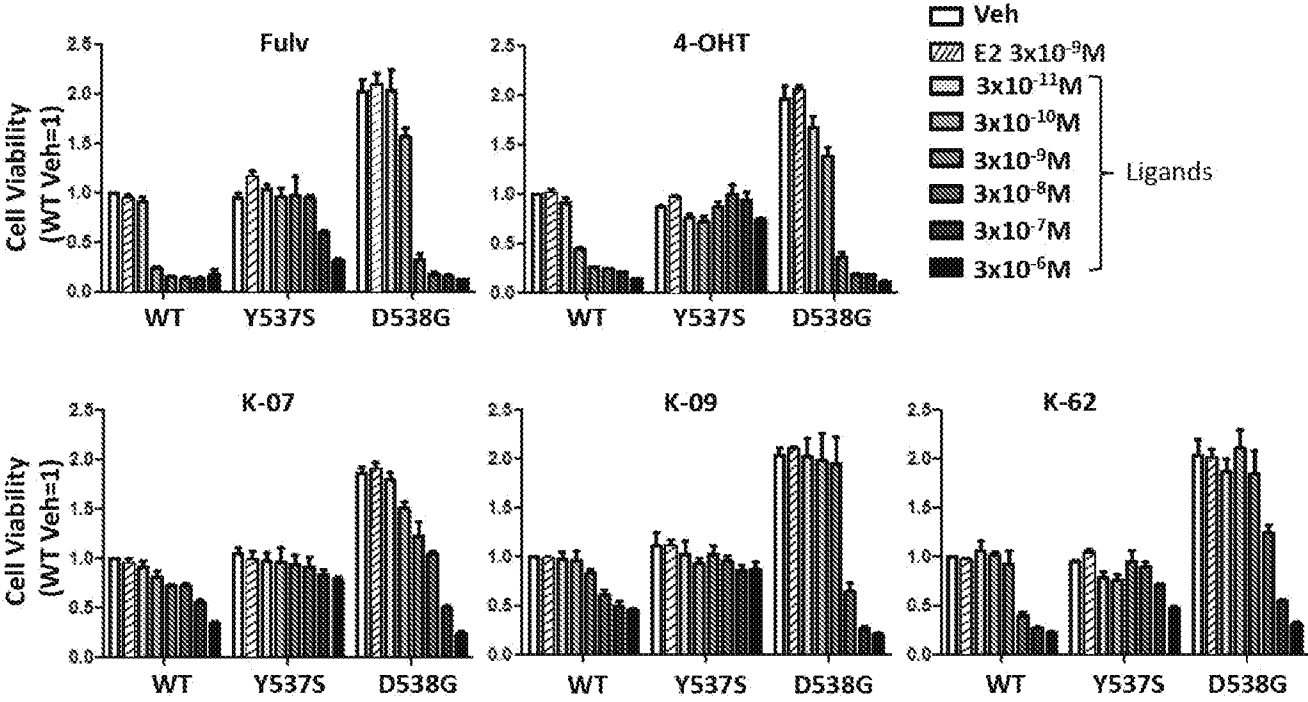


FIG. 18

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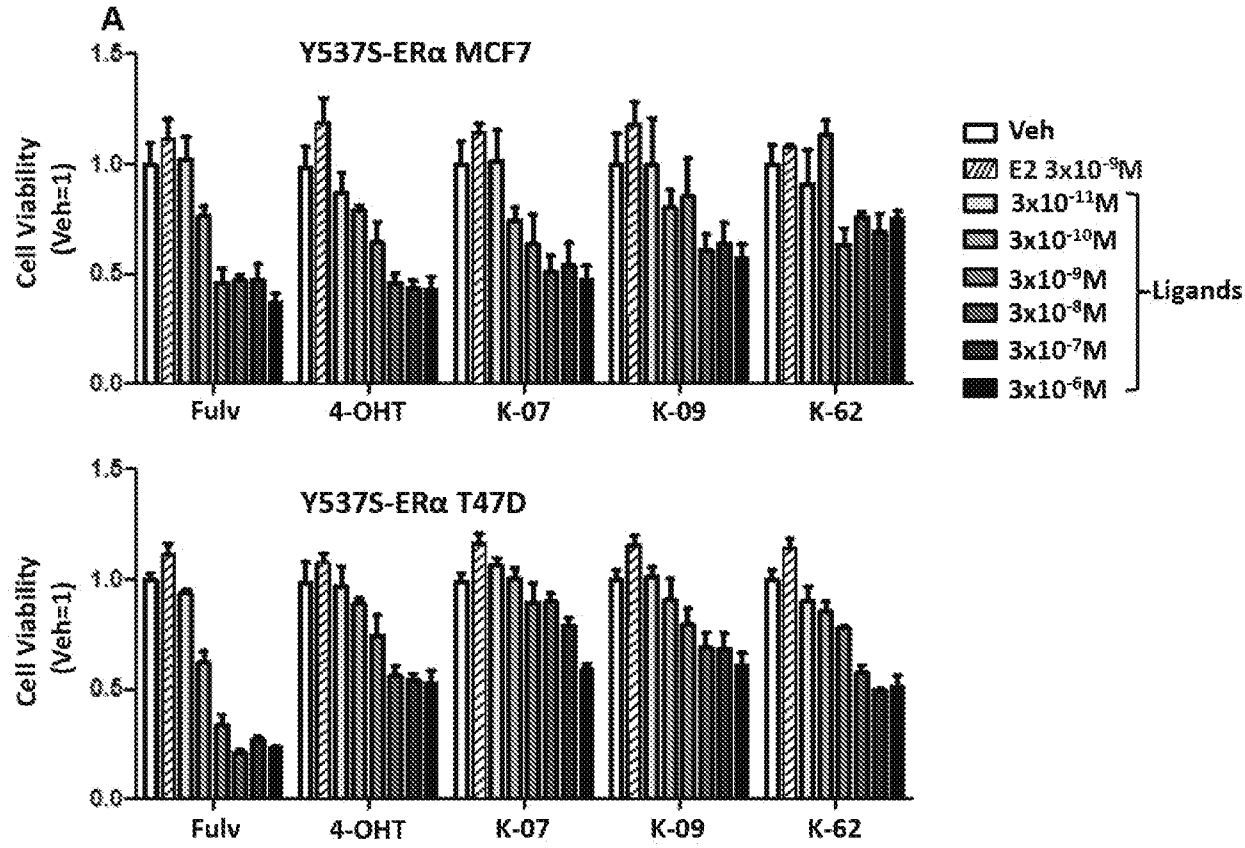


FIG. 19A

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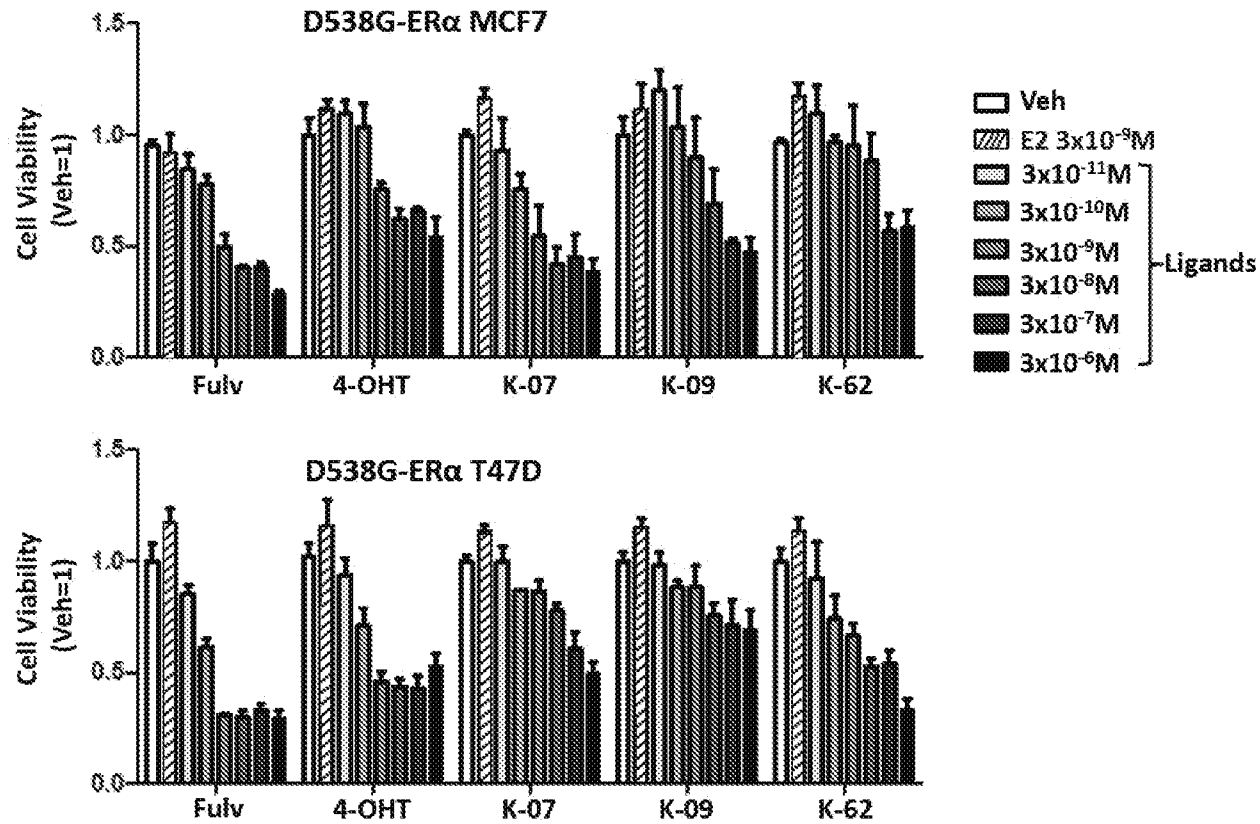


FIG. 19B

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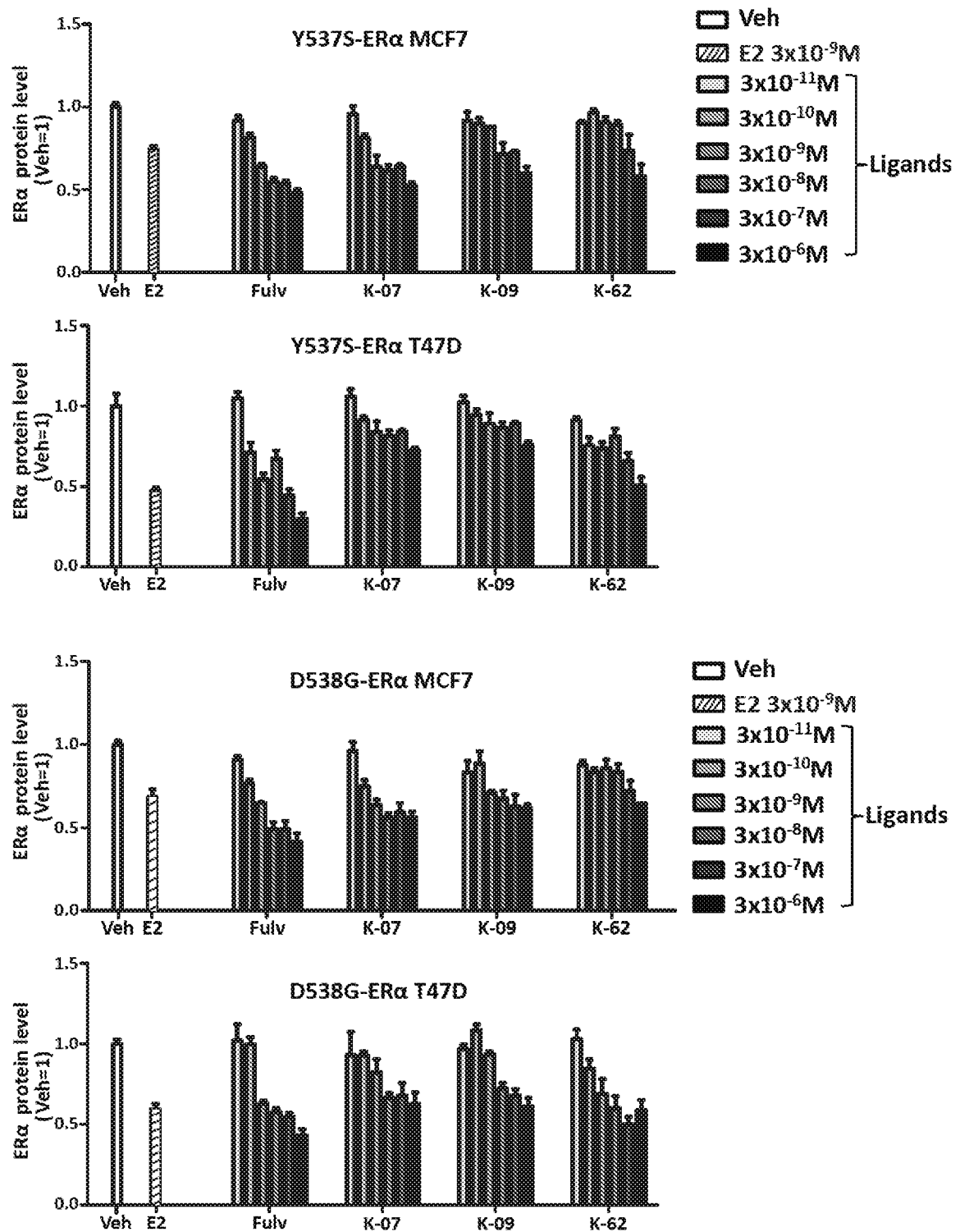


FIG. 20

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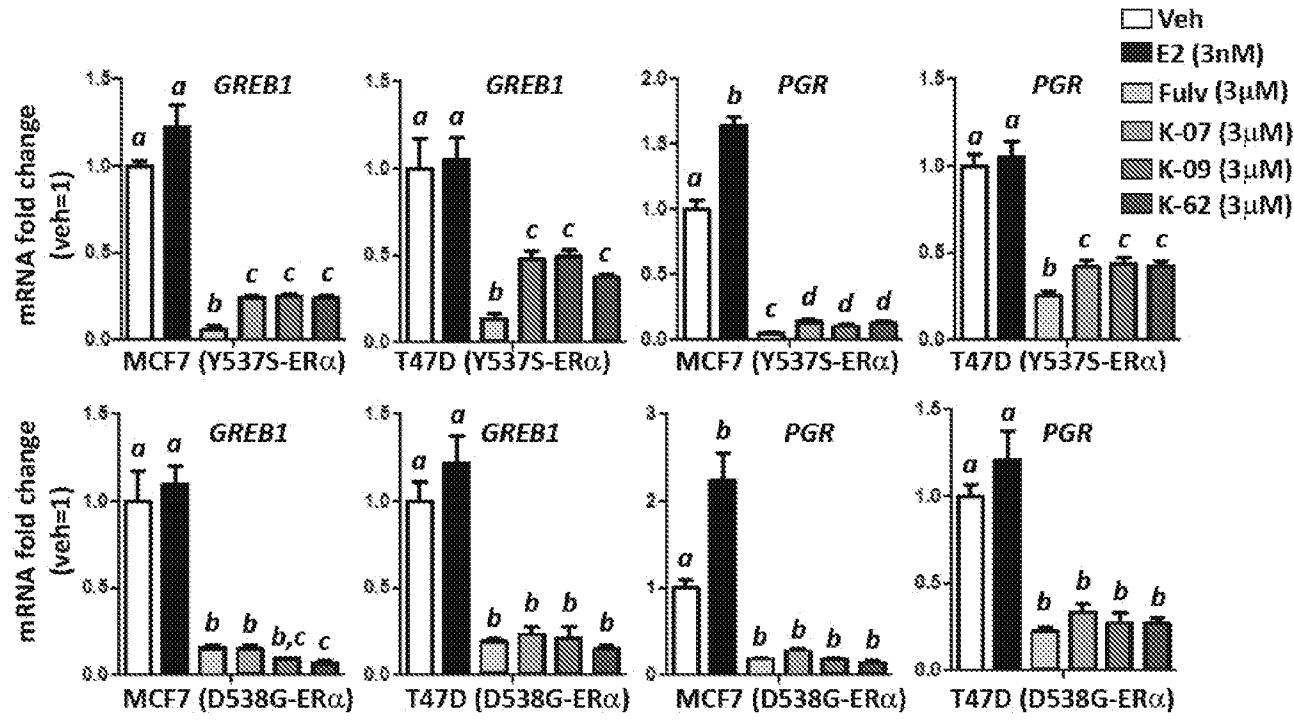


FIG. 21

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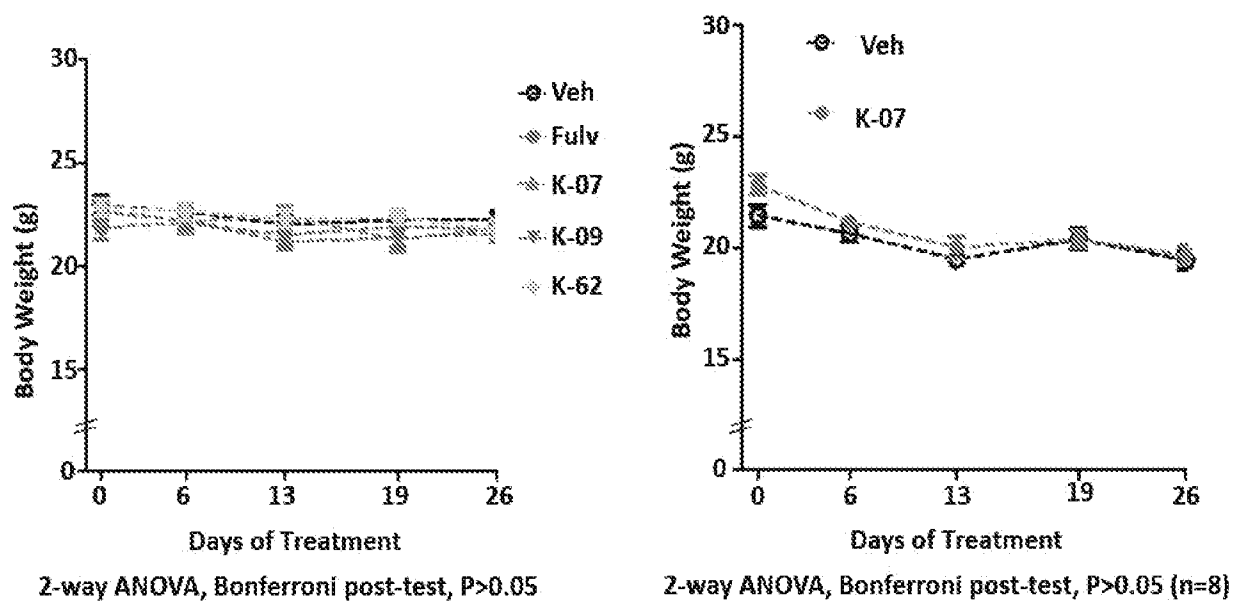


FIG. 22

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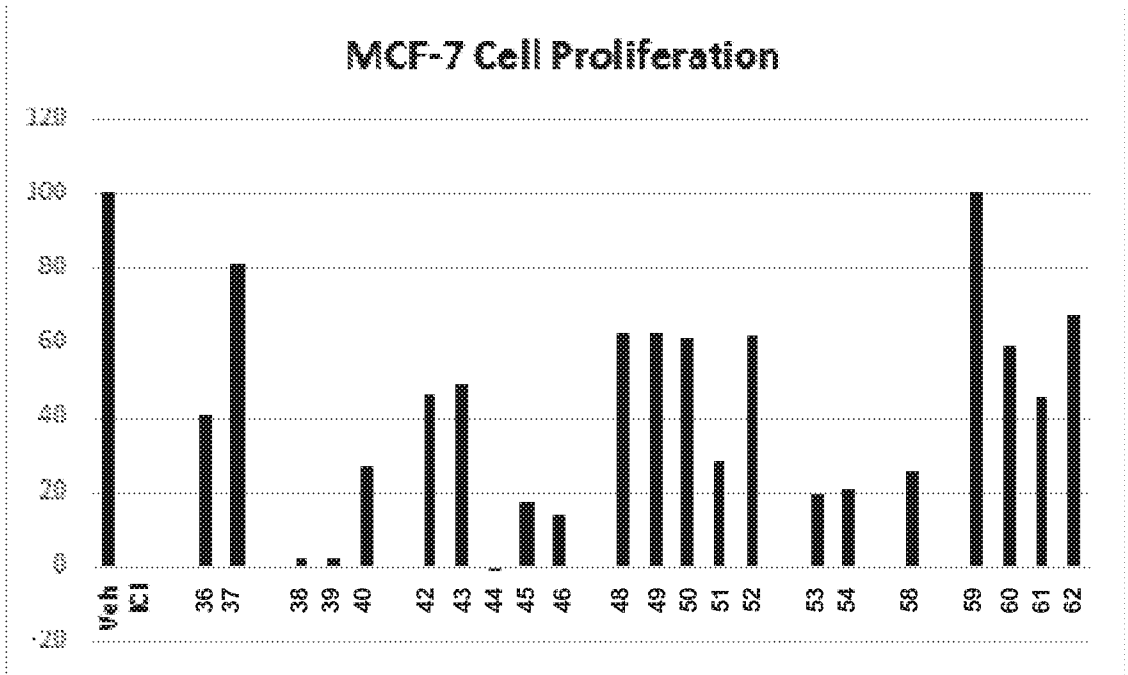


FIG. 23

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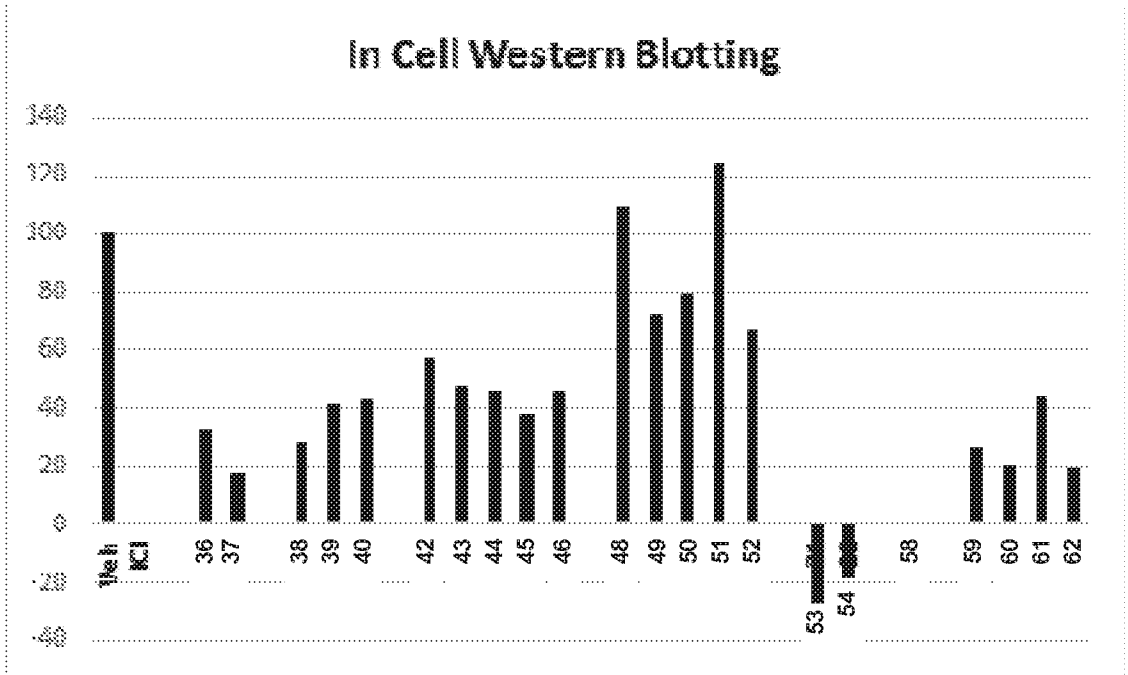


FIG. 24

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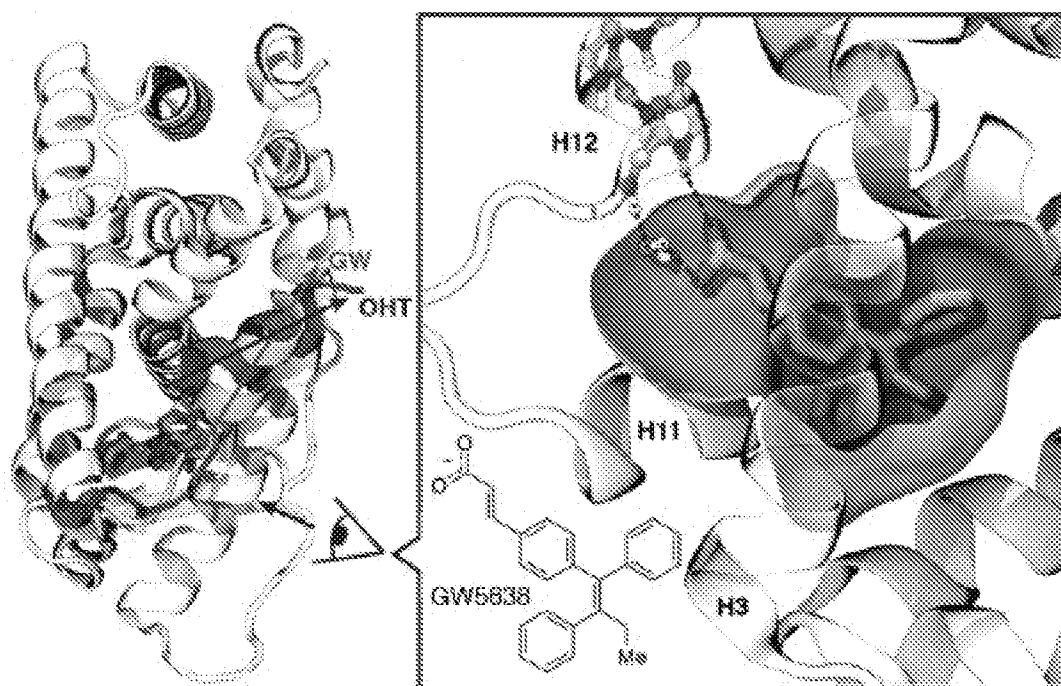


FIG. 25

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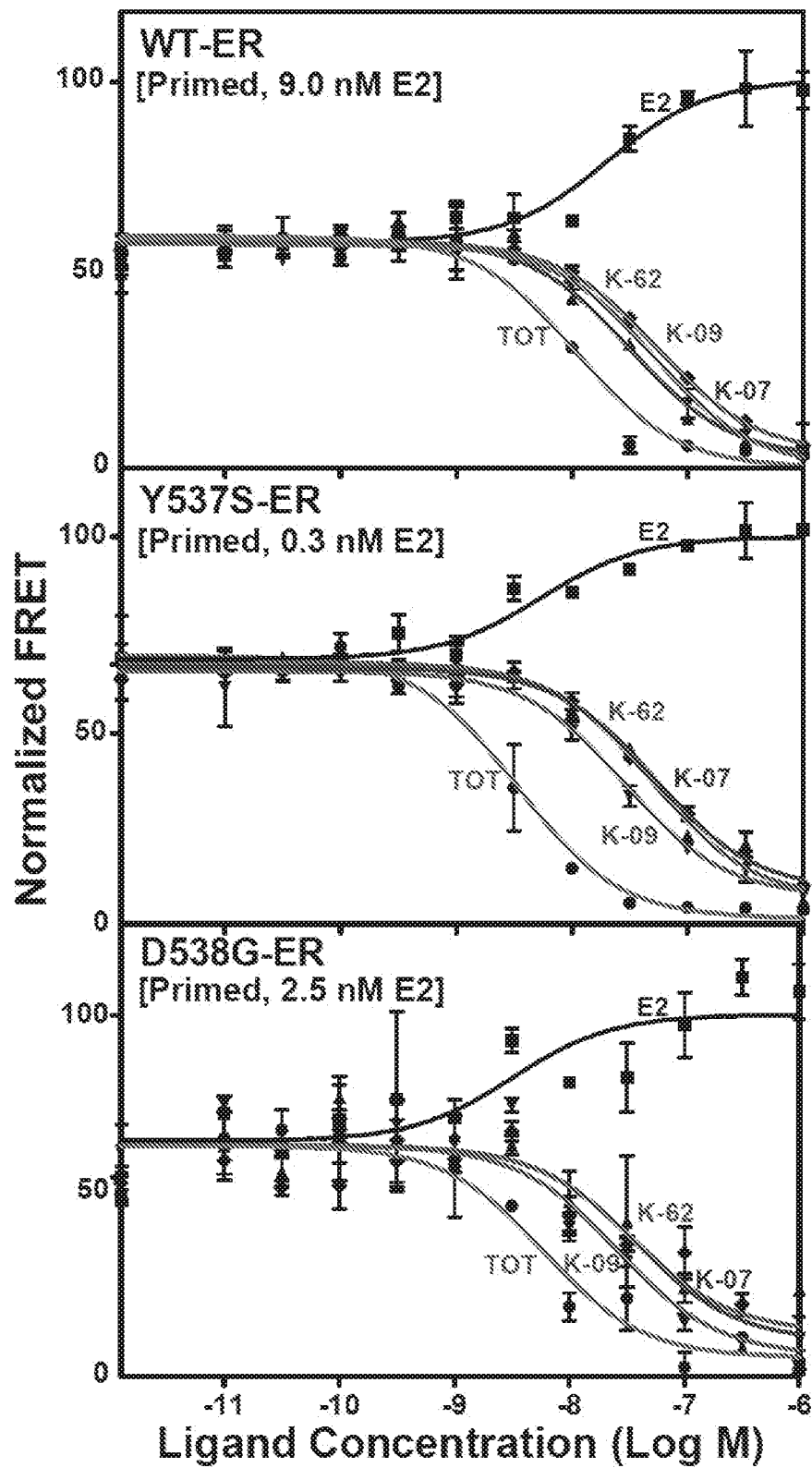


FIG. 26

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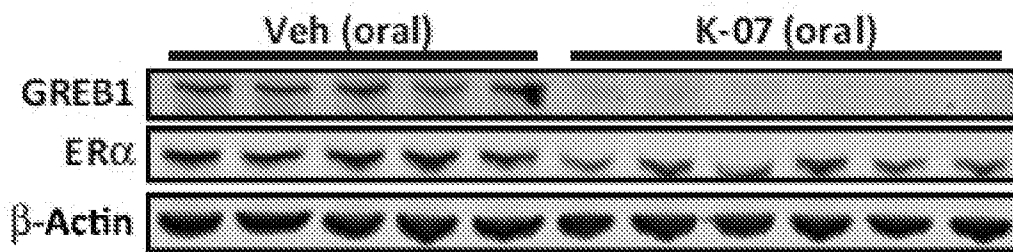


FIG. 27A

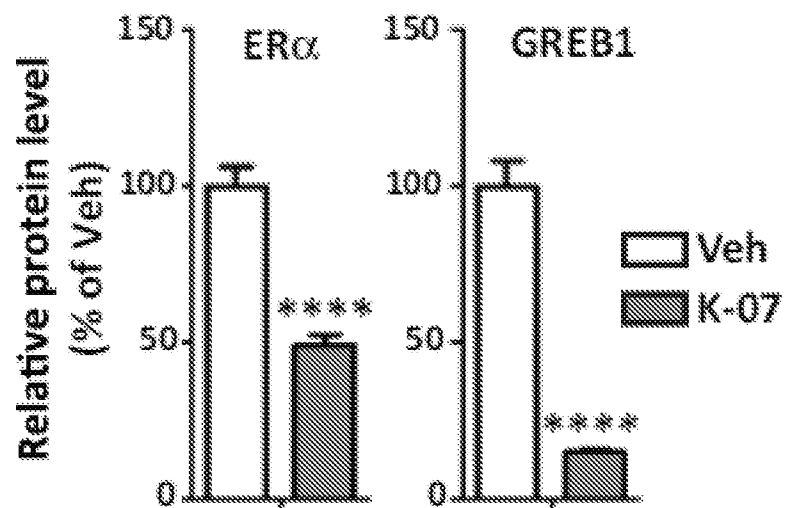


FIG. 27B

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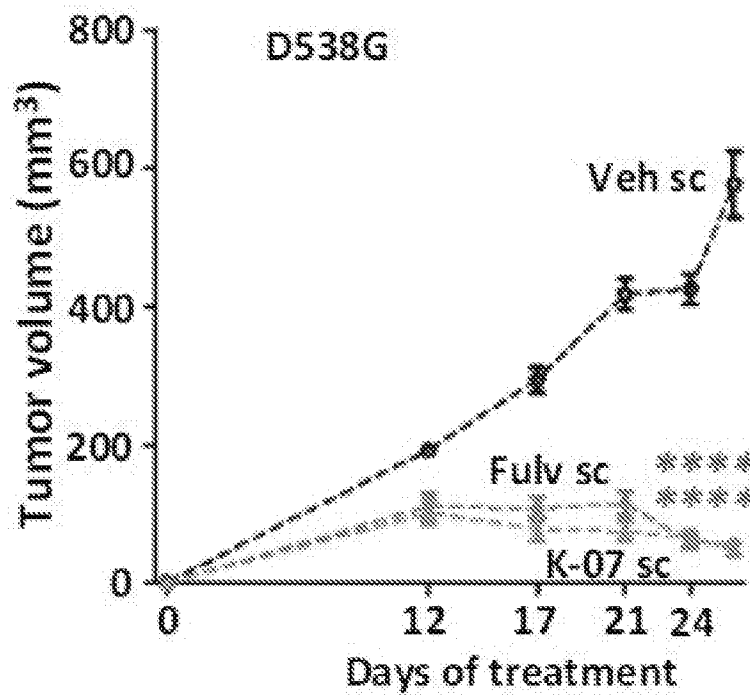


FIG. 28A

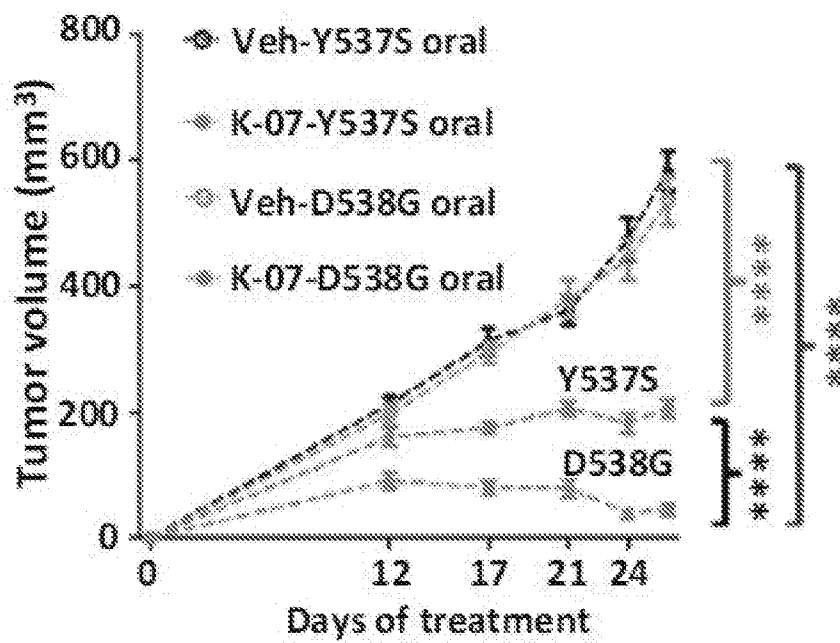


FIG. 28B

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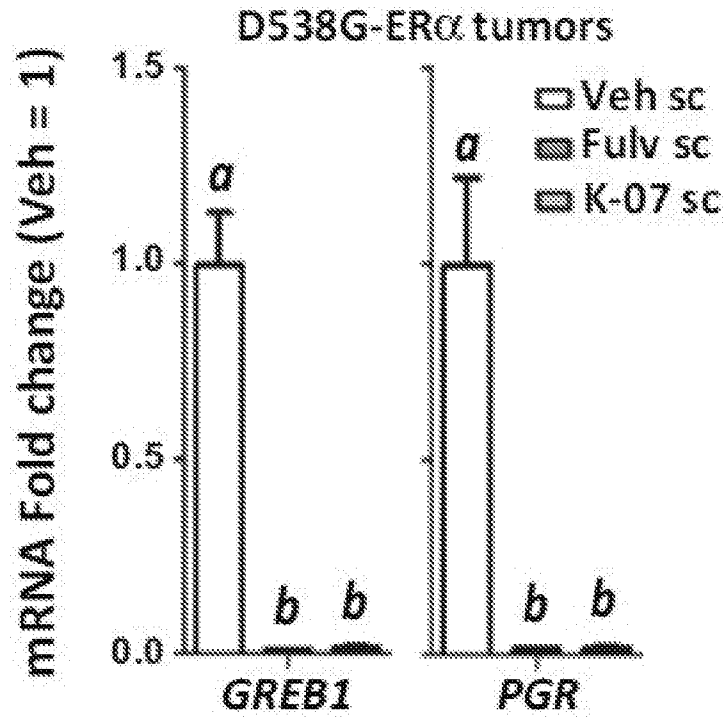


FIG. 28C

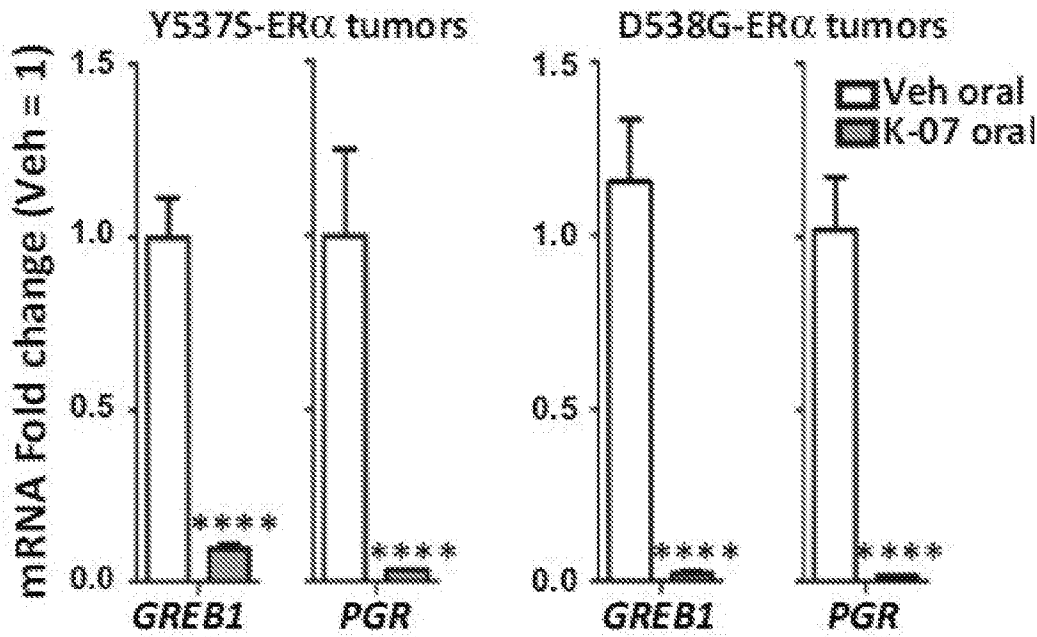


FIG. 28D

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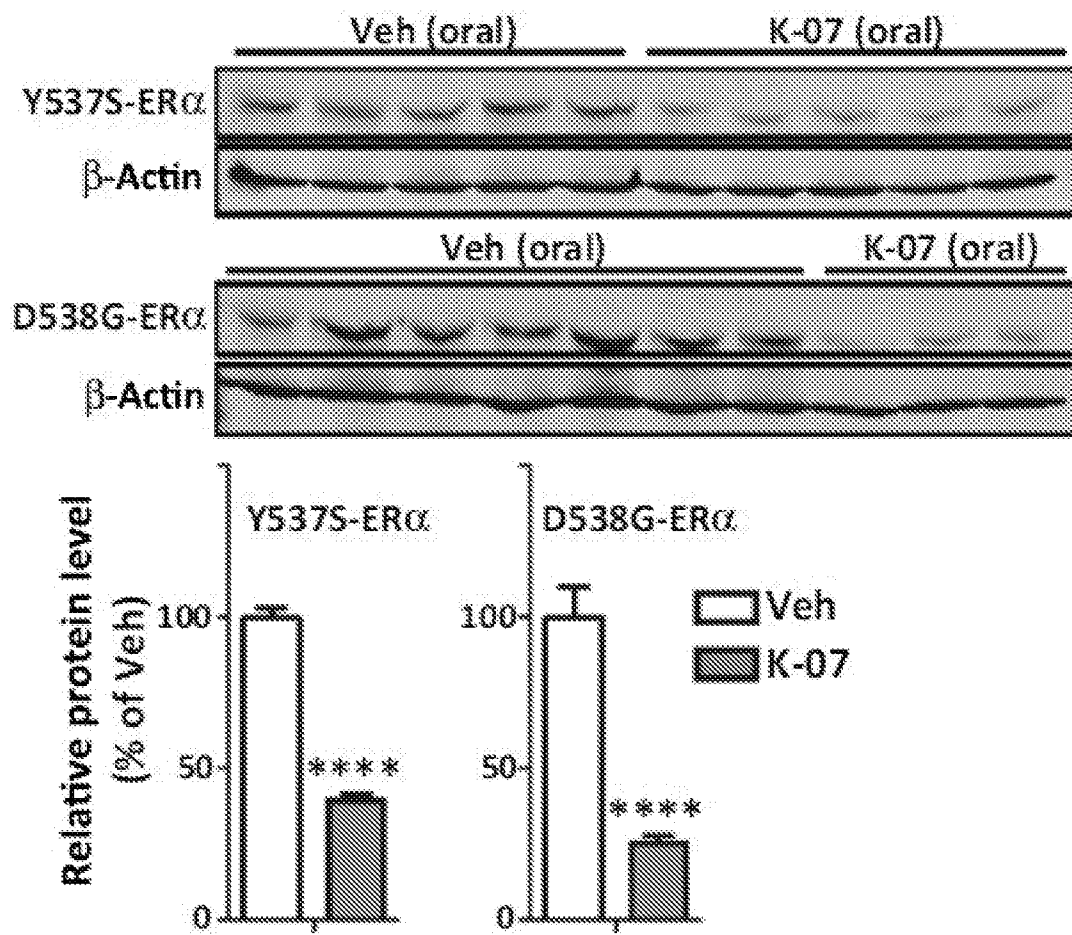


FIG. 28E

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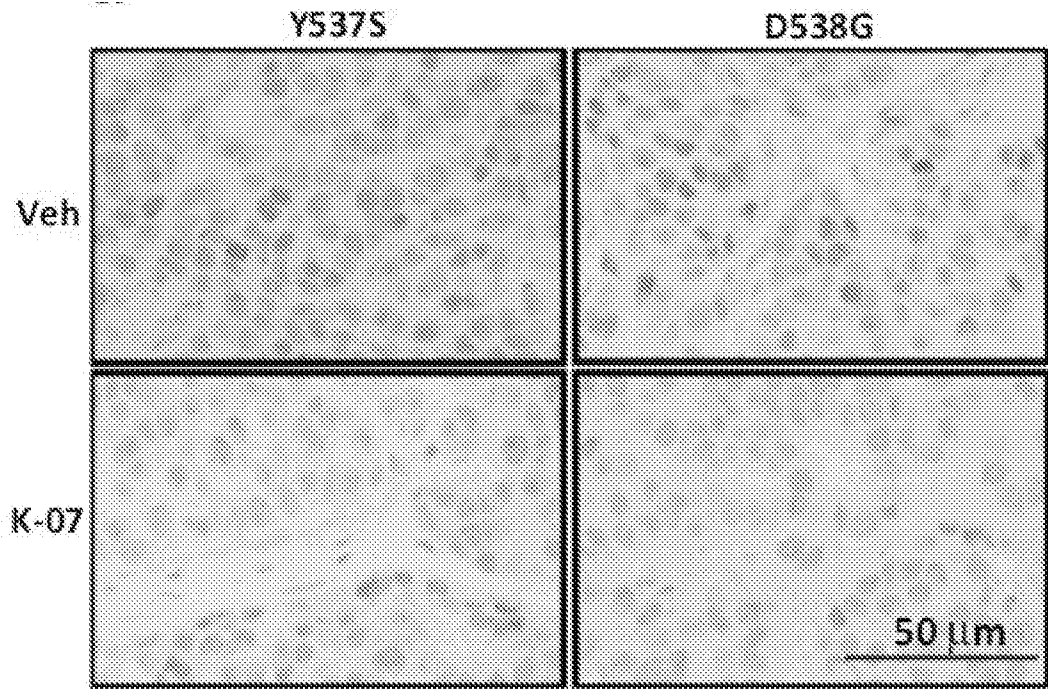


FIG. 28F

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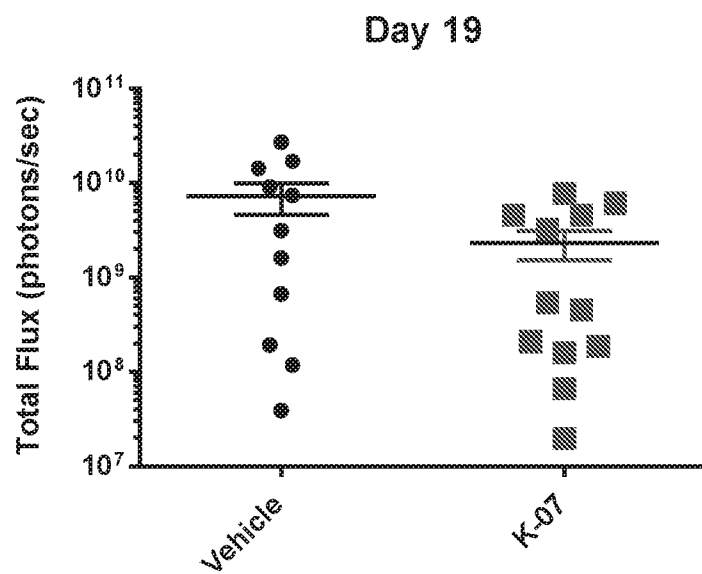


FIG. 29A

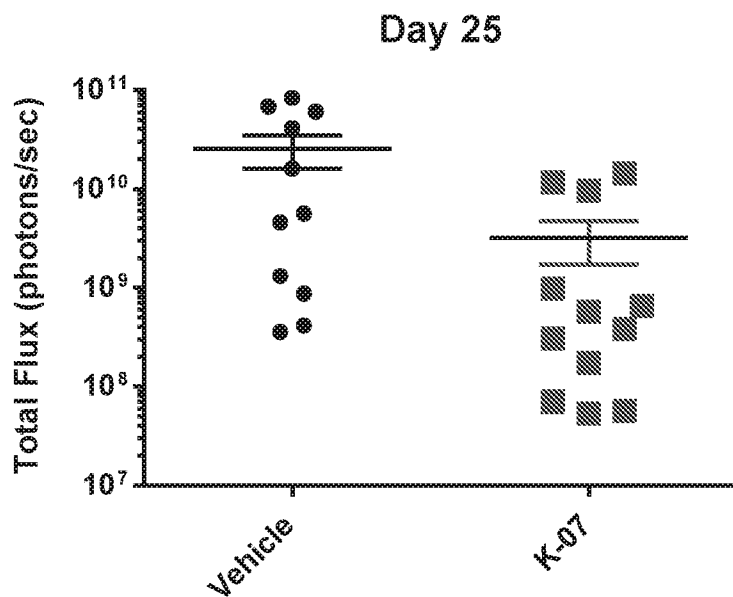


FIG. 29B

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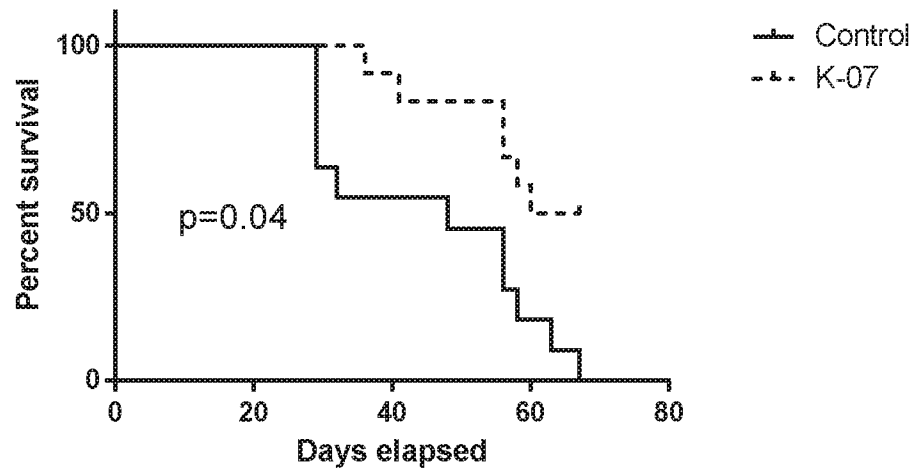
Survival of Mice with D538G MCF7 cells -intracardiac injection

FIG. 29C

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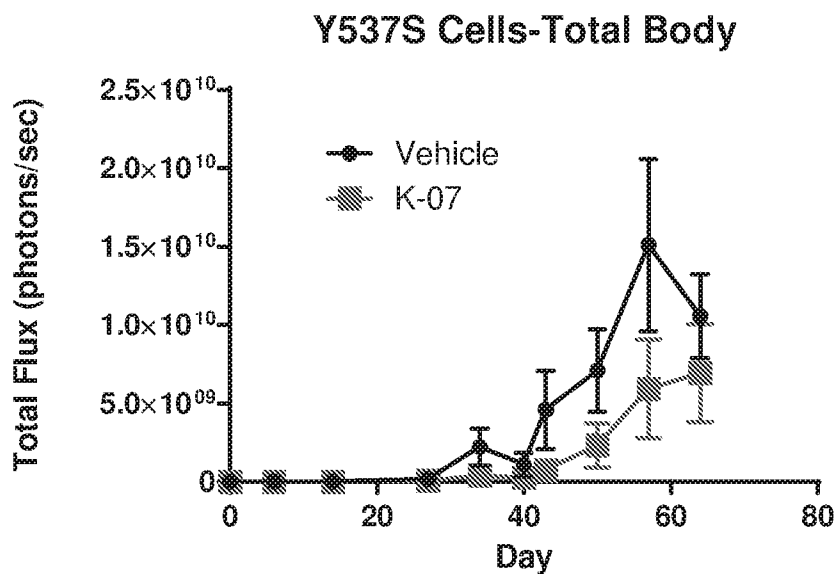


FIG. 30A

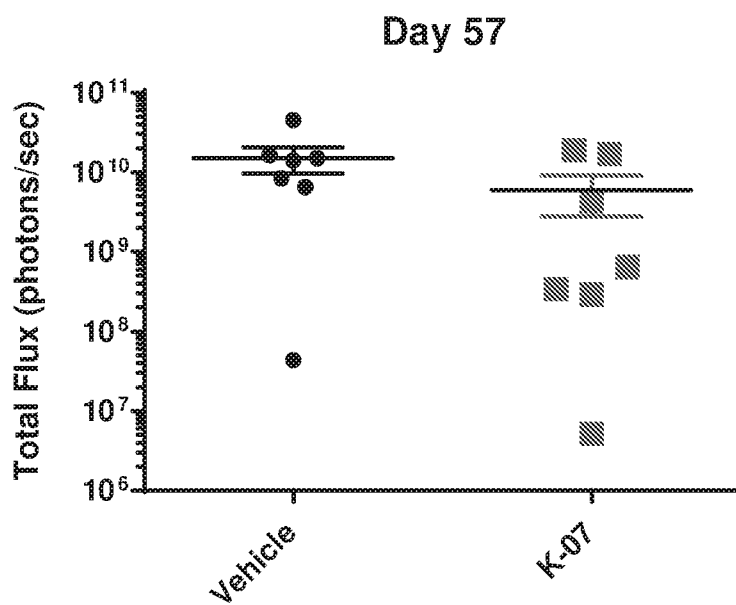


FIG. 30B

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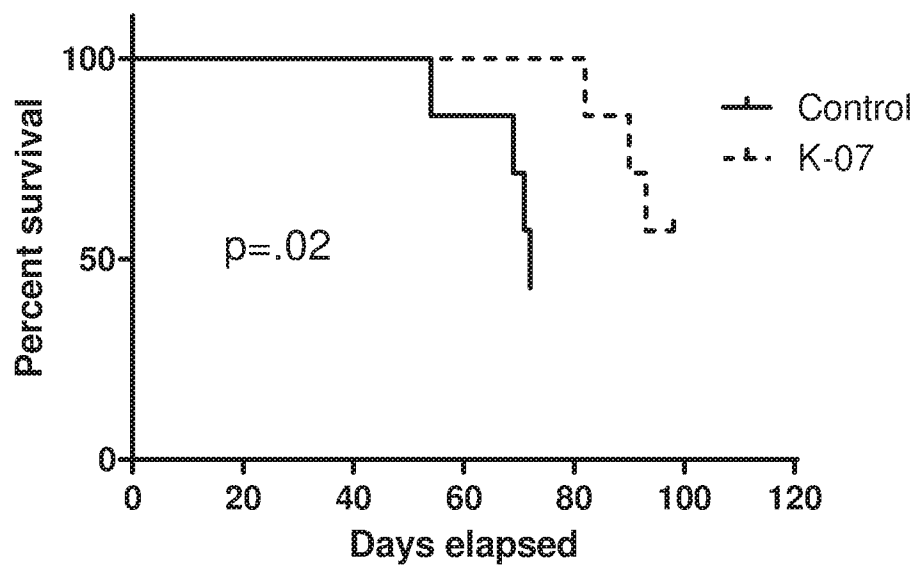
Overall Survival of Mice with Y537S MCF7 Cells

FIG. 30C

44/45

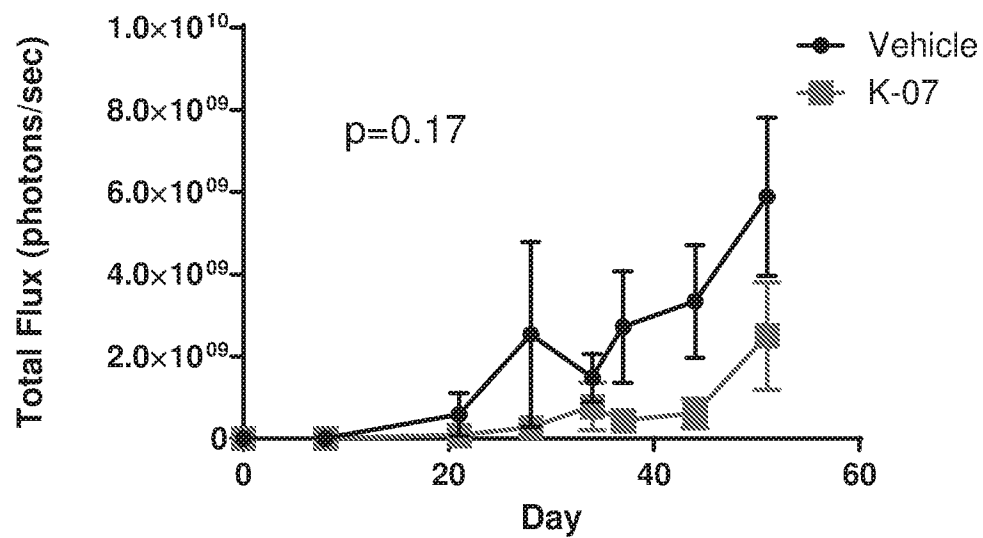


FIG. 31A

Overall Survival of Mice with D538G MCF7 Cells

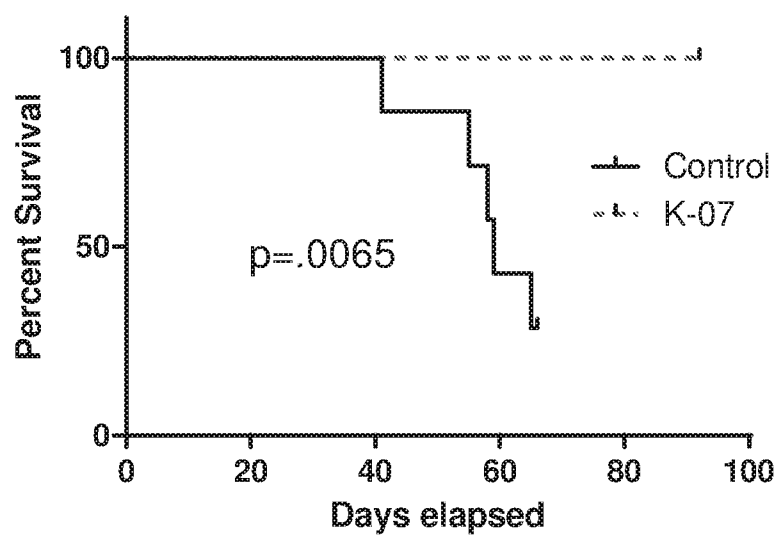


FIG. 31B

	WT-ER	Y537S-ER	D538G-ER
E2 Priming conc. (nmol/L) ^b	9	0.3	2.5
E2 (K _d ; nmol/L)	0.22 ± 0.11	1.40 ± 0.54	1.77 ± 0.66
Cheng-Prusoff correction: 1 + [(E2)/K _d] ^c	42	12	2.4
Ligand		K_i (nmol/L; fold increase over WT)	
Trans-hydroxytamoxifen			
	IC ₅₀ nmol/L ^d	3.4	6.0
	K _i nmol/L ^e	2.8	13
	(fold change from WT) ^f	(11×)	(5×)
K-07	IC ₅₀ nmol/L ^d	49	38
	K _i nmol/L ^e	41	16
	(fold change from WT) ^f	(54×)	(21×)
	IC ₅₀ nmol/L ^d	29	26
K-09	K _i nmol/L ^e	24	11
	(fold change from WT) ^f	(20×)	(9.2×)
	IC ₅₀ nmol/L ^d	53	36
	K _i nmol/L ^e	44	16
K-62	(fold change from WT) ^f	(34×)	(12×)

^aBinding of E2 was determined by direct Scatchard binding assay using tritiated E2 (28). Binding of other ligands was determined by a competitive radiometric assay using tritiated E₂ and increasing concentrations of ligand (28).

^bThe concentration of E2 needed to recruit SRC3 binding to about 50% of maximum to each receptor. It differs from WT versus mutant ERs because of different levels of constitutive activity and E2-binding affinity of these ERs.

^cThis factor is required to convert IC₅₀ values to K_i values.

^dIC₅₀ values are read from the inhibition curves shown in Supplementary Fig. S2.

^eK_i values are determined by dividing the IC₅₀ values by the Cheng-Prusoff correction factor.

^fFold change from WT is determined for each AE by dividing the K_i value for the mutant-ER by the K_i value for WT-ER.

FIG. 32

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2018/024144

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

10(completely); 1, 2, 5, 8, 9, 22-38(partially)

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2018/024144

A. CLASSIFICATION OF SUBJECT MATTER INV. A61K31/05 A61K31/165 C07C39/23 C07C235/40 A61P35/00 ADD.											
According to International Patent Classification (IPC) or to both national classification and IPC											
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) A61K C07C Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) EPO-Internal, WPI Data											
C. DOCUMENTS CONSIDERED TO BE RELEVANT <table border="1"> <thead> <tr> <th>Category*</th> <th>Citation of document, with indication, where appropriate, of the relevant passages</th> <th>Relevant to claim No.</th> </tr> </thead> <tbody> <tr> <td>X</td> <td>MUTHYALA R S ET AL: "BRIDGED BICYCLIC CORES CONTAINING A 1,1-DIARYLETHYLENE MOTIF ARE HIGH-AFFINITY SUBTYPE-SELECTIVE LIGANDS FOR THE ESTROGEN RECEPTOR", JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY, vol. 46, no. 9, 1 January 2003 (2003-01-01), pages 1589-1602, XP001204850, ISSN: 0022-2623, DOI: 10.1021/JM0204800</td> <td>1,2,5,8, 22,24-38</td> </tr> <tr> <td>A</td> <td>the whole document ----- -/--</td> <td>9,10,23</td> </tr> </tbody> </table>			Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.	X	MUTHYALA R S ET AL: "BRIDGED BICYCLIC CORES CONTAINING A 1,1-DIARYLETHYLENE MOTIF ARE HIGH-AFFINITY SUBTYPE-SELECTIVE LIGANDS FOR THE ESTROGEN RECEPTOR", JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY, vol. 46, no. 9, 1 January 2003 (2003-01-01), pages 1589-1602, XP001204850, ISSN: 0022-2623, DOI: 10.1021/JM0204800	1,2,5,8, 22,24-38	A	the whole document ----- -/--	9,10,23
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.									
X	MUTHYALA R S ET AL: "BRIDGED BICYCLIC CORES CONTAINING A 1,1-DIARYLETHYLENE MOTIF ARE HIGH-AFFINITY SUBTYPE-SELECTIVE LIGANDS FOR THE ESTROGEN RECEPTOR", JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY, vol. 46, no. 9, 1 January 2003 (2003-01-01), pages 1589-1602, XP001204850, ISSN: 0022-2623, DOI: 10.1021/JM0204800	1,2,5,8, 22,24-38									
A	the whole document ----- -/--	9,10,23									
☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.											
* Special categories of cited documents : "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier application or patent but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family											
Date of the actual completion of the international search		Date of mailing of the international search report									
11 June 2018		22/08/2018									
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016		Authorized officer Seelmann, Marielle									

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2018/024144

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE Reaxys [Online] 1 January 1994 (1994-01-01), Hasegawa Takeshi et al., Bulletin of the Chemical Society of Japan, 67(2), 462-472 (1994): "Case enlargement of 1,4-Bis(hydroxymethyl)pentacyclo(4.2.0.0(2 ,5).0(3,8).0(4,7))octane to a tetracyclo(4.3.0.0(3,9).0(4,7))nonane system in formic acid", XP002781500, Database accession no. XRN=6948432 and XRN=6949076 abstract -----	1,8
X	DATABASE Reaxys [Online] Elsevier; 1 January 1983 (1983-01-01), Willy Friedrichsen et al., Zeitschrift für Naturforschung, Teil B: anorganische Chemie, organische Chemie, 38(4), 504-515 (1983): "Cycloaddition of ketenes with fulvenes", XP002781501, Database accession no. XRN = 6231581 abstract -----	1,8
X	US 3 636 166 A (LEDNICER DANIEL) 18 January 1972 (1972-01-18)	1,5,8,24
Y	in particular examples 6-8,11 and 17;	2,22, 25-38
A	the whole document	9,10,23
X	GB 1 260 716 A (SCHERICO LTD [CH]) 19 January 1972 (1972-01-19)	1,5,8,24
Y	at least claims 1-5;	2,22, 25-38
A	the whole document	9,10,23
X	FR 1 376 466 A (EASTMAN KODAK CO [US]) 31 October 1964 (1964-10-31) at least examples 11-13; the whole document -----	1,5,8
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INTERNATIONAL SEARCH REPORT

International application No

PCT/US2018/024144

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	E.BOSCH ET AL.,: "Catalytic epoxidation of hindered olefins with dioxygen.", J.AM.CHEM.SOC., vol. 118, 1 January 1996 (1996-01-01), pages 1319-1329, XP002781506, page 1320; compounds 4-5 -----	1,2,8

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Information on patent family members

International application No

PCT/US2018/024144

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			BE 729943 A	17-09-1969
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FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 10(completely); 1, 2, 5, 8, 9, 22-38(partially)

compounds (I) with Q = bond

2. claims: 6, 7, 11-15(completely); 1-5, 9, 17-38(partially)

compounds (I) with Q not a bond

3. claims: 16(completely); 1-5, 8, 17-38(partially)

compounds (I) with at least one $X_i = N$
