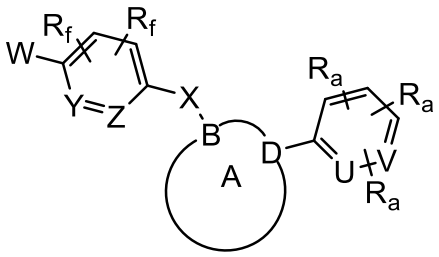
endothelial cells, bone, and male prostate tissue. Different tissues have different degrees of sensitivity to and activity of endogenous estrogens, so SERMs produce estrogenic or antiestrogenic effects depending on the specific tissue in question as well as the percentage of intrinsic activity (IA) of the SERM. Moreover, their levels in various tissues may change in response to physical development, aging or disease state. Antagonizing at the ER can either occur through competitive inhibition, wherein one ligand displaces a more agonistic ligand (eg 17β-estradiol) and signals to a lesser degree or not at all relative to the agonist ligand. There is a second mode of inhibiting ER-agonist signaling and this comprises the binding of a ligand to ER and inducing a conformation or conformations that trigger the degradation of the ER in the proteasome. Often, the degradation is triggered by ubiquination and/or palmoylation of ER subsequent to a binding event of the degradation-triggering compound. Compounds that bind ER and accelerate its degradation are often referred to as selective estrogen receptor degraders ("SERDs"). Referring to a compound as a SERM or SERD is a general way to focus on that aspect of its pharmacology. As it turns out, many compounds that function as SERMs, meaning they have at least some agonist activity in some (but not all) ER-expressing tissues, can also trigger at least some receptor degradation. Accordingly, it should be appreciated that many if not most of the compounds falling under the embodiments of this invention represent a spectrum of SERM/SERD activity. Whether SERMs, SERDs and SERM/SERDs, the compounds of the present disclosure are able to achieve the methods disclosed herein.

SUMMARY

[0004a] In a first aspect of the present disclosure, there is provided a compound according to formula I'



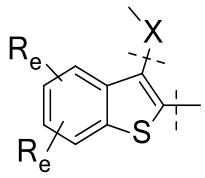
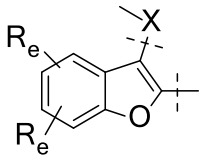
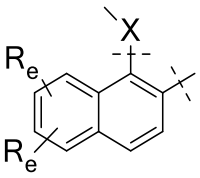
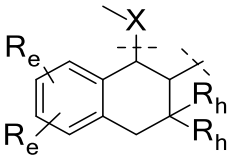
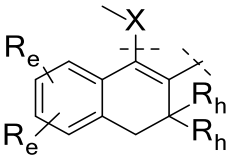
I'

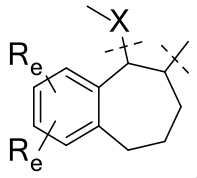
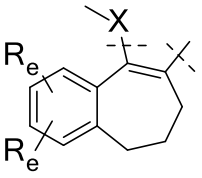
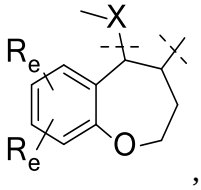
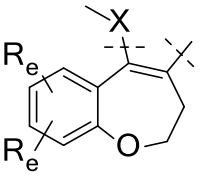
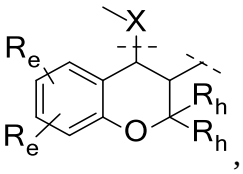
wherein:

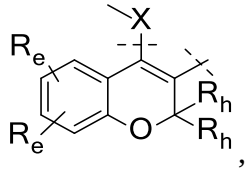
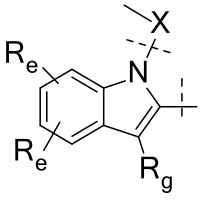
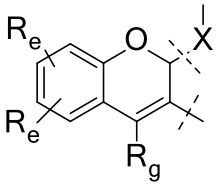
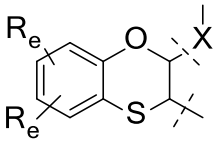
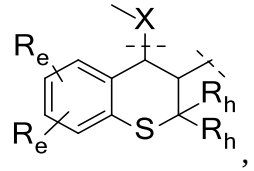
B is nitrogen or carbon;

D is carbon;

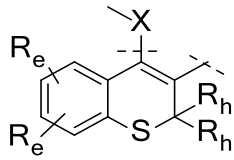
A is a fused ring system selected from the group consisting of:

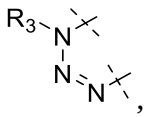
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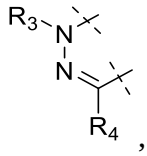
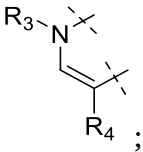
, , , , ,

, , , , ,

and

;

each R_e is independently selected from hydrogen, halogen, OH, O(CO)R, O(CO)NR_1R_2, O(SO_2)NR_1R_2, or wherein two adjacent R_e together form: ,

, or ;

R is C_1-C_6 alkyl or aryl;

R_1 and R_2 are each independently hydrogen or C_1-C_6 alkyl;

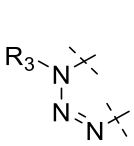
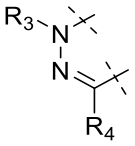
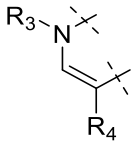
each R_3 is hydrogen, C_1-C_{12} acyl; C_1-C_{12} acyloxy;

each R_4 is independently hydrogen, C_1-C_3 alkyl, fluorine or chlorine;

each R_h is independently selected from hydrogen or CH_3;

R_g is hydrogen, C_1-C_3 alkyl, C_1-C_3 fluoroalkyl, CN, fluorine, chlorine or bromine;

each R_a is independently selected from: H, C_1-C_3 alkyl, C_1-C_3 fluoroalkyl, phenyl (optionally substituted with 1-3 groups selected from fluorine, chlorine, C_1-C_3 alkyl, CN,

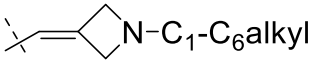
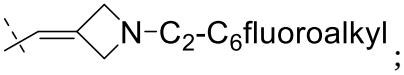
OC_1-C_3 alkyl, OH), OH, OC_{1-3}alkyl, CN, fluorine, chlorine, O(CO)R, $O(CO)NR_1R_2$, $O(SO_2)NR_1R_2$, or two adjacent Ra together form: , , or ;

X is O, S, CH_2, NH or a bond when B is carbon, or CH_2 or a bond when B is nitrogen;

Y and Z are each independently selected from CR_f or N;

U and V are each independently selected from CR_a or N;

each R_f is independently H, C_1-C_3 alkyl, OC_1-C_3 alkyl, fluorine or chlorine; and

W is –CHR'-CHR'-NH-C_1-C_4alkyl, -CHR'-CHR'-NH-C_1-C_4fluoroalkyl, -CHR'-CHR'-NH-C_3-C_6cycloalkyl, -CHR'-CHR'-NH-C_1-C_4alkyl-C_3-C_6cycloalkyl, , or ;

wherein each R' is independently H or C_1-C_3alkyl;

or a pharmaceutically acceptable salt thereof.

[0004b] In another aspect of the present disclosure, there is provided a compound selected from:

1-(4-(2-(Ethylamino)ethyl)benzyl)-2-(4-methoxyphenyl)-3-methyl-1*H*-indol-5-ol;

1-(4-(2-(Cyclopropylamino)ethyl)benzyl)-2-(4-methoxyphenyl)-3-methyl-1*H*-indol-5-ol;

1-(4-(2-(Isopropylamino)ethyl)benzyl)-2-(4-methoxyphenyl)-3-methyl-1*H*-indol-5-ol;

1-(4-(2-(Cyclohexylamino)ethyl)benzyl)-2-(4-methoxyphenyl)-3-methyl-1H-indol-5-ol;

2-(4-Methoxyphenyl)-3-methyl-1-(4-(2-((2,2,2-trifluoroethyl)amino)ethyl)benzyl)-1*H*-indol-5-ol;

1-(4-(2-(Cyclopropylamino)ethyl)benzyl)-3-fluoro-2-(4-methoxyphenyl)-1*H*-indol-5-ol;

1-(4-(2-(Ethylamino)ethyl)benzyl)-3-fluoro-2-(4-methoxyphenyl)-1*H*-indol-5-ol;

3-Chloro-1-(4-(2-(ethylamino)ethyl)benzyl)-2-(4-methoxyphenyl)-1*H*-indol-5-ol;

1-(4-(2-(Cyclopropylamino)ethyl)benzyl)-3-fluoro-2-(o-tolyl)-1H-indol-5-ol;

3-Fluoro-2-(2-methoxyphenyl)-1-(4-(2-(propylamino)ethyl)benzyl)-1H-indol-5-ol;

1-(4-(2-(Cyclobutylamino)ethyl)benzyl)-2-(2,6-dimethylphenyl)-3-fluoro-1*H*-indol-5-ol;

2-(2,6-Dimethylphenyl)-1-(4-(2-(ethylamino)ethyl)benzyl)-3-fluoro-1*H*-indol-5-ol;

1-(4-(2-(Cyclopropylamino)ethyl)benzyl)-3-fluoro-2-(4-hydroxy-2-methylphenyl)-1*H*-indol-5-ol;

3-Fluoro-1-(4-(2-((2-fluoroethyl)amino)ethyl)benzyl)-2-(4-methoxy-2-methylphenyl)-1H-indol-5-ol;

3-Fluoro-1-(4-(2-((3-fluoropropyl)amino)ethyl)benzyl)-2-(4-methoxy-2-methylphenyl)-1H-indol-5-ol;
1-(4-(2-(Cyclopropylamino)ethyl)benzyl)-3-fluoro-2-(4-fluoro-2-methylphenyl)-1*H*-indol-5-ol;
3-Fluoro-2-(4-methoxy-2-methylphenyl)-1-(4-(2-(propylamino)ethyl)benzyl)-1H-indol-5-o;l
2-([1,1'-Biphenyl]-2-yl)-3-fluoro-1-(4-(2-(propylamino)ethyl)benzyl)-1H-indol-5-ol;
1-(4-(2-(Ethylamino)ethyl)benzyl)-3-fluoro-2-(o-tolyl)-1H-indol-5-ol;
1-(4-(2-(Cyclobutylamino)ethyl)benzyl)-3-fluoro-2-(o-tolyl)-1H-indol-5-ol;
3-Fluoro-1-(4-(2-(propylamino)ethyl)benzyl)-2-(o-tolyl)-1H-indol-5-ol;
1-(4-(2-(Butylamino)ethyl)benzyl)-3-fluoro-2-(o-tolyl)-1*H*-indol-5-ol;
3-Fluoro-1-(4-(2-((3-fluoropropyl)amino)ethyl)benzyl)-2-(o-tolyl)-1H-indol-5-ol;
3-Fluoro-1-(4-(2-((2-fluoroethyl)amino)ethyl)benzyl)-2-(o-tolyl)-1H-indol-5-ol;
1-(4-(2-(Cyclopropylamino)propyl)benzyl)-3-fluoro-2-(o-tolyl)-1H-indol-5-o;l
1-(4-(2-((Cyclopropylmethyl)amino)ethyl)benzyl)-3-fluoro-2-(2-(trifluoromethyl)phenyl)-1*H*-indol-5-ol;
1-(4-(2-(Cyclopropylamino)ethyl)benzyl)-3-fluoro-2-(2-(trifluoromethyl)phenyl)-1*H*-indol-5-ol;
1-(4-(2-(Ethylamino)ethyl)benzyl)-3-fluoro-2-(2-(trifluoromethyl)phenyl)-1H-indol-5-o;l
2-(2-Chlorophenyl)-1-(4-(2-(cyclopropylamino)ethyl)benzyl)-3-fluoro-1H-indol-5-ol;
N-Ethyl-2-(4-((8-fluoro-7-(o-tolyl)pyrrolo[3,2-e]indazol-6(3H)-yl)methyl)phenyl)ethan-1-amine;
N-(Cyclopropylmethyl)-2-(4-((8-fluoro-7-(o-tolyl)pyrrolo[3,2-e]indazol-6(3*H*)-yl)methyl)phenyl)ethan-1-amine;
N-(4-((8-Fluoro-7-(o-tolyl)pyrrolo[3,2-e]indazol-6(3*H*)-yl)methyl)phenethyl)cyclobutanamine;
N-(4-((8-Fluoro-7-(o-tolyl)pyrrolo[3,2-e]indazol-6(3*H*)-yl)methyl)phenethyl)cyclopropanamine;
N-(4-((8-fluoro-7-(o-tolyl)pyrrolo[3,2-e]indazol-6(3*H*)-yl)methyl)phenethyl)propan-1-amine;
3-Fluoro-*N*-(4-((8-fluoro-7-(o-tolyl)pyrrolo[3,2-e]indazol-6(3*H*)-yl)methyl)phenethyl)propan-1-amine;
(5R,6S)-5-(4-(2-(Ethylamino)ethyl)phenyl)-6-phenyl-5,6,7,8-tetrahydronaphthalen-2-ol;
(5R,6S)-5-(4-(2-((Cyclopropylmethyl)amino)ethyl)phenyl)-6-phenyl-5,6,7,8-tetrahydronaphthalen-2-ol;
(5R,6S)-5-(4-(2-(Ethylamino)ethyl)phenyl)-6-(o-tolyl)-5,6,7,8-tetrahydronaphthalen-2-ol;

(5R,6S)-5-(4-(2-((cyclopropylmethyl)amino)ethyl)phenyl)-6-(o-tolyl)-5,6,7,8-tetrahydronaphthalen-2-ol;
5-(4-(2-(Ethylamino)ethyl)phenyl)-6-(4-isopropylphenyl)-5,6,7,8-tetrahydronaphthalen-2-ol;
6-(4-Isopropylphenyl)-5-(4-(2-(propylamino)ethyl)phenyl)-5,6,7,8-tetrahydronaphthalen-2-ol;
5-(4-(2-((Cyclopropylmethyl)amino)ethyl)phenyl)-6-(4-isopropylphenyl)-5,6,7,8-tetrahydronaphthalen-2-ol;
3-(4-(2-(Cyclopropylamino)ethyl)phenoxy)-2-(o-tolyl)benzo[b]thiophen-6-ol;
3-(4-(2-((Cyclopropylmethyl)amino)ethyl)phenoxy)-2-(o-tolyl)benzo[b]thiophen-6-ol;
3-(4-((1-Propylazetidin-3-ylidene)methyl)phenoxy)-2-(o-tolyl)benzo[*b*]thiophen-6-ol;
1-(4-(2-((Cyclopropylmethyl)amino)ethyl)benzyl)-2-(4-methoxyphenyl)-3-methyl-1H-indol-5-ol;
1-(4-(2-((Cyclopropylmethyl)amino)ethyl)benzyl)-3-fluoro-2-(o-tolyl)-1H-indol-5-ol;
2-Fluoro-N-(4-((8-fluoro-7-(o-tolyl)pyrrolo[3,2-e]indazol-6(3H)yl)methyl)phenethyl)ethan-1-amine;
5-(4-(2-(Cyclopropylamino)ethyl)benzyl)-4-(o-tolyl)-2,3-dihydrobenzo[*b*]oxepin-8-ol; and
5-(4-(2-(Ethylamino)ethyl)benzyl)-4-(o-tolyl)-2,3-dihydrobenzo[*b*]oxepin-8-ol.

[0004c] In yet another aspect of the present disclosure, there is provided a pharmaceutical composition comprising a compound as disclosed herein and a pharmaceutically acceptable excipient.

[0004d] In a further aspect of the present disclosure, there is provided a use of a compound as disclosed herein or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating a disease, syndrome, illness, or symptom associated with insufficient or overabundant estrogen levels in a mammal in need thereof.

[0004e] In another aspect of the present disclosure, there is provided a use of a compound as disclosed herein or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating a cancer selected from the group consisting of prostate cancer, breast cancer, endometrial cancer, lung cancer, hepatocellular cancer, lymphoma, multiple endocrine neoplasia, vaginal cancer, renal cancer, thyroid cancer, testicular cancer, leukemia, and ovarian cancer in a mammal in need thereof.

[0004f] In yet another aspect of the present disclosure, there is provided a compound as disclosed herein or a pharmaceutically acceptable salt thereof for use in therapy.

[0005] In one example, presented herein are compounds of Formulas I to VII, I' to X', or a pharmaceutically acceptable salt, solvate or prodrug thereof, that modify the effects of endogeneous estrogens acting through ER and/or trigger ER degradation, and therefore, are useful as agents for the treatment or prevention of diseases or conditions in which the actions of estrogens and/or estrogen receptors are involved in the etiology or pathology of the disease or condition or contribute to at least one symptom of the disease or condition and wherein such actions of estrogens and/or estrogen receptors are undesirable. In some examples, compounds disclosed herein are selective estrogen receptor degrader compounds.

[0006] In one example, compounds of Formulas I to VII, I' to X', or a pharmaceutically acceptable salt, solvate or prodrug thereof, are useful for the treatment of ER-related diseases or conditions including, but not limited to, ER-α dysfunction associated with cancer such as,

breast cancer, lung cancer, colorectal cancer, endometrial cancer, prostate cancer, ovarian and uterine cancer, including metastatic cancers.

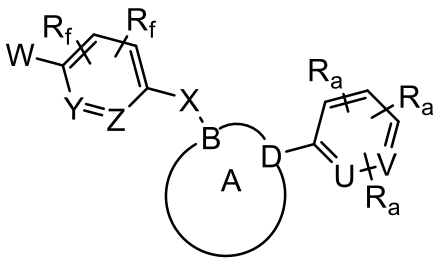
[0007] In one example, described herein are compounds of Formulas I to VII, I' to X', and pharmaceutically acceptable salts, solvates, metabolites and prodrugs thereof. Compounds described herein are estrogen receptor modulators. In some examples, the compound of Formulas I to VII or I' to X' is an estrogen receptor antagonist. In some examples, the compound of Formulas I to VII or I' to X' displays minimal estrogen receptor agonist activity. In some examples, in the context of treating cancers, the compound of Formulas I to VII or I' to X' may offer improved therapeutic activity characterized by complete or longer-lasting tumor regression, a lower incidence or rate of development of resistance to treatment, and/or a reduction in tumor invasiveness.

[0008] In some examples, compounds disclosed herein have high specificity for the estrogen receptor and have desirable, tissue-selective pharmacological activities. Desirable, tissue-selective pharmacological activities include, but are not limited to, ER antagonist activity in breast cells and no ER agonist activity in uterine cells. In some examples, compounds disclosed herein are estrogen receptor degraders that display full estrogen receptor antagonist activity with negligible or minimal estrogen receptor agonist activity.

[0009] In some examples, compounds disclosed herein are estrogen receptor degraders. In some examples, compounds disclosed herein are estrogen receptor antagonists. In some examples, compounds disclosed herein have minimal or negligible estrogen receptor agonist activity.

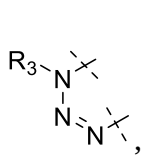
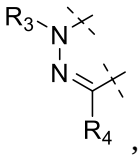
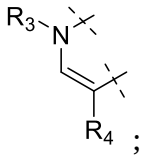
[00010] In some examples, presented herein are compounds selected from the group consisting of active metabolites, tautomers, pharmaceutically acceptable solvates, pharmaceutically acceptable salts, and prodrugs of a compound of Formulas I to VII or I' to X'.

[00011] In certain examples, the present disclosure describes a compound of Formula I:



I

wherein:

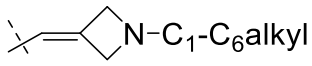
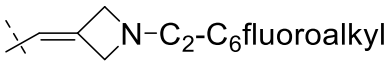
OH), OH, OC_{1-3}alkyl, CN, fluorine, chlorine, bromine, O(CO)R, $O(CO)NR_1R_2$, OPO_3, OSO_3,$O(SO_2)NR_1R_2$, or two adjacent R_a together form: , , or ;

X is O, S, CH_2, NH or a bond when B is carbon, or CH_2 or a bond when B is nitrogen;

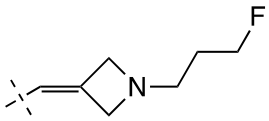
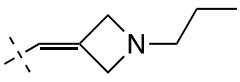
Y and Z are each independently selected from CR_f or N;

U and V are each independently selected from CR_a or N;

each R_f is independently H, C_1-C_3 alkyl, OC_1-C_3 alkyl, fluorine or chlorine; and

W is –CHR'-CHR'-NH-C_1-C_4alkyl, -CHR'-CHR'-NH-C_1-C_4fluoroalkyl, -CHR'-CHR'-NH-C_3-C_6cycloalkyl, -CHR'-CHR'-NH-C_1-C_4alkyl-C_3-C_6cycloalkyl, , or ; wherein each R' is independently H or C_1-C_3alkyl;

or a pharmaceutically acceptable salt thereof.

[00012] In some examples, W is –CH_2-CH_2-NH-CH_2-CH_2-CH_3; in some examplesW is –CH_2-CH_2-NH-CH_2-CH_2-CH_2F; in some examplesW is ; in certain examples, W is .

[00013] In certain examples, provided herein are pharmaceutical compositions comprising a compound selected from the group consisting of formulas I-VII, I' to X', and all structural examplesdescribed herein and at least one pharmaceutically acceptable excipient.

[00014] In certain examples, provided herein is a method of modulating an estrogen receptor in a cell, comprising the administration of a compound to said cell wherein said compound is selected from the group consisting of formulas I-VII, I' to X', and all the structural examplesdescribed herein, or a pharmaceutically acceptable salt thereof.

[00015] In certain examples, provided herein is a method of identifying a compound capable of modulating an estrogen receptor comprising contacting a cell expressing an estrogen receptor with a compound according to formula I, and monitoring the effect of the compound on the cell.

[00016] Also described herein is a prodrug of a compound selected from the group consisting of formulas I-VII, I' to X', and all structural examplesdescribed herein. Also

described herein is a pharmaceutically acceptable salt of a prodrug of a compound selected from the group consisting of formulas I-VII, I' to X', and all structural examplesdescribed herein. In some examples, the pharmaceutically acceptable salt of the prodrug of a compound of Formulas I-VII, I' to X', is a hydrochloride salt.

[00017] In some examples, described herein is a pharmaceutical composition comprising a compound selected from the group consisting of formulas I-VII, I' to X', and all structural examplesdescribed herein or a pharmaceutically acceptable salt or prodrug of a compound selected from the group consisting of formulas I-VII, I' to X', and all structural examplesdescribed herein. In some examples, the pharmaceutical composition is formulated for intravenous injection, subcutaneous injection, oral administration, or topical administration. In some examples, the pharmaceutical composition is a tablet, a pill, a capsule, a liquid, a suspension, a gel, a dispersion, a solution, an emulsion, an ointment, or a lotion.

[00018] This present disclosure also provides a method of treating (e.g., preventing, or ameliorating the symptoms associated with, or reducing the incidence of, reducing the pathogenesis of, facilitating the recovery from or delaying the onset of) a disease, syndrome, illness, or symptom associated with insufficient or overabundant estrogen levels in a mammal in need thereof, wherein said method comprises the administration to said mammal of an effective amount of a compound selected from the group consisting of formulas I-VII, I' to X', and all structural examplesdescribed herein or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a compound of formulas I-VII, I' to X', or one of the structural examplesdescribed herein, or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable excipient. In a particular example, the mammal is a human.

[00019] In certain examples, this present disclosure describes a method of treating (e.g., preventing, or ameliorating the symptoms associated with, or reducing the incidence of, reducing the pathogenesis of, facilitating the recovery from or delaying the onset of) prostate cancer, breast cancer, endometrial cancer, lung cancer, hepatocellular cancer, lymphoma, multiple endocrine neoplasia, vaginal cancer, renal cancer, thyroid cancer, testicular cancer, leukemia, and ovarian cancer in a mammal in need thereof comprising the administration to said mammal of a compound selected from the group consisting of formulas I-VII, I' to X', and all structural examplesdescribed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a compound selected from the group consisting of formulas I-VII, I' to X', and all structural examplesdescribed herein including pharmaceutically acceptable salts thereof and a pharmaceutically acceptable excipient. In an

example, the mammal is a human. In some examples, the cancer is positive for the expression of ESR1. In certain examples, the cancers are resistant to prior lines of treatment (e.g., prior endocrinological therapy). In certain examples, the cancer progresses after exposure to one or more agents selected from the group consisting of tamoxifen, toremifene, letrozole, aromasin, anastrazole, and faslodex. In some examples, the treatment is in adjuvant setting and in some examples the treatment is in the metastatic setting. In certain examples, SERD and/or SERMS compounds disclosed herein are combined with other active compounds including, cdk4/6 inhibitors, PI3k inhibitors, mTOR inhibitors, taxanes, and Her2 inhibitors.

DETAILED DESCRIPTION OF THE INVENTION

[00020] As employed above and throughout the disclosure, the following terms, unless otherwise indicated, shall be understood to have the following meanings.

[00021] Unless otherwise stated, the following terms used in this application, including the specification and claims, have the definitions given below. It must be noted that, as used in the specification and the appended claims, the singular forms "a," "an" and "the" include plural referents unless the context clearly dictates otherwise. Unless otherwise indicated, conventional methods of mass spectroscopy, NMR, HPLC, protein chemistry, biochemistry, recombinant DNA techniques and pharmacology are employed. In this application, the use of "or" or "and" means "and/or" unless stated otherwise. Furthermore, use of the term "including" as well as other forms, such as "include", "includes," and "included," is not limiting. The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described.

[00022] The term "bond" or "single bond" refers to a chemical bond between two atoms, or two moieties when the atoms joined by the bond are considered to be part of larger substructure. In one aspect, when a group described herein is a bond, the referenced group is absent thereby allowing a bond to be formed between the remaining identified groups.

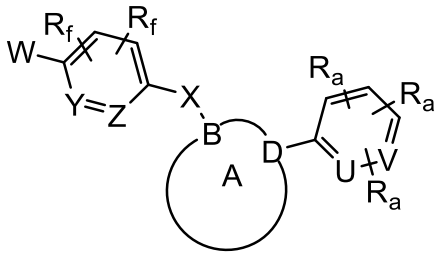
[00023] The term "moiety" refers to a specific segment or functional group of a molecule. Chemical moieties are often recognized chemical entities embedded in or appended to a molecule.

[00024] In some situations, compounds may exist as tautomers. All tautomers are included within the scope of the compounds presented herein.

[00025] The term "modulate" as used herein, means to interact with a target either directly or indirectly so as to alter the activity of the target, including, by way of example only, to

What is claimed is:

1. A compound according to formula I’



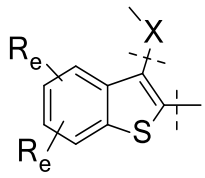
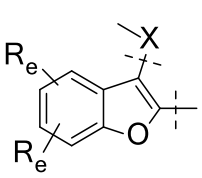
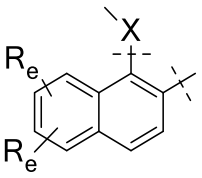
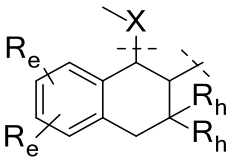
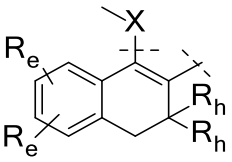
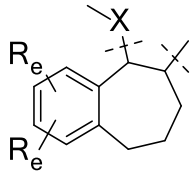
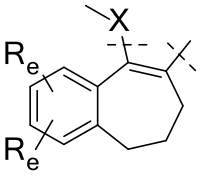
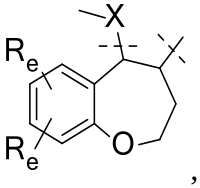
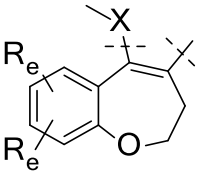
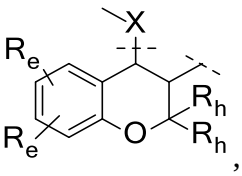
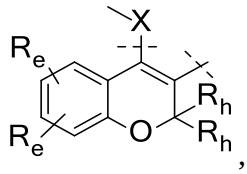
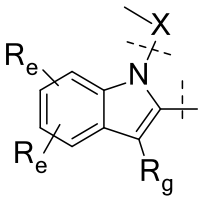
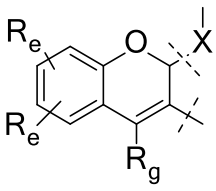
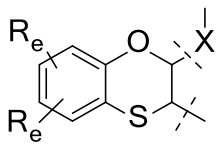
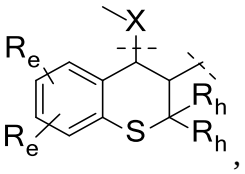
I’

wherein:

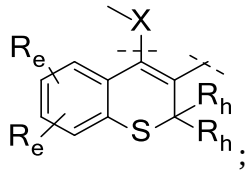
B is nitrogen or carbon;

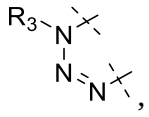
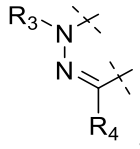
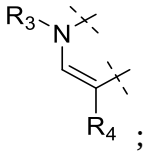
D is carbon;

A is a fused ring system selected from the group consisting of:

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and

;

each R_e is independently selected from hydrogen, halogen, OH, O(CO)R, $O(CO)NR_1R_2$, $O(SO_2)NR_1R_2$, or wherein two adjacent R_e together form: , , or ;

R is C_1-C_6 alkyl or aryl;

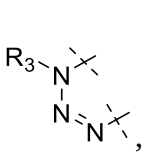
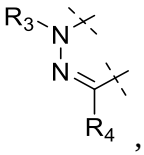
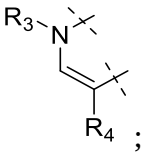
R_1 and R_2 are each independently hydrogen or C_1-C_6 alkyl;

each R_3 is hydrogen, C_1-C_{12} acyl; C_1-C_{12} acyloxy;

each R_4 is independently hydrogen, C_1-C_3 alkyl, fluorine or chlorine;

each R_h is independently selected from hydrogen or CH_3;

R_g is hydrogen, C_1-C_3 alkyl, C_1-C_3 fluoroalkyl, CN, fluorine, chlorine or bromine;

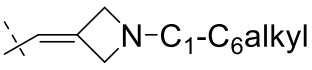
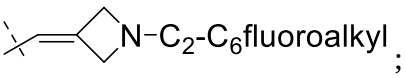
each R_a is independently selected from: H, C_1-C_3 alkyl, C_1-C_3 fluoroalkyl, phenyl (optionally substituted with 1-3 groups selected from fluorine, chlorine, C_1-C_3 alkyl, CN, OC_1-C_3 alkyl, OH), OH, OC_{1-3}alkyl, CN, fluorine, chlorine, O(CO)R, $O(CO)NR_1R_2$, $O(SO_2)NR_1R_2$, or two adjacent Ra together form: , , or ;

X is O, S, CH_2, NH or a bond when B is carbon, or CH_2 or a bond when B is nitrogen;

Y and Z are each independently selected from CR_f or N;

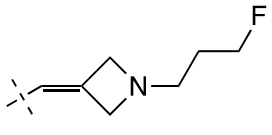
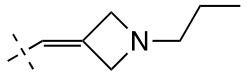
U and V are each independently selected from CR_a or N;

each R_f is independently H, C_1-C_3 alkyl, OC_1-C_3 alkyl, fluorine or chlorine; and

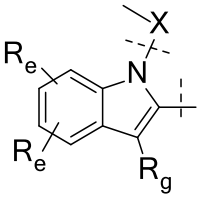
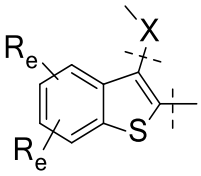
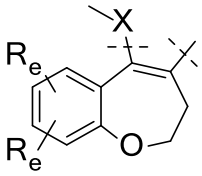
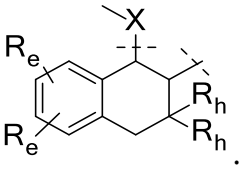
W is –CHR'-CHR'-NH-C_1-C_4alkyl, -CHR'-CHR'-NH-C_1-C_4fluoroalkyl, -CHR'-CHR'-NH-C_3-C_6cycloalkyl, -CHR'-CHR'-NH-C_1-C_4alkyl-C_3-C_6cycloalkyl, , or ;

wherein each R' is independently H or C_1-C_3alkyl;

or a pharmaceutically acceptable salt thereof.

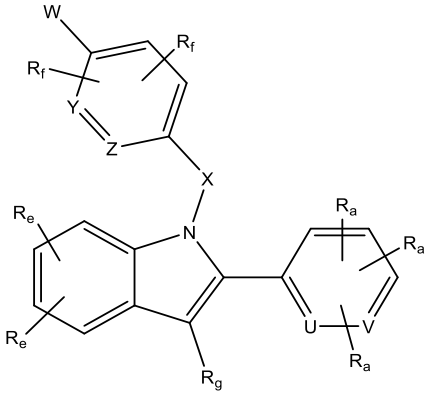
2. The compound of claim 1, wherein W is $–CH_2-CH_2-NH-CH_2-CH_2-CH_3$; $–CH_2-CH_2-NH-CH_2-CH_2-CH_2F$;  ; or  , or a pharmaceutically acceptable salt thereof.

3. The compound of claim 1, wherein A is:

 ,  ,  , or  .

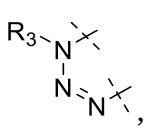
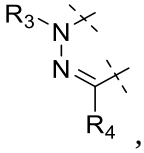
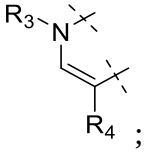
4. The compound of claim 1, wherein Y and Z are each CR_f and U and V are each CR_a.

5. The compound of claim 1, having a structure according to formula II'



II'

wherein:

each R_a is independently selected from H, C_1-C_3 alkyl, phenyl (optionally substituted with 1-3 groups selected from fluorine, chlorine, C_1-C_3 alkyl, CN, OC_1-C_3 alkyl, OH), OH, OC_1-$_3$alkyl, CN, fluorine, chlorine, O(CO)R, $O(CO)NR_1R_2$, $O(SO_2)NR_1R_2$, or two adjacent R_a together form:  ,  , or  ;

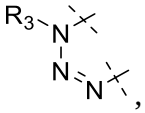
R is C_1-C_6 alkyl or aryl;

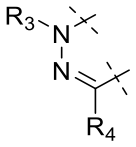
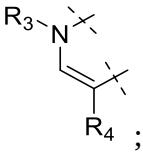
R_1 and R_2 are each independently hydrogen or C_1-C_6 alkyl;

each R_3 is independently hydrogen; C_1-C_{12} acyl or C_1-C_{12} acyloxy ;

each R_4 is independently hydrogen, C_1-C_3 alkyl, fluorine or chlorine;

each R_e is independently selected from hydrogen, halogen, OH, O(CO)R,

O(CO)NR_1R_2, O(SO_2)NR_1R_2, or wherein two adjacent R_e together form: ,

 , or  ;

each R_f is independently H, C_1-C_3 alkyl, OC_1-C_3 alkyl, fluorine or chlorine;

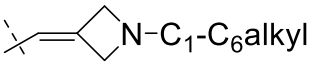
R_g is hydrogen, C_1-C_3 alkyl, C_1-C_3 fluoroalkyl, CN, fluorine, chlorine or bromine;

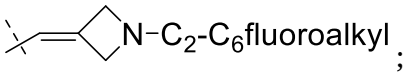
X is CH_2 or a bond;

Y and Z are each independently selected from CR_f or N;

U and V are each independently selected from CR_a or N; and

W is –CHR'-CHR'-NH-C_1-C_4alkyl, -CHR'-CHR'-NH-C_1-C_4fluoroalkyl, -CHR'-CHR'-NH-C_3-C_6cycloalkyl, -CHR'-CHR'-NH-C_1-C_4alkyl-C_3-C_6cycloalkyl,



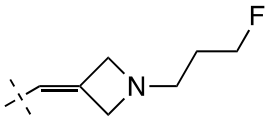
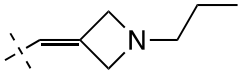
, or 

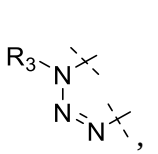
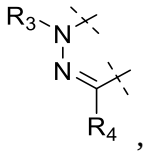
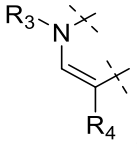
;

wherein each R' is independently H or C_1-C_3alkyl;

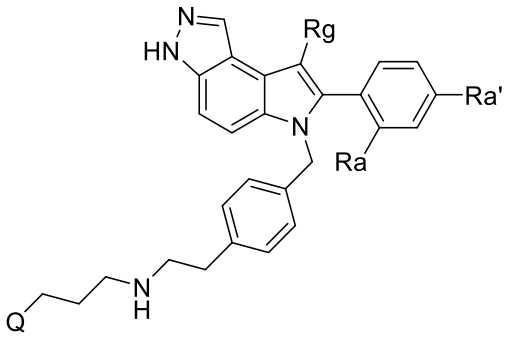
or a pharmaceutically acceptable salt thereof.

6. The compound of claim 5, wherein: X is CH_2; Y and Z are each CR_f; U and V are each CR_a; R_g is F, Cl or CH_3; each R_a is independently selected from H, OH, CH_3 and Cl; each R_f is H; and W is –CH_2-CH_2-NH-CH_2-CH_2-CH_3, –CH_2-CH_2-NH-CH_2-CH_2-CH_2F,

 , or  ; or a pharmaceutically acceptable salt thereof.

7. The compound of claim 6, wherein each R_e is independently selected from hydrogen or OH, or wherein two adjacent R_e together form: , , or  ; and wherein R_3 is H and R_4 is H.

8. The compound of claim 1, having a structure according to formula III':



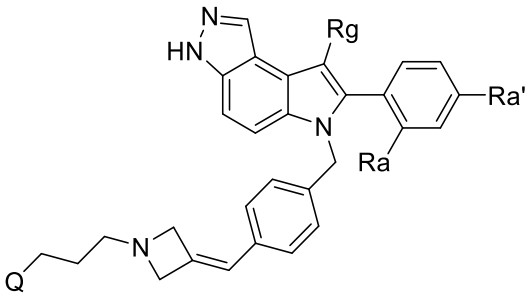
III'

wherein: Q is H or F; Rg is F, Cl, or CH_3; Ra is CH_3, Cl or OMe; and Ra' is H, F or OH; or a pharmaceutically acceptable salt thereof.

9. The compound of claim 8, wherein Rg is F.

10. The compound of claim 9, wherein Ra is CH_3 and Ra' is H.

11. The compound of claim 1, having a structure according to formula IV':



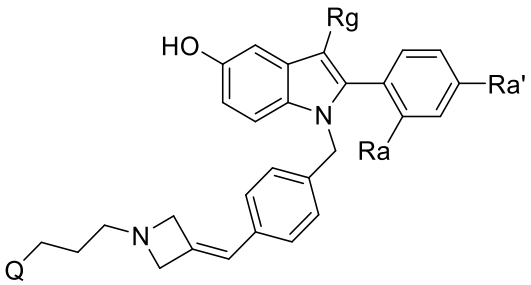
IV'

wherein: Q is H or F; Rg is F, Cl, or CH_3; Ra is CH_3, Cl or OMe; and Ra' is H, F or OH; or a pharmaceutically acceptable salt thereof.

12. The compound of claim 11, wherein Rg is F.

13. The compound of claim 12, wherein Ra is CH_3 and Ra' is H.

14. The compound of claim 1, having a structure according to formula V':



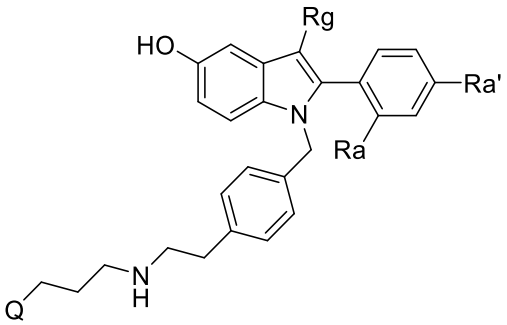
V'

wherein: Q is H or F; Rg is F, Cl, or CH_3; Ra is CH_3, Cl or OMe; and Ra' is H, F or OH; or a pharmaceutically acceptable salt thereof.

15. The compound of claim 14, wherein Rg is F.

16. The compound of claim 15, wherein Ra is CH_3 and Ra' is H.

17. The compound of claim 1, having a structure according to formula VI':



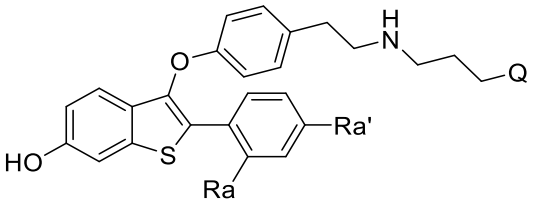
VI'

wherein: Q is H or F; Rg is F, Cl, or CH3; Ra is CH_3, Cl or OMe; and Ra' is H, F or OH; or a pharmaceutically acceptable salt thereof.

18. The compound of claim 17, wherein Rg is F.

19. The compound of claim 18, wherein Ra is CH_3 and Ra' is H.

20. The compound of claim 1, having a structure according to formula VII':

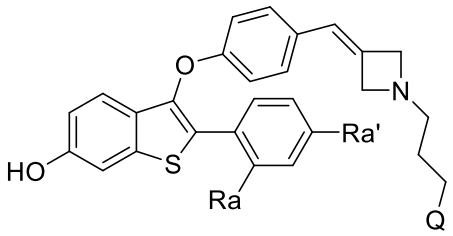


VII'

wherein: Q is H or F; Ra is CH_3, Cl or OMe; and Ra' is H, F or OH; or a pharmaceutically acceptable salt thereof.

21. The compound of claim 20, wherein Ra is CH_3 and Ra' is H.

22. The compound of claim 1, having a structure according to formula VIII':

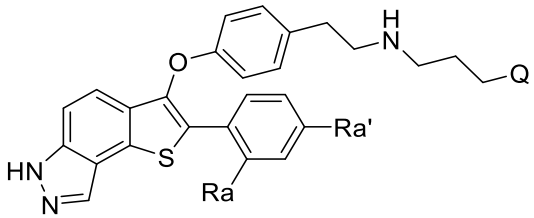


VIII'

wherein: Q is H or F; Ra is CH_3, Cl or OMe; and Ra' is H, F or OH; or a pharmaceutically acceptable salt thereof.

23. The compound of claim 22, wherein Ra is CH_3 and Ra' is H.

24. The compound of claim 1, having a structure according to formula IX':

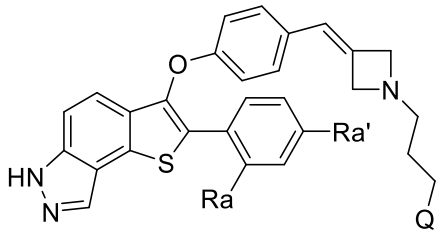


IX'

wherein: Q is H or F; Ra is CH_3, Cl or OMe; and Ra' is H, F or OH; or a pharmaceutically acceptable salt thereof.

25. The compound of claim 24, wherein Ra is CH_3 and Ra' is H.

26. The compound of claim 1, having a structure according to formula X':



X'

wherein: Q is H or F; Ra is CH_3, Cl or OMe; and Ra' is H, F or OH; or a pharmaceutically acceptable salt thereof.

27. The compound of claim 26, wherein Ra is CH_3 and Ra' is H.

28. A compound selected from:

1-(4-(2-(Ethylamino)ethyl)benzyl)-2-(4-methoxyphenyl)-3-methyl-1*H*-indol-5-ol;

1-(4-(2-(Cyclopropylamino)ethyl)benzyl)-2-(4-methoxyphenyl)-3-methyl-1*H*-indol-5-ol;

1-(4-(2-(Isopropylamino)ethyl)benzyl)-2-(4-methoxyphenyl)-3-methyl-1*H*-indol-5-ol;

1-(4-(2-(Cyclohexylamino)ethyl)benzyl)-2-(4-methoxyphenyl)-3-methyl-1H-indol-5-ol;

2-(4-Methoxyphenyl)-3-methyl-1-(4-(2-((2,2,2-trifluoroethyl)amino)ethyl)benzyl)-1*H*-indol-5-ol;

1-(4-(2-(Cyclopropylamino)ethyl)benzyl)-3-fluoro-2-(4-methoxyphenyl)-1*H*-indol-5-ol;

1-(4-(2-(Ethylamino)ethyl)benzyl)-3-fluoro-2-(4-methoxyphenyl)-1*H*-indol-5-ol;

3-Chloro-1-(4-(2-(ethylamino)ethyl)benzyl)-2-(4-methoxyphenyl)-1*H*-indol-5-ol;

1-(4-(2-(Cyclopropylamino)ethyl)benzyl)-3-fluoro-2-(o-tolyl)-1H-indol-5-ol;

3-Fluoro-2-(2-methoxyphenyl)-1-(4-(2-(propylamino)ethyl)benzyl)-1H-indol-5-ol;

1-(4-(2-(Cyclobutylamino)ethyl)benzyl)-2-(2,6-dimethylphenyl)-3-fluoro-1*H*-indol-5-ol;

2-(2,6-Dimethylphenyl)-1-(4-(2-(ethylamino)ethyl)benzyl)-3-fluoro-1*H*-indol-5-ol;

1-(4-(2-(Cyclopropylamino)ethyl)benzyl)-3-fluoro-2-(4-hydroxy-2-methylphenyl)-1*H*-indol-5-ol;

3-Fluoro-1-(4-(2-((2-fluoroethyl)amino)ethyl)benzyl)-2-(4-methoxy-2-methylphenyl)-1H-indol-5-ol;

3-Fluoro-1-(4-(2-((3-fluoropropyl)amino)ethyl)benzyl)-2-(4-methoxy-2-methylphenyl)-1H-indol-5-ol;

1-(4-(2-(Cyclopropylamino)ethyl)benzyl)-3-fluoro-2-(4-fluoro-2-methylphenyl)-1*H*-indol-5-ol;

3-Fluoro-2-(4-methoxy-2-methylphenyl)-1-(4-(2-(propylamino)ethyl)benzyl)-1H-indol-5-o;l

2-([1,1'-Biphenyl]-2-yl)-3-fluoro-1-(4-(2-(propylamino)ethyl)benzyl)-1H-indol-5-ol;

1-(4-(2-(Ethylamino)ethyl)benzyl)-3-fluoro-2-(o-tolyl)-1H-indol-5-ol;

1-(4-(2-(Cyclobutylamino)ethyl)benzyl)-3-fluoro-2-(o-tolyl)-1H-indol-5-ol;

3-Fluoro-1-(4-(2-(propylamino)ethyl)benzyl)-2-(o-tolyl)-1H-indol-5-ol;

1-(4-(2-(Butylamino)ethyl)benzyl)-3-fluoro-2-(o-tolyl)-1*H*-indol-5-ol;

3-Fluoro-1-(4-(2-((3-fluoropropyl)amino)ethyl)benzyl)-2-(o-tolyl)-1H-indol-5-ol;

3-Fluoro-1-(4-(2-((2-fluoroethyl)amino)ethyl)benzyl)-2-(o-tolyl)-1H-indol-5-ol;

1-(4-(2-(Cyclopropylamino)propyl)benzyl)-3-fluoro-2-(o-tolyl)-1H-indol-5-o;l

1-(4-(2-((Cyclopropylmethyl)amino)ethyl)benzyl)-3-fluoro-2-(2-(trifluoromethyl)phenyl)-1*H*-indol-5-ol;

1-(4-(2-(Cyclopropylamino)ethyl)benzyl)-3-fluoro-2-(2-(trifluoromethyl)phenyl)-1*H*-indol-5-ol;

1-(4-(2-(Ethylamino)ethyl)benzyl)-3-fluoro-2-(2-(trifluoromethyl)phenyl)-1H-indol-5-o;l

2-(2-Chlorophenyl)-1-(4-(2-(cyclopropylamino)ethyl)benzyl)-3-fluoro-1H-indol-5-ol;

N-Ethyl-2-(4-((8-fluoro-7-(o-tolyl)pyrrolo[3,2-e]indazol-6(3H)-yl)methyl)phenyl)ethan-1-amine;

N-(Cyclopropylmethyl)-2-(4-((8-fluoro-7-(o-tolyl)pyrrolo[3,2-e]indazol-6(3*H*)-yl)methyl)phenyl)ethan-1-amine;

N-(4-((8-Fluoro-7-(o-tolyl)pyrrolo[3,2-e]indazol-6(3*H*)-yl)methyl)phenethyl)cyclobutanamine;

N-(4-((8-Fluoro-7-(o-tolyl)pyrrolo[3,2-e]indazol-6(3*H*)-yl)methyl)phenethyl)cyclopropanamine;

N-(4-((8-fluoro-7-(o-tolyl)pyrrolo[3,2-e]indazol-6(3*H*)-yl)methyl)phenethyl)propan-1-amine;

3-Fluoro-*N*-(4-((8-fluoro-7-(o-tolyl)pyrrolo[3,2-e]indazol-6(3*H*)-yl)methyl)phenethyl)propan-1-amine;

(5R,6S)-5-(4-(2-(Ethylamino)ethyl)phenyl)-6-phenyl-5,6,7,8-tetrahydronaphthalen-2-ol;

(5R,6S)-5-(4-(2-((Cyclopropylmethyl)amino)ethyl)phenyl)-6-phenyl-5,6,7,8-tetrahydronaphthalen-2-ol;

(5R,6S)-5-(4-(2-(Ethylamino)ethyl)phenyl)-6-(o-tolyl)-5,6,7,8-tetrahydronaphthalen-2-ol;

(5R,6S)-5-(4-(2-((cyclopropylmethyl)amino)ethyl)phenyl)-6-(o-tolyl)-5,6,7,8-tetrahydronaphthalen-2-ol;

5-(4-(2-(Ethylamino)ethyl)phenyl)-6-(4-isopropylphenyl)-5,6,7,8-tetrahydronaphthalen-2-ol;
6-(4-Isopropylphenyl)-5-(4-(2-(propylamino)ethyl)phenyl)-5,6,7,8-tetrahydronaphthalen-2-ol;
5-(4-(2-((Cyclopropylmethyl)amino)ethyl)phenyl)-6-(4-isopropylphenyl)-5,6,7,8-tetrahydronaphthalen-2-ol;
3-(4-(2-(Cyclopropylamino)ethyl)phenoxy)-2-(o-tolyl)benzo[b]thiophen-6-ol;
3-(4-(2-((Cyclopropylmethyl)amino)ethyl)phenoxy)-2-(o-tolyl)benzo[b]thiophen-6-ol;
3-(4-((1-Propylazetidin-3-ylidene)methyl)phenoxy)-2-(o-tolyl)benzo[*b*]thiophen-6-ol;
1-(4-(2-((Cyclopropylmethyl)amino)ethyl)benzyl)-2-(4-methoxyphenyl)-3-methyl-1H-indol-5-ol;
1-(4-(2-((Cyclopropylmethyl)amino)ethyl)benzyl)-3-fluoro-2-(o-tolyl)-1H-indol-5-ol;
2-Fluoro-N-(4-((8-fluoro-7-(o-tolyl)pyrrolo[3,2-e]indazol-6(3H)yl)methyl)phenethyl)ethan-1-amine;
5-(4-(2-(Cyclopropylamino)ethyl)benzyl)-4-(o-tolyl)-2,3-dihydrobenzo[*b*]oxepin-8-ol; and
5-(4-(2-(Ethylamino)ethyl)benzyl)-4-(o-tolyl)-2,3-dihydrobenzo[*b*]oxepin-8-ol.

29. A pharmaceutical composition comprising a compound of any one of claims 1-28 and a pharmaceutically acceptable excipient.

30. Use of a compound of any one of claims 1-28 or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating a disease, syndrome, illness, or symptom associated with insufficient or overabundant estrogen levels in a mammal in need thereof.

31. Use of a compound of any one of claims 1-28 or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating a cancer selected from the group consisting of prostate cancer, breast cancer, endometrial cancer, lung cancer, hepatocellular cancer, lymphoma, multiple endocrine neoplasia, vaginal cancer, renal cancer, thyroid cancer, testicular cancer, leukemia, and ovarian cancer in a mammal in need thereof.

32. A compound of any one of claims 1-28 or a pharmaceutically acceptable salt thereof for use in therapy.