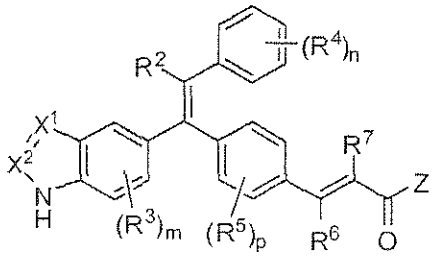
α dysfunction associated with cancer (e.g. bone cancer, breast cancer, colorectal cancer, endometrial cancer, prostate cancer, ovarian and uterine cancer), leiomyoma (e.g. uterine leiomyoma), central nervous system (CNS) defects (e.g. alcoholism, migraine), cardiovascular system defects (e.g. aortic aneurysm, susceptibility to myocardial infarction, aortic valve sclerosis, cardiovascular disease, coronary artery disease, hypertension), hematological system defects (e.g. deep vein thrombosis), immune and inflammation diseases (e.g. Graves' Disease, arthritis, mulitple sclerosis, cirrhosis), susceptibility to infection (e.g. hepatitis B, chronic liver disease), metabolic defects (e.g. bone density, cholestasis, hypospadias, obesity, osteoarthritis, osteopenia, osteoporosis), neurological defects (e.g. Alzheimer's disease, Parkinson's disease, migraine, vertigo), psychiatric defects (e.g. anorexia nervosa, attention deficity hyperactivity disorder (ADHD), dementia, major depressive disorder, psychosis) and reproductive defects (e.g. age of menarche, endometriosis, infertility).

[0007] In one aspect, described herein are compounds of Formula (I), pharmaceutically acceptable salts, solvates, metabolites and prodrugs thereof. Compounds of Formula (I) are estrogen receptor modulators. In some embodiments, the compound of Formula (I) is an estrogen receptor antagonist. In some embodiments, the compound of Formula (I) is an estrogen receptor degrader. In some embodiments, the compound of Formula (I) is an estrogen receptor antagonist as well as an estrogen receptor degrader. In some embodiments, the compound of Formula (I) displays miminal or no estrogen receptor agonist activity. In some embodiments, in the context of treating cancers, the compound of Formula (I) 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.

[0007a] In one aspect, there is provided a compound that has the structure of Formula (XII):



Formula (XII)

wherein,

X^1 is CH, CR^3 or N;

X^2 is N, CH, or CR^3;

Z is -OH or $-OR^{10}$;

R^2 is C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4deuteroalkyl, C_3-C_6cycloalkyl, or -C_1-C_4alkylene-W;

W is hydroxy, halogen, CN, C_1-C_4alkyl, C_1-C_4haloalkyl, C_1-C_4alkoxy, C_1-C_4haloalkoxy, and C_3-C_6cycloalkyl;

each R^3 is independently halogen, C_1-C_4alkyl, or C_1-C_4fluoroalkyl;

each R^4 is independently halogen, -CN, $-OR^9$, $-S(=O)_2R^{10}$, C_1-C_4alkyl, C_1-C_4fluoroalkyl, or C_1-C_4heteroalkyl;

each R^5 is independently halogen, -CN, $-OR^9$, $-S(=O)_2R^{10}$, C_1-C_4alkyl, C_1-C_4fluoroalkyl, or C_1-C_4heteroalkyl;

R^6 is H, C_1-C_4alkyl, or halogen;

R^7 is H, C_1-C_4alkyl, or halogen;

R^9 is H, C_1-C_6alkyl, C_1-C_6fluoroalkyl, or C_3-C_6cycloalkyl;

R^{10} is C_1-C_6alkyl;

m is 0, 1, or 2;

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

p is 0, 1, or 2;

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

[0007b] In one aspect, there is provided a pharmaceutically acceptable salt of a compound as defined above.

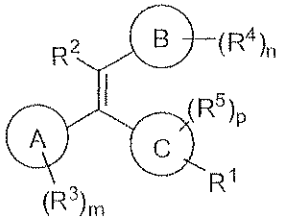
[0007c] In one aspect, there is provided a pharmaceutical composition comprising a compound as defined above, or a pharmaceutically acceptable salt, or N-oxide thereof and at least one pharmaceutically acceptable inactive ingredient.

[0007d] In one aspect, there is provided a compound as defined above, or a pharmaceutically acceptable salt, or N-oxide thereof, for use in medicine.

[0007e] In one aspect, there is provided a compound as defined above, or a pharmaceutically acceptable salt, or N-oxide thereof, for use in the treatment of cancer in a mammal.

[0007f] In one aspect, there is provided a compound as defined above, or a pharmaceutically acceptable salt, or N-oxide thereof, for use in the treatment of bone cancer, breast cancer, colorectal cancer, endometrial cancer, prostate cancer, ovarian cancer, uterine cancer, cervical cancer, lung cancer, leiomyoma, uterine leiomyoma, alcoholism, migraine, aortic aneurysm, susceptibility to myocardial infarction, aortic valve sclerosis, cardiovascular disease, coronary artery disease, hypertension, deep vein thrombosis, Graves' Disease, arthritis, multiple sclerosis, cirrhosis, hepatitis B, chronic liver disease, bone density, cholestasis, hypospadias, obesity, osteoarthritis, osteopenia, osteoporosis, Alzheimer's disease, Parkinson's disease, migraine, vertigo, anorexia nervosa, attention deficit hyperactivity disorder (ADHD), dementia, major depressive disorder, psychosis, age of menarche, endometriosis, or infertility in a mammal.

[0008] In one aspect, provided herein is a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, metabolite or prodrug thereof:



Formula (I)

wherein,

ring A is indanyl, indenyl, naphthyl, 5- or 6-membered monocyclic heteroaryl, or 8-, 9- or 10-membered bicyclic heterocycle;

ring B is phenyl, indanyl, indenyl, naphthyl, 5- or 6-membered monocyclic heteroaryl or 8-, 9- or 10-membered bicyclic heterocycle;

ring C is phenyl, indanyl, indenyl, naphthyl, 5- or 6-membered monocyclic heteroaryl or 8-, 9- or 10-membered bicyclic heterocycle;

R^1 is Y, -X-C_1-C_6alkylene-Y, -C_1-C_6alkylene-Y, -C_2-C_6alkynylene-Y, -C(R^6)=C(R^7)-Y, -X-C_1-C_6alkynylene-Y, -X-C_3-C_6cycloalkylene-Y or –C_3-C_6cycloalkylene-Y;

X is NR^8, O, S, S(=O) or $S(=O)_2$;