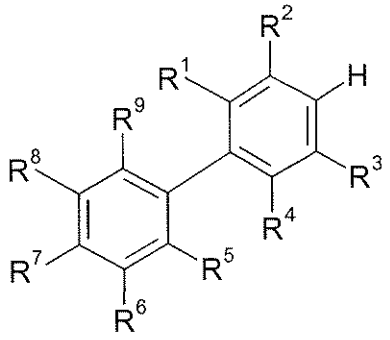
Claims

1. A compound of formula (I) or a pharmaceutically acceptable ester, amide, carbamate or salt thereof, including a salt of such an ester, amide or carbamate



(I)

in which

R^1 is selected from the group consisting of optionally substituted 5-10 membered heterocyclyl, optionally substituted phenyl, optionally substituted naphthyl, optionally substituted C_{3-8}cycloalkyl, optionally substituted C_{5-6}cycloalkenyl, optionally substituted phenylC_{2-4}alkenyl, C_{2-8}alkenyl, haloC_{2-8}alkenyl, dihaloC_{2-8}alkenyl, trihaloC_{2-8}alkenyl, and C_{3-8}cycloalkylC_{2-4}alkenyl, wherein when said heterocyclyl, phenyl or naphthyl group or part of group is substituted, it is substituted with from 1 to 5 substituents, each substituent being independently selected from the group consisting of OR^A, $N(R^B)_2$, halogen, cyano, nitro, -C(O)C_{1-4}alkyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, haloC_{1-6} alkyl, dihaloC_{1-6}alkyl and trihaloC_{1-6}alkyl, and when said C_{3-8}cycloalkyl or C_{5-6}cycloalkenyl group is substituted, it is substituted with 1, 2 or 3 substituents selected from C_{1-5}alkyl, C_{1-5}alkenyl , C_{1-5}alkynyl, C_{1-5}alkyl substituted with up to 3 halogen atoms, -CO-C_{1-5}alkyl, and halogen;

R^2 is selected from the group consisting of -C(NH_2)=N-OH, -C(O)N(R^C)$_2$, cyano, -CHO, -CH=N-OH, -C(O)NH-OH, -C(CO_2H)=N-OH, -C(O-C_{1-4}alkyl)=NH, -C(NH_2)=N-NH_2, -C(O)-C(O)-NH_2, -C(O)CO_2H, -CO_2H, -CH_2-CO_2H, -CH(OH)CO_2H, -CH_2NH-$CONH_2$, ~~-~~C_{1-6}alkyl-NH_2, ~~C_{1-6}alkyl-OH,~~ CH_2SO_3H, -NH-C(NH_2)=NH, -NH-C(O)NH_2, -N=C(-NH-CH_2CH_2-NH-), ~~$N(R^B)_2$, $N(OH)_2$,~~ $NHSO_2R^D$, -S-CN, -S-C(NH_2)=NH, -S-C(NH_2)=N-OH, $SO_2N(R^E)_2$, SO_3H, cyanoC_{1-6}alkyl~~-~~, and optionally substituted 5-10 membered heterocyclyl containing from one to three nitrogen atoms, wherein when said heterocyclyl group is substituted, it is substituted with from 1 to 3 substituents, each substituent being independently selected from the group consisting of OR^A, $N(R^B)_2$, halogen, cyano, nitro, -C(O)C_{1-4}alkyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, haloC_{1-6} alkyl, dihaloC_{1-6}alkyl and trihaloC_{1-6}alkyl;

3. A compound as claimed in claim 2, in which R^1 is selected from the group consisting of optionally substituted 5-10 membered heterocyclyl, optionally substituted phenyl, optionally substituted naphthyl, optionally substituted C_{5-6}cycloalkenyl, optionally substituted phenylC_{2-4}alkenyl, C_{2-8}alkenyl, C_{3-8}cycloalkyl, and C_{3-8}cycloalkylC_{2-4}alkenyl, wherein when said heterocyclyl or phenyl or naphthyl group or part of group is substituted, it is substituted with from 1 to 5 substituents, each substituent being independently selected from the group consisting of OR^A, halogen, C_{1-6}alkyl, haloC_{1-6} alkyl, dihaloC_{1-6}alkyl and trihaloC_{1-6}alkyl, and wherein where said optionally substituted C_{5-6}cycloalkenyl group is substituted, it is substituted with 1 or two substituents selected from halogen atoms and methyl groups.

4. A compound as claimed in any one of the preceding claims, in which R^1 represents an optionally substituted isoxazolyl, isothiazolyl, pyrrolyl, pyrazolyl, pyridyl or pyrrolidinyl group.

5. A compound as claimed in any one of the preceding claims, in which R^2 is selected from the group consisting of -C(NH_2)=N-OH, -C(O)N(R^C)$_2$, cyano, -CHO, -CH=N-OH, -C(O)NH-OH, -C(CO_2H)=N-OH, -C(O-C_{1-4}alkyl)=NH, -C(NH_2)=N-NH_2, -C(O)-C(O)-NH_2, -CH_2NH-$CONH_2$, -C_{1-6}alkyl-NH_2, -NH-C(NH_2)=NH, -NH-C(O)NH_2, -N=C(-NH-CH_2CH_2-NH-), ~~N(OH)$_2$~~, -S-CN, -S-C(NH_2)=NH, -S-C(NH_2)=N-OH, cyanoC_{1-6}alkyl-, and an optionally substituted 5-6 membered heterocyclyl containing from one to three nitrogen atoms; wherein when said heterocyclyl group is substituted, it is substituted with from 1 to 3 substituents, each substituent being independently selected from the group consisting of OH, halogen, cyano, nitro, C_{1-4}alkyl, haloC_{1-4} alkyl, dihaloC_{1-4}alkyl and trihaloC_{1-4}alkyl.

6. A compound as claimed in claim 5, in which R^2 represents -C(NH_2)=N-OH, -C(O)NH_2, -CH=N-OH, cyano, or pyrazolyl.

7. A compound as claimed in any one of the preceding claims, in which R^3 is selected from the group consisting of hydrogen, halogen, cyano, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkylC_{1-6}alkyl, haloC_{1-6}alkyl, dihaloC_{1-6}alkyl, trihaloC_{1-6}alkyl, phenyl, and phenylC_{1-4}alkyl.

8. A compound as claimed in claim 7, in which R^3 represents halogen, cyano, C_{1-6}alkyl, C_{2-6}alkenyl, trihaloC_{1-6}alkyl, phenyl, or phenylC_{1-2}alkyl.

9. A compound as claimed in any one of the preceding claims, in which each of R^5, R^6, R^8 and R^9 is independently selected from the group consisting of hydrogen, OR^A, N(R^B)$_2$, halogen, cyano, nitro, C_{1-6}alkyl, haloC_{1-6} alkyl, dihaloC_{1-6}alkyl and trihaloC_{1-6}alkyl.

3'-chloro-2-(3,5-dimethylisoxazol-4-yl)-5'-fluoro-N',4'-dihydroxy-5-(trifluoromethyl)-[1,1'-biphenyl]-3-carboximidamide

3-chloro-3",5,5"-trifluoro-N',4-dihydroxy-5'-(trifluoromethyl)-[1,1':2',1"-terphenyl]-3'-carboximidamide

3-chloro-5,5"-difluoro-N',4-dihydroxy-2"-methoxy-5'-(trifluoromethyl)-[1,1':2',1"-terphenyl]-3'-carboximidamide

3-chloro-5-fluoro-N',4-dihydroxy-2"-methoxy-5'-(trifluoromethyl)-[1,1':2',1"-terphenyl]-3'-carboximidamide

5'-chloro-3",5"-difluoro-N'-hydroxy-4-methoxy-3-methyl-[1,1':2',1"-terphenyl]-3'-carboximidamide

5'-chloro-3",5"-difluoro-N',4-dihydroxy-3-methyl-[1,1':2',1"-terphenyl]-3'-carboximidamide

5-chloro-2-(3,5-dimethylisoxazol-4-yl)-N',4'-dihydroxy-3'-methyl-[1,1'-biphenyl]-3-carboximidamide

5'-chloro-N',4-dihydroxy-2",3-dimethyl-[1,1':2',1"-terphenyl]-3'-carboximidamide

5'-chloro-5"-fluoro-N',4-dihydroxy-2"-methoxy-3-methyl-[1,1':2',1"-terphenyl]-3'-carboximidamide

5'-chloro-5"-fluoro-4-hydroxy-2"-methoxy-3-methyl-[1,1':2',1"-terphenyl]-3'-carboxamide

5'-chloro-3",5"-difluoro-N',4-dihydroxy-3-isopropyl-[1,1':2',1"-terphenyl]-3'-carboximidamide

2'-(3,5-dimethylisoxazol-4-yl)-3'-(1H-1,2,3-triazol-4-yl)-5'-(trifluoromethyl)-[1,1'-biphenyl]-4-ol

N',4-dihydroxy-5'-(trifluoromethoxy)-[1,1':2',1"-terphenyl]-3'-carboximidamide

3",5"-difluoro-N',4-dihydroxy-5'-(trifluoromethoxy)-[1,1':2',1"-terphenyl]-3'-carboximidamide

5"-chloro-N',4-dihydroxy-2"-methoxy-5'-(trifluoromethoxy)-[1,1':2',1"-terphenyl]-3'-carboximidamide

4-hydroxy-5'-(trifluoromethoxy)-[1,1':2',1"-terphenyl]-3'-carboxamide

3",5"-difluoro-4-hydroxy-5'-(trifluoromethoxy)-[1,1':2',1"-terphenyl]-3'-carboxamide

N',4-dihydroxy-5'-isopropyl-[1,1':2',1"-terphenyl]-3'-carboximidamide

3",5"-difluoro-N',4-dihydroxy-5'-isopropyl-[1,1':2',1"-terphenyl]-3'-carboximidamide

5"-chloro-N',4-dihydroxy-5'-isopropyl-2"-methoxy-[1,1':2',1"-terphenyl]-3'-carboximidamide

4-amino-5'-isopropyl-[1,1':2',1"-terphenyl]-3'-carboxamide

3",5"-difluoro-4-hydroxy-5'-isopropyl-[1,1':2',1"-terphenyl]-3'-carboxamide

2-(3-cyanofuran-2-yl)-N',4'-dihydroxy-5-(trifluoromethyl)-[1,1'-biphenyl]-3-carboximidamide

2-(4-cyano-1-methyl-1H-pyrazol-5-yl)-N',4'-dihydroxy-5-(trifluoromethyl)-[1,1'-biphenyl]-3-carboximidamide

2"-cyano-N',4-dihydroxy-5'-(trifluoromethyl)-[1,1':2',1"-terphenyl]-3'-carboximidamide

2-(3-cyano-1-methyl-1H-pyrrol-2-yl)-N',4'-dihydroxy-5-(trifluoromethyl)-[1,1'-biphenyl]-3-carboximidamide

~~2'-(3,5-dimethylisoxazol-4-yl)-3'-(hydroxymethyl)-5'-(trifluoromethyl)-[1,1'-biphenyl]-4-ol~~

5'-cyano-3",5"-difluoro-N',4-dihydroxy-[1,1':2',1"-terphenyl]-3'-carboximidamide

N',4'-dihydroxy-2-(pyrrolidin-1-yl)-5-(trifluoromethyl)-[1,1'-biphenyl]-3-carboximidamide

4-chloro-3',5'-difluoro-N'-hydroxy-6-(1H-indazol-5-yl)-[1,1'-biphenyl]-2-carboximidamide

6-(1H-benzo[d]imidazol-5-yl)-4-chloro-3',5'-difluoro-N'-hydroxy-[1,1'-biphenyl]-2-carboximidamide

4-chloro-3',5'-difluoro-N'-hydroxy-6-(1H-indol-5-yl)-[1,1'-biphenyl]-2-carboximidamide

17. The compound as claimed in any one of claims 1 to 16 together with a further therapeutic agent, for simultaneous, sequential or separate administration.

18. A pharmaceutical composition which comprises a compound as claimed in any one of claims 1 to 16, together with a pharmaceutically acceptable carrier.

19. The compound as claimed in any one of claims 1 to 17, or the composition as claimed in claim 18, for use as a medicament.

20. The compound as claimed in any one of claims 1 to 17, or the composition as claimed in claim 18, for use in the treatment or prophylaxis of a condition associated with a disease or disorder associated with estrogen receptor activity.

21. Use of a compound as claimed in any one of claims 1 to 17, for the manufacture of a medicament for the treatment or prophylaxis of a condition associated with a disease or disorder associated with estrogen receptor activity.

~~22. A method for the treatment or prophylaxis of a disease or disorder associated with estrogen receptor activity in a mammal, which comprises administering to the mammal a therapeutically effective amount of a compound as claimed in any one of claims 1 to 17 or a composition as claimed in claim 18.~~

~~23~~22. Use of a compound as claimed in any one of claims 1 to 16 in labelled form as a diagnostic agent for the diagnosis of conditions associated with a disease or disorder associated with estrogen receptor activity.

~~24~~23. Use of a compound as claimed in any one of claims 1 to 16 or a labelled form of such a compound as a reference compound in a method of identifying ligands for the estrogen receptor.

~~25~~24. A compound or composition as claimed in claim 20, or a use as claimed in claim 21 or ~~23~~22, ~~or a method as claimed in claim 22,~~ wherein the condition associated with a disease or disorder associated with estrogen receptor activity is selected from bone loss, bone fractures, osteoporosis, cartilage degeneration, endometriosis, uterine fibroid disease, hot flushes, increased levels of LDL cholesterol, cardiovascular disease, impairment of cognitive functioning, age-related mild cognitive impairment, cerebral degenerative disorders, restenosis, gynecomastia, vascular smooth muscle cell proliferation, obesity, incontinence, anxiety, depression, perimenopausal depression, post-partum depression, premenstrual syndrome, manic depression, dementia, obsessive compulsive behavior, attention deficit disorder,

attention deficit hyperactivity disorder, sleep disorders, irritability, impulsivity, anger management, hearing disorders, multiple sclerosis, Parkinson's disease, Alzheimer's disease, Huntington's disease, amyotrophic lateral sclerosis, spinal cord injury, stroke, autoimmune disease, inflammation, IBD, IBS, sexual dysfunction, hypertension, retinal degeneration, lung cancer, colon cancer, breast cancer, uterus cancer, prostate cancer, the bile duct cancer form named cholangiocarcinoma, benign prostatic hyperplasia, lower urinary tract symptoms, overactive bladder, interstitial cystitis, painful bladder symptoms, vaginal atrophy, wound healing, chronic pain, sepsis, inflammatory and neuropathic pain, ovarian cancer, melanoma, lymphoma, atherosclerosis, left ventricular hypertrophy, congestive heart failure, mesothelioma, gallbladder cancer and extra-hepatic cholangiocarcinoma.

~~26~~25. A compound or composition as claimed in claim 20, or a use as claimed in claim 21 or ~~23~~22~~, or a method as claimed in claim 22~~, wherein the condition associated with a disease or disorder associated with estrogen receptor activity is selected from bone loss, bone fractures, osteoporosis, cartilage degeneration, endometriosis, uterine fibroid disease, hot flushes, increased levels of LDL cholesterol, cardiovascular disease, restenosis, gynecomastia, vascular smooth muscle cell proliferation, obesity, incontinence, anxiety, depression, perimenopausal depression, post-partum depression, premenstrual syndrome, manic depression, dementia, obsessive compulsive behavior, attention deficit disorder, attention deficit hyperactivity disorder, sleep disorders, irritability, impulsivity, anger management, hearing disorders, spinal cord injury, stroke, autoimmune disease, inflammation, IBD, IBS, sexual dysfunction, hypertension, retinal degeneration, lung cancer, colon cancer, breast cancer, uterus cancer, prostate cancer, the bile duct cancer form named cholangiocarcinoma, benign prostatic hyperplasia, lower urinary tract symptoms, overactive bladder, interstitial cystitis, painful bladder symptoms, vaginal atrophy, wound healing, chronic pain, sepsis, inflammatory and neuropathic pain, ovarian cancer, melanoma, lymphoma, atherosclerosis, left ventricular hypertrophy, congestive heart failure, mesothelioma, gallbladder cancer and extra-hepatic cholangiocarcinoma.