The efficacy of the natural estrogen, 17β-estradiol, for the treatment of various forms of depressive illness has also been demonstrated and it has been suggested that the anti-depressant activity of estrogen may be mediated via regulation of tryptophan hydroxylase activity and subsequent serotonin synthesis (See, e.g., Lu N Z, Shlaes T A, Cundlah C, Dziennis S E, Lyle R E, Bethea C L, "Ovarian steroid action on tryptophan hydroxylase protein and serotonin compared to localization of ovarian steroid receptors in midbrain of guinea pigs." Endocrine 11:257-267, 1999). The pleiotropic nature of natural estrogen precludes its widespread, more chronic use due to the increased risk of proliferative effects on breast, uterine and ovarian tissues. The identification of the estrogen receptor, ERβ, has provided a means by which to identify more selective estrogen agents which have the desired anti-depressant activity in the absence of the proliferative effects which are mediated by ERα. Thus, it has been shown that therapeutic agents having ERβ-selectivity are potentially effective in the treatment of depression.

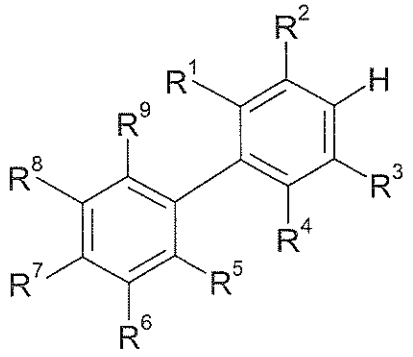
What is needed in the art are compounds that can produce the same positive responses as estrogen replacement therapy without the negative side effects. Also needed are estrogen-like compounds that exert selective effects on different tissues of the body.

The synthesis of a series of polysubstituted biphenyl compounds and their binding affinity towards the human recombinant estrogen receptor alpha is disclosed in D. Lesuisse et al, *Bioorg. Med. Chem. Lett.*, **2001**, *11*, 1709-1712. A series of 4-hydroxy-biphenyl-carbaldehyde oxime derivatives and their binding affinity towards the estrogen receptor (ER) subtypes ERα and ERβ is disclosed in C. Yang et al, *Bioorg. Med. Chem. Lett.*, **2004**, *12*, 2553-2570 and also in WO 2004/099122. Further aryl-carbaldehyde oxime derivatives and their use as estrogenic agents are described in WO 2004/103941. Certain other biphenyl compounds and their use in the treatment of multiple sclerosis are disclosed in WO 2006/105442.

The compounds of the present invention are ligands for estrogen receptors and as such may be useful for treatment or prevention of a variety of conditions related to estrogen functioning.

Summary of the Invention

In one aspect, there is provided a compound of formula (I) or a pharmaceutically acceptable salt thereof



(I)

in which

R^1 is selected from the group consisting of optionally substituted 5-10 membered heterocyclyl containing one or more oxygen, nitrogen and/or sulphur atoms, 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, -CH_2SO_3H, -NH-C(NH_2)=NH, -NH-C(O)NH_2, -N=C(-NH-CH_2CH_2-NH-), $NHSO_2R^D$, -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;

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, optionally substituted phenyl, optionally substituted phenylC_{1-4}alkyl, optionally substituted 5-10 membered heterocyclyl containing one or more oxygen, nitrogen and/or sulphur atoms, and optionally substituted

5-10 membered heterocyclylC_{1-4}alkyl, the heterocyclyl part of the group containing one or more oxygen, nitrogen and/or sulphur atoms, wherein when said phenyl or heterocyclyl 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_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, haloC_{1-6}alkyl, dihaloC_{1-6}alkyl and trihaloC_{1-6}alkyl;

R^4 is selected from the group consisting of hydrogen, halogen, cyano, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, and haloC_{1-6}alkyl, dihaloC_{1-6}alkyl, and trihaloC_{1-6}alkyl;

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(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;

R^7 is OR^A;

or R^6 and R^7 may, together with the atoms they are attached to, form a 5-, 6- or 7- membered cyclic group optionally containing one to three heteroatoms selected from O, N and S, said 5-, 6- or 7- membered cyclic group being optionally substituted with one of more groups selected from OR^A, cyano, nitro, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halo C_{1-6} alkyl, dihalo C_{1-6} alkyl and trihalo C_{1-6} alkyl; and

each R^A, each R^B, each R^C, each R^D and each R^E is independently selected from the group consisting of hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl and C_{3-8}cycloalkylC_{1-6}alkyl; each optionally substituted by from 1 to 3 halogen atoms.

Also disclosed is ~~This invention provides~~ 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

substituent being independently selected from the group consisting of OR^A, $N(R^B)_2$, halogen cyano, nitro, 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;

R^4 is selected from the group consisting of hydrogen, halogen, cyano, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, and haloC_{1-6}alkyl, dihaloC_{1-6}alkyl, and trihaloC_{1-6}alkyl;

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(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;

R^7 is OR^A;

or R^6 and R^7 may, together with the atoms they are attached to, form a 5-, 6- or 7- membered cyclic group optionally containing one to three heteroatoms selected from O, N and S, said 5-, 6- or 7- membered cyclic group being optionally substituted with one of more groups selected from OR^A, cyano, nitro, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halo C_{1-6} alkyl, dihalo C_{1-6} alkyl and trihalo C_{1-6} alkyl; and

each R^A, each R^B, each R^C, each R^D and each R^E is independently selected from the group consisting of hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl and C_{3-8}cycloalkylC_{1-6}alkyl; each optionally substituted by from 1 to 3 halogen atoms.

In another aspect, there is provided a pharmaceutical composition which comprises a compound as described herein, together with a pharmaceutically acceptable carrier.

In yet another aspect, there is provided the compound as described herein, or the composition as described herein, for use as a medicament.

In yet another aspect, there is provided the compound as described herein, or the composition as described herein, for use in the treatment or prophylaxis of a condition associated with a disease or disorder associated with estrogen receptor activity.

In yet another aspect, there is provided the use of a compound as described herein, 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, wherein the condition associated with a disease or disorder associated with estrogen receptor activity is selected from the group consisting of bone fractures, osteoporosis, cartilage degeneration, endometriosis, uterine fibroid disease, hot flushes, 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.

In yet another aspect, there is provided the use of a compound as described herein, 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, wherein the condition associated with a disease or disorder associated with estrogen receptor activity is selected from the group consisting of bone fractures, osteoporosis, cartilage degeneration, endometriosis, uterine fibroid disease, hot flushes, 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.

In yet another aspect, there is provided the in vitro use of a compound as described herein in labelled form as a diagnostic agent for the diagnosis of conditions associated with a disease or disorder associated with estrogen receptor activity.

In yet another aspect, there is provided the use of a compound as described herein or a labelled form of such a compound as a reference compound in a method of identifying ligands for the estrogen receptor.

Compounds of the invention have surprisingly been found to be ligands of the estrogen receptor. The compounds accordingly have use in the treatment or prophylaxis of conditions associated with estrogen receptor activity.

Detailed Description of Invention

The compounds of the invention may contain chiral (asymmetric) centers or the molecule as a whole may be chiral. The individual stereoisomers (enantiomers and diastereoisomers) and mixtures of these are within the scope of the present invention.

Certain compounds of the invention contain an oxime group which may be present as the (E) or (Z) oxime isomer. The individual (E) and (Z) oxime isomers and mixtures of these are within the scope of the present invention. Throughout the specification, where the oxime structure is shown with a wavy line bond, this indicates either that a single isomer is present but the stereochemistry is unknown, or that a mixture of both isomers is present.

degeneration, endometriosis, uterine fibroid disease, hot flushes, 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.

23. In vitro use~~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. The use of claim 23 for *in vitro* use.~~

2425. 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.

2526. A compound or composition as claimed in claim 20, or a use as claimed in claim 23, wherein the condition associated with a disease or disorder associated with estrogen receptor activity is selected from the group consisting of bone fractures, osteoporosis, cartilage degeneration, endometriosis, uterine fibroid disease, hot flushes, 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.

2627. A compound or composition as claimed in claim 20, or a use as claimed in claim 23, wherein the condition associated with a disease or disorder associated with estrogen receptor activity is selected from the group consisting of bone fractures, osteoporosis, cartilage degeneration, endometriosis, uterine fibroid disease, hot flushes, 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.