(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
15 October 2009 (15.10.2009)

PCT

(10) International Publication Number
WO 2009/124968 A1

(51) International Patent Classification:
A61K 31/343 (2006.01) *A61K 31/443* (2006.01)
C07D 307/80 (2006.01) *A61K 31/4709* (2006.01)
A61K 31/381 (2006.01) *C07D 405/04* (2006.01)
A61K 31/4025 (2006.01) *C07D 407/04* (2006.01)
A61K 31/4155 (2006.01) *C07D 409/04* (2006.01)
A61K 31/416 (2006.01) *C07D 417/04* (2006.01)
A61K 31/427 (2006.01) *A61P 35/00* (2006.01)

(21) International Application Number:
PCT/EP2009/054220

(22) International Filing Date:
8 April 2009 (08.04.2009)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0806656.5 11 April 2008 (11.04.2008) GB

(71) Applicant *(for all designated States except US)*: **KARO BIO AB** [SE/SE]; Novum, S-141 57 Huddinge (SE).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **NÖTEBERG, Daniel** [SE/SE]; c/o Karo Bio AB, Novum, S-141 57 Huddinge (SE). **KALLIN, Elisabet** [SE/SE]; c/o Karo Bio AB, Novum, S-141 57 Huddinge (SE). **WENNERSTÅL, Mattias** [SE/SE]; c/o Karo Bio AB, Novum, S-141 57 Huddinge (SE).

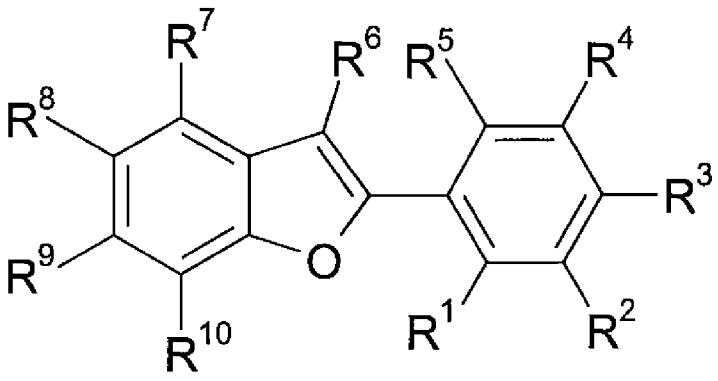
(74) Agents: **SCOTT, Susan Margaret** et al.; Abel & Imray, 20 Red Lion Street, London WC1R 4PQ (GB).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report (Art. 21(3))*

(54) Title: NOVEL ESTROGEN RECEPTOR LIGANDS



(I)

(57) Abstract: The invention provides a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable ester, amide, solvate or salt thereof, including a salt of such an ester or amide, and a solvate of such an ester, amide or salt: wherein R^3 is selected from the group consisting of OR^A; -CHO; -C(O)C_{1-4}alkyl; -C(O)phenyl; -O-C(O)R^A; and N(R^B)2; R^6 is selected from certain cyclic groups defined in the specification; and the remaining groups are defined in the specification; together with a pharmaceutically acceptable carrier. Most of the compounds are novel. The invention also provides the use of such compounds in the treatment or prophylaxis of a condition associated with a disease or disorder associated with estrogen receptor activity.

WO 2009/124968 A1

Novel Estrogen Receptor Ligands

Field of Invention

This invention relates to compounds which are estrogen receptor ligands and are preferably selective for the estrogen receptor β isoform, to methods of preparing such compounds and to methods for using such compounds in treatment of diseases related to the estrogen receptor such as depressive disorders, anxiety disorders, Alzheimer's disease, cognitive disorders, osteoporosis, elevated blood triglyceride levels, atherosclerosis, endometriosis, urinary incontinence, autoimmune disease, and cancer of the lung, colon, breast, uterus and prostate.

Background of Invention

The estrogen receptor (ER) is a ligand activated mammalian transcription factor involved in the up and down regulation of gene expression. The natural hormone for the estrogen receptor is β-17-estradiol (E2) and closely related metabolites. Binding of estradiol to the estrogen receptor causes a dimerization of the receptor and the dimer in turn binds to estrogen response elements (ERE's) on DNA. The ER/DNA complex recruits other transcription factors responsible for the transcription of DNA downstream from the ERE into mRNA which is eventually translated into protein. Alternatively the interaction of ER with DNA may be indirect through the intermediacy of other transcription factors, most notably fos and jun. Since the expression of a large number of genes is regulated by the estrogen receptor and since the estrogen receptor is expressed in many cell types, modulation of the estrogen receptor through binding of either natural hormones or synthetic ER ligands can have profound effects on the physiology and pathophysiology of the organism.

Historically it has been believed there was only one estrogen receptor. However a second subtype (ER-β) has been discovered. While both the "classical" ER-α and the more recently discovered ER-β are widely distributed in different tissues, they nevertheless display markedly different cell type and tissue distributions. Therefore synthetic ligands which are either ER-α or ER-β selective may preserve the beneficial effects of estrogen while reducing the risk of undesirable side effects.

Estrogens are critical for sexual development in females. In addition, estrogens play an important role in maintaining bone density, regulation of blood lipid levels, and appear to have

neuroprotective effects. Consequently decreased estrogen production in post-menopausal women is associated with a number of diseases such as osteoporosis, atherosclerosis, depression and cognitive disorders. Conversely certain types of proliferative diseases such as breast and uterine cancer and endometriosis are stimulated by estrogens and therefore antiestrogens (*i.e.*, estrogen antagonists) have utility in the prevention and treatment of these types of disorders.

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 preclude 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 particularly effective in the treatment of depression.

Certain benzofuran compounds are known *per se* from European Journal of Organic Chemistry, 2005, (12), 2481-2490; Australian Journal of Chemistry 1999, 52(8), 767-774; Bulletin de la Societe Chimique de France, 1974, (9,-10 pt. 2), 2225-2232; and Comptes Rendus des Seances de l'Academie des Sciences, Serie C: Sciences Chimiques, 1967, 265(5), 320-323. None of these documents disclose that the compounds have any biological activity.

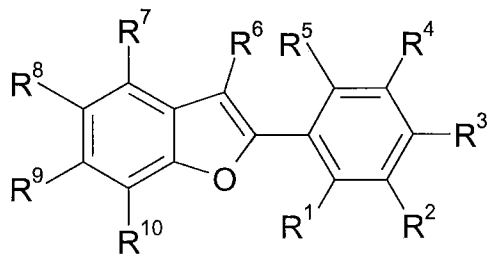
Certain benzofurans are known to have biological activity at estrogen receptors, see Anti-cancer Drug Design 1991, 6(5), 417-426; DE 41 17 512; WO 03/051860; and WO 2007/047204.

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 compounds used in 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 including bone loss, bone fractures, osteoporosis, cartilage degeneration, endometriosis, uterine fibroid disease, hot flashes, increased levels of LDL cholesterol, cardiovascular disease, impairment of cognitive functioning, cerebral degenerative disorders, restenosis, gynecomastia, vascular smooth muscle cell proliferation, obesity, incontinence, anxiety, depression, autoimmune disease, and lung, colon, breast, uterus, and prostate cancer.

Summary of the Invention

The present inventors have found that certain benzofuran compounds have valuable biological activity. Those compounds comprise a compound of formula (I) or a pharmaceutically acceptable ester, amide, solvate or salt thereof, including a salt of such an ester or amide, and a solvate of such an ester, amide or salt:



(I)

wherein R^1, R^2, R^4 and R^5 are each independently selected from the group consisting of hydrogen, OR^A, 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^3 is selected from the group consisting of OR^A; -CHO; -C(O)C_{1-4}alkyl; -C(O)phenyl; -O-C(O)R^A; and $N(R^B)_2$ in which each R^B is independently selected from the group consisting of hydrogen, -C(O)C_{1-4}alkyl, -C(O)phenyl, -SO_2C_{1-4}alkyl, -SO_2phenyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkyl-C_{1-6}alkyl, C_{6-10}aryl, C_{6-10}aryl-C_{1-6}alkyl, C_{5-10}heterocyclyl and C_{5-10}heterocyclyl-C_{1-6} alkyl;

or R^3 and R^4 together with the atoms to which they are attached, 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 1 or 2 groups selected from OR^A, 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^6 is selected from the group consisting of C_{3-8}cycloalkyl, C_{3-8}cycloalkyl-C_{1-6}alkyl, C_{3-8}cycloalkyl-C_{1-6}alkenyl, phenyl, biphenyl, phenyl-C(=CH_2)-, and C_{5-10}heterocyclyl, wherein said phenyl, biphenyl, phenyl-C(=CH_2)- or C_{5-10}heterocyclyl group is unsubstituted or substituted on the ring with 1 to 3 substituents, each substituent being selected from the group consisting of OR^A; halogen; cyano; nitro; -CHO; -C(O)C_{1-6}alkyl; C_{1-6}alkyl, C_{1-6}alkoxy or C_{1-6}alkoxyalkyl optionally substituted by 1 to 3 halogen atoms; C_{2-6}alkenyl optionally substituted by halogen or cyano; C_{2-6}alkynyl; SO_2H; SO_2C_{1-6}alkyl; SH; and SC_{1-6}alkyl;

R^8 is OR^A;

R^7, R^9 and R^{10} are each independently selected from the group consisting of hydrogen, OR^A, halogen, cyano, nitro, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C(O)H, C(O)C_{1-6}alkyl, haloC_{1-6}alkyl, dihaloC_{1-6}alkyl, trihaloC_{1-6}alkyl, cyanoC_{1-6}alkyl, and C_{1-4}alkoxyC_{1-6}alkyl; and

R^A is selected from the group consisting of hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkyl-C_{1-6}alkyl, C_{6-10}aryl and C_{6-10} aryl-C_{1-6}alkyl.

The compounds defined above have 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.

Accordingly the invention provides a pharmaceutical composition which comprises a compound as defined above together with a pharmaceutically acceptable carrier; a compound as defined above for use as a medicament; use of a compound as defined above 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; and 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 defined above. Most of the compounds as defined above are novel, and the invention therefore further

provides those compounds *per se*, said compounds being those defined above with the provisos that (i) if all of R^2, R^3, R^8 and R^9 represent methoxy groups and all of R^1, R^4, R^5, R^7 and R^{10} represent hydrogen atoms, then R^6 represents a group other than phenyl or 3,4-dimethoxyphenyl; (ii) if both R^3 and R^8 represent methoxy groups, R^2 represents an isopropoxy group, R^9 represents a hydroxy or an isopropoxy group, and all of R^1, R^4, R^5, R^7 and R^{10} represent hydrogen atoms, then R^6 represents a group other than 3,4,5-trimethoxyphenyl; and (iii) if both of R^3 and R^8 represent methoxy groups and all of R^1, R^2, R^4, R^5, R^7, R^9 and R^{10} represent hydrogen atoms, then R^6 represents a group other than phenyl.

Detailed Description of Invention

The compounds used in 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.

The present invention uses compounds that are estrogen receptor ligands. The term "estrogen receptor ligand" as used herein is intended to cover any moiety which binds to an estrogen receptor. The ligand may act as an agonist, a partial agonist, an antagonist or a partial antagonist. The ligand may be ERβ selective or display mixed ERα and ERβ activity. For example, the ligand may act both as an agonist or a partial agonist of ERβ and as an antagonist or a partial antagonist of ERα. In general, however, the compounds have an improved combination of activity (generally agonist activity, most of the compounds being) and selectivity for the β receptor.

Preferably R^A is selected from the group consisting of hydrogen, C_{1-4}alkyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkyl-C_{1-4} alkyl, phenyl and benzyl. More preferably, R^A is selected from the group consisting of hydrogen, C_{1-4}alkyl and C_{3-6}cycloalkyl. Most preferably, R^A is selected from the group consisting of hydrogen and C_{1-4}alkyl, for example R^A may be hydrogen.

Preferably R^1, R^2, and R^5 are each independently selected from the group consisting of hydrogen, OR^A, halogen, cyano, nitro, C_{1-4}alkyl, haloC_{1-4}alkyl, dihaloC_{1-4}alkyl and trihaloC_{1-4}alkyl. More preferably R^1, R^2 and R^5 are each independently selected from the group consisting of hydrogen, OR^A, halogen, cyano, halomethyl, dihalomethyl and trihalomethyl. Most preferably R^1, R^2, and R^5 are each independently selected from hydrogen, hydroxy, halogen (for example chlorine or

fluorine), cyano, methyl and trifluoromethyl. Preferably at least 1, for example at least 2, for example all 3, of R^1, R^2, and R^5 represent hydrogen.

In one preferred embodiment, R^3 is selected from the group consisting of OR^A and $N(R^B)_2$, in which R^A has one of the preferred meanings given above and each R^B is independently selected from the group consisting of hydrogen, C_{1-4}alkyl, and C_{3-6}cycloalkyl, especially hydrogen and C_{1-4}alkyl. Especially, R^3 represents a hydroxy group. In one embodiment, when R^3 represents -OC_{1-4}alkyl, suitably R^8 represents a group other than -OC_{1-4}alkyl; for example when R^3 represents –OCH_3, suitably R^8 represents a group other than –OCH_3.

In one preferred embodiment, R^4 represents one of the preferred groups mentioned above for R^1, R^2, and R^5.

In a further preferred embodiment, R^3 and R^4, together with the atoms to which they are attached, form a 5-, 6- or 7- membered cyclic group optionally containing one to three heteroatoms selected from O, N and S, preferably N, said 5-, 6- or 7- membered cyclic group being optionally substituted with 1 or 2 groups selected from OR^A, 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. Preferably R^3 and R^4 together represent an -NH-CH=N-, -NH-N=CH- or -CH-CH-NH- group, in which case said heterocycle together with the phenyl ring to which it is fused is a benzimidazole, indole or, especially, indazole, group. In a heterocycle comprising R^3 and R^4 together, the atom adjacent the phenyl ring in the R^3 position is preferably a heteroatom, especially a nitrogen atom. A heterocycle comprising R^3 and R^4 is preferably unsubstituted.

R^6 is preferably selected from the group consisting of C_{3-6}cycloalkyl, C_{3-6}cycloalkyl-C_{1-2}alkyl, C_{3-6}cycloalkyl-C_{1-2}alkenyl, phenyl, biphenyl, phenyl-C(=CH_2)-, and C_{5-7}heterocyclyl wherein said phenyl, biphenyl, phenyl-C(=CH_2)- or C_{5-10}heterocyclyl group is unsubstituted or substituted on the ring with 1 or 2 substituents, each substituent being selected from the group consisting of OR^A; halogen (for example chlorine or fluorine); cyano; and C_{1-4}alkyl or C_{1-4}alkoxy optionally substituted by 1 to 3 halogen atoms. Most preferably, R^6 is an aromatic group, for example a phenyl or aromatic C_5heterocyclyl group, with optional substitution of said group as described above. Preferred C_5heterocyclyl groups include thiophenyl, thiazolyl, furanyl, pyrazolyl, pyrrolyl, oxazolyl and imidazolyl, especially furanyl, thiophenyl and

pyrazolyl. For example, R^6 may represent a phenyl group or a C_5heterocyclyl group optionally substituted by one of the above substituents.

R^7, R^9 and R^{10} are preferably each independently selected from the group consisting of hydrogen, OR^A, halogen, cyano, C_{1-4}alkyl, haloC_{1-4}alkyl, dihaloC_{1-4}alkyl and trihaloC_{1-4}alkyl. More preferably, R^7, R^9 and R^{10} are each independently selected from the group consisting of hydrogen, OR^A, halogen, cyano, halomethyl, dihalomethyl and trihalomethyl. Most preferably R^7, R^9 and R^{10} are each independently selected from hydrogen, hydroxy, halogen (for example chlorine or fluorine), cyano, methyl and trifluoromethyl. Preferably at least 1, for example at least 2, for example all 3, of R^7, R^9 and R^{10} represent hydrogen.

Accordingly, in one preferred group of compounds:

R^A represents C_{1-4}alkyl or, especially, hydrogen;

R^1, R^2, and R^5 are each independently selected from the group consisting of hydrogen, OR^A, halogen (for example chlorine or fluorine), cyano, halomethyl, dihalomethyl and trihalomethyl; preferably at least 1, for example at least 2, for example all 3, of R^1, R^2, and R^5 represent hydrogen;

R^3 represents $N(R^B)_2$, in which each R^B independently represents hydrogen and C_{1-4}alkyl, or, preferably, OR^A;

R^4 represents one of the preferred groups mentioned above for R^1, R^2, and R^5; or

R^3 and R^4 together represent an -NH-CH=N-, -CH=CH-NH- or, especially, -NH-N=CH- group;

R^6 represents an aromatic group, for example a phenyl or a C_5heterocyclyl group, which can either be unsubstituted or substituted on the ring with 1 or 2 substituents, each substituent being selected from the group consisting of OR^A; halogen (for example chlorine or fluorine); cyano; and C_{1-4}alkyl or C_{1-4}alkoxy optionally substituted by 1 to 3 halogen atoms;

R^7, R^9 and R^{10} each independently represent hydrogen, OR^A, halogen (for example chlorine or fluorine), cyano, halomethyl, dihalomethyl and trihalomethyl, especially hydrogen, hydroxy, halogen, cyano, methyl and trifluoromethyl, preferably at least 1, for example at least 2, for example all 3, of R^7, R^9 and R^{10} being hydrogen.

Compounds of the formula I include, but are not limited to, the following:

2-(4-Hydroxy-phenyl)-7-methyl-3-phenyl-benzofuran-5-ol;

5-Hydroxy-2-(4-hydroxy-phenyl)-3-phenyl-benzofuran-7-carbonitrile;

2-(2-Fluoro-4-hydroxy-phenyl)-7-methyl-3-phenyl-benzofuran-5-ol;

7-Dibromomethyl-2-(4-hydroxy-phenyl)-3-phenyl-benzofuran-5-ol;

[5-Hydroxy-2-(4-hydroxy-phenyl)-3-phenyl-benzofuran-7-yl]-acetonitrile;

2-(4-Hydroxy-phenyl)-7-(1-methoxy-ethyl)-3-phenyl-benzofuran-5-ol;

7-Difluoromethyl-2-(4-hydroxy-phenyl)-3-phenyl-benzofuran-5-ol;

2-(4-Hydroxy-phenyl)-3-phenyl-7-vinyl-benzofuran-5-ol;

2-(4-Hydroxy-phenyl)-3-thiophen-3-yl-7-trifluoromethyl-benzofuran-5-ol;

7-Fluoro-2-(1H-indazol-5-yl)-3-thiophen-3-yl-benzofuran-5-ol;

2-[7-Chloro-5-hydroxy-2-(4-hydroxy-phenyl)-benzofuran-3-yl]-furan-3-carbonitrile;

2-(4-Hydroxy-phenyl)-7-methyl-3-thiophen-3-yl-benzofuran-5-ol;

3-(2,5-Difluoro-phenyl)-2-(4-hydroxy-phenyl)-7-methyl-benzofuran-5-ol;

3-[5-Hydroxy-2-(4-hydroxy-phenyl)-7-methyl-benzofuran-3-yl]-benzonitrile;

2-(4-Hydroxy-phenyl)-7-methyl-3-m-tolyl-benzofuran-5-ol;

2-(4-Hydroxy-phenyl)-7-methyl-3-thiophen-2-yl-benzofuran-5-ol;

2-(4-Hydroxy-phenyl)-7-methyl-3-pyridin-3-yl-benzofuran-5-ol;

2-[5-Hydroxy-2-(4-hydroxy-phenyl)-7-methyl-benzofuran-3-yl]-benzonitrile;

2-(4-Hydroxy-phenyl)-7-methyl-3-(3-nitro-phenyl)-benzofuran-5-ol;

5-[5-Hydroxy-2-(4-hydroxy-phenyl)-7-methyl-benzofuran-3-yl]-thiophene-2-carbaldehyde;

3-(3,5-Difluoro-phenyl)-2-(4-hydroxy-phenyl)-7-methyl-benzofuran-5-ol;

3-(3,5-Dichloro-phenyl)-2-(4-hydroxy-phenyl)-7-methyl-benzofuran-5-ol;

2-(4-Hydroxy-phenyl)-7-methyl-3-(2-phenoxy-phenyl)-benzofuran-5-ol;

3-Biphenyl-2-yl-2-(4-hydroxy-phenyl)-7-methyl-benzofuran-5-ol;

3-(2-Hydroxy-phenyl)-2-(4-hydroxy-phenyl)-7-methyl-benzofuran-5-ol;

1-{3-[5-Hydroxy-2-(4-hydroxy-phenyl)-7-methyl-benzofuran-3-yl]-phenyl}-ethanone;

2-(4-Hydroxy-phenyl)-3-(3-methanesulfonyl-phenyl)-7-methyl-benzofuran-5-ol;

3-(3-Ethylsulfanyl-phenyl)-2-(4-hydroxy-phenyl)-7-methyl-benzofuran-5-ol;

2-(4-Hydroxy-phenyl)-7-methyl-3-quinolin-5-yl-benzofuran-5-ol;

1-{5-[5-Hydroxy-2-(4-hydroxy-phenyl)-7-methyl-benzofuran-3-yl]-thiophen-2-yl}-ethanone;

2-(4-Hydroxy-phenyl)-7-methyl-2',3'-dihydro-[3,5']bibenzofuranyl-5-ol;

2-(4-Hydroxy-phenyl)-7-methyl-3-(3-trifluoromethoxy-phenyl)-benzofuran-5-ol;

3-(2-Fluoro-pyridin-3-yl)-2-(4-hydroxy-phenyl)-7-methyl-benzofuran-5-ol;

3-Benzo[b]thiophen-2-yl-2-(4-hydroxy-phenyl)-7-methyl-benzofuran-5-ol;

2-(4-Hydroxy-phenyl)-7-methyl-3-(1-methyl-1H-pyrazol-4-yl)-benzofuran-5-ol;

2-(4-Hydroxy-phenyl)-7-methyl-3-(1-phenyl-vinyl)-benzofuran-5-ol;

2-(4-Hydroxy-phenyl)-7-methyl-3-pyridin-4-yl-benzofuran-5-ol;

2-(4-Hydroxy-phenyl)-7-methyl-3-(1-methyl-1H-pyrrol-2-yl)-benzofuran-5-ol;

3-(3,5-Dimethyl-isoxazol-4-yl)-2-(4-hydroxy-phenyl)-7-methyl-benzofuran-5-ol;

3-(5-Fluoro-2-methyl-phenyl)-2-(4-hydroxy-phenyl)-7-methyl-benzofuran-5-ol;

3-[1-(4-Fluoro-phenyl)-vinyl]-2-(4-hydroxy-phenyl)-7-methyl-benzofuran-5-ol;

3-Cyclopropyl-2-(4-hydroxy-phenyl)-7-methyl-benzofuran-5-ol;

3-(5-Fluoro-2-methoxy-phenyl)-2-(4-hydroxy-phenyl)-7-methyl-benzofuran-5-ol;

2-(4-Hydroxy-phenyl)-7-methyl-3-(1H-pyrrol-2-yl)-benzofuran-5-ol;

3-Furan-2-yl-2-(4-hydroxy-phenyl)-7-methyl-benzofuran-5-ol;

2-(4-Hydroxy-phenyl)-7-methyl-3-thiazol-5-yl-benzofuran-5-ol;

2-(4-Hydroxy-phenyl)-3-(2-methoxy-thiazol-4-yl)-7-methyl-benzofuran-5-ol;

2-(4-Hydroxy-phenyl)-7-methyl-3-thiazol-2-yl-benzofuran-5-ol;

2-(4-Hydroxy-phenyl)-3-(2-isopropyl-phenyl)-7-methyl-benzofuran-5-ol;

3-(2-Ethyl-phenyl)-2-(4-hydroxy-phenyl)-7-methyl-benzofuran-5-ol;

(E)-3-{2-[5-Hydroxy-2-(4-hydroxy-phenyl)-7-methyl-benzofuran-3-yl]-phenyl}-acrylonitrile;

3-(2-Butoxy-phenyl)-2-(4-hydroxy-phenyl)-7-methyl-benzofuran-5-ol;

2-(4-Hydroxy-phenyl)-7-methyl-3-(2-trifluoromethoxy-phenyl)-benzofuran-5-ol;

4-[5-Hydroxy-2-(4-hydroxy-phenyl)-7-methyl-benzofuran-3-yl]-thiophene-2-carbaldehyde;

3-((E)-2-Cyclopropyl-vinyl)-2-(4-hydroxy-phenyl)-7-methyl-benzofuran-5-ol;

2-(4-Hydroxy-phenyl)-7-methyl-3-(3-methyl-thiophen-2-yl)-benzofuran-5-ol;

2-[5-Hydroxy-2-(4-hydroxy-phenyl)-7-methyl-benzofuran-3-yl]-thiophene-3-carbaldehyde;

2-[5-Hydroxy-2-(4-hydroxy-phenyl)-7-methyl-benzofuran-3-yl]-thiophene-3-carbonitrile;

7-Bromomethyl-2-(4-hydroxy-phenyl)-3-phenyl-benzofuran-5-ol;

5-Hydroxy-2-(4-hydroxy-phenyl)-3-thiophen-3-yl-benzofuran-7-carbonitrile;

5-Hydroxy-2-(4-hydroxy-phenyl)-3-phenyl-benzofuran-7-carbaldehyde;
7-Chloro-2-(4-hydroxy-phenyl)-3-phenyl-benzofuran-5-ol;
7-Chloro-2-(4-hydroxy-phenyl)-3-thiophen-3-yl-benzofuran-5-ol;
5-Hydroxy-2-(4-hydroxy-phenyl)-3-thiophen-3-yl-benzofuran-7-carbaldehyde;
2-(4-Hydroxy-phenyl)-3-thiophen-3-yl-7-vinyl-benzofuran-5-ol;
2-[7-Chloro-5-hydroxy-2-(4-hydroxy-phenyl)-benzofuran-3-yl]-thiophene-3-carbonitrile;
3-(3-Cyano-furan-2-yl)-5-hydroxy-2-(4-hydroxy-phenyl)-benzofuran-7-carbonitrile;
2-[5-Hydroxy-2-(4-hydroxy-phenyl)-7-trifluoromethyl-benzofuran-3-yl]-furan-3-carbonitrile;
2-[2-(3-Fluoro-4-hydroxy-phenyl)-5-hydroxy-7-methyl-benzofuran-3-yl]-furan-3-carbonitrile;
2-(4-Hydroxy-phenyl)-6-methyl-3-phenyl-benzofuran-5-ol;
2-(2,5-Difluoro-4-hydroxy-phenyl)-7-methyl-3-phenyl-benzofuran-5-ol;
2-(2,6-Difluoro-4-hydroxy-phenyl)-7-methyl-3-phenyl-benzofuran-5-ol;
2-(3-Fluoro-4-hydroxy-phenyl)-7-methyl-3-phenyl-benzofuran-5-ol;
2-(1H-Indazol-5-yl)-7-methyl-3-phenyl-benzofuran-5-ol;
2-(3,5-Difluoro-4-hydroxy-phenyl)-7-methyl-3-phenyl-benzofuran-5-ol;
2-(3-Chloro-5-fluoro-4-hydroxy-phenyl)-7-methyl-3-phenyl-benzofuran-5-ol;
5-(5-Methoxy-7-methyl-3-phenyl-benzofuran-2-yl)-1H-indazole;
2-(3-Fluoro-4-hydroxy-phenyl)-7-methyl-3-thiophen-3-yl-benzofuran-5-ol;
2-(2-Fluoro-4-hydroxy-phenyl)-7-methyl-3-thiophen-3-yl-benzofuran-5-ol;
2-(2,6-Difluoro-4-hydroxy-phenyl)-7-methyl-3-thiophen-3-yl-benzofuran-5-ol;
2-(3-Chloro-5-fluoro-4-hydroxy-phenyl)-7-methyl-3-thiophen-3-yl-benzofuran-5-ol;
2-[2-(3-Chloro-5-fluoro-4-hydroxy-phenyl)-5-hydroxy-7-methyl-benzofuran-3-yl]-furan-3-carbonitrile; and
2-[7-Fluoro-5-hydroxy-2-(1H-indazol-5-yl)-benzofuran-3-yl]-furan-3-carbonitrile.

The compound names given above were generated in accordance with IUPAC by the ACD Labs 8.0/name program, version 8.05 and/or with ISIS DRAW Autonom 2000.

Depending upon the substituents present in compounds of the formula I, the compounds may form esters, amides and/or salts. Salts and solvates of compounds of formula (I) which are suitable for use in medicine are those wherein a counterion or associated solvent is pharmaceutically acceptable. However, salts and solvates having non-pharmaceutically acceptable counterions or associated solvents are within the scope of the present invention, for

example, for use as intermediates in the preparation of the compounds of formula (I) and their pharmaceutically acceptable salts, solvates and physiologically functional derivatives. By the term "physiologically functional derivative" is meant a chemical derivative of a compound of formula (I) having the same physiological function as the free compound of formula (I), for example, by being convertible in the body thereto. Esters and amides are examples of physiologically functional derivatives.

Suitable salts include those formed by reaction of basic groups in the compound of formula I with organic or inorganic acids. In particular, suitable salts include those formed with mineral acids, strong organic carboxylic acids, such as alkanecarboxylic acids of 1 to 4 carbon atoms which are unsubstituted or substituted, for example, by halogen, such as saturated or unsaturated dicarboxylic acids, such as hydroxycarboxylic acids, such as amino acids, or with organic sulfonic acids, such as (C_1-C_4)-alkyl- or aryl-sulfonic acids which are unsubstituted or substituted, for example by halogen. Pharmaceutically acceptable acid addition salts include those formed from hydrochloric, hydrobromic, sulphuric, nitric, citric, tartaric, acetic, phosphoric, lactic, pyruvic, acetic, trifluoroacetic, succinic, perchloric, fumaric, maleic, glycolic, lactic, salicylic, oxaloacetic, methanesulfonic, ethanesulfonic, p-toluenesulfonic, formic, benzoic, malonic, naphthalene-2-sulfonic, benzenesulfonic, isethionic, ascorbic, malic, phthalic, aspartic, and glutamic acids, lysine and arginine. Other acids such as oxalic, while not in themselves pharmaceutically acceptable, may be useful as intermediates in obtaining the compounds and their pharmaceutical acceptable acid addition salts.

Pharmaceutically acceptable esters and amides of the compounds of formula (I) may have an appropriate group, for example an OH group or an NR^3 group, converted by reaction with an appropriate acid.

Those skilled in the art of organic chemistry will appreciate that many organic compounds can form complexes with solvents in which they are reacted or from which they are precipitated or crystallized. These complexes are known as "solvates". For example, a complex with water is known as a "hydrate".

A compound which, upon administration to the recipient, is capable of being converted into a compound of formula (I) as described above, or an active metabolite or residue thereof, is known

as a "prodrug". A prodrug may, for example, be converted within the body, e. g. by hydrolysis in the blood, into its active form that has medical effects. Pharmaceutical acceptable prodrugs are described in T. Higuchi and V. Stella, Prodrugs as Novel Delivery Systems, Vol. 14 of the A. C. S. Symposium Series (1976); "Design of Prodrugs" ed. H. Bundgaard, Elsevier, 1985; and in Edward B. Roche, ed., Bioreversible Carriers in Drug Design, American Pharmaceutical Association and Pergamon Press, 1987, which are incorporated herein by reference.

The following definitions apply to the terms as used throughout this specification, unless otherwise limited in specific instances.

As used herein, the term "alkyl" means both straight and branched chain saturated hydrocarbon groups. Examples of alkyl groups include methyl, ethyl, n-propyl, iso-propyl, n-butyl, t-butyl, i-butyl, sec-butyl, pentyl and hexyl groups. Among unbranched alkyl groups, there are preferred methyl, ethyl, n-propyl, iso-propyl, n-butyl groups. Among branched alkyl groups, there may be mentioned t-butyl, i-butyl, 1-ethylpropyl and 1-ethylbutyl groups.

As used herein, the term "alkoxy" means the group O-alkyl, where "alkyl" is used as described above. Examples of alkoxy groups include methoxy and ethoxy groups. Other examples include propoxy and butoxy.

As used herein, the term "alkenyl" means both straight and branched chain unsaturated hydrocarbon groups with at least one carbon carbon double bond. Examples of alkenyl groups include ethenyl, propenyl, butenyl, pentenyl and hexenyl. Preferred alkenyl groups include ethenyl, 1- propenyl and 2- propenyl.

As used herein, the term "alkynyl" means both straight and branched chain unsaturated hydrocarbon groups with at least one carbon carbon triple bond. Examples of alkynyl groups include ethynyl, propynyl, butynyl, pentynyl and hexynyl. Preferred alkynyl groups include ethynyl 1- propynyl and 2- propynyl.

As used herein, the term "cycloalkyl" means a saturated group in a ring system. A cycloalkyl group can be monocyclic or bicyclic. A bicyclic group may, for example, be fused or bridged. Examples of monocyclic cycloalkyl groups include cyclopropyl, cyclobutyl and cyclopentyl.

Other examples of monocyclic cycloalkyl groups are cyclohexyl, cycloheptyl and cyclooctyl. Examples of bicyclic cycloalkyl groups include bicyclo [2. 2.1]hept-2-yl. Preferably, the cycloalkyl group is monocyclic.

As used herein, the term "aryl" means a monocyclic or bicyclic aromatic carbocyclic group. Examples of aryl groups include phenyl and naphthyl. A naphthyl group may be attached through the 1 or the 2 position. In a bicyclic aromatic group, one of the rings may, for example, be partially saturated. Examples of such groups include indanyl and tetrahydronaphthyl. Specifically, the term C_{5-10} aryl is used herein to mean a group comprising from 5 to 10 carbon atoms in a monocyclic or bicyclic aromatic group. A particularly preferred C_{5-10} aryl group is phenyl.

As used herein, the term "halogen" means fluorine, chlorine, bromine or iodine. Fluorine, chlorine and bromine are particularly preferred.

As used herein, the term "haloalkyl" means an alkyl group having a halogen substituent, the terms "alkyl" and "halogen" being understood to have the meanings outlined above. Similarly, the term "dihaloalkyl" means an alkyl group having two halogen substituents and the term "trihaloalkyl" means an alkyl group having three halogen substituents. Examples of haloalkyl groups include fluoromethyl, chloromethyl, bromomethyl, fluoromethyl, fluoropropyl and fluorobutyl groups; examples of dihaloalkyl groups include difluoromethyl and difluoroethyl groups; examples of triihaloalkyl groups include trifluoromethyl and trifluoroethyl groups.

As used herein, the term "heterocyclyl" means an aromatic or a non-aromatic cyclic group of carbon atoms wherein from one to three of the carbon atoms is/are replaced by one or more heteroatoms independently selected from nitrogen, oxygen or sulfur. A heterocyclyl group may, for example, be monocyclic or bicyclic. In a bicyclic heterocyclyl group there may be one or more heteroatoms in each ring, or only in one of the rings. A heteroatom is preferably O or N. Heterocyclyl groups containing a suitable nitrogen atom include the corresponding N-oxides. Examples of monocyclic heterocycloalkyl rings include aziridinyl, azetidinyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, piperidinyl, piperazinyl, tetrahydrofuranyl, tetrahydropyranyl, morpholinyl, thiomorpholinyl and azepanyl.

Examples of bicyclic heterocyclic rings in which one of the rings is non-aromatic include dihydrobenzofuranyl, indanyl, indolinyl, isoindolinyl, tetrahydroisoquinolinyl, tetrahydroquinolyl and benzoazepanyl.

Examples of monocyclic heteroaryl groups include furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, pyridyl, triazolyl, triazinyl, pyridazyl, pyrimidinyl, isothiazolyl, isoxazolyl, pyrazinyl, pyrazolyl and pyrimidinyl; examples of bicyclic heteroaryl groups include quinoxalinyl, quinazolinyl, pyridopyrazinyl, benzoxazolyl, benzothiophenyl, benzimidazolyl, naphthyridinyl, quinolinyl, benzofuranyl, indolyl, benzothiazolyl, oxazolyl[4,5-b]pyridiyl, pyridopyrimidinyl, isoquinolinyl and benzodroxazole.

Examples of preferred heterocyclyl groups include piperidinyl, tetrahydrofuranyl, tetrahydropyranyl, pyridyl, pyrimidyl and indolyl. Preferred heterocyclyl groups also include thiophenyl, thiazolyl, furanyl, pyrazolyl, pyrrolyl and imidazolyl.

As used herein the term "cycloalkylalkyl" means a group cycloalkyl-alkyl- attached through the alkyl group, "cycloalkyl" and "alkyl" being understood to have the meanings outlined above.

As mentioned above, the compounds defined herein have activity as estrogen receptor ligands. The compounds have activity as estrogen receptor modulators, and may be agonists, partial agonists, antagonists, or partial antagonists of the estrogen receptor.

The compounds may thus be used in the treatment of diseases or disorders associated with estrogen receptor activity. In particular, the compounds that are agonists or partial agonists of the estrogen receptor (which includes most of the compounds of the invention) may be used in the treatment of diseases or disorders for which selective agonists or partial agonists of the estrogen receptor are indicated. Compounds that are antagonists or partial antagonists of the estrogen receptor may be used in the treatment of diseases or disorders for which selective antagonists or partial antagonists of the estrogen receptor are indicated.

Clinical conditions for which an agonist or partial agonist is indicated include, but are not limited to, bone loss, bone fractures, osteoporosis, cartilage degeneration, endometriosis, uterine fibroid disease, hot flashes, increased levels of LDL cholesterol, cardiovascular disease, impairment of

cognitive functioning, cerebral degenerative disorders, restenosis, gynecomastia, vascular smooth muscle cell proliferation, obesity, incontinence, anxiety, depression, autoimmune disease, inflammation, IBD, IBS, sexual dysfunction, hypertension, retinal degeneration, and lung, colon, breast, uterus, and prostate cancer, and/or disorders related to estrogen functioning.

The compounds find particular application in the treatment or prophylaxis of the following: bone loss, bone fractures, osteoporosis, cartilage degeneration, endometriosis, uterine fibroid disease, hot flashes, increased levels of LDL cholesterol, cardiovascular disease, impairment of cognitive functioning, cerebral degenerative disorders, restenosis, gynecomastia, vascular smooth muscle cell proliferation, obesity, incontinence, anxiety, depression, autoimmune disease, inflammation, IBD, IBS, sexual dysfunction, hypertension, retinal degeneration, and lung, colon, breast, uterus, and prostate cancer, and/or disorders related to estrogen functioning.

The amount of active ingredient which is required to achieve a therapeutic effect will, of course, vary with the particular compound, the route of administration, the subject under treatment, including the type, species, age, weight, sex, and medical condition of the subject and the renal and hepatic function of the subject, and the particular disorder or disease being treated, as well as its severity. An ordinarily skilled physician, veterinarian or clinician can readily determine and prescribe the effective amount of the drug required to prevent, counter or arrest the progress of the condition.

Oral dosages of the present invention, when used for the indicated effects, will range between about 0.01 mg per kg of body weight per day (mg/kg/day) to about 100 mg/kg/day, preferably 0.01 mg per kg of body weight per day (mg/kg/day) to 10 mg/kg/day, and most preferably 0.1 to 5.0 mg/kg/day, for adult humans. For oral administration, the compositions are preferably provided in the form of tablets or other forms of presentation provided in discrete units containing 0.01, 0.05, 0.1, 0.5, 1.0, 2.5, 5.0, 10.0, 15.0, 25.0, 50.0, 100, and 500 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. A medicament typically contains from about 0.01 mg to about 500 mg of the active ingredient, preferably from about 1 mg to about 100 mg of active ingredient. Intravenously, the most preferred doses will range from about 0.1 to about 10 mg/kg/minute during a constant rate infusion. Advantageously, compounds of the present invention may be administered in a single

daily dose, or the total daily dosage may be administered in divided doses of two, three or four times daily. Furthermore, preferred compounds for the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using those forms of transdermal skin patches well known to those of ordinary skill in the art. To be administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen.

While it is possible for the active ingredient to be administered alone, it is preferable for it to be present in a pharmaceutical formulation or composition. Accordingly, the invention provides a pharmaceutical formulation comprising a compound of the general formula I or a pharmaceutically acceptable ester, amide, solvate or salt thereof, including a salt of such an ester or amide, and a solvate of such asn ester amide or salt, and a pharmaceutically acceptable diluent, excipient or carrier (collectively referred to herein as "carrier" materials). Pharmaceutical compositions of the invention may take the form of a pharmaceutical formulation as described below.

The pharmaceutical formulations according to the invention include those suitable for oral, parenteral (including subcutaneous, intradermal, intramuscular, intravenous [bolus or infusion], and intraarticular), inhalation (including fine particle dusts or mists which may be generated by means of various types of metered does pressurized aerosols), nebulizers or insufflators, rectal, intraperitoneal and topical (including dermal, buccal, sublingual, and intraocular) administration, although the most suitable route may depend upon, for example, the condition and disorder of the recipient.

The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing the active ingredient into association with the carrier which constitutes one or more accessory ingredients. In general the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both and then, if necessary, shaping the product into the desired formulation.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets, pills or tablets each containing a predetermined amount

of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous liquid or a non-aqueous liquid, for example as elixirs, tinctures, suspensions or syrups; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary or paste.

A tablet may be made by compression or moulding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, lubricating, surface active or dispersing agent. Moulded tablets may be made by moulding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredient therein. The present compounds can, for example, be administered in a form suitable for immediate release or extended release. Immediate release or extended release can be achieved by the use of suitable pharmaceutical compositions comprising the present compounds, or, particularly in the case of extended release, by the use of devices such as subcutaneous implants or osmotic pumps. The present compounds can also be administered liposomally.

Exemplary compositions for oral administration include suspensions which can contain, for example, microcrystalline cellulose for imparting bulk, alginic acid or sodium alginate as a suspending agent, methylcellulose as a viscosity enhancer, and sweeteners or flavoring agents such as those known in the art; and immediate release tablets which can contain, for example, microcrystalline cellulose, dicalcium phosphate, starch, magnesium stearate, calcium sulfate, sorbitol, glucose and/or lactose and/or other excipients, binders, extenders, disintegrants, diluents and lubricants such as those known in the art. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes and the like. Disintegrators include without limitation starch, methylcellulose, agar, bentonite, xanthan gum and the like. The compounds of formula (I) can also be delivered through the oral cavity by sublingual and/or buccal administration. Molded tablets, compressed tablets or freeze-dried tablets are exemplary forms which may be used. Exemplary compositions include those formulating the present compound(s) with fast dissolving diluents such as mannitol, lactose, sucrose and/or cyclodextrins. Also included in such formulations may be high molecular weight

excipients such as celluloses (avicel) or polyethylene glycols (PEG). Such formulations can also include an excipient to aid mucosal adhesion such as hydroxy propyl cellulose (HPC), hydroxy propyl methyl cellulose (HPMC), sodium carboxy methyl cellulose (SCMC), maleic anhydride copolymer (e.g., Gantrez), and agents to control release such as polyacrylic copolymer (e.g. Carbopol 934). Lubricants, glidants, flavors, coloring agents and stabilizers may also be added for ease of fabrication and use. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. For oral administration in liquid form, the oral drug components can be combined with any oral, non-toxic, pharmaceutically acceptable inert carrier such as ethanol, glycerol, water, and the like.

The compounds can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, 1,2-dipalmitoylphosphatidylcholine, phosphatidyl ethanolamine (cephaline) , or phosphatidylcholine (lecithin).

Formulations for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilised) condition requiring only the addition of the sterile liquid carrier, for example saline or water-for-injection, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described. Exemplary compositions for parenteral administration include injectable solutions or suspensions which can contain, for example, suitable non-toxic, parenterally acceptable diluents or solvents, such as mannitol, 1,3-butanediol, water, Ringer's solution, an isotonic sodium chloride solution, or other suitable dispersing or wetting and suspending agents, including synthetic mono- or diglycerides, and fatty acids, including oleic acid, or Cremaphor.

Exemplary compositions for nasal, aerosol or inhalation administration include solutions in saline, which can contain, for example, benzyl alcohol or other suitable preservatives, absorption

promoters to enhance bioavailability, and/or other solubilizing or dispersing agents such as those known in the art.

Formulations for rectal administration may be presented as a suppository with the usual carriers such as cocoa butter, synthetic glyceride esters or polyethylene glycol. Such carriers are typically solid at ordinary temperatures, but liquefy and/or dissolve in the rectal cavity to release the drug.

Formulations for topical administration in the mouth, for example buccally or sublingually, include lozenges comprising the active ingredient in a flavoured basis such as sucrose and acacia or tragacanth, and pastilles comprising the active ingredient in a basis such as gelatin and glycerine or sucrose and acacia. Exemplary compositions for topical administration include a topical carrier such as Plastibase (mineral oil gelled with polyethylene).

Preferred unit dosage formulations are those containing an effective dose, as hereinbefore recited, or an appropriate fraction thereof, of the active ingredient.

It should be understood that in addition to the ingredients particularly mentioned above, the formulations of this invention may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavouring agents.

Whilst a compound as defined herein may be used as the sole active ingredient in a medicament, it is also possible for the compound to be used in combination with one or more further active agents. Such further active agents may be further compounds as defined herein, or they may be different therapeutic agents, for example an antidepressant, an anxiolytic, an anti-psychotic, or an agent useful in the prevention or treatment of osteoporosis or other pharmaceutically active material. For example, the compounds as defined herein may be effectively administered in combination with effective amounts of other agents such as an antidepressant, an anxiolytic, an anti-psychotic, an organic bisphosphonate or a cathepsin K inhibitor. Nonlimiting examples of antidepressants include noradrenaline reuptake inhibitors (NRI), selective serotonin reuptake inhibitors, monoamine oxidase inhibitors, tricyclic antidepressants (TCA), dopamine reuptake inhibitors (DRI), opioids, selective sèretonic reuptake enhancers, tetracyclic antidepressants,

reversible inhibitors of monoamine oxidase, melatonin agonists, serotonin and noradrenaline reuptake inhibitors (SNRI), corticotropin releasing factor antagonists, α-adrenoreceptor antagonists, 5HT1α receptor agonists and antagonists, lithium and atypical anti-psychotics. Examples of antidepressants of the SSRI class include Fluoxetine and Sertraline; examples of antidepressants of the SNRI class Venlafaxine, Citalopram, Paroxetine, Escitalopram, Fluvoxamine; examples of antidepressants of the SNRI class include Duloxetine; examples of antidepressants of the DRI and NRI classes include Bupropion; examples of antidepressants of the TCA class include Amitriptyline and Dothiepin (Dosulepin). Examples of atypical antipsychotics include: Clozapine, Olanzapine, Risperidone, Quetiapine, Ziprasidone and Dopamine partial agonists. Nonlimiting examples of anxiolytics include benzodiazepines and non-benzodiazapines. Examples of benzodiazapines include lorazepam, alprazolam, and diazepam. Examples of non-benzodiazapines include Buspirone (Buspar®), barbiturates and meprobamate. One or more of those further anti-depressants may be used in combination.

Nonlimiting examples of said organic bisphosphonates include adendronate, clodronate, etidronate, ibandronate, incadronate, minodronate, neridronate, risedronate, piridronate, pamidronate, tiludronate, zoledronate, pharmaceutically acceptable salts or esters thereof, and mixtures thereof. Preferred organic biphosphonates include alendronate and pharmaceutically acceptable salts and mixtures thereof. Most preferred is alendronate monosodium trihydrate.

The precise dosage of the bisphosphonate will vary with the dosing schedule, the oral potency of the particular bisphosphonate chosen, the age, size, sex and condition of the mammal or human, the nature and severity of the disorder to be treated, and other relevant medical and physical factors. Thus, a precise pharmaceutically effective amount cannot be specified in advance and can be readily determined by the caregiver or clinician. An appropriate amount can be determined by routine experimentation from animal models and human clinical studies. Generally, an appropriate amount of bisphosphonate is chosen to obtain a bone resorption inhibiting effect, i.e. a bone resorption inhibiting amount of the bisphonsphonate is administered. For humans, an effective oral dose of bisphosphonate is typically from about 1.5 to about 6000 μg/kg of body weight and preferably about 10 to about 2000 μg/kg of body weight.

For human oral compositions comprising alendronate, pharmaceutically acceptable salts thereof, or pharmaceutically acceptable derivatives thereof, a unit dosage typically comprises from about

8.75 mg to about 140 mg of the alendronate compound, on an alendronic acid active weight basis, i.e. on the basis of the corresponding acid.

The compounds as defined herein can be used in combination with other agents useful for treating estrogen-mediated conditions. The individual components of such combinations can be administered separately at different times during the course of therapy or concurrently in divided or single combination forms. The present invention is therefore to be understood as embracing all such regimes of simultaneous or alternating treatment and the term "administering" is to be interpreted accordingly. It will be understood that the scope of combinations of the compounds of this invention with other agents useful for treating estrogen-mediated conditions includes in principle any combination with any pharmaceutical composition useful for treating disorders related to estrogen functioning.

The above other therapeutic agents, when employed in combination with the compounds as defined herein, may be used, for example, in those amounts indicated in the Physicians' Desk Reference (PDR) or as otherwise determined by one of ordinary skill in the art.

Where the compounds are utilized in combination with one or more other therapeutic agent(s), either concurrently or sequentially, the following combination ratios and dosage ranges are preferred:

When combined with an antidepressant, an anxiolytic, an anti-psychotic, an organic bisphosphonate or a cathepsin K inhibitor, the compounds defined herein may be employed in a weight ratio to the additional agent within the range from about 10:1 to about 1:10.

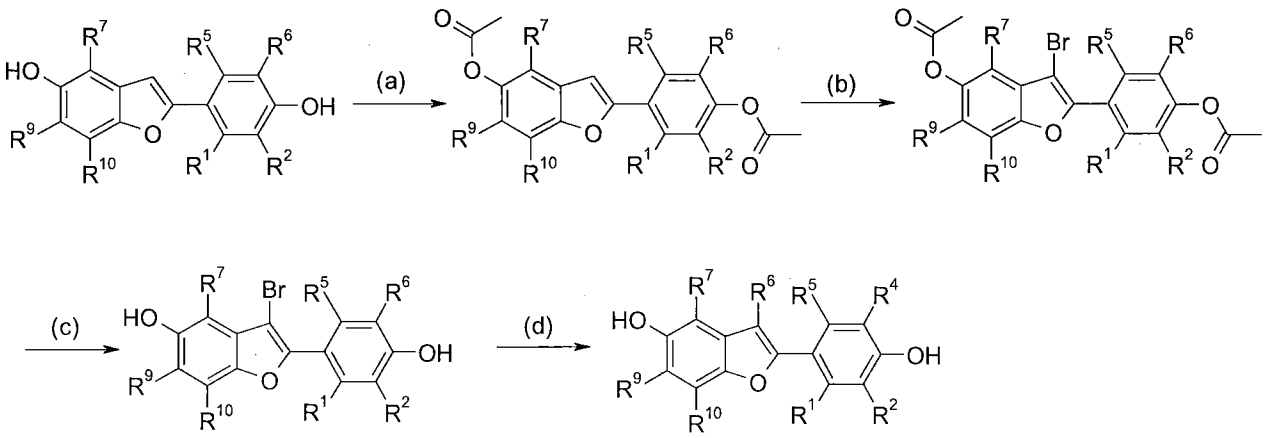
The compounds of the invention as described above also find use, optionally in labelled form, as a diagnostic agent for the diagnosis of conditions associated with malfunction of the estrogen receptor. For example, such a compound may be radioactively labelled.

The compounds of the invention as described above, optionally in labelled form, also find use as a reference compound in methods of discovering other agonists, partial agonists, antagonists or partial antagonists of the estrogen receptor. Thus, the invention provides a method of discovering a ligand of the estrogen receptor which comprises use of a compound as defined

herein such a compound of the invention in labelled form, as a reference compound. For example, such a method may involve a competitive binding experiment in which binding of a compound to the estrogen receptor is reduced by the presence of a further compound which has estrogen receptor-binding characteristics, for example stronger estrogen receptor-binding characteristics than the compound of the invention in question.

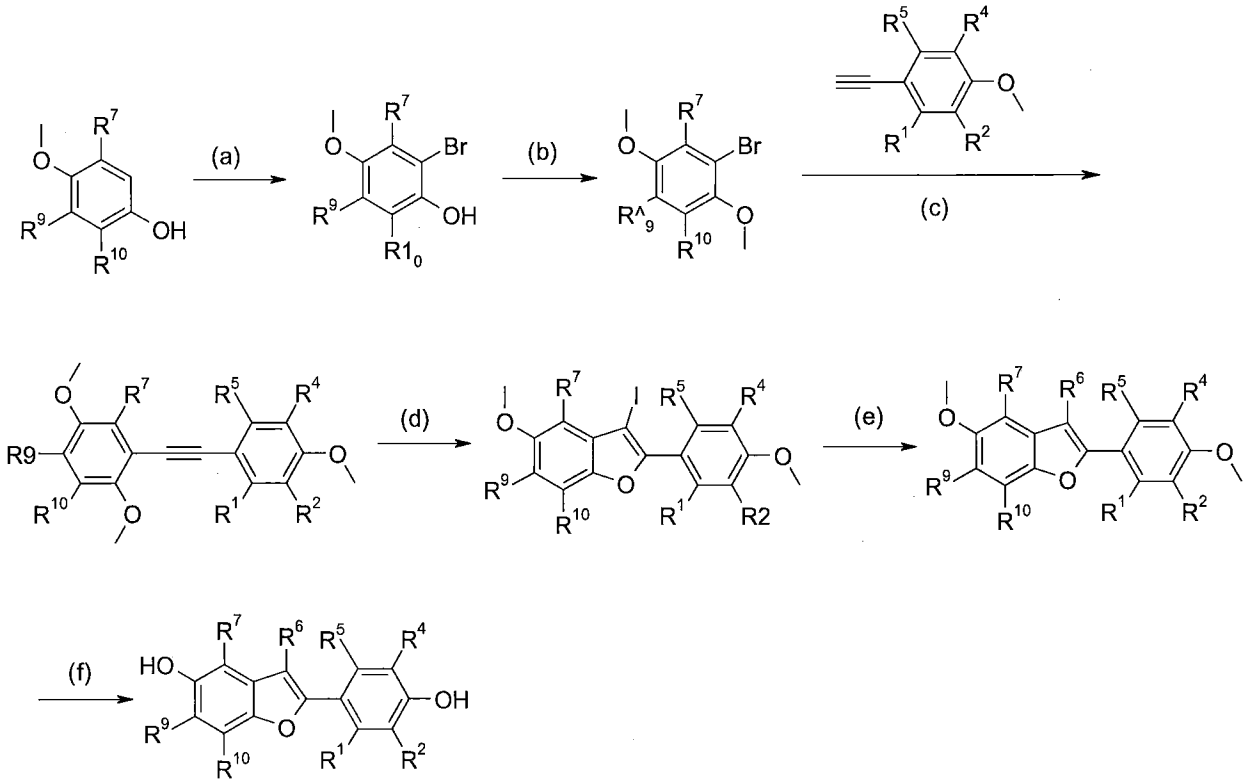
Numerous synthetic routes to the compounds of the present invention can be devised by any person skilled in the art and the possible synthetic routes described below do not limit the invention. Many methods exist in the literature for the synthesis of benzofurans, and a number of possible synthetic routes are shown schematically below. Where appropriate, any initially produced compound as defined herein can be converted into another compound as defined herein by known methods.

Scheme 1



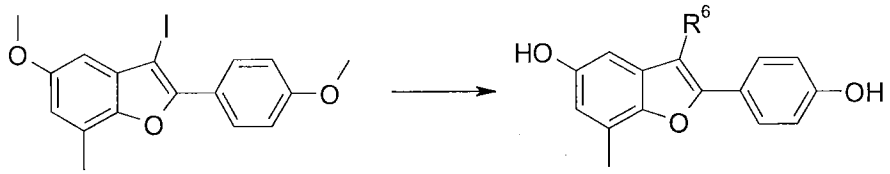
(a) NaOAc, Ac_2O; (b) Br_2, $CHCl_3$; (c) KOH, EtOH; (d) $R6B(OH)_2$,$Pd(OAc)_2$, 2-Dicyclohexylphosphino-2',6'-dimethoxy-1,1'biphenyl, K_2CO_3, toluene

Scheme 2



(a) Br_2, $CHCl_3$; (b) 1,8-Diazabicyclo[5.4.0]undec-7-ene, CH_3I, acetone; (c) X-Phos, $Pd(AcCN)_2Cl_2$, Cs_2CO_3,EtCN; (d) I_2, CH_2Cl_2; (e) $PhB(OH)_2$,2-Dicyclohexylphosphino-2',6'-dimethoxy-1,1'-biphenyl, $Pd(OAc)_2$, K_2CO_3, toluene, ethanol; (f) BBr_3, CH_2Cl_2;

Scheme 3



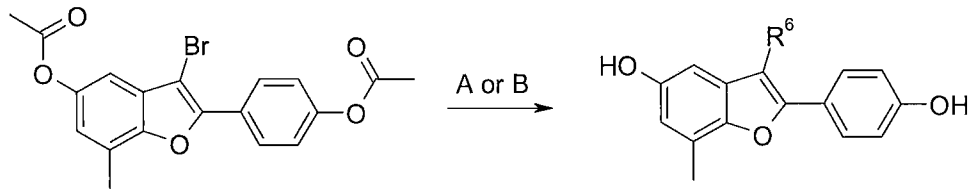
When using Scheme 3, the following general process was used. Boronic acids (0.1 mmol, 2 eq) were weighed into microwave vials. Sodium carbonate (11 mg, 0.1 mmol, 2 eq) was dissolved in water (0.5 ml) and added. The benzofuran (20 mg, 0.05 mmol, 1 eq) was dissolved in DME (1 ml) and added. Tetrakis (2 mg, 0.0015 mmol, 0.03 eq) was dissolved in ethanol (0.5 ml), and added. The vials were flushed with nitrogen, capped and irradiated in a microwave oven at 140 degrees for 3 minutes. The reaction mixtures were filtered into prep. HPLC vials, and chromatographed in acidic buffer using 20-100 % water/acetonitrile gradient. UV-peaks in the range 16 - 24 minutes were collected. For the majority of the reactions a major uv-peak elutes at

around 18 min. Fraction tubes were evaporated, the residues dissolved in acetone and transferred to preweighed vials. The vials were evaporated to dryness, kept under vacuum overnight and weighed.

The dried compounds were dissolved in DCM (1 ml) containing cyclohexene (21 ul) in vials with septa, flushed with nitrogen and cooled in alumina blocks in dry ice/ acetone bath. Boron tribromide (1 M solution in DCM, 200 uL) was added with a syringe. The vials were allowed to reach 10 degrees and then kept at 4 degrees over night.

The reactions were cooled, quenched with MeOH (100 ul), diluted with DCM containing 10% MeOH (1 ml), and washed with sat.sodium bicarbonate. The sodium bicarbonate solution was washed once more with DCM (1 ml). The phases were separated using a phase separation membrane. The organic phase was evaporated to dryness and subjected to reversed phase preparative HPLC. Appropriate fractions were combined and evaporated, and identified by 1H-NMR and LC/MS. Purity was determined by analytical HPLC.

Scheme 4



Two variants on Scheme 4 were used, as follows.

Method A.

Boronic acids or pinacolates (0.2 mmole, 2 eq) were weighed into microwave vials. Cesium carbonate (0.2 mmole, 2 eq) was dissolved in water (326 mg/ml), and 0.2 ml of this solution was added to each vial. 2-(4-acetoxy-phenyl)-3-bromo-7-methyl-benzofuran-5-yl ester (0.1 mmole,1 eq) was dissolved in dioxane (19.7 mg/ml) and 2 ml of this solution was added to each vial. Tetrakis(triphenylphosphine)palladium (5 mol%) was added as dry powder to each vial. Magnets were added, the vials were flushed with nitrogen, capped and run in microwave at 150 degrees for 60 minutes. The reaction mixtures were filtered and evaporated. The residues were dissolved in dry methanol (2 ml) and THF (200 ul), and treated with a few drops of 1M sodium methoxide solution for 3 hours at room temp. The reaction mixtures were neutralized with H^+ resin (Amberlyst 15) for 15 min, filtered and chromatographed on preparative reversed phase HPLC.

Appropriate fractions were combined and evaporated, and identified by ^{1}H-NMR and LC/MS. Purity was determined by analytical HPLC.

Method B

Acetic acid 2-(4-acetoxy-phenyl)-3-bromo-7-methyl-benzofuran-5-yl ester (30 mg, 0.074 mmol, 1 eq) was dissolved in dry DMF and dispensed into the vials. LiCl (23 mg, 0.52 mmol, 7 eq) and tetrakis (0.05 eq) were added with a spatula. The vials were again flushed with nitrogen. The tin reagents were added with a pipette (0.089 mmol, 1.2 eq). The vials were capped and run in microwave at 100 degrees for 10 minutes.

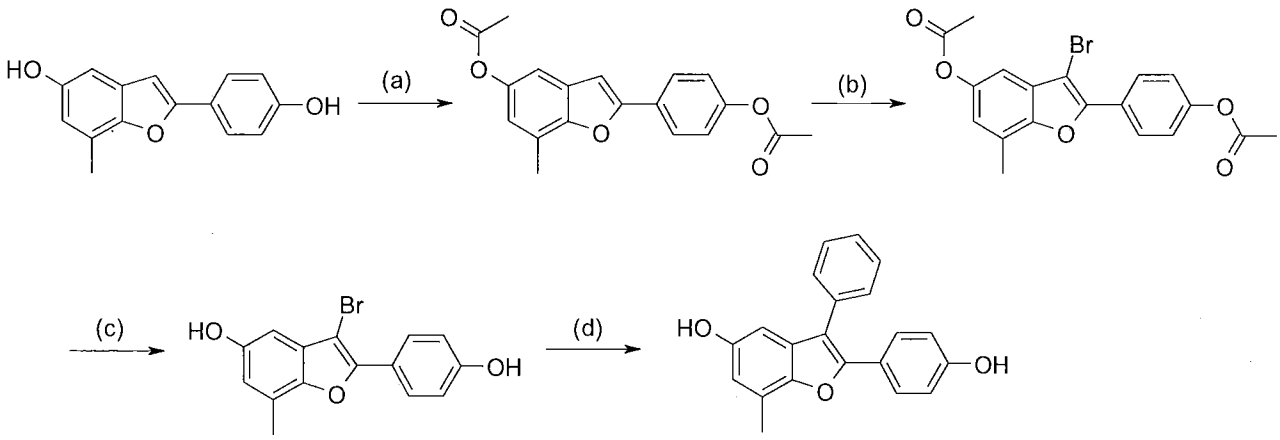
The solvents were removed by vacuum centrifugation, and the residue was dissolved in dry methanol (2 ml). A few drops of 1M sodium methoxide solution were added. The solution was stirred at room temp for 20 min, neutralized with Amberlyst 15 (H^+ resin), filtered, evaporated to 1.5 ml by applying nitrogen flow, and purified by prep HPLC using 20-50% ACN, 20 min acidic gradient.

The following Examples illustrate the invention.

Example 1

2-(4-Hydroxy-phenyl)-7-methyl-3-phenyl-benzofuran-5-ol (E1)

Scheme 1



(a) NaOAc, Ac_2O; (b) Br_2, $CHCl_3$; (c) KOH, EtOH; (d) $PhB(OH)_2$,$Pd(OAc)_2$, 2-Dicyclohexylphosphino-2',6'-dimethoxy-1,1'biphenyl, K_2CO_3, toluene

(a) Acetic acid 2-(4-acetoxy-phenyl)-7-methyl-benzofuran-5-yl ester

2-(4-Hydroxy-phenyl)-7-methyl-benzofuran-5-ol (prepared according to WO03/51860; 16 mg, 0.067 mmol) and sodium acetate (8 mg, 0.13 mmol) were mixed with acetic anhydride (1 mL)

and stirred at room temperature overnight. Methanol (1 mL) was added and the mixture was stirred for 30 minutes, then saturated aqueous sodium bicarbonate (3 mL) was added, the mixture was extracted with CH_2Cl_2 and filtered through an isolute phase separator. The organic phase was evaporated to give the title compound in quantitative yield.

(b) Acetic acid 2-(4-acetoxy-phenyl)-3-bromo-7-methyl-benzofuran-5-yl ester

Acetic acid 2-(4-acetoxy-phenyl)-7-methyl-benzofuran-5-yl ester (24 mg, 0.067 mmol) was dissolved in $CHCl_3$ (1 mL), the mixture was cooled to 0 °C, bromine (3.5 µL, 0.067 mmol) was added, the mixture was stirred at 0 °C for one hour, then at room temperature for 2 h. The solvent was evaporated to give the title compound in quantitative yield.

(c) 3-Bromo-2-(4-hydroxy-phenyl)-7-methyl-benzofuran-5-ol

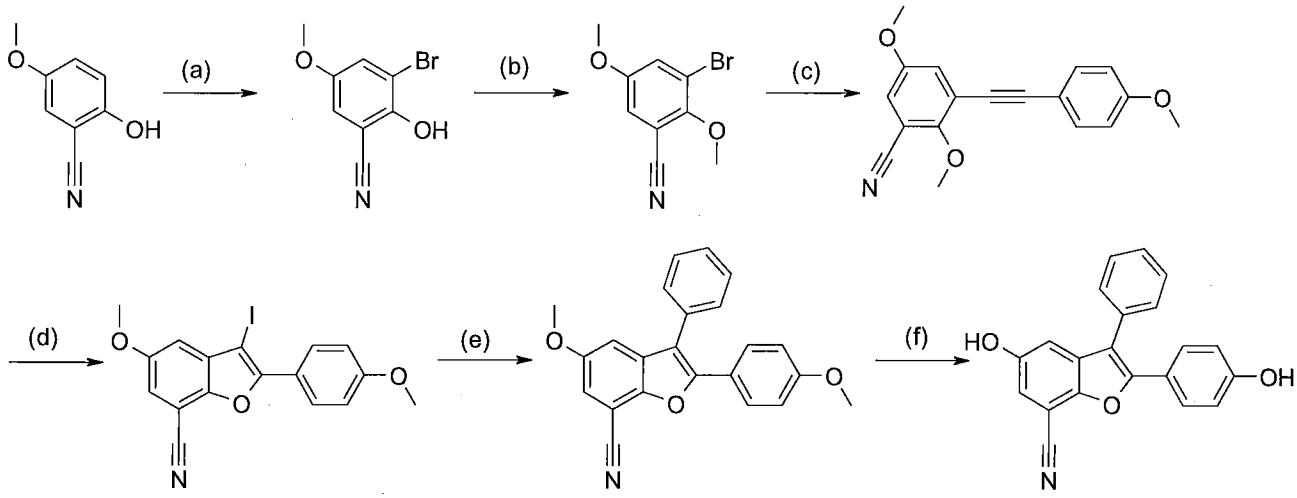
To a solution of acetic acid 2-(4-acetoxy-phenyl)-3-bromo-7-methyl-benzofuran-5-yl ester (2 mg, 4.5 µmol) in EtOH (0.5 mL) at room temperature was added KOH (2 mg, 0.032 mmol) and the mixture was stirred for 30 minutes. A few drops of aqueous HCl (2 M) were added to adjust the pH to 1. The mixture was diluted with water and extracted with CH_2Cl_2, then filtered through a phase separator, and the organic phase was evaporated to give the title compound in quantitative yield.

(d) 2-(4-Hydroxy-phenyl)-7-methyl-3-phenyl-benzofuran-5-ol

A mixture of acetic acid 2-(4-acetoxy-phenyl)-3-bromo-7-methyl-benzofuran-5-yl ester (8 mg, 0.018 mmol), 2-dicyclohexylphosphino-2',6'-dimethoxy-1-1'-biphenyl (0.4 mg, 0.001 mmol), palladium acetate (0.1 mg, 0.0004 mmol), potassium carbonate (5.2 mg, 0.038 mmol), and phenylboronic acid (4.4 mg, 0.036 mmol) in toluene (0.5 mL) was stirred at 90 °C overnight. After cooling, water and CH_2Cl_2 were added, and the mixture was filtered through a phase separator. The organic phase was evaporated and the residue was purified by preparative HPLC to give the title compound (3 mg, 52 %). ES/MS m/z: 317 (M+H), 315.1 (M-H); ^{1}H NMR (acetone-d6, 500MHz): 7.66-7.61 (m, 4H), 7.18 (dd, 1H, J=4.4, 1.6Hz), 6.96 (m, 2H), 6.84 (m, 1H), 6.77 (m, 1H) and 2.52 (s, 3H).

Example 2: 5-Hydroxy-2-(4-hydroxy-phenyl)-3-phenyl-benzofuran-7-carbonitrile (E2)

Scheme 2



(a) Br_2, $CHCl_3$; (b) 1,8-Diazabicyclo[5.4.0]undec-7-ene, CH_3I, acetone; (c) 1-Ethynyl-4-methoxybenzene, X-Phos, $Pd(AcCN)_2Cl_2$, Cs_2CO_3,EtCN; (d) I_2, CH_2Cl_2; (e) $PhB(OH)_2$,2-Dicyclohexylphosphino-2',6'-dimethoxy-1,1'-biphenyl, $Pd(OAc)_2$, K_2CO_3, toluene, ethanol; (f) BBr_3, CH_2Cl_2;

(a) 3-Bromo-2-hydroxy-5-methoxy-benzonitrile

To an ice cold solution of 2-Hydroxy-5-methoxy-benzonitrile (1.00 g, 6.71 mmol) in $CHCl_3$ (50 mL) was added dropwise over a period of 30 minutes a solution of bromine (345 µL, 6.71 mmol) in $CHCl_3$ (50 mL) and the mixture was stirred at 0 °C for another 30 minutes. The mixture was washed with an excess of an aqueous solution of sodium bisulfite until the orange bromine color faded, and was then filtered through a phase separator. The organic phase was evaporated to give 1.53 g (100 %) of the title compound.

(b) 3-Bromo-2,5-dimethoxy-benzonitrile

To a stirred solution of 3-Bromo-2-hydroxy-5-methoxy-benzonitrile (1.53 g, 6.71 mmol) and iodomethane (4.10 mL, 65.8 mmol) in acetone (100 mL) was added dropwise over 1 h a solution of 1,8-diazabicyclo[5.4.0]undec-7-ene (3.92 mL, 26.3 mmol) in acetone (50 mL). After addition was complete the reaction mixture was stirred for another hour, then ~80 % of the solvent was evaporated, and the residue was diluted with water and extracted with CH_2Cl_2. It was then filtered through a phase separator, the organic phase was evaporated and the residue was purified by column chromatography (mobile phase: CH_2Cl_2 – isohexane 1:1) to give the title compound (1.62 g, 100%).

(c) 2,5-Dimethoxy-3-(4-methoxy-phenylethynyl)-benzonitrile

3-Bromo-2,5-dimethoxy-benzonitrile (505 mg, 2.07 mmol), dicyclohexyl-(2',4',6'-triisopropyl-biphenyl-2-yl)-phosphane (30 mg, 0.062 mmol), bisacetonitrile palladium (II) chloride (5 mg, 0.021 mmol), cesium carbonate (1.35 g, 4.14 mmol) and propionitrile (15 mL) were stirred at reflux under a flow of nitrogen gas. A solution of 1-ethynyl-4-methoxy-benzene (287 mg, 2.17 mmol) in propionitrile (5 mL) was added *via* syringe dropwise over 30 minutes and after addition was complete the mixture was stirred at reflux for an additional 2 h. After cooling and dilution with water the mixture was extracted with CH_2Cl_2, filtered through a phase separator, the organic phase was evaporated and the residue was purified by column chromatography (mobile phase: CH_2Cl_2 – isohexane 1:2) to give the title compound (550 mg, 91%).

(d) 3-Iodo-5-methoxy-2-(4-methoxy-phenyl)-benzofuran-7-carbonitrile

To a solution of 2,5-dimethoxy-3-(4-methoxy-phenylethynyl)-benzonitrile (550 mg, 1.88 mmol) in CH_2Cl_2 (15 mL) that was kept dark using aluminum foil around the reaction vessel, iodine (952 mg, 3.76 mmol) was added and the mixture was stirred at room temperature for 3 h. An excess of an aqueous solution of $NaHSO_3$ was added and the mixture was stirred until the violet iodine color had faded. It was then filtered through a phase separator, the organic phase was evaporated and the residue was purified by column chromatography (mobile phase: CH_2Cl_2 – isohexane 1:1) to give the title compound (762 mg, 100 %). Reference for the iodocyclization: *J. Org. Chem.* **2005**, *70*, 10292-20296.

(e) 5-Methoxy-2-(4-methoxy-phenyl)-3-phenyl-benzofuran-7-carbonitrile

A mixture of 3-iodo-5-methoxy-2-(4-methoxy-phenyl)-benzofuran-7-carbonitrile (20 mg, 0.049 mmol), dicyclohexyl-(2',6'-dimethoxy-biphenyl-2-yl)-phosphane (1.6 mg, 0.004 mmol), palladium acetate (0.23 mg, 0.001 mmol), potassium carbonate (14 mg, 0.098 mmol), phenylboronic acid (12 mg, 0.098 mmol), toluene (0.9 mL) and EtOH (0.1 mL) was stirred at room temperature overnight. The mixture was then diluted with CH_2Cl_2, washed with water, and filtered through a phase separator. The organic phase was evaporated and the residue was purified by column chromatography (mobile phase CH_2Cl_2 – isohexane 1:1) to give the title compound (17 mg, 97 %).

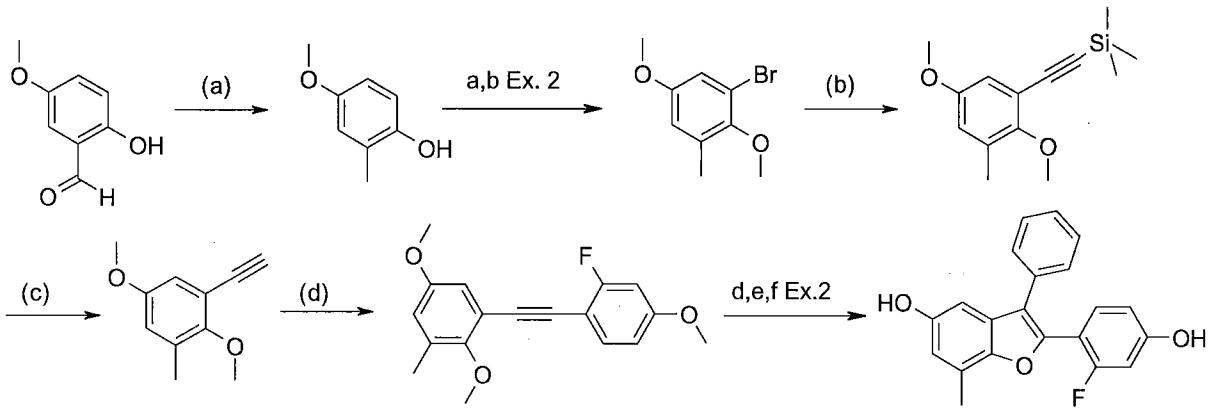
(f) 5-Hydroxy-2-(4-hydroxy-phenyl)-3-phenyl-benzofuran-7-carbonitrile

A solution of boron tribromide in CH_2Cl_2 (1 M, 240 µL, 0.24 mmol) was added to a stirred solution of 5-methoxy-2-(4-methoxy-phenyl)-3-phenyl-benzofuran-7-carbonitrile (17 mg, 0.048

mmol) and the mixture was stirred at room temperature for 1 h. The reaction was quenched with methanol, washed with $NaHCO_3$ (saq), and filtered through a phase separator. The organic phase was evaporated and the residue was purified by column chromatography (mobile phase CH_2Cl_2 – methanol 19:1) to give the title compound (13 mg, 83 %). ES/MS m/z : 328.1 (M+H), 326.2 (M-H); ^1H NMR (MeOH-d4, 500MHz): 7.45-7.50 (m, 2H), 7.39-7.45 (m, 5H), 7.0-7.03 (m, 2H), 6.71-6.75 (m, 2H).

Example 3: 2-(2-Fluoro-4-hydroxy-phenyl)-7-methyl-3-phenyl-benzofuran-5-ol (E3)

Scheme 3



(a) 1.EtOCOCl, Et_3N, THF 2. NaBH4 (aq); (b) Trimethylsilylacetylene, X-Phos, $Pd(AcCN)_2Cl_2$, Cs_2CO_3, EtCN; (c) Tetrabutylammonium fluoride, THF; (d) 4-Bromo-3-Fluoroanisole, X-Phos, $Pd(AcCN)_2Cl_2$, Cs_2CO_3, EtCN

(a) 4-Methoxy-2-methyl-phenol

The title compound was obtained from 2-hydroxy-5-methoxy-benzaldehyde using the method described in *Chem Pharm Bull 27* (6), **1979**, *pp 1490-1494*: Ethyl chloroformate (571 µL, 6.0 mmol) was added dropwise over a period of 30 minutes to an ice cold solution of 2-hydroxy-5-methoxy-benzaldehyde (624 µL, 5.0 mmol) and triethyl amine (832 µL, 6.0 mmol) in THF (5 mL) and the mixture was stirred at °C for 30 more minutes. The precipitate was filtered off and the filtrate was dropwise over a period of 45 minutes added to an ice cold solution of $NaBH_4$ (756 mg, 20 mmol) in water (7.5 mL). The resulting mixture was stirred at room temperature for 90 minutes, then diluted with water, acidified to pH < 2 with 2 M HCl and extracted with ether. The organic phase was dried ($MgSO_4$) and evaporated. When 90 % of the ether had evaporated a precipitate formed that was filtered away. The title compound was in the filtrate. Quantitative yield.

(b) (2,5-Dimethoxy-3-methyl-phenylethynyl)-trimethyl-silane

1-Bromo-2,5-dimethoxy-3-methyl-benzene (prepared from 4-methoxy-2-methyl-phenol according to the first steps of method 2, 1.62 g, 6.61 mmol), dicyclohexyl-(2',4',6'-triisopropyl-biphenyl-2-yl)-phosphane (94 mg, 0.20 mmol), bisacetonitrile palladium (II) chloride (17 mg, 0.066 mmol), cesium carbonate (4.31 g, 13.2 mmol) and propionitrile (40 mL) were stirred at reflux under a flow of nitrogen gas. Ethynyl-trimethyl-silane (2.04 mL, 13.2 mmol) was added *via* syringe and the mixture was stirred at reflux for an additional 2 h. After cooling and dilution with water the mixture was extracted with CH_2Cl_2, and filtered through a phase separator. The organic phase was evaporated and the residue was purified by column chromatography (mobile phase: CH_2Cl_2 – isohexane 1:3) to give the title compound (312 mg, 19 %) along with a considerable amount of 1-Ethynyl-2,5-dimethoxy-3-methyl-benzene (242 mg, 21 %).

(c) 1-Ethynyl-2,5-dimethoxy-3-methyl-benzene

To a solution of (2,5-dimethoxy-3-methyl-phenylethynyl)-trimethyl-silane (312 mg, 1.26 mmol) in THF (10 mL) was added tetrabutylammonium fluoride hydrate (362 mg, 1.38 mmol) and the mixture was stirred at room temperature for 1 h. The mixture was diluted with ether and washed with water, the phases were separated, and the organic phase was dried ($MgSO_4$), filtered and evaporated. The residue was filtered through a silica plug (2 g) using CH_2Cl_2 as the eluent to give the title product in quantitative yield.

(d) 1-(2-Fluoro-4-methoxy-phenylethynyl)-2,5-dimethoxy-3-methyl-benzene

1-Bromo-2-fluoro-4-methoxy-benzene (47 mg, 0.23 mmol), dicyclohexyl-(2',4',6'-triisopropyl-biphenyl-2-yl)-phosphane (3 mg, 0.0068 mmol), bisacetonitrile palladium (II) chloride (0.6 mg, 0.0023 mmol), cesium carbonate (150 mg, 0.46 mmol) and propionitrile (0.5 mL) were stirred at reflux under a flow of nitrogen gas. A solution of 1-ethynyl-2,5-dimethoxy-3-methyl-benzene (40 mg, 0.23 mmol) in propionitrile (0.5 mL) was added *via* syringe and the mixture was stirred at reflux for an additional 2 h. After cooling and dilution with water the mixture was extracted with CH_2Cl_2 and filtered through a phase separator. The organic phase was evaporated and the residue was purified by column chromatography (mobile phase: CH_2Cl_2 – isohexane 1:1) to give the title compound (58 mg, 84 %).

2-(2-Fluoro-4-hydroxy-phenyl)-7-methyl-3-phenyl-benzofuran-5-ol

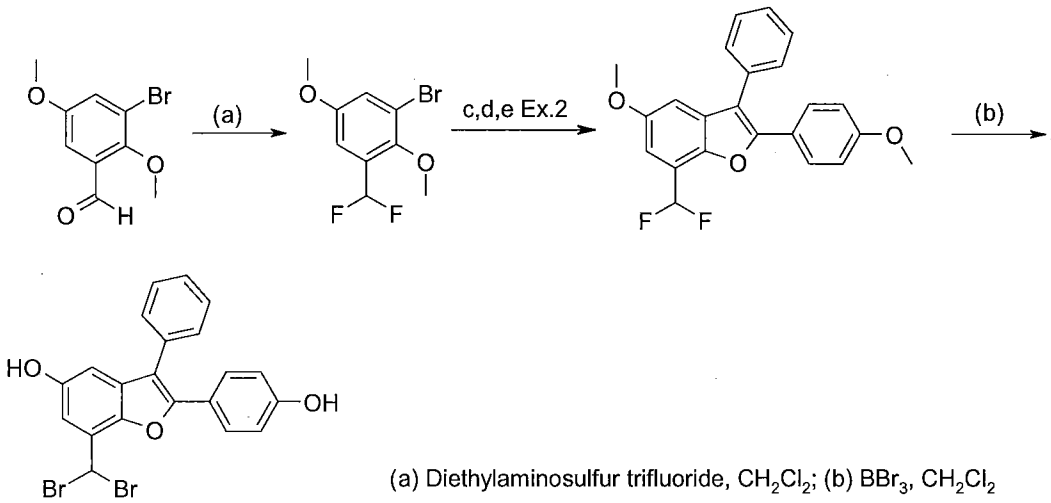
The title compound was prepared from 1-(2-fluoro-4-methoxy-phenylethynyl)-2,5-dimethoxy-3-methyl-benzene in the three final steps described in method 2. ES/MS m/z: 353.3 (M+H), 351.4

(M-H); ^{1}H NMR (MeOH-d4, 500MHz): 7.33-7.39 (m, 4 H), 7.26-7.31 (m, 3H), 6.80 (d, 2.23 Hz, 1H), 6.64-6.66 (m, 1H), 6.62 (dd, 2.24 Hz, 8.56 Hz, 1H), 6.52 (dd, 2.50 Hz, 12.00 Hz, 1H), 2.48 (s, 3H).

Example 4

7-Dibromomethyl-2-(4-hydroxy-phenyl)-3-phenyl-benzofuran-5-ol (E4)

Scheme 4



(a) Diethylaminosulfur trifluoride, CH_2Cl_2; (b) BBr_3, CH_2Cl_2

(a) 1-Bromo-3-difluoromethyl-2,5-dimethoxy-benzene

To a plastic tube containing a solution of 3-bromo-2,5-dimethoxy-benzaldehyde (prepared from 2-hydroxy-5-methoxy-benzaldehyde according to the first steps of method 2, 108 mg, 0.44 mmol) in CH_2Cl_2 (3 mL) was added diethylaminosulfur trifluoride (291 µL, 2.2 mmol) and the mixture was stirred at 40 °C overnight. After cooling the mixture was poured into water, filtered through a phase separator. The organic phase was evaporated and the residue was purified by column chromatography (mobile phase: CH_2Cl_2 – isohexane 1:3 to give the title compound (96 mg, 82 %).

(b) 7-Dibromomethyl-2-(4-hydroxy-phenyl)-3-phenyl-benzofuran-5-ol

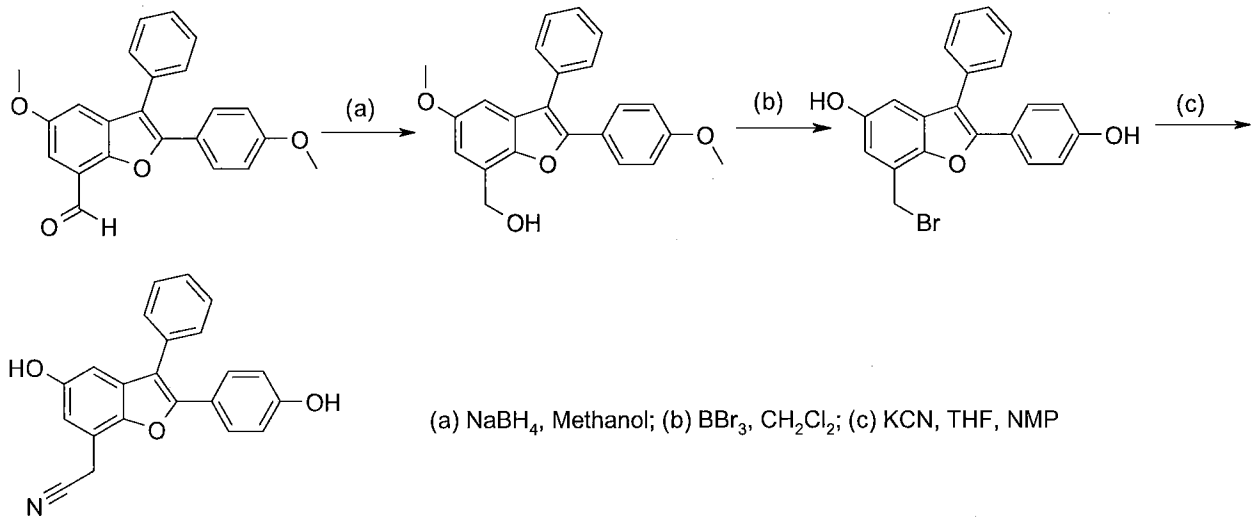
A solution of boron tribromide in CH_2Cl_2 (1 M, 220 µL, 0.22 mmol) was added to a stirred solution of 7-difluoromethyl-5-methoxy-2-(4-methoxy-phenyl)-3-phenyl-benzofuran (prepared from 1-bromo-3-difluoromethyl-2,5-dimethoxy-benzene according to method 2, 17 mg, 0.045 mmol) and the mixture was stirred at room temperature for 1 h. The reaction was quenched with methanol, washed with $NaHCO_3$ (saq), and filtered through a phase separator. The organic

phase was evaporated and the residue was purified by column chromatography (mobile phase CH_2Cl_2 – methanol 19:1) to give the title compound (5 mg, 23 %). ^1H NMR ($CDCl_3$, 500MHz): 7.58-7.61 (m, 2H), 7.43-7.49 (m, 4H), 7.38-7.42 (m, 1H), 7.22 (s, 1H), 7.19 (d, 2.46 Hz, 1H), 6.85-6.89 (m, 3H).

Example 5

[5-Hydroxy-2-(4-hydroxy-phenyl)-3-phenyl-benzofuran-7-yl]-acetonitrile (E5)

Scheme 5



(a) [5-Methoxy-2-(4-methoxy-phenyl)-3-phenyl-benzofuran-7-yl]-methanol

To a solution of 5-methoxy-2-(4-methoxy-phenyl)-3-phenylbenzofuran-7-carbaldehyde (prepared from 2-hydroxy-5-methoxy-benzaldehyde according to method 2, 53 mg, 0.15 mmol) in methanol (3 mL) was added $NaBH_4$ (11 mg, 0.30 mmol) and the mixture was stirred at room temperature for 1 h. The reaction was quenched with 1 M HCl (aq) and the mixture was diluted with water. The title compound precipitated and was isolated by filtration. Yield: 50 mg (94%).

(b) 7-Bromomethyl-2-(4-hydroxy-phenyl)-3-phenyl-benzofuran-5-ol

To an ice cold solution of [5-methoxy-2-(4-methoxy-phenyl)-3-phenyl-benzofuran-7-yl]-methanol (50 mg, 0.14 mmol) in CH_2Cl_2 (3 mL) was added a 1 M solution of BBr_3 in CH_2Cl_2 (0.56 mL, 0.56 mmol) and the mixture was stirred at 0 °C for 4 h. The reaction was quenched by the addition of methanol, washed with sodium bicarbonate (saq), and filtered through a phase separator. The organic phase was evaporated and the residue was purified by column

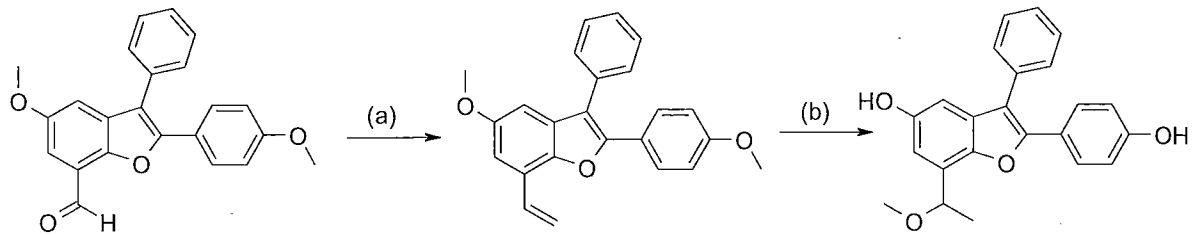
chromatography (mobile phase: CH_2Cl_2 – methanol 39:1) to give the title compound (26 mg, 44%).

(c) [5-Hydroxy-2-(4-hydroxy-phenyl)-3-phenyl-benzofuran-7-yl]-acetonitrile

Potassium cyanide (3 mg, 0.039 mmol) and 7-bromomethyl-2-(4-hydroxy-phenyl)-3-phenyl-benzofuran-5-ol (14 mg, 0.035 mmol) were suspended in a 3:1 mixture of THF and NMP (0. 5 mL) and the mixture was stirred at 60 °C overnight. Sodium bicarbonate (saq) was added and the mixture was extracted with a 4:1 mixture of CH_2Cl_2 and methanol, and filtered through a phase separator. The organic phase was evaporated and the residue was purified by column chromatography (mobile phase: CH_2Cl_2 – methanol 39:1) to give the title compound (2 mg, 17 %). ES/MS m/z: 342.2 (M+H), 340 (M-H); ^{1}H NMR: (MeOH-d4, 500 MHz): 7.38-7.50 (m, 7H), 6.83 (d, 2.37 Hz, 1H), 6.75 (d, 2.37 Hz, 1H), 6.71-6.74 (m, 2H), 4.16 (s, 2H).

Example 6: 2-(4-Hydroxy-phenyl)-7-(1-methoxy-ethyl)-3-phenyl-benzofuran-5-ol (E6)

Scheme 6



(a) BuLi, Ph_3PCH_3Br, THF; (b) 1. BF_3SMe_2, cyclohexene, CH_2Cl_2, 2. Methanol

(a) 5-Methoxy-2-(4-methoxy-phenyl)-3-phenyl-7-vinyl-benzofuran

Butyllithium (2.5 M in hexanes, 0.08 mL, 0.2 mmol) was added to an ice cold slurry of methyltriphenylphosphinium bromide in THF (1 mL). The mixture was stirred at 0 °C for 15 minutes. 5-Methoxy-2-(4-methoxy-phenyl)-3-phenylbenzofuran-7-carbaldehyde (36 mg, 0.10 mmol) was added and the mixture was stirred at 50 °C for three hours. The reaction was quenched by the careful addition of 2 M HCl, extracted with CH_2Cl_2, filtered through a phase separator, the organic phase was evaporated and the residue was purified by column chromatography (mobile phase: CH_2Cl_2 – isohexane 1:2) to give the title compound (20 mg, 89%).

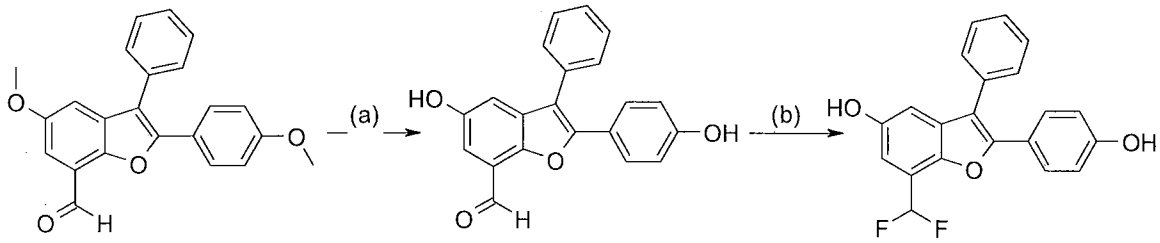
(b)2-(4-Hydroxy-phenyl)-7-(1-methoxy-ethyl)-3-phenyl-benzofuran-5-ol

5-Methoxy-2-(4-methoxy-phenyl)-3-phenyl-7-vinyl-benzofuran (12 mg, 0.034 mmol) and cyclohexene (34 µL, 0.34 mmol) were dissolved in CH_2Cl_2 (1 mL) and stirred at room temperature. $BF_3 \cdot S(CH_3)_2$ (14 µL, 0.135 mmol) was added and the mixture was stirred at room temperature overnight. Methanol was added, followed by $NaHCO_3$ (saq). After filtration through a phase separator the organic phase was evaporated and the residue was purified by column chromatography (mobile phase: CH_2Cl_2 – methanol 39:1) to give the title compound (2 mg, 15 %). ES/MS m/z: 361.4 (M+H), 359.2 (M-H); ^{1}H NMR: (MeOH-d4, 500 MHz): 7.37-7.50 (m, 7H), 6.78 (d, 2.43 Hz, 1H), 6.70-6.74 (m, 2H), 6.69 (d, 2.43 Hz, 1H), 4.91 (q, 6.55 Hz, 1H), 3.34 (s, 1H), 1.60 (d, 6.55 Hz, 3H).

Example 7

7-Difluoromethyl-2-(4-hydroxy-phenyl)-3-phenyl-benzofuran-5-ol (E7)

Scheme 7



(a) 1. BF_3SMe_2, CH_2Cl_2, Cyclohexene 2. Methanol; (b) Diethylaminosulfur trifluoride, CH_2Cl_2

(a) 5-Hydroxy-2-(4-hydroxy-phenyl)-3-phenyl-benzofuran-7-carbaldehyde

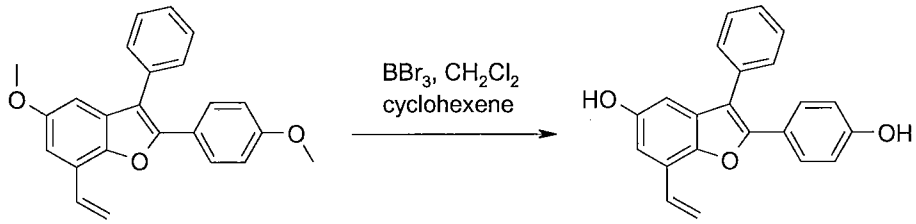
5-Methoxy-2-(4-methoxy-phenyl)-3-phenylbenzofuran-7-carbaldehyde (80 mg, 0.22 mmol) and cyclohexene (220 µL, 2.2 mmol) were dissolved in CH_2Cl_2 (3 mL) and stirred at room temperature. $BF_3 \cdot S(CH_3)_2$ (56 µL, 0.54 mmol) was added and the mixture was stirred at room temperature overnight. Methanol was added, followed by $NaHCO_3$ (saq). After filtration through a phase separator the organic phase was evaporated and the residue was purified by column chromatography (mobile phase: CH_2Cl_2 – methanol 39:1) to give the title compound (20 mg, 27%).

(b) 7-Difluoromethyl-2-(4-hydroxy-phenyl)-3-phenyl-benzofuran-5-ol

A solution of 5-hydroxy-2-(4-hydroxy-phenyl)-3-phenyl-benzofuran-7-carbaldehyde (15 mg, 0.045 mmol) and diethylaminosulfur trifluoride (22 µL, 0.18 mmol) in CH_2Cl_2 (0.5 mL) was stirred overnight at 40 °C in a plastic tube. After cooling, the reaction was quenched by the addition of methanol and the mixture was washed with $NaHCO_3$ (saq). After filtration through a phase separator the organic phase was evaporated and the residue was purified by column chromatography (mobile phase: CH_2Cl_2 – methanol 19:1) to give the title compound (5 mg, 31 %). ES/MS m/z: 353.3 (M+H), 351.3 (M-H); ^{1}H NMR: (MeOH-d4, 500 MHz): 7.39-7.51 (m, 7H), 7.18 (t, 55.13 Hz, 1H), 6.93-6.95 (m, 1H), 6.87-6.89 (m, 1H), 6.71-6.75 (m, 2H).

Example 8: 2-(4-Hydroxy-phenyl)-3-phenyl-7-vinyl-benzofuran-5-ol (8)

Scheme 8

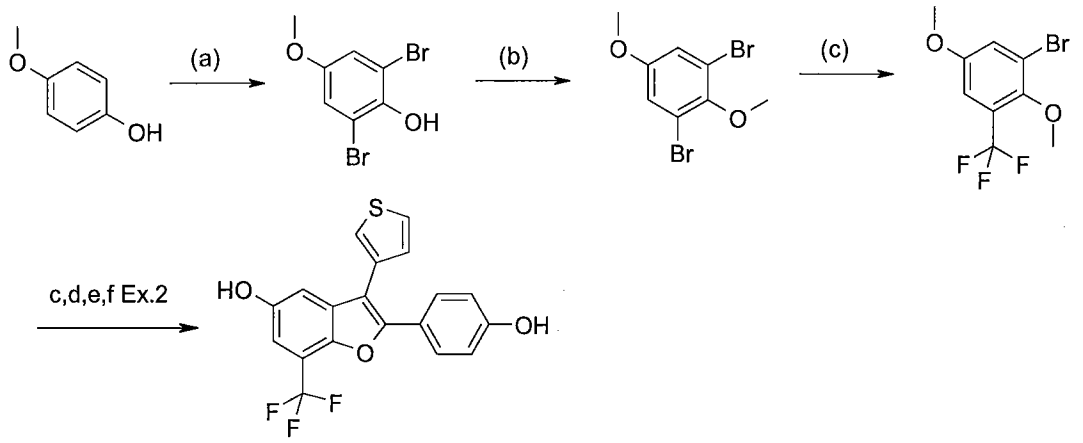


2-(4-Hydroxy-phenyl)-3-phenyl-7-vinyl-benzofuran-5-ol

To a solution of 5-methoxy-2-(4-methoxy-phenyl)-3-phenyl-7-vinyl-benzofuran (prepared according to method 6, 4 mg, 0.011 mmol) and cyclohexene (23 µL, 0.22 mmol) was added BBr_3 (1 M in CH_2Cl_2, 56 µL, 0.056 mmol) at -78 °C. The mixture was then stored in the freezer (-18 °C) overnight. The reaction was quenched with water, washed with $NaHCO_3$ (saq), and filtered through a phase separator. The organic phase was evaporated and the residue was purified by column chromatography (mobile phase: CH_2Cl_2 – methanol 39:1) to give the title compound (2 mg, 54 %). ES/MS m/z: 329.1 (M+H), 327.2 (M-H); ^{1}H NMR: (MeOH-d4, 500 MHz): 7.38-7.50 (m, 7H), 6.97 (dd, 13.37 Hz, 17.76 Hz, 1H), 6.81 (d, 2.52 Hz, 1H), 6.71-6.75 (m, 2H), 6.69 (d, 2.52 Hz, 1H), 6.25 (dd, 1.35 Hz, 17.76 Hz, 1H), 5.52 (dd, 1.35 Hz, 11.37 Hz, 1H).

Example 9

2-(4-Hydroxy-phenyl)-3-thiophen-3-yl-7-trifluoromethyl-benzofuran-5-ol (E9)



(a) Br_2, MeOH; (b) 1,8-Diazabicyclo[5.4.0]undec-7-ene, CH_3I, Acetone; (c) Methyl fluorosulphonyldifluoroacetate, CuI, DMF

(a) 2,6-Dibromo-4-methoxy-phenol

A solution of 4-methoxyphenol (5.72 g, 46.1 mmol) in MeOH (80 mL) was cooled to 0 °C while stirring. A solution of Br_2 (4.97 mL, 96.8 mmol) in MeOH (20 mL) was added dropwise and the resulting mixture was stirred at room temperature for 3 h. The reaction was quenched by the addition of aqueous solutions of $NaHCO_3$ and $NaHSO_3$.When gas evolution ceased and the bromine color had faded, water was added and a thick yellowish precipitate was formed. The precipitate was filtered off and recrystallized from MeOH-H_2O to give the title product (5.20 g, 40 %).

(b) 1,3-Dibromo-2,5-dimethoxy-benzene

To a stirred solution of 2,6-dibromo-4-methoxy-phenol (5.2 g, 18.4 mmol) and CH_3I (11.5 mL, 184 mmol) in dry acetone (50 mL) was added a solution of 1,8-diazabicyclo[5.4.0]undec-7-ene (13.8 mL, 92.2 mmol) in dry acetone (50 mL) dropwise during 30 min. When the addition was complete the reaction mixture was stirred at room temp for 30 minutes. The mixture was poured into 2 M HCl (aq) and extracted with ether. The organic phase was dried, filtered and evaporated and the residue was purified by column chromatography (mobile phase CH_2Cl_2-isohexane 9:1 → 1:1) to give the desired bisether as a colorless liquid.

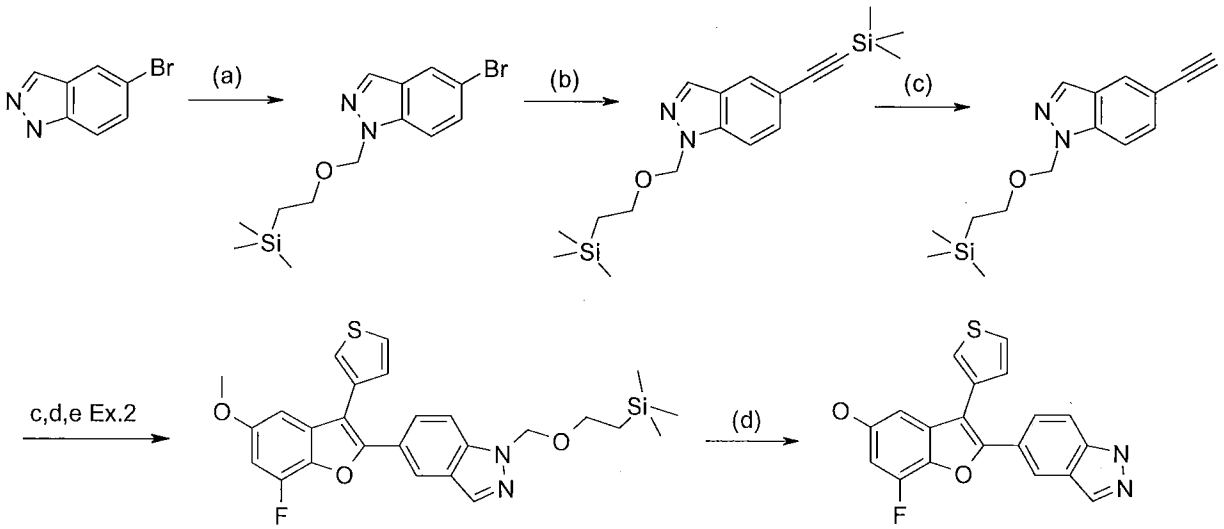
(c) 1-Bromo-2,5-dimethoxy-3-trifluoromethyl-benzene

To a stirred solution of 1,3-dibromo-2,5-dimethoxy-benzene (353 mg, 1.19 mmol) and difluoro-fluorosulfonyl-acetic acid methyl ester (455 µL, 3.58 mmol) in DMF (1 mL) under N_2 was added CuI (227 mg, 1.19 mmol). The mixture was then stirred at 80 °C over three days under N_2. The reaction was worked up by cooling, dilution with CH_2Cl_2, washing with water, and filtering through a phase separator. The organic phase was evaporated and the residue was purified by column chromatography (mobile phase CH_2Cl_2 - isohexane 1:9 → 1:1) to give the title compound (60 mg, 18 %).

2-(4-Hydroxy-phenyl)-3-thiophen-3-yl-7-trifluoromethyl-benzofuran-5-ol

The title compound was prepared from 1-bromo-2,5-dimethoxy-3-trifluoromethyl-benzene in the four final steps described in example 2. ES/MS m/z: 377.2 (M+H), 375.2 (M-H).

Example 10: 7-Fluoro-2-(1H-indazol-5-yl)-3-thiophen-3-yl-benzofuran-5-ol (E10)



(a) Tetrabutylammonium bromide, 2-(Trimethylsilyl)ethoxymethyl chloride; (b) Trimethylsilylacetylene, X-Phos, $Pd(AcCN)_2Cl_2$, Cs_2CO_3, EtCN; (c) Tetrabutylammonium fluoride; (d) BBr_3, CH_2Cl_2, Cyclohexene

(a) 5-Bromo-1-(2-trimethylsilanyl-ethoxymethyl)-1H-indazole

A mixture of the 5-bromo-1H-indazole (2.00 g, 10.15 mmol), tetrabutylammonium bromide (33 mg, 0.10 mmol) and 2 M NaOH (aq, 10.15 mL, 20.3 mmol) in CH_2Cl_2 (30 mL) was cooled in an ice bath, a solution of (2-chloromethoxy-ethyl)-trimethyl-silane in CH_2Cl_2 (20 mL) was added dropwise during 30 minutes and the mixture was stirred at 0 °C for 1 h then allowed to warm to room temperature and stirred for one additional hour. The mixture was filtered through a phase separator, the organic phase was evaporated to give the title compound and the regioisomeric 5-

bromo-2-(2-trimethylsilanyl-ethoxymethyl)-2H-indazole in a 3:1 ratio in a combined quantitative yield.

(b) 1-(2-Trimethylsilanyl-ethoxymethyl)-5-trimethylsilanylethynyl-1H-indazole

A mixture of 5-bromo-1-(2-trimethylsilanyl-ethoxymethyl)-1H-indazole (3.32 g, 10.15 mmol), dicyclohexyl-(2',4',6'-triisopropyl-biphenyl-2-yl)-phosphane (387 mg, 0.81 mmol), bisacetonitrile palladium (II) chloride (53 mg, 0.20 mmol), cesium carbonate (6.61 g, 20.30 mmol), and propionitrile (60 mL) was stirred at to 80 °C under argon. Ethynyl-trimethyl-silane (4.3 mL, 30.5 mmol) was added via syringe and the mixture was stirred at 80 °C for 2 h. The mixture was cooled, diluted with water and ether; the phases were separated, the organic phase was dried, filtered, and evaporated and the residue was purified by column chromatography (mobile phase: CH_2Cl_2 - isohexane 1:9 → 1:0) to give the title compound (3.10 g, 89 %).

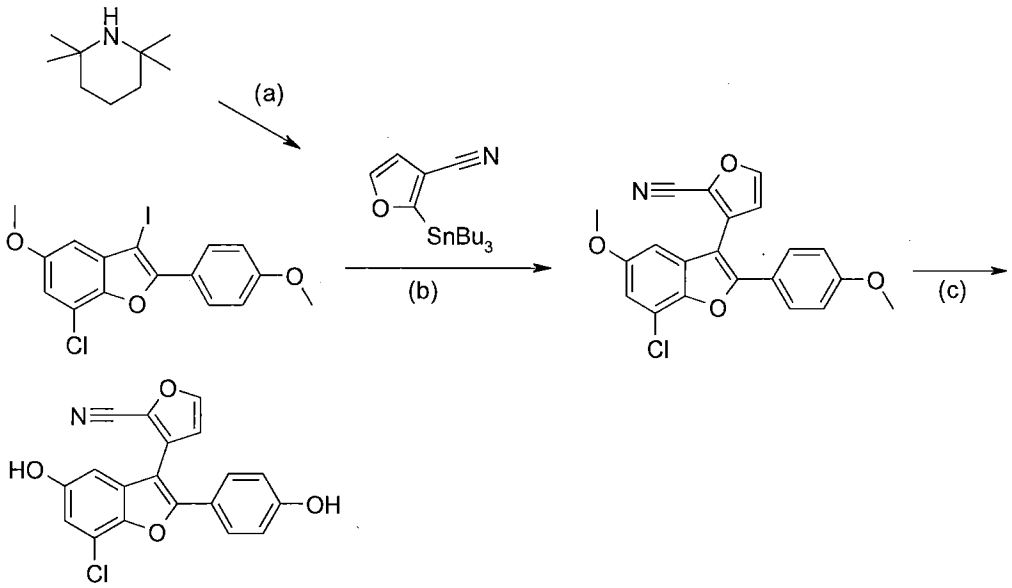
(c) 5-Ethynyl-1-(2-trimethylsilanyl-ethoxymethyl)-1H-indazole

1-(2-Trimethylsilanyl-ethoxymethyl)-5-trimethylsilanylethynyl-1H-indazole (357 mg, 1.04 mmol), tetrabutylammonium fluoride hydrate (271 mg, 1.04 mmol), and acetonitrile (10 mL) were mixed and stirred at 0 °C for 10 minutes. The solvent was evaporated and the residue was filtered through a 5 g silica plug. The title compound (235 mmol, 83 %) was eluted with a mixture of CH_2Cl_2 and isohexane (1:1).

(d) 7-Fluoro-2-(1H-indazol-5-yl)-3-thiophen-3-yl-benzofuran-5-ol

To a solution of 5-(7-fluoro-5-methoxy-3-thiophen-3-yl-benzofuran-2-yl)-1-(2-trimethylsilanyl-ethoxymethyl)-1H-indazole (prepared from 2-fluoro-4-methoxy-phenol and eventually 5-ethynyl-1-(2-trimethylsilanyl-ethoxymethyl)-1H-indazole according to method 2, 20 mg, 0.04 mmol) and cyclohexene (82 µL, 0.81 mmol) in CH_2Cl_2 (1 mL) at 6 °C was added BBr_3 (1 M in CH_2Cl_2, 0.40 mL, 0.40 mmol) and the mixture was left at that temperature overnight. The reaction was quenched with water, pH was adjusted to ~10 with sodium carbonate (saq), extracted with EtOAc, the phases were separated, the organic phase was dried (Na_2CO_3), filtered, and evaporated. The residue was purified by column chromatography (mobile phase: CH_2Cl_2 – methanol 99:1 → 19:1) to give the title compound (4.3 mg, 30 %). ES/MS m/z: 351.1 (M+1), 349.1 (M-1); ^{1}H NMR (MeOH-d4, 500 MHz): 8.09-8.10 (m, 1H), 8.06 (d, 093 Hz, 1H), 7.63 (dd, 1.52 Hz, 8.81 Hz, 1H), 7.58 (dd, 2.83 Hz, 5.04 Hz, 1H), 7.53 (dd, 1.27 Hz, 3.14 Hz, 1H), 7.49-7.52 (m, 1H), 7.12 (dd, 1.28 Hz, 5.03 Hz, 1H), 6.69 (d, 2.14 Hz, 1H), 6.61 (dd, 2.14 Hz, 12.05 Hz, 1H).

Example 11: 2-[7-Chloro-5-hydroxy-2-(4-hydroxy-phenyl)-benzofuran-3-yl]-furan-3-carbonitrile (E11)



(a) 1. BuLi, THF 2. 3-Furonitrile 3. Bu_3SnCl; (b) $Pd(PPh_3)_2Cl_2$, dioxane; (c) BBr_3, CH_2Cl_2

(a) 2-Tributylstannanyl-furan-3-carbonitrile

Butyllithium (1.6 M in hexanes, 3.3 mL, 5.24 mmol) was added to an ice cold solution of 2,2,6,6-tetramethylpiperidine (1.00 mL, 5.90 mmol) in THF (10 mL). The solution was stirred at 0 °C for 30 minutes, then cooled to -78 °C. A solution of furan-3-carbonitrile (610 mg, 6.56 mmol) in THF (10 mL) was added dropwise over 30 minutes and the mixture was stirred for 2 h at -78 °C. A solution of tributyltin chloride in THF (2 mL) was added dropwise over 30 minutes and the mixture was stirred overnight. The temperature was allowed to rise to room temperature during that time. The reaction was quenched by the addition of NH_4Cl (saq), extracted with $CHCl_3$, filtered through a phase separator. The organic phase was evaporated and the residue was purified by column chromatography (mobile phase CH_2Cl_2 - isohexane 0:1 → 1:1) to give the title compound (992 mg, 50 %).

(b) 3-[7-Chloro-5-methoxy-2-(4-methoxy-phenyl)-benzofuran-3-yl]-furan-2-carbonitrile

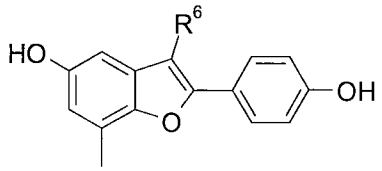
7-Chloro-3-iodo-5-methoxy-2-(4-methoxy-phenyl)-benzofuran (prepared from 2-chloro-4-methoxy-phenol according to method 2, 24 mg, 0.06 mmol), 2-tributylstannanyl-furan-3-carbonitrile (29 mg, 0.08 mmol) and $Pd(PPh_3)_2Cl_2$ (4 mg, 0.01 mmol) was mixed with dioxane (0.5 mL) under nitrogen in a microwave vial. The reaction was run in a microwave reactor at 130 °C for 40 min. NH_4Cl (saq), was added, and the mixture was extracted with $CHCl_3$ and filtered

through a phase separator. The organic phase was evaporated and the residue was purified by column chromatography (mobile phase: CH_2Cl_2 - isohexane 1:3 → 1:0) to give the title compound (17 mg, 77 %).

(c) 3-[7-Chloro-5-hydroxy-2-(4-hydroxy-phenyl)-benzofuran-3-yl]-furan-2-carbonitrile

To an ice cold solution of 3-[7-chloro-5-methoxy-2-(4-methoxy-phenyl)-benzofuran-3-yl]-furan-2-carbonitrile (17 mg, 0.04mmol) in CH_2Cl_2 (1 mL) was added BBr_3 (1 M in CH_2Cl_2, 0.45 mL, 0.45 mmol). The mixture was stored in the refrigerator at 6 °C overnight without stirring. The reaction was quenched by the addition of $NaHCO_3$ (saq), extracted with CH_2Cl_2 - MeOH 19:1, and filtered through a phase separator. The organic phase was evaporated and the residue was purified by column chromatography (mobile phase CH_2Cl_2 - MeOH 1:0 → 9:1) to give the title compound (1 mg, 6 %). ES/MS m/z: 352 (M+1), 350 (M-1); ^{1}H NMR (MeOH-d4, 500 MHz): 7.85 (d, 2.02 Hz, 1H), 7.71 (d, 8.61 Hz, 1H), 7.44-7.49 (m, 2H), 6.93 (d, 2.00 Hz, 1H), 6.83-6.90 (m, 3H).

The following example compounds were synthesized using the procedures described above.



E 12 2-(4-Hydroxy-phenyl)-7-methyl-3-thiophen-3-yl-benzofuran-5-ol

R^6 = thiophen-3-yl

ES/MS m/z: 323.6 (pos. M + H), 321.6 (neg. M – H); ^{1}H NMR (acetone-d6, 500MHz): 7.66-7.61 (m, 4H), 7.18 (dd, 1H, J=4.4, 1.6Hz), 6.96 (m, 2H), 6.84 (m, 1H), 6.77 (m, 1H) and 2.52 (s, 3H).

E 13 3-(2,5-Difluoro-phenyl)-2-(4-hydroxy-phenyl)-7-methyl-benzofuran-5-ol

R^6 = 2,5-difluoro-phenyl

ES/MS m/z: 353.7 (pos. M + H), 351.7 (neg. M – H); ^{1}H NMR (acetone-d6, 500MHz): 7.57 (m, 2H), 7.36 (m, 1H), 7.31 (m, 1H), 6.97 (m, 2H), 6.80 (m, 1H), 6.70 (m, 1H) and 2.55 (s, 3H).

E 14 3-[5-Hydroxy-2-(4-hydroxy-phenyl)-7-methyl-benzofuran-3-yl]-benzonitrile

R^6 = 3-cyano-phenyl

ES/MS m/z: 342.7 (pos. M + H), 340.7 (neg. M – H); ^{1}H NMR (acetone-d6, 500MHz): 7.89 (m, 1H), 7.85-7.81 (m, 2H), 7.73 (m, 1H), 7.54 (m, 2H), 6.96 (m, 2H), 6.80 (m, 2H) and 2.54 (s, 3H).

E 15 2-(4-Hydroxy-phenyl)-7-methyl-3-m-tolyl-benzofuran-5-ol

R^6 = 3-methyl-phenyl

ES/MS m/z: 331.7 (pos. M + H), 329.7 (neg. M – H); ^{1}H NMR (acetone-d6, 500MHz): 7.58 (m, 2H), 7.39 (t, 1H, J=7.7Hz), 7.32 (m, 1H), 7.26 (m, 1H), 6.92 (m, 2H), 6.77 (m, 1H), 6.73 (m, 1H), 2.54 (s, 3H) and 2.38 (s, 3H).

E 16 2-(4-Hydroxy-phenyl)-7-methyl-3-thiophen-2-yl-benzofuran-5-ol

R^6 = thiophen-2-yl

ES/MS m/z: 321.6 (neg. M – H); ^{1}H NMR (acetone-d6, 500MHz): 7.66 (m, 2H), 7.61 (dd, 1H, J=4.8, 1.5Hz), 7.24-7.21 (m, 2H), 6.97 (m, 2H), 6.84 (m, 1H), 6.79 (m, 1H) and 2.53 (s, 3H).

E 17 2-(4-Hydroxy-phenyl)-7-methyl-3-pyridin-3-yl-benzofuran-5-ol

R^6 = pyridin-3-yl

ES/MS m/z: 318.7 (neg. M + H); ^{1}H NMR (acetone-d6, 500MHz): 8.68 (dd, 1H, J=2.3, 0.9Hz), 8.63 (dd, 1H, J=5.0, 1.7Hz), 7.90 (m, 1H), 7.55 (m, 2H), 7.51 (m, 1H), 6.96 (m, 2H), 6.80 (m, 1H), 6.78 (m, 1H) and 2.55 (s, 3H).

E 18 2-[5-Hydroxy-2-(4-hydroxy-phenyl)-7-methyl-benzofuran-3-yl]-benzonitrile

R^6 = 2-cyano-phenyl

ES/MS m/z: 342.3 (pos. M + H), 340.2 (neg. M – H); ^{1}H NMR (acetone-d6, 500MHz): 7.96 (m, 1H), 7.89 (m 1H), 7.71 (m, 1H), 7.47 (m, 2H), 7.05 (m, 1H), 6.94 (m, 2H), 6.81 (m, 1H), 6.63 (m, 1H) and 2.57 (s, 3H).

E 19 2-(4-Hydroxy-phenyl)-7-methyl-3-(3-nitro-phenyl)-benzofuran-5-ol

R^6 = 3-nitro-phenyl

ES/MS m/z: 362.0 (pos. M + H), 360.0 (neg. M – H); ^{1}H NMR (acetone-d6, 500MHz): 8.33 (m, 1H), 8.27 (m, 1H), 7.91 (m, 1H), 7.80 (dd, 1H, J=7.6, 8.1Hz), 7.50 (m, 2H), 6.87 (m, 2H), 6.75-6.73 (m, 2H) and 2.52 (s, 3H).

E 20 5-[5-Hydroxy-2-(4-hydroxy-phenyl)-7-methyl-benzofuran-3-yl]-thiophene-2-carbaldehyde

R^6 = 5-thiophene-2-carbaldehyde

ES/MS m/z: 349.0 (neg. M – H); ^{1}H NMR (acetone-d6, 500MHz): 9.98 (s, 1H), 8.02 (d, 1H,

J=3.9Hz), 7.60 (m, 2H), 7.38 (d, 1H, J=3.9Hz), 6.94 (m, 2H), 6.92 (m, 1H), 6.75 (m, 1H) and 2.50 (s, 3H).

E 21 3-(3,5-Difluoro-phenyl)-2-(4-hydroxy-phenyl)-7-methyl-benzofuran-5-ol

R^6 = 3,5-difluoro-phenyl

ES/MS m/z: 351.0 (neg. M – H); ^{1}H NMR (acetone-d6, 500MHz): 7.50 (m, 2H), 7.11-7.04 (m, 3H), 6.89 (m, 2H), 6.73-6.71 (m, 2H) and 2.50 (s, 3H).

E 22 3-(3,5-Dichloro-phenyl)-2-(4-hydroxy-phenyl)-7-methyl-benzofuran-5-ol

R^6 = 3,5-dichloro-phenyl

ES/MS m/z: 383+385 (neg. M – H); ^{1}H NMR (acetone-d6, 500MHz): 7.52 (t, 1H, J=1.9Hz), 7.50 (m, 2H), 7.45 (m, 2H), 6.90 (m, 2H), 6.72-6.70 (m, 2H) and 2.50 (s, 3H).

E 23 2-(4-Hydroxy-phenyl)-7-methyl-3-(2-phenoxy-phenyl)-benzofuran-5-ol

R^6 = 2-phenoxy-phenyl

ES/MS m/z: 407.0 (neg. M – H); ^{1}H NMR (acetone-d6, 500MHz): 7.51 (m, 2H), 7.49-7.44 (m, 2H), 7.28 (m, 1H), 7.21-7.17 (m, 2H), 7.04 (m, 1H), 6.96 (m, 1H), 6.84 (m, 2H), 6.76 (m, 2H), 6.65 (m, 1H), 6.63 (m, 1H) and 2.45 (s, 3H).

E 24 3-Biphenyl-2-yl-2-(4-hydroxy-phenyl)-7-methyl-benzofuran-5-ol

R^6 = biphenyl-2yl

ES/MS m/z: 391.0 (neg. M – H); ^{1}H NMR (acetone-d6, 500MHz): 7.56 (m, 1H), 7.52-7.49 (m, 2H), 7.45 (m, 1H), 7.32 (m, 2H), 7.13-7.10 (m, 2H), 7.06-7.04 (m, 3H), 6.75 (m, 2H), 6.58 (m, 1H), 6.39 (m, 1H) and 2.43 (s, 3H).

E 25 3-(2-Hydroxy-phenyl)-2-(4-hydroxy-phenyl)-7-methyl-benzofuran-5-ol

R^6 = 2-hydroxy-phenyl

ES/MS m/z: 331.0 (neg. M – H); ^{1}H NMR (acetone-d6, 500MHz): 7.50 (m, 2H), 7.29 (m, 1H), 7.23 (dd, 1H, J=7.6, 1.6Hz), 7.04 (dd, 1H, J=8.3, 1.0Hz), 6.95 (m, 1H), 6.78 (m, 2H), 6.63 (m, 1H), 6.48 (m, 1H) and 2.48 (s, 3H).

E 26 1-{3-[5-Hydroxy-2-(4-hydroxy-phenyl)-7-methyl-benzofuran-3-yl]-phenyl}-ethanone

R^6=4-Acetyl-phenyl

ES/MS m/z: 357.0 (neg. M – H); ^{1}H NMR (acetone-d6, 500MHz): 8.10 (m, 1H), 8.02 (m, 1H), 7.70 (m, 1H), 7.64 (m, 1H), 7.49 (m, 2H), 6.84 (m, 2H), 6.71-6.70 (m, 2H), 2.60 (s, 3H) and 2.51 (s, 3H).

E 27 2-(4-Hydroxy-phenyl)-3-(3-methanesulfonyl-phenyl)-7-methyl-benzofuran-5-ol

R^6 = 3-methanesulfonyl-phenyl

ES/MS m/z: 393.0 (neg. M – H); ^{1}H NMR (acetone-d6, 500MHz): 8.05 (m, 1H), 7.97 (m, 1H), 7.81 (m, 1H), 7.77 (m, 1H), 7.49 (m, 2H), 6.87 (m, 2H), 6.74-6.72 (m, 2H), 3.17 (s, 3H) and 2.51 (s, 3H).

E 28 3-(3-Ethylsulfanyl-phenyl)-2-(4-hydroxy-phenyl)-7-methyl-benzofuran-5-ol

R^6 = 3-ethylsulfanyl-phenyl

ES/MS m/z: 375.0 (neg. M – H); ^{1}H NMR (acetone-d6, 500MHz): 7.50 (m, 2H), 7.44 (m, 1H), 7.41 (m, 1H), 7.36 (m, 1H), 7.28 (m, 1H), 6.85 (m, 2H), 6.69 (m, 2H), 2.97 (q, 2H, J=7.3Hz), 2.50 (s, 3H) and 1.27 (t, 3H, J=7.3Hz).

E 29 2-(4-Hydroxy-phenyl)-7-methyl-3-quinolin-5-yl-benzofuran-5-ol

R^6 = quinolin-5-yl

ES/MS m/z: (neg. M – H); ^{1}H NMR (acetone-d6, 500MHz): 8.94 (dd, 1H, J=4.1, 1.6Hz), 8.18 (m, 1H), 8.04 (m, 1H), 7.90 (dd, 1H, J=8.5, 7.1Hz), 7.66 (dd, 1H, J=7.1, 1.2Hz), 7.39 (dd, 1H, J=8.5, 4.1Hz), 7.33 (m, 2H), 6.72-6.69 (m, 3H), 6.28 (d, 1H, J=2.0Hz) and 2.57 (s, 3H).

E 30 1-{5-[5-Hydroxy-2-(4-hydroxy-phenyl)-7-methyl-benzofuran-3-yl]-thiophen-2-yl}-ethanone

R^6=4-Acetyl-thiophene-2-yl

ES/MS m/z: 363.0 (neg. M – H); ^{1}H NMR (acetone-d6, 500MHz): 7.90 (d, 1H, J=3.8Hz), 7.60 (m, 2H), 7.26 (d, 1H, J=3.8Hz), 6.92 (m, 2H), 6.90 (m, 1H), 6.73 (m, 1H), 2.57 (s, 3H) and 2.49 (s, 3H).

E 31 2-(4-Hydroxy-phenyl)-7-methyl-2',3'-dihydro-[3,5']bibenzofuranyl-5-ol

R^6=1-Phenyl-vinyl

ES/MS m/z: 357 (neg. M-H); ^{1}H NMR (acetone-d6, 500MHz): 7.55 (m, 2H), 7.29 (d, 1H, J=2.1Hz), 7.18 (dd, 1H, J=8.2, 2.1Hz), 7.00 (d, 1H, J=8.2Hz), 6.83 (m, 2H), 6.71 (m, 1H), 6.66 (m, 1H), 3.72 (t, 2H, J=7.4Hz), 3.22 (t, 2H, J=7.4Hz) and 2.49 (s, 3H).

E 32 2-(4-Hydroxy-phenyl)-7-methyl-3-(3-trifluoromethoxy-phenyl)-benzofuran-5-ol

R^6 = 3-trifluoromethoxy-phenyl

ES/MS m/z: 399.0 (neg. M – H); ^{1}H NMR (acetone-d6, 500MHz): 7.64 (m, 1H), 7.52-7.48 (m, 3H), 7.40-7.36 (m, 2H), 6.86 (m, 2H), 6,71 (m, 2H) and 2.50 (s, 3H).

E 33 3-(2-Fluoro-pyridin-3-yl)-2-(4-hydroxy-phenyl)-7-methyl-benzofuran-5-ol

R^6 = 2-fluoro-pyridin-3-yl

ES/MS m/z: 334.0 (neg. M – H); ^{1}H NMR (acetone-d6, 500MHz): 8.32 (m, 1H), 8.03 (m, 1H), 7.48 (m, 1H), 7.46 (m, 2H), 6.87 (m, 2H), 6.71 (m, 1H), 6.57 (m, 1H) and 2.52 (s, 3H).

E 34 3-Benzo[b]thiophen-2-yl-2-(4-hydroxy-phenyl)-7-methyl-benzofuran-5-ol

R^6 = benzo[b]thiophen-2-yl

ES/MS m/z: 373.3 (pos. M +H), 371.3 (neg. M – H).

E 35 2-(4-Hydroxy-phenyl)-7-methyl-3-(1-methyl-1H-pyrazol-4-yl)-benzofuran-5-ol

R^6 = 1-methyl-1H-pyrazol-4-yl

ES/MS m/z: 321.3 (pos. M + H).

E 36 2-(4-Hydroxy-phenyl)-7-methyl-3-(1-phenyl-vinyl)-benzofuran-5-ol

R^6 = 1-phenyl-vinyl

ES/MS m/z: 343.3 (pos. M + H).

E 37 2-(4-Hydroxy-phenyl)-7-methyl-3-pyridin-4-yl-benzofuran-5-ol

R^6 = pyridine-4-yl

ES/MS m/z: 318.3 (pos. M + H).

E 38 2-(4-Hydroxy-phenyl)-7-methyl-3-(1-methyl-1H-pyrrol-2-yl)-benzofuran-5-ol

R^6 = 1-methyl-1H-pyrrol-2-yl

ES/MS m/z: 320.4 (pos. M + H).

E 39 3-(3,5-Dimethyl-isoxazol-4-yl)-2-(4-hydroxy-phenyl)-7-methyl-benzofuran-5-ol

R^6 = 3,5-dimethyl-isoxazol-4-yl

ES/MS m/z: 336.3 (pos. M + H), 334.3 (neg. M – H); ^{1}H NMR (acetone-d6, 500MHz): 7.53 (m, 2H), 6.91 (m, 2H), 6.70 (m, 1H), 6.52 (m, 1H), 2.51 (s, 3H), 2.24 (s, 3H) and 1.99 (s, 3H).

E 40 3-(5-Fluoro-2-methyl-phenyl)-2-(4-hydroxy-phenyl)-7-methyl-benzofuran-5-ol

R^6 = 5-fluoro-2-methyl-phenyl

ES/MS m/z: 349.3 (pos. M + H), 347.3 (neg. M – H); ^{1}H NMR (acetone-d6, 500MHz): 7.44-7.39 (m, 3H), 7.15 (m, 1H), 7.08 (dd, 1H, J=9.5, 2.8Hz), 6.82 (m, 2H), 6.69 (m, 1H), 6.40 (m, 1H), 2.52 (s, 3H) and 2.06 (s, 3H).

E 41 3-[1-(4-Fluoro-phenyl)-vinyl]-2-(4-hydroxy-phenyl)-7-methyl-benzofuran-5-ol

R^6 = 1-(4-fluoro-phenyl)-vinyl

ES/MS m/z: 361.4 (pos. M + H), 359.4 (neg. M – H); ^{1}H NMR (acetone-d6, 500MHz): 7.66 (m, 2H), 7.51 (m, 2H), 7.06 (m, 2H), 6.82 (m, 2H), 6.66 (m, 1H), 6.48 (m, 1H), 6.01 (d, 1H, J=1.0Hz), 5.45 (d, 1H; J=1.0Hz), 2.50 (s, 3H).

E 42 3-Cyclopropyl-2-(4-hydroxy-phenyl)-7-methyl-benzofuran-5-ol

R^6 = cyclopropyl

ES/MS m/z: 279.4 (neg. M – H).

E 43 3-(5-Fluoro-2-methoxy-phenyl)-2-(4-hydroxy-phenyl)-7-methyl-benzofuran-5-ol

R^6 = 5-fluoro-2-methoxy-phenyl

ES/MS m/z: 365.3 (pos. M + H), 363.3 (neg. M – H); ^{1}H NMR (acetone-d6, 500MHz): 7.46 (m, 2H), 7.22-7.15 (m, 2H), 7.09 (dd, 1H, J=9.1, 2.9Hz), 6.82 (m, 2H), 6.66 (m, 1H), 6.50 (m, 1H), 3.65 (s, 3H) and 2.50 (s, 3H).

E 44 2-(4-Hydroxy-phenyl)-7-methyl-3-(1H-pyrrol-2-yl)-benzofuran-5-ol

R^6 = 1H-pyrrol-2-yl

ES/MS m/z: 306.3 (pos. M + H), 304.3 (neg. M – H); ^{1}H NMR (acetone-d6, 500MHz): 7.55 (m, 2H), 6.93 (m, 1H), 6.85 (m, 2H), 6.76 (m, 1H), 6.66 (m, 1H), 6.29-6.26 (m, 2H) and 2.48 (s, 3H).

E 45 3-Furan-2-yl-2-(4-hydroxy-phenyl)-7-methyl-benzofuran-5-ol

R^6 = furan-2-yl

ES/MS m/z: 307.3 (pos. M + H), 305.3 (neg. M – H); ^{1}H NMR (acetone-d6, 500MHz): 7.67 (t, 1H, J=1.3Hz), 7.64 (m, 2H), 6.98 (d, 1H, J=1.3Hz), 6.94 (m, 2H), 6.71 (m, 1H), 6.62-6.60 (m, 2H) and 2.48 (s, 3H).

E 46 2-(4-Hydroxy-phenyl)-7-methyl-3-thiazol-5-yl-benzofuran-5-ol

R^6 = thiazol-5-yl

ES/MS m/z: 324.3 (pos. M + H), 322.3 (neg. M – H); ^{1}H NMR (acetone-d6, 500MHz): 9.10 (s, 1H), 7.97 (s, 1H), 7.56 (m, 2H), 6.91 (m, 2H), 6.75-6.72 (m, 2H) and 2.50 (s, 3H).

E 47 2-(4-Hydroxy-phenyl)-3-(2-methoxy-thiazol-4-yl)-7-methyl-benzofuran-5-ol

R^6 = 2-methoxy-thiazol-4-yl

ES/MS m/z: 354.3 (pos. M + H), 352.2 (neg. M – H); ^{1}H NMR (acetone-d6, 500MHz): 7.60

(m, 2H), 6.96 (m, 2H), 6.72 (m, 1H), 6.66 (m, 1H), 6.47 (s, 1H), 3.01 (s, 3H) and 2.51 (s, 3H).

E 48 2-(4-Hydroxy-phenyl)-7-methyl-3-thiazol-2-yl-benzofuran-5-ol

R^6 = thiazol-2-yl

ES/MS m/z: 324.2 (pos. M + H), 322.2 (neg. M – H); ^{1}H NMR (acetone-d6, 500MHz): very weak 9.10 (s, 1H), 7.97 (s, 1H), 7.57 (m, 2H), 6.91 (m, 2H), 6.75 (m, 1H), 6.73 (m, 1H) and 2.50 (s, 3H).

E 49 2-(4-Hydroxy-phenyl)-3-(2-isopropyl-phenyl)-7-methyl-benzofuran-5-ol

R^6 = 2-isopropyl-phenyl

ES/MS m/z: 359.3 (pos. M + H), 357.3 (neg. M – H); ^{1}H NMR (acetone-d6, 500MHz): 7.54 (dd, 1H, J=7.8, 1.2Hz), 7.47 (m, 1H), 7.41 (m, 2H), 7.32 (m, 1H), 7.23 (dd, 1H, J=7.5, 1.4Hz), 6.78 (m, 2H), 6.67 (m, 1H), 6.36 (m, 1H), 2.93 (m, 1H), 2.52 (s, 3H), 1.10 (d, 3H, J=6.9Hz) and 1.00 (d, 3H, J=6.9Hz).

E 50 3-(2-Ethyl-phenyl)-2-(4-hydroxy-phenyl)-7-methyl-benzofuran-5-ol

R^6 = 2-ethyl-phenyl

ES/MS m/z: 345.3 (pos. M + H), 343.3 (neg. M – H); ^{1}H NMR (acetone-d6, 500MHz): 7.46-7.40 (m, 4H), 7.33 (m, 1H), 7.26 (m, 1H), 6.78 (m, 2H), 6.66 (m, 1H), 6.35 (m, 1H), 2.52 (s, 3H), 2.48 (m, 2H) and 0.96 (t, 3H, J07.5Hz).

E 51 (E)-3-{2-[5-Hydroxy-2-(4-hydroxy-phenyl)-7-methyl-benzofuran-3-yl]-phenyl}-acrylonitrile

R^6=2-((E)-2-Cyano-vinyl)-phenyl

ES/MS m/z: 368.3 (pos. M + H), 366.3 (neg. M – H); ^{1}H NMR (acetone-d6, 500MHz): not pure 7.64-7.55 (m, 3H), 7.47 (dd, 1H, J=7.6, 1.4Hz), 7.38-7.31 (m, 3H), 6.80 (m, 2H), 6.71 (m, 1H), 6.39 (m, 1H), 6.20 (d, 1H, J=16.6Hz) and 2.53 (s, 3H).

E 52 3-(2-Butoxy-phenyl)-2-(4-hydroxy-phenyl)-7-methyl-benzofuran-5-ol

R^6 = 2-butoxy-phenyl

ES/MS m/z: 389.3 (pos. M + H), 387.3 (neg. M – H); ^{1}H NMR (acetone-d6, 500MHz): 7.47 (m, 2H), 7.40 (m, 1H), 7.34 (dd, 1H, J=7.4, 1.7Hz), 7.13 (d, 1H, J=8.0Hz), 7.06 (m, 1H), 6.80 (m, 2H), 6.64 (m, 2H), 6.53 (m, 1H), 3.88 (m, 2H), 2.50 (s, 3H), 1.34 (m, 2H), 1.10 (m, 2H) and 0.71 (t, 3H, J=7.3Hz).

E 53 2-(4-Hydroxy-phenyl)-7-methyl-3-(2-trifluoromethoxy-phenyl)-benzofuran-5-ol

R^6 = 2-trifluoromethoxy-phenyl

ES/MS m/z: 401.3 (pos. M + H), 399.3 (neg. M – H); ^{1}H NMR (acetone-d6, 500MHz): 7.62 (m, 1H), 7.55-7.52 (m, 3H), 7.42 (m, 2H), 6.83 (m, 2H), 6.68 (m, 1H), 6.50 (m, 1H) and 2.51 (s, 3H).

E 54 4-[5-Hydroxy-2-(4-hydroxy-phenyl)-7-methyl-benzofuran-3-yl]-thiophene-2-carbaldehyde

R^6 = thiophen-2-carbaldehyde

ES/MS m/z: 351.3 (pos. M + H), 349.2 (neg. M – H); ^{1}H NMR (acetone-d6, 500MHz): 10.03 (s, 1H), 8.09 (s, 1H), 8.03 (s, 1H), 7.55 (m, 2H), 6.89 (m, 2H), 6.76 (m, 1H), 6.71 (m, 1H) and 2.50 (s, 3H).

E 55 3-((E)-2-Cyclopropyl-vinyl)-2-(4-hydroxy-phenyl)-7-methyl-benzofuran-5-ol

R^6 = (E)-2-cyclopropyl-vinyl

ES/MS m/z: 307.3 (pos. M + H), 305.3 (neg. M – H); ^{1}H NMR (acetone-d6, 500MHz): 7.67 (m, 2H), 7.02-6.99 (m, 3H), 6.73-6.65 (m, 2H), 5.85 (dd, 1H, J=16.0, 9.1Hz), 2.53 (s, 3H), 1.66 (m, 1H), 0.85 (m, 2H) and 0.57 (m, 2H).

E 56 2-(4-Hydroxy-phenyl)-7-methyl-3-(3-methyl-thiophen-2-yl)-benzofuran-5-ol

R^6 = 3-methyl-thiophen-2-yl

ES/MS m/z: 410.3 (pos. M + H), 408.3 (neg. M – H); ^{1}H NMR (acetone-d6, 500MHz): 7.54 (d, 1H, J=5.1Hz), 7.52 (m, 2H), 7.08 (d, 1H, J=5.1Hz), 6.85 (m, 2H), 6.68 (m, 1H), 6.59 (m, 1H), 2.51 (s, 3H) and 1.99 (s, 3H).

E 57 2-[5-Hydroxy-2-(4-hydroxy-phenyl)-7-methyl-benzofuran-3-yl]-thiophene-3-carbaldehyde

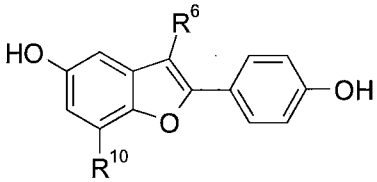
R^6=thiophene-2-yl-3-carbaldehyde

ES/MS m/z: 349.2 (pos. M + H), 347.2 (neg. M – H).

E 58 2-[5-Hydroxy-2-(4-hydroxy-phenyl)-7-methyl-benzofuran-3-yl]-thiophene-3-carbonitrile

R^6 = 3-cyano-thiophen-2-yl

ES/MS m/z: 410.3 (pos. M + H), 408.3 (neg. M – H); ^{1}H NMR (acetone-d6, 500MHz): 7.54 (d, 1H, J=5.1Hz), 7.52 (m, 2H), 7.08 (d, 1H, J=5.1Hz), 6.85 (m, 2H), 6.68 (m, 1H), 6.59 (m, 1H), 2.51 (s, 3H) and 1.99 (s, 3H).



5

E 59 7-Bromomethyl-2-(4-hydroxy-phenyl)-3-phenyl-benzofuran-5-ol

R^6 = phenyl R^{10} = bromomethyl

ES/MS m/z: 395.0 + 397.1 (pos. M + H), 393.1 + 394.9 (neg. M – H); ^{1}H NMR MeOH-d4: 7.35-7.47 (m, 7H), 6.80 (d, 2.40 Hz, 1H), 6.70-6.74 (m, 3H), 4.79 (s, 2H).

E 60 5-Hydroxy-2-(4-hydroxy-phenyl)-3-thiophen-3-yl-benzofuran-7-carbonitrile

R^6 = thiophen-3-yl R^{10} = cyano

ES/MS m/z: 344.4 (pos. M + H), 393.1 + 332.2 (neg. M – H); ^{1}H NMR MeOH-d4: 7.59 (dd, 2.87 Hz, 5.02 Hz, 1 H), 7.52 (dd, 1.30 Hz, 2.87 Hz, 1 H), 7.48-7.52 (m, 2H), 7.10-7.14 (m, 2H), 7.03 (d, 2.51 Hz, 1H), 6.77-6.81 (m, 2H)

E 61 5-Hydroxy-2-(4-hydroxy-phenyl)-3-phenyl-benzofuran-7-carbaldehyde

R^6 = phenyl, R^{10} = carbaldehyde

ES/MS m/z: 331.3 (pos. M + H), 329.3 (neg. M – H); ^{1}H NMR MeOH-d4: 10.44 (s, 1H), 3.40-3.51 (m, 7H), 7.21 (d, 2.52 Hz, 1H), 7.06 (d, 2.53 Hz, 1H), 6.71-6.76 (m, 2H)

E 62 7-Chloro-2-(4-hydroxy-phenyl)-3-phenyl-benzofuran-5-ol

R^6 = phenyl R^{10} = chloro

ES/MS m/z: 337.2 (pos. M + H), 335.3 (neg. M – H); ^{1}H NMR MeOH-d4: 7.45-7.50 (m, 2H), 7.38-7.45 (m, 5H), 6.80 (d, 2.22 Hz, 1H), 6.71-6.75 (m, 2H), 6.69 (d, 2.22 Hz, 1H).

E 63 7-Chloro-2-(4-hydroxy-phenyl)-3-thiophen-3-yl-benzofuran-5-ol

R^6 = thiophen-3-yl R^{10} = chloro

ES/MS m/z: 343.2 (pos. M + H), 341.2 (neg. M – H); ^{1}H NMR MeOH-d4: 7.56 (dd, 2.85 Hz, 5.02 Hz, 1H), 7.46-7.50 (m, 3H), 7.11 (dd, 1.25 Hz, 5.00 Hz, 1H), 6.80 (d, 2.25 Hz, 1H), 6.75-6.79 (m, 3H).

E 64 5-Hydroxy-2-(4-hydroxy-phenyl)-3-thiophen-3-yl-benzofuran-7-carbaldehyde

R^6 = thiophen-3-yl, R^{10} = carbaldehyde

ES/MS m/z: 337.2 (pos. M + H), 335.2 (neg. M – H); ^{1}H NMR MeOH-d4: 10.45 (s, 1H), 7.59 (dd, 2.97 Hz, 4.88 Hz, 1H), 7.52-7.57 (m, 3H), 7.22-7.24 (m, 1H), 7.14-7.16 (m, 2H), 6.86-6.81 (m, 2H)

E 65 2-(4-Hydroxy-phenyl)-3-thiophen-3-yl-7-vinyl-benzofuran-5-ol

R^6 = thiophen-3-yl R^{10} = vinyl

ES/MS m/z: 335.3 (pos. M + H), 333.2 (neg. M – H); ^{1}H NMR MeOH-d4: 7.56 (dd, 3.10 Hz, 5.06 Hz, 1H), 7.46-7.52 (m, 3H), 7.13 (dd, 1.24 Hz, 5.03 Hz, 1H), 6.96 (dd, 11.25 Hz, 17.77 Hz, 1H), 6.81 (d, 2.36 Hz, 1H), 6.74-6.80 (m, 3H), 6.23 (dd, 1.36 Hz, 11.32 Hz), 5.52 (dd, 1.36 Hz, 11.32 Hz, 1H)

E 66 2-[7-Chloro-5-hydroxy-2-(4-hydroxy-phenyl)-benzofuran-3-yl]-thiophene-3-carbonitrile

R^6 = 3-cyano-thiophen-2-yl R^{10} = chloro

ES/MS m/z: 368.2 (pos. M + H), 366.2 (neg. M – H).

E 67 3-(3-Cyano-furan-2-yl)-5-hydroxy-2-(4-hydroxy-phenyl)-benzofuran-7-carbonitrile

R^6 = 3-cyano-furan-2yl R^{10} = cyano

ES/MS m/z: 343.1 (pos. M + H), 341.1 (neg. M – H). ^{1}H NMR MeOH-d4: 7.87 (d, 1.93 Hz, 1H), 7.48-7.52 (m, 2H), 7.24 (d, 2.23 Hz, 1H), 7.14 (d, 2.22 Hz, 1H), 6.95 (d, 1.91 Hz, 1H), 6.86-6.90 (m, 2H).

E 68 2-[5-Hydroxy-2-(4-hydroxy-phenyl)-7-trifluoromethyl-benzofuran-3-yl]-furan-3-carbonitrile

R^6 = 3-cyano-furan-2yl R^{10} = trifluoromethyl

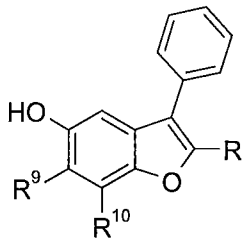
ES/MS m/z: 386.1 (pos. M + H), 384.0 (neg. M – H). ^{1}H NMR MeOH-d4: 7.86 (d, 2.21 Hz, 1H), 7.44-7.49 (m, 2H), 7.15 (d, 2.24 Hz, 1H), 7.08 (d, 2.30 Hz, 1H), 6.83-6.90 (m, 3H).

E 69 2-[2-(3-Fluoro-4-hydroxy-phenyl)-5-hydroxy-7-methyl-benzofuran-3-yl]-furan-3-carbonitrile

R^6 = 3-cyano-furan-2yl R= 3-fluoro-4-hydroxy-phenyl

ES/MS m/z: 350.1 (pos. M + H), 348.1 (neg. M – H). ^{1}H NMR MeOH-d4: 7.84 (d, 2.19 Hz,

1H), 7.30 (dd, 2.05 Hz, 12.06 Hz, 1H), 7.22-7.26 (m, 1H), 6.97 (t, 8.78 Hz, 1H), 6.92 (d, 2.21 Hz, 1H), 6.77 (d, 2.21 Hz, 1H), 6.68-6.71 (m, 1H), 2.51 (s, 3H).

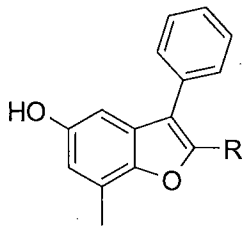


E 70 2-(4-Hydroxy-phenyl)-6-methyl-3-phenyl-benzofuran-5-ol

R = 4-hydroxyphenyl R^9 = methyl

R^{10} = hydrogen

ES/MS m/z: 317.0 (pos. M + H), 315.1 (neg. M – H). ^{1}H NMR MeOH-d4: 7.34-7.48 (m, 7H), 7.22 (s, 1H), 6.76 (s, 1H), 6.68-6.72 (m, 2H), 2.30 (s, 1H).



E 71 2-(2,5-Difluoro-4-hydroxy-phenyl)-7-methyl-3-phenyl-benzofuran-5-ol

R = 2,5-difluoro-4-hydroxy-phenyl

ES/MS m/z: 335.6 (pos. M +H), 333.4 (neg. M – H); ^{1}H NMR MeOH-d4: 7.34-7.42 (m, 4H), 7.29-7.34 (m, 1H), 7.15 (dd, 6.61 Hz, 11.34 Hz, 1 H), 6.79 (d, 2.21 Hz, 1 H), 6.63-6.69 (m, 2H), 2.48 (s, 3H)

E 72 2-(2,6-Difluoro-4-hydroxy-phenyl)-7-methyl-3-phenyl-benzofuran-5-ol

R = 2,6-difluoro-4-hydroxy-phenyl

ES/MS m/z: 335.6 (pos. M +H), 333.1 (neg. M – H); ^{1}H NMR MeOH-d4: 7.33-7.38 (m, 4H), 7.26-7.30 (m, 1H), 6.87 (d, 2.45 Hz, 1H), 6.69 (d, 2.45 Hz, 1H), 6.42 (d, 9.37 Hz, 2H), 2.47 (s, 3H)

E 73 2-(3-Fluoro-4-hydroxy-phenyl)-7-methyl-3-phenyl-benzofuran-5-ol

R = 3-fluoro-4-hydroxy-phenyl

ES/MS m/z: 353.3 (pos. M +H), 351.4 (neg. M – H); ^{1}H NMR MeOH-d4: 7.46-7.51 (m, 2H),

7.39-7.44 (m, 3H), 7.20-7.26 (m, 2H), 6.81-6.86 (m, 1H), 6.63 (d, 2.27 Hz, 1H), 6.58 (d, 2.27 Hz, 1H), 2.50 (s, 3H)

E 74 2-(1H-Indazol-5-yl)-7-methyl-3-phenyl-benzofuran-5-ol

R = 1H-indazol-5-yl

ES/MS m/z: 341.3 (pos. M +H), 339.1 (neg. M – H); ^{1}H NMR MeOH-d4: 8.04-8.06 (m, 1H),7.97-8.01 (m, 1H), 7.56-7.59 (m, 1H), 7.35-7.47 (m, 6H), 6.68 (d, 2.18 Hz, 1H), 6.63-6.66 (m, 1H), 2.54 (s, 3H).

E 75 2-(3,5-Difluoro-4-hydroxy-phenyl)-7-methyl-3-phenyl-benzofuran-5-ol

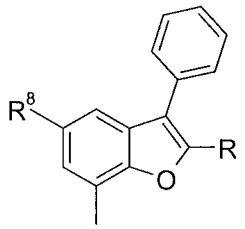
R = 3,5-difluoro-4-hydroxy-phenyl

ES/MS m/z: 353.2 (pos. M + H), 351.3 (neg. M – H); ^{1}H NMR MeOH-d4: 7.49-7.54 (m, 2H), 7.42-7.47 (m, 3H), 7.07-7.11 (m, 2H), 6.65 (d, 2.28 Hz, 1H), 6.56 (d, 2.28 Hz, 1H)

E 76 2-(3-Chloro-5-fluoro-4-hydroxy-phenyl)-7-methyl-3-phenyl-benzofuran-5-ol

R = 3-chloro-5-fluoro-4-hydroxy-phenyl

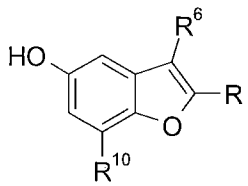
ES/MS m/z: 368.9 (pos. M + H), 367.0 (neg. M – H); ^{1}H NMR MeOH-d4: 7.48-7.54 (m, 2H), 4.41-7.47 (m, 3H), 7.33-7.35 (m, 1H), 7.17 (dd, 2.21 Hz, 11.79 Hz, 1H), 6.64-6.66 (m, 1H), 7.57 (d, 2.30 Hz, 1H), 2.51 (s, 3H)



E 77 5-(5-Methoxy-7-methyl-3-phenyl-benzofuran-2-yl)-1H-indazole

R = 1H-indazole R^8 = methoxy

ES/MS m/z: 355.4 (pos. M + H), 353.2 (neg. M – H). ^{1}H NMR $CDCl_3$: 8.10-8.13 (m, 2H), 7.66 (d, 8.73 Hz, 1H), 7.40-7.53 (m, 6H), 6.76-6.79 (m, 2H), 3.80 (s, 3H), 2.60 (s, 3H)



E 78 2-(3-Fluoro-4-hydroxy-phenyl)-7-methyl-3-thiophen-3-yl-benzofuran-5-ol

R^6 = thiophen-3-yl R = 3-fluoro-4-hydroxy-phenyl

R^{10} = methyl

ES/MS m/z: 341.3 (pos. M + H), 339.1 (neg. M – H); ^{1}H NMR MeOH-d4: 7.58 (dd, 3.16 Hz, 4.73 Hz, 1H), 7.48 (dd, 1.28 Hz, 3.16 Hz, 1H), 7.27-7.31 (m, 2H), 7.13 (dd, 1.25 Hz, 4.73 Hz, 1H), 6.85-6.90 (m, 1H), 6.64-6.66 (m, 1H), 6.62-6.63 (m, 1H), 2.50 (s, 3H)

E 79 2-(2-Fluoro-4-hydroxy-phenyl)-7-methyl-3-thiophen-3-yl-benzofuran-5-ol

R^6 = thiophen-3-yl R = 2-fluoro-4-hydroxy-phenyl

R^{10} = methyl

ES/MS m/z: 341.3 (pos. M + H), 339.1 (neg. M – H); ^{1}H NMR MeOH-d4: 7.42 (dd, 2.83 Hz, 5.04 Hz, 1H), 7.38 (dd, 1.25 Hz, 2.83 Hz, 1H), 7.30 (t, 8.49 Hz, 1H), 7.03 (dd, 1.26 Hz, 5.04 Hz, 1H), 6.88-6.89 (m, 1H), 6.63-6.66 (m, 2H), 6.57 (dd, 2.22 Hz, 11.67 Hz, 1H), 2.47 (s, 3H)

E 80 2-(2,6-Difluoro-4-hydroxy-phenyl)-7-methyl-3-thiophen-3-yl-benzofuran-5-ol

R^6 = thiophen-3-yl R = 2,6-difluoro-4-hydroxy-phenyl

R^{10} = methyl

ES/MS m/z: 359.3 (pos. M + H), 357.1 (neg. M – H); ^{1}H NMR MeOH-d4: 7.42 (dd, 2.83 Hz, 5.00 Hz, 1H), 7.38 (dd, 1.28 Hz, 2.83 Hz, 1H), 7.05 (dd, 1.28 Hz, 5.00 Hz, 1H), 6.96 (d, 2.50 Hz, 1H), 6.69 (d, 2.50 Hz, 1H), 6.47 (d, 9.27 Hz, 1H), 2.46 (s, 3H)

E 81 2-(3-Chloro-5-fluoro-4-hydroxy-phenyl)-7-methyl-3-thiophen-3-yl-benzofuran-5-ol

R^6 = thiophen-3-yl R = 3-chloro-5-fluoro-4-hydroxy-phenyl

R^{10} = methyl

ES/MS m/z: 373.1 (neg. M – H); ^{1}H NMR MeOH-d4: 7.62 (dd, 2.84 Hz, 5.04 Hz, 1H), 7.50 (dd, 1.27 Hz, 2.84 Hz, 1H), 7.40 (t, 1.87 Hz, 1H), 7.24 (1.93 Hz, 5.04 Hz), 7.14 (dd, 1.27 Hz, 5.04 Hz, 1H), 6.63-6.66 (m, 2H), 2.50 (s, 3H)

E 82 2-[2-(3-Chloro-5-fluoro-4-hydroxy-phenyl)-5-hydroxy-7-methyl-benzofuran-3-yl]-furan-3-carbonitrile

R^6 = 3-cyano-furan-2yl R = 3-chloro-5-fluoro-4-hydroxy-phenyl

R^{10} = methyl

ES/MS m/z: 384.0 (pos. M + H), 382.0 (neg. M – H). ^{1}H NMR MeOH-d4: 7.87 (d, 1.97 Hz, 1H), 7.35-7.38 (m, 1H), 7.26 (dd, 2.14 Hz, 11.36 Hz, 1H), 6.94 (d, 1.95 Hz, 1H), 6.79 (d, 2.22 Hz, 1H), 6.72 (d, 2.16 Hz, 1H), 2.52 (s, 3H)

E 83 2-[7-Fluoro-5-hydroxy-2-(1H-indazol-5-yl)-benzofuran-3-yl]-furan-3-carbonitrile

R^6 = 3-cyano-furan-2yl R = 1H-indazol-5-yl

R^{10} = fluoro

ES/MS m/z: 360.0 (pos. M + H), 358.1 (neg. M – H). ^{1}H NMR MeOH-d4: 8.12-8.15 (m, 2H), 7.87 (d, 2.19 Hz, 1H), 7.61-7.64 (m, 1H), 7.58 (dd, 1.55 Hz, 8.11 Hz, 1H), 6.94 (d, 2.19 Hz, 1H), 6.81 (d, 2.19 Hz, 1H), 6.70 (dd, 2.22 Hz, 12.30 Hz, 1H)

Example 84: Description of the Estrogen Receptor Binding Assays

The estrogen receptor ligand binding assays are designed as scintillation proximity assays (SPA), employing the use of tritiated estradiol (^{3}H-E2) and recombinant expressed biotinylated estrogen receptor binding domains. The binding domains of human ERα (ERα-LBD, pET-N-AT #1, aa 301-595) and ERβ (ERβ-LBD, pET-N-AT #1, aa 255-530) proteins are produced in E.coli ((BL21, (DE3), pBirA)) at 22 C in 2xLB medium supplemented with 50 uM biotin. After 3 h of IPTG induction (0.55 mM), cells are harvested by centrifugation at 7300xg for 15 min and cell pellets stored frozen in -20C. Extraction of ERα and ERβ are performed using 5 g of cells suspended in 50 mL of extraction buffer (50 mM Tris, pH 8.0, 100 mM KCl, 4 mM EDTA, 4 mM DDT and 0.1 mM PMSF). The cell suspension is run twice through a Microfluidizer M-110L (Microfluidics) and centrifuged at 15,000xg for 60 min. The supernatant is aliquoted and stored in -70C.

Dilute ERα-LBD or ERβ-LBD extracts in assay buffer (18 mM K_2HPO_4, 2 mM KH_2PO_4, 20 mM Na_8MoO_4, 1 mM EDTA, 1mM TCEP) 1:676 and 1:517 for alpha and beta respectively. The diluted receptor concentrations should be 900 fmol/L. Preincubate the extracts with streptavidin coated polyvinyltoluene SPA beads (RPNQ0007, GE Healthcare) at a concentration of 0.43 mg/mL for 1hr at room temperature.

Test compounds are evaluated over a range of concentrations from 157 µM to 37.5 pM. The test compound stock solutions should be made in 100% DMSO at 5x of the final concentration desired for testing in the assay. The amount of DMSO in the test wells of the 384 well plate will be 20%. Add 18µl aliquots of test compounds to the assay plates followed by 35µl of the preincubated receptor/SPA bead mix and finally add 35µl of 3nM ^{3}H-E2. Cover the plates with a

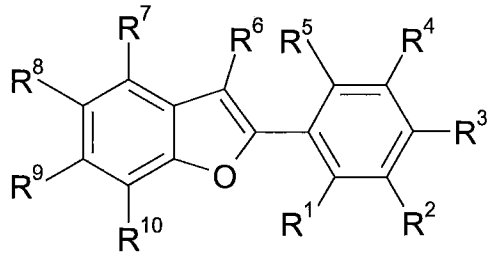
plastic sealer, centrifuge for 1 minute at 1000 rpm and equilibrate over night on a shaker at room temperature. The following morning, centrifuge the plates 5 minutes at 2000 rpm and measure on a plate scintillation counter e.g. a PerkinElmer Microbeta 1450 Trilux.

For compounds able to displace 3[H]-E2 from the receptor an IC_{50}-value (the concentration required to inhibit 50% of the binding of 3[H]-E2) is determined by a non-linear four parameter logistic model; b = ((bmax-bmin)/(1+(I/IC_{50})S))+bmin I is added concentration of binding inhibitor, IC_{50} is the concentration of inhibitor at half maximal binding and S is a slope factor. The Microbeta-instrument generates the mean cpm (counts per minute) value / minute and corrects for individual variations between the detectors thus generating corrected cpm values.

The compounds of Examples 1-84 exhibit binding affinities to the estrogen receptor α-subtype in the range of IC_{50} 1 to 10,000 nM or to the estrogen receptor β-subtype in the range of IC_{50} 1 to 10,000 nM.

Claims

1. A pharmaceutical composition which comprises a compound of formula (I) or a pharmaceutically acceptable ester, amide, solvate or salt thereof, including a salt of such an ester or amide, and a solvate of such an ester, amide or salt:



(I)

wherein R^1, R^2, R^4 and R^5 are each independently selected from the group consisting of hydrogen, OR^A, 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^3 is selected from the group consisting of OR^A; -CHO; -C(O)C_{1-4}alkyl; -C(O)phenyl; -O-C(O)R^A; and $N(R^B)_2$ in which each R^B is independently selected from the group consisting of hydrogen, -C(O)C_{1-4}alkyl, -C(O)phenyl, -SO_2C_{1-4}alkyl, -SO_2phenyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkyl-C_{1-6}alkyl, C_{6-10}aryl, C_{6-10}aryl-C_{1-6}alkyl, C_{5-10}heterocyclyl and C_{5-10}heterocyclyl-C_{1-6} alkyl;

or R^3 and R^4 together with the atoms to which they are attached, 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 1 or 2 groups selected from OR^A, 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^6 is selected from the group consisting of C_{3-8}cycloalkyl, C_{3-8}cycloalkyl-C_{1-6}alkyl, C_{3-8}cycloalkyl-C_{1-6}alkenyl, phenyl, biphenyl, phenyl-C(=CH_2)-, and C_{5-10}heterocyclyl, wherein said phenyl, biphenyl, phenyl-C(=CH_2)- or C_{5-10}heterocyclyl group is unsubstituted or substituted on the ring with 1 to 3 substituents, each substituent being selected from the group consisting of OR^A; halogen; cyano; nitro; -CHO; -CO.C_{1-6}alkyl; C_{1-6}alkyl, C_{1-6}alkoxy or

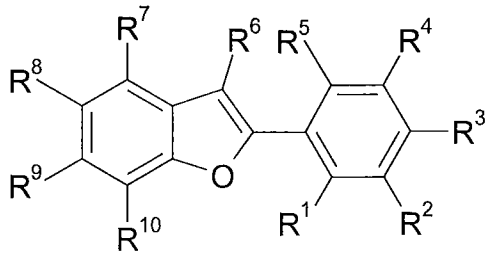
C_{1-6}alkoxyalkyl optionally substituted by 1 to 3 halogen atoms; C_{2-6}alkenyl optionally substituted by halogen or cyano; C_{2-6}alkynyl; SO_2H; SO_2C_{1-6}alkyl; SH; and SC_{1-6}alkyl;

R^8 is OR^A;

R^7, R^9 and R^{10} are each independently selected from the group consisting of hydrogen, OR^A, halogen, cyano, nitro, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C(O)H, $C(O)C_{1-6}$alkyl, haloC_{1-6}alkyl, dihaloC_{1-6}alkyl, trihaloC_{1-6}alkyl, cyanoC_{1-6}alkyl, and C_{1-4}alkoxyC_{1-6}alkyl; and

R^A is selected from the group consisting of hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkyl-C_{1-6}alkyl, C_{6-10}aryl and C_{6-10} aryl-C_{1-6}alkyl;
together with a pharmaceutically acceptable carrier.

2. A compound of formula (I) or a pharmaceutically acceptable ester, amide, solvate or salt thereof, including a salt of such an ester or amide, and a solvate of such an ester, amide or salt:



(I)

wherein R^1, R^2, R^4 and R^5 are each independently selected from the group consisting of hydrogen, OR^A, 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^3 is selected from the group consisting of OR^A; -CHO; $-C(O)C_{1-4}$alkyl; -C(O)phenyl; $-O-C(O)R^A$; and $N(R^B)_2$ in which each R^B is independently selected from the group consisting of hydrogen, $-C(O)C_{1-4}$alkyl, -C(O)phenyl, $-SO_2C_{1-4}$alkyl, $-SO_2$phenyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkyl-C_{1-6}alkyl, C_{6-10}aryl, C_{6-10}aryl-C_{1-6}alkyl, C_{5-10}heterocyclyl and C_{5-10}heterocyclyl-C_{1-6} alkyl;

or R^3 and R^4 together with the atoms to which they are attached, 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 1 or 2 groups selected from OR^A, 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^6 is selected from the group consisting of C_{3-8}cycloalkyl, C_{3-8}cycloalkyl-C_{1-6}alkyl, C_{3-8}cycloalkyl-C_{1-6}alkenyl, phenyl, biphenyl, phenyl-C(=CH_2)-, and C_{5-10}heterocyclyl, wherein said phenyl, biphenyl, phenyl-C(=CH_2)- or C_{5-10}heterocyclyl group is unsubstituted or substituted on the ring with 1 to 3 substituents, each substituent being selected from the group consisting of OR^A; halogen; cyano; nitro; -CHO; -CO.C_{1-6}alkyl; C_{1-6}alkyl, C_{1-6}alkoxy or C_{1-6}alkoxyalkyl optionally substituted by 1 to 3 halogen atoms; C_{2-6}alkenyl optionally substituted by halogen or cyano; C_{2-6}alkynyl; SO_2H; SO_2C_{1-6}alkyl; SH; and SC_{1-6}alkyl;

R^8 is OR^A;

R^7, R^9 and R^{10} are each independently selected from the group consisting of hydrogen, OR^A, halogen, cyano, nitro, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C(O)H, C(O)C_{1-6}alkyl, haloC_{1-6}alkyl, dihaloC_{1-6}alkyl, trihaloC_{1-6}alkyl, cyanoC_{1-6}alkyl, and C_{1-4}alkoxyC_{1-6}alkyl; and

R^A is selected from the group consisting of hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkyl-C_{1-6}alkyl, C_{6-10}aryl and C_{6-10} aryl-C_{1-6}alkyl;
with the provisos that (i) if all of R^2, R^3, R^8 and R^9 represent methoxy groups and all of R^1, R^4, R^5, R^7 and R^{10} represent hydrogen atoms, then R^6 represents a group other than phenyl or 3,4-dimethoxyphenyl; (ii) if both R^3 and R^8 represent methoxy groups, R^2 represents an isopropoxy group, R^9 represents a hydroxy or an isopropoxy group and all of R^1, R^4, R^5, R^7 and R^{10} represent hydrogen atoms, then R^6 represents a group other than 3,4,5-trimethoxyphenyl; and (iii) if both of R^3 and R^8 represent methoxy groups and all of R^1, R^2, R^4, R^5, R^7, R^9 and R^{10} represent hydrogen atoms, then R^6 represents a group other than phenyl.

3. A composition or a compound as claimed in either claim 1 or claim 2, in which R^1, R^2, and R^5 are each independently selected from the group consisting of hydrogen, OR^A, halogen, cyano, nitro, C_{1-4}alkyl, haloC_{1-4}alkyl, dihaloC_{1-4}alkyl and trihaloC_{1-4}alkyl.

4. A composition or a compound as claimed in claim 3, in which R^1, R^2 and R^5 are each independently selected from the group consisting of hydrogen, hydroxy, halogen, cyano, methyl and trifluoromethyl.

5. A composition or a compound as claimed in any one of the preceding claims, in which R^3 is selected from the group consisting of OR^A and $N(R^B)_2$, in which each R^B is independently selected from the group consisting of hydrogen, C_{1-4}alkyl, and C_{3-6}cycloalkyl.

6. A composition or a compound as claimed in claim 5, in which R^3 represents a hydroxy group.

7. A composition or a compound as claimed in any one of the preceding claims, in which R^4 represents hydrogen, OR^A, halogen, cyano, nitro, C_{1-4}alkyl, haloC_{1-4}alkyl, dihaloC_{1-4}alkyl or trihaloC_{1-4}alkyl.

8. A composition or a compound as claimed in claim 7, in which R^4 represents hydrogen, hydroxy, halogen, cyano, methyl or trifluoromethyl.

9. A composition or a compound as claimed in any one of claims 1 to 4, in which R^3 and R^4 together represent an -NH-CH=N-, -NH-N=CH- or -CH-CH-NH- group.

10. A composition or a compound as claimed in any one of the preceding claims, in which R^6 is selected from the group consisting of C_{3-6}cycloalkyl, C_{3-6}cycloalkyl-C_{1-2}alkyl, C_{3-6}cycloalkyl-C_{1-2}alkenyl, phenyl, biphenyl, phenyl-$C(=CH_2)$-, and C_{5-7}heterocyclyl wherein said phenyl, biphenyl, phenyl-$C(=CH_2)$- or C_{5-10}heterocyclyl group is unsubstituted or substituted on the ring with 1 or 2 substituents, each substituent being selected from the group consisting of OR^A; halogen; cyano; and C_{1-4}alkyl or C_{1-4}alkoxy optionally substituted by 1 to 3 halogen atoms.

11. A composition or a compound as claimed in claim 10, in which R^6 is an aromatic group.

12. A composition or a compound as claimed in either claim 10 or claim 11, in which R^6 is an optionally substituted phenyl or C_5heterocyclyl group.

13. A composition or a compound as claimed in any one of the preceding claims, in which R^7, R^9 and R^{10} are each independently selected from the group consisting of hydrogen, OR^A, halogen, cyano, C_{1-4}alkyl, haloC_{1-4}alkyl, dihaloC_{1-4}alkyl and trihaloC_{1-4}alkyl.

14. A composition or a compound as claimed in claim 13, in which R^7, R^9 and R^{10} are each independently selected from hydrogen, hydroxy, halogen, cyano, methyl and trifluoromethyl.

15. A composition or a compound as claimed in any one of the preceding claims, in which R^A is selected from the group consisting of hydrogen, C_{1-4}alkyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkyl-C_{1-4} alkyl, phenyl and benzyl.

16. A compound or a composition as claimed in claim 15, in which R^A represents hydrogen or C_{1-4}alkyl.

17. A composition as claimed in claim 1 or a compound as claimed in claim 2, in which:

R^A represents C_{1-4}alkyl or hydrogen;

R^1, R^2, and R^5 are each independently selected from the group consisting of hydrogen, OR^A, halogen, cyano, halomethyl, dihalomethyl and trihalomethyl;

R^3 represents OR^A or $N(R^B)_2$, in which each R^B independently represents hydrogen or C_{1-4}alkyl;

R^4 represents one of the preferred groups mentioned above for R^1, R^2, and R^5; or

R^3 and R^4 together represent an -NH-N=CH- group;

R^6 represents phenyl or a C_5heterocyclyl group which can either be unsubstituted or substituted on the ring with 1 or 2 substituents, each substituent being selected from the group consisting of OR^A; halogen; cyano; and C_{1-4}alkyl or C_{1-4}alkoxy optionally substituted by 1 to 3 halogen atoms; and

R^7, R^9 and R^{10} each independently represent hydrogen, OR^A, halogen, cyano, halomethyl, dihalomethyl and trihalomethyl.

18. A composition or a compound as claimed in claim 17, in which at least one of R^1, R^2, and R^5 represents hydrogen; R^3 represents OR^A; or R^3 and R^4 together represent an -NH-CH=N-, -NH-N=CH- or -CH=CH-NH- group; R^6 represents phenyl or a C_5heterocyclyl group optionally substituted by cyano; and R^7, R^9 and R^{10} each independently represent hydrogen, hydroxy, halogen, cyano, methyl and trifluoromethyl, at least one of R^7, R^9 and R^{10} being hydrogen.

19. A compound as claimed in claim 2, which is:
2-(4-Hydroxy-phenyl)-7-methyl-3-phenyl-benzofuran-5-ol;
5-Hydroxy-2-(4-hydroxy-phenyl)-3-phenyl-benzofuran-7-carbonitrile;
2-(2-Fluoro-4-hydroxy-phenyl)-7-methyl-3-phenyl-benzofuran-5-ol;
7-Dibromomethyl-2-(4-hydroxy-phenyl)-3-phenyl-benzofuran-5-ol;
[5-Hydroxy-2-(4-hydroxy-phenyl)-3-phenyl-benzofuran-7-yl]-acetonitrile;
2-(4-Hydroxy-phenyl)-7-(1-methoxy-ethyl)-3-phenyl-benzofuran-5-ol;
7-Difluoromethyl-2-(4-hydroxy-phenyl)-3-phenyl-benzofuran-5-ol;
2-(4-Hydroxy-phenyl)-3-phenyl-7-vinyl-benzofuran-5-ol;
2-(4-Hydroxy-phenyl)-3-thiophen-3-yl-7-trifluoromethyl-benzofuran-5-ol;
7-Fluoro-2-(1H-indazol-5-yl)-3-thiophen-3-yl-benzofuran-5-ol;
2-[7-Chloro-5-hydroxy-2-(4-hydroxy-phenyl)-benzofuran-3-yl]-furan-3-carbonitrile;
2-(4-Hydroxy-phenyl)-7-methyl-3-thiophen-3-yl-benzofuran-5-ol;
3-(2,5-Difluoro-phenyl)-2-(4-hydroxy-phenyl)-7-methyl-benzofuran-5-ol;
3-[5-Hydroxy-2-(4-hydroxy-phenyl)-7-methyl-benzofuran-3-yl]-benzonitrile;
2-(4-Hydroxy-phenyl)-7-methyl-3-m-tolyl-benzofuran-5-ol;
2-(4-Hydroxy-phenyl)-7-methyl-3-thiophen-2-yl-benzofuran-5-ol;
2-(4-Hydroxy-phenyl)-7-methyl-3-pyridin-3-yl-benzofuran-5-ol;
2-[5-Hydroxy-2-(4-hydroxy-phenyl)-7-methyl-benzofuran-3-yl]-benzonitrile;
2-(4-Hydroxy-phenyl)-7-methyl-3-(3-nitro-phenyl)-benzofuran-5-ol;
5-[5-Hydroxy-2-(4-hydroxy-phenyl)-7-methyl-benzofuran-3-yl]-thiophene-2-carbaldehyde;
3-(3,5-Difluoro-phenyl)-2-(4-hydroxy-phenyl)-7-methyl-benzofuran-5-ol;
3-(3,5-Dichloro-phenyl)-2-(4-hydroxy-phenyl)-7-methyl-benzofuran-5-ol;
2-(4-Hydroxy-phenyl)-7-methyl-3-(2-phenoxy-phenyl)-benzofuran-5-ol;

3-Biphenyl-2-yl-2-(4-hydroxy-phenyl)-7-methyl-benzofuran-5-ol;

3-(2-Hydroxy-phenyl)-2-(4-hydroxy-phenyl)-7-methyl-benzofuran-5-ol;

1-{3-[5-Hydroxy-2-(4-hydroxy-phenyl)-7-methyl-benzofuran-3-yl]-phenyl}-ethanone;

2-(4-Hydroxy-phenyl)-3-(3-methanesulfonyl-phenyl)-7-methyl-benzofuran-5-ol;

3-(3-Ethylsulfanyl-phenyl)-2-(4-hydroxy-phenyl)-7-methyl-benzofuran-5-ol;

2-(4-Hydroxy-phenyl)-7-methyl-3-quinolin-5-yl-benzofuran-5-ol;

1-{5-[5-Hydroxy-2-(4-hydroxy-phenyl)-7-methyl-benzofuran-3-yl]-thiophen-2-yl}-ethanone;

2-(4-Hydroxy-phenyl)-7-methyl-2',3'-dihydro-[3,5']bibenzofuranyl-5-ol;

2-(4-Hydroxy-phenyl)-7-methyl-3-(3-trifluoromethoxy-phenyl)-benzofuran-5-ol;

3-(2-Fluoro-pyridin-3-yl)-2-(4-hydroxy-phenyl)-7-methyl-benzofuran-5-ol;

3-Benzo[b]thiophen-2-yl-2-(4-hydroxy-phenyl)-7-methyl-benzofuran-5-ol;

2-(4-Hydroxy-phenyl)-7-methyl-3-(1-methyl-1H-pyrazol-4-yl)-benzofuran-5-ol;

2-(4-Hydroxy-phenyl)-7-methyl-3-(1-phenyl-vinyl)-benzofuran-5-ol;

2-(4-Hydroxy-phenyl)-7-methyl-3-pyridin-4-yl-benzofuran-5-ol;

2-(4-Hydroxy-phenyl)-7-methyl-3-(1-methyl-1H-pyrrol-2-yl)-benzofuran-5-ol;

3-(3,5-Dimethyl-isoxazol-4-yl)-2-(4-hydroxy-phenyl)-7-methyl-benzofuran-5-ol;

3-(5-Fluoro-2-methyl-phenyl)-2-(4-hydroxy-phenyl)-7-methyl-benzofuran-5-ol;

3-[1-(4-Fluoro-phenyl)-vinyl]-2-(4-hydroxy-phenyl)-7-methyl-benzofuran-5-ol;

3-Cyclopropyl-2-(4-hydroxy-phenyl)-7-methyl-benzofuran-5-ol;

3-(5-Fluoro-2-methoxy-phenyl)-2-(4-hydroxy-phenyl)-7-methyl-benzofuran-5-ol;

2-(4-Hydroxy-phenyl)-7-methyl-3-(1H-pyrrol-2-yl)-benzofuran-5-ol;

3-Furan-2-yl-2-(4-hydroxy-phenyl)-7-methyl-benzofuran-5-ol;

2-(4-Hydroxy-phenyl)-7-methyl-3-thiazol-5-yl-benzofuran-5-ol;

2-(4-Hydroxy-phenyl)-3-(2-methoxy-thiazol-4-yl)-7-methyl-benzofuran-5-ol;

2-(4-Hydroxy-phenyl)-7-methyl-3-thiazol-2-yl-benzofuran-5-ol;

2-(4-Hydroxy-phenyl)-3-(2-isopropyl-phenyl)-7-methyl-benzofuran-5-ol;

3-(2-Ethyl-phenyl)-2-(4-hydroxy-phenyl)-7-methyl-benzofuran-5-ol;

(E)-3-{2-[5-Hydroxy-2-(4-hydroxy-phenyl)-7-methyl-benzofuran-3-yl]-phenyl}-acrylonitrile;

3-(2-Butoxy-phenyl)-2-(4-hydroxy-phenyl)-7-methyl-benzofuran-5-ol;

2-(4-Hydroxy-phenyl)-7-methyl-3-(2-trifluoromethoxy-phenyl)-benzofuran-5-ol;

4-[5-Hydroxy-2-(4-hydroxy-phenyl)-7-methyl-benzofuran-3-yl]-thiophene-2-carbaldehyde;

3-((E)-2-Cyclopropyl-vinyl)-2-(4-hydroxy-phenyl)-7-methyl-benzofuran-5-ol;

2-(4-Hydroxy-phenyl)-7-methyl-3-(3-methyl-thiophen-2-yl)-benzofuran-5-ol;

2-[5-Hydroxy-2-(4-hydroxy-phenyl)-7-methyl-benzofuran-3-yl]-thiophene-3-carbaldehyde;
2-[5-Hydroxy-2-(4-hydroxy-phenyl)-7-methyl-benzofuran-3-yl]-thiophene-3-carbonitrile;
7-Bromomethyl-2-(4-hydroxy-phenyl)-3-phenyl-benzofuran-5-ol;
5-Hydroxy-2-(4-hydroxy-phenyl)-3-thiophen-3-yl-benzofuran-7-carbonitrile;
5-Hydroxy-2-(4-hydroxy-phenyl)-3-phenyl-benzofuran-7-carbaldehyde;
7-Chloro-2-(4-hydroxy-phenyl)-3-phenyl-benzofuran-5-ol;
7-Chloro-2-(4-hydroxy-phenyl)-3-thiophen-3-yl-benzofuran-5-ol;
5-Hydroxy-2-(4-hydroxy-phenyl)-3-thiophen-3-yl-benzofuran-7-carbaldehyde;
2-(4-Hydroxy-phenyl)-3-thiophen-3-yl-7-vinyl-benzofuran-5-ol;
2-[7-Chloro-5-hydroxy-2-(4-hydroxy-phenyl)-benzofuran-3-yl]-thiophene-3-carbonitrile;
3-(3-Cyano-furan-2-yl)-5-hydroxy-2-(4-hydroxy-phenyl)-benzofuran-7-carbonitrile;
2-[5-Hydroxy-2-(4-hydroxy-phenyl)-7-trifluoromethyl-benzofuran-3-yl]-furan-3-carbonitrile;
2-[2-(3-Fluoro-4-hydroxy-phenyl)-5-hydroxy-7-methyl-benzofuran-3-yl]-furan-3-carbonitrile;
2-(4-Hydroxy-phenyl)-6-methyl-3-phenyl-benzofuran-5-ol;
2-(2,5-Difluoro-4-hydroxy-phenyl)-7-methyl-3-phenyl-benzofuran-5-ol;
2-(2,6-Difluoro-4-hydroxy-phenyl)-7-methyl-3-phenyl-benzofuran-5-ol;
2-(3-Fluoro-4-hydroxy-phenyl)-7-methyl-3-phenyl-benzofuran-5-ol;
2-(1H-Indazol-5-yl)-7-methyl-3-phenyl-benzofuran-5-ol;
2-(3,5-Difluoro-4-hydroxy-phenyl)-7-methyl-3-phenyl-benzofuran-5-ol;
2-(3-Chloro-5-fluoro-4-hydroxy-phenyl)-7-methyl-3-phenyl-benzofuran-5-ol;
5-(5-Methoxy-7-methyl-3-phenyl-benzofuran-2-yl)-1H-indazole;
2-(3-Fluoro-4-hydroxy-phenyl)-7-methyl-3-thiophen-3-yl-benzofuran-5-ol;
2-(2-Fluoro-4-hydroxy-phenyl)-7-methyl-3-thiophen-3-yl-benzofuran-5-ol;
2-(2,6-Difluoro-4-hydroxy-phenyl)-7-methyl-3-thiophen-3-yl-benzofuran-5-ol;
2-(3-Chloro-5-fluoro-4-hydroxy-phenyl)-7-methyl-3-thiophen-3-yl-benzofuran-5-ol;
2-[2-(3-Chloro-5-fluoro-4-hydroxy-phenyl)-5-hydroxy-7-methyl-benzofuran-3-yl]-furan-3-carbonitrile; or
2-[7-Fluoro-5-hydroxy-2-(1H-indazol-5-yl)-benzofuran-3-yl]-furan-3-carbonitrile;
or a pharmaceutically acceptable ester, amide, solvate or salt thereof, including a salt of such an ester or amide, and a solvate of such an ester, amide or salt.

20. A pharmaceutical composition as claimed in claim 1, which comprises a compound as claimed in claim 19, together with a pharmaceutically acceptable carrier.

21. A composition or a compound as claimed in any one of claims 1 to 20, for use as a medicament.

22. A composition or a compound as claimed in claim 21, for use in the treatment or prophylaxis of a condition associated with a disease or disorder associated with estrogen receptor activity.

23. Use of a composition or a compound as claimed in any one of claims 1 to 20, 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.

24. 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 composition or a compound as claimed in any one of claims 1 to 20.

25. Use of a compound as claimed in any one of claims 2 to 19 in labelled form as a diagnostic agent for the diagnosis of conditions associated with a disease or disorder associated with estrogen receptor activity, or use of a compound as claimed in any one of claims 2 to 19 or a labelled form of such a compound as a reference compound in a method of identifying ligands for the estrogen receptor.

26. A composition, a compound, a method or a use as claimed in any one of claims 21 to 25, 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 flashes, increased levels of LDL cholesterol, cardiovascular disease, impairment of cognitive functioning, cerebral degenerative disorders, restenosis, gynecomastia, vascular smooth muscle cell proliferation, obesity, incontinence, anxiety, depression, autoimmune disease, inflammation, IBD, IBS, sexual dysfunction, hypertension, retinal degeneration and lung, colon, breast, uterus, and prostate cancer.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2009/054220

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/343 C07D307/80 A61K31/381 A61K31/4025 A61K31/4155
A61K31/416 A61K31/427 A61K31/443 A61K31/4709 C07D405/04
C07D407/04 C07D409/04 C07D417/04 A61P35/00

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 C07D

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 practical, search terms used)
EPO-Internal, WPI Data, BIOSIS, EMBASE, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 516 257 A (SCHERING AG [DE]) 2 December 1992 (1992-12-02) claim 1	1-26
Y	ERBER S ET AL: "2 PHENYLBENZO-B-FURANS RELATIONSHIPS BETWEEN STRUCTURE ESTROGEN RECEPTOR AFFINITY AND CYTOSTATIC ACTIVITY AGAINST MAMMARY TUMOR CELLS" ANTI-CANCER DRUG DESIGN, vol. 6, no. 5, 1991, pages 417-426, XP009117620 ISSN: 0266-9536 tables II,IV; compound 14A	1-26
Y	WO 03/051860 A (WYETH CORP [US]) 26 June 2003 (2003-06-26) claim 1	1-26

-/--

[X] Further documents are listed in the continuation of Box C.

[X] 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 document 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
3 June 2009	15/06/2009

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Steendijk, Martin

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2009/054220

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 3 658 833 A (KABAS GUGLIELMO ET AL) 25 April 1972 (1972-04-25) column 13 -----	2-5,7,8, 10-17
X	BANWELL M G ET AL: "Synthesis, X-ray crystal structure and tubulin-binding properties of a benzofuran analogue of the potent cytotoxic agent combretastatin A4" AUSTRALIAN JOURNAL OF CHEMISTRY, CSIRO, AU, vol. 52, no. 8, 1 January 1999 (1999-01-01), pages 767-774, XP002904956 ISSN: 0004-9425 page 768; compound 4 page 770, right-hand column -----	1-5,7,8, 10-18
A	CHURRUCA, FATIMA ET AL: "A new, expeditious entry to the benzophenanthrofuran framework by a Pd-catalyzed C- and O-arylation/PIFA-mediated oxidative coupling sequence" EUROPEAN JOURNAL OF ORGANIC CHEMISTRY , (12), 2481-2490 CODEN: EJOCFK; ISSN: 1434-193X, 2005, XP002530269 table 2; compounds 3G,3K -----	2
A	DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; PERROT, CLAUDE ET AL: "Synthesis of substituted 2,3-diarylbenzo[b]furans. Rearrangement" XP002530270 retrieved from STN Database accession no. 1975:97904 RN: 16841-82-0 abstract & BULLETIN DE LA SOCIETE CHIMIQUE DE FRANCE , (9-10, PT. 2), 2225-32 CODEN: BSCFAS; ISSN: 0037-8968, 1974, -----	2

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2009/054220

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0516257 A	02-12-1992	AT 169295 T	15-08-1998
		AU 670746 B2	01-08-1996
		AU 1887092 A	08-01-1993
		CA 2110062 A1	10-12-1992
		DE 4117512 A1	26-11-1992
		WO 9221669 A1	10-12-1992
		FI 935220 A	24-11-1993
		HU 65680 A2	28-07-1994
		IE 921934 A1	02-12-1992
		JP 3179100 B2	25-06-2001
		JP 6507615 T	01-09-1994
		NO 934248 A	24-11-1993
		RU 2120443 C1	20-10-1998
		US 5470854 A	28-11-1995
WO 03051860 A	26-06-2003	AT 416170 T	15-12-2008
		AU 2002366356 A1	30-06-2003
		BR 0215058 A	06-06-2006
		CA 2470352 A1	26-06-2003
		CN 1606551 A	13-04-2005
		EP 1458700 A2	22-09-2004
		JP 2006506315 T	23-02-2006
		MX PA04005784 A	13-09-2004
		US 2006074128 A1	06-04-2006
US 3658833 A	25-04-1972	CA 939358 A1	01-01-1974
		CH 512623 A	31-12-1970
		CH 986269 D	31-12-1970
		DE 2031819 A1	11-03-1971
		ES 381189 A1	01-12-1972
		FR 2051383 A5	02-04-1971
		GB 1315536 A	02-05-1973
		NL 7009484 A	29-12-1970