

10-ARYL-11H-BENZO[b]FLUORENE DERIVATIVES AND ANALOGS FOR MEDICINAL USE

The invention relates to a non-steroidal compound with affinity for
5 estrogen receptors and to a method for selective estrogen receptor modulation (SERM) with such a compound and to the use of such a compound for the manufacture of a medicine for estrogen-receptor related treatments.

10 Compounds with affinity for estrogen receptors have found long-standing utility in the treatment of a variety of medical indications and in regimes for contraceptive purposes. Despite the long history of the field there still is a need for more effective, safer and more economical compounds than the existing ones. This need is the more pressing in view of advancement
15 in health care in other areas, which has led to an increasingly longer life span. This is in particular a problem for women for whom the decline in estrogenic hormones at menopause is drastic and has negative consequences for bone strength and cardiovascular functions. For the control or prevention of estrogen sensitive tumor growth, compounds are
20 needed which are antagonists, partial antagonists or tissue selective agonists for estrogen receptors.

The discovery of subtypes of estrogen receptors, there being an α -subtype ($ER\alpha$) and a β -subtype ($ER\beta$) of such receptors (Mosselman et al., FEBS Letters vol. 392 (1996) pp. 49-53 as well as EP -A- 0 798 378), offers the
25 possibility to influence one particular subtype of those two receptors more selectively, immanently resulting in more effective treatments or treatments with less side effects. Since these receptors have a different distribution in human tissue, the finding of compounds which possess a selective affinity for either of the two is an important technical progress,
30 making it possible to provide a more selective treatment in estrogen-receptor related medical treatments, such as those for contraception and for treatment of menopausal complaints, osteoporosis, and estrogen dependent tumour control, with a lower burden of estrogen-related side-effects.

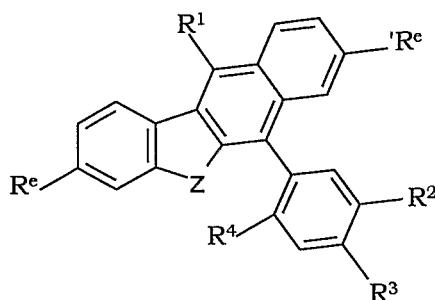
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This invention pertains to non-steroidal estrogenic compounds with a 10-aryl-11H-benzo[b]fluorene or a 7-aryl-5,6-dihydrobenz[a]anthracene

skeleton. Compounds with a 10-phenyl-11*H*-benzo[*b*]fluorene skeleton are described as products from enediyne thermocyclisation [Schmittl, M., *Z. Naturforsch., B: Chem. Sci.* (1998), **53**, 1015-1020] and from [4+2] cycloaddition reactions of diarylacetylenes [Rodriguez, D., *Org. Lett.* 5 (2000), **2**, 1497-1500], but no medicinal activity of these compounds is known. Indeno[1,2-*g*]quinolines with interactions with nuclear receptors are disclosed in WO 96 19458. Despite the keen interest in compounds with affinity for the estrogen receptor, new compounds with a 10-aryl-11*H*-benzo[*b*]fluorene or 7-aryl-5,6-dihydrobenz[*a*]anthracene skeleton 10 and affinity for the estrogen receptor cannot be learnt from these documents.

The present invention resides in the finding that compounds with an unsaturated or partially unsaturated four-ring skeleton with hydroxyl 15 substitutions at specific locations, i.e. 2,8-dihydroxy-10-aryl-11*H*-benzo[*b*]fluorene and 3,9-dihydroxy-7-aryl-5,6-dihydrobenz[*a*]anthracene, possess surprisingly high antagonism for ER β . Some of these compounds also show ER α antagonism or ER α agonism.

20 Specifically, the invention provides non-steroidal compounds having the formula 1



Formula 1

25 wherein:

R^e and 'R^e are OH, optionally independently etherified or esterified;

Z is -CH₂- or -CH₂CH₂-;

R¹ is H, halogen, CF₃, or (1C-4C)alkyl;

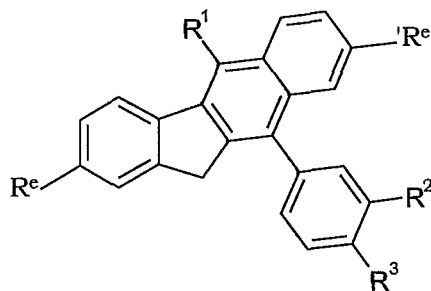
30 R², R³ and R⁴ are independently H, halogen, -CF₃, -OCF₃, (1C-8C)Alkyl, hydroxy, (1C-8C)alkyloxy, aryloxy, aryl(1C-8C)alkyl, halo(1C-8C)alkyl, -O(CH₂)_mX, wherein X is halogen or phenyl and m = 2-4; -

$O(CH_2)_mNR_aR_b$, $-S(CH_2)_mNR_aR_b$ or $-(CH_2)_mNR_aR_b$, wherein $m = 2-4$
 and wherein R_a , R_b are independently (1C-8C)alkyl, (2C-8C)alkenyl,
 (2C-8C)alkynyl, or aryl, optionally substituted with halogen, $-CF_3$, $-$
 OCF_3 , $-CN$, $-NO_2$, $-OH$, (1C-8C)alkoxy, aryloxy, carboxyl, (1C-
 5 8C)alkylthio, carboxylate, (1C-8C)alkyl, aryl, aryl(1C-8C)alkyl,
 halo(1C-8C)alkyl or R_a and R_b form a 3-8 membered ring structure,
 optionally substituted with halogen, $-CF_3$, $-OCF_3$, $-CN$, $-NO_2$,
 hydroxy, hydroxy(1C-4C)alkyl, (1C-8C)alkoxy, aryloxy, (1C-
 8C)alkylthio, carboxyl, carboxylate, (1C-8C)alkyl, aryl, aryl(1C-
 10 8C)alkyl, halo(1C-8C)alkyl.

Preferred compounds of the invention can be obtained by selecting $-CH_2-$
 for Z and hydrogen for R^4 in formula 1. For R^1 it is preferred to select
 compounds having H, halogen or CF_3 . Compounds with R^1 in formula 1
 15 is halogen, whereby chlorine is most preferred, are particularly potent
 and selective for the $ER\beta$.

Another embodiment of the invention is a non-steroidal compound with a
 10-Aryl-11H-benzo[*b*]fluorene skeleton having the formula 2

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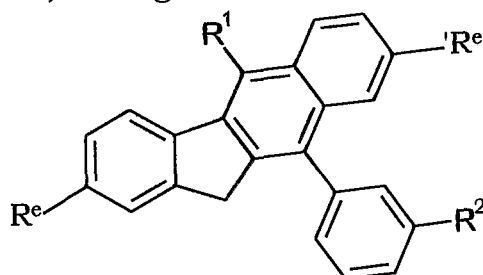


Formula 2

wherein:
 R^e and R^e are OH, optionally independently etherified or esterified;
 25 R^1 is H, halogen or CF_3 ;
 R^2 and R^3 are independently H, halogen, $-CF_3$, $-OCF_3$, (1C-8C)Alkyl,
 hydroxy, (1C-8C)alkyloxy, aryloxy, aryl(1C-8C)alkyl, halo(1C-
 8C)alkyl, $-O(CH_2)_mNR_aR_b$, $-S(CH_2)_mNR_aR_b$ or $-(CH_2)_mNR_aR_b$, wherein
 $m = 2-4$ and R_a , R_b are independently (1C-8C)alkyl, (2C-8C)alkenyl,
 30 (2C-8C)alkynyl, or aryl, optionally substituted with halogen, $-CF_3$, $-$
 OCF_3 , $-CN$, $-NO_2$, $-OH$, (1C-8C)alkoxy, aryloxy, carboxyl, (1C-

- 8C)alkylthio, carboxylate, (1C-8C)alkyl, aryl, aryl(1C-8C)alkyl, halo(1C-8C)alkyl or R_a and R_b form a 3-8 membered ring structure, optionally substituted with halogen, $-CF_3$, $-OCF_3$, $-CN$, $-NO_2$, hydroxy, (1C-8C)alkoxy, aryloxy, (1C-8C)alkylthio, carboxyl, carboxylate, (1C-8C)alkyl, aryl, aryl(1C-8C)alkyl, halo(1C-8C)alkyl.

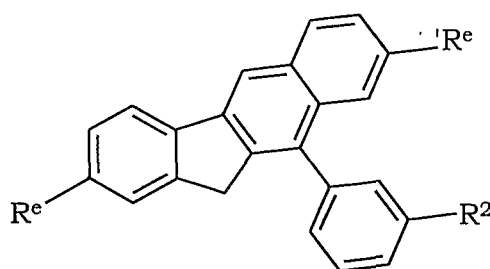
For compounds, having formula 3,



Formula 3

- it is preferred to select those in which R^e and R^e are OH, optionally independently etherified or esterified; R^1 is H, halogen, CF_3 ; R^2 is $-O(CH_2)_mNR_aR_b$, wherein $m = 2-3$ and R_a , R_b are independently (1C-5C)alkyl or (3C-5C)alkenyl, optionally substituted with OH or methoxy, or R_a and R_b form a 4-7 membered ring structure selected from the list: azetidine, pyrrolidine, 3-pyrroline, piperidine, piperazine, tetrahydropyridine, morpholine, thiomorpholine, thiazolidine, homopiperidine, tetrahydroquinoline and 6-azabicyclo[3.2.1]octane, which 4-7 membered ring structure can optionally be substituted with OH, methoxy, acetyl, carboxylate, (1C-3C)alkyl, phenyl, benzyl, and phenylethyl.

In particular, a very effective compound is made available by this invention by selecting a compound having formula 4:



Formula 4

wherein:

R^e and 'R^e are OH, optionally independently etherified or esterified;

R² is (3C-6C)alkyloxy, -O(CH₂)_mX (wherein X is halogen or phenyl and

5 m = 2-3), or -O(CH₂)_mNR_aR_b, (wherein m = 2-3), whereby R_a, R_b are
independently (1C-5C)alkyl or (3C-5C)alkenyl, optionally substituted
with OH or methoxy, or R_a and R_b form a 4-7 membered ring
structure selected from the list: azetidine, pyrrolidine, 3-pyrroline,
piperidine, piperazine, tetrahydropyridine, morpholine,
10 thiomorpholine, thiazolidine, homopiperidine, tetrahydroquinoline
and 6-azabicyclo[3.2.1]octane, which 4-7 membered ring structure
can optionally be substituted with OH, hydroxy(1C-2C)alkyl,
methoxy, acetyl, carboxylate, (1C-3C)alkyl, phenyl, benzyl, and
phenylethyl.

15

In those cases that the compound in formulas 1-4 contain a basic amine
function, the compound may be used as a free base or as a
pharmaceutically acceptable salt such as hydrochloride, acetate, oxalate,
tartrate, citrate, phosphate, maleate or fumarate.

20

The ester and ether compounds in the collection of compounds according
to the invention often have activity as prodrug. A prodrug is defined as
being a compound which converts in the body of a recipient to a
compound as defined by the formulas 1 to 4 and to the free hydroxyl
25 compounds of the above defined compounds. Preferred ester and ether
prodrugs are carboxylic acid esters or alkyl ethers on one or both
hydroxyl groups, and more preferred prodrugs are (2C-6C)carboxylic acid
esters, such as esters of (iso)butanoic acid, or (1C-4C) alkyl ethers.

In general, the hydroxy groups can for example be substituted by

30 alkyl*oxy, alkenyl*oxy, acyl*oxy, aroyloxy, alk*oxycarbonyloxy, sulfonyl
groups or phosphate groups, whereby the carbon chain length of the
groups denoted with an asterisk (*) is not considered to be sharply
delimited, while aroyl generally will comprise a phenyl, pyridinyl or
pyrimidyl, which groups can have substitutions customary in the art,
35 such as alkyl*oxy, hydroxy, halogen, nitro, cyano, and (mono-, or
dialkyl*-)-amino. The length of the alkyl, alkenyl and acyl groups is
selected depending on the desired properties of the prodrugs, whereby

the longer chained prodrugs with for example lauryl or caproyl chains are more suitable for sustained release and depot preparations. It is known that such substituents spontaneously hydrolyse or are enzymatically hydrolysed to the free hydroxyl substituents on the skeleton of the
5 compound. Such prodrugs will have biological activity comparable to the compounds to which they are converted in the body of the recipients. The active compound to which a prodrug is converted is called the parent compound. The onset of action and duration of action as well as the distribution in the body of a prodrug may differ from such properties of
10 the parent compound.

Substitution variants of the compounds of the present invention are possible for similar use. A substitution variant is defined to be a compound which comprises in its molecular structure the structure as
15 defined by the formula I. The skilled person inspecting the group of compounds provided by the present invention will immediately understand that modification by a substituent to the skeleton can yield a compound with similar biological activity as the compound without this particular substituent. It is common practise in the art to test such
20 substitution variants for the expected biological activity so that it is a routine skill to obtain useful substitution variants of compounds according to the invention.

Other terms used in this description have the following meaning:

- 25 alkyl is a branched or unbranched alkyl group, for example methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, tert-butyl, hexyl, octyl, capryl, or lauryl;
alkenyl is a branched or unbranched alkenyl group, such as ethenyl, 2-butenyl, etc.;
- 30 alkynyl is a branched or unbranched alkynyl group, such as ethynyl and propynyl;
halogen refers to fluorine, chlorine, bromine and iodine;
aryl is a mono- or polycyclic, homo- or heterocyclic aromatic ring system, such as phenyl, naphthyl or pyridinyl; a monocyclic ring with 6 atoms is
35 preferred for use;

a ring system or structure is referring to a chemical group in which all atoms are involved in formed rings, which rings can be saturated or (partially) unsaturated and comprise C, O, S or N atoms;

aroyl is arylcarbonyl such as a benzoyl group;

5 alkanoyl means a formyl or alkylcarbonyl group such as formyl, acetyl and propanoyl;

acyl is a (substituent-)carbonyl group, such as an aroyl or alkanoyl;

carboxyl is a -COOH substituent, making the compound an organic acid;

carboxylate is an ester or salt of a carboxyl substituent.

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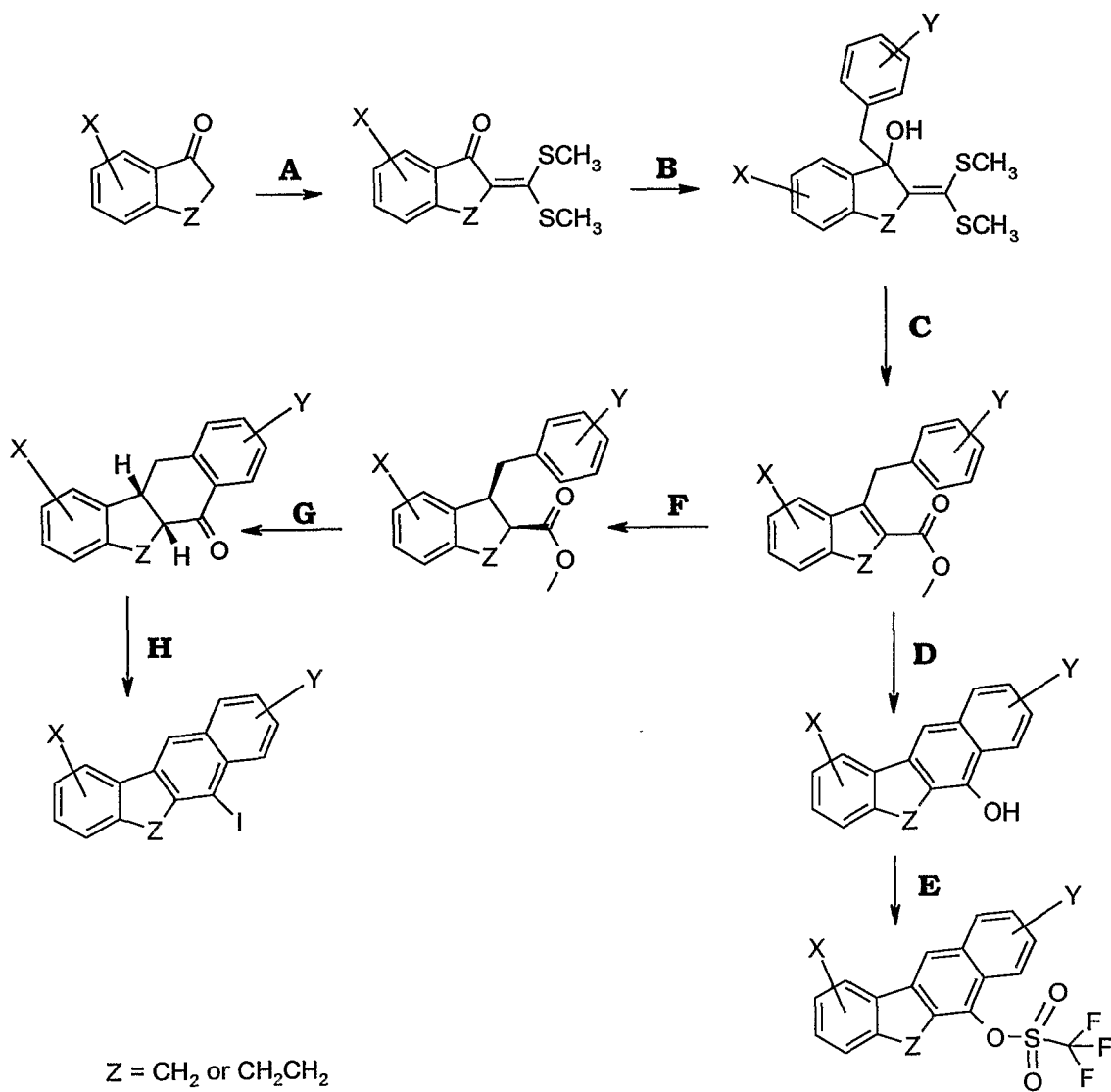
The prefixes (1C-4C), (2C-4C) etc. have the usual meaning to restrict the meaning of the indicated group to those with 1 to 4, 2 to 4 etc. carbon atoms.

15 The estrogen-receptor affinity profile of the compounds according to the present invention, makes them suitable for use in estrogen-receptor related medical treatments, in the sense that these compounds are improved anti-estrogens, partial anti-estrogen, partial estrogens or selective (partial) (anti-)estrogens. Estrogen-receptor related medical
20 treatments specifically named are those for contraception or for treatment or prevention of benign prostate hypertrophy, cardiovascular disorders, menopausal complaints, osteoporosis, estrogen dependent tumour control or central nervous system disorders such as depression or Alzheimer's disease. In particular those compounds which have
25 selective affinity for the ER β receptor are suitable for estrogen-receptor related medical treatments under diminished estrogen-related side-effects. This is most desirable when these compounds are used in the treatment of osteoporosis, cardiovascular disorders and central nervous system disorders such as depression or Alzheimer's disease. Selective
30 blockade of ER β -receptors with compounds of this invention can be used to prevent and reduce malignant tumor growth and hyperplasias. The receptor selectivity helps to effectuate tissue selectivity. Those tissues rich in ER β -receptors can be protected by ER β -receptor antagonists from the risk of stimulation of growth by estrogenic agonists. The latter can be
35 of endogenous origin or from exogenous origine when administered during estrogenic treatment, for example for hormone replacement after menopause. Tissues that can benefit from protection in view of the

presence of ER β -receptors are prostate, testes (human), lung, colon and endometrium. In particular, endometrium proliferation can be reduced by ER β antagonists of the invention.

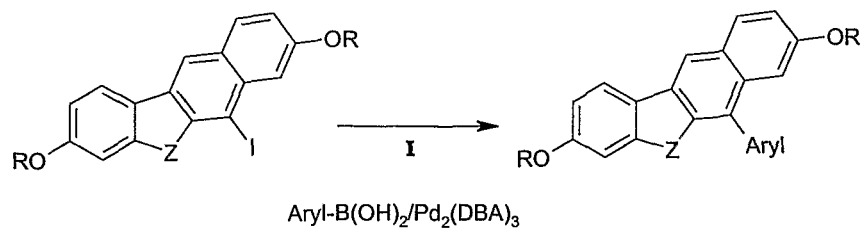
- 5 The compounds of the invention can be produced by various methods known in the art of organic chemistry in general. More specifically the routes of synthesis as illustrated in the schemes and examples can be used.

Scheme 1. A general procedure that can be used to prepare compounds of the invention



5

Scheme 2



R is protecting group

With reference to scheme 1, the benzofluorene ($Z=CH_2$) and the benzanthracene ($Z=CH_2CH_2$) skeleton can be assembled in an identical manner. In step **A** adequately substituted indanones or tetralones are treated with CS_2 under appropriate basic conditions to introduce a
5 dithioketene function (in fact serving as a carboxylate equivalent), after which procedure reaction with an organometallic derivative of a substituted benzylhalide (preferably a Grignard derivative) in step **B**, followed by alcoholysis (step **C**) leads to an α,β -unsaturated ester. At this stage an acid catalyzed cyclization (step **D**) immediately leads to the
10 phenolic benzofluorene (or benzanthracene). Conversion of this into a reactive intermediate (like triflate) in step **E** allows the introduction of the desired functionalities (like aryl groups, carboxylates etc) by means of known organometallic techniques.

If the mentioned α,β -unsaturated ester is first hydrogenated in step **F**
15 prior to cyclization (step **G**), the indicated ketones become available. They may be easily converted into the aromatic iodide in step **H**. These, under circumstances may be more reactive than the afore-mentioned triflates and provide valuable alternatives for functionalization (step **I** in scheme 2).

20 Ester prodrugs can be made by esterification of compounds with free hydroxyl groups by reaction with appropriate acyl chlorides in pyridine. Free dihydroxy compounds having formula 1 can be made by hydrolysis of ether precursors.

25 The present invention also relates to a pharmaceutical composition comprising the non-steroidal compound according to the invention mixed with a pharmaceutically acceptable auxiliary, such as described in the standard reference Gennaro *et al*, *Remington: The Science and Practice of Pharmacy*, (20th ed., Lippincott Williams & Wilkins, 2000, see
30 especially Part 5: Pharmaceutical Manufacturing). Suitable auxiliaries are made available in e.g. the Handbook of Pharmaceutical Excipients (2nd Edition, Editors A. Wade and P.J. Weller; American Pharmaceutical Association; Washington; The Pharmaceutical Press; London, 1994). The mixture of the compounds according to the invention and the
35 pharmaceutically acceptable auxiliary may be compressed into solid dosage units, such as pills, tablets, or be processed into capsules or suppositories. By means of pharmaceutically suitable liquids the

compounds can also be applied as an injection preparation in the form of a solution, suspension, emulsion, or as a spray, e.g. nasal spray. For making dosage units, e.g. tablets, the use of conventional additives such as fillers, colorants, polymeric binders and the like is contemplated. In
5 general any pharmaceutically acceptable additive which does not interfere with the function of the active compounds can be used. The compounds of the invention may also be included in an implant, a vaginal ring, a patch, a gel, and any other preparation for sustained release.

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Suitable carriers with which the compositions can be administered include lactose, starch, cellulose derivatives and the like, or mixtures thereof used in suitable amounts.

15 Furthermore, the invention relates to the use of the non-steroidal compound according to the invention for the manufacture of a medicament for estrogen-receptor related treatments and treatment of estrogen-receptor related disorders such as peri- and/or post-menopausal complaints. Thus the invention also pertains to the medical
20 indications of peri- and/or post-menopausal (climacteric) complaints and osteoporosis, i.e. a method of treatment in the field of hormone replacement therapy (HRT), comprising the administration to a patient, being a woman, of a compound as described hereinbefore (in a suitable pharmaceutical dosage form).

25

Further, the invention relates to the use of the non-steroidal compound according to the invention in the manufacture of a medicament having contraceptive activity. Thus the invention also pertains to the medical indication of contraception, i.e. a method of contraception comprising the
30 administration to a subject, being a woman or a female animal, of a progestogen and an estrogen as is customary in the field, wherein the estrogen is a compound as described hereinbefore (in a suitable pharmaceutical dosage form).

35 Finally the invention relates to the use of the non-steroidal compound for the manufacture of a medicament having selective estrogenic and/or

anti-estrogenic activity, such a medicament being generally suitable in the area of HRT (hormone replacement therapy).

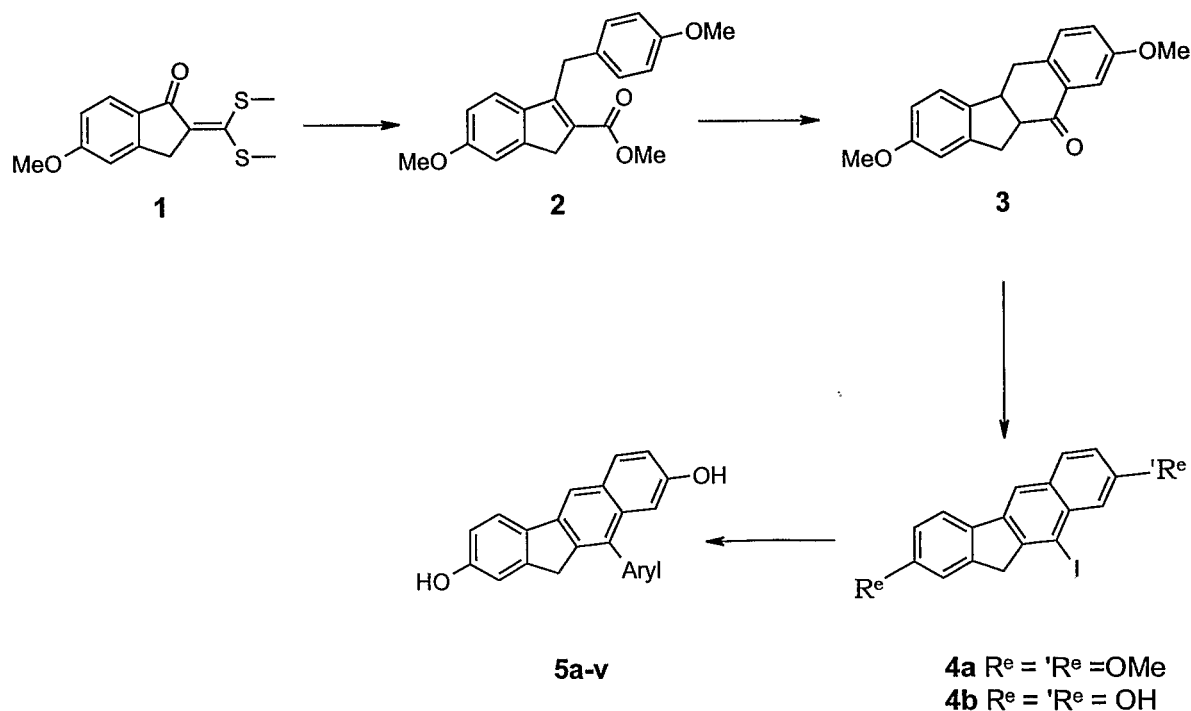
The dosage amounts of the present compounds will be of the normal order for estrogenic compounds, e.g. of the order of 0.01 to 100 mg per administration.

The invention is further illustrated hereinafter with reference to some unlimitative examples and the corresponding formula schemes referred to. Compounds are identified by numbers (in bold letter type) with reference to the corresponding numbers in the schemes. Abbreviations used in the schemes: Me is methyl, Bn is benzyl, ph is phenyl, aryl represents the substituted phenyl as in formula 1.

15 **EXAMPLES**

Example 1

20 **Scheme 3**



Preparation of precursor 10-iodo-2,8-dihydroxy-11H-benzo[b]fluorene (4b).

- 59 ml 4-methoxybenzyl-magnesium chloride (0.2 M in diethyl ether) was added to **1** [J.V. Ram and M. Nath, *Indian J. Chem. Sect.B*; **34**, 416-422 (1995)] (11.6 mmol) in 70 ml THF at 0°C and the reaction mixture was
- 5 stirred for 0.5 hour at 20°C. The mixture was poured into saturated aq. NH₄Cl, extracted with diethyl ether and dried over MgSO₄. After evaporation of the solvent the crude product was purified by chromatography on silica gel (heptane/ethyl acetate). The pure fractions were concentrated and the material obtained was taken up in 95 ml
- 10 methanol and treated with BF₃.Et₂O (28 mmol). After 0.5 hour the temperature was raised to 65°C and after 0.5 hour the reaction mixture was poured into water, extracted with CH₂Cl₂ and the organic layer washed with NaHCO₃ (aq). The extract was dried over MgSO₄, concentrated and the residue was recrystallised from methanol to afford
- 15 pure **2** in 45% yield (R_f = 0.48 heptane/ethyl acetate (3:2)).
- A mixture of **2** (5 mmol) and palladium on carbon (10% Pd (w/w), 300 mg) in 120 ml ethanol/acetic acid (5:1) was stirred under an atmosphere of hydrogen for 1 hour. The catalyst was removed by filtration and the filtrate was concentrated.
- 20 The residue was dissolved in methanesulfonic acid and stirred at 90°C for 15 minutes after which the mixture was poured into ice water and extracted with ethyl acetate. The organic layer was washed with NaHCO₃(aq) and dried over MgSO₄. Chromatography on silica gel (heptane/ethyl acetate) gave pure **3** in 85% yield. (R_f = 0.49
- 25 heptane/ethyl acetate (2:1)); MP 96-98°C.
- The compound **3** (0.34 mmol) was dissolved in ethanol and 1 ml hydrazine monohydrate was added. After 4 hours refluxing, water was added and the hydrazone was extracted with CH₂Cl₂. The organic layer was washed with water, dried and concentrated. The residue was taken
- 30 up in 1.5 ml triethylamine and 0.2 g iodine in 0.7 ml THF was added at 0°C. After 1 hour the reaction mixture was diluted with toluene, poured into ice water and extracted with toluene. The organic layer was washed with 1N HCl and saturated NaHCO₃(aq), dried over MgSO₄ and concentrated. The residue was dissolved in 8 ml m-xylene/toluene (2:1)
- 35 palladium on carbon (10% w/w, 100 mg) was added and the mixture was heated at 125°C for 2 hours. After cooling the catalyst was filtered off, the filtrate was concentrated and the residue was purified on silica gel

(heptane/ethyl acetate). The appropriate fractions were collected and concentrated to give pure **4a**. Compound **4a** was dissolved in 30 mL CH₂Cl₂ and treated with BBr₃ (3.5 mmol). After 1 hour another 2.1 mmol of BBr₃ was added. After 1.5 hours the mixture was carefully poured into
 5 sat. NaHCO₃ (aq) and extracted with ethyl acetate. The organic layer was dried over MgSO₄ and concentrated. Chromatography on silica gel (toluene/ethyl acetate) afforded pure **4b** in 62% yield. (R_f = 0.50 toluene/ethyl acetate (4:1)); ESI-MS : M+H = 375.2, M-H = 373.0.

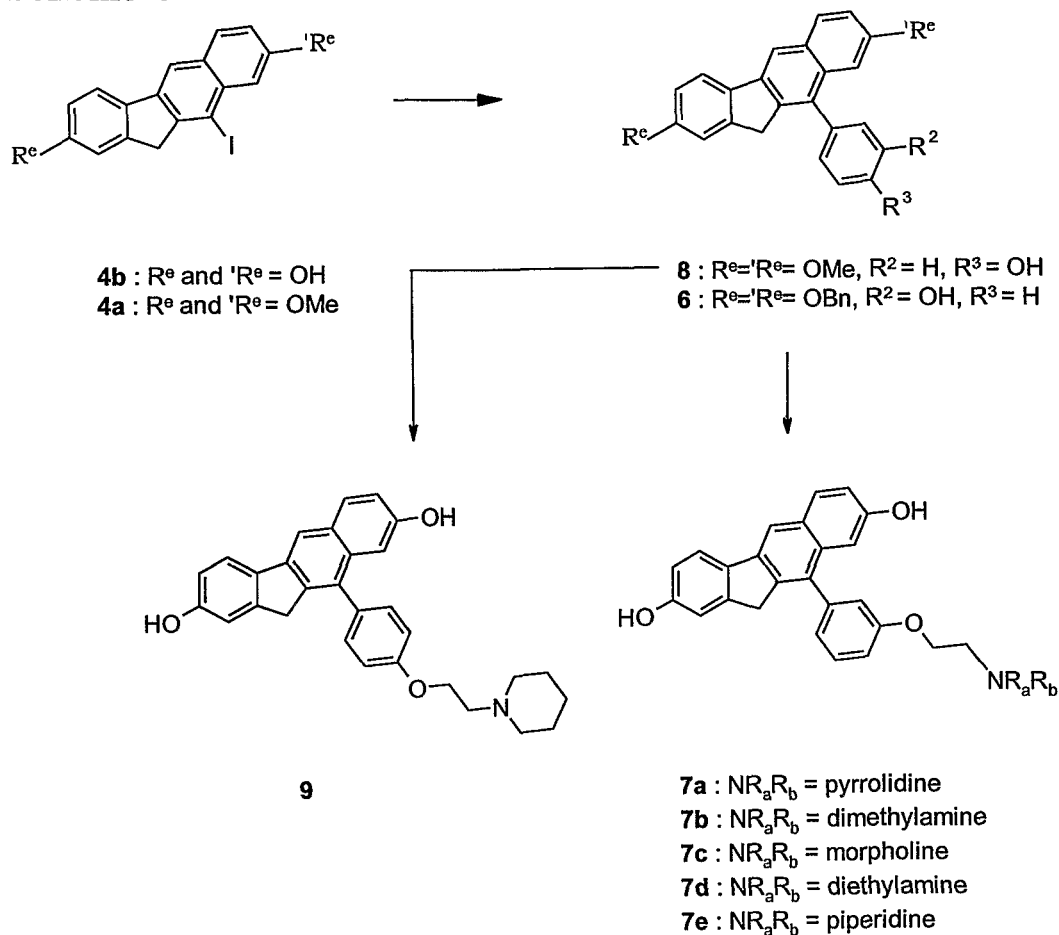
10 *General procedure to prepare compounds 5a-v (10-aryl-2,8-dihydroxy-11H-benzo[b]fluorenes)*

(reference to scheme 3)

A mixture of 10-iodo-benzofluorene derivative **4** (27 μmol), 3 mg Pd₂(dba)₃, 0.2 M Na₂CO₃(aq), 30 μmol arylboronic acid and 1 ml 2-
 15 methoxy-ethanol was heated for 5 hours at 55° C. Ethyl acetate and water were added to the reaction mixture and the organic layer was separated, dried over MgSO₄ and concentrated. The residue was purified on silica gel (toluene/ethylacetate) to give pure **5a-v** (yields 14-52 %).

Compound	ARYL	Yield (%)	[M-H]
5a	4-chlorophenyl	37	[M-H] = 357.2
5b	2-naphthyl	44	[M-H] = 373.2
5c	3-methoxyphenyl	32	[M-H] = 353.4
5d	3-trifluoromethylphenyl	54	[M-H] = 391.3
5e	4-methylphenyl	42	[M-H] = 337.4
5f	3-chloro-4-fluorophenyl	40	[M-H] = 375.2
5g	3,4-methylenedioxophenyl	49	[M-H] = 367.4
5h	4-phenylphenyl	55	[M-H] = 399.4
5i	2-benzothiazole	30	[M-H] = 379.4
5j	3-fluorophenyl	27	[M-H] = 341.4
5k	4-methoxyphenyl	27	[M-H] = 353.4
5l	4-fluorophenyl	52	[M-H] = 341.4
5m	3,4-dichlorophenyl	14	[M-H] = 390.8
5n	3-chlorophenyl	37	[M-H] = 357.0
5o	4-trifluoromethylphenyl	22	[M-H] = 391.4
5p	3-methylphenyl	21	[M-H] = 337.2

5q	3-isopropylphenyl	40	[M-H] = 365.0
5r	4-trifluoromethoxyphenyl	41	[M-H] = 407.2
5s	3-fluoro-4-phenylphenyl	22	[M-H] = 417.0
5t	4-methylthiophenyl	32	[M-H] = 371.2
5u	2-trifluoromethylphenyl	20	[M-H] = 391.0
5v	Phenyl	25	[M-H] = 323.2

Example 2**Scheme 4****5 Compound 7a-d**

A mixture of **4b** (0.94 mmol), potassium carbonate (3.0 mmol) and benzyl bromide (2.1 mmol) in acetone (10 ml) was refluxed overnight after which the mixture was poured into water and extracted with ethyl acetate. The organic layer was dried over MgSO₄, concentrated and purified by chromatography on silica gel (heptane/ethyl acetate).

The purified product (0.43 mmol) was taken up in 2-methoxyethanol (16 ml) and Pd₂(dba)₃ (36 μmol), 3-hydroxyphenylboronic acid pinacolester (0.45 mmol) and Na₂CO₃ (2M in water, 2 ml) were added. The mixture was stirred for 30 minutes at 60°C, poured into water and extracted with ethyl acetate. The organic layer was dried over MgSO₄, concentrated and purified by chromatography on silica gel (CH₂Cl₂/methanol) to give pure **6** in 56% yield. (R_f = 0.34 (heptane/ethyl acetate (7:3))).

A mixture of **6** (48 μ mol), 1-(2-chloroethyl)pyrrolidine hydrochloride (76 μ mol) and cesium carbonate (0.15 mmol) in acetonitrile (2 ml) was stirred for 3 hours at 50°C. The mixture was poured into water and extracted with ethyl acetate, the organic extract was dried over MgSO_4 , the solvent evaporated and the residue was purified by chromatography on silica gel (CH_2Cl_2 /methanol). The pure fractions were concentrated and the material obtained was dissolved in ethyl acetate (3 ml). Pd/C (10% w/w, 25 mg) and 3 drops of acetic acid were added and the mixture was stirred under an atmosphere of hydrogen for 5 hours. The catalyst was removed by filtration and the filtrate was concentrated. The residue was purified by chromatography on silica gel (CH_2Cl_2 /methanol) to yield pure **7a** in 22% yield. $R_f = 0.14$ (CH_2Cl_2 /methanol (9:1)), ESI-MS: $M+H = 438.4$, $M-H = 436.2$.

15 *Compound 7b*

Compound **7b** was prepared from **6** in 5% yield, in the same fashion as described for the preparation of **7a**, using 2-dimethylaminoethyl chloride hydrochloride ($R_f = 0.18$ CH_2Cl_2 /methanol (9:1)); ESI-MS: $M+H = 412.4$, $M-H = 410.4$.

20

Compound 7c

Compound **7c** was prepared from **6** in 32% yield, in the same fashion as described for the preparation of **7a**, using 1-(2-chloroethyl)morpholine hydrochloride instead of 1-(2-chloroethyl)pyrrolidine hydrochloride ($R_f = 0.21$ CH_2Cl_2 /methanol (9:1)); ESI-MS: $M+H = 454.4$, $M-H = 452.2$.

Compound 7d

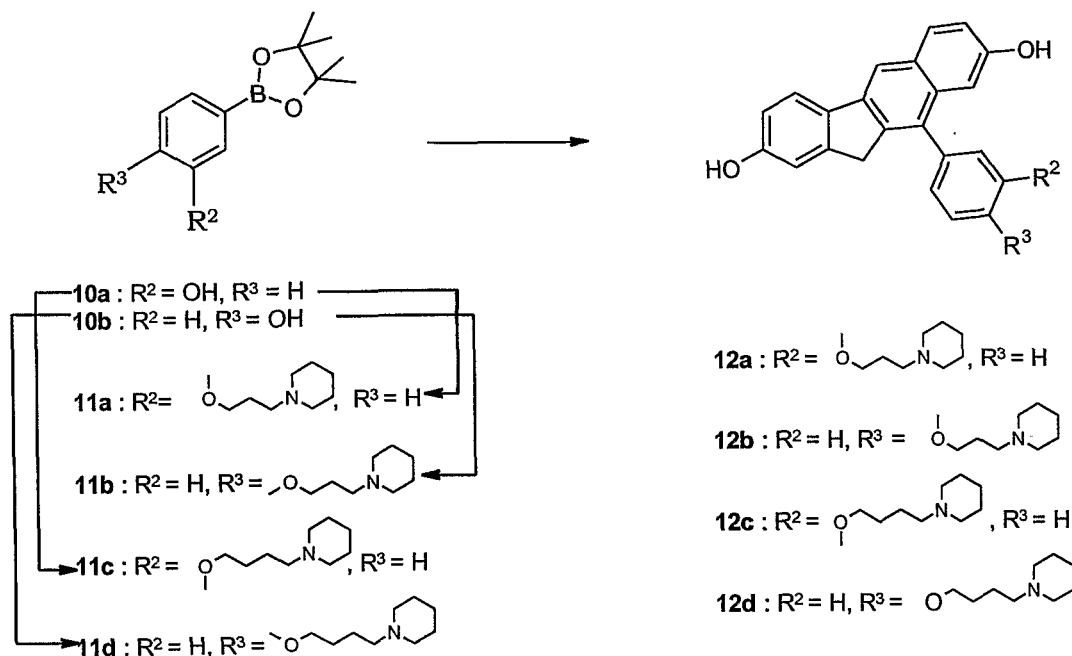
Compound **7d** was prepared from **6** in 65% yield, in the same fashion as described for the preparation of **7a**, using 2-diethylaminoethyl chloride hydrochloride instead of 1-(2-chloroethyl)pyrrolidine hydrochloride ($R_f = 0.17$ CH_2Cl_2 /methanol (9:1)); ESI-MS: $M+H = 440.4$, $M-H = 438.2$.

Compound 7e

Compound **7e** was prepared from **6** in 18% yield, as described for the preparation of **7a**, using 1-(2-chloroethyl)piperidine hydrochloride instead of 1-(2-chloroethyl)pyrrolidine hydrochloride ($R_f = 0.15$ CH_2Cl_2 /methanol (9:1)); ESI-MS: $M+H = 452.4$, $M-H = 450.2$.

Compound 9

- A mixture of **4a** (0.30 mmol), Pd₂(dba)₃ (0.40 μmol), 4-hydroxyphenylboronic acid (0.30 mmol) and sodium carbonate (2 M in water, 4 ml) in 12 ml 2-methoxyethanol was stirred at 60°C. After 30 minutes the mixture was poured into water and extracted with ethyl acetate. The organic extract was dried over MgSO₄, concentrated and purified by chromatography on silica gel (toluene/ethyl acetate) to give **8** in 65% yield. R_f = 0.24 (toluene/ethyl acetate (8:2)).
- 10 Compound **8** (0.16 mmol) was dissolved in toluene (3 ml). Sodium hydride (0.4 mmol) and 1-(2-chloroethyl)piperidine hydrochloride (0.2 mmol) were added and the mixture was refluxed for 3.5 hours. The reaction mixture was poured into water and extracted with ethyl acetate. The organic extract was dried over MgSO₄, concentrated and purified by
- 15 chromatography on silica gel (toluene/methanol). The pure fractions were collected and concentrated, the material obtained (46 μmol) was dissolved in CH₂Cl₂ and treated with ethanethiol (0.62 mmol) and aluminum chloride (95 μmol) at RT. After 16 hours the dark red mixture was poured into water and extracted with ethyl acetate. The
- 20 organic extract was dried over MgSO₄, concentrated and purified by chromatography on silica gel (CH₂Cl₂/methanol) to give **9** in 22% yield. R_f = 0.23 (toluene/methanol (85:15)), ESI-MS : M+H = 452.4, M-H = 450.2.

Example 3**Scheme 5**

5

Compound 12a

A mixture of 3-hydroxyphenylboronic acid pinacolester **10a** (0.68 mmol), cesium carbonate (0.68 mmol) and 1-bromo-3-chloropropane (0.80 mmol) in acetonitrile (3 ml) was stirred overnight at RT. Additional cesium carbonate (0.31 mmol) and 1-bromo-3-chloropropane (0.4 mmol) were added and the mixture was stirred overnight at 60°C. The mixture was poured into water and extracted with CH_2Cl_2 . The CH_2Cl_2 -layer was dried over MgSO_4 , concentrated and purified by chromatography on silica gel (toluene/ethyl acetate). The purified product was dissolved in piperidine and stirred for 48 hours at 45°C. The solid material (piperidine.HCl) was filtered off and the filtrate was concentrated to give **11a** in 88% yield. $R_f = 0.05$ (toluene/ethyl acetate (4:1)).

A mixture of **4b** (67 μmol), **11a** (86 μmol), $\text{PdCl}_2(\text{dppf})_2$ (5 μmol) and sodium carbonate (2 M in water, 0.25 ml) in 2.5 ml 2-methoxyethanol was stirred at 90°C. After 2 hours the mixture was poured into water and extracted with ethyl acetate. The organic extract was dried over MgSO_4 , concentrated and purified by chromatography on silica gel (CH_2Cl_2 /methanol). The appropriate fractions were collected and

concentrated, the material obtained was recrystallised from CHCl_3 to give **12a** in 38% yield. $R_f = 0.42$ (CH_2Cl_2 /methanol (85:15)).

Compound **12b**

5 A mixture of 4-hydroxyphenylboronic acid pinacolester **10b** (0.68 mmol), potassium hydroxide (2.1 mmol) and 1-bromo-3-chloropropane (2.8 mmol) in methanol (2 ml) was refluxed for 24 hours. The mixture was poured into water and extracted with ethyl acetate. The organic extract was dried over MgSO_4 , concentrated and purified by chromatography on
10 silica gel (toluene/ethyl acetate). The purified product was dissolved in piperidine and stirred overnight at 50°C . The solid material (piperidine.HCl) was filtered off and the filtrate was concentrated to give **11b** in 80% yield. $R_f = 0.10$ (toluene/methanol (9:1)).

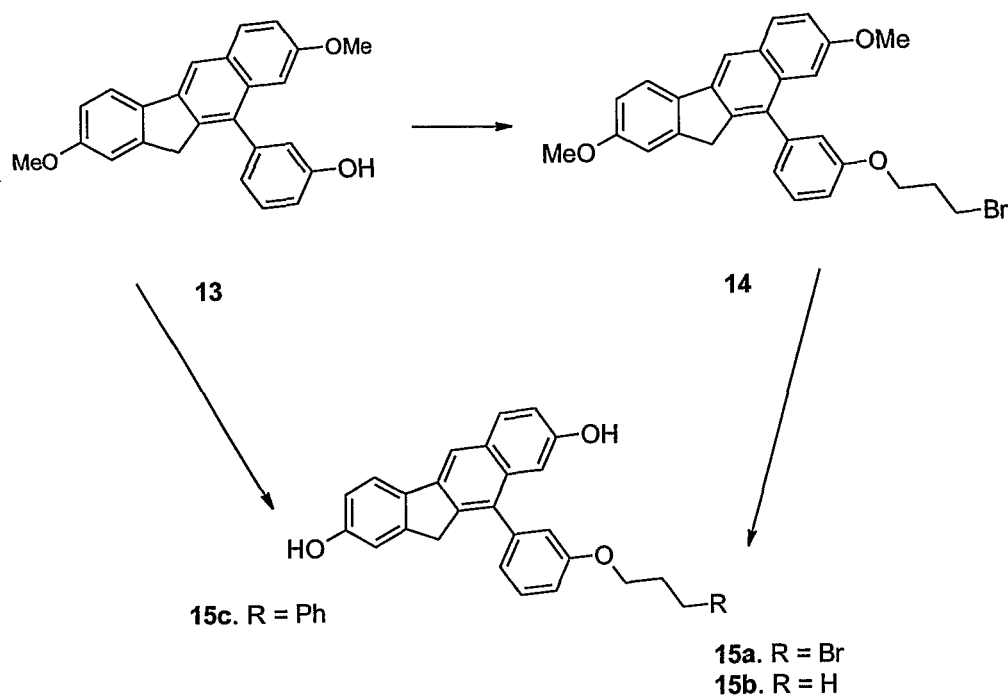
Compound **12b** was prepared from **4a** and **11b** in 20% yield, in a similar
15 fashion as described for the preparation of **12a**. $R_f = 0.42$ (CH_2Cl_2 /methanol (85:15)), ESI-MS : $M+H = 466.4$, $M-H = 464.6$

Compound **12c**

Compound **12c** was prepared from **10a** in 25% yield, as described for the
20 preparation of **12a**, using 1-bromo-4-chloro-butane instead of 1-bromo-3-chloro-propane. $R_f = 0.21$ (CH_2Cl_2 /methanol (8:2)), ESI-MS : $M+H = 480.6$, $M-H = 478.2$

Compound **12d**

25 To mixture of 1,4-diiodobutane (5 mmol) and cesium carbonate (0.68 mmol) in acetonitrile (2 ml) was portionwise added 4-hydroxyphenylboronic acid pinacolester **10b** (0.68 mmol) at 40°C . After 2.5 hours water was added and the mixture was extracted with ethyl acetate. The organic layer was dried over MgSO_4 , concentrated and
30 purified by chromatography on silica gel (heptane/toluene). The purified product was dissolved in piperidine and stirred at RT for 2 hours. The solid material (piperidine.HI) was filtered off and the filtrate was concentrated to give **11d** in 32% yield. $R_f = 0.55$ (toluene/methanol (8:2)). Compound **12d** was prepared from **4b** and **11d** in 13% yield, in a similar
35 fashion as described for the preparation of **12a**. $R_f = 0.22$ (CH_2Cl_2 /methanol (8:2)), ESI-MS : $M+H = 480.4$, $M-H = 478.2$

Example 4**Scheme 6**

5

Compound 14

A mixture of 2.03 mmole of 1,3-dibromopropane and 1.02 mmole of potassium carbonate in 10 ml of acetone was warmed to 40 °C. To this solution 0.51 mmole of **13** in 10 ml of acetone was added dropwise and the reaction mixture was stirred at 40 °C for 23 hours. An additional mixture of 2.03 mmole of 1,3-dibromopropane and 1.02 mmole of potassium carbonate in 5 ml of acetone was added and the reaction mixture stirred for 4 hours at reflux temperature. The reaction mixture was taken up in ethyl acetate and water, washed with water and saturated NaCl solution, dried over MgSO₄ and concentrated. The crude product was purified by chromatography on silica gel (heptane/ethyl acetate) to give pure **14** in 65% yield.

R_f = 0.64 (heptane/diethylether (7:3))

20

Compound 15a

82 µmole of **14** was dissolved in 6 ml of dry CH₂Cl₂. 327 µmole of BF₃·S(CH₃)₂ was added and the solution was stirred at room temperature

for 16 hours. The reaction mixture was taken up in ethyl acetate, washed with water and saturated NaHCO_3 solution, dried over MgSO_4 and concentrated. The crude product was purified by chromatography on silica gel (CH_2Cl_2 /methanol) to give pure **15a** in 93% yield.

5 Rf = 0.47 (CH_2Cl_2 /methanol (9:1))

Compound 15b

22 μM of bromide **14** was refluxed for 1.5 hours with 100 μM LiAlH_4 in THF. Water and ethyl acetate were added to the reaction mixture and the
10 organic layer was separated, dried over MgSO_4 and concentrated. The residue was purified on silicagel (methylene/ methanol) to give pure 3'-O-propyl compound **15b** in yield 37%. Rf = 0.40 (heptane-ethyl acetate 7:3).

Compound 15c

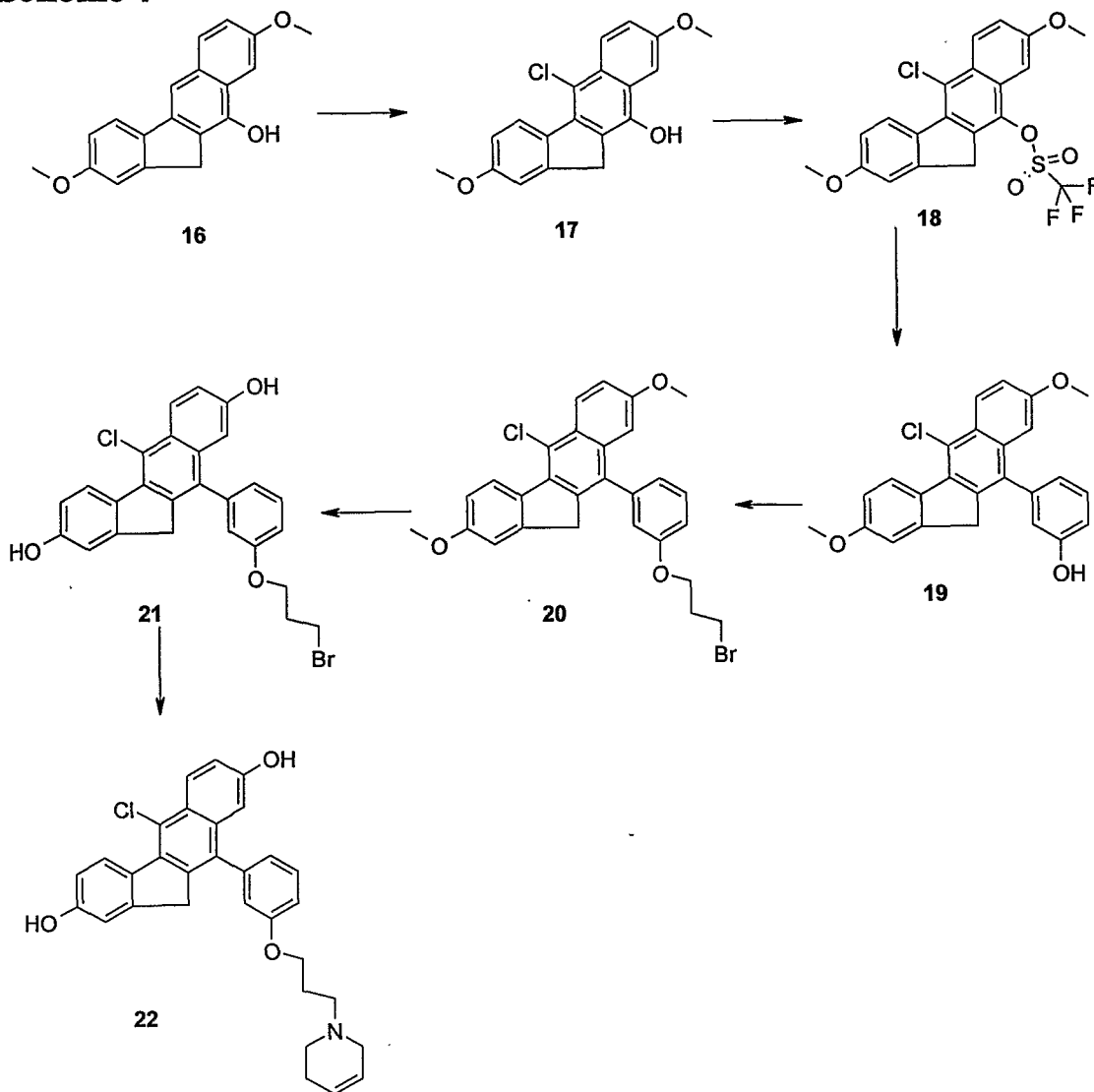
15 54 μM of compound **13** was reacted with 1.7 mM 1-bromo-3-phenylpropane in the presence of 1.7 mM K_2CO_3 in 3 ml acetone at room temperature. After 24 hours the salts were removed by filtration. The filtrate was concentrated and redissolved in methylene chloride. The mixture was extracted with water, dried over MgSO_4 and concentrated.

20 The residue was purified by chromatography on silica gel (heptane/ethylacetate). (yield= 88%).

47 μM of the resulting product was demethylated with 1.9 mM $(\text{CH}_3)_3\text{S}.\text{BF}_3$ in CH_2Cl_2 for one night. Ethyl acetate and water were added to the reaction mixture and the organic layer was separated, dried over
25 MgSO_4 and concentrated. The residue was purified on silica gel (heptane / ethylacetate) to give pure compound **15c** in yield=57%. Rf 0.7 (heptane ethyl acetate 8:2)

Example 5

23

Scheme 7*2,8-dimethoxy-10-hydroxy-11H-benzo[b]fluorene (Compound 16)*

- 5 The compound 2,8-dimethoxy-10-hydroxy-11H-benzo[b]fluorene (Compound **16**) 1 was prepared from its corresponding ester as explained above for step 4 in scheme 1. An amount of 3 g of the corresponding unsaturated ester was added in small portions over a few minutes to 30 ml of methanesulphonic acid at 60°C. After stirring for ½ hr the
- 10 cyclization was complete. The mixture was then poured onto ice water and stirred for an additional ½ hr. The product was filtered, washed with water and thoroughly dried over P₂O₅, to give 2.2 gr of compound **16**.

R_f 0.38 (heptane / eth. ac. 7/3). NMR (DMSO) 3.82, 3.88 (2x3, s, OCH₃), 3.95 (s, 2, CH₂). 9.57 (s, 1, OH), 6.97, 7.11, 7.20, 7.55, 7.51, 7.75, 7.80 (7H's, aromatic protons)

5 **5-chloro-2,8-dimethoxy-10-hydroxy-11H-benzo[b]fluorene (Compound 17)**

To a solution of 800 mg of compound **16** in 10 ml of DMF was added 850 mg of 2,2,3,4,5,6-hexachlorocyclohexa3,5-diene in small portions over 5 minutes. The mixture was stirred for 1 hr and then poured into 50 ml of water. The dark reaction product was extracted with ethyl acetate and
10 purified by chromatography over silica gel (heptane / ethyl acetate as eluent), to provide 380 mg of **17** as a brown solid; R_f 0.38 (hept. / ethyl ac. 6/4) , R_f (starting material) 0.44. NMR (DMSO) 3.85, 3.92 (2xs, 6, OCH₃) 4.03 (s, 2, CH₂), 7.03, 7.30, 8.13, 8.38 (2x AB, 4, Ar-H) , 7.25 , 7.61 (2x br.s, 2, Ar-H).

15

Compound 18

To a solution of 900 mg of **17** in 8 ml of pyridine was added at 0°C 700µl of trifluoromethanesulphonic anhydride. Stirring was performed for 1 hr at RT followed by pouring into water and additional stirring for 15 min.
20 followed by filtration of the crude product. Purification was achieved by chromatography over silicagel, to provide 800 mg of triflate **18**; Mp 165-168°C. NMR (CDCl₃) 3.90 , 3.96 (2x s , 6 , OCH₃), 4.18 (s, 2, CH₂), 7.0, 7.09, 7.29, 7.35, 8.11, 8.47 (6H, Ar-H).

25 **Compound 19**

A mixture of 210 mg of triflate **18**, 220 mg of 3-hydroxyphenyl-pinacolborane, 200 mg of K₃PO₄, 15 mg of As(PPh)₃, 15 mg of PdCl₂.PPh₃, 0.5 ml of water and 5 ml of dioxane was heated at 100°C for 1,5 hr under a nitrogen atmosphere. The reaction was poured into water and extracted
30 with ethyl acetate. Chromatography of the resulting material provided 215 mg of **19** as an amorphous product; R_f 0.35 (hept./ethyl ac. 7/3), Mp 184-185°C. NMR (CDCl₃) 3.74, 3.87 (s, 6, OCH₃), 3.80 (s, 2, CH₂) , 6.82-7.0 (m, 6, Ar-H), 7.25, 7.40, 8.38, 8.53 (4H, Ar-H).

35 **Compound 20**

A mixture of 200 mg of **19**, 500 mg of powdered K₂CO₃, 1.25 ml of 1,3-dibromopropane and 10 ml of acetonitrile was heated at 55°C for 3 hr.

The reaction was diluted with water and extracted with ethyl acetate. The crude product was purified by chromatography on silica gel (hept. / ethyl acetate) , to provide 220 mg of **20**; R_f 0.63 (hept./eth.ac. 7/3) ; NMR ($CDCl_3$) 3.65 (t,3, CH_2Br), 2.33 (m, 2, CH_2), 4.13 (t, 2, CH_2O), 3.78 (s, 2, CH_2).

Compound 21

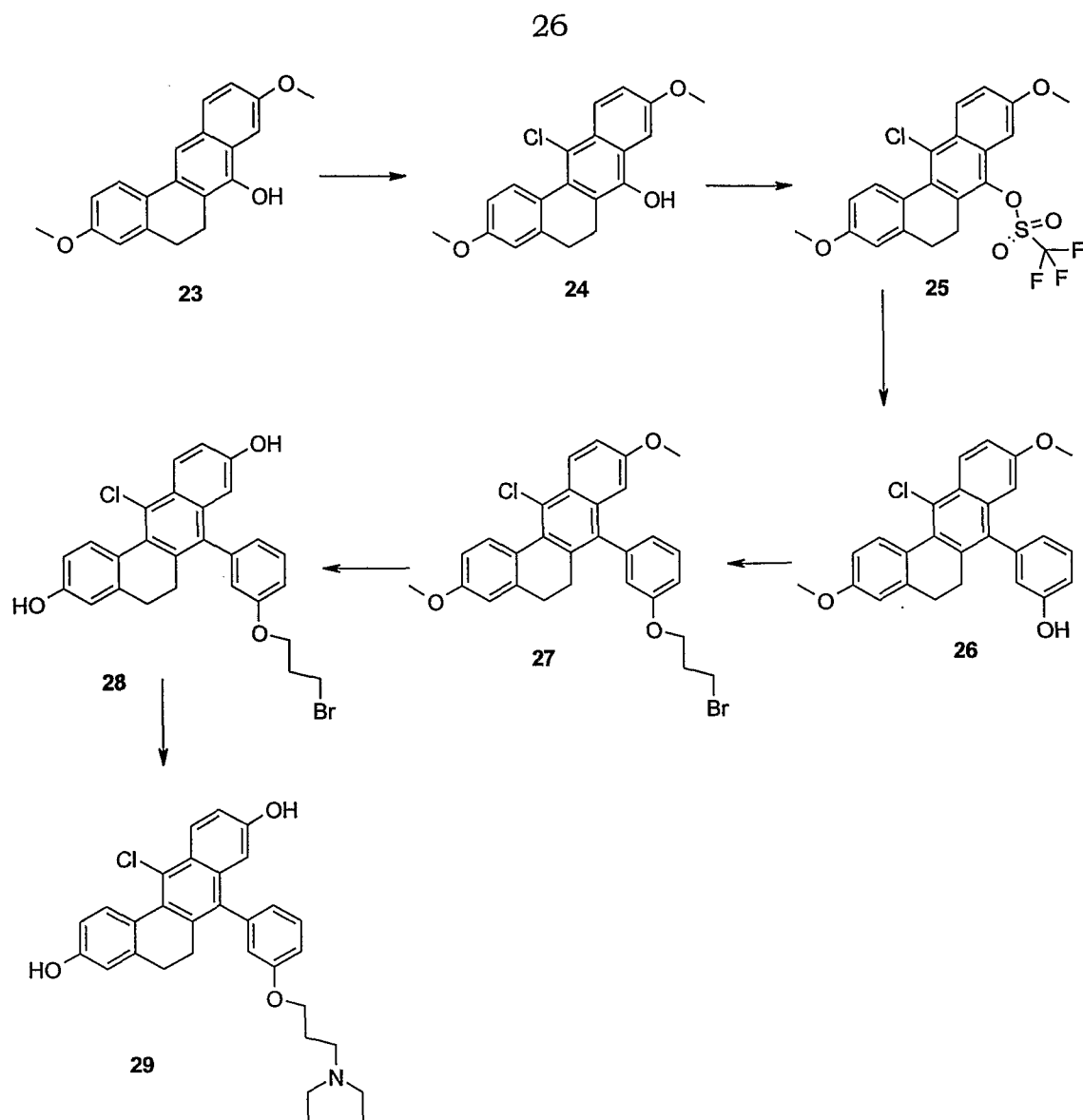
To a solution of 220 mg of **20** in 7 ml of methylenechloride was added 1.5 ml of BF_3 .dimethylsulfide complex. The mixture was stirred until completion of the reaction (5 hr). The reaction was poured into water and the product extracted with ethyl acetate. Chromatography provided 210 mg of **21** as a colorless amorphous material; R_f 0.25 (hept./ eth.ac. 7/3) . NMR ($CDCl_3$) 3.67 (t,3, CH_2Br), 2.33 (m, 2, CH_2), 4.15 (t, 2, CH_2O), 3.77 (s, 2, CH_2).

Compound 22

A mixture of 70 mg of **21**, 0.3 ml of 1,2,5,6-tetrahydropyridine and 3 ml of acetonitrile was heated at 55°C for ½ hr. The mixture was then poured onto 5% $NaHCO_3$ and extracted with ethyl acetate. The product was purified by passing through a short silica column (CH_2Cl_2/CH_3OH). The product thus obtained was converted into a HCl salt by treatment of a solution the free base in methanol/ether with 1M HCl/ether. The hydrochloride salt thus obtained was freeze-dried from water to obtain 45 mg of amorphous **22**. NMR (DMSO) 9.77 , 9.82 (2x s, 2, OH's), 5.70 and 5.88 (2x m, 2, tetrahydropyridine), 8.32, 8.20, 7.52, 7.21, 7.08, 6.98, 6.87 (10, aromatic H's).

Example 6

Scheme 8



3,9-dimethoxy-7-hydroxy-5,6-dihydro-benz[a]anthracene (compounds **23**)
 and 12-chloro-3,9-dimethoxy-7-hydroxy-5,6-dihydro-benz[a]anthracene
 5 (compound **24**)

The compound 3,9-dimethoxy-7-hydroxy-5,6-dihydro-benz[a]anthracene (compounds **23**) was prepared analogously to compound **16** in example 5. To a solution of 600 mg of **23** in 10 ml of DMF was added in portions 600 mg of 2,3,4,4,5,6-hexachlorocyclohexa-2,5-dien-1-one. The mixture
 10 was then stirred at 40°C for 4 hr. Then the reaction was poured into water and the product extracted with ethyl acetate. The crude material was passed through a silicagel column (hept./ eth.ac.) and finally triturated with heptane-diisopropyl ether to provide 280 mg of **24** as

orange crystals; Mp 140-141°C, R_f 0.28 (hept./eth.ac. 7/3) starting material R_f 0.30.

Compound 25

- 5 To a solution of 300 mg of **24** in 3 ml of pyridine was added 200 μ l of triflic anhydride. The mixture was stirred for 1 hr at rt, and then poured into water and extracted with ethyl acetate.. The product was purified over silica gel and afforded 220 mg of **25** as a white solid; Mp 122-124; R_f 0.70 (hept./ethyl ac. 7/3).

10

Compound 26

- A mixture of 210 mg of **25**, 220 mg of 3-hydroxyphenylpinacolborane, 200 mg of K_3PO_4 15 mg of $(PPh_3)As$, 15 mg of $PdCl_2(PPh_3)_2$, 0.5 ml of water and 5 ml of dioxane was heated at 100°C for 1.5 hr. The mixture
15 was then poured into water and extracted with ethyl acetate. Chromatography over silica gel provided 215 mg of **26** as an oil; R_f 0.28 (hept. / ethyl acetate 7/3) . NMR (DMSO) 2.56 (4, CH_2CH_2), 3.67, 3.80 (2x s, 6, OCH_3), 8.32, 8.18, 7.33, 6.93, 6.70 (10, Ar-H's), 9.64 (s, 1, OH).

20 **Compound 27**

- A mixture of 215 mg of **26**, 500 mg of K_2CO_3 , 1.2 ml of 1,3-dibromopropane and 10 ml of acetonitrile was heated at 55°C for 2.5 hr. The reaction was then poured in water and extracted with ethyl acetate. Chromatography provided 220 mg of **27** as a colorless oil ; R_f 0.60
25 (hept./ethyl acetate 7/3) . NMR ($CDCl_3$) 2.60 (m, 4, CH_2CH_2), 2.30 (m, 2, CH_2), 3.60 (t, 2, CH_2Br) , 4.13 (t, 2, CH_2O) , 3.72, 3.87 (2x s, 6, OCH_3).

Compound 28

- To a solution of 190 mg of **27** in 7 ml of methylenechloride was added 1.5
30 ml of BF_3 .dimethylsulfide complex. After stirring at rt for 4 hr the mixture was poured onto water and extracted with ethyl acetate. Chromatography of the crude product gave 150 mg of essentially pure **28**; R_f 0.20 (hept./ethyl ac. 7/3); NMR (DMSO) 2.27 (m, 2, CH_2), 2.50 (m, 4, CH_2CH_2), 3.68 (t, 2, CH_2Br), 4.12 (t, 2, CH_2O), 9.68, 9.82 (2xs, 2, OH).

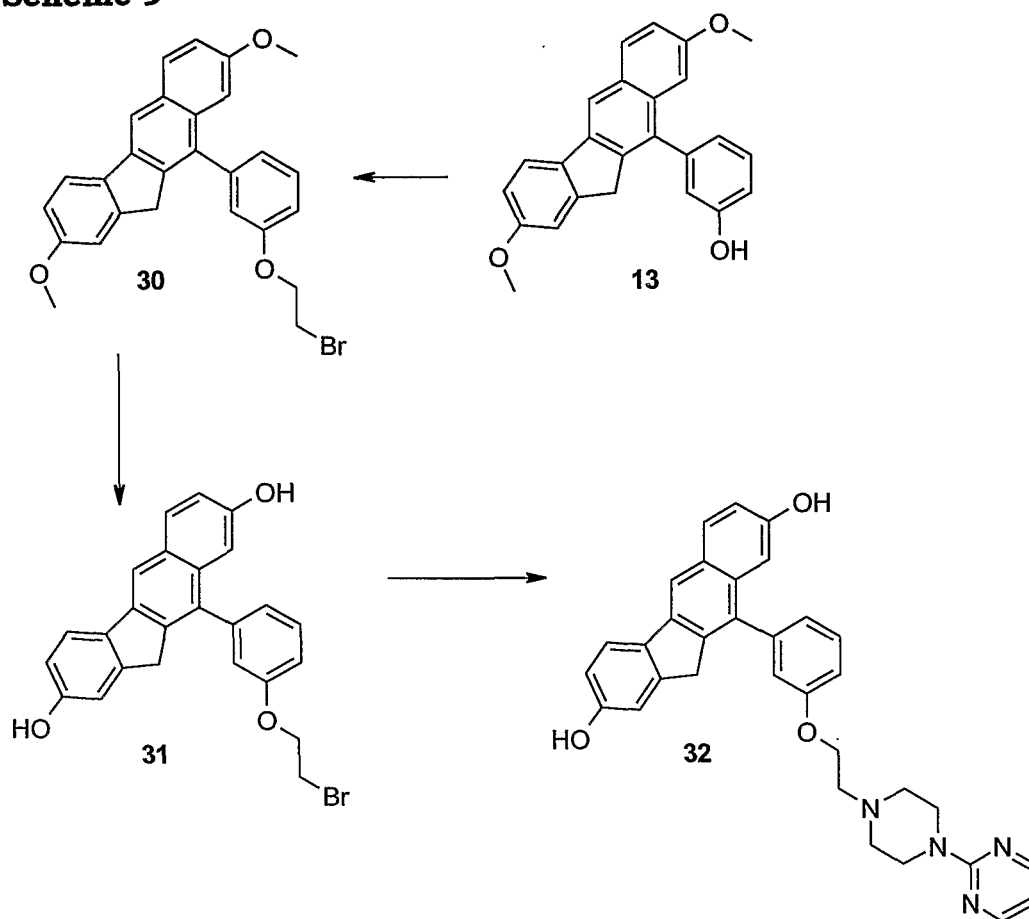
35

Compound 29

28

A mixture of 60 mg of **28**, 0.4 ml of pyrrolidine and 3 ml of acetonitrile was stirred at 50°C for ½ hr. The mixture was then poured into 5% NaHCO₃ and extracted with ethyl acetate. The product was purified by passing through a short silica column (CH₂Cl₂/CH₃OH as eluent) and then converted into a HCl salt by treatment with 1M HCl / ether. The resulting hydrochloride was freeze dried from water to give 35 mg of **29**; R_f 0.20 (CH₂Cl₂/CH₃OH/HOAc 90/10/1); NMR (DMSO) 9.70 and 9.82 (2x s, 2H, OH's), 8.22, 8.05, 7.48 7.17, 7.06, 6.88, 6.84, 6.76, 6.70, 6.62 (m, 10H, Ar-H's), 4.10 (t, 2, CH₂O).

10

Example 7**Scheme 9**

15

Compound 30

A mixture of 300 mg of compound **13**, 900 mg of powdered K₂CO₃, 2 ml of 1,2-dibromopropane and 8 ml of acetonitrile was heated at 55°C for 16

hr. The reaction was diluted with water and extracted with ethyl acetate. The crude product was purified by chromatography on silica gel (hept. / ethyl acetate), to provide 310 mg of **30**; R_f 0.50 (hept./eth.ac. 7/3) ; NMR ($CDCl_3$) 3.67 (t,3, CH_2Br), 4.35 (t, 2, CH_2O), 3.79 (s, 2, CH_2), 3.75, 3.87 (2x s, 6, OCH_3).

Compound **31**

To a solution of 310 mg of **30** in 6 ml of methylenechloride was added 2 ml of BF_3 .dimethylsulfide complex. The mixture was stirred until completion of the reaction (5 hr). The reaction was poured into water and the product extracted with ethyl acetate. Chromatography provided 290 mg of **31** as a colorless amorphous material; R_f 0.19 (hept./ eth.ac. 7/3) . NMR ($CDCl_3$) 3.67 (t,3, CH_2Br), 4.35 (t, 2, CH_2O), 3.76 (s, 2, CH_2).

15 Compound **32**

A mixture of 60 mg of **31** 0.3 g of 2-pyrimidinylpiperazine and 2 ml of acetoneitrile was heated at 50°C for 16 hr. The mixture was then diluted with water and the product extracted with ethyl acetate. The organic material was passed through a short silica column (a gradient of CH_2Cl_2 / CH_3OH as eluent), to provide essentially pure **32** as the free base. This was dissolved in a small amount of ethyl acetate and treated with 1M HCl in ether to give the HCl salt. This was freeze dried from water to provide 48 mg of amorphous HCl salt of **32**. R_f 0.82 (CH_2Cl_2 - CH_3OH - acetic acid 9/1/0,1) ; NMR (DMSO) 4.50 (m , 2, CH_2O), 6.76 , 6.84, 6.88, 6.96, 7.05, 7.09, 7.16, 7.21 ,7.55, 8.21, 8.32, 8.44 (resp. 1H, 1H, 1H, 1H, 1H, 1H, 1H, 1H, 1H, 1H, 1H, 2H's ; Ar-H's).

Example 8

30 Biological activity

Determination of competitive binding to cytoplasmic human estrogen receptor α or β from recombinant CHO cells is used to estimate the relative affinity (potency ratio) of a test compound for estrogen receptors present in the cytosol of recombinant Chinese hamster ovary (CHO) cells, stably transfected with the human estrogen receptor α (hER α) or β receptor (hER β), as compared with 17 β -estradiol (E_2).

The estrogenic and antiestrogenic activity of compounds is determined in an in vitro bioassay with recombinant Chinese hamster ovary (CHO) cells stably co-transfected with the human estrogen receptor α (hER α) or β receptor (hER β), the rat oxytocin promoter (RO) and the luciferase
5 reporter gene (LUC). The estrogenic activity (potency ratio) of a test compound to stimulate the transactivation of the enzyme luciferase mediated via the estrogen receptors hER α or hER β is compared with the standard estrogen estradiol. The antiestrogenic activity (potency ratio) of a test compound to inhibit the transactivation of the enzyme luciferase
10 mediated via the estrogen receptors hER α or hER β by the estrogen estradiol is compared with the standard ICI 164.384 (= (7 α ,17 β)-N-butyl-3,17-dihydroxy-N-methylestra-1,3,5(10)-triene-7-undecanamide).

Results

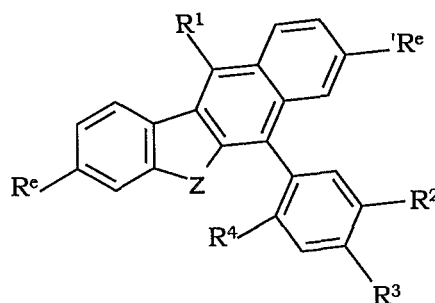
Compound	ER β antagonism
5a	+
5b	+
5c	+
5d	+
5e	++
5f	+
5g	+
5h	+
5i	+
5j	+
5k	+
5l	++
5m	++
5n	+
5o	+
5p	+
5q	+
5r	++

Compound	ER β antagonism
5s	+
5t	+
5u	++
5v	+
7a	+++
7b	+++
7c	+++
7d	+++
7e	+++
9	++
12a	+++
12b	++
12c	+++
12d	+
14	++
17a	+++
17b	++
17c	++

5 > 5% (relative to ICI): +
 > 40% : ++
 > 100%: +++

Claims

1. A compound having the formula 1



5

Formula 1

wherein:

Rᵉ and 'Rᵉ are OH, optionally independently etherified or esterified;

10 Z is -CH₂- or -CH₂CH₂-;

R¹ is H, halogen, CF₃, or (1C-4C)alkyl;

R², R³ and R⁴ are independently H, halogen, -CF₃, -OCF₃, (1C-8C)Alkyl, hydroxy, (1C-8C)alkyloxy, aryloxy, aryl(1C-8C)alkyl, halo(1C-8C)alkyl, -O(CH₂)ₘX, wherein X is halogen or phenyl and m = 2-4; -

15 O(CH₂)ₘNRₐRᵇ, -S(CH₂)ₘNRₐRᵇ or -(CH₂)ₘNRₐRᵇ, wherein m = 2-4 and Rₐ, Rᵇ are independently (1C-8C)alkyl, (2C-8C)alkenyl, (2C-8C)alkynyl, or aryl, optionally substituted with halogen, -CF₃, -OCF₃, -CN, -NO₂, -OH, (1C-8C)alkoxy, aryloxy, carboxyl, (1C-8C)alkylthio, carboxylate, (1C-8C)alkyl, aryl, aryl(1C-8C)alkyl, halo(1C-8C)alkyl or

20 Rₐ and Rᵇ form a 3-8 membered ring structure, optionally substituted with halogen, -CF₃, -OCF₃, -CN, -NO₂, hydroxy, hydroxy(1C-4C)alkyl, (1C-8C)alkoxy, aryloxy, (1C-8C)alkylthio, carboxyl, carboxylate, (1C-8C)alkyl, aryl, aryl(1C-8C)alkyl, halo(1C-8C)alkyl.

25

2. A compound according to claim 1, characterised in that Z is -CH₂- and R⁴ is H.

3. A compound according to claim 1 or 2, characterised in that R¹ is H, halogen or CF₃.

30

4. A compound according to anyone of claims 1-3, characterised in that R^1 is halogen.
5. A compound according to claim 2, characterised in that
- 5 R^1 is H;
 R^3 is H;
 R^2 is (3C-6C)alkyloxy, $-O(CH_2)_mX$, wherein X is halogen or phenyl and $m = 2-3$, or $-O(CH_2)_mNR_aR_b$, wherein $m = 2-3$ and R_a, R_b are independently (1C-5C)alkyl or (3C-5C)alkenyl, optionally substituted
- 10 with OH or methoxy, or R_a and R_b form a 4-7 membered ring structure selected from the list: azetidine, pyrrolidine, 3-pyrroline, piperidine, piperazine, tetrahydropyridine, morpholine, thiomorpholine, thiazolidine, homopiperidine, tetrahydroquinoline and 6-azabicyclo[3.2.1]octane, which 4-7 membered ring structure
- 15 can optionally be substituted with OH, hydroxy(1C-2C)alkyl, methoxy, acetyl, carboxylate, (1C-3C)alkyl, phenyl, benzyl, and phenylethyl.
6. A compound according to any one of claim 1-5 for use as a medicine
- 20 7. The use of a compound according to any one of claims 1-5 for the manufacture of a medicine for use in estrogen-receptor related treatments.
- 25 8. A pharmaceutical composition comprising a compound according to anyone of claim 1-6