2-PHENYL-1-[4-(2-AMINOETHOXY)-BENZYL]-INDOLE IN COMBINATION WITH ESTROGENS

The present invention relates to the use of new 2-Phenyl-1-[4-(2-Aminoethoxy)-Benzyl]-Indole compounds which are useful as estrogenic agents, in conjunction with estrogens, as well as pharmaceutical compositions and methods of treatment utilizing these compounds.

Background of the Invention

The use of hormone replacement therapy for bone loss prevention in post-menopausal women is well precedented. The normal protocol calls for estrogen supplementation using such formulations containing estrone, estriol, ethynyl estradiol, 17ß-estradiol, esterified estrogens, or conjugated estrogens isolated from natural sources (i.e. Premarin® conjugated estrogens from Wyeth-Ayerst) or synthetic estrogens. In some patients, therapy may be contraindicated due to the proliferative effects of unopposed estrogens (estrogens not given in combination with progestins) have on uterine tissue. This proliferation is associated with increased risk for endometriosis and/or endometrial cancer. The effects of unopposed estrogens on breast tissue are less clear, but are of some concern. The need for estrogens which can maintain the bone sparing effect while minimizing the proliferative effects in the uterus and breast is evident. Certain nonsteroidal antiestrogens have been shown to maintain bone mass in the ovariectomized rat model as well as in human clinical trials. Tamoxifen (sold as Novadex® brand tamoxifen citrate by Zeneca Pharmaceuticals, Wilmington, Delaware), for example, is a useful palliative for the treatment of breast cancer and has been demonstrated to exert an estrogen agonist-like effect on the bone, in humans. However, it is also a partial agonist in the uterus and this is cause for some concern. Raloxifene, a benzothiophene antiestrogen, has been shown to stimulate uterine growth in the ovariectomized rat to a lesser extent than Tamoxifen while maintaining the ability to spare bone. A suitable review of tissue selective estrogens is seen in the article "Tissue-Selective Actions Of Estrogen Analogs", *Bone* Vol. 17, No. 4, October 1995, 181S-190S.

The use of indoles as estrogen antagonists has been reported by Von Angerer, Chemical Abstracts, Vol. 99, No. 7 (1983), Abstract No. 53886u. Also, see, J.Med.Chem. 1990, 33, 2635-2640; J.Med.Chem. 1987, 30, 131-136. Also see Ger. Offen., DE 3821148 A1 891228 and WO 96/03375. These prior art compounds share structural similarities with the present compounds, but are functionally different. For compounds containing a basic amine, there is no phenyl group to rigidify the side chain.

WO A 95 17383 (Karo Bio AB) describes indole antiestrogens with long straight chains. Another related patent WO A 93 10741 describes 5-Hydroxyindoles with a broad range of side chains. WO 93/23374 (Otsuka Pharmaceuticals, Japan) describes compounds sharing structural similarities with those of the present invention, except with the structure referred to as R_3 in the present formulas I and II, below, is defined as thioalkyl and the reference discloses no such compounds having chains from the indole nitrogen having the same structure as the ones provided by the present invention.

In their article *Postmenopausal Hormone replacement therapy with estrogen periodically supplemented with antiestrogen*, Am. J. Obstet. Gynecol., Vol. 140, No. 7, 1981, pp. 787-792, Kauppila et al. describe their study of postmenopausal estrogen therapy of seven-week estrogen regimens followed by 10-day treatments with the antiestrogen clomiphene citrate.

Also, in their article *Comparison of Megestrol Acetate and Clomiphene Citrate as Supplemental Medication in Posmenopausal Oestrogen Replacement Therapy,* Arch. Gynecol. (1983) 234:49-58, Kauppila et al. describe combination therapies in postmenopausal women of estrogen with random supplementation of megestrol acetate or clomiphene citrate.

U.S. Patent No. 4,894,373 (Young) teaches the use of antiestrogens, including clomiphene and its isomers, citrates and derivatives, in the absence of estrogen for treating menopausal symptoms and treating or preventing osteoporosis. U.S. Patent No. 5,552,401 (Cullinan et al.) describes benzothiophene compounds as useful for the treatment of various medical indications associated with post-menopausal syndrome,

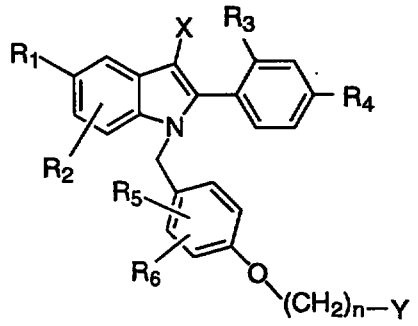
and uterine fibroid disease, endometriosis, and aortal smooth muscle cell proliferation, the compounds being used in pharmaceutical formulations optionally containing estrogen or progestin. U.S. Patents Nos. 5,646,137 and 5,591,753 (both issued to Black et al.) discloses methods of treating osteoporosis with formulations of raloxefine-type arylbenzothiophene compounds in conjunction with a progestin selected from medroxyprogesterone, norethindrone or norethynodrel, or pharmaceutically acceptable salts thereof. U.S Pat. No. 5,550,107 (Labrie) claims an invention comprising the treatment of breast or endometrial cancer with an antiestrogen together with at least one compound selected from the group of an androgen, a progestin, at least one inhibitor of sex steroid formation, expecially 17ß-hydroxysteroid dehydrogenase and aromatase activity, at least one inhibitor of prolactin secretion, one inhibitor of growth hormone secretion and one inhibitor of ACTH secretion. U.S. Pat. No. 5,672,609 (Bryant et al.) discloses pyridine compounds useful in treating post menopausal syndrome and formulations therefore containing estrogen or progestin. U.S. Pat. No. 5,534,527 (Black et al.) teaches the use of aroylbenzothiophenes and estrogens in the inhibition of bone loss.

Description of the Invention

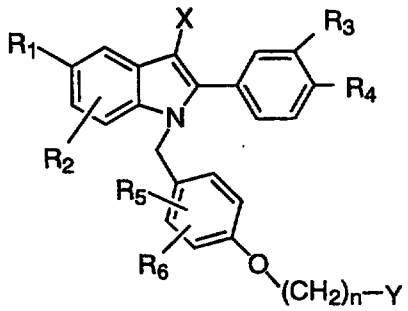
The present invention provides pharmaceutical formulations, and methods for using them, comprising compounds of formulas (I) and (II), below, in conjunction with estrogens, preferably in conjunction with one or more pharmaceutically acceptable carriers or excipients. Among the uses of the present formulations is alleviating the symptoms of post-menopausal syndrome in women, including peri-menopausal and post-menopausal symptoms. The present formulations and methods of treatment can be used to minimize undesirable side effects of estrogen treatment or therapy and may be used to minimize the amounts of estrogen(s) necessary for a particular regimen.

Compounds of the general structure type shown in formulas (I) and (II) are estrogen agonists/antagonists useful for the treatment of diseases associated with estrogen deficiency and are disclosed in EP-A-0802183 published 22 October 1997, the contents of which are incorporated herein by reference . The compounds are capable of antagonizing the effects of 17β- estradiol while showing little uterine stimulation when dosed alone.

The present invention includes, in conjunction with one or more estrogens, the use of compounds of formulas (I) or (II), below:



or



(I) (II)

wherein:

R_1 is selected from H, OH or the C_1-C_{12} esters (straight chain or branched) or C_1-C_{12} (straight chain or branched or cyclic) alkyl ethers thereof, or halogens; or C_1-C_4 halogenated ethers including trifluoromethyl ether and trichloromethyl ether.

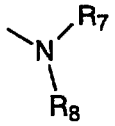
R_2, R_3, R_4, R_5 and R_6 are independently selected from H, OH or the C_1-C_{12} esters (straight chain or branched) or C_1-C_{12} alkyl ethers (straight chain or branched or cyclic) thereof, halogens, or C_1-C_4 halogenated ethers including trifluoromethyl ether and trichloromethyl ether, cyano, C_1-C_6 alkyl (straight chain or branched), or trifluoromethyl, with the proviso that, when R_1 is H, R_2 is not OH.

X is selected from H, C_1-C_6 alkyl, cyano, nitro, trifuoromethyl, halogen;

n is 2 or 3;

Y is selected from:

a) the moiety:



wherein R_7 and R_8 are independently selected from H, C_1-C_6 alkyl, or phenyl optionally substituted by CN, C_1-C_6 alkyl (straight chain or branched), C_1-C_6 alkoxy (straight chain or branched), halogen, -OH, $-CF_3$, or $-OCF_3$; or R_7 and R_8 are concatenated together as $-(CH_2)p-$, wherein p is an integer of from 2 to 6, preferably 4

to 6, the ring so formed is optionally substituted with 1-3 substituents selected from C_1-C_3 alkyl, trifluoromethyl, halogen, hydrogen, phenyl, nitro and -CN;

b) a five-membered saturated, unsaturated or partially unsaturated heterocycle containing up to two heteroatoms selected from the group consisting of -O-, -NH-, -N(C_1C_4 alkyl)-, -N=, and -$S(O)_m$-, wherein m is an integer of from 0-2, optionally substituted with 1-3 substituents independently selected from hydroxyl, halo, C_1-C_4 alkyl, trihalomethyl, C_1-C_4 alkoxy, trihalomethoxy, C_1-C_4 acyloxy, C_1-C_4 alkylthio, C_1-C_4 alkylsulfinyl, C_1-C_4 alkylsulfonyl, hydroxy (C_1-C_4)alkyl, -CO_2H, -CN-, -$CONHR_1$-, -NH_2, C_1-C_4alkylamino, di-(C_1-C_4)alkylamino, -$NHSO_2R_1$, -$NHCOR_1$, -NO_2, and phenyl optionally substituted with 1-3 (C_1-C_4)alkyl, wherein R_1 is as defined above or C_1-C_6 alkyl;

c) a six-membered saturated, unsaturated or partially unsaturated heterocycle containing up to two heteroatoms selected from the group consisting of -O-, -NH-, -N(C_1C_4 alkyl)-, -N=, and -$S(O)_m$-, wherein m is an integer of from 0-2, optionally substituted with 1-3 substituents independently selected from the group consisting of hydrogen, hydroxyl, halo, C_1-C_4 alkyl, trihalomethyl, C_1-C_4 alkoxy, trihalomethoxy, C_1-C_4 acyloxy, C_1-C_4 alkylthio, C_1-C_4 alkylsulfinyl, C_1-C_4 alkylsulfonyl, hydroxy (C_1-C_4)alkyl, -CO_2H-, -CN-, -$CONHR_1$-, -NH_2-, C_1-C_4 alkylamino, di(C_1-C_4)alkylamino, -$NHSO_2R_1$-, -$NHCOR_1$-, -NO_2, and phenyl optionally substituted with 1-3 (C_1-C_4)alkyl;

d) a seven-membered saturated, unsaturated or partially unsaturated heterocycle containing up to two heteroatoms selected from the group consisting of -O-, -NH-, -N(C_1C_4 alkyl)-, -N=, and -$S(O)_m$-, wherein m is an integer of from 0-2, optionally substituted with 1-3 substituents independently selected from the group consisting of hydrogen, hydroxyl, halo, C_1-C_4 alkyl, trihalomethyl, C_1-C_4 alkoxy, trihalomethoxy, C_1-C_4 acyloxy, C_1-C_4 alkylthio, C_1-C_4 alkylsulfinyl, C_1-C_4 alkylsulfonyl, hydroxy (C_1-C_4)alkyl, -CO_2H-, -CN, -$CONHR_1$-, -NH_2, C_1-C_4 alkylamino, di(C_1-C_4)alkylamino, -$NHSO_2R_1$, -$NHCOR_1$, -NO_2, and phenyl optionally substituted with 1-3 (C_1-C_4)alkyl;; or

e) a bicyclic heterocycle containing from 6-12 carbon atoms either bridged or fused and containing up to two heteroatoms selected from the group consisting of -O-, -NH-, -N(C_1C_4 alkyl)-, and -$S(O)_m$-, wherein m is an integer of from 0-2, optionally substituted with 1-3 substituents independently selected from the group consisting of hydrogen, hydroxyl, halo, C_1-C_4 alkyl, trihalomethyl, C_1-C_4 alkoxy, trihalomethoxy, C_1-C_4 acyloxy, C_1-C_4 alkylthio, C_1-C_4 alkylsulfinyl, C_1-C_4 alkylsulfonyl, hydroxy (C_1-C_4)alkyl, -CO_2H, -CN, -$CONHR_1$-, -NH_2, C_1-C_4 alkylamino, di(C_1-C_4)alkylamino, -$NHSO_2R_1$, -$NHCOR_1$, -NO_2, and phenyl optionally substituted with 1-3 (C_1-C_4) alkyl;

and the pharmaceutically acceptable salts thereof.

The more preferred formulations of this invention are those having, along with one or more pharmaceutical carriers or excipients:

a) one or more estrogens; and

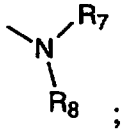
b) one or more compounds selected from the general structures I or II, above, wherein:

R_1 is selected from H, OH or the C_1-C_{12} esters or alkyl ethers thereof, halogen;

R_2, R_3, R_4, R_5, and R_6 are independently selected from H, OH or the C_1-C_{12} esters or alkyl ethers thereof, halogen, cyano, C_1-C_6 alkyl, or trihalomethyl, preferably trifluoromethyl, with the proviso that, when R_1 is H, R_2 is not OH;

X is selected from H, C_1-C_6 alkyl, cyano, nitro, triflouromethyl, halogen;

Y is the moiety



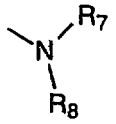
;

R_7 and R_8 are selected independently from H, C_1-C_6 alkyl, or combined by -(CH_2)p-, wherein p is an integer of from 2 to 6, so as to form a ring, the ring being optionally substituted by up to three substituents selected from the group of hydrogen, hydroxyl, halo, C_1-C_4 alkyl, trihalomethyl, C_1-C_4 alkoxy, trihalomethoxy, C_1-C_4 alkylthio, C_1-C_4 alkylsulfinyl, C_1-C_4 alkylsulfonyl, hydroxy (C_1-C_4)alkyl, -CO_2H, -CN, -CONH(C_1-C_4)alkyl, -NH_2, C_1-C_4 alkylamino, C_1-C_4 dialkylamino, -$NHSO_2$(C_1-C_4)alkyl, -NHCO(C_1-C_4)alkyl and -NO_2;

and the pharmaceutically acceptable salts thereof.

The rings formed by a concatenated R_7 and R_8, mentioned above, may include, but are not limited to, aziridine, azetidine, pyrrolidine, piperidine, hexamethyleneamine or heptamethyleneamine rings.

The most preferred compounds of the present formulations are those having the structural formulas I or II, above, wherein R_1 is OH; R_2 - R_6 are as defined above; X is selected from the group of Cl, NO_2, CN, CF_3, or CH_3; and Y is the moiety



and R_7 and R_8 are concatenated together as $-(CH_2)_r-$, wherein r is an integer of from 4 to 6, to form a ring optionally substituted by up to three subsituents selected from the group of hydrogen, hydroxyl, halo, C_1-C_4 alkyl, trihalomethyl, C_1-C_4alkoxy, trihalomethoxy, C_1-C_4 alkylthio, C_1-C_4 alkylsulfinyl, C_1-C_4 alkylsulfonyl, hydroxy (C_1-C_4)alkyl, $-CO_2H$, -CN, $-CONH(C_1$-$C_4)$alkyl, $-NH_2$, C_1-C_4alkylamino, di-(C_1-C_4)alkylamino, $-NHSO_2(C_1$-$C_4)$alkyl, $-NHCO(C_1$-$C_4)$alkyl and $-NO_2$;
and the pharmaceutically acceptable salts thereof.

In another embodiment of this invention, when R_7 and R_8 are concatenated together as $-(CH_2)p-$, wherein p is an integer of from 2 to 6, preferably 4 to 6, the ring so formed is optionally substituted with 1-3 substituents selected from C_1-C_3 alkyl, trifluoromethyl, halogen, phenyl, nitro and -CN.

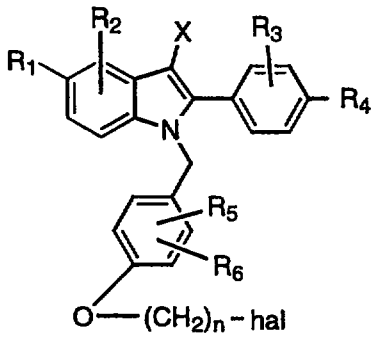
The invention includes sulfate, sulfamates and sulfate esters of phenolic groups. Sulfates can be readily prepared by the reaction of the free phenolic compounds with sulfur trioxide complexed with an amine such as pyridine, trimethylamine, triethylamine, etc. Sulfamates can be prepared by treating the free phenolic compound with the desired amino or alkylamino or dialkylamino sulfamyl chloride in the presence of a suitable base such as pyridine. Sulfate esters can be prepared by reaction of the free phenol with the desired alkanesulfonyl chloride in the presence of a suitable base such as pyridine. Additionally, this invention includes compounds containing

phosphates at the phenol as well as dialkyl phoshates. Phosphates can be prepared by reaction of the phenol with the appropriate chlorophosphate. The dialkylphosphates can be hydrolyzed to yield the free phosphates. Phosphinates are also claimed where the phenol is reacted with the desired dialkylphosphinic chloride to yield the desired dialkylphosphinate of the phenol.

The invention includes acceptable salt forms formed from the addition reaction with either inorganic or organic acids. Inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sufuric acid, phoshoric acid, nitric acid useful as well as organic acids such as acetic acid,propionic acid, citric acid, maleic acid, malic acid, tartaric acid, phthalic acid, succinic acid, methanesulfonic acid, toluenesulfonic acid, napthalenesulfonic acid, camphorsulfonic acid, benzenesulfonic acid are useful. It is known that compounds possessing a basic nitrogen can be complexed with many different acids (both protic and non-protic) and usually it is preferred to administer a compound of this invention in the form of an acid addition salt. Additionally, this invention includes quaternary ammonium salts of the compounds herein. These can be prepared by reacting the nucleophilic amines of the side chain with a suitably reactive alkylating agent such as an alkyl halide or benzyl halide.

The compounds utilized in this invention are prepared by a process which comprises one of the following:

a) reacting a compound of formula



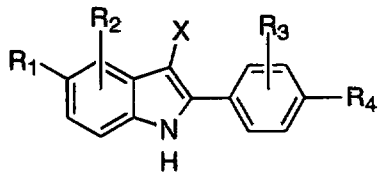
wherein n, R_1-R_6 and X are as defined above and hal is chlorine or bromine with a compound of formula:

HNR7R8

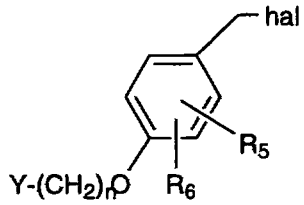
where R7 and R8 are as defined above to give a corresponding compound of formula I or II;

or

b) reacting a compound of formula



wherein R1-R4 and X are as defined above in the presence of a base, e.g NaH, with a compound of formula



wherein n, R5, R6 and Y are as defined above and hal is a halogen, e.g Cl or Br to give a corresponding compound of Formula I ;

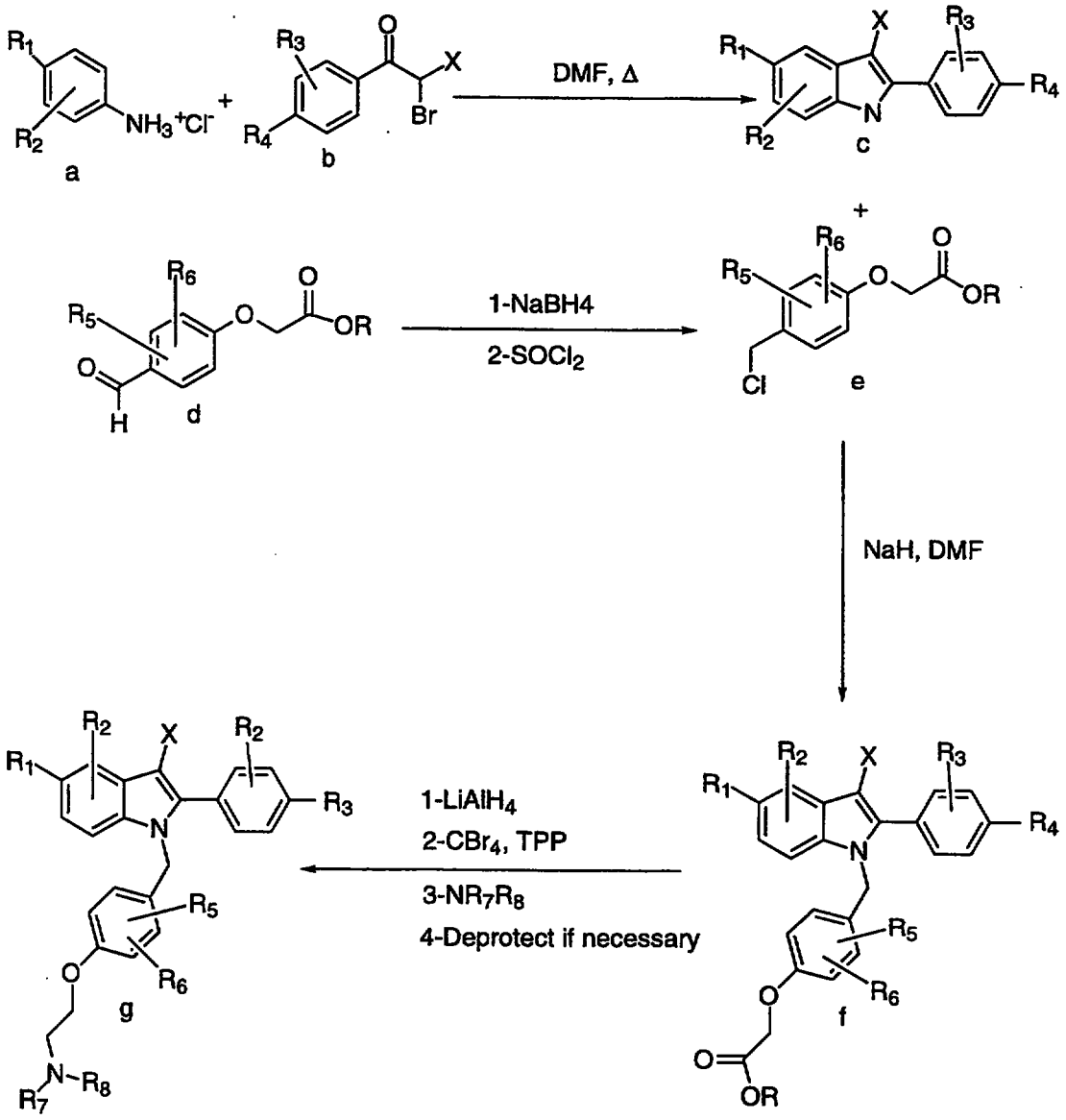
if necessary protecting any reactive substituent groups during each process above and removing same; and

if desired converting a phenolic group present to a phosphate, sulfate, sulfamate or sulfate ester; and further if desired converting the compound of formula I or II to a pharmaceutically acceptable salt.

Methods

Compounds of this invention can be synthesized in a general sense according to Scheme 1, below.

Scheme 1

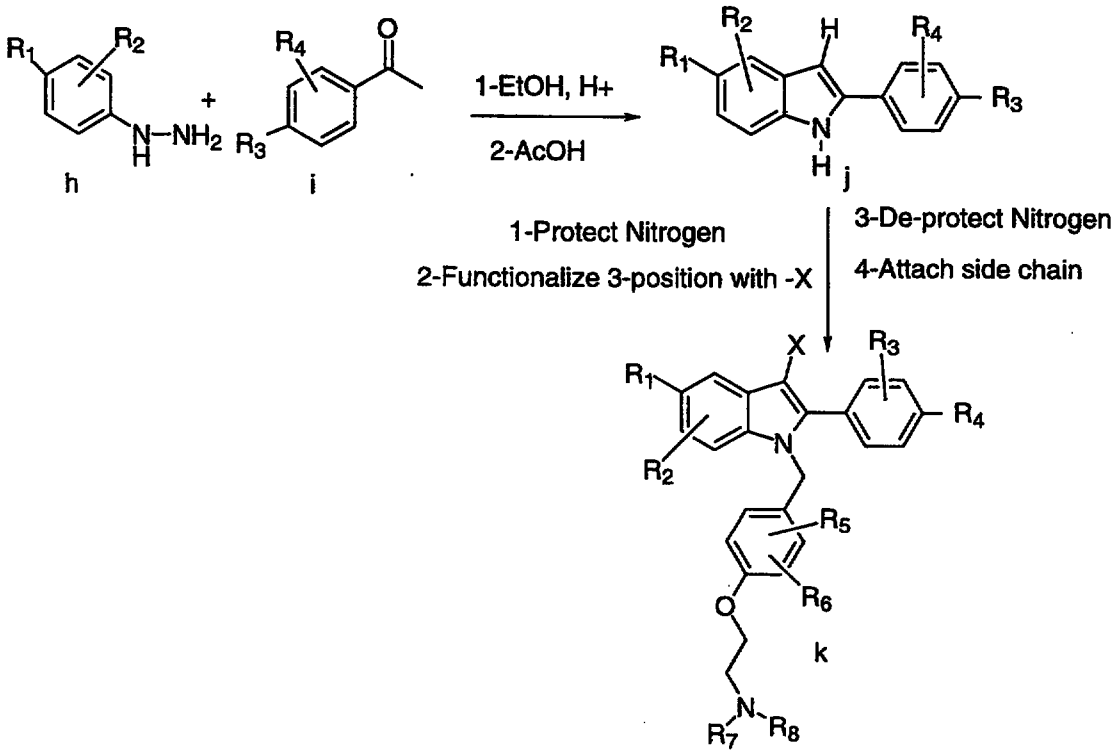


The initial indole synthesis is accomplished by heating an appropriately substituted alpha-bromo ketone (b) with the desired aniline (a) in DMF to form the indole (c). The product is then alkylated with a benzyl chloride (e) to give the substituted indole (f). The benzyl chloride (e) can be readily prepared from the aldehyde (d) in 2 steps as given. Product (g) can be prepared from (f) by reduction of the ester, conversion of the alcohol to a bromide, displacement of the bromide with the

desired amine in a suitable solvent such as THF or DMF, and finally, deprotection if necessary. Deprotection is necessary when either R_1 or R_2 or both is a protected phenol. The preferred protecting group is a benzyl group which can be conveniently removed by several conventional methods, especially hydrogenolysis.

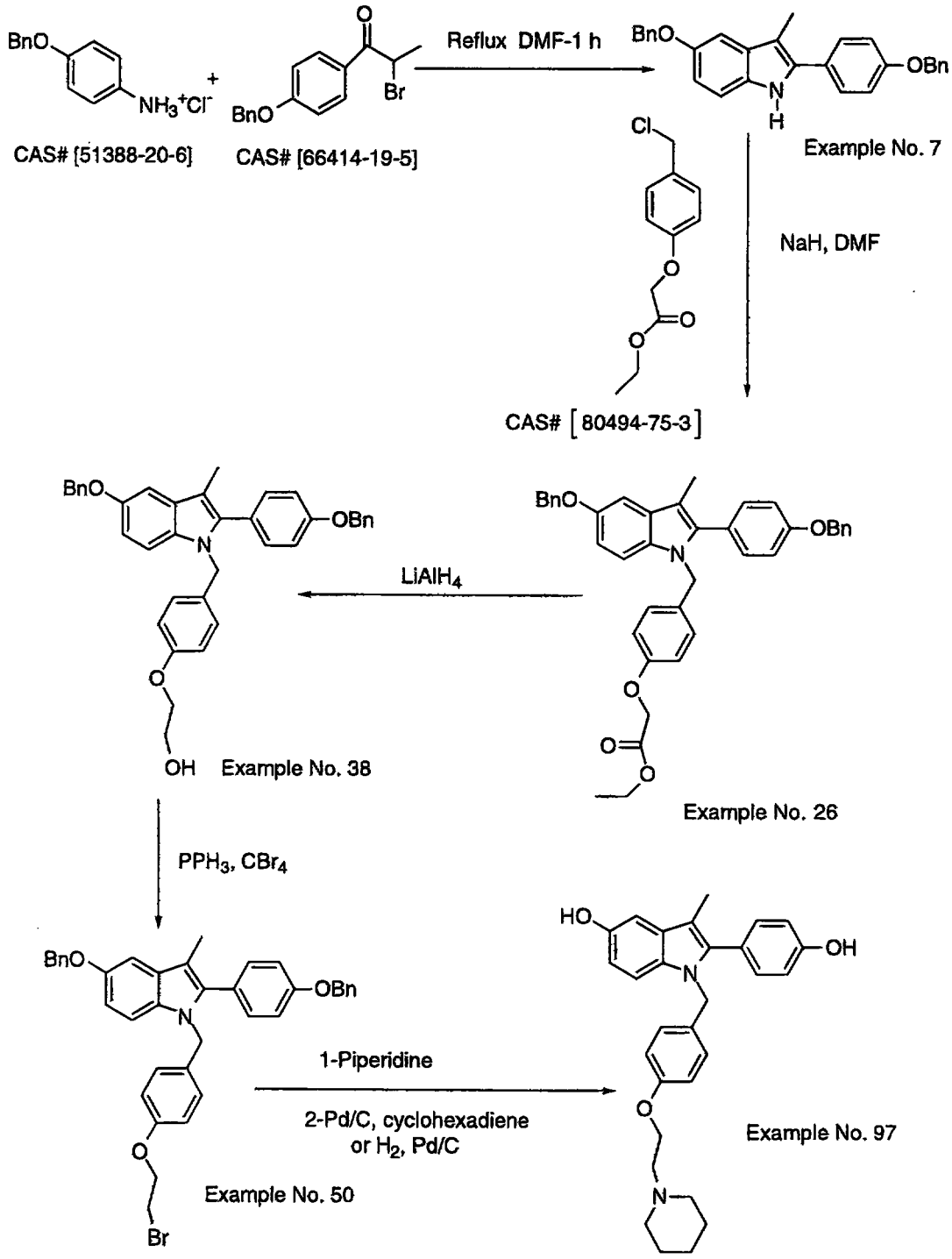
For the synthesis of compounds with X=H, halogen, trifluoromethyl, cyano, nitro, an alternative synthesis shown in scheme 2 may be preferable. The formation of halogens at the 3-position can be easily performed with such reagents as N-chlorosuccinamide, N-bromosuccinamide, or N-iodosuccinamide. A 3-Iodoindole compound obtained can be used as a precursor to the 3-trifluoromethyl compound by a coupling reaction utilizing a palladium catalyst and bistrifluoromethyl mercury (II). A compound with a cyano group in the 3-position can be prepared by electrophilic cyanation or alternatively the 3-position can be formylated (with a formyl iminium salt, for example) then the formyl group converted to an oxime and subsequently dehydrated to a nitrile. Alternatively, the 3-cyano compound can be synthesized by reaction of the 3-unsubstituted indole with chlorosulfonylisocyanate followed by triethylamine. A compound with the nitro group in the 3-position can be prepared by treating the indole with sodium nitrite and acetic acid. One skilled in the art recognizes these routes are not limiting and other routes are also available.

Scheme 2



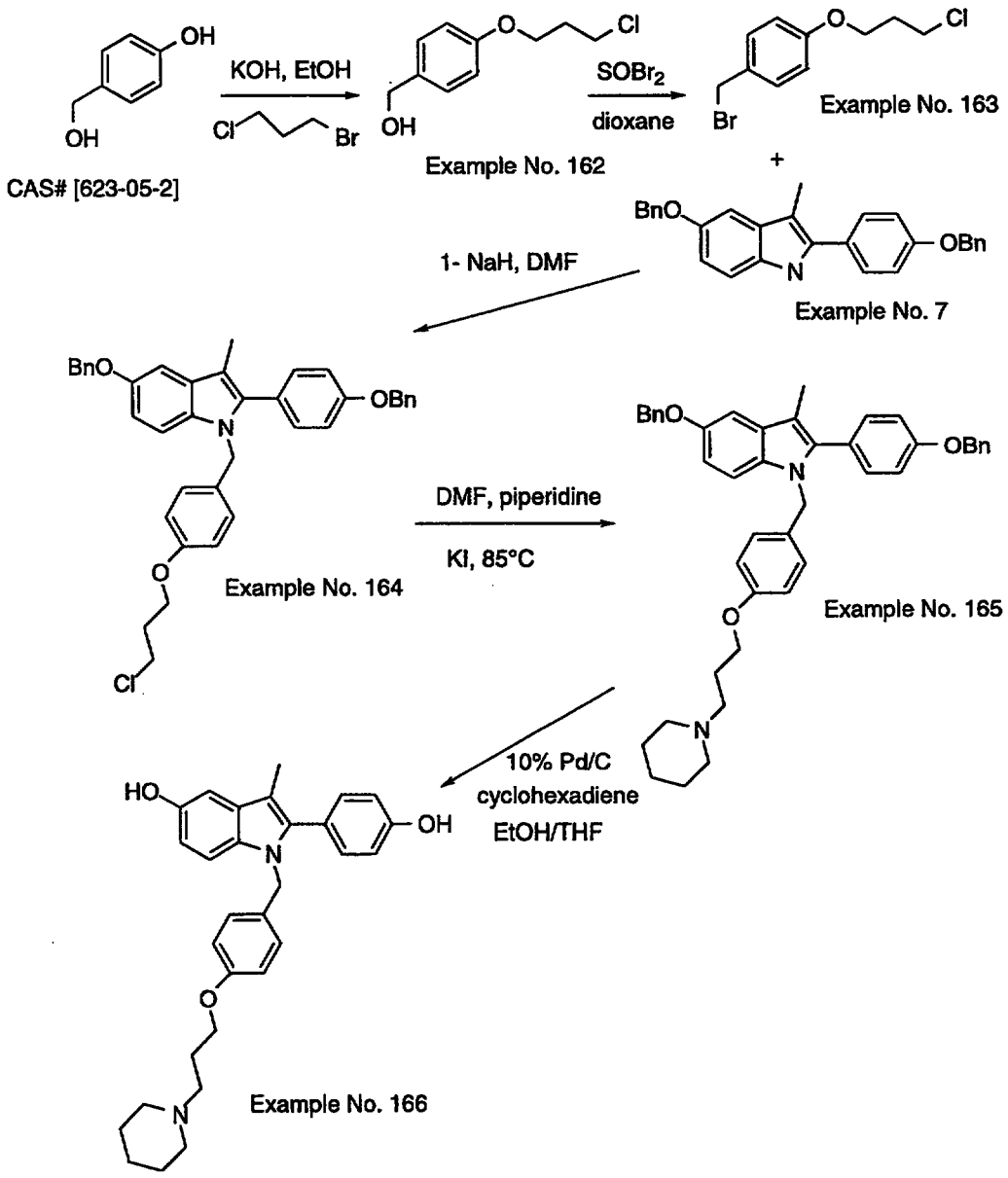
Synthesis of selected representative examples are given in the following schemes:

Scheme 3



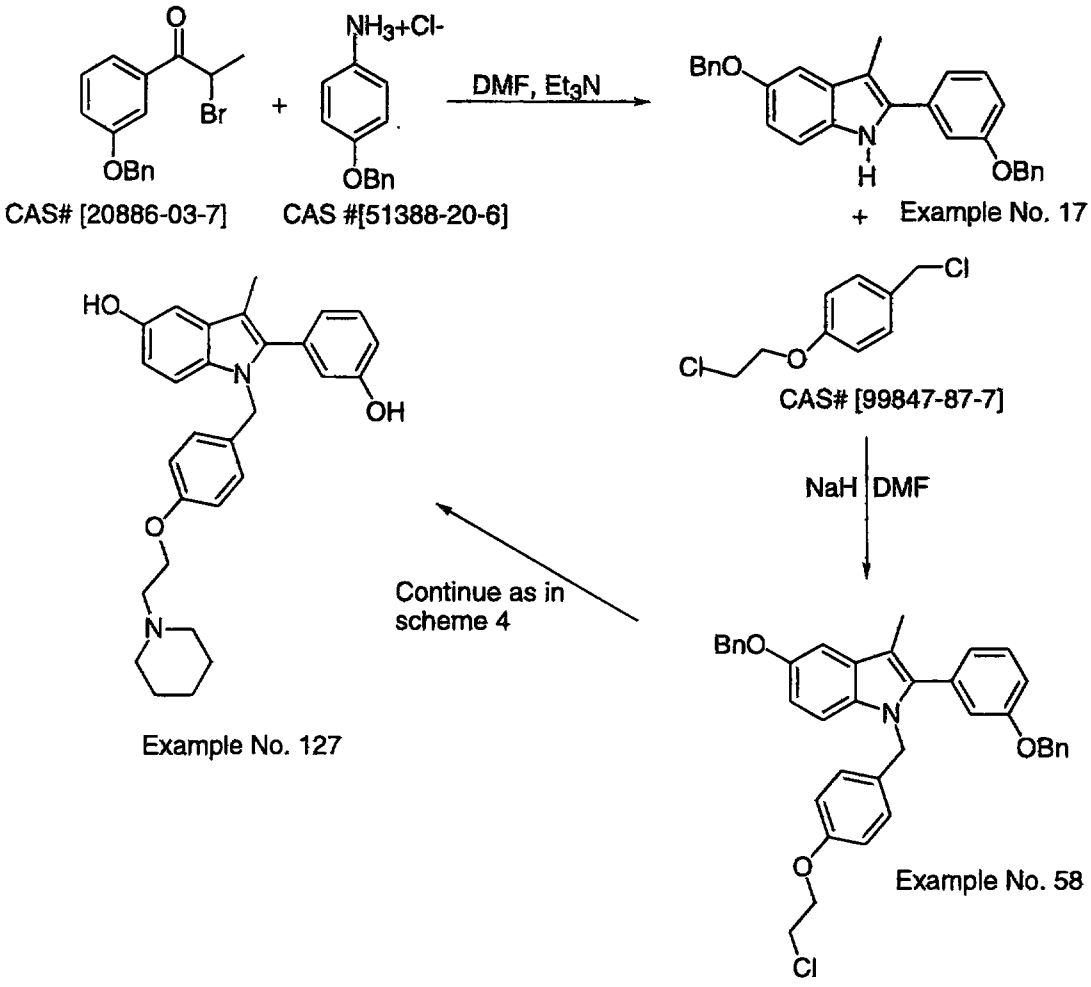
The synthesis of analogues with a 3-carbon chain (example No. 166) between the oxygen and the basic amine can be accomplished as shown in scheme 4.

Scheme 4



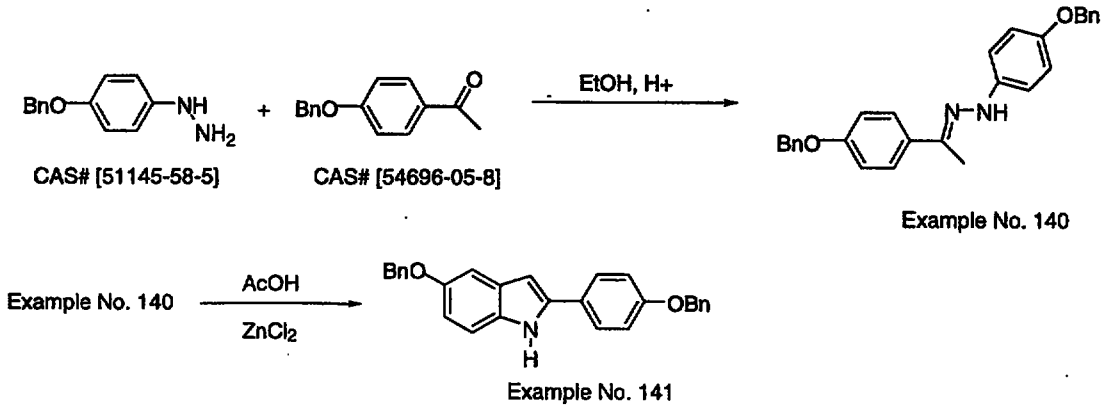
The synthetic procedure shown in scheme 4 may be used for compounds with two carbon chains analogous to example No. 97 in scheme 3. This is shown in scheme 4a for the synthesis of example No. 127.

Scheme 4a



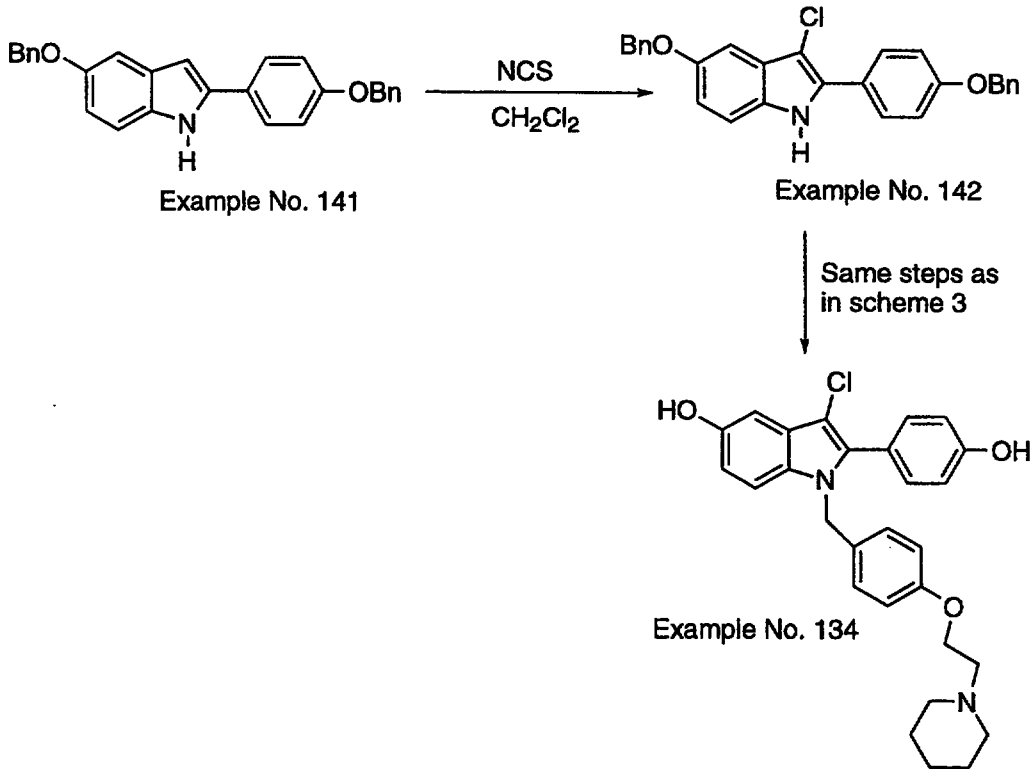
The synthesis of indoles with alternative substituents (CN, Cl) at the 3-position of the indole both utilize the 3-unsubstituted indole No. 141 for a precursor. The indole is synthesized by the Fisher method utilizing the hydrazone derived from the condensation of 4-benzyloxyacetophenone CAS No. [54696-05-8] and 4-benzyloxyphenylhydrazine CAS No. [51145-58-5]. The hydrazone No. 140 is then cyclized in acetic acid using zinc chloride to afford the desired indole No. 141. This synthesis can be seen in scheme 5.

Scheme 5



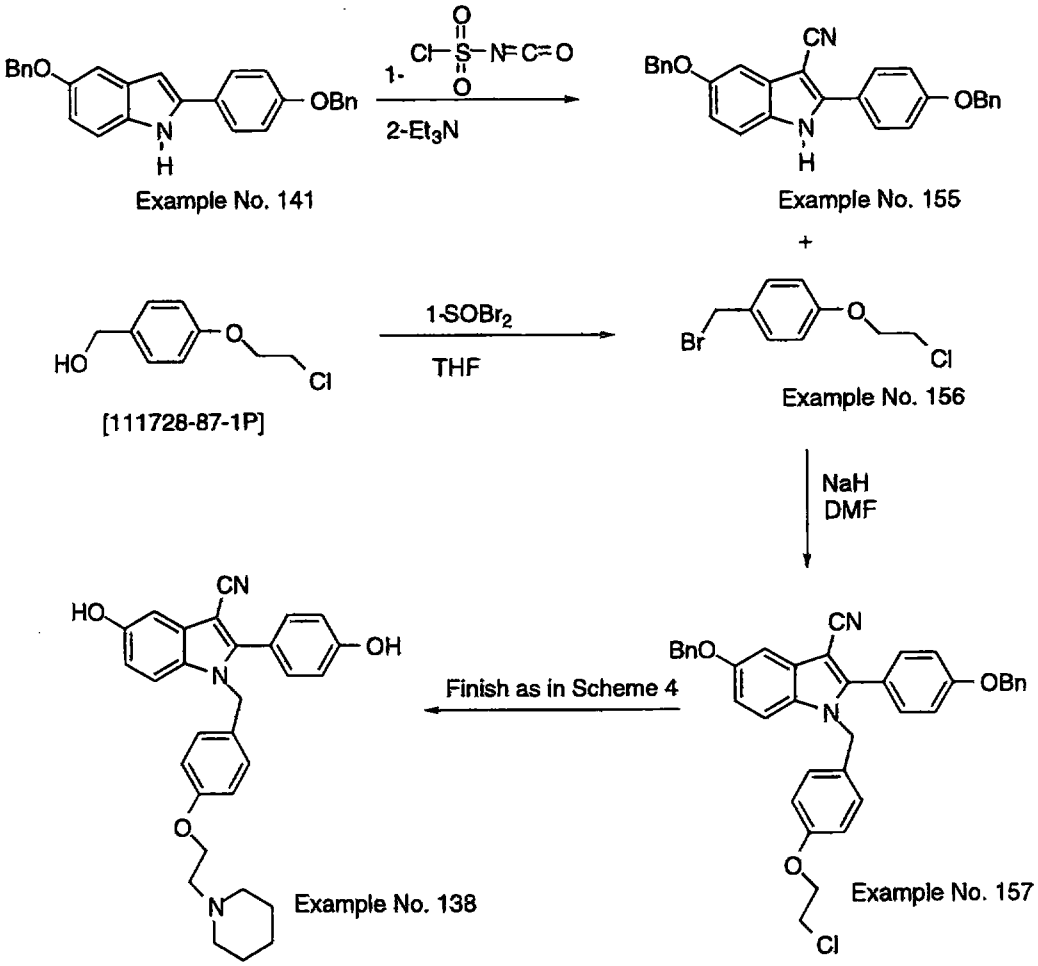
The synthesis of 3-Chloroindole compounds is demonstrated for example No. 134 and shown, *infra,* in scheme 6. The indole No. 141 from scheme 5 is chlorinated with N-chlorosuccinamide. The 3-Chloroindole No. 142, thus obtained, is taken to the final product in analogous fashion to that shown in scheme 3.

Scheme 6



3-Cyano analogues are synthesized from the precursor indole No. 141 as shown in Scheme 7. Reaction of the precursor indole No. 141 with chlorosulfonyl isocyanate followed by addition of triethylamine yields the 3-Cyanoindole No. 155. The side chain is made by conversion of the benzylic alcohol of CAS No. [111728-87-1] to the benzylic bromide No. 156 using thionyl bromide in THF. The indole is alkylated by the side chain in DMF using sodium hydride to give the intermediate No. 157. This can then be taken to the final product No. 138 in an analogous fashion to that shown in scheme 4.

Scheme 7



The compounds of Formulas (I) and (II) are partial estrogen agonists and display high affinity for the estrogen receptor. Unlike many estrogens, however, these

compounds do not cause increases in uterine wet weight. These compounds are antiestrogenic in the uterus and can completely antagonize the trophic effects of estrogen agonists in uterine tissue. These compounds are useful in treating or preventing mammal disease states or syndromes which are caused or associated with an estrogen deficiency. This tissue selectivity allows their use for desirable estrogenic activity in certain tissues, such as bone, while limiting that activity in others, such as uterine tissue.

Estrogens useful in the formulations of this invention include estrone, estriol, equilin, estradiene, equilenin, ethinyl estradiol, 17β-estradiol, 17α-dihydroequilenin, 17β-dihydroequilenin (U.S. Patent 2,834,712), 17α-dihydroequilin, 17β-dihydroequilin, menstranol and conjugated estrogenic hormones, such as those in Wyeth-Ayerst Laboratories' Premarin® products. Phytoestrogens, such as equol or enterolactone, may also be used in the present formulations and methods. A preferred embodiment of this invention comprises pharmaceutical compositions and methods of treatment utilizing conjugated estrogenic hormones, such as those in Wyeth-Ayerst Laboratories' Premarin® products, with one or more compounds of Formulas (I) or (III) listed herein. Esterified estrogens, such as those sold by Solvay Pharmaceuticals, Inc. under the Estratab® tradename, may also be used with the present formulations. Also preferred for use with the present invention are the salts of the applicable estrogens, most preferably the sodium salts. Examples of these preferred salts are Sodium estrone sulfate, Sodium equilin sulfate, Sodium 17alpha-dihydroequilin sulfate, Sodium 17alpha-estradiol sulfate, Sodium Delta8,9- dehydroestrone sulfate, Sodium equilenin sulfate, Sodium 17beta-dihydroequilin sulfate, Sodium 17alpha-dihydroequilenin sulfate, Sodium 17beta-estradiol sulfate, Sodium 17beta-dihydroequilenin sulfate, Estrone 3-sodium sulfate, Equilin 3-sodium sulfate, 17alpha-Dihydroequilin 3-sodium sulfate, 3beta-Hydroxy-estra-5(10),7-dien-17-one 3-sodium sulfate, 5alpha-Pregnan-3beta-20R-diol 20-sodium sulfate, 5alpha-Pregnan-3beta,16alpha-diol-20-one 3-sodium sulfate, delta(8,9)-Dehydroestrone 3-sodium sulfate, Estra-3beta, 17alpha-diol 3-sodium sulfate, 3beta-Hydroxy-estr-5(10)-en-17-one 3-sodium sulfate or 5alpha-Pregnan-3beta,16alpha,20R-triol 3-sodium sulfate. Preferred salts of estrone include, but are not limited to, the sodium and piperate salts.

The present compounds of Formulas (I) and (II) are tissue selective compounds having the ability to behave like estrogen agonists, such as by lowering cholesterol and preventing bone loss, or like estrogen antagonists. Therefore, these compounds in the present formulations are useful for treating many maladies including osteoporosis, prostatic hypertrophy, infertility, breast cancer, endometrial hyperplasia, endometrial cancer, endometriosis, cystic glandular hyperplasia, uterine hyperplasia, cervical hyperplasia, benign prostatic hyperplasia, cardiovascular disease, contraception, Alzheimer's disease and melanoma. The formulations of this invention may also be used to treat bone loss resulting from secondary osteoporosis, including that categorized as endocrine in nature, including that resulting from glucocorticoid excess, hyperparathyroidism, hyperthyroidism, hypogonadism, hyperprolactinemia, and diabetes mellitus. The bone loss may also be the drug-induced, such as that resulting from heparin treatments, alcohol consumption, or the use of tobacco, barbiturates or corticosteroids. The drug-induced loss of bone may also stem from treatment with gonadotropin releasing hormone (GnRH or LHRH) or synthetic GnRH antagonists or agonists, such as the leuprolide acetate injectable sold by TAP Pharmaceuticals Inc. under the tradename LUPRON® or the goserelin acetate implant sold by Zeneca Pharmaceuticals under the Zoladex® tradename. Such bone loss may also result from immobilization of the individual, chronic renal failure, malabsorption syndrome, hepatic disease, chronic obstructive lung disease, rheumatoid arthritis, or sarcoidosis.

Additionally, these formulations can be used for hormone replacement therapy in post-menopausal women or in other estrogen deficiency states where estrogen supplementation would be beneficial. The symbiotic activity of the compounds and estrogen(s) of the present methods of treatment are particularly of interest in overcoming the unwanted consequences of estrogen therapy, such as breakthrough bleeding and/or excessive endometrial stimulation, which may lead to endometrial hyperplasia or endometriosis. These formulations, therefore, may be used in methods of treating or preventing excessive estrogenic uterine stimulation in a mammal.

The formulations of this invention may also be used in methods of treatment for bone loss, which may result from an imbalance in an individual's formation of new bone tissues and the resorption of older tissues, leading to a net loss of bone. Such bone depletion results in a range of individuals, particularly in post-menopausal

women, women who have undergone hysterectomy/oophorectomy, those receiving or who have received extended corticosteroid therapies, those experiencing gonadal dysgenesis, and those suffering from Cushing's syndrome. Special needs for bone replacement can also be addressed using these formulations in individuals with bone fractures, defective bone structures, and those receiving bone-related surgeries and/or the implantation of prosthesis. In addition to those problems described above, these formulations can be used in treatments for osteoarthritis, Paget's disease, osteomalacia, osteohalisteresis, endometrial cancer, multiple myeloma and other forms of cancer having deleterious effects on bone tissues. Methods of treating the maladies listed herein are understood to comprise administering to an individual in need of such treatment a pharmaceutically effective amount of one or more of the compounds of Formulas (I) and (II), or a pharmaceutically acceptable salt thereof, in conjunction with a therapeutically desirable amount of an estrogen. This invention also includes pharmaceutical compositions utilizing one or more of the present compounds, and/or the pharmaceutically acceptable salts thereof, along with one or more pharmaceutically acceptable carriers, excipients, etc.

Estrogens regulate a number of physiological processes. The primary target tissues for estrogens include the reproductive tract (ovary; uterus; vagina), mammary tissue, skeleton, cardiovascular system and the central nervous system (CNS). The reduction in circulating estrogens results in a number of changes. There is a cessation in reproductive function with an associated amenorrhea, uterine atrophy, and increase in vaginal dryness (lack of keratinization). Mammary tissue becomes relatively quiescent. There is an increase in the rate of loss of bone mass (2-7%) compared to the normal 0.5-1.0%/year that is seen in all individuals over the age of 35. A change in lipid profile occurs with increases in Low Density Lipoprotein (LDL) and decreases in High Density Lipoprotein (HDL) commonly measured and an associated increased risk of a cardiovascular event (heart attack, stroke). Changes in the central nervous system include an increase in vasomotor symptoms (hot flush) and potentially changes in cognition and memory.

Estrogen replacement therapy (ERT) normalizes some of these changes, particularly those associated with the cardiovascular system (reduced LDL, increased HDL, reduced risk of heart attack), the skeleton (maintenance of bone mass, reduced

fracture risk), and central nervous system (reduction in frequency and severity of the hot flush). While the reproductive tract responds, it is not all positive. On the positive side, vaginal dryness is alleviated. However , negative uterine responses include hypertrophy and hyperplasia, along with some menstrual-like bleeding. The breast is also affected and there are data correlating exogenous estrogen therapy with an increased risk of breast cancer.

Currently, women with intact uteri are generally not prescribed estrogens alone, but estrogens in combination with a progestin to reduce uterine stimulation. While the risks of endometrial cancer are reduced to non-hormone treated levels, the other side effects of progestins reduce compliance in women on hormone replacement.

The tissue selective estrogen (TSE) compounds of this invention provide positive skeletal and cardiovascular affects similar to estrogens, without the negative effects associated with the uterus and breast. The combinations of TSEs and estrogens derive the positive effects of estrogens on the CNS, bone and cardiovascular, with the combination providing complimentary or additive effects on the bone and cardiovascular systems. The major variable is the TSEs ability to block estrogenic influence on the uterus and breast, which are the two major negative effects of unopposed estrogens.

It is understood that the dosage, regimen and mode of administration of these compounds of Formulas (I) and (II) will vary according to the malady and the individual being treated and will be subjected to the judgment of the medical practitioner involved. It is preferred that the administration of one or more of the compounds herein begins at a low dose and be increased until the desired effects are achieved. Similarly, it will be understood that the dosage(s) of the estrogen(s) utilized in the present formulations will be selected according to conventional methods. It is most preferred that the dosage will be monitored to achieve the desired result with the minimum of estrogen(s) necessary.

Effective administration of these compounds of Formulas (I) and (II) may be given at a dose of from about 0.01 mg/day to about 1,000 mg/day. Preferably, administration will be from about 1 mg/day to about 600 mg/day in a single dose or in

two or more divided doses. Most preferably a daily dose of between about 1 mg/day and about 150 mg/day will be administered. Such doses may be administered in any manner useful in directing the active compounds herein to the recipient, including orally, parenterally (including intravenous, intraperitoneal and subcutaneous injections, implants, etc.), intravaginally and transdermally. For the purposes of this disclosure, transdermal administrations are understood to include all administrations across the surface of the body and the inner linings of bodily passages including epithelial and mucosal tissues. Such administrations may be carried out using the present compounds, or pharmaceutically acceptable salts thereof, in lotions, creams, foams, patches, suspensions, solutions, and suppositories (rectal and vaginal).

Oral formulations containing the active compounds of Formulas (I) and (II) may comprise any conventionally used oral forms, including tablets, capsules, buccal forms, troches, lozenges and oral liquids, suspensions or solutions. Capsules may contain mixtures of the active compound(s) with inert fillers and/or diluents such as the pharmaceutically acceptable starches (e.g. corn, potato or tapioca starch), sugars, artificial sweetening agents, powdered celluloses, such as crystalline and microcrystalline celluloses, flours, gelatins, gums, etc. Useful tablet formulations may be made by conventional compression, wet granulation or dry granulation methods and utilize pharmaceutically acceptable diluents, binding agents, lubricants, disintegrants, suspending or stabilizing agents, including, but not limited to, magnesium stearate, stearic acid, talc, sodium lauryl sulfate, microcrystalline cellulose, carboxymethylcellulose calcium, polyvinylpyrrolidone, gelatin, alginic acid, acacia gum, xanthan gum, sodium citrate, complex silicates, calcium carbonate, glycine, dextrin, sucrose, sorbitol, dicalcium phosphate, calcium sulfate, lactose, kaolin, mannitol, sodium chloride, talc, dry starches and powdered sugar. Oral formulations herein may utilize standard delay or time release formulations to alter the absorption of the active compound(s). Suppository formulations may be made from traditional materials, including cocoa butter, with or without the addition of waxes to alter the suppository's melting point, and glycerin. Water soluble suppository bases, such as polyethylene glycols of various molecular weights, may also be used.

It will be understood that the estrogen of this invention will be administered in the dosages of conventional regimens, according to the recipient's tolerance and the particular treatment or maintenance schedule intended. The compounds of Formulas (I) and (II) herein will be administered in an amount necessary to agonize or antagonize the estrogen(s) of the formulation's activity to the level desired. When conjugated estrogens, USP, are used, it is preferred that the daily doseage is from 0.1 mg to 5.0 mg, more preferably between about 0.3 mg and about 2.5 mg, most preferably between about 0.3 and about 1.25 mg/day. For mestranol or ethynyl estradiol a daily dosage may be from about 1 μg to about 0.15 mg/day and a dosage of from about 1 μg to about 0.3 mg/day may be used for ethynyl estradiol, preferably between about 2 μg to about .15 mg/day of ethynyl estradiol.

The compounds of this invention can be formulated neat or with a pharmaceutical carrier for administration, the proportion of which is determined by the solubility and chemical nature of the compound, chosen route of administration and standard pharmacological practice. The pharmaceutical carrier may be solid or liquid.

A solid carrier can include one or more substances which may also act as flavoring agents, lubricants, solubilizers, suspending agents, fillers, glidants, compression aids, binders or tablet-disintegrating agents; it can also be an encapsulating material. In powders, the carrier is a finely divided solid which is in admixture with the finely divided active ingredient. In tablets, the active ingredient is mixed with a carrier having the necessary compression properties in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contain up to 99% of the active ingredient. Suitable solid carriers include, for example, calcium phosphate, magnesium stearate, talc, sugars, lactose, dextrin, starch, gelatin, cellulose, methyl cellulose, sodium carboxymethyl cellulose, polyvinylpyrrolidine, low melting waxes and ion exchange resins.

Liquid carriers are used in preparing solutions, suspensions, emulsions, syrups, elixirs and pressurized compositions. The active ingredient can be dissolved or suspended in a pharmaceutically acceptable liquid carrier such as water, an organic solvent, a mixture of both or pharmaceutically acceptable oils or fats. The liquid carrier can contain other suitable pharmaceutical additives such as solubilizers, emulsifiers,

buffers, preservatives, sweeteners, flavoring agents, suspending agents, thickening agents, colors, viscosity regulators, stabilizers or osmo-regulators. Suitable examples of liquid carriers for oral and parenteral administration include water (partially containing additives as above, e.g. cellulose derivatives, preferably sodium carboxymethyl cellulose solution), alcohols (including monohydric alcohols and polyhydric alcohols, e.g. glycols) and their derivatives, lethicins, and oils (e.g. fractionated coconut oil and arachis oil). For parenteral administration, the carrier can also be an oily ester such as ethyl oleate and isopropyl myristate. Sterile liquid carriers are useful in sterile liquid form compositions for parenteral administration. The liquid carrier for pressurized compositions can be halogenated hydrocarbon or other pharmaceutically acceptable propellant.

Liquid pharmaceutical compositions which are sterile solutions or suspensions can be utilized by, for example, intramuscular, intraperitoneal or subcutaneous injection. Sterile solutions can also be administered intravenously. The compounds of this invention can also be administered orally either in liquid or solid composition form.

The compounds of this invention may be administered rectally or vaginally in the form of a conventional suppository, creams, gels, etc. For administration by intranasal or intrabronchial inhalation or insufflation, the compounds of this invention may be formulated into an aqueous or partially aqueous solution, which can then be utilized in the form of an aerosol. The compounds of this invention may also be administered transdermally through the use of a transdermal patch containing the active compound and a carrier that is inert to the active compound, is non toxic to the skin, and allows delivery of the agent for systemic absorption into the blood stream via the skin. The carrier may take any number of forms such as creams and ointments, pastes, gels, and occlusive devices. The creams and ointments may be viscous liquid or semisolid emulsions of either the oil-in-water or water-in-oil type. Pastes comprised of absorptive powders dispersed in petroleum or hydrophilic petroleum containing the active ingredient may also be suitable. A variety of occlusive devices may be used to release the active ingredient into the blood stream such as a semipermeable membrane covering a reservoir containing the active ingredient with or without a carrier, or a matrix containing the active ingredient. Other occlusive devices are known in the literature.

The dosage requirements vary with the particular compositions employed, the route of administration, the severity of the symptoms presented and the particular subject being treated. Treatment will generally be initiated with small dosages less than the optimum dose of the compound. Thereafter the dosage is increased until the optimum effect under the circumstances is reached; precise dosages for oral, parenteral, transdermal, rectal or vaginal suppositories, nasal, or intrabronchial and other administrations will be determined by the administering physician based on experience with the individual subject treated. Preferably, the pharmaceutical composition is in unit dosage form, e.g. as tablets or capsules. In such form, the composition is sub-divided in unit dose containing appropriate quantities of the active ingredient; the unit dosage forms can be packaged compositions, for example, packeted powders, vials, ampoules, prefilled syringes or sachets containing liquids. The unit dosage form can be, for example, a capsule or tablet itself, or it can be the appropriate number of any such compositions in package form.

The compound(s) of Formulas (I) and (II) and the estrogen(s) of the present formulations may be administered in separate dosage units, such as separate pills, tablets, powders, etc., or combined into one formulation. When optimum dosages for the compounds of Formulas (I) and (II) and the estrogens of these formulations have been determined, it may preferable to incorporate both into a single formulation for ease of administration. It is also understood that the formulations herein may or may not include other pharmaceutically active components.

Solvents used for the reactions described herein were anhydrous Aldrich Sure Seal^{TM} without further purification. Reagents were typically Aldrich and used without further purification. All reactions were carried out under a nitrogen atmosphere. Chromatography was performed using 230-400 mesh silica gel (Merck Grade 60, Aldrich Chemical Company). Thin layer chromatography was performed with Silica Gel 60 F_{254} plates from EM Science. ^1H NMR spectra were obtained on a Bruker AM-400 instrument in DMSO and chemical shifts reported in ppm. Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer diffraction grating or Perkin-Elmer 784 spectrophotometers. Mass spectra were recorded on a Kratos MS 50 or Finnigan 8230

mass spectrometers. Elemental analyses were obtained with a Perkin-Elmer 2400 elemental analyzer. Analysis values for compounds with CHN analysis reported were within 0.4% of theoretical values.

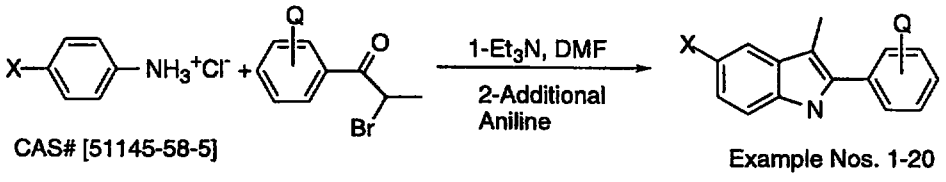
Synthesis of α-bromo ketones

Method a

The synthesis of the alpha bromo ketones is conveniantly accomplished by simply dissolving the starting phenyl ketone in ethyl ether (0.05-0.10 M) and at room temperature, 1.1 equivalents of bromine is added in dropwise. The reaction can be monitored by TLC for consumption of starting materials. The reaction is worked up by washing with an aqueous sodium bicarbonate solution followed by a 10% aqueous sodium sulfite solution. The ether layer is washed with brine and dried over magnesium sulfate. Concentration of the reaction mixture typically yields the bromoketones in good yield and purity. The bromoketones were taken "as is" (without purification or characterization) to the next step.

3-Methyl indoles

Scheme 8



CAS# [51145-58-5]

Example Nos. 1-20

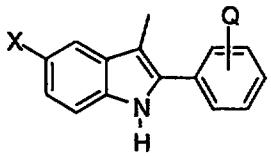


Table 1

Example No.	X	Q
No. 1	H	H
No. 1a	F	OBn
No. 2	H	4'-Obn
No. 6	OBn	4'-OEt
No. 7	OBn	4'-OBn
No. 8	OBn	4'-F
No. 9	OBn	3'-OMe,4'-OBn
No. 10	OBn	3',4'-OCH_2O-
No. 11	OBn	4'-O-iPr
No. 12	OBn	4'-O-Cp
No. 13	OBn	4'-CF_3
No. 14	OBn	4'-CH_3
No. 15	OBn	4'-Cl
No. 16	OBn	2'-OMe,4'-OMe
No. 17	OBn	3'-OBn
No. 18	OBn	4'-OBn,3'-F
No. 19	OBn	3'-OMe
No. 20	OBn	4'-OCF_3

Method 1

Illustrated For Example No. 7

5-Benzyloxy-2-(4-benzyloxy-phenyl)-3-methyl-1H-indole

A flask was charged with 4-benzyloxyaniline hydrochloride CAS No. [51145-58-5]. (45 g, 0.23 mol), 4'-benzyloxy-2-bromophenylpropiophenone CAS No. [66414-19-5] (21g, 0.066 mol), and 50 mL DMF. The reaction was heated at reflux for 30 minutes and then cooled to rt and then partitioned between 250 mL EtOAc and 100 mL 1N HCl (aq). The EtOAc was washed with $NaHCO_3$ (aq) and brine, then dried over $MgSO_4$. The solution was concentrated and the residue taken up in CH_2Cl_2 and hexanes added to precipitate out 25g of a crude solid. The solid was dissolved in

CH_2Cl_2 and evaporated onto silica gel and chromatographed using CH_2Cl_2/Hexane (1:5) to yield 9.2 g of a tan solid (33%): Mp = 150-152°C; ^1H NMR (DMSO) 10.88 (s, 1 H), 7.56 (d, 2 H, J = 8.8 Hz), 7.48 (d, 4 H, J = 7.9 Hz), 7.42-7.29 (m, 6 H), 7.21 (d, 1 H, J = 7.0 Hz), 7.13 (d, 2 H, J = 8.8 Hz), 7.08 (d, 1 H, J = 2.2 Hz), 6.94 (dd, 1 H, J = 8.8, 2.4 Hz), 5.16 (s, 2 H), 5.11 (s, 2 H), 2.33 (s, 3 H); IR (KBr) 3470, 2880, 2820, 1620 cm^{-1}; MS eI m/z 419.

Method 2 (shown in scheme 8)

Also Illustrated For Example No. 7

Reagents used were same as in method 1 except the additional use of triethylamine in this method. The bromoketone CAS No. [66414-19-5] (50.0 g, 0.16 mol) in 200 mL DMF was treated with the aniline hydrochloride CAS No. [51145-58-5] (44 g, 0.22 mol) and the reaction purged with nitrogen for about 10 minutes. The triethylamine (54.6 mL) was added and the reaction was heated at 120°C for 2 hours. TLC analysis (EtOAc/hexanes) shows the starting material has dissappeared forming a more polar spot. The reaction mixture is allowed to cool down and an additional 48 g of the aniline hydrochloride was added. The reaction was heated to 150°C for 2 hours. An additional 5 grams of the aniline hydrochloride was added and the reaction was heated at 150°C for an additional 30 minutes. The reaction mixture is allowed to cool to room temperature and then poured into approximately 1.5 liters of water and extracted with 2 liters of ethyl acetate. Solids are dissolved with additional ethyl acetate as neccessary. The ethyl acetate layer is washed with 1 liter of 1 N NaOH solution aq., 1 liter of water, brine, then dried over magnesium sulfate and filtered. The organic layers were concentrated down to yield a crude solid which is stirred with 500 mL of methanol and filtered. This solid is then stirred with 500 mL of ethyl ether and filtered. The solid is stirred alternatively with methanol and ether until it is of whitish color and has a melting point similar to that described for No. 7 in method 1. Reaction yields 36 grams of product.

Physical Data for Indoles

The following 3-methyl indoles (No. 1- No. 20) were synthesized according to the procedure outlined in scheme 2 using method 2 using the appropriately substituted bromoketones (prepared as given above) and anilines (commercially available; Aldrich) as starting materials.

Example No. 1 2-Phenyl-3-methyl-1H-indole
Mp = 90 -94°C; ^{1}H NMR (DMSO) 11.13 (s, 1 H), 7.68 - 7.64 (m, 2 H), 7.54 - 7.46 (m, 3 H), 7.37 - 7.32 (m, 2 H), 7.12 - 7.06 (m, 1 H), 7.03 - 6.97 (m, 1 H), 2.40 (s, 3 H); MS eI m/z 207 (M+).

Example No. 1a 5-Flouro-2-(4-benzyloxy-phenyl)-3-methyl-1H-indole
Mp = 143 - 146°C.

Example No. 2 2-(4-Benzyloxy-phenyl)-3-methyl-1H-indole
Mp = 118 - 120°C; ^{1}H NMR (DMSO) 11.03 (s, 1 H), 7.57 (dd, 2 H, J = 2.0 Hz, 6.6 Hz), 7.48 - 7.46 (m, 3 H), 7.44 - 7.28 (m, 4 H), 7.18 - 7.11 (m, 2 H), 7.08 - 7.03 (m, 1 H), 7.0 - 6.95 (m, 1 H), 5.16 (s, 2 H), 2.36 (s, 3 H); MS eI m/z 313 (M+).

Example No. 3 5-Benzyloxy-2-phenyl-3-methyl-1H-indole
Mp = 141-144°C; ^{1}H NMR(DMSO) 10.98 (s, 1 H), 7.65-7.61 (m, 2 H), 7.51-7.44 (m, 4 H), 7.42-7.28 (m, 4 H), 7.23 (d, 1 H, J = 8.8Hz), 7.10 (d, 1 H, J = 2.5Hz), 6.80 (d, 1 H , J = 6.0Hz), 5.10 (s, 2 H), 2.36 (s, 3 H); MS eI m/z 313 (M+).

Example No. 4 5-Benzyloxy-2-(4-methoxy-phenyl)-3-methyl-1H-indole
Mp =158°C; ^{1}H NMR 10.85 (brs, 1 H), 7.56 (d, 2 H, J = 8.8 Hz), 7.48 (d, 2 H, J = 8.3 Hz), 7.45 - 7.36 (m, 2 H), 7.34 -7.28 (m, 1 H), 7.21 (d, 1 H, J = 8.6 Hz), 7.09 - 7.04 (m, 3 H), 6.79 (dd, 1 H, J = 8.8 Hz), 5.11 (s, 2 H), 3.80 (s, 3 H), 2.33 (s, 3 H); IR (KBr) 3400, 2900, 1610 cm^{-1}; MS eI m/z 343 (M+); CHN calcd for $C_{23}H_{21}NO_2$ + 0.25 H_2O.

Example No. 5 5-methoxy-2-(4-methoxy-phenyl)-3-methyl-1H-indole
Mp = 139 - 142°C; ^{1}H NMR (DMSO) 10.85 (s , 1 H), 7.57 (d , 2 H , J = 8.8 Hz), 7.19 (d , 1 H , J = 8.6 Hz), 7.04 (d, 2 H, J = 6.8 Hz), 6.95 (d , 1H , J = 2.2 Hz), 6.71 (dd , 1H , J = 8.5 Hz , J = 2.4 Hz), 3.80 (s , 3 H), 3.76 (s , 3 H), 2.33 (s , 3 H); MS eI m/z 267 (M+); CHN calc for $C_{17}H_{17}NO_2$.

Example No. 6 5-Benzyloxy-2-(4-ethoxy-phenyl)-3-methyl-1H-indole
Mp = 143-145°C;^{1}H NMR (DMSO) 10.86 (s , 1H), 7.54 (d , 2 H, J = 8.5 Hz), 7.46 (d, 2 H , J = 7.3 Hz), 7.41-7.37 (m , 2 H), 7.32-7.30 (m, 1 H), 7.20 (d, 1 H, J = 8.6 Hz), 7.05 (d , 1 H), 7.03 (d, 2 H, J = 8.8 Hz), 6.79 (dd , 1 H, J = 8.6 Hz, J = 2.4 Hz), 5.10 (s, 2 H), 4.07 (q , 2 H, J = 6.8 Hz), 2.32 (s , 3 H), 1.34 (t , 3 H, J = 7.0 Hz); MS eI m/z 357 (M+).

Example No. 8 5-Benzyloxy-2-(4-fluoro-phenyl)-3-methyl) -1H-indole
Mp = 132°C; ^{1}H NMR (DMSO) 11.0 (s, 1 H), 7.68-7.64 (m, 2 H), 7.49-7.47 (m, 2 H), 7.41-7.31 (m, 5 H), 7.23 (d, 1 H, J = 8.8 Hz), 7.10 (d, 1 H, J = 2.4 Hz), 6.82 (dd, 1 H, J = 8.8, 2.4 Hz), 5.11 (s, 2 H), 2.34 (s, 3 H); MS EI m/z 331; CHN calcd for $C_{22}H_{18}FNO$.

Example No. 9 5-Benzyloxy-2-(4-benzyloxy-3-methoxy-phenyl)-3-methyl-1H-indole
Mp = 155 -158°C ; ^{1}H NMR (DMSO) 10.88 (s , 1H), 7.50 - 7.45 (m , 4 H), 7.41 - 7.35 (m ,6H), 7.22 - 7.20 (m , 2 H), 7.14 (s , 2 H) , 7.08 (d , 1H , J = 2.2Hz), 6.78 (dd, 1H, J = 8.5 Hz, J = 2.4Hz), 5.13 (s , 2H) , 5.11(s , 2H), 3.85 (s, 3H), 2.35 (s , 3H); MS eI m/z 449 (M+).

Example No. 10 2-Benzo[1,3]dioxol-5-yl-5-benzyloxy-3-methyl-1H-indole
Mp = 142-145°C; ^{1}H NMR (DMSO) 10.86 (s , 1H), 7.48 (d , 2 H , J = 7.0 Hz), 7.40 - 7.30 (m , 3 H), 7.20 (m , 2 H), 7.10 - 7.05 (m, 3 H), 6.78 (dd, 1 H, J = 8.8 Hz, J = 2.4 Hz), 6.06 (s, 2 H), 5.10 (s, 2 H), 2.31 (s , 3 H); MS eI m/z 357 (M+); CHN calc for $C_{23}H_{19}NO_3$.

Example No. 11 **5-Benzyloxy-2-(4-isopropoxy-phenyl)-3-methyl) -1H-indole**

Mp = 136 - 138°C; ^{1}H NMR (DMSO) 10.86 (s, 1 H), 7.55 - 7.51 (m, 2 H), 7.50 - 7.47 (d, 2 H, J = 7.3 Hz), 7.40 - 7.34 (m, 2 H), 7.39 - 7.28 (m, 1 H), 7.20 (d, 1 H, J = 8.7 Hz), 7.06 (d, 1 H, J = 2.2 Hz), 7.02 (d, 2 H, J = 8.8 Hz), 6.77 (dd, 1 H, J = 2.4 Hz, 8.8 Hz); 5.10 (s, 2 H), 4.68 - 4.62 (m, 1 H), 2.32 (s, 3 H), 1.28 (d, 6 H, J = 6.0 Hz); MS eI m/z 371 (M+).

Example No. 12 **5-Benzyloxy-2-(4-cyclopenyloxy-phenyl)-3-methyl-1H-indole**

Mp = 161 - 167°C; ^{1}H NMR (DMSO) 10.85 (s, 1 H), 7.53 (d, 2 H, J = 8.8 Hz), 7.47 (d, 2 H, J = 8.4 Hz), 7.40 - 7.36 (m, 2 H), 7.33 - 7.28 (m, 1 H), 7.20 (d, 1 H, J = 8.6 Hz), 7.07 (d, 1 H, J = 2.4 Hz), 7.01 (d, 2 H, J = 8.8 Hz), 6.78 (dd, 1 H, J = 8.6 Hz, 2.2 Hz), 5.10 (s, 2 H), 4.88 - 4.84 (m, 1 H), 2.32 (s, 3 H), 1.99 - 1.88 (m, 2 H), 1.78 - 1.69 (m, 4 H), 1.64 - 1.52 (m, 2 H); IR (KBr) 3400, 2920, 1600 cm^{-1}; MS eI m/z 397 (M+); CHN calcd for $C_{27}H_{27}NO_2 + 0.25\ H_2O$.

Example No. 13 **5-Benzyloxy-2-(4-triflouromethyl-phenyl)-3-methyl-1H-indole**

^{1}H NMR (DMSO) 11.0 (br s, 1 H), 7.87 - 7.82 (m, 4 H), 7.48 (d, 2 H, J = 8.8 Hz), 7.44 - 7.35 (m, 2 H), 7.34 - 7.26 (m, 2 H), 7.15 (d, 1 H, J = 2.2 Hz), 6.87 (dd, 1 H, J = 8.6 Hz, 2.4 Hz), 5.12 (s, 2 H), 2.41 (s, 3 H); CHN calcd for $C_{23}H_{18}F_3NO$.

Example No. 14 **5-Benzyloxy-2-(4-methyl-phenyl)-3-methyl-1H-indole**

Mp = 144 - 146°C; ^{1}H NMR (DMSO) 10.91 (s, 1 H), 7.56 - 7.20 (m, 10 H), 7.08 (d, 1 H, J = 2.4 Hz), 6.80 (dd, 1 H, J = 2.4 Hz, 8.6 Hz), 5.11 (s, 2 H), 2.34 (s, 3 H), 2.34 (s, 3 H); MS eI m/z 327(M+).

Example No. 15 **5-Benzyloxy-2-(4-chloro-phenyl)-3-methyl-1H-indole**

Mp = 134-136°C; ^{1}H NMR (DMSO) 11.04 (s , 1H), 7.65 (d , 2H, J = 8.3Hz), 7.53 (d , 2 H , J = 8.5Hz), 7.47 (d , 2 H , J = 6.8 Hz), 7.41 - 7.37 (m , 2H), 7.31 - 7.28 (m , 1H), 7.25 (d , 1H , J = 8.5 Hz), 7.11 (d , 1 H , J = 2.4Hz), 6.82

(dd , 1H , J =8.8 Hz , J = 2.4 Hz), 5.11 (s , 2H), 2.35 (s , 3H); IR (KBr) 3380, 1210 cm^{-1}, Ms eI m/z 347 (M+); CHN calc for $C_{22}H_{18}ClNO_2$.

Example No. 16 5-Benzyloxy-2-(2,4-dimethoxy-phenyl)-3-methyl-1H-indole

Oil; ^1H NMR (DMSO) 10.58 (s, 1 H), 7.50 - 7.18 (m, 7 H), 7.04 (d, 1 H, J = 2.4 Hz), 6.76 (dd, 1 H, J = 2.3 Hz, 8.6 Hz), 6.69 - 6.62 (m, 2 H), 5.11 (s, 2 H), 3.82 (s, 3 H), 3.78 (s, 3 H), 2.12 (s, 3 H).

Example No. 17 5-Benzyloxy-2-(3-benzyloxy-phenyl)-3-methyl-1H-indole

Mp = 83 - 86°C

Exampe No. 18 5-Benzyloxy-2-(4-benzyloxy-3-fluoro-phenyl)-3-methyl-1H-indole

Mp = 135 - 137°C; ^1H NMR (DMSO) 10.94 (s, 1 H), 7.50 - 7.31 (m, 13 H), 7.22 (d, 1 H, J = 8.6 Hz), 7.10 (d, 1 H, J = 2.2 Hz), 6.81 (dd, 1 H, J = 8.6 Hz, 2.2 Hz), 5.23 (s, 2 H), 5.11 (s, 2 H), 2.34 (s, 3 H); MS eI m/Z 437 (M+); CHN calcd for $C_{29}H_{24}FNO_2$.

Example No. 19 5-Benzyloxy-2-(3-methoxy-phenyl)-3-methyl-1H-indole

Mp = 107 - 109°C; ^1H NMR (DMSO) 11.00 (s, 1 H), 7.51 - 7.48 (m, 2 H), 7.43 - 7.20 (m, 7 H), 7.13 - 7.12 (d, 1 H, J = 2.1 Hz), 6.93 - 6.90 (dd, 1 H, J = 2.3 Hz, J = 5.7 Hz), 6.86 - 6.82 (dd, 1 H, J = 2.3 Hz, J = 6.3 Hz), 5.12 (s, 2 H), 3.83 (s, 3 H), 2.38 (s, 3 H); IR (KBr) 3400, 2900, 1600 cm^{-1}; MS eI m/z 343 (M+); CHN calcd for $C_{23}H_{21}NO_2$.

Example No. 20 5-Benzyloxy-3-methyl-2-(4-trifluoromethoxy-phenyl)-1H-indole

Mp = 127 - 128°C; ^1H NMR (DMSO) 11.07 (s, 1 H), 7.77 - 7.74 (dd, 2 H, J = 1.8 Hz, J = 5.0 Hz), 7.50 - 7.48 (d, 4 H, J = 8.3 Hz), 7.42 - 7.25 (m, 4 H), 7.14 - 7.13 (d, 1 H, J = 2.2 Hz), 6.87 - 6.83

(dd, 1 H, J = 2.3 Hz, J = 6.3 Hz), 5.13 (s, 2 H), 2.37 (s, 3 H); IR (KBr) 3360, 1600 cm^{-1}; MS eI m/z 396 (M+); CHN calcd for $C_{23}H_{18}F_3NO_2$.

3-Methylindole acetic acid ethyl esters

Scheme 9

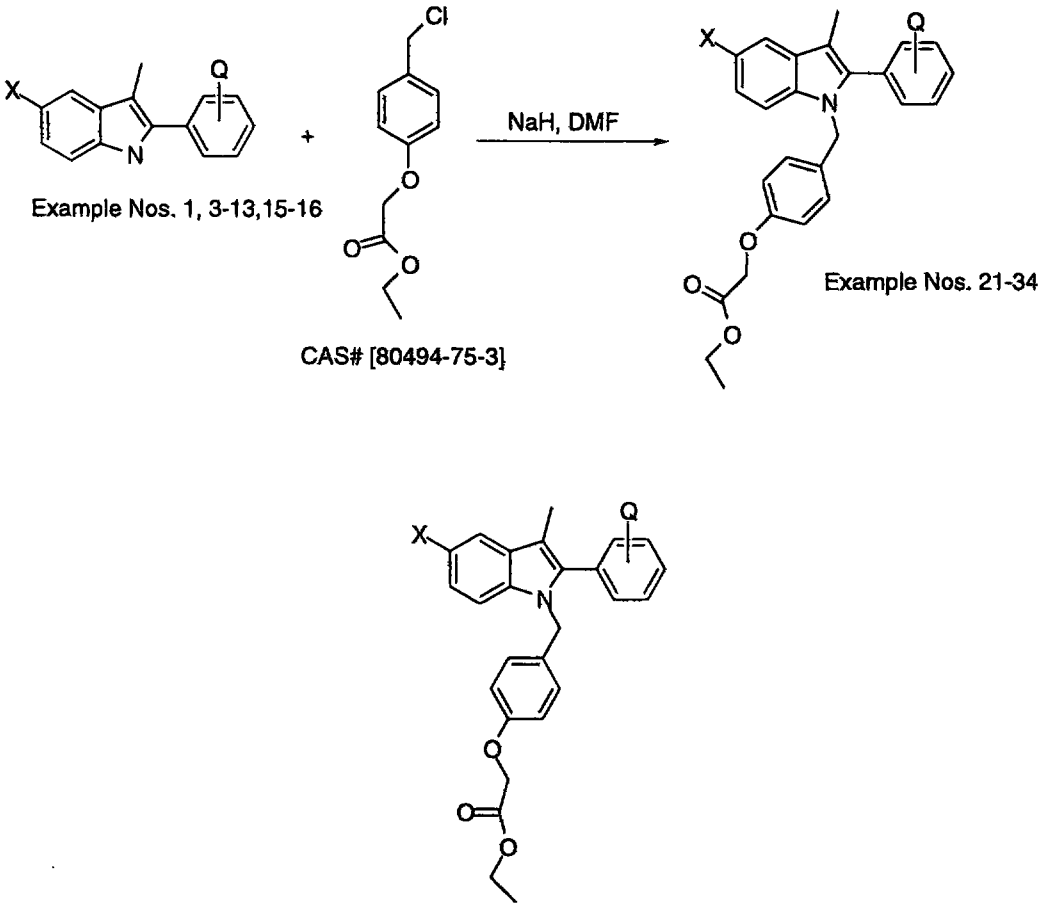


Table 2

Example No.	X	Q
No. 21	H	H
No. 22	OBn	H
No. 23	OBn	4'-OMe
No. 24	OMe	4'-OMe
No. 25	OBn	4'-OEt
No. 26	OBn	4'-OBn
No. 27	OBn	4'-F
No. 28	OBn	3'-OMe,4'-OBn
No. 29	OBn	4'-O-iPr
No. 30	OBn	3',4'-OCH_2O-
No. 31	OBn	4'-OCp
No. 32	OBn	4'-CF_3
No. 33	OBn	4'-Cl
No. 34	OBn	2'-OMe, 4'-OMe

Experimental Procedure For 3-Methylindole Acetic Acid Ethyl Esters Synthesis Method 3 Illustrated For Example No. 26

{4-[5-Benzyloxy-2-(4-benzyloxy-phenyl)-3-methyl-indol-1-ylmethyl]-phenoxy}-acetic acid ethyl ester

A solution of 5-Benzyloxy-2-(4-benzyloxy-phenyl)-3-methyl-1H-indole (indole example No. 7) (32g, 77 mmol) in DMF (0.15 L) was cooled to 0°C and treated with sodium hydride (2.2 g, 89 mmol). The reaction was stirred for 20 minutes and then the benzyl chloride CAS No. [80494-75-3] (29g, 127 mmol) was added and the reaction stirred for 18 hours at room temperature. The reaction mixture was poured into water and extracted with ethyl acetate. The ethyl acetate was washed with brine and dried over magnesium sulfate. The ethyl acetate was concentrated and triturated with ether to obtain 21 g of a white solid. The filtrate was concentrated and triturated with ether to

give an additional 7 g of white solid for a total yield of 28 g: Mp = 129-131°C; ^{1}H NMR (DMSO) 7.47 (d, 4 H, J = 7.2 Hz), 7.39 (q, 4 H, J = 7.9 Hz), 7.36-7.32 (m, 1 H), 7.29 (d, 2 H, J = 8.8 Hz), 7.19 (d, 1 H, J = 9.0 Hz), 7.13-7.09 (m, 4 H), 6.80 (dd, 1 H, J = 8.8, 2.4 Hz), 6.73 (s, 4 H), 5.16 (s, 2 H), 5.13 (s, 2 H), 5.11 (s, 2 H), 4.66 (s, 2 H), 4.11 (q, 2 H, J = 7.2 Hz), 2.15 (s, 3 H), 1.16 (t, 3 H, J = 7.2 Hz); MS eI m/z 612.

Physical Data For Indole Ethyl Esters

The following indole alkylation products were prepared according to scheme 9 using method 3 with the appropriately substituted 3-methyl indole selected from (No. 1- No. 16) as the starting material.

Example No. 21 {4-[2-Phenyl-3-methyl-indol-1-ylmethyl]-phenoxy}-acetic acid ethyl ester

Oil; ^{1}H NMR (DMSO) 7.57 - 7.30 (m, 7 H), 7.13 - 7.02 (m, 2 H), 6.77 - 6.70 (m, 4 H), 5.22 (s, 2 H), 4.65 (s, 2 H), 4.09 (q, 2 H, J = 7.2 Hz), 2.20 (s, 3 H), 1.15 (t, 3 H, J = 7.0 Hz); MS eI m/z 399 (M+).

Example No. 22 {4-[5-Benzyloxy-2-phenyl-3-methyl-indol-1-ylmethyl]-phenoxy}-acetic acid ethyl ester

Oil; ^{1}H NMR(DMSO) 7.50 - 7.40 (m, 10 H), 7.22 (d, 1 H , J = 8.4Hz), 7.14 (d , 1H ,J = 2.5Hz), 6.83 (d, 1 H, J = 2.5 Hz), 6.72 (s , 4 H), 5.18 (s , 2 H), 5.11 (s, 2 H), 4.65 (s, 2 H), 4.10 (q, 2 H, J = 7.2 Hz), 2.16 (s, 3 H), 1.14 (t , 3 H , J = 7.0Hz); MS eI m/z 505 (M+).

Example No. 23 {4-[5-Benzyloxy-2-(4-methoxy-phenyl)-3-methyl-indol-1-ylmethyl]-phenoxy}-acetic acid ethyl ester

Mp = 90 - 96°C; ^{1}H NMR (DMSO) 7.47 (d, 2 H, J = 6.8 Hz), 7.41 - 7.37 (m, 2 H), 7.33 - 7.27 (m, 3 H), 7.19 (d, 1 H, J = 8.8 Hz), 7.12 (d, 1 H, J = 2.4 Hz), 7.03 (d, 2 H, J = 8.8 Hz), 6.80 (dd, 1 H, J = 8.8 Hz, 2.4 Hz), 6.74 (s, 4 H), 5.16 (s, 2 H), 5.11 (s, 2 H), 4.65 (s, 2 H), 4.11 (q, 2 H, J = 7.0 Hz), 3.79 (s, 3 H), 2.15 (s, 3 H), 1.16 (t, 3 H, J = 7.0 Hz); IR (KBr) 2990, 2900, 1760, 1610 cm-1; MS FAB m/z 536 (M+H+).

Example No. 24 **{4-[5-Methoxy-2-(4-methoxy-phenyl)-3-methyl-indol-1-ylmethyl]-phenoxy}-acetic acid ethyl ester**

Mp = 109-113°C; ^{1}H NMR (DMSO) 7.27 (d , 2 H , J = 8.8Hz), 7.17 (d , 1H , J= 8.8 Hz), 7.03 (d , 2 H J = 8.6 Hz) , 6.99 (d , 1 H , J = 2.5 Hz), 6.78 - 6.70 (m , 5 H) , 5.15 (s , 2H), 4.65 (s , 2 H), 4.11 (q , 2 H, J = 7.0 Hz), 3.78 (s , 3 H), 3.76 (s, 3 H), 2.15 (s , 3 H), 1.15 (t , 3 H , J = 7.1 Hz); MS eI m/z 459 (M+).

Example No. 25 **{4-[5-Benzyloxy-2-(4-ethoxy-phenyl)-3-methyl-indol-1-ylmethyl]-phenoxy}-acetic acid ethyl ester**

Mp = 113-115°C; ^{1}H NMR (DMSO) 7.45 (d , 2 H , J =7.3 Hz), 7.40 - 7.25 (m , 5 H), 7.17 (d , 1 H , J =8.8 Hz), 7.11 (d , 1 H , J =2.2 Hz), 7.01 (d , 2 H , J = 6.8 Hz), 6.78 (dd , 1 H , J = 8.8Hz, J = 2.4 Hz), 6.73 (s , 4 H), 5.15 (s, 2 H), 5.10 (s , 2 H), 4.65 (s , 2 H), 4.15 - 4.01 (m , 4 H), 2.14 (s , 3H), 1.33 (t , 3 H, J = 5.7 Hz), 1.16 (t , 3 H, J= 7.1 Hz); MS eI m/z 549 (M+).

Example No. 27 **{4-[5-Benzyloxy-2-(4-flouro-phenyl)-3-methyl-indol-1-ylmethyl]-phenoxy}-acetic acid ethyl ester**

^{1}H NMR (DMSO) 7.50 - 7.15 (m, 16 H), 5.20 (s, 2 H), 5.12 (s, 2 H), 4.62 (s, 2 H), 4.13 (q, 2 H, J = 7.1 Hz), 2.18 (s, 3 H), 1.20 (t, 3 H, J = 7.1 Hz).

Example No. 28 **{4-[5-Benzyloxy-2-(3-methoxy-4-benzyloxy)-3-methyl-indol-1-ylmethyl]-phenoxy}-acetic acid ethyl ester**

Foam; ^{1}H NMR (DMSO) 7.50 - 7.30 (m , 10 H), 7.22 (d, 2H, J = 9.1 Hz), 7.13 (d, 2 H, J = 8.6 Hz), 6.85 - 6.70 (m, 6 H), 5.17 (s, 2H), 5.13 (s, 2H), 5.11 (s, 2 H), 4.66 (s , 2 H), 4.14 (m , 2H), 3.61 (s, 3 H), 2.17 (s, 3 H), 1.16 (t, 3 H, J = 7.0 Hz).

Example No. 29 **{4-[5-Benzyloxy-2-(4-isopropoxy-phenyl)-3-methyl-indol-1-ylmethyl]-phenoxy}-acetic acid ethyl ester**

Oil; ^{1}H NMR (DMSO) 7.46 (d, 2H, J = 7.7 Hz), 7.42 - 7.28 (m, 3 H), 7.25 (d, 2 H, J = 8.7 Hz), 7.17 (d, 1 H, J = 8.7 Hz), 7.11 (d, 1 H, J = 2.4 Hz), 6.99 (d, 2 H, J = 8.6 Hz), 6.79 (dd, 1 H, J = 2.4 Hz, 8.8 Hz), 6.73 (s, 4 H), 5.15 (s, 2 H), 5.10 (s, 2 H), 4.70 - 4.60 (m, 3 H), 4.10 (q, 2 H, J = 7.0 Hz), 2.15

(s, 3 H), 1.27 (d, 6 H, J = 5.9 Hz), 1.16 (t, 3 H, J = 7.1 Hz); MS eI m/z 563 (M+).

Example No. 30 {4-[5-Benzyloxy-2-(3,4-methlyenedioxy-benzyloxy)-3-methyl-indol-1-ylmethyl]-phenoxy}-acetic acid ethyl ester

Oil; ^{1}H NMR (DMSO) 7.45 (d, 2 H, J = 7.0 Hz), 7.37 (m , 2 H), 7.32 (m , 1 H), 7.19 (d , 1H, J = 8.8 Hz), 7.11 (d, 1 H, J = 2.2 Hz), 7.00 (d , 1 H, J = 7.9 Hz), 6.90 (d , 1 H, 5.0 Hz), 6.82 - 6.75 (m , 6H), 6.07 (s , 2H), 5.16 (s , 2 H), 5.10 (s, 2H), 4.65 (s ,2 H), 4.10 (m , 2 H), 2.15 (s , 3 H) , 1.15 (t , 3 H , J = 7.0 Hz); MS eI m/z 549 (M+).

Example No. 31 {4-[5-Benzyloxy-2-(4-cyclopentyloxy-phenyl)-3-methyl-indol-1-ylmethyl]-phenoxy}-acetic acid ethyl ester

Mp = 96-98°C; ^{1}H NMR (DMSO) 7.47 (d, 1 H, J = 7.2 Hz), 7.40 - 7.36 (m, 2 H), 7.33 - 7.30 (m, 1 H), 7.26 (m, 2 H), 7.18 (d, 1 H, J = 8.8 Hz), 7.11 (d, 1 H, J = 2.4 Hz), 6.98 (d, 2 H, J = 8.8 Hz), 6.79 (dd, 1 H, J = 8.8 Hz, 2.4 Hz), 6.74 (s, 5 H), 5.15 (s, 2 H), 5.11 (s, 2 H), 4.86 - 4.80 (m, 1 H), 4.66 (s, 2 H), 4.13 (q, 2 H, J = 7.2 Hz), 2.15 (s, 3 H), 1.98 - 1.85 (m, 2 H), 1.79 - 1.65 (m, 4 H), 1.62 - 1.55 (m, 2 H), 1.16 (t, 3 H, J = 7.0 Hz); IR (KBr) 2950, 2910, 2890, 1760, 1610 cm^{-1}; MS eI m/z 589 (M+); CHN calcd for C:77.39 H:6.67 N: 2.38 Found: C:76.76 H:6.63 N:2.27.

Example No. 32 {4-[5-Benzyloxy-3-methyl-2-(4-trifluoromethyl-phenyl)-indol-1-ylmethyl]-phenoxy}-acetic acid ethyl ester

Mp = 221°C; ^{1}H NMR (DMSO) 7.83 (d, 2 H, J = 8.1 Hz), 7.60 (d, 2 H, J = 7.9 Hz), 7.48 (d, 2 H, J = 8.4 Hz), 7.40 -7.36 (m, 4 H), 7.18 (d, 1 H, J = 2.4 Hz), 6.86 (dd, 1 H, J = 8.8 Hz, 2.4 Hz), 6.72 (s, 4 H), 5.21 (s, 2 H), 5.12 (s, 2 H), 4.65 (s, 2 H), 4.11 (q, 2 H, J = 7.2 Hz), 2.20 (s, 3 H), 1.16 (t, 3 H, J = 7.0 Hz); IR (KBr) 2920, 1730 cm-1; MS eI m/z 573 (M+); CHN calcd for $C_{34}H_{30}F_3NO_4$ + 0.25 H_2O.

Example No. 33 {4-[5-Benzyloxy-2-(4-chlorophenyl)-3-methyl-indol-1-ylmethyl]-phenoxy}-acetic acid ethyl ester

Mp = 99-101°C; ^{1}H NMR (DMSO) 7.52 (d, 2 H, J = 8.6Hz), 7.46 (d, 2 H , J = 6.8 Hz), 7.42 - 7.38 (m ,4 H), 7.36 (m , 1H), 7.25

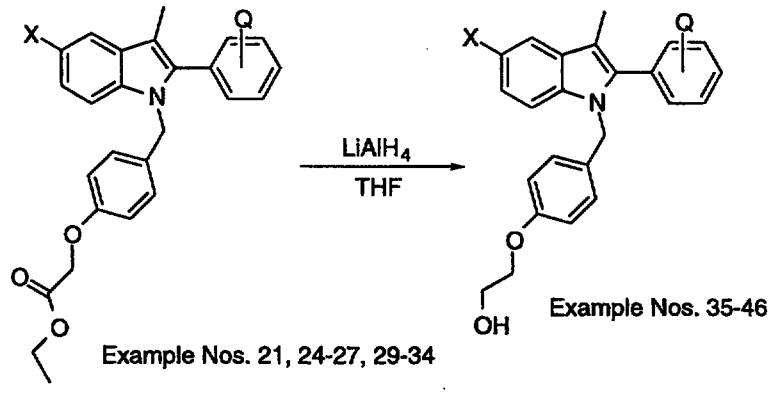
(d ,1 H , J = 9.0Hz),7.14 (d , 1 H , J = 2.4Hz), 6.83 (dd , 1 H , J = 8.8Hz , J = 2.5 Hz), 6.72 (s, 4 H), 5.18 (s , 2 H), 5.11(s , 2 H), 4.65 (s , 2 H), 4.11 (q , 2 H, J = 7.2 Hz), 2.16 (s , 3 H), 1.15 (t , 3H , J = 7.2 Hz); MS eI m/z 539 (M+); CHN calc for $C_{33}H_{30}ClNO_4$.

Example No. 34 **{4-[5-Benzyloxy-2-(2,4-dimethoxy)-3-methyl-indol-1-ylmethyl]-phenoxy}-acetic acid ethyl ester**

Oil; ^1H NMR (DMSO) 7.30 - 6.45 (m, 15 H), 4.95 (s, 2 H), 4.75 - 4.65 (m, 2 H), 4.50 (s, 2 H), 3.97 (q, 2 H, J = 7.1 Hz), 3.65 (s, 3 H), 3.51 (s, 3 H), 1.87 (3 H), 1.01 (t, 3 H, J = 7.1 Hz).

3-Methylindole phenylethanols

Scheme 10



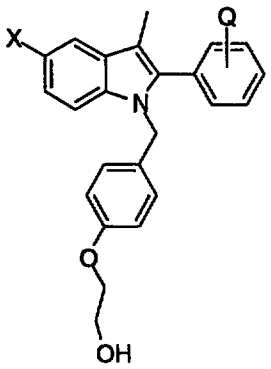


Table 3

Example No.	X	Q
No. 35	H	H
No. 36	OMe	4'-OMe
No. 37	OBn	4'-OEt
No. 38	OBn	4'-OBn
No. 39	OBn	4'-F
No. 40	OBn	3',4'-OCH_2O-
No. 41	OBn	4'-O-iPr
No. 42	OBn	4'-OCp
No. 43	OBn	4'-CF_3
No. 44	OBn	4'-CH_3
No. 45	OBn	4'-Cl
No. 46	OBn	2'-OMe, 4'-OMe

Experimental Procedure For 3-Methylindole Phenethanols Synthesis Method 4

Illustrated For Example No. 38

2-{4-[5-Benzyloxy-2-(4-benzyloxy-phenyl)-3-methyl-indol-1-ylmethyl]-phenoxy}-ethanol

A solution of No. 26 from previous step (5.5 g, 8.8 mmol) in THF (50 mL) was cooled to 0°C and a solution of $LiAlH_4$ (10mL, 1 M) in THF was added dropwise. After 30 minutes at 0°C the reaction was carefully quenched with water, and partitioned between EtOAc and 1 N HCl. The EtOAc was dried with $MgSO_4$, concentrated, and chromatographed on silica gel EtOAc/hexane (2:3) to yield 4.0 g of No. 38 as a white foam: ^1H NMR (DMSO) 7.48-7.46 (m, 4 H), 7.42-7.27 (m, 8 H), 7.20 (d, 1 H, J = 8.8 Hz), 7.12-7.10 (m, 3 H), 6.80 (dd, 1 H, J = 8.8, 2.4 Hz), 6.73 (s, 4 H), 5.15 (s, 2 H), 5.13 (s, 2 H), 5.11 (s, 2 H), 4.80 (t, 1 H, J = 5.5 Hz), 3.86 (t, 2 H, J = 4.8 Hz), 3.63 (q, 2 H, J = 5.3 Hz), 2.15 (s, 3 H).

Physical Data For Indole Phenethanols

Following compounds were made according to scheme 10 and method 4 using the appropriately substituted indole ethyl ester selected from No. 21- No. 34.

Example No. 35 2-{4-[2-phenyl-3-methyl-indol-1-ylmethyl]-phenoxy}-ethanol

Oil; ^{1}H NMR (DMSO) 7.57 - 7.32 (m, 7 H), 7.13 - 7.02 (m, 2 H), 6.74 (s, 4 H), 5.21 (s, 2 H), 4.80 (s, 1 H), 3.86 - 3.83 (m, 2 H), 3.62 (s, 2 H), 2.20 (s, 3 H); MS eI m/z 357 (M+).

Example No. 36 2-{4-[5-methoxy-2-(4-methoxy-phenyl)-3-methyl-indol-1-ylmethyl]-phenoxy}-ethanol

Oil; ^{1}H NMR (DMSO) 7.27 (d, 2 H , J = 8.8Hz),7.17 (d, 1 H, J = 8.8 Hz), 7.03 (d, 2 H J = 8.6 Hz) , 6.99 (d , 1 H , J = 2.5 Hz), 6.78 - 6.70 (m , 5 H) , 5.14 (s, 2 H), 4.80 (brs, 1H), 3.85 (t , 2 H, J = 5.0 Hz), 3.78 (s , 3H), 3.76 (s, 3 H), 3.63 (t , 2H , J = 5.0 Hz), 2.16 (s , 3H); MS eI m/z 417 (M+).

Example No. 37 2-{4-[5-benzyloxy-2-(4-ethoxy-phenyl)-3-methyl-indol-1-ylmethyl]-phenoxy}-ethanol

Foam; ^{1}H NMR (DMSO) 7.45 (d , 2 H , J =7.3 Hz), 7.40 - 7.25 (m , 5 H), 7.17 (d , 1 H , J = 8.8 Hz), 7.11 (d , 1 H , J =2.2 Hz), 7.01 (d , 2 H , J = 6.8 Hz), 6.78 (dd , 1 H , J = 8.8Hz, J = 2.4 Hz), 6.73 (s , 4H), 5.15 (s, 2 H), 5.10 (s , 2H), 4.80 (brs, 1 H), 4.06 (q , 2 H, J = 6.8 Hz), 3.85 (t , 2 H , J = 5.0 Hz), 3.63 (t , 2H , J = 4.8 Hz), 2.14 (s , 3H), 1.33 (t , 3H, J = 6.9 Hz); MS eI m/z 507 (M+).

Example No. 39 2-{4-[5-benzyloxy-2-(4-flouro-phenyl)-3-methyl-indol-1-ylmethyl]-phenoxy}-ethanol

^{1}H NMR (DMSO) 7.40 - 6.60 (m, 16 H), 5.10 (s, 1 H), 5.07 (s, 2 H), 5.02 (s, 2 H), 3.76 (t, 2 H, J = 4.9 Hz), 3.53 (t, 2 H, J = 5.0 Hz), 2.06 (s, 3 H).

Example No. 40 **2-{4-[5-benzyloxy-2-(3,4-methylenedioxy-phenyl)-3-methyl-indol-1-ylmethyl]-phenoxy}-ethanol**

Oil; ^{1}H NMR (DMSO) 7.45 (d, 2 H ,J = 7.0 Hz), 7.37 (m , 2 H), 7.32 (m, 1 H), 7.19 (d, 1H, J = 8.8 Hz), 7.11 (d, 1 H, J = 2.2 Hz), 7.00 (d, 1 H, J = 7.9 Hz), 6.90 (d, 1 H ,5.0 Hz), 6.82 - 6.75 (m , 6H), 6.07 (s , 2 H), 5.16 (s , 2 H), 5.10 (s , 2 H), 3.86 (t , 2 H , J = 5.0 Hz), 3.63 (t , 2 H , J = 5.0 Hz), 2.15 (s, 3 H); MS eI m/z 507 (M+).

Example No. 41 **2-{4-[5-Benzyloxy-2-(4-isopropoxy-phenyl)-3-methyl-indol-1-ylmethyl]-phenoxy}-ethanol**

Foam; ^{1}H NMR (DMSO) 7.46 (d, 2H, J = 7.7 Hz), 7.42 - 7.28 (m, 3 H), 7.25 (d, 2 H, J = 8.7 Hz), 7.17 (d, 1 H, J = 8.7 Hz), 7.11 (d, 1 H, J = 2.4 Hz), 6.99 (d, 2 H, J = 8.6 Hz), 6.79 (dd, 1 H, J = 2.4 Hz, 8.8 Hz), 6.73 (s, 4 H), 5.14 (s, 2 H), 5.10 (s, 2 H), 4.80 (bs, 1 H), 4.70 - 4.60 (m, 1 H), 3.85 (t, 2 H, J = 4.8 Hz), 3.63 (t, 2 H, J = 5.1 Hz), 2.13 (s, 3 H), 1.30 (d, 6 H, J = 5.9 Hz); MS eI m/z 521 (M+).

Example No. 42 **2-{4-[5-Benzyloxy-2-(4-cyclopentyloxy-phenyl)-3-methyl-indol-1-ylmethyl]-phenoxy}-ethanol**

Mp = 129-131°C; ^{1}H NMR (DMSO) 7.47 (d, 2 H, J = 7.2 Hz), 7.38 (t, 2 H, J = 7.2 Hz), 7.33 - 7.28 (m, 1 H), 7.25 (d, 2 H, J = 8.8 Hz), 7.18 (d, 1 H, J = 8.8 Hz), 7.11 (d, 1 H, J = 2.4 Hz), 6.98 (d, 2 H, J = 8.8 Hz), 6.79 (dd, 1 H, J = 8.8 Hz, 2.4 Hz), 6.74 (s, 4H), 5.15 (s, 2 H), 5.11 (s, 2 H), 4.84 - 4.80 (m, 1 H), 4.79 (t, 1 H, J = 5.7 Hz), 3.86 (t, 2 H, J = 4.8 Hz), 3.63 (q, 2 H, J = 5.1 Hz), 2.15 (s, 3 H), 1.96 - 1.87 (m, 2 H), 1.77 - 1.65 (m, 4 H), 1.62 - 1.53 (m, 2 H); IR (KBr) 3490 br, 2920, 1620 cm-1; MS eI m/Z 547 (M+).

Example No. 43 **2-{4-[5-Benzyloxy-2-(4-triflouromethyl-phenyl)-3-methyl-indol-1-ylmethyl]-phenoxy}-ethanol**

Foam; ^{1}H NMR (DMSO) 7.83 (d, 2 H, J = 8.1 Hz), 7.59 (d, 2 H, J = 7.9 Hz), 7.47 (d, 2 H, J = 8.3 Hz), 7.42 - 7.36 (m, 2 H), 7.35 - 7.29 (m, 2 H), 7.18 (d, 1 H, J = 2.4 Hz), 6.87 (dd, 1 H, J = 8.1 Hz, 2.4 Hz), 6.77 - 6.68 (m, 4 H), 5.21 (s, 2 H), 5.12 (s, 2 H), 4.81 (br s, 1 H), 3.85 (t, 2 H, J = 5.1 Hz), 3.63 (t, 2 H, J = 5.1 Hz), 2.19 (s, 3 H); MS eI m/z 531.

Example No. 44 **2-{4-[5-Benzyloxy-2-(4-methyl-phenyl)-3-methyl-indol-1-ylmethyl]-phenoxy}-ethanol**

Oil; ^{1}H NMR (DMSO) 7.46 (d, 2 H, J = 7.2 Hz), 7.45 - 7.18 (m, 8 H), 7.12 (d, 1 H, J = 2.4 Hz), 6.81 (dd, 1 H, J = 2.4 Hz, 8.6 Hz), 6.73 (s, 4 H), 5.15 (s, 2 H), 5.10 (s, 2 H), 4.80 (bs, 1 H), 3.85 (t, 2 H, J = 4.8 Hz), 3.63 (t, 2 H, J = 4.9 Hz), 2.34 (s, 3 H), 2.15 (s, 3 H); MS eI m/z 477 (M+).

Example No. 45 **2-{4-[5-Benzyloxy-2-(4-choro-phenyl)-3-methyl-indol-1-ylmethyl]-phenoxy}-ethanol**

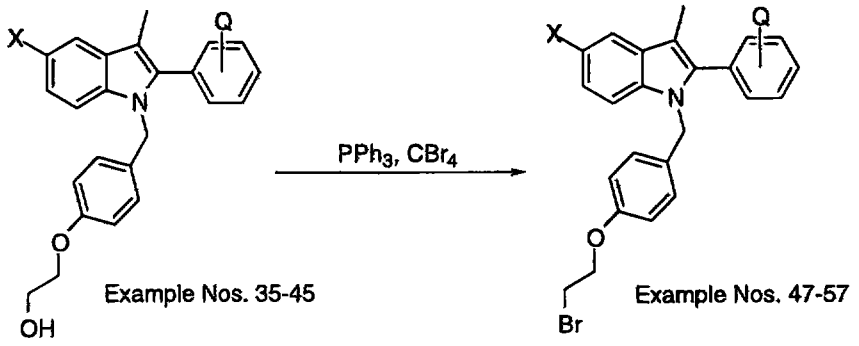
Mp = 110 - 113°C; ^{1}H NMR (DMSO) 7.52 (d , 2 H, J = 8.6Hz), 7.46 (d, 2 H, J = 6.8Hz), 7.38 (m ,4 H), 7.42 - 7.37 (m , 1 H), 7.25 (d, 1 H, J = 9.0Hz), 7.14 (d, 1 H, J = 2.4Hz), 6.83 (dd ,1H, J = 8.8Hz , J = 2.5 Hz), 6.76 - 6.70 (m, 4 H), 5.17 (s , 2 H), 5.11 (s ,2H), 3.85 (t , 2H , J = 5.2Hz), 3.63 (t , 2H , J= 5.0 Hz), 2.16 (s , 3 H); MS eI m/z 497 (M+).

Example No. 46 **2-{4-[5-Benzyloxy-2-(2,4-dimethoxy-phenyl)-3-methyl-indol-1-ylmethyl]-phenoxy}-ethanol**

Oil; ^{1}H NMR (DMSO) 7.46 (d, 2 H, J = 7.5 Hz), 7.39 - 7.35 (m, 2 H), 7.31 - 7.28 (m, 1H), 7.16 - 7.06 (m, 3 H), 6.82 - 6.72 (m, 5 H), 6.68 (d, 1 H, J = 2.2 Hz), 6.61 (dd, 1 H, J = 2.4 Hz, 8.3 Hz), 5.0 (s, 1 H), 4.88 (s, 2 H), 4.85 (d, 1H, J = 6.3 Hz), 4.69 (d, 1 H, J = 6.3 Hz), 3.63 (t, 2 H, J = 6.9 Hz), 3.58 (s, 3 H), 3.46 (s, 3 H), 3.40 (t, 2 H, J = 6.9 Hz), 1.80 (s, 3 H).

Data for 3-methylindole phenylethyl bromides

Scheme 11



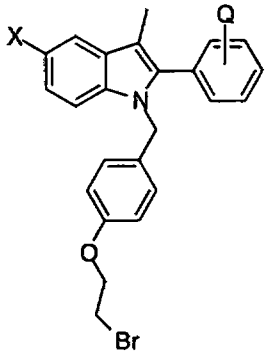


Table 4

Example No.	X	Q
No. 47	H	H
No. 48	OMe	4'-OMe
No. 49	OBn	4'-OEt
No. 50	OBn	4'-OBn

Table 4 (Cont'd)

Example No.	X	Q
No. 51	OBn	4'-F
No. 52	OBn	3',4'-OCH_2O-
No. 52a	OBn	3'-OMe, 4'-OBn
No. 53	OBn	4'-O-iPr
No. 54	OBn	4'-OCp
No. 55	OBn	4'-CF_3
No. 56	OBn	4'-CH_3
No. 57	OBn	4'-Cl

Experimental Procedure For 3-Methylindole Phenethyl bromide Synthesis
Method 5
Illustrated For Example No. 50

Example No. 50
5-Benzyloxy-2-(4-benzyloxy-phenyl)-1-[4-(2-bromo-ethoxy)-benzyl]-3-methyl-1H-indole

To a solution of example No. 38 (3.3 g, 5.8 mmol) in THF (50 mL) was added CBr_4 (2.9 g, 8.7 mmol) and PPH_3 (2.3 g, 8.7 mmol). The reaction was stirred at rt for 3 h and then concentrated and chromatographed on silica gel using a gradient elution from EtOAc/hexane (1:4) to EtOAc to give 3.2 g of a white solid: Mp = 131-134°C; ^1H NMR (DMSO) 7.64-7.30 (m, 10 H), 7.29 (d, 2 H, J = 8.8 Hz), 7.20 (d, 1 H, J = 8.8 Hz), 7.12-7.09 (m, 3 H), 6.80 (dd, 1 H, J = 8.8, 2.4 Hz), 6.77-6.73 (m, 4 H), 5.16 (s, 2 H), 5.13 (s, 2 H), 5.11 (s, 2 H), 4.20 (t, 2 H, J = 5.3 Hz), 3.73 (t, 2 H, J = 5.5 Hz), 2.15 (s, 3 H); MS FAB 631/633 ($M+H^+$, Br present).

Physical Data for Indole Phenethyl Bromides

The following compounds were made according to scheme 11 as described in Method 5 using the appropriately substituted indole selected from No. 35- No. 45.

Example No. 47 **1-[4-(2-bromo-ethoxy)-benzyl]-2-phenyl-3-methyl-1H-indole**

Oil; ^{1}H NMR (DMSO) 7.57 - 7.32 (m, 7 H), 7.13 - 7.02 (m, 2 H), 6.74 (s, 4 H), 5.21 (s, 2 H), 4.19 (t, 2 H, J = 5.2 Hz), 3.71 (t, 2 H, J = 5.5 Hz), 2.20 (s, 3 H); MS eI m/z 419 (M+).

Example No. 48 **5-Methoxy-2-(4-methoxy-phenyl)-1-[4-(2-bromo-ethoxy)-benzyl]-3-methyl-1H-indole**

Oil; ^{1}H NMR (DMSO) 7.27 (d , 2 H , J = 8.8Hz),7.17 (d, 1H, J = 8.8 Hz), 7.03 (d , 2 H J = 8.6 Hz) , 6.99 (d , 1 H , J = 2.5 Hz), 6.80 - 6.69 (m , 5 H) , 5.14 (s, 2H), 4.19 (t , 2H , J = 5.4 Hz), 3.78 (s , 3 H), 3.76 (s , 3 H), 3.72 (t , 2H , J = 5.5 Hz), 2.16 (s , 3H); MS eI m/z 479 (M+).

Example No. 49 **5-Benzyloxy-2-(4-ethoxy-phenyl)-1-[4-(2-bromo-ethoxy)-benzyl]-3-methyl-1H-indole**

Mp = 118-120°C; ^{1}H NMR (DMSO) 7.45 (d , 2 H , J =7.3 Hz), 7.41 - 7.26 (m , 5 H), 7.17 (d , 1 H , J = 8.8 Hz), 7.11 (d , 1 H , J =2.2 Hz), 7.01 (d , 2 H , J = 6.8 Hz), 6.78 (dd , 1 H , J = 8.8Hz, J = 2.4 Hz), 6.78 - 6.74 (m , 4 H), 5.15 (s, 2 H), 5.10 (s , 2 H), 4.22 - 4.18 (m, 2 H), 4.04 (q , 2 H, J = 6.8 Hz), 3.72 (t , 2 H , J = 5.5 Hz), 2.14 (s , 3 H), 1.33 (t , 3 H , J = 7.0Hz); MS eI m/z 569 (M+).

Example No. 51 **5-Benzyloxy-1-[4-(2-bromo-ethoxy)-benzyl]-2-(4-fluoro-phenyl)-3-methyl-1H-indole**

Mp = 114-116°C; ^{1}H NMR (DMSO) 7.47 (m, 2 H), 7.45 - 7.20 (m, 8 H), 7.14 (d, 1 H, J = 2.4 Hz), 6.83 (dd, 1 H, J = 2.7 Hz, 9.0 Hz), 6.80 - 6.70 (m, 4 H), 5.16 (s, 2 H), 5.11 (s, 2H), 4.19 (t, 2 H, J = 5.27 Hz), 3.72 (t, 2 H, J = 6.4 Hz), 2.15 (s, 3 H); MS eI m/z 543 (M+); CHN calc for $C_{31}H_{27}BrFNO_2$.

Example No. 52 **2-Benzo[1,3]dioxyl-5-yl-5-benzyloxy-1-[4-(2-bromo-ethoxy)-benzyl]-3-methyl-1H-indole**

Mp = 133-136°C; ^{1}H NMR (DMSO) 7.45 (d, 2 H, J = 7.0 Hz), 7.41-7.38 (m , 2 H), 7.35-7.30 (m , 1 H), 7.19 (d ,1 H, J = 8.8 Hz), 7.11 (d, 1 H, J = 2.2 Hz), 7.00 (d, 1 H, J = 7.9 Hz), 6.90 (d , 1 H, 1.4 Hz), 6.82 - 6.78 (m, 2H), 6.77 (s, 4 H), 6.07 (s, 2 H), 5.16 (s, 2 H), 5.10 (s, 2 H), 4.20 (t , 2 H, J = 5.5Hz), 3.73 (t , 2H, J = 5.2Hz), 2.15 (s , 3H); MS eI m/z 569 (M+).

Example No. 52a **5-Benzyloxy-1-[4-(2-bromo-ethoxy)-benzyl]-2-(3-methoxy-4-benzyloxy-phenyl)-3-methyl-1H-indole**

Foam; ^{1}H NMR (DMSO) 7.47 - 7.42 (m, 4 H), 7.40 - 7.30 (m, 6 H), 7.20 (d, 1 H, J = 8.8 Hz), 7.12 - 7.10 (m, 2 H), 6.86 - 6.84 (m, 2 H), 6.81 (dd, 1 H, J = 8.8 Hz, 2.4 Hz), 6.78 (s, 4 H), 5.17 (s, 2 H), 5.11 (s, 2 H), 5.10 (s, 2 H), 4.20 (t, 2 H, J = 5.0 Hz), 3.72 (t, 2 H, J = 5.4 Hz), 3.63 (s, 3 H), 2.17 (s, 3 H); MS FAB m/z 662 (M+H+).

Example No. 53 **5-Benzyloxy-1-[4-(2-bromo-ethoxy)-benzyl]-2-(4-isopropoxy-phenyl)-3-methyl-1H-indole**

Mp = 125 - 128°C; ^{1}H NMR (DMSO) 7.46 (d, 2H, J = 7.7 Hz), 7.42 - 7.28 (m, 3 H), 7.25 (d, 2 H, J = 8.7 Hz), 7.17 (d, 1 H, J = 8.7 Hz), 7.11 (d, 1 H, J = 2.4 Hz), 6.99 (d, 2 H, J = 8.6 Hz), 6.79 (dd, 1 H, J = 2.4 Hz, 8.8 Hz), 6.73 (s, 4 H), 5.14 (s, 2 H), 5.10 (s, 2 H), 4.70 - 4.60 (m, 1 H), 4.19 (t, 2 H, J = 5.3 Hz), 3.72 (t, 2 H, J = 4.4 Hz), 2.13 (s, 3 H), 1.30 (d, 6 H, J = 5.9 Hz); MS eI m/z 583 (M+).

Example No. 54 **5-Benzyloxy-1-[4-(2-bromo-ethoxy)-benzyl]-2-(4-cyclopentyloxy-phenyl)-3-methyl-1H-indole**

Mp = 110 - 112°C; 7.47 (d, 2 H, J = 7.0 Hz), 7.38 (t, 2 H, J = 7.0 Hz), 7.35 - 7.28 (m, 1 H), 7.25 (d, 2 H, J = 8.8 Hz), 7.18 (d, 1 H, J = 8.8 Hz), 7.11 (d, 1 H, J = 2.4 Hz), 6.98 (d, 2 H, J = 8.6 Hz), 6.79 (dd, 1 H, J = 8.6 Hz, 2.4 Hz), 6.78 - 6.74 (m, 4 H), 5.16 (s, 2 H), 5.11 (s, 2 H), 4.86 - 4.83 (m, 1 H), 4.20 (t, 2 H, J = 5.3 Hz), 3.73 (t, 2 H, J = 5.5 Hz), 2.15 (s, 3 H), 2.00 - 1.87 (m, 2 H), 1.79 - 1.65 (m, 4 H), 1.63 - 1.56 (m, 2 H); IR (KBr) 2950, 2910, 1610 cm-1; MS eI m/z 609, 611 (M+, Br present).

Example No. 55 **5-Benzyloxy-1-[4-(2-bromo-ethoxy)-benzyl]-3-methyl-2-(4-trifluoromethyl-phenyl)-1H-indole**

Mp = 106 -109°C; ^{1}H NMR (DMSO) 7.83 (d, 2 H, J = 8.1 Hz), 7.60 (d, 2 H, J = 7.9 Hz),7.35 - 7.29 (m, 2 H), 7.48 (d, 2 H, J = 8.6 Hz), 7.39 (t, 2 H, J = 7.0 Hz), 7.18 (d, 1 H, J = 2.2 Hz), 6.87 (dd, 1 H, J = 9.0 Hz, 2.6 Hz), 6.77 - 6.71 (m, 4 H), 5.22 (s, 2 H), 5.12 (s, 2 H), 4.20 (t, 2 H, J = 5.3 Hz), 3.72 (t, 2 H, J = 5.3 Hz), 2.20 (s, 3 H); IR (KBr) 2910, 2850, 1620 cm-1; MS eI m/z 595, 593 (M+)

Example No. 56 **5-Benzyloxy-1-[4-(2-bromo-ethoxy)-benzyl]-3-methyl-2-(4-methyl-phenyl)-1H-indole**

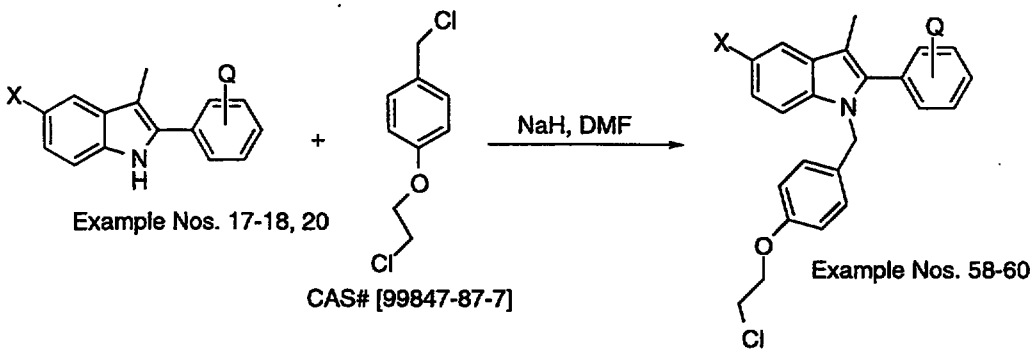
Mp = 82 - 95°C; ^{1}H NMR (DMSO) 7.46 (d, 2 H, J = 7.2 Hz), 7.45 - 7.18 (m, 8 H), 7.12 (d, 1 H, J = 2.4 Hz), 6.81 (dd, 1 H, J = 2.4 Hz, 8.6 Hz), 6.73 (s, 4 H), 5.15 (s, 2 H), 5.10 (s, 2 H), 4.19 (t, 2 H, J = 5.3 Hz), 3.72 (t, 2 H, J = 4.4 Hz), 2.34 (s, 3 H), 2.15 (s, 3 H); MS eI m/z 539 (M+).

Example No. 57 **5-Benzyloxy-1-[4-(2-bromo-ethoxy)-benzyl]-3-methyl-2-(4-chloro-phenyl)-1H-indole**

^{1}H NMR (DMSO) 7.52 (d ,2H, J = 8.6Hz),7.46 (d , 2H , J = 6.8Hz), 7.38 (m ,4 H),7.36 (m , 1H),7.25 (d ,1H , J = 9.0Hz),7.14 (d , 1H , J = 2.4Hz), 6.83 (dd , 1H , J = 8.8Hz , J = 2.5 Hz), 6.72 (m ,4H), 5.17 (s , 2H), 5.11 (s ,2H), 4.19 (t , 2H , J = 5.5 Hz), 3.72 (t , 2H , J = 5.5 Hz), 2.16 (s , 3H); MS eI m/z 559 (M+).

Data for some 3-methylindole phenylethyl chlorides used as intermediates

Scheme 12



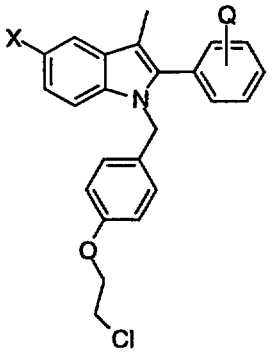


Table 5

Example No.	X	Q
No. 58	OBn	3'-OBn
No. 59	OBn	3'-F, 4'-OBn
No. 60	OBn	4'-OCF_3

Experimental Procedure For 3-Methylindole Phenethylchloride Synthesis

Method 5a

Illustrated For Example No. 58

5-Benzyloxy-2-(3-benzyloxy-phenyl)-1-[4-(2-chloro-ethoxy)-benzyl]-3-methyl-1H-indole

To a solution of 9.7 g (0.0231 mol) of 5-benzyloxy-3-methyl-2-(3-benzyloxy-phenyl)-1H-indole (indole example No. 17) in 80 mL of dry DMF was added 0.85 g of sodium hydride (60% in mineral oil). After allowing this mixture to stir for 30 minutes (until no more bubbling was indicated), 4.8 g of 1-chloromethyl-4-(2-chloro-ethoxy)-benzene CAS No. [99847-87-7] was added. The reaction mixture was allowed to react at room temperature overnight. 200 mL of ethyl acetate were added to the reaction mixture and then washed with water (3 x 100 mL). The organic solution was collected, washed with saturated brine, removed, dried over magnesium sulfate, filtered and evaporated to dryness in a rotary evaporator. The product was recrystallized in ethyl acetate.

Mp = 125 - 127°C; ^{1}H NMR (DMSO) 7.48 - 7.46 (d, 2 H, J = 6.8 Hz), 7.40 - 7.35 (m, 7 H), 7.33 - 7.28 (m, 2 H), 7.23 - 7.21 (d, 1 H, J = 8.8 Hz), 7.13 - 7.12 (d, 1 H, J = 2.2 Hz), 7.07 - 7.04 (m, 1 H), 6.94 - 6.92 (d, 2 H, J = 6.1 Hz), 6.83 - 6.80 (dd, 1 H, J = 2.5 Hz, J = 6.3 Hz), 6.78 - 6.72 (m, 4 H), 5.14 (s, 2 H), 5.11 (s, 2 H), 5.04 (s, 2 H), 4.13 - 4.10 (t, 2 H, J = 5.1 Hz), 3.86 - 3.84 (t, 2 H, J = 5.1 Hz), 2.14 (s, 3 H); IR 3420, 2900 cm^{-1}; MS eI m/z 587 (M+); CHN calcd for $C_{38}H_{34}ClNO_3$.

Physical Data for Indole Phenethyl Chlorides

The following compounds were made according to scheme 12 as described in Method 5a using the appropriately substituted indoles No. 18, No. 20.

Example No. 59 5-Benzyloxy-2-(4-benzyloxy-3-fluoro-phenyl)-1-[4-(2-chloro-ethoxy)-benzyl]-3-methyl-1H-indole

Mp = 88-91°C; ^{1}H NMR (DMSO) 7.49-7.43 (m, 4H), 7.43-7.28 (m, 7H), 7.26-7.21 (m, 2H), 7.13-7.09 (m, 2H), 6.88-6.72 (m, 5H), 5.21 (s, 2H), 5.18 (s, 2H), 5.11

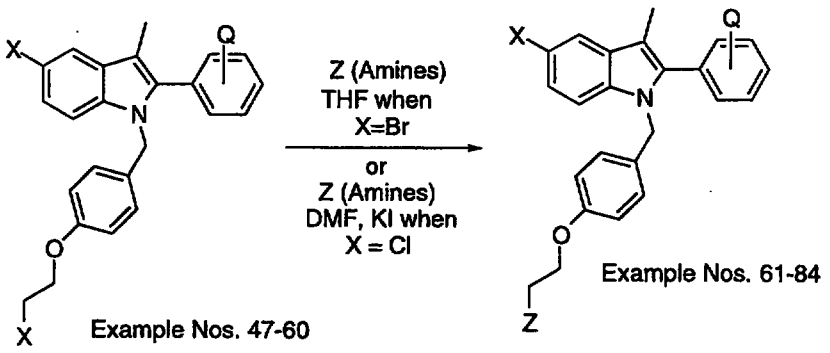
(s, 2H), 4.13 (t, 2H, J = 5.2 Hz), 3.87 (t, 2H, J =5.2 Hz), 2.16 (s, 3H); MS eI m/Z 605 (M+); CHN calcd for $C_{38}H_{33}ClFNO_3$.

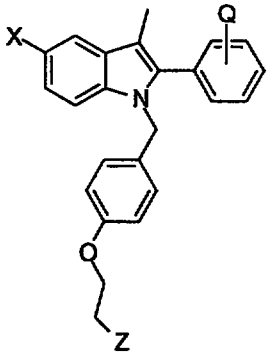
Example No. 60 5-Benzyloxy-1-[4-(2-chloro-ethoxy)-benzyl]-3-methyl-2-(4-trifluoromethoxy-phenyl)-1H-indole

Mp = 108 - 110°C; ^1H NMR (DMSO) 7.49 - 7.48 (m, 6 H), 7.40 - 7.25 (m, 4 H), 7.17 - 7.16 (d, 1 H, J = 2.9 Hz), 6.88 - 6.84 (m, 1 H), 6.77 - 6.72 (m, 4 H), 5.20 (s, 2 H), 5.14 - 5.13 (d, 2 H, J = 2.3 Hz), 4.16 - 4.11 (m, 2 H), 3.89 - 3.84 (m, 2 H), 2.19 - 2.17 (m, 3 H); IR 3400, 2900, 1600 cm^{-1}; MS eI m/z 566 (M+); CHN calcd for $C_{32}H_{27}ClF_3NO_3 + 0.25\ H_2O$.

Aminoethoxy indoles

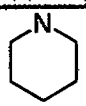
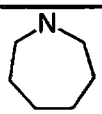
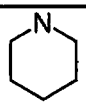
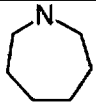
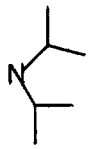
Scheme 13





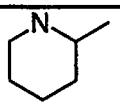
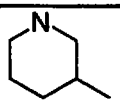
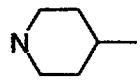
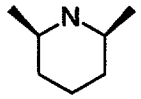
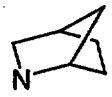
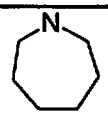
5

Table 6

Example No.	X	Q	Z
No. 61	OBn	4'-OEt	
No. 62	OBn	H	
No. 63	OBn	4'-OBn	
No. 64	OBn	4'-OBn	
No. 65	OBn	4'-OBn	

5

Table 6 (Cont'd)

Example No.	X	Q	Z
No. 66	OBn	4'-OBn	
No. 66a	OBn	4'-OBn	
No. 67	OBn	4'-OBn	
No. 68	OBn	4'-OBn	
No. 69	OBn	4'-OBn	
No. 70	OBn	4'-OBn	
No. 71	OBn	4'-OBn	
No. 71a	OBn	4'-OBn	
No. 72	OBn	4'-F	

5

Table 6 (Cont'd)

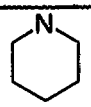
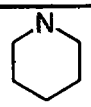
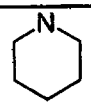
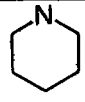
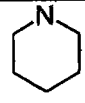
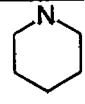
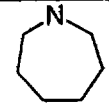
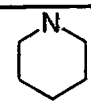
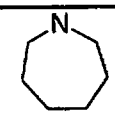
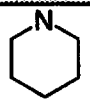
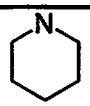
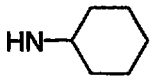
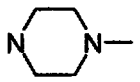
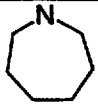
Example No.	X	Q	Z
No. 72a	OBn	4'-F	
No. 72b	OBn	4'-Cl	
No. 73	OBn	3',4'-OCH_2O-	
No. 74	OBn	4'-O-iPr	
No. 75	OBn	4'-CH_3	
No. 76	OBn	3'-OBn	
No. 77	OBn	3'-OBn	
No. 78	OBn	4'-OBn,3'-F	
No. 79	OBn	4'-OBn,3'-F	

Table 6 (Cont'd)

Example No.	X	Q	Z
No. 80	OBn	3'-OMe	
No. 81	OBn	4'-OCF_3	
No. 82	OBn	4'-OBn	
No. 83	OBn	4'-OBn	
No. 84	OBn	3'-OMe	

Experimental Procedure For 3-Methyl aminoethoxyindole Synthesis

Method 6

Illustrated For Example No. 63

Substitution of the Bromide

5-Benzyloxy-2-(4-benzyloxy-phenyl)-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indole

A solution of example No. 50 (3.2 g, 5.0 mmol) in THF (50 mL) was treated with piperidine (5.0 mL, 50 mmol) and heated to reflux. After 5 hours, the reaction mixture was concentrated and taken up in EtOAc, washed with saturated $NaHCO_3$, dried over $MgSO_4$ and column chromatographed on silica gel using a gradient elution of EtOAc/Hexane to EtOAc. The product (2.7 g) was a white solid with a Mp = 93-95°C; ^1H NMR (DMSO) 7.48-7.46 (m, 4 H), 7.42-7.38 (m, 4 H), 7.38-7.32 (m, 2 H), 7.29 (d, 2 H, J = 8.8 Hz), 7.19 (d, 1 H, J = 9.0 Hz), 7.12-7.10 (m, 3 H), 6.80 (dd, 1 H, J = 8.8, 2.4 Hz), 6.73 (s, 4 H), 5.15 (s, 2 H), 5.13 (s, 2 H), 5.11 (s, 2 H), 3.93 (t, 2

H, J = 5.7 Hz), 2.60-2.50 (m, 2 H), 2.41-2.30 (m, 4 H), 2.15 (s, 3 H), 1.47-1.42 (m, 4 H), 1.36-1.32 (m, 2 H); MS FAB 637 ($M+H^+$).

Alternative Procedure

Method 6a

Substitution of chlorides

Synthesis illustrated for product No. 76

Example No. 76 5-Benzyloxy-2-(3-benzyloxy-phenyl)-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indole

To a solution of 1.1 g (0.00953 mol) of 5-benzyloxy-2-(3-benzyloxy-phenyl-1-[4-(2-chloro-ethoxy)-benzyl]-3-methyl-1H-indole (example No. 58) in 10 mL of DMF was added 1.1 mL (0.0112 mol) of piperidine, and 0.93 g (00561 mol) of potassium iodide. The reaction mixture was heated to ~40-50° C for 4 hours. After cooling the reaction mixture to room temperature, 150 mL of ethyl acetate were added and the mixture was washed with water (3 x 100 mL). The organic solution was collected, washed with saturated brine, removed, dried over magnesium sulfate, filtered and evaporated to yield 1.0 g of product of the product after purification.

Mp = 125 - 126°C; ^{1}H NMR (DMSO) 7.48 - 7.45 (d, 2 H, J = 7.2 Hz), 7.41 - 7.35 (m, 7 H), 7.33 - 7.28 (m, 2 H), 7.23 - 7.21 (d, 1 H, J = 9.0 Hz), 7.13 - 7.12 (d, 1 H, J = 2.4 Hz), 7.06 - 7.03 (m, 1 H), 6.95 - 6.91 (m, 2 H), 6.83 - 6.80 (dd, 1 H, J = 2.4 Hz, J = 6.3 Hz), 6.75 - 6.70 (m, 4 H), 5.13 (s, 2 H), 5.11 (s, 2 H), 5.02 (s, 2 H), 3.93 - 3.90 (t, 2 H, J = 6.0 Hz), 2.56 - 2.53 (t, 2 H, J = 5.9 Hz), 2.49 - 2.48 (m, 4 H), 2.14 (s, 3 H), 1.46 - 1.40 (m, 4 H), 1.35 - 1.31 (m, 2 H); IR (KBr) 3400, 2900 cm^{-1}; MS eI m/z 636 (M+); CHN calcd for $C_{43}H_{44}N_2O_3 + 0.25\ H_2O$.

Physical data for the amine substituted compounds

The following compounds were prepared by scheme 13 using method 6. Except for examples No. 76- No. 84 which were prepared using method 6a.

Example No. 61 **5-Benzyloxy-2-(4-ethoxy-phenyl)-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indole**

Mp = 188 - 191°C; ^{1}H NMR (DMSO) 7.45 (d , 2 H , J =7.3 Hz), 7.40 - 7.25 (m , 5 H), 7.17 (d , 1 H , J = 8.8 Hz), 7.11 (d , 1 H , J =2.2 Hz), 7.01 (d , 2 H , J = 6.8 Hz), 6.78 (dd , 1 H , J = 8.8Hz, J = 2.4 Hz), 6.73 (s , 4H), 5.15 (s, 2 H), 5.10 (s , 2H), 4.05 (q, 2H, J = 6.8 Hz), 3.93 (t, 2H , J = 6.0 Hz), 2.55 (t , 2H, J = 5.7 Hz), 2.41 - 2.35 (m , 4 H), 2.14 (s , 3 H), 1.46 - 1.40 (m , 4H), 1.38 - 1.30 (m, 5 H); MS eI m/z 574 (M+).

Example No. 62 **5-Benzyloxy-2-phenyl-3-methyl-1-[4-(2-azepan-1-yl-ethoxy)-benzyl]-1H-indole**

Oil; ^{1}H NMR (DMSO) 7.50-7.43 (m , 4 H), 7.42-7.37 (m , 5 H), 7.33-7.30(m , 1 H), 7.22 (d , 1 H, J = 8.8 Hz), 7.14 (d , 1 H , J = 2.4 Hz), 6.81 (d , 1 H , J = 6.6 Hz), 6.72 (s , 4 H), 5.18 (s, 2 H), 5.11 (s , 2 H), 3.90 (t , 2 H , J = 6.1 Hz), 2.81-2.75 (m , 2 H), 2.68-2.59 (m , 4 H), 2.16 (s , 3 H), 1.58-1.43 (m , 8 H); MS eI m/z 544 (M+).

Example No. 64 **5-Benzyloxy-2-(4-benzyloxy-phenyl)-3-methyl-1-[4-(2-azepan-1-yl-ethoxy)-benzyl]-1H-indole**

Mp = 106 - 107°C; ^{1}H NMR (DMSO) 7.47 (d, 4 H, J = 8.3 Hz), 7.41 - 7.36 (m, 4 H), 7.36 - 7.30 (m, 2 H), 7.29 (d, 2 H, J = 8.8 Hz), 7.19 (d, 1 H, J = 8.8 Hz), 7.14 - 7.10 (m, 3 H), 6.80 (dd, 1 H, J = 8.8 Hz), 6.73 (s, 4 H), 5.15 (s, 2 H), 5.13 (s, 2 H), 5.11 (s, 2 H), 3.90 (t, 2 H, J = 5.9 Hz), 2.76 (t, 2 H, J = 5.9 Hz), 2.64 - 2.56 (m, 4 H), 2.15 (s, 3 H), 1.58 - 1.44 (m, 8 H); MS FAB m/z 651 (M+H+).

Example No. 65 **5-Benzyloxy-2-(4-benzyloxy-phenyl)-3-methyl-1-[4-(2-diisopropylamino-1-yl-ethoxy)-benzyl]-1H-indole**

Mp = 148 - 150°C; ^{1}H NMR (DMSO) 7.47 (d, 4 H, J = 8.3 Hz), 7.41 - 7.36 (m, 4 H), 7.36 - 7.32 (m, 2 H), 7.28 (d, 2 H, J = 8.8 Hz), 7.19 (d, 1 H, J = 9.0 Hz), 7.13 - 7.08 (m, 3 H), 6.80 (dd, 1 H, J = 8.8 Hz, 2.4 Hz), 6.76 - 6.68 (m, 4 H), 5.14 (s, 2 H), 5.13 (s, 2 H), 5.11 (s, 2 H), 3.75 (t, 2 H, J = 7.0 Hz), 2.95 (m, 2 H), 2.67 (t, 2 H, J = 7.0 Hz), 2.15 (s, 3 H), 0.93 (d, 12 H, J = 6.4 Hz); MS FAB m/z 653 (M+H+).

Example No. 66 **5-Benzyloxy-2-(4-benzyloxy-phenyl)-3-methyl-1-[4-(2-butyl-methylamino-1-ylethoxy)-benzyl]-1H-indole**
Mp = 101 - 104°C; ^{1}H NMR (DMSO) 7.45 (d , 4 H ,J = 7.5 Hz) , 7.40 - 7.25 (m , 8 H), 7.19 (d , 1 H ,J = 8.8 Hz), 7.12-7.08 (m , 3 H), 6.80 (dd , 1 H , J = 6.5 Hz, J = 2.4 Hz), 6.72 (s, 4 H), 5.14 (s , 2 H) , 5.13 (s, 2 H), 5.10 (s , 2 H), 3.91 (t , 2 H , J = 5.9 Hz), 2.64-2.59 (m , 2H), 2.35-2.29 (m, 2 H), 2.17 (s , 3 H), 2.14 (s , 3 H), 1.40-1.31 (m , 2 H), 1.25-1.19 (m , 2 H), 0.83 (t , 3 H, 7.2 Hz); MS eI m/z 638 (M+).

Example No. 66a **5-Benzyloxy-2-(4-benzyloxy-phenyl)-3-methyl-1-{4-dimethylamino)-ethoxy]-benzyl}-1H-indole**
Mp = 123-124°C

Example No. 67 **5-Benzyloxy-2-(4-benzyloxy-phenyl)-3-methyl-1-{4-[2-(2-methyl-piperidin-1-yl)-ethoxy]-benzyl}-1H-indole**
Mp = 121°C

Example No. 68 **5-Benzyloxy-2-(4-benzyloxy-phenyl)-3-methyl-1-{4-[2-(3-methyl-piperidin-1-yl)-ethoxy]-benzyl}-1H-indole**
Mp = 90°C

Example No. 69 **5-Benzyloxy-2-(4-benzyloxy-phenyl)-3-methyl-1-{4-[2-(4-methyl-piperidin-1-yl)-ethoxy]-benzyl}-1H-indole**
Mp = 98°C; ^{1}H NMR (DMSO) 7.46 (d, 4 H, J = 7.2 Hz), 7.42 - 7.36 (m, 4 H), 7.36 - 7.31 (m, 2 H), 7.28 (d, 2 H, J = 8.6 Hz), 7.19 (d, 1 H, J = 9.0 Hz), 7.12 - 7.10 (m, 3 H), 6.80 (dd, 1 H, J = 8.8 Hz, 2.4 Hz), 6.73 (s, 4 H), 5.15 (s, 2 H), 5.13 (s, 2 H), 5.11 (s, 2 H), 3.93 (t, 2 H, J = 5.9 Hz), 2.85 - 2.78 (m, 2 H), 2.62 - 2.56 (m, 2 H), 2.15 (s, 3 H), 1.97 - 1.87 (m, 2 H), 1.55 - 1.47 (m, 2 H), 1.30 - 1.20 (m, 1 H), 1.15 - 1.02 (m, 2 H), 0.85 (d, 3 H, J = 6.6 Hz); MS esI m/z 651 (M+1)+.

Example No. 70 **5-Benzyloxy-2-(4-benzyloxy-phenyl)-3-methyl-1{4-[2-((cis)-2,6-Dimethyl-piperidin-1-yl)-ethoxy]-benzyl}-1H-indole**
Mp = 106 - 107°C; ^{1}H NMR (DMSO) 7.46 (d, 4 H, J = 8.1 Hz), 7.42 - 7.36 (m, 4 H), 7.37 - 7.31 (m, 2 H), 7.29 (d, 2 H, J = 8.8 Hz), 7.18 (d, 1 H, J = 8.8 Hz), 7.14 -

7.09 (m, 3 H), 6.80 (dd, 1 H, J = 8.8 Hz, 2.4 Hz), 6.72 (s, 4 H), 5.14 (s, 2 H), 5.13 (s, 2 H), 5.11 (s, 2 H), 3.84 (t, 2 H, J = 7.0 Hz), 2.84 (t, 2 H, J = 6.6 Hz), 2.44 - 2.37 (m, 2 H), 2.15 (s, 3 H), 1.60 - 1.43 (m, 3 H), 1.32 - 1.18 (m, 1 H), 1.16 - 1.06 (m, 2 H), 1.01 (d, 6 H, J = 6.2 Hz).

Example No. 71 **5-Benzyloxy-2-(4-benzyloxy-phenyl)-3-methyl-{4-[2-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]oct-6-yl)-ethoxy]-benzyl}-1H-indole**

Mp = 107°C; MS ESI m/z 705 (M+1)+

Example No. 71a **(1S,4R)-5-Benzyloxy-2-(4-benzyloxy-phenyl)-3-methyl{4-[2-(2-Aza-bicyclo [2.2.1] hept-2-yl)-ethoxy]-benzyl}-1H-indole**

The (1S,2R)- 2-aza-bicyclo [2.2.1] heptane used to substitute the bromide was prepared according to the procedure outlined in Syn. Comm. 26(3), 577-584 (1996).

Mp = 95 - 100°C; ^{1}H NMR (DMSO) 7.32 - 6.55 (m, 21 H), 5.10 - 4.90 (m, 6 H), 3.69 (t, 2 H, J = 5.9 Hz), 2.65 - 2.5 (m, 3 H), 2.10 (s, 2 H), 2.0 (s, 3 H), 1.50 - 1.0 (m, 7 H).

Example No. 72 **5-Benzyloxy-2-(4-flouro-phenyl)-3-methyl-1-[4-(2-azepan-1-yl-ethoxy)-benzyl]-1H-indole**

Oil; ^{1}H NMR (DMSO) 7.50 - 7.43 (m, 2 H), 7.42 - 7.33 (m, 4 H), 7.32 - 7.20 (m, 4 H), 7.13 (d, 1 H, J = 2.4 Hz), 6.83 (dd, 1 H, J = 2.4 Hz, 6.7 Hz), 6.71 (s, 4 H), 5.14 (s, 2 H), 5.11 (s, 2 H), 3.89 (t, 2 H, J = 5.9 Hz), 3.20 (m, 4 H), 2.74 (t, 2 H, J = 6.0 Hz), 2.15 (s, 3 H), 1.60 - 1.40 (m, 8 H); MS eI m/z 562 (M+).

Example No. 72a **5-Benzyloxy-2-(4-flouro-phenyl)-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indole**

Oil; ^{1}H NMR (DMSO) 7.32 - 6.53 (m, 16 H), 5.00 (s, 2 H), 4.96 (s, 2 H), 3.77 (t, 2 H, J = 5.8 Hz), 3.22 - 3.14 (m, 4 H), 2.40 (t, 2 H, J = 5.8 Hz), 2.0 (s, 3 H), 1.29 - 1.17 (m, 6 H).

Example No. 72b **5-Benzyloxy-2-(4-chloro-phenyl)-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indole**

Oil; ^{1}H NMR (DMSO) 7.52 (d, 2 H, J = 8.6 Hz), 7.46 (d, 2 H, J = 6.8 Hz), 7.41 - 7.37 (m, 4 H), 7.35 - 7.29 (m, 1 H), 7.25 (d, 1 H, J = 9.0 Hz), 7.14 (d, 1 H, J = 2.4 Hz), 6.83 (dd, 1 H, J = 8.8 Hz, 2.5 Hz), 6.72 - 6.65 (m, 4 H), 5.16 (s, 2 H), 5.11 (s, 2 H), 3.90 (t, 2 H, J = 5.9 Hz), 2.55 (t, 2 H, J = 6.0 Hz), 2.41 - 2.26 (m, 4 H), 2.16 (s, 3 H), 1.44 - 1.39 (m, 4 H), 1.38 - 1.29 (m, 2 H); MS eI m/z 564 (M+).

Example No. 73 **5-Benzyloxy-2-[3,4-methylenedioxy-phenyl]-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indole**

Foam; ^{1}H NMR (DMSO) 7.45 (d, 2 H ,J = 7.0 Hz), 7.41-7.37 (m, 2 H), 7.33-7.29 (m, 1 H), 7.19 (d, 1H, J = 8.8 Hz), 7.11 (d, 1 H, J = 2.2 Hz), 7.00 (d, 1 H, J = 7.9 Hz), 6.90 (d, 1 H, 1.4 Hz), 6.82 - 6.78 (m , 2H), 6.74 (s, 4 H), 6.07 (s , 2 H), 5.16 (s , 2 H), 5.10 (s , 2 H), 3.93 (t , 2H, J = 6.0 Hz), 2.56 (t , 2 H , J = 6.0Hz), 2.41-2.35 (m , 4H), 2.15 (s , 3H), 1.48-1.41 (m, 4H), 1.38-1.28 (m , 2H); MS eI m/z 574 (M+).

Example No. 74 **5-Benzyloxy-2-[4-isopropoxy-phenyl]-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indole**

Foam; ^{1}H NMR (DMSO) 7.46 (d, 2H, J = 7.7 Hz), 7.42 - 7.28 (m, 3 H), 7.25 (d, 2 H, J = 8.7 Hz), 7.17 (d, 1 H, J = 8.7 Hz), 7.11 (d, 1 H, J = 2.4 Hz), 6.99 (d, 2 H, J = 8.6 Hz), 6.79 (dd, 1 H, J = 2.4 Hz, 8.8 Hz), 6.73 (s, 4 H), 5.14 (s, 2 H), 5.10 (s, 2 H), 4.70 - 4.60 (m, 1 H), 3.92 (t, 2 H, J = 5.7 Hz), 2.55 (t, 2 H, 5.7 Hz), 2.40 - 2.30 (bs, 4 H), 2.15 (s, 3 H), 1.50 - 1.40 (m, 4 H), 1.40 - 1.30 (m, 2 H), 1.28 (d, 6 H, J = 6.2 Hz); MS eI m/z 588 (M+).

Example No. 75 **5-Benzyloxy-2-[4-methyl-phenyl]-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indole**

Oil; ^{1}H NMR (DMSO) 7.46 (d, 2 H, J = 7.2 Hz), 7.45 - 7.18 (m, 8 H), 7.12 (d, 1 H, J = 2.4 Hz), 6.81 (dd, 1 H, J = 2.4 Hz, 8.6 Hz), 6.73 (s, 4 H), 5.15 (s, 2 H), 5.10 (s, 2 H), 3.92 (t, 2 H, J = 5.9 Hz), 2.55 (t, 2 H, J = 5.9 Hz), 2.45 - 2.30 (m, 7 H), 2.10 (s, 3 H), 1.50 - 1.40 (m, 4 H), 1.48 - 1.35 (m, 2 H); MS eI m/z 544 (M+).

Example No. 77 **1-[4-(2-Azepan-1-yl-ethoxy)-benzyl]-5-benzyloxy-2-(3-benzyloxy-phenyl)-3-methyl-1H-indole**

Mp = 103 - 105°C; ^{1}H NMR (DMSO) 7.47 - 7.45 (d, 2 H, J = 8.1 Hz), 7.41 - 7.35 (m, 7 H), 7.32 - 7.29 (t, 2 H, 7.0 Hz), 7.23 - 7.21 (d, 1 H, J = 8.7 Hz), 7.13 - 7.12 (d, 1 H, J = 2.1 Hz), 7.06 - 7.03 (m, 1 H), 6.95 - 6.91 (m, 2 H), 6.83 - 6.80 (m, 1 H), 6.75 - 6.73 (m, 4 H), 5.13 (s, 2 H), 5.11 (s, 2 H), 5.02 (s, 2 H), 3.90 - 3.87 (t, 2 H, J = 6.0 Hz), 2.76 - 2.73 (t, 2 H, J = 6.0 Hz), 2.49 - 2.48 (m, 4 H), 2.13 (s, 3 H), 1.51 (s, 8 H); IR 3400, 2900 cm^{-1}; MS eI m/z 650 (M+); CHN calcd for $C_{44}H_{46}N_2O_3$.

Example No. 78 **5-Benzyloxy-2-(4-benzyloxy-3-fluoro-phenyl)-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indole**

Mp = 125-128°C; ^{1}H NMR (DMSO) 7.50 - 7.45 (m, 4 H), 7.43 - 7.28 (m, 7 H), 7.26 - 7.20 (m, 2 H), 7.14 - 7.09 (m, 2 H), 6.82 (dd, 1 H, J = 2.4 Hz, 8.8 Hz), 6.72 (s, 4 H), 5.21 (s, 2 H), 5.16 (s, 2 H), 5.11 (s, 2 H), 3.94 (t, 2 H, J = 5.8 Hz), 2.62 - 2.56 (m, 2 H), 2.41 - 2.36 (m, 4 H), 2.15 (s, 3 H), 1.45 - 1.40 (m, 4 H), 1.40 - 1.31 (m, 2 H); MS eI m/Z 654 (M+); CHN calcd for $C_{43}H_{43}FN_2O_3$.

Example No. 79 **5-Benzyloxy-2-(4-benzyloxy-3-fluoro-phenyl)-3-methyl-1-[4-(2-azepan-1-yl-ethoxy)-benzyl]-1H-indole**

Mp = 122-124°C; ^{1}H NMR (DMSO) 7.50 - 7.28 (m, 10 H), 7.26 - 7.20 (m, 2 H), 7.15 - 7.10 (m, 2 H), 6.88 - 6.76 (m, 2 H), 6.70 (s, 4 H), 5.22 (s, 2H), 5.16 (s, 2H), 5.11 (s, 2H), 3.92 - 3.86 (m, 2H), 2.82 - 2.65 (m, 2H), 2.65 - 2.55 (m, 4H), 2.15 (s, 3H), 1.60 - 1.4 (m, 8H); MS eI m/Z 668 (M+); CHN calcd for $C_{44}H_{45}FN_2O_3$.

Example No. 80 **5-Benzyloxy-2-(3-methoxy-phenyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-3-methyl-1H-indole**

Mp 86 - 87°C; ^{1}H NMR (DMSO) 7.50 - 7.49 (m, 2 H), 7.46 - 7.31 (m, 4 H), 7.24 - 7.21 (d, 1 H, J = 8.8 Hz), 7.15 - 7.14 (d, 1 H, J = 2.3 Hz), 7.00 - 6.93 (m, 2 H), 6.88 - 6.81 (m, 2 H), 6.75 (s, 4 H), 5.18 (s, 2 H), 5.12 (s, 2 H), 3.96 - 3.92 (t, 2 H, J = 5.9 Hz), 3.71 (s, 3 H), 2.59 - 2.55 (t, 2 H, J = 5.8 Hz), 2.37 (s, 4 H), 2.18 (s, 3 H), 1.49 - 1.42 (m, 4 H), 1.37 - 1.34 (m, 2 H); MS eI m/z 561 (M+); CHN calcd for $C_{37}H_{40}N_2O_3 + 0.25\ H_2O$.

Example No. 81 **5-Benzyloxy-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-2-(4-trifluoromethoxy-phenyl)-1H-indole**

Mp = 107 - 108°C; ^{1}H NMR (DMSO) 7.52 - 7.45 (m, 6 H), 7.41 - 7.26 (m, 4 H), 7.17 - 7.16 (d, 1 H, J = 2.3 Hz), 6.87 - 6.84 (dd, 1 H, J = 2.3 Hz, J = 6.4 Hz), 6.75 - 6.68 (m, 4 H), 5.18 (s, 2 H), 5.13 (s, 2 H), 3.95 - 3.91 (t, 2 H, J = 5.9 Hz), 2.58 - 2.54 (t, 2 H, J = 5.9 Hz), 2.38 - 2.34 (m, 4 H), 2.17 – 2.15 (s, 3 H), 1.49 - 1.42 (m, 4 H), 1.35 - 1.34 (d, 2 H, J = 4.9 Hz); IR 3400, 2900, 1600 cm^{-1}; MS eI m/z 615 (M+); CHN calcd for $C_{37}H_{37}F_3N_2O_3$.

Example No. 82 **(2-{4-[5-Benzyloxy-2-(4-benzyloxy-phenyl)-3-methyl-indol-1-ylmethyl]-phenoxy}-ethyl)-cyclohexyl-amine**

Mp = 87-90°C; ^{1}H NMR (DMSO) 7.46(dd, 4H, J= 6.9Hz, 0.6Hz), 7.42-7.27 (m, 9H), 7.19 (d, 1H, J= 9Hz), 7.14-7.08 (m, 3H), 6.80 (dd, 1H, J= 6.4Hz, 2.4Hz), 6.75- 6.70 (m, 4H), 5.15(s, 2H), 5.13 (s, 2H), 5.13(s, 2H), 3.89 (t, 2H, J= 5.6), 2.84 (m, 2H), 2.48 (m, 1H), 2.14 (s, 3H), 1.80 (m, 2H), 1.65 (m, 2H), 1.61 (m, 1H), 0.96-1.19 (m, 5H); MS eI m/Z 650 (M+); CHN calcd for $C_{44}H_{46}N_2O_4$.

Example No. 83 **5-Benzyloxy-2-(4-benzyloxy-phenyl)-3-methyl-1-{4-methylpiperazin-1-yl)-ethoxy]-benzyl}-1H-indole**

Mp = 88-91°C; ^{1}H NMR (DMSO) 7.47 (m, 4H), 7.26-7.42 (m, 8H), 7.19 (d, 1H, J= 8.8), 7.10-1.12 (m, 3H), 6.80 (q, 1H, J= 6.3Hz, 2.4Hz), 6.73 (m, 4H), 5.15 (s, 2H), 5.13 (s, 2H), 5.11 (s, 2H), 3.94 (t, 2H, J= 5.9Hz), 2.59 (t, 2H), 2.42 (m, 4H), 2.29 (m, 4H), 2.15 (s, 3H), 2.12 (s, 3H); MS eI m/Z 652 (M+); CHN calcd for $C_{43}H_{45}N_3O_3$.

Example No. 84 **1-[4-(2-Azepan-1-yl-ethoxy)-benzyl]-5-benzyloxy-2-(3-methoxy-phenyl)-3-methyl-1H-indole**

Mp = 103 - 105°C; ^{1}H NMR (DMSO) 7.47 - 7.45 (d, 2 H, J = 8.1 Hz), 7.41 - 7.35 (m, 7 H), 7.32 - 7.29 (t, 2 H, 7.0 Hz), 7.23 - 7.21 (d, 1 H, J = 8.7 Hz), 7.13 - 7.12 (d, 1 H, J = 2.1 Hz), 7.06 - 7.03 (m, 1 H), 6.95 - 6.91 (m, 2 H), 6.83 - 6.80 (m, 1 H), 6.75 - 6.73 (m, 4 H), 5.13 (s, 2 H), 5.11 (s, 2 H), 5.02 (s, 2 H), 3.90 - 3.87 (t, 2

H, J = 6.0 Hz), 2.76 - 2.73 (t, 2 H, J = 6.0 Hz), 2.49 - 2.48 (m, 4 H), 2.13 (s, 3 H), 1.51 (s, 8 H); IR 3400, 2900 cm^{-1}; MS eI m/z 650 (M+); CHN calcd for $C_{44}H_{46}N_2O_3$.

Data and procedures for compounds From Table 11 (ER Receptor Data Table, *infra*) of Text

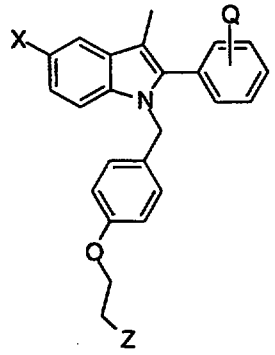
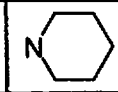
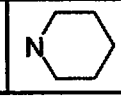
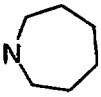
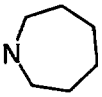
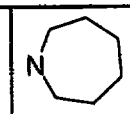
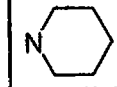
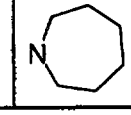


Table 7

Example No.	X	Q	Z
No. 85	H	H	
No. 86	H	4'-OH	

5

Table 7 (Cont'd)

Example No.	X	Q	Z
No. 87	OH	H	
No. 88	OMe	4'-OH	
No. 89	OH	4'-OMe	
No. 90	OMe	4'-OMe	
No. 91	OMe	4'-OMe	
No. 92	OH	4'-OEt	
No. 93	OH	4'-OEt	
No. 94	F	4'-OH	
No. 95	OH	H	
No. 96	OH	4'-OH	
No. 97	OH	4'-OH	
No. 98	OH	4'-OH	

5

Table 7 (Cont'd)

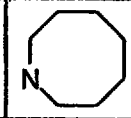
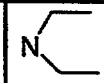
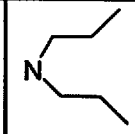
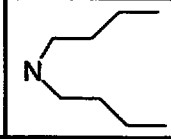
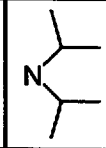
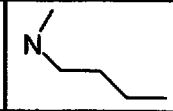
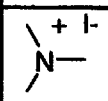
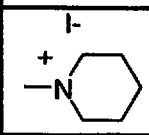
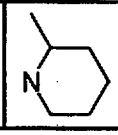
Example No.	X	Q	Z
No. 99	OH	4'-OH	
No. 100	OH	4'-OH	
No. 101	OH	4'-OH	
No. 102	OH	4'-OH	
No. 103	OH	4'-OH	
No. 104	OH	4'-OH	
No. 105	OH	4'-OH	
No. 106	OH	4'-OH	
No. 107	OH	4'-OH	
No. 108	OH	4'-OH	

Table 7 (Cont'd)

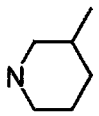
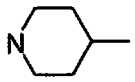
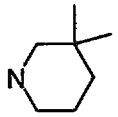
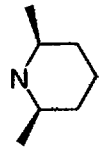
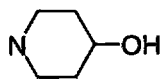
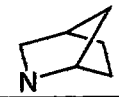
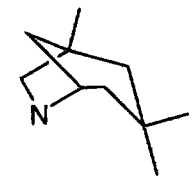
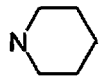
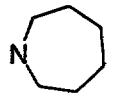
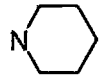
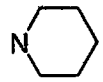
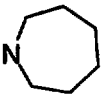
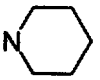
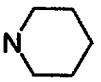
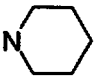
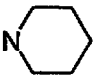
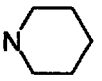
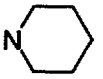
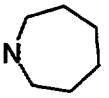
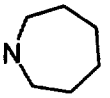
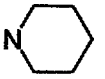
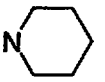
Example No.	X	Q	Z
No. 109	OH	4'-OH	
No. 110	OH	4'-OH	
No. 111	OH	4'-OH	
No. 112	OH	4'-OH	
No. 113	OH	4'-OH	
No. 114	OH	4'-OH	
No. 115	OH	4'-OH	
No. 116	OH	4'-F	
No. 117	OH	4'-F	
No. 118	OH	3'-OMe,4'-OH	
No. 119	OH	3',4'-OCH_2O-	

Table 7 (Cont'd)

Example No.	X	Q	Z
No. 120	OH	4'-O-iPr	
No. 121	OH	4'-O-iPr	
No. 122	OH	4'-O-Cp	
No. 123	OH	4'-CF_3	
No. 124	OH	4'-CH_3	
No. 125	OH	4'-Cl	
No. 126	OH	2',4',-Dimethoxy	
No. 127	OH	3'-OH	
No. 128	OH	3'-OH	
No. 129	OH	4'-OH,3'-F	
No. 130	OH	4'-OH, 3'-F	
No. 131	OH	3'-OMe	
No. 132	OH	4'-OCF_3	

Hydrogenation of Indoles Containing Benzyl Ether(s)
Method 7
Illustrated For Example No. 97

2-(4-Hydroxy-phenyl)-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indol-5-ol

A suspension of 10% Pd/C (1.1 g) in EtOH was treated with a solution of No. 63 (2.2 g, 3.4 mmol) in THF/EtOH. Cyclohexadiene (6.0 mL, 63 mmol) was added and the reaction was stirred for 48 hours. The catalyst was filtered through Celite and the reaction mixture was concentrated and chromatographed on silica gel using a gradient elution of MeOH/CH_2Cl_2 (1:19 to 1:10) to yield 0.8 g of the product as a white solid. Mp =109-113°C; CHN calc'd for $C_{29}H_{32}N_2O_3$ + 0.5 H_2O; ^1H NMR 9.64 (s, 1 H), 8.67 (s, 1 H), 7.14 (d, 2 H, J = 8.6 Hz), 7.05 (d, 1 H, J = 8.6 Hz), 6.84 (d, 2 H, J = 8.8 Hz), 6.79 (d, 1 H, J = 2.2 Hz), 6.74 (s, 4 H), 6.56 (dd, 1 H, J = 8.8, 2.4 Hz), 5.09 (s, 2 H), 3.95-3.93 (m, 2 H), 2.60-2.51 (m, 2 H), 2.39-2.38 (m, 4 H), 2.09 (s, 3 H), 1.46-1.45 (m, 4 H), 1.35-1.34 (m, 2 H); IR (KBr) 3350 (br), 2920, 1620, 1510 cm-1; MS (EI) m/z 456.

Alternatively, the compounds may be dissolved in a THF/EtOH solution (or other appropriate solvent) and hydrogenated with H_2 and 10% Pd/C using either a ballon or Parr Hydrogenator. Either procedure is effective. In many of the examples, the compounds were made into acid addition salts. The procedure for the preparation of an HCl salt is given below (Method 8).

Method 8

1.0 g of Example No. 97 free base from the hydrogenation procedure above in a large test tube was dissolved in 20 mL of MeOH. This was treated with slow addition of 2.6 mL 1.0 N HCl and then 4.0 mL deionized water. The tube was partially opened to the atmosphere to encourage slow evaporation of the solvents. After about ten minutes, crystals began to appear and after 4 hours the solution was filtered and the solid crystals washed with water. The product was present as 0.42 g of white crystalline plates with a melting point of 184-185°C. The mother liquor yielded an

additional crop of 0.30 g of white solid with a melting point of 177-182°C. CHN calc'd for $C_{29}H_{32}N_2O_3$ + HCL + 1 H_2O.

Alternatively, the compounds can be made into quaternary ammonium salts. An example procedure for the synthesis of example No. 107 is given below (Method 9).

Method 9

Example No. 107 2-(4-Hydroxy-phenyl)-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indol-5-ol methiodide

0.8g of example No. 97 was dissolved in 18 mL THF and treated with 2 mL of methyl iodide. The solution was heated to reflux for an hour. The reaction was allowed to come to room temperature and the solids filtered to yield 0.72 g as a crystalline solid. Mp = 214 - 217°C, CHN calcd for $C_{29}H_{32}N_2O_3$ + CH_3I + 0.5 H_2O.

Example No. 106 2-(4-Hydroxy-phenyl)-3-methyl-1-[4-(2-dimethyl-1-yl-ethoxy)-benzyl]-1H-indol-5-ol methiodide was prepared similarly to No. 106 except using No. 100 for starting material: Mp = 245 - 250°C; ^{1}H NMR (DMSO) 9.66 (s, 1 H), 8.69 (s, 1 H), 7.16 (d, 2 H, J = 8.4 Hz), 7.05 (d, 1 H, J = 8.8 Hz), 6.84 (d, 1 H, J = 8.6 Hz), 6.81 - 6.75 (m, 6H), 6.56 (dd, 1 H, J = 2.4 Hz, 8.7 Hz), 5.12 (s, 2 H), 4.34 (m, 2 H), 3.70 (t, 2 H, J = 4.6 Hz), 3.11 (s, 9 H), 2.09 (s, 3 H); IR (KBr) 3250, 1500, 1250; MS eI m/z 416 (M+); CHN calcd for $C_{26}H_{28}N_2O_3$ + 1.09 CH_3I + 0.8 H_2O.

Physical Data for final, deprotected compounds

The following compounds are either free bases, HCl salts or acetate salts. They were prepared according to the procedure outlined in method 7 using the appropriate benzyl ether for precursor. Where a compound from table 1 does not contain a free phenolic functionality, then it was unnecessary to debenzylate it and method 7 not applied. The physical data for these compounds (No. 85, No. 90- No. 91) is still presented below.

Example No. 85 **4-{3-Methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indole} (HCl)**

Mp = 134 - 137°C; ^{1}H NMR (DMSO) 10.33 (s, 1H), 7.56 - 7.38 (m, 6 H), 7.32 (d, 1 H, J = 8.1 Hz), 7.14 - 7.0 (m, 2 H), 6.80 (s, 4 H), 5.24 (s, 2 H), 4.28 (t, 2 H, J = 5.0 Hz), 3.50 - 3.40 (m, 4 H), 3.0 -2.95 (m, 2 H), 2.10 (s, 3 H), 1.80 - 1.60 (m, 5 H), 1.40 - 1.35 (m, 1 H); IR 3400, 2900, 1510, 1250 cm^{-1}; MS (+) FAB m/z 425 $[M+H]^+$; CHN calcd for $C_{29}H_{32}N_2O$ + 1.0 HCl + 1.0 H_2O.

Example No. 86 **4-{3-Methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indol-2-yl}-phenol hydrochloride (HCl)**

Mp = 192 - 194°C; 1H NMR (DMSO), 10.28 (s, 1 H), 9.75 (s, 1 H), 7.51 - 7.49 (m, 1H), 7.27 (dd, 1 H, J = 7.0 Hz, 0.7 Hz), 7.18 (d, 2 H, J = 7.6 Hz), 7.09 - 7.02 (m, 2 H), 6.86 (d, 2 H, J = 8.6 Hz), 6.80 (s, 4 H), 5.20 (s, 2 H), 4.28 (t, 2 H, J = 4.9 Hz), 3.50 - 3.35 (m, 4 H), 3.0 - 2.85 (m, 2 H), 2.20 (s, 3 H), 1.80 - 1.60 (m, 5 H), 1.40 - 1.30 (m, 1 H); IR 3400, 3100, 2600, 1500, 1225 cm^{-1}; MS eI m/z 440 (M+); CHN calc for $C_{29}H_{32}N_2O_2$ + 1 HCl.

Example No. 87 **3-Methyl-2-phenyl-1-[4-(2-piperidine-1-yl-ethoxy)-benzyl]-1H-indol-5-ol (HCl)**

Mp = 228-230°C; ^{1}H NMR 10.1 (brs , 1 H), 8.76 (s, 1 H), 7.55 - 7.45 (m , 5 H),7.10 (d , 1 H , J = 8.8 Hz), 6.85 - 6.80 (m , 5 H), 6.61 (d , 1 H , J = 8.8 Hz), 5.15 (s, 2 H), 4.25 (t , 2 H, J = 4.8 Hz), 3.47-3.35 (m , 4 H), 2.96-2.87 (m , 2 H), 2.12 (s , 3 H), 1.75-1.65 (m , 5 H), 1.31-1.28 (m , 1 H); MS eI m/z 440 (M+); CHN calcd for $C_{29}H_{32}N_2O_2$ + 1 HCL + .33 H_2O; IR (KBr) 3200, 2500, 1450, 1200 cm -1.

Example No. 88 **4-{5-Methoxy-3-methyl-1-{4-[2-(piperidin-1-yl)-ethoxy]-benzyl}-1H-indol-2-yl}-phenol**

Mpt = 87-90°C; ^{1}H NMR (DMSO) 9.67 (s, 1 H), 7.16 (d, 2 H, J = 8.6 Hz), 7.16 (1 H buried), 6.98 (d, 1 H, J = 2.4 Hz), 6.85 (d, 2 H, J= 8.6 Hz), 6.73 (s, 4 H), 6.69 (dd, 1 H, J = 8.8, 2.4 Hz), 5.13 (s, 2 H), 3.94 (t, 2 H, J = 5.7 Hz), 3.76 (s, 3 H), 2.63-2.50 (m, 2 H), 2.43-2.31 (m, 4 H), 2.15 (s, 3 H), 1.49-1.40 (m, 4 H), 1.39-

1.25 (m, 2 H); IR (KBr) 3400 (br), 2920, 1610, 1520 cm^{-1}; MS eI m/z 470; CHN calcd for $C_{30}H_{34}N_2O_3 + 0.1\ H_2O$.

Example No. 89 **2-(4-methoxy-phenyl)-3-methyl-1-{4-[2-(piperidin-1-yl)-ethoxy]-benzyl}-1H-indol-5-ol**

Mp = 188-189°C; ^1H NMR (DMSO) 8.70 (s, 1 H), 7.27 (d, 2 H, J = 8.6 Hz), 7.06 (d, 1 H, J = 8.6 Hz), 7.02 (d, 2 H, J = 8.8 Hz), 6.81 (d, 1 H, J= 2.2 Hz), 6.73 (s, 4 H), 6.58 (dd, 1 H, J = 8.8, 2.4 Hz), 5.10 (s, 2 H), 3.93 (t, 2 H, J = 5.9 Hz), 3.79 (s, 3 H), 2.56 (t, 2 H, J = 5.9 Hz), 2.41-2.32 (m, 4 H), 2.10 (s, 3 H), 1.47-1.41 (m, 4 H), 1.34-1.31 (m, 2 H); MS eI m/z 470; CHN calcd for $C_{30}H_{34}N_2O_3 + 0.1\ H_2O$.

Example No. 90 **5-Methoxy-2-(4-methoxy-phenyl)-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indole (HCL)**

Mp = 188-191°C; ^1H NMR (DMSO) 10.35 (brs , 1 H), 7.27 (d , 2 H , J = 8.8Hz), 7.17 (d , 1H , J= 8.8 Hz), 7.03 (d , 2 H J = 8.6 Hz) , 6.99 (d , 1 H , J = 2.5 Hz), 6.82 - 6.78 (m , 4 H), 6.71 (dd , 1 H , J = 8.8 Hz , J = 2.5 Hz), 5.17 (s, 2 H), 4.31 - 4.22 (m , 2H), 3.79 (s , 3H), 3.76 (s , 3H), 3.43 - 3.36 (m ,4 H), 2.97 - 2.83 (m , 2 H), 2.16 (s, 3 H), 1.80 - 1.59 (m ,5 H) , 1.41 - 1.26 (m , 1H); IR (KBr) 2920 ,1450 , 1250 cm -1; MS eI m/z 484 (M+); CHN calc for $C_{31}H_{36}N_2O_3$ + 1 HCL.

Example No. 91 **1-[4-(2-Azepan-1-yl-ethoxy)-benzyl]-5-methoxy-2-(4-methoxy-phenyl)-3-methyl-1H-indole (HCL)**

Mp = 161-163°C; ^1H NMR (DMSO) 10.65 (brs , 1H), 7.27 (d, 2 H , J = 8.8Hz), 7.17 (d, 1H , J = 8.8 Hz), 7.03 (d, 2 H J = 8.6 Hz) , 6.99 (d , 1 H , J = 2.5 Hz), 6.82 - 6.77 (m, 4 H) ,6.71 (dd, 1 H, J = 8.8 Hz, J = 2.5 Hz), 5.17 (s, 2 H), 4.27 (m, 2H), 3.79 (s, 3H), 3.76 (s, 3H), 3.44 - 3.30 (m, 4 H), 3.17 (m , 2H), 2.16 (s , 3H), 1.82 - 1.77 (m, 4 H), 1.63 - 1.48 (m, 4 H); MS eI m/z 499 (M+); CHN calc for $C_{32}H_{38}N_2O_3$ + 1 HCl.

Example No. 92 **2-(4-Ethoxy-phenyl)-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indol-5-ol**

Mp = 173-175°C ; ^1H NMR (DMSO) 8.69 (s , 1 H), 7.25 (d , 2 H , J = 8.8Hz), 7.04 (d , 1H, J = 8.8 Hz), 6.99 (dd , 2 H , J = 6.8 Hz , J = 2.0 Hz),

6.80 (d , 1 H , J = 2.2 Hz), 6.73 (s ,4H), 6.59 (dd , 1 H , J = 8.5 J = 2.2), 5.09 (s , 2H), 4.05 (q , 2 H, J = 7.03 Hz), 3.93 (t , 2 H , J = 6.0 Hz), 2.62 - 2.56 (m , 2H), 2.41 - 2.36 (m ,4 H), 2.09 (s , 3H), 1.45 - 1.41 (m , 4H), 1.38 - 1.30 (m , 5H); MS eI m/z 484 (M+); CHN calc for $C_{31}H_{36}N_2O_3$ + .25H_2O.

Example No. 93 **1-[4-(2-Azepan-1-yl-ethoxy)-benzyl]-2-(4-ethoxy-phenyl)-3-methyl-1H-indol-5-ol**

Mp = 133-135°C; ^{1}H NMR (DMSO) 8.69 (s , 1 H), 7.25 (d , 2 H , J = 8.8Hz), 7.04 (d , 1H, J = 8.8 Hz), 6.99 (dd , 2 H , J = 6.8 Hz , J = 2.0 Hz), 6.80 (d , 1 H , J = 2.2Hz), 6.73 (s ,4H), 6.59 (dd , 1 H , J = 8.5 Hz, J = 2.2 Hz), 5.09 (s , 2H), 4.05 (q , 2H, J = 7.03 Hz), 3.90 (t , 2H , J = 6.1 Hz), 2.75 (t , 2H , J = 6.0 Hz), 2.62 - 2.58 (m , 4 H), 2.09 (s , 3 H),1.58 - 1.44 (m , 8 H), 1.33 (t , 3H , J = 7.0 Hz); IR (KBr) 2930 , 1470 , 1250 CM^{-1}; MS eI m/z 498 (M+); CHN calc for $C_{32}H_{38}N_2O_3$.

Example No. 94 **4-{5-Fluoro-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indol-2-yl}-phenol (HCl)**

Mp = 223-225°C; ^{1}H NMR (DMSO) 10.30 (br s , 1H), 7.27 - 7.23 (m , 2 H), 7.17 (d , 2 H , J = 8.6 Hz), 6.88 - 6.79 (m , 7H), 5.20 (s , 2H), 4.28 (t , 2H , J = 5.0 Hz), 3.42 - 3.35 (m , 4 H), 3.00 - 2.85 (m , 2 H), 2.14 (s , 3 H), 1.78 - 1.70 (m , 4 H) , 1.67 - 1.59 (m , 1 H), 1.40 - 1.26 (m , 1 H); MS eI m/z 458 (M+).

Example No. 95 **1-[4-(2-Azepan-1-yl-ethoxy)-benzyl]-3-methyl-2-phenyl-1H-indol-5-ol (HCl)**

Mp = 203-204°C ; ^{1}H NMR (DMSO) 10.50 (brs , 1 H), 8.80 (s , 1 H), 7.50 - 7.38 (m, 5 H); 7.10 (d , 1 H, J = 8.8Hz), 6.83 - 6.77 (m , 5 H), 6.60 (d , 1 H , J = 6.6 Hz), 5.15 (s , 2H), 4.26 (t , 2 H , J = 5.2 Hz), 3.45 - 3.35 (m , 4 H), 3.21-3.10 (m , 2 H), 2.12 (s, 3H), 1.85-1.75 (m , 4 H) , 1.70 - 1.51 (m , 4 H); MS eI m/z 454 (M+); CHN calc for $C_{30}H_{34}N_2O_2$ + 1 HCl.

Example No. 96 2-(4-Hydroxy-phenyl)-3-methyl-1-[4-(2-pyrollidin-1-yl-ethoxy)-benzyl]-1H-indol-5-ol

Mp = 105-110°C; CHN calc'd for $C_{28}H_{30}N_2O_3$ + 0.4 H_2O; ^1H NMR (DMSO) 9.65 (s, 1 H), 8.67 (s, 1 H), 7.15 (d, 2 H, J = 8.6 Hz), 7.05 (d, 1 H, J = 8.6 Hz), 6.84 (d, 2 H, J = 2 H), 6.79 (d, 1 H, J = 2.4 Hz), 6.56 (dd, 1 H, J = 8.6, 2.2 Hz), 6.74 (s, 4 H), 5.09 (s, 2 H), 3.95 (t, 2 H, J = 5.7 Hz), 3.39-3.23 (m, 4 H), 2.80-2.75 (m, 2 H), 2.09 (s, 3 H), 1.67-1.64 (m, 4 H); IR (KBr) 3410 (br), 1620, 1510 cm^{-1}; MS (EI) m/z 442

Example No. 97 1-[4-(2-Azepan-1-yl-ethoxy)-benzyl]-2-(4-hydroxy-phenyl)-3-methyl-1H-indol-5-ol (HCl)

Mp = 168 - 171°C; ^1H NMR (DMSO) 10.11 (br s, 1 H), 9.70 (s, 1 H), 8.71 (s, 1 H); 7.15 (d, 2 H, J = 8.6 Hz), 7.05 (d, 1 H, J = 8.8 Hz), 6.85 (d, 2 H, J = 8.8 Hz), 6.80 - 6.77 (m, 5 H), 6.56 (dd, 1 H, J = 8.8 Hz, 2.2 Hz), 5.11 (s, 2 H), 4.26 (t, 2 H, J = 4.6 Hz), 3.48 - 3.30 (m, 4 H), 3.22 - 3.08 (m, 2 H), 2.09 (s, 3 H), 1.83 - 1.76 (m, 4 H), 1.67 - 1.48 (m, 4 H); IR (KBr) 3500 br, 3250 br, 2900, 1610; MS FAB m/z 471 (M+H+); CHN calcd for $C_{30}H_{34}N_2O_3$ + 2.5 H_2O + HCl.

Example No. 98 Acetate Salt of Example No. 97

Made by the precipitation of No. 97 free base from acetone and acetic acid.

Mp = 174 - 178°C

Example No. 99 1-[4-(2-Azocan-1-yl-ethoxy)-benzyl]-2-(4-hydroxy-phenyl)-3-methyl-1H-indol-5-ol

Mp = 98 - 102°C; ^1H NMR (DMSO) 9.63 (s, 1 H), 8.68 (s, 1 H), 7.15 - 7.13 (m, 2 H), 7.05 (d, 1 H, J = 8.5 Hz), 6.83 (dd, 2 H, J = 2.0 Hz, 6.6 Hz), 6.79 (d, 1 H, J = 2.2 Hz), 6.73 (s, 4 H), 6.55 (dd, 1 H, J = 2.2 Hz, 8.6 Hz), 5.08 (s, 2 H), 3.89 (t, 2 H, J = 5.7 Hz), 2.74 (t, 2 H, J = 5.4 Hz), 2.55 (bs, 4 H), 2.08 (s, 3 H), 1.55 (s, 2 H), 1.46 (s, 8 H); IR 3400, 2900, 1250 cm^{-1}; MS ei m/z 484 (M+); CHN calcd for $C_{31}H_{36}N_2O_3$ + .30 H_2O.

Example No. 100 **2-(4-Hydroxy-phenyl)-3-methyl-1-[4-(2-dimethyl-1-yl-ethoxy)-benzyl]-1H-indol-5-ol**

Mp = 95 - 105°C; IR (KBr) 3400 br, 2900, 1610 cm^{-1}; MS eI m/z 416 (M+); CHN calcd for $C_{26}H_{28}N_2O_3$ + 0.5 H_2O.

Example No. 101 **2-(4-Hydroxy-phenyl)-3-methyl-1-[4-(2-diethyl-1-yl-ethoxy)-benzyl]-1H-indol-5-ol**

Mp = 100-107°C; CHN calc'd for C_{28} H_{32} N_2O_3 + 0.25 H_2O; ^1H NMR (DMSO) 9.64 (s, 1 H), 8.67 (s, 1 H), 7.14 (d, 2 H, J = 8.6 Hz), 7.05 (d, 1 H, J = 8.8 Hz), 6.84 (d, 2 H, J = 8.6 Hz), 6.79 (d, 1 H, 2.2 Hz), 6.74 (s, 4 H), 6.56 (dd, 1 H, J = 8.8, 2.4 Hz), 5.09 (s, 2 H), 3.95-3.85 (m, 2 H), 2.80-2.60 (m, 2 H), 2.58-2.40 (m, 4 H), 2.09 (s, 3 H), 0.93 (t, 6 H, J = 7.0 Hz); IR (KBr) 3410 (br), 2950, 1610, 1510 cm^{-1}; MS FAB 445 (M+H+).

Example No. 102 **1-[4-(2-Dipropylamino-ethoxy)-benzyl]-2-(4-hydroxy-phenyl)-3-methyl-1H-indol-5-ol**

Mp = 83 - 86°C; ^1H NMR (DMSO) 9.64 (s, 1 H), 8.67 (s, 1 H), 7.14 (d, 2 H, J = 8.6), 7.04 (d, 1 H, J = 8.6 Hz), 6.83 (d, 2 H, J = 8.6 Hz), 6.78 (d, 1 H, J = 2.2 Hz), 6.72 (m, 4 H), 6.55 (dd, 1 H, J = 2.4 Hz, 8.2 Hz), 5.08 (s, 2 H), 3.88 (t, 2 H, J = 6.0 Hz), 2.80 - 2.63 (m, 2 H), 2.59 - 2.45 (m, 4 H), 2.10 (s, 3 H), 1.41 - 1.30 (m, 4 H), 0.79 (t, 6 H, J = 7.3 Hz); IR 3400, 2900, 1250; MS FAB m/z 473 [M+H+]; CHN calcd for $C_{30}H_{36}N_2O_3$ + .20 H_2O.

Example No. 103 **1-[4-(2-Dibutylamino-ethoxy)-benzyl]-2-(4-hydroxy-phenyl)-3-methyl-1H-indol-5-ol**

Foam; ^1H NMR (DMSO) 9.63 (s, 1H), 8.66 (s , 1 H), 7.15 (d , 2 H, J = 8.6 Hz), 7.05 (d , 1 H , J = 8.8 Hz) , 6.83 (d, 2 H, J = 8.6 Hz), 6.79 (d, 1 H, J = 4.2 Hz), 6.78 - 6.71 (m, 4 H), 6.55 (dd , 1 H , J = 8.6 Hz J = 2.4 Hz), 5.10 (s, 2 H), 3.88 (t , 2 H, J = 5.5 Hz), 2.68-2.62 (m , 2H), 2.42-2.34 (m, 4 H), 2.08 (s , 3 H), 1.38 - 1.19 (m , 8H), 0.82 (t , 6 H, J = 7.2 Hz); IR (KBr) 3400, 1450 cm -1; MS eI m/z 501 (M+).

Example No. 104 **1-[4-(2-Diisopropylamino-ethoxy)-benzyl]-2-(4-hydroxy-phenyl)-3-methyl-1H-indol-5-ol**

Mp = 96 - 102°C; ^{1}H NMR (DMSO) 9.64 (s, 1 H), 8.67 (s, 1 H), 7.14 (d, 2 H, J = 8.6 Hz), 7.04 (d, 1 H, J = 8.6 Hz), 6.83 (d, 2 H, J = 8.6 Hz), 6.79 (d, 1 H, J = 2.4 Hz), 6.77 - 6.69 (m, 4 H), 6.56 (dd, 1 H, J = 8.6 Hz, 2.2 Hz), 5.08 (s, 2 H), 3.75 (t, 2 H, J = 7.0 Hz), 3.01 - 2.92 (m, 2 H), 2.67 (t, 2 H, J = 7.0 Hz), 2.09 (s, 3 H), 0.93 (d, 12 H, 6.6 Hz); IR (KBr) 3400 br, 2940, 1620 cm-1; MS FAB m/z 473 (M+H+); CHN calcd for $C_{30}H_{36}N_2O_3$ + 0.5 H_2O.

Example No. 105 **1-{4-[2-(Butyl-methyl-amino)-ethoxy]-benzyl}-2-(4-hydroxy-phenyl)-3-methyl-1H-indol-5-ol**

Mp = 102-107°C; ^{1}H NMR (DMSO) 9.60 (s , 1H), 8.67 (s, 1H),7.14 (d , 2 H , J = 8.4 Hz), 7.04 (d , 1 H , J = 8.6 Hz), 6.82 (d , 2 H , J = 8.8 Hz), 6.78 (d , 1 H , J= 2.3 Hz), 6.73 (s , 4 H), 6.55 (dd , 1 H , J = 8.8 Hz, J = 2.4 Hz), 5.08 (s , 2 H), 3.92 (t , 2H , J =6.0 Hz), 2.64-2.59 (m , 2 H), 2.38-2.29(m , 2 H), 2.20 (br s, 3 H), 2.08 (s, 3 H), 1.40-1.31 (m , 2 H), 1.25-1.19 (m , 2 H), 0.83 (t , 3 H , 7.2 Hz); IR (KBr) 3420 ,1460 , 1230 cm^{-1}; MS eI m/z 638 (M+).

Example No. 108 **2-(4-Hydroxy-phenyl)-3-methyl-1-{4-[2-(2-methyl-piperidin-1-yl)-ethoxy]-benzyl}-1H-indol-5-ol**

Mp = 121 - 123°C; ^{1}H NMR (DMSO) 9.65 (s, 1 H), 8.68 (s, 1 H), 7.14 (d, 2 H, J = 8.6 Hz), 7.04 (d, 1 H, J = 8.8 Hz), 6.84 (d, 2 H, J = 8.6 Hz), 6.79 (d, 1 H, J = 2.0 Hz), 6.74 (s, 4 H), 6.56 (dd, 1 H, J = 8.8 Hz, 2.4 Hz), 5.09 (s, 2 H), 3.97 - 3.86 (m, 2 H), 2.95 - 2.73 (m, 2 H), 2.62 - 2.53 (m, 1 H), 2.36 - 2.14 (m, 2 H), 2.09 (s, 3 H), 1.61 - 1.30 (m, 4 H), 1.28 - 1.09 (m, 2 H), 0.98 (d, 3 H, J = 5.1 Hz); IR (KBr) 3400, 2920, 2850, 1610 cm^{-1}; CHN calcd for $C_{30}H_{34}N_2O_3$ + 0.25 H_2O.

Example No. 109 **2-(4-Hydroxy-phenyl)-3-methyl-1-{4-[2-(3-methyl-piperdin-1-yl)-ethoxy]-benzyl}-1H-indol-5-ol**

Mp = 121 - 123°C; ^{1}H NMR (DMSO) 9.64 (s, 1 H), 8.67 (s, 1 H), 7.14 (dd, 2 H, J = 8.3 Hz, 1.4 Hz), 7.04 (dd, 1 H, J = 8.6 Hz, 1.2 Hz), 6.84 (dd, 2 H, J = 8.6 Hz, 1.7 Hz), 6.79 (s, 1 H), 6.79 (s, 4 H), 6.56

(d, 1 H, J = 8.6 Hz), 5.08 (s, 2 H), 3.94 (t, 2 H, J = 5.0 Hz), 2.86 - 2.71 (m, 2 H), 2.63 - 2.50 (m, 2 H), 2.48 (s, 3 H), 1.92 - 1.79 (m, 2 H), 1.63 - 1.35 (m, 5 H), 0.79 (d, 3 H, J = 5.2 Hz); IR (KBr) 3400, 2910, 1625 cm^{-1}; CHN calcd for $C_{30}H_{34}N_2O_3$ + 0.25 H_2O.

Example No. 110 **2-(4-Hydroxy-phenyl)-3-methyl-1-{4-[2-(4-methyl-piperidin-1-yl)-ethoxy]-benzyl}-1H-indol-5-ol (HCl)**

Mp = 154 - 162°C; ^1H NMR (DMSO) 10.00 (brs, 1 H), 9.71 (s, 1 H), 8.71 (s, 1 H), 7.15 (d, 2 H, J = 8.6 Hz), 7.05 (d, 1 H, J = 8.6 Hz), 6.85 (d, 2 H, J = 8.6 Hz), 6.83 - 6.77 (m, 4 H), 6.57 (dd, 1 H, J = 8.6 Hz, 2.2 Hz), 5.11 (s, 2 H), 4.27 (t, 2 H, J = 4.8 Hz), 3.51 - 3.35 (m, 4 H), 3.01 - 2.87 (m, 2 H), 2.09 (s, 3 H), 1.74 (d, 2 H, J = 13.4 Hz), 1.61 - 1.37 (m, 4 H), 0.88 (d, 3 H, J = 6.4 Hz); IR (KBr) 3410, 2910, 1620 cm^{-1}; MS el m/z 470 (M+H+); CHN calcd for $C_{30}H_{34}N_2O_3$ + HCl + 2 H_2O.

Example No. 111 **1-{4-[2-(3,3-Dimethyl-piperidin-1-yl)-ethoxy]-benzyl}-2-(4-hydroxy-phenyl)-3-methyl-1H-indol-5-ol**

Mp = 100°C; ^1H NMR (DMSO) 9.65 (s, 1 H), 8.67 (s, 1 H), 7.15 (d, 2 H, J = 8.6 Hz), 7.05 (d, 1 H, J = 8.8 Hz), 6.84 (d, 2 H, J = 8.6 Hz), 6.79 (d, 1 H, J = 2.4 Hz), 6.74 (s, 4 H), 6.56 (dd, 1 H, J = 8.8, 2.4 Hz), 5.09 (s, 2 H), 3.93 (t, 2 H, J = 5.7 Hz), 2.60-2.50 (m, 2 H), 2.37-2.25 (m, 2 H), 2.09 (s, 3 H), 2.10-1.99 (m, 2 H), 1.46 (t, 2 H, J = 5.9 Hz), 1.13 (t, 2 H, J = 6.4 Hz), 0.86 (s, 6 H); MS el m/z 484.

Example No. 112 **1-{4-[2-((cis)-2,6-Dimethyl-piperidin-1-yl)-ethoxy]-benzyl}-2-(4-hydroxy-phenyl)-3-methyl-1H-indol-5-ol**

Mp = 114 - 121°C; ^1H NMR (DMSO) 9.62 (s, 1 H), 8.64 (s, 1 H), 7.11 (d, 2 H, J = 8.6 Hz), 7.01 (d, 1 H, J = 8.6 Hz), 6.81 (d, 2 H, J = 8.8 Hz), 6.76 (d, 1 H, J = 2.2 Hz), 6.72 - 6.66 (m, 4 H), 6.53 (dd, 1 H, J = 8.6 Hz, 2.2 Hz), 5.06 (s, 2 H), 3.86 - 3.72 (m, 2 H), 2.86 - 2.76 (m, 2 H), 2.43 - 2.35 (m, 2 H), 2.06 (s, 3 H), 1.78 - 1.59 (m, 3 H), 1.29 - 1.17 (m, 1 H), 1.12 - 0.92 (m, 8 H); IR (KBr) 3400 br, 2920, 1630 cm-1; MS FAB m/z 485 (M+H+); CHN calcd for $C_{31}H_{36}N_2O_3$ + 0.1 acetone + 0.75 H_2O.

Example No. 113 **2-(4-Hydroxy-phenyl)-1-{4-[2-(4-hydroxy-piperidin-1-yl)-ethoxy]-benzyl}-3-methyl-1H-indol-5-ol**

Mp = 80 - 90°C; 1H NMR (DMSO) 9.66 (s, 1 H), 8.68 (s, 1 H), 7.15 (d, 2 H, J = 7.6 Hz), 7.04 (d, 1 H, J = 8.8 Hz), 6.84 (dd, 2 H, J = 2.0 Hz, 6.6 Hz), 6.78 (d, 1 H, 2.2 Hz), 6.73 (s, 4 H), 6.55 (dd, 1 H, J = 2.2 Hz, 8.6 Hz), 5.09 (s, 2 H), 4.50 (d, 1 H, J = 4.2 Hz), 3.92 (t, 2 H, J = 5.8 Hz), 3.40 (m, 2 H), 2.72 (m, 2 H), 2.60 (m, 2 H), 2.10 (s, 3 H), 2.15-2.05 (m, 1 H), 1.75-1.63 (m, 2 H), 1.42 - 1.28 (m, 2 H); IR (KBr) 3400, 2900, 1250 cm^{-1}; MS eI m/z 472 (M+); CHN calcd for $C_{29}H_{32}N_2O_4$ + .11 CH_2Cl_2.

Example No. 114 **(1S,4R)-1-{4-[2-(2-Aza-bicyclo [2.2.1] hept-2-yl)-ethoxy]-benzyl}-2-(4-hydroxy-phenyl)-3-methyl-1H-indol-5-ol**

Mp = 125 - 130°C; ^1H NMR (DMSO) 9.65 (s, 1 H), 8.67 (s, 1 H), 7.13 (d, 2 H, J = 8.6 Hz), 7.04 (d, 1 H, J = 8.5 Hz), 6.83 (dd, 2 H, J = 2.0 Hz, 6.6 Hz), 6.78 (d, 1 H, J = 2.2 Hz), 6.73 (s, 4 H), 6.55 (dd, 1 H, J = 2.2 Hz, 8.6 Hz), 5.08 (s, 2 H), 3.95 - 3.8 (m, 2 H), 2.90 - 2.70 (3 H), 2.30 - 2.20 (m, 2 H), 2.10 (s, 3 H), 1.70 - 1.60 (m, 1 H), 1.60 - 1.30 (m, 4 H), 1.25 - 1.15 (m, 2 H); IR (KBr) 3400, 2950, 1500; MS (+) FAB m/z 469 $[M+H]^+$; CHN calcd for $C_{30}H_{32}N_2O_3$ + .34 EtOAc.

Example No. 115 **2-(4-Hydroxy-phenyl)-3-methyl-1-{4-[2-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]oct-6-yl)-ethoxy]-benzyl}-1H-indol-5-ol**

Mp = 98 - 100°C; ^1H NMR (DMSO) 9.64 (s, 1 H), 8.67 (s, 1 H), 7.14 (d, 2 H, J = 8.6 Hz), 7.05 (d, 1 H, J = 8.6 Hz), 6.84 (d, 2 H, J = 8.6 Hz), 6.79 (d, 1 H, J = 2.4 Hz), 6.75 - 6.69 (m, 4 H), 6.56 (dd, 1 H, J = 8.6 Hz, 2.4 Hz), 5.08 (s, 2 H), 3.83 (t, 2 H, J= 5.9 Hz), 3.12 - 3.07 (m, 1 H), 2.94 - 2.87 (m, 1 H), 2.85 (d, 1 H, J = 9.2 Hz), 2.78 - 2.70 (m, 1 H), 2.17 (d, 1 H, J = 9.2 Hz), 2.09 (s, 3 H), 1.55 - 1.42 (m, 2 H), 1.29 (q, 2 H, J = 13.6 Hz), 1.14 (s, 3 H), 1.11 - 1.02 (m, 2 H), 0.96 (s, 3 H), 0.82 (s, 3 H); IR (KBr) 3400 br, 2940, 2900, 1630 cm^{-1}; MS ESI m/z 525 (M+H+); CHN calcd for $C_{34}H_{40}N_2O_3$ + 0.5 H_2O.

Example No. 116 **2-(4-Fluoro-phenyl)-3-methyl-1-[4-(2-piperidine-1-yl-ethoxy)-benzyl]-1H-indol-5-ol (HCl)**

Mp = 201 - 203°C; ^1H NMR (DMSO) 10.22 (s, 1 H), 8.78 (s, 1 H), 7.45 - 7.35

(m, 2 H), 7.34 - 7.25 (m, 2 H), 7.11 (d, 1 H, J = 8.6 Hz), 6.90 - 6.70 (m, 5 H), 6.61 (dd, 1 H, J = 2.4 Hz, 8.8 Hz), 5.15 (s, 2 H), 4.27 (t, 2 H, 4.8 Hz), 3.50 - 3.34 (m, 4 H), 3.0 - 2.85 (m, 2 H), 2.10 (s, 3 H), 1.80 (m, 5 H), 1.40 - 1.25 (m, 1 H); MS eI m/z 458 (M+); CHN calcd for $C_{29}H_{31}FN_2O_2$ + 1 HCl.

Example No. 117 **1-[4-(2-Azepan-1-yl-ethoxy)-benzyl]-2-(4-fluoro-phenyl)-3-methyl-1H-indol-5-ol**

Mp = 181 - 184°C; ^{1}H NMR (DMSO) 10.68 (s, 1 H), 8.80 (s, 1 H), 7.50 - 7.36 (m, 2 H), 7.34 - 7.26 (m, 2 H), 7.12 (d, 1 H, J = 8.8 Hz), 6.86 - 6.73 (m, 5 H), 6.63 (dd, 1H, J = 2.2 Hz, 8.5 Hz), 5.13 (s, 2H), 4.29 (t, 2 H, J = 5.2 Hz), 3.50 - 3.30 (m, 4 H), 3.20 - 3.08 (m, 2 H), 2.11 (s, 3 H), 1.90 - 1.70 (m, 4 H), 1.68 - 1.45 (m, 4 H); IR (KBr) 3500, 3100, 2910, 1450, 1250 cm^{-1}; MS e/I m/z 472 (M+); CHN calcd for $C_{30}H_{33}FN_2O_2$ + 1 HCl.

Example No. 118 **2-(3-Methoxy-4-hydroxy-phenyl)-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indol-5-ol (HCl)**

Mp = 161-163°C ; ^{1}H NMR (DMSO) 10.12 (brs, 1H) , 9.25 (s, 1 H), 8.71 (s , 1H), 7.05 (d, 1H , J = 8.5Hz), 6.85 - 6.79 (m, 8 H), 6.57 (dd , 1H , J = 8.5Hz , J = 2.2Hz), 5.13 (s , 2H), 4.27 (t , 2H , J = 5.0Hz), 3.64 (s , 3H), 3.44 - 3.37 (m , 4 H), 2.93 - 2.85 (m , 2H), 2.11 (s , 3H), 1.80 - 1.60 (m , 5 H), 1.40 - 1.25 (m , 1H); MS eI m/z 486 (M+); CHN calc for $C_{30}H_{34}N_2O_4$ + 1HCL + 1 H_2O; IR (KBr) 3190, 1470, 1230 cm^{-1}.

Example No. 119 **2-Benzo[1,3]dioxol-5-yl-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indol-5-ol (HCL)**

Mp = 122-125°C ; ^{1}H NMR (DMSO) 9.80 (brs , 1 H), 8.73 (s , 1 H),7.07 (d , 1 H, J = 8.7 Hz), 7.02 (d , 1 H, J = 8.0 Hz) , 6.89 (d , 1 H,J = 1.7 Hz), 6.80 - 6.75 (m , 6 H), 6.58 (dd , 1 H , J = 6.4 Hz, J = 2.2Hz), 6.06 (s , 2H), 5.13 (s, 2H), 4.30 - 4.19 (m , 2 H), 3.51 - 3.30 (m , 4 H), 2.99-2.85 (m, 2 H), 2.10 (s , 3 H), 1.81-1.59 (m , 5 H), 1.41-1.26 (m , 1 H); MS eI m/z 484(M+); CHN calc for $C_{30}H_{32}N_2O_4$ + HCl +.26 H_2O.

Example No. 120 **2-(4-Isopropoxy-phenyl)-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indol-5-ol (HCl)**

Mp = 120 - 125°C; ^{1}H NMR (DMSO) 10.18 (s, 1 H), 8.73 (s, 1 H), 7.25 (d, 2 H, J = 8.6 Hz), 7.04 (d, 1 H, J = 8.8 Hz), 6.99 (d, 2 H, J = 8.8 Hz), 6.82 - 6.80 (m, 5 H), 6.59 (dd, 1 H, J = 2.2 Hz, 8.6 Hz), 5.12 (s, 2 H), 4.67 - 4.61 (m, 1 H), 4.27 (t, 2 H, J = 4.8 Hz), 3.50 - 3.35 (m, 4 H), 3.0 - 2.85 (m, 2 H), 2.10 (s, 3 H), 1.80 - 1.60 (m, 5 H), 1.40 - 1.25 (m, 7 H); IR (KBr) 3400, 3000, 1500, 1250; MS eI m/z 498 (M+); CHN calcd for $C_{32}H_{38}N_2O_3$ + 1.0 HCl + .70 H_2O.

Example No. 121 **1-[4-(2-Azepan-1-yl-ethoxy)-benzyl]-2-(4-isopropoxy-phenyl)-3-methyl-1H-indol-5-ol (HCl)**

Mp = 120 - 125°C; ^{1}H NMR (DMSO) 10.36 (s, 1 H), 8.73 (s, 1 H), 7.26 - 7.23 (m, 2 H), 7.05 (d, 1 H, J = 8.8 Hz), 7.01 - 6.98 (m, 2 H), 6.85 - 6.75 (m, 5 H), 6.57 (dd, 1 H, J = 2.2 Hz, 8.6 Hz), 5.12 (s, 2 H), 4.67 - 4.61 (m, 1 H), 4.27 (t, 2 H, J = 4.8 Hz), 3.50 - 3.30 (m, 4 H), 3.20 - 3.10 (m, 2 H), 2.10 (s, 3 H), 1.85 - 1.75 (m, 4 H), 1.65 - 1.50 (m, 4 H), 1.27 (d, 6 H, J = 6.1 Hz); IR (KBr) 3400, 1500, 1250: MS eI m/z 512 (M+); Calcd for $C_{33}H_{40}N_2O_3$ + 1.0 HCl + .5 H_2O.

Example No. 122 **2-(4-Cyclopenyloxy-phenyl)-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indol-5-ol**

Mp = 121 - 135°C; ^{1}H NMR (DMSO) 9.80 (br s, 1 H), 8.72 (s, 1 H), 7.24 (d, 2 H, J = 8.8 Hz), 7.05 (d, 1 H, J = 8.8 Hz), 6.98 (d, 2 H, J = 8.8 Hz), 6.83 - 6.78 (m, 5 H), 6.57 (dd, 1 H, J = 8.8 Hz, 2.4 Hz), 5.13 (s, 2 H), 4.86 - 4.82 (m, 1 H), 4.25 (t, 2 H, J = 4.8 Hz), 3.50 - 3.38 (m, 4 H), 2.92 (q, 2 H, J = 8.8 Hz), 2.11 (s, 3 H), 1.98 - 1.85 (m, 2 H), 1.81 - 1.56 (m, 11 H), 1.41 - 1.29 (m, 1 H); IR (KBr) 3400 , 2920, 1620 cm-1; MS eI m/z 524 (M+); CHN calcd for $C_{34}H_{40}N_2O_3$ + 0.5 H_2O.

Example No. 123 **3-Methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-2-(4-trifluoromethyl-phenyl)-1H-indol-5-ol**

Mp = 174°C; ^{1}H NMR (DMSO) 8.8 (s, 1 H), 7.82 (d, 2 H, J = 8.1 Hz), 7.59 (d, 2 H, J = 7.9 Hz), 7.17 (d, 1 H, J = 8.6 Hz), 6.86 (d, 1 H, J = 2.4 Hz), 6.75 - 6.68 (m, 4 H), 6.65 (dd, 1 H, J = 8.8 Hz, 2.4 Hz), 5.16 (s, 2 H), 3.93 (t, 2 H, J = 5.7 Hz), 2.62

- 2.56 (m, 2 H), 2.42 - 2.32 (m, 4 H), 2.15 (s, 3 H), 1.48 - 1.40 (m, 4 H), 1.39 - 1.29 (m, 2 H); IR (KBr) 3410, 2910, 2850, 1620 cm-1; MS eI m/z 508 (M+); CHN calcd for $C_{30}H_{31}F_3N_2O_2$ + 0.25 H_2O.

Example No. 124 **3-Methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-2-p-tolyl-1H-indol-5-ol**

Mp = 162 - 164°C; ^{1}H NMR (DMSO) 8.70 (s, 1 H), 7.28 - 7.24 (m, 4 H), 7.07 (d, 1 H, J = 8,4 Hz), 6.81 (d, 1 H, J = 2.2 Hz), 6.73 (s, 4 H), 6.58 (dd, 1 H, J = 2.4 Hz, 8.8 Hz), 5.11 (s, 2 H), 3.92 (t, 2 H, J = 5.9 Hz), 2.55 (t, 2 H, J = 5.9 Hz), 2.45 - 2.30 (m, 7 H), 2.10 (s, 3 H), 1.50 - 1.40 (m, 4 H), 1.48 - 1.35 (m, 2 H); IR (KBr) 3400, 2900, 1200; MS eI m/z 454 (M+); CHN calcd for $C_{30}H_{34}N_2O_2$.

Example No. 125 **2-(4-Chloro-phenyl)-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indol-5-ol (HCL)**

Mp = 161-164°C; ^{1}H NMR (DMSO) 10.12 (brs , 1H), 8.80 (s , 1H), 7.53 (d , 2H , J = 8.3 Hz), 7.36 (d , 2H , J = 8.8 Hz), 7.12 (d , 1 H , J = 8.8Hz), 6.85-6.75 (m, 5 H), 6.63 (dd , 1H , J = 8.8 Hz , J = 2.4 Hz), 5.14 (s , 2H), 4.29-4.22 (m , 2H), 3.45-3.36 (m , 4 H), 2.97 - 2.84 (m , 2H) , 2.11 (s , 3H), 1.83 - 1.61 (m , 5H), 1.37 - 1.25 (m , 1H); MS eI m/z 475 (M+); CHN calc for $C_{29}H_{31}ClN_2O_2$ +HCL + .25 H_2O.

Example No. 126 **2-(2,4-Dimethoxy-phenyl)-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indol-5-ol**

Mp = 85 - 92°C; ^{1}H NMR (DMSO) 8.62 (s, 1 H), 7.10 (d, 1 H, J = 8.4 Hz), 7.01 (d, 1 H, J = 8.6 Hz), 6.80 - 6.70 (m, 5 H), 6.69 (d, 1 H, 2.2 Hz), 6.59 (dd, 1 H, J = 2.4 Hz, 8.5 Hz), 6.52 (dd, 1 H, J = 2.4 Hz, 8.8 Hz), 5.02 (d, 1 H, J = 6.5 Hz), 4.83 (d, 1 H, J = 6.3 Hz), 4.0 - 3.90 (m, 2 H), 3.80 (s, 3 H), 3.67 (s, 3 H), 2.65 - 2.50 (m, 2 H), 2.45 - 2.30 (m, 4 H), 2.0 (s, 3 H), 1.55 - 1.40 (m, 4 H), 1.39 - 1.30 (m, 2 H); IR (KBr) 3400, 2900, 1520, 1250; MS eI m/z 500 (M+); CHN calcd for $C_{31}H_{36}N_2O_4$ + .05 CH_2Cl_2.

Example No. 127 **2-(3-Hydroxy-phenyl)-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indol-5-ol**

Mp = 115 - 118°C; ^{1}H NMR (DMSO) 9.57 (s, 1 H), 8.71 (s, 1 H), 7.27 - 7.23 (t, 1 H, J = 8.1 Hz), 7.06 - 7.04 (d, 1 H, J = 8.8 Hz), 6.81 - 6.74 (m, 8 H), 6.59 - 6.56 (dd, 1 H, J = 2.3 Hz, J = 6.3 Hz), 5.12 (s, 2 H), 3.94 - 3.91 (t, 2 H, J = 5.9 Hz), 2.57 - 2.54 (t, 2 H, J = 5.8 Hz), 2.36 (s, 4 H), 2.11 (s, 3 H), 1.45 - 1.41 (m, 4 H), 1.34 - 1.33 (m, 2 H); IR (KBr) 3400, 2900 cm^{-1}; MS eI m/z 456 (M+); CHN calcd for $C_{29}H_{32}N_2O_3$ + 1.0 H_2O.

Example No. 128 **1-[4-(2-Azepan-1-yl-ethoxy)-benzyl]-2-(3-hydroxy-phenyl)-3-methyl-1H-indole-5-ol**

Mp = 94 - 97°C; ^{1}H NMR (DMSO) 9.58 (s, 1 H), 8.71 (s, 1 H), 7.27 - 7.23 (t, 1 H, J = 7.9 Hz), 7.07 - 7.04 (d, 1 H, J = 8.7 Hz), 6.81 - 6.74 (m, 8 H), 6.59 - 6.56 (dd, 1 H, J = 2.4 Hz, J = 6.3 Hz), 5.12 (s, 2 H), 3.9 (m, 2 H), 2.80 (s, 2 H), 2.65 (s, 4 H), 2.11 (s, 3 H), 1.54 - 1.50 (m, 8 H); IR 3400, 2900 cm^{-1}; MS eI m/z 470 (M+); CHN calcd for $C_{30}H_{34}N_2O_3$ + 0.75 H_2O + 0.23 Ethyl Acetate.

Example No. 129 **2-(3-Fluoro-4-hydroxy-phenyl)-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indol-5-ol**

Mp = 117-119°C; ^{1}H NMR (DMSO) 10.1 (s, 1H), 8.71 (s, 1H), 7.10 - 6.95 (m, 4 H), 6.80 (d, 1H, J = 2.2Hz), 6.74 (s, 4H), 6.59 (dd, 1H, J = 2.2 Hz, 8.5 Hz), 5.1 (s, 2H), 3.93 (t, 2H, J = 5.9 Hz), 2.56 (t, 2H, J = 5.8 Hz), 2.44 - 2.30 (m, 4H), 2.10 (s, 3 H), 1.45 -1.40 (m, 4H), 1.36 -1.32 (m, 2H); MS eI m/Z 475 (M+); CHN calcd for $C_{29}H_{31}FN_2O_3$.

Example No. 130 **2-(3-Fluoro-4-hydroxy-phenyl)-3-methyl-1-[4-(azepan-1-yl-ethoxy)-benzyl]-1H-indol-5-ol**

Mp = 88 - 91°C; ^{1}H NMR (DMSO) 10.10 (s, 1H), 8.71 (s, 1H), 7.12 - 6.94 (m, 4 H), 6.80(d, 1 H, J = 2.2 Hz), 6.74 (s, 4 H), 6.58 (dd, 1 H, J = 2.2 Hz, 8.5 Hz), 5.10 (s, 2 H), 3.91(t, 2 H, J = 5.9 Hz), 2.76 (t, 2 H, J = 5.9), 2.62 - 2.60 (m, 4H), 2.10 (s, 3H), 1.70 - 1.40 (m, 8 H); MS eI m/Z 488 (M+); CHN calcd for $C_{30}H_{33}FN_2O_3$.

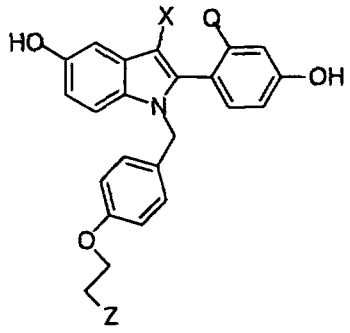
Example No. 131 **2-(3-Methoxy-phenyl)-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indole-5-ol**

Mp = 120 - 123°C; ^{1}H NMR (DMSO) 8.76 (s, 1 H), 7.42 - 7.46 (t, 1 H, J = 7.9 Hz), 7.12 - 7.09 (d, 1 H, J = 8.7 Hz), 6.99 - 6.92 (m, 2 H), 6.86 - 6.83 (m, 2 H), 6.76 (s, 4 H), 6.63 - 6.60 (dd, 1 H, J = 2.1 Hz, J = 6.5 Hz), 5.14 (s, 2 H), 3.96 - 3.92(t, 2 H, J = 5.9 Hz), 3.70 (s, 3 H), 2.59 - 2.55 (t, 2 H, J = 5.9 Hz), 2.37 (s, 4 H), 2.14 (s, 3 H), 1.49 - 1.44 (m, 4 H), 1.35 - 1.34 (m, 2 H); IR 3400, 2950, 1600 cm^{-1}; MS eI m/z 471 (M+); CHN calcd for $C_{30}H_{34}N_2O_3$.

Example No. 132 **3-Methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-2-(4-trifluoromethoxy-phenyl)-1H-indole-5-ol**

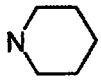
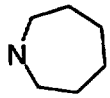
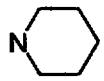
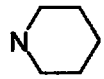
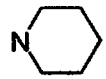
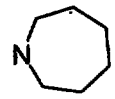
Mp = 122 - 125°C; ^{1}H NMR (DMSO) 8.80 (s, 1 H), 7.51 - 7.45 (m, 4 H), 7.17 - 7.14 (d, 1 H, J = 8.7 Hz), 6.85 - 6.84 (d, 1 H, J = 2.0 Hz), 6.75 - 6.69 (m, 4 H), 6.66 - 6.62 (m, 1 H), 5.14 (s, 2 H), 3.95 - 3.92 (t, 2 H, J = 5.8 Hz), 2.59 - 2.55 (t, 2 H, J = 5.6 Hz), 2.49 - 2.38 (m, 4 H), 2.13 (s, 3 H), 1.47 - 1.44 (m, 4 H), 1.36 - 1.34 (d, 2 H, J = 4.8 Hz); IR 3400, 2900, 1600 cm^{-1}; MS eI m/z 525 (M+); CHN calcd for $C_{30}H_{31}F_3N_2O_3 + 0.25\ H_2O$.

Synthetic procedures and physical data for compounds substituted with chloro, ethyl or cyano groups at the 3-position of the indole



5

Table 8

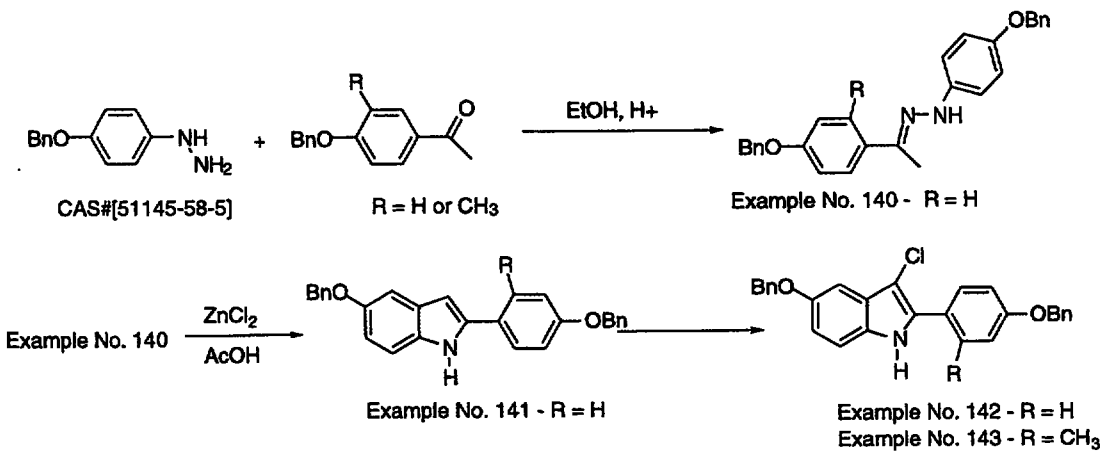
Example No.	X	Q	Z
No. 133	Cl	H	
No. 134	Cl	H	
No. 135	Cl	H	
No. 136	Cl	CH_3	
No. 137	Et	H	
No. 138	CN	H	
No. 139	CN	H	

Synthesis of 3-chloro analogues No. 133- No. 136

10

Scheme 14

Synthesis of 3-chloroindole



Example No. 140 Formation of hydrazone

4-Benzyloxyphenylhydrazine CAS No. [51145-58-5] (50.0 g, 233.4 mmol) was mixed with 4-benzyloxyacetophenone CAS No. [54696-05-8] (63.0 g, 280.0 mmol) in pure ethanol (800 mL). A catalytic amount of acetic acid (5 drops) was added. The reaction was heated to reflux for 2.5 hrs. During the course of refluxing, the condensed product solidified out of the hot solution. The reaction was cooled down to rt. The desired product was collected by vacuum filtration as a light yellow solid (85 g, 86%). Mp = 165-174°C; ^{1}H NMR (DMSO) 8.91 (s, 1 H), 7.68 (d, 2 H, J = 8.8 Hz), 7.48 - 7.32 (m, 10 H), 7.12 (d, 2 H, J = 9 Hz), 7.00 (d, 2 H, J = 8.8 Hz), 6.88 (d, 2 H, J = 9.0 Hz). 5.11 (s, 2 H), 5.01 (s, 2 H), 2.17 (s, 3 H); MS eI m/z 422 (M+).

Example No. 141 Formation of indole from hydrazone: 5-Benzyloxy-2-(4-benzyloxy-phenyl)-1H-indole

A flask was charged with N-(4-Benzyloxy-phenyl)-N'-[1-(4-benzyloxy-phenyl)-ethylidene]-hydrazine (No. 140) (10.0 g, 23.7 mmol), $ZnCl_2$ (8.06 g, 59.17 mmol), acetic acid (70 mL). The reaction flask was heated to 105 °C for no more than 20 min. During the heating period, the reaction was monitored carefully by TLC for the disappearance of the starting material. The progress of the reaction could be shown as the product solidified out of the solution while heating. The reaction was then cooled to rt and more product crashed out was observed. The reaction content was poured into a separatory funnel containing ether (100 mL) and H_2O (200 mL), which was shaken vigorously. The insoluble residue as the desired product stayed in the ether layer which was collected by vacuum filtration. The product was further purified by trituration in ether to give a light gray solid (4.4 g, 46%)

Mp = 202 - 204°C; ^{1}H NMR (DMSO) 11.24 (s, 1 H), 7.73 (d, 2 H, J = 8.8 Hz), 7.48 - 7.41(m, 4 H), 7.45 - 7.27 (m, 6 H), 7.25 (d, 1 H, J = 8.6 Hz), 7.12 - 7.04 (m, 3 H), 6.77 (dd, 1 H, J = 2.4 Hz, 8.6 Hz), 6.65 (d, 1 H, J = 1.5 Hz), 5.14 (s, 2 H), 5.08 (s, 2 H); IR 3420, 3000, 1625 cm^{-1}; MS eI m/z 405 (M+); CHN calcd for $C_{28}H_{23}NO_2 + 0.40\ H_2O$.

Example No. 142 Chlorination of indole to render 5-Benzyloxy-3-chloro-2-(4-benzyloxy-phenyl)-1H-indole

A flask was charged with 5-Benzyloxy-2-(4-benzyloxy-phenyl)-1H-indole No. 141 (8.0 g, 20.0 mmole) and CH_2Cl_2 (50ml).The reaction was cooled to 0°C and n-chlorosuccinimide(2.9g , 22mmole) was added . The reaction was stirred at 0°C for 20min. The reaction was then washed with 10% sodium sulfite solution,dried over $MgSO_4$, and concentrated.To the resulting brown solid was added MeOH and the mixture was stirred for 15 min.The solid was filtered to give 6.8g of a tan solid (78%). Mp = 157-160°C ; ^{1}H NMR (DMSO) 11.5 (s , 1 H), 7.80 (d , 2 H , J = 7.0 Hz), 7.42 - 7.28 (m , 11 H), 7.17 (d, 2 H , J = 8.7 Hz), 7.01 (d , 1 H , J = 2.2Hz), 6.88 (dd , 1 H, J = 8.8 Hz, J = 2.4 Hz), 5.17 (s , 2H), 5.13 (s , 2H); MS eI m/z 439 (M+).

Example No. 143 5-Benzyloxy-3-chloro-2-(2-methyl-4-benzyloxy-phenyl)-1H-indole

This indole synthesized analogously to indole No. 142 immediately preceding: Mp = ^{1}H NMR (DMSO) 11.34 (s , 1 H), 7.48 - 7.44 (m , 4 H), 7.42 - 7.24 (m , 8 H), 7.02 (dd , 2 H , J = 9.3 Hz , J = 2.4 Hz), 6.95 (dd , 1 H , J = 8.4 Hz , J = 2.6Hz), 6.88 (dd , 1 H, J = 8.8Hz, J =2.4 Hz), 5.16 (s , 2 H), 5.14 (s , 2 H), 2.23 (s ,3 H); MS eI m/z 453 (M+).

Example No. 144 Alkylation of indole to give {4-[5-Benzyloxy-2-(4-benzyloxy-phenyl)-3-chloro-indol-1-ylmethyl]-phenoxy}-acetic acid ethyl ester

This procedure was performed analogously to that outlined for the synthesis of 3-methyl indole acetic acid ethyl esters outlined in method 3.
Mp = 90-94°C; ^{1}H NMR (DMSO) 7.45 (d , 4H, J= 7.8 Hz),7.41 - 7.26 (m, 9H), 7.14 (d , 2 H , J = 8.7 Hz), 7.04 (d , 1 H , J = 2.4 Hz), 6.91
(dd, 1 H, J = 9.0Hz, J = 2.5 Hz), 6.80-6.74 (m, 4H), 5.24 (s , 2H), 5.15 (s , 2H), 5.14 (s , 2H), 4.66 (s , 2 H), 4.12 (q, 2H, J = 7.2 Hz), 1.16 (t , 3H , J = 7.5 Hz); MS eI m/z 631(M+).

Example No. 145 Reduction of No. 144 to render No. 145 2-{4-[5-Benzyloxy-2-(4-benzyloxy-phenyl)-3-chloro-indol-1-ylmethyl]-phenoxy}-ethanol

This reaction was performed analogously to that outlined for the synthesis of 3-methyl indoles outlined in method 4. Compound was not purified or characterized, but used as obtained for the next step.

Example No. 146 Bromination of No. 145 to render Benzyloxy-2-(4-benzyloxy-phenyl)-1-[4-(2-bromo-ethoxy)-benzyl]-3-chloro-1H-indole

This reaction was performed analogously to that outlined for the synthesis of 3-methyl indoles outlined in method 5. Mp = 155-158°C; ^{1}H NMR (DMSO) 7.45 (d ,4 H, J= 7.8 Hz),7.41 - 7.25 (m , 9H), 7.14 (d , 2 H , J = 8.7 Hz), 7.04 (d , 1 H , J = 2.4 Hz), 6.91 (dd, 1 H, J = 9.0Hz, J = 2.5 Hz), 6.74 (s, 4H), 5.24 (s , 2 H), 5.15 (s , 2H), 5.14 (s , 2 H), 4.20 (t , 2 H, J= 5.3Hz), 3.74 (t , 2 H , J = 5.3 Hz); MS eI m/z 651 (M+).

Example No. 147 Substitution of No. 146 with piperidine to render 5-Benzyloxy-2-(4-benzyloxy-phenyl)-3-chloro-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indole

This reaction performed analogously to that outlined for the synthesis of 3-methyl indoles outlined in method 6, using piperidine to substitute the bromide.
Mp 96-98°C; ^{1}H NMR (DMSO) 7.45 (d , 4 H, J= 7.8 Hz), 7.40 - 7.30 (m , 9 H), 7.14 (d, 2 H , J = 8.7 Hz), 7.04 (d , 1 H , J = 2.4 Hz), 6.91 (dd, 1 H, J = 9.0Hz, J = 2.5 Hz), 6.74 (s, 4 H), 5.24 (s , 2H), 5.15 (s , 2 H), 5.14 (s , 2 H), 3.93 (t , 2 H, J = 6.0 Hz), 2.56 (t , 2 H , J= 6.0 Hz), 2.41-2.32 (m , 4 H), 1.48-1.39 (m , 4 H), 1.38-1.31 (m , 2 H).

Example No. 148 **5-Benzyloxy-2-(4-benzyloxy-phenyl)-3-chloro-1-[4-(2-azepan-1-yl-ethoxy)-benzyl]-1H-indole**

Reaction performed the same as above except the substituting amine used was hexamethyleneamine.

Mp = 94-97°C; ^{1}H NMR (DMSO) 7.45 (d , 4H, J= 7.8 Hz), 7.42 - 7.30 (m , 9H), 7.14 (d , 2 H , J = 8.7 Hz), 7.04 (d , 1 H , J = 2.4 Hz), 6.91 (dd, 1 H, J = 9.0Hz, J = 2.5 Hz), 6.74 (s, 4 H), 5.24 (s , 2H), 5.15 (s , 2H), 5.14 (s , 2H), 3.93 (t , 2 H, J = 6.0 Hz), 2.75 (t, 2H, J = 6.0 Hz), 2.63-2.59 (m , 4 H), 1.58-1.44 (m , 8 H); MS eI m/z 671 (M+).

Example No. 149 **5-Benzyloxy-2-(2-methyl-4-benzyloxy-phenyl)-3-chloro-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indole**

Reactions to make this compound analogous to those used to make No. 147.

Oil; ^{1}H NMR(DMSO) 7.50 - 7.29 (m , 11 H), 7.17 (d , 1 H , J = 8.4Hz), 7.05 (d, 1 H, J = 2.4Hz), 7.02 (d , 1H, J = 2.4Hz), 6.93 - 6.85 (m, 2 H) , 6.75 - 6.65 (m , 4H), 5.14 (s , 2H), 5.13 (s , 2H) , 5.07 (m , 2 H), 3.92 (t , 2 H , J = 5.9Hz), 2.55 (t , 2H , J = 5.9Hz), 2.42 - 2.29 (m , 4 H), 1.94 (s , 3H), 1.44 - 1.40 (m ,4 H), 1.38 - 1.34 (m , 2H).

Example No. 133 **3-Chloro-2-(4-hydroxy-phenyl)-1-[4-(2-pyrrolidin-1-yl-ethoxy)-benzyl]-1H-indol-5-ol (Hcl)**

Synthesized as described for example No. 134.

Mp = 233-235°C; ^{1}H NMR (DMSO) 10.50 (s, 1 H), 9.88 (s, 1 H), 9.01 (s, 1 H), 7.30 - 7.20 (m, 3 H), 6.90 - 6.80 (m, 7 H), 6.68 (dd, 1 H, J = 2.4, Hz, 8.8 Hz), 5.20 (s, 2 H), 4.22 (t, 2 H, J = 4.8 Hz), 3.47 (t, 2 H, J = 4.8 Hz), 3.10 (bm, 4 H), 1.90 (s, 4 H); IR (KBr) 3400, 1625, 1475, 825 cm^{-1}; MS eI m/z 462 (M+); CHN calcd for $C_{27}H_{27}ClN_2O_3$ + 1 HCl + .75 H_2O.

Example No. 134 Removal of benzyl ethers to render 3-Chloro-2-(4-hydroxy-phenyl)-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indol-5-ol (HCl)

Benzyl ethers were removed analogously to that procedure outlined for 3-methyl indoles outlined in method 7. This compound was then converted to the hydrochloride salt as described previously in method 8; Mp = 207-209°C; ^{1}H NMR (DMSO) 10.10 (bs , 1 H), 9.86 (s , 1H), 9.07 (s , 1 H), 7.26 (d, 2 H, J = 8.6 Hz), 7.22 (d, 1 H, J = 8.8 Hz), 6.87 (d , 2 H , J = 8.6Hz), 6.81 - 6.78 (m , 5 H), 6.65 (dd , 1 H, J = 8.8 Hz, J = 2.2 Hz), 5.20 (s, 2 H), 4.27 (t , 2H, J = 5.0Hz), 3.44 - 3.37 (m , 4 H), 3.00 - 2.85 (m , 2 H), 1.81-1.60 (m , 5H), 1.41 - 1.26 (m ,1 H); IR (KBr) 3350, 1470 ,1250 CM -1; MS eI m/z 476 (M+); CHN calc for $C_{28}H_{29}ClN_2O_3$ + HCL + 1.5 H_2O.

Example No. 135 3-Chloro-2-(4-hydroxy-phenyl)-1-[4-(2-azepan-1-yl-ethoxy)-benzyl]-1H-indol-5-ol (Hcl)

Synthesized as described for No. 134.

Mp = 196-198°C; ^{1}H NMR (DMSO) 10.10 (brs , 1 H), 9.86 (s , 1H), 9.07 (s , 1 H), 7.26 (d, 2 H, J = 8.8 Hz), 7.22 (d , 1 H, J = 9.0 Hz), 6.87 (d , 2 H , J = 8.6Hz), 6.84 - 6.78 (m , 5 H), 6.65 (dd , 1 H, J = 8.8 Hz, J = 2.2 Hz), 5.20 (s, 2 H), 4.27 (t , 2H, J = 5.0Hz), 3.45-3.30 (m , 4 H), 3.21-3.10 (m , 2 H), 1.82-1.76 (m , 4 H), 1.65 - 1.46 (m , 4 H); MS eI m/z 491 (M+);

CHN calc for $C_{29}H_{31}ClN_2O_3$ + 1 HCl + .37 H_2O; IR (KBr) 3400 , 3200, 1450, 1125

Example No. 136 3-Chloro-2-(4-hydroxy-2-methyl-phenyl)-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indol-5-ol

Synthesized as described for No. 134 except the compound was not converted into a salt.

Foam; ^{1}H NMR (DMSO) 9.64 (s , 1H), 9.01 (s , 1H), 7.25 (d, 1 H, J = 8.8Hz), 7.03 (d , 1 H , J = 8.1 Hz), 6.79 (d , 1 H , J= 2.4 Hz), 6.78 - 6.65 (m , 7 H), 5.06 - 4.92 (m , 2 H), 3.94 (t, 2 H, J = 5.9 Hz), 2.62 - 2.57 (m , 2 H) , 2.42 - 2.32 (m , 4 H) , 1.90 (s , 3 H), 1.48- 1.40 (m , 4 H), 1.40 - 1.32 (m, 2 H); MS eI m/z 490 (M+); IR (KBr) 3430, 2900 , 1450 cm^{-1}; CHN calc for $C_{29}H_{31}ClN_2O_3$ + 1.0 H_2O.

Synthesis of 3-ethylindole analogue No. 137

This compound was synthesized in exact analogy to the example given for 3-methylindoles, supra, using methods a and 2-8. The only difference is that the starting material used is 4'-(benzyloxy)-Butyrophenone CAS No. [26945-71-1] instead of 4'-(benzyloxy)-Propiophenone. Data for intermediates is as follows.

Example No. 150 5-Benzyloxy-2-(4-benzyloxy-phenyl)-3-ethyl-1H-indole

Mp = 101 - 108°C; MS eI m/z 433 (M+).

Example No. 151 {4-[5-Benzyloxy-2-(4-benzyloxy-phenyl)-3-ethyl-indol-1-ylmethyl]-phenoxy}-acetic acid ethyl ester

Mp = 72 - 75°C; MS eI m/z 625 (M+).

Example No. 152 2-{4-[5-Benzyloxy-2-(4-benzyloxy-phenyl)-3-ethyl-indol-1-ylmethyl]-phenoxy}-ethanol

Mp = 105 - 113 °C; MS eI m/z 583 (M+).

Example No. 153 Benzyloxy-2-(4-benzyloxy-phenyl)-1-[4-(2-bromo-ethoxy)-benzyl]-3-ethyl-1H-indole

Mp = 140°C (decomp.); MS eI m/z 647, 645 (M+, Br present).

Example No. 154 5-Benzyloxy-2-(4-benzyloxy-phenyl)-3-ethyl-1-[4-(2-piperidin -1-yl-ethoxy)-benzyl]-1H-indole

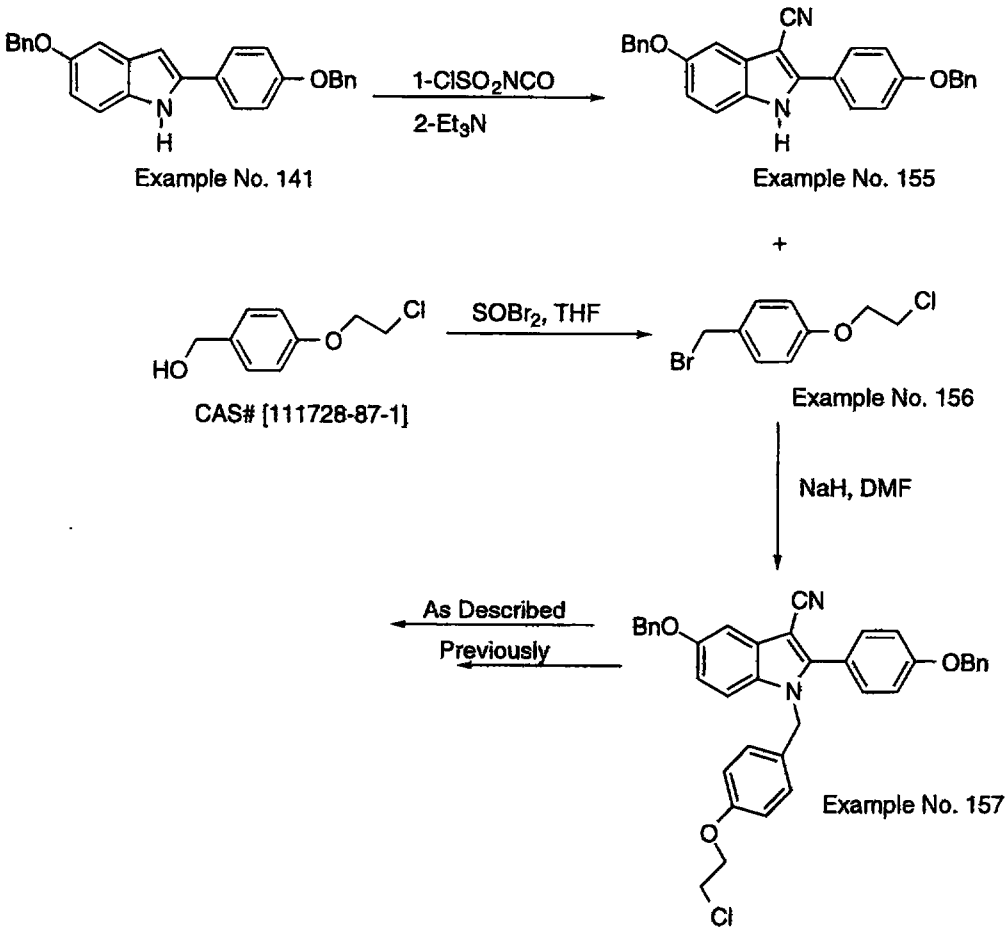
Mp = 92 - 96°C; ^{1}H NMR (DMSO) 7.47 (d, 4 H, J = 7.2 Hz), 7.42 - 7.39 (m, 4 H), 7.36 - 7.30 (m, 2 H), 7.27 (d, 2 H, J = 8.6 Hz), 7.18 (d, 1 H, J = 8.8 Hz), 7.14 (d, 1 H, J = 2.4 Hz), 7.10 (d, 2 H, J = 8.8 Hz), 6.79 (dd, 1 H, J = 8.8 Hz, 2.2 Hz), 6.73 (s, 4 H), 5.13 (s, 2 H), 5.11 (s, 4 H), 3.93 (t, 2 H, J = 5.9 Hz), 2.62 - 2.53 (m, 4 H), 2.40 - 2.33 (m, 4 H), 1.49 - 1.42 (m, 4 H), 1.37 - 1.30 (m, 2 H), 1.10 (t, 3 H, J = 7.2 Hz); MS eI m/z 650 (M+H+).

Example No. 137 **2-(4-Hydroxy-phenyl)-3-ethyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indol-5-ol (HCl)**

Mp = 160 - 164°C; ^{1}H NMR (DMSO) 9.78 (br s, 1 H), 9.69 (s, 1 H), 8.69 (s, 1 H), 7.14 (d, 2 H, J = 8.6 Hz), 7.05 (d, 1 H, J = 8.6 Hz), 6.87 - 6.78 (m, 7 H), 6.56 (dd, 1 H, J = 8.8 Hz, 2.4 Hz), 5.08 (s, 2 H), 4.25 (t, 2 H, J = 4.4 Hz), 3.45 - 3.38 (m, 5 H), 3.00 - 2.86 (m, 2 H), 2.57 - 2.50 (m, 2 H), 1.83 - 1.59 (m, 5 H), 1.41 - 1.28 (m, 1 H), 1.10 (t, 2 H, J = 7.5 Hz); IR (KBr) 3400 br, 3200 br, 2920, 1610 cm-1; MS eI m/z 470 (M+); CHN calcd for $C_{30}H_{34}N_2O_3$ + HCl + 1.5 H_2O.

Scheme 15

Synthesis of 3-cyanoindole analogues



Example No. 155 5-Benzyloxy-3-cyano-2- (4-benzyloxy-phenyl)-1H-indole

In a reaction flask 5-Benzyloxy-2-(4-benzyloxy-phenyl)-1H-indole No. 141 (5.90 g, 14.6 mmol) was mixed with CH_2Cl_2 (90 mL) was cooled down to 0°C (the starting material did not completely dissolve in CH_2Cl_2). While stirring vigorously, a solution of chlorosulfonyl isocyanate (2.26 g, 16.0 mmol) in CH_2Cl_2 (25 mL) was added dropwise over a period of 45 min. The reaction was run at 0°C for 2 hrs while detected by TLC for the formation of the insoluble N-chlorosulfonylamide intermediate. After this period, Et_3N (1.47 g, 14.6 mL) in CH_2Cl_2 (25 mL) was added dropwise over 45 min at 0°C. The insoluble residue became soluble in the reaction solvent as the Et_3N addition was approaching completion. The reaction was let go for the additional 1 hr at 0°C and 2 hrs at rt. The progress of the reaction could be observed by the insoluble solid formation of the product as the reaction time went on. The solvent was stripped down and the solid residue purified by trituration with methanol to yield (4.0 g, 63.8 %). Mp = 238 - 242°C; ^1H NMR (DMSO) 12.31 (s, 1 H), 7.88 (d, 2 H, J = 8.8 Hz), 7.48 (d, 4 H, J = 7.25 Hz), 7.55 - 7.30 (m, 7 H), 7.23 (d, 2 H, J = 8.8 Hz), 7.14 (d, 1 H, J = 2.4 Hz), 6.97 (dd, 1 H, J = 2.2 Hz, 8.8 Hz), 5.20 (s, 2 H), 5.17 (s, 2 H); MS eI m/z 430 (M+).

Example No. 156 4-(2-Chloroethoxy)benzylbromide

To 4-(2-Chloroethoxy)benzylalcohol CAS No. [111728-87-1] (6.4 g, 34.31 mmol) in dioxane (100 mL) at 0°c was added slowly thionylbromide (7.13 g, 34.31 mmol). The reaction was run at 0°C after 5 min. The reaction mixture was diluted with ether (200 mL) and washed with H_2O (1x30 mL) then $NaHCO_3$ (2x25 mL), and brine (30 mL). The organic extract was dried over $MgSO_4$ and concentrated. The crude product was purified by silica gel chromatography (15% EtOAc/Hex) to yield 5.0 g (58%) of the desired product. Mp = 64-66°C; ^1H NMR (DMSO) 7.37 (d, 2 H, J = 8.8 Hz), 6.93 (d, 2 H, J = 8.8 Hz), 4.68 (s, 2 H), 4.24 (t, 2 H, J = 5.05 Hz), 3.93 (t, 2 H, J = 5.27 Hz); MS eI m/z 248 (M+).

Example No. 157 Benzyloxy-2-(4-benzyloxy-phenyl)-1-[4-(2-chloro-ethoxy)-benzyl]-3-cyano-1H-indole

In a reaction flask the 3-cyano indole starting material No. 155 (2.86 g, 6.64 mmol) was dissolved in DMF (25 mL) at 0°C was added NaH (191.2 mg, 8 mmol) slowly. The reaction was stirred at 0°C for 20 min. In a separate reaction flask containing 4-(2-Chloroethoxy)benzylbromide No. 156 (1.81 g, 7.28 mmol) in DMF (15 mL) at 0°C, the above prepared indole anion solution taken up by syringe was added slowly. The reaction was stirred at 0 °C for 20 min and promoted to rt for 1 h. The reaction was quenched with a few drops of H_2O. The reaction mixture was partitioned between EtOAc (2x100 mL) and H_20 (80 mL). The organic extract was washed with brine (80 mL), dried over $MgSO_4$, and concentrated.The crude product was purified by trituration with ether to give the product as a white solid (2.80 g, 70.4%). Mp = 160-162°C; ^{1}H NMR (DMSO) 7.53 - 7.28 (m, 13 H), 7.23 (m, 3 H), 6.97 (dd, 1 H, J = 2.4 Hz, 9.0 Hz), 6.86 - 6.78 (m, 4 H), 5.37 (s, 2 H), 5.18 (s, 4 H), 4.15 (t, 2 H, J = 4.8 Hz), 3.87 (t, 2 H, J = 5.3 Hz); MS eI m/z 598 (M+).

Example No. 's 158 and 159

Substitution of the chloro group with piperidine and hexamethyleneamine was performed analogously to the procedure outlined in method 6 using No. 157 as a starting material, *supra*.

Example No. 158 5-Benzyloxy-2-(4-benzyloxy-phenyl)-3-cyano-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indole

Mp = 148 - 150 °C; ^{1}H NMR (DMSO) 7.54 - 7.30 (m, 13 H), 7.25 - 7.18 (m, 3 H), 6.98 (dd, 1 H, J = 2.4 Hz, 9.0 Hz), 6.84 - 6.74 (m, 4 H), 5.35 (s, 2 H), 5.17 (s, 4 H), 3.94 (t, 2 H, 5.9 Hz), 2.55 (t, 2 H, 5.7 Hz), 2.35 (bs, 4 H), 1.50 - 1.40 (m, 4 H), 1.38 - 1.25 (m, 2 H); IR 3400, 2910, 2250, 1250 cm^{-1}; MS FAB 648 [M+H]+.

Example No. 159 **5-Benzyloxy-2-(4-benzyloxy-phenyl)-3-cyano-1-[4-(2-azepan-1-yl-ethoxy)-benzyl]-1H-indole**

^{1}H NMR (DMSO) 8.60 (br s, 1 H), 7.60 - 7.28 (m, 12 H), 7.25 - 7.16 (m, 3 H), 6.97 (dd, 1 H, J = 2.4 Hz, 9.0 Hz), 6.88 - 6.75 (m, 4 H), 5.35 (s, 2 H), 5.17 (s, 4 H), 3.92 (t, 2 H, J = 6.2 Hz), 3.08-3.00 (m, 2 H), 2.77 (t, 2 H, J = 5.9 Hz), 2.63 (t, 4 H, J = 4.8 Hz), 1.78 - 1.68 (m, 2 H), 1.60 - 1.40 (m, 4 H); MS eI m/z 661 (M+).

Examples No. 138 and No. 139

Benzyl ethers were removed by hydrogen transfer using 1,4 cyclohexadiene and 10% Pd/C as described in method 7. Compounds were converted into their respective hydrochloride salts as described in method 8.

Example No. 138 **5-Hydroxy-2-(4-Hydroxy-phenyl)-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indole-3-carbonitrile (HCl)**

Mp = 173 - 175°C; ^{1}H NMR (DMSO) 10.40 (s, 1 H), 10.12 (s, 1 H), 9.40 (s, 1 H), 7.38 (m, 2 H), 7.30 (d, 1 H, J = 8.8 Hz), 7.02 - 6.90 (m, 3 H), 6.88 (s, 4 H), 6.75 (dd, 1 H, J = 2.4 Hz, 9Hz), 5.33 (s, 2 H), 4.30 (t, 2 H, J = 4.8 Hz), 3.51 - 3.38 (m, 4 H), 2.92 (m, 2 H), 1.85 - 1.73 (m, 4 H), 1.68 - 1.59 (m, 1 H), 1.26 - 1.21 (m, 1 H); IR 3400, 2200, 1250 cm-1; MS eI m/z 467 (M+); CHN calcd for $C_{29}H_{29}N_3O_3$ + 1.0 HCl + 1.0 H_2O.

Example No. 139 **1-[4-(2-Azepan-1-yl-ethoxy)-benzyl]-5-hydroxy-2-(4-hydroxy-phenyl)-1H-indole-3-cabonitrile (HCl)**

Mp = 160 - 163°C; ^{1}H NMR (DMSO) 10.22 (s, 1 H), 10.08 (s, 1 H), 9.35 (s, 1 H), 7.40 - 7.37 (m, 2 H), 7.30 (d, 1 H, 8.8 Hz), 7.0 - 6.90 (m, 3 H), 6.87 (s, 4 H), 6.74 (dd, 1 H, J = 2.41 Hz, 9 Hz), 5.33 (s, 2 H), 4.27 (t, 2 H, J = 5.0 Hz), 3.50 - 3.30 (m, 4 H), 3.20 (m, 2 H), 1.85 - 1.70 (m, 4 H), 1.65 - 1.50 (m, 4 H); IR 3300, 2200, 1250 cm^{-1}; MS eI m/z 481 (M+); CHN calc for $C_{30}H_{31}N_3O_3$ + 1 HCl + 1 H_2O.

Esters of Indole No. 's 97 and 98

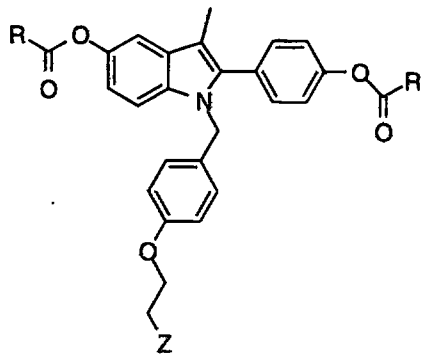
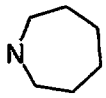
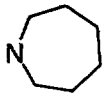


Table 9

Example No.	R	Z
No. 160	Et	
No. 161	t-Bu	
No. 162	t-Bu	

Method 9

Example No. 162 Di-pivalate ester of 2-(4-Hydroxy-phenyl)-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indol-5-ol

Example No. 97 free base was used as the starting material for this synthesis. No. 97 (1.0 g, 2.5 mmol) in 20 mL CH_2Cl_2 was treated with diisopropylethylamine (0.7g, 6.3 mmol) and cataltic DMAP. The reaction was cooled to 0°C and treated with pivaloyl chloride (0.7 mL, 5.6 mmol) and allowed to come to rt and stirred overnight. The reaction was worked up by diluting with CH_2Cl_2 and washing with water and brine. After drying over $MgSO_4$ the solution was concentrated and chromatographed on silica gel ($MeOH/CH_2Cl_2$, 1:19) to yield the desired material as an orange foam (1.08 g). This material was then taken up in 15 mL ethyl acetate and treated with 2.5 mL of a 1M HCl/Et_2O solution. Hexane was added until the solution turned cloudy. The product precipitated out as the HCl salt. This material was recrystallized from ethyl

acetate/hexane to yield 0.42 g of pure No. 162: Mp = 182 - 185°C; CHN calcd for $C_{39}H_{48}N_2O_5$ + HCl + 0.25 H_2O.

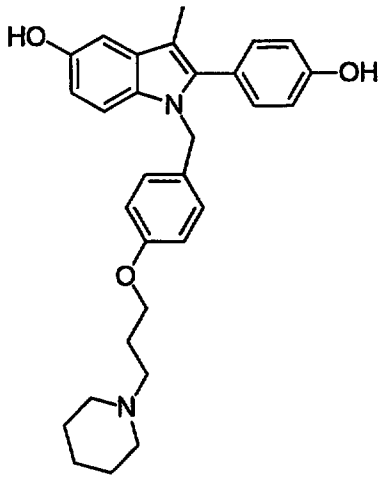
Example No. 160 Di-propionate of 1-[4-(2-Azepan-1-yl-ethoxy)-benzyl]-2-(4-hydroxy-phenyl)-3-methyl-1H-indol-5-ol (HCl)

Compound was prepared analogously to example No. 162 except the starting material used was example No. 98 and the acylating agent used was propionyl chloride: Mp = 170.5 - 172°C; CHN calcd for $C_{36}H_{42}N_2O_5$ + HCl + 0.75 H_2O; MS FAB 605 (M+Na)+.

Example No. 161 Di-pivalate of 1-[4-(2-Azepan-1-yl-ethoxy)-benzyl]-2-(4-hydroxy-phenyl)-3-methyl-1H-indol-5-ol (HCl)

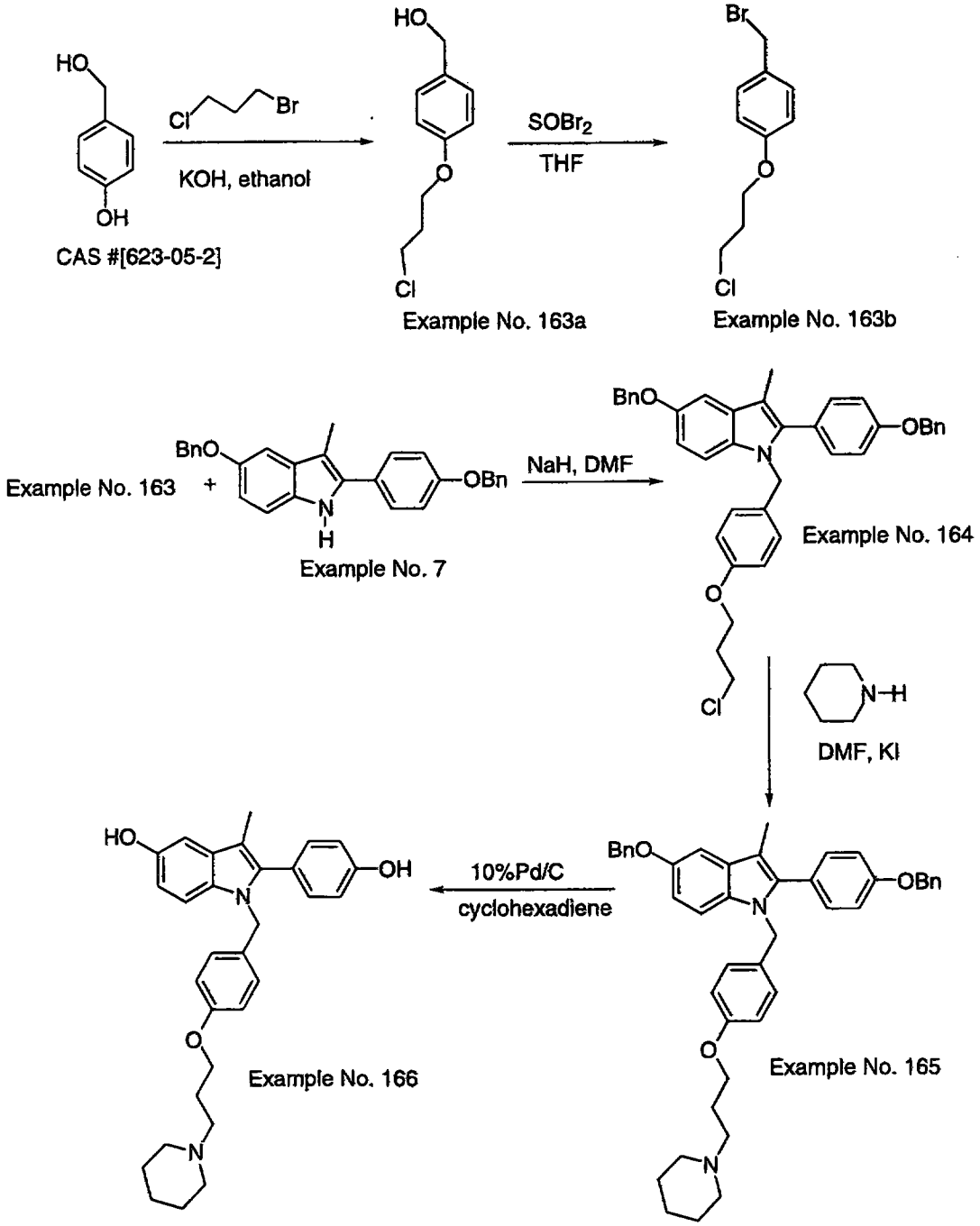
Compound was prepared analogously to example No. 162 except the starting material used was example No. 98: Mp = 143 - 151°C; CHN calcd for $C_{40}H_{50}N_2O_5$ + HCl + 0.75 H_2O.

Experimental for example No. 166



Scheme 16

Synthesis of No. 166



EXAMPLE No. 166
2-(4-Hydroxy-phenyl)-3-methyl-1-{4-[3-(piperidin-1-yl)-propoxy]-benzyl}-1H-indol-5-ol

The title compound was prepared according to Scheme 16 and the steps provided below:

Method 11

Example No. 163a **4-(3-chloropropoxy)-benzyl alcohol**

A solution of 4-hydroxy benzyl alcohol CAS No. [623-05-2] (10g, 80.5 mmol) in ethanol (70 mL) was treated with 1, 3 bromochloro propane (16.0g , 100 mmol) and potassium hydroxide (5.0 g, 89 mmol) was refluxed for 2 hours. The solution was cooled and filtered and then the filtrate concentrated. The concentrate was taken up in ether and washed with water, brine and dried over magnesium sulfate. The material was chromatographed on silica gel using ethyl acetate/hexanes (3:7) to yield 11.6 g of the product as a white solid: Mp = 65°C; ^{1}H NMR (DMSO) 7.21 (d, 2 H, J = 8.8 Hz), 6.88 (d, 2 H, J = 8.8 Hz), 5.03 (t, 1 H, J = 5.7 Hz), 4.40 (d, 2H, J = 5.5 Hz), 4.05 (t, 2 H, J = 6.1 Hz), 3.77 (t, 2 H, J = 6.4 Hz); MS eI m/z 200.

Method 12

Example No. 163b **4-(3-chloropropoxy)-benzyl bromide**

A solution consisting of 4-(3-chloropropoxy)-benzyl alcohol No. 162 (10.6 g, 52.8 mmol) in dioxane (0.125 l) was cooled to 0° C and treated with a dropwise addition of thionyl bromide (12.0 g, 58.0 mmol). After 10 minutes the reaction was complete. The dioxane was diluted with ethyl ether and washed with water, brine, and then dried over $MgSO_4$. The material was concentrated down to yield 15 g of an oil: ^{1}H NMR (DMSO) 7.36 (d, 2 H, J = 8.8 Hz), 6.92 (d, 2 H, J = 8.6 Hz), 4.68 (s, 2 H), 4.08 (t, 2 H, J = 5.9 Hz), 3.77 (t, 2 H, J = 6.4 Hz); MS (FAB) 266 ($M+H^+$).

Method 13

Example No. 164 5-Benzyloxy-2-(4-benzyloxy-phenyl)-1-[4-(3-chloro-propoxy)-benzyl]-3-methyl-1H-indole

A solution consisting of 5-Benzyloxy-2-(4-benzyloxy-phenyl)-3-methyl-1H-indole No. 7 (6.5 g, 15.5 mmol) in DMF (60 mL) was cooled to 0°C and treated with addition of sodium hydride (0.68 g, 17.0 mmol) and stirred for 20 minutes. A solution of 4-(3-chloropropoxy)-benzyl bromide No. 163 in DMF (10 mL) was then added slowly. The reaction was allowed to come to rt and stirred for 2 hours. The reaction was poured into water and extracted with ethyl acetate. The ethyl acetate was washed with water, brine and dried over magnesium sulfate and concentrated. The concentrate was treated with methanol and 5 g of the desired product precipitated as a white solid with a melting point of 130-132°C.

Method 14

Example No. 165 5-Benzyloxy-2-(4-benzyloxy-phenyl)-1-[4-(3-piperidin-1-yl-propoxy)-benzyl]-3-methyl-1H-indole

A solution of 5-Benzyloxy-2-(4-benzyloxy-phenyl)-1-[4-(3-chloro-propoxy)-benzyl]-3-methyl-1H-indole No. 164 (3g, 5.1 mmol), potassium iodide (2.5 g, 15.3 mmol) and piperidine (3.0 mL, 30.6 mmol) were heated in DMF (30 mL) at 100°C for 18 hours. The reaction was worked up by pouring into water and extracting with ethyl acetate. The organic layer was washed with water, brine and dried over magnesium sulfate. The solution was concentrated to an oil and the product precipitated out by adding methanol. The product was obtained as a white solid: Mp = 104-106°C; ^{1}H NMR (DMSO) 7.47 (d, 4 H, J = 7.5 Hz), 7.38 (q, 4 H, J = 7.9 Hz), 7.36-7.30 (m, 1 H), 7.28 (d, 2 H, J = 8.3 Hz), 7.19 (d, 1 H, J = 8.8 Hz), 7.12-7.10 (m, 4 H), 6.80 (dd, 1 H, J = 8.8, 2.0 Hz), 6.72 (s, 4 H), 5.14 (s, 2 H), 5.13 (s, 2 H), 5.11 (s, 2 H), 3.86 (t, 2 H, J = 6.4 Hz), 2.35-2.20 (m, 6 H), 2.14 (s, 3 H), 1.78-1.75 (m, 2 H), 1.47-1.42 (m,4 H), 1.40-1.31 (m, 2 H); MS eI m/z 650.

Method 15

Example No. 166 2-(4-Hydroxy-phenyl)-3-methyl-1-{4-[3-(piperidin-1-yl)-propoxy]-benzyl}-1H-indol-5-ol

A solution of 5-Benzyloxy-2-(4-benzyloxy-phenyl)-1-[4-(3-piperidin-1-yl-propoxy)-benzyl]-3-methyl-1H-indole No. 165 (2.35 g) in tetrahydrofuran (25 mL) and ethanol (25 mL) was added to 2.3 g of 10% palladium on carbon. Cyclohexadiene (10 mL) was added and the reaction allowed to stir at room temperature for 18 hours. The catalyst was filtered through celite and the reaction mixture was concentrated and chromatographed on silica gel using dichloromethane/methanol (4:1) to elute the product (0.8 g) as a white foam: Mp = 125-130°C; ^{1}H NMR 9.68 (s, 1 H), 8.70 (s, 1 H), 7.15 (d, 2 H, J = 8.6 Hz), 7.05 (d, 1 H, J = 8.8 Hz), 6.85 (d, 2 H, J = 8.6 Hz), 6.80 (d, 1 H, J = 2.4 Hz), 6.74 (d, 4 H, J = 2.6 Hz), 6.57 (dd, 1 H, J = 8.6, 2.2 Hz), 5.09 (s, 2 H), 3.88 (t, 2 H, J = 6.4 Hz), 3.60-3.15 (m, 2 H), 2.62-2.38 (m, 4 H), 2.09 (s, 3 H), 1.92-1.78 (m, 2 H), 1.55-1.43 (m, 4 H), 1.42-1.30 (m, 2 H); IR (KBr) 3400 (br), 2900, 1620, 1515 cm-1; MS eI m/z 470.

Synthesis of No. 167 and No. 168

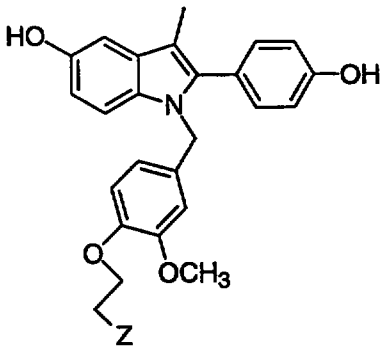
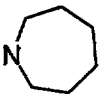
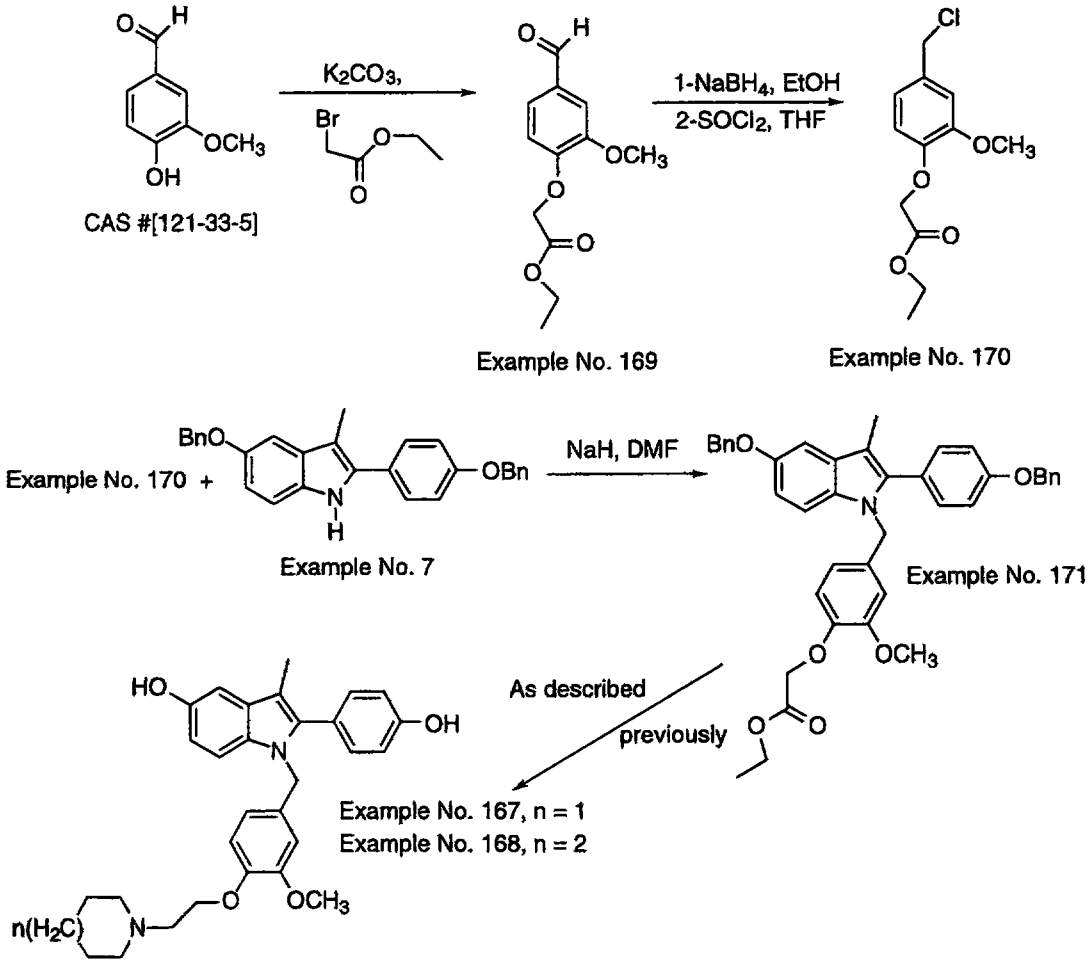


Table 10

Example No.	Z
No. 167	
No. 168	

Scheme 17

Synthetic scheme for examples No. 167 and No. 168



Synthesis of example No. 167
2-(4-Hydroxy-phenyl)-1-[3-methoxy-4-(2-piperidin-1-yl-ethoxy)-benzyl]-3-methyl-1H-indol-5-ol

Example No. 169 (4-Formyl-2-methoxy-phenoxy)-acetic acid ethyl ester

A flask containing vanillin (20g, 0.13 mol), ethyl bromoacetate (28.4g, 0.17 mol) and potassium carbonate (32.7 g, 0.24 mol) and acetone 200 mL were heated to reflux for 3 hours. The reaction was allowed to come to rt. The acetone was stripped off and the residue partitioned between water and ethyl acetate. The ethyl acetate was washed with brine and dried over magnesium sulfate. The organic layer was concentrated and the solid triturated with hexanes to yield 28.4 grams of example No. 169.

Mp = 56 - 59 °C; ^{1}H NMR (DMSO) 9.83 (s, 1 H), 7.50 (dd, 1 H, J = 2.0 Hz, 8.3 Hz), 7.42 (d, 1 H, J = 1.7 Hz), 7.07 (d, 1 H, J = 8.4 Hz), 4.91 (s, 2 H), 4.16 (q, 2 H, J = 7.2 Hz), 3.84 (s, 3 H), 1.20 (t, 3 H, J = 7.1 Hz); MS eI m/z 238 (M+); CHN calcd for $C_{12}H_{14}O_5$.

Example No. 170 (4-Chloromethyl-2-methoxy-phenoxy)-acetic acid ethyl ester

A solution of example No. 169 (28.8g, 0.119 mol) in 600 mL of EtOH/THF(1:1) was treated with sodium borohydride (2.25 g, 0.06 mol) at 0°C and stirred for 45 minutes. The solvents were evaporated and the reaction mixture diluted with ethyl acetate and washed with 1N HCl solution. The product thus obtained (14.2 g, 0.059 mol) as an oil was dissolved in 140 mL of THF and cooled to 0°C. This solution was then treated with dropwise addition of thionyl chloride (7.38g, 0.062 mol) at)°C. After 1 hour the reaction was poured into 400 mL of water and extracted with ether. The ether layer was washed with a sodium bicarbonate solution and dried over magnesium sulfate. This was concentrated and chromatographed by silica gel chromatography using ethyl acetate/hexanes (1:9). The product was obtained as 10.5 g of a white solid. Mp = 64 - 66°C; ^{1}H NMR (DMSO) 7.06 (d, 1 H, J = 2.0 Hz), 6.91 (dd, 1 H, J = 2.0 Hz, 2.2 Hz), 6.83 (d, 1 H, J = 2.1 Hz), 4.75 (s, 2 H), 4.70 (s, 2 H), 4.13 (q, 2 H, J = 7.2 Hz), 3,77 (s, 3 H), 1.19 (t, 3 H, J = 7.1 Hz); MS eI m/z 258 (M+); CHN calcd for $C_{12}H_{15}ClO_4$.

Example No. 171 {2-Methoxy-4-[5-benzyloxy-2-(4-benzyloxy-phenyl)-3-methyl-indol-1-ylmethyl]-phenoxy}-acetic acid ethyl ester

Alkylation of the indole No. 7 was performed as described previously in Method No. 3 using example No. 170 as the electrophile.

Mp = 120 - 123°C; ^{1}H NMR (DMSO) 7.48 - 7.20 (m, 13 H), 7.18 - 7.10 (m, 3 H), 6.80 (dd, 1 H, J = 2.5 Hz, 8.8 Hz), 6.64 (d, 1 H, J = 8.4 Hz), 6.52 (d, 1 H, J = 2.0 Hz), 6.24 (dd, 1 H, J = 1.9 Hz, 8.1 Hz), 5.13 (s, 4 H), 5.10 (s, 2 H), 4.61 (s, 2 H), 4.10 (q, 2 H, J = 7.0 Hz), 3.58 (s, 3 H), 2.15 (s, 3 H), 1.15 (t, 3 H, J = 7.0 Hz); MS eI m/z 641 (M+).

Example No. 172 2-{2-Methoxy-4-[5-benzyloxy-2-(4-benzyloxy-phenyl)-3-methyl-indol-1-ylmethyl]-phenoxy}-ethanol

Reduction of the ester No. 171 was performed as described previously in Method 4.

Mp = 86 - 90°C; ^{1}H NMR (DMSO) 7.48 - 7.20 (m, 13 H), 7.18 - 7.10 (m, 3 H), 6.80 (dd, 1 H, J = 2.5 Hz, 8.8 Hz), 6.64 (d, 1 H, J = 8.4 Hz), 6.52 (d, 1 H, J = 2.0 Hz), 6.24 (dd, 1 H, J = 1.9 Hz, 8.1 Hz), 5.13 (s, 4 H), 5.10 (s, 2 H), 4.76 (t, 1 H, J = 5.5 Hz), 3.83 (t, 2 H, J = 5.1 Hz), 3.63 (q, 2 H, J = 5.3 Hz), 3.56 (s, 3 H), 2.15 (s, 3 H); MS eI m/z 599 (M+).

Example No. 173 5-Benzyloxy-2-(4-benzyloxy-phenyl)-1-[3-methoxy-4-(2-bromo-ethoxy)-benzyl]-3-methyl-1H-indole

Conversion of the alcohol of example No. 172 to the bromide was performed analogously to that described in Method 5.

Mp = 150 - 152°C; ^{1}H NMR (DMSO) 7.48 - 7.20 (m, 13 H), 7.18 - 7.10 (m, 3 H), 6.80 (dd, 1 H, J = 2.5 Hz, 8.8 Hz), 6.64 (d, 1 H, J = 8.4 Hz), 6.52 (d, 1 H, J = 2.0 Hz), 6.24 (dd, 1 H, J = 1.9 Hz, 8.1 Hz), 5.13 (s, 4 H), 5.10 (s, 2 H), 4.15 (t, 2 H, J = 5.3 Hz), 3.70 (t, 2 H, J = 5.7 Hz), 3.58 (s, 3 H), 2.15 (s, 3 H); MS eI m/z 661 (M+).

Example No. 174 5-Benzyloxy-2-(4-benzyloxy-phenyl)-3-methyl-1-[3-Methoxy-4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indole

Substitution of the bromide with piperidine was performed as described previously in Method 6.

^{1}H NMR (DMSO) 7.48 - 7.20 (m, 13 H), 7.18 - 7.10 (m, 3 H), 6.80

(dd, 1 H, J = 2.5 Hz, 8.8 Hz), 6.64 (d, 1 H, J = 8.4 Hz), 6.52 (d, 1 H, J = 2.0 Hz), 6.24 (dd, 1 H, J = 1.9 Hz, 8.1 Hz), 5.13 (s, 4 H), 5.10 (s, 2 H), 3.90 (t, 2 H, J = 5.7 Hz), 3.55 (s, 3 H), 2.62 - 2.50 (bs, 2 H), 2.45 - 2.30 (bs, 4 H), 2.15 (s, 3 H), 1.50 - 1.40 (m, 4 H), 1.40 - 1.35 (m, 2 H); MS FAB m/z 667 (M+H+).

Example No. 175 **5-Benzyloxy-2-(4-benzyloxy-phenyl)-3-methyl-1-[2-Methoxy-4-(2-azepan-1-yl-ethoxy)-benzyl]-1H-indole**

Reaction performed exactly as for No. 174 except hexamethyleneamine was used to displace the bromide in place of piperidine.

Foam; ^{1}H NMR (DMSO) 7.48 - 7.20 (m, 13 H), 7.18 - 7.10 (m, 3 H), 6.80 (dd, 1 H, J = 2.5 Hz, 8.8 Hz), 6.64 (d, 1 H, J = 8.4 Hz), 6.52 (d, 1 H, J = 2.0 Hz), 6.24 (dd, 1 H, J = 1.9 Hz, 8.1 Hz), 5.13 (s, 4 H), 5.10 (s, 2 H), 3.90 (t, 2 H, J = 5.7 Hz), 3.55 (s, 3 H), 2.85 - 2.70 (bs, 2 H), 2.70 - 2.55 (s, 4 H), 2.10 (s, 3 H), 1.60 - 1.15 (m, 8 H); MS FAB m/z 681 (M+H+)

Example No. 167 **2-(4-Hydroxy-phenyl)-1-[3-methoxy-4-(2-piperidin-1-yl-ethoxy)-benzyl]-3-methyl-1H-indol-5-ol**

Compound No. 173 was hydrogenated by transfer hydrogenation as described previously in Method 7. Compound was isolated as the hydrochloride salt by dissolving in ether and treating with 1.2 equivalents of 1N ether/HCl solution (this is a variation of method 8).

Mp = 123 - 127 °C; ^{1}H NMR (DMSO) 10.20 (bs, 1 H), 9.72 (s, 1 H), 8.71 (s, 1 H), 7.17 (d, 2 H, J = 8.6 Hz), 7.11 (d, 1 H, J = 8.8 Hz), 6.87 (d, 2 H, J = 8.6 Hz), 6.79 (m, 2 H), 6.57 (dd, 1 H, J = 2.4 Hz, 8.8 Hz), 6.55 (d, 1 H, J = 1.7 Hz), 6.33 (dd, 1 H, J = 1.7 Hz, 8.1 Hz), 5.11 (s, 2 H), 4.23 (t, 2 H, J = 4.8 Hz), 3.60 (s, 3 H), 3.45 (m, 2 H), 3.35 (m, 2 H), 2.95 (m, 2 H), 2.10 (s, 3 H), 1.70 (m, 5 H), 1.35 (m, 1 H); IR 3500, 1500, 1275 cm^{-1}; MS (+) FAB m/z 487 $(M+H)^+$; CHN calcd for $C_{30}H_{34}N_2O_4$ + 1 HCl + 1.0 H_2O.

Example No. 168 **2-(4-Hydroxy-phenyl)-1-[3-methoxy-4-(2-azepan-1-yl-ethoxy)-benzyl]-3-methyl-1H-indol-5-ol**

Prepared in the same way as that described for example No. 167.

Mp = 142 - 146 °C; ^{1}H NMR (DMSO) 10.36 (s, 1 H), 9.72 (s, 1 H), 8.71 (s, 1 H), 7.18 (d, 2 H, J = 8.3 Hz), 7.11 (d, 1 H, J = 8.6 Hz), 6.87 (d, 2 H, J = 8.3 Hz), 6.82 (d, 1 H, J = 8.1 Hz), 6.79 (d, 1 H, J = 2.2 Hz), 6.57 (dd, 1 H, J = 2.2 Hz, 8.6 Hz), 6.55 (d, 1 H, J = 1.8 Hz), 6.33 (dd, 1 H, J = 1.5 Hz, 8.1 Hz), 5.11 (s, 2 H), 4.24 (t, 2 H, J = 4.6 Hz), 3.60 (s, 3 H), 3.40 (m, 4 H), 3.20 (m, 2 H), 2.10 (s, 3 H), 1.75 (m, 4 H), 1.55 (m, 4 H); IR (KBr) 3300, 1500, 1270, 1200 cm^{-1}; MS (+) FAB m/z 501 $(M+H)^+$; CHN calcd for $C_{31}H_{36}N_2O_4$ + 1.0 HCl + 0.12 CH_3OH.

Biological Data

Method 16

***In vitro* estrogen receptor binding assay**

Receptor preparation

CHO cells overexpressing the estrogen receptor were grown in 150 mm^2 dishes in DMEM + 10% dextran coated charcoal, stripped fetal bovine serum. The plates were washed twice with PBS and once with 10mM Tris-HCl, pH 7.4, 1mM EDTA. Cells were harvested by scraping the surface and then the cell suspension was placed on ice. Cells were disrupted with a hand-held motorized tissue grinder using two, 10-second bursts. The crude preparation was centrifuged at 12,000g for 20 minutes followed by a 60 minute spin at 100,000g to produce a ribosome free cytosol. The cytosol was then frozen and stored at -80°C. Protein concentration of the cytosol was estimated using the BCA assay with reference standard protein.

Binding assay conditions

The competition assay was performed in a 96-well plate (polystyrene*) which binds <2.0% of the total input [^{3}H]-17β-estradiol and each data point was gathered in triplicate. 100uG/100uL of the receptor preparation was aliquoted per well. A saturating dose of 2.5 nM [^{3}H]17β-estradiol + competitor (or buffer) in a 50 uL volume was added in the preliminary competition when 100x and 500x competitor were evaluated, only 0.8 nM [^{3}H] 17β-estradiol was used. The plate was incubated at room

temperature for 2.5 h. At the end of this incubation period 150 uL of ice-cold dextran coated charcoal (5% activated charcoal coated with 0.05% 69K dextran) was added to each well and the plate was immediately centrifuged at 99g for 5 minutes at 4°C. 200 uL of the supernatant solution was then removed for scintillation counting. Samples were counted to 2% or 10 minutes, whichever occurs first. Because polystyrene absorbs a small amount of [^{3}H]17β-estradiol, wells containing radioactivity and cytosol, but not processed with charcoal were included to quantitate amounts of available isotope. Also, wells containing radioactivity but no cytosol were processed with charcoal to estimate unremovable DPM of [^{3}H] 17β-estradiol. Corning No. 25880-96, 96-well plates were used because they have proven to bind the least amount of estradiol.

Analysis of results

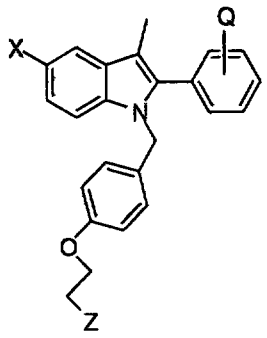
Counts per minute (CPM) of radioactivity were automatically converted to disintegrated per minute (DPM) by the Beckman LS 7500 Scintillation Counter using a set of quenched standards to generate a H No. for each sample. To calculate the % of estradiol binding in the presence of 100 or fold 500 fold competitor the following formula was applied:

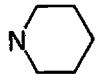
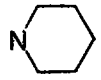
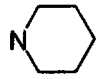
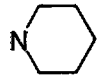
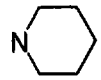
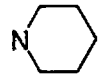
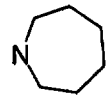
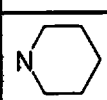
((DPM sample-DPM not removed by charcoal /(DPM estradiol-DPM not removed by charcoal)) x 100% = % of estradiol binding

For the generation of IC_{50} curves, % binding is plotted vs compound. IC_{50}'s are generated for compounds that show >30% competition at 500x competitor concentration. For a description of these methods, see Hulme, E.C., ed. 1992. Receptor-Ligand Interactions: A Practical Approach. IRL Press, New York.(see especially chapter 8).

Table 11

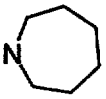
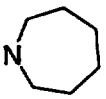
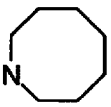
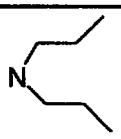
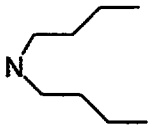
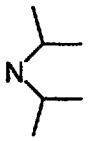
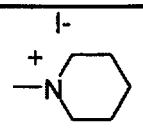
Estrogen Receptor Binding



Example No.	X	Q	Z	Receptor Binding IC50's uM
No. 85	H	H		0.45
No. 86	H	4'-OH		0.12
No. 87	OH	H		0.030
No. 88	OMe	4'-OH		0.35
No. 89	OH	4'-OMe		0.30
No. 90	OMe	4'-OMe		0.60
No. 91	OMe	4'-OMe		0.52
No. 92	OH	4'-OEt		0.062

5

Table 11 (Cont'd)

Example No.	X	Q	Z	Receptor Binding IC50's uM
No. 93	OH	4'-OEt		0.090
No. 94	F	4'-OH		0.20
No. 97	OH	4'-OH		0.060
No. 98	OH	4'-OH		0.050
No. 99	OH	4'-OH		0.03
No. 100	OH	4'-OH		0.06
No. 101	OH	4'-OH		0.04
No. 102	OH	4'-OH		0.08
No. 103	OH	4'-OH		0.2
No. 104	OH	4'-OH		0.1
No. 105	OH	4'-OH		0.028
No. 106	OH	4'-OH		0.1
No. 107	OH	4'-OH		0.06

5 **Table 11 (Cont'd)**

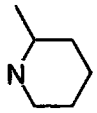
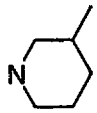
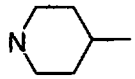
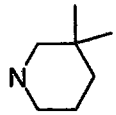
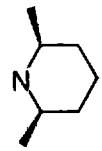
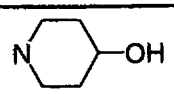
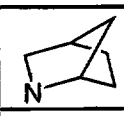
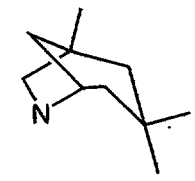
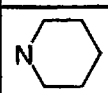
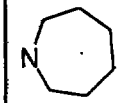
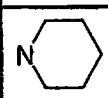
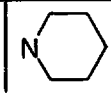
Example No.	X	Q	Z	Receptor Binding IC50's uM
No. 108	OH	4'-OH		0.02
No. 109	OH	4'-OH		0.17
No. 110	OH	4'-OH		0.037
No. 111	OH	4'-OH		0.15
No. 112	OH	4'-OH		0.07
No. 113	OH	4'-OH		0.047
No. 114	OH	4'-OH		0.001
No. 115	OH	4'-OH		0.15
No. 116	OH	4'-Fl		0.04
No. 117	OH	4'-Fl		0.10
No. 118	OH	3'-OMe,4'-OH		N/A
No. 119	OH	3',4'-OCH_2O-		0.070

Table 11 (Cont'd)

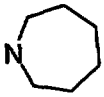
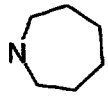
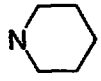
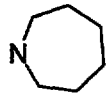
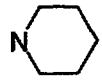
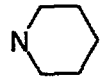
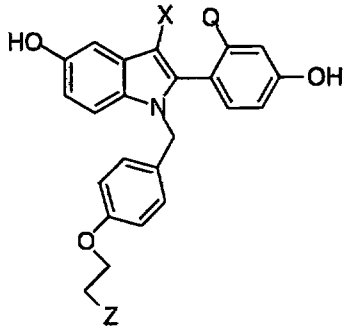
Example No.	X	Q	Z	Receptor Binding IC50's uM
No. 120	OH	4'-O-iPr		0.10
No. 121	OH	4'-O-iPr		0.080
No. 122	OH	4'-O-Cp		0.080
No. 123	OH	4'-CF_3		0.17
No. 124	OH	4'-CH_3		0.11
No. 125	OH	4'-Cl		0.11
No. 126	OH	2',4',-Dimethoxy		N/A
No. 127	OH	3'-OH		0.019
No. 128	OH	3'-OH		0.009
No. 129	OH	4'-OH,3'-Fl		0.0055
No. 130	OH	4'-OH, 3'-Fl		0.013
No. 131	OH	3'-OMe		0.12
No. 132	OH	4'-OCF_3		0.05

Table 12

Estrogen Receptor Binding



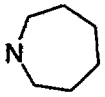
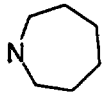
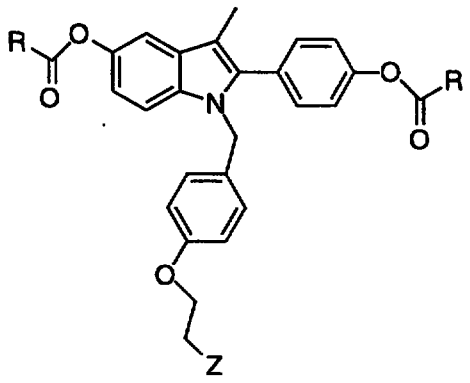
Example No.	X	Q	Z	Receptor Binding IC50's uM
No. 133	Cl	H		0.004
No. 134	Cl	H		0.024
No. 135	Cl	H		0.029
No. 136	Cl	CH_3		0.013
No. 137	Et	H		0.15
No. 138	CN	H		0.011
No. 139	CN	H		0.023

Table 13

Estrogen Receptor Binding



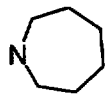
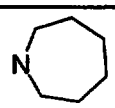
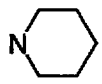
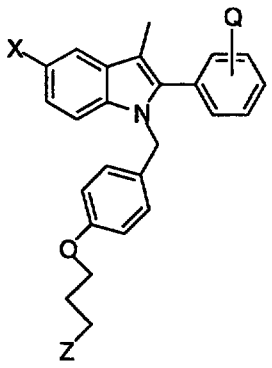
Example No.	R	Z	Receptor Binding IC50's uM
No. 160	Et		N/A
No. 161	t-Bu		N/A
No. 162	t-Bu		Does not Bind

Table 14

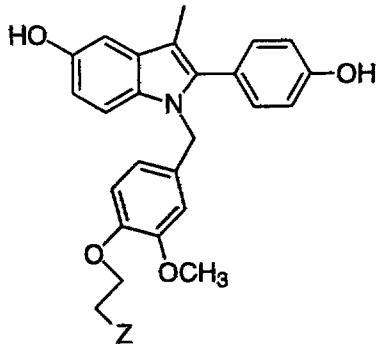
Estrogen Receptor Binding

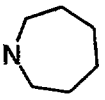


Example No.	X	Q	Z	Receptor Binding IC50's uM
No. 166	OH	4'-OH		0.099

Table 15

Estrogen Receptor Binding



Example No.	Z	Receptor Binding IC50's uM
No. 167		0.08
No. 168		0.057

Method 17

Ishikawa Cell Alkaline Phosphatase Assay

Cell Maintenance and Treatment:

Ishikawa cells were maintained in DMEM/F12 (50%:50%) containing phenol red + 10% fetal bovine serum and the medium was supplemented with 2 mM Glutamax, 1% Pen/Strap and 1 mM sodium pyruvate. Five days prior to the beginning of each experiment (treatment of cells) the medium was changed to phenol red-free

DMEM/F12 + 10% dextran coated charcoal stripped serum. On the day before treatment, cells were harvested using 0.5% trypsin/EDTA and plated at a density of 5 X 10^4 cells/well in 96-well tissue culture plates. Test compounds were dosed at 10^{-6}, 10^{-7} and 10^{-8}M in addition to 10^{-6} M (compound) + 10^{-9} M 17β- estradiol to evaluate the ability of the compounds to function as antiestrogens. Cells were treated for 48 h prior to assay. Each 96-well plate contained a 17β–estradiol control. Sample population for at each dose was n=8.

Alkaline Phosphatase Assay:

At the end of 48h the media is aspirated and cells are washed three times with phosphate buffered saline (PBS). 50μL of lysis buffer (0.1 M Tris-HCl, pH 9.8, 0.2% Triton X-100) is added to each well. Plates are placed at -80°C for a minimum of 15 minutes. Plates are thawed at 37°C followed by the addition of 150μL of 0.1 M Tris-HCl, pH 9.8, containing 4 mM para-nitrophenylphosphate (pNPP) to each well (final concentration, 3 mM pNPP).

Absorbance and slope calculations were made using the KineticCalc Application program (Bio-Tek Instruments, Inc., Winooski, VT). Results are expressed as the mean +/- S.D. of the rate of enzyme reaction (slope) averaged over the linear portion of the kinetic reaction curve (optical density readings every 5 minutes for 30 minutes absorbance reading). Results for compounds are summarized as percent of response related to 1 nM 17β–estradiol.

Various compounds were assayed for estrogenic activity by the alkaline phosphatase method and corresponding ED50 values (95% C.I.) were calculated. The four listed in the following were used as as reference standards:

17β-estradiol	0.03 nM
17α-estradiol	1.42 nM
estriol	0.13 nM
estrone	0.36 nM

A description of these methods is described by Holinka, C.F., Hata, H., Kuramoto, H. and Gurpide, E. (1986) Effects of steroid hormones and antisteroids on alkaline phosphatase activity in human endometrial cancer cells (Ishikawa Line). Cancer Research, 46:2771-2774, and by Littlefield, B.A., Gurpide, E., Markiewicz, L., McKinley, B. and Hochberg, R.B. (1990) A simple and sensitive microtiter plate estrogen bioassay based on stimulation alkaline phosphatase in Ishikawa cells; Estrogen action of D5 adrenal steroids. Endocrinology, 6:2757-2762.

Ishikawa Alkaline Phosphatase Assay

Compound	% Activation
17β-estradiol	100% activity
tamoxifen	0% activity (45% with 1 nM 17β-estradiol)
raloxifene	5% activity (5% with 1 nM 17β-estradiol)
Example No. 98	1% activity (1% with 1 nM 17β-estradiol)

Method No. 18

2X VIT ERE Infection Assay

Cell Maintenance and Treatment

Chinese Hamster Ovary cells (CHO) which had been stably transfected with the human estrogen receptor were maintained in DMEM + 10% fetal bovine serum (FBS). 48h prior to treatment the growth medium was replaced with DMEM lacking phenol red + 10% dextran coated charcoal stripped FBS (treatment medium). Cells were plated at a density of 5000 cells/well in 96-well plates containing 200 μL of medium/well.

Calcium Phoshate Transfection

Reporter DNA (Promega plasmid pGL2 containing two tandem copies of the vitellogenin ERE in front of the minimal thymidine kinase promoter driving the luciferase gene) was combined with the B-galactosidase expression plasmid pCH110 (Pharmacia) and carrier DNA (pTZ18U) in the following ratio:

10uG of reporter DNA
5uG of pCH110DNA
5 uG of pTZ18U
20 uG of DNA/1 mL of transfection solution

The DNA (20uG) was dissolved in 500 uL of 250 mM sterile $CaCl_2$ and added dropwise to 500 uL of 2 X HeBS (0.28 M NaCl, 50 mM HEPES, 1.5 mM Na_2HPO_4, pH 7.05) and incubated at room temperature for 20 minutes. 20 uL of this mixture was added to each well of cells and remained on the cells for 16 h. At the end of this incubation the precipitate was removed, the cells were washed with media, fresh treatment media was replaced and the cells were treated with either vehicle, 1 nM 17β-estradiol, 1uM compound or 1 uM compound + 1 nM 17β-estradiol (tests for estrogen antagonism). Each treatment condition was performed on 8 wells (n=8) which were incubated for 24 h prior to the luciferase assay.

Luciferase Assay

After 24h exposure to compounds, the media was removed and each well washed with 2 X with 125 uL of PBS lacking Mg^{++} and Ca^{++}. After removing the PBS, 25 uL of Promega lysis buffer was added to each well and allowed to stand at room temperature for 15 min, followed by 15 min at -80°C and 15 min at 37°C. 20 uL of lysate was transferred to an opaque 96 well plate for luciferase activity evaluation and the remaining lysate (5 uL) was used for the B-galactosidase activity evaluation (normalize transfection). The luciferan substrate (Promega) was added in 100 uL aliquots to each well automatically by the luminometer and the light produced (relative light units) was read 10 seconds after addition.

Infection Luciferase Assay (Standards)

Compound	% Activation
17β-estradiol	100% activity
estriol	38% activity
tamoxifen	0% activity (10% with 1 nM 17β-estradiol)

raloxifene 0% activity (0% with 1 nM 17β-estradiol)

B-Galactosidase Assay

To the remaining 5 uL of lysate 45 uL of PBS was added. Then 50 uL of Promega B-galactosidase 2X assay buffer was added, mixed well and incubated at 37°C for 1 hour. A plate containing a standard curve (0.1 to 1.5 milliunits in triplicate) was set up for each experimental run. The plates were analyzed on a Molecular Devices spectrophotometric plate reader at 410 nm. The optical densities for the unknown were converted to milliunits of activity by mathematical extrapolation from the standard curve.

Analysis of Results

The luciferase data was generated as relative light units (RLUs) accumulated during a 10 second measurement and automatically transferred to a JMP (SAS Inc) file where background RLUs were subtracted. The B-galactosidase values were automatically imported into the file and these values were divided into the RLUs to normalize the data. The mean and standard deviations were determined from a n=8 for each treatment. Compounds activity was compared to 17β-estradiol for each plate. Percentage of activity as compared to 17β-estradiol was calculated using the formula %=((Estradiol-control)/(compound value)) X 100. These techniques are described by Tzukerman, M.T., Esty, A., Santiso-Mere, D., Danielian, P., Parker, M.G., Stein, R.B., Pike, J.W. and McDonnel, D.P. (1994). Human estrogen receptor transactivational capacity was determined by both cellular and promoter context and mediated by two functionally distinct intramolecular regions (see Molecular Endocrinology, 8:21-30).

Table 16

Infection Luciferase Activity

Example No.	1 uM	1 uM + 17β estradiol
No. 85	-2	43
No. 86	-5	2
No. 87	0	0
No. 88	4	44
No. 89	16	18
No. 90	3	58
No. 91	-3	56
No. 92	-4	-2
No. 93	-3	-2
No. 94	-5	15
No. 95	-4	-4
No. 96	12	8
No. 97	-4	-5
No. 98	5	5
No. 99	5	6
No. 100	9	10
No. 101	14	9
No. 102	9	10
No. 103	13	10
No. 104	7	7
No. 105	5	5
No. 106	10	81
No. 107	-1	54
No. 108	11	10
No. 109	6	5
No. 110	8	10
No. 111	25	23
No. 112	10	10
No. 113	14	16
No. 114	1	-1
No. 115	11	10
No. 116	-1	1
No. 117	0	1
No. 118	N/A	N/A
No. 119	-1	-1
No. 120	-1	1
No. 121	0	1
No. 122	1	5
No. 123	-1	1

Table 16 (Cont'd)
Infection Luciferase Activity

Example No.	1 uM	1 uM + 17β estradiol
No. 124	-2	-2
No. 125	-3	-2
No. 126	-1	0
No. 127	-3	-4
No. 132	-5	-2
No. 133	7	9
No. 134	9	5
No. 135	7	3
No. 136	16	10
No. 137	6	8
No. 138	-2	-1
No. 139	-12	-13
No. 160	N/A	N/A
No. 161	N/A	N/A
No. 162	-14	-13
No. 166	25	23
No. 167	4	10
No. 168	3	7

Method No. 19

Rat Uterotrophic/Antiuterotrophic Bioassay

The estrogenic and antiestrogenic properties of the compounds were determined in an immature rat uterotrophic assay (4 day) that (as described previously by L.J.Black and R.L.Goode, Life Sciences, **26**, 1453 (1980)). Immature Sprague-Dawley rats (female, 18 days old) were tested in groups of six. The animals were treated by daily ip injection with 10 uG compound, 100 uG compound, (100 uG compound + 1 uG 17β-estradiol) to check antiestrogenicity, and 1 uG 17β-estradiol, with 50% DMSO/50% saline as the injection vehicle. On day 4 the animals were sacrificed by CO_2 asphyxiation and their uteri were removed and stripped of excess lipid, any fluid removed and the wet weight determined. A small section of one horn was submitted for histology and the remainder used to isolate total RNA in order to evaluate complement component 3 gene expression.

Table 17

3 Day Rat Immature Uterine Assay

	Uterine wt mg	Uterine wt mg	Uterine wt mg	Uterine wt mg
Example No.	100 uG cmpd	100 uG cmpd + 1uG 17β-estradiol	1 uG 17β-estradiol	Vehicle
Tamoxifen	71.4 mg	N/A	98.2 mg	42.7 mg
No. 85	41.1 mg	92.4 mg	94.4 mg	26.6 mg
No. 94	28.1 mg	93.7 mg	88.5 mg	22.3 mg
No. 97	27.4 mg	24.3 mg	63.2 mg	30.7 mg
No. 98	29.4 mg	27.9 mg	94.1 mg	35.9 mg
No. 100	59.9 mg	68.7 mg	91.9 mg	23.4 mg
No. 101	65.1 mg	71.0 mg	113.7 mg	27.7 mg
No. 122	46.7 mg	38.7 mg	103.4 mg	30.3 mg
No. 123	39.2 mg	61.4 mg	94.4 mg	26.1 mg
No. 138	28.4 mg	37.9 mg	93.9 mg	24.6 mg
No. 139	30.4 mg	45.0 mg	82.1 mg	20.5 mg
No. 168	43.2 mg	81.7 mg	98.9 mg	25.5 mg

Method No. 20

6-Week Ovariectomized Rat Model

Female Sprague Dawley CD rats, ovx or sham ovx, were obtained 1 day after surgery from Taconic Farm (weight range 240 - 275 g). They were housed 3 or 4 rats/cage in a room on a 14/10 (light/dark) schedule and provided with food (Purina 500 rat chow) and water ad libitum. Treatment for all studies began 1 day after the animals arrival and dosed 5 or 7 days per week as indicated for 6 weeks. A group of age matched sham operated rats not receiving any treatment served as an intact, estrogen replete control group for each study. All treatments were prepared in 1% tween 80 in normal saline at defined concentrations so that the treatment volume was 0.1mL/100g body weight. 17-beta estradiol was dissolved in corn oil (20 uG/mL) and delivered subcutaneously, 0.1 mL/rat. All dosages were adjusted at three week intervals according to group mean body weight measurements.

Five weeks after the initiation of treatment and one week prior to the termination of the study, each rat was evaluated for bone mineral density (BMD). The BMD's of the proximal tibiae (PT) and fourth lumbar vertabrae (L4) were measured in anesthetized rats using a dual energy X-ray absorptiometer (Eclipse XR-26, Norland Corp. Ft. Atkins, WI). The dual energy X-ray absorptiometer (DXA) measurements for each rat were performed as follows: Fifteen minutes prior to DXA measurements, the rat was anesthetized with an intraperitoneal injection of 100 mg/kg ketamine (Bristol Laboratories, Syracuse, NY) and 0.75 mg/kg acepromazine (Aveco, Ft.Dodge, IA). The rat was placed on an acrylic table under the DXA scanner perpendicular to its path; the limbs were extended and secured with paper tape to the surface of the table. A preliminary scan was performed at a scan speed of 50 mm/second with a scan resolution of 1.5 mm X 1.5 mm to determine the region of interest in PT and L4. Small subject software was employed at a scan speed of 10mm/second with resolution of 0.5 mm X 0.5 mm for final BMD measurements. The software allows the operator to define a 1.5 cm wide area to cover the total length of L4. The BMDs for respective sites were computed by the software as a function of the attenuation of the dual beam (46.8 KeV and 80 KeV) X-ray generated by the source underneath the subject and the detector travelling along the defined area above the subject. The data for BMD values (expressed in g/cm2) and individual scans were stored for statistical analysis.

One week after BMD evaluation the rats were sacrificed by carbon dioxide suffocation and blood collected for cholesterol determination. The uteri were removed and the weights taken. Total cholesterol is determined using a Boehringer-Mannheim Hitachi 911 clinical analyzer using the Cholesterol/HP kit. Statitstics were compared using one-way analysis of variance with Dunnet's test.

Table 18

6-Week Ovariectomized Rat Study Of Example No. 98

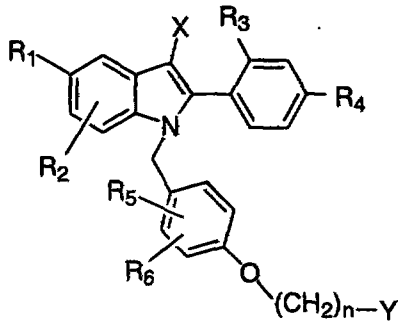
Treatment	BMD (mg/cm^2)[a,b] Proximal Tibia	BMD (mg/cm^2)[a,b] L_4	Body Weight (g)[a,c]	Uterine Weight (mg)[a,c]	Cholesterol (mg/dl)[a,c]
Study [d]					
Sham (Intact)	0.211** ±0.003	0.183* ±0.003	43.0* ±6.0	426.4** ±25.0	71.6** ±5.0
Vehicle (Ovx)	0.189 ±0.004	0.169 ±0.004	62.7 ±8.2	118.2 ±7.8	87.2 ±3.0
Example No. 98 0.3mg/kg, p.o.	0.210** ±0.003	0.173 ±0.003	46.8 ±6.6	149.3 ±4.4	59.0** ±2.2
Raloxifene 3mg/kg, p.o.	0.207** ±0.006	0.170 ±0.003	25.3** ±5.4	191.6** ±9.3	55.0** ±2.4
17ß-Estradiol 2µg/rat, s.c.	0.224** ±0.004	0.169 ±0.004	33.1** ±4.9	426.0** ±18.4	95.5 ±3.9

[a] Mean ± SEM
[b] Following 5 weeks of treatment
[c] Following 6 weeks of treatment
[d] Daily treatment x7 days/week x6 weeks

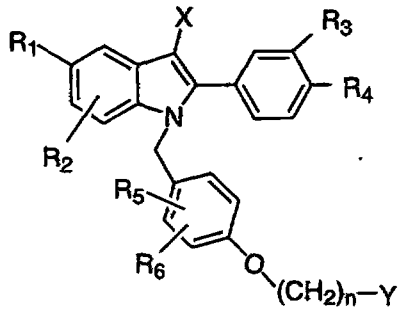
*$p < 0.05$ vs corresponding Vehicle value
**$p < 0.01$ vs corresponding Vehicle value

CLAIMS:

1. A pharmaceutical composition comprising one or more estrogens and a compound having the structure:



or



(I) (II)

wherein:

R_1 is selected from H, OH or the C_1-C_{12} esters (straight chain or branched) or C_1-C_{12} (straight chain or branched or cyclic) alkyl ethers thereof, or halogens; or C_1-C_4 halogenated ethers including trifluoromethyl ether and trichloromethyl ether.

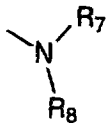
R_2, R_3, R_4, R_5, and R_6 are independently selected from H, OH or the C_1-C_{12} esters (straight chain or branched) or C_1-C_{12} alkyl ethers (straight chain or branched or cyclic) thereof, halogens, or C_1-C_4 halogenated ethers including trifluoromethyl ether and trichloromethyl ether, cyano, C_1-C_6 alkyl (straight chain or branched), or trifluoromethyl, with the proviso that, when R_1 is H, R_2 is not OH.

X is selected from H, C_1-C_6 alkyl, cyano, nitro, trifluoromethyl, halogen;

n is 2 or 3;

Y is selected from:

a) the moiety:



wherein R_7 and R_8 are independently selected from H, C_1-C_6 alkyl, or phenyl optionally substituted by CN, C_1-C_6 alkyl (straight chain or branched), C_1-C_6 alkoxy (straight chain or branched), halogen, -OH, $-CF_3$ or $-OCF_3$; or R_7 and R_8 are concatenated together as $-(CH_2)p-$, wherein p is an integer of from 2 to 6, preferably 4

to 6, the ring so formed is optionally substituted with 1-3 substituents selected from C_1-C_3 alkyl, trifluoromethyl, halogen, hydrogen, phenyl, nitro and -CN

b) a five-, six- or seven- membered saturated, unsaturated or partially unsaturated heterocycle containing up to two heteroatoms selected from -O-, -NH-, -N(C_1C_4 alkyl)-, -N= and -$S(O)_m$-, wherein m is an integer of from 0-2, optionally substituted with 1-3 substituents independently selected from hydroxyl, halo, C_1-C_4 alkyl, trihalomethyl, C_1-C_4alkoxy, trihalomethoxy, C_1-C_4acyloxy, C_1-C_4alkylthio, C_1-C_4alkylsulfinyl, C_1-C_4 alkylsulfonyl, hydroxy(C_1-C_4)alkyl, -CO_2H, -CN, -$CONHR_1$, -NH_2, C_1-C_4alkylamino, di-(C_1-C_4)alkylamino, -$NHSO_2R_1$, -$NHCOR_1$, -NO_2, and phenyl optionally substituted with 1-3 (C_1-C_4)alkyl, wherein R_1 is as defined above or C_1-C_6 alkyl ;

c) a bicyclic heterocycle containing from 6-12 carbon atoms either bridged or fused and containing up to two heteroatoms selected from -O-, -NH-, -N(C_1C_4 alkyl)-, and -$S(O)_m$-, wherein m is an integer of from 0-2, optionally substituted with 1-3 substituents independently selected hydroxyl, halo, C_1-C_4 alkyl, trihalomethyl, C_1-C_4 alkoxy, trihalomethoxy, C_1-C_4 acyloxy, C_1-C_4 alkylthio, C_1-C_4 alkylsulfinyl, C_1-C_4 alkylsulfonyl, hydroxy(C_1-C_4)alkyl, -CO_2H, -CN-, -$CONHR_1$-, -NH_2, C_1-C_4 alkylamino, di(C_1-C_4)alkylamino, -$NHSO_2R_1$, -$NHCOR_1$, -NO_2, and phenyl optionally substituted with 1-3 (C_1-C_4) alkyl;

or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or excipient.

2. A pharmaceutical composition of Claim 1 wherein:

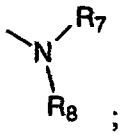
R_1 is selected from H, OH or the C_1-C_4 esters or alkyl ethers thereof, halogen;

R_2, R_3, R_4, R_5, and R_6 are independently selected from H, OH or the C_1-C_4 esters or alkyl ethers thereof, halogen, cyano, C_1-C_6 alkyl, or trifluoromethyl, with the proviso that, when R_1 is H, R_2 is not OH;

X is selected from H, C_1-C_6 alkyl, cyano, nitro, trifluoromethyl, halogen;

Y is the moiety





;

R_7 and R_8 are selected independently from H, C_1-C_6 alkyl, or combined by -$(CH_2)p$-, wherein p is an integer of from 2 to 6, so as to form a ring, the ring being optionally substituted by up to three substituents selected from hydroxyl, halo, C_1-C_4 alkyl, trihalomethyl, C_1-C_4 alkoxy, trihalomethoxy, C_1-C_4 alkylthio, C_1-C_4 alkylsulfinyl, C_1-C_4 alkylsulfonyl, hydroxy (C_1-C_4)alkyl, -CO_2H, -CN, -CONH(C_1-C_4)alkyl, -NH_2, C_1-C_4 alkylamino, di-(C_1-C_4)alkylamino, -$NHSO_2$(C_1-C_4)alkyl, -NHCO(C_1-C_4)alkyl and -NO_2;

or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or excipient.

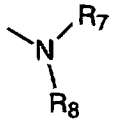
3. A pharmaceutical composition of Claim 1 wherein:

R_1 is OH;

R_2, R_3, R_4, R_5, and R_6 are independently selected from H, OH or the C_1-C_4 esters or alkyl ethers thereof, halogen, cyano, C_1-C_6 alkyl, or trifluoromethyl, with the proviso that, when R_1 is H, R_2 is not OH;

X is selected from the group of Cl, NO_2, CN, CF_3, or CH_3;

Y is the moiety



; and

R_7 and R_8 are concatenated together as -$(CH_2)_r$-, wherein r is an integer of from 4 to 6, to form a ring optionally substituted by up to three subsituents selected from hydroxyl, halo, C_1-C_4 alkyl, trihalomethyl, C_1-C_4 alkoxy, trihalomethoxy, C_1-C_4 alkylthio, C_1-C_4 alkylsulfinyl, C_1-C_4 alkylsulfonyl, hydroxy (C_1-C_4)alkyl, -CO_2H, -CN, -CONH(C_1-C_4)alkyl, -NH_2, C_1-C_4 alkylamino, di-(C_1-C_4)alkylamino, -$NHSO_2$(C_1-C_4)alkyl, -NHCO(C_1-C_4)alkyl and -NO_2;

or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or excipient.



4. A pharmaceutical composition of Claim 1 in which the compound is 5-benzyloxy-2-(4-ethoxyphenyl)-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)benzyl]-1H-indole or a pharmaceutically acceptable salt thereof.

5. A pharmaceutical composition of Claim 1 in which the compound is 1-[4-(2-azepan-1-yl-ethoxy)benzyl]-2-(4-hydroxy-phenyl)-3-methyl-1H-indol-5-ol or a pharmaceutically acceptable salt thereof.

6. A pharmaceutical composition of Claim 1 in which the compound is 4-{3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)benzyl]-1H-indole} or a pharmaceutically acceptable salt thereof.

7. A pharmaceutical composition of Claim 1 in which the compound is 4-{5-fluoro-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indol-2-yl}-phenol or a pharmaceutically acceptable salt thereof.

8. A pharmaceutical composition of Claim 1 in which the compound is 1-[4-(2-azepan-1-yl-ethoxy)-benzyl]-2-(4-hydroxy-phenyl)-3-methyl-1H-indol-5-ol or a pharmaceutically acceptable salt thereof.

9. A pharmaceutical composition of Claim 1 in which the compound is 2-(4-hydroxyphenyl)-3-methyl-1-[4-(2-dimethyl-1-yl-ethoxy)benzyl]-1H-indol-5-ol or a pharmaceutically acceptable salt thereof.

10. A pharmaceutical composition of Claim 1 in which the compound is 2-(4-hydroxyphenyl)-3-methyl-1-[4-(2-diethyl-1-yl-ethoxy)benzyl]-1H-indol-5-ol or a pharmaceutically acceptable salt thereof.

11. A pharmaceutical composition of Claim 1 in which the compound is 2-(4-cyclopenyloxyphenyl)-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)benzyl]-1H-indol-5-ol or a pharmaceutically acceptable salt thereof.



12. A pharmaceutical composition of Claim 1 in which the compound is 3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)benzyl]-2-(4-trifluoromethylphenyl)-1H-indol-5-ol or a pharmaceutically acceptable salt thereof.

13. A pharmaceutical composition of Claim 1 in which the compound is 2-(4-hydroxyphenyl)-1-[3-methoxy-4-(2-piperidin-1-ylethoxy)benzyl]-3-methyl-1H-indol-5-ol or a pharmaceutically acceptable salt thereof.

14. A pharmaceutical composition of Claim 1 in which the compound is 2-(4-hydroxyphenyl)-1-[3-methoxy-4-(2-azepan-1-yl-ethoxy)benzyl]-3-methyl-1H-indol-5-ol or a pharmaceutically acceptable salt thereof.

15. A pharmaceutical composition of any one of Claims 1 to 14 wherein the one or more estrogens are selected from equilin, equilenin, estradiene, ethinyl estradiol, 17β-estradiol, 17alpha-dihydroequilenin, 17β-dihydroequilenin, menstranol, conjugated estrogens, estrone, 17alpha-estradiol sulfate, Delta8,9- dehydroestrone, equol or enterolactone; or a pharmaceutically acceptable salt or ester thereof.

16. A pharmaceutical composition of Claim 15 wherein the pharmaceutically acceptable salt of the one or more estrogens is a sodium salt.

17. A method of treating or preventing bone loss in a mammal, the method comprising administering to a mammal in need thereof an effective amount of an estrogen and an effective amount of a compound of any one of Claims 1 to 14, or a pharmaceutically acceptable salt thereof.

18. A method of treating or preventing disease states or syndromes which are caused or associated with an estrogen deficiency in a mammal, the method comprising administering to a mammal in need thereof an effective amount of an estrogen and an effective amount of a compound of any one of Claims 1 to 14, or a pharmaceutically acceptable salt thereof.

19. A method of treating or preventing cardiovascular disease in a mammal, the method comprising administering to a mammal in need thereof an effective amount



of an estrogen and an effective amount of a compound of any one of Claims 1 to 14, or a pharmaceutically acceptable salt thereof.

20. A method of treating or preventing disease in a mammal which result from proliferation or abnormal development, actions or growth of endometrial or endometrial-like tissue, the method comprising administering to a mammal in need thereof an effective amount of an estrogen and an effective amount of a compound of any one of Claims 1 to 14, or a pharmaceutically acceptable salt thereof.

21. A method of treatment of Claim 20 wherein the disease is endometriosis.

22. A product comprising one or more estrogens and a compound having the structure (I) or (II) as claimed in any one 1 to 14 as a combined preparation for simultaneous , separate or sequential use in the treatment or prevention of cardiovascular disease, or a disease in a mammal which results from proliferation or abnormal development, actions or growth of endometrial or endometrial-like tissue, or disease states or syndromes which are caused or associated with an estrogen deficiency

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
A61K 31/40, 31/565

A1

(11) International Publication Number: WO 99/59581

(43) International Publication Date: 25 November 1999 (25.11.99)

(21) International Application Number: PCT/US99/10217

(22) International Filing Date: 11 May 1999 (11.05.99)

(30) Priority Data:
09/079,561 15 May 1998 (15.05.98) US

(71) Applicant: AMERICAN HOME PRODUCTS CORPORATION [US/US]; Five Giralda Farms, Madison, NJ 07940-0874 (US).

(72) Inventors: PICKAR, James, Harrison; 816 Crum Creek Road, Springfield, PA 19064 (US). KOMM, Barry, Samuel; 1506 Melrose Avenue, Havertown, PA 19083 (US).

(74) Agents: ECK, Steven, R.; American Home Products Corporation, Patent Law Dept.- 2B, One Campus Drive, Parsippany, NJ 07054 (US) et al.

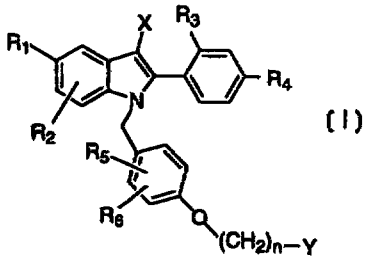
(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published

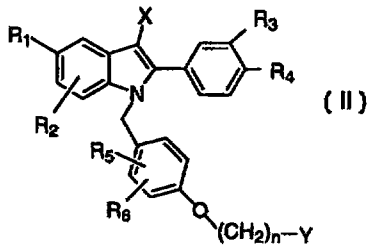
With international search report.

Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: 2-PHENYL-1-[4-(2-AMINOETHOXY)-BENZYL]-INDOLE IN COMBINATION WITH ESTROGENS



(I)



(II)

(57) Abstract

The present invention relates to new formulations containing one or more estrogens and 2- phenyl- 1-[4-(2-aminoethoxy)benzyl]-Indole compounds which are useful as estrogenic agents, as well as pharmaceutical compositions and methods of treatment utilizing these compounds, which have general structures (I) or (II).