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# Diaryl naphthyl methanes a novel class of anti-implantation agents

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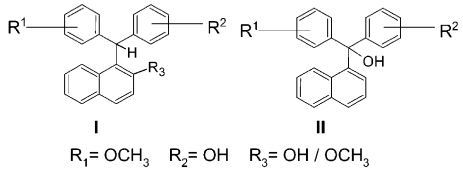
**Abstract**—Diaryl naphthyl methanes and the corresponding 1, 2, 3, 4- and 5, 6, 7, 8-tetrahydro naphthyl methane derivatives have been synthesized as novel estrogen receptor binding ligands. The secondary and tertiary amino alkoxy derivatives of diaryl naphthyl and tetrahydro naphthyl methane interact with the estrogen receptor to elicit promising estrogenic, antiestrogenic and implantation inhibition activities in rats. The most active compounds in this series are **7**, **9** and **20**, cent percent active in preventing implantation in rats at 2.5 mgkg$^{-1}$ dose.


## 1. Introduction

The importance of estrogen antagonists as pharmaceuticals lies in their tissue selective activity. Although the molecular requirement for estrogen agonist and antagonist actions has been worked out to a large extent, their tissue selective action is poorly understood. Therefore, synthesis and biological evaluation of new estrogen agonists and antagonists continues for an in-depth understanding of their site and mechanism of action.[1–3]

Most of the estrogen antagonists known today including ormeloxifene,[4,5] the first non-steroidal oral contraceptive introduced by our group, possess triaryl ethylene (TAE) frame work,[6] present in an acyclic or cyclic form. The estrogen receptor (ER) model proposed by us earlier[7] (Fig. 1) and later supported by X-ray studies reported by Brzozowski et al.,[8] suggested presence of subsites on ER active site corresponding to estrogen agonist and antagonist actions. Looking for a deviation from TAEs for a possibly better tissue selective action and utilizing the above information on receptor model, development of novel diaryl naphthyl methane molecules was conceived. We report here our work on diaryl naphthyl methane and corresponding 1, 2, 3, 4- and 5, 6, 7, 8-tetrahydro naphthyl methane derivatives which furnished a large number of compounds possessing estrogenic, antiestrogenic and promising antiimplantation activities.

It was conceived that a diaryl naphthyl methane molecule carrying a basic side chain on an aryl residue may interact with ER and therefore, exhibit estrogen agonistic/antagonistic activity. Thus, prototypes **I** and **II** were synthesized.[9] However, such compounds were found to be inactive. This inactivity was presumably due to the presence of hydroxyl functions (OH and OR) at an inappropriate location (lypophilic sites). This is supported by the observation that prototype **III** now reported, lacking such hydrophilic residues showed significant antifertility activity.




The most promising compounds **7**, **9** and **20** were found to be active at 2.5 mgkg$^{-1}$ dose in rats when administered orally on day 1–7 postcoitum. However, in the single day administration it was active only at a dose of 15 mgkg$^{-1}$. This reduced activity may be assigned to a likely metabolism of the triaryl methane residue, wherein a facile formation of a methane free radical[10] is possible or poor absorption from the gastrointestinal tract.

In view of the above observation, synthesis of corresponding 1,2,3,4-tetrahydronaphthalenes **IV** was undertaken. During this synthesis, 5,6,7,8-tetrahydronaphthalenes **V** were also formed.[11] Interestingly both these prototypes were found to be active.

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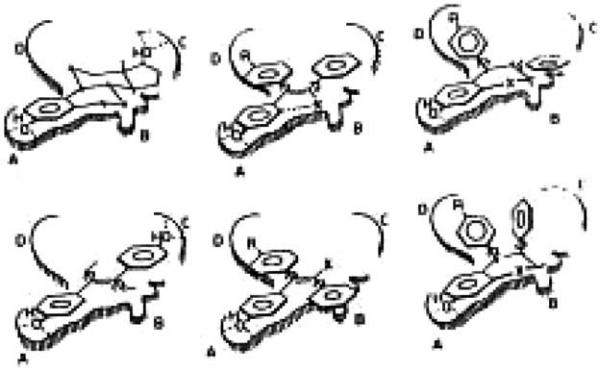

**Figure 1.** Possible regions of the ligand binding site of oestrogen receptor involved in binding of the steroidal, stilbene, cis and trans triarylethylene and triarylethane estrogens.

Compounds substituted with a tertiary aminoethoxy or a 3-substituted amino-2-hydroxy propyloxy group at the *para* position of an aryl residue elicited antifertility activity at doses varying from 1–10 mgkg$^{-1}$ day$^{-1}$.

## 2. Chemistry

Synthesis of diaryl naphthyl methane derivatives was carried out starting with α-naphthoic acid **1**. Condensation of α-naphthoic acid with anisole in the presence of polyphosphoric acid produced 4-methoxy-naphthophenone 2 which on reduction with sodium borohydride gave (4-methoxyphenyl)-naphth-1-yl-carbinol **3** (Scheme). A Friedel-Crafts reaction on the carbinol **3** with phenol furnished (4-methoxyphenyl)-(4-hydroxyphenyl)-naphth-1-yl methane **4** as the main product along with other side products. Similarly, Friedel–Crafts reaction on the o-cresol generated (4-methoxyphenyl)-(4-hydroxy-3-methyl phenyl)-naphth-1-yl-methane **5**. When m-cresol was used in the above Friedel–Crafts reaction (4-methoxyphenyl)-(4-hydroxy-2-methyl phenyl)-naphth-1-yl methane **6** was obtained in major amounts (Table 1). Carrying out Friedel–Crafts reaction twice, instead of generating diaryl naphthyl methane through Friedel–Crafts on naphthaldehyde was necessary as to have selectivity of the substituent on the two aryl residues.

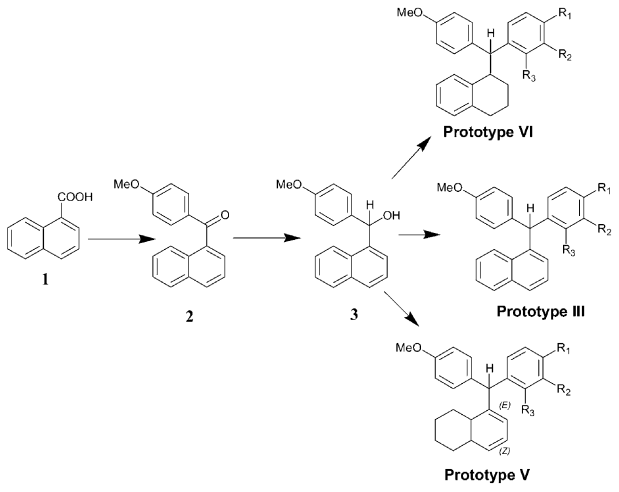


**Table 1.**

| S. No | Prototype | $R_1$ | $R_2$ | $R_3$ |
|---|---|---|---|---|
| 4 | III | OH | H | H |
| 5 | III | OH | $CH_3$ | H |
| 6 | III | OH | H | $CH_3$ |
| 7 | III | 2-Pyrrolidin-1-yl-ethoxy | H | H |
| 8 | III | 2-Pyrrolidin-1-yl-ethoxy | $CH_3$ | H |
| 9 | III | 2-Pyrrolidin-1-yl-ethoxy | H | $CH_3$ |
| 10 | III | (Butyl-methyl-amino)-methoxy | H | H |
| 11 | III | Dimethylamino-methoxy | H | H |
| 12 | III | 2-Diethylamino-ethoxy | $CH_3$ | H |
| 13 | III | 2-Diethylamino-ethoxy | H | $CH_3$ |
| 14 | III | 2-Piperidin-1-yl-ethoxy | H | H |
| 15 | III | 2-Piperidin-1-yl-ethoxy | CH3 | H |
| 16 | IV | OH | H | H |
| 17 | IV | OH | $CH_3$ | H |
| 18 | IV | 2-Pyrrolidin-1-yl-ethoxy | H | H |
| 19 | IV | 2-Pyrrolidin-1-yl-ethoxy | $CH_3$ | H |
| 20 | IV | 2-Piperidin-1-yl-ethoxy | H | H |
| 21 | IV | 2-Piperidin-1-yl-ethoxy | $CH_3$ | H |
| 22 | IV | 2-Diethylamino-ethoxy | H | H |
| 23 | IV | 2-Diethylamino-ethoxy | $CH_3$ | H |
| 24 | V | OH | H | H |
| 25 | V | OH | $CH_3$ | H |
| 26 | V | 2-Pyrrolidin-1-yl-ethoxy | H | H |
| 27 | V | 2-Pyrrolidin-1-yl-ethoxy | $CH_3$ | H |
| 28 | V | 2-Piperidin-1-yl-ethoxy | H | H |
| 29 | V | 2-Piperidin-1-yl-ethoxy | $CH_3$ | H |
| 30 | V | 2-Diethylamino-ethoxy | H | H |
| 31 | V | 2-Diethylamino-ethoxy | $CH_3$ | H |
| 32 | III | Oxiranyl-methyloxy | H | H |
| 33 | III | Oxiranyl-methyloxy | $CH_3$ | **H** |
| 34 | III | 3-Butylamino-2-hydroxy-1-propyloxy | H | H |
| 35 | III | 3-Butylamino-2-hydroxy-1-propyloxy | $CH_3$ | **H** |
| 36 | III | 3-Propylamino-2-hydroxy-1-propyloxy | H | H |
| 37 | III | 3-Cyclopropylamino-2-hydroxy-1-propyloxy | H | H |
| 38 | III | 3-Pyrrolidin-1-yl-2-hydroxy-1-propyloxy | H | $CH_3$ |
| 39 | III | 3-Piperidin-1-yl-2-hydroxy-1-propyloxy | H | H |
| 40 | III | 3-Morpholin-4-yl-2-hydroxy-1-propyloxy | H | H |
| 41 | III | 3-Piperazin-1-yl-2-hydroxy-1-propyloxy | H | H |
| 42 | III | 3-Cyclohexyl-2-hydroxy-1-propyloxy | H | H |
| 43 | III | 3-Diethylamino-2-hydroxy-1-propyloxy | H | H |
| 44 | IV | Oxiranyl-methyloxy | H | H |
| 45 | IV | Oxiranyl-methyloxy | $CH_3$ | H |
| 46 | IV | 3-Butylamino-2-hydroxy-1-propyloxy | H | H |
| 47 | IV | 3-Butylamino-2-hydroxy-1-propyloxy | $CH_3$ | H |
| 48 | IV | 3-Dibutylamino-2-hydroxy-1-propyloxy | H | |
| 49 | V | Oxiranyl-methyloxy | H | H |
| 50 | V | Oxiranyl-methyloxy | $CH_3$ | H |
| 51 | V | 3-Butylamino-2-hydroxy-1-propyloxy | H | H |
| 52 | V | 3-Butylamino-2-hydroxy-1-propyloxy | $CH_3$ | H |

Catalytic hydrogenation of the above naphthyl derivatives **4**, **5** and **6** using Raney nickel as catalyst furnished corresponding 1, 2, 3, 4- and 5, 6, 7, 8-tetrahydronaphth-1-yl-methane derivatives **16**–**17** and **24**–**25** respectively (Table 1).

A substituted amino alkyl group, generally a basic requirement for estrogen antagonistic activity,[12–15] was introduced in the phenol derivatives **4**–**6** and their corresponding tetrahydro derivatives **16**–**17** and **24**–**25** for the preparation of the desired compounds. A tertiary amino alkyl group was introduced by reacting the phenol derivative with a tertiary amino alkyl halide (Table 1). When the substituted phenol was first reacted with epichlorohydrin and subsequently with a primary or secondary amine, it yielded 3-substitutedamino-2-hydroxypropyl derivatives (Table 1).

Similarly, aminoalkoxy derivatives of 1, 2, 3, 4- and 5, 6, 7, 8-tetrahydro-naphth-1-yl-methane derivatives were also prepared (Table 1). Compounds thus prepared were routinely screened for antiimplantation activity. Compounds showing cent percent activity at 10 $mgkg^{-1}$ or lower doses were generally evaluated for the Relative Binding Affinity (RBA) for ER, estrogenic and anti-estrogenic activities. Results are shown in Table 2.

All these compounds thus prepared were obtained as racemates. An effective separation into pure enantiomeric forms through optical resolution of their salts with di-p-toluoyl-D-tartaric acid and di-p-toluolyl-L-tartaric acid could not be achieved. Also, diastereomeric forms of prototype IV have not been separated.

## 3. Results and discussion

On the basis of Structure Activity Relationship (SAR) studies carried out on antiestrogenic molecules prepared in our laboratory and else where, we had earlier proposed an estrogen receptor model.[7] The receptor was analyzed as composed of four subunits ABCD (Fig. 1), wherein sub sites A to C presumably interact with estrogenic component. Sub site D is the antiestrogen binding site where the nitrogen containing basic side chain of antiestrogens interact.

The validity of this model received support from the X-ray studies with raloxifene bound receptor[8] which suggested that the extent of anti-estrogenicity much depend upon positioning of the anti-estrogenic basic chain, which in turn is structure dependent. Therefore, subtle changes in the molecular structure may bring about significant changes in the agonist to antagonist ratio of the compound, which determines its particular pharmaceutical usage. Novel diaryl naphthyl methane derivatives were designed to fit into the ER model.

A study of the 3-D molecular structure of diaryl naphthyl methane, its comparison with estradiol and the potent antiestrogen centchroman on silicon graphics Indy R 4000 workstation employing Molecular Simulations software (Insight II[16] and Discover[17]) was carried out. Structures were built in builder module of Insight II software. The 3-D structures were later optimized for their geometry using CVFF forcefield[18] and the energy minimization was performed using steepest descent, conjugate gradient, Newton Raphsons algorithms in sequence followed by Quasi Newton Raphson (va09a) implemented in the discover module by using 0.001

**Table 2.**

| S. No. | Dose ($mgkg^{-1}$) | Efficacy (%) | RBA% of Estradiol | Estrogenicity (% increase in uterine weight) | Antiestrogenicity (% inhibition in ethynyl estradiol induced uterine weight gain) |
|---|---|---|---|---|---|
| 7 | 2.5 | 100 | 14 | 171 | 42 |
| | 1 | 75 | | | |
| 8 | 10 | 100 | 0.078 | ND | ND |
| 9 | 2.5 | 100 | 0.80 | 202 | 46 |
| 14 | 10 | 100 | 0.80 | 120 | 42 |
| 15 | 10 | 100 | 0.029 | ND | |
| | 5 | Inactive | | | |
| 18 | 10 | 100 | 6.126 | 168 | 29 |
| | 7.5 | 199 | ND | ND | ND |
| | 5 | 75 | | | |
| 20 | 2.5 | 100 | 5.15 | 200 | 41 |
| 21 | 5 | 100 | 1.15 | 143 | 25 |
| | 2.5 | 67 | | | |
| 22 | 10 | 100 | 5.158 | ND | ND |
| 23 | 10 | 100 | 0.771 | ND | ND |
| 26 | 5 | 100 | 14.27 | 105 | 26 |
| | 2.5 | 67 | | | |
| | 1 | 50 | | | |
| 29 | 10 | 100 | 0.78 | ND | ND |
| 30 | 15 | 100 | 0.62 | ND | ND |
| | 10 | 75 | | | |
| 34 | 10 | 100 | ND | ND | ND |
| 37 | 10 | 100 | 0.84 | 196 | 36 |
| 38 | 5 | 100 | 0.293 | 159 | 34 |
| | 2.5 | Inactive | | 18 | 10 |
| 39 | 15 | 100 | 10.48 | 196 | 31 |
| | 10 | 66.6 | | | |
| 40 | 15 | 100 | 0.68 | 150 | 34 |
| | 5 | Inactive | | 1961 | 35 |
| 42 | 10 | 100 | 0.76 | 169 | 25 |
| 46 | 5 | 100 | 5.14 | 119 | 14 |
| | 2.5 | Inactive | | | |
| 47 | 5 | 100 | 2.66 | 132 | 25 |
| | 2.5 | Inactive | | | |
| 48 | 5 | 100 | 17.28 | 129 | 27 |
| 52 | 10 | 75 | 33.49 | 133 | 20 |

kcalmol$^{-1}$ energy gradient convergence and maximum number of iteration set to 1000. Energy minimized structures were stored in MDL format.

The conformational resemblances of the molecules were assessed using the RMS fitting option of the Search-Compare[19] module. One-to-one correspondences for atoms in the molecules to be superimposed were specified. The RMS fit between the superimposed molecules was noted. Figure 2 shows molecular similarity of diaryl naphthyl methane with estradiol. The RMS fit value was found to be 0.665287. This would suggest the binding of the molecule to the receptor at the active site where estradiol binds. Superimposition of the diaryl naphthyl methane molecule on to the antiestrogen centchroman shown in Figure 2, with RMS fit value of 0.662630, shows that in both the molecules the nitrogen containing basic residue is similarly disposed.

In our X-ray based studies reported earlier,[20] we have shown that potent antiestrogens like tamoxifen, nafoxidene and centchroman show similar disposition in space. Thus, the present study correlates diaryl naphthyl methanes with other antiestrogens, which explains its antiestrogenic behavior.

Interestingly, A ring reduced diaryl naphthyl methanes were found to be equipotent as B ring reduced compounds. This may be explained on the basis of molecular modeling studies, which suggest (Fig. 2) that the molecule could be alternatively superimposed on to estradiol with the D ring of estradiol overlaying A ring of the diaryl naphthyl methane, (RMS fit value 0.089109).

These compounds were synthesized as antiimplantation agents wherein antiestrogenic property of the compound interferes with the implantation process in rats. However, a weak estrogenic profile may be helpful in proper regulation of the reproductive processes. Significant activity was observed only in basic chain added compounds Table 2. Compounds **7**, **9** and **20** found to be active at 2.5 mgkg$^{-1}$ dose were most active ones of this series. Unlike 3, 4-diaryl chromenes and chromans[21] wherein a 3-substitutedamino-2-hydroxypropyloxy group added compound showed better activity as compared to 2-tertiary aminoethoxy, in this series the latter group

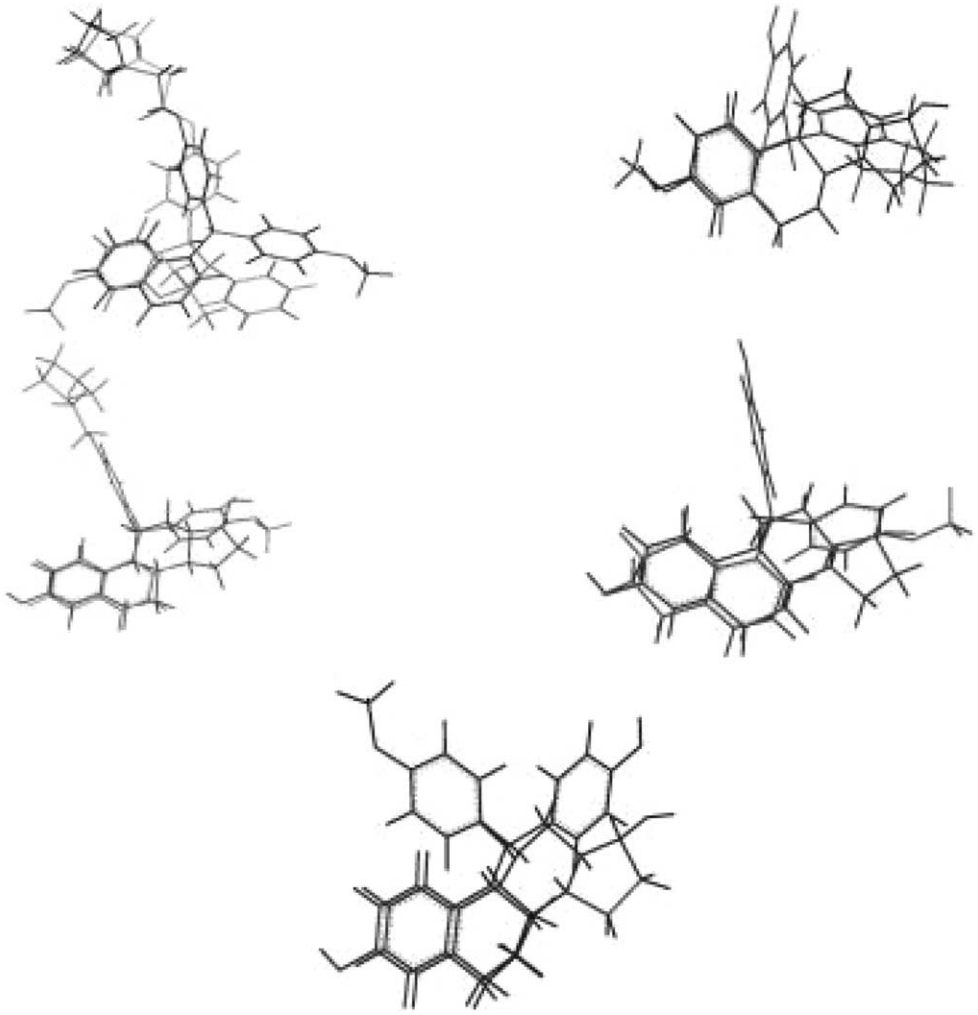

**Figure 2.** Superposition of (a) centchroman with diaryl naphthyl methane, (b) diaryl naphthyl methane with estradiol, (c) diaryl naphthyl methane (A ring reduced) with A ring of estradiol, (d) diaryl naphthyl methane (B ring reduced) with D ring of estradiol and (e) diaryl naphthyl methane (B ring reduced) with estradiol.

was found to be better. Since the compounds did not possess a free phenolic group, their RBA values were of low order.

It has been earlier shown[22] that a phenolic residue in the estradiol binding zone, on substitution with a basic chain, produces compounds with lower RBA value compared to the phenol whereas a similar substitution when carried out on a phenolic residue present in anti-estrogen binding zone enhances the RBA of the compound. In the present series it was observed that incorporation of a basic residue in prototype **IV** resulted in a decrease of RBA whereas a similar change in prototype **V** had a reverse effect. However, hydroxy compounds in all three prototypes were either less active or inactive, thereby suggesting that the biological activity is not through removal of the basic chain and a consequent estrogenic effect produced by the hydroxy group thus generated. It is likely that under the present situation, the diphenyl methyl residue attached to naphthyl ring enjoys a free rotation thereby the phenolic residue may occupy a position in the estrogen binding zone when unsubstituted or on the antiestrogen binding zone when a basic residue is attached.

## 4. Experimental

### 4.1. (4-Methoxy-phenyl)-1-(naphth-1-yl)-ketone (2)

A mixture of naphthoic acid (10 g, 0.057 mol), anisole (18 mL, 0.165 mol) and polyphosphoric acid (100 g) was taken in r.b. flask. The reaction mixture was heated for 10–12 h on water bath at 80 °C. The reaction mixture was then poured onto ice and extracted with ethyl acetate. Excess of naphthoic acid was washed off with sodium bicarbonate and then organic layer was washed with water till neutral, dried over sodium sulphate and concentrated. The oily residue thus obtained was crystallized from benzene–hexane.

### 4.2. (4-Methoxy-phenyl)-1-naphth-1-yl-carbinol (3)

Naphthophenone (10 g, 0.038 mol) was dissolved in 100 mL of methanol. To the stirred reaction mixture, sodium borohydride (2.5 g, 0.66 mol) was added slowly and stirring continued for 4–5 h. Then methanol was distilled off and the reaction mixture was extracted with ethyl acetate. The organic layer was washed with water, dried over sodium sulphate and concentrated. The oily residue thus obtained was crystallized from benzene–hexane.

### 4.3. General procedure for preparation of compounds 4–6

A mixture of (4-methoxy-phenyl)-naphth-1-yl-carbinol (1.0 mmol) and substituted phenol (1.0 mmol) was taken in a mixture of dry benzene and dry pentane (1:1). To this stirred solution, $AlC_{13}$ (1.0 mmol) was added at 0–4 °C. After 15 min tin (lV) chloride (1.5 mmol)) was added and stirring continued for 4–5 h. Reaction mixture was decomposed with ice-cold water (200 mL) containing 0.5 mL concd HCl, and extracted with ethyl acetate. The organic layer was washed with water, dried over sodium sulphate and concentrated. This crude product was purified by flash column chromatography on silica gel using 5% ethyl acetate in hexane as eluant.

### 4.4. General procedure for preparation of compounds 7–9, 11–15, 18–23 and 26–31

A mixture of substituted (4-methoxyphenyl)-(4-hydroxyphenyl)-naphth-1-yl-methane (1 mmol), anhydrous potassium carbonate (3 fold excess by weight), tertiary amino alkyl halide chain (2 mmol) and dry acetone (as solvent) was refluxed for 8–12 h. Potassium carbonate was filtered off, acetone was distilled off and residue was diluted with water, dried over sodium sulphate and concentrated. The oil thus obtained was treated with ethanolic HCl. The solvent was evaporated off and compound was crystallized from absolute alcohol and dry ether, filtered under anhydrous condition (hygroscopic) and dried in Abderhalden drying apparatus.

### 4.5. (4-Methoxyphenyl)-(4-pyrrolidinoethoxy-phenyl)-naphth-1-yl-methane *N*-methyl iodide (10)

A mixture of (4-methoxyphenyl)-(4-pyrrolodinoethoxy-phenyl)-naphth-1-yl-methane (0.5 g, 1.14 mmol), methyl iodide (0.3 mL, 4.81 mmol) anhydrous potassium carbonate (1 g, 7.24 mmol) in dry acetone (20 mL) was refluxed for 15 h. Acetone was distilled off. Reaction mixture was extracted with ethyl acetate, washed with water, dried over anhydrous sodium sulphate and concentrated to give the desired product.

### 4.6. General procedure for preparation of compounds 16–17 and 24–25

A mixture of substituted (4-methoxy-phenyl)-(4-hydroxyphenyl)-naphth-1-yl-methane (8 mmol) in methanol (as solvent) and Raney nickel (3 g) was hydrogenated at 40–50 psi pressure for 6–8 h. Then catalyst was filtered off and methanol was distilled off. The crude product was purified by flash column chromatography on silica gel using 5% ethyl acetate–hexane as eluant.

### 4.7. General procedure for preparation of compounds 32–33, 44–45 and 49–50

A mixture of substituted (4-methoxy-phenyl)-(4-hydroxyphenyl)-naphth-1-yl-methane (1 mmol), anhydrous potassium carbonate (3-fold excess by weight) and epichlorohydrine (as solvent) was refluxed for 10–12 h at 120 °C. The reaction mixture was filtered and solvent was distilled off. The residue was dissolved in ether, washed with NaOH (10%) and water, dried over sodium sulphate and concentrated to give oil. This oil was purified by column chromatography on silica gel using hexane–chloroform as eluant. General procedure for preparation of compounds **34–43**, **46–48** and **51–52**. A mixture of substituted (4-methoxy phenyl)-(4-(2,3-epoxypropyloxy)-phenyl))-naphth-1-yl methane (1 mmol), amine (1 mmol) and ethanol (as solvent) was refluxed for 3–4 h. Ethanol was distilled off and the

residue was passed through basic alumina column using hexane–benzene as eluant.

### 4.8. Characterization of products

**4.8.1. (4-Methoxyphenyl)-1-naphth-1-yl-ketone (2).** Yield: 11.5 g (75.5%), mp 97 °C, IR (KBr, $cm^{-1}$): 1500, 1580, 1600 (ArH), 1660 (C=O); $^1H$ NMR (δ, $CDCl_3$) 3.85 (s, 3H, OMe), 6.85–7.15 (m, 4H, ArH), 7.7–7.8 (m, 7H, ArH), MS *m/z* 262. Anal. ($C_{18}H_{14}O_2$), C, 82.4; H, 5.38, Found: C, 82.23; H, 5.31.

**4.8.2. (4-Methoxyphenyl)-1-naphth-1-yl-carbinol (3).** Yield: 9.2 g (91.3%), mp. 92 °C, IR (KBr, $cm^{-1}$) 1500, 1600 (ArH), 3200 (HO), $^1H$ NMR (δ, $CDCl_3$) 2.5 (s, 1H, OH), 3.7 (s, 3H, OMe), 6.40 (s, 1H, CH), 6.8 (dd, 2H, ArH), 7.23 (dd, 2H, ArH), 7.23–7.53 (m, 3H, naphth), 7.63 (d, 1H, naphth), 7.74 (d, 1H, naphth), 7.82 (d, 1H, naphth), 7.92 (d, 1H, naphth); MS *m/z* 264. Anal. ($C_{18}H_{16}O_2$), C, 81.79; H, 6.10, Found: C, 81.83; H, 5.94.

**4.8.3. (4-Methoxyphenyl)-(4-hydroxy phenyl)-naphth-1-yl-methane (4).** Yield: 73%, mp 140 °C, IR (KBr, $cm^{-1}$) 1244 (OMe), 1444, 1508, 1604 (ArH), 2954 (CH), 3298 (OH); $^1H$ NMR ($CDCl_3$) 6.70–6.74 (dd, 2H, *meta* to OH), 6.78–6.82 (dd, 2H, *ortho* to OH), 6.91–6.93 (dd, 2H, *meta* to OMe), 6.94 (dd, 2H, *ortho* to OMe), 7.30 (m, 1H, naphth), 7.34–7.35 (m, 2H, naphth), 7.40–7.41 (dd, 1H, naphth), 7.70–7.74 (d, 1H, naphth), 7.81 (d, 1H, naphth), 7.94 (d, 1H, naphth), 3.76 (s, 3H, MeO), 6.14 (s, 1H, CH), 4.6 (s, 1H, OH); MS *m/z* 340. Anal. ($C_{24}H_{20}O_2$), C,84.68; H,5.92. Found: C, 84.55; H, 5.84.

**4.8.4. (4-Methoxyphenyl)-(3-methyl-4-hydroxy phenyl)-naphth-1-yl-methane (5).** Yield: 67.16%, mp 126–128 °C, IR (KBr, cm−1) 1240 (OMe), 1500, 1600 (ArH), 3379 (OH); $^1H$ NMR ($CDCl_3$) 2.14 (s, 3H, $CH_3$) 3.74 (s, 3H, OMe), 4.61 (s, 1H, OH), 6.12 (s, 1H, CH), 6.64 (dd, 1H, ArH, *ortho* to OH), 6.74 (dd, 1H, ArH, *meta* to OH), 7.01 (dd, 2H, ArH, *meta* to OMe), 6.93 (d, 1H, naphth), 6.8 (dd, 2H, *ortho* to OMe), 6.86 (s, 1H, ArH, *ortho* to $CH_3$), 7.32–7.43 (m, 3H, naphth), 7.72 (d, 1H, naphth), 7.84 (d, 1H, naphth), 7.94 (d, 1H, naphth); MS *m/z* 354. Anal. ($C_{25}H_{22}O_2$), C, 84.72 and H, 6.26 Found: C, 84.53; H, 6.20.

**4.8.5. (4-Methoxyphenyl)-(2-methyl-4-hydroxy phenyl)-naphtha-1-yl-methane (6).** Yield: 73.08%, mp 110 °C, IR (KBr, $cm^{-2}$) 1454, 1508, 1584, 1616 (ArH), 2974 (CH), 1242 (OMe), 3344 (OH); $^1H$ NMR ($CDCl_3$) 6.53–6.55 (dd, 1H, *meta* to OH), 6.58–6.64 (dd, 1H, *ortho* to OH), 6.65–6.66 (dd, 2H, *meta* to OMe), 6.93–6.97 (dd, 2H, *ortho* to OMe), 7.73–7.77 (d, 1H, naphth), 7.87 (d, 1H, naphth), 7.83 (d, 1H, naphth), 7.30–7.41 (m, 4H, naphth), 3.77 (s, 3H, MeO), 4.74 (s, 1H, OH), 6.16 (s, 1H, CH), 2.16 (s, 3H, $CH_3$), 7.27 (s, 1H, *ortho* to OH); MS *m/z* 354. Anal. ($C_{25}H_{22}O_2$), C, 84.72 and H, 6.26 Found: C, 84.42; H, 6.32.

**4.8.6. (4-Methoxyphenyl)-(4-pyrrolidinoethoxy-phenyl)-naphth-1-yl-methane hydrochloride (7).** Yield: 56.26%, mp 212 °C, IR (KBr, $cm^{-1}$) 1500, 1580, 1600 (ArH), 3380 (Amine); $^1H$ NMR (δ, $CDCl_3$) 1.6–1.8 (m, 4H, 2×$CH_2$ pyrrolidine), 2.42–2.6 (m, 4H, 2×N $CH_2$ pyrrolidine), 2.77 (t, 2H, $CH_2N$ $J=5$ Hz), 3.65 (s, 3H, OMe), 4.21 (t, 2H, $OCH_2$ $J=3.6$ Hz), 6.05 (s, 1H, CH), 6.65–7.65 (m, 15H, ArH); MS *m/z* 437. Anal. ($C_{30}H_{32}O_2NCl$), C, 76.01; H, 6.80; N, 2.95 Found: C, 76.23; H, 6.57; N, 2.68.

**4.8.7. (4-Methoxyphenyl)-(3-methyl-4-pyrrolidinoethoxy-phenyl)-naphth-1-yl-methane hydrochloride (8).** Yield: 46%, mp 140–143 °C, IR (KBr, $cm^{-1}$) 1500, 1600 (ArH), 3320 (amine); $^1H$ NMR (δ, $CDCl_3$) 1.3–1.7 (m, 4H, 2×$CH_2$ pyrrolidine), 2.14 (s, 3H, $CH_3$), 2.4–2.6 (m, 4H, 2×$NCH_2$ pyrrolidine), 2.7 (t, 2H, $NCH_2$), 3.7 (s, 3H, OMe), 4.1 (t, 2H, $OCH_2$), 6.1 (s, 1H, CH), 6.6–8.0 (m, 14H, ArH); MS *m/z* 451. Anal. ($C_{31}H_{34}O_2NCl$), C, 82.45; H, 7.37; N, 3.10 Found: C, 82.26; H, 6.97; N, 2.88.

**4.8.8. (4-Methoxyphenyl)-(2-methyl-4-pyrrolidinoethoxy-phenyl)-naphth-1-yl-methane (9).** Yield: 61.22%, oil; IR (Neat, cm−1) 1460, 1512, 1606 (ArH), 1215 (OMe), 2929 (CH), 3685 (Amine); $^1H$ NMR (δ, $CDCl_3$) 2.85 (t, 2H, $CH_2N$), 3.77 (s, 3H, OMe), 4.03–4.10 (t, 2H, $OCH_2$), 6.58–7.84 (m, 14H, ArH), 6.16 (s, 1H, CH), 1.9–1.29 (m, 4H, 2×$CH_2$ pyrrolidine), 1.79–2.04 (m, 4H, 2×$NCH_2$ pyrrolidine); MS *m/z* 451.

**4.8.9. (4-Methoxyphenyl)-(4-pyrrolidinoethoxy-phenyl)-naphth-1-yl-methane *N*-methyl iodide (10).** Yield: 0.41 g (63.42%), mp 70 °C, IR (KBr, $cm^{-1}$) 1461, 1508, 1554, 1608 (ArH), 2925 (CH),1244 (OMe), 3759 (amine); $^1H$ NMR (δ, $CDCl_3$) 6.1 (s, 1H, CH), 6.7–7.8 (m, 15H, ArH), 2.3 (m, 4H, 2×$NCH_2$ pyrrolidine), 3.36 (s, 3H, $NCH_3$), 3.8–4.1 (t, 2H, $CH_2N$), 4.3–4.4 (t, 2H, $OCH_2$), 3.78 (s, 3H, OMe), 1.2–1.3 (m, 4H, 2×$CH_2$ pyrrolidine); MS *m/z* 452 [M + −127].

**4.8.10. (4-Methoxyphenyl)-(4-diethylaminoethoxy-phenyl)-naphth-1-yl-methane (11).** Yield: 48.78%, oil; IR (Neat, $cm^{-1}$) 1500, 1580, 1600 (ArH), 3360 (Amine); $^1H$ NMR (δ, $CDCl_3$): 0.97 (t, 6H, 2×$CH_3$ $J=5$ Hz), 2.54 (q, 4H, 2×$CH_2$ $J=5$ Hz), 2.78 (t, 2H, $CH_2N$), 3.65 (s, 3H, OMe), 3.92 (t, 2H, OCH2 $J=5$ Hz), 6.05 (s, 1H, CH), 6.65–7.65 (m, 15H, ArH); MS *m/z* 439.

**4.8.11. (4-Methoxyphenyl)-(3-methyl-4-(*N*-*N*-diethylamino ethoxy-phenyl)-naphth-1-yl-methane hydrochloride (12).** Yield: 49.09%; mp 115–116 °C; IR (KBr, $cm^{-1}$): 1500, 1600 (ArH), 3370 (amine); $^1H$ NMR (δ, $CDCl_3$): 1.1–1.3 (m, 6H, 2×$CH_3$), 2.17 (s, 3H, $CH_3$), 2.5–3.0 (m, 6H, 3×$NCH_2$), 3.7 (s, 3H, OMe), 4.0 (t, 2H, $OCH_2$), 6.1 (s, 1H, CH), 6.7–8.0 (m, 14H, ArH); MS *m/z* 453.

**4.8.12. 4-Methoxyphenyl-2-methyl-4-diethylaminoethoxy)-phenyl-naphth-1-yl-methane (13).** Yield: 72.99%, oil; IR (Neat, $cm^{-1}$) 1463, 1506, 1583, 1614 (ArH), 2976 (CH), 3225 (OH), 1217 (OMe), 3425 (amine); $^1H$ NMR ($CDCl_3$) 1.0–1.07 (t, 6H, 2×$CH_3$), 2.58 (t, 2H, $NCH_2$), 3.77 (s, 3H, OMe), 3.96 (t, 2H, $OCH_2$), 6.57–7.86 (m, 14H, ArH), 6.16 (s, 1H, CH), 2.5 (q, 4H, 2×$NCH_2$); MS *m/z* 453.

**4.8.13. (4-Methoxyphenyl)-(4-piperidinoethoxy-phenyl)-naphth-1-yl-methane (14).** Yield: 66.1%, oil; IR (Neat, $cm^{-1}$) 1510, 1608, 1695 (ArH), 3371 (amine); $^1H$ NMR

(δ, $CDCl_3$) 1.60–1.62 (m, 6H, 3×$CH_2$ of piperidine ring), 2.49–2.52 (m, 4H, 2×$NCH_2$ piperidine), 2.78 (t, 2H, $NCH_2$), 3.79 (s, 3H, OMe), 4.06–4.10 (t, 2H, $OCH_2$), 6.16 (s, 1H, CH), 6.80–7.80 (m, 15H, ArH); MS *m*/*z* 451.

**4.8.14. (4-Methoxyphenyl)-(3-methyl-4-piperidinoethoxyphenyl)-naphth-1-yl-methane (15).** Yield: 55.23%, oil; IR (Neat, $cm^{-1}$) 1506 (ArH), 3260 (amine); $^1H$ NMR (δ, $CDCl_3$) 1.60–1.62 (m, 6H, 3×$CH_2$ of piperidine ring), 2.47–2.51 (m, 4H, 2×$NCH_2$), 2.78 (t, 2H, $NCH_2$), 3.74 (s, 3H, OMe), 4.0 (t, 2H, $OCH_2$), 6.1 (s, 1H, CH), 6.6–8.0 (m, 14H, ArH); MS *m*/*z* 465.

**4.8.15. (4-Methoxyphenyl)-(4-hydroxyphenyl)-1,2,3,4-tetrahydronaphth-1-yl-methane (16).** Yield: 29%; oil; IR (Neat, $cm^{-1}$): 1454, 1510, 1608 (ArH), 3320 (OH); $^1H$ NMR (δ, $CDCl_3$): 1.55–1.99 (m, 4H, 2×$CH_2$ naphth), 2.73–2.93 (m, 2H, $CH_2$ naphth), 3.46 (m, 1H, CH naphth), 3.73 (s, 3H, OMe), 4.0 (d, 1H, CH), 4.6 (2s, 1H, OH), 6.33–7.23 (m, 12H, ArH); MS *m*/*z* 344.

**4.8.16. (4-Methoxyphenyl)-(3-methyl-4-hydroxyphenyl)-1,2,3,4-tetrahydronaphth-1-yl-methane (17).** Yield: 31.5%; IR (Neat, $cm^{-1}$): 1602 (ArH), 3374 (OH); $^1H$ NMR (δ, $CDCl_3$): 1.5–1.9 (m, 4H, 2×$CH_2$ naphth), 2.16 (s, 3H, $CH_3$), 2.7–2.8 (m, 2H, $CH_2$ naphth), 3.5 (m, 1H, CH naphth), 3.7 (s, 3H, OMe), 3.9 (d, 1H, CH), 4.6 (2s, 1H, OH), 6.3–7.23 (m, 11H, ArH); MS *m*/*z* 358.

**4.8.17. (4-Methoxyphenyl)-(4-pyrrolidinoethoxyphenyl)-1,2,3,4-tetrahydronaphth-1-yl-methanehydrochloride (18).** Yield: 68.35%, mp 148 °C; IR (KBr, $cm^{-1}$) 1452, 1510, 1610 (ArH), 3435 (amine); $^1H$ NMR (δ, $CDCl_3$) 1.6–1.8 (m, 8H, 2×$CH_2$ naphth and 2×$CH_2$ pyrrolidine), 2.66 (m, 4H, 2×NCH2 pyrrolidine), 2.9–3.0 (m, 4H, N-$CH_2$ and $CH_2$ naphth), 3.52 (m, 1H, CH naphth), 3.74 (s, 3H, OMe), 3.98–4.08 (m, 3H, $OCH_2$ and CH), 6.35–7.26 (m, 12H, ArH); MS *m*/*z* 441.

**4.8.18. (4-Methoxyphenyl)-(3-methyl-4-pyrrolidinoethoxy phenyl)-1,2,3,4-tetrahydro naphth-1-yl-methane (19).** Yield: 44%, oil; mp 148 °C; IR (Neat, cm−1) 1510, 1583, 1608 (ArH), 3400 (amine) 2931 (CH); $^1H$ NMR (δ, $CDCl_3$) 1.26–1.83 (m, 8H, 2×$CH_2$ naphth and 2×$CH_2$ pyrrolidine), 2.1–2.2 (2s, 3H, $CH_3$ — due to restricted rotation), 2.64 (m, 4H, 2×$NCH_2$ pyrrolidine), 2.86–2.92 (m, 4H, N-$CH_2$ and $CH_2$ naphth), 3.49 (m, 1H, CH naphth), 3.72–3.77 (s, 3H, OMe), 3.94 (d, 1H, CH), 4.0 (t, 2H, $OCH_2$), 6.28–7.25 (m, 11H, ArH); MS *m*/*z* 455.

**4.8.19. (4-Methoxyphenyl)-(4-piperidinoethoxyphenyl)-1,2,3,4-tetrahydronaphth-1-yl-methane (20).** Yield: 58.6%, oil; IR (Neat, cm−1) 1456, 1508, 1608 (ArH), 3433 (amine), 1247 (OMe); $^1H$ NMR (δ, $CDCl_3$) 1.45–1.82 (m, 10H, 2×$CH_2$ naphth and 3×$CH_2$ piperidine), 2.48–2.49 (m, 4H, 2×$NCH_2$ piperidine), 2.81–2.83 (m, 4H, N-$CH_2$ and $CH_2$ naphth), 3.51 (m, 1H, CH naphth), 3.75 (s, 3H, OMe), 3.97–4.07 (m, 3H, OCH2 and CH), 6.32–7.25 (m, 12H, ArH); MS *m*/*z* 455.

**4.8.20. (4-Methoxyphenyl)-(3-methyl-4-piperidinoethoxy phenyl)-1,2,3,4-tetrahydronaphth-1-yl-methane (21).** Yield: 72%, oil; IR (Neat, $cm^{-1}$) 1458, 1506, 1583, 1610 (ArH), 3400 (amine) 2931 (CH); $^1H$ NMR (δ, $CDCl_3$) 1.25–1.83 (m, 10H, 2×$CH_2$ naphth and 3×$CH_2$ piperidine), 2.09–2.19 (2s, 3H, $CH_3$ — due to restricted rotation), 2.51–2.53 (m, 4H, 2×$NCH_2$ piperidine), 2.76–2.81 (m, 4H, N-$CH_2$ and $CH_2$ naphth), 3.49 (m, 1H, CH naphth), 3.72 (s, 3H, OMe), 3.94 (d, 1H CH), 4.03–4.09 (m, 2H, $OCH_2$), 6.67–7.23 (m, 11H, ArH); MS *m*/*z* 469.

**4.8.21. (4-Methoxyphenyl)-(4-*N*-*N*-diethylaminoethoxyphenyl)-1,2,3,4-tetrahydro naphth-1-yl-methane (22).** Yield: 62.5%, oil; IR (Neat, $cm^{-1}$) 1463, 1510, 1581, 1608 (ArH), 3340 (amine); $^1H$ NMR (δ, $CDCl_3$) 1.07 (s, 6H, $CH_3$), 1.81–1.82 (m, 4H, 2×$CH_2$ naphth), 2.62–2.64 (m, 4H, 2×$NCH_2$), 2.81–2.88 (m, 4H, N-$CH_2$ and $CH_2$ naphth), 3.46–3.48 (m, 1H, CH naphth), 3.73 (s, 3H, OMe), 3.97–4.04 (m, 3H, $OCH_2$ and CH), 6.35–7.25 (m, 12H, ArH); MS *m*/*z* 443.

**4.8.22. 4-Methoxyphenyl-3-methyl-4-diethylaminoethoxy phenyl)-1,2,3,4-tetrahydronaphth-1-yl-methane (23).** Yield: 67.6%, oil; IR (Neat, $cm^{-1}$) 1510, 1606 (ArH), 2976 (CH), 1215 (OMe), 3411 (amine), $^1H$ NMR (δ, $CDCl_3$) 1.25–1.26 (m, 6H, 2×$CH_3$), 1.5–2.0 (m, 4H, 2×$CH_2$ naphth), 2.0–2.2 (2s, 3H, $CH_3$ — due o restricted rotation), 2.59–2.63 (m, 4H, 2×$NCH_2$), 2.84–2.92 (m, 4H, $NCH_2$ and $CH_2$ naphth), 3.49 (m, 1H, CH naphth), 3.73 (s, 3H, OMe), 4.01 (m, 3H, $OCH_2$ and CH), 6.67–7.23 (m, 11H, ArH); MS *m*/*z* 457.

**4.8.23. (4-Methoxyphenyl)-(4-hydroxyphenyl)-5,6,7,8-tetrahydronaphth-1-yl-methane (24).** Yield: 26%, mp 154–157 °C; IR (KBr, $cm^{-1}$) 1506, 1602 (ArH), 1245 (OMe), 3429 (OH); $^1H$ NMR (δ, $CDCl_3$) 1.73 (m, 4H, 2×$CH_2$ naphth), 2.59 (m, 2H, $CH_2$ naphth), 2.79 (m, 2H, 2×$CH_2$ naphth), 3.79 (s, 3H, OMe), 5.54 (s, 1H, CH), 4.43 (s, 1H, OH), 6.60–7.0 (m, 11H, ArH); MS *m*/*z* 344.

**4.8.24. (4-Methoxyphenyl)-(3-methyl-4-hydroxyphenyl)-5,6,7,8-tetrahydronaphth-1-yl-methane (25).** Yield: 28.7%, oil; IR (Neat, $cm^{-1}$) 1500, 1610 (ArH), 3520 (OH); $^1H$ NMR (δ, $CDCl_3$) 1.7 (bs, 4H, 2×$CH_2$ naphth), 2.16 (s, 3H, $CH_3$), 2.6 (m, 2H, $CH_2$ naphth), 2.8 (bs, 2H, 2×$CH_2$ naphth), 3.75 (s, 3H, OMe), 5.5 (s, 1H, CH), 4.6 (s, 1H, OH), 6.6–7.0 (m, 10H, ArH); MS *m*/*z* 358.

**4.8.25. (4-Methoxyphenyl)-(4-pyrrolidinoethoxyphenyl)-5,6,7,8-tetrahydronaphth-1-yl-methane hydrochloride (26).** Yield: 42.30%, mp 196–198 °C; IR (KBr, $cm^{-1}$) 1510, 1608 (ArH), 1217 (OMe), 3435 (amine); $^1H$ NMR (δ, $CDCl_3$) 1.71 (m, 4H, 2×$CH_2$ naphth) 2.08–2.24 (broad m, 4H, 2×$CH_2$ pyrrolidine), 2.57 (m, 2H, $CH_2$ naphth), 2.98 (t, 2H, $NCH_2$), 3.46 (m, 4H, 2×N-$CH_2$ pyrrolidine), 3.78 (s, 3H, OMe), 3.86–4.0 (t, 2H, $OCH_2$), 5.54 (s, 1H, CH), 6.58–6.81(m, 11H, ArH); MS *m*/*z* 441. Anal. ($C_{31}H_{34}O_3NCl$), C, 73.87; H, 6.80; N, 2.78 Found: C, 74.12; H, 7.14; N, 2.92.

**4.8.26. (4-Methoxyphenyl)-(3-methyl-4-pyrrolidinoethoxy phenyl)-5,6,7,8-tetrahydro naphth-1-yl-methane (27).** Yield: 48.5%, oil; IR (Neat, $cm^{-1}$) 1461, 1506, 1583, 1608 (ArH), 1217 (OMe), 3390 (amine); $^1H$ NMR (δ, $CDCl_3$) 1.70–1.72 (m, 4H, 2×$CH_2$ naphth), 2.17 (s, 3H, $CH_3$),

2.63–2.67 (m, 6H, 2×$CH_2$ pyrrolidine and $CH_2$ naphth), 2.78 (m, 2H, $CH_2$ naphth), 2.91–2.93 (t, 2H, N-$CH_2$), 3.47–3.67 (m, 4H, $NCH_2$), 3.78 (s, 3H, OMe), 4.0–4.1 (t, 2H, $OCH_2$), 5.5 (s, 1H, CH), 6.70–6.99 (m, 10H, ArH); MS *m*/*z* 455.

**4.8.27. (4-Methoxyphenyl)-(4-piperidinoethoxyphenyl)-5,6,7,8-tetrahydronaphth-1-yl-methane (28).** Yield: 55.89%, oil; IR (Neat, $cm^{-1}$) 1508, 1583, 1608 (ArH), 3306 (amine); $^1H$ NMR (δ, $CDCl_3$) 1.57–1.73 (m, 10H, 2×$CH_2$ naphth and 3×$CH_2$ piperidine), 2.4–2.5 (m, 4H, 2×$NCH_2$ piperidine), 2.60–2.64 (m, 2H, $CH_2$ naphth), 2.75–2.79 (m, 4H, $CH_2$ naphth and $NCH_2$), 3.79 (s, 3H, OMe), 4.0–4.1 (t, 2H, $OCH_2$), 5.5 (s, 1H, CH), 6.6–7.0 (m, 11H, ArH); MS *m*/*z* 455.

**4.8.28. (4-Methoxyphenyl)-(3-methyl-4-piperidinoethoxy phenyl)-5,6,7,8-tetrahydro naphth-1-yl-methane (29).** Yield: 51.7%, oil; IR (Neat, $cm^{-1}$) 1512, 1610 (ArH), 3398 (amine) 2935 (CH), 1215 (OMe); $^1H$ NMR (δ, $CDCl_3$) 1.57–1.73 (m, 10H, 2×$CH_2$ naphth and 3×$CH_2$ piperidine), 2.14 (s, 3H, $CH_3$), 2.4–2.5 (m, 4H, 2×$NCH_2$ piperidine), 2.60–2.64 (m, 2H, $CH_2$ naphth), 2.75–2.79 (m, 4H, $CH_2$ naphth and $NCH_2$), 5.5 (m, 1H, CH), 3.79 (s, 3H, OMe), 3.99 (t, 2H $OCH_2$), 6.6–7.2 (m, 10H, ArH); MS *m*/*z* 469.

**4.8.29. (4-Methoxyphenyl)-(4-*N*-*N*-diethylaminoethoxy-phenyl)-5,6,7,8-tetrahydro naphth-1-yl-methane (30).** Yield: 69.76%, oil; IR (Neat, $cm^{-1}$) 1508, 1583, 1608 (ArH), 3354 (amine); $^1H$ NMR (δ, $CDCl_3$) 1.04 (m, 6H, 2×$CH_3$), 1.72 (broad s, 4H, 2×$CH_2$), 2.60–2.67 (m, 6H, $CH_2$ naphth and 2×$NCH_2$), 2.79–2.89 (m, 4H, N-$CH_2$ and $CH_2$ naphth), 5.5 (s, 1H, CH naphth), 3.74 (s, 3H, OMe), 4.0 (t, 2H, $OCH_2$), 6.6–7.0 (m, 11H, ArH); MS *m*/*z* 443.

**4.8.30. 4-Methoxyphenyl-2-methyl-4-diethylaminoethoxy phenyl)-5,6,7,8-tetrahydro naphth-1-yl-methane (31).** Yield: 53.21%, oil; IR (Neat, $cm^{-1}$) 1461, 1506, 1608 (ArH), 2972 (CH), 3413 (amine), 1217 (OMe); $^1H$ NMR (δ, $CDCl_3$) 1.23 (m, 6H, 2×$CH_3$), 1.62–1.77 (m, 4H, 2×$CH_2$ naphth), 2.12 (s, 3H, $CH_3$), 2.53–2.69 (m, 6H, $CH_2$ naphth and 2×$NCH_2$) 2.7–2.8 (m, 2H, $CH_2$ naphth), 3.77 (s, 3H, OMe), 4.0 (t, 2H, $OCH_2$), 6.6–7.0 (m, 10H, ArH), 5.5 (s, 1H, CH), 2.9 (m, 2H, $NCH_2$); MS *m*/*z* 457.

**4.8.31. (4-Methoxyphenyl)-[4-(2,3-epoxypropyloxy)-phenyl]-naphth-1-yl-methane (32).** Yield: 78.99%, oil; IR (Neat, $cm^{-1}$) 1483, 1514, 1610 (ArH), 761 (C–O), 2950 (CH), 1217 (OMe), $^1H$ NMR (δ, $CDCl_3$) 2.56 (d, 2H, $CH_2$ epoxide), 3.15 (m, 1H, CH epoxide) 3.65 (s, 3H, OMe), .9 (d, 2H, OCH2), 6.05 (s, 1H, CH), 6.6–7.8 (m, 15H, ArH); MS *m*/*z* 396.

**4.8.32. (4-Methoxyphenyl)-[3-methyl-4-(2,3-epoxypropyl-oxy)-phenyl]-naphth-1-yl-methane (33).** Yield: 66.9%, oil; IR (Neat, $cm^{-1}$) 1510, 1604 (ArH), 760 (C–O), 2971 (CH), 1217 (OMe), $^1H$ NMR (δ, $CDCl_3$) 2.17 (s, 3H, $CH_3$), 2.6–3.0 (d, 2H, $CH_2$ epoxide), 3.3 (m, 1H, CH epoxide), 3.75 (s, 3H, OMe), 3.9 (d, 2H, $OCH_2$), 6.10 (s, 1H, CH), 6.6–8.0 (m, 14H, ArH); MS *m*/*z* 410.

**4.8.33. (4-Methoxyphenyl)-[4-(2-hydroxy-3-*n*-butylamino propyloxy)-phenyl]-naphth-1-yl-methane (34).** Yield: 58.27%), oil; IR (Neat, $cm^{-1}$) 1461, 1508, 1600 (ArH), 2974 (CH), 1230 (OMe), 3478 (OH), 3413 (amine). $^1H$ NMR (δ, $CDCl_3$) 1.4 (m, 9H, $NCH_2C_3H_7$), 2.7 (d, 2H, $NCH_2$), 2.9 (m, 1H, NH), 3.95 (d, 2H, $OCH_2$), 3.75 (s, 3H, OMe), 4.0 (m, 1H, CHOH), 6.7–7.8 (m, 15H, ArH), 6.15 (s, 1H, CH); MS *m*/*z* 469.

**4.8.34. (4-Methoxyphenyl)-[3-methyl-4-(2-hydroxy-3-*n*-butyl aminopropyloxy)-phenyl]-naphth-1-yl-methane (35).** Yield: 41.6%), mp 138 °C; IR (KBr, $cm^{-1}$) 1510, 1600 (ArH), 2980 (CH), 1230 (OMe), 3450 (OH), 3443 (amine); $^1H$ NMR (δ, $CDCl_3$) 1.4 (m, 9H, $NCH_2C_3H_7$), 2.16 (s, 3H, $CH_3$), 2.7 (d, 2H, $NCH_2$), 2.9 (m, 1H, NH), 3.95 (d, 2H, $OCH_2$), 3.75 (s, 3H, OMe), 4.1 (m, 1H, CHOH), 6.7-8.0 (m, 14H, ArH), 6.15 (s, 1H, CH); MS *m*/*z* 483.

**4.8.35. (4-Methoxyphenyl)-[4-(2-hydroxy-3-*n*-propylamino propyloxy)-phenyl]-naphth-1-yl-methane (36).** Yield: 65.27%, oil; IR (Neat, $cm^{-1}$) 1473, 1519 (ArH), 2960 (CH), 3685 (OH), 1215 (OMe), 3685 (OH), 1215 (OMe), 3766 (amine); $^1H$ NMR (δ, $CDCl_3$) 1.18–1.36 (m, 7H, $C_3H_7$), 3.95 (m, 1H, NH), 2.77 (d, 2H, $CH_2N$), 3.7 (s, 3H, OMe), 3.8 (d, 2H, $OCH_2$), 4.16 (s, 1H, CHOH), 6.71–7.88 (m, 15H, ArH), 6.09 (s, 1H, CH), MS *m*/*z* 455.

**4.8.36. (4-Methoxyphenyl)-[4-(2-hydroxy-3-cyclopropyl-amino propyloxy)-phenyl]-naphth-1-yl-methane (37).** Yield: 46.62%, oil; IR (Neat, $cm^{-1}$): 1600 (ArH), 2980 (CH), 1230 (OMe), 3451 (OH), 3434 (amine); $^1H$ NMR (δ, $CDCl_3$) 1.7–2.2 (m, 5H, cyclopropyl), 2.7 (d, 2H, $NCH_2$), 2.8 (m, 1H, NH), 3.96 (d, 2H, $OCH_2$), 3.7 (s, 3H, OMe), 4.0 (m, 1H, CHOH), 6.7–7.9 (m, 15H, ArH), 6.15 (s, 1H, CH); MS *m*/*z* 453.

**4.8.37. (4-Methoxyphenyl)-[4-(2-hydroxy-3-pyrrolidino propyloxy)-phenyl]-naphth-1-yl-methane (38).** Yield: 83.68%, oil; mp 210 °C; IR (KBr, $cm^{-1}$) 1461, 1508, 1612 (ArH), 2929 (CH), 1245 (OMe), 3478 (OH), 3413, 3762 (amine); $^1H$ NMR (δ, $CDCl_3$) 1.6–1.77 (m, 4H, 2×$CH_2$ of pyrrolidine), 2.78–2.79 (d, 2H, $NCH_2$), 3.95 (d, 2H, $OCH_2$), 3.7 (s, 3H, OMe), 4.01 (m, 1H, CHOH), 6.79–7.97 (m, 15H, ArH), 6.15 (s, 1H, CH), 2.5–2.6 (m, 4H, 2×$NCH_2$ pyrrolidine); MS *m*/*z* 467.

**4.8.38. (4-Methoxyphenyl)-[4-(2-hydroxy-3-piperidinopropyl oxy)-phenyl]-naphth-1-yl-methane hydrochloride (39).** Yield: 48.33%, mp 220 °C; IR (KBr, $cm^{-1}$) 1461, 1512, 1612 (ArH), 2945 (CH), 1245, 1305 (OMe), 3421 (OH), 3705 (amine); $^1H$ NMR (δ, $CDCl_3$) 1.5–1.6 (m, 6H, 3×$CH_2$ piperidine), 2.2–2.5 (m, 4H, 2×$NCH_2$ piperidine), 2.74 (d, 2H, $NCH_2$), 4.0–4.1 (d, 2H, $OCH_2$), 3.7 (s, 3H, OMe), 5.3 (s, 1H, CHOH), 6.7–7.9 (m, 15H, ArH), 6.1 (s, 1H, CH); MS *m*/*z* 481 [M + −37]. Anal. ($C_{32}H_{36}O_3NCl$), C, 74.19; H, 7.00; N, 2.70 Found: C, 74.38; H, 7.26; N 2.79.

**4.8.39. (4-Methoxyphenyl)-[4-(2-hydroxy-3-morpholino propyloxy)-phenyl]-naphth-1-yl-methane hydrochloride (40).** Yield: 59.36%, mp 207 °C; IR (KBr, $cm^{-1}$) 1456,

1508, 1608 (ArH), 2935 (CH), 1245, 1301 (OMe), 3417 (OH), 3759 (amine); $^1$H NMR (δ, $CDCl_3$) 2.32 (m, 4H, $NCH_2$), 4.2 (d, 2H, $OCH_2$), 3.7 (s, 3H, OMe), 4.2 (m, 1H, CHOH), 6.76–7.75 (m, 15H, ArH), 3.5–3.6 (m, 4H, $CH_2O$), 2.8 (d, 2H, $CH_2N$); MS $m/z$ 483 [M + −37]. Anal. ($C_{31}H_{34}O_4NCl$), C, 71.59; H, 6.59; N, 2.69 Found: C, 71.38; H, 7.00; N, 2.89.

**4.8.40. (4-Methoxyphenyl)-[4-(2-hydroxy-3-piperazino propyloxy)-phenyl]-naphth-1-yl-methane hydrochloride (41).** Yield: 68.78%, mp: 200 °C, IR (KBr, cm$^{-1}$)1507, 1556, 1607 (ArH), 2932 (CH), 3404 (OH), 1217 (OMe), 3768 (amine), $^1$H NMR (δ, $CDCl_3$): 2.81 (m, 1H, NH), 2.83 (d, 2H, $CH_2N$), 3.76 (s, 3H, OMe), 3.94 (d, 2H, $OCH_2$), 4.0 (m, 1H, CHOH), 6.81–7.82 (m, 15H, ArH), 6.1 (s, 1H, CH), 2.79 (m, 8H, 4×$CH_2$ piperazine); MS $m/z$ 482 [M + −37].

**4.8.41. (4-Methoxyphenyl)-[4-(2-hydroxy-3-cyclohexylamino propyloxy)-phenyl]-naphth-1-yl-methane hydrochloride (42).** Yield: 56.44%, mp 140 °C, IR (KBr, cm$^{-1}$) 1461, 1508, 1608 (ArH), 2937 (CH), 1241 (OMe), 3481 (OH), 3419, 3749 (amine); $^1$H NMR (δ, $CDCl_3$) 1.17–1.27 (m, 11H, CH & $CH_2$ of cyclohexyl), 2.8 (d, 2H, $NCH_2$), 3.76 (s, 3H, OMe), 3.94–3.96 (d, 2H, $OCH_2$), 5.2 (s, 1H, CHOH), 6.75–7.8 (m, 15H, ArH), 6.13 (s, 1H, CH), 4.68 (s, 1H, NH); MS $m/z$ 495.

**4.8.42. (4-Methoxyphenyl)-[4-(2-hydroxy-3-diethylamino propyloxy)-phenyl]-naphth-1-yl-methane (43).** Yield: 50.66%, oil; IR (Neat, cm$^{-1}$) 1400, 1508, 1608 (ArH), 2927 (CH), 3246 (OH), 1249 (OMe), 3371(amine), $^1$H NMR (δ, $CDCl_3$) 1.0–1.07 (t, 6H, $N(CH_2CH_3)_2$), 2.58–2.65 (q, 4H, $N(CH_2CH_3)_2$), 3.77 (s, 3H, OMe), 3.95 (d, 2H, $OCH_2$), 4.01 (m, 1H, CHOH), 6.80–7.81 (m, 15H, ArH), 6.15 (s, 1H, CH), 2.74 (d, 2H, $CH_2N$); MS $m/z$ 469.

**4.8.43. (4-Methoxyphenyl)-[4-(2,3-epoxypropyloxy)-phenyl]-1,2,3,4-tetrahydronaphth-1-yl-methane (44).** Yield: 94.8%, oil; IR (Neat, cm$^{-1}$) 1456, 1508, 1583, 1608 (ArH), 2933 (CH), 1217 (OMe), $^1$H NMR (δ, $CDCl_3$) 1.58–1.83 (m, 4H, 2×$CH_2$ naphth), 2.74–2.88 (m, 4H, $CH_2$ naphth and $CH_2$ epoxide), 3.48 (m, 1H, CH epoxide), 3.51 (m, 1H, CH naphth), 3.75 (s, 3H, OMe), 4.1–4.3 (m, 3H, $OCH_2$ and CH), 6.37–7.24 (m, 12H, ArH); MS $m/z$ 400.

**4.8.44. (4-Methoxyphenyl)-[3-methyl-4-(2,3-epoxypropyloxy)-phenyl]-1,2,3,4-tetrahydro naphth-1-yl-methane (45).** Yield: 88.4%, oil; IR (Neat, cm$^{-1}$) 1461, 1510, 1608 (ArH), 1247 (OMe), $^1$H NMR (δ, $CDCl_3$) 1.59–1.86 (m, 4H, 2×$CH_2$ naphth), 2.13–2.23 (s, 3H, $CH_3$), 2.80–2.92 (m, 4H, $CH_2$ naphth and $CH_2$ epoxide), 3.48 (m, 1H, CH epoxide), 3.49–3.50 (m, 1H, CH naphth), 3.74 (s, 3H, OMe), 3.93–3.99 (m, 2H, $OCH_2$), 4.17 (d, 1H, CH), 6.3-7.24 (m, 11H, ArH); MS $m/z$ 414.

**4.8.45. (4-Methoxyphenyl)-[4-(2-hydroxy-3-n-butylamino propyloxy)-phenyl]-1,2,3,4-tetrahydronaphth-1-yl-methane (46).** Yield: 48.93%), oil; IR (Neat, cm$^{-1}$): 1472, 1510, 1608 (ArH), 2931 (CH), 1217 (OMe), 3377 (OH), 3749 (amine); $^1$H NMR (δ, $CDCl_3$); 1.26–1.49 (m, 11H, 2×$CH_2$ naphth and $CH_2C_3H_7$), 2.64–2.85 (m, 6H, $CH_2$ naphth and $CH_2NCH_2$), 3.48 (m, 1H, CH naphth), 3.74 (s, 3H, OMe), 3.91–4.02 (m, 4H, $OCH_2$, CH and CHOH), 6.69–7.26 (m, 12H, ArH); MS $m/z$ 473.

**4.8.46. (4-Methoxyphenyl)-[3-methyl-4-(2-hydroxy-3-*n*-butyl amino propyloxy)-phenyl]-1,2,3,4-tetrahydronaphth-1-yl-methane (47).** Yield: 60.05%), oil; IR (Neat, cm$^{-1}$) 1460, 1506, 1579,1608 (ArH), 2929 (CH), 1217 (OMe), 3377 (OH), 3709 (amine); $^1$H NMR (δ, $CDCl_3$); 1.26–1.80 (m, 11H, 2×$CH_2$ naphth and $CH_2C_3H_7$), 2.11–2.21 (2s, 3H, $CH_3$ due to restricted rotation) 2.64–2.88 (m, 6H, CH2 naphth and $CH_2NCH_2$), 3.48 (m, 1H, CH naphth), 3.73 (s, 3H, OMe), 3.91–3.98 (m, 4H, $OCH_2$, CH and CHOH), 6.3–7.2 (m, 11H, ArH); MS $m/z$ 487.

**4.8.47. (4-Methoxyphenyl)-[4-(2-hydroxy-3-*n*-dibutyl aminopropyloxy)-phenyl]-1,2,3,4-tetra hydronaphth-1-yl-methane (48).** Yield: 49.3%), oil; IR (Neat, cm$^{-1}$): 1461, 1510, 1608 (ArH), 2933 (CH), 1217 (OMe), 3375 (OH), 3749 (amine); $^1$H NMR (δ, $CDCl_3$); 1.29–1.42 (m, 14H, 2×$C_3H_7$), 1.43–1.79 (m, 4H, 2×$CH_2$ naphth), 2.42–2.56 (m, 6H, 3×$NCH_2$), 2.64–2.88 (m, 2H, $CH_2$ naphth) 3.46–3.48 (m, 1H, CH naphth), 3.72 (s, 3H, OMe), 4.0 (m, 4H, $OCH_2$, CH and CHOH), 6.31–7.20 (m, 12H, ArH); MS $m/z$ 529.

**4.8.48. (4-Methoxyphenyl)-[4-(2,3-epoxypropyloxy)-phenyl]-5,6,7,8-tetrahydronaphth-1-yl-methane (49).** Yield: 78.39%, oil; IR (Neat, cm$^{-1}$) 1461, 1510, 1610 (ArH), 2931 (CH), 1217 (OMe), $^1$H NMR (δ, $CDCl_3$) 1.71–1.73 (m, 4H, 2×$CH_2$ naphth), 2.59 (m, 2H, $CH_2$ naphth), 2.8–2.9 (m, 4H, $CH_2$ naphth and $CH_2$ epoxide), 3.15 (m, 1H, CH epoxide), 3.78 (s, 3H, OMe), 3.9–4.1 (d, 1H, $OCH_2$, $J = 5.9$ Hz), 4.17–4.19 (d, 1H, $OCH_2$, $J = 5.9$ Hz), 5.53 (s, 1H, CH), 6.6–7.0 (m, 11H, ArH); MS $m/z$ 400.

**4.8.49. (4-Methoxyphenyl)-[3-methyl-4-(2,3-epoxypropyloxy)-phenyl]-5,6,7,8-tetrahydro naphth-1-yl-methane (50).** Yield: 82.37%, oil; IR (Neat, cm$^{-1}$) 1458, 1504, 1583, 1608 (ArH), 2927 (CH), 1217 (OMe), $^1$H NMR (δ, $CDCl_3$) 1.65–1.75 (m, 4H, 2×$CH_2$ naphth), 2.15 (s, 3H, $CH_3$), 2.53–2.64 (m, 2H, $CH_2$ naphth), 2.7–2.8 (m, 4H, $CH_2$ naphth and $CH_2$ epoxide), 3.3–3.9 (m, 1H, CH epoxide), 3.70 (s, 3H, OMe), 3.9–4.0 (d, 1H, $OCH_2$, $J = 5.8$ Hz), 4.1–4.2 (d, 1H, $OCH_2$, $J = 5.8$ Hz), 5.5 (s, 1H, CH), 6.6–7.0 (m, 10H, ArH); MS $m/z$ 413.

**4.8.50. (4-Methoxyphenyl)-[4-(2-hydroxy-3-n-butyl amino-propyloxy)-phenyl]-5,6,7,8-tetra hydronaphth-1-yl-methane (51).** Yield: 69.75%), oil; IR (Neat, cm$^{-1}$): 1460, 1510, 1581, 1608 (ArH), 2933 (CH), 1230 (OMe), 3377 (OH), 3759 (amine); $^1$H NMR (δ, $CDCl_3$); 1.71 (m, 11H, 2×$CH_2$ naphth and $C_3H_7$), 2.58–2.78 (m, 2H, $CH_2$ naphth), 2.85–3.0 (m, 6H, $CH_2$ naphth, $CH_2NCH_2$), 3.77 (s, 3H, OMe), 3.95–4.0 (m, 3H, $OCH_2$ and CHOH), 6.59–6.99 (m, 11H, ArH), 5.53 (s, 1H, CH); MS $m/z$ 473.

**4.8.51. (4-Methoxyphenyl)-[3-methyl-4-(2-hydroxy-3-*n*-butylaminopropyloxy)-phenyl]-5,6,7,8-tetrahydro naphth-1-yl-methane (52).** Yield: 52.79%), oil; IR (Neat, cm$^{-1}$):

1458, 1506, 1610 (ArH), 2935 (CH), 1230 (OMe), 3367 (OH), 3749 (amine); $^1$H NMR (δ, $CDCl_3$); 1.20–1.75 (m, 11H, 2×$CH_2$ naphth and $C_3H_7$), 2.14 (s, 3H, $CH_3$), 2.52–2.62 (m, 2H, $CH_2$ naphth), 2.72–2.92 (m, 6H, $CH_2$ naphth, $CH_2NCH_2$), 3.74 (s, 3H, OMe), 3.9–4.0 (d, 2H, $OCH_2$), 4.02–4.17 (m, 1H, CHOH), 6.6–7.0 (m, 10H, ArH), 5.51 (s, 1H, CH); MS *m*/*z* 487.

### 4.9. Materials and spectroscopic methods

Mps were determined in open capillary with a Büchi-530 melting point apparatus and are uncorrected. $^1$H NMR spectra were recorded on a Brucker WM (400 MHz) spectrometer using TMS as reference. IR spectra were obtained in neat/KBr discs on a model Perkin–Elmer Ac-1 spectrophotometer and are expressed in reciprocal centimeters. EI mass spectra were obtained at 70 eV using a JEOL JMS-D 300 spectrometer. Elemental analyses (C, H) were carried out on a Carlo Erba-1108 elemental analyzer. TLC was performed on 7×3 cm thin layer analytical plates (SRL). Chemicals were obtained from Fluka, Aldrich and Across and were used as receive under otherwise noted. The following experiments represent typical experimental procedures employed in the preparation of the compounds given in Table 1.

### 4.10. Estrogen agonistic activity

Twenty one day old immature female Sprague–Dawley rats were bilaterally ovariectomized under light ether anesthesia and after post-operative rest for 7 days were randomized into different treatment groups. Each rat received the compound of the invention once daily for 3 consecutive days on days 28–30 of age by oral route. A separate group of animals received only the vehicle for similar duration served as control. At autopsy 24 h after the last treatment on day 31 of age, vaginal smear of each rat was taken and uterus was carefully excised, gently blotted, weighed. Premature opening of vagina, cornification of vaginal epithelium and increase in uterine fresh weight were taken as parameters for evaluation of estrogen agonistic activity in comparison to rats of vehicle control group. The objective was to evaluate estrogen agonistic effect of the compounds on the uterus and vagina. Compounds exhibiting no or negligible estrogen agonistic activity in this assay were identified for further development as antiimplantation agents.

### 4.11. Estrogen antagonistic activity

Twenty-one-day-old immature female Sprague–Dawley rats were bilaterally ovariectomized under light ether anesthesia and after post-operative rest for 7 days were randomized into different treatment groups. Each rat received the compound of the invention and 0.02 mg $kg^{-1}$ dose of 17 α-ethynylestradiol in 10% ethanol-distilled water once daily for 3 consecutive days on days 28–30 of age by oral route. A separate group of animals receiving only 17 α-ethynylestradiol (0.02 mg$kg^{-1}$) in 10% ethanol-distilled water for similar duration were used for comparison. At autopsy on day 31 of age vaginal smear of each rat was taken and uterus was carefully excised, gently blotted, weighed and fixed for histology. Inhibition in ethynylestradiol induced cornification of vaginal epithelium and increase in uterine fresh weight were taken as parameters for evaluation of estrogen antagonistic effect of the compounds. Compounds exhibiting potent estrogen antagonistic activity in this assay were identified for further development as antiimplantation agents.

### 4.12. Antiimplantation screening

Antiimplantation activity of the compounds was studied in sperm positive adult (180–220 g) Sprague–Dawley female albino rats mated to coeval males of proven fertility. The compounds were administered orally as a suspension in gum acacia to colony bread adult mated female rats on days 1–5 post-coitum using five to seven animals in each group. The animals were examined by laprotomy on day 10 of pregnancy for the number and status of implantations and corpora lutea. The results were scored as positive only if implantations were totally absent in both the uterine horns of each animal.

### 4.13. Estrogen receptor binding affinity

The relative binding affinity (RBA) of the compounds for estrogen receptor was determined by competition assay, employing radiolabeled estradiol ($^3$H-$E_2$) as the reference compound. The test ligands and ($^3$H-$E_2$) were incubated (4 °C) with cytosol estrogen receptors obtained from immature 20–21 days old rat uteri. Aliquot of the uterine cytosol (200 μL concd 1 uterus per mL) prepared in TEA buffer (10 mM TRIS, 1.5 mM EDTA, 0.02% sodium azide, pH 7.4) were incubated in triplicate with a fixed concentration of radiolabeled estradiol with or without various concentrations of the competitor substance dissolved in 60 μL of the TEA buffer containing DMF as co solvent (final concentration of DMF in the incubation medium never exceeded 5%) for 18 h at 4 °C. At the end of this period, dextran coated charcoal (DCC) (5% Norit 0.5% dextran) suspension in 100 μL of TEA buffer was added into each tube, which were briefly vortexed and allowed to stand for 15 min. DCC was precipitated by centrifugation (800 *g*×10 min) and the supernatants counted for radioactivity in 10 mL of a dioxane-based scintillation fluid. RBA of the text compound was computed from a graph plotted between percent bound radioactivity verses log concentration of the test substance. At 50% inhibition, log of the competitor concentration relative to that of estradiol, gave the affinity of the test compound to estrogen receptor relative to estradiol. This when multiplied with 100 gave the percentage value designated as RBA (Table 2).

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