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# Substituted phenanthrenes with basic amino side chains: A new series of anti-breast cancer agents☆

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**Abstract**—In the course of our search for new anti-breast cancer agents, substituted phenanthrenes with basic amino side chains were synthesized and some of them showed remarkable antiproliferative activity against ER +ve MCF-7 cell line with $IC_{50}$ in the range of 3.53–22.25 μM. One of the compounds **15ca** showed anti-breast cancer activity in 7,12-dimethylbenz[*a*]anthracene (DMBA) induced hormone-dependent mammary tumor in rat and the activity was comparable to that shown by tamoxifen.


## 1. Introduction

Stimulation of estrogen receptors (ER) by endogenous estrogens plays an important role in both male and female physiology.[1] Estrogen stimulation is implicated in the development of breast cancer.[2] The blockade of estrogen action is a major approach for the treatment of estrogen-dependent breast cancer.[3] Consequently, many estrogen receptor ligands with antiestrogenic effect are being developed with the aim of preventing estrogen mediated growth. Triarylethylenes such as tamoxifen **1** (TAM) are the first successful series of potent selective estrogen receptor modulators (SERMs) with antiestrogenic activity that was developed for the treatment and prevention of ER positive breast cancer.[4] However, because these antiestrogens generally possess partial estrogenic activity in some estrogen target tissues such as bone, uterus, and liver,[5] considerable efforts have been made to the search of pure antiestrogens without estrogenic activity.[6] This approach has resulted in the development of steroidal and non-steroidal pure antiestrogens (**2**, **3**, and **4** in Fig. 1) which compete with endogenous estradiol for ER binding and directly interact with growth factors, thereby inhibiting estrogen action.

Phenanthrenes and their substituted analogs are well known to exhibit various biological activities such as

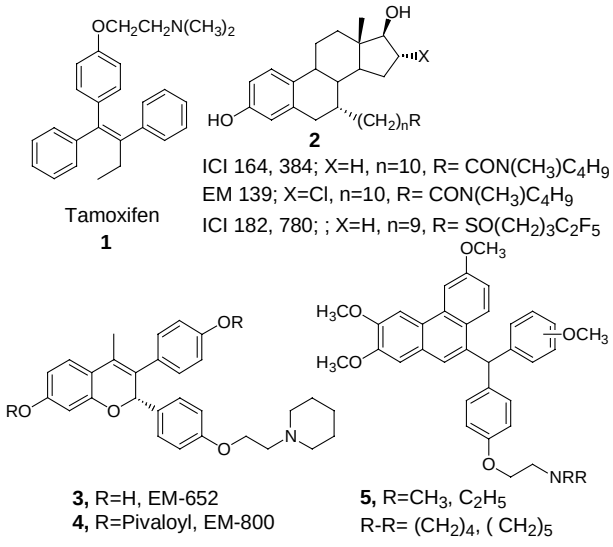


**Figure 1.** Structures of the estrogen receptor ligands.

*Keywords*: Substituted phenanthrenes; Anti-breast cancer agents; Basic amino side chain.
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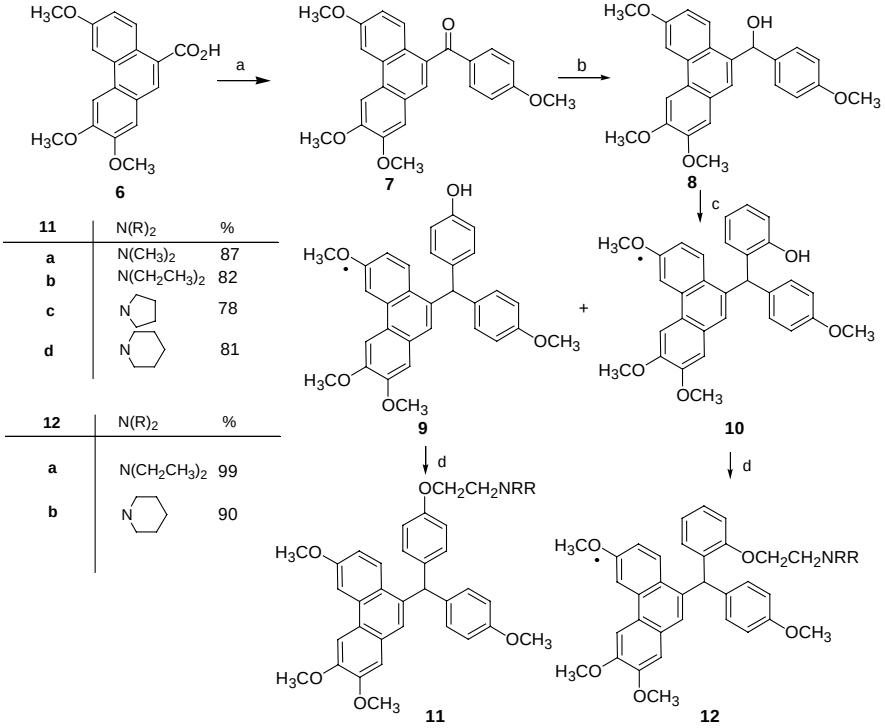
antimicrobial,[7a] cytotoxic,[7b] antifungal,[7c] and antimalarial.[7d] Recently, diaryloxy methano phenanthrene derivatives having antitubercular activity are reported from our laboratory.[8] Particularly, we have been interested in the relationship between substituted phenanthrenes and anti-breast cancer activities as some of the phenanthrene derivatives are known to exhibit antiproliferative effect against breast cancer cells.[9] It is well known that most of the compounds having high relative binding affinity to estrogen receptor possess at least one or two strategically placed hydroxy or methoxy groups in their structure.[10] On the other hand, there are considerable literature reports that 7α substituted estradiol derivatives especially **ICI 164**, **182**, **384**, **780**, and **EM-139** are having antiestrogenic activity on breast cancer cells.[11] Thus, we presume that methoxy substituted phenanthrene will mimic the skeleton of estradiol for receptor binding and substitution at position nine of phenanthrene nucleus might act as 7α substituent in **2** and thus will exert antiestrogenic effect on breast cancer cells. Thus, we have designed the compound **5** as our target molecule with various amines as side chains and evaluated their antiproliferative activity against estrogen responsive MCF-7 cell lines.

## 2. Results and discussion

### 2.1. Chemistry

To synthesize the target molecule as described in Figure 1, **11** and **12** were selected. Literature procedure was followed to synthesize the trimethoxy-phenanthrene-9-carboxylic acid **6**.[12] Treatment of **6** with anisole in the presence of PPA gave the methanone derivative **7** (58%) which on reduction with LAH furnished the carbinol **8** in 83% yield. Friedel–Crafts arylation with phenol in the presence of concd. $H_2SO_4$ and benzene furnished **9** as major product and **10** as minor one by nucleophilic attack of phenol through *para* and *ortho* position on the carbinol carbon atom of **8**, respectively. The reaction between **9** and **10** with alkylaminohydrochloride chains in the presence of $K_2CO_3$ and acetone led to the formation of **11a–d** and **12a–b**, respectively, in good yields, Scheme 1. Since all the six compounds were crystallizable solids, they were used as such for evaluation of their anti-breast cancer activity, Tables 1 and 2.

Out of six compounds **11a–d**, **12a–b** synthesized, only one compound **11a** was showing antiproliferative activity with $IC_{50}$ 21.80 against ER +ve MCF-7 cell line. To rationalize our pharmacological results, we performed comparative docking of compound **11a** with 4-hydroxytamoxifen (OHT) in estrogen receptor (ERα) using MOE software. From Figure 2, it is evident that the compound **11a** does not fit well into the ERα ligand binding pocket. The improper orientation of **11a** in ERα may be due to the steric hindrance of methoxy functionality of phenanthrene. Thus, we presumed that the compounds lacking methoxy on phenanthrene may be suitable for binding with ERα ligand binding pocket. The comparative docking study of compound **15bc** and OHT with ERα shows encouraging results and as




**Scheme 1.** Synthesis of (2-{4-[(4-methoxy-phenyl)-(2,3,6-trimethoxy-phenanthren-9-yl)-methyl]-phenoxy}-ethyl)-alkylamine derivatives **11** and **12**. Reagents and conditions: (a) anisole, PPA, 58%; (b) LAH, THF, 83%; (c) Phenol, concd. $H_2SO_4$, benzene, 65%; (d) $ClCH_2CH_2NRR{\cdot}HCl$, $K_2CO_3$, acetone, 78–99%.

**Table 1.** In vitro anti-breast cancer activities of **11a–d**, **12a–b**, **15**·HCl, **16**·HCl, and **18**·HCl, against human breast cancer cell line ER +ve MCF-7

| Serial No. | Compound | $IC_{50}$ (μM) (MCF-7)[a] |
|---|---|---|
| 1 | **11a** | 21.80 |
| 2 | **11b** | NA |
| 3 | **11c** | NA |
| 4 | **11d** | NA |
| 5 | **12a** | NA |
| 6 | **12b** | NA |
| 7 | **15aa** | NA |
| 8 | **15ab** | NA |
| 9 | **15ac** | NA |
| 10 | **15ad** | NA |
| 11 | **15ba** | NA |
| 12 | **15bb** | NA |
| 13 | **15bc** | 3.53 |
| 14 | **15bd** | 5.97 |
| 15 | **15ca** | 3.88 |
| 16 | **15cb** | 4.29 |
| 17 | **15cc** | 6.50 |
| 18 | **15cd** | 7.91 |
| 19 | **16ca** | NA |
| 20 | **16cb** | NA |
| 21 | **16cc** | NA |
| 22 | **16cd** | 22.25 |
| 23 | **18a** | NA |
| 24 | **18b** | NA |
| 25 | **18c** | 9.97 |
| 26 | **18d** | 4.94 |
| 27 | **18e** | NA |
| 28 | **18f** | NA |
| 29 | **18g** | 20.19 |
| 30 | Tamoxifen | 12.48 |

[a] $IC_{50}$ values for anti-breast cancer activity of ligands using ER +ve and −ve cell lines viz. MCF-7 and MDA MB-453, respectively, using tamoxifen as a positive control. The results are representative of one of three similar experiments each performed in triplicate. Each datum depicts the $IC_{50}$ for each ligand. The deviation in each case was less than 5% and 'NA' represents ligands that were found to be inactive at 25 μM in either of the two cell types in which the SRB assays were conducted.

expected **15bc** orients well in pocket through hydrogen bonding with ARG 394 and GLU 353 residues of ERα (Fig. 3). Thus, the feasible synthetic strategies toward compounds **15** and **16** were undertaken.

Toward the objective, the compounds **13a–c**[8] and **14a–c**[8] were reacted with different alkylamine hydrochlorides in the presence of $K_2CO_3$ and acetone to furnish **15** and**16** in good yield (Scheme 2). By treatment of amines **15** and **16** with ethanolic hydrogen chloride the corresponding salts **15**·HCl and **16**·HCl were prepared. The salts **15**·HCl and **16**·HCl were tested and found to be active against MCF-7 cell lines in vitro with $IC_{50}$ in the range of 3.53–22.25 μM (Table 1). Therefore, 4-[(2 or 3 or 4-methoxy-phenyl)-phenanthren-9-yl-methyl]-phenol derivatives were selected as active pharmacophores and further synthetic transformations were performed. From close analysis of the structures of **15** and **16**, it is clear that the aminoalkyl containing basic ether side chain is responsible for its modulating influence on antagonistic efficacy among diaryloxymethanophenanthrene pharmacophore. Thus, we became interested to study the

**Table 2.** In vitro anti-breast cancer activities of **11a–d**, **12a–b**, **15**·HCl, **16**·HCl, and **18**·HCl, against ER −ve MDA MB-453 cell line

| Serial No. | Compound | $IC_{50}$ (μM) (MDA MB-453)[a] |
|---|---|---|
| 1 | **11a** | 2.75 |
| 2 | **11b** | 3.50 |
| 3 | **11c** | 3.50 |
| 4 | **11d** | 5.75 |
| 5 | **12a** | 5.80 |
| 6 | **12b** | NA |
| 7 | **15ad** | NA |
| 8 | **15ca** | NA |
| 9 | **15cb** | 6.2 |
| 10 | **15cd** | 10.0 |
| 11 | **16cd** | 7.33 |
| 12 | **18c** | 6.30 |
| 13 | **18d** | 2.75 |
| 14 | **18e** | NA |
| 15 | **18f** | NA |
| 16 | Tamoxifen | 13.50 |

[a] $IC_{50}$ values for anti-breast cancer activity of ligands using ER +ve and −ve cell lines viz. MCF-7 and MDA MB-453, respectively, using tamoxifen as a positive control. The results are representative of one of three similar experiments each performed in triplicate. Each datum depicts the $IC_{50}$ for each ligand. The deviation in each case was less than 5% and 'NA' represents ligands that were found to be inactive at 25 μM in either of the two cell types in which the SRB assays were conducted.

effect of ether side chain containing various aminoalkyl groups on the pharmacophore.

Toward this objective, **13c** was treated with epichlorohydrin in the presence of $K_2CO_3$ to furnish epoxides **17** in good yield (86%). The epoxide **17**, in turn, reacted with commercially available different amines to afford a variety of 1-aminopropan-2-ol derivatives **18** (64–96%, Scheme 3) through nucleophilic reaction of amines onto less hindered side of the epoxide. By treatment of **18** with ethanolic hydrochloride, the corresponding salts **18**·HCl were prepared and tested against MCF-7 and MDA MB-453 cell lines in vitro (Tables 1 and 2).

## 2.2. Biology

**2.2.1. Determination of anti-breast cancer activity in vitro.** The activities of the compounds against MCF-7 and MDA MB-453 cell lines were determined through SRB (Sulforhodamine B) antiproliferative activity assay and the results are shown in Tables 1 and 2.

**2.2.2. Structure–activity relationship.** From the comparison of the data of compounds (Table 1), it is evident that compounds lacking methoxy groups on the phenanthrene nucleus gave lower $IC_{50}$ agsinst ER +ve MCF-7 cell line. Compounds containing an *ortho*-methoxy group were found to be inactive, whereas molecules containing *meta*-methoxy and *para*-methoxy groups except for **15ba** and **15bb**, were active. The contribution of the basic ether chain to estrogen antagonistic activity of the phenanthrene is structure as well as position specific. The protype is active with the chain at *para* position and inactive with chain at *ortho* position of the phenyl ring. The activity increased with the decrease of

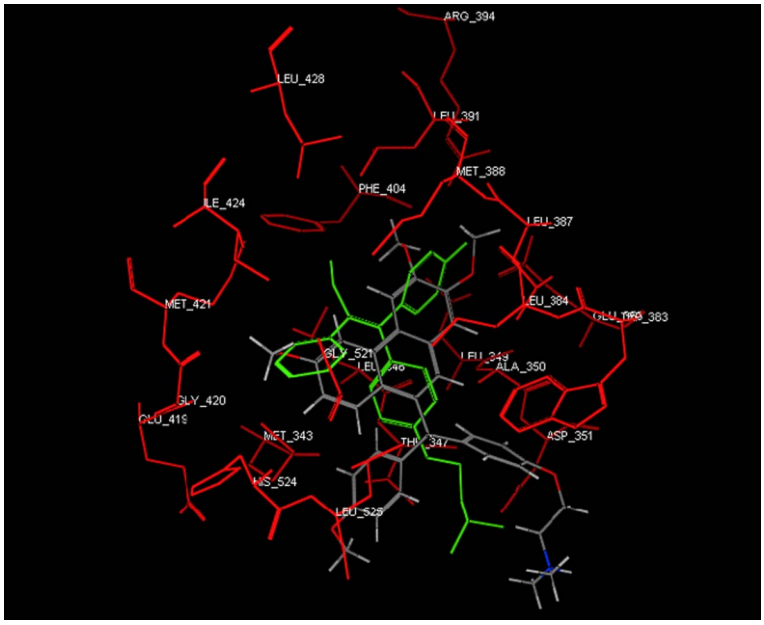



**Figure 2.** Comparative docking orientation and predicted receptor interactions for compound **11a** (gray), 4-hydroxytamoxifen (OHT, green), and ERα (red) (PDB ID3ERT).

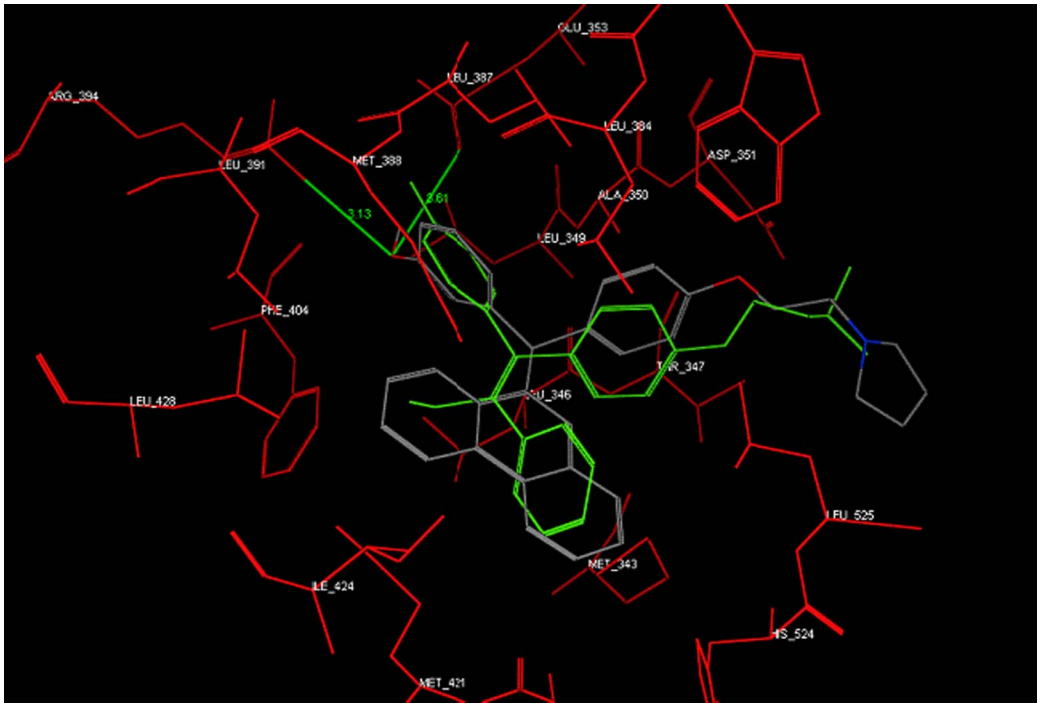
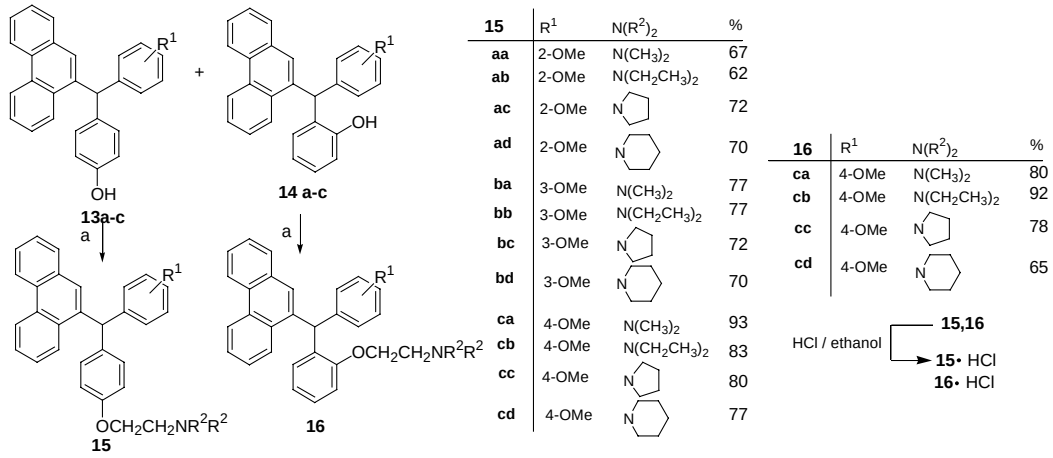



**Figure 3.** Comparative docking orientation and predicted receptor interactions for compound **15bc** (gray), 4-hydroxytamoxifen (OHT, green), and ERα (red) (PDB ID3ERT).

the length of alkyl group on nitrogen. This was evident from MIC values of piperidino ether **15bd** and **15cd** (5.91 and 7.91 μM, respectively), pyrolidone ether **15bc** and **15cc** (3.53 and 6.50 μM, respectively), diethylamino ether **15cb** (4.29 μM), and dimethylamino ether **15ca** (3.88 μM). In 1-aminopropan-2-ol derivatives (**18a**–**g**), compounds having *N*-methylpiperazine, cyclohexylamine or cyclopropyl amine in the side chain impart better antagonistic activity than the compounds having pyrrolidine, piperidine, morpholine or *N*-benzylpiperazine amino group.

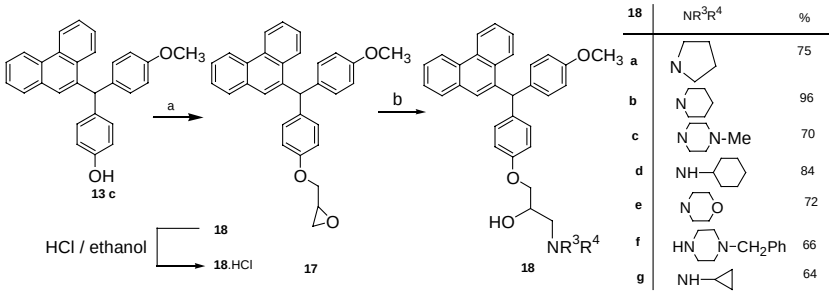
It is also interesting to note from $IC_{50}$ values of **11a**–**d**, **12a**–**b**, **15ad**, **15cb**, **15cd**, **16cd**, and **18c**–**f** against ER −ve MDA MB-453 (Table 2) that **11a**–**d** and **12a**–**b** containing methoxy groups on phenanthrene gave lower $IC_{50}$ against ER −ve MDA MB-453 in comparison of $IC_{50}$ (Table 1) against ER +ve MCF-7. The specificity




| 15 | $R^1$ | $N(R^2)_2$ | % |
|---|---|---|---|
| aa | 2-OMe | $N(CH_3)_2$ | 67 |
| ab | 2-OMe | $N(CH_2CH_3)_2$ | 62 |
| ac | 2-OMe | N | 72 |
| ad | 2-OMe | N | 70 |
| ba | 3-OMe | $N(CH_3)_2$ | 77 |
| bb | 3-OMe | $N(CH_2CH_3)_2$ | 77 |
| bc | 3-OMe | N | 72 |
| bd | 3-OMe | N | 70 |
| ca | 4-OMe | $N(CH_3)_2$ | 93 |
| cb | 4-OMe | $N(CH_2CH_3)_2$ | 83 |
| cc | 4-OMe | N | 80 |
| cd | 4-OMe | N | 77 |

| 16 | $R^1$ | $N(R^2)_2$ | % |
|---|---|---|---|
| ca | 4-OMe | $N(CH_3)_2$ | 80 |
| cb | 4-OMe | $N(CH_2CH_3)_2$ | 92 |
| cc | 4-OMe | N | 78 |
| cd | 4-OMe | N | 65 |

**Scheme 2.** Synthesis of 4-[(2 or 3 or 4-methoxy-phenyl)-phenanthren-9-yl-methyl]-phenols **13a–c**, **14a–c**, 1-(2-{4-[2 or 3 or 4-methoxy-phenyl)-phenanthren-9-yl-methyl]-phenoxy}-ethyl)-*N*,*N*-dialkylamines **15**, **16**, and their hydrochlorides **15**·HCl and **16**·HCl. Reagents and conditions: (a) $ClCH_2CH_2N(R^2)_2$·HCl, $K_2CO_3$, acetone, 62–93%.




| 18 | $NR^3R^4$ | % |
|---|---|---|
| a | N | 75 |
| b | N | 96 |
| c | N-Me | 70 |
| d | NH | 84 |
| e | O | 72 |
| f | N-$CH_2$Ph | 66 |
| g | NH | 64 |

**Scheme 3.** Synthesis of 1-amino-3-{4-[(4-methoxy-phenyl)-phenanthren-9-yl-methyl]-phenoxy}-propan-2-ols **18a–g**. Reagents and conditions: (a) epichlorohydrin, $K_2CO_3$, 86%; (b) $HNR^3R^4$, ethanol, 64–96%.

may be due to the presence of methoxy groups of **11a–d** and **12a–b**, Figures 2 and 3. Compounds **15cb**, **15cd**, and **16cd** containing *para*-methoxy groups gave better anti-proliferative activity than **15ad** with *ortho*-methoxy functionality. **18c–d** containing *N*-methylpiperazine and cyclohexyl amine showed enhanced activity than **18e–f** containing morpholine and *N*-benzylpiperazine rings, Table 2.

Since the objective was to develop estrogen responsive anti-breast cancer agents, **15ca** was selected to find its activity in vivo because of a lower $IC_{50}$ value against the ER +ve MCF-7 cell line in vitro. From Figure 4, it is evident that **15ca** at 10 mg/kg dose level effectively inhibited the growth and induced significant regression of mammary tumors. By the end of third week of treatment, the tumors regressed to almost 50% of their 0-day size. The compound was however ineffective at 20 mg/kg dose (data not shown). Also, all animals of both the dose groups died in the fourth week of treatment. The mortality largely appeared to be due to anorexia, which was evident in the third week of treatment.

## 3. Conclusion

The analysis of in vitro data of the compounds **11a–d**, **12a–b**, **15**·HCl, **16**·HCl, and **18**·HCl clearly suggests that

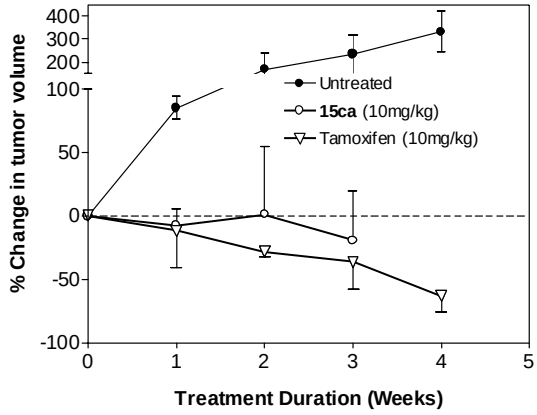



**Figure 4.** The data of compound **15ca** in vivo.

this class of compounds appears to have anti-breast cancer activity. The compound **15ca** seems to protect the mice from the challenge of tumor and this protection is dose dependent. We are reporting for the first time that diaryloxymethano phenanthrenes might be a suitable pharmacophore for developing novel anti-breast cancer agents. A rational and logical design of a compound retaining the anti-breast cancer activity without toxicity may be a favorable molecule. Synthesis of the compounds and their biological evaluation toward this direction are currently underway.

## 4. Experimental details

### 4.1. (4-Methoxy-phenyl)-(2,3,6-trimethoxy-phenanthren-9-yl)-methanone (7)

A mixture of trimethoxy-phenanthrene-9-carboxylic acid **6** (5 g, 16.02 mmol), PPA (50 g),and anisole (2.5 g, 23.14 mmol) was taken and heated for 2 h at 100 °C. The reaction mixture was poured into ice-cold water and extracted with ethyl acetate, washed with $NaHCO_3$, and dried over anhydrous $Na_2SO_4$. Column chromatography over silica gel and elution with 40% ethyl acetate in hexane furnished the methanone **7**: white solid (3.73 g, 58%), mp 147 °C, IR (KBr): 2934, 1600, 1511, 1425, 1248 $cm^{-1}$, $^1H$ NMR ($CDCl_3$, 200 MHz): $\delta$ 8.01 (d, 1H, $J = 7$ Hz), 7.89 (s, 1H), 7.86 (s, 1H), 7.85 (d, 2H, $J = 8$ Hz), 7.58 (s, 1H), 7.14 (s, 1H), 7.13 (d, 1H, $J = 7.8$ Hz), 6.89 (d, 2H, $J = 7$ Hz), 4.08 (s, 3H), 3.96 (s, 6H), 3.81 (s, 3H); MS: 402 ($M^+$). Anal. Calcd for $C_{25}H_{22}O_5$: C, 74.61; H, 5.51. Found: C, 74.57; H, 5.45.

### 4.2. (4-Methoxy-phenyl)-(2,3,6-trimethoxy-phenanthren-9-yl)-methanol (8)

The methanone **7** (2.0 g, 4.97 mmol) was taken in dry THF (60 mL) at 0 °C and LAH (380 mg, 10.27 mmol) was added in portions into it and the reaction mixture was stirred for 2 h. Excess LAH was destroyed by slow addition of ethyl acetate and solvent was distilled off. Extraction with ethyl acetate and elution of 40% ethyl acetate in hexane over silica gel furnished the methanol **8**: white solid (1.67 g, 83%), mp 176 °C, IR (KBr): 2929, 1611, 1511, 1464, 1248, 1160, 1034, 760 $cm^{-1}$, $^1H$ NMR ($CDCl_3$, 200 MHz): $\delta$ 7.90 (d, 1H, $J = 8.4$ Hz), 7.85 (s, 1H), 7.79 (s, 1H), 7.64 (s, 1H), 7.31 (d, 2H, $J = 8.6$ Hz), 7.15 (s, 1H), 7.07 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 2.6$ Hz), 6.82 (d, 2H, $J = 8.6$ Hz), 6.37 (s, 1H), 4.07 (s, 3H), 3.99 (s, 3H), 3.95 (s, 3H), 3.75 (s, 3H), 1.80 (br s, 1H); MS: 404 ($M^+$). Anal. Calcd for $C_{25}H_{24}O_5$: C, 74.24; H, 5.98. Found: C, 74.28; H, 6.03.

### 4.3. Representative Friedel–Crafts alkylation

To a solution of carbinol **8** (1.5 g, 3.71 mmol) and phenol (523 mg, 5.57 mmol) in dry benzene (15 mL), catalytic amount of concd. $H_2SO_4$ was added and the reaction mixture was refluxed at 80 °C for 1 h. It was cooled to room temperature, treated with saturated $NaHCO_3$, and extracted with ethyl acetate. The organic layer was washed with water and dried over anhydrous $Na_2SO_4$. Column chromatography over silica gel and elution with 15% ethyl acetate in hexane furnished the desired compound (1.15 g, *ortho* and *para* together, 65%).

### 4.4. 4-[(4-Methoxy-phenyl)-(2,3,6-trimethoxy-phenanthren-9-yl)-methyl]-phenol (9)

Pale yellow solid (810 mg), mp 175 °C, IR (KBr): 2929, 1611, 1465, 1243, 1033 $cm^{-1}$, $^1H$ NMR ($CDCl_3$, 200 MHz): $\delta$ 7.93 (d, 1H, $J = 7$ Hz), 7.90 (s, 1H), 7.88 (s, 1H), 7.10 (d, 1H, $J = 7$ Hz), 7.07 (s, 1H), 7.04 (d, 2H, $J = 8$ Hz), 7.02 (d, 1H, $J = 7$ Hz), 6.99 (d, 1H, $J = 8$ Hz), 6.88 (d, 1H, $J = 7$ Hz), 6.85 (s, 1H), 6.82 (d, 2H, $J = 8$ Hz), 6.77 (d, 1H, $J = 7$ Hz), 6.08 (s, 1H), 4.95 (br s, 1H), 4.07 (s, 3H), 3.93 (s, 6H), 3.78 (s, 3H); MS: 480 ($M^+$). Anal. Calcd for $C_{31}H_{28}O_5$): C, 77.48; H, 5.87. Found: C, 77.41; H, 5.94.

### 4.5. 2-[(4-Methoxy-phenyl)-(2,3,6-trimethoxy-phenanthren-9-yl)-methyl]-phenol (10)

Pale yellow solid (340 mg), mp 150 °C, IR (KBr): 2935, 1614, 1510, 1460, 1245, 1033 $cm^{-1}$, $^1H$ NMR ($CDCl_3$, 200 MHz): $\delta$ 7.92 (d, 1H, $J = 7$ Hz), 7.89 (s, 1H), 7.86 (s, 1H), 7.18 (d, 1H, $J = 7$ Hz), 7.14 (s, 1H), 7.11 (d, 1H, $J = 8$ Hz), 7.10 (d, 2H, $J = 7$ Hz), 7.09 (d, 2H, $J = 8$ Hz), 6.87 (s, 1H), 6.83 (d, 1H, $J = 8$ Hz), 6.80 (d, 2 H, $J = 8$Hz), 6.31 (s, 1H), 4.97 (br s, 1H), 4.09 (s, 3H), 3.95 (s, 6H), 3.79 (s, 3H); MS: 480 ($M^+$). Anal. Calcd $C_{31}H_{28}O_5$: C, 77.48; H, 5.87. Found: C, 77.53; H, 5.83.

### 4.6. Representative chain reaction

A mixture of compounds **9** or **10** (300 mg, 0.625 mmol), anhydrous $K_2CO_3$ (431 mg, 3.12 mmol), aminohydrochloride chain (0.93 mmol), and dry acetone (10 mL) was refluxed for 7 h. $K_2CO_3$ was filtered off and acetone was removed. The residue was diluted with water and extracted with ethyl acetate. The organic layer was washed with water, brine, and dried over anhydrous $Na_2SO_4$. Column chromatography over silica gel and elution with 30% ethyl acetate in hexane furnished the compound. The product was dissolved in absolute ethanol (10 mL) and ethanolic HCl was added dropwise untill the pH of the mixture became acidic. Ethanol was removed in vacuo. The residue was recrystallized from a mixture of absolute ethanol and dry ether to give the compound as hydrochloride salt.

### 4.7. (2-{4-[(4-Methoxy-phenyl)-(2,3,6-trimethoxy-phenanthren-9-yl)-methyl]- phenoxy}-ethyl)-dimethyl-amine (11a)

Pale yellow solid (300 mg, 87%), mp 100 °C, IR (KBr): 2934, 1614, 1509, 1462, 1244, 1032 $cm^{-1}$, $^1H$ NMR ($CDCl_3$, 200 MHz): $\delta$ 7.94 (d, 1H, $J = 8$ Hz), 7.89 (s, 1H), 7.87 (s, 1H), 7.10 (d, 1H, $J = 7.8$ Hz), 7.07 (s, 1H), 7.02 (d, 4H, $J = 8.2$ Hz), 6.89 (s, 1H), 6.82 (d, 4H, $J = 8.2$ Hz), 4.09 (s, 3H), 4.05 (t, 2H, $J = 7$ Hz), 3.97 (s, 6H), 3.78 (s, 3H), 2.71 (t, 2H, $J = 7$ Hz), 2.32 (s, 6H); MS: 552 ($M^+$), Anal. Calcd for $C_{35}H_{37}NO_5$: C, 76.20; H, 6.76; N, 2.54. Found: C, 77.29; H, 6.69; N, 2.57.

### 4.8. Diethyl-(2-{4-[(4-methoxy-phenyl)-(2,3,6-trimethoxy-phenanthren-9-yl)-methyl]-phenoxy}-ethyl)-amine (11b)

Pale yellow solid (300 mg, 82%), mp 105 °C, IR (KBr): 2962, 1612, 1509, 1463, 1246, 1034 $cm^{-1}$, $^1H$ NMR ($CDCl_3$, 200 MHz): $\delta$ 7.95 (d, 1H, $J = 8$ Hz), 7.91 (s, 1H), 7.88 (s, 1H), 7.10 (d, 1H, $J = 7.8$ Hz), 7.05 (d, 4H, $J = 8.4$ Hz), 7.02 (s, 1H), 6.92 (s, 1H), 6.85 (d, 4H, $J = 8.4$ Hz), 6.11 (s, 1H), 4.11 (s, 3H), 4.06 (t, 2H, $J =$ 7 Hz), 3.99 (s, 6H), 3.80 (s, 3H), 2.90 (t, 2H, $J = 7$ Hz), 2.67 (q, 4H, $J = 7$ Hz), 1.09 (t, 2H, $J = 7$ Hz); MS: 580

($M^{1+}$), Anal. Calcd for $C_{37}H_{41}NO_5$: C, 76.66; H, 7.13; N, 2.42. Found: C, 76.71; H, 7.19; N, 2.39.

### 4.9. 1-(2-{4-[(4-Methoxy-phenyl)-(2,3,6-trimethoxy-phenanthren-9-yl)-methyl]-phenoxy}-ethyl)-pyrrolidine (11c)

Light brown solid (270 mg, 78%), mp 173 °C, IR (KBr): 2933, 1612, 1509, 1247, 1036 $cm^{-1}$, $^1H$ NMR ($CDCl_3$, 200 MHz): $\delta$ 7.94 (d, 1H, $J$ = 8 Hz), 7.90 (s, 1H), 7.85 (s, 1H), 7.10 (d, 1H, $J$ = 7.8 Hz), 7.02 (s, 1H), 6.90 (s, 1H), 6.82 (d, 4H, $J$ = 8.4 Hz), 6.08 (s, 1H), 4.08 (s, 3H), 4.04 (t, 2H, $J$ = 6 Hz), 3.96 (s, 6H), 3.77 (s, 3H), 2.88 (t, 2H, $J$ = 6 Hz), 2.61–2.59 (m, 4H), 1.82–1.76 (m, 4H); MS: 578 ($M^{1+}$), Anal. Calcd for $C_{37}H_{39}NO_5$: C, 76.92; H, 6.80; N, 2.42. Found: C, 76.99; H, 6.89; N, 2.49.

### 4.10. 1-(2-{4-[(4-Methoxy-phenyl)-(2,3,6-trimethoxy-phenanthren-9-yl)-methyl]-phenoxy}-ethyl)-piperidine (11d)

Pale yellow solid (300 mg, 81%), mp 107 °C, IR (KBr): 2930, 1612, 1509, 1463, 1245, 1036 $cm^{-1}$, $^1H$ NMR ($CDCl_3$, 200 MHz): $\delta$ 7.93 (d, 1H, $J$ = 8 Hz), 7.90 (s, 1H), 7.86 (s, 1H), 7.10 (d, 2H, $J$ = 7.8 Hz), 7.06 (d, 4H, $J$ = 8.2 Hz), 6.90 (s, 1H), 6.82 (d, 4H, $J$ = 8.2 Hz), 4.08 (t, 2H, $J$ = 7 Hz), 4.07 (s, 3H), 3.96 (s, 6H), 3.78 (s, 3H), 2.75 (t, 2H, $J$ = 7 Hz), 2.49 (t, 4H, $J$ = 7 Hz), 1.62–1.40 (m, 6H); MS: 592 ($M^{1+}$), Anal. Calcd for $C_{38}H_{41}NO_5$: C, 77.13; H, 6.98; N, 2.37. Found: C, 77.09; H, 6.91; N, 2.32.

### 4.11. Diethyl-(2-{2-[(4-methoxy-phenyl)-(2,3,6-trimethoxy-phenanthren-9-yl)-methyl]-phenoxy}-ethyl)-amine (12a)

Pale yellow solid (370 mg, 99%), mp 175 °C, IR (KBr): 2964, 1613, 1510, 1244, 1043, 757 $cm^{-1}$, $^1H$ NMR ($CDCl_3$, 200 MHz): $\delta$ 7.93 (d, 1H, $J$ = 8 Hz), 7.90 (s, 1H), 7.87 (s, 1H), 7.21 (m, 1H), 7.10 (d, 1H, $J$ = 7.8 Hz), 7.09 (d, 1H, $J$ = 7.8 Hz), 7.03 (d, 2H, $J$ = 8.4 Hz), 6.93 (s, 1H), 6.89 (d, 1H, $J$ = 8 Hz), 6.83 (d, 1H, $J$ = 7.8 Hz), 6.82 (s, 1H), 6.81 (d, 2H, $J$ = 8.4 Hz), 6.48 (s, 1H), 4.09 (s, 3H), 3.97 (t, 2H, $J$ = 6 Hz), 3.96 (s, 6H), 3.79 (s, 3H), 2.58 (t, 2H, $J$ = 6 Hz), 2.39 (q, 4H, $J$ = 7 Hz), 0.85 (t, 6H, $J$ = 7.8 Hz); MS: 580 ($M^{1+}$). Anal. Calcd for $C_{37}H_{41}NO_5$: C, 76.66; H, 7.13; N, 2.42. Found: C, 76.60; H, 7.07; N, 2.38.

### 4.12. 1-(2-{2-[(4-Methoxy-phenyl)-(2,3,6-trimethoxy-phenanthren-9-yl)-methyl]-phenoxy}-ethyl)-piperidine (12b)

Pale yellow solid, mp 171 °C (270 mg, 90%), IR (KBr): 2933, 1614, 1511, 1244, 1036, 754 $cm^{-1}$, $^1H$ NMR ($CDCl_3$, 200 MHz): $\delta$ 7.93 (d, 1H, $J$ = 8 Hz), 7.90 (s, 1H), 7.86 (s, 1H), 7.20 (m, 1H), 7.10 (d, 1H, $J$ = 7.8 Hz), 7.09 (d, 1H, $J$ = 7.8 Hz), 7.03 (d, 2H, $J$ = 8.4 Hz), 6.92 (s, 1H), 6.86 (d, 1H, $J$ = 8 Hz), 6.83 (d, 1H, $J$ = 7.8 Hz), 6.82 (s, 1H), 6.80 (d, 2H, $J$ = 8.2 Hz), 6.48 (s, 1H), 4.09 (s, 3H), 4.03 (t, 2H, $J$ = 7 Hz), 3.97 (s, 6H), 3.78 (s, 3H), 2.52 (t, 2H, $J$ = 6 Hz), 2.19–2.16 (m, 4H), 1.35–1.22 (m, 6H); MS: 592 ($M^{1+}$). Anal. Calcd for $C_{38}H_{41}NO_5$: C, 77.13; H, 6.98; N, 2.37. Found: C, 77.17; H, 7.02; N, 2.43.

Syntheses of **15** and **16** are reported earlier (Ref. 8).

### 4.13. 2-{4-[(4-Methoxy-phenyl)-phenanthren-9-yl-methyl]-phenoxymethyl}-oxirane (17)

The compound **13c** (2.0 g, 5.12 mmol) and anhydrous $K_2CO_3$ (2.52 g, 18.23 mmol) were taken in epichlorohydrin (75 mL) and refluxed for 12 h. $K_2CO_3$ was filtered off and epichlorohydrin was removed in vacuo. The residue was diluted with water and extracted with ethyl acetate. The organic layer was washed with water, brine, and dried over anhydrous $Na_2SO_4$. Column chromatography over silica gel and elution with 20% ethyl acetate in hexane furnished the epoxide **17**. Pale yellow solid (1.97 g, 86%), mp 90 °C, IR (KBr): 3017, 1608, 1508, 1456, 1246, 1178, 1037 $cm^{-1}$ , $^1H$ NMR ($CDCl_3$, 200 MHz): $\delta$ 8.71 (d, 1H, $J$ = 8.2 Hz), 8.64 (d, 1H, $J$ = 8 Hz), 8.02 (d, 1H, $J$ = 8 Hz), 7.69–7.47 (m, 5H), 7.13 (s, 1H), 7.05 (d, 4H, $J$ = 8.2 Hz), 6.83 (d, 4H, $J$ = 8.2 Hz), 6.14 (s, 1H), 4.16 (dd, 1H, $J_1$ = 10 Hz, $J_2$ = 3.2 Hz), 3.93 (dd, 1H, $J_1$ = 10 Hz, $J_2$ = 5.6 Hz), 3.77 (s, 3H), 3.33–3.20 (m, 1H), 2.90–2.85 (m, 1H), 2.74–2.71 (m, 1H); MS: 446 ($M^+$). Anal. Calcd for $C_{31}H_{26}O_3$: C, 83.38; H, 5.87. Found: C, 83.42; H, 5.83.

### 4.14. Representative epoxide opening reactions with amines

The compound **17** (300 mg, 0.67 mmol) and amine (1.05 mmol) were dissolved in ethanol (20 mL) and refluxed for 7 h. The ethanol was removed and the residue was diluted with water and extracted with ethyl acetate. The organic layer was washed with water, brine, and dried over anhydrous $Na_2SO_4$. Column chromatography over silica gel and elution with 5% methanol in chloroform furnished the title compound given below. The aminopropan-2-ol derivatives were dissolved in absolute ethanol (15 mL) and ethanolic HCl was added dropwise untill the pH of the mixture became acidic. Ethanol was removed in vacuo. The residue was recrystallized from a mixture of absolute ethanol and dry ether.

### 4.15. 1-{4-[(4-Methoxy-phenyl)-phenanthren-9-yl-methyl]-phenoxy}-3-pyrrolidin-1-yl-propan-2-ol (18a)

Pale yellow solid, mp 110 °C (260 mg, 75%), IR (KBr): 3011, 1606, 1508, 1457, 1246, 1038, 754 $cm^{-1}$, $^1H$ NMR ($CDCl_3$, 200 MHz): $\delta$ 8.70 (d, 1H, $J$ = 8 Hz), 8.64 (d, 1H, $J$ = 8.2 Hz), 8.01 (d, 1H, $J$ = 8.2 Hz), 7.64–7.47 (m, 5H), 7.13 (s, 1H), 7.04 (d, 4H, $J$ = 8.4 Hz), 6.81 (d, 4H, $J$ = 8.4 Hz), 6.13 (s, 1H), 5.76 (br s, 1H), 4.25 (m, 1H), 4.02–3.87 (m, 2H), 3.77 (s, 3H), 3.11–2.92 (m, 6H), 2.03–1.93 (m, 4H); MS: 518 ($M^{1+}$). Anal. Calcd for $C_{35}H_{35}NO_3$: C, 81.21; H, 6.81; N, 2.71. Found: C, 81.25; H, 6.87; N, 2.78.

### 4.16. 1-{4-[(4-Methoxy-phenyl)-phenanthren-9-yl-methyl]-phenoxy}-3-piperidin-1-yl-propan-2-ol (18b)

Pale yellow solid, mp 105 °C (340 mg, 96%), IR (KBr): 2934, 1607, 1507, 1246, 1177, 1037, 755 $cm^{-1}$, $^1H$

NMR ($CDCl_3$, 200 MHz): $\delta$ 8.71 (d, 1H, $J$ = 8.2 Hz), 8.64 (d, 1H, $J$ = 8 Hz), 8.02 (d, 1H, $J$ = 8.2 Hz), 7.69–7.47 (m, 5H), 7.14 (s, 1H), 7.05 (d, 4H, $J$ = 8.4 Hz), 6.82 (d, 4H, $J$ = 8.4 Hz), 6.14 (s, 1H), 4.11 (m, 1H), 3.96–3.92 (m, 2H), 3.78 (s, 3H), 3.51 (br s, 1H), 2.69–2.42 (m, 6H), 1.51–1.45 (m, 6H); MS: 532 ($M^{1+}$). Anal. Calcd for $C_{36}H_{37}NO_3$: C, 81.32; H, 7.01; N, 2.63. Found: C, 81.39; H, 7.08; N, 2.68.

### 4.17. 1-{4-[(4-Methoxy-phenyl)-phenanthren-9-yl-methyl]-phenoxy }-3-(4-methyl-piperazin-1-yl)-propan-2-ol (18c)

Pale yellow solid, mp 195 °C (256 mg, 70%), IR (KBr): 3016, 1668, 1508, 1455, 1245, 1219, 768 $cm^{-1}$, $^1H$ NMR ($CDCl_3$, 200 MHz): $\delta$ 8.71 (d, 1H, $J$ = 8.4 Hz), 8.65 (d, 1H, $J$ = 8.4 Hz), 8.03 (d, 1H, $J$ = 8 Hz), 7.69–7.47 (m, 5H), 7.14 (s, 1H), 7.05 (d, 4H, $J$ = 8.4 Hz), 6.83 (d, 4H, $J$ = 8.4 Hz), 6.14 (s, 1H), 4.08–4.04 (m, 1H), 3.96–3.94 (m, 2H), 3.78 (s, 3H), 2.75–2.34 (m, 10H), 2.29 (s, 3H); MS: 547 ($M^{1+}$). Anal. Calcd for $C_{36}H_{38}N_2O_3$: C, 79.01; H, 7.01; N, 5.12. Found: C, 79.05; H, 7.11; N, 5.17.

### 4.18. 1-Cyclohexylamino-3-{4-[(4-methoxy-phenyl)-phenanthren-9-yl-methyl]-phenoxy}-propan-2-ol (18d)

Pale yellow solid, mp 155 °C (307 mg, 84%), IR (KBr): 2939, 1608, 1509, 1408, 1246, 1219, 1040, 766 $cm^{-1}$, $^1H$ NMR ($CDCl_3$, 200 MHz): $\delta$ 8.71 (d, 1H, $J$ = 8.2 Hz), 8.65 (d, 1H, $J$ = 7.8 Hz), 7.99 (d, 1H, $J$ = 8.2 Hz), 7.65–7.47 (m, 5H), 7.13 (s, 1H), 7.04 (d, 4H, $J$ = 8.4 Hz), 6.84 (d, 4H, $J$ = 8.4 Hz), 6.13 (s, 1H), 4.20 (br s, 1H), 4.07–4.04 (m, 1H), 3.95–3.88 (m, 2H), 3.78 (s, 3H), 2.95–2.86 (m, 3H), 1.86–1.64 (m, 4H), 1.32–1.13 (m, 6H); MS: 546 ($M^{1+}$). Anal. Calcd for $C_{37}H_{39}NO_3$): C, 81.43; H, 7.20; N, 2.57. Found: C, 81.37; H, 7.26; N, 2.49.

### 4.19. 1-{4-[(4-Methoxy-phenyl)-phenanthren-9-yl-methyl]-phenoxy}-3-morpholin-4-yl-propan-2-ol (18e)

Pale yellow solid, mp 120 °C (257 mg, 72%), IR (KBr): 3417, 1609, 1504, 1449, 1243, 1113, 1032, 747 $cm^{-1}$, $^1H$ NMR ($CDCl_3$, 200 MHz): $\delta$ 8.71 (d, 1H, $J$ = 8.2 Hz), 8.65 (d, 1H, $J$ = 8.2 Hz), 8.03 (d, 1H, $J$ = 8 Hz), 7.69–7.44 (m, 5H), 7.14 (s, 1H), 7.05 (d, 4H, $J$ = 8.4 Hz), 6.84 (d, 4H, $J$ = 8.4 Hz), 6.14 (s, 1H), 4.13–4.06 (m, 1H), 3.97–3.95 (m, 2H), 3.78 (s, 3H), 3.74–3.70 (m, 4H), 2.68–2.42 (m, 6H); MS: 534 ($M^{1+}$). Anal. Calcd for $C_{35}H_{35}NO_4$: C, 78.77; H, 6.61; N, 2.62. Found: C, 78.72; H, 6.66; N, 2.68.

### 4.20. 1-(4-Benzyl-piperazin-1-yl)-3-{4-[(4-methoxy-phenyl) -phenanthren-9-yl-methyl]-phenoxy}-propan-2-ol (18f)

Pale yellow solid, mp 175 °C (250 mg, 60%), IR (KBr): 3020, 1216, 758, 669 $cm^{-1}$, $^1H$ NMR ($CDCl_3$, 200 MHz): $\delta$ 8.71 (d, 1H, $J$ = 8.2 Hz), 8.64 (d, 1H, $J$ = 8.2 Hz), 8.02 (d, 1H, $J$ = 8.2 Hz), 7.64–7.47 (m, 5H), 7.30–7.25 (m, 5H), 7.13 (s, 1H), 7.05 (d, 4H, $J$ = 8.4 Hz), 6.82 (d, 4H, $J$ = 8.4 Hz), 6.14 (s, 1H), 4.09–4.05 (m, 1H), 3.94 (d, 2H, $J$ = 4.8 Hz), 3.78 (s, 3H), 3.51 (s, 2H), 3.01–2.50 (m, 10H); MS: 623 ($M^{1+}$). Anal. Calcd for $C_{42}H_{42}N_2O_3$: C, 81.00; H, 6.80; N, 4.50. Found: C, 81.09; H, 6.86; N, 4.55.

### 4.21. 1-Cyclopropylamino-3-{4-[(4-methoxy-phenyl)-phenanthren-9-yl-methyl]-phenoxy}-propan-2-ol (18g)

Pale yellow solid, mp 115 °C (216 mg, 64%), IR (KBr): 3015, 1607, 1508, 1456, 1243, 1178, 1037, 743 $cm^{-1}$, $^1H$ NMR ($CDCl_3$, 200 MHz): $\delta$ 8.71 (d, 1H, $J$ = 8.2 Hz), 8.64 (d, 1H, $J$ = 8.2 Hz), 8.02 (d, 1H, $J$ = 8.2 Hz), 7.69–7.44 (m, 5H), 7.14 (s, 1H), 7.05 (d, 4H, $J$ = 8.4 Hz), 6.82 (d, 4H, $J$ = 8.4 Hz), 6.14 (s, 1H), 4.07–4.03 (m, 1H), 3.95–3.88 (m, 2H), 3.78 (s, 3H), 2.94–2.82 (m, 2H), 2.38 (br s, 1H), 0.47–0.36 (m, 4H); MS: 504 ($M^{1+}$). Anal. Calcd for $C_{34}H_{33}NO_3$: C, 81.08; H, 6.60; N, 2.78. Found: C, 81.01; H, 6.54; N, 2.68.

### 4.22. Test procedure for the evaluation of antiproliferative cytotoxic activity in vitro

The procedure is based on the following methods: new colorimetric assay for anticancer drug screening, Skehan et al.[13] and feasibility of high-flux anticancer drug screen using a diverse panel of cultured human tumor cell lines Saxena et al.[14]

Briefly, a fully confluent flask of MCF-7 cells was trypsinized and $10^4$ cells/well were plated in a 96-well flat-bottomed plate in 200 µl minimum essential medium (MEM), pH 7.4, and allowed to attach for 24 h at 37 °C in a humidified $CO_2$ incubator. Subsequently, the compound of invention dissolved in DMSO or ethanol was added at specified concentration and further incubated for 48 h as before. The cells were then fixed in 50 µl cold 50% TCA and incubated for 1 h at 4 °C. The supernatant was discarded and the plate was washed five times with deionized water and air-dried. Hundred microliters of 0.4% (w/v) Sulforhodamine B (SRB) in 1% acetic acid was added to each well and incubated at room temperature for 30 min. Unbound SRB was removed by five washes with chilled 1% acetic acid and the plate was air-dried. Two hundred microliters of unbuffered 10 mM Tris base was added to solubilize the bound stain for 5 min at room temperature and OD was read at 560 nm in a plate reader. The graph is plotted between OD and concentration, and $IC_{50}$ is calculated with respect to tamoxifen that is used as positive control.

### 4.23. In vivo evaluation of anti-breast cancer activity

The Huggins[15] rat model of 7,12-dimethylbenz[*a*]anthracene induced hormone responsive breast cancer was used for evaluating the anti-cancer potential of the compound. Groups of rats ($n$ = 3/per group) with palpable (0.5 cm diameter) tumor were given by oral gavage the compound **15ca** (10 and 20 mg/kg dose levels), tamoxifen (10 mg/kg) or the vehicle (1% gum acacia) only (untreated control), once daily for 4 weeks. Tamoxifen was used as a standard SERM for comparison. Tumor dimensions were measured at least once weekly during the period of treatment and the tumor volume

was calculated using the formula for ellipsoids. The effect of the treatment was expressed as % change in tumor volume.

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