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# Syntheses of 2-methoxyestradiol and eugenol template based diarylpropenes as non-steroidal anticancer agents

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Syntheses of 2-methoxyestradiol (**1**) and eugenol (**6**) template based conformationally flexible and rigid diarylpropenes, **14(a–l)** and **20(a–e)**, as nonsteroidal anticancer agents have been performed. The synthesized compounds were evaluated for their anticancer activity in *in vitro* using a panel of human cancer cell lines *viz.* MCF-7, A549, DU 145, KB and MDA-MB-231by SRB assay. Compounds **14i**, **14k** and **15a** showed significant anticancer activity at $IC_{50}$ between 10.27 μM to 27.91 μM in different cancer cell lines. The most active molecule, **14k**, inhibited proliferation of cells by inducing apoptosis and arresting the cell cycle at the G2/M phase. *In vitro* toxicity of these compounds (**14i**, **14k** and **15a**) in healthy hepatic monocyte (THP-1) cells showed high selectivity of compounds towards cancerous *vs.* healthy cells.

## Introduction

2-Methoxyestradiol (**2ME2**, **2**), a metabolite of 17β-estradiol (**1**), possess potent antiproliferative, antiangiogenic and proapoptotic activities and is now an investigational drug for cancer chemotherapy under the trade name Panzem® (Fig. 1).[1–8] In humans, **2ME2** is formed *via* transformation of estradiol (**1**) to 2-hydroxyestradiol (2OHE2) which is finally converted into **2ME2** with the help of hepatic cytochrome P450 and catechol-*O*-transferase enzymes.[9,10] The antiproliferative activity of **2ME2** is independent of estrogen receptors (ERs) since it has very weak interactions with ERs, rather it acts through its binding with the colchicine binding site of β-tubulin protein.[11–15]

Structurally, the presence of a phenyl ring bearing a hydroxy and methoxy group in the tetracyclic steroidal framework is a prime requirement for biological activity of **2ME2**. Similarly, some natural products such as combretastatin **CA4** (**3**), isoeugenol (**4**) and dehydrozingerone (**5**) which also possess a phenyl ring bearing a hydroxy and methoxy group similar to **2ME2** (**2**) are reported to have diverse biological activities including anticancer activity.[16,17]

Furthermore, eugenol (**6**), another structurally similar natural product, present in *ocimum sanctum L* (sweet basil) and clove (*syzygium aromaticum L*) displays diverse biological activities such as antimicrobial, antioxidant, and anticancer activities *etc.* (Fig. 1).[18,19] In two independent studies, the weak anticancer activity of **6** was potentiated by use of gemcitabine (**7**) and **2ME2** respectively in combination therapy.[20,21] These observations concluded that eugenol (**6**) has synergetic effect on cell proliferation inhibition. In literature, a substituted diarylpropene derivative isolated from *Dalbergia paviflora* (leguminosae) has been reported for significant cell proliferation inhibitory activity.[22] Following this lead, Ito *et al.* synthesized different non-target specific diarylpropene analogues as cancer

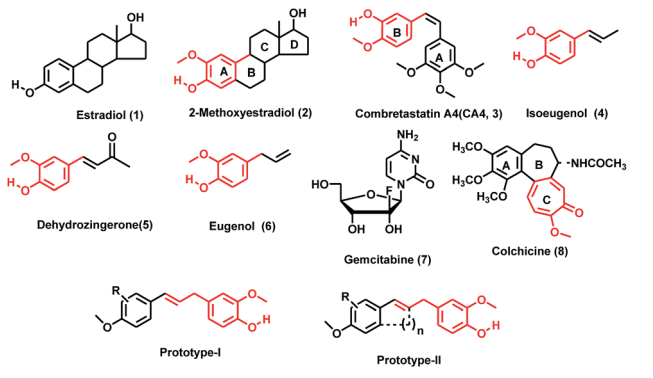


Fig. 1 Estradiol derivatives, cytotoxic phytomolecules and designed Prototype I and II.

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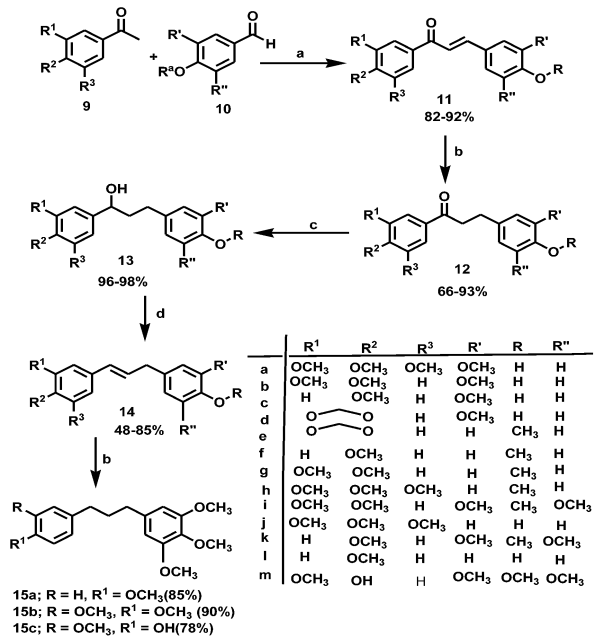
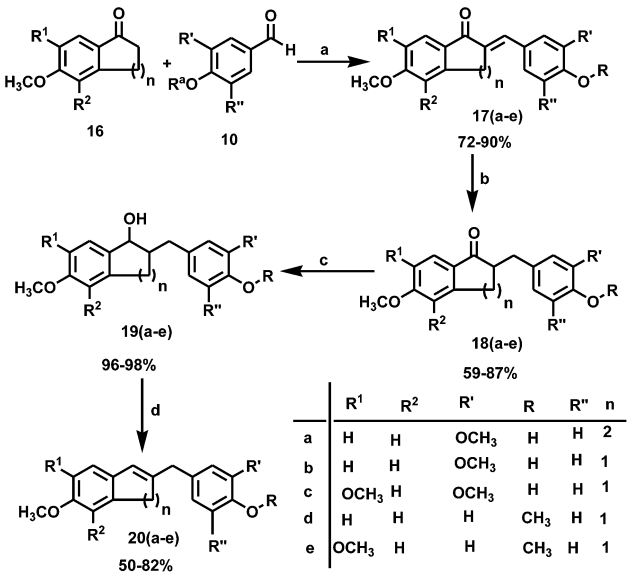



Scheme 1 Reagent and conditions (a) KOH in ethanol, 35–40 °C; (b) 10% Pd/C, ethylacetate–methanol (1 : 1), 35–40 °C; (c) sodium borohydride, dry ethanol, 35–40 °C; (d) HCl, methanol, reflux. [a] In case of hydroxy derivatives of **10**, R = THP which was deprotected during workup and gave hydroxy derivative of **11**.




Scheme 2 Reagent and conditions (a) (i) KOH in ethanol, 35–40 °C (ii) HCl; (b) 10% Pd/C, ethylacetate–methaol (1 : 1), 35–40 °C; (c) sodium borohydride, dry ethanol, 35–40 °C; (d) HCl, methanol, reflux. [a] In case of hydroxy derivatives of **10**, R = THP which was deprotected during workup and gave hydroxy derivative of **17**.

chemo-preventive agents and evaluated them in a single cancer cell line using curcumin as positive control.[23]

In view of the fact that main clinical demerit of **2ME2** is limited bioavailability due to its transformation into glucuronoids and 17β-hydroxydehydrogenase **(17β-HSD)** mediated conversion of **2ME2** into 2-methoxyestrone **(2ME1)**, there is a need to develop non-steroidal mimics of **2ME2** which can have similar mode of action and devoid of many side effects associated with **2ME2.**[24,25]

Realizing the biological potential of diarylpropene pharmacophore and its suitability with the objective of present study, different target oriented (*i.e.* estrogen receptor(ER) and/or tubulin protein), 2-methoxyestradiol (**2ME2**) and eugenol (**6**) template based conformationally flexible and rigid diarylpropenes of type **I** and **II** have been synthesized as non-steroidal cancer chemotherapeutic agents and evaluated for their cytotoxic activity in different cancer cell lines (specially in ER + cell line) for cancer chemotherapy (Fig. 1).

The proposed prototypes will have a phenyl ring bearing a hydroxy and methoxy group similar to **2ME2** (**2**), **CA4** (**3**) and eugenol (**6**), and a cytostatic portion which could possibly encompass the region homologous to the rings C and D complex of **2ME2.**

## Results and discussion

### Chemistry

The synthesis of prototype-**I** was started through base catalyzed Aldol condensation of substituted acetophenone (**9**) and benzaldehyde (**10**) at room temperature which gave diaryl propenones (**11**) in 82–92% yields (Scheme 1). NMR spectroscopic analyses of diarylpropenone derivatives (**11**) revealed trans stereochemistry across the C=C bond. Diarylpropenones (**11**) were subjected to catalytic hydrogenation using 10% palladium adsorbed on charcoal (Pd/C) in ethylacetate–methanol mixture (8 : 2) at normal pressure and temperature for about 3 h which yielded diarylpropanones (**12**) in 66–93% yields. Subsequently, reduction of **12** using sodium borohydride at room temperature yielded diarylpropanols (**13**) as racemic mixture in quantitative yields. The racemic mixture of compound **13** on dehydration in presence of HCl in ethanol at reflux for 1 h gave desired diarylpropenes (**14**) in 48–85% yields.

Proton NMR spectroscopic analyses of diarylpropene derivatives (**14**) showed coupling constant (*J* value) in the range of 15.6 to 15.9 Hertz for olefinic proton which revealed trans stereochemistry across the C=C bond. For SAR study, compound **15** was proposed to be synthesized from compound **14k**. Synthesis of **15** was done through catalytic hydrogenation of **14k** using 10% palladium adsorbed on charcoal (Pd/C) in ethylacetate–methanol mixture (8 : 2) at normal pressure and temperature for about 1 h, yielded **15** in 78–90% yield.

The synthesis of target compounds of prototype (**II**) was made using same methodology used for synthesis of prototype-**I** (Scheme 2). Cyclic ketones (**16**) such as 6-methoxytetralone, 5-methoxyindanone, 4,5-dimethoxyindanone and substituted benzaldehyde (**10**) were used as starting materials to generate chalcones (**17**) which on reduction of C=C double bond using catalytic hydrogenation gave compound **18** as racemic mixture. Compound **18** on sodium borohydride reduction yielded **19** as diasteromeric mixture. Compound **19** on dehydration under acidic reaction conditions yielded compound **20**. Generally,

Table 1 *In vitro* anticancer activity of compounds **14 (a–l)**, **15 (a–c)** and **20 (a–e)** using SRB assay ($IC_{50}$ in μM)[b,c] and *in vitro* cytotoxicity in THP-1 Cells using resazurin assay ($CC_{50}$ in μM)

| | | $IC_{50}$ (μM) (mean ± SE) | | | | | $CC_{50}$ (μM) |
|---|---|---|---|---|---|---|---|
| S no | Compound | MCF-7 | A549 | DU145 | KB | MDA-MB-231 | THP-1 |
| 1 | **14a** | 66.32 ± 8.55 | 37.00 ± 3.72 | 44.60 ± 3.59 | 20.10 ± 4.47 | 60.84 ± 4.58 | — |
| 2 | **14b** | 78.72 ± 6.54 | 55.90 ± 6.64 | 72.22 ± 2.70 | 58.11 ± 7.31 | >100 | — |
| 3 | **14c** | 54.59 ± 2.03 | 48.35 ± 4.99 | 60.01 ± 2.98 | 42.58 ± 4.58 | 66.44 ± 1.66 | — |
| 4 | **14d** | 54.57 ± 1.03 | 50.69 ± 5.77 | 58.34 ± 3.59 | 41.05 ± 4.47 | 65.79 ± 0.17 | — |
| 5 | **14e** | >50 | >50 | >50 | >50 | — | — |
| 6 | **14f** | >100 | >100 | >100 | >100 | >100 | — |
| 7 | **14g** | 68.74[a] | 52.40[a] | >100 | 53.83 ± 11.30 | >100 | — |
| 8 | **14h** | 45.28 ± 26.78 | 23.06[a] | 31.49[a] | 38.01 ± 27.49 | >100 | — |
| 9 | **14i** | 16.03 ± 1.54 | 16.45 ± 0.45 | 26.53 ± 7.19 | 19.12 ± 10.47 | — | 150 |
| 10 | **14j** | 34.44 ± 2.13 | 32.67 ± 1.48 | >50 | 38.752[a] | — | — |
| 11 | **14k** | 14.27 ± 1.11 | 10.27 ± 0.86 | 17.99 ± 12.96 | — | — | 300 |
| 12 | **14l** | 56.45 ± 1.77 | 47.66 ± 5.52 | 64.29 ± 2.33 | 39.14 ± 4.48 | 65.23 ± 1.16 | — |
| 13 | **20a** | 48.08 ± 0.85 | 46.85 ± 6.95 | 59.81 ± 1.91 | 31.94 ± 2.83 | 56.96 ± 1.43 | — |
| 14 | **20b** | >100 | >100 | >100 | 46.23[a] | >100 | — |
| 15 | **20c** | 71.80 ± 4.95 | 66.39 ± 6.77 | 81.97 ± 4.23 | 51.53 ± 6.05 | >100 | — |
| 16 | **20d** | 58.82[a] | >100 | >100 | 53.84 ± 19.11 | >100 | — |
| 17 | **20e** | 79.70[a] | 67.16[a] | >100 | 56.66 ± 18.69 | >100 | — |
| 18 | **15a** | 13.42 ± 4.03 | 11.73 ± 1.34 | 21.56 ± 5.25 | 14.97 ± 9.61 | — | 300 |
| 19 | **15b** | >100[a] | >100[a] | >100[a] | >100[a] | >100[a] | 300 |
| 20 | **15c** | 57.80 ± 9.96 | 14.45[a] | 33.69[a] | <6.25[a] | — | 100 |
| 21 | **Eugenol** | 40.69[a] | 33.50 ± 1.14 | 33.19 ± 2.74 | 38.58[a] | — | — |
| 22 | **TAM** | 8.74 ± 1.17 | 10.37 ± 0.84 | 12.14 ± 0.62 | 11.40 ± 2.02 | 8.41 ± 1.15 | — |
| 23 | **2ME2** | >30[a] | 7.51[a] | — | <1.73[a] | >30[a] | — |

[a] Although the compounds had been tested thrice in this cell line, value of one assay was >50 (a) or >100 (b), therefore it could not be included in calculation of mean and SE. [b] Values are represented as mean $IC_{50}$ value ± SE of three independent experiments, (−) = not done. [c] Cell lines used: A549 (lung carcinoma), DU 145 (prostate carcinoma), KB (oral carcinoma contaminated with HeLa cells), MCF-7 (ER+ breast adenocarcinoma) and MDA-MB-231 (ER− breast adenocarcinoma).

yields at each step of the synthesis were good and comparable to the corresponding open chain analogues (Scheme 1).

The synthesized compounds were characterized by the use of different spectroscopic techniques *viz.* NMR, IR, mass spectrometry.

### HPLC analysis

The purity of compounds **14 (a–l)**, **15 (a–c)** and **20 (a–e)** was determined using high-low chromatographic approach on reverse phase solid matrix $C_{18}$ coupled with photo diode array (PDA) detector with gradient mobile phase composition of acetonitrile–water (80 : 20, v/v) with and without acid additives at a flow rate of 1.0 mL $min^{-1}$. Peak area normalization method of high-low chromatographic analysis was adopted to determine the chromatographic purity and the concentration of every identified HPLC peak of compounds in the absence of primary standards. The purity of the compounds ranged 98–99%.

### Biology

The compounds **14 (a–l)**, **15(a–c)** and **20 (a–e)** were investigated for their anticancer activity in *in vitro* model in a panel of human cancer cell lines *viz.* A549 (lung carcinoma), DU 145 (prostate carcinoma), KB (oral carcinoma contaminated with HeLa cells), MCF-7 (ER+ breast adenocarcinoma) and MDA-MB-231 (ER− breast adenocarcinoma) using SRB assay. Further, Docking experiments were performed for the most active compound **14k** using β-tubulin protein and estrogen receptor α to predict the possible mode of action.

### *In vitro* anticancer activity

The anticancer activity of compounds, **14 (a–l)**, **15 (a–c)** and **20 (a–e)** is described by half maximal inhibitory concentration ($IC_{50}$) value in Table 1. Most of the compounds have shown anticancer activity at $IC_{50}$ value between 10.27 μM to 81.97 μM in different cancer cell lines under study. In these experiments, tamoxifen (**TAM**), 2-methoxyestradiol (**2ME2**) and eugenol (**6**) were used as positive control (Table 1). Out of twenty compounds, compounds **14i**, **14k** and **15a** showed significant anticancer activity at $IC_{50}$ between 10.27 μM to 27.91 μM in different cancer cell lines comparable to tamoxifen (TAM), 2-methoxyestradiol (**2ME2**) and eugenol (**6**) (Table 1). Compound **14k** was found to be most active compound among two series.

### *In vitro* toxicity in healthy hepatomonocyte (THP-1) cells

Compound **14i**, **14k** and **15 (a–c)** were further evaluated for their inherent toxicity in healthy hepatic monocyte (THP-1) cells *in vitro* to know their selectivity towards cancerous cell *vs.* healthy cells. The toxicity results showed that compounds **14k**, **15a** and

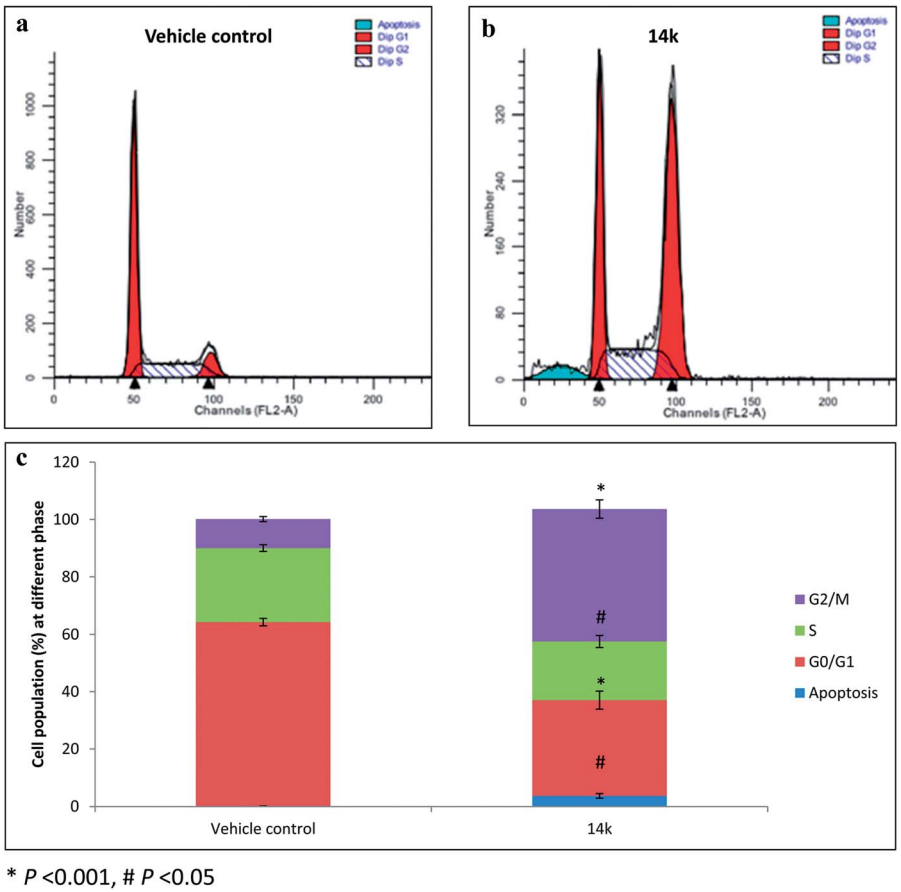



Fig. 2 Effect of **14k** on cell division cycle (a, b) MCF-7 cells were treated with **14k** at $IC_{50}$ concentrations for 24 h. After staining with PI, cells were subjected to flow cytometry. (c) Histogram showing average population cells in various phases (G1, G2, S) of cell cycle (mean ± S.E. of three independent assays, each performed in duplicate). #$P$ < 0.05, *$P$ < 0.001 compared with vehicle treated controls.

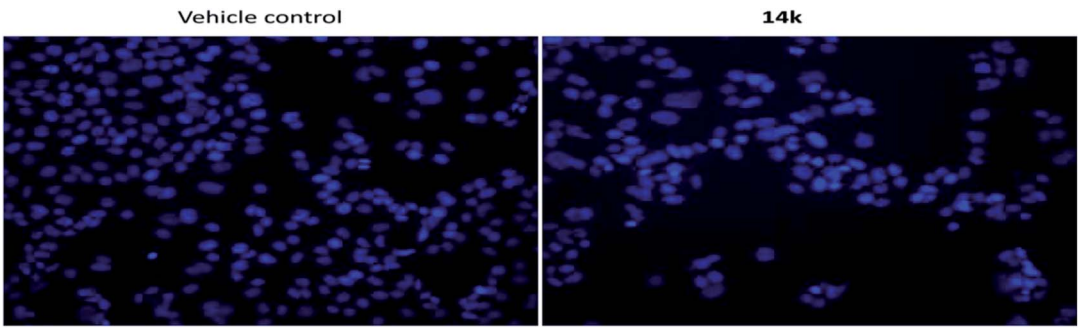



Fig. 3 **14k** induced apoptosis in MCF-7 cells, MCF-7 cells were treated with the compound at $IC_{50}$ concentrations for 24 h at 37 °C. Cells were stained with DAPI and images acquired on a fluorescent microscope (Nikon, Japan) using 20× objective.

**15b** did not show any toxicity to the healthy cells at 300 μM concentration whereas, compound **14i** and **15c** was devoid of any toxicity to the healthy THP-1 cells at 150 μM and 100 μM concentrations respectively. The toxicity assessment results and anticancer activities of ($IC_{50}$ value) of these compounds (**14i**, **14k** and **15a**) showed many fold selectivity towards cancerous cell *vs.* healthy cells.

## Cell division cycle study

Being a potent molecule of the both series, compound **14k** was further studied for detailed biological characterization. For this purpose, estrogen receptor (ER) positive human breast cancer cell line (MCF-7) was selected for subsequent biological assays. The effect of **14k** on cell division cycle was studied. After 24 h incubation with the compound at 15 μM concentration (near

$IC_{50}$ value), **14k** showed significant accumulation of G2/M population compared to the vehicle treated controls (Fig. 2a–c). This was associated with significant decrease in cells at S and G0/G1 phase.

We further investigated ability of **14k** to trigger apoptosis in MCF-7 cells. Cells were exposed to the compound at $IC_{50}$ concentration for 24 h, stained with DAPI and were observed under fluorescent microscope for fragmented nuclei, a hallmark of apoptosis. Compound **14k** caused marked fragmentation of MCF-7 cellular nuclei in comparison to the vehicle control group (Fig. 3).

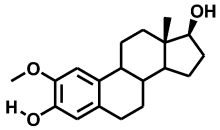
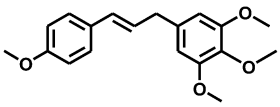
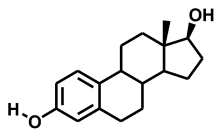
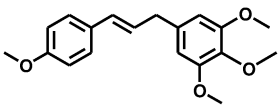
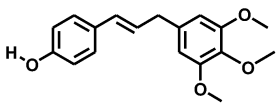
### Structure–activity relationship (SAR) study

Further, the structure–activity (SAR) relationship of synthesized compounds revealed that position of double bond in these molecules had great impact on their biological activity. Compound **14h** and **14k** are positional isomers with respect to the position of double bond (C=C). Both compounds bear a methoxyphenyl group and a trimethoxyphenyl group linked together by $-HC{=}CH-CH_2$ linker. Compound **14k** showed better activity (at $IC_{50}$ 10.27 μM to 17.99 μM) than **14h** (at $IC_{50}$ 23.06 μM to 45.28 μM) in all cancer cell lines. The observed difference in their activity might be due to position of the double bond. Based on their observation, Amato *et al.* have shown that ring A of **2ME2** is homologous to the ring C of colchicines (**8**) and ring B of the combretastin-A4 (CA4, **3**) and the remaining nonplanar part is homologous to the rings C and D complex.[26] Similarly, it is possible that structural arrangement of compound **14k** allows it to interact with β-tubulin for its cytotoxic activity in general and has ER mediated selectivity for cytotoxic activity in ER positive cells (MCF-7 cells) in particular. This was further supported by docking experiment (discussed below). Removal of double bond from **14k** (compound **15a**) did not affect anticancer activity of **14k**, however, in case of **14i**, removal of C=C double bond (compound **15b**) abolished the biological activity. The anticancer activity of **14k** and **15a** in ER positive cancer cells (MCF-7 cells) can be assumed due to better structural complementarities of these derivatives with ligand binding pocket of ER.

### Docking study

To verify our assumptions, docking experiments were performed (Table 2) for compound **14k** on β-tubulin and estrogen receptor-α (Fig. 4b and 5b). Docking of **14k** at colchicine binding site showed good binding within colchicine binding site of β-tubulin with binding energy of $-5.34$ kcal $mol^{-1}$ and inhibitory constant ($K_i$ value) of 121.87 μM. It had a hydrogen bond (H-bond) interactions *via* oxygen atom of trimethoxyphenyl group with bond distance of 3.06 Å with Cys β241amino acid of β-tubulin similar to colchicine (**5**) and **2ME2** (**2**).[27,28]

Table 2 Docking interactions of **2ME2**, **14k** on β-tubulin and **14k**, **14k′** and 17-β-estradiol, on estrogen receptor-α (ERα)

| Name/Pubchem ID | Structure | Binding energy (kcal $mol^{-1}$) | $K_i$ value (inhibitory constant) | Hydrogen bond | Number of rotatable bonds |
|---|---|---|---|---|---|
| **(A) β-tubulin receptor** | | | | | |
| 2-methoxyestradiol (**2ME-2**) (CID_66414) |  | −6.42 | 19.67 μM | Cys241: HG, Lys352: HZ3, Asn349: O | 3 |
| **14k** |  | −5.34 | 121.87 μM | Cys241: HG | 7 |
| **(B) Estrogen receptor** | | | | | |
| 17-β-Estradiol |  | −9.83 | 62.57 nM | His524: HD1, Arg394: HH21, Glu353: OE1 | 3 |
| **14k** |  | −5.9 | 47.33 μM | Leu327: HN | 7 |
| **14k′** |  | −5.26 | 138.5 μM | Glu353: OE2, Ile326:HN | 7 |

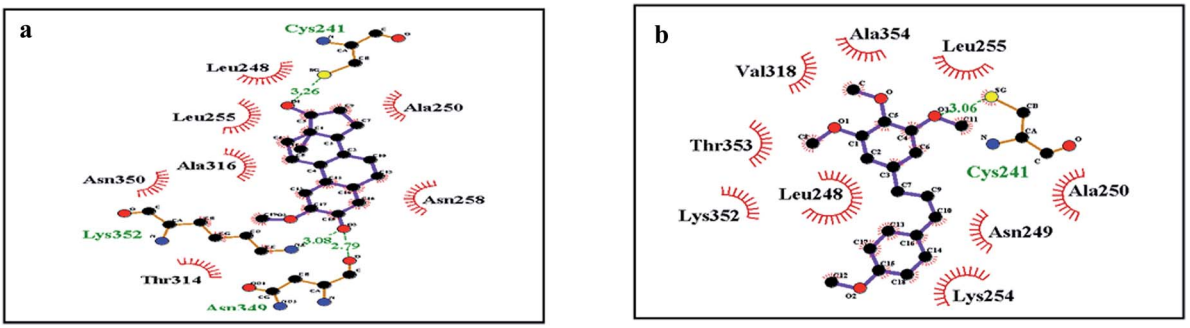



Fig. 4 (a and b) Docking poses of 2-methoxyestradiol (**2ME2**, 2) & **14k** within colchicine binding site of β-tubulin.

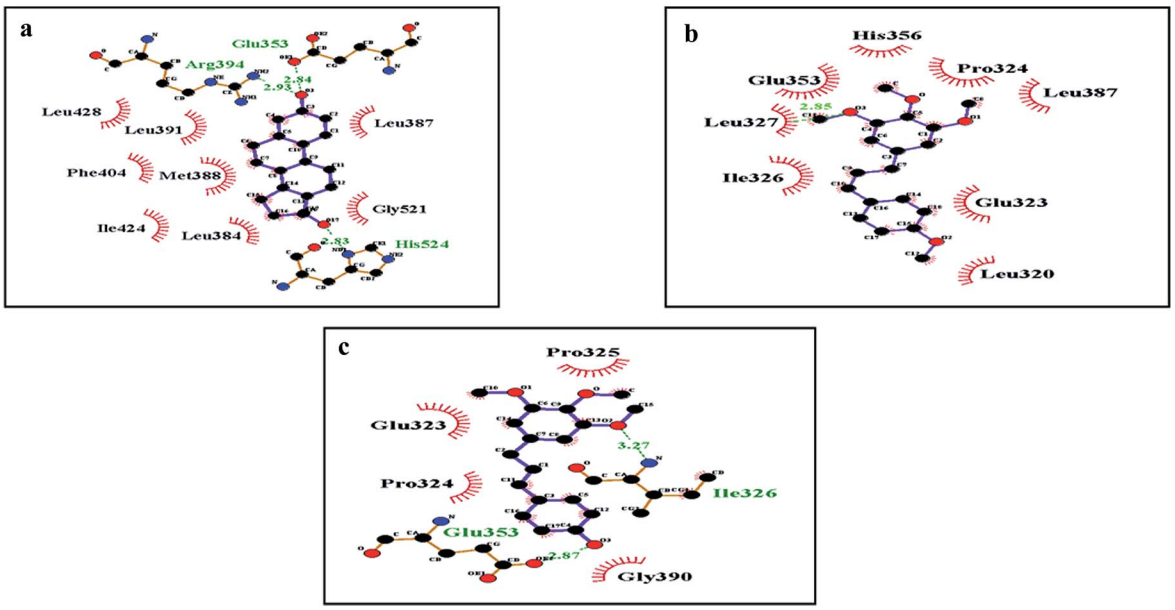



Fig. 5 (a) Docking pose of compound 17β-estradiol (**1**) of within LBD of Estrogen Receptor-α, (b) Docking pose of compound **14K** within LBD Estrogen Receptor-α, (c) Docking pose of compound **14K′** within LBD of within LBD of Estrogen Receptor-α.

Further, docking of **14k** on ER-α [PDB:1A52] showed one H-bond interaction between trimethoxyphenyl group of **14k** with Leu327 of ligand binding pocket (LBP) having bond distance of 2.85 Å in a region encompassed by rings C and D (Fig. 5a). The binding energy and inhibitory constant for **14k** were found to be −5.9 kcal $mol^{-1}$ and 47.33 μM respectively (Fig. 5b). Interestingly, a virtual hydroxyl derivative of **14k** (**14k′**) showed one H-bond interaction between trimethoxyphenyl group and Ile326 in a region encompassed by rings C and D of 17β-estradiol (**1**) with bond distance of 3.27 Å (Fig. 5c). Additionally, there is one more H-bond interaction between hydroxyl group of ring A of **14k′** and Glu353 with bond distance of 2.87 Å. The binding energy and inhibition constant for **14k′** were found to be −5.26 kcal $mol^{-1}$ and 138.5 μM respectively.

## Conclusion

In conclusions, 2-methoxyestradiol (**1**) and eugenol (**6**) template based conformationally flexible and rigid diarylpropenes of type **I** and **II**, established significant anticancer activity. Compounds **14i**, **14k** and **15a** showed potential cytotoxicites against various human cancer cell lines and were found to be non-toxic against healthy hepatic monocyte (THP-1) cells. Anti-cancer activity of the most potent molecule (**14k**) was found to be mediated through induction of apoptosis by arresting cells at G2/M phase of division cycle. In the both series, conformationally flexible diarylpropenes were more active than structurally rigid analogues possibly due to molecular flexibility. Further structural modifications of these diarylpropenes may lead to a good lead in future for development of ER selective anticancer drug molecules.

## Experimental section

### General

The reagents and the solvents used in this study were of analytical grade and used without further purification. All the reactions were monitored on Merck aluminium thin layer

chromatography (TLC, $UV_{254\ nm}$) plates. Column chromatography was carried out on silica gel (60–120 mesh). The melting points were determined on Buchi melting point M560 apparatus in open capillaries and are uncorrected. Commercial reagents were used without purification. $^1H$ and $^{13}C$ NMR spectra were recorded on a Bruker WM-300 (300 MHz) using $CDCl_3$ and DMSO-$d_6$ as the solvent. Chemical shift are reported in parts per million shift ($\delta$-value) based on the middle peak of the solvent ($CDCl_3$–DMSO-$d_6$) ($\delta$ 75.00 ppm for $^{13}C$ NMR) as the internal standard. Signal patterns are indicated as s, singlet; bs, broad singlet; d, doublet; dd, double doublet; t, triplet; m, multiplet; brm, broad multiplet. Coupling constants ($J$) are given in Hertz. Infrared (IR) spectra were recorded on a Perkin-Elmer AX-1 spectrophotometer in KBr disc and reported in wave number ($cm^{-1}$). ESI mass spectra were recorded on Shimadzu LC-MS and LC-MS-MS APC3000 (Applied Biosystems) after dissolving the compounds in acetonitrile and methanol.

### General procedure for the synthesis of compounds (11a–m)

**(*E*)-3-(3,4,5-Trimethoxyphenyl)-1-(4-methoxyphenyl)prop-2-en-1-one (11k).** In a round bottomed flask compound **9** ($R_1 = R_3$ = H, $R_2$ = $OCH_3$, 2.00 g, 13.00 mmol) was dissolved into methanol (20 mL) and methanolic KOH (10%, 20 mL) was added to this solution drop wise on ice bath. After 20 minutes, compound **10** ($R'$=$R''$=$OCH_3$, R=$CH_3$, 2.62 g, 13.00 mmol) dissolved in methanol (15 mL) was added to reaction mixture. The reaction mixture was allowed to stir at ice bath for 30 minutes and afterwards at room temperature for 12 h. The progress of reaction was monitored using TLC. After completion of reaction, solvent was evaporated followed by drop wise addition of dilute HCl was made and pH of the content was adjusted to acidic. The content was extracted with ethyl acetate. The organic layer was then separated and dried over anhydrous sodium sulphate ($Na_2SO_4$) and concentrated. The crude material was purified by crystallization by methanol which yielded pure compound **11k** as yellow solid. Yield: (3.58 g), 82%; m.p. 134–135 °C; $R_f$: 0.34 (30% ethyl acetate–hexane); IR (KBr, $\nu_{max}$ $cm^{-1}$): 3448, 1656, 1601, 1504, 1460, 1220, 1118, 1029, 998; $^1H$ NMR ($CDCl_3$, 300 MHz, $\delta$ ppm): 3.83–3.91 (m, 12H, 4 × $OCH_3$), 6.85 (s, 2H, ArH), 6.97 (d, $J$ = 9.0 Hz, 2H, ArH), 7.40 (d, $J$ = 15.6 Hz, 1H, CH), 7.70 (d, $J$ = 15.3 Hz, 1H, CH), 8.02 (d, $J$ = 8.7 Hz, 2H, ArH); $^{13}C$ NMR ($CDCl_3$, 75 MHz, $\delta$ ppm): 55.89 ($OCH_3$), 56.63 (2 × $OCH_3$), 61.39 ($OCH_3$), 106.02 (2 × C), 114.24 (2 × C), 121.66, 130.99, 131.20 (2 × C), 131.54, 140.71, 144.53, 153.88, 163.81 (2 × C), 189.09 (C=O); ESIMS ($C_{19}H_{20}O_5$): $m/z$ = 329 $[M + H]^+$ .

**3-(4-Hydroxy-3-methoxyphenyl)-1-(3,4,5-trimethoxyphenyl)-prop-2-en-1-one (11a).** Yield: (2.52 g), 77%; m.p. Oil °C; $R_f$: 0.22 (30% ethyl acetate–hexane); IR (KBr, $\nu_{max}$ $cm^{-1}$): 3369, 2933, 1651, 1576, 1509, 1340, 1156, 1124, 1028, 793; $^1H$ NMR ($CDCl_3$, 300 MHz, $\delta$ ppm): 3.93–3.95 (m, 12H, 4 × $OCH_3$), 6.95 (d, $J$ = 8.1 Hz, 1H, ArH), 7.11 (d, $J$ = 1.5 Hz, 1H, ArH), 7.22–7.42 (m, 4H, ArH), 7.75 (d, $J$ = 15.6 Hz, 1H, CH); $^{13}C$ NMR ($CDCl_3$, 75 MHz, $\delta$ ppm): 56.45 ($OCH_3$), 56.87 (2 × $OCH_3$), 61.35 ($OCH_3$), 106.66 (2 × C), 110.93, 115.37, 119.99, 123.39, 127.89, 134.23, 145.57, 147.27, 148.77, 153.54 (3 × C), 189.88 (C=O); ESIMS ($C_{19}H_{20}O_6$): $m/z$ = 345 $[M + H]^+$, 367 $[M + Na]^+$.

**3-(4-Hydroxy-3-methoxyphenyl)-1-(3,4-dimethoxyphenyl)-prop-2-en-1-one (11b).** Yield: (2.84 g), 82%; m.p. 128–129 °C; $R_f$: 0.20 (30% ethyl acetate–hexane); IR (KBr, $\nu_{max}$ $cm^{-1}$): 3333, 1644, 1588, 1559, 1510, 1024, 801, 722; $^1H$ NMR ($CDCl_3$, 300 MHz, $\delta$ ppm): 3.92–3.95 (m, 9H, 3 × $OCH_3$), 6.04 (bs, 1H, OH), 6.90–6.96 (m, 2H, ArH), 7.11 (s, 1H, ArH), 7.20–7.29 (m, 1H, ArH), 7.36–7.41 (d, $J$ = 15.3 Hz, 1H, CH), 7.57–7.65 (m, 2H, ArH), 7.69 (d, $J$ = 11.7 Hz, 1H, CH); $^{13}C$ NMR ($CDCl_3$, 75 MHz, $\delta$ ppm): 56.42 ($OCH_3$), 56.47 (2 × $OCH_3$), 110.38, 110.67, 111.31, 115.32, 119.79, 123.27, 123.43, 128.06, 131.98, 144.78, 147.25, 148.59, 149.65, 153.55, 189.60 (C=O); ESIMS ($C_{18}H_{18}O_5$): $m/z$ = 315 $[M + H]^+$, 337 $[M + Na]^+$, 353 $[M + K]^+$.

**3-(4-Hydroxy-3-methoxyphenyl)-1-(4-methoxyphenyl)prop-2-en-1-one (11c).** Yield: (3.10 g), 82%; m.p. 157–158 °C; $R_f$: 0.30 (30% ethyl acetate–hexane); IR (KBr, $\nu_{max}$ $cm^{-1}$): 3317, 1651, 1591, 1426, 1278, 1220, 1172, 1025, 981, 820; $^1H$ NMR ($CDCl_3$, 300 MHz, $\delta$ ppm): 3.87 (s, 3H, $OCH_3$), 3.94 (s, 3H, $OCH_3$), 6.03 (s, 1H, OH), 6.91–6.98 (m, 3H, ArH), 7.12 (s, 1H, ArH), 7.19–7.25 (m, 1H, ArH), 7.38 (d, $J$ = 15.3 Hz, 1H, CH), 7.68 (d, $J$ = 14.4 Hz, 1H, CH), 8.02 (d, $J$ = 8.7 Hz, 2H, ArH); $^{13}C$ NMR ($CDCl_3$, 75 MHz, $\delta$ ppm): 55.90 ($OCH_3$), 56.42($OCH_3$), 110.46, 114.20 (2 × C), 115.28, 119.93, 123.57, 128.05, 131.14 (2 × C), 131.72, 144.79, 147.21, 148.54, 163.69, 189.27(C=O); ESIMS ($C_{17}H_{16}O_4$): $m/z$ = 285 $[M + H]^+$, 307 $[M + Na]^+$.

**1-(Benzo[*d*][1,3]dioxol-6-yl)-3-(4-hydroxy-3-methoxyphenyl)-prop-2-en-1-one (11d).** Yield: (3.34 g), 92%; m.p. 153–154 °C; $R_f$: 0.50 (10% ethyl acetate–hexane); IR (KBr, $\nu_{max}$ $cm^{-1}$): 3265, 1641, 1596, 1563, 1501, 1450, 1258, 1034, 843, 801; $^1H$ NMR ($CDCl_3$, 300 MHz, $\delta$ ppm): 3.95 (s, 3H, $OCH_3$), 6.05 (s, 3H, OH and $OCH_2$), 6.88 (d, $J$ = 8.1 Hz, 1H, ArH), 6.94 (d, $J$ = 8.1 Hz, 1H, ArH), 7.11 (s, 1H, ArH), 7.19 (d, $J$ = 8.1 Hz, 1H, ArH), 7.32 (d, $J$ = 15.6 Hz, 1H, CH), 7.51 (s, 1H, ArH), 7.63 (d, $J$ = 8.1 Hz, 1H, ArH), 7.73 (d, $J$ = 15.6 Hz, 1H, CH); $^{13}C$ NMR ($CDCl_3$, 75 MHz, $\delta$ ppm): 56.43 ($OCH_3$), 102.23 ($CH_2$), 108.28, 108.84, 110.44, 115.29, 119.76, 123.66, 124.90, 127.97, 133.62, 145.04, 147.24, 148.63 (2 × C), 151.63, 188.77 (C=O); ESIMS ($C_{17}H_{14}O_5$): $m/z$ = 299 $[M + H]^+$, 321 $[M + Na]^+$.

**1-(Benzo[*d*][1,3]dioxol-5-yl)-3-(4-methoxyphenyl)prop-2-en-1-one (11e).** Yield: (2.68 g), 78%; m.p. 147–148 °C; $R_f$: 0.44 (20% ethyl acetate–hexane); IR (KBr, $\nu_{max}$ $cm^{-1}$): 2905, 2840, 1648, 1580, 1502, 1441, 1249, 1031, 929, 805; $^1H$ NMR ($CDCl_3$, 300 MHz, $\delta$ ppm): 3.83 (s, 3H, $OCH_3$), 6.03 (s, 2H, $CH_2$), 6.85–6.92 (m, 3H, ArH), 7.75 (d, $J$ = 15.6 Hz, 1H, CH), 7.50–7.63 (m, 4H, ArH), 7.35 (d, $J$ = 15.6 Hz, 1H, CH); $^{13}C$ NMR ($CDCl_3$, 75 MHz, $\delta$ ppm): 55.79 ($OCH_3$), 102.20 ($CH_2$), 108.27, 108.83, 114.81 (2 × C), 119.85, 124.85, 128.16, 130.51 (2 × C), 133.68, 144.47, 148.64, 151.91, 162.00, 188.69 (C=O); ESIMS ($C_{17}H_{14}O_4$): $m/z$ = 305 $[M + Na]^+$.

**1,3-Bis(4-methoxyphenyl)prop-2-en-1-one (11f).** Yield: (2.89 g), 81%; m.p. 98–99 °C; $R_f$: 0.40 (30% ethyl acetate–hexane); IR (KBr, $\nu_{max}$ $cm^{-1}$): 2954, 2841, 1655, 1594, 1506, 1330, 1253, 1216, 1168, 1018, 817; $^1H$ NMR ($CDCl_3$, 300 MHz, $\delta$ ppm): 3.84 (s, 3H, $OCH_3$), 3.88 (s, 3H, $OCH_3$), 6.91–6.98 (m, 4H, ArH), 7.41 (d, $J$ = 15.3 Hz, 1H, CH), 7.59 (d, $J$ = 8.7 Hz, 2H, ArH), 7.77 (d, $J$ = 15.6 Hz, 1H, CH), 8.02 (d, $J$ = 9.0 Hz, 2H, ArH); $^{13}C$ NMR ($CDCl_3$, 75

MHz, $\delta$ ppm): 55.79 ($OCH_3$), 55.86 ($OCH_3$), 114.19 (2 × C), 114.80 (2 × C), 120.04, 128.26, 130.48 (2 × C), 131.09 (2 × C), 131.80, 144.20, 161.93, 163.68, 189.19 (C═O); ESIMS ($C_{17}H_{16}O_3$): $m/z$ = 269 $[M + H]^+$.

**1-(3,4-Dimethoxyphenyl)-3-(4-methoxyphenyl)prop-2-en-1-one (11g).** Yield: (2.98 g), 90%; m.p. 86–87 °C; $R_f$: 0.15 (20% ethyl acetate–hexane); IR (KBr, $\nu_{max}$ $cm^{-1}$): 3057, 3005, 1650, 1571, 1507, 1248, 1158, 1026, 823, 796, 766; $^1$H NMR ($CDCl_3$, 300 MHz, $\delta$ ppm): 3.85–3.96 (m, 9H, 3 × $OCH_3$), 6.91–6.95 (m, 3H, ArH), 7.43 (d, $J$ = 15.6 Hz, 1H, CH), 7.58–7.69 (m, 4H, ArH), 7.75–7.81 (d, $J$ = 15.6 Hz, 1H, CH); $^{13}$C MR ($CDCl_3$, 75 MHz, $\delta$ ppm): 55.80 ($OCH_3$), 56.45 (2 × $OCH_3$), 110.40, 111.26, 114.80 (2 × C), 119.80, 123.22, 128.23, 130.51 (2 × C), 132.02, 144.22, 149.63, 153.51, 161.94, 189.05 (C═O); ESIMS ($C_{18}H_{18}O_4$): $m/z$ = 299 $[M + H]^+$, 321 $[M - H]^+$.

**1-(3,4,5-Trimethoxyphenyl)-3-(4-methoxyphenyl)prop-2-en-1-one (11h).** Yield: (2.81 g), 90%; m.p. 99–100 °C; $R_f$: 0.24 (20% ethyl acetate–hexane); IR (KBr, $\nu_{max}$ $cm^{-1}$): 2939, 2838, 1655, 1573, 1457, 1028, 993, 821, 707; $^1$H NMR (acetone-$D_6$, 300 MHz, $\delta$ ppm): 3.77 (s, 3H, $OCH_3$), 3.78 (s, 3H, $OCH_3$), 3.81 (s, 6H, 2 × $OCH_3$), 6.99 (d, $J$ = 9.0 Hz, 2H, ArH), 7.43 (s, 2H, ArH), 7.74–7.77(m, 4H, ArH and CH); $^{13}$C NMR ($CDCl_3$, 75 MHz, $\delta$ ppm): 55.31 ($OCH_3$), 56.18 (2 × $OCH_3$), 60.22 ($OCH_3$), 106.58 (2 × C), 114.74 (2 × C), 119.84, 128.21, 130.82 (2 × C), 134.19, 142.98, 144.04, 153.83 (2 × C), 162.19, 188.19 (C═O); ESIMS ($C_{19}H_{20}O_5$): $m/z$ = 329 $[M + H]^+$.

**3-(3,4,5-Trimethoxyphenyl)-1-(3,4-dimethoxyphenyl)prop-2-en-1-one (11i).** Yield: (3.58 g), 90%; m.p. 126–127 °C; $R_f$: 0.20 (30% ethyl acetate–hexane); IR (KBr, $\nu_{max}$ $cm^{-1}$): 2998, 2947, 2833, 1657, 1583, 1511, 1465, 1416, 1268, 1124, 1023, 818, 766; $^1$H NMR ($CDCl_3$, 300 MHz, $\delta$ ppm): 3.81–3.85 (m, 15H, 5 × $OCH_3$), 6.87–6.94 (m, 3H, ArH), 7.43 (d, $J$ = 15.6 Hz, 1H, CH), 7.62–7.74 (m, 3H, CH and ArH); $^{13}$C NMR ($CDCl_3$, 75 MHz, $\delta$ ppm): 56.48 (2 × $OCH_3$), 56.64 (2 × $OCH_3$), 61.39 ($OCH_3$), 106.04 (2 × C), 110.34, 111.25, 121.46, 123.41, 130.97, 131.77, 140.72, 144.54, 149.70, 153.67, 153.87 (2 × C), 188.97 (C═O); ESIMS ($C_{20}H_{22}O_6$): $m/z$ = 381$[M + Na]^+$, 397$[M + K]^+$.

**3-(4-Hydroxyphenyl)-1-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (11j).** Yield: (2.69 g), 90%; m.p. 155–156 °C; $R_f$: 0.20 (30% ethyl acetate–hexane); IR (KBr, $\nu_{max}$ $cm^{-1}$): 3404, 2937, 1586, 1509, 1236, 1125, 1002, 830; $^1$H NMR ($CDCl_3$, 300 MHz, $\delta$ ppm): 3.85–3.95 (m, 9H, 3 × $OCH_3$), 6.89 (d, $J$ = 8.7 Hz, 2H, ArH), 7.27 (s, 2H, ArH), 7.36 (d, $J$ = 15.3 Hz, 1H, CH), 7.51–7.56 (m, 2H, ArH), 7.75 (d, $J$ = 15.6 Hz, 1H, CH); $^{13}$C MR ($CDCl_3$, 75 MHz, $\delta$ ppm): 55.75 (2 × $OCH_3$), 60.22 ($OCH_3$), 105.36, 115.60 (2 × C), 117.76, 125.50, 129.89 (2 × C), 133.34, 144.54, 152.45 (2 × C), 159.70, 188.54 (C═O); ESIMS ($C_{18}H_{18}O_5$): $m/z$ = 313 $[M - H]^+$, 315 $[M + H]^+$.

**3-(4-Hydroxyphenyl)-1-(4-methoxyphenyl)prop-2-en-1-one (11l).** Yield: (2.68 g), 79%; m.p. 179–180 °C; $R_f$: 0.30 (30% ethyl acetate–hexane); $^1$H NMR (DMSO-$d_6$, 300 MHz, $\delta$ ppm): 3.38 (s, 3H, $OCH_3$), 6.82 (d, $J$ = 8.4 Hz, 2H, ArH), 7.05 (d, $J$ = 8.4 Hz, 2H, ArH), 7.60–7.74 (m, 4H, CH and ArH), 8.11 (d, $J$ = 8.7 Hz, 2H, ArH); $^{13}$C NMR (DMSO-$d_6$, 75 MHz, $\delta$ ppm): 55.56 ($OCH_3$), 113.98 (2 × C), 115.84 (2 × C), 118.45, 125.96, 130.75 (2 × C), 130.82, 130.92 (2 × C), 143.68, 160.00, 163.03, 187.30 (C═O); ESIMS ($C_{16}H_{14}O_3$): $m/z$ = 255 $[M + H]^+$, 277 $[M + Na]^+$.

**3-(3,4,5-Trimethoxyphenyl)-1-(4-hydroxy-3-methoxyphenyl)-prop-2-en-1-one (11m).** Yield: (2.65 g), 64%; m.p. 183–186 °C; $R_f$: 0.20 (30% ethyl acetate–hexane); $^1$H NMR ($CDCl_3$, 300 MHz, $\delta$ ppm): 3.89–3.96 (m, 12H, 4 × $OCH_3$), 6.24 (s, 1H, OH), 6.85 (s, 2H, ArH), 6.98 (d, $J$ = 7.5 Hz, 1H, ArH), 7.41 (d, $J$ = 15.6 Hz, 1H, CH), 7.62–7.65 (m, 2H, ArH), 7.71 (d, $J$ = 15.6 Hz, 1H, CH); ($CDCl_3$, 75 MHz, $\delta$ ppm): 56.34 ($OCH_3$), 56.66 (2 × $OCH_3$), 61.37 $OCH_3$, 106.13 (2 × C), 110.96, 114.17, 121.43, 124.04, 130.98, 131.47, 140.82, 144.52, 147.38, 150.83, 153.90 (2 × C), 188.90 (C═O); ESIMS ($C_{19}H_{20}O_6$): $m/z$ = 345 $[M + H]^+$, 367 $[M + Na]^+$.

## General procedure for the synthesis of compounds (12a–m)

**3-(3,4,5-Trimethoxyphenyl)-1-(4-methoxyphenyl)propan-1-one (12k).** Compound **11k** (1.00 g, 3.04 mmol) was taken in a round bottomed flask and dissolved in ethyl acetate–methanol mixture (8 : 2). The mixture was flushed with nitrogen gas and palladium charcoal (Pd/C, 5% wt) (0.10 g) was added and hydrogen gas was passed to it for 3 h. The progress of reaction was monitored by TLC. After completion of the reaction, the solvent was evaporated and crude material was worked up using ethyl acetate and water. The organic layer was the separated, dried anhydrous sodium sulphate ($Na_2SO_4$) and concentrated. The crude was purified by column chromatography on silica gel (100–200 mesh size) using ethyl acetate–hexane (12 : 88) as eluents which yielded pure compound **12k** as white solid. Yield: (0.88 g), 88%; m.p. 94–95 °C; $R_f$: 0.52 (30% ethyl acetate–hexane); IR (KBr, $\nu_{max}$ $cm^{-1}$): 2938, 2837, 1683, 1251, 1178, 1124, 1012, 845; $^1$H NMR ($CDCl_3$, 300 MHz, $\delta$ ppm): 2.99 (t, $J$ = 7.5 Hz, 2H, $CH_2$), 3.23 (t, $J$ = 7.5 Hz, 2H, $CH_2$), 3.81–3.85 (m, 12H, 4 × $OCH_3$), 6.45 (s, 2H, ArH), 6.92 (d, $J$ = 8.7 Hz, 2H, ArH), 7.93 (d, $J$ = 8.7 Hz, 2H, ArH); $^{13}$C NMR ($CDCl_3$, 75 MHz, $\delta$ ppm): 31.21 ($CH_2$), 40.59 ($CH_2$), 55.85 ($OCH_3$), 56.50 (2 × $OCH_3$), 61.22 ($OCH_3$), 105.87, 114.14 (2 × C), 130.42, 130.69 (2 × C), 137.66 (2 × C), 153.61 (3 × C), 163.90, 198.21 (C═O); ESIMS ($C_{19}H_{22}O_5$): $m/z$ = 353 $[M + H]^+$, 369 $[M + K]^+$.

**3-(4-Hydroxy-3-methoxyphenyl)-1-(3,4,5-trimethoxyphenyl)-propan-1-one (12a).** Yield: (0.93 g), 92%; m.p. 122–123 °C; $R_f$: 0.54 (20% ethyl acetate–hexane); IR (KBr, $\nu_{max}$ $cm^{-1}$): 3411, 2934, 2840, 1667, 1265, 1236, 1127, 1029, 998, 851; $^1$H NMR ($CDCl_3$, 300 MHz, $\delta$ ppm): 2.98 (t, $J$ = 7.3 Hz, 2H, $CH_2$), 3.22 (t, $J$ = 7.3 Hz, 2H, $CH_2$), 3.86–3.90 (m, 12H, 4 × $OCH_3$), 5.55 (s, 1H, OH), 6.73, (bs, 2H, ArH), 6.70 (d, $J$ = 7.8 Hz, 1H, ArH), 7.22 (s, 2H, ArH); $^{13}$C NMR ($CDCl_3$, 75 MHz, $\delta$ ppm): 30.56 ($CH_2$), 41.11 ($CH_2$), 56.30 ($OCH_3$), 56.71 (2 × $OCH_3$), 61.33 ($OCH_3$), 106.00 (2 × C), 111.65, 114.82, 121.28, 132.61, 133.61, 143.02, 144.42, 146.88, 153.47 (2 × C), 198.65 (C═O); ESIMS ($C_{19}H_{22}O_6$): $m/z$ = 345 $[M - H]^+$, 369 $[M + Na]^+$.

**3-(4-Hydroxy-3-methoxyphenyl)-1-(3,4-dimethoxyphenyl)-propan-1-one (12b).** Yield: (0.83 g), 82%; m.p. 141–142 °C; $R_f$: 0.25 (30% ethyl acetate–hexane); IR (KBr, $\nu_{max}$ $cm^{-1}$): 3355, 1648, 1019, 792; $^1$H NMR ($CDCl_3$, 300 MHz, $\delta$ ppm): 2.88–2.93 (m, 2H, $CH_2$), 3.12–3.17 (m, 2H, $CH_2$), 3.79 (s, 3H, $OCH_3$), 3.84 (bs, 6H, 2 × $OCH_3$), 5.46 (s, 1H, OH), 6.65–6.67 (m, 2H, ArH), 6.75–6.81 (m, 2H, ArH), 7.45–7.51 (m, 2H, ArH); $^{13}$C NMR ($CDCl_3$, 75 MHz, $\delta$ ppm): 32.18 ($CH_2$), 36.76 ($CH_2$), 49.71 ($OCH_3$), 55.63 ($OCH_3$), 56.49 ($OCH_3$), 104.83, 107.83, 114.28 (2 × C),

129.72, 130.26 (2 × C), 132.11, 149.41, 149.88, 155.99, 158.51, 207.04 (C═O); ESIMS ($C_{18}H_{20}O_5$): $m/z$ = 339 $[M + Na]^+$, 354 $[M + K]^+$.

**3-(4-Hydroxy-3-methoxyphenyl)-1-(4-methoxyphenyl)propan-1-one (12c).** Yield: (0.86 g), 85%; m.p. 112–113 °C; $R_f$: 0.50 (30% ethyl acetate–hexane); IR (KBr, $\nu_{max}$ $cm^{-1}$): 3504, 1671, 978, 822, 780; $^1H$ NMR ($CDCl_3$, 300 MHz, $\delta$ ppm): 2.91 (bs, 2H, $CH_2$), 3.24 (t, $J$ = 7.6 Hz, 2H, $CH_2$), 3.81 (s, 3H, $OCH_3$), 3.87 (s, 3H, $OCH_3$), 6.72 (bs, 2H, ArH), 6.89 (s, 1H, ArH), 7.00 (d, $J$ = 9.0 Hz, 2H, ArH), 7.33 (s, 1H, OH), 7.98 (d, $J$ = 9.0 Hz, 2H, ArH); $^{13}C$ NMR ($CDCl_3$, 75 MHz, $\delta$ ppm): 30.20 ($CH_2$), 40.36 ($CH_2$), 55.40 ($OCH_3$), 55.74 ($OCH_3$), 112.52, 114.06 (2 × C), 115.17, 121.11, 130.54 (2 × C), 130.63, 133.38, 145.20, 147.72, 163.86, 197.63(C═O); ESIMS ($C_{17}H_{18}O_4$): $m/z$ = 287 $[M + H]^+$, 309 $[M + Na]^+$.

**1-(Benzo[*d*][1,3]dioxol-6-yl)-3-(4-hydroxy-3-methoxyphenyl)-propan-1-one (12d).** Yield: (0.66 g), 66%; m.p. 80–81 °C; $R_f$: 0.31 (30% ethyl acetate–hexane); IR (KBr, $\nu_{max}$ $cm^{-1}$): 3495, 2930, 1677, 1251, 1033, 982, 928, 866, 823; $^1H$ NMR ($CDCl_3$, 1d DMSO-$d_6$, 300 MHz, $\delta$ ppm): 2.94–2.99 (m, 2H, $CH_2$), 3.15–3.20 (m, 2H, $CH_2$), 3.86 (s, 3H, $OCH_3$), 5.54 (s, 1H, OH), 6.02 (s, 2H, $OCH_2O$), 6.65–6.77 (m, 2H, ArH), 6.81–6.86 (m, 2H, ArH), 7.42 (s, 1H, ArH), 7.54 (d, $J$ = 8.4 Hz, 1H, ArH); $^{13}C$ NMR ($CDCl_3$, 1d DMSO-$d_6$, 75 MHz, $\delta$ ppm): 30.54 ($CH_2$), 40.94 ($CH_2$), 56.30 ($OCH_3$), 102.22 ($CH_2$), 108.26, 111.59, 114.78, 121.26, 124.65, 132.24, 133.64, 144.36, 146.85, 148.59 (2 × C), 152.11, 197.91 (C═O); ESIMS ($C_{17}H_{16}O_5$): $m/z$ = 299 $[M - H]^+$, 323 $[M + Na]^+$.

**1-(Benzo[*d*][1,3]dioxol-5-yl)-3-(4-methoxyphenyl)propan-1-one (12e).** Yield: (0.92 g), 92%; m.p. 51–52 °C; $R_f$: 0.64 (30% ethyl acetate–hexane); IR (KBr, $\nu_{max}$ $cm^{-1}$): 2911, 1666, 1242, 1034, 814, 785; $^1H$ NMR (acetone-$D_6$, 300 MHz, $\delta$ ppm): 2.91 (t, $J$ = 7.5 Hz, 2H, $CH_2$), 3.22 (t, $J$ = 7.5 Hz, 2H, $CH_2$), 3.73 (s, 3H, $OCH_3$), 6.08 (s, 2H, $CH_2$), 6.82 (d, $J$ = 8.4 Hz, 2H, ArH), 6.91 (d, $J$ = 8.1 Hz, 1H, ArH), 7.18 (d, $J$ = 8.4 Hz, 2H, ArH), 7.42 (d, $J$ = 1.5 Hz, 1H, ArH), 7.63 (d, $J$ = 8.1 Hz, 1H, ArH); $^{13}C$ NMR (acetone-$D_6$, 75 MHz, $\delta$ ppm): 29.59 ($CH_2$), 40.26 ($CH_2$), 54.94 ($OCH_3$), 102.45 ($CH_2$), 107.72, 108.11, 114.09 (2 × C), 124.57, 129.72 (2 × C), 130.40, 133.88, 148.64, 152.05, 158.52, 197.10; ESIMS ($C_{17}H_{16}O_4$): $m/z$ = 307 $[M + Na]^+$.

**1,3-Bis(4-methoxyphenyl)propan-1-one (12f).** Yield: (0.86 g), 86%; $R_f$: 0.42 (20% ethyl acetate–hexane); IR (KBr, $\nu_{max}$ $cm^{-1}$): 2934, 1680, 1032, 823, 742, 691; $^1H$ NMR (acetone-$D_6$, 300 MHz, $\delta$ ppm): 2.98 (t, $J$ = 7.5 Hz, 2H, $CH_2$), 3.34 (t, $J$ = 7.5 Hz, 2H, $CH_2$), 3.77 (s, 6H, 2 × $OCH_3$), 6.86 (d, $J$ = 8.7 Hz, 2H, ArH), 7.23 (d, $J$ = 8.4 Hz, 2H, ArH), 7.53 (d, $J$ = 8.1 Hz, 2H, ArH), 8.03 (d, $J$ = 7.5 Hz, 2H, ArH); ESIMS ($C_{17}H_{18}O_3$): $m/z$ = 261 $[M + H]^+$, 283 $[M + Na]^+$.

**1-(3,4,5-Trimethoxyphenyl)-3-(4-methoxyphenyl)propan-1-one (12h).** Yield: (0.80 g), 80%; m.p. 91–92 °C; $R_f$: 0.53 (30% ethyl acetate–hexane); IR (KBr, $\nu_{max}$ $cm^{-1}$): 3003, 2935, 1675, 1246, 1122, 1008, 816, 763; $^1H$ NMR ($CDCl_3$, 300 MHz, $\delta$ ppm): 2.99 (t, $J$ = 7.3 Hz, 2H, $CH_2$), 3.22 (t, $J$ = 7.5 Hz, 2H, $CH_2$), 3.77 (s, 3H, $OCH_3$), 3.89 (bs, 9H, 3 × $OCH_3$), 6.84 (d, $J$ = 8.4 Hz, 2H, ArH), 7.15–7.19 (m, 4H, ArH); $^{13}C$ NMR ($CDCl_3$, 75 MHz, $\delta$ ppm): 29.93 ($CH_2$), 40.97 ($CH_2$), 55.66 ($OCH_3$), 56.71 (2 × $OCH_3$), 61.31 ($OCH_3$), 106.02 (2 × C), 114.39 (2 × C), 129.78 (2 × C), 132.62, 133.73, 143.03, 153.48 (2 × C), 158.47, 198.53 (C═O); ESIMS ($C_{19}H_{22}O_5$): $m/z$ = 353 $[M + Na]^+$, 369 $[M + K]^+$.

**1-(3,4-Dimethoxyphenyl)-3-(4-methoxyphenyl)propan-1-one (12g).** Yield: (0.81 g), 80%; m.p. 64–65 °C; $R_f$: 0.31 (30% ethyl acetate–hexane); IR (KBr, $\nu_{max}$ $cm^{-1}$): 3447, 3004, 2931, 1668, 1263, 1156, 1026, 889, 822, 767; $^1H$ NMR ($CDCl_3$, 300 MHz, $\delta$ ppm): 2.99 (t, $J$ = 7.6 Hz, 2H, $CH_2$), 3.21 (t, $J$ = 7.6 Hz, 2H, $CH_2$), 3.77 (s, 3H, $OCH_3$), 3.91–3.93 (m, 6H, 2 × $OCH_3$), 6.82–6.87 (m, 3H, ArH), 7.16 (d, $J$ = 8.1 Hz, 2H, ArH), 7.52–7.58 (m, 2H, ArH); $^{13}C$ NMR ($CDCl_3$, 75 MHz, $\delta$ ppm): 30.02 ($CH_2$), 40.65 ($CH_2$), 55.66 ($OCH_3$), 56.38 ($OCH_3$), 56.43($OCH_3$), 110.44, 110.63, 114.34 (2 × C), 123.04, 129.75 (2 × C), 130.60, 133.80, 149.45, 153.65, 158.39, 198.45 (C═O); ESIMS ($C_{18}H_{20}O_4$): $m/z$ = 323 $[M + Na]^+$, 339 $[M + K]^+$.

**3-(3,4,5-Trimethoxyphenyl)-1-(3,4-dimethoxyphenyl)propan-1-one (12i).** Yield: (0.93 g), 93%; m.p. 95–96 °C; $R_f$: 0.28 (30% ethyl acetate–hexane); IR (KBr, $\nu_{max}$ $cm^{-1}$): 2941, 2839, 1678, 1009, 872, 776; $^1H$ NMR (acetone-$D_6$, 300 MHz, $\delta$ ppm): 2.90–2.95 (m, 2H, $OCH_2$), 3.26–3.31 (m, 2H, $CH_2$), 3.67 (s, 3H, $OCH_3$), 3.78 (s, 6H, 2 × $OCH_3$), 3.85–3.87 (m, 6H, 2 × $OCH_3$), 6.59 (s, 2H, ArH), 7.01 (d, $J$ = 8.4 Hz, 1H, ArH), 7.52 (d, $J$ = 2.1 Hz, 1H, ArH), 7.66 (dd, $J$ = 2.1 and 2.1 Hz, 1H, ArH); $^{13}C$ NMR ($CDCl_3$, 75 MHz, $\delta$ ppm): 31.00 ($CH_2$), 39.99 ($CH_2$), 55.00 ($OCH_3$), 55.87(2 × $OCH_3$), 55.69 ($OCH_3$), 59.96 ($OCH_3$), 106.30 (2 × C), 110.89, 111.00, 122.90, 130.61, 137.02, 137.77, 149.65, 153.78 (2 × C), 154.00, 197.64 (C═O); ESIMS ($C_{20}H_{24}O_6$): $m/z$ = 283 $[M + Na]^+$, 399 $[M + K]^+$.

**3-(4-Hydroxyphenyl)-1-(3,4,5-trimethoxyphenyl)propan-1-one (12j).** Yield: (0.68 g), 68%; m.p. 141–142 °C; $R_f$: 0.29 (30% ethyl acetate–hexane); IR (KBr, $\nu_{max}$ $cm^{-1}$): 3439, 2990, 1664, 1230, 1124, 999, 826, 775; $^1H$ NMR (acetone-$D_6$, 300 MHz, $\delta$ ppm): 2.89 (t, $J$ = 7.2 Hz, 2H, $CH_2$), 3.24–3.29 (m, 2H, $CH_2$), 3.78 (s, 3H, $OCH_3$), 3.87 (s, 6H, 2 × $OCH_3$), 6.73 (d, $J$ = 9.0 Hz, 2H, ArH), 7.09 (d, $J$ = 7.8 Hz, 2H, ArH), 7.29 (s, 2H, ArH), 8.15 (bs, 1H, OH); $^{13}C$ NMR (acetone-$D_6$, 75 MHz, $\delta$ ppm): 29.97 ($CH_2$), 40.70 ($CH_2$), 56.30 (2 × $OCH_3$), 60.38 ($OCH_3$), 106.29 (2 × C), 115.74 (2 × C), 129.98 (2 × C), 132.86, 133.14, 153.95(3 × C), 156.26, 198.30 (C═O); ESIMS ($C_{18}H_{20}O_5$): $m/z$ = 315 $[M + H]^+$, 339 $[M + 2H + Na]^+$.

**3-(4-Hydroxyphenyl)-1-(4-methoxyphenyl)propan-1-one (12l).** Yield: (0.85 g), 85%; m.p. 82–83 °C; $R_f$: 0.40 (30% ethyl acetate–hexane); $^1H$ NMR ($CDCl_3$, 300 MHz, $\delta$ ppm): 2.97 (t, $J$ = 7. 5 Hz, 2H, $CH_2$), 3.21 (t, $J$ = 7.6 Hz, 2H, $CH_2$), 3.85 (s, 3H, $OCH_3$), 6.06 (bs, 1H, OH), 6.78 (d, $J$ = 8.4 Hz, 2H, ArH), 6.92 (d, $J$ = 9.0 Hz, 2H, ArH), 7.08 (d, $J$ = 8.1 Hz, 2H, ArH), 7.94 (d, $J$ = 8.7 Hz, 2H, ArH); $^{13}C$ NMR ($CDCl_3$, 75 MHz, $\delta$ ppm): 29.56 ($CH_2$), 40.37 ($CH_2$), 55.44 ($OCH_3$), 113.73 (2 × C), 115.36 (2 × C), 129.44 (2 × C), 129.76, 130.42 (2 × C), 133.04, 154.14, 163.51, 198.86 (C═O); ESIMS ($C_{16}H_{16}O_3$): $m/z$ = 257 $[M + H]^+$, 279 $[M + Na]^+$.

**3-(3,4,5-Trimethoxyphenyl)-1-(4-hydroxy-3-methoxyphenyl)-propan-1-one (12m).** Yield: (0.80 g) 80%; $R_f$: 0.0.37 (30% ethyl acetate–hexane); $^1H$ NMR ($CDCl_3$, 300 MHz, $\delta$ ppm): 2.99 (t, $J$ = 7.5 Hz, 2H, $CH_2$), 3.21 (t, $J$ = 7.5 Hz, 2H, $CH_2$), 3.79–3.83 (m, 12H, 4 × $OCH_3$), 6.46 (s, 2H, ArH), 6.97 (d, $J$ = 8.1 Hz, 1H, ArH), 7.60–7.63 (m, 2H, ArH); $^{13}C$ NMR ($CDCl_3$, 75 MHz, $\delta$ ppm): 31.20 ($CH_2$), 40.63 ($CH_2$), 55.85 ($OCH_3$), 56.23 (2 × $OCH_3$), 61.22 ($OCH_3$), 105.87, 114.14 (2 × C), 130.42, 130.69, 137.66 (2 × C), 153.61 (3 × C), 156.8, 163.90, 198.21 (C═O); ESIMS ($C_{19}H_{22}O_6$): $m/z$ = 346 $[M + H]^+$.

### General procedure for the synthesis of compounds (13a–m)

**1-(4-Methoxyphenyl)-3-(3,4,5-trimethoxyphenyl)propan-1-ol (13k).** In a round bottomed flask, compound **12k** (0.86 g, 2.60 mmol) was dissolved in methanol and kept at 0 °C for 15–20 minutes. To this mixture sodium borohydride ($NaBH_4$, 0.29 g, 7.80 mmol), was added and reaction was transferred to room temperature after half an hour. The progress of reaction was monitored by TLC (30% ethyl acetate–hexane). After completion of reaction, solvent was taken off and the reaction mixture was treated with $NH_4Cl$ and worked up using ethyl acetate and water. The organic layer was the separated, dried anhydrous sodium sulphate ($Na_2SO_4$) and concentrated. The crude solid material was purified by washing it with hexane which yielded pure compound **13k** as white solid in 98% (3.58 g), yield which was further processed for hydrolysis as such. The experimental procedure used for synthesis of compound **13a–m** is same as described for compound **13k**. The molar ratio of reactants was same for synthesis of all derivatives.

### General procedure for the synthesis of compounds (14a–m)

**5-(4-Methoxycinnamyl)-1,2,3-trimethoxybenzene (14k).** In a round bottomed flask, compound **13k** (0.83 g, 2.50 mmol) was dissolved in ethanol and conc. HCl (1 mL) was added to it. The reaction mixture was transferred for reflux. The progress of reaction was monitored by TLC (30% ethyl acetate–hexane). After completion of reaction, solvent was taken off and the reaction mixture was worked up using ethyl acetate and water. The organic layer was the separated, dried over anhydrous sodium sulphate ($Na_2SO_4$) and concentrated. The crude solid material was purified by column chromatography on silica gel (100–200 mesh size) using hexane as eluents which yielded pure compound **14k** as white solid. Yield: (0.44 g), 54%; m.p. 61–62 °C; $R_f$: 0.45 (30% ethyl acetate–hexane); IR (KBr, $\nu_{max}$ $cm^{-1}$): 2936, 2835, 1593, 1507, 1459, 1330, 1239, 1120, 1017, 832; $^1H$ NMR ($CDCl_3$, 300 MHz, $\delta$ ppm): 3.46 (d, $J = 6.6$ Hz, 2H, $CH_2$), 3.80–3.84 (m, 12H, 4 × $OCH_3$), 6.16–6.24 (m, 1H, CH), 6.39–6.45 (m, 3H, CH and ArH), 6.84 (d, $J = 8.7$ Hz, 2H, ArH), 7.30 (d, $J = 8.7$ Hz, 2H, ArH); $^{13}C$ NMR ($CDCl_3$, 75 MHz, $\delta$ ppm): 40.09 ($CH_2$), 55.69 ($OCH_3$), 56.51 (2 × $OCH_3$), 61.25 ($OCH_3$), 106.00 (2 × C), 114.38 (2 × C), 127.19, 127.67 (2 × C), 130.65, 130.95, 136.00, 153.65 (3 × C), 159.35; ESIMS ($C_{19}H_{22}O_4$): $m/z = 337$ $[M + Na]^+$, 353 $[M + K]^+$.

**4-(3,4,5-Trimethoxycinnamyl)-2-methoxyphenol (14a).** Yield: (0.38 g), 48%; m.p. Oil; $R_f$: 0.37 (30% ethyl acetate–hexane); IR (KBr, $\nu_{max}$ $cm^{-1}$): 3424, 2937, 2837, 1582, 1509, 1458, 1236, 1124, 787; $^1H$ NMR ($CDCl_3$, 300 MHz, $\delta$ ppm): 3.46 (d, $J = 6.0$ Hz, 2H, $CH_2$), 3.80–3.89 (m, 12H, 4 × $OCH_3$), 5.52 (s, 1H, OH), 6.21–6.28 (m, 1H, CH), 6.35 (d, $J = 15.9$ Hz, 1H, CH), 6.58 (s, 2H, ArH), 6.72–6.75 (m, 2H, ArH), 6.86 (d, $J = 8.4$ Hz, 1H, ArH); $^{13}C$ NMR ($CDCl_3$, 75 MHz, $\delta$ ppm): 39.35 ($CH_2$), 56.33 ($OCH_3$), 56.49 (2 × $OCH_3$), 61.30 ($OCH_3$), 103.70 (2 × C), 111.70, 114.76, 121.76, 129.60, 131.03, 132.31, 133.66, 137.99, 144.51, 146.95, 153.72 (2 × C); ESIMS ($C_{19}H_{24}O_6$): $m/z = 331$ $[M + H]^+$, 329 $[M - H]^+$.

**4-(3,4-Dimethoxycinnamyl)-2-methoxyphenol (14b).** Yield: (0.59 g), 63%; m.p. 103–134 °C; $R_f$: 0.4 (20% ethyl acetate–hexane); IR (KBr, $\nu_{max}$ $cm^{-1}$): 3488, 1513, 1462, 1264, 1139, 1025, 814, 766; $^1H$ NMR ($CDCl_3$, 300 MHz, $\delta$ ppm): 3.46 (d, $J = 6.3$ Hz, 2H, $CH_2$), 3.87 (bs, 9H, 3 × $OCH_3$), 5.52 (bs, 1H, OH), 6.17–6.24 (m, 1H, CH), 6.37 (d, $J = 15.9$ Hz, 1H, CH), 6.73–6.91 (m, 6H, ArH); $^{13}C$ NMR ($CDCl_3$, 75 MHz, $\delta$ ppm): 39.43 ($CH_2$), 56.22 ($OCH_3$), 56.34 (2 × $OCH_3$), 109.03, 111.57, 111.64, 114.71, 119.53, 121.71, 128.16, 130.78, 131.07, 132.61, 144.42, 146.91, 148.86, 149.44; ESIMS ($C_{18}H_{20}O_4$): $m/z = 323$ $[M + Na]^+$.

**4-(4-Methoxycinnamyl)-2-methoxyphenol (14c).** Yield: (0.42 g), 50%; m.p. 92–93 °C; $R_f$: 0.57 (30% ethyl acetate–hexane); IR (KBr, $\nu_{max}$ $cm^{-1}$): 3435, 1606, 1512, 1459, 1435, 1265, 1237, 1028, 834, 786; $^1H$ NMR ($CDCl_3$, 300 MHz, $\delta$ ppm): 3.41 (d, $J = 6.6$ Hz, 2H, $CH_2$), 3.76 (s, 3H, $OCH_3$), 3.80 (s, 3H, $OCH_3$), 6.18–6.28 (m, 1H, CH), 6.40 (d, $J = 15.6$ Hz, 1H, CH), 6.66–6.86 (m, 5H, ArH), 7.32 (d, $J = 8.7$ Hz, 2H, ArH), 7.38 (s, 1H, OH); $^{13}C$ NMR ($CDCl_3$, 75 MHz, $\delta$ ppm): 39.01 ($CH_2$), 55.02 ($OCH_3$), 55.75 ($OCH_3$), 112.52, 114.26 (3 × C), 115.27, 121.29, 127.54 (2 × C), 127.94, 130.21, 130.80, 145.33, 147.82, 159.44; ESIMS ($C_{17}H_{18}O_3$): $m/z =$ 293 $[M + Na]^+$, 309 $[M + K]^+$.

**4-(3-(Benzo[*d*][1,3]dioxol-6-yl)allyl)-2-methoxyphenol (14d).** Yield: (0.66 g), 85%; m.p. 78–79 °C; $R_f$: 0.6 (10% ethyl acetate–hexane); IR (KBr, $\nu_{max}$ $cm^{-1}$): 3455, 1607, 1500, 1444, 1253, 1035, 880, 794; $^1H$ NMR ($CDCl_3$, 300 MHz, $\delta$ ppm): 3.45 (d, $J = 6.3$ Hz, 2H, $CH_2$), 3.87 (s, 3H, $OCH_3$), 5.53 (s, 1H, OH), 5.93 (bs, 2H, $CH_2$), 6.11–6.21 (m, 1H, ArH), 6.32–6.37 (d, $J = 15.6$ Hz, 1H, ArH), 6.72–6.80 (m, 4H, CH and ArH), 6.85–6.91(m, 2H, ArH); $^{13}C$ NMR ($CDCl_3$, 75 MHz, $\delta$ ppm): 39.32 ($CH_2$), 56.31 ($OCH_3$), 101.37 ($CH_2$), 105.95, 108.64, 111.57, 114.71, 120.95, 121.65, 128.30, 130.73, 132.45, 132.54, 144.40, 146.90, 147.20, 148.37; ESIMS ($C_{17}H_{16}O_4$): $m/z = 285$ $[M + H]^+$, 307 $[M + Na]^+$, 323 $[M + K]^+$.

**5-(3-(4-Methoxyphenyl)prop-1-enyl)benzo[*d*][1,3]dioxole (14e).** Yield: (0.42 g), 54%; m.p. oil; $R_f$: 0.80 (30% ethyl acetate–hexane); IR (KBr, $\nu_{max}$ $cm^{-1}$): 2924, 1609, 1508, 1443, 1246, 1038, 934, 816; $^1H$ NMR ($CDCl_3$, 300 MHz, $\delta$ ppm): 3.46 (d, $J = 6.6$ Hz, 2H, $CH_2$), 3.79 (s, 3H, $OCH_3$), 6.49 (s, 2H, $CH_2$), 6.11–6.21 (m, 1H, CH), 6.34 (d, $J = 15.6$ Hz, 1H, CH), 6.69–6.90 (m, 5H, ArH), 7.14 (d, $J = 8.4$ Hz, 2H, ArH); $^{13}C$ NMR ($CDCl_3$, 75 MHz, $\delta$ ppm): 38.72 ($CH_2$), 55.69 ($OCH_3$), 101.34 ($CH_2$), 105.97, 108.61, 114.34 (2 × C), 120.90, 128.39, 129.95 (2 × C), 130.71, 132.52, 132.72, 147.17, 148.36, 158.49; ESIMS ($C_{17}H_{16}O_3$): $m/z = 307$ $[M + K]^+$.

**1,3-Bis(4-methoxyphenyl)prop-1-ene (14f).** Yield: (0.37 g), 48%; m.p. 63–64 °C; $R_f$: 0.85 (30% ethyl acetate–hexane); IR (KBr, $\nu_{max}$ $cm^{-1}$): 2953, 2902, 1609, 1510, 1243, 1032, 823; $^1H$ NMR (acetone-$D_6$, 300 MHz, $\delta$ ppm): 3.44 (d, $J = 6.6$ Hz, 2H, $CH_2$), 3.76(bs, 6H, 2 × $OCH_3$), 6.18–6.28 (m, 1H, CH), 6.40 (d, $J = 15.9$ Hz, 1H, CH), 6.85 (d, $J = 8.4$ Hz, 4H, ArH), 7.15 (d, $J = 8.1$ Hz, 2H, ArH), 7.32 (d, $J = 8.7$ Hz, 2H, ArH); $^{13}C$ NMR (acetone-$D_6$, 75 MHz, $\delta$ ppm): 38.48 ($CH_2$), 54.97 ($OCH_3$), 55.02 ($OCH_3$), 114.17 (2 × C), 114.20 (2 × C), 127.54 (2 × C), 127.81, 129.82 (2 × C), 130.36, 130.76, 132.82, 158.66, 159.48; ESIMS ($C_{17}H_{18}O_2$): $m/z = 253$ $[M - H]^+$, 255$[M + H]^+$, 277 $[M + Na]^+$.

**1,2-Dimethoxy-4-(3-(4-methoxyphenyl)prop-1-enyl)benzene (14g).** Yield: (0.47 g), 60%; m.p. 48–49 °C; $R_f$: 0.61 (30% ethyl acetate–hexane); IR (KBr, $\nu_{max}$ $cm^{-1}$): 2930, 2839, 1605, 1509, 1268, 1240, 1126, 1019, 966, 818; $^1H$ NMR ($CDCl_3$, 300 MHz, $\delta$ ppm): 3.48 (d, $J = 6.3$ Hz, 2H, $CH_2$), 3.80–3.88 (m, 9H, 3 × $OCH_3$), 6.15–6.25 (m, 1H, CH), 6.37 (d, $J = 15.9$ Hz, 1H, CH), 6.78–6.91 (m, 5H, ArH), 7.17 (d, $J = 8.4$ Hz, 2H, ArH); $^{13}C$ NMR ($CDCl_3$, 75

MHz, $\delta$ ppm): 38.82 ($CH_2$), 55.69 ($OCH_3$), 56.20 ($OCH_3$), 56.34 ($OCH_3$), 109.05, 111.60, 114.32 (2 × C), 119.52, 128.23, 130.02 (2 × C), 130.75, 131.13, 132.79, 148.84, 149.43, 158.49; ESIMS ($C_{18}H_{20}O_3$): $m/z$ = 283 $[M - H]^+$, 285 $[M + H]^+$, 307 $[M + Na]^+$.

**1,2,3-Trimethoxy-5-(3-(4-methoxyphenyl)prop-1-enyl)benzene (14h).** Yield: (0.38 g), 48%; m.p. 69–71 °C; $R_f$: 0.78 (30% ethyl acetate–hexane); IR (KBr, $\nu_{max}$ $cm^{-1}$): 2936, 2835, 1583, 1508, 1459, 1419, 1243, 1123, 1027, 819; $^1$H NMR ($CDCl_3$, 300 MHz, $\delta$ ppm): 3.51 (d, $J$ = 6.0 Hz, 2H, $CH_2$), 3.82–3.96 (m, 12H, 4 × $OCH_3$), 6.23–6.32 (m, 1H, CH), 6.52 (d, $J$ = 15.6 Hz, 1H, CH),6.61 (s, 2H, ArH), 6.84–6.91 (m, 2H, ArH), 7.12–7.20 (m, 2H, ArH); $^{13}$C NMR ($CDCl_3$, 75 MHz, $\delta$ ppm): 38.77 ($CH_2$), 55.69 ($OCH_3$), 56.50 (2 × $OCH_3$), 61.32 ($OCH_3$), 103.59 (2 × C), 114.35 (2 × C), 129.69, 130.06 (2 × C), 131.00, 132.49, 133.70, 153.64 (3 × C), 158.54; ESIMS ($C_{19}H_{22}O_4$): $m/z$ = 337 $[M + Na]^+$.

**1,2-Dimethoxy-4-(3-(3,4,5-trimethoxyphenyl)prop-1-enyl)-benzene (14i).** Yield: (0.40 g), 51%; m.p. 67–68 °C; $R_f$: 0.71 (30% ethyl acetate–hexane); IR (KBr, $\nu_{max}$ $cm^{-1}$): 2934, 2835, 1588, 1510, 1458, 1236, 1127, 1024, 823; $^1$H NMR ($CDCl_3$, 300 MHz, $\delta$ ppm): 3.47 (d, $J$ = 6.6 Hz, 2H, $CH_2$), 3.82–3.88 (m, 15H, 5 × $OCH_3$), 6.16–6.24 (m, 1H, CH), 6.37–6.45 (m, 3H, CH and ArH), 6.72 (d, $J$ = 8.4 Hz, 1H, ArH), 6.80 (d, $J$ = 9.3 Hz, 1H, ArH), 6.90 (d, $J$ = 8.4 Hz, 1H, ArH); $^{13}$C NMR ($CDCl_3$, 75 MHz, $\delta$ ppm): 40.09 ($CH_2$), 56.25 ($OCH_3$), 56.35 ($OCH_3$), 56.53 (2 × $OCH_3$), 61.25 ($OCH_3$), 106.10 (2 × C), 109.21, 111.67, 119.58, 127.50, 130.98, 131.18, 136.48, 148.99, 149.49, 153.68 (3 × C); ESIMS ($C_{20}H_{24}O_5$): $m/z$ = 367 $[M + Na]^+$, 369 $[M + 2 + Na]^+$.

**4-(3,4,5-Trimethoxycinnamyl)phenol (14j).** Yield: (0.41 g), 52%; m.p. 124–125 °C; $R_f$: 0.46 (30% ethyl acetate–hexane); IR (KBr, $\nu_{max}$ $cm^{-1}$): 3355, 3001, 2935, 2836, 1584, 1511, 1454, 1418, 1237, 1125, 1003, 830, 781; $^1$H NMR ($CDCl_3$, 300 MHz, $\delta$ ppm): 3.44 (dd, $J$ = 0.9 and 0.5 Hz, 2H, $CH_2$), 3.80–3.85 (m, 9H, 3 × $OCH_3$), 6.18–6.37 (m, 2H, CH), 6.57 (s, 2H, ArH), 6.78 (d, $J$ = 8.4 Hz, 2H, ArH), 7.10 (d, $J$ = 8.4 Hz, 2H, ArH); ESIMS ($C_{18}H_{20}O_4$): $m/z$ = 301 $[M + H]^+$, 323 $[M + Na]^+$.

**4-(4-Methoxycinnamyl)phenol (14l).** Yield: (0.39 g), 50%; m.p. 73–74 °C; $R_f$: 0.43 (30% ethyl acetate–hexane); IR (KBr, $\nu_{max}$ $cm^{-1}$): 3370, 1605, 1511, 1242, 1026, 831; $^1$H NMR ($CDCl_3$, 300 MHz, $\delta$ ppm): 3.39 (d, $J$ = 6.6 Hz, 2H, $CH_2$), 3.73 (s, 3H, $OCH_3$), 4.95 (bs, 1H, OH), 6.08–6.17 (m, 1H, CH), 6.31 (d, $J$ = 15.9 Hz, 1H, CH), 6.70–6.79 (m, 4H, ArH), 6.95 (d, $J$ = 8.4 Hz, 2H, ArH), 7.19–7.24 (m, 2H, ArH); $^{13}$C NMR ($CDCl_3$, 75 MHz, $\delta$ ppm): 38.84 ($CH_2$), 55.74 ($OCH_3$), 114.38 (2 × C), 115.71 (2 × C), 127.64 (2 × C), 127.94, 130.20 (2 × C), 130.54, 130.84, 133.00, 154.31, 159.19; ESIMS ($C_{16}H_{16}O_2$): $m/z$ = 293 $[M + Na]^+$, 309 $[M + K]^+$.

**3-(3,4,5-Trimethoxyphenyl)-1-(4-hydroxy-3-methoxyphenyl)-prop-1-ene (14m).** Yield: (0.45 g), 57%; oil; $R_f$: 0.30 (30% ethyl acetate–hexane); $^1$H NMR ($CDCl_3$, 300 MHz, $\delta$ ppm): 3.39 (d, $J$ = 6.3 Hz, 2H, $CH_2$), 3.75–3.86 (m, 12H, 4 × $OCH_3$), 5.54 (s, 1H, OH), 6.04–6.14 (m, 1H, CH), 6.29–6.34 (m, 1H, CH), 6.38 (s, 2H, ArH), 6.76–6.82 (m, 3H, ArH); ESIMS ($C_{19}H_{22}O_5$): $m/z$ = 331 $[M + H]^+$, 353 $[M + Na]^+$.

### General procedure for the synthesis of (15a–c)

**1,2,3-Trimethoxy-5-(3-(4-methoxyphenyl)propyl)benzene (15a).** Compound **14k** (0.80 g, 2.54 mmol) was taken in a round bottomed flask and dissolved in ethyl acetate–methanol mixture (8 : 2). The mixture was flushed with nitrogen gas and palladium charcoal (Pd/C, 5% wt) (0.08 g) was added and hydrogen gas was passed to it for 1 h. The progress of reaction was monitored by TLC. After completion of the reaction, the solvent was evaporated and crude material was worked up using ethyl acetate and water. The organic layer was the separated, dried anhydrous sodium sulphate ($Na_2SO_4$) and concentrated. The crude was purified by column chromatography on silica gel (100–200 mesh size) using ethyl acetate–hexane (12 : 88) as eluents which yielded pure compound **15** as white solid. Yield: (0.68 g), 85%; m.p. 56–57 °C; $R_f$: 0.80 (30% ethyl acetate–hexane); IR (KBr, $\nu_{max}$ $cm^{-1}$): 2933, 2837, 1588, 1509, 1457, 1242, 1125, 1006, 829; $^1$H NMR ($CDCl_3$, 300 MHz, $\delta$ ppm): 1.90–2.00 (m, 2H, $CH_2$), 2.59–2.66 (m, 4H, 2 × $CH_2$), 3.82–3.87 (m, 12H, 4 × $OCH_3$), 6.42 (s, 2H, ArH), 6.87 (d, $J$ = 8.7 Hz, 2H, ArH), 7.14 (d, $J$ = 8.4 Hz, 2H, ArH); $^{13}$C NMR ($CDCl_3$, 75 MHz, $\delta$ ppm): 33.58 ($CH_2$), 34.96 ($CH_2$), 36.19 ($CH_2$), 55.66 ($OCH_3$), 56.47 (2 × $OCH_3$), 61.52 ($OCH_3$), 105.75 (2 × C), 114.16 (2 × C), 129.72 (2 × C), 134.65, 136.50, 138.54, 153.48 (2 × C), 158.19; ESIMS ($C_{19}H_{24}O_4$): $m/z$ = 316 $[M]^+$, 339 $[M + Na]^+$.

**1,2-Dimethoxy-4-(3-(3,4,5-trimethoxyphenyl)propyl)benzene (15b).** Yield: (0.72 g), 90%; m.p. 52–53 °C; $R_f$: 0.30 (30% ethyl acetate–hexane); IR (KBr, $\nu_{max}$ $cm^{-1}$): 2939, 2837, 1589, 1514, 1463, 1239, 1130, 1029, 1003, 823, 766; $^1$H NMR ($CDCl_3$, 300 MHz, $\delta$ ppm): 1.90–2.01 (m, 2H, $CH_2$), 2.59–2.66 (m, 4H, 2 × $CH_2$), 3.85–3.89 (m, 12H, 4 × $OCH_3$), 6.42 (s, 2H, ArH), 6.74–6.77 (m, 2H, ArH), 6.81–6.84 (d, $J$ = 7.8 Hz, 1H, ArH); $^{13}$C NMR ($CDCl_3$, 75 MHz, $\delta$ ppm): 33.48, 33.46, 36.21, 56.26 ($OCH_3$), 56.36 (2 × $OCH_3$), 61.22 ($OCH_3$), 105.86 (2 × C), 111.77, 112.35, 120.67 (2 × C), 135.26, 136.61, 138.45, 147.66, 149.30, 153.50; ESIMS ($C_{20}H_{26}O_5$): $m/z$ = 347$[M + H]^+$, 369 $[M + Na]^+$.

### 2-Methoxy-4-(3-(3,4,5-trimethoxyphenyl)propyl)phenol (15c)

Yield: (0.63 g), 78%; m.p. 83–84 °C; $R_f$: 0.45 (30% ethyl acetate–hexane); $^1$H NMR ($CDCl_3$, 300 MHz, $\delta$ ppm): 1.79–1.89 (m, 2H, $CH_2$), 2.48–2.53 (t, $J$ = 2.7 Hz, 4H, 2 × $CH_2$), 3.73–3.82 (m, 12H, 4 × $OCH_3$), 5.51 (s, 1H, CH), 6.32 (s, 2H, ArH), 6.57–6.60 (dd, $J$ = 1.8 and 1.8 Hz, 1H, ArH), 6.71–6.75(m, 2H, ArH); $^{13}$C NMR ($CDCl_3$, 75 MHz, $\delta$ ppm): 33.35, 35.20, 36.13, 56.42, 56.48 (2 × $OCH_3$), 61.23, 105.83 (2 × C), 111.04, 115.09, 120.13, 135.97, 136.56, 138.51, 145.16, 145.91, 153.48 (2 × C); ESIMS ($C_{19}H_{24}O_5$): $m/z$ = 333 $[M + H]^+$.

### General procedure for the synthesis of compounds (17a–e)

**2-(4-Hydroxy-3-methoxybenzylidene)-3,4-dihydro-6-methoxy-naphthalen-1(2H)-one (17a).** In a round bottomed flask compound **16** ($R_1$ = $R_2$ = H, $n$ = 2) (2.00 g, 11.36 mmol) was dissolved into methanol (20 mL) and methanolic KOH (10%, 20 mL) was added to this solution drop wise on ice bath. After 20 minutes, compound **10** (R′ = $OCH_3$, R = H, 2.63 g, 11.36 mmol) dissolved in methanol (15 mL) was added to reaction mixture. The reaction mixture was allowed to stir at ice bath for 30 minutes and afterwards at room temperature for 12 h. The progress of reaction was monitored using TLC. After completion of reaction, solvent was evaporated followed by drop wise

addition of dilute HCl and pH of the content was adjusted to acidic. The content was extracted with ethyl acetate. The organic layer was then separated and dried over anhydrous sodium sulphate ($Na_2SO_4$) and concentrated. The crude material was purified by crystallization by methanol which yielded pure compound **17a** as yellow solid. Yield: (2.53 g), 72%; m.p. 129–130 °C; $R_f$: 0.18 (20% ethyl acetate–hexane); IR (KBr, $\nu_{max}$ $cm^{-1}$): 3182, 1637, 1597, 1556, 1522, 1255, 1127, 1093, 1034, 867, 826, 765; $^1H$ NMR ($CDCl_3$, 300 MHz, $\delta$ ppm): 2.88–2.93(m, 2H, $CH_2$), 3.12 (bs, 2H, $CH_2$), 3.86(s, 3H, $OCH_3$), 3.90(s, 3H, $OCH_3$), 5.93(s, 1H, OH), 6.70(s, 1H, ArH), 6.86 (dd, $J$ = 2.4 &2.1 Hz, 1H, ArH), 6.96–7.03 (m, 3H, ArH), 7.78 (s, 1H, ArH), 8.09 (d, $J$ = 8.7 Hz, 1H, ArH); $^{13}C$ NMR ($CDCl_3$, 75 MHz, $\delta$ ppm): 27.71 ($CH_2$), 29.61 ($CH_2$), 55.83 ($OCH_3$), 56.83($OCH_3$), 112.66, 113.19, 113.65, 114.85, 124.08, 127.58, 128.75, 131.09, 134.14, 136.77, 145.95, 146.70, 146.82, 163.90, 187.15(C═O); ESIMS ($C_{19}H1_8O_4$): $m/z$ = 309$[M - 1]^+$, 333 $[M + Na]^+$.

**2-(4-Hydroxy-3-methoxybenzylidene)-2,3-dihydro-5-methoxyinden-1-one (17b).** Yield: (3.02 g), 83%; m.p. 199–201 °C; $R_f$: 0.09 (20% ethyl acetate–hexane); IR (KBr, $\nu_{max}$ $cm^{-1}$): 3490, 1681, 1624, 1589, 1521, 1267, 1092, 1028, 837, 811; $^1H$ NMR (DMSO-$d_6$, 300 MHz, $\delta$ ppm): 3.75–3.79 (m, 6H, 2 × $OCH_3$), 3.94 (bs, 2H, $CH_2$), 6.79–6.82 (d, $J$ = 8.1 Hz, ArH), 6.90–6.93 (d, $J$ = 8.4 HZ, 1H, ArH), 7.09–7.14 (m, 2H, ArH), 7.21–7.47 (m, 4H, CH and ArH), 7.59–7.62 (d, $J$ = 8.4 Hz, 1H, ArH); $^{13}C$ NMR (DMSO-$d_6$, 75 MHz, $\delta$ ppm): 32.80, 56.52, 56.60, 110.92, 115.23, 149.53, 148.67, 133.24, 133.12, 133.24, 148.67, 149.53, 153.60, 165.53, 192.53 (C═O); ESIMS ($C_{18}H_{16}O_4$): $m/z$ = 297 $[M + H]^+$, 323 $[M + Na]^+$.

**2-(4-Hydroxy-3-methoxybenzylidene)-2,3-dihydro-5,6-dimethoxyinden-1-one (17c).** Yield: (2.92 g), 86%; m.p. 140–141 °C; $R_f$: 0.11 (30% ethyl acetate–hexane); IR (KBr, $\nu_{max}$ $cm^{-1}$): 3424, 1672, 1578, 1505, 1311, 817, 714; $^1H$ NMR ($CDCl_3$, 300 MHz, $\delta$ ppm): 3.79–3.85 (m, 11H, 3 × $OCH_3$ and $CH_2$), 6.77–6.87 (m, 2H, ArH), 7.01–7.07 (m, 2H, ArH), 7.16 (s, 1H, CH), 7.36 (s, 1H, ArH); $^{13}C$ NMR ($CDCl_3$, 75 MHz, $\delta$ ppm): 32.41 ($CH_2$), 55.28 ($OCH_3$), 56.42 ($OCH_3$), 58.58 ($OCH_3$), 105.26, 107.65, 113.96, 116.03, 125.12, 127.86, 131.50, 132.91, 133.21, 144.94, 147.86, 148.57, 149.85, 155.48, 193.45 (C═O); ESIMS ($C_{19}H_{18}O_5$): $m/z$ = 327 $[M + H]^+$, 349 $[M + Na]^+$.

**2-(4-Methoxybenzylidene)-2,3-dihydro-5-methoxyinden-1-one (17d).** Yield: (2.55 g), 74%; m.p. 145–146 °C; $R_f$: 0.15 (20% ethyl acetate–hexane); IR (KBr, $\nu_{max}$ $cm^{-1}$): 1684, 1597, 1504, 1256, 1125, 1022, 808; $^1H$ NMR ($CDCl_3$, 300 MHz, $\delta$ ppm): 3.84–3.92 (m, 8H, CH and 2 × $OCH_3$), 6.91–6.97 (m, 4H, ArH), 7.55–7.60 (m, CH and ArH), 7.82 (d, $J$ = 8.4 Hz, 1H, ArH); $^{13}C$ NMR ($CDCl_3$, 75 MHz, $\delta$ ppm): 32.92 ($CH_2$), 55.77 ($OCH_3$), 56.05 ($OCH_3$), 110.13, 114.81 (2 × C), 115.49, 126.42, 128.71, 132.03, 132.72 (2 × C), 132.91, 133.34, 152.76, 161.03, 165.44, 193.27 (C═O); ESIMS ($C_{18}H_{16}O_3$): $m/z$ = 303 $[M + Na]^+$, 319 $[M + K]^+$.

**2-(4-Methoxybenzylidene)-2,3-dihydro-5,6-dimethoxyinden-1-one (17e).** Yield: (2.90 g), 90%; m.p. 191–192 °C; $R_f$: 0.46 (30% ethyl acetate–hexane); IR (KBr, $\nu_{max}$ $cm^{-1}$): 1684, 1597, 1504, 1256, 1125, 1022, 808; $^1H$ NMR ($CDCl_3$, 300 MHz, $\delta$ ppm): 3.83–4.20 (m, 11H, $CH_2$ and 3 × $OCH_3$), 6.92–6.94 (m, 3H, ArH), 7.29 (s, 1H, CH), 7.52–7.58 (m, 3H, ArH); $^{13}C$ NMR ($CDCl_3$, 75 MHz, $\delta$ ppm): 32.55 ($CH_2$), 55.76 ($OCH_3$), 56.53 ($OCH_3$), 56.64 ($OCH_3$), 105.49, 107.61, 114.81 (2 × C), 128.75, 131.68, 132.60 (2 × C), 132.67, 133.56, 145.02, 150.00, 155.62, 161.02, 193.57 (C═O); ESIMS ($C_{19}H_{18}O_4$): $m/z$ = 333 $[M + Na]^+$.

## General procedure for the synthesis of compounds (18a–e)

**2-(4-Hydroxy-3-methoxybenzyl)-3,4-dihydro-6-methoxynaphthalen-1(2H)-one (18a).** Compound **17a** (1.00 g, 3.23 mmol) was taken in a round bottomed flask and dissolved in ethyl acetate–methanol mixture (8 : 2). The mixture was flushed with nitrogen gas and palladium charcoal (Pd/C, 5% wt) (0.10 g) was added and hydrogen gas was passed to it for 3 h. The progress of reaction was monitored by TLC. After completion of the reaction, the solvent was evaporated and crude material was worked up using ethyl acetate and water. The organic layer was the separated, dried anhydrous sodium sulphate ($Na_2SO_4$) and concentrated. The crude was purified by column chromatography on silica gel (100–200 mesh size) using ethyl acetate–hexane (12 : 88) as eluents which yielded pure compound **18a** as white solid. Yield: (0.72 g), 72%; m.p. 114–115 °C; $R_f$: 0.40 (30% ethyl acetate–hexane); IR (KBr, $\nu_{max}$ $cm^{-1}$): 3353, 2932, 1663, 850; $^1H$ NMR ($CDCl_3$, 300 MHz, $\delta$ ppm): 1.67 (s, 2H, $CH_2$), 2.56–2.68 (m, 2H, $CH_2$), 2.85–2.89 (m, 2H, $CH_2$), 3.35–3.39 (m, 1H, CH), 3.84–3.86 (m, 6H, 2 × $OCH_3$), 5.53 (s, 1H, OH), 6.66–6.74 (m, 3H, ArH), 6.80–6.84 (m, 2H, ArH), 8.03 (d, $J$ = 9.0 Hz, 1H, ArH); $^{13}C$ NMR ($CDCl_3$, 75 MHz, $\delta$ ppm): 28.00 ($CH_2$), 29.29 ($CH_2$), 35.87($CH_2$), 49.73 (CH), 55.81 ($OCH_3$), 56.32 ($OCH_3$), 112.11, 112.85, 113.59, 114.54, 122.35, 126.55, 130.38, 132.41, 144.36, 146.87, 146.95, 163.90, 198.75 (C═O); ESIMS ($C_{19}H_{20}O_4$): $m/z$ = 335 $[M + Na]^+$.

**2-(4-Hydroxy-3-methoxybenzyl)-2,3-dihydro-5-methoxyinden-1-one (18b).** Yield: (0.59 g), 59%; m.p. 120–121 °C; $R_f$: 0.37 (40% ethyl acetate–hexane); IR (KBr, $\nu_{max}$ $cm^{-1}$): 3376, 1681, 1593, 1517, 1251, 849, 814; $^1H$ NMR ($CDCl_3$, 300 MHz, $\delta$ ppm): 2.63 (dd, $J$ = 9.6 and 9.9 Hz, 1H, CH of $CH_2$), 2.80 (dd, $J$ = 3.0 and 3.0 Hz, 1H, CH of $CH_2$), 2.89–2.98 (m, 1H, CH), 3.10 (dd, $J$ = 7.5 and 7.5 Hz, 1H, CH of $CH_2$), 3.22–3.28 (dd, $J$ = 3.9 and 4.2 Hz, 1H, CH of $CH_2$), 3.84 (s, 6H, $OCH_3$), 5.55 (s, 1H, OH), 6.68–6.73 (m, 2H, ArH), 6.81–6.83 (m, 2H, ArH), 6.88 (d, $J$ = 8.4 Hz, 1H, ArH), 7.69 (d, $J$ = 8.4 Hz, 1H, ArH); $^{13}C$ NMR ($CDCl_3$, 75 MHz, $\delta$ ppm): 31.29 ($CH_2$), 32.44 ($CH_2$), 49.67, 56.01 ($OCH_3$), 56.29 ($OCH_3$), 110.09, 111.84, 114.60, 115.82, 122.03, 126.01, 130.30, 131.91, 144.52, 146.92, 157.16, 165.84, 206.63 (C═O); ESIMS ($C_{18}H_{18}O_4$): $m/z$ = 299 $[M + H]^+$, 321 $[M + Na]^+$.

**2-(4-Hydroxy-3-methoxybenzyl)-2,3-dihydro-5,6-dimethoxyinden-1-one (18c).** Yield: (0.70 g), 70%; m.p. 137–138 °C; $R_f$: 0.27 (30% ethyl acetate–hexane); IR (KBr, $\nu_{max}$ $cm^{-1}$): 3387, 2988, 2939, 1676, 1216, 1035, 972, 846, 803, 665: $^1H$ NMR ($CDCl_3$, 300 MHz, $\delta$ ppm): 2.57–2.65 (m, 1H, CH of $CH_2$), 2.76 (d, $J$ = 16.8 Hz, 1H, CH), 2.93 (bs, 1H, CH), 3.04–3.09 (m, 1H, CH), 3.25 (d, $J$ = 13.8, Hz, 1H, CH), 3.83–3.92 (m, 9H, 3 × $OCH_3$), 5.06 (s, 1H, OH), 6.68–6.73 (m, 2H, ArH), 6.84 (bs, 2H, ArH), 7.25 (s, 1H, ArH); $^{13}C$ NMR ($CDCl_3$, 75 MHz, $\delta$ ppm): 32.17 ($CH_2$), 37.39 ($CH_2$), 49.79, 55.29 ($OCH_3$), 56.49 ($OCH_3$), 56.59 ($OCH_3$), 104.79, 107.86, 111.86, 114.62, 122.00, 129.71, 131.95, 144.53, 146.92, 149.51, 149.91, 156.04, 207.12 (C═O); ESIMS ($C_{19}H_{20}O_5$): $m/z$ = 329 $[M + H]^+$.

**2-(4-Methoxybenzyl)-2,3-dihydro-5-methoxyinden-1-one (18d).** Yield: (0.87 g), 87%; m.p. 85–86 °C; $R_f$: 0.57 (30% ethyl acetate–hexane); IR (KBr, $\nu_{max}$ $cm^{-1}$): 2916, 2841, 1689, 1251, 1023, 840, 689; $^1H$ NMR ($CDCl_3$, 300 MHz, $\delta$ ppm): 2.58–2.66 (m, 1H, CH of $CH_2$)2.78 (dd, $J$ = 3.6 and 3.6 Hz, 1H, CH of $CH_2$), 2.89–2.98 (m, 1H, CH), 3.09 (dd, $J$ = 7.5 and 7.8 Hz, 1H, CH of $CH_2$), 3.28 (dd, $J$ = 4.2 and 4.2 Hz, 1H, CH of $CH_2$), 3.78 (s, 3H, $OCH_3$), 3.85 (s, 3H, $OCH_3$), 6.80–6.90 (m, 4H, ArH), 7.14 (d, $J$ = 8.4 Hz, 2H, ArH), 7.69 (d, $J$ = 8.4 Hz, 1H, ArH); $^{13}C$ NMR ($CDCl_3$, 75 MHz, $\delta$ ppm): 32.50($CH_2$), 36.68 ($CH_2$), 49.61 (CH), 55.63 ($OCH_3$), 55.99 ($OCH_3$), 110.11, 114.31 (2 × C), 115.75, 126.04, 130.27 (3 × C), 132.10, 157.04, 158.54, 165.81, 206.46 (C═O); ESIMS ($C_{18}H_{18}O_3$): $m/z$ = 283 $[M + H]^+$, 305 $[M + Na]^+$.

**2-(4-Methoxybenzyl)-2,3-dihydro-5,6-dimethoxyinden-1-one (18e).** Yield: (0.73 g), 73%; m.p. 122–123 °C; $R_f$: 0.13 (30% ethyl acetate–hexane); IR (KBr, $\nu_{max}$ $cm^{-1}$): 2947, 2926, 1691, 1602, 1506, 1464, 1259, 810, 778; $^1H$ NMR ($CDCl_3$, 300 MHz, $\delta$ ppm): 2.58–2.65 (m, 1H, CH of $CH_2$), 2.71–2.78 (dd, $J$ = 3.0 and 3.0 Hz, 1H, CH of $CH_2$), 2.89–2.97 (m, 1H, CH), 3.01–3.09 (m, 1H, CH of $CH_2$), 3.24–3.30 (dd, $J$ = 4.2 and 4.2 Hz, 1H, CH of $CH_2$), 3.77 (s, 3H, $OCH_3$), 3.82–3.925 (m, 6H, 2 × $OCH_3$), 6.81 (d, $J$ = 8.7 Hz, 3H, ArH), 7.12–7.18 (m, 3H, ArH); $^{13}C$ NMR ($CDCl_3$, 75 MHz, $\delta$ ppm): 32.18 ($CH_2$), 36.76 ($CH_2$), 49.71 (CH), 55.63 ($OCH_3$), 56.49 ($OCH_3$), 56.57 ($OCH_3$), 104.83, 107.83, 114.28 (2 × C), 129.72, 130.26 (2 × C), 132.11, 149.41, 149.88, 155.99, 158.51, 207.04 (C═O); ESIMS ($C_{19}H_{20}O_4$): $m/z$ = 313 $[M + H]^+$, 335 $[M + Na]^+$.

### General procedure for the synthesis of compounds (19a–e)

In a round bottomed flask, compound **18a** (0.60 g, 1.92 mmol) was dissolved in methanol and kept at 0 °C for 15–20 minutes. To this mixture sodium borohydride ($NaBH_4$, 0.22 g, 5.76 mmol), was added and reaction was transferred to room temperature after half an hour. The progress of reaction was monitored by TLC (30% ethyl acetate–hexane). After completion of reaction, solvent was taken off and the reaction mixture was treated with $NH_4Cl$ and worked up using ethyl acetate and water. The organic layer was the separated, dried anhydrous sodium sulphate ($Na_2SO_4$) and concentrated. The crude solid material was purified by washing it with hexane which yielded pure compound **19a** as white solid in 98% (0.54 g) yield which was further processed for hydrolysis as such. The experimental procedure used for synthesis of compound **19b–m** is same as described above. The molar ratio of reactants was same for synthesis of all derivatives.

### General procedure for the synthesis of compounds (20a–e)

**4-((1,2-Dihydro-7-methoxynaphthalen-3-yl)methyl)-2-methoxyphenol (20a).** In a round bottomed flask, compound **19a** (0.97 g, 2.93 mmol) was dissolved in ethanol and conc. HCl (1 mL) was added to it. The reaction mixture was transferred for reflux. The progress of reaction was monitored by TLC (30% ethyl acetate–hexane). After completion of reaction, solvent was taken off and the reaction mixture was worked up using ethyl acetate and water. The organic layer was the separated, dried over anhydrous sodium sulphate ($Na_2SO_4$) and concentrated. The crude solid material was purified by column chromatography on silica gel (100–200 mesh size) using hexane as eluents which yielded pure compound **20a** as white solid. Yield: (0.75 g), 82%; m.p. 72–73 °C; $R_f$: 0.50 (20% ethyl acetate–hexane); IR (KBr, $\nu_{max}$ $cm^{-1}$): 3386, 2935, 1607, 1511, 1432, 1266, 1240, 1152, 1033, 802, 738; $^1H$ NMR ($CDCl_3$, 300 MHz, $\delta$ ppm): 2.17 (t, $J$ = 7.9 Hz, 2H, $CH_2$), 2.76 (t, $J$ = 7.9 Hz, 2H, $CH_2$), 3.42 (s, 2H, $CH_2$), 3.79 (s, 3H, $OCH_3$), 3.86 (s, 3H, $OCH_3$), 5.53 (s, 1H, OH), 6.21 (s, 1H, CH), 6.67–6.73 (m, 4H, ArH), 6.861 (d, $J$ = 8.4 Hz, 1H, ArH), 6.94 (d, $J$ = 8.1 Hz, 1H, ArH); $^{13}C$ NMR ($CDCl_3$, 75 MHz, $\delta$ ppm): 27.07 ($CH_2$), 29.15 ($CH_2$), 43.83 ($CH_2$), 55.69 ($OCH_3$), 56.32 ($OCH_3$), 111.51, 111.80, 113.98, 114.54, 122.17, 123.44, 126.89, 128.36, 131.94, 136.55, 138.93, 144.41, 146.87, 158.70; ESIMS ($C_{19}H_{20}O_3$): $m/z$ = 319 $[M + Na]^+$, 335 $[M + K]^+$.

**2-Methoxy-4-((6-methoxy-1*H*-inden-2-yl)methyl)phenol (20b).** Yield: (0.60 g), 66%; m.p. 108–109 °C; $R_f$: 0.58 (30% ethyl acetate–hexane); IR (KBr, $\nu_{max}$ $cm^{-1}$): 3434, 2932, 1604, 1515, 1473, 1275, 1237, 1034, 869, 821; $^1H$ NMR (acetone-$d_6$, 300 MHz, $\delta$ ppm): 3.22 (bs, 2H, $CH_2$), 3.68 (s, 2H, $CH_2$), 3.74 (s, 3H, $OCH_3$), 3.80 (s, 3H, $OCH_3$), 6.41 (s, 1H, CH), 6.69–6.78 (m, 4H, ArH), 6.85 (bs, 1H, ArH), 6.96 (bs, 1H, ArH), 7.12 (d, $J$ = 8.1 Hz, 1H, ArH), 7.36 (bs, 1H, OH); $^{13}C$ NMR (acetone-$d_6$, 75 MHz, $\delta$ ppm): 37.43 ($CH_2$), 40.85 ($CH_2$), 55.16 ($OCH_3$), 55.74 ($OCH_3$), 110.60, 111.92, 112.73, 115.22, 120.55, 121.60, 126.79, 132.07, 138.85, 145.36, 145.66, 147.80, 148.24, 157.87; ESIMS ($C_{18}H_{18}O_3$): $m/z$ = 283 $[M + H]^+$, 305 $[M + Na]^+$.

**2-methoxy-4-((5,6-dimethoxy-1*H*-inden-2-yl)methyl)phenol (20c).** Yield: (0.65 g), 71%; m.p. 116–117 °C; $R_f$: 0.38 (30% ethyl acetate–hexane); IR (KBr, $\nu_{max}$ $cm^{-1}$): 3412. 2963, 2924, 1607, 1513, 1487, 1461, 1298, 1269, 855; $^1H$ NMR (acetone-$d_6$, 300 MHz, $\delta$ ppm): 3.18 (s, 2H, $CH_2$), 3.68 (s, 2H, $CH_2$), 3.75–3.89 (m, 9H, 3 × $OCH_3$), 6.39 (s, 1H, CH), 6.67–6.77 (m, 2H, ArH), 6.84–6.89 (m, 2H, ArH), 7.15 (s, 1H, ArH); $^{13}C$ NMR (acetone-$d_6$, 75 MHz, $\delta$ ppm): 37.43 ($CH_2$), 40.73 ($CH_2$), 55.77 ($OCH_3$), 55.95 ($OCH_3$), 56.22 ($OCH_3$), 105.56, 109.72, 112.75, 115.21, 121.58, 127.17, 132.19, 136.27, 138.86, 145.37, 147.58, 147.81, 149.15, 149.30; ESIMS ($C_{19}H_{20}O_4$): $m/z$ = 313 $[M + H]^+$, 335 $[M + Na]^+$.

**2-(4-methoxybenzyl)-6-methoxy-1*H*-indene (20d).** Yield: (0.45 g), 50%; m.p. 83–84 °C; $R_f$: 0.6 (30% ethyl acetate–hexane); IR (KBr, $\nu_{max}$ $cm^{-1}$): 3006, 2927, 2837, 1606, 1511, 1464, 1232, 1243, 1179, 1106, 1030, 859, 809, 745; $^1H$ NMR (acetone-$D_6$, 300 MHz, $\delta$ ppm): 3.21 (s, 2H, $CH_2$), 3.70–3.83 (m, 8H, $CH_2$ and 2 × $OCH_3$), 6.39 (s, 1H, ArH), 6.75 (d, $J$ = 8.1 Hz, 1H, ArH), 6.84–6.96 (m, 3H, ArH), 7.11–7.18 (m, 3H, CH and ArH); $^{13}C$ NMR (acetone-$D_6$, 75 MHz, $\delta$ ppm): 36.89 ($CH_2$), 40.83 ($CH_2$), 54.96 ($OCH_3$), 55.16 ($OCH_3$), 110.60, 111.95, 114.16 (2 × C), 120.56, 120.89, 126.89, 130.08 (2 × C), 132.70, 145.63, 148.12, 157.92, 158.68; ESIMS ($C_{18}H_{18}O_2$): $m/z$ = 267 $[M + H]^+$, 265 $[M - H]^+$.

**2-(4-methoxybenzyl)-5,6-dimethoxy-1*H*-indene (20e).** Yield: (0.57 g), 62%; m.p. 94.0–95 °C; $R_f$: 0.6 (30% ethyl acetate–hexane); IR (KBr, $\nu_{max}$ $cm^{-1}$): 2941, 2834, 1609, 1507, 1460, 1320, 1242, 1101, 1033, 853, 823; $^1H$ NMR ($CDCl_3$, 300 MHz, $\delta$ ppm): 3.20 (s, 2H, $CH_2$), 3.79–3.87 (m, 11H, $CH_2$ and 3 × $OCH_3$), 6.39 (s, 1H, CH), 6.83–6.85 (m, 3H, ArH), 6.95 (bs, 1H, ArH), 7.13 (d, $J$ = 8.4 Hz, 2H, ArH); $^{13}C$ NMR (acetone-$D_6$, 75 MHz, $\delta$ ppm): 36.89 ($CH_2$), 40.70 ($CH_2$), 54.96 ($OCH_3$), 55.91 ($OCH_3$), 56.17 ($OCH_3$), 105.46, 109.60, 114.13 (2 × C), 127.27, 130.07 (2 × C),

132.81, 136.20, 138.76, 147.55, 149.03, 149.27, 158.64; ESIMS ($C_{19}H_{20}O_3$): $m/z$ = 297 $[M + H]^+$, 319 $[M + Na]^+$.

### HPLC analysis

Liquid chromatography based generic methods are widely applicable for the pharmaceutical industry to identify, quantify and determine the purity of small organic compounds. The purity of compounds was determined using high-low chromatographic approach. LC-PDA-MS (Shimadzu, Japan) consisting of an analytical column (Phenomenex, $C_{18}$ 250 × 4.6 mm, 5 mm), pumps (LC-20AD), injector and PDA (SPD-M20A), was used for analysis. Gradient elution covering a wide range of solvent polarity *viz.* methanol–water, acetonitrile–water with and without acid additives, was tried on diverse stationary phases. Finally, a better separation was achieved with a mobile phase composition of acetonitrile–water (80 : 20, v/v). A flow rate of 1.0 mL $min^{-1}$ and column temperature of 27 °C was maintained throughout the run.

### *In vitro* anticancer activity

**Assessment of cell growth inhibition.** *In vitro* anticancer activity of test compounds was studied by Sulphorhodamine B (SRB) dye based plate assay. In brief, $10^4$ cells per well were added in 96-well culture plates and incubated at 37 °C in 5% $CO_2$ concentration. After overnight incubation of cells, serial dilutions of test compound were added to the wells. Untreated cells served as control. After 48 h, cells were fixed with ice-cold Tri-chloroacetic acid (50% w/v, 100 μl per well), stained with SRB (0.4% w/v in 1% acetic acid, 50 μl per well), washed and air-dried. Bound dye was solubilised with 10 mM Tris base (150 μl per well) and absorbance was read at 540 nm on a plate reader. The cytotoxic effect of compound was calculated as % inhibition in cell growth as per formula: [1-(Absorbance of drug treated cells/Absorbance of untreated cells) × 100]. Determination of 50% inhibitory concentration ($IC_{50}$) was based on dose-response curves.

**Cell cycle analysis by flowcytometry.** Cell cycle distribution was measured in concentration and time dependent manner by flow cytometric analysis of PI-stained cellular DNA, as described earlier.[13] Briefly, MCF-7 cells ($4 \times 10^5$ per well) were seeded in 6-well culture plate and grown overnight (37 °C, 5% $CO_2$). Compound treated cells were harvested by trypsinization and fixed (30 min, 4 °C) with ice-cold 70% ethanol at indicated time points. The pellets were washed with PBS and re-suspended in a solution containing PI (20 mg $ml^{-1}$), Triton X100 (0.1%) and RNase (1 mg $ml^{-1}$) in PBS. After incubation (45 min, in the dark, 37 °C), cells were analysed on a FACS Calibur flow cytometer (BD Biosciences). Distribution of cells in different phases of cell cycle was calculated using "Cell Quest" software.

**Detection of fragmented nuclei by DAPI staining.** To observe the nuclear morphology, cells ($10^4$ per well) were grown overnight in 96-well plates and treated with **14k** at $IC_{50}$ concentration. After 24 h incubation with test compound, cells were fixed with 4% formaldehyde (50 μl per well), washed with PBS and permeabilized with 0.1% Triton X100 (50 μl per well). After washing with PBS, cells were stained with DAPI (2 μg $mL^{-1}$, 50 μl per well) for 15 min in dark. Images were acquired with 20× objective using a fluorescent microscope (Nikon, Japan).

***In vitro* cytotoxicity in THP-1 cells.** The compounds were tested for its cytotoxicity against THP-1 cell line *in vitro* using resazurin assay (Roy *et al.*, 2011). Briefly, $10^4$–$10^6$ cells per well were seeded in 96-well plate in 200 μl RPMI supplemented with heat inactivated fetal bovine serum (10% v/v) and incubated at 37 °C with 5% $CO_2$ for overnight. Cells were exposed to different dilutions of test compounds and standard (Rifampin) in triplicate ranging from 400 to 6.25 μM concentration with two fold dilutions. After 48 h 20 μl of resazurin (0.02% w/v) was added in each well and further incubated for 4–5 h. The colour change from purple to pink was assessed visually and fluorescence was measured at 530 ± 25 nm and 590 ± 25 nm for excitation and emission respectively in Synergy Biotek plate reader. $CC_{50}$ values (50% cytotoxic concentrations) were calculated by plotting fluorescence values using Microsoft excel template.

### Ligand and protein preparation for docking experiments

Estrogen receptor (PDB: 1A52; 17-β-estradiol bound) and β-tubulin (PDB: 1SA0; colchicine bound) were retrieved from RCSB Protein Data Bank. Ligand Explorer viewer and PDBsum (http://www.ebi.ac.uk/pdbsum/) were used to inspect the binding site residues and their interactions with bound ligands. This showed that 17β-estradiol has interactions *via* hydrogen bond with His524, Arg394 and Glu353 in bound state with chain A. Surrounding residues at this active site included Leu346, Leu387, Leu391, Phe404, Met388, Ala350, Ile424 and Leu525. Whereas, colchicine bound active site of β-tubulin protein showed colchicine interaction *via* hydrogen bond with Cys241 in bound state with chain B. Surrounding residues at this active site also included Leu255, Asn258, Ala316, Ile378, Leu242, Val238, Ala250 and Lys254.

The test compounds were drawn using chemsketch (http://www.acdlabs.com) and the SMILES format of these structures were converted into 3D coordinate file in .pdb format using online SMILE translation tool (http://cactus.nci.nih.gov/translate/). Energy minimization of these compounds was performed using ligand preparation tool of Discovery studio 2.5 and PRODRG server (http://davapc1.bioch.dundee.ac.wy.prodrg). Estrogen receptor chain A and β-tubulin chain B were used for docking studies after removing heteroatoms and water molecules. Proteins were energy minimized using Swiss-pdb viewer 4.01 (http://www.expasy.org/spdbv) by applying GROMOS96 force field to compute energy and to execute energy minimization. AutoDock 4.2 software (http://www.scripps.edu) was used to execute docking experiments following Lamarckian Genetic algorithm (hybrid of genetic and local search algorithm) and using default docking parameters. Best docked conformation of each ligand based on docking parameters and binding site residues interactions were selected among top 10 docked conformations of each ligand generated during docking. LigPlot Plus version v.1.4.4 (Roman Laskowski, 2009) was used to generate schematic diagram of protein-ligand interactions for a given ligand in a PDB file. Colchicine and 2-methoxyestradiol (known tubulin inhibitors) were also docked on β-tubulin and

results obtained were compared with test compounds, diarylpropene derivatives on β-tubulin. Similarly, 17β-estradiol (known estrogen receptor alpha inhibitor) was docked on estrogen receptor to compare the results obtained with test compounds, diarylpropene derivatives on estrogen receptor alpha.

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