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# 2,3,5-Substituted tetrahydrofurans as cancer chemopreventives. Part 1: Synthesis and anti-cancer activities of 5-hydroxymethyl-2,3-diaryl-tetrahydro-furan-3-ols

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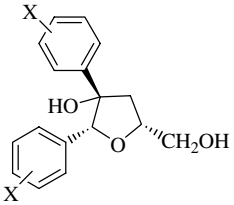
**Abstract**—The allylation of appropriate benzoin in presence of indium metal followed by *m*-CPBA mediated cyclization gave 5-hydroxymethyl-2,3-diaryl-tetrahydro-furan-3-ols. Investigations on 59 human tumor cell lines of these compounds identify four compounds exhibiting significant growth inhibition of tumor cells at particular cell lines. Compound **12** is very specific toward CCRF-CEM and SR cell lines of leukemia.


## 1. Introduction

The over-expression of COX-2 in the cancer cells, leading to tumor promotion, activation of epidermal growth factor receptor, inhibition of apoptosis, promotion of angiogenesis, etc., has established a close correlation between the arachidonic acid metabolism and cancer progression.[1] The role of COX-2 in the cancer cells has been further supported by the fact that non-steroidal anti-inflammatory drugs like aspirin, nimesulide (moderately selective COX-2 inhibitors) and the coxibs like celecoxib (selective COX-2 inhibitor) have been proven to be effective in the treatment of cancer when used in combination with other anti-cancer drugs.[2]

The use of highly selective COX-2 inhibitors reduces the synthesis of prostacyclin, a vasodilator, and shunts the arachidonic acid metabolism toward LOX pathway leading to cardiac toxicity.[3] To develop new therapeutic treatments targeting COX-2, it is desirable to design new molecules with either moderate COX-2 inhibition or dual COX-2/5-LOX inhibition so that the side effects could be avoided. Besides the investigations on some known drugs like aspirin, ibuprofen, indomethacin, celecoxib, etc.[2] for their anti-cancer activities, a series of pyrazole based COX-2/5-LOX inhibitors have been explored for their properties of cell proliferation and/or apoptosis induction.[4]

In order to develop COX-2 inhibitors as cancer chemopreventives, here, we report the synthesis and anti-cancer activities of 5-hydroxymethyl-2,3-diaryl-tetrahydrofuran-3-ols (Fig. 1), the phenyl substituted analogues of 5-hydroxymethyl-2,3-diphenyl-tetrahydrofuran-3-ol, one of the moderate COX-2 inhibitors.[5] The investigations at 59 human tumor cell lines identify compounds **12**, **13**, **14**, and **15** exhibiting significant anti-cancer activities at sub-micromolar concentrations against various cell lines.




X = 4-Cl, 2-Cl, 4-F, 4-OMe, 4-$SO_2$Me

**Figure 1.**

*Keywords*: COX-2; Cancer propagation; 2,3-Diaryltetrahydrofurans; Benzoins; Allylation; Epoxidation; 59 Human tumor cell lines; Anti-cancer agents.
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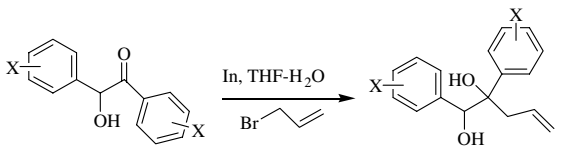
## 2. Results

### 2.1. Chemistry

The compounds have been prepared using our earlier reported synthetic methodology.[5,6] Stirring the solutions of benzoin **1**–**5**, allyl bromide, and indium metal in THF–$H_2O$ (2:1) at 0 °C provided the allylated products **6**–**10**. (Scheme 1).

Treatment of compound **10** with oxone (2 eq) in THF–$H_2O$ (1:1) at 0 °C provided the corresponding sulfonylmethyl substituted compound **11** (90%), mp 145 °C (Scheme 2).

Compounds **6**–**9** and **11** on treatment with *m*-chloroperbenzoic acid (*m*-CPBA) (2 equiv) in dry $CHCl_3$ at 0 °C gave respective compounds **12**–**16** which from their NMR spectral data (and based on X-ray structure of 5-hydroxymethyl-2,3-diphenyl-tetrahydrofuran-3-ol) have been assigned $2R^*$, $3S^*$, $5R^*$ configurations at the three chiral centers.[6] (Scheme 3).



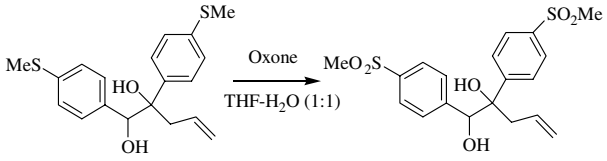

**1-5**

**1**: X = 4-Cl
**2**: X = 2-Cl
**3**: X = 4-F
**4**: X = 4-OMe
**5**: X = 4-SMe

**6-10**

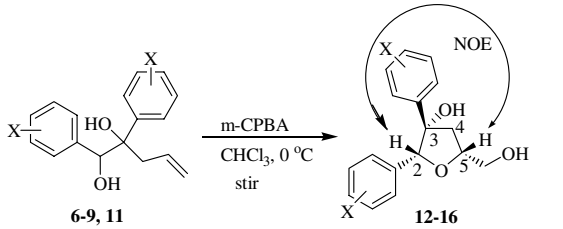
**6**: X = 4-Cl (80%)
**7**: X = 2-Cl (79%)
**8**: X = 4-F (75%)
**9**: X = 4-OMe (72%)
**10**: X = 4-SMe (82%)

**Scheme 1.**




**10** **11** (90%)

**Scheme 2.**




**6-9, 11** **12-16**

**12**: X = 4-Cl (58%)
**13**: X = 2-Cl (55%)
**14**: X = 4-F (61%)
**15**: X = 4-OMe (55%)
**16**: X = 4-$SO_2$Me (56%)

**Scheme 3.**

### 2.2. Biology

The anti-cancer activities of all the compounds have been tested at 59 human tumor cell lines representing leukemia, melanoma, and cancers of the lung, colon, brain, ovary, breast, prostate as well as kidney, following the standard procedure.[7] The results of these studies are represented as percent growth inhibition at $10^{-8}$ M, $10^{-7}$ M, $10^{-6}$ M, $10^{-5}$ M, and $10^{-4}$ M concentrations along with the 50% growth inhibition concentrations ($GI_{50}$), total growth inhibitions (TGI), and 50% lethal concentrations ($LC_{50}$). The concentrations of these compounds representing growth inhibition of 50% ($GI_{50}$) have been given in Table 1, while other data have been given in Supplementary part.

## 3. Discussion

The results of the anti-cancer activities of the compounds over the 59 human tumor cell lines indicate the potential of these compounds for the treatment of cancer. The substitution pattern at the two phenyl rings highly influences the anti-cancer properties of these compounds. Compounds **12** and **13** carrying chlorine at *para*- and *ortho*-positions, respectively, of two phenyl rings show best anti-cancer activities with average $GI_{50}$ over all the 59 cancer cell lines as $1.99 \times 10^{-5}$ M and $2.20 \times 10^{-5}$ M, respectively. Remarkably, these values are comparable to the average $GI_{50}$ of 5-fluorouracil ($1.77 \times 10^{-5}$ M),[8] a clinically used anti-cancer drug. Moreover, compound **12** exhibits $GI_{50}$ $4.63 \times 10^{-7}$ M and $2.02 \times 10^{-7}$ M at CCRF-CEM and SR cell lines of leukemia showing, respectively, 71% and 87% growth inhibition of tumor cells at $10^{-6}$ M concentration. At HS 578T cell line of breast cancer, 21% growth inhibition has been observed with compound **12** at $10^{-8}$ M concentration. With compound **13**, 27% and 36% growth inhibitions at concentrations $10^{-6}$ M and $10^{-5}$ M, respectively, have been observed for NCI-H522 cell line of non-small cell lung cancer (NSCLC) and an inhibition of 15%, 28%, 32%, and 46% at $10^{-8}$ M, $10^{-7}$M, $10^{-6}$ M, and $10^{-5}$ M, respectively, has been seen for the growth of IGROV1 cell line of ovarian cancer.

Compounds **14** and **15** with fluorine and methoxy groups at *para*-positions of two phenyl rings have average $GI_{50}$ $9.50 \times 10^{-5}$ M and $9.33 \times 10^{-5}$ M, respectively, which are considerably less than the average $GI_{50}$ of compounds **12** and **13**. However, compound **14** shows 13% growth inhibition at $10^{-8}$ M concentration for HOP-92 cell line of NSCLC and 29% growth inhibition at $10^{-7}$ M concentration for HS 578T cell line of breast cancer. Compound **15** exhibits 46% and 36% growth inhibition at $10^{-6}$ M concentration for CCRF-CEM and SR cell lines of leukemia. The replacements of chlorines from the phenyl rings of compound **12** with sulfonyl methyl groups as in compound **16** have decreased the average $GI_{50}$ of this compound to $1.0 \times 10^{-4}$ M.

These investigations show the specificity of a compound for a particular cell line and decisively point toward the efficacy of compounds **12** and **13** toward a number of

**Table 1.** Concentrations of compounds resulting in growth inhibitions of 50% (log $GI_{50}$) of in vitro human tumor cell lines

| Panel/Cell line | Compound | | | | | |
|---|---|---|---|---|---|---|
| | **12** | **13** | **14** | **15** | **16** | 5-Fluorouracil |
| *Leukemia* | | | | | | |
| CCRF-CEM | −6.33 | −4.56 | >−4.00 | >−4.00 | >−4.00 | −4.5 |
| HL-60 (TB) | −4.76 | −4.78 | >−4.00 | −4.41 | >−4.00 | −4.7 |
| K-562 | −4.60 | −4.70 | >−4.00 | >−4.00 | >−4.00 | −4.7 |
| MOLT-4 | −4.75 | −4.77 | >−4.00 | >−4.00 | >−4.00 | −4.9 |
| RPMI-8226 | −4.86 | −4.66 | >−4.00 | >−4.00 | >−4.00 | −5.3 |
| SR | −4.69 | −4.77 | >−4.00 | −4.30 | >−4.00 | −5.4 |
| *Non-small cell lung cancer* | | | | | | |
| A549/ATCC | −4.53 | −4.64 | >−4.00 | >−4.00 | >−4.00 | −5.7 |
| EKVX | −4.74 | −4.72 | >−4.00 | >−4.00 | >−4.00 | −3.5 |
| HOP-62 | −4.68 | −4.50 | >−4.00 | >−4.00 | >−4.00 | −4.7 |
| HOP-92 | −4.77 | −4.65 | −4.18 | −4.02 | >4.00 | −3.8 |
| NCI-H226 | −4.58 | −4.58 | >−4.00 | >−4.00 | >4.00 | −3.6 |
| NCI-H23 | −4.61 | −4.59 | >−4.00 | >−4.00 | >−4.00 | −4.9 |
| NCI-H322M | −4.45 | −4.49 | >−4.00 | >−4.00 | >−4.00 | −4.7 |
| NCI-H460 | −4.70 | −4.70 | >−4.00 | >−4.00 | >−4.00 | −6.0 |
| NCI-H522 | −4.58 | −4.87 | >−4.00 | >−4.00 | >−4.00 | −4.4 |
| *Colon cancer* | | | | | | |
| COLO 205 | −4.59 | −4.83 | >−4.00 | >−4.00 | >−4.00 | −5.2 |
| HCC-2998 | −4.62 | −4.53 | >−4.00 | >−4.00 | >−4.00 | −5.8 |
| HCT-116 | −4.76 | −4.59 | −4.04 | >−4.00 | >4.00 | −6.4 |
| HCT-15 | −4.50 | −4.55 | >−4.00 | >−4.00 | >−4.00 | −5.2 |
| HT29 | −4.62 | −4.77 | >−4.00 | >−4.00 | >4.00 | −5.2 |
| KM12 | −4.69 | −4.59 | >−4.00 | >−4.00 | >−4.00 | −5.0 |
| SW-620 | −4.56 | −4.52 | >−4.00 | >−4.00 | >−4.00 | −4.6 |
| *CNS cancer* | | | | | | |
| SF-268 | −4.57 | −4.62 | >−4.00 | >−4.00 | >−4.00 | −4.3 |
| SF-295 | −4.52 | −4.57 | >−4.00 | >−4.00 | >−4.00 | −4.3 |
| SF-539 | −4.63 | −4.65 | >−4.00 | >−4.00 | >−4.00 | −5.9 |
| SNB-19 | −4.42 | −4.50 | >−4.00 | >−4.00 | >−4.00 | −3.9 |
| SNB-75 | −4.64 | −4.68 | >−4.00 | >−4.00 | >−4.00 | −3.7 |
| U251 | −4.61 | −4.55 | >−4.00 | >−4.00 | >−4.00 | −4.4 |
| *Melanoma* | | | | | | |
| LOX IMVI | −4.75 | −4.77 | >−4.00 | >−4.00 | >−4.00 | −5.2 |
| MALME-3M | −4.67 | −4.67 | >−4.00 | >−4.00 | >−4.00 | −4.7 |
| SK-MEL-28 | −4.54 | −4.58 | >−4.00 | >−4.00 | >−4.00 | −4.3 |
| SK-MEL-5 | −4.82 | −4.77 | >−4.00 | >−4.00 | >−4.00 | −4.9 |
| UACC-257 | −4.67 | −4.72 | >−4.00 | >−4.00 | >−4.00 | −4.0 |
| UACC-62 | −4.80 | −4.78 | >−4.00 | >−4.00 | >−4.00 | −4.9 |
| *Ovarian cancer* | | | | | | |
| IGROV1 | Nd | −4.96 | −4.23 | >−4.00 | >−4.00 | −4.9 |
| OVCAR-3 | −4.58 | −4.71 | >−4.00 | >−4.00 | >−4.00 | −4.6 |
| OVCAR-4 | −4.49 | −4.61 | >−4.00 | >−4.00 | >−4.00 | −4.2 |
| OVCAR-5 | −4.59 | −4.64 | >−4.00 | >−4.00 | >−4.00 | −3.8 |
| OVCAR-8 | −4.51 | −4.58 | >−4.00 | >−4.00 | >−4.00 | −4.7 |
| SK-OV-3 | −4.40 | −4.63 | >−4.00 | >−4.00 | >−4.00 | −3.8 |
| *Renal cancer* | | | | | | |
| 786-0 | −4.65 | −4.58 | >−4.00 | >−4.00 | >−4.00 | −4.9 |
| A498 | −4.61 | −4.64 | >−4.00 | >−4.00 | >−4.00 | −5.0 |
| ACHN | −4.55 | −4.56 | >−4.00 | >−4.00 | >−4.00 | −5.0 |
| CAKI-1 | −4.57 | −4.49 | >−4.00 | >−4.00 | >−4.00 | −5.4 |
| RXF 393 | −4.68 | −4.73 | −4.28 | −4.55 | >−4.00 | −4.3 |
| SN12C | −4.77 | −4.68 | >−4.00 | >−4.00 | >−4.00 | −4.6 |
| TK-10 | −4.52 | −4.68 | >−4.00 | >−4.00 | >−4.00 | −3.9 |
| UO-31 | −4.71 | −4.64 | >−4.00 | >−4.00 | >−4.00 | −5.3 |
| *Prostate cancer* | | | | | | |
| PC-3 | −4.70 | −4.62 | >4.00 | >−4.00 | >−4.00 | −4.3 |
| DU-145 | −4.66 | −4.57 | >4.00 | >−4.00 | >−4.00 | −5.0 |
| *Breast cancer* | | | | | | |
| MCF7 | −4.52 | −4.57 | >−4.00 | >−4.00 | >−4.00 | −5.8 |

**Table 1** (*continued*)

| Panel/Cell line | Compound | | | | | |
|---|---|---|---|---|---|---|
| | **12** | **13** | **14** | **15** | **16** | 5-Fluorouracil |
| NCI/ADR-RES | −4.52 | −4.53 | >−4.00 | >−4.00 | >−4.00 | −4.4 |
| MDA-MB-2321/ATCC | −4.71 | −4.73 | >−4.00 | >−4.00 | >−4.00 | −3.3 |
| HS 578T | −4.74 | −4.79 | −4.35 | −4.40 | >−4.00 | −3.6 |
| MDA-MB-435 | −4.64 | −4.79 | >−4.00 | >−4.00 | >−4.00 | −5.0 |
| BT-549 | −4.78 | −4.77 | >−4.00 | >−4.00 | >−4.00 | −4.0 |

nd: not done (the evaluation has not been performed at this cell line).

cancer cell lines while compounds **14** and **15** show activity against HOP-92, HS 578T, and CCRF-CEM cell lines. The anti-cancer properties of these compounds along with their potential as moderate COX-2 inhibitors could provide a dual advantage in the chemotherapy of cancer.

## 4. Conclusions

Appreciable anti-cancer activities have been observed for compounds **12**, **13**, **14**, and **15** at various human tumor cell lines. Compound **12** is highly specific for CCRF-CEM and SR cell lines of leukemia showing 71% and 87% growth inhibition of tumor cells at $10^{-6}$ M concentration.

## 5. Experimental

### 5.1. General details

Melting points were determined in capillaries and are uncorrected. $^{1}H$ and $^{13}C$ NMR spectra were run on JEOL 300 MHz and 75 MHz NMR, respectively, using $CDCl_3$ as solvent. Chemical shifts are given in ppm with TMS as an internal reference. *J* values are given in Hertz. Chromatography was performed with silica 100–200 mesh and reactions were monitored by thin layer chromatography (TLC) with silica plates coated with silica gel HF-254.

### 5.2. General procedure: Synthesis of substituted benzoins

Mixing of the solutions of appropriate benzaldehyde (24 mmol) in alcohol and NaCN (10 mmol) in water was followed by refluxing for 1 h. The reaction mixture was washed with sodium bicarbonate solution and extracted with ether. Removal of ether and column chromatography of the residue using ethyl acetate and hexane as eluent provided the pure benzoins.

**5.2.1. 1,2-Bis-(4-chloro-phenyl)-2-hydroxy-ethanone (1).** Yield 39%; light yellow solid, mp 78 °C ($CHCl_3$); IR (KBr, $cm^{-1}$): 1678 (C=O), 3380 (OH); $^{1}H$ NMR (300 MHz): $\delta$ 4.51 (d, $J$ = 5.7 Hz, 1H, OH, exchanges with $D_2O$), 5.88 (d, $J$ = 4.5 Hz 1H, CH), 7.24 (d, $J$ = 8.4 Hz, 2H, ArH), 7.30 (d, $J$ = 8.4 Hz, 2H, ArH), 7.38 (d, $J$ = 8.4 Hz, 2H, ArH), 7.82 (d, $J$ = 8.4 Hz, 2H, ArH); $^{13}C$ NMR (normal/DEPT-135) (75 MHz): $\delta$ 75.43 (+ve, CH), 129.01 (+ve, CH), 129.38 (+ve, CH), 129.46 (+ve, CH), 130.38 (+ve, CH), 131.53 (ab, C), 134.71 (ab, C), 137.12 (ab, C), 140.64 (ab, C), 197.46 (ab, C=O); FAB-MS *m/z* 281 ($M^+$); Anal. calcd for $C_{14}H_{10}Cl_2O_2$; C, 59.81; H, 3.59 Found: C, 59.53%, H, 3.34%.

**5.2.2. 1,2-Bis-(2-chloro-phenyl)-2-hydroxy-ethanone (2).** Yield 40%; light yellow solid, mp 58 °C ($CHCl_3$) (lit.[9] mp 58 °C); IR (KBr, $cm^{-1}$): 1701 (C=O), 3584 (OH); $^{1}H$ NMR (300 MHz): $\delta$ 4.44 (s, 1H, OH, exchanges with $D_2O$), 6.35 (s, 1H, CH), 7.16–7.28 (m, 6H, ArH), 7.30–7.38 (m, 2H, ArH); $^{13}C$ NMR (normal/DEPT-135) (75 MHz): $\delta$ 75.38 (+ve, CH), 126.51 (+ve, CH), 127.32 (+ve, CH), 128.98 (+ve, CH), 129.27 (+ve, CH), 129.92 (ab, C), 129.98 (+ve, CH), 130.46 (+ve, CH), 132.31 (+ve, CH), 133.81 (ab, C), 134.70 (ab, C), 135.40 (ab, C), 197.46 (ab, C=O); FAB-MS *m/z* 281 ($M^+$); Anal. calcd for $C_{14}H_{10}Cl_2O_2$; C, 59.81; H, 3.59 Found: C, 59.52%, H, 3.36%.

**5.2.3. 1,2-Bis-(4-fluoro-phenyl)-2-hydroxy-ethanone (3).** Yield 45%; white solid, mp 67 °C ($CHCl_3$); IR (KBr, $cm^{-1}$): 1683 (C=O), 3375 (OH); $^{1}H$ NMR (300 MHz): $\delta$ 4.49 (bs, 1H, OH, exchanges with $D_2O$), 5.91 (s, 1H, CH), 6.95-7.10 (m, 4H, ArH), 7.24–7.32 (m, 2H, ArH), 7.90–7.95 (m, 2H, ArH); $^{13}C$ NMR (normal/DEPT-135) (75 MHz): $\delta$ 75.30 (+ve, CH), 115.74 (+ve, CH), 116.32 (+ve, CH), 129.45 (+ve, CH), 129.56 (+ve, CH), 131.77 (+ve, CH), 131.89 (+ve, CH), 161.08 (ab, C), 164.33 (ab, C), 164.36 (ab, C), 197.16 (ab, C=O); FAB-MS *m/z* 248 ($M^+$); Anal. calcd for $C_{14}H_{10}F_2O_2$; C 67.74, H 4.06. Found: C 67.45%, H 4.01%.

**5.2.4. 2-Hydroxy-1,2-bis-(4-methoxy-phenyl)-ethanone (4).** Yield 38%; white solid, mp 42 °C ($CHCl_3$); IR (KBr, $cm^{-1}$): 1666 (C=O), 3392 (OH); $^{1}H$ NMR (300 MHz): $\delta$ 3.75 (s, 3H, $OCH_3$), $\delta$ 3.82 (s, 3H, $OCH_3$), 4.59 (d, $J$ = 6.0 Hz, 1H, OH, exchanges with $D_2O$), 5.85 (d, $J$ = 6.0 Hz 1H, CH), 6.82 (d, $J$ = 5.1 Hz, 2H, ArH), 6.86 (d, $J$ = 5.1 Hz, 2H, ArH), 7.24 (d, $J$ = 8.4 Hz, 2H, ArH), 7.89 (d, $J$ = 8.4 Hz, 2H, ArH); $^{13}C$ NMR (normal/DEPT-135) (75 MHz): $\delta$ 55.18 (+ve, $CH_3$), 55.43 (+ve, $CH_3$), 75.19 (+ve, CH), 113.87 (+ve, CH), 114.45 (+ve, CH), 126.24 (ab, C), 128.96 (+ve, CH), 131.52(ab, C), 131.79 (+ve, CH), 159.58 (ab, C), 163.93 (ab, C), 197.27 (ab, C=O); FAB-MS *m/z* 272 ($M^+$); Anal. calcd for $C_{16}H_{16}O_4$; C 70.57, H 5.92. Found: C 70.35%, H 5.76%.

**5.2.5. 2-Hydroxy-1,2-bis-(4-methylsulfanyl-phenyl)-ethanone (5).** Yield 50%; white solid, mp 106 °C ($CHCl_3$); IR (KBr, $cm^{-1}$): 1677 (C=O), 3400 (OH); $^{1}H$ NMR

(300 MHz): $\delta$ 2.43 (s, 3 H, $SCH_3$), $\delta$ 2.47 (s, 3H, $SCH_3$), 5.85 (s, 1H, CH), 7.16–7.24 (m, 6H, ArH), 7.80 (dd, $^1J$ = 6.6 hz, $^2J$ = 1.8 Hz, 2H, ArH); $^{13}$C NMR (normal/DEPT-135) (75 MHz): $\delta$ 14.50 (+ve, $CH_3$), 15.43 (+ve, $CH_3$), 75.43 (+ve, CH), 124.79 (+ve, CH), 126.80 (+ve, CH), 128.12 (+ve, CH), 129.33 (ab, C), 129.43 (+ve, CH), 135.84 (ab, C), 139.24 (ab, C), 147.46 (ab, C), 197.54 (ab, C=O); FAB-MS *m/z* 304 ($M^+$); Anal. calcd for $C_{16}H_{16}O_2S_2$; C 63.13, H 5.30. Found: C 63.01%, H 5.13%.

### 5.3. Indium mediated allylation of substituted benzoins homoallylic alcohols

Substituted benzoin **1**–**5** (5 mmol), allyl bromide (7.5 mmol), and indium metal (5 mmol) were taken in THF–$H_2O$ (2:1) mixture (10 ml) and the reaction mixture was stirred at 0 °C until the indium metal was dissolved. The turbid reaction mixture was treated with 4N HCl and was extracted with $CHCl_3$ (3× 25 ml). The organic phase was dried over $Na_2SO_4$. The solvent was distilled off at low temperature and the residue was column chromatographed (silica gel, 60–120 mesh) using ethyl acetate, hexane as eluents to isolate pure homoallylic alcohol.

**5.3.1. (1*R**, 2*S**)-1,2-Bis(4-chloro-phenyl)-pent-4-ene-1,2-diol (6).** 80%, white solid, mp 92 °C, $^1$H NMR (300 MHz): IR (KBr, cm$^{-1}$): 3348 (OH), 3421 (OH); $\delta$ 2.61 (bs, 2H, 2 x OH), 2.71 (dd, $^1J$ = 14 Hz, $^2J$ = 8.7 Hz, 1H, 1H of $CH_2$), 2.87 (dd, $^1J$ = 14 Hz, $^2J$ = 5.4 Hz, 1H, 1H of $CH_2$), 4.72 (s, 1H, CH), 5.12–5.21 (m, 2H,=$CH_2$), 5.49–5.59 (m, 1H, CH), 6.92–7.26 (m, 8H, ArH); $^{13}$C NMR (normal/DEPT-135) (75 MHz): $\delta$ 42.54 (−ve, $CH_2$), 77.97(ab, C), 79.68 (+ve, CH), 120.49 (−ve, $CH_2$), 127.75 (+ve, CH), 127.99 (+ve, CH), 129.14 (+ve, CH), 131.54 (+ve, CH), 132.55 (+ve, CH), 133.03 (ab, C), 133.59 (ab, C), 137.62 (ab, C) 139.84 (ab, C); FAB-MS *m/z* 323, 325, 327 (100:69:1) ($M^+$); Anal. calcd for $C_{17}H_{16}O_2Cl_2$; C 63.17, H 4.99. Found: C 63.0%, H 4.7%.

**5.3.2. (1*R**, 2*S**)-1,2-Bis-(2-chloro-phenyl)-pent-4-ene-1,2-diol (7).** Yield 79%; white solid, mp 114 °C ($CHCl_3$); IR (KBr, cm$^{-1}$): 3350 (OH), 3425 (OH); $^1$H NMR (300 MHz): $\delta$ 2.81 (s, 1H, OH, exchanges with $D_2O$), 2.94 (dd, $^1J$ = 14.4 Hz, $^2J$ = 8.7 Hz, 1H, 1H of $CH_2$), 3.66 (dd, $^1J$ = 14.4 Hz, $^2J$ = 6.0 Hz, 1H, 1H of $CH_2$), 5.08–5.24 (m, 2H, =$CH_2$), 5.46–5.61 (m, 1H, =CH), 5.93 (s, 1H, CH), 7.02–7.08 (m, 4H, ArH), 7.14–7.20 (m, 2H, ArH), 7.51–7.54 (m, 1H, ArH), 7.57–7.61 (m, 1H, ArH); $^{13}$C NMR (normal/DEPT-135) (75 MHz): $\delta$ 42.08 (−ve, $CH_2$), 72.54 (+ve, CH), 78.97 (ab, C), 119.73 (−ve, $CH_2$), 126.17 (+ve, CH), 126.24 (+ve, CH), 128.45 (+ve, CH), 128.70 (+ve, CH), 129.18 (+ve, CH), 129.88 (+ve, CH), 130.23 (+ve, CH), 130.81 (+ve, CH), 131.01 (ab, C), 133.32 (+ve, CH), 134.07 (ab, C), 137.48 (ab, C), 139.00 (ab, C); FAB-MS *m/z* 323 ($M^+$); Anal. calcd for $C_{17}H_{16}Cl_2O_2$; C 63.17, H 4.99. Found: C 63.05%, H 4.89%.

**5.3.3. (1*R**, 2*S**)-1,2-Bis-(4-fluoro-phenyl)-pent-4-ene-1,2-diol (8).** Yield 75%; white solid, mp 60 °C ($CHCl_3$); IR (KBr, cm$^{-1}$): 3342 (OH), 3420 (OH); $^1$H NMR (300 MHz): $\delta$ 2.73 (dd, $^1J$ = 14.1 Hz, $^2J$ = 8.4 Hz, 1H, 1H of $CH_2$), 2.85 (dd, $^1J$ = 14.1 Hz, $^2J$ = 5.7 Hz, 1H, 1H of $CH_2$), 4.69 (s, 1H, CH), 5.08–5.27 (m, 2H,=$CH_2$), 5.47–5.61 (m, 1H, =CH), 6.78–6.94 (m, 6H, ArH), 6.01–7.25 (m, 2H, ArH; $^{13}$C NMR (normal/DEPT-135) (75 MHz): $\delta$ 42.52 (−ve, $CH_2$), 77.98 (ab, C), 79.63 (+ve, CH), 114.15 (+ve, CH), 114.43 (+ve, CH), 120.10 (−ve, $CH_2$), 128.14 (+ve, CH), 129.27 (+ve, CH), 132.75 (+ve, CH), 134.91 (ab, C), 136.90 (ab, C), 160.12 (ab, C), 163.36 (ab, C); FAB-MS *m/z* 290 ($M^+$); Anal. calcd for $C_{17}H_{16}F_2O_2$; C 70.33, H 5.56. Found: C 70.01%, H 5.25%.

**5.3.4. (1*R**, 2*S**)-1,2-Bis(4-methoxy-phenyl)-pent-4-ene-1,2-diol (9).** 72%, white solid, mp 90 °C; IR (KBr, cm$^{-1}$): 3369 (OH), 3404 (OH); $^1$H NMR (300 MHz): $\delta$ 2.59 (bs, 2H, 2xOH, exchanges with $D_2O$), 2.68 (dd, $^1J$ = 14 Hz, $^2J$ = 8.7 Hz, 1H, 1H of $CH_2$), 2.85 (dd, $^1J$ = 14 Hz, $^2J$ = 5.4 Hz, 1H, 1H of $CH_2$), 3.73 (s, 3H, $OCH_3$), 3.75 (s, 3H, $OCH_3$), 4.74 (s, 1H, CH), 5.07–5.18 (m, 2H, =$CH_2$), 5.52–5.63 (m, 1H, CH), 6.67 (d, $J$ = 9 hz, 2H, Ar-3H), 6.72 (d, $J$ = 9 Hz, 2H, ArH), 6.91 (d, $J$ = 9 Hz, 2H, ArH), 7.03 (d, $J$ = 9 Hz, 2H, ArH); The decoupling of 2H doublet at $\delta$ 6.91 converts doublet at $\delta$ 6.67 into singlet and decoupling of doublet at $\delta$ 7.03 converts doublet at $\delta$ 6.72 into singlet. This indicates that two doublets at $\delta$ 7.03 and $\delta$ 6.72 and two doublets at $\delta$ 6.67 and $\delta$ 6.91 are due to protons of the same ring.$^{13}$C NMR (normal/DEPT-135) (75 MHz): $\delta$ 42.39 (−ve, $CH_2$), 55.04 (+ve, $OCH_3$), 55.37 (+ve, $OCH_3$), 78.14 (ab, C), 80.11 (+ve, CH), 112.74 (+ve, CH), 112.79 (+ve, CH), 119.54 (−ve, $CH_2$), 127.85 (+ve, CH), 128.93 (+ve, CH), 131.49 (ab, C), 133.42 (+ve, CH), 133.45 (ab, C), 158.33 (ab, C), 158.91 (ab, C). FAB-MS *m/z* 314 ($M^+$); Anal. calcd for $C_{19}H_{22}O_{4;}$C 72.59, H 7.05% Found C 72.30%, H 6.98%.

**5.3.5. (1*R**, 2*S**)-1,2-Bis-(4-methanesulfanyl-phenyl)-pent-4-ene-1,2-diol (10).** Yield 82%; white solid, mp 112 °C ($CHCl_3$); IR (KBr, cm$^{-1}$): 3375 (OH), 3420 (OH); $^1$H NMR (300 MHz): $\delta$ 2.43 (s, 3H, $SCH_3$), 2.45 (s, 3H, $SCH_3$), 2.57 (s, 1H, OH, exchanges with $D_2O$), 2.70 (dd, $^1J$ = 14.1 Hz, $^2J$ = 8.4 Hz, 1H, 1H of $CH_2$), 2.87 (dd, $^1J$ = 14.1 Hz, $^2J$ = 5.7 Hz, 1H, 1H of $CH_2$), 4.74 (s, 1H, CH), 5.08–5.19 (m, 2H,=$CH_2$), 5.49–5.62 (m, 1H, =CH), 6.93 (d, $J$ = 8.4 Hz, 2H, ArH), 7.03–7.12 (m, 6H, ArH); $^{13}$C NMR (normal/DEPT-135) (75 MHz): $\delta$ 15.61 (+ve, $CH_3$), 15.62 (+ve, $CH_3$), 42.37 (−ve, $CH_2$), 78.12 (ab, C), 80.06 (+ve, CH), 120.01 (−ve, $CH_2$), 125.52 (+ve, CH), 125.63 (+ve, CH), 127.15 (+ve, CH), 128.29 (+ve, CH), 133.02 (+ve, CH), 136.04 (ab, C), 139.82 (ab, C), 142.35 (ab, C), 142.65 (ab, C); FAB-MS *m/z* 346 ($M^+$); Anal. calcd for $C_{19}H_{22}O_2S_2$; C 65.86, H 6.40. Found: C 65.62%, H 6.34%.

### 5.4. Oxone mediated conversion of methane sulfanyl (10) to methanesulfonyl (11)

To the ice cold solution of 1,2-Bis-(4-methanesulfanyl-phenyl)-pent-4-ene-1,2-diol (10 mmol) in THF–$H_2O$ (1:1) was added oxone (20 mmol) and the reaction mixture

was stirred at 0 °C for 2 h. After the completion of reaction (TLC monitoring), the reaction mixture was extracted with ethyl acetate. The organic phase was dried over $Na_2SO_4$. The solvent was distilled off under vacuum and the pure compound was isolated by washing with $CHCl_3$–diethyl ether (1:20).

**5.4.1. (1*R**, 2*S**)-1,2-Bis-(4-methanesulfonyl-phenyl)-pent-4-ene-1,2-diol (11).** Yield 90%; white solid, mp 145 °C ($CH_3OH$); IR (KBr, $cm^{-1}$): 3370 (OH), 3405 (OH); $^1H$ NMR (300 MHz): $\delta$ 2.84 (dd, $^1J$ = 14.1 Hz, $^2J$ = 8.4 Hz, 1H, 1H of $CH_2$), 2.96 (dd, $^1J$ = 14.1 Hz, $^2J$ = 6.0 Hz, 1H, 1H of $CH_2$), 2.98 (s, 3H, $SO_2CH_3$), 3.02 (s, 3H, $SO_2CH_3$), 4.89 (s, 1H, CH), 5.09–5.19 (m, 2H,=$CH_2$), 5.43–5.57 (m, 1H, =CH), 7.22 (d, $J$ = 7.5 hz, 2H, ArH), 7.40 (d,$J$ = 7.5 Hz, 2H, ArH), 7.62 (d,$J$ = 7.5 Hz, 2H, ArH), 7.74 (d,$J$ = 7.5 Hz, 2H, ArH); $^{13}C$ NMR (normal/DEPT-135) (75 MHz): $\delta$ 42.57 (−ve, $CH_2$), 44.18 (+ve, $CH_3$), 44.24 (+ve, $CH_3$), 78.71 (ab, C), 79.44 (+ve, CH), 122.46 (−ve, $CH_2$), 126.86 (+ve, CH), 127.13 (+ve, CH), 127.83 (+ve, CH), 129.22 (+ve, CH), 130.41 (+ve, CH), 144.69 (ab, C), 160.55 (ab, C), 161.13 (ab, C), 162.28 (ab, C); FAB-MS *m*/*z* 410 ($M^+$); Anal. calcd for $C_{19}H_{22}O_6S_2$; C 55.59, H 5.40. Found: C 55.33%, H 5.16%.

### 5.5. *m*-CPBA mediated cyclization of homoallylic alcohols

*m*-CPBA (10 mmol) was added to an ice cold solution of appropriate homoallylic alcohol (**6**–**9**, **11**) (5 mmol) in $CH_2Cl_2$ and the reaction mixture was stirred for 24 h at 0 °C (TLC monitoring). The reaction mixture was neutralized with sodium bicarbonate followed by extraction with $CH_2Cl_2$. The organic layer was dried over anhydrous sodium sulfate and distilled off. The residue was column chromatographed (silica gel 100–200) using ethyl acetate, hexane as eluents to get pure product.

**5.5.1. (2*R**, 3*S**, 5*R**)-2,3-Bis-(4-chloro-phenyl)-5-hydroxymethyl-tetrahydro-furan-3-ol (12).** Yield 58%; white solid, mp 120 °C (ethanol); IR (KBr, $cm^{-1}$): 3400 (OH); $^1H$ NMR (300 MHz): $\delta$ 2.42 (dd, $^1J$ = 14.1 Hz, $^2J$ = 3.3 Hz, 1H, H-4), 2.95 (dd, $^1J$ = 14.1 Hz, $^2J$ = 10.0 Hz, 1H, H-4), 3.73 (dd, $^1J$ = 11.4 Hz, $^2J$ = 2.1 Hz, 1H, C$H_2$OH), 4.09 (dd, $^1J$ = 6.0 Hz, $^2J$ = 4.2 Hz, 1H, C$H_2$OH), 4.55–4.61 (m, 1H, H-5), 4.99 (s, 1H, H-2), 6.95 (d, $J$ = 8.4 Hz, 2H, ArH), 7.17 (d, $J$ = 8.4 Hz, 2H, ArH), 7.33 (d, $J$ = 2.1 Hz, 4H, ArH); $^{13}C$ NMR (normal/DEPT-135) (75 MHz): $\delta$ 44.73 (−ve, C-4), 64.31 (−ve, $CH_2OH$), 77.00 (+ve, C-5), 80.89 (ab, C-3), 89.45 (+ve, C-2), 127.04 (+ve, CH), 127.96 (+ve, CH), 128.14 (+ve, CH), 128.44 (+ve, CH), 133.12 (ab, C), 133.74 (ab, C) 139.24 (ab, C). The observation of NOE between H-2 and H-5 shows their syn orientation. FAB-MS *m*/*z* 321 ($M^+$- $H_2O$); Anal. calcd for $C_{17}H_{16}Cl_2O_3$; C 60.19%, H 4.75%. Found: C 60.28%, H 4.59%.

**5.5.2. (2*R**, 3*S**, 5*R**)-2,3-Bis-(2-chloro-phenyl)-5-hydroxymethyl-tetrahydro-furan-3-ol (13).** Yield 55%; white solid, mp 90 °C (ethanol); IR (KBr, $cm^{-1}$): 3407 (OH); $^1H$ NMR (300 MHz): $\delta$ 2.23 (dd, $^1J$ = 14.1 Hz, $^2J$ = 5.1 Hz, 1H, H-4), 3.68 (dd, $^1J$ = 14.1 Hz, $^2J$ = 9.9 Hz, 1H, H-4), 3.80 (dd, $^1J$ = 11.7 Hz, $^2J$ = 3.3 Hz, 1H, C$H_2$OH), 4.11 (dd, $^1J$ = 11.4 Hz, $^2J$ = 2.1 Hz, 1H, C$H_2$OH), 4.65–4.72 (m, 1H, H-5), 6.24 (s, 1H, H-2), 7.12–7.31 (m, 5H, ArH), 7.38 (dd, $^1J$ = 7.5 Hz, $^2J$ = 2.1 Hz, 1H, ArH), 7.52 (dd, $^1J$ = 7.5 Hz, $^2J$ = 2.1 Hz, 1H, ArH), 7.77 (dd, $^1J$ = 7.8 Hz, $^2J$ = 1.5 Hz, 1H, ArH); $^{13}C$ NMR (normal/DEPT-135) (75 MHz): $\delta$ 41.46 (−ve, C-4), 64.49 (−ve, $CH_2OH$), 77.29 (+ve, C-5), 81.34 (ab, C-3), 82.20 (+ve, C-2), 126.17 (+ve, CH), 126.85 (+ve, CH), 128.66 (+ve, CH), 128.85 (+ve, CH), 129.05 (+ve, CH), 129.33 (+ve, CH), 130.56 (+ve, CH), 131.106 (+ve, CH), 131.82 (ab, C), 133.14 (ab, C) 133.52 (ab, C), 137.64 (ab, C). FAB-MS *m*/*z* 321 ($M^+$-$H_2O$); Anal. calcd for $C_{17}H_{16}Cl_2O_3$; C 60.19%, H 4.75%. Found: C 60.11%, H 4.83%.

**5.5.3. (2*R**, 3*S**, 5*R**)-2,3-Bis-(4-fluoro-phenyl)-5-hydroxymethyl-tetrahydro-furan-3-ol (14).** Yield 61%; white solid, mp 70 °C (ethanol); IR (KBr, $cm^{-1}$): 3395 (OH); $^1H$ NMR (300 MHz): $\delta$ 2.44 (dd, $^1J$ = 13.8 Hz, $^2J$ = 3.6 Hz, 1H, H-4), 2.85 (dd, $^1J$ = 13.8 Hz, $^2J$ = 10.2 Hz, 1H, H-4), 3.78 (dd, $^1J$ = 11.4 Hz, $^2J$ = 2.7 Hz, 1H, C$H_2$OH), 4.11 (dd, $^1J$ = 11.4 Hz, $^2J$ = 2.1 Hz, 1H, C$H_2$OH), 4.59 (ddd, $^1J$ = 11.4 Hz, $^2J$ = 5.7 Hz, $^3J$ = 2.4 Hz, 1H, H-5), 5.04 (s, 1H, H-2), 6.87–6.94 (m, 2H, ArH), 6.98–7.06 (m, 4H, ArH), 7.36 (d, $J$ = 5.1 Hz, 1H, ArH), 7.39 (d, $J$ = 5.1 Hz, 1H, ArH); $^{13}C$ NMR (normal/DEPT-135) (75 MHz): $\delta$ 44.65 (−ve, C-4), 64.42 (−ve, $CH_2OH$), 76.58 (+ve, C-5), 80.86 (ab, C-3), 89.47 (+ve, C-2), 114.58 (+ve, CH), 114.86 (+ve, CH), 114.97 (+ve, CH), 115.25 (+ve, CH), 127.20 (+ve, CH), 127.31 (+ve, CH), 128.58 (+ve, CH), 130.87 (+ve, CH), 130.87 (ab, C), 131.62 (ab, C), 132.5 (ab, C), 133.72 (ab, C). FAB-MS *m*/*z* 289 ($M^+$-OH); Anal. calcd for $C_{17}H_{16}F_2O_3$; C 66.66%, H 5.27%. Found: C 66.73%, H 5.40%.

**5.5.4. (2*R**, 3*S**, 5*R**)-5-Hydroxymethyl-2,3-bis-(4-methoxy-phenyl)-tetrahydro-furan-3-ol (15).** Yield 55%; white solid, mp 105 °C (ethanol); IR (KBr, $cm^{-1}$): 3420 (OH); $^1H$ NMR (300 MHz): $\delta$ 2.38 (dd, $^1J$ = 14.1 Hz, $^2J$ = 3.3 Hz, 1H, H-4), 2.78 (dd, $^1J$ = 14.1 Hz, $^2J$ = 9.9 Hz, 1H, H-4), 3.72 (dd, $^1J$ = 13.5 Hz, $^2J$ = 2.4 Hz, 1H, C$H_2$OH), 3.73 (s, 3H, $OCH_3$), 3.79 (s, 3H, $OCH_3$), 4.01 (dd, $^1J$ = 13.5 Hz, $^2J$ = 1.8 Hz, 1H, C$H_2$OH), 4.52–4.56 (m, 1H, H-5), 5.05 (s, 1H, H-2), 6.74 (d, $J$ = 8.4 Hz, 2H, ArH), 6.86 (d, $J$ = 8.7 Hz, 2H, ArH), 6.99 (d, $J$ = 8.4 Hz, 2H, ArH), 7.29 (d, $J$ = 8.7 Hz, 2H, ArH); $^{13}C$ NMR (normal/DEPT-135) (75 MHz): $\delta$ 44.42 (−ve, C-4), 55.09 (+ve, $CH_3$), 55.18 (+ve, $CH_3$), 64.61 (−ve, $CH_2OH$), 77.12 (+ve, C-5), 81.11 (ab, C-3), 89.41 (+ve, C-2), 113.32 (+ve, CH), 113.55 (+ve, CH), 126.62 (+ve, CH), 127.13 (ab, C), 128.09 (+ve, CH), 133.23 (ab, C), 158.55 (ab, C) 159.28 (ab, C). FAB-MS *m*/*z* 313 ($M^+$- OH); Anal. calcd for $C_{19}H_{22}O_5$; C 69.07%, H 6.71%. Found: C 69.25%, H 6.89%.

**5.5.5. (2*R**, 3*S**, 5*R**)-5-Hydroxymethyl-2,3-bis-(4- methanesulfonyl-phenyl)-tetrahydro-furan-3-ol (16).** Yield 56%; white solid, mp 160 °C (ethanol); IR (KBr,

$cm^{-1}$): 3405 (OH); $^1H$ NMR (300 MHz): $\delta$ 2.60 (dd, $^1J$ = 14.7 Hz, $^2J$ = 2.70 Hz, 1H, H-4), 3.03 (dd, $^1J$ = 14.7 Hz, $^2J$ = 9.9 Hz, 1H, H-4), 3.13 (s, 3H, $CH_3$), 3.22 (s, 3H, $CH_3$), 3.93 (d, $J$ = 11.7 hz', 1H, $CH_2OH$), 4.27 (d, $J$ = 12.0 Hz, 1H, $CH_2OH$), 4.82–4.86 (m, 1H, H-5), 5.34 (s, 1H, H-2), 7.20 (d, $J$ = 8.7 Hz, 2H, ArH), 7.68 (d, $J$ = 8.4 Hz, 2H, ArH), 7.28 (d, $J$ = 8.1 Hz, 2H, ArH), 7.99 (d, $J$ = 8.4 Hz, 2H, ArH); $^{13}C$ NMR (normal/DEPT-135) (75 MHz): $\delta$ 44.19 (+ve, $CH_3$), 44.36 (+ve, $CH_3$), 44.84 (−ve, C-4), 64.09 (−ve, $CH_2OH$), 77.42 (+ve, C-5), 82.56 (ab, C-3), 88.96 (+ve, C-2), 126.86 (+ve, CH), 127.06 (+ve, CH), 127.87 (+ve, CH), 127.92 (+ve, CH), 138.88 (ab, C), 138.90 (ab, C), 140.08 (ab, C), 146.08 (ab, C). FAB-MS *m/z* 427 ($M^+$+1); Anal. calcd for $C_{19}H_{22}O_7S_2$; C 53.51%, H 5.20%, S 15.04%. Found: C 53.59%, H 5.32%, S 15.01%.

**In vitro anti-cancer activities**: The detailed evaluations for anti-cancer activities at 59 human tumor cell lines were carried out by screening unit of NCI at NIH, Bethesda, USA. The compounds were evaluated at five concentrations viz. $10^{-4}$ M, $10^{-5}$ M, $10^{-6}$ M, $10^{-7}$ M, and $10^{-8}$ M. The percentage growth of tumor cells was calculated at each cell line for each concentration of the compound. The results are expressed as growth inhibition of 50% ($GI_{50}$) which is the concentration of the compound causing 50% reduction in the net protein increase (as measured by SRB staining) in control cells during drug incubation, Total Growth Inhibition (TGI), and $LC_{50}$ indicating the net loss of cells following treatment. However, in these studies the particular cellular target of the compounds has not been identified.

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## Supplementary data

In vitro testing results of these compounds showing percent growth of tumor cells of various cell lines at five concentrations, Total Growth Inhibition, and $LC_{50}$ values are given. X-ray structure of 5-hydroxymethyl-2,3-diphenyl-tetrahydro-furan-3-ol has been given, based upon which the relative configurations have been assigned at different chiral centers of compounds **12**–**16**. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmc.2007.04.004.

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