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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

# Multicomponent one-pot synthesis of 2-naphthol derivatives and evaluation of their anticancer activity

**Biswanath Das · Cheruku Ravindra Reddy · Jajula Kashanna · Suman Kumar Mamidyala · Chityal Ganesh Kumar**

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**Abstract** Treatment of 2-naphthol with aldehydes and allyl tributyl stannane or anisole in the presence of $AlCl_3$ at 0°C to room temperature afforded its 1-alkyl derivatives in high yields (76–83%) within 4–8 h. The products were evaluated for their cytotoxic activity against four human cancer cell lines. The most potent compound (**5d**) showed $IC_{50}$ of 1.2 ± 1.1, 1.6 ± 1.0, 0.9 ± 0.1, and 0.8 ± 0.4 μM against Hep $G_2$, A549, MDA 231, and HeLa cell lines, respectively, and its activity was found to be comparable to that of doxorubicin.

**Keywords** 2-Naphthol derivatives · Multicomponent synthesis · $AlCl_3$ · Anticancer activity · Doxorubicin

## Introduction

2-naphthol derivatives are valuable pharmacologic compounds possessing various important biological properties such as antiinflammatory, antibacterial, hypotensive, and bradycardiac activities (Shen *et al.*, 1999, Huang *et al.*, 2003, Chopade *et al.*, 2010). Some of these compounds have recently been prepared by different workers (Shen *et al.*, 1999, Khodaei *et al.*, 2006, Selvam and Perumal, 2006, Das *et al.*, 2007, 2009, 2010, Srihari *et al.*, 2007, Shaterian *et al.*, 2008, Mahdavinia and Bigdeli, 2009, Zhao *et al.*, 2007). However, the multistep procedures are the disadvantages in many of these methods. Herein, we report a simple and efficient one-pot synthesis of different 2-naphthol derivatives. The anticancer activity of these compounds has also been evaluated.

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## Chemistry

In continuation of our work (Das *et al.*, 2007, 2009) on the development of useful synthetic methodologies, we have observed that 2-naphthol (**1**) when treated with aldehydes (**2**) and allyl tributyl stannane (**3**) or anisole (**4**) using $AlCl_3$ as a catalyst afforded its 1-alkyl derivatives (**5** or **6**) at 0°C to room temperature (Scheme 1).

Various 2-naphthol derivatives (**5**, **6**) have been prepared using different aldehydes (**2**) following the above three-component one-pot synthetic method (Table 1). These derivatives included 4,4-diarylbent-1-ene compounds (**5a**–**5g**) and triaryl methanes (**6a**–**6d**). The former were formed within 4–6 h, while the latter in 6–8 h. The yields of the products were high (76–83%). The structures of these derivatives were established from their spectral (IR, $^1H$, $^{13}C$ NMR, and MS) and analytical data. All the prepared compounds were optically inactive.

The mechanism of this multicomponent synthesis involves the initial reaction of 2-naphthol (**1**) with aldehydes (**2**) in the presence of $AlCl_3$ to form the orthoquinone methide intermediate A (Van De Water and Pettus, 2002) which was subsequently attacked by the nucleophile, allyl tributyl stannane (**3**) or anisole (**4**) to afford the products (Scheme 2).

**Scheme 1**

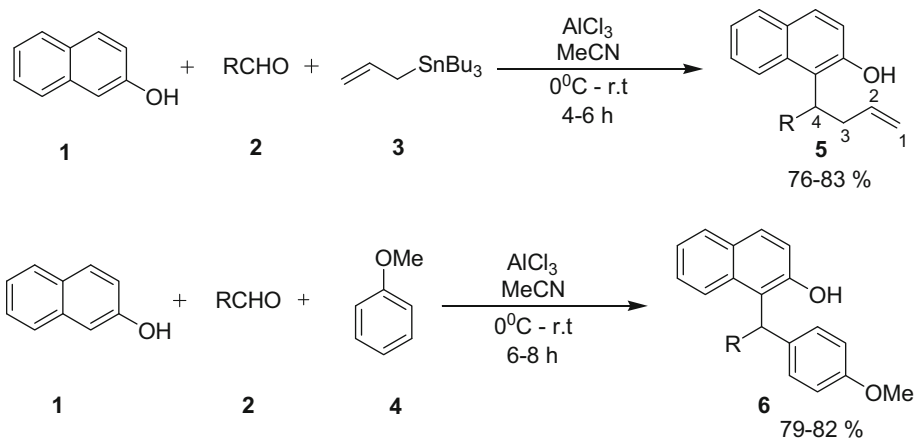



**Table 1** Synthesis of 2-naphthol derivatives (**5**, **6**)

| Entry | *R* | Time (h) | Product | Yield[c](%) |
|---|---|---|---|---|
| 1 | $C_6H_5$ | 5.0 | **5a**[a] | 79 |
| 2 | $C_6H_5$ | 7.0 | **6a**[b] | 81 |
| 3 | 4-Me–$C_6H_4$ | 4.0 | **5b**[a] | 83 |
| 4 | 4-i–Pr–$C_6H_4$ | 4.5 | **5c**[a] | 81 |
| 5 | 4-i–Pr–$C_6H_4$ | 6.0 | **6b**[b] | 82 |
| 6 | 4-F–$C_6H_4$ | 6.0 | **5d**[a] | 78 |
| 7 | 2-F–$C_6H_4$ | 6.5 | **5e**[a] | 77 |
| 8 | 3-F–$C_6H_4$ | 7.0 | **5f**[a] | 80 |
| 9 | 4-F–$C_6H_4$ | 8.0 | **6c**[b] | 79 |
| 10 | 4-Cl–$C_6H_4$ | 6.0 | **5g**[a] | 76 |
| 11 | 4-Cl–$C_6H_4$ | 8.0 | **6d**[b] | 79 |

The structures of the products were established from their spectral (IR, $^1$H, $^{13}$C NMR, and ESI–MS) data

[a] 2-naphthol (1 mmol), aldehyde (1 mmol), allyl tributyl stannane (1.2 mmol), and $AlCl_3$ (10 mol %) were used

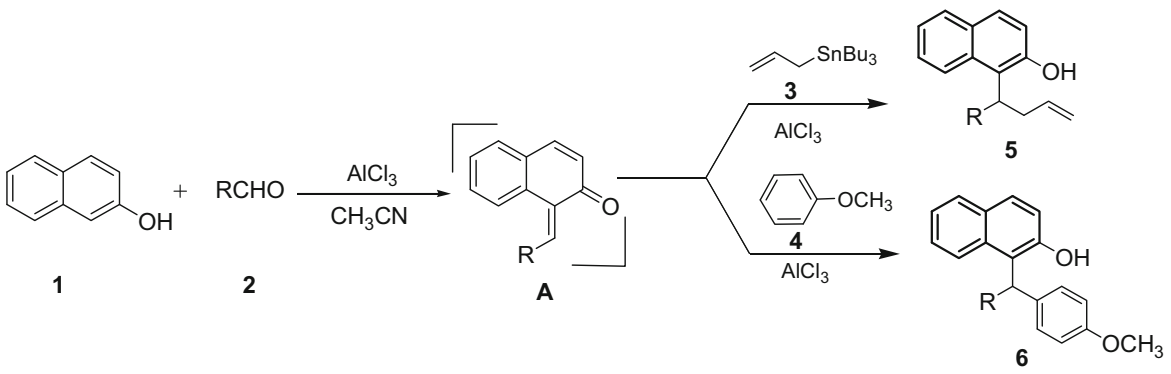
[b] 2-naphthol (1 mmol), aldehyde (1 mmol), anisole (1.2 mmol), and $AlCl_3$ (10 mol %) were used

[c] Isolated yields after purification

The catalyst, $AlCl_3$ is easily available and less expensive. It catalyses the present multicomponent synthesis efficiently for the preparation of 2-naphthol derivatives. It works under mild reaction conditions. The reaction was conducted at 0°C to room temperature. The ether linkage was not affected.

## Bioactivity

The synthetic 2-naphthol derivatives (**5**, **6**) were evaluated for their in vitro cytotoxic activity against four human cancer cell lines including liver (Hep $G_2$), lung (A 549), breast (MDA 231), and cervical (HeLa) by applying MTT assay (Navarra *et al.*, 2010). Doxorubicin was used as a positive control and DMSO as a negative control. $IC_{50}$ values were determined for each compound (Table 2; Fig. 1). The data indicate that the 2-naphthol derivatives containing a propylene chain at the C-1 alkyl group (compounds **5**) are generally more active compared with those having an aromatic ring at the same position (compounds **6**). Moreover, among the products **5**, the compound which contains an unsubstituted phenyl ring (**5a**) exhibits low activity (Table 2, entry 1). However, a compound with a substituted phenyl ring showed higher activity (entries 3, 4, 6, 8). The most active compound, **5d** (entry 6) contains a 4-fluoro phenyl ring and it possess $IC_{50}$ of 1.2 ± 1.1, 1.6 ± 1.0, 0.9 ± 0.1, and 0.8 ± 0.4 μM against Hep $G_2$,




**Scheme 2**

**Table 2** $IC_{50}$ values (μM) of test compounds against different cancer cell lines

| Entry | Sample code | $IC_{50}$ values (μM)[a] | | | |
|---|---|---|---|---|---|
| | | HepG2 | A549 | MDA231 | HeLa |
| 1 | **5a** | 53.0 ± 2.1 | 59.0 ± 3.2 | 33.0 ± 1.4 | 76.0 ± 3.6 |
| 2 | **6a** | 6.2 ± 1.6 | 6.1 ± 2.4 | 5.8 ± 2.5 | 6.3 ± 1.7 |
| 3 | **5b** | 5.6 ± 1.5 | 6.8 ± 1.2 | 6.0 ± 1.4 | 6.2 ± 1.5 |
| 4 | **5c** | 15.0 ± 2.1 | 13.5 ± 3.2 | 16.5 ± 4.5 | 12.5 ± 3.2 |
| 5 | **6b** | 44.0 ± 3.5 | 50.0 ± 2.1 | 37.8 ± 2.8 | 33.0 ± 4.6 |
| 6 | **5d** | 1.2 ± 1.1 | 1.6 ± 1.0 | <1 ± 0.1 | <1 ± 0.4 |
| 7 | **5e** | 9.7 ± 1.5 | 7.8 ± 1.9 | 6.6 ± 1.2 | 6.8 ± 2.1 |
| 8 | **5f** | 6.5 ± 0.9 | 8.6 ± 1.3 | 9.1 ± 1.9 | 8.8 ± 1.1 |
| 9 | **6c** | 14.0 ± 3.5 | 17.2 ± 4.1 | 12.5 ± 2.1 | 11 ± 2.0 |
| 10 | **5 g** | 7.4 ± 1.1 | 9.6 ± 1.2 | 7.6 ± 1.1 | 6.4 ± 1.2 |
| 11 | **6d** | 42.0 ± 3.7 | 44.6 ± 2.4 | 33.2 ± 2.1 | 29.4 ± 2.7 |
| 12 | Doxorubicin | 1.2 ± 0.5 | <1 ± 0.1 | <1 ± 0.1 | <1 ± 0.2 |

No inhibition of growth was observed when 1% DMSO was used as negative control

[a] All tests were performed in duplicate ($n = 2$) and values are represented as mean ± standard deviations

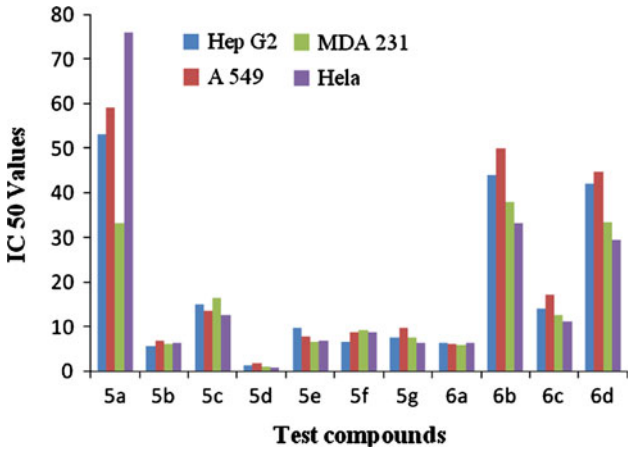



**Fig. 1** $IC_{50}$ values of the test compounds

A 549, MDA 231, and HeLa cell lines, respectively. The activity of the compound is comparable to that of doxorubicin (Table 2). The regioisomers **5e** (containing a 2-fluoro phenyl ring) and **5f** (containing a 3-fluoro phenyl ring) of **5a** exhibited lower activity. The other three compounds **5b**, **5g**, **6a** also possess impressive cytotoxic activity.

## Conclusions

In conclusion, we have developed an efficient method for the conversion of 2-naphthol into its derivatives by reaction with aldehydes and allyl tributyl stannane or anisole in the presence of $AlCl_3$ at 0°C to room temperature. The mild reaction conditions, high yields, operational simplicity, and one-pot conversion are the advantages of the method. The evaluation of cytotoxic property of these 2-naphthol derivatives identified a compound having activity comparable to that of doxorubicin.

## Experimental

### General

All commercially available reagents were used directly without further purification unless otherwise stated. The solvents used were all of AR grade and were distilled under a positive pressure of dry nitrogen atmosphere wherever necessary. The progress of the reactions was monitored by analytical thin layer chromatography (TLC) performed on Merck Silica Gel 60 $F_{254}$ plates. Column chromatography was carried out using silica gel 60–120 mesh (Qingdao Marine Chemical, China). IR spectra were recorded on a Perkin-Elmer RX1 FT-IR spectrophotometer and mass spectra on VG-Autospec micromass. NMR spectra were recorded on Gemini 200 MHz spectrometer with tetramethylsilane as internal standard using $CDCl_3$. The chemical shifts are expressed as $\delta$ values in parts per million (ppm) and the coupling constants ($J$) are given in Hertz (Hz). Yields were of purified compounds and were not optimized. Optical rotations were measured with JASCO DIP 300 digital polarimeter at 25°C.

### General experimental procedure

$AlCl_3$ (10 mol %) was added to a solution of a 2-naphthol (1 mmol), aldehyde (1 mmol), and allyl tributyl stannane or anisole (1.2 mmol) in MeCN (5 ml) at 0°C under $N_2$ atmosphere. The mixture was stirred at room temperature and the reaction was monitored by TLC. After completion, the solvent was removed from the reaction mixture, and water and EtOAc (10 ml each) were added. The organic layer was separated and concentrated. The residue was subjected to column chromatography (silica gel, hexane–EtOAc) to obtain a pure product (**5** or **6**).

### The spectral and analytical data of the unknown products

*1-[1-(4-isopropylphenyl)but-3-enyl]naphthalen-2-ol (**5c**)*

IR: 3449, 1637, 1462, 1219 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 8.02, (1H, d, $J = 8.0$ Hz, Ar–H), 7.71 (1H, d, $J = 8.0$ Hz, Ar–H), 7.60 (1H, d, $J = 8.0$ Hz, Ar–H), 7.40

(1H, *t*, $J = 8.0$ Hz, Ar–H), 7.31–7.20 (4H, m, Ar–H), 7.12 (2H, d, $J = 8.0$ Hz, Ar–H), 6.93 (1H, d, $J = 8.0$ Hz, Ar–H), 5.69 (1H, m, H-2), 5.10–4.92 (2H, m, $H_2$-1), 4.87 (1H, brd, $J = 8.0$ Hz, H-4), 3.13 (1H, m, $CHMe_2$), 3.01–2.81 (2H, m, $H_2$-3), 1.22 (6H, *t*, $J = 7.0$ Hz, $CHMe_2$); $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ 152.2 (Ar–C), 147.0 (Ar–C), 143.4 (Ar–C), 137.0 (Ar–C), 134.6 (C-2), 129.9 (Ar–C), 128.8 (Ar–C), 128.2 (Ar–C), 127.9 (Ar–C), 127.1 (Ar–C), 126.8 (Ar–C), 123.2 (Ar–C), 122.1 (Ar–C), 119.4 (Ar–C), 117.9 (Ar–C), 116.4 (C-1), 40.3 (C-4), 36.2 (C-3), 34.2 ($CHMe_2$), 24.1 ($CHMe_2$); ESIMS: *m/z* 317 $[M + H]^{+\cdot}$; Anal. Calc for $C_{23}H_{24}O$: C 87.34, H 7.60%; Found: C 87.45, H 7.58%.

*1-[1-(4-fluorophenyl)but-3-enyl]naphthalen-2-ol (**5d**)*

IR: 3448, 1630, 1509, 1461, 1270, 1224 $cm^{-1}$; $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 7.91 (1H, d, $J = 8.0$ Hz, Ar–H), 7.70 (1H, d, $J = 8.0$ Hz, Ar–H), 7.58 (1H, d, $J = 8.0$ Hz, Ar–H), 7.39–7.02 (4H, m, Ar–H), 6.98–6.82 (3H, m, Ar–H), 5.69 (1H, m, H-2), 5.10–4.98 (2H, m, $H_2$-1), 4.82 (1H, brd, $J = 7.0$ Hz, H-4), 3.19–3.01 (2H, m, $H_2$-3); $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ 160.2 (d, $J = 280.0$ Hz, Ar–C–F), 151.9 (Ar–C), 137.1 (Ar–C), 133.5 (C-2), 131.1 (Ar–C), 131.0 (Ar–C), 129.9 (Ar–C), 128.8 (Ar–C), 126.8 (Ar–C), 124.3 (Ar–C), 123.2 (Ar–C), 123.0 (Ar–C), 122.0 (Ar–C), 119.1 (Ar–C), 119.0 (d, $J = 8.0$ Hz, Ar–C), 116.2 (C-1), 40.5 (C-4), 36.9 (C-3); ESIMS: *m/z* 293 $[M + H]^{+\cdot}$; Anal. Calc for $C_{20}H_{17}FO$: C 82.19, H 5.82%; Found: C 82.28, H 5.78%.

*1-[1-(2-fluorophenyl)but-3-enyl]naphthalen-2-ol (**5e**)*

IR: 3450, 1632, 1514, 1465, 1231 $cm^{-1}$; $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 7.89 (1H, d, $J = 8.0$ Hz, Ar–H), 7.72 (1H, d, $J = 8.0$ Hz, Ar–H), 7.58 (1H, d, $J = 8.0$ Hz, Ar–H), 7.55 (1H, *t*, $J = 8.0$ Hz, Ar–H), 7.36–6.92 (3H, m, Ar–H), 6.89–6.80 (3H, m, Ar–H), 5.71 (1H, m, H-2), 5.17–4.92 (2H, m, $H_2$-1), 4.87 (1H, brd, $J = 7.0$ Hz, H-4), 3.20–3.04 (2H, m, $H_2$-3); $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ 160.5 (d, $J = 280.0$ Hz, Ar–C–F), 151.7 (Ar–C), 132.8 (C-2), 131.2 (Ar–C), 131.4 (d, $J = 8.0$ Hz, Ar–C), 129.5 (Ar–C), 128.7 (Ar–C), 128.0 (Ar–C), 127.2 (Ar–C), 126.5 (Ar–C), 125.2 (Ar–C), 124.8 (Ar–C), 123.1 (Ar–C), 123.0 (Ar–C), 121.7 (Ar–C), 119.1 (Ar–C), 118.6 (d, $J = 8.0$ Hz, Ar–C), 116.2 (C-1), 40.3 (C-4), 36.5 (C-3); ESIMS: *m/z* 293 $[M + H]^{+\cdot}$; Anal. Calc for $C_{20}H_{17}FO$: C 82.19, H 5.82%; Found: C 82.12, H 5.84%.

*1-[1-(3-fluorophenyl)but-3-enyl]naphthalen-2-ol (**5f**)*

IR: 3447, 1628, 1512, 1464, 1218 $cm^{-1}$; $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 7.87 (1H, d, $J = 8.0$ Hz, Ar–H), 7.68 (1H, d, $J = 8.0$ Hz, Ar–H), 7.54 (1H, d, $J = 8.0$ Hz, Ar–H), 7.36–6.92 (4H, m), 6.88–6.78 (3H, m, Ar–H), 5.62 (1H, m, H-2), 5.12–4.96 (2H, m, $H_2$-1), 4.83 (1H, brd, $J = 7.0$ Hz, H-4), 3.17–3.02 (2H, m, $H_2$-3); $^{13}$CNMR (50 MHz, $CDCl_3$): $\delta$ 162.7 (d, $J = 280.0$ Hz, Ar–C–F), 151.2 (Ar–C), 143.8 (Ar–C), 134.1 (C-2), 131.3 (Ar–C), 131.1 (Ar–C), 129.5 (Ar–C), 128.7 (Ar–C), 126.4 (Ar–C), 124.2 (Ar–C), 124.1 (Ar–C), 123.7 (Ar–C), 122.8 (Ar–C), 121.6 (Ar–C), 118.8 (Ar–C), 118.3 (d, $J = 8.0$ Hz, Ar–C), 116.7 (C-1), 114.2 (d, $J = 8.0$ Hz, Ar–C), 41.0 (C-4), 36.7 (C-3); ESIMS: *m/z* 293 $[M + H]^{+\cdot}$; Anal. Calc for $C_{20}H_{17}FO$: C 82.19, H 5.82%; Found: C 82.31, H 5.86%.

*1-[1-(4-chlorophenyl)but-3-enyl]naphthalen-2-ol (**5g**)*

IR: 3448, 1629, 1491, 1462, 1366, 1237 $cm^{-1}$; $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 7.91 (1H, d, $J = 8.0$ Hz, Ar–H), 7.70 (1H, d, $J = 8.0$ Hz, Ar–H), 7.58 (1H, d, $J = 8.0$ Hz, Ar–H), 7.40–7.04 (6H, m, Ar–H), 6.93 (1H, d, $J = 8.0$ Hz, Ar–H), 5.68 (1H, m, H-2), 5.08–4.92 (2H, m, $H_2$-1), 4.82 (1H, brd, $J = 7.0$ Hz, H-4), 3.18–2.98 (2H, m, $H_2$-3); $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ 151.8 (Ar–C–Cl), 142.2 (Ar–C), 137.0 (Ar–C), 135.3 (Ar–C), 133.4 (C-2), 129.9, (Ar–C), 129.1 (Ar–C), 128.2 (Ar–C), 126.4 (Ar–C), 124.2 (Ar–C), 124.0 (Ar–C), 122.8 (Ar–C), 121.7 (Ar–C), 119.1 (Ar–C), 118.9 (Ar–C), 116.2 (C-1), 40.7 (C-4), 36.2 (C-3); ESIMS: *m/z* 309, 311 $[M + H]^{+\cdot}$; Anal. Calc for $C_{20}H_{17}ClO$: C 77.80, H 8.15%; Found: C 77.89, H 8.09%.

*1-[(4-fluorophenyl)(4-methoxyphenyl)methyl]naphthalen-2-ol (**6c**)*

IR: 3468, 1626, 1603, 1508, 1463, 1248 $cm^{-1}$; $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 7.86 (1H, d, $J = 8.0$ Hz, Ar–H), 7.73–7.61 (2H, m, Ar–H), 7.55 (1H, d, $J = 8.0$ Hz, Ar–H), 7.38–7.12 (4H, m, Ar–H), 7.06 (2H, d, $J = 8.0$ Hz, Ar–H), 7.02–6.91 (2H, m, Ar–H), 6.80 (2H, d, $J = 8.0$ Hz, Ar–H), 6.27 (1H, s, Ar–H), 5.22 (1H, brs, $CHAr_3$), 3.72 (3H, s, OMe); $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ 156.1, (d, $J = 280.0$ Hz Ar–C), 154.0 (Ar–C), 152.9 (Ar–C), 137.8 (Ar–C), 132.2 (Ar–C), 130.8 (Ar–C), 130.1 (Ar–C), 130.0 (Ar–C), 129.1 (Ar–C), 127.9 (Ar–C), 126.9 (Ar–C), 126.6 (Ar–C), 123.2 (Ar–C), 122.8 (Ar–C), 120.0 (Ar–C), 118.1 (Ar–C), 116.2, (d, $J = 10.0$ Hz, Ar–C), 114.7 (Ar–C), 54.9 (OMe), 47.1 ($CHAr_3$),; ESIMS: *m/z* 381 $[M + Na]^{+\cdot}$; Anal. Calc for $C_{24}H_{19}FO_2$: C 80.45, H 5.31%; Found: C 80.58, H 5.27%.

*1-[(4-chlorophenyl)(4-methoxyphenyl)methyl]naphthalen-2-ol (**6d**)*

IR: 3468, 1627, 1603, 1509, 1463, 1246 $cm^{-1}$; $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 7.78 (1H, d, $J = 8.0$ Hz, Ar–H), 7.63 (1H, d, $J = 8.0$ Hz, Ar–H), 7.61 (1H, d, $J = 8.0$ Hz,

Ar–H), 7.30–7.12 (4H, m, Ar–H), 7.10 (2H, d, $J = 8.0$ Hz, Ar–H), 7.01 (2H, d, $J = 8.0$ Hz, Ar–H), 6.92 (1H, d, $J = 8.0$ Hz, Ar–H), 6.72 (2H, d, $J = 8.0$ Hz, Ar–H), 6.19 (1H, s, Ar–H), 5.09 (1H, brs, $CHAr_3$), 3.69 (3H, s, OMe); $^{13}C$ NMR (50 MHz, $CDCl_3$): $\delta$ 159.0 (Ar–C), 152.9 (Ar–C), 140.4 (Ar–C), 133.1 (Ar–C), 133.0 (Ar–C), 130.5 (Ar–C), 130.0(Ar–C), 129.9 (Ar–C), 128.9 (Ar–C), 128.0 (Ar–C), 127.1 (Ar–C), 124.7 (Ar–C), 124.4 (Ar–C), 123.5 (Ar–C), 122.9 (Ar–C), 119.9 (Ar–C), 119.3 (Ar–C), 114.9 (Ar–C), 55.2 (OMe), 47.1 ($CHAr_3$; ESIMS: *m/z* 375, 377 $[M + H]^{+\cdot}$; Anal. Calc for $C_{24}H_{19}ClO_2$: C 76.90, H 5.07%; Found: C 76.82, H 5.13%.

### Evaluation of cytotoxic activity

Cell lines used for testing in vitro cytotoxicity included HepG2 derived from human hepatocellular liver carcinoma cells (ATCC No. HB-8065), A549 derived from human lung adenocarcinoma epithelial cells (ATCC No. CCL-185), MDA231 derived from human breast adenocarcinoma cells (ATCC No. HTB-26) and HeLa derived from human cervical cancer cells (ATCC No. CCL-2). These cell lines were obtained from American Type Culture Collection, Manassas, VA, USA.

All tumor cell lines were maintained in a Modified Eagle's medium (Sigma-Aldrich, USA) supplemented with 10% fetal bovine serum (Sigma), along with 1% non-essential amino acids without L-glutamine (Sigma), 0.2% sodium bicarbonate, 1% sodium pyruvate (Sigma), and 1% of antibiotic mixture (10,000 units penicillin and 10 mg streptomycin per ml, Sigma). The cells were washed and resuspended in the above medium and 100 µl of this suspension was seeded in 96-well flat bottom plates. The cells were maintained at 37°C in a humidified 5% $CO_2$ incubator (Model 2406 Shellab $CO_2$ incubator, Sheldon manufacturing, Cornelius, OR, USA). After 24 h of incubation, the cells were treated for 2 days with eleven test compounds at concentrations ranging from 0.1 to 100 µM in DMSO (1% final concentration) and were assayed at the end of the second day. Each assay was performed with two internal controls: (1) an $IC_0$ with cells only, (2) an $IC_{100}$ with media only. After 48 h of incubation, the cells were subjected to MTT colorimetric assay (5 mg $ml^{-1}$ MTT). The effect of the different test compounds on the viability of tumor cell lines was measured at the wavelength of 540 nm on a multimode reader (Infinite® M200, Tecan, Switzerland). Dose–response curves were plotted for the test compounds and controls after correction by subtracting the background absorbance from that of the blanks. The $IC_{50}$ values (50% inhibitory concentration) were calculated from the plotted absorbance data for the dose–response curves. $IC_{50}$ values (in µM) are expressed as the average of two independent experiments.

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