DOI:10.7598/cst2018.1522
ISSN:2278-3458

Chemical Science Transactions
2018, **7(4),** 656-666

**RESEARCH ARTICLE**

# Synthesis and Bioevaluation Study of Benzofuran Linked Tetralones as Antimitotic Agent

B. UMESHA[1], A. SOWBHAGY[2] and Y. B. BASAVARAJU[1*]

[1]Department of Studies in Chemistry, University of Mysore, Manasagangotri, Mysore - 570006, Karnataka, India

[2]Department of Studies in Organic Chemistry, University of Mysore, Manasagangotri, Mysore - 570006, Karnataka, India

*basavaraju_yb@yahoo.co.in*

Received 24 March 2018 / Accepted 15 April 2018

**Abstract:** A series of new benzofuran linked tetralones **(5a-h)** have been prepared by chalcone route of Claisen-Schmidt condensation reaction in the presence of sodium hydroxide, 1-(benzofuran-6-yl)-ethanone **(1)** reacts with substituted benzaldehyde **(2a-h)** followed by cyclopropanation of 1-(benzofuran-6-yl)-3-phenylprop-2-en-1-one **(3a-h)** with trimethylsulfoxonium iodide (TMSOI) in the presence of sodium hydride and Friedel-Craft's intramolecular cyclization reaction of benzofuran-6-yl(2-phenylcyclopropyl)methanone **(4a-h)** in the presence of anhyd. stannic chloride and acetic anhydride. The target molecules were characterized by spectral and elemental analysis and also screened for their antimitotic activity by onion root method. Taken together, our results indicated that among the entire synthesized analogues, the two new compounds **5e** and **5f** bearing electron donating methoxy group on *para* and 3,4,5-position of the phenyl moiety respectively exhibits even good antimitotic activity than other compounds.

**Keywords:** Chalcones, Substituted bezaldehyde, Onion root tip method, Antimitotic activity

## Introduction

Aryltetralin lignan represent a significant subclass of lignans. Many of these aryltetralin lignans are derived from traditional herbs and have received increasing attention over the past decades for their interesting bioactivities[1]. Podophyllotoxin (Figure 1), **(1)** is a naturally occurring aryl tetralin lignan obtained from a number of plant species of the podophyllum family[2] such as *Berberidaceae* and *Mayapple P. peltatum* and is known as antimicrotubule agent which is considered as potent destabilizers for microtubule formation in colchicine binding site[3]. The biological activity of podophyllotoxin has led to extensive structural modifications, resulting in several clinically useful compounds. Podophyllotoxin, exhibits anticancer[4-7], antitumor and antiproliferative activity[8,9]. Podophyllotoxin and 4'-*o*-demethylepipodophyllotoxin which have shown inhibitory activity against numerous types of tumor cells. Hundreds of derivatives of these compounds have been designed and include etoposide, teniposide and

etopophos which are more potent antitumor agents than 4'-*o*-demethylepipodophyllotoxin. These have been approved for many years for clinical use in the treatment of various types of cancers (breast, testicular, small cell lung cancer, lymphomas, Kaposi's sarcoma, nonlymphocytic leukemia)[10-13].

On the other hand heterocyclic rings and in particular, the benzofuran is an important moiety for the synthesis of pharmaceutical compounds with different activities and good safety profiles. Benzofurans have been drawn as promising structural units in the field of medicinal chemistry. Benzofuran derivatives are a class of most important heterocyclic moieties, which have drawn considerable attention over past year. Benzofuran is known to possess important biological properties and potential applications[14]. Natural and synthetic compounds containing benzofuran fragment displaying a broad range of biological activities such as antimicrobials, anti-inflammatory and analgesic[15], anticancer[16], antioxidant agents[17], antitumor[18], antitubercular[19,20] and anti-inflammatory[21].

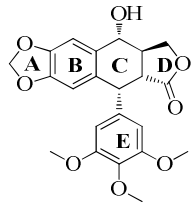



**Figure 1.** Structure of podophyllotoxin (**1**)

The literature survey approaching to synthesis of benzofuran linked with tetralone moiety indicate the lack of reference available. In view of this, on continuation of our research interest in the synthesis and biological evaluation of podophyllotoxin analogous[22], we have synthesized benzofuran linked tetralones in one compact structure for the purpose of increasing the antimitotic activity.

## Experimental

All the reagents and chemicals of analytical grade have been purchased from the CDH chemicals and were used for the synthesis without further purification. Melting point of the synthesized compounds **(5a-h)** was determined by open capillary method and is uncorrected. The IR spectra were recorded on a FT-IR instrument in KBr disc. The $^{1}$H NMR (400 MHz) spectra were recorded on Agilent 400MR DD2 spectrometer using $CDCl_3$ as a solvent. $^{13}$C NMR (100 MHz) spectra were recorded on Agilent 400MR DD2 spectrometer using $CDCl_3$ solvent. The chemical shifts were expressed in $\delta$ values relative to the tetramethyl silane as an internal reference. The mass spectra were recorded by Waters, USA on Synapt G2 HDMS/ACQUITY UPLC instrument. The elemental analysis was recorded on a Perkin-Elmer 2400 instrument. The purity of the compounds was checked by thin layer chromatography on silica gel glass plates in benzene and ethyl acetate mixture (7:0.5). The synthesized compounds **(5a-h)** were purified by column chromatography using silica gel (60-120 mesh) as adsorbent and benzene as eluent.

### Synthesis

*General procedure for the synthesis of chalcones (**3a-h**)*

2-Benzofuranyl methyl ketone (1.6 g, 10 mmol) **(2)** and substituted aldehydes **(2a-h)** (10 mmol) were stirred in water (40 mL) and ethanol (25 mL) mixture in the presence of sodium

hydroxide (2.00 g, 0.05 mol) at 15-30 $^{o}$C for 4 h. The reaction mixture was kept overnight in an ice bath. The precipitated products were filtered and recrystallized from ethanol.

*1-(Benzofuran-2-yl)-3-phenylprop-2-en-1-one* ***(3a)***

Color: Dark yellow solid, m.p: 102-104 $^{o}$C, Yield 85%, IR(KBr)$\nu_{max}$(cm$^{-1}$)**:** 1672 (C=O), 1458 (CH=CH), 1584 (C=C), 2947 (-CH); $^{1}$H NMR (DMSO-$d_6$ 400 MHz) δ ppm: 6.83-7.80 (m, 10H, Ar-Hs), 7.14 (d, 1H, *J* = 14.8 Hz, *β*-CH), 6.56 (d, 1H, *J* = 14.8 Hz, *α*-CH); $^{13}$C NMR (DMSO-$d_6$ 100 MHz) δ ppm: 174.8, 163.5, 155.0, 145.4, 130.2, 128.2, 128.0, 125.9, 125.3, 122.7, 122.3, 121.4, 119.2, 116.0, 113.5; MS (ESI) *m/z*: 248.03 ($M^+$); Anal.calcd. for $C_{17}H_{12}O_2$, C, 82.24; H, 4.87; found: C, 82.21; H, 4.85%.

*1-(Benzofuran-2-yl)-3-(4-chlorophenyl)prop-2-en-1-one* ***(3b)***

Color: Light yeollow solid, m.p: 110-112 $^{o}$C, Yield 81%, IR(KBr)$\nu_{max}$(cm$^{-1}$)**:** 1668 (C=O), 1450 (CH=CH), 1593 (C=C), 2958 (-CH); $^{1}$H NMR (DMSO-$d_6$ 400 MHz) δ ppm: 6.94-7.72 (m, 9H, Ar-Hs), 7.02 (d, 1H, *J* = 13.2 Hz, *β*-CH), 6.52 (d, 1H, *J* = 13.2 Hz, *α*-CH); $^{13}$C NMR (DMSO-$d_6$ 100 MHz) δ ppm: 177.1, 162.5, 158.2, 149.1, 136.5, 131.3, 129.5, 129.1, 125.3, 124.1, 123.7, 121.0, 120.2, 114.6, 110.2; MS (ESI) *m/z*: 282.07 ($M^+$); Anal.calcd. for $C_{17}H_{11}ClO_2$, C, 72.22; H, 3.92; found: C, 72.25; H, 3.88%.

*1-(Benzofuran-2-yl)-3-(4-fluorophenyl)prop-2-en-1-one* ***(3c)***

Color: Light yellow solid, m.p: 124-126 $^{o}$C, Yield 74%, IR(KBr)$\nu_{max}$(cm$^{-1}$)**:** 1660 (C=O), 1458 (CH=CH), 1597 (C=C), 2946 (-CH); $^{1}$H NMR (DMSO-$d_6$ 400 MHz) δ ppm: 6.72-7.66 (m, 9H, Ar-Hs), 7.07 (d, 1H, *J* = 15.0 Hz, *β*-CH), 6.64 (d, 1H, *J* = 15.0 Hz, *α*-CH); $^{13}$C NMR (DMSO-$d_6$ 100 MHz) δ ppm: 176.3, 165.1, 162.2, 157.1, 142.6, 134.3, 130.8, 127.1, 123.5, 122.0, 121.9, 120.3, 116.2, 115.3, 111.0; MS (ESI) *m/z*: 266.32 ($M^+$); Anal.calcd. for $C_{17}H_{11}FO_2$, C, 76.68; H, 4.16; found: C, 76.63; H, 4.15%.

*1-(Benzofuran-2-yl)-3-(4-nitrophenyl)prop-2-en-1-one* ***(3d)***

Color: Brown solid, m.p: 120-122 $^{o}$C, Yield 65%, IR(KBr)$\nu_{max}$(cm$^{-1}$)**:** 1665 (C=O), 1453 (CH=CH), 1592 (C=C), 2940 (-CH); $^{1}$H NMR (DMSO-$d_6$ 400 MHz) δ ppm: 6.78-7.74 (m, 9H, Ar-Hs), 7.12 (d, 1H, *J* = 14.2 Hz, *β*-CH), 6.67 (d, 1H, *J* = 14.2 Hz, *α*-CH); $^{13}$C NMR (DMSO-$d_6$ 100 MHz) δ ppm: 177.1, 163.5, 152.2, 146.1, 144.6, 141.5, 129.6, 125.4, 124.2, 123.5, 123.0, 120.3, 120.0, 112.8, 109.0; MS (ESI) *m/z*: 293.13 ($M^+$); Anal.calcd. for $C_{17}H_{11}NO_4$, C, 69.62; H, 3.78; N, 4.78; found: C, 69.63; H, 3.81; N, 4.74%.

*1-(Benzofuran-2-yl)-3-(4-methoxyphenyl)prop-2-en-1-one* ***(3e)***

Color: Dark yellow solid, m.p: 116-118 $^{o}$C, Yield 79%, IR(KBr)$\nu_{max}$(cm$^{-1}$)**:** 1669 (C=O), 1455 (CH=CH), 1588 (C=C), 2952 (-CH); $^{1}$H NMR (DMSO-$d_6$ 400 MHz) δ ppm: 6.72-7.80 (m, 9H, Ar-Hs), 7.24 (d, 1H, *J* = 13.8 Hz, *β*-CH), 6.72 (d, 1H, *J* = 13.8 Hz, *α*-CH), 3.84 (s, 3H, $OCH_3$); $^{13}$C NMR (DMSO-$d_6$ 100 MHz) δ ppm: 171.0, 162.2, 156.2, 150.6, 143.5, 133.2, 127.2, 126.3, 122.3, 121.9, 120.1, 116.0, 112.8, 110.5, 53.2; MS (ESI) *m/z*: 278.07 ($M^+$); Anal.calcd. for $C_{18}H_{14}O_3$, C, 77.68; H, 5.07; found: C, 77.71; H, 5.03%.

*1-(Benzofuran-2-yl)-3-(3,4,5-trimethoxyphenyl)prop-2-en-1-one* ***(3f)***

Color: Dark yellow solid, m.p: 132-134 $^{o}$C, Yield 82%, IR(KBr)$\nu_{max}$(cm$^{-1}$)**:** 1661 (C=O), 1461 (CH=CH), 1578 (C=C), 2964 (-CH); $^{1}$H NMR (DMSO-$d_6$ 400 MHz) δ ppm: 6.61-7.64 (m, 7H, Ar-Hs), 7.04 (d, 1H, *J* = 14.4 Hz, *β*-CH), 6.77 (d, 1H, *J* = 14.4 Hz, *α*-CH), 3.87 (s, 9H, $OCH_3$); $^{13}$C NMR (DMSO-$d_6$ 100 MHz) δ ppm: 172.8, 162.5, 158.6, 145.6, 150.3, 135.1, 127.2, 126.0, 125.9 122.1, 121.0, 120.3, 115.1, 111.2, 103.1, 60.2, 56.5; MS (ESI) *m/z*: 338.15 ($M^+$); Anal.calcd. for $C_{20}H_{18}O_5$, C, 70.99; H, 5.36; found: C, 70.97; H, 5.33%.

*1-(Benzofuran-2-yl)-3-(p-tolyl)prop-2-en-1-one* ***(3g)***

Color: Yellow solid, m.p: 122-124 $^{o}$C, Yield 76%, IR(KBr)$\nu_{max}$(cm$^{-1}$)**:** 1663 (C=O), 1464 (CH=CH), 1572 (C=C), 2960 (-CH); $^{1}$H NMR (DMSO-$d_6$ 400 MHz) δ ppm: 6.75-7.72 (m, 9H, Ar-Hs), 7.10 (d, 1H, *J* = 14.0 Hz, *β*-CH), 6.72 (d, 1H, *J* = 14.0 Hz, *α*-CH), 2.42 (s, 3H, $CH_3$); $^{13}$C NMR (DMSO-$d_6$ 100 MHz) δ ppm: 177.1, 160.0, 155.8, 143.5, 136.1, 132.0, 128.5, 128.0, 126.3, 124.5, 123.8, 122.3, 120.3, 114.1, 108.5, 21.7; MS (ESI) *m/z*: 262.14 ($M^+$); Anal.calcd. for $C_{18}H_{14}O_2$, C, 82.42; H, 5.38; found: C, 82.46; H, 5.35%.

*1-(Benzofuran-2-yl)-3-(3,4-dimethylphenyl)prop-2-en-1-one* ***(3h)***

Color: Light yellow solid, m.p: 126-128 $^{o}$C, Yield 69%, IR(KBr)$\nu_{max}$(cm$^{-1}$)**:** 1667 (C=O), 1461 (CH=CH), 1575 (C=C), 2955 (-CH); $^{1}$H NMR (DMSO-$d_6$ 400 MHz) δ ppm: 6.68-7.79 (m, 8H, Ar-Hs), 7.06 (d, 1H, *J* = 13.1 Hz, *β*-CH), 6.79 (d, 1H, *J* = 13.1 Hz, *α*-CH), 2.39 (s, 6H, $CH_3$); $^{13}$C NMR (DMSO-$d_6$ 100 MHz) δ ppm: 171.6, 164.9, 152.6, 142.6, 136.2, 136.0, 132.9, 132.5, 131.2, 128.2, 125.9, 124.3, 122.5, 121.7, 120.1, 113.6, 108.1, 19.5, 18.1; MS (ESI) *m/z*: 276.05 ($M^+$); Anal.calcd. for $C_{19}H_{16}O_2$, C, 82.58; H, 5.84; found: C, 82.55; H, 5.81%.

*General procedure for the synthesis of cyclopropyl ketones* ***(4a-h)***

Sodium hydride (0.13 g of 5.5 mmol) was added in portions to the stirred suspensions of trimethylsulfoxonium iodide (1.21 g of 5.5 mmol) in dry dimethyl sulfoxide (DMSO) (20 mL) under nitrogen gas atmosphere. The reaction mixture was stirred for 10 mins at 25-30 $^{o}$C (until the evolution of the $H_2$ gas ceased). Chalcones (5 mmol*)* **(3a-h)** in dry DMSO (15 mL) were added drop wise during 30 mins to the above solution. The reaction mass was stirred at 26-28 $^{o}$C for 2 h and raised the temperature to 50-60 $^{o}$C for 1 h. The completion of the reaction was confirmed by TLC and the reaction mixture was poured into water (20 mL). The precipitated gummy residue was extracted into chloroform. The combined organic layer was washed with water, dried over anhyd. $Na_2SO_4$ and concentrated under reduced pressure. the products were recrystallized from ethanol.

*Benzofuran-2-yl(2-phenylcyclopropyl)methanone* ***(4a)***

Color: Light brown solid, m.p: 111-113 $^{o}$C, Yield 70%, IR(KBr)$\nu_{max}$(cm$^{-1}$)**:** 3152-2963 (Ar-CH), 1660 (C=O); $^{1}$H NMR (DMSO-$d_6$ 400 MHz) δ ppm: 8.08-7.14 (m, 10H, Ar-H), 2.32-2.12 (m, 2H, cyclopropyl-CH), 0.74 (d, 2H, *J* = 4.4 Hz, cyclopropyl-$CH_2$); $^{13}$C NMR (DMSO-$d_6$ 100 MHz) δ ppm: 185.8, 162.0, 152.6, 142.8, 128.6, 127.6, 125.4, 124.9, 123.7, 120.5, 111.3, 25.7, 23.9, 14.8; MS (ESI) *m/z*: 262.14 ($M^+$). Anal.calcd. for $C_{18}H_{14}O_2$: C, 82.42; H, 5.38; found: C, 82.45; H, 5.35%.

*Benzofuran-2-yl(2-(4-chlorophenyl)cyclopropyl)methanone* ***(4b)***

Color: Brown solid, m.p: 119-121 $^{o}$C, Yield 65%, IR(KBr)$\nu_{max}$(cm$^{-1}$)**:** 3142-2960 (Ar-CH), 1664 (C=O); $^{1}$H NMR (DMSO-$d_6$ 400 MHz) δ ppm: 8.02-7.11 (m, 9H, Ar-H), 2.42-2.23 (m, 2H, cyclopropyl-CH), 0.70 (d, 2H, *J* = 3.2 Hz, cyclopropyl-$CH_2$); $^{13}$C NMR (DMSO-$d_6$ 100 MHz) δ ppm: 188.4, 160.1, 153.4, 139.5, 130.5, 128.5, 127.3, 126.8, 124.7, 123.8, 120.4, 111.2, 103.5, 25.9, 23.4, 14.1; MS (ESI) *m/z*: 296.11 ($M^+$). Anal.calcd. for $C_{18}H_{13}ClO_2$: C, 72.85; H, 4.42; found: C, 72.89; H, 4.40%.

*Benzofuran-2-yl(2-(4-fluorophenyl)cyclopropyl)methanone* ***(4c)***

Color: Brown solid, m.p: 132-134 $^{o}$C, Yield 64%, IR(KBr)$\nu_{max}$(cm$^{-1}$)**:** 3122-2954 (Ar-CH), 1672 (C=O); $^{1}$H NMR (DMSO-$d_6$ 400 MHz) δ ppm: 7.86-7.31 (m, 9H, Ar-H), 2.34-2.15 (m,

2H, cyclopropyl-CH), 0.92 (d, 2H, *J* = 5.8 Hz, cyclopropyl-$CH_2$); $^{13}$C NMR (DMSO-$d_6$ 100 MHz) δ ppm: 187.9, 160.8, 159.1, 153.6, 137.9, 128.4, 127.6, 124.2, 120.5, 114.6, 110.9, 102.8, 25.3, 13.9, 14.8; MS (ESI) *m/z*: 280.01 ($M^+$). Anal. Calcd. for $C_{18}H_{13}FO_2$: C, 77.13; H, 4.67; found: C, 77.14; H, 4.63%.

*Benzofuran-2-yl(2-(4-nitrophenyl)cyclopropyl)methanone* ***(4d)***

Color: Dark brown semisolid, m.p: 125-127 °C, Yield 68%, IR(KBr)$\nu_{max}$($cm^{-1}$)**:** 3110-2940 (Ar-CH), 1677 (C=O); $^1$H NMR (DMSO-$d_6$ 400 MHz) δ ppm: 7.91-7.22 (m, 9H, Ar-H), 2.30-2.10 (m, 2H, cyclopropyl-CH), 0.83 (d, 2H, *J* = 4.2 Hz, cyclopropyl-$CH_2$); $^{13}$C NMR (DMSO-$d_6$ 100 MHz) δ ppm: 186.5, 155.9, 151.9, 147.3, 144.6, 127.6, 125.4, 124.3, 123.5, 120.6, 111.1, 103.4, 25.6, 22.8, 14.0; MS (ESI) *m/z*: 307.17 ($M^+$). Anal.calcd. for $C_{18}H_{13}NO_4$: C, 77.13; H, 4.67; found: C, 77.14; H, 4.63%.

*Benzofuran-2-yl(2-(4-methoxyphenyl)cyclopropyl)methanone* ***(4e)***

Color: Dark brown solid, m.p: 128-130 °C, Yield 72%, IR(KBr)$\nu_{max}$($cm^{-1}$)**:** 3122-2951 (Ar-CH), 1659 (C=O); $^1$H NMR (DMSO-$d_6$ 400 MHz) δ ppm: 7.83-7.17 (m, 9H, Ar-H), 3.81 (s, 3H, $OCH_3$), 2.45-2.25 (m, 2H, cyclopropyl-CH), 0.69 (d, 2H, *J* = 3.8 Hz, cyclopropyl-$CH_2$); $^{13}$C NMR (DMSO-$d_6$ 100 MHz) δ ppm: 188.1, 160.2, 157.0, 153.9, 134.5, 127.2, 126.0, 124.8, 123.8, 120.5, 113.0, 111.5, 103.5, 55.3, 25.4, 23.7, 14.9; MS (ESI) *m/z*: 292.14 ($M^+$). Anal.calcd. for $C_{19}H_{16}O_3$: C, 78.06; H, 5.52; found: C, 78.01; H, 5.50%.

*Benzofuran-2-yl(2-(3,4,5-trimethoxyphenyl)cyclopropyl)methanone* ***(4f)***

Color: Dark brown semisolid, m.p: 134-136 °C, Yield 75%, IR(KBr)$\nu_{max}$($cm^{-1}$)**:** 3131-2956 (Ar-CH), 1662 (C=O); $^1$H NMR (DMSO-$d_6$ 400 MHz) δ ppm: 7.83-7.17 (m, 7H, Ar-H), 3.85 (s, 9H, $OCH_3$), 2.40-2.23 (m, 2H, cyclopropyl-CH), 0.72 (d, 2H, *J* = 5.1 Hz, cyclopropyl-$CH_2$); $^{13}$C NMR (DMSO-$d_6$ 100 MHz) δ ppm: 187.8, 160.2, 153.4, 152.7, 137.2, 135.6, 127.6, 124.6, 123.0, 120.5, 110.9, 103.4, 102.1, 60.4, 56.0, 25.4, 23.4, 14.0; MS (ESI) *m/z*: 292.19 ($M^+$). Anal.calcd. for $C_{21}H_{20}O_5$: C, 78.06; H, 5.52; found: C, 78.01; H, 5.50%.

*Benzofuran-2-yl(2-(p-tolyl)cyclopropyl)methanone* ***(4g)***

Color: Light brown solid, m.p: 135-137 °C, Yield 69%, IR(KBr)$\nu_{max}$($cm^{-1}$)**:** 3141-2943 (Ar-CH), 1664 (C=O); $^1$H NMR (DMSO-$d_6$ 400 MHz) δ ppm: 7.81-6.98 (m, 9H, Ar-H), 2.45 (s, 3H, $CH_3$), 2.39-2.28 (m, 2H, cyclopropyl-CH), 0.79 (d, 2H, *J* = 3.3 Hz, cyclopropyl-$CH_2$); $^{13}$C NMR (DMSO-$d_6$ 100 MHz) δ ppm: 188.1, 160.8, 153.4, 138.4, 134.6, 126.7, 124.2, 123.4, 120.6, 110.6, 103.8, 25.7, 23.7, 21.6, 14.0; MS (ESI) *m/z*: 276.15 ($M^+$). Anal.calcd. for $C_{19}H_{16}O_2$: C, 82.58; H, 5.84; found: C, 82.55; H, 5.82%.

*Benzofuran-2-yl(2-(3,4-dimethylphenyl)cyclopropyl)methanone* ***(4h)***

Color: Dark brown solid, m.p: 131-133 °C, Yield 65%, IR(KBr)$\nu_{max}$($cm^{-1}$)**:** 3139-2959 (Ar-CH), 1669 (C=O); $^1$H NMR (DMSO-$d_6$ 400 MHz) δ ppm: 7.77-7.14 (m, 8H, Ar-H), 2.41 (s, 6H, $CH_3$), 2.32-2.13 (m, 2H, cyclopropyl-CH), 0.67 (d, 2H, *J* = 3.9 Hz, cyclopropyl-$CH_2$); $^{13}$C NMR (DMSO-$d_6$ 100 MHz) δ ppm: 188.1, 160.4, 153.4, 140.6, 136.1, 133.4, 129.8, 126.4, 127.6, 124.6, 123.6, 121.4, 120.4, 111.2, 103.9, 25.4, 13.9, 18.7, 19.7, 14.6; MS (ESI) *m/z*: 290.17 ($M^+$). Anal.calcd. for $C_{20}H_{18}O_2$: C, 82.73; H, 6.25; found: C, 82.75; H, 6.22%.

*General procedure for the synthesis of benzofuran linked tetralones (5a-h)*

Cyclopropyl ketones (5 mmol) **(4a-h)** were dissolved in dry dichloromethane (50 mL). Acetic anhydride (0.51 mL, 5.5 mmol) and anhyd. stannic chloride (0.65 mL, 5.5 mmol) were

added under nitrogen gas atmosphere. The resultant reaction mixture was stirred at 25-28 $^{o}$C for 3 h. The completion of reaction was known by TLC. The reaction mixture was poured into 5% NaOH solution (20 mL), the product was extracted into dichloromethane. The organic layer was washed with 5% HCl followed by water, dried over anhyd. $Na_2SO_4$ and concentrated *under vacuum* using a rotary evaporator to give brown residue. The product was purified by column chromatography using silica gel (60-120 mesh) as adsorbent and benzene as eluent. The benzene solution was concentrated to a small volume (20 mL) and hexane (100 mL) was added drop wise to give solid products in good yields.

*1-Phenyl-2,3-dihydrodibenzo[b,d]furan-4(1H)-one* ***(5a)***

Color: Dark brown solid, m.p: 122-124 $^{o}$C, Yield 70%, IR(KBr) $\nu_{max}$(cm$^{-1}$)**:** 3132-2942 (Ar-CH), 1674 (C=O); $^{1}$H NMR (DMSO-$d_6$ 400 MHz) δ ppm: 7.86-7.19 (m, 9H, Ar-H), 4.07 (t, 1H, *J* = 5.2 Hz, CH), 2.43-2.10 (m, 4H, $CH_2$); $^{13}$C NMR (DMSO-$d_6$ 100 MHz) δ ppm: 184.8, 161.0, 156.7, 140.5, 132.4, 128.6, 128.4, 127.6, 126.0, 124.3, 123.5, 119.7, 111.3, 39.4, 32.4, 32.6; MS (ESI) *m/z*: 262.05 ($M^+$). Anal.calcd. for $C_{18}H_{14}O_2$: C, 82.42; H, 5.38; found: C, 82.43; H, 5.34%.

*1-(4-Chlorophenyl)-2,3-dihydrodibenzo[b,d]furan-4(1H)-one* ***(5b)***

Color: Dark brown gummy, Yield-61%, IR (KBr)$\nu_{max}$(cm$^{-1}$)**:** 3136-2940 (Ar-CH), 1662 (C=O); $^{1}$H NMR (DMSO-$d_6$ 400 MHz) δ ppm: 7.78-7.22 (m, 8H, Ar-H), 4.10 (t, 1H, *J* = 5.2 Hz, CH), 2.41-2.14 (m, 4H, $CH_2$); $^{13}$C NMR (DMSO-$d_6$ 100 MHz) δ ppm: 185.1, 160.4, 156.4, 139.7, 132.5, 131.4, 129.4, 128.6, 127.4, 124.2, 119.3, 110.9, 39.7, 32.5, 31.6; MS (ESI) *m/z*: 296.11 ($M^+$). Anal.calcd. for $C_{18}H_{13}ClO_2$: C, 72.85; H, 4.42; found: C, 72.81; H, 4.40%.

*1-(4-Fluorophenyl)-2,3-dihydrodibenzo[b,d]furan-4(1H)-one* ***(5c)***

Color: Dark brown gummy, Yield-66%, IR (KBr)$\nu_{max}$(cm$^{-1}$)**:** 3142-2960 (Ar-CH), 1674 (C=O); $^{1}$H NMR (DMSO-$d_6$ 400 MHz) δ ppm: 7.58-7.10 (m, 8H, Ar-H), 4.22 (t, 1H, *J* = 4.3 Hz, CH), 2.39-2.11 (m, 4H, $CH_2$); $^{13}$C NMR (DMSO-$d_6$ 100 MHz) δ ppm: 185.3, 161.3, 160.5, 156.8, 136.5, 132.6, 129.7, 127.4, 124.3, 123.4, 119.6, 115.8, 111.1, 39.4, 32.6, 30.1; MS (ESI) *m/z*: 280.14 ($M^+$). Anal.calcd. for $C_{18}H_{13}FO_2$: C, 77.13; H, 4.67; found: C, 77.10; H, 4.65%.

*1-(4-Nitrophenyl)-2,3-dihydrodibenzo[b,d]furan-4(1H)-one* ***(5d)***

Color: Brown gummy, Yield-58%, IR (KBr)$\nu_{max}$(cm$^{-1}$)**:** 3138-2943 (Ar-CH), 1668 (C=O); $^{1}$H NMR (DMSO-$d_6$ 400 MHz) δ ppm: 7.64-7.18 (m, 8H, Ar-H), 4.14 (t, 1H, *J* = 3.1 Hz, CH), 2.58-2.25 (m, 4H, $CH_2$); $^{13}$C NMR (DMSO-$d_6$ 100 MHz) δ ppm: 184.9, 161.3, 156.7, 147.3, 145.8, 132.7, 129.8. 127.4, 124.3, 124.0, 123.8, 119.8, 111.0, 39.7, 32.9, 32.0; MS (ESI) *m/z*: 307.11 ($M^+$). Anal.calcd. for $C_{18}H_{13}NO_4$: C, 70.35; H, 4.26; N, 4.56; found: C, 70.39; H, 4.28; N, 4.52%.

*1-(4-Methoxyphenyl)-2,3-dihydrodibenzo[b,d]furan-4(1H)-one* ***(5e)***

Color: Dark brown solid, m.p: 143-145 $^{o}$C, Yield-68%, IR (KBr)$\nu_{max}$(cm$^{-1}$)**:** 3130-2932 (Ar-CH), 1668 (C=O); $^{1}$H NMR (DMSO-$d_6$ 400 MHz) δ ppm: 7.68-7.12 (m, 8H, Ar-H), 4.16 (t, 1H, *J* = 3.7 Hz, CH), 3.82 (s, 3H, $OCH_3$), 2.50-2.21 (m, 4H, $CH_2$); $^{13}$C NMR (DMSO-$d_6$ 100 MHz) δ ppm: 182.6, 160.5, 157.3, 156.9, 133.5, 132.9, 129.7, 127.6, 124.6, 123.5, 119.5, 114.3, 110.9, 55.4, 39.54, 32.6, 31.5; MS (ESI) *m/z*: 292.14 ($M^+$). Anal.calcd. for $C_{19}H_{16}O_2$: C, 78.06; H, 5.52; found: C, 78.03; H, 5.55%.

*1-(3,4,5-Trimethoxyphenyl)-2,3-dihydrodibenzo[b,d]furan-4(1H)-one* ***(5f)***

Color: Brown solid, m.p: 149-151 °C, Yield-73%, IR (KBr)$\nu_{max}$($cm^{-1}$)**:** 3136-2938 (Ar-CH), 1660 (C=O); $^1$H NMR (DMSO-$d_6$ 400 MHz) δ ppm: 7.34-7.10 (m, 6H, Ar-H), 4.13 (t, 1H, *J* = 3.5 Hz, CH), 3.79 (s, 9H, $OCH_3$), 2.36-2.18 (m, 4H, $CH_2$); $^{13}$C NMR (DMSO-$d_6$ 100 MHz) δ ppm: 183.6, 160.9, 156.3, 153.8, 136.8, 133.6, 132.7, 127.5. 124.8, 123.7, 119.6, 111.0, 106.6, 60.4, 56.8, 39.0, 32.9, 31.9; MS (ESI) *m/z*: 352.15 ($M^+$). Anal.calcd. for $C_{21}H_{20}O_5$: C, 71.58; H, 5.72; found: C, 71.60; H, 5.75%.

*1-(p-Tolyl)-2,3-dihydrodibenzo[b,d]furan-4(1H)-one* ***(5g)***

Color: Brown gummy, Yield-64%, IR (KBr)$\nu_{max}$($cm^{-1}$)**:** 3144-2920 (Ar-CH), 1665 (C=O); $^1$H NMR (DMSO-$d_6$ 400 MHz) δ ppm: 7.39-7.25 (m, 8H, Ar-H), 4.15 (t, 1H, *J* = 3.0 Hz, CH), 2.47 (s, 3H, $CH_3$), 2.30-2.10 (m, 4H, $CH_2$); $^{13}$C NMR (DMSO-$d_6$ 100 MHz) δ ppm: 185.1, 161.8, 156.8. 137.8, 135.6, 132.6, 132.7, 129.4, 128.3, 127.1, 124.9, 123.6, 119.8, 111.0, 39.7, 32.5, 32.1, 21.5; MS (ESI) *m/z*: 276.16 ($M^+$). Anal.calcd. for $C_{19}H_{16}O_2$: C, 82.58; H, 5.84; found: C, 82.62; H, 5.80%.

*1-(3,4-Dimethylphenyl)-2,3-dihydrodibenzo[b,d]furan-4(1H)-one* ***(5h)***

Color: Brown solid, m.p: 144-146 °C, Yield-60%, IR (KBr)$\nu_{max}$($cm^{-1}$)**:** 3140-2928 (Ar-CH), 1669 (C=O); $^1$H NMR (DMSO-$d_6$ 400 MHz) δ ppm: 7.52-7.20 (m, 7H, Ar-H), 4.18 (t, 1H, *J* = 2.8 Hz, CH), 2.44 (s, 6H, $CH_3$), 2.28-2.16 (m, 4H, $CH_2$); $^{13}$C NMR (DMSO-$d_6$ 100 MHz) δ ppm: 185.3, 160.4, 156.4, 136.7, 135.4, 134.9, 132.5, 130.4, 129.8, 127.8, 125.6, 124.0, 123.1, 119.7, 111.1, 39.1, 32.5, 31.9, 19.5, 18.2; MS (ESI) *m/z*: 290.19 ($M^+$). Anal.calcd. for $C_{20}H_{18}O_2$: C, 82.73; H, 6.25; found: C, 82.75; H, 6.23%.

*Antimitotic studies*

The antimitotic activity of benzofuran linked tetralones **(5a-h)** were examined using onion root tip method. Materials used are aceto-orcein solution, compound microscope, glass slides, cover slips, hydrochloric acid (0.1 N), Carney's solution II, 3 % ethanol and tested samples (0.1 mg/mL). To study the effect of benzofuran linked tetralones on somatic cells, onion base was immersed to an extent of about half a centimeter in a sample tube and control solution tube in a glass (7x3), after removing the old roots from it and immersion is continued for 24 h intervals respectively for germination. After this, the germinated root tips were removed and were fixed in Carney's solution II (alcohol and acetic acid in 3:1 ratio respectively) for 24 h. After 24 h Carney's solution II was decanted carefully and the root tips were washed with preserving solvent (70% ethanol). The fixed root tips were persevered in 70% ethanol in refrigerator. The root tips were taken in watch glass and stained with a drop of aceto-orcein stain and a drop of 1 N HCl (7:1). The glass slides were warmed and kept for 1 h. The roots were taken on a clean glass slide and squashed using 45% acetic acid following the method of Levan[23]. A microscope cover glass was placed on the material and then pressure was applied on a cover glass to ensure uniform spreading. The cover glass was sealed with molten paraffin wax and slide was observed under microscope. Mitotic Index (*M. I.*) was calculated by following method of Fissceja[24]. The mitotic index was determined by examination of minimum of zone cells. Three replicates were made for each calculation. The slides were observed under microscope and photographed.

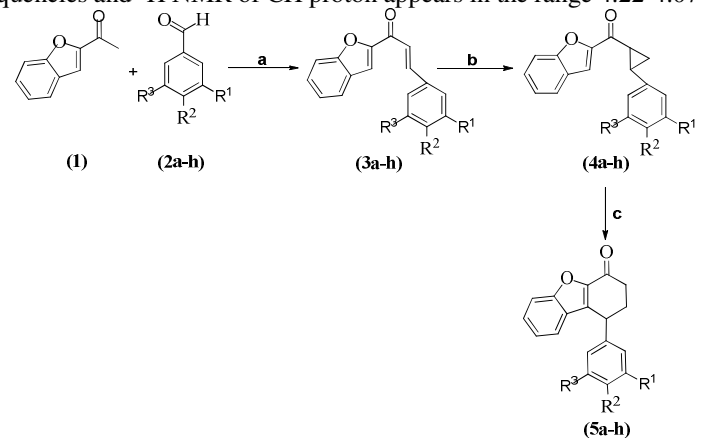
$$M.I = \frac{\text{Total number of dividing cells}}{\text{Total number of cells examined}} X100 \quad (1)$$

The percentage of the number of dividing cells compared to the control and the percent inhibition of mitosis by antimitotic agent at concentration (0.1 mg/mL) against a control was calculated[25].

## Results and Discussion

### *Chemistry*

The synthesis of benzofuran linked tetralones **(5a-h)** has been carried out by chalcone route (Scheme 1). The substituted 1-(benzofuran-6-yl)-3-phenylprop-2-en-1-one **(3a-h)** were prepared in high yields by Claisen-Schmidt condensation reaction of 1-(benzofuran-6-yl)ethanone **(1)** with substituted benzaldehyde **(2a-h)** in the presence of sodium hydroxide in water-methanol mixture[26]. The structures of the compounds **(3a-h)** were confirmed by IR and $^1$H NMR spectral studies. IR spectra of compounds **(3a-h)** showed the C=C stretching frequency in the range 1572-1595 cm$^{-1}$ and $^1$H NMR showed the absence of aldehyde proton at 9.87 ppm. The substituted benzofuran-6-yl(2-phenylcyclopropyl)-methanone **(4a-h)** were prepared in good yields by the reaction of 1-(benzofuran-6-yl)-3-phenylprop-2-en-1-one **(3a-h)** with trimethylsulfoxonium iodide (TMSOI) in the presence of sodium hydride in dry DMSO. The sodium hydride acts as a base which abstracts a proton from the methyl group in trimethylsulfoxonium iodide to form a dimethylsulfoxonium methylide. It attacks nucleophilically the $\beta$-carbon atom of the 1-(benzofuran-6-yl)-3-phenylprop-2-en-1-one which acts as Michael receptors to form an enolate ion, which undergoes nucleophilic attack on the methylene carbon atom bearing the dimethyl-sulfoxonium cation intramolecularly finally to form the desired benzofuran-6-yl(2-phenylcyclopropyl)methanone. The structure of compounds **(4a-h)** was confirmed by IR spectra. In its IR spectra exhibit C=O stretching band in the range 1677-1659 cm$^{-1}$ and $^1$H NMR showed the cyclopropane CH and $CH_2$ peak at the range 0.92-0.69 and 2.45-2.10 ppm respectively. Benzofuran linked tetralones **(5a-h)** were prepared in good yields by the Friedel-Craft's intramolecular cyclization reaction of benzofuran-6-yl(2-phenylcyclopropyl-)methanone **(4a-h)** in the presence of anhyd stannic chloride and acetic anhydride in dry dichloromethane. The benzofuran-6-yl(2-phenylcyclopropyl)methanone undergo electrophilic ring opening in the presence of Lewis acid to give benzylcarbocationic intermediate which is intramolecularly attacked by aryl ring $\pi$-electrons resulting in the formation of a six membered ring with a pendant carbocation. This readily gives up proton to form benzofuran linked tetralones. Acetic anhydride facilitates the formation of desired benzofuran linked tetralones. In its IR spectra appeared absorption bands in the range 3144-2920 cm$^{-1}$ and 1774-1660 cm$^{-1}$ corresponds to aromatic C-H and C=O stretching frequencies and $^1$H NMR of CH proton appears in the range 4.22-4.07 ppm.




**Scheme 1** Synthetic protocol of benzofuran linked tetralones **(5a–h)**

*Reagents and conditions:* ***(a)*** *NaOH, EtOH-$H_2O$, r.t.;* ***(b)*** *NaH, DMSOI, DMSO;* ***(c)*** *$Ac_2O$, Anhyd. $SnCl_4$, Dry $CH_2Cl_2$*

*Antimitotic activity*

Antimitotic activity of test compounds **(5a-h)** was evaluated by onion root tip method. *Allium Cepa* has been used to evaluate the antimitotic activity of benzofuran linked tetralones **(5a–h)** by onion root tip method. Onion roots in synthesized compounds of 0.1 mg/mL at 24 h exhibited changes in chromosomes and shape of the cells with elongated appearance. The results obtained as % Inhibition are presented in given Table 1. It is more attractive to speculate the observation that the result of the antimitotic activity of the different compounds of benzofuran linked tetralones appeared to be related to benzofuran unit and substituents on the phenyl ring.

The results of antimitotic activity revealed that the majority of the synthesized compounds showed varying % inhibition compared with control. All compounds exhibited moderate to good activity (47-80% inhibition) compared to control (100% inhibition) was observed after onion roots in synthesized compounds of 0.1 mg/mL at 24 h by exhibited changes in chromosomes and shape of the cells. Compounds **5e** and **5f** were maximally active (77-80% inhibition) due to the presence of electron donating methoxy group(s) at *para* and 3,4,5-positions respectively on phenyl ring. Compounds **5g** and **5h** containing methyl group on *para* position and 3,4-positions of phenyl ring showed moderate antimitotic activity (65-73% inhibition) compared to control, followed by **5a** having no group on phenyl ring. Further, compounds **5b, 5c** and **5d** showed less activity (47-60% inhibition) because presence of electron withdrawing substituent particularly chloro, fluoro and nitro group at *para* position of phenyl ring.

**Table 1.** % Inhibition of benzofuran linked tetralones **(5a–h)** compared to control by onion root tip method

| Compounds | Entry R | | | % Dividing cells | % Dividing cells compared to control | % Inhibition |
|---|---|---|---|---|---|---|
| Control | $R^1$ | $R^2$ | $R^3$ | 40.15 | 100.00 | 100.00 |
| **5a** | H | H | H | 12.01 | 29.91 | 70.08 |
| **5b** | H | Cl | H | 16.31 | 40.62 | 59.38 |
| **5c** | H | F | H | 21.19 | 52.77 | 47.23 |
| **5d** | H | $NO_2$ | H | 19.06 | 47.47 | 52.53 |
| **5e** | H | $OCH_3$ | H | 09.18 | 22.41 | 77.59 |
| **5f** | $OCH_3$ | $OCH_3$ | $OCH_3$ | 8.01 | 19.95 | 80.05 |
| **5g** | H | $CH_3$ | H | 13.89 | 34.59 | 65.41 |
| **5h** | $CH_3$ | $CH_3$ | H | 11.14 | 27.74 | 72.26 |

## Conclusion

In view of this study, we report the preparation of benzofuran linked tetralones **(5a-h)** bearing different substituents on the phenyl ring by chalcone route. In the first step, chalcones were prepared in high yields by Claisen-Schmidt condensation reaction. The chalcones and trimethylsulfoxonium iodide (TMSOI) were a good synthon in the presence of sodium hydride for the synthesis of cyclopropanone. Finally benzofuran linked tetralones were prepared by the Friedel-Craft's intramolecular cyclization reaction. To all the compounds, the antimitotic activity was evaluated by onion root tip method. All synthesized benzofuran linked tetralones **(5a-h)** exhibited promising antimitotic activity compared to control. Compound **5e** and **5f** were exhibited effective antimitotic activity than remaining compounds. By this result, the prepared benzofuran linked tetralones are promising building blocks for medicinal and materials chemistry.

*Acknowledgment*

The authors are grateful to the University Grants Commission, Government of India, for granting UGC-PDFSS. The authors are also thankful to IOE, University of Mysore for providing spectral facilities.

## References

1. Foley P, Eghbali N and Anastas P T, *J Nat Prod.,* 2010, **73(5)**, 811-813; DOI:10.1021/np900667h
2. Lee K H, Beers S A, Mori M, Wang Z Q, Kuo Y H, Li L, Liu S Y, Chang J Y, Han F S and Chen Y C, *J Med Chem.,* 1990, **33(5)**, 1364-1368; DOI:10.1021/jm00167a013
3. Huanhuan Li, Tao Liu, Hongxia Xuan, Senbiao Fang and Chunyan Zhao, *Med Chem Res.,* 2014, **23(11)**, 4713-4723; DOI:10.1007/s00044-014-1028-7
4. Stahelin H F and Von Wartburg A, *Cancer Res.,* 1991, **51(1)**, 5-15.
5. Bhattacharyya D, Hazra S, Banerjee A, Datta R, Kumar D, Chakrabarti S and Chattopadhyay S, *Plant Mol Biol.,* 2016, **92(1-2)**, 1-23; DOI:10.1007/s11103-016-0492-5
6. Bohrin L and Rosen B, *Drug Discov Today,* 1996, **1(8)**, 343-351; DOI:10.1016/1359-6446(96)10028-3
7. Zhang L, Chen F, Wang J, Chen Y Z, Zhang Z Q, Lin Y and Zhu X L, *RSC Adv.,* 2015, **5**, 97816-97823; DOI:10.1039/C5RA21217K
8. Ikeda R, Nagao T, Okabe H, Nakano Y, Matsunaga H, Katano M and Mori M, *Chem Pharm Bull.,* 1998, **46**, 871-874.
9. Muto N, Tomokuni T, Haramoto M, Tatemoto H, Nakanishi T, Inatomi Y, Murata H and Inada A, *Biosci Biotechnol Biochem.,* 2008, **72(2)**, 477-484; DOI:10.1271/bbb.70570
10. Liu Y Q, Tian J, Qian K, Zhao X B, Morris-Natschke S L, Yang L, Nan X, Tian X and Lee K H, *Med Res Rev.,* 2015, **35(1)**, 1-62; DOI:10.1002/med.21319
11. Baldwin E L and Osheroff N, *Curr Med Chem.,* 2005, **5**, 363-372.
12. Kamal A, Arifuddin M, Dastidar S G and Kumar B A, *Bioorg Med Chem.,* 2003, **11(23)**, 5135-5142; DOI:10.1016/j.bmc.2003.08.019
13. Kamal A, Kumar B A and Arifuddin M, *Tetrahedron Lett.,* 2003, **44(46)**, 8457-8459; DOI:10.1016/j.tetlet.2003.09.110
14. Tejpal Singh Chundawat, Nutan Sharma and Sunita Bhagat, *Med Chem Res.,* 2014, **23(3)**, 1350-1359; DOI:10.1007/s00044-013-0735-9
15. Rajanarendar E, Govardhan Reddy K, Krishna S R, Shireesha B, Reddy Y N and Rajam M V, *Med Chem Res.,* 2013, **22**, 6143-6153; DOI:10.1007/s00044-013-0598-0
16. Karatas F, Koca M, Kara H and Servi S, *Eur J Med Chem.,* 2006, **41(5)**, 664-669; DOI:10.1016/j.ejmech.2006.01.003
17. Agatsuma T, Furukawa H, Hayakawa I, Shioya R and Sugano Y, *Bioorg Med Chem Lett.,* 2004, **14(13)**, 3411-3414; DOI:10.1016/j.bmcl.2004.04.079
18. Manna K and Agrawal Y K, *Eur J Med Chem.,* 2010, **45(9)**, 3831-3839; DOI:10.1016/j.ejmech.2010.05.035
19. Manna K and Agrawal Y K, *Med Chem Res.,* 2011, **20(3)**, 300-306; DOI:10.1007/s00044-010-9322-5
20. Saberi M R, Vinh T K, Yee W S, Griffiths B J N, Evans P J and Simons C, *J Med Chem.,* 2006, **49(3)**, 1016-1022; DOI:10.1021/jm0508282

21. Bigler L, Spirli C, Fiorotto R, Pettenazzo A, Duner E, Baritussio A, Follath F and Riem H H, *Eur J Med Chem.,* 2007, **42(6)**, 861-867; DOI:10.1016/j.ejmech.2006.12.031
22. Umesha B, Basavaraju Y B and Mahendra C, *Med Chem Res.,* 2015, **24(1)**, 142-151; DOI:10.1007/s00044-014-1100-3
23. Levan A, *Hereditas,* 1938, **24(4)**, 471-486; DOI:10.1111/j.1601-5223.1938.tb03221.x
24. Fissceja G, *Hereditas,* 1985, **102(1)**, 99-112; DOI:10.1111/j.1601-5223.1985.tb00471.x
25. Hakala T R, Lange P A and Fraley E F, Method *in vitro* in all Mediated and Tumor Immunity; In: Bloom B R and David J R, Ed.; Academic Press:New York, 1976, 451.
26. Umesha B and Basavaraju Y B, *Russ J Bioorg Chem.,* 2014, **40(4)**, 467-476; DOI:10.1134/S106816201404013X