European Journal of Chemistry 5 (4) (2014) 584-587

European Journal of Chemistry

Journal homepage: www.eurjchem.com

Synthesis and study of antimicrobial activity of new tetralone esters

Krishna Mudeenahally Hucchegowda, Basavaraju Yeriyur Basavaiah *, Umesha Basavaiah and Shivakumar Santhekasalagere Basavaiah

Department of Studies in Chemistry, University of Mysore, Manasagangotri, Mysore-570 006, Karnataka, India

**Corresponding author at: Department of Studies in Chemistry, University of Mysore, Manasagangotri, Mysore-570 006, Karnataka, India. Tel.: +91.948.0441804. Fax: +91.821.2421263. E-mail address: basavaraju_yb@yahoo.co.in (Y.B. Basavaraju).*

ARTICLE INFORMATION

DOI: 10.5155/eurjchem.5.4.584-587.1093

Received: 17 May 2014
Received in revised form: 28 June 2014
Accepted: 01 July 2014
Online: 31 December 2014

KEYWORDS

Tetralone esters
Cyclopropanation
Antimicrobial activity
Friedel-Crafts acylation
Claisen-Schmidt reaction
Ethyl monochloro acetate

ABSTRACT

Podophyllotoxin belongs to the class of cyclolignan family of natural products, which exhibits strong antimitotic, anti-AIDS (HIV), antitropical skin disease, antimalarial, virucidal, fungicidal and other biological activities. The new tetralone esters (9a-d) of podophyllotoxin analogues were synthesized in good yields by chalcone route to study their structure-activity relationship. All the products obtained were characterized by spectral and elemental analysis data and they were screened for antimicrobial activity. Compounds 9b and 9c were shown significant antibacterial and antifungal activities.

1. Introduction

Podophyllotoxin (**1**) is a strong antimitotic agent [1,2]. Podophyllin is a resinous extract of two important medicinal plants *Podophyllum emodi* and *Podophyllum peltatum* belonging to the family of Berberidaceae [3-6]. It has also been extracted from many other plants of podophyllum species. Podophyllotoxin and its derivatives also exhibit strong antiviral and neoplastic activity [7]. The use of podophyllotoxin in cancer chemotherapy is restricted due to its toxic side effects and unfavourable solubility.

The semi-synthetic derivatives of podophyllotoxin, etoposide (VP-16, **2**), teniposide (VM-26, **3**) are used in the treatment of cancers, including small-cell lung cancer, lymphoma, testicular carcinoma and Kaposi's sarcoma (Figure 1) [8,9]. Some of its synthetic derivatives exhibit cathartic, cytotoxic and anticancer activities [10-12]. In view of these reports, it was decided to synthesize new tetralone esters (**9a-d**) to study their structure activity relationship by modifying structures of podophyllotoxin.

2. Experimental

2.1. Materials and methods

All reagents and chemicals were purchased from Merck chemicals and were used without further purification. Melting points were determined by open capillary method and are uncorrected. The IR spectra were recorded on a FT-IR in KBr disc or Nujol. The ^{1}H NMR spectra were recorded on Jeol 300MHz and Jeol GSX-400 spectrometer using $CDCl_3$ or DMSO-d_6 as solvent and TMS as an internal reference. ^{13}C NMR (100 MHz) spectra were recorded on Bruker DRX-400 instrument with DMSO-d_6 solvent. The chemical shifts were expressed in δ ppm values. The mass spectra (ESI-MS) were recorded by Bruker daltonics on ESQUIRE-3000 instrument.

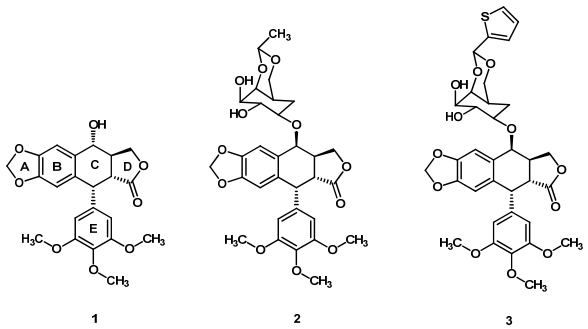
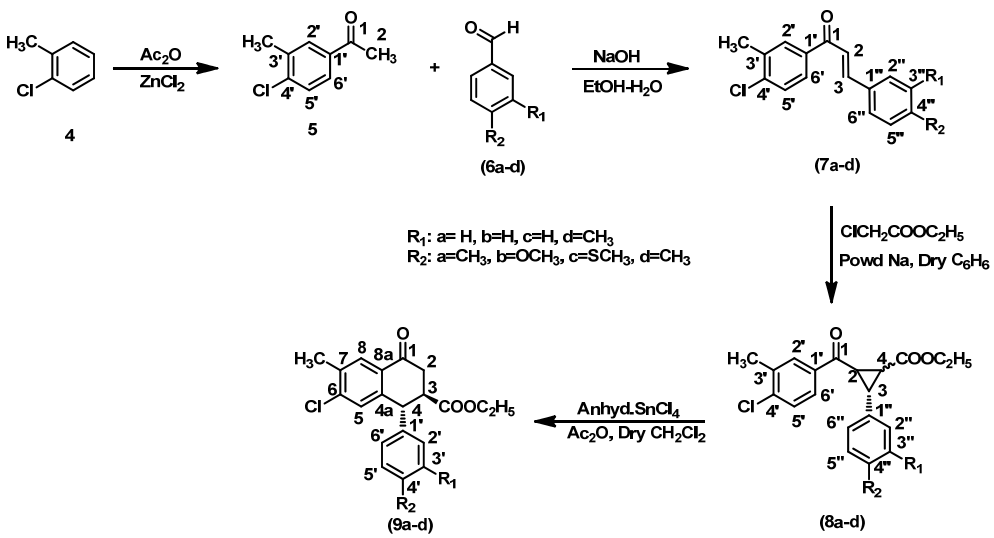


Figure 1. The structure of podophyllotoxin (**1**) and its semi synthetic derivatives etoposide (**2**) and teniposide (**3**).

ISSN 2153-2249 (Print) / ISSN 2153-2257 (Online)
http://dx.doi.org/10.5155/eurjchem.5.4.584-587.1093



Scheme 1

The purity of the compounds was checked by TLC on silica gel glass plates in benzene:ethyl acetate mixture (7:0.5, *v*:*v*). The compounds were purified by column chromatography using silica gel (60-120 mesh) as adsorbent and benzene as eluent.

2.2. Synthesis

2.2.1. Synthesis of acetophenone (5)

2-Chloro toluene (**4**) (10 g, 0.079 mol) in acetic anhydride (50 mL) containing fused zinc chloride (10.76 g, 0.079 mol) were stirred at room temperature for 12 h. After usual workup, the product was obtained and it was recrystallized from ethanol (Scheme 1).

4'-Chloro-3'-methyl-acetophenone (**5**): Color: Colourless liquid. Yield: 93.81%. B.p.: 104-105 °C. IR (KBr, *ν*, cm^{-1}): 1673 (C=O), 1598 (C=C). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 2.32 (s, 3H, CH_3), 2.49-2.54 (s, 3H, $COCH_3$), 7.34-7.73 (m, 3H, Ar-H). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 199.4 (C-1), 138.6 (C-4'), 135.5 (C-3'), 134.7 (C-1'), 130.3 (C-2'), 127.9 (C-5'), 126.8 (C-6'), 28.8 (C-2), 14.9 (3'-CH_3). MS (ESI, *m/z*): 168.03 (M$^+$). Anal. calcd. for C_9H_9ClO: C, 64.11; H, 5.38. Found: C, 64.08; H, 5.35%.

2.2.2. General procedure for the synthesis of chalcones (7a-d)

4'-Chloro-3'-methyl-acetophenone (**5**) (5 g, 0.0296 mol) and substituted benzaldehydes (**6a-d**) (0.0296 mol) were stirred vigorously in water (40 mL) and ethanol (25 mL) mixture in the presence of sodium hydroxide (1.18 g, 0.0296 mol) at 15-30 °C for 4h. The reaction mixture was kept overnight in an ice bath. The precipitated products were filtered and recrystallized from ethanol (Scheme 1).

1-(4'-Chloro-3'-methyl-phenyl)-3-(4''-methylphenyl)-prop-2-ene-1-one (**7a**): Color: Pale yellow solid. Yield: 98.6%. M.p.: 96-98 °C. IR (KBr, *ν*, cm^{-1}): 1665 (C=O), 1594 (C=C). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 2.32 (s, 3H, CH_3), 2.36 (s, 3H, CH_3), 7.04-7.62 (m, 8H, Ar-H, *α*-CH), 8.02 (d, 1H, *J*=12Hz, *β*-CH). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 188.9 (C-1), 144.7 (C-3), 139.5 (C-4'), 137.1 (C-4''), 136.3 (C-3'), 135.2 (C-1'), 131.8 (C-1''), 130.7 (C-2'), 128.9 (C-5'), 128.1 (C-3'', C-5''), 127.9 (C-6'), 126.1 (C-2'', C-6''), 121.1 (C-2), 23.8 (4''-CH_3), 14.9 (3'-CH_3). MS (ESI, *m/z*): 270.08 (M$^+$). Anal. calcd. for $C_{17}H_{15}ClO$: C, 75.41; H, 5.58. Found: C, 75.38; H, 5.54%.

1-(4'-Chloro-3'-methyl-phenyl)-3-(4''-methoxyphenyl)-prop-2-ene-1-one (**7b**): Color: Yellow solid. Yield: 92.3%. M.p.: 102-104 °C. IR (KBr, *ν*, cm^{-1}): 1662 (C=O), 1591 (C=C). ^{1}H NMR (400 MHz, DMSO, δ, ppm): 2.31 (s, 3H, CH_3), 3.82 (s, 3H, OCH_3), 6.84-7.78 (m, 8H, Ar-H, *α*-CH), 8.05 (d, 1H, *J*=13Hz, *β*-CH). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 188.8 (C-1), 159.2 (C-4''), 145.1 (C-3), 139.9 (C-4'), 136.4 (C-3'), 135.4 (C-1'), 131.3 (C-2'), 129.1 (C-5'), 128.1 (C-6'), 127.2 (C-1''), 127 (C-2'', C-6''), 121.3 (C-2), 114.1 (C-3'', C-5''), 55.7 (OCH_3), 15.1 (3'-CH_3). MS (ESI, *m/z*): 286.08 (M$^+$). Anal. calcd. for $C_{17}H_{15}ClO_2$: C, 71.20; H, 5.27. Found: C, 71.18; H, 5.24%.

1-(4'-Chloro-3'-methyl-phenyl)-3-(4''-methylthiophenyl)-prop-2-ene-1-one (**7c**): Color: Yellow solid. Yield: 91.6%. M.p.: 109-111 °C. IR (KBr, *ν*, cm^{-1}): 1667 (C=O), 1598 (C=C). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 2.33 (s, 3H, CH_3), 2.51 (s, 3H, SCH_3), 7.26-7.62 (m, 8H, Ar-H, *α*-CH), 8.04 (d, 1H, *J*=12Hz, *β*-CH). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 189.1 (C-1), 145.1 (C-3), 139.9 (C-4'), 136.2 (C-3'), 135.8 (C-1'), 135.1 (C-4''), 131.2 (C-1'', C-2'), 129.1 (C-5'), 128.1 (C-6'), 126.2 (C-3'', C-5''), 125.9 (C-2'', C-6''), 121.1 (C-2), 15.1 (3'-CH_3), 14.8 (SCH_3). MS (ESI, *m/z*): 302.05 (M$^+$). Anal. calcd. for $C_{17}H_{15}ClOS$: C, 67.43; H, 4.99. Found: C, 67.41; H, 4.96%.

1-(4'-Chloro-3'-methyl-phenyl)-3-(3'',4''-dimethylphenyl)-prop-2-ene-1-one (**7d**): Color: Yellow solid. Yield: 94.7%. M.p.: 121-123 °C. IR (KBr, *ν*, cm^{-1}): 1665 (C=O), 1597 (C=C). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 2.34 (s, 3H, 3'-CH_3), 2.34 (s, 3H, 3''-CH_3), 2.34 (s, 3H, 4''-CH_3), 6.63-7.95 (m, 7H, Ar-H, *α*-CH), 8.06 (d, 1H, *J*=12Hz, *β*-CH). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 189.3 (C-1), 144.8 (C-3), 140.1 (C-4'), 136.7 (C-3''), 136.1 (C-3'), 135.8 (C-4''), 135.2 (C-1'), 132.1 (C-1''), 131.5 (C-2'), 129.2 (C-5'), 128.6 (C-5''), 128.1 (C-6'), 126.1 (C-2''), 123.1 (C-6''), 121.2 (C-2), 18.1 (3''-CH_3), 17.3 (4''-CH_3), 14.9 (3'-CH_3). MS (ESI, *m/z*): 284.10 (M$^+$). Anal. calcd. for $C_{18}H_{17}ClO$: C, 75.92; H, 6.02. Found: C, 75.89; H, 6.01%.

2.2.3. General procedure for the synthesis of cyclopropyl keto esters (8a-d)

Chalcones (**7a-d**) (0.0184 mol), freshly distilled ethyl monochloro acetate (2.25 g, 0.0184 mol) and powdered sodium (0.8 g, 0.0368 mol) were stirred in dry benzene (120 mL) at room temperature for 30 h. The unreacted sodium and its salts were filtered off. The filtrate was washed with 5% aqueous sodium hydroxide solution (2 × 50 mL), 2% brine solution (2 × 50 mL) and dried over anhydrous sodium sulphate. The solvent

was removed by distillation to give a crude product, which was purified by column chromatography using chloroform as eluent. The products were recrystallized from ethanol (Scheme 1).

Ethyl-2-(4'-chloro-3'-methyl-benzoyl)-3-(4''-methylphenyl)-cyclopropane-1-carboxylate (**8a**): Color: Brown solid. Yield: 86.3%. M.p.: 113-115 °C. IR (KBr, *ν*, cm^{-1}): 1741 (COO), 1675 (C=O), 1597 (C=C). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 1.12-1.31 (t, 3H, *J*=4Hz, $COOCH_2CH_3$), 1.94-2.78 (m, 3H, cyclopro-CH), 2.31 (s, 3H, 3'-CH_3), 2.34 (s, 3H, 4''-CH_3), 4.05-4.13 (q, 2H, *J*=4Hz, $COOCH_2CH_3$), 6.97-7.66 (m, 7H, Ar-H). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 192.3 (C-1), 170.8 (COO), 140.2 (C-1''), 138.6 (C-4'), 135.3 (C-3'), 134.4 (C-1', C-4''), 130.2 (C-2'), 128.6 (C-5'), 128.1 (C-3'', C-5''), 127 (C-6'), 124.6 (C-2'', C-6''), 61.5 ($COOCH_2CH_3$), 35.9 (C-3), 33.2 (C-4), 31.1 (C-2), 24.1 (4''-CH_3), 15.1 (3''-CH_3), 13.8 ($COOCH_2CH_3$). MS (ESI, *m/z*): 356.12 (M^+). Anal. calcd. for $C_{21}H_{21}ClO_3$: C, 70.68; H, 5.93. Found: C, 70.66; H, 5.91%.

Ethyl-2-(4'-chloro-3'-methyl-benzoyl)-3-(4''-methoxyphenyl)-cyclopropane-1-carboxylate (**8b**): Color: Brown solid. Yield: 82%. M.p.: 103-105 °C. IR (KBr, *ν*, cm^{-1}): 1735 (COO), 1674 (C=O), 1595 (C=C). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 0.98-1.29(t, 3H, *J*=4Hz, $COOCH_2CH_3$), 1.95-2.75(m, 3H, cyclopro-CH), 2.35 (s, 3H, CH_3), 3.82 (s, 3H, OCH_3), 4.05-4.15(q, 2H, *J*=4Hz, $COOCH_2CH_3$), 6.67-7.68 (m, 7H, Ar-H). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 191.9 (C-1), 171.2 (COO), 156.8 (C-4''), 138.4 (C-4'), 135.2 (C-3'), 134.9 (C-1''), 134.2 (C-1'), 130.2 (C-2'), 128.3 (C-5'), 126.7 (C-6'), 125.8 (C-2'', C-6''), 113.3 (C-3'', C-5''), 61.6 ($COOCH_2CH_3$), 55.3 (OCH_3), 36.1 (C-3), 33.2 (C-4), 29.9 (C-2), 14.8 (3'-CH_3), 13.9 ($COOCH_2CH_3$). MS (ESI, *m/z*): 372.11 (M^+). Anal. calcd. for $C_{21}H_{21}ClO_4$: C, 67.65; H, 5.68. Found: C, 67.61; H, 5.64%.

Ethyl-2-(4'-chloro-3'-methyl-benzoyl)-3-(4''-meththio phenyl)-cyclopropane-1-carboxylate (**8c**): Color: Brown solid. Yield: 84.6%. M.p.: 120-122 °C. IR (KBr, *ν*, cm^{-1}): 1740 (COO), 1678 (C=O), 1598 (C=C). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 0.99-1.29 (t, 3H, *J*=4Hz, $COOCH_2CH_3$), 1.92-2.74 (m, 3H, cyclopro-CH), 2.34 (s, 3H, CH_3), 2.51 (s, 3H, SCH_3), 3.96-4.16 (q, 2H, *J*=4Hz, $COOCH_2CH_3$), 7.01-7.66 (m, 7H, Ar-H). ^{13}C NMR (100 MHz, DMSO-d_6,δ, ppm): 191.7 (C-1), 170.9 (COO), 139.8 (C-1''), 138.2 (C-4'), 135.4 (C-3'), 134.2 (C-1'), 132.2 (C-4''), 130.1 (C-2'), 128.4 (C-5''), 126.7 (C-6'), 126 (C-3'', C-5''), 125 (C-2'', C-6''), 61.4 ($COOCH_2CH_3$), 36 (C-3), 33.1 (C-4), 30.8 (C-2), 15 (3'-CH_3), 14.6 (SCH_3), 13.7 ($COOCH_2CH_3$). MS (ESI, *m/z*): 388.09 (M^+). Anal. calcd. for $C_{21}H_{21}ClO_3S$: C, 64.85; H, 5.44. Found: C, 64.83; H, 5.41%.

Ethyl-2-(4'-chloro-3'-methyl-benzoyl)-3-(3'',4''-dimethyl phenyl)-cyclopropane-1-carboxylate (**8d**): Color: Brown solid. Yield: 87.3%. M.p.: 130-132 °C. IR (KBr, *ν*, cm^{-1}): 1738 (COO), 1677 (C=O), 1593 (C=C). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 0.98-1.30 (t, 3H, *J*=4Hz, $COOCH_2CH_3$), 1.92-2.73 (m, 3H, cyclopro-CH), 2.30 (s, 3H, 3'-CH_3), 2.33 (s, 3H, 3''-CH_3), 2.36 (s, 3H, 4''-CH_3), 4.07-4.12 (q, 2H, *J*=4Hz, $COOCH_2CH_3$), 6.81-7.64 (m, 6H, Ar-H). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 191.5 (C-1), 170.6 (COO), 139.5 (C-1'), 138.3 (C-4'), 135.8 (C-3''), 134.8 (C-3'), 134.4 (C-1'), 133.1 (C-4''), 129.8 (C-2'), 128.2 (C-5'), 127.9 (C-5''), 126.8 (C-6'), 126.1 (C-2''), 121.7 (C-6''), 61.2 ($COOCH_2CH_3$), 36.2 (C-3), 33.2 (C-4), 30.6 (C-2), 18.1 (3''-CH_3), 17.7 (4''-CH_3), 14.6 (3'-CH_3), 14 ($COOCH_2CH_3$). MS (ESI, *m/z*): 370.13 (M^+). Anal. calcd. for $C_{22}H_{23}ClO_3$: C, 71.25; H, 6.25. Found: C, 71.23; H, 6.22%.

2.2.4. General procedure for the synthesis of tetralone esters (9a-d)

A solution of cyclopropyl keto esters (**8a-d**) (0.0140 mol) in dry dichloromethane (75 mL) was added dropwise to a magnetically stirred solution of anhydrous Stannic chloride (3.65 g, 0.0140 mol) and acetic anhydride (2.86 g, 0.0280 mol) in dichloromethane (75 mL) for half anone h at 0 °C and further stirred for 6 h. After treating the reaction mixture with 5 N HCl solution (50 mL), the organic layer was washed with 10% NaOH solution (2 × 50 mL) and finally with water. The crude product was purified by column chromatography using benzene as eluent (Scheme 1).

3-Ethylcarboxy-4-(4'-methylphenyl)-6-chloro-7-methyl-1-tetralone (**9a**): Color: Reddish brown semi solid. Yield: 87.3%. IR (KBr, *ν*, cm^{-1}): 1745 (CO), 1698 (C=O), 1592 (C=C). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 0.98-1.30 (t, 3H, *J*=4Hz, $COOCH_2CH_3$), 2.31 (s, 3H, 7-CH_3), 2.35 (s, 3H, 4'-CH_3), 2.76-3.02 (dd, 2H, CH_2), 3.63 (q, 1H, *J*=4Hz, CH), 4.11-4.22 (q, 2H, *J*=4Hz, $COOCH_2CH_3$), 4.66 (d, 1H, *J*=12Hz, CH), 7.15-7.58 (m, 6H, Ar-H). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 196.7 (C-1), 172.8 (COO), 139.9 (C-1'), 138.8 (C-6), 138.3 (C-4a), 135.4 (C-4'), 133.1 (C-7), 131.6 (C-8a), 130.7 (C-8), 129.2 (C-3', C-5'), 127.7 (C-2', C-6'), 127.6 (C-5), 61.5 ($COOCH_2CH_3$), 45.1 (C-4), 40.8 (C-3), 37.2 (C-2), 24 (4'-CH_3), 14.8 (7-CH_3), 13.9 ($COOCH_2CH_3$). MS (ESI, *m/z*): 356.12 (M^+). Anal. calcd. for $C_{21}H_{21}ClO_3$: C, 70.68; H, 5.93. Found: C, 70.65; H, 5.91%.

3-Ethylcarboxy-4-(4'-methoxyphenyl)-6-chloro-7-methyl-1-tetralone (**9b**): Color: Reddish brown semi solid. Yield: 82.6%. IR (KBr, *ν*, cm^{-1}): 1742 (CO), 1696 (C=O), 1594 (C=C). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 1.28 (t, 3H, *J*=4Hz, $COOCH_2CH_3$), 2.33 (s, 3H, CH_3), 2.73-3.04 (dd, 2H, CH_2), 3.62 (q, 1H, *J*=3Hz, CH), 3.82 (s, 3H, OCH_3), 4.19 (q, 2H, *J*=4Hz, $COOCH_2CH_3$), 4.68 (d, 1H, *J*=12Hz, CH), 6.92-7.57 (m, 6H, Ar-H). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 196.3 (C-1), 173.1 (COO), 157.8 (C-4'), 139.1 (C-6), 138.6 (C-4a), 135.1 (C-1'), 132.9 (C-7), 131.9 (C-8a), 130.6 (C-8), 129 (C-2', C-6'), 127.2 (C-5), 114.2 (C-3', C-5'), 61.3 ($COOCH_2CH_3$), 55.4 (OCH_3), 45.2 (C-4), 40.6 (C-3), 37.2 (C-2), 15 (7-CH_3), 13.7 ($COOCH_2CH_3$). MS (ESI, *m/z*): 372.11 (M^+). Anal. calcd. for $C_{21}H_{21}ClO_4$: C, 67.65; H, 5.68. Found: C, 67.62; H, 5.66%.

3-Ethylcarboxy-4-(4'-methylthiophenyl)-6-chloro-7-methyl-1-tetralone (**9c**): Color: Reddish brown semi solid. Yield: 89.4%. IR (KBr, *ν*, cm^{-1}): 1748 (CO), 1691 (C=O), 1583 (C=C). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 1.28 (t, 3H, *J*=4Hz, $COOCH_2CH_3$), 2.34 (s, 3H, CH_3), 2.53 (s, 3H, SCH_3), 2.74-3.03 (dd, 2H, CH_2), 3.60 (q, 1H, *J*=3Hz, CH), 4.21 (q, 2H, *J*=4Hz, $COOCH_2CH_3$), 4.67 (d, 1H, *J*=4Hz, CH), 7.13-7.56 (m, 6H, Ar-H). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 196.5 (C-1), 172.3 (COO), 138.8 (C-4'), 139.1 (C-6), 138.2 (C-4a), 133.4 (C-4'), 133 (C-7), 131.4 (C-8a), 130.9 (C-8), 128.3 (C-2', C-6'), 127.4 (C-5), 127.1 (C-3', C-5'), 61.5 ($COOCH_2CH_3$), 45.4 (C-4), 41.2 (C-3), 37.6 (C-2), 14.6 (7-CH_3), 13.9(SCH_3), 13.2 ($COOCH_2CH_3$). MS (ESI, *m/z*): 388.09 (M^+). Anal. calcd. for $C_{21}H_{21}ClO_3S$: C, 64.85; H, 5.44. Found: C, 64.83; H, 5.41%.

3-Ethylcarboxy-4-(3',4'-dimethylphenyl)-6-chloro-7-methyl-1-tetralone (**9d**): Color: Reddish brown semi solid. Yield: 79.8%. IR (KBr, *ν*, cm^{-1}): 1744 (CO), 1693 (C=O), 1599 (C=C). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 1.15-1.29 (t, 3H, *J*=4Hz, $COOCH_2CH_3$), 2.32 (s, 3H, 7-CH_3), 2.34 (s, 3H, 3'-CH_3), 2.35 (s, 3H, 4'-CH_3), 2.71-3.02 (dd, 2H, CH_2), 3.62 (q, 1H, *J*=3Hz, CH), 4.18-4.22 (q, 2H, *J*=4Hz, $COOCH_2CH_3$), 4.68 (d, 1H, *J*=4Hz, CH), 6.97-7.57 (m, 5H, Ar-H). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 195.7 (C-1), 172.1 (COO), 139.3 (C-1'), 138.5 (C-6), 138 (C-4a), 137.1 (C-3'), 134.2 (C-4'), 133.1 (C-7), 131.6 (C-8a), 130.9 (C-8), 129.3 (C-2'), 128.6 (C-5'), 127.5 (C-5), 125 (C-6'), 61.1 ($COOCH_2CH_3$), 45.8 (C-4), 41 (C-3'), 37.4 (C-2), 18 (3'-CH_3), 17.8 (4'-CH_3), 15(7-CH_3), 13.9 ($COOCH_2CH_3$). MS (ESI, *m/z*): 370.13 (M^+). Anal. calcd. for$C_{22}H_{23}ClO_3$: C, 71.25; H, 6.25. Found: C, 71.23; H, 6.24%.

2.3. Antimicrobial activity

The newly synthesized compounds (**9a-d**) were evaluated for their *in vitro* antibacterial activity against the gram positive bacteria *Staphylococcus aureus* and the gram negative bacteria *Escherichia coli* by disc diffusion method [13]. The bioassay was carried out using Mueller-Hinton agar (Hi-Media) medium. Ciprofloxacin was used as a standard. Simillarly the *in vitro* antifungal activity was evaluated for the compounds **9a-d**

against *Aspergillis niger* and *Candida albicans* (recultured) by disc diffusion method [14] with Sabouraud's dextrose agar (Hi-Media). Clotrimazole was used as a standard. Each compound was tested at a concentration of 100µg/mL in DMSO for both activities. The plates were incubated at 35 °C for 24 h and the resulting zone of inhibition (in mm) was measured.

3. Results and discussion

3.1. Chemistry

In this paper, the chalcone route has been followed with some changes in experimental procedure to synthesize new tetralone esters (**9a-d**) (Scheme 1) [15,16]. The 4'-chloro-3'-methyl-acetophenone (**5**) was prepared in high yield by Friedel-Crafts acylation reaction of 2-chloro toluene (**4**) with acetic anhydride in the presence of fused zinc chloride [17]. The structure of acetophenone was confirmed by IR and ^{1}H NMR spectra. The IR spectra showed C=C stretching frequency at 1598 cm^{-1} and C=O stretching frequency at 1673 cm^{-1}. The ^{1}H NMR spectra signals corresponding to $COCH_3$ appeared at 2.49-2.54 ppm.

The chalcones (**7a-d**) were prepared in excellent yields by Claisen-Schmidt reaction of 4'-chloro-3'-methyl-acetophenone (**5**) with benzaldehydes (**6a-d**) in the presence of sodium hydroxide in water-ethanol mixture [18]. The structures of chalcones were confirmed by IR and ^{1}H NMR spectra. The IR spectra of chalcones showed C=C stretching frequency in the range of 1591-1598 cm^{-1} and C=O stretching frequency in the range of 1662-1667 cm^{-1}. The ^{1}H NMR spectra signals corresponding to α-CH and β-CH of chalcones appeared at 7.62-7.95 ppm and 8.02-8.06 ppm with coupling constant J = 12 Hz.

The cyclopropyl keto esters (**8a-d**) were prepared in good yields by the reaction of chalcones (**7a-d**) with ethyl monochloro acetate in the presence of powdered sodium in dry benzene [19]. The IR spectra showed stretching frequencies at 1593-1598, 1674-1678 and 1735-1741 cm^{-1} for C=C, C=O and ester C=O of cyclopropyl keto esters respectively. The ^{1}H NMR spectra signals of cyclopropyl CH protons appeared at 1.92-2.78 ppm.

The tetralone esters (**9a-d**) were prepared in good yields by intramolecular cyclization of cyclopropyl keto esters (**8a-d**) in the presence of anhydrous stannic chloride and acetic anhydride in dry dichloromethane [20,21]. The structures of tetralone esters were based on IR, ^{1}H NMR, Mass spectra and elemental analysis data. The IR stretching frequencies of compounds (**9a-d**) showed at 1592-1599, 1691-1698 and 1742-1748 cm^{-1} for C=C, C=O and ester C=O, respectively. The ^{1}H NMR spectra signals appeared at 0.98-1.30 ppm and 4.11-4.22 ppm for CH_2 and CH_3 protons of tetralone esters with a coupling constant J = 4 Hz.

3.2. Antimicrobial activity

3.2.1. Antibacterial activity

The synthesized compounds **9a-d** were screened for their antibacterial activity. The compound **9a** has low activity compared to standard (Ciprofloxacin) and compounds **9b-d** against *Escherichia coli*a nd *Staphylococcus aureus* at a concentration of 100µg/mL. Compound **9d** has moderate activity and compounds **9b** and **9c** exhibited better activities compared to ciprofloxacin and compounds **9a** and **9d** at the same concentration. The bacterial zones of inhibition (in mm) values were summarized in Table 1.

3.2.2. Antifungal activity

The synthesized compounds **9a-d** were screened for their antifungal activity. Compounds **9b** and **9c** are more active when compared to standard (Clotrimazole). The compound **9a** exhibited low activity and the compound **9d** exhibited moderate activity against *Aspergillis niger* and *Candida albicans* at a concentration of 100µg/mL. The fungal zones of inhibition (in mm) values were summarized in Table 2.

Table1. Antibacterial activity of the synthesized compounds **9a-d**.

Compound	Zone of inhibition in (mm)	
	E. coli	*S. aureus*
9a	9	11
9b	12	14
9c	27	28
9d	29	26
Ciprofloxacin	21	23

Table 2. Antifungal activity of the synthesized compounds **9a-d**.

Compound	Zone of inhibition in (mm)	
	A. niger	*C. albicans*
9a	8	10
9b	14	15
9c	23	24
9d	25	23
Clotrimazole	22	20

4. Conclusion

The new tetralone esters **9a-d** were synthesized in good yields. They were screened for their antimicrobial activities. All the compounds exhibited better activities.

Acknowledgement

The authors are thankful to the director, Central Drug Research Institute (CDRI), Lucknow and Indian Institute of Technology (IIT), Chennai, for providing NMR, Mass spectra and elemental analysis data for our research compounds.

References

[1]. Smissman, E. E.; Murray, R. J.; McChesney, J. D. *J. Med. Chem.* **1976**, *19*, 148-153.
[2]. Jungi, W. F.; Senn, H. J. *Cancer Chemother. Rep.* **1975**, *59*, 737-742.
[3]. Podwyssotzki, V. *Arch. Exp. Pathol. Pharmakol.* **1880**, *13*, 29-52.
[4]. Jackson, D. E.; Dewick, P. M. *Phytochemistry* **1985**, *24*, 2407-2409.
[5]. Yalamati, D.; William, L. *Curr. Med. Chem.* **1998**, *5*, 205-252.
[6]. Kelly, M. G.; Hartwell, J. L. *J. Natl. Cancer Inst.* **1954**, *14*, 967-1010.
[7]. Canel, C.; Moraes, R. M.; Dayan, F. E.; Ferreira, D. *Phytochemistry* **2000**, *54*, 115-120.
[8]. Imbert, T. F. *Biochimie* **1998**, *80(3)*, 207-222.
[9]. Gordaliza, M.; Garcia, P. A.; Miguel del Corral, J. M.; Castro, M. A.; Gomez-Zurita, M. A. *Toxicon* **2004**, *44*, 441-459.
[10]. Rivera, G. *Cancer Chemother. Rep.* **1975**, *59*, 743-749.
[11]. Sathisha, A. D.; Hemakumar, K. H.; Basavaraju, Y. B. *Ind. J. Heterocycl. Chem.* **2007**, *17*, 15-18.
[12]. Lee, C. T. L.; Lin, V. C. K. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 2897-2902.
[13]. Bauer, A. W.; Kirby, W. M.; Sherris, J. C. *Am. J. Clin. Pathol.* **1966**, *39*, 493-496.
[14]. Booth, J.; Boyland, E. *Biochem. J.* **1966**, *34*, 125-135.
[15]. Basavaraju, Y. B.; Raju, D.; Anupama, N. *Int. J. Pharm. Sci. Rev. Res.* **2013**, *21*, 305-309.
[16]. Umesha, B.; Basavaraju, Y. B. *Eur. J. Chem.* **2013**, *4(3)*, 235-239.
[17]. Sadashivamurthy, B.; Basavaraju, Y. B. *Ind. J. Heterocycl. Chem.* **2006**, *15*, 259-262.
[18]. Furniss, B. S.; Hannaford, A. J.; Smith, P. W. G.; Tatchell, A. R. Vogels text book of practical organic chemistry, 5th edition, ELBS Longman, New York, 1989.
[19]. Lokanatha Rai, K. M.; Murthy, C. A.; Radhakrishna, P. M. *Synth. Commun.* **1990**, *20*, 1273-1277.
[20]. Vyas, D. M.; Skonezhy, M. P.; Jenkins, T. A.; Doyle, T. W. *Tetrahedron Lett.* **1986**, *27*, 3099-3102.
[21]. Sadashivamurthy, B.; Basavaraju, Y. B. *Bulg. Chem. Commun.* **2005**, *37*, 135-139.