Journal of Chemical, Biological and Physical Sciences

An International Peer Review E-3 Journal of Sciences

*Available online at*www.jcbsc.org

Section A: Chemical Sciences

CODEN (USA): JCBPAT Research Article

Synthesis, Characterization and Antimicrobial Activity of Some 5-Aryl-(*2E, 4E*)-Pentadienoic Acid Derivatives

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Received: 25 May 2014; **Revised:** 05 June 2014; **Accepted:** 10 June 2014

Abstract: A number of (*2E, 4E*)-5-(aryl)-3-methoxypenta-2, 4-dienoic acids (2a-e) have been prepared in good yields by condensation of ethyl (2*E*)-3-methoxybut-2-enoate with substituted benzaldehyde in KOH/DMSO solution. Similarly, reaction of **2** with benzyl bromide in dry acetone as the solvent and in presence of K_2CO_3 as a base afforded a series of pentadienoate derivatives (3a-e). Structures of these newly synthesized compounds derivatives were confirmed by IR, ^{1}H NMR, ^{13}C NMR, and MS spectra and by elemental analysis. Moreover, the prepared compounds were evaluated *in vitro* for their antibacterial and antifungal activities.

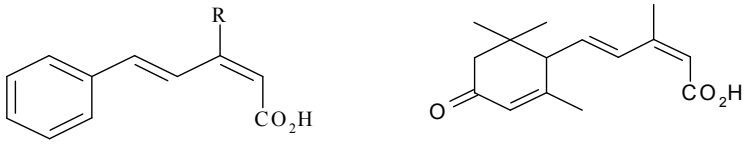
Keywords: 5-Aryl-3-alkoxy-(*2E, 4E*)-2, 4-pentadienoic acids, abscisic acid, KOH /DMSO, antibacterial and antifungal activities.

INTRODUCTION

Pentadienoic acid derivatives (I) have been a subject of interest in our laboratory [1-4]. Our attraction to this area of research arose from the fact that these compounds are structurally related to an important plant growth inhibitor, abscisic acid (ABA) (II) whose biological activity depends on certain structural features: A free carboxyl group, a six-membered ring that contains a double bond in the α or β positions, and the

configuration of C-2 double bond must be *cis* [2]. These features are in fact present in pentadienoic acid (PDA) derivatives [2]. In addition, some pentadienoic acids have retinoid-like biological activity [5, 6] as well as many other applications in plant chemistry, as plant growth regulators, in industry as adhesive compounds[7] and in medicinal chemistry as anti-diabetic agents[8] antimalarial[9] for the prevention or treatment of hyperuricemia, for reducing the serum uric acid level of a subject[10] for treatment of liver disorders[11] and for chemotherapy in the treatment of inflammation, atherosclerosis, restenosis, and immune disorders[12-14]. Moreover, some amide derivatives are able to prevent the excessive bone desorption associated with osteoporosis[15-17] and are employed as anti-allergic agents with antihistaminic and anti slow-reacting substance (SRS) activities[18] and in combination with anti-infective drugs for treatment of infectious diseases. Similarly, others such as N-phenylethyl-5-phenyl-2, 4-pentadienamide were used as blood platelet aggregation inhibitors and as antifungal agents[19-21].

A number of reports dealing with the synthesis of structurally related compounds such as 2, 4-pentadienoic acids (I) have appeared in the literature. Condensation of ethyl *β*-alkyl (or alkoxy) crotonates with carbonyl compounds in presence of lithium diisopropylamide (LDA), sodium hydride, lithium or sodium amide was employed as a method to prepare a number of these acids in 48-97% yields[1, 8-12]. Similarly, the reaction of phosphorous, arsenic, or tellurium ylides with some aldehydes and ketones afforded the corresponding dienoic acids through Wittig-type reactions[13-15]. In addition to synthetic procedures, we have undertaken calculations to predict, in a simple way, the strength of activity of 5-aryl-3-alkoxy-(2*E*,4*E*)-2,4-pentadienoic acids as new plant growth regulators from the value of total dipole moment (TDM) in the molecule under investigation using AM1 semi-empirical quantum mechanical methods. The validity of this hypothesis was checked by comparisons with experimental results obtained by other investigations.



(I) (II)

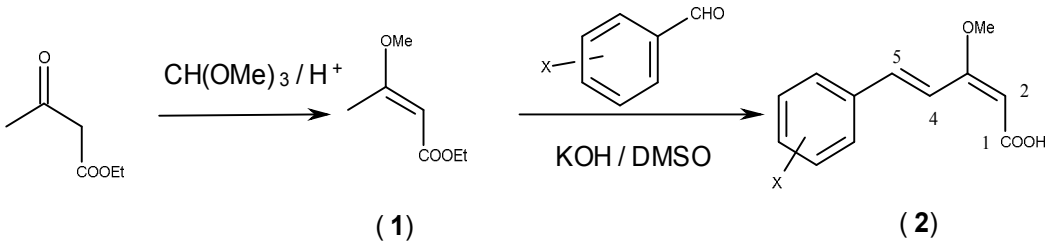
Figure 1: Structures of pentadienoic acid (PDA) derivative (I) and abscisic acid (ABA) (II).

In view of the wide interest in the chemistry of alkenoic acids, we describe, herein, the synthesis and characterization of (*2E, 4E*)-5-(aryl)-3-methoxypenta-2, 4-dienoic acids (2a-e), with expected biological activities, from ethyl (*2E*)-3-methoxybut-2-enoate (1). The synthetic strategy involved KOH as a base in DMSO as a solvent instead of other solvent/base combinations reported in the literature [1]. Additionally, the synthesis and characterization of some benzyl-(*2E, 4E*)-5-(aryl)-3-methoxypenta-2, 4-dienoate derivatives (3a-e) are also described. The antimicrobial activity of the synthesized compounds was investigated in vitro.

RESULTS AND DISCUSSION

Chemistry: Ethyl (*2E*)-3-methoxybut-2-enoate (**1**) required in this study was prepared according to a published procedure [4, 22] which involves the reaction of ethyl acetoacetate and trimethyl orthoformate, followed by addition of concentrated hydrochloric acid. Immediate distillation of the reaction mixture afforded the desired product as a mixture of *E*- and *Z*- isomers, with the *E*- isomer as the major product, in

a 96% yield. Condensation of **(1)** with substituted benzaldehyde using DMSO as solvent and KOH as base afforded (*2E, 4E*)-5-(aryl)-3-methoxypenta-2, 4-dienoic acid **(2a-e)** in good yields (**Scheme 1**).



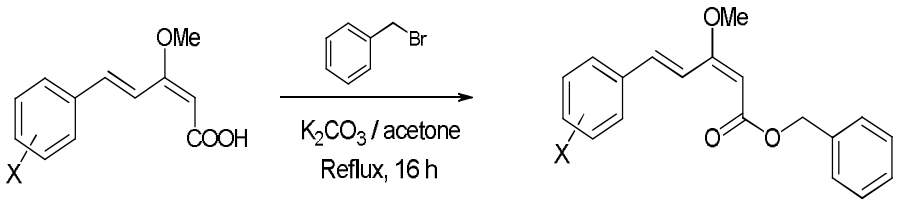
(**1**) (**2**)

Compounds (**2**)

	a	b	c	d	e
X	3-Cl	4-Cl	2,4-Cl,Cl	3,4-Cl,Cl	4- NO_2

Scheme 1: Synthesis of compounds 2a-e.

Similarly, reaction of 2 with benzyl bromide in dry acetone as solvent and in presence of K_2CO_3 as a base, yielded compounds (3a-e) in moderate to good yield as shown in **Scheme 2**.



(**2**) (**3**)

Compounds (**2**) and (**3**)

	a	b	c	d	e
X	3-Cl	4-Cl	2,4-Cl,Cl	3,4-Cl,Cl	4-NO_2

Scheme 2: Synthesis of compounds 3a-e.

The structures of the prepared compounds were confirmed by NMR, mass spectrometry, and elemental analysis. The ^{1}H and ^{13}CNMR spectra of all prepared compounds are in total agreement with the suggested structures. The H-2 signal resonated at a slightly higher chemical shift than H-4 and H-5 signals. The (*4E*)-stereochemistry was confirmed from the coupling constant value (J = 16 Hz) for H-4 and H-5 signals for all synthesized compounds ($J_{cis} \approx 12.5$ Hz). DEPT experiments were employed to differentiate secondary and quaternary carbons from primary and tertiary ones. Additional support of the proposed structures comes from mass spectral data; HRMS of the prepared compounds showed the correct molecular ions as suggested by their molecular formulas. In conclusion, we have prepared a number of new (*2E, 4E*)-5-(aryl)-3-methoxypenta-2, 4-dienoic acids (2a-e) from ethyl (2*E*)-3-methoxybut-2-enoate (1).

Although similar compounds have been prepared and characterized in the literature, our compounds were prepared using different experimental conditions, which to the best of our knowledge were not used before. In the past, people employed sodium hydride in THF while in our syntheses we have used potassium hydroxide/DMSO.

Antimicrobial Activity of the Synthesized Compounds: The antimicrobial activity of the synthesized compounds was studied *in vitro* against different pathogens as shown in **Table 1**. Results revealed that compounds 2c, 2d, 2e, and 3e displayed antibacterial activities against tested Gram positive bacteria (*S. aureus* and *S. pneumonia*). However, none of the prepared compounds showed any activity against Gram negative bacteria and against selected fungal plant pathogens (data was not presented). The highest antibacterial activity was achieved from compound 2d against *S. pneumonia* where the inhibition zone was 15 ± 0.2 mm indicating moderate effect compared to the control antibiotics employed.

Table-1: Effect of compounds **2a-e** and **3b-e** on selected Human pathogens.

Compound and control antibiotics	**Zone of inhibition (mm) in pathogen's cultures**				
	S. aureus	***K. oxytoca***	***S. pneumonia***	***E. coli***	***P.aeruginosa***
2a	ND	ND	ND	ND	ND
2b	ND	ND	ND	ND	ND
2c	7±2	ND	7±2	ND	ND
2d	10±2	ND	15±2	ND	ND
2e	ND	ND	10±2	ND	ND
3b	ND	ND	ND	ND	ND
3c	ND	ND	ND	ND	ND
3d	ND	ND	ND	ND	ND
3e	13±2	ND	9±2	ND	ND
Amoxicillin	20±1	20 ± 1	20 ± 2	20 ± 1	20±1
Streptomycin	18±5	18 ± 5	19 ± 4	19 ± 5	21±1
Bacteriocin	23±1	27 ± 1	23 ± 1	21 ± 1	23±1

ND: not detected

EXPERIMENTAL

Materials and Equipment: All chemicals used in this investigation were obtained from commercial sources (Across, Merck, and Fluka) and were used as received without further purification with the exception of trimethyl orthoformate which was distilled before being used. Progress of reactions was monitored by thin layer chromatography (TLC), using glass plates pre-coated with silica gel (E. Merck Kiesegel 60 F254 layer thickness 0.25 mm). Melting points were measured on a Stuart scientific melting point apparatus in open capillary tubes and were uncorrected. Infrared spectra (IR) were obtained, as potassium bromide (KBr) discs, on Nicolet-MAGNA-IR-560 spectrophotometer; only characteristic peaks are indicated in wave number (cm^{-1}). ^{1}H and ^{13}C NMR spectra were recorded with the aid of a Bruker DPX 300 MHz spectrometer (Germany) with $CDCl_3$ or DMSO-d_6 as solvent and TMS as the internal standard. Chemical shifts are expressed in δ units; *J* values for ^{1}H–^{1}H coupling constants are given in Hertz. High resolution mass spectra (HRMS) were obtained using an electrospray ion trap (ESI) technique by collision-induced dissociation on a Bruker APEX-4 (7-Tesla) instrument (Bremen, Germany).

The samples were dissolved in acetonitrile, diluted in spray solution (methanol/water 1:1 v/v +0.1% formic acid) and infused using a syringe pump with a flow rate of 2 mL/min. External calibration was conducted using arginine cluster in a mass range *m/z* 175-871. Elemental analyses were performed on a Euro-Vector Euro, C, H, N and S elemental analyzer (EA3000); the obtained results agreed with the calculated percentages to within ±0.4%. Compounds were checked for their purity by TLC using glass plates, precoated with silica gel 60 GF254, supplied by Fluka.

Synthesis of Ethyl 3-methoxy-(*2E*)-butenoate (1)

The title compound was synthesized according to published procedures[4, 22].

General procedure for preparation of 5-aryl-3-methoxy-(*2E,4E*)-2,4-pentadienoic acids (2a-e): Compounds 2a-e were synthesized and purified according to the following general procedure: to a solution of 6.0 g (0.040 mol) of ethyl (*2E*)-3-methoxybut-2-enoate (1) in 9.5 mL of dimethylsulfoxide (DMSO) were added 0.040 mol of the appropriate aldehyde and 4.66 g (0.040 mol) of 50% aqueous potassium hydroxide solution and the mixture was heated at 100 °C for about 4 h. After cooling, the mixture was diluted with 100 mL of water and extracted with diethyl ether (3x100 mL). Dilute HCl was added, with stirring, to the aqueous layer to bring the pH of solution to 3.5-4. The precipitated crude product was filtered, washed repeatedly with water and dried. It was then, suspended in 50 mL of ethanol, filtered off, and dried to give the desired products (2a-e).

Synthesis of Benzyl -(*2E, 4E*)- 5-(aryl) - 3-methoxypenta-2, 4-dienoate (3a-e)

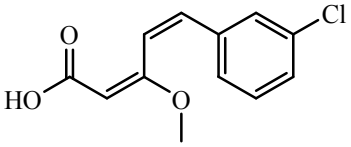
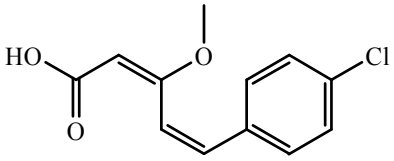
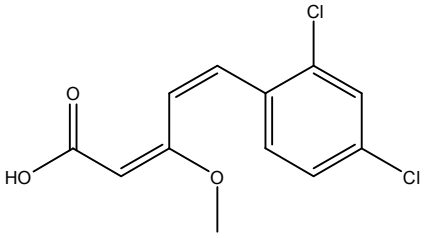
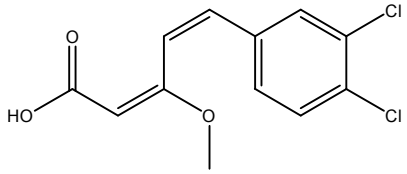
The following general procedure was employed for the synthesis of compounds (3a-e): to a stirred solution of 0.004 mol of the appropriate acid (2a-e) in 20 mL of acetone was added 1.2 g (0.008 mol) of solid potassium carbonate.

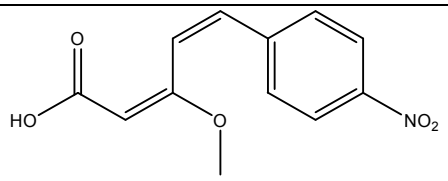
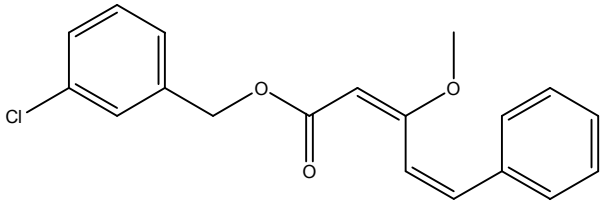
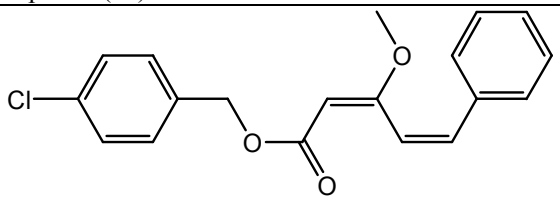
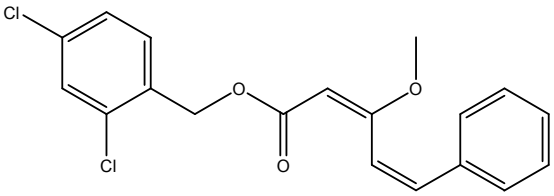
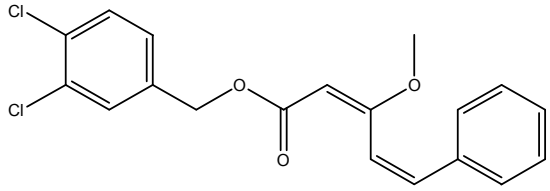
Table-2: Characterization data of prepared compounds.

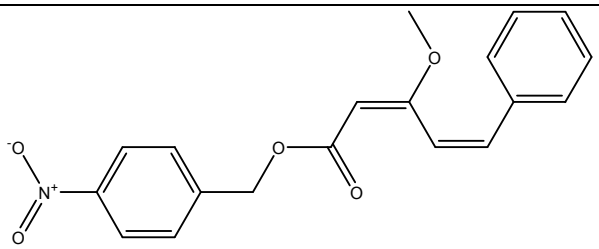
Compound	Formula	Mol.Wt.	% Calculated, %(found)			% Yield	M.P °C
			C	H	N		
2a	$C_{12}H_{11}ClO_3$	238.67	60.39 (60.56)	4.65 (4.43)		32	175-176
2b	$C_{12}H_{11}ClO_3$	238.67	60.39 (60.34)	4.65 (4.54)		67	167-170
2c	$C_{12}H_{10}Cl_2O_3$	273.12	52.77 (52.74)	3.69 (3.40)		83	170-171
2d	$C_{12}H_{10}Cl_2O_3$	273.12	52.77 (52.82)	3.69 (3.52)		56	203-205
2e	$C_{12}H_{11}NO_5$	249.23	57.83 (57.92)	4.45 (4.42)		60	195-197
3a	$C_{19}H_{17}ClO_3$	328.80	69.41 (69.38)	5.21 (5.09)		58	84-88
3b	$C_{19}H_{17}ClO_3$	328.80	69.41 (70.01)	5.21 (5.12)		77	92-95
3c	$C_{19}H_{16}Cl_2O_3$	363.24	62.83 (62.64)	4.44 (4.22)		74	76-77
3d	$C_{19}H_{16}Cl_2O_3$	363.24	62.83 (62.60)	4.44 (4.23)		41	103-106
3e	$C_{19}H_{17}NO_5$	339.35	67.25 (67.45)	5.05 (4.64)	4.13 (4.16)	23	66-68

The mixture was stirred at room temperature for 10 min followed by the addition of 0.684 g (0.004 mol) of benzyl bromide. The mixture was then refluxed for 16 h and the solid was filtered off. The solvent was removed under reduced pressure and the solid crude was recrystallized from ether to afford compounds 3a-e in pure form. The composition and properties of the prepared compounds are summarized in **Tables 2** and **3**.

Table-3: Spectral data of newly prepared compounds.

Compound (2a)	**Spectral data**
 (*2E,4E*)-5-(3-chlorophenyl)-3-methoxypenta-2,4-dienoic acid	IR (KBr), $\tilde{\nu}$ /cm^{-1}: 1677.8, 1633, 1583. ^{1}H NMR ($CDCl_3$): δ 3.69 (s, 3H), 5.19 (s, 1H), 7.17 (d, *J* = 16 Hz, 1H), 7.35-7.50 (m, 4H) 8.00 (d, *J* = 16 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 56.1, 94.6, 122.1, 127.3, 128.3, 129.1, 130.5, 131.2, 133.0, 134.2, 165.6, 168.4. HRMS (ESI) *m/z*: calcd for ($C_{12}H_{12}ClO_3$) $[M+H]^+$ 239.04750; found 239.04695
Compound (2b)	**Spectral data**
 *(2E,4E)*-5-(4-chlorophenyl)-3-methoxypenta-2,4-dienoic acid	IR (KBr), $\tilde{\nu}$ /cm^{-1}: 1675, 1629, 1589 ^{1}H NMR ($CDCl_3$): δ 3.68 (s, 3H), 5.17 (s, 1H), 7.16 (d, *J* = 16 Hz, 1H), 7.38 (d, *J* = 8 Hz, 2H), 7.89 (d, *J* = 8 Hz, 2H), 8.00 (d, *J* = 16 Hz, 1H). ^{13}C NMR($CDCl_3$): δ 56.1, 94.2, 121.2, 128.3, 129.4, 131.6, 133.3, 133.9, 135.1, 138.3, 166.4, 168.5 HRMS (ESI) *m/z*: calcd for ($C_{12}H_{12}ClO_3$) $[M+H]^+$ 239.04750; found 239.04695
Compound (2c)	**Spectral data**
 (*2E,4E*)-5-(2,4-dichlorophenyl)-3-methoxypenta-2,4-dienoic acid	IR (KBr), $\tilde{\nu}$ /cm^{-1}: 1682, 1631, 1580 ^{1}H NMR (DMSO-d_6): δ 3.76 (s, 3H), 5.26 (s, 1H), 7.40 (d, *J* = 16 Hz, 1H), 7.45-7.69 (m, 3H), 8.03 (d, *J* = 16 Hz, 1H). ^{13}C NMR (DMSO-d_6): δ 56.3, 95.2, 124.0, 128.5, 129.8, 130.5, 132.8, 133.5, 134.2, 134.5, 165.1, 168.3. HRMS (ESI) *m/z*: calcd for ($C_{12}H_9Cl_2O_3$) $[M-H]^-$ 270.99287; found 270.99342
Compound (2d)	**Spectral data**
 (*2E,4E*)-5-(3,4-dichlorophenyl)-3-methoxypenta-2,4-dienoic acid	IR (KBr), $\tilde{\nu}$ /cm^{-1}: 1678, 1629, 1572. ^{1}H NMR (DMSO-d_6): δ 3.69 (s, 3H), 5.20 (s, 1H), 7.16 (d, *J* = 16 Hz, 1H), 7.44-7.73 (m, 3H), 7.99 (d, *J* = 16 Hz, 1H). ^{13}C NMR (DMSO-d_6): δ 56.1, 94.9, 122.6, 127.3, 129.7, 131.9, 132.0, 132.2, 132.9, 137.1, 165.4, 168.3. HRMS (ESI) *m/z*: calcd for ($C_{12}H_{11}Cl_2O_3$) $[M+H]^+$ 273.00852; found 273.00798
Compound (2e)	**Spectral data**
	IR (KBr), $\tilde{\nu}$ /cm^{-1}:1692, 1604, 1540 ^{1}H NMR (DMSO-d_6): δ 3.76 (s, 3H), 4.64 (s, 1H), 7.32 (d, *J* =

 *(2E,4E*)-3-methoxy-5-(4-nitrophenyl)penta-2,4-dienoic acid	16 Hz, 1H), 8.13(d, *J* = 16 Hz, 1H), 8.17 (d, *J* = 8 Hz, 2H), 8.35 (d, *J* = 8 Hz, 2H). ^{13}C NMR (DMSO-d_6): δ 62.5, 95.7, 123.6, 124.23, 128.7, 131.2, 136.85, 141.8, 147.2, 166.3, 168.19. HRMS (ESI) *m/z*: Calcd for ($C_{12}H_{11}NO_5$) $[M+H]^+$ 250.07155; found 250.07112
Compound (3a)	**Spectral data**
 *(2E,4E*)-3-chlorobenzyl3-methoxy-5-phenylpenta-2,4-dienoate	IR (KBr), $\tilde{\nu}$ /cm^{-1}: 1702, 1636, 1581, 1288, 1134, 1191.5 ^{1}HNMR (DMSO-d_6): δ 3.77 (s, 3H), 5.16 (s, 2H), 5.36 (s, 1H), 7.28 (d, *J* = 16 Hz, 1H), 7.35 -7.50 (m, 9H), 8.03 (d, *J* = 16 Hz, 1H). ^{13}C NMR δ: 56.5, 65.55, 93.5, 121.8, 129.3, 166.4, 166.8, 126.2-138.3 (Ar-C) HRMS (ESI) *m/z*: calcd for ($C_{19}H_{18}ClO_3$) $[M+H]^+$ 329.09445; found 329.09390
Compound (3b)	**Spectral data**
 *(2E,4E*)-4-chlorobenzyl 3-methoxy-5-phenylpenta-2,4-dienoate	IR (KBr), $\tilde{\nu}$ /cm^{-1}:1701, 1636, 1584, 1278, 1149, 1191 ^{1}H NMR (DMSO-d_6): δ 3.77 (s, 3H), 5.19 (s, 2H), 5.35 (s, 1H), 7.28 (d, *J* = 16 Hz, 1H), 7.33–7.66 (m, 9H), 8.00 (d, *J* = 16 Hz, 1H). ^{13}C NMR (DMSO-d$_6$): δ 56.4, 65.5, 93.1, 121.0, 129.5, 166.4, 166.9, 128.4-137.0 (Ar-C) HRMS (ESI) *m/z*: calcd for ($C_{19}H_{18}ClO_3$) $[M+H]^+$ 329.09445; found 329.09390
compound: (3c)	**Spectral data**
 *(2E,4E*)-2,4-dichlorobenzyl 3-methoxy-5-phenylpenta-2,4-dienoate	IR (KBr), $\tilde{\nu}$ /cm^{-1}: 1698, 1634, 1579, 1280, 1140, 1194 ^{1}H NMR (DMSO-d_6): δ 3.78 (s, 3H), 5.15 (s, 2H), 5.40 (s, 1H), 7.36 (m, 5H), 7.32–7.52 (m, 9H), 8.03 (d, *J* = 16 Hz, 1H). ^{13}C NMR (DMSO-d$_6$): δ 56.6, 65.6, 94.1, 123.6, 129.9, 165.9, 166.7, 128.4-136.8 (Ar-C) HRMS (ESI) *m/z*: calcd for ($C_{19}H_{17}Cl_2O_3$) $[M+H]^+$ 363.05547; found 363.05493
compound: (3d)	**Spectral data**
 *(2E,4E*)-3,4-dichlorobenzyl 3-methoxy-5-phenylpenta-2,4-dienoate	IR (KBr), $\tilde{\nu}$ /cm^{-1}: 1698, 1639, 1584, 1280, 1133, 1189 ^{1}H NMR (DMSO-d_6): δ 3.77 (s, 3H), 5.16 (s, 2H), 5.37 (s, 1H), 7.27(d, *J* = 16 Hz, 1H), 7.37 (m, 1H), 7.41 (m, 3H), 7.54 (dd, *J* = 8.4, 10.2 Hz, 1H), 7.66 (d, *J* = 8 Hz, 1H), 7.79 (s, 1H), 8.01 (d, *J* = 16 Hz, 1H) ^{13}C NMR (DMSO-d$_6$): δ 55.5, 66.5, 93.7, 122.3, 129.4, 166.2, 166.8, 127.3-136.9 (Ar-C) HRMS (ESI) *m/z*: calcd for ($C_{19}H_{17}Cl_2O_3$) $[M+H]^+$ 363.05547; found 363.05493
compound: (3e)	**Spectral data**

 *(2E,4E*)-4-nitrobenzyl 3-methoxy-5-phenylpenta-2,4-dienoate	IR (KBr), /cm–1: 1712, 1635, 1601, 1522, 1277, 1121 1H NMR (DMSO-d6): δ 3.23 (s, 3H), 5.41 (s, 2H), 5.55 (s, 1H), 8.2 (d, J =16 Hz, 1H), 7.31–7.51 (m, 8), 7.40 (d, J = 16 Hz, 1H) 13C NMR (DMSO-d6): δ 62.5, 66.5, 103.3, 124.2, 143.8, 164.6, 168.2, 124.3-143.7 (Ar-C) HRMS (ESI) m/z: calcd for (C19H17NO5) [M+H]+ 340.11850; found 340.11795

BIOLOGICAL EVALUATION

Antimicrobial Susceptibility: The *in vitro* antibacterial activity of the synthesized compounds was determined by the agar well diffusion method, using 5 bacterial strains namely: *Staphylococcus aureus* ATCC 92701, *Streptococcus pneumonia* ATCC 6303, *Escherichia coli* ATCC 10145, *Klebsiella oxytoca* ATCC 13182, and *Pseudomonas aeruginosa* ATCC 29737. The test bacteria were cultured in nutrient broth at 37 °C for 18 h. Autoclaved Mueller Hinton agar (MHA) medium was cooled down to 40 °C, and then 1 mL of above bacterial suspension (10^6 cfu/mL) was mixed with 15 mL of this medium, poured into a sterile Petri dish and allowed to set. Test compounds were prepared by dissolving 2 mg of each compound in 100 µL of dimethyl sulfoxide (DMSO). Wells of 6 mm in diameter were made on the solidified medium using a sterile cork borer and filled with 50 µL of each compound. Antibiotic disks (10 µg/disk), including Streptomycin, Amoxicillin, and Bacteriocin, were used along with 50 µL of mixture of DMSO were used as control. Culture plates were incubated at 37 °C for 24 h and the antibacterial activity was determined by measuring the diameter of inhibition zone around the well. Each experiment was repeated twice.

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