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Synthesis, Characterizations and Antibacterial Activity of (*E*)-1-(4-(3-chlorophenoxy)-2-chlorophenyl)-3-phenylprop-2-ene-1-one Derivatives

Rohidas Gilbile[1,2], Devanand B. Shinde[1]*, B.Ram[2] and B.Balram[2]

1. Department of Chemical Technology, Dr. Babasaheb Ambedkar Marahtwada University, Aurangabad-431004, MS, **INDIA**
2. Green Evolution Laboratories, Wangapally Village, Nalgonda, 500085, Telangana State, **INDIA**

Email: rohidasgilbile2015@gmail.com

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ABSTRACT

The growth of new styryl ketones has revealed therapeutic efficacy for the management of several diseases. Styryl ketones having an α, β unsaturated carbonyl group are versatile synthons for various chemical transformations and taken an important place in organic chemistry, the research in this area is encouraged because of development of bacterial resistance to widely used antibiotics of this type. The present paper describes the synthesis and antibacterial activity of novel styryl ketone derivatives derived from 1-(4-(3-chlorophenoxy)2-chlorophenyl)ethanone.

Keywords: Styryl ketone, Antibacterial Activity, 3-Chlorophenol, 2, 4-Dichloroacetophenone.

INTRODUCTION

Infectious diseases caused by bacteria have increased tremendously in recent years. Though many significant advances have been made in antibacterial therapy, the widespread use and misuse of antibiotics have caused the emergence of bacterial resistance to antibiotics [1-3]. Styryl ketones are 1,3-diphenyl-2-propene-1-one, in which two aromatic rings are linked by a three carbon α, β-unsaturated carbonyl system and are a chemical class that has shown promising therapeutic efficacy for the management of several diseases. Many papers have been presented in the literature with references to structural modifications of the styryl template [4]. Natural and synthetic styryl ketones have shown broad spectrum of biological activities such as anti-inflammatory [5], antituberculosis [6], antifungal [7], antimalarial [8], antileish-manicidal [9], anticancer [10-14], antitumour [15], antibacterial [16] and as inhibitors of mycobacterial FAS-II and PknG [17]. Encouraged by the various biological activities associated with styryl ketone derivatives we report herein the synthesis, characterization and antibacterial activity of six new styryl ketone derivatives derived from 1-(4-(3-chlorophenoxy)2-chlorophenyl)ethanone.

MATERIALS AND METHODS

The solvents were purified according to standard procedures prior to use, and all commercial chemicals were used as received. For thin-layer chromatography (TLC) analysis, Merck pre-coated Plates (silica gel 60 F254) were used and spots were visualized with UV light. Merck silica gel 60 (230-400 mesh) was used for flash column chromatography and the eluting solvents are indicated in the procedures. Melting point (mp) determinations were performed by using Mel-temp apparatus and are uncorrected. ^{1}H NMR spectra were recorded in Varian MR-400 MHz instrument. Chemical shifts are reported in δ parts per million (ppm) downfield from tetramethylsilane (TMS) with reference to internal standard and the signals were reported as s (singlet), d (doublet), dd (doublet of doublet), t (triplet), q (quartet), m (multiplet) and coupling constants in Hz. The mass spectra were recorded on Agilent ion trap MS. Infrared (IR) spectra were recorded on a Perkin Elmer FT-IR spectrometer.

Preparation of 1-(4-(3-chlorophenoxy)2-chlorophenyl)ethanone (3): To a stirred mixture of 3-chloro phenol (**2**) (1.0 mmol), cesium carbonate (1.5 mmol), CuI (0.02 mmol) in N,N-dimethylformamide (15 mL) was added slowly a pre-mixed solution of 2,4-dichloroacetophenone (**1)** (2.5 mmol) in N,N-dimethylformamide (5 mL) at room temperature. The reaction mixture was stirred at 110°C for 12.0 h. The reaction was quenched with water and extracted with ethyl acetate. The organic layer was washed with water and saturated sodium chloride, dried over magnesium sulphate, filtered and the solvent was evaporated under vacuum to afford compound **3**. Pale yellow solid; Yield: 1.19g, 80%; m.p. 110−115^{o}C; IR (KBr): ν_{max} 3088, 2930, 1741, 1663 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.63 (s, 3H), 6.84 (d, 1H, J = 7.0 Hz), 6.95 (d, 2H, J = 7.8 Hz), 7.15 (d, 1H, J = 7.6 Hz), 7.34 (d, 2H, J = 7.8 Hz), 7.8 (d, 1H, J = 7.6 Hz) ; ESI MS: m/z (rel.abund. %): 280.10 (M$^+$, 100).

General experimental procedure for the preparation of styryl derivatives (4a-e):1-(4-(3-chloro phenoxy)2-chlorophenyl)ethanone (200 mg, 1.0 mmol) was added to a solution of NaOH (4 eq) in methanol at room temperature and stirred for 5-10 min. To this reaction mixture was added appropriate benzaldehydes **a-e** (2.0 mmol) and stirred at room temperature for 6 h. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with brine solution, dried over anhydrous sodium sulphate filtered and concentrated under reduced pressure, to obtain the crude compounds. The crude compounds were purified by washing several times with pet-ether or sometimes they were purified by column chromatography using silica gel (60-120 mesh). Yields of the products varied between 80- 88%.

(*E*)-1-(4-(3-chlorophenoxy)-2-chlorophenyl)-3-phenylprop-2-en-1-one (4a): Pale yellow solid; Yield 83%; m.p.116-117 ^{o}C; IR (KBr): υ_{max} 3084, 2888, 1744, 1645, 1575, 1460, 1385, 1265, 1145, 985, 880, 785, 650 cm^{-1}; ^{1}H NMR: (400MHz, DMSO-d$_6$): δ 7.68 (d, 1H, *J* = 7.2 Hz), 7.54 (d, 1H, *J* = 15.4 Hz), 7.42 (d, 2H, *J* = 7.8 Hz), 7.38-7.30 (m, 3H), 7.25 (d, 1H, *J* = 15.0 Hz), 7.20 (dd, 1H, *J* = 7.84, 7.64 Hz), 7.15 (t, 1H, *J* = 7.8 Hz), 7.0 (d, 1H, *J* = 7.8 Hz), 6.90 (dd, 1H, *J* = 7.4,7.8 Hz), 6.64 (s, 2H); ESI-MS: m/z (rel.abund. %): 369.2 (M$^+$, 100).

(*E*)-1-(4-(3-chlorophenoxy)-2-chlorophenyl)-3-(4-methoxyphenyl)prop-2-en-1-one (4b): Pale yellow solid; Yield 80%; m.p.: 96-97^{o}C; IR (KBr): υ_{max} 3064, 2890, 1741, 1640, 1575, 1540, 1465, 1445, 1388, 1356, 1288, 1265, 1135, 984, 945, 858, 780, 645 cm^{-1}; ^{1}H NMR: (400MHz, DMSO-d$_6$): δ 7.71 (d, 2H, *J* = 7.4 Hz), 7.88 (d, 1H, *J* = 15.8 Hz), 7.68 (d, 2H, *J* = 7.8 Hz), 7.54 (d, 1H, *J* = 15.6 Hz), 7.44 (dd, 1H, *J* = 7.6, 7.58 Hz), 7.48 (d, 1H, *J* = 7.4 Hz), 7.38 (d, 1H, *J* = 7.8 Hz), 7.26 (d, 2H, *J* = 7.8 Hz), 7.18 (d, 2H, *J* = 7.8 Hz), 3.89 (s,3H); ESI-MS: m/z (rel.abund. %): 399.64 (M$^+$, 100).

(*E*)-1-(4-(3-chlorophenoxy)-2-chlorophenyl)-3-(2,4-dimethoxyphenyl)prop-2-en-1-one(4c):Pale brown solid; Yield 85%; m.p.106-107^{o}C; IR (KBr): υ_{max} 3044, 2898, 1745, 1644, 1578, 1548, 1460, 1425, 1385, 1350, 1285, 1265, 1170, 1135, 1040, 980, 945, 890, 858, 780, 672, 645 cm^{-1}; ^{1}H NMR: (400MHz, DMSO-

d_6): δ 7.78 (d, 2H, *J* = 7.4 Hz), 7.70 (d, 1H, *J* = 15.8 Hz), 7.52 (d, 2H, *J* = 7.8 Hz), 7.44 (d, 1H, *J* = 15.6 Hz), 7.20 (dd, 1H, *J* = 7.6, 7.5 Hz), 7.28 (d, 2H, *J* = 7.4 Hz), 7.18 (d, 1H, *J* = 7.8 Hz), 7.12 (d, 2H, *J* = 7.8 Hz), 6.84 (d, 1H, *J* = 7.8 Hz), 3.78 (s,6H); ESI-MS: m/z (rel.abund. %): 429.40 (M^+, 100).

(*E*)-1-(4-(3-chlorophenoxy)-2-chlorophenyl)-3-(2,5-dimethoxyphenyl)prop-2-en-1-one (4d): Pale yellow solid; Yield 82%; m.p. 126-127^{o}C; IR (KBr): υ_{max} 3048, 2958, 1741, 1641, 1575, 1538, 1462, 1430, 1390, 1356, 1288, 1261, 1168, 1128, 1027, 996, 978, 934, 898, 862, 787, 680, 645 cm^{-1}; ^{1}H NMR: (400MHz, DMSO-d_6): δ 7.82 (d, 1H, *J* = 7.6 Hz), 7.74 (d, 1H, *J* = 15.8 Hz), 7.48 (d, 2H, *J* = 8.0 Hz), 7.34 (d, 1H, *J* = 15.6 Hz), 7.28 (dd, 1H, *J* = 7.8, 7.7 Hz), 7.25 (d, 2H, *J* = 7.4 Hz), 7.1 (d, 1H, *J* = 7.8 Hz), 7.15 (s, 2H, *J* = 7.8 Hz), 6.98 (d, 1H, *J* = 7.8 Hz), 3.78 (s, 6H); ESI-MS: m/z (rel.abund. %): 429.40 (M^+, 100).

(*E*)-1-(4-(3-chlorophenoxy)-2-chlorophenyl)-3-(3,4,-dimethoxyphenyl)prop-2-en-1-one (4e):Yellow solid; Yield 84%; m.p.: 114-116^{o}C; IR (KBr): υ_{max} 3060, 2928, 1741, 1641, 1575, 1528, 1452, 1410, 1370, 1336, 1268, 1241, 1188, 1148, 1037, 990, 987, 924, 889, 852, 797, 782, 688, 640 cm^{-1}; ^{1}H NMR: (400MHz, DMSO-d_6): δ 7.80 (d, 1H, *J* = 7.6 Hz), 7.54 (d, 1H, *J* = 15.4 Hz), 7.30 (d, 2H, *J* = 8.4 Hz), 7.20 (d, 1H, *J* = 15.0 Hz), 7.14 (dd, 1H, *J* = 7.84, 7.64 Hz), 7.05 (t, 1H, *J* = 7.4 Hz), 7.0 (d, 2H, *J* = 7.8 Hz), 6.94 (d, 1H, *J* = 7.8 Hz), 6.82 (d, 2H, *J* = 7.8 Hz), 3.78 (s,6H); ESI-MS: m/z (rel.abund. %): 429.40 (M^+, 100).

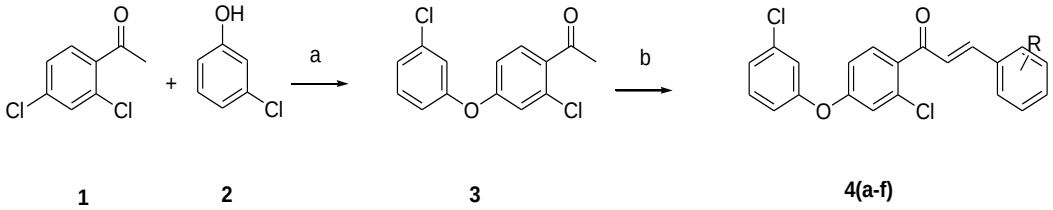
(*E*)-1-(4-(3-chlorophenoxy)-2-chlorophenyl)-3-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (4f): Yellow solid; Yield 88%; m.p.134-136^{0}C; IR (KBr): υ_{max} 3063, 2948, 1741, 1651, 1584, 1521, 1472, 1428, 1388, 1346, 1268, 1241, 1198, 1140, 1037, 996, 987, 924, 889, 852, 797, 782, 710, 688, 658 cm^{-1}; ^{1}H NMR: (400MHz, DMSO-d_6): δ 7.83 (d, 1H, *J* = 7.4 Hz), 7.54 (d, 1H, *J* = 15.4 Hz), 7.32 (d, 2H, *J* = 8.4 Hz), 7.15-7.20 (d, 1H, *J* = 15.0 Hz), 7.14 (dd, 1H, *J* = 8.84, 8.64 Hz), 7.05 (t, 1H, *J* = 7.4 Hz), 7.0 (d, 1H, *J* = 7.8 Hz), 6.94 (dd, 1H, *J* = 7.4,7.8 Hz), 6.72 (s, 2H), 3.92 (s, 3H), 3.84 (s,6H); ESI-MS: m/z (rel.abund. %): 459.60 (M^+, 100).

Antibacterial Bioassay: The antibacterial activity of all the synthesized compounds (**4a-f**) were screened against different Gram-positive (*Staphylococcus aureus and Streptococcus pyogenes)* and Gram-negative (*Escherichia coli* and *Pseudomonas aeruginosa*) organisms by measuring zone of inhibition. The antibacterial activity was performed by agar diffusion method [18-19] at the concentration level of 50µg mL^{-1}. Ampicillin was used as standard drug at a concentration of 50 µg mL^{-1}. Nutrient agar was used as culture media and DMSO was used as solvent control. The results of the antibacterial activity are shown in **Table 1**.

RESULTS AND DISCUSSION

Chemistry: The synthesis of six new styryl derivatives **4a-f** is illustrated in **scheme 1**. Etherification of 2, 4 dichloroacetophenone **1** was carried out by using 3-chlorophenol **2**, CuI and Cs_2CO_3 in DMF at 110^{o}C for 12 h to afford 1-(4-(3-chlorophenoxy)-2-chlorophenyl)ethanone **3.** Claisen-Schmidt condensation of compound **3** with various benzaldehydes (**a –f**) was carried in presence of sodium hydroxide in methanol at room temperature for 6 h to afford styryl ketone derivatives **4a-f** in 80-88%. All the newly synthesized styryl ketone derivatives **4a-f** was characterized by ^{1} H NMR, IR and mass spectral data. As a representative example, the ^{1}H NMR spectrum of compound **4f** indicated the following signals: the singlets at 3.80 ppm, 3.90 ppm indicated the presence of a, -O**C**$\mathbf{H_3}$ and signals at 7.15 and 7.52 (doublet with J = 15.0 Hz) represents the –CH=CH- olefinic protons. All the other aromatic protons were observed at expected regions. The ^{1}H NMR data for all the styryl derivatives **4a–f** were also is in agreement with the assigned structures. The IR spectral data of all the compounds **4a-f** indicated the presence of distinctive functional groups such as –C=O, -CH=CH str in the range 1740-1640 and 1644-1618, 1610-1590 cm^{-1}. The mass spectra of compounds showed (M+1) peaks, is in agreement with their molecular formula.

Antibacterial Evaluation: Antibacterial evaluation data (Zone of inhibition) of the synthesized styryl derivatives **4a–f** is presented in **table 1**. It is observed from the table 1 that compounds **4c**, **4d** and **4f** exhibited excellent activity and compounds **4b** and **4e** displayed equipotent activity (zone of inhibition similar to the standard drug ampicillin) while the compound **4a** showed moderate activity when tested against all the bacterial strains (Gram positive and Gram negative bacteria as mentioned in Table **1**). In general it observed that the compounds having R = 2,4 dimethoxy, 2,5 dimethoxy and 3,4,5 trimethoxy moiety in the scaffold exhibited excellent activity while the compounds having R= 4 methoxy and 3,4 dimethoxy substituent in the scaffold showed equipotent activity and with R = H showed moderate activity, therefore it can be concluded that a further structural activity studies is needed to achieve a promising anti-bacterial drug candidate.



1 **2** **3** **4(a-f)**

R= **4a**: H, **4b**: 4-OMe, **4c**: 2, 4-OMe, **4d**: 2,5-OMe, **4e**: 3,4-OMe, **4f**: 3,4,5-OMe

Scheme 1. Synthesis of styryl ketone derivatives **4a – 4f**

Experimental Conditions: a) CuI, Cs_2CO_3, DMF, 110 ^oC, 12 h; b) Benzaldehydes (a-f), NaOH, methanol, 6 h.

Table-1 Results of Antibacterial Activity of Compounds **4a-f** (Concentration used 50 µg/mL of DMSO)

Compound No.	**R**	*Gram negative*		*Gram positive*	
		E.coli ***MTCC 443***	*P.aeruginosa* ***MTCC 424***	*S.aureus* ***MTCC 96***	*S.pyogenes* ***MTCC 442***
		Zones of Inhibition of compounds 4a –4f in mm			
4a	**H**	**11**	**10**	**10**	**11**
4b	**4-OMe**	**16**	**15**	**14**	**16**
4c	**2,4 -OMe**	**20**	**19**	**16**	**18**
4d	**2,5 -OMe**	**20**	**19**	**16**	**18**
4e	**3,4-OMe**	**16**	**15**	**14**	**16**
4f	**3,4,5-OMe**	**20**	**19**	**16**	**18**
Standard Drug	Ampicillin (50 µg/mL of DMSO)	**16**	**15**	**14**	**16**

APPLICATIONS

The newly synthesized styryl ketones derivatives **4a-f** was found to exhibit significant antibacterial activity and further exploration of the main scaffold may lead to a promising antibacterial agent.

CONCLUSIONS

In conclusion, we have synthesized and characterized six new styryl ketone derivatives **4a-f** and tested for their prospective antibacterial activities at the concentrations 50 µg mL^{-1} with reference to the standard

antibacterial drug ampicillin. Compounds having R = 2,4 dimethoxy, 2,5 dimethoxy and 3,4,5 trimethoxy moiety in the main scaffold exhibited excellent activity while the remaining compounds showed either equipotent or moderate activity when tested against all the bacterial strains (Gram positive and Gram negative bacteria).

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AUTHORS' ADDRESSES

1. **Dr. Balram Bhavani**
Associate Director, Green Evolution Laboratories,
Wangapally Village, Nalgonda, 500 085,
Telangana, India
E-mail: bharathram09@gmail.com, Ph: 9866522817

2. **Rohidas Gilbile**
Principal Scientist,Green Evolution Laboratories,
Wangapally Village, Nalgonda, 500 085,
Telangana, India
E-mail: rohidasgilbile2015@gmail.com, Ph: 7702683053

3. **Dr. Ram Bhavani**
Director, Green Evolution Laboratories,
Wangapally Village, Nalgonda, 500 085,
Telangana, India
E-mail: ram_19_73@yahoo.co.in, Ph: 8179802942

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