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RESEARCH ARTICLE

Synthesis and Biological Studies of Novel Chalcones of Vanillin Analogue

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ABSTRACT

Novel series of 3-Methoxy-4-(2, 4-Dichlorophenylmethoxy) chalcone derivatives were synthesized using various acetophenones with 3-methoxy-4-(2, 4-dichlorophenylmethoxy) benzaldehyde. The aldehyde was prepared by the condensation of vanillin with 2, 4-Dichlorobenzylchloride. The characterization of these chalcone derivatives were established on the basis of IR, NMR, Mass and elemental analyses. The synthesized chalcone derivatives were screened for their *in vitro* antimicrobial testing.

KEYWORDS

Vanillin, Chalcone, Anti Microbial Testing

INTRODUCTION

The chemistry of chalcones has generated intensive scientific studies throughout the world.

Chalcones form a major class of natural products with widespread distribution throughout the plant kingdom. Natural chalcones occur mainly as flower pigments and have also been found in heartwood, bark, leaves, fruits and roots of many trees, plants and vegetables. Chalcone derivatives are very versatile as physiologically active compounds and substrates for the evaluation of various organic syntheses. Chalcones are also key precursors in the synthesis of many biologically important heterocycles such as benzothiazepine, pyrazolines, cyanopyridine, pyrimidine, thiopyrimidine, cyclohexenone and flavones. Naturally occurring and synthetic chalcones show interesting biological activity such as Antitumor[1], Anticancer[2], Antitubercular[3,4], Anti HIV[5], Antimicrobial[6-8], Antiinflammatory[9], Antimalarial[10,11], Insecticidal[12], Antiparasitic[13], Cardiovascular[14] and Antiplasmodial[15]. The introduction of a halogen into the benzenoid part of these α, β-unsaturated ketones enhances their biological activity[16]. Brief account of various modifications reported on chalcones, which resulted in a variety of biological and pharmacological activities.

Numerous methods are available for the synthesis of chalcones; the most convenient method is the one that involves condensation of equimolar quantities of a substituted acetophenone with substituted aldehydes in the presence of aqueous alcoholic alkali.

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MATERIAL AND METHODS

The materials like vanillin, 2, 4-Dichlorobenzyl chloride and various substituted acetophenones are of analytical grade and used without further purification.

Melting points of synthesized compounds were taken in open capillary method and are uncorrected. Elemental analyses (% of C, H & N) of the compounds were performed on a model

2400 Perkin–Elmer elemental analyzer. Infrared spectra (4000–400 cm^{-1}, using KBr discs) of the samples were recorded on Shimadzu-435 Spectrophotometer and ^1H NMR spectra on Bruker Advance 400MHz spectrometer with $CDCl_3$ as a solvent and tetramethyl silane (TMS) as internal standard.

The chemical shift was measured in parts per million (ppm). The antimicrobial activity of purified compounds was done by Cup-plate agar diffusion method. Purity of the compounds is checked by thin layer chromatography (TLC) plates.

Synthesis of 3-methoxy-4-(2, 4-Dichlorophenylmethoxy) benzaldehyde

The solution of Vanillin (1.53g, 0.01M) in DMF (6ml) was stirred at 60˚C in water bath with 2,4-Dichlorobenzyl chloride(1.95g, 0.01M) and anhydrous $K_2CO_{3(s)}$ (2.76gm, 0.02M) for four hours, after four hours, product was cooled at room temperature and precipitated by water addition. The separated white solid was filtered and leached in Methanol.

Synthesis of 3-Methoxy-4-(2, 4-Dichlorophenylmethoxy)-4'-bromo chalcone

To the solution of 3-methoxy-4-(2,4-Dichlorophenylmethoxy)benzaldehyde (3.11, 0.01M) in Methanol (25ml) was stirred with 4-bromoacetophenone (1.99gm, 0.01M) and 20% NaOH 5ml for 12 hrs keep it aside for overnight, separated greenish yellow color product was filtered and recrystallized from ethanol. Similarly, other 3-Methoxy-4-(2, 4-Dichlorophenylmethoxy) chalcones were synthesized (Scheme 1).

Spectral Data of Synthesized Compounds

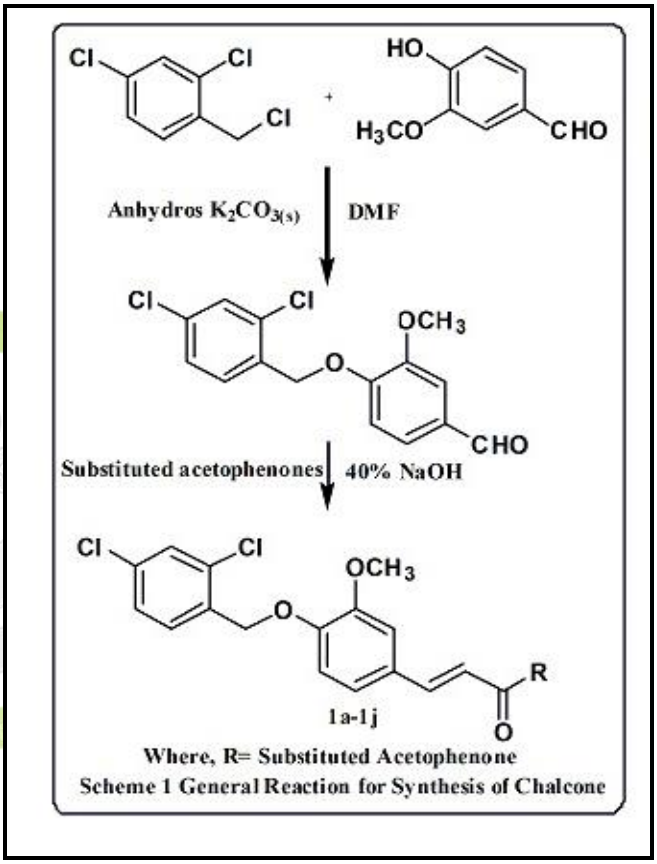
3-methoxy-4-(2,4-Dichlorophenylmethoxy) benzaldehyde

Yield 96%, M P: 103˚C; IR (KBr): ν 2923(-CHO), 1260(-OCH_3), 672(-C-Cl), 1241 (Ar-O-CH_2) cm^{-1}, ^1H-NMR ($CDCl_3$): δ 9.86(s, 1H,-CHO), 5.25(s, 2H,-O-CH_2-), 7.28-7.71(m, 6H, ArH), 3.84 (s, 3H, -OCH_3). Mass (m/z): 311, Molecular formula: $C_{15}H_{12}O_3Cl_2$

Compound (1a)

3-Methoxy-4-(2,4-Dichlorophenylmethoxy) chalcone

IR (KBr): ν 1265(-OCH_3), 674(-C-Cl), 1653(-CO-CH=CH-), 1242(Ar-O-CH_2) cm^{-1}, ^1H-NMR($CDCl_3$): δ 5.21(s, 2H, -O-CH_2-), 3.89(s, 3H, -OCH_3), 7.83-7.87 (d, 1H, 15.6Hz, =CH-Ar), 7.72-7.76(d, 1H, 16.4Hz, -CO-CH=), 7.13-8.12(m, 11H, Ar-H), Mass (m/z): 413



Scheme 1 General Reaction for Synthesis of Chalcone

Compound (1b)

3-Methoxy-4-(2,4-Dichlorophenylmethoxy)-4'-bromo chalcone

IR (KBr): ν 1261(-OCH_3), 673(-C-Cl), 1653(-CO-CH=CH-), 1240(Ar-O-CH_2) cm^{-1}, ^1H-NMR($CDCl_3$): δ 5.20(s, 2H, -O-CH_2-), 3.88(s, 3H, -OCH_3), 7.82-7.86 (d, 1H, 15.6Hz, =CH-Ar), 7.71-7.75(d, 1H, 16.4Hz, -CO-CH=), 7.12-8.11(m, 10H, Ar-H), Mass (m/z): 492

Compound (1c)

3-Methoxy-4-(2,4-Dichlorophenylmethoxy)-4'-chloro chalcone

IR (KBr): ν 1260(-OCH_3), 673(-C-Cl), 1653(-CO-CH=CH-), 1242(Ar-O-CH_2) cm^{-1}, ^{1}H-NMR($CDCl_3$): δ 5.20(s, 2H, -O-CH_2-), 3.88(s, 3H, -OCH_3), 7.82-7.86 (d, 1H, 15.6Hz, =CH-Ar), 7.71-7.75(d, 1H, 16.4Hz, -CO-CH=), 7.12-8.16(m, 10H, Ar-H), Mass(m/z): 447

Compound (1d)

3-Methoxy-4-(2,4-Dichlorophenylmethoxy)-2'-chloro chalcone

IR (KBr): ν 1261(-OCH_3), 673(-C-Cl), 1653(-CO-CH=CH-), 1242(Ar-O-CH_2) cm^{-1}, ^{1}H-NMR($CDCl_3$): δ 5.20(s, 2H, -O-CH_2-), 3.92(s, 3H, -OCH_3), 7.82-7.86 (d, 1H, 15.6Hz, =CH-Ar), 7.71-7.75(d, 1H, 16.4Hz, -CO-CH=), 7.15-8.13(m, 10H, Ar-H), Mass(m/z): 447

Compound (1e)

3-Methoxy-4-(2,4-Dichlorophenylmethoxy)-2',4'-dichloro chalcone

IR (KBr): ν 1262(-OCH_3), 670(-C-Cl), 1655(-CO-CH=CH-), 1244(Ar-O-CH_2) cm^{-1}, ^{1}H-NMR($CDCl_3$): δ 5.19(s, 2H, -O-CH_2-), 3.87(s, 3H, -OCH_3), 7.82-7.86 (d, 1H, 15.6Hz, =CH-Ar), 7.70-7.74(d, 1H, 16.4Hz, -CO-CH=), 7.09-8.10(m, 9H, Ar-H), Mass (m/z): 482

Antimicrobial Screening

The sample of synthesized compounds for antimicrobial activity was prepared at concentration 40µg/ml in DMSO. In case of antibacterial activity, the plates were incubated at 37°C for 24 hours and for antifungal activity the plates were incubated at 30°C for 48 hours. The antibacterial activity was checked against *Gram positive* bacteria *Staphylococcus aureus (S aureus)* and *Bacillus subtilis (B subtilis)*, *Gram negative* bacteria *Pseudomonas aeruginosa (P aeruginosa)* and *Escherichia coli (E coli)*. The antifungal activity was checked against fungi *Aspergillus niger (A niger)* and *Candida albicans (C albicans)*. The results were compared with stand drugs Sparfloxacin, Benzyl penicillin and Fluconazole. (Table 2)

RESULTS AND DISCUSSION

The novel 3-methoxy-4-(2,4-Dichlorophenylmethoxy) benzaldehyde was synthesized by refluxing vanillin with 2,4-Dichlorobenzyl chloride in the presence of anhydrous potassium carbonate in dimethyl formamide (DMF), the resulting novel benzaldehyde was reacted with substituted acetophenones in the presence of sodium hydroxide and ethanol as solvent to got corresponding chalcones **1a-1j** with excellent yield. The analytical and physical data of the synthesized compounds are given. (Table 1)

IR Spectral Studies

The FT−IR spectra of synthesized 3-methoxy-4-(2,4-Dichlorophenylmethoxy)benzaldehyde show a strong band at stretching frequency in of 1240 cm^{-1} (sy str) which is characteristic of Ar−O−CH_2 group. No peak appeared in the range of 3400–3300 cm^{-1}, which indicated the disappearance of the –OH group of vanillin. The 3-Methoxy-4-(2,4-Dichlorophenylmethoxy) chalcones show absorption bands in the range of 1653-1656 cm^{-1} for carbonyl group[17] ν(C=O str) of α, β-unsaturated ketone and 1590-1597 cm^{-1} for aromatic double bonds ν(C=C). In addition characteristic strong bands at 1240-1247 cm^{-1} for Ar−O−CH_2 and sharp band at 972 cm^{-1} ν(=C-H bend) for (-CH=CH-) group in chalcone were observed.

^{1}H NMR Spectral Studies

Two prominent doublets at δ 7.71–7.75 and 7.82–7.86 ppm with coupling constant (*J* ~ 16Hz) appeared in the ^{1}H-NMR spectra of chalcones, which corresponds to the α- and β-hydrogen atoms of the olefinic double bond of the α, β-unsaturated carbonyl compound. The large coupling constant values confirmed that the chalcones possess *trans* (*E*)-configurations[18]. The aromatic protons of the chalcones appeared downfield between δ 7.09 to 8.38 ppm in the aromatic region of the spectrum. The characteristic methylene protons of Ar−O−CH_2− appeared as singlet in range δ 5.19-5.24 ppm in aldehyde as well as in chalcones.

Mass Spectral Studies

The molecular ion peak (m/e) is equivalent to their molecular weight of proposed compound and the fragmentation pattern of synthesized

Table 1: Analytical and Physical Data of the Synthesized Compounds

Comp	-R	Molecular formula	Mol. Wt.	M.P ^{0}C	% yield	Elemental analysis					
						Calculated (%)			Found (%)		
						C	H	N	C	H	N
1a	-C_6H_5	$C_{23}H_{18}Cl_2O_3$	413	109	87	66.84	4.39	-	66.80	4.31	-
1b	-4-Br C_6H_4	$C_{23}H_{17}BrCl_2O_3$	492	163	89	56.13	3.48	-	56.43	3.43	-
1c	-4-Cl-C_6H_4	$C_{23}H_{17}Cl_3O_3$	447	182	78	61.70	3.83	-	61.19	3.88	-
1d	-2-Cl-C_6H_4	$C_{23}H_{17}Cl_3O_3$	447	153	96	61.70	3.83	-	61.21	3.85	-
1e	-2,4-Cl_2-C_6H_3	$C_{23}H_{16}Cl_4O_3$	482	197	95	57.29	3.84	-	57.18	3.29	-
1f	-4-OH-C_6H_4	$C_{23}H_{18}Cl_2O_4$	429	121	77	64.35	4.81	-	63.01	4.56	-
1g	-2-OH-C_6H_4	$C_{23}H_{18}Cl_2O_4$	429	155	78	64.35	4.81	-	63.07	4.79	-
1h	-4-OCH_3-C_6H_4	$C_{24}H_{20}Cl_2O_4$	443	140	96	65.02	4.55	-	65.11	4.50	-
1i	-2-NO_2-C_6H_4	$C_{23}H_{17}Cl_2NO_5$	458	146	94	60.28	3.74	3.06	59.97	3.82	3.09
1j	-4-NO_2-C_6H_4	$C_{23}H_{17}Cl_2NO_5$	458	134	92	60.28	3.74	3.06	60.04	3.71	3.14

Table 2: Antimicrobial Screening Data of the Synthesized Compounds

Comp	-R	Molecular formula	Antibacterial activity (zone of inhibition in mm)				Antifungal activity (zone of inhibition in mm)	
			S. aureus	*B. subtilis*	*P. aeruginosa*	*E. coli*	*A. niger*	*C. albicans*
1a	-C_6H_5	$C_{23}H_{18}Cl_2O_3$	11	10	09	12	12	13
1b	-4-Br-C_6H_4	$C_{23}H_{17}BrCl_2O_3$	15	12	12	13	10	12
1c	-4-Cl-C_6H_4	$C_{23}H_{17}Cl_3O_3$	12	14	10	12	14	19
1d	-2-Cl-C_6H_4	$C_{23}H_{17}Cl_3O_3$	13	15	13	11	20	11
1e	-2,4-Cl_2-C_6H_3	$C_{23}H_{16}Cl_4O_3$	10	12	10	14	12	13
1f	-4-OH-C_6H_4	$C_{23}H_{18}Cl_2O_4$	07	13	09	07	16	10
1g	-2-OH-C_6H_4	$C_{23}H_{18}Cl_2O_4$	09	07	10	08	10	06
1h	-4-OCH_3-C_6H_4	$C_{24}H_{20}Cl_2O_4$	09	12	07	11	09	12
1i	-2-NO_2-C_6H_4	$C_{23}H_{17}Cl_2NO_5$	10	08	07	09	12	09
1j	-4-NO_2-C_6H_4	$C_{23}H_{17}Cl_2NO_5$	11	11	10	08	15	15
	Sparfloxacin		24	25	25	22	-	-
	Benzyl penicillin		18	17	16	16	-	-
	Fluconazole		-	-	-	-	22	20

compounds matche to the typical fragmentation pattern of the chalcones that further confirming the structures of the compounds. The elemental analysis (% of C, H and O) data found is equivalent to their calculated value.

Antimicrobial Activity

From antimicrobial screening data of synthesized compounds show that compound **1c** and **1d** has good antifungal activity against *C albicans* and *A niger*. The compound **1b** and **1d** has also moderate activity against *S aureus* and *B subtilis* respectively (Table 2).

CONCLUSION

In the present work, a series of chalcone using aldehyde and various substituted acetophenones were synthesized and characterized. The antimicrobial activities of synthesized compounds show good results compared to standard drugs data, especially halogenated compounds were more active against some microbes. Further investigation with appropriate structural modification of the above compounds may result in therapeutically useful products. On the basis of analytical data and spectral data, the structure and geometry (*trans*) were proposed for all the chalcones.

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