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Solvent free synthesis of some chalcones and their effect on Bovine Serum Albumin

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ABSTRACT

Substituted 1,3-diphenyl-2-propen-1-ones were synthesized via solvent free synthesis and their effect on bovine serum albumin was evaluated. It was observed that the synthesized chalcones interacted with the serum protein irrespective of the type and position of the substituent and resulted in its precipitation.

Key words :1,3-diphenylpropenones, Chalcones, Interaction, Bovine Serum Albumin.

INTRODUCTION

Chalcones have been a subject of great interest for chemists and biochemists all over due to several reasons; their ease of synthesis, vast and interesting pharmacological activities synthetic and natural chalcones possess and their potential to be used as important synthetic intermediate for their reaction with different types of reagents have provided altogether diverse areas of interest. Chalcones are well known intermediates for synthesizing various heterocyclic compounds. The compounds with the backbone of chalcones have been reported to possess various biological activities such as antimicrobial[1], anti-inflammatory[2], analgesic[3], antiplatelet[4], antiulcerative[5], antimalarial[6], anticancer[7], antiviral[8], antileishmanial[9], antioxidant[10], antitubercular[11], antihyperglycemic[12], immunomodulatory[13], inhibition of chemical mediators release[14], inhibition of leukotriene B_4 [15], inhibition of tyrosinase[16] and inhibition of aldose reductase[17] activities. The diverse biological activities possessed by different chalcones as reported in literature inspired us to look for the interactions of chalcones with serum albumin, a major serum protein responsible for the transportation of various compounds including drugs to the target site[18]. The transported drug can exhibit pharmacological action by interacting with biomolecules, may be enzymes, proteins, receptors, nucleic acids etc. In the present work we first report the solvent free synthesis of substituted 1,3-diphenyl-2-propen-1-ones, their structural analysis and evaluation of effect of these chalcones on bovine serum albumin.

MATERIALS AND METHODS

The reactions were monitored by thin layer chromatography. Thin layer chromatography was performed with silica-gel G (suspended in $CHCI_3$-EtOH) and plates were viewed under Iodine vapors. Melting points were determined by electrochemical capillary melting points apparatus and are uncorrected. Elisa plate reader was used for measuring absorbance in the visible range. The Spectrofuge was used for centrifugation purpose.

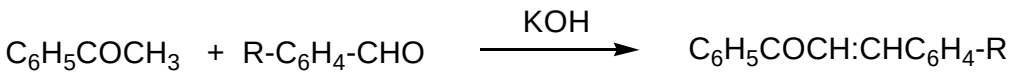
Synthesis of Chalcones- Substituted chalcones (2-3, 5-9) of acetophenone were synthesized by solvent free synthesis [19]. Acetophenone, substituted benzaldehyde and KOH were mixed thoroughly in 1:1:2 molar ratios in pestle mortar. The mixture first went into solution and thereafter it solidified. The solid was washed properly with water. The precipitates obtained were filtered, dried and recrystallized with alcohol.

The chalcones 1, 4 and 10 could not be prepared in pure form as by the above procedure and therefore were synthesized by the method earlier used [20]. Mixture of acetophenone (0.01 mole) and substituted aryl aldehydes (0.01 mole) was stored in an ice cold solution of potassium hydroxide (0.03 mole). The reaction mixture was kept overnight at room temperature and then it was poured into crushed ice and acidified with dilute hydrochloric acid. The chalcone derivative precipitates out as solid. Then it was filtered and recrystallised from ethanol. The purity of the products was confirmed through TLC. Their structures were confirmed by their melting points, IR data and 1HNMR analysis compiled in the following tables I, II, and III.

Reaction of chalcones with Bovine Serum Albumin: To 10 ml solution of 0.1mM BSA added 1ml solution of 50 mM chalcone solution drop wise with constant stirring. The pH of the solution was 5.5. The interaction between chalcone and BSA resulted in precipitation of protein from the solution. The remaining protein was estimated by biuret method [21]. The results are presented in figure 1.

RESULTS AND DISCUSSION

The profound biological activities possessed by chalcones and their potential to be used as synthones for the synthesis of large number of heterocyclic compounds have generated considerable interest in the synthesis of a large number of substituted chalcones. One of the most widely used method employed for the synthesis of chalcones involved Claisen-Schmidt condensation of substituted benzaldehyde with the acetophenones in the presence of a base.



R= H-, o-Cl-, m-Cl-, p-Cl-, o-OCH_3, m-OCH_3, p-OCH_3, o-NO_2, m-NO_2, p-NO_2

In the present work we report the synthesis of substituted 1,3-diphenylpropenones under solvent free conditions. The chalcones thus obtained were in quantitative yields (table I). The process is fast and the product is obtained in fifteen to 30 min. The resulting chalcones were identified with the help of spectral studies.

Table I Physical Parameters and Elemental Analysis of Synthesized Chalcones (C_6H_5-CO-CH:CH-Ar)

Comp. No	Ar-	Mol. Formula	Mol. Wt.	M.Pt.(lit) °C	Rf value	% Yield	Elemental analysis (Calculated)				
							%C	%H	%O	%N	%Cl
1	C_6H_5-	$C_{15}H_{12}O$	208	58 (58)	0.871	94·23	86.54	5.77	7.69	--	--
2	*o*-Cl-C_6H_4-	$C_{15}H_{11}ClO$	242	51 (49-52)	0.886	82·47	74.38	4.55	6.61	--	14.46
3	*m*-Cl-C_6H_4-	$C_{15}H_{11}ClO$	242	69 (70-72)	0.900	86·59	74.38	4.55	6.61	--	14.46
4	*p*-Cl-C_6H_4-	$C_{15}H_{11}ClO$	242	110 (110-113)	0.900	92·75	74.38	4.55	6.61	--	14.46
5	*o*-OMe-C_6H_4-	$C_{16}H_{14}O_2$	238	55 (56-59)	0.828	90.54	80.67	5.88	13.45	--	--
6	*m*-OMe-C_6H_4-	$C_{16}H_{14}O_2$	238	56-58 (69-71)	0.735	86.13	80.67	5.88	13.45	--	--
7	*p*-OMe-C_6H_4-	$C_{16}H_{14}O_2$	238	76 (75-76)	0.687	95.79	80.67	5.88	13.45	--	--
8	*o*-NO_2-C_6H_4-	$C_{15}H_{11}NO_3$	253	128 (124-128)	0.663	89.32	71.15	4.35	18.97	5.53	--
9	*m*-NO_2-C_6H_4-	$C_{15}H_{11}NO_3$	253	145 (146)	0.735	94.46	71.15	4.35	18.97	5.53	--
10	*p*-NO_2-C_6H_4-	$C_{15}H_{11}NO_3$	253	158 (157-159)	0.747	76.87	71.15	4.35	18.97	5.53	--

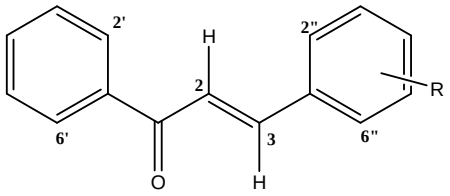
In the IR spectra of chalcones 1-10 the >C=0 group absorption was present at 1640 – 1652 cm^{-1}. This suggests the presence of highly conjugated system (table II).

Table II IR Data [υ_{max}(cm^{-1})] of Chalcones (C_6H_5-CO-CH:CH-Ar)

Compound No	Ar-	[C=O]	[C=C]	[CH]	[O-N-O sym]	[O-N-O asym]
1	C_6H_5-	1666	1605	3055	-	-
2	*o*-Cl-C_6H_4-	1659	1605	3078	-	-
3	*m*-Cl-C_6H_4-	1659	1605	3063	-	-
4	*p*-Cl-C_6H_4-	1659	1597	3063	-	-
5	*o*-OMe-C_6H_4-	1659	1597	3063	-	-
6	*m*-OMe-C_6H_4-	1659	1597	3063	-	-
7	*p*-OMe-C_6H_4-	1659	1597	3009	-	-
8	*o*-NO_2-C_6H_4-	1666	1605	2916	1342	1512
9	*m*-NO_2-C_6H_4-	1659	1605	3070	1350	1528
10	*p*-NO_2-C_6H_4-	1659	1597	3070	1342	1512

In ^{1}HNMR ($CDCl_3$) spectrum, the C-2 and C-3 protons are observed as doublets with coupling constant ~ 16 Hz. which shows that stereochemistry across C-2, C-3 double bond is Trans. The other protons were revealed at their respective position as detailed in table III.

Table III ^{1}HNMR ($CDCl_3$) Data Obtained for Chalcones (C_6H_5-CO-CH:CH-Ar) δ:



Comp. No	Ar-	H-2	H-3	J_{23}(Hz)	H-3', H-4', H-5', Ar-H	H-2', H-6'	3H, -OCH_3
1	**C_6H_5-**	7.56, d	7.85, d	15.9	7.69-7.43, m	8.05, dd, J_o=8.1Hz, J_m=1.2Hz	-
2	***o*-Cl-C_6H_4-**	7.34, d	7.81, d	15.9	7.61-7.38, m	8.04, d, J_o=7.2 Hz	-
3	***m*-Cl-C_6H_4-**	7.63, d	7.77, d	15.6	7.66-7.35, m	8.05, d, J_o=7.2 Hz	-
4	***p*-Cl-C_6H_4-**	7.53, d	7.78, d	15.9	7.64-7.40, m	8.04, d, J_o=7.2 Hz	-
5	***o*-OMe-C_6H_4-**	7.63, d	8.15, d	15.9	7.67-6.86, m	8.04, d, J_o=6.6 Hz	3.94, s
6	***m*-OMe-C_6H_4-**	7.65, d	8.15, d	15.9	7.64-7.37, m	8.04, d, J_o=7.2 Hz	3.94, s
7	***p*-OMe-C_6H_4-**	7.44, d	7.82, d	15.3	7.49-6.96, m	8.03, d, J_o=7.2 Hz	3.94, s
8	***o*-NO_2-C_6H_4-**	7.34, d	8.16, d	15.9	8.10-7.52, m	8.04, d, J_o=7.5 Hz	-
9	***m*-NO_2-C_6H_4-**	7.68, d	7.86, d	15.9	8.53-7.53, m	8.07, dd, J_o=8.4Hz, J_m=1.8Hz	-
10	***p*-NO_2-C_6H_4-**	7.42, d	7.81, d	15.9	8.21-7.48, m	8.07, dd, J_o=7.5Hz	-

After establishing the structures of the synthesized chalcones, further studies on interaction of chalcones with bovine serum albumin was conducted. Albumin is a soluble, monomeric protein which comprises about one-half of the blood serum protein. Albumin functions primarily as a carrier protein for steroids, fatty acids, and thyroid hormones.

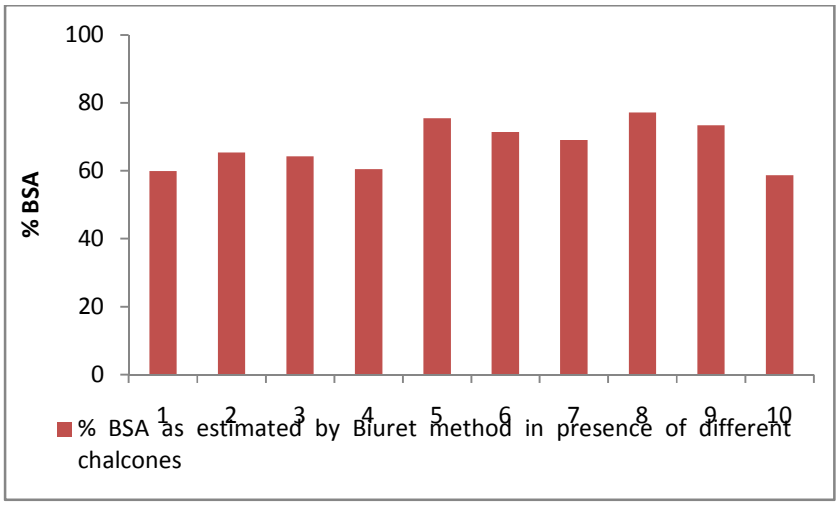


Fig. I Effect of 1-phenyl-3-(substituted phenyl)prop-2-en-1-ones on bovine serum albumin

It is also responsible for the transportation of drugs. The figure I represent the results of the serum protein left in solution after interaction with chalcones. The chalcones possessing α,β-unsaturated ketone moiety are highly reactive. It is well reported that these 1,3-diarylpropenones are used as synthons for the synthesis of different types of heterocycles [22]. In proteins a number of side chain groups such as thiol, amino, imidazole, alcohol etc. are available for reaction with this reactive moiety. We propose that nucleophilic groups of BSA react with α,β-unsaturated group and results in complex formation. The resulting interactions may cause a change in the three dimensional structure of albumin under study. These interactions may result

in denaturation or change in the native structure of BSA and finally resulting its precipitation. Similar interactions have been reported earlier [20] between chalcones and serum proteins.

CONCLUSION

Chalcones react with the side chain groups of bovine serum albumin and results in its precipitation.

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