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Research Article

SYNTHESIS OF NOVEL CHALCONES OF SCHIFF'S BASES AND TO STUDY THEIR EFFECT ON BOVINE SERUM ALBUMIN

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ABSTRACT

Objective: Some novel chalcones consisting –unsaturated carbonyl group and C=N bond were synthesized i.e. 1-(4-(benzylideneamino)phenyl)-3-phenylprop-2-en-1-ones and studied the influence of their presence on bovine serum albumin.
Methods: 1-(4-(benzylideneamino)phenyl)-3-phenylprop-2-en-1-ones were synthesized by the reaction of substituted benzaldehydes with 1-((4-benzylideneamino)phenyl)ethanone and in the presence of a base. The structures were confirmed by their IR and ^{1}HNMR spectra. After establishing the structures of 1-(4-(benzylideneamino)phenyl)-3-phenylprop-2-en-1-ones, their effect were observed on BSA in solution.
Results: Out of synthesized chalcones, 1-(4-(4-(3-phenylallylideneamino)phenyl)-3-p-tolylprop-2-en-1-one is most reactive chalcone as it decreased the availability of BSA in solution to maximum extent.
Conclusion: 1-(4-(benzylideneamino)phenyl)-3-phenylprop-2-en-1-ones interact with the bovine serum albumin which is responsible for the transportation of a number of compounds.

Keywords: Bovine serum albumin, interaction studies, chalcones.

INTRODUCTION

Albumin, generally regarded as serum albumin or plasma albumin, is the most abundant protein in the circulatory system and contributes 80% to colloid osmotic blood pressure. It has now been determined that serum albumin is chiefly responsible for the maintenance of blood pH. In mammals albumin is synthesized initially as preproalbumin by the liver. After removal of the signal peptide, the resultant proalbumin is further processed by removal of the six-residue propeptide from the new N-terminus. The albumin released into circulation possesses a half-life of 19 days. It has both high-affinity and secondary binding sites, optimizing the roles that fatty acids, metals, disulfides, and other molecules play in cellular metabolism.

There is growing interest in the pharmalogical potential of natural products. Chalcones[1] constitute an important group of natural products. Chemically, they consist of open chain flavanoids in which the two aromatic rings are joined by a three carbon α,β-unsaturated carbonyl system. They go through an assortment of chemical reactions and are found advantageous in synthesis of pyrazoline, isoxazole and a variety of heterocyclic compounds. In synthesizing a range of therapeutic compounds, chalcones impart key role. They have shown worth mentioning therapeutic efficacy for the treatment of various diseases. Chalcone based derivatives have gained attention since they own simple structures, and diverse pharmacological actions. The presence of a reactive α,β-unsaturated keto function in chalcones is found to be responsible for their pharmacological activities[2]. In last years a variety of chalcones have been reviewed for their a wide variety of pharmacological effects including antimalarial[3-6], antiplatelet[7], antiviral[8-10], antibacterial[11-13], antitubercular[15,16], antifungal[17, antitumor[18], antileishmanial[19], analgesic[20-21], antiulcerative[22], antihyperglycemic[23], antioxidant[24], antiinvasive[25], cytotoxic[26] and enzyme inhibitory properties[27,28]. We have reported the interaction of some series of chalcones with BSA. In continuation of our previous work, with 1-(5'-chloro-2'-hydroxyphenyl)-3-(4"-substituted phenyl)-prop-2-en-1-one and their methoxy derivatives[29], 1-phenyl-3-(substituted phenyl)-prop-2-en-1-one[30], 1-(2'-furyl)-3-(substitutedphenyl)-prop-2-en-1-one[31], 1-(2'-thienyl)-3-(substitutedphenyl)-prop-2-en-1-one[32], 1-(4-hydroxyphenyl)-3-(substitutedphenyl)-2-propen-1-ones and 1-(4-nitrophenyl)-3-(substitutedphenyl)-2-propen-1-ones[33], 1-biphenyl-3-(substitutedphenyl)-2-propen-1-ones[34], bischalcones[35] with bovine serum albumin, we here report the interaction of bovine serum albumin with 1-(4-(benzylideneamino)phenyl)-3-phenylprop-2-en-1-ones. This protein is involved in the transportation of a number of compounds including drugs. It is also reported that there is about 80% primary sequence identity between bovine serum albumin and human serum albumin[36], it is also suggested that the present study performed with BSA can give an insight about the interaction of chalcones with human serum albumin.

EXPERIMENTAL

MATERIALS AND METHODS

The reaction progress and purity of products were monitored by thin layer chromatography. Thin layer chromatography was performed with silica-gel G (suspended in $CHCl_3$-EtOH) and plates were viewed under Iodine vapors. Melting points were determined by electrochemical capillary Melting points apparatus and are uncorrected. Elisa plate reader, Systronic make was used for measusring absorbance in the visible range. The Lab-India made Spectrofuge (model 16M) was used for centrifugation purpose.

Synthesis of Chalcones- A series of chalcones 1-(4-(benzylideneamino)phenyl)-3- phenylprop-2-en-1-ones was synthesized by two step reaction.

Synthesis of 1-((4-benzylideneamino)phenyl)ethanone-

A mixture of 4-aminoacetophenone (0.01moles) and substituted benzaldehyde (0.01 moles) was refluxed for 6 hr in distilled ethanol (50 mL). The solution was kept for cooling at room temperature, and the solid formed was filtered off, washed with water, dried and recrystallized from ethanol.

Synthesis of 1-((4-benzylideneamino)phenyl)-3-phenylprop-2-en-1-one-

substituted benzaldehyde (0.01 mole) with 1-((4-benzylideneamino)phenyl)ethanone (0.01 mole) in presence of potassium hydroxide (0.01 mole) was grinded respectively with a mortar and pestle. The progress of reaction and the purity of the products were confirmed through TLC. The structures were confirmed by their IR and ^{1}HNMR spectra, reported in Table1 & 2.

Table 1: Physical Parameters and IR Data [υ max (cm^{-1})] of Chalcones ($RC_6H_4CH=NC_6H_4$-CO-CH=CH-C_6H_4R')

Comp No	R, R'	Mol. Formula	Mol. Wt.	M.P° C	% yield	IR Data [υ max (cm^{-1})] [C=O]	[C=C]	[C=N]	[O-N-Osym]	[O-N-Oasym]
1.	*p*-NO_2, *m*-Cl	$C_{22}H_{15}N_2O_3Cl$	391.5	220-223	82	1657	1599	1674	1344	1536
2.	*p*-NO_2, *p*-Cl	$C_{22}H_{15}N_2O_3Cl$	391.5	225-227	71	1657	1599	1674	1333	1519
3.	*p*-NO_2, *m*-OMe	$C_{23}H_{18}NO_2$	340	234-239	69	1657	1596	1671	1335	1525
4.	*p*-NO_2, *p*-OMe	$C_{23}H_{18}NO_2$	340	195-199	81	1657	1603	1673	1339	1527
5.	*p*-NO_2, *p*-CH_3	$C_{23}H_{18}N_2O_3$	370	183-186	75	1657	1598	1675	1349	1522
6.	*p*-NO_2, *p*-NO2	$C_{22}H_{15}N_3O_5$	402	155-159	79	1657	1599	1675	1330	1521
7.	*p*-Br, *p*-CH_3	$C_{23}H_{18}NOBr$	404	188-192	72	1658	1595	1671	1335	1528
8.	*p*-Br, *p*-NO2	$C_{22}H_{15}N_2O_3Br$	436	172-177	66	1651	1595	1673	1342	1528
9.	*p*-$N(CH_3)_2$, *p*-CH_3	$C_{25}H_{24}N_2O$	368	200-205	88	1650	1597	1675	1343	1529
10.	*p*-CH_3, *p*-CH_3	$C_{24}H_{21}NO$	339	210-215	90	1649	1591	1675	1335	1528
11.	*p*-CH_3, *p*-NO2	$C_{23}H_{18}N_2O_3$	370	221-229	81	1658	1595	1671	1342	1528
12.	$C_6H_5CH=CH$-	$C_{31}H_{25}NO$	427	298-304	67	1654	1590	1672	1344	1529

Table 2: ^{1}HNMR (δ ppm) Data for Chalcones ($RC_6H_4CH=NC_6H_4$-CO-CH=CH-C_6H_4R')

Comp No	R, R'	H-2	H-3	J_{2-3} (Hz) -	Ar-H	3H,-OCH3	C-H, N=CH
1.	*p*-NO_2, *m*-Cl	6.965 (d)	7.850 (d)	15.5	7.199-8.343(m)	-	8.32
2.	*p*-NO_2, *p*-Cl	7.357 (d)	8.061 (d)	15.7	7.156-8.456(m)	-	8.37
3.	*p*-NO_2, *m*-OMe	7.450 (d)	7.882 (d)	15.7	7.129-8.526(m)	3.824	8.49
4.	*p*-NO_2, *p*-OMe	7.450 (d)	7.882 (d)	15.7	7.129-8.526(m)	3.932	8.59
5.	*p*-NO_2, *p*-CH_3	7.439 (d)	7.841 (d)	15.8	7.156-8.456(m)	-	8.32
6.	*p*-NO_2, *p*-NO2	7.412 (d)	8.101 (d)	15.8	7.129-8.526(m)	-	8.52
7.	*p*-Br, *p*-CH_3	7.548 (d)	8.029 (d)	15.6	7.118-8.299(m)	-	8.61
8.	*p*-Br, *p*-NO2	7.397 (d)	7.685 (d)	15.3	7.199-8.343(m)	-	8.12
9.	*p*-$N(CH_3)_2$, *p*-CH_3	6.671 (d)	7.546 (d)	15.3	7.156-8.456(m)	-	8.69
10	*p*-CH_3, *p*-CH_3	6.965 (d)	7.850 (d)	15.5	7.199-8.343(m)	-	8.38
11	*p*-CH_3, *p*-NO2	7.357 (d)	8.061 (d)	15.7	7.145-8.421(m)	-	8.39
12	$C_6H_5CH=CH$-, *p*-CH_3	7.450 (d)	7.882 (d)	15.7	7.239-8.578(m)	-	8.47

In Table 2 ^{1}HNMR ($CDCl_3$) data of different chalcones are presented. It was observed that C-2 and C-3 protons resonated as doublets with coupling constant ~ 15 Hz. The stereochemistry across C-2, C-3 double bond is Trans. The other protons were revealed at their respective position.

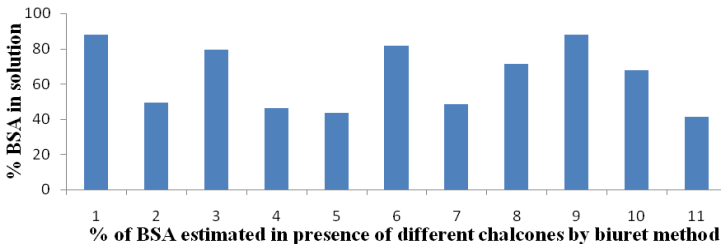
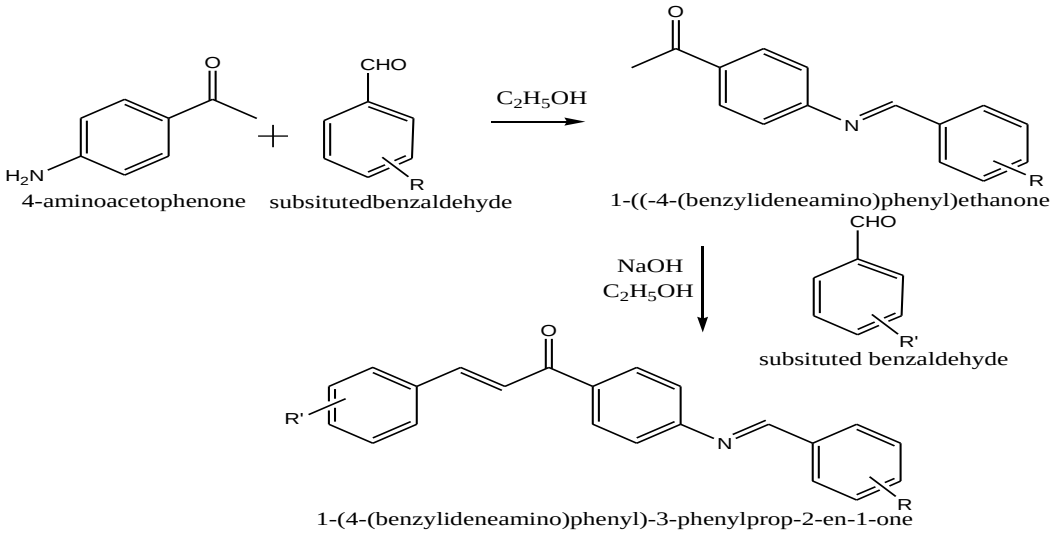


Figure 1: The results presented are calculated as % of BSA left in solution after Interactionwith chalcone with respect to control where no chalcone was added but an equal amount of solvent was added

Reaction of chalcones with Bovine Serum Albumin- To 10 ml solution of 0.1mM BSA, 1ml solution of 50 mM chalcone solution was added drop wise with constant stirring. After interaction between chalcone and BSA, some albumin gets precipitated. The remaining protein in solution was estimated by biuret method [36].



RESULTS AND DISCUSSION

The method used for the synthesis of chalcones involves Claisen-Schmidt condensation of substituted arylaldehyde with the arylmethylketone with the help of mortar and pestle by solvent free synthesis. In the present work we report the synthesis of one series i.e. 1-((4-benzylideneamino)phenyl)-3-phenylprop-2-en-1-ones by the reaction of substituted benzaldehydes with 1-((4-benzylideneamino)phenyl)ethanone and in the presence of a base. For this, 1-((4-benzylideneamino)phenyl)ethanone was synthesized by condensation of 4-aminoacetophenone and substituted benzaldehyde in alcohol with removal of water. The synthesis of different chalcones was established by their spectral data. In the IR spectra of chalcones (1-12) as mentioned in table 1, the peak at 1651 – 1659 cm^{-1} represent >C=O stretching vibrations which indicate the presence of carbonyl group in conjugation with highly unsaturated system and the results suggests the presence of α, β – unsaturated carbonyl group in the synthesized compounds. And the peak at 1640-1690 cm^{-1} represent >C=N stretching vibrations which indicate the presence of benzylideneamino group The synthesis of chalcones is characterized by the presence of two doublets around δ 7.4 - 6.7 and δ 8.1 - 7.4. These represents C-2 and C-3 protons and the geometry across the double bond has been found out to be trans as doublets with coupling constant $J_{2,3}$ is ~ 15.7 - 15.0 Hz. The aryl and other protons were revealed at their respective position. After establishing the structures of 1-((4-benzylideneamino)phenyl)-3-phenylprop-2-en-1-ones their effect was observed on BSA in solution.

We have earlier reported spetrophotometric analysis of BSA in presence of different series of chalcones[29-36]. In the present work, the results are presented on the basis of interaction of serum protein with synthesized 1-((4-benzylideneamino)phenyl)-3-phenylprop-2-en-1-ones (Figure 1). The chalcones possess α, β-unsaturated ketone moiety and are therefore highly reactive. The moiety C2-C3 double bond is most nucleophilic group available and therefore has been used as a tool for the synthesis of large number of heterocycle compound [26]. In proteins also, a number of side chain groups such as thiol, amino, imidazole, alcohol etc. are available. Any of these nucleophilic groups can react with C2-C3 double bond of chalcones. We propose that nucleophilic groups of BSA react with α, β-unsaturated group in an effective manner. The results suggest that 1-(4-(4-(3-phenylallylideneamino)phenyl)-3-p-tolylprop-2-en-1-one is most reactive chalcone as it decreased the availability of BSA in solution to maximum extent. The resulting interactions may cause a change in the three dimensional structure of albumin under study and finally resulting its precipitation out of solution.

CONCLUSION

To conclude, we have synthesized a series i.e. 1-((4-benzylideneamino)phenyl)-3-phenylprop-2-en-1-ones; by Claisen-Schmidt condensation successfully and has been characterized with the help of IR and ^1H NMR spectra. These α, β-unsaturated compounds may possess diverse pharmacological activities. It has been found that the synthesized chalcones interact with the bovine serum albumin, a protein mainly responsible for the transportation of a number of compounds.

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