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Studies on inclusion complexes of 2-[4-(5'-benzylidene-4'-oxo-3'- phenyl thiazolidinyl-2'-imino)benzoyl]aminoimino-5-benzylidene-3-phenyl-4-thiazolidinone with β-cyclodextrin

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ABSTRACT

Thiazolidinones and its derivatives are good pharamacores and showing wide spectrum of fungicidal, antibacterial and tubercolostic activities. A series of 2-[4-(5'-benzylidene-4'-oxo-3'-phenylthiazolidinyl-2'-imino) benzoyl] aminoimino-5-benzylidene-3-phenyl-4-thiazolidinone have been synthesized starting from p-Aminobenzoic acid .To enhance the solubility of these synthesized compounds, the inclusion complexes were prepared with β-cyclodextrin. The synthesis of compounds and their inclusion complexes have been ascertained from the changes in spectral characteristics and their analytical data.

Key words: 4-Thiazolidinone**,** p-Aminobenzoic acid ,β-cyclodextrin, inclusion complexes, .

INTRODUCTION

4-thiazolidinones are well known for their versatile physiological activities like antibacterial [1], anti HIV [2-3], anti-tubercular [4], antihistaminic [5] antimicrobial [6-8] etc. The nucleus is also known as wonder nucleus because it gives out different derivatives with all different types of biological activities. The presence of N-C-S linkage in the compounds has been shown to have hypnotic [9] and anti-cancer [10-12] activities etc. All these facts were driving force to develop some new thiazolidinone and their derivatives with wide structural variation. But these therapeutic agents possess low intrinsic aqueous solubility. One of the promising approaches is to encapsulate the drug in the hydrophobic cavity of cyclodextrin [13] and with it to try to increase the bioavailability which may produce better biological activity. Cyclodextrins are one of the most widely used synthetic model host cavities, which provide a conical cavity for the water insoluble guests to be encapsulated, thereby making them water soluble [14]. Out of all the known cyclodextrins, β-cyclodextrin is usually considered for inclusion complex formation because it is, least toxic [15] cheaper, easily available and highly stable towards heat and oxidation [16-18].

The aim of the present work was to synthesize 2-[4-(4-oxo-3-phenylthiazolidinyl-2-imino)benzoyl]aminoimino-3-phenyl-4- thiazolidinone in their purest forms starting from Ethyl p-Aminobenzoate and prepare its inclusion complexes with β-cyclodextrin in 1:5 ratio . The formation of compounds and their inclusion complexes have been ascertained from elemental analysis, melting point data and study of spectral characteristics.

MATERIALS AND METHODS

Apparatus and Materials

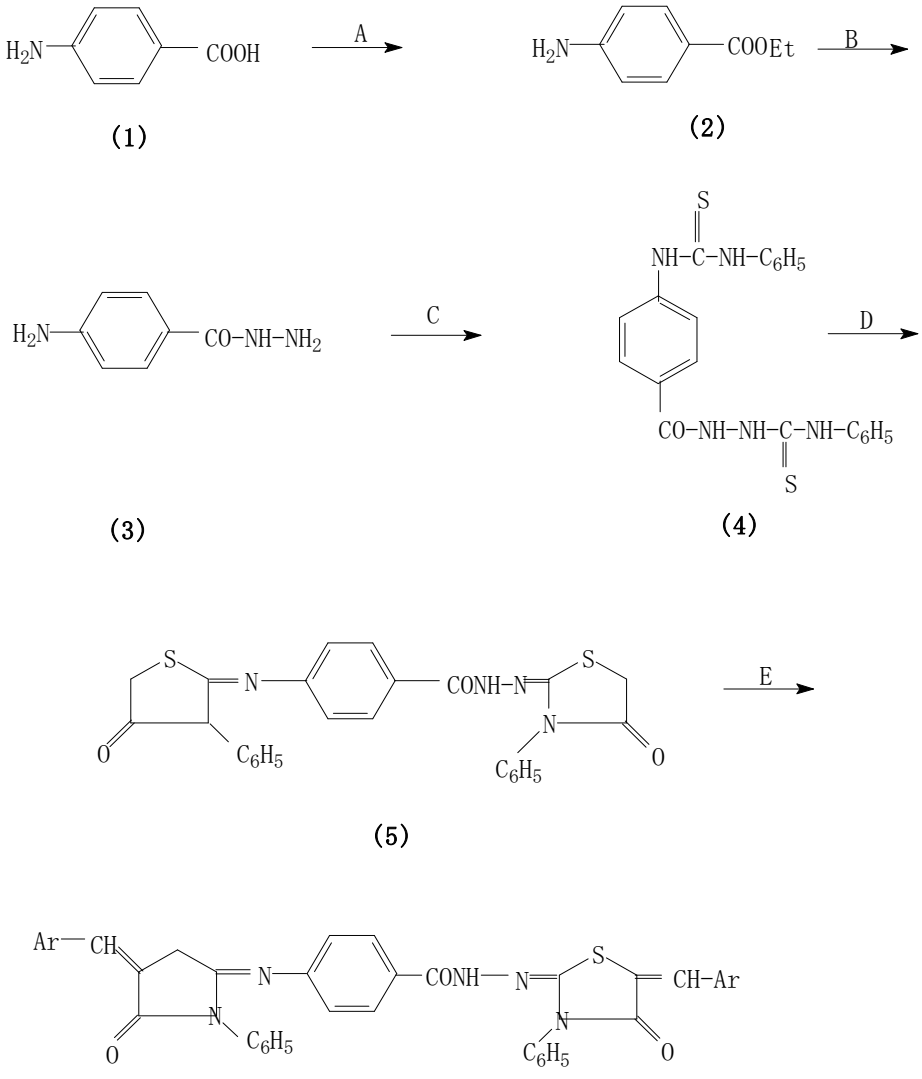
All the chemicals of acceptable standards were procured from local market. Double distilled water to be used as solvent was prepared in the laboratory. Phenylisothiocyanate used as a reagent was also prepare in the laboratory.

Electronic spectra were recorded on Shimadzu UV-1700 Spectrophotometer and IR spectra were recorded in KBr pellets in Shimadzu 8400 FTIR Spectrophotometer. Melting points were recorded by open capillary method.

Method

Synthesis of ethyl p-amino benzoate- p-Amino benzoic acid(11gm, 80 mole) was added to a solution of absolute ethanol (80ml) saturated with dry HCl gas and the mixture was refluxed on a water bath for two hours. The hot solution was poured in to large volume of water and the resulting solution was neutralizing by addition of 1N sodium bicarbonate solution. The precipitate ester was filtered, dried over anhydrous Na_2SO_4 and was recrystalised from rectified sprite. Yield-5 gm (45.40%)

SCHEME



Where **A**=C_2H_5OH, **B**=NH_2NH_2, **C**=$C_2H_5OH+C_6H_5NCS$, **D**=$ClCH_2COOH$+An.CH_3COONa, **E**=C_6H_5CHO+An.CH_3COONa

Synthesis of p-aminobenzoyl hydrazine- A mixture of hydrazine hydrate (10ml), ethyl p-amino benzoate (5gm) was refluxed slowly for one and half an hour. After cooling hydrazide separate out as colourless needles. It was filtered, washed with water, dried and recrystallised from ethanol. Yield-1.5 gm (33.30%)

synthesis of 1-(p-phenylthioureidobenzoyl)-4-phenyl thiosemicarbazide- To stirred solution of p-Aminobenzoyl hydrazine (1.5gm,10mmole) in absolute ethanol (10ml), phenyl isothiocyanate(2.7gm,20mmole) was added during a period of ten minutes and then it was refluxed for water bath for three hours. After cooling, the colourless solid separated was filtered , dried and recrystalised from ethanol. Yield-1.05 gm (70%)

Synthesis of 2-[4-(4-oxo-3-phenylthiazolidinyl-2-imino) benzoyl] aminoimino-3-phenyl-4-thiazolidinone-A mixture of 1-(P-Phenylthioureidobenzoyl)-4-phenyl thiosemicarbazide (2.1 gm, 5mmole), chloroacetic acid(1 gm, 10mmole) and anhydrous sodium acetate(0.2 gm) in absolute ethanol (20 ml) was refluxed on a water bath. After one hour of reflux everything went into solution and the refluxed was continued for another three hours. The excess of solvent was removed and the pasty mass was triturated with crushed ice. The solid separated was filtered, dried in air and recrystalised from ethanol. Yield-.88 gm (40%)

Synthesis of 2-[4-(5'-benzylidene-4'-oxo-3'-phenylthiazolidinyl imino)benzoyl]aminoimino-5-benzylidene-3-phenyl-4-thiazolidinone- A mixture of 2-[4-(4-oxo-3-phenylthiazolidinyl-2-imino) benzoyl] aminoimino-3-phenyl-4-thiazolidinone (1.7 gm, 3 m mole), benzaldehyde(0.3 gm, 6 m mole) and anhydrous sodium acetate (0.3 gm) in glacial acetic acid (15ml) was refluxed slowly for three hours. After cooling the solution was poured in to crushed ice and the resulting yellow solid separated was filtered, dried and recrystalised from ethanol,

Aqueous Phase solubility study:
The aqueous solubility of compound at various concentration of β-cyclodextrin was studied by Higuchi and Corners method [19]. Accurately weighed sample of these compounds was shaken in rotary flash shaker at room temperature in a series of conical flask for a period of 48 hours till the attainment of equilibrium. The solutions were filtered through whatmann-42 filter paper and were analyzed in a UV-visible spectrophotometer. The various values of absorbance at λ-max were plotted against different concentrations of β –cyclodextrin. From the phase solubility plots, the thermodynamic stability constant (K_T) of the inclusion complexes are determined using Benesi Hilderbrand relation:

$$\frac{1}{\Delta A} = \frac{1}{\Delta \epsilon} + \frac{1}{K\,[Guest]_o \Delta \epsilon} X \frac{1}{[\beta\text{-}CD]_o}$$

Where ΔA is change in absorbance, Δϵ is change in molar extension coefficient, $[Guest]_o$ is concentration of compound in inclusion complex and $[\beta\text{-}CD]_o$ is molar concentration of β-CD.

Synthesis of inclusion complexes:
From phase solubility study the 1:5 ratio of thiazolidinone and β –cyclodextrin gives maximum absorbance. So inclusion complexes of the compounds 6A,6B,6C and 6D are prepared with β –cylodextrin in 1:5 ratio as per co-precipitation method[20]. The solutions of these compound in recquired concentrations were added drop by drop to β –cyclodextrin solution of the required concentration. The mixtures were stirred for a period of 48 hours and filtered. The filtrate was cooled for 48 hours in refrigerators. Finally, the precipitate obtained was filtered and washed with distilled water and dried in air for 48 hours.

RESULTS AND DISCUSSION

Thiazolidinone derivatives have low solubility in polar solvent which may be a limiting factor in reducing their pharmacological activities. The solubility and therapeutic activity of these compounds can be enhanced significantly by forming inclusion complexes with cyclodextrins. The analytical and spectral data of the synthesized compounds and their inclusion complexes are included in Table-I and Table-II. The formations of the compounds are ascertained from the study of the spectral characteristics and elemental sulphur composition. The IR data and sulphur composition nearly match with the expected values.

The formation of inclusion complexes of the compounds with β-cyclodextrin is confirmed from the changes in melting points of the inclusion complexes with their respective compounds. The melting point of the compounds 6A,6B,6C and 6D are190^{o}C,140^{o}C,128 ^{o}C and 178^{o}C respectively, whereas the melting point of their corresponding inclusion complexes are195^{o}C,147^{o}C,136^{o}C, and 183^{o}C .respectively. It is due to the fact that extra amount of thermal energy is required to bring the molecules out of the cavity of the β-cyclodextrin.

The formation of colour of the synthesized compounds 6A,6B,6C and 6D are yellow, deep yellow, pale yellow and yellow. Similarly the colour of their corresponding inclusion complex are light yellowish, brownish yellow, yellow, and pale yellow respectively.

In case of IR data of 6A it is seen that the IR frequencies are found to be formed at 3253(N-H str), 3053(C-H str, Ar),1637(C=O str), 1712(C=O str), 1494(C=N str), 758(C-S str), 842(C-N str) in the compound as excepected .Similarly the IR data of inclusion complexes of 6A show charectestics absorption at 3200-3500(O-H str,broad), 2924(C-H str, Ar),1696(C=O str), 1498(C=N str), 760(C-S str), 860(C-N str), in the compounds. Similarly the IR

data of complexes 6B, 6C and 6D their inclusion complexes is found to be absorbed at the suitable characteristic frequency. In case of IR data for all compounds, it is seen that the IR frequencies (C=O) undergo downward shift and the peaks become broader, weaker and smoother. But in case of NH stretching vibration, the frequency undergoes a shift towards higher wave number after inclusion complex formation. All these changes noticeably demonstrate transference of compounds into the cavity of β-cyclodextrin and development of weak interaction like H-bonding, Vannder Waals forces, hydrophobic interactions in between the host and guest molecules[21,22].

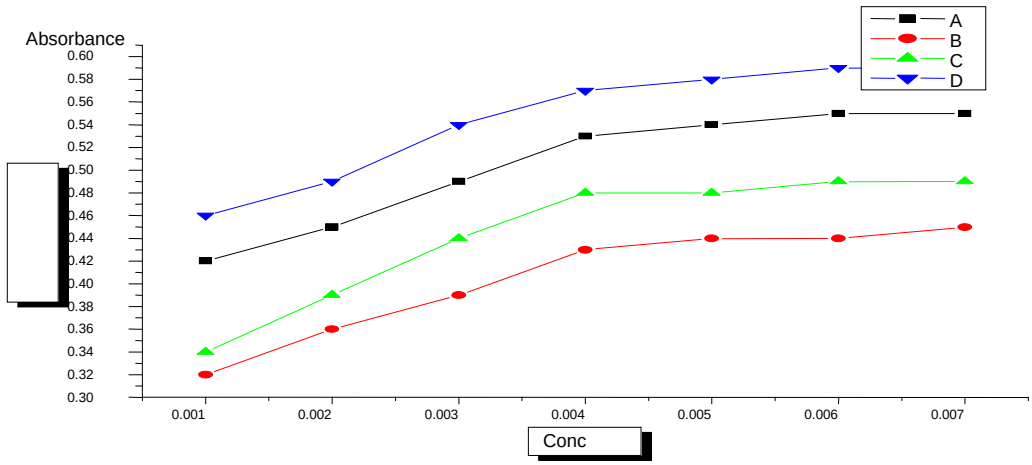
Table-1 : Physical properties of the compounds with and without inclusion complex

Sl No.	Compound/ complex	substituent	Colour	Yield	Melting Point (ºC)	Elemental Analysis (%) (Theoretical) (Experimental) C	H	N	O	S
1	Compound- 6A	phenyl	yellow	47%	190	69.13 (69.2)	3.99 (4)	10.33 (10)	7.09 (7.0)	9.453 (9.5)
2	Inclusion complex of comp. 6A	phenyl	Light yellow	52%	195					
3	Compound- 6B	p-Anisyl	Deep yellow	44%	140	66.76 (66.8)	4.2 (4.2)	9.5 (9.6)	10.85 (10.7)	8.68 8.6
4	Inclusion complex of comp. 6B	p-Anisyl	yellow	45%	147					
5	Compound- 6C	p-Chlorophenyl	Pale yellow	39%	128	62.73 (62.8)	3.35 (3.4)	9.38 (9.3)	6.43 (6.4)	8.58 (8.6)
6	Inclusion complex of comp.6C	p-Chlorophenyl	light yellow	62%	136					
7	Compound- 6D	p-Nitrophenyl	Yellow	51%	178	61.02 (61.00)	3.26 (3.3)	12.78 (12.7)	14.6 (14.6)	8.34 (8.4)
8	Inclusion complex of comp. 6D	p-Nitrophenyl	Pale yellow	46%	183					

Table-2 : Spectral data of the compounds with and without inclusion complex

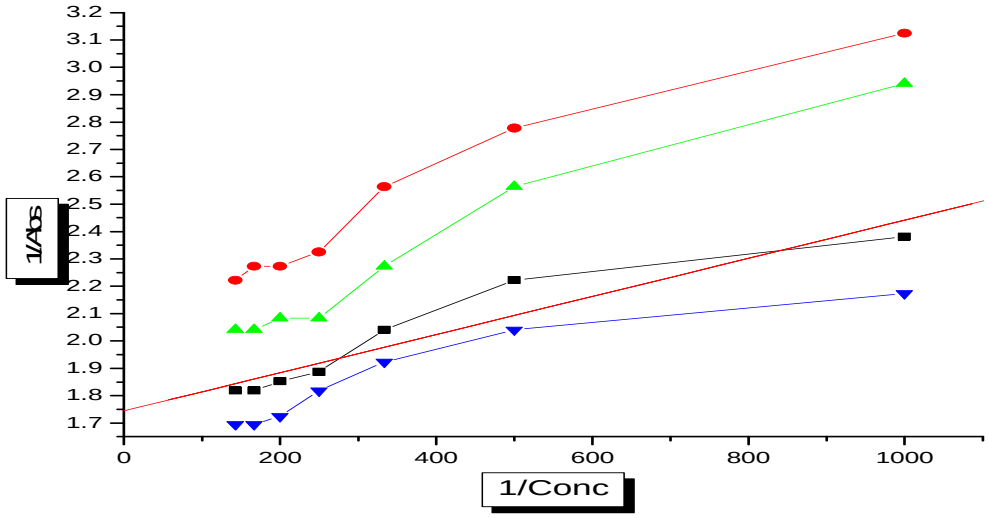
Sl No.	Compound/ Complex	substituent	UV λ_{Max}(nm)	IR(KBr) cm^{-1}
1	Compound- 6A	phenyl	274	3253(N-H str), 3053(C-H str, Ar),1637(C=O str), 1712(C=O str), 1494(C=N str), 758(C-S str), 842(C-N str),
2	Inclusion complex of comp. 6A	phenyl	269	3200-3500(O-H str,broad), 2924(C-H str, Ar),1696(C=O str), 1498(C=N str), 760(C-S str), 860(C-N str),
3	Compound- 6B	p-Anisyl	262	1105(C-O-C str),3245(N-H str), 3052(C-H str, Ar),1642(C=O str), 1705(C=O str), 1489(C=N str), 744(C-S str), 840(C-N str),
4	Inclusion complex of comp. 6B	p-Anisyl	259	3200-3500(O-H str,broad), 1113(C-O-C str), 3064(C-H str, Ar),1644(C=O str), 1710(C=O str), 1495(C=N str), 758(C-S str), 857(C-N str),
5	Compound- 6C	p-Chlorophenyl	255	3251(N-H str), 3075(C-H str, Ar),1640(C=O str), 1706(C=O str), 1495(C=N str),736,703(C-Cl str) 756(C-S str), 840(C-N str),
6	Inclusion complex of comp.6C	p-Chlorophenyl	251	3200-3500(O-H str,broad), 3078(C-H str, Ar),1646(C=O str), 1716(C=O str), 1498(C=N str),738,715(C-Cl str) 759(C-S str), 847(C-N str),
7	Compound- 6D	p-Nitro phenyl	263	3249(N-H str), 3055(C-H str, Ar),1636(C=O str), 1711(C=O str), 1537,1350(N=O str)1493(C=N str), 758(C-S str), 841(C-N str), 765(N-O str)
8	Inclusion complexof comp. 6D	p-Nitro phenyl	261	3200-3500(O-H str,broad), 3061(C-H str, Ar),1642(C=O str), 1718(C=O str), 1541,1356(N=O str)1494(C=N str), 764(C-S str), 8415C-N str), 767(N-O str)

FIGURE-1: AQUEOUS PHASE SOLUBILITY OF THE COMPOUNDS



A- PHENYL, B- P-ANISYL, C- P-NITROPHENYL , D- P-CHLOROPHENYL

FIGURE-2 PLOT OF 1/ABSORBANCE VS. 1/ [B-CD] *β*



A- PHENYL, B- P-ANISYL, C- P-NITROPHENYL , D- P-CHLOROPHENYL

CONCLUSION

From the above results and discussions, it is clear that solubility of 2-[4-(5'-benzylidene-4'-oxo-3'-phenylthiazolidinyl-2'-imino)benzoyl]aminoimino-5-benzylidene-3-phenyl-4-thiazolidinone increase significantly by the formation of inclusion complexes with *β*-cyclodextrin which can be used as a very good analytical tool for increasing bio accessibility of the drugs.

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