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A Comparative Study of the Inclusion Complexes of 2-[5'-benzylidene-2'-phenyl-4'-oxo-1', 3'-thiazolidine]-1, 3-benzothiazole and 2-[5'-(*p*-*N*,*N*-dimethylamino-benzylidene)-2'-phenyl-4'-oxo-1', 3'-thiazolidine]-1, 3-benzothiazole with β-Cyclodextrin

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Abstract: The compounds 2-[5'-benzylidene-2'-phenyl-4'-oxo-1',3'-thiazolidine] -1,3-benzothiazole and 2-[5'-(p-*N*,*N*-dimethylaminobenzylidene)-2'-phenyl-4'-oxo-1',3'-thiazolidine]-1,3-benzothiazole have been synthesized in their purest forms starting from 2-aminobenzothiazole. The inclusion complexes of the above compounds have been prepared with β-cyclodextrin to increase their solubility and bioaccessibility in polar medium. The formation of inclusion complexes have been ascertained by study of spectral characteristic before and after inclusion complex formation. The stability of inclusion complexes and nature of interaction between the host and guest are known from the determination of thermodynamic parameters. Further the antibacterial and antifungal activities of the compounds are determined which is found to increase significantly after inclusion complex formation

Keywords: 2-Aminobenzothiazole, Inclusion complex, β-Cyclodextrin, Antimicrobial activity.

Introduction

The derivatives of benzothiazole exhibit a wide spectrum of pharmacological activities such as antitubercular[1], antimicrobial[2], antifugicidal[3-5] and antiallergic[6]. The amino of (-NH_2) group of 2-aminobenzothiazole can be used as a very good target for condensing with 2-oxo-azetidine and their 5-benzylidene moieties generating a series of 2-[5'-(aryldene)-2'-*p*-substituted phenyl-4'-oxo-1',3'-thiazolidine]-1,3-benzothiazole which have significant antimicrobial activities[7-16]. These compounds being insoluble in polar medium may have poor pharmacological activities[17]. The solubility of these compounds can be enhanced by forming inclusion (host-guest) complexes with β-cyclodextrins (β-CD) which in turn increase their solubility and drug efficiency[18].

In the present work, an attempt has been made to synthesize 2-[5'-benzylidene-2'-phenyl-4'-oxo-1', 3'-thiazolidine]-1, 3-benzothiazole(**IIIA**) and 2-[5'-(*p-N,N*-dimethylamino-benzylidene)-2'-phenyl-4'-oxo-1',3'-thiazolidine]-1,3-benzothiazole(**IIIB**) and to prepare their inclusion complexes with β-CD. The formation of compounds and their inclusion complexes have been ascertained by the study of spectral characteristics. Thermodynamic parameters of the inclusion complexes have been calculated to have an idea about the stability of the compounds with in β-CD cavity. Finally antibacterial and antifungal activities of the compounds have been determined to examine whether the inclusion complex formation is enhancing the bioaccesibility of the compounds or not.

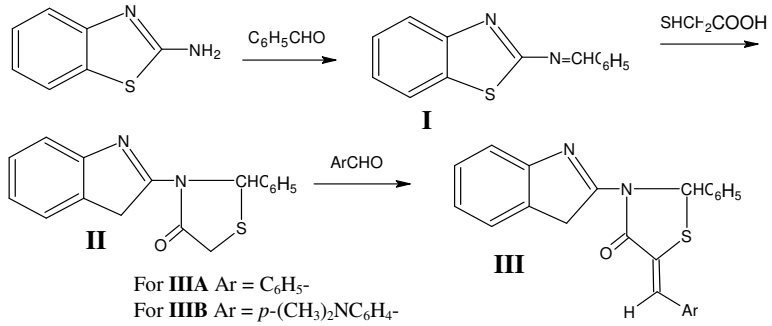
Experimental

The elemental analysis of the compounds synthesized has been performed in a CHN analyzer. Electronic spectra are recorded on shimadzu UV-1700 spectrophotometers while IR spectra are recorded in KBr pallets in the range of 400-4000 cm^{-1} region in a shimadzu 8400 S FTIR spectrophotometer. Melting points are recorded by open capillary method.

The pure compounds have been synthesized as per the method described by Srivastava *et al*[33]. Equimolar solution of 2-aminobenzothiazole (5 g, 0.03 mol) and benzaldehyde (3.38 mL, 0.03 mol) with few drops of glacial acetic acid in MeOH (50 mL) was refluxed on water with bath for about 1 h. The solvent was removed *in vacuo* and the residue was purified over the column of silica gel using $CHCl_3$.The product was recrystallized from ethanol to give 2-*N*-(benzyledine)-imino-1, 3-benzothiazole**(I).**

A mixture of the compound **I** (3g, 0.01 mL) and thioglycolic acid (0.91 mL, 0.01 mol) in the presence of $ZnCl_2$ in benzene (50 mL) is refluxed on a water bath for about 15 h. The solvent was removed *in vacuo* and the residue was purified over the column of silica gel using $CHCl_3$ as an eluent.The product was recrystallized from ethanol to afford compound 2-[2'-(phenyl)-4'- oxo-1', 3'-thiazolidine]-1, 3-benzothiazole**(II).**

Equimolar solution of the compound **II** (2 g, 0.006 mol) and benzaldehyde (0.65 mL, 0.006 mol) in dioxane (20 mL) in the presence of C_2H_5OK was refluxed on a water bath for about 6 h. The solvent was removed *in vacuo* and the residue was purified over the column of silica gel using $CHCl_3$ as an eluent. The product was recrystallized from ethanol to yield compound 2-[5'-benzylidene-2'-phenyl-4'-oxo-1',3'-thiazolidine]-1,3-benzothiazole(**IIIA).** Similarly the compound **IIIB** was synthesized as per the procedure given above using p-*N,N*-dimethylaminobenzaldehyde in place of benzaldehyde. The synthesis of compound **IIIA** and **IIIB** are shown in Scheme 1**.**



Scheme 1

The aqueous phase solubility of compound IIIA and IIIB at various concentration of β -CD have been studied by Higuchi Connors method[19]. Accurately weighed sample of these

compounds in quantities exceeding their aqueous solubility were shaken in a rotary flash shaker at room temperature with aqueous solution of β-CD in increasing concentration in a series of stoppered conical flasks for a period of 48 h till equilibrium is established.

The solutions were filtered through Whatman No 1 paper and were analysed in a UV-Vis spectrophotometer at 200-400 nm range. The various values of OD at λ_{max} have been plotted against different concentration of β-CD. The inclusion complexes of compounds **IIIA** and **IIIB** have been prepared as per Nayak *et al*[32]. The solutions of the synthesized compound were prepared in required concentration (0.05 mM) and were added drop wise to previously stirred β–CD solution. The mixture were stirred at room temperature for 48 h and filtered. Then the contents are cooled for another 48 h in refrigerator. Finally the precipitate obtained are filtered through G-4 crucible, washed with double distilled water and dried in air for 24 h.

The thermodynamic stability constant (K_T) at room temperature of the inclusion complexes have been calculated using Benesi-Hilderbrand relation[20]. The stability constant K (during deencapsulation) of the complexes are calculated with increasing temperature. The slope of the linear plot of ln K against 1/T gives rise to the calculation of ΔH (change in enthalpy) and then ΔS (change in entropy) was calculated using the integrated form of the van't-Hoff equation.

$$\ln K = (-\Delta H/RT) + \Delta S/R$$

The value of ΔG was calculated from the value of K_T at 298 K using the equation

$$\Delta G = -RT \ln K_T$$

The antibacterial and antifungal properties of compounds (**IIIA** and **IIIB**) and their inclusion complexes with β-CD have been studied as per Cappuccino[21] and Cooper[22-23] respectively.

Results and Discussion

The synthesis of compound **IIIA** and **IIIB** have been confirmed from elemental analysis and IR data as shown in the Table 1.The elemental composition nearly matches with theoretical data. The Infrared data of $C=O_{str}$ at 1689.73, $C=CHAr_{str}$ at 1639.38. C-N at 1294.15, N-HC-S_{str}at 3049.25 *etc* suggest formation of compound **IIIA**. The Infrared data of $C=O_{str}$ at 1685.52, $C=CHAr_{str}$ at 1635.37, C-N at 1319.22, N-HC-S_{str} at 3323.12 *etc*. suggests formation of compound **IIIB**. In addition, both compounds **IIIA** and **IIIB** differ significantly in their melting points (Table 1)**.**

Table 1. Analytical data of compound (**IIIA** & **IIIB**) and their inclusion complex with β-cyclodextrin

No	Compound	M.P °C	Elemental Analysis Found(calculated)% C	H	N	O/S	λ_{max} nm	IR(KBr) cm^{-1}
1	Compound IIIA	203	71.48 (71.2)	4.12 (4.3)	3.6 (3.4)	20.8 (21.1)	261	1689.53(C=O),cyclic 1639.38(C=CHAr) 1294.15(C-N) 3049.25((N-CH-S)
2	Inclusion complex of compound IIIA with β-cyclodextrin	212	-	-	-	-	259	1676.03(C=O),cyclic 1629.74(C=CHAr) 3047.32(N-CH-S)
3	Compound IIIB	204	71.538 (71.1)	5.0 (5.13)	8.07 (7.9)	15.392 (15.87)	353	1685.52(C=O),cyclic 1635.37(C=CHAr) 1319.22(C-N) 3323.12((N-CH-S)
4	Inclusion complex of compound IIIB with β-cyclodextrin	213	-	-	-	-	351	1668.53 (C=O),cyclic 1627.75(C=CHAr) 1317.22(C-N) 3309.62(N-CH-S)

The synthesis of inclusion complexes of compounds **IIIA** and **IIIB** have been confirmed from melting point data and spectral characteristics (UV-Vis and IR)(Table 1) The melting point of **IIIA** and its inclusion complex are 203^0 and 212^0 C respectively. The melting point of **IIIB** and its inclusion complex are 204^0 and 214^0 C respectively. A higher melting point of inclusion complexes than their compounds (**IIIA** and **IIIB**) are due to the fact that extra amount of thermal energy is required for the compound to be brought out of β-CD cavity. .

The drug recipient interactions are better identified by employing UV and IR spectrophotometry as useful tool[24]. The absorption maxima are shown to undergo a distinct blue shift of 2 nm after their inclusion complex formation with β-CD (Table 1, Figure 1.1**,** Figure 1.2).These observation clearly demonstrate transference of the compound from a more protic environment to a less protic environment (cavity of β-CD)**.** The compound and β-CD interaction leading to inclusion complex formation is further supported by IR data (Table 1). It is seen that the IR stretching frequencies due to different bonds C=O, N-HC-S, C=CHAr *etc* in case compound **IIIA** and **IIIB** undergo a downward shift towards lower energy and the peaks become broader, weaker and smoother. Such changes in IR spectral characteristics due to the inclusion complex formation may be attributed to development of weak interactions like H- bonding van der Waals forces and hydrophobic interactions between host and guest molecules[25].

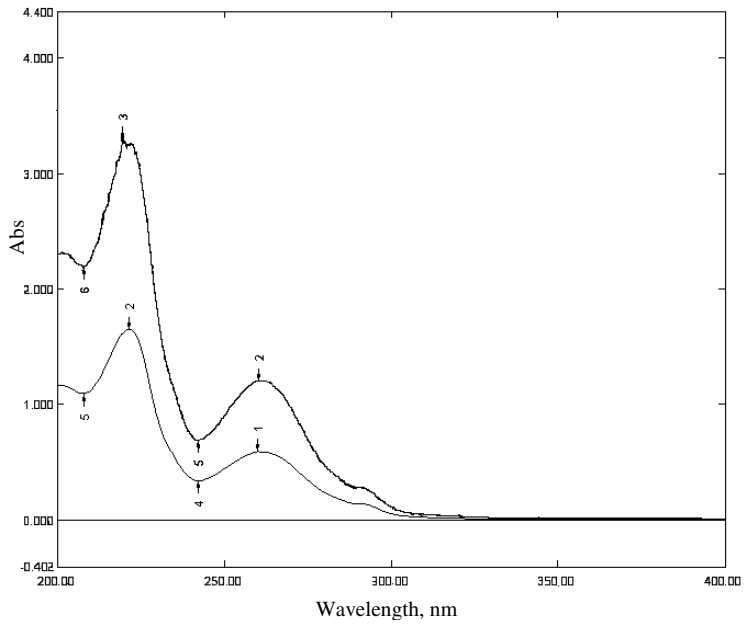


Figure 1.1. Comparison of UV spectra of **IIIA** (lower curve) and its inclusion complex (upper curve)

The phase solubility plots of **IIIA** and **IIIB** in a solution of β-CD is shown in the Figure 2. In both the cases, it is seen that there is a linear increase in solubility of the compounds with increasing concentration of β-CD. At a higher concentration of β-CD, a small negative deviation is observed. Since the slopes of plots are less than unity, the stoichiometry of the inclusion complexes[26] is 1:1.

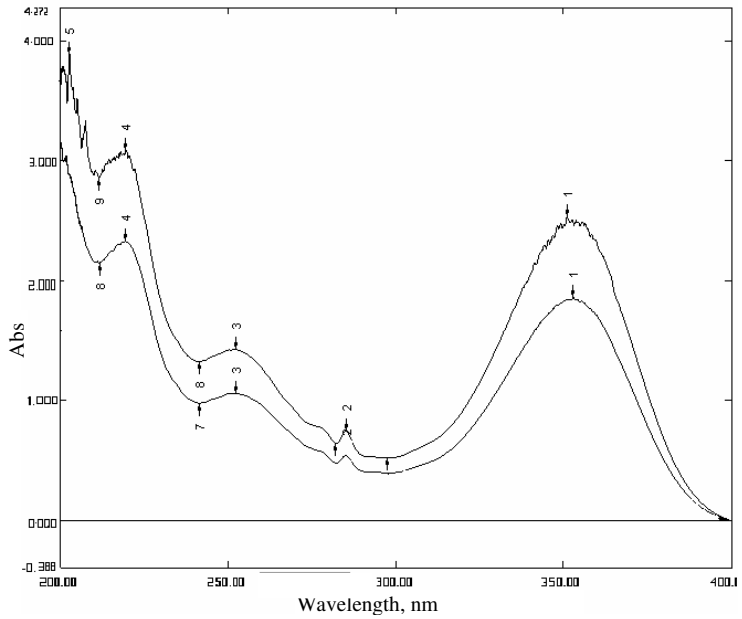


Figure 1.2. Comparison of UV spectra IIIB (lower curve) and its inclusion complex (upper curve)

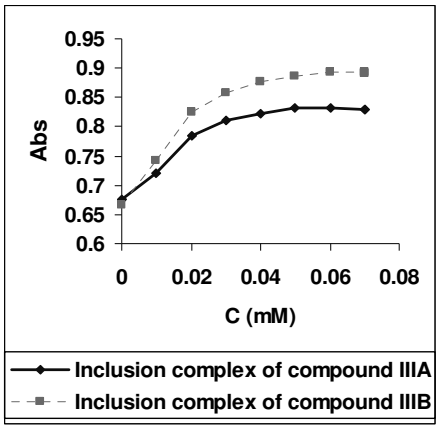


Figure 2. Phase solubility plot of compound **IIIA** and **IIIB**

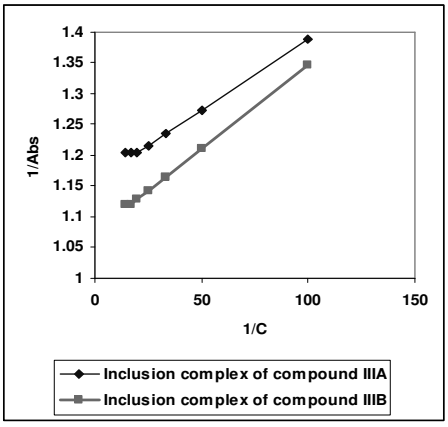


Figure 3. Plot of absorbance^{-1} *vs.* $1/[\beta\text{-CD}]_0$ of compound **IIIA** and **IIIB**

The thermodynamic stability constants (K_T) of inclusion complexes are determined by following Benesi-Hilderbrand reaction:

$$1/\Delta A = 1/\Delta \epsilon + 1/K[\text{guest}]_0 \, \Delta \epsilon \, .1/[\beta\text{-CD}]_0$$

Where ΔA is change in absorbance [guest]0 is concentration of compound in inclusion complex and [β-CD]0 is molar concentration of β-CD

A good linear correlation (Figure 3) is obtained for a plot of $1/\Delta A$ verses $[1/\beta\text{-CD}]_0$ for compounds **IIIA** and **IIIB**. The values of K_T for the complexes are calculated using the relation:

$$K_T = \text{Intercept/Slope}$$

The K_T values for the inclusion complexes of **IIIA** and **IIIB** with β-CD are found to be 522.42 M^{-1} and 390.5M^{-1} respectively. Lower value K_T for inclusion complex of **IIIB** than that of **IIIA** clearly indicates that the stability of inclusion complex of **IIIA** is more than that of **IIIB**. Further the data obtained are with in 100 to 1000M^{-1} (ideal values) indicating appreciable stability for the inclusion complexes[27].

The thermodynamic parameters associated with encapsulation of compounds **IIIA** and **IIIB** with β-CD for 1:1 stoichiometries have been calculated by determining the K values at different temperatures. The K values are found to decrease with increasing temperature (deencapsulation) as expected for an exothermic process[28,29]. The plot of ln K as a function of inverse absolute temperature produced a linear plot (Figure 4). In such a case, the slope corresponds to (-ΔH/ R).From these values and the value of K_T at 298 K, ΔG, ΔS and ΔH have been calculated (Table 2)

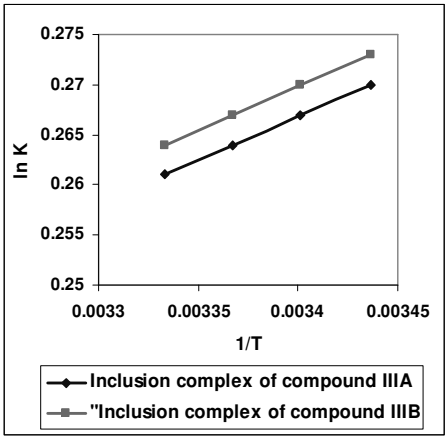


Figure 4. Plot of ln K *vs.* 1/Temperature of compound **IIIA** and **IIIB**

Table 2. Thermodynamical data of inclusion complex of compound (**IIIA** and **IIIB**) at 298 K

No	Compound	K, M^{-1}	ΔG, kJ/mol	ΔH, kJ/mol	ΔS, kJ/mol
1	Inclusion complex of IIIA with β-cyclodextrin	522.42	-15.5086	-0.725	0.05199
2	Inclusion complex IIIB with β-cyclodextrin	396.5	-14.84	-0.725	-0.00025

As can be seen from the table, ΔG values are negative for both the complexes. The data clearly demonstrates spontaneous formation of both the inclusion complexes. Secondly a negative value of ΔH and a positive value of ΔS at 298 K for compound **IIIA** suggest the complex formation to be an exothermic and enthalpy controlled process which may be due to the stabilization of compound with in the cavity of β-CD by weak intermolecular forces as suggested earlier[30-32]. In case of inclusion complex of **IIIB**, both ΔH and ΔS are negative which indicate the complex formation is energetically allowed but entropy forbidden. The negative value of entropy change may be due to steric hindrance with in β-CD cavity which may be correlated with its lower value of stability constant (Table 2).

The data obtained from antibacterial and antifungal studies of compounds **IIIA** and **IIIB** suggest that both the antibacterial (*E.coli*) and antifungal activities (*P.notatum*) increase significantly after the formation of inclusion complexes (Table 3). This may be

attributed to enhanced solubility of the drug. As the solubility increases, the drug becomes more bioacccessibile to specific tissues leading to increased drug activity.

Table 3. Pharmacological data of compound (**IIIA** and **IIIB**) and their inclusion complex and their inclusion complex with β-cyclodextrin

No	Compound	Conc. µgm/mL	Antibacterial activity, Zone of Inhibition of *E.Coli* (Diameter), mm	Antifungal activity Zone of Inhibition of *Pencilinium Notatum* (Diameter), mm
1	Compound IIIA	0.05	9	7
2	Inclusion complex of compound IIIA With *β*-cyclodextrin	0.05	12	14
3	Compound IIIB	0.05	10	11
4	Inclusion complex of compound IIIB with *β*-cyclodextrin	0.05	13	19

Conclusion

From the above results and discussions, it is clear that the solubility of compound **IIIA** and **IIIB** can be improved by inclusion complex formation with β-CD which is a very good analytical tool for enhancing the bioavailability of drugs. Further the study furnishes information about the participation of non-covalent intermolecular forces in between the guest (drug) and host β-cyclodextrin.

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