



Research Article

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Studies on Inclusion complexes of 3-[4-(4'-oxothiazolidinyl-2-imino)-aryl]-5,6-dihydro-5-oxothiazolo[2,3-a] triazole derivatives with β -cyclodextrin

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ABSTRACT

A number of compounds containing two thiazolidinone moieties, one fused to a triazole ring and other in the form of a side chain have been synthesized starting from p-Aminobenzoyl hydrazine in purest forms. Their corresponding inclusion complexes have been prepared with β -cyclodextrin so as to increase their solubility in polar medium. The formation of the compounds and their inclusion complexes have been ascertained from their elemental and spectral analysis. The antibacterial activities of the compounds and their inclusion complexes have been evaluated. It is found that the inclusion complex formation increases the antibacterial activities significantly.

Keywords: Thiazolidinone, p-Aminobenzoylhydrazine, Inclusion complex, β -cyclodextrin, Antibacterial activities.

INTRODUCTION

Thiazolidinones and their derivatives[1-5] exhibit a wide spectrum of pharmacological activities namely antibacterial, antifungal, antihistaminic, antimicrobial, antitubercular etc. Triazole units are also important pharmacophores for designing several chemotherapeutic agents [6]. Compounds containing two thiazolidinone moieties one fused to a triazole ring and the other in the form of a side chain have been synthesized starting from p-Aminobenzoylhydrazine. Poor solubility of these compounds in the polar medium may be a limiting factor reducing bio-accessibility of these compounds and hence lowering their drug efficiency. One of the ways to increase solubility of these compounds is to form inclusion(host-guest) complexes with β -cyclodextrin(β -CD), which in turn increases their solubility and drug efficiency [7-9]. So, in this paper an attempt has been made to synthesize a number of 3-[4-(4'-oxothiazolidinyl-2-imino)-aryl]-5,6-dihydro-5-oxothiazolo [2,3-a] triazole derivatives in their purest form and to prepare their inclusion complexes with β -cyclodextrin. The formation of the compound and their inclusion complexes have been ascertained by the study of physical and spectral characteristics. An attempt has also been made to examine whether inclusion complex formation enhances antibacterial activity of the drug or not.

EXPERIMENTAL SECTION

Apparatus and Materials

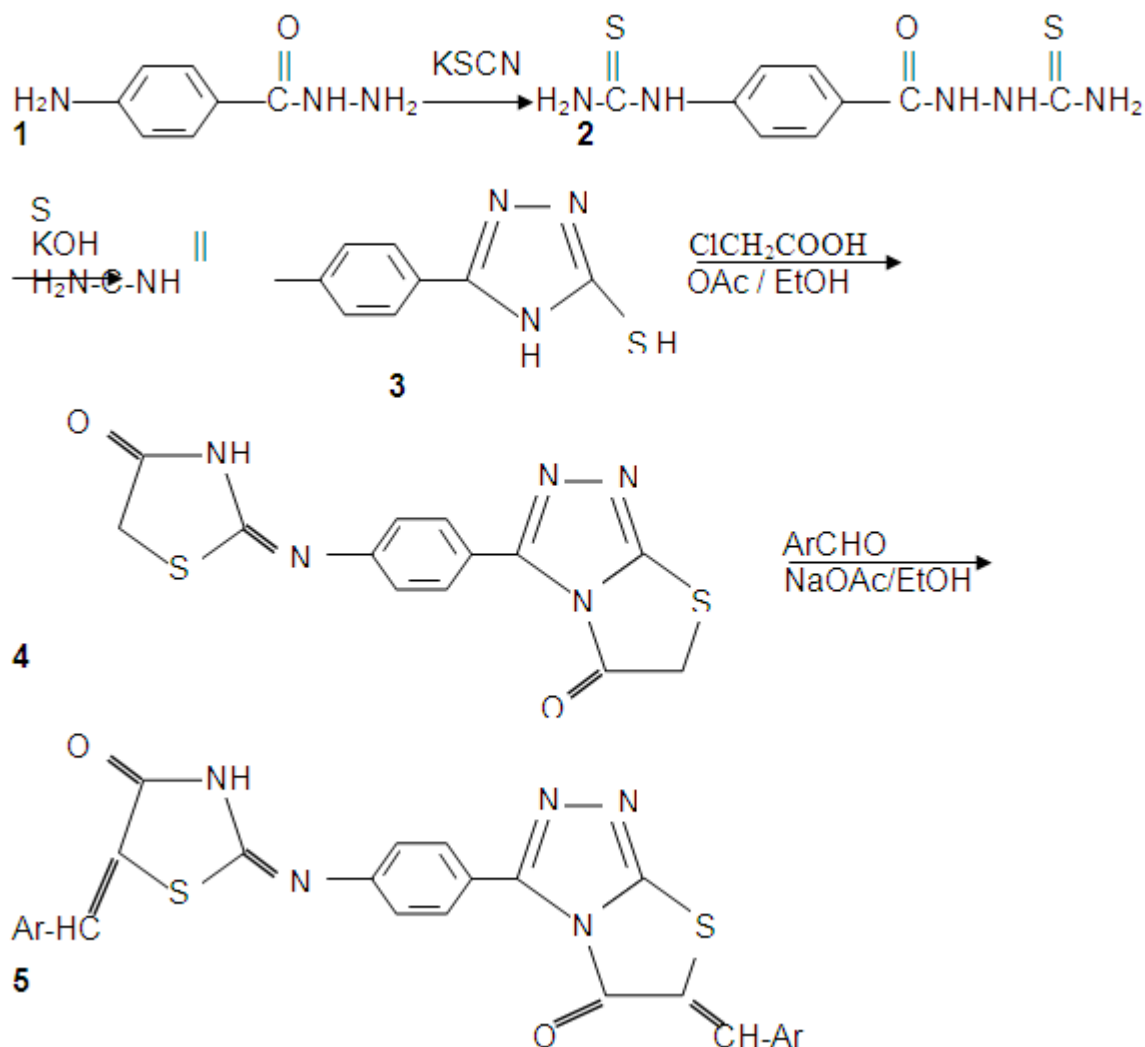
All the chemicals are procured from local market. Double distilled water is used as the solvent for dilution was prepared in the laboratory. The electronic spectra were recorded on Shimadzu UV-1700 Spectrophotometer while IR-spectra were recorded in KBr pellets in 400-4000 cm^{-1} region on a Shimadzu 8400 FTIR Spectro photometer. Melting points were recorded in open capillary method and are uncorrected.

Synthesis of compounds

The compounds in the purest form were synthesized as per the method describe by Garnaiket.al [6] 1987 (Scheme-1)

Step-1: Synthesis of 1-(4-Thioureidobenzoyl) thiosemicarbazide(2)

A mixture of p-aminobenzoyl hydrazine (1.5 gm, 10mmole), potassium thiocyanate (4gm, 40 mmole), con.HCl (10 ml) and water (50 ml) was refluxed for 3hr. After cooling the resulting yellow solid was dried and recrystallized from ethanol, (yield-1.57gm, 62%), m.p. 200°C (Found: S, 23.60 C₉H₁₁N₅S₂O requires; S, 23.79%); $\nu_{\text{max}}^{\text{KBr}}$: 3500-3150 (-NH-,broad), 1680(C=O), 1610, 1590 and 1440cm⁻¹.

**(Scheme-1)****Step-2: Synthesis of 5-(4-Thioureidophenyl) -2-mercapto-s-triazole(3)**

A suspension of the 1-(4-thioureidobenzoyl) thiosemicarbazide (2.7gm, 10mmol) and 10% KOH solution (30ml) was refluxed slowly for 3hr. the mixture was then cooled to room temperature and filtered. The filtrate was neutralized by the gradual addition of glacial acetic acid. The resulting colourless solid was dried and recrystallised from ethanol, (yield- 1.3gm (65%), m.p. 250°C (found: S, 25.2 C₉N₅S₂H₉ requires: S 25.49%); $\nu_{\text{max}}^{\text{KBr}}$ 3410-3100 (-NH- broad), 2420 (SH), 1600, 1560 and 1415cm⁻¹.

Step-3: Synthesis of 3-[4-(4'-Oxothiazolidinyl-2-imino) phenyl] – 5,6 – dihydro-5-oxothiazolo [2,3 -a] triazole (4)

A mixture of 3 (2.51gm, 10mmol), monochloroacetic acid (2gm, 20mmol) and anhydrous sodium acetate (0.5gm) in ethanol (50ml) was refluxed on a water bath for 4hr. The excess of solvent was then evaporated and the resulting slurry was poured into crushed ice. The resulting light yellow solid was filtered off, dried and recrystallized from ethanol (1.46gm, 50%), m.p. 190°C (found: S, 19.0 C₁₃N₅S₂O₂H₉ requires: S, 19.3%); $\nu_{\text{max}}^{\text{KBr}}$ 3210 (-NH-broad), 2955(-CH₂-stretch), 1710 and 1730 (two carbonyls in different environment), 1600, 1570 and 1500 cm⁻¹.

Step-4: Synthesis of 3-[4-(5-Benzylidene-4-Oxothiazolidinyl)-2-imino] phenyl-6-benzylidene-5,6-dihydro-5-oxothiazolo [2,3-a] triazole (5; Ar= C₆H₅)

A mixture of **4** (1.1gm, 3mmol), benzaldehyde (0.7gm, 6mmol) and anhydrous sodium acetate (0.5gm) in glacial acetic acid (10ml) was refluxed for 2.5hr. After cooling the deep yellow solution was poured into crushed ice and the resulting yellow solid was dried and recrystallized from acetic acid (0.65gm, 60%), m.p. 205°C (found: S, 12.4% C₂₇N₅S₂O₂H₁₇ requires S, 12.6%); $\nu_{\text{max}}^{\text{KBr}}$ 3200 (-NH- broad), 1725 and 1740 (carbonyl in different environment), 1620, 1590, 1510 and 1430 cm⁻¹.

Synthesis of Inclusion complexes

The inclusion complexes of the compounds(A,B,C,D&E) with β -cyclodextrin were prepared as per co-precipitation method[10].The solution of the compounds are prepared in required concentration (0.03mM) and added drop wise to a previously stirred β -cyclodextrin solution. The mixtures are stirred at room temperature for 48 hrs.and filtered. Then the content is cooled for another 48 hrs.in a refrigerator. Finally, the precipitate is filtered through G-4 crucible, washed with distilled water and dried in air for 24 hrs.

Aqueous phase solubility study

The aqueous phase solubility of all the compounds have been studied as per Higuchi Connors method[11]. An accurately weight of the compounds were shaken in rotary flask 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 on UV-visible spectrophotometer. Value of λ_{max} were plotted against different concentration of β -cyclodextrin. From the phase solubility plots, the thermodynamic stability constant (KT)of the inclusion complexes are determined using BenesiHilderbrand relation:

$$\frac{1}{\Delta A} = \frac{1}{\Delta \epsilon} + \frac{1}{K [\text{Guest}]_0 \Delta \epsilon} \times \frac{1}{[\beta\text{-CD}]_0}$$

Where ΔA is change in absorbance, $\Delta \epsilon$ is change in molar extension coefficient, $[\text{Guest}]_0$ is concentration of compound in inclusion complex and $[\beta\text{-CD}]_0$ is molar concentration of β -CD.

Study of Antibacterial activity

The antibacterial activities of the compounds and their inclusion complexes with β -cyclodextrin have been studied against E.coli and S.aureus per Cappuccino[13](1999).

RESULTS AND DISCUSSION

The analytical data of the compounds and their inclusion complexes are given in Table-I. 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. Similarly the formation of inclusion complexes of the compounds with β -cyclodextrin is confirmed from the changes in melting points of the inclusion complexes than their respective compounds. 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. 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 N-H stretching vibration, the frequency undergoes a shift towards higher wave number after inclusion complex formation. All these changes clearly demonstrate transference of compounds into the cavity of β -cyclodextrin and development of weak interaction like H-bonding, vander Waals forces, hydrophobic interactions in between the host and guest molecules. The determination of the thermodynamic stability constants (Table-I) of inclusion complexes indicate that the value remains within 100 to 1000 M⁻¹ and hence all inclusion complexes have appreciable stability. The data obtained from antibacterial studies (Table-II) of all compounds and their corresponding inclusion complexes against two well-known bacteria E.coli and S. aureus clearly suggest that inclusion complex formation increases the antibacterial activities significantly. This may be attributed to enhance solubility of the compounds which makes the compounds more bio accessible to specific tissues leading to increased drug activity.

Table – I: Analytical data of compounds and their inclusion complexes with β -cyclodextrin

Sl. No	Compound/complex	Ar.	Color	MP In °C	% of yield	K	% of S found/ calculated	IR(KBr)
1.	Compound 5A	Phenyl	Yellow	205	60	-	12.4/ 12.6	3200 (b)(NH) 1725 (C=O), 1740
2.	Inclusion complex of comp. 5A		Light yellow	210	40	320	-	3250(NH) 1702(C=O), 1732
3.	Compound 5B	p-Anisyl	Deep yellow	140	66	-	11.0/ 11.2	3230(b)(NH) 1710(C=O), 1730
4.	Inclusion complex of comp. 5B	-	Yellow	152	45	300	-	3248(NH) 1700 (C=O), 1724
5.	Compound 5C	p-Chloro phenyl	Pale yellow	128	60	-	11.01/ 11.10	3220 (NH) 1720(C=O), 1740
6.	Inclusion complex of comp. 5C	-	Light yellow	136	40	280	-	3230(NH) 1716(C=O), 1730
7.	Compound 5D	p-Bromo phenyl	Yellow	146	55	-	8.86/ 9.14	3210 (NH) 1715 (C=O), 1730
8.	Inclusion complex of comp. 5D	-	Pale yellow	151	40	330	-	3228 (NH) 1710 (C=O), 1725
9.	Compound 5E	p-Nitro Phenyl	Yellow	178	50	-	9.61/ 9.73	3222(NH) 1700 (C=O), 1718
10.	Inclusion complex of comp. 5E		Pale yellow	184	60	210	-	3215(NH) 1700 (C=O), 1720

Table-II: Antibacterial studies of the compounds and their Inclusion complexes

Sl. No.	Compounds	Con ^c in μ g/ml	E.coil DZI	S. Aureus DZI
1.	Compound 5A	0.05	9	7
2.	Inclusion complex of comp. 5A	0.05	13	9
3.	Compound 5B	0.05	14	10
4.	Inclusion complex of comp. 5B	0.05	16	13
5.	Compound 5C	0.05	14	10
6.	Inclusion complex of comp. 5C	0.05	17	12
7.	Compound 5D	0.05	14	13
8.	Inclusion complex of comp. 5D	0.05	16	15
9.	Compound 5E	0.05	16	14
10.	Inclusion complex of comp. 5E	0.05	18	16

CONCLUSION

From the above results and discussions, it is clear that solubility of thiazolidinones and their diaryl derivative 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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