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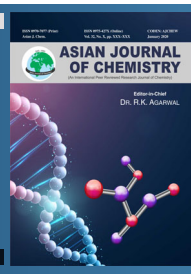


# Inclusion Complexes of Some Substituted 4-Thiazolidinones with Activating and Deactivating Group

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Some substituted 4-thiazolidinones have been prepared by taking 2-hydrazinobenzothiazole as a staring material. Polar solvent water makes less solubility of these compounds. Hence inclusions of compounds are prepared by taking suitable ratio of compound and β-cyclodextrin. The purpose of this work is to synthesize more soluble and more bioaccesible compounds. The synthesized compounds and their inclusions are known from the study of their thermodynamic properties and spectral characteristics (UV, IR and NMR). Pharmaceutical activity of the compounds and inclusion can be performed by using the bacteria namely *E. coli*, *S. aureus* and *P. vulgaris*. Considering and discussing all the matters, it has been found that inclusion formation shows more antibacterial activity than simple compound.

**Keywords: 4-Thiazolidinone, β-Cyclodextrin, *Escherichia coli*, Antibacterial activity.**

## INTRODUCTION

Drugs and medicines are basic needs of the society with mainly heterocyclic structures. These compound′s have their importance due to their nature, applicability and utility. Out of available compounds few are similar with earlier structure while some of them are new to mankind. Synthesization, evaluation and determination of chemotherapeutic potential of organic compounds are the prime work of organic chemists. By using modern techniques like sophisticated analytical instruments and spectroscopic methods, we are able to find the structure of compounds. Out of them, thiazolidinone is one of the well known heterocyclic compounds which contains nitrogen and sulphur in a five membered ring besides a carbonyl group. The substituted thiazolidinones are well known for their biological activities such as antimicrobial [1,2], antioxidant [3], anti-HIV [4], antihistaminic [5], anticonvulsant [6,7], anti-inflammatory [8-10]. The objective of this studey is to formulate three compounds of substituted 4-thiazolidinone derivatives from 2-hydrazinobenzothiazole. Since the compounds has poor solubility, hence they cannot provide maximum bioaccessibility. But there are various methods like addition of surface active agents, salt formation, crystal engineering, addition of ionic liquids and inclusion formation for increasing aqueous solubility of soluble drugs. Among these methods inclusion formation with cyclodextrin is useful for solubility of poorly water soluble drugs [11,12]. Improvements with regards to solubility, tolerability and bio-availability of the generated complex takes place with respect to original drug molecule.

This work reports a synthesis of a supramolecule by comb-4-thiazolidinines with β-cyclodextrin. During the past two decades, cyclodextrin and their derivatives draw a substantial attraction due to formation of large no of complex molecules with drugs. Cyclodextrins (CDs) are glucopyranose units held by β-(1,4) bonds containing six to more than 100 glucose units. There are three different types of CDs like α, β and γ-CDs consisting of six, seven and eight glucose units, respectively. Inclusion complexes can be prepared from CDs having wide range of hydrophobic molecules. In aqueous solutions, the hydrophobic CDs are occupied by water molecules which are bound by weak forces with drug to form complexes. One or two hydrophobic molecules can be entrapped by one to three CDs depending upon internal cavity size [13]. Different concentration of β-cyclodextrin has been taken to carry the experiment with the compound solution to know the best encapsulation ratios of the compound. Since, these three compounds are less soluble in water, hence an effort is made to build a supramolecule with β-cyclodextrin to make it better solubility in polar

solvent. The best way for the solubility of drug is to insert it into the cavity of β-cyclodextrin and to make it more the bioavailability which may turn out for more biological functions. Cyclodextrin is able to provide a conical cavity for the water insoluble thiazolidinone to be encapsulated by using host model cavities and makes it more water soluble. For this reason, β-cyclodextrins selected on account of its least toxicity, low-cost and easily availability in the market [14-16]. In order to prepare required compound, β-cyclodextrin has been encapsulated with of three compounds of 2-(benzothiazolyl-2′)-hydrazino-5-arylidene-4-thiazolidinone derivatives. The spectral and thermal studies of compounds and their inclusions have proved their formation. Besides this, antibacterial activity of compounds and their corresponding inclusions were matched.

## EXPERIMENTAL

2-Hydrazinobenzothiazole and other used chemicals are purchased from Himedia company. Melting points of the synthesized compounds and inclusions was determined by using open capillary method and are uncorrected. UV spectra of compounds spectra were measured on Shimadzu UV-1700 Spectrophotometer while at the same time IR-spectra were recorded in KBr pellets in 4000-400 $cm^{-1}$ region on a Shimadzu 8400 FTIR Spectrophotometer. Chemical shifts are analysed with the help of TMS as an internal standard. $^1H$ NMR spectra ($CDCl_3$) are scanned on a DRX-300 (300MHz) spectrophotometer and δ scale.

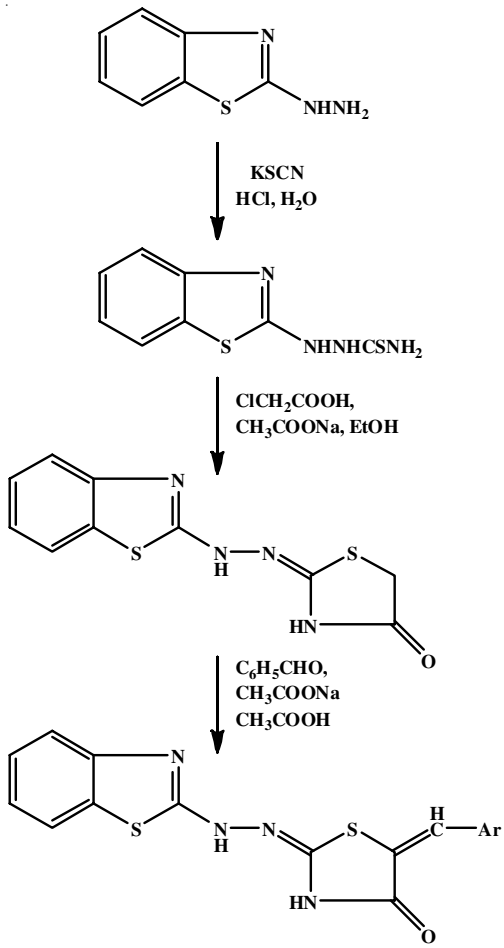
**Synthesis of compounds:** A reported method is adopted for the synthesis of compound K [17] (**Scheme-I**).

**Synthesis of 1-(benzothiazolyl-2′)thiosemicarbazide:** To synthesize 1-(benzothiazolyl-2′)thiosemicarbazide, 2-hydrazinobenzothiazole (1.65 g) mixed with 2 g of KSCN and added 2.0 mL of conc. HCl. Poured the mixture into a round bottom flask containing 10 mL of water. Refluxed the flask slowly for 3 h and then cooled to room temperature. Finally, yellow solid is formed which was filtrated and recrystallized using ethanol. m.p.: 141 °C, yield: 0.7 g (40 %).

**Synthesis of 2-(benzothiazolyl-2′)hydrazino-4-thiazolidinone:** 1-(Benzothiazolyl-2′)thiosemicarbazide (2.02 g) in a round bottom flask and added 0.2 g anhydrous sodium acetate. The solution was stirred for 2 min followed by the addition of 0.9 g monochloroacetic acid and 15 mL of absolute ethanol and refluxed for 3 h. The excess solvent was removed and the obtained white solid washed with cold water, filtered and recrystallized with alcohol. Yield: 1.3 g (69 %), m.p. 158-160 ºC.

**Synthesis of 2-(Benzothiazolyl-2′)hydrazino-5-arylidene-4-thiazolidinone (compound K):** 2-(Benzothiazolyl-2′)hydrazino-4-thiazolidinone (2.18 g) with 0.9 g of benzaldehyde and added 1.0 g fused sodium acetate dissolved in 15 mL of glacial acetic acid and refluxed for 4 h. Thereafter, the solution was poured into ice-cold water, which on drying yields yellow solid compound. Further, the product was washed with water and recrys-tallized with ethanol. Yield: 2.1 g (59 %), m.p. 202 ºC. Compounds L and M can be prepared by the same way as at can be done for compound K. Instead of benzaldehde, *o*-chlorobenzaldehyde and *p*-chlorobenzaldehyde is used.

**Aqueous phase solubility study:** Higuchi Connors method [18] is used to find the aqueous phase solubility of all the compounds. An exact amount of compound is added in a series of




**Scheme-I:** Sythetic scheme of compound **K**

conical flasks. All the conical flasks has to be shaked for 48 h in a rotary flask shaker at room temperature until it reached to the equilibrium point. The contents present in the conical flask were filtered by using Whatmann No. 42 filter paper. UV-visible spectrophotometer in the range of 200-400 nm is used for the analysis of the solution.

**Preparation of inclusion complexes:** An appropriate amount of compounds K, L and M with β-cyclodextrin inclusion complexes are prepared by adopting co-precipitation method [19-22]. For this purpose, concentrated (0.03 mM) solution of compound is taken. Simultaneously, β-cyclodextrin solutions were carried with required concentration and mixed with the solutions of compound with constant stirring at room temperature for 48 h. After filtration, the solid compound was refrigerated for 48 h.

**Antibacterial activity:** The antibacterial activity of the synthesized compounds were performed by using cup-plate method [23,24]. For the testing the compounds and their inclusions, DMSO having a concentration of 500 μg/mL is prepared. The bacterial strains of *E. coli* (MTCC 40), *S. aureus* (MTCC 87) and *P. vulgaris* (MTCC 426) were inoculated into 100 mL of the sterile nutrient broth and incubated of about 37 ºC for 24 h. McFarland method is adopted for the standardization of density of bacterial suspension. To carry the process, a uniform diameter of 6 mm consisting of agar plates, after inoculating them separately with the test organisms aseptically. The drug (500 μg/mL) and the test compounds (500 μg/mL) were intro-

duced with the help of micropipette and the plates were placed at 8-10 ºC for right diffusion of drug into the media. After 2 h of cold incubation, the petri plates were transferred to incubator placed at 37 ºC for 18-24 h.

## RESULTS AND DISCUSSION

Thiazolidinone derivatives exhibit less pharmacological activities on account of their less solubility in polar solvents. The formation of inclusion complex of thiazolidinone makes the augmentation of solubility and therapeutic potential in a noticeable amount. In an encapsulation of compound with β-cyclodextrins, its solubility and therapeutic activity can be enhanced significantly. Table-1 provides the analytical data of synthesized compounds and their inclusions. Analysis of the spectral characteristics and elemental analysis evidences formation of compounds and their inclusion complexes (Table-2).

The changes in melting points of inclusion complexes with their respective compounds indicates its inclusion complex formation with β-cyclodextrin. This accounts that some excess thermal energy is essential to bring the molecules out of the hollow space of β-cyclodextrin.

The IR data of inclusion complexes of compound K show characteristics absorption at 750, 1246, 1597, 1730, 2962 and 3315 $cm^{-1}$ indicating the presence of C-S, C-C, C-N, C=O, C-H and N-H bonds, respectively in the compounds. Likewise compounds L and M with their inclusion complexes are found to be absorbed at the proper characteristic frequency (Table-2). The develop-ment of weak interaction like H-bonding, van der Waals forces, hydrophobic interactions in between the host and guest molecules [25] leads to all these changes evidently demonstrate transference of compounds into the cavity of β-cyclodextrin . After the formation of inclusion complexes, UV spectra of the compounds are found to be increased. The δ values of inclusion complexes are found to be less as compared to the parent compound. This indicates that PMR signals are shifted towards upfield in the inclusion complex on account of notable shielding factor which arises through encapsulation within the cavity of β-cyclodextrin.

With increasing concentration of β-cyclodextrin, the solubility of these compounds increase linearly which can be determined from aqueous phase solubility study. The slopes of all the plots were not as much of as unity because of stoichiometry of these complexes are 1:1. By using Benesi-Hilderband relation [21], thermodynamic stability constants ($K_T$) of inclusion complexes were determined. Good linear correlations were obtained for a plot of inverse of ΔA *versus* inverse of $[\beta\text{-CD}]_o$ for compounds. Subsequently, the $K_T$ values of inclusion complexes of comp-ounds with β-cyclodextrin were found to be 313,295 and 276 $M^{-1}$, respectively (Table-3), which were remained within 100 to 1000 $M^{-1}$ (ideal values) representing substantial stabilities for the inclusion complexes through host-guest interaction like van der Waal′s force, hydrophobic interaction, *etc*. [26-28]. The interaction of the compound with β-cyclodextrin for 1:1 stoichiometry were calculated by determining stability constant ($K_T$ values) with the help of thermodynamic parameter at different temperatures. With increase in temperature, $K_T$ values were found to be decreasing.

The value of diameter of zone of inhibition formed by the compounds and their corresponding inclusion complexes against *E. coli*, *S. aureus* and *P. vulgaris* are shown in Table-4. Thus, it is found that inclusion complex formation increases the antibacterial activities considerably extent. Compound

TABLE-1
PHYSICAL DATA OF THE COMPOUNDS AND THEIR INCLUSION COMPLEXES

| Compound/Complex | Ar. | Colour | m.p. (°C) | Yield (%) |
|---|---|---|---|---|
| Compound **K** | Phenyl | Brownish red | 202 | 59 |
| Inclusion complex of compound **K** | | Light yellowish | 208 | 40 |
| Compound **L** | *o*-ClPh | Deep Yellow | 161 | 65 |
| Inclusion complex of compound **L** | | Brownish yellow | 168 | 41 |
| Compound **M** | *p*-ClPh | Dull brown | 135 | 55 |
| Inclusion complex of compound **M** | | Pale yellow | 144 | 45 |

TABLE-2
SPECTRAL DATA OF THE COMPOUNDS AND THEIR INCLUSION COMPLEXES

| Compound/ Complexes | $UV_{\lambda_{max}}$ | IR (KBr, $\nu_{max}$, $cm^{-1}$) | $^1H$ NMR |
|---|---|---|---|
| Compound **K** | 267 | 748.38 (C-S *str.*), 1494.83 (C=C *str.*), 1595.13 (C=N *str.*), 1728.22 (C=O *str.*), 3111.18, 2960.73 (N-H *str.*) | $^1H$ NMR ($CDCl_3$): δ 7.28 (s, 1H, N-H), 7.50 (s, 1H, C-NH), 7.30 (s, 1H, C-H), 7.32-7.48 (m, 8H, Ar-H) |
| Compound **K** with β-CD | 273 | 750.31 (C-S *str.*), 1456.26, 1496.76 (C=C *str.*), 1597.06 (C=N *str.*), 3315.63, 2962.66 (N-H *str.*) | $^1H$ NMR ($CDCl_3$): δ 7.30 (s, 1H, N-H), 7.48 (s, 1H, C-NH), 7.39 (s, 1H, C-H), 7.28-7.50 (m, 8H, Ar-H) |
| Compound **L** | 277 | 667.37 (C-Cl *str.*), 748.38 (C-S *str.*), 1494.83 (C=C *str.*), 1595.13 (C=N *str.*), 1730 (C=O *str.*), 3111.18, 3037.89 (N-H *str.*) | $^1H$ NMR ($CDCl_3$): δ 7.28 (s, 1H, N-H), 7.74 (s, 1H, C-NH), 7.31 (s, 1H, C-H), 7.53-7.73 (m, 6H, Ar-H) |
| Compound **L** with β-CD | 281 | 667 (C-Cl *str.*), 748 (C-S *str.*), 1496 (C=C *str.*), 1597 (C=N *str.*), 1732 (C=O *str.*), 3280, 3111, (N-H *str.*) | $^1H$ NMR ($CDCl_3$): δ 7.29 (s, 1H, N-H), 7.50 (s, 1H, C-NH), 7.48 (s, 1H, C-H), 7.28-7.41 (m, 13H, Ar-H) |
| Compound **M** | 278 | 667 (C-Cl *str.*)), 748. (C-S *str.*), 850.61, 1338.60 (N=O *str.*), 1494 (C=C *str.*), 1595 (C=N *str.*), 1732 (C=O *str.*), 2916.37 (Ar-H *str.*), 3112, 3037 (N-H *str.*) | $^1H$ NMR ($CDCl_3$): δ 7.28 (s, 1H, N-H), 7.74 (s, 1H, C-NH), 7.32 (s, 1H, C-H), 7.36-7.73 (m, 8H, Ar-H) |
| Compound **M** with β-CD | 285 | 667 (C-Cl *str.*), 750 (C-S *str.*), 1128 (C-N *str.*), 1494 (C=C *str.*), 1670 (C=N *str.*), 3159 (N-H *str.*) | $^1H$ NMR ($CDCl_3$): δ 7.29 (s, 1H, N-H), 7.74 (s, 1H, C-NH), 7.73 (s, 1H, C-H), 7.30-7.72 (m, 14H, Ar-H) |

TABLE-3
EQULIBRIUM CONSTANT AND FREE ENERGY CHANGE OF INCLUSION COMPLEXES

| Inclusion complex of compound | Equlibrium constant ($K_T$) | ΔG (kJ/mol) |
|---|---|---|
| **K** | 313 | -14.332 |
| **L** | 295 | -14.184 |
| **M** | 276 | -14.018 |

TABLE-4
ANTIBACTERIAL ACTIVITIES OF THE COMPOUNDS AND THEIR INCLUSION COMPLEXES

| Compounds/complexes | Diameter of zone of inhibition (mm) | | |
|---|---|---|---|
| | *E. coli* | *S. aureus* | *P. vulgaris* |
| Compound **K** | 12 | 11 | 10 |
| Inclusion complex of comp. **K** | 14 | 13 | 12 |
| Compound L | 16 | 15 | 14 |
| Inclusion complex of comp. **L** | 18 | 17 | 16 |
| Compound **M** | 16 | 15 | 15 |
| Inclusion complex of comp. **M** | 21 | 19 | 20 |
| Control | – | – | – |
| Standard | 28 | 27 | 26 |

containing *p*-chloro derivative exhibited maximum activity than that of other two compounds among the tested substances against all the bacterial strains. On account of more solubility the compounds becomes more bioaccessible to specific tissues leading to increased drug activity.

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## CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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