



Research Article

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**Antioxidant Activities of Inclusion Complexes of 2-(Benzothiazolyl-2')  
Hydrazono-3-Phenyl 5-Arylidene- 4- Thiazolidinone Derivatives with  $\beta$ -  
Cyclodextrin**

**Simanchal Dash<sup>1</sup>, B. K. Garnaik<sup>2\*</sup>**

<sup>1</sup>Department of Chemistry, Roland Institute of Technology, Surya Vihar, Berhampur, Odisha, India

<sup>2</sup>P. G. Department of Chemistry, Berhampur University, Bhanja Bihar, Odisha, India

**ABSTRACT**

The present study focused on the preparation and antioxidant studies of inclusion complexes of some compounds of 4-Thiazolidinone derivatives with  $\beta$ -cyclodextrin. The inclusion complex has been prepared in order to increase solubility and bio-accessibility of the parent compound. The experiment was conducted by taking 2-Hydrazinobenzothiazole as a starting material and a series of compounds and their inclusion is prepared from it. Taking into account on their physical, thermal and spectral characteristics (UV, IR and NMR), the formation of compounds and their inclusion complex are confirmed. From the antioxidant activities of compounds and inclusion complex, it has been found that inclusion complex has displayed more effectively than the original compounds.

**Keywords:** 4-Thiazolidinone, phase solubility study, inclusion complexes,  $\beta$ -cyclodextrin, antioxidant activities.

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**INTRODUCTION**

Antioxidant works as a prime agent in number of biological and pathological activities in all living organisms. [1] Antioxidants have to facilitate for scavenging reactive oxygen species and free radicals to prevent maximum diseases. [2-3] Hence to prevent and treat the diseases caused by free radicals or reactive oxygen species, it is essential to find useful antioxidants for scavenging such dreaded species.

Heterocyclic compounds containing nitrogen and sulphur have a great importance in pharmaceutical and medicinal chemistry.

A large number of pharmacologist and chemists worked on condensed 4-Thiazolidinone due to their significant therapeutic and other biological properties. As a result there is a wide application of 4-Thiazolidinone. Different substituted 4-thiazolidinone has been found to be possessed diverse type of activities like antimicrobial [4-5], antioxidant [6], anti-HIV [7], antihistaminic [8], anti-convulsant [8-10], anti-inflammatory. [11-13]

In the present work, 2-hydrazinobenzothiazoles is taken as starting material, five compounds has been prepared from it. Since the compounds have poor solubility, hence they cannot provide maximum bio-accessibility. So our objective is to develop a supramolecule by combining organic compound with  $\beta$ -cyclodextrin. Different concentration of  $\beta$ -cyclodextrin has been taken with the compound solution to know the best encapsulation of the

**\*Corresponding author: Dr. B. K. Garnaik,**  
P. G. Department of Chemistry, Berhampur University,  
Bhanja Bihar, Odisha, India;

**E-mail:** [bama\\_61@rediffmail.com](mailto:bama_61@rediffmail.com)

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compound. Among the available cyclodextrin,  $\beta$ -cyclodextrin is chosen on account of its availability, cost-effectiveness and less-toxic in nature. [14-16] Inclusion complexes are prepared by encapsulating the 2-(Benzothiazolyl-2')hydrazono-3-phenyl-5-arylidene-4-Thiazolidinone derivatives with  $\beta$ -cyclodextrin. The compound and their inclusion complexes are tested for their physical, thermal and spectral characteristics. Antioxidant activities of the synthesized compounds and their inclusion complexes have been studied.

## MATERIAL AND METHODS

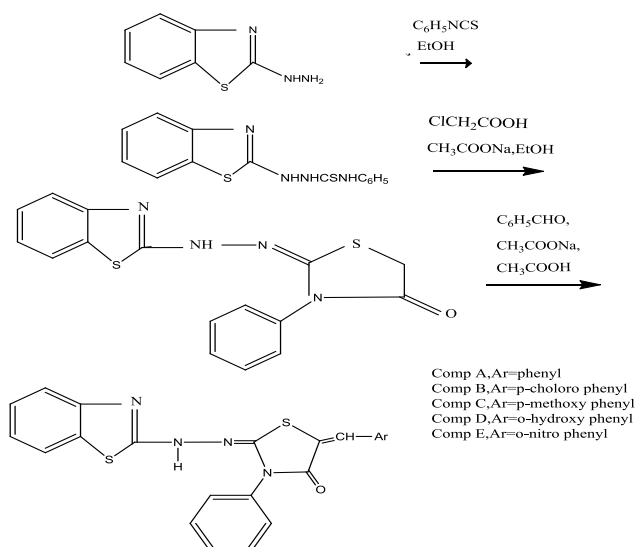
### Apparatus and Materials

All the chemicals used during the present work are procured with analytical reagent grade and purchased from Himedia Laboratories Pvt. Limited, Mumbai, India. In the laboratory Double distilled water was prepared and it is used as the solvent for dilution purpose. The electronic spectra were recorded on Shimadzu UV-1700 Spectrophotometer while IR-spectra were recorded in KBr pellets in 400-4000  $\text{cm}^{-1}$  region on a Shimadzu 8400 FTIR Spectrophotometer.  $^1\text{H}$  NMR spectra ( $\text{CDCl}_3$ ) are scanned on a DRX-300 (300MHz) spectrophotometer using TMS as internal standard and chemical shifts are expressed in  $\delta$  scale. Purity of synthesized compounds has been checked by sulphur detection and homogeneity has been checked by TLC using silica gel. Open capillary method was used to know the melting point of the compounds and are uncorrected.

### Synthesis of compounds

The compounds were synthesized as per the method described by Garnaik *et.al* [17] scheme-I.

SCHEME-1



Compound A: 2-(Benzothiazolyl-2')hydrazono-3-phenyl 5-arylidene-4-thiazolidinone

Compound B: 2-(Benzothiazolyl-2')hydrazono-3-phenyl 5-p-chloro arylidene-4-thiazolidinone

Compound C: 2-(Benzothiazolyl-2')hydrazono-3-phenyl 5-p-methoxy arylidene-4-thiazolidinone

Compound D: 2-(Benzothiazolyl-2')hydrazono-3-phenyl 5-o-hydroxy arylidene-4-thiazolidinone

Compound E: 2-(Benzothiazolyl-2')hydrazono-3-phenyl 5-o-nitro arylidene-4-thiazolidinone

### Step-1: Procedure for synthesis of 1-(Benzothiazolyl-2') 4-phenyl thiosemicarbazide

2-hydrazinobenzothiazole (1.65 g, 10 mmole) is taken in a 100 mL round bottom flask with ethanol (10 ml) as solvent and add Phenyl isothiocyanate (1.35 g, 10 mmole) with stirring for 5 minutes. Reflux and stir the resulting solution with half an hour and then cool. The resulting solid filtered and recrystallised from ethanol. M.P. 179°C, yield-2.1 g (70%), (Found S, 21.2%,  $\text{C}_{14}\text{H}_{12}\text{N}_4\text{S}_2$  requires S, 21.4%)

### Step-2: Procedure for synthesis of 2-(Benzothiazolyl-2') hydrazono-3-phenyl- 4-thiazolidinone

Take a mixture of 1-(Benzothiazolyl-2') 4-phenyl thiosemicarbazide (0.06 g, 2 mmole), monochloroacetic acid (0.25 g, 2 mmole) and anhydrous sodium acetate (0.2 g) in absolute ethanol (10 ml) in a 100 mL round bottom flask and refluxed for three hour. The surplus of solvent was removed and poured into cold water. The crystals formed was filtered, washed with hot water, and recrystallised from ethanol, M.P. 166°C, yield-0.3 g (44%), (Found: S, 18.80%  $\text{C}_{16}\text{H}_{12}\text{N}_4\text{OS}_2$  requires S, 18.95%). IR (KBr  $\text{Ucm}^{-1}$ ): 746.45 (C-S str), 1487.12 (C=C str) 1556.55 (C=N str), 1714.72(C=O str), 3030.17(Ar-H str), 3226.91(N-H str).

### Step-3: Procedure for synthesis of 2-(Benzothiazolyl-2') hydrazono-3-phenyl 5-arylidene-4-thiazolidinone (Compound A)

Take 15 mL of glacial acetic acid in 100 mL round bottom flask and add a mixture of 2-(benzothiazolyl-2')hydrazono-3-phenyl 4-thiazolidinone (0.35 g, 2 mmole), benzaldehyde (0.22 g, 2 mmole), fused sodium acetate (1 g) and reflux for four hour. Pale yellow solution is formed during the above step, put it into ice cold water and remove the excess water from it. Dry the compound and recrystallised from ethanol, m.p. 122°C, yield-0.28 g (63%). (Found: S, 14.07%  $\text{C}_{23}\text{H}_{17}\text{N}_4\text{OS}_2$  requires S, 14.91%). In this procedure compound A is prepared. Similarly Compounds B, C, D and E can be prepared by using the same procedure and taking different aldehydes in the last step. The physical and spectral data of the compounds is given in the Table 1 and 2.

### Synthesis of Inclusion complexes:

The inclusion complexes of 4-substituted thiazolidinone derivative are prepared according to co-precipitation method. [18-20] Required concentrations of compound solution are prepared and added drop wise to a previously stirred  $\beta$ -cyclodextrin solution. Stir the mixture at room temperature for 48 hour and filtered. Then the content is cooled for another 48 hour in a refrigerator. At the end, the precipitate is filtered through G-4 crucible, washed with distilled water and dried in air for 24hour.

### Preparation of solution for Antioxidant study

Tagashira and Ohtake [21] method of DPPH (2, 2-Diphenyl-1-picrylhydrazyl) scavenging assay is used for screening the antioxidant activity of the synthesized compounds. Test sample solution is prepared in two different concentrations of 100 $\mu\text{g}/\text{ml}$  and 500 $\mu\text{g}/\text{ml}$  in

ethanolic DPPH. After vortexing, the mixture is incubated for 10 minutes at room temperature. The measurement of absorbance of the samples is taken at 517 nm. Taking the difference of absorbance between a test sample and a control, the activity of the sample is calculated. Ascorbic acid is used as reference substance.

$$\% \text{ Inhibition} = (A_0 - A_1) / A_0 \times 100$$

Where  $A_0$  was the absorbance of the control and  $A_1$  was the absorbance of the sample.

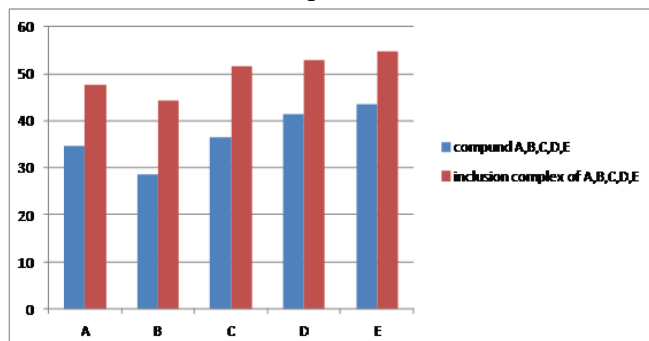


Fig. 1: Percentage of inhibition at 500 µg/ml of sample with DPPH

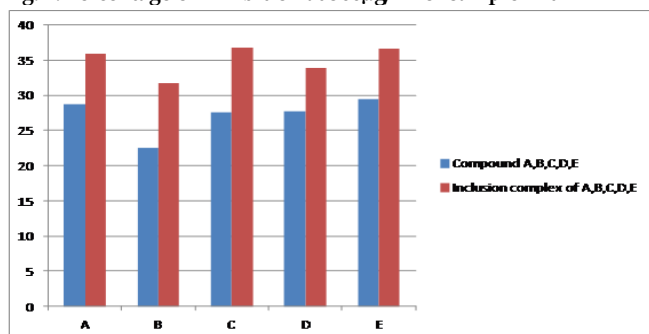


Fig. 2: Percentage of inhibition at 100 µg/ml of sample with DPPH

## RESULTS AND DISCUSSION

The five compounds of 4-thiazolidinone derivatives like A, B, C, D and E are synthesized in their pure crystalline states. The inclusion complexes of the compounds are prepared with  $\beta$ -cyclodextrin. The changes in the melting point, colour and spectral characteristics substantiate the formation of inclusion complex. An increased melting point of inclusion complexes of respective compounds may be featured through the fact that a supplementary thermal energy is required for deencapsulation from the  $\beta$ -cyclodextrin cavity (Table 1). The spectral data of UV, IR and  $^1\text{H}$  NMR of compounds A, B, C, D, E and their inclusion complexes are found to be absorbed at the appropriate characteristic frequency (Table 2).

Table 1: Physical properties of compounds and their inclusions

| Compound/Complex            | Substituent      | Colour          | M.P. in $^{\circ}\text{C}$ | % of yield |
|-----------------------------|------------------|-----------------|----------------------------|------------|
| Compound A                  | Phenyl           | Yellow          | 122                        | 63         |
| Compound A with $\beta$ -CD |                  | Yellowish white | 145                        | 45         |
| Compound B                  | P-Chloro phenyl  | Brown           | 190                        | 65         |
| Compound B with $\beta$ -CD |                  | Pale brown      | 205                        | 50         |
| Compound C                  | P-methoxy phenyl | Yellow          | 201                        | 63         |
| Compound C with $\beta$ -CD |                  | Yellowish white | 225                        | 48         |
| Compound D                  | O-Hydroxy phenyl | Light yellow    | 180                        | 60         |
| Compound D with $\beta$ -CD |                  | Yellowish white | 197                        | 50         |
| Compound E                  | O-Nitro phenyl   | Brown           | 170                        | 61         |
| Compound E with $\beta$ -CD |                  | Brownish white  | 193                        | 45         |

In case of UV data, it is found to inclusion complexes are absorbed some higher frequency than the parent compound. In case of IR data for all compounds, it is found that the IR frequencies of inclusion complex are found to be changed on account of the factors like H-bonding, van der Waals forces, in the cavity of  $\beta$ -cyclodextrin. [22] The comparison between the  $\delta$  values of compounds and their inclusion complexes revealed that the  $\delta$  values of PMR signals of compounds are shifted towards up field in the inclusion complex which could be explained on the caging based shielding phenomenon within the interior cavity of  $\beta$ -cyclodextrin.

The free radical entrapping activity of the compound increases significantly after caging in the core of  $\beta$ -Cyclodextrin. This can be correlated to the higher solubility of the compounds due to inclusion complex formation there by increasing the bioaccessibility. Higher the bioaccessibility of the compounds more is the entrapping reactive oxygen species or free radicals character, thereby escalating antioxidant character of the compounds. [23-24] The antioxidant activities or radical scavenging activity (RSA) of the compounds and their inclusion complexes are given (Table 3 and Figure 1 and 2). The RSA of the compounds increases appreciably after the formation of the inclusion complex.

The synthesized compounds and their inclusion complexes have been tested at two different concentrations of 100 µg/ml and 500 µg/ml to know their antioxidant potential (Figure 1 and 2). All the compounds and their inclusion complexes exhibited DPPH radical scavenging activity in a dose dependent manner. Among the different compounds and their inclusion complexes synthesized. The percentage of inhibition of compounds A, B, C, D and E are 28.80%, 22.60%, 27.60%, 27.80% and 29.40%. Similarly the percentage of inhibition of inclusion complexes of the corresponding compounds are 35.87%, 31.80%, 36.80%, 33.90% and 36.70% respectively. The compound E is found to be maximum inhibition of 29.4% and inclusion complex of C shows maximum inhibition of 36.80% which is highest among tested compounds at 100 µg/ml. The percentage of inhibition of compounds A, B, C, D and E are 34.60%, 28.70%, 36.50%, 41.50% and 43.40%. Similarly the inclusion complexes of the corresponding compounds are 47.80%, 44.40%, 51.60%, 52.80% and 54.60% respectively.

**Table 2: Spectral data of synthesized compounds and their inclusions.**

| S. No. | Compound/complexes    | UV <sub>λmax</sub> | IR(KBr) cm <sup>-1</sup>  | <sup>1</sup> H NMR   |
|--------|-----------------------|--------------------|---|--|
| 1      | Compound -A           | 275                | 742.59(C-Sstr), 1492.60(C=C Str), 1589.34(C=N str), 1645.28(C=O str), 3194.12(N-H str)  | <sup>1</sup> H NMR (CDCl <sub>3</sub> ): δ 6.81-8.23 (d, 6H, Ar-H), 4.23(s,1H,C-NH),7.58(s,1H,C-H),7.34-7.61 (m,8H, Ar-H)                          |
| 2      | Compound-A with β-CD  | 278                | 746.45(C-Sstr), 1494.83(C=C str), 1581.83(C=N str), 1714.12(C=O str), 3224.34(N-H str)  | <sup>1</sup> H NMR (CDCl <sub>3</sub> ): δ 6.12-7.81 (d, 6H, Ar-H), 3.83 (s,1H,C-NH),7.11(s,1H,C-H),6.82-7.24 (m,8H, Ar-H)                         |
| 3      | Compound -B           | 265                | 692.44(C-Cl str), 744.52(C-S str), 1487.12(C=C Str), 1583.56(C=N str), 2916.37(Ar-Hstr)1701.22, 1645.28(C=O str), 3197.89(N-H str)            | <sup>1</sup> H NMR (CDCl <sub>3</sub> ): δ 6.95-8.6 (d, 6H, Ar-H), 4.4(s,1H,C-NH),7.80(s,1H,C-H),7.56-7.9 (t,8H, Ar-H)                             |
| 4      | Compound -B with β-CD | 267                | 692.44(C-Clstr), 746.45(C-S str), 1489.05(C=C Str), 153 9.20(C=Nstr), 1714.72(C=O str), 3030.17(Ar-Hstr), 3325.28, 3194.12(N-H str)           | <sup>1</sup> H NMR (CDCl <sub>3</sub> ): δ 6.3 -7.45 (d, 6H, Ar-H), 3.9 (s,1H,C-NH),7.25(s,1H,C-H),6.9-7.3 (t,8H, Ar-H)                            |
| 5      | Compound -C           | 296                | 748.38(C-Sstr), 1425.40(C=Nstr), 1494.83(C=C Str), 1593.20(C=N str), 1712.97 (C=O), 3062.96(Ar-HStr)  | <sup>1</sup> H NMR (CDCl <sub>3</sub> ): δ 6.6-8.5 (d, 6H, Ar-H), 4.3(s,1H,C-NH),7.65(s,1H,C-H),7.3-7.6 (t,8H, Ar-H),3.95 (s,3H,OCH <sub>3</sub> ) |
| 6      | Compound -C with β-CD | 299                | 748.38(C-Sstr), 1417.60(C-NStr), 1456.26(C=Cstr), 1508.33(C=N str), 1699.29, 1637.56(C=O str), 3331.07(N-H str)                               | <sup>1</sup> H NMR (CDCl <sub>3</sub> ): δ 6.1-7.8 (d, 6H, Ar-H), 3.7 (s,1H,C-NH),7.5(s,1H,C-H),6.6-7.1 (t,8H, Ar-H)3.65 (s,3H,OCH <sub>3</sub> )  |
| 7      | Compound -D           | 271                | 692.44(C-Cl str), 744.52(C-S str), 1487.12(C=C Str), 1583.56(C=N str), 2920.23(Ar-Hstr), 1699.29(C=O str), 2358.94, 1373.32, 1153.43, 1010.70 | <sup>1</sup> H NMR (CDCl <sub>3</sub> ): δ 6.62 -7.81 (d, 6H, Ar-H), 4.53(s,1H,C-NH),7.71(s,1H,C-H),6.91-7.62 (m,8H, Ar-H) 5.13 (s, 1H, OH)        |
| 8      | Compound -D with β-CD | 275                | 692.44, 748.38(C-S str), 1494.83(C=C Str), 153 9.20(C=Nstr), 1697.36(C=O str), 3062.96(Ar-Hstr), 1423.47, 1317.38, 1159.22                    | <sup>1</sup> H NMR (CDCl <sub>3</sub> ): δ 6.41-7.52 (d, 6H, Ar-H), 4.13 (s,1H,C-NH),7.23(s,1H,C-H),6.44-7.12 (m,8H, Ar-H) 5.11 (s,1H, OH)         |
| 9      | Compound -E           | 276                | 742.59(C-Sstr), 850.61, 1338.60(N=Ostr), 1616.35(C=C Str), 1450.26(C=N str), 1696.36 (C=Ostr), 2916.37(Ar-HStr), 3196.50 (N-Hstr)             | <sup>1</sup> H NMR (CDCl <sub>3</sub> ): δ 6.72-7.44 (d, 6H, Ar-H), 4.34(s,1H,C-NH),7.91(s,1H,C-H),7.51-7.92(m,8H, Ar-H)                           |
| 10     | Compound -E with β-CD | 281                | 690.52(C-Cl str), 748.38(C-S str), 1157.92(C-N str), 1494.83(C=C Str), 1597.60(C=N str), 2922.16(Ar-Hstr)                                     | <sup>1</sup> H NMR (CDCl <sub>3</sub> ): δ 6.33-7.12 (d, 6H, Ar-H), 4.14 (s,1H,C-NH),7.33(s,1H,C-H),7.11-7.54 (m,8H, Ar-H)                         |

**Table 3: Antioxidant studies of the compounds with and without inclusion complexes at conc. (100µg/ml) and conc. (500µg/ml) at absorbance of 517 nm**

| Types compound | Conc. (100µg/ml) |                   | Conc. (500µg/ml) |                   |
|----------------|------------------|-------------------|------------------|-------------------|
|                | Compound         | Inclusion complex | Compound         | Inclusion complex |
| Compound A     | 0.875            | 0.788             | 0.804            | 0.642             |
| Compound B     | 0.952            | 0.838             | 0.876            | 0.683             |
| Compound C     | 0.890            | 0.777             | 0.781            | 0.580             |
| Compound D     | 0.888            | 0.813             | 0.719            | 0.580             |
| Compound E     | 0.868            | 0.778             | 0.696            | 0.558             |

The DPPH radical scavenging activity of the compound E is found to be maximum inhibition of 43.40% and inclusion complex of compound E shows maximum inhibition of 54.60% which is highest among tested compounds at a concentration of 500µg/ml. From the above study, it is observed that the solubility and bioaccessibility of the drug is found to be increased after the formation of the inclusion complexes. The study further proves that, there is a considerable increase in anti-oxidant activities of the inclusion complexes.

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