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Article

Biological Significance of some Inclusion Complexes of 4-Thiazolidinone Derivatives with β-Cyclodextrin

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ABSTRACT

A new series of compounds of (2-Benzothiazolyl-2')hydrazono-3-phenyl-5-arylidene-4-thiazolidinone derivatives and 2-phenyl-(3-benzothiazolyl-2')hydrazono-5-arylidene-4-thiazolidinone derivative *4(a-i)* are prepared from 2-hydrazinobenzothiazole taking as a starting material. The inclusion complexes of respective compounds can be prepared with *β*-cyclodextrins using the co-precipitation method. These synthesized compounds and their inclusions have been characterized with their spectral, analytical data and screened for their antibacterial activities. With the formation of inclusion complexes, the compounds show more biological activeness as compared to the parent compounds. Finally, the antibacterial study proves that the inclusion complexes of *4d* show greater efficiency towards *Staphylococcus aureus* whereas *4e* shows greater efficiency against *Escherichia coli* bacteria's respectively.

Key words: Antibacterial activities, Biological activeness, *Escherichia coli*, Inclusion complexes.

1. INTRODUCTION

The life become more complicated with the infections caused by multi drug-resistant gram-positive pathogens and these are found to be a frighten rate in hospitals and community places. Infections rose by these organisms make a drastic challenge to the scientific community and require suitable therapy to search appropriate antibacterial agents. Heterocycles of small size ring bearing nitrogen, sulfur, and oxygen gained absolute importance for a long time on account of their medicinal properties. In this context heterocyclic compounds such as pyridine, benzothiazole, and 4-thiazolidinone moieties would provide better interesting biological results. Considering all the above facts, we attempted to prepare ten biological active compounds to evaluate their antibacterial activities. The results revealed from the screening of the compounds and inclusion complexes show that the inclusion complexes show better activity as compared to parent compound. Further, the biological activeness of the compounds prompted us to synthesize some new compounds of 4-thiazolidinone derivatives. The study deals with the preparation of some 4-thiazolidinone derivatives starting from 2-hydrazinobenzothiazole in two different schemes. The board range of biological activeness of heterocyclic moieties makes its advantages not only discovery of new drugs but also the development of it. We have an interest in heterocyclic moieties due to their broad range of biological activeness and leading a path for the development of new pharmaceutical molecules.

The multi behavior activities of 4-thiazolidinone in the area of biological aspect brought the attention of chemistry to research over it. They have to show different biological activities like antimicrobial [1,2], antioxidant [3], anti-viral [4], anti-diabetic [5], anti-convulsant [6,7], and anti-inflammatory [8-10]. The present communication brings the antibacterial studies of series of compounds starting from 2-hydrazinobenzothiazole. Since the compounds show less solubility in the aqueous medium. So to get better solubility of the compounds, its inclusion complexes are prepared with non-toxic oligosaccharides namely β-cyclodextrins [11-13]. In this context characterization of compounds with regard to their physical, spectral, and thermal has been performed for confirmation of compounds and their inclusion complexes. Furthermore, antibacterial activities of the compounds and inclusion complexes have been carried out.

2. EXPERIMENTAL

2.1. Apparatus and Material

Compounds and inclusion complexes melting points are determined using open capillary method. To know electronic spectra of sample Shimadzu ultraviolet (UV)-1700 Spectrophotometer is used. Structures are confirmed with the help of Shimadzu 8400 FTIR spectrometer recorded using KBr pellets and ^{1}H NMR spectra ($CDCl_3$) are scanned on a DRX-300 (300 MHz) spectrophotometer using TMS as internal standard. The chemical shifts are reported in ppm. Chemicals belonging analytical grade are used in the process and they brought from Merck and Himedia company, Mumbai, India. Double distilled water was used during the experimental work prepared in the laboratory.

2.2. Synthesis of Compounds

The synthesis of compounds has been performed by the method adopted as per Garnaik *et al*. [14] Scheme 1.

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2.2.1. 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 min. Reflux and stir the resulting solution with half an hour and then cool. The resulting solid was filtered and recrystallized from ethanol. Melting point of compound is 179°C and yield is 2.1 g (70%) (Found S, 21.2%, $C_{14}H_{12}N_4S_2$ requires S, 21.4%).

2.2.2. Synthesis of 2-(Benzothiazolyl-2') hydrazono-3-phenyl-4-thiazolidinone

Take a mixture of 1-(Benzothiazolyl-2') 4-phenyl thiosemicarbazide (0.06 gm, 2mmole), monochloroacetic acid (0.25 gm, 2 mmole) and anhydrous sodium acetate (0.2 gm) in absolute ethanol (10 ml) in a 100mL round bottom flask and refluxed for 3h. The surplus of solvent was removed and poured into cold water. The crystals formed were filtered, washed with hot water, and recrystallized from ethanol, melting point of compound is 166°C and yield is 0.3 g. (44%) (Found: S, 18.80% $C_{16}H_{12}N_4OS_2$ requires S, 18.95%).

2.2.3. Synthesis of 2-(benzothiazolyl-2') hydrazono-3-phenyl 5-arylidene-4-thiazolidinone (Compound 4a)

Take 15mL 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 m mole), fused sodium acetate (1 g) and reflux for 4 h. 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 recrystallize it from ethanol, melting point of compound is 122°C and yield is 0.28 g (63%). (Found: S, 14.07% $C_{23}H_{17}N_4OS_2$ requires S, 14.91%). Similarly, compounds 4b, 4c, 4d, and 4e can be prepared using the same procedure and taking different aldehydes in the last step.

2.2.4. Preparation of Schiff's base (compound 2)

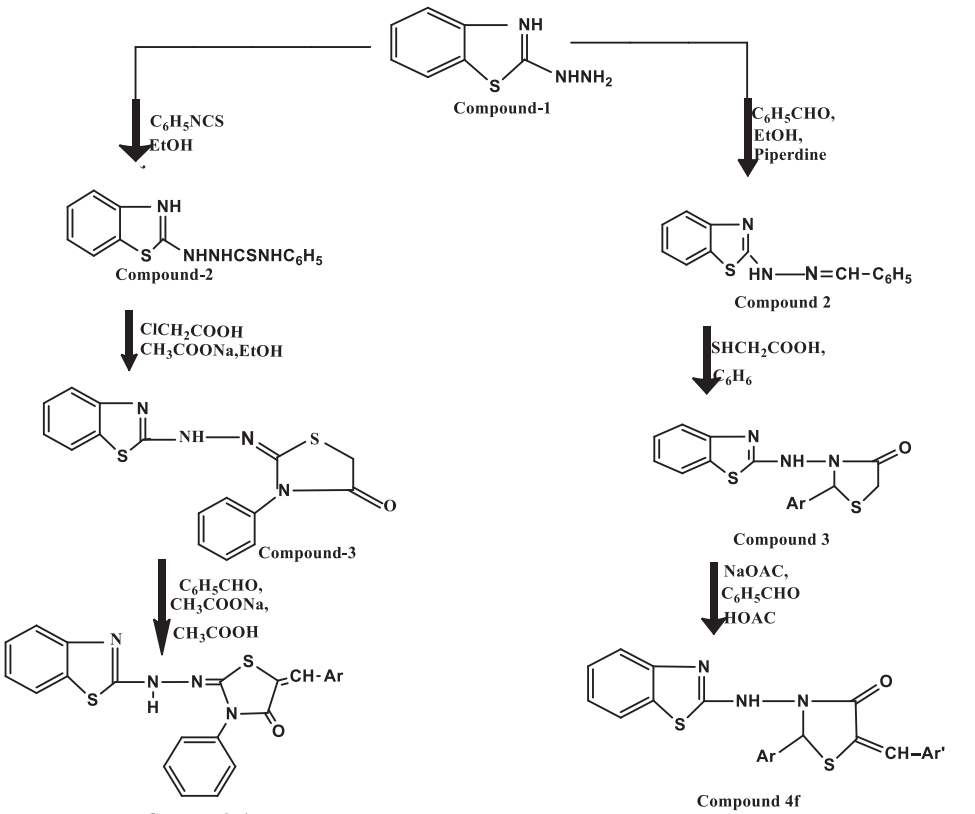
A mixture of compound 1 (10 m mole) and benzaldehyde (10 m mole) containing 4–6 drops of piperidine in 20 Ml. ethanol was refluxed in a water bath for 4hrs. The solvent was cooled at room temperature and decompose into ice-cold water. The product obtained was filtered and washed with cold water. The compound so obtained dried and recrystallized from ethanol. Melting point is 218°C and yield is 2.1 g (70%).

2.2.5. Synthesis of 3-(benzothiazolyl-2')hydrazono-2-phenyl-4--thiazolidinone (Compound3)

A mixture of compound 2 (1 m mole) was added with mercaptoacetic acid of (1 m mole) with stirring in dry benzene (15 ml). Continually stirred the mixture for 6 h and refluxed for 4 h. The product formed was filtered, dried, and recrystallized from ethanol to yield the product. Melting point is 215°C, and yield is 0.22 g (68%).

2.2.6. Synthesis of 2-phenyl3-(Benzothiazolyl-2')hydrazono-5-arylidene-4-thiazolidinone(Compound-4f)

A mixture of compound 3 (1 m mole), benzaldehyde (1m mole) and a pinch of anhydrous sodium acetate in glacial acetic acid of 10 ml. was



Comp 4a,Ar=phenyl
Comp 4b,Ar=p-choloro phenyl
Comp 4c,Ar=p-methoxy phenyl
Comp 4d,Ar=o-hydroxy phenyl
Comp 4e,Ar=o-nitro phenyl

Comp 4f,Ar=Phenyl, Ar'=phenyl
Comp 4g-Ar=Phenyl , Ar'=P-Anisaldehyde
Comp 4h-Ar=O-Chloro phenyl , Ar'=Phenyl
Comp 4i-Ar=O-Chlorophenyl, Ar'=P-Anisaldehyde
Comp 4j,-Ar=P-Ansialdehyde, Ar'=P-Anisaldehyde

Scheme 1: Synthesis of 2-(Benzothiazolyl-2')hydrazono-3-phenyl 5-arylidene-4-thiazolidinone and other compounds

Compound **4a:** 2-(Benzothiazolyl-2')hydrazono-3-phenyl 5-arylidene-4-thiazolidinone
Compound **4b:** 2-(Benzothiazolyl-2')hydrazono-3-phenyl 5-p-chloro arylidene-4-thiazolidinone
Compound **4c:** 2-(Benzothiazolyl-2')hydrazono-3-phenyl 5-p-methoxy arylidene-4-thiazolidinone
Compound **4d:** 2-(Benzothiazolyl-2')hydrazono-3-phenyl 5-o-hydroxy arylidene-4-thiazolidinone
Compound **4e:** 2-(Benzothiazolyl-2')hydrazono-3-phenyl 5-o-nitro arylidene-4-thiazolidinone

Scheme 2: Synthesis of 2-Phenyl 3-(Benzothiazolyl-2') hydrazono- 5-arylidene- 4-thiazolidinone and other compounds

refluxed for 4 h. The complete mixture is taken into cool condition and poured into cold water. The product thus separated was filtered, washed with water, dried, and recrystallized from ethanol. Melting point is 210°C and yield is 0.24 g (60%). Above systematic procedure is used to prepare compound 4f whereas compound 4g is prepared by adopting same method but using p-anisaldehyde instead of benzaldehyde in the last step. On the same way compounds 4h, 4i, and 4j can be prepared by using different aldehydes in the first and last step respectively.

Compound 4f; 2-Phenyl 3-(Benzothiazolyl-2')hydrazono- 5-arylidene-4-thiazolidinone

Compound 4g; 2-Phenyl 3-(Benzothiazolyl-2') hydrazono- 5-p-anisilidiene-4-thiazolidinone
Compound 4h: 2-o-Chloro phenyl 3-(Benzothiazolyl-2')hydrazono-5-arylidene-4-thiazolidinone
Compound 4i: 2-o-Chloro phenyl 3-(Benzothiazolyl-2') hydrazono- 5-p-anisilidiene-4-thiazolidinone
Compound 4j: 2-p-anisilidienyl3-(benzothiazolyl-2')hydrazono-5-p-anisilidiene-4-thiazolidinone.

2.3. Aqueous Phase Solubility Study

Higuchi Connors method [15] is used to determine to know aqueous phase solubility of 4-thiazolidinone derivatives compound at different conc. of β-cyclodextrin. For this, a specific amount of the substance is taken in a conical flask with varied concentrations of β-cyclodextrin (0–10 mM). At room temperature solutions are shaking in a rotatory flask shaker for periods of 48 h till it reached at equilibrium. Filtration of solution is carried through the Whatman filter paper and is analyzed by UV visible spectrometer. Finally, absorbance values of λmax were plotted against changed concentrations of β-cyclodextrin to know the ratio of compound formation.

2.4. Synthesis of Inclusion Complexes

The set of compounds of 4-Thiazolidinone derivatives makes inclusion complexes with β-CD using co-precipitation method [16-19]. To start the process, prepare the required concentrations of compound solution and mixed drop wise to an earlier well-stirred β-cyclodextrin solution. To get a complete homogenous mixture of the compound keep it 48 h at room temperature and then filtered. Cool the content in a refrigerator for another 48 h. For filtration of precipitate, G-4 is crucible is used and wash the solution with distilled water at last step. The resulted compound dried for another 24 h.

2.5. Evaluation of Antibacterial Activity

The antibacterial study of compounds and their corresponding inclusion complex has been performed using cup plate method [20]. The drugs tetracycline is used as a standard for the comparison of compounds and inclusion complexes. Materials employed in testing were test tubes, micropipette, whatmann No. 1 filter paper, dimethyl sulphoxide (DMSO), tetracycline, Petri plate, refrigerator, incubator, distilled water, bacterial cultures. To avoid contamination all the required apparatus were sterilized before use and necessary precautions were taken. Two different microorganisms such as *Staphylococcus aureus* and *Escherichia coli* are used to carrying out the process. The cultures were maintained on their respective media in slants at 4°C. The slants were sub-cultured to their respective media and kept 24 h for bacteria at 37°C. One day before test, the bacterium was inoculated into 25 mL of sterilized nutrient broth which was prepared in a similar manner as that of the nutrient broth media. Inoculated sub-cultured broths were kept at room temperature. The growth thus obtained was used as inoculums for the test. In order to prepare desired concentration of synthesized compounds to test upon standard bacterial strains, DMSO used as a diluents. According to the method, DMSO with strength of 500 μg/ml were taken and solution of compounds, as well as inclusion, has been prepared with same concentration. Then two bacteria *E. coli* and *S. aureus* were inoculated into 100 mL of the sterile nutrient broth. Further, it has been incubated at a temperature of approximately 37°C for 24 h. Mac Farland method is used to standardize the density of bacterial suspension. Standardized diameter of agar plates was used to inoculate them one after other with the test organisms aseptically. Micropipette is used to take the drug test solutions in a plate and then the plates were kept inside the refrigerator for 2 h with a temperature maintaining at the range of 8–10°C for right dispersal of drug into the media. Then transferred the petri plates into incubator with a temperature of nearly 38°C for 22 h. The results were obtained by comparing inhibition zone of test compounds with standard drug (Tetracyline). The zone of inhibition can be found using venire scale in the Petri plates and data are presented in (Table 2).

3. RESULTS AND DISCUSSION

For the present work, the various substituted 4-thiazolidinone derivatives are prepared from 2-hydrazinobenzothiazole as given in the Schemes 1 and 2. In this context, ten derivatives of 4-thiazolidinedione compounds 4(a-i) are synthesized in their own state in pure crystalline form. With the help of β-cyclodextrin also their respective inclusion complex are prepared as usual way as described in the procedure. The change in their physical and spectral characters acknowledges the formation of the inclusion complex. There is an increase in the melting point of inclusion complexes as compared to the original compounds and it is due to the additional heat energy required for encapsulation from the β-cyclodextrin cavity (Table 3).

The structures of these 4-thiazolidinone derivatives and their inclusion complexes were confirmed on the basis of elemental analysis, UV, IR, and ^{1}H NMR spectra. On comparing the spectral nature between compounds and inclusion complexes, it is found to be varied and this happens due to some change in inclusion complexes. Spectral values of UV, IR, and ^{1}H NMR of compounds and their inclusion complexes are absorbed in suitable frequency as shown in (Table 1). While comparing UV data of compound and inclusion complexes, it has been interfered that inclusion complexes are absorbed at more frequency as that of compounds. There happens deviation of spectral characters of compounds with their respective inclusion complexes. Similarly, the IR data of other respective compounds and their inclusions are found to be absorbed with the proper characteristic frequency. IR frequencies of inclusion complexes changed from that of the compounds after its formation and these changes take place due to the transference of compounds into the cavity of β-cyclodextrin. These changes accounts due to the creation of weak forces such as H-bonding, Vander Waals forces, hydrophobic interactions in between the two combing species, i.e.,

Table 1: Spectral properties of compounds and their inclusion

Compound/inclusion	UVλ_{max}	IR (KBr) cm^{-1}	^{1}H NMR in $CDCl_3$
Comp. 4a	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)	^{1}H NMR ($CDCl_3$): 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)
Inclusion 4a	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)	^{1}H NMR ($CDCl_3$): 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)
Comp. 4b	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)	^{1}H NMR ($CDCl_3$): 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)
Inclusion 4b	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)	^{1}H NMR ($CDCl_3$): 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)
Comp. 4c	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)	^{1}H NMR ($CDCl_3$): 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_3)
Inclusion 4c	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)	^{1}H NMR ($CDCl_3$): 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_3)
Comp. 4d	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	^{1}H NMR ($CDCl_3$): 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)
Inclusion 4d	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	^{1}H NMR ($CDCl_3$): 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)
Comp. 4e	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)	^{1}H NMR ($CDCl_3$): 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)
Inclusion 4e	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),	^{1}H NMR ($CDCl_3$): 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)
Comp. 4f	298	744.52 (CSstr), 1166.93, 1444.68 (C-Nstr) 1510.26 (C=C Str), 1625.99 (C=Cstr), 1728.22 (C=Ostr), 3082.25, 2916.37 (Ar-Hstr)	^{1}H NMR ($CDCl_3$): δ 6.93–8.02 (d, 6H, Ar-H), 4.02 (s, 1H, C-NH), 7.56 (s, 1H, C-H), 7.31–7.68 (t, 8H, Ar-H)
Inclusion 4f	285	752.24 (C-Sstr), 937.40 (N-C Sstr) 1442.75 (C=Cstr), 1612.49 (C=C aro), 1658.78 (C=Ostr), 2920.23 (Ar-H str), 3267.41 (N-H str)	^{1}H NMR ($CDCl_3$): δ 6.94–8.01 (d, 6H, Ar-H), 3.87 (s, 1H, C-NH), 7.15 (s, 1H, C-H), 6.96–7.96 (t, 8H, Ar-H)
Comp. 4g	278	744.52 (C-Sstr), 894.97 (C Nstr) 1573.91 (C=C Str), 1691.57 (C=Nstr), 2916.37 (Ar-Hstr) 1759.08 (C=O str), 3360.00(N-str)	^{1}H NMR ($CDCl_3$): δ 6.96–8.01 (d, 6H, Ar-H), 3.87 (s, 1H, C-NH), 7.70 (s, 1H, C-H), 7.18–7.70 (t, 8H, Ar-H)
Inclusion 4g	267	738.74 (C-Sstr), 943.19(N-C Sstr), 1251.80 (C Nstr), 1510.26 (C=CStr), 1610.20 (C=Nstr), 3174.83 (N-H str	^{1}H NMR ($CDCl_3$): δ 6.93–7.67 (d, 6H, Ar-H), 3.9 (s, 1H, C-NH), 7.28 (s, 1H, C-H), 6.96–7.39 (t, 8H, Ar-H)
Comp. 4h	277	655.80 (C-Clstr), 738.74 (C-Sstr), 1367.53 (C-Nstr), 1573.91, 1510.26 (C=CStr), 1610.56 (C=Nstr), 1658.78 (C=Ostr), 3190.26 (N-H str)	^{1}H NMR ($CDCl_3$): δ 7.26–8.25 (d, 6H, Ar-H), 4.62 (s, 1H, C-NH), 7.50 (s, 1H, C-H), 7.3–7.8 (t, 8H, Ar-H)

(Contd...)

Table 1: (***Continued***)

Compound/inclusion	UVλ_{max}	IR (KBr) cm^{-1}	^{1}H NMR in $CDCl_3$
Inclusion 4h	267	705.95 (C-Clstr), 734.88 (C-Sstr), 939.33 (N-C Sstr), 1321.24 (CNstr), 1512.19 (C=CStr), 1610.56 (C=Nstr), 3217.27 (N-Hstr)	^{1}H NMR ($CDCl_3$): δ 7.21–8.03 (d, 6H, Ar-H), 3.59 (s, 1H, C-NH), 7.28 (s, 1H, C-H)
Comp. 4i	273	659.66 (C-Clstr), 705.96 (C-S str), 1321.26 (C-Nstr), 1510.26 (C=CStr), 1610.56 (C=Nstr), 2929.87 (Ar-Hstr), 3224.89 (N-H str)	^{1}H NMR ($CDCl_3$): δ 7.18–8.45 (d, 6H, Ar-H), 3.86 (s, 1H, C-NH), 7.32 (s, 1H, C-H), 6.94–8.08 (t, 8H, Ar-H) 3.86 (s, 3H, OCH_3)
Inclusion 4i	265	674.01 (C-Clstr), 736.31 (C-Sstr), 945.12 (N-C-Sstr), 1510.26 (C=CStr), 1610.56 (C=Nstr), 1658.78 (C=Ostr), 2929.87 (Ar-Hstr), 3201.83 (N-H str)	^{1}H NMR ($CDCl_3$): δ 7.18–8.44 (d, 6H, Ar-H), 3.87 (s, 1H, C-NH), 7.28 (s, 1H, C-H), 6.69–7.71 (t, 8H, Ar-H) 3.87 (s, 3H, OCH_3)
Comp. 4j	297	692.44 (C-Clstr), 746.45 (C-S str), 1489.05 (C=CStr), 1539.20 (C=Nstr), 1714.72 (C=Ostr), 3030.17 (ArHstr), 3325.28, 3194.12 (N-H str)	^{1}H NMR ($CDCl_3$): δ 6.89–8.18 (d, 5H, Ar-H), 4.0 (s, 1H, C-NH), 7.60 (s, 1H, C-H), 7.30–7.63 (t, 8H, Ar-H)
Inclusion 4j	299	748.38 (CSstr), 1425.40 (C=Nstr), 1494.83 (C=CStr), 1593.20 (C=Nstr), 1712.97 (C=O), 3062.96 (Ar-HStr	^{1}H NMR ($CDCl_3$): δ 6.93–7.97 (d, 5H, Ar-H), 4.1 (s, 1H, C-NH), 7.63 (s, 1H, C-H), 7.34–7.61 (t, 8H, Ar-H)

Table 2: Antibacterial studies of the compounds and their inclusion complexes

S. No.	Compound	Diameter of zone of inhibition			
		Gram-negative bacteria *Escherichia coli*		Gram-positive bacteria *Staphylococcus aureus*	
		Compound	Inclusion complexes	Compound	Inclusion complexes
1.	4a	7	11	9	13
2.	4b	10	15	10	15
3.	4c	11	16	11	14
4.	4d	11	15	8	13
5.	4e	8	15	10	16
6.	4f	11	13	9	11
7.	4g	10	12	10	11
8.	4h	9	12	12	14
9.	4i	10	13	11	13
10.	4j	10	11	12	14

host and guest molecules [21-23]. Besides this, there is also change in δ values of the inclusion complexes with respect to their original compounds. There is a change in PMR signals in the inclusion complex as compared to parent compound due to encapsulation induced shielding within the cavity of β-cyclodextrin. The comparison between the δ values of compounds and their inclusion complexes revealed that the δ values of PMR signal are changed after the formation of complexes.

The thermal parameter K_T of the inclusion complex can be determined with the help of Benesi-Hilderband relation [24]. The K_T values of inclusion complexes of compounds from 4a to 4i has been determined. For compound 4a, it is found to be 526.123. All other compounds obtained are also remain in the expected range of 100–1000 M^{-1} signifying their stabilities for the inclusion complexes by the way of host-guest interaction such as Vander Waal's force and hydrophobic interaction. [21-23]. The free energy of activation of the compound is −15.627. Negative value of Gibb's free energy change implies for doing some useful work and ΔG° become favorable for the reaction to happen.

From the antibacterial studies against two selected bacterial strains such as *E. coli* and *S. aureus,* it's found that the diameter of the zone of inhibition of inclusion complexes noticeably high as compared to the compounds against which its tested as given in Table 2. From the experiment, it has been confirmed that the inclusion complex of compound 4e exhibited maximum activity against *E. coli* than that of other complexes whereas compound 4d shows maximum activity towards *S. aureus* with relevance to other complexes. The noticeable improvement of antibacterial activity of the inclusion complexes on account of more solubility of compounds within the aqueous medium that creating them more bio-accessible and effective towards specific tissues as a result which efficiency of drug increased.

Table 3: Physical properties of compounds and their inclusion

Compound/complex	Molecular formula	Colour	M.P. in °C	% of yield	Elemental analysis		
					Calculated (Found)		
					C	H	N
Compound 4a	$C_{23}H_{16}N_4S_2O$	Yellow	122	63	64.46 (64.36)	3.76 (3.66)	13.07 (12.97)
Comp. 4a with β-CD		Yellowish white	145	45			
Comp. 4b	$C_{23}H_{15}N_4S_2OCl$	Brown	190	65	59.66 (59.56)	3.26 (3.26)	12.10 (12.00)
Comp. 4b with β-CD		Pale brown	205	50			
Comp. 4c	$C_{24}H_{18}N_4S_2O_2$	Yellow	201	63	62.86 (62.96)	3.95 (3.85)	12.21 (12.11)
Comp. 4c with β-CD		Yellowish white	225	48			
Comp. 4d	$C_{23}H_{16}N_4S_2O_2$	Light yellow	180	60	62.14 (62.04)	3.62 (3.72)	12.60 (12.50)
Comp. 4d with β-CD		Yellowish white	197	50			
Comp. 4e	$C_{23}H_{15}N_5S_2O_3$	Brown	170	61	58.34 (58.24)	3.19 (3.09)	14.78 (14.88)
Comp.E with β-CD		Brownish white	193	45			
Comp. 4f	$C_{23}H_{18}N_3OS_2$	Yellow	170	60	66.48 (66.38)	04.12 (04.02)	10.11 (10.00)
Comp. 4f with β-CD		Yellowish white	182	45			
Comp. 4g	$C_{24}H_{20}N_3O_2S_2$	Pale Yellow	175	62	64.69 (64.49)	4.29 (3.09)	4.43 (4.13)
Comp 4g with β-CD		Yellowish white	183	40			
Comp. 4h	$C_{23}H_{17}N_3OS_2Cl$	Brown	225	63	61.39 (61.25)	3.58 (3.35)	9.93 (9.13)
Comp. 4h with β-CD		Brownish white	229	48			
Comp. –4i	$C_{24}H_{19}N_3O_2S_2Cl$	Light Brown	232	55	60.05 (60.15)	3.77 (3.87)	8.75 (8.85)
Comp. 4i with β-CD		Reddish white	237	40			
Comp. 4j	$C_{25}H_{22}N_3O_3S_2$	Pale red	180	60	63.14 (63.04)	4.45 (4.35)	8.83 (8.73)
Comp. 4j with β-CD		Reddish white	187	45			

4. CONCLUSION

This work involved with preparation some of the compounds of 4-thiazolidinone and their inclusion with β-cyclodextrin and characterized by their spectral, thermal, and antibacterial nature. Proper molecular interactions have leaded the formation of complex which is found to point out more active nature than the original compounds. Complex formation with β-cyclodextrin is an excellent process to get better aqueous dissolution of inadequately water-soluble drugs. Thus, inclusion complexes show more bio-accessibility of the drug as a result of which it minimizes doses of drug and its related ill effect.

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