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Research Article

Thermal, Spectral, Antibacterial and Antifungal Research On β-Cyclodextrin-Inclusion Complexes Of 2-Cyclohexylimino-3-Phenyl-5-Arylidene-4-Thiazolidinone derivatives.

Chinmaya Guru[1*], Nutan Maharana[2], Rabinarayana Sahu[3] B. K. Garnaik[4]

P. G. Department of Chemistry, Berhampur University, Bhanja Bihar, Odisha E-mail: guruchinmay6@gmail.com

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ARTICLE INFO

ABSTRACT

We have synthesized substituted 4-thiazolidinones using unsymmetrical thiourea, derived from cyclohexylamine and phenyl isothiocyanate as starting materials. The solubility of these compounds is reduced in polar solvents (water). Therefore, the incorporation of compounds is achieved by selecting an appropriate ratio between the component and β-cyclodextrin. The objective of this study is to produce molecules that are both more soluble and more bio accessible. The research has established the thermodynamic characteristics and spectral properties (UV, IR, and NMR) of the synthesized compounds and their constituents. The compounds' antibacterial and antifungal activities and incorporation can be assessed using bacteria like *Escherichia coli* and *Bacillus subtilis* and fungi like *Candida albicans* and *Aspergillus niger*.
. Analysis and thought have led to the conclusion that inclusion formation is more effective against bacteria than a single molecule.

Keywords: 4-Thiazolidinone, β-Cyclodextrin, *Bacillus subtilis* ,*Aspergillus niger*, antibacterial and antifungal activities.

1.INTRODUCTION

Society relies on drugs and medications, which are primarily heterocyclic in structure. These compounds are significant for their nature, applicability, and utility. Organic chemists focus on synthesizing, evaluating, and determining the chemotherapeutic potential of organic substances. Current techniques, such as sophisticated analytical tools and spectroscopic approaches, can determine compound structures. Thiazolidinone, a heterocyclic molecule with nitrogen, sulphur, and a carbonyl group over a five-membered ring, is well-known. Some of the biological effects that substituted thiazolidinones are known for are their ability to fight bacteria, viruses, histamine, seizures, and inflammation [1],[2],[3],[4],[5],[6]. Four substituted 4-thiazolidinone derivatives from unsymmetrical thiourea **N1 – Cyclohexyl- N2- Phenylthiourea** are the goal of this study. The poor dissolution of the chemicals prevents them from being as bioavailable as possible. When these compounds form an inclusion complex with β-cyclodextrins, their solubility and bio accessibility are greatly improved [7]. β-Cyclodextrin is often the one that is selected for inclusion complex formation among all the cyclodextrins that are known to exist, because it is readily accessible, relatively inexpensive, and very resistant to heat and oxidation [7], [8], [9].
In this study, we construct a supramolecule from β-cyclodextrin and 4-thiazolidinines. In the last two decades, cyclodextrin and its derivatives have gained popularity due to their ability to create complex compounds with pharmaceuticals. Cyclodextrins (CDs) include six or more than 100 glucose units, joined by β-(1,4) linkages. Three CD types—α, β, and γ-CDs have six, seven, or eight glucose units at their core.
CDs with various hydrophobic compounds can form inclusion complexes. In aqueous solutions, water molecules occupy hydrophobic CDs and form complexes with the drug through weak forces. One to three CDs can entrap one or two hydrophobic molecules, depending on cavity size [10]. Experiments used varying amounts of β-cyclodextrin to determine the optimal encapsulation ratios for the molecule. Inserting the drug into the β-cyclodextrin cavity improves its solubility, increasing its bioavailability, and potentially enhancing its biological functions. Cyclodextrin makes a cone-shaped hole for thiazolidinone, which doesn't dissolve in

water. The host then makes it dissolve in water by creating cavities [11]. The selection of β-cyclodextrins was based on their low toxicity, low cost, and market availability [12]. To create the desired compound, we encapsulated β-cyclodextrin in four 2-cyclohexylimino-3-phenyl-5-arylidene-4-thiazolidinone derivatives. Spectroscopic and thermal measurements have confirmed the compounds' synthesis and inclusions. Compounds and inclusion complexes were also compared for antibacterial and antifungal activities.

2. EXPERIMENTAL

2.1 Apparatus and Material

Himedia is the source of cyclohexylamine, phenyl isothiocyanate, and other chemicals. We used the open capillary method to determine the melting points of the produced compounds and inclusions. While the Shimadzu 8400 FTIR Spectrophotometer captured infrared spectra in the 4000-400 cm^{-1} area from KBr pellets, the Shimadzu UV-1700 Spectrophotometer obtained compound UV spectra. We can analyse chemical changes using TMS as an internal reference. ^1H NMR spectra ($CDCl_3$) are scanned using a DRX-300 (300 MHz) spectrophotometer and δ scale.

2.2 Synthesis of compound:

The Mineati Sen & Co. method is used to synthesize chemical K (Scheme-1).

2.2.1. N1 – Cyclohexyl- N2- Phenylthiourea (C-I)

After adding seven milliliters of phenyl isothiocyanate, we left the mixture of five milliliters of cyclohexylamine (50 mmol) in fifteen milliliters of rectified spirit to reflux for four hours. Filtered, spirit washed, dried, and recrystallized from the ethanol was the process that followed after the sediment had settled to the bottom of the cooling tank.

M.P. 150°C, yield-4gm (70%), (Found S, 13.69 $C_{13}H_{18}N_2S_2$ requires S, 13.67%)

2.2.2.-Cyclohexylimino-3-phenyl – 4 - thiazolidinone (C-II)

Over the course of four hours, a solution was refluxed containing 2.1 g of cyclohexylphenylthiourea (9 mmol) in 20 ml of 100% alcohol, 1 g of monochloroacetic acid (10 mmol), and 0.5 g of anhydrous sodium citrate. We removed the solvent by distillation and ground the solid with cold water. We obtained the crude solid after filtration, washing with hot water, drying, and crystallization from ethanol. Yield: -1.74 gm (71%), melting point: -130 to 148 °C Since the crystallized solid was a crude one, it was purified through repeated crystallization using ethanol to obtain the desired chemical in the form of a pale yellow solid.

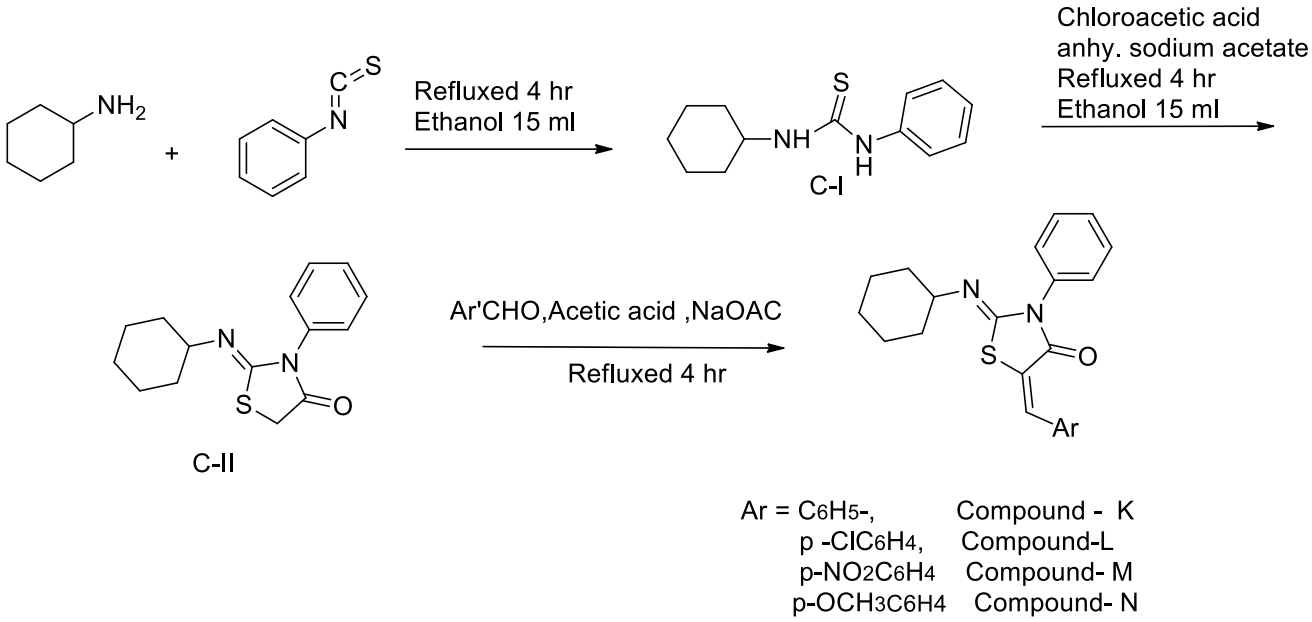
m.p.- 98°C, yield -1.1 gm (Found S, 11.69 $C_{15}H_{18}N_2OS$ requires S, 11.67%)

2.2.3. 2- Cyclohexylimino – 3- phenyl -5- benzylidene-4- thiazolidinone (K)

"By refluxing 2-cyclohexylimino-3-phenyl-4-thiazolidinone (0.8 g, 2 mmol), benzaldehyde (0.17 g, 2 mmol), and anhydrous sodium acetate (0.5 g) in glacial acetic acid (15 ml) for 4 hours, the benzylidene derivative was isolated as a yellow solid.

M.P. – 185°C, yield – 0.62gm (53%).(Found S, 8.1, $C_{22}H_{21}N_2OSCl$ requires S, 8.07 %)

Similarly, the other compounds of the series (L, M, and N) were prepared by using p-chlorobenzaldehyde and p-nitrobenzaldehyde, respectively."



Scheme-1

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2.3 SYNTHESIS OF INCLUSION COMPLEX

2.3.1. Phase solubility measurements:

The β-cyclodextrin concentration was determined by using the Higuchi-Connor technique. [13] An accurately measured amount of these compounds, in excess of their water solubility, was mixed with 50 ml of β - cyclodextrin solutions ranging from 0 to 10 mM in a series of stoppered conical flasks and shaken at room temperature for 48 hours. After the suspensions had equilibrated, they were filtered using Whatmann-42 filter paper and tested for sample content in a UV-visible spectrophotometer operating in the 3000A°–4500 A°range. Plotted against varying concentrations of β - cyclodextrin are the distinct absorbance values at maximum. After drying, we recrystallized the material using ethanol as the solvent.

2.3.2 Synthesis of inclusion complexes:-

Using the co-precipitation method [14], chemicals K, L, M, and N were mixed with β-cyclodextrin to make inclusion complexes. We gradually supplemented the β-cyclodextrin solution with the appropriate concentrations of these compounds, adding them drop by drop. We vigorously mixed the solutions over the course of 48 hours. We filtered the agitated solutions. We used refrigerators to chill the filtrates for an entire day. We subjected the collected precipitates to filtration, water washing, and subsequent drying in an open environment for a day.

2.3.3 Study of thermodynamic properties:-

The Benesi Hilderbrand relation [15] determines inclusion complex thermodynamic stability constant KT.
Benesi Hilderbrand relation $1/\Delta A = 1/\Delta\epsilon + 1/K_T [\text{Guest}]_o . \Delta\epsilon . [\beta\text{-CD}]_o$
ΔA represents absorbance change, Δϵ ' represents molar extension coefficient change, [Guest]o represents compound concentration in inclusion complex, and $[\beta\text{-CD}]_o$ represents β-CD molar concentration.
K_T = Intercept/Slope
From the slope of the linear plot of lnK vs. 1/T, and can be calculated.
The values of ΔH and ΔS can be determined by analyzing the slope of the linear plot of lnK vs 1/T.
from vant Hoff's equation
ln K= ΔH/RT- ΔS/R
At 298 K, ΔG was computed using the equation: ΔG = - RT ln K.

2.4. Biological Evaluation

2.4 .1 Experimental procedure for Antibacterial study:

The cup-plate method [14] was employed to investigate the antibacterial properties of drugs and inclusion complexes. The procedure involved using dimethyl sulphoxide with a concentration of 500 µg/ml to make a solution of chemicals and inclusion with the same concentration. The sterile nutritional broth was infected with

two bacteria, namely E. coli and B. subtilis, in a volume of 100 ml. We also incubated the sample for 24 hours at a temperature of approximately 37 °C. The test organisms were aseptically inoculated onto agar plates using a standardized diameter. We used a micropipette to precisely place the medication and test solutions on a plate. The next step was to chill the plates in the fridge for at least two hours, ideally between 8 and 10 degrees Celsius. We aimed to distribute the medicine evenly throughout the medium. After that, the petri dishes were placed in an incubator that was preheated to around 38 °C and left there for 22 hours. After that, using the venire scale on the Petri plates, one may calculate the zone of inhibition. Table 3 presents the results in tabular form.

2.4.2. Experimental procedure for Antifungal activity:

We used disc diffusion to test the compounds and their inclusion complexes for antifungal properties [16]. We introduced the 72-hour fungus culture to Sabouraud's dextrose agar plates. We used *Aspergillus niger* and *Candida albicans* as fungal pathogens in this study. We produced cultures in test tubes using Sabouraud Dextrose Broth. We prepared lawn cultures by swabbing the surface of Sabouraud's Dextrose Agar plates with a sterilized cotton swab. We used a cork borer to make aseptic wells 5 minutes after the agar surface had dried. The DMSO-saturated wells were filled with a solution containing the produced chemical and inclusion complexes at a conc. of 500 µg/ml. As a standard, the test organisms have been exposed to 20 µg/ml of gliseofulvin. We incubated the plates at 28° C for at least 24 to 48 hours. We measured the zones of inhibition to the millimetre using a precise scale. When compared to nakedly produced compounds, inclusion complexes exhibit significantly higher potency against both test organisms utilized in this work, according to the investigation of antifungal screening results.

3.Results and Discussion

Four 2-cyclohexylimino-3-phenyl-5-arylidene-4-thiazolidinone derivatives (K,L, M, and N) have been successfully synthesized in their purest forms, as depicted in Scheme 1. As a result of their lower solubility in polar solvents, thiazolidinone derivatives display a lower level of pharmacological activity. Forming an inclusion complex of thiazolidinone improves its solubility and therapeutic efficacy. When a chemical is encapsulated with β-cyclodextrins, it is possible to greatly boost both its solubility and its medicinal action.

3.1. Physiochemical & Spectral Study

Table 1 presents the physicochemical characteristics of the produced compounds and their inclusions. There is proof that the compounds have joined with β-cyclodextrin by looking at how the melting points of the complexes change when they are mixed with their own compounds. These molecules require more thermal energy than is required to extract them from the β-cyclodextrin hollow area. Compound and inclusion complex synthesis is shown by elemental analysis and spectrum properties (Table 2).

. The compound K inclusion complex infrared (IR) data shows distinct absorption at 751, 1499, 1351, 1720, 2920, 1522, and 748 cm^{-1}. Depending on the absorption spectra, the compounds may include C-S, C=C, C-N, C=O, Ar-H, C=N str, or C-S bonds, respectively. Chemicals L, M, and N and their inclusion complexes absorb the right frequency (Table 2). These alterations ensure compound transport into the cyclodextrin cavity by weak hydrogen bonds, van der Waals forces, and hydrophobic interactions between host and guest molecules [17].

. It has been found that the compounds' UV spectra have grown since inclusion complexes were developed. The research reveals that the inclusion complexes have values lower than those of the parent chemical. The -β cyclodextrin cavity encapsulation has a strong shielding effect, which suggests that the inclusion complex has moved PMR signals to the up field.

3.2 Phase Solubility Study

Figure 1 shows that the concentration of β-cyclodextrin increases the solubility of these compounds linearly. The results of an aqueous-phase solubility test will reveal this. Even though these complexes have a stoichiometry of 1:1, the slopes of the plots were not as close to unity as they could have been.

3.3. Evaluation of thermodynamics parameters

The Benesi-Hilderband connection helped us calculate inclusion complex thermodynamic stability constants (K_T) [15]. As shown in figure 2, substances showed strong linear associations when plotting ΔA inverse versus [β-CD]o. Additional study revealed K_T values of 778, 362, 461, and 426 M^{-1} for compounds having β-cyclodextrin (refer to Table 3). Their ideal range was 100 to 1000 M^{-1}, which they maintained.

Because of host-guest interactions, including hydrophobic interaction and van der Waal's force, these results show that the inclusion complexes are quite stable. The results can be found on pages 26–28, along with references [18], [19], and [20]. The calculations were made easier by determining the stability constant (KT) values at various temperatures and assuming a 1:1 stoichiometry. This helped with the calculation of the related thermodynamic parameters, such as the ΔG value at 298K ($\triangle G = -2.303RT \log K$). Formation of inclusion complexes is a naturally occurring and thermodynamically allowed process, as all of the inclusion complexes in Table 3 show a negative value for the free energy changes [17] and [21].

3.4. Antibacterial activities Study

Table 4 shows the zone of inhibition diameter values for the compounds and their inclusion complexes against *E. coli* and *B. subtilis*. **Figures 2 and 3.**

Inclusion complex formation significantly enhances antibacterial activity, as seen here. Among the chemicals studied, the compound containing the p-nitroderivative had the highest activity against all of the tested bacterial strains, outperforming the other three compounds. When chemicals are more soluble, they are easier for the body to absorb and use as medicine because they can reach more tissues.

3.5. Antifungal activities study

As shown in Table 5 and Figure 4, the inclusion complex of compounds M inhibits *Candida albicans* with the highest zone of inhibition (15 mm), followed by K (13 mm), L (13 mm), and N (10 mm). Table 5 and Figure 5 show that the inclusion complex of chemicals K inhibits *Aspergillus niger* the most (14 mm), followed by L (9 mm), M (13 mm), and N (11 mm).

The zone of inhibition of the standard drug is found to be greater than that of the tested compounds and their complexes. The activity of the drug may be due to its interaction with the cell plasma. The drug can interact properly with sensitive fungal species while falling to interact with resistant fungal species.

Table: 1 Physical data on compounds and inclusion complexes

Physical data on compounds and inclusion complexes				
Compound/ Complex	**Ar.**	**Colour**	**M.P. (°C)**	**Yield (%)**
C- K	Phenyl	Brownish red	160	53%
I.C. K		Light yellowish	172	43%
C-L	p-ClPh	Deep Yellow	185	45%
I.C- L		Brownish yellow	192	35%
C-M	P-NO_2-pPh	Dull brown	174	57%
I.C-M		Pale yellow	182	45%
C-N	p-OCH_3Ph	Brownish red	166	49%
I.C. – N		Brownish yellow	173	39%

Table: 2 Spectral data of the compounds and their inclusion complexes

	U.V. λmax		
C- K	275	748. (C-S str.), 1494 (C=C str.), 1347 (C-N str.), 1715 (C=O str.), 2916(Ar-H str.), 1520 (C=N str).	^{1}H NMR (CDCl3):, 7.32 (s, 1H, C=C-H),, 7.16-8.92 (m, 10H, Ar-H), 1.80-1.38 (m, 10H, Cyclohexyl proton)
I.C. K	281	751. (C-S str.), 1499 (C=C str.), 1351 (C-N str.), 1720 (C=O str.), 2920 (Ar-H str.), 1522 (C=N str).748. (C-S str.)	^{1}HNMR (CDCl3):, 7.30 (s, 1H, C=C-H),, 7.04-8.62 (m, 10H, Ar-H), 1.76-1.35 (m, 10H, Cyclohexyl proton)
C - L	282	667 (C-Cl str.),749. (C-S str.),1530(C=N str.), 850.61, 1338.60 (N=O str.), 1494 (C=C str.), 1351 (C-N str.), 1717 (C=O str.), 2918 (Ar-H str.)	^{1}H NMR (CDCl3):, 7.33 (s, 1H, C=C-H),, 7.06-8.51 (m, 9H, Ar-H), 1.80-1.41 (m, 11H, Cyclohexyl proton)
I.C. L	286	669 (C-Cl str.),752 (C-S str.),1533 (C=N str.), 850.61, 1341.04 (N=O str.), 1496 (C=C str.), 1347 (C-N str.), 1722 (C=O str.), 2922.08 (Ar-H str.)	^{1}H NMR (CDCl3):7.31 (s, 1H, C=C-H),, 7.02-8.45 (m, 9H, Ar-H), 1.79-1.38 (m, 11H, Cyclohexyl proton)
C-M	278	750(C-S str.),1545 (C=N str.) 1339 (N=O str.), 1494 (C=C str.), 1347 (C-N str.), 1719 (C=O str.), 2916.37 (Ar-H str.)	^{1}H NMR(CDCl3):, 7.33 (s, 1H, C=C-H),, 7.1-8.69 (m, 9H, Ar-H), 1.81-1.42(m, 10H, Cyclohexyl proton)
I.C. M	281	752(C-S str.),1547 (C=N str.) 1342 (N=O str.), 1496(C=C str.), 1349 (C-N str.), 1721 (C=O str.), 2916.37 (Ar-H str.)	^{1}H NMR (CDCl3):, 7.32 (s, 1H, C=C-H),, 7.09-8.66 (m, 9H, Ar-H), 1.79-1.38(m, 10H, Cyclohexyl proton)
C-N	284	3076-3115 (Ar-H_{str}), 1380.06 (C=N str.),1500.62(C=C_{str}),1352.10(C-N_{str}), 1722(C=O str.),1150 (C-Ostr), 2830 (w,C-H str in OCH3)	^{1}H NMR (CDCl3):, 7.37 (s, 1H, C=C-H), , 7.18-8.92 (m, 9H, Ar-H),3.84-3.88(s, 3H, OCH_3) 1.82-1.39 (m, 10H, Cyclohexyl proton)
I.C-N	289	3078-3117 (Ar-H_{str}), 1382 (C=N str.),1503(C=C_{str}),1354(C-N_{str}), 9439(N-C-S_{str}), 696.30 (C-N_{str}) 1725(C=O str.),1152 (C-Ostr), 2830 (w,C-H str in OCH3)	^{1}H NMR (CDCl3):7.35 (s,1H, C=C-H), , 7.16-8.72 (m, 9H, Ar-H),3.82-3.85(s, 3H, OCH_3) 1.79-1.37 (m,10H, Cyclohexyl proton)

Table: 3 Equlibrium constant and free energy change of inclusion complexes

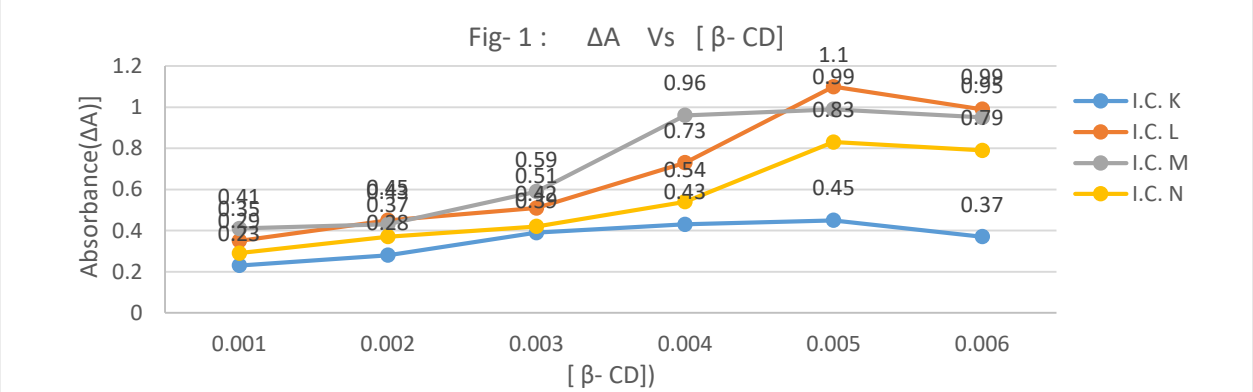
Sl. No	Inclusion complex of Compound	Equilibrium Constant (K) in M^{-1}	ΔG (kJ/mol)
1	I.C.K	778	-16.49
2	I.C.L	362	-14.59
3	I.C.M	461	-15.19
4	I.C.N	426	-15.01

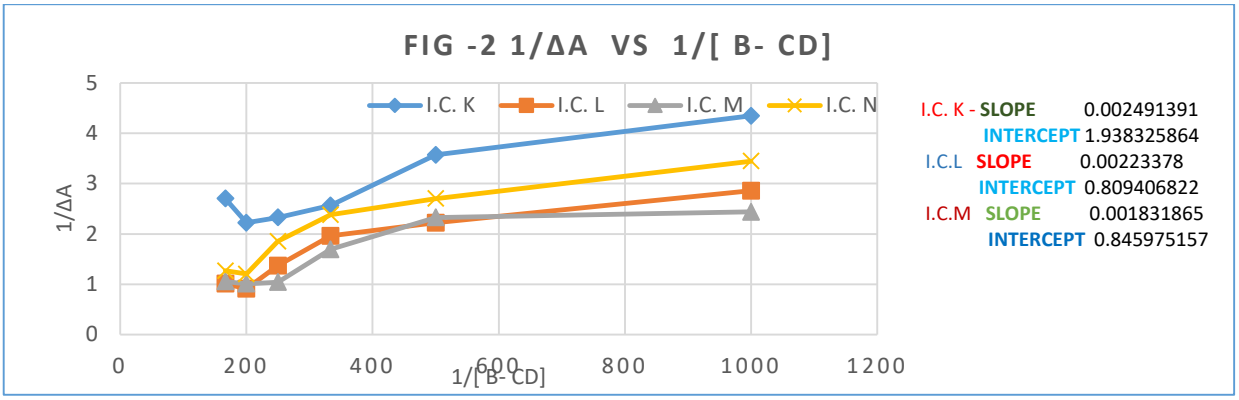
Table: 4 Antibacterial activity of the synthesized compounds & their complexes

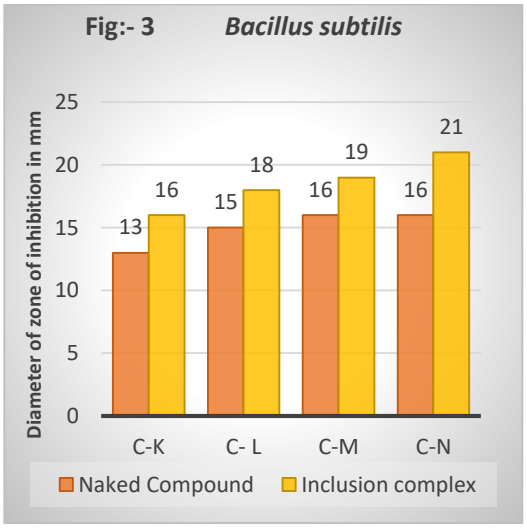
Compound/Complex	Diameter of zone of inhibition(mm)	
	Escherichia coli	***Bacillus subtilis***
Comp- K	9	13
I.C. K	12	16
Comp-L	11	17
I.C.- L	16	22
Comp-M	14	16
I.C.- M	17	19
Comp-N	13	16
I.C.- N	16	21

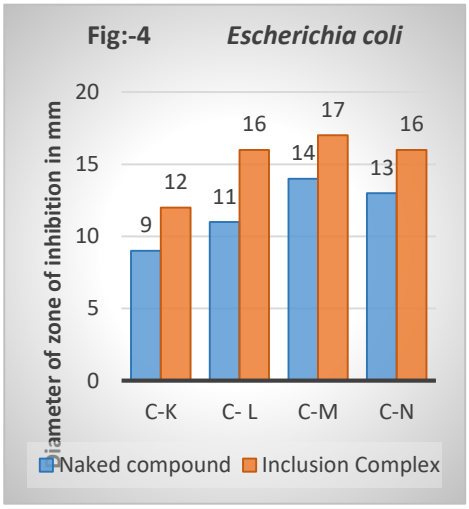
Table -5 Antifungal activity of the synthesized compounds & their complexes

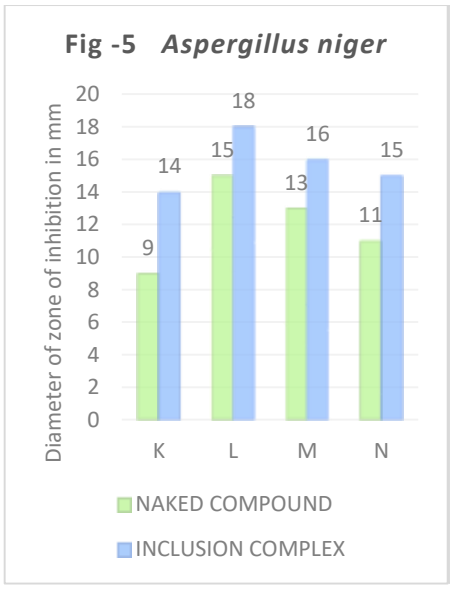
Sl. No.	Compound/Inclusion complex	Diameter of zone of inhibition (mm)	
		Candida albicans	***Aspergillus niger***
1	Comp- K	4	9
	I.C.K	13	14
2	Comp- L	9	3
	I.C.L	13	11
3	Comp- M	10	7
	I.C.M	15	13
4	Comp- N	6	6
	I.C.N	10	11”

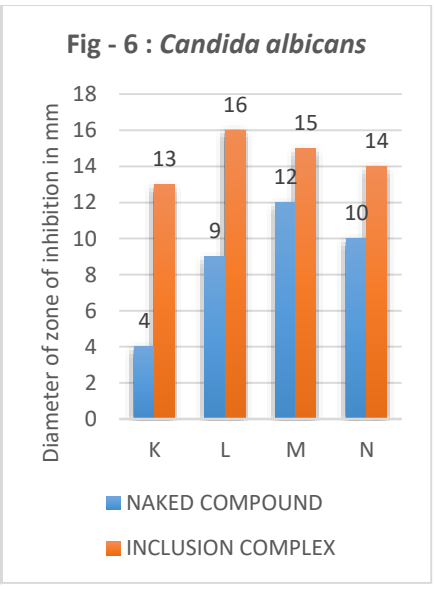












4.Conclusion:

To summarize, the results show that the synthesized compounds, namely the derivatives K, L, M, and N of 2-Cyclohexylimino-3-Phenyl-5-Arylidene-4-Thiazolidinone, exhibit significant improvements in their solubility, bioavailability, thermodynamic stability, and antibacterial and antifungal activities when they form inclusion complexes with β-cyclodextrin.

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