WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.453
Volume 14, Issue 6, 1044-1057. Research Article ISSN 2277–7105

SYNTHESIS OF INCLUSION COMPLEXES OF SOME HETEROCYCLICS WITH B-CYCLODEXTRIN FOR PHARMACOLOGICAL ACTIVITY

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Article Received on
27 Jan. 2025,

Revised on 16 Feb. 2025,
Accepted on 08 March 2025

DOI: 10.20959/wjpr20256-35944

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ABSTRACT

Heterocyclic compounds may be classified into aliphatic and aromatic. The aliphatic heterocyclics are the cyclic analogues of amines, ethers, thioethers, amides, etc. There properties are particularly influenced by the presence of strain in the ring. The heterocyclic compounds may have three, four, five, six or seven membered rings. Thiazolidin-4-ones and its derivatives have played an important role in medicine, because of their diverse chemical reactivity and broad spectrum of biological activities such as anti-cancer, analgesic, anti-inflammatory, antidepressant, antidiabetic, anti-viral, anti-convulsant, anti-bacterial and anti-fungal activities. These above facts were acts as an inspiration to develop some new 4-thiazolidinone derivatives. But these therapeutic agents acquire low aqueous solubility, which in a major challenge for formulation chemists that can be solved by various technological approaches during the pharmaceutical product development stage. Several difficulties are faced in designing formulations for better absorption and with enhanced bioavailability. One of the important approaches is to encapsulate the drug in the hydrophobic cavity of cyclodextrin to produce inclusion complex and to increase the bioavailability. Cyclodextrins are one of the most commonly used host cavities, which provide a conical cavity for the water insoluble drugs to be encapsulated there by making them more water soluble, improve bioavailability, get better stability, decline volatility, conversion of liquid or gas into solid form, reduce side effects etc.

KEYWORDS: Heterocyclic, Thiazolidin-4-one, Cyclodextrin, Complex, Solubility, Bioavailability

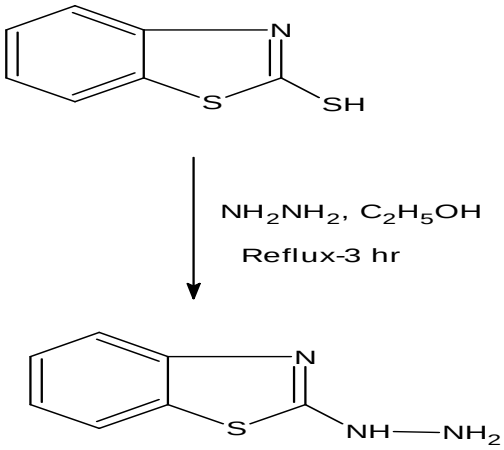
INTRODUCTION

Heterocyclic compounds have been recognized as the most important organic compounds. They have contributed to the development of society from a biological and industrial point of views as well as to the understanding of life processes and to the efforts to improve the quality of life. They participate in most important biochemical processes and are the constituents of DNA and RNA in the living cells. It has been established that half of the medicines consist of heterocyclic compounds. The heterocyclic ring comprises the core of the active moiety or pharmacophore. Especially sulphur and nitrogen containing heterocyclic compounds, possessing broad-spectrum of biological activities, widely occur in nature in the form of alkaloids, vitamins, pigments and as constituents of plant and animal cells Heterocyclic compounds may be classified into aliphatic and aromatic. The aliphatic heterocyclic's are the cyclic analogues of amines, ethers, thioethers, amides, etc. There properties are particularly influenced by the presence of strain in the ring. These compounds generally consist of small (3 and 4member) and common (5 to 7 member) ring systems. Furthermore, these compounds also comply with the general rule proposed by Huckel. This rule states that aromatic is obtained in cyclic conjugated and planar systems containing (4n+2) π electrons. The heterocyclic compounds may have three, four-, five-, six- or seven-member ring.

MATERIALS AND METHODS

All the chemicals and solvents used in the present study were procured from S. D. Fine-Chem. Ltd., Mumbai, and Sigma-Aldrich Chemie, Germany. Culture media for antimicrobial screening were procured from HiMedia Laboratories, Mumbai.

Methods: **Preparation of Hydrazinobenzothiazole (Compound-M-1):** To a warm solution of 2-mercaptobenzothiazole (1.7 gm,10 mmole) in absolute ethanol (10 ml), hydrazine hydrate 99% (1 ml) was added and the resulting solution was refluxed on a water bath for 2-3 hours. It was concentrated and cooled during which crystals of the desired compounds separated. It was filtered and washed with ethanol (Compound-M-1).

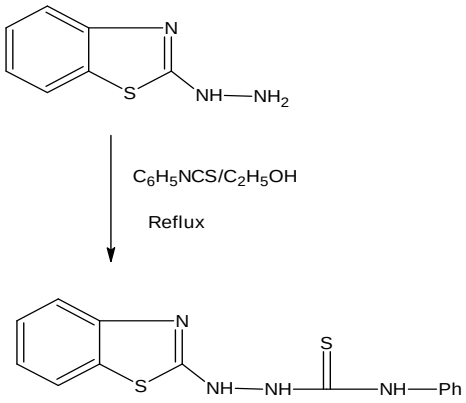


(Compound-M-2)

Molecular Formula = $C_{14}H_{12}N_4S_2$

Molecular weight = 300.40

Preparation of1-(Benzothiazolyl-2')-4-phenylthiosemicarbazide (Compound-M-2): To a solution of 2-hydrazinobenzothiazole (1.65 gm, 10 mmole) in ethanol (10ml), phenyl isothiocyanate (1.35gm, 10mmole) was added with stirring during a period of 5 minutes. The resulting solution was refluxed with stirring for half an hour and cooled. The crystals obtained were filtered and recrystallised from ethanol (Compound-M-2).



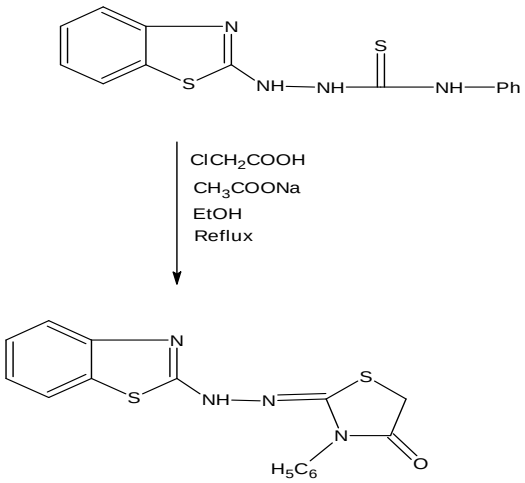
(Compound-M-2)

Molecular Formula = $C_{14}H_{12}N_4S_2$

Molecular weight = 300.40

Preparation of 2-(Benzothiazolyl-2') azino-3-phenyl-4-thiazolidinone (Compound-M-3): A mixture of 1-(benzothiazolyl-2')-4-phenylthiosemicarbazide (0.6 gm, 2 mmole), monochloroacetic acid (0.25 gm, 2 mmole) and anhydrous sodium acetate (0.2gm) in absolute ethanol (10 ml) was refluxed for three hours. The excess of solvent was evaporated,

cooled and poured into ice cold water. The resulting solid was filtered off, washed with hot water and recrystallised from ethanol (Compound-M-3).

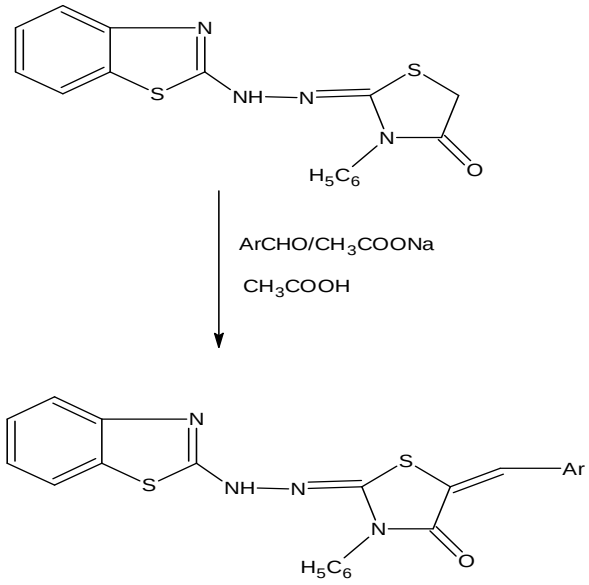


(Compound-M-3)

Molecular Formula = $C_{16}H_{12}N_4OS_2$

Molecular weight = 340.42

Preparation of 2-(Benzothiazolyl-2') azino-3-phenyl-5-benzylidene-4-thiazolidinone (Compound-M-4): This was prepared from 2-(benzothiazolyl-2-azino-3-phenyl-4-thiazolidinone (0.35gm) and benzaldehyde (0.22 gm) by following the above general procedure (Compound-M-4).

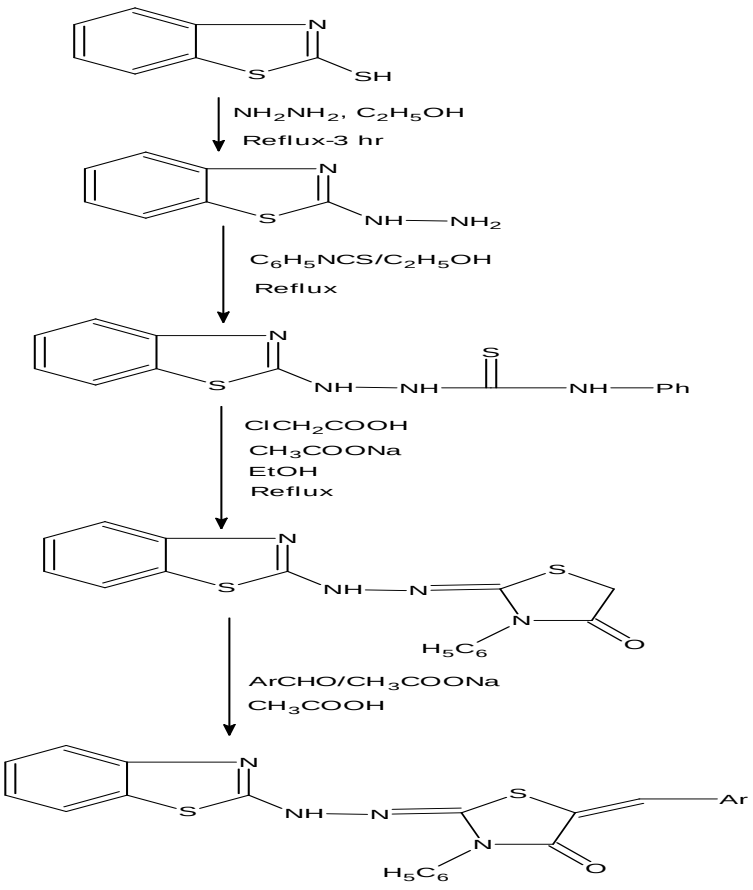


(Compound-M-4)

Molecular Formula = $C_{23}H_{16}N_4OS_2$

Molecular weight = 428.53

Aim and scope of the present work: The importance of 4-thiazolidinone derivatives occupies a unique position in the field of chemistry, due to its various biological activities. These are analgesic 12, anticancer 13-16, anti-inflammatory 17-20, antidepressant 21, ant diabetic 22 , antiviral 23-24, anticonvulsant 25-26, antibacterial and antifungal activities 27-39. These above facts were acts as an inspiration to develop some new 4-thiazolidinone derivatives. But these therapeutic agents acquire low aqueous solubility, which in a major challenge for formulation chemists that can be solved by various technological approaches during the pharmaceutical product development stage. Several difficulties are faced in designing formulations for better absorption and with enhanced bioavailability. One of the important approaches is to encapsulate the drug in the hydrophobic cavity of cyclodextrin to produce inclusion complex and to increase the bioavailability. Cyclodextrins are one of the most commonly used host cavities, which provide a conical cavity for the water insoluble drugs to been capsulated there by making them more water soluble, improve bioavailability, get better stability, decline volatility, conversion of liquid or gas into solid form, reduce side effects etc. From the literature review study it was observed that 4-thiazolidinonederivatives are an important for medicinal, industrial and agricultural point of view. In view of all these above information, it was planned to synthesize some 4-thiazolidine derivatives.



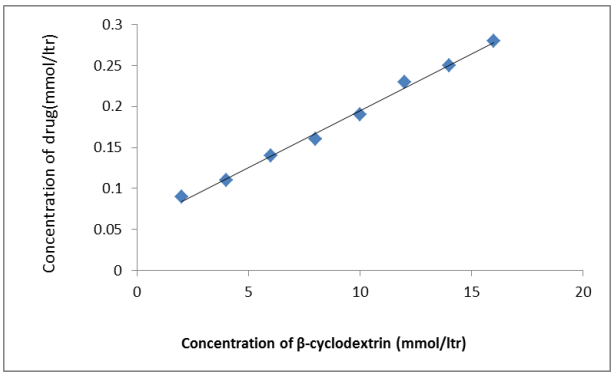
Out of alpha, beta and gamma cyclodextrins, β-cyclodextrin is known to be more suitable for inclusion complex formation because of the following benefits. It has suitable cavity diameter for guest molecules. Its production procedure does not require sophisticated technologies. It is cost-effective, least toxic and easily available. These above facts prompted us to synthesize some thiazolidinone derivatives and prepare the inclusion complex with β-cyclodextrin. Along with this an attempt was also taken into account to test whether complex formation improved the antibacterial activity of the drug or not. In the present study we have synthesized 2-(Benzothiazolyl-2') azino-3-phenyl-5-benzylidene-4-thiazolidinone derivatives starting from 2-mercaptobenzothiazole (scheme-I). When 2-mercaptobenzothiazole is refluxed with absolute ethanol in presence of hydrazine hydrate for 2-3hours it gives hydrazinobenzothiazole (M-1). Then it was refluxed slowly with stirring for half an hour with phenyl isothiocyanate to produce 1-(Benzothiazolyl-2')-4-phenylthiosemicarbazide (M-2). A mixture of 1-(benzothiazolyl-2')-4-phenylthiosemicarbazide (M-2), monochloroaceticacid and anhydrous sodium acetate in absolute ethanol was refluxed for three hours to provide 2-(Benzothiazolyl-2') azino-3-phenyl-4-thiazolidinone (M-3). A suspension of the above 2-(Benzothiazolyl-2') azino-3-phenyl-4-thiazolidinone (M-3) in benzaldehyde was refluxed slowly for three hours to deliver 2-(Benzothiazolyl-2') azino-3-phenyl-5-benzylidene-4-thiazolidinone (M-4). Finally the inclusion complex of compound M-4 was also prepared.

Spectral study: The FTIR spectra of the synthesized compounds were recorded by ShimadzuFTIR spectrophotometer using KBr disks. For all measurements 20 scans in the range of 400 cm^{-1} with a spectral resolution 1 cm^{-1} was recorded**.**

The FTIR data (fig.3.1-3.4) have been used as tool to detect the conformation of the formation of inclusion complex and to know the factors responsible for the stability of the complex. It was found that there was a shift in IR signals towards lower energy and the peak becomes broader and weaker which may be due to the encapsulation of compound within the cavity of β-cyclodextrin.

Phase solubility study: The affinity between β-Cyclodextrin and the synthesized compound in water can be evaluated by phase-solubility study. In the present study phase solubility study was performed according to the method reported by Higuchi and Connors. To carry out this study 4-thiazolidinone derivatives in amount that exceeded its solubility, was taken in a vial in which 25 ml of distilled water (pH 6.8) containing various concentration of β-Cyclodextrin was added. Then the flasks were sealed and shaken for 48 hours at 25°C.

Subsequently, the aliquots were withdrawn, using a syringe and samples were filtered immediately through a Whatman filter paper and diluted. A portion of the sample was analysed by UV spectrophotometer against blank prepared in the same concentration of β-cyclodextrin in water.[48] The various values of the absorbance at λ_{max} are plotted against different concentrations of β-cyclodextrin to obtain the phase solubility curve (Fig.-4.1).



Preparation of inclusion complex: The inclusion complex of the compound M-4 with β-cyclodextrin was prepared as per co-precipitation method. In a 100ml beaker containing 50 ml of double distilled water accurately weighed quantity of β-cyclodextrin was taken. The content was stirred for half an hour. The required quantity of the compound M-4 was taken in a 250 ml dry conical flask and to this 50 ml of double distilled water was added. The content was placed in the magnetic stirrer and it was stirred well. Then the β-cyclodextrin solution was poured slowly into this. The mixture was formed by this was stirred continuously for 48 hours at room temperature. Then the prepared solution was placed in refrigerator for 48 hours which produces as light turbid solution. Then the solution was passed through a silica gel column. Then the solution was filtered. The filtrate was dried in the oven at 60^{o}C for 24 hours which gives a white coloured solid substance. Finally, it was collected carefully which gives the inclusion complex of the compound and β-cyclodextrin.[48]

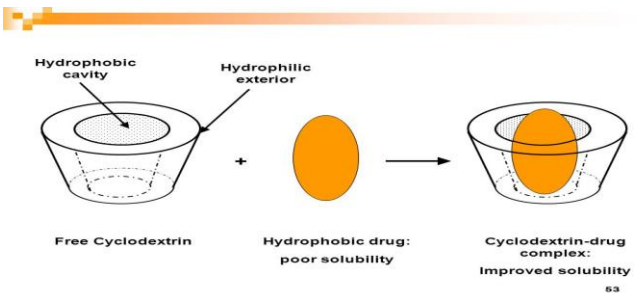


Figure 4: 2 Schematic representation of the association of free CD and drug to form drug-CD complex.

Study of thermodynamic properties: Thermodynamic data of the synthesized compounds and their inclusion complexes.

Compounds and their complex	KM^{-1}	ΔG KJ/mol	ΔH KJ/mol	ΔS KJ/mol
M-1	159	-10.12	-2.07	0.029
M-2	162	-10.12	-2.37	0.036
M-3	160	-10.21	-2.28	0.032
M-4	176	-11.25	-2.96	0.058
Inclusion Complex	271	-16.34	-3.77	0.066

There are various classes of heterocyclic compounds; among them thiazolidinone derivatives constitute an important class of bioactive compounds. The different methods of preparation of 4-thiazolidinone derivatives and a brief review on various biological activities of 4-thiazolidinones are discussed in chapter-1. The chief biological activities of 4-thiazolidinones included in this first chapter are anticancer, analgesic, anti-inflammatory, antidepressant, anticonvulsant, antidiabetic, antibacterial and antifungal activities.

One of the major weaknesses of thiazolidinone derivatives has low aqueous solubility which is a limiting factor to diminish their pharmacological activities. The solubility and pharmacological activities of thiazolidinone derivatives can be enhanced significantly by forming inclusion complexes with cyclodextrins. Out of α, β and ϒ cyclodextrins, β-cyclodextrin is well known for its better host for inclusion complex formation because it is more stable, cheaper and easily available. A brief review on cyclodextrins, their chemical structure, types of cyclodextrins, properties of cyclodextrin, approaches for preparation of inclusion complexes, mechanism of complex formation, characterization techniques of drug-cyclodextrin complex and finally applications of cyclodextrins in different fields such as drug in formulation.

The synthesis of 2-(Benzothiazolyl-2') azino-3-phenyl-5-benzylidene-4-thiazolidinone and its inclusion complex. After preparation of the titled compounds their melting points were determined. Molecular formula, molecular weight, melting point and yield of the synthesized compounds were given in table-6.1. The formations of the compounds are ascertained by melting point determination (table-6.1) and spectral analysis (figure-3.1-3.4).

The phase-solubility curve for the inclusion complex formation between synthesized compound (M-4) and β-cyclodextrin is given in figure-. This plot revealed that the aqueous

solubility of compound increase linearly as a function of β-Cyclodextrin concentration. The linear host-guest correlation with slope of less than one suggested the formation of a 1:1 complex with respect to β-cyclodextrin concentration.

As mentioned earlier that thiazolidinone derivatives have low aqueous solubility, therefore the solubility of the synthesized compounds can be increased by the formation of inclusion complexes with β-cyclodextrin, a renowned encapsulating oligosaccharides having hydrophobic core and hydrophilic surface. Before the preparation of inclusion complex, aqueous phase solubility of the compound has been studied in order to determine the optimum concentration of compounds required for inclusion complex formation. The formation of inclusion complexes have been established from their changes in colour, melting point and spectral characteristics of the compounds. After the inclusion complex formation, there has been an increase in melting point, a blue shift of UV-absorption maximum (λ_{max}), an increase in absorbance, shifting of IR-frequencies towards lower energy, broadening and weakening of IR-signals. An increase in melting point has been attributed to requirement of higher thermal energy to bring the guest molecules out of the cavity of the guest which gives information about the formation of inclusion complex. The changes in characteristic absorption peaks of UV and IR have been explained in terms of changes of compounds from protic to aprotic phase (figure-3.1-3.4).

The various thermodynamic parameters like change in free energy (ΔG), change in enthalpy (ΔH) and change in entropy (ΔS) have been determined from temperature dependency of stability constant, van't Hoff reaction isotherm and Gibbs-Helmholtz equation. The entropy forbidden inclusion complex formation may be due to steric strain in between host and guest. The negative entropy factor is suggested to be compensated by the larger energy factor which was described in table-4.1.

After the preparation of inclusion complex of the compound M-4, the synthesized compounds along with their inclusion complex are screened against Pseudomonas aeruginosa. The brief information about the bacterial strains used for this study including their images was given in Chapter-5. The results of the antibacterial study showed that the compound and their inclusion complexes were sensitive to the test bacteria. It is observed that the zone of inhibition increased from uncomplexed state (naked compounds) to complex state. This may be due to the enhancement of stability and increase the bioavailability of the complexes as compared to the pure compound (figure-6.1).

Table 6.1: Physical properties of the synthesized compounds.

Compounds	M.F.	M.W.	M.P.(ºC)	% Yield
M-1	$C_7H_7N_3S$	165.21	191	73
M-2	$C_{14}H_{12}N_4S_2$	300.40	179	70
M-3	$C_{16}H_{12}N_4OS_2$	340.42	166	44
M-4	$C_{23}H_{16}N_4OS_2$	428.53	122	63

Antibacterial activity of the compound M-4 and its inclusion complexes: The synthesized compounds and their inclusion complexes are tested for their antibacterial activity by disc diffusion method using P. aeruginosa. Muller Hinton broth was used as nutrient medium to grow and dilute the drug suspension for test. DMSO was used as a diluent which not effected the growth of microbes. The study was done at the concentration of 100mg/ml. the result of the study is depicted in figure-6.1.

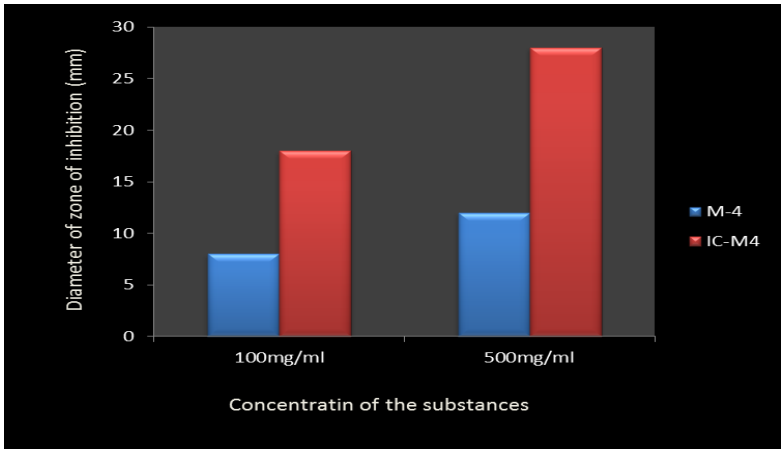


Figure 6.1: Antibacterial activity of the compound M-4 and its inclusion complexes.

CONCLUSION

From the present investigation, it may be concluded that the formation of inclusion complexes of the synthesized compounds modifies the physicochemical as well as biological properties of the molecules which includes solubility, dissolution rate as well as antibacterial activity etc. Thus, the aim of the present investigation is successfully completed.

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