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Microwave Synthesis and Evaluation of Silver Complexes of Thiocarbohydrazide Schiff Bases for their Biological Activity

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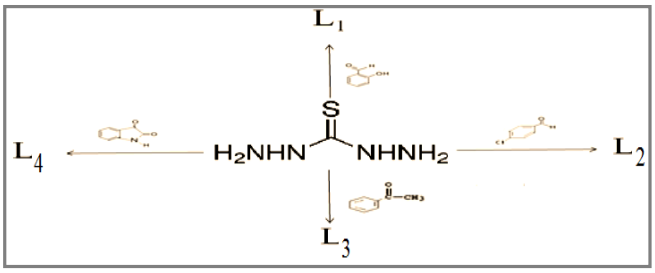
ABSTRACT

Thiocarbohydrazide, Schiff bases of thiocarbohydrazide and their silver complexes have been synthesized under microwave irradiation. The synthesized Schiff bases and their complexes have been characterized by elemental analysis, FTIR and NMR spectroscopy. They have also been screened in vitro for their antibacterial and antifungal activities against two bacteria namely Escherichia coli and Staphylococcus aureus and two fungi Candida albicans and Aspergillus niger.

Graphical Abstract



Keywords: Microwave, Irradiation, Thiocarbohydrazide, Schiff base, Albicans.

INTRODUCTION

Thiocarbohydrazide (TCH), a thiocarbonyl compound was discovered in 1908 by R. Stolle. Wilson and Gula were the first to begin studies on this new molecule. Audrieth reinvestigated and improved the original synthesis of TCH and Sandstrom and Beyer were among the first to use TCH in heterocyclic synthesis. TCH has several uses, but the major use is in Transmission and Scanning Electron Microscopy (TEM and SEM). One reason, that is TCH is such a versatile reagent and is an osmiophillic, which enables it to be used in cooperation with many osmium reagents, especially and most commonly osmium tetroxide (OsO_4). Another reason for TCH is it has an indefinite shelf life, due to its simple purification process.

Thiocarbohydrazide is widely used in organic synthesis and important raw materials of Metribuzin of highly efficient broad-spectrum herbicide. They are also described for use as fogging agents and are considered as safe, storable, and cool-burning pyrotechnic compounds for dissemination of smoke, chemical warfare agents. On the other hand, thiocarbohydrazides are used in performing a highly selective heavy metal ion adsorbent and as complexing agents for the solvent extraction separation methods [**1**].

Schiff bases of thiocarbohydrazide are a class of important compounds in medicinal and pharmaceutical field as they show biological activities including antibacterial [**2-3**], antifungal [**4-7**], anticancer [**8-12**] and herbicidal activities.

Herein, we have described, microwave synthesis of TCH (Thiocarbohydrazide), Schiff bases of TCH and their silver complexes. They have been evaluated for their antifungal and antimicrobial activities. The objective is to develop new antimicrobial agent to fight the microbial infections.

MATERIALS AND METHODS

All the chemicals required for synthesis were purchased from commercial shop and were used without further purification. The synthesis were carried out in a Scientific Microwave Synthesizer Model: CATA-2R of capacity 32 litre with a maximum power output of 850W and microwave frequency 2450 MHz. Completion of reaction was monitored by performing TLC[13]. Elemental composition was determined by elemental analyzer at SAIF, Cochin. For IR spectra, Perkin Elmer FT-IR spectrometer within 350-4000 cm^{-1} range was used by employing KBr disc method. Reports of Antibacterial and Antifungal activities of synthesized compounds were obtained from Bio-Genics, Research and Training Centre in Biotechnology, Hubli, Karnataka as diameter of Inhibition Zones in mm.

General procedure:

Microwave Synthesis of Thiocarbohydrazide: TCH is synthesized by Hydrazinolysis of Carbon Disulfide as it is the cheapest method. 50 ml Hydrazine hydrate was added into 150 mL of distilled water. To this mixture, 15.2 g of CS_2 was added drop wise slowly for one hour with continuous stirring [**14**].

This mixture was transferred in to a round bottomed flask and irradiated with microwave for 30 min at 450W. The temperature of reaction mixture was maintained in between 80-90°C .The progress of the reaction and purity of the products was monitored by TLC using silica gel. After the completion of the reaction, the content of the flask was cooled. The white solid separated was filtered and recrystallized from distilled water.

Synthesis of Schiff Bases: Methanolic solutions of TCH and methanolic solution of aldehyde (Salicylaldehyde/Isatin/ p-chlorobenzaldehyde/ Acetophenone) in 2:1 ratio were mixed thoroughly and few drops of glacial acetic acid was added [**15**]. The mixture was subjected to microwave irradiation at an interval of 1 min at 450 W for about 8-10 min. The progress of the reaction and purity of the products were monitored by TLC using silica gel. After the completion of the reaction, the obtained product was poured into ice cold distilled water and stirred well. Solid separated was filtered and recrystallized from alcohol. The crystalline products were dried under reduced pressure over anhydrous calcium chloride and kept in a desiccator till further use.

Synthesis of Silver Complexes: Synthesis of Silver complexes was carried out in the absence of light [**16**]. The equimolar solutions of ligand and $AgNO_3$ in methanol were mixed thoroughly in 1:1 ratio and the resulting mixture was then irradiated in the microwave synthesizer at an interval of 2 min at 500 W for about 15-20 min. The progress of the reaction and purity of the products were checked by

TLC using silica gel. After the completion of the reaction, the obtained product was poured into cold distilled water and stirred well. The solid separated was filtered off, re-crystallized from methanol and finally washed with petroleum ether. The final product was dried under reduced pressure over anhydrous calcium chloride and the products were also stored in the dark at all times.

Detection Method:

Detection of Silver in Synthesized Complexes: Approximately 1g of each complex was dissolved in of 20ml dilute Nitric acid and boiled to expel brown fumes [**17**]. It is then diluted with double distilled water, heated and dil. HCl (3:100) was added slowly with constant stirring until precipitation is completed. The presence of Silver in complexes is confirmed by the appearance of precipitate.

Evaluation of Silver Complexes for their Biological Activity: The synthesized ligands and their silver complexes were tested for their in vitro antibacterial activity against *Staphylococcus aureus* and *Escherichia coli* and antifungal activity against *Aspergillus niger* and *Candida albicans* at 25, 50, 250, 500 and 1000 µg mL^{-1} of concentrations in DMSO solvent by Agar diffusion method. Antimicrobial activities are measured in terms of diameter of inhibition zone in mm and are compared with Ciprofloxacin and Amphotericin respectively [**18-20**].

RESULTS AND DISCUSSION

Elemental analysis: Micro analytical data of synthesized compounds with proposed empirical formula are given in the following table 1. The results obtained from elemental analytical measurements are in good agreement with calculated results from the empirical formula of each compound. From elemental analysis, it is confirmed that the metal-ligand ratio in complexes is 1:1.

Table 1.Elemental Analysis Data

S. No.	Ligand/ Complex	Empirical Formula	% of elements, found (Calculated)			
			C	H	N	S
1	L_1	$C_{15}H_{14}N_4O_2S$	57.15 (57.32)	4.60 (4.46)	17.80 (17.83)	10.24 (10.19)
2	L_2	$C_{17}H_{12}N_6O_2S$	56.80 (56.04)	3.38 (3.29)	23.45 (23.07)	8.94 (8.79)
3	L_3	$C_{15}H_{12}N_4O_2SCl_2$	47.01 (46.99)	3.24 (3.13)	15.02 (14.62)	8.51 (8.35)
4	L_4	$C_{17}H_{18}N_4S$	65.94 (65.80)	5.84 (5.80)	18.06 (18.83)	10.36 (10.32)
5	C_1	$C_{15}H_{12}N_4O_2SAg_2$	35.15 (34.09)	2.60 (2.27)	10.80 (10.60)	11.02 (10.19)
6	C_2	$C_{17}H_{12}N_6O_2SAg_2$	35.15 (35.17)	2.20 (2.06)	14.80 (14.48)	5.02 (5.51)
7	C_3	$C_{15}H_{12}N_4O_2SCl_2Ag_2$	31.15 (30.05)	2.20 (2.00)	9.80 (9.35)	5.22 (5.34)
8	C_4	$C_{17}H_{18}N_4SAg_2$	35.15 (36.55)	3.20 (3.22)	11.80 (10.03)	5.62 (5.73)

IR Spectral Analysis of synthesized compounds: For confirmation of formation of Schiff base ligands, the IR spectra of ligands are compared with that of TCH **[21-24].** It has been observed that the two peaks at 3273 and 3203 for symmetrical & asymmetrical stretching vibrations of $–NH_2$ group of TCH are disappeared and new band is appeared in the region 1615-1634 cm^{-1} in the IR spectra of ligands which is assigned to C=N group stretching vibration. From these observations, formation of Schiff bases is confirmed. The single bands in the region 3425-3448 cm^{-1} in the IR spectra of ligands is assigned to stretching vibrations of N-H group. Further, to understand the mode of co-ordination of ligand with silver ion, the IR spectra of ligands are compared with that of their silver complex. After careful observations, it has found that, the IR spectrum of ligand L_1 shows the strong OH band at 3148 cm^{-1}, as a part of a broad band comprising the N-H and C-H stretching vibrations in between

3000 cm^{-1} and 3436 cm^{-1}. This OH band is disappeared in the IR spectrum of its complex indicating the involvement of OH group in the co-ordination. All the complexes have shown shift in the band for C=N group stretching vibrations. This indicates that C=N group is involved in coordination with silver ion.

The shift in NH of TCH, C=O and C=S bands in the complexes shows that N, O and S atoms are co-ordinated with silver ion. New appeared bands in lower region are assigned to M-N and M-O. Some important IR bands of ligands and complexes are cited in the table 2.

Table 2.IR Spectral data of Ligands and Complexes

Ligand / Complex	-NH	C=N (Azomethine)	C=O (Lactonyl)	-OH (Aromatic)	C=S	M-N	M-O
L_1	3436	1615	--	3148	1278	--	754
L_2	3427	1627	1695	--	1258	--	--
L_3	3425	1628	--	--	1247	--	--
L_4	3448	1634	--	--	1228	--	--
C_1	3424	1617	--	Disappeared	1267	578	--
C_2	3436	1622	1699	--	1245	579	--
C_3	3432	1631	--	--	Disappeared	514	--
C_4	3442	1629	--	--	Disappeared	512	--

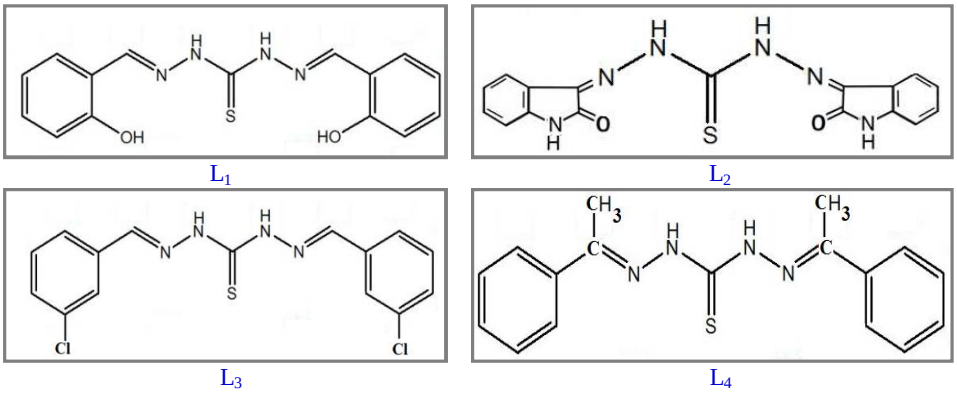
L_1- Schiff base of TCH and Salicylaldehyde
L_2- Schiff base of TCH and Isatin
L_3-Schiff base of TCH and p-chlorobenzaldehyde
L_4- Schiff base of TCH and Acetophenone
C_1- Silver complex of L_1
C_2- Silver complex of L_2
C_3- Silver complex of L_3
C_4- Silver complex of L_4

NMR Analysis: The 1H NMR Spectral data are placed in the table 3. The shift in signal of Azomethine, TCH and Phenolic proton in complexes supports their involvement in co-ordination.

Table 3. NMR Spectral data of ligands and complexes

Ligand / Complex	-NH Protons	HC=N (Azomethine)	Aromatic Proton	Phenolic OH Proton	O-H bonding
L_1	8.5,8.8	8.1	6.8-7.5	10,11.6	--
L_2	10.6,10.2	8.6	6.8-8.2	--	--
L_3	14.3,12.5,11.3,9.1	--	6.9-7.8	--	9.9,10.7
L_4	14.6,12.2,11.3,8.7	--	6.9-7.9	--	9.9,10.7
C_1	11.5,9.9	8.2	7.2-8.1	--	--
C_2	12,10.9	8.6	7.2-8.1	--	--
C_3	10.9,10.2	--	7.2-8.1	--	--
C_4	10.5,10.2	--	7.2-8.1	--	--

On the basis of Elemental, IR and NMR Spectral data analysis, the structures in figure 1 has been proposed for synthesized ligands and structures in figure 2 for complexes.



L_1 L_2 L_3 L_4

Figure 1. Structures of Ligands

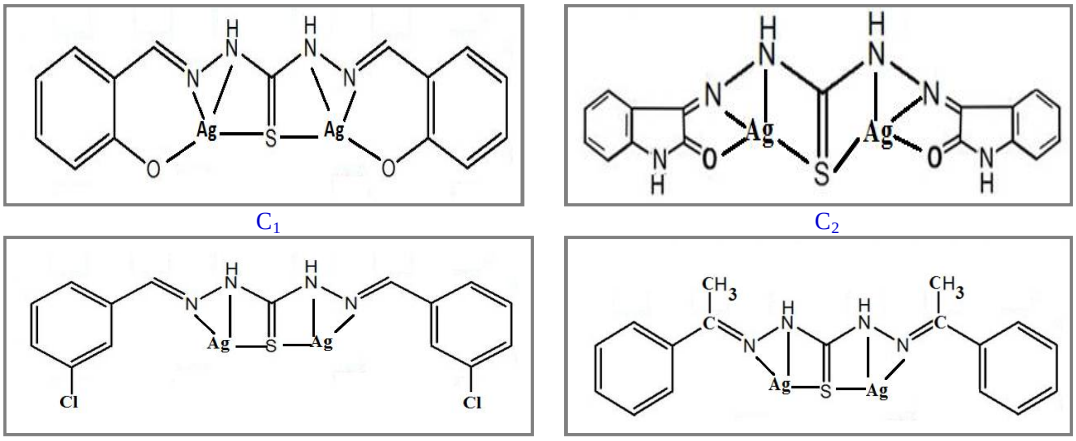


Figure 2. Structures of complexes**.**

Antimicrobial Analysis: The antibacterial and antifungal activities of synthesized compounds are recorded as diameter of inhibition zone. They are found inactive against selected fungi and the antibacterial activities are mentioned in the tables 4.

Table 4. Diameter of inhibition zone of ligands and complexes on selected bacteria

Ligands and Complexes	Antibacterial activity											
	S. aureus						*E. coli*					
	Concentration µg mL^{-1}						*Concentration* µg mL^{-1}					
	25	50	100	250	500	1000	25	50	100	250	500	1000
L_1	0	0	0	0	3	6	0	0	0	0	0	4
L_2	0	0	0	0	0	0	0	0	0	0	0	3
L_3	0	0	0	0	0	0	0	0	0	0	0	0
L_4	0	0	0	0	0	0	0	0	0	0	0	0
C_1	0	0	0	0	0	0	0	0	0	0	0	0
C_2	0	0	0	0	0	0	0	0	0	0	0	0
C_3	0	0	0	0	0	3	0	0	0	3	5	7
C_4	0	0	0	0	3	7	0	0	0	0	0	4
Ciprofloxacin	25	28	31	34	36	***	26	29	32	34	38	*

*** and * means Inhibition zones were too big to measure

APPLICATION

The synthesis of thiocarbohydrazide derivatives can be used as antimicrobial agent.

CONCLUSION

Microwave synthesis has shown spectacular reduction in reaction time. Ligands are co-ordinated with silver ion through N, O and S atoms. All the synthesized ligands and complexes are found inactive against selected fungal strains. They have not shown appreciable antibacterial activities against selected bacterial strains.

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