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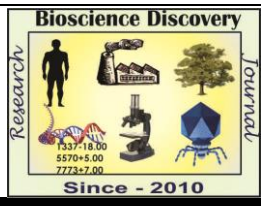

Synthesis, Characterisation and Biological Activities of Some Aromatic Thiocarbohydrazones

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Abstract

Three new derivatives of thiocarbohydrazide have been synthesized by reacting thiocarbohydrazide with equivalent amount aromatic aldehydes in ethanol medium at refluxing conditions. These three new derivatives of thiocarbohydrazide were characterized by elemental, spectral (Uv-visible, IR, NMR and mass) analyses. These three new derivatives of thiocarbohydrazide were tested for the evaluation of antibacterial activity against *Staphylococcus aureus* and *Escherichia coli* and antifungal activity against *Aspergillus niger* and *Rhizopus sps*. These compounds are biologically active in very low concentration.

INTRODUCTION

Study of thiocarbohydrazide and its derivatives is of great interest due to the wide use of these compounds and their valuable reactions. Thiocarbohydrazones are prepared by reaction between Thiocarbohydrazides with aldehydes or ketones; or Thiocarbohydrazones are Schiff bases formed by condensation of between thiocarbohydrazides with aldehyde or ketones (Li and Xu *et al.*, 2008).

Carbohydrazide and thiocarbohydrazide are hydrazine derivatives of carbonic and thiocarbonic acids. Thiocarbohydrazides are more widely used in heterocyclic synthesis as contain the functional group RNHCSNHR which is key for the synthesis of many organic heterocyclic ring systems. Macrocycles synthesized in the reactions of thiocarbohydrazide with polycarbonyl compounds and their complexes with the salts of divalent metals are effective fungistatic agents (Naik and Annigeri *et al.*, 2002), while the cytotoxicity of the carbohydrazones and thiocarbohydrazones displayed activity comparable with or exceeding that of melphalan (Dimmock and Kumar *et al.*, 1997).

Thiocarbohydrazide Schiff bases are a class of important compounds in medicinal and pharmaceutical field. They show biological activities including antibacterial (El-masry **and** Fahmy *et al.*, 2000; Baseer and Jadhav et *al.*, 2000; Nalawade and Nalawade *et al.*, 2015; Hodnett and Dunn *et al.*, 1970), antifungal (Nalawade and Nalawade *et al.*, 2015; Samadhiya and Halve *et al.*, 2001; Nandi and Chaudhri *et al.*, 1984) and anticancer (Hodnett and Dunn *et al.*, 1970; Samadhiya and Halve *et al.*, 2001; Nandi and Chaudhri *et al.*, 1984) activities. Furthermore, Schiff bases are utilized as starting materials in the synthesis of industrial (Metwally and Khalifa *et al.*, 2012) and biological compounds (Nandi and Chaudhri *et al.*, 1984; Metwally and Khalifa *et al.*, 2012; Ali and Chowdhary *et al.*, 1970; Scovill and Klayman *et al.*, 1982; Bindu and Kurup *et al.*, 1998).

In present work**,** we have reacted Thiocarbohydrazide with equivalent amount of aromatic aldehydes in ethanol medium at refluxing

conditions to give substituted benzaldehyde thiocarbohydrazones in high yield, provided the reactant ratio was carefully controlled, the reaction could afforded the desired monosubstituted products in high selectivity and no 1,5-disubstitued byproducts were observed (Li and Xu *et al.*, 2008). These three newly synthesized derivatives thiocarbohydrazide viz. (E)-N'-(4-Fluorobenzylidene) hydrazine carbothiohydrazide (F-TCH), (E)-N'-(4-Chlorobenzylidene) hydrazine carbothiohydrazide (Cl-TCH), (E)-N'-(4-Bromobenzylidene) hydrazine carbothiohydrazide (Br-TCH**)** which were characterized by elemental, Uv-visible, IR, NMR and mass spectra. The compounds were tested for the evaluation of antibacterial activity against *Staphylococcus aureus* and *Escherichia coli* and antifungal activity against *Aspergillus niger* and *Rhizopus sps*. The compounds are biologically active in very low concentration.

MATERIALS AND METHODS

Instrumentation

All chemicals used were of analytical grade, from SD Fine. Melting points of all the synthesized compounds were determined by open capillary tube method, these are uncorrected. The purity of all compounds was checked by TLC which was run on Silica Gel G plates using nHexane and Ethyl acetate (8:2). Spots were visualized under ultraviolet light. IR spectra were recorded on Bruker FT-IR spectrophotometer by using KBr pellets technique. ^{1}HNMR was recorded on Bruker AMX 200 MHz spectrophotometer by using DMSO as solvent. Mass spectra were recorded on YOKUDELNA-ES$^+$2000. The microanalysis of C, H, and N were estimated by elemental analyzer (Perkin Elmer 2400), at SAIF, CDRI, Lucknow, India. The UV-visible spectra were recorded in amyl acetate solvent on Shimatzu UV-1800 with quartz cells of 1 cm path length.

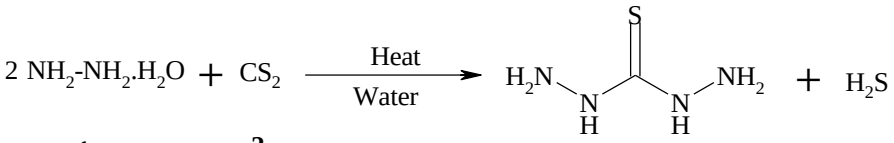
Synthesis of New Derivatives of Thiocarbohydrazide

It is two step manufacturing process.

a. Preparation of thiocarbohydrazide (TCH) –

It is synthesized by various methods (Li and Xu *et al*., 2008); Metwally and Khalifa *et al*., 2012; Authenrith and Hefner *et al.*, 1925) one of them (Li and Xu *et al*., 2008) is as follows. Initially 25 ml of hydrazine hydrate and 25ml water was placed in a 100 ml in round bottom flask .The temperature of solution was lowered to 10° C and 12.5 ml of carbon disulfide was dropped in round bottom flask. Now the above solution was refluxed by using water condenser about 1.5 hours. The temperature of flask was maintained about 80 to 85° C. Reaction was monitored with TLC. The temperature was then lowered to 10° C. Now the flask was cooled in ice cold water. The product obtained was filtered, recrystallised with hot water and washed with water.

Reaction:



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b. Synthesis of Schiff Bases of thiocarbohydrazide

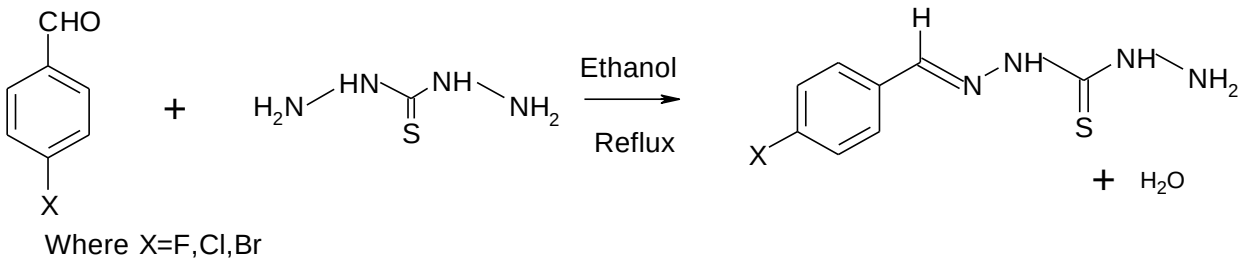
In a 100 ml round bottom flask equimolar amount of aromatic aldehyde (*p*-fluoro benzaldehyde, /*p*-chloro benzaldehyde / *p*-bromo benzaldehyde) and thiocarbohydrazide was taken and dissolved in ethanol and 2-3 drops of glacial acetic acid was added as a catalyst. The above reaction mixture was refluxed by using water condenser along with magnetic stirring. The completion of reaction was indicated by the TLC. Then the product was filtered. After natural cooling, crystals of thiocarbohydrazone were obtained. Melting point and yield of F-TCH (5a), Cl-TCH(5b), Br-TCH(5c) was recorded in table1.

Biological Evaluation

Antibacterial and antifungal activity

Antibacterial and antifungal activity of 5a,5b,5c were tested by serial dilution technique (Spooner D I and Sykes *et al.*,1972).Eight test tubes containing 5 ml of sterile nutrient / sabouraud broth were inoculated with 0.02ml of 24 h old culture of bacteria *Staphylococcus aureus* and *Escherichia coli* and fungi *Aspergillus niger* and *Rhizopus sps*. respectively.

General Reaction:



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Different amounts of F-TCH, Cl-TCH, Br-TCH in ethanol were aseptically added with the help of sterile pipettes from the stock solution 200 µg/ml to 5 ml quantities of respective media so as to reach the concentration from 1µg/ml to 20µg/ml. All test tubes were inoculated at 37^0C and at room temperature for bacteria and fungi respectively. Test tubes inoculated with organism were observed for presence of turbidity after 24h and 48h respectively. The lowest concentration of in F-TCH, Cl-TCH, Br-TCH inhibiting the growth of organism was determined as MIC value.

RESULTS AND DISCUSSION

When hydrazine hydrate taken twice moles as compared with the carbon disulphide and refluxed in distilled water thiocarbohydrazide (TCH) is formed. The pure TCH formed is then dissolved in hot alcohol and then appropriate aldehyde in 1:1 molar proportion added. Catalytic amount of glacial acetic acid catalyses the reaction and the reaction went very smoothly to afford the Schiff bases of Thiocarbohydrazide (Thiocarbohydrazone).The elemental analysis data(C,H,N,S and X) of Thiocarbohydrazones,

Table1: Physical data of the synthesized compounds:

Melting Point-TCH-175^{0}C and yield-65%

Compound	Solvent	Physical state with colour	M. P.	Yield	Time
F-TCH	Ethanol	Solid,white	202 ºC	99%	2 hr.
Cl-TCH	Ethanol	Solid,white	200 ºC	92%	3 hr.
Br-TCH	Ethanol	Solid,faint yellow	208 ºC	90%	3 hr.

Table 2, showed that they may be represented by the formula $C_8H_9N_4SX$.The purity of Thiocarbohydrazones was confirmed by TLC, IR, NMR spectra .

Table 2: Composition and elemental analysis of thiocarbohydrazone

				Calculated(Found)%				
Entry	Molecular formula	Molecular weight	M.P.	C	H	N	S	X
F-TCH	$C_8H_9N_4SF$	212	202	45.28 (45.29)	4.24 (4.25)	26.41 (26.40)	15.09 (15.08)	8.96
Cl-TCH	$C_8H_9N_4SF$	218	200	44.03	4.12	25.68	14.67	16.05
Br-TCH	$C_8H_9N_4SF$	273	208	35.16	3.29	20.51	11.72	29.3

Spectral Data

^{1}H NMR Spectra:

A survey of literature reveals that the NMR spectroscopy has been proved useful in establishing the structure and nature of many Schiff bases. The ^{1}H NMR spectra of Schiff base was recorded in d6-dimethylsulfoxide (DMSO-d6) solution using Me_4Si (TMS) as internal standard. The single peak at 8.60,7.94 and 7.97 ppm in compound F-TCH, Cl-TCH, Br-TCH are due to CH=N, azomethine proton showing formation of Schiff bases, which were formed by condensation of Thiocarbohydrazide (TCH) with aromatic aldehyde. Doublet at 4.72, 4.66 and 4.99 in compound F-TCH, Cl-TCH, Br-TCH are due to NH_2 proton in thiocarbohydrazide.

Infrared Spectra

The IR spectra provide valuable information regarding the nature of functional group in the Schiff bases of thiocarbohydrazide.

It was noted that a pair of bands at 3434.33 cm^{-1} and 3648.42 cm^{-1} in compound 5a;3271.26 cm^{-1} and 3385.05 cm^{-1} in compound 5b and at 3227.02 cm^{-1} and 2965.23 cm^{-1} in compound 5c are corresponding to $\nu(NH_2)$ present in the spectra of the thiocarbohydrazones (Kumar G *et al*., 1972). The value of ν(C=N) stretching vibration in IR spectra of Thiocarbohydrazones, show band at 1645.35,1650,1677.31 cm^{-1} indicates that expected C=N (azomethine gr) in imino compound formed by condensation of Thiocarbohydrazide (TCH) with aromatic aldehyde.

Compound (5a): (E)-N'-(4- Fluoro benzylidene) hydrazinecarbothiohydrazide(F-TCH)

IR (KBr) cm^{-1}: C=N 1602, and N-H 3434.33 and 3648.42.

^{1}HNMR (DMSO) δ ppm: 4.72 (d, 2H, NH_2), 7.29-8.15 (m, 4H, Aromatic), 8.60 (s, 1H, CH), 11.61 (s, 1H, NH). 11.93 (s, 1H, NH).

Mass(m/z): 212.01, 145.13.

Compound (5b): (E)-N'- (4- Chloro benzylidene) hydrazinecarbothiohydrazide(Cl-TCH)

IR (KBr) cm^{-1}: C=N 1600, and N-H 3271.26, 3385.05.

^{1}HNMR (DMSO) δ ppm: 4.66 (d, 2H, NH_2), 7.29-7.76 (m, 4H, Aromatic), 7.94 (s, 1H, CH), 11.44 (s, 1H, NH), 9.56 (s, 1H, NH).

Mass(m/z): 229.08, 231.08.

Compound(5c): (E)-N'- (4- Bromo benzylidene) hydrazinecarbothiohydrazide (Br-TCH)

IR (KBr) cm^{-1}: C=N 1587, and N-H 3227.02 and 2965.23.

^{1}HNMR (DMSO) δ ppm: 4.90 (d, 2H, NH_2), 7.57-7.84 (m, 4H, Aromatic), 7.97 (s, 1H, CH), 9.93 (s, 1H, NH). 11.50 (s, 1H, NH).

Mass(m/z): 273.02, 275.05.

Electronic spectra

Electronic spectral data of the thiocarbohydrazones were recorded in amyl acetate solutions. Each thiocarbohydrazones derivative shows several intense absorptions bands in the visible and ultraviolet regions. These wide range bands seem to be due to both the π→π* and n→π* of benzene ring or azomethine (-C=N) groups (Carlin and Devi *et al.*, 1965). The bands at the 216-297 nm region are assigned to intramolecular π→π* transitions and the bands at the 321-410 nm are attributed to n→π* transitions of benzene ring or azomethine (-C=N) groups.The band at 382 nm corresponds to the transition of azomethine group (Lever *et al.*, 1984).

Antibacterial and antifungal activity

The antibacterial and antifungal activities for F-TCH, Cl-TCH and Br-TCH are shown in table (3a, 3b and, 3c). All the three compounds show antibacterial and antifungal activity. The F-TCH and Cl-TCH show more antibacterial and antifungal activity than Br-TCH.

Table 3 a : Antibacterial and antifungal activity of F-TCH

Antibacterial activity				Antifungal activity			
Quantity of Stock Solution	Conc. in µg/ml	Growth(+)/ Inhibition (-) for		Quantity of Stock Solution	Conc. in µg/ml	Growth(+)/ Inhibition (-) for	
		Staphylococcus aureus	*Escherichia coli*			*Aspergillus niger*	*Rhizopus spe*
0.05	2	+	+	0.05	2	+	+
0.1	4	+	+	0.1	4	+	+
0.2	8	+	+	0.2	8	+	+
0.3	12	-	+	0.3	12	-	-
0.4	16	-	-	0.4	16	-	-
0.5	20	-	_	0.5	20	-	-

Table 3b: Antibacterial and antifungal activity of Cl-TCH

Antibacterial activity				Antifungal activity			
Quantity of Stock Solution	Conc. in µg/ml	Growth(+)/ Inhibition (-) for		Quantity of Stock Solution	Conc. in µg/ml	Growth(+)/ Inhibition (-) for	
		Staphylococcus aureus	*Escherichia coli*			*Aspergillus niger*	*Rhizopus spe*
0.05	2	+	+	0.05	2	+	+
0.1	4	+	+	0.1	4	+	+
0.2	8	+	+	0.2	8	+	+
0.3	12	-	+	0.3	12	+	+
0.4	16	-	-	0.4	16	-	-
0.5	20	-	_	0.5	20	-	-

Table 3c: Antibacterial and antifungal activity of Br-TCH

Antibacterial activity				Antifungal activity			
Quantity of Stock Solution	Conc. in µg/ml	Growth(+)/ Inhibition (-) for		Quantity of Stock Solution	Conc. in µg/ml	Growth(+)/ Inhibition (-) for	
		Staphylococcus aureus	*Escherichia coli*			*Aspergillus niger*	*Rhizopus spe*
0.05	2	+	+	0.05	2	+	+
0.1	4	+	+	0.1	4	+	+
0.2	8	+	+	0.2	8	+	+
0.3	12	+	+	0.3	12	-	+
0.4	16	-	+	0.4	16	-	-
0.5	20	-	_	0.5	20	-	-

Here we conclude that the present method for the synthesis of thiocarbohydrazone is easy, clean and efficient. Preparation and purification of thiocarbohydrazone is easy and rapid ;it requires low cost of chemicals. Greater % yields are obtained in ethanol medium. These thiocarbohydrazones (F-TCH, Cl-TCH and Br-TCH) are found to be biologically active. The Compounds F-TCH and Cl-TCH show better antibacterial and antifungal activity than Br-TCH.

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