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Original Article

Synthesis and Evaluation of Thiosemicarbazone Derivatives as Potent Antimicrobial Agent

Madhavi Pardeshi*[1], Kratika Daniel[2], Sachin K Jain[2], Sudha Vengurlekar[2]

[1]Research Scholar, Oriental College of Pharmacy & Research, Oriental university, Indore, MP

[2]Professor, Oriental College of Pharmacy & Research, Oriental university, Indore, MP

[*]Corresponding Author: Madhavi Pardeshi

Abstract:
The present study focuses on the design, synthesis, characterization, and biological evaluation of novel 1-(substituted phenyl)-4-phenylthiosemicarbazide derivatives as promising antimicrobial agents. Recognizing the global challenge of infectious diseases and rising antimicrobial resistance, the research aimed to develop new drug candidates with improved efficacy and safety. All derivatives (3a–3e) were synthesized through the condensation of phenyl thiosemicarbazide with various aryl aldehydes and characterized using melting point determination, thin-layer chromatography, and FTIR spectroscopy.

Keywords – Antimicrobial, Thiosemicarbazide, FTIR spectroscopy, Drug.

1. Introduction

Heterocycles have significantly advanced society from both biological and industrial perspectives, enhancing the quality of life. In recent discards, numerous scientists have synthesized a range of bioactive heterocyclic compounds. Sulfur and nitrogen-containing compounds, particularly thiosemicarbazides, garner considerable attention in the domain of medicinal chemistry [2]. Consequently, numerous novel compounds are introduced to this domain annually. Thiosemicarbazides and thiosemicarbazones, which include sulfur and nitrogen, exhibit potential pharmacological effects [3]. Thiosemicarbazide (NH2-NH-CSNH2) is the most basic hydrazine derivative of thiocarbamic acid. The chemical behavior of thiosemicarbazide resembles that of its counterpart semicarbazide; however, it exhibits greater chemical versatility due to the thione group compared to the keto group, which accounts for the more diverse behavior of thiosemicarbazide [5]. The application of these derivatives in organic synthesis has become a conventional method for the production of various heterocyclic compounds [6]. Owing to the presence of multiple reactive centers, these compounds serve as advantageous precursors for the synthesis of nitrogen- and sulfur-containing heterocyclic compounds, including pyrazoles, thiazoles, thiadiazoles, thiadiazines, triazoles, pyrimidines, triazines, zolotriazines, and thiazolotriazines, among others [7]. Thiosemicarbazide's capacity to form complexes with zinc, iron, nickel, copper, and other metal cations, which are crucial in biological processes. The main objective of the study is to synthesize and characterize some novel Thiosemicarbazone derivatives as potent antimicrobial agent

Experimental Work

Synthesis of 1,4-substituted Phenylthio-semicarbazide (3 a-e) – 1 gm of Phenyl thiosemicarbazone was dissolved in 10 mL of methanol in RBF, then added 10 ml of Substituted benzaldehyde to flask with continuous stirring. 2 - 3 drops of glacial acetic acid were used to catalyse the reaction. Heated the reaction mixture under reflux for 3 hrs at 60 -70^{o}C. Completion of reaction was monitored through TLC using solvent, hexane: ethyl acetate, 7 : 3 as mobile phase. Then the reaction was stopped, and product

obtained was filtered and the excess solvent was distilled under reduced pressure, Recrystallize the crude product from ethanol to obtain 1,4-substituted diphenyl thio semicarbazide (3a – e).

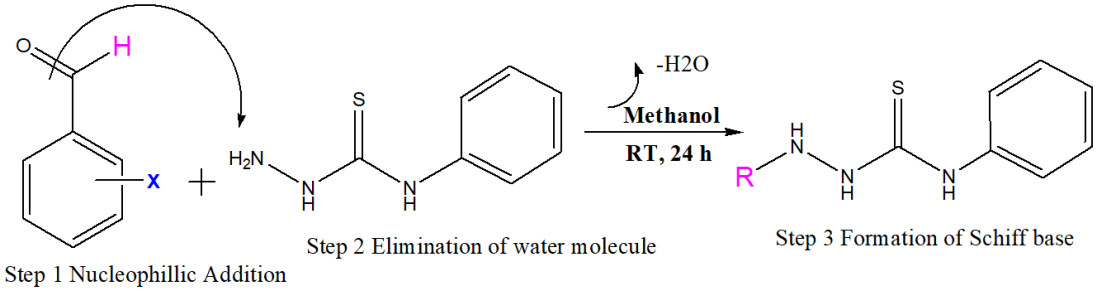

Figure 1. Reaction Mechanism of Thiosemicarbazone derivative 3(a-e)

Anti-Microbial Activity –

Antimicrobial activity consists of antibacterial & Antifungal Activity, all the synthesized compounds were tested for antimicrobial activity again bacterial & fungal strain.

Standard Drug – Ciprofloxacine (5 µg/mL)

Test Compounds - Dissolved the compounds (3a – e) in DMSO to obtain test concentrations (25, 50, 100 µg/mL).

Préparations of Nutrient Medium – Poured molten Mueller Hinton Agar into sterile Petri dishes and allow to solidify.

Procedure - Swab the entire agar surface with the test microbial culture (10 µl). Used a sterile cork borer to punch wells (approximate 6 mm diameter). Added 10 µL of each concentration into the respective wells. Included wells for positive control (Standard Drug ciprofloxacin 5 µg/ml). Incubated all petri plates at 37^{o}C for 24 hrs

Observation - Measured the zone of inhibition (in mm) using a transparent scale. Each reading taken in triplicate and one way ANOVA was used the observation was made in terms of mean ± sem. All observations were summarized in Table 1

Result & Discussion

This study includes the synthesis of novel thiosemicarbazone derivatives, examining their antimicrobial and anthelmintic properties. Thiosemicarbazone serves as a multifaceted pharmacophore, demonstrating a broad spectrum of biological activities. The range of actions encompasses antibacterial, analgesic, anti-inflammatory, ulcerogenic, anticonvulsant, anticancer, antitumor, and anthelmintic effects. The present research work was comprised of synthesis of new Benzimidazole derivatives as an antimicrobial and anthelmintic agent. It was reported in the literature that thiosemicarbazone increases the probability of off good anthelmintic and antimicrobial, because of presence heterocyclic moiety, aromatic ring & electron withdrawing agents possesed the potential and showed excellent anthelmintic and antimicrobial activity.

Chemistry of Synthesis – Thiosemicarbzone derivatives (figure 2) was synthesised in a single pot reaction, from Phenyl thiosemicarbazone was dissolved in methanol and substituted benzaldehyde to obtain 1,4-substituted phenyl thiosemicarbazide derivatives. The schematic representation was displayed in figure 2.

Reaction Mechanism - The amino group (–NH2) of phenyl thiosemicarbazide condenses with the carbonyl group (–CHO) of benzaldehyde forming a C=N (Schiff base) linkage. The reaction mechanisms are comprised of three steps - Step 1 Nucleophilic Addition, Step 2: Elimination of Water, Step 3: Schiff Base Formation.

Characterization of Compounds - Completion of reaction was monitored through TLC using solvent, hexane: ethyl acetate, 7 : 3 as mobile phase was used as a solvent and Iodine was used to develop the TLC plates. All Physical characteristics and spectral analysis such as Melting Point, Colour, Yield, *rf*, were summarized in **Table 1**.

Table 1 - Physical Characteristics and Spectral Data of all Compounds

S. No.	Compound Name with code	Colour	M.P. (^oC)	% Yield	R_f
1.	1,4-diphenylthiosemicarbazide (3a)	Pale yellow	132 -134	41.33	0.74.
2.	1-(4-chlorophenyl)-4-phenylthiosemicarbazide (3b)	Off-white	143 -145	40.28	0.58
3.	1-(4-hydroxy-2-methoxyphenyl)-4-phenylthiosemicarbazide (3c)	Yellow	136 -138	34.23	0.62
4.	1-(4-hydroxyphenyl)-4-phenylthiosemicarbazide (3d)	Pale Yellow	180 -182	40.67	0.43
5.	1-(furan-2-yl)-4-phenylthiosemicarbazide (3e)	Pale Brown	162 - 164	43.11	0.33

Antimicrobial Activity

Numerous pathogenic microorganisms exhibiting antibiotic resistance have been recognised as a significant worldwide health threat to both humans and animals. The rise of antibiotic resistance in microorganisms is neither unprecedented nor surprising. The emergence of novel resistance variations among several bacterial pathogens and commensal species is becoming concerning. The antimicrobial efficacy of the benzotriazole nitrogen-containing heterocyclic compound was assessed utilising the established disc-diffusion method, with ciprofloxacin as the reference drug against Gram-positive (Staphylococcus aureus), Gram-negative (Escherichia coli and Pseudomonas aeruginosa) bacteria, and Candida albicans as the fungal strain. The antibacterial activity of the synthesised compound was assessed by measuring the zone of inhibition (ZOI) in millimetres (mm) and comparing it to the standard medication as a reference parameter. All information is presented in Table 2.

Table 2. Antimicrobial activity data at 100µg/ml (after 24 hr)

S.NO.	COMPOUNDS	ZONE OF INHIBITION (mm) after 24 hr		
		Antibacterial		Antifungal
		S. aureus	*E. coli*	*C. albicans*
1	1,4-diphenylthiosemicarbazide (3a)	10.33±0.33	12.33±0.33	9.67±0.66
2	1-(4-chlorophenyl)-4-phenylthiosemicarbazide (3b)	14.00±0.57	14.33±0.33	12.00±0.57
3	1-(4-hydroxy-2-methoxyphenyl)-4-phenylthiosemicarbazide (3c)	13.00±0.94	15.67±0.33	15.33±0.33
4	1-(4-hydroxyphenyl)-4-phenylthiosemicarbazide (3d)	20.33±0.88	19.67±1.20	21.00±1.15
5	1-(furan-2-yl)-4-phenylthiosemicarbazide (3e)	24.00±0.57	27.33±1.76	25.67±0.33
6	Ciprofloxacin	32.19±1.58	33.00±0.57	33.12±1.58

It has been observed from the table and figure that Compound **3e** possessed maximum antimicrobial activity against all strain.

Conclusion

The present investigation focused on the synthesis, characterization, and evaluation of a novel series of 1-(substituted phenyl)-4-phenylthiosemicarbazide derivatives (compounds 3a–e) as promising antimicrobial agents and Compound **3e** possessed maximum antimicrobial activity against all strain.. Recognizing the global health burden posed by infectious diseases and the growing challenge of antimicrobial resistance, this research aimed to identify new pharmacophores that can address urgent medical needs.

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