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GREEN SYNTHESIS AND ANTIMICROBIAL EVALUATION OF SOME THIOSEMICARBAZONE AND SEMICARBAZONE DERIVATIVES

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ABSTRACT
The interaction of substituted pyridine carboxaldehyde with thiosemicarbazide and semicarbazide *via* a greener approach resulted in the synthesis of thiosemicarbazone and semicarbazone derivatives; respectively. The resultant compounds were synthesized in aqueous media and were characterized by FTIR and ^{1}H-NMR spectral studies.
The antimicrobial evaluation of the final compounds has proven that they are active against the strains (*S. aureus*, *P. aeruginosa*, *A. niger,* and *C. glabrata*) incorporating the microdilution method.
Keywords: Azomethine, Green synthesis, Semicabazones, Thiosemicarbazones, Antimicrobial Activities.
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INTRODUCTION

Thiosemicarbazones and semicarbazones have been widely studied as they can be easily synthesized by the condensation of carbazides and carbonyl compounds *via the* formation of an azomethine bond (>C=N-).[1] Azomethine derivatives have significant applications as dyes, polymers, and catalysts[2-4] in addition to their biological significance including antifungal, antibacterial, antitumor, antihypertensive, antimalarial, antiprotozoal, antiviral, anti-inflammatory, anticancer.[5-17] It has been evident that the N-atom of the azomethine entity is associated with the formation of H-bond along with active centers and disrupts the normal cell processes.[18] The azomethine-metal complexes on the other hand have been widely investigated for their anticancer and herbicidal significance.[19] The present conditions provoke newer drugs imparting microbial inhibition properties against different pathogens; along with a feasible and relatively easier synthetic approach.[20-22] Here, in this work, we report the green synthesis and antimicrobial significance of some Thiosemicarbazone and Semicarbazone derivatives. These synthesized analogs have shown promising activities against bacterial as well as fungal strains.

EXPERIMENTAL

All the commercial chemicals and reagents (procured from Sigma Aldrich/Merck) were used as such without any purification. IR spectra were noted with the KBr pellet method on a Perkin Elmer FTIR spectrophotometer (Version: 10.4.00) in the range 4000-600 cm^{-1}. ^{1}H-NMR spectra were noted using TMS as the internal reference on Bruker Ascend 300 MHz system in DMSO-d_6. Melting points were determined using an Electrothermal apparatus and were uncorrected.

Green Synthesis of Substituted Thiosemicarbazones (Scheme-1)

A mixture of pyridine carboxaldehyde (**A1**, 0.001 mole), thiosemicarbazide (**B**, 0.001 mole), and sodium acetate (0.001 mole) in water (20 mL) was refluxed for about an hour. Contents were cooled and the precipitate obtained was filtered, washed with ice-cold water twice, and dried in an electric oven to obtain compound **D1** as a powdered solid (m.p.: 212-214˚C, Yield: 97%). A similar procedure with **A2**, **A3,** and **A4** resulted in the synthesis of compounds **D2**, **D3,** and **D4**; respectively.

Green Synthesis of Substituted Semicarbazones (Scheme-1)

A mixture of pyridine carboxaldehyde (**A1**, 0.001 mole), semicarbazide hydrochloride (**C**, 0.001 mole), and sodium acetate (0.001 mole) in water (20 mL) was refluxed for about an hour. Contents were cooled and the precipitate obtained was filtered, washed with ice-cold water twice, and dried in an electric oven

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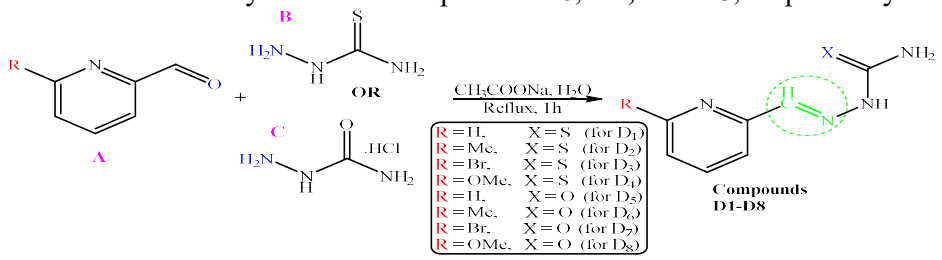
to obtain compound **D5** as a powdered solid (m.p.: 190-192°C, Yield: 89%). A similar procedure with **A2**, **A3,** and **A4** resulted in the synthesis of compounds **D6**, **D7,** and **D8**; respectively.



Scheme-1: Green Synthesis of Substituted Thiosemicarbazones and Semicarbazones

RESULTS AND DISCUSSION

The syntheses of thiosemicarbazone (**D1-D4**) and semicarbazone (**D5-D8**) derivatives were carried out *via a* greener approach in aqueous media using substituted pyridine carboxaldehyde (**A1-A4**), thiosemicabazide (**B**) and semicarbazide hydrochloride (**C**) through a simple condensation pathway (Scheme1). All the resultant final compounds were obtained as powdered solids. They were found to be thermally stable and were obtained in excellent yields (86-98%). Physical and analytical data are presented in Table-1.

Table-1: Physical and Analytical Data for the Synthesized Derivatives D1-D8

S. No.	Compound	Molecular Formula	M.P. (°C)	Yield (%)
1	D1 (R = H; X = S)	$C_7H_8SN_4$	212-214	97
2	D2 (R = Me; X = S)	$C_8H_{10}SN_4$	196-198	86
3	D3 (R = Br; X = S)	$C_7H_7BrSN_4$	191-193	92
4	D4 (R = OMe; X = S)	$C_8H_{10}OSN_4$	223-225	90
5	D5 (R = H; X = O)	$C_7H_8ON_4$	190-192	89
6	D6 (R = Me; X = O)	$C_8H_{10}ON_4$	217-218	87
7	D7 (R = Br; X = O)	$C_7H_7BrON_4$	230-232	92
8	D8 (R = OMe; X = O)	$C_8H_{10}O_2N_4$	192-193	98

IR Spectra

IR Spectra of all the derivatives were noted in the region 4000-600 cm^{-1}. These spectra were comparatively studied based on some key peaks. The dual signals in the region 3270-3115 cm^{-1} in spectra of derivatives **D1-D8** have been accounted for $\nu(NH_2)$ and peaks observed in the region 3180-2970 cm^{-1} have been attributed to ν(NH). Peaks recorded in spectra in the region 1625-1585 cm^{-1} are assigned to ν(>C=N) of the synthesized analogs which depict the formation of azomethine bond.[23, 24] Moreover, peaks in the region 1085-1065 cm^{-1} in **D1-D4** and 1710-1680 cm^{-1} in **D5-D8** can be assigned to ν(C=S) and ν(C=O) of the thioemicarbazone and semicarbazone groups; respectively (Table-2). For instance; in the IR spectrum of derivative **D1** (Fig.-1) two peaks appear at 3270 and 3255 cm^{-1} due to the amino (NH_2) group. The NH group appears at 3180 cm^{-1}, and C=N, C=S groups appear at 1620, 1085 cm^{-1}; respectively.

Table-2: IR Spectral Readings for the Synthesized Derivatives D1-D8

S. No.	Compound	$\upsilon(NH_2)$	υ(NH)	υ(C=O)	υ(C=N)	υ(C=S)
1	D1 (R = H; X = S)	3270, 3255	3180	---	1620	1085
2	D2 (R = Me; X = S)	3245, 3115	2970	---	1615	1070
3	D3 (R = Br; X = S)	3280, 3260	3130	---	1625	1080
4	D4 (R = OMe; X = S)	3370, 3265	3170	---	1610	1065
5	D5 (R = H; X = O)	3250, 3160	3080	1685	1585	---
6	D6 (R = Me; X = O)	3275, 3165	3095	1605	1595	---
7	D7 (R = Br; X = O)	3270, 3140	3100	1710	1585	---
8	D8 (R = OMe; X = O)	3235, 3170	3075	1680	1590	---

^{1}H-NMR Spectra

The presence of signals observed in the 11.77-10.46 ppm region in the proton spectra of compounds **D1-D8** can be attributed to >NH group.[25] Additionally, signals observed in the typical 8.56-6.58 ppm region are assigned to aromatic protons in the proton spectra of all the compounds. Signals observed in compounds

D2, and **D6** around 2.44-2.43 ppm region have been assigned to the methyl (-CH_3) group; whereas, signals observed in compounds **D4**, and **D8** around 3.87-3.84 ppm are assigned for the methoxy (-OMe) group (Table-3). For instance, in the ^{1}H-NMR spectrum of derivative **D1** (Fig.-2); the aromatic protons appear at δ 7.32 (t, 1H), 7.82 (t, 1H), 8.29 (d, 1H), 8.52 (d, 1H); while the CH-N appears at δ 8.10 (s, 1H), NH at 11.67 (s, 1H), and terminal amine at δ 8.21 (s, 1H).

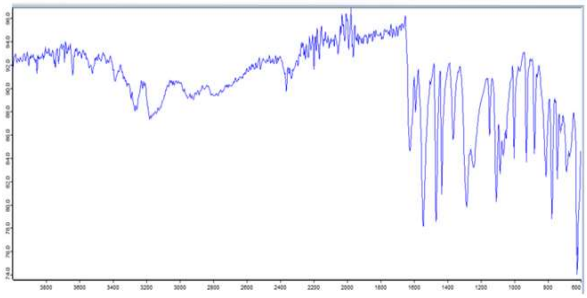


Fig.-1: IR Spectrum for the Derivative D1

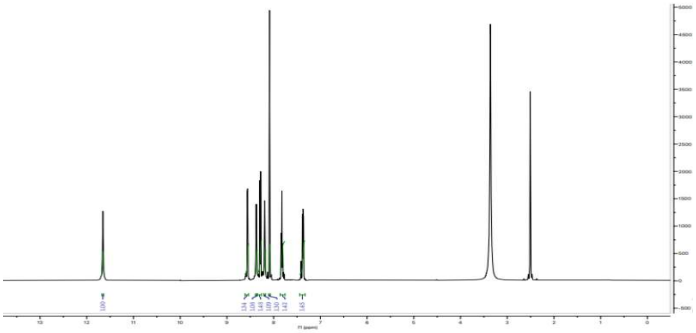


Fig.-2: ^{1}H-NMR Spectrum for the Derivative D1

Table-3: ^{1}H-NMR Spectral Readings for the Synthesized Derivatives D1-D8

S. No.	Compound	^{1}H NMR (500 MHz, DMSO–d_6)
1	D1 (R = H; X = S)	*δ* 11.67 (s, 1H), 8.52 (d, 1H), 8.29 (d, 1H), 8.25 (s, 1H), 8.21 (s, 1H), 8.10 (s, 1H), 7.82 (t, 1H),7.32 (t, 1H)
2	D2 (R = Me; X = S)	*δ* 11.61 (s, 1H), 8.32 (s, 1H),8.13 (s, 1H), 8.06 (d, 1H), 8.01 (s, 1H), 7.68 (t, 1H), 7.20 (d, 1H),2.44 (s, 3H)
3	D3 (R = Br; X = S)	*δ* 11.77 (s, 1H), 8.47 (s, 1 H), 8.35 (d, 1H), 8.29 (s, 1H), 7.99 (s, 1H), 7.72 (t, 1H), 7.62 (d, 1H)
4	D4 (R = OMe; X = S)	*δ* 11.63 (s, 1H), 8.34 (s, 1H), 8.11 (s, 1H), 7.94 (s, 1H), 7.85 (d, 1H),7.69 (t, 1H), 6.77 (d, 1H),3.84 (s, 3H)
5	D5 (R = H; X = O)	*δ* 10.53 (s, 1H), 8.56-8.54 (d, 1H), 8.18-8.16 (d, 1H), 7.90 (s, 1H), 7.83-7.80 (t, 1H), 7.35-7.33 (m, 1H),6.66 (s, 1H)
6	D6 (R = Me; X = O)	*δ* 10.46 (s, 1H), 7.93-7.91 (d, 1H), 7.81 (s, 1H), 7.66-7.64 (t, 1H),7.16-7.15 (d, 1H), 6.58 (s, 1H),2.43 (s, 3H)
7	D7 (R = Br; X = O)	*δ* 10.61 (s, 1H), 8.18-8.17 (d, 1H), 7.74 (s, 1H), 7.73-7.72 (t, 1H),7.55-7.54 (d, 1H), 6.68 (s, 1H)
8	D8 (R = OMe; X = O)	*δ* 10.52 (s, 1H), 7.76-7.71 (m, 2H), 7.79 (s, 1H), 7.78-7.77 (d, 1H) 6.62 (s, 1H), 3.87 (s, 3H)

Antibacterial Evaluation

The synthesized thiosemicarbazone and semicarbazone derivatives were evaluated for their antimicrobial activities against *S. aureus* ATCC 25923*, P. aeruginosa* ATCC 9027, *C. glabrata* ATCC 15545 and *A. niger* ATCC 1015. Ciprofloxacin was used as the control drug for antibacterial activity and Itraconazole for antifungal activity.[26, 27] Antimicrobial evaluation of compounds (**D1-D8**) reveals that they show appreciable activities against all the strains. Compound **D5** (R = H; X = O) showed the best activities against all the strains with respect to the other analogs. Overall; the analogs depicted better antibacterial significance compared to their antifungal activities.

Table-4: Antimicrobial Activity Results for the Synthesized Derivatives D1-D8

S. No.	Compound	MIC concentrations (ug/ml)			
		S. aureus ATCC 25923	*P. aeruginosa* ATCC 9027	*C. glabrata* ATCC 15545	*A. niger* ATCC 1015
1	D1	250	500	1500	1500
2	D2	500	500	1500	1000
3	D3	250	250	1000	1500
4	D4	500	250	1000	1500
5	D5	100	100	1000	500
6	D6	500	500	1000	1000
7	D7	750	1000	2000	2000
8	D8	500	500	1000	1000
9	Ciprofloxacin	25	25	---	---
10	Itraconazole	---	---	10	5

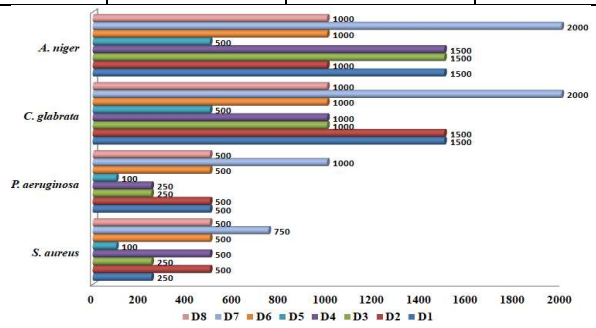


Fig.-3: Antimicrobial Activities of Synthesized Derivatives D1-D8

CONCLUSION

In the presented work; green synthesis of some thiosemicarbazone and semicarbazone derivatives has been reported. An azomethine bond was formed by the chemical interaction of thiosemicarbazide or semicarbazide (**C**) with respective substituted pyridine carboxaldehyde. These synthesized compounds were analyzed based on their FTIR and ^{1}H-NMR spectral studies. The antimicrobial evaluation of these derivatives depicted their biological significance against bacterial and fungal strains.

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CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

All the authors contributed significantly to this manuscript, participated in reviewing/editing, and approved the final draft for publication. The research profile of the authors can be verified from their ORCID IDs, given below:

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