

## Synthesis and Antibacterial Activity of Semicarbazones and Thiosemicarbazones

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Aryl semicarbazones and thiosemicarbazones have been synthesized by the condensation of aromatic carbonyl compounds with semicarbazide and thiosemicarbazide compounds respectively. The compounds have been characterized on the basis of analytical and spectral data. They have been screened for antibacterial activity by agar double dilution method. Some of them have significant activity against *Escherichia coli*, *Staphylococcus aureus* and *Pseudomonas aeruginosa*.

**Key Words:** Semicarbazones and Thiosemicarbazones, Antibacterial activity.

### INTRODUCTION

Semicarbazones and thiosemicarbazones are of much interest due to a wide spectrum of biological activities<sup>1</sup>. Semicarbazides, the raw compounds of semicarbazones, have been observed to be active against *S. aureus*<sup>2</sup>, *C. albicans*<sup>3</sup> and *S. typhi*<sup>4</sup>. Recently Pandeya and coworkers reviewed the bioactivity of semicarbazones; they exhibited aniconvulsant<sup>5,6</sup>, antitubercular<sup>7</sup> activities. Alves *et al.*<sup>8</sup> synthesized *p*-bromophenoxy acetaldehyde thiosemicarbazone found active against vaccinia and polio type L. virus. Thiosemicarbazones have been reported to show anticancer<sup>9</sup>, antiinflammatory<sup>10</sup> and fungicidal<sup>11</sup> activities. Considering the biological potential of semicarbazones and thiosemicarbazones, herein, the synthesis of some of these derivatives is reported and evaluated for antibacterial activities.

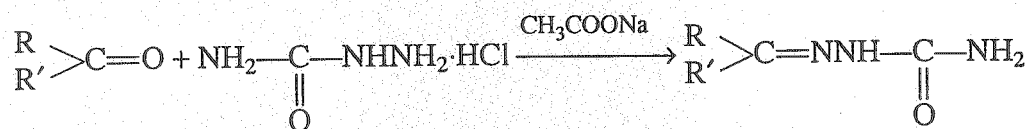
### EXPERIMENTAL

Melting points were determined in open capillary and the literature values were generally in agreement with the observed values. UV and IR spectra were recorded on Jasco Model 7800 and PCFT spectrophotometers respectively. The PMR spectra were recorded on a Jeol FX90Q spectrometer using TMS as an internal standard. PMR, physical and analytical data are given in Table-1.

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N-Semicarbazones were synthesized by the following general equation:



where R = H, CH<sub>3</sub>; R' = Ph, substituted Ph

TABLE-I  
PMR, PHYSICAL AND ANALYTICAL DATA OF SEMICARBAZONES AND THIOSEMICARBAZONES

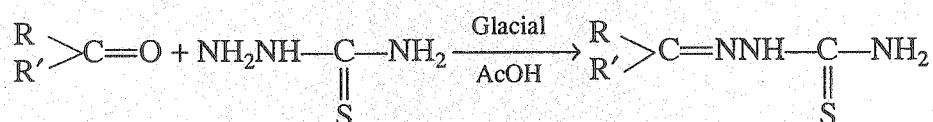
Compd. No.	R	R'	m.f. (m.p., °C)	PMR (CDCl <sub>3</sub> /DMSO-d <sub>6</sub> , δ)	Elemental analysis, Found/Calcd. (%)	
					C	N
I	CH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub>	C <sub>9</sub> H <sub>11</sub> ON <sub>3</sub> (215)	9.8 (bs, 1H, NH) 5.9 (s, 2H, CONH <sub>2</sub> ) 2.30 (s, 3H, CH <sub>3</sub> )	60.77 (60.98)	23.89 (23.72)
II	CH <sub>3</sub>	<i>m</i> -C <sub>6</sub> H <sub>4</sub> NH <sub>2</sub>	C <sub>6</sub> H <sub>12</sub> ON <sub>4</sub> (203)	9.8 (bs, 1H, NH) 3.5 (s, 2H, ArNH <sub>2</sub> ) 2.30 (s, 3H, CH <sub>3</sub> )	56.05 (56.21)	29.01 (29.16)
III	CH <sub>3</sub>	<i>p</i> -C <sub>6</sub> H <sub>4</sub> NH <sub>2</sub>	C <sub>9</sub> H <sub>12</sub> ON <sub>4</sub> (276)	9.7 (bs, 1H, NH) 7.5 (d, 2H, <i>o</i> - to ArNH <sub>2</sub> ) 5.85 (s, 2H, CONH <sub>2</sub> )	56.32 (56.21)	29.29 (29.16)
IV	CH <sub>3</sub>	<i>p</i> -C <sub>6</sub> H <sub>4</sub> Cl	C <sub>9</sub> H <sub>10</sub> ON <sub>3</sub> Cl (205)	7.9 (s, 2H, <i>o</i> - to aromatic group) 7.8 (d, 2H, <i>o</i> - to aromatic Cl group) 2.20 (s, 3H, CH <sub>3</sub> )	50.84 (51.05)	20.14 (19.86)
V	H	<i>o</i> -C <sub>6</sub> H <sub>4</sub> OH	C <sub>8</sub> H <sub>9</sub> O <sub>2</sub> N <sub>3</sub> (225)	9.8 (bs, 1H, NH) 5.9 (s, 2H, CONH <sub>2</sub> ) 2.30 (s, Ar-C-H)	53.86 (53.60)	23.19 (23.46)
VI	H	C <sub>6</sub> H <sub>5</sub>	C <sub>15</sub> H <sub>12</sub> O <sub>3</sub> N <sub>4</sub> (115)	9.7 (bs, 1H, NH) 7.4 (d, 2H, meta to aromatic NO <sub>2</sub> group) 2.30 (s, Ar-C-H)	58.91 (59.13)	19.79 (19.71)
VII	CH <sub>3</sub>	<i>p</i> -C <sub>6</sub> H <sub>4</sub> Cl	C <sub>9</sub> H <sub>10</sub> N <sub>3</sub> S (86)	9.8 (bs, 1H, NH) 7.9 (d, 2H, <i>o</i> - to aromatic Cl group) 2.20 (s, 3H, CH <sub>3</sub> )	47.27 (47.45)	18.20 (18.46)
VIII	CH <sub>3</sub>	<i>p</i> -C <sub>6</sub> H <sub>4</sub> NH <sub>2</sub>	C <sub>9</sub> H <sub>12</sub> N <sub>4</sub> S (180)	7.6 (d, 2H, <i>o</i> - to aromatic NH <sub>2</sub> ) 6.7 (s, 2H, CSNH <sub>2</sub> ) 2.35 (s, 3H, CH <sub>3</sub> )	51.68 (51.87)	27.11 (26.91)

#### Preparation of acetophenone semicarbazone<sup>12</sup>

A solution of semicarbazide hydrochloride (0.01 mol in 25 mL water) was added slowly into the solution of acetophenone (0.01 mL in 15 mL of ethanol) containing 2g of sodium acetate with constant stirring. The reaction mixture was

refluxed for 1/2 h and then cooled for crystallization. Similarly other semicarbazones were prepared.

N-Thiosemicarbazones were synthesized by the following equation:

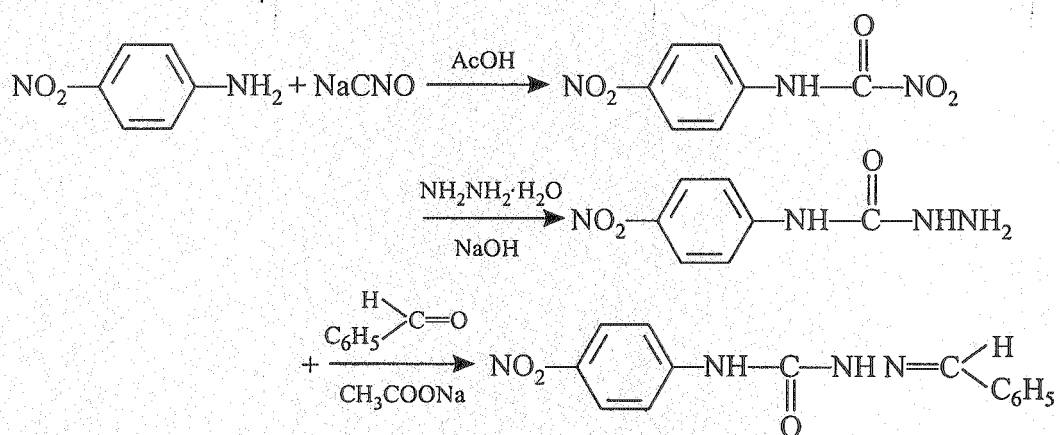


where R = H, CH<sub>3</sub>; R' = Ph, substituted Ph

### Preparation of Acetophenone thiosemicarbazone<sup>12</sup>

A solution of thiosemicarbazide (0.01 mol in 10 mL ethanol) was added slowly into the solution of acetophenone (0.01 mol in 15 mL ethanol) containing 2 mL of glacial acetic acid with constant stirring. The reaction mixture was refluxed for half hour and then cooled for crystallization. Similarly other N-thiosemicarbazones were prepared.

### Preparation of 4-(4'-nitrophenyl) benzaldehyde semicarbazone



The reaction of substituted aniline with sodium cyanate in presence of acetic acid gave substituted phenyl urea. This on reaction with hydrazine hydrate affords 4-(4'-substituted phenyl) semicarbazide, which on usual reaction with benzaldehyde gave 4-(4'-nitro phenyl) benzaldehyde(II) semicarbazone.

**Agar double dilution method<sup>13</sup>:** Graded amount of synthesized compounds were incorporated into measured amount of MH agar media. The media was subsequently inoculated and incorporated. Stock solution of test compounds were prepared in dimethyl formamide or dimethyl sulphoxide with a concentration of 100 mg/mL. The stock solution was then serially double diluted and used for study, 1 mL of this solution was added into each sterilized petri-dish containing graded amount of MH agar media (previously cooled to 60°C). Under aseptic conditions the dilute bacterial suspension was inoculated as spots using sterilized swabs. After inoculation, the plates were incubated at 37°C for 24 h. The MIC, the lowest concentration of the test drug that inhibited the growth of bacteria on agar plate was noted. The antibacterial data of test compounds are given in Table-2.

IR (KBr,  $\text{cm}^{-1}$ ) of compound I: 3470  $\nu(\text{N—H})$ , 3320  $\nu_{\text{asym}}(\text{NH})$ , 3190  $\nu_{\text{sym}}(\text{NH})$ , 1740  $\nu(\text{C=O})$ , 1450  $\nu(\text{C}\equiv\text{C ring})$ , 1380  $\delta(\text{C—H})$ , 750  $\delta(\text{Ar—H})$ .

IR (KBr,  $\text{cm}^{-1}$ ) of compound II: 3470  $\nu(\text{N—H})$ , 3330  $\nu_{\text{asym}}(\text{N—H})$ , 3200  $\nu_{\text{sym}}(\text{N—H})$ , 1590  $\delta(\text{N—H})$ , 1710  $\nu(\text{C=O})$ , 1610  $\nu(\text{C=N})$ , 775  $\delta(\text{Ar—H})$ .

IR (KBr,  $\text{cm}^{-1}$ ) of compound III: 3335  $\nu_{\text{asym}}(\text{N—H})$ , 3180  $\nu_{\text{sym}}(\text{NH})$ , 1720  $\nu(\text{C=O})$ , 1600  $\delta(\text{N—H})$ , 1400  $\delta(\text{C—H})$ , 780  $\delta(\text{Ar—H})$ .

IR (KBr,  $\text{cm}^{-1}$ ) of compound IV: 3350  $\nu_{\text{asym}}(\text{NH})$ , 3175  $\nu_{\text{sym}}(\text{NH})$ , 1710  $\nu(\text{C=O})$ , 1620  $\nu(\text{C=N})$ , 1490  $\nu(\text{C}\equiv\text{C})$ , 1380  $\delta(\text{C—H})$ , 780  $\delta(\text{Ar—H})$ .

IR (KBr,  $\text{cm}^{-1}$ ) of compound V: 3500  $\nu(\text{O—H})$ , 3480  $\nu(\text{N—H})$ , 3340  $\nu_{\text{asym}}(\text{N—H})$ , 3200  $\nu_{\text{sym}}(\text{NH})$ , 3080  $\nu(\text{Ar—C—H})$ , 1740  $\nu(\text{C=O})$ , 1200  $\nu(\text{C—O})$ , 750  $\delta(\text{Ar—H})$ .

IR (KBr,  $\text{cm}^{-1}$ ) of compound VI: 3335  $\nu_{\text{asym}}(\text{N—H})$ , 3150  $\nu_{\text{sym}}(\text{N—H})$ , 1590  $\delta(\text{N—H})$ , 1550  $\nu_{\text{asym}}(\text{N}\equiv\text{O})$ , 1460  $\nu(\text{C}\equiv\text{C ring})$ , 1340  $\nu_{\text{sym}}(\text{N}\equiv\text{O})$ , 760  $\delta(\text{Ar—H})$ .

IR (KBr,  $\text{cm}^{-1}$ ) of compound VII: 3450  $\nu(\text{N—H})$ , 3350  $\nu_{\text{asym}}(\text{N—H})$ , 3180  $\nu_{\text{sym}}(\text{N—H})$ , 1450  $\nu(\text{C}\equiv\text{C ring})$ , 1390  $\delta(\text{C—H})$ , 1280  $\nu(\text{N—CS—N})$ , 1210  $\nu(\text{C=S})$ , 790  $\delta(\text{Ar—H})$ .

IR (KBr,  $\text{cm}^{-1}$ ) of compound VIII: 3320  $\nu_{\text{asym}}(\text{N—H})$ , 3160  $\nu_{\text{sym}}(\text{N—H})$ , 1600  $\delta(\text{N—H})$ , 1400  $\delta(\text{C—H})$ , 1280  $\nu(\text{N—CS—N})$ , 1190  $\nu(\text{C=S})$ , 750  $\delta(\text{Ar—H})$ .

TABLE-2  
ANTIBACTERIAL ACTIVITY DATA OF SEMICARBAZONES AND  
THIOSEMICARBAZONES

S. No.	Compounds	Antibacterial activity		
		<i>E. coli</i>	<i>S. aureus</i>	<i>P. aeruginosa</i>
I	Acetophenone semicarbazone	19.53	625	2500
II	3-Amino acetophenone semicarbazone	78.12	19.53	1250
III	4-Amino acetophenone semicarbazone	156.25	9.76	2500
IV	4-Chloro acetophenone semicarbazone	19.53	9.76	19.53
V	2-Hydroxy benzaldehyde semicarbazone	1250	19.53	2500
VI	4-(4'-Nitro phenyl) benzaldehyde semicarbazone	19.53	9.76	9.76
VII	4-Chloro acetophenone thiosemicarbazone	19.50	9.80	9.80
VIII	4-Amino acetophenone thiosemicarbazone	312.50	78.10	39.10
IX	Trimethoprim	19.53	> 5000	5000

## RESULTS AND DISCUSSION

The compounds I–VIII have been characterised on the basis of satisfactory analytical and spectral data (Table-I). The UV spectra of the compounds showed absorption maxima of 271–325 nm. The IR spectra exhibited bands at  $1590 \pm 10$ ,  $1620 \pm 10$ , 1710–1740 and 3150–3350  $\text{cm}^{-1}$  which have been assigned due to N—H bending, C=N stretching, C=O stretching and N—H stretching respectively. One more IR band at 1190–1210  $\text{cm}^{-1}$  showed absorption due to C=S stretching. The N—H proton appeared as a broad singlet in offset ( $\delta$ , 9.7–9.8) region of PMR spectrum and was D<sub>2</sub>O exchangeable.

Out of the eight compounds, synthesized in the series, six compounds showed good antibacterial activity against *Staphylococcus aureus* while 4-amino, 4-chloro substituted acetophenone semicarbazones, 4-4'-nitrophenyl] benzaldehyde semicarbazone and 4-chloro acetophenone thiosemicarbazone showed MIC values at 9.76–9.8 µg/mL in the same test. The compounds IV, VI and VII exhibited antibacterial activity against *E. coli* at MIC values 19.5 µg/mL. The compounds IV, VI and VII exhibited antibacterial activity against *Pseudomonas aeruginosa* at MIC values 19.53, 9.76 and 9.8 µg/mL respectively. Compounds I, IV, VI and VII have same potency as standard drug trimethoprim against *E. coli*, but highly potent against other species than trimethoprim. Among all the synthesized compounds, VI and VII were considered best and found active against all the three types of bacteria tested.

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