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Synthesis, characterization and antifungal activity of thiosemicarbazides and thiosemicarbazones

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Abstract : Thiosemicarbazides (1, 2 and 3) were synthesized by reacting aniline with carbon disulfide followed by addition of hydrazine or phenyl hydrazine or 2,4-dinitrophenyl hydrazine respectively. Different substituted benzaldehydes were condensed with 4-phenylthiosemicarbazide to afford respective thiosemicarbazones (4-15). Antifungal activity of the synthesized compounds exhibited that thiosemicarbazides were more effective than thiosemicarbazones against *Macrophomina phaseolina* and *Fusarium moniliforme*. All the synthesized compounds registered less activity than bavistin against both fungi at all concentrations.

Keywords : Thiosemicarbazides, hydrazine derivatives, thiosemicarbazones, antifungal activity, ED_{50}.

Introduction

Heteroatoms have constituted one of the largest areas of research in organic chemistry. It deals with the study of organic compounds containing at least one hetero atom, such as sulfur, oxygen or nitrogen. The presence of heteroatom results in significant changes in the molecular structure due to the availability of unshared pair of electrons and the difference in electronegativity between heteroatoms and carbon.

Among sulfur and nitrogen containing organic compounds, thiosemicarbazides and thiosemicarbazones have potential biological activities. Thiosemicarbazide is the simplest hydrazine derivative of thiocarbamic acid. The addition of hydrazine to various isothiocyanates is one of the convenient reaction for the synthesis of substituted thiosemicarbazides, which are of great interest not only in terms of a possible study of biological activity, but also as starting compound for the synthesis. The chemical behaviour of thiosemicarbazide is similar to its analogue semicarbazide, however is of greater chemical versatility of thione group as compared to keto group and is responsible for more varied behaviour of thiosemicarbazide. Thiosemicarbazone is formed when ammonia related compound (nucleophiles) such as thiosemicarbazide is added to the carbonyl group (C=O).

A better understanding of their biological activity can be derived from their oxidation mechanisms. It is widely accepted that the prerequisite for thio compounds to express their physiological effects is through S-oxygenation[1]. These compounds possess potentially beneficial biological activity, such as antifungal[2], antibacterial[3], antiviral[4], antimalarial[5] and antitumor activity[6] owing to their ability to diffuse through the semipermeable membrane of cell lines[7–9].

Throughout history, the plant diseases have made a significant impact on the food supply and human welfare[10]. Although, a number of fungicides have been synthesized by the scientists to control such diseases, but due to their cost, non-availability and environment sustainability, there is still a severe need to synthesize new and easily available fungicides. In the present investigation, we have synthesised thiosemicarbazides and thiosemicarbazone derivatives to evaluate their antifungal potential.

Results and discussion

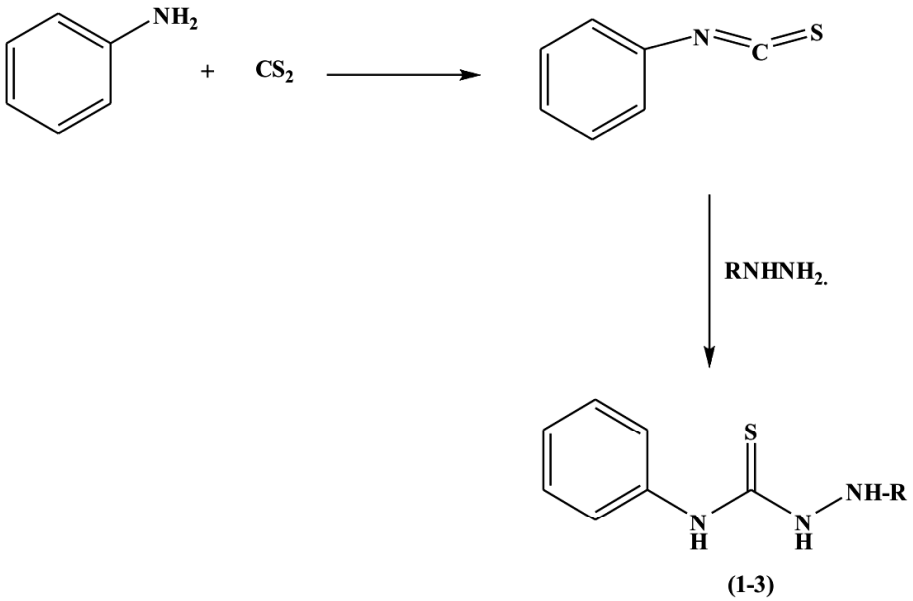
Three thiosemicarbazides (**1-3**) were synthesized by using aniline, carbon disulphide and hydrazine derivatives as depicted in Fig. 1. However 4-phenyl thiosemicarbazide (**1**) was reported in literature[11] but its preparation was done by different method. Thiosemicarbazones (**4-15**) were prepared by adding substituted aldehyde to the solution of 4-phenyl thiosemicarbazide as shown in Fig. 2. Physical data (yield, melting point, R_f, state and colour) of compounds were determined (Table 1). All compounds were characterized by their spectral data (IR and ^{1}H NMR).

IR data :

IR spectra of the thiosemicarbazides showed the formation of C=S bond by observing band at 1286–1306 cm^{-1}. In thiosemicarbazones, stretching band corresponding to C=N appeared at 1600–1612 cm^{-1}. Broad peaks due to -NH- stretching and -OH- stretching were observed at 3364–3534 cm^{-1} and 3365–3450 cm^{-1} respectively. Therefore formation of compounds (**1-15**) was confirmed.

^{1}H NMR data :

In ^{1}H NMR spectra for thiosemicarbazides (**1-3**), -NH- protons namely **a**, **b** and **c** were present in three different types of environments (Fig. 3). The protons at position **a** exhibited singlet from 8.87–9.71 ppm, whereas singlet for protons on position **b** were observed in the range of 8.14–9.63 ppm. In case of protons present on **c**, two different values of -NH- were recorded, for compound (**1**) broad peak as singlet for most shielded protons at 4.7 was observed, whereas compounds (**2**) and (**3**) ex-



(1-3)

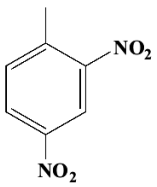
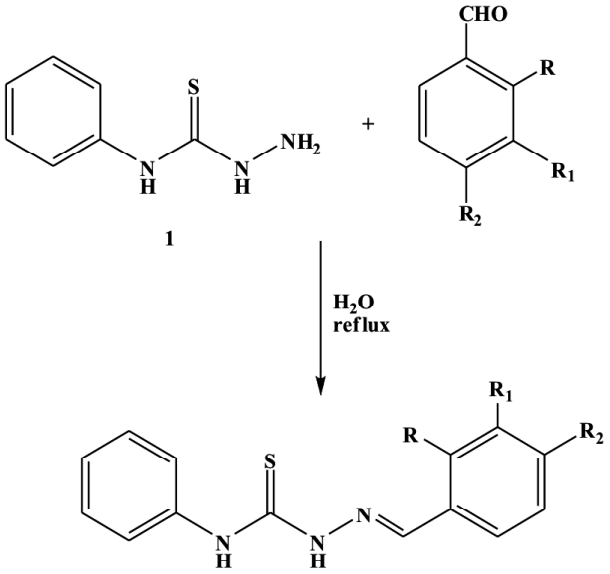
Compd.	R
1	-H
2	-C_6H_5
3	

Fig. 1



4	R=H, R_1=H, R_2=H
5	R=H, R_1=Cl, R_2=H
6	R=H, R_1=H, R_2=Cl
7	R=NO_2, R_1=H, R_2=H
8	R=H, R_1=NO_2, R_2=H
9	R=H, R_1=H, R_2=NO_2
10	R=H, R_1=OCH_3, R_2=H
11	R=H, R_1=H, R_2= OCH_3
12	R=OH, R_1=H, R_2=H
13	R=H, R_1=H, R_2=OH
14	R=H, R_1=OCH_3, R_2=OH
15	R=OCH_3, R_1=OCH_3, R_2=OH

Fig. 2

hibited peaks at 9.63 and 9.71 ppm respectively. In thiosemicarbazones (**4-15**), the most deshielded protons at position **a′** and **b′** (Fig. 4), appeared as a singlet between 9.31–12.05 and 9.09–10.91 ppm respectively. The presence of singlet in the range 7.80–8.53 ppm due to azomethenic proton present at position **d** (Fig. 4). Multiplet due to overlapped protons in the range of 6.81–7.98 ppm was observed for all aromatic protons.

Antifungal activity :

Synthesized compounds were evaluated for their *in vitro* antifungal activity against *F. moniliforme* and *M. phaseolina*. The percent inhibition against *F. moniliforme* is collated in Table 2 and Table 3 and of *M. phaseolina* in

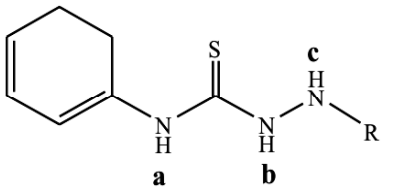


Fig. 3

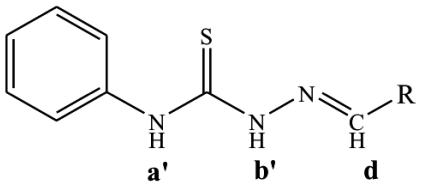


Fig. 4

Table 5 and Table 6. Whereas ED_{50} values for *F. moniliforme* and *M. phaseolina* are given in Table 4 and Table 7 respectively. Bavistin was used as standard against both the test fungi. Thiosemicarbazide **1** had the most interesting antifungal activity among all synthesized compounds. Substitution on the aromatic ring influenced antifungal activity. Thus, compounds **4** and **15** having no substitution and tri substitution (two methoxy groups at 3rd and 5th position and hydroxy at 4th position) respectively on the benzene nucleus had the lowest ED_{50}. However none of the compounds showed better control than standard bavistin against both the tested fungi (Figs. 5 and 6).

Experimental

General :

All the recorded melting points were determined in open capillaries and are uncorrected. Structures of compounds were confirmed by routine spectrometric analysis. IR and ^{1}H NMR spectra were got scanned from Sophisticated Analytical Instrumentation Facility (SAIF), Central Instrument Laboratory (CIL), Panjab University, Chandigarh. The IR spectra of compounds were recorded using KBr discs on Perkin-Elmer FTIR spectrophotometer. ^{1}H NMR spectra were recorded on a Bruker Avance II 400 MHz instrument using TMS as an internal standard. The chemical shifts were expressed in δ (ppm) val-

Table 1. Physical parameters of different thiosemicarbazides and thiosemicarbazones

Compd.	Molecular formula	Color	Yield (%)	Melting point (°C)	*R_f[a]	Elemental analysis (%) : Found (Calcd.)			
						C	H	N	S
1	$C_7H_9N_3S$	White	77	138–139	0.54	50.27 (50.29)	5.43 (5.42)	25.12 (25.14)	19.19 (19.16)
2	$C_{13}H_{13}N_3S$	White	82	131–132	0.53	64.18 (64.19)	5.35 (5.34)	17.29 (17.28)	13.15 (13.16)
3	$C_{13}H_{11}N_5O_4S$	Light brown	66	98–99	0.53	46.85 (46.84)	3.31 (3.30)	21.01 (21.02)	9.54 (9.60)
4	$C_{14}H_{13}N_3S$	White	89	193–194	0.54	65.87 (65.86)	5.07 (5.09)	16.49 (16.47)	12.51 (12.54)
5	$C_{14}H_{12}ClN_3S$	Off-white	91	194–195	0.53	58.01 (58.03)	4.12 (4.14)	14.53 (14.50)	11.01 (11.05)
6	$C_{14}H_{12}ClN_3S$	White	88	199–200	0.55	58.02 (58.03)	4.14 (4.14)	14.52 (14.50)	11.03 (11.05)
7	$C_{14}H_{13}N_4O_2S$	Yellow	85	189–190	0.52	55.83 (55.81)	4.30 (4.31)	18.62 (18.60)	10.59 (10.63)
8	$C_{14}H_{13}N_4O_2S$	Orange	89	180–181	0.54	55.82 (55.81)	4.32 (4.31)	18.62 (18.60)	10.61 (10.63)
9	$C_{14}H_{13}N_4O_2S$	Orange	87	183–184	0.53	55.80 (55.81)	4.33 (4.31)	18.61 (18.60)	10.64 (10.63)
10	$C_{15}H_{15}N_3OS$	Off-white	92	154–155	0.54	63.12 (63.15)	5.28 (5.26)	14.72 (14.73)	11.21 (11.22)
11	$C_{15}H_{15}N_3OS$	White	88	178–179	0.53	63.16 (63.15)	5.23 (5.26)	14.71 (14.73)	11.20 (11.22)
12	$C_{14}H_{13}N_3OS$	Pale yellow	86	175–176	0.53	61.98 (61.99)	4.80 (4.79)	15.46 (15.49)	11.81 (11.80)
13	$C_{14}H_{13}N_3OS$	Pale yellow	91	170–171	0.54	61.97 (61.99)	4.77 (4.79)	15.48 (15.49)	11.78 (11.80)
14	$C_{15}H_{15}N_3O_2S$	White	85	176–177	0.53	59.78 (59.80)	4.99 (4.98)	13.93 (13.95)	10.64 (10.63)
15	$C_{16}H_{17}N_3O_3S$	Yellow	89	140–141	0.56	57.98 (58.00)	5.13 (5.13)	12.65 (12.68)	9.71 (9.68)

[a]Mobile phase for thin layer chromatography is dichloromethane.

All compounds were obtained in solid form.

Table 2. Percent inhibition (*I*) by different thiosemicarbazides against *Fusarium moniliforme* at different concentrations (μg/mL)

Compd.	Percent inhibition (*I*)				
	50	100	250	500	1000
1	34.42	48.23	67.22	73.78	78.14
2	32.78	47.54	62.30	72.22	77.04
3	26.22	37.70	45.90	49.09	62.3
Bavistin	100	100	100	100	100
CD (p = 0.05)	NS	0.081	NS	0.007	0.04

ues and the abbreviations 's' and 'm' stands for singlet and multiplet respectively. C, H, N and S analysis and Mass spectra were done in Punjab Agricultural University, Ludhiana. All the compounds gave satisfactory C, H, N and S analysis that was recorded on Vario EL III Elementor CHNS analyser. Mass spectra were recorded in terms of mass to charge ratio (*m/z*) on waters LCMS Quattro MicroTM API.

Table 3. Percent inhibition (*I*) by different thiosemicarbazones against *Fusarium moniliforme* at different concentrations (µg/mL)

Compd.	Percent inhibition (*I*)				
	50	100	250	500	1000
4	6.55	9.83	13.11	16.39	27.86
5	1.63	18.03	34.42	37.70	40.98
6	16.37	19.67	22.95	34.42	54.09
7	14.75	24.60	36.06	52.45	57.37
8	26.23	31.47	36.06	45.18	50.82
9	18.03	29.51	39.34	55.37	60.65
10	27.86	40.98	50.80	57.73	60.65
11	34.42	47.54	55.73	59.01	62.29
12	18.03	21.31	29.5	40.98	59.01
13	31.14	44.20	50.81	55.73	59.02
14	0	9.83	13.11	16.39	27.86
15	24.59	29.51	26.06	47.54	50.81
Bavistin	100	100	100	100	100
CD (p = 0.05)	NS	0.015	0.031	NS	0.075

Table 4. ED_{50} of different thiosemicarbazides and thiosemicarbazones against *Fusarium moniliforme*

Compd.	ED_{50} (µg/mL)
1	117
2	124
3	510
4	*a*
5	*a*
6	900
7	700
8	950
9	400
10	250
11	175
12	780
13	255
14	*a*
15	990
Bavistin	8

[a]Represents ED_{50} more than 1000 µg/mL.

General method for synthesis of thiosemicarbazides **(1-3)** :

In a 150 mL round bottommed flask, solution of aniline (0.01 mole) in ammonia (2 mL) was taken. Carbon disulphide (0.01 mole) was added slowly along with ethanol and stirred vigorously for 2 h. Then the solution of sodium carbonate (0.01 mole) and chloroacetic acid (0.01 mole) in distilled water was added to it followed by addition of different hydrazine derivatives (0.01 mole), reaction mixture was refluxed for 3 h on water bath. The resulting solid product was obtained on cooling and pure product was obtained after recrystallization.

Table 5. Percent inhibition (*I*) by different thiosemicarbazides against *Macrophomina phaseolina* at different concentrations (µg/mL)

Compd.	Percent inhibition (*I*)				
	50	100	250	500	1000
1	35.59	46.53	67.21	75.40	85.56
2	22.95	27.86	50.91	65.49	80.24
3	22.95	27.86	50.81	54.09	57.37
Bavistin	81.96	83.60	85.25	100	100
CD (p = 0.05)	NS	NS	NS	0.007	0.08

Table 6. Percent inhibition (*I*) by different thiosemicarbazones against *Macrophomina phaseolina* at different concentrations (µg/mL)

Compd.	Percent inhibition (*I*)				
	50	100	250	500	1000
4	14.75	19.67	22.95	26.22	40.81
5	31.14	44.2	50.81	55.73	59.01
6	27.86	40.98	47.81	58.73	62.29
7	26.22	39.34	45.9	54.09	63.49
8	31.14	42.26	50.08	55.73	59.01
9	24.59	37.7	50.1	54.09	59.02
10	14.79	19.67	26.22	34.42	55.73
11	18.03	21.31	27.86	45.9	60.65
12	50	59.01	62.29	27.21	72.13
13	21.31	31.14	40.98	55.73	63.93
14	26.22	29.5	36.06	47.54	50.8
15	9.83	13.11	18.03	19.67	22.92
Bavistin	81.96	83.60	85.25	100	100
CD (p = 0.05)	0.026	NS	0.018	NS	0.086

General method for synthesis of thiosemicarbazones **(4-15)** :

Equimolar amounts of substituted benzaldehyde (0.01 mole) was added to the aqueous solution of 4-phenyl thiosemicarbazide (**1**). Reaction mixture was refluxed for 4 h. The progress of reaction was monitored by thin layer chromatography (TLC) from time to time. After completion of reaction, the contents were kept at room temperature and solid obtained was filtered. The pure product was obtained after recrystallization from ethanol.

Table 7. ED_{50} of different thiosemicarbazides and thiosemicarbazones against *Macrophomina phaseolina*

Compd.	ED_{50} (μg/mL)
1	155
2	240
3	255
4	*a*
5	260
6	303
7	362
8	253
9	263
10	905
11	764
12	175
13	400
14	*a*
15	*a*
Bavistin	10

[a]Represents ED_{50} more than 1000 μg/mL.

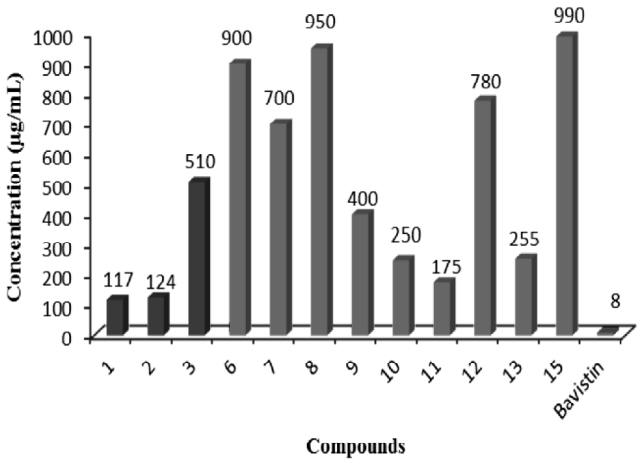


Fig. 5. Antifungal activity of thiosemicarbazides (**1-3**) and thiosemicarbazones (**4-15**) in terms of ED_{50} values against *Fusarium monaliforme*.

Antifungal activity :

A culture of the test fungi was grown on Potato Dextrose Agar (PDA) medium for certain period (generally 7 days) at ambient temperature (25 ± 1 °C) for growth. Stock solution (1000 μg/mL) of test compounds was prepared in dimethyl sulphoxide and further dilutions were done (500, 250, 100, 50 μg/mL) and stored at 4 °C for further use. After solidification, small disc (0.5 cm dia.) of the fungus culture was cut with a sterile cork borer

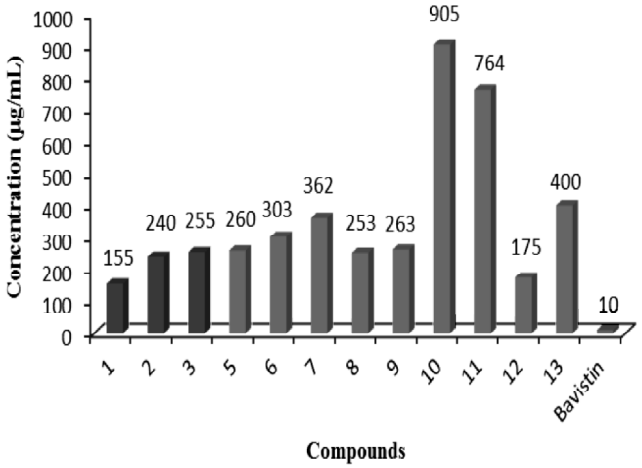


Fig. 6. Antifungal activity of thiosemicarbazides (**1-3**) and thiosemicarbazones (**4-15**) in terms of ED_{50} values against *Macrophomina phaseolina*.

and transferred aseptically upside down at the centre of Petri dish. Petri plates were incubated in BOD incubator at 25 ± 1 °C. Two fungi viz. *Fusarium moniliforme* and *Macrophomina phaseolina* were selected for bioassay. Growth of fungal colony was measured after every 24 h till the fungus in the control plates completely occupied it. Three replications were maintained for each treatment. The percent growth inhibition over control was calculated using the formula

$$I = \frac{100(C - T)}{C}$$

where, I = inhibition percentage, C = growth in control, T = growth in treatment.

4-Phenylthiosemicarbazide (**1**) : Yield : 77%; m.p. 138–139 °C; IR (KBr, cm^{-1}) : 3531 (ν_{as} N-H-str.), 3302 (ν_s N-H str.), 3060 (Ar C-H str.), 1639, 1596, 1527, 1497 (Ar C=C str.), 1391 (C-N str.), 1286 (C=S str.), 775 (N-H bending) and 737 (Ar C-H bending); ^{1}H NMR (400 MHz $CDCl_3$, δ, ppm) : 9.71 (1H, s, N**H at a**), 9.05 (1H, s, N**H at b**), 7.07–7.65 (5H, m, Ar-**H**) and 4.77 (2H, bs, NH_2 **at c**); LC-MS (EI, 70 eV), *m/z* 167.05 (M^+).

1,4-Diphenylthiosemicarbazide (**2**) : Yield : 82%; m.p. 131–132 °C; IR (KBr, cm^{-1}) : 3534 (N-H str.), 3045 (Ar C-H str.), 1634, 1598, 1532, 1493 (Ar C=C str.), 1397 (C-N str.), 1296 (C=S str.), 772 (N-H bending) and 735 (Ar C-H bending); ^{1}H NMR (400 MHz DMSO, δ, ppm) :

9.66 (1H, s, N**H at a**), 9.63 (1H, s, N**H at c**), 8.14 (1H, s, N**H at b**) and 7.97–6.81 (10H, m, Ar-**H**).

1-(2,4-Dinitrophenyl)-4-phenylthiosemicarbazide (**3**) : Yield : 66%; m.p. 98–99 °C; IR (KBr, cm^{-1}) : 3484 (N-H str.), 3055 (Ar C-H str.), 1624, 1591, 1535, 1496 (Ar C=C str.), 1540 (ν_{as} NO_2 str.), 1370 (ν_s NO_2 str.), 1399 (C-N str.), 1301 (C=S str.), 769 (N-H bending) and 738 (Ar C-H bending); ^{1}H NMR (400 MHz DMSO, δ, ppm) : 9.71 (1H, s, N**H at c**), 9.63 (1H, s, N**H at b**), 8.87 (1H, s, N**H at c**) and 7.09–7.63 (8H, m, Ar-**H**); LC-MS (EI, 70 eV), *m/z* 967.58 (M^+).

1-Benzylidene-4-phenylthiosemicarbazide (**4**) : Yield : 89%; m.p. 193–194 °C; IR (KBr, cm^{-1}) : 3364 (N-H str.), 1635, 1580, 1534, 1495 (Ar C=C str.), 1600 (C=N str.), 1396 (C-N str.), 1295 (C=S str.), 743 (NH bending), 738 (Ar C-H bending) and 696 (Ar C-C bending); ^{1}H NMR (400 MHz DMSO, δ, ppm) : 11.65 (1H, s, N**H at a′**), 10.11 (1H, s, N**H at b′**) , 8.48 (1H, s, C**H**=N **at d**) and 7.07–7.98 (10H, m, Ar-**H**).

1-(2-Chlorobenzylidene)-4-phenylthiosemicarbazide (**5**) : Yield : 91%; m.p. 194–195 °C; IR (KBr, cm^{-1}) : 3364 (N-H str.), 1635, 1580, 1534, 1495 (Ar C=C str.), 1600 (C=N str.), 1396 (C-N str.), 1295 (C=S str.), 743 (NH bending) and 738 (Ar C-H bending); ^{1}H NMR (400 MHz DMSO, δ, ppm) : 11.85 (1H, s, N**H at a′**), 10.09 (1H, s, N**H at b′**), 8.23 (1H, s, C**H**=N **at d**) and 7.13–7.93 (9H, m, Ar-**H**).

1-(4-Chlorobenzylidene)-4-phenylthiosemicarbazide (**6**) : Yield : 88%; m.p. 199–200 °C; IR (KBr, cm^{-1}) : 3365 (N-H str.), 3044 (Ar C-H str.), 1630, 1550, 1540, 1495 (Ar C=C str.), 1609 (C=N str.), 1397 (C-N str.), 1290 (C=S str.), 738 (C-Cl str.), 767 (NH bending) and 746 (Ar C-H bending); ^{1}H NMR (400 MHz DMSO, δ, ppm) : 11.47 (1H, s, N**H at a′**), 10.14 (1H, s, N**H at b′**), 8.11 (1H, s, C**H**=N **at d**) and 7.20–7.90 (9H, m, Ar-**H**); LC-MS (EI, 70 eV), *m/z* 289.04 (M^+).

1-(2-Nitrobenzylidene)-4-phenylthiosemicarbazide (**7**) : Yield : 85%; m.p. 189–190 °C; IR (KBr, cm^{-1}) : 3369 (N-H str.), 3041 (Ar C-H str.), 1633, 1591, 1531, 1499 (Ar C=C str.), 1606 (C=N str.), 1545 (ν_{as} NO_2 str.), 1370 (ν_s NO_2 str.), 1395 (C-N str.), 1301 (C=S str.), 774 (N-H bending) and 747 (Ar C-H bending); ^{1}H NMR (400 MHz DMSO, δ, ppm) : 12.05 (1H, s, N**H at a′**), 10.24 (1H, s, N**H at b′**), 8.21 (1H, s, C**H**=N **at d**) and 7.19–7.80 (9H, m, Ar-**H**).

1-(3-Nitrobenzylidene)-4-phenylthiosemicarbazide (**8**) : Yield : 89%; m.p. 180–181 °C; IR (KBr, cm^{-1}) : 3370 (N-H str.), 3031 (Ar C-H str.), 1635, 1596, 1535, 1497 (Ar C=C str.), 1605 (C=N str.), 1547 (ν_{as} NO_2 str.), 1375 (ν_s NO_2 str.), 1390 (C-N str.), 1306 (C=S str.), 776 (N-H bending) and 746 (Ar C-H bending); ^{1}H NMR (400 MHz DMSO, δ, ppm) : 11.85 (1H, s, N**H at a′**), 10.09 (1H, s, N**H at b′**), 8.22 (1H, s, C**H**=N **at d**) and 7.17–7.92 (9H, m, Ar-**H**); LC-MS (EI, 70 eV), *m/z* 300.07 (M^+).

1-(4-Nitrobenzylidene)-4-phenylthiosemicarbazide (**9**) : Yield : 87%; m.p. 183–184 °C; IR (KBr, cm^{-1}) : 3368 (N-H str.), 3040 (Ar C-H str.), 1632, 1590, 1530, 1498 (Ar C=C str.), 1605 (C=N str.), 1547 (ν_{as} NO_2 str.), 1365 (ν_s NO_2 str.), 1394 (C-N str.), 1300 (C=S str.), 779 (N-H bending) and 735 (Ar C-H bending); ^{1}H NMR (400 MHz DMSO, δ, ppm) : 11.95 (1H, s, N**H at a′**), 10.91 (1H, s, N**H at b′**), 8.34 (1H, s, C**H**=N **at d**) and 7.27–7.95 (9H, m, Ar-**H**).

1-(3-Methoxybenzylidene)-4-phenylthiosemicarbazide (**10**) : Yield : 92%; m.p. 154–155 °C; IR (KBr, cm^{-1}) : 3364 (N-H str.), 3035 (Ar C-H str.), 1635, 1599, 1534, 1495 (Ar C=C str.), 1600 (C=N str.), 1396 (C-N str.), 1295 (C=S str.), 1073 (C-O str.), 767 (N-H bending) and 738 (Ar C-H bending); ^{1}H NMR (400 MHz $CDCl_3$, δ, ppm) : 9.42 (1H, s, N**H at a′**), 9.09 (1H, s, N**H at b′**), 8.02 (1H, s, C**H**=N **at d**), 7.18–7.94 (9H, m, Ar-**H**) and 4.11 (3H, s, -OC**H$_3$**); LC-MS (EI, 70 eV), *m/z* 285.09 (M^+).

1-(4-Methoxybenzylidene)-4-phenylthiosemicarbazide (**11**) : Yield : 88%; m.p. 178–179 °C; IR (KBr, cm^{-1}) : 3369 (N-H str.), 3041 (Ar C-H str.), 1633, 1591, 1531, 1499 (Ar C=C str.), 1606 (C=N str.), 1395 (C-N str.), 1301 (C=S str.), 1080 (C-O str.), 773 (N-H bending) and 739 (Ar C-H bending); ^{1}H NMR (400 MHz DMSO, δ, ppm) : 9.31 (1H, s, N**H at a′**), 9.17 (1H, s, N**H at b′**), 7.80 (1H, s, C**H**=N **at d**), 6.93–7.68 (9H, m, Ar-**H**) and 3.86 (3H, s, -OC**H$_3$**).

1-(2-Hydroxybenzylidene)-4-phenylthiosemicarbazide (**12**) : Yield : 86%; m.p. 175–176 °C; IR (KBr, cm^{-1}) : 3450 (N-H str. and OH str.), 3044 (Ar C-H str.), 1630,

1580, 1540, 1498 (Ar C=C str.), 1609 (C=N str.), 1397 (C-N str.), 1290 (C=S str.), 765 (N-H bending) and 739 (Ar C-H bending); ^{1}H NMR (400 MHz $CDCl_3$, δ, ppm) : 11.65 (1H, s, O**H**), 10.85 (1H, s, N**H at a′**), 9.09 (1H, s, N**H at b′**), 8.36 (1H, s, C**H**=N **at d**) and 7.17–7.92 (9H, m, Ar-**H**).

1-(4-Hydroxybenzylidene)-4-phenylthiosemicarbazide (**13**) : Yield : 91%; m.p. 170–171 °C; IR (KBr, cm^{-1}) : 3368 (N-H str. and OH str.), 3040 (Ar C-H str.), 1632, 1590, 1530, 1498 (Ar C=C str.), 1605 (C=N str.), 1394 (C-N str.), 1300 (C=S str.), 767 (N-H bending) and 738 (Ar C-H bending); ^{1}H NMR (400 MHz $CDCl_3$, δ, ppm) : 11.38 (1H, s, O**H**), 9.58 (1H, s, N**H at a′**), 9.33 (1H, s, N**H at b′**), 8.39 (1H, s, C**H**=N **at d**) and 7.07–7.90 (9H, m, Ar-**H**); LC-MS (EI, 70 eV), *m/z* 271.08 (M^+).

1-(4-Hydroxy-3-methoxybenzylidene)-4-phenylthiosemicarbazide (**14**) : Yield : 85%; m.p. 176–177 °C; IR (KBr, cm^{-1}) : 3365 (N-H str. and OH str.), 3036 (Ar C-H-str.), 1639, 1596, 1534, 1496 (Ar C=C str.), 1610 (C=N str.), 1389 (C-N str.), 1299 (C=S str.), 1078 (C-O str.), 768 (N-H bending) and 740 (Ar C-H bending); ^{1}H NMR (400 MHz $CDCl_3$, δ, ppm) : 11.46 (1H, s, O**H**), 10.65 (1H, s, N**H at a′**), 9.19 (1H, s, N**H at b′**), 8.43 (1H, s, C**H**=N **at d**), 7.17–7.92 (8H, m, Ar-**H**) and 4.21 (3H, s, O**CH$_3$**); LC-MS (EI, 70 eV), *m/z* 301.09 (M^+).

1-(4-Hydroxy-3,5-dimethoxybenzylidene)-4-phenylthiosemicarbazide (**15**) : Yield : 89%; m.p. 140–141 °C; IR (KBr, cm^{-1}) : 3366 (N-H str. and OH str.), 3038 (Ar C-H str.), 1633, 1594, 1532, 1498 (Ar C=C str.), 1612 (C=N str.), 1395 (C-N str.), 1296 C=S str.), 1080 (C-O str.), 764 (N-H bending) and 745 (Ar C-H bending); ^{1}H NMR (400 MHz DMSO, δ, ppm) : 11.61 (1H, s, O**H**), 10.67 (1H, s, N**H at a′**), 10.09 (1H, s, N**H at b′**), 8.53 (1H, s, C**H**=N **at d**), 7.27–7.82 (7H, m, Ar-**H**) and 4.32 (6H, s, O**CH$_3$**).

Conclusions

Thiosemicarbazides (**1-3**) were prepared by the reaction of aniline and CS_2, followed by addition of hydrazine derivatives. Water based method was used for the synthesis of thiosemicarbazone (**4-15**). Thiosemicarbazides were found to be more active than thiosemicarbazones at all the concentrations against both the test fungi. However the compounds with least and maximum substitution were proved to be least effective. All the synthesized compounds registered less activity than bavistin at all the concentrations against both the test fungi.

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