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Synthesis and characterization of substituted acetophenone-4, 4-dimethyl-3-thiosemicarbazone derivatives with an evaluation of antimicrobial and antioxidant activities

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ABSTRACT

Thiosemicarbazones are organic compounds; these are widely used in the medical field. It is primarily in the manufacture of pharmaceutical drugs and bio molecules. These compounds have the azomethine functional group (-N=CH-) used to derive organic open chain and heterocyclic compounds. Thiosemicarbazones are similar to semicarbazones, and carbonyl group oxygen is replaced by sulphur. Thiosemicarbazone contains nitrogen and sulfur atoms, so they are used as ligands in coordination chemistry and form metal complexes. Thiosemicarbazone and its metal complexes are used in a variety of ways. It is especially widely used in the preparation of polymers and biochemicals products. Thiosemicarbazone and its metal complexes are closely correlated with biological properties and act as antioxidants, antifungals, antimicrobials and anticancer. Subsequently, in the current study, substituted thiosemicarbazones were synthesized and examined for their antimicrobial and antioxidant activity. Newly substituted thiosemicarbazones were obtained from the respective acetophenones and thiosemicarbazides. The structure of the newly prepared compounds was confirmed by spectroscopic studies such as IR, ^{1}H, ^{13}C NMR, Mass and elemental analysis. The antimicrobial activity of all the new compounds showed significant activity against the selected bacteria and fungi in the studies. The compound TZ04 exhibited good antioxidant activity compared with standard ascorbic acid and butylated hydroxytoluene.

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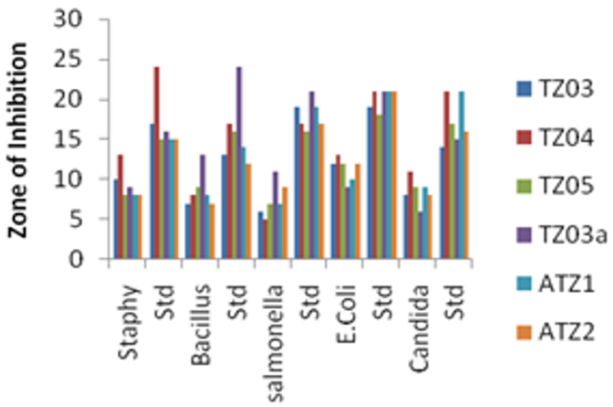
INTRODUCTION

Thiosemicarbazones is a thiourea derivative, and the general formula is $R_1R_2C=N–NH–CS–NR'R''$. R_1, R_2, R' and R" may be alkyl/aryl/hydragen or heterocyclic part (Reddy *et al.*, 2016). Thiosemicarbazones are generally prepared from condensation of carbonyl compounds and thiosemicarbazide with alcohol and dehydrating agents. Chemically, Thiosemicarbazones are generally known as Schiff base compounds and contain azomethine (–C=N–) group (Mohan *et al.*, 2018). In the presences, azomethein group thiosemicarbazones are intermediate and form heterocyclic compounds (Salman *et al.*, 2017) with suitable agents and also forms, metal complexes (Suvarapu *et al.*, 2012) with metal

ions due to in the presence of N and S donor atoms. The derivatives of thiosemicarbazones in organic and metal bonding compounds are of high biological importance.

Due to this, many organic and organo metallic thiosemicarbazone derivatives are the focus of the majority of structural and medical research such as antibacterial (ño Mosquera *et al.*, 2018), anti fungal (de Oliveira Paiva *et al.*, 2014), antimicrobial and antioxidant (Kumar *et al.*, 2018), antiviral (Padmanabhan *et al.*, 2017), antiamoebic (Abid *et al.*, 2008), anticonvulsant (Nevagi *et al.*, 2014), anti-HIV (Rauf *et al.*, 2019), antimalarial (Pingaew *et al.*, 2010), antitumor (Zhang *et al.*, 2017), anticancer (Su *et al.*, 2013), neurotropic (Lukevics *et al.*, 1994), antitrypanosomal (Haraguchi *et al.*, 2011), antituberculosis (Velezheva *et al.*, 2016), analgesic (Srivastava *et al.*, 2011) and anti-inflammatory (De Oliveira *et al.*, 2016) activity. The biological activity of thiosemicarbazones is based on the formation of metal chelates.

The biological activity of metal complexes varies from metal ions or ligands, and this is indicated to increase or decrease the biological activity of many metal complexes. Based on the above information, we have studied the synthesis, characterization, antimicrobial and antioxidant activities of the substituted acetophenone-4,4-dimethyl-3-thiosemi carbazones. A thin layer chromatography was used to determine the purity of the compounds. The structures of the synthesized compounds were determined by spectral and elemental analysis. The physical properties of the synthesized compounds are given in the experimental section, and all newly synthesized compounds were screened to antimicrobial and antioxidant activity.



Graph 1: Antimicrobial activity.

MATERIALS AND METHODS

The chemicals used in this study are brought from Sigma-Aldrich Chemicals and was used directly in the experimental part without refinement. The compounds were synthesized by the reporting method (Kumar *et al.*, 2018), and the method is described in Scheme 1 and Table 1.

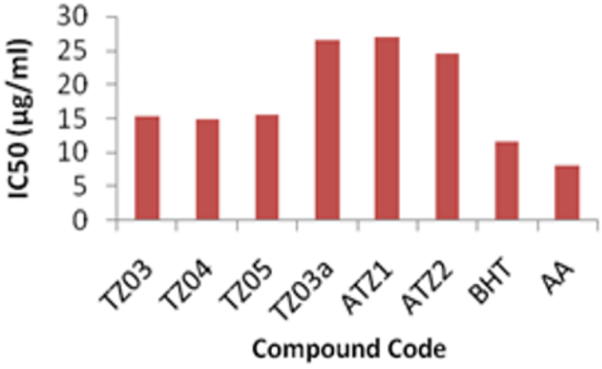
Reaction completion was checked and confirmed by thin-layer chromatography. The melting points were determined and are uncorrected using the open capillary tube method. The structures of the products were confirmed by elemental and spectral analysis.

Synthesis of 2-[1-(4-chlorophenyl) ethylidene]-*N*,*N*-dimethylhydrazine carbothioamide (TZ03)

An equimolar (0.01 mol) mixture of 4-Chloroaceto phenone and 4,4-Dimethyl-3-thiosemicarbazide was dissolved in ethanol (20 ml) with five drops of acetic acid and were refluxed for 6–7 hours at 70–80°C. Thin-layer chromatography techniques checked purity.

After the reaction was done, the synthesized compound (TZ03) was separated. The extracted product was recrystallized with ethanol.

Similarly, other compounds (TZ04, TZ05, TZ03a, ATZ1 and ATZ2) were synthesized by using the same procedure.



Graph 2: Antioxidant activity.

2-[1-(4-chlorophenyl) ethylidene]-*N*,*N*-dimethyl hydrazinecarbothioamide (TZ03)

Yield 68%; m.p 203°C IR (cm^{-1}): 3471 (NH), 3062 (C-H), 2985 (C-H), 1589 (C=N), 1504 (C-C); ^{1}H NMR (400 MHz) δ: 11.39 (s, 1H), 7.82 (d, J=10.4, 2H), 7.44 (d, J=10.8, 2H), 3.11 (s, 6H), 2.29 (s, 3H) ppm; ^{13}C NMR (100 MHz) δ:177.5 (C_2), 147.4 (C_5), 135.6 (C_6), 128.2 (C_7 and C_{11}), 128.9 (C_8 and C_{10}), 136.6 (C_9), 23.3 (C_{12}), 42.6 (C_{13} and C_{14}) ppm; EI-MS (m/z): 255 [M^+]; $C_{11}H_{14}ClN_3S$; Elemental analysis-calcd: C,

51.65; H, 5.51; N, 16.42 (%); found: C, 51.66; H, 5.52; N, 16.43 (%).

2-[1-(4-bromophenyl)ethylidene]-*N, N-dimethyl* hydrazinecarbothioamide (TZ04)

Yield 71%; m.p 209°C IR (cm^{-1}): 3425 (NH), 3070 (C-H), 2985 (C-H), 1527 (C=N), 1604 (C-C); ^{1}H NMR (400 MHz) δ: 11.37 (s, 1H), 7.90 (d, *J*=9.6, 2H), 7.44 (d, *J*=9.2, 2H), 3.12 (s, 6H), 2.25 (s, 3H) ppm; ^{13}C NMR (100 MHz) δ: 177.6 (C_2), 147.4 (C_5), 136.5 (C_6), 128.6 (C_7 and $C_{11,}$), 131.7 (C_8 and C_{10}), 125.4 (C_9),

23.2 (C_{12}), 42.1 (C_{13} and C_{14}) ppm; EI-MS (m/z): 299 [M^+]; $C_{11}H_{14}BrN_3S$; Elemental analysis-calcd: C, 44.01; H, 4.66; N, 14.00 (%); found: C, 44.02; H, 4.69; N, 13.99 (%).

N-dimethyl-2-(1-[4-(propan-2-yl)phenyl] ethylidene) hydrazinecarbo thioamide (TZ05)

Yield 67 %; m.p 202°C IR (cm^{-1}): 3448 (NH), 3062 (C-H), 2985 (C-H), 1527 (C=N), 1604 (C-C); ^{1}H NMR (400 MHz) δ: 11.71 (s, 1H), 7.40 (d, *J*=10.4, 2H), 7.06 (d, *J*=8.4, 2H), 3.14 (s, 6H), 2.87–2.64 (sep,1H), 2.33 (s, 3H), 1.16 (d, *J*=36.4, 6H) ppm; ^{13}C NMR (100 MHz) δ:177.5 (C_2), 147.4 (C_5), 134.7 (C_6), 126.8 (C_7 and $C_{11,}$), 126.2 (C_8 & C_{10}), 150.7 (C_9), 23.3 (C_{12}), 42.5 (C_{13} and C_{14}), 33.2 (isoprop-C_{15}), 23.3 (isoprop CH-C_{16} & C_{17}) ppm; EI-MS (m/z): 263 [M^+]; $C_{14}H_{21}N_3S$; Elemental analysis-calcd: C, 63.87; H, 7.98; N, 15.96 (%); found: C, 63.84; H, 8.04; N, 15.95 (%).

2-[1-(3,4-dimethoxyphenyl)ethylidene]-N,N-dimethylhydrazinecarbo thioamide (TZ03a)

Yield 69 %; m.p 208°C IR (cm^{-1}): 3439 (NH), 3049 (C-H), 2949 (C-H), 1593 (C=N), 1597 (C-C); ^{1}H NMR (400 MHz) δ: 11.49 (s, 1H), 7.72–7.68 (m, 1H), 7.64 (d, *J*=7.6,1H), 7.19 (d, *J*=1.6,1H), 3.10 (s, 6H), 2.46 (s, 6H, OCH_3), 2.29 (s, 3H) ppm; ^{13}C NMR (100 MHz) δ: 177.5 (C_2), 168.8 (C_5), 111.4 (C_6), 162.5 (C_7), 103.7 (C_8), 162.2 (C_9), 108.6 (C_{10}), 129.8 ($C_{11,}$), 23.2 (C_{12}), 57.8 (C_{R2} & C_{R3}), 42.4 (C_{13} &C_{14}) ppm; EI-MS (m/z): 281 [M^+]; $C_{13}H_{19}N_3SO_2$ Elemental analysis-calcd: C, 55.51; H, 6.76; N, 14.94 (%); found: C, 55.49; H, 6.81; N, 14.93 (%).

2-[1-(3,4-dimethylphenyl)ethylidene]-N,N-dimethylhydrazinecarbo thioamide (ATZ1)

Yield 71 %; m.p 211°C IR (cm^{-1}): 3361 (NH), 3075 (C-H), 2944 (C-H), 1572 (C=N), 1552 (C-C); ^{1}H NMR (400 MHz) δ: 11.49 (s, 1H), 7.72–7.68 (m, 1H), 7.66 (d, *J*=2, 1H), 7.16 (d, *J*=26.8, 1H), 3.10 (s, 6H), 2.46 (s, 6H, CH_3), 2.29 (s, 3H) ppm; ^{13}C NMR (100 MHz) δ:177.5 (C_2), 147.4 (C_5), 130.9 (C_6), 129.3 (C_7), 136.9 (C_8), 139.1 (C_9), 132.2 (C_{10}), 124.0 ($C_{11,}$), 23.3 (C_{12}), 42.5 (C_{13} & C_{14}), 18.8 (C_{R2} & C_{R3}) ppm; EI-MS (m/z): 249 [M^+]; $C_{13}H_{19}N_3S$; Elemental analysis-calcd: C, 62.65; H, 7.63; N, 16.86 (%); found: C, 62.61; H, 7.68; N, 16.85 (%).

2-[1-(2,4-dihydroxyphenyl)ethylidene]-N,N-dimethylhydrazinecarbo thioamide (ATZ2)

Yield 73 %; m.p 196°C; IR (cm^{-1}): 3488 (NH), 3088 (C-H), 2974 (C-H), 1559 (C=N), 1519 (C-C); ^{1}H NMR (400 MHz) δ: 11.44 (s, 1H), 10.91 (s, 1H), 9.98 (s, 1H), 7.63 (d, *J*=8, 1H), 7.21-7.13 (m, 1H),7.07 (d, *J*=12.4, 1H),3.11 (s, 6H), 2.59 (s. 3H) ppm; ^{13}C NMR (100 MHz) δ: 177.5 (C=S), 147.4 (C=N), 127.3 (C_6), 114.3 (C_7), 149.9 (C_8), 152.1 (C_9), 111.9 (C_{10}), 121.2 ($C_{11,}$), 23.2 (C_{12}), 42.6 (C_{13} & C_{14}); EI-MS (m/z): 253 [M^+]; $C_{11}H_{15}N_3O_2S$; Elemental analysis-calcd: C, 52.17; H, 5.92; N, 16.60 (%); found: C, 52.15; H, 5.97; N, 16.59 (%).

Antimicrobial activity

The Kirby-Bauer disc diffusion method (Hussain *et al.*, 2016) of *in vitro* antibacterial activity was used to evaluate all the synthesized compounds. Bacteria such as *B.subtilis*, *S.aureus*, *S.typhi* and *E.coli* were used to test the activity of the compounds. Ciprofloxacin was used as the reference antibacterial drug. For the anti fungal assay, *Candida albicans* was used to test the activity of the compounds. Fluconazole was kept as the standard drug. The inhibition zone of synthesized compounds was compared with standard drugs. The results of the zone of inhibition for the antimicrobial activity of the synthesized compounds are given in Table 2.

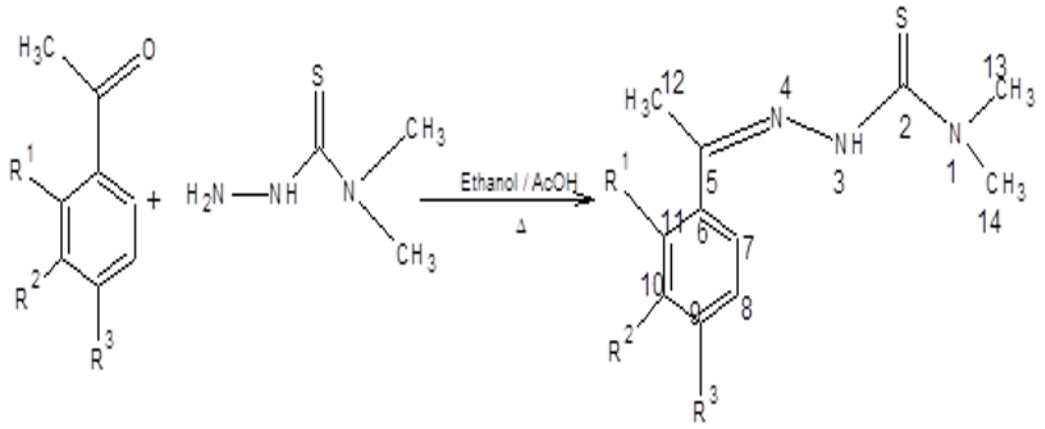
Antioxidant activity

All synthesized compounds for antioxidant activity were screened using the DPPH evaluation method (Meeran and Hussain, 2017). The antioxidant data of all the samples are given in Table 3. DPPH method is a reduction principle of the purple DPPH (free radical) reduced and changes to yellow colored diphenylpicrylhydrazine. The remaining purple colored DPPH exhibited maximum absorption of 517 nm. The 2 ml different concentration of the synthesized compounds or standards were added with 2ml of DPPH solution (0.1 mM), and these are kept in the dark. After 20 min of incubation at 37°C, the solution absorbance was measured at 517 nm. AA and BHA were used as positive controls. The following formula was used to calculate the percentage of inhibition.

Inhibition (%) = (blank OD–sample OD/blank OD)×100.

RESULTS AND DISCUSSION

The final compounds were purified by re crystallization with ethanol. The structure of the



Scheme 1: Synthesis of substituted acetophenone-4, 4-dimethyl-3-thiosemicarbazones.

Table 1: Compound code of substituted acetophenone-4, 4-dimethyl-3-thiosemicarbazones.

Compound Code	TZ03	TZ04	TZ05	TZ03a	ATZ1	ATZ2
R1	H	H	H	H	H	OH
R2	H	H	H	OMe	Me	H
R3	Cl	Br	CHMe2	OMe	Me	OH

Table 2: Antimicrobial activity of the synthesized compounds.

Sample Code	Zone of inhibition (mm) of synthesized compounds																			
	Antibacterial activity																Antifungal activity			
	Staphylococcus aureus				*Bacillus subtilis*				*Salmonella typhi*				*Escherichia coli*				*Candida albicans*			
	100 mcg	50 mcg	25 mcg	std	100 mcg	50 mcg	25 mcg	std	100 mcg	50 mcg	25 mcg	std	100 mcg	50 mcg	25 mcg	std	100 mcg	50 mcg	25 mcg	std
TZ03	10	7	4	17	7	3	-	13	6	4	-	19	12	8	6	19	8	-	-	24
TZ04	13	5	2	24	8	6	5	17	5	3	-	17	13	7	4	21	11	9	-	21
TZ05	8	6	4	15	9	6	5	16	7	5	3	16	12	8	6	18	8	7	3	17
TZ03a	9	7	6	16	13	9	5	24	11	8	4	21	9	8	5	21	6	4	-	15
ATZ1	8	5	3	15	8	6	5	14	7	3	-	19	10	7	4	21	9	7	4	21
ATZ2	8	6	3	15	7	5	4	12	9	6	5	17	12	5	8	21	8	6	3	16

Table 3: Antioxidant activity of synthesized compounds.

Compound	Concentration (μg/ml)					IC50 (μg/ml)*
	20	40	60	80	100	
TZ03	49.03	59.47	66.22	70.08	74.82	15.22
TZ04	50.27	59.2	64.68	70.96	75.58	14.83
TZ05	49.63	59.33	65.75	70.48	76.06	15.46
TZ03a	47.41	53.49	67.09	72.47	80.37	26.5
ATZ1	45.93	58.07	63.35	71.92	82.19	26.96
ATZ2	74.06	65.17	64.06	65.17	74.06	24.49
BHT	54.59	64.19	72.57	81.94	94.16	11.52
AA	58.1	64.81	75.06	87.74	98.21	8.09

*Average of three independent determinations

compounds was confirmed based on spectral and elemental analysis. The spectral characterization of 2-[1-(4-chlorophenyl) ethylidene]-*N*, *N*-dimethylhydrazinecarbothioamide (TZ03) is described as an example. The IR spectrum revealed 3471, 3062 & 2985 and 1589 cm^{-1} values respectively. It is obtained due to the compound which contains the characteristics of groups of amide NH, aromatic & aliphatic CH and imine C = N respectively. ^{1}H NMR spectrum reported a singlet at δ 11.39 ppm assignable to NH proton. Two doublets at δ 7.82 (J=10.4) ppm and δ 7.44 (J=10.8Hz) ppm each for two protons are assignable to H-7, H-11 and H-8, H-10 respectively.

A singlet at δ 3.11 ppm for six protons is due to -$N(CH_3)_2$ and a singlet at δ 2.29 ppm is related to C_5–CH_3 protons. The ^{13}C NMR spectral results are described below. The signal exhibited at δ177.5 ppm due to the thiocarbonyl carbon (C=S) and the carbon of C=N showed at δ147.4 ppm. The aromatic carbons C_6, [C_7 and C_{11}], [C_8 and C_{10}] and C_9 appeared at δ 135.6, 128.2, 128.9 and 136.6ppm respectively. The methyl carbon, C_{12} is observed at 23.3ppm and the peak at 42.6 ppm due to Dimethyl carbons of C_{13} and C_{14} (NMe_2) respectively. The mass spectrum of the molecular ion peak is reported at 255 [M^+]. This value refers to the molecular weight of the compound. Hence, the above spectral data are compatible with the structure of the desired product, 2-[1-(4-chlorophenyl) ethylidene]-*N*, *N*-dimethylhydrazinecarbothioamide.

All synthesized compounds were screened for *in vitro* antimicrobial activity by the Kirby-Bauer disc diffusion method. The inhibition zone was compared with standards. The results of the antibacterial and anti fungal activity are given in Table 2 and Graph 1. The newly synthesized compounds showed significant activity against selected bacteria. High anti fungal activity was observed in the TZ04 compared to other compounds due to the Bromo substitution of TZ04. The results of the antioxidant activity of synthesized compounds at different concentrations are shown in Table 3. The calculated IC_{50} values are given in Table 3 and Graph 2. The most active compound among the synthesized compounds is TZ04, which gave an IC_{50} value of 14.8 μg/ml, while AA and BHA gave 8.09 and 11.52 μg/ml respectively.

CONCLUSIONS

Serious substituted acetophenone-4,4-dimethyl-3-thiosemicarbazones derivatives have been synthesized, and the elemental and spectral analysis confirmed the structures of the compounds. Newly synthesized compounds exhibited significant antimicrobial activity against selected bacteria and fungi. The compound TZ04 showed high antioxidant activity. Finally, 2-[1-(4-bromophenyl)ethylidene]-*N*, *N*-dimethylhydrazinecarbothio amide is observed to have good anti fungal and high antioxidant activity.

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Conflict of Interest

The authors declare that they have no conflict of interest for this study.

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