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New Halogenated Thiosemicarbazones as Potential Antimicrobial Agents: synthesis and spectral characterization

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ABSTRACT

Three new chalcogenic thiosemicarbazones (3,4-difluoroacetophenone thiosemicarbazone(**1**), 2-bromo-4'-chloroacetophenone thiosemicarbazone(**2**) and 2, 4'-dibromoacetophenone thiosemicarbazone(**3**) are synthesized by using a conventional one step processes in which the respective halo-substituted acetophenones are condensed with thiosemicarbazide to result in the formation of the product. The chalcogenic thiosemicarbazones are then characterized by the spectroscopic techniques like FT-IR, FT-Raman, UV-Vis, ^{1}H and ^{13}C NMR (^{19}F for **1**), HR-MS and LC-MS, TG-DTA. The compound **1** is unambiguously characterized by single crystal X-ray diffraction and is found to have monoclinic system. These compounds were further tested for their antimicrobial activity against some human pathogens like *E. coli*, *B. subtilis*, *P. aureginosa* and *S. aureus*. The MIC values have suggested that these are potential antimicrobial agents.

INTRODUCTION

Sulphur gained prominent status through its versatile biological capability and is being used from ancient Greeks as fungicidal agent. It is the third most abundant mineral in the total percentage of body weight of a human being.

The high impact of sulphur as pesticide is understood in the early 1820s itself.The rapid inter conversion of the allotropes of sulphur in vapour state stood responsible for the usage of this system as the high temperature thermochemical solar energy conversion system (Clark and Dowling, 2004). Sulphur containing organic compounds had replaced the inorganic sulphur compounds as agrochemicals (Lamberth, 2004). The chalcogenic thiosemicarbazones are getting appreciation all around as the compounds of wide biological activities. The usage of these compounds was started early in the 1800s as potential extractants for the recovery of the rare and familiar metal ions because of their chelating ability (Dominguez*et al.,* 2002). From past few decades they have been identified as the ligands that can form the complexes with various transition and non-transition metal ions (Enyedy*et al.,* 2011; Kang*et al.,* 1997; Mehta*et al.,* 2009; Rai*et al.,* 2009). Moreover their function as antimicrobial (Menichetti*et al.,* 2004; Singh*et al.,* 2007), antifungal (Arguelles*et al.,* 2009), antidiabetic (Kulkarni*et al.,* 2012) and antitumour (Ma *et al.,* 2008; Lessa*et al.,* 2011; Kowol*et al.,* 2012; Li *et al.,* 2013)agents are highly appreciable and are comparable with the drugs having the similar functional groups that are available in the market. Triapine is the one among this category that is tested asan anticancer agent against a variety of tumor cell lines which is under phase I and II clinical trials because of its high efficiency as an iron chelator (Nutting *et al.,* 2009; Knox *et al.,* 2007; Ma *et al.,* 2008). The high efficacy of these compounds as biologically active agents is asserted with the presence of the sulphur atom. Sulphur containing compounds are also found to play a key role in the field of fluorescent dyes (Rucker *et al.,* 2003), polymers,liquid crystals (Al-Dujali*et al.,* 2001) etc. In the present study we synthesized three novel halogen substituted thiosemicarbazones and characterized them with spectroscopic techniques. With the help of vast literature survey proving the efficiency of these

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thiosemicarbazones as biological agents, we conducted the antimicrobial assays for these compounds against the human pathogens like *E. coli*, *B. subtilis*, *S. aureus*. In the near future we are planning to synthesize the transition metal complexes of these chelating ligands and study their antioxidant and anticancer activities.

MATERIALS AND METHODS

Chemicals

All the chemicals used in the study are of analytical grade unless reported. The organic chemicals 3,4-difluoroacetophenone are purchased from Sigma Aldrich,2-bromo-4□-chloroacetophenone and 2, 4'-dibromoacetophenone were purchased from Avra synthesis pvt ltd. Thiosemicarbazideis obtained from Sd-Fine chemicals. Organic solvents used are of GR grade and are used without further purification.

Physical measurements

A Shimadzu 2450 UV-Vis spectrophotometer equipped with a 1.0 cm quartz cell was used for the absorbance studies. Elemental analysis(CHN) was performed using SEM attached Oxford instruments Inca Penta FETX3.

Infrared spectra are recorded in solid state using KBr pellets on JASCO FTIR 5300 spectrophotometer in the range of 4000-600cm^{-1}. The NMR spectrum is recorded on a Bruker(400MHz) spectrometer at 300ºK, using DMSO-d^6 as a solvent and tetramethylsilane(TMS) as an internal reference compound. Mass spectra of the compoundsare recorded in ESI mode using Bruker HRMS at University of Hyderabad. X-ray powder diffraction data are collected on a Philips X'pert Pro X-ray powder diffractometer equipped with X'cellerator detector at room temperature. The scan range, step size, and time per step are2θ= 5.00 to 40, 0.028 and 30s, respectively.

EXPERIMENTAL

Synthesis

A series of the halo substituted thiosemcarbazone ligands **1, 2**and **3** are synthesized by using a modified procedure (Metwally*et al.,* 2011; Refat*et al.,* 2012).

To the hot ethanolic solution of thiosemicarbazide, the respective halo substituted acetophenone in ethanol is added slowly under constant stirring. The mixture is refluxed for about 4 hours and the colored solution obtained is evaporated under reduced pressure to obtain the solid compound. Purity of the compounds is checked by TLC techniques. **Scheme. 1** shows the synthesisprocedure.

3,4-difluoroacetophenone thiosemicarbazone(1)

Pale yellow colored crystals, yield: 78%. Elemental analysis for $C_9H_9N_3F_2S$(%): Calc. C, 47; H, 3.96; N, 18.33;S, 13.99; Found,C, 47.08; H, 3.92; N, 18.37;S, 13.98; HR-MS (m/z): 230 $[C_9H_9N_3F_2S]^+$. NMR spectra (Bruker, 400 MHz, DMSO- d^6, ppm): ^{1}H-NMR; δ = 2.26 (3H, s, CH_3), 7.2-7.6 (3H, Ar-H), 8.1 (2H, s, NH_2), 10.25 (1H, br, s, NH); ^{13}C-NMR; δ = 179.4(C1), 146.0 (C2), 14.2 (C3), 135.7 (C4),115.8 (C5), 149.5 (C6), 150.9 (C7), 117.3 (C8) and 124.1 (C9).^{19}F NMR; δ = -137.8 (C6F), -138.6 (C7F). IR (KBr, cm^{-1}): 3417 s, 3232-3147 br, (υ NH_2); 1596 s, (υ C=N + υ C=C); 1365 m, 880 m, (υ C=S).

2-bromo-4'-chloroacetophenonethiosemicarbazone(2)

Light brownish yellow colored compound yield: 63%. Elemental analysis(%) for $C_9H_9BrClN_3S$: Calc. C,35.26; H,2.96; N, 13.70;S, 10.46; found. C,35.48; H,2.92; N,13.62;S, 10.45; HRMS(m/z): 306 $[C_9H_9BrClN_3S]^+$. IR (KBr, cm^{-1}): 3453 br, 3310-3146 br, (υ NH_2); 1629 s, (υ C=N + υ C=C); 1351 m, 832 m, (υ C=S). NMR spectra (Bruker, 400 MHz, DMSO - d^6, ppm): ^{1}H-NMR; δ = 1.98 (2H, s, CH_2), 7.50 (2H, d Ar-H), 7.66 (2H, d Ar-H) 9.35 (2H, s, NH_2), 10.16 (1H, br, s, NH); ^{13}C-NMR; δ = 177.43(C1), 150.71 (C2), 65.5 (C3), 132.0 (C4), 125.9 (C5 & C9), 127.9 (C6 & C8), 136.7 (C7).

2, 4'-dibromoacetophenonethiosemicarbazone(3)

Yellowish brown color compound, yield: 74%. Elemental analysis(%) for $C_9H_9Br_2N_3S$: Calc. C 30.79, H 2.58, N 11.97, S 9.13; found C 30.84, H 2.55, N 11.91, S 9.12; HRMS (m/z): 351 $[C_9H_9Br_2N_3S]^+$. IR (KBr, cm^{-1}): 3441 br, 3034 br, (υ NH_2); 1629 s, (υ C=N + υ C=C); 1383 w, 827 m, (υ C=S).NMR spectra (Bruker, 400 MHz, DMSO- d^6, ppm): ^{1}H-NMR; δ = 4.01 (2H, s, CH_2), 7.50 (2H, d Ar-H), 7.91 (2H, d Ar-H) 9.42 (2H, s, NH_2), 10.21 (1H, br, s, NH);^{13}C-NMR; δ = 178.43(C1), 154.02 (C2), 65.5 (C3), 132.15 (C4), 132.0 (C5 & C9), 132.04 (C6 & C8), 136.7 (C7).

Antimicrobial activity

The synthesized compounds **1**, **2** and **3**are subjected for invitro antimicrobial assay against some gram negative bacteria like *E. coli*, *B. subtilis*,*P. aeruginosa*and a gram positive *S. aureus* by the agar disc diffusion method (Menichetti*et al.,* 2004). The pathogens are sub cultured in nutrient agar medium by incubating at 37^{o}C for 24 hours.

A bacterial suspension of about10^{-5}CFU/mL is mixed and poured on to the agar medium in an agar plate maintained at 40^{o}C in a laminar flow cabinet. The minimum inhibitory concentrations of the three synthesized compounds arepredicted by preparing different concentrations (5.0, 10.0, 25.0 and 50.0 µg/ml) by serial dilution of the test samples that are previously dissolved in 0.1percent DMSO.

Filter paper discs of about 6.0 mm in diameter are soaked in the samples of varying concentration and are fixed on to the nutrient agar medium. Ciprofloxacin(30 µg/mL) is used as positive control and filter paper discs wetted with 0.1 percent DMSO are used as negative control. The result obtained from antimicrobial activity is assed after incubating the samples for about 24 hours at 37 ^{o}C. Each experiment is performed in duplicate.

RESULTS AND DISCUSSION

Infrared spectra

Infrared spectral studies primarily helped in the structural confirmation of the synthesized compounds by identifying the bands corresponding to the important functional groups. A strong intense band observed at 1596, 1629 and 1629 cm^{-1} respectively for **1**, **2** and **3** corresponding to the stretching frequency of the azomethine group while the thione function the compounds are observed at 880, 832 and 827 cm^{-1}(Joseph *et al.,* 2006; Seena*et al.,* 2012).

^{1}H, ^{13}C and ^{19}F NMR spectra

The significant evidence for the formation of **1, 2**and **3**is obtained from NMR spectral analysis. The ^{1}H NMR, ^{13}C NMR and ^{19}F NMR spectra of **1**are recorded in DMSO-d^{6} using tetramethylsilane(TMS) as the internal reference compound. The ^{1}H NMR spectrum has shown a singlet of three protons intensity at δ2.26 ppm indicating three methyl protons (attached to C3 carbon). -NH_2 protons are also observed as singlet at δ8.15ppm with a small shoulder at δ8.19 because of the partial hydrogen bonding interaction between one of the two hydrogen atoms with the iminic nitrogen and a broad peak appearing at δ10.25 ppm indicates an N-H proton proving the thione form of **1**. The compounds having *E* confirmation shows the NH proton signals in between 9-12 ppm (Ali *et al.,* 2012).

The aromatic protons are observed in the range of δ7.6-7.2 ppm among which theproton attached to C9 carbon is observed as quartet due toortho and meta coupling. For the compounds **2** and **3**a similar pattern of the chemical shift values for -NH_2 and NH protons are observed (9.35, 9.42 ppm and 10.16, 10.21 ppm respectively).

The presence of the bromo substitution at the C3 carbon of the compounds **2** and **3** allowed the protons to appear at 1.98 and 4.01 ppm respectively.^{13}C nmr has shown a peak at δ179.4, 177.43 and 178.43ppm for C1 a thioamide carbon, the carbon with imine function (C2 carbon) of the three compounds are observed at δ146.0, 150.71 and 154.02 ppm. Two signals each as doublets for the fluorine atoms attached to C6 and C7 carbons of compound **1** are found at δ149.5 and 150.9ppm respectively. C8 and C5 carbons are also found as doublets at δ116 and 115.8ppm and C3 carbon has shown a peak at δ14.2ppm. C4,C9 and C2 carbon peaks are observed at δ135.7, 124.1 and 146.0 ppm respectively.

For the compounds **2** and **3**, the aromatic carbon atoms C6 and C8 are observed at is observed at δ127.9 and 132.04 ppm. While the remaining two aromatic carbons C5 and C9 are found as singlets at δ125.9 and 132.0 ppm. C4 and C3 carbons are found at δ132.0, 65.5for compound **2** and at δ132.15, 65.5 ppm for compound **3** respectively.

^{19}FNMR of the same has shown two peaks each one as doublet at δ–137.8 and –138.6 ppm respectively. A brief summary on the ^{13}C NMR spectral data for the three compounds were presented in the **Table. 1**.

UV-Vis spectra

The UV-Vis spectra of compounds **1,2** and**3**are studied using UV-Vis 2450 Schimadzu instrument, in saturated ethyl acetate and DMSO solutions with the respective solvent as blank. The electronic spectra of compound **1** in ethylacetateshowed a strong band at 313 nm (31,949cm^{-1}), which corresponds to the $\pi \rightarrow \pi^*$ transitions of the phenyl ring and the imine nitrogen function of the thiosemicarbazone. The compounds**2** and **3**in DMSO showed the bandswith an absorption maxima at 317 nm (31,545 cm^{-1}), 389 nm (25,706 cm^{-1})and 352 nm(28,409 cm^{-1})respectively (Raphea*et al.,* 2007).

The shift in the absorption bands of both **2** and **3** are assertable for the increased π donor capacity of the halogen present at the para position of the aromatic ring. The appearance of these intra ligand charge transfer $\pi \rightarrow \pi^*$ bands υ_2 of compound **2** and υ_1 of compound **3** in the visible range are responsible for the colour of these compounds. Characteristic $\pi \rightarrow \pi^*$ transitions of the chromophoric functions are responsible for the high intensity of these compounds.

The band gap calculated for the compounds from the UV-Vis spectra gave an insight into the semiconducting property(0.5-4.0 eV) which was further supported by the data obtained from the electrochemical response.**Fig. 1.** Shows the spectra obtained for the compounds.

Powder X-ray diffraction studies

Intense sharp peaks at specific 2θ angles confirm the crystalline nature of the synthesized molecules **1**, **2** and **3** and are quite different from each other (**Fig. 2**).From the spectrum it is clear that the compounds have high amount of crystalline nature in between 20-30 °C, which after increase in temperature, slowly changed to non-crystalline substance.

Antimicrobial activity

Results of the antimicrobial activity was evaluated after incubation for 24 hours at 37 ^{o}C for the compounds **1**, **2** and **3**have shown significant antimicrobial activity against these tested human pathogens. The compound **1**with the fluorine substitution on the aromatic ring induced the cytotoxicity and stood responsible for the comparable activity with the standard antibioticciprofloxacin. The minimum inhibitory concentration expressed in terms of µg/ml and the inhibition zones (mm) at different concentration of the synthesized compounds in 0.1% DMSO to the standard drug ciprofloxacin (30 µg/mL) with respect to each microorganism are given in the **Table 2**.

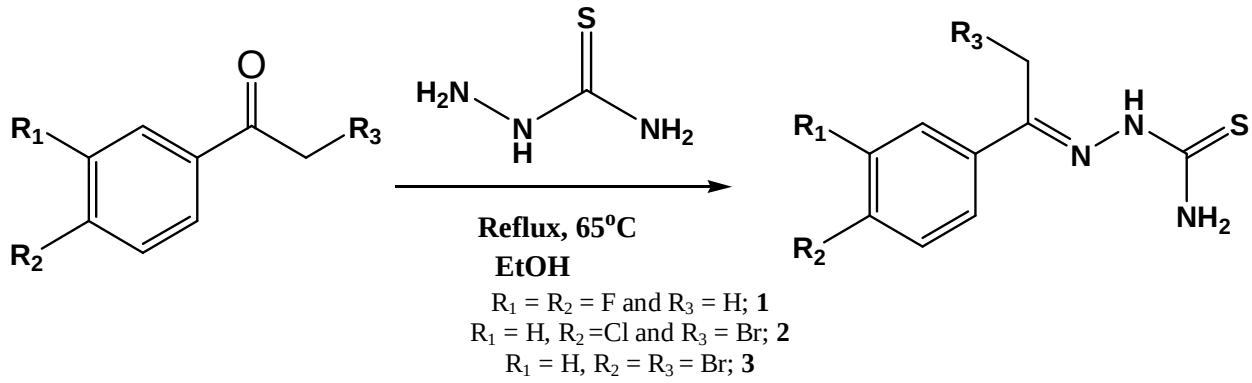
The compound 1 exerted its high potency of antimicrobial activity towards the gram negative *B. subtilis* and *P. aureginosa*by showing the inhibiting activity at a concentration of10 µg/ml whose activity can be ascertained to the presence of the fluoro substitution. The same comopound 1 showed its inability to inhibit the growth of the gram positive microorganism *S. arueus*. Mostly the activity of the compounds are showing a trend of **1**>**2**>**3**.

Table. 1: Summary of the ^{13}C NMR data for the compounds **1**, **2** and **3**.

Compound	C1	C2	C3	C4	C5	C6	C7	C8	C9
1	179.4	146.0	14.2	135.7	115.8	149.5	150.9	116.0	124.1
2	177.43	150.7	65.5	132.0	125.9	127.9	136.7	127.9	125.9
3	178.4	154.0	65.5	132.15	132.0	132.4	136.7	132.4	132.0

Table. 2: Antimicrobial activity of the compounds **1**, **2** and **3** compared against the standard drug ciprofloxacin (30 µg/ml). MIC in µg/ml and Zone of inhibition in mm.

Compound	1		2		3		ciprofloxacin
	MIC	Zone	MIC	Zone	MIC	Zone	Zone
B. subtilis	10	7±0.5	25	12±2	50	13±1	15±0.7
S. aureus	-	-	10	8±0.6	25	8±0.2	13±0.3
P. aureginosa	10	15±0.3	50	14±0.3	50	11±1	15±0.1
E. coli	25	9±1	25	6±2	50	8±2	11±0.4



$R_1 = R_2 = F$ and $R_3 = H$; **1**
$R_1 = H$, $R_2 = Cl$ and $R_3 = Br$; **2**
$R_1 = H$, $R_2 = R_3 = Br$; **3**

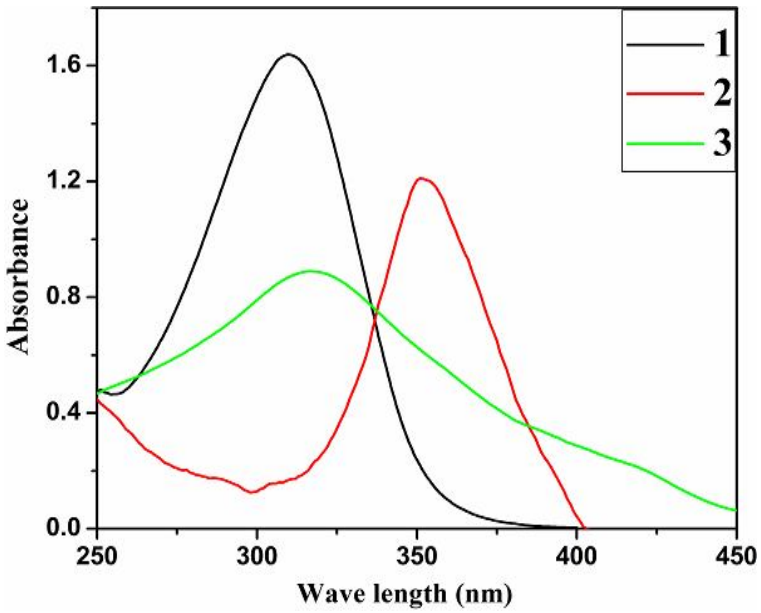


Fig. 1. UV-Vis spectra for compounds **1**,**2** and **3** taken as 1 x 10^{-4} M dmso solution.

CONCLUSION

The halo substituted thiosemicarbazones were synthesized by a simple one step condensation processes. The IR spectroscopy and NMR spectroscopy provided a convenient approach to elucidate the structure of the synthesized compounds. The antimicrobial activity studies suggested that the compounds are potential agents of biological importance. Among all the compounds tested the fluoro substituted compound **1** was found to be more active than the remaining compounds.

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