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ORIGINAL PAPER

Synthesis and X-ray Crystal Structure of 2 and 4-Trifluoromethyl Substituted Phenyl Semicarbazone and Thiosemicarbazone

T. K. Venkatachalam[1] · Paul V. Bernhardt[2] · Gregory K. Pierens[1] · David C. Reutens[1]

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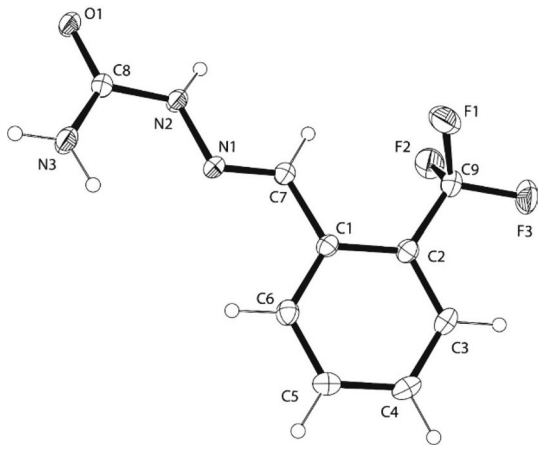
Abstract NMR and single crystal X-ray structure data for four structurally similar semicarbazones and thiosemicarbazones were compared. In solution, proton NMR showed considerable variation in their chemical shift values especially for the NH_2 protons. In the case of the semicarbazones this peak appeared as a broad singlet with an integration ratio of two while for the thiosemicarbazones the amino group showed two distinct singlets with marked chemical shift differences. This is attributed to the differences in the canonical forms of the thiosemicarbazone amino group and the semicarbazone analogue. Additionally, we provide evidence that the 2-trifluoromethyl phenyl substituted semicarbazone (**2**) formed an intermolecular hydrogen bond with one of the hydrogens of the NH_2 group while this was totally absent in the thiosemicarbazone. We explain this by the restricted rotation of the CN bond in the thiosemicarbazone due to its double bond character compared to the less restricted rotation in semicarbazone compound.

Graphical Abstract NMR and single crystal X-ray structure data for four structurally similar semicarbazones and thiosemicarbazones were compared for their hydrogen bonding characteristics.



Keywords Semicarbazones · NMR · X-ray crystal structure · Hydrogen bond

Introduction

Semicarbazones and thiosemicarbazones are compounds, which can be easily obtained by the condensation of an aldehyde with either semicarbazide or thiosemicarbazide in a single step. These compounds were known from the early part of the nineteenth century. Although the preparation of these simple compounds has been described in the literature, the biological activity profiles of these compounds were only studied in the latter part of the last century. A variety of thiosemicarbazones/semicarbazones show a wide range of biological activities including being effective against tuberculosis [1] and cancer [2–5]. Apart from being biologically active, these compounds have the capacity to complex with various metal ions, and some

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✉ T. K. Venkatachalam
t.venkatachalam@uq.edu.au

[1] Centre for Advanced Imaging, The University of Queensland, Brisbane 4072, Australia

[2] School of Chemistry and Molecular Biosciences, The University of Queensland, Brisbane 4072, Australia

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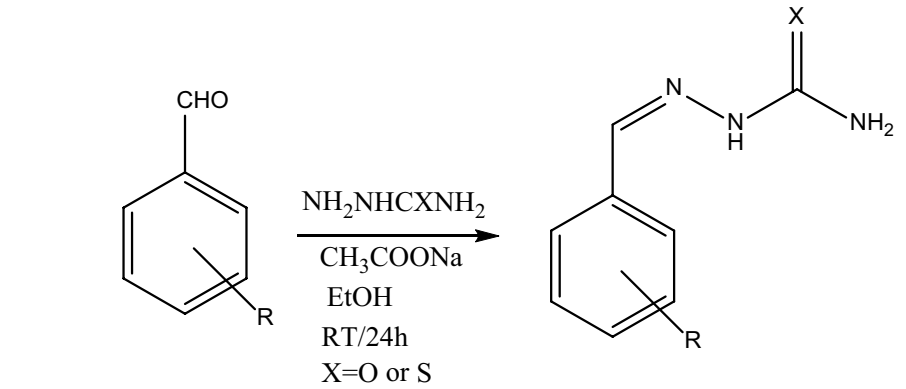
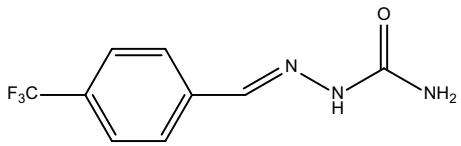
Scheme 1 General synthetic scheme for synthesis of semicarbazone and thiosemicarbazones and the structures of semicarbazones and thiosemicarbazones used in the present study





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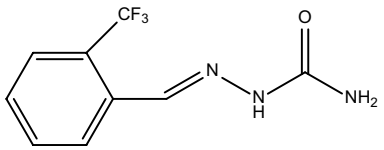

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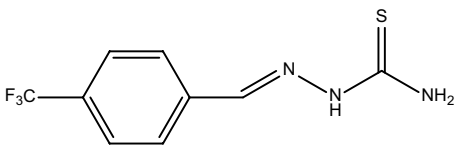

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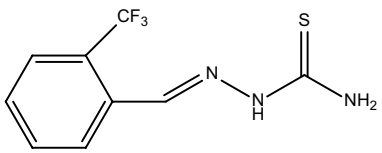

(4)

of the metal complexes also possess marked biological activity. Iron complexes of thiosemicarbazone derivatives have been found to be effective anti-cancer agents [6–13] (see Kalinowski et al. [14] for a detailed review on the use of thiosemicarbazones for cancer treatment). Lobana et al. [15] have compiled a detailed review on the bonding and structural characteristics of thiosemicarbazones in particular and reported the development of strategies for the preparation of newer derivatives and their potential applications. In recent years attachment of radiometals to thiosemicarbazones has been undertaken to develop cancer imaging agents [16–21]. Several single crystal X-ray diffraction studies of both semicarbazones and thiosemicarabzones have been published. The 4-pyridyl semicarbazone and its zinc, cobalt and cadmium complexes, [22] crystal structures of complexes of 2-pyridyl semicarbazone [23–28] and the X-ray crystal structures of both the ligand and the cadmium and indium chelates of 4-nitrophenyl thiosemicarbazones [29, 30] have previously been described.

We studied the structural features of new thiosemicarbazone derivatives containing the trifluoromethyl group in their structural framework.

Experimental

All chemicals were obtained from Sigma-Aldrich and used without further purification. NMR spectra were recorded in deuterated dimethylsulfoxide and the chemical shifts were referenced by the DMSO protons at 2.54 ppm. The NMR data were acquired on a Bruker 700 MHz NMR spectrometer equipped with a cryoprobe. The proton spectra where acquired with a sweep width of 15 ppm centered at 7 ppm. The carbon spectra were acquired with a sweep width of 220 ppm centered at 110 ppm. The COSY experiments were acquired with a sweep width of 15 ppm using a 90° pulse of 9 µs with 256 increments. The ^{13}C HSQC spectrum was acquired with sweep widths of 18 and 160 ppm for proton and carbon respectively and the carbon centered at 80 ppm. Additionally, HMBC spectral data was also acquired to establish the structures of the compounds (^{13}C sweep width of 220 ppm). The raw data were multiplied by an exponential or shifted sine squared function before performing the Fourier transform.

Physical constants of compounds: 4-triflouromethyl phenyl semicarbazone and thiosemicarbazone data have been reported in our earlier publication [31] and the data for

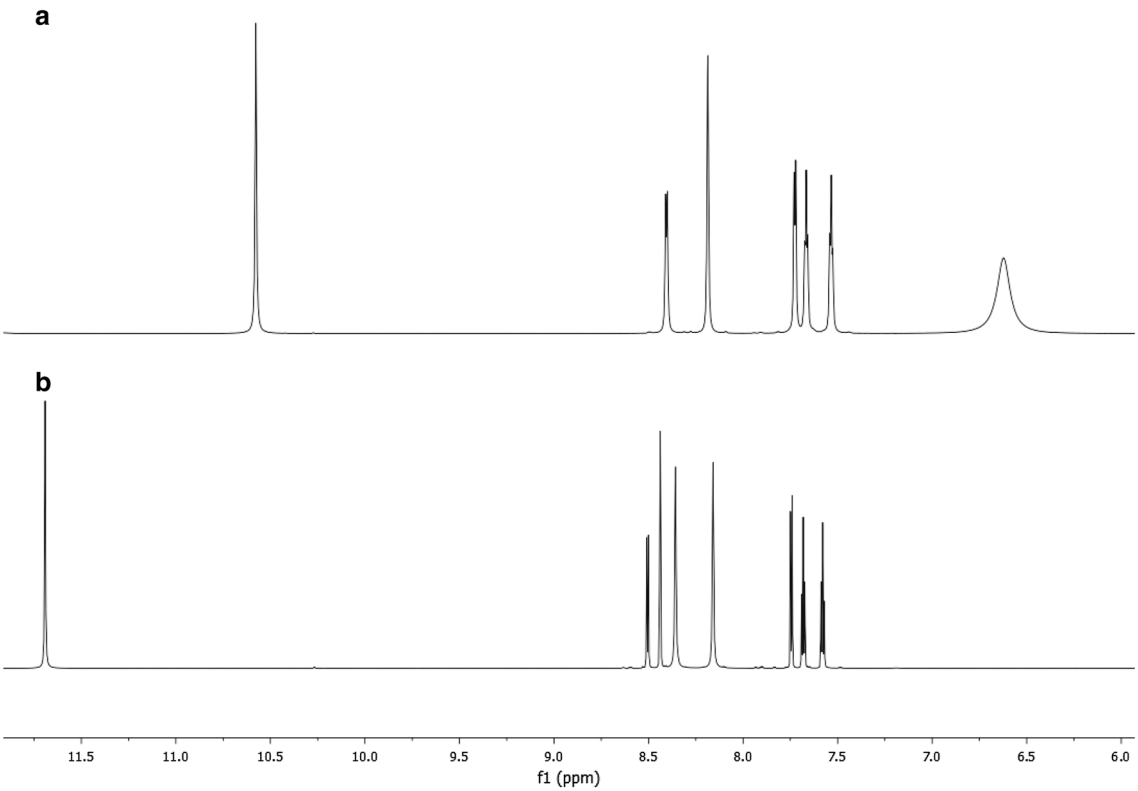

Fig. 1 ^{1}H NMR spectra of **a** 2-CF_3 phenyl semicarbazone (**2**) and **b** 2-CF_3 phenyl thiosemicarbazone (**4**) in d_6-DMSO at room temperature

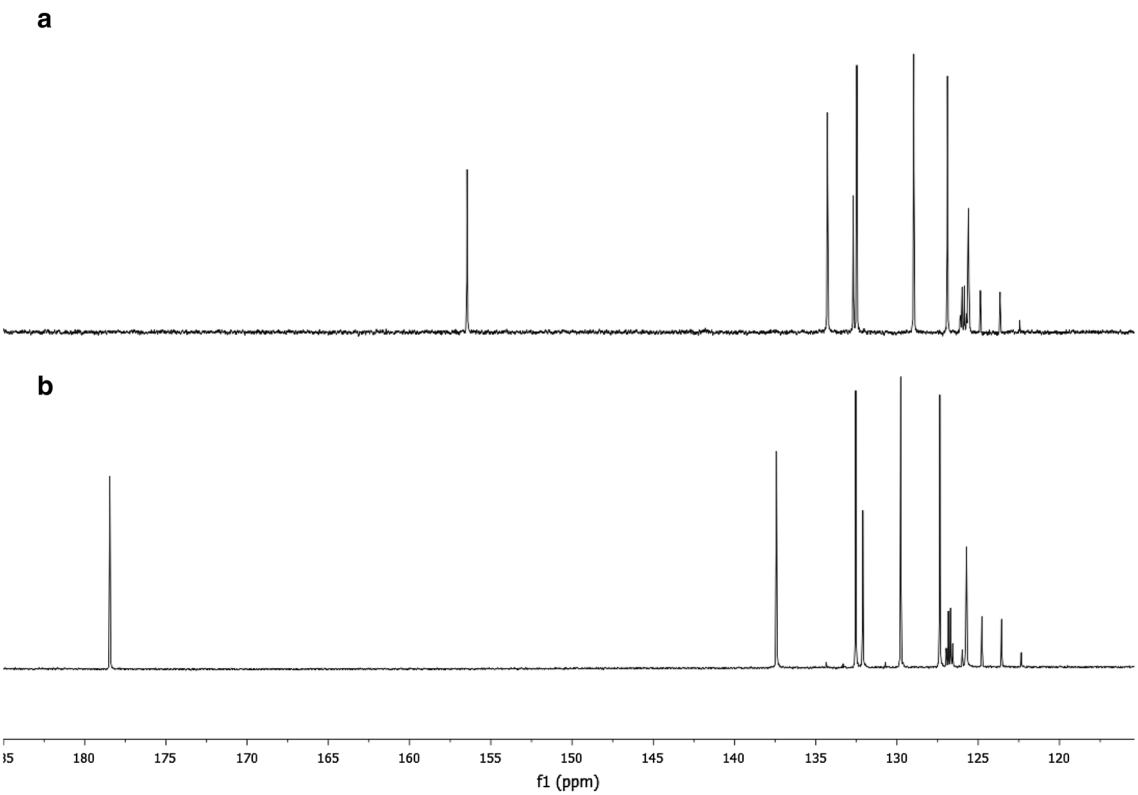

Fig. 2 ^{13}C NMR spectra of 2-CF_3 phenyl semicarbazone (**2**) (**a**) and 2-CF_3 phenyl thiosemicarbazone (**4**) (**b**) in d_6-DMSO at room temperature

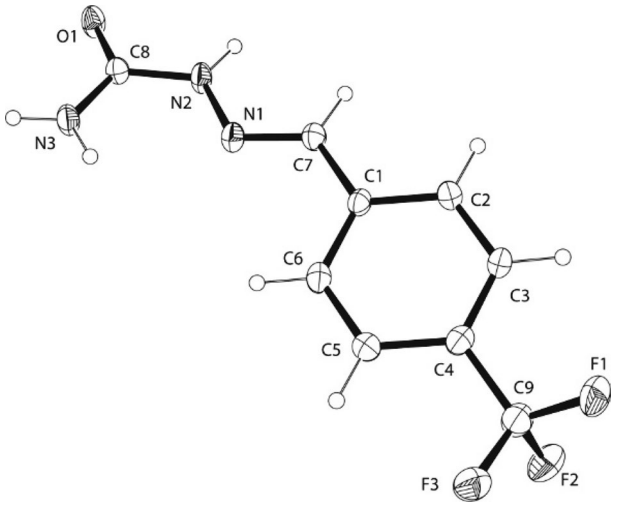

Fig. 3 Molecular structure of 4-CF_3 phenyl semicarbazone (**1**) (30% ellipsoid probability)

2-triflouromethyl phenyl semicarbazone and thiosemicarbazone are as follows:

2-CF_3-Phenyl semicarbazone (**2**): ^{1}H NMR (d_6-DMSO): δ ppm: 10.57 (s, 1H), 8.41–8.40 (d, 1H, J = 7.0 Hz), 8.19 (s, 1H), 7.73–7.72 (d, 1H, J = 7.0 Hz), 7.67–7.65 (t, 1H), 7.54–7.52 (t, 1H), 6.62 (bs, 2H, NH_2); ^{13}C NMR (d_6-DMSO): δ ppm: 156.5, 134.3, 132.7, 132.5, 128.9, 126.9, 125.9–123.7 (m, CF3), 125.6, 124.8.

2-CF_3-Phenyl-thiosemicarbazone (**4**): ^{1}H NMR (d_6-DMSO): δ ppm: 11.69 (s, 1H), 8.51–8.50 (d, 1H, J = 7.0 Hz), 8.44 (s, 1H), 8.36 (s, 1H), 8.16 (s, 1H), 7.75–7.74 (d, 1HJ = 7.0 Hz), 7.69–7.67 (t, 1H), 7.58–7.57 (t, 1H); ^{13}C NMR (d_6-DMSO): δ ppm 178.4, 137.4, 132.5, 132.1, 129.7, 127.4, 126.8, 125.7, 124.2.

X-ray Crystallography

X-ray quality single crystals were obtained by slow diffusion of methylene chloride into methanol solutions. Crystallographic data were acquired at 190 K on an Oxford Diffraction Gemini CCD diffractometer employing graphite-monochromated Mo Kα radiation (0.71073 Å) and operating within the range $2 < 2\theta < 50°$. Temperature control was achieved with an Oxford Cryosystems Desktop Cooler. Data reduction and empirical absorption corrections (semi-empirical from equivalents) were performed with Oxford Diffraction CrysAlisPro software [32]. The structure was solved by direct methods with SHELXS and refined by full-matrix least-squares analysis with SHELXL-97 [33] within the WinGX graphical user interface [34]. All non-H atoms were refined with anisotropic thermal parameters. All hydrogen bonds were included at calculated positions and constrained to their parent N- or C-atom using a riding model. The molecular structure diagrams were produced with ORTEP3 [34]. The packing diagrams were drawn with PLUTON [35]. The crystal data in CIF format have been deposited at the Cambridge Crystallographic Data Centre with deposition numbers 1440272–1440275.

Results and Discussion

The synthesis of semicarbazone and thiosemicarbazone was achieved following Scheme 1, that is, 2- or 4-substituted trifluoromethyl benzaldehyde was condensed with either semicarbazide hydrochloride or thiosemicarbazide hydrochloride in the presence of sodium acetate in ethanol to furnish the required compounds. The compounds were further purified by recrystallization from methanol to yield analytically pure products.

The trifluoromethyl substituted compounds were synthesised because the CF_3 group constitutes an important group in medicinal chemistry due to its peculiar chemical properties centering on its hydrophobic nature, electron rich environment and hydrogen bonding capacity. It can also confer high in vivo stability to molecules [36–38]. The compounds were further characterized using various NMR techniques including COSY, HMBC and HSQC. The ^{1}H NMR data of the compounds are shown in Fig. 1a, b for the respective compounds. The ^{1}H NMR of 2-trifluoromethyl phenyl semicarbazone (**2**) showed a singlet at 10.5 ppm for the isolated NH proton followed by doublets for the protons in the phenyl ring and an additional singlet for the CH protons. A broad peak at 6.62 ppm was assigned to NH_2 protons with an integration value of 2. The ^{13}C NMR spectrum of the compound (Fig. 2a) showed nine carbons as expected. The C=O carbon appeared at 156.5 ppm followed by other carbons in the structure. It is interesting to note that the CF_3 carbon showed multiple couplings, and the peak was centred at 126.2 ppm. Figure 1b represents the ^{1}H NMR spectrum of the 2-trifluoromethyl phenyl substituted thiosemicarbazone (**4**) in dimethyl sulfoxide solvent. In accordance with the structure of the molecule, the NH proton appeared at 11.7 ppm followed by the aromatic proton signals further upfield. The spectrum also showed a singlet for each of the NH_2 protons respectively. Figure 2b shows the ^{13}C spectrum for the same compound in d_6-DMSO solvent. Once again we observed the C=O peak at 178.4 ppm similar to that obtained for the 2-trifluoromethyl substituted phenyl semicarbazone, except it was shifted downfield as expected for thio compounds. We also observed the CF_3 carbon peak as a quartet centered at 126.8 ppm confirming the presence of this group in the structure of the molecule. This carbon is shifted upfield relative to the 4-substituted trifluoromethyl group of the semicarbazone [31].

Table 1 Crystal parameters for all the compounds

Compounds #	(**1**)	(**2**)	(**3**)	(**4**)	
Empirical formula	$C_9H_8F_3N_3O$	$C_9H_8F_3N_3O$	$C_9H_8F_3N_3S$	$C_9H_8F_3N_3S$	
Formula weight	231.18	231.18	247.24	247.24	
Temperature	190 (2) K	190 (2) K	190 (2) K	190 (2) K	
Wavelength	0.71073 Å	0.71073 Å	0.71073 Å	0.71073 Å	
Crystal system	Monoclinic	Monoclinic	Monoclinic	Monoclinic	
Space group	$P2_1/c$	$P2_1/c$	$P2_1/c$	$P2_1/n$	
Unit cell dimensions	a = 14.706 (3) Å	a = 7.4630 (7 Å	a = 15.8160 (13) Å	a = 6.8489 (17) Å	
	b = 5.1088 (10) Å, β = 102.976 (19)°	b = 6.4315 (6) Å, β = 90.803 (8)°	b = 8.4856 (5) Å, β = 104.826 (8)°	b = 8.555 (3) Å, β = 94.716 (18)°	
	c = 13.204 (2) Å	c = 20.892 (2) Å	c = 8.4410 (7) Å	c = 18.048 (4) Å	
Volume	966.7 (3) $Å^3$	1002.71 (17) $Å^3$	1095.14 (14) $Å^3$	1053.9 (5) $Å^3$	
Z	4	4	4	4	
Density (calculated)	1.588 Mg/m^3	1.531 Mg/m^3	1.500 Mg/m^3	1.558 Mg/m^3	
Absorption coefficient	0.147 mm^{-1}	0.141 mm^{-1}	0.312 mm^{-1}	0.324 mm^{-1}	
F(000)	472	472	504	504	
Crystal size	0.4 × 0.3 × 0.06 mm^3	0.4 × 0.15 × 0.15 mm^3	0.6 × 0.3 × 0.1 mm^3	0.4 × 0.1 × 0.1 mm^3	
Theta range for data collection	3.75°–24.99°	3.33°–24.99°	3.46°–25.00°	3.28°–24.99°	
Index ranges	$-17 \le h \le 17$, $-3 \le k \le 6$, $-14 \le l \le 15$	$-4 \le h \le 8$, $-4 \le k \le 7$, $-24 \le l \le 24$	$-18 \le h \le 18$, $-10 \le k \le 10$, $-9 \le l \le 10$	$-6 \le h \le 8$, $-10 \le k \le 10$, $-21 \le l \le 21$	
Reflections collected	3002		3634	8470	2452
Independent reflections	1692 [R(int) = 0.0516]		1763 [R(int) = 0.0329]	1923 [R(int) = 0.0405]	2452 [R(int) = 0.0000]
Completeness to theta = 24.99°	99.8%		99.3%	99.8%	99.8%
Absorption correction	Semi-empirical from equivalents		Semi-empirical from equivalents	Semi-empirical from equivalents	Semi-empirical from equivalents
Max. and min. transmission	1 and 0.30435		1 and 0.98219	1 and 0.88951	1 and 0.38827
Refinement method	Full-matrix least-squares on F^2		Full-matrix least-squares on F^2	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Data/restraints/parameters	1692/0/145		1763/0/145	1923/0/173	2452/0/147
Goodness-of-fit on F2	0.997		1.092	1.169	0.975
Final R indices [I > 2sigma(I)]	R1 = 0.0593, wR2 = 0.1179		R1 = 0.0435, wR2 = 0.0911	R1 = 0.0516, wR2 = 0.1109	R1 = 0.0707, wR2 = 0.1720
R indices (all data)	R1 = 0.1115, wR2 = 0.1468		R1 = 0.0641, wR2 = 0.1034	R1 = 0.0627, wR2 = 0.1154	R1 = 0.1134, wR2 = 0.1880, 0.010 (3)
Largest diff. peak and hole	0.226 and −0.297 e $Å^{-3}$		0.187 and −0.216 e $Å^{-3}$	0.283 and −0.245 e $Å^{-3}$	0.327 and −0.339 e $Å^{-3}$

Single Crystal X-ray Studies of 2- and 4-Trifluoromethyl Substituted Phenyl Semicarbazone and Thiosemicarbazones

Figure 3 shows the molecular structure of 4-trifluoromethyl phenyl semicarbazone (**1**). The crystal data along with the collection parameters are shown in Table 1. Table 2 shows selected bond lengths. The bond lengths and angles were as expected. It appears from the crystal structure that the CF_3 group is in the same plane as that of the semicarbazone moiety. It is also evident that the N2–H proton is intact and therefore this compound exists as a keto tautomer instead of the enol configuration, which is not observed for this semicarbazone, although it is known that these semicarbazones can exhibit keto-enol tautomerism. Furthermore we find that the compound exists as an anti-conformer. The N1–N2 bond length in the structure is 1.374 (4) Å, which is consistent with the reported value for the phenyl semicarbazone (1.355 (4) Å). The C8–O1 bond is 1.237 (4) Å, which is consistent with the expected value for a C=O compound (1.227 (3) Å) [39].

Table 2 Selected bond lengths and angles of semicarbazones/thiosemicarbazones

Compound (**1**)				Compound (**2**)			
Bonds	Lengths	Bonds	Angles	Bonds	Lengths	Bonds	Angles
C(1)–C(6)	1.395 (5)	C(6)–C(1)–C(2)	118.0 (3)	C(1)–C(6)	1.395 (3)	C(6)–C(1)–C(2)	118.02 (19)
C(1)–C(2)	1.396 (4)	C(6)–C(1)–C(7)	122.8 (3)	C(1)–C(2)	1.402 (3)	C(6)–C(1)–C(7)	119.37 (19)
C(1)–C(7)	1.447 (5)	C(2)–C(1)–C(7)	119.1 (3)	C(1)–C(7)	1.47(3)	C(2)–C(1)–C(7)	122.61 (19)
C(2)–C(3)	1.388 (5)	C(3)–C(2)–C(1)	120.3 (3)	C(2)–C(3)	1.391 (3)	C(3)–C(2)–C(1)	120.2 (2)
C(3)–C(4)	1.374 (5)	C(4)–C(3)–C(2)	121.0 (3)	C(2)–C(9)	1.488 (3)	C(3)–C(2)–C(9)	118.7 (2)
C(4)–C(5)	1.397 (4)	C(3)–C(4)–C(5)	119.3 (3)	C(3)–C(4)	1.375 (3)	C(1)–C(2)–C(9)	121.05 (19)
C(4)–C(9)	1.489 (5)	C(3)–C(4)–C(9)	120.0 (3)	C(4)–C(5)	1.374 (3)	C(4)–C(3)–C(2)	120.4 (2)
C(5)–C(6)	1.376 (5)	C(5)–C(4)–C(9)	120.6 (3)	C(5)–C(6)	1.380 (3)	C(5)–C(4)–C(3)	120.0 (2)
C(7)–N(1)	1.291 (4)	C(6)–C(5)–C(4)	119.9 (3)	C(7)–N(1)	1.275 (3)	C(4)–C(5)–C(6)	120.3 (2)
C(8)–O(1)	1.237 (4)	C(5)–C(6–C(1)	121.5 (3)	C(8)–O(1)	1.239 (2)	C(5)–C(6)–C(1)	121.0 (2)
C(8)–N(3)	1.319 (4)	N(1)–C(7)–C(1)	121.8 (3)	C(8)–N(3)	1.334 (3)	N(1)–C(7)–C(1)	119.43 (19)
C(8)–N(2)	1.373 (4)	O(1)–C(8)–N(3)	124.8 (3)	C(8)–N(2)	1.364 (3)	O(1)–C(8)–N(3)	123.78 (19)
C(9)–F(3)	1.339 (4)	O(1)–C(8)–N(2)	118.5 (3)	C(9)–F(1)	1.339 (3)	O(1)–C(8)–N(2)	119.70 (19)
C(9)–F(1)	1.344 (4)	N(3)–C(8)–N(2)	116.7 (3)	C(9)–F(3)	1.340 (2)	N(3)–C(8)–N(2)	116.51 (19)
C(9)–F(2)	1.351 (4)	F(3)–C(9)–F(1)	106.6 (3)	C(9)–F(2)	1.347 (3)	F(1)–C(9)–F(3)	105.60 (18)
N(1)–N(2)	1.374 (4)	F(3)–C(9)–F(2)	106.1 (3)	N(1)–N(2)	1.369 (2)	F(1)–C(9)–F(2)	105.49 (19)
Compound (**3**)				Compound (**4**)			
Bonds	Lengths	Bonds	Angles	Bonds	Lengths	Bonds	Angles
C(1)–C(2)	1.380 (4)	C(2)–C(1)–C(6)	118.8 (3)	C(1)–C(6)	1.374 (6)	C(6)–C(1)–C(2)	118.3 (4)
C(1)–C(6)	1.387 (4)	C(2)–C(1)–C(7)	119.6 (3)	C(1)–C(2)	1.396 (6)	C(6)–C(1)–C(7)	119.3 (4)
C(1)–C(7)	1.461(4)	C(6)–C(1)–C(7)	121.5 (3)	C(1)–C(7)	1.464 (7)	C(2)–C(1)–C(7)	122.3 (4)
C(2)–C(3)	1.385 (4)	C(1)–C(2)–C(3)	121.0 (3)	C(2)–C(3)	1.392 (6)	C(3)–C(2)–C(1)	120.3 (5)
C(3)–C(4)	1.373 (5)	C(4)–C(3)–C(2)	119.5 (3)	C(2)–C(9)	1.495 (6)	C(3)–C(2)–C(9)	118.4 (4)
C(4)–C(5)	1.385 (5)	C(3)–C(4)–C(5)	120.2 (3)	C(3)–C(4)	1.373 (7)	C(1)–C(2)–C(9)	121.3 (4)
C(4)–C(9)	1.494 (5)	C(3)–C(4)–C(9)	120.5 (3)	C(4)–C(5)	1.365 (8)	C(4)–C(3)–C(2)	119.7 (5)
C(5)–C(6)	1.375 (4)	C(5)–C(4)–C(9)	119.3 (3)	C(5)–C(6)	1.379 (6)	C(5)–C(4)–C(3)	120.2 (4)
C(7)–N(1)	1.275 (4)	C(6)–C(5)–C(4)	119.9 (3)	C(7)–N(1)	1.269 (6)	C(4)–C(5)–C(6)	120.3 (5)
C(8)–N(3)	1.319 (4)	C(5)–C(6)–C(1)	120.6 (3)	C(8)–N(3)	1.299 (6)	C(1)–C(6)–C(5)	121.1 (5)
C(8)–N(2)	1.347(3)	N(1)–C(7)–C(1)	120.5 (3)	C(8)–N(2)	1.343 (6)	N(1)–C(7)–C(1)	120.5 (4)
C(8)–S(1)	1.687 (3)	N(3)–C(8)–N(2)	117.3 (2)	C(8)–S(1)	1.699 (4)	N(3)–C(8)–N(2)	118.2 (4)
C(9)–F(2′)	1.220 (11)	N(3)–C(8)–S(1)	123.3 (2)	C(9)–F(2)	1.330 (6)	N(3)–C(8)–S(1)	123.1 (4)
C(9)–F(1′)	1.259 (13)	N(2)–C(8)–S(1)	119.5 (2)	C(9)–F(1)	1.330 (6)	N(2)–C(8)–S(1)	118.6 (4)
C(9)–F(3)	1.298 (9)	F(2′)–C(9)–F(1′)	117.9 (13)	C(9)–F(3)	1.332 (5)	F(2)–C(9)–F(1)	104.7 (4)
C(9)–F(2)	1.316 (9)	F(3)–C(9)–F(2)	108.6 (8)	N(1)–N(2)	1.364 (5)	F(2)–C(9)–F(3)	107.2 (5)
						F(1)–C(9)–F(3)	106.6 (4)

Table 3 shows the hydrogen bonds observed for **1**. The N–H protons are all involved in H-bonding. Examination of the crystal packing diagram of this compound revealed (Fig. 4) one intramolecular and three intermolecular hydrogen bonds (Table 3) two hydrogen bonds. Interestingly, the CF_3 group at the 4-position of the molecule was not involved in an intermolecular hydrogen bond similar to that observed for **2** described below.

Figure 5 shows the molecular structure of 2-trifluomethyl phenyl substituted semicarbazone (**2**). Selected bond lengths for this compound are listed in Table 2. We observe a similar trend regarding the bond lengths as observed for **1**. In compound **2**, we observed the keto form. Furthermore it also showed an anti-conformer configuration similar to **1**. Examination of the intra and intermolecular hydrogen bonding characteristics for the compound revealed interesting results (Table 3). As observed for the previous compound, the N–H groups are involved in H-bonding. Additionally, intermolecular hydrogen bonding observed between the fluorine atom and the H3

Table 3 Hydrogen bonds for compounds (**1**)–(**4**)

Compound #	D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
1	N(2)–H(2A)...O(1)#1	0.88	2.05	2.865 (4)	153.3
	N(3)–H(3A)...O(1)#2	0.88	2.02	2.876 (4)	164.2
2	N(2)–H(2)...O(1)#1	0.88	2.03	2.894 (2)	166.7
	N(3)–H(3A)...O(1)#2	0.88	2.06	2.937 (2)	174.2
	N(3)–H(3B)...F(2)#3	0.88	2.34	3.118 (2)	146.8
3	N(2)–H(2A)...S(1)#1	0.88	2.52	3.386 (2)	169.9
	N(3)–H(3B)...S(1)#2	0.88	2.61	3.443 (2)	158.7
4	N(3)–H(3B)...S(1)#1	0.88	2.51	3.386 (4)	171.1
	N(2)–H(2)...S(1)#2	0.88	2.53	3.393 (4)	166.5

Symmetry transformations used to generate equivalent atoms (**1**): #1 −x+1, −y+2, −z+2 #2 −x+1, y−1/2, −z+5/2

(**2**): #1 −x+1, −y+2, −z+1 #2 −x+2, −y+2, −z+1 #3 x+1, y, z;(**3**): #1 −x+1, y+1/2, −z+1/2 #2 −x+1, y−1/2, −z+1/2

(**4**) #1 −x+1/2, y−1/2, −z+5/2 #2 −x+1/2, y+1/2, −z+5/2

atom of the molecule with a donor–acceptor distance of 3.118 (2) Å (Fig. 6). It is intriguing that the 4-CF_3 group substituted phenyl semicarbazone analogue did not show the presence of such an intermolecular hydrogen bond. We believe that perhaps the proximity of the CF_3 group at position 2 might have influenced the formation of the intermolecular hydrogen bond. If this rationale is correct then we should anticipate a similar outcome in the case of 2-CF_3 substituted phenyl thiosemicarbazone's X-ray crystal structure.

Figure 7 shows the molecular structure of 4-CF_3 substitued phenyl thiosemicarbazone (**3**). This molecule also showed that the trifluoromethyl group is in the same plane as the thiosemicarbazone moiety. Again, we observe the keto form with anti-conformer similar to the afore-discussed compounds. Table 2 shows selected bond lengths for **3**; they are within expected ranges. We observe the classical hydrogen bonds N2–H2…S1 and N3–H3B…S1 [3.386 (2) and 3.443 (2)] (see Table 3). In **3** (Fig. 8). A weak interaction with quite unfavourable donor-H-acceptor angle in N3–H…N1 (104°) is also apparent. This type of weak intramolecular between the imine N atom and the adjacent NH group was also reported for N4-substituted thiosemicarbazones [40].

In order to complete the series and compare the crystal structure characteristics, we prepared the 2-trifluoromethyl substituted phenyl thiosemicarbazone (**4**) to understand whether this compound forms a similar type of intermolecular hydrogen bond with the fluorine and the

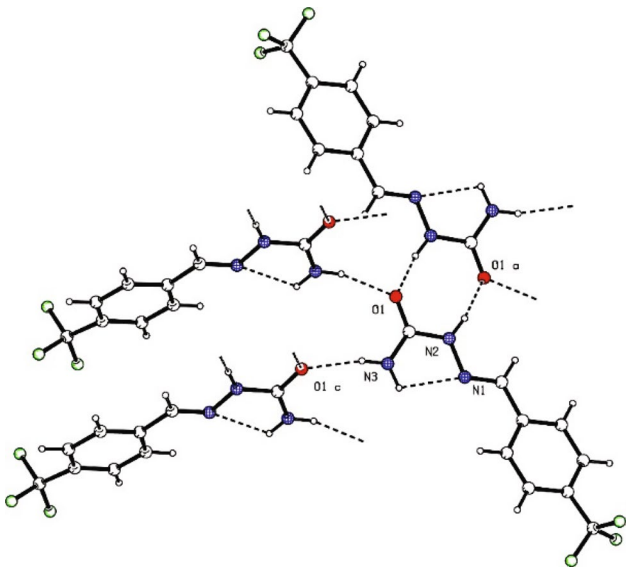

Fig. 4 Crystal packing diagram for 4-CF_3 phenyl semicarbazone (**1**)

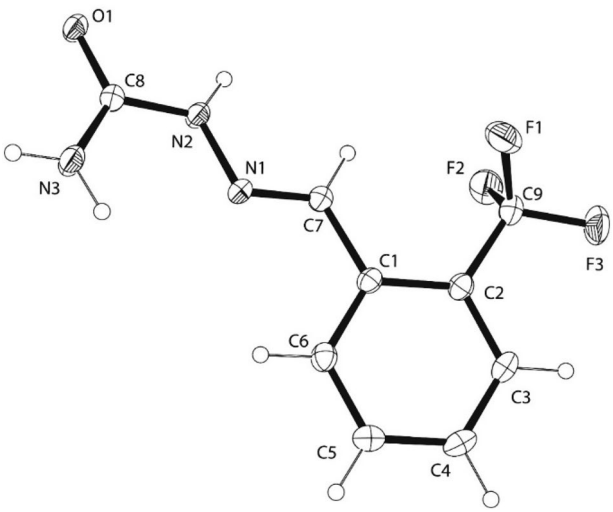

Fig. 5 Molecular structure of 2-CF_3 phenyl semicarbazone (**2**) (30% ellipsoid probability)

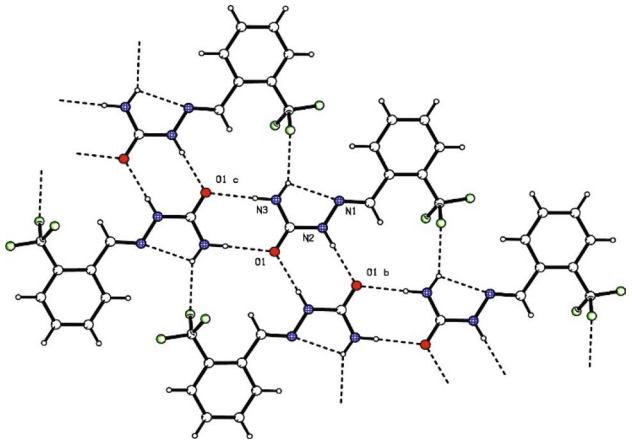

Fig. 6 Crystal packing diagram for 2-CF_3 phenyl semicarbazone (**2**) (see the new intermolecular hydrogen bonding between F and N3–H)

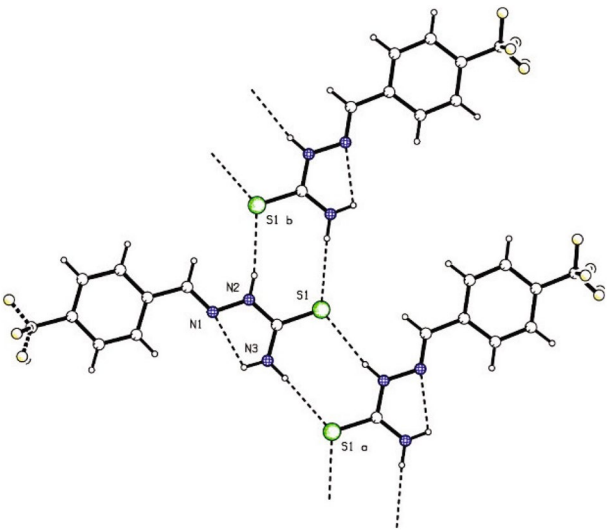

Fig. 8 Crystal packing diagram for 4-CF_3 phenyl thiosemicarbazone (**3**)

N–H(3) group as seen in (**2**). Figure 9 shows the molecular structure of **4**. Selected bond lengths are shown in Table 2. The bond length of C(8)–S(1) is 1.699(4) Å confirms the C=S (thioketo) character of the compound. However, and in contrast to **2**, in **4** no intermolecular hydrogen bond between the fluorine atoms of the trifluromethyl group and the NH group was observed (Fig. 10). This puzzling observation may be rationalized by the electronegativity differences between oxygen and sulphur. More importantly, we propose the existence of an equilibrium between a neutral and a zwitterionic structure for the thiosemicarbazone, and a lower tendency to form such a species for the oxygen analogue. Further proof of this comes from the ^{1}H NMR spectra of both the compounds (see the NMR spectra). At least in solution (DMSO solvent) we see that the NH_2 protons appear as a broad singlet in the case of the semicarbazones while the same functional group exhibits distinct singlets in the thiosemicarbazone analogue, demonstrating that the protons are in different environments on the NMR timescale.

Thus a close look at the hydrogen bond formation between the trifluoromethyl group attached in 2-position of the phenyl ring of these semicarbazone and thiosemicarbazone revealed the importance of the canonical

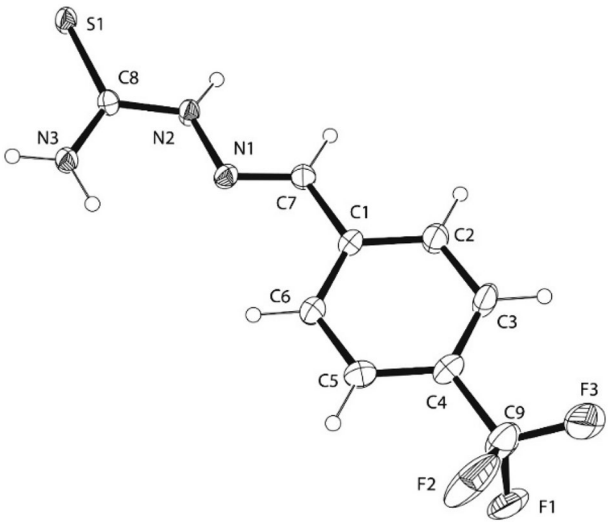

Fig. 7 Molecular structure of 4-CF_3 phenyl thiosemicarbazone (**3**) (30% ellipsoid probability)

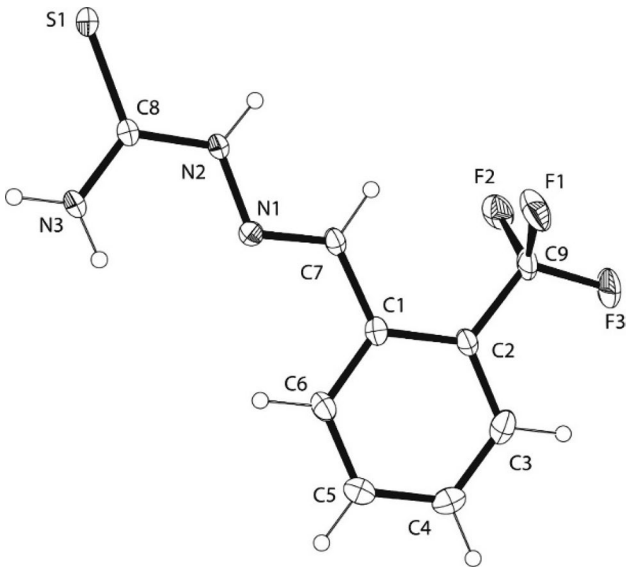

Fig. 9 X-ray crystal structure of 2-trifluoromethyl phenyl thiosemicarbazone (**4**) (30% ellipsoid probability)

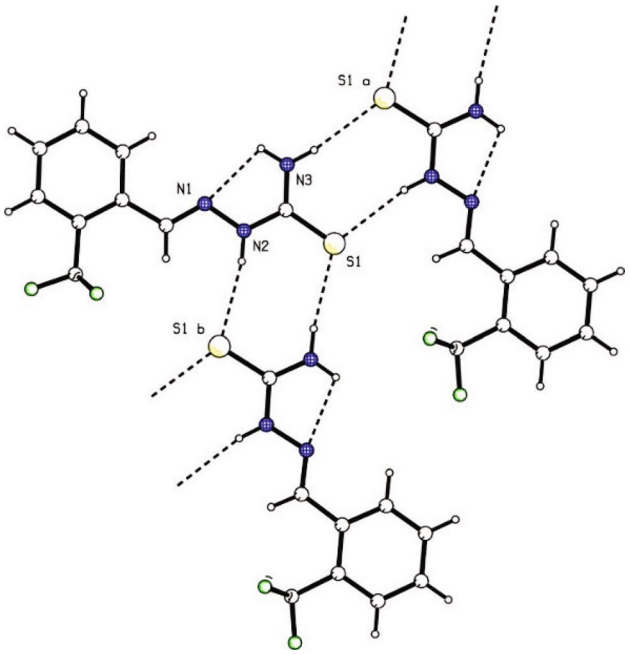

Fig. 10 Crystal packing diagram of 2-trifluoromethyl phenyl thiosemicarbazone (**4**) (note: there is no intermolecular hydrogen bond with fluorine atoms in this molecule)

structure associated with the latter than the former. Further work is in progress to synthesize additional new flouro substituted semi and thiosemicarbazones and to establish their hydrogen bonding characteristics along with optimizing strategies to radio label with positron emitting isotopes for imaging purposes.

Conclusion

In summary we have determined the single crystal X-ray crystal structure of four structurally similar semi and thiosemicarbazones. The ^{1}H NMR in dimethyl sulfoxide showed considerable differences between the semi and thiosemicarbazones NH_2 group and the ^{13}C spectral data was consistent with the ^{1}H NMR data. The NH_2 group in the semicarbazone appeared as a broad singlet with an integration ratio of 2 while in thiosemicarbazone the protons of the NH_2 group appeared well separated as a broad singlet with an integration ratio of 1. In terms of hydrogen bonding characteristics, there was not much change in the 4-trifluoromethyl substituted semi and thiosemicarbazones. However, we observe that in the case of 2-trifluoromethyl substituted semicarbazone that the fluorine atom of this group formed an intermolecular hydrogen bond with one of the protons of the NH group while this feature was absent in the case of thiosemicarbazone with similar structure.

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