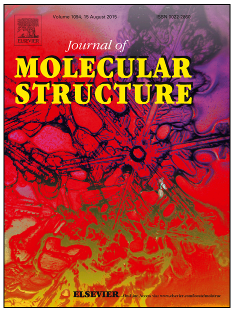

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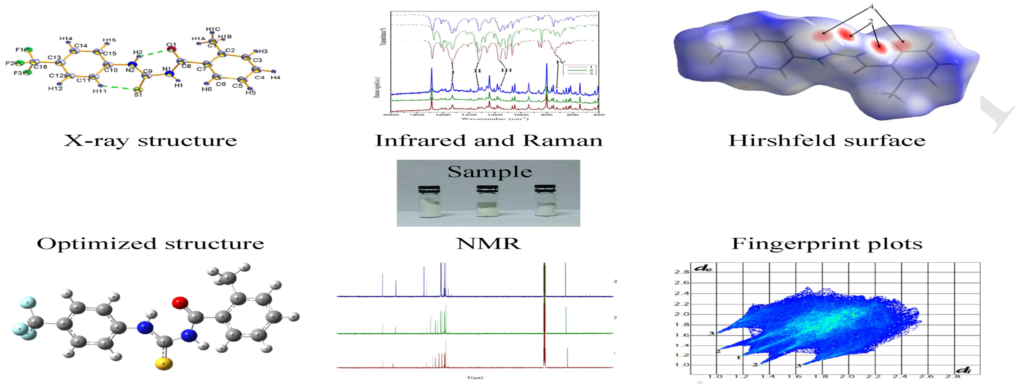
Graphical abstract: The three novel isomeric acyl thiourea compounds were firstly prepared and characterized by some spectroscopic techniques. The molecular structure of compounds **1** and **3** was determined by X-ray diffraction analysis. A detailed analysis of the intermolecular contacts in the compounds **1** and **3** have been performed based on the Hirshfeld surfaces, their 2D fingerprint plots and the enrichment ratios. Conformational aspects are also discussed in terms of the vibrational spectra.



Synthesis, structural characterization and quantum chemical calculations on 1-(isomeric methylbenzoyl)-3-(4-trifluoromethylphenyl)thioureas

Lei Qiao[a], Yu Zhang[a], Wei Hu[a], Jiajia Guo[a], Wenli Cao[a], Zimei Ding[a], Zhiwei Guo[a], An Fan[a], Jirong Song[b] and Jie Huang[a,*]

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Abstract: The 1-(isomeric methylbenzoyl)-3-(4-trifluoromethylphenyl)thioureas (**1-3**) have been synthesized using the reaction of 2-methylbenzoyl isothiocyanate, 3-methylbenzoyl isothiocyanate and 4-methylbenzoyl isothiocyanate with 4-aminotrifluorotoluene in dry tetrahydrofuran in good yields. The series of compounds were characterized by FT-IR and Raman (vibrational spectra), multinuclear (^{1}H and ^{13}C) NMR, mass spectrometry and elemental analyses techniques. Structural and conformational properties of compounds **1** and **3** were determined by the X-ray single crystal diffraction. A detailed analysis of the intermolecular actions in the two crystal structures has been performed based on the Hirshfeld surfaces and their two-dimensional fingerprint plots. Different hydrogen bonds were formed in the compounds **1** and **3**, which have important impact to the FT-IR spectrum. In addition, vibrational spectral characteristics of compounds **1-3** have been studied by FT-IR and Raman, along with the quantum chemical calculations at the B3LYP/6-311++G (d, p) level of approximation.

Keywords: 1-(isomeric methylbenzoyl)-3-(4-trifluoromethylphenyl)thioureas; X-ray single crystal analysis; Quantum chemical calculation; Hydrogen bonds; Hirshfeld surface

1. Introduction

Acyl thiourea derivatives have become the center of attraction to the scientific community for a widely diversity applications [1] such as antiviral [2, 3], antimicrobial [4-6], anti-HIV [7], herbicidal [8], antitumor [9, 10], anti-inflammatory [11], insecticidal [12] and fungicidal properties [13]. Furthermore, it can also be used in heterocyclic syntheses [14-17] and anion recognition materials [18-20]. In addition, thiourea derivatives are exceptionally versatile ligands in Coordination Chemistry [21], able to coordinate with the transition metals such as Ni(Ⅱ), Cu(Ⅱ), Co(Ⅱ), Fe(Ⅲ) [22, 23], Zn(Ⅱ) [24], Pd(Ⅱ) [25] and Ru(Ⅱ) [26] ions as neutral monobasic or dibasic ligands.

Very recently, thiourea derivatives are placed at a prestigious status as evidenced by the fact that the

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molecular structure of the class of compounds prior to their use in various applied fields [1]. M.G. Woldu *et al.* [27] demonstrated that the four main forms of acyl thiourea derivatives can be denoted as S, U, M and Z, which the letters reflect the position of the C=O and C=S double bonds relative to the drawn N-H bond. Aamer Saeed *et al.* [28] and Raúl Ramos Cairo *et al.* [29] also pronounced that Hirshfeld surfaces analysis is an impressive tool for evaluating intermolecular interaction in a series of thioureas compounds. It is note that the emergence of quantum chemistry does accelerate the study process of molecular structure. The quantum chemistry method is one of most effective means to explain molecular structure such as the infrared spectrum and raman activity [30-33], maximum absorption bands of UV-Vis [34], structure parameters and downfield and upfield of ^{1}H and ^{13}C chemical shifts [35]. Furthermore, the electronic properties which were calculated by the quantum chemistry can well explain the structure-activity relationship of organic compounds [36]. Gil *et al.* performed thermodynamic [37] and non-linear optical (NLO) behavior [38] for thiourea derivatives using the density functional method (DFT) with different basis sets. Aamer Saeed *et al*. [39, 40] calculated the electronic and reactivity properties of thiourea compounds by the natural bond orbital analysis using the quantum chemical calculation.

Many reports on 1-(acyl/aroyl)-3-(2-, 3- and 4-substituted alkyl/ aryl)thioureas can be found in the literatures [32，35, 41]. Less attention, however, has been received by the isomeric 1-(2-, 3- and 4-substituted aroyl)-3-(alkyl/aryl)thioureas. Herein we report the preparation and spectroscopic and conformational properties of 1-(isomeric methylphenyl)-3-(4-trifluoromethylphenyl)thioureas. In this article, two crystal structures have been determined by X-ray diffraction. The intermolecular contacts have been preformed based on the Hirshfeld surfaces and their associated 2D fingerprint plots. The FT-IR, Raman, mass spectra and NMR spectroscopic properties were determined and discussed. We also validated the FT-IR and Raman and analyzed those properties by the quantum chemical calculations using GAUSSIAN 09W program [42].

2. Experimental

2.1. Materials and measurements

The solvent tetrahydrofuran, ethyl acetate, N, N - dimethyl formamide (DMF), dichloro sulfoxide and ethanol were of analytical grade quality and were used without further purification (E. Merck). The reagents potassium thiocyanate, 4-aminotrifluorotoluene, 2-methylbenzoic acid, 3-methylbenzoic acid and 4-methylbenzoic acid were purchased from Aldrich and were of analytical grade and used as received. Microwave syntheses were carried out using a BILON-CW-1000 microwave synthesizer with the appropriate absorption power settings. Melting points were recorded using a Cossim KER3100-08S apparatus and were uncorrected. Elemental analyses were conducted using an ELEMENTAR Vario EL □ elemental analyzer. ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were determined in dimethylsulfoxide-d_6 at 400 MHz and 100 MHz using a Bruker spectrophotometer. ^{1}H NMR (400 MHz): internal standard solvent DMSO-d_6 (2.50 ppm from TMS): internal standard TMS; ^{13}C NMR (100 MHz): internal standard solvent DMSO-d_6 (39.96 ppm from TMS): internal standard TMS; the splitting of proton resonances in the reported ^{1}H NMR spectra were remarked as s=singlet, d=double, t=triplet dd=doublet of doublets, dt=doublet of triplets and m=multiple; coupling constants are reported in Hz. Mass spectra were recorded on a MAT-112-S spectrometer at 70 eV.

2.2. Synthesis and characterization

A solution of prepared heterogeneous methyl benzoyl chloride (1.32-1.35 ml, 10 mmol) in dry tetrahydrofuran (40 mL) was added drop wise to a three-necked round-bottomed flask containing potassium thiocyanate (1.4577 g, 15 mmol). The mixtures were refluxed for approximately 2 hours at 60 □. A solution of 4-aminotrifluorotoluene (1.5307 g, 9.5 mmol) in tetrahydrofuran (20 mL) was added and reacted in microwave heating 60-65□ for about 90 seconds. The resulting mixture was pushed into 500 mL water and filtered off, washed with ethanol and dried in vacuo. The forming compounds were grown at room temperature from organic solvent (acetonitrile and ethyl acetate) for single crystals of compounds **1** and **3**, respectively.

2.2.1. Synthesis of 1-(2-methylphenyl)-3-(4-trifluoromethylphenyl)thiourea, (1)

White solid; Yield: 83.49%; m.p.: 187.8-188.1 □; FT-IR (KBr): ν, cm^{-1} 3355 (w, free N-H), 3154 (w, assoc H-N), 2919 (w, Ar-CH), 1681 (s, C=O), 1158 (m, ν_s(NCN)), 763 (m, C=S). ^{1}H NMR (400 MHz, DMSO-d_6): δ, ppm 12.69 (s, 1H, NH), 11.87 (s, 1H, NH), 7.99 (d, J=8.4 Hz, 2H, Ar-H), 7.80 (d, J=8.6 Hz, 2H, Ar-H), 7.58-7.41 (m, 2H, Ar-H), 7.31 (t, J=7.6 Hz, 2H, Ar-H), 2.44 (s, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO): δ, ppm 179.94 (C=S), 170.92 (C=O), 136.61 (Ar-C), 134.34 (Ar-C), 131.53 (Ar-C), 131.14 (2C), 128.68 (2C), 126.25 (Ar-C), 126.03 (m, 2C), 125.05 (2C), 123.23 (CF_3), 19.96 (CH_3). Anal. Calc. for $C_{16}H_{13}F_3N_2OS$ (MW=338.35) in wt%: C, 56.80; H, 3.87; N, 8.28. Found: C, 56.82; H, 3.79; N, 8.30. EI MS (70 eV) m/z: 338.41 $[M]^+$.

2.2.2. Synthesis of 1-(3-methylphenyl)-3-(4-trifluoromethylphenyl)thiourea, (2)

Pale yellow solid; Yield: 80.69%; m.p.: 114.6-116.4 □; FT-IR (KBr): ν, cm^{-1} 3357 (w, free N-H), 3246 (w, assoc H-N), 2922 (w, Ar-CH), 1666 (s, C=O), 1154 (m, ν_s(NCN)), 772 (m, C=S). ^{1}H NMR (400 MHz, DMSO-d_6): δ, ppm 12.77 (s, 1H, NH), 11.67 (s, 1H, NH), 7.97 (d, J=8.4 Hz, 2H, Ar-H), 7.80 (dd, J=17.7, 9.2 Hz, 2H, Ar-H), 7.46 (dt, J=15.1, 7.6 Hz, 2H, Ar-H), 2.40 (s, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO): δ, ppm 179.94 (C=S), 168.73 (C=O), 142.15 (Ar-C), 138.33 (Ar-C), 134.32 (Ar-C), 132.39(2C), 129.64 (2C), 128.87 (Ar-C), 126.29 (m, 2C), 125.10 (2C), 123.22 (CF_3), 21.28 (CH_3). Anal. Calc. for $C_{16}H_{13}F_3N_2OS$ (MW=338.35) in wt%: C, 56.80; H, 3.87; N, 8.28. Found: C, 56.79; H, 3.82; N, 8.25. EI MS (70 eV) m/z: 338.39 $[M]^+$.

2.2.3. Synthesis of 1-(4-methylphenyl)-3-(4-trifluoromethylphenyl)thiourea, (3)

White solid; Yield: 79.70%; m.p.: 154.9-156.5 □; FT-IR (KBr): v, cm^{-1} 3351 (w, free N-H), 3208 (w, assoc H-N), 2931 (w, Ar-CH), 1679 (s, C=O), 1158 (m, v_s(NCN)), 766 (m, C=S). ^1H NMR (400 MHz, DMSO-d_6): δ, ppm 12.81 (s, 1H, NH), 11.63 (s, 1H, NH), 7.99-7.91 (m, 4H, Ar-H), 7.79 (d, J=8.59 Hz, 2H, Ar-H), 7.36 (d, J=8.06 Hz, 2H, Ar-H), 2.40 (s, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO): δ, ppm 179.98 (C=S), 168.48 (C=O), 144.24 (Ar-C), 142.16 (Ar-C), 129.55 (Ar-C), 129.51(2C), 129.32 (2C), 126.78 (Ar-C), 126.23 (m, 2C), 125.03 (2C), 123.22 (CF_3), 21.63 (CH_3). Anal. Calc. for $C_{16}H_{13}F_3N_2OS$ (MW=338.35) in wt%: C, 56.80; H, 3.87; N, 8.28. Found: C, 56.78; H, 3.78; N, 8.29. EI MS (70 eV) m/z: 338.34 $[M]^+$.

2.3. Vibrational spectroscopy

Solid-phase infrared spectra (KBr pellets) were recorded in the 4000-400 cm^{-1} range on a Bruker EQUINOX 55 FT-IR spectrometer. The FT-Raman spectra were recorded in the region 2000-100 cm^{-1} using a Bruker IFS 66v spectrometer equipped with Ar^+ laser source operating at 514.5 nm line with of spectral width 2 cm^{-1}.

2.4. Quantum chemical calculations

Quantum chemical calculations were performed with the GAUSSIAN 09W program package by using the B3LYP DFT hybrid methods. The files of X-ray structure were sever as the initial geometry and fully optimized for compounds **1** and **3**. The conformational analysis of compound **2** also was performed around all bonds having free rotation to obtain the most stable conformer [36]. The valence triple-ξ basis set augmented with diffuse and polarization functions in both the hydrogen and heavy atom [6-311++G (d, p)] were applied to optimize geometry parameter and to calculate frequency [43]. The Raman activities (in Å4/amu) calculated with the GAUSSIAN 09W program was converted to corresponding Raman intensities. The calculated vibrational properties corresponding in all cases to potential energy minima for which no imaginary frequency was found.

2.5. X-ray data collection, structure solution and refinement

Single crystal X-ray experiments were performed with Mo *Kα* radiation (λ=0.071073 nm) with Bruker APEX-II CCD diffractometer. SHELXS 97 was used for structure solution and refinement using the direct methods [44]. All the non-hydrogen atoms were obtained by the full-matrix-block least-squares method on F^2 with anisotropic thermal parameters [45]. The hydrogen atoms were located in difference Fourier maps and refined at idealized positions riding on the relevant carbon or nitrogen atoms with C-H=0.095 nm and N-H=0.088 nm and with isotropic displacement $U_{iso}(H)=1.2U_{eq}(C, N)$. All molecular plots and packing diagrams were drawn using Diamond program [46] and additional metrical data were calculated using PLATON [47]. The intermolecular contacts of compounds **1** and **3** were drawn in **Fig. S1** using Mercury program [48].

2.6. Hirshfeld surface computational method

Hirshfeld surfaces and their 2D fingerprint plots [49-52] were performed by the CrystalExplorer 3.1 software [53]. The Hirshfeld surface is becoming a valuable tool for decoding and quantifying the intermolecular interactions in a whole-of-molecule approach [54-56]. The Hirshfeld surfaces analysis on acyl thiourea derivatives were firstly reported by Aamer Saeed and coworkers [**57**], which is a quite big breakthrough in the acyl thioureas field. In order to explore the intermolecular contacts and their types in a molecule crystal, the d_{norm} (normalized contact distance) parameter were involved and defined for the follow equation:

$$d_{norm}=(d_i- r_i^{vdW})/ r_i^{vdW} +(d_e+ r_e^{vdW})/ r_e^{vdW} \qquad [58]$$

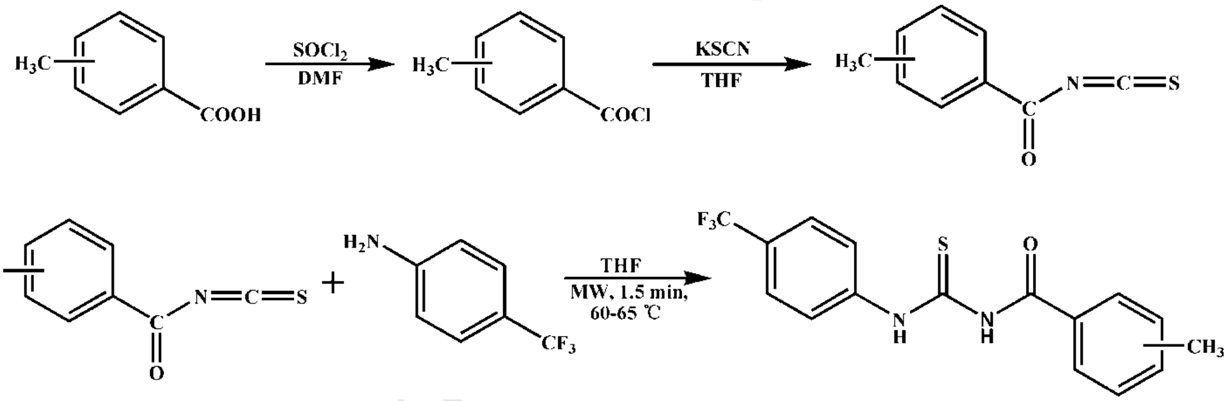
The parameters d_i and d_e were defined as the distances from the points on the surface to the nearest nucleus inside and outside the surface, respectively. The r^{vdW} is the van der Waals radius of the appropriate atom internal or external to the surface. The red scale on the Hirshfeld surface (d_{norm} is negative)-white (d_{norm} is equal to zero)-blue (d_{norm} is positive) was introduced to visualize the intermolecular contacts. The 3D d_{norm} surfaces were mapped over a fixed color of -0.27 (red) to 1.2 **Å** (blue). The fingerprint plots were displayed by using the translated 0.8-3.0 Å range and including reciprocal contacts. The shape index was mapped in the color range of -1.0 au (concave) to 1.0 au (concave) Å. The curvedness was mapped by default.

3. Results and discussion

3.1 Synthesis and characterization

The synthetic pathway to the title 1-(isomeric methylphenyl)-3-(4-trifluoromethylphenyl)thioureas is shown in **Scheme 1**[59]. Those corresponding isomeric methyl benzoyl isothiocyanate were produced by reaction of corresponding methyl benzoyl chloride with potassium thiocyanate in dry tetrahydrofuran. After reaction, 4-aminotrifluorotoluene was added into three-necked round-bottomed flask to generate the title compounds in 79.70%-83.49% yields. The products **1** and **3** were recrystallized with acetonitrile and ethyl acetate to shape the crystal suitable for the X-ray crystal diffraction, respectively.

In the ^{1}H NMR spectra of all synthesized thiourea compounds, the protons of the two -NH groups are obtained as single peak at 12.69-12.81 ppm and 11.61-11.87 ppm, respectively. The protons of benzene rings are observed at 7.31-7.99 ppm and the protons of methyl group appeared at 2.40-2.44 ppm in the title compounds. In the ^{13}C NMR spectra the characteristic phenyl signals are observed at δ 136.6-125.1, 142.2-125.1 and 144.2-125.0 for compounds **1**, **2** and **3**, respectively. The signals of the carbonyl and thiocarbonyl are found around δ 179.94 and 170.92 for **1**, δ 179.94 and 168.78 for **2**, δ 179.98 and 168.48 for 3 as well. The carbons of trifluoromethyl groups are observed at 123.23 ppm in all compounds. The FT-IR spectra of synthesized thioureas **1**, **2** and **3** show intense and characteristic absorptions at 3355, 3357 and 3351 cm^{-1} for N-H(1), 3154, 3246 and 3208 cm^{-1} for H-N(2), 2919, 2922 and 2931 cm^{-1} for (C-H, Ph), 1523, 1521 and 1525 cm^{-1} for (C=C, Ph), 1107, 1104 and 1101 cm^{-1} for (C-F), at 1681, 1666 and 1679 cm^{-1} for the carbonyl, 763, 772 and 766 cm^{-1} for thiocarbonyl, respectively. The detail of vibrational spectra would be discussed in the following part.



(1) 2-CH_3, (2) 3-CH_3, (3) 4-CH_3

Scheme 1. Synthesis of 1-(isomeric methylphenyl)-3-(4-trifluoromethylphenyl)thioureas.

3.2. Molecular and crystal structure

Crystals of compounds **1** and **3** were grown by slow evaporation of acetonitrile and ethyl acetate at room temperature, respectively. Data collections and structure refinement details are summarized in **Table 1**. Some selected bond lengths, bond angles and dihedral angles are in normal ranges and comparable to those in experiment data as shown in **Table 2** together with the calculated values at the B3LYP level in gas. The two crystal structures with atomic labeling and intramolecular hydrogen bonds are depicted in **Fig. 1** and **Fig. 2**, respectively. The computed molecular structures are shown in **Fig. 3**. Intra- and intermolecular hydrogen bond parameters are listed in **Table 3**. The X-ray result of the synthesized thiourea derivatives exhibit that **1** crystallized in triclinic system with space group of P-1, while **3** crystallized in orthorhombic system with space group of Pbca. The unit cell dimensions for **1** and **3** are $a=7.431(3)$ Å, $b=7.762(4)$ Å, $c=14.075(7)$ Å, $\alpha=100.619(9)°$, $\beta=96.159(8)°$, $\gamma=91.718(8)°$, $V=792.3(6)$ Å^3 *and* $Z=2$; and $a=6.622(2)$ Å, $b=15.490(5)$ Å, $c=31.130(10)$ Å, $\alpha=\beta=\gamma=90°$, $V=3193.3(19)$ Å^3 *and* $Z=8$, respectively.

The C8-S1 and C9-O1 bond lengths both show the expected double-bond character in two crystal structures, which can be demonstrated using the quantum chemical calculation (see **Fig. 3**). The C9(O1)-N1, C8(S1)-N1 and C8(S1)-N2 bond lengths indicate the partial double-bond character typical for this type of compounds which are in good agreement with the report related trifluoromethyl substituted benzene species [60-63]. Compared to the unsubstituted 1-benzoyl-3-phenylthioureas, the trifluoromethyl substitution at C4 does not result in any significant effect on these bond lengths which are consistent with the paper reported [64]. The molecular structures of **1** and **3** which possess methyl group at different positions consist of similar thiourea cores (-CONHCSNH-). The cores are mostly planar with O-C-N-C and C-N-C-S torsion angles of 2.759° and 174.942° for **1**, 6.631° and 164.192° for **3** as well. The dihedral angle between the C2-C7 plane and the C10-C15 plane are 13.50° and 37.75° for compounds **1** and **3**, respectively. The compounds **1** and **3** of the corresponding angles with respect to the (N/C/S/N/C/O) plane are 47.82° and 69.59° for the C2-C7 plane and 60.78° and 34.16° for the C10-C15 plane, respectively. Dihedral angles between these carbonyl thiourea planes and the phenyl rings with the methyl group measure for **1**: 60.78° and for **3**: 34.16°, which can be attributed to the effects of methyl group of steric hindrance.

Crystal packing patterns show intermolecular N-H···O hydrogen bonds for **1** (-*x*, 1-*y*, 1-*z*) and **3** (1-*x*, 1-*y*, 1-*z*), forming centrosymmetric dimmers, as shown in **Figs. 4** and **5**, with N-H···O contacts of 3.151(5) and 3.162(5) Å, respectively. Meanwhile, intramolecular N-H···O hydrogen bonds form S (6) ring [65] and contribute to the relative planarity of the acyl thiourea moieties in compounds **1** (**Fig. 1**) and **3** (**Fig. 2**). The intermolecular hydrogen bonds linking X-H···S=C forms parallelograms in all two compounds. The crystal packing of compound **1** is stabilized by N-H···S (1-*x*, -*y*, 1-*z*) hydrogen bonds, wherein atom S as an acceptor forming R_2^2 (8) ring as well as on compassion with the reported data for related molecules [33]. Noted that the intramolecular C-H···S hydrogen bonds in compound **1** form a S (6) rings and contribute to the relative planarity of the acyl thiourea moieties, as is shown in **Fig 1**. The packing diagram of compound **3** shows the intermolecular C-H···S (-0.5+*x*, 1.5-*y*, 1-*z*) actions form R_2^2 (12) motif, as is shown in **Fig 5**.

The C-H···π interactions were calculated using the PLATON program. The parameters of compound **1** are not satisfy with the conditions of C-H···π interactions. However, in the crystal packing patterns of compound **3**, the C-H···π interactions are formed between the H15 on the phenyl ring and the C2-C7 ring with a symmetry code: 1-*x*, 1-*y*, 1-*z*. The distance of 2.98 Å between H15 and the centroid of C2-C7 ring is content with the range the C-H···π interactions. The distance between H15 and the nearest carbon atom in the phenyl ring is 3.612(5) Å (the detail parameters see **Table S3**).

Table 1.

Data collections and structure refinement details for compounds **1** and **3**.

Compound	Compound **1**	Compound **3**
Chemical formula	$C_{16}H_{13}F_3N_2OS$	$C_{16}H_{13}F_3N_2OS$
Formula weight	338.34	338.34
Temperature (K)	296(2)	296(2)
Wavelength (Å)	0.71073	0.71073
a (Å)	7.431(3)	6.622(2)
b (Å)	7.762(4)	15.490(5)
c (Å)	14.075(7)	31.130(10)
α (degree)	100.619(9)	90
β (degree)	96.159(8)	90
γ (degree)	91.718(8)	90
Volume (Å^3)	792.3(6)	3193.3(19)
Z	2	8
Dc (Mg/m^3)	1.418	1.408
Crystal system	Triclinic	Orthorhombic
Space group	P-1	Pbca
Index ranges	$-8 \le h \le 8$, $-9 \le k \le 5$, $-16 \le l \le 15$	$-7 \le h \le 7$, $-8 \le k \le 8$, $-36 \le l \le 25$
Absorption Coefficient (μ)	0.240	0.238
F (000)	348	1392
Theta range for data collection (^{o})	1.48 to 25.09	1.31 to 25.10
Reflections collected	3968	14853
Independent reflections	2793	2832
R (int)	0.0226	0.0609
Goodness-of-fit on F^2 (S)	1.020	1.051
R (all data)	R1 = 0.0951, wR2 = 0.1958	R1 = 0.1056, wR2 = 0.2324

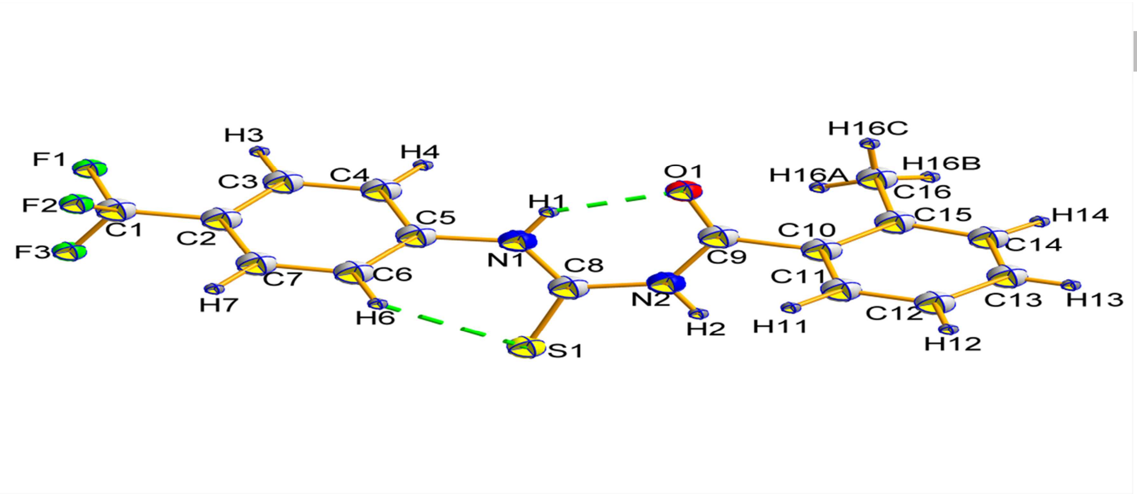


Fig. 1. Molecular structure of compound **1** in a single crystal at 296K (with the thermal ellipsoids shown at a 50% probability level). Intramolecular N-H···O and C-H··S hydrogen bonds are shown as a light green dashed line.

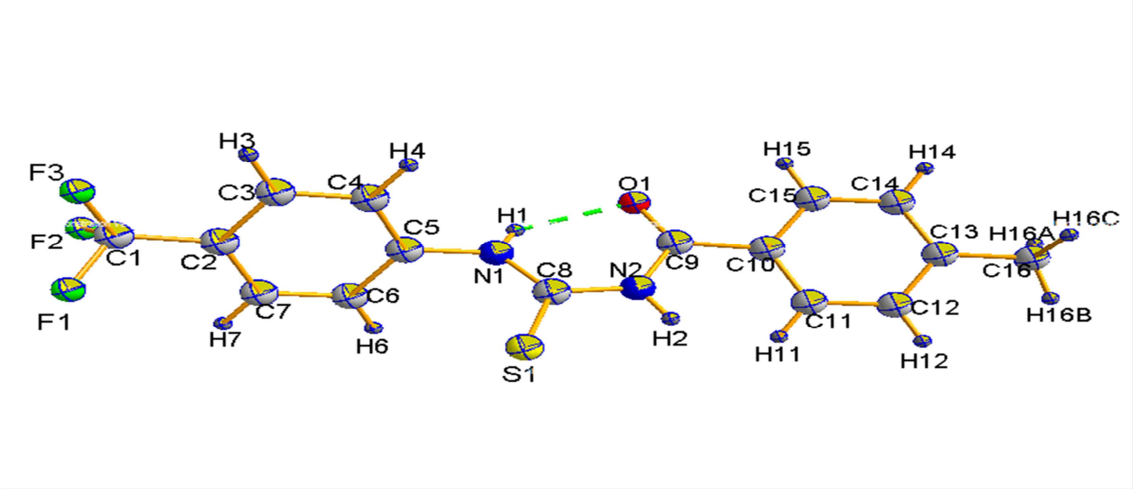


Fig. 2. Molecular structure of compound **3** in a single crystal at 296K (with the thermal ellipsoids shown at a 50% probability level). Intramolecular N-H···O hydrogenbond is shown as a light green dashed line.

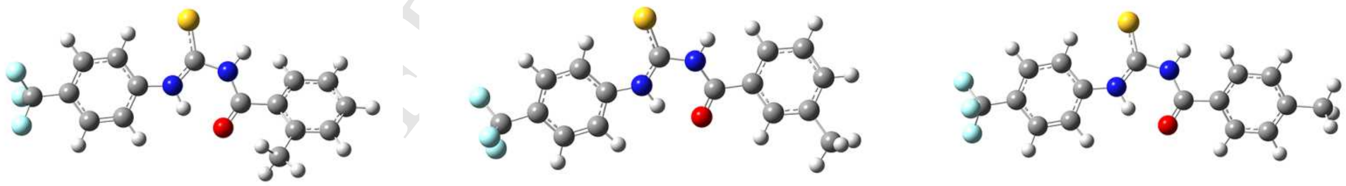


Fig. 3. Computed molecular structures of **1** (left), **2** (middle) and **3** (right).

Table 2.

Selected bond lengths [Å] and angles [^{o}] for compounds **1** and **3**. Computed values at the B3LYP/6-311++G (d, p) level of approximation for compounds **1**, **2** and **3**.

Compound	**1**		**2**	**3**	
Parameter	Experimental	Calculated	Calculated	Experimental	Calculated
Bond distances					

C8=S1	1.643(4)	1.669(3)	1.669(7)		1.669(4)	1.670(1)
C9=O1	1.213(4)	1.227(9)	1.228(8)		1.218(5)	1.229(3)
N1-C5	1.421(4)	1.407(5)	1.407(2)		1.436(5)	1.407(1)
N1-C8	1.344(4)	1.351(3)	1.350(9)		1.337(5)	1.350(8)
N2-C8	1.390(4)	1.410(6)	1.410(1)		1.389(5)	1.409(6)
N2-C9	1.380(4)	1.385(3)	1.382(8)		1.391(5)	1.383(5)
Bond angles						
N1-C8=S1	126.1(3)	129.6(6)	129.6(7)		124.9(3)	129.6(4)
N1-C8-N2	115.0(3)	113.5(1)	113.5(6)		117.3(4)	113.5(8)
N2-C8=S1	118.8(2)	116.8(3)	116.7(6)		117.8(3)	116.7(8)
N2-C9=O1	123.1(3)	122.3(4)	122.3(6)		121.9(4)	122.2(4)
Dihedral angles						
S1=C8-N2-C9	174.942(31)	178.471(87)	179.252(46)		164.192(33)	179.204(56)
O1=C9-N2-C8	2.759(62)	4.692(68)	3.837(67)		6.631(65)	3.782(83)

Table 3.

Hydrogen bonds for compounds **1** and **3** [Å and °].

Compound	Donor-Hydrogen··· Acceptor	D-H (Å)	H···A (Å)	D··· A (Å)	D-H···A (°)
1	N1-H1···O1	0.8600	1.9700	2.665(4)	137.000
	N1-H1···O1^{a}	0.8600	2.4700	3.151(5)	137.000
	C6-H6···S1	0.9300	2.8600	3.231(4)	105.000
	N2-H2···S1^{b}	0.8600	2.7100	3.651(4)	172.000
3	N1-H1···O1^{c}	0.8600	2.4700	3.162(5)	138.000
	N1-H1···O1	0.8600	2.0800	2.707(5)	130.000
	C11-H11···S1^{d}	0.9300	2.7800	3.593(5)	146.000

Symmetry equivalent position: (a) -*x*, 1-*y*, 1-*z*; (b) 1-*x*, -*y*, 1-*z*; (c) 1-*x*,1- *y*, 1-*z*; (d) -1-*x*, 1.5+*y*, 1.5-*z*.

(a)

(b)

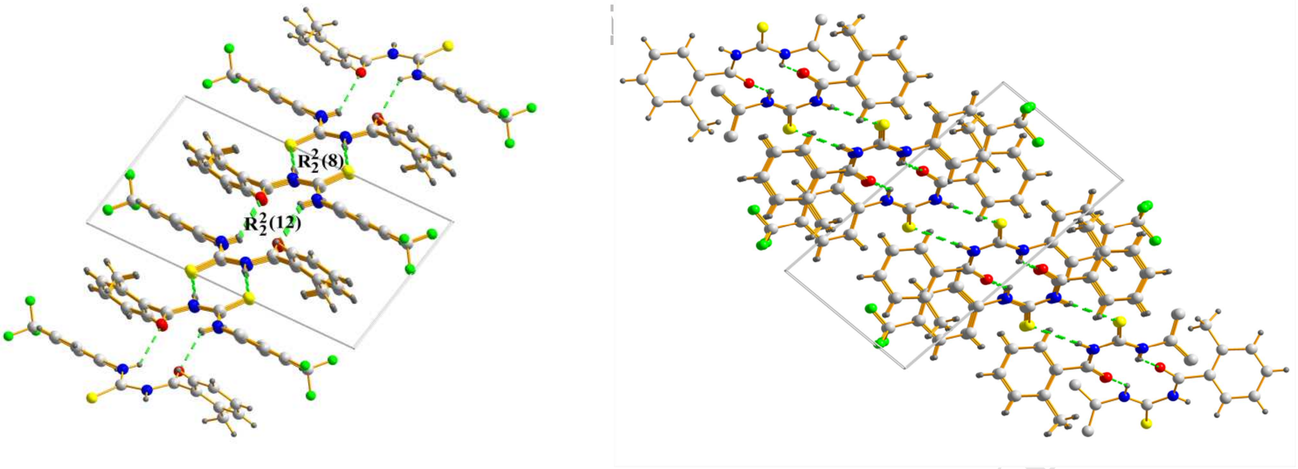


Fig. 4. Packing diagrams of the compound **1**; (a) viewed along the a axis; (b) viewed along the b axis.

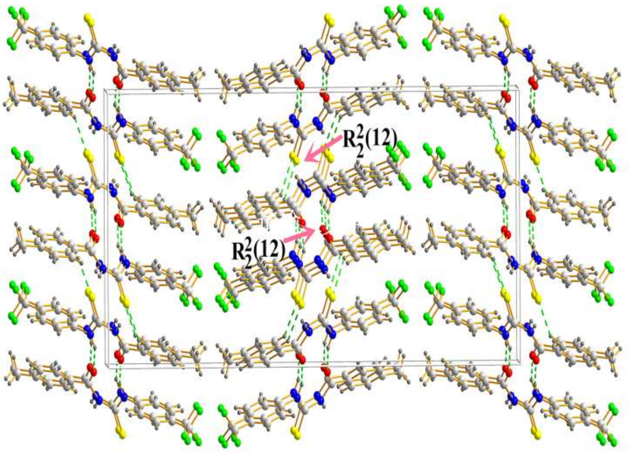


Fig. 5. Packing diagram of the compound **3** viewed along the a axis.

3.3. Hirshfeld surface analysis

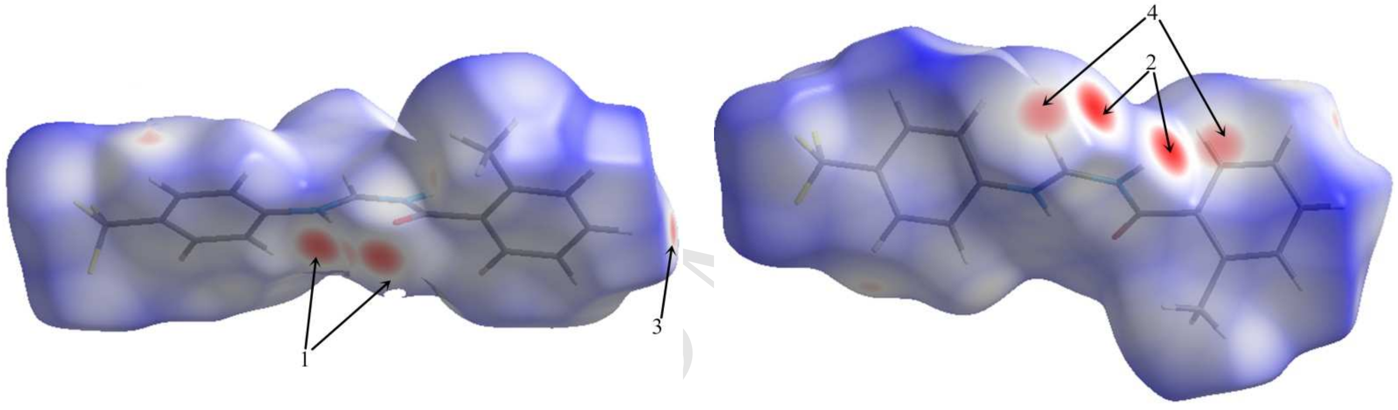
The Hirshfeld surfaces and their two-dimensional fingerprint plots were performed for the purpose of analyzing and quantizing structure properties in relation to packing patterns. The geometric parameters of hydrogen bonds for compounds **1** and **3** are listed in **Table 3.**

The intermolecular contacts of compounds **1** and **3** were analyzed using the Hirshfeld surfaces, which are shown as **Fig. 6**. The d_{norm} map of compounds **1** and **3** show a pair of adjacent deep-red regions (labeled 1) which demonstrate the strong N-H···O hydrogen bonds (**Table 3**) forming R_2^2(12) dimers in the corresponding crystal packing patterns (**Fig. 4(a)** and **Fig. 5**). The compound **1** also exhibit red regions close to both sulfur atom and hydrogen atom (labeled 2), as a result of N-H···S hydrogen bond forming R_2^2(8) loops, such as illustrated in the **Fig. 4(a)** and discussed in the crystal packing analysis. It is noted that the intermolercular contacts are formed by the C=S group with the C-H of the benzene ring instead of the N-H group in the compound **3** (labeled 2). Meanwhile, as can be seen in the compound **3** the red regions occur near to the S atom, which is due to form bifurcate C-H···S hydrogen bonds (labeled 3 and 4). Differently, when we look at to the Hirshfeld surface of compound **1** again, it is observed that the S atom and the C atom of the benzene ring is involved in a C···S intermolecular contact (labeled 4), resulting in a red color in the Hirshfeld surface. In addition, the compound **1** also show red regions near to both the F atom and the H atom of methyl, which is form the F···H intermolecular contact (labeled 3).

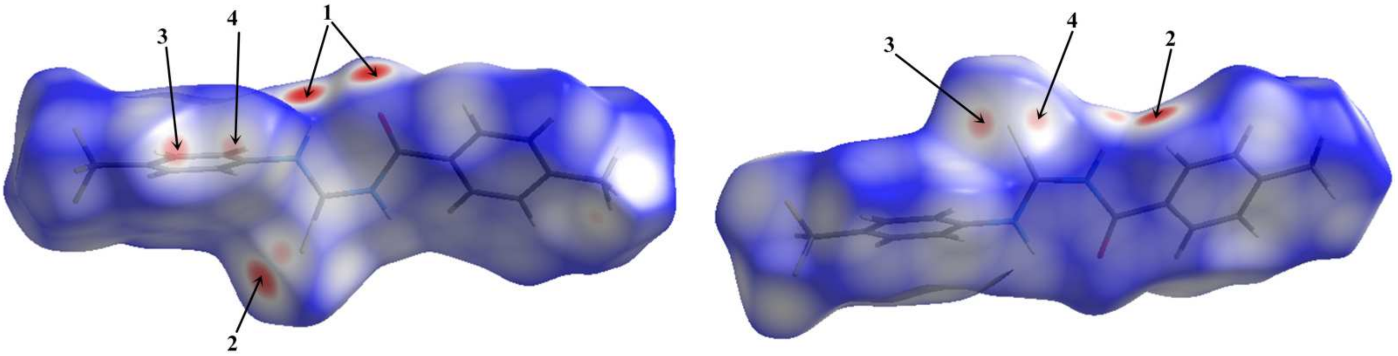
Their 2D fingerprint plots of the main intermolecular contacts for compounds **1** and **3** are depicted in **Fig. 7**. Although the structure **1** is very similar to the structure **3**, the fingerprint plots are quite different (**Fig. 7A**). The H···H contact of compound **3** shows a sharper spike (labeled 1 in **Fig. 7A**) centered near a sum of 2.3 Å (d_i+d_e) than the spike centered near a sum of 2.4 Å (d_i+d_e) for compound **1** (labeled 1 in **Fig. 7A**). The O···H (labeled 2 in **Fig. 7A**) and S···H (labeled 3 in **Fig. 7A**) intermolecular contacts are a pair of sharp spikes with a center near a sum of 2.3 and 2.5 Å (d_i+d_e) for compound **1**, 2.3 and 2.6 Å (d_i+d_e) for compound **3**, correspond to N-H···O and N-H···S hydrogen bonds for compound **1**, N-H···O and C-H···S hydrogen bonds for compound **3**, respectively. The F···H contact have a pair of spikes attached to the O···H contact, which is centered near a sum of 2.5 and 2.6 Å (d_i+d_e) for compounds **1** and **3**, respectively. In addition, the hydrophobic intermolecular contacts (C···H and C···C) are shown in **Fig. 7C** and **Fig. 7D**. Hence, the intra- and intermolecular hydrogen bonds together with the hydrophobic intermolecular contacts provide forces for self-assembly in the compounds **1** and **3**.

The two molecular surfaces connecting each other in crystals can be explained by complementary hollows (red) and bumps (blue) on the Shape index. The planar stacking arrangements must meet the condition of the relatively flat surface (green) on curvedness [58]. In the curvedness for compounds **1** and **3**, they all meet the condition of the relatively flat surfaces. However, there do not show the complementary hollows and bumps in phenyl regions of Shape index of compounds **1** and **3** in **Fig. 8**. So the π-π stacking interactions do not exist.

The enrichment ratios of the main intermolecular contacts were calculated using the method reported by C. Jelsch and coworkers [66]. The result of the enrichment ratios for compounds **1** and **3** are shown in **Table 4** (complete information is provided in **Table S1**). It is noted that the H···H intermolecular contacts are lightly impoverished in compounds **1** (E_{HH}=0.78) and **3** (E_{HH}=0.88) with the percentage of R_{HH} being 32.83% for compound **1** and 32.60% for compound **3**, respectively, which is quite different with the reported paper [28]. Meanwhile, it is observed that the O···H, S···H, F···H and C···H contacts are highly favored for compounds **1** and **3**, with the enriched ratio of E_{OH}, E_{SH}, E_{FH} and E_{CH} being 1.49, 1.35, 1.49 and 1.03 for compound **1** and 1.44, 1.37, 1.24 and 0.96 for compound **3**, respectively. The high values of E_{OH}, E_{SH}, E_{FH} and E_{CH} and are helpful for explaining that the H···H intermolecular contacts are lightly impoverished in compounds **1** and **3**, which is because H···H, O···H, S···H, F···H and C-H contacts are presumably in competition. There is an obvious difference that the N···H intermolecular contacts in the compounds **1** and **3** have a great gap in the value of E_{NH}. More concretely, the N···H intermolecular contact is slightly favoured for compound **1** (E_{NH}=0.92) and impoverished for compound **3** (E_{NH}=0.47). This fact demonstrated the E_{NH} ratios and the corresponding random contacts do not remain relativity, which consist with the reported research [28]. Compound **1** and compound **3** have also the second difference in the F···F intermolecular contacts. The F···F intermolecular contact has a highly enriched (E_{FF}=1.43) for compound **3** but a slightly impoverished for compound **1** (E_{FF}=0.56). The third difference between compound **1** and compound **3** is that the former have a highly enriched (E_{CS}=1.31) but the latter have a slightly impoverished (E_{CS}=0.68) in the C···S contacts (**Fig. S1**). The C···C contacts are highly enriched (E_{CC}=1.38) for compound **1** with the percentage of R_{CC} merely being 2.7, enriched (E_{CC}=1.96) for compound **3** with the percentage of R_{CC} only being 4.3. The C···O contacts are very impoverishedfor compounds **1** (E_{CO}=0.32) and **3** (E_{CO}=0.32).



Compound **1**

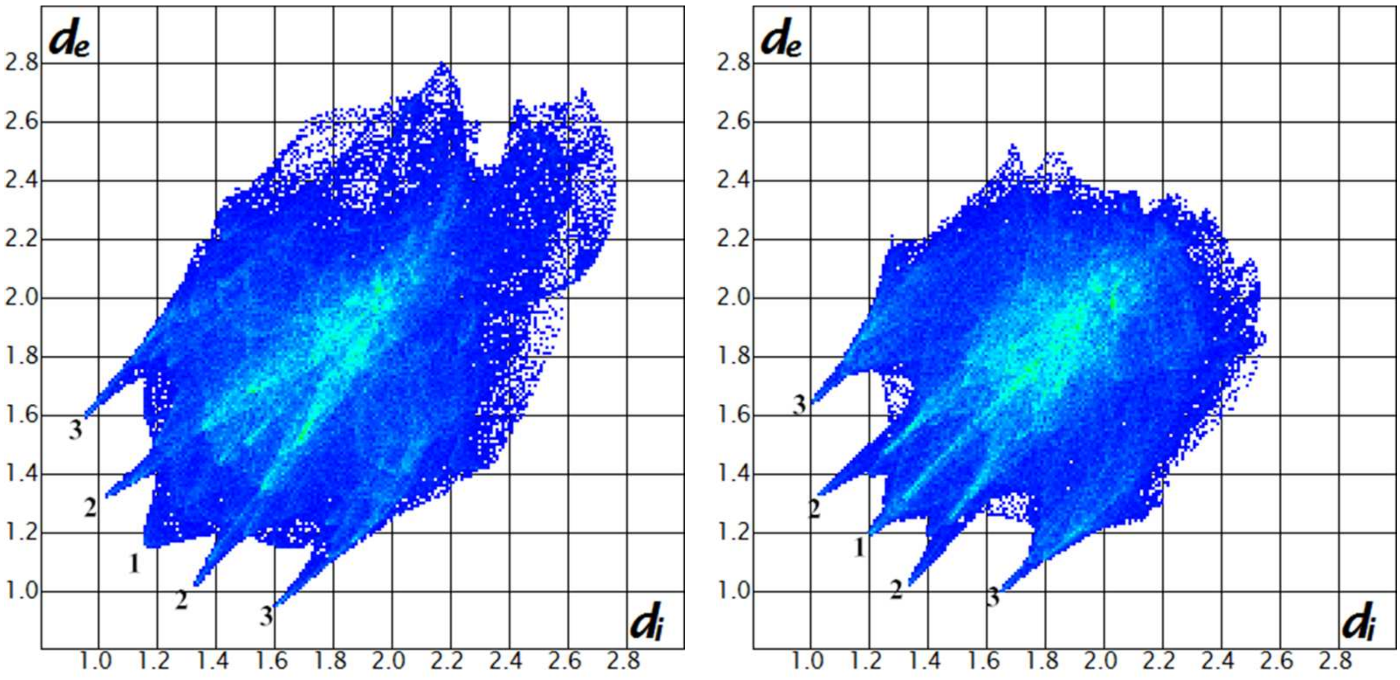


Compound **3**

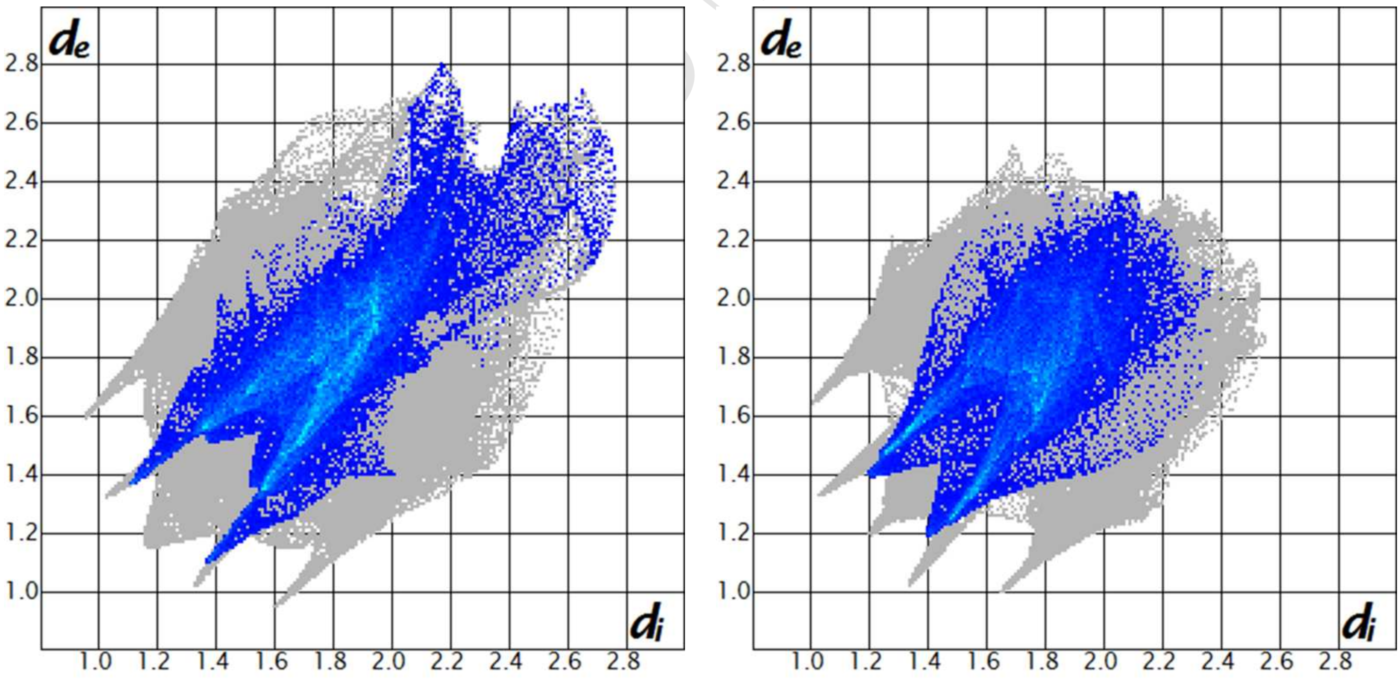
Fig. 6. Pictures of the Hirshfeld surface in two orientations for compounds **1** and **3** with thermal ellipsoids plotted at 50% probability level. The right column is rotated by 180° around the horizontal axis of the plot. Number arrows are described

either in **Table 3** or in the text.

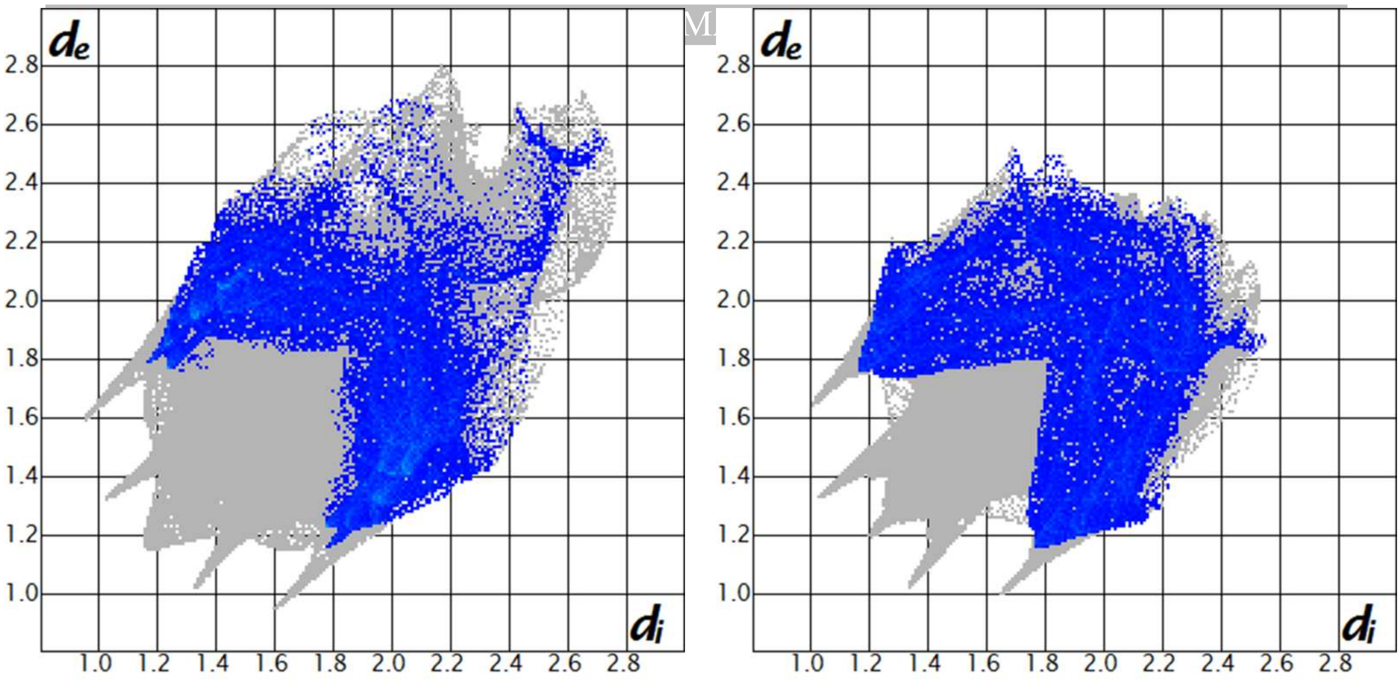
(A) The fingerprint plots H···H, O···H and S···H.



(B) The fingerprint plots F···H.



(C) The fingerprint plots C···H.



(D) The fingerprint plots C···C.

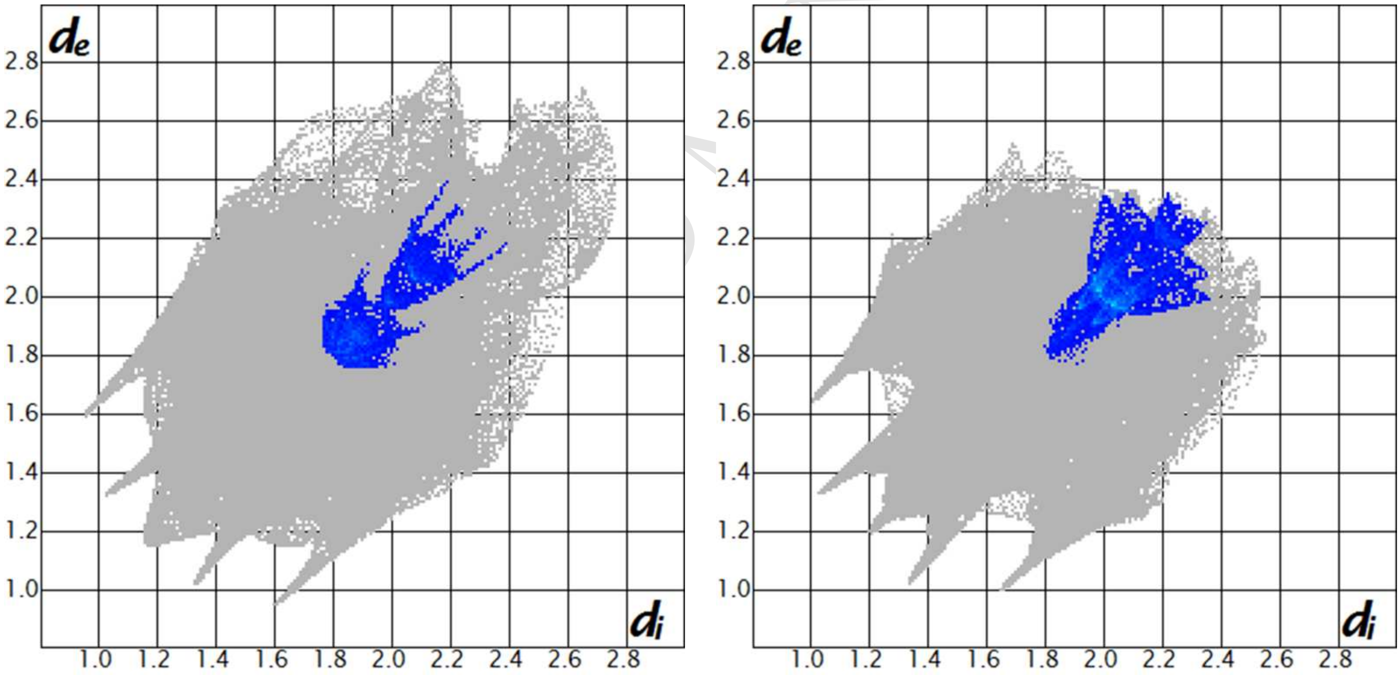
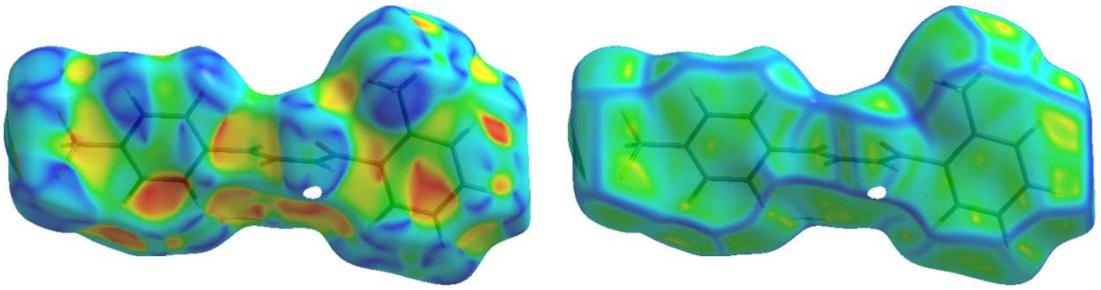
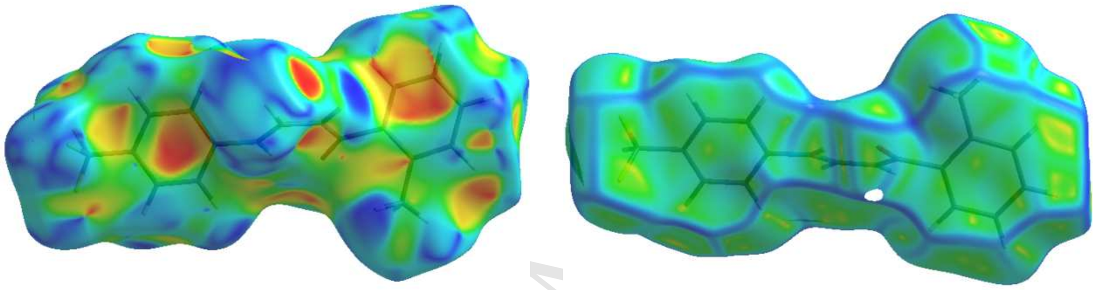


Fig. 7. The fingerprint plots (A-D) for compounds **1** (left) and **3** (right). The numbers 1, 2 and 3 in the (A) represent H···H, O···H and S···H intermolecular contacts, respectively. The pictures B, C and D show F···H, C···H and C···C intermolecular contacts, respectively.

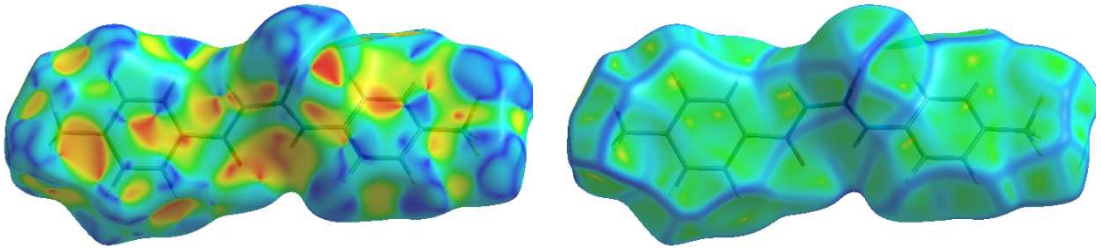
Compound **1 (A)**



Compound **1 (B)**



Compound **3 (A)**



Compound **3 (B)**

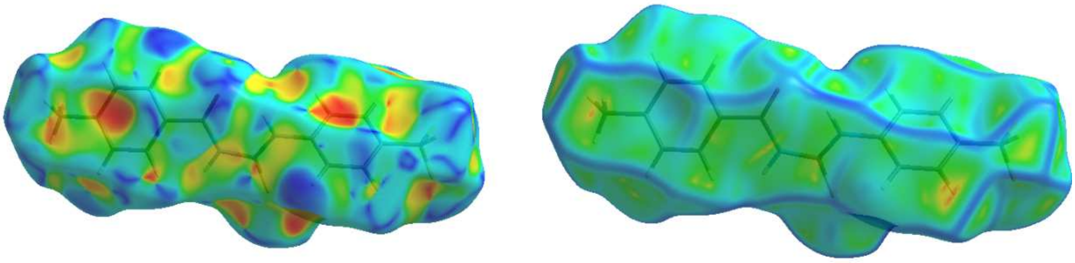


Fig. 8. Hirshfeld surfaces for compounds **1** and **3** mapped with shape index (the left column) and curvedness (the right column). The letters “A” and “B” represent front and back views of the same group of molecules.

Table 4.

Enrichment ratios E_{XY} of the main intermolecular interactions for compounds **1** and **3**.

Interaction	1	3
H···H	0.78	0.88
C···H	1.03	0.96
N···H	0.92	0.47
O···H	1.49	1.44
S···H	1.35	1.37
F···H	1.49	1.24
C···C	1.38	1.96
C···O	0.32	0.08
C···S	1.31	0.68
F···F	0.56	1.43

[*] E_{XY} value for random contacts R_{XY} lower than 0.9% was not calculated.

3.4. ^{1}H and ^{13}C NMR spectra

^{1}H NMR and ^{13}C NMR spectra were determined in DMSO-d_6 solution at 400 and 100 MHz, respectively, using a Bruker spectrophotometer. All three thiourea compounds exhibit the corresponding group characteristics in the same ^{1}H NMR spectra (**Fig. 9**). The proton of C=O-N-H group of compound **1**

(11.87 ppm) is at a lower field compared with compounds **2** (11.67 ppm) and **3** (11.63 ppm) in ^{1}H NMR. Again the carbon of C=O group for compound **1** is at a lower field that is similar to their ^{1}H NMR spectra (**Fig. 10**). The protons of methyl group of compound **1** is at δ 2.44 ppm which is bigger that the shifts of compounds **2** and **3**. The shifts of the carbon of methyl groups are arranged in following order: (1) < (2) < (3). The shifts of the proton and carbon of phenyl ring are different due to the different site of methyl group. The isomerization has slight influence on the position of chemical shift from the view of the whole NMR spectra which is in consistent with the conclusion reported by H.M. Abosadiya [35].

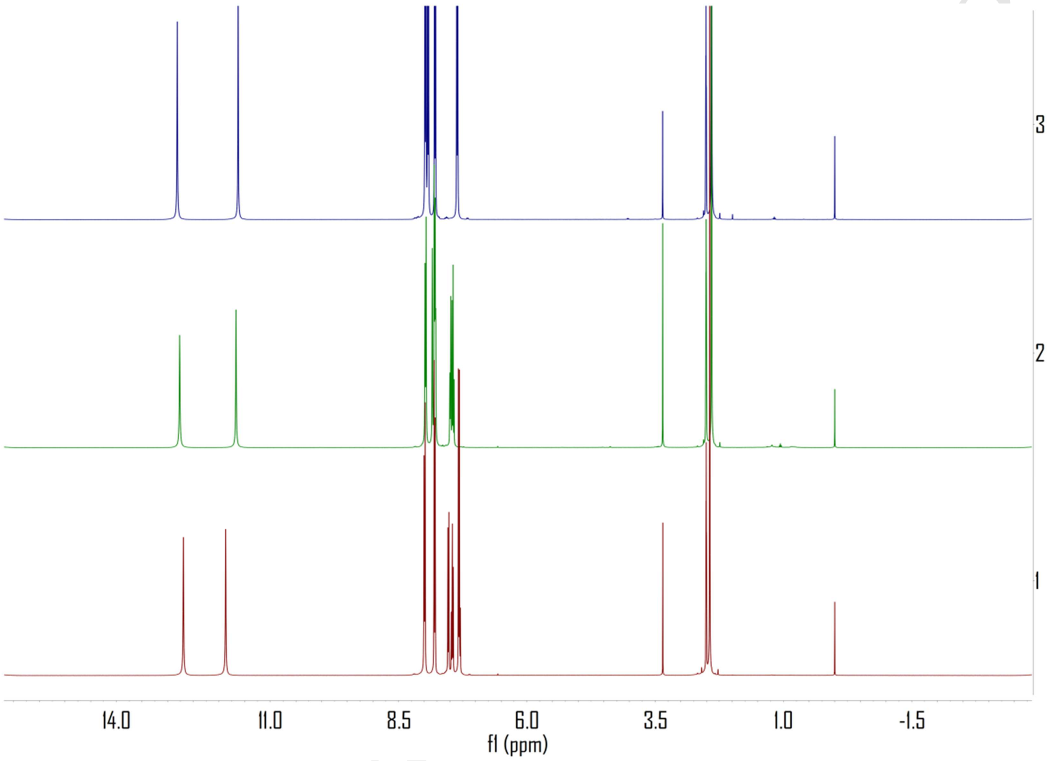


Fig. 9. The ^{1}H NMR spectra of compounds **1**, **2** and **3**.

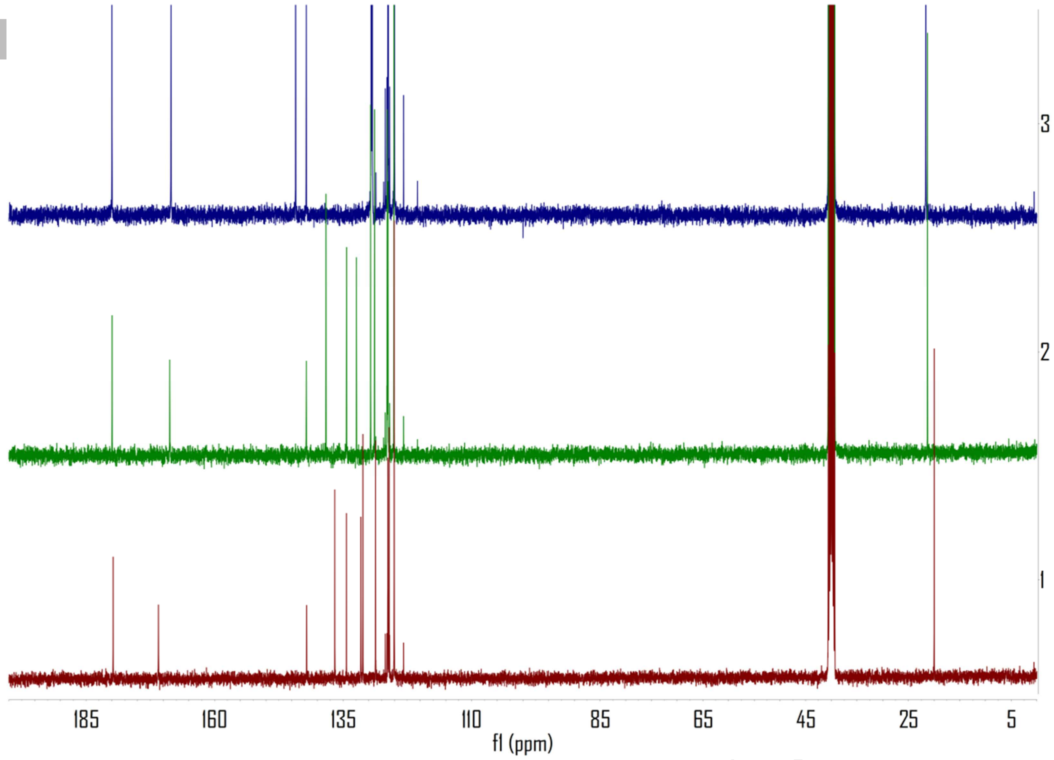


Fig. 10. The ^{13}C NMR spectra of compounds **1**, **2** and **3**.

3.5. Vibrational analysis

The vibrational spectra have a plenty of indistinguishable absorptions for the title compounds. In order to explain clearly assignments of the observed infrared absorption, the theoretically calculated vibrational analysis were performed using B3LYP/6-311++G (d, p). The geometric parameters are in good agreement with the experimental ones (**Table 2**) and the computed harmonic frequencies are listed in **Table 5**.

In the infrared spectra broad absorptions are observed at 3355 cm^{-1} for compound **1**, 3357 cm^{-1} for compound **2**, 3351 cm^{-1} for compound **3** which all could be assigned to the formation of C=O···H-N intramolecular hydrogen bonds [67]. It noted that the infrared spectrum of compound **1** is quite different from compounds **2** and **3** for which the spectrum 1 becomes wide in width and the spike generates a red shift phenomenon at 3154 cm^{-1} (see **Fig. S9**). It also proves that the compound **1** forms the N-H···S=C (1-*x*, -*y*, 1-*z*) intermolecular hydrogen bond while the hydrogen bond do not be involved in compound **3**. The phenomena indicate that compound **2** is more similar with **3** in molecular conformation. But the isomerization effect on virbration modes is negligible from the view of the whole FT-IR spectra that is also in consistent with the conclusion reported by H.M. Abosadiya [35].

Fig. 11 shows the Raman and IR spectra of the title compound in the 2000-400 cm^{-1} range. Many signals originate in both the central thiourea moiety and the substituent groups. The strong IR absorptions at 1681, 1666 and 1679 cm^{-1} for compounds **1-3**, respectively, are assigned to the C=O stretching modes. Very strong counterparts are observed in the Raman spectra at 1688, 1673 and 1679 cm^{-1} for the three compounds. Calculated frequencies for this mode are also very similar for the three isomers [1717 (**1**), 1714 (**2**) and 1713 (**3**)]. The relative low frequency value for υ(C=O) is in accordance with the formation C=O···H-N intermolecular hydrogen bonds. In addition, this phenomenon also can be explained as being a result of conjugated resonance interactions between the carbonyl and the phenyl ring in title compounds. It is noted that the υ(C=O) modes appreciably couple with the C-N stretching modes and the N-H bending modes in the similar compounds [31, 32].

The δ(N-H) (□) deformation modes of the amide and thioamide group are expected to appear absorptions in the 1600-1500 cm^{-1} range of the FT-IR spectrum. The FT-IR spectrum of the title compounds appear a middle intense bands at 1523, 1521 and 1525 cm^{-1} for compounds **1**, **2** and **3**, respectively, which are assigned as δ(N1-H). The Raman spikes correspond to middle intense signals at 1528, 1528 and 1526 cm^{-1}, respectively. Meanwhile, the most intense infrared absorptions appear at 1501 and 1503 cm^{-1} for compounds **1** and **3**, which are assigned as δ(N2-H). The calculated values at δ(N1-H) and δ(N2-H) at 1600 and 1539 cm^{-1} for **1**, 1601 and 1542 cm^{-1} for **2**, 1599 and 1534 cm^{-1} for **3** are in good agreement with the experiment values.

In the region between 1400 and 1100 cm^{-1} in the FT-IR spectra of the title compounds contains some medium intensity absorptions from skeletal motions, especially including the vibrations of υ(C-N) in the thiourea cores. Due to the vibrational properties reported for the similar compounds, it is expected to appear in the 1400-1300 cm^{-1} region for symmetric and antisymmetric stretching modes of C-N. The NCN antisymmetric stretching modes for the thiourea moiety (thioamide band Ⅱ) is assigned at 1312, 1324 and 1312 cm^{-1} for compounds **1**-**3**, respectively, which is in good agreement with the Raman values. Computed values are 1369, 1371 and 1373 cm^{-1}, which are slightly higher than the experiment, by using the B3LYP/6-311G++ (d, p) level. The symmetric υ_{as}(NCN) stretching mode (thioamide band Ⅲ) is assigned at 1158, 1154 and 1158 cm^{-1} for compounds **1**-**3**, respectively. The Raman counterparts are observed as signals of intensities of 1167, 1163 and 1161 cm^{-1}, respectively.

It is worthy to note that weak FT-IR absorptions centered at 763, 772 and 766 cm^{-1} with weak intensity Raman signals are assigned to the υ(C=S) modes for compounds **1**-**3**, respectively, in good agreement with the calculated values (see band Ⅳ of **Fig. 11**). The formation of C=S···H-X intermolecular hydrogen bonds seems to deeply affect the frequency of the υ(C=S) modes compared with the related report which υ(C=S) is assigned to the absorption appeared at 1325 cm^{-1} [68].

The norm modes associated with the υ(C-H) and υ(C=C) stretching vibrations of the phenyl rings are observed in the typical range with values located in the 3050-2850 cm^{-1} and below 1600 cm^{-1}, respectively. The C-F stretching vibrations are observed at 1107, 1104 and 1101 cm^{-1}, which are in good agreement with the calculated values.

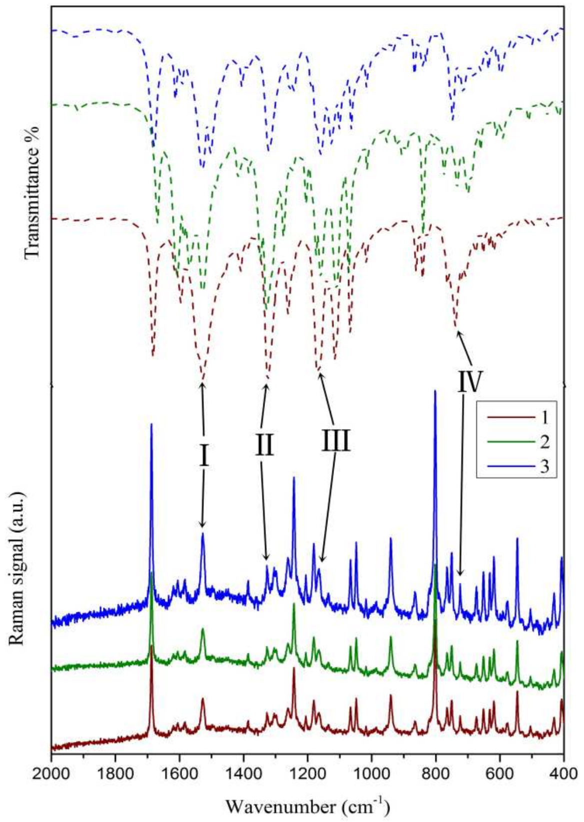


Fig. 11. FT-IR (the dashed lines) and FT-Raman (the solid lines) spectra for compounds **1**, **2** and **3** in the 2000-400 cm^{-1} region.

Table 5

Experimental and theoretical (B3LYP/6-311++G**) vibrational data (cm^{-1}) with a tentative assignment for the title compounds.

FTIR[a]			FT-Raman[a]			Calculated[b]			Proposed assignment approximate description[c]
1	**2**	**3**	**1**	**2**	**3**	**1**	**2**	**3**	
3355 vw	3357 w	3351 w				3607(42.0)	3612(39.9)	3616(38.4)	ν(N2-H)
3154 m, br	3246 m	3208 sh				3328(406.3)	3322(418.8)	3319(431.2)	ν(N1-H)
3025w	3036 w	3071 w				3240(11.1)	3239(10.9)	3240(11.0)	ν(C-H)
2919 vw	2922 m	2931vw				3201(1.0)	3202(1.0)	3202(1.0)	ν(C-H)
2849 vw	2851 w	2848 vw				3198(1.1)	3198(1.1)	3198(1.1)	ν(C-H)

1681 s	1666 s	1679 s	1688 s	1673 s	1679 s	1717(121.1)	1714(94.0)	1713(103.9)	ν(C=O)
	1603 s	1611 s	1619 w	1617 w	1617 w	1660(37.3)	1660(35.4)	1660(32.0)	ν(C-C)
1594 m	1586 m	1592 m	1594 w	1591 w		1648(556.9)	1649(376.9)	1644(645.1)	ν(C-C)
1523 vs	1521 s	1525 s	1528 m	1528 m	1526 m	1600(326.8)	1601(323.9)	1599(373.3)	δ(N2-H)
1501 vs		1513 vs				1539(412.3)	1542(372.9)	1534(219.6)	δ(N1-H)
1408 m	1417 m	1405 m				1446(24.0)	1445(23.9)	1447(24.3)	ν(C-C)
1312 vs	1324 s	1312 s	1326 w	1329 w	1327 w	1369(545.1)	1371(592.8)	1373(630.6)	ν_{as} (N-C-N)
1259 m, sh	1272 m	1256 m				1277(117.9)	1286(131.5)	1282(150.8)	ν(C8-C2)
1243 m, sh	1246	1244 m	1243 s	1247 s	1238 s	1259(7.2)	1262(2.9)	1250(26.9)	δ(C-H)
1158 vs	1154 s	1158 vs	1167 w	1163 w	1161 w	1170(163.8)	1162(288.6)	1165(267.9)	ν_s(N-C-N)
1107 s	1104 vs	1101 vs				1120(119.8)	1121(28.0)	1121(133.0)	ν(C-F)
1064 s	1069 s	1063 s	1066 m	1067 m	1066m	1076(189.2)	1076(197.4)	1087(12.7)	ν(C=S)/ ν_s(CNC)
1015 m	1014 m	1017 m	1018 w	1017 w	1019 w	1028(49.8)	1028(48.8)	1028(51.8)	δ(CCC)
962 w	953 w	961 w				972(4.2)	969(0.8)	970(3.0)	δ(N-C7-N)
	923 w	934 w	941 m	932 m	936 m	968(0.6)	967(5.7)	968(0.7)	δ(C-H)
861m	890 w	866 m	866 w		868 w	873(11.2)		872(8.2)	δ(NC=O)
840 m	837 s	841s			837 m	864(82.8)	863(84.2)	864(75.6)	δ(C-H)
763 s	772 m	766 s	724 w	730 w	727 w	774(20.8)	774(28.2)	756(20.4)	ν(C=S)
705 m		715 m				718(0.5)		702(2.0)	ρ(C-H)
675 m, sh	686 m, sh	678m	676 w	684 w		692(4.9)	696(10.0)	689(6.9)	ρ(C-H, Ph)
650 m	660 m	660 m	652 w	658 w	659 w	670(49.1)	670(21.2)	654(6.0)	ρ(N2-H)
632 m	629 w	636 m	631 w	628 w	636 w	661(38.9)	644(37.2)	638(41.4)	δ(C=O)
618 m	611 m	610 m	619 m	612 m	608 m	610(7.5)	607(9.5)	614(14.4)	oop(C=S)
600 s, sh	590 s,sh	592 m, sh				593(12.1)	593(13.6)	606(20.4)	ρ(C-H)
557vw	551 w	549 w, sh	547 m	546 m	546 m	555(0.4)	569(0.5)	564(1.5)	ρ(C-H)
	510 w	507 w, sh	506 w	505 w	505 w	513(6.7)	514(9.4)	513(5.8)	δ(CCC)
492 w		498 w				503(3.0)	508(2.5)	490(6.9)	ρ(C-H)
	452 w	451 w				462(2.2)	462 (9.5)	443(9.1)	δ(CCC)
			365 m	365 m	365 m	378(2.2)	366(0.4)	360(11.5)	δ(SCN)
			314 w	312 w	311 w	334(18.8)	339(28.0)	335(14.0)	δ(CCC)
			190 s	190 s	190 s	196(0.9)	195(1.2)	196(0.9)	ρ(NCS)

[a] FT-IR of solid in KBr pellets, FT-Raman of finely powered solid. Bind intensity: vs = very strong, s = strong, m = medium, w = weak, vw = very weak, sh=shoulder bond.

[b] Scaled computed values for S form. In parentheses relative bond strengths IR intensities [in km/mol].

[c] ν: stretching (subscripts s and as refer to symmetric and antisymmetric modes, respectively), δ: deformation, ρ: rocking, oop: out of plane deformation modes.

4. Conclusion

Three novel 1-(isomeric methylbenzoyl)-3-(4-trifluoromethylphenyl)thioureas have been synthesized and fully determined by spectroscopy techniques. The structural and conformational properties of compounds **1** and **3** were determined by the X-ray single crystal diffraction. The Hirshfeld surfaces, fingerprint plots and the enrichment ratios were carried out to clearly explain the intermolecular interactions and their quantitative contributions to the crystal packing of the two thiourea compounds. The FT-IR spectra revealed that the structure **2** is more similar with structure **3** rather than structure **1** by comparing to the value of wavelength. And the isomerization effect has slight effect on the whole FT-IR and NMR spectra. The main normal modes have been analyzed by the joint analysis of the FT-IR spectra, the Raman spectra and the corresponding calculated values.

Acknowledgements

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Appendix A. Supplementary material

Crystallographic data for the structures reported in this paper have been deposited with Cambridge Crystallographic Data Center as supplementary publication nos. CCDC 1517869 for **1** and CCDC 1519303 for **3**. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).” Other supporting materials can be found in the Electronic Supplementary Material of this paper.

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Highlights:

1. The three isomeric acyl thiourea compounds were firstly prepared and characterized.

2. Intermolecular contacts were explored using both the Hirshfeld surfaces and their 2D fingerprint plots.

3. Conformational aspects are discussed in terms of the X-ray diffraction analysis and the vibrational spectra.

4. The computed vibrational spectra are in good agreement with the experimental results.