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# Fluorinated pyrazolinic thiosemicarbazones: selective synthesis and computational analysis

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RESEARCH ARTICLE

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ABSTRACT

Thiosemicarbazones are a class of iminic organosulfur compounds synthesized by condensation reaction between a thiosemicarbazide and an aldehyde or ketone. Such compounds present a wide range of biological activities, either as sole organic compounds or in association with metallic species. The fluorinated pyrazoline cyclic thiosemicarbazones described herein were synthesized from 4,4,4-trifluoro-1-phenyl-1,3-butanedione and three thiosemicarbazides. The reactions resulted in thiosemicarbazones 1, 2, and 3, with 51, 70, and 71% yields, respectively. which were characterized by elemental analysis, FTIR, $^{1}$H and $^{19}$F{$^{1}$H} NMR, mass spectrometry and single crystal X-ray diffraction. The spectral data confirm that the thiosemicarbazones are cyclic the both in solid state and solution, as no evidence of ring-chain tautomerism has been observed. Additionally, single-crystal X-ray diffraction studies revealed that the compounds mentioned above crystallized in centrosymmetric space groups, two of them in monoclinic $P2_1/n$ and the last one in triclinic $P\bar{1}$. Theoretical free energies of formation were calculated using the DFT methodology, and the results indicate that the ring isomer is significantly more stable than the chain isomer; thus, no ring-chain isomerism is expected to form, in agreement with the experimental data.

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## 1. Introduction

Thiosemicarbazones are a class of iminic organosulfur compounds synthesized by a condensation reaction between a thiosemicarbazide and an aldehyde or ketone followed by water elimination [1-3]. The general synthesis of a thiosemicarbazone is presented in Scheme 1. These compounds are known for their structural versatility and wide range of biological activities. In addition to the substituent effect ($R_1$, $R_2$, $R_3$, or $R_4$, see Scheme 1) [4-7], the biological activity of thiosemicarbazones can be modulated by the possibility of forming heterocycles [8-11]. Some heterocycles derived from thiosemicarbazones are shown in Figure 1.

Another strategy that has been used to improve the biological activity of thiosemicarbazone is the insertion of fluorine atoms in its structure [12-14]. Fluorination has long been described as a potent approach in drug design due to the high electronegativity of fluorine and the small atomic radius, which can affect the pharmacological properties of a molecule [15,16]. Therefore, fluorine-containing groups, such as fluorophenyl (-ArF) and trifluoromethyl (-$CF_3$), are found in the structure of several commercially available drugs. As examples, we can highlight the anticancer drugs Apatulamide® [17] and Selinexor® [18], both contain the -$CF_3$ group.

The last feature that allows modulation of the biological activity of thiosemicarbazones is their ability to form highly stable metal complexes. Coordination to a metallic center typically occurs through the sulfur and iminic nitrogen atoms, forming a five-membered chelate ring. Eventually, other donor atoms in the substituent groups may also bond to the metal [19-21]. In addition to its high stability, several studies have revealed that coordination with a metal element can significantly increase the biological activity of thiosemicarbazones [3,22,23]. This class of compounds is versatile for medicinal applications, including antiviral [24] and antibacterial activity [25]. A notable example is the copper(II) complex Cu-ATSM, which is in an ongoing Phase III clinical trial for the treatment of amyotrophic lateral sclerosis [26], and its radioactive counterpart, $^{64}$Cu-ATSM, currently used for hypoxia imaging [27]. Other thiosemicarbazones are in advanced clinical trials for cancer treatment [28,29]. Thus, given the relevance of the properties and applications of thiosemicarbazones, this study reports the synthesis and structural characterization of three fluorinated cyclic thiosemicarbazones


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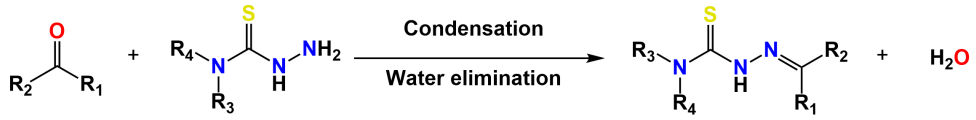
**Table 1.** Crystallographic data and details of diffraction experiments of compounds **1**, **2**, and **3**.

| Compound | 1 | 2 | 3 |
|---|---|---|---|
| Empirical formula | $C_{11}H_{10}F_3N_3OS$ | $C_{12}H_{12}F_3N_3OS$ | $C_{26}H_{28}F_6N_6O_2S_2$ |
| Formula weight (g mol$^{-1}$) | 289.28 | 303.31 | 634.66 |
| Temperature (K) | 296(2) | 296(2) | 293(2) |
| Wavelength (Å) | 0.71073 | 0.71073 | 0.71073 |
| Crystal system | Triclinic | Monoclinic | Triclinic |
| Space Group | $P\bar{1}$ | $P2_1/n$ | $P\bar{1}$ |
| Unit cell dimensions | a = 10.1734(3) Å | a = 7.6478(2) Å | a = 7.222(5) Å |
| | α = 67.8990(10)° | α = 90° | α = 78.470(5)° |
| | b = 11.2434(3) Å | b = 18.9380(7) Å | b = 13.815(5) Å |
| | β = 84.5050(10)° | β = 107.665(2)° | β = 78.234(5)° |
| | c = 13.6339(4) Å | c = 9.7766(3) Å | c = 15.268(5) Å |
| | γ = 63.2540(10)° | γ = 90° | γ = 85.995(5)° |
| Volume (Å$^3$) | 1285.21(6) | 1349.22(8) | 1464.4(12) |
| Z | 4 | 4 | 2 |
| Absorption coefficient (mm$^{-1}$) | 0.283 | 0.274 | 0.256 |
| Crystal size (mm$^3$) | 0.36 x 0.23 x 0.16 | 0.68 x 0.11 x 0.04 | 0.92 x 0.18 x 0.14 |
| θ range for data collection (°) | 1.618 to 25.043 | 2.151 to 25.048 | 1.388 to 25.399 |
| Index ranges | $-12 \le h \le 12$ | $-9 \le h \le 9$ | $-8 \le h \le 8$ |
| | $-8 \le k \le 13$ | $-21 \le k \le 21$ | $-16 \le k \le 16$ |
| | $-16 \le l \le 16$ | $-11 \le l \le 11$ | $-18 \le l \le 18$ |
| Reflections collected | 15312 | 9285 | 18754 |
| Data/restraints/parameters | 4534/0/345 | 2385/0/183 | 5372/0/383 |
| Absorption correction | Multi-scan | Multi-scan | Multi-scan |
| Goodness-of-Fit on F$^2$ | 1.020 | 1.031 | 1.037 |
| Final R indices [$I > 2\sigma(I)$] | $R_1$ = 0.0358 | $R_1$ = 0.0396 | $R_1$ = 0.0435 |
| | $wR_2$ = 0.0912 | $wR_2$ = 0.0991 | $wR_2$ = 0.0981 |
| R indices (all data) | $R_1$ = 0.0417 | $R_1$ = 0.0522 | $R_1$ = 0.0778 |
| | $wR_2$ = 0.0961 | $wR_2$ = 0.1095 | $wR_2$ = 0.1143 |




**Scheme 1.** Structure of a thiosemicarbazone and the general procedure for its synthesis.

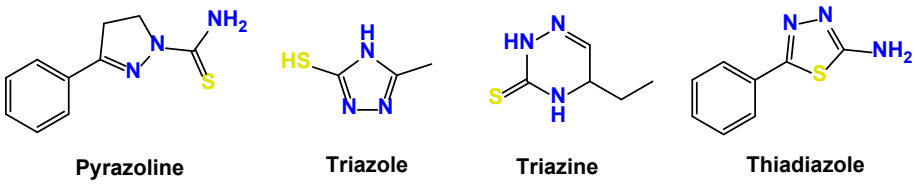



**Figure 1.** Some heterocycles derived from thiosemicarbazones.

containing a pyrazoline ring. Theoretical investigations on the cyclization energy of formation have also been conducted using the DFT methodology.

## 2. Experimental

### *2.1. Chemicals and reagents*

All chemicals, reagents, and solvents were purchased from Sigma-Aldrich and used as received.

### *2.2. Instrumentation*

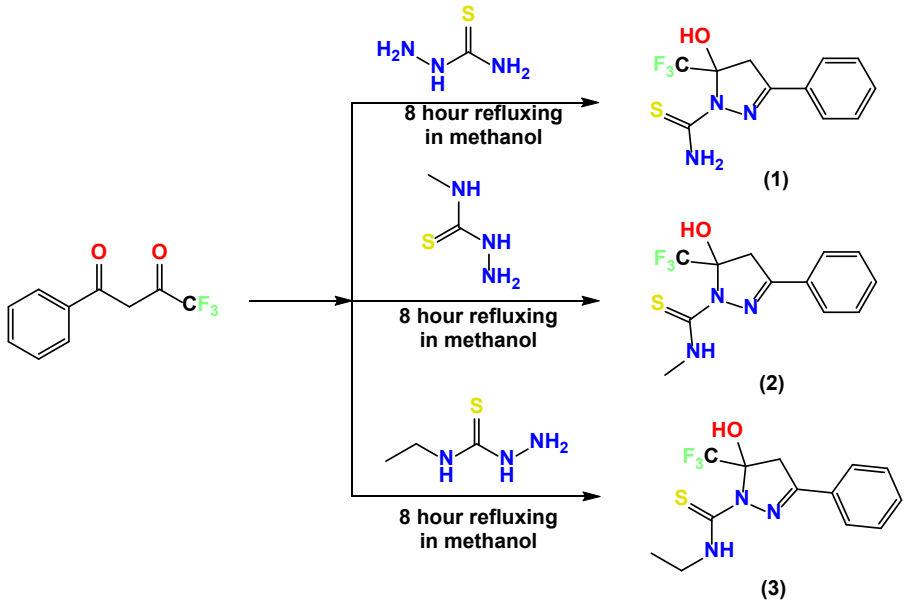
FTIR spectra were measured as KBr pellets on an IR Prestige-21 (Shimadzu Co.) spectrophotometer between 4000 and 400 cm$^{-1}$. Elemental analyzes were performed on a Flash 2000 organic CHNS-O elemental analyzer. The $^1$H and $^{19}$F{$^1$H} NMR spectra were recorded on an Agilent 500/54 premium shielded spectrometer. Samples were prepared in DMSO-$d^6$, at room temperature. The chemical shifts (δ) for $^1$H and $^{19}$F{$^1$H} are quoted in ppm with reference to TMS and the deuterium lock signal, respectively. Electrospray ionization high-resolution mass spectrometry was conducted on an Agilent 6210 ESI-TOF spectrometer. The samples were prepared in acetonitrile and injected directly into the ionization source for analysis in negative mode.

### *2.3. Crystal structure determination*

Single crystal X-ray diffraction was carried out on a Bruker APEX II Duo diffractometer, using graphite monochromated Mo-K$_\alpha$ (λ = 0.71073 Å) radiation. Cell determination and data reduction were processed with SAINT software. The multi-scan method was used for absorption correction. Structures were solved by direct methods with SHELXS 97 [30]. All non-hydrogen atoms were refined anisotropically with SHELXL 2014 [31]. Hydrogen atoms were refined isotropically according to the riding model method with SHELXL 2014. The crystal data and structural refinement parameters are in Table 1.

### *2.4. Computational calculations*

The calculations were performed using Gaussian 09 software, Revision E.01 (Gaussian, Inc., USA). For all calculations, the density functional theory (DFT) was used, combining the functional B3LYP with the basis set 6-31G(d,p) [32].




**Scheme 2.** Synthesis of cyclic thiosemicarbazones **1**, **2**, and **3**.

The compounds were optimized in their geometries, and the vibrational frequencies were calculated in a methanol medium using the polarizable continuum model with the integral equation formalism variant (IEFPCM) [33] to account for the solvent effect of methanol. Optimizations were carried out taking the X-ray structures reported in this work as the starting points.

### *2.5. Synthesis*

Thiosemicarbazones were synthesized according to a general procedure in the literature [34]. In a round bottom flask equipped with a magnetic stirrer bar and containing 15.0 mL of methanol, 2.4 mmol of 4,4,4-trifluoro-1-phenyl-1,3-butanedione and 2.2 mmol of the desired thiosemicarbazide (3-thiosemicarbazide, 4-methyl-3-thiosemicarbazide, or 4-ethyl-3-thiosemicarbazide) were added. The solution was stirred at reflux for eight hours, cooled to room temperature, and placed in a freezer overnight. The white crystalline precipitate was filtered off, washed with cold methanol, dried under reduced pressure, and characterized by $^{1}$H and $^{19}$F{$^{1}$H} NMR, FTIR, and mass spectrometry. Suitable single crystals were obtained for XRD analyzes.

*5-Hydroxy-3-phenyl-5-(trifluoromethyl)-4, 5-dihydro-1H-pyrazole-1-carbothioamide* (**1**): Color: White. Yield: 51%. Anal. calcd. for $C_{11}H_{10}F_3N_3OS$: C, 45.67; H, 3.48; N, 14.53%. Found: C, 46.15; H, 3.38; N, 14.54%. FT-IR (KBr, ν, cm$^{-1}$): ν(O–H): 3437; $\nu_{as}$(N–H): 3294; $\nu_{s}$(N–H): 3146; ν(C=N): 1591; ν(C–F): 1186-1150; ν(C=S): 831. $^{1}$H NMR (500 MHz, DMSO-$d_6$, δ, ppm): 8.82 (s, 1H, C–N$H_2$), 8.49 (s, 1H, C–O*H*), 8.47 (s, 1H, C–N$H_2$), 7.97-7.89 (m, 2H, Ar–*H*), 7.58-7.44 (m, 3H, Ar–*H*), 4.05 (d, $^{2}J_{HH}$ = 19.1 Hz, 1H, –C$H_2$–), 3.79 (dq, $^{2}J_{HH}$ = 19.1 Hz, $^{4}J_{HF}$ = 1.6 Hz, 1H, –C$H_2$–). $^{19}$F{$^{1}$H} NMR (376 MHz, DMSO-$d_6$, ppm): –81.34. ESI HRMS (*m/z*): [M–H]$^-$ calculated for $C_{11}H_9F_3N_3OS$: 288.04239; found: 288.04228.

*5-Hydroxy-N-methyl-3-phenyl-5-(trifluoromethyl)-4, 5-dihydro-1H-pyrazole-1-carbothioamide* (**2**): Color: White. Yield: 70%. Anal. calcd. for $C_{12}H_{12}F_3N_3OS$: C, 47.52; H, 3.99; N 13.85%. Found: C, 48.32; H, 3.94; N, 13.79%. FT-IR (KBr, ν, cm$^{-1}$): ν(O–H): 3316; ν(N–H): 3088; ν(C=N): 1603; ν(C–F): 1184-1150; ν(C=S): 824. $^{1}$H NMR (500 MHz, DMSO-$d_6$, δ, ppm): 9.09 (q, $^{3}J_{HH}$ = 4.5 Hz, 1H, C–N*H*–C), 8.33 (s, 1H, C–O*H*), 7.96 – 7.90 (m, 2H, Ar–*H*), 7.57 – 7.46 (m, 3H, Ar–*H*), 4.05 (d, $^{2}J_{HH}$ = 19.1 Hz, 1H, –C$H_2$–), 3.77 (dq, $^{2}J_{HH}$ = 19.0 Hz, $^{4}J_{HF}$ = 1.6 Hz, 1H, –C$H_2$–), 3.01 (d, $^{3}J_{HH}$ = 4.6 Hz, 3H, N–C$H_3$). $^{19}$F{$^{1}$H} NMR (376 MHz, DMSO-$d_6$, ppm): –81.12. ESI HRMS (*m/z*): [M–H]$^-$ calculated for $C_{12}H_{11}F_3N_3OS$: 302.05804; found: 302.05773.

*N-Ethyl-5-hydroxy-3-phenyl-5-(trifluoromethyl)-4, 5-dihydro-1H-pyrazole-1-carbothioamide* (**3**): Color: White. Yield: 75%. Anal. calcd. for $C_{13}H_{14}F_3N_3OS$: C, 49.20; H, 4.45; N, 13.24%. Found: C, 49.85; H, 4.51; N, 13.24%. FT-IR (KBr, ν, cm$^{-1}$): ν(O–H): 3310; ν(N–H): 3088; ν(C=N): 1605; ν(C–F): 1177-1138; ν(C=S): 820. $^{1}$H NMR (500 MHz, DMSO-$d_6$, δ, ppm): 9.11 (t, $^{3}J_{HH}$ = 5.9 Hz, 1H, C–N*H*–C), 8.39 (s, 1H, C–O*H*), 7.97 – 7.91 (m, 2H, Ar–*H*), 7.58 – 7.47 (m, 3H, Ar–H), 4.05 (d, $^{2}J_{HH}$ = 19.1 Hz, 1H, –C$H_2$–), 3.78 (dq, $^{2}J_{HH}$ = 19.1 Hz, $^{4}J_{HF}$ = 1.6 Hz, 1H, –C$H_2$–), 3.66 – 3.50 (m, 2H, N–C$H_2$–C$H_3$), 1.17 (t, $^{3}J_{HH}$ = 7.1 Hz, 3H, N–C$H_2$–C$H_3$). $^{19}$F{$^{1}$H} NMR (376 MHz, DMSO-$d_6$, ppm): –81.03. ESI HRMS (*m/z*): [M – H]$^-$ calculated for $C_{13}H_{13}F_3N_3OS$: 316.07369; found: 316.07514.

## 3. Results and discussion

### *3.1. Synthesis and spectroscopic characterization*

The reactions of 4,4,4-trifluoro-1-phenyl-1,3-butanedione with 3-thiosemicarbazide, 4-methyl-3-thiosemicarbazide and 4-ethyl-3-thiosemicarbazide resulted in cyclic thiosemicarbazones **1**, **2**, and **3**, with 51, 71 and 75% yield, respectively. The synthesis, summarized in Scheme 2, consisted of condensation reactions followed by the elimination of a water molecule. All compounds were obtained as white crystalline solids that are air and light-stable. The compounds were characterized by $^{1}$H and $^{19}$F{$^{1}$H} NMR, FTIR, mass spectrometry and single crystal X-ray diffraction, confirming that the compounds have the proposed structures.

In the $^{1}$H NMR spectra, all hydrogens in the proposed structures were assigned. The spectra are given in the Supplementary Material. The presence of two signals for the methylene hydrogens ($H_a$ and $H_b$) indicates that the compounds are in a cyclic form. Figure 2 shows a section of the $^{1}$H NMR spectrum of thiosemicarbazone **1**, as an example of the cyclized structure in solution. The $H_a$ and $H_b$ protons of compound **1** couple to each other with $^{2}J_{HH}$ = 19.1 Hz. However, their signals resonate as two different splitting patterns: a doublet at 4.05 ppm and a doublet of quartets at 3.79 ppm.

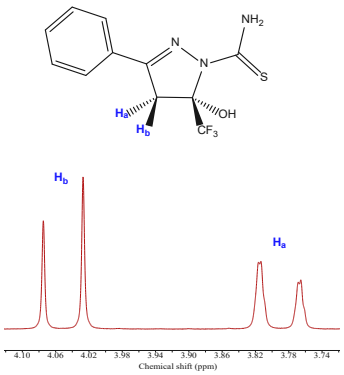



**Figure 2.** Section of the $^{1}$H NMR spectrum of thiosemicarbazone **1**, showing the peaks for the methylene hydrogens.

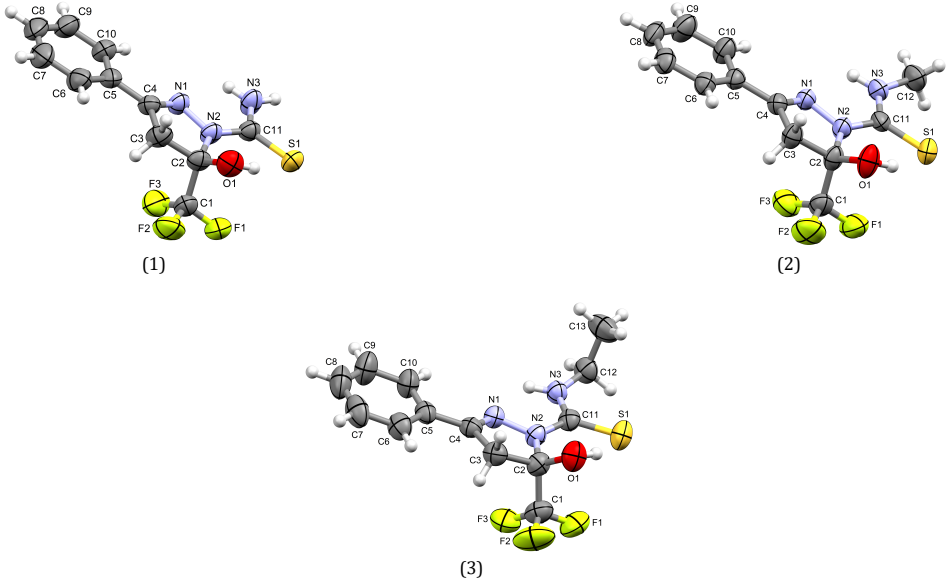



**Figure 3.** Molecular structure of thiosemicarbazones **1**, **2**, and **3**, from left to right, obtained from single crystal XRD data. The ellipsoids were drawn at 50% probability level.

The quartet arises from coupling to $^{19}$F ($^{4}J_{HF}$ = 1.6 Hz), and is probably attributable to the hydrogen atom in the anti-position relative to the trifluoromethyl group, consistent with the Karplus relationship for vicinal couplings [35]. The same pattern is also observed for the other two thiosemicarbazones. As expected, only one signal was observed in the $^{19}$F{$^{1}$H} NMR spectra, which is assigned to the fluorine atoms in the trifluoromethyl group. The full $^{19}$F{H} NMR spectra are in the Supplementary Material.

In the IR spectra, the formation of thiosemicarbazones is evidenced by the presence of the ν(O–H) vibrational mode, which appears as a sharp strong to medium intensity band around 3310-3406 cm$^{-1}$, and by the disappearance of the strong band around 1630-1670 cm$^{-1}$, assigned to the ν(C=O) of the β-diketone carbonyl group. The ν(N–H) was found at 3088-3294 cm$^{-1}$; for compound **1**, both asymmetrical and symmetrical ν(N–H) were observed. In the region between 1591-1634 cm$^{-1}$, the coupling between ν(C=N) and δ(C–C–C) of the pyrazoline ring appeared as a sharp band of medium-to-low intensity, while the ν(C–N) and δ(N–H) coupling of the thioamide group was found as a strong band at 1460 to 1591 cm$^{-1}$. The ν(C=S) is found at the 820-858 cm$^{-1}$ range and is coupled to the thioamide δ(N–C–N) vibrational mode. The ν(C–F) was observed around 1134-1186 cm$^{-1}$. As a characteristic of the $CF_3$ group, the ν(C–F) appears as a group of bands due to a combination of asymmetrical and symmetrical stretchings. The infrared spectra are in the Supplementary Material and the assignments were based on the theoretical infrared spectra obtained by calculating the vibrational frequencies and the literature [36]. The mass spectra show the molecular ion peaks that correspond to the proposed structures for all three thiosemicarbazones: for compound **1**, $[M–H]^-$ (*m/z* 288.04228); for compound **2**, $[M–H]^-$ (*m/z* 302.05773); and for compound **3**, $[M–H]^-$ (*m/z* 316.07514). A small fragmentation was observed in the spectra of compounds **2** and **3**. All mass spectra are in the Supplementary Material.

### *3.2. Single crystal X-ray diffraction*

Single crystals of compounds **1**, **2** and **3** were obtained and analyzed. The X-ray diffraction results confirm the proposed structures and are in accordance with the spectroscopic data. The structures of compounds **1**, **2**, and **3** are shown in Figure 3. Selected bond lengths and angles are presented in Table 2.

X-ray structures confirm the presence of the pyrazoline ring, in which the lengths of the C4–N1 bonds indicate a double bond character [37], consistent with the presence of an imine group. In the pyrazoline ring, it is also possible to see the conformation of the methylene hydrogens, where one is in *syn* position relative to the trifluoromethyl group, while the other is in *anti*-position, in accordance with the $^{1}$H NMR data.

**Table 2.** Selected bond lengths (Å) and angles (°) for structures of compounds **1**, **2**, and **3**.

| Bonds and angles | 1 | 2 | 3 |
|---|---|---|---|
| C11–S1 | 1.6926(18) | 1.686(2) | 1.682(3) |
| C4–N1 | 1.282(2) | 1.282(3) | 1.278(3) |
| C11–N2 | 1.354(2) | 1.360(3) | 1.371(3) |
| C11–N3 | 1.321(2) | 1.321(3) | 1.324(3) |
| N1–N2 | 1.4043(19) | 1.400(2) | 1.404(3) |
| C2–O1 | 1.377(2) | 1.379(3) | 1.382(3) |
| C2–N2 | 1.477(2) | 1.481(3) | 1.475(3) |
| C1–F * | 1.326(3) | 1.330(3) | 1.327(3) |
| S1–C11–N2 | 122.07(13) | 121.77(18) | 121.72(19) |
| S1–C11–N3 | 122.33(15) | 123.29(17) | 123.58(19) |
| N2–C11–N3 | 115.60(16) | 114.94(19) | 114.7(2) |
| C1–C2–O1 | 109.90(15) | 110.1(2) | 109.6(2) |
| C3–C2–N2 | 101.09(14) | 101.36(17) | 101.17(19) |
| N1–C4–C3 | 113.36(16) | 113.52(19) | 113.6(2) |
| C2–C3–C4 | 103.36(15) | 102.61(18) | 103.33(19) |
| N1–N2–C2 | 111.88(14) | 111.74(17) | 112.16(17) |
| S1–C11–N2 | 122.07(13) | 121.77(18) | 121.72(19) |

* Mean bond length.

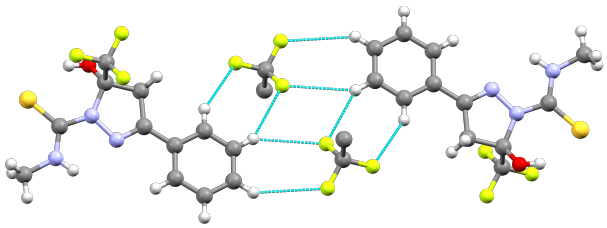
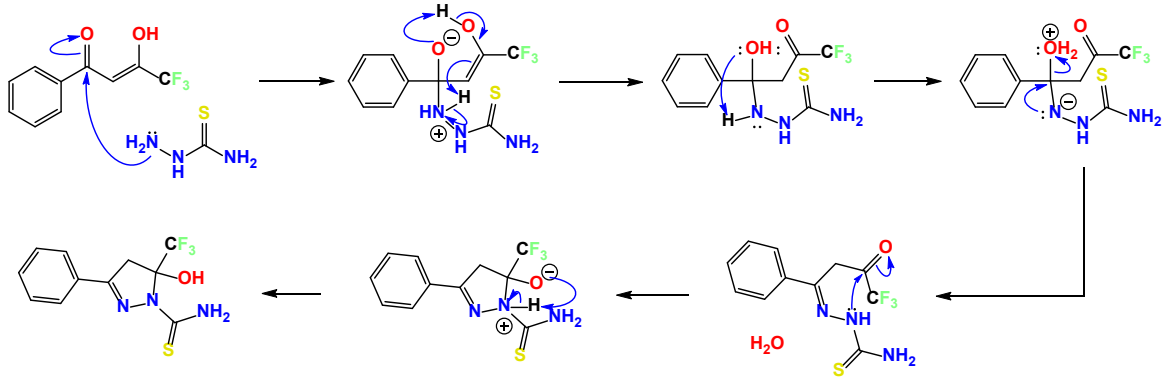
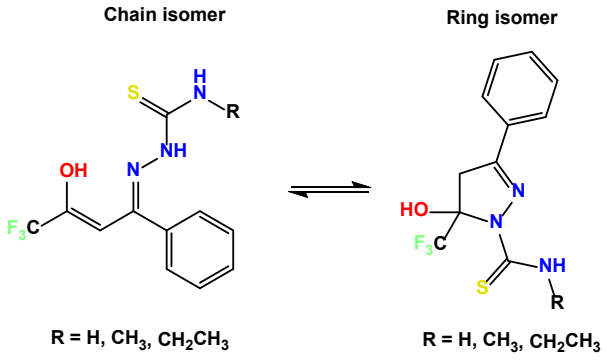


**Figure 4.** Net of F···H–$C_{arom.}$ intermolecular interactions, depicted by blue dashed lines, in the crystal packing of thiosemicarbazone **2**. Some atoms were omitted for better visualization.



**Scheme 3.** Proposed mechanism for the formation of the thiosemicarbazones reported in this work.




**Scheme 4.** Possible ring-chain isomerism that could occur in the thiosemicarbazones described in this work.

The C11–S1 bond lengths also suggest a double bond character [37] and are consistent with the crystallographic data of other thiosemicarbazones [38-40].

Regarding the overall conformation of the thiosemicarbazones, one interesting feature that has been observed in the crystal structures is the *quasi*-coplanarity of the phenyl and pyrazoline rings. The average dihedral angle between the planes containing the rings is 3.2°.

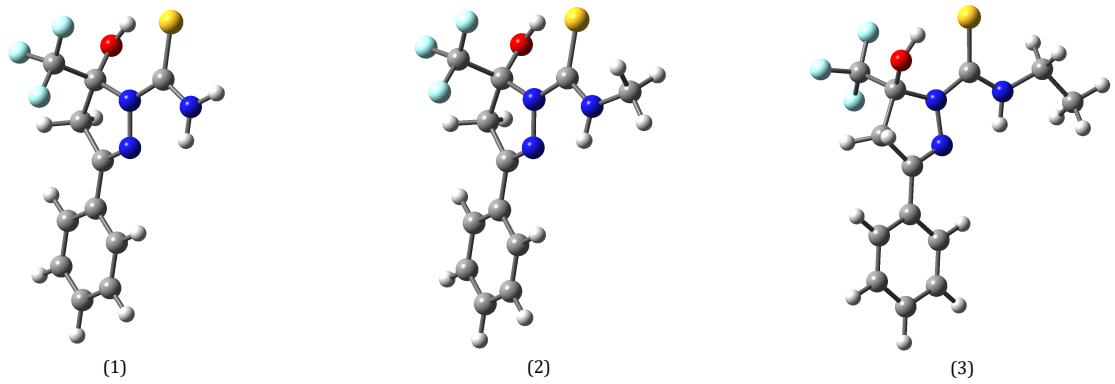



**Figure 5.** Optimized structures of thiosemicarbazones **1**, **2**, and **3**, from left to right.

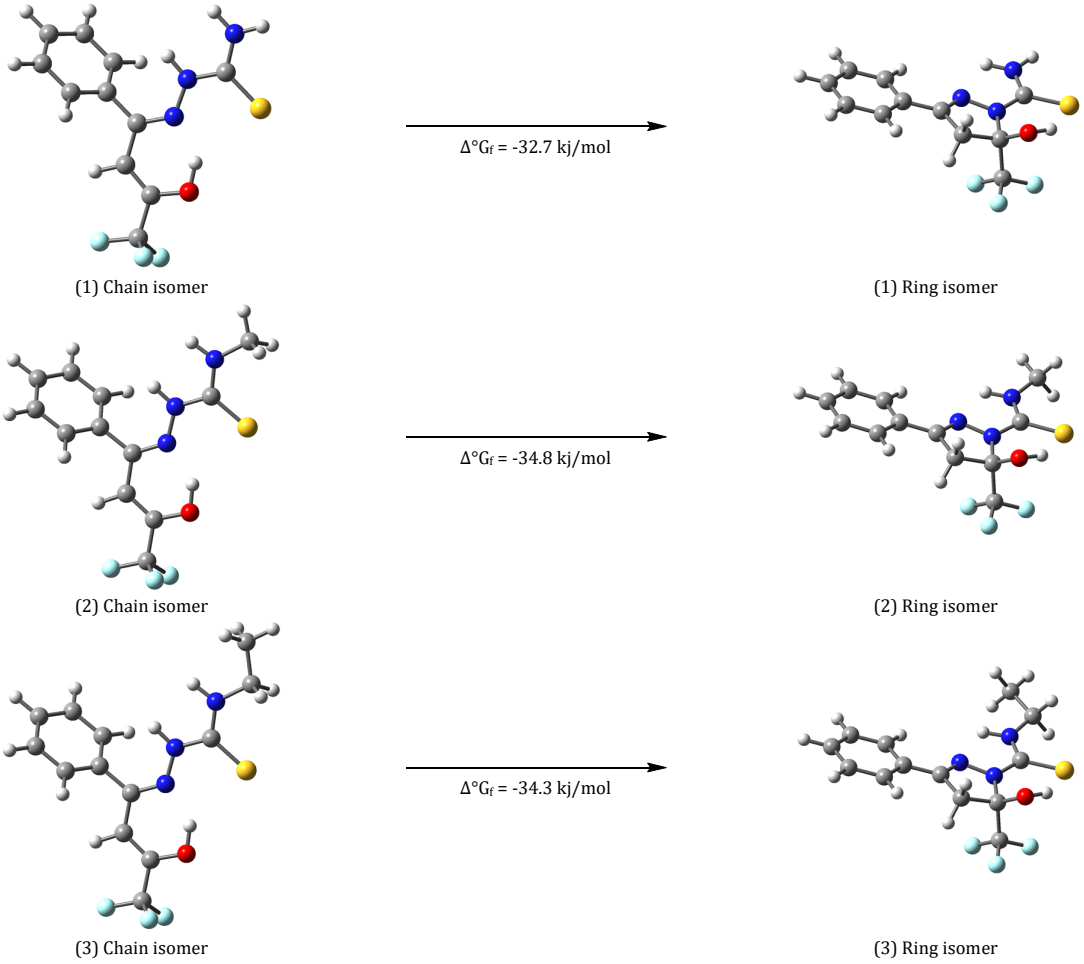



**Figure 6.** Calculated free energy of cyclization of thiosemicarbazones **1**, **2** and **3**.

A deeper investigation on the molecular interactions that stabilize crystal packing revealed a possible net of F···H–$C_{arom.}$ intermolecular interactions (Figure 4) influencing this coplanarity.

### *3.3. Synthetic structural features*

Based on the structure of the isolated product, the proposed mechanism for product formation, shown in Scheme 3, and the calculated free energy of thiosemicarbazone formation, we briefly discuss some synthetic structural features for this type of reaction. It is known that iminic compounds derived from β-diketones, *i.e.* the thiosemicarbazones described in this work, can present ring-chain isomerization [41,42]; thus, two isomers can coexist, as shown in Scheme 4. However, the structural experimental data obtained for the studied thiosemicarbazones, particularly single-crystal XRD and NMR, show that this equilibrium does not occur and the thiosemicarbazones are in cyclic form both in solid state and in solution.

According to the proposed mechanism, an intramolecular nucleophilic attack occurs, which promotes acyclization. To gain insights into this process, we optimized the structures of the thiosemicarbazones and conducted a computational analysis on the energy of cyclization in this system. The results

indicate that the formation of the rings stabilizes the thiosemicarbazones by an average value of –33.9 kJ/mol. This stabilization energy indicates that the ring isomer is significantly more stable than the chain isomer, corroborating the fact that the ring form is the only one found in the solid state or in solution. The optimized structures and the calculated free energies of cyclization for thiosemicarbazones **1**, **2** and **3** are presented, respectively, in Figures 5 and 6.

## 4. Conclusions

In this work, the synthesis and characterization of three fluorinated cyclic thiosemicarbazones are described in full detail. The elemental analysis and mass spectrometry confirm that the compounds have the proposed empirical formulas, while infrared spectroscopy shows that the condensation reactions were successful. The NMR data indicate that the thiosemicarbazones exist in a cyclic form in solution and that no ring-chain isomerization occurs. All hydrogen and fluorine atoms in the structures have been assigned. The single-crystal X-ray results also confirm the proposed structures, in accordance with the spectroscopic data. The calculated free energy of formation shows that cyclization is energetically advantageous and stabilizes the thiosemicarbazones, which explains why only the ring isomer is present in solution and in the solid state.

## Supporting information

CCDC-2420370, 2420371, 2420372 contains the supplementary crystallographic data for this paper, for compounds **1**, **2** and **3**, respectively. These data can be obtained free of charge via https://www.ccdc.cam.ac.uk/structures/, or by e-mailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(0)1223-336033.

Electronic Supplemental Information (ESI) available: Crystal data in CIF format. Copies of infrared spectrum, $^{1}H$ and $^{19}F\{^{1}H\}$ NMR, mass spectrometry of all new compounds. The online version of this article contains supplementary material, which is available to authorized users.

## Disclosure statement

Conflict of interest: The authors declare that they have no conflict of interest.
Ethical approval: Any animal or human data is acquired or used in this article. No ethical approval is necessary.
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## CRediT authorship contribution statement

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