

Proceedings

Synthesis and Characterization of Some 5-Acetylbarbituric Based Thiosemicarbazone Derivatives [†]

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Abstract: A new series of 5-acetylbarbituric based thiosemicarbazones named 5-acetylbarbituric hydrazine-1-carbothioamide (Acb4NDH, **1**), N-methyl-(5-acetylbarbituric)hydrazine-1-carbothioamide (Acb4NM, **2**), N-ethyl-(5-acetylbarbituric)hydrazine-1-carbothioamide (Acb4NE, **3**), N,N-dimethyl-(5-acetylbarbituric)hydrazine-1-carbothioamide (Acb4NDM, **4**), N'-piperidine-(5-acetylbarbituric)-1-carbothiohydrazide (Acb4Npip, **5**) and N'-hexamethyleneimine-(5-acetylbarbituric)-1-carbothiohydrazide (Acb4Nhexim, **6**), has been synthesized from 5-acetylbarbituric acid and *N*-unsubstituted/substituted thiosemicarbazides. The synthesized compounds were well characterized by elemental analyses, FT-IR, ¹H, ¹³C NMR and mass spectroscopic methods. Three-dimensional molecular structures of three compounds (**1**, **2** and **6**) and of *N*,₃-dimethyl-4-(5-(methylamino)-1,3,4^λ4-thiadiazol-2-yl)-5-oxo-2,5-dihydro-1*H*-pyrazole-1-carbothioamide ethyl sulfate salt (**7**) were determined by single crystal X-ray crystallography. The compounds were evaluated for their in vitro cytotoxicity against HeLa-229 cancer cell line.

Keywords: Thiosemicarbazones; 5-acetylbarbituric acid; heterocyclics; single crystal; cytotoxicity

1. Introduction

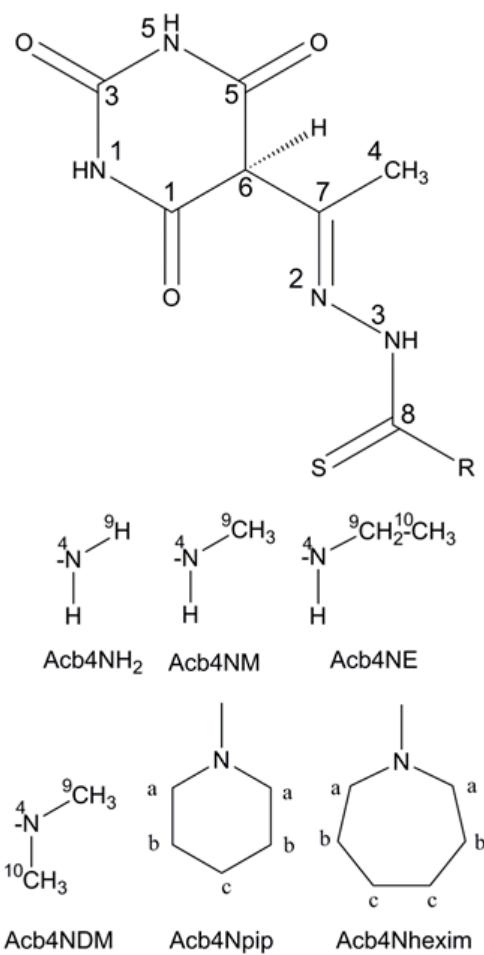
The use of thiosemicarbazides or thiosemicarbazones in organic synthesis has become a classic strategy for the preparation of different heterocycles. Numerous researchers have reported the S/N regioselective nucleophilic completion in the synthesis of heterocyclic compounds by intramolecular cyclization reactions. Changes in reaction conditions can induce an S or an N attack to eventually provide different cyclic products from a single starting material [1]. Also thiosemicarbazones are a class of ligand that has considerable interest for medicinal chemists due to their therapeutic potential. It is believed that the presence of the sulfur atom and its ability to bind to metals in the biological system is the main reason for biological activities, such as anticancer, antitumor, antifungal, antibacterial, antimarial, antiviral and anti-HIV, and its mechanism of action probably involves the inhibition of ribonucleotide reductase, converting ribonucleotides into deoxyribonucleotides. In addition, thiosemicarbazones that have an aromatic heterocyclic moiety appear to have improved biological activities [2]. In general, the thiosemicarbazones are easy to synthesize and their structure can be modified in multiple ways. In some cases, small modifications result in dramatic changes to the chemistry allowing a rational design of metal complex stability, redox potentials, membrane permeability and, ultimately, biological activity. A condensation reaction between a thiosemicarbazide and an aldehyde or ketone gives a thiosemicarbazone [3].

Alternatively, reactions between the methyl ester of imidopicolinic acid and thiosemicarbazides also cause thiosemicarbazones [4].

On the other hand, the medical importance of many pyrimidine derivatives is significant since they have antineoplastic, antiviral, antibiotic and anti-inflammatory properties, among other biological activities. Many synthetic molecules containing pyrimidine, such as certain barbituric acid derivatives or the sulfadiazine, are also important as synthetic drugs and chemotherapeutic agents, and have been developed using the small 5-acetylbarbiturate moieties as the main building block in their preparation [5].

Then, in the light of the above facts about thiosemicarbazones and barbituric acid derivatives, it is likely that the combination of both types of compounds may lead to new biologically active agents. For that reason, we have undertaken the reaction between such bioactive moieties, already tested previously [1,6].

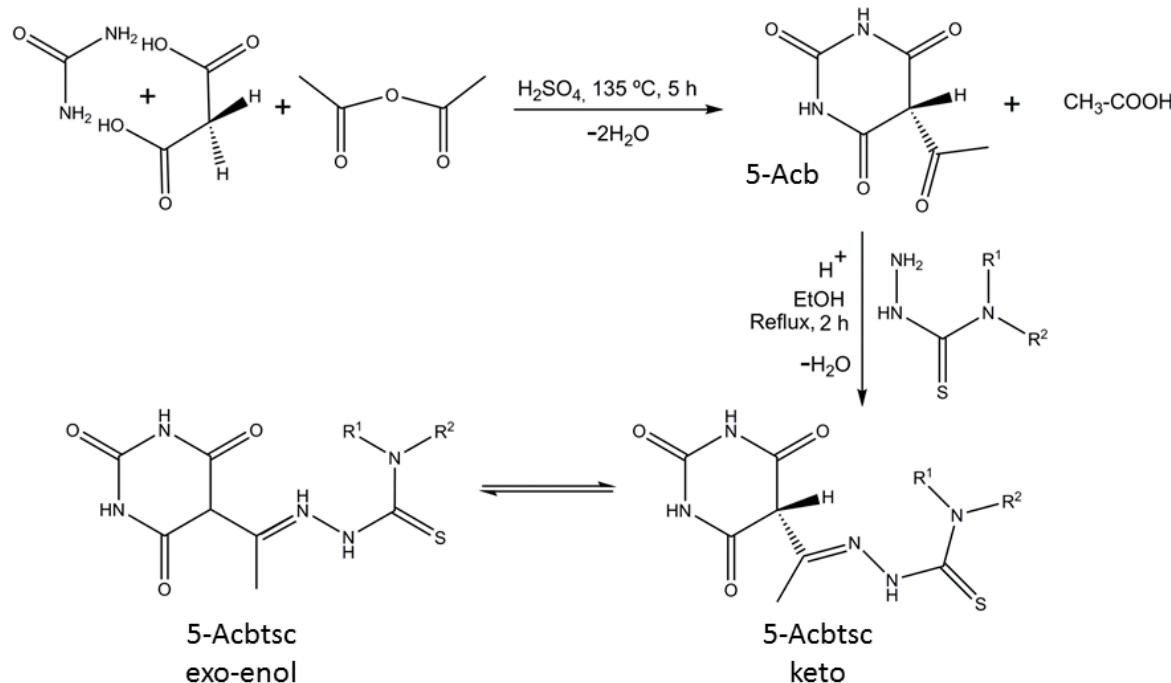
Herein, we present the synthesis of some new thiosemicarbazone derivatives (Scheme 1) via the condensation of the 5-acetylbarbituric acid and N-unsubstituted/substituted thiosemicarbazides. All structures of the newly synthesized materials were confirmed by both elemental and spectral (FT-IR, ^1H , ^{13}C NMR and mass) tools. The crystalline and molecular structure of three thiosemicarbazones and of *N*, 3-dimethyl-4-(5-(methylamino)-1,3,4 λ^4 -thiadiazol-2-yl)-5-oxo-2,5-dihydro-1*H*-pyrazole-1-carbothioamide ethyl sulfate salt, obtained serendipitously, were determined by X-ray diffraction of single-crystals. In addition, the results of the cytotoxic activity of thiosemicarbazones have been evaluated to determine in vitro antiproliferative activity against the HeLa-229 cell line (human cervical carcinoma).



Scheme 1. List of the synthesized 5-acetylbarbituric based thiosemicarbazone compounds.

2. Materials and Methods

All reagents and solvents were commercial products that were used as received, without further purification. 5-Acetylbarbituric acid (5-Acb) was prepared according to literature procedure [7]. The thiosemicarbazones (5-Acbtsc) were prepared by condensation reactions between 5-Acb and the unsubstituted/substituted thiosemicarbazides [1,6], as follows (Scheme 2):



Scheme 2. Synthesis pathway of 5-acetylbarbituric acid and thiosemicarbazones and tautomeric behavior of 5-acetylbarbiturate.

A mixture of 5-acetylbarbituric acid (0.01 mol) and of the corresponding thiosemicarbazide (0.01 mol) in 96% ethyl alcohol (45 mL) with 2 drops of conc. H₂SO₄ was heated under reflux for 2 h, cooled, and stirred for 3 d at room temperature. The precipitate was filtered off and recrystallised from ethanol.

5-acetylbarbituric hydrazine-1-carbothioamide (Acb4NDH, 1). Colorless solid, 80.9% yield; m.p. 270 °C to 272 °C. ¹H NMR (DMSO-d₆, δ/ppm): 2.5 (3H, Me), 8.1 (2H, N4H₂), 10.1 (1H, N3H), 10.6 (1H, N1H), 10.8 (1H, N5H), 13.0 (1H, N2H). ¹³C NMR (DMSO-d₆, δ/ppm): 15.7 (C-4), 88.8 (C-6), 149.6 (C-3), 167.9 (C-7), 174.0 (C-1, C-5), 181.0 (C-8). IR (KBr, v/cm⁻¹): 3430s, 3297m, 3211s,br, 3104m, v(N-H), 1725s v(C=O), 1664s δ(NH), 1627s,br, 1553s [v(C=N)+v(C=C)], 1377m, 1282s, 1239s [v(C=S)+v(C=N)], 1039m v(N-N), 830w v(C=S). MS m/z, (%): 243 (M⁺, 2). Anal. Calc. for C₇H₉N₅O₃S (243.24): C, 34.6; H, 3.7; N, 28.8; S, 13.2. Found: C, 34.9; H, 3.7; N, 28.0; S, 12.9%.

Suitable crystals for X-ray diffraction were grown at room temperature as Acb4NDH·DMSO (1·DMSO), after two weeks, from solutions prepared for NMR studies.

N-methyl-(5-acetylbarbituric)hydrazine-1-carbothioamide (Acb4NM, 2). Colorless solid, 78.4% yield; m.p. 260 °C to 262 °C. ¹H NMR (DMSO-d₆, δ/ppm): 2.5 (3H, Me), 2.9 (3H, N4M), 8.3 (1H, N4H), 9.9 (1H, N3H), 10.6 (1H, N1H), 10.8 (1H, N5H), 13.1 (1H, N2H). ¹³C NMR (DMSO-d₆, δ/ppm): 14.1 (C-9), 15.8 (C-4), 89.6. (C-6), 167.5 (C-7), 149.6 (C-3), 174.1 (C-1, C-5), 181.0 (C-8). IR (KBr, v/cm⁻¹): 3329m, 3184m, 3211m, 3066m, v(N-H), 1718s v(C=O), 1655w δ(NH), 1633s,br, 1575s, 1517m[v(C=N)+v(C=C)], 1382m, 1362m, 1296m, 1236m [v(C=S)+v(C=N)], 1047w v(N-N), 831m v(C=S). MS m/z, (%): 257 (M⁺, 24). Anal. Calc. for C₈H₁₁N₅O₃S (257.27): C, 37.3; H, 4.3; N, 27.2; S, 12.5. Found: C, 37.8; H, 4.4; N, 26.9; S, 12.1%.

Suitable crystals for X-ray diffraction were grown as Acb4NM (2), after a short time, from the mother liquors, and as N,3-dimethyl-4-(5-(methylamino)-1,3,4^λ-thiadiazol-2-yl)-5-oxo-2,5-dihydro

-1H-pyrazole-1-carbothioamide, ethyl sulfate salt (**7**) by slow evaporation of the mother liquors from the recrystallization three weeks later.

N-ethyl-(5-acetylbarbituric)hydrazine-1-carbothioamide (Acb4NE, **3**). Colorless solid, 78.4% yield; m.p. 270 °C to 272 °C. ¹H NMR (DMSO-d₆, δ/ppm): 1.1 (3H, N4CH₃), 2.5 (3H, Me), 3.4(2H, N4CH₂), 8.4 (1H, N4H), 9.9 (1H, N3H), 10.8 (1H, N5H), 10.6 (1H, N1H), 13.1 (1H, N2H). ¹³C NMR (DMSO-d₆, δ/ppm): 14.1 (C-10), 15.8 (C-4), -(C-9), 89.6 (C-6), 167.5 (C-7), 149.6 (C-3), 174.1 (C-1, C-5), 181.0 (C-8). IR (KBr, ν/cm⁻¹): 3329m, 3184m, 3111w, 3066w, ν(N-H), 1701s ν(C=O), 1659s δ(NH), 1572s, 1550s [ν(C=N)+ν(C=C)], 1298w, 1272m [ν(C=S)+ν(C=N)], 1051wm ν(N-N), 802m ν(C=S). MS *m/z*, (%): 271 (M⁺, 3). Anal. Calc. for C₉H₁₃N₅O₃S (271.29): C, 39.9; H, 4.8; N, 25.8; S, 11.8. Found: C, 40.1; H, 4.7; N, 25.6; S, 11.2%.

N,N-dimethyl-(5-acetylbarbituric)hydrazine-1-carbothioamide (Acb4NDM, **4**). Yellow solid, 60.7% yield; m.p. 280 °C to 282 °C. ¹H NMR (DMSO-d₆, δ/ppm): 2.5 (1H, C6H), 2.6 (3H, Me), 3.1 (6H, N4Me₂), 10.5 (1H, N1H), 10.5 (1H, N5H), 13.5 (1H, N2H). ¹³C NMR (DMSO-d₆, δ/ppm): 16.3 (C-4), 40.6 (C-9, C10), 88.3 (C-6), 150.0 (C-3), 165.9 (C-7), 171.3 (C-1, C-5), 181.4 (C-8). IR (KBr, ν/cm⁻¹): 3380m,br, 3172m, 3106w, ν(N-H), 1728s ν(C=O), 1664s δ(NH), 1617s, 1577s, 1530s, [ν(C=N)+ν(C=C)], 1375s, 1318s, 1235m [ν(C=S)+ν(C=N)], 1069w ν(N-N), 839m ν(C=S). MS *m/z*, (%): 271 (M⁺, 36). Anal. Calc. for C₉H₁₃N₅O₃S (271.29): C, 39.9; H, 4.8; N, 25.8; S, 11.8. Found: C, 39.9; H, 4.7; N, 25.5; S, 11.7%.

N'-piperidine-(5-acetylbarbituric)-1-carbothiohydrazide (Acb4Npip, **5**). Beige solid, 75.8% yield; m.p. > 300 °C. ¹H NMR (DMSO-d₆, δ/ppm): 1.6 (Hc), 1.6 (Hb), 2.5 (1H, C6H), 2.6 (3H, Me), 3.8 (Ha), 10.5 (1H, N1H), 10.5 (1H, N5H), 13.6 (1H, N2H). ¹³C NMR (DMSO-d₆, δ/ppm): 16.17 (C-4), 23.8 (Cc), 25.4 (Cb), 49.1 (Ca), 87.9 (C-6), 149.8 (C-3), 170.1 (C-7), 174.1 (C-1, C-5), 180.1 (C-8). IR (KBr, ν/cm⁻¹): 3341m,br, 3183m,br, 3111m, ν(N-H), 1718s ν(C=O), 1675s δ(NH), 1636s, 1577s, 1512s, [ν(C=N)+ν(C=C)], 1380m, 1357m, 1302m, 1273m, 1248m [ν(C=S)+ν(C=N)], 1041w ν(N-N), 831m ν(C=S). MS *m/z*, (%): 226 ([C₇H₆O₃N₄S]⁺, 39). Anal. Calc. for C₁₂H₁₇N₅O₃S (311.36): C, 46.3; H, 5.5; N, 22.5; S, 10.3. Found: C, 45.8; H, 5.5; N, 22.0; S, 9.8%.

N'-hexamethyleneimine-(5-acetylbarbituric)-1-carbothiohydrazide (Acb4Nhixim, **6**). Colorless solid, 68.8% yield; m.p. > 300 °C. ¹H NMR (DMSO-d₆, δ/ppm): 1.5 (Hb), 1.7 (Hc), 2.5 (1H, C6H), 2.5 (3H, Me), 3.9 (Ha), 10.8 (1H, N5H), 10.8 (1H, N1H), 13.5 (1H, N2H). ¹³C NMR (DMSO-d₆, δ/ppm): 16.1 (C-4), 88.3 (C-6), 149.9 (C-3), 171.8 (C-7), 174.2 (C-1, C-5), 180.5 (C-8). IR (KBr, ν/cm⁻¹): 3338m, 3178m,br, 3019m, ν(N-H), 1728s ν(C=O), 1623s δ(NH), 1578s, 1516sh [ν(C=N)+ν(C=C)], 1366m, 1316m, 1273m, 1241w [ν(C=S)+ν(C=N)], 1040w ν(N-N), 831w ν(C=S). MS *m/z*, (%): 198 ([C₇H₁₀O₃N₄]⁺, 23). Anal. Calc. for C₁₃H₁₉N₅O₃S (243.24): C, 48.0; H, 5.9; N, 21.5; S, 9.8. Found: C, 48.0; H, 5.7; N, 21.5; S, 9.5%.

Crystals suitable for X-ray diffraction were grown as Acb4Nhixim·H₂O, (6·H₂O) by slow evaporation of the mother liquors from the recrystallization after two weeks.

Microanalyses (C, H and N) were carried out in a Carlo-Erba 1108 elemental analyser. FT-IR spectra were recorded from KBr pellets over the range 4000–400 cm⁻¹ on a Bruker IFS-66v spectrometer. ¹H and ¹³C NMR spectra in DMSO-d₆ were run on Bruker AMX 300 and WM 300 instruments, respectively, using TMS as internal reference. For X-ray analysis, intensity data were collected at 100 K on a Bruker X8 KappaAPEXII diffractometer. Structures were solved by direct methods followed by difference Fourier calculations, and were refined by a full-matrix least-squares procedure using SHELXLTL. The structures of **1**·DMSO, **2**, **6**·H₂O and **7** were deposited at the Cambridge Crystallographic Data Centre with CCDC Nos. 1961790–1961793, respectively.

3. Results and Discussion

The 5-acetylbarbituric acid preparation is an acid-catalyzed one-pot three-component reaction between the malonic acid, urea and acetic anhydride constitutes a relatively facile synthesis of the 5-acetylbarbituric acid. The first step in the mechanism is believed to be the condensation between the acid and urea to generate the cyclized product, barbituric acid, where the α-carbon has a reactive hydrogen atom and is quite acidic (pKa = 4.01) because of the additional aromatic stabilization of the carbanion. In a second step, the intermediate generated acts as an electrophile for the Friedel–Crafts acylation using acetic anhydride. As shown in Scheme 2, 5-acetylbarbituric acid in condensation

with thiosemizarbazides, in the presence of concentrated sulfuric acid (a few drops), in absolute alcohol, produced *N*-(Substituted)-5-acetylbarbituric thiosemicarbazones **1–6**. The infrared spectra of these compounds showed characteristic absorption bands attributed to N-H, C=O and C=S bonds. The ¹H NMR spectra of these synthesized compounds, showed two characteristic signals in the range of δ 2.5 to 2.6 ppm and 13.0 to 13.6 ppm due to C-CH₃ and N2H protons, respectively. The ¹H NMR spectra of Acb4NDH and the *N*-monosubstituted thiosemicarbazones (**1–3**) show a signal in the range of 9.9–10.1 ppm due to the N3H proton, while in the spectra of the *N*-disubstituted thiosemicarbazones (**4–6**), this signal is absent, appearing a new signal at 2.45 ppm attributed to the proton C6H (Figure 1). This fact reflects the keto/exo-enol tautomerism present in solution (Scheme 2). In ¹³C NMR spectra, the signals around 150 and 170 ppm correspond to carbonyls, and another around 181 ppm to thiocarbonyl.

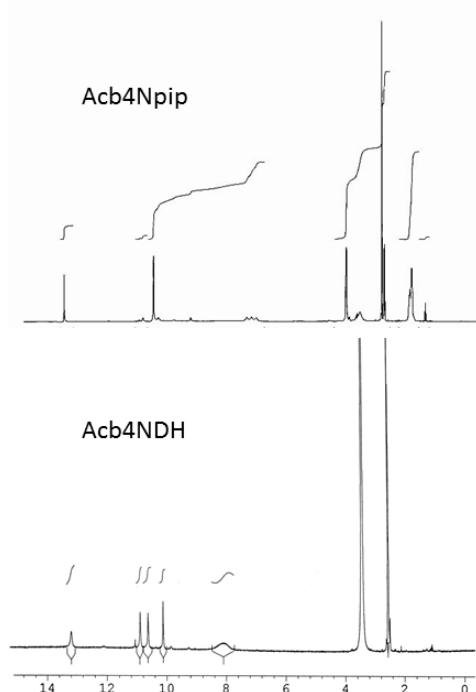


Figure 1. ¹H NMR spectra of thiosemicarbazones **1** (down) and **6** (top), showing the signals corresponding to the different tautomeric forms.

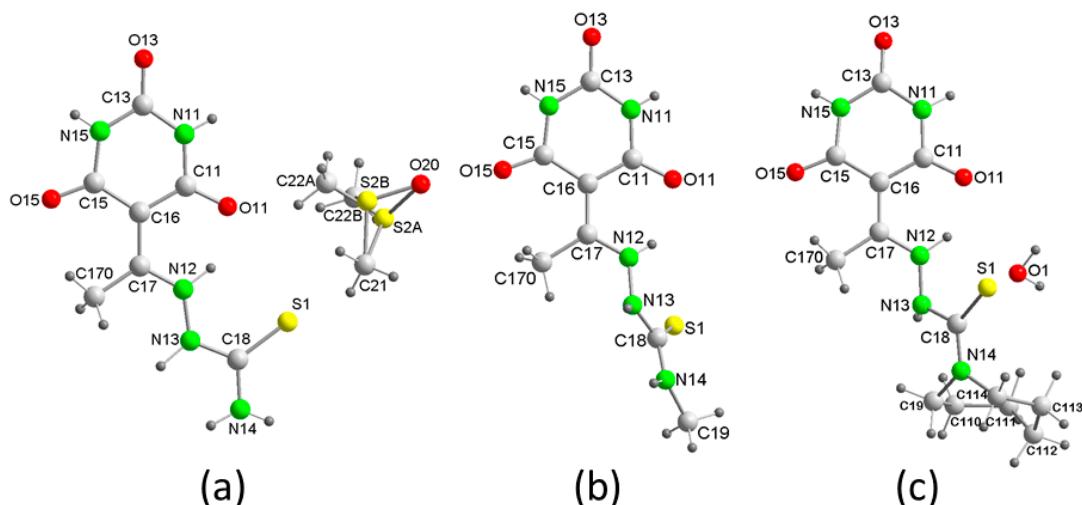


Figure 2. Perspective view of: (a) Acb4NDH·DMSO (1-DMSO), (b) Acb4NM (2) and (c) Acb4Nhexim·H₂O, (6-H₂O), showing the asymmetrical unit and the atom-numbering scheme.

3.1. Structural

For compounds **1**, **2** and **6** was made a single-crystal X-ray diffraction analysis. The crystal data of this thiosemicarbazones is: Compound **1**·DMSO crystallizes in the $P\bar{1}$ triclinic space group and unit cell dimensions $a = 8.1322(3)$ Å, $b = 8.9386(4)$ Å, $c = 10.0589(2)$ Å, $\alpha = 78.839(3)^\circ$, $\beta = 85.285(3)^\circ$, $\gamma = 74.452(4)^\circ$ and $V = 690.75(4)$ Å³. Compound **2** crystallizes in the $P2_1/c$ monoclinic space group and unit cell dimensions $a = 11.7397(5)$ Å, $b = 6.7208(3)$ Å, $c = 13.9717(5)$ Å, $\beta = 106.404(2)^\circ$, and $V = 1057.50(8)$ Å³. Compound **6**·H₂O crystallizes in the $P2_1/n$ monoclinic space group and unit cell dimensions $a = 6.3848(10)$ Å, $b = 28.301(6)$ Å, $c = 8.7678(17)$ Å, $\beta = 100.462(6)^\circ$, and $V = 1558.0(5)$ Å³.

An analysis of the distances and bond angles in each of the compounds showed that they do not differ significantly from the values found in other heterocyclic thiosemicarbazones [8]. The asymmetric unit for **1**, **2** and **6** are shown in Figure 2.

Although in the solid phase the three thiosemicarbazones are presented in the tautomeric form exo-enol, in regard to the molecular structure there are some differences between them. The molecule of **1** is flat with a maximum deviation of its atoms from the least-squares plane of 0.054 Å (N15) and a torsion angle C17-N12-N13-C18 of $-176.9(3)^\circ$, while in **2** and **6** the planes barbiturate and thiosemicarbazide are rotated with respect to each other, the torsion angle C17-N12-N13-C18 being 129.9(2) and $-135.3(5)^\circ$, respectively. In addition, while in **1** the atom N13 is contained in the plane formed by the atoms N12/H13/C18 [deviation 0.004(12) Å], in **2** and **6** such atom is not contained in the referred plane [deviation $-0.132(12)$ and 0.279(22) Å, respectively].

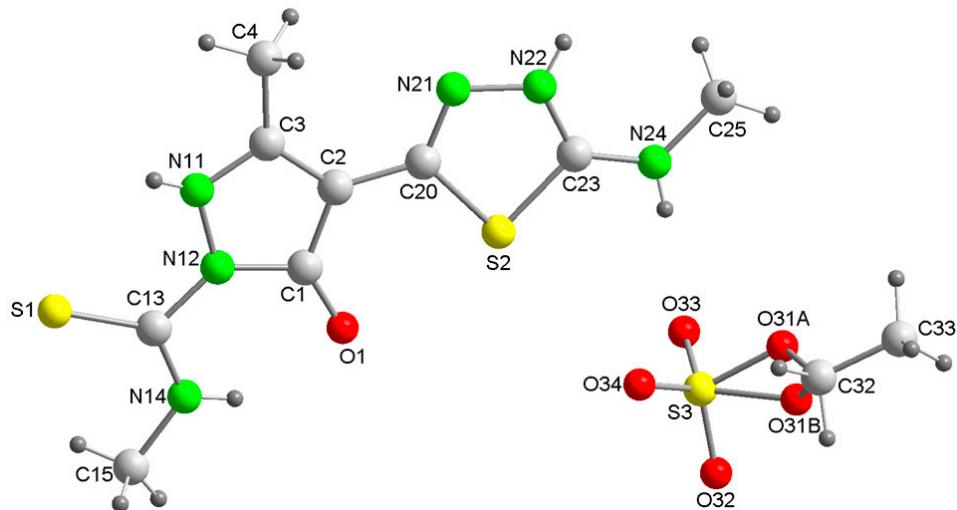


Figure 3. Perspective view of compound **7** showing the asymmetrical unit and the atom-numbering scheme.

N,3-Dimethyl-4-(5-(methylamino)-1,3,4λ⁴-thiadiazol-2-yl)-5-oxo-2,5-dihydro-1*H*-pyrazole-1-carbothioamide ethyl sulfate salt (**7**), was obtained serendipitously in the synthesis of compound **2** as an unexpected one-pot reaction where malonic acid, 4-Methyl-3-thiosemicarbazide, acetic anhydride, concentrated sulfuric acid (as a catalyst and as an adsorbent to remove water formed in the reaction) and absolute ethanol (as solvent) are involved. It is believed the mechanism may contain the following sequence of stages: (a) a double condensation between a molecule of malonic acid and two of thiosemicarbazide, (b) cyclization to form the 1,3,6-thiadiazole ring, (c) Friedel–Crafts acylation at the carbon alpha (directly adjacent to both carbonyl groups), (d) cyclization to form the pyrazol-3-one ring, (e) esterification between ethanol and sulfuric acid to give monoethylester of sulfuric acid and finally, (f) protonation to form the salt. The structure of the new compound was established by X-ray diffractometry.

Compound **7** crystallizes in the $P2_1/c$ monoclinic space group and unit cell dimensions $a = 6.9663(5)$ Å, $b = 30.7597(12)$ Å, $c = 8.6746(6)$ Å, $\beta = 104.412(6)^\circ$, and $V = 1800.3(2)$ Å³. The asymmetric unit for **7** is shown in Figure 3.

In the sulfate monoethyl ether anion of the molecule of **7**, the O31 is disordered over two positions with occupancy factor for each of 0.74(2) for O31A and 0.26(2) for O31B. For its part, the cation is completely flat. The root-mean-square deviation of atomic positions is 0.031. In the crystalline structure, each anion is linked by hydrogen bonding N-H···O to three nearest neighboring cations, forming a robust 3D network.

3.2. Antiproliferative Activity

The in vitro anticancer activity of **1–6** was determined in human cervical cancer cells (HeLa-229) by the colorimetric MTT assay with an exposure time of 72 h. The percentage of inhibition of cell growth for all thiosemicarbazones is in the range of values from 6 to 32 demonstrating low antiproliferative activity.

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Conflicts of Interest: The authors declare no conflict of interest.

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