

Novel 1,3-oxathiole derivatives: Efficient one-pot synthesis, antitumor efficiency, X-ray crystallographic, Hirshfeld surface, and Fukui function analysis

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ABSTRACT

An efficient one-pot access of two novel 1,3-oxathiole derivatives namely, ethyl (Z)-2-(4-acetyl-5-methyl-1,3-oxathiol-2-ylidene)-2-cyanoacetate; **7a** and ethyl (Z)-2-(1-cyano-2-ethoxy-2-oxoethylidene)-5-methyl-1,3-oxathiole-4-carboxylate; **7b** is described. The title compounds were prepared from the reaction of ethyl 2-cyanoacetate with carbon disulfide and 3-chloropentane-2,4-dione or ethyl 2-chloro-3-oxobutanoate in a K₂CO₃/DMF mixture. Their chemical structures were fully identified and characterized using spectral (IR, NMR, MS) and X-ray single-crystal structure analysis. The molecules of **7a** and **7b** are connected in the 3D via C—H...O and π - π stacking interactions, respectively. Using Hirshfeld analysis, the H...H, O...H, and N...H contacts dominate the molecular packing of **7a** 28.3, 25.0, and 15.9 %, respectively, while 38.8, 20.3 and 15.0 % for **7b**, respectively. The local reactivity was determined using Fukui functions and dual descriptor indices. According to the Fukui function, the susceptibility to nucleophilic attack was mainly detected on C2, C5, C6, and O7 in **7a**, and C2, C5, and O7 in **7b**. The in vitro cytotoxicity of the synthesized compounds was evaluated against cancer cell lines: MCF-7 (breast cancer), HepG2 (liver cancer), and HCT116 (colorectal cancer). Compound **7a** is particularly effective against HepG2 cells with an IC₅₀ value of 7.8 $\pm$ 0.7 μ g/mL and impacts MCF-7 and HCT116 with IC₅₀ values of 26.5 $\pm$ 1.8 and 26.3 $\pm$ 1.4 μ g/mL, respectively. In contrast, compound **7b** has moderate activity against HepG2 but limited effect on the other two lines.

1. Introduction

Cancer ranks among the foremost causes of mortality globally, necessitating ongoing research and the innovation of new anticancer agents [1]. By 2030, cancer is anticipated to impact approximately 26 million new cases, resulting in 17 million fatalities annually [2]. Many researchers dedicate their sincere efforts to synthesizing novel potent heterocyclic motifs to address the pressing need to discover potent chemotherapeutic agents to mitigate the problems associated with currently available anticancer medications such as toxicity and drug

resistance.

In contrast to the wide publications about azoles, the 1,3-oxathiole derivatives are rare in the literature, and some of the reported compounds were found to possess anti-proliferative [3–5], anti-inflammatory [6–8] and alkaline phosphatase inhibition [9]. Encouraged by these results and in continuation of our efforts to construct new sulfur-containing heterocycles of potential pharmacological activities [10–17], we examined the reaction of ethyl 2-cyanoacetate with CS₂ and 3-chloropentane-2,4-dione or ethyl 2-chloro-3-oxobutanoate in K₂CO₃/DMF mixture. Interestingly, the

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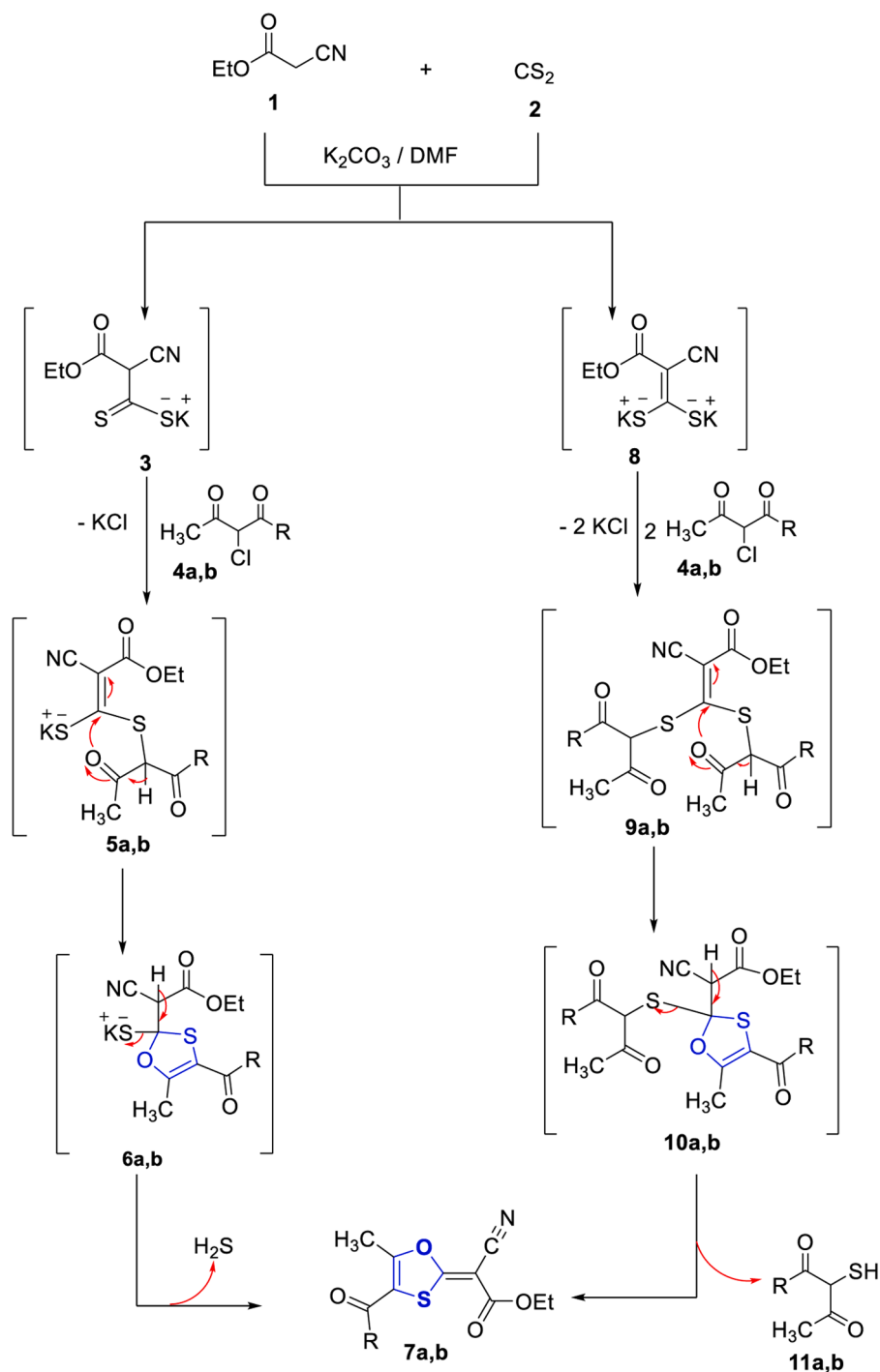
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7	a	b
R	CH ₃	CH ₃ CH ₂ O

Scheme 1. Synthesis of 1,3-oxathioles 7a,b.

reaction afforded two new 1,3-oxathiole derivatives **7a,b**. Their anti-cancer activity was assessed against MCF-7, HepG2, and HCT-116 cell lines using the sulforhodamine B (SRB) assay.

2. Material and methods

2.1. Chemistry

2.1.1. General remarks

All the melting points were measured using a Gallen Kamp apparatus.

(ThermoFisher Scientific, Paisley, UK) in open glass capillaries and were uncorrected. Infrared (IR) spectra were recorded using the KBr disk technique on a Perkin Elmer FT-IR spectrophotometer 1000 (Perkin Elmer, Waltham, MA, USA). NMR spectra (^1H and ^{13}C) were measured using A Bruker advanced NMR spectrometer operating at 400 MHz in deuterated DMSO at Cairo University Microanalytical Unit, Faculty of Pharmacy, Egypt.

Mass spectra were measured using a Q-ToF micro mass spectrometer at Panjab University, Chandigarh, India. Elemental Analysis was measured in Vario Elemental Analyzer III (Vario, Germany). Anticancer measurements were carried out at the Tissue Culture and Cancer Biology Research Laboratory, King Khalid University, KSA

2.1.2. Synthetic procedures

2.1.2.1. Synthetic approach to 1,3-oxathiole derivatives 7a,b. To a stirred solution of anhydrous K_2CO_3 (0.276 g, 20 mmol) in DMF (20 mL), ethyl 2-cyanoacetate (**1**) (1.13 g, 1.06 mL, 10 mmol) was added. After stirring for 20 mins, CS_2 (**2**) (0.76 g, 0.60 mL, 10 mmol) was added. Stirring continued for 30 mins, then 3-chloropentane-2,4-dione (**4a**) (2.69 g, 2.34 mL, 20 mmol) or ethyl 2-chloro-3-oxobutanoate (**4b**) (3.29 g, 2.76 mL, 20 mmol) was added portion-wise. Then, the reaction mixture was stirred at room temperature for an additional six hours. The resulting mixture was poured into an ice/water mixture and neutralized using dilute HCl. The precipitated solid products were filtered, and recrystallized from ethanol to give the title compounds **7a,b**, respectively.

Ethyl (Z)-2-(4-acetyl-5-methyl-1,3-oxathiol-2-ylidene)-2-cyanoacetate (7a).

Yield 85 %; m.p.: 130 °C (EtOH); IR (KBr) ν 1670 (C=O), 2214 ($\text{C}\equiv\text{N}$), 2989 (CH aliphatic) cm^{-1} ; ^1H NMR (DMSO- d_6) δ 1.27 (t, 3H, CH_3 , $J = 7.1$ Hz), 2.55 (s, 3H, CH_3), 2.67 (s, 3H, CH_3), 4.26 (q, 2H, CH_2 , $J = 7.1$ Hz); ^{13}C NMR (DMSO- d_6) δ 14.58, 15.09, 29.74, 62.07, 75.53, 113.64, 121.62, 158.14, 164.66, 181.34, 190.52. Anal. Calcd for $\text{C}_{11}\text{H}_{11}\text{NO}_4\text{S}$ (253.27): C, 52.17; H, 4.38; N, 5.53. Found: C, 52.23; H, 4.31; N, 5.48.

Ethyl (Z)-2-(1-cyano-2-ethoxy-2-oxoethylidene)-5-methyl-1,3-oxathiole-4-carboxylate (7b).

Yield 87 %; m.p.: 170 °C (EtOH); IR (KBr) ν 1682, 1728 ($2\text{C}=\text{O}$), 2218 ($\text{C}\equiv\text{N}$), 2997 (CH aliphatic) cm^{-1} ; MS: Q-TOF micro mass: calcd for $[\text{M} + \text{H}]^+$ $m/z = 284.29$, found 284.058. ^1H NMR (DMSO- d_6) δ 1.27, 1.31 (2t, 6H, 2 CH_3), 2.61 (s, 3H, CH_3), 4.25, 4.32 (2q, 4H, 2 CH_2); ^{13}C NMR (DMSO- d_6) δ 14.19, 14.38, 14.61, 62.15, 62.72, 75.53, 110.46, 113.64, 160.11, 164.84, 181.56. Anal. Calcd for $\text{C}_{12}\text{H}_{13}\text{NO}_5\text{S}$ (283.29): C, 50.88; H, 4.63; N, 4.94. Found: C, 50.75; H, 4.71; N, 4.88.

2.2. X-ray crystallography

The compounds of **7a** and **7b** were obtained as single crystals by slow evaporation from ethanol solution of the pure compound at room temperature. Data were collected on a Bruker APEX-II D8 Venture area diffractometer, equipped with graphite monochromatic Mo $\text{K}\alpha$ radiation, $\lambda = 0.71073$ Å at 293 (2) K. Cell refinement and data reduction were carried out by Bruker SAINT. SHELXT [18,19] was used to solve structures. The final refinement was carried out by full-matrix least-squares techniques with anisotropic thermal data for nonhydrogen atoms on F . The crystallographic data of compounds **7a** (CCDC 2,386,459) and **7b** (CCDC 1,974,705) are available on request (free of charge) from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

2.3. Fukui functions analysis

Fukui function calculations were carried out to examine the chemical reactivity and structural characteristics of 1,3-oxathiole molecules **7a** and **7b** using the Gaussian 09 W and viewed on GaussView 6.0. The molecular structures were optimized using Density Functional Theory (DFT) with Becke's three-parameter functional (B3LYB) method, applying the 6-311++G(d,p) basis set [20], and utilizing the UCA-FUKUI V 2.0 packages. Additionally, natural bond orbital (NBO) analysis was conducted using the NBO program within Gaussian 09 W, employing the POP=NBO keyword [21]. The condensed Fukui function and associated parameters were determined with the UCA-FUKUI tool [22]. All calculations were conducted on a laptop with a 13th Gen Intel® Core™ i7-1360P @ 2.20 GHz processor and 16.0 GB ram.

2.4. Hirshfeld surface analysis

The topology analyses were performed using the Crystal Explorer 17.5 program [23].

2.5. The in vitro anticancer assessment

The anticancer effectiveness of synthetic compounds was evaluated using the sulforhodamine B (SRB) assay. MCF-7, HepG2, and HCT 116 cell lines were plated at a density of 2×10^3 cells per well in 96-well plates and allowed to adhere for 24 h before being treated with nano-emulsion formulations. Various concentrations of the formulations (0, 0.01, 0.1, 1, 10, 100, and 1000 $\mu\text{g/mL}$) were applied to the wells, and the cells were incubated for 72 h at 37 °C. After this incubation period, the

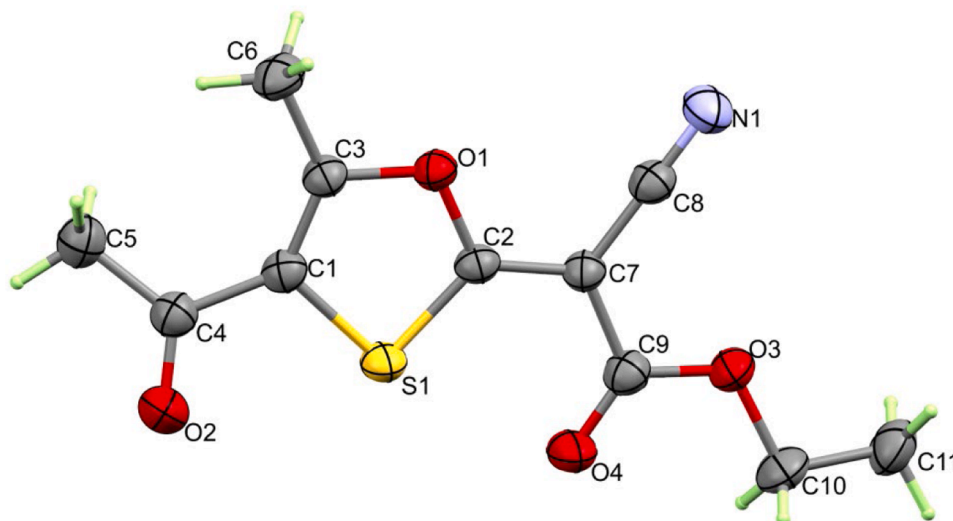


Fig. 1. X-ray structure of **7a**.

Table 1
Experimental details.

Identification code	7a	7b
CCDC	2,386,459	1,974,705
Empirical formula	C ₁₁ H ₁₁ NO ₄ S	C ₁₂ H ₁₃ NO ₅ S
Formula weight	253.27	283.29
Temperature/K	293(2)	293(2)
Crystal system	monoclinic	monoclinic
Space group	P2 ₁ /c	P2 ₁ /c
a/Å	11.4381(7)	7.0587(3)
b/Å	14.1667(8)	15.7129(8)
c/Å	7.3657(3)	12.5234(6)
α/°	90	90
β/°	93.985(4)	92.538(2)
γ/°	90	90
Volume/Å ³	1190.65(11)	1387.64(11)
Z	4	4
ρ _{calc} /cm ³	1.413	1.356
μ/mm ^{−1}	0.274	0.248
F(000)	528.0	592.0
Crystal size/mm ³	0.19 × 0.17 × 0.1	0.447 × 0.265 × 0.152
Radiation	MoKα (λ = 0.71073)	MoKα (λ = 0.71073)
2θ range for data collection/°	6.77 to 54.848	4.162 to 54.994
Index ranges	−14 ≤ h ≤ 13, −18 ≤ k ≤ 18, −9 ≤ l ≤ 8	−9 ≤ h ≤ 9, −20 ≤ k ≤ 20, −16 ≤ l ≤ 16
Reflections collected	9229	60,959
Independent reflections	2475 [R _{int} = 0.1112, R _{sigma} = 0.0698]	3183 [R _{int} = 0.0533, R _{sigma} = 0.0213]
Data/restraints/parameters	2475/0/157	3183/0/195
Goodness-of-fit on F ²	1.073	1.142
Final R indexes [I ≥ 2σ (I)]	R ₁ = 0.0819, wR ₂ = 0.2435	R ₁ = 0.0502, wR ₂ = 0.1136
Final R indexes [all data]	R ₁ = 0.1076, wR ₂ = 0.2993	R ₁ = 0.0680, wR ₂ = 0.1269
Largest diff. peak/hole / e Å ^{−3}	0.37/0.47	0.21/0.23

culture media was replaced with 150 μL of 10 % trichloroacetic acid (TCA) and incubated for 1 hour at 4 °C, followed by five washes with distilled water. The cells were then stained with 50 μL of a 0.04 % w/v SRB solution and incubated for 10 mins at 25 °C in the dark. Afterward, the excess stain was removed with 1 % acetic acid, and 100 μL of 10 mM Tris base solution (pH=10.5) was added to each well to dissolve the protein-bound dye. Finally, the optical density was measured using a microplate reader set to 540 nm [24]

Table 2
Selected geometric parameters (Å, °) for 7a and 7b

1,3-Oxathiole 7a				1,3-Oxathiole 7a			
Bond distances				Bond distances			
S1—C2	1.708(3)	C3—C1	1.335(4)	S1—C6	1.7213 (17)	O3—C6	1.343 (2)
S1—C1	1.755(4)	C3—C6	1.476(5)	S1—C8	1.7560 (19)	O3—C7	1.389 (2)
O1—C3	1.396(4)	C2—C7	1.366(5)	O1—C2	1.512 (8)	O4—C9	1.194 (3)
O1—C2	1.367(4)	C7—C9	1.453(5)	O1—C3	1.324 (2)	O5—C9	1.329 (3)
O3—C9	1.330(5)	C7—C8	1.420(5)	O1—C2X	1.444 (7)	O5—C10	1.462 (2)
O3—C10	1.458(5)	C1—C4	1.480(6)	O2—C3	1.210 (2)	N1—C5	1.134 (3)
O4—C9	1.212(5)	C4—C5	1.477(6)				
O2—C4	1.201(4)	C10—C11	1.477(7)				
N1—C8	1.148(4)						
Bond angles				Bond angles			
C2—S1—C1	89.44(16)	C3—C1—S1	112.0(3)	C6—S1—C8	88.80 (9)	S1—C6—C4	126.90 (14)
C2—O1—C3	111.9(2)	C3—C1—C4	133.2(3)	C2—O1—C3	117.8 (4)	O3—C6—C4	120.12 (15)
C9—O3—C10	116.2(3)	C4—C1—S1	114.8(3)	C2X—O1—C3	112.9 (3)	S1—C6—O3	112.98 (12)
O1—C3—C6	112.6(3)	O3—C9—C7	112.6(3)	C6—O3—C7	112.85 (13)	O3—C7—C12	113.83 (17)
C1—C3—O1	113.5(3)	O4—C9—O3	124.5(4)	C9—O5—C10	116.39 (18)	O3—C7—C8	113.13 (16)
C1—C3—C6	133.9(4)	O4—C9—C7	122.9(4)	O1—C2—C1	112.6 (6)	S1—C8—C9	120.76 (15)
O1—C2—S1	113.1(2)	N1—C8—C7	178.7(4)	O1—C2X—C1X	113.7 (9)	S1—C8—C7	112.24 (14)
C7—C2—S1	127.1(3)	O2—C4—C1	117.7(4)	O1—C3—O2	124.38 (19)	O4—C9—O5	125.52 (19)
C7—C2—O1	119.8(3)	O2—C4—C5	121.8(4)	O1—C3—C4	112.77 (16)	O5—C9—C8	109.83 (17)
C2—C7—C9	118.6(3)	C5—C4—C1	120.4(3)	O2—C3—C4	122.85 (18)	O4—C9—C8	124.7 (2)
C2—C7—C8	120.7(3)	O3—C10—C11	108.7(4)	N1—C5—C4	179.7 (2)	O5—C10—C11	107.6 (2)
C8—C7—C9	120.7(3)						

3. Results and discussion

3.1. Synthesis and characterization

The reaction of equimolar ratios of ethyl 2-cyanoacetate (**1**), CS₂ (**2**), and 3-chloropentane-2,4-dione (**4a**) or ethyl 2-chloro-3-oxobutanoate (**4b**) in presence of K₂CO₃/DMF mixture gave 1,3-oxathioles **7a,b**, respectively in ~ 65 % yields. In anticipation of the low yield of the previous reaction, the same reaction was repeated using two molar ratios of **4a,b**, where the compounds **7a,b** were isolated in 85 and 87 % yields, respectively.

As shown in Scheme 1, synthesis of **7a,b** could proceed by one of two routes. In route A, the reaction of **1** with **2** afforded potassium salt **3** which reacted with one mole of either **4a** or **4b** to afford S-alkylated intermediates **5a,b**. Intramolecular cyclization of **5a,b** followed by elimination of H₂S afforded final products **7a,b**. While in route B, the reaction of **1** with **2** afforded di potassium salt **8** which reacted with two moles of either **4a** or **4b** to give **9a,b**. Similarly, intramolecular cyclization of **9a,b** followed by removal of mercapto derivatives **11a,b** yielded final products **7a,b**.

Chemical structures of 1,3-oxathioles **7a,b** were appropriately characterized by both spectral data (IR, NMR, MS) and X-ray analysis. For example, the ¹H NMR spectrum of compound **7a** exhibited two singlet signals at δ 2.55 and 2.67 ppm for two methyl protons. Protons of the ethoxy group are shown as a triplet at δ 1.27 ppm (J = 7.1 Hz) and a quartet at δ 4.26 ppm (J = 7.1 Hz). Also, the chemical shift values in the C-13 NMR spectra of **7a,b** confirmed the formation of 1,3-oxathiole structures **7** [Figs. S5 and S8, SI file].

Moreover, single crystal X-ray diffraction of **7a** (Fig. 1) and **7b** (Fig. 3) confirm the established structures.

3.2. X-ray analysis

For compounds **7a** and **7b**, the crystallographic data and refinement information are summarized in Table 1. The selected bond lengths and bond angles listed in Table 2 are normal ranges [25].

For compound **7a**, the asymmetric unit contains one molecule as shown in Fig.1.

The molecules are connected in the 3D via C—H...O contacts shown in Fig. 2 which belong to van der Waals interactions. The donor...acceptor and hydrogen acceptor distances are 3.221(5) and 2.49 Å, respectively while the donor-hydrogen...acceptor angle is 133° A view

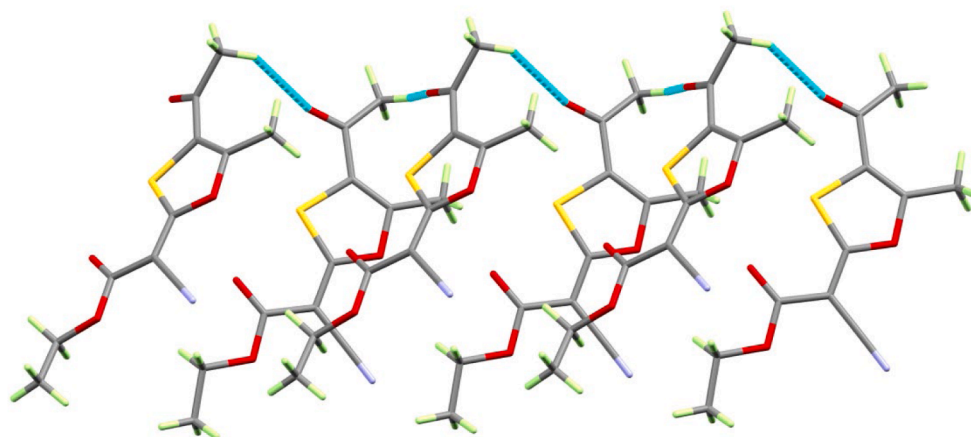


Fig. 2. Molecular packing via C5-H...O2 interaction for 7a.

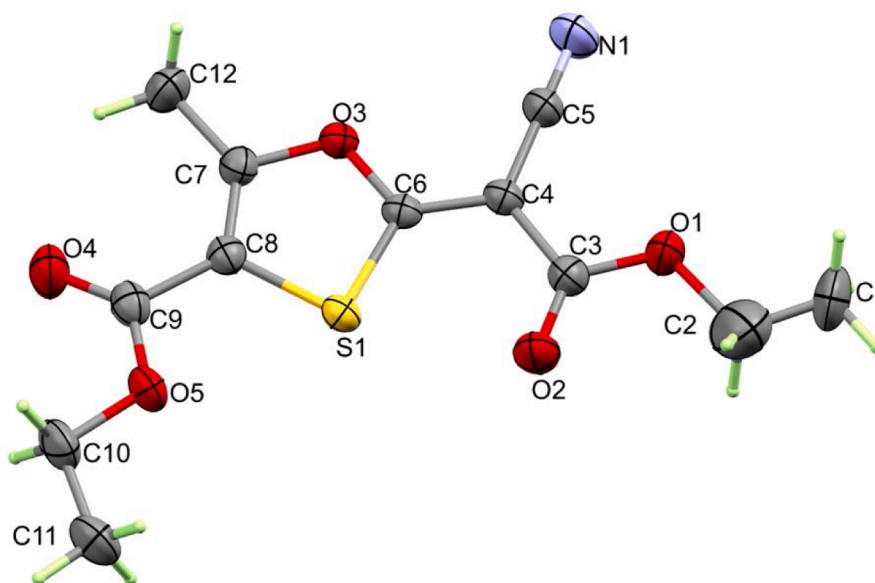


Fig. 3. X-ray structure of 7b

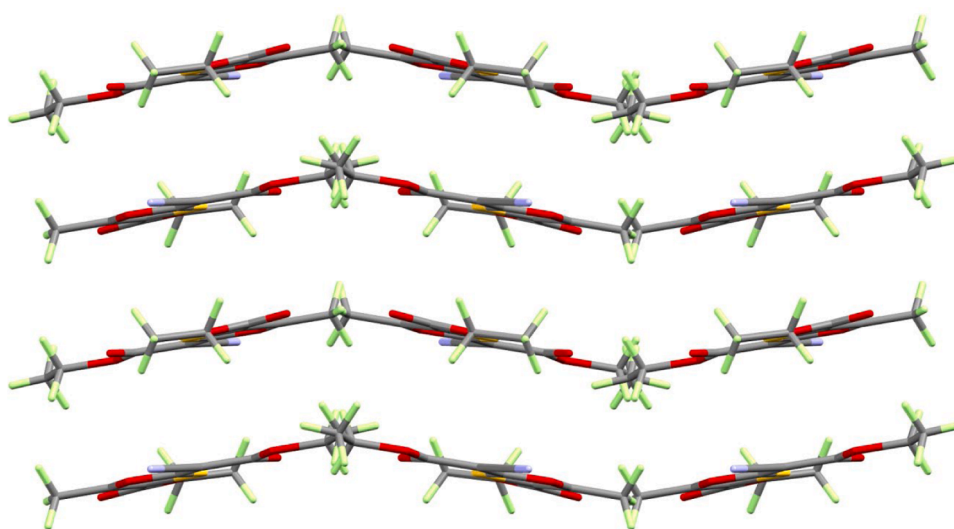


Fig. 4. Molecular packing of 7b along *ab*-plane.

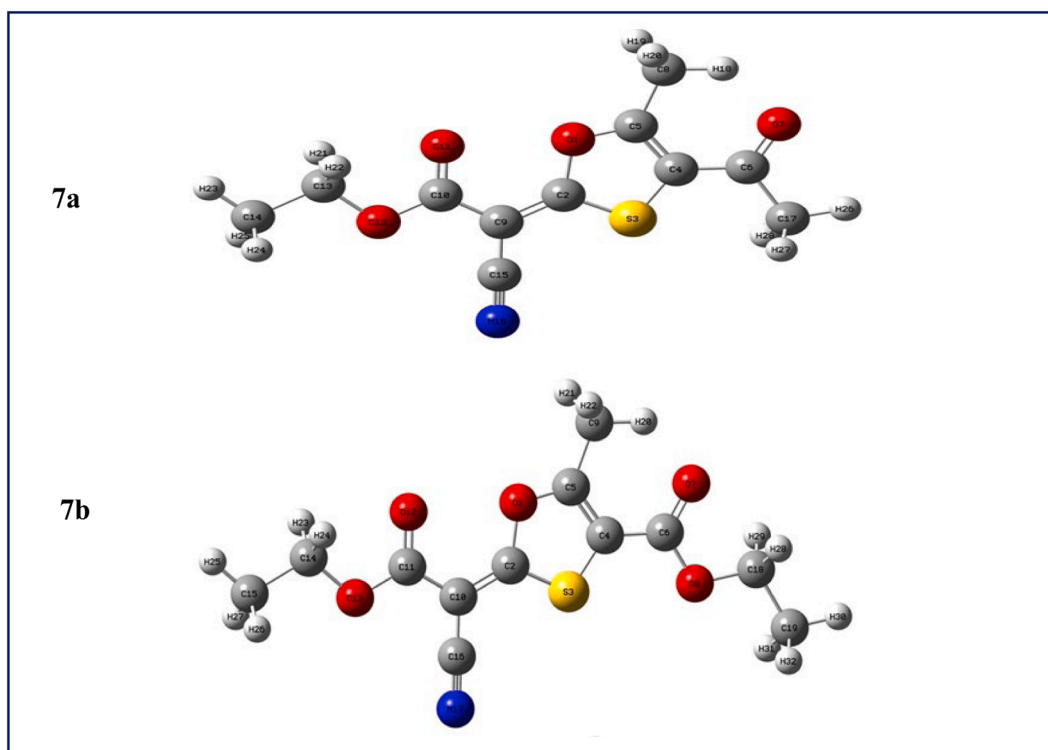


Fig. 5. The optimized structures of oxathioles 7a,b.

of the packing scheme along the *ab* plane is shown in Fig. S1.

The asymmetric unit of **7b** contains one independent molecule as shown in Fig. 3. All the bond lengths and angles are in normal ranges [25]. Two positions with an occupancy of 0.63:0.37 are observed for the terminal ethyl group C1-C2 in the molecule.

The disorder in the ethyl group is shown in Fig. S2 (Supplementary data).

In the crystal packing, the molecules are packed parallel to one another allowing the presence of π - π stacking interactions between the 1,3-oxathiole ring systems (Fig. 4). The C6...S1 distance is 3.491(1) Å while the two ring centroids separation is 3.811 Å (Fig. S3).

3.3. Fukui functions

The optimized structures of 1,3-oxathiole **7a** and **7b** are shown in Fig. 5. The Fukui function is known as the most common tool for analyzing a molecule's chemical reactivity and selectivity during a reaction [26]. It helps to identify the most favorable sites within a compound for electrophilic, nucleophilic, and radical attacks, as shown by the following equations [27],

$$\text{For electrophilic attack: } f_k^- = q_k(N_0) - q_k(N_0 - 1)$$

$$\text{For nucleophilic attack: } f_k^+ = q_k(N_0 + 1) - q_k(N_0)$$

$$\text{For radical attack: } f_k^0 = \frac{1}{2}(f_k^+ + f_k^-)$$

Where q_k corresponds to the electronic population of atom k in the

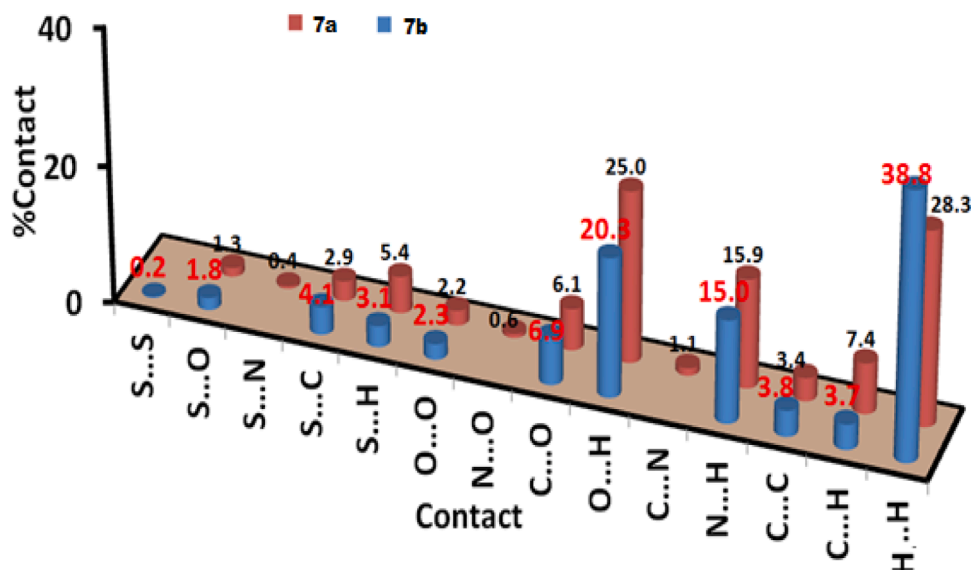


Fig. 6. Contacts contributed to the molecular packing based on Hirshfeld analysis.

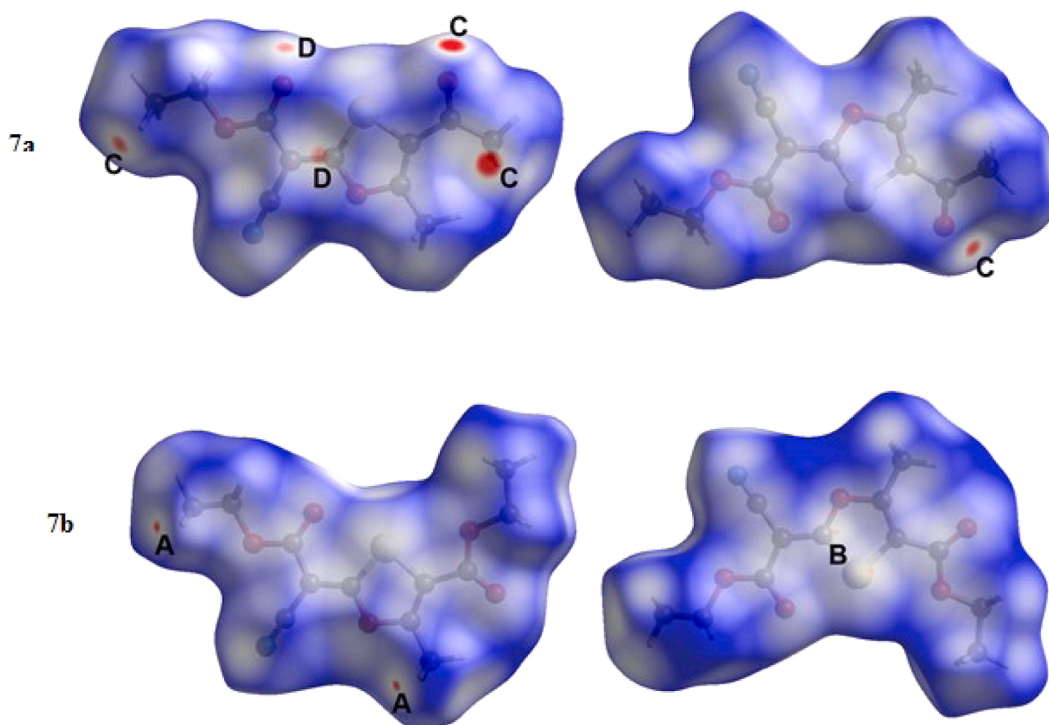


Fig. 7. Hirshfeld d_{norm} maps showing the most important contacts: A) H...H; B) C...S; C) O...H and D) C...O.

molecule in its neutral (N_0), anionic ($N_0 + 1$), and cationic ($N_0 - 1$) states.

Moreover, selectivity towards nucleophilic or electrophilic attack can be predicted using values of f_k^- , f_k^+ , and Dual Descriptor index. Dual Descriptor index is calculated by $\Delta f(r) = [f^+(r) - f^-(r)]$. If $\Delta f(r) > 0$, the atom is selective for a nucleophilic attack. However, if $\Delta f(r) < 0$, it is hard to be attacked by a nucleophile and may be preferred for an electrophilic attack. Values of f_k^- , f_k^+ , f_k^0 , and $\Delta f(r)$ are shown in Table S1.

For oxathiole (**7a**), C2, C5, C6, and O7 showed the most favorable sites for the nucleophilic attack, whereas S3, C9, O11, and N16 are the most preferred atoms for electrophilic attack. In addition, S3, O7, C9, and N16 showed the most preferred atoms for the radical attack as shown in Table S1.

For 1,3-oxathiole **7b**, the obtained results showed that C2, C5, and O7 are the most preferred atoms for the nucleophilic attack (high positive f^+ values and $\Delta f(r)$ is more than 0), whereas O1, S3, C10, and N17

are the most preferred atoms for electrophilic attack (high positive f^- values and $\Delta f(r)$ is less than 0). Based on f^0 values, S3, O7, C10, and N17 showed the most preferred atoms for radical attack.

3.4. Hirshfeld surface analysis

The presence of intermolecular interaction between molecular units in the crystal is important for crystal stability. Hirshfeld maps (d_{norm} , shape index, and curvedness) are important for analyzing these non-covalent interactions. All possible contacts that occurred in the studied compounds are shown in Fig. 6. The most dominant non-covalent interactions in the crystal structure of both compounds are the H...H, O...H, and N...H contacts. Their percentages for **7a** are 28.3, 25.0 and 15.9 %, respectively, while 38.8, 20.3 and 15.0 % for **7b**, respectively.

In terms of importance, not all these non-covalent interactions have

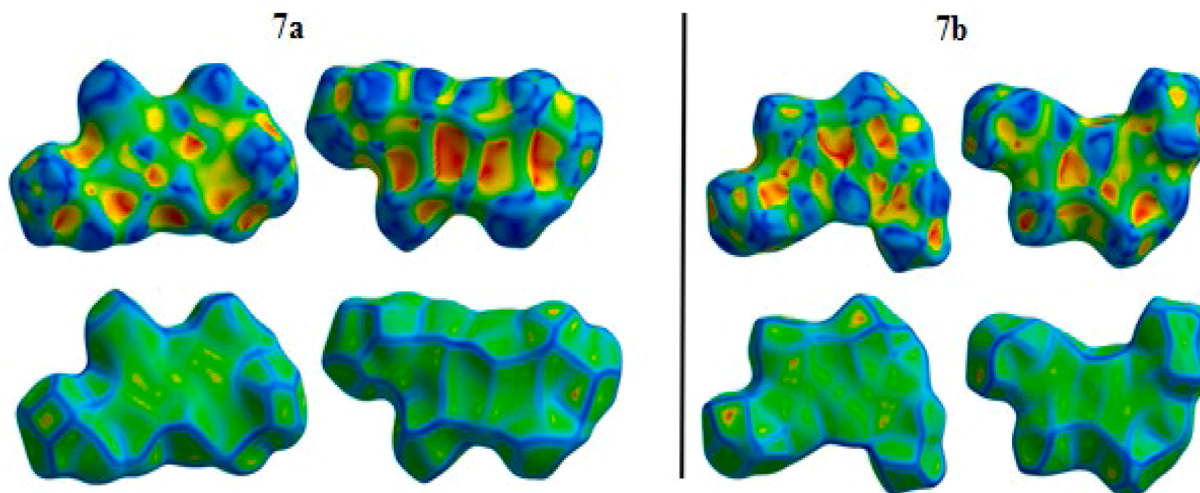


Fig. 8. Shape index and curvedness maps for **7a** and **7b**

Table 3

The cytotoxic effects of 7a,b on human solid tumor cancer cells.

Compound	IC ₅₀ (μg/mL)		
	MCF-7	HepG2	HCT-116
Doxorubicin (Dox)	0.92 ± 0.091	0.62 ± 0.04	1.2 ± 0.12
7a	26.5 ± 1.8	7.8 ± 0.7	26.3 ± 1.4
7b	≥ 100	52.3 ± 1.1	≥ 100

great importance in molecular packing. The d_{norm} map with red spots showing the most significant contacts in the molecular packing is presented in Fig. 7.

For 7a, the important contacts are O...H and C...O interactions where the O2...H00I, O2...H00F and C2...O4 have the shortest contact distances of 2.404, 2.489 and 3.153 Å, respectively.

In the case of 7b, there are two important contacts which are the H...H and C...S contacts where the H1B...H12B and C6...S1 distances are 2.133 and 3.491 Å, respectively.

In Fig. 8, the shape index and curvedness maps are presented. These maps are important for examining the presence of π - π interactions or not. The red-blue triangle in the shape index of 7a but not in 7b in addition to the presence of a flat green area in the curvedness maps of the former is considered evidence of the presence of π - π stacking interactions in 7a. The C4...C8, C3...C7, and C2...C2 contacts have

distances of 3.429, 3.512, and 3.544 Å, respectively where all are slightly larger than twice the van der Waals radii of carbon.

3.5. Antitumor evaluation of 1,3-oxathiole derivatives 7a,b

The study evaluated the cytotoxic and antiproliferative effects of synthesized compounds 7a,b on three cancer cell lines: MCF-7 (breast cancer), HepG2 (liver cancer), and HCT116 (colorectal cancer). The goal was to determine how effectively these compounds could inhibit the growth and proliferation of these specific cancer cell lines. Sulforhodamine B (SRB) assay was used for cytotoxicity screening [24]

The relationship between cytotoxicity of anticancer drugs and anti-tumor activity highlights the importance of IC₅₀ values in evaluating their efficacy. Samples with low IC₅₀ values may successfully target malignant tumors at lower doses, thereby increasing their usefulness in cancer treatment. Low IC₅₀ indicates suppression of cell proliferation and effective anti-tumor activity.

As presented in Table 3 and Fig 9, compound 7a was found to be the most toxic to HepG2 cells, exhibiting an IC₅₀ value of 7.8 ± 0.7 μg/mL. Its effects on MCF-7 and HCT116 cells were similar, with IC₅₀ values of 26.5 ± 1.8 and 26.3 ± 1.4 μg/mL, respectively. Meanwhile, compound 7b showed promising cytotoxicity and antiproliferative activity against HepG2 cells, with an IC₅₀ of 52.3 ± 1.1 μg/mL. However, this compound had weak toxicity on the MCF-7 and HCT116 cell lines, with IC₅₀ values

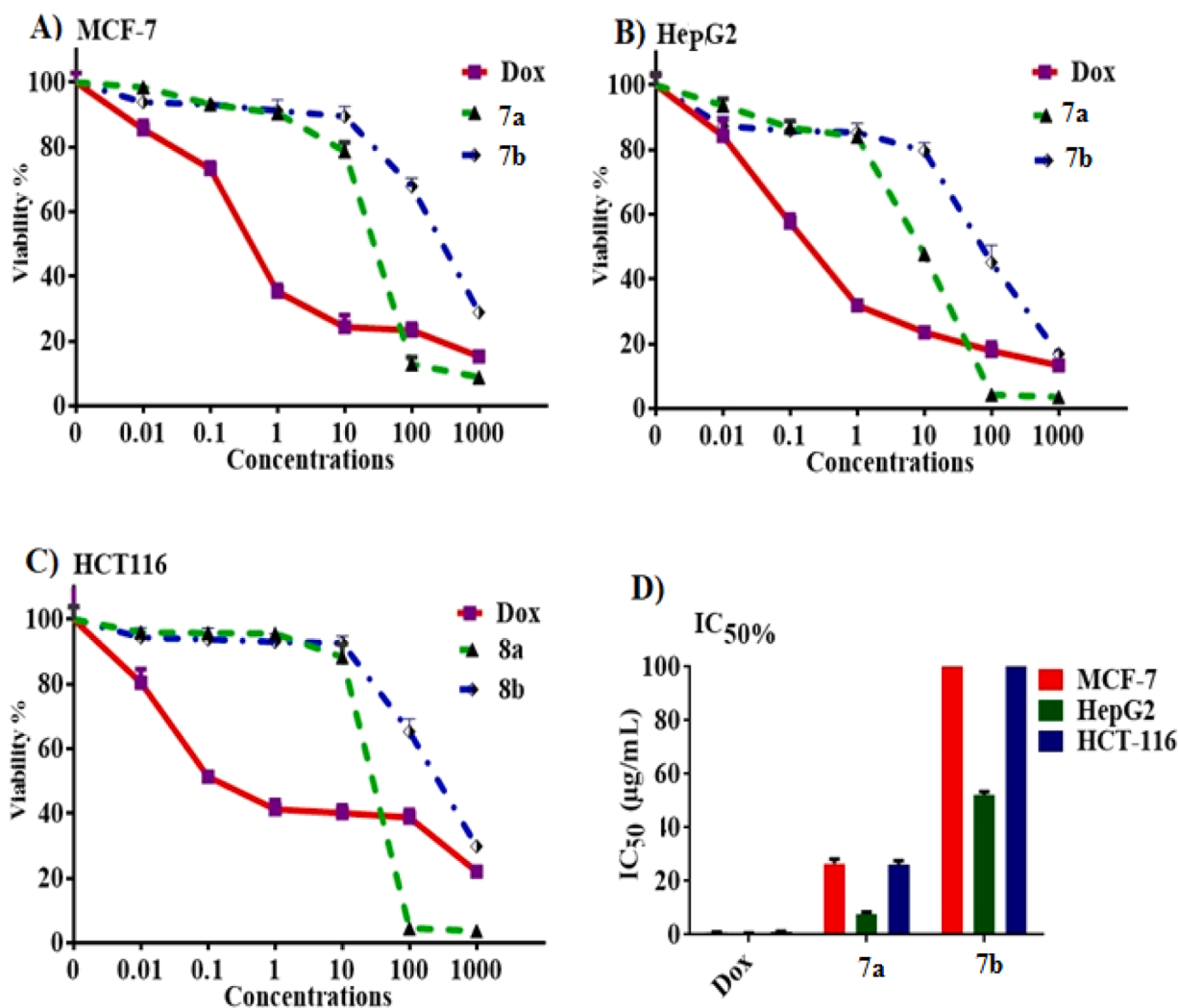


Fig. 9. Dose-Response Curves for MCF-7 (A), HepG2 (B), and HCT116 Cells (C), along with the IC₅₀ values for compounds 7a and 7b (D) after 72 h of treatment with varying concentrations (0–1000 μg/mL). Data are presented as Mean ± SD.

exceeding 100 µg/mL.

4. Conclusions

We succeeded in preparing two novel 1,3-oxathiole derivatives for the first time using a one-pot method. Chemical structures of synthesized compounds have been confirmed using spectral and X-ray analysis, these compounds reveal significant differences in the cytotoxic and anti-proliferative effects on MCF-7, HepG2, and HCT116 cancer cell lines. Compound **7a** stands out as the most effective agent against HepG2 cells and shows notable activity on MCF-7 and HCT116 cells, indicating its potential for further development in cancer treatment. Conversely, compound **7b** demonstrates moderate effectiveness against HepG2 but limited activity on the other cell lines.

The supramolecular structure of **7a** and **7b** were investigated using Hirshfeld analysis. For the former, the H...H (28.3 %), O...H (25.0 %), and N...H (15.9 %) dominate the molecular packing of **7a**. Their percentages in the latter are 38.8, 20.3 and 15.0 %, respectively.

CRediT authorship contribution statement

Abdullatif Bin Muhsinah: Writing – review & editing, Resources, Methodology, Investigation, Funding acquisition. **Nabila A. Kheder**: Writing – review & editing, Writing – original draft, Supervision, Methodology, Formal analysis, Data curation. **Saied M. Soliman**: Writing – review & editing, Writing – original draft, Validation, Software, Investigation, Data curation. **Hazem A. Ghabbour**: Software, Formal analysis, Data curation. **Ismail A. Elhaty**: Writing – review & editing, Writing – original draft, Software, Investigation, Formal analysis, Data curation. **Nehad H. Gad**: Writing – review & editing, Writing – original draft, Validation, Data curation. **Yahia N. Mabkhot**: Writing – review & editing, Writing – original draft, Visualization, Validation, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no competing interests.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.molstruc.2025.141663](https://doi.org/10.1016/j.molstruc.2025.141663).

Data availability

Data will be made available on request.

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