

# X-ray crystal structure of new monohydrate of 2-thioxoimidazolidin-4-one derivative and structural comparison with its analogs; visualizing intermolecular interactions with Hirshfeld surface analysis

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**Abstract** This article describes X-ray crystal structure analysis of *N*-(5-oxo-2-thioxoimidazolidin-1-yl)thiophene-2-carboxamide monohydrate (**1**). The title compound crystallizes in the triclinic space group  $P\bar{1}$  with  $a = 6.5688(6)$ ,  $b = 7.9479(7)$ ,  $c = 10.8830(8)$  Å,  $\alpha = 102.343(7)$ ,  $\beta = 94.837(7)$ ,  $\gamma = 100.309(7)^\circ$ , and  $Z = 2$ . The molecule of **1** consists of a 2-thiohydantoin ring substituted in the N3-position by a thiophene-carboxamide system. The thiophene ring is rotationally disordered; the disorder is of the flip type with an occupancy ratio of 0.742(3):0.258(3) [74:26%]. Molecular and crystal structure of **1** was compared and discussed with amino and hydrate analogs. Moreover, Hirshfeld surface analysis was used for visually analyzing intermolecular interactions in crystal structures.

**Keywords** Hirshfeld surface analysis · Fingerprint plots · 2-Thiohydantoin · 2-thioxoimidazolidin-4-one · Four-coordinated water

## Introduction

2-Thiohydantoin (2-thioxoimidazolidin-4-ones) are 2-thio analogs of hydantoin (imidazolidine-2,4-diones). Hydantoin and thiohydantoin are present in the wide

range of active compounds, such as therapeutics, fungicides, and herbicides [1, 2]. Moreover, thiohydantoin is present in natural products [3].

These compounds are constituted by five-membered heterocyclic systems, carry thioamide and amide groups in molecules, which provide multiple atoms with donor and acceptor features. Because of these unique structural components, hydantoin and 2-thiohydantoin furnish an interesting feature in structural chemistry. Furthermore, thiohydantoin and hydantoin have been used in crystal engineering as spacers in metallo-organic frameworks [4] and represent significant building blocks for combinatorial chemistry libraries [5, 6].

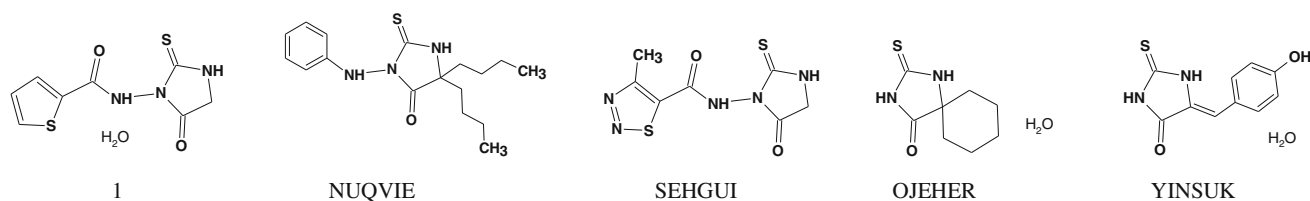
2-Thiohydantoin exists as two polymorphs: I  $P2_1/c$  [7], II  $P\bar{1}$  [8], and its core can easily be modified. We have added thiophene-carboxamide moiety onto the heterocycle core, in N3-position; the crystal structures of biologically active thiophene-carboxamide derivatives have already been reported [9, 10].

Compounds, such as 2-thiohydantoin derivatives, with an amino linkage at the N3-position are relatively uncommon and only two structures have so far been determined and deposited in Cambridge Structural Database (CSD version 5.32 + 3 updates; refcodes: NUQVIE and SEHGUI [11]). The title compound is a member of this class. In addition, it should be noted that only three structures of hydrates of 2-thiohydantoin derivatives (1,3,5-substituted) have so far been deposited in CSD (refcodes: KIDBAA, OJEHER, and YINSUK), Scheme 1.

Considering the above mentioned facts and in continuation of our work of 2-thiohydantoin derivatives [12], we describe herein the X-ray crystal structure analysis of *N*-(5-oxo-2-thioxoimidazolidin-1-yl)thiophene-2-carboxamide monohydrate (**1**) or 3-substituted 2-thiohydantoin

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**Scheme 1** 2-Thiohydantoin derivatives, with the amino linkage at the N3-position

monohydrate. Its molecular and crystal structure was compared with amino and hydrate analogs.

Structure activity relationship (SAR) studies provide medicinal chemists valuable information that is useful for drug design and prediction of drug activity. Since different conformations of the ligand result in different values of the descriptors used in the SAR analysis an important step in SAR is the correct choice of a conformation states. We therefore carried out extensive conformational searches for title thiohydantoin at the molecular mechanics level in order to compare structures obtained from different force fields with the X-ray data.

## Experimental

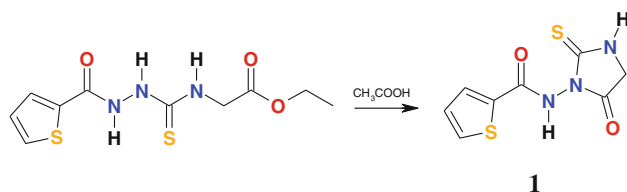
### Synthesis

Title compound was obtained as a product of the dehydrocyclization of 4-ethoxycarbonylmethyl-1-(thiophen-2-yl)-carbonylthiosemicarbazide in glacial acetic acid according to procedure described previously [13], Scheme 2.

### Crystallography

Crystallographic measurements were performed on an Oxford Diffraction Xcalibur CCD diffractometer with the graphite-monochromatized Mo  $K_{\alpha}$  radiation ( $\lambda = 0.71073$  Å) at the temperature of 100(2) K. Data sets were collected using the  $\omega$  scan technique, with an angular scan width of  $0.75^{\circ}$ . Programs CrysAlis CCD and CrysAlis Red [14] were used for data collection, cell refinement, and data reduction. The data were corrected for Lorentz and polarization effects. Furthermore, a multi-scan absorption correction was applied.

Crystal structures were solved by direct methods using SHELXS-97 [15] and full-matrix least-squares refinement on  $F^2$  was performed using SHELXL-97 [16] (both



**Scheme 2** Brief synthesis scheme

operating under WinGX program, version 1.80.05 [17]). Non-H atoms were refined with anisotropic displacement parameters. H atom bonded to N atoms were found from the difference Fourier map, the other H atoms were positioned geometrically. Displacement parameters of all H atoms were fixed ( $1.2 U_{eq}$  of the atom to which they are bonded); their positions were refined using riding model.

The thiophene ring is rotationally disordered by ca  $180^{\circ}$  over two sites with occupancies of 0.742(3) and 0.258(3). Different types of atoms (S and C) occupy positions that are virtually the same, which influence their  $U_{ij}$  values. The alternative positions of S and C atoms were constrained to have the same  $U_{ij}$  components (the restraints used in SHELXL were EADP, ISOR, and DFIX).

Details of the unit cell, data collection and refinement are summarized in Table 1 (see also Supplementary Data).

### Hirshfeld surface

Hirshfeld surface defines the contour of shape occupied by a molecule in the crystal structure and is constructed basing on the electron distribution calculated as the sum of spherical atom electron densities [18]. Some properties can be mapped on Hirshfeld surface: (i)  $d_e$  is the distance from the Hirshfeld surface to the nearest nucleus outside the surface, (ii)  $d_i$  is the corresponding distance to the nearest nucleus inside the surface, and (iii)  $d_{norm}$  is a normalized contact distance and is the sum of these two ( $d_i$  and  $d_e$ ) normalized by the van der Waals radii quantities. Where atoms make intermolecular contacts closer than the sum of their van der Waals radii, these contacts will be highlighted in red on the  $d_{norm}$  surface. Longer contacts are blue, and contacts around the sum of van der Waals radii are white [19].

All Hirshfeld 3D surfaces were generated using the program CrystalExplorer 2.1 [20], only the major component of the disordered thiophene ring was included. Moreover, 2D fingerprint plots (introduced by Spackman and McKinnon [21]) which clearly identify each type of intermolecular interactions were produced. They not only indicate which intermolecular interactions are present, but also the relative area of the surface corresponding to each kind of interaction. The most obvious characteristics of these plots are their pseudo-mirror symmetry about the diagonal where  $d_i = d_e$ . The pseudo-mirror symmetry of the 2D plots is a direct

**Table 1** Crystal data and structure refinement for **1**

	<b>1</b>
Unit-cell formula	C <sub>8</sub> H <sub>7</sub> N <sub>3</sub> O <sub>2</sub> S <sub>2</sub> ·H <sub>2</sub> O
Formula weight	259.3
Temperature (K)	100(2)
Crystal system	Triclinic
Space group	<i>P</i> $\bar{1}$
<i>a</i> (Å)	6.5688(6)
<i>b</i> (Å)	7.9479(7)
<i>c</i> (Å)	10.8830(8)
$\alpha$ (°)	102.343(7)
$\beta$ (°)	94.837(7)
$\gamma$ (°)	100.309(7)
<i>V</i> (Å <sup>3</sup> )	541.63(8)
<i>Z</i>	2
<i>D<sub>x</sub></i> (g cm <sup>-3</sup> )	1.59
$\mu$ (mm <sup>-1</sup> )	0.487
<i>F</i> (000)	268
Crystal size (mm)	0.35 × 0.2 × 0.15
$\theta$ range (°)	2.68–29.91
<i>hkl</i> ranges	−9 ≤ <i>h</i> ≤ 9 −11 ≤ <i>k</i> ≤ 10 0 ≤ <i>l</i> ≤ 14
Refl. collected	4367
Refl. unique, <i>R</i> <sub>int</sub>	2716, 0.0283
Data/parameters	2716/152
Goodness-of-fit	0.923
<i>R</i> <sub>1</sub> , <i>wR</i> <sub>2</sub> [ <i>I</i> > 2 $\sigma$ ( <i>I</i> )]	0.0422, 0.0887
<i>R</i> <sub>1</sub> , <i>wR</i> <sub>2</sub> [all data]	0.0700, 0.0952
max/min $\Delta\rho$ (eÅ <sup>-3</sup> )	0.49/−0.43

consequence of the molecule having both donor and acceptor roles in the same intermolecular interaction.

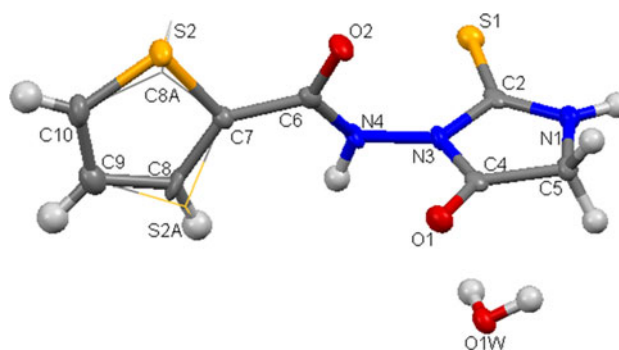
### Computational details

Conformational search engine of the HyperChem program (Hypercube Inc.) was used at the MM level of theory using AMBER99, CHARMM27, MM+, and OPLS force fields as implemented in version 8.0.1 with Random Walk search method and convergence criterion set to 0.1 kcal·mol<sup>-1</sup> Å<sup>-1</sup>. The geometry of the most stable conformers were then reoptimized to gradients of 0.01 kcal·mol<sup>-1</sup> Å<sup>-1</sup>.

## Results and discussion

### Molecular structure

The molecule of **1** consists of a 2-thiohydantoin ring substituted in the N3-position by a thiophene-carboxamide system (Fig. 1).



**Fig. 1** The structure of the title compound with atom labels and 50% probability ellipsoids for non-H atoms. Both orientations of the disordered thiophene ring are shown

The thiophene ring is rotationally disordered (flip disorder) by ca 180° (around the single C6–C7 bond, to which it is attached) over two sites causing the existence of two isomeric molecules (*cis*- and *trans*-O<sub>carboxamide</sub>:S<sub>thiophene</sub>) in the crystal structure. These two orientations of thiophene ring are not equivalent. The site-occupation factors are 0.742(3) and 0.258(3), and the dihedral angle between two occupancy components, major (*cis*) and minor (*trans*), is 4.7(2)°. Disorder of this kind is often observed in structures of simple thiophene derivatives, e.g., in the family of thiophene-carboxamides [22, 23].

Bond lengths in disordered thiophene ring are as follows: (i) S2/S2a–C 1.634(3)–1.709(2), (ii) C–C 1.385(6)/1.521(15), (iii) C=C 1.350(3)–1.443(6) Å, and result from the alternative positions of S and C atoms, which occupy approximately the same position. The carboxamide and thiohydantoin systems have bond lengths within normal ranges [12, 24].

The most significant bond distances and angles are listed in Table 2.

As expected, both thiophene and thiohydantoin moiety are almost planar. The maximum deviations from the least-squares planes are 0.044(2) Å for the C9 atom (*trans* component) from the thiophene ring and 0.032(1) Å for the N3 atom from the thiohydantoin moiety. The two rings moieties are almost perpendicular; they orient at an angle of 87.1(1)° (*cis* component of thiophene ring)/82.5(3)° (*trans* component of thiophene ring) in relation to each other. Carboxamide unit is nearly coplanar with the thiophene ring; the maximum deviation from their mean plane (*cis* component of thiophene ring was taken into consideration) is 0.199(2) Å for the N4 atom.

The molecule of **1** was fitted to other amino-2-thiohydantoin derivatives (refcodes: NUQVIE and SEHGUI [11]). This molecular fit of three molecules through the thiohydantoin system showed that this fragment is very rigid (Fig. 2), while relative differences in orientation of

**Table 2** Selected geometric parameters for **1**

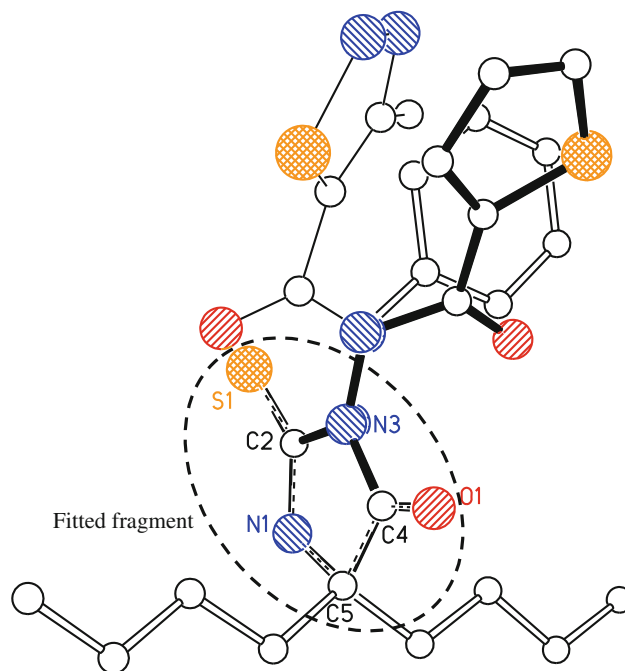
1	
Bond lengths (Å)	
N1–C2	1.331(3)
C2–N3	1.402(3)
N3–C4	1.380(3)
C4–C5	1.503(3)
C5–N1	1.458(3)
C2–S1	1.659(2)
C4–O1	1.215(3)
Bond angles (°)	
O2–C6–N4	121.6(2)
C6–N4–N3	118.1(2)
C7–C6–N4	116.3(2)
N3–C2–S1	125.3(2)
N3–C4–O1	124.0(2)
C2–N3–C4	113.1(2)
Torsion angles (°)	
S2–C7–C6–N4	–164.1(2)
C8–C7–C6–N4	16.7(5)
C7–C6–N4–N3	–161.6(2)
C6–N4–N3–C2	–113.5(2)
C6–N4–N3–C4	66.0(2)
N4–N3–C4–O1	–1.1(3)
N4–N3–C2–S1	2.5(3)
O2–C6–N4–N3	19.8(3)

the carbonyl O atom of carboxamide moiety for **1** and SEHGUI are observed.

### Crystal structure of **1**

In crystal structure of *N*-(5-oxo-2-thioxoimidazolidin-1-yl)thiophene-2-carboxamide hydrate, there are four potential hydrogen-bond acceptors (two O and two S) and two potential hydrogen-bond donors (two –NH). Moreover, water molecule has both double-donor and -acceptor hydrogen-bond functionality. Therefore, in crystal structure of **1**, various kinds of hydrogen bonds are observed: C–H···O, C–H···S, N–H···S, N–H···O, and O–H···O. Selected geometrical parameters and values, characterizing interactions are collected in Table 3.

Molecules of **1** form two types of centrosymmetric dimers, in which molecules are linked by (i) C–H···O and (ii) C–H···S hydrogen bonds. In both cases, dimers are made via thiohydantoin moiety, the C<sub>5</sub>H<sub>2</sub> group acts as the double-donor; C<sub>5</sub>–H<sub>5a</sub>···O1- and C<sub>5</sub>–H<sub>5b</sub>···S1-dimer results in formation of R<sub>2</sub><sup>2</sup>(8) and R<sub>2</sub><sup>2</sup>(10) graph-set motif, respectively [25]. Molecules connected by these dimers form tapes running parallel to the (1 $\bar{1}$ 1) net plane, Fig. 3.



**Fig. 2** Molecular fit of the molecules **1** (solid line), SEHGUI (full line) and NUQVIE (open line). Fitted fragment is labeled, and hydrogen atoms are omitted for clarity

Subsequently, parallel tapes are joined by very weak the C<sub>8</sub><sup>thiophene-cis</sup>–H<sub>8</sub>···O<sub>2</sub><sup>carboxamide</sup> interaction to form the three-dimensional crystal network.

In addition, there is N–H···S interaction in crystal structure—an intramolecular. This N–H···S interaction joins the amino N<sub>4</sub> atom and the thiophene S<sub>2a</sub> atom (*trans* component). It forms a five-membered ring, the motif is S(5), fused with the thiophene system locking the molecular conformation and limiting conformational flexibility, Table 3.

By analyzing the crystal packing of **1**, S···S and S···O contacts were observed; S<sub>2a</sub><sup>thiophene-trans</sup>···S<sub>2a</sub><sup>thiophene-trans</sup> distance is 3.67(1) Å [symmetry code: 1 – x, 1 – y, –z], and S<sub>2a</sub><sup>thiophene-trans</sup>···O<sub>2</sub><sup>carboxamide</sup> distance is 3.24(1) Å [symmetry code: x + 1, y, z]. They are almost equal the sum of the van der Waals radii of two atoms involved in contacts [26].

The N–H···O and O–H···O hydrogen bonds are **1**···water interactions (Table 3; Fig. 4). Hydrogen-bonding configuration observed for water molecule is tetrahedral (double-donor and -acceptor). Water molecule acts as a double proton acceptor for –NH groups (N<sub>1</sub><sup>thiohydantoin</sup>–H<sub>1n</sub>···O<sub>1w</sub> and N<sub>4</sub><sup>carboxamide</sup>–H<sub>4n</sub>···O<sub>1w</sub>) and a double proton donor to O=C groups (O<sub>1w</sub>–H<sub>1w1</sub>···O<sub>1</sub><sup>thiohydantoin</sup> and O<sub>1w</sub>–H<sub>2w1</sub>···O<sub>2</sub><sup>carboxamide</sup>).

In the hydrogen bonds hierarchy, the N–H···O and O–H···O are stronger than the C–H···O, C–H···S, and

**Table 3** Geometry of hydrogen bonds for **1**

D–H...A	D–H (Å)	H...A (Å)	D...A (Å)	DHA (°)
C5–H5a...O1 <sup>(i)</sup>	0.97	2.60	3.352(3)	134
C5–H5b...S1 <sup>(ii)</sup>	0.97	2.83	3.525(2)	129
C8–H8...O2 <sup>(iii)</sup>	0.93	2.72	3.601(5)	157
N4–H4n...S2a	0.88	2.65	3.011(4)	106
N1–H1n...O1w <sup>(iv)</sup>	0.91	1.93	2.833(2)	170
N4–H4n...O1w <sup>(v)</sup>	0.88	2.00	2.825(2)	156
O1w–H1w1...O1	0.81	1.93	2.737(2)	177
O1w–H2w1...O2 <sup>(i)</sup>	0.84	1.95	2.754(2)	160

Symmetry codes (i)  $-x, 1 - y, 1 - z$ ; (ii)  $1 - x, 2 - y, 1 - z$ ; (iii)  $x + 1, y, z$ ; (iv)  $x, y + 1, z$ ; (v)  $1 - x, 1 - y, 1 - z$

N–H...S ones, so it seems that four-coordinated water is the major crystal structure-determining component.

There are no water...water,  $\pi\cdots\pi$ , and C–H... $\pi$  interactions within the crystal structure.

Comparison of crystal structure of **1** with amino and hydrate analogs

A search of the CSD [11] revealed that only six structures (with coordinates available) relevant for comparison have been deposited: (i) two polymorphs (THHYDT and THHYDT02), (ii) two derivatives with an amino linkage at the N3-position (NUQVIE and SEHGUI), and (iii) two structures of hydrates of 2-thiohydantoin derivatives/1,3,5-substituted (OJEHER and YINSUK). Only one of these compounds has very similar substitution moiety that we have used in this study—SEHGUI, Scheme 1.

The hydrogen-bonding patterns were examined to show similarities and differences in arrangement of crystal nets, particularly participation of thiohydantoin moiety in intermolecular interactions.

In crystal structure of the polymorph I of thiohydantoin, THHYDT, two N–H...O hydrogen bonds have been found. One of these, related by the centre of symmetry, forms dimer, and another one joins dimers to form sheets. In turn, structure of the polymorph II, THHYDT02, is stabilized by two kinds of cyclic dimers, the adjacent molecules are connected through N–H...O and N–H...S hydrogen bonds, respectively.

In contrast to **1**, thiohydantoin...thiohydantoin dimers are not observed in NUQVIE and SEHGUI (amino N3-derivatives). Examination of the hydrogen bonding patterns for NUQVIE shows formation N<sub>thiohydantoin</sub>–H...O<sub>thiohydantoin</sub>

chain and N<sub>amino</sub>–H...S<sub>thiohydantoin</sub> dimer, while in SEHGUI centrosymmetric N<sub>thiohydantoin</sub>–H...O<sub>carboxamide</sub> dimer is produced, further dimers are linked by N<sub>carboxamide</sub>–H...N<sub>thiadiazole</sub> hydrogen bonds.

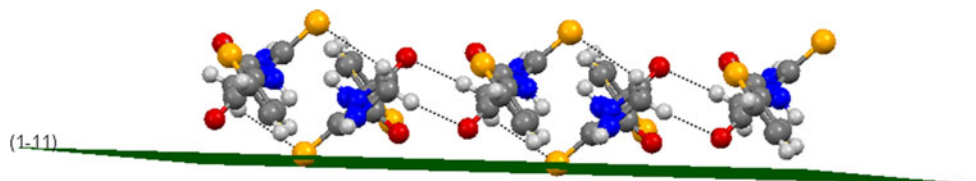
The next step is comparison of hydrates of 2-thiohydantoin derivatives, precisely hydrates which were defined to search as 1,3,5-substituted.

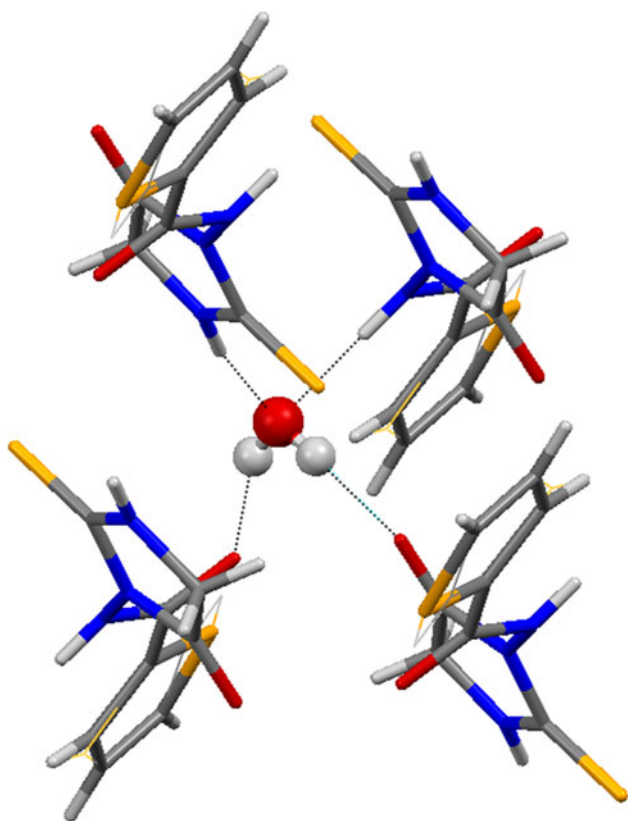
OJEHER—monohydrate—has the same potential for hydrogen-bond formation as THHYDT and/or THHYDT02, excluding water molecule, but has steric bulk in the form of cyclohexane ring—spiro ring. Observed hydrogen bonds, in OJEHER, suggest that the water molecule participates as a proton donor forming intermolecular O–H...O<sub>thiohydantoin</sub> hydrogen bond and as a proton acceptor forming N<sub>thiohydantoin</sub>–H...O hydrogen bond. Thiohydantoin units are interconnected by the N–H...S hydrogen bonds in zig-zag chain.

Analysis of hydrogen bonds in YINSUK (not described previously by the Authors) reveals that all potential donor/acceptor groups are involved in intermolecular interactions. And so, thiohydantoin moieties are linked via two types of dimers, they are formed by N–H...O and N–H...S hydrogen bonds, respectively, and what is more molecules are also joined by cyclic O<sub>hydroxyl</sub>–H...O<sub>hydroxyl</sub> dimer. Water molecules interact together to form O–H...O dimer, besides they are entangled, as donors in O–H...O<sub>hydroxyl</sub> hydrogen bonds.

Summarizing the most important information, should be noted:

- C–H...O- and C–H...S-thiohydantoin-dimers are produced only in **1**.
- N–H...O- and/or N–H...S-thiohydantoin-dimers are formed in THHYDT, THHYDT02, and YINSUK.

**Fig. 3** Tape formation by C–H...O and C–H...S dimers



**Fig. 4** Tetrahedral hydrogen-bonding configuration observed for water molecule

- (iii) The presence of amino/carboxamide group determined arrangement of intermolecular interactions. In crystal structure of two amino-2-thiohydantoin

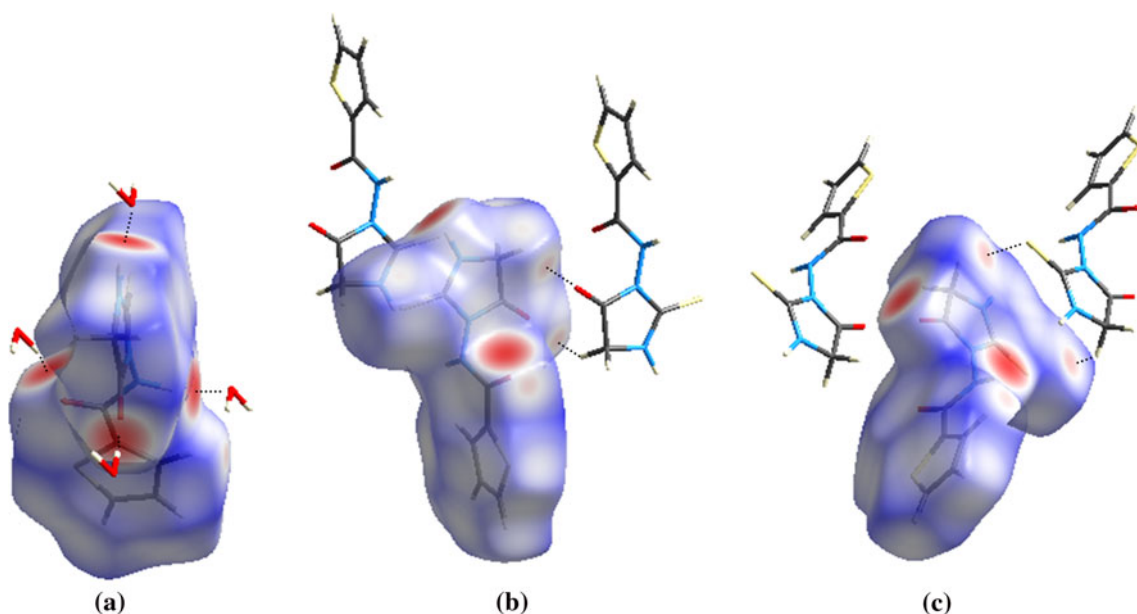
derivatives (NUQVIE and SEHGUI) none thiohydantoin...thiohydantoin dimers are observed.

- (iv) N–H...O- and N–H...S-thiohydantoin-chain manner is observed in NUQVIE and OJEHER, respectively.
- (v) Because water molecule displays a wide range of orientational flexibility in crystals of thiohydantoin derivatives hydrates, it is the major crystal structure-determining component forming strong hydrogen bonds, with itself and thiohydantoin derivatives. This results in the creation of the three-dimensional crystal network.

#### Hirshfeld surface analysis

Hirshfeld surfaces of molecule in crystal **1** were generated; only major (*cis*) component of disordered thiophene ring was used. Surfaces mapped with the  $d_{\text{norm}}$  are shown in Fig. 5. The dominant interactions can be seen in the Hirshfeld surface plots as the brightest red areas, highlighting both acceptors and donors. The most intense spots occur above O=C and N–H groups, Fig. 5a. They correspond to strong N–H...O and O–H...O hydrogen bonds, which are **1**...water interactions (see Table 3; Fig. 4) and show their significant participation in the crystal structure. Decreased but significant spots are also observed over thiohydantoin atoms: S, O, and H (CH<sub>2</sub>—on opposite sides) as would be expected for C–H...O and C–H...S dimers formation, Figs. 3 and 5b, c.

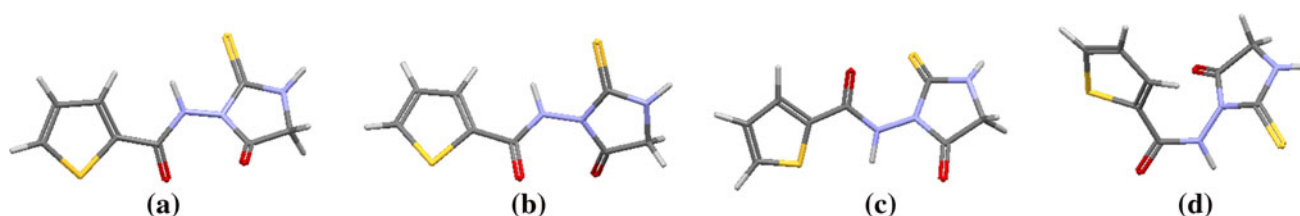
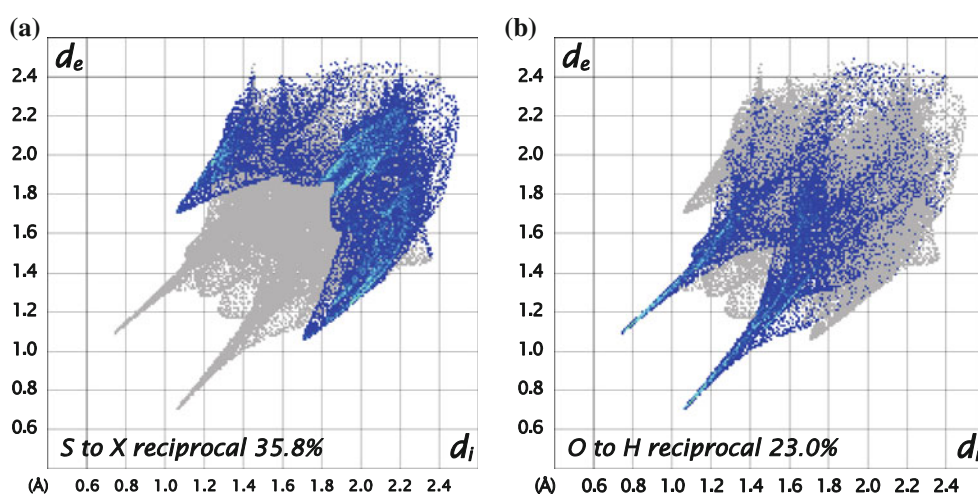
Fingerprint plots were produced to show the relative contribution of different intermolecular interactions to the



**Fig. 5** The Hirshfeld surfaces mapped with  $d_{\text{norm}}$  for **1** molecule. The surfaces are partially transparent for clarity; only the major (*cis*) component of the disordered thiophene ring was used. (a) The most

intense *red spots* correspond to strong **1**...water interactions. Decreased *red spots* correspond to (b) C–H...O and (c) C–H...S dimers formation (Color figure online)

**Fig. 6** Decomposed fingerprint plots for **1** showing contacts between (a) S...X/X...S (where X = H, C, S, O, N) and (b) O...H/H...O



**Fig. 7** Most stable conformations obtained from (a) AMBER, (b) CHARMM, (c) MM+, and (d) OPLS force fields

Hirshfeld surface, Fig. 6. From this simple analysis, it appears that the crystal structure is determined by S...X/X...S [35.8%, where X = H (23.6%,  $(d_e + d_i)_{\min} \approx 2.8$  Å); C (6.5%); S (2.4%); O (2.8%); N (0.5%)] and O...H/H...O interactions (23.0%,  $(d_e + d_i)_{\min} \approx 1.8$  Å). It should be noted that the structure is also dominated by H...H contacts (22.0%).

The inspection of contacts between other atom types pointed out that there are no significant  $\pi \cdots \pi$  interactions within the crystal **1** (C...C contacts make 1.0% of the surface area).

### Computational study

We used the conformational search engine implemented in HyperChem with four force fields used: AMBER99, CHARMM27, MM+, and OPLS. The most stable structures of **1** obtained from each force field are presented in

Fig. 7. Table 4 compares their main geometric differences, namely torsion angles of the conformers of the lowest energy (the atom numbering scheme is given in Fig. 1) and the root-mean-squared (RMS) error compared to the crystal structure obtained experimentally. As can be seen, the best fit to the crystal structure is obtained when OPLS force field is employed. Using this force field we have compared stabilities of *cis* and *trans* conformers. The obtained difference of only 0.15 kcal·mol<sup>-1</sup> indicates that both conformers might be present in crystal structure.

### Conclusions

The X-ray crystal structure analysis of *N*-(5-oxo-2-thioxoimidazolidin-1-yl)thiophene-2-carboxamide monohydrate (**1**) was described and discussed with amino and hydrate analogs.

**Table 4** Torsion angles of the conformers of **1** with the lowest energies

	AMBER99	CHARMM27	MM+	OPLS
RMS error (Å)	2.73	2.74	2.81	2.61
Torsion angles (°)				
S2–C7–C6–N4	175.9	–168.2	–2.1	141.0
C8–C7–C6–N4	–4.6	12.7	177.9	–41.5
C7–C6–N4–N3	–177.5	176.6	–173.4	–7.4
C6–N4–N3–C2	152.4	–149.8	–32.1	131.8
C6–N4–N3–C4	–46.1	42.4	143.8	–61.6

The thiophene ring is rotationally (flip) disordered over two sites causing the existence of two isomeric molecules (*cis*- and *trans*-O<sub>carboxamide</sub>:S<sub>thiophene</sub>) in the crystal structure. These two orientations of thiophene ring are not equivalent; the site-occupation factors are 0.742(3) and 0.258(3).

In crystal structure of **1**, C–H...O/S, N–H...S, N–H...O, and O–H...O hydrogen bonds are observed, which are **1**...**1**, **1**...**1**, **1**...H<sub>2</sub>O, and H<sub>2</sub>O...**1**, respectively. By C–H...O and C–H...S intermolecular interactions, molecules of **1** form two types of centrosymmetric dimers with graph-set notation of R<sub>2</sub><sup>2</sup>(8) and R<sub>2</sub><sup>2</sup>(10), respectively. In both cases, dimers are made via thiohydantoin moiety, and this is the first example of C–H...O- and C–H...S-thiohydantoin dimers observed in the solid state. Fingerprint plots (in the wake of Hirshfeld surface analysis) confirmed that crystal structure is determined by S...X/X...S and O...H/H...O interactions, and  $\pi$ ... $\pi$  interactions are not observed within the crystal.

Search of the CSD [11] revealed that only six structures relevant for comparison have been deposited, and only one of these compounds has very similar substitution moiety to that we have used in this study—SEHGUI (amino N3-derivatives). In contrast to **1**, thiohydantoin...thiohydantoin dimers are not observed in SEHGUI. Examination of the hydrogen-bonding patterns for SEHGUI shows formation of centrosymmetric N<sub>thiohydantoin</sub>–H...O<sub>carboxamide</sub> dimer.

In this study, the data from X-ray crystal structure analysis of **1** have been compared with the results from AMBER, CHARMM, MM+, and OPLS force fields implemented in HyperChem. The best fit to the crystal structure was obtained when OPLS force field was employed. Using this force field stabilities of *cis* and *trans* conformers were compared. The obtained difference of only 0.15 kcal·mol<sup>−1</sup> indicated that both conformers might be present in crystal structure.

## Supplementary data

CCDC 848572 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via [http://www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif), by e-mailing [data\\_request@ccdc.cam.ac.uk](mailto: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.

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