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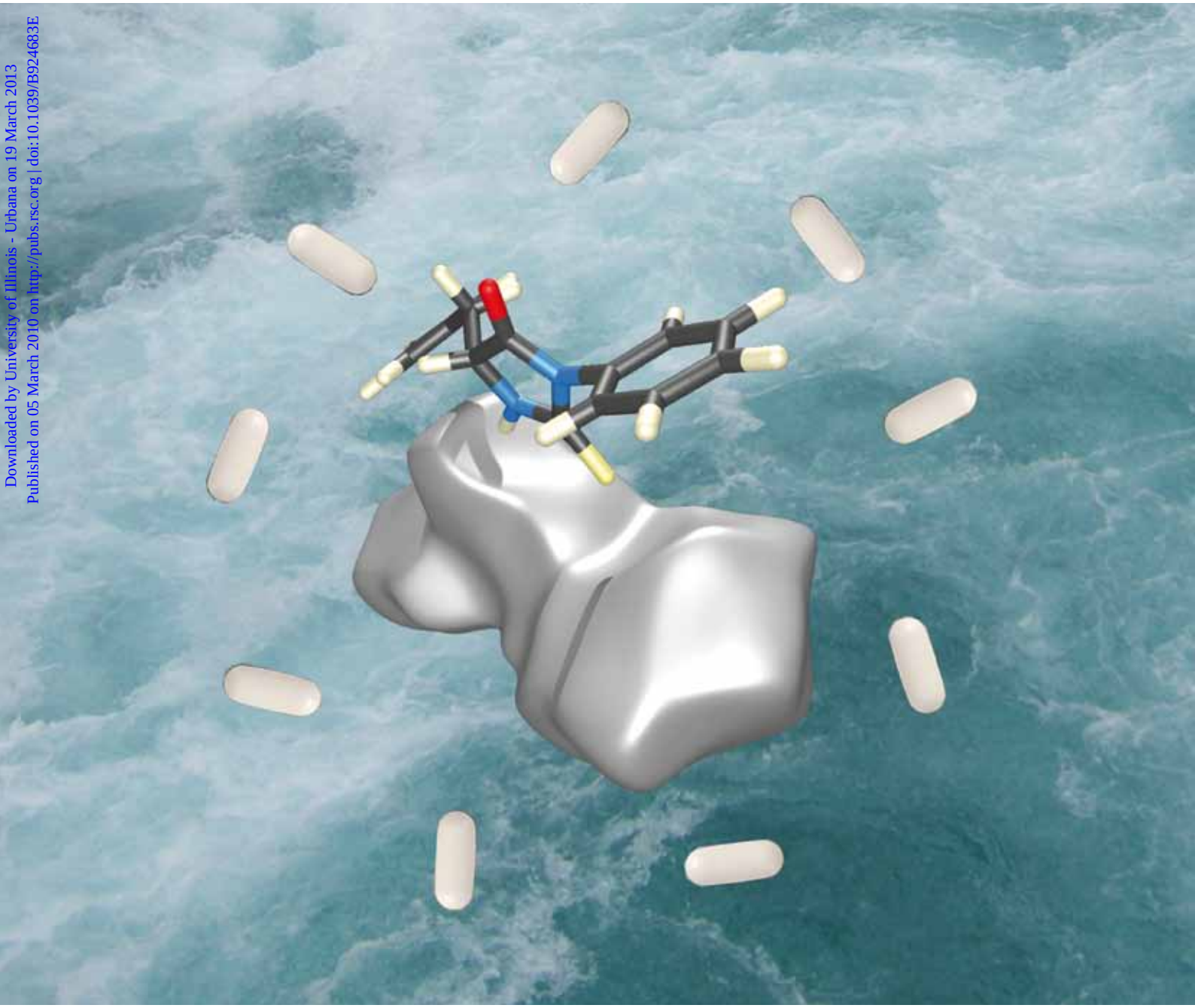

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Hydrogen bonded dimers *vs.* one-dimensional chains in 2-thiooxoimidazolidin-4-one (thiohydantoin) drug derivatives†

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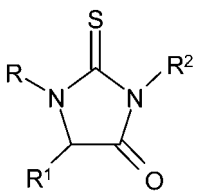
Hydantoins have been known as medicinally active compounds since the 1940s and thiohydantoin derivatives are currently undergoing clinical trials as potent androgen receptor antagonist drugs. Control of solid state properties including the formation of drug polymorphs is important to the pharmaceutical industry, and frequently results from different H-bonded motifs. N–H thiohydantoins show formation of H-bonded arrays in the solid state. Two novel and five known thiohydantoin derivatives were synthesised *via* reaction of alkyl isothiocyanates with amino acid methyl esters. X-Ray crystallographic data were obtained for all seven compounds showing that four of the structures contain hydrogen bonded dimeric units linked *via* N–H···S interactions and three of the structures have N–H···O linked H-bonded chains.

Introduction

The hydantoin or imidazolidine-2,4-dione heterocycle is present in a wide range of biologically active compounds including therapeutic drugs for the treatment of seizures and antitumour compounds.[1–4] Thiohydantoins, where one of the oxygens is replaced by a sulfur, have also been used as anti-convulsant agents[5] and are present in fungicides, herbicides and natural products.[6,7] Both of these heterocycles are commonly used as templates in combinatorial chemistry libraries.[8,9] However, the overriding current medicinal interest comes from the recent application of thiohydantoins as androgen receptor antagonists which are now in clinical trials for the treatment of hormone independent prostate cancers.[10–13] This work links with our ongoing efforts to investigate new antagonists of cellular receptors.[14–17]



Thiohydantoin

We have investigated the potential for thiohydantoin compounds to form H-bonded arrays in the solid state, which is relevant to crystalline drug morphology.[18,19] A fine energetic balance between different H-bonded arrangements can result in the isolation of different polymorphs, which can either be desirable or problematic.[19–21] In addition there is considerable general interest in the controlled formation of hydrogen bonded arrays in the solid state, particularly in relation to the competition of sulfur and oxygen as H-bond acceptors.[22]

The thiohydantoin backbone can easily be modified in an attempt to probe the factors that induce the preference for one structural type over another. Groups can be added to provide steric bulk or offer the potential for further intermolecular interactions such as π···π stacking. We have incorporated benzyl, phenyl, propyl and allyl substituents onto the heterocycle backbone in the R^1 and R^2 positions. We then crystallised the compounds to determine whether any preference is shown for the weaker N–H···S bond over N–H···O bonds and how this relates to structural type.

Previous studies of 5-substituted hydantoins and thiazolines have used these units to assemble H-bonded arrays. For example, monosubstituted hydantoins or thiazolines which can potentially form triply hydrogen bonded dimers have been studied.[23] Thiohydantoins have also been used in crystal engineering as spacers in metallo-organic frameworks.[24] In these polymeric metal complexes the thiohydantoin amine group at the 3-position was deprotonated and coordinated to caesium along with bridging O and S donors. In our work we have included a substituent in the 3-position which blocks formation of N–H···O dimeric interactions. On ruling out the most energetically favourable interaction the remaining choice is formation of either an eight membered ring dimer with N–H···S=C H-bonds or a 1D H-bonded chain with N–H···O=C interactions. This should offer a finer energetic balance between H-bonded structures and increased potential for drug polymorph formation. In this study, our aim was to gain insight into interactions that may control the topology.

Results and discussion

A series of compounds was synthesised which are substituted in the 3- and 5-positions, see Fig. 1, with groups of different rigidity and varying potential to form π interactions. The five membered thiohydantoin ring can be formed by cyclisation with an

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† Electronic supplementary information (ESI) available: CIF and platon.lst (CALC ALL) files are included for all X-ray structures. Hirshfeld surfaces and fingerprint plots calculated for the X-ray structures found in the CSD. CCDC reference numbers 756015–756021. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b924683e

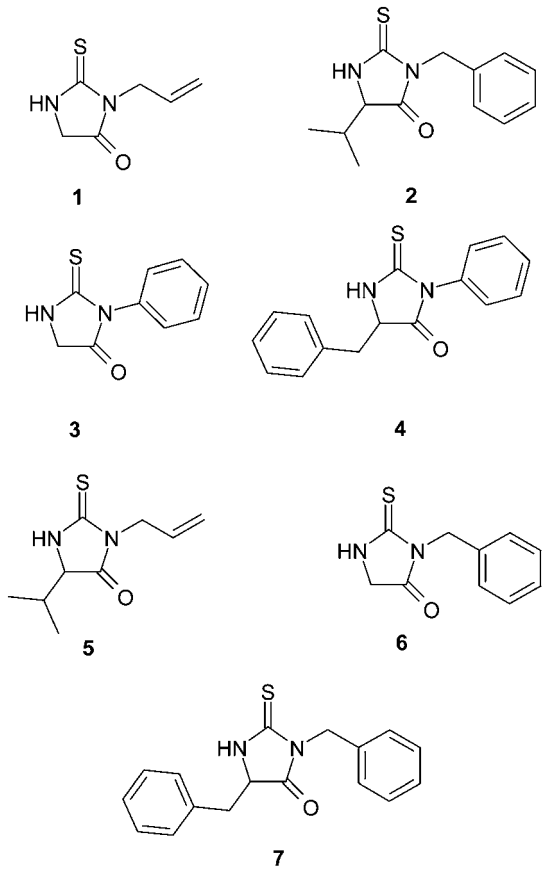


Fig. 1 Thiohydantoin derivatives synthesised and structurally characterised in this study.

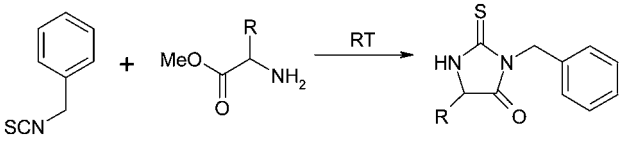
isothiocyanate derivative. Of the seven compounds selected for this study, two of the thioimidazolidones have not been reported previously but none had been crystallographically characterised.

These compounds have the potential for intermolecular H-bonding interactions *via* an N–H group with either or both of the O and S atoms. 5-(2-Pyridylmethylene)-2-thiohydantoin has previously been used in crystal engineering as a component potentially offering an ADA hydrogen bonding arrangement.[23] The structure showed formation of a 2D 'tape' network composed of hydrogen bonded dimers. There were additional interactions with intramolecular H-bonding to the pyridyl N and a $\pi\cdots\pi$ interaction with the pyridyl ring.

Dimers with N–H···S H-bonds have also previously been observed in the solid state for related compounds.[25] Thermodynamically the stronger N–H···O interaction should be preferred over the N–H···S interaction. However, in the solid state structure other factors such as accommodation of bulky groups and π interactions can affect this energetic balance. Combinations of four substituents (allyl, benzyl, phenyl and isopropyl) were used with the N–H retained at the 1-position.

Synthesis

The imidazolidine-2,4-dione core and its mixed thio–oxo equivalent are common five membered rings that can easily be synthesised. There are a number of routes to produce such



Scheme 1 Synthesis of a thiohydantoin derivative from an isothiocyanate compound.

compounds including the Bucherer–Bergs route and a highly efficient microwave assisted version of the Biltz synthesis.[26–28] The thiohydantoin core can also easily be functionalised in the 5-position after cyclisation. However, our selected route was to exploit the reaction of methyl ester derivatives of amino acids with alkyl isothiocyanates to give the cyclic derivatives in high yields. All compounds synthesised from chiral amino acids produced racemic mixtures of products.

Methyl esters of amino acids were reacted with isothiocyanates, see Scheme 1, to cyclise, forming the five membered rings in an analogous fashion to the common reaction of isocyanates or phosgene to form hydantoin heterocycles. Of the seven compounds produced (**1–7**), see Fig. 1, the *N*-benzyl derivatives **2** and **7** have not previously been synthesised. The remaining compounds (**1** and **3–6**) have previously been made using a variety of synthetic procedures.

The most common route to produce these compounds involves a similar cyclisation using the amino acid rather than the methyl ester. This method has been used to synthesise **1**, **3**, **4** and **5**.[29,30] Compound **4** has also been made by reaction of the amino acid with a dithiocarbamate,[31] and as a single diastereoisomer from Fmoc protected phenylalanine using a microwave procedure.[32,33] Compound **6** has been synthesised by a number of procedures[34,35] including a stepwise process involving isolation and cyclisation of a thiourea derivative.[36] Yields for these processes are variable but, in comparison to the direct reactions of the amino acids with isothiocyanates, our use of commercially available methyl esters results in higher yields (>90%) in all cases. The compounds were characterised by ^{1}H and ^{13}C NMR and all crystals were grown by the same method. Slow evaporation of a mixture of hexane and ethyl acetate gave diffraction quality crystals for structure determination. Single crystal X-ray diffraction studies unambiguously determined the structures of these compounds.

Structural studies

The crystallographic details for the seven structures are given in Tables 1 and 2, and selected bond lengths and angles are listed in Table 3. Two structural types were identified: H-bonded dimers and one-dimensional H-bonded chains. The dimeric structures involve the neighbouring N–H and sulfur group acting as donor and acceptor respectively to form intermolecular interactions. In all of these molecules the related O dimer cannot form as the neighbouring N1 position is substituted. Thus the alternative possibility is the formation of a chain type structure where the N–H···O interaction is present.

In these molecules where the acceptor : donor ratio is 2 : 1 a direct choice is offered between a sulfur and an oxygen

Table 1 Crystal data for the single crystal X-ray structures of **1** to **4**

	1	**2**	**3**	**4**
Formula	$C_6H_6N_2OS$	$C_{13}H_{16}N_2OS$	$C_9H_8N_2OS$	$C_{16}H_{12}N_2OS$
M_r	154.19	248.34	192.23	282.35
Crystal system	Monoclinic	Monoclinic	Monoclinic	Monoclinic
Space group	$P2_1/c$	$P2_1/c$	$P2_1/c$	$C2/c$
a/Å	9.3380(13)	5.0267(9)	12.377(4)	28.380(6)
b/Å	6.3930(5)	11.2601(12)	5.6900(12)	5.0073(6)
c/Å	13.1620(18)	22.199(4)	12.515(4)	20.811(4)
β/°	108.753(11)	94.545(14)	91.27(3)	106.952(16)
Volume/Å^3	774.03(16)	1252.5(3)	881.1(5)	2828.9(9)
Z	4	4	4	8
Density (calc.)/Mg m^{-3}	1.376	1.317	1.449	1.326
μMoKα/mm^{-1}	0.364	0.244	0.323	0.225
T/K	150	150	400	150
θ range/°	3.27 to 34.74	2.58 to 34.76	3.62 to 34.75	2.87 to 30.00
Measured reflections	7718	27 326	8162	11 195
Unique reflections [R_{int}]	3169 [0.0606]	5327 [0.1370]	3714 [0.0992]	4096 [0.0839]
Completeness (θ)/°	98.5% (34.74)	98.8% (34.76)	97.9% (34.75)	99.6% (30.0)
Goodness-of-fit on F^2	0.956	0.853	1.176	1.034
$R1$, w$R2$ ($I > 2\sigma(I)$)	0.0382, 0.938	0.0493, 0.1021	0.1199, 0.3058	0.1072, 0.3080
$R1$, w$R2$ (all data)	0.0666, 0.1024	0.1816, 0.1410	0.2063, 0.4126	0.1901, 0.3591
Extinction coefficient	0.002(3)	0.024(3)	0.043(6)	0.006(2)
Largest diff. peak and hole/e Å^{-3}	0.410 and −0.396	0.495 and −0.833	0.763 and −0.820	1.370 and −0.644

acceptor. The steric bulk appears to prohibit formation of multiple interactions.

H-bonded dimers

Four of the structures determined, **1–4**, contain the H-bonded dimer motif held together by two N–H···S bonds with the donor to acceptor distances in the range from 3.32 to 3.40 Å and the D–H···A angle varying between 158.6 to 177.4°, see Fig. 2 and Table 4. Crystal packing diagrams are shown in Fig. 2, see **1**(c), **2**(c), **3**(c) and **4**(c). The structural parameters are further discussed later in comparison with the related compounds deposited in the Cambridge Structural Database.

Compound **1** is not substituted in the C5 (R^1) position and has an allyl substituent at the N1 (R^2) position. There are two intermolecular close approaches from C–H groups to the carbonyl oxygen with the most significant from the H-atom on one of the allyl carbons (C5–H5···O1 3.315(2) Å, 145°). This may have some impact on the orientation of the dimeric units in the structure.

The remaining three structures all contain phenyl or benzyl substituents, offering the potential for π···π type interactions. However, the dimeric units are not aligned to optimise stacking interactions between the benzene rings but CH···π interactions are observed. As there may be a fine energetic balance differentiating the type of H-bonded network, these weak interactions could contribute to the structural type. Steric interactions in packing the molecules together are also likely to be important. The key factor remains the formation of strong interactions in the N–H···S dimeric unit. Structure **3** is most similar to **1** in terms

Table 2 Crystal data for the single crystal X-ray structures of **5** to **7**

	5	**6**	**7**
Formula	$C_9H_{14}N_2OS$	$C_{18}H_{10}N_2OS$	$C_{17}H_{16}N_2OS$
M_r	198.28	206.26	296.38
Crystal system	Monoclinic	Monoclinic	Monoclinic
Space group	$P2_1/c$	$C2/c$	$P2_1/n$
a/Å	9.5863(11)	21.9470(19)	9.0344(11)
b/Å	9.2632(7)	8.2582(8)	17.331(13)
c/Å	11.9253(12)	11.4242(9)	9.5981(11)
β/°	95.960(9)	115.115(6)	101.028(10)
Volume/Å^3	1053.24(18)	1936.1(3)	1475.1(3)
Z	4	4	4
Density (calc.)/Mg m^{-3}	1.250	1.415	1.335
μMoKα/mm^{-1}	0.272	0.300	0.219
T/K	150	150	150
θ range/°	2.79 to 34.77	2.60 to 34.78	2.58 to 34.78
Measured reflections	12 811	10 104	20 656
Unique reflections [R_{int}]	4526 [0.0356]	4002 [0.0406]	6254 [0.1200]
Completeness (θ)/°	99.0% (34.77)	95.6% (34.78)	97.9% (34.78)
Goodness-of-fit on F^2	1.130	1.377	1.042
$R1$, w$R2$ ($I > 2\sigma(I)$)	0.0501, 01372	0.0411, 0.1249	0.0736, 0.1932
$R1$, w$R2$ (all data)	0.0675, 0.1486	0.0493, 0.1298	0.1188, 0.2374
Extinction coefficient	0.043(7)	0.0020(2)	0.097(11)
Largest diff. peak and hole/e Å^{-3}	0.585 and −0.448	0.452 and −0.387	0.744 and −0.814

Table 3 Selected bond lengths (Å) for structures **1** to **7**

	1	2	3	4	5	6	7
C(1)–S(1)	1.6700(11)	1.665(2)	1.666(5)	1.630(4)	1.6568(11)	1.6557(10)	1.652(2)
C(2)–O(1)	1.2079(15)	1.204(3)	1.214(5)	1.237(6)	1.2174(14)	1.2190(13)	1.213(2)
C(1)–N(2)	1.3319(15)	1.330(3)	1.331(5)	1.340(5)	1.3329(15)	1.3319(13)	1.335(2)
C(1)–N(1)	1.3827(16)	1.380(3)	1.387(5)	1.383(5)	1.3963(14)	1.3959(12)	1.397(2)
C(2)–N(1)	1.3875(14)	1.383(3)	1.391(5)	1.383(7)	1.3700(15)	1.3716(13)	1.372(2)
C(2)–C(3)	1.5082(18)	1.513(3)	1.497(6)	1.511(7)	1.5164(17)	1.5114(15)	1.515(2)
C(3)–N(2)	1.4535(16)	1.453(3)	1.447(6)	1.476(6)	1.4549(15)	1.4488(14)	1.450(2)

of substitution pattern with close approaches from two of the phenyl protons to carbonyl oxygens in neighbouring molecules appearing to influence the twist of the phenyl ring (C6–H6···O1 and C9–H9···O 3.246(5) Å/166° and 3.388(5) Å/166° respectively). These interactions link dimeric units throughout the structure. There is also a weak intermolecular CH···π interaction from H3A on C3.

Compounds **2** and **4** have significantly greater steric bulk as they are substituted in both the 3- and 5-positions. Compound **2** does not have any π···π interactions between the flexible benzyl groups. There are only very weak intermolecular interactions in addition to the dimeric H-bonding with a CH···O distance/angle of 3.366(3) Å, 140° for the C12 methyl group (H12C). Compound **4** again has no π···π interactions between benzene rings despite the presence of both phenyl and benzyl substituents. The most significant additional interactions are probably the intermolecular ones between the benzene ring CH and neighbouring oxygen or sulfur atoms.

One-dimensional H-bonded chains

The other structural type observed in this work shows formation of 1D chains in the solid state, see Fig. 3. In this case the hydrogen bond is formed between the ring N–H and the carbonyl oxygen of a neighbouring thiohydantoin molecule. Three structures of this type were characterised (compounds **5–7**), see Table 3 for bond lengths and angles, and Table 4 for H-bonding parameters.

The 3-allyl-5-propyl thiohydantoin **5** forms one-dimensional hydrogen bonded chains *via* a single H-bond between the carbonyl oxygen and the amine ring N1 position. The steric bulk of the propyl group appears to inhibit formation of the eight membered ring NH···S H-bonded dimer. There do not appear to be any other significant inter- or intramolecular interactions.

The inclusion of a benzyl substituent in the 3-position of **6** may disfavour formation of an optimised dimeric species to preferentially give one-dimensional chains with N–H···O H-bonds. Crystal packing may also affect the structural preference in this case. The benzyl group is twisted to be almost perpendicular to the thiohydantoin ring plane (N1–C4–C5–C10 torsion angle = 106.52(11)°). The packing places the benzylic groups together in a layer on either side of the H-bonded chains. No π···π interactions or other significant intermolecular interactions are observed but the hydrophobic benzyl groups are grouped together.

In **7**, both phenyl rings are twisted to accommodate the chain structure formed by the hydrogen bonding. However, in contrast to the structures observed for **5** and **6**, the orientation of the hydantoin ring in the hydrogen bonded chain alternates along the chain. There are two intermolecular CH···π interactions from a C–H on each of the phenyl rings.

Hirshfeld surfaces

Another method for the analysis of intermolecular contacts that offers a whole-of-the-molecule approach is the use of Hirshfeld surfaces.[37,38] This method was used to generate pictures of the surfaces in which the significant intermolecular contacts are highlighted, see Fig. 4A. The dominant interactions between N–H and S to form the dimeric species can be seen in the Hirshfeld surface plots as the brightest red areas for **1–4**. Fingerprint plots were produced to show the intermolecular surface contact distances with the regions highlighted for the O···H and S···H interactions, Fig. 4B and 4C respectively. The plots are reciprocal and so both donor and acceptor interactions are included. Similar patterns are observed for all four compounds with the importance of CH···O intermolecular contacts particularly notable for compounds **1** and **3** matching the previous analysis. This can be observed on both the Hirshfeld surfaces and the fingerprint plots.

The Hirshfeld surfaces of compounds **5–7** show the most significant interactions (red) on opposite sides of the molecule as would be expected for chain formation and the fingerprint plots show shorter O···H interactions and longer S···H distances as expected.

The relative contribution of different interactions to the Hirshfeld surface was calculated. Due to varying number and types of carbon containing substituents they are not directly comparable across the series but offer some insight into the effects of adding different substituents onto the thiohydantoin backbone. No significant π···π interactions are observed with C···C close contacts making up less than 1.1% of the surface area for each of **1–7**. C···H intermolecular contacts vary significantly with the different substituents present. Where an aryl substituent is present (in compounds **2**, **3**, **4**, **6**, and **7**) the relative contribution to the surface area for C···H intermolecular contacts is in the range of 16.0 to 22.8%.

Comparison with known thiohydantoin X-ray structures

A search of the Cambridge Structural Database[39] (CSD) revealed that *ca.* 60 structures had been deposited which contain the thiohydantoin heterocyclic backbone, however, many are not relevant for comparison as the heterocycle is part of a larger polycyclic structure or has a substitution pattern which does not allow for H-bonding. Eight structures (with coordinates available) were identified with both a thiohydantoin core and an N–H group available for hydrogen bonding at the 1-position. They

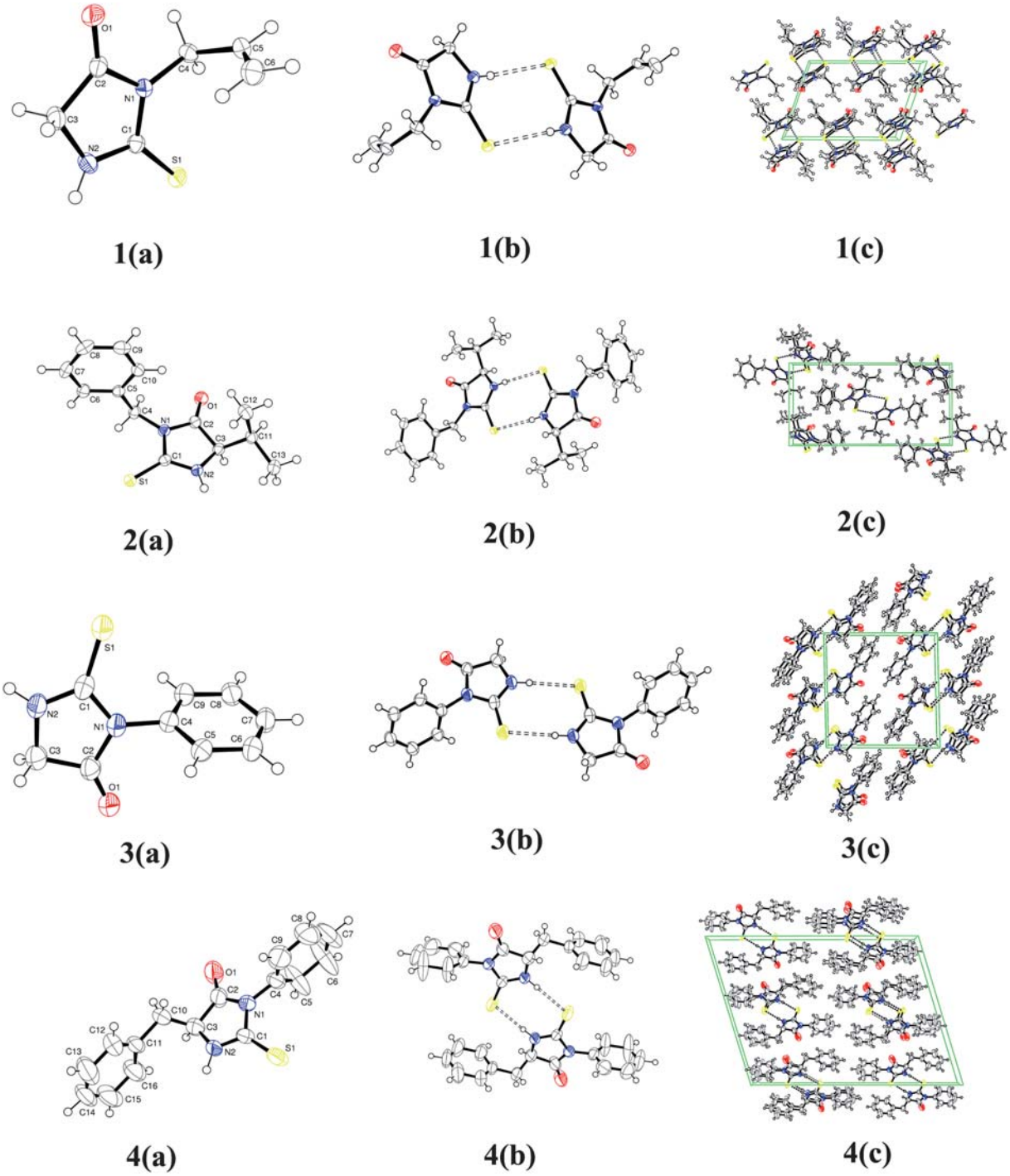


Fig. 2 The X-ray crystal structures of compounds **1** to **4**. (a) A labelled ORTEP plot (ellipsoids at 50% probability level) of the molecule in the asymmetric unit. (b) The H-bonded dimer with H···S interactions represented by a dashed line. (c) Packing of the dimers is shown, aligned to most clearly indicate how they pack. The unit cell outline is shown in green.

can be divided into four categories: the unsubstituted thiohydantoin, a 5 monosubstituted derivative, 3,5-substituted derivatives and 5-disubstituted derivatives, see Fig. 5. Only one of these compounds has the same substitution pattern that we have used in this study (EHXBY).

The H-bonding patterns were analysed showing the O chains and S dimers that have been observed in our work but also some different H-bonding patterns, particularly where the N3 position was also available for H-bonding or other species were present within the crystal lattice, such as iodine.

The unsubstituted thiohydantoin (THHYDT) has two H-bonds formed with the O atom and the S does not participate in H-bonding.[40] This is expected for a system where there is no steric bulk or other factors directing the interactions away from the most favourable H-bond donor–acceptor pair. An O dimer forms with H-bonding from the N–H in the 3-position (between

Table 4 H-bonding parameters for structures of **1** to **7** and relevant literature structures

D–H···A	Type of H-bonding	D–H/Å	H···A/Å	D···A/Å	Angle (D–H···A)/°	
1 (N–H···S)	S dimer	0.88	2.568	3.403(1)	158.60(12)	$-x, 1-y, -z$
2 (N–H···S)	S dimer	0.88	2.52	3.393(2)	170.3(2)	$1-x, 1-y, 1-z$
3 (N–H···S)	S dimer	0.88	2.44	3.308(4)	168.1(4)	$-x, 1-y, -z$
4 (N–H···S)	S dimer	0.910(6)	2.410(6)	3.316(4)	177.4(5)	$½-x, 5/2-y, -z$
5 (N–H···O)	O chain	0.830(2)	2.042(2)	2.869(2)	174.01(18)	$x, ½-y, -½-z$
6 (N–H···O)	O chain	0.88	2.041	2.914(1)	171.67(11)	$x, 1-y, -½+z$
7 (N–H···O)	O chain	0.88	1.945	2.801(2)	163.9(2)	$-½+x, ½-y, -½+z$
THHYDT	O dimer	0.829	2.097	2.916	169.3	
THHYDT	Other N–H···O	0.912	2.022	2.928	172.5	
YINGIM	O dimer	0.848/0.834	2.027/2.012	2.856/2.836	165.8/169.8	
YINGIM	S dimer	0.842/0.792	2.519/2.601	3.358/3.386	174.2/171.0	
NUTVIH	S dimer	0.841	2.556	3.394	174.3	
NUTVIH	O chain	0.869	2.248	3.094	164.6	
KUWDOV	O dimer	0.809	2.128	2.874	153.5	
EHXBY	S dimer	1.09	2.355	3.396	159.2	
HAFLEF	O chain	0.896	1.946	2.794	157.2	
WUSJID	O chain	0.824	2.153	2.967	170.1	
LEVWAL	S dimer	0.806	2.569	3.373	175.0	

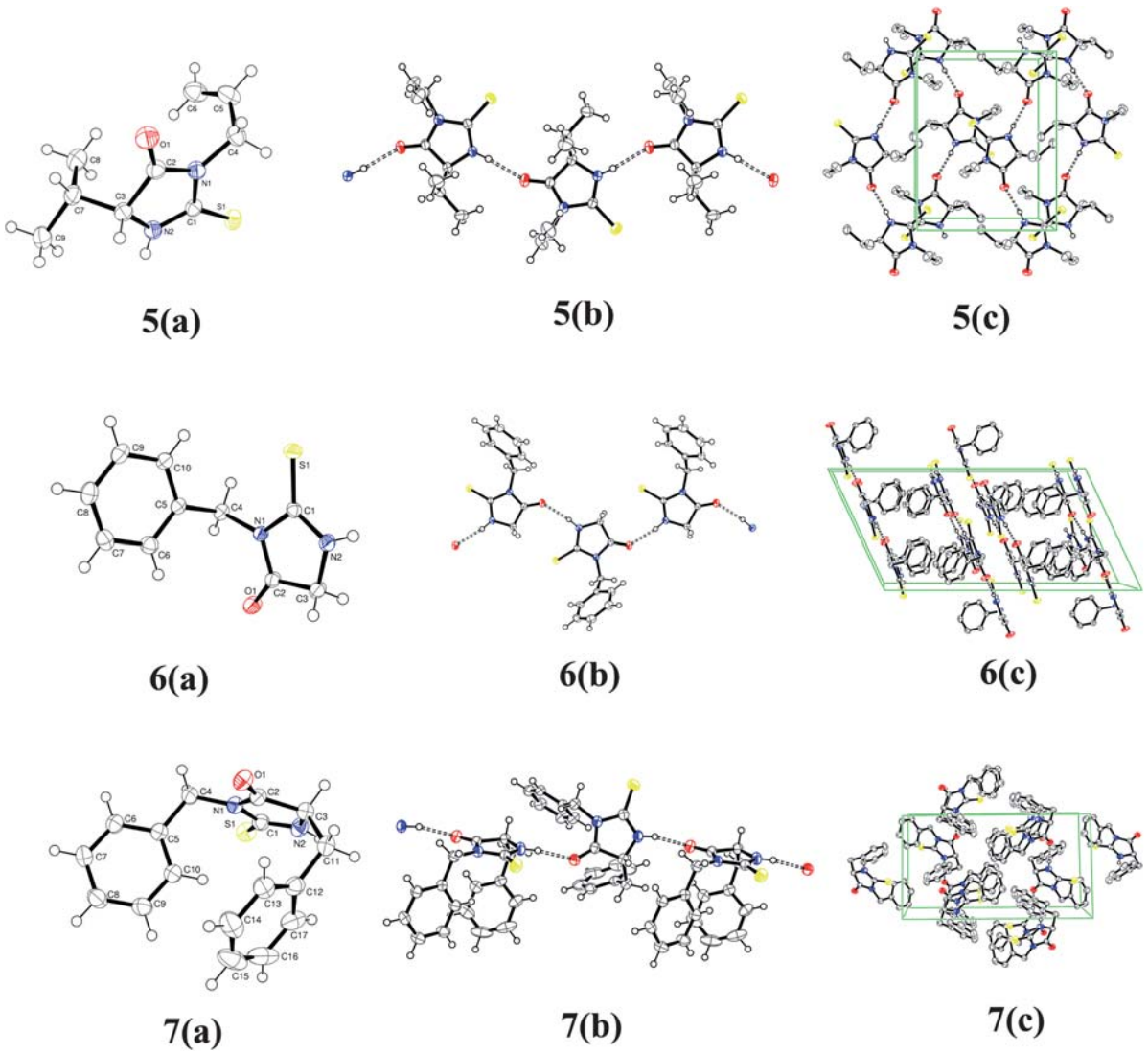


Fig. 3 The X-ray crystal structures of compounds **5** to **7**. (a) A labelled ORTEP plot (ellipsoids at 50% probability level) of the molecule in the asymmetric unit. (b) The H-bonded 1D chains with the H···O interactions represented by a dashed line. (c) Packing of the molecules is shown, aligned to give the clearest view. The unit cell outline is shown in green.

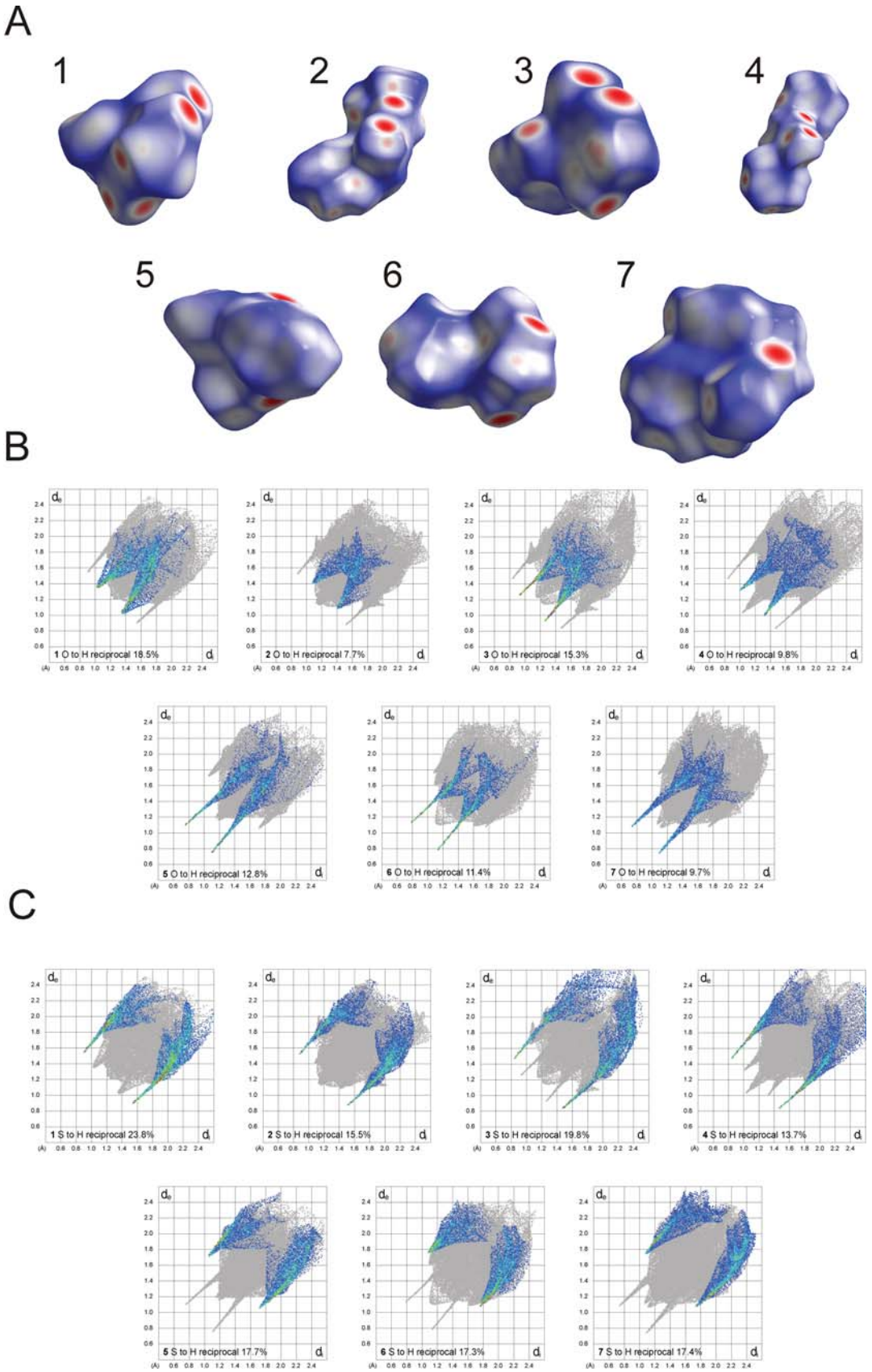


Fig. 4 Hirshfeld surface analysis of compounds **1–7**. (A) Hirshfeld surface of compounds **1–7** mapped with d_{norm} which highlights both donor and acceptor equally. (B) Fingerprint plots for compounds **1–7** resolved into O···H contacts. The full fingerprint appears beneath each decomposed plot in grey. (C) Fingerprint plots for compounds **1–7** resolved into S···H contacts. The full fingerprint appears beneath each decomposed plot in grey.

the C═S and C═O). The N–H in the 1-position also has an intermolecular H-bond to O in a neighbouring molecule.

5-Phenylthiohydantoin (YINGIM) has the same potential for hydrogen bond formation as thiohydantoin (THHYDT) but with additional steric bulk in the form of a single substituent in the 5-position. As with THHYDT the structure shows the formation of O dimers with the N–H in the 3-position. But in this case H-bonded S dimers are also present to give an overall three dimensional structure.[41] There are no π···π interactions and although there are some reasonable distances for C–H···π interactions, all the angles to the phenyl ring centroid are below 130°.

The next step in increasing steric bulk is to add a further group at the 5-position to give the 5-disubstituted derivatives (NUTVIH and KUWDOV). 5-Diphenylthiohydantoin (NUTVIH) shows a combination of O chains and S dimers with no significant further interactions (no π···π or strong C–H to π interactions are observed).[42] The 5-dimethylhydantoin (KUWDOV) unfortunately does not offer an appropriate comparison as it is co-crystallised with iodine (I_2).[43] Unsurprisingly the iodine in the crystal lattice interacts with the sulfur blocking any possibility for its involvement in H-bonding interactions. This gives discrete O-bonded dimers, as would be predicted for this co-crystallised mixture.

The 3,5-disubstituted derivative which matches the substitution pattern in our work is 3-ethyl 5-(4-methoxybenzyl) thiohydantoin (EHXBY).[44] The two 5-benzyl structures we synthesised adopt different H-bonding motifs and so do not give predictive structural information for such derivatives. This compound forms sulfur H-bonded dimers, as was observed for compound **4**. No significant C–H to π interactions are present but there are two intermolecular C–H···O hydrogen bonds at reasonable donor–acceptor distances and angles (3.53 Å/159° and 3.32 Å/148°).

Bulkier derivatives are also known with a 3,5-trisubstituted pattern where the 5-position is disubstituted. This increase in steric bulk appears to disfavour the formation of sulfur H-bonded dimers to give structures with H-bonded chains formed by interaction with the carbonyl oxygen. The 3-methyl 5-dimethyl thiohydantoin (HAFLEF)[45] and the 3-ethyl 5-diphenyl thiohydantoin (WUSJID)[28] both give the chain type structures. There are no significant additional interactions in the HAFLEF structure. In the WUSJID structure the molecules are arranged to maintain the H-bonding and to accommodate the bulky phenyl substituents. There are two C–H to π interactions at *ca.* 3.7 Å with angles over 140° but no further significant intermolecular H-bonding interactions.

The final structure identified is also a 3,5-trisubstituted thiohydantoin but in this case with a long alkyl chain in the 3-position. For this 3-hexyl 5-diphenyl thiohydantoin (LEVWAL), H-bonded dimers with the sulfur acceptor are observed.[46] This changeover appears to be due to the packing of the long alkyl chains which would interfere with O-chain formation as the layers of S-dimers are formed with the oxygens pointing between the layers. No other significant interactions were observed.

Examination of the hydrogen bonding parameters for the seven structures from this work and the additional eight known structures shows reasonable consistency in the N–H···O and N–H···S distances, see Table 4. The donor to acceptor distances are in the range 3.3 to 3.4 Å for the sulfur acceptor and 2.8 to 3.1 Å for the oxygen acceptor. The longest N to O distance is observed for a structure with multiple H-bonded networks (NUTVIH). The lowest D–H···A angle is 154°, but this is for the KUWDOV structure where iodine is incorporated in the crystal structure and S···I interactions will be optimised. The remaining angles are in the range 157 to 177°.

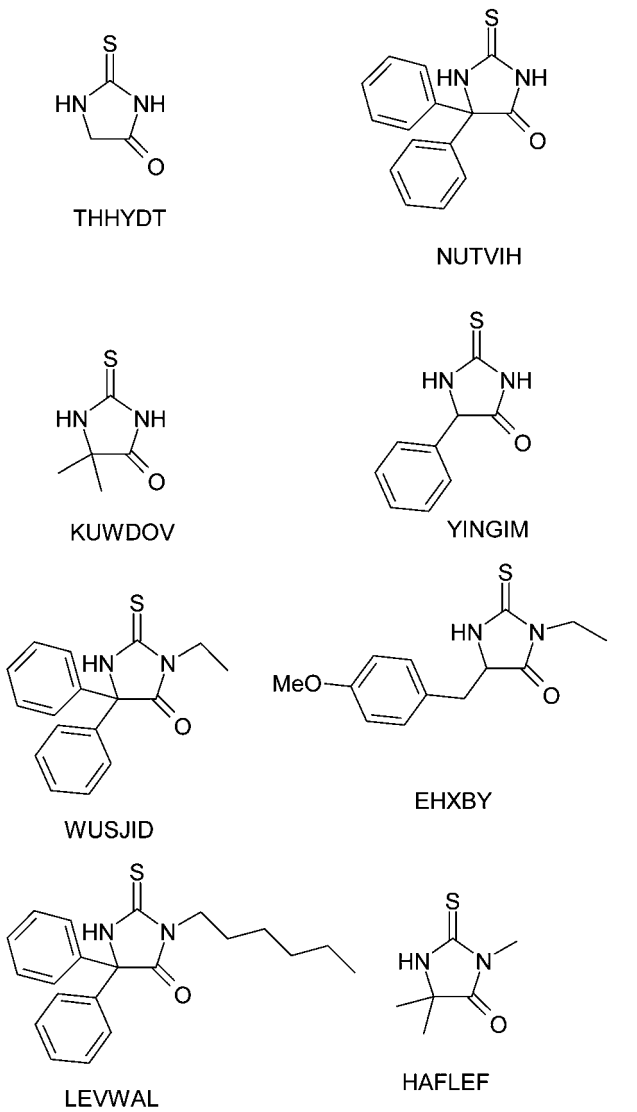


Fig. 5 Thiohydantoin derivatives deposited in the crystallographic database.

The Hirshfeld surfaces were calculated for the literature structures along with fingerprint plots in which either O···H or S···H interactions highlighted (Fig. S1–S3)†. The thiohydantoin structure THHYDT has over 50% of the relative contribution to the Hirshfeld surface area from either O···H or S···H close contacts (25.2% and 29.2% respectively). This contrasts with the hexyldiphenyl substituted LEVWAL where 60.7% of the surface area is contributed by H···H contacts, reflecting both the larger number of alkyl and aryl groups and the reduced potential for H-bonding interactions with O and S.

Conclusions

In our compounds (**1–7**), we have blocked formation of oxygen acceptor H-bonded O dimers in thiohydantoins as anticipated.

This has given a series of compounds which adopt one of two structural types, either H-bonded dimers or 1D chains.

No clear relationship is obvious between the substituent on the N-position and the structural type. Both of the *N*-phenyl compounds (**3** and **4**) form dimers but the similarly bulky *N*-benzyl compounds (**2**, **6** and **7**) adopt either chains or dimers with no obvious reasons for structure selection. It may be that the more rigid phenyl substituents encourage formation of the rotationally inflexible dimers.

The 3 and 5 substituents can be accommodated by the formation of infinite H-bonded chains with this motif allowing for variation in the relative twist of neighbouring rings. Steric bulk clearly plays a role. A comparison of **1** and **5** suggests increased steric bulk in the 5-position favours chain formation. It is also interesting to see the variation for the LEVWAL structure which uses hydrophobic interactions to bring *N*-hexyl substituents together and forms a sulfur H-bonded dimer where oxygen H-bonded chains might have been predicted.

$\pi\cdots\pi$ interactions are not a key driving force in formation of these structures. However, the weaker C–H to π type interactions could tip the balance in favour of which structural type is adopted. Computational energy calculations could be of value in predicting structures for this class of compounds.

We plan to study more variants of these compounds to determine if further rationalisation is possible. It does appear that there is a fine energetic balance between the two structural types. Conceivably both structural types could be observed for thiohydantoin derivatives with certain combinations of substituents to give crystalline polymorphs. The existence of polymorphs is of significant interest due to the potential pharmaceutical applications of these compounds.

Experimental

All reagents and solvents were purchased from Sigma-Aldrich, Lancaster or Fisher and were used as supplied unless otherwise stated.

All ^{1}H NMR and proton decoupled ^{13}C NMR spectra were collected on a Jeol JNM-LA400 spectrometer at 400 and 100 MHz respectively, and referenced against residual solvent signals.

Synthetic procedure to prepare substituted 2-thioxoimidazolidin-4-one derivatives

To a solution of hydrochloride salts of the amino acid methyl ester and alkyl/aryl isothiocyanate (1 equiv.) in CH_2Cl_2 (20 mL) at room temperature was added triethylamine (2 equiv.) and the reaction mixture was stirred for an hour. The solution was given an aqueous wash (1 × 10 mL) and the organic phase dried over Na_2SO_4. The solvent was removed under reduced pressure and the crude product purified by short filtration column (flash silica) using dichloromethane–ethyl acetate (9 : 1) as an eluent to give the desired product as a white solid in more than 90% yield.

X-Ray quality crystals were obtained by slow evaporation using hexane–ethyl acetate (9 : 1) as a solvent for crystallisation.

Compound 1 (R^1 = H, R^2 = allyl). ^{1}H NMR (400 MHz, CD_2Cl_2) δ 4.01 (s, 2H, H_{CH_2}), 4.33 (td, 2H, J = 5.64 Hz and 1.40 Hz, H_{CH_2}), 5.10–5.17 (m, 2H, $H_{=CH_2}$), 5.73–5.82 (m, 1H, $H_{=CH}$), 7.53 (br s, 1H, H_{NH}). ^{13}C NMR (100 MHz, CD_2Cl_2) δ 43.45, 48.93, 118.13, 131.31, 171.65, 185.09.

Compound 2 (R^1 = i-Pr, R^2 = Bn). ^{1}H NMR (400 MHz, acetone-d_6) δ 4.36 (s, 2H, H_{CH2}), 7.35–7.37 (m, 2H, H_{Ar}), 7.43–7.53 (m, 3H, H_{Ar}), 9.11 (br s, 1H, H_{NH}). ^{13}C NMR (100 MHz, acetone-d_6) δ 49.65, 129.23, 129.38, 129.63, 134.87, 172.38, 185.53.

Compound 3 (R^1 = H, R^2 = Ph). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.77 (d, 3H, J = 7.00 Hz, H_{CH3}), 0.96 (d, 3H, J = 7.00 Hz, H_{CH3}), 2.14–2.22 (m, 1H, H_{CH}), 3.91 (dd, 1H, J = 3.64 Hz and 1.12 Hz, H_{CH}), 4.91 (d, 2H, J = 2.52 Hz, H_{CH2}), 7.16–7.24 (m, 3H, H_{Ar}), 7.35–7.38 (m, 2H, H_{Ar}), 8.16 (br s, 1H, H_{NH}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.17, 18.77, 44.39, 64.55, 127.82, 128.41, 128.61, 135.61, 173.52, 184.09.

Compound 4 (R^1 = Bn, R^2 = Ph). ^{1}H NMR (400 MHz, CD_2Cl_2) δ 3.04 (dd, 1H, J = 14.08 Hz and 6.44 Hz, H_{CH2}), 3.19 (dd, 1H, J = 14.08 Hz and 4.24 Hz, H_{CH2}), 4.39–4.42 (m, 1H, H_{CH}), 6.89–6.93 (m, 2H, H_{Ar}), 7.15–7.17 (m, 2H, H_{Ar}), 7.22–7.27 (m, 3H, H_{Ar}), 7.32–7.38 (m, 3H, H_{Ar}), 8.26 (br s, 1H, H_{NH}). ^{13}C NMR (100 MHz, CD_2Cl_2) δ 37.27, 60.76, 127.68, 128.07, 128.76, 129.04, 129.19, 129.50, 132.33, 133.81, 172.71, 183.51.

Compound 5 (R^1 = i-Pr, R^2 = allyl). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86 (d, 3H, J = 6.76 Hz, H_{CH3}), 1.03 (d, 3H, J = 6.76 Hz, H_{CH3}), 2.24 (m, 1H, H_{CH}), 3.98 (dd, 1H, J = 3.92 Hz and 1.40 Hz, H_{CH}), 4.34 (td, 2H, J = 5.60 Hz and 1.40 Hz, H_{CH2}), 5.12–5.21 (m, 2H, $H_{=CH2}$), 5.72–5.81 (m, 1H, $H_{=CH}$), 8.56 (br s, 1H, H_{NH}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.15, 18.80, 30.72, 42.90, 64.64, 118.39, 130.52, 173.31, 183.81.

Compound 6 (R^1 = H, R^2 = Bn). ^{1}H NMR (400 MHz, acetone-d_6) δ 3.73 (s, 2H, H_{CH2}), 4.57 (s, 2H, H_{CH2}), 6.82–6.91 (m, 3H, H_{Ar}), 7.03–7.06 (m, 2H, H_{Ar}), 8.40 (br s, 1H, H_{NH}). ^{13}C NMR (100 MHz, acetone-d_6) δ 43.37, 47.84, 126.87, 127.59, 127.84, 135.48, 171.26, 183.86.

Compound 7 (R^1 = Bn, R^2 = Bn). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.83 (dd, 1H, J = 14.04 Hz and 8.16 Hz, H_{CH_2}), 3.17 (dd, 1H, J = 14.04 Hz and 4.24 Hz, H_{CH_2}), 4.23 (dq, 1H, J = 4.24 Hz and 1.12 Hz, H_{CH_1}), 4.82 (s, 2H, H_{CH_2}), 7.04–7.07 (m, 2H, H_{Ar}), 7.14–7.19 (m, 8H, H_{Ar}), 7.75 (br s, 1H, H_{NH}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 37.14, 44.37, 60.38, 127.53, 127.68, 128.34, 128.41, 128.89, 129.14, 134.28, 135.31, 173.12, 183.48.

X-Ray crystallography†

Diffraction datasets were collected on a Stöe IPDS-II imaging plate diffractometer using MoKα radiation (λ = 0.71073 Å). The temperature of each crystal was kept at 150 K during data collection and controlled using the Oxford Cryosystems Cryostream Cooler.[47] All structures were solved using direct methods (SHELXS) and refined against F^2 (SHELXL).[48,49] H atoms were either located on the difference map or placed in idealised positions and refined using a riding model with C–H = 0.97 Å, N–H = 0.91 Å and U_{iso}(H) = 1.2 (or 1.5 for some H atoms) times U_{eq} of the carrier atom. The WinGX package was used for

refinement and production of data tables, and ORTEP-3 used for structure visualisation.[50,51] All ORTEP representations show ellipsoids at the 50% probability level. Analysis of the H-bonded and π-interactions was carried out using PLATON for both our structures and the literature compounds.[52] CrystalExplorer was used to produce Hirshfeld surface plots based on d_{norm} and decomposed 2D fingerprint plots to show the relative contribution for specified contacts to the intermolecular contact surface.[53]

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