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A Close Insight into the Nature of Intermolecular Interactions in View Article Online Dihydropyrimidine-2(1H)-thione Derivatives <sup>†</sup>

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<sup>†</sup> Electronic supplementary information (ESI) available: Ring puckering parameters and endocyclic torsion angles for compounds 1-4 are given in Tables S1 and S2, respectively. Topological and geometrical parameters for the main intermolecular interactions of compounds 1-4 are shown in Tables S3-S6, respectively. Interaction energies for molecular pairs involving H...H contacts and electrostatic potentials in 1–4 and related compounds are shown in Table S7 and S8, respectively. Overlay diagram for independent molecules of compound 1 is shown in Figure S1. Packing diagrams, as well as intermolecular energies for the respective molecular pairs for compounds 1-4 are given in Figures S2-S5, respectively. Hirshfeld surfaces of compound 1 is shown in Figure S6. Figure S7 shows the relative contributions of intermolecular contacts to the Hirshfeld surface area and full 2D fingerprint plots are displayed in Figure S8. Hirshfeld surface mapped with electrostatic potentials (ESP) and 3D-deformation density maps for compounds 1-4 are shown in Figures S9-S12, respectively.

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## Abstract

The crystal structures of four 1-(R-phenyl)-4,4,6-trimethyl-3,4-dihydropyrimidine-2(*1H*)-thione derivatives [R = 2-chloro (1), 2,3-di-chloro (2), 2,4-di-methyl (3), and 4-methoxy (4)] have been determined and an analysis of their molecular conformations was carried out. A comparative study of intermolecular interactions -including eight closely related structures from CSD- was performed and the degree of isostructurality was quantified. Intermolecular interactions have been characterized in the periodic system electron density and the topological analysis highlights the role of N–H···S=C hydrogen bonds in the stabilization of different supramolecular architectures. PIXEL lattice energy calculations revealed that the dispersion component is the major contribution, with an important role of the coulombic term to the total energy. Interaction energies for molecular pairs involving strong N–H···S=C hydrogen bonds indicate a dominant contribution to packing stabilization coming from coulombic components. Hirshfeld surfaces and fingerprint plots allowed us to visualize different intermolecular contacts and its relative contributions to total surface in each compound. The analysis of electrostatic potentials (ESP) correlates well with the computed energies characterizing the strength of different interactions.

**Keywords:** dihydropyrimidine, crystal structure, Pixel energy, Hirshfeld surfaces, electrostatic potential, deformation density.

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Non-covalent interactions play an essential role in supramolecular chemistry, molecular biology and crystal engineering.<sup>1</sup> It is well known that strong hydrogen bonds have been preferably used as tools for the design of materials with specific desirable properties.<sup>2</sup> In absence of strong hydrogen bonds however, other kind of non-covalent interactions can be dominant and therefore responsible for crystal stability. The hydrogen bond do not represent an exclusively electrostatic interaction but a complex combination of at least four components such as electrostatic (acid/base), polarization (hard/soft), van der Waals (dispersion/repulsion), and covalent (charge transfer). The electrostatic nature is clearly dominant in strong hydrogen bonds, particularly if donor and acceptor atoms are very electronegative, but the proportion of electrostatic character can vary, even in the case of weaker interactions. In this direction, the study of non-covalent interactions in sulfur-containing compounds is attracting continuous attention in crystal engineering,<sup>3</sup> mainly because of the high polarizability of the electron density at the sulfur atom.. Thus, the versatility of the thioamide [-C(S)NH<sub>2</sub>],<sup>4, 5</sup> triazole-thione<sup>6, 7</sup> and thiosemicarbazone<sup>8</sup> functional groups as a key moiety for crystal engineering has recently been recognized.

Dihydropyrimidine-2-thiones are heterocyclic compounds having a pyrimidine ring system.<sup>9, 10</sup> This class of compounds are usually obtained by variations of well known three-component reaction early reported by Pietro Biginelli.<sup>11, 12</sup> In recent years, a considerable increased interest has been directed at the role and effect of dihydropyrimidine-2-thiones in a variety of biological activities.<sup>13, 14</sup>

In this work, the crystal structures of four novel 1-(R-phenyl)-4,4,6-trimethyl-3,4dihydropyrimidine-2(*1H*)-thione derivatives [see Scheme 1, R = 2-chloro (1), 2,3-dichloro (2), 2,4-dimethyl (3) and 4-methoxy (4)], have been determined using single-crystal X-ray analysis.

Scheme 1. General structure of 1-(R-phenyl)-4,4,6-trimethyl-3,4-dihydropyrimidine\_2f/Hde Online bol: 10.1039/C6CE02619B thiones.



The aims of this article are (1) to analyze the conformational stability of the 3,4dihydropyrimidine-2(1H)-thione moiety by varying the phenyl substitution at the 1- position, and (2) to determine the intermolecular interactions governing the crystal structure of the 3,4dihydropyrimidine-2(1H)-thione and how conserved are these interactions upon substitution. To pursuing these goals, a molecular conformation analysis and a detailed characterization of intermolecular contacts were carried out for these four compounds as well as for eight other closely related structures found in CSD. Also, a comprehensive analysis of intermolecular interaction has been performed by applying a battery of complementary tools, including: (1) the topology of the electron density obtained from a periodic quantum calculation was analyzed within the context of the Bader's theory of atoms in molecules (AIM)<sup>15</sup> to characterize the intermolecular interactions, (2) lattice energies and intermolecular interaction energies associated to different molecular pairs have been calculated in order to determine the energy components contributing to crystal stabilization,<sup>16, 17</sup> (3) Hirshfeld surface based tools, such as  $d_{\text{norm}}$ , shape index and curvedness surface properties,<sup>18, 19</sup> have been used for exploration of the packing modes and visualization of intermolecular interactions, (4) quantitative pictures of intermolecular contacts, including the relative percentage of each type of interaction have been obtained from fingerprint plots and their decompositions,<sup>20, 21</sup> and (5) the intermolecular interactions have been analyzed in terms of a combined quantitative study based on electrostatic potential (ESP) and 3D deformation density maps.<sup>22</sup>

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# 2- Experimental

**2.1- Preparation of 1-(R-phenyl)-4,4,6-trimethyl-3,4-dihydropyrimidine-2**(*1H*)-**thione derivatives**. In an attempt to obtain the corresponding acyl thiourea derivative, Yamin et al.<sup>23, 24</sup> isolated 1-phenyl-4,4,6-trimethyl-3,4-dihydropyrimidine-2-(1*H*)thione from the reaction between cinnamoyl isothiocyanate and aniline in acetone. We demonstrated that 1-aryl-4,4,6-trimethyl-3,4-dihydropyrimidine-2-(1*H*)thiones are in fact formed by the reaction of aniline, KSCN and 4-methylpent-3-en-2-one, an aldol condensation product of acetone formed *in situ* from acetone used as solvent.<sup>9, 10,25</sup> Following this general method, suitable substituted anilines (1.0 mmol) were added portion wise to a stirred suspension of potassium thiocyanate (1.0 mmol) in 4-methylpent-3-en-2-one (1.20 mmol) at room temperature. The reaction mixture was heated at 50-60 °C for 3-5 hours and the progress was followed by TLC. On completion, the reaction mixture was cooled to room temperature and poured into ice-water. The precipitated compounds were recrystallized from ethanol to afford the purified dihydropyrimidine-2-thiones (1-4) in good to excellent yields (Scheme 2).



R= 2-Cl (1), 2,3-Cl<sub>2</sub> (2), 2,4-(CH<sub>3</sub>) (3), 4-MeO (4)

**Scheme 2.** Green synthesis of 1-(R-phenyl)-4,4,6-trimethyl-3,4-dihydropyrimidine-2(*1H*)-thiones **1-4**.

**1-(2-Chlorophenyl)-4,4,6-trimethyl-3,4-dihydropyrimidine-2(1***H***)-thione (1), 10.1039/CCEP02619B crystalline solid; Yield; 92%, R<sub>f</sub>: 0.31; m.p: 123-124°C; IR (neat): 3390 (NH), 3029 (=C-H stretch), 1645 (CS-NH), 1576 (C=C), 1297 (C-N): <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 300 MHz): \delta 7.88 (s, 1H, N-H), 7.22-6.45 (m, 5H, Ar-H), 4.25 (s, 1H, Csp<sup>2</sup>-H), 1.41 (s, 3H, Csp<sup>2</sup>-CH<sub>3</sub>) 1.28 (s, 3H, CH<sub>3</sub>), 1.24 (s, 3H, CH<sub>3</sub>); <sup>13</sup>C-NMR (CDCl<sub>3</sub>, 75 MHz): \delta 187.5 (CSNH), 138.1 (-C=C-), 137.3, 135.2, 134.7, 131.7, 130.4, 129.8, 110.6 (-H-C=C-), 57.4 ((CH<sub>3</sub>)<sub>2</sub>-C-), 34.2 ((CH<sub>3</sub>)<sub>2</sub>-), 33.4 (-C-CH<sub>3</sub>). Elemental analysis C<sub>13</sub>H<sub>15</sub>ClN<sub>2</sub>S: calc (%): C 58.97, H 5.23, Cl 13.26, N 10.54, S 12.01; found (%): C 58.94, H 5.27, Cl 13.28, N 10.53, S 12.00.** 

**1-(2,3-Di-chlorophenyl)-4,4,6-trimethyl-3,4-dihydropyrimidine-2(1***H***)-thione (<b>2**). Brown crystalline solid; Yield; 81%, R<sub>f</sub>: 0.33; m.p: 130-131°C; IR (neat): 3401 (NH), 3087 (=C-H stretch), 1694 (CS-NH), 1598 (C=C), 1307 (C-N): <sup>1</sup>H-NMR ((CD<sub>3</sub>)<sub>2</sub>CO, 300 MHz):  $\delta$  7.99 (s, 1H, N-H), 7.64-7.29 (m, 5H, Ar-H), 5.04 (q, 1H, *J*= 1.2 Hz, Csp<sup>2</sup>-H), 1.52 (d, 3H, *J*=1.2 Hz, Csp<sup>2</sup>-CH<sub>3</sub>) 1.44-1.41 (s, 6H, 2×CH<sub>3</sub>); <sup>13</sup>C-NMR ((CD<sub>3</sub>)<sub>2</sub>CO, 75 MHz):  $\delta$  183.1 (CSNH), 137.5 (-C=C-), 137.1, 135.9, 132.8, 128.5, 128.1, 127.6, 107.9 (-H-C=C-), 57.1 ((CH<sub>3</sub>)<sub>2</sub>-C-), 33.6 (CH<sub>3</sub>)<sub>2</sub>-), 32.7 (-C-CH<sub>3</sub>). GC-MS: 300 (M<sup>+</sup>), 285, 265 (100 %), 249, 226, 185. Elemental analysis C<sub>13</sub>H<sub>14</sub>Cl<sub>2</sub>N<sub>2</sub>S: calc (%): C 51.95, H 4.56, Cl 23.50, N 9.33, S 10.65; found (%): C 51.98, H 4.53, Cl 23.54, N 9.31, S 10.63.

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**1-(2,4-Dimethylphenyl)-4,4,6-trimethyl-3,4-dihydropyrimidine-2(1***H***)-thione (3). White crystalline solid; Yield; 85%, R<sub>f</sub>: 0.32; m.p: 150-151°C; IR (neat): 3320 (NH), 3082 (=C-H stretch), 1697 (CS-NH), 1535 (C=C), 1290 (C-N): <sup>1</sup>H-NMR ((CD<sub>3</sub>)<sub>2</sub>CO, 300MHz): δ 7.72 (s, 1H, N-H), 7.08-6.89 (m, 3H, Ar-H), 4.97 (q, 1H,** *J***=1.2 Hz, Csp<sup>2</sup>-H), 2.31 (s, 3H, Ar-CH<sub>3</sub>), 2.17 (s, 3H, Ar-CH<sub>3</sub>), 1.44 (d, 3H,** *J***= 1.2 Hz, Csp<sup>2</sup>-CH<sub>3</sub>), 1.39 (6H, 2×CH<sub>3</sub>); <sup>13</sup>C-NMR ((CD<sub>3</sub>)<sub>2</sub>CO, 75 MHz): δ 177.2 (CSNH), 138.1 (-C=C-), 137.5, 136.5, 131.8, 130.8, 129.9, 128.8, 109.2 (-H-C=C-), 51.8 ((CH<sub>3</sub>)<sub>2</sub>-), 30.8 ((CH<sub>3</sub>)<sub>2</sub>-C-), 20.2 (-C-CH<sub>3</sub>), 19.6 (2×Ar-CH<sub>3</sub>): GC-MS: 260 (M<sup>+</sup>),** 

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245 (100%), 179, 163, 79. Elemental analysis C<sub>15</sub>H<sub>20</sub>N<sub>2</sub>S: calc (%): C 69.14, H 7.79 N MO APPe Online S 12.35; found (%): C 69.17, H 7.75, N 10.71, S 12.37.

**1-(4-Methoxyphenyl)-4,4,6-trimethyl-3,4-dihydropyrimidine-2**(1*H*)-thione (4). Red crystalline solid; Yield; 87%,  $R_f$ : 0.47; m.p: 163-164°C; IR (neat): 3355 (NH), 3045 (=C-H stretch), 1700 (CS-NH), 1585 (C=C), 1301 (C-N): <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 300MHz):  $\delta$  7.81 (s, 1H, N-H), 7.65-6.17 (m, 5H, Ar-H), 4.61 (s, 1H, Csp<sup>2</sup>-H), 3.71 (s, 3H, Ar-OCH<sub>3</sub>), 1.64 (s, 3H, Csp<sup>2</sup>-CH<sub>3</sub>) 1.24 (s, 3H, CH<sub>3</sub>), 1.21 (s, 3H, CH<sub>3</sub>); <sup>13</sup>C-NMR (CDCl<sub>3</sub>, 75MHz):  $\delta$  186.5 (CSNH), 137.9 (-C=C-), 134.7, 126.3, 121.9, 120.2, 111.2 (-H-C=C-), 57.9 ((CH<sub>3</sub>)<sub>2</sub>-C-), 54.6 (Ar-OCH<sub>3</sub>), 33.8 ((CH<sub>3</sub>)<sub>2</sub>-), 32.4 (-C-CH<sub>3</sub>). LC-MS (m/z) %: [M+H]<sup>+</sup> 263.6 (100%). Elemental analysis C<sub>14</sub>H<sub>18</sub>N<sub>2</sub>OS: calc (%): C 64.05, H 6.96, N 10.64, O 6.15, S 12.21; found (%): C 64.03, H 6.93, N 10.66, O 6.16, S 12.20.

Instrumentation. Melting points were determined using a Gallenkamp melting point apparatus (MP-D) and are uncorrected. Infrared spectra were recorded using a Shimadzu IR 460 as KBr pellets. <sup>1</sup>H-NMR spectra were obtained using a Bruker 300 NMR MHz spectrometer in deuterated solvents using TMS as an internal reference. <sup>13</sup>CNMR spectra were obtained by (75 MHz) NMR spectrometer in deuterated solvents. MS were recorded using an EI source (70 eV) on Agilent technologies 6890N (GC) and an inert mass selective detector 5973 mass spectrometer. Gaseous helium was used as mobile phase with the pressure in the column head equal to 100 kPa. The column used was a 19091J-433 HP-5 of 30 m x 0.32 mm x 0.25 mm film thickness. Approximately 1  $\mu$ L volume of the compounds dissolved in CHCl<sub>3</sub> or acetone were chromatographed under the following conditions: the injection temperature was 200 °C, the initial column temperature (70 °C) was held for 2 min, then increased to 200 °C at 10 °C/min and held for 4 min after elevated to 250 °C at 10 °C/min and held for 2 min more. In the spectrometer the source was kept at 200 °C. Thin layer chromatography (TLC) was conducted

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on 0.25 mm silica gel plates (60 F254, Merck). Elemental analyses were conducted Virtsinge Online DOI: 10.1039/C6CE02619B CHNS 932 LECO instrument.

*X-ray data collection and structure refinement*. The crystal and refinement data for compounds **1-4** are listed in Table 1. Data were collected at 130(2) K on a Bruker AXS SMART APEX diffractometer using MoK $\alpha$  radiation. Structure solved by direct methods and full-matrix least-squares refinement on  $F^2$  by using SHELX.<sup>26</sup> All non-hydrogen atoms were refined anisotropically, and all H atoms were derived from difference maps, then placed at idealized positions and then refined using the riding model. Methyl-H atoms were allowed to rotate but not to tip. The ring puckering parameters and geometric parameters of  $\pi$ -stacking were calculated with PLATON for Windows Taskbar v1.17.<sup>27</sup> Molecular structures were plotted using Olex2,<sup>28</sup> and the packing diagrams were generated using MERCURY.<sup>29</sup>

Full crystallographic data have been deposited with the Cambridge Crystallographic Data Centre (CCDC-1504146, 1504147, 1504148, 1504149 for **1-4**, respectively). Enquiries for data can be directed to: Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, UK, CB2 1EZ or (e-mail) deposit@ccdc.cam.ac.uk or (fax) +44 (0) 1223 336033.

	(1)	(2)	(3)	(4)
Empirical formula	$C_{13}H_{15}ClN_2S$	$C_{13}H_{14}Cl_2N_2S$	$C_{15}H_{20}N_2S$	$C_{14}H_{18}N_2OS$
Formula weight	266.78	301.22	260.39	262.36
Temperature / K	130(2)	130(2)	130(2)	130(2)
Crystalsystem	monoclinic	monoclinic	monoclinic	triclinic
Spacegroup	$P2_1/c$	$P2_1/c$	$P2_1/n$	P-1
Unit cell dimensions	a = 14.214(2)Å b = 9.8017(14)Å c = 19.392(3)Å	a = 12.072(4)Å b = 7.010(2)Å c = 17.035(5)Å	a = 12.228(3)Å b = 8.896(2)Å c = 14.798(4)Å	a = 8.729(3)Å b = 9.683(3)Å c = 10.503(4)Å $\alpha = 64.578(5)^{\circ}$
	$p = 95.548(4)^{\circ}$	$\beta = 101.402(7)^{\circ}$	$p = 113.100(0)^{\circ}$	$\beta = 78.685(6)^{\circ}$ $\gamma = 63.892(6)^{\circ}$
Volume / Å <sup>3</sup>	2689.0(7)	1413.2(7)	1480.1(6)	719.9(4)
Ζ	8	4	4	2
$ ho_{ m calc.}$ / mg mm <sup>-3</sup>	1.318	1.416	1.169	1.210
$\mu$ / mm <sup>-1</sup>	0.419	0.520	0.204	0.216
F(000)	1120	624	560	280

Table 1. Crystal data and structure refinement for compounds 1-4.

Page	9	of	33	
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Crystal size / mm <sup>3</sup>	0.32 x 0.16 x 0.12	0.23 x 0.11 x 0.04	0.38 x 0.06 x 0.03	0.48 x 0.21 xie0.04 cle Online
Theta range for data collection	1.44 to 27.87°	1.72 to 27.88°	$1.84$ to $27.88^{\circ}$	2.15 to 27.10°
Index ranges	$-18 \le h \le 18$	$-15 \le h \le 15$	$-15 \le h \le 16$	$-11 \le h \le 8$
	$-12 \le k \le 12$	$-9 \le k \le 9$	$-11 \le k \le 11$	$-12 \le k \le 11$
	$-25 \le l \le 25$	$-22 \le l \le 21$	$-19 \le l \le 18$	$-13 \le l \le 13$
Reflections collected	24935	12844	13456	5079
Independent reflections	6406 [ <i>R</i> (int) =	3377 [ <i>R</i> (int) =	3524 [ <i>R</i> (int) =	3133 [ <i>R</i> (int) =
	0.057]	0.089]	0.100]	0.067]
Data/restraints/parameters	6406/0/309	3377/0/164	3524/0/168	3133/0/167
Goodness-of-fit on $F^2$	0.934	1.008	0.765	0.824
Final <i>R</i> indexes $[I > 2\sigma(I)]$	R1 = 0.0499	R1 = 0.0537	R1 = 0.0544	R1 = 0.0522
	wR2 = 0.1064	wR2 = 0.1075	wR2 = 0.0865	wR2 = 0.0852
Largest diff. peak/hole / e Å <sup>-3</sup>	0.569/ -0.379	0.563 / -0.371	0.376 / -0.327	0.241 / -0.268

**Topological analysis.** Periodic calculations were performed at the B3LYP/6-31G(d,p) level with Crystal14 code.<sup>30</sup> Using the experimental estimations as the starting point, the coordinates of the hydrogen atoms in the crystal were optimized to minimize the B3LYP/6-31G\*\* crystal energy with heavy atom coordinates and cell parameters fixed at their experimental values. The topology of the resulting electron density was then analyzed using the TOPOND14 code.<sup>31,32</sup> For consistency with the periodic results, molecular and supramolecular electron densities were also analyzed with TOPOND98 from calculations performed with Crystal98 using geometry optimized with Crystal09.

*Lattice and interaction energies.* Lattice energy and intermolecular interaction energies for specific molecular pairs were calculated using the CLP (Coulomb–London–Pauli) approach implemented in the PIXEL program package.<sup>33, 34</sup>

*Hirshfeld surface calculations*. Hirshfeld surfaces and their associated two-dimensional fingerprint plots<sup>35-38</sup> were plotted using *CrystalExplorer*3.0 software.<sup>39</sup> The  $d_{norm}$  (normalized contact distance) surface and the breakdown of two-dimensional fingerprint plots were used for decoding and quantifying intermolecular interactions in the crystal lattice. The fingerprint plots can be decomposed to highlight particular atom pair close contacts,<sup>40</sup> which overlap in the full fingerprint. The  $d_{norm}$  is a symmetric function of distances to the surface from nuclei inside and outside the Hirshfeld surface ( $d_i$  and  $d_e$ , respectively), relative to their respective van der Waals

radii. 3D  $d_{norm}$  surfaces were mapped over a fixed color scale of -0.135 au (red) -0.460 eÅrate Online (blue). The 2D fingerprint plots were displayed by using the translated 0.6–2.6 Å range, and including reciprocal contacts. Electrostatic potentials on 0.008 e/au<sup>3</sup> isosurfaces were calculated at the HF/6-31G\* level by using Tonto program<sup>41</sup> integrated into *CrystalExplorer*. 3Ddeformation densities were plotted over the electron density isosurface (0.008 e/au<sup>3</sup>), charge depleted (CD) and charge concentrated (CC) regions were colored in red and blue, respectively.

The similarity/dissimilarity between the structures was evaluated using XPac2.0,<sup>42</sup> which allows identify and compare "supramolecular constructs" (SC) for pair of structures with the same space group and similar cell dimensions. The SC are sub-components of complete crystal structures of 0D, 1D (row of molecules match), 2D (layer of molecules match) and 3D similarity (isostructural systems). Furthermore, the XPac method establishes the dissimilarity index 'x' and the stretch parameter D as a measure of how far two crystal structures differ from perfect geometrical similarity.

# 3. Results

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# 3.1-Conformational Analysis

Molecular structures for compounds **1-4** are shown in Figures 1. In compound **1** there are two independent molecules (A and B) in the asymmetric unit. An overlay diagram of the molecules shows that the molecule A is virtually super-imposable upon the molecule B (Figure S1, ESI), and the *r.m.s* deviations with and without inversion are 1.712 and 0.54 Å, respectively, matching all non-H atoms. The major difference between the matched molecules is found in the twist of the axial-CH<sub>3</sub> with respect to C-Cl group, C107-C101...C114-Cl1 and C207-C201...C214-Cl2 pseudo-torsion angles being -172.8(2) and -3.4(2)° for molecules A and B, respectively. These results indicate that the axial-CH<sub>3</sub> and C-Cl groups lie on opposite sides of the heterocyclic plane in molecule A, and on the same side in molecule B.

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**Figure 1.** Views of the molecular structures of compounds **1-4** (two independent molecules, A and B, for compound **1**). Displacement ellipsoids are drawn at the 50% probability level. Atoms numbering are given and H-atoms are omitted for clarity.



In all structures rings are twisted each other around the N2-C(Ph) bond. The mean planes of the heterocyclic rings through four coplanar atoms make dihedral angles of 87.0(1)(average), 85.4(1), 87.7(1) and  $83.6(1)^{\circ}$  with the benzene ring for compounds **1**-**4**, respectively, as found in other families of 3,4-dihydropyrimidine-2(*1H*)-thione/one derivatives.<sup>43, 44</sup> However, the benzene ring is equatorial in structures **1**-**4**, and axial in the referred compounds,<sup>43, 44</sup> leading to extended and folded molecular conformations, respectively.

The ring puckering parameters<sup>45</sup> and the endocyclic torsion angles for the pyrimidine ring are shown in Tables S1 and S2 (ESI).

# 3.2-Crystal structures: a topological description

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A brief description of crystal structures of compounds **1-4** based on the main close shell online interactions characterized from an AIM topological analysis of the corresponding electron densities follows. The strategy consists in associating substructures of growing dimensionality with interactions of decreasing strength, using at this respect the criterion based on the values at the critical point of the electron density and the positive curvature of the Laplacian.<sup>46</sup>

The basic structural block in compound **1** is set up from two molecules that are linked through two N–H···S interactions (I and II in Table S3, ESI, and Figure 2), these being the most relevant from the topological view point. The computed H···S distances and N–H···S angles are 2.42/2.60 Å and 161/146°, for the two molecules (A/B) within the asymmetric unit, respectively (see Table S3), in qualitative good agreement with the experimental data (2.54/2.71 Å and 162/147°). Molecules in the pair are also linked each other by a H<sub>me</sub>···S interaction (VII). Connections between pairs through four S···H<sub>R</sub> interactions (III, IV, VI, and VIII) give rise to infinite chains along *a* axis direction (see Figure 2). Cl···H<sub>me</sub> interactions (V) acting between chains in two different directions complete the main three dimensional interaction network.

**Figure 2.** (a) Chain of pseudo-centrosymmetric pairs of molecules along *a* axis direction; (b) consecutive shackles of three chains in the crystal structure of compound **1**.



In compound **2** molecules are linked through one N–H…S, two H<sub>R</sub>…S and one H<sub>me</sub>…S interactions (I, II, III and IV in Table S4, ESI, and Figure 3) giving rise to infinite chains along *b* axis direction. Chains linked each other through pairs of H<sub>me</sub>…S interactions (VI in Table S3, ESI, and Figure 3) form layers parallel to (1 0 0). The main three dimensional interaction network is completed by Cl2…Cl2 interactions (V) connecting layers each other (see Figure 3). The computed  $d_{Cl}$ …Cl distance 3.38 Å, in perfect agreement with the experimental value.

Figure 3. (a) *b* axis direction view of a chain; (b) *b* axis direction view of two layers of compound 2.



The basic structural blocks of compounds **3** are centrosymmetric molecular pairs whose molecules are linked through a pair of rather strong N–H···S interactions, geometrically characterized by d<sub>H···S</sub> and  $\theta_{D-H···S}$  of 2.37 Å and 164°, respectively (I in Table S5 ESI, and Figure 4). Molecules in a pair are also linked each other by a pair of H<sub>me</sub>···S interactions (IV). Connections between molecular pairs through pairs of S···H<sub>R</sub> interactions (II) give rise to infinite chains along [1  $\overline{1}$  1] (see Figure 4). On the other hand, a second set of S···H<sub>R</sub> interactions (III) link centrosymmetric pairs in infinite chains along *b* axis direction. Combination of the two chain kinds originates layers parallel to ( $\overline{2}$  0 2).

**Figure 4.** (a) View along a direction perpendicular to  $(\overline{2} \ 0 \ 2)$  of infinite chains along  $[1 \ \overline{1} \ 1]$  and along *b* axis; (b) Layer view along *b* axis direction for compound **3**.

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For compound **4**, the basic substructures are also the centrosymmetric molecular pairs whose molecules are linked through a pair of NH···S interactions (computed  $d_{H...S}$  and  $\theta_{D-H...S}$ values are 2.42Å and 159°, respectively, see I in Table S6, ESI, and Figure 5). Connections between such molecular pairs through pairs of O···H<sub>me</sub> interactions (II) give rise to infinite chains along *a* axis direction (see Figure 5). Pairs of S···H<sub>R</sub> interactions (III) link chains each other originating layers parallel to (0 0 1). Connection between neighbor layers through O···H<sub>me</sub> interactions (IV) completes the main three dimensional interaction network.

Figure 5. (a) Infinite chain along *a* axis direction; (b) layer view along *a* axis direction of compound 4.

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# 3.3- Structural motifs and interaction energies

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For each crystal under consideration lattice energy and intermolecular interaction energies for specific molecular pairs were calculated using the CLP (Coulomb–London–Pauli) approach which enables partitioning of the total energy into their coulombic, polarization, dispersion and repulsion contributions. These results are summarized in Table 2.

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Table	2.	Lattice	energies	(kJ	$mol^{-1}$ )	partitioned	into	coulombic	$(E_{\rm coul}),$	polarization Ver Article Online DOI: 10.1039/C5CE02619B	
dispersion ( $E_{disp}$ ) and repulsion ( $E_{rep}$ ) components for <b>1–4</b> and related compounds.											

Compound	Ecoul	$E_{ m pol}$	$E_{ m disp}$	Erep	Етот
1	-75.6	-38.2	-148.6	124.7	-137.7
2	-71.1	-38.9	-161.3	121.8	-149.4
3	-72.2	-40.6	-138.2	115.3	-135.7
4	-86.4	-41.4	-143.8	123.1	-148.4
IJUGEA	-82.1	-40.5	-151.8	130.3	-144.2
DUNZIW	-74.8	-40.6	-154.1	122.8	-146.7
EVEWIM	-66.3	-32.7	-119.0	91.7	-126.2
VAGSUR	-68.9	-37.7	-127.3	102.2	-131.8
IMARIY	-74.3	-41.8	-133.1	116.0	-133.1
PUJYID	-66.7	-35.5	-141.5	110.7	-133.0
FAXVOQ-I	-69.9	-35.5	-130.8	105.0	-131.3
FAXVOQ-II	-65.3	-29.8	-132.2	97.5	-129.8

Detailed diagrams of crystal packing for structures 1-4 are shown in Figures S2-S5 (ESI) respectively, and the geometry of relevant intermolecular hydrogen bonds is listed in Table 3 (Column 4) following the distance criteria<sup>47</sup> for crystal packing analysis of supramolecular motif. In order to compare the packing modes of 1-4 with similar structures, a search of the (CSD,<sup>48</sup>  $1.19^{49}$ ) database ConOuest for 4,4,6-trimethyl-3,4crystal structural dihydropyrimidine-2(1H)-thione moiety was undertaken, yielding eight hits: two structures correspond to the *meta* (IJUGEA)<sup>50, 51</sup> and *para* (DUNZIW)<sup>9</sup> isomers of compound **1**. Other two related structures contain mono-substituents fluorine (EVEWIM)<sup>52</sup> and bromine (VAGSUR)<sup>53</sup> on the phenyl ring, while two structures are the ortho-methyl (IMARIY)<sup>25</sup> and meta-methyl isomers (PUJYID).<sup>10</sup> The unsubstituted compound is present as orthorhombic (FAXVOQ-I)<sup>23</sup> and triclinic (FAXVOQ-II)<sup>24</sup> polymorphs. Relevant data for these structures are also included in Table 3.

**Table 3**. Interaction energies ( $E_{\text{TOT}}$ ) partitioned into coulombic, polarization, dispersion and repulsion contributions (kJ mol<sup>-1</sup>) for various molecular pairs in **1**–**4** and related compounds.

	Compound	Symmetry	Involved	$d(\mathbf{H}\cdot\cdot\cdot A),$	Centroid	$E_{ m coul}$	$E_{ m pol}$	$E_{\rm disp}$	Erep	Етот
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		Interactions	$\angle D$ —H····A	distance			View Ar	ticle Online	
1	x, <sup>1</sup> /2-y,- <sup>1</sup> /2+Z	N11-H1A•••S2,	2.539(1), 162	7.534	-66.5	-38.4	-38.1	74.8	-68.2
		N21-H2A•••S1	2.707(1), 147						
	-x,1-y,1-z	C110-H11A···S1	2.901(1), 168	5.774	-28.4	-17.6	-44.4	42.6	-47.8
	x,-1+y,z	C207-H20G···Cl1	2.788(1), 172	8.532	-6.2	-3.2	-20.4	14.0	-15.9
	-x,2-y,1-z	$Cg \cdot \cdot \cdot Cg$	$4.104(1)^{a}$	7.746	-25.0	-9.5	-38.0	29.5	-43.0
2	-x,-1/2+y,1/2-z	N1-H1A· ··S1,	2.65(2), 163	7.135	-45.0	-25.5	-40.7	50.2	-61.0
		C9-H9A···S1	2.931(1), 161						
	$1-x,\frac{1}{2}+y,\frac{1}{2}-z$	C6-H6C•••Cl1	3.179(1), 128	6.841	-5.0	-2.5	-32.7	14.8	-25.4
	$1-x, -\frac{1}{2}+y, \frac{1}{2}-z$	Cl1···C12	$3.985(1)^{b}$	6.841	-5.0	-2.5	-32.7	14.8	-25.4
	1-x,1-y,-z	Cl2•••Cl2	$3.381(2)^{c}$	11.536	-2.8	-1.6	-8.8	9.1	-4.1
3	1-x,2-y,2-z	N1-H1A• ••S1	2.48 (2), 164	7.781	-80.7	-52.2	-40.1	94.3	-78.7
	$-\frac{1}{2}+x, 1.5-y, -\frac{1}{2}+z$	C5-H5A•••S1	2.989(1), 128	7.606	-14.1	-8.0	-28.4	22.4	-28.2
4	-x,2-y,-z	N2-H2···S1	2.529(1), 160	8.154	-79.1	-47.0	-39.5	87.5	-78 0
	1-x,1-y,-z	C3-H3A•••S1	2.929(1), 154	6.043	-28.1	-14.4	-40.4	34.5	-48.5
	-1+x,y,z	C12-H12A•••01	2.47(1), 154	8.729	-15.0	-5.7	-24.8	17.7	-27. 8
	2-x,-y,1-z	С7-Н7В•••О1	2.671(2), 130	12.869	-6.7	-2.5	-10.8	8.7	-112
IJUGEA	2-x,2-y,1-z	N1-H1A• ••S1	2.583(1), 162	7.944	-73.6	-43.2	-38.1	81.3	-75.0
	1-x,2-y,-z	С9-Н9•••С11	3.021(1), 120	5.773	-27.6	-14.1	-46.9	41.6	-47.0
DUNZIW	1-x,y,½-z	N3-H1•••S1	2.59(3), 169	8.299	-68.4	-45.0	-37.5	79.9	-71.0
	1.5-x,1.5-y,2-z	C15-H15· ··Cl1	3.049(1), 158	11.476	-3.0	-1.8	-12.7	7.5	-10.C
EVEWIM	1-x,-y,1-z	N1-H1A• ••S1	2.571(1), 162	7.628	-69.8	-41.2	-36.5	77.4	-//ບ 🗘
	-1+x,y,z	C3-H3A•••F1	2.649(2), 153	8.814	-8.5	-2.6	-15.1	7.5	-18.7
VAGSUR	-x,-y,-z	N2-H1•••S1	2.426(3), 170	7.920	-75.4	-48.7	-38.5	87.4	-1.1
•	x, <sup>1</sup> /2-y, <sup>1</sup> /2+Z	С5-Н8•••Ѕ1	2.981(3), 127	7.501	-13.3	-7.2	-27.1	20.6	-27.1
	1-x,1/2+y,1/2-z	C7-H11···Br1	3.072(2), 123	6.689	-3.6	-1.7	-24.2	11.2	-18 -
IMARIY	1-x,1-y,-z	N2-H2· ··S1	2.54(3), 169	7.347	-80.4	-52.8	-39.6	94.6	-76.1
·	<sup>1</sup> / <sub>2</sub> +x, <sup>1</sup> / <sub>2</sub> -y, <sup>1</sup> / <sub>2</sub> +z	C9-H9A•••S1	2.938(1), 130	7.586	-15.6	-8.3	-27.5	24.5	-26.8
PUJYID	x,y,z	N1-H1N• <b>··</b> S2,	2.621(1),151	7.528	-61.4	-40.2	-37.1	72.5	-66.2
		N3-H3N•••S1	2.596(1), 163						
FAXVOQ-I	x,y,z	N2-H2A· ··S2,	2.608(1), 158	7.292	-66.5	-38.9	-35.5	69.1	-71.7
		N4-H4A• ••S1	2.636(1), 167						
	-½+x,y,½-z	C12-H12A· ••S1	2.968(1), 155	5.063	-22.8	-13.5	-52.5	43.4	-45.5
FAXVOQ-II	1-x,1-y,2-z	N2-H2A• ••S1	2.707(1), 148	7.256	-61.4	-31.5	-36.6	64.3	-6: ?
	x,-1+y,z	C13-H13A•••S1	2.921(1), 166	8.649	-10.2	-4.8	-17.7	12.7	-26.1
C	<sup><i>i</i></sup> Inter-centroid dis	tance, Cg is the cent	roid of C109-C114	ring; <sup><i>b</i></sup> Cl····C	distance;	<sup>b</sup> Cl···Cl	distance	•	
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de	escription of the m	iam intermolecular	interactions using	g mirshield s	surface a	narysis I	have be	en	1
ca	urried out. Figure	6 shows surfaces m	happed over the d	norm propert	y, in a si	milar o	rientatio	on.	
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# 3.4- Hirshfeld surface analysis

For a better comprehension of the crystal packing for compounds 1-4, a complete description of the main intermolecular interactions using Hirshfeld surface analysis have been carried out. Figure 6 shows surfaces mapped over the  $d_{norm}$  property, in a similar orientation. The surfaces are shown as transparent to allow visualization of the molecules. Contacts with distances equal to the sum of the van der Waals radii are represented as white regions and the contacts with distances shorter than and longer than van der Waals radii are shown as red and blue colors, respectively.

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**Figure 6**. Views of the Hirshfeld surfaces mapped with  $d_{norm}$  in two orientations: from the vertical and back view (180° rotated around the vertical axis of the plot). Close contacts are labeled as follows: (1) S...H, (2) Cl...H, (3) H...H, (4) C...H, (5) O...H, (6) C...C, and (7) Cl...Cl.



A close examination with *Shape index* and *Curvedness*, which are Hirshfeld surface properties generally used to identify planar stacking arrangements,<sup>37</sup> was performed. The pattern of touching red and blue triangles on the *shape index* surfaces is characteristic of  $\pi$ - $\pi$ stacking.<sup>37</sup> This type of interaction is also evident as relatively large and green flat regions delineated by blue circles on the corresponding *Curvedness* surfaces.<sup>40</sup>

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The full two-dimensional fingerprint plots and decomposed fingerprint plots of the main Online internolecular interactions are depicted in Figure 7, and the relative contributions of individual intermolecular interactions to the Hirshfeld surface area of structures **1-4** and full two-dimensional fingerprint plots for eight related compounds are shown in Figures S7 and S8, respectively (ESI). For IJUGEA, our data are in close agreement with the Hirshfeld surface analysis recently reported by Babashkina et al.<sup>51</sup>

Figure 7. Full and decomposed 2D fingerprint plots of intermolecular contacts for 1-4.



3.5- Electrostatic potential and 3D deformation density

The surprising energy results about the relevance of the coulombic contributions formed in Control 1039/CECE2619B the studied structures prompted us to enhance the study of intermolecular interactions by analyzing the electrostatic potential (ESP) maps.<sup>54</sup> The ESP maps of compounds **1-4** are presented in Figures S9a-S12a in the ESI, and the magnitudes of electrostatic potentials for all twelve structures are given in Table S8 (ESI). In general, the ESP maps show an asymmetric charge distribution in the molecules, generating relevant polarization effects as reflected by high dipole moments ranging from 4.87 D for VAGSUR to 5.86 D for compound **3** (Table S8).

# **4-Discussion**

The dihydropyrimidine-2(1H)-thione rings of the studied species adopt a puckered conformation, and a description based on the canonical conformations for six-membered rings is given. In structure **1** (Mol. A), the pyrimidine ring adopts an intermediate conformation between a  ${}^{2}E$  and  ${}^{2}S_{1}$  screw-boat form, whereas in structures **1** (Mol. B) and **2** an E<sub>2</sub> envelope conformation with C101 and C1 atoms as flap atoms, respectively, is adopted. In compound **3** the heterocyclic ring adopts a conformation which is best described as an intermediate between a  ${}^{6}S_{1}$  screw-boat and  ${}^{6}H_{1}$  half-chair form. An E<sub>4</sub> envelope with apex at C10 atom for structure **4** is observed. The validity of these descriptions is borne out by the corresponding endocyclic torsion angles (Table S2, ESI). The thionyl and 4-methyl groups all have equatorial orientations, while the two 6-methyl groups present pseudo-equatorial orientations.

The similarity/dissimilarity between the twelve closely related structures was quantitatively analyzed.<sup>55</sup> The pair of *ortho*-substituted VAGSUR/IMARIY compounds revealed the presence of 3D-SC showing a high degree of isostructurality as reflected by 'x' and D values of 2.6 and 0.13 Å, respectively. The similarity/dissimilarity was also examined for the pairs **3**/IMARIY and **3**/VAGSUR structures, which showed SC with minor but similar degree of isostructurality, as reflected by ('x', D) values of (8.2, 0.49 Å) and (8.4, 0.36 Å),

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respectively. In spite of the same space group and relative similar cell dimensions for PUINALD Online and FAXVOQ-I structures, no significant structural similarity was found in this pair of compounds. No other pair of compounds presents isostructurality.

The topological analysis of the electron densities highlights the preponderance of N-H...S interactions in the stabilization of the crystal packing of the whole series of compounds here studied. In compound 1, two N-H. S interactions are observed for the two independent molecules in the asymmetric unit. For compounds 3 and 4 centrosymmetric molecular pairs are observed whose molecules are linked through such a pair of N-H...S interactions. Furthermore, non classical H<sub>me</sub>...S and S...H<sub>R</sub> are significant contributors in the stabilization of the dihydropyrimidine-2(1H)-thione synthon, as observed for compounds 1-4, and Cl. H<sub>me</sub> and  $Cl \cdots Cl$  are also observed for the chlorinated species 1 and 2.

Lattice energy values (Table 2) show that the dispersion energy  $(E_{disp})$  is the major contribution towards the crystal stabilization for all compounds as generally expected for organic species, with similar percentages ranging from 53.0 % in compound 4 to 59.5 % in compound 2. However, the coulombic component  $(E_{coul})$  is very significant for all structures representing the second higher contributor ranging from 26.2 % (compound 2) to 31.8 % (compound 4). A complementary description is obtained when the results of intermolecular energy calculations for selected molecular pairs are considered, as shown in Table 3. The occurrence of N-H...S hydrogen bonds forming  $R_2^2(8)$  motifs is a common feature for all structures except in compound 2 (Figures S2 and S3, ESI), generating molecular pairs with highest energy stabilization (from -78.7 kJ/mol for compound 3 to -61.0 kJ/mol for compound 2) in comparison with molecular pairs involving other types of contacts. PIXEL energies also reveal that the highest contribution towards the crystal stabilization in all compounds comes from coulombic component (40.5-47.8 %) only for molecular pairs involving N-H···S interactions, while for remaining interactions the dispersion energy is dominant.

The four chloro-substituted compounds here analyzed (1, 2, IJUGEA and DUNZIW Contrepresent the higher lattice energy values, indicating the relevant role of the chlorine atom in the crystal stabilization of these compounds. In these molecules, weak C–H····Cl hydrogen bonds are formed, creating dimers where the cohesive energy is ranging from -10 kJ/mol for DUNZIW to -25.4 kJ/mol for structure 2. On the other hand, VAGSUR and IMARIY compounds present similar dispersion (-127.3 and -133.1 kJ/mol) and total lattice energies (-131.8 and -133.1 kJ/mol). In the case of FAXVOQ-I and FAXVOQ-II polymorphic forms, the cohesive energy in the lattice is very similar, being the former more stable only in 1.5 kJ/mol. This suggests that changes in the space symmetry do not alter the total lattice energy of the unsubstituted compound.

Crystal packing of structure **1** is also characterized by the appearance of C-H...S hydrogen bonds generating  $R_2^2(12)$  motifs (-48.7 kJ/mol), which alternate with strong  $R_2^2(9)$ ring patterns along the *a*-axis (Figure S2). In the case of structure **2**, the lower coulombic contribution of 40.5 % can be attributed to an alternated combination of N-H...S and C-H...S hydrogen bonds forming weaker  $R_2^2(10)$  dimers (Figure S3) in two different molecular pairs with the same pairing energy (-61.0 kJ/mol). Unlike remaining structures, the  $R_2^2(9)$  rings involved in a pair molecular amounting up to 78.7 kJ/mol are interconnected by weaker C-H...S hydrogen bonds in structure **3** (Figure S4, ESI), which are associated to a lower intermolecular energy (-28.2 kJ/mol).

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In structure **4**, a  $R_2^2(14)$  descriptor is also observed interacting through weak C–H···S hydrogen bonds, as well as weak C–H···O hydrogen bonds due to the C7 atom in the molecule at (x, y, z) acting as donor to the O1 atom of methoxy group in the molecule at (2-x, -y, 1-z). This interaction generates dimers (-11.2 kJ/mol) with the formation of  $R_2^2(6)$  rings (Figure S5, ESI) and long inter-centroid distance of 12.869 Å. Another molecular pair involves C-H···O

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hydrogen bonds with increased intermolecular energy (-27.8 kJ/mol) and shorter centroid Online DOI: 10.1039/C6CE02619B distance of 8.729 Å.

The Hirshfeld surface analysis is in sound agreement with the computed interaction energy values. Thus, the large and red regions labeled 1 in Figure 6 are dominant in the  $d_{norm}$ maps for all compounds, and represent H…S contacts attributed to N–H…S hydrogen bonds, which form  $\mathbb{R}^2_2(\mathbf{9})$  cyclic dimers through the two larger and very close regions exhibiting similar brightness as in structures **1**, **3** and **4**. In the case of structure **2**, the two larger red spots are apart to each other and exhibit different brightness, indicating the combined participation of N–H and C–H donors where the sulfur atom acts as bifurcated acceptor. In compounds **1** and **2**, a pale blue to white spot labeled 2 on the front view of the surfaces shows Cl…H contacts associated to weak C–H…Cl hydrogen bonds. In compound **1**, distinctively to the others, a small red region labeled 6 depicts the presence of C…C contacts indicating  $\pi$ -stacking interactions [characterized by Cg…Cg= 4.104(1) Å and slippage = 2.435(1) Å], providing additional stabilization (-43.0 kJ/mol) to crystal packing (see also Figure S6).

In all structures, a significant presence of H…H, S…H and C…H contacts are found. The H…H interactions are highlighted in the middle of scattered points in full 2D fingerprint maps, with minimum values of ( $d_e + d_i$ ) around 2.4 Å. As expected, the H…H contacts are associated to molecular pairs with intermolecular energies (Table S7, ESI) lower than -15 kJ/mol for most of structures, being the dispersive forces the highest contributor (56-93 %) towards the packing stabilization, with  $E_{disp}$  values from -7.4 to -45.7 kJ/mol. The repulsion energy values are in the range 3.1-27.3 kJ/mol.

The Cl···H/H···Cl interactions are present in the two chloro-substituted compounds (1-2). In structure 1 two asymmetrical spikes appear in the fingerprint plot, which spread up to the shorter distance of  $(d_e + d_i) \approx 2.67$  Å at bottom right region, and  $(d_e + d_i) \approx 3.03$  Å at top left region, which indicate Cl···H/H····Cl contacts occurring between molecules A and B in the

asymmetric unit. The fingerprint plot of **2** ( $d_e + d_i \approx 3.10$  Å) displays two symmetrical Vietner Online Spikes contributing 22.5 % to the Hirshfeld surface area. The contributions to the Hirshfeld surface area due to Cl···H/H···Cl contacts are similar for monochloro-substituted compounds **1** (14.6 %) and IJUGEA (15.8 %, in good agreement with the value of 16.3 % reported in ref <sup>51</sup>), while significant Cl···C/C···Cl and Cl···Cl contacts are found for compound **2**, comprising 5.1 and 3.7 %, respectively.

The molecular ESP for molecule A of structure **1** (Figure S9a, ESI) reveals a highly polar molecule with a deep red region of strongly negative electrostatic potential (-0.082 au) surrounding the S2 atom, and a complementary deep blue region of strongly positive electrostatic potential (0.112 au) near the H1A hydrogen atom. These ESP values favor the formation of strong N–H···S contacts in this structure, supported by the high intermolecular energy value of -68.2 kJ/mol. In addition, an electronegative C–Cl group (-0.017 au on the surface) and an electropositive C–H group (0.043 au) are responsible for the formation of H···Cl contacts, which are electrostatically favored, and represent the weakest C207-H20G···Cl1 hydrogen bond interaction (-15.9 kJ/mol) in the self-assembly of structure **1**.

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For the 2,3-di-chloro-substituted compound **2**, high electropositive potential is observed near the H-atoms involving N–H···S (0.174 au) and C–H···S (0.139 au) hydrogen bonds (Figure S10a, ESI). These two intermolecular contacts are associated to a molecular pair with the highest interaction energy (-61.0 kJ/mol). It is interesting to note the reduced electronegative potentials of -0.027 and -0.022 au around the S1 atom in structure **2**. This can be explained considering that the sulfur atom participates as an acceptor in the formation of four hydrogen bonds and the total negative charge is distributed around the periphery of the S1 atom.

The molecular ESP surface for structure **3** (Figure S11a, ESI) displays similar electrostatic features to that in structure **1**, with a deep red region of strongly electronegative

potential (-0.086 au) surrounding the S1 atom, and a complementary deep blue area of strongler Online DOI: 10.1039/CCEE02619B electropositive potential (0.117 au) near the H1A hydrogen atom.

Like in structures 1-3, the ESP map of structure 4 (Figure S12a) shows strong N2–H2…S1 hydrogen bonds (-78.0 kJ/mol) as result of the high electrostatic interaction (-0.087/0.109 au) between complementary regions. Moreover, an electronegative O-atom and an electropositive H7B hydrogen atom with lower potentials of -0.063 au and 0.018 au, respectively, give rise to weaker C–H…O hydrogen bonds forming  $R_2^2(6)$  motifs associated to a molecular pair with minor interaction energy (-11.2 kJ/mol).

3D deformation density maps through the common N–H····S hydrogen bonds for compounds 1-4 (Figures S9b-12b, ESI) and additionally the Cl····Cl halogen bond<sup>56</sup> for structure 2 (Figure S10b) were also calculated for a better comprehension of the attractive nature in these interactions. It is clearly visible in all structures that the charge concentration (CC) region around the S-atom is attracted towards the charge depleted (CD) region on the Hatom of NH group in a neighbor molecule, confirming the formation of  $R_2^2(9)$  cyclic dimers through N–H···S hydrogen bonds. Finally, the map of structure 2 (Figure S10b) displays an interaction between two CD regions representing Cl2····Cl2 halogen bond, associated with a slightly attractive interaction (the E<sub>TOT</sub> is -4.1 kJ/mol, see Table 3). The characteristic asphericity of the electron distribution around terminally-bonded chlorine atoms,<sup>57</sup> reflects the high repulsion component of the lattice energy (9.1 kJ/mol, see Table 3) for this molecular pair.

# **5-Conclusions**

The crystal structures of four 4,4,6-trimethyl-3,4-dihydropyrimidine-2(1H)-thione derivatives were determined by single crystal X-ray diffraction. A complete investigation of the crystal packing was performed, including a comparison with eight closely related structures. Lattice energy determination indicates that the coulombic component has a relevant

contribution (around 30 %) to the total energy for all compounds. In the same direction of the online online on the same direction of the second sec

The presence of halogen substituents, mainly Cl atoms, offers the possibility of establishing further intermolecular interactions. The electrostatic potentials calculated for the three types of hydrogen bonds observed in the crystal packing vary in the same way for both chloro-substituted compounds, being highest for N–H…S hydrogen bond and lowest for C–H…Cl hydrogen bond. This is a clear evidence of the relative strength of these interactions, decreasing in the order N-H…S < C–H…S < C–H…Cl for compounds 1-4.

In summary, the nature of intermolecular interactions in crystal structures of dihydropyrimidine derivatives was fully analyzed, and it can be useful for the prediction of supramolecular motifs in this type of compounds. The occurrence of N-H…S=C hydrogen bonds forming  $R_2^2(\mathbf{S})$  motifs can be anticipated for the 3,4-dihydropyrimidine-2(*1H*)-thione group. This interaction is governed by coulombic components with minor influence of the 1-phenyl substitution.

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The cyclic pyrimidine-thione synthon is characterized through a complete analysis of intermolecular interactions for a series of twelve closely related dihydropyrimidine-2(1H)-thiones.

