ASM Sc. J., 15, 2021
https://doi.org/10.32802/asmscj.2020.495

Hirshfeld Surface Investigation of Intermolecular Interaction of N-Aroyl-N’-(2-pyridyl)thiourea Derivatives

Rafie Draman[1*] and Mohd Sukeri Mohd Yusof[2]

[1]*Faculty of Applied Science. Universiti Teknologi MARA. Terengganu Branch, Bukit Besi Campus*
[2]*Faculty of Science and Marine Environment. Universiti Malaysia Terengganu*

A detailed analysis of the intermolecular interactions of the crystalline structure of thiourea derivatives namely 1-(3-Methylbenzoyl)-3-(6-methyl-2-pyridyl)-thiourea, N-(2-Furoyl)-N’-(6-methyl-2-pyridyl)thiourea, 2-Methyl-N-[(3-methyl-2-pyridyl)-carbamothioyl]benzamide and 1-(4-Chlorobenzoyl)-3-(3-methylpyridin-2-yl)thiourea have been performed based on the Hirshfeld surfaces and their associated two-dimensional fingerprint plots. The result showed that the structures were stabilized by H···H, H···S, O···H, N···H, C–H···π, and $\pi\cdots\pi$ intermolecular interactions, which contribute mostly to the packing of the species in the crystal. The three largest contributions to the packing of the molecules in the crystals were provided by H···H, C–H···S and C··· H intermolecular interactions.

Keywords: thiourea; intermolecular interactions; hirshfeld surfaces; crystal structure

I. INTRODUCTION

Thiourea derivatives become a promising compound in material chemistry because they can form intra- and intermolecular hydrogen bonds. The combination of intra- and intermolecular hydrogen bonding strongly affects the chemical properties of these compounds (Custelcean, 2008; Obrzud et *al.* 2014; Solmaz *et al.* 2018; Saeed & Flörke 2007; Saeed. 2010). There are two conformational balances around the –C(C=O)–N–(C=S)N– moiety core of thiourea derivative compounds have been experimentally produced, which are *trans-cis* and *cis-trans* stabilized by intramolecular hydrogen bond of N–H···O and N–H···N respectively (Saeed *et a*l. 2014; Woldu & Dillen, 2008). In crystal packing, the majority of thiourea compounds displayed a characteristic intermolecular pattern forming dimers via N–H···S hydrogen bonding (Gomes *et al.* 2010). Some of the thiourea compounds the N–H group forming both an intramolecular and intermolecular N–H···O hydrogen bonds (Gunasekaran *et al.* 2010).

Hirshfeld surface analysis is the powerful tool to investigate and understand the characteristic of intermolecular contact relative to van der Waals radii within a crystal structure or as a surface around the molecule. This can be done by analysing 3D d_{norm} and 2D fingerprint plot (McKinnon *et al.* 2007; McKinnon *et al.* 2004). Recently, this system has been applied to investigate structure-directing interactions (Martin *et al.* 2015), intermolecular interactions in crystalline (Saeed *et al.* 2015; Martins *et al.* 2017; Sivajeyanthi *et al.* 2017; Lai *et al.* 2018; Boukhssas *et al.* 2018; Rajasekar *et al.* 2015) and supramolecular self-assembly (Saeed *et al.* 2016; Gumus *et al.* 2018; Seth *et al.* 2011).

Inspired by the relationship of the promising application of thiourea compound, availability of Crystallographic Information File (CIF) and a powerful tool, we decided to analyse our previously synthesized and reported compounds namely 1-(3-Methylbenzoyl)-3-(6-methyl-2-pyridyl)-thiourea (Yusof *et al.* 2006), N-(2-Furoyl)-N’-(6-methyl-2-pyridyl)thiourea (Hassan *et al.* 2007), 2-Methyl-N-[(3-methyl-2-pyridyl)-carbamothioyl]benzamide (Yamin *et al.*

---

*Corresponding author’s e-mail: rafiedraman@gmail.com

2008) and 1-(4-Chlorobenzoyl)-3-(3-methylpyridin-2-yl)thiourea (Yusof *et al.* 2011), designated as C1, C2, C3 and C4 respectively. This study aims to analyse the similarity and dissimilarity of intermolecular interaction in crystal packing.

II. COMPUTATIONAL METHOD

Crystal Explorer 17.5 (Turner *et al.* 2017) program is used to calculate Hirshfeld surface and the associated fingerprint plots by feeding it with the CIF file format as a structure input. A Hirshfeld surface is the outer contour of the space which a molecule or an atom consumes in a crystalline environment. Hirshfeld surfaces were mapped with d_{norm} property where it is a normalized contact distance, based on both d_e and d_i (distance from the point to the nearest nucleus external and internal to the surface respectively) and the van der Waals radii of the atom internal (r_i^{vdw}) and external (r_e^{vdw}), provide a 3D picture of intermolecular close contacts in a crystal. The d_{norm} is calculated equation (1), enables identification of the regions of particular importance to intermolecular interactions (Seth *et al.* 2011):

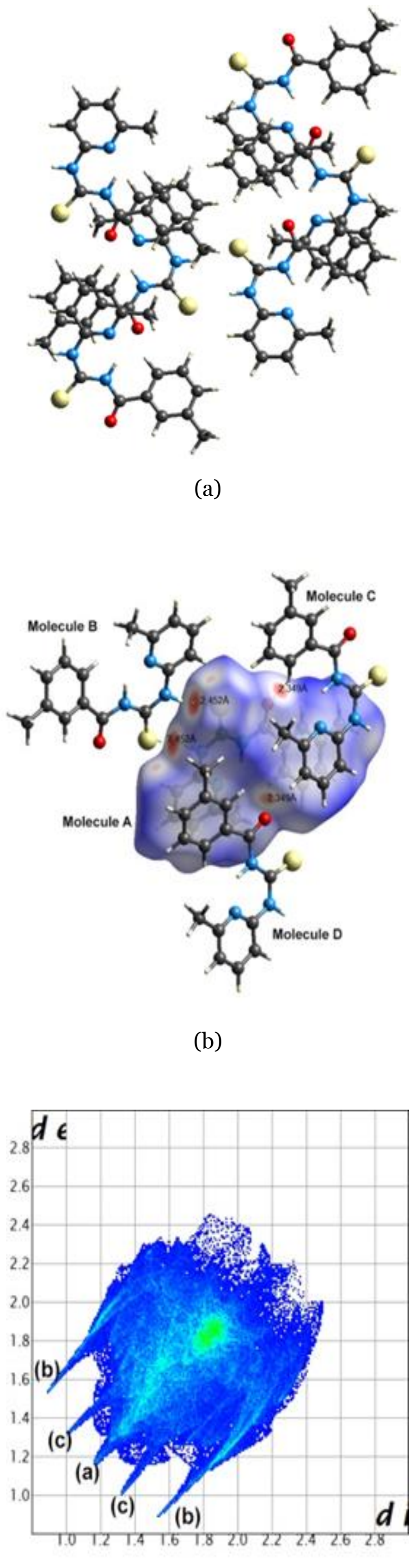
$$d_{norm} = \frac{(d_i - r_i^{vdw})}{r_i^{vdw}} + \frac{(d_e - r_e^{vdw})}{r_e^{vdw}} \qquad (1)$$

The value of the d_{norm} is negative or positive when intermolecular contacts are, respectively, shorter or longer than vdW separations. Because of the symmetry between d_e and d_i in the expression for d_{norm}, where two Hirshfeld surfaces touch, both will display a red spot identical in colour intensity as well as size and shape. The d_{norm} values are mapped onto the Hirshfeld surface using a red–blue-white colour scheme: red regions correspond to closer contacts and negative d_{norm} value, the blue regions correspond to longer contacts and positive d_{norm} value and the white regions are those where the distance of contacts is exactly the vdW separation and with a d_{norm} value of zero. The combination of d_e and d_i in the form of a 2D fingerprint plot are used for decoding and quantifying intermolecular interactions in the crystal lattice (McKinnon *et al.* 2007; Spackman & Jayatilaka, 2009).

III. RESULT AND DISCUSSION

The molecules of C1 are zig-zagging with eclipse between pyridyl and methyl benzyl groups between layer along the *'b'* axis. Therefore, the π-π base interaction plays a critical role in the solid-state of the structure, indicated by the blue-whitish colour. The N—H···S hydrogen bond and C—H···O contact self-assembly with the bond length of 2.452Å and 2.349 Å covered 14.5% and 10.2% (Table 1) respectively, indicated by the red spot on the d_{norm} plot (Figure 1b). This two self-assembly are shown in the fingerprint plot (Figure 1c) where the pairwise spike of C—H···O and N—H···S, with d_e + d_i sum of 2.6 Å and 3.2 Å label (a) and (b) respectively. The N—H···S/S···H—N intermolecular hydrogen bond originated from two molecules A - B within the layer but O···H—C and C—H···O intermolecular close contact occur between the layer of molecules A-C and A-D respectively.

Molecular stacking of C2 is in an eclipsed manner along the 'a' axis (Figure 2a). The d_{norm} plot (Figure 2b) shows reciprocal N—H···S hydrogen bond contact self-assembly of molecule A--B, with the bond length of 2.419Å indicated by the red spot. Furthermore, it is observed that the oxygen atom of the furoyl ring, oxygen atom of the carbonyl and nitrogen atom of the pyridyl ring are not involved in any close intermolecular contact, resulting in white-to-blue gradient colour. They involve in C—H···O and C—H···N contacts intermolecular van der Waals interaction between layers. In addition, methyl substituent form that C—H···π interaction with thiourea moiety conjugated system. The fingerprint plot (Figure 2c) only has three spikes where they belong to H···H contact with d_e + d_i sum of 2.4 Å labelled (a) covered 36.5 %, and a pair of N--H···S (b) contact (d_e + d_i = 3.0 Å) covered 17.9 % of the Hirshfeld surface. Both wings contributed to C···H/H···C contact. The O···H contacts (c) with less sharp spikes centred on (d_e + d_i) of 2.8 Å, attributed to C—H···O face to face contact contribute about 12.4 % of Hirshfeld surface. Another face to face interaction includes C—H···N van der Waals and C···C contact for π-π interaction leading to π stacking arrangement of the crystal is in the centre of the fingerprint plot.



(a)

(b)

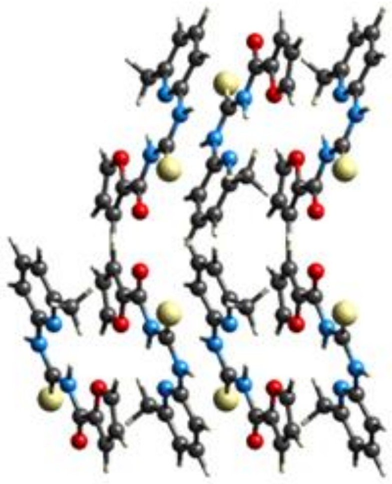
(c)

Figure 1. (a) Packing diagram, (b) d_{norm} surfaces and (c) Fingerprint plot of C1

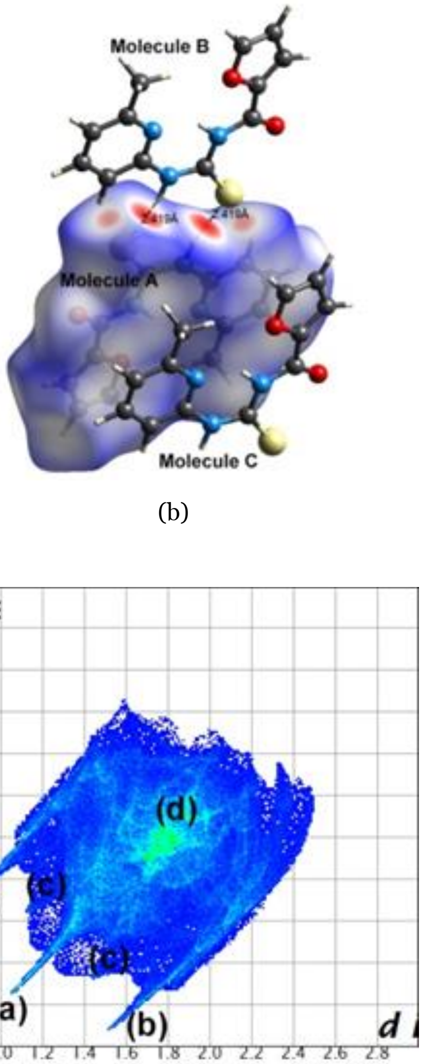
Table 1. Percentage of various intermolecular contacts contributed to the Hirshfeld surface

Interaction	Percentage of Hirshfeld, d_{norm} plot (%)			
	C1	C2	C3	C4
S···H	14.5	17.9	13.3	12.9
O···H	10.2	12.4	6.4	5.4
N···H	6.2	4.6	8.5	8.9
H···H	44.8	36.5	46.0	30.7
C···H	12.5	12.7	18.8	18.5
C···C	10.1	7.0	3.7	3.4
Cl···H				12.7
C···O				2.4

C3, the molecules pack in a herringbone arrangement along the *'c'* axis, stack in an eclipsed manner along the *'b'* axis and zigzag chain is visible when viewed from the *'a'* axis (Figure 3a). Methyl substituent on both pyridyl and phenyl ring give massive repulsion to sulphur and oxygen respectively, causing both rings largely twisted relative to the thiourea moiety. There is two major interaction that causes self-assembly for this compound. One is the N--H···O/O···H—N hydrogen bond for self-assembly of molecule A and C, and two is the N—H···C/C···H—N hydrogen bond contact form a reciprocal arrangement of molecule A and B, with the bond length of 2.183 Å and 2.513 Å respectively. Another close contact is the interaction in which C—H···S hydrogen bond diagonally interact between molecule A and D.



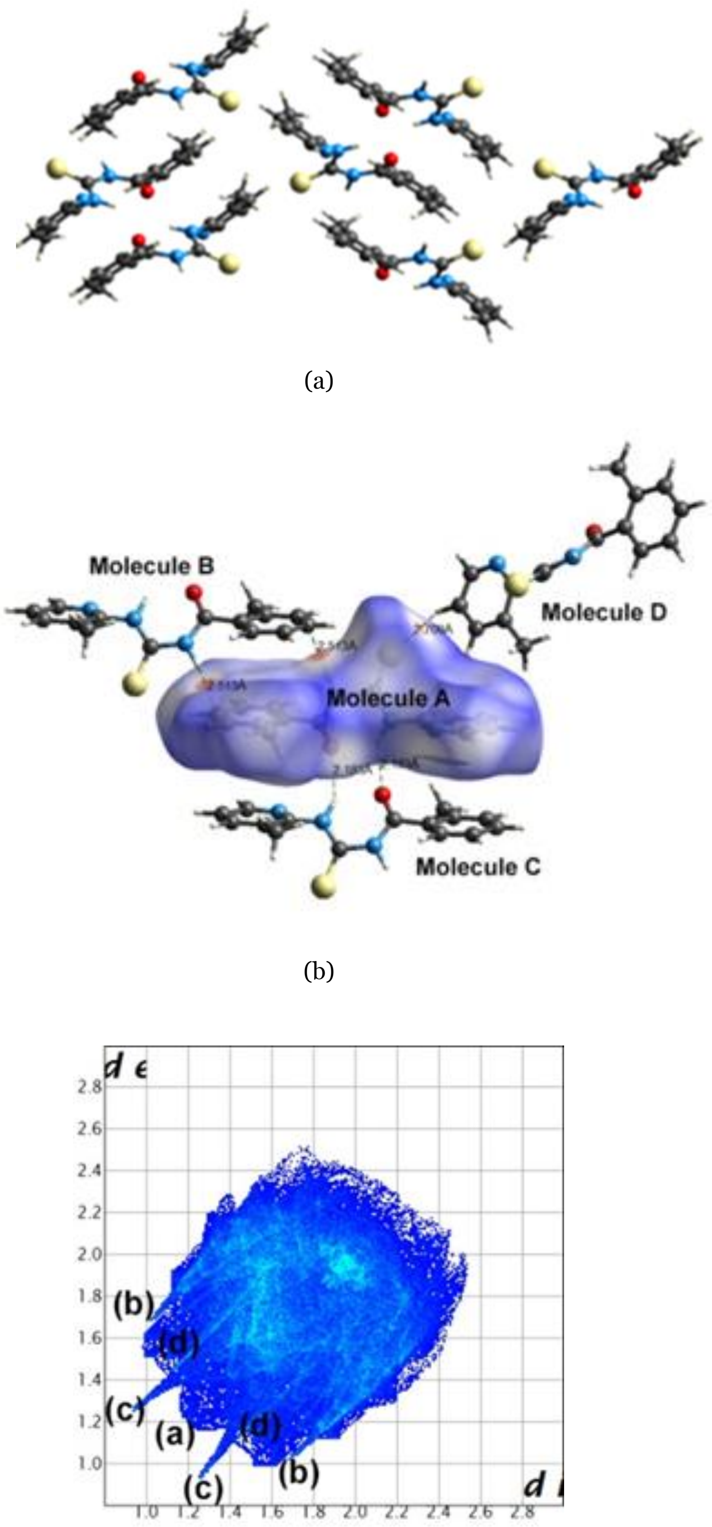
(a)



(b)

Figure 2. (a) Packing diagram, (b) d_{norm} surfaces and (c) Fingerprint plot of C2

On the other hand, there was increment between the interaction of C···H (18.8%) and N···H (8.5 %). Besides, the H···H spike is observed, but it is not as sharp as C1 and C2. All of these contacts were indicated by a deep red spot on the d_{norm} plot of Hirshfeld surface (Figure 3b). 2D fingerprint plot (Figure 3c) provides crucial insight of interaction differences between *cis-trans* and *trans-cis* conformation. Although it is dominated by H···H contacts (a) same as C1 and C2, C···C and O···H contact are significantly reduced to 3.7% and 6.4% respectively. Sharp spike for O···H interaction (c) with the sum value of $d_e + d_i$ is 2.6 Å is the closest contact for this compound. S···H spike (b) is lost because of overlapping of N···H and C···H (d) in fingerprint plot.



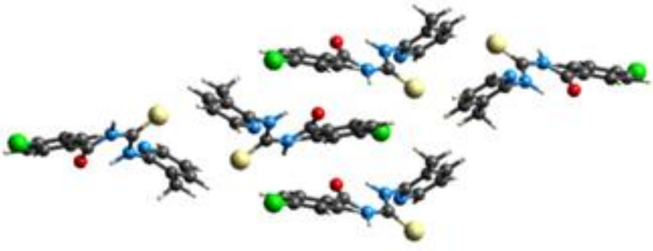
(a)

(b)

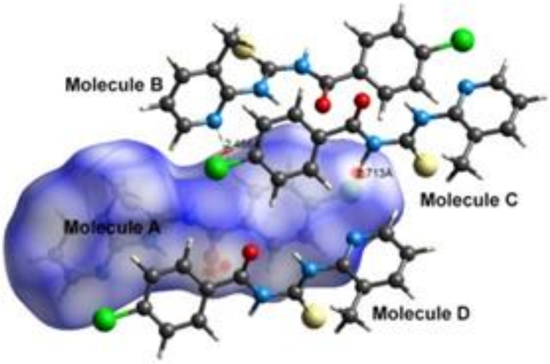
(c)

Figure 3. (a) Packing diagram, (b) d_{norm} surfaces and (c) Fingerprint plot of C3

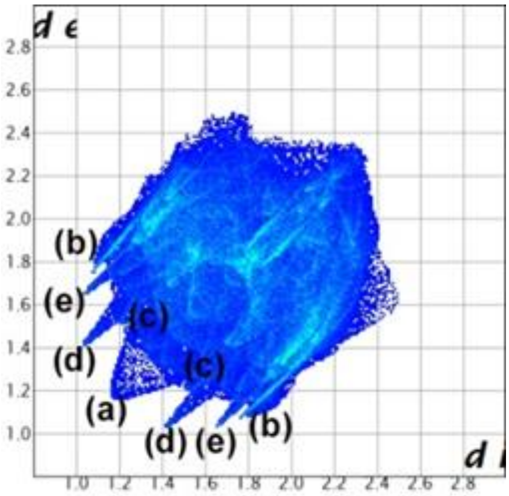
Molecules are stacked in an eclipsed manner down the *'b'* axis in C4 (Figure 4a). The twisted pyridyl ring caused by repulsion between methyl substituent and sulphur atom forbid it to form hydrogen bond instead allows nitrogen atom of pyridyl ring form C—H···N hydrogen-bonded between molecule A and B about 2.466Å. The halogen atom (Cl) produces contact between molecule A and C through Cl···H--N dipole interaction about 2.713 Å. Two adjacent red spots between molecule A and D in C4 are the contact of O···C for typical centrosymmetric loops. All are indicated by the red spot on d_{norm} plot (Figure 4b). White areas observed are side to side intermolecular contact in crystal packing. Fingerprint plot of C4 (Figure 4c) shows that H···H (a) and N···H (b) contacts have the same $d_e + d_i$ value of 2.4Å and covered 30.7% and 5.4%. of Hirsfeld plot respectively and it is the lowest compare to C1, C2 and C3. The third spike is the Cl···H contact (e). The two wings of the plot are the interaction of S···H and C···H contact overlapping each other (b), and O···H contact is concentrated in the middle of the plot (c).



(a)



(b)



(c)

Figure 4. (a) Packing diagram, (b) d_{norm} surfaces and (c) Fingerprint plot of C4

IV. CONCLUSION

The solid structures of Compound C1-C4 are stabilized π···π stacking interactions and H···H the contact is the main contribution of intermolecular interaction. Heterocyclic aromatic atom contributes to non-conventional C–H···O and C–H···N hydrogen bond, and substituent group plays a major contribution to C–H···π intermolecular interaction and extra dipole interaction C–H···Cl. The type of intermolecular interaction depends on the constituent of the structure. The position and the orientation of the intermolecular interaction depend on the conformation and orientation of the molecule in the crystalline structure. Generally, the molecule that has the same constituent, but different position substituent group should have the same type of interaction but in different location and orientation.

V. REFERENCES

Boukhssas, S, Aouine, Y, Faraj, H, Alami, A, El Hallaoui, A, Tijani, N, Yamni, K, Zouihri, H, Mrani, D & Lachkar, M. 2018, 'Hirshfeld Surface Analysis and DFT calculations of 1-phenyl-N-(benzomethyl)-N-({1-[(2-benzo-4-methyl-4,5-dihydro-1,3-oxazol-4-yl)methyl]-1H-1,2,3-triazol-4-yl}methyl)methanamine', *J. Mater. Environ. Sci.*, vol. 9, no. 8, pp. 2254-2262.

Custelcean, R 2008, 'Crystal engineering with urea and thiourea hydrogen-bonding groups', *Chemical Communications*, vol. 3, pp. 295-307.

Gomes, LR, Santos, LMNBF, Coutinho, JA, Schröder, B & Low, JN 2010, 'N′-Benzoyl-N, N-diethylthiourea: a monoclinic polymorph', *Acta Crystallographica Section E: Structure Reports Online*, vol. 66, no. 4, pp. o870-o870.

Gumus, L, Solmaz, U, Binzet, G, Keskin, E, Arslan, B & Arslan, H 2018, 'Supramolecular self-assembly of new thiourea derivatives directed by intermolecular hydrogen bonds and weak interactions: crystal structures and Hirshfeld surface analysis', *Research on Chemical Intermediate*, pp. 1-30.

Gunasekaran, N, Karvembu, R, Ng, SW & Tiekink, ER 2010, '1-Benzoyl-3, 3-bis (propan-2-yl) thiourea', *Acta Crystallographica Section E: Structure Reports Online*, vol. 66, no. 8, pp. o2113-o2113.

Hassan, NNN, Kadir, MA., Yusof, MSM, & Yamin, BM 2007, 'N-(2-Furoyl)-N′-(6-methyl-2-pyridyl) thiourea', *Acta Crystallographica Section E: Structure Reports Online*, vol. 63, no. 11, pp. o4224-o4224

Lai, LC, Rahman, CNBCA, Tahir, MIM, Ravoof, TB, Jotani, MM & Tiekink, ER 2018, '3-Methyl-1-{(E)-[1-(4-methylpyridin-2-yl) ethylidene] amino} thiourea: crystal structure and Hirshfeld surface analysis', *Acta Crystallographica Section E: Crystallographic Communications*, vol. 74, no. 2, pp. 256-260.

Martin, AD, Britton, J, Easun, TL, Blake, AJ, Lewis, W & Schröder, M 2015, 'Hirshfeld surface investigation of structure-directing interactions within dipicolinic acid derivatives', *Crystal Growth & Design*, vol. 15, no. 4, pp. 1697-1706

Martins, BB, Bresolin, L, de Farias, RL, de Oliveira, AB & Gervini, VC 2017, 'Crystal structure, Hirshfeld analysis and molecular docking with the vascular endothelial growth factor receptor-2 of (3Z)-5-fluoro-3-(hydroxyimino) indolin-2-one', *Acta Crystallographica Section E: Crystallographic Communications*, vol. 73, no. 7, pp. 987-992.

McKinnon, JJ, Jayatilaka, D, & Spackman, MA 2007, 'Towards quantitative analysis of intermolecular interactions with Hirshfeld surfaces', *Chemical Communications*, vol. 37, pp. 3814-3816.

McKinnon, JJ, Spackman, MA, & Mitchell, AS 2004, 'Novel tools for visualizing and exploring intermolecular interactions in molecular crystals', *Acta Crystallographica Section B*, vol. 60, no. 6, pp. 627-668.

McKinnon, JJ, Jayatilaka, D & Spackman, MA 2007, 'Towards quantitative analysis of intermolecular interactions with Hirshfeld surfaces', *Chemical Communications*, vol. 37, pp. 3814-3816.

Obrzud, M, Rospenk, M & Koll, A 2014, 'Self-aggregation mechanisms of N-alkyl derivatives of urea and thiourea', *Physical Chemistry Chemical Physics*, vol. 16, no. 7, pp. 3209-3219.

Rajasekar, M, Muthu, K, Aditya Prasad, A, Agilandeshwari, R & Meenakshisundaram, SP 2015, 'Synthesis, growth, structure and characterization of molybdenum zinc thiourea complex crystals', *Acta Crystallographica Section B: Structural Science, Crystal Engineering and Materials*, vol. 71, no. 3, pp. 285-292.

Saeed, A, Ashraf, S, Flörke, U, Espinoza, ZYD, rben, MF & Pérez, H 2016, 'Supramolecular self-assembly of a coumarine-based acylthiourea synthon directed by π-stacking interactions: Crystal structure and Hirshfeld surface analysis', *Journal of Molecular Structure*, vol. 1111, pp. 76-83.

Saeed, A, Bolte, M, Erben, MF, & Pérez, H 2015, 'Intermolecular interactions in crystalline 1-(adamantane-1-carbonyl)-3-substituted thioureas with Hirshfeld surface analysis', *Cryst. Eng. Comm.*, vol. 17, no. 39, pp. 7551-7563.

Saeed, A, Erben, MF, & Flörke, U 2010, 'Effect of fluorine substitution on the crystal structures and vibrational properties of phenylthiourea isomers', *Journal of Molecular Structure*, vol. 982., no. 1, pp. 91-99.

Saeed, A, & Flörke, U 2007, '1-(3-Methoxyphenyl)-3-(4-methylbenzoyl) thiourea', *Acta Crystallographica Section E: Structure Reports Online*, vol. 63, no. 9, pp. o3695-o3695.

Saeed, A, Flörke, U, & Erben, MF 2014, 'A review on the chemistry, coordination, structure and biological properties of 1-(acyl/aroyl)-3-(substituted) thioureas', *Journal of Sulfur Chemistry*, vol. 35, no. 3, pp. 318-355.

Seth, SK, Saha, NC, Ghosh, S & Kar, T 2011, 'Structural elucidation and electronic properties of two pyrazole derivatives: A combined X-ray, Hirshfeld surface analyses and quantum mechanical study', *Chemical Physics Letters*, vol. 506, no. 4, pp. 309-314.

Seth, SK, Sarkar, D, Roy, A & Kar, T 2011, 'Insight into supramolecular self-assembly directed by weak interactions in acetophenone derivatives: crystal structures and Hirshfeld surface analyses', *Cryst. Eng. Comm.*, vol. 13, no. 22, pp. 6728-6741.

Sivajeyanthi, P, Jeevaraj, M, Edison, B & Balasubramani, K 2017, 'Crystal structure and Hirshfeld surface analysis of (E)-4-amino-N-[1-(4-methylphenyl)ethylidene] benzohydrazide', *Acta Crystallographica Section E: Crystallographic Communications*, vol. 73, no. 7, pp. 1029-1032.

Solmaz, U, Gumus, I, Binzet, G, Celik, O, Balci, GK, Dogen, A & Arslan, H 2018, 'Synthesis, characterization, crystal structure, and antimicrobial studies of novel thiourea derivative ligands and their platinum complexes', *Journal of Coordination Chemistry*, vol. 71, no. 2, pp. 200-218.

Spackman, MA. & Jayatilaka, D 2009, 'Hirshfeld surface analysis', *Cryst. Eng. Comm.*, vol. 11, no. 1, pp.19-32.

Turner, MJ, MacKinnon, JJ, Wolff, SK, Grimwood, DJ, Spackman, PR, Jayatilaka, D & Spackma, MA 2017, *Crystal Explorer Ver. 17.5*, The University of Western Australia.

Woldu, MG & Dillen, J 2008, 'A quantum mechanical study of the stability and structural properties of substituted acylthiourea compounds', *Theoretical Chemistry Accounts*, vol. 121, no. 1-2, pp. 71-82.

Yamin, BM, Yousuf, S, Yusof, MSM, & Jusoh, RH 2008, '2-Methyl-N-[(3-methyl-2-pyridyl)carbamothioyl] benzamide', Ac*ta Crystallographica Section E: Structure Reports Online*, vol. 64, no. 5, pp. o833-o833.

Yusof, MSM, Tajuddin, NA & Yamin, BM 2006, '1-(3-Methylbenzoyl)-3-(6-methyl-2-pyridyl) thiourea', *Acta Crystallographica Section E: Structure Reports Online*, vol. 62, no. 8, pp. o3242-o3244.

Yusof, MSM, Mushtari, NA, Kadir, MA, & Yamin, BM 2011, '1-(4-Chlorobenzoyl)-3-(3-methylpyridin-2-yl) thiourea', *Acta Crystallographica Section E: Structure Reports Online*, vol. 67, no. 9, pp. o2367-o2367.