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Synthesis and Structural Characterization of Isostructural 4-(4-Aryl)-2-(5-(4-fluorophenyl)-3-(1-(4-fluorophenyl)-5-methyl-1*H*-1,2,3-triazol-4-yl)-4,5-dihydro-1*H*-pyrazol-1-yl)thiazoles

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Abstract: 4-(4-Chlorophenyl)-2-(5-(4-fluorophenyl)-3-(1-(4-fluorophenyl)-5-methyl-1*H*-1,2,3-triazol-4-yl)-4,5-dihydro-1*H*-pyrazol-1-yl)thiazole (**4**) and 4-(4-fluorophenyl)-2-(5-(4-fluorophenyl)-3-(1-(4-fluorophenyl)-5-methyl-1*H*-1,2,3-triazol-4-yl)-4,5-dihydro-1*H*-pyrazol-1-yl)thiazole (**5**) have been synthesized in high yields. Crystallization of **4** and **5** from dimethylformamide solvent produced samples suitable for structure determination by single crystal diffraction. The materials are isostructural with triclinic, P$\bar{1}$ and symmetry and comprise two independent molecules in the asymmetric unit. The two independent molecules in the asymmetric unit assume similar conformation. The molecule is essentially planar apart from one of the two fluorophenyl groups, which is oriented roughly perpendicular to the plane of the rest of the molecule.

Keywords: crystal structure; heterocycle; 1,2,3-triazole; 1,3-thiazole; biological activity; 4,5-dihydro-1*H*-pyrazole; synthesis

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1. Introduction

The progressive development of microbial resistance to current drugs is of global concern and, consequently, the design and synthesis of new medications are an ongoing challenge [1]. The majority (85%) of biologically active compounds contain different heterocycles and hence the synthesis of new molecules is important for the quest to generate potential additions to the established heterocyclic systems for therapeutic use [2].

1,2,3-Triazoles are highly stable heterocycles that have a wide range of medicinal applications [3]. They have anti-HIV, anticancer, antibacterial, anti-inflammatory, antitubercular and antiviral activities [4–16]. The common synthetic routes for 1,2,3-triazoles include 1,3-dipolar cycloaddition between azides and terminal alkynes [17]. However, the procedure results in a mixture of 1,4-disubstituted and 1,5-disubstituted 1,2,3-triazoles due to poor regioselectivity. The use of a copper(I)-catalyzed version of azide–alkyne cycloaddition and click chemistry approaches resulted in the production of various substituted 1,2,3-triazoles in high yields [18–22].

Pyrazoline-containing heterocycles are involved in different therapeutic applications. They are used as antimicrobial, anti-inflammatory, analgesic, antidepressant and anticancer agents [23–25]. Many pyrazolines exist in vitamins, pigments, alkaloids and cells of many plants and animals [26]. Substituted pyrazolines can be synthesized in one-pot procedures. For example, condensation of carbonyl compounds and hydrazine hydrochloride in methanol for 1 h at 65 °C produced substituted pyrazolines [27]. They can also be produced from 3-butynol and arylhydrazines through hydrohydrazination in the presence of a catalyst containing zinc [28].

1,3-Thiazoles exist in nature and have diverse pharmacological applications as bioactive compounds. For example, tiazofurin, ritonavir, ravuconazole, nitazoxanide, fanetizole, meloxicam, fentiazac, nizatidine and thiamethoxam act as antimicrobial agents [29,30]. The synthesis of compounds containing the thiazole system is therefore a useful venture due to their potential for medicinal applications. Recent synthetic procedures for 1,3-thiazoles include a copper-catalyzed oxidative reaction of aldehydes and amines in the presence of sulfur [31]. Furthermore, the Hantzsch condensation of thiourea and 2-bromoacetophenones provided 2-aminothiazoles [32]. Recently, we have synthesized a number of heterocycles containing pyrazole, thiazole and 1,2,3-triazole moieties [33,34] and some crystal structures have been established [35,36].

This work involved the synthesis of 4-(4-chlorophenyl)-2-(5-(4-fluorophenyl)-3-(1-(4-fluorophenyl)-5-methyl-1*H*-1,2,3-triazol-4-yl)-4,5-dihydro-1*H*-pyrazol-1-yl)thiazole (**4**) and 4-(4-fluorophenyl)-2-(5-(4-fluorophenyl)-3-(1-(4-fluorophenyl)-5-methyl-1*H*-1,2,3-triazol-4-yl)-4,5-dihydro-1*H*-pyrazol-1-yl)thiazole (**5**). The crystal structures obtained enabled a comparison of the structural properties of the materials; the structures are identical in this case. The study of isostructurality in crystalline solids contributes to the general understanding of the factors that may be important in the design of solid materials for particular applications [37]. Investigation of the properties of isostructural materials containing different substituents continues to attract interest [38–41], including compounds in which different halogens have been exchanged [42–44]. Although it is not surprising that two similar molecules can display similar structural properties, it is not a certainty that this will be the case. Thus, for example, 3-chlorocinnamic acid and 3-bromocinnamic acid can display different crystal structures [45] and, indeed, one molecule can crystallize in more than one crystal structure type, as observed for 3-chlorobenzoic acid [46,47].

Compounds **4** and **5** allow a comparison of isostructural chloro and bromo derivatives of 4-(4-aryl)-2-(5-(4-fluorophenyl)-3-(1-(4-fluorophenyl)-5-methyl-1*H*-1,2,3-triazol -4-yl)-4,5-dihydro-1*H*-pyrazol-1-yl)thiazole. Rationalization of intermolecular contacts may, for example, reveal information about possible interactions with binding sites in therapeutic application. A potential application of **4** and **5** and related compounds is as therapeutics. An example is 4-(4-chlorophenyl)-2-(5-(4-fluorophenyl)-3-(5-methyl-1-*p*-tolyl-1*H*-1,2,3-triazol-4-yl)-4,5-dihydro-1*H*-pyrazol-1-yl)thiazole, which displays antimicrobial activity [48]. However, the focus of this work was the synthesis and characterization of new materials.

2. Materials and Methods

2.1. General

IR spectra of compounds **4** and **5** were recorded on a AIM-9000 Shimadzu spectrometer. ^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectra of compounds **4** and **5** were recorded on JEOL spectrometers in DMSO-d_6 as solvent. Compound **1** was synthesized following a reported procedure [49]. The IR, ^{1}H and ^{13}C NMR spectra, CIFs and checkcif reports for compounds **4** and **5** are available in the supplementary material.

2.2. Synthesis of **2**

A mixture of **1** (1.20 g, 5.0 mmol) and 4-fluorobenzaldehyde (0.62 g, 5.0 mmol) in EtOH (15 mL) containing NaOH (0.8 g) was stirred for 4 h at room temperature. The solid obtained was added to an ice/water (100 mL) mixture, filtered, dried and recrystallized from dimethylformamide to produce colorless crystals of **2** (M.p. 168–170 °C) in 90% yield.

2.3. Synthesis of **3**

A mixture of **2** (0.97 g, 3.0 mmol) and thiosemicarbazide (0.30 g, 3.0 mmol) in EtOH (15 mL) containing NaOH (0.30 g, 2.5 mol) was refluxed for 2 h. The solid formed upon cooling was filtered, dried and recrystallized from dimethylformamide to produce colorless crystals of **3** (M.p. 229–231 °C) in 87% yield.

*2.4. Synthesis of **4** and **5***

A mixture of **3** (0.40 g, 1.0 mmol) and 4-chloro- or 4-bromophenacyl bromide (1.0 mmol) in dry EtOH (15 mL) was refluxed for 2 h. The solid produced was filtered, dried and recrystallized from dimethylformamide to produce **4** (M.p. 267–268 °C) in 82% yield or **5** (M.p. 275–276 °C) in 85% yield, respectively, as pale-yellow crystals. **Compound 4:** IR (KBr) ν_{max}: 1544 (C=N) and 1604 (C=C) cm^{-1}. ^{1}H NMR: δ 2.47 (s, 3H, Me), 3.42 (dd, *J* = 3.5 and 17.2 Hz, 1H), 4.16 (dd, *J* = 11.3 and 17.2 Hz, 1H), 5.66 (m, 1H), 7.18 (t, *J* = 7.7 Hz, 2H, Ar), 7.36–7.39 (m, 3H, Ar), 7.46–7.49 (m, 4H, Ar) and 7.70–7.71 (m, 4H, Ar). ^{13}C NMR: δ 10.47, 44.85, 63.16, 105.78, 115.91 (d, J_{C-F} = 21.5 Hz), 117.25 (d, J_{C-F} = 22.7 Hz), 127.71, 128.31 (d, J_{C-F} = 8.4 Hz), 129.08, 129.34 (d, J_{C-F} = 8.3 Hz), 132.34, 132.53, 134.69 (d, J_{C-F} = 88.2 Hz), 137.86 (d, J_{C-F} = 78.7 Hz), 148.28, 149.86, 161.58 (d, J_{C-F} = 121.6 Hz), 162.55 (d, J_{C-F} = 122.5 Hz) and 165.18. **Compound 5:** IR (KBr) ν_{max}: 1572 (C=N) and 1602 (C=C) cm^{-1}. ^{1}H NMR: δ 2.47 (s, 3H, Me), 3.43 (dd, *J* = 3.6 and 18.1, 1H), 4.15 (dd, *J* = 11.4 and 18.1 Hz, 1H), 5.65 (m, 1H), 7.18 (t, *J* = 7.8 Hz, 2H, Ar), 7.38 (s, 1H, Ar), 7.49–7.52 (m, 6H, Ar), 7.62 (d, *J* = 7.8 Hz, 2H, Ar) and 7.64–7.65 (m, 2H, Ar). ^{13}C NMR: δ 10.48, 44.84, 63.14, 105.87, 115.91 (d, J_{C-F} = 21.5 Hz), 117.25 (d, J_{C-F} = 22.7 Hz), 121.12, 128.01, 128.30 (d, J_{C-F} = 8.3 Hz), 129.36 (d, J_{C-F} = 8.3 Hz), 131,99, 132.33, 134.36 (d, J_{C-F} = 45.3 Hz), 137.86 (d, J_{C-F} = 78.7 Hz), 148.29, 148.29, 149.90, 161.57 (d, J_{C-F} = 120.4 Hz), 163.53 (d, J_{C-F} = 121.3 Hz) and 165.17.

2.5. X-ray Crystal Structure

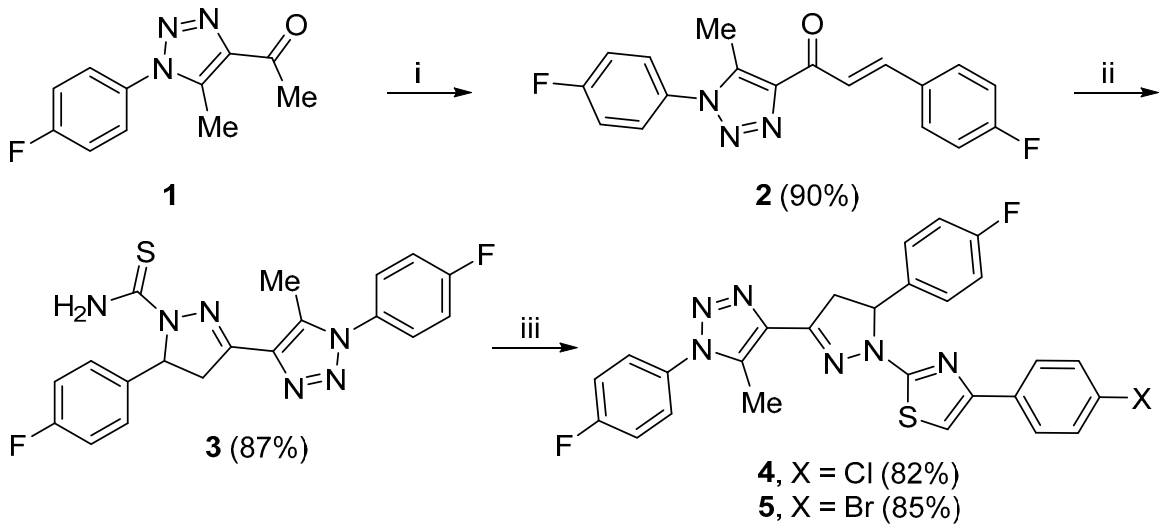
Single-crystal XRD data were recorded at ambient temperature on an Agilent SuperNova Dual Atlas diffractometer (mirror monochromator, MoKα (λ = 0.71073 Å) radiation). Crystal structures were solved by direct methods using SHELXS [50] and refined using SHELXL2018 [51]. Non-hydrogen atoms were refined with anisotropic displacement parameters. Hydrogen atoms were inserted in idealized positions and refined using a riding model with Uiso(H) set to 1.2 or 1.5 times the value of Ueq(C) for the atoms to which they are bonded. CCDC 2077559 and 2077560 contain the supplementary crystallographic data for this paper. Hirshfeld surfaces were calculated using CrystalExplorer [52,53].

3. Results and Discussion

*3.1. Synthesis of Compounds **4** and **5***

Compounds **4** and **5** were synthesized using a multi-step reaction from 1-(1-(4-fluorophenyl)-5-methyl-1*H*-1,2,3-triazol-4-yl)ethanone (**1**) via 3-(4-fluorophenyl)-1-(1-(4-fluorophenyl)-5-methyl-1*H*-1,2,3-triazol-4-yl)prop-2-en-1-one (**2**) and 5-(4-fluorophenyl)-3-(1-(4-fluorophenyl)-5-methyl-1*H*-1,2,3-triazol-4-yl)-4,5-dihydro-1*H*-pyrazole-1-carbothio amide (**3**) as intermediates. Reaction of **3** and 2,4′-dibromoacetophenone or 2-bromo-4′-chloroacetophenone under reflux in ethanol (EtOH) produced 4-(4-chlorophenyl)-2-(5-(4-fluorophenyl)-3-(1-(4-fluorophenyl)-5-methyl-1*H*-1,2,3-triazol-4-yl)-4,5-dihydro-1*H*-pyrazol-1-yl)thiazole (**4**) or 4-(4-bromophenyl)-2-(5-(4-fluorophenyl)-3-(1-(4-fluorophenyl)-5-methyl-1*H*-1,2,3-triazol-4-yl)-4,5-dihydro-1*H*-pyrazol-1-yl)thiazole (**5**) in 82% or 85% yield, respectively (Scheme 1).

The structures of compounds **4** and **5** were confirmed using IR, ^{1}H and ^{13}C NMR spectroscopy. The IR spectra showed characteristic absorption bands in the 1544–1572 cm^{-1} and 1602–1604 cm^{-1} regions due to the stretching vibrations of the C=N and C=C groups, respectively. The ^{1}H NMR spectra showed separate peaks for the methylene protons in the pyrazoline moiety, indicating that they are diastereotopic. In addition, the ^{13}C NMR spectra confirmed the coupling between carbon and fluorine atoms and showed overlap between the signals of some carbons.



Scheme 1. Synthesis of **4** and **5**.

*3.2. Crystal Structures of **4** and **5***

Compounds **4** and **5** are isostructural as evidenced by their similar unit cell parameters and triclinic, P$\bar{1}$, symmetry (Table 1). The molecules of **4** and **5** comprise linked systems of rings (Figure 1). The rings are chloro/bromo-phenyl [**A** (C1-C6, Cl1/Br1), (C28-C33, Cl2/Br2)], thiazolyl [**B** (C7-C9, N1, S1), (C34-C36, N7, S2)], pyrazolyl [**C** (C10-C12, N2, N3), (C37-C39, N8, N9)], fluorophenyl [**D** (C13-C18, F1), (C40-C45, F3)], methyltriazolyl [**E** (C19-C21, N4-N6), C46-C48, N10-N12)] and a second fluorophenyl [**F** (C22-C27, F2), (C49-C54, F4)].

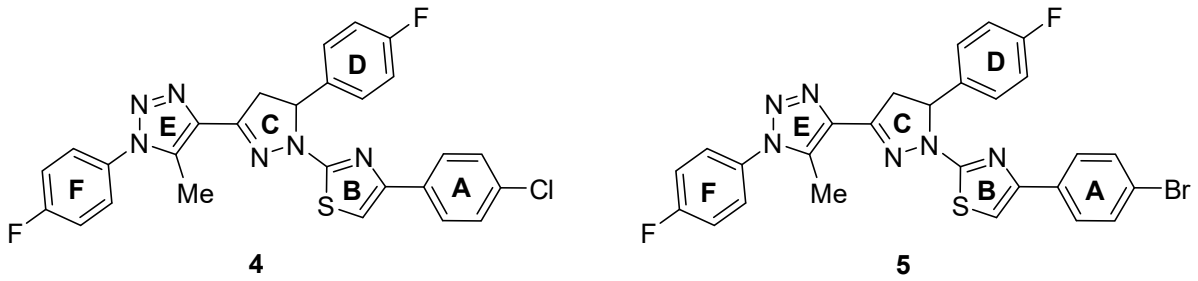


Figure 1. Ring systems in compounds **4** and **5**.

The asymmetric unit in both structures contains two independent molecules (Figure 2a,b). Products **4** and **5** were obtained as racemic mixtures and the two molecules in the asymmetric unit are enantiomers with C10 and C37 as chiral centers. In all the molecules, rings **A**, **B**, **C** and **E** are almost coplanar with twist angles between adjacent rings in the range 3.58(1)° to 13.38(13)° (Table 2). Ring **F** is twisted by ca 30° and **D** is almost perpendicular to the plane of **A**, **B**, **C** and **E**. The two independent molecules in each structure have similar conformations although they are not identical. Additionally, molecular conformations are similar in both crystal structures.

Table 1. Crystal and structure refinement data for **4** and **5**.

	4	**5**
Formula	$C_{27}H_{19}ClF_2N_6S$	$C_{27}H_{19}BrF_2N_6S$
Formula weight	532.99	577.45
Temperature/K	293(2)	293(2)
Wavelength/Å	0.71073	0.71073
Crystal system	Triclinic	Triclinic
Space group	$P\bar{1}$	$P\bar{1}$
a/Å	7.7344(6)	7.7607(3)
b/Å	18.2778(12)	18.2950(11)
c/Å	19.4909(12)	19.5252(14)
α/°	116.181(6)	115.910(6)
β/°	96.410(6)	96.971(4)
γ/°	92.091(6)	92.567(4)
Volume/Å^3	2445.9(3)	2460.2(3)
Z	4	4
Density (calculated)/Mg m^{-3}	1.447	1.559
μ/mm^{-1}	0.287	1.801
F(000)	1096	1168
Crystal size/mm^3	0.270 × 0.065 × 0.026	0.623 × 0.148 × 0.118
Reflections collected	23,275	23,703
Independent reflections	11,546	11,617
R(int)	0.0496	0.0448
Data/parameters	11,546/670	11,617/669
Goodness-of-fit on F^2	1.014	1.032
R1 [I > 2σ(I)]	0.0652	0.0669
wR2 [I > 2σ (I)]	0.1239	0.1722
R1 (all data)	0.1802	0.1364
wR2 (all data)	0.1666	0.2137
Extinction coefficient	0.0012(3)	n/a
Largest diff. peak and hole/e.Å^{-3}	0.238 and −0.243	0.689 and −0.680

Table 2. Inter-ring twist angles (°) and centroid-to-centroid distances (Å). (The centroid-to-centroid distances shown are longer than is conventionally shown for π–π contacts but are used in this case for ease of comparison of the structures. (i) and (ii) refer to the first and second independent molecules).

Inter-Ring Twist Angle	**4(i)**	**4(ii)**	**5(i)**	**5(ii)**
A–B	9.44 (11)	13.38 (10)	9.68 (13)	13.36 (14)
B–C	3.58 (14)	5.30 (15)	5.17 (17)	5.03 (20)
C–D	88.15 (1)	84.53 (13)	88.15 (16)	84.17 (16)
C–E	10.39 (15)	10.78 (16)	10.86 (18)	10.53 (21)
E–F	33.09 (9)	32.59 (10)	35.39 (11)	31.86(13)
Centroid-centroid distance	**4**	**5**		
d1	3.75(1)	3.73(1)		
d2	4.05(1)	4.09(1)		
d3	3.81(1)	3.79(1)		
d4	4.14(1)	4.20(1)		

The following discussion applies to the structures of both **4** and **5**, although only the former is used for illustration. In the crystals, the molecules are stacked parallel to the *a*-axis (Figure 3). In the stack, the mean plane of the fragment containing rings **A**, **B**, **C** and **E** is parallel to (10-1) in one stack and to (201) in the adjacent stack in the direction of the b-axis (Figure 4). Within a given stack, there is very limited π–π interaction between aromatic rings of neighboring molecules. The closest rings in the stack are fluorophenyl/chlorophenyl in **4** (Figure 5) and fluorophenyl/bromophenyl in **5** and the distances between the ring centroids are in the range from 3.73 Å to 4.20 Å (d1–d4 in Table 2). The planes of the rings

involved are not parallel and the angles between the rings of neighboring molecules are 12.18° and 14.42° for **4** and the corresponding angles are 12.95° and 13.70° for **5**.

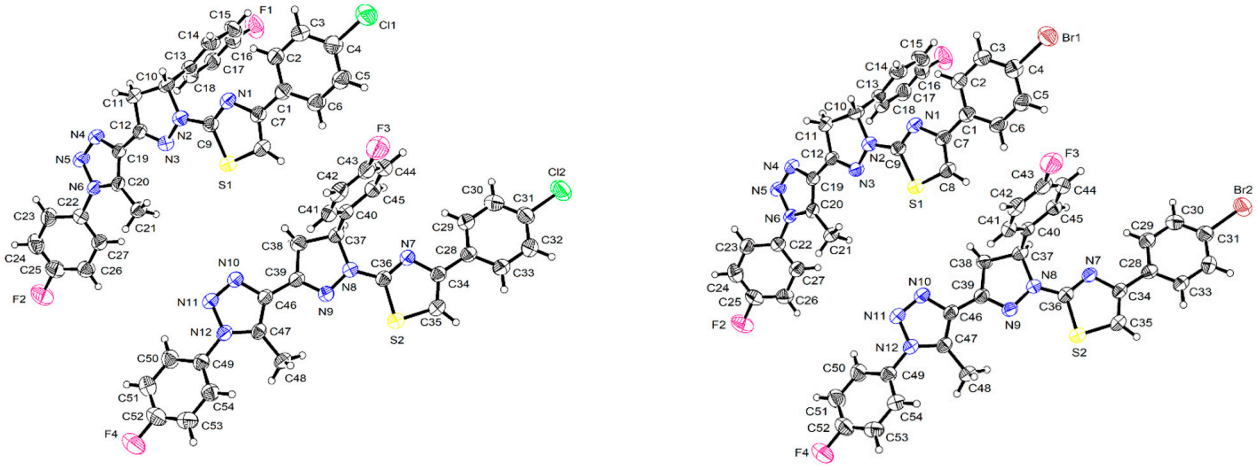


Figure 2. Ortep representation of the asymmetric unit showing 50% probability ellipsoids for (**a**): **4** and (**b**): **5**.

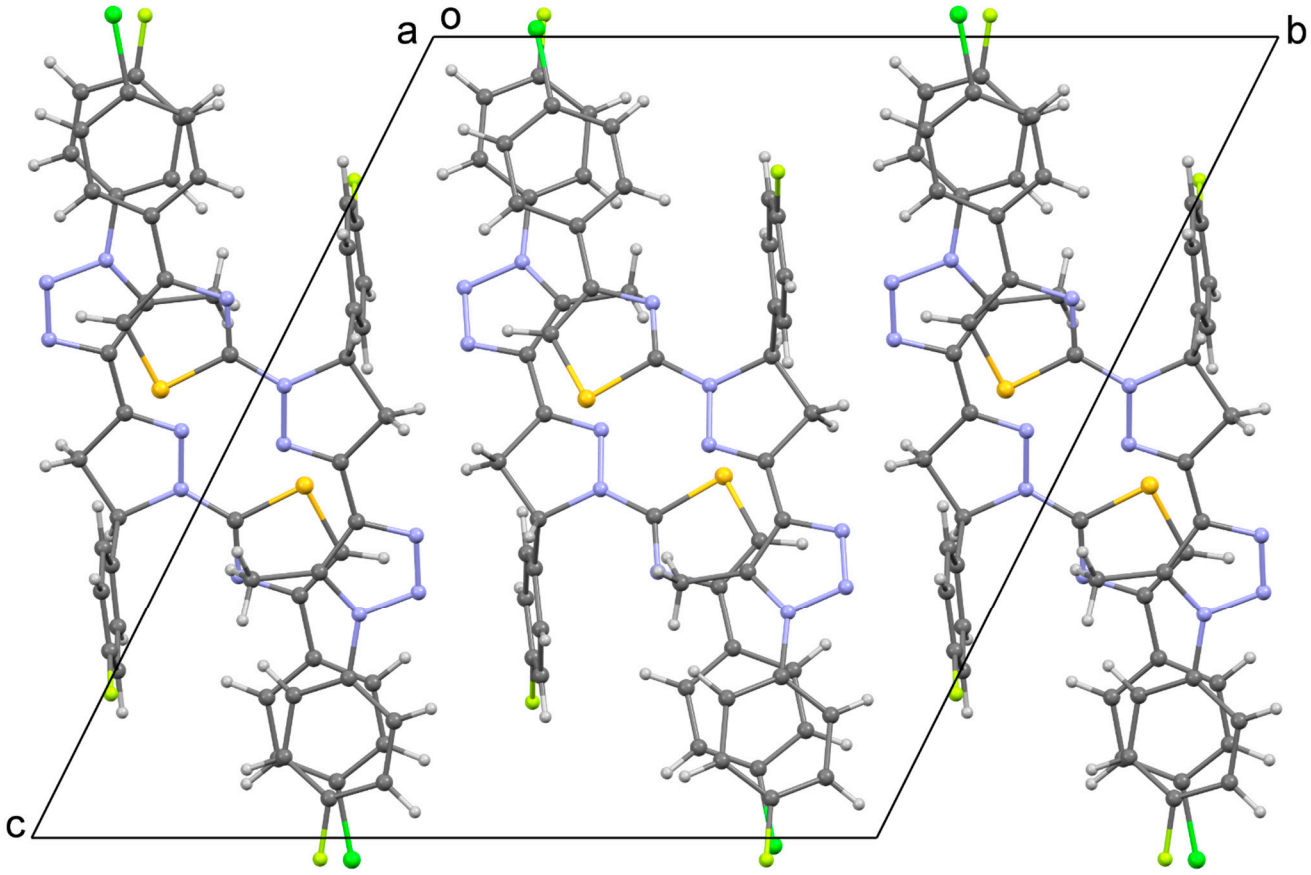


Figure 3. The crystal structure packing in **4** viewed down the *a*-axis.

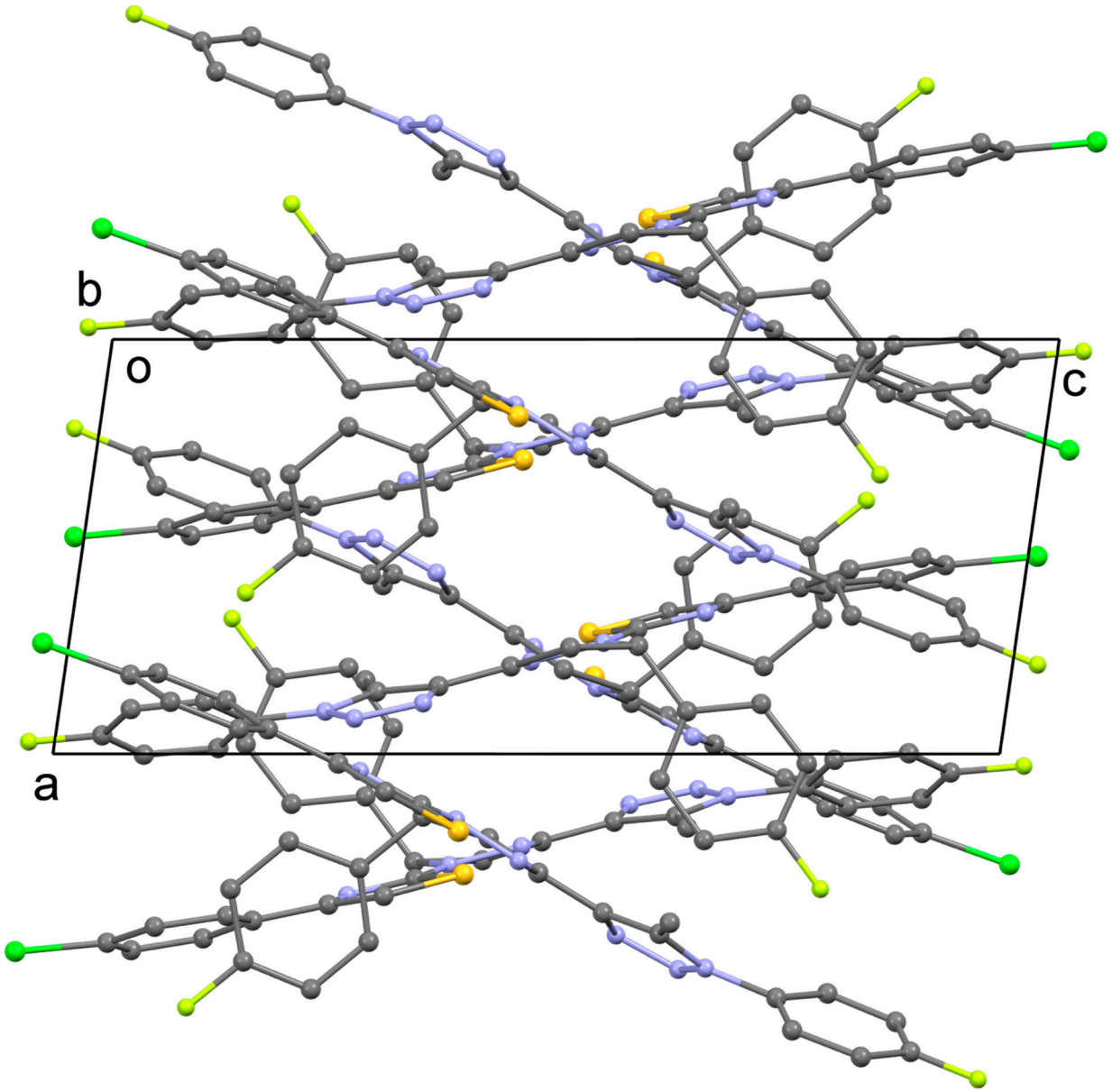


Figure 4. The crystal structure of **4** viewed down the *b*-axis with hydrogen atoms omitted for clarity.

Generally, an asymmetric unit comprising one molecule would be expected in such a structure as the second enantiomer can be generated by inversion symmetry. However, the structures of **4** and **5** comprise two independent molecules with slightly different conformations in order to attain the most efficient molecular packing in the crystal. An alternative method to maximize packing efficiency would be by the incorporation of solvent molecules, for example.

The crystals of **4** and **5** are isostructural despite the different halogen substituents, which are Cl and Br, respectively. The difference in the calculated densities of 1.447 Mg m^{-3} and 1.559 Mg m^{-3} is consistent with the presence of chlorine and bromine atoms in the structures. Despite the different halogen substituents, the molecules have assumed essentially the same crystal structure but with slight adjustment of conformation and intermolecular contacts by virtue of the larger size of the Br atom rendering the molecular volume of **5** about 1% greater than that of **4**.

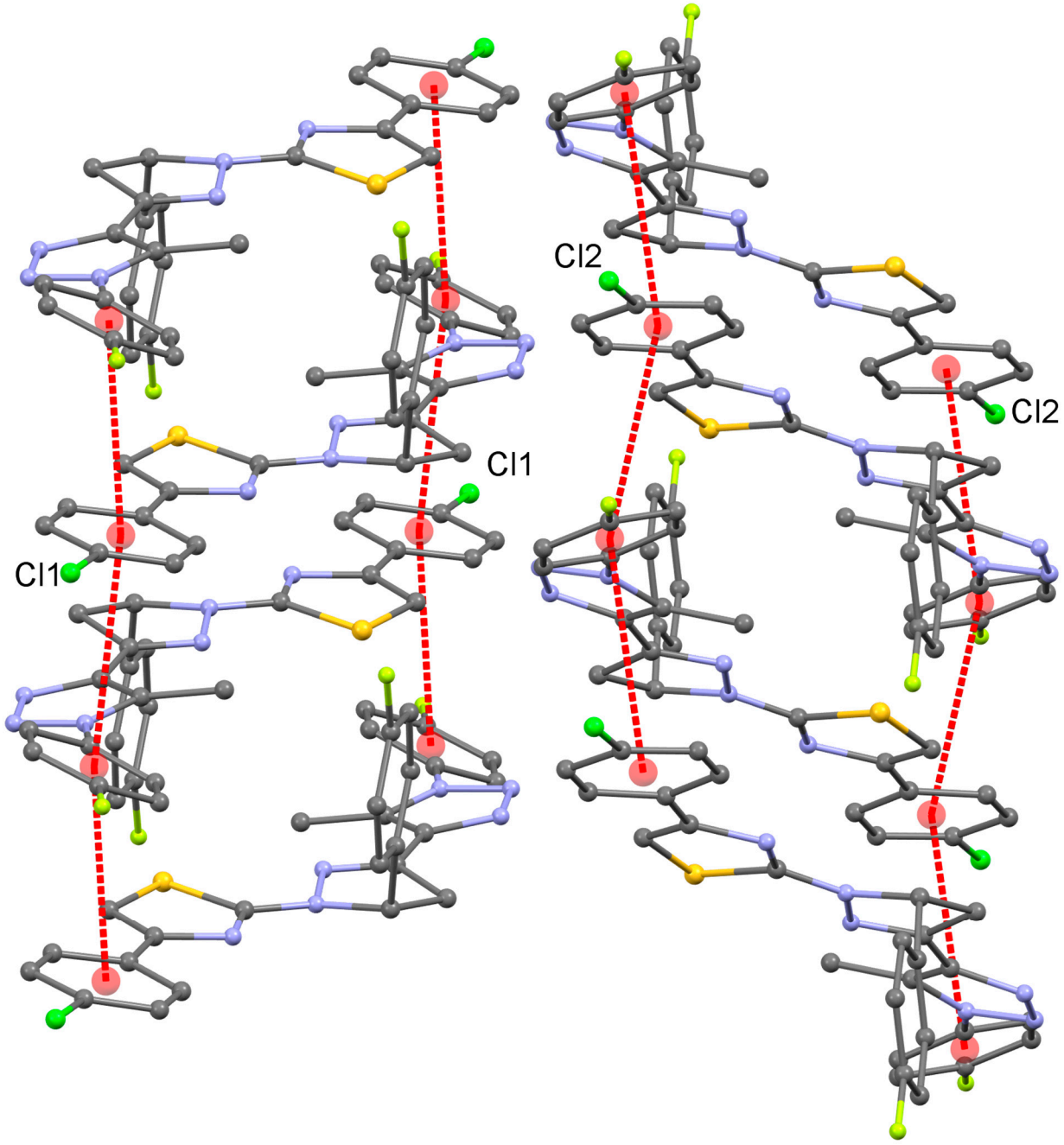


Figure 5. A segment of the crystal structure of **4** viewed approximately along the *c*-axis showing the stacking of molecules with ring centroid separation shown as red dashed lines.

For the title compounds, the substituents on rings **A**, **D** and **F** are (**4**: Cl, F and F) and (**5**: Br, F and F). Crystal structures have also been reported for molecules with other substituents on the same rings, namely (**6**: Cl, F and Me) [48], (**7**: H, Cl and Me) [54], (**8**: Br, F and Me) [55] and (**9**: H, F and Me) [56]. Molecular conformation in structures **6–9** is similar to that in **4** and **5** since rings **A**, **B**, **C** and **E** are roughly coplanar, ring **F** is twisted and ring **D** is oriented out of the plane. However, unlike **4** and **5**, the other crystal structures have just one molecule in the asymmetric unit. Exchanging F for methyl (**5** vs. **8**) and (**4** vs. **6**) results in different crystal structures, as does the replacement of Cl by F (**7** vs. **9**). In contrast, the crystal structures in which Cl and Br are exchanged (**6** vs. **8**) are identical, which is an observation consistent with the results obtained in this work for **4** and **5**.

The Hirshfeld surfaces show different intermolecular contacts for the two independent molecules of each structure. The surfaces are shown in Figure 6b,d for **4** and Figure 7b,d for **5**. The red regions clearly indicate that the intermolecular contacts are not identical for the two independent molecules of the same structure. Conversely, the contacts are essentially the same for the corresponding molecules in **4** and **5**. Highlighted in the fingerprint plots in Figure 6a,c for **4** and Figure 7a,c for **5** are the contributions by chlorine and bromine. The plots follow the same pattern as the Hirshfeld surfaces; the two independent molecules of the same structure show differences whereas comparable molecules from different structures have similar characteristics. The contributions in **4** by Cl are 3.7% and 4.1% for the two independent molecules and 3.9% and 4.2% by Br for **5**.

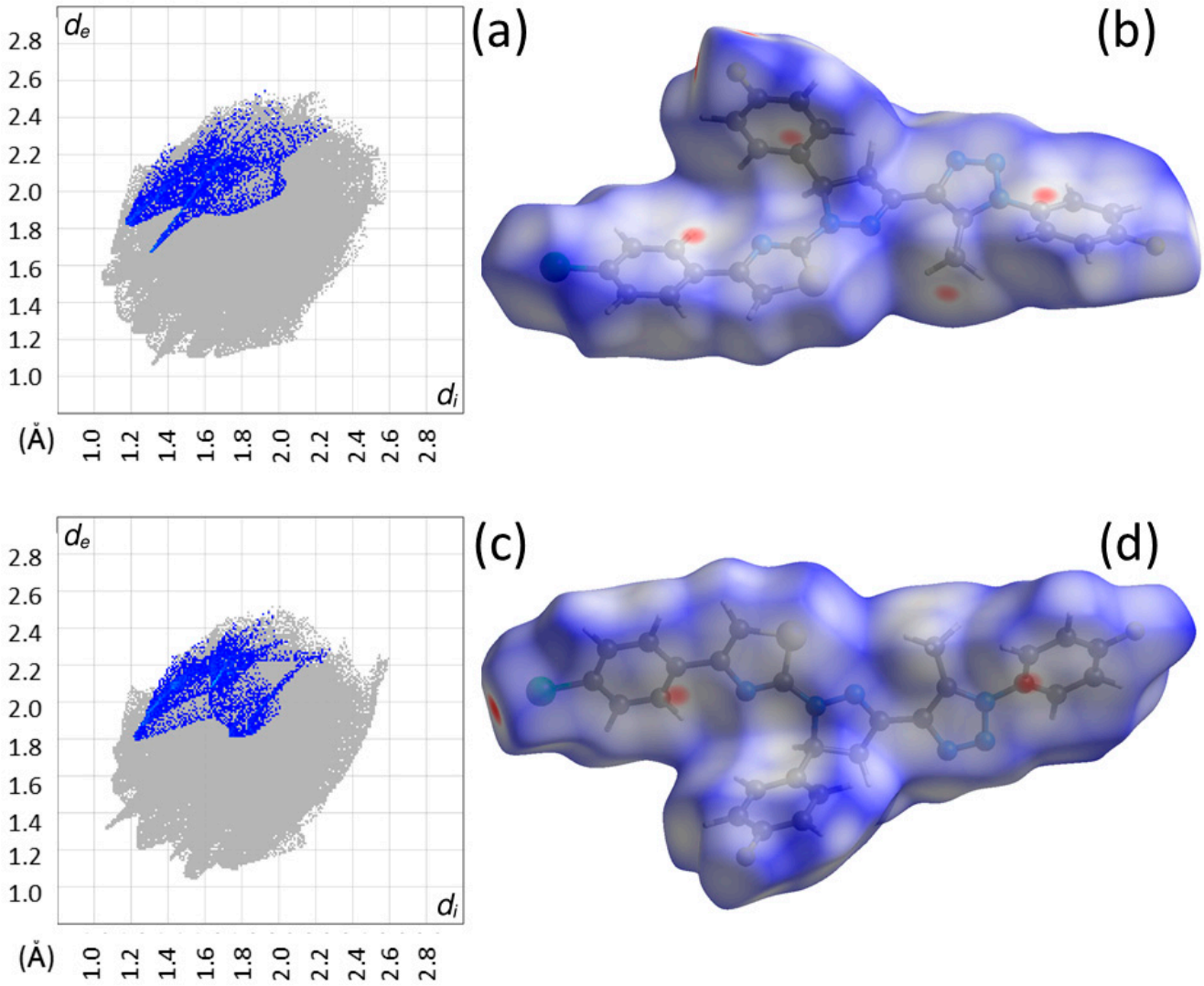


Figure 6. (**a**): Two-dimensional fingerprint plot for one independent molecule of **4** with Cl interactions highlighted; (**b**): the associated Hirshfeld surface. (**c**): Two-dimensional fingerprint plot for the second independent molecule with Cl interactions highlighted; (**d**): the associated Hirshfeld surface.

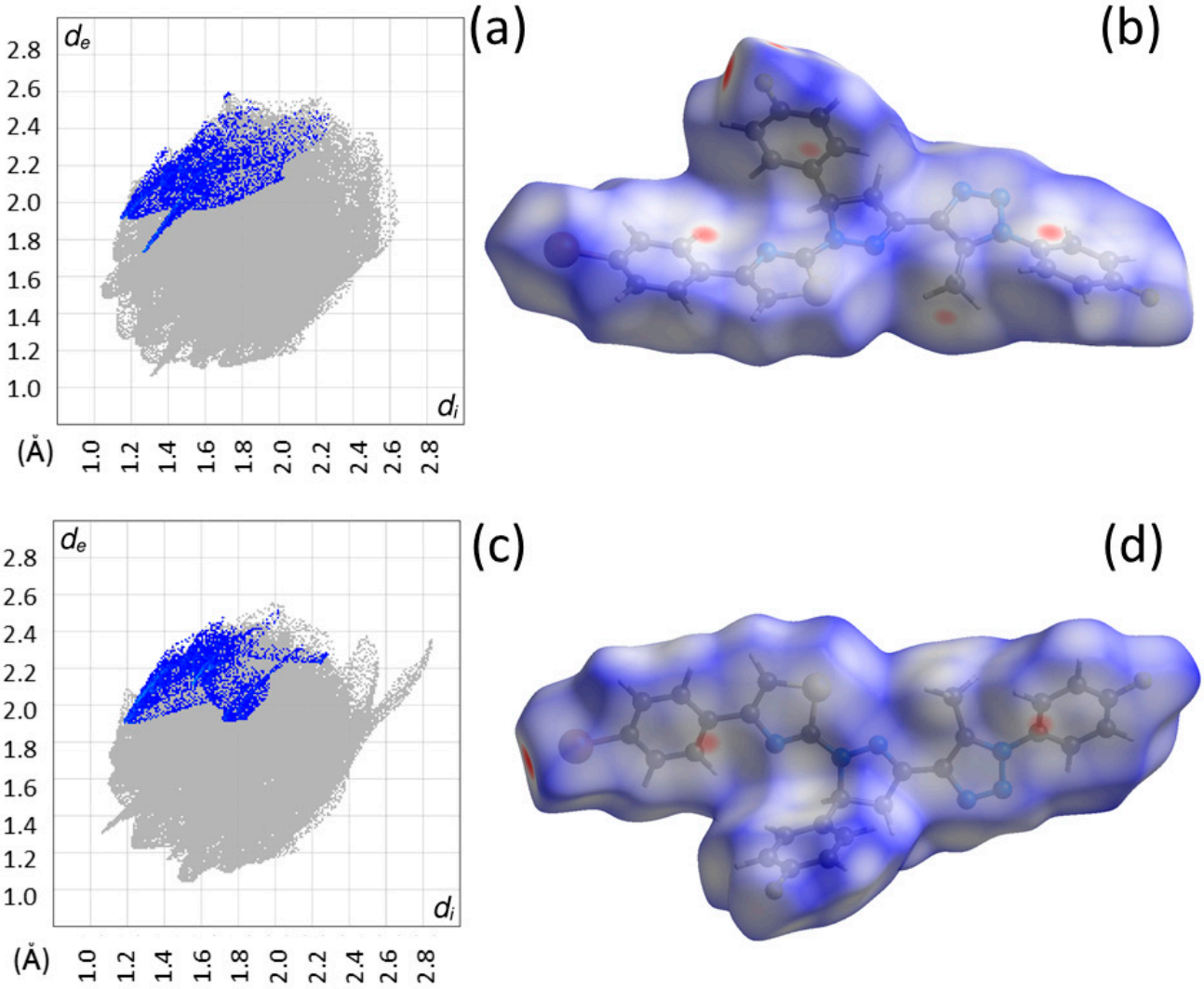


Figure 7. (**a**): Two-dimensional fingerprint plot for one independent molecule of **5** with Br interactions highlighted; (**b**): the associated Hirshfeld surface. (**c**): Two-dimensional fingerprint plot for the second independent molecule with Br interactions highlighted; (**d**): the associated Hirshfeld surface.

4. Conclusions

Two materials, 4-(4-chlorophenyl)-2-(5-(4-fluorophenyl)-3-(1-(4-fluorophenyl)-5- methyl -1*H*-1,2,3-triazol-4-yl)-4,5-dihydro-1*H*-pyrazol-1-yl)thiazole (**4**) and 4-(4-fluorophenyl)-2-(5-(4-fluorophenyl)-3-(1-(4-fluorophenyl)-5-methyl-1*H*-1,2,3-triazol-4-yl)-4,5-dihydro-1*H*-pyrazol-1-yl)thiazole (**5**), have been synthesized in high yields and characterized spectroscopically. The materials have been recrystallized using dimethylformamide as the solvent and their structures have been established by single crystal diffraction. The two materials are isostructural and contain two independent molecules in the asymmetric unit. The two independent molecules in each structure have similar conformations although they are not identical. The crystal structures of **4** and **5** are identical but with slight adjustments necessary to accommodate the different halogen (Cl and Br) substituents. Comparison with related materials shows similarity in molecular conformation but with different crystal packing.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/cryst11070795/s1, IR, ^{1}H and ^{13}C NMR spectra, CIFs and checkcif reports for compounds **4** and **5**.

Author Contributions: Conceptualization: B.M.K. and G.A.E.-H.; methodology: B.M.K., B.F.A.-W. and G.A.E.-H.; X-ray crystal structures: B.M.K.; investigation: B.M.K., B.F.A.-W. and G.A.E.-H.; writing—original draft preparation: B.M.K., B.F.A.-W. and G.A.E.-H.; writing—review and editing: B.M.K. and G.A.E.-H. All authors have read and agreed to the published version of the manuscript.

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