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Afshan Banu[a]; Ravi S. Lamani[b]; I. M. Khazi[b]; Noor Shahina Begum[a]
[a] Department of Studies in Chemistry, Bangalore University, Bangalore, India [b] Department of Chemistry, Karnatak University, Dharwad, India

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Synthesis and Crystal Structure of 2-(4-Fluorobenzyl)-6-Phenylimidazo-[2,1-*b*][1,3,4]Thiadiazole-5-Carbaldehyde

AFSHAN BANU,[1] RAVI S. LAMANI,[2] I. M. KHAZI,[2] AND NOOR SHAHINA BEGUM[1]

[1]Department of Studies in Chemistry, Bangalore University, Bangalore, India
[2]Department of Chemistry, Karnatak University, Dharwad, India

The crystal and molecular structure of 2-(4-fluoro-benzyl)-6-phenyl-imidazo[2,1-b][1,3,4]thiadiazole-5-carbaldehyde is described. The compound crystallizes in the monoclinic space group $P2_1/n$ with $a = 7.419(3)$ Å, $b = 8.287(3)$ Å, $c = 25.734(10)$ Å, $\beta = 91.686(8)°$, $V = 1{,}581.6(10)$ Å^3, $z = 4$. The crystal structure is stabilized by intermolecular C-H . . . N, C-H . . . O, and C-H . . . F interactions.

Keywords C-H . . . N, C-H . . . O, and C-H . . . F weak interactions; crystal structure; imidazole thiadiazole derivative

Introduction

Imidazo[2,1-b][1,3,4]thiadiazole derivatives with pharmacophoric substituents have promising biological and pharmacological activities, because the imidazo-[2,1-b][1,3,4]thiadiazole ring is bioisosteric with the imidazo[2,1-b][1,3,4]thiazole ring present in the well-known anthelmintic drug Tetramisole [1]. Consequently, a large number of imidazo[2,1-b][1,3,4]thiadiazole derivatives have been reported to possess diverse pharmacological properties such as anticancer [2], antitubercular [3], antibacterial [4], antifungal [5], anticonvulsant, analgesic [6], and antisecretory [7] activities. Moreover, much interest has been focused on the anti-inflammatory [8], cardiotonic [9], diuretic [10], and herbicidal [11] activities displayed by compounds incorporating this heterocyclic system. In the field of modern medicinal chemistry it has been found that the fluorinated compounds in general, and fluorinated heterocyclic compounds in particular, are of much interest. It is reported that if a fluorine atom is incorporated into these compounds, the course of the reaction as well as the biological properties are altered. The oxidative and thermal stability of these compounds increases due to accumulation of fluorine atoms on carbon. These fluorinated drugs possess metabolically nondegradable properties leading to an increase in lipid solubility, which will further enhance the rate of absorption and transport of the drug

Address correspondence to Dr. Noor Shahina Begum, Department of Chemistry, Central College Campus, Dr. B.R. Ambedkar Street, Bangalore University, Bangalore 560001, Karnataka, India. E-mail: noorsb@rediffmail.com

in vivo [12]. In view of the above facts and in continuation of our search for various biologically active molecules [3,13,14], we attempted the synthesis and structure analysis of the title compound. Additionally, it is an intermediate required for the synthesis of thiazolidine-2,4-dione derivative, which is an expected antidiabetic agent.

Synthesis and Method of Crystallization

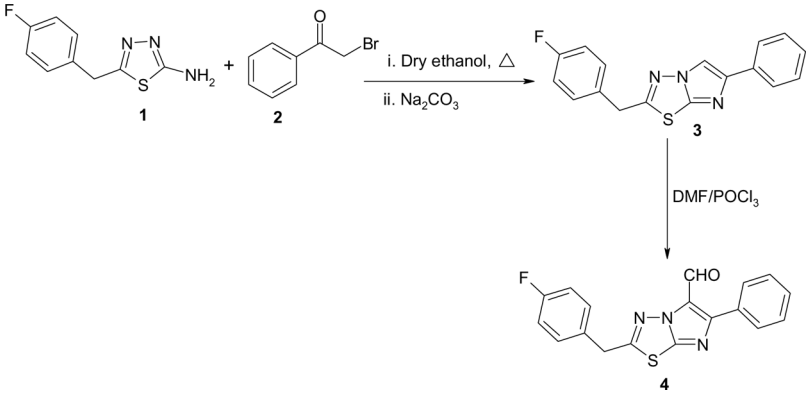
The title compound was prepared in two stages as shown in Scheme 1. The reaction of 2-amino-5-(4-fluorobenzyl)-1,3,4-thiadiazole [15] (**1**) and phenacyl bromide (**2**) in boiling ethanol afforded the 2-(4-fluorobenzyl)-6-phenylimidazo[2,1-*b*][1,3,4]thiadiazole (**3**) as hydrobromide salt, which was neutralized by sodium carbonate solution to get the free base. It was subjected to Vilsmeier-Haack reaction to yield 2-(4-fluorobenzyl)-6-phenylimidazo[2,1-*b*][1,3,4]thiadiazole-5-carbaldehyde (**4**). The structures of the synthesized compounds were established by analytical and spectral data and confirmed by X-ray crystal structure analysis.

Preparation of 2-(4-Fluorobenzyl)-6-Phenylimidazo[2,1-b][1,3,4]Thiadiazole(3)

A mixture of equimolar quantities of 2-amino-(4-fluorobenyl)-1,3,4-thiadiazole (**1**) (2.69, 0.013 mol) and phenacyl bromide (**2**) compound (2.4 g, 0.01 mol) was refluxed in dry ethanol for 16 h. The excess of solvent was distilled off and the solid hydrobromide salt that separated was collected by filtration, suspended in water, and neutralized by aqueous sodium carbonate solution to get free base (**3**). It was filtered, washed with water, dried, and recrystallized from ethanol.

Preparation of 2-(4-Fluorobenzyl)-6-Phenylimidazo [2,1-b] [1,3,4]Thiadiazole Carbaldehyde (4)

Vilsmeier Haack reagent was prepared by adding phosphorous oxychloride (3 mL) in dimethylformamide (20 mL) at 0°C with stirring. At the same temperature, 2-(4-fluorobenzyl)-6-arylimidazo[2,1-b][1,3,4]thiadiazole (**3**) (2.5 g, 0.008 mol) was added to the reagent and stirred at 0°C–5°C for 30 min. The mixture was further stirred for 2 h at room temperature and then at 60°C for additional 2 h. The reaction mixture was cooled in an ice-water bath and quenched with 5 mL water. The reaction



Scheme 1. Preparation of compound **4**.

mixture was basified with aq. sodium carbonate (10%) solution with cooling and further stirred at 80°C–90°C for 2 h. After cooling, the mixture was diluted with water and extracted with chloroform (30 mL × 3). The combined extracts were washed with water (100 mL × 3) and dried over anhydrous sodium sulfate. Solvent was removed under vacuum and the solid obtained was recrystallized from chloroform to afford yellow crystals in excellent yields.

Experimental

Melting points were determined in open capillaries. Infrared (IR) spectra was recorded on Nicolet Fourier transform infrared (FTIR) 410 spectrophotometer, ^{1}H nuclear magnetic resonance (NMR) spectra were recorded on a Varian RXZ-300 MHz spectrometer University Science Instrument Centre, Karnatak University Dharwad, Karnataka using tetramethyl silane (TMS) as internal standard.

Table 1. Crystal data and structure refinement

CCDC deposit no.	693225
Empirical formula	$C_{18}H_{12}FN_3OS$
Formula weight	336.36
Temperature	293(2) K
Wavelength (Å)	0.71073
Crystal system	Monoclinic
Space group	$P2_1/n$
Unit cell dimensions	
a (Å)	7.419(3)
b (Å)	8.287(3)
c (Å)	25.734(10)
β (°)	91.686(8)
Volume (Å^3)	1581.6(10)
Z	4
Calculated density (Mg/m^3)	1.413
Absorption coefficient (mm^{-1})	0.225
F(000)	692
Crystal size	0.4 mm × 0.35 mm × 0.3 mm
Theta range for data collection	2.58–28.37°.
Limiting indices	$-9 \le h \le 9$, $-10 \le k \le 11$, $-18 \le l \le 34$
Reflections collected/unique	10,140/3,876 [R(int) = 0.0476]
Completeness to theta	28.37 98.3%
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	3,876/0/241
Goodness-of-fit on F^2	0.961
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0559$, $wR_2 = 0.1318$
R indices (all data)	$R_1 = 0.1175$, $wR_2 = 0.1674$
Largest diff. peak and hole (eÅ^{-3})	0.307 and −0.215

Physical Measurements

The infrared spectra of imidazo[2,1-b][1,3,4]thiadiazole do not contain an absorption band due to carbonyl and amino functionalities, confirming the formation of imidazothiadiazole. The ^{1}H NMR spectra ($CDCl_3$) showed appropriate signals due to different protons present in the molecule. The formylation product showed the band due to aldehydic proton in the NMR spectrum. The absence of a singlet due to C_5-H was considered as the confirmation of the formylation at C_5.

Compound (**3**), yield 75%, m.p. 168–170°C; IR (KBr) νcm^{-1}: 3,124, 2,923, 2,853, 1,602, 1,507; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.29 (s, 2H, CH_2), 7.06–7.44 (m, 7H, Ar-H), 7.83 (d, $J = 7.2$ Hz, 2H, Ar-H), 7.98 (s, 1H, C_5-H, imidazole), ^{13}C NMR (150 MHz, $CDCl_3$) δ: 43.2, 116.9, 121, 126, 128, 129.6, 130.1, 132.1, 132.6, 135.5, 160.1, 136.5, 1648. Anal. calcd. for $C_{17}H_{12}FN_3S$: C, 66.01; H, 3.88; N, 13.59; Found: C, 66.10; H, 3.82; N, 13.62%.

Compound (**4**), yield 75%, m.p. 110–112°C; IR (KBr) νcm^{-1}: 2,924, 2,854, 1,676, 1,602, 1,523; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.45 (s, 2H, CH_2), 7.07–7.13 (t, 1H, $J = 8.52$ Hz, Ar-H), 7.32–7.84 (m, 8H), 10.04 (s, 1H, CHO). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 46.5, 116.1, 125.0, 127.6, 131.2, 132.0, 134.7, 135.0, 135.9, 136.4, 144.1,

Table 2. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameter ($\times 10^3$) nonhydrogen atoms

Atoms	x	y	z	U(eq)
C(1)	5,750(4)	4,545(4)	1,606(1)	57(1)
C(2)	6,197(3)	3,266(3)	1,223(1)	52(1)
C(3)	7,185(3)	851(3)	787(1)	49(1)
C(4)	6,226(4)	2,748(3)	−431(1)	63(1)
C(5)	6,781(3)	1,627(3)	−31(1)	45(1)
C(6)	7,450(3)	48(3)	6(1)	46(1)
C(7)	7,896(3)	−1,143(3)	−394(1)	48(1)
C(8)	7,708(4)	−838(4)	−925(1)	58(1)
C(9)	8,149(4)	−2,015(4)	−1,282(1)	67(1)
C(10)	8,778(4)	−3,488(4)	−1,119(1)	67(1)
C(11)	8,977(4)	−3,803(4)	−603(1)	71(1)
C(12)	8,544(4)	−2,651(3)	−240(1)	62(1)
C(13)	7,425(3)	5,441(3)	1,791(1)	51(1)
C(14)	8,030(4)	6,742(3)	1,512(1)	64(1)
C(15)	9,600(5)	7,530(4)	1,656(2)	80(1)
C(16)	10,560(4)	6,987(5)	2,081(2)	83(1)
C(17)	10,021(5)	5,705(5)	2,371(1)	80(1)
C(18)	8,431(4)	4,940(4)	2,224(1)	67(1)
N(1)	7,683(3)	−419(2)	520(1)	51(1)
N(2)	6,640(3)	2,099(2)	485(1)	46(1)
N(3)	6,077(3)	3,486(2)	721(1)	51(1)
O(1)	6,290(3)	2,571(2)	−898(1)	80(1)
F(1)	12,118(3)	7,741(3)	2,228(1)	132(1)
S(1)	6,995(1)	1,370(1)	1,431(1)	59(1)

160.1, 164.0, 192.6. Anal. calcd. for $C_{18}H_{12}FN_3OS$: C, 64.09; H, 3.56; N, 12.46; Found: C, 64.13; H, 3.49; N, 12.42%.

Crystal Structure Determination

The X-ray diffraction data were collected on a Bruker Smart CCD Area Detector System (I.I.Sc, Bangalore). Intensity data were collected up to a maximum of 28.37° for the compound in the ω–ϕ scan mode. The data were reduced using SAINTPLUS [16]. A total of 10,140 reflections were collected, resulting in 3,876 independent reflections, of which the number of reflections satisfying $I > 2\ \sigma(I)$ criteria was 2,017. These were treated as observed. The structure was solved by direct methods and difference Fourier synthesis using SHELXS97 [17]. The positions of all nonhydrogen atoms were included in the full-matrix least-square refinement using SHELXL97 [18]. Anisotropic refinement using full-matrix least-square procedures was carried out for a few cycles until convergence was reached. Then the hydrogen atoms were fixed geometrically. The R factor after final convergence was 0.0559 and the maximum and minimum values of residual electron density were 0.307 and −0.215 eÅ^{-3}. Molecular diagrams were generated using ORTEP [19]. The mean plane calculation was done using the program PARST [20].

Table 3. Anisotropic displacement parameters ($\times 10^4$) of non hydrogen atoms

Atoms	U11	U22	U33	U23	U13	U12
C(1)	54(2)	60(2)	56(2)	−2(1)	6(1)	2(1)
C(2)	48(1)	52(2)	56(2)	2(1)	2(1)	−1(1)
C(3)	45(1)	50(2)	51(2)	10(1)	−3(1)	−2(1)
C(4)	78(2)	52(2)	58(2)	6(1)	2(2)	7(1)
C(5)	42(1)	49(2)	46(2)	4(1)	1(1)	−5(1)
C(6)	39(1)	48(1)	50(2)	2(1)	−1(1)	−5(1)
C(7)	38(1)	51(2)	54(2)	0(1)	−2(1)	−5(1)
C(8)	55(2)	57(2)	61(2)	1(1)	1(1)	−4(1)
C(9)	64(2)	76(2)	62(2)	−12(2)	−1(1)	−2(2)
C(10)	56(2)	73(2)	73(2)	−19(2)	0(2)	7(1)
C(11)	71(2)	61(2)	80(2)	−4(2)	−3(2)	15(2)
C(12)	63(2)	60(2)	60(2)	0(2)	−6(2)	8(1)
C(13)	60(2)	49(2)	45(2)	−4(1)	6(1)	7(1)
C(14)	73(2)	54(2)	64(2)	4(1)	2(2)	4(1)
C(15)	83(2)	60(2)	95(3)	−5(2)	9(2)	−12(2)
C(16)	68(2)	92(3)	89(3)	−37(2)	1(2)	15(2)
C(17)	81(2)	103(3)	55(2)	−19(2)	−13(2)	6(2)
C(18)	83(2)	75(2)	42(2)	1(1)	4(1)	−2(2)
N(1)	54(1)	47(1)	53(1)	1(1)	−1(1)	1(1)
N(2)	49(1)	40(1)	49(1)	4(1)	1(1)	1(1)
N(3)	51(1)	45(1)	56(1)	−1(1)	0(1)	1(1)
O(1)	114(2)	71(1)	54(1)	12(1)	0(1)	23(1)
F(1)	98(2)	150(2)	148(2)	−49(2)	−14(1)	−45(2)
S(1)	70(1)	59(1)	49(1)	5(1)	−1(1)	5(1)

Results and Discussion

The Details of crystal data and refinements are given in Table 1. Table 2 gives the list of atomic coordinates and equivalent isotropic displacement parameters of the nonhydrogen atoms. Table 3 gives the list of anisotropic displacement parameters of the nonhydrogen atoms. The bond lengths and bond angles of all the nonhydrogen atoms are given in Tables 4 and 5. The selected torsion angles are listed in Table 6. All nonbonded interactions are tabulated in Table 7. The ORTEP diagram of the molecule with thermal ellipsoids drawn at 50% probability is shown in Fig. 1. Figures 2, 3, and 4 show the packing of molecules in the crystal structure.

The imidazothiadiazole and aryl ring are planar with a dihedral angle of 0.942(3)° between them. The fluoro benzyl ring is inclined at an angle of 74° to these imidazothiadiazole and aryl ring systems. The carbaldehyde group is coplanar with an imidazothiadiazole ring and *cis* to the phenyl ring and the fluoro group is coplanar with the benzyl ring. The carbonyl group has a *cis* orientation with respect to the C5=C6 double bond, which leads to a strong intramolecular hydrogen bond.

Table 4. Bond lengths [Å]

Atoms	Lengths
S(1)-C(3)	1.720(3)
S(1)-C(2)	1.757(3)
N(2)-C(3)	1.349(3)
N(2)-N(3)	1.371(3)
N(2)-C(5)	1.391(3)
N(3)-C(2)	1.305(3)
N(1)-C(3)	1.317(3)
N(1)-C(6)	1.385(3)
C(6)-C(5)	1.401(3)
C(6)-C(7)	1.471(3)
C(5)-C(4)	1.438(4)
C(7)-C(8)	1.392(4)
C(7)-C(12)	1.393(4)
C(8)-C(9)	1.386(4)
C(2)-C(1)	1.491(4)
O(1)-C(4)	1.214(3)
C(13)-C(14)	1.377(4)
C(13)-C(18)	1.386(3)
C(13)-C(1)	1.513(4)
C(12)-C(11)	1.381(4)
C(18)-C(17)	1.382(4)
C(14)-C(15)	1.376(4)
C(10)-C(11)	1.357(4)
C(10)-C(9)	1.369(4)
C(17)-C(16)	1.365(5)
C(16)-F(1)	1.358(3)
C(16)-C(15)	1.365(5)

Table 5. Bond angles [°]

Atoms	Angles
C(3)-S(1)-C(2)	88.11(12)
C(3)-N(2)-N(3)	118.5(2)
C(3)-N(2)-C(5)	107.8(2)
N(3)-N(2)-C(5)	133.71(19)
C(2)-N(3)-N(2)	108.0(2)
C(3)-N(1)-C(6)	104.3(2)
N(1)-C(6)-C(5)	111.1(2)
N(1)-C(6)-C(7)	117.2(2)
N(2)-C(5)-C(6)	103.57(19)
N(2)-C(5)-C(4)	118.2(2)
N(1)-C(3)-N(2)	113.3(2)
N(1)-C(3)-S(1)	137.3(2)
N(2)-C(3)-S(1)	109.42(19)
N(3)-C(2)-C(1)	123.0(2)
N(3)-C(2)-S(1)	116.00(19)
C(1)-C(2)-S(1)	120.9(2)
O(1)-C(4)-C(5)	127.7(3)
O(1)-C(4)-H(4)	116.1
F(1)-C(16)-C(17)	117.9(4)
F(1)-C(16)-C(15)	119.4(4)

The C-N bond length in the imidazole ring are longer than that of a typical C=N bond but shorter than that of a C-N bond, indicating electron delocalization in the ring.

Table 6. Selected Torsion angles (°)

C(5)-N(2)-N(3)-C(2)	179.0(2)
C(3)-N(1)-C(6)-C(7)	−179.76(19)
N(3)-N(2)-C(5)-C(6)	−179.8(2)
C(3)-N(2)-C(5)-C(4)	178.4(2)
C(7)-C(6)-C(5)-N(2)	179.6(2)
N(1)-C(6)-C(5)-C(4)	−177.7(3)
C(6)-N(1)-C(3)-S(1)	179.0(2)
N(3)-N(2)-C(3)-N(1)	179.57(19)
C(5)-N(2)-C(3)-S(1)	−178.97(15)
C(2)-S(1)-C(3)-N(1)	−179.1(3)
N(1)-C(6)-C(7)-C(8)	179.3(2)
N(2)-N(3)-C(2)-C(1)	178.0(2)
C(3)-S(1)-C(2)-C(1)	−177.8(2)
N(3)-C(2)-C(1)-C(13)	95.7(3)
S(1)-C(2)-C(1)-C(13)	82.2(3)
N(2)-C(5)-C(4)-O(1)	178.0(3)
C(18)-C(17)-C(16)-F(1)	179.7(3)
F(1)-C(16)-C(15)-C(14)	179.6(3)

Table 7. Nonbonded interactions and possible hydrogen bonds (Å, °)

D—H···A	D—H	H···A	D···A	D—H···A
C8-H8...O1	0.954(1)	2.127(1)	3.016(4)	154(2)
C14-H14...N1[a]	0.930(3)	2.755(2)	3.477(4)	135(0)
C4-H4...N3[b]	1.023(5)	2.389(5)	3.340(4)	154(2)
C14-H14...O1[c]	0.930(3)	2.827(2)	3.577 (4)	138(0)
C1-H1A...O1[c]	1.023(5)	2.827(2)	3.340(4)	154(2)
C17-H17...F1[d]	0.930(3)	2.715(2)	3.388(4)	129(0)

[a] x + y + 1,+z;
[b] x + 1,−y + 1, −z;
[c] x + 1, −y + 1, −z;
[d] −x + 1/2 + 2, +y −1/2, −z + 1/2.
D = donor; A = acceptor; H = hydrogen.

The thiadiazole moiety displays differences in the bond lengths of the pairs of bonds C3-N2/C6-N1 and S1-C2/S1-C3 due to the fused imidazole ring as well as the different groups that are attached on either side of the imidazothiadiazole ring system. The difference in bond lengths S1-C3 [1.720(3) Å] and S1-C2 [1.757(3) Å] indicates that the resonance effect caused by the imidazole ring is stronger than that caused by the thiadiazole ring. The imidazole and thiadiazole parts show different π conjugations, due to their fused nature as well as the groups attached to them. This is evident from the C-N bond length similarities in the imidazole ring (having values intermediate between those of single and double bonds) compared to the C-S bond length differences in the thiadiazole ring. As a result, the imidazole part of this imidazothiadiazole system is more resonance stabilized. Additionally, the imidazothiadiazole entity is generally planar and rigid.

The molecular structure is primarily stabilized by a strong intramolecular C8-H8...O1 hydrogen bond [C8-H8 = 0.954(1) Å, H8...O1 = 2.127(1) Å, C8...O1 = 3.016(4) Å and the angle C8-H8...O1 = 154(2)°] leading to the formation of a pseudo-seven-membered hydrogen-bonded pattern with graph set S(7), thus locking the molecular conformation and eliminating conformational flexibility.

The crystal structure is stabilized by intermolecular interactions into a three-dimensional framework structure by the combination of C-H...N, C-H...O, and

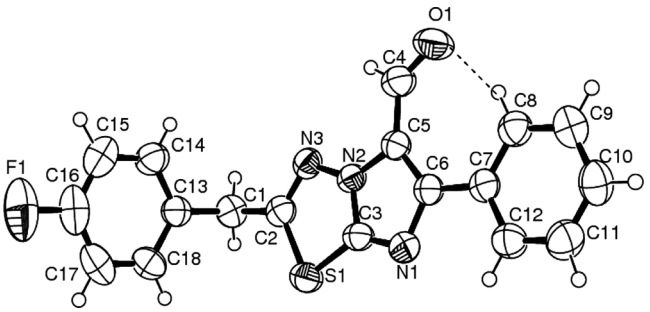


FIGURE 1. ORTEP view of compound **4** showing 50% probability ellipsoids and the atom numbering scheme. Dotted line indicates intramolecular C8-H8...O1 interaction.

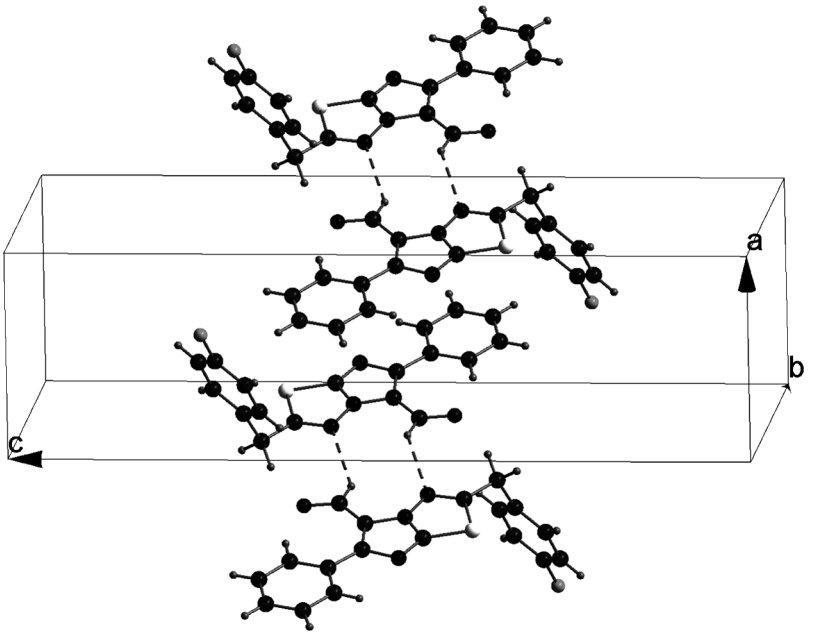


FIGURE 2. Crystal structure of **4** viewed along the *b* axis. Dotted lines indicate intermolecular C-H . . . N interaction.

C-H . . . F. Hydrogen bonds with C-H as donor play a significant role, functional and structural, contributing to the overall stability of the molecular packing. The framework is composed of two different C-H . . . N interactions; the first is from C14 to its neighbor N1 linking the molecule in terms of zig-zag, chain-like structure and the

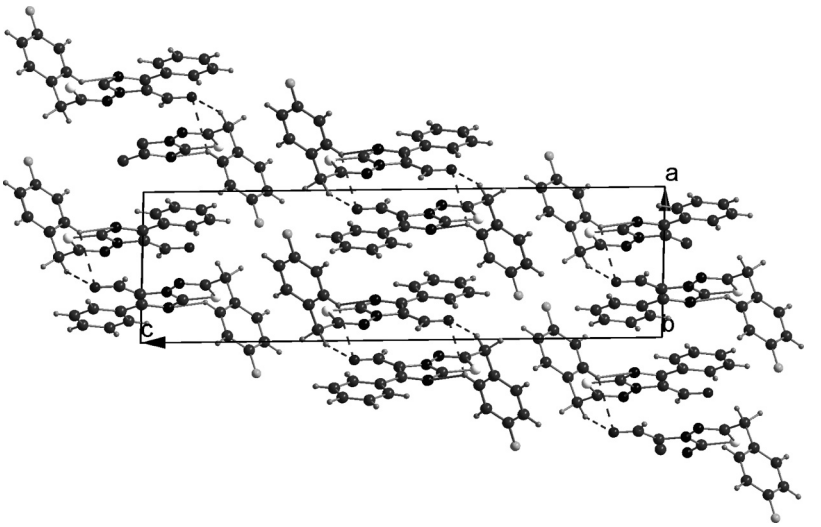


FIGURE 3. Crystal structure of **4** viewed along the *b* axis. Dotted lines indicate intermolecular C-H . . . O interaction generating bifurcated bonds.

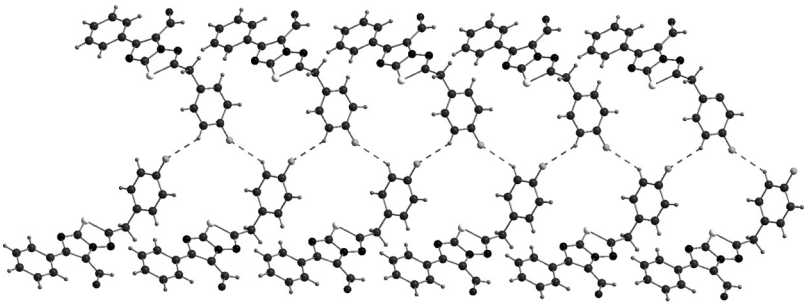


FIGURE 4. Crystal structure of **4** representing two-dimensional sheet-like structure. Dotted lines indicate intermolecular C-H . . . F interactions.

second C-H . . . N interaction between C4 and N3 form head-to-head dimers corresponding to graph set notation of $R_2^2(10)$ (Fig. 2). There are two different C-H . . . O interactions; in the first the molecules are linked by paired C-H . . . O hydrogen bonds into centrosymmetric dimers corresponding to graph set notation $R_2^2(18)$ and the second generate bifurcated bonds from two donors, C1 and C14, to the same acceptor, O1 along the b axis (Fig. 3). The C-H . . . F interactions create self-assembly in terms of a two-dimensional sheet-like structure along the crystallographic b axis (Fig. 4). The dependence of the strength of the C-H . . . X interaction on C-H group acidity [21] meant that the selected compounds should have as large a number of acidic C-H groups as possible [22]. Thus, we concluded on the basis of Cambridge Structural Database (CSD) and computational studies that the C-F group does not favor the formation of F . . . F contacts as do the C-Cl, C-Br, and C-I groups [23]. This difference between F and the other halogens has been noted in several other studies [24]. The presence of the fluoro substituent on the benzene ring enhances the acidity of the C-H groups. There are no aromatic π-π stacking interactions. The supramolecular aggregation in this structure is thus limited to the C-H . . . N, C-H . . . O, and C-H . . . F intermolecular interactions giving overall stability to the structure.

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