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ORIGINAL ARTICLE

Synthesis, spectroscopic and crystal structure analysis of 2-(4-fluorobenzyl)-6-(4-methoxyphenyl)imidazo[2,1-b]-[1,3,4]thiadiazole and its morpholinomethyl derivative

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KEYWORDS

Imidazo[2,1-b] 1,3,4-thiadiazoles;
Crystal structure;
Morpholinomethyl derivative;
Weak interactions: C–H...O, C–H...N, C–H...F and π–π stacking

Abstract The preparation of 2-(4-fluorobenzyl)-6-(4-methoxyphenyl)-5-morpholin-1-ylmethyl imidazo[2,1-b][1,3,4]thiadiazole via the intermediate 2-(4-fluorobenzyl)-6-(4-methoxyphenyl)Imidazo[2,1-b][1,3,4] thiadiazole is described. Elemental analysis, IR spectrum, ^{1}H NMR and X-ray crystal structure analyses were carried out to determine the compositions and molecular structures of the two compounds. The crystal packing exhibits intermolecular C–H···O, C–H···N, C–H···F and π–π stacking interactions leading to the formation of the supramolecular network.

1. Introduction

Imidazole[2,1-b][1,3,4]thiadiazole derivatives have been of interest to the medicinal chemists for many years because of their anticancer (Terzioglu and Gursoy, 2003), antitubercular (Gadad et al., 2004), antibacterial (Gadad et al., 2000; Mohan and Varman, 1999),antifungal (Andotra et al., 1997), anticonvulsant, analgesic(Khazi et al., 1996) and antisecretory (Andreani et al., 2000) activities. This is due to the fact that the imidazole [2,1-b][1,3,4] thiadiazole system is similar in part to Levamisole, a well-known immune modulator (Amery et al., 1984; Renoux and Renoux, 1974). Moreover Mannich bases of many heterocycles are known for diverse biological activities (Kumar, 2010). The authors have recently reported that Mannich bases of imidazole [2,1-b][1,3,4] thiadiazoles possess considerable antitubercular and antimicrobial activities

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(Hegde et al., 2006). One such Mannich reaction is discussed here.

Apart from this, fluorinated compounds in general and fluorinated heterocyclic compounds in particular, are the focus of much interest in modern medicinal chemistry. In other classes of antitumour compounds, e.g. the anthracycline antibiotics (Miller and Stoodley, 2010), the substitution of a hydrogen atom for a fluorine atom in the tetracyclic ring system was found to possess better antitumour properties (Animati et al., 1996). In recent years there have been reports that the incorporation of fluorine atom could alter the course of the reaction as well as enhance the biological properties. Accumulation of fluorine on carbon leads to increased oxidative and thermal stabilities. Thus fluorinated drugs, being metabolically non-degradable, are regarded as useful therapeutic agents. Further, such drugs have increased lipid solubility, resulting in an increased rate of absorption and transport *in vivo* (Strunecka et al., 2004; Kevin Park et al., 2001). In view of the above facts and in continuation of our search for various biologically active molecules (Kolavi et al., 2006a, b; Hegde et al., 2006), we report herein the structural studies on 2-(4-fluorobenzyl)-6-(4-methoxyphenyl)imidazo[2,1-b][1,3,4] thiadiazole and its morpholinomethyl derivative.

The syntheses of these compounds were followed by measurement of their analytical data and subsequent spectroscopic analyses using IR and ^{1}H NMR techniques to confirm the presence of the supposed ring systems, the presence of fluoro and methoxy substituent as well as the signals for the existence of various protons.

The two compounds were subjected to single crystal X-ray diffraction analyses so that their supramolecular structures could be investigated in terms of possible intermolecular interactions.

2. Experimental

2.1. Materials

All reagents were obtained from commercial sources. Solvents were dried and purified with known conventional methods.

2.2. Analytical methods

The melting points were determined in open capillaries and are uncorrected. The IR spectra were recorded as KBr discs using a Nicolet FT-IR 410 spectrophotometer. ^{1}H NMR spectra were recorded on a Varian RXZ-300 MHz spectrometer using TMS as internal reference compound. C, H and N were estimated on a Heraus CHN rapid analyzer at Karnatak University, Dharwad, India. The title compound was prepared in two stages as shown in Scheme 1.

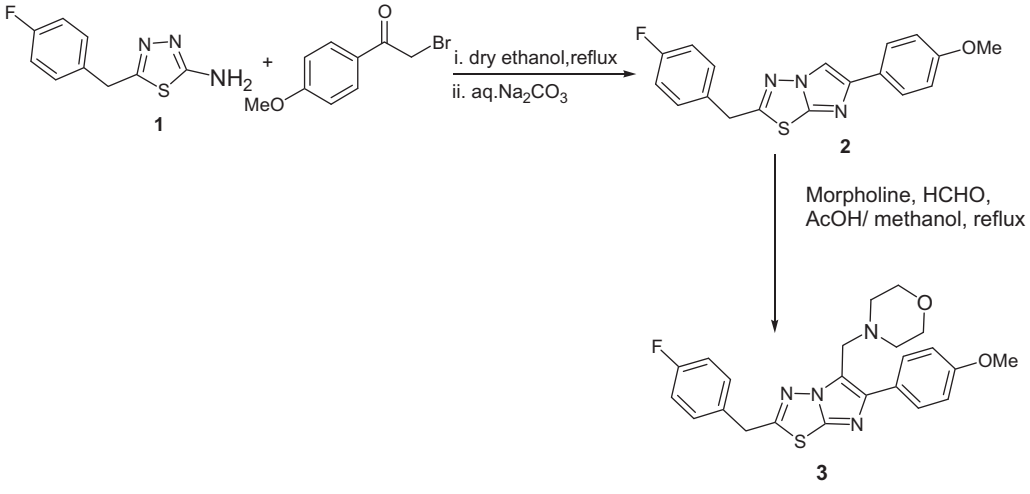
2.3. Procedure for the preparation of 2-(4-fluorobenzyl)-6-(4-methoxyphenyl)imidazo[2,1-b][1,3,4] thiadiazole (2) and its morpholinomethyl derivative (3)

A mixture of 5-(4-fluorobenzyl)-1,3,4-thiadiazol-2-amine (**1**) (Eberle et al., 1972) (2.69 g, 0.01 mol) and *p*-methoxy phenacyl bromide (0.01 mol) was refluxed in dry ethanol for 12 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 (**2**). It was filtered, washed with water, dried and recrystallized from ethanol and dioxane mixture to afford white needles. Yield 65% (3.78 g).

A mixture of 2-(4-fluorobenzyl)-6-(4-methoxyphenyl)imidazo[2,1-b][1,3,4] thiadiazole (**2**) (2.19 g, 0.005 mol), morpholine (0.87 g, 0.01 mol), formalin (1 mL) and acetic acid (1 mL) in methanol (20 mL) was refluxed for 10 h (monitored by TLC). Reaction mixture was diluted with water and extracted with chloroform (3 × 30 mL). The combined chloroform extract was washed with water (3 × 30 mL) and dried over anhydrous sodium sulfate. The solvent was removed under vacuum and the residue was recrystallized from benzene and hexane mixture to afford yellow crystalline solid. Yield 85% (2.16 g).

2.3.1. 2-(4-Fluorobenzyl)-6-(4-methoxyphenyl)imidazo[2,1-b][1,3,4] thiadiazole (2)

Yield 65%; m.p. 151–153 °C; IR (KBr) ν (cm^{-1}): 3010, 2834, 2812, 1610, 1509; ^{1}H NMR [300 MHz, $CDCl_3$]: δ: 3.84 (s, 3H, OCH_3), 4.26 (s, 2H, CH_2), 6.93-7.74 (m, 8H, Ar-H), 7.88 (s, 1H, C_5–H, imidazole). Anal. calcd. for $C_{18}H_{14}FN_3OS$:



Scheme 1 Syntheses of compounds **2** and **3**.

C, 63.71; H, 4.12; N, 12.38. Found: C, 63.74; H, 4.09; N, 12.41%, Mass *m*/*z*: 339 (m^+).

*2.3.2. 2-(4-Fluorobenzyl)-6-(4-methoxyphenyl)-5-morpholin-1-ylmethyl-imidazo[2,1-b][1,3,4]thiadiazole (**3**)*

Yield 85%; m.p. 135–137 °C; IR (KBr) υ (cm^{-1}): 3041, 2829, 2824, 1608, 1510; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.57 (t, 4H, C_3, C_5-H, morpholine), 3.73 (t, 4H, C_2, C_6-H,morpholine), 3.86 (s, 3H, OCH_3), 3.90 (s, 2H, CH_2N), 4.30 (s, 2H, CH_2), 6.97–7.89 (m, 8H, Ar-H), Anal. calcd. for $C_{23}H_{23}FN_4O_2S$: C, 63.01; H, 5.25; N, 12.78. Found: C, 63.03; H, 5.21; N, 12.75%, Mass *m*/*z*: 438 (m^+).

3. X-ray diffraction analysis

The X-ray diffraction data, for both compound (**2**) and compound (**3**) were collected on a Bruker Smart CCD Area Detector System at I.I.Sc., Bangalore, using MoKα (0.71073 Å) radiation for the crystal. The data were reduced using SAINT-PLUS (Bruker, 1998). The structure was solved by direct methods using SHELXS97 (Sheldrick, 1997) and difference Fourier synthesis using SHELXL97 (Sheldrick, 1997). The positions and anisotropic displacement parameters of all non-hydrogen atoms were included in the full-matrix least-square refinement using SHELXL97 (Sheldrick, 1997)and the procedures were carried out for a few cycles until convergence was reached. The H atoms were placed at calculated positions in the riding model approximation (C–H 0.93 Å); their temperature factors were set to 1.2 times those of the equivalent isotropic temperature factors of the parent atoms. All other non-H atoms were refined anisotropically. Molecular diagrams were generated using ORTEP (Farrugia, 1997). The mean plane calculation was done using the program PARST (Nardelli, 1983).

*3.1. Compound (**2**)*

Intensity data were collected up to a maximum of 28.34° for the compound in the ω-scan mode. A total of 9702 reflections were collected, resulting in 3910 independent reflections of which the number of reflections satisfying $I > 2\ \sigma(I)$ criteria were 1782. These were treated as observed. The R factor after final convergence was 0.0618 and the maximum and minimum values of residual electron density were 0.232 and -0.247 e $Å^{-3}$.

*3.2. Compound (**3**)*

Intensity data were collected up to a maximum of 25.0° for the compound in the ω-scan mode. A total of 5430 reflections were collected, resulting in 3631 independent reflections of which the number of reflections satisfying $I > 2\ \sigma(I)$ criteria were 2768. These were treated as observed. The R factor after final convergence was 0.0547 and the maximum and minimum values of residual electron density were 0.532 and -0.326 e$Å^{-3}$.

4. Results and discussion

4.1. Chemistry

The reaction of 2-(4-fluorobenzyl)-6-(4-methoxyphenyl)imidazo[2,1-b][1,3,4]thiadiazole (**2**) with p-methoxy-ω-bromoacetophenone is refluxed in ethanol afforded the hydrobromide salts of imdazole(2,1-b)1,3,4-thiadiazole which on basification with aqueous sodium carbonate solution gave the free base (**2**) in good yield.

The structure of (**2**) was confirmed by IR, NMR and mass spectral data. The absence of νNH_2 band in the IR Spectrum and appearance of C5-H in the ^{1}H NMR spectrum established the formation of compound (**2**). The Mannich raeaction of (**2**) with morpholine and formalin afforded compound (**3**). The structure of (**3**) was established by its analytical and spectral data. In the ^{1}H NMR spectra the absence of peak around 7.88 ppm indicates that the proton at C-5 position of the imidazole group is not available. The protons corresponding to the morpholine ring are indicated by the peaks at 2.57 and 3.73 ppm .These structures were further confirmed by mass spectral data and single crystal X-ray analysis. A number of compounds containing 2-benzyl-6-phenyl-imidazo[2,1-b][1,3,4] thiadiazole as the basic structural unit with various substituents have been synthesized earlier and spectroscopically analyzed and reported (Badiger et al., 2009; Gupta et al., 1993). Good quality single crystals suitable for crystallographic studies could be grown by slow evaporation technique using ethanol and chloroform solvents for compounds (**2**) and (**3**), respectively. In the present work we report the synthesis and spectroscopic analysis of the two title compounds with more emphasis laid on weak interactions.

4.2. Crystallography

The details of the crystal data and refinements are given in Tables 1 and 2 for the compounds (**2**) and (**3**), respectively. The selected bond distances and angles for compound (**2**) and (**3**)

Table 1 Crystal data and structure refinement for (**2**).

Empirical formula	C18 H14 F N3 O S
Formula weight	339.38
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system, space group	Monoclinic, P 21/n
Unit cell dimensions	
a = 11.119(7) Å	
b = 5.667(4) Å	
c = 25.385(5) Å	
β = 91.185(13)°	
Volume	1599.1(14) $Å^3$
z	4
Calculated density	1.410 Mg/m^3
Absorption coefficient	0.223 mm^{-1}
F(000)	704
Crystal size	0.40 × 0.35 × 0.30 mm
Theta range for data collection	3.00–28.34°
Limiting indices	$-14 \leqslant h \leqslant 14$, $-7 \leqslant k \leqslant 5$, $-33 \leqslant 1 \leqslant 28$
Reflections collected/unique	9702/3910 [R(int) = 0.0623]
Completeness to theta	28.34 97.7%
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	3910/0/218
Goodness-of-fit on F^2	0.968
Final R indices [I > 2sigma(I)]	$R1$ = 0.0618, w$R2$ = 0.1487
R indices (all data)	$R1$ = 0.1336, w$R2$ = 0.1945
Largest diff. peak and hole	0.232 and -0.247 e$Å^{-3}$

Table 2 Crystal data and structure refinement for (**3**).

Empirical formula	C23 H23 F N4 O2 S
Formula weight	438.51
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system, space group	Triclinic, P-1
Unit cell dimensions	
a = 7.4400(9) Å	
b = 10.5011(13) Å	
c = 14.2403(18) Å	
α = 88.108(2)°	
β = 80.189(2)°	
γ = 72.735(2)°	
Volume	1046.7(2) Å^3
z	2
Calculated density	1.391 Mg/m^3
Absorption coefficient	0.192 mm^{-1}
F(000)	460
Crystal size	0.40 × 0.35 × 0.30 mm
Theta range for data collection	2.03 to 25.00 °.
Limiting indices	$-8 \leqslant h \leqslant 7$, $-12 \leqslant k \leqslant 11$, $-16 \leqslant l \leqslant 16$
Reflections collected/unique	5430/3631 [R(int) = 0.0244]
Completeness to theta	25.00% 98.3%
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	3631/0/281
Goodness-of-fit on F^2	0.997
Final R indices [I > 2sigma(I)]	$R1$ = 0.0547, w$R2$ = 0.1430
R indices (all data)	$R1$ = 0.0731, w$R2$ = 0.1687
Largest diff. peak and hole	0.532 and −0.326 eÅ^{-3}

Table 3 Selected bond lengths (Å) and angles (°) for compound (**2**).

S(1)–C(9)	1.723(3)	C(9)–S(1)–C(10)	88.36(15)
S(1)–C(10)	1.760(3)	C(9)–N(1)–C(7)	104.5(2)
N(1)–C(9)	1.312(3)	C(10)–N(2)–N(3)	109.0(2)
N(1)–C(7)	1.391(3)	C(9)–N(3)–C(8)	107.6(2)
N(2)–C(10)	1.291(4)	C(9)–N(3)–N(2)	118.1(3)
N(2)–N(3)	1.365(3)	C(8)–N(3)–N(2)	134.2(2)
N(3)–C(9)	1.361(3)	C(1)–O(1)–C(18)	118.7(3)
N(3)–C(8)	1.365(4)	C(8)–C(7)–N(1)	110.5(3)
F(1)–C(15)	1.355(4)	N(1)–C(7)–C(4)	120.6(2)
O(1)–C(1)	1.371(4)	N(3)–C(8)–C(7)	105.3(2)
O(1)–C(18)	1.422(4)	N(1)–C(9)–N(3)	112.1(3)
C(7)–C(8)	1.369(3)	N(1)–C(9)–S(1)	139.1(2)
C(10)–C(11)	1.487(4)	N(3)–C(9)–S(1)	108.8(2)
		N(2)–C(10)–S(1)	115.7(2)
		C(11)–C(10)–S(1)	121.0(3)

are given in Tables 3 and 4, respectively. Tables 5 and 6 give their respective hydrogen bond interactions. The ORTEP diagrams of the molecules **2** and **3** are shown in Figs. 1 and 2, respectively. Figs. 3 and 4 show the hydrogen bond interactions in crystal structure of (**2**) and (**3**), respectively.

Molecule (**2**) (Fig. 1) crystallizes in the monoclinic space group $P2_1/n$. The imidazo-thiadiazole and methoxyphenyl rings are coplanar with only 7.9° between them. Fluorobenzyl ring is inclined at an angle of 68.8° to these two ring systems. The methoxy group is *cis* to imidazo-thiadiazole and benzene ring.

Molecule (**3**) (Fig. 2) crystallizes in the triclinic space group *P-1*. The presence of morpholinomethyl ring decreases the pla-

Table 4 Selected bond lengths (Å) and angles (°) for compound (**3**).

S(1)–C(9)	1.727(3)	C(1)–O(1)–C(23)	117.5(2)
S(1)–C(10)	1.770(3)	C(20)–O(2)–C(21)	110.3(2)
F(1)–C(15)	1.364(3)	C(10)–N(1)–N(2)	108.5(2)
O(1)–C(1)	1.372(3)	C(9)–N(2)–N(1)	118.3(2)
O(1)–C(23)	1.416(4)	N(1)–N(2)–C(8)	133.2(2)
O(2)–C(20)	1.424(3)	C(9)–N(3)–C(7)	104.0(2)
O(2)–C(21)	1.428(4)	C(18)–N(4)–C(19)	111.7(2)
N(1)–C(10)	1.295(3)	O(1)–C(1)–C(2)	115.2(2)
N(1)–N(2)	1.373(3)	O(1)–C(1)–C(6)	124.7(3)
N(2)–C(9)	1.361(3)	C(8)–C(7)–N(3)	111.5(2)
N(2)–C(8)	1.386(3)	N(3)–C(7)–C(4)	120.3(2)
N(3)–C(9)	1.314(4)	N(2)–C(8)–C(7)	103.5(2)
N(3)–C(7)	1.401(3)	N(2)–C(8)–C(18)	122.5(2)
N(4)–C(18)	1.462(3)	N(3)–C(9)–N(2)	112.5(2)
N(4)–C(19)	1.462(3)	N(3)–C(9)–S(1)	138.4(2)
N(4)–C(22)	1.470(3)	N(2)–C(9)–S(1)	109.1(2)
C(8)–C(18)	1.492(4)	N(1)–C(10)–C(11)	122.6(3)
C(10)–C(11)	1.491(4)	N(1)–C(10)–S(1)	116.0(2)
C(11)–C(12)	1.514(4)	C(11)–C(10)–S(1)	121.3(2)
C(12)–C(13)	1.385(4)	C(16)–C(15)–F(1)	118.1(3)
C(19)–C(20)	1.514(4)	F(1)–C(15)–C(14)	119.0(3)
C(21)–C(22)	1.507(4)	N(4)–C(18)–C(8)	113.7(2)
		N(4)–C(19)–C(20)	110.7(2)
		O(2)–C(20)–C(19)	111.3(2)

Table 5 Non-bonded interactions and possible hydrogen bonds (Å, °) for compound (**2**) (D: donor; A: acceptor; H: hydrogen).

D–H···A	D–H	H···A	D···A	D–H···A
C11–H11B...N1	0.970(3)	2.532(2)	3.456(4)	159 (4)

Symmetry code: $-x + 1/2 + 1$, $+y - 1/2$, $-z + 1/2$.

Table 6 Non-bonded interactions and possible hydrogen bonds (Å, °) for compound (**3**) (D: donor; A: acceptor; H: hydrogen).

D–H···A	D–H	H···A	D···A	D—H···A
C3–H3...N4	0.930(3)	2.523(2)	3.379(4)	153
C13–H13...O2^{i}	0.930(3)	2.566(2)	3.407(3)	150
C11–H11A O2^{i}	0.970(3)	2.664(2)	3.525(4)	148
C23–H23C...N3^{ii}	0.960(3)	2.871(2)	3.471(4)	121
C17–H17...N3^{iii}	0.930(3)	2.584(3)	3.457(4)	156
C19–H19B...F1^{iv}	0.970(3)	2.666(2)	3.517(4)	146

Symmetry code: (0) x,y,z; (i) $-x + 1,-y,-z + 1$; (ii) $-x + 2,-y + 1,-z$; (iii) $x - 1, +y, +z$; (iv) $x + 1, +y - 1, +z$.

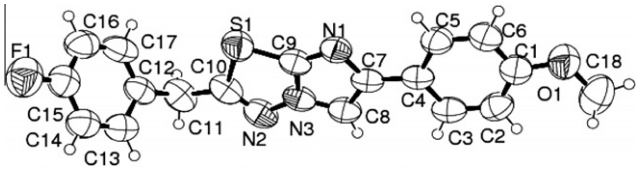


Figure 1 ORTEP diagram of compound (**2**), showing 50% probability displacement ellipsoids and the atom-numbering scheme.

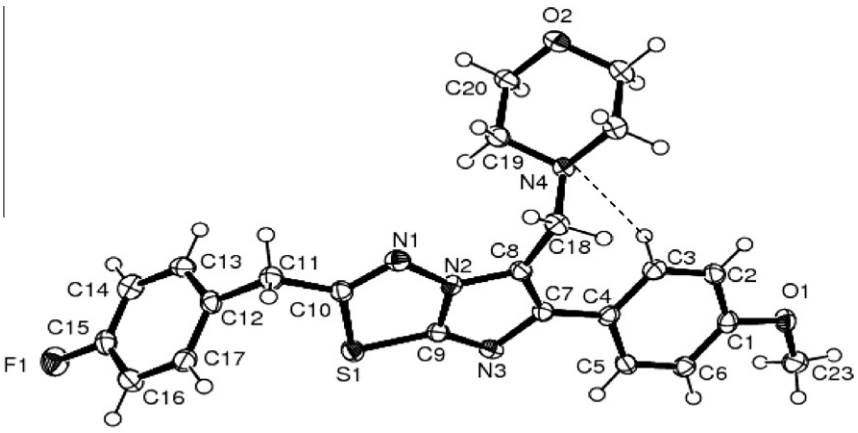


Figure 2 ORTEP diagram of compound (**3**), showing 50% probability displacement ellipsoids and the atom-numbering scheme. Dotted line indicates intramolecular C3–H3...N4 interaction.

narity of the molecule. This can be seen in the angle between imidazo-thiadiazole and methoxyphenyl rings increasing to 17.45° and that between fluorobenzyl and imidazo-thiadiazole increasing to 79.21°. The morpholinomethyl ring is almost orthogonal to imidazo-thiadiazole ring at an angle of 85.58°. A weak intramolecular C–H...N hydrogen bond interaction, which forms an S(7) graph-set motif, helps to establish the relative conformations of the ring systems involved. The morpholinomethyl moiety adopts a conventional chair conformation with oxygen and nitrogen atoms deviating from the plane and occupying apical and base positions respectively. The bond lengths and angles in morpholinomethyl ring conform to standard values (Parkin et al., 2004).

In the crystal structure of (**2**), there are C–H...N interactions (Fig. 3) (C11–H11B ...N1) linking the molecules through centrosymmetric dimers corresponding to the graph set (Bernstein et al., 1995) $R_2^2(12)$, along the crystallographic '*c*' axis. Additionally there are F...F short contacts (3.081 Å), providing cohesion. The aggregation is further reinforced by π–π stacking interactions with the shortest distance being 3.502 Å, between C16 and C18 atoms.

In the crystal structure of (**3**), there are C–H...O, C–H...N and C–H...F interactions. The C–H...O interaction generates a bifurcated bond from two donors, C11 and C13 to the same acceptor, O2 connecting the molecules into chain along the '*b*' axis (Fig. 4). Further, the C–H...N interactions also result in bifurcated bond from two donors, C17 and C23 to the same acceptor, N3 linking the dimers so formed into a tape pattern along the '*c*' axis (Fig. 5).

But the donor-acceptor distance is the least in the C–H...F interaction (3.517 Å) compared to those in C–H...O (3.525 Å) and C–H...N (3.457 Å), this makes the C–H...F bond a successful competitor for the C–H donor. This is unusual since

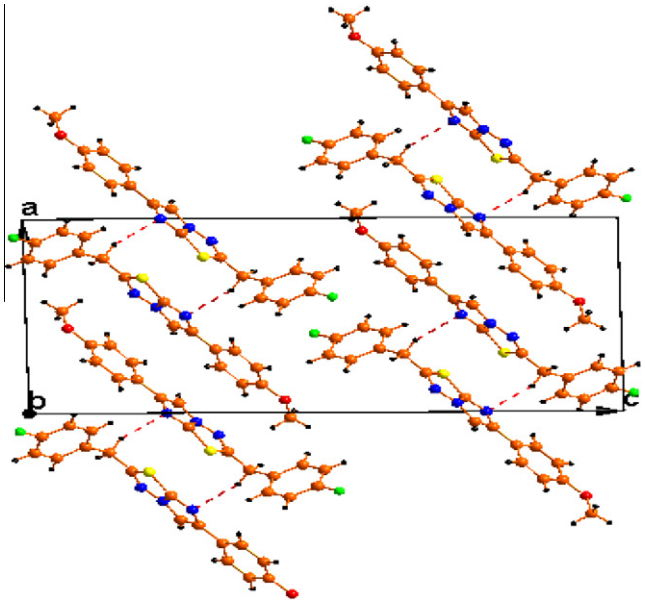


Figure 3 Packing of the molecules in crystal of (**2**) viewed along the '*b*' axis. Dotted lines indicate C–H...N intermolecular interactions resulting in dimers.

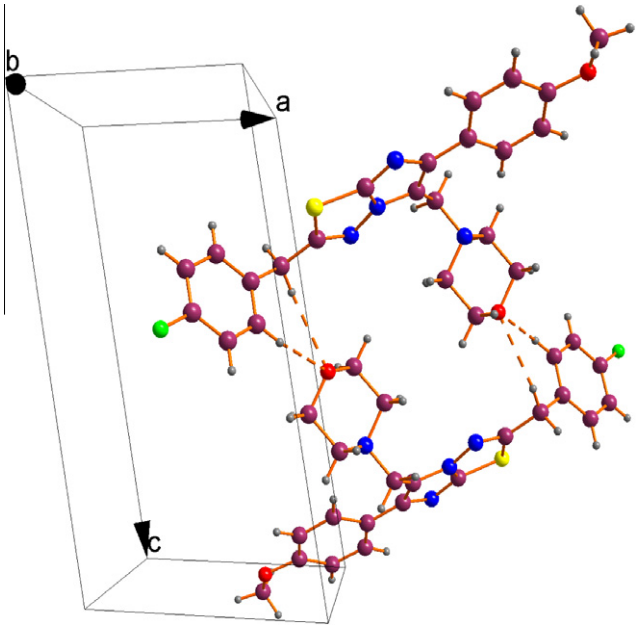


Figure 4 Packing of the molecules of (**3**) with dotted lines indicating C–H...O intermolecular interactions generating a bifurcated bond along the '*b*' axis.

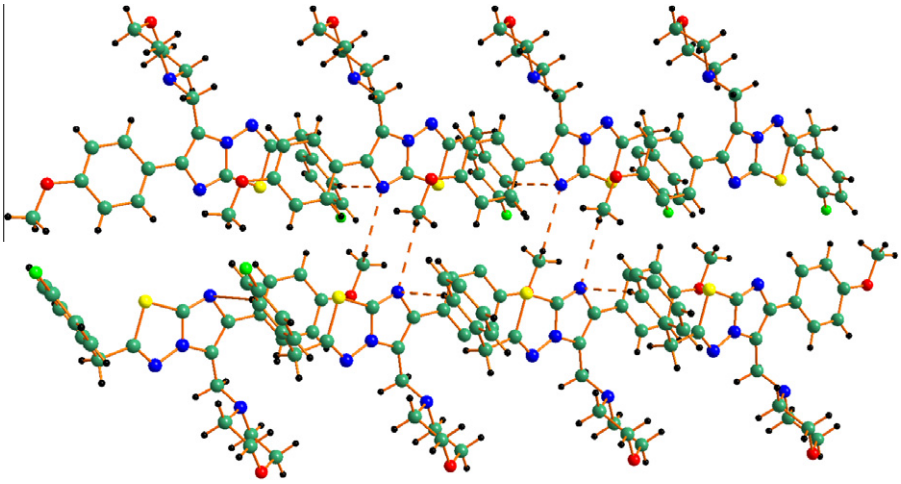


Figure 5 View of the molecular packing in (**3**), showing C–H...N interactions along the '*c*' axis.

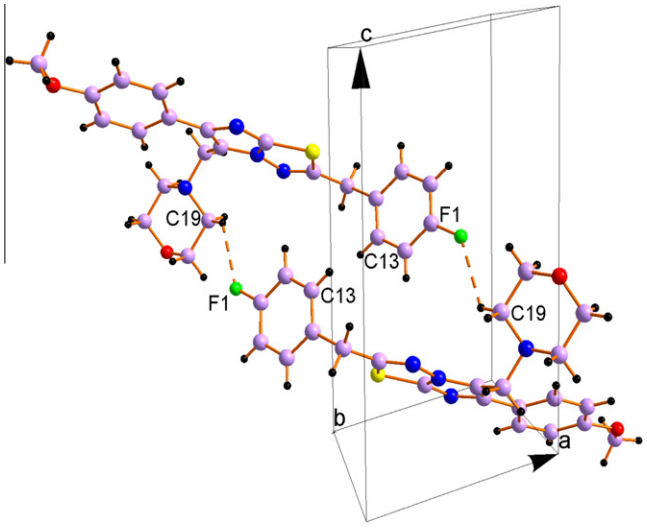


Figure 6 Packing of the molecules of (**3**) with dotted lines indicating C–H...F intermolecular interactions generating cyclic dimers along the '*b*' axis.

it happens in the presence of oxygen and nitrogen which are strong acceptor atoms, thus making the C–H...F interaction an important structure-directing entity. The molecules are linked by paired C–H...F hydrogen bonds into cyclic dimers corresponding to the graph set (Bernstein et al., 1995) notation $R_2^2(28)$ (Fig. 6).

The molecular packing is further stabilized by π–π stacking interactions between fluorobenzyl rings with the shortest centroid-centroid distance being 3.45 Å for C13–C13 carbons [Cg–Cg symmetry code: $-x, 1-y, 1-z$].

Notably, there are no F...F contacts, which shows that fluorine would form C–H...F interactions rather than F...F contacts. This distinctly different behavior of F from other heavier halogens that prefer halogen-halogen interactions has been observed in many organo fluorine compounds (Brock et al., 1978; Weiss et al., 1997; Thalladi et al., 1998).

The presence of fluorine atoms attached to the aromatic ring increases the acidity of the aromatic hydrogen atoms as is generally observed with aromatic compounds (Estarellas et al., 2008) and the strength of any C–H...X interaction (X = halogen) depends on C–H group acidity. Regarding the location of the F atom, the flourobenzyl group is attached to the thiadiazole part of imidazo-thiadiazole system. It is well known that the imidazole and thiadiazole parts show different π conjugations, owing to their fused nature. The imidazole part of this imidazo-thiadiazole system is more resonance stabilized. Additionally, the imidazo-thiadiazole entity is generally planar and rigid.

The crystal packing of compound (**3**) establishes the fact that the so-called elusive C–H...F interaction can be as important as C–H...O and C–H...N interactions in achieving a cohesive self assembly. Supramolecular synthons based on this weak interaction can be useful building blocks for construction of crystalline superstructures. The prospects for such systematic design of structures are worth exploring.

5. Conclusion

This work describes the synthesis of an imidazo[2,1-*b*]-[1,3,4]thiadiazole derivative and its subsequent aminomethylation in a Mannich reaction to give its corresponding 5-(morpholinomethyl) derivative. Additionally, the X-ray analysis was carried out in order to establish a supramolecular assembly with the specific aim of assessing various weak interactions including fluorine interaction that control the architecture of organic solids.

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