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Crystal structure of *N*-ethyl-4-[3-(trifluoromethyl)-phenyl]piperazine-1-carbothioamide, $C_{14}H_{18}F_3N_3S$

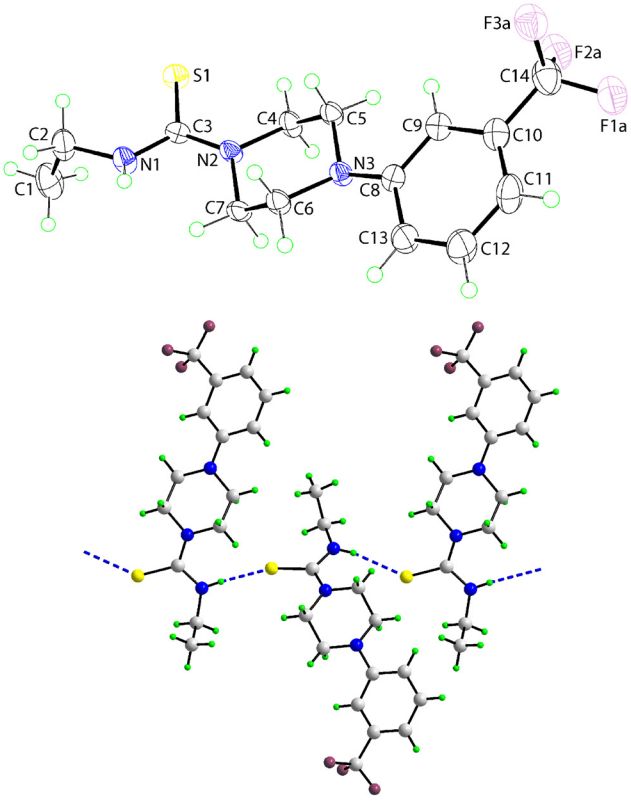

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Table 1: Data collection and handling.

Crystal:	Plate, colourless
Size:	0.19 × 0.06 × 0.03 mm
Wavelength:	Cu *K*α radiation (1.54184 Å)
μ:	2.18 mm^{-1}
Diffractometer, scan mode:	SuperNova, ω-scans
θ_{max}, completeness:	74.5°, >99%
$N(hkl)_{measured}$, $N(hkl)_{unique}$, R_{int}:	15,788, 3093, 0.016
Criterion for I_{obs}, $N(hkl)_{gt}$:	$I_{obs} > 2\ \sigma(I_{obs})$, 2960
$N(param)_{refined}$:	223
Programmes:	CrysAlis^{Pro} [1], SHELX [2, 3], OLEX2 [4]

Abstract

$C_{14}H_{18}F_3N_3S$, monoclinic, $P2_1/c$ (no. 14), a = 4.61919(4) Å, b = 29.1507(3) Å, c = 11.27803(10) Å, β = 94.4768(8)°, V = 1513.99(3) Å^3, Z = 4, $R_{gt}(F)$ = 0.0588, $wR_{ref}(F^2)$ = 0.1579, T = 160 K.

CCDC no.: 2211988

The molecular structure and supramolecular chain in the crystal are shown in the figure. Table 1 contains crystallographic data and Table 2 contains the list of the atoms including atomic coordinates and displacement parameters.

Source of material

Ethyl isothiocyanate (436 mg, 5.0 mmol) was added to a solution of 1-(3-trifluoromethylphenyl)piperazine (1.15 g, 5.0 mmol) in ethanol (8 mL), and the mixture was heated under reflux for 1 h. Water (15 mL) was added and the mixture was stirred for further 30 min at room temperature. The precipitated crude product was filtered, washed with water, dried and crystallised from aqueous ethanol to yield 1.49 g (94%) of the title compound (I) as colourless plates. M.pt: 380–381 K (uncorrected). **^{1}H NMR** ($CDCl_3$, 500.13 MHz): δ 1.30 (t, 3H, CH_3, J = 7.5 Hz), 3.26–3.28 (m, 4H, Piperazine–H), 3.96 (t, 4H, Piperazine–H, J = 7.0 Hz), 4.40 (q, 2H, CH_3, J = 7.5 Hz), 6.88–6.89 (m, 1H, Ar–H), 7.26–7.42 (m, 4H, Ar–H & NH). **^{13}C NMR** ($CDCl_3$, 125.76 MHz): δ 14.66 (CH_3),

Table 2: Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å^2).

	x	*y*	*z*	U_{iso}*/U_{eq}
F1A[a]	0.4357 (7)	0.58429 (9)	0.6886 (3)	0.0474 (5)
F1B[b]	0.3499 (13)	0.58397 (15)	0.7181 (5)	0.0486 (6)
F2A[a]	0.2987 (8)	0.54297 (12)	0.5417 (2)	0.0476 (5)
F2B[b]	0.3990 (13)	0.5475 (2)	0.5534 (4)	0.0470 (6)
F3A[a]	0.0078 (6)	0.55534 (12)	0.6761 (3)	0.0490 (5)
F3B[b]	−0.0038 (7)	0.5406 (2)	0.6326 (6)	0.0480 (6)
N1	−0.0072 (5)	0.22093 (7)	0.65401 (18)	0.0303 (4)
H1	0.030 (7)	0.2288 (11)	0.724 (3)	0.036 (8)*
N2	0.1803 (4)	0.28986 (6)	0.59848 (16)	0.0259 (4)
N3	0.3860 (4)	0.37736 (6)	0.68388 (16)	0.0255 (4)
S1	−0.14082 (13)	0.24423 (2)	0.42956 (5)	0.0308 (2)
C1	0.0077 (8)	0.13887 (10)	0.6014 (3)	0.0518 (8)
H1A	0.091089	0.146572	0.526609	0.078*
H1B	−0.114146	0.111468	0.589903	0.078*
H1C	0.164508	0.132875	0.663057	0.078*
C2	−0.1743 (6)	0.17842 (9)	0.6392 (2)	0.0397 (6)
H2A	−0.338581	0.183240	0.578665	0.048*
H2B	−0.255863	0.170638	0.715243	0.048*
C3	0.0232 (5)	0.25208 (7)	0.56815 (19)	0.0235 (4)
C4	0.2233 (6)	0.32746 (8)	0.51589 (19)	0.0296 (5)
H4A	0.080032	0.324900	0.446205	0.036*
H4B	0.420077	0.325286	0.487260	0.036*
C5	0.1886 (5)	0.37352 (8)	0.57601 (19)	0.0272 (5)
H5A	0.230083	0.398459	0.520192	0.033*
H5B	−0.014348	0.377036	0.596975	0.033*
C6	0.3377 (5)	0.33956 (8)	0.76581 (19)	0.0273 (5)
H6A	0.138233	0.341476	0.791780	0.033*
H6B	0.475838	0.342147	0.837163	0.033*
C7	0.3790 (5)	0.29401 (8)	0.7059 (2)	0.0276 (5)
H7A	0.582014	0.291312	0.684401	0.033*
H7B	0.341862	0.268811	0.761588	0.033*
C8	0.4369 (5)	0.42106 (8)	0.7331 (2)	0.0263 (5)
C9	0.3234 (5)	0.46090 (8)	0.6790 (2)	0.0285 (5)
H9	0.193717	0.458766	0.609566	0.034*
C10	0.3992 (5)	0.50383 (8)	0.7263 (2)	0.0322 (5)
C11	0.5772 (7)	0.50860 (9)	0.8290 (2)	0.0422 (6)
H11	0.623244	0.538034	0.861293	0.051*
C12	0.6876 (7)	0.46900 (10)	0.8840 (3)	0.0488 (7)
H12	0.810089	0.471421	0.955373	0.059*
C13	0.6226 (6)	0.42604 (9)	0.8367 (2)	0.0384 (6)
H13	0.704986	0.399548	0.875030	0.046*
C14	0.2839 (5)	0.54539 (9)	0.6596 (2)	0.0442 (5)

Occupancies: [a]0.642 (5), [b]0.358 (5).

39.98 (CH_2), 52.50, 54.82 (Piperazine–C), 112.06, 114.20, 119.62, 130.76, 132.25, 150.14 (Ar–C), 124.86 (CF_3), 179.84 (C=S). ESI–MS, m/z: 318.4 $[M+H]^+$.

Experimental details

The C-bound H atoms were geometrically placed (C–H = 0.95–0.99 Å) and refined as riding with U_{iso}(H) = 1.2–1.5U_{eq}(C). The N-bound H atom was located in a difference map and refined using isotropic approximation. The F atoms of the $-CF_3$ group are disordered over two positions. Some restraints had to be used to correct the geometry of the disordered components (SADI) and the thermal parameters of the constituent atoms (SIMU). At the conclusion of the refinement, the major component of the disorder had a site occupancy = 0.642(5). The maximum and minimum electron density peaks of 1.04 and 0.65 e Å^{-3}, respectively, were located 0.86 and 0.36 Å from the F1a atom.

Discussion

The piperazine scaffold has been identified as a privileged structure in drug discovery and various piperazine-based derivatives are currently employed as efficient chemotherapeutic agents [5, 6]. Several piperazine-1-carbothioamide derivatives were reported to possess potent anti-bacterial [7, 8] and anti-inflammatory [9] activities. It was in this context that the crystal and molecular structures of the title hybrid piperazine-1-carbothioamide derivative, (I), were studied.

The molecular structure of (I) is shown in the upper image of the figure (50% probability ellipsoids; only the major component of the disordered $-CF_3$ group is shown). The C3–N2–C7–C6 torsion angle is –135.4(2)°, indicating a significant twist about the C7–N2 bond, in order to reduce steric congestion. Despite this rotation, a close intramolecular H1···H7b contact of 1.88 Å as well as a C7···H1 contact of 2.51 Å are evident. The C3–N1 [1.343(3) Å] and C3–N2 [1.348(3) Å] bond lengths are experimentally equivalent; the C3–S1 bond length is 1.698(2) Å. Further twists in the molecule are manifested in the dihedral angle between the CN_2S chromosphere and terminal phenyl ring of 34.00(9)°. The 1,4-di-substituted piperazine ring has a conformation of a chair.

There are two closely related piperazine derivatives in the literature, each of which has a terminal, unsubstituted phenyl ring. In the simplest derivative of these, the N-bound substituent is an adamantan-1-yl group [10] while in the second literature molecule the nitrogen atom is connected to a more complicated fused, three-ring system comprising a five-, six- and five-ring sequence [11]. The equivalent C3–S1 bond lengths in the literature precedents of 1.694(4) and 1.692(4) Å, respectively, are the same as in (I). While for the adamantan-1-yl derivative [adam] the C3–N1 and C3–N3 bond lengths [1.351(4) & 1.369(4) Å] are indistinguishable, there is evidence of disparities in these bonds [1.336(5) & 1.371(6) Å] in the second literature molecule.

As illustrated in the lower view of the figure, supramolecular chains are apparent in the crystal. The molecules in the chain are related by glide symmetry along [001] and are connected by amine–N–H···S(thione) hydrogen bonds [N1–H1···S1^{i}: H1···S1^{i} = 2.63(3) Å, N1···S1^{i} = 3.372(2) Å with angle at H1 = 151(3)° for symmetry operation (i): x, 1/2 – y, 1/2 + z]. While no N–H···S hydrogen bonds are noted in the crystal of the literature adamantan-1-yl structure, probably owing to the bulk of the N-bound substituent, linear chains are apparent in the second literature structure. Connections between zigzag chains in (I), to form an undulating supramolecular layer are of the type C–H···F with the shortest of these being a piperazine-methylene–C–H···F interaction [C5–H5a···F3b^{ii}: H5a···F3b^{ii} = 2.52 Å, C5···F3b^{ii} = 3.390(6) Å with angle at H5a = 147° for (ii): 1 – x, 1 – y, 1 – z], i.e. involving an atom comprising a minor component of the disordered residue. The chains stack along the a-axis in an ···ABA··· sequence without directional between them.

In order to gain a greater appreciation of the supramolecular association, an analysis for the calculated Hirshfeld surfaces was conducted employing CrystalExplorer 17 [12] in accord with standard methods [13]. The Hirshfeld surfaces were calculated for both the major and minor components of the disordered –CF_3 group. The differences in percentage contributions to the surfaces from either component of the disorder were no greater than 1.0% so the following discussion is based on calculations performed for the major component. By far the greater contribution to the Hirshfeld surface was from H···H contacts, i.e. 46.2%. Significant contributions also came from F···H/H···F [22.9%], S···H/H···S [11.2%] and C···H/H···C [8.9%] contacts. Relatively minor contributions to the surface were of the type N···H/H···N [3.2%], F···C/C···F [3.0%] and F···F [2.7%]. The only other contribution to the Hirshfeld surface greater than 0.1% was from C···C contacts, i.e. 1.7%.

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