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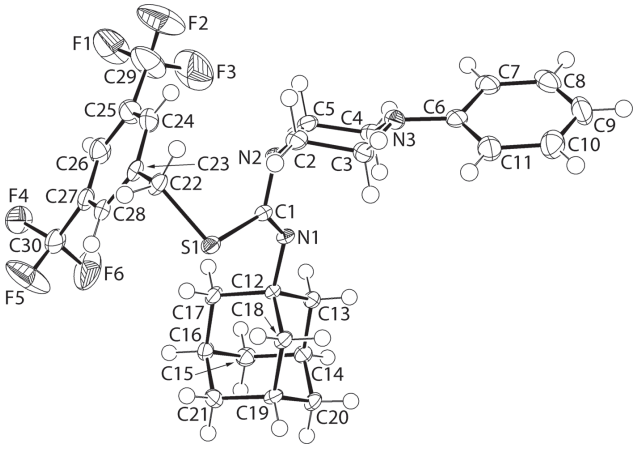
Crystal structure of 3,5-bis(trifluoromethyl)benzyl (*Z*)-*N'*-(adamantan-1-yl)-4-phenylpiperazine-1-carbothioimidate, $C_{30}H_{33}F_6N_3S$



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Abstract

$C_{30}H_{33}F_6N_3S$, triclinic, $P\bar{1}$ (no. 2), $a = 9.3012(5)$ Å, $b = 10.2734(5)$ Å, $c = 15.1850(8)$ Å, $\alpha = 81.982(2)°$, $\beta = 78.696(2)°$, $\gamma = 83.882(2)°$, $V = 1404.25(13)$ Å^3, $Z = 2$, $R_{gt}(F) = 0.0779$, $wR_{ref}(F^2) = 0.2499$, $T = 293(2)$ K.

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

Table 1: Data collection and handling.

Crystal:	Slab, colorless
Size:	0.58 × 0.47 × 0.07 mm
Wavelength:	Mo $K\alpha$ radiation (0.71073 Å)
μ:	0.18 mm^{-1}
Diffractometer, scan mode:	Bruker APEX-II, φ and ω-scans
θ_{max}, completeness:	33.2°, >99%
$N(hkl)_{measured}$, $N(hkl)_{unique}$, R_{int}:	48368, 10750, 0.095
Criterion for I_{obs}, $N(hkl)_{gt}$:	$I_{obs} > 2\ \sigma(I_{obs})$, 7424
$N(param)_{refined}$:	398
Programs:	Bruker programs [1], SHELX [2, 3], ORTEP [4]

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

Atom	*x*	*y*	*z*	U_{iso}*/U_{eq}
S1	0.98386(5)	0.51000(4)	0.66054(3)	0.01323(12)
N1	0.69696(17)	0.60257(15)	0.64402(11)	0.0122(3)
N2	0.86822(17)	0.75759(15)	0.62935(11)	0.0129(3)
N3	0.82652(17)	0.92552(15)	0.46515(11)	0.0141(3)
F1[a]	0.6835(5)	0.8971(3)	1.02509(18)	0.0589(9)
F2[a]	0.8013(4)	0.9811(2)	0.8977(2)	0.0610(9)
F3[a]	0.5984(4)	0.9168(3)	0.9015(2)	0.0706(9)
F1′[b]	0.8490(9)	0.9393(6)	0.9780(5)	0.0619(13)
F2′[b]	0.7236(12)	0.9677(7)	0.8762(5)	0.0598(14)
F3′[b]	0.6193(10)	0.8858(9)	1.0038(6)	0.0622(15)
F4	0.72337(19)	0.41464(15)	1.10754(9)	0.0349(4)
F5	0.8472(2)	0.29227(15)	1.01309(12)	0.0573(6)
F6	0.6274(3)	0.3624(2)	1.00252(14)	0.0643(7)
C1	0.82839(19)	0.62775(17)	0.64263(12)	0.0116(3)
C2	0.9920(2)	0.79314(18)	0.55694(13)	0.0150(3)
H2A	1.0694	0.7219	0.5558	0.018*
H2B	1.0313	0.8711	0.5692	0.018*
C3	0.9452(2)	0.81997(18)	0.46506(13)	0.0144(3)
H3A	1.0287	0.8450	0.4188	0.017*
H3B	0.9121	0.7403	0.4508	0.017*
C4	0.7000(2)	0.89565(18)	0.53841(13)	0.0148(3)
H4A	0.6542	0.8212	0.5262	0.018*
H4B	0.6276	0.9710	0.5404	0.018*
C5	0.7496(2)	0.86352(18)	0.62956(13)	0.0146(3)
H5A	0.7829	0.9422	0.6452	0.017*

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Table 2 (continued)

Atom	x	y	z	U_{iso}*/U_{eq}
H5B	0.6663	0.8377	0.6757	0.017*
C6	0.7924(2)	0.97605(18)	0.37967(14)	0.0156(4)
C7	0.6890(2)	1.08575(19)	0.37243(16)	0.0200(4)
H7	0.6424	1.1225	0.4243	0.024*
C8	0.6557(2)	1.1396(2)	0.28977(17)	0.0253(5)
H8	0.5862	1.2114	0.2867	0.030*
C9	0.7252(3)	1.0876(2)	0.21042(17)	0.0281(5)
H9	0.7018	1.1236	0.1548	0.034*
C10	0.8297(3)	0.9814(2)	0.21635(16)	0.0262(5)
H10	0.8783	0.9469	0.1640	0.031*
C11	0.8626(2)	0.9256(2)	0.29992(15)	0.0201(4)
H11	0.9323	0.8539	0.3026	0.024*
C12	0.63842(19)	0.47279(17)	0.66558(12)	0.0105(3)
C13	0.47856(19)	0.49282(17)	0.65042(13)	0.0131(3)
H13A	0.4230	0.5544	0.6899	0.016*
H13B	0.4769	0.5306	0.5884	0.016*
C14	0.4059(2)	0.36227(18)	0.66950(13)	0.0142(3)
H14	0.3044	0.3778	0.6592	0.017*
C15	0.4064(2)	0.30470(19)	0.76833(13)	0.0162(4)
H15A	0.3500	0.3650	0.8084	0.019*
H15B	0.3611	0.2217	0.7812	0.019*
C16	0.5654(2)	0.28244(19)	0.78459(13)	0.0152(3)
H16	0.5656	0.2454	0.8476	0.018*
C17	0.6379(2)	0.41381(18)	0.76491(12)	0.0139(3)
H17A	0.7380	0.3991	0.7758	0.017*
H17B	0.5840	0.4752	0.8051	0.017*
C18	0.7227(2)	0.37406(17)	0.60209(12)	0.0127(3)
H18A	0.7217	0.4103	0.5397	0.015*
H18B	0.8243	0.3595	0.6102	0.015*
C19	0.6515(2)	0.24254(17)	0.62253(13)	0.0135(3)
H19	0.7073	0.1803	0.5825	0.016*
C20	0.4927(2)	0.26407(18)	0.60698(13)	0.0149(3)
H20A	0.4478	0.1809	0.6198	0.018*
H20B	0.4911	0.2984	0.5443	0.018*
C21	0.6524(2)	0.18559(18)	0.72137(13)	0.0159(4)
H21A	0.7529	0.1701	0.7315	0.019*
H21B	0.6084	0.1019	0.7342	0.019*
C22	1.0637(2)	0.5927(2)	0.73707(13)	0.0160(4)
H22A	1.1509	0.5404	0.7517	0.019*
H22B	1.0929	0.6780	0.7070	0.019*
C23	0.9554(2)	0.61106(19)	0.82258(13)	0.0150(3)
C24	0.8961(2)	0.7359(2)	0.84203(14)	0.0205(4)
H24	0.9264	0.8099	0.8029	0.025*
C25	0.7908(3)	0.7504(2)	0.92038(15)	0.0243(4)
C26	0.7426(3)	0.6411(2)	0.97887(14)	0.0230(4)
H26	0.6706	0.6509	1.0300	0.028*
C27	0.8041(2)	0.5168(2)	0.95945(14)	0.0192(4)
C28	0.9100(2)	0.50135(19)	0.88264(13)	0.0167(4)
H28	0.9510	0.4174	0.8711	0.020*
C29[a]	0.7186(4)	0.8848(4)	0.9376(2)	0.0486(8)
C29′[b]	0.7479(9)	0.8848(11)	0.9475(5)	0.0535(10)
C30	0.7503(3)	0.3973(2)	1.02066(15)	0.0255(5)

Occupancies: [a] = 0.716(3), [b] = 284(3)

Source of material

3,5-Bis(trifluoromethyl)benzyl bromide (614 mg, 2.0 mmol) and anhydrous potassium carbonate (276 mg, 2 mmol) were added to an anhydrous acetone (15 mL) solution of *N*-(adamantan-1-yl)-4-phenylpiperazine-1-carbothioamide (711 mg, 2 mmol), and the mixture was heated under reflux for 4 h. The solvent was then distilled off *in vacuo* and the resulting residue was washed with water (20 mL), dried and crystallized from aqueous ethanol to yield 872 mg (75%) of the title compound as colourless crystals. *M*.pt: 386–388 K. Single crystals suitable for X-ray analysis were obtained by the slow evaporation of its $CHCl_3$:EtOH (1:1; 5 mL) solution held at room temperature. **^{1}H NMR** ($CDCl_3$, 700.17 MHz): δ 1.58 (s, 6H, adamantane-CH_2), 1.69 (s, 6H, adamantane-CH_2), 1.95−1.97 (m, 3H, adamantane-CH), 3.29–3.31 (m, 4H, piperazine-H), 3.40–3.42 (m, 4H, piperazine-H), 4.04 (s, 2H, benzylic CH_2), 6.93–7.02 (m, 3H, Ar−H), 7.29 (s, 1H, Ar−H), 7.32–7.34 (m, 2H, Ar−H), 7.78 (s, 2H, Ar−H). **^{13}C{^{1}H} NMR** ($CDCl_3$, 176.08 MHz): δ 29.80, 35.51, 36.44, 54.80 (adamantane-C), 37.31 (benzylic CH_2), 49.0, 49.13 (piperazine-C), 116.28, 120.12, 129.16, 129.24, 131.44, 131.63, 141.30, 147.50 (Ar−C), 124.04 (CF_3), 151.19 (C=N). **ESI-MS**, m/*z*: 582.2 [*M* + H]+.

Experimental details

The C-bound H atoms were geometrically placed (C−H = 0.93–0.98 Å) and refined as riding with U_{iso}(H) = 1.2U_{eq}(C). Disorder was resolved for the C25-bound CF_3 group with two distinct sites modelled. The site occupancy factor for the major component refined to 0.716(3). Standard restraints in SHELXL [3], such as SADI and SIMU, were employed. The maximum and minimum residual electron density peaks of 1.14 and 1.35 e Å^{-3}, respectively, were located 0.80 and 0.73 Å from the F1′ and S1 atoms, respectively.

Discussion

Recently, a series of adamantane-isothiourea hybrid derivatives were synthesized and demonstrated to exhibit a broad spectrum of anti-bacterial activity [5]. The motivation for the synthesis of these potential drugs was twofold. Firstly, the adamantane cage, known to be highly lipophilic, is a crucial pharmacophore in a number of drugs [6]. A key example is that of the drug amantadine, an effective anti-viral agent for influenza A viruses [7] as well as being a potent anti-parkinsonian agent [8]. Subsequently, adamantane derivatives have been shown to exhibit diversified pharmocological potential, including anti-viral [9], anti-cancer [10], anti-bacterial and anti-fungal [11], anti-malarial [12] and anti-diabetic [13] activities. Secondly, and in the same way, isothiourea derivatives are known to display

significant anti-viral [14], anti-cancer [15] and anti-bacterial [16] activities. With such a diverse range of pharmacological profiles exhibited by both adamantane and isothiourea derivatives, it was thought their combination through the synthesis of adamantane-isothiourea hybrid molecules would lead to even more efficient therapeutic agents [5]. Herein, the crystal and molecular structures of the title compound are described in continuation of complementary structural studies of these new anti-bacterial agents [17].

The molecule [systematic name: 3,5-bis(trifluoromethyl) benzyl 4-phenyl-*N*-(tricyclo[3.3.1.1^{3,7}]decan-1-yl)piperazine-1-carboximidothioate] is shown in the figure (70% displacement ellipsoids; the minor component of the disordered CF_3 has been omitted). The central CN_2S chromophore is strictly planar with the r.m.s. deviation of the least-squares plane through the C1, N1, N2 and S1 atoms being 0.0068 Å. There is a *Z* configuration about the C1=N1 bond [1.272(2) Å], and the piperazinyl ring has a chair conformation. The conformational relationship between the central plane and the piperazinyl ring approaches orthogonal with the dihedral angle between the least-squares planes through the residues being 70.42(7)°. The dihedral angle between the least-squares planes through the piperazinyl and the N3-bound phenyl ring is 28.47(6)°, indicating a twisted conformation. To a first approximation, the di-substituted benzyl residue is folded back over the rest of the molecule. Nevertheless, the residue is inclined towards the piperazinyl group as reflected in the values of the C22—S1—C1—N2 and C22—S1—C1—N1 torsion angles of 42.75(15) and −135.09(17)°, respectively. Generally the geometric parameters are in the expected ranges [18, 19].

The most prominent feature of the molecular packing are weak methylene-C—H···N(piperazinyl) interactions between centrosymmetrically related molecules [C2—H2b···N3^{i}: H2b···N3^{i} = 2.53 Å, C2···N3^{i} = 3.444(2) Å with an angle at H2b = 157° for symmetry operation i: $2-x$, $2-y$, $1-z$], leading to dimeric aggregates. There are no other directional interactions connecting molecules. Globally, molecules assemble into double layers that stack along the *c* axis direction. The CF_3 groups project to either side of the layers and inter-digitate with successive layers. Reflecting the packing, the calculated Hirshfeld surfaces [20, 21] show a dominance of H···H [48.6%], F···H/H···F [28.1%], C···H/H···C [10.2%] and F···F [6.3%] contacts to the overall surface.

There are two literature precedents for the title compound, namely derivatives with 4-nitrobenzyl [5] and 4-bromobenzyl [22] groups. There are non-trivial differences in the conformations in these molecules. While there is nearly an orthogonal relationship between the central plane and the piperazinyl ring in the title structure, these residues are closer to co-planar in the literature structures, with comparable dihedral angles of 32.2(3) and 34.78(7)°, respectively.

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