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Crystal structures of vortioxetine and its methanol monosolvate

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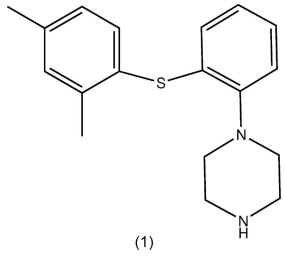
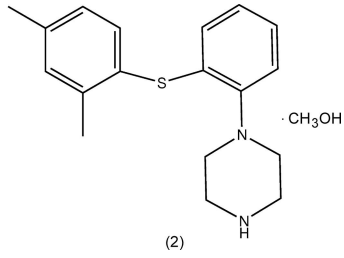
Vortioxetine, $C_{18}H_{22}N_2S$, (1), systematic name 1-{2-[(2,4-dimethylphenyl)sulfanyl]phenyl}piperazine, a new drug used to treat patients with major depressive disorder, has been crystallized as the free base and its methanol monosolvate, $C_{18}H_{22}N_2S{\cdot}CH_3OH$, (2). In both structures, the vortioxetine molecules have similar conformations: in (1), the dihedral angle between the aromatic rings is 80.04 (16)° and in (2) it is 84.94 (13)°. The C—S—C bond angle in (1) is 102.76 (14)° and the corresponding angle in (2) is 103.41 (11)°. The piperazine ring adopts a chair conformation with the exocyclic N—C bond in a pseudo-equatorial orientation in both structures. No directional interactions beyond normal van der Waals contacts could be identified in the crystal of (1), whereas in (2), the vortioxetine and methanol molecules are linked by N—H···O and O—H···N hydrogen bonds, generating [001] chains.

1. Chemical context

Major depressive disorder (MDD) is a disabling mental illness responsible for almost 66 million disability-adjusted life-years globally (Bidzan *et al.*, 2012). The medications most often prescribed for depression include the selective serotonin reuptake inhibitors (SSRIs) and the serotonin norepinephrine reuptake inhibitors (SNRIs). As several neurotransmitter pathways may be involved in MDD, antidepressants possessing two or more complementary modes of action (*i.e.* multimodal) have been a focus of MDD therapy for some time (Richelson, 2013). One such antidepressant is vortioxetine.

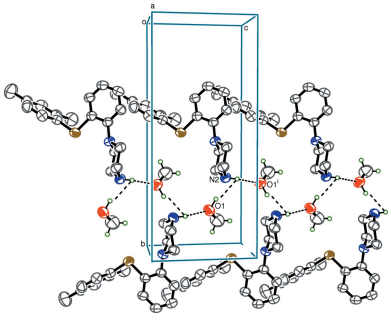


(1)



(2)

Vortioxetine is an investigational multi-modal antidepressant that is believed to work through a combination of two pharmacological modes of action: serotonin (5-HT) reuptake inhibition and 5-HT receptor activity (du Jardin *et al.*, 2014; Hussar *et al.*, 2014). In 2013, vortioxetine hydrobromide was approved by the US Food and Drug Administration (FDA) for the once-daily treatment of adults with MDD in the USA (Gibb & Deeks, 2014. The patent of Benny *et al.* (2007) discloses crystalline vortioxetine base and a variety of crys-



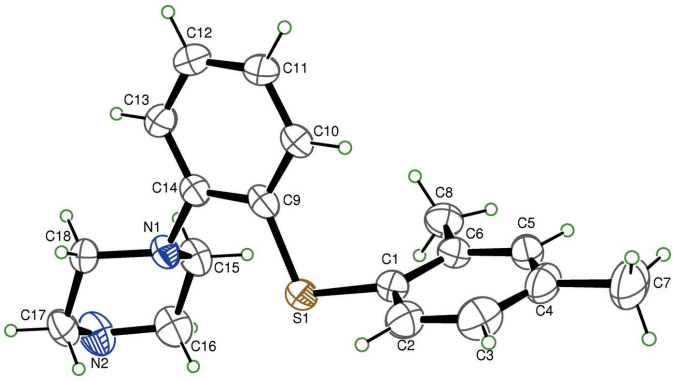


Figure 1
The molecular structure of compound (1), showing 50% probability displacement ellipsoids.

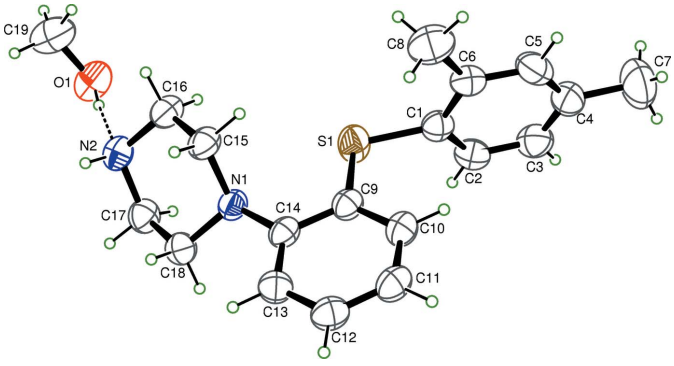


Figure 2
The molecular structure of compound (2), showing 50% probability displacement ellipsoids.

talline vortioxetine salts, comprising polymorphs of vortioxetine hydrobromide as well as a hemihydrate and an ethyl acetate solvate thereof, and crystalline vortioxetine hydrochloride and a monohydrate thereof. Crystalline vortioxetine mesylate, mesohydrogentartrate, hydrogenmaleate and hydrogen sulfate are also disclosed. However, there are few reports on the single-crystal X-ray structure of vortioxetine base and its salts. As part of our ongoing structural studies of pharmaceutical compounds, the crystal structures of vortioxetine free base (1), and its methanol solvate (2), have been determined and reported here.

2. Structural commentary

The asymmetric unit of (1) consists of one vortioxetine molecule and that of compound (2) consists of one vortioxetine molecule and one methanol molecule. Views of the asymmetric units of (1) and (2), with atom labelling, are presented in Figs. 1 and 2, respectively. In both structures, the two benzene rings bridged by the S atom, are almost perpendicular to one another. The dihedral angles between the planes of these benzene rings is 80.04 (16)° in compound (1) and 84.94 (13)° in compound(2). The S atom is nearly coplanar with the benzene rings as indicated by C1—S1—C9—C14 torsion angles of 176.0 (2) for (1) and −176.04 (18)° for (2).

Table 1
Hydrogen-bond geometry (Å, °) for (2).

D—H···A	D—H	H···A	D···A	D—H···A
N2—H2A···O1^{i}	0.86	2.15	2.930 (3)	151
O1—H1···N2	0.82	1.93	2.744 (3)	171

Symmetry code: (i) $x, -y+\frac{1}{2}, z+\frac{1}{2}$.

The piperazine ring of both structures adopts a chair conformation with the exocyclic N1—C14 bond in a pseudo equatorial orientation. Atoms N1 and N2 deviate from the best fit plane through the remaining four C atoms by 0.683 (1) and 0.637 (1) Å in (1) and by 0.698 (1) and −0.562 Å in (2).

3. Supramolecular features

There are no hydrogen bonds or π–π stacking interactions linking the molecules in (1), while in (2) the presence of the additional methanol solvent molecule results in the formation of zigzag chains mediated by alternating O1—H1···N2 and N2—H2A···O1^{i} [symmetry code: (i) $x, -y+\frac{1}{2}, z+\frac{1}{2}$] hydrogen bonds propagating along the c-axis direction (Table 1). a packing diagram for (2) is shown in Fig. 3.

4. Synthesis and crystallization

Vortioxetine was supplied by Zhejiang Jingxin Pharmaceutical Co., Ltd. Crystals of (1) and (2) suitable for X-ray diffraction were recrystallized by slow evaporation from acetonitrile and methanol–water solutions, respectively, at room temperature over a few days.

5. Refinement

Crystal data, data collection and structure refinement details are summarized in Table 2. All H atoms were placed in idealized positions and refined as riding, with C—H = 0.93–0.97, N—H = 0.86 and O—H = 0.82 Å and U_{iso}(H) = 1.2U_{eq} or 1.5U_{eq}(carrier atom).

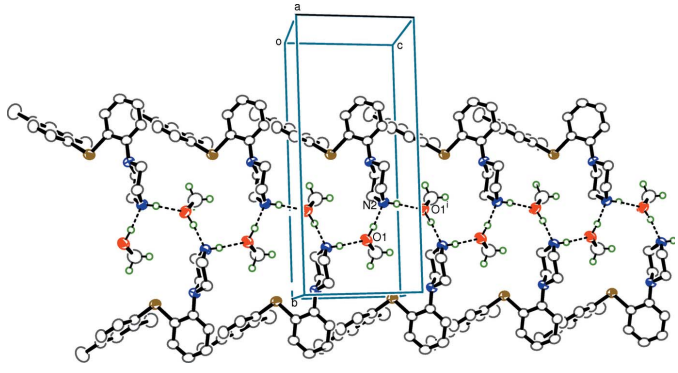


Figure 3
Part of the crystal packing of compound (2), viewed along the a axis. Hydrogen bonds are shown as dashed lines. H atoms not involved in hydrogen bonding have been omitted for clarity.

Table 2
Experimental details.

	(1)	(2)
Crystal data		
Chemical formula	$C_{18}H_{22}N_2S$	$C_{18}H_{22}N_2S{\cdot}CH_4O$
M_r	298.44	330.48
Crystal system, space group	Triclinic, $P\overline{1}$	Monoclinic, $P2_1/c$
Temperature (K)	296	296
a, b, c (Å)	7.6160 (4), 8.3267 (5), 13.9011 (7)	13.2100 (7), 18.1500 (9), 8.1746 (4)
α, β, γ (°)	84.999 (2), 77.631 (1), 74.347 (2)	90, 104.378 (2), 90
V (Å^3)	828.75 (8)	1898.57 (17)
Z	2	4
Radiation type	Mo $K\alpha$	Mo $K\alpha$
μ (mm^{-1})	0.19	0.18
Crystal size (mm)	0.48 × 0.38 × 0.16	0.38 × 0.33 × 0.28
Data collection		
Diffractometer	Rigaku R-AXIS RAPID/ZJUG	Rigaku R-AXIS RAPID/ZJUG
Absorption correction	Multi-scan (*ABSCOR*: Higashi, 1995)	Multi-scan (*ABSCOR*: Higashi, 1995)
T_{min}, T_{max}	0.904, 0.970	0.928, 0.952
No. of measured, independent and observed $[I > 2\sigma(I)]$ reflections	8178, 3756, 2072	18365, 4331, 2468
R_{int}	0.053	0.054
$(\sin\theta/\lambda)_{max}$ (Å^{-1})	0.649	0.648
Refinement		
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.056, 0.185, 1.00	0.052, 0.156, 1.00
No. of reflections	3756	4331
No. of parameters	193	213
H-atom treatment	H-atom parameters constrained	H-atom parameters constrained
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.40, −0.37	0.25, −0.25

Computer programs: *PROCESS-AUTO* and *CrystalStructure* (Rigaku, 2007), *SHELXS97* and *SHELXL97* (Sheldrick, 2008) and *ORTEP-3 for Windows* and *WinGX* (Farrugia, 2012).

Acknowledgements

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supporting information

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Computing details

For both compounds, data collection: *PROCESS-AUTO* (Rigaku, 2007); cell refinement: *PROCESS-AUTO* (Rigaku, 2007); data reduction: *CrystalStructure* (Rigaku, 2007); program(s) used to solve structure: *SHELXS97* (Sheldrick, 2008); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008); molecular graphics: *ORTEP-3 for Windows* (Farrugia, 2012); software used to prepare material for publication: *WinGX* (Farrugia, 2012).

(1) 1-{2-[(2,4-Dimethylphenyl)sulfanyl]phenyl}piperazine

Crystal data

$C_{18}H_{22}N_2S$
M_r = 298.44
Triclinic, $P\overline{1}$
Hall symbol: -P 1
a = 7.6160 (4) Å
b = 8.3267 (5) Å
c = 13.9011 (7) Å
α = 84.999 (2)°
β = 77.631 (1)°
γ = 74.347 (2)°
V = 828.75 (8) Å^3
Z = 2
$F(000)$ = 320
D_x = 1.196 Mg m^{-3}
Mo $K\alpha$ radiation, λ = 0.71073 Å
Cell parameters from 5189 reflections
θ = 3.0–27.4°
μ = 0.19 mm^{-1}
T = 296 K
Chunk, colorless
0.48 × 0.38 × 0.16 mm

Data collection

Rigaku R-AXIS RAPID/ZJUG diffractometer
Radiation source: rotating anode
Graphite monochromator
Detector resolution: 10.00 pixels mm^{-1}
ω scans
Absorption correction: multi-scan (ABSCOR: Higashi, 1995)
T_{min} = 0.904, T_{max} = 0.970
8178 measured reflections
3756 independent reflections
2072 reflections with $I > 2\sigma(I)$
R_{int} = 0.053
θ_{max} = 27.5°, θ_{min} = 3.0°
h = −9→9
k = −10→10
l = −18→17

Refinement

Refinement on F^2
Least-squares matrix: full
$R[F^2 > 2\sigma(F^2)]$ = 0.056
$wR(F^2)$ = 0.185
S = 1.00
3756 reflections
193 parameters
0 restraints
Primary atom site location: structure-invariant direct methods
Secondary atom site location: difference Fourier map
Hydrogen site location: inferred from neighbouring sites
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0622P)^2 + 0.7569P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.40 e Å^{-3}
$\Delta\rho_{min}$ = −0.37 e Å^{-3}

Extinction correction: SHELXL97 (Sheldrick, 2008), $Fc^*=kFc[1+0.001xFc^2\lambda^3/\sin(2\theta)]^{-1/4}$

Extinction coefficient: 0.072 (7)

Special details

Geometry. All e.s.d.'s (except the e.s.d. in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell e.s.d.'s are taken into account individually in the estimation of e.s.d.'s in distances, angles and torsion angles; correlations between e.s.d.'s in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell e.s.d.'s is used for estimating e.s.d.'s involving l.s. planes.

Refinement. Refinement of F^2 against ALL reflections. The weighted *R*-factor *wR* and goodness of fit *S* are based on F^2, conventional *R*-factors *R* are based on *F*, with *F* set to zero for negative F^2. The threshold expression of $F^2 > \sigma(F^2)$ is used only for calculating *R*-factors(gt) *etc*. and is not relevant to the choice of reflections for refinement. *R*-factors based on F^2 are statistically about twice as large as those based on *F*, and *R*- factors based on ALL data will be even larger.

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å²)

	x	*y*	*z*	U_{iso}*/U_{eq}
C1	0.6391 (4)	0.3576 (4)	0.1355 (2)	0.0428 (7)
C2	0.6226 (5)	0.1944 (5)	0.1467 (3)	0.0549 (8)
H2	0.5698	0.1559	0.2079	0.066*
C3	0.6828 (5)	0.0891 (5)	0.0688 (3)	0.0641 (10)
H3	0.6711	−0.0198	0.0781	0.077*
C4	0.7608 (5)	0.1436 (5)	−0.0235 (3)	0.0575 (9)
C5	0.7753 (4)	0.3054 (5)	−0.0349 (2)	0.0520 (8)
H5	0.8265	0.3428	−0.0969	0.062*
C6	0.7165 (4)	0.4163 (4)	0.0425 (2)	0.0446 (7)
C7	0.8231 (6)	0.0284 (6)	−0.1104 (3)	0.0894 (14)
H7A	0.8791	0.0843	−0.1673	0.134*
H7B	0.7174	−0.0007	−0.1241	0.134*
H7C	0.9121	−0.0710	−0.0948	0.134*
C8	0.7350 (5)	0.5916 (4)	0.0254 (3)	0.0573 (9)
H8A	0.8268	0.6061	0.0592	0.086*
H8B	0.6175	0.6680	0.0498	0.086*
H8C	0.7727	0.6130	−0.0440	0.086*
C9	0.7492 (4)	0.5017 (4)	0.2771 (2)	0.0429 (7)
C10	0.9282 (4)	0.4087 (4)	0.2382 (2)	0.0478 (8)
H10	0.9473	0.3388	0.1862	0.057*
C11	1.0770 (4)	0.4193 (4)	0.2761 (2)	0.0526 (8)
H11	1.1958	0.3563	0.2496	0.063*
C12	1.0515 (4)	0.5228 (5)	0.3533 (2)	0.0568 (9)
H12	1.1525	0.5293	0.3789	0.068*
C13	0.8738 (4)	0.6169 (4)	0.3921 (2)	0.0523 (8)
H13	0.8565	0.6869	0.4438	0.063*
C14	0.7213 (4)	0.6081 (4)	0.3550 (2)	0.0420 (7)
C15	0.4781 (5)	0.8573 (4)	0.3382 (2)	0.0542 (8)
H15A	0.5081	0.8376	0.2681	0.065*
H15B	0.5450	0.9350	0.3504	0.065*
C16	0.2704 (5)	0.9311 (5)	0.3705 (3)	0.0643 (10)
H16A	0.2338	1.0370	0.3356	0.077*
H16B	0.2040	0.8566	0.3535	0.077*

C17	0.2816 (5)	0.8026 (5)	0.5307 (2)	0.0561 (9)
H17A	0.2164	0.7227	0.5196	0.067*
H17B	0.2516	0.8238	0.6006	0.067*
C18	0.4901 (4)	0.7287 (4)	0.4994 (2)	0.0485 (8)
H18A	0.5568	0.8049	0.5140	0.058*
H18B	0.5278	0.6242	0.5354	0.058*
N1	0.5348 (3)	0.7000 (3)	0.39293 (16)	0.0425 (6)
N2	0.2190 (4)	0.9568 (4)	0.4764 (2)	0.0692 (9)
H2A	0.1597	1.0506	0.5030	0.083*
S1	0.54672 (10)	0.48897 (12)	0.23790 (6)	0.0524 (3)

Atomic displacement parameters (Å²)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
C1	0.0376 (15)	0.0479 (18)	0.0434 (15)	−0.0111 (13)	−0.0076 (12)	−0.0052 (13)
C2	0.0553 (19)	0.057 (2)	0.0552 (19)	−0.0189 (16)	−0.0121 (16)	−0.0012 (16)
C3	0.069 (2)	0.048 (2)	0.079 (3)	−0.0141 (17)	−0.022 (2)	−0.0033 (18)
C4	0.0539 (19)	0.058 (2)	0.061 (2)	−0.0015 (16)	−0.0194 (17)	−0.0219 (17)
C5	0.0440 (17)	0.067 (2)	0.0425 (16)	−0.0091 (15)	−0.0087 (14)	−0.0079 (15)
C6	0.0372 (15)	0.0502 (19)	0.0458 (16)	−0.0103 (13)	−0.0077 (13)	−0.0024 (13)
C7	0.088 (3)	0.095 (3)	0.086 (3)	−0.005 (3)	−0.023 (2)	−0.048 (3)
C8	0.055 (2)	0.055 (2)	0.064 (2)	−0.0212 (16)	−0.0089 (16)	0.0014 (17)
C9	0.0402 (15)	0.0448 (18)	0.0375 (14)	−0.0075 (13)	0.0005 (12)	0.0006 (12)
C10	0.0390 (15)	0.056 (2)	0.0437 (16)	−0.0090 (14)	0.0006 (13)	−0.0094 (14)
C11	0.0346 (15)	0.066 (2)	0.0540 (18)	−0.0071 (14)	−0.0076 (14)	−0.0083 (16)
C12	0.0426 (17)	0.074 (3)	0.058 (2)	−0.0168 (16)	−0.0161 (15)	−0.0066 (17)
C13	0.0475 (18)	0.065 (2)	0.0488 (17)	−0.0172 (15)	−0.0110 (15)	−0.0141 (15)
C14	0.0410 (15)	0.0452 (18)	0.0378 (14)	−0.0113 (13)	−0.0035 (12)	−0.0012 (12)
C15	0.059 (2)	0.048 (2)	0.0475 (17)	−0.0077 (15)	−0.0032 (15)	0.0013 (14)
C16	0.064 (2)	0.051 (2)	0.065 (2)	0.0022 (17)	−0.0102 (18)	0.0045 (17)
C17	0.0546 (19)	0.061 (2)	0.0459 (17)	−0.0119 (16)	0.0054 (15)	−0.0107 (15)
C18	0.0516 (18)	0.057 (2)	0.0376 (15)	−0.0142 (15)	−0.0066 (13)	−0.0097 (14)
N1	0.0423 (13)	0.0423 (15)	0.0367 (12)	−0.0054 (11)	−0.0013 (10)	−0.0033 (10)
N2	0.071 (2)	0.0517 (19)	0.0656 (18)	0.0063 (15)	0.0048 (16)	−0.0124 (15)
S1	0.0349 (4)	0.0732 (6)	0.0475 (5)	−0.0108 (4)	−0.0023 (3)	−0.0186 (4)

Geometric parameters (Å, º)

C1—C2	1.391 (5)	C11—C12	1.384 (5)
C1—C6	1.406 (4)	C11—H11	0.9300
C1—S1	1.773 (3)	C12—C13	1.388 (4)
C2—C3	1.373 (5)	C12—H12	0.9300
C2—H2	0.9300	C13—C14	1.389 (4)
C3—C4	1.386 (5)	C13—H13	0.9300
C3—H3	0.9300	C14—N1	1.430 (4)
C4—C5	1.374 (5)	C15—N1	1.464 (4)
C4—C7	1.522 (5)	C15—C16	1.517 (5)
C5—C6	1.398 (4)	C15—H15A	0.9700

C5—H5	0.9300	C15—H15B	0.9700
C6—C8	1.497 (5)	C16—N2	1.459 (4)
C7—H7A	0.9600	C16—H16A	0.9700
C7—H7B	0.9600	C16—H16B	0.9700
C7—H7C	0.9600	C17—N2	1.449 (4)
C8—H8A	0.9600	C17—C18	1.521 (4)
C8—H8B	0.9600	C17—H17A	0.9700
C8—H8C	0.9600	C17—H17B	0.9700
C9—C10	1.392 (4)	C18—N1	1.472 (4)
C9—C14	1.403 (4)	C18—H18A	0.9700
C9—S1	1.773 (3)	C18—H18B	0.9700
C10—C11	1.373 (4)	N2—H2A	0.8600
C10—H10	0.9300		

C2—C1—C6	119.3 (3)	C11—C12—H12	120.3
C2—C1—S1	118.4 (2)	C13—C12—H12	120.3
C6—C1—S1	122.2 (2)	C14—C13—C12	121.1 (3)
C3—C2—C1	121.2 (3)	C14—C13—H13	119.5
C3—C2—H2	119.4	C12—C13—H13	119.5
C1—C2—H2	119.4	C13—C14—C9	118.9 (3)
C2—C3—C4	120.6 (4)	C13—C14—N1	123.5 (3)
C2—C3—H3	119.7	C9—C14—N1	117.5 (3)
C4—C3—H3	119.7	N1—C15—C16	109.5 (3)
C5—C4—C3	118.3 (3)	N1—C15—H15A	109.8
C5—C4—C7	121.0 (4)	C16—C15—H15A	109.8
C3—C4—C7	120.7 (4)	N1—C15—H15B	109.8
C4—C5—C6	122.9 (3)	C16—C15—H15B	109.8
C4—C5—H5	118.6	H15A—C15—H15B	108.2
C6—C5—H5	118.6	N2—C16—C15	111.3 (3)
C5—C6—C1	117.7 (3)	N2—C16—H16A	109.4
C5—C6—C8	120.4 (3)	C15—C16—H16A	109.4
C1—C6—C8	121.9 (3)	N2—C16—H16B	109.4
C4—C7—H7A	109.5	C15—C16—H16B	109.4
C4—C7—H7B	109.5	H16A—C16—H16B	108.0
H7A—C7—H7B	109.5	N2—C17—C18	111.5 (3)
C4—C7—H7C	109.5	N2—C17—H17A	109.3
H7A—C7—H7C	109.5	C18—C17—H17A	109.3
H7B—C7—H7C	109.5	N2—C17—H17B	109.3
C6—C8—H8A	109.5	C18—C17—H17B	109.3
C6—C8—H8B	109.5	H17A—C17—H17B	108.0
H8A—C8—H8B	109.5	N1—C18—C17	108.9 (3)
C6—C8—H8C	109.5	N1—C18—H18A	109.9
H8A—C8—H8C	109.5	C17—C18—H18A	109.9
H8B—C8—H8C	109.5	N1—C18—H18B	109.9
C10—C9—C14	119.6 (3)	C17—C18—H18B	109.9
C10—C9—S1	124.1 (2)	H18A—C18—H18B	108.3
C14—C9—S1	116.3 (2)	C14—N1—C15	112.9 (2)
C11—C10—C9	120.5 (3)	C14—N1—C18	115.5 (2)

C11—C10—H10	119.7	C15—N1—C18	110.2 (2)
C9—C10—H10	119.7	C17—N2—C16	110.8 (3)
C10—C11—C12	120.6 (3)	C17—N2—H2A	124.6
C10—C11—H11	119.7	C16—N2—H2A	124.6
C12—C11—H11	119.7	C9—S1—C1	102.76 (14)
C11—C12—C13	119.3 (3)		

C6—C1—C2—C3	0.9 (5)	C10—C9—C14—C13	−0.6 (4)
S1—C1—C2—C3	176.7 (3)	S1—C9—C14—C13	176.8 (2)
C1—C2—C3—C4	−0.4 (5)	C10—C9—C14—N1	−179.5 (3)
C2—C3—C4—C5	−0.3 (5)	S1—C9—C14—N1	−2.1 (3)
C2—C3—C4—C7	−178.4 (3)	N1—C15—C16—N2	57.3 (4)
C3—C4—C5—C6	0.6 (5)	N2—C17—C18—N1	−57.9 (4)
C7—C4—C5—C6	178.7 (3)	C13—C14—N1—C15	95.2 (4)
C4—C5—C6—C1	−0.1 (5)	C9—C14—N1—C15	−85.9 (3)
C4—C5—C6—C8	−179.7 (3)	C13—C14—N1—C18	−32.8 (4)
C2—C1—C6—C5	−0.6 (4)	C9—C14—N1—C18	146.1 (3)
S1—C1—C6—C5	−176.2 (2)	C16—C15—N1—C14	169.7 (3)
C2—C1—C6—C8	178.9 (3)	C16—C15—N1—C18	−59.5 (4)
S1—C1—C6—C8	3.3 (4)	C17—C18—N1—C14	−171.1 (3)
C14—C9—C10—C11	0.6 (5)	C17—C18—N1—C15	59.5 (3)
S1—C9—C10—C11	−176.6 (2)	C18—C17—N2—C16	56.1 (4)
C9—C10—C11—C12	−0.1 (5)	C15—C16—N2—C17	−55.7 (4)
C10—C11—C12—C13	−0.3 (5)	C10—C9—S1—C1	−6.7 (3)
C11—C12—C13—C14	0.3 (5)	C14—C9—S1—C1	176.0 (2)
C12—C13—C14—C9	0.1 (5)	C2—C1—S1—C9	106.2 (3)
C12—C13—C14—N1	179.0 (3)	C6—C1—S1—C9	−78.2 (3)

(2) 1-{2-[(2,4-Dimethylphenyl)sulfanyl]phenyl}piperazine methanol monosolvate

Crystal data

$C_{18}H_{22}N_2S·CH_4O$
M_r = 330.48
Monoclinic, $P2_1/c$
Hall symbol: -P 2ybc
a = 13.2100 (7) Å
b = 18.1500 (9) Å
c = 8.1746 (4) Å
β = 104.378 (2)°
V = 1898.57 (17) Å^3
Z = 4
$F(000)$ = 712
D_x = 1.156 Mg m^{-3}
Mo $K\alpha$ radiation, λ = 0.71073 Å
Cell parameters from 10380 reflections
θ = 3.2–27.4°
μ = 0.18 mm^{-1}
T = 296 K
Chunk, colorless
0.38 × 0.33 × 0.28 mm

Data collection

Rigaku R-AXIS RAPID/ZJUG diffractometer
Radiation source: rotating anode
Graphite monochromator
Detector resolution: 10.00 pixels mm^{-1}
ω scans
Absorption correction: multi-scan (ABSCOR: Higashi, 1995)
T_{min} = 0.928, T_{max} = 0.952
18365 measured reflections
4331 independent reflections
2468 reflections with $I > 2\sigma(I)$
R_{int} = 0.054

θ_{max} = 27.4°, θ_{min} = 3.2°
h = −16→17
k = −23→23
l = −10→10

Refinement

Refinement on F^2
Least-squares matrix: full
$R[F^2 > 2\sigma(F^2)]$ = 0.052
$wR(F^2)$ = 0.156
S = 1.00
4331 reflections
213 parameters
0 restraints
Primary atom site location: structure-invariant direct methods
Secondary atom site location: difference Fourier map
Hydrogen site location: inferred from neighbouring sites
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0598P)^2 + 0.7465P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.001
$\Delta\rho_{max}$ = 0.25 e Å^{-3}
$\Delta\rho_{min}$ = −0.25 e Å^{-3}
Extinction correction: SHELXL97 (Sheldrick, 2008), $Fc^*=kFc[1+0.001xFc^2\lambda^3/\sin(2\theta)]^{-1/4}$
Extinction coefficient: 0.032 (3)

Special details

Geometry. All e.s.d.'s (except the e.s.d. in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell e.s.d.'s are taken into account individually in the estimation of e.s.d.'s in distances, angles and torsion angles; correlations between e.s.d.'s in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell e.s.d.'s is used for estimating e.s.d.'s involving l.s. planes.
Refinement. Refinement of F^2 against ALL reflections. The weighted R-factor wR and goodness of fit S are based on F^2, conventional R-factors R are based on F, with F set to zero for negative F^2. The threshold expression of $F^2 > \sigma(F^2)$ is used only for calculating R-factors(gt) *etc*. and is not relevant to the choice of reflections for refinement. R-factors based on F^2 are statistically about twice as large as those based on F, and R- factors based on ALL data will be even larger.

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å²)

	x	y	z	U_{iso}*/U_{eq}
C16	0.7959 (2)	0.35981 (14)	0.6308 (3)	0.0631 (7)
H16A	0.7446	0.3322	0.6726	0.076*
H16B	0.7810	0.3521	0.5097	0.076*
C15	0.78325 (19)	0.44056 (13)	0.6641 (3)	0.0590 (6)
H15A	0.7148	0.4573	0.6018	0.071*
H15B	0.7892	0.4484	0.7835	0.071*
C18	0.96814 (19)	0.45883 (14)	0.7082 (3)	0.0604 (6)
H18A	0.9744	0.4667	0.8277	0.073*
H18B	1.0219	0.4875	0.6754	0.073*
C17	0.9822 (2)	0.37770 (14)	0.6748 (3)	0.0628 (7)
H17A	0.9841	0.3717	0.5577	0.075*
H17B	1.0490	0.3615	0.7446	0.075*
C14	0.84554 (18)	0.55978 (12)	0.5953 (3)	0.0500 (5)
C13	0.89399 (19)	0.61073 (14)	0.7155 (3)	0.0579 (6)
H13	0.9419	0.5948	0.8126	0.069*
C12	0.8721 (2)	0.68494 (14)	0.6929 (3)	0.0644 (7)
H12	0.9049	0.7186	0.7747	0.077*
C11	0.8017 (2)	0.70901 (14)	0.5493 (3)	0.0645 (7)
H11	0.7865	0.7590	0.5348	0.077*
C10	0.7535 (2)	0.65945 (13)	0.4267 (3)	0.0600 (6)
H10	0.7056	0.6761	0.3302	0.072*

C9	0.77610 (18)	0.58456 (12)	0.4466 (3)	0.0520 (6)
C1	0.6514 (2)	0.56877 (13)	0.1194 (3)	0.0560 (6)
C6	0.5482 (2)	0.58898 (14)	0.1102 (3)	0.0612 (6)
C5	0.4947 (2)	0.62711 (16)	−0.0328 (4)	0.0738 (8)
H5	0.4261	0.6413	−0.0401	0.089*
C4	0.5387 (2)	0.64500 (16)	−0.1649 (3)	0.0723 (8)
C3	0.6398 (2)	0.62274 (17)	−0.1533 (3)	0.0743 (8)
H3	0.6708	0.6328	−0.2413	0.089*
C2	0.6953 (2)	0.58576 (15)	−0.0131 (3)	0.0650 (7)
H2	0.7638	0.5718	−0.0070	0.078*
C8	0.4960 (3)	0.5711 (2)	0.2494 (4)	0.0946 (10)
H8A	0.4280	0.5935	0.2252	0.142*
H8B	0.5376	0.5897	0.3546	0.142*
H8C	0.4890	0.5186	0.2571	0.142*
C7	0.4764 (3)	0.6864 (2)	−0.3175 (5)	0.1267 (15)
H7A	0.5232	0.7121	−0.3704	0.190*
H7B	0.4311	0.7212	−0.2825	0.190*
H7C	0.4351	0.6523	−0.3962	0.190*
C19	0.8246 (3)	0.1517 (2)	0.6374 (5)	0.1043 (11)
H19A	0.8628	0.1474	0.7534	0.156*
H19B	0.8153	0.1036	0.5866	0.156*
H19C	0.7576	0.1734	0.6317	0.156*
N1	0.86499 (14)	0.48236 (10)	0.6108 (2)	0.0520 (5)
N2	0.89994 (17)	0.33031 (11)	0.7085 (2)	0.0601 (5)
H2A	0.9160	0.3296	0.8171	0.090*
O1	0.87917 (19)	0.19532 (11)	0.5525 (2)	0.0848 (6)
H1	0.8925	0.2349	0.6017	0.127*
S1	0.72717 (6)	0.51680 (4)	0.29023 (9)	0.0699 (3)

Atomic displacement parameters (Å²)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
C16	0.0652 (16)	0.0537 (14)	0.0744 (16)	−0.0033 (12)	0.0246 (13)	0.0061 (12)
C15	0.0560 (15)	0.0559 (15)	0.0708 (15)	0.0007 (11)	0.0263 (12)	0.0091 (12)
C18	0.0550 (15)	0.0564 (15)	0.0679 (15)	0.0030 (12)	0.0117 (12)	0.0056 (12)
C17	0.0605 (15)	0.0587 (16)	0.0700 (15)	0.0089 (12)	0.0179 (12)	0.0051 (12)
C14	0.0514 (13)	0.0455 (13)	0.0583 (13)	0.0004 (10)	0.0232 (10)	0.0031 (10)
C13	0.0568 (15)	0.0582 (15)	0.0588 (14)	−0.0015 (12)	0.0149 (11)	−0.0027 (11)
C12	0.0692 (17)	0.0522 (15)	0.0726 (16)	−0.0061 (13)	0.0193 (13)	−0.0104 (12)
C11	0.0738 (17)	0.0441 (13)	0.0795 (17)	0.0015 (12)	0.0265 (14)	−0.0004 (12)
C10	0.0660 (16)	0.0479 (14)	0.0657 (15)	0.0032 (12)	0.0158 (12)	0.0040 (11)
C9	0.0538 (14)	0.0469 (13)	0.0585 (13)	0.0014 (11)	0.0197 (11)	0.0017 (10)
C1	0.0587 (15)	0.0494 (13)	0.0603 (14)	−0.0020 (11)	0.0154 (11)	−0.0061 (10)
C6	0.0576 (15)	0.0588 (15)	0.0684 (15)	−0.0071 (12)	0.0183 (12)	−0.0078 (12)
C5	0.0520 (15)	0.0746 (19)	0.087 (2)	0.0034 (13)	0.0023 (14)	−0.0083 (15)
C4	0.076 (2)	0.0682 (18)	0.0647 (16)	−0.0061 (15)	0.0024 (14)	0.0004 (13)
C3	0.079 (2)	0.084 (2)	0.0612 (16)	−0.0154 (16)	0.0194 (14)	−0.0003 (14)
C2	0.0552 (15)	0.0723 (18)	0.0686 (16)	−0.0039 (13)	0.0173 (12)	−0.0070 (13)

C8	0.089 (2)	0.106 (3)	0.102 (2)	−0.012 (2)	0.0492 (19)	−0.0035 (19)
C7	0.138 (4)	0.125 (3)	0.094 (3)	0.014 (3)	−0.014 (2)	0.026 (2)
C19	0.111 (3)	0.101 (3)	0.113 (3)	−0.031 (2)	0.049 (2)	−0.009 (2)
N1	0.0503 (11)	0.0459 (11)	0.0609 (11)	0.0022 (9)	0.0158 (9)	0.0081 (8)
N2	0.0708 (14)	0.0516 (12)	0.0599 (12)	0.0050 (10)	0.0201 (10)	0.0058 (9)
O1	0.1255 (18)	0.0678 (13)	0.0686 (12)	−0.0129 (12)	0.0384 (12)	−0.0116 (9)
S1	0.0871 (5)	0.0482 (4)	0.0669 (4)	0.0070 (3)	0.0050 (3)	−0.0044 (3)

Geometric parameters (Å, º)

C16—N2	1.465 (3)	C9—S1	1.776 (2)
C16—C15	1.507 (4)	C1—C2	1.384 (3)
C16—H16A	0.9700	C1—C6	1.395 (4)
C16—H16B	0.9700	C1—S1	1.774 (2)
C15—N1	1.471 (3)	C6—C5	1.391 (4)
C15—H15A	0.9700	C6—C8	1.506 (4)
C15—H15B	0.9700	C5—C4	1.386 (4)
C18—N1	1.461 (3)	C5—H5	0.9300
C18—C17	1.517 (3)	C4—C3	1.376 (4)
C18—H18A	0.9700	C4—C7	1.513 (4)
C18—H18B	0.9700	C3—C2	1.373 (4)
C17—N2	1.464 (3)	C3—H3	0.9300
C17—H17A	0.9700	C2—H2	0.9300
C17—H17B	0.9700	C8—H8A	0.9600
C14—C13	1.385 (3)	C8—H8B	0.9600
C14—C9	1.403 (3)	C8—H8C	0.9600
C14—N1	1.428 (3)	C7—H7A	0.9600
C13—C12	1.380 (3)	C7—H7B	0.9600
C13—H13	0.9300	C7—H7C	0.9600
C12—C11	1.375 (4)	C19—O1	1.370 (4)
C12—H12	0.9300	C19—H19A	0.9600
C11—C10	1.379 (3)	C19—H19B	0.9600
C11—H11	0.9300	C19—H19C	0.9600
C10—C9	1.393 (3)	N2—H2A	0.8598
C10—H10	0.9300	O1—H1	0.8200
N2—C16—C15	114.3 (2)	C2—C1—S1	118.1 (2)
N2—C16—H16A	108.7	C6—C1—S1	122.3 (2)
C15—C16—H16A	108.7	C5—C6—C1	117.5 (2)
N2—C16—H16B	108.7	C5—C6—C8	120.7 (3)
C15—C16—H16B	108.7	C1—C6—C8	121.8 (3)
H16A—C16—H16B	107.6	C4—C5—C6	123.2 (3)
N1—C15—C16	109.0 (2)	C4—C5—H5	118.4
N1—C15—H15A	109.9	C6—C5—H5	118.4
C16—C15—H15A	109.9	C3—C4—C5	117.7 (3)
N1—C15—H15B	109.9	C3—C4—C7	121.5 (3)
C16—C15—H15B	109.9	C5—C4—C7	120.8 (3)
H15A—C15—H15B	108.3	C2—C3—C4	120.6 (3)

N1—C18—C17	109.0 (2)	C2—C3—H3	119.7
N1—C18—H18A	109.9	C4—C3—H3	119.7
C17—C18—H18A	109.9	C3—C2—C1	121.5 (3)
N1—C18—H18B	109.9	C3—C2—H2	119.3
C17—C18—H18B	109.9	C1—C2—H2	119.3
H18A—C18—H18B	108.3	C6—C8—H8A	109.5
N2—C17—C18	114.0 (2)	C6—C8—H8B	109.5
N2—C17—H17A	108.8	H8A—C8—H8B	109.5
C18—C17—H17A	108.8	C6—C8—H8C	109.5
N2—C17—H17B	108.8	H8A—C8—H8C	109.5
C18—C17—H17B	108.8	H8B—C8—H8C	109.5
H17A—C17—H17B	107.7	C4—C7—H7A	109.5
C13—C14—C9	119.2 (2)	C4—C7—H7B	109.5
C13—C14—N1	123.6 (2)	H7A—C7—H7B	109.5
C9—C14—N1	117.2 (2)	C4—C7—H7C	109.5
C12—C13—C14	120.8 (2)	H7A—C7—H7C	109.5
C12—C13—H13	119.6	H7B—C7—H7C	109.5
C14—C13—H13	119.6	O1—C19—H19A	109.5
C11—C12—C13	120.0 (2)	O1—C19—H19B	109.5
C11—C12—H12	120.0	H19A—C19—H19B	109.5
C13—C12—H12	120.0	O1—C19—H19C	109.5
C12—C11—C10	120.4 (2)	H19A—C19—H19C	109.5
C12—C11—H11	119.8	H19B—C19—H19C	109.5
C10—C11—H11	119.8	C14—N1—C18	117.31 (19)
C11—C10—C9	120.3 (2)	C14—N1—C15	113.85 (18)
C11—C10—H10	119.9	C18—N1—C15	109.97 (18)
C9—C10—H10	119.9	C17—N2—C16	111.36 (19)
C10—C9—C14	119.3 (2)	C17—N2—H2A	101.4
C10—C9—S1	124.22 (18)	C16—N2—H2A	114.7
C14—C9—S1	116.39 (17)	C19—O1—H1	109.5
C2—C1—C6	119.5 (2)	C1—S1—C9	103.41 (11)

N2—C16—C15—N1	54.9 (3)	C6—C5—C4—C7	179.9 (3)
N1—C18—C17—N2	−55.2 (3)	C5—C4—C3—C2	−1.6 (4)
C9—C14—C13—C12	2.2 (4)	C7—C4—C3—C2	179.4 (3)
N1—C14—C13—C12	179.8 (2)	C4—C3—C2—C1	0.9 (4)
C14—C13—C12—C11	−0.3 (4)	C6—C1—C2—C3	0.6 (4)
C13—C12—C11—C10	−0.6 (4)	S1—C1—C2—C3	176.9 (2)
C12—C11—C10—C9	−0.4 (4)	C13—C14—N1—C18	−28.7 (3)
C11—C10—C9—C14	2.3 (4)	C9—C14—N1—C18	149.0 (2)
C11—C10—C9—S1	−174.67 (19)	C13—C14—N1—C15	101.7 (3)
C13—C14—C9—C10	−3.1 (3)	C9—C14—N1—C15	−80.6 (3)
N1—C14—C9—C10	179.1 (2)	C17—C18—N1—C14	−166.5 (2)
C13—C14—C9—S1	174.04 (18)	C17—C18—N1—C15	61.3 (3)
N1—C14—C9—S1	−3.7 (3)	C16—C15—N1—C14	164.7 (2)
C2—C1—C6—C5	−1.3 (4)	C16—C15—N1—C18	−61.3 (3)
S1—C1—C6—C5	−177.42 (19)	C18—C17—N2—C16	48.1 (3)
C2—C1—C6—C8	179.2 (3)	C15—C16—N2—C17	−48.2 (3)

S1—C1—C6—C8	3.0 (4)	C2—C1—S1—C9	100.2 (2)
C1—C6—C5—C4	0.6 (4)	C6—C1—S1—C9	−83.6 (2)
C8—C6—C5—C4	−179.9 (3)	C10—C9—S1—C1	1.0 (2)
C6—C5—C4—C3	0.9 (4)	C14—C9—S1—C1	−176.04 (18)

Hydrogen-bond geometry (Å, º)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N2—H2*A*···O1^{i}	0.86	2.15	2.930 (3)	151
O1—H1···N2	0.82	1.93	2.744 (3)	171

Symmetry code: (i) *x*, −*y*+1/2, *z*+1/2.