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N-(3-Methoxy-5-methylpyrazin-2-yl)-2-[4-(1,3,4-oxadiazol-2-yl)phenyl]pyridine-3-sulfonamide (ZD4054 Form 1)

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Key indicators

Single-crystal X-ray study
T = 293 K
Mean σ(C–C) = 0.003 Å
R factor = 0.047
wR factor = 0.127
Data-to-parameter ratio = 15.9

For details of how these key indicators were automatically derived from the article, see http://journals.iucr.org/e.

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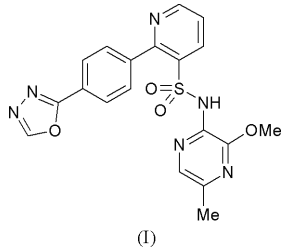
The title compound, $C_{19}H_{16}N_6O_4S$, crystallizes from *N*-methylpyridine in the centrosymmetric space group $P2_1/n$ with four molecules in the unit cell. The molecule has 11 heteroatoms, of which only one is protonated. This potential hydrogen-bond donor, *viz*. the NH amide group, participates in both intra- and intermolecular hydrogen-bond interactions, thus contributing to the stabilization of the molecular conformation and the linking of molecules as dimers. The hairpin-like folded molecule is arranged with three of its four aromatic rings in two parallel planes intersected by a sulfonamide moiety. In this way, the molecules stack efficiently, facilitated by short-range van der Waals forces. No residual volume for solvent inclusion was found.

Comment

Studies reported by Adsmond & Grant (2001) on hydrogen bonding in sulfonamides, in which S=O···H—N hydrogen-bond interactions are common (present 50 times in 39 sulfonamide structures), prompted the structural study of the title sulfonamide molecule, (I).



(I)

The molecular conformation of the title compound (ZD4054 Form 1), (I), is presented in Fig. 1 together with the adopted atomic numbering. Three of the four aromatic ring planes are almost parallel. The dicoupled oxadiazolylphenyl planes on one side of the sulfonamide group and the methoxy-substituted pyrazinyl ring on the other side deviate by 3.1 (1)° from each other. The pyridinyl ring is twisted by 63 (2)° to these planes. The hairpin-like torsion angles C14—C9—S1—N2 and C9—S1—N2—C3 are −47.97 (18) and −47.76 (17)°, respectively (Table 1). The methoxy group is well conjugated within the pyrazinyl ring plane, with a maximum deviation of 0.086 (3) Å. The molecular bond lengths and angles are normal, except for distances close to the sulfonamide group (Table 1).

The protonated N2—H amide group engages in a shared three-center hydrogen-bond scheme and participates in both intra- and intermolecular hydrogen-bond interactions (Table 2). The intermolecular N—H···N hydrogen bonds link

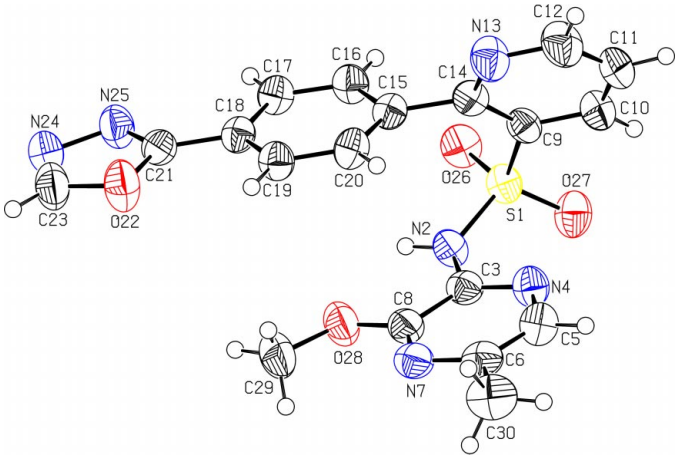


Figure 1
*ORTEP*II (Johnson, 1976) view of (I) showing the atom-labelling scheme. Displacement ellipsoids of non-H atoms are drawn at the 50% probability level.

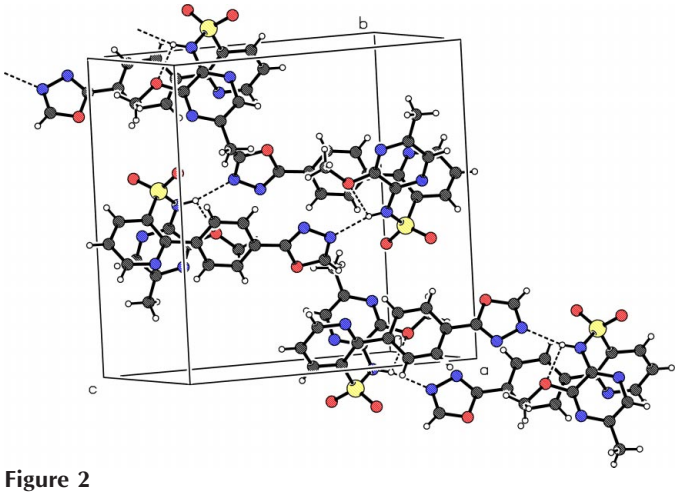


Figure 2
Part of the molecular packing scheme of (I). Dashed lines indicate hydrogen-bond interactions.

inversion-symmetry-related molecules together in a head-to tail fashion (Fig. 2) into dimers (Fig. 3), with the graph-set motif $R_2^2(26)$ (Bernstein *et al.*, 1995). The antiparallel head-to-tail framework is often found among non-polar molecules, which in this way induce soft C—H···*X* (*X* = N, O) and C—H···π interactions that facilitate the molecular packing contacts. It is interesting to note that the type of hydrogen bonding which consists of either S═O···H—N chains (50 occurrences) or $R_2^2(8)$ rings (10 occurrences) are absent in the ZD4054 structure (Adsmond & Grant, 2001). The only classical intermolecular hydrogen bond found here is the aromatic N—H···N hydrogen bond. This type of interaction is present 16 times in the sulfonamides but is always present together with other hydrogen bonds (Adsmond & Grant, 2001). The availability of the interaction observed in ZD4054 is most probably a consequence of the extended planarity caused by the intramolecular phenyl–methoxy hydrogen-bond formation and the planar orientation of the oxadiazolylphenyl rings. The packing coefficient of ZD4054 is 68.1% (Kitaigorodskij, 1973), reflecting an efficient molecular packing arrangement.

Experimental

Crystals of (I) were prepared on industrial scale, involving crystallization with cooling from the solvent *N*-methylpyrollidin-2-one. The crystallization was initiated by addition of water as an antisolvent, thus producing crystals of sufficient quality for the single-crystal X-ray determination.

Crystal data

$C_{19}H_{16}N_6O_4S$
M_r = 424.44
Monoclinic, $P2_1/n$
a = 8.310 (1) Å
b = 15.132 (1) Å
c = 15.414 (1) Å
β = 90.79 (1)°
V = 1938.1 (3) Å^3
Z = 4
D_x = 1.455 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 7434 reflections
θ = 3.6–27.5°
μ = 0.21 mm^{-1}
T = 293 (2) K
Rhombohedron, colourless
0.17 × 0.17 × 0.08 mm

Data collection

Nonius KappaCCD diffractometer
φ and ω scans with κ offset
Absorption correction: none
7434 measured reflections
4382 independent reflections
2604 reflections with $I > 2\sigma(I)$
R_{int} = 0.035
θ_{max} = 27.5°
$h = -10 \rightarrow 10$
$k = -17 \rightarrow 19$
$l = -19 \rightarrow 19$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.047
$wR(F^2)$ = 0.127
S = 0.97
4382 reflections
276 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0686P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.21 e Å^{-3}
$\Delta\rho_{min}$ = −0.34 e Å^{-3}

Table 1
Selected geometric parameters (Å, °).

S1—O27	1.4247 (13)	N4—C3	1.305 (2)
S1—O26	1.4309 (14)	N4—C5	1.359 (3)
S1—N2	1.6284 (18)	N7—C8	1.304 (3)
S1—C9	1.779 (2)	N7—C6	1.357 (3)
O22—C23	1.354 (3)	N13—C14	1.341 (3)
O22—C21	1.356 (3)	N13—C12	1.343 (3)
O28—C8	1.344 (2)	N24—C23	1.267 (3)
O28—C29	1.439 (3)	N24—N25	1.401 (2)
N2—C3	1.403 (3)	N25—C21	1.277 (3)
O26—S1—O27	117.77 (9)	N4—C3—C8	121.41 (18)
O26—S1—N2	105.13 (9)	N4—C5—C6	123.2 (2)
O26—S1—C9	111.20 (8)	N7—C6—C30	117.5 (2)
O27—S1—N2	110.29 (9)	N7—C6—C5	120.46 (19)
O27—S1—C9	106.17 (9)	O28—C8—N7	122.68 (19)
N2—S1—C9	105.72 (9)	O28—C8—C3	114.97 (18)
C21—O22—C23	102.21 (18)	N7—C8—C3	122.35 (18)
C8—O28—C29	117.97 (18)	S1—C9—C10	116.52 (15)
S1—N2—C3	123.67 (14)	S1—C9—C14	124.09 (15)
C3—N4—C5	115.75 (18)	N13—C12—C11	124.5 (2)
C6—N7—C8	116.76 (18)	N13—C14—C15	114.60 (17)
C12—N13—C14	117.66 (19)	N13—C14—C9	121.07 (18)
N25—N24—C23	105.89 (18)	O22—C21—N25	112.23 (18)
N24—N25—C21	106.44 (18)	O22—C21—C18	119.41 (17)
N2—C3—C8	118.73 (17)	N25—C21—C18	128.36 (19)
N2—C3—N4	119.83 (18)	O22—C23—N24	113.2 (2)
C9—S1—N2—C3	−47.76 (17)	S1—N2—C3—N4	−16.4 (3)
C14—C9—S1—N2	−47.97 (18)	S1—C9—C14—C15	−2.7 (3)

Table 2
Hydrogen-bonding geometry (Å, °).

D—H···A	D—H	H···A	D···A	D—H···A
N2—H2···O28	0.88 (2)	2.34 (2)	2.661 (2)	101.7 (18)
N2—H2···N24^{i}	0.88 (2)	2.08 (2)	2.938 (2)	166 (2)
C10—H10···O27	0.93	2.40	2.807 (3)	106
C19—H19···O27^{ii}	0.93	2.54	3.322 (3)	142

Symmetry codes: (i) $2-x, -y, -z$; (ii) $\frac{3}{2}-x+, \frac{1}{2}+y+, \frac{1}{2}-z+$.

After identification in difference Fourier maps, aromatic and methyl H atoms were constrained to ideal-geometry positions, with C—H distances of 0.93 and 0.96 Å, respectively. Only atom H2, which participates in hydrogen bonding, was allowed to refine freely. One common U value was refined to 0.064 (2) Å^2 for the aromatic H atoms, and another was refined to 0.105 (4) Å^2 for the methyl H atoms. The highest residual electron-density peak was located close to atom C18 and the deepest hole close to atom S1.

Data collection: *KappaCCD Software* (Nonius, 2000); cell refinement: *HKL SCALEPACK* (Otwinowski & Minor, 1997); data reduction: *SCALEPACK* and *DENZO-SMN* (Otwinowski & Minor, 1997); program(s) used to solve structure: *SIR*92 (Altomare *et al.*, 1992); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *ORTEP*II (Johnson, 1976), *PLATON* (Spek, 2003) and *MERCURY* (Bruno *et al.*, 2002); software used to prepare material for publication: *PLATON*.

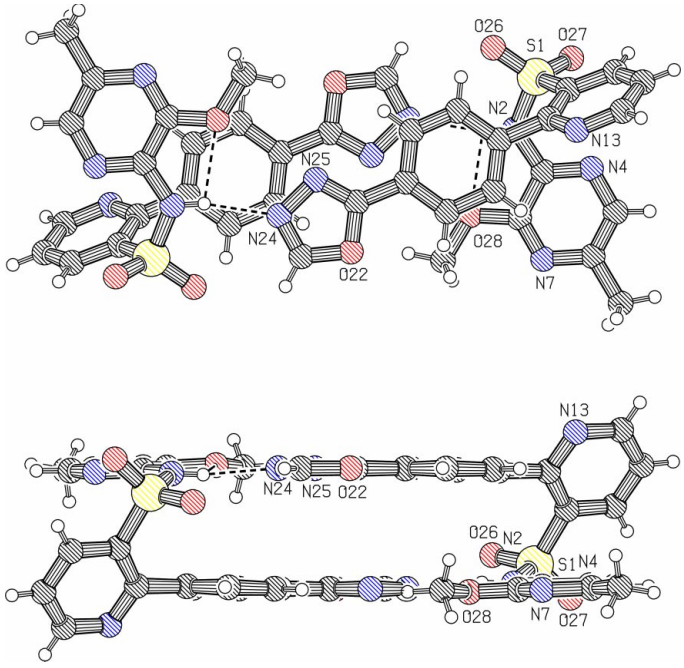


Figure 3
The hydrogen-bonded (dashed lines) dimer, viewed in two perpendicular orientations.

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