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4,6-Dimethyl-2-[4-(4-nitrophenyl)piperazin-1-ylmethyl]isothiazolo[5,4-*b*]pyridin-3(2*H*)-one

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Key indicators

Single-crystal X-ray study
T = 293 K
Mean σ(C–C) = 0.002 Å
R factor = 0.042
wR factor = 0.134
Data-to-parameter ratio = 11.4

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

In the structure of the title compound, $C_{19}H_{21}N_5O_3S$, the piperazine ring adopts a slightly deformed chair conformation, with puckering parameters Q = 0.534 (2) Å and θ = 22.2 (2)° and an almost flat configuration of the piperazine N atom bonded to the benzene ring. This deformation is caused by the strong conjugation effect of the lone pair of the N atom with the π-electron system of the benzene ring in the arylpiperazine part of the molecule. The molecular packing is influenced by weak π–π interactions of the isothiazolopyridine systems, with a shortest centroid-to-centroid separation of 3.5113 (14) Å between pyridine rings.

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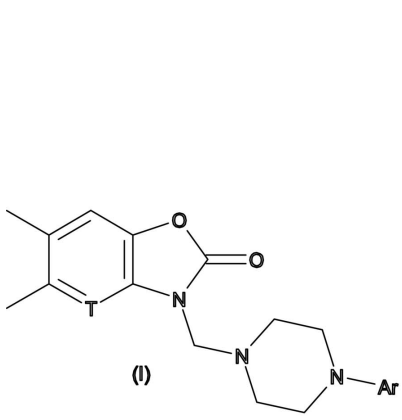
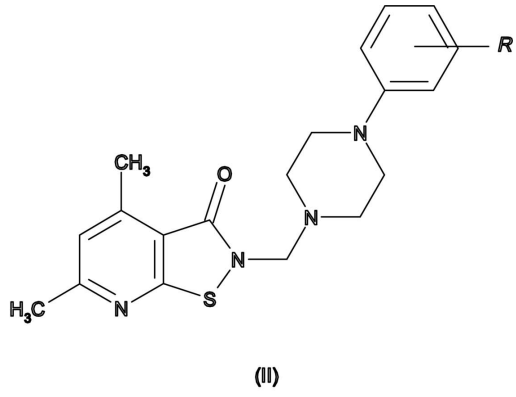
Comment

Benzoxazolines and oxazolopyridinones of the Mannich base type with a pharmacophoric 4-arylpiperazine moiety, (I), possess significant analgesic activity (Flouzat *et al.*, 1993; Palaska *et al.*, 1995; Viaud *et al.*, 1995). In this context, we described the synthesis and analgesic action of a series of related Mannich base derivatives of isothiazolo[5,4-*b*]pyridine of the general structure (II) (Malinka *et al.*, 2005). Because of the observation that reduction of the electron density in the aromatic ring of the 4-arylpiperazine substructure leads to an increase of analgesic action, most of the isothiazolopyridines (II) were prepared by incorporating the 4-arylpiperazine group possessing 2-chloro (II*a*), 2-fluoro (II*b*), 3-trifluoromethyl (II*c*), or 4-nitro (II*d*), substituents, which are electron-attracting in nature.



(I)

T = CH, N



(II)

(IIa) *R* = 2-Cl, (IIb) *R* = 2-F, (IIc) *R* = 3-CF_3, (IId) *R* = 4-NO_2, (IIe) *R* = H, (IIf) *R* = 2-OCH_3, (IIg) *R* = 2-CH_3,

In order to extend the structure–activity (SAR) studies and to find a useful model for toxicity and analgesia assessment within a series of isothiazolopyridines of type (II) and their

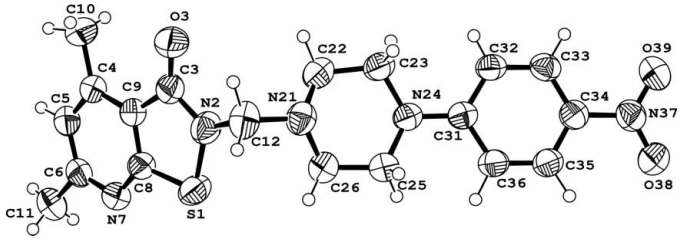


Figure 1
A view of the molecule of (II*d*), showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level. H atoms are represented as small spheres of arbitrary radii.

analogs yet to be synthesized, theoretical investigations were undertaken. As a part of these studies, the crystal structure of the 4-nitrophenylpiperazine derivative (II*d*) was evaluated for comparison of the preferred conformation and charge (electron) distribution within the 4-nitrophenylpiperazine grouping with that of isothiazolopyridines (II*e*) (R = H), (II*f*) (R = 2-OCH_3) and (II*g*) (R = 2-CH_3) described previously (Karczmarzyk & Malinka, 2004). Biheterocyclic compounds with an S—N bond are derivatives rarely mentioned in the literature. The Cambridge Structural Database (CSD; Version 5.26 of November 2004; Allen, 2002; Bruno *et al.*, 2002) reveals only 27 organic structures with an isothiazole unit.

The geometry (bond lengths, angles and planarity) of the isothiazolopyridine ring is very similar in (II*d*) (Fig. 1) and the related structures (II*e*), (II*f*) and (II*g*). The pyridine and isothiazole rings are planar to within 0.004 (1) and 0.017 (1) Å, respectively, and they are inclined at an angle of 2.16 (8)°. The asymmetry in the values of the exocyclic angles at C3 [128.52 (16) and 122.74 (16)°] is characteristic of both 2-arylpiperazine-substituted derivatives (II*e*), (II*f*) and (II*g*), and the unsubstituted parent 4,6-dimethylisothiazolo[5,4-*b*]-pyridin-3(2*H*)-one (Karczmarzyk & Malinka, 2004). This is due to the steric effect of the bulky methyl, carbonyl and methylene groups on adjacent positions of the isothiazolopyridine rings.

The conformation of the (4-nitrophenyl)piperazine substituent is described by the torsion angles S1—N2—C12—N21, N2—C12—N21—C22 and N2—C12—N21—C26 of 81.3 (2), 66.8 (2) and −63.6 (2)°, respectively. These torsion angles indicate that the orientation of the substituent in relation to the fused bicyclic system is similar to that observed in (II*g*) and partially opposite to that found in (II*e*) and (II*f*) (Karczmarzyk & Malinka, 2004).

The piperazine ring adopts a slightly deformed chair conformation with puckering parameters of Q = 0.534 (2) Å and θ = 22.2 (2)° (Cremer & Pople, 1975). This deformation is caused by the relative flatness of the pyramidal configuration of N24; this atom is displaced from the equatorial plane of the piperazine ring by 0.416 (2) Å, while atom N21 is displaced by 0.722 (2) Å on the opposite side. The N24—C31 bond length of 1.375 (2) Å, significantly shorter than an average non-conjugated C_{ar}—N (Nsp^3, pyramidal) single bond of 1.426 (11) Å (Allen *et al.*, 1987), and the sum of the bond angles around N24 of 351.76° show that the lone pair at N24 is strongly conjugated with the π system of the benzene ring. A similar conjugation effect for the lone pair of the tertiary N atom is observed for the unsubstituted phenyl ring in (II*e*), but in the case of (II*d*) this conjugation is considerably stronger because of the electron-withdrawing capacity of the nitro group. The near coplanarity of the piperazine and benzene rings, and of the benzene ring with the nitro group, described by the torsion angles C23—N24—C31—C32 of −19.4 (2)° and C33—C34—N37—O39 of 7.3 (2)°, is favorable for the propagation of this effect in the 4-nitrophenylpiperazine substituent. The geometry of the nitrophenyl group does not distort significantly from C_{2v} symmetry characteristic of this system.

There are no classical hydrogen bonds present in the crystal structure of (II*d*). The molecular packing in the crystal is influenced by the presence of weak π–π interactions (Spek, 2003). The isothiazolopyridine systems belonging to inversion-related molecules overlap each other, forming molecular stacks in the [100] direction, with centroid-to-centroid separations of 3.5115 (14) Å between pyridine and ($-x$, $1-y$, $-z$) rings, and 3.7447 (14) Å between five-membered isothiazole (x, y, z) and pyridine ($1-x$, $1-y$, $-z$) rings. These π–π distances are longer than the 3.35 Å observed in graphite but they are comparable to a van der Waals distance of about 3.5 Å for the carbon aromatic skeleton. Similar overlapping occurs for pairs of benzene rings, with the shortest intermolecular contact C31···C33^{i} = 3.332 (2) Å [symmetry code: (i) $-x+1$, $-y+1$, $-z+1$]. Additionally, only one weak C—H···O interaction is observed [C12—H121 = 1.03 (3) Å, H121···O3 = 2.39 (3) Å, C12···O3 = 2.850 (2) Å and C12—H121···O3 = 106 (2)°].

Experimental

The title compound (Malinka *et al.*, 2005) was prepared from 2-hydroxymethyl-4,6-dimethylisothiazolo[5,4-*b*]pyridin-3(2*H*)-one and commercially available *N*-(4-nitrophenyl)piperazine, according to the method of Malinka & Rutkowska (1997). Crystals suitable for X-ray diffraction analysis were grown by slow evaporation of a hexane solution.

Crystal data

$C_{19}H_{21}N_5O_3S$
M_r = 399.47
Triclinic, $P\overline{1}$
a = 7.879 (2) Å
b = 8.825 (2) Å
c = 14.927 (3) Å
α = 99.94 (3)°
β = 101.43 (3)°
γ = 109.04 (3)°
V = 929.6 (5) Å^3
Z = 2
D_x = 1.427 Mg m^{-3}
Cu $K\alpha$ radiation
Cell parameters from 704 reflections
θ = 3.0–69.5°
μ = 1.82 mm^{-1}
T = 293 (2) K
Prism, yellow
0.35 × 0.25 × 0.15 mm

Data collection

Bruker SMART APEX CCD diffractometer
ω scans
Absorption correction: multi-scan [*SADABS* (Sheldrick, 2002), based on the method of Blessing (1995)]
T_{min} = 0.633, T_{max} = 0.764
10692 measured reflections
3403 independent reflections
3190 reflections with $I > 2\sigma(I)$
R_{int} = 0.017
θ_{max} = 70.1°
$h = -8 \rightarrow 9$
$k = -10 \rightarrow 10$
$l = -18 \rightarrow 18$

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F_o^2) + (0.0961P)^2 + 0.0935P]$ where $P = (F_o^2 + 2F_c^2)/3$
$R[F^2 > 2\sigma(F^2)] = 0.042$	$(\Delta/\sigma)_{max} < 0.001$
$wR(F^2) = 0.135$	$\Delta\rho_{max} = 0.20$ e Å^{-3}
$S = 1.05$	$\Delta\rho_{min} = -0.28$ e Å^{-3}
3403 reflections	
298 parameters	
H atoms treated by a mixture of independent and constrained refinement	

Table 1
Selected geometric parameters (Å, °).

S1—N2	1.7078 (16)	N21—C22	1.442 (2)
S1—C8	1.7369 (18)	N21—C26	1.451 (2)
O3—C3	1.222 (2)	N24—C31	1.375 (2)
O38—N37	1.229 (2)	N24—C23	1.465 (2)
O39—N37	1.2213 (19)	N24—C25	1.470 (2)
N2—C3	1.380 (2)	N37—C34	1.443 (2)
N2—C12	1.484 (2)	C3—C9	1.465 (2)
N21—C12	1.432 (2)	C8—C9	1.392 (2)
N2—S1—C8	90.62 (8)	C23—N24—C25	117.30 (13)
C3—N2—C12	122.11 (16)	O39—N37—O38	122.17 (15)
C3—N2—S1	115.84 (12)	O39—N37—C34	119.13 (15)
C12—N2—S1	120.20 (13)	O38—N37—C34	118.70 (13)
C12—N21—C22	116.90 (15)	O3—C3—N2	122.74 (16)
C12—N21—C26	116.25 (15)	O3—C3—C9	128.52 (16)
C22—N21—C26	108.59 (14)	N2—C3—C9	108.74 (14)
C31—N24—C23	118.29 (12)	C9—C8—S1	111.91 (13)
C31—N24—C25	116.17 (12)	C8—C9—C3	112.81 (14)
C22—N21—C12—N2	66.8 (2)	C23—N24—C31—C32	−19.4 (2)
C26—N21—C12—N2	−63.6 (2)	O39—N37—C34—C33	7.3 (2)
S1—N2—C12—N21	81.3 (2)		

The H atoms were located in a difference Fourier map and their coordinates were refined isotropically [C—H = 0.88 (3)–1.04 (3) Å and U_{iso}(H) = 1.5U_{eq}(C)], except for those attached to the methyl C atoms, which were positioned geometrically and treated as riding on their parent C atoms [C—H = 0.96 Å and U_{iso}(H) = 1.5U_{eq}(C)].

Data collection: *SMART* (Bruker, 1999); cell refinement: *SMART*; data reduction: *SAINT* (Bruker, 1999); program(s) used to solve structure: *SIR92* (Altomare *et al.*, 1993); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *ORTEP-3 for Windows* (Farrugia, 1997); software used to prepare material for publication: *SHELXL97* and *WinGX* (Farrugia, 1999).

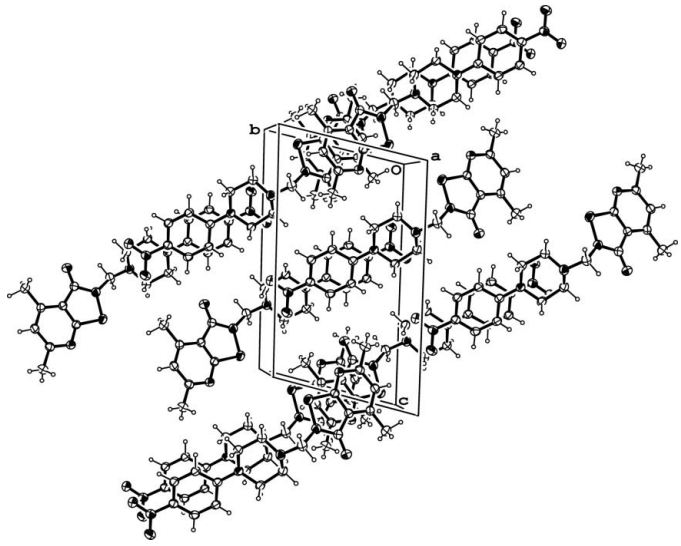


Figure 2
The molecular packing of (II*d*).

References

Allen, F. H. (2002). *Acta Cryst.* B**58**, 380–388.

Allen, F. H., Kennard, O., Watson, D. G., Brammer, L. Orpen, A. G. & Taylor, R. (1987). *J. Chem. Soc. Perkin Trans. 2*, pp. S1–S19..

Altomare, A., Cascarano, G., Giacovazzo, C. & Guagliardi, A. (1993). *J. Appl. Cryst.* **26**, 343–350.

Blessing, R. H. (1995). *Acta Cryst.* A**51**, 33–38.

Bruker (1999). *SMART* and *SAINT*. Bruker AXS Inc., Madison, Wisconsin, USA.

Bruno, I. J., Cole, J. C., Edgington, P. R., Kessler, M., Macrae, C. F., McCare, P., Pearson, J. & Taylor, R. (2002). *Acta Cryst.* B**58**, 389–397.

Cremer, D. & Pople, J. A. (1975). *J. Am. Chem. Soc.* **97**, 1354–1358.

Farrugia, L. J. (1997). *J. Appl. Cryst.* **30**, 565.

Farrugia, L. J. (1999). *J. Appl. Cryst.* **32**, 837–838.

Flouzat, C., Bresson, Y., Mattio, A., Bonnet, J. & Guillaument, G. (1993). *J. Med. Chem.* **36**, 497–503.

Karczmarzyk, Z. & Malinka, W. (2004). *J. Chem. Crystallogr.* **34**, 453–458.

Malinka, W. & Rutkowska, M. (1997). *Farmaco*, **52**, 595–601.

Malinka, W., Świątek, P., Filipek, B., Sapa, J., Jezierska, A. & Koll, A. (2005). In preparation.

Palaska, E., Unlu, S., Özkanli, F., Pilli, G., Erdogan, H., Safak, C., Demirdamar, R. & Gümüsel, B. (1995). *Arzneim.-Forsch. Drug Res.* **45**, 693–696.

Sheldrick, G. M. (1997) *SHELXL97*. University of Göttingen, Germany.

Sheldrick, G. M. (2002) *SADABS*. Version 2.06. University of Göttingen, Germany.

Spek, A. L. (2003). *J. Appl. Cryst.* **36**, 7–13.

Viaud, M. C., Jamoneau, P., Flouzat, C., Bizot-Espirad, J. G., Pfeifer, B., Renard, P., Caignard, D. H., Adam, G. & Guillaument, G. (1995). *J. Med. Chem.* **38**, 1278–1286.