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N-*tert*-Butyl-*N*′-(2-cyclohexylamino-5-nitrobenzenesulfonyl)urea, BM531, a dual-acting agent for thromboxane receptor antagonism and thromboxane synthase inhibition

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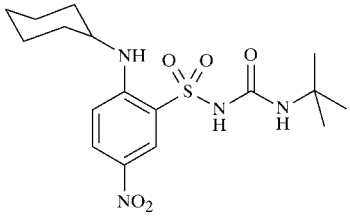
The title compound (BM531), $C_{17}H_{26}N_4O_5S$, has been designed for use as both a thromboxane synthase inhibitor (TXSI) and a thromboxane receptor antagonist (TXRA). We report here the X-ray crystal structure determination of the compound.

Comment

N-*tert*-Butyl-*N*′-(2-cyclohexylamino-5-nitrobenzenesulfonyl)-urea, BM531, (I), is a thromboxane synthase inhibitor (TXSI) and a thromboxane receptor antagonist (TXRA) (Dogné *et al.*, 2001). It crystallizes in space group $P2_1/n$ with two molecules, *A* and *B*, in the asymmetric unit (Fig. 1). A stretched conformation is observed for each molecule and the two NH moieties (N3 and N4) of the sulfonylurea group are



BM531

opposite the carbonyl moiety, and the nitro group is not in the same plane as the phenyl group. Subtle differences between the two molecules can be highlighted from analysis of the O—N2*A*/*B*—C10*A*/*B*—C and S1—N3—C13—N4 torsion angles, which differ by 10 and 7°, respectively, in molecules *A* and *B* (Table 1).

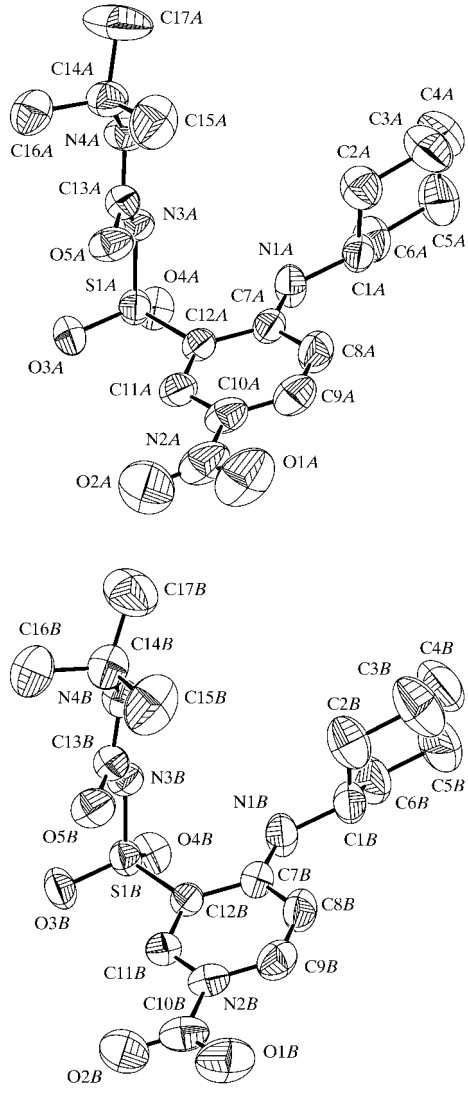


Figure 1
Views of the two molecules in the asymmetric unit of BM531. Displacement ellipsoids are drawn at the 50% probability level and H atoms have been omitted for clarity.

Previously, five conformations, depending on the torsion angles along the sulfonylurea group (Fig. 2), have been reported for this class of compounds, namely α, β, γ and δ for 3-pyridylsulfonylurea and sulfonylcyanoguanidine (Masereel *et al.*, 1995), and ε for *N*-(5-nitrobenzenesulfonyl)urea (Michaux *et al.*, 2001) (Table 3). According to these conventions, both molecules of BM531 in the asymmetric unit adopt

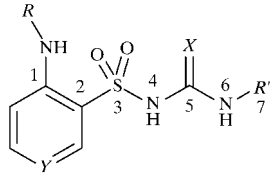


Figure 2
The definition of the theoretical torsion angles along the sulfonylurea group in this class of compounds. Thus, φ_1 is the angle 1–2–3–4, φ_2 is 2–3–4–5, φ_3 is 3–4–5–6 and φ_4 is 4–5–6–7; see also Table 3.

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the ε conformation (Table 4). Moreover, this particular conformation was also found in another dual-action *N*-(5-nitrobenzenesulfonyl)urea molecule, BM567 (Michaux *et al.*, 2001). As in BM567, one intramolecular hydrogen bond in BM531 (N1*A*—H12*A*···O4*A*/N1*B*—H12*B*···O4*B*) involves one O atom of the sulfonyl group and imposes this conformation on BM531 (Table 2). Intermolecular hydrogen bonds were also observed in the crystal packing (Table 2 and Fig. 3). These involve the sulfonylurea moiety, which could be a potential anchoring point for binding with one of the two enzymes.

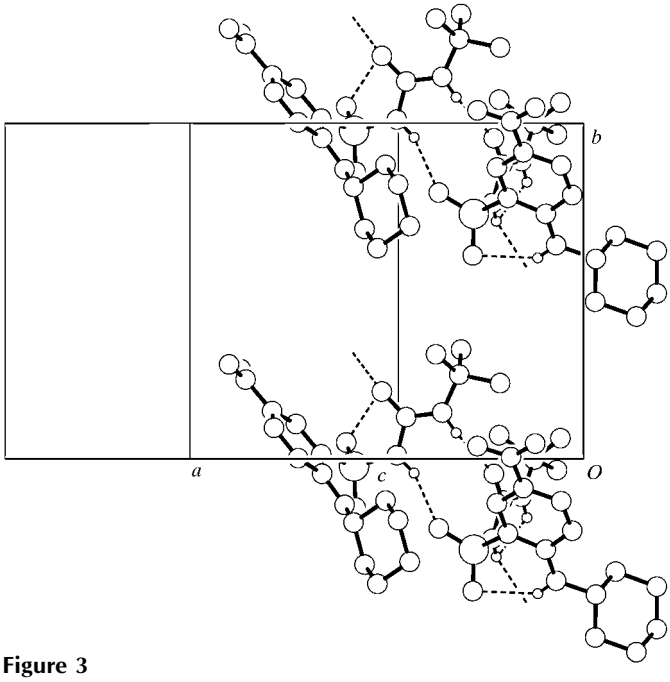

Figure 3
A packing diagram for BM531.

In addition, the crystal packing of BM531 also involves C—H···O interactions that may be classified as weak donor–strong acceptor hydrogen bonds (Desiraju & Steiner, 1999). Indeed, H···*A* distances are between 2 and 3 Å, *D*···*A* distances between 3 and 4 Å and *X*—H···*A* angles between 90 and 180° (Table 2). The phenyl, *tert*-butyl and sulfonyl groups of BM531 are involved in these hydrogen bonds. Three of these interactions are intramolecular hydrogen bonds (Table 2), which should contribute in part to the molecular conformation of the sulfonylurea group of BM531.

In preliminary conclusion, from the two examples analysed to date, the ε conformation in *N*-(5-nitrobenzenesulfonyl)urea molecules seems convenient for both thromboxane synthase inhibition and thromboxane receptor antagonism. The active site of these targets would favour such a conformation. In addition, the sulfonylurea group of these compounds would form favourable interactions with the two targets.

Experimental

Colourless crystals of BM531 suitable for X-ray analysis were obtained by slow evaporation of an ethanol–toluene (1:2) solution.

Crystal data

$C_{17}H_{26}N_4O_5S$
M_r = 398.49
Monoclinic, $P2_1/n$
a = 14.447 (5) Å
b = 11.579 (5) Å
c = 24.981 (5) Å
β = 95.195 (5)°
V = 4162 (2) Å^3
Z = 8
D_x = 1.272 Mg m^{-3}
Cu $K\alpha$ radiation
Cell parameters from 25 reflections
θ = 30–40°
μ = 1.68 mm^{-1}
T = 293 (2) K
Polyhedral, colourless
0.42 × 0.17 × 0.13 mm

Data collection

Enraf–Nonius CAD-4 diffractometer
$\theta/2\theta$ scans
Absorption correction: analytical (de Meulenaer & Tompa, 1965)
T_{min} = 0.539, T_{max} = 0.811
11 170 measured reflections
8166 independent reflections
5832 reflections with $I > 2\sigma(I)$
R_{int} = 0.018
θ_{max} = 71.9°
$h = -17 \rightarrow 12$
$k = 0 \rightarrow 14$
$l = -30 \rightarrow 30$
3 standard reflections
every 200 reflections
frequency: 60 min
intensity decay: 5%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.047
$wR(F^2)$ = 0.136
S = 1.04
8166 reflections
487 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0713P)^2 + 0.7284P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.003
$\Delta\rho_{max}$ = 0.21 e Å^{-3}
$\Delta\rho_{min}$ = −0.51 e Å^{-3}

H atoms were treated as riding, with N—H distances of 0.86 Å and C—H distances in the range 0.93–0.98 Å.

Table 1
Selected torsion angles (°).

O1*A*—N2*A*—C10*A*—C11*A*	−168.7 (2)
O2*A*—N2*A*—C10*A*—C9*A*	−169.8 (3)
O1*A*—N2*A*—C10*A*—C9*A*	10.3 (4)
O2*A*—N2*A*—C10*A*—C11*A*	11.2 (4)
S1*A*—N3*A*—C13*A*—N4*A*	179.76 (14)
O1*B*—N2*B*—C10*B*—C11*B*	−179.0 (2)
O2*B*—N2*B*—C10*B*—C9*B*	−179.5 (2)
O1*B*—N2*B*—C10*B*—C9*B*	−0.4 (4)
O2*B*—N2*B*—C10*B*—C11*B*	2.0 (4)
S1*B*—N3*B*—C13*B*—N4*B*	172.15 (15)

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

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N1*A*—H12*A*···O4*A*	0.86	2.22	2.919 (3)	139
N1*B*—H12*B*···O4*B*	0.86	2.25	2.935 (3)	137
N3*A*—H16*A*···O3*B*	0.86	2.31	3.094 (3)	153
N3*B*—H16*B*···O3*A*^{i}	0.86	2.29	3.045 (3)	147
N3*B*—H16*B*···O5*A*^{i}	0.86	2.60	3.252 (3)	134
N4*A*—H17*A*···O5*B*	0.86	2.21	2.936 (3)	142
N4*B*—H17*B*···O5*A*^{i}	0.86	2.20	2.893 (3)	137
C2*B*—H2*B*···O1*B*^{ii}	0.97	2.50	3.457 (4)	168
C15*A*—H19*A*···O5*A*	0.96	2.42	3.022 (4)	121
C15*B*—H19*B*···O5*B*	0.96	2.40	3.002 (5)	120
C16*A*—H21*A*···O5*A*	0.96	2.55	3.109 (3)	117
C16*B*—H21*B*···O5*B*	0.96	2.57	3.154 (4)	119
C16*A*—H22*A*···O4*B*^{iii}	0.96	2.55	3.414 (3)	150
C16*B*—H22*B*···O4*A*^{iv}	0.96	2.59	3.399 (3)	142

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

Table 3
Theoretical torsion angles (°) along the sulfonylurea group for the α, β, γ, δ and ε conformations.

The numbers 1–7 refer to the positions defined in Fig. 2.

Conformer	φ_1 (1–2–3–4)	φ_2 (2–3–4–5)	φ_3 (3–4–5–6)	φ_4 (4–5–6–7)
α	−90	90	180	180
β	90	90	180	0
γ	90	90	180	180
δ	90	90	0	180
ε	−90	−90	180	180

Table 4
Torsion angles (°) for the ε conformation of the two asymmetric molecules of (I).

	φ_1	φ_2	φ_3	φ_4
Molecule *A*	−63.75 (19)	−60.5 (2)	179.7 (1)	174.3 (2)
Molecule *B*	−62.8 (2)	−57.5 (2)	172.2 (1)	178.3 (2)

Data collection: *CAD*-4 *Software* (Enraf–Nonius, 1989); cell refinement: *CAD*-4 *Software*; data reduction: *HELENA* (Spek, 1997); program(s) used to solve structure: *SIR*97 (Altomare *et al.*, 1999); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *PLATON* (Spek, 1990); software used to prepare material for publication: *SHELXL*97.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: GG1135). Services for accessing these data are described at the back of the journal.

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