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Terbogrel, a dual-acting agent for thromboxane receptor antagonism and thromboxane synthase inhibition

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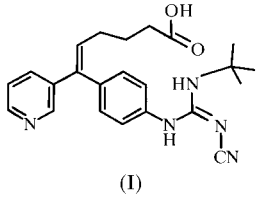
Terbogrel, (*E*)-6-[4-(3-*tert*-butyl-2-cyanoguanidino)phenyl]-6-(3-pyridyl)hex-5-enoic acid, $C_{23}H_{27}N_5O_2$, a mixed thromboxane A_2 receptor antagonist and thromboxane A_2 synthase inhibitor, shows a hairpin-like conformation stabilized by an intramolecular hydrogen bond. A structural feature characteristic of the thromboxane A_2 synthase inhibitor mode is observed: a distance of 8.4257 (19) Å between the pyridine N atom and the carboxyl group.

Comment

Terbogrel, (I), is a combined thromboxane A_2 receptor antagonist (TRA) and thromboxane A_2 synthase inhibitor (TxSI; Soyka *et al.*, 1999). In order to understand this dual mode of action, the structural properties of the compound have been studied and the results are presented here.



(I)

A folded hairpin-like conformer is observed in (I) (Fig. 1), confirming the assumption of Andersen *et al.* (1976) that TXA_2 receptor binding requires a prostaglandin conformation, with a U-shaped or approximately parallel arrangement of the α and ω side chains (the so-called hairpin conformation hypothesis). Such a conformation was also observed in *S*-145, a potent TRA, by Ezumi *et al.* (1990).

The crystal packing of (I) reveals mainly intra- and intermolecular hydrogen bonds (Table 1). The hairpin-like conformation is stabilized by an intramolecular hydrogen bond between N5—H5 and the terminal carboxyl (O29) of the molecule (Fig. 1), as predicted by Takasuka *et al.* (1991). Intermolecular hydrogen bonds are found between atom N9 of the cyanoguanidine group and N10—H10. Thus 'clippers' seem to be formed between the molecules. Another intermolecular bond is observed between atom N22 of the pyridine and the carboxyl function. All these groups are thought to be potential anchoring sites for the TXA_2 receptor.

In the case of TxSIs, the essential structural features for activity are a basic N atom (here, a 3-substituted pyridine) and a carboxylic acid group separated by a distance of 8–10 Å (Iizuka *et al.*, 1981). In (I), a distance of 8.4257 (19) Å is observed between N22 and O30.

In conclusion, two structural features of terbogrel can support its dual action: its hairpin-like conformation for the TRA mode, and the two groups separated by 8.4257 (19) Å for the TxSI mode.

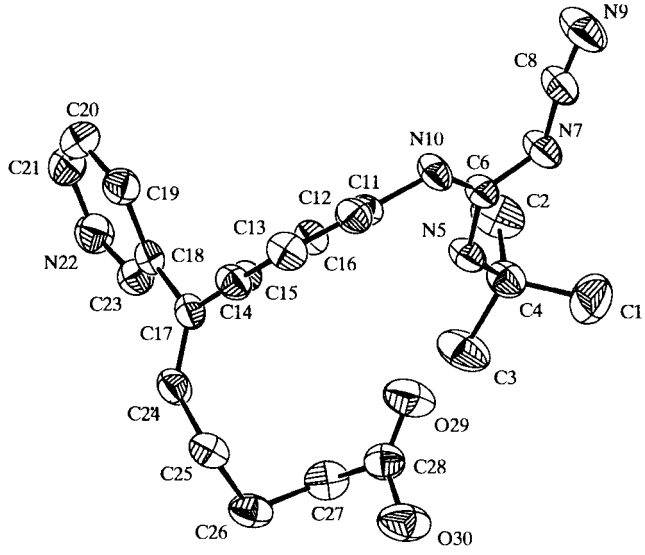


Figure 1
ORTEP (Johnson, 1965) representation of (I) showing the hairpin-like conformation. Displacement ellipsoids are drawn at the 50% probability level and H atoms have been omitted for clarity.

Experimental

Terbogrel (0.173 g) was dissolved in acetic acid (1 ml). This solution was then diluted with water (2 ml) and stored for 48 h at room temperature, after which time crystals of (I) formed.

Crystal data

$C_{23}H_{27}N_5O_2$
M_r = 405.50
Monoclinic, $P2_1/c$
a = 14.9340 (10) Å
b = 10.1150 (10) Å
c = 15.7400 (10) Å
β = 113.049 (5)°
V = 2187.8 (3) Å^3
Z = 4
D_x = 1.231 Mg m^{-3}
Cu $K\alpha$ radiation
Cell parameters from 25 reflections
θ = 30–40°
μ = 0.651 mm^{-1}
T = 293 (2) K
Polyhedral, colourless
0.48 × 0.35 × 0.14 mm

Data collection

Enraf–Nonius CAD-4 diffractometer
$\theta/2\theta$ scans
Absorption correction: ψ scan (North *et al.*, 1968)
T_{min} = 0.813, T_{max} = 0.913
5986 measured reflections
4252 independent reflections
3571 reflections with $I > 2\sigma(I)$
R_{int} = 0.013
θ_{max} = 71.88°
$h = -18 \rightarrow 15$
$k = -8 \rightarrow 12$
$l = 0 \rightarrow 19$
3 standard reflections
every 200 reflections
frequency: 60 min
intensity decay: 6%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.036
$wR(F^2)$ = 0.105
S = 1.047
4252 reflections
288 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0492P)^2 + 0.4729P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.001
$\Delta\rho_{max}$ = 0.20 e Å^{-3}
$\Delta\rho_{min}$ = −0.18 e Å^{-3}
Extinction correction: *SHELXL*97 (Sheldrick, 1997)
Extinction coefficient: 0.0021 (2)

Table 1
Hydrogen-bonding geometry (Å, °).

D—H···A	D—H	H···A	D···A	D—H···A
N5—H5···O29	0.865(17)	2.206 (18)	3.019 (2)	156.4 (14)
N10—H10···N9^{i}	0.877(17)	2.159 (17)	3.014 (2)	165.0 (16)
O30—H30···N22^{ii}	1.01(3)	1.69 (3)	2.677 (2)	164 (3)

Symmetry codes: (i) $2-x, -y, 1-z$; (ii) $x, y-1, z$.

H atoms H5, H10, H24 and H30 were located in difference Fourier maps and then refined. All other H atoms were calculated geometrically and restrained to ride on their parent atoms (C—H = -.93–0.97 Å), with U_{eq}(H) fixed to $1.2U_{eq}$ of the parent atoms.

Data collection: *CAD*-4 *EXPRESS* (Enraf–Nonius, 1992); cell refinement: *CAD*-4 *EXPRESS*; data reduction: *HELENA* (Spek, 1997); program(s) used to solve structure: *SIR*97 (Altomare *et al.*, 1998); 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: GS1099). Services for accessing these data are described at the back of the journal.

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