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Inhibitor of HIV-1 reverse transcriptase: *N'*-(5-bromo-2-pyridyl)-*N*-[2-(2,5-dimethoxyphenyl)ethyl]thiourea

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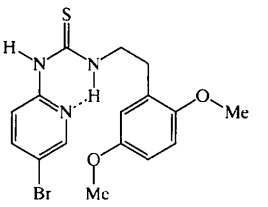
Abstract

The crystal structure of the title compound, $C_{16}H_{18}BrN_3O_2S$ (HI-236), a potent non-nucleoside inhibitor of HIV-1 reverse transcriptase, revealed an intramolecular hydrogen bond between a thiourea N atom and the pyridyl-N atom [N—H···N = 2.671 (3) Å, graph-set motif $S_1^1(6)$] that imparts a more rigid conformation to the molecule. A second hydrogen bond between a thiourea N atom and the thiocarbonyl-S atom [N—H2···S = 3.403 (2) Å, graph-set motif $R_2^2(8)$] was observed between inversion-related molecules of HI-236. The first-level hydrogen-bond graph-set notation for HI-236 was determined to be $S_1^1(6)R_2^2(8)$.

Comment

We recently reported the anti-human immunodeficiency virus (HIV) activity of a thiourea derivative, *N'*-(5-bromo-2-pyridyl)-*N*-[2-(2,5-dimethoxyphenyl)-ethyl]thiourea (HI-236, wild type $HTLV_{IIIB}$ IC_{50}p24 $< 0.001\ \mu M$) (Mao *et al.*, 1999). The identification of HI-236 was aided by structure-based drug design methods which relied on the construction of a composite binding pocket to represent the available binding space in the non-nucleoside inhibitor (NNI or NNRTI) binding site of HIV reverse transcriptase (RT) (Mao *et al.*, 1998, 1999; Sudbeck *et al.*, 1998; Vig *et al.*, 1998*a*,*b*). HI-236 was highly effective against the multidrug-resistant HIV-1 strain RT-MDR (IC_{50} = 5 n*M*) which contains mutations at RT residues Val-74, Leu-41, Ala-106, and Tyr-215 (Mao *et al.*, 1999).



HI-236

The X-ray crystal structure of HI-236 (Fig. 1) showed that the molecule contains an intramolecular hydrogen bond between N3—H3*A* and N1 that locks the molecule into a more rigid conformation and imparts a more compact molecular shape. The presence of this hydrogen bond is consistent with modeling studies undertaken to predict how the inhibitor could bind to the NNI binding site of HIV RT. Modeling studies which docked the HI-236 molecule into the binding site of RT showed that the compact conformation resulting from the hydrogen bond would allow the molecule to easily fit into the NNI binding site (Mao *et al.*, 1999). An extended conformation resulting from a 180° rotation about the N2—C6 bond, however, would hinder the binding of HI-236 in the NNI binding site of RT. An approximation of the dihedral angle between the two aromatic ring planes in the crystal structure of HI-236 can be described by the N3—C7—C8—C9 dihedral angle which was observed to be 66°.

† On the Drug Discovery Program.

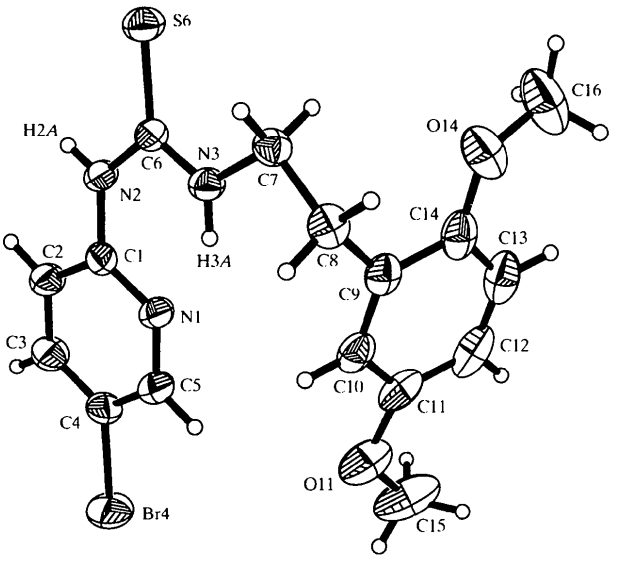


Fig. 1. *ORTEP*II (Johnson, 1976) plot of of HI-236 at 295 K. Displacement ellipsoids are shown at the 30% probability level.

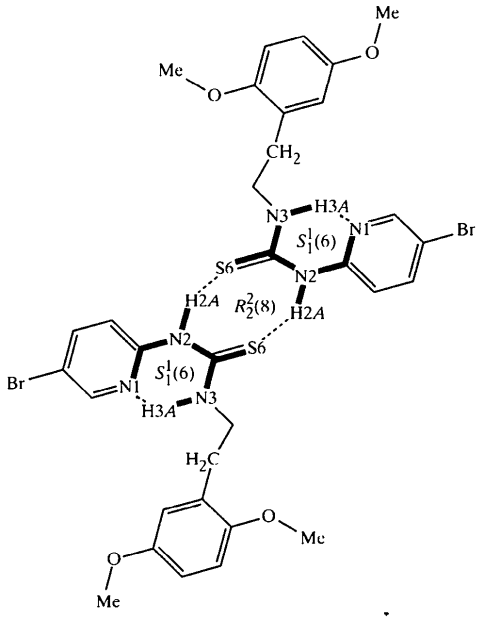


Fig. 2. Hydrogen-bond patterns observed in the X-ray crystal structure of HI-236, described by the first-level hydrogen-bond graph-set notation $S_1^1(6)R_2^2(8)$.

The hydrogen-bond pattern for HI-236 can be described in hydrogen-bond graph-set notation (Bernstein *et al.*, 1990, 1995; Etter, 1990, 1991; Etter *et al.*, 1990). The crystal structure of HI-236 contains only two different hydrogen bonds: N3—H3*A*···N1 and N2—H2*A*···S6 (Fig. 2). The intramolecular hydrogen bond between N3—H3*A* and N1 can be described in graph-set notation as $S_1^1(6)$ (S = self, involving one donor, one acceptor, and six atoms comprising the shortest path through the molecule from the acceptor to the donor). The intermolecular hydrogen bond between N2—H2*A* and S6 of two inversion-related molecules forms a hydrogen-bonded dimer described by a ring motif, $R_2^2(8)$ [R = ring, involving two donors, two acceptors, and eight atoms in the hydrogen-bond motif (ring)]. The two different hydrogen bonds observed in the crystal structure of HI-236 can be summarized by the first-level hydrogen-bond graph-set notation, $S_1^1(6)R_2^2(8)$.

Experimental

The title compound HI-236 was synthesized as reported previously (Vig *et al.*, 1998*b*). Crystals of HI-236 were grown from 2-propanol by slow evaporation at room temperature. The specimen crystal was mounted on a glass fiber using epoxy resin.

Crystal data

$C_{16}H_{18}BrN_3O_2S$
M_r = 396.30
Monoclinic
$P2_1/c$
a = 4.4957 (3) Å
b = 18.8581 (13) Å
c = 20.8480 (15) Å
β = 91.685 (1)°
V = 1766.7 (2) Å^3
Z = 4
D_x = 1.490 Mg m^{-3}
D_m not measured

Mo $K\alpha$ radiation
λ = 0.71073 Å
Cell parameters from 3027 reflections
θ = 1.46–27.52°
μ = 2.457 mm^{-1}
T = 295 (2) K
Needle
0.60 × 0.16 × 0.08 mm
Colorless

Data collection

Bruker SMART CCD area-detector diffractometer
φ and ω scans
Absorption correction: empirical (*SADABS*; Sheldrick, 1996)
T_{min} = 0.32, T_{max} = 0.83
10 751 measured reflections
3984 independent reflections

2022 reflections with $I > 2\sigma(I)$
R_{int} = 0.034
θ_{max} = 27.52°
$h = -5 \rightarrow 5$
$k = -21 \rightarrow 24$
$l = -26 \rightarrow 23$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.037
$wR(F^2)$ = 0.097
S = 0.87
3984 reflections
218 parameters
H atoms treated by a mixture of independent and constrained refinement

$w = 1/[\sigma^2(F_o^2) + (0.0513P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.001
$\Delta\rho_{max}$ = 0.35 e Å^{-3}
$\Delta\rho_{min}$ = −0.42 e Å^{-3}
Extinction correction: none
Scattering factors from *International Tables for Crystallography* (Vol. C)

Table 1. *Selected geometric parameters (Å, °)*

Br4—C4	1.897 (2)	O14—C14	1.372 (4)
S6—C6	1.674 (2)	O14—C16	1.412 (4)
O11—C11	1.368 (4)	N2—C6	1.375 (3)
O11—C15	1.438 (4)	N3—C6	1.318 (3)
C11—O11—C15	117.2 (3)	N3—C6—S6	122.9 (2)
C14—O14—C16	118.7 (3)	N2—C6—S6	119.60 (19)
N3—C6—N2	117.5 (2)		
N3—C7—C8—C9	65.7 (3)	C16—O14—C14—C13	15.4 (4)
C15—O11—C11—C12	0.1 (5)		

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

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N2—H2*A*···S6^{i}	0.81 (2)	2.62 (3)	3.403 (2)	165 (2)
N3—H3*A*···N1	0.84 (2)	1.98 (3)	2.671 (3)	138 (2)

Symmetry code: (i) $1-x, -y, -z$.

H atoms were placed at ideal positions and refined as riding atoms with relative isotropic displacement parameters except for H2*A* and H3*A* (Fig. 1), which were located in the electron-density difference map and refined isotropically.

Data collection: *SMART* (Bruker, 1998*a*). Cell refinement: *SAINT* (Bruker, 1998*a*). Data reduction: *SHELXTL* (Bruker, 1998*b*). Program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1990). Program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997). Molecular graphics: *SHELXTL*. Software used to prepare material for publication: *SHELXTL*.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: BK1492). Services for accessing these data are described at the back of the journal.

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rac-(3*R*,5*S*)-5-(1-Cyclopropyl-1-methylethyl)-3,5-diphenyl-2,3,4,5-tetrahydrofuran-2-one, a triclinic structure with local monoclinic pseudosymmetry

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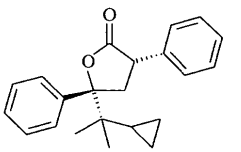
Abstract

The crystal packing in the title compound, $C_{22}H_{24}O_2$, shows layers with pseudo-monoclinic symmetry. The two independent molecules are related by local $2_1/b$ pseudosymmetry. Adjacent layers are displaced by a distance of about 1.17 Å in the *a* direction, resulting in an overall triclinic symmetry of the structure. The packing of the layers shows intermolecular C—H···π(arene) interactions.

Comment

The structure of the title compound, (I), contains two crystallographically independent molecules. Both molecules have very similar conformations. Corresponding torsion angles of the molecules differ by no more than 6°. The two independent molecules (Fig. 1) are related by a non-crystallographic glide plane perpendicular to the *a* axis, with a translation of *b*/2. The equation of the plane expressed in crystal coordinates is approximately: $8.430x + 0.347y + 1.236z = 2.764$. The angle between this plane and the *b* axis is 1.4°. Thus, the pseudo-glide plane is almost continuous in the crystallographic *b* direction. In the *c* direction, however, the pseudo-glide plane only acts in one unit cell and shows a shift of about 1.17 Å along **a** between adjacent cells (Fig. 2). The pseudo-glide symmetry can be combined with the crystallographic inversion center at $(0,0,\frac{1}{2})$ to give an additional pseudo-twofold screw axis parallel



(I)