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YC-1, an activation inductor of soluble guanylyl cyclase

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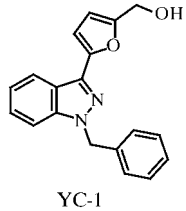
The crystal structure of 1-benzyl-3-(5-hydroxymethyl-2-furyl)-indazole, $C_{19}H_{16}N_2O_2$, showed that the furan O and indazole N atoms lie on the same face of the molecule. The crystal packing consists of intermolecular hydrogen bonding, and indazole–indazole and indazole–phenyl interactions.

Comment

The benzylindazole derivative YC-1 [1-benzyl-3-(5-hydroxymethyl-2-furyl)indazole] has been described as an inhibitor of platelet aggregation (Ko *et al.*, 1994; Wu *et al.*, 1995) and smooth muscle cell proliferation (Yu *et al.*, 1995). Recently, it has been demonstrated that YC-1 induces activation of soluble guanylyl cyclase (sGC) probably by binding to an allosteric site which sensitizes the sGC enzyme towards its gaseous activators (NO and CO) by reducing the ligand dissociation rate from the haem group (Friebe & Koesling, 1998; Denninger & Marletta, 1999; Kharitonov *et al.*, 1999; Friebe *et al.*, 1999; Schelvis *et al.*, 1999). Considering YC-1 as a



YC-1

lead to design new sGC activators with potential therapeutic interest with respect to cardiovascular diseases, we are engaged in a program aiming to synthesize new analogues possessing the same structural features as YC-1 and in particular having the same spatial arrangement of the three putative interaction centres with the enzyme: two N atoms of the indazole ring, the O atom of the furan ring and the O atom of the alcohol group. In order to model these interactions, we needed to determine the three-dimensional structure of a stable conformation of YC-1. The first molecular modelling trials were unable to define the relative orientation of the furan and indazole rings, *i.e.* if the O atom of the furan lies *cis* or *trans* with respect to the N9 atom of the indazole nucleus with certainty.

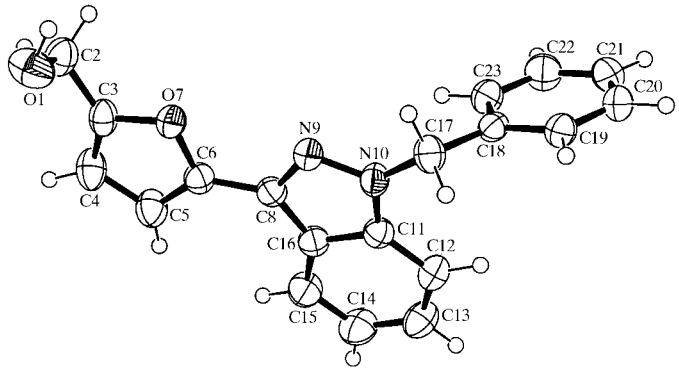


Figure 1
View of YC-1 showing the labelling of the non-H atoms. Displacement ellipsoids are shown at 50% probability levels and H atoms are drawn as small circles of arbitrary radii.

In the resulting crystal structure, the furan and indazole rings are quasi-coplanar (Fig. 1). The ring heteroatoms, *i.e.* the furan O (O7) and indazole N atoms (N9, N10), lie on the same face of the molecule, *i.e.* in the *cis* conformation. The angle

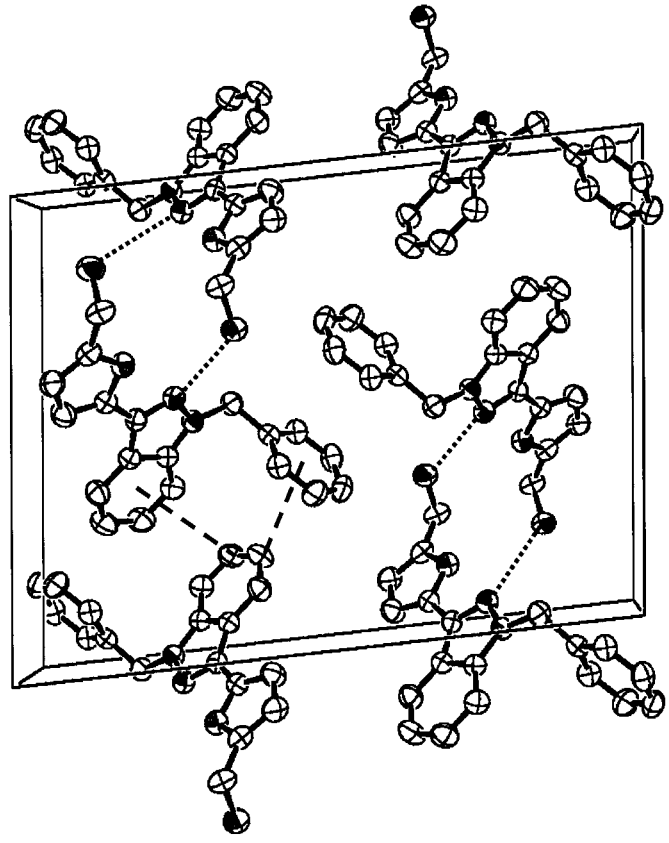


Figure 2
The crystal packing of YC-1 molecules projected on the *ac* plane. H atoms have been omitted for clarity. Dashed lines indicate the hydrogen bonds and interactions between the aromatic rings.

between the planes of the two rings is about 5.4 (1)°. The third ring, the phenyl of the benzyl group, adopts an approximately perpendicular position with respect to the two rings mentioned above, the angle being 77.87 (4)°.

The crystal packing is stabilized by intermolecular hydrogen bonding and interactions between the aromatic rings of the molecule. An intermolecular hydrogen bond forms between the N9 atom of the indazole ring and the hydroxymethyl O1—H1 group of the furan ring of a neighbouring molecule [N9···H1($\frac{1}{2}-x,-\frac{1}{2}+y,\frac{1}{2}-z$) = 1.93 (3) Å; Table 1 and Fig. 2]. The intermolecular distances observed between the aromatic rings of neighbouring molecules suggest two interactions as the most important: indazole–indazole and indazole–phenyl (Fig. 2), for which a T-shaped arrangement was observed. Such an arrangement has been shown to result in favourable intermolecular attractive forces (Koch & Egert, 1995). For indazole–indazole T-shaped arrangements, the shortest distance corresponds to a C13—H13···*Cg*1 interaction, with an H13···*Cg*1 distance of 3.18 Å (*Cg*1 is the centroid of the indazole phenyl ring with symmetry code $\frac{3}{2}-x,\ y-\frac{1}{2},\frac{1}{2}-z$). For indazole–phenyl T-shaped arrangements, the shortest distance corresponds to a C14—H14···*Cg*2 interaction, with an H14···*Cg*2 distance of 3.07 Å (*Cg*2 is the centroid of the phenyl ring with symmetry code $\frac{3}{2}-x,\frac{1}{2}+y,\frac{1}{2}-z$).

Experimental

Suitable red transparent crystals of the compound, synthesized according to Collot *et al.* (1999), were grown by slow evaporation from a hexane solution at room temperature.

Crystal data

$C_{19}H_{16}N_2O_2$
M_r = 304.34
Monoclinic, $P2_1/n$
a = 14.3450 (10) Å
b = 5.6905 (7) Å
c = 18.7140 (10) Å
β = 96.064 (9)°
V = 1519.1 (2) Å^3
Z = 4
D_x = 1.331 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 25 reflections
θ = 8–14°
μ = 0.088 mm^{-1}
T = 293 (2) K
Prism, translucent pale red
0.6 × 0.4 × 0.3 mm

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

D—H···A	D—H	H···A	D···A	D—H···A
O1—H1···N9^{i}	0.96 (3)	1.93 (3)	2.831 (2)	156 (2)

Symmetry code: (i) $\frac{1}{2}-x,\frac{1}{2}+y,\frac{1}{2}-z$.

Data collection

Enraf–Nonius CAD-4 diffractometer
$\theta/2\theta$ scans
3412 measured reflections
3314 independent reflections
2522 reflections with $I > 2\sigma(I)$
R_{int} = 0.012
θ_{max} = 27°
$h = -18 \rightarrow 18$
$k = 0 \rightarrow 7$
$l = 0 \rightarrow 23$
3 standard reflections
frequency: 60 min
intensity decay: 3%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.045
$wR(F^2)$ = 0.140
S = 1.060
3314 reflections
272 parameters
All H atoms refined
$w = 1/[\sigma^2(F_o^2) + (0.0797P)^2 + 0.1614P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.002
$\Delta\rho_{max}$ = 0.17 e Å^{-3}
$\Delta\rho_{min}$ = −0.26 e Å^{-3}

All H atoms were found in the difference electron-density map with bond lengths and angles close to well established geometrical criteria [C—H 0.92 (2)–1.02 (2) Å]. They were refined with isotropic displacement parameters.

Data collection: *CAD*-4-*PC* (Enraf–Nonius, 1994); cell refinement: *CAD*-4-*PC*; data reduction: *Xtal*3.2 (Hall *et al.*, 1992); program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1997); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *ORTEP*-3 (Farrugia, 1997); software used to prepare material for publication: *SHELXL*97.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: GS1090). Services for accessing these data are described at the back of the journal.

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