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(2*R**,3*R**,6*S**)-*N*,6-Bis(4-fluorophenyl)-2-(4-hydroxyphenyl)-3,4,5,6-tetrahydro-2*H*-pyran-3-carboxamide

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Key indicators

Single-crystal X-ray study
T = 273 K
Mean σ(C–C) = 0.004 Å
R factor = 0.044
wR factor = 0.101
Data-to-parameter ratio = 8.4

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

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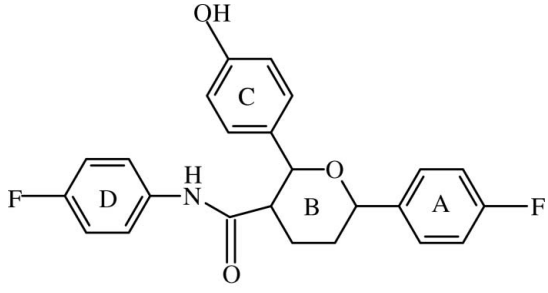
The molecule of the title compound, $C_{24}H_{21}F_2NO_2$, has a T-shaped form in the crystal structure. The central tetrahydropyran ring shows a chair conformation. All substituents are equatorially attached to this ring. The crystal packing is stabilized by N—H···O, O—H···O and C—H···π(arene) interactions.

Comment

Ezetimibe, which was approved in late 2002 for the use either alone or in combination with a statin (simvastatin, atorvastatin, lovistatin or pravastatin), is the only example to date of a drug that involves inhibition of intestinal cholesterol absorption (Clader, 2004; Rosenblum *et al.*, 1998). Ezetimibe is effective as monotherapy since some preclinical studies show that it can induce hepatic cholesterol synthesis (Sudhop *et al.*, 2002). The crystal structure of ezetimibe has already been published by our group (Ravikumar & Sridhar, 2005). The title compound, (I), was obtained by performing a further reaction with ezetimibe and we present here its crystal structure.



(I)

The title compound posesses three stereogenic centres whose relative configurations are C7 (*S*), C10 (*R*) and C11 (*R*) (Fig. 1). The molecule has a T-shaped form with the tetra-

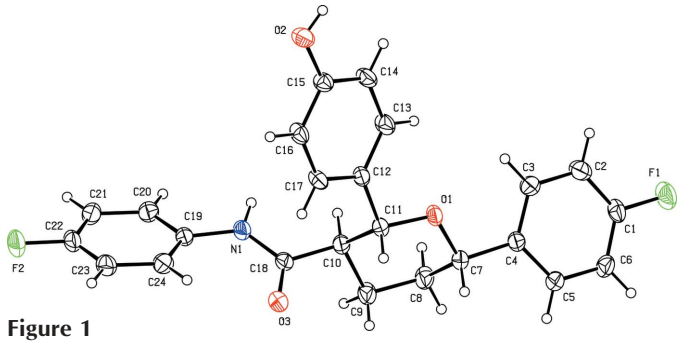


Figure 1
A view of (I) with the atomic numbering scheme. Displacement ellipsoids are drawn at the 30% probability level.

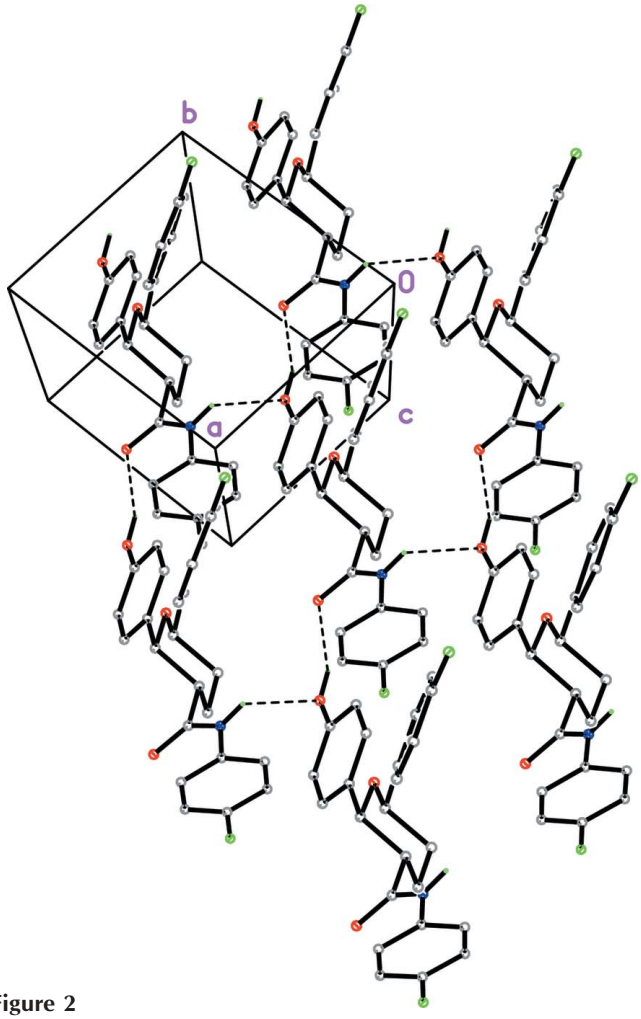


Figure 2
A packing diagram of (I), showing the O—H···O and N—H···O interactions as dashed lines. H atoms not involved in hydrogen bonding have been omitted for clarity.

hydropyran ring (ring *B*) as the junction point. Ring *B* has a chair conformation. All substituents are attached to it in equatorial positions. The C10—C18—N1—C19 torsion angle of 177.2 (2)° shows the antiperiplanar conformation of the amide bond. The carbonyl group is not coplanar with the fluorophenyl ring (Table 1). The two F atoms of rings *A* and *D* are separated by a distance of 16.013 (4) Å. The crystal structure is stabilized by an extensive hydrogen-bonding network (Table 2). Hydroxyl atom O2 acts as donor to carbonyl atom O3 and as acceptor from amide atom N1. In addition, weak intramolecular C—H···O and C—H···π interactions have also been found in the crystal packing.

Experimental

Ezetimibe (650 mg) was added to HCl (10 ml) containing 30% acetonitrile solution (7 ml HCl + 3 ml acetonitrile). The reaction was heated at 353 K for 8 h. The solvent was removed under vacuum at 323 K and the aqueous phase was extracted with methylene chloride (3 × 3 ml). The combined organic layer was washed with brine. The organic phase was dried over sodium sulfate and was distilled completely to afford a white powder, which was purified by column chromatography using chloroform and methanol (10% solution). The product was isolated and characterized. Suitable single crystals were obtained on recrystallization of the compound from methanol. MS: 409 [M^+]; ^{1}H NMR ($CDCl_3$): 1.5–1.6 (2*H*, *m*, CH_2 at b), 2.06–2.17 (2H, *m*, CH_2 at a), 2.7–2.8 (1H, *m*, CH at e), 4.6 (1*H*, *d*, CH at c), 4.7 (1H, *d*, CH at d), 6.74–6.76 (2H, *m*, Ar—H × 2), 7.11–7.20 (2H, *m*, Ar—H × 2), 7.22–7.29 (4H, *m*, Ar—H × 4), 7.47–7.51 (4*H*, *m*, Ar—H × 4), 9.914 (1*H*, s, N—H). ^{13}C NMR: 29.317 (C at a), 34.089 (C at b), 52.88 (C at c), 80.744 (C at d), 83.271 (C at c), 115.804 (Ar-c), 116.076 (Ar-c × 4), 116.353 (Ar-c), 123.684 (Ar-c), 128.842 (Ar-c), 128.949 (Ar-c), 129.505 (Ar-c × 4), 133.055 (Ar-c), 140.302 (Ar-c), 158.313 (Ar-c), 174.414 (C at f). IR (C m^{-1}): 3316.2 (NH-st); 1655 (C═O st); 1609, 1547, 1508 (N—H bend); 1213 (C—N st).

Crystal data

$C_{24}H_{21}F_2NO_3$	Z = 1
M_r = 409.42	D_x = 1.365 Mg m^{-3}
Triclinic, *P*1	Mo *K*α radiation
a = 6.1397 (5) Å	Cell parameters from 2320 reflections
b = 7.6596 (7) Å	θ = 2.8–26.8°
c = 11.1439 (10) Å	μ = 0.10 mm^{-1}
α = 72.484 (1)°	T = 273 (2) K
β = 89.979 (1)°	Block, colourless
γ = 85.553 (2)°	0.22 × 0.18 × 0.16 mm
V = 498.12 (8) Å^3	

Data collection

Bruker SMART APEX CCD area-detector diffractometer	2121 reflections with $I > 2\sigma(I)$
ω scans	R_{int} = 0.024
Absorption correction: none	θ_{max} = 28.0°
5763 measured reflections	$h = -8 \rightarrow 8$
2282 independent reflections	$k = -10 \rightarrow 9$
	$l = -14 \rightarrow 14$

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F_o^2) + (0.051P)^2 + 0.0636P]$ where $P = (F_o^2 + 2F_c^2)/3$
$R[F^2 > 2\sigma(F^2)]$ = 0.044	$(\Delta/\sigma)_{max} < 0.001$
$wR(F^2)$ = 0.101	$\Delta\rho_{max}$ = 0.22 e Å^{-3}
S = 1.05	$\Delta\rho_{min}$ = −0.20 e Å^{-3}
2282 reflections	
272 parameters	
H-atom parameters constrained	

Table 1
Selected geometric parameters (Å, °).

C1—F1	1.354 (3)	C18—N1	1.349 (3)
C15—O2	1.373 (3)	C19—N1	1.419 (3)
C18—O3	1.223 (3)	C22—F2	1.368 (3)
O3—C18—N1—C19	−0.8 (4)	C24—C19—N1—C18	24.9 (4)

Table 2
Hydrogen-bond geometry (Å, °).

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N1—H1···O2^{i}	0.86	2.24	2.903 (3)	134
O2—H2···O3^{ii}	0.82	1.98	2.739 (3)	153
C17—H17···F1^{iii}	0.93	2.55	3.178 (3)	125
C24—H24···O3	0.93	2.39	2.929 (4)	117
C2—H2*A*···*Cg*2^{iv}	0.93	2.83	3.515	131
C5—H5···*Cg*2^{v}	0.93	2.86	3.575	134
C9—H9*B*···*Cg*1^{i}	0.97	2.78	3.662	152

Symmetry codes: (i) $x, y-1, z$; (ii) $x-1, y+1, z$; (iii) $x+1, y, z+1$; (iv) $x-1, y+1, z-1$; (v) $x, y, z-1$. Notes: *Cg*1 is the centroid of ring C12–C17 and *Cg*2 of ring C19–C24.

All H atoms were placed in idealized positions and allowed to ride on their parent atoms, with C—H = 0.93–0.97 Å, O—H = 0.82 Å and N—H = 0.86 Å, and with U_{iso}(H) = 1.2U_{eq}(C,*N*,*O*). In addition, the torsion angle about the C—OH bond was refined. In the absence of significant anomalous scattering effects, the absolute configuration could not be established by this analysis. Therefore, it was arbitrarily assigned and the Friedel pairs were merged.

Data collection: *SMART* (Bruker, 2001); cell refinement: *SAINT* (Bruker, 2001); data reduction: *SAINT*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 1997); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *ORTEP3* (Farrugia, 1997) and *PLATON* (Spek, 2003); software used to prepare material for publication: *SHELXL97* and *PARST* (Nardelli, 1995).

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