Acta Crystallographica Section E
Structure Reports Online
ISSN 1600-5368

(*S*)-4-[2-(3-Cyanobenzamido)-3-hydroxypropyl]phenyl 3-cyanobenzoate

Sumaira Umbreen, Sabine Foro* and Boris Schmidt

Clemens-Schöpf-Institut für Organische Chemie und Biochemie, Technische Universität Darmstadt, Petersenstraße 22, D-64287 Darmstadt, Germany

Correspondence e-mail: foro@tu-darmstadt.de

Key indicators

Single-crystal X-ray study
T = 299 K
Mean σ(C–C) = 0.005 Å
R factor = 0.038
wR factor = 0.079
Data-to-parameter ratio = 8.4

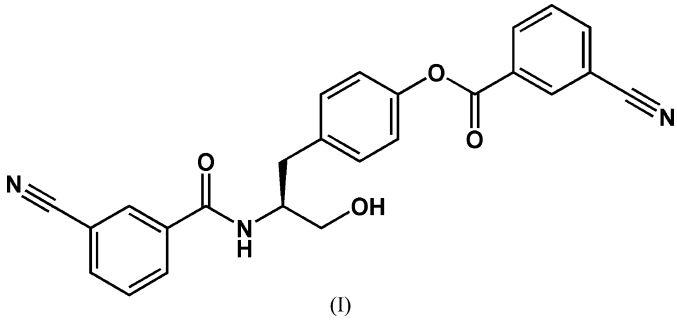
For details of how these key indicators were automatically derived from the article, see http://journals.iucr.org/e.

Received 17 May 2006
Accepted 24 May 2006

Non-planar molecules of the title compound, $C_{25}H_{19}N_4O_3$, are linked by intermolecular N—H···O, O—H···N and C—H···O hydrogen bonds to form a three-dimensional network.

Comment

The accumulation of β-amyloid peptide (Aβ) in the brain is thought to be a primary cause for the progression of Alzheimer's disease (Selkoe, 2001). Since Aβ is generated from the cleavage of β-amyloid precursor protein (APP) by proteolytic enzymes, β- and γ-secretases (Sinha & Lieberburg, 1999), these two secretases represent potential therapeutic targets (Schmidt *et al.*, 2005). The identification of β-secretase (Vassar *et al.*, 1999) prompted us to develop effective inhibitors against this enzyme. β-Secretase belongs to an aspartyl protease family, similar to HIV protease. The majority of potent inhibitors of BACE are still peptide-based transition state analogues according to several reviews (Schmidt, 2003; Schmidt *et al.*, 2005, 2006). Hydroxyethylenes, statines, norstatines, bisstatines, hydroxyethylamines and hydroxyethylureas were employed. The hydroxyethylenes delivered the first highly potent inhibitors. The compound (*S*)-4-[2-(3-cyanobenzoamido)-3-hydroxypropyl]phenyl 3-cyanobenzoate (I), is an important precurser for hydroxyethylene amides. In the reaction of 3-cyanobenzoic acid with L-tyrosinol, we obtained compound (I) as the major and unexpected product. X-ray studies of the title compound, (I), have been carried out to obtain detailed structural information and the results are presented here.



(I)

The three intermolecular N—H···O, O—H···N and C—H···O hydrogen bonds form a three-dimensional network. Details of the hydrogen-bonding geometry are given in Table 1. The dihedral angles C8—O2—C9—C14 and N2—C18—C19—C24 are 95.5 (3) and −34.2 (4)°, respectively indicating non-planarity in the molecule of (I).

Experimental

Ethyl-3-(3′-dimethylaminopropyl)carbodiimide hydrochloride (979 mg, 5.11 mmol) and *N*-hydroxybenzotriazole hydrate (828 mg, 6.13 mmol) were added to a solution of 3-cyanobenzoic acid (751 mg, 5.11 mmol) dissolved in CH_2Cl_2 (10 ml). The resulting mixture was stirred at ambient temperature for 5 min, then treated with L-tyrosinol (1.02 ml, 6.13 mmol) and triethylamine (1.42 ml, 10.22 mmol) for 6 h. CH_2Cl_2 (20 ml) was added, and the solution was washed with HCl (0.1 *N*, 5 × 30 ml), $NaHCO_3$ saturated solution (3 × 30 ml) and brine (1 × 30 ml), dried over Na_2SO_4 and concentrated to obtain the title compound, (I), as colourless crystals (1.5 g, 69%). Single crystals of (I) suitable for X-ray data collection were obtained by slow evaporation of a methanol/dichloromethane (2:8) solution.

Crystal data

$C_{25}H_{19}N_3O_4$
M_r = 425.43
Monoclinic, *C*2
a = 32.665 (9) Å
b = 4.778 (1) Å
c = 15.015 (4) Å
β = 113.19 (2)°
V = 2154.1 (9) Å^3
Z = 4
D_x = 1.312 Mg m^{-3}
Mo *K*α radiation
μ = 0.09 mm^{-1}
T = 299 (2) K
Nneedle, colourless
0.50 × 0.08 × 0.02 mm

Data collection

Oxford Diffraction Xcalibur diffractometer with Sapphire CCD detector
ω and φ scans
Absorption correction: analytical (*CrysAlis RED*; Oxford Diffraction, 2004)
T_{min} = 0.974, T_{max} = 0.998
7760 measured reflections
2438 independent reflections
1261 reflections with $I > 2\sigma(I)$
R_{int} = 0.052
θ_{max} = 26.4°

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.038
$wR(F^2)$ = 0.079
S = 0.88
2438 reflections
289 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0294P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.15 e Å^{-3}
$\Delta\rho_{min}$ = −0.14 e Å^{-3}

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

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N2—H2N···O4^{i}	0.86	2.14	2.889 (4)	145
O3—H3O···N1^{ii}	0.82	2.19	3.007 (5)	173
C11—H11···O1^{iii}	0.93	2.53	3.414 (4)	159

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

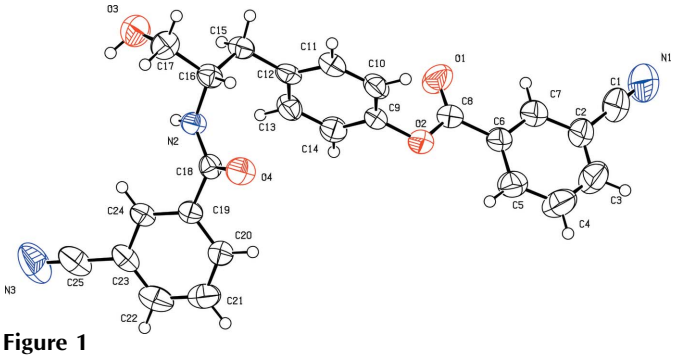


Figure 1
Molecular structure of (I), showing the atom labelling and displacement ellipsoids drawn at the 50% probability level.

H atoms were positioned with idealized geometry and were refined using a riding model, with C—H in the range 0.93–0.98 Å, O—H = 0.82 Å and N—H = 0.86 Å. U_{iso}(H) values were set equal to 1.2U_{eq} of the parent atom. In the absence of significant anamalous dispersion effects, Friedel pairs were merged and the $\Delta f''$ term set to zero. The absolute configuration was assigned according to the known absolute configuration of the educt L-tyrosinol.

Data collection: *CrysAlis CCD* (Oxford Diffraction, 2003); cell refinement: *CrysAlis RED* (Oxford Diffraction, 2004); data reduction: *CrysAlis RED*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 1997); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *PLATON* (Spek, 2003); software used to prepare material for publication: *SHELXL97*.

The authors thank Professor Dr Hartmut Fuess, FG Strukturforschung, FB Material- und Geowissenschaften, Technische Universität Darmstadt, Petersenstr. 23, 64287 Darmstadt, for diffractometer time.

References

Oxford Diffraction (2003). *CrysAlis CCD*. Oxford Diffraction Ltd., Köln, Germany.
Oxford Diffraction (2004). *CrysAlis RED*. Oxford Diffraction Ltd., Köln, Germany.
Schmidt, B. (2003). *Chembiochem*, **4**, 367–378.
Schmidt, B., Baumann, S., Braun, H. A. & Larbig, G. (2006). *Curr. Top. Med. Chem.* **6**, 377–392.
Schmidt, B., Braun, H. A. & Narlawar, R. (2005). *Curr. Med. Chem.* **12**, 1677–1695.
Selkoe, D. J. (2001). *Nat. Phys. Rev.* **81**, 741–766.
Sheldrick, G. M. (1997). *SHELXS97* and *SHELXL97*. University of Göttingen, Germany.
Sinha, S. & Lieberburg, I. (1999). *Proc. Natl Acad. Sci. USA*, **96**, 11049–11053.
Spek, A. L. (2003). *J. Appl. Cryst.* **36**, 7–13.
Vassar, R., Bennett, B. D., Babu-Khan, S., Kahn, S., Mendiaz, E. A., Denis, P., Teplow, D. B., Ross, S., Amarante, P., Loeloff, R., Luo, Y., Fisher, S., Fuller, J., Edenson, S., Lile, J. *et al.* (1999). *Science*, **286**, 753–766.