Wei Sun, Zhi-Ling Zhu, Li-Min Zuo, Ting Zhao, Ming-Hui Zhu and Guang-Zhi Shan*

Crystal structure of *tert*-butyl (*R*)-(1-(benzylamino)-3-methoxy-1-oxopropan-2-yl) carbamate, C₁₆H₂₄N₂O₄

Table 1: Data collection and handling.

Crystal:	Block, clear light colourless
Size:	0.28 × 0.19 × 0.15 mm
Wavelength:	Cu K α radiation (1.54184 Å)
μ :	0.72 mm ⁻¹
Diffractometer, scan mode:	Xcalibur, ω -scans
$\theta_{\max}$, completeness:	66.9°, >99%
$N(hkl)_{\text{measured}}$, $N(hkl)_{\text{unique}}$, R_{int} :	24014, 2949, 0.043
Criterion for I_{obs} , $N(hkl)_{\text{gt}}$:	$I_{\text{obs}} > 2 \sigma(I_{\text{obs}})$, 2650
$N(\text{param})_{\text{refined}}$:	204
Programs:	CrysAlis ^{PRO} [1], SHELX [2], SUPERFLIP [3], OLEX2 [4]

<https://doi.org/10.1515/ncrs-2018-0219>

Received June 27, 2018; accepted August 26, 2018; available online September 18, 2018

Abstract

C₁₆H₂₄N₂O₄, monoclinic, $P2_1$ (no. 4), $a = 10.7872(2)$ Å, $b = 5.02626(11)$ Å, $c = 15.5479(3)$ Å, $\beta = 94.2278(17)^\circ$, $V = 840.70(3)$ Å³, $Z = 2$, $R_{\text{gt}}(F) = 0.0337$, $wR_{\text{ref}}(F^2) = 0.0871$, $T = 293(2)$ K.

CCDC no.: 1863961

The asymmetric unit of the title crystal structure is shown in the figure. Tables 1 and 2 contain details of the measurement method and a list of the atoms including atomic coordinates and displacement parameters.

Source of material

The title compound was synthesized according to a reported procedure [5]. Single crystals suitable for X-ray diffraction were obtained by slow evaporation from ethyl acetate at room temperature.

*Corresponding author: Guang-Zhi Shan, Institute of Medicinal Biotechnology, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100050, P.R. China, e-mail: shanguangzhi@imb.pumc.edu.cn

Wei Sun, Zhi-Ling Zhu, Li-Min Zuo, Ting Zhao and Ming-Hui Zhu: Institute of Medicinal Biotechnology, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100050, P.R. China

Table 2: Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å²).

Atom	<i>x</i>	<i>y</i>	<i>z</i>	$U_{\text{iso}}^*/U_{\text{eq}}$
O1	0.93691(16)	−0.0318(4)	0.78192(13)	0.0573(5)
O3	1.20050(17)	0.3403(3)	0.56779(10)	0.0564(5)
O4	1.1616(2)	0.6900(4)	0.65359(13)	0.0664(6)
N2	1.12537(18)	0.2669(4)	0.69396(12)	0.0470(5)
H2	1.1308	0.1018	0.6802	0.056*
O2	1.12205(17)	0.2756(4)	0.93128(11)	0.0656(5)
C8	0.9496(2)	0.2114(5)	0.78138(14)	0.0416(5)
C12	1.1619(2)	0.4537(5)	0.63973(15)	0.0443(6)
N1	0.85488(17)	0.3803(4)	0.78451(13)	0.0496(5)
H1	0.8690	0.5487	0.7849	0.060*
C9	1.0770(2)	0.3382(5)	0.77528(14)	0.0423(5)
H9	1.0692	0.5321	0.7787	0.051*
C1	0.6416(2)	0.4921(6)	0.81831(16)	0.0511(6)
C2	0.6622(3)	0.6066(6)	0.89848(17)	0.0595(7)
H2A	0.7322	0.5592	0.9336	0.071*
C10	1.1665(2)	0.2404(6)	0.84898(15)	0.0534(6)
H10A	1.1828	0.0528	0.8405	0.064*
H10B	1.2447	0.3347	0.8470	0.064*
C13	1.2393(3)	0.5104(6)	0.49688(16)	0.0567(7)
C7	0.7278(2)	0.2844(7)	0.7872(2)	0.0682(8)
H7A	0.7274	0.1311	0.8251	0.082*
H7B	0.6974	0.2272	0.7299	0.082*
C6	0.5369(3)	0.5676(8)	0.76782(19)	0.0717(8)
H6	0.5211	0.4940	0.7132	0.086*
C3	0.5802(3)	0.7909(7)	0.92735(19)	0.0686(8)
H3	0.5955	0.8668	0.9816	0.082*

Table 2 (continued)

Atom	<i>x</i>	<i>y</i>	<i>z</i>	<i>U</i> _{iso} [*] / <i>U</i> _{eq}
C5	0.4551(3)	0.7527(9)	0.7979(3)	0.0875(11)
H5	0.3846	0.8016	0.7635	0.105*
C4	0.4770(3)	0.8626(7)	0.8770(2)	0.0781(10)
H4	0.4218	0.9865	0.8969	0.094*
C16	1.3534(3)	0.6659(8)	0.5278(2)	0.0862(12)
H16A	1.3309	0.8018	0.5671	0.129*
H16B	1.3889	0.7467	0.4793	0.129*
H16C	1.4131	0.5484	0.5565	0.129*
C11	1.1195(3)	0.5447(8)	0.9584(2)	0.0795(9)
H11A	1.0580	0.6402	0.9228	0.119*
H11B	1.1996	0.6238	0.9533	0.119*
H11C	1.0991	0.5524	1.0174	0.119*
C14	1.1332(3)	0.6807(7)	0.4626(2)	0.0736(9)
H14A	1.0603	0.5725	0.4518	0.110*
H14B	1.1537	0.7633	0.4098	0.110*
H14C	1.1174	0.8155	0.5042	0.110*
C15	1.2724(6)	0.3089(8)	0.4294(2)	0.132(2)
H15A	1.3332	0.1868	0.4545	0.197*
H15B	1.3057	0.3998	0.3820	0.197*
H15C	1.1991	0.2126	0.4091	0.197*

Experimental details

All H atoms were positioned geometrically and constrained to ride on the parent atoms, N–H = 0.86 Å, C–H = 0.93–0.98 Å with $U_{\text{iso}}(\text{H}) = 1.5U_{\text{eq}}(\text{methyl C})$ or $1.2U_{\text{eq}}(\text{C, N})$ for other H atoms.

Discussion

The title compound is an important intermediate of the Lacosamide synthesis. Lacosamide (trade name Vimpat) is an anticonvulsant drug approved for the adjunctive treatment of partial-onset seizures and neuropathic pain [6, 7]. Lacosamide has a dual mechanism underlying its anticonvulsant and analgesic activity. It selectively enhances slow inactivation of voltage-gated sodium channels and regulates the collapse response mediator protein 2 (CRMP2) [8, 9].

The asymmetric unit of the title compound contains one single target molecule. The torsion angle of C9–C10–O2–C10 is $-71.0(3)^\circ$. There are several weaker intramolecular C–H $\cdots$ O non-classical hydrogen bonds in the crystal structure. The components are linked by weak classical intermolecular N–H $\cdots$ O hydrogen bonds to form chains propagating along [010]. These hydrogen bonds contribute to the stabilization of the crystal packing.

Acknowledgements: This work was supported by CAMS Initiative for Innovative Medicine (2017-I2M-1-012).

References

1. Rigaku Oxford Diffraction: CrysAlis PRO Software system, version 1.171.39.32a, Rigaku Corporation, Oxford, UK (2017).
2. Sheldrick, G. M.: Crystal structure refinement with SHELXL. *Acta Crystallogr.* **C71** (2015) 3–8.
3. Palatinus, L.; Chapuis, G.: SUPERFLIP: a computer program for the solution of crystal structures by charge flipping in arbitrary dimensions. *J. Appl. Cryst.* **40** (2007) 786–790.
4. Dolomanov, O. V.; Bourhis, L. J.; Gildea, R. J.; Howard, J. A. K.; Puschmann, H.: OLEX2: a complete structure solution, refinement and analysis program. *J. Appl. Cryst.* **42** (2009) 339–341.
5. Aratikatla, E. K.; Bhattacharya, A. K.: Chiral pool approach for the synthesis of functionalized amino acids: synthesis of antiepileptic drug (*R*)-lacosamide. *Tetrahedron Lett.* **56** (2015) 5802–5803.
6. Beyreuther, B. K.; Freitag, J.; Heers, C.; Krebsfanger, N.; Scharfenecker, U.; Thomas, U.: Lacosamide: a review of preclinical properties. *CNS Drug Rev.* **13** (2007) 21–42.
7. Doty, P.; Rudd, G. D.; Stoehr, T.; Thomas, D.: Lacosamide. *Neurotherapeutics* **4** (2007) 145–148.
8. Perucca, E.; Perucca, U.; Clincke, G.; Kirkpatrick, P.: Lacosamide. *Nat. Rev. Drug Discov.* **7** (2008) 973–974.
9. Errington, A. C.; Stoehr, T.; Heers, C.; Lees, G.: The investigational anticonvulsant lacosamide selectively enhances slow inactivation of voltage-gated sodium channels. *Mol. Pharmacol.* **73** (2008) 157–169.