Crystal Structure of (Z)-($\pm$)-2-(3,5-dimethoxyphenyl)-4-(4-methoxybenzylidene)tetrahydrofuran-3-carboxylic Acid

Tian-tian WANG,[†] Zhi-liang LV, Ji-lu FENG, Hai-ling SUN, Jia LIU, and Ke LI*

Department of Medicinal Chemistry, School of Pharmacy, Second Military Medical University, Shanghai 200433, PR China

The title compound, (Z)-($\pm$)-2-(3,5-dimethoxyphenyl)-4-(4-methoxybenzylidene)tetrahydrofuran-3-carboxylic acid crystallizes in the triclinic system, space group *P*1, with the following unit-cell parameters: *a* = 8.768(5), *b* = 9.974(6), *c* = 11.576(6) Å, α = 100.586(7), β = 93.277(7), γ = 111.067(6)°, *Z* = 2. The crystal structure was solved by direct methods using single-crystal X-ray diffraction data, and refined by full-matrix least-squares procedures to a final *R*-value of 0.0597 for 3172 observed reflections with *I* > 2 σ (*I*). The crystal structure is stabilized by intermolecular C–H...O hydrogen-bonding interactions.

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Tetrahydrofuran lignans are important five-numbered oxygen-containing heterocyclic compounds isolated from a variety of plant sources. Owing to their diverse bioactivities, viz. antiviral,¹ antifungal,² anti-inflammatory,³ and antioxidant.⁴ This important class of heterocyclic products has therefore draw interest to constantly develop synthetic methodologies of such compounds. In our previous study, we found that some of the tetrahydrofuran derivatives showed good inhibition to HIV-1 virus and anti-tumor activitise.⁵ Also, chemical modifications of the compound structure seem to be a promising route to obtain compounds with good biological activity, but with lower toxicity and fewer side effects. In this study, we synthesized the lead compound. We also carried out X-ray studies to obtain more information on the structure and geometrical features of this title compound. The synthesis and chemical structure of the title compound is shown in Fig. 1.

The title compound, (Z)-($\pm$)-2-(3,5-dimethoxyphenyl)-4-(4-methoxybenzylidene)tetrahydrofuran-3-carboxylic acid (Fig. 1), was synthesized from (Z)-($\pm$)-ethyl-4-(4-methoxy)benzylidene-2-(3,5-dimethoxyphenyl)-tetrahydrofuran-3,3-dicarboxylate (3 mmol), and KOH (20%, 10 eq) in THF at room temperature (20 – 25°C) for 3 h. Then, the product was poured into ice water and the crude product, which was separated out, was filtered and recrystallized from ethanol. Yield: 0.944 g (85%); m.p., (167.3 – 168.2°C); *R*_f, 0.30 (Petroleum Ether : Ethyl Acetate : Acetic Acid = 300:120:5). Colorless crystals, suitable for X-ray diffraction

analysis, were grown by slow evaporation of an ethanol/acetone (1:1) solution.

X-ray intensity data were collected at room temperature on a Bruker CCD area-detector diffractometer equipped with graphite monochromated Mo *K* α radiation (λ = 0.71073 Å). A total of 3820 reflections were measured, out of which 3172 were found

Table 1 Crystal and experiment data

Identification code	f80905b
Empirical formula	C ₂₁ H ₂₂ O ₆
Formula weight	370.39
Temperature	293(2)K
Wavelength	0.71073 Å
Crystal system, space group	triclinic, <i>P</i> 1
Unit cell dimensions	<i>a</i> = 8.768(5) Å α = 100.586(7)° <i>b</i> = 9.974(6) Å β = 93.277(7)° <i>c</i> = 11.576(6) Å γ = 111.067(6)°
Volume	920.2(9) Å ³
<i>Z</i> , Calculated density	2, 1.337 Mg/m ³
Absorption coefficient	0.098 mm ⁻¹
<i>F</i> (0 0 0)	392
Crystal size	0.24 × 0.15 × 0.10 mm
Theta range for data collection	1.81 to 25.01°
Limiting indices	−10 ≤ <i>h</i> ≤ 10, −11 ≤ <i>k</i> ≤ 9, −13 ≤ <i>l</i> ≤ 13
Reflections collected/unique	3820/3172 [<i>R</i> (int) = 0.0357]
Completeness to theta = 25.01	97.5%
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9903 and 0.9769
Refinement method	full-matrix least-squares on <i>F</i> ²
Data/restraints/parameters	3172/0/251
Goodness-of-fit on <i>F</i> ²	1.035
Final <i>R</i> indices [<i>I</i> > 2 σ (<i>I</i>)]:	<i>R</i> ₁ = 0.0597, <i>wR</i> ₂ = 0.1652
<i>R</i> indices (all data):	<i>R</i> ₁ = 0.0695, <i>wR</i> ₂ = 0.1731
Largest diff. peak and hole	0.248 and −0.303 e.Å ⁻³

CCDC 703808 contains the supplementary crystallographic data for this paper. these data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif

Fig. 1 Structure and synthesis of the title compound.

[†] To whom correspondence should be addressed.
E-mail: junrui_sh@yahoo.cn

Fig. 2 ORTEP view of the molecule with displacement ellipsoids drawn at the 50% probability level. H atoms are shown as small spheres of arbitrary radii.

Table 2 Selected bond lengths (Å) and bond angles (°)

O(1)-C(4)	1.427(2)	C(13)-O(3)	1.278(2)
O(1)-C(1)	1.433(2)	C(7)-O(4)	1.369(2)
C(1)-C(5)	1.498(3)	C(11)-O(4)	1.403(3)
C(1)-C(2)	1.527(3)	C(9)-O(5)	1.367(2)
C(2)-C(3)	1.523(3)	C(12)-O(5)	1.415(3)
C(2)-C(13)	1.504(2)	C(18)-O(6)	1.368(2)
C(3)-C(4)	1.507(3)	C(21)-O(6)	1.410(3)
C(3)-C(14)	1.324(3)	C(14)-C(15)	1.462(3)
C(13)-O(2)	1.241(2)		
C(4)-O(1)-C(1)	106.33(14)	C(6)-C(5)-C(1)	120.13(17)
O(1)-C(1)-C(5)	110.42(15)	C(10)-C(5)-C(1)	119.84(17)
O(1)-C(1)-C(2)	103.17(14)	O(4)-C(7)-C(8)	123.4(2)
C(5)-C(1)-C(2)	114.38(15)	O(4)-C(7)-C(6)	115.79(19)
C(13)-C(2)-C(3)	113.61(15)	O(5)-C(9)-C(10)	124.91(18)
C(13)-C(2)-C(1)	14.11(15)	O(5)-C(9)-C(8)	113.91(18)
C(3)-C(2)-C(1)	103.40(14)	O(2)-C(13)-O(3)	123.33(17)
C(14)-C(3)-C(4)	130.14(17)	O(2)-C(13)-C(2)	120.71(16)
C(14)-C(3)-C(2)	124.62(16)	O(3)-C(13)-C(2)	115.95(16)
C(4)-C(3)-C(2)	105.16(15)	C(3)-C(14)-C(15)	131.75(18)
O(1)-C(4)-C(3)	105.83(15)	O(6)-C(18)-C(19)	124.38(19)

to be unique ($-10 \leq h \leq 10$, $-11 \leq k \leq 9$, $-13 \leq l \leq 13$). Data were corrected for Lorentz and polarization factors. The structure was solved by direct methods and refined on F^2 by full-matrix least-squares procedures using SHELXTL-97.⁶ Non-hydrogen atoms were refined with anisotropic displacement parameters. All H atoms were positioned geometrically, and treated using a riding model, fixing the aromatic and methyl C-H distances at 0.93 and 0.96 Å with $U_{\text{iso}}(\text{H}) = 1.2$ or $1.5U_{\text{eq}}(\text{C})$. The final R-value of 0.0597. A summary of the crystallographic information is given in Table 1, selected bond lengths and bond angles are given in Table 2. An ORTEP-3 drawing of the title compound along with the atom numbering is shown in Fig. 2.

The bond lengths and bond angles observed in the structure are within the expected ranges. The C-C bond length in the phenyl ring is in the range 1.370(3) – 1.398(3) Å. Also, the single-bond length of C-C is in the range of 1.47 – 1.53 Å, except for C14-C15. The bond length of C14-C15 is 1.462(3) Å. Due to a conjugation effect, it has some extent to a double-bond character, so the bond length is a little shorter than for normal

Table 3 Hydrogen-bond parameters (Å, °)

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(3)-H(3)...O(2)#1	1.14(3)	1.48(3)	2.614(2)	173(3)

Symmetry transformations used to generate equivalent atoms: #1 $-x+1, -y+2, -z+2$.

single-bond length. The double-bond character of C3-C14 and C13-O2 is confirmed by the distances 1.324(3) and 1.241(2) Å, respectively. Because of electron delocalization, the bond length of the single bond C13-O3 [1.278(2)] Å is shorter than for normal C-O single bond C1-O1 [1.427(2)] and C4-O1 [1.433(2)] Å. The bond lengths of C1-O1 [1.427(2)] and C4-O1 [1.433(2)] Å lie in the normal range of the single C-O [1.43] Å bond length. The tetrahydrofuran ring takes an envelope conformation. The conformation of the tetrahydrofuran ring moiety linking C5-10 phenyl ring plane, carboxyl plane and C3-C14-20 plane determines the characteristic shape of the molecule. The relevant torsion angles (O1-C1-C2-C3, C1-C2-C3-C4, C2-C3-C4-O1, C3-C4-O1-C1, and C2-C3-C14-C15) are 31.39(17), -11.08(19), -13.20(20), 34.50(20), and -178.43(19)°, respectively. The dihedral angles with respect to the three plane to the tetrahydrofuran ring is 84.55(10), 11.69(19), 65.01(15)°, respectively. The ring plane and for carboxyl plane linking to the tetrahydrofuran ring adopt a *trans*-conformation. Also, the dihedral angle between the two plane is 83.52(13)°. The crystal structure of the title compound is stabilized by intermolecular O(3)-H(3)...O(2) hydrogen-bonding interactions (Table 3).

Acknowledgements

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References

1. J. X. Pu, X. M. Gao, C. Lei, W. L. Xiao, R. R. Wang, L. B. Yang, Y. Zhao, L. M. Li, S. X. Huang, Y. T. Zheng, and H. D. Sun, *Chem. Pharm. Bull.*, **2008**, *56*, 1143.
2. A. Akiyama, S. Yamauchi, T. Nakato, M. Maruyama, T. Sugahara, T. Kishada, *Biosci. Biotechnol. Biochem.*, **2007**, *71*, 1028.
3. J. Ma, D. Moul, H. Yang, P. Alexander, P. Reneta, D. Ruth, E. L. Peter, J. K. Edward, and R. Ilya, *Phytochemistry*, **2007**, *68*, 1172.
4. W. S. Lee, Y. Baek, J. R. Kim, K. H. Cho, D. E. Sok, and T. S. Jeong, *Bioorg. Med. Chem. Lett.*, **2004**, *14*, 5623.
5. D. ZH. Zhou, Y. H. Yi, and Q. Y. Wu, Studies on the Anti-HIV Leading Compounds from *Torreya Grandis* cv. Merrilli and Structure Modifications (D)., **2004**.
6. G. M. Sheldrick, SHELXS97 and SHELXL97, **1997**, University of Göttingen Germany.