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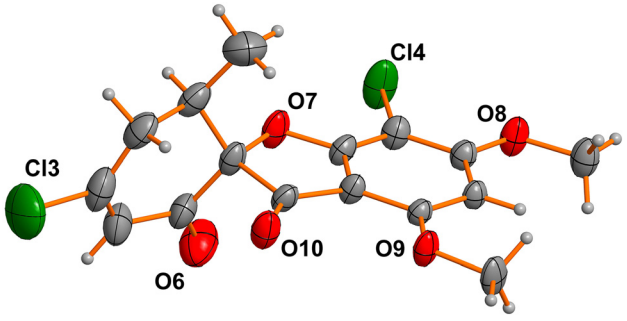
The crystal structure of 4′-chloro-griseofulvin: (2*S*,6′*R*)-4′,7-dichloro-4,6-dimethoxy-6′-methyl-3*H*-spiro[benzofuran-2,1′-cyclohexan]-3′-ene-2′,3-dione, $C_{16}H_{14}Cl_2O_5$



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Abstract

$C_{16}H_{14}Cl_2O_5$, orthorhombic, $P2_12_12_1$ (no. 19), a = 8.6429 (4) Å, b = 11.3361 (6) Å, c = 33.9029 (11) Å, V = 3321.7 (3) Å^3, Z = 8, $R_{gt}(F)$ = 0.0635, w$R_{ref}(F^2)$ = 0.1630, T = 293(2) K.

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Table 1 contains crystallographic data and Table 2 contains the list of the atoms including atomic coordinates and displacement parameters.

Table 1: Data collection and handling.

Crystal:	Colourless block
Size:	0.20 × 0.12 × 0.10 mm
Wavelength:	CuKα radiation (1.54184 Å)
μ:	3.72 mm^{-1}
Diffractometer, scan mode:	Xcalibur, ω
θ_{max}, completeness:	71.8°, >99 %
$N(hkl)_{measured}$, $N(hkl)_{unique}$, R_{int}:	12,583, 6346, 0.059
Criterion for I_{obs}, $N(hkl)_{gt}$:	$I_{obs} > 2\sigma(I_{obs})$, 4807
$N(param)_{refined}$:	421
Programs:	Olex2,[1] Shelx[2,3]

1 Source of materials

The title compound was synthesized by using our previously reported method[4,5] that 2′-hydroxy-griseofulvin (339 mg, 1.0 mmol) reacted with phosphorylchloride (0.56 mL, 5 mmol) in a solution of dioxane (28 mL), and LiCl (212 mg, 5 mmol) was added. Then the mixture was refluxed for about 30 min, cooled to room temperature and sat. aq. sodium carbonate was added until it is slightly basic (pH 7–8). Then extracted with DCM (3 × 20 mL) and the combined organic phases were dried by sodium sulphate anhydrous and concentrated. The residue was purified by column chromatography DCM and the white solid (121 mg) was obtained, yield 45 %. This white solid was recrystallized to obtain colourless crystals from solution (DCM:methanol 5:1) by natural cooling method at room temperature.

2 Experimental details

A suitable crystal was selected and tested on a Xcalibur, Eos, Gemini diffractometer. Using Olex2,[1] the structure was solved with the Shelxt[2] structure solution program using Intrinsic Phasing and refined with the Shelxl[3] refinement package using Least Squares minimisation.

3 Comment

Griseofulvin, a natural product, is the first oral antifungal agent which was used for the treatment of dermatomycoses in humans.[6] Hundreds of griseofulvin analogues have been

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

Atom	*x*	*y*	*z*	U_{iso}*/U_{eq}
C1	0.7618 (9)	0.1383 (8)	0.3599 (2)	0.0433 (18)
C2	0.6984 (10)	0.0542 (6)	0.3374 (2)	0.0418 (17)
H2	0.7121	−0.0246	0.3442	0.050*
C3	0.6085 (9)	0.0844 (6)	0.3026 (2)	0.0353 (15)
C4	0.6071 (7)	0.2147 (5)	0.29020 (16)	0.0263 (12)
C5	0.6117 (8)	0.2987 (6)	0.32557 (17)	0.0303 (14)
H5	0.5163	0.2865	0.3407	0.036*
C6	0.7481 (8)	0.2666 (7)	0.35274 (17)	0.0397 (16)
H6A	0.8434	0.2949	0.3409	0.048*
H6B	0.7352	0.3066	0.3778	0.048*
C7	0.7359 (7)	0.2306 (6)	0.25888 (15)	0.0255 (12)
C8	0.6547 (6)	0.2359 (5)	0.22156 (16)	0.0250 (11)
C9	0.7043 (6)	0.2406 (5)	0.18208 (15)	0.0237 (11)
C10	0.5948 (7)	0.2418 (6)	0.15252 (15)	0.0277 (12)
H10	0.6257	0.2438	0.1263	0.033*
C11	0.4374 (7)	0.2400 (6)	0.16190 (16)	0.0266 (12)
C12	0.3865 (6)	0.2385 (6)	0.20118 (16)	0.0263 (12)
C13	0.4968 (6)	0.2357 (5)	0.22964 (15)	0.0232 (11)
C14	0.6168 (11)	0.4274 (7)	0.3137 (2)	0.052 (2)
H14A	0.7102	0.4427	0.2993	0.077*
H14B	0.6143	0.4759	0.3369	0.077*
H14C	0.5290	0.4453	0.2974	0.077*
C15	0.9148 (7)	0.2482 (8)	0.13682 (16)	0.0387 (15)
H15A	0.8729	0.1839	0.1218	0.058*
H15B	1.0257	0.2437	0.1367	0.058*
H15C	0.8826	0.3216	0.1253	0.058*
C16	0.3673 (10)	0.2364 (11)	0.09365 (19)	0.073 (3)
H16A	0.2760	0.2324	0.0776	0.109*
H16B	0.4299	0.1677	0.0891	0.109*
H16C	0.4252	0.3058	0.0869	0.109*
C17	0.4577 (12)	0.5656 (8)	0.5052 (2)	0.059 (2)
C18	0.5663 (11)	0.5070 (9)	0.4868 (2)	0.058 (2)
H18	0.6688	0.5305	0.4898	0.070*
C19	0.5309 (10)	0.4057 (8)	0.46188 (19)	0.0463 (18)
C20	0.3603 (9)	0.3781 (6)	0.45557 (18)	0.0362 (16)
C21	0.2607 (10)	0.4071 (7)	0.4918 (2)	0.0460 (18)
H21	0.2939	0.3548	0.5132	0.055*
C22	0.2917 (11)	0.5347 (7)	0.5053 (2)	0.050 (2)
H22A	0.2368	0.5885	0.4880	0.060*
H22B	0.2510	0.5451	0.5317	0.060*
C23	0.3012 (9)	0.4436 (5)	0.41779 (17)	0.0324 (14)
C24	0.2640 (9)	0.3504 (5)	0.39048 (18)	0.0303 (15)
C25	0.2076 (8)	0.3504 (5)	0.35139 (17)	0.0270 (13)
C26	0.1856 (7)	0.2425 (5)	0.33266 (15)	0.0275 (11)
H26	0.1480	0.2408	0.3070	0.033*
C27	0.2196 (8)	0.1355 (6)	0.35205 (18)	0.0311 (14)
C28	0.2786 (9)	0.1352 (6)	0.39079 (19)	0.0360 (16)
C29	0.2964 (8)	0.2427 (6)	0.40859 (16)	0.0331 (13)
C30	0.0884 (12)	0.3836 (10)	0.4846 (3)	0.075 (3)
H30A	0.0506	0.4366	0.4647	0.112*
H30B	0.0320	0.3957	0.5087	0.112*
H30C	0.0747	0.3037	0.4759	0.112*
C31	0.1252 (11)	0.4599 (7)	0.2952 (2)	0.047 (2)
H31A	0.2041	0.4273	0.2785	0.070*
H31B	0.1058	0.5402	0.2877	0.070*
H31C	0.0319	0.4147	0.2924	0.070*
C32	0.1411 (10)	0.0231 (6)	0.2959 (2)	0.0451 (19)
H32A	0.2125	0.0606	0.2782	0.068*
H32B	0.0427	0.0623	0.2945	0.068*
H32C	0.1289	−0.0581	0.2886	0.068*
Cl1	0.8741 (3)	0.0986 (3)	0.40005 (6)	0.0749 (8)
Cl2	0.19155 (16)	0.23935 (17)	0.21261 (4)	0.0377 (4)
Cl3	0.5048 (4)	0.6916 (3)	0.53154 (10)	0.1003 (11)
Cl4	0.3193 (4)	0.00695 (16)	0.41503 (6)	0.0640 (7)
O1	0.5416 (8)	0.0109 (5)	0.28270 (19)	0.0639 (18)
O2	0.8737 (5)	0.2326 (5)	0.26670 (12)	0.0361 (11)
O3	0.8599 (4)	0.2414 (4)	0.17650 (11)	0.0299 (9)
O4	0.3243 (5)	0.2411 (5)	0.13414 (12)	0.0419 (11)
O5	0.4639 (4)	0.2336 (4)	0.26919 (11)	0.0297 (9)
O6	0.6320 (8)	0.3498 (7)	0.44516 (19)	0.075 (2)
O7	0.3468 (6)	0.2541 (4)	0.44650 (12)	0.0457 (12)
O8	0.1995 (7)	0.0301 (4)	0.33553 (14)	0.0434 (13)
O9	0.1758 (7)	0.4561 (4)	0.33564 (13)	0.0392 (12)
O10	0.2990 (8)	0.5503 (4)	0.41525 (14)	0.0479 (13)

synthesized[7] and used for bioactivity screening. Recently, we found griseofulvin analogues exhibiting excellent antifungal activities against phytopathogenic fungi.[1,8] The title compound (2*S*,6′*R*)-4′,7-dichloro-4,6-dimethoxy-6′-methyl-3*H*-spiro[benzo-furan-2,1′-cyclohexan]-3′-ene-2′,3-dione was synthesized by using 2′-hydroxy-griseofulvin as starting material, and the structure was determined by X-ray single crystal diffraction. It is a key chemical intermediate which was used for synthesis of the 4′-position griseofulvin analogues.[8]

The asymmetric unit of the title structure contains two crystallographically independent molecules, and one of these molecules is shown in the figure. In the molecule, the bond length of Cl1–C1 and Cl2–C12 are 1.731(7) Å and 1.729(6) Å respectively. The angle of O2–C7–C8 is 131.5(5)°, the bond lengths and angles of the title compound are similar to the structures of natural product griseofulvin[9] and 2′-chloro-griseofulvin.[2] The plane (C8/C9/C10/C11/C12/C13) of benzene ring and the plane (O5/C4/C7/C8/C13) of furan ring are approximately in the same plane and their dihedral angle is only 3.81°. The plane (O5/C4/C7/C8/C13) of furan ring and the plane (C4/C3/C2) of cyclohexanone present a dihedral angle of about 79.19°. Cyclohexanone ring (C1/C2/C3/C4/C5/C6) has a half-chair conformation. All geometric parameters are in the expected ranges.

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Conflict of interest statement: The authors declare no conflicts of interest regarding this article.

References

1. 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. Crystallogr.* **2009**, *42*, 339–341.
2. Sheldrick, G. M. SHELXTL – Integrated Space-Group and Crystal-Structure Determination. *Acta Crystallogr.* **2015**, *A71*, 3–8.
3. Sheldrick, G. M. Crystal Structure Refinement with SHELXL. *Acta Crystallogr.* **2015**, *C71*, 3–8.
4. Bai, Y.-B.; Zhang, M.; Li, D.; Zhao, Y.; Huang, L.-Z.; Gao, J.-M. Synthesis and Antifungal Activity of Derivatives of the Natural Product Griseofulvin Against Phytopathogenic Fungi. *J. Agric. Food Chem.* **2023**, *71*, 6236–6248.
5. Zhang, M.; Bai, Y.-B. The Crystal Structure of (2*R*,6′*R*)-2′,7-Dichloro-4,6-Dimethoxy-6′-Methyl-3*H*-Spiro[Benzofuran-2,1′-Cyclohexan]-2′-Ene-3,4′-Dione, $C_{16}H_{14}Cl_2O_5$. *Z. Kristallogr. N. Cryst. Struct.* **2023**, *238*, 185–187.
6. Oxford, A. E.; Raistrick, H.; Simonart, P. Studies in the Biochemistry of Micro-Organisms: Griseofulvin, $C_{17}H_{17}O_6Cl$, A Metabolic Product of *Penicillium griseofulvum* Dierckx. *Biochem. J.* **1939**, *33*, 240–248.
7. Dong, N.; Li, X.; Wang, F.; Cheng, J.-P. Asymmetric Michael-Aldol Tandem Reaction of 2-Substituted Benzofuran-3-Ones and Enones: A Facile Synthesis of Griseofulvin Analogues. *Org. Lett.* **2013**, *15*, 4896–4899.
8. Bai, Y.-B.; Gao, Y.-Q.; Nie, X.-D.; Tuong, T.-M.-L.; Li, D.; Gao, J.-M. Antifungal Activity of Griseofulvin Derivatives Against Phytopathogenic Fungi In Vitro and In Vivo and Three-Dimensional Quantitative Structure-Activity Relationship Analysis. *J. Agric. Food Chem.* **2019**, *67*, 6125–6132.
9. Nirmala, K. A.; Sakegowda, D. S.; Duax, W. L. Crystal Structure of Griseofulvin. *J. Crystallogr. Spectrosc. Res.* **1982**, *12*, 415–423.