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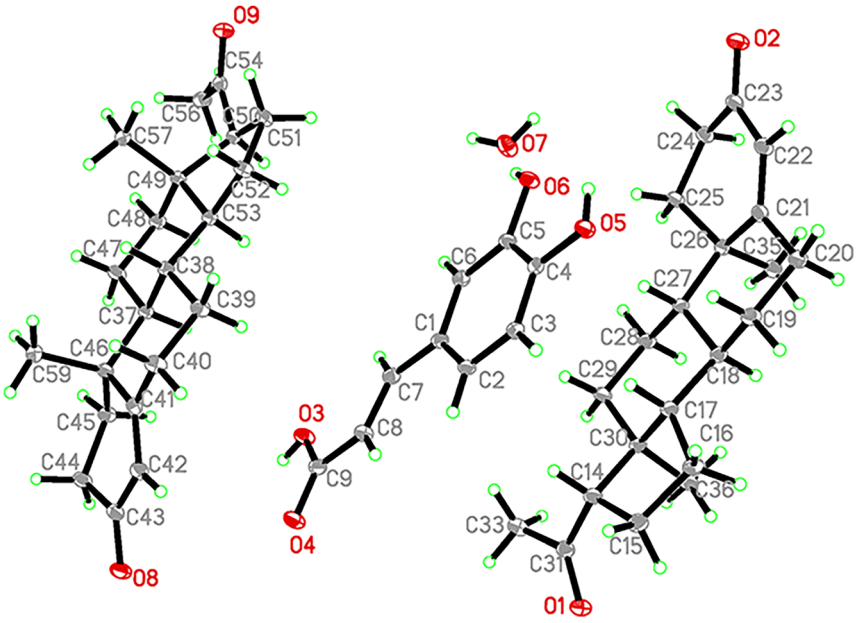
The cocrystal of caffeic acid — progesterone — water (1/2/1), $C_{51}H_{70}O_9$



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Abstract

$C_{51}H_{70}O_9$, triclinic, space group $P1$ (no. 1), a = 7.67650(10) Å, b = 11.9494(2) Å, c = 13.8656(2) Å, α = 114.055(1)°, β = 103.568(1)°, γ = 93.456(1)°, V = 1111.46(3) Å^3, Z = 1, T = 100(11) K.

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The molecular structure is shown in the figure. Table 1 contains the crystallographic data and the list of the atoms including atomic coordinates and displacement parameters can be found in the cif-file attached to this article.

Table 1: Data collection and handling.

Crystal:	Clear light colourless block
Size:	0.14 × 0.12 × 0.10 mm
Wavelength:	Cu $K\alpha$ radiation (1.54184 Å)
μ:	0.66 mm^{-1}
Diffractometer, scan mode:	Rigaku XtaLAB, ω scans
θ_{max}, completeness:	74.2°, 99 %
$N(hkl)_{measured}$, $N(hkl)_{unique}$, R_{int}:	10,987, 5,428, 0.020
Criterion for I_{obs}, $N(hkl)_{gt}$:	$I_{obs} > 2\sigma(I_{obs})$, 5,348
$N(param)_{refined}$:	553
Programs:	Rigaku,[1] Olex2,[2] SHELX[3]

1 Source of materials

Equimolar quantities of progesterone (31.5 mg, 0.1 mmol) and caffeic acid (18.0 mg, 0.1 mmol) were dissolved in a 5 mL ethanol/water (v/v = 2:1) solution. The mixture was vigorously stirred for 20 min to ensure complete dissolution. Then the solution was subjected to slow solvent evaporation at room temperature. After 7 days, colorless block crystals were obtained.

2 Experimental details

Using Olex2,[2] the structure was refined with the SHELXL[3] refinement package using least squares minimisation. All H atoms bonded to C or O were idealized and refined using riding model.

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3 Comment

Progesterone (PROG) is a key steroid hormone that plays a crucial role in reproductive health.[4] However, PROG has a water solubility of only 5.46 mg/L at room temperature, which suggests it has low oral bioavailability and poor absorption in the body.[5] In recent years, various methods have been developed to improve drug dissolution and bioavailability.[6] Co-crystallization involves the formation of a crystalline complex between progesterone and special cocrystal former, which could significantly improve its pharmacological properties and clinical efficacy. For example, the cocrystal of PROG and isophthalic acid (IPA), showed approximately 3–4 times improvements in $AUC0_{-24h}$ and $AUC_{0-\infty}$, compared with the free PROG.[7] Here, we have firstly prepared the cocrystal of PROG and caffeic acid (CA).

The asymmetric unit of the title compound contains two PROG molecules, one CA molecule, and one water molecule. Hydrogen bonds play a crucial role in the formation of the cocrystal. The –OH and –COOH groups of CA act as hydrogen bond acceptors, forming O–H···O hydrogen bonds with the –C=O groups of PROG molecules, connecting adjacent PROG molecules to create a two-dimensional layered hydrogen bond network. Furthermore, water molecules link the layers of CA through O–H···O bonds, resulting in a three-dimensional network structure. Geometric parameters are in general in the expected ranges.[8,9]

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