Crystal structure of 2(*R*)-(5-fluorouracil-1-yl)acetyl-2-phenylglycin dimethylformamide solvate, C₁₄H₁₂FN₃O₅ · C₃H₇NO

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Abstract

C₁₇H₁₉FN₄O₆, monoclinic, *P*12₁/*c*1 (no. 14), *a* = 5.2042(5) Å, *b* = 21.778(2) Å, *c* = 16.932(2) Å, β = 101.165(2)°, *V* = 1882.7 Å³, *Z* = 4, *R*_{gt}(*F*) = 0.068, *wR*_{ref}(*F*²) = 0.198, *T* = 298 K.

Source of material

The starting material 5-fluoro-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-1-acetic acid was prepared from 5-fluorouracil and bromoacetic acid following the method of the literature [1]. The

key intermediate methyl 2(*R*)-(5-fluorouracil-1-aceto)amino-2-phenyl acetate was synthesized from 5-fluorouracil-1-acetic acid, dicyclohexyl carbodiimide (dcc), and 1-hydroxybenzotriazole (btOH). A solution (25 ml) of dcc (0.024 mol) in dimethylformamide (dmf) was dropped in a dmf solution (75 ml) of 5-fluorouracil-1-acetic acid (0.02 mol) and btOH (0.02 mol) at 273 K. After 5 h reaction at room temperature, methyl 2(*R*)-amino-2-phenyl acetate (0.02 mol) and triethylamine (0.02 mol) were added to the above mixture. After 4 h stirring, a white solid methyl 2(*R*)-(5-fluorouracil-1-aceto)amino-2-phenyl acetate was obtained after filtration, reduced pressure distillation of dmf, and column chromatography separation. The title compound was obtained by hydrolysis with 1 M sodium hydroxide solution. The purified product was dissolved in 95 % ethanol and single crystals were separated after 10 d. Mass, IR, ¹H NMR and ¹³C NMR are available in the CIF.

Discussion

5-Fluorouracil (5FU) is an antimetabolite with good antitumor activity but has side effects [1–3]. Much attention has been paid to the derivatives of 5FU and their anticancer activities [4–6]. In an extension of this research, we report the crystal structure of a peptide derivative of 5FU, 2(*R*)-(5-fluorouracil-1-yl)acetyl-2-phenylglycin.

The atoms (C1, C2, C3, C4, N1 and N2) in the heterocyclic ring and the atoms (C9–C14) of the benzene ring are essentially planar with r.m.s. deviations of 0.0104 Å and 0.0100 Å, respectively. The dihedral angle between the two rings is 53.8(2)°. Moreover, the N3—C6 bond distance (1.327(5) Å) is shorter than a typical C—N bond length (1.443(4) Å) [7] indicating the electron delocalization of the atoms O3, C6 and N3. In the crystal structure, 2(*R*)-(5-fluorouracil-1-yl)acetyl-2-phenylglycin and *N,N*-dimethylformamide solvent molecules are linked by intermolecular O4—H4···O6, N3—H3···O2ⁱ (i: *x*, −*y*+³/₂, *z*−¹/₂) and N2—H2···O5ⁱⁱ (ii: *x*, −*y*+³/₂, *z*−¹/₂) hydrogen bonds to produce a zigzag chain along [001] direction (figure, bottom).

Table 1. Data collection and handling.

Crystal:	colorless block, size 0.14 × 0.15 × 0.26 mm
Wavelength:	Mo <i>K</i> _α radiation (0.71073 Å)
μ :	1.13 cm ^{−1}
Diffractionmeter, scan mode:	Bruker APEX SMART CCD, ϕ/ω
2 θ _{max} :	50.02°
<i>N</i> (<i>hkl</i>) _{measured} , <i>N</i> (<i>hkl</i>) _{unique} :	9665, 3321
Criterion for <i>I</i> _{obs} , <i>N</i> (<i>hkl</i>) _{gt} :	<i>I</i> _{obs} > 2 σ (<i>I</i> _{obs}), 2514
<i>N</i> (<i>param</i>) _{refined} :	255
Programs:	SHELXS-97 [8], SHELXL-97 [9], SHELXTL [10]

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Table 2. Atomic coordinates and displacement parameters (in Å²).

Atom	Site	<i>x</i>	<i>y</i>	<i>z</i>	<i>U</i> _{iso}
H(4)	4e	0.5867	0.5725	0.3535	0.081
H(2)	4e	−0.0129	0.8159	−0.1286	0.058
H(3)	4e	−0.0363	0.6671	0.2043	0.047
H(4A)	4e	−0.5745	0.6917	−0.0404	0.058
H(5A)	4e	−0.3669	0.7116	0.0945	0.059
H(5B)	4e	−0.1546	0.7636	0.1133	0.059
H(7)	4e	0.4095	0.6227	0.1680	0.050
H(10)	4e	0.4238	0.5391	0.0823	0.088
H(11)	4e	0.3159	0.4390	0.0433	0.114
H(12)	4e	−0.0054	0.3887	0.0908	0.099

Table 2. Continued.

Atom	Site	<i>x</i>	<i>y</i>	<i>z</i>	<i>U</i> _{iso}
H(13)	4e	−0.2128	0.4347	0.1825	0.093
H(14)	4e	−0.1040	0.5347	0.2231	0.076
H(15A)	4e	0.4319	0.6352	0.6208	0.167
H(15B)	4e	0.7112	0.6375	0.6758	0.167
H(15C)	4e	0.5270	0.5812	0.6805	0.167
H(16A)	4e	0.9760	0.5265	0.5623	0.196
H(16B)	4e	0.8442	0.5024	0.6321	0.196
H(16C)	4e	1.0386	0.5581	0.6470	0.196
H(17)	4e	0.4518	0.6136	0.4910	0.092

Table 3. Atomic coordinates and displacement parameters (in Å²).

Atom	Site	<i>x</i>	<i>y</i>	<i>z</i>	<i>U</i> ₁₁	<i>U</i> ₂₂	<i>U</i> ₃₃	<i>U</i> ₁₂	<i>U</i> ₁₃	<i>U</i> ₂₃
F(1)	4e	−0.6716(7)	0.6986(2)	−0.1899(2)	0.079(2)	0.111(3)	0.059(2)	−0.037(2)	−0.001(2)	0.006(2)
O(1)	4e	0.0957(8)	0.8075(2)	0.0162(2)	0.089(3)	0.072(3)	0.040(2)	−0.025(2)	0.003(2)	0.005(2)
O(2)	4e	−0.3137(7)	0.7755(2)	−0.2420(2)	0.075(2)	0.083(3)	0.027(2)	−0.008(2)	0.012(2)	0.007(2)
O(3)	4e	0.1300(6)	0.6648(2)	0.0441(2)	0.063(2)	0.058(2)	0.038(2)	0.006(2)	0.023(2)	0.005(2)
O(4)	4e	0.5521(7)	0.5750(2)	0.3043(2)	0.065(2)	0.097(3)	0.038(2)	0.039(2)	−0.001(2)	−0.010(2)
O(5)	4e	0.2354(7)	0.6350(2)	0.3279(2)	0.066(2)	0.072(2)	0.030(2)	0.025(2)	0.010(2)	−0.007(2)
N(1)	4e	−0.2617(8)	0.7456(2)	−0.0048(2)	0.052(2)	0.050(2)	0.030(2)	0.003(2)	0.012(2)	0.011(2)
N(2)	4e	−0.1198(7)	0.7911(2)	−0.1120(2)	0.055(2)	0.056(3)	0.034(2)	−0.009(2)	0.011(2)	0.013(2)
N(3)	4e	0.0540(7)	0.6556(2)	0.1694(2)	0.043(2)	0.052(2)	0.023(2)	0.013(2)	0.011(1)	−0.000(2)
C(1)	4e	−0.081(1)	0.7830(2)	−0.0299(3)	0.058(3)	0.046(3)	0.035(2)	−0.001(2)	0.008(2)	0.002(2)
C(2)	4e	−0.3053(9)	0.7651(2)	−0.1707(3)	0.047(3)	0.052(3)	0.036(3)	0.007(2)	0.012(2)	0.003(2)
C(3)	4e	−0.4781(9)	0.7255(2)	−0.1373(3)	0.047(3)	0.061(3)	0.040(3)	−0.013(2)	0.005(2)	0.007(2)
C(4)	4e	−0.4561(9)	0.7172(2)	−0.0592(3)	0.048(3)	0.047(3)	0.054(3)	0.000(2)	0.020(2)	0.016(2)
C(5)	4e	−0.209(1)	0.7278(2)	0.0801(3)	0.062(3)	0.057(3)	0.033(2)	0.002(3)	0.019(2)	0.011(2)
C(6)	4e	0.0058(9)	0.6795(2)	0.0959(2)	0.049(3)	0.041(3)	0.030(2)	−0.004(2)	0.013(2)	−0.005(2)
C(7)	4e	0.2591(9)	0.6100(2)	0.1911(2)	0.043(3)	0.051(3)	0.032(2)	0.006(2)	0.010(2)	−0.006(2)
C(8)	4e	0.3449(9)	0.6085(2)	0.2826(3)	0.043(3)	0.044(3)	0.034(2)	0.008(2)	0.003(2)	−0.010(2)
C(9)	4e	0.1782(8)	0.5461(2)	0.1601(2)	0.036(2)	0.054(3)	0.028(2)	0.007(2)	−0.000(2)	−0.002(2)
C(10)	4e	0.298(1)	0.5181(3)	0.1039(4)	0.079(4)	0.082(5)	0.066(4)	−0.002(3)	0.031(3)	−0.026(3)
C(11)	4e	0.230(2)	0.4585(4)	0.0796(4)	0.113(6)	0.092(6)	0.083(5)	0.005(5)	0.026(4)	−0.052(4)
C(12)	4e	0.040(1)	0.4284(3)	0.1083(4)	0.090(5)	0.065(4)	0.082(5)	0.001(4)	−0.010(4)	−0.025(4)
C(13)	4e	−0.084(1)	0.4556(3)	0.1623(4)	0.079(4)	0.072(5)	0.077(4)	−0.019(3)	0.007(3)	−0.006(4)
C(14)	4e	−0.016(1)	0.5154(3)	0.1873(3)	0.071(4)	0.066(4)	0.054(3)	−0.005(3)	0.017(3)	−0.013(3)
O(6)	4e	0.6856(9)	0.5619(2)	0.4532(2)	0.102(3)	0.106(4)	0.048(2)	0.030(3)	−0.006(2)	0.006(2)
N(4)	4e	0.688(1)	0.5803(2)	0.5835(3)	0.087(4)	0.084(4)	0.047(3)	−0.015(3)	−0.002(3)	0.017(3)
C(15)	4e	0.581(2)	0.6112(4)	0.6453(4)	0.148(7)	0.124(7)	0.061(4)	−0.011(6)	0.018(4)	0.003(5)
C(16)	4e	0.905(2)	0.5383(5)	0.6083(4)	0.105(6)	0.20(1)	0.073(5)	0.037(6)	−0.018(4)	0.041(6)
C(17)	4e	0.595(1)	0.5876(3)	0.5063(4)	0.094(5)	0.071(4)	0.055(4)	0.001(4)	−0.007(3)	0.011(3)

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