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5-Fluoro-1-octanoyluracil

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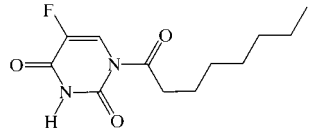
The crystal structure of 5-fluoro-1-octanoyluracil [5-fluoro-1-octanoylpyrimidine-2,4(1*H*,3*H*)-dione, $C_{12}H_{17}FN_2O_3$], a lipophilic prodrug of 5-fluorouracil, is described. The 5-fluoropyrimidine-2,4(1*H*,3*H*)-dione moiety is similar to the known structure of 1-acetyl-5-fluorouracil. The 1-octanoyl group and the 5-fluorouracil moiety are essentially coplanar, with the octanoyl carbonyl group oriented towards the the ring C—H group and away from the nearer ring carbonyl group. The torsion angle C—N—C—O (from the ring CH group to the octanoyl carbonyl group) of 9.2 (2)° is similar to the corresponding torsion angles reported for 1-acetyl-5-fluorouracil (17.3 and 1.6°) and 1,3-diacetyl-5-fluorouracil (8.8°).

Comment

The antimetabolite 5-fluorouracil is used for the treatment of solid tumors such as gastrointestinal adenocarcinoma, breast cancer and squamous cell carcinoma of the head and neck (Iyer & Ratain, 1999). 5-Fluorouracil cannot be administered orally because of its unpredictable absorption, non-linear pharmacokinetics and a high interpatient variance. Numerous 5-fluorouracil analogues have been synthesized to improve the delivery of 5-fluorouracil (Iyer & Ratain, 1999; Lamont & Schilsky, 1999; Ozaki, 1996). After delivery to the target tissue, these analogues are subject to chemical or enzymatic hydrolysis *in vivo* and release 5-fluorouracil (Bundgaard *et al.*, 1983; Møllgaard *et al.*, 1982). There is currently growing interest in lipophilic 1- and 3-acyl derivatives for transdermal drug delivery. Despite this potential application of acyl-5-fluorouracil derivatives, only the crystal structures of two acyl derivatives, namely 1-acetyl- and 1,3-diacetyl-5-fluorouracil, have been described (Beall *et al.*, 1993).

The structures of both 1-acetyl- and 1-octanoyl-5-fluorouracil, *i.e.* the 5-fluoropyrimidine-2,4(1*H*,3*H*)-dione system, are very similar. The 1-octanoyl group and the 5-fluorouracil moiety of the title compound, (I), are essentially coplanar, with the C7═O7 carbonyl group oriented towards the C6—H group and away from the C2═O2 group. The torsion angle C6—N1—C7—O7 is 9.2 (2)° and is similar to the torsion angles reported for 1-acetyl-5-fluorouracil (17.3 and 1.6°) and 1,3-diacetyl-5-fluorouracil (8.8°) (Beall *et al.*, 1993). Most likely, the slight differences are due to packing effects in the crystal. Thus, the carbonyl of the 1-acyl group can be conjugated with the pyrimidine-2,4(1*H*,3*H*)-dione ring system. As a result of the orientation of the acyl group, the partially positive carbonyl C7 atom is easily accessible to nucleophiles such as hydroxide, and the hydrolysis of 1-acyl-5-fluorouracil derivatives is fast. For example, the half-life of 1-acetyl-5-fluorouracil is about 4.8 min (Beall *et al.*, 1993).



(I)

Experimental

5-Fluoro-1-octanoyluracil was synthesized by acylation of 5-fluorouracil with octanoyl chloride (Roberts & Sloan, 1999; Taylor & Sloan, 1998). White crystals were obtained upon crystallization from diethyl ether at 253 K (m.p. 336–338 K). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.88 (*t*, $-CH_3$, J = 6.8 Hz, 3H), 1.20–1.42 (*m*, 8H), 1.72 (*q*, $-CH_2CH_2CON$, J = 7.4 Hz, 2H), 3.12 (*t*, $-CH_2CON$, J = 7.4 Hz, 2H), (*d*, –CH═CF–, J = 6.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.04 ($-CH_3$), 22.56, 24.37, 28.84, 28.94, 31.59, 39.04, 121.75 (═CH–, J_{CF} = 27 Hz), 141.26 (═CF-, J_{CF} = 182 Hz), 147.75 (N—CO—NH), 156.62 (═CF—CO—NH, J_{CF} = 21 Hz), 171.98 (acyl CO); ^{19}F NMR ($CDCl_3$): δ −161.10 (*d*, 6.0 Hz); IR (cm^{-1}): 1738 and 1704 [ν(C═O)]; MS *m*/*z* (relative intensity, %): 256 (1, M^+), 127 (100, $C_8H_{15}O^+$), 57 (84), 43 (31).

Crystal data

$C_{12}H_{17}FN_2O_3$	D_x = 1.347 Mg m^{-3}
M_r = 256.28	Mo $K\alpha$ radiation
Triclinic, $P\overline{1}$	Cell parameters from 4236 reflections
a = 5.4500 (11) Å	θ = 1.00–25.35°
b = 9.7410 (19) Å	μ = 0.107 mm^{-1}
c = 12.307 (3) Å	T = 173 (1) K
α = 80.27 (3)°	Irregular plate-like fragment, colourless
β = 85.97 (3)°	0.32 × 0.20 × 0.04 mm
γ = 79.13 (3)°	
V = 631.9 (2) Å^3	
Z = 2	

Data collection

Nonius KappaCCD diffractometer	θ_{max} = 25.23°
ω scans at fixed χ = 55°	$h = -6 \rightarrow 6$
4358 measured reflections	$k = -11 \rightarrow 11$
2277 independent reflections	$l = -14 \rightarrow 14$
1562 reflections with $I > 2\sigma(I)$	Intensity decay: <1%
R_{int} = 0.034	

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F_o^2) + (0.0424P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$R[F^2 > 2\sigma(F^2)]$ = 0.041	$(\Delta/\sigma)_{max} < 0.001$
$wR(F^2)$ = 0.100	$\Delta\rho_{max}$ = 0.21 e Å^{-3}
S = 1.046	$\Delta\rho_{min}$ = −0.20 e Å^{-3}
2277 reflections	Extinction correction: *SHELXL97*
165 parameters	Extinction coefficient: 0.048 (5)
H-atom parameters constrained	

Table 1
Selected geometric parameters (Å, °).

N1—C6	1.3950 (19)	C5—F5	1.3490 (18)
N1—C2	1.410 (2)	O7—C7	1.2084 (18)
N1—C7	1.449 (2)	C7—C8	1.500 (2)
C2—O2	1.2074 (18)	C8—C9	1.527 (2)
C2—N3	1.3766 (19)	C9—C10	1.517 (2)
N3—C4	1.3714 (19)	C10—C11	1.523 (2)
C4—O4	1.2282 (18)	C11—C12	1.520 (2)
C4—C5	1.440 (2)	C12—C13	1.514 (2)
C5—C6	1.316 (2)	C13—C14	1.517 (2)
C6—N1—C2	120.36 (14)	F5—C5—C4	116.15 (14)
C6—N1—C7	115.90 (13)	C5—C6—N1	121.15 (15)
C2—N1—C7	123.71 (13)	O7—C7—N1	116.73 (14)
O2—C2—N3	121.57 (14)	O7—C7—C8	123.48 (15)
O2—C2—N1	124.02 (15)	N1—C7—C8	119.78 (14)
N3—C2—N1	114.41 (14)	C7—C8—C9	111.77 (14)
C4—N3—C2	128.42 (14)	C10—C9—C8	112.19 (13)
O4—C4—N3	122.42 (15)	C9—C10—C11	114.19 (14)
O4—C4—C5	125.06 (16)	C12—C11—C10	113.52 (14)
N3—C4—C5	112.53 (15)	C13—C12—C11	114.28 (14)
C6—C5—F5	120.89 (14)	C12—C13—C14	113.15 (14)
C6—C5—C4	122.95 (16)		

Data collection: *COLLECT* (Nonius, 1998); cell refinement: *SCALEPACK* (Otwinowski & Minor, 1997); data reduction: *DENZO–SMN* (Otwinowski & Minor, 1997); program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1997); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); software used to prepare material for publication: *SHELXL*97 (Sheldrick, 1997) and local programs.

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