organic compounds

7-(5-Carboxypentyl)-1,3-dimethyl-xanthine monohydrate

José João Carvalho, Franziska Emmerling* and Rudolf J. Schneider

Federal Institute for Materials Research and Testing, Department of Analytical Chemistry, Reference Materials, Richard-Willstätter-Strasse 11, D-12489 Berlin-Adlershof, Germany

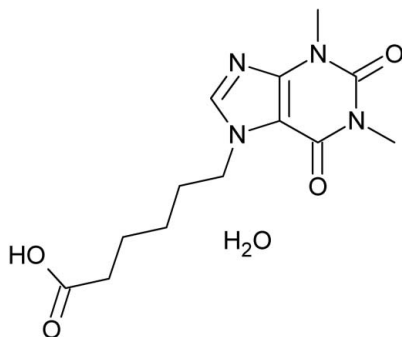Correspondence e-mail: franziska.emmerling@bam.de

The title compound [systematic name: 6-(1,3-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-7-yl)hexanoic acid monohydrate, CAS 61444–23-3], $C_{13}H_{18}N_4O_4 \cdot H_2O$, was synthesized and crystallized from ethyl acetate. Hydrogen bonds between xanthine and water molecules contribute to the formation of layers parallel to (10$\bar{2}$).

Related literature

For related literature, see: Allen (2002); Barone & Roberts (1996); Birkett & Miners (1991); Cook *et al.* (1976); Derollez *et al.* (2005); Edwards *et al.* (1997); Fenske (2007); Fickling *et al.* (1990); Kolpin *et al.* (2002); Leyland-Jones & Wong (2000); McDonagh (1991); Newton *et al.* (1981); Sutor (1958); Wahlländer *et al.* (1990).

Experimental

Crystal data

$C_{13}H_{18}N_4O_4 \cdot H_2O$	V = 1501 (2) Å^3
M_r = 312.33	Z = 4
Monoclinic, $P2_1/c$	Mo $K\alpha$ radiation
a = 4.370 (4) Å	μ = 0.11 mm^{-1}
b = 34.55 (2) Å	T = 291 (2) K
c = 9.960 (9) Å	$0.25 \times 0.1 \times 0.08$ mm
β = 93.21 (3)°	

Data collection

Bruker APEX CCD area-detector diffractometer	10307 measured reflections
Absorption correction: multi-scan (*SADABS*; Bruker, 2001)	3520 independent reflections
T_{min} = 0.97, T_{max} = 0.99	1861 reflections with $I > 2\sigma(I)$
	R_{int} = 0.096

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.048	H atoms treated by a mixture of independent and constrained refinement
$wR(F^2)$ = 0.158	
S = 0.86	
3520 reflections	$\Delta\rho_{max}$ = 0.19 e Å^{-3}
203 parameters	$\Delta\rho_{min}$ = −0.20 e Å^{-3}

Table 1
Hydrogen-bond geometry (Å, °).

D—H$\cdots A$	D—H	H$\cdots A$	$D \cdots A$	D—H$\cdots A$
O1W—H1$A\cdots$O1^i	0.79 (2)	2.00 (2)	2.764 (4)	163 (6)
O1W—H1$B\cdots$N9^{ii}	0.80 (4)	1.98 (5)	2.786 (6)	179 (7)
O3—H3$\cdots$O1W^{iii}	0.82	1.80	2.590 (5)	162

Symmetry codes: (i) $-x + 1, y + \frac{1}{2}, -z + \frac{1}{2}$; (ii) $-x, -y + 1, -z$; (iii) $x - 1, y, z$.

Data collection: *SMART* (Bruker, 2001); cell refinement: *SAINT* (Bruker, 2001); data reduction: *SAINT*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 1997); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *ORTEPIII* (Burnett & Johnson, 1996) and *SHELXTL* (Sheldrick, 2001); software used to prepare material for publication: *SHELXTL*.

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supplementary materials

7-(5-Carboxypentyl)-1,3-dimethylxanthine monohydrate

J. J. Carvalho, F. Emmerling and **R. J. Schneider**

Comment

7-(5-Carboxypentyl)-1,3-dimethylxanthine (Fig. 1) is a carboxylic acid derivative of caffeine and can be used to couple the xanthine moiety to labels (fluorescent, luminescent, colorimetric, radioactive, *etc*.), biomolecules (immunoassay tracer enzymes, immunogenic carrier proteins, coating proteins, *etc*.) or solid phases (microtitre plates, chip surfaces, affinity supports *etc*.) to construct assays and methods for the determination of caffeine.

Caffeine (1,3,7-trimethylxanthine) is a stimulant alkaloid whose annual world consumption exceeds 22 million tons (Fenske, 2007). Caffeine is an important analyte in pharmacology and pharmacokinetics serving as a metabolic probe for hepatic biotransformation (Wahlländer *et al.*, 1990) and for renal clearance (Birkett and Miners, 1991), analyzed in blood, saliva and urine. Radioimmunoassay (Cook *et al.*, 1976) and ELISA (Fickling *et al.*, 1990) has been used in the past being replaced by Enzyme Multiplied Immunoassay Technique (EMIT) as the most common format (McDonagh *et al.*, 1991).

About 1.8% of unmetabolized caffeine is excreted *via* urine (Newton *et al.*, 1981) but daily intake is about 4 mg kg^{-1} body weight for US consumers (Barone *et al.*, 1996) giving rise to high loads discharged into the waste water system. Kolpin *et al.* (2002) found caffeine in more than 70% of surface water samples taken all over the US in concentrations ranging from 0.1 µg L^{-1} to 5.7 µg L^{-1}.

The title compound has been synthesized before (Cook *et al.*, 1976), but the three-dimensional-crystal structure has not been reported so far while necessary for the understanding of the cross-reactivity of caffeine monoclonal antibodies against related xanthines.

The average C—N, C—C and C—O distances in the title compound (Fig. 1) are in good agreement with those in the caffeine molecule (Edwards *et al.*, 1997; Derollez *et al.*, 2005) and comparable compounds in the CSD (Version 5.27; Allen, 2002, for example Sutor, 1958). Analysis of the crystal packing shows that the molecules are linked *via* hydrogen bonds to result in a layer structure. The relevant hydrogen-bonding geometries and the symmetry codes are listed in Table 2. A s illustrated in Fig. 2, intermolecular O—H⋯N and O—H⋯O hydrogen bonds, involving the O atoms of aqua ligands and the N atoms of imidazole and a carboxylic O atom contribute to the hydrogen bonding. The center-to-center (DC) and center-to-plane (DP) distances between two neighboring almost parallel (interplanar angle α=0.62°) imidazole and adjacent pyrimidine rings are 3.545 (4)Å (DC) and 3.341 and 3.336Å (DP), revealing the existence of π-π stacking interactions, which further stabilize the structure.

Experimental

The title compound was synthesized starting from theophylline. Briefly theophylline was reacted with 6-bromohexanoic acid ethyl ester in a solvent system consisting of potassium carbonate (21 m*M*) in anhydrous dimethylformamide (DMF). The mixture was kept at 60°C under reflux conditions for 14 h. The cleavage of the ethyl ester was achieved by 10% sodium hydroxide in DMF at 110°C under reflux for 30 min. The solvent was evaporated and the residue dissolved in water. 6 N

hydrochloric acid was added to protonate the carboxylic acid group. Sodium chloride was added and the compound extracted by liquid-liquid extraction with ethyl acetate. Yields were 89% and 92% for the both reaction steps, respectively.

Colourless, needleshaped crystals of the compound were grown by solvent evaporation from ethyl acetate at room temperature. *M.p.* 124°C (DSC, onset, 0.75 mg; loss of crystal water at 106°C). NMR data: ^1H *NMR* (400 MHz, DMSO), δ(p.p.m.): 8.07 (s,1*H*), 4.22 (t,2*H*), 3.41 (s,3*H*), 3.22 (s,3*H*), 2.19 (t,2*H*), 1.50 (m,2*H*), 1.22 (m,2*H*); the carboxylic acid proton exchanges. ^{13}C *NMR* (400 MHz, DMSO) δ(p.p.m.): 174.3 (COOH), 154.3 (C-6'), 151.0 (C-2'), 148.4 (C-4'), 142.4 (CH), 105.9 (C-5'), 46.0 (CH2), 33.4 (CH2), 29.9 (CH3), 29.4 (CH2), 27.6 (CH3), 25.1 (CH2), 23.8 (CH2); Mass spectrum: 295.0 ($[M+H]^+$, 100%), 317.1 ($[M+Na]^+$, 34%. 277.4 (32%), 229.3 (18%), 181.0 ([theophylline+H]$^+$, 14%).

Refinement

The hydrogen atoms were located in difference maps but positioned with idealized geometry and refined using the riding model, with C—H = 0.93–0.97 Å, and $U_{iso}(H) = 1.2U_{eq}$(parent atom).
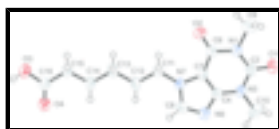
Figures

Fig. 1. *ORTEP-3* representation of (I) with the atomic labeling of the asymmetric unit and co-ordination sphere, shown with 50% probability displacement ellipsoids.
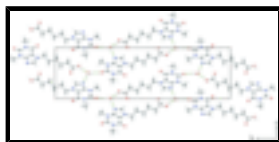
Fig. 2. View of the layers array of (I), formed *via* strong hydrogen-bonding interactions (indicated by green lines).

6-(1,3-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-7-yl)hexanoic acid monohydrate

Crystal data

$C_{13}H_{18}N_4O_4 \cdot H_2O$	$F_{000} = 664$
$M_r = 312.33$	$D_x = 1.382$ Mg m^{-3}
Monoclinic, $P2_1/c$	Mo $K\alpha$ radiation $\lambda = 0.71073$ Å
Hall symbol: -P 2ybc	Cell parameters from 128 reflections
$a = 4.370$ (4) Å	$\theta = 3.5–29.6º$
$b = 34.55$ (2) Å	$\mu = 0.11$ mm^{-1}
$c = 9.960$ (9) Å	$T = 291$ (2) K
$\beta = 93.21$ (3)º	Needle, colourless
$V = 1501$ (2) Å^3	$0.25 \times 0.1 \times 0.08$ mm
$Z = 4$	

Data collection

Bruker APEX CCD area-detector diffractometer	1861 reflections with $I > 2\sigma(I)$

Monochromator: graphite	$R_{int} = 0.096$
$T = 292(2)$ K	$\theta_{max} = 27.9°$
ω scans	$\theta_{min} = 1.2°$
Absorption correction: multi-scan (SADABS; Bruker, 2001)	$h = -5 \rightarrow 5$
$T_{min} = 0.97$, $T_{max} = 0.99$	$k = -35 \rightarrow 44$
10307 measured reflections	$l = -12 \rightarrow 11$
3520 independent reflections	

Refinement

Refinement on F^2	Secondary atom site location: difference Fourier map
Least-squares matrix: full	Hydrogen site location: inferred from neighbouring sites
$R[F^2 > 2\sigma(F^2)] = 0.048$	H atoms treated by a mixture of independent and constrained refinement
$wR(F^2) = 0.158$	$w = 1/[\sigma^2(F_o^2) + (0.0723P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$S = 0.86$	$(\Delta/\sigma)_{max} = 0.031$
3520 reflections	$\Delta\rho_{max} = 0.19$ e Å^{-3}
203 parameters	$\Delta\rho_{min} = -0.20$ e Å^{-3}
Primary atom site location: structure-invariant direct methods	Extinction correction: none

Special details

Geometry. All e.s.d.'s (except the e.s.d. in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell e.s.d.'s are taken into account individually in the estimation of e.s.d.'s in distances, angles and torsion angles; correlations between e.s.d.'s in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell e.s.d.'s is used for estimating e.s.d.'s involving l.s. planes.

Refinement. Refinement of F^2 against ALL reflections. The weighted R-factor wR and goodness of fit S are based on F^2, conventional R-factors R are based on F, with F set to zero for negative F^2. The threshold expression of $F^2 > 2sigma(F^2)$ is used only for calculating R-factors(gt) *etc*. and is not relevant to the choice of reflections for refinement. R-factors based on F^2 are statistically about twice as large as those based on F, and R– factors based on ALL data will be even larger.

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters ($Å^2$)

	x	y	z	U_{iso}*/U_{eq}
O1	0.6656 (6)	0.26684 (7)	0.4862 (3)	0.0647 (8)
O2	0.6266 (6)	0.39794 (7)	0.5376 (2)	0.0538 (7)
O3	−0.3153 (7)	0.63559 (7)	0.1447 (3)	0.0803 (10)
H3	−0.4073	0.6489	0.0875	0.120*
O4	−0.4681 (7)	0.58849 (7)	0.0088 (3)	0.0773 (9)
O1W	0.3703 (10)	0.68701 (8)	0.0072 (4)	0.1010 (12)
H1A	0.395 (14)	0.7096 (6)	0.003 (6)	0.152*
H1B	0.263 (12)	0.6786 (16)	−0.054 (4)	0.152*
N1	0.6354 (6)	0.33202 (8)	0.5114 (3)	0.0446 (7)

N3	0.3446 (7)	0.29961 (7)	0.3420 (3)	0.0469 (8)
N7	0.1420 (6)	0.39731 (7)	0.3044 (3)	0.0437 (7)
N9	0.0103 (7)	0.34122 (8)	0.2042 (3)	0.0519 (8)
C2	0.5525 (8)	0.29755 (10)	0.4475 (4)	0.0486 (9)
C4	0.2218 (8)	0.33503 (9)	0.3049 (3)	0.0434 (9)
C5	0.3098 (8)	0.36827 (9)	0.3684 (3)	0.0415 (8)
C6	0.5302 (8)	0.36947 (9)	0.4767 (3)	0.0418 (8)
C8	−0.0300 (9)	0.37944 (10)	0.2077 (4)	0.0524 (10)
H8	−0.1654	0.3925	0.1483	0.063*
C9	0.8520 (9)	0.32890 (10)	0.6276 (3)	0.0577 (10)
H9A	0.7428	0.3234	0.7064	0.087*
H9B	0.9610	0.3529	0.6399	0.087*
H9C	0.9948	0.3084	0.6131	0.087*
C10	0.2521 (9)	0.26402 (10)	0.2716 (4)	0.0657 (12)
H10A	0.4281	0.2522	0.2351	0.099*
H10B	0.1034	0.2700	0.1999	0.099*
H10C	0.1639	0.2465	0.3334	0.099*
C11	0.1366 (9)	0.43804 (9)	0.3433 (3)	0.0508 (10)
H11A	0.3439	0.4464	0.3686	0.061*
H11B	0.0157	0.4408	0.4215	0.061*
C12	0.0055 (9)	0.46391 (9)	0.2332 (3)	0.0557 (10)
H12A	−0.1976	0.4548	0.2045	0.067*
H12B	0.1329	0.4623	0.1567	0.067*
C13	−0.0156 (9)	0.50577 (9)	0.2763 (3)	0.0544 (10)
H13A	−0.1430	0.5074	0.3528	0.065*
H13B	0.1876	0.5149	0.3052	0.065*
C14	−0.1457 (9)	0.53182 (9)	0.1672 (3)	0.0565 (10)
H14A	−0.3467	0.5223	0.1369	0.068*
H14B	−0.0155	0.5306	0.0915	0.068*
C15	−0.1745 (9)	0.57328 (9)	0.2096 (4)	0.0572 (10)
H15A	−0.2834	0.5741	0.2917	0.069*
H15B	0.0294	0.5835	0.2300	0.069*
C16	−0.3345 (8)	0.59884 (10)	0.1092 (4)	0.0506 (9)

Atomic displacement parameters ($Å^2$)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
O1	0.080 (2)	0.0363 (14)	0.0758 (18)	0.0091 (14)	−0.0110 (15)	0.0073 (13)
O2	0.0639 (17)	0.0407 (14)	0.0550 (15)	−0.0025 (12)	−0.0125 (12)	−0.0065 (12)
O3	0.120 (3)	0.0362 (15)	0.0799 (19)	0.0077 (15)	−0.0402 (17)	−0.0002 (14)
O4	0.110 (2)	0.0457 (15)	0.0710 (18)	0.0130 (16)	−0.0422 (17)	−0.0064 (14)
O1W	0.141 (3)	0.0350 (15)	0.118 (3)	0.0056 (19)	−0.072 (2)	−0.0037 (18)
N1	0.0492 (18)	0.0375 (16)	0.0460 (17)	0.0010 (14)	−0.0081 (14)	0.0035 (13)
N3	0.059 (2)	0.0297 (16)	0.0505 (18)	0.0010 (14)	−0.0058 (15)	−0.0040 (13)
N7	0.0563 (19)	0.0301 (15)	0.0431 (16)	0.0024 (14)	−0.0106 (14)	−0.0009 (13)
N9	0.061 (2)	0.0421 (18)	0.0514 (18)	0.0004 (15)	−0.0099 (16)	−0.0029 (14)
C2	0.052 (2)	0.038 (2)	0.056 (2)	0.0040 (18)	0.0028 (19)	0.0017 (18)
C4	0.049 (2)	0.0362 (19)	0.045 (2)	0.0010 (17)	−0.0018 (18)	0.0005 (17)

C5	0.052 (2)	0.0315 (18)	0.0404 (19)	−0.0006 (16)	−0.0031 (17)	0.0017 (15)
C6	0.044 (2)	0.039 (2)	0.041 (2)	0.0016 (17)	−0.0008 (17)	0.0016 (16)
C8	0.061 (3)	0.042 (2)	0.053 (2)	0.0048 (19)	−0.0106 (19)	0.0013 (18)
C9	0.061 (3)	0.055 (2)	0.055 (2)	0.0041 (19)	−0.013 (2)	0.0067 (19)
C10	0.078 (3)	0.043 (2)	0.075 (3)	0.000 (2)	−0.003 (2)	−0.017 (2)
C11	0.063 (3)	0.0321 (18)	0.056 (2)	0.0027 (17)	−0.0093 (19)	0.0007 (17)
C12	0.072 (3)	0.039 (2)	0.055 (2)	0.0112 (19)	−0.011 (2)	0.0015 (17)
C13	0.068 (3)	0.040 (2)	0.054 (2)	0.0110 (19)	−0.0054 (19)	0.0030 (17)
C14	0.077 (3)	0.039 (2)	0.051 (2)	0.0072 (19)	−0.014 (2)	0.0013 (17)
C15	0.073 (3)	0.038 (2)	0.058 (2)	0.0100 (19)	−0.021 (2)	−0.0008 (17)
C16	0.058 (3)	0.037 (2)	0.055 (2)	0.0026 (18)	−0.005 (2)	0.0003 (18)

Geometric parameters (Å, °)

O1—C2	1.224 (4)	C9—H9A	0.9600
O2—C6	1.218 (4)	C9—H9B	0.9600
O3—C16	1.320 (4)	C9—H9C	0.9600
O3—H3	0.8200	C10—H10A	0.9600
O4—C16	1.185 (4)	C10—H10B	0.9600
O1W—H1A	0.789 (19)	C10—H10C	0.9600
O1W—H1B	0.80 (2)	C11—C12	1.503 (4)
N1—C2	1.389 (4)	C11—H11A	0.9700
N1—C6	1.410 (4)	C11—H11B	0.9700
N1—C9	1.457 (4)	C12—C13	1.513 (5)
N3—C2	1.352 (4)	C12—H12A	0.9700
N3—C4	1.379 (4)	C12—H12B	0.9700
N3—C10	1.462 (4)	C13—C14	1.498 (4)
N7—C8	1.339 (4)	C13—H13A	0.9700
N7—C5	1.378 (4)	C13—H13B	0.9700
N7—C11	1.460 (4)	C14—C15	1.501 (5)
N9—C8	1.333 (4)	C14—H14A	0.9700
N9—C4	1.343 (4)	C14—H14B	0.9700
C4—C5	1.356 (4)	C15—C16	1.480 (5)
C5—C6	1.406 (5)	C15—H15A	0.9700
C8—H8	0.9300	C15—H15B	0.9700
C16—O3—H3	109.5	N3—C10—H10C	109.5
H1A—O1W—H1B	113 (6)	H10A—C10—H10C	109.5
C2—N1—C6	127.0 (3)	H10B—C10—H10C	109.5
C2—N1—C9	116.2 (3)	N7—C11—C12	113.0 (3)
C6—N1—C9	116.8 (3)	N7—C11—H11A	109.0
C2—N3—C4	119.3 (3)	C12—C11—H11A	109.0
C2—N3—C10	119.0 (3)	N7—C11—H11B	109.0
C4—N3—C10	121.7 (3)	C12—C11—H11B	109.0
C8—N7—C5	105.1 (3)	H11A—C11—H11B	107.8
C8—N7—C11	128.2 (3)	C11—C12—C13	112.8 (3)
C5—N7—C11	126.5 (3)	C11—C12—H12A	109.0
C8—N9—C4	103.0 (3)	C13—C12—H12A	109.0
O1—C2—N3	122.2 (3)	C11—C12—H12B	109.0
O1—C2—N1	120.6 (3)	C13—C12—H12B	109.0

N3—C2—N1	117.2 (3)	H12A—C12—H12B	107.8
N9—C4—C5	112.3 (3)	C14—C13—C12	113.2 (3)
N9—C4—N3	125.7 (3)	C14—C13—H13A	108.9
C5—C4—N3	122.1 (3)	C12—C13—H13A	108.9
C4—C5—N7	105.7 (3)	C14—C13—H13B	108.9
C4—C5—C6	123.2 (3)	C12—C13—H13B	108.9
N7—C5—C6	131.1 (3)	H13A—C13—H13B	107.7
O2—C6—C5	127.5 (3)	C13—C14—C15	113.8 (3)
O2—C6—N1	121.4 (3)	C13—C14—H14A	108.8
C5—C6—N1	111.1 (3)	C15—C14—H14A	108.8
N9—C8—N7	114.0 (3)	C13—C14—H14B	108.8
N9—C8—H8	123.0	C15—C14—H14B	108.8
N7—C8—H8	123.0	H14A—C14—H14B	107.7
N1—C9—H9A	109.5	C16—C15—C14	115.1 (3)
N1—C9—H9B	109.5	C16—C15—H15A	108.5
H9A—C9—H9B	109.5	C14—C15—H15A	108.5
N1—C9—H9C	109.5	C16—C15—H15B	108.5
H9A—C9—H9C	109.5	C14—C15—H15B	108.5
H9B—C9—H9C	109.5	H15A—C15—H15B	107.5
N3—C10—H10A	109.5	O4—C16—O3	122.5 (3)
N3—C10—H10B	109.5	O4—C16—C15	125.6 (3)
H10A—C10—H10B	109.5	O3—C16—C15	111.9 (3)

Hydrogen-bond geometry (Å, °)

D—H···A	D—H	H···A	D···A	D—H···A
O1W—H1A···O1[i]	0.79 (2)	2.00 (2)	2.764 (4)	163 (6)
O1W—H1B···N9[ii]	0.80 (4)	1.98 (5)	2.786 (6)	179 (7)
O3—H3···O1W[iii]	0.82	1.80	2.590 (5)	162

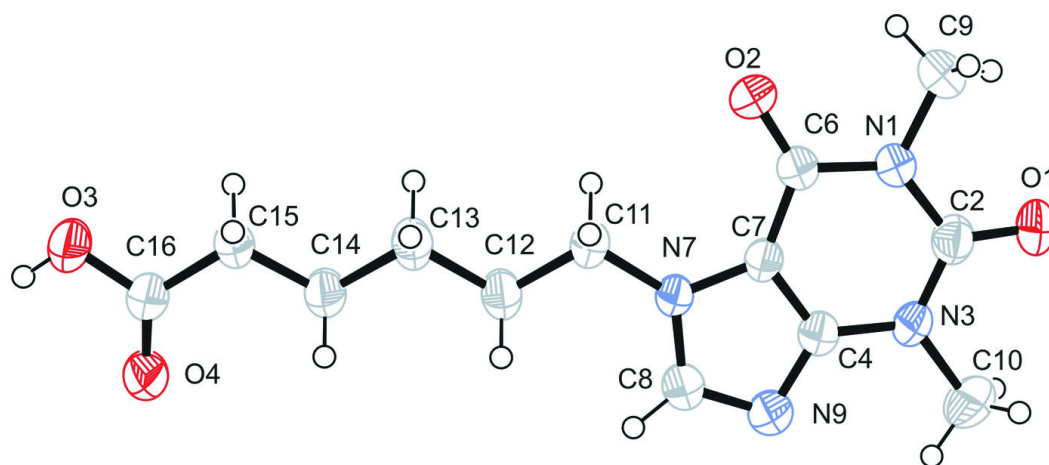Symmetry codes: (i) $-x+1, y+1/2, -z+1/2$; (ii) $-x, -y+1, -z$; (iii) $x-1, y, z$.

Fig. 1

Fig. 2