

## Crystal Structure of (–)-7-[(7*S*)-7-Amino-5-azaspiro[2.4]hept-5-yl]-8-chloro-6-fluoro-1-[(1*R*,2*S*)-2-fluorocyclopropyl]-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acid (Sitafloxacin) Sesquihydrate

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Sitafloxacin (DU-6859) is a newly developed fluoroquinolone antibacterial agent. Its antibacterial activity is significantly better than those of other quinolones.<sup>1</sup> Three hydrate forms (hemihydrate, monohydrate and sesquihydrate) and three anhydrate forms ( $\alpha$ ,  $\beta$  and  $\gamma$ -forms) of sitafloxacin crystals have been found so far. The polymorphic and pseudopolymorphic crystals show different physicochemical properties. The crystal structure of the  $\beta$ -form has been already reported.<sup>2</sup> In this paper, we report the X-ray structure of the sesquihydrate.

The crystal used for the X-ray analysis was yellowish prismatic, and its size was approximately 0.20×0.18×0.10 mm<sup>3</sup>. The crystal and experimental data are listed in Table 1. Intensity data were collected in the  $\omega$ -2 $\theta$  scan mode using

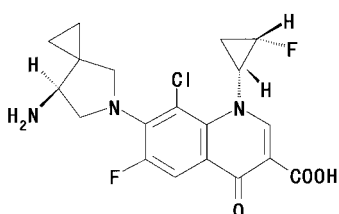


Fig. 1 Chemical structure of sitafloxacin.

Table 1 Crystal and experimental data

Formula:	C <sub>19</sub> H <sub>18</sub> ClF <sub>2</sub> N <sub>3</sub> O <sub>3</sub> ·1.5H <sub>2</sub> O
Formula weight:	436.84
Crystal system:	orthorhombic
Space group:	<i>P</i> 2 <sub>1</sub> 2 <sub>1</sub> 2 <sub>1</sub> Z = 8
<i>a</i> =	13.749(4) Å
<i>b</i> =	20.990(5) Å
<i>c</i> =	13.609(2) Å
<i>V</i> =	3927.4 Å <sup>3</sup>
<i>D</i> <sub>x</sub> =	1.49 g/cm <sup>3</sup>
$\mu$ (Cu K $\alpha$ ) =	2.23 mm <sup>-1</sup>
No. of reflections used =	2867
<i>T</i> =	295 K
<i>R</i> =	0.065, <i>R</i> <sub>w</sub> = 0.052
Minimum residual density =	-0.34 eÅ <sup>-1</sup>
Maximum residual density =	0.75 eÅ <sup>-1</sup>
Measurement:	RIGAKU AFC5RU
Program system:	KPPXRAY
Structure determination:	MULTAN88
Refinement:	block-diagonal

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graphite-monochromated Cu K $\alpha$  radiation ( $\lambda$  = 1.5478 Å). The structure was solved by direct method, and refined by block-diagonal least-squares method. Non-hydrogen atoms were refined anisotropically. Hydrogen atoms were located in the difference Fourier map and refined isotropically. The highest peak in the map was assigned as an extra water molecule (O54). The hydration number of this crystal is known to vary from 1.5 to 2.0 according to relative humidity. Since the crystal used in this experiment was treated in an ordinary circumstance, the occupancy value of the extra water was assumed to be 0.5.

The final atomic coordinates and equivalent temperature factors of non-hydrogen atoms are listed in Table 2. Selected bond distances and angles are listed in Table 3. The bond distances and angles are within expected values.

The two independent sitafloxacin molecules in the unit cell take slightly different conformations (Fig. 2). The quinolone rings in either molecule do not take planar conformation, because of steric hindrance between the CL atom and a cyclopropyl ring. Comparing these conformations with that of  $\beta$ -form, the azacyclopentyl ring takes quite different orientations. C10(C30)–C11(C31)–N02(N22)–C14(C34) take *trans* conformation in this crystal, while the corresponding bond takes *gauche* conformation in  $\beta$ -form.

In addition to this conformational difference, ionization states of the sitafloxacin molecules are different between the two

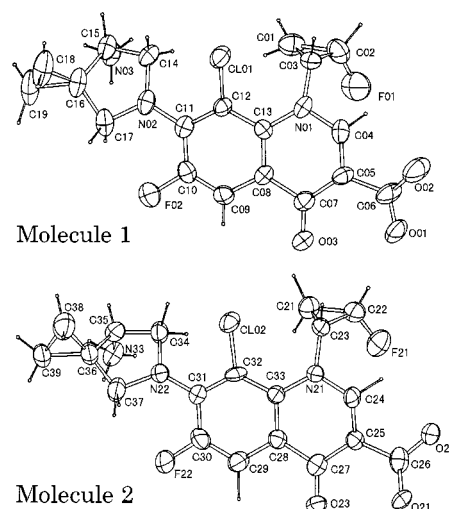


Fig. 2 Molecular drawing of sitafloxacin in sesquihydrate form with atom numbering.

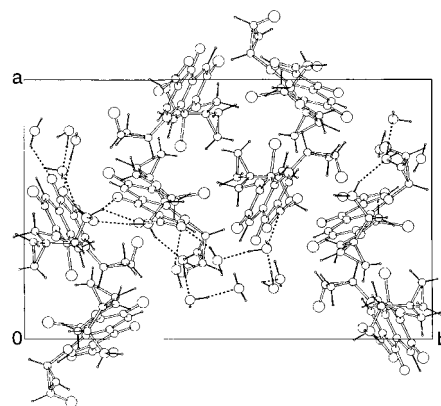
Table 2 Atomic coordinates and equivalent temperature factors,  $U_{eq}$ , of non-hydrogen atoms

Atom	x	y	z	$U_{eq}$
CL01	0.0652(2)	0.9418(1)	0.6777(2)	.048(1)
CL21	-0.2540(2)	0.6160(1)	0.5215(2)	.0455(9)
F01	-0.2396(4)	0.8867(3)	0.4772(5)	.081(3)
F02	0.1428(4)	0.7084(2)	0.7106(4)	.062(3)
F21	-0.1257(4)	0.7780(3)	0.7765(4)	.064(3)
F22	0.0707(5)	0.5227(3)	0.4322(4)	.088(3)
C01	-0.1638(7)	0.9246(5)	0.6239(7)	.054(4)
C02	-0.2066(7)	0.9370(5)	0.5286(8)	.061(4)
C03	-0.1003(7)	0.9444(4)	0.5386(7)	.045(3)
C04	-0.0516(7)	0.8841(4)	0.3947(6)	.042(3)
C05	-0.0215(7)	0.8327(4)	0.3440(6)	.040(4)
C06	-0.0469(8)	0.8340(4)	0.2356(7)	.053(4)
C07	0.0229(6)	0.7800(4)	0.3966(6)	.040(3)
C08	0.0385(6)	0.7912(4)	0.5032(6)	.031(3)
C09	0.0835(7)	0.7463(4)	0.5620(6)	.037(3)
C10	0.0996(6)	0.7567(4)	0.6579(6)	.040(3)
C11	0.0795(6)	0.8139(4)	0.7056(6)	.036(3)
C12	0.0457(6)	0.8617(4)	0.6449(6)	.033(3)
C13	0.0151(6)	0.8493(4)	0.5479(6)	.031(3)
C14	0.0321(7)	0.8695(4)	0.8625(6)	.041(4)
C15	0.0316(7)	0.8458(4)	0.9687(7)	.045(4)
C16	0.1253(7)	0.8078(5)	0.9712(7)	.052(4)
C17	0.1363(7)	0.7761(5)	0.8733(7)	.049(3)
C18	0.2153(8)	0.8365(6)	1.0218(8)	.084(5)
C19	0.1635(8)	0.7767(6)	1.0617(7)	.078(5)
C21	-0.2022(7)	0.7480(4)	0.6212(7)	.045(4)
C22	-0.2103(7)	0.7620(4)	0.7268(7)	.049(4)
C23	-0.2209(6)	0.6951(4)	0.6932(6)	.036(3)
C24	-0.1065(7)	0.6495(4)	0.8099(6)	.036(3)
C25	-0.0229(6)	0.6221(4)	0.8399(6)	.034(3)
C26	0.0045(7)	0.6284(4)	0.9468(6)	.045(4)
C27	0.0378(7)	0.5901(4)	0.7677(6)	.039(3)
C28	-0.0045(7)	0.5865(4)	0.6688(6)	.036(3)
C29	0.0478(7)	0.5530(4)	0.5958(7)	.044(4)
C30	0.0143(7)	0.5514(4)	0.5005(7)	.049(4)
C31	-0.0747(7)	0.5783(4)	0.4713(6)	.039(3)
C32	-0.1291(6)	0.6055(4)	0.5468(6)	.036(3)
C33	-0.0943(6)	0.6142(4)	0.6433(6)	.033(3)
C34	-0.1499(7)	0.6337(4)	0.3294(6)	.043(4)
C35	-0.1269(7)	0.6250(4)	0.2211(7)	.045(4)
C36	-0.1296(7)	0.5543(4)	0.2099(7)	.045(4)
C37	-0.0833(8)	0.5274(4)	0.3013(7)	.057(4)
C38	-0.2186(8)	0.5250(5)	0.1661(8)	.065(5)
C39	-0.1243(8)	0.5225(5)	0.1128(7)	.059(4)
N01	-0.0389(5)	0.8942(3)	0.4951(5)	.039(3)
N02	0.0937(5)	0.8238(3)	0.8069(5)	.042(3)
N03	-0.0533(6)	0.8042(3)	0.9921(5)	.045(3)
N21	-0.1424(5)	0.6493(3)	0.7158(5)	.034(3)
N22	-0.1028(5)	0.5786(3)	0.3741(5)	.041(3)
N23	-0.0311(6)	0.6530(4)	0.1951(5)	.049(3)
O01	-0.0502(5)	0.7821(3)	0.1925(4)	.061(3)
O02	-0.0648(7)	0.8857(3)	0.1964(5)	.086(3)
O03	0.0499(5)	0.7297(3)	0.3595(4)	.055(3)
O21	0.0705(5)	0.5952(3)	0.9795(4)	.062(3)
O22	-0.0435(5)	0.6703(3)	0.9931(4)	.049(3)
O23	0.1190(4)	0.5684(3)	0.7843(4)	.047(2)
O51	0.1958(6)	0.4735(4)	0.2407(7)	.106(4)
O52	0.1510(7)	0.5946(4)	0.1757(7)	.127(5)
O53	0.2685(9)	0.6273(6)	-0.0674(9)	.054(4)
O54*	0.305(1)	0.6112(9)	0.062(1)	.133(8)

$$U_{eq} = 1/3 (U_{11}(aa^*)^2 + U_{22}(bb^*)^2 + U_{33}(cc^*)^2 + 2U_{12}(aa^*bb^*)\cos\gamma + 2U_{13}(aa^*cc^*)\cos\beta + 2U_{23}(bb^*cc^*)\cos\alpha).$$

\* occupancy 0.5 (fixed).

crystal forms. The difference Fourier map show protonation of amino groups and dissociation of carboxyl groups in this crystal. The molecules in the present crystal are in zwitterionic form, while the molecule in  $\beta$ -form as a neutral form. Crystal packing is shown in Fig. 3 and hydrogen bonds are listed in Table 4. The amino N03 atom in molecule **1** forms

Fig. 3 Crystal packing of sitafloxacin sesquihydrate, looked down the  $c$ -axis.Table 3 Selected bond distances ( $\text{\AA}$ ) and bond and torsion angles ( $^\circ$ )

C11—N02	1.41(1)	C31—N22	1.38(1)
C06—O01	1.24(1)	C26—O21	1.23(1)
C06—O02	1.23(1)	C26—O22	1.27(1)
C07—O03	1.23(1)	C27—O23	1.23(1)
C15—N03	1.49(1)	C35—N23	1.49(1)
C10—C11—N02	123.8(7)	C30—C31—N22	121.2(8)
C12—C11—N02	121.7(7)	C32—C31—N22	123.7(8)
C05—C06—O01	117.0(8)	C25—C26—O21	119.0(7)
C05—C06—O02	118.8(8)	C25—C26—O22	114.2(8)
O01—C06—O02	124.2(9)	O21—C26—O22	126.8(8)
C05—C07—O03	125.4(8)	C25—C27—O23	124.7(8)
C08—C07—O03	119.6(7)	C28—C27—O23	120.7(8)
C10—C11—C12—CL01	-153.7(4)	C30—C31—C32—CL21	-160.8(5)
C10—C11—C12—C13	13.2(8)	C30—C31—C32—C33	8.7(9)
C12—C11—N02—C14	32.1(8)	C32—C31—N22—C34	39.6(9)
C12—C11—N02—C17	-175.7(5)	C32—C31—N22—C37	-146.3(6)

Table 4 Hydrogen-bonding geometry ( $\text{\AA}$ ,  $^\circ$ )

Donor	H	Acceptor	D...A	H...A	H-D...A	H...A...D
N03	HN03C	O01 <sup>i</sup>	2.767(9)	1.81(4)	2(2)	1(1)
N03	HN03B	O22	2.814(9)	1.93(4)	16(3)	8(2)
N03	HN03A	O54 <sup>ii</sup>	2.74(2)	1.97(5)	16(3)	6(1)
N23	HN23C	O22 <sup>iii</sup>	2.778(9)	1.78(5)	8(4)	5(2)
N23	HN23A	O52	2.80(1)	1.99(5)	16(3)	7(1)
N23	HN23B	O03	2.97(1)	2.15(6)	29(3)	13(2)
O51	HO51A	O02 <sup>iv</sup>	2.72(1)	2.00(4)	17(3)	6(1)
O52	HO52A	O21 <sup>iii</sup>	2.89(1)	1.95(6)	1(2)	0.6(9)
O52	HO52B	O51	2.76(1)	1.85(5)	8(3)	4(1)
O53	HO53A	O21 <sup>iii</sup>	2.88(1)	1.88(8)	2(3)	1(2)
O54	HO54A	O52	2.65(2)	1.53(6)	5(3)	3(2)

Symmetry code: (i)  $+x, +y, 1+z$ ; (ii)  $-1/2+x, 3/2-y, 1-z$ ; (iii)  $+x, +y, -1+z$ ; (iv)  $-x, -1/2+y, 1/2-z$ .

intermolecular hydrogen bonds with the two carboxyl groups (O01 and O22) and one water molecule (O54). All hydrogen atoms of the N23 amino group participate in intermolecular hydrogen bonds. The water molecules in the crystal form a hydrogen bonding linkage, N03—O54—O52—O51—O02, between the sitafloxacin molecules.

## References

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2. K. Yamazaki and M. Suzuki, *Anal. Sci.*, **1998**, *14*, 463.