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Moxifloxacinium chloride–water–methanol (2/1/1), a novel antibacterial agent

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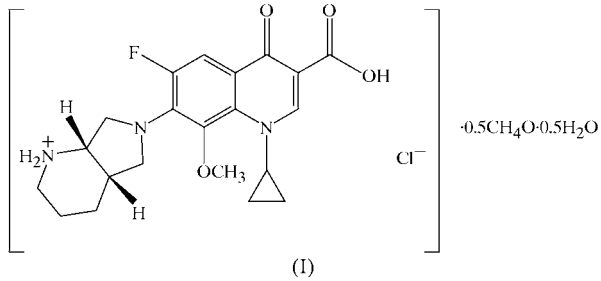
Moxifloxacin, a novel fluoroquinolone with a broad spectrum of antibacterial activity, is available as the solvated monohydrochloride salt 7-[(*S*,*S*)-2-aza-8-azoniabicyclo[4.3.0]-non-8-yl]-1-cyclopropyl-6-fluoro-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid chloride–water–methanol (2/1/1), $C_{21}H_{25}FN_3O_4^+\cdot Cl^-\cdot 0.5H_2O\cdot 0.5CH_3OH$. The asymmetric unit contains two cations, two chloride ions, a molecule of water and one methanol molecule. The two cations adopt conformations that differ by an almost 180° rotation with respect to the piperidinopyrrolidine side chain. The cyclopropyl ring and the methoxy group are not coplanar with the quinoline ring system. The carboxylic acid function, the protonated terminal piperidyl N atom, the water molecule, the chloride ion and the methanol molecule participate in O—H···O, O—H···Cl, N—H···O and N—H···Cl hydrogen bonding, linking the molecules into extended two-dimensional networks.

Comment

Development of resistance to antimicrobial agents and the emergence of multiresistant pathogens have generated worldwide concern in the medicinal community. The fluoroquinolone class of antimicrobial agents is being used empirically in an increasing number of patients because of the resistance developed to the more traditional antimicrobial agents. Fluoroquinolones are active against a wide range of multiresistant pathogens, as they act against different molecular targets compared with other antimicrobial agents (Hooper, 2000). All fluoroquinolones are analogues of the basic quinoline pharmacore (Fig. 1), and distinct antimicrobial and pharmacological activities have been defined for each modification of the molecular structure (Domagala, 1994; Tillotson, 1996).

Moxifloxacin is a novel third-generation fluoroquinolone, the antimicrobial activity of which depends upon inhibition of DNA gyrase (bacterial topoisomerase II), an enzyme necessary for DNA replication, transcription, repair and recombination (von Keutz & Schluter, 1999). Moxifloxacin, a chiral (*S*,*S*)-8-methoxyfluoroquinolone derivative formulated as a hydrochloride salt, is supplied as a film-covered tablet, Avelox, developed by Bayer Pharmaceuticals Corporation and marketed in the USA by Schering–Plough. Moxifloxacin is the only topical fluroquinolone without added preservatives and is formulated at a physiological pH of 6.8 compared with 6.0 for gatifloxacin. Moxifloxacin is highly effective against Gram-positive organisms, has better pharmacokinetic properties and has no precipitates. Because moxifloxacin is self-preserved, it has minimal toxicity and is safe and effective for children, including newborns. Recently, the US Food and Drug Administration has approved the once-daily antibiotic Avelox for the treatment of complicated skin and skin structure infections in adults caused by methicillin-susceptible *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumoniae* or *Enterobacter cloacae*. In a continuation of our ongoing programmes on the structural elucidation of drug molecules and to gain further insight into structure–activity relationships, the crystal structure of moxifloxacin hydrochloride–water–methanol (2/1/1), (I), was determined and is reported here.



(I)

The bond distances and angles in (I) are in normal ranges (Allen *et al.*, 1987) and are comparable to the corresponding values observed in similar compounds (Sivalakshmidevi *et al.*, 2000; Prasanna & Guru Row, 2001; Sun *et al.*, 2004; Li *et al.*, 2005). The asymmetric unit consists of two independent moxifloxacin cations (unprimed and primed atoms in Fig. 2) protonated at the terminal piperidyl N atom, two chloride anions, one water molecule and one methanol molecule. The conformations of the two cations differ principally by a rotation of the piperidinopyrrolidine ring system about the C7—N2 bond by nearly 180°. If one ignores the uniqueness in the configuration of the piperidinopyrrolidine ring system introduced by the presence of atom N3, the skeletons of the two symmetry-independent cations appear to be related by a pseudo-centre of inversion. After inversion of the primed molecule, the r.m.s. deviation for superimposing the quinoline systems in the asymmetric unit is 0.025 Å (Fig. 3).

An earlier study indicated that substitution at the N1 position is important for antibacterial activity (Albrecht, 1977). The cyclopropyl group is by far the optimal group at this position because of its favourable combination of steric, spatial and through-space electronic interactions (Chu & Fernandes, 1989). The orientation of the plane of the cyclopropyl ring is practically perpendicular to that of the quinoline system [C1—N1—C11—C12 and C1—N1—C11—C13 are −113.7 (4) and −43.3 (5)°, respectively, for the unprimed cation and 116.0 (4) and 48.6 (6)° for the primed cation]. The

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quinoline ring system is essentially planar and the dihedral angles between the planes of the cyclopropyl and quinoline ring systems are 69.6 (2) and 71.1 (2)° for the unprimed and primed cations, respectively. The corresponding angles are 56.2° in 2-hydroxyethanaminium enrofloxacin (Sun *et al.*, 2004), 60.8° in sparfloxacin (Miyamoto *et al.*, 1990), 78.8 and 70.9° in sitafloxacin sesquihydrate (Suzuki *et al.*, 2000), 56.0° in ciprofloxacin hydrochloride (Turel & Golobic, 2003), and 56.5 and 54.6° in ciprofloxacin lactate (Prasanna & Guru Row, 2001).

The positions of the substituents at atoms C2 and C3, having an interaction between the carboxylic acid group and the carbonyl group, are generally considered necessary for the binding of quinolones to DNA gyrase (Schentag & Domagala, 1985). Carboxyl atom O1 forms an intramolecular hydrogen bond with the carbonyl group O3. This hydrogen bond forms a quasi-six-membered ring. The coplanarity between the 3-carbonyl group and the carboxylic acid group is reflected by the C3—C2—C10—O1 and C10—C2—C3—O3 torsion angles of 2.8 (6) and −1.3 (6)°, respectively, for the unprimed cation and −4.3 (6) and 1.2 (6)° for the primed cation.

An analysis of quinolones, using an automated computer structure evaluation program, concluded that cell permeability is predominantly controlled by the nature of the C7 substituent (Klopman *et al.*, 1987). The nature of the C7 substituent is known to influence quinoline activity in Gram-positive and Gram-negative bacteria (Bryskier & Chantot, 1995), and also the target preference of fluoroquinolones (Alovero *et al.*, 2000). The most common C7 substituents are substituted piperazin-1-yl groups (norfloxacin, ciprofloxacin, enrofloxacin, perfloxacin, ofloxacin, difloxacin, fleroxacin and amifloxacin). Moxifloxacin has the bulkiest C7 substituent, a fused bicyclic system composed of a pyrrolidine and a piperidine ring, of the currently available fluoroquinolone agents, which prevents active efflux associated with the NorA or pmrA genes seen in certain Gram-positive bacteria (Blondeau, 1999; Pestova *et al.*, 2000). An important aspect of the title compound is the orientation of its piperidinopyrrolidine

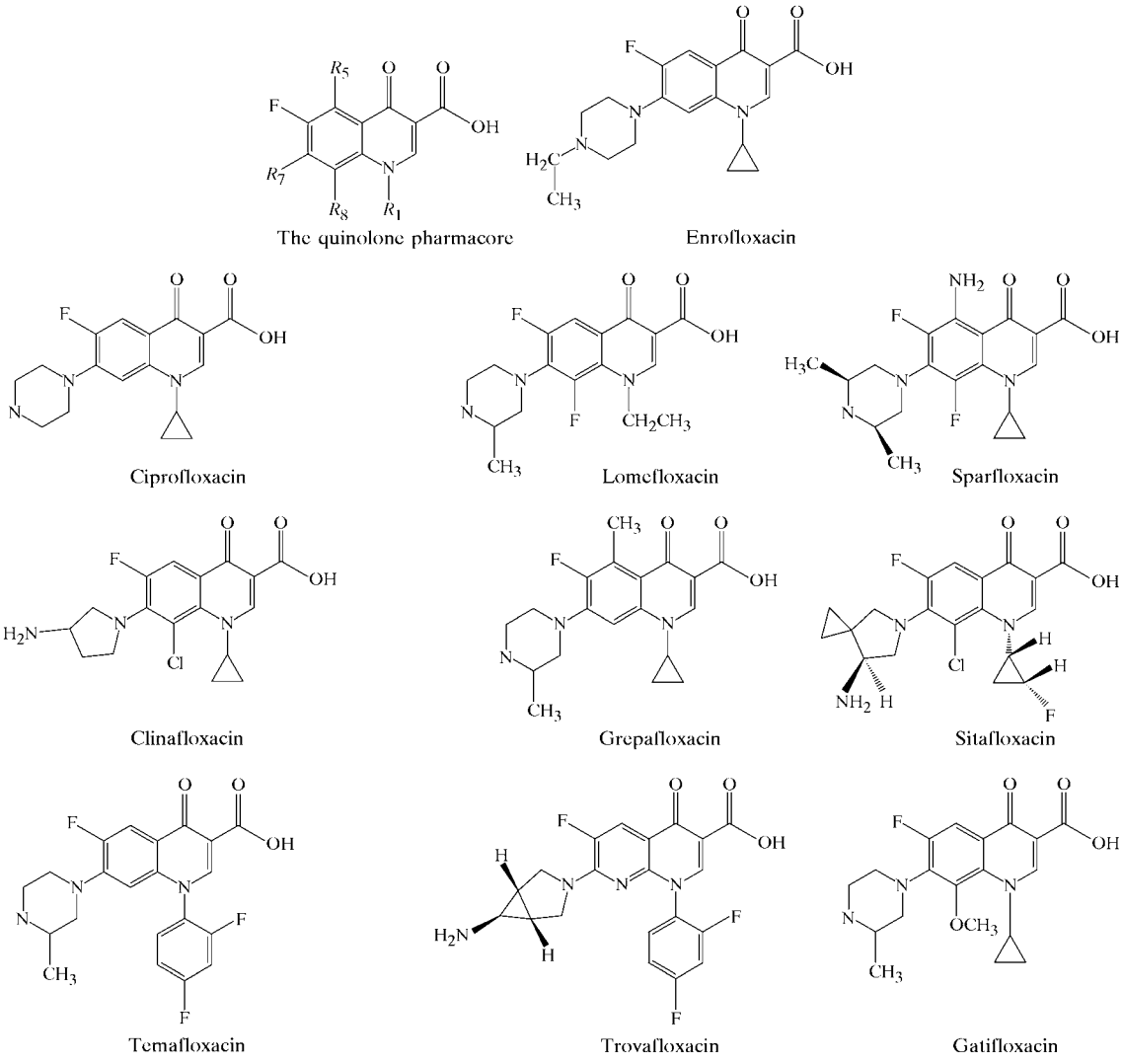

Figure 1
Structural modifications of fluoroquinolones.

side chain. In the unprimed cation, it is rotated so that atom C15 is facing away from the F atom to give a *transoid* arrangement [C6—C7—N2—C15 = 152.9 (4)°], while in the primed cation, this relationship is *cisoid* and the corresponding torsion angle is 17.3 (6)°. It is thus almost as if the piperidinopyrrolidine ring in the unprimed cation has been rotated by 180° to yield the primed cation. This arrangement is further supported by the N2—C15—C16—N3 torsion angle of −154.9 (3)° in the unprimed cation and −84.1 (4)° in the primed cation, perhaps providing the accessibility of the piperidine N atom to hydrogen bonding. This conformational arrangement may be contributing to the different modes of hydrogen bonding in the cations. The orientation of the piperazine ring, one of the smallest substituents observed at C7, has a C6—C7—N2—C15 torsion angle of 67.4° in ciprofloxacin hydrochloride, 58.9 (2)° in 2-hydroxethanaminium enrofloxacin and −73.3 (7)° in sparfloxacin. Atoms N3 and O2, which occupy the two terminal positions of the cation in the title compound, are separated by distances of 11.722 (5) and 11.467 (5) Å for the unprimed and primed cations, respectively. The corresponding distances found in similar antibacterial agents are 11.23 Å (ciprofloxacin hydrochloride), 11.49 and 11.33 Å (ciprofloxacin lactate), 11.39 Å (2-hydroxethanaminium enrofloxacin), 10.83 and 10.99 Å (sitafloxacin sesquihydrate), and 11.23 Å (sparfloxacin). The piperidine ring in (I) adopts a chair conformation with the exposed N atom participating in the hydrogen-bonding interactions. The pyrrolidine ring favours a half-chair conformation twisted on atoms C16–C20 for both cations. An overlay (Fig. 4) of the title compound with other similar antibacterial agents, by superimposing the quinoline systems, reveals the conformational similarities.

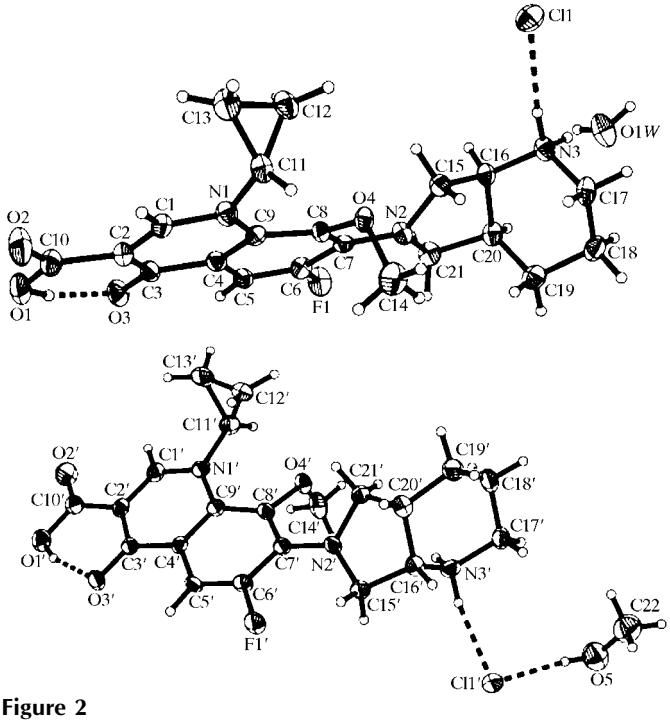

Figure 2
The asymmetric unit of the title compound, showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 30% probability level and H atoms are shown as small spheres of arbitrary radii. Hydrogen bonds are shown as dashed lines.

The methoxy group on atom C8 in moxifloxacin is thought to contribute to enhanced activity and lower selection of resistant mutants of Gram-positive bacteria compared with the C8-unsubstituted analogue (Marutani *et al.*, 1993). The C14—O4 methoxy group is almost perpendicular to the plane of the quinoline ring system [C14—O4—C8—C9 = 95.4 (4) and −80.2 (4)° for the unprimed and primed cations, respectively].

Different modes of hydrogen-bonding interactions, *viz.* cation–cation, cation–water, cation–chloride ion, methanol–chloride ion and water–chloride ion, stabilize the molecules in the crystal structure (Table 1 and Fig. 5) . The two H atoms at atom N3′ of the piperidine ring in the primed cation participate in hydrogen bonding with chloride ions, while in the unprimed cation the corresponding H atoms participate in hydrogen bonding with one chloride ion and with a water molecule. The water molecule acts as a donor in hydrogen

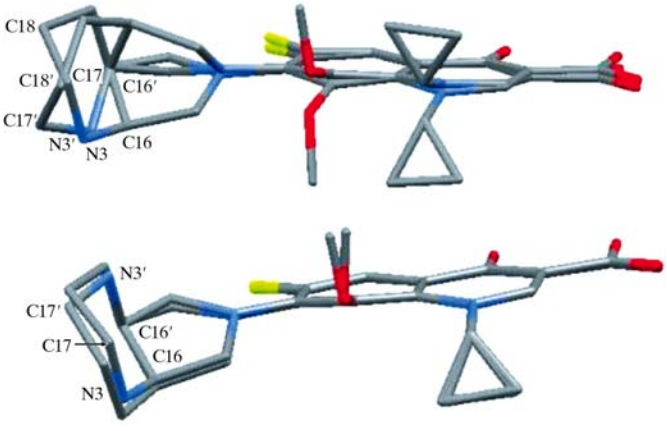

Figure 3
The least-squares fit between the skeletons of the two independent cations in (I) (top) and with the primed cation inverted (bottom). The quinolone ring system was fitted and H atoms were omitted for clarity.

Figure 4
An overlay of the skeletons of some antibacterial molecules, *viz.* the primed cation of (I) (labelled 1), ciprofloxacin hydrochloride (labelled 2), 2-hydroxyethanaminium enrofloxacin (labelled 3) and sitafloxacin sesquihydrate (labelled 4).

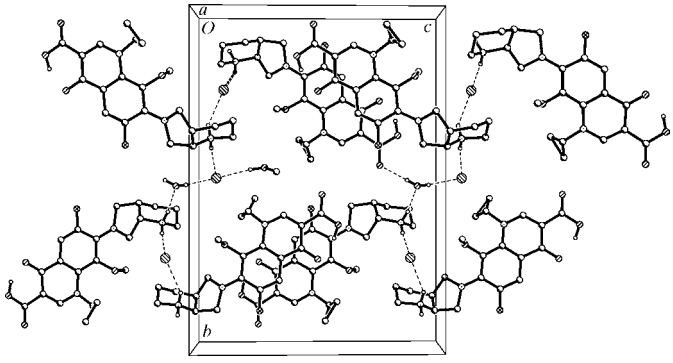

Figure 5
Part of the crystal packing of (I), shown with extracellular molecules to illustrate the water–chloride ion–methanol network. Hydrogen bonds are shown as dashed lines. H atoms not involved in hydrogen bonding have been omitted for clarity.

bonds with a chloride ion and the carbonyl O atom of the carboxylic acid group of the unprimed cation. The methanol molecule forms a hydrogen bond with a chloride ion. Taken together, the hydrogen bonds link all of the components of the structure into extended two-dimensional networks which lie parallel to the $(10\overline{1})$ plane.

The crystal structure of (I) may be viewed in the context of a molecular model for the quinoline–gyrase–DNA complex proposed by Shen *et al.* (1989). According to this model, substituents on atoms N1 and C8 are envisaged as providing the necessary hydrophobic interactions. Binding to DNA is suggested through a hydrogen-bonding domain on the drug comprising the C2 carboxylic acid group and the carbonyl group at C3, while the substituent on atom C7 is involved in drug–enzyme interactions. In (I), the perpendicular orientation of the planes of the cyclopropyl and methoxy groups with respect to that of the quinoline skeleton may possibly be providing the hydrophobic interactions. The coplanar arrangement between the carboxylic acid group and the carbonyl group – the hydrogen-bonding domain of the drug – may be facilitating the required binding to DNA. Despite the presence of a bulky fused bicyclic system substituent on atom C7, the drug–enzyme interaction is possible through the cationic terminal piperidine N atom.

Experimental

To obtain crystals suitable for X-ray studies, moxifloxacin hydrochloride (Neuland Laboratories Ltd, Hyderabad) was dissolved in a methanol–water solution (80:20) and the solution was allowed to evaporate slowly.

Crystal data

$C_{21}H_{25}FN_3O_4^+\cdot Cl^-\cdot 0.5H_2O\cdot 0.5CH_4O$
M_r = 462.92
Monoclinic, $P2_1$
a = 6.828 (2) Å
b = 20.929 (6) Å
c = 15.357 (5) Å
β = 92.007 (5)°
V = 2193.4 (11) Å^3
Z = 4
D_x = 1.402 Mg m^{-3}
Mo $K\alpha$ radiation
μ = 0.22 mm^{-1}
T = 273 (2) K
Block, colourless
0.21 × 0.19 × 0.09 mm

Data collection

Bruker SMART APEX CCD area-detector diffractometer
ω scan
19500 measured reflections
7616 independent reflections
5008 reflections with $I > 2\sigma(I)$
R_{int} = 0.076
θ_{max} = 25.0°

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.049
$wR(F^2)$ = 0.104
S = 0.90
7616 reflections
607 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0384P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.26 e Å^{-3}
$\Delta\rho_{min}$ = −0.24 e Å^{-3}
Absolute structure: Flack & Bernardinelli (2000), 3643 Friedel pairs
Flack parameter: 0.12 (6)

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

D—H···A	D—H	H···A	D···A	D—H···A
N3—H31···O1W	0.913 (18)	1.84 (2)	2.736 (5)	167 (3)
N3—H32···Cl1	0.92 (4)	2.23 (2)	3.149 (4)	174 (4)
O1—H2···O3	0.93 (6)	1.64 (6)	2.487 (4)	150 (5)
N3′—H33···Cl1′	0.905 (19)	2.20 (2)	3.059 (4)	159 (3)
N3′—H34···Cl1^{i}	0.893 (19)	2.48 (3)	3.263 (4)	147 (3)
O1′—H2′···O3′	0.90 (4)	1.68 (4)	2.541 (4)	159 (4)
O5—H51···Cl1′	0.94 (2)	2.27 (2)	3.210 (5)	174 (7)
O1W—H1W···O2^{ii}	0.80 (4)	1.99 (2)	2.790 (5)	169 (5)
O1W—H2W···Cl1′^{ii}	0.84 (4)	2.30 (2)	3.126 (4)	171 (6)

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

All O- and N-bound H atoms were located in a difference electron-density map and refined with O—H bond-length restraints of 0.82 (2) (water molecule) and 0.92 (2) Å (carboxylic acid and methanol), and N—H bond-length restraints of 0.90 (2) Å. H atoms attached to C atoms were positioned geometrically and refined as riding atoms [aromatic C—H = 0.93 Å, methine C—H = 0.98 Å and methylene C—H = 0.97 Å, with U_{iso}(H) = 1.2U_{eq}(C), and methyl C—H = 0.96 Å, with U_{iso}(H) = 1.5U_{eq}(C)]. The methyl groups were allowed to rotate but not to tip. The absolute configuration of the procured material was known in advance and was confirmed by unambiguous refinement of the absolute structure parameter (Flack & Bernardinelli, 2000).

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: *SHELXTL/PC* (Sheldrick, 1990) and *MERCURY* (Macrae *et al.*, 2006); software used to prepare material for publication: *SHELXL97*.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: LN3009). Services for accessing these data are described at the back of the journal.

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