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A novel oxazolidinone antibiotic: RWJ-416457

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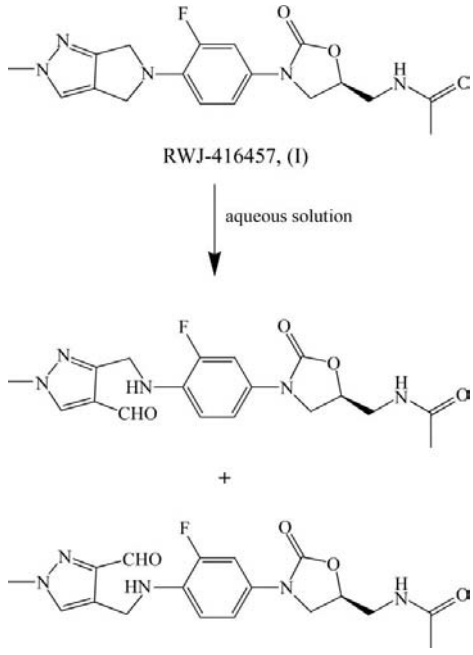
The crystal structure of the antibiotic drug candidate RWJ-416457 (systematic name: *N*-{(5*S*)-3-[4-(5,6-dihydro-2*H*,4*H*-2-methylpyrrolo[3,4-*c*]pyrazol-5-yl)-3-fluorophenyl]-2-oxo-1,3-oxazolidin-5-yl}acetamide), $C_{18}H_{20}FN_5O_3$, which belongs to the first new class of antibiotics discovered in the past 30 years, has been determined at 150 K. Each molecule of this drug donates one hydrogen bond to a neighboring molecule and accepts one hydrogen bond to give $(O{=}C{-}R{-}N{-}H\cdots O{=}C{-}R{-}N{-}H\cdots)_n$ linkages along the *b*-axis direction. The compound contains a pyrrolopyrazole ring, which, owing to its uncommon structure, has been shown to have particular effectiveness against multi-drug-resistant bacteria.

Comment

The title compound, RWJ-416457, (I) (Foleno *et al.*, 2007), belongs to the oxazolidinone class of compounds, which are the first new class of antibiotics discovered in the past 30 years (Dresser & Rybak, 1998). Compound (I) is a novel antibiotic drug candidate which inhibits the growth of Gram-positive clinical pathogens, including health-care-associated methicillin-resistant *Staphylococcus aureus* (MRSA). Although prone to oxidation in aqueous solution, (I) is stable to oxidation as a crystalline solid. Compound (I) degrades *via* an oxidative mechanism in solution to give ring-opened species of the pyrrolopyrazole. The degradation is enhanced at lower pH and in the presence of metals such as copper and iron. Particular care was taken during characterization of the drug substance to analyze for trace metals. Crystals of the title compound were grown from a mixture of dimethyl sulfoxide (DMSO) and water.

Compound (I) (Fig. 1) has two carbonyl O atoms that can serve as hydrogen-bond acceptors and one secondary amide N atom that can act as a hydrogen-bond donor. It is found in the crystal structure that each molecule of (I) donates one N—H hydrogen bond to a neighboring molecule and accepts one hydrogen bond. Together, the intermolecular interactions form $(O{=}C{-}R{-}N{-}H\cdots O{=}C{-}R{-}N{-}H\cdots)_n$ linkages along the *b*-axis direction (Fig. 2). The urethane carbonyl group of the oxazolidinone ring accepts the N—H hydrogen bond; the secondary amide carbonyl group is not involved in hydrogen bonding. There is no evidence of F···F short contacts, or C—H···π or π–π interactions between the aromatic rings.



Compound (I) is optically pure from the chemical synthesis, being assembled from the enantiopure chiral starting material of the oxazolidinone ring (*S* configuration at the lone chiral center on the molecule). This oxazolidinone ring is known to be a key component of the antibacterial properties of the compound. Unique to compound (I) is its pyrrolopyrazole ring system (Table 1). A search of the Cambridge Structural Database (CSD; Version 1.11 of September 2009; Allen, 2002) for the pyrrolopyrazole ring system indicated that this moiety has not been previously characterized structurally. The rarity of this ring system is a likely contributor to the effectiveness of the molecule in combating bacteria that show resistance to

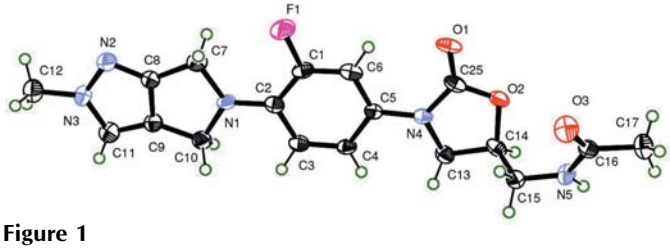


Figure 1
A view of the molecule of (I), showing the atom-numbering scheme. Anisotropic displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii.

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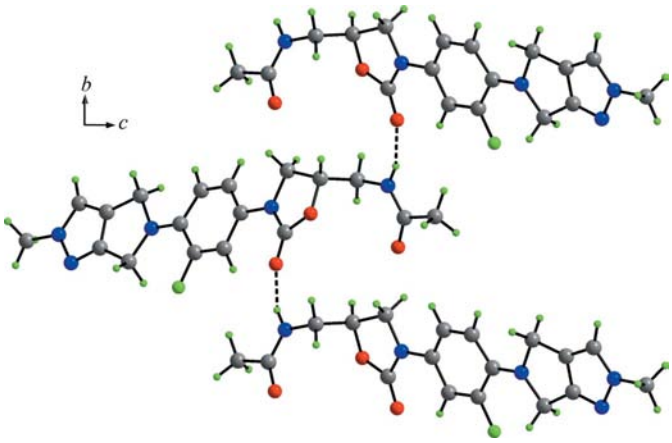

Figure 2
Hydrogen bonding in the RWJ-416457 crystal, forming a simple linear motif [graph set $C(7)$].

other treatments (Foleno *et al.*, 2007). This bicyclic eight-membered ring is also highly reactive, as observed from its solution chemistry in which ring opening occurs when the N1—C7 or N1—C10 bonds break. The degradation products are reactive aldehydes, which are susceptible to nucleophilic addition. Within living cells, the presence of aldehydes is undesirable, and these degradation products may alter the antibacterial nature of the compound.

One key observation for (I) is its long-term chemical stability as a crystalline material compared with its short solution half-life. The layers of hydrogen-bonded molecules likely act as protective barriers against oxygen attack on the bicyclic ring. Large-scale molecular motions are also forbidden in the solid state, so the cleavage of the pyrrolo-pyrazole ring and rearrangement to the aldehydes is less favorable. The molecule is free of such constraints in solution, resulting in rapid degradation of the compound.

The crystalline form of this compound provides further stability because of its low solubility in water. At 5.8 ng ml^{-1}, the equilibrium solubility does not allow for significant amounts of compound to be in solution at any given time. Dissolved drug substance is a requirement for the solution-mediated degradation pathway. The crystalline drug has a further advantage because crystallization also acts as a purification step in removing metals and acid, which can persist beyond the final synthetic step, causing degradation of the drug candidate during its shelf-life. In light of the solution deficiencies of this compound, the drug in its crystalline form is therefore essential for stable storage as a drug candidate in the clinic.

Experimental

RWJ-416457 (75.4 mg; 0.20 mol) was added to DMSO (1 ml, 0.63 mol) in water at 353 K. Malonic acid (1.186 g, 11.39 mol) was added to the solution to increase the solubility of (I). The solution of (I) and malonic acid was passed through a 0.2 µm filter and the filtrate was left to cool in a glass vial at room temperature. Single crystals of the title compound appeared after 1 d.

Crystal data

$C_{18}H_{20}FN_5O_3$
M_r = 373.39
Monoclinic, $P2_1$
a = 4.8358 (17) Å
b = 10.293 (4) Å
c = 17.403 (6) Å
β = 97.524 (10)°
V = 858.7 (5) Å^3
Z = 2
Mo $K\alpha$ radiation
μ = 0.11 mm^{-1}
T = 150 K
0.31 × 0.04 × 0.01 mm

Data collection

Bruker–Nonius Kappa APEXII CCD diffractometer
Absorption correction: multi-scan (*APEX2*; Bruker, 2006)
T_{min} = 1.00, T_{max} = 1.00
5186 measured reflections
1725 independent reflections
1180 reflections with $I > 2\sigma(I)$
R_{int} = 0.041
Standard reflections: 0

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.049
$wR(F^2)$ = 0.087
S = 0.96
1725 reflections
245 parameters
1 restraint
H-atom parameters constrained
$\Delta\rho_{max}$ = 0.52 e Å^{-3}
$\Delta\rho_{min}$ = −0.49 e Å^{-3}

Table 1
Selected bond lengths (Å).

N1—C10	1.472 (7)	C7—C8	1.504 (8)
N2—N3	1.356 (7)	C8—C9	1.378 (8)
N2—C8	1.343 (7)	C9—C11	1.376 (8)
N3—C11	1.348 (7)		

Structure determination of (I) was initiated in space group $P2_1$ as indicated from the observed metric constants, intensity statistics and systematic absences. Subsequent structure solution and refinement confirmed this choice; however, least-squares refinement failed to improve $R1 < 17\%$ for $F^2 > 2\sigma(F^2)$. Twinning was suspected, and close inspection of the frames for the full data collection revealed a number of extra reflections that did not overlap with the original unit cell. Domain searching analysis using *ROTAX* (Cooper *et al.*, 2002) revealed a twin law [0.998, 0, $\overline{0.005}$/0, $\overline{1}$, 0/$\overline{0.999}$, 0, $\overline{0.998}$], as well as an optimized 'twin tolerance' parameter of 0.022 Å^{-1}, which identified the overlapping and separate reflections from the two domains (Cooper *et al.*, 2002). The analysis and successful refinement demonstrated that the crystal was a twin lattice quasi-symmetry twin (Donnay & Donnay, 1974; Giacovazzo, 1992) with a rotation about [102] and small twin obliquity (Donnay & Donnay, 1972), ω = 0.46°. Scale factors for the two twin components were constrained to sum to 1.0, with the value of the major twin component scale refining to 0.8037 (17). Least-squares refinement of the data on F^2 using this twin law led to significant improvement [$R1$ = 4.9% for $F^2 > 2\sigma(F^2)$]. In an attempt to improve the data, *CELL_NOW* (Sheldrick, 2003) was run on the original data, yielding a numerically identical twin law. The data were integrated using the two-domain .p4p file, and *TWINABS* (Sheldrick, 2002) was used to generate HKLF4 and HKLF5 files. The refinement using these files was not significantly different, with marginally higher R values, from that using the *ROTAX* procedure described above, and thus the original refinement was retained. The molecules are ordered and closely packed (Kitaigorodskii packing index KPI = 71.4%) (Spek, 2009).

After location in electron-density difference maps, H atoms were first regularized with the use of restraints [C—H = 0.93 (2)–0.98 (2) Å, N—H = 0.86 (2) Å, H—C—H = 109.5 (20)°, H—N—H restrained to be equal ±2° and U_{iso}(H) = 1.2–1.5U_{eq} ±0.002 Å^2 of the parent atom], after which the positions were refined as riding.

Data collection: *APEX2* (Bruker, 2006); cell refinement: *APEX2*; data reduction: *APEX2*; program(s) used to solve structure: *SHELXS86* (Sheldrick, 2008); program(s) used to refine structure: *CRYSTALS* (Betteridge *et al.*, 2003); molecular graphics: *DIAMOND* (Crystal Impact, 2009); software used to prepare material for publication: *publCIF* (Westrip, 2010).

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: MX3027). Services for accessing these data are described at the back of the journal.

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