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3-(4-Fluorophenyl)-1-methyl-4-(4-pyridyl)-quinolin-2(1*H*)-one

Christian Peifer,[a]* Dieter Schollmeyer,[b] Katrin Kinkel[a] and Stefan Laufer[a]

[a]Pharmazeutisches Institut, Auf der Morgenstelle 8, Universität Tübingen, 72076 Tübingen, Germany, and [b]Institut für Organische Chemie der Universität Mainz, Duesbergweg 10-14, 55099 Mainz, Germany

Correspondence e-mail: christian.peifer@uni-tuebingen.de

Key indicators

Single-crystal X-ray study
T = 193 K
Mean σ(C–C) = 0.002 Å
R factor = 0.049
wR factor = 0.164
Data-to-parameter ratio = 17.2

For details of how these key indicators were automatically derived from the article, see http://journals.iucr.org/e.

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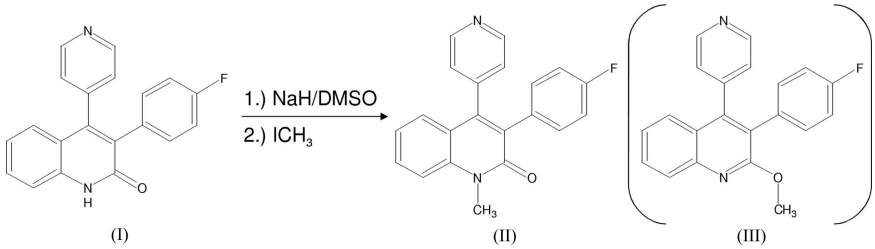
The title compound, $C_{21}H_{15}FN_2O$, was synthesized in the course of our studies of p38 mitogen-activated protein kinase inhibitors. It has been investigated by ^1H and ^{13}C NMR spectroscopy and was proven by X-ray crystallographic analysis to be the *N*-methyl rather than the *O*-methyl isomer. In the crystal structure, a three-dimensional network is formed consisting of quinolinone aromatic stacking interactions and weak C—H···O and C—H···N hydrogen bonds.

Comment

The title compound, (II) (Fig. 1), bearing the vicinal pyridine/4-*F*-phenyl combination as a core structure, was prepared in an approach to develop novel ATP-competitive inhibitors of p38 mitogen-activated protein kinase (p38MAPK; Kumar *et al.*, 2003). Compound (II) was synthesized as a derivative of the biologically active compound (I) (Peifer *et al.*, 2007), which was designed by analogy with p38MAPK inhibitors such as SB203580 (Cuenda *et al.*, 1995). Concerning the binding mode of these compounds in the ATP binding pocket of p38MAPK, the pyridine N atom is considered to accept a hydrogen bond from the Met109 residue, the 4-*F*-phenyl group is situated in a hydrophobic pocket, while the lactam O atom accepts a hydrogen bond from Lys53. In contrast, the NH group is not involved in interactions with p38MAPK (Fig. 2, left-hand side). However, the lactam group of (I) possesses a typical vicinal hydrogen bond donor–acceptor system potentially capable of interacting *via* an alternative binding mode with the hinge region of other kinases (Liao, 2007), such as VEGF-R2 (Fig. 2, right-hand side). Thus, keeping the pyridine/4-*F*-phenyl pharmacophore of (I) but methylating the lactam N atom in order to prevent the hydrogen-bond donor system is of particular interest in our structure–activity relationship studies.



N-Methylamides are commonly prepared by the reaction of methyl iodide with the salt of the amide. In this study, compound (II) was synthesized *via* deprotonation of (I) followed by addition of MeI (see scheme). Since (I), as a cyclic amide, exhibits keto–enol tautomerism, methylation of

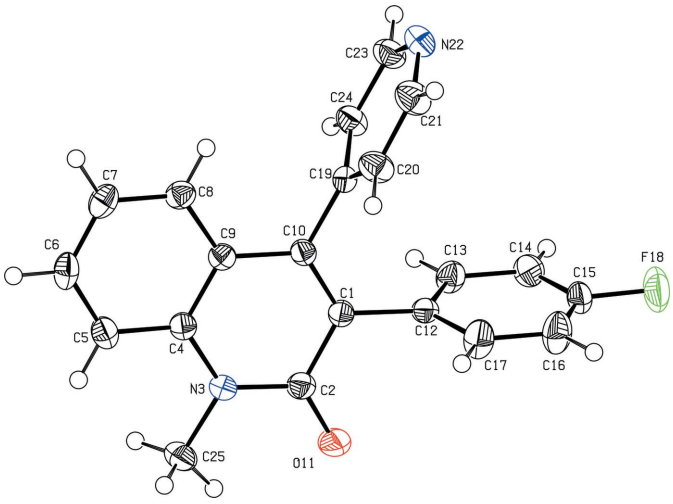


Figure 1
The molecular structure of (II). Displacement ellipsoids are drawn at the 50% probability level and H atoms are depicted as circles of arbitrary size.

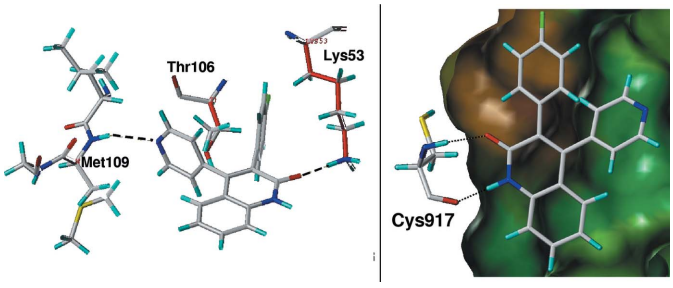


Figure 2
The modelled binding mode (*SYBYL*; Tripos Associates Inc., 1996) of (I) in the ATP binding pocket of p38MAPK (left-hand side; PDB code 1CM8) and VEGF-R2 (right-hand side; PDB code 1YWN). Key amino acid residues and significant hydrogen-bond interactions (dashed lines) are shown.

deprotonated (I) could lead to (II) or (III) (Kazuko *et al.*, 1980). A selective method for *N*-methylation of amides and lactams has been published (Bassindale *et al.*, 2000). However, in this study, we used the simple technique for methylation, and it was difficult by NMR analysis to conclude whether (II) is the *N*-methyl or the methoxy derivative. X-ray crystallographic analysis was thus useful to prove that the compound is the *N*-methyl isomer.

Concerning the molecular geometry of (II), we found the 1-methylquinolin-2(1*H*)-one core-defining pyridine/quinolinone with an exocyclic bond angle of 120.83 (14)° (C1⋯C10—C19) and 4-*F*-phenyl/quinolinone with an angle of 121.93 (14)° (C10⋯C1—C12). The corresponding exocyclic bond angles for (I) are 120.13 (17) and 123.35 (17)° (Peifer *et al.*, 2006), indicating that the methylation has a minor impact on the molecular geometry of (II). However, the dihedral angle between the planes of the pyridine (C19–C24) and quinolinone (C1/C2/O11/N3/C4–C10) systems is 70.08 (8)° in (I) *versus* 88.17 (7)° in (II), probably as a consequence of different crystal packing. In the crystal structure of (II), aromatic stacking interactions of symmetry-related quinolinone groups, with a distance of 3.706 (3) Å (centroid-to-centroid of rings C4–C9), and weak hydrogen bonds (Table 1) are formed (Fig. 3).

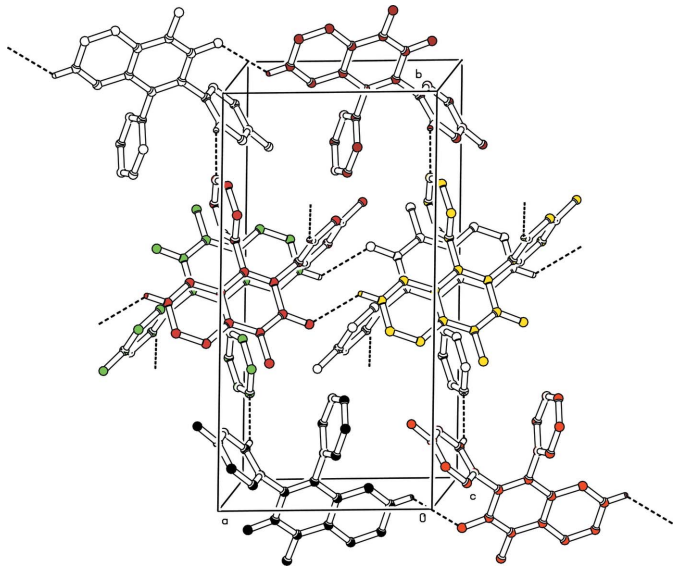


Figure 3
Part of the packing diagram of (II). Dashed lines indicate hydrogen bonds. Only important H atoms are shown. Symmetry-related molecules are drawn in different colours to indicate clearly the molecular connectivity.

Experimental

A dry three-necked round-bottomed flask was charged with (I) (1 mmol) and NaH (60%; 85 mg) in dry dimethyl sulfoxide (5 ml) under an Ar stream. The mixture was stirred at room temperature for 30 min and then MeI (0.11 ml) was added. The progress of the reaction was monitored by thin-layer chromatography until all starting material (I) disappeared, to form solely (II) {ethyl acetate–hexanes 3:1 *v*/*v*; R_f[(II)] = 0.4, R_f[(I)] = 0.3}. After 30 min, water (10 ml) was added, and the mixture was extracted with ethyl acetate (20 ml), dried over Na_2SO_4 and evaporated. The residue was purified by flash column chromatography using ethyl acetate–hexanes (2:1 *v*/*v*) to yield 94% of (II). Crystals of (II) suitable for X-ray crystallographic analysis were grown at 278 K as colourless blocks from an ethanol solution, by slow evaporation.

Crystal data

$C_{21}H_{15}FN_2O$
M_r = 330.36
Monoclinic, $P2_1/n$
a = 9.3217 (6) Å
b = 18.1539 (11) Å
c = 9.9297 (7) Å
β = 105.259 (4)°
V = 1621.12 (18) Å^3
Z = 4
Mo $K\alpha$ radiation
μ = 0.09 mm^{-1}
T = 193 (2) K
0.49 × 0.24 × 0.09 mm

Data collection

Bruker SMART APEX2 CCD area-detector diffractometer
Absorption correction: multi-scan (*CORINC*; Dräger & Gattow, 1971)
T_{min} = 0.939, T_{max} = 0.992
10801 measured reflections
3895 independent reflections
2765 reflections with $I > 2\sigma(I)$
R_{int} = 0.042

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.049$	227 parameters
$wR(F^2) = 0.164$	H-atom parameters constrained
$S = 1.04$	$\Delta\rho_{max} = 0.28$ e Å^{-3}
3895 reflections	$\Delta\rho_{min} = -0.24$ e Å^{-3}

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

D—H···A	D—H	H···A	D···A	D—H···A
C7—H7···O11^{i}	0.95	2.58	3.282 (2)	130
C13—H13···N22^{ii}	0.95	2.60	3.387 (2)	141

Symmetry codes: (i) $x+1, y, z$; (ii) $x-\frac{1}{2}, -y+\frac{3}{2}, z-\frac{1}{2}$.

H atoms were placed in calculated positions and refined with C—H bond lengths constrained to 0.95 (aromatic CH) or 0.98 Å (methyl CH_3), and with $U_{iso}(H) = 1.5U_{eq}(C)$ for the methyl group or $1.2U_{eq}(C)$ otherwise.

Data collection: *APEX2* (Bruker, 2006); cell refinement: *APEX2*; data reduction: *APEX2*; program(s) used to solve structure: *SIR92* (Altomare *et al.*, 1994); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *ORTEPII* (Johnson, 1976) and *SYBYL* (Tripos Associates Inc., 1996); software used to prepare material for publication: *SHELXL97* and *PLATON* (Spek, 2003).

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