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

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Key indicators

Single-crystal X-ray study
T = 193 K
Mean σ(C–C) = 0.003 Å
R factor = 0.047
wR factor = 0.125
Data-to-parameter ratio = 12.8

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

The title compound, $C_{20}H_{13}FN_2O$, has the quinolin-2(1*H*)-one unit in the lactam form. The molecules form rows along the *b* axis *via* N—H···N hydrogen bonds

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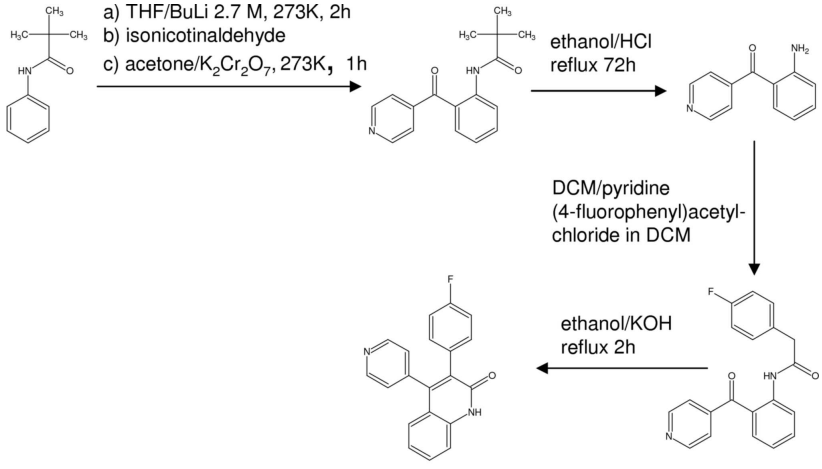
Comment

The title compound, (I), bearing the 3,4-diarylquinolin-2(1*H*)-one system as a core structural element was prepared in an approach to synthesize a novel ATP-competitive inhibitor of p38 mitogen-activated protein kinase (p38MAPK), a well characterized drug target in cytokine signalling pathways involved in the inflammatory process (Kumar *et al.*, 2003). Compound (I) was designed by analogy to first-generation p38MAPK inhibitors such as compound SB203580 (Cuenda *et al.*, 1995). Prototypical pyridinyl/fluorphenyl imidazole inhibitors such as SB203580 consist of a central pharmacophore, which is the vicinal pyridine/fluorphenyl system, connected to a five-membered ring (Peifer *et al.*, 2006).



(I)

In this study, we replaced the five-membered ring by a 3,4-diarylquinolin-2(1*H*)-one unit to study the impact of the modified molecular geometry on inhibitory activity towards the kinase. Among the number of synthetic methods for preparing 3,4-diarylquinolin-2(1*H*)-one (Kadnikov & Larock, 2004; Fuerstner & Hupperts, 1995), ring closure to form the quinolin-2(1*H*)-one system was achieved in high yield in this synthesis by a Knoevenagel reaction (see scheme). However, the crystal structure analysis revealed that the quinolin-2(1*H*)-one unit adopts the lactam form (see Fig. 1) and not the tautomeric 3-(4-fluorophenyl)-4-(4-pyridyl)quinolin-2-ol form.

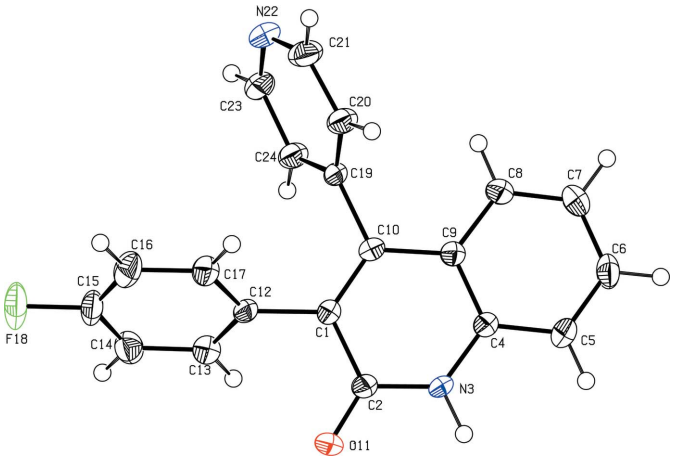


Figure 1
ORTEPII (Johnson, 1976) perspective view of (I). Displacement ellipsoids are drawn at the 50% probability level. H atoms are depicted as circles of arbitrary size.

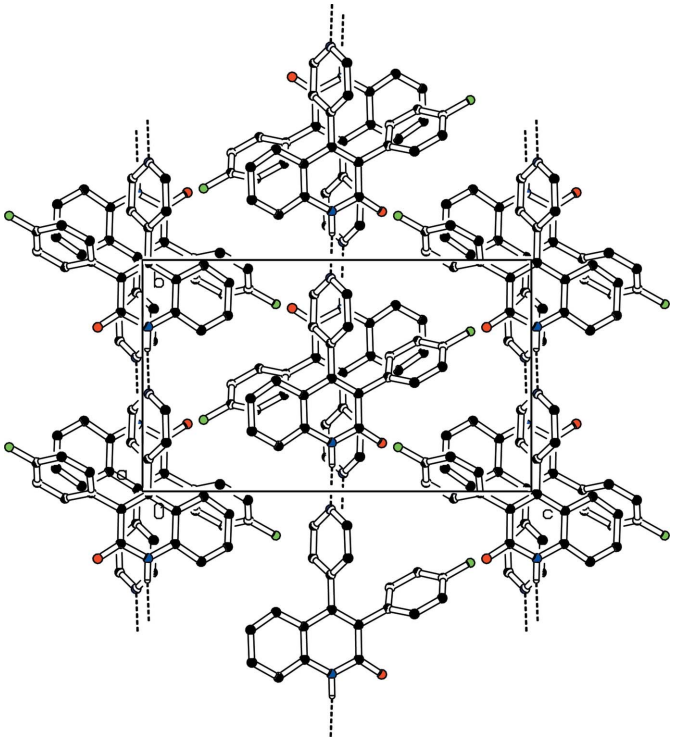


Figure 2
A packing diagram for (I), viewed along the *a* axis. Dashed lines indicate hydrogen bonds. Only H atoms bonded to nitrogen are shown.

The NH group forms an intermolecular hydrogen bond to the pyridine N atom. As a result, the molecules form rows parallel to the *b* axis (see Fig. 2). The pyridine N atom is considered to accept a hydrogen bond of amino acid residue Met109 in the ATP-binding pocket of p38MAPK by anology to the aminopyrimidine group of the original substrate ATP (see Fig. 3). Thus, this hydrogen bond is of particular interest in the light of our molecular modelling studies with this compound.

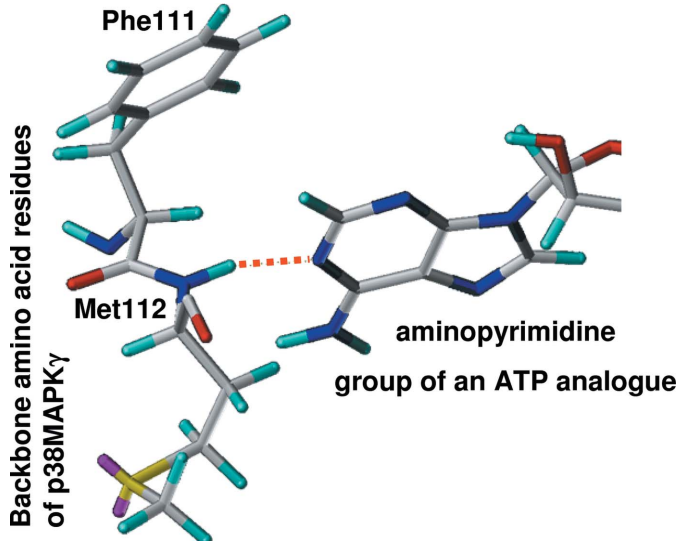


Figure 3
The crystal structure of an ATP-analogue in the ATP-binding pocket of p38MAPK-gamma (pdb code: 1CM8). A significant hydrogen-bond interaction is shown from Met112 to the aminopyrimidine group of the ATP analogue with a distance of 1.88 Å; for clarity, Met112 is equivalent to Met109 in p38MAPK-alpha, however, p38MAPK-gamma was used as a homologous model because no adequate data exist for p38MAPK-alpha.

Experimental

N-Pivaloylaniline (1.063 g, 6 mmol) was dissolved in dry tetrahydrofuran (THF) under an argon athmosphere and cooled to 273 K. At this temperature, 4.5 ml of a solution of *n*-BuLi (2.7 *M* in heptane) was added dropwise. After stirring 2 h in an ice bath, isonicotinaldehyde (1.070 g, 10 mmol) isonicotinaldehyde in THF (5 ml) was added and the reaction stirred overnight. Purification yielded a colourless thick oil, which was immediately used for Jones oxidation. The oil was dissolved in acetone, cooled in an ice bath, and the Jones reagent was added dropwise until the colour remained red. After stirring for 1 h, the whole mixture was extracted over a short column of silica gel and used for deprotection in 100 ml ethanol/10 ml concentrated HCl, which was refluxed for 72 h to yield (2-aminophenyl)(pyridin-4-yl)methanone. (4-Fluorophenyl)acetic acid (154 mg, 1 mmol) and PCl_5 (210 mg, 1 mmol) in dichloromethane (DCM, 4 ml) were stirred overnight. The reaction was then cooled to 273 K and a solution of 200 mg of (2-aminophenyl)(pyridin-4-yl)methanone in 5 ml dry DCM/100 mg dry pyridine was added. After stirring overnight, work-up gave 2-(4-fluorophenyl)-*N*-(2-isonicotinoylphenyl)acetamide. This compound was dissolved in 30 ml ethanol/50 mg KOH and refluxed for 2 h to yield the title compound. Crystals suitable for analysis were obtained by slow evaporation of an ethanol solution of (I).

Crystal data

$C_{20}H_{13}FN_2O$
M_r = 316.33
Monoclinic, $P2_1/n$
a = 9.434 (5) Å
b = 9.9087 (16) Å
c = 16.789 (9) Å
β = 97.32 (3)°
V = 1556.7 (12) Å^3
Z = 4
D_x = 1.350 Mg m^{-3}
Cu $K\alpha$ radiation
μ = 0.76 mm^{-1}
T = 193 (2) K
Needle, colourless
0.32 × 0.10 × 0.10 mm

Data collection

Enraf–Nonius CAD-4 diffractometer
$\theta/2\omega$ scans
Absorption correction: none
2956 measured reflections
2956 independent reflections
2184 reflections with $I > 2\sigma(I)$
$\theta_{max} = 69.9^{\circ}$
3 standard reflections
frequency: 60 min
intensity decay: 4%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.047$
$wR(F^2) = 0.125$
$S = 1.02$
2956 reflections
231 parameters
Only H-atom displacement parameters refined
$w = 1/[\sigma^2(F_o^2) + (0.0544P)^2 + 0.4397P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max} = 0.19$ e Å^{-3}
$\Delta\rho_{min} = -0.24$ e Å^{-3}

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

D—H···A	D—H	H···A	D···A	D—H···A
N3—H3···N22^{i}	0.94 (3)	1.93 (3)	2.867 (2)	174 (1)

Symmetry code: (i) $x, y-1, z$.

H atoms were placed at calculated positions (except for H3, which was located in a Fourier map). The individual U_{iso} values were refined freely. Positional parameters were refined using a riding-motion model (C—H = 0.95 Å). The distance N3—H3 was refined.

Data collection: *CAD-4 Software* (Enraf–Nonius, 1989); cell refinement: *CAD-4 Software*; data reduction: *CORINC* (Dräger & Gattow, 1971); program(s) used to solve structure: *SIR92* (Altomare *et al.*, 1994); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *PLATON* (Spek, 2005); software used to prepare material for publication: *SHELXL97*.

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