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4-[5-(4-Fluorophenyl)-3-isopropylisoxazol-4-yl]-pyridine

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Key indicators

Single-crystal X-ray study
T = 293 K
Mean σ(C–C) = 0.003 Å
R factor = 0.056
wR factor = 0.150
Data-to-parameter ratio = 17.7

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

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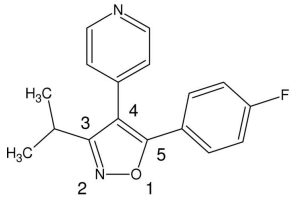
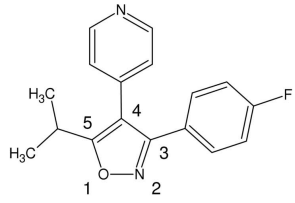
In the title compound, $C_{17}H_{15}FN_2O$, the exocyclic bond angles at the C atoms of the isoxazole ring bearing the pyridyl and 4-fluorophenyl substituents are 129.66 (17) and 134.58 (16)°, respectively. The structure was determined in a study of the molecular geometry of isoxazole derivatives with biological activity as MAPK inhibitors.

Comment

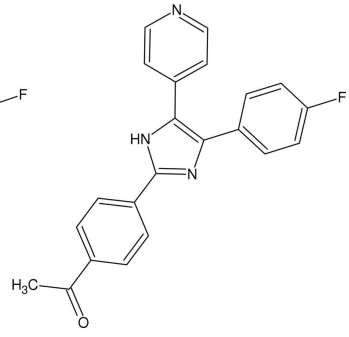
In this study, the title compound, (I), bearing a 4,5-diarylisoxazole group as a core component, was prepared as an isomer of the 3,4-diarylisoxazole [(II); Peifer, Abadleh *et al.*, 2006] (see scheme 1), an ATP-competitive inhibitor of p38 mitogen-activated protein kinase (p38MAPK). This kinase is considered to be a validated drug target in inflammatory processes and therefore inhibitors of p38MAPK provide therapeutic benefit (Boldt & Kolch, 2004; Lee *et al.*, 1994).



(I)



(II)



SB203580

Most small-molecule inhibitors such as the first-generation compound SB203580 (Cuenda *et al.*, 1995) are ATP-competitive ligands to the ATP binding site of MAPK and they consist of a central pharmacophore which, in a basic concept, is the vicinal pyridine/fluorophenyl system connected to a five-membered ring (Peifer, Wagner & Laufer, 2006). However, by testing (I) and (II) in the *in vitro* p38-alpha MAPK assay (Laufer *et al.*, 2005), both compounds were found to possess biological activity. Since the pharmacophore is bound to the isoxazole system in isomer (I) at the 4,5- and in (II) at the 3,4-positions, we were particularly interested to evaluate the molecular geometry of the compounds using X-ray crystallography. Analysis of these structures revealed that compound (I) (Fig. 1) has exocyclic bond angles of 129.66 (17) (C4—C5—C15) and 134.58 (16)° (C5—C4—C9), whereas compound (II) has corresponding exocyclic bond angles of 129.9 (2) and 130.0 (2)° (Peifer, Abadleh *et al.*, 2006). The consequence is a different distance between the aromatic systems, *e.g.* from

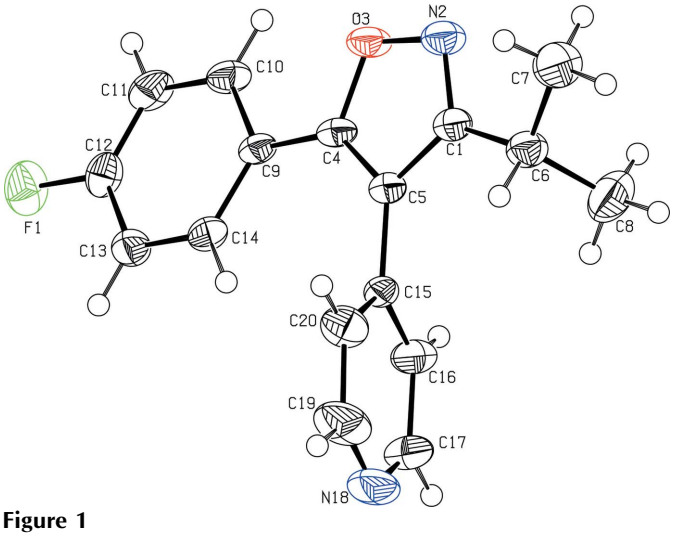


Figure 1
The molecular structure of (I). Displacement ellipsoids are drawn at the 50% probability level. H atoms are depicted as circles of arbitrary size.

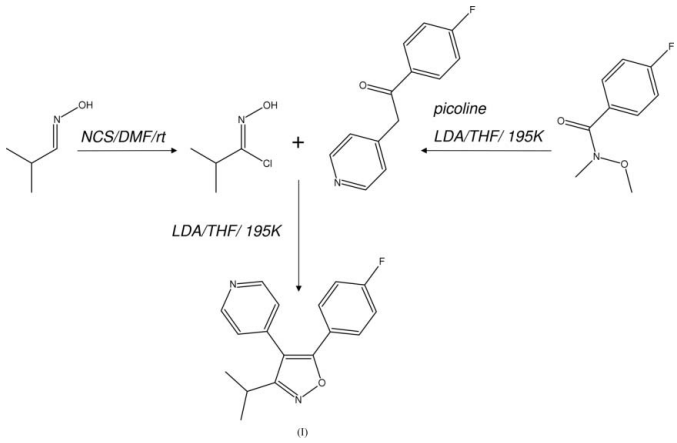
pyridine (py) N (N18) to F (F1), the distance is 8.14 Å in (I) and 7.96 Å in (II). In both (I) and (II), the aromatic six-membered rings are twisted relative to each other, with a dihedral angle of 76.30 (7)° in (I) and 76.3 (1)° in (II). However, SB203580 in its complex with p38-α MAPK has exocyclic bond angles of 131.5 and 131.4°, and a $N_{py}\cdots F$ distance of 8.28 Å, and the 4-*F*-phenyl and pyridine rings have a dihedral angle of 72.4° (pdb code 1A9u; Wang *et al.*, 1998). Therefore, compounds (I) and (II), with comparable molecular geometry to SB203580 and biological activity for p38-alpha MAPK, demonstrate that the isoxazole ring is favorable for ligand-protein interactions. These results may be useful in molecular modeling of ligand-protein docking.

Experimental

For the synthesis of isobutyryl chloride oxime (see scheme 2), isobutyraldehyde oxime (69 mmol) was dissolved in DMF (10 ml) at room temperature (rt), *N*-chlorosuccinimide (NCS, 50 mmol) was added slowly and the reaction mixture was stirred at rt for 2 h. The reaction was quenched by adding water and the mixture extracted with diethyl ether (200 ml). The organic phase was washed with cold brine three times and separated, dried over Na_2SO_4 and kept at 278 K, whereupon a white solid precipitated, yielding 95% of isobutyryl chloride oxime.

For the synthesis of 1-(4-fluorophenyl)-2-pyridin-4-ylethanone, diisopropylamine (138 mmol) in THF (150 ml) was cooled to 195 K under argon, *n*-butyllithium (1.6 *M* in hexanes, 50 ml) was added and the mixture stirred for 1 h (preparation of LDA). Picoline (92 mmol) in THF was added dropwise and, after 1 h, 4-fluoro-*N*-methoxy-*N*-methylbenzamide (92 mmol) in THF was added. The reaction mixture was then warmed to 273 K over a period of 2 h.

Among the number of synthetic methods for preparing 4,5-diarylisoxazoles (Hansen *et al.*, 1980; Dominguez *et al.*, 1996), in this study the ring closure to form the isoxazole ring was conveniently achieved by reaction of 3.8 mmol 1-(4-fluorophenyl)-2-(4-pyridyl)ethanone with 15.2 mmol LDA and 15.2 mmol isobutyryl chloride oxime in THF at 195 K over a period of 3 h. After warming to rt, water was added carefully and the mixture extracted with ethyl acetate (200 ml). The organic phase was separated, dried over Na_2SO_4 and evaporated to give an oil, which was purified by column chromatography (ethyl acetate–hexanes, 4/6) to yield 40% of (I) as a white solid. Crystals of (I) for X-ray analysis precipitated at 278 K from an ethyl acetate solution on slow evaporation.



Crystal data

$C_{17}H_{15}FN_2O$
M_r = 282.31
Monoclinic, $C2/c$
a = 14.1426 (10) Å
b = 11.8646 (9) Å
c = 17.8516 (13) Å
β = 105.475 (4)°
V = 2886.8 (4) Å^3
Z = 8
D_x = 1.299 Mg m^{-3}
Mo $K\alpha$ radiation
μ = 0.09 mm^{-1}
T = 293 (2) K
Block, colorless
0.53 × 0.41 × 0.30 mm

Data collection

Bruker SMART CCD diffractometer
ω scans
Absorption correction: none
11215 measured reflections
3556 independent reflections
1995 reflections with $I > 2\sigma(I)$
R_{int} = 0.130
θ_{max} = 28.4°

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.056
$wR(F^2)$ = 0.151
S = 0.89
3556 reflections
201 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.076P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.23 e Å^{-3}
$\Delta\rho_{min}$ = −0.27 e Å^{-3}

The high R_{int} value is presumably due to a local detector problem which could not be resolved during measurement procedure. H atoms were placed at calculated positions, with C—H = 0.93 (aromatic) or 0.96–0.98 Å (Csp^3), and refined as riding, with U_{iso}(H) = 1.2 or 1.5 times U_{eq}(C).

Data collection: *SMART* (Bruker, 1998); cell refinement: *SAINT* (Bruker, 1998); data reduction: *SAINT*; program(s) used to solve structure: *SIR92* (Altomare *et al.*, 1994); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *PLATON* (Spek, 2003); software used to prepare material for publication: *SHELXL97*.

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