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

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Key indicators

Single-crystal X-ray study
T = 298 K
Mean σ(C–C) = 0.004 Å
Disorder in main residue
R factor = 0.066
wR factor = 0.198
Data-to-parameter ratio = 13.4

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

The molecular structure of the title compound, $C_{17}H_{15}FN_2O$, was determined in the course of our studies on mitogen-activated protein kinase inhibitors. The exocyclic bond angles at the carbon atoms of the isoxazole ring bearing the pyridyl and 4-fluorophenyl rings are 130.0 (2) and 129.2 (2)°, respectively. The pyridine and 4-fluorophenyl rings are twisted relative to the isoxazole ring by 80.2 (2) and 19.1 (1)°, respectively.

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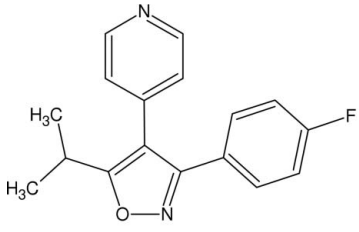
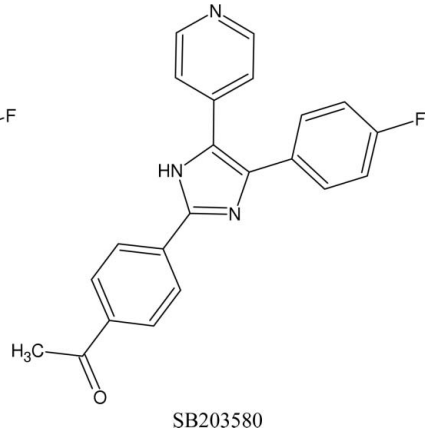
Comment

We have described the background to this work in a previous paper (Peifer *et al.*, 2006), in which the structure of an isomer of the title compound, (I), is reported and the two structures are briefly compared. Mitogen-activated protein kinases (MAPKs) use ATP as cofactor to phosphorylate serine/threonine residues in cytokine signalling pathways such as interleukin-1β and tumor necrosis factor-alpha (Kumar *et al.*, 2003). In humans, to date 11 members of the highly homologous MAPK superfamily have been identified (Boldt & Kolch, 2004). Among them, p38-alpha MAPK and JNK3 are considered in particular to be validated drug targets in inflammatory processes, and therefore inhibitors of these MAPKs provide therapeutic benefit (Lee *et al.*, 1994). Most small-molecule inhibitors such as the first-generation inhibitor SB203580 (see scheme; Cuenda *et al.*, 1995) bind in the ATP binding pocket and, at the molecular level, the pyridine N atom accepts a key hydrogen bond from the protein, while the fluorophenyl group is situated in a hydrophobic pocket, causing selectivity over other protein kinases (Wang *et al.*, 1998; Wilson *et al.*, 1997). Accordingly, the pharmacophore unit is the vicinal pyridine/fluorophenyl system connected to a five-membered heterocycle core.



(I)



SB203580

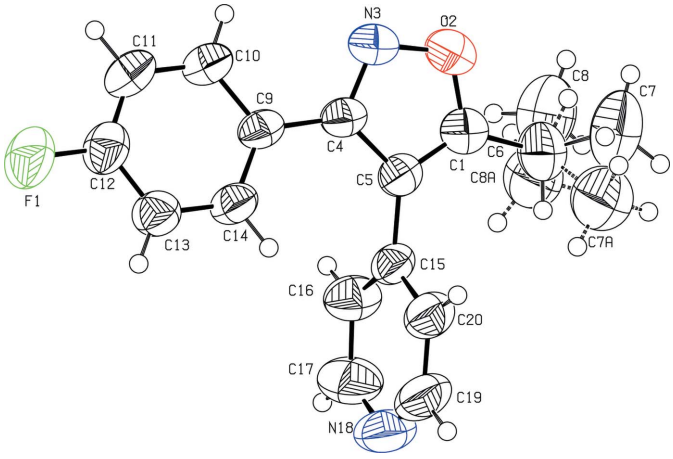


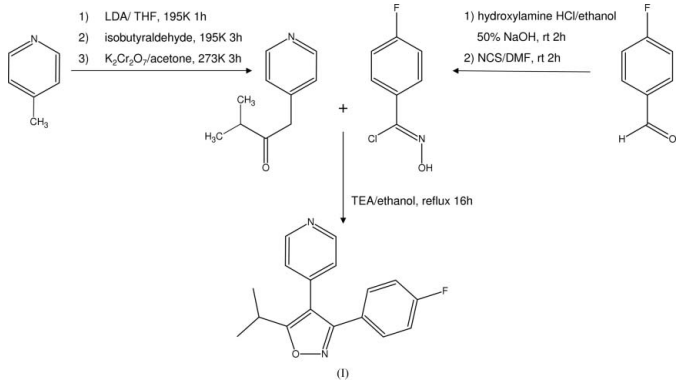
Figure 1
The molecular structure of (I). Displacement ellipsoids are drawn at the 50% probability level. H atoms are depicted as circles of arbitrary size. Both disorder components of the isopropyl group are shown.

As described previously (Peifer *et al.*, 2006), the title compound, (I), and its isomer in which the O and N atoms are exchanged in the isoxazole ring, were designed as ATP-competitive inhibitors in which the central isoxazole unit acts as a carrier for the vicinal pyridine/fluorophenyl pharmacophore. Compound (I) (Fig. 1) has exocyclic bond angles of 130.0 (2)° for C15—C5—C4 and 129.9 (2)° for C5—C4—C9, compared with 134.58 (16) and 129.66 (17)°, respectively, in the isomer. The aromatic 4-fluorophenyl and pyridyl rings are not coplanar but are twisted relative to each other, with a dihedral angle of 76.3 (1)°. Accordingly, compound (I) is shown to have molecular geometry comparable to that of SB203580. Compound (I) was found to be active in the *in vitro* p38MAPK assay (Laufer *et al.*, 2005), indicating that it forms important ligand–protein interactions comparable to SB203580.

Experimental

The synthesis of precursors and the isoxazole ring closure are shown in the reaction scheme below.

For the preparation of 3-methyl-1-pyridin-4-ylbutan-2-one, diisopropylamine (12.0 mmol) in THF (20 ml) and *n*-butyllithium in hexanes (8.25 ml, 1.6 *M*, 1.1 equivalents) were stirred for 1 h at 195 K (preparation of LDA). Picoline (11.0 mmol) in THF (20 ml) was added and stirred for 1 h at 195 K followed by isobutyraldehyde (11.1 mmol) in THF (20 ml), with further stirring for 3 h at this temperature. The reaction was warmed to room temperature (rt), quenched by adding water and the mixture extracted with ethyl acetate (200 ml). The organic phase was separated, dried over Na_2SO_4 and evaporated. The residue was dissolved in 5 ml acetone and Jones' reagent ($K_2Cr_2O_7$) was added dropwise until the colour changed from yellow to brown. The reaction mixture was stirred at rt for 2 h. Purification by flash chromatography using ethyl acetate/hexanes (1:1) yielded 3-methyl-1-pyridin-4-ylbutan-2-one (52%) as a pale-yellow oil. For the preparation of 4-fluorobenzoyl chloride oxime, 4-fluorobenzaldeyde oxime (15.1 mmol) was dissolved in DMF (5 ml). *N*-chlorosuccinimide (NCS, 15.7 mmol) was added and the mixture 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 evaporated. The residue was kept at 278 K, and 4-fluorobenzoyl chloride oxime precipitated as a white solid (yield 95%). Among the number of synthetic methods for preparing 3,4-diarylisoxazoles (Di Nunno *et al.*, 2004), in this study the ring closure to form the isoxazole ring was conveniently achieved by the reaction of 2.5 mmol 3-methyl-1-(pyridine-4-yl)butan-2-one with 4.3 mmol 4-fluorobenzoyl chloride oxime in ethanol (10 ml), catalysed by triethylamine (1 ml). The reaction mixture was stirred for 4 h at rt, then refluxed for 16 h. After cooling to rt, water (50 ml) was added and the mixture extracted with ethyl acetate (200 ml), dried over Na_2SO_4 and evaporated. The oily brown product was purified by column chromatography using ethyl acetate/hexanes (10:1). Crystals of (I) suitable 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 = 15.490 (2) Å
b = 11.4393 (9) Å
c = 17.878 (3) Å
β = 110.838 (7)°
V = 2960.7 (7) Å^3
Z = 8
D_x = 1.267 Mg m^{-3}
Cu $K\alpha$ radiation
μ = 0.73 mm^{-1}
T = 298 (2) K
Needle, colourless
0.51 × 0.16 × 0.16 mm

Data collection

Enraf–Nonius CAD-4 diffractometer
$\omega/2\theta$ scans
Absorption correction: none
2894 measured reflections
2797 independent reflections
2167 reflections with $I > 2\sigma(I)$
R_{int} = 0.017
θ_{max} = 69.9°
3 standard reflections
frequency: 60 min
intensity decay: 5%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.066
$wR(F^2)$ = 0.198
S = 1.05
2797 reflections
209 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.1116P)^2 + 1.374P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.41 e Å^{-3}
$\Delta\rho_{min}$ = −0.24 e Å^{-3}
Extinction correction: *SHELXL97*
Extinction coefficient: 0.0047 (5)

H atoms were placed at calculated positions, with C—H = 0.93–0.98 Å, and refined as riding, with U_{iso}(H) = 1.2 or 1.5U_{eq}(C). The disorderd isopropyl group was refined with bond lengths restrained to 1.540 (5) Å and fixed occupancy factors of 0.8 and 0.2, giving sensible displacement parameters for both components, which were approximated to isotropic behaviour.

Data collection: *CAD-4 Software* (Enraf–Nonius, 1989); cell refinement: *CAD-4 Software*; data reduction: *CORINC* (Dräger *et al.*, 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, 2003); software used to prepare material for publication: *SHELXL97*.

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