organic compounds

4-(4-Fluorophenyl)-2-methyl-3-(1-oxy-4-pyridyl)isoxazol-5(2H)-one

Simona Margutti,[a] Dieter Schollmeyer[b] and Stefan Laufer[a]*

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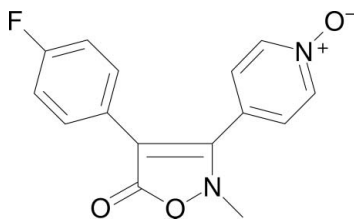Correspondence e-mail: stefan.laufer@uni-tuebingen.de

The crystal structure of the title compound, $C_{15}H_{11}FN_2O_3$, was determined as part of a study on the biological activity of isoxazolone derivatives as p38 mitogen-activated protein kinase (MAPK) inhibitors. The dihedral angles between rings are isoxazole/benzene = 55.0 (3)°, isoxazole/pyridine = 33.8 (2)° and benzene/pyridine = 58.1 (2)°.

Related literature

Isoxazolones as potent inhibitors of p38 MAP kinases were first described by Laughlin et al. (2005). For related literature, see: Adams et al. (1998); Clark et al. (2002); De Laszlo et al. (1998); Foster et al. (2000); Laufer & Wagner (2002); Laufer et al. (2006); Ohkawa et al. (2001); Revesz et al. (2000); Wang et al. (1998).

Experimental

Crystal data

$C_{15}H_{11}FN_2O_3$	$Z = 8$
$M_r = 286.26$	Cu $K\alpha$ radiation
Tetragonal, $P4_32_12$	$\mu = 0.97$ mm^{-1}
$a = 10.0828$ (6) Å	$T = 193$ (2) K
$c = 25.257$ (5) Å	$0.40 \times 0.20 \times 0.10$ mm
$V = 2567.6$ (6) Å^3	

Data collection

Enraf–Nonius CAD-4 diffractometer	1488 independent reflections
Absorption correction: multi-scan (*MULABS*; Blessing, 1995)	1129 reflections with $I > 2\sigma(I)$
$T_{min} = 0.60$, $T_{max} = 0.88$	$R_{int} = 0.081$
5114 measured reflections	3 standard reflections frequency: 60 min intensity decay: 5%

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.068$	191 parameters
$wR(F^2) = 0.192$	H-atom parameters constrained
$S = 1.00$	$\Delta\rho_{max} = 0.45$ e Å^{-3}
1488 reflections	$\Delta\rho_{min} = -0.34$ e Å^{-3}

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, 2003); software used to prepare material for publication: *SHELXL97*.

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supporting information

4-(4-Fluorophenyl)-2-methyl-3-(1-oxy-4-pyridyl)isoxazol-5(2*H*)-one

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S1. Comment

Compound **(II)** (Fig. 2) was prepared in the course of our study on isoxazolones derivatives bearing the typical vicinal 4-pyridyl and 4-fluorophenyl pharmacophores of MAP Kinase inhibitors. Isoxazolones are described in the literature as inhibitors for p38 MAP Kinase (Laughlin *et al.*, 2005; Clark *et al.*, 2002).

The prototypical pyridinylimidazole SB 203580 is one of the best studied p38 inhibitors reported until now. Figure 1 shows the most important interactions between the ATP binding sites of p38 kinase and the imidazole inhibitor SB203580 (Wang *et al.*, 1998). The 4-fluorophenyl ring of SB203580 occupies a hydrophobic back pocket, enhancing selectivity. Vicinal to this interaction site, the 4-pyridinyl ring forms a hydrogen bond from the backbone NH group of Met 109 of p38 MAP Kinase (Fig. 1).

However, certain liver toxicities, such as increased liver size and increased cytochrome P450 induction, have been reported (Foster *et al.*, 2000; Adams *et al.*, 1998). In light of this potential toxicity and the risks associated with developing human drugs, a continuing need exists for potent new small-molecule inhibitors of cytokine production with improved pharmacokinetic and safety profiles.

Several research groups have undertaken studies in which the imidazole ring was replaced by other 5- or 6- membered heterocycles (Laufer & Wagner, 2002; De Laszlo *et al.*, 1998; Laufer *et al.*, 2006; Revesz *et al.*, 2000; Ohkawa *et al.*, 2001). Replacement of the core heterocycle represents a strategy to dissect inhibition of p38 from interferences with cytochrome P450 (CYP450).

Accordingly, and based on the research published by Laughlin *et al.* (2005), we plan to prepare derivatives of isoxazolones in order to obtain more accurate and comparable information about this class of compounds as p38 MAP Kinase inhibitors in terms of biological activity.

The data presented here show the isoxazolone system is almost planar (Fig. 2). It is oriented at a dihedral angle of 55.0 (3)° to the fluorophenyl ring and 33.8 (2)° to the oxy-pyridine system. There are no significant intermolecular interactions.

S2. Experimental

For the synthesis of 2-(4-fluorophenyl)-3-oxo-3-pyridin-4-yl-N-oxide-propionic acid ethyl ester (see Fig. 3), to a suspension of 10 g (72 mmol) of isonicotinic acid N-oxide in 15 ml of DMF, 19.7 g (121 mmol) of CDI were added. The reaction mixture was stirred at 298 K for 1 h. The limpid solution was then cooled at 273 K and 13.3 g (72 mmol) of (4-fluorophenyl)acetic acid ethyl ester and 4.1 g (168 mmol) of NaH were added. The reaction mixture was stirred at 273 K for 15 min, then the temperature was raised to 298 K and kept under vigorous stirring for 4 h. The reaction mixture was then poured into water/ice, the pH adjusted to 6, and the solution extracted with ethyl acetate. The combined organic layers were then collected, dried over Na_2SO_4 and concentrated under vacuum, affording an oil that was chromatographed over SiO_2 using acetone as eluent, yielding 80% of 2-(4-fluorophenyl)-3-oxo-3-pyridin-4-yl-N-oxide-propionic acid ethyl

ester.

For the synthesis of **(I)**, a suspension of 1.0 g (3.3 mmol) of 2-(4-fluorophenyl)-3-oxo-3-pyridin-4-yl-N-oxide-propionic acid ethyl ester and 0.3 g (4.0 mmol) of hydroxylamine hydrochloride in 0.5 ml of H_2O was warmed to 353 K. 3 ml of MeOH were added and the resulting solution refluxed for 4 h. The reaction mixture was then cooled to 298 K and stored at 277 K overnight, whereupon a yellow solid precipitated, yielding 83% of **(I)**.

For the synthesis of **(II)**, a suspension of 0.71 g (2.6 mmol) of **(I)** in 1 ml of DMF was added to 0.620 ml (4.5 mmol) of Et_3N and refluxed for 2 h. The reaction mixture was then cooled to 298 K, added to 0.231 ml (3.75 mmol) of iodomethane and stirred at 298 K for 2 h. Ethyl acetate was then added and the resulting precipitate separated by filtration and then crystalized from MeOH, yielding 40% of **(II)**.

S3. Refinement

Hydrogen atoms attached to carbon were placed at calculated positions with C—H = 0.95 Å (aromatic) or 0.99–1.00 Å (sp^3 C). All H atoms were refined with U_{eq} = 1.2 or 1.5 times U_{eq} of the parent atom).
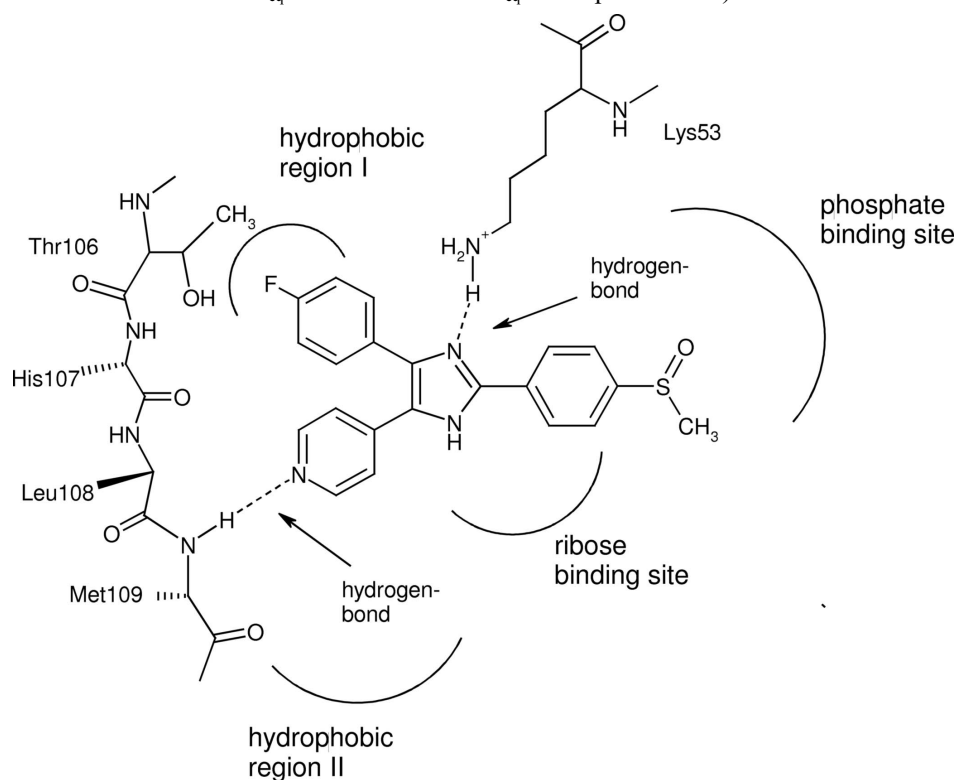
Figure 1

Schematic drawing of important interactions between the prototypical pyridin-4-yl imidazole inhibitor SB 203580 and the ATP binding site of p38.
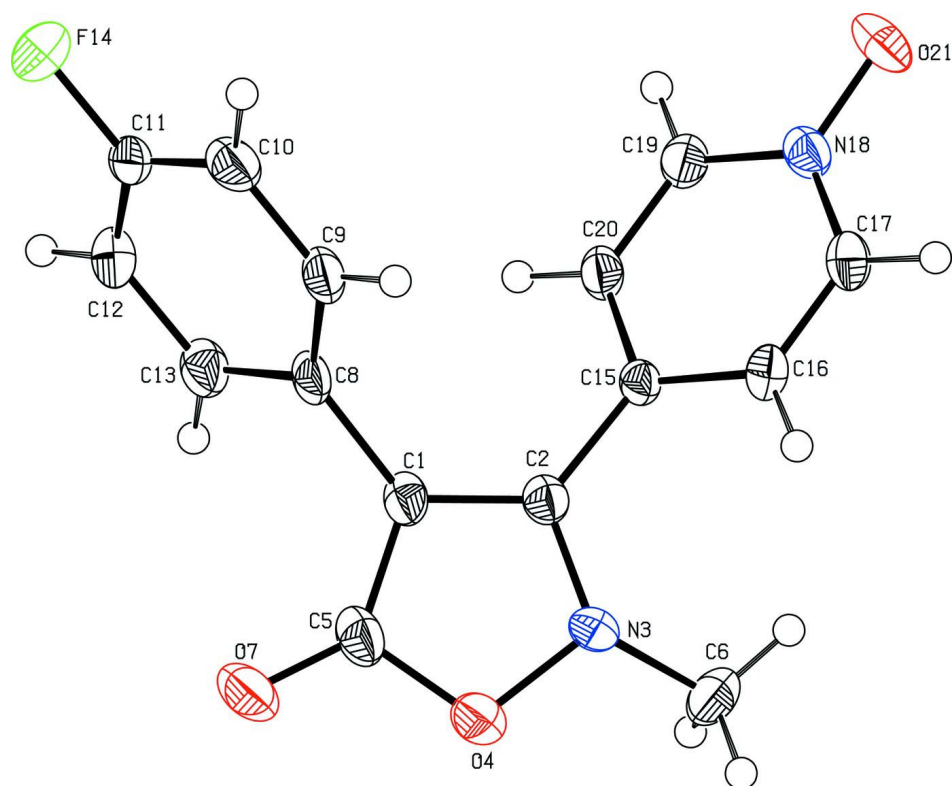
Figure 2

PLATON (Spek, 2003) view of (II). Displacement ellipsoids are drawn at the 50% probability level. H atoms are depicted as circles of arbitrary size.
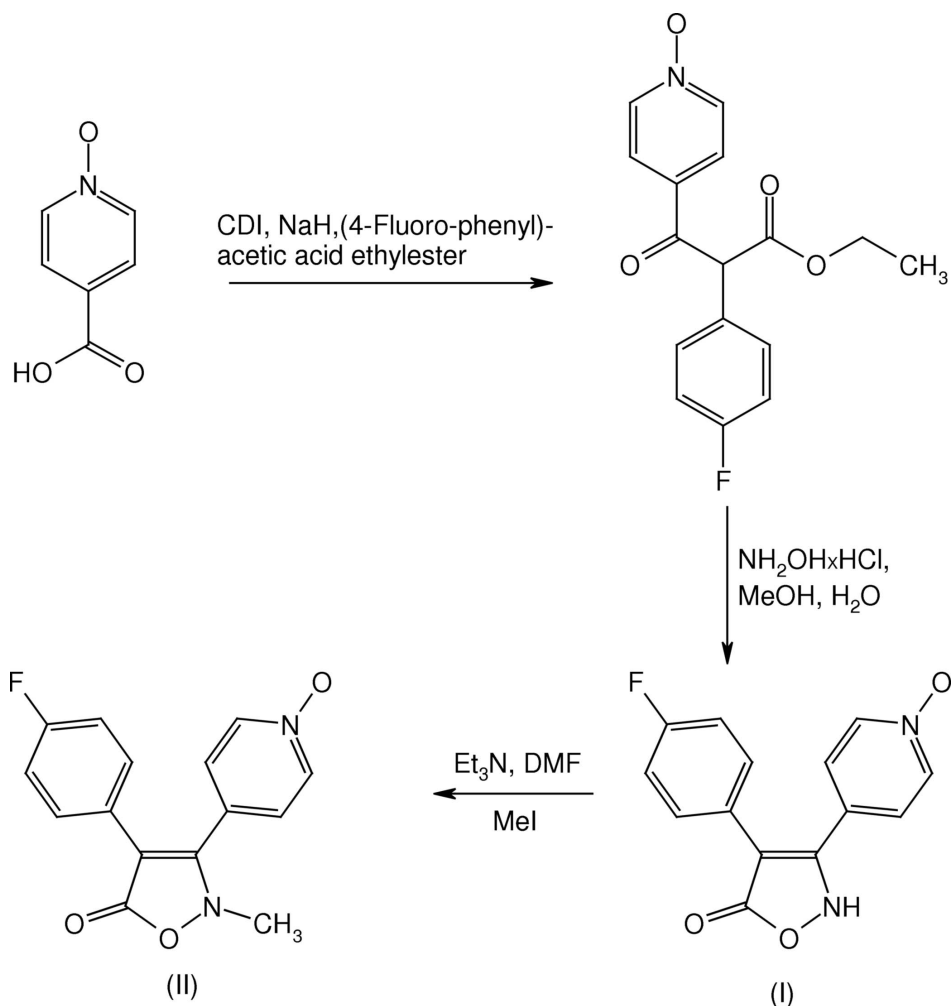
Figure 3
Synthesis of (II).

4-(4-Fluorophenyl)-2-methyl-3-(1-oxy-4-pyridyl)isoxazol-5(2H)-one

Crystal data

$C_{15}H_{11}FN_2O_3$	$D_x = 1.481$ Mg m^{-3}
$M_r = 286.26$	Cu $K\alpha$ radiation, $\lambda = 1.54178$ Å
Tetragonal, $P4_32_12$	Cell parameters from 25 reflections
Hall symbol: P 4nw 2abw	$\theta = 20–32°$
$a = 10.0828$ (6) Å	$\mu = 0.97$ mm^{-1}
$c = 25.257$ (5) Å	$T = 193$ K
$V = 2567.6$ (6) Å^3	Block, yellow
$Z = 8$	$0.40 \times 0.20 \times 0.10$ mm
$F(000) = 1184$	

Data collection

Enraf–Nonius CAD-4 diffractometer	Absorption correction: multi-scan (*MULABS*; Blessing, 1995)
Radiation source: rotating anode	$T_{min} = 0.60$, $T_{max} = 0.88$
Graphite monochromator	5114 measured reflections
$\theta/2\omega$ scans	1488 independent reflections

1129 reflections with $I > 2\sigma(I)$	$k = -12 \rightarrow 12$
$R_{int} = 0.081$	$l = -23 \rightarrow 30$
$\theta_{max} = 69.8°$, $\theta_{min} = 4.7°$	3 standard reflections every 60 min
$h = -12 \rightarrow 12$	intensity decay: 5%

Refinement

Refinement on F^2	Secondary atom site location: difference Fourier map
Least-squares matrix: full	
$R[F^2 > 2\sigma(F^2)] = 0.068$	Hydrogen site location: inferred from neighbouring sites
$wR(F^2) = 0.192$	
$S = 1.00$	H-atom parameters constrained
1488 reflections	$w = 1/[\sigma^2(F_o^2) + (0.149P)^2]$
191 parameters	where $P = (F_o^2 + 2F_c^2)/3$
0 restraints	$(\Delta/\sigma)_{max} < 0.001$
Primary atom site location: structure-invariant direct methods	$\Delta\rho_{max} = 0.45$ e Å⁻³
	$\Delta\rho_{min} = -0.34$ e Å⁻³

Special details

Geometry. All e.s.d.'s (except the e.s.d. in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell e.s.d.'s are taken into account individually in the estimation of e.s.d.'s in distances, angles and torsion angles; correlations between e.s.d.'s in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell e.s.d.'s is used for estimating e.s.d.'s involving l.s. planes.

Refinement. Refinement of F^2 against ALL reflections. Friedel Pairs merged (MERG 3 instruction). The weighted R-factor wR and goodness of fit S are based on F^2, conventional R-factors R are based on F, with F set to zero for negative F^2. The threshold expression of $F^2 > \sigma(F^2)$ is used only for calculating R-factors(gt) *etc*. and is not relevant to the choice of reflections for refinement. R-factors based on F^2 are statistically about twice as large as those based on F, and R-factors based on ALL data will be even larger.

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å²)

	x	y	z	$U_{iso}*/U_{eq}$
C1	0.4167 (4)	0.0719 (4)	0.3006 (2)	0.0248 (11)
C2	0.3537 (4)	0.1885 (4)	0.2905 (2)	0.0231 (10)
N3	0.2782 (4)	0.1781 (4)	0.24613 (17)	0.0272 (10)
O4	0.2804 (4)	0.0427 (3)	0.23076 (16)	0.0346 (9)
C5	0.3701 (5)	−0.0233 (5)	0.2641 (2)	0.0302 (11)
C6	0.1515 (5)	0.2379 (6)	0.2342 (2)	0.0366 (13)
H6A	0.0806	0.1855	0.2505	0.055*
H6B	0.1387	0.2403	0.1958	0.055*
H6C	0.1493	0.3284	0.2483	0.055*
O7	0.3926 (4)	−0.1402 (4)	0.25595 (18)	0.0409 (10)
C8	0.5231 (4)	0.0446 (4)	0.3400 (2)	0.0262 (11)
C9	0.6393 (5)	0.1185 (5)	0.3410 (2)	0.0290 (11)
H9	0.6499	0.1896	0.3167	0.035*
C10	0.7405 (5)	0.0908 (5)	0.3767 (3)	0.0348 (13)
H10	0.8198	0.1415	0.3774	0.042*
C11	0.7207 (5)	−0.0138 (5)	0.4112 (2)	0.0300 (12)
C12	0.6096 (5)	−0.0891 (5)	0.4118 (2)	0.0315 (12)
H12	0.6000	−0.1598	0.4364	0.038*
C13	0.5100 (5)	−0.0603 (5)	0.3757 (3)	0.0313 (12)
H13	0.4318	−0.1128	0.3752	0.038*

F14	0.8198 (3)	−0.0417 (3)	0.44649 (16)	0.0477 (10)
C15	0.3631 (4)	0.3142 (4)	0.31988 (19)	0.0198 (10)
C16	0.3580 (4)	0.4384 (4)	0.2958 (2)	0.0253 (11)
H16	0.3448	0.4438	0.2586	0.030*
C17	0.3714 (5)	0.5514 (5)	0.3240 (2)	0.0265 (11)
H17	0.3655	0.6347	0.3066	0.032*
N18	0.3934 (4)	0.5467 (4)	0.37729 (18)	0.0253 (9)
C19	0.3954 (5)	0.4264 (5)	0.4021 (2)	0.0270 (11)
H19	0.4076	0.4228	0.4394	0.032*
C20	0.3804 (4)	0.3122 (4)	0.3746 (2)	0.0254 (10)
H20	0.3817	0.2298	0.3929	0.030*
O21	0.4120 (4)	0.6544 (3)	0.40417 (17)	0.0395 (10)

Atomic displacement parameters (Å^2)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
C1	0.0148 (19)	0.020 (2)	0.039 (3)	0.0011 (17)	0.0004 (19)	0.000 (2)
C2	0.022 (2)	0.021 (2)	0.027 (3)	0.0009 (17)	0.0007 (19)	−0.0004 (19)
N3	0.033 (2)	0.0243 (18)	0.025 (2)	0.0040 (17)	−0.0053 (18)	−0.0087 (17)
O4	0.0338 (19)	0.0286 (17)	0.041 (2)	0.0032 (15)	−0.0063 (17)	−0.0105 (16)
C5	0.025 (2)	0.022 (2)	0.043 (3)	0.0028 (19)	0.004 (2)	−0.004 (2)
C6	0.036 (3)	0.041 (3)	0.033 (3)	0.010 (2)	−0.011 (2)	0.002 (2)
O7	0.040 (2)	0.0289 (18)	0.053 (3)	0.0000 (15)	−0.002 (2)	−0.0161 (18)
C8	0.019 (2)	0.017 (2)	0.042 (3)	0.0062 (17)	−0.002 (2)	−0.005 (2)
C9	0.026 (2)	0.018 (2)	0.042 (3)	0.0040 (17)	−0.002 (2)	−0.002 (2)
C10	0.024 (2)	0.028 (2)	0.053 (4)	0.002 (2)	−0.004 (2)	−0.013 (2)
C11	0.025 (2)	0.024 (2)	0.041 (3)	0.0109 (19)	−0.010 (2)	−0.012 (2)
C12	0.035 (3)	0.023 (2)	0.037 (3)	0.007 (2)	−0.002 (2)	0.001 (2)
C13	0.022 (2)	0.023 (2)	0.048 (3)	0.001 (2)	−0.001 (2)	0.000 (2)
F14	0.0400 (17)	0.0448 (18)	0.058 (2)	0.0099 (15)	−0.0234 (17)	−0.0034 (17)
C15	0.0172 (19)	0.0174 (19)	0.025 (3)	0.0021 (15)	−0.0003 (18)	−0.0017 (18)
C16	0.025 (2)	0.022 (2)	0.028 (3)	0.0062 (18)	0.000 (2)	0.003 (2)
C17	0.029 (2)	0.020 (2)	0.030 (3)	0.0014 (18)	0.003 (2)	0.006 (2)
N18	0.0232 (19)	0.0212 (19)	0.031 (3)	0.0019 (15)	0.0016 (17)	−0.0046 (18)
C19	0.030 (2)	0.025 (2)	0.026 (3)	0.0051 (19)	−0.002 (2)	0.000 (2)
C20	0.025 (2)	0.018 (2)	0.033 (3)	0.0015 (18)	−0.002 (2)	0.0027 (19)
O21	0.049 (2)	0.0213 (17)	0.048 (3)	−0.0046 (15)	−0.0001 (19)	−0.0107 (17)

Geometric parameters (Å, º)

C1—C2	1.360 (6)	C10—H10	0.950
C1—C5	1.412 (7)	C11—C12	1.354 (7)
C1—C8	1.489 (7)	C11—F14	1.368 (6)
C2—N3	1.359 (6)	C12—C13	1.388 (7)
C2—C15	1.472 (6)	C12—H12	0.950
N3—O4	1.419 (5)	C13—H13	0.950
N3—C6	1.444 (6)	C15—C16	1.393 (6)
O4—C5	1.403 (6)	C15—C20	1.394 (7)

C5—O7	1.218 (6)	C16—C17	1.350 (7)
C6—H6A	0.980	C16—H16	0.950
C6—H6B	0.980	C17—N18	1.364 (7)
C6—H6C	0.980	C17—H17	0.950
C8—C9	1.389 (6)	N18—O21	1.293 (5)
C8—C13	1.395 (7)	N18—C19	1.366 (6)
C9—C10	1.391 (8)	C19—C20	1.352 (7)
C9—H9	0.950	C19—H19	0.950
C10—C11	1.382 (8)	C20—H20	0.950
C2—C1—C5	108.0 (4)	C12—C11—F14	118.8 (5)
C2—C1—C8	128.4 (4)	C12—C11—C10	123.7 (5)
C5—C1—C8	123.5 (4)	F14—C11—C10	117.5 (5)
N3—C2—C1	110.5 (4)	C11—C12—C13	118.3 (5)
N3—C2—C15	121.2 (4)	C11—C12—H12	120.9
C1—C2—C15	128.3 (5)	C13—C12—H12	120.9
C2—N3—O4	106.9 (4)	C12—C13—C8	121.0 (5)
C2—N3—C6	129.5 (4)	C12—C13—H13	119.5
O4—N3—C6	111.0 (4)	C8—C13—H13	119.5
C5—O4—N3	107.6 (4)	C16—C15—C20	116.8 (4)
O7—C5—O4	118.6 (5)	C16—C15—C2	123.5 (4)
O7—C5—C1	134.9 (5)	C20—C15—C2	119.7 (4)
O4—C5—C1	106.5 (4)	C17—C16—C15	121.6 (5)
N3—C6—H6A	109.5	C17—C16—H16	119.2
N3—C6—H6B	109.5	C15—C16—H16	119.2
H6A—C6—H6B	109.5	C16—C17—N18	120.5 (4)
N3—C6—H6C	109.5	C16—C17—H17	119.7
H6A—C6—H6C	109.5	N18—C17—H17	119.7
H6B—C6—H6C	109.5	O21—N18—C17	120.8 (4)
C9—C8—C13	118.4 (5)	O21—N18—C19	120.2 (4)
C9—C8—C1	121.4 (5)	C17—N18—C19	119.0 (4)
C13—C8—C1	120.2 (4)	C20—C19—N18	121.3 (5)
C8—C9—C10	121.5 (5)	C20—C19—H19	119.4
C8—C9—H9	119.2	N18—C19—H19	119.4
C10—C9—H9	119.2	C19—C20—C15	120.7 (4)
C11—C10—C9	117.2 (5)	C19—C20—H20	119.6
C11—C10—H10	121.4	C15—C20—H20	119.6
C9—C10—H10	121.4		
C5—C1—C2—N3	−5.8 (6)	C8—C9—C10—C11	0.2 (8)
C8—C1—C2—N3	170.2 (5)	C9—C10—C11—C12	0.0 (8)
C5—C1—C2—C15	176.1 (4)	C9—C10—C11—F14	180.0 (4)
C8—C1—C2—C15	−7.9 (8)	F14—C11—C12—C13	−179.7 (5)
C1—C2—N3—O4	7.4 (5)	C10—C11—C12—C13	0.3 (8)
C15—C2—N3—O4	−174.4 (4)	C11—C12—C13—C8	−0.9 (8)
C1—C2—N3—C6	144.7 (5)	C9—C8—C13—C12	1.1 (8)
C15—C2—N3—C6	−37.1 (7)	C1—C8—C13—C12	178.5 (5)
C2—N3—O4—C5	−6.0 (5)	N3—C2—C15—C16	−33.2 (7)

C6—N3—O4—C5	−151.9 (4)	C1—C2—C15—C16	144.7 (5)
N3—O4—C5—O7	−176.3 (5)	N3—C2—C15—C20	148.1 (5)
N3—O4—C5—C1	2.5 (5)	C1—C2—C15—C20	−34.1 (7)
C2—C1—C5—O7	−179.6 (6)	C20—C15—C16—C17	1.0 (6)
C8—C1—C5—O7	4.1 (10)	C2—C15—C16—C17	−177.8 (5)
C2—C1—C5—O4	1.9 (6)	C15—C16—C17—N18	1.5 (7)
C8—C1—C5—O4	−174.4 (4)	C16—C17—N18—O21	177.0 (4)
C2—C1—C8—C9	−54.3 (8)	C16—C17—N18—C19	−3.1 (7)
C5—C1—C8—C9	121.2 (5)	O21—N18—C19—C20	−177.9 (4)
C2—C1—C8—C13	128.4 (6)	C17—N18—C19—C20	2.2 (7)
C5—C1—C8—C13	−56.1 (7)	N18—C19—C20—C15	0.3 (7)
C13—C8—C9—C10	−0.7 (8)	C16—C15—C20—C19	−1.9 (7)
C1—C8—C9—C10	−178.1 (5)	C2—C15—C20—C19	176.9 (4)