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4-[4-(4-Fluorophenyl)-2-methyl-5-oxo-2,5-dihydroisoxazol-3-yl]-1-methylpyridinium iodide–4-[3-(4-fluorophenyl)-2-methyl-5-oxo-2,5-dihydroisoxazol-4-yl]-1-methylpyridinium iodide (0.6/0.4)

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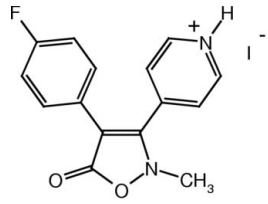
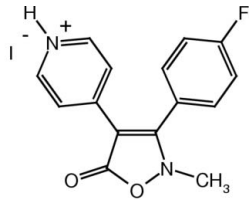
Key indicators: single-crystal X-ray study; T = 193 K; mean σ(C–C) = 0.006 Å; disorder in main residue; R factor = 0.040; wR factor = 0.115; data-to-parameter ratio = 20.7.

The crystal structure of the title compound, $C_{16}H_{16}FN_2O_2^+\cdot I^-$, was determined as part of a study of the biological activity of isoxazolone derivatives as p38 mitogen-activated protein kinase (MAPK) inhibitors. The X-ray crystal structure of 4-[4-(4-fluorophenyl)-2-methyl-5-oxo-2,5-dihydroisoxazol-3-yl]-1-methylpyridinium iodide showed the presence of the regioisomer 4-[3-(4-fluorophenyl)-2-methyl-5-oxo-2,5-dihydroisoxazol-4-yl]-1-methylpyridinium iodide. The synthesis of the former compound was achieved by reacting 4-(4-fluorophenyl)-3-(4-pyridyl)isoxazol-5(2*H*)-one after treatment with Et_3N in dimethylformamide, with iodomethane. The unexpected formation of the regioisomer could be explained by a rearrangement occurring *via* aziridine of the isoxazolone compound. The regioisomers have site occupancies of 0.632 (4)/0.368 (4). The two six members rings make a dihedral angle of 66.8 (2)°.

Related literature

For general background on the pharmaceutical applications of isoxazolones, see: Laughlin *et al.* (2005); Clark *et al.* (2002); Wang *et al.* (1998); Foster *et al.* (2000); Adams *et al.* (1998); Laufer & Wagner (2002); de Laszlo *et al.* (1998); Laufer *et al.* (2005, 2006); Revesz *et al.* (2000); Ohkawa *et al.* (2001). The aziridine rearrangement of isoxazolones was described by Nishiwaki & Saito (1971) and Sauers (1990).

Experimental

Crystal data

$C_{15}H_{12}FN_2O_2^+\cdot I^-$
M_r = 398.17
Monoclinic, $P2_1/c$
a = 10.2804 (4) Å
b = 20.5895 (9) Å
c = 7.4907 (3) Å
β = 96.8828 (14)°
V = 1574.12 (11) Å^3
Z = 4
Mo $K\alpha$ radiation
μ = 2.05 mm^{-1}
T = 193 (2) K
0.52 × 0.20 × 0.08 mm

Data collection

Bruker SMART APEXII CCD diffractometer
Absorption correction: multi-scan (*APEX2*; Bruker, 2006)
T_{min} = 0.415, T_{max} = 0.853
27681 measured reflections
3897 independent reflections
3369 reflections with $I > 2\sigma(I)$
R_{int} = 0.126

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.040
$wR(F^2)$ = 0.115
S = 1.07
3897 reflections
188 parameters
H-atom parameters constrained
$\Delta\rho_{max}$ = 1.60 e Å^{-3}
$\Delta\rho_{min}$ = −0.51 e Å^{-3}

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: *ORTEP* (Johnson, 1968) and *PLATON* (Spek, 2003); software used to prepare material for publication: *SHELXL97*.

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Supplementary data and figures for this paper are available from the IUCr electronic archives (Reference: BT2577).

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supplementary materials

Acta Cryst. (2008). E**64**, o298-o299 [**doi:10.1107/S1600536807055985**]

4-[4-(4-Fluorophenyl)-2-methyl-5-oxo-2,5-dihydroisoxazol-3-yl]-1-methylpyridinium iodide-4-[3-(4-fluorophenyl)-2-methyl-5-oxo-2,5-dihydroisoxazol-4-yl]-1-methylpyridinium iodide (0.6/0.4)

S. Margutti, D. Schollmeyer and S. Laufer

Comment

Compound **(II)** (Scheme 1) 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. Fig. 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 gaining selectivity. Vicinal to this interaction site, 4-pyridinyl moiety 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 exist for potent new small molecules 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 representing a strategy to dissect inhibition of p38 from interferences with cytochrome P450 (CYP450).

Accordingly, and based on the research published by Laughlin and co-authors (Laughlin *et al.*, 2005), we plane to prepare *N*-alkylated derivatives of compound **(I)** in order to get more accurate and comparable information about isoxazolones as p38 MAP Kinase inhibitors in terms of biological activity.

By testing compounds **(I)** and **(II)** in the *in vitro* p38-alpha MAPK assay (Laufer *et al.*, 2005), only compound **(I)** was found to posses biological activity.

The loss of the biological activity of compound **(II)** can be attributed to the absence of hydrogen bond donor on the pyridine ring and, consequentely, impossibility of interaction with Met109.

Experimental

For the synthesis of 2-(4-Fluoro-phenyl)-3-oxo-3-pyridin-4-yl-propionic acid ethyl ester (see scheme 1), to a suspension of 3.3 g (26.8 mmol) of isonicotinic acid in 15 ml of DMF, 7.3 g (45 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 5 g (27.4 mmol) of (4-Fluoro-phenyl)-acetic acid ethyl and 1.7 g (70.8 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 was then poured into water/ice, the pH adjusted to value 6 and extracted with ethylacetate. 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 *y* ielding 75% of 2-(4-Fluoro-phenyl)-3-oxo-3-pyridin-4-yl-propionic acid ethyl ester. For the synthesis of **(I)**, a suspension of 5.2 g (18.1 mmol) of 2-(4-Fluoro-phenyl)-3-oxo-3-pyridin −4-yl-propionic acid ethyl ester and 1.41 g (20.27 mmol) of hydroxylamine hydrochloride in 1.5 ml of H_2O was warmed to 353 K. 8 ml of MeOH were added and the resulting solution allowed to reflux 4 h. The reaction mixture was then cooled to 298 K and stored at 277 K overnight whereupon a yellow solide precipitated, yielding 75% of **(I)**. For the synthesis of **(II)** and **(III)**, a suspension of 620 mg (2.5 mmol) of **(I)** in 1 ml of DMF was added of 0.620 ml (4.5 mmol) of Et3N and refluxed for 2 h. The reaction mixture was then cooled at 298 K, added of 0.231 ml (3.75 mmol) of iodomethane and stirred at 298 K for 2 h. The reaction mixture was then added of ethylacetate and the resulting precipitate separated by filtration and then crystalized from MeOH yielding 54% of **(II)** and **(III)**.

Refinement

Hydrogen atoms attached to carbons were placed at calculated positions with C—H = 0.95 A% (aromatic) or 0.99–1.00 Å (sp^3 C-atom). All H atoms were refined with isotropic displacement parameters (set at 1.2–1.5 times of the U_{eq} of the parent atom). The regioisomers (II) and (III) have s.o.f.s of 0.632 (4)/0.368 (4). The coordinates and a.d.p.'s of the disorderd C, N and F atoms were constrained to be equal to achieve a good convergence of the refinement procedure.

Figures

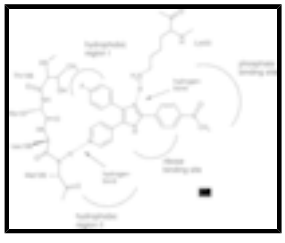


Fig. 1. Schematic drawing of important interactions between the prototypical pyridin-4-yl imidazole inhibitor SB 203580 and the ATP binding site of p38.

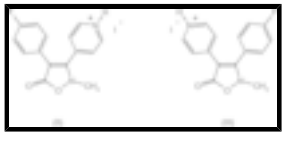


Fig. 2. Schematic drawings of 4-[4-(4-Fluoro-phenyl)-2-methyl-5-oxo-2,5-dihydro-isoxazol-3-yl]-1-methyl- pyridinium iodide, (II), and 4-[3-(4-Fluoro-phenyl)-2-methyl-5-oxo-2,5-dihydro-isoxazol-3-yl]-1-methyl- pyridinium iodide, (III).

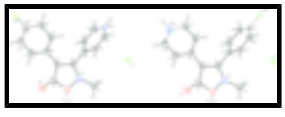


Fig. 3. *ORTEP* (Johnson, 1968) view of (II) and (III). Displacement ellipsoids are drawn at the 50% probability level. H atoms are depicted as circles of arbitrary size.

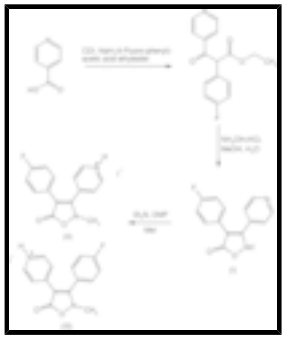


Fig. 4. The formation of the title compound.

4-[4-(4-Fluorophenyl)-2-methyl-5-oxo-2,5-dihydroisoxazol-3-yl]-1- methylpyridinium iodide– 4-[3-(4-fluorophenyl)-2-methyl-5-oxo-2,5-dihydroisoxazol-4-yl]-1-methyl- pyridinium iodide (0.6/0.4)

Crystal data

$C_{15}H_{12}FN_2O_2^+ \cdot I^-$	$F_{000} = 776$
$M_r = 398.17$	$D_x = 1.680$ Mg m^{-3}
Monoclinic, $P2_1/c$	Mo $K\alpha$ radiation $\lambda = 0.71069$ Å
Hall symbol: -P 2ybc	Cell parameters from 6868 reflections
$a = 10.2804$ (4) Å	$\theta = 2.7$–28.3º
$b = 20.5895$ (9) Å	$\mu = 2.05$ mm^{-1}
$c = 7.4907$ (3) Å	$T = 193$ (2) K
$\beta = 96.8828$ (14)º	Block, brown
$V = 1574.12$ (11) Å^3	0.52 × 0.20 × 0.08 mm
$Z = 4$	

Data collection

Bruker APEXII CCD diffractometer	3369 reflections with $I > 2\sigma(I)$
Monochromator: graphite	$R_{int} = 0.126$
$T = 193$(2) K	$\theta_{max} = 28.4$º
CCD scan	$\theta_{min} = 2.0$º
Absorption correction: multi-scan (APEX2; Bruker, 2006)	$h = -13 \rightarrow 13$
$T_{min} = 0.415$, $T_{max} = 0.853$	$k = -27 \rightarrow 27$
27681 measured reflections	$l = -9 \rightarrow 9$
3897 independent reflections	

Refinement

Refinement on F^2	Secondary atom site location: difference Fourier map
Least-squares matrix: full	Hydrogen site location: inferred from neighbouring sites
$R[F^2 > 2\sigma(F^2)] = 0.040$	H-atom parameters constrained
$wR(F^2) = 0.115$	$w = 1/[\sigma^2(F_o^2) + (0.0617P)^2 + 2.8681P]$ where $P = (F_o^2 + 2F_c^2)/3$
$S = 1.07$	$(\Delta/\sigma)_{max} = 0.001$
3897 reflections	$\Delta\rho_{max} = 1.60$ e Å^{-3}
188 parameters	$\Delta\rho_{min} = -0.51$ e Å^{-3}
Primary atom site location: structure-invariant direct methods	Extinction correction: none

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. 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 $F^2 > 2\text{sigma}(F^2)$ 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 ($Å^2$)

	x	*y*	*z*	U_{iso}*/U_{eq}	Occ. (<1)
F1A	1.0107 (3)	0.20467 (16)	1.6192 (4)	0.0292 (4)	0.632 (4)
F1B	0.3217 (5)	0.1835 (3)	0.8219 (7)	0.0292 (4)	0.368 (4)
C1	0.9450 (4)	0.08719 (19)	0.9398 (5)	0.0327 (7)	
C2	0.8322 (4)	0.07466 (19)	0.8261 (5)	0.0333 (7)	
N3	0.8565 (3)	0.0373 (2)	0.6894 (5)	0.0458 (9)	
O4	0.9887 (3)	0.02271 (16)	0.7079 (4)	0.0439 (7)	
C5	1.0475 (4)	0.0546 (2)	0.8619 (6)	0.0384 (8)	
C6	0.7766 (4)	0.0089 (2)	0.5375 (6)	0.0408 (9)	
H6A	0.8320	−0.0168	0.4667	0.061*	
H6B	0.7337	0.0435	0.4623	0.061*	
H6C	0.7100	−0.0191	0.5806	0.061*	
O7	1.1646 (3)	0.04901 (16)	0.8994 (5)	0.0489 (8)	
C8	0.9607 (4)	0.12052 (18)	1.1149 (5)	0.0332 (8)	
C9	0.8538 (4)	0.1315 (2)	1.2097 (6)	0.0359 (8)	
H9	0.7687	0.1187	1.1584	0.043*	
C10	0.8700 (4)	0.1609 (2)	1.3781 (6)	0.0399 (9)	
H10	0.7969	0.1691	1.4412	0.048*	
C11A	0.9937 (5)	0.1776 (2)	1.4501 (6)	0.0462 (9)	0.632 (4)
N11B	0.9937 (5)	0.1776 (2)	1.4501 (6)	0.0462 (9)	0.368 (4)
H11B	1.0046	0.1958	1.5571	0.055*	0.368 (4)
C12	1.1020 (4)	0.1672 (2)	1.3625 (6)	0.0458 (10)	
H12	1.1868	0.1795	1.4162	0.055*	
C13	1.0846 (4)	0.1386 (2)	1.1952 (6)	0.0413 (9)	
H13	1.1586	0.1310	1.1333	0.050*	
C15	0.6988 (4)	0.10094 (19)	0.8287 (5)	0.0312 (7)	
C16	0.5906 (4)	0.06123 (19)	0.8311 (5)	0.0336 (7)	
H16	0.6003	0.0153	0.8348	0.040*	
C17	0.4681 (4)	0.0892 (2)	0.8282 (5)	0.0352 (8)	
H17	0.3932	0.0623	0.8308	0.042*	
N18A	0.4542 (3)	0.15364 (17)	0.8217 (4)	0.0292 (4)	0.632 (4)
H18A	0.3753	0.1705	0.8193	0.035*	0.632 (4)
C18B	0.4542 (3)	0.15364 (17)	0.8217 (4)	0.0292 (4)	0.368 (4)
C19	0.5569 (4)	0.1931 (2)	0.8188 (6)	0.0364 (8)	

H19	0.5441	0.2388	0.8156	0.044*
C20	0.6822 (4)	0.16808 (19)	0.8204 (5)	0.0354 (8)
H20	0.7552	0.1961	0.8160	0.042*
I1	0.47781 (2)	0.126317 (12)	0.31747 (3)	0.03385 (11)

Atomic displacement parameters (Å^2)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
F1A	0.0284 (10)	0.0371 (11)	0.0211 (9)	0.0016 (8)	−0.0013 (7)	−0.0038 (8)
F1B	0.0284 (10)	0.0371 (11)	0.0211 (9)	0.0016 (8)	−0.0013 (7)	−0.0038 (8)
C1	0.0289 (17)	0.0352 (19)	0.0353 (18)	0.0032 (14)	0.0087 (14)	0.0040 (14)
C2	0.0329 (18)	0.0339 (19)	0.0339 (18)	0.0020 (14)	0.0065 (14)	0.0026 (14)
N3	0.0312 (17)	0.061 (2)	0.045 (2)	0.0125 (16)	0.0037 (15)	−0.0117 (17)
O4	0.0336 (14)	0.0525 (18)	0.0474 (17)	0.0086 (13)	0.0122 (12)	−0.0064 (14)
C5	0.0325 (19)	0.038 (2)	0.045 (2)	0.0013 (16)	0.0092 (16)	0.0042 (16)
C6	0.040 (2)	0.042 (2)	0.042 (2)	0.0019 (17)	0.0108 (17)	−0.0077 (17)
O7	0.0292 (14)	0.0528 (18)	0.067 (2)	0.0032 (12)	0.0151 (14)	0.0009 (16)
C8	0.0303 (18)	0.0346 (19)	0.0349 (19)	−0.0006 (14)	0.0047 (15)	0.0048 (14)
C9	0.0286 (17)	0.046 (2)	0.0336 (19)	0.0007 (15)	0.0036 (15)	0.0009 (15)
C10	0.037 (2)	0.048 (2)	0.035 (2)	0.0035 (17)	0.0049 (16)	−0.0002 (17)
C11A	0.055 (2)	0.043 (2)	0.039 (2)	−0.0025 (18)	−0.0002 (18)	0.0000 (17)
N11B	0.055 (2)	0.043 (2)	0.039 (2)	−0.0025 (18)	−0.0002 (18)	0.0000 (17)
C12	0.037 (2)	0.050 (3)	0.048 (2)	−0.0095 (18)	−0.0029 (18)	0.0029 (19)
C13	0.0297 (19)	0.048 (2)	0.047 (2)	−0.0043 (16)	0.0057 (17)	0.0058 (18)
C15	0.0331 (17)	0.0352 (18)	0.0257 (16)	0.0025 (14)	0.0045 (13)	−0.0009 (14)
C16	0.0372 (19)	0.0332 (18)	0.0313 (17)	−0.0009 (15)	0.0079 (15)	−0.0007 (14)
C17	0.0360 (19)	0.038 (2)	0.0323 (18)	−0.0024 (15)	0.0063 (15)	−0.0016 (14)
N18A	0.0284 (10)	0.0371 (11)	0.0211 (9)	0.0016 (8)	−0.0013 (7)	−0.0038 (8)
C18B	0.0284 (10)	0.0371 (11)	0.0211 (9)	0.0016 (8)	−0.0013 (7)	−0.0038 (8)
C19	0.0344 (18)	0.0363 (19)	0.0381 (19)	0.0028 (15)	0.0025 (15)	0.0013 (15)
C20	0.0318 (18)	0.0329 (19)	0.041 (2)	−0.0005 (14)	0.0037 (15)	−0.0014 (15)
I1	0.03172 (15)	0.03684 (16)	0.03268 (16)	−0.00256 (9)	0.00260 (10)	−0.00114 (9)

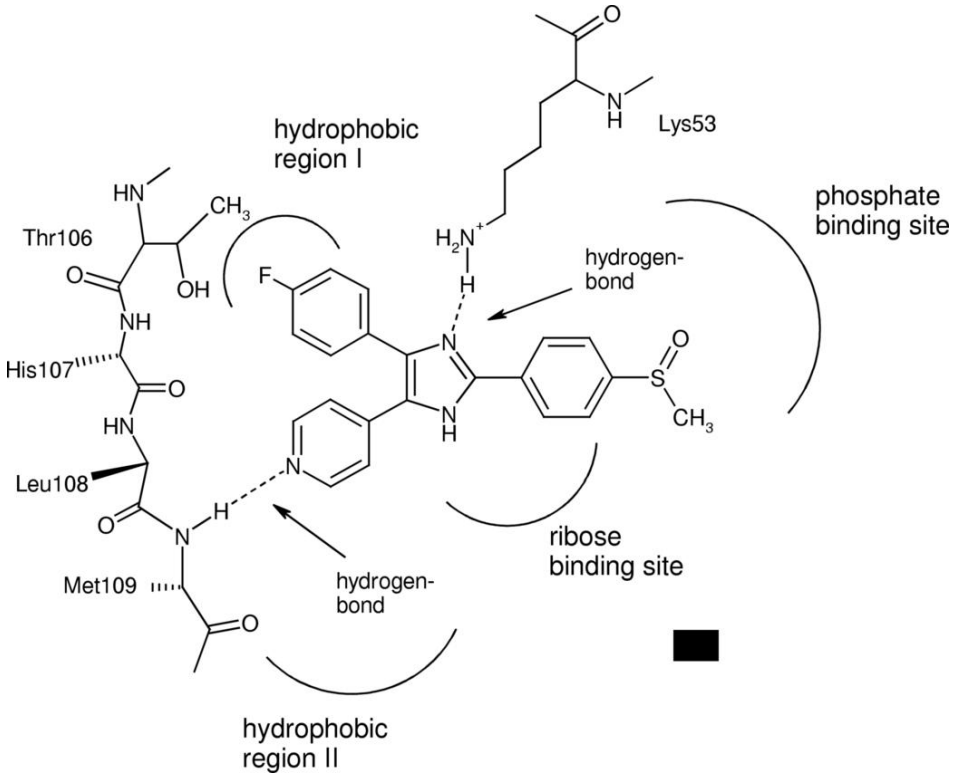
Geometric parameters (Å, °)

F1A—C11A	1.376 (5)	C10—C11A	1.365 (6)
C1—C2	1.378 (5)	C10—H10	0.9500
C1—C5	1.431 (5)	C11A—C12	1.375 (7)
C1—C8	1.472 (5)	C12—C13	1.378 (7)
C2—N3	1.328 (5)	C12—H12	0.9500
C2—C15	1.477 (5)	C13—H13	0.9500
N3—O4	1.383 (4)	C15—C16	1.383 (5)
N3—C6	1.444 (6)	C15—C20	1.393 (6)
O4—C5	1.400 (5)	C16—C17	1.382 (5)
C5—O7	1.208 (5)	C16—H16	0.9500
C6—H6A	0.9800	C17—N18A	1.336 (6)
C6—H6B	0.9800	C17—H17	0.9500
C6—H6C	0.9800	N18A—C19	1.334 (5)
C8—C13	1.392 (6)	N18A—H18A	0.8800

C8—C9	1.397 (6)	C19—C20	1.386 (5)
C9—C10	1.390 (6)	C19—H19	0.9500
C9—H9	0.9500	C20—H20	0.9500
C2—C1—C5	105.4 (3)	C10—C11A—C12	122.8 (4)
C2—C1—C8	129.2 (3)	C10—C11A—F1A	118.4 (4)
C5—C1—C8	125.1 (4)	C12—C11A—F1A	118.8 (4)
N3—C2—C1	111.3 (3)	C11A—C12—C13	118.5 (4)
N3—C2—C15	118.9 (3)	C11A—C12—H12	120.8
C1—C2—C15	129.6 (4)	C13—C12—H12	120.8
C2—N3—O4	108.8 (3)	C12—C13—C8	121.3 (4)
C2—N3—C6	134.4 (4)	C12—C13—H13	119.4
O4—N3—C6	116.8 (3)	C8—C13—H13	119.4
N3—O4—C5	107.6 (3)	C16—C15—C20	119.5 (3)
O7—C5—O4	117.8 (4)	C16—C15—C2	122.2 (4)
O7—C5—C1	135.3 (4)	C20—C15—C2	118.1 (3)
O4—C5—C1	106.9 (3)	C17—C16—C15	119.1 (4)
N3—C6—H6A	109.5	C17—C16—H16	120.4
N3—C6—H6B	109.5	C15—C16—H16	120.4
H6A—C6—H6B	109.5	N18A—C17—C16	120.5 (4)
N3—C6—H6C	109.5	N18A—C17—H17	119.7
H6A—C6—H6C	109.5	C16—C17—H17	119.7
H6B—C6—H6C	109.5	C19—N18A—C17	121.6 (3)
C13—C8—C9	118.2 (4)	C19—N18A—H18A	119.2
C13—C8—C1	120.4 (4)	C17—N18A—H18A	119.2
C9—C8—C1	121.3 (4)	N18A—C19—C20	120.7 (4)
C10—C9—C8	121.1 (4)	N18A—C19—H19	119.6
C10—C9—H9	119.5	C20—C19—H19	119.6
C8—C9—H9	119.5	C19—C20—C15	118.5 (4)
C11A—C10—C9	118.2 (4)	C19—C20—H20	120.7
C11A—C10—H10	120.9	C15—C20—H20	120.7
C9—C10—H10	120.9		
C5—C1—C2—N3	0.7 (5)	C1—C8—C9—C10	177.6 (4)
C8—C1—C2—N3	−173.3 (4)	C8—C9—C10—C11A	−1.2 (6)
C5—C1—C2—C15	−173.3 (4)	C9—C10—C11A—C12	0.7 (7)
C8—C1—C2—C15	12.7 (7)	C9—C10—C11A—F1A	−177.8 (4)
C1—C2—N3—O4	0.6 (5)	C10—C11A—C12—C13	−0.1 (7)
C15—C2—N3—O4	175.3 (3)	F1A—C11A—C12—C13	178.4 (4)
C1—C2—N3—C6	178.3 (5)	C11A—C12—C13—C8	0.2 (7)
C15—C2—N3—C6	−7.0 (8)	C9—C8—C13—C12	−0.7 (6)
C2—N3—O4—C5	−1.7 (5)	C1—C8—C13—C12	−177.1 (4)
C6—N3—O4—C5	−179.9 (4)	N3—C2—C15—C16	60.6 (5)
N3—O4—C5—O7	−178.4 (4)	C1—C2—C15—C16	−125.8 (5)
N3—O4—C5—C1	2.1 (4)	N3—C2—C15—C20	−116.6 (4)
C2—C1—C5—O7	178.9 (5)	C1—C2—C15—C20	57.0 (6)
C8—C1—C5—O7	−6.8 (8)	C20—C15—C16—C17	−1.0 (5)
C2—C1—C5—O4	−1.7 (4)	C2—C15—C16—C17	−178.1 (3)
C8—C1—C5—O4	172.6 (3)	C15—C16—C17—N18A	0.5 (5)
C2—C1—C8—C13	−168.6 (4)	C16—C17—N18A—C19	−0.4 (5)

C5—C1—C8—C13	18.5 (6)	C17—N18A—C19—C20	0.7 (6)
C2—C1—C8—C9	15.1 (6)	N18A—C19—C20—C15	−1.2 (6)
C5—C1—C8—C9	−157.8 (4)	C16—C15—C20—C19	1.4 (6)
C13—C8—C9—C10	1.3 (6)	C2—C15—C20—C19	178.6 (4)

Fig. 1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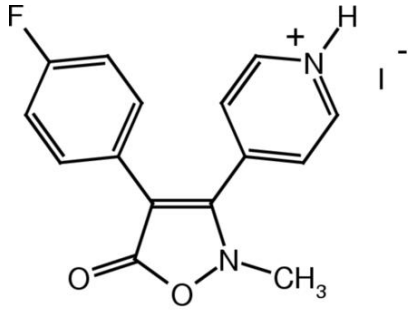
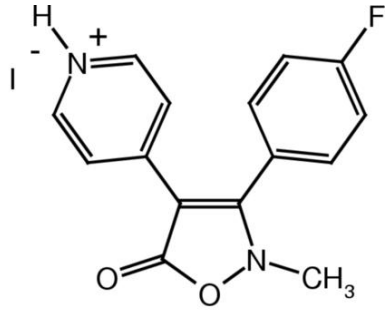
Lys53
phosphate
binding site
Thr106
hydrogen-
bond
His107
Leu108
ribose
binding site
hydrogen-
bond
Met109
hydrophobic
region II

Fig. 2

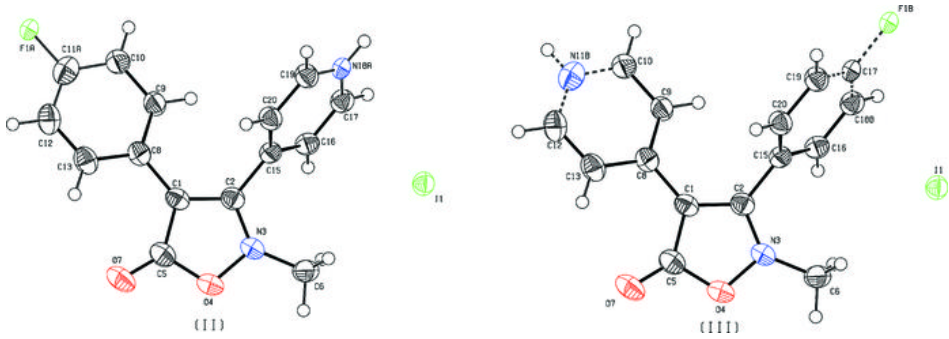


(II)



(III)

Fig. 3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C10
C9
C19
N18A
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N3
O7
C5
O4
C6
(II)
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C9
C19
C17
C20
C12
C13
C8
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C15
C16
C18
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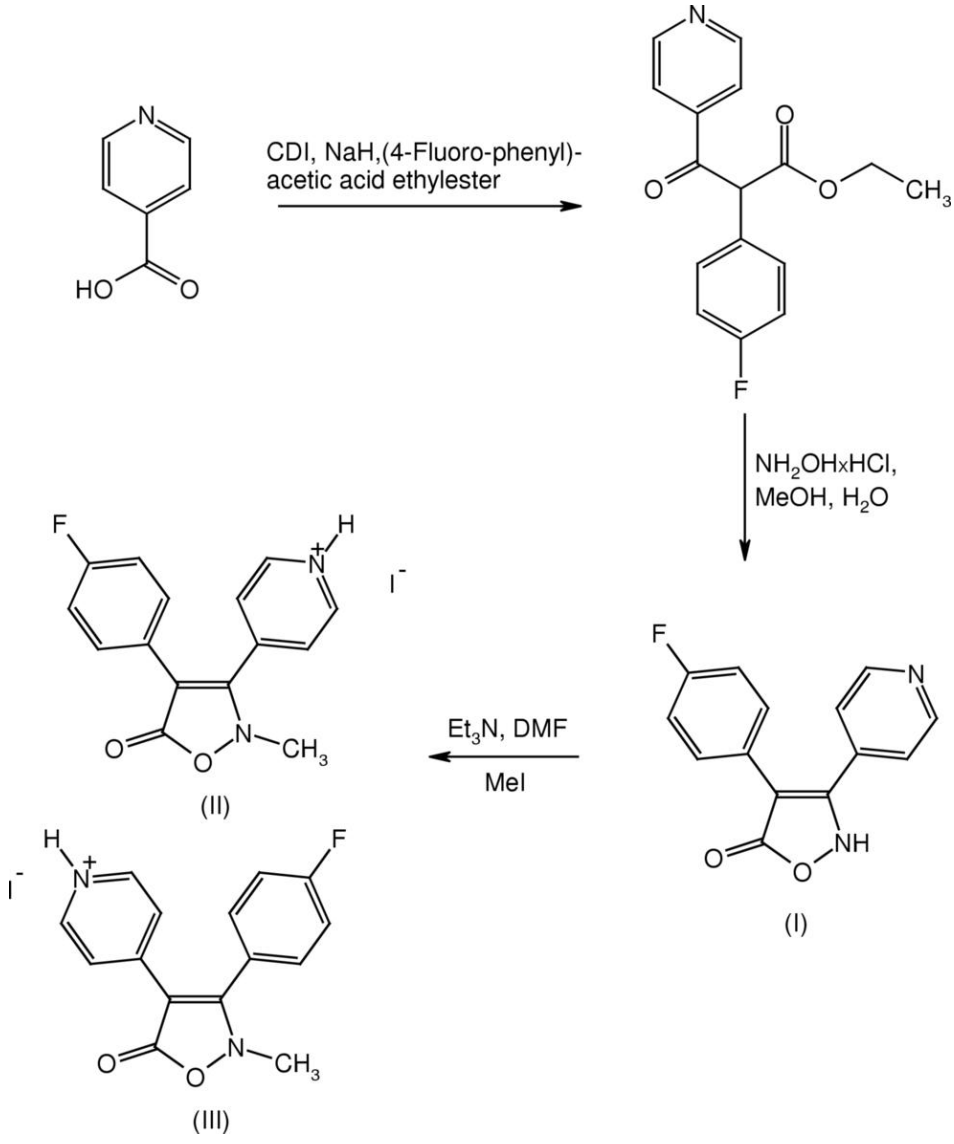
N3
O7
C5
O4
C6
(III)

Fig. 4


CDI, NaH,(4-Fluoro-phenyl)-acetic acid ethylester
NH2OHxHCl, MeOH, H2O
Et3N, DMF
MeI
(I)
(II)
(III)