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5-Methyl-*N*-[2-(trifluoromethyl)phenyl]-isoxazole-4-carboxamide

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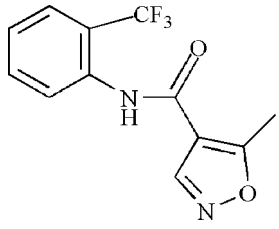
Key indicators: single-crystal X-ray study; T = 293 K; mean σ(C–C) = 0.006 Å; R factor = 0.062; wR factor = 0.164; data-to-parameter ratio = 12.8.

In the title compound, $C_{12}H_9F_3N_2O_2$, the benzene ring is nearly perpendicular to the isoxazole ring, making a dihedral angle of 82.97 (2)°. In the crystal, molecules are linked by N—H···O hydrogen bonds into a supramolecular chain running along the c axis.

Related literature

For applications of leflunomide [systematic name: 5-methyl-*N*-[4-(trifluoromethyl) phenyl]-isoxazole-4-carboxamide] in the treatment of rheumatoid arthritis, see: Shaw *et al.* (2011); Schattenkirchner (2000). For leflunomide analogs, see: Huang *et al.* (2003); Wang *et al.* (2011).



Experimental

Crystal data

$C_{12}H_9F_3N_2O_2$
M_r = 270.21
Monoclinic, $P2_1/c$
a = 15.839 (3) Å
b = 8.3260 (17) Å
c = 9.4250 (19) Å
β = 101.29 (3)°
V = 1218.9 (4) Å^3
Z = 4
Mo $K\alpha$ radiation
μ = 0.13 mm^{-1}
T = 293 K
0.20 × 0.10 × 0.10 mm

Data collection

Enref–Nonius CAD-4 diffractometer
Absorption correction: ψ scan (North *et al.*, 1968)
T_{min} = 0.974, T_{max} = 0.987
2193 measured reflections
2193 independent reflections
1125 reflections with $I > 2\sigma(I)$
3 standard reflections every 200 reflections
intensity decay: 1%

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.062
$wR(F^2)$ = 0.164
S = 1.00
2193 reflections
172 parameters
H-atom parameters constrained
$\Delta\rho_{max}$ = 0.19 e Å^{-3}
$\Delta\rho_{min}$ = −0.19 e Å^{-3}

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

D—H···A	D—H	H···A	D···A	D—H···A
N1—H1A···O1^{i}	0.86	2.13	2.855 (3)	142

Symmetry code: (i) $x, -y+\frac{1}{2}, z+\frac{1}{2}$.

Data collection: *CAD-4 EXPRESS* (Enraf–Nonius, 1994); cell refinement: *CAD-4 EXPRESS*; data reduction: *XCAD4* (Harms & Wocadlo,1995); program(s) used to solve structure: *SHELXTL* (Sheldrick, 2008); program(s) used to refine structure: *SHELXTL*; molecular graphics: *SHELXTL*; software used to prepare material for publication: *SHELXTL*.

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Supplementary data and figures for this paper are available from the IUCr electronic archives (Reference: XU5516).

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supplementary materials

Acta Cryst. (2012). E**68**, o1450 [doi:10.1107/S1600536812016467]

5-Methyl-*N*-[2-(trifluoromethyl)phenyl]isoxazole-4-carboxamide

De-Cai Wang, Jiang-Kai Qiu, Hai-Xi Zhu, Ping Wei and Ping-Kai Ou-Yang

Comment

Leflunomide is one of the most effective isoxazole-containing disease-modifying drugs for treating rheumatoid arthritis (Shaw *et al.*, 2011; Schattenkirchner, 2000). Many leflunomide analogs have been synthesized and exhibit potent immunomodulating effect (Huang, *et al.*, 2003). In our previous work, some anolog has been sucessfully sythesized (Wang *et al.*, 2011). In this paper, one new leflunomide analog N-(2,4-difluorophenyl)-5-methylisoxazole-4-carboxamide monohydrate, was synthesized as a novel and potent immunomodulating drugs. We report herein its crystal structure.

As illustrated in Fig. 1, the molecular structure of the title compound is not planar. The C1-C6 benzene and the C9-C11/N2/O2 isoxazole ring is almost perpendicular to each other with the dihedral angle of 82.97 (2) °. The central nitrogen atom (N1) and carbon atom (C8) are nearly coplanar with the benzene ring and the isoxazole rings [N1-C5-C6-C1 torsion angles = -176.7 (3) ° and C8-C9-C10-O2 torsion angles = -177.9 (3) °], respectively. The length of the C11=N2 double bond is 1.295 (5) Å, slightly longer than standard 1.28 Å value of a C=N double bond. The crystal structure is stabilized by N—H···O hydrogen bonds(Table 1).

Experimental

A solution of 0.05 mole of 5-methylisoxazole-4-carboxylic acid chloride (7.3 g) in 20 ml of acetonitrile is added dropwise, while stirring, to 0.1 mole of 2-(trifluoromethyl)aniline (16.1g),dissolved in 150 ml of acetonitrile at room temperature.After stirring for 40 minutes, the precipitated 2-(trifluoromethyl)aniline hydrochloride is filtered off and washed with 100 ml portions of acetonitrile, and the combined filtrates are concentrated under reduced pressure.9.6g(69.51% of theory) of white crystalline 5-methyl-N-(2-(trifluoromethyl)phenyl)isoxazole-4- carboxamide are thus obtained. Crystals of (I) suitable for X-ray diffraction were obtained by slow evaporation of an methylbenzene solution.

Refinement

H atoms were placed at calculated positions and were treated as riding on the parent C or N atoms with C—H = 0.96 (methyl), 0.97 (methylene) and N—H = 0.86 Å, U_{iso}(H) = 1.2 or 1.5 U_{eq}(C,N).

Computing details

Data collection: *CAD-4 EXPRESS* (Enraf–Nonius, 1994); cell refinement: *CAD-4 EXPRESS* (Enraf–Nonius, 1994); data reduction: *XCAD4* (Harms & Wocadlo,1995); program(s) used to solve structure: *SHELXTL* (Sheldrick, 2008); program(s) used to refine structure: *SHELXTL* (Sheldrick, 2008); molecular graphics: *SHELXTL* (Sheldrick, 2008); software used to prepare material for publication: *SHELXTL* (Sheldrick, 2008).

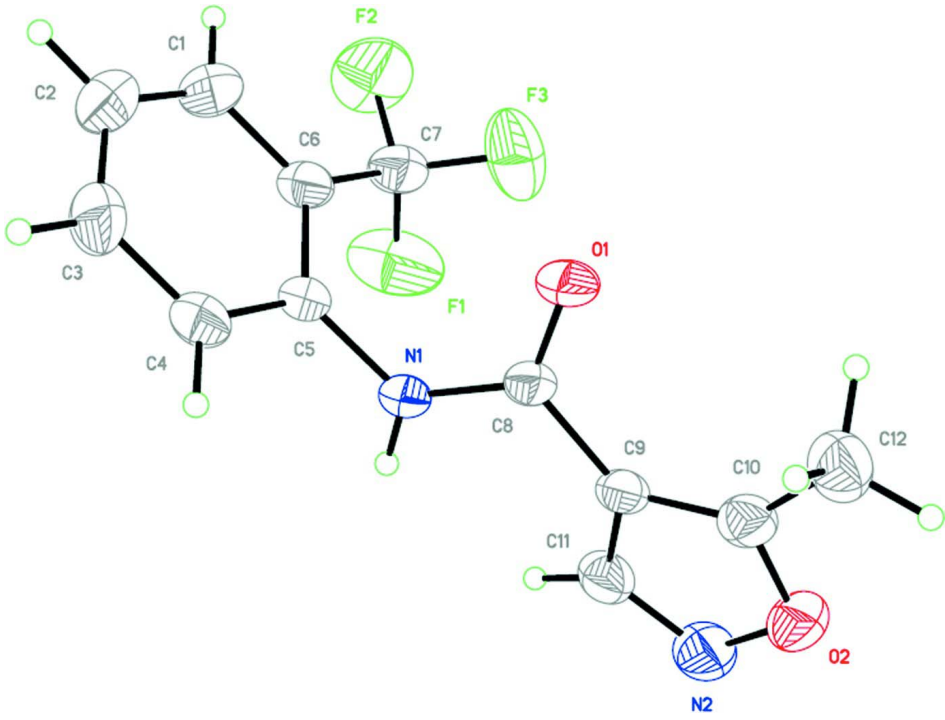

Figure 1

The structure of the title compound, showing the atomic numbering scheme. Non-H atoms are shown with 30% probability displacement ellipsoids.

5-Methyl-*N*-[2-(trifluoromethyl)phenyl]isoxazole-4-carboxamide

Crystal data

$C_{12}H_9F_3N_2O_2$
$M_r = 270.21$
Monoclinic, $P2_1/c$
Hall symbol: -P 2ybc
$a = 15.839\ (3)$ Å
$b = 8.3260\ (17)$ Å
$c = 9.4250\ (19)$ Å
$\beta = 101.29\ (3)°$
$V = 1218.9\ (4)$ Å^3
$Z = 4$
$F(000) = 552$
$D_x = 1.472$ Mg m^{-3}
Mo $K\alpha$ radiation, $\lambda = 0.71073$ Å
Cell parameters from 25 reflections
$\theta = 9–13°$
$\mu = 0.13$ mm^{-1}
$T = 293$ K
Block, colorless
0.20 × 0.10 × 0.10 mm

Data collection

Enref–Nonius CAD-4 diffractometer
Radiation source: fine-focus sealed tube
Graphite monochromator
$\omega/2\theta$ scans
Absorption correction: ψ scan (North *et al.*, 1968)
$T_{min} = 0.974$, $T_{max} = 0.987$
2193 measured reflections
2193 independent reflections
1125 reflections with $I > 2\sigma(I)$
$R_{int} = 0.000$
$\theta_{max} = 25.2°$, $\theta_{min} = 1.3°$
$h = -18\rightarrow18$
$k = 0\rightarrow9$
$l = 0\rightarrow11$
3 standard reflections every 200 reflections
intensity decay: 1%

Refinement

Refinement on F^2
Least-squares matrix: full
$R[F^2 > 2\sigma(F^2)] = 0.062$
$wR(F^2) = 0.164$
$S = 1.00$
2193 reflections
172 parameters
0 restraints
Primary atom site location: structure-invariant direct methods
Secondary atom site location: difference Fourier map
Hydrogen site location: inferred from neighbouring sites
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.068P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max} = 0.19$ e Å^{-3}
$\Delta\rho_{min} = -0.19$ e Å^{-3}

Special details

Geometry. All esds (except the esd in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell esds are taken into account individually in the estimation of esds in distances, angles and torsion angles; correlations between esds in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell esds is used for estimating esds 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 $F^2 > 2$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}
N1	0.73554 (18)	0.2300 (3)	0.9712 (3)	0.0540 (8)
H1A	0.7386	0.2533	1.0610	0.065*
O1	0.67807 (16)	0.2925 (3)	0.7394 (2)	0.0647 (8)
F1	0.9108 (2)	0.3541 (4)	1.0116 (3)	0.1322 (13)
C1	0.9018 (3)	−0.0106 (6)	0.8447 (4)	0.0732 (12)
H1B	0.9526	0.0039	0.8108	0.088*
O2	0.55089 (19)	0.6534 (3)	0.9342 (3)	0.0782 (9)
N2	0.6083 (3)	0.6480 (4)	1.0694 (4)	0.0790 (11)
F2	0.97802 (18)	0.2773 (4)	0.8551 (4)	0.1233 (11)
C2	0.8701 (3)	−0.1615 (6)	0.8525 (5)	0.0844 (14)
H2B	0.8989	−0.2489	0.8232	0.101*
F3	0.85728 (19)	0.3827 (3)	0.7915 (3)	0.1128 (10)
C3	0.7957 (3)	−0.1853 (5)	0.9035 (5)	0.0805 (13)
H3A	0.7746	−0.2886	0.9103	0.097*
C4	0.7526 (3)	−0.0551 (5)	0.9447 (4)	0.0650 (11)
H4A	0.7023	−0.0707	0.9797	0.078*
C5	0.7837 (2)	0.0983 (4)	0.9344 (3)	0.0512 (9)
C6	0.8601 (2)	0.1205 (5)	0.8858 (4)	0.0574 (10)
C7	0.9005 (3)	0.2832 (5)	0.8849 (5)	0.0680 (11)
C8	0.6852 (2)	0.3198 (4)	0.8696 (4)	0.0486 (9)
C9	0.6396 (2)	0.4541 (4)	0.9236 (4)	0.0488 (9)
C10	0.5722 (3)	0.5371 (5)	0.8487 (4)	0.0589 (10)
C11	0.6589 (3)	0.5281 (5)	1.0597 (4)	0.0641 (11)
H11A	0.7029	0.4948	1.1343	0.077*
C12	0.5197 (3)	0.5268 (5)	0.7026 (4)	0.0761 (12)
H12A	0.4770	0.6101	0.6897	0.114*

H12B	0.4919	0.4240	0.6897	0.114*
H12C	0.5559	0.5397	0.6327	0.114*

Atomic displacement parameters (Å²)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
N1	0.066 (2)	0.0617 (19)	0.0402 (15)	0.0153 (17)	0.0235 (14)	0.0065 (15)
O1	0.0783 (18)	0.0810 (19)	0.0400 (13)	0.0171 (15)	0.0239 (12)	−0.0014 (13)
F1	0.172 (3)	0.127 (3)	0.112 (2)	−0.071 (2)	0.062 (2)	−0.0454 (19)
C1	0.064 (3)	0.081 (3)	0.083 (3)	0.013 (2)	0.035 (2)	0.003 (2)
O2	0.093 (2)	0.0569 (17)	0.094 (2)	0.0188 (16)	0.0402 (19)	0.0020 (16)
N2	0.111 (3)	0.063 (2)	0.069 (2)	0.010 (2)	0.035 (2)	−0.0060 (19)
F2	0.0791 (18)	0.124 (2)	0.182 (3)	−0.0192 (18)	0.0619 (19)	0.010 (2)
C2	0.091 (3)	0.071 (3)	0.100 (4)	0.022 (3)	0.040 (3)	0.003 (3)
F3	0.108 (2)	0.087 (2)	0.135 (3)	−0.0171 (17)	0.0032 (18)	0.0453 (18)
C3	0.097 (3)	0.049 (3)	0.102 (3)	0.003 (2)	0.034 (3)	0.014 (2)
C4	0.065 (3)	0.068 (3)	0.070 (3)	−0.001 (2)	0.033 (2)	0.015 (2)
C5	0.059 (2)	0.054 (2)	0.045 (2)	0.0066 (19)	0.0234 (18)	0.0067 (16)
C6	0.058 (2)	0.069 (3)	0.050 (2)	0.006 (2)	0.0218 (18)	0.0051 (19)
C7	0.065 (3)	0.075 (3)	0.071 (3)	0.000 (2)	0.033 (2)	0.004 (2)
C8	0.050 (2)	0.049 (2)	0.052 (2)	0.0024 (18)	0.0254 (17)	0.0047 (17)
C9	0.061 (2)	0.044 (2)	0.0470 (19)	−0.0004 (18)	0.0261 (17)	0.0010 (17)
C10	0.064 (3)	0.049 (2)	0.070 (2)	−0.004 (2)	0.030 (2)	0.004 (2)
C11	0.091 (3)	0.056 (2)	0.051 (2)	0.003 (2)	0.026 (2)	0.0006 (19)
C12	0.076 (3)	0.072 (3)	0.081 (3)	−0.001 (2)	0.017 (2)	0.015 (2)

Geometric parameters (Å, º)

N1—C8	1.346 (4)	C3—C4	1.377 (5)
N1—C5	1.417 (4)	C3—H3A	0.9300
N1—H1A	0.8600	C4—C5	1.379 (5)
O1—C8	1.231 (4)	C4—H4A	0.9300
F1—C7	1.314 (4)	C5—C6	1.387 (4)
C1—C2	1.361 (6)	C6—C7	1.499 (5)
C1—C6	1.370 (5)	C8—C9	1.475 (4)
C1—H1B	0.9300	C9—C10	1.350 (5)
O2—C10	1.345 (4)	C9—C11	1.401 (5)
O2—N2	1.415 (4)	C10—C12	1.465 (5)
N2—C11	1.295 (5)	C11—H11A	0.9300
F2—C7	1.312 (4)	C12—H12A	0.9600
C2—C3	1.370 (6)	C12—H12B	0.9600
C2—H2B	0.9300	C12—H12C	0.9600
F3—C7	1.302 (5)		
C8—N1—C5	121.8 (3)	F3—C7—F1	106.5 (4)
C8—N1—H1A	119.1	F2—C7—F1	104.9 (4)
C5—N1—H1A	119.1	F3—C7—C6	114.2 (4)
C2—C1—C6	121.1 (4)	F2—C7—C6	112.7 (4)
C2—C1—H1B	119.5	F1—C7—C6	112.2 (3)
C6—C1—H1B	119.5	O1—C8—N1	122.2 (3)

C10—O2—N2	108.9 (3)	O1—C8—C9	121.8 (3)
C11—N2—O2	105.0 (3)	N1—C8—C9	115.9 (3)
C1—C2—C3	120.3 (4)	C10—C9—C11	105.2 (3)
C1—C2—H2B	119.9	C10—C9—C8	126.8 (3)
C3—C2—H2B	119.9	C11—C9—C8	128.0 (4)
C2—C3—C4	119.5 (4)	O2—C10—C9	108.7 (3)
C2—C3—H3A	120.3	O2—C10—C12	116.3 (4)
C4—C3—H3A	120.3	C9—C10—C12	135.0 (4)
C3—C4—C5	120.4 (3)	N2—C11—C9	112.2 (4)
C3—C4—H4A	119.8	N2—C11—H11A	123.9
C5—C4—H4A	119.8	C9—C11—H11A	123.9
C4—C5—C6	119.5 (3)	C10—C12—H12A	109.5
C4—C5—N1	118.9 (3)	C10—C12—H12B	109.5
C6—C5—N1	121.6 (3)	H12A—C12—H12B	109.5
C1—C6—C5	119.2 (4)	C10—C12—H12C	109.5
C1—C6—C7	119.2 (3)	H12A—C12—H12C	109.5
C5—C6—C7	121.6 (3)	H12B—C12—H12C	109.5
F3—C7—F2	105.6 (3)		

C10—O2—N2—C11	−1.6 (4)	C1—C6—C7—F1	−123.8 (4)
C6—C1—C2—C3	−0.7 (7)	C5—C6—C7—F1	52.7 (5)
C1—C2—C3—C4	1.0 (7)	C5—N1—C8—O1	0.1 (5)
C2—C3—C4—C5	0.2 (6)	C5—N1—C8—C9	−179.3 (3)
C3—C4—C5—C6	−1.7 (6)	O1—C8—C9—C10	16.6 (5)
C3—C4—C5—N1	177.1 (4)	N1—C8—C9—C10	−163.9 (3)
C8—N1—C5—C4	−100.9 (4)	O1—C8—C9—C11	−160.1 (3)
C8—N1—C5—C6	77.9 (4)	N1—C8—C9—C11	19.4 (5)
C2—C1—C6—C5	−0.8 (6)	N2—O2—C10—C9	1.4 (4)
C2—C1—C6—C7	175.8 (4)	N2—O2—C10—C12	−179.2 (3)
C4—C5—C6—C1	2.0 (5)	C11—C9—C10—O2	−0.7 (4)
N1—C5—C6—C1	−176.7 (3)	C8—C9—C10—O2	−177.9 (3)
C4—C5—C6—C7	−174.5 (4)	C11—C9—C10—C12	−180.0 (4)
N1—C5—C6—C7	6.7 (5)	C8—C9—C10—C12	2.8 (6)
C1—C6—C7—F3	114.9 (4)	O2—N2—C11—C9	1.2 (4)
C5—C6—C7—F3	−68.6 (5)	C10—C9—C11—N2	−0.4 (4)
C1—C6—C7—F2	−5.7 (6)	C8—C9—C11—N2	176.9 (3)
C5—C6—C7—F2	170.9 (4)		

Hydrogen-bond geometry (Å, º)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N1—H1*A*···O1^{i}	0.86	2.13	2.855 (3)	142

Symmetry code: (i) *x*, −*y*+1/2, *z*+1/2.