



Crystal structure of pirfenidone (5-methyl-1-phenyl-1*H*-pyridin-2-one): an active pharmaceutical ingredient (API)

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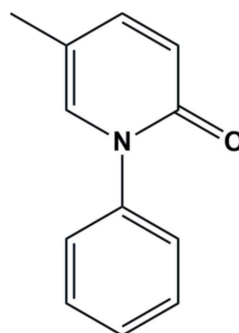
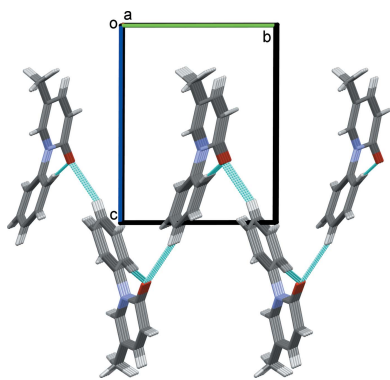
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The crystal structure of pirfenidone, C₁₂H₁₁NO [alternative name: 5-methyl-1-phenylpyridin-2(1*H*)-one], an active pharmaceutical ingredient (API) approved in Europe and Japan for the treatment of Idiopathic pulmonary fibrosis (IPF), is reported here for the first time. It was crystallized from toluene by the temperature gradient technique, and crystallizes in the chiral monoclinic space group *P*2₁. The phenyl and pyridone rings are inclined to each other by 50.30 (11)°. In the crystal, molecules are linked by C–H···O hydrogen bonds involving the same acceptor atom, forming undulating layers lying parallel to the *ab* plane.

1. Chemical context

Idiopathic Pulmonary Fibrosis (IPF) is a lung disease characterized by cough, scars and dyspnea that leads to progressive and irreversible loss of lung function. Pirfenidone (systematic name: 5-methyl-1-phenyl-1*H*-pyridin-2-one) has been approved in Japan since 2008 (Pirespa[®]) and in Europe since 2011 (Esbriet[®]) for the treatment of IPF, even if its mechanism of action has not been completely elucidated (Richeldi *et al.*, 2011). Different synthetic approaches have been reported, mainly relying on *N*-arylation reactions of 5-methyl-2-pyridone (Liu *et al.*, 2009; Crifar *et al.*, 2014; Jung *et al.*, 2016; Falb *et al.*, 2017). Pirfenidone has been known since 1974 (Gadekar, 1974) and its antifibrotic properties were described in 1990 (Margolin, 1990). Nevertheless, despite its formulation as oral tablets, no information on the solid-state structure of this compound has been reported to date. In the present study, we report and analyse the crystal structure of pirfenidone.



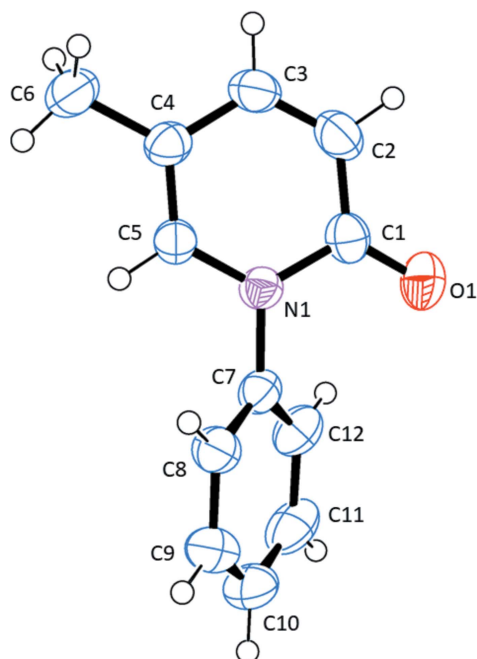


Figure 1
A view of the molecular structure of pirfenidone with the atom labelling. Displacement ellipsoids are drawn at the 50% probability level.

2. Structural commentary

The molecular structure of pirfenidone is shown in Fig. 1. This axially chiral molecule crystallizes in the monoclinic space group $P2_1$, with one molecule in a general position. The molecule is far from planar with the phenyl (C7–C12) and pyridinone (N1/C1–C5) rings subtending a dihedral angle of $50.30(11)^\circ$.

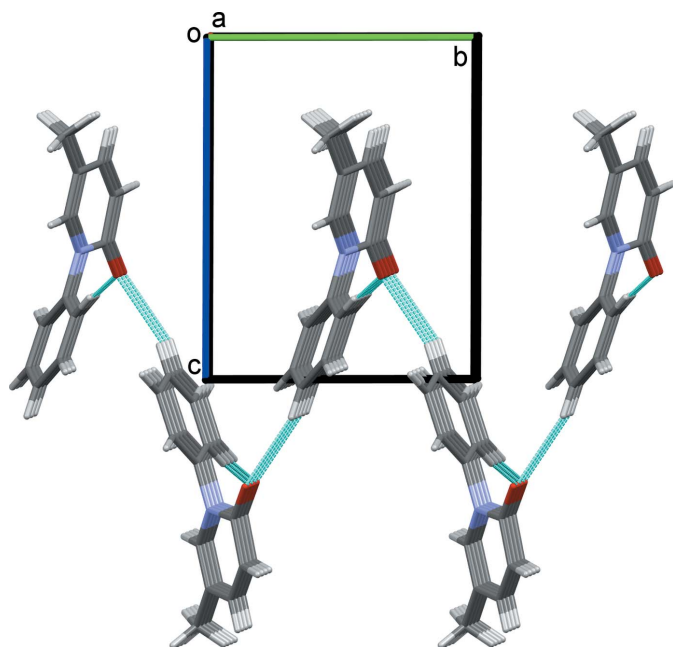


Figure 2
A view along the a axis of the crystal packing of pirfenidone. The C–H...O hydrogen bonds (see Table 1) are shown as dashed lines.

Table 1
Hydrogen-bond geometry (\AA , $^\circ$).

$D-H\cdots A$	$D-H$	$H\cdots A$	$D\cdots A$	$D-H\cdots A$
C8–H8...O1 ⁱ	0.93	2.33	3.203 (3)	156
C10–H10...O1 ⁱⁱ	0.93	2.46	3.310 (3)	152

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

3. Supramolecular features

In the crystal, molecules are linked by C–H...O hydrogen bonds involving the same acceptor atom (Table 1), forming an undulating network, enclosing $R_4^3(20)$ ring motifs, and lying parallel to the ab plane (Figs. 2 and 3). The $R_4^3(20)$ ring motifs are clearly visible in Fig. 3. There are no other significant intermolecular contacts present according to the analysis of the crystal structure using *PLATON* (Spek, 2009).

4. Database Survey

A search of the Cambridge Structural Database (CSD, Version 5.40, February 2019; Groom *et al.*, 2016) for 1-phenylpyridin-2(*1H*)-ones, excluding structures with ring atoms being included in further cyclic moieties, gave 40 hits (see supporting information file S1). Only six of these compounds involve an unsubstituted phenyl ring as in the title compound. When considering compounds with no substituent in position-6 of the pyridinone ring (on atom C5 in the title compound; Fig. 1) only three structures fit this extra criteria, *viz.* *S*-ethyl 2-oxo-1-phenyl-1,2-dihydro-3-pyridinecarbothioate (CSD refcode NOLBIA; Liu *et al.*, 2008), monoclinic space group $P2_1$, 4-chloro-6-oxo-1-phenyl-1,6-dihydropyridine-3-carbaldehyde (QIWFIM; Xiang *et al.*, 2008), monoclinic space group $P2_1/c$, and methyl 5-benzoyl-2-oxo-1-phenyl-1,2-dihydropyridine-4-carboxylate (TEMKIH; Shao *et al.*, 2012), orthorhombic space group $Pna2_1$ with two independent molecules in the asymmetric unit. In these three compounds, the phenyl ring is inclined to the pyridone ring by *ca* $65.50, 64.66$ and $55.83/57.12^\circ$, respectively. This dihedral angle in the title compound, pirfenidone, is $50.30(11)^\circ$. In the other three

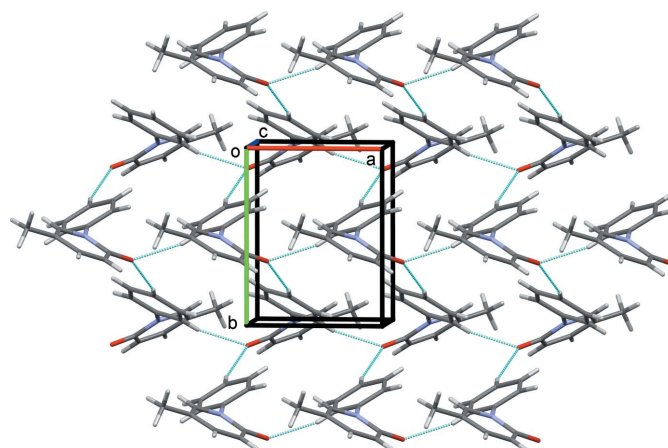


Figure 3
A view along the c axis of the crystal packing of pirfenidone. The C–H...O hydrogen bonds (see Table 1) are shown as dashed lines.

Table 2
Experimental details.

Crystal data	
Chemical formula	C ₁₂ H ₁₁ NO
<i>M_r</i>	185.22
Crystal system, space group	Monoclinic, <i>P</i> 2 ₁
Temperature (K)	293
<i>a</i> , <i>b</i> , <i>c</i> (Å)	6.2525 (8), 7.797 (1), 10.2810 (13)
β (°)	104.744 (2)
<i>V</i> (Å ³)	484.70 (11)
<i>Z</i>	2
Radiation type	Mo <i>K</i> α
μ (mm ⁻¹)	0.08
Crystal size (mm)	0.50 × 0.45 × 0.05
Data collection	
Diffractometer	Bruker SMART APEX CCD
Absorption correction	Multi-scan (<i>SADABS</i> ; Bruker, 2010)
<i>T_{min}</i> , <i>T_{max}</i>	0.692, 0.746
No. of measured, independent and observed [<i>I</i> > 2 σ (<i>I</i>)] reflections	4547, 2128, 1879
<i>R_{int}</i>	0.019
(<i>sin</i> θ / λ) _{max} (Å ⁻¹)	0.643
Refinement	
<i>R</i> [<i>F</i> ² > 2 σ (<i>F</i> ²)], <i>wR</i> (<i>F</i> ²), <i>S</i>	0.037, 0.095, 1.04
No. of reflections	2128
No. of parameters	127
No. of restraints	1
H-atom treatment	H-atom parameters constrained
$\Delta\rho_{\max}$, $\Delta\rho_{\min}$ (e Å ⁻³)	0.11, -0.20
Absolute structure	Flack <i>x</i> determined using 762 quotients [(<i>I</i> ⁺) - (<i>I</i> ⁻)] / [(<i>I</i> ⁺) + (<i>I</i> ⁻)] (Parsons <i>et al.</i> , 2013)
Absolute structure parameter	0.3 (4)

Computer programs: *APEX2* and *SAINT* (Bruker, 2010), *SHELXT2017* (Sheldrick, 2015a), *SHELXL2017* (Sheldrick, 2015b), *ORTEP-3 for Windows* (Farrugia, 2012), *Mercury* (Macrae *et al.*, 2008), *PLATON* (Spek, 2009) and *PUBLICIF* (Westrip, 2010).

compounds [AQIKIV (Gorobets *et al.*, 2010), BAFPUV (Dyachenko *et al.*, 2011) and WEDCEP (Allais *et al.*, 2012) – see supporting information file S1] with a substituent in position-6 of the pyridinone ring the corresponding dihedral angle varies from *ca* 73.02 to 89.28° as a result of steric hindrance.

5. Synthesis and crystallization

Pirfenidone was obtained in > 99.5% purity according to the method published previously (Mossotti *et al.*, 2018). Single crystals were grown in the following way: approximately 100 mg of pirfenidone in 2 mL of toluene was heated until complete dissolution. The flask with this solution was then closed and kept at 273–278 K. Well-formed colourless crystals of pirfenidone were obtained after 1 week. The melting point of this crystal form, determined by DSC analysis (heating rate 10 K min⁻¹), is 383 K. This crystallization procedure must be performed in order to grow single crystals suitable for X-ray diffraction analysis and not with the aim of increasing the purity of the product. It is worth nothing that the industrial process is already optimized for the isolation of a pure API (> 99.5%) and a further crystallization step is not needed to improve its purity. We performed several other crystallization trials in order to search for other possible forms of pirfeni-

done; however, each crystallization attempt gave rise to the same crystal form.

6. Refinement

Crystal data, data collection and structure refinement details are summarized in Table 2. The H atoms were included in calculated positions and treated as riding: C–H = 0.93–0.96 Å with *U*_{iso}(H) = 1.5*U*_{eq}(C-methyl) and 1.2*U*_{eq}(C) for other H atoms.

Acknowledgements

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Computing details

Data collection: *APEX2* (Bruker, 2010); cell refinement: *S SAINT* (Bruker, 2010); data reduction: *S SAINT* (Bruker, 2010); program(s) used to solve structure: *SHELXT2017* (Sheldrick, 2015a); program(s) used to refine structure: *SHELXL2017* (Sheldrick, 2015b); molecular graphics: *ORTEP-3 for Windows* (Farrugia, 2012) and *Mercury* (Macrae *et al.*, 2008); software used to prepare material for publication: *SHELXL2017* (Sheldrick, 2015b), *PLATON* (Spek, 2009) and *publCIF* (Westrip, 2010).

5-Methyl-1-phenylpyridin-2(1*H*)-one

Crystal data

$C_{12}H_{11}NO$	$D_x = 1.269 \text{ Mg m}^{-3}$
$M_r = 185.22$	Melting point: 375 K
Monoclinic, $P2_1$	Mo $K\alpha$ radiation, $\lambda = 0.71073 \text{ \AA}$
$a = 6.2525 (8) \text{ \AA}$	Cell parameters from 2547 reflections
$b = 7.797 (1) \text{ \AA}$	$\theta = 3.3\text{--}27.2^\circ$
$c = 10.2810 (13) \text{ \AA}$	$\mu = 0.08 \text{ mm}^{-1}$
$\beta = 104.744 (2)^\circ$	$T = 293 \text{ K}$
$V = 484.70 (11) \text{ \AA}^3$	Plate, colourless
$Z = 2$	$0.50 \times 0.45 \times 0.05 \text{ mm}$
$F(000) = 196$	

Data collection

Bruker SMART APEX CCD diffractometer	2128 independent reflections
ω scans	1879 reflections with $I > 2\sigma(I)$
Absorption correction: multi-scan (SADABS; Bruker, 2010)	$R_{\text{int}} = 0.019$
$T_{\text{min}} = 0.692$, $T_{\text{max}} = 0.746$	$\theta_{\text{max}} = 27.2^\circ$, $\theta_{\text{min}} = 2.1^\circ$
4547 measured reflections	$h = -8 \rightarrow 8$
	$k = -9 \rightarrow 10$
	$l = -13 \rightarrow 13$

Refinement

Refinement on F^2	1 restraint
Least-squares matrix: full	Hydrogen site location: inferred from neighbouring sites
$R[F^2 > 2\sigma(F^2)] = 0.037$	H-atom parameters constrained
$wR(F^2) = 0.095$	$w = 1/[\sigma^2(F_o^2) + (0.0528P)^2 + 0.0476P]$
$S = 1.04$	where $P = (F_o^2 + 2F_c^2)/3$
2128 reflections	$(\Delta/\sigma)_{\text{max}} < 0.001$
127 parameters	

$$\Delta\rho_{\max} = 0.11 \text{ e } \text{\AA}^{-3}$$

$$\Delta\rho_{\min} = -0.20 \text{ e } \text{\AA}^{-3}$$

Absolute structure: Flack x determined using
762 quotients $[(F^-)-(F)]/[(F^+)+(F)]$ (Parsons *et al.*,
2013)
Absolute structure parameter: 0.3 (4)

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. none

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (\AA^2)

	x	y	z	$U_{\text{iso}}^*/U_{\text{eq}}$
N1	0.7599 (2)	0.5275 (2)	0.62509 (16)	0.0382 (4)
O1	1.0951 (2)	0.6634 (3)	0.69330 (17)	0.0602 (5)
C1	0.9386 (3)	0.6188 (3)	0.6002 (2)	0.0437 (5)
C5	0.5769 (3)	0.4849 (3)	0.5233 (2)	0.0395 (5)
H5	0.460421	0.428046	0.545647	0.047*
C7	0.7635 (3)	0.4782 (3)	0.76141 (19)	0.0401 (5)
C4	0.5595 (3)	0.5219 (3)	0.3929 (2)	0.0430 (5)
C12	0.9445 (4)	0.3913 (3)	0.8390 (2)	0.0497 (5)
H12	1.066616	0.368712	0.805687	0.060*
C8	0.5830 (3)	0.5134 (3)	0.8108 (2)	0.0481 (5)
H8	0.462114	0.572084	0.758231	0.058*
C6	0.3599 (4)	0.4732 (3)	0.2835 (2)	0.0579 (6)
H6A	0.400128	0.387266	0.227127	0.087*
H6B	0.304346	0.572565	0.230447	0.087*
H6C	0.247695	0.428652	0.322817	0.087*
C11	0.9409 (5)	0.3383 (3)	0.9672 (2)	0.0616 (7)
H11	1.061057	0.278817	1.019737	0.074*
C3	0.7416 (4)	0.6079 (3)	0.3637 (2)	0.0527 (6)
H3	0.737708	0.633055	0.274701	0.063*
C2	0.9189 (4)	0.6537 (3)	0.4608 (2)	0.0540 (6)
H2	1.033979	0.710617	0.436893	0.065*
C9	0.5836 (4)	0.4604 (4)	0.9395 (2)	0.0623 (7)
H9	0.462501	0.484254	0.973553	0.075*
C10	0.7616 (5)	0.3728 (4)	1.0174 (2)	0.0649 (7)
H10	0.760634	0.337171	1.103577	0.078*

Atomic displacement parameters (\AA^2)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
N1	0.0355 (8)	0.0426 (9)	0.0362 (8)	0.0009 (8)	0.0084 (7)	0.0007 (7)
O1	0.0399 (8)	0.0725 (11)	0.0631 (11)	-0.0111 (8)	0.0038 (7)	-0.0046 (9)
C1	0.0368 (10)	0.0430 (12)	0.0524 (12)	0.0007 (9)	0.0134 (9)	-0.0023 (10)
C5	0.0380 (9)	0.0395 (11)	0.0398 (10)	-0.0026 (9)	0.0078 (8)	0.0011 (9)
C7	0.0411 (10)	0.0397 (11)	0.0362 (10)	-0.0013 (8)	0.0034 (8)	0.0002 (8)

C4	0.0524 (11)	0.0376 (11)	0.0376 (10)	-0.0009 (10)	0.0087 (9)	-0.0001 (9)
C12	0.0496 (12)	0.0478 (12)	0.0459 (12)	0.0081 (10)	0.0017 (10)	-0.0051 (10)
C8	0.0395 (10)	0.0602 (13)	0.0435 (11)	-0.0003 (10)	0.0082 (8)	0.0070 (11)
C6	0.0705 (15)	0.0570 (15)	0.0399 (11)	-0.0077 (13)	0.0026 (11)	-0.0004 (11)
C11	0.0708 (16)	0.0522 (14)	0.0469 (13)	0.0053 (12)	-0.0126 (12)	0.0046 (11)
C3	0.0694 (15)	0.0522 (14)	0.0410 (11)	-0.0091 (11)	0.0224 (11)	0.0002 (10)
C2	0.0559 (13)	0.0556 (14)	0.0576 (14)	-0.0113 (12)	0.0276 (11)	-0.0015 (11)
C9	0.0595 (14)	0.0851 (19)	0.0450 (13)	-0.0110 (13)	0.0183 (11)	0.0036 (13)
C10	0.0826 (19)	0.0688 (17)	0.0378 (12)	-0.0134 (16)	0.0054 (12)	0.0103 (12)

Geometric parameters (Å, °)

N1—C5	1.381 (2)	C8—C9	1.386 (3)
N1—C1	1.402 (2)	C8—H8	0.9300
N1—C7	1.448 (3)	C6—H6A	0.9600
O1—C1	1.232 (3)	C6—H6B	0.9600
C1—C2	1.432 (3)	C6—H6C	0.9600
C5—C4	1.349 (3)	C11—C10	1.375 (4)
C5—H5	0.9300	C11—H11	0.9300
C7—C8	1.378 (3)	C3—C2	1.338 (3)
C7—C12	1.384 (3)	C3—H3	0.9300
C4—C3	1.417 (3)	C2—H2	0.9300
C4—C6	1.501 (3)	C9—C10	1.376 (4)
C12—C11	1.386 (4)	C9—H9	0.9300
C12—H12	0.9300	C10—H10	0.9300
C5—N1—C1	121.93 (17)	C4—C6—H6A	109.5
C5—N1—C7	118.39 (16)	C4—C6—H6B	109.5
C1—N1—C7	119.67 (16)	H6A—C6—H6B	109.5
O1—C1—N1	120.88 (19)	C4—C6—H6C	109.5
O1—C1—C2	124.9 (2)	H6A—C6—H6C	109.5
N1—C1—C2	114.20 (18)	H6B—C6—H6C	109.5
C4—C5—N1	122.94 (19)	C10—C11—C12	120.7 (2)
C4—C5—H5	118.5	C10—C11—H11	119.7
N1—C5—H5	118.5	C12—C11—H11	119.7
C8—C7—C12	120.74 (19)	C2—C3—C4	121.7 (2)
C8—C7—N1	119.42 (17)	C2—C3—H3	119.1
C12—C7—N1	119.81 (19)	C4—C3—H3	119.1
C5—C4—C3	116.47 (19)	C3—C2—C1	122.6 (2)
C5—C4—C6	122.2 (2)	C3—C2—H2	118.7
C3—C4—C6	121.4 (2)	C1—C2—H2	118.7
C7—C12—C11	119.0 (2)	C10—C9—C8	120.6 (2)
C7—C12—H12	120.5	C10—C9—H9	119.7
C11—C12—H12	120.5	C8—C9—H9	119.7
C7—C8—C9	119.3 (2)	C11—C10—C9	119.7 (2)
C7—C8—H8	120.4	C11—C10—H10	120.2
C9—C8—H8	120.4	C9—C10—H10	120.2

Hydrogen-bond geometry (Å, °)

<i>D</i> —H \cdots <i>A</i>	<i>D</i> —H	H \cdots <i>A</i>	<i>D</i> \cdots <i>A</i>	<i>D</i> —H \cdots <i>A</i>
C8—H8 \cdots O1 ⁱ	0.93	2.33	3.203 (3)	156
C10—H10 \cdots O1 ⁱⁱ	0.93	2.46	3.310 (3)	152

Symmetry codes: (i) $x-1, y, z$; (ii) $-x+2, y-1/2, -z+2$.