

π -Stacked hydrogen-bonded chains of rings in 2,4-difluorobenzaldehyde isonicotinoylhydrazone and hydrogen-bonded sheets in 2,3-dichlorobenzaldehyde isonicotinoylhydrazone

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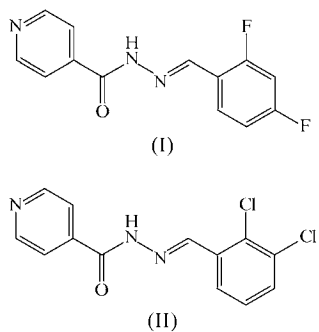
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The difluorinated ring in 2,4-difluorobenzaldehyde isonicotinoylhydrazone, C₁₃H₉F₂N₃O, (I), is disordered over two sets of sites with unequal occupancy. The molecules of (I) are linked by a combination of N—H···O and C—H···O hydrogen bonds into chains of rings, which are linked into sheets by a single π – π stacking interaction. In 2,3-dichlorobenzaldehyde isonicotinoylhydrazone, C₁₃H₉Cl₂N₃O, (II), the molecules are linked by a combination of N—H···N, C—H···N and C—H···O hydrogen bonds into sheets of R₄⁴(14) and R₄⁴(26) rings.

Comment

Tuberculosis is again a worldwide problem, due in part to the advent of multi-drug resistant strains and the association of tuberculosis with human immunodeficiency virus infection in AIDS. A first-line drug used in combination with other drugs



for the treatment of tuberculosis is isoniazid (isonicotinoylhydrazine). As part of a study of new derivatives of isoniazid, we now report the structures of 2,4-difluoro-

benzaldehyde isonicotinoylhydrazone, (I), and 2,3-dichlorobenzaldehyde isonicotinoylhydrazone, (II).

The leading torsion angles (Table 1) indicate that, while the molecules of compound (II) are nearly planar, in those of compound (I) not only is the central spacer unit between atoms C14 and C21 non-planar, but each of the rings, particularly the pyridyl ring, is twisted away from the mean plane of the adjacent spacer atoms.

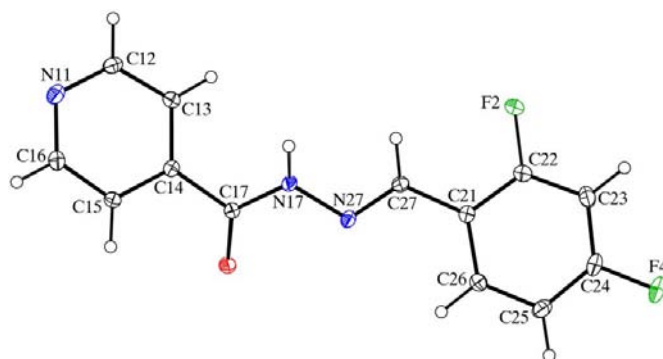


Figure 1
The major conformer (see *Comment*) of compound (I), showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 30% probability level.

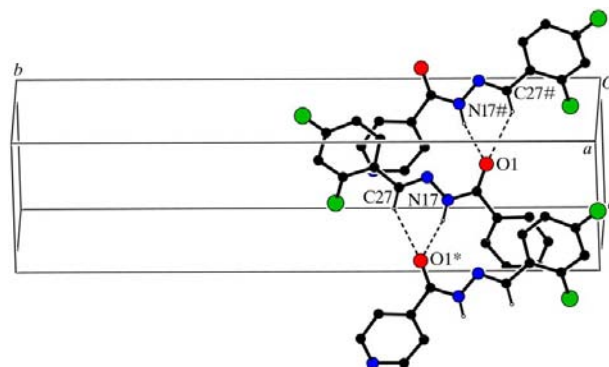


Figure 2
Part of the crystal structure of compound (I), showing the formation of a chain of rings along [101]. For the sake of clarity, only the major conformer is shown, and H atoms not involved in the motif shown have been omitted. Atoms marked with an asterisk (*) or a hash (#) are at the symmetry positions $(\frac{1}{2} + x, \frac{1}{2} - y, \frac{1}{2} + z)$ and $(-\frac{1}{2} + x, \frac{1}{2} - y, -\frac{1}{2} + z)$, respectively.

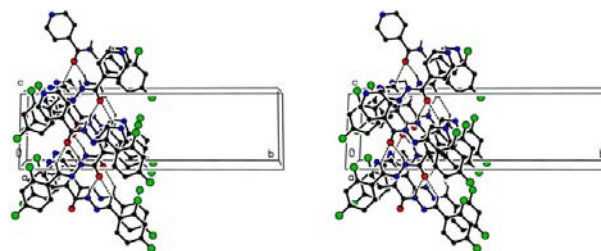


Figure 3
A stereoview of part of the crystal structure of compound (I), showing the formation of an (010) sheet of π -stacked [101] chains. For the sake of clarity, only the major conformer is shown and H atoms not involved in the motifs shown have been omitted.

Compound (I) (Fig. 1) exhibits orientational disorder of the difluorinated ring, such that one of the F atoms appears to be disordered over sites bonded to C22 and C26. The major conformer, with this F atom occupying the site designated F2, has occupancy 0.760 (3), while the minor conformer, with the disordered F atom occupying the site designated F6, has occupancy 0.240 (3).

The molecules of compound (I) are linked by a combination of N—H···O and C—H···O hydrogen bonds (Table 2) into a chain of rings, and these chains are linked into sheets by a single π – π stacking interaction. Atoms N17 and C27 in the molecule at (x, y, z) both act as hydrogen-bond donors to atom O1 in the molecule at $(\frac{1}{2} + x, \frac{1}{2} - y, \frac{1}{2} + z)$, so forming a $C(4)C(7)[R_2^1(6)]$ chain of rings (Bernstein *et al.*, 1995) running

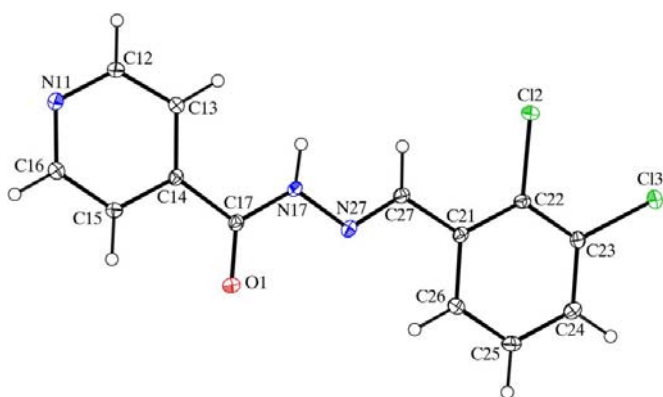


Figure 4
The molecule of compound (II), showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 30% probability level.

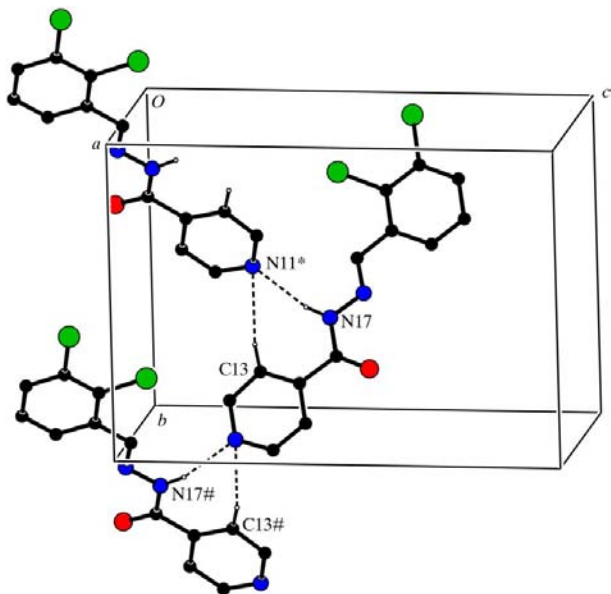


Figure 5
Part of the crystal structure of compound (II), showing the formation of a chain of rings along [010]. For the sake of clarity, H atoms not involved in the motif shown have been omitted. Atoms marked with an asterisk (*) or a hash (#) are at the symmetry positions $(1 - x, -\frac{1}{2} + y, \frac{1}{2} - z)$ and $(1 - x, \frac{1}{2} + y, \frac{1}{2} - z)$, respectively.

parallel to the [101] direction and generated by the n -glide plane at $y = \frac{1}{4}$ (Fig. 2).

The aryl ring in the molecule at (x, y, z) and the pyridyl ring in the molecules at $(\frac{1}{2} + x, \frac{1}{2} - y, -\frac{1}{2} + z)$ and $(-\frac{1}{2} + x, \frac{1}{2} - y, \frac{1}{2} + z)$ are almost parallel, with a dihedral angle of only $0.6(2)^\circ$ between adjacent rings; the corresponding ring–centroid separations are $3.754(2) \text{ \AA}$, with an interplanar spacing of *ca* 3.394 \AA and a ring offset of *ca* 1.60 \AA . This interaction thus forms a chain parallel to the $[10\bar{1}]$ direction, which links the hydrogen-bonded [101] chains into an (010) sheet lying in the domain $-0.01 < y < 0.51$ (Fig. 3). A second such sheet, related to the first by inversion and generated by the n -glide plane at $y = \frac{3}{4}$, lies in the domain $0.49 < y < 1.01$, but there are no direction-specific interactions between adjacent (010) sheets.

The molecules of compound (II) (Fig. 4) are fully ordered, and they are linked into sheets by a combination of N—H···N, C—H···N and C—H···O hydrogen bonds. Atoms N17 and C13 in the molecule at (x, y, z) both act as hydrogen-bond donors to pyridyl atom N11 in the molecule at $(1 - x, -\frac{1}{2} + y, \frac{1}{2} - z)$, so forming a $C(4)C(7)[R_2^1(7)]$ chain of rings running parallel to the [010] direction and generated by the 2_1 screw axis along $(\frac{1}{2}, y, \frac{1}{4})$ (Fig. 5). In addition, atom C12 in the molecule at (x, y, z) acts as hydrogen-bond donor to atom O1 in the molecule at $(x, \frac{3}{2} - y, -\frac{1}{2} + z)$, so forming a $C(6)$ chain

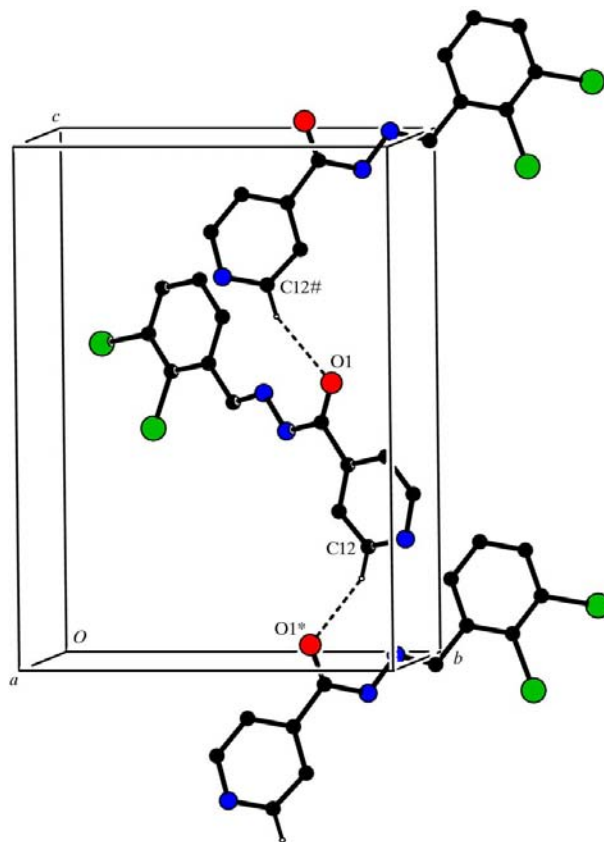


Figure 6
Part of the crystal structure of compound (II), showing the formation of a $C(6)$ chain along [001]. For the sake of clarity, H atoms not involved in the motif shown have been omitted. Atoms marked with an asterisk (*) or a hash (#) are at the symmetry positions $(x, \frac{3}{2} - y, -\frac{1}{2} + z)$ and $(x, \frac{3}{2} - y, \frac{1}{2} + z)$, respectively.

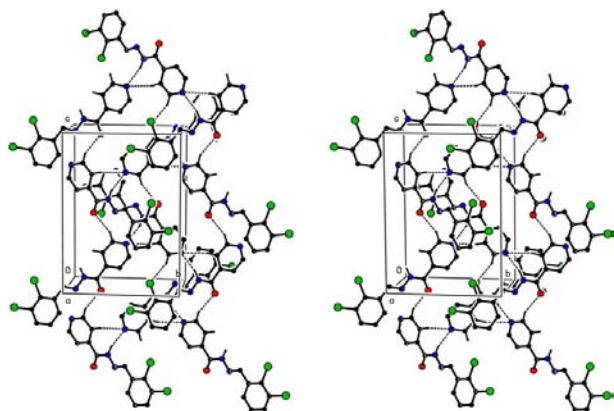


Figure 7

A stereoview of part of the crystal structure of compound (II), showing the formation of a hydrogen-bonded (100) sheet. For the sake of clarity, H atoms not involved in the motifs shown have been omitted.

running parallel to the [001] direction and generated by the *c*-glide plane at $y = \frac{3}{4}$ (Fig. 6). The combination of the [010] and [001] chains then generates a sheet parallel to (100) containing alternating $R_4^4(14)$ and $R_4^4(26)$ rings, where each type of ring is centrosymmetric (Fig. 7). There are no direction-specific interactions between adjacent sheets.

Experimental

Equimolar mixtures of isoniazid (2 mmol) and the appropriate dihalobenzaldehyde (2 mmol) in tetrahydrofuran (20 ml) containing a catalytic amount of triethylamine were heated under reflux for 6 h in an atmosphere of dinitrogen. After cooling, the mixtures were concentrated under reduced pressure and the residues were purified by column chromatography on silica gel, eluting with a hexane–ethyl acetate gradient, to give pure samples of compounds (I) and (II). Crystallization from ethanol solutions gave crystals suitable for single-crystal X-ray diffraction. For (I), m.p. 501–503 K; for (II), m.p. 511–512 K. Spectroscopic analysis, for (I): ^1H NMR (DMSO- d_6): δ 12.43 (1H, s, NH), 8.82 (2H, d, $J = 5.5$ Hz), 8.67 (1H, s), 8.02 (1H, dd, $J = 15.5$ and 8.5 Hz), 7.85 (2H, d, $J = 5.5$ Hz), 7.40 (1H, dd, $J = 9.5$ and 11.0 Hz), 7.23 (1H, dd, $J = 8.5$ and 8.5 Hz); ^{13}C NMR (DMSO- d_6): δ : 163.4 (dd, $J = 13.2$ and 250.5 Hz), 161.6, 161.1 (dd, $J = 11.1$ and 251.4 Hz), 150.4, 140.9, 140.1, 128.0 (d, $J = 8.2$ Hz), 121.4, 118.4 (d, $J = 10.1$ Hz), 112.7 (d, $J = 21.9$ Hz), 104.5 (t, $J = 25.5$ Hz); for (II): ^1H NMR (DMSO- d_6): δ 12.35 (1H, s, NH), 8.88 (1H, s), 8.79 (2H, d, $J = 5.5$ Hz), 7.98 (1H, d, $J = 8.0$ Hz), 7.83 (2H, d, $J = 5.5$ Hz), 7.71 (1H, d, $J = 7.5$ Hz), 7.45 (1H, dd, $J = 7.5$ and 8.0 Hz); ^{13}C NMR (DMSO- d_6): δ 161.7, 150.4, 149.6, 144.6, 140.0, 133.7, 132.4, 131.8, 128.5, 125.6, 121.5; IR (KBr, ν , cm^{-1}), for (I): 3177 (NH) and 1654 (CO); for (II): 3188 (NH) and 1686 (CO).

Compound (I)

Crystal data

$\text{C}_{13}\text{H}_9\text{F}_2\text{N}_3\text{O}$
 $M_r = 261.23$
 Monoclinic, $P2_1/n$
 $a = 6.8859$ (3) Å
 $b = 24.7258$ (12) Å
 $c = 7.2582$ (2) Å
 $\beta = 107.953$ (2)°
 $V = 1175.61$ (8) Å³
 $Z = 4$

$D_x = 1.476$ Mg m⁻³
 Mo $K\alpha$ radiation
 Cell parameters from 2658 reflections
 $\theta = 3.2$ – 27.5 °
 $\mu = 0.12$ mm⁻¹
 $T = 120$ (2) K
 Block, colourless
 $0.60 \times 0.35 \times 0.10$ mm

Data collection

Nonius KappaCCD area-detector diffractometer
 φ and ω scans
 Absorption correction: multi-scan (SADABS; Sheldrick, 2003)
 $T_{\min} = 0.946$, $T_{\max} = 0.988$
 10256 measured reflections

2658 independent reflections
 2231 reflections with $I > 2\sigma(I)$
 $R_{\text{int}} = 0.031$
 $\theta_{\text{max}} = 27.5$ °
 $h = -8 \rightarrow 8$
 $k = -32 \rightarrow 30$
 $l = -9 \rightarrow 9$

Refinement

Refinement on F^2
 $R[F^2 > 2\sigma(F^2)] = 0.041$
 $wR(F^2) = 0.101$
 $S = 1.07$
 2658 reflections
 178 parameters
 H-atom parameters constrained

$w = 1/[\sigma^2(F_o^2) + (0.035P)^2 + 0.6726P]$
 where $P = (F_o^2 + 2F_c^2)/3$
 $(\Delta/\sigma)_{\text{max}} = 0.001$
 $\Delta\rho_{\text{max}} = 0.25$ e Å⁻³
 $\Delta\rho_{\text{min}} = -0.28$ e Å⁻³

Table 1

Selected torsion angles (°) for compounds (I) and (II).

	(I)	(II)
C13–C14–C17–N17	39.21 (19)	–1.9 (2)
C14–C17–N17–N27	178.39 (12)	–175.12 (12)
C17–N17–N27–C27	169.28 (13)	176.30 (13)
N17–N27–C27–C21	176.72 (12)	–178.28 (12)
N27–C27–C21–C22	168.76 (14)	–173.32 (13)

Table 2

Hydrogen-bond geometry (Å, °) for (I).

<i>D</i> –H... <i>A</i>	<i>D</i> –H	H... <i>A</i>	<i>D</i> ... <i>A</i>	<i>D</i> –H... <i>A</i>
N17–H17...O1 ¹	0.88	1.97	2.826 (2)	164
C27–H27...O1 ¹	0.95	2.49	3.261 (2)	138

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

Compound (II)

Crystal data

$\text{C}_{13}\text{H}_9\text{Cl}_2\text{N}_3\text{O}$
 $M_r = 294.13$
 Monoclinic, $P2_1/c$
 $a = 7.7369$ (2) Å
 $b = 10.7764$ (4) Å
 $c = 14.9091$ (5) Å
 $\beta = 90.2400$ (18)°
 $V = 1243.05$ (7) Å³
 $Z = 4$
 $D_x = 1.572$ Mg m⁻³

Mo $K\alpha$ radiation
 Cell parameters from 2833 reflections
 $\theta = 3.2$ – 27.5 °
 $\mu = 0.52$ mm⁻¹
 $T = 120$ (2) K
 Plate, colourless
 $0.30 \times 0.10 \times 0.07$ mm

Data collection

Nonius KappaCCD area-detector diffractometer
 φ and ω scans
 Absorption correction: multi-scan (SADABS; Sheldrick, 2003)
 $T_{\min} = 0.861$, $T_{\max} = 0.965$
 18370 measured reflections

2833 independent reflections
 2466 reflections with $I > 2\sigma(I)$
 $R_{\text{int}} = 0.033$
 $\theta_{\text{max}} = 27.5$ °
 $h = -10 \rightarrow 9$
 $k = -13 \rightarrow 13$
 $l = -19 \rightarrow 19$

Refinement

Refinement on F^2
 $R[F^2 > 2\sigma(F^2)] = 0.031$
 $wR(F^2) = 0.099$
 $S = 1.15$
 2833 reflections
 172 parameters
 H-atom parameters constrained

$w = 1/[\sigma^2(F_o^2) + (0.0574P)^2 + 0.238P]$
 where $P = (F_o^2 + 2F_c^2)/3$
 $(\Delta/\sigma)_{\text{max}} = 0.001$
 $\Delta\rho_{\text{max}} = 0.42$ e Å⁻³
 $\Delta\rho_{\text{min}} = -0.49$ e Å⁻³

Table 3
Hydrogen-bond geometry (Å, °) for (II).

<i>D</i> —H... <i>A</i>	<i>D</i> —H	H... <i>A</i>	<i>D</i> ... <i>A</i>	<i>D</i> —H... <i>A</i>
N17—H17...N11 ⁱ	0.88	2.22	3.079 (2)	164
C12—H12...O1 ⁱⁱ	0.95	2.45	3.338 (2)	155
C13—H13...N11 ⁱ	0.95	2.59	3.512 (2)	164

Symmetry codes: (i) $-x + 1, y - \frac{1}{2}, -z + \frac{1}{2}$; (ii) $x, -y + \frac{3}{2}, z - \frac{1}{2}$.

The space groups $P2_1/n$ for (I) and $P2_1/c$ for (II) were uniquely assigned from the systematic absences. All H atoms were located in difference maps and then treated as riding atoms, with distances C—H = 0.95 Å and N—H = 0.88 Å, and with $U_{\text{iso}}(\text{H}) = 1.2U_{\text{eq}}(\text{C}, \text{N})$. In compound (I), the disordered difluorinated ring was modelled using partially occupied hydrogen and fluorine sites adjacent to atoms C22 and C26, with the occupancies of the partially occupied hydrogen and partially occupied fluorine sites each constrained to sum to unity. The site-occupancy factors then refined to 0.760 (3) and 0.240 (3).

For both compounds, data collection: *COLLECT* (Nonius, 1999); cell refinement: *DENZO* (Otwinowski & Minor, 1997) and *COLLECT*; data reduction: *DENZO* and *COLLECT*; program(s) used to solve structure: *OSCAIL* (McArdle, 2003) and *SHELXS97* (Sheldrick, 1997); program(s) used to refine structure: *OSCAIL* and *SHELXL97* (Sheldrick, 1997); molecular graphics: *PLATON* (Spek,

2003); software used to prepare material for publication: *SHELXL97* and *PRPKAPPA* (Ferguson, 1999).

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: SK1868). Services for accessing these data are described at the back of the journal.

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