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Three 5*H*-indeno[1,2-*c*]pyridazin-5-one derivatives, potent type-B monoamine oxidase inhibitors

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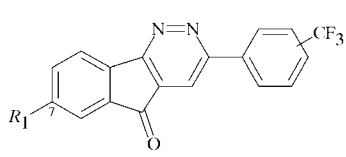
The structures of three compounds, namely 7-methoxy-2-[3-(trifluoromethyl)phenyl]-9*H*-indeno[1,2-*c*]pyridazin-9-one, $C_{19}H_{11}F_3N_2O_2$, (I*d*), 6-methoxy-2-[3-(trifluoromethyl)phenyl]-9*H*-indeno[1,2-*c*]pyridazin-9-one, $C_{19}H_{11}F_3N_2O_2$, (II*d*), and 2-methyl-6-(4,4,4-trifluorobutoxy)-9*H*-indeno[1,2-*c*]pyridazin-9-one, $C_{16}H_{13}F_3N_2O_2$, (II*f*), which are potent reversible type-B monoamine oxidase (MAO-B) inhibitors, are presented and discussed. Compounds (I*d*) and (II*d*) crystallize in a nearly planar conformation. The crystal structures are stabilized by weak C—H···O hydrogen bonds. The packing is dominated by π–π stacking interactions between the heterocyclic central moieties of centrosymmetrically related molecules. In compound (II*f*), the trifluoroethyl termination is almost perpendicular to the plane of the ring.

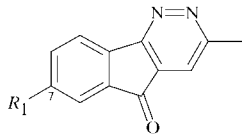
Comment

The 5*H*-indeno[1,2-*c*]pyridazin-5-ones (I*a*)–(I*e*) have been described by Testa (Kneubühler *et al.*, 1993, 1995) to be reversible and selective MAO-B inhibitors. As part of a project aiming to improve the biological activity of compounds of this family, we recently described a general MAO-B pharmacophore. This led to the rational design of compounds (I*f*) and (II*f*), bearing a hydrophobic 4,4,4-trifluorobutoxy side chain on positions 7 and 6, respectively, of the indeno[1,2-*c*]pyridazin-5-one ring (Ooms *et al.*, 2003). [The values of IC_{50} given for compounds (I*a*)–(I*d*) are taken from Kneubühler *et al.* (1995).]

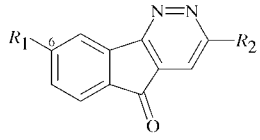
We intended to synthesize (I*f*), possessing the side chain on position 7, using the strategy successfully used by Testa (Kneubühler *et al.*, 1995) to produce two related compounds, *viz*. (I*c*) and (I*d*). Surprisingly, we found that the resulting product possesses the isomeric structure (II*f*), with the side chain on position 6.



	R_1	CF_3	IC_{50} (μM)
(I*a*)	H	*p*	0.09
(I*b*)	H	*m*	0.28
(I*c*)	HO	*m*	5.10
(I*d*)	MeO	*m*	1.31



	R_1
(I*e*)	MeO
(I*f*)	$CF_3(CH_2)_3O$



	R_1	R_2
(II*d*)	MeO	3-CF_3Ph
(II*f*)	$CF_3(CH_2)_3O$	Me

In order to validate the results obtained by Testa, we repeated the synthesis of (I*d*). We found that the major isomer (47% yield, yellow, m.p. 487 K, ^{1}H NMR spectrum identical to that published) was in fact (II*d*) and not (I*d*), as proved unambiguously by the X-ray crystal data. The minor product (3.5% yield, orange, m.p. 477 K), on the other hand, presented the structure (I*d*), again proved by X-ray crystallography.

Compound (I*d*) (Fig. 1), the minor isomer, crystallized in the triclinic $P\overline{1}$ space group. This compound possesses the methoxy group on position C7 of the 5*H*-indeno[1,2-*c*]-pyridazine ring [O2—C7—C8—C9 torsion angle −178.7 (2)°]. The dihedral angle between the phenyl ring *D* and the adjacent pyridazine ring *C* is approximately 19° (Fig. 1). Atom C10 acts as a donor for a weak intermolecular C—H···O hydrogen bond with carboxyl atom O1 (Table 1). The crystal packing is dominated by π–π stacking interactions between the centrosymmetrically related molecules (Fig. 2 and Table 2). The stacking geometry is such that rings *A*, *B* and *C* of one molecule are superimposed on rings *C*, *B* and *A*, respectively, of a symmetry-related molecule at $(1-x, 1-y, -z)$. On the

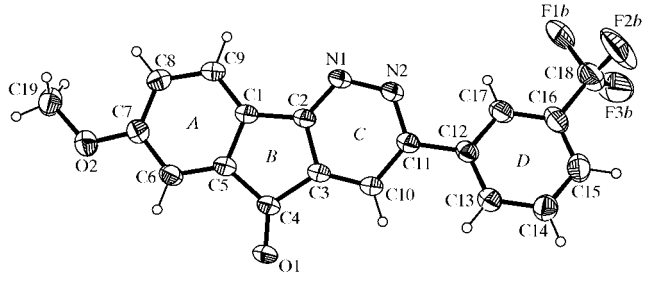


Figure 1
The molecular structure of compound (I*d*). Displacement ellipsoids are drawn at the 30% probability level and H atoms are shown as small spheres of arbitrary radii. For clarity, only one of the disordered CF_3 groups is shown.

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other hand, π–π stacking interactions arise between one molecule and its symmetry-related molecule at ($-x$, $2-y$, $-z$) (Table 2).

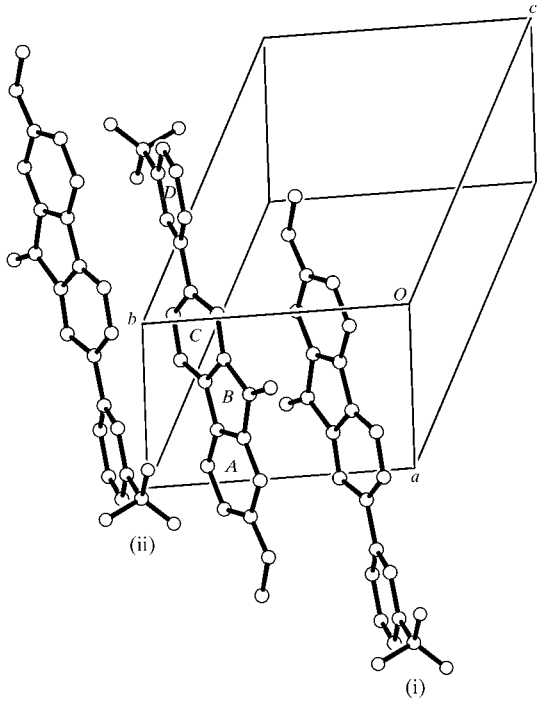

Figure 2
A packing diagram for compound (I*d*), illustrating the π–π stacking network. For clarity, H atoms have been omitted and only the major conformations of the disordered F atoms are shown. [Symmetry codes: (i) $1-x$, $1-y$, $-z$; (ii) $-x$, $2-y$, $-z$.]

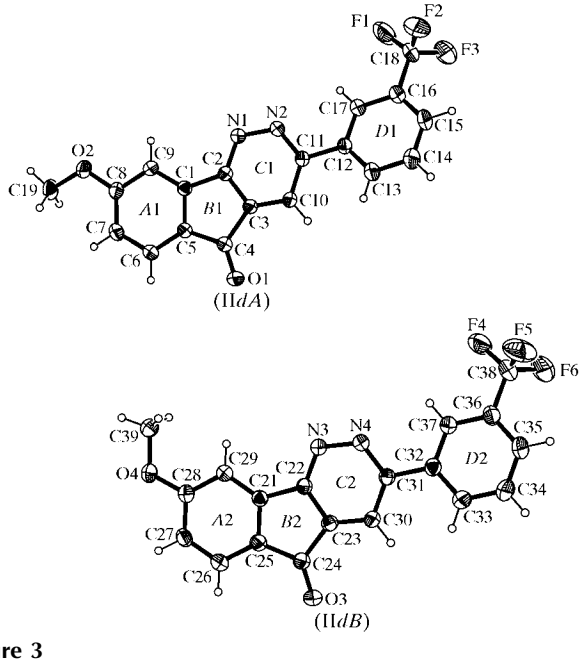

Figure 3
The molecular structures of the two molecules of compound (II*d*). Displacement ellipsoids are drawn at the 30% probability level and H atoms are shown as small spheres of arbitrary radii. For clarity, only one of the disordered CF_3 groups is shown.

Compound (II*d*) (Fig. 3), the major isomer, also crystallized in the triclinic $P\overline{1}$ space group. In this compound, the asymmetric unit contains two independent molecules, one, (II*dA*), with the methoxy group located on position 6 (atom C8) of the 5*H*-indeno[1,2-*c*]pyridazine ring and defined by a C19—O2—C8—C9 torsion angle of 169.8 (2)°, and the other, (II*dB*), with the methoxy group also located at the same position 6 (atom C28) but with a value for the same torsion angle of 0.5 (3)°. This leads to an arrangement in which atom C10 in molecule (II*dA*) acts as a donor for a weak intermolecular C—H···O hydrogen bond with carboxyl atom O3 in (II*dB*) (Table 3). Atoms C30 and C33 in molecule (II*dB*) are also donors for weak intermolecular C—H···O hydrogen bonds with carboxyl atom O1 of a neighbouring (II*dA*) molecule (Table 3). The

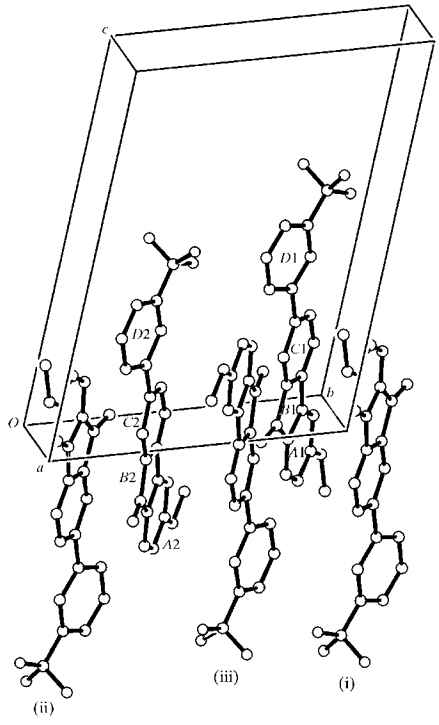

Figure 4
A packing diagram for compound (II*d*), illustrating the π–π stacking network. H atoms have been omitted for clarity. [Symmetry codes: (i) $1-x$, $2-y$, $-z$, for (II*dA*); (ii) $1-x$, $1-y$, $-z$, for (II*dA*); (iii) $2-x$, $1-y$, $-z$, for (II*dB*).]

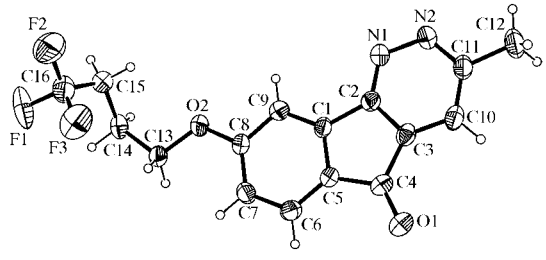

Figure 5
The molecular structure of compound (II*f*). Displacement ellipsoids are drawn at the 30% probability level and H atoms are shown as small spheres of arbitrary radii.

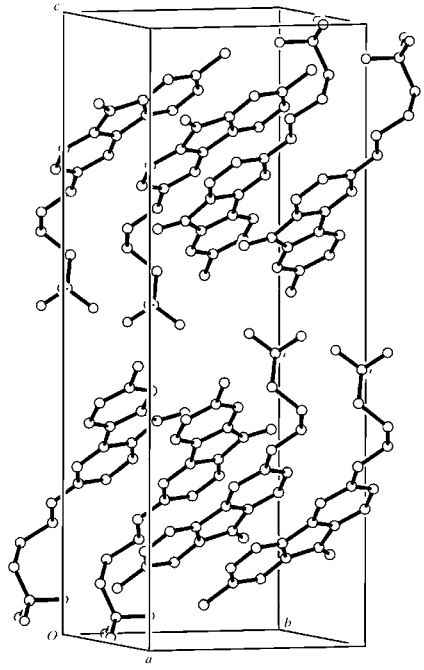

Figure 6
A packing diagram for compound (II*f*), illustrating the π–π stacking network leading to a parallel arrangement along the *a* axis. H atoms have been omitted for clarity.

crystal packing is dominated by π–π stacking interactions between the heterocyclic central moiety of (II*dA*) and its centrosymmetrically related structure at $(1-x, 2-y, -z)$, and between the heterocyclic central moiety of (II*dB*) and its centrosymmetrically related structure at $(2-x, 1-y, -z)$ (Fig. 4 and Table 4). Other π–π stacking interactions arise between (II*dA*) and a symmetry-related (II*dB*) molecule situated at $(1-x, 1-y, -z)$, and also between (II*dB*) and a symmetry-related (II*dA*) molecule at $(1-x, 1-y, -z)$ (Fig. 4 and Table 4).

Derivative (II*f*), bearing a hydrophobic 4,4,4-trifluorobutoxy side chain at position 6 (atom C8), crystallized in the monoclinic $P2_1/c$ space group (Fig. 5). The molecular structure of (II*f*) shows a nearly planar conformation of the 5*H*-indeno[1,2-*c*]pyridazin-5-one ring, except for the trifluoroethyl termination of the side chain, which is almost perpendicular to the plane of the ring [O2—C13—C14—C15 torsion angle −60.6 (5)° and C13—C14—C15 bond angle 116.6 (4)°]. Atom C14 acts as a donor for a weak intermolecular C—H···O hydrogen bond with carboxyl atom O1 of a neighbouring molecule (Table 5). The crystalline cohesion is maintained by π–π stacking interactions between one molecule and the translated structures at $(x-1, y, z)$ and $(1+x, y, z)$, leading to a parallel arrangement along the *a* axis (Fig. 6).

Experimental

The syntheses of compounds (I*d*), (II*d*) and (II*f*) will be reported elsewhere. The compounds were crystallized by slow overnight evaporation of acetonitrile solutions.

Compound (I*d*)

Crystal data

$C_{19}H_{11}F_3N_2O_2$
$M_r = 356.30$
Triclinic, $P\overline{1}$
$a = 7.768$ (2) Å
$b = 8.750$ (2) Å
$c = 12.703$ (2) Å
$\alpha = 89.01$ (1)°
$\beta = 81.59$ (2)°
$\gamma = 68.05$ (1)°
$V = 791.6$ (3) Å^3
$Z = 2$
$D_x = 1.495$ Mg m^{-3}
Cu $K\alpha$ radiation
Cell parameters from 24 reflections
$\theta = 14$–47°
$\mu = 1.05$ mm^{-1}
$T = 293$ (2) K
Prism, yellow
0.30 × 0.18 × 0.04 mm

Data collection

Enraf–Nonius CAD-4 diffractometer
$\theta/2\theta$ scans
Absorption correction: analytical (Alcock, 1970)
$T_{min} = 0.743$, $T_{max} = 0.959$
3495 measured reflections
3273 independent reflections
2692 reflections with $I > 2\sigma(I)$
$R_{int} = 0.015$
$\theta_{max} = 75.1°$
$h = -9 \rightarrow 9$
$k = -10 \rightarrow 0$
$l = -15 \rightarrow 15$
3 standard reflections
every 200 reflections
frequency: 60 min
intensity decay: 3%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.048$
$wR(F^2) = 0.139$
$S = 1.03$
3273 reflections
263 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0722P)^2 + 0.1799P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} = 0.004$
$\Delta\rho_{max} = 0.20$ e Å^{-3}
$\Delta\rho_{min} = -0.22$ e Å^{-3}

Compound (II*d*)

Crystal data

$C_{19}H_{11}F_3N_2O_2$
$M_r = 356.30$
Triclinic, $P\overline{1}$
$a = 10.306$ (1) Å
$b = 10.798$ (1) Å
$c = 14.986$ (1) Å
$\alpha = 73.453$ (6)°
$\beta = 79.592$ (7)°
$\gamma = 89.422$ (7)°
$V = 1570.8$ (2) Å^3
$Z = 4$
$D_x = 1.507$ Mg m^{-3}
Cu $K\alpha$ radiation
Cell parameters from 24 reflections
$\theta = 18$–42°
$\mu = 1.06$ mm^{-1}
$T = 293$ (2) K
Plate, yellow
0.38 × 0.15 × 0.04 mm

Table 1
Hydrogen-bonding geometry (Å, °) for (I*d*).

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
C10—H10···O1^{i}	0.93	2.54	3.408 (2)	156

Symmetry code: (i) $-x, 1-y, -z$.

Table 2
Geometry of short *Cg*···*Cg* ring interactions for (I*d*).

Cgi and *Cgj* denote the centres of gravity for rings *i* and *j* in (I*d*), and α is the dihedral angle between the planes of rings *i* and *j*.

Cgi	*Cgj*	*Cgi*···*Cgj* (Å)	α (°)
CgA	*CgC*^{i}	3.722 (1)	0.27 (13)
CgA	*CgD*^{ii}	3.885 (1)	18.56 (11)
CgB	*CgB*^{i}	3.427 (1)	0.00 (15)
CgB	*CgD*^{ii}	3.811 (1)	18.75 (12)
CgC	*CgC*^{ii}	3.841 (1)	0.00 (15)

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

Data collection

Enraf–Nonius CAD-4 diffractometer
$\theta/2\theta$ scans
Absorption correction: analytical (Alcock, 1970)
T_{min} = 0.689, T_{max} = 0.959
6538 measured reflections
6193 independent reflections
4032 reflections with $I > 2\sigma(I)$
R_{int} = 0.015
θ_{max} = 71.9°
$h = -12 \rightarrow 12$
$k = -13 \rightarrow 0$
$l = -18 \rightarrow 17$
3 standard reflections
every 200 reflections
frequency: 60 min
intensity decay: 2%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.048
$wR(F^2)$ = 0.147
S = 1.04
6193 reflections
498 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.065P)^2 + 0.4238P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.001
$\Delta\rho_{max}$ = 0.22 e Å^{-3}
$\Delta\rho_{min}$ = −0.27 e Å^{-3}

Table 3
Hydrogen-bonding geometry (Å, °) for (II*d*).

D—H···A	D—H	H···A	D···A	D—H···A
C10—H10···O3^{i}	0.93	2.50	3.418 (3)	168
C33—H33···O1^{i}	0.93	2.58	3.320 (3)	137
C30—H30···O1^{i}	0.93	2.42	3.322 (3)	164

Symmetry code: (i) $2 - x, 1 - y, -z$.

Table 4
Geometry of short $Cg\cdots Cg$ ring interactions for (II*d*).

Cgi and *Cgj* denote the centres of gravity for rings *i* and *j* in (II*d*), and α is the dihedral angle between the planes of rings *i* and *j*.

Cgi	*Cgj*	*Cgi*···*Cgj* (Å)	α (°)
*CgA*1	*CgC*2^{ii}	3.686 (1)	5.17 (11)
*CgA*2	*CgD*2^{iii}	3.874 (1)	15.66 (15)
*CgB*1	*CgB*1^{i}	3.464 (1)	0.00 (14)
*CgC*1	*CgA*1^{i}	3.753 (1)	1.86 (12)
*CgC*1	*CgA*2^{ii}	3.587 (1)	6.77 (11)
*CgC*2	*CgB*2^{iii}	3.525 (1)	1.82 (11)

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

Compound (II*f*)

Crystal data

$C_{16}H_{13}F_3N_2O_2$
M_r = 322.28
Monoclinic, $P2_1/c$
a = 4.918 (2) Å
b = 11.978 (6) Å
c = 24.659 (5) Å
β = 96.65 (2)°
V = 1442.8 (10) Å^3
Z = 4
D_x = 1.484 Mg m^{-3}
Cu $K\alpha$ radiation
Cell parameters from 25 reflections
θ = 30–38°
μ = 1.08 mm^{-1}
T = 293 (2) K
Needle, yellow
0.40 × 0.10 × 0.10 mm

Data collection

Enraf–Nonius CAD-4 diffractometer
$\theta/2\theta$ scans
Absorption correction: ψ scan (North *et al.*, 1968)
T_{min} = 0.672, T_{max} = 0.900
4511 measured reflections
2816 independent reflections
1160 reflections with $I > 2\sigma(I)$
R_{int} = 0.057
θ_{max} = 71.9°
$h = -6 \rightarrow 0$
$k = -14 \rightarrow 10$
$l = -30 \rightarrow 30$
3 standard reflections
every 200 reflections
frequency: 60 min
intensity decay: 6%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.068
$wR(F^2)$ = 0.249
S = 0.98
2816 reflections
209 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.1307P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.25 e Å^{-3}
$\Delta\rho_{min}$ = −0.26 e Å^{-3}

Table 5
Hydrogen-bonding geometry (Å, °) for (II*f*).

D—H···A	D—H	H···A	D···A	D—H···A
C15—H15*B*···O1^{i}	0.97	2.60	3.309 (6)	130

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

In all three compounds, the trifluoromethyl groups present very large ellipsoids. In two cases, for (I*d*) and (II*dB*), a disordered model with the trifluoromethyl group distributed over two sites could be defined, whereas no satisfactory models could be defined for (II*dA*) and (II*f*). The disordered models were constrained to have chemically reasonable dimensions, whereas restraints on the anisotropic displacement parameters were used for all trifluoromethyl groups. The H atoms were introduced geometrically and treated as riding, with C—H distances of 0.93–0.96 Å and with U_{iso}(H) = $1.2U_{eq}$(C).

For all three compounds, data collection: *CAD*-4 *EXPRESS* (Enraf–Nonius, 1995); cell refinement: *CAD*-4 *EXPRESS*. For compounds (I*d*) and (II*d*), data reduction: *PLATON* (Spek, 2003). For compound (II*f*), data reduction: *HELENA* (Spek, 1997). For all three compounds, program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1997); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *ORTEP*III (Burnett & Johnson, 1996) and *ORTEP*-3 *for Windows* (Farrugia, 1997); software used to prepare material for publication: *SHELXL*97.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: DN1056). Services for accessing these data are described at the back of the journal.

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