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Two polymorphs of safinamide, a selective and reversible inhibitor of monoamine oxidase B

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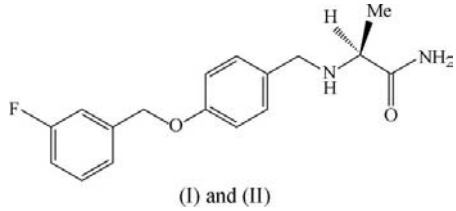
Two polymorphs of safinamide {systematic name: (2*S*)-2-[4-(3-fluorobenzyloxy)benzylamino]propionamide}, $C_{17}H_{19}FN_2O_2$, a potent selective and reversible monoamine oxidase B (MAO-B) inhibitor, are described. Both forms are orthorhombic and regarded as conformational polymorphs due to the differences in the orientation of the 3-fluorobenzyloxy and propanamide groups. Both structures pack with layers in the *ac* plane. In polymorph (I), the layers have discrete wide and narrow regions which are complementary when located next to adjacent layers. In polymorph (II), the layer has long flanges protruding from each side, which interdigitate when packed with the adjacent layers. N—H···O hydrogen bonds are present in both structures, whereas N—H···F hydrogen bonding is seen in polymorph (I), while N—H···N hydrogen bonding is seen in polymorph (II).

Comment

Monoamine oxidases (MAOs) are flavin adenine dinucleotide (FAD) containing enzymes localized in the outer mitochondrial membrane. Two different isoenzymatic forms have been identified, MAO-A and MAO-B, which differ in their amino acid sequences, three-dimensional structures, substrate specificity and sensitivity to inhibitors. Safinamide, a derivative of the chemical class of aminoamides, has been developed by Newron Pharmaceuticals, Bresso, Italy, and was initially reported by Pharmacia & Upjohn as a potent anticonvulsant (Pevarello *et al.*, 1998). It acts by means of multiple mechanisms of action that comprise MAO-B and dopamine uptake inhibition, sodium and calcium channel modulation, and reduction of glutamate release in the central nervous system (Caccia *et al.*, 2006). Due to its excellent therapeutic properties and safety margin, safinamide has been developed as an anti-Parkinsonian and anticonvulsant agent.

Polymorphism is often characterized as the ability of a drug substance to exist as two or more crystalline phases that have different arrangements and/or conformations of the molecules in the crystal lattice (Grant, 1999). The last decade has witnessed many developments in the design and characterization of polymorphs, due to increased awareness of the possibility of multiple crystal forms of a substance, the utility that may be derived from preparing a crystal form with enhanced properties, and the potential intellectual property implications of new crystal forms.

The present study is a continuation of our investigation of the structural characterization of pharmaceutical compounds (Ravikumar & Sridhar, 2007; Ravikumar *et al.*, 2008; Ravikumar & Sridhar, 2009). We report here the crystal structures of two polymorphic forms of safinamide, denoted (I) and (II).



(I) and (II)

Both polymorphs crystallize in the space group $P2_12_12_1$ and were assigned the known handedness (the asymmetric centre C15 has the *S* configuration). The molecular structures observed in polymorphs (I) and (II) are composed of a central aromatic ring substituted at C8 by a fluorobenzyloxy group and at C11 by an alaninamide group (Figs. 1 and 2). The bond lengths in the two structures are the same to within 3σ. The exocyclic bond angles involving atom C1 differ by up to 4.7° (Table 1); the sense of these deviations suggests interactions

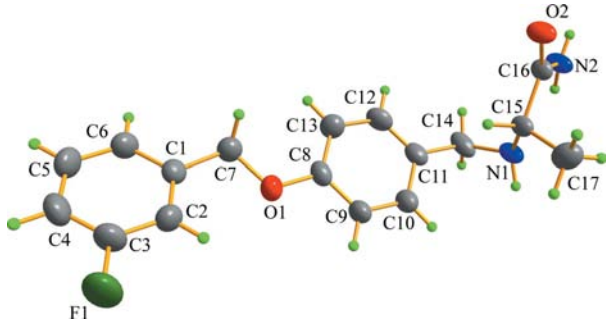


Figure 1
A perspective drawing of (I), showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 30% probability level and H atoms are shown as small spheres of arbitrary radii.

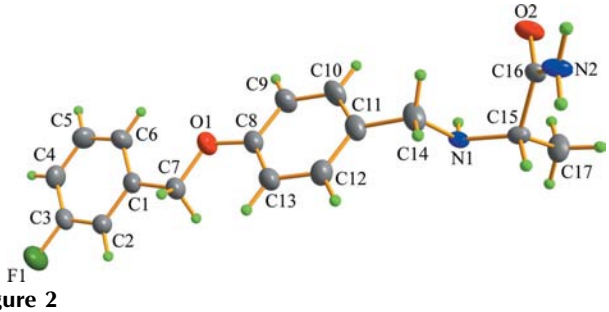


Figure 2
A perspective drawing of (II), showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 30% probability level and H atoms are shown as small spheres of arbitrary radii.

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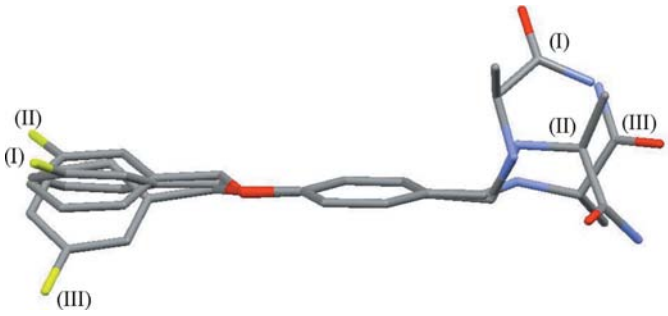

Figure 3
A superposition of the molecular conformations of safinamide molecules. The overlay was made by making a least-squares fit through the central aromatic ring system (C8–C13) of safinamide polymorph (I). The labels and r.m.s. deviations (Å) are as follows: safinamide polymorph (II), 0.012; extracted structure of safinamide from safinamide–human monoamine oxidase complex, (III), 0.025. H atoms have been omitted for clarity.

between atoms O1 and C2 [in (I)] or C6 [in (II)], possibly associated with weak intramolecular C—H···O hydrogen bonds (Tables 2 and 3). The slight variation in bond angles involving amine atom N1 may be attributed to its involvement in different types of hydrogen-bonding interactions. The significant conformational differences between polymorphs (I) and (II) are in the orientations of the fluorobenzyloxy and alaninamide groups in relation to the central aromatic ring. The fluoro-substituted ring is *cisoid* [C2—C1—C7—O1 = 16.8 (5)°] to ether atom O1 in (I), while it is *transoid* [C2—C1—C7—O1 = 171.2 (3)°] in (II). Similarly, the alaninamide group is in a −*sc*,−*sc*,−*sp* orientation in (I), but is in a −*ap*,*sc*,*ac* orientation in (II).

It is noteworthy that in the crystal structure of the complex safinamide–human monoamine oxidase, (III) [Binda *et al.*, 2007; Protein Data Bank (Berman *et al.*, 2000) entry 2V5Z], the extracted ligand structure (Fig. 3) shows another significant difference in the orientation of the C8 and C11 substituents (C2—C1—C7—O1 = −44.8° and the alaninamide group is in an −*ap*,−*ac*,−*sc* orientation). It is interesting to note that the alaninamide chain is in an extended conformation in the extracted ligand structure and perhaps it may be speculated that a third polymorph of the title compound is possible with such features.

Substantial differences in the molecular packing of the polymorphs are observed. Both (I) and (II) pack with layers in the *ac* plane. In (I), the layers have discrete wide and narrow regions which are complementary when located next to adjacent layers. In (II), the layer has long flanges protruding from each side, which interdigitate when packed with the adjacent layers.

The amide groups are associated to form the core of the hydrogen-bonding networks in (I) (Table 2). Amide atom N2 connects two adjacent molecules by N—H···O=C hydrogen bonding involving only the amide groups, creating an $R_3^2(8)$ graph-set motif (Etter, 1990; Etter *et al.*, 1990; Bernstein *et al.*, 1995). The hydrogen-bonded amide groups are coplanar, forming a ribbon-like packing motif along the *a* axis (Fig. 4). Amine atom N1 forms an N—H···F interaction with an adjacent fluorobenzyl group, developing a helical hydrogen-bonded catemer along the *a* axis and cross-linking neighbouring ribbon-like motifs along the *c* axis to give the two-dimensional supramolecular hydrogen-bonded network.

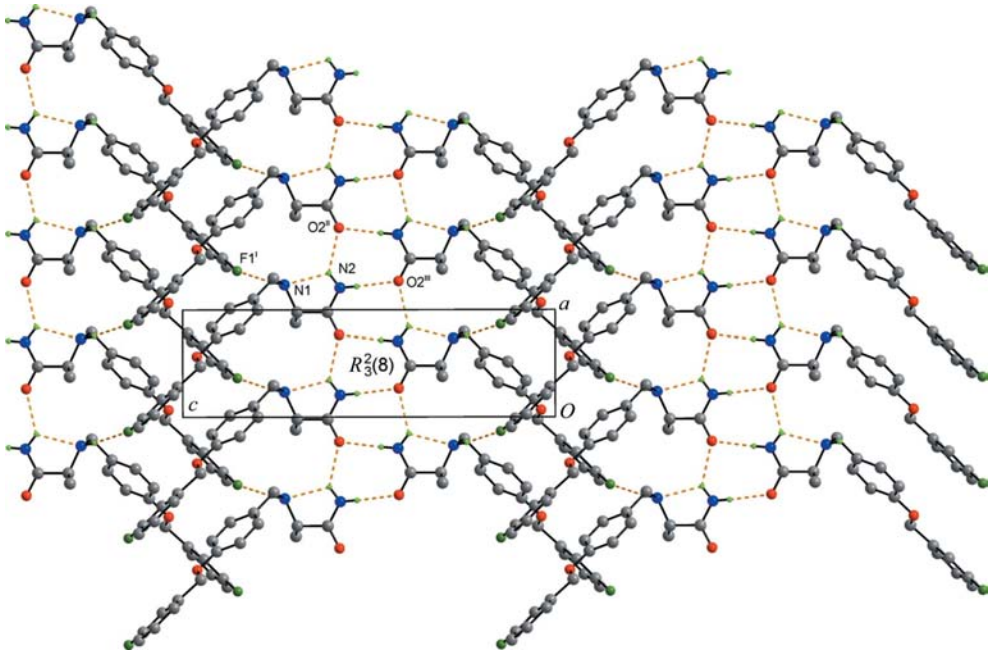

Figure 4
A partial packing diagram for (I), showing extracellular molecules, depicting the ribbon-like packing motif generated by N—H···O hydrogen bonds, along with N—H···F helical hydrogen-bonded catemers. Hydrogen bonds are shown as dashed lines and H atoms not involved in hydrogen bonding have been omitted for clarity. Selected atoms of the molecules present in the asymmetric unit are labelled, primarily to provide a key for the coding of the atoms. [Symmetry codes: (i) $x+\frac{3}{2}, -y+\frac{1}{2}, -z+2$; (ii) $x+1, y, z$; (iii) $x+\frac{1}{2}, -y+\frac{1}{2}, -z+1$.]

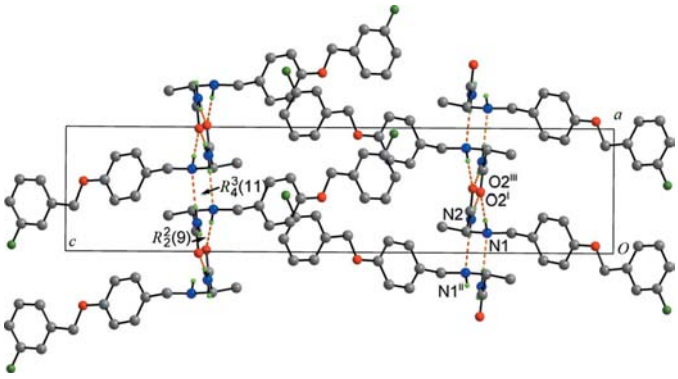

Figure 5
A partial packing diagram for (II), showing extracellular molecules, depicting the ribbon-like pattern generated by the N—H···O and N—H···N hydrogen bonds (dashed lines). H atoms not involved in hydrogen bonding have been omitted for clarity. Selected atoms of the molecules present in the asymmetric unit are labelled, primarily to provide a key for the coding of the atoms. Atom O2^{iii} lies exactly behind atom O2^{i}. [Symmetry codes: (i) $-x+1, y-\frac{1}{2}, -z+\frac{1}{2}$; (ii) $-x, y+\frac{1}{2}, -z+\frac{1}{2}$; (iii) $-x+1, y+\frac{1}{2}, -z+\frac{1}{2}$.]

Fig. 5 illustrates the packing for (II), wherein one N2—H group forms an N—H···O=C interaction with another amide group (Table 3). This generates a ribbon-like pattern of $R_2^2(9)$ motifs along the *a* axis. The second amide H atom bound to N2 forms an N—H···N hydrogen bond to an amine group, generating an $R_4^3(11)$ motif in combination with N—H···O hydrogen bonds, resulting in an infinite two-dimensional supramolecular hydrogen-bonded network. A stacking interaction between pairs of aromatic and fluorobenzyl rings [centroid–centroid separation = 3.875 (2) Å; symmetry code: $-\frac{1}{2}+x, \frac{3}{2}-y, -z$] occurs between adjacent layers. The F atom in (II) is involved in an intermolecular C—H···F interaction. Ether atom O1 is not involved in any intermolecular hydrogen-bonding interactions in either polymorph.

In conclusion, it can be seen that the two polymorphic structures, *viz.* (I) and (II), which differ significantly in the orientation of the two substituents at C8 and C11, give rise to two different modifications of the crystal packing.

Experimental

Plate-shaped single crystals of polymorph (I) were obtained by slow evaporation of the title compound (Pevarello *et al.*, 1998; 25 mg) from benzene (10 ml) and hexane (2 ml) solutions stirred and warmed slightly over a steam bath for 10 min. Needle-shaped crystals of polymorph (II) were obtained by slow evaporation from ethyl acetate (8 ml) and hexane (2 ml) solutions stirred and warmed slightly over a steam bath for 10 min.

Compound (I)

Crystal data

$C_{17}H_{19}FN_2O_2$
M_r = 302.34
Orthorhombic, $P2_12_12_1$
a = 5.1127 (5) Å
b = 17.8516 (16) Å
c = 17.8746 (1) Å
V = 1631.4 (2) Å^3
Z = 4
Mo $K\alpha$ radiation
μ = 0.09 mm^{-1}
T = 294 K
0.14 × 0.10 × 0.06 mm

Data collection

Bruker SMART APEX CCD area-detector diffractometer
15763 measured reflections
1698 independent reflections
1179 reflections with $I > 2\sigma(I)$
R_{int} = 0.057

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.042
$wR(F^2)$ = 0.113
S = 0.97
1698 reflections
212 parameters
H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max}$ = 0.15 e Å^{-3}
$\Delta\rho_{min}$ = −0.12 e Å^{-3}

Compound (II)

Crystal data

$C_{17}H_{19}FN_2O_2$
M_r = 302.34
Orthorhombic, $P2_12_12_1$
a = 6.6297 (9) Å
b = 8.1015 (12) Å
c = 29.268 (4) Å
V = 1572.0 (4) Å^3
Z = 4
Mo $K\alpha$ radiation
μ = 0.09 mm^{-1}
T = 294 K
0.15 × 0.10 × 0.05 mm

Table 1
Selected geometric parameters (°) for polymorphs (I) and (II).

	(I)	(II)
C2—C1—C6	118.5 (4)	119.1 (3)
C2—C1—C7	122.4 (4)	117.7 (3)
C6—C1—C7	119.0 (4)	123.2 (3)
N1—C14—C11	116.7 (3)	113.3 (2)
N1—C15—C16	111.7 (3)	113.1 (2)
N1—C15—C17	111.8 (3)	109.4 (2)
C14—N1—C15	116.0 (3)	112.8 (2)
C11—C14—N1—C15	−52.8 (5)	−173.8 (3)
C16—C15—N1—C14	−84.7 (4)	−46.8 (3)
N1—C15—C16—N2	−20.1 (5)	119.6 (3)

Table 2
Hydrogen-bond geometry (Å, °) for (I).

D—H···A	D—H	H···A	D···A	D—H···A
N1—H1N···F1^{i}	0.88 (4)	2.17 (4)	3.046 (4)	174 (5)
N2—H2N···N1	0.88 (4)	2.23 (4)	2.693 (4)	113 (3)
N2—H2N···O2^{ii}	0.88 (4)	2.25 (4)	2.885 (4)	128 (3)
N2—H3N···O2^{iii}	0.84 (3)	2.10 (3)	2.940 (3)	177 (3)
C2—H2···O1	0.93	2.41	2.729 (5)	100

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

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

D—H···A	D—H	H···A	D···A	D—H···A
N1—H1N···O2^{i}	0.89 (3)	2.33 (3)	3.212 (3)	171 (2)
N2—H2N···N1^{ii}	0.86 (4)	2.13 (4)	2.981 (3)	171 (3)
N2—H3N···O2^{iii}	0.85 (3)	2.10 (3)	2.916 (3)	160 (3)
C6—H6···O1	0.93	2.41	2.746 (4)	101
C5—H5···F1^{iv}	0.93	2.41	3.274 (4)	155

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

Data collection

Bruker SMART APEX CCD area-detector diffractometer
15166 measured reflections
1636 independent reflections
1573 reflections with $I > 2\sigma(I)$
$R_{int} = 0.025$

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.043$
$wR(F^2) = 0.121$
$S = 1.22$
1636 reflections
212 parameters
H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max} = 0.19$ e Å^{-3}
$\Delta\rho_{min} = -0.17$ e Å^{-3}

All N-bound H atoms were located in difference Fourier maps, and their positions and isotropic displacement parameters were located and refined. All other H atoms were located in a difference density map but were positioned geometrically and included as riding atoms, with C—H = 0.93–0.98 Å and U_{iso}(H) = 1.5U_{eq}(C) for methyl or 1.2U_{eq}(C) for all other H atoms. In the absence of significant anomalous scattering effects, Friedel pairs were merged. The absolute configuration of safinamide was known in advance.

For both compounds, data collection: *SMART* (Bruker, 2001); cell refinement: *SAINT* (Bruker, 2001); data reduction: *SAINT*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 2008); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008); molecular graphics: *DIAMOND* (Brandenburg & Putz, 2005) and *Mercury* (Macrae *et al.*, 2008); software used to prepare material for publication: *SHELXL97*.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: SF3130). Services for accessing these data are described at the back of the journal.

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