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3-[4-(4-Fluorophenyl)piperazin-1-ylmethyl]-5-methyl-1,3-benzoxazol-2(3*H*)-one and 3-[4-(2-fluorophenyl)-piperazin-1-ylmethyl]-5-methyl-1,3-benzoxazol-2(3*H*)-one

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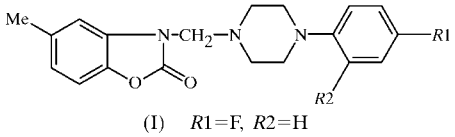
The title compounds, both $C_{19}H_{20}FN_3O_2$, contain essentially planar benzoxazolinone ring systems, within which the C—N bond distances and angles do not differ significantly between the two compounds. In both cases, the piperazine ring adopts an almost perfect chair conformation and the benzoxazolinone ring system lies nearly perpendicular to it. The structures contain intermolecular C—H···O contacts, and the interactions between the benzoxazolinone and fluorophenylpiperazine portions of the molecules are segregated.

Comment

Benzoxazolinones have been investigated primarily for their medicinal value as central nervous system depressants, exhibiting analgesic, antipyritic, anticonvulsant, hypnotic and skeletal muscle relaxant activities (Sam & Valentine, 1969). In addition, many investigations of 1,3-benzoxazolin-2-ones have shown that compounds with this structure have anti-inflammatory, antineplastic and antimicrobial activities (Clark & Pessolano, 1953; Varma & Nobles, 1968; Varma & Kapoor, 1979; Vaccher *et al.*, 1986; Erol *et al.*, 1989; Kalcheva *et al.*, 1990; Gökhan *et al.*, 1996; Köksal *et al.*, 2002). The medical value of these derivatives prompted us to synthesize 3-substituted benzoxazolin-2-ones and clarify their structures.



(I) *R*1=F, *R*2=H
(II) *R*2=F, *R*1=H

The pharmacological results indicate that the title compounds, (I) and (II), possess good analgesic activity, coupled with notable anti-inflammatory properties (Okun *et al.*, 1963). Moreover, these title compounds show a remarkable gastric tolerance. It also seems that, as far as the chemical structures of the title compounds are concerned, compounds bearing chloro and fluoro substituents show increased analgesic–anti-inflammatory activities.

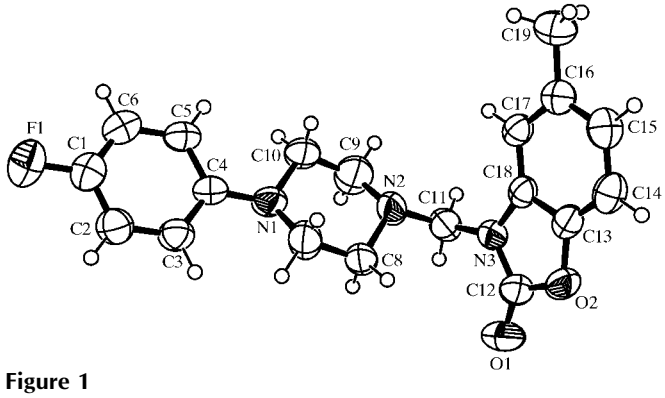


Figure 1
The structure of (I), showing 50% probability displacement ellipsoids and the atom-numbering scheme.

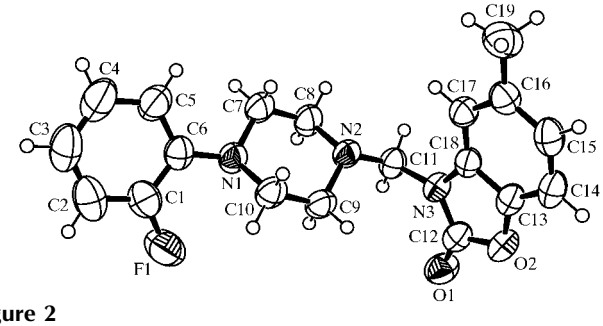


Figure 2
The structure of (II), showing 50% probability displacement ellipsoids and the atom-numbering scheme.

In order to obtain information about the stereochemistry of the molecules and to confirm the assigned structures, X-ray analyses were undertaken.

In (I) (Fig. 1 and Table 1), because the benzene and oxazolinone rings are almost parallel to one another, the benzoxazolinone ring system is essentially planar; this conformation is consistent with the findings of Koysal *et al.* (2003). The deviations from the plane of the nine-membered benzoxazolinone ring system for atoms C12, C13, C15 and C18 are 0.029 (4), −0.011 (3), 0.015 (3) and −0.012 (3) Å. The plane through the C atoms of the piperazine ring makes a dihedral angle of 89.72 (15)° with the benzoxazolinone ring system. The piperazine moiety adopts an almost perfect chair conformation [the puckering parameters (Cremer & Pople, 1975) are q_2 = 0.050 (4) Å, q_3 = 0.508 (4) Å, Q_T = 0.5101 Å, φ = 201 (5)° and θ = 5.3 (4)°].

Compound (II) (Fig. 2 and Table 3) is similar in that it also contains a planar benzoxazolinone ring system, the maximum deviation from the plane being 0.021 (1) Å for atom C12. The benzoxazolinone ring system, like that in (I), is nearly perpendicular to the piperazine ring, the dihedral angle in (II) being 82.64 (6)°. The piperazine ring in (II) also adopts a chair conformation [q_2 = 0.0113 (13) Å, q_3 = −0.5861 (15) Å, Q_T = 0.5862 (15) Å, φ = 187 (8)° and θ = 178.73 (13)°].

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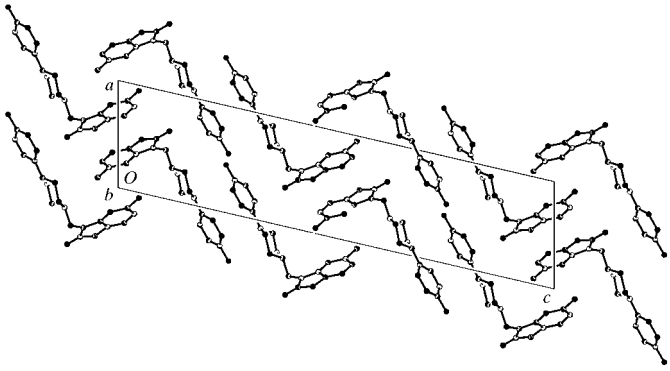

Figure 3
The packing of molecules of (I) in the unit cell.

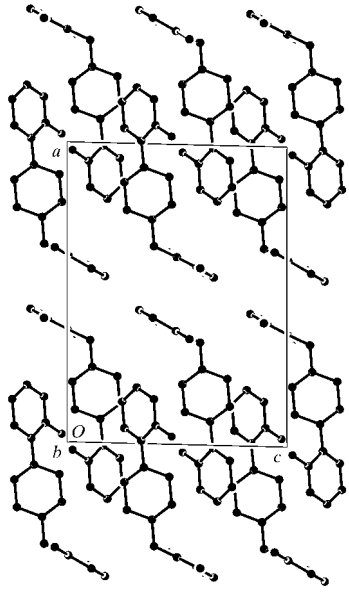

Figure 4
The packing of molecules of (II) in the unit cell.

The structure of compound (I) contains intermolecular C5—H5···O1^{i} and C14—H14···O2^{ii} contacts (Table 2), which link the molecules into discrete pairs across crystallographic centres of symmetry (Fig. 3). Compound (II) contains only an intermolecular C14—H14···O1^{iii} contact (Table 4). The compounds differ in that, in (I), the acceptor O atom is within the oxazolinone ring, while in (II), the acceptor is the C═O group exo to the ring. Therefore, the intermolecular interactions in (II) link the molecules into infinite chains rather than the discrete dimers found in (I) (Fig. 4).

$\pi-\pi$ stacking interactions are present in both (I) and (II). In both compounds, the benzoxazolinone ring systems align in an antiparallel manner. In the closest interaction (with a perpendicular separation of 3.4 Å), the lateral offset is small, while the longer interaction (with a perpendicular separation of 3.6 Å) has a larger lateral offset.

Experimental

The title compounds were prepared *via* the Mannich reaction, using arylpiperazine derivatives, formaldehyde and 5-methyl-1,3-benzoxazolin-2-one, prepared *via* a modification of the procedure described by Bywater *et al.* (1945), using 4-methyl-2-aminophenol (0.1 mol) and urea (0.12 mol). The mixture was fused at 418–423 K for 4 h in a preheated oil bath, and the residue was recrystallized from water (yield 59.69%, m.p. 394–395 K). For the preparation of (I) and (II), formalin (0.12 mol, 37% *w*/*v*) was added to a vigorously stirred solution of the appropriate substituted piperazine derivative (0.1 mol) and 5-methyl-1,3-benzoxazolin-2-one (0.1 mol) in methanol, and the mixture refluxed on a water bath for 1 h. The resulting mixture was poured on to crushed ice and the solid product was separated by filtration, dried and crystallized from ethanol–water. The structures of the compounds were checked by IR, ^{1}H NMR and elemental analysis. For (I): yield 82.58%; m.p. 440–441 K; analysis calculated for $C_{19}H_{20}FN_3O_2$: C 66.85, H 5.91, O 12.31%; found: C 66.92, H 5.78, O 12.12%; IR (KBr, cm^{-1}): 3200, 2824 (C—H), 1790 (C═O); ^{1}H NMR ($CDCl_3$): δ 7.1–6.8 (*s*, 7H), 4.7 (*s*, 2H), 3.3–3.0 (*s*, 4H), 2.9–2.5 (*s*, 4H), 2.3 (*s*, 3H). For (II): yield 80.06%; m.p. 417–418 K; analysis calculated for $C_{19}H_{20}FN_3O_2$: C 66.85, H 5.91, O 12.31%; found: C 66.37, H 6.34, O 11.95%; IR (KBr, cm^{-1}): 3200, 2924 (C—H), 1771 (C═O); ^{1}H NMR ($CDCl_3$): δ 7.3–6.8 (*m*, 7H), 4.8 (*s*, 2H), 3.3–3.0 (*d*, 4H), 2.9–2.6 (*d*, 4H), 2.4 (*s*, 3H).

Compound (I)

Crystal data

$C_{19}H_{20}FN_3O_2$	D_x = 1.357 Mg m^{-3}
M_r = 341.22	Mo $K\alpha$ radiation
Monoclinic, $P2_1/c$	Cell parameters from 10 038 reflections
a = 8.1788 (6) Å	θ = 0.0–29.4°
b = 6.1512 (4) Å	μ = 0.10 mm^{-1}
c = 34.090 (3) Å	T = 293 (2) K
β = 103.067 (7)°	Prism, colourless
V = 1670.6 (2) Å^3	0.62 × 0.48 × 0.35 mm
Z = 4	

Data collection

Stoe IPDS-II diffractometer	3072 independent reflections
ω scans	2368 reflections with $I > 2\sigma(I)$
Absorption correction: by integration (*X-RED*32; Stoe & Cie, 2002)	R_{int} = 0.028
	θ_{max} = 26.0°
T_{min} = 0.940, T_{max} = 0.969	$h = -10 \rightarrow 9$
7820 measured reflections	$k = -7 \rightarrow 7$
	$l = -42 \rightarrow 42$

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F_o^2) + (0.1428P)^2 + 0.916P]$ where $P = (F_o^2 + 2F_c^2)/3$
$R[F^2 > 2\sigma(F^2)]$ = 0.080	
$wR(F^2)$ = 0.250	$(\Delta/\sigma)_{max} < 0.001$
S = 1.07	$\Delta\rho_{max}$ = 0.95 e Å^{-3}
3072 reflections	$\Delta\rho_{min}$ = −0.43 e Å^{-3}
240 parameters	
H-atom parameters constrained	

Table 1
Selected geometric parameters (Å, °) for (I).

F1—C1	1.350 (4)	N2—C9	1.399 (5)
O1—C12	1.194 (4)	N2—C8	1.450 (4)
O2—C12	1.377 (4)	N2—C11	1.451 (4)
O2—C13	1.397 (4)	N3—C12	1.364 (4)
N1—C7	1.385 (4)	N3—C18	1.386 (4)
N1—C4	1.402 (4)	N3—C11	1.452 (4)
N1—C10	1.460 (4)		
N1—C7—C8	113.6 (3)	N2—C11—N3	110.2 (3)
N2—C8—C7	110.9 (3)	O1—C12—N3	129.9 (4)
N2—C9—C10	113.0 (3)	O1—C12—O2	122.4 (3)
N1—C10—C9	111.5 (3)		
C7—N1—C4—C5	150.7 (4)	N1—C7—C8—N2	50.8 (5)
C10—N1—C4—C5	8.4 (5)	N2—C9—C10—N1	−54.9 (5)

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

D—H···A	D—H	H···A	D···A	D—H···A
C5—H5···O1^{i}	0.93	2.58	3.268 (4)	131
C14—H14···O2^{ii}	0.93	2.65	3.547 (4)	163

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

Compound (II)

Crystal data

$C_{19}H_{20}FN_3O_2$	$D_x = 1.314$ Mg m^{-3}
$M_r = 341.22$	Mo $K\alpha$ radiation
Monoclinic, $P2_1/c$	Cell parameters from 19 436 reflections
$a = 15.7467$ (10) Å	$\theta = 0.0$–$29.5°$
$b = 9.5470$ (4) Å	$\mu = 0.09$ mm^{-1}
$c = 11.4779$ (6) Å	$T = 293$ (2) K
$\beta = 91.422$ (5)°	Prism, colourless
$V = 1724.98$ (16) Å^3	0.60 × 0.42 × 0.31 mm
$Z = 4$	

Data collection

Stoe IPDS-II diffractometer	3392 independent reflections
ω scans	2779 reflections with $I > 2\sigma(I)$
Absorption correction: by integration (*X-RED*32; Stoe & Cie, 2002)	$R_{int} = 0.093$
	$\theta_{max} = 26.0°$
$T_{min} = 0.878$, $T_{max} = 0.980$	$h = -19 \rightarrow 19$
24 265 measured reflections	$k = -11 \rightarrow 11$
	$l = -14 \rightarrow 13$

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F_o^2) + (0.0658P)^2 + 0.1274P]$ where $P = (F_o^2 + 2F_c^2)/3$
$R[F^2 > 2\sigma(F^2)] = 0.041$	
$wR(F^2) = 0.124$	
$S = 1.07$	$(\Delta/\sigma)_{max} < 0.001$
3392 reflections	$\Delta\rho_{max} = 0.21$ e Å^{-3}
246 parameters	$\Delta\rho_{min} = -0.15$ e Å^{-3}
H-atom parameters constrained	Extinction correction: *SHELXL*97
	Extinction coefficient: 0.015 (2)

Table 3
Selected geometric parameters (Å, °) for (II).

F1—C1	1.351 (2)	N2—C11	1.4429 (16)
O1—C12	1.1970 (18)	N2—C9	1.4535 (17)
O2—C12	1.3810 (17)	N2—C8	1.4553 (16)
O2—C13	1.3872 (17)	N3—C12	1.3628 (17)
N1—C6	1.4134 (17)	N3—C18	1.3905 (17)
N1—C7	1.4530 (18)	N3—C11	1.4518 (15)
N1—C10	1.4620 (17)		
N1—C7—C8	109.66 (12)	N1—C10—C9	109.88 (11)
N2—C8—C7	110.41 (12)	O1—C12—N3	129.86 (13)
N2—C9—C10	110.30 (11)	O1—C12—O2	122.46 (12)
C7—N1—C6—C5	−12.2 (2)	N2—C9—C10—N1	58.71 (16)
C10—N1—C6—C5	117.40 (17)	C18—N3—C11—N2	−66.38 (16)
N1—C7—C8—N2	−59.02 (18)		

Table 4
Hydrogen-bonding geometry (Å, °) for (II).

D—H···A	D—H	H···A	D···A	D—H···A
C14—H14···O1^{iii}	0.93	2.57	3.4680 (18)	163

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

H atoms were located geometrically and treated using a riding model, with C—H distances of 0.93 (aromatic), 0.97 (CH_2) and 0.96 Å (CH_3).

For both compounds, data collection: *X-AREA* (Stoe & Cie, 2002); cell refinement: *X-AREA*; data reduction: *X-RED*32 (Stoe & Cie, 2002); 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); software used to prepare material for publication: *WinGX* (Farrugia, 1997) and *PARST* (Nardelli, 1995).

Supplementary data for this paper are available from the IUCr electronic archives (Reference: AV1163). Services for accessing these data are described at the back of the journal.

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