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1-(2-Bromo-5-methoxyphenyl)-8-chloro-6-(2-fluorophenyl)-4*H*-1,2,4-triazolo[4,3-*a*][1,4]benzodiazepine

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Key indicators

Single-crystal X-ray study
T = 120 K
Mean σ(C–C) = 0.003 Å
R factor = 0.035
wR factor = 0.075
Data-to-parameter ratio = 16.4

For details of how these key indicators were automatically derived from the article, see http://journals.iucr.org/e.

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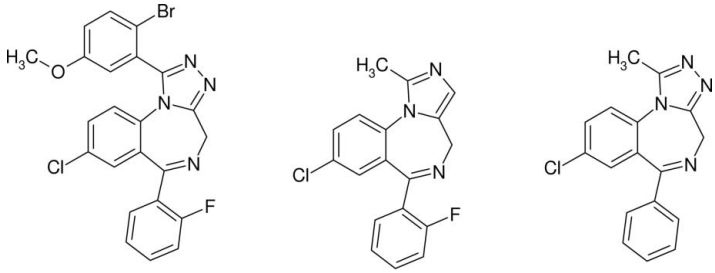
The title compound, $C_{23}H_{15}BrClFN_4O$, is an analogue of sedatives such as midazolam and alprazolam. Its geometrical parameters are normal and comparable with those of related compounds. The only possible significant intermolecular interaction is a C—H···O bond.

Comment

1,4-Benzodiazepine derivatives are widely used as daytime sedatives, tranquilizers, sleep inducers, anaesthetics, anticonvulsants and muscle relaxants (Block *et al.*, 1989; Di Braccio *et al.*, 2001; Hollister, 1983; Moroz, 2004). Five-atom heterocyclic fused benzodiazepine ring systems occupy a prominent place among drugs for treatment of central nervous system (CNS) disorders (Robol *et al.*, 1996; Wang *et al.*, 1999; Novelli *et al.*, 1999; Evans *et al.*, 2001).



(I) (II) (III)

The title compound, (I), $C_{23}H_{15}BrClFN_4O$, (Fig. 1), which appears to have promising physiological properties, comparable with those of diazepam (Valium), is a structural analogue of well known CNS depressant drugs such as midazolam, (II),

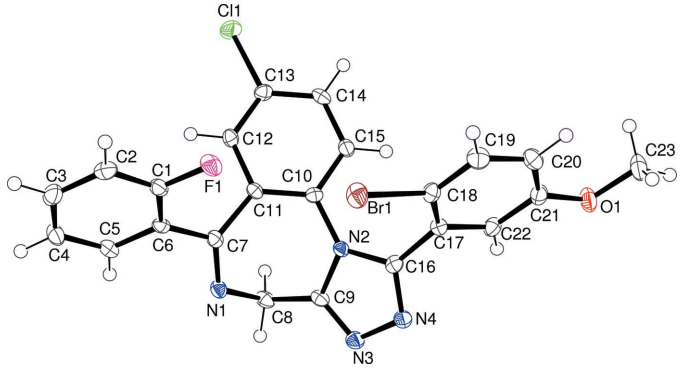


Figure 1
View of (I), showing 30% probability displacement ellipsoids and arbitrary spheres for the H atoms.

and alprazolam, $C_{17}H_{13}ClN_4$, (III). To confirm the structural relationship of (I) to these drugs, its crystal structure is presented here.

The geometrical parameters for (I) fall within their expected ranges (Allen *et al.*, 1995), although the C10—N2—C16 bond angle of 131.51 (18)° is notably obtuse. Atom C7 is displaced from the fluorobenzene mean plane by 0.108 (4) Å. The Br atom is significantly displaced [by 0.154 (3) Å] from the plane of the benzenel ring to which it is attached. The dihedral angles between the various rings in (I) are as follows, where a single atom is used to identify its five- or six-membered ring: C1/C12 62.23 (10); C1/C17 6.12 (11); C1/N3 50.99 (11); C12/C17 64.24 (10); C12/N3 38.05 (11); N3/C17 56.43 (11)°.

The bond distances within the five-membered ring (Table 1) suggest that the C9—N3 and C16—N4 bonds have far more double-bond character than do N3—N4, C9—N2 and C16—N2, *i.e.* the canonical form shown in the scheme is probably the most significant contributor to the overall structure. The bond angle sums about atoms C7 (359.6°), C9 (360.0°), C16 (360.0°) and N2 (359.7°) suggest that all these atoms are well regarded as being sp^2 hybridized.

The seven-membered diazepine ring (C7/C11/C10/N2/C9/C8/N1) in (I) is far from planar, and its shape approximates to a twist chair (Hendrickson, 1967) with a pseudo-twofold axis passing through C9 and the C7—C11 bond midpoint, if such a description is valid for a seven-membered ring containing multiple bonds. However, the pattern of the torsion angles of the seven-membered ring is also close to reflecting C_s symmetry. In the structure of alprazolam dihydrate (Vega *et al.*, 1999), a similar ring conformation was described as a boat. In this description applied to (I), atoms C7, C9, N1 and N2 form the bottom of the boat (r.m.s. deviation from the mean plane = 0.017 Å), C8 the prow, and C10 and C11 the stern [deviations from the C7/C9/N1/N2 mean plane = 0.686 (3), 0.666 (3) and 0.698 (3) Å, respectively].

The crystal packing in (I), shown in Fig. 2, results in $(10\bar{1})$ sheets of molecules. Apart from a possible C—H···N interaction (Table 2), which might help to provide coherence between adjacent $(10\bar{1})$ sheets, there are few significant intermolecular interactions in (I). Any π–π stacking must be extremely weak, the smallest centroid···centroid separation being 4.11 Å. No C—H···π interactions were identified in a *PLATON* (Spek, 2003) analysis of (I).

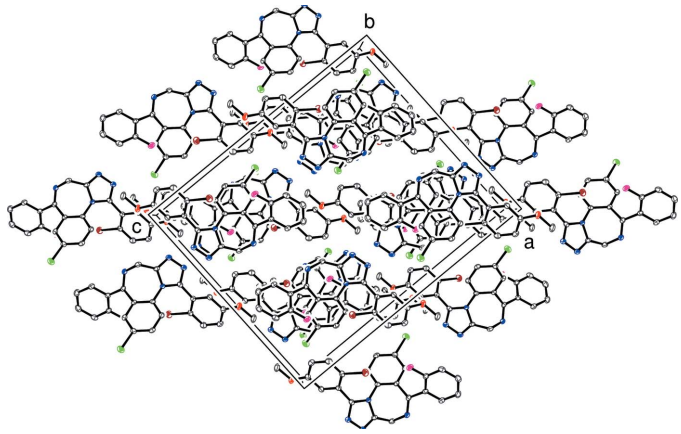


Figure 2
The packing in (I), viewed approximately down [010]. H atoms have been omitted.

Experimental

7-Chloro-5-(2-fluorophenyl)-1,3-dihydro-2*H*-1,4-benzodiazepine-2-thione (3.06 g, 0.01 mol) was reacted with 2-bromo-5-methoxy benzoic hydrazide (2.45 g, 0.01 mol) by refluxing in *n*-butanol (50 ml) with a catalytic amount of acetic acid (0.1 ml) to result in crude (I). The crude product was purified by silica-gel column chromatograpy using dichloromethane as eluent (yield 78%) and recrystallized from acetone as pale-yellow crystals (m.p. 493 K). FT–IR (KBr, cm^{-1}): 3055 and 2926 (–CH), 1609 (–C═N), 1482 ($-CH_2$), 1297 (Ar—F), 1018 (Ar—Cl). ^{1}H NMR ($CDCl_3$, δ, p.p.m.): 3.82 (*s*, 3H, $-OCH_3$), 4.22 (*d*, *J* = 13.2 Hz, 1H, $-CH_2$), 5.64 (*d*, *J* = 13.2 Hz, 1H, $-CH_2$), 6.85 (*d*, *J* = 8.4 Hz, 1H, ArH), 6.95 (*dd*, *J* = 8.7 and 9.3 Hz, 2H, Ar—H), 7.07 (*t*, 1H, Ar—H), 7.16–7.32 (*m*, 1H, Ar—H), 7.45–7.52 (*m*, 4H, Ar—H), 7.67 (*t*, 1H, Ar—H). ^{13}C NMR ($CDCl_3$, 75 MHz, δ, p.p.m.): 46.34, 55.70, 116.23, 116.53, 118.93, 124.64, 129.24, 130.25, 131.58, 132.58, 133.37, 134.29, 155.30, 159.15, 165.38.

Crystal data

$C_{23}H_{15}BrClFN_4O$
M_r = 497.75
Monoclinic, *C*2/*c*
a = 17.0109 (6) Å
b = 11.5436 (4) Å
c = 20.6095 (6) Å
β = 92.2816 (17)°
V = 4043.8 (2) Å^3
Z = 8
D_x = 1.635 Mg m^{-3}
Mo *K*α radiation
Cell parameters from 4476 reflections
θ = 2.9–27.5°
μ = 2.20 mm^{-1}
T = 120 (2) K
Block, pale yellow
0.36 × 0.32 × 0.24 mm

Data collection

Nonius KappaCCD diffractometer
ω and φ scans
Absorption correction: multi-scan (*SADABS*; Bruker, 2003)
T_{min} = 0.505, T_{max} = 0.620
17959 measured reflections
4636 independent reflections
3545 reflections with $I > 2\sigma(I)$
R_{int} = 0.043
θ_{max} = 27.5°
h = −19 → 22
k = −14 → 14
l = −26 → 26

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.035
$wR(F^2)$ = 0.075
S = 1.03
4636 reflections
282 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0276P)^2 + 3.972P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.001
$\Delta\rho_{max}$ = 0.41 e Å^{-3}
$\Delta\rho_{min}$ = −0.52 e Å^{-3}
Extinction correction: *SHELXL97*
Extinction coefficient: 0.00038 (7)

Table 1
Selected geometric parameters (Å, °).

C6—C7	1.493 (3)	C9—N2	1.380 (3)
C7—N1	1.283 (3)	C16—N4	1.314 (3)
C7—C11	1.496 (3)	C16—N2	1.383 (3)
C9—N3	1.302 (3)	N3—N4	1.390 (3)
F1—C1—C6—C7	−6.3 (3)	C16—C17—C18—Br1	1.2 (3)
N1—C8—C9—N3	113.4 (2)	C15—C10—N2—C16	34.3 (3)
N1—C8—C9—N2	−66.0 (3)		

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

D—H···A	D—H	H···A	D···A	D—H···A
C2—H2···N4^{i}	0.95	2.42	3.244 (3)	145

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

H atoms were positioned geometrically (C—H = 0.95–0.99 Å) and refined as riding, with U_{iso}(H) = 1.2U_{eq}(carrier) or 1.5U_{eq}(methyl carrier). The methyl group was rotated to fit the electron density.

Data collection: *COLLECT* (Nonius, 1998); cell refinement: *SCALEPACK* (Otwinowski & Minor, 1997); data reduction: *SCALEPACK*, *DENZO* (Otwinowski & Minor, 1997) and *SORTAV* (Blessing, 1995); program(s) used to solve structure: *SHELXS97* (Sheldrick, 1997); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *ORTEP-3* (Farrugia, 1997); software used to prepare material for publication: *SHELXL97*.

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