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N-Piperonyl analogue of the atypical antipsychotic clozapine

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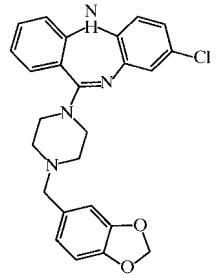
The crystal structure of 11-[4-(1,3-benzodioxol-5-ylmethyl)-piperazino]-8-chloro-5*H*-dibenzo[*b*,*e*][1,4]diazepine, $C_{25}H_{23}ClN_4O_2$, confirms the buckled nature of the dibenzodiazepine nucleus, with the central seven-membered heterocycle in a boat conformation and the dihedral angle between the planes of the aromatic rings being similar to that found for the parent compound, clozapine. The piperazine ring displays an almost perfect chair conformation, with the piperonyl group assuming an equatorial orientation. The relative position of the dibenzodiazepine and piperazine ring systems is controlled by the planarity of the piperazine N atom in the amidine moiety.

Comment

Schizophrenia is a debilitating mental disorder characterized by the chaotic jumbling and breakdown of internal thought processes. The symptoms of this disease can be divided into two distinct categories, positive (delusions and hallucinations) and negative (social and emotional withdrawal). Therapeutics used to treat this disorder fall into two clinical classes, typical and atypical. Typical antipsychotics exhibit efficacy against the positive symptoms of schizophrenia but, as an undesirable side effect, have a propensity to induce movement disorders such as Parkinsonism. Atypical antipsychotics, on the other hand, are efficacious against both the positive and negative symptoms of schizophrenia, and are virtually devoid of such side effects.

Clozapine is an atypical antipsychotic drug unparalleled in its efficacy against treatment-resistant schizophrenia. The therapeutic action of clozapine against delusions and hallucinations is thought to be due, in part, to its affinity and selectivity for dopamine-D_4 receptors (Van-Tol *et al.*, 1991; Seeman, 1992). These findings have sparked considerable interest in the area of selective D_4 ligands (Boyfield *et al.*, 1996; Mansbach *et al.*, 1998) and our research attention has been directed towards the synthesis of a family of clozapine analogues. The title compound, (I), has been patented as a selective dopamine-D_4 antagonist (Tehim *et al.*, 1998) for potential use in the treatment of anxiety and schizophrenia, while the related dibenzoxazepine, formed by solitary isosteric replacement of NH by O, displays approximately 20-fold greater selectivity for the D_4 receptor compared with the D_2 receptor, this latter dopamine receptor subtype having been implicated in drug-induced movement disorders (Kufferle *et al.*, 1997). Our interest in the crystal structure of (I) (Fig. 1)was to examine the effect of the arylmethyl substituent on the geometries of the piperazine ring and the tricyclic nucleus, relative to clozapine.



(I)

The conformation of the clozapine moiety in (I) is similar to that observed in the parent compound, clozapine (Petcher & Weber, 1976), showing the buckled nature of the dibenzodiazepine nucleus with the central seven-membered heterocycle in a boat conformation. The dihedral angle between the planes of the benzene rings (defined as the obtuse angle subtended by the plane normals) is 120.73 (6)°, similar to the 115° observed in clozapine, while the dihedral angles between

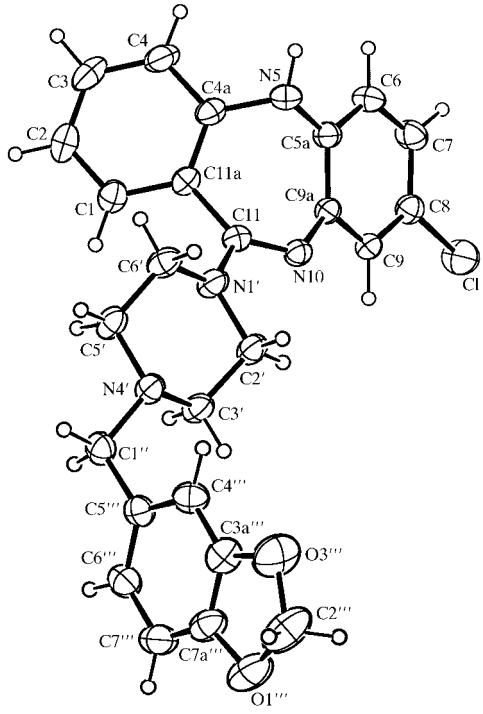


Figure 1
An *ORTEP*II (Johnson, 1976) drawing of (I) with displacement ellipsoids at the 50% probability level. H atoms are shown as spheres of radius 0.1 Å.

the plane of the four C atoms in the piperizine ring and the chloro-substituted and unsubstituted aromatic rings are 29.67 (10) and 33.85 (10)°, respectively (for clozapine, the angles are 40.5 and 31.8°, respectively), a consequence of the planarity of the piperazine N atom in the amidine moiety and the partial double-bond character of N1′—C11. As in clozapine, the piperazine ring in (I) adopts an almost perfect chair conformation, with the piperonyl group assuming an equatorial orientation. The nine atoms of this group are coplanar, with the orientation such that the dihedral angle between this plane and the plane of the C atoms in the piperazine ring is 80.21 (6)°, while the torsion angles C5′—N4′—C1″—C5‴ and N4′—C1″—C5‴—C4‴ are −167.71 (14) and 42.8 (2)°, respectively.

There is a very weak hydrogen-bonded interaction between the H atom on N5 and N10 of an adjacent molecule [N5···N10^{i} 3.291 (2), N5—H(N5) 0.88 (2) and H(N5)···N10^{i} 2.46 (2) Å, and N5—H(N5)···N10^{i} 159 (2)°; symmetry code: (i) $x, \frac{1}{2}-y, -\frac{1}{2}+z$]. This is achieved, despite the sterically congested area around N10, by the dibenzodiazepine rings of the two molecules being almost perpendicular, the dihedral angle between the C4a—N5—C5a and C9a^{i}—N10^{i}—C11^{i} planes being 89.32 (17)°. No such interaction was found for clozapine.

Experimental

Compound (I) was synthesized using a modification of the literature procedure for the synthesis of clozapine (Schneider, 1976). The method entailed reaction of 8-chloro-10,11-dihydro-5*H*-dibenzo[*b*,*e*][1,4]diazepin-11-one and the titanium tetraamine complex of *N*-piperonylpiperazine in anisole. The crude product was purified by flash chromatography (Still *et al.*, 1978) and the product recrystallized from dichloromethane–hexane as bright yellow prisms (m.p. 429–430 K, yield: 50%).

Table 1
Selected geometric parameters (Å, °).

Cl—C8	1.740 (2)	N1′—C6′	1.464 (2)
N5—C5a	1.415 (2)	N4′—C3′	1.457 (2)
N5—C4a	1.418 (2)	N4′—C5′	1.459 (2)
N10—C11	1.293 (2)	N4′—C1″	1.463 (2)
N10—C9a	1.403 (2)	C4a—C11a	1.394 (2)
N1′—C11	1.363 (2)	C5a—C9a	1.406 (2)
N1′—C2′	1.462 (2)	C11—C11a	1.489 (2)
C5a—N5—C4a	114.25 (13)	C5′—N4′—C1″	111.91 (13)
C11—N10—C9a	123.24 (12)	C4—C4a—N5	121.0 (2)
C11—N1′—C2′	120.69 (12)	C6—C5a—N5	121.42 (14)
C11—N1′—C6′	125.19 (13)	C8—C9—C9a	121.22 (14)
C2′—N1′—C6′	111.27 (13)	N10—C11—N1′	118.19 (13)
C3′—N4′—C5′	109.66 (12)	N10—C11—C11a	125.33 (13)
C3′—N4′—C1″	109.87 (13)	N1′—C11—C11a	116.18 (12)
C5a—N5—C4a—C11a	64.0 (2)	C6′—N1′—C11—C11a	−32.6 (2)
C4a—N5—C5a—C9a	−61.1 (2)	N5—C4a—C11a—C11	3.5 (2)
C11—N10—C9a—C5a	41.4 (2)	N10—C11—C11a—C4a	−46.5 (2)
N5—C5a—C9a—N10	−9.1 (2)	C3′—N4′—C1″—C5‴	70.2 (2)
C9a—N10—C11—C11a	6.4 (2)	C5′—N4′—C1″—C5‴	−167.71 (14)
C2′—N1′—C11—N10	−5.9 (2)	N4′—C1″—C5‴—C6‴	−138.3 (2)
C6′—N1′—C11—N10	153.3 (2)	N4′—C1″—C5‴—C4‴	42.8 (2)
C2′—N1′—C11—C11a	168.2 (2)		

Crystal data

$C_{25}H_{23}ClN_4O_2$	D_x = 1.311 Mg m^{-3}
M_r = 446.92	Mo $K\alpha$ radiation
Monoclinic, $P2_1/c$	Cell parameters from 25 reflections
a = 13.097 (2) Å	θ = 11.3–16.3°
b = 16.169 (2) Å	μ = 0.198 mm^{-1}
c = 10.752 (2) Å	T = 293 (1) K
β = 95.818 (12)°	Prism, intense yellow
V = 2265.2 (6) Å^3	0.60 × 0.57 × 0.53 mm
Z = 4	

Data collection

Enraf–Nonius CAD-4 MACH-S diffractometer	R_{int} = 0.012
$\omega/2\theta$ scans	θ_{max} = 27.47°
Absorption correction: Gaussian (*SHELX*76; Sheldrick, 1976)	$h = -16 \rightarrow 16$
T_{min} = 0.893, T_{max} = 0.918	$k = -1 \rightarrow 20$
6392 measured reflections	$l = -1 \rightarrow 13$
5171 independent reflections	3 standard reflections
3884 reflections with $I > 2\sigma(I)$	frequency: 150 min
	intensity decay: none

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F_o^2) + (0.0454P)^2 + 0.5782P]$ where $P = (F_o^2 + 2F_c^2)/3$
$R[F^2 > 2\sigma(F^2)]$ = 0.039	$(\Delta/\sigma)_{max}$ = −0.001
$wR(F^2)$ = 0.097	$\Delta\rho_{max}$ = 0.184 e Å^{-3}
S = 1.063	$\Delta\rho_{min}$ = −0.250 e Å^{-3}
5169 reflections	Extinction correction: *SHELXL*93 (Sheldrick, 1993)
382 parameters	Extinction coefficient: 0.0085 (8)
All H-atom parameters refined	

Refined C—H distances are in the range 0.93 (2)–1.04 (2) Å.

Data collection: *CAD*-4 *Software* (Enraf–Nonius, 1989); cell refinement: *CAD*-4 *Software*; data reduction: *PROCESS_DATA* (Gable *et al.*, 1993); program(s) used to solve structure: *SHELXS*86 (Sheldrick, 1990); program(s) used to refine structure: *SHELXL*93 (Sheldrick, 1993); molecular graphics: *ORTEP*II (Johnson, 1976); software used to prepare material for publication: *SHELXL*93.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: TA1272). Services for accessing these data are described at the back of the journal.

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