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4-Chloro-*N*-[4-(8-chloro-5*H*-dibenzo[*b*,e][1,4]-diazepin-11-yl)-1-methylpiperazinio]benzamidate dichloromethane solvate

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Key indicators

Single-crystal X-ray study
T = 123 K
Mean σ(C–C) = 0.003 Å
R factor = 0.053
wR factor = 0.111
Data-to-parameter ratio = 22.8

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

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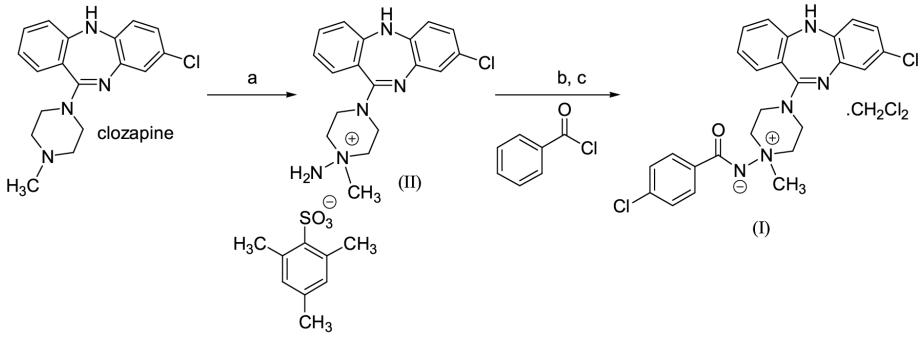
The structure of the title compound, $C_{25}H_{23}Cl_2N_5O\cdot CH_2Cl_2$, confirms the presence of the buckled nature of the dibenzodiazepine nucleus, with the central seven-membered heterocycle in a boat conformation, the dihedral angle between the planes of the aromatic rings being similar to that found for the parent compound, clozapine and related structures. The piperazine ring displays an almost perfect chair conformation, with the methyl and chlorobenzimide groups assuming equatorial and axial orientations, respectively, at the cationic nitrogen site. At the other piperazine N atom, the dibenzodiazepine nucleus assumes an axial orientation. The relative positions of the dibenzodiazepine and piperazine ring systems is controlled by the planarity of the piperazine N atom in the amidine moiety.

Comment

Aminimides are functional groups that possess pharmaceutically desirable physiochemical properties as a result of their zwitterionic character. These inner salts are reported to result in enhanced solubility in protic, aprotic and non-polar media (Rutenber *et al.*, 1996). Recently, there have been reports describing the use of the aminimide moiety in azole antifungal agents (Abel *et al.*, 1998) and peptidomimetic inhibitors of elastase (Peisach *et al.*, 1995) and HIV-1 protease (Rutenber *et al.*, 1996). This interesting property led us to consider the use of aminimides in the synthesis of analogues of clozapine, an atypical antipsychotic used clinically in the treatment of schizophrenia.



Reagent and conditions: (a) $MesSO_3NH_2$, CH_2Cl_2, 0°C, 20 min. (b) NaH, DMF, -15°C-RT, 7h. (c) (I) recrystallised from dichloromethane/hexane.

Our interest in the crystal structure of (I) (Fig. 1) was to examine its solid state structure, investigating the influence of the aminimide functionality on the conformation of the tricyclic nucleus and the piperazine ring. We were also interested in obtaining further structural information relating to the aminimide functional group, as molecular modelling

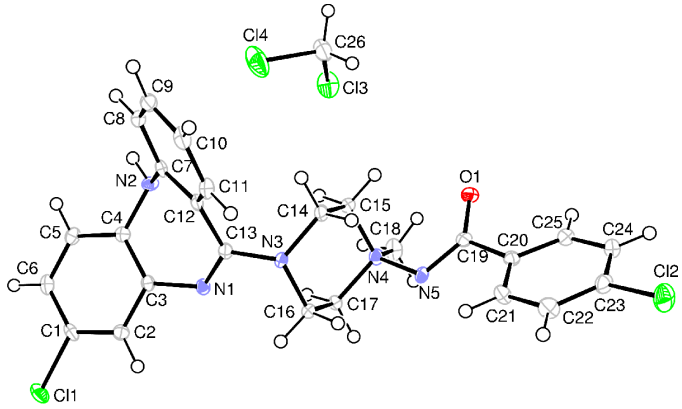


Figure 1
ORTEP-3 (Farrugia, 1997) view of (I) (50% probability displacement ellipsoids).

programs are not adequately parameterized for this moiety. We report here the X-ray crystal structure of an aminimide-containing analogue of clozapine.

The conformation of (I) shows 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 aromatic rings is 123.65 (6)°, which is similar to the 115° observed for the prototypical atypical antipsychotic clozapine (Petcher & Weber, 1976). The dihedral angles between the plane of the four C atoms in the piperazine ring and the C1–C6 and C7–C12 aromatic rings are 89.15 (6) and 61.49 (8)°, respectively, a consequence of the planarity of the piperazine N atom in the amidine moiety and the partial double-bond character of the N3—C13 bond. The piperazine ring adopts an almost perfect chair conformation, with the methyl and chlorobenzimide groups assuming equatorial and axial orientations, respectively, whilst the dibenzodiazepine nucleus assumes an axial orientation.

Experimental

The title compound, (I), was prepared in two steps, according to the scheme, from commercially available clozapine (Neve, 1999). A solution of *O*-mesitylenesulfonylhydroxylamine (3.1 mmol) was added dropwise to an ice-cold stirred solution of clozapine (3.1 mmol) in dichloromethane, after which stirring was continued for a further 20 min. Hexane was added to the reaction mixture to precipitate the product, which was collected by filtration. Recrystallization from ethyl acetate/methanol gave the intermediate salt (II) as bright yellow needles (yield 82%, m.p. 456–457 K. Sodium hydride (0.74 mmol, 60% dispersion oil) was washed with anhydrous hexane, dried under a continuous stream of dry nitrogen and cooled to 258 K (dry ice/benzyl alcohol). A solution of (II) (0.18 mmol) and 4-chlorobenzoyl chloride (0.22 mmol) in anhydrous *N*,*N*-dimethylformamide was added dropwise to the dry sodium hydride with stirring over a period of 5 min. The mixture was maintained at 258 K for 7 h and then allowed to warm to room temperature overnight. The solvent was removed *in vacuo* to afford an orange solid, which was resuspended in ethyl acetate, and a white solid was removed by filtration. The filtrate was concentrated and the resulting residue was purified by flash column chromatography (ethyl acetate/methanol, 10:1) to afford a bright yellow solid (yield 85%). Recrystallization from chloroform/hexane gave the title compound (yield 40%) as yellow needles. Pale yellow needles of (I) suitable for X-ray diffraction studies were grown from a dichloromethane/hexane mixture (m.p. 441–443 K).

Crystal data

$C_{25}H_{23}Cl_2N_5O\cdot CH_2Cl_2$	D_x = 1.46 Mg m^{-3}
M_r = 565.31	Mo $K\alpha$ radiation
Monoclinic, $P2_1/n$	Cell parameters from 41 694 reflections
a = 14.1386 (2) Å	θ = 3–30°
b = 9.9659 (1) Å	μ = 0.49 mm^{-1}
c = 18.2523 (3) Å	T = 123 (2) K
β = 90.2765 (5)°	Acicular, yellow
V = 2571.79 (6) Å^3	0.35 × 0.08 × 0.08 mm
Z = 4	

Data collection

Nonius KappaCCD area-detector diffractometer	4972 reflections with $I > 2\sigma(I)$
φ and ω scans	R_{int} = 0.070
Absorption correction: none	θ_{max} = 30.0°
41 694 measured reflections	$h = -19 \rightarrow 19$
7441 independent reflections	$k = -13 \rightarrow 12$
	$l = -25 \rightarrow 25$

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F_o^2) + (0.0419P)^2 + 1.7861P]$ where $P = (F_o^2 + 2F_c^2)/3$
$R[F^2 > 2\sigma(F^2)]$ = 0.053	$(\Delta/\sigma)_{max}$ = 0.001
$wR(F^2)$ = 0.111	$\Delta\rho_{max}$ = 0.58 e Å^{-3}
S = 1.02	$\Delta\rho_{min}$ = −0.74 e Å^{-3}
7441 reflections	
326 parameters	
H-atom paramters constrained	

Table 1
Hydrogen-bonding geometry (Å, °).

D—H···A	D—H	H···A	D···A	D—H···A
N2—H1N···O1^{i}	0.84	2.09	2.918 (2)	167

Symmetry code: (i) $\frac{3}{2} - x, y - \frac{1}{2}, \frac{1}{2} - z$.

Most H atoms were constrained in the riding-model approximation,with C---H = 0.95, 0.99 and 0.98 Å for $CH_{aromatic}$, CH_2 and CH_3 H atoms, respectively, and with U_{iso}(H) = 1.5U_{eq}(C) for methyl H atoms and 1.2U_{eq}(C) for the remaining H atoms. The H atom on N2 was located in a difference Fourier map and then constrained to ride on the N atom with U_{iso}(H) = 1.2U_{eq}(N).

Data collection: *COLLECT* (Bruker, 1997–2004); cell refinement: *SCALEPACK* (Otwinowski & Minor, 1997); data reduction: *DENZO* (Otwinowski & Minor, 1997) and *SCALEPACK*; program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1997); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *ORTEP*-3 *for Windows* (Farrugia, 1997); software used to prepare material for publication: *WinGX* (Farrugia, 1999).

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