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5,5′-(Piperazine-1,4-diyl)bis(8-chloropyrido-[2,3-*b*][1,5]benzoxazepine)

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Key indicators

Single-crystal X-ray study
T = 123 K
Mean σ(C–C) = 0.002 Å
R factor = 0.040
wR factor = 0.104
Data-to-parameter ratio = 16.6

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

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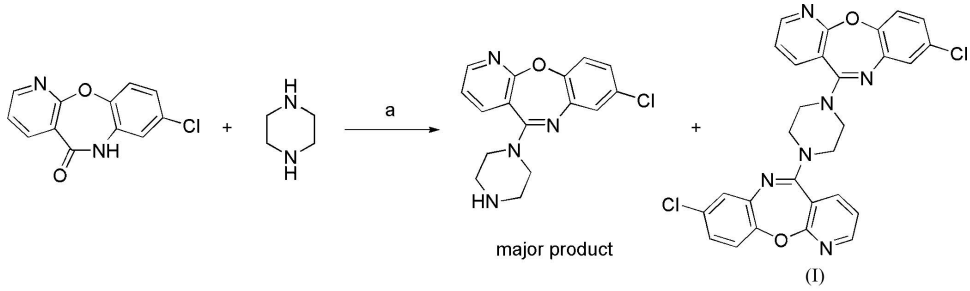
The centrosymmetric title compound, $C_{28}H_{20}Cl_2N_6O_2$, features a tricyclic framework with the characteristic V-shape of the pyridobenzoxazepine nucleus and with the central seven-membered heterocycle having a classical boat conformation. The piperazine ring displays an almost-perfect chair conformation, with the tricyclic nuclei assuming a pseudo-equatorial orientation.

Comment

Clozapine is an efficacious atypical antipsychotic used in the treatment of schizophrenia (Andreasen *et al.*, 1994; Gerlach, 1991). However, clozapine is found to induce a 1–2% incidence of agranulocytosis, a blood dyscrasia which can be fatal in some cases (Veys *et al.*, 1992; Gerson & Meltzer, 1992). Our anti-psychotic drug discovery programme (Capuano *et al.*, 2002, 2003) entails the synthesis of structurally related compounds that contain a tricyclic motif attached to piperazine, with an additional π-system anchored to the distal N atom of the piperazine ring system by a suitable spacer. The NH group of the central seven-membered ring of clozapine has been isosterically replaced with O, and the adjacent benzene ring replaced with a pyridine ring, affording the 'pyridobenzoxazepine' structural class. To expedite the chemical synthesis programme, we envisaged the synthetic utility of 8-chloro-5-piperazinopyrido[2,3-*b*][1,5]benzoxazepine (desmethyl JL13) as a versatile intermediate towards a library of clozapine-like analogues through parallel synthesis. During the synthesis, the title compound, (I), was isolated as a by-product, purified and structurally characterized by X-ray diffraction.



Reagents and conditions: (a) $TiCl_4$/toluene,1,4-dioxane, Δ, 24 h.

The molecule of compound (I) (Fig. 1) is located about a centre of inversion and exhibits the characteristic buckled nature of the pyridobenzoxazepine nucleus, with the central seven-membered heterocycle in a classical boat conformation. The dihedral angle between the planes of the aromatic rings (defined as the obtuse angle subtended by the plane normals)

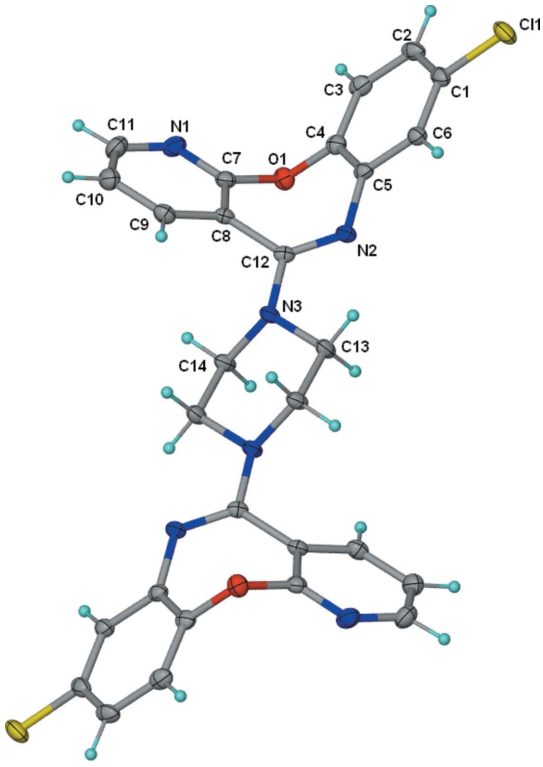


Figure 1
The molecular structure of (I), showing the atomic labelling scheme. Displacement ellipsoids are drawn at the 50% probability level. Unlabelled atoms are related to labelled atoms by $2-x, 2-y, 1-z$.

is 120.04 (5)°, which is comparable with the values of 113.99 (7)° observed for 8-chloro-5-(4-methylpiperazin-1-yl)-11*H*-pyrido[2,3-*b*][1,5]benzoxazepine (JL13) (Dupont & Liégeois, 2003) and 115° observed for the prototype atypical anti-psychotic drug clozapine (Petcher & Weber, 1976). The piperazine ring adopts a chair conformation, with the tricyclic group assuming a pseudo-equatorial orientation, by virtue of the sp^2-like nature of the piperazine N atoms (sum of angles = 347.2°). However, the piperazine ring is rotated slightly away from the pyridyl ring, as shown by the torsion angles N2—C12—N3—C13 = 4.5 (2)° and C8—C12—N3—C14 = 51.5 (2)° [for JL13 and clozapine, the corresponding angles are −1.4 (2) and 37.2 (2)° (Dupont & Liégeois, 2003) and 9 and −34° (Petcher & Weber, 1976), respectively].

There are no significant interactions between molecules of (I), which pack parallel to the *c* axis.

Experimental

Compound (I) was synthesized (Vom, 2006) according to the scheme from the tricyclic lactam 8-chlorobenzo[*b*]pyrido[3,2-*f*][1,4]oxazepin-5(6*H*)-one (Liégeois *et al.*, 1994) and commercially available anhydrous piperazine in the presence of the Lewis acid titanium tetrachloride To a stirred solution of piperazine (2.67 g, 30.3 mmol) in anhydrous 1,4-dioxane (30 ml) was added a solution of titanium tetrachloride in dry toluene (1.0 *M*, 6.7 ml, 6.7 mmol). A hot solution of the tricyclic lactam (1.50 g, 6.06 mmol) in anhydrous 1,4-dioxane (85 ml) was then added to the titanium–amine complex and the reaction mixture heated at reflux for 24 h. Following work-up, the title compound was purified by flash chromatography (silica gel, ethyl acetate) and recrystallized from CH_2Cl_2–hexane (3:1) as yellow prismatic crystals suitable for X-ray crystallography (1.4% yield; m.p. 596–597 K). ^{1}H NMR (300 MHz, $CDCl_3$, δ, p.p.m.): 3.66 (8H, *br s*, H2′, H3′, H5′, H6′), 6.99 (2H, *d*, *J* = 8.5 Hz, H9, H9″), 7.17–7.28 (6H, *m*, H3, H7, H10, H3″, H7″, H10″), 7.77 (2H, *d*, *J* = 7.5 Hz, H4, H4″), 8.45 (2H, *br s*, H2, H2″).

Crystal data

$C_{28}H_{20}Cl_2N_6O_2$
M_r = 543.40
Monoclinic, $P2_1/c$
a = 8.6940 (2) Å
b = 8.9993 (2) Å
c = 16.2542 (4) Å
β = 102.089 (1)°
V = 1243.52 (5) Å^3
Z = 2
D_x = 1.451 Mg m^{-3}
Mo $K\alpha$ radiation
μ = 0.30 mm^{-1}
T = 123 (2) K
Prism, pale yellow
0.20 × 0.10 × 0.10 mm

Data collection

Enraf–Nonius KappaCCD area-detector diffractometer
φ and ω scans
Absorption correction: multi-scan (*SORTAV*; Blessing 1997)
T_{min} = 0.932, T_{max} = 0.971
13846 measured reflections
2860 independent reflections
2080 reflections with $I > 2\sigma(I)$
R_{int} = 0.044
θ_{max} = 27.5°

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.040
$wR(F^2)$ = 0.104
S = 1.05
2860 reflections
172 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0512P)^2 + 0.2669P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.30 e Å^{-3}
$\Delta\rho_{min}$ = −0.29 e Å^{-3}

All H atoms were included in the riding-model approximation, with C—H distances in the range 0.95–0.99 Å and with U_{iso}(H) = 1.2U_{eq}(C).

Data collection: *COLLECT* (Bruker, 2004); cell refinement: *HKL2000* (Bruker, 2004); data reduction: *HKL2000*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 1997); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *X-SEED* (Barbour, 2001) and *POV-RAY* (Cason, 2003); software used to prepare material for publication: *SHELXL97*.

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