Acta Crystallographica Section C
Crystal Structure Communications
ISSN 0108-2701

Ethyl 5-isopropoxy-4-methyl-β-carboline-3-carboxylate: structural determinants of benzodiazepine-receptor antagonism

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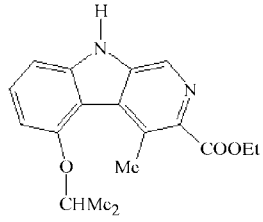
Received 16 February 2005
Accepted 18 February 2005
Online 25 March 2005

Molecules of the title compound, $C_{18}H_{20}N_2O_3$, are linked into ribbons by N—H···O and N—H···N hydrogen bonds. Stereochemical comparison with Ro 15-1788 (*viz*. ethyl 8-fluoro-5,6-dihydro-5-methyl-6-oxo-4*H*-imidazo[1,5-*a*][1,4]-benzodiazepine-3-carboxylate) has identified three electronegative N and O atoms in the molecule as features likely to be responsible for its activity as a benzodiazepine-receptor antagonist.

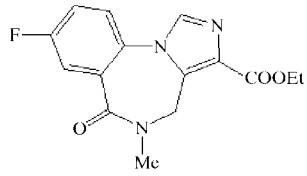
Comment

The title compound (ZK 93426) is a member of the β-carbolines, a class of compounds that bind to the benzodiazepine receptor (BDZR) and elicit a wide range of neurological effects, *i.e.* agonist (anxiolytic, sedative and anticonvulsant), antagonist and inverse agonist (anxiogenic and convulsant) activities (Braestrup & Nielsen, 1993). ZK 93426 was reported to bind with high affinity to benzodiazepine receptors and act as a BDZR antagonist (Jensen *et al.*, 1984). The structure of ZK 93426 is presented in Fig. 1; bond distances and angles are consistent with normal values. The 13-atom ring system shows a slightly bowed configuration, with a maximum deviation of 0.109 (2) Å for atom C7, significantly higher than in the more planar systems found in other reported β-carboline crystal structures (Bertolasi *et al.*, 1984; Kubicki & Codding, 2001). The two O atoms of the ethoxycarbonyl moiety are not coplanar with the tricyclic system, with atoms O2 and O3 lying 1.12 and −0.5 Å, respectively, out of the mean plane, in contrast to the situation in the previously reported structures. Atoms O1 and C9 of the isopropoxy group deviate from the plane of the tricyclic system by 0.2 and 0.3 Å, respectively.

As in other β-carbolinecarboxylate structures, the H atom at atom N9 in ZK 93426 forms two (bifurcated) hydrogen bonds, one with the carbonyl O atom and another with atom N2 of a symmetry-related molecule (Table 1). The crystal packing is presented in Fig. 2. The hydrogen-bonded molecules form infinite ribbons running parallel to the *c* axis, with van der Waals interactions between them.



ZK 93426



Ro 15-1788

We have compared (Fig. 3) the structure of ZK 93426 with that of Ro 15-1788 (ethyl 8-fluoro-5,6-dihydro-5-methyl-6-oxo-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine-3-carboxylate; Hempel *et al.*, 1987), a chemically different BDZR antagonist, in order to correlate pharmacological properties with stereochemical features. The structures were superposed by maximizing the fit of four atoms in each (N2, O2, O1 and C5 in ZK 93426, with similar functions in Ro 15-1788). No bond rota-

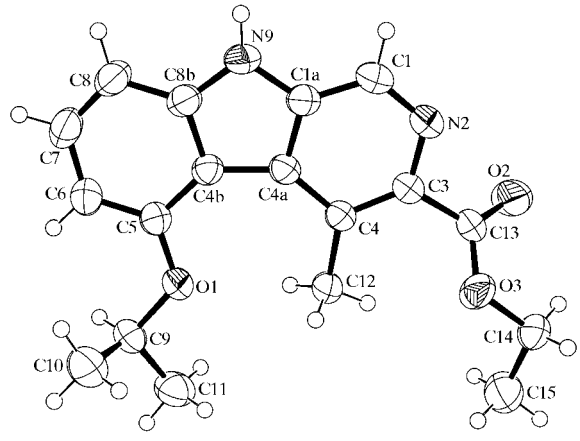


Figure 1
The molecular structure of ZK 93426, showing 50% probability displacement ellipsoids. H atoms are drawn as small circles of arbitrary radii.

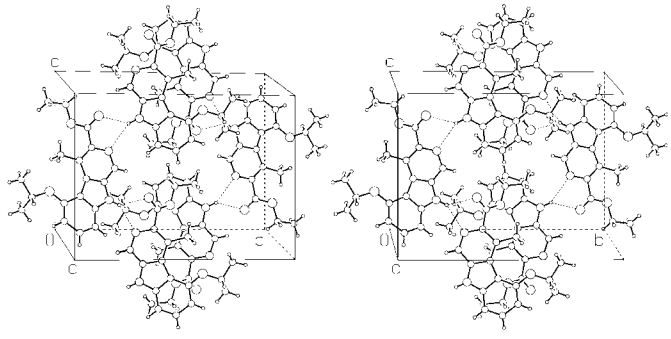


Figure 2
A stereoview of the molecular packing and hydrogen-bond scheme. All atoms are drawn as spheres of arbitrary radii. Only the H atoms involved in hydrogen bonds are shown.

‡ Deceased.

 DOI: 10.1107/S0108270105005457

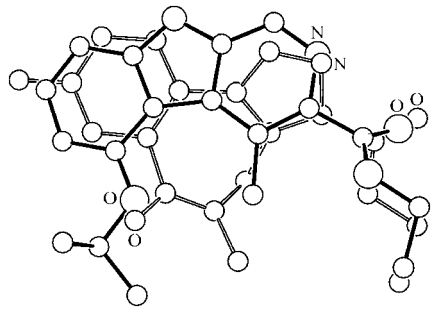


Figure 3
The superposition of ZK 93426 (large circles, filled bonds) with Ro 15-1788.

tions or other molecular alterations were performed. As is evident from the superposition, hydrophobic portions of both structures occupy similar regions in space, and three electronegative N and O atoms in each molecule superpose closely. The results are persuasive that these common features are the likely determinants for the common pharmacological activity of these compounds.

Experimental

The title compound was crystallized from a methanol–benzene mixture. Compound (I) was warmed first in methanol to dissolve all of the powder and then benzene was added until a slight cloudiness appeared; the mixture was filtered through a glass frit and allowed to stand in a covered beaker. White hexagonal needle-shaped crystals grew in about 5 d.

Crystal data

$C_{18}H_{20}N_2O_3$
M_r = 312.36
Monoclinic, $P2_1/c$
a = 8.5190 (9) Å
b = 16.2110 (15) Å
c = 11.862 (2) Å
β = 104.46 (2)°
V = 1586.3 (4) Å^3
Z = 4
D_x = 1.308 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 32 reflections
θ = 10–22°
μ = 0.09 mm^{-1}
T = 294 (2) K
Hexagonal needle, white
0.50 × 0.30 × 0.25 mm

Data collection

Enraf–Nonius CAD-4 diffractometer
$\omega/2\theta$ scans
2777 measured reflections
2777 independent reflections
2135 reflections with $I > 2\sigma(I)$
θ_{max} = 25.0°
$h = -10 \rightarrow 9$
$k = 0 \rightarrow 19$
$l = 0 \rightarrow 14$
3 standard reflections
every 100 reflections
intensity decay: 1%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.039
$wR(F^2)$ = 0.107
S = 1.01
2777 reflections
288 parameters
All H-atom parameters refined
$w = 1/[\sigma^2(F_o^2) + (0.0451P)^2 + 0.3655P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.002
$\Delta\rho_{max}$ = 0.24 e Å^{-3}
$\Delta\rho_{min}$ = −0.19 e Å^{-3}

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

D—H···A	D—H	H···A	D···A	D—H···A
N9—H9···O2^{i}	0.85 (2)	2.27 (2)	2.984 (2)	142 (2)
N9—H9···N2^{i}	0.85 (2)	2.51 (2)	3.266 (2)	148 (2)

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

Since all H atoms were refined independently, it is not surprising that some heavy-atom–hydrogen geometrical parameters differ slightly from standard values [C—H = 0.94 (3)–1.05 (2) Å].

Data collection: *CAD-4 Software* (Enraf–Nonius, 1989); cell refinement: *CAD-4 Software*; data reduction: *DATRDN* (Stewart, 1976); program(s) used to solve structure: *MULTAN80* (Main *et al.*, 1980); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *ORTEP-3 for Windows* (Farrugia, 1997); software used to prepare material for publication: *SHELXL97*.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: GD1376). Services for accessing these data are described at the back of the journal.

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