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5-Phenyl-9*H*-1,3-dioxolo[4,5-*h*][2,3]-benzodiazepin-8(7*H*)-one

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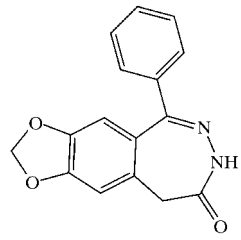
The title compound, $C_{16}H_{12}N_2O_3$, is a novel potent and selective non-competitive antagonist at AMPA/kainate receptors [AMPA is 2-amino-3-(3-hydroxy-5-methylisoxazol-4-yl)-propionic acid and kainate is 3-carboxymethyl-4-isopropenylpyrrolidine-2-carboxylic acid]. The crystal structure has been determined at room temperature by X-ray diffraction and the seven-membered ring shows the usual boat conformation. The energy stabilization of the crystal packing of the title compound by significant hydrogen-bond interactions is discussed using theoretical computations.

Comment

There is increasing evidence of the potential therapeutic utility of glutamate receptor antagonists in the treatment of several neurodegenerative disorders, including stroke and epilepsy. In the course of our studies on the modulation of glutamate receptor function, we have identified novel potent and selective non-competitive AMPA receptor antagonists based on the 2,3-benzodiazepine nucleus (Zappalá *et al.*, 2001). In previous publications (De Sarro *et al.*, 1998; Grasso *et al.*, 1999, 2001), we reported chemical and biological studies of a new series of 1-aryl-3,5-dihydro-7,8-methylenedioxy-4*H*-2,3-benzodiazepin-4-ones, and their 1,2,3,5-tetrahydro analogues and 3-*N*-alkylcarbamoyl derivatives, which have been shown to possess remarkable anticonvulsant properties, acting as non-competitive antagonists at the AMPA receptor complexes. Structure–activity relationship studies revealed that several structural features, such as an amino group on the phenyl ring or a methylcarbamoyl moiety at the N3 position, are important to maintain and/or potentiate the pharmacological properties of these molecules. This paper describes the crystal structure analysis of the title compound, (I), which represents the reference compound of this class of allosteric modulators.

The results of this investigation will be used to compare the molecular geometry of (I) with those of the analogous 2,3-benzodiazepines reported in the literature (Anderson *et al.*, 1996; Bruno *et al.*, 2001; Harkness, 2001) and to provide better understanding of the structural characteristics necessary for AMPA receptor antagonists.



(I)

Among the various literature reports of benzodiazepine crystal structures, the 1,2- or 2,3-derivatives are uncommon, as we have already pointed out (Bruno *et al.*, 2001). A systematic search of the Cambridge Structural Database (CSD, Version 5.23; Allen, 2002) retrieved 11 compounds containing 2,3-benzodiazepines, omnifariously substituted, and six 1,2-diazepines. By considering the N—N interaction in this set of 2,3-derivatives, seven 4-substituted 1-methyl-1*H*-2,3-benzodiazepines show a double bond (Gould & Gould, 1974; Blake *et al.*, 1995), while one is a 2,3-benzodiazepine 2-oxide (Walkinshaw, 1985).

The diazepinone fragment of (I) shows geometrical features very close to those found in the 4,5-dihydro-7,8-dimethoxy-1-phenyl-3*H*-2,3-benzodiazepin-4-one parent compound (Bruno *et al.*, 2001). The few significant bond differences are no greater than 0.016 Å and are observed for the atoms involved in intermolecular hydrogen bonds. Due to the weaker hydrogen-bond interactions involving the carbonyl O atom, the C1—O1 bond distance is shorter than the corresponding distance in the parent compound [1.217 (3) *versus* 1.231 (2) Å]. The seven-membered ring of (I) shows the usual boat conformation with mirror pseudosymmetry. The puckering parameters for the C1/N2/N3/C4–C7 ring are Δ_S(C7) = 0.028 (1), Q = 0.869 (2) Å, φ_2 = 100.0 (1)°, φ_3 = 152.4 (6)° and θ = 76.87 (1)° (Cremer & Pople, 1975).

The phenyl group attached at C4 appears more rotated with respect to the central fragment in (I) than in the parent compound, due to molecular packing influences, as evidenced by the C5—C4—C12—C17 torsion angles [−29.7 (2)° in the parent compound *versus* −49.3 (2)° in (I)]. The whole benzodioxole fragment is quite flat [the maximum deviation from the mean plane is 0.078 (1) Å for atom C18] and it is able to produce intermolecular stacking interactions of 3.395 (1) Å between adjacent slightly bent planes [7.63 (1)°] along the crystallographic *c* axis. The bond distances and angles of the benzodioxole fragment are in good agreement with the corresponding values in recently reported compounds containing this fragment, for example 5-(2-hydroxy-3,3,3-trifluoropropanoyl)-1,3-benzodioxole (Singh *et al.*, 2001).

The molecular packing of (I) is also determined by two pairs of weak N—H···N and Csp^2—H···O intermolecular hydrogen-bond interactions, connecting each molecule to two different centrosymmetric units in a 'head-to-tail' arrange-

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ment. The resulting packing is characterized by flat polymeric ribbons parallel to the crystallographic *a* axis.

Conventional 'strong' hydrogen bonds (*e.g.* O—H···O, N—H···O, N—H···N, *etc*) are often the key in supramolecular organization (Desiraju & Steiner, 1999). Recently, 'weak' C—H···O hydrogen bonds have been studied and many of their properties are well understood (Taylor & Kennard, 1982; Berkovitch-Yellin & Leiserowitz, 1984; Steiner, 2000). In order to understand the role played by these hydrogen bonds in determining the molecular packing observed in (I), a series of *ab initio* calculations were carried out using *GAUSSIAN*98 (Frisch *et al.*, 1998). The single-point energy (SPE) was computed on the molecular geometries obtained directly from the X-ray diffraction analysis. The SPE calculations, at the HF/6-31+G(*d*,*p*) level, were performed on the trimeric hydrogen-bonded aggregate and on both different types of dimer (N—H···N and C═O···H—C interconnected), as well as on the monomer. The complexation energy was obtained as the difference between the energy of the corresponding dimer and the doubled energy of the isolated monomer. The stabilization energies due to the intermolecular hydrogen bonds are 8.62 and 25.94 kJ mol^{-1} for the N—H···N and C═O···H—C dimer aggregates, respectively, while the corresponding value for the combined trimer is 34.56 kJ mol^{-1}. The largest stabilization energy of 17.32 kJ mol^{-1}, calculated for the C═O···H—C dimer with respect to the N—H···N dimer, is essentially due to the geometrical features of the hydrogen bonds involved.

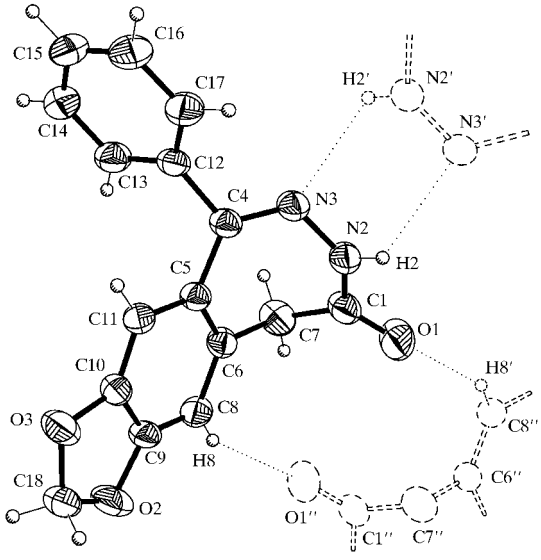

Figure 1
A perspective view of the molecule of (I), showing the atomic numbering scheme for the asymmetric unit. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii. Dotted lines represent hydrogen bonds to symmetry-related molecules, which are drawn with dashed bonds and empty ellipsoids. Primes and double primes indicate molecules at symmetry positions $(1-x, 2-y, 1-z)$ and $(2-x, 2-y, 1-z)$, respectively.

The same level of calculation was performed on 3,5-dihydrobenzo[*d*][2,3]diazepin-4-one, considered as a model of (I), and on its two dimeric models, created to simulate the corresponding dimers of (I) in the solid state. Their geometries were optimized without symmetry restrictions. The complexation energies were computed as before, by considering the isolated monomer geometry as appearing in the corresponding dimer. Since we are interested only in the relative energies, the basis set superposition errors and zero-point energy were not taken into account in all calculations. The bond distances and angles of the optimized geometries, as well as those of the seven-membered ring conformation, are in good agreement with the X-ray diffraction data, except for the bond distances of atoms involved in the hydrogen bonds.

In the gas phase, the computed complexation energies of the N—H···N and C═O···H—C dimers are 26.11 and 31.30 kJ mol^{-1}, respectively. Hence, the value of the trimer aggregate must be assumed to be 57.41 kJ mol^{-1}. In the gas phase, we obtained the greatest possible value of the interaction energy for the same hydrogen bonds as were observed in the solid state. The value computed for the X-ray trimeric fragment in the solid state is about 40% less than the corresponding value in the gas phase and this confirms the expected stabilization of the crystal packing by the hydrogen bonds.

Experimental

The title compound was obtained as described previously by De Sarro *et al.* (1995). Suitable single crystals were obtained by recrystallization from an ethanol solution.

Crystal data

$C_{16}H_{12}N_2O_3$
M_r = 280.28
Monoclinic, $P2_1/c$
a = 10.638 (2) Å
b = 17.857 (4) Å
c = 6.958 (1) Å
β = 91.42 (3)°
V = 1321.4 (4) Å^3
Z = 4
D_x = 1.409 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 35 reflections
θ = 6.7–17.5°
μ = 0.10 mm^{-1}
T = 293 (2) K
Irregular, colourless
0.50 × 0.25 × 0.12 mm

Table 1
Selected geometric parameters (Å, °).

O1—C1	1.217 (3)	C5—C6	1.393 (3)
C1—N2	1.366 (3)	C9—O2	1.369 (2)
C1—C7	1.504 (3)	C9—C10	1.376 (3)
N2—N3	1.390 (2)	C10—O3	1.374 (3)
N3—C4	1.286 (3)	O2—C18	1.433 (3)
C4—C5	1.479 (3)	C18—O3	1.418 (3)
C4—C12	1.485 (3)		
O1—C1—N2	120.2 (2)	C6—C5—C4	121.6 (2)
O1—C1—C7	123.6 (2)	C6—C7—C1	109.2 (2)
N2—C1—C7	116.2 (2)	O2—C9—C10	109.8 (2)
C1—N2—N3	128.6 (2)	C9—C10—O3	109.9 (2)
C4—N3—N2	120.7 (2)	C9—O2—C18	105.7 (2)
N3—C4—C5	126.4 (2)	O3—C18—O2	108.1 (2)
N3—C4—C12	116.1 (2)	C10—O3—C18	105.9 (2)
C5—C4—C12	117.4 (2)		
O1—C1—N2—N3	166.8 (2)	C10—C9—O2—C18	−5.0 (2)
C1—N2—N3—C4	49.3 (3)	C9—C10—O3—C18	4.4 (2)

Data collection

Siemens *P*4 diffractometer
ω scans
2770 measured reflections
2315 independent reflections
1727 reflections with $I > 2\sigma(I)$
$R_{int} = 0.048$
$\theta_{max} = 25.1^{\circ}$
$h = -12 \rightarrow 12$
$k = -21 \rightarrow 0$
$l = 0 \rightarrow 8$
3 standard reflections
every 197 reflections
intensity decay: none

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.056$
$wR(F^2) = 0.151$
$S = 0.94$
2315 reflections
190 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.1078P)^2 + 0.2546P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} = 0.018$
$\Delta\rho_{max} = 0.22$ e Å^{-3}
$\Delta\rho_{min} = -0.27$ e Å^{-3}

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

D—H···A	D—H	H···A	D···A	D—H···A
N2—H2···N3^{i}	0.86	2.45	3.030 (3)	126
C8—H8···O1^{ii}	0.93	2.58	3.431 (3)	152

Symmetry codes: (i) $1-x, 2-y, 1-z$; (ii) $2-x, 2-y, 1-z$.

Reflection intensities were evaluated by profile fitting of a 96-step peak scan using the 2θ shells procedure (Diamond, 1969) and then corrected for Lorentz polarization effects. $\sigma(I)$ values were estimated from counting statistics. H atoms were located in idealized positions, with N—H = 0.86 Å and C—H = 0.93–0.97 Å, and allowed to ride on their parent C atoms, with isotropic displacement parameters related to the refined values of their corresponding parent atoms.

Data collection: *P*3/*V* (Siemens, 1989); cell refinement: *P*3/*V*; data reduction: *SHELXTL-Plus* (Siemens, 1990); program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1990); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *XPW* in *SHELXTL* (Siemens, 1996); software used to prepare material for publication: locally modified *PARST*97 (Nardelli, 1995) and *SHELXL*97.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: NA1590). Services for accessing these data are described at the back of the journal.

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