Acta Crystallographica Section E
Structure Reports Online
ISSN 1600-5368

3-Hydroxy-6-methyl-2-[4-(3-trifluoromethylphenyl)piperazin-1-ylmethyl]-4*H*-pyran-4-one

Yavuz Köysal,[a]* Şamil Işık[a] and Mutlu Dilsiz Aytemir[b]

[a]Department of Physics, Faculty of Arts and Sciences, Ondokuz Mayıs University, Kurupelit 55139, Samsun, Turkey, and [b]Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Hacettepe University, Sıhhiye, Ankara, Turkey

Correspondence e-mail: yavuzk@omu.edu.tr

Key indicators

Single-crystal X-ray study
T = 293 K
Mean σ(C–C) = 0.005 Å
Disorder in main residue
R factor = 0.050
wR factor = 0.121
Data-to-parameter ratio = 12.8

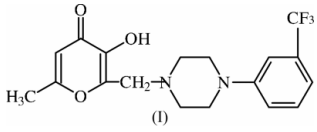
For details of how these key indicators were automatically derived from the article, see http://journals.iucr.org/e.

Received 25 November 2003
Accepted 12 December 2003
Online 19 December 2003

In the structure of the title compound, 3-hydroxy-6-methyl-2-[4-(3-trifluoromethylphenyl)piperazin-1-ylmethyl]-4*H*-pyran-4-one, $C_{18}H_{19}F_3N_2O_3$, the piperazine ring displays an almost perfect chair conformation, with the substituents at the N atoms lying in equatorial positions. The conformation of the molecule is determined by intra- and intermolecular hydrogen bonds.

Comment

The treatment of epilepsy is still a major problem because of uncontrolled seizures and medication toxicity (Martin, 2001). Antiepileptics, which are used symptomatically in the treatment of epilepsy, must be administered for a long time, even throughout the patient's life-time. Although there are number of antiepileptic drugs available on the market, development of new compounds for anticonvulsant therapy is important as there is the risk of developing tolerance or side effects. Moreover, it is still not possible to control some types of epilepsy (Martin, 2001; Schäfer, 1985; Wilson *et al.*, 1971; Aytemir *et al.*, 2004).



(I)

Anticonvulsant agents are found in several different chemical classes, such as hydantoins, barbiturates, oxazolidinediones, succinimides, acylureides, glutarimides, benzodiazepines, secondary or tertiary alcohols, dibenzazepine derivatives, valproic acid and derivatives, γ-aminobutyric acid (GABA) analogues and miscellaneous agents (Kordkovos, 1988). GABA has been suggested to be the major inhibitory neurotransmitter in the central nervous system (Enna & Maggi, 1979). In the literature, maltol (2-methyl-3-hydroxy-4*H*-pyran-4-one) has been reported as belonging to a group of compounds found to have anticonvulsant activity (Kimura *et al.*, 1980; Aoyagi *et al.*, 1974). Maltol was also shown to have a central depressing activity in mice (Kimura *et al.*, 1980). According to activity studies, the title compound, (I), has been found to be very active against scMET (subcutaneous Metrazol) at all doses after 4 h and at a dose of 300 mg kg^{-1} after half an hour.

The molecular structure of (I) is shown in Fig. 1 and selected geometric parameters are given in Table 1. The bond lengths and angles are in agreement with those in a related structure reported in the literature (Thirumurugan *et al.*, 1998). The piperazine ring adopts a chair conformation. The plane through the C atoms of the piperazine ring makes a

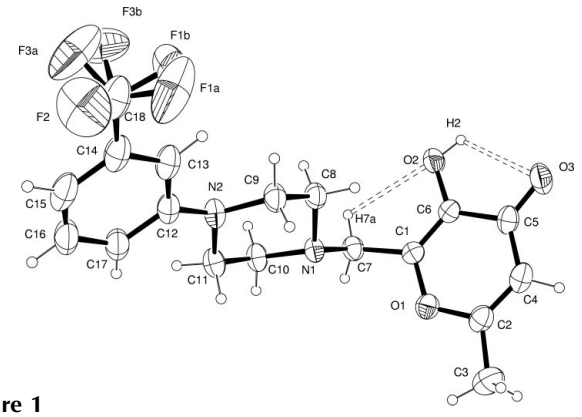


Figure 1
The structure of (I), showing 30% probability displacement ellipsoids and the atom-numbering scheme. Intramolecular hydrogen bonds are shown as double dashed lines. Both disorder components are shown.

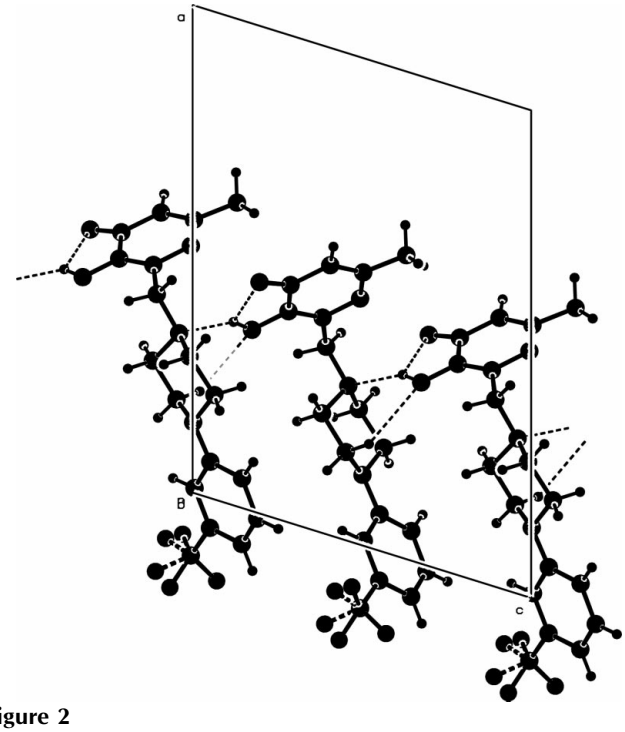


Figure 2
The crystal packing of (I), with the hydrogen bonding shown as dashed lines.

dihedral angle of 16.7 (1)° with the CF_3-substituted phenyl ring, and an angle of 89.3 (1)° with the pyran-4-one ring with the hydroxyl substituent, O2. The hydroxyl group forms an intramolecular hydrogen bond with carbonyl atom O3 (Fig. 1 and Table 2). There is also a short intramolecular contact involving atoms C7—H7*A* and O2.

In the crystal structure of (I), symmetry-related molecules are linked by intermolecular hydrogen bonds; details are given in Table 2 and Fig. 2.

Experimental

3-Hydroxy-6-methyl-2-[4-(3-trifluoromethylphenyl)piperazin-1-ylmethyl]-4*H*-pyran-4-one was synthesized as a Mannich base. Compound (I) was prepared by reaction of 1-(α,α,α-trifluoro-*m*-tolyl)piperazine with 5-hydroxy-2-methyl-4*H*-pyran-4-one (allomaltol) and formaldehyde. 2-Chloromethyl-5-hydroxy-4*H*-pyran-4-one (cholorokojic acid) was synthesized as described by Ellis *et al.* (1996) (yield 76%; m.p. 439–440 K). For the synthesis of 5-hydroxy-2-methyl-4*H*-pyran-4-one (allomaltol), cholorokojic acid (30 g, 0.187 mol, 1 equivalent) was added to distilled water (100 ml) and heated to 323 K with stirring. Zinc dust (24.4 g, 0.375 mol, 2 equivalents) was then added, followed by the dropwise addition of concentrated hydrochloric acid (56 ml, 3 equivalents) over 1 h with vigorous stirring, maintaining the temperature between 343 and 353 K. The reaction mixture was stirred for a further 3 h at 343 K. Excess zinc was removed by hot filtration and the filtrate extracted with dichloromethane (3 × 200 ml). The combined organic extracts were dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to yield the crude product. Recrystallization from 2-propanol afforded allomaltol as colourless plates (14.8 g, 63%; m.p 425–426 K). This was then used for the synthesis of (I). For (I), 3-hydroxy-6-methyl-2-[4-(3-trifluoromethylphenyl)piperazin-1-ylmethyl]-4*H*-pyran-4-one: yield 78%, m.p. 418–419 K. Analysis calculated: C 58.69, H 5.20, N 7.60%; found: C 58.61, H 5.46, N 7.60%. Spectroscopic analysis: IR (KBr, ν, cm^{-1}): 1632 (C═O), 1458 (C═C), 1363,1253 (C—O); ^{1}H NMR ($CDCl_3$, 80 MHz, δ, p.p.m.): 2.25 (*s*, 3H), 2.70 (*t*, 4H), 3.15 (*t*, 4H), 3.70 (*s*, 2H), 6.20 (*s*, 1H), 7.00–7.40 (*m*, 4H).

Crystal data

$C_{18}H_{19}F_3N_2O_3$	D_x = 1.391 Mg m^{-3}
M_r = 368.36	Mo $K\alpha$ radiation
Monoclinic, $P2_1/c$	Cell parameters from 3360 reflections
a = 15.5021 (15) Å	θ = 1.9–23.2°
b = 10.5534 (16) Å	μ = 0.12 mm^{-1}
c = 11.2637 (11) Å	T = 293 (2) K
β = 107.294 (8)°	Prism, colourless
V = 1759.4 (4) $Å^3$	0.80 × 0.32 × 0.06 mm
Z = 4	

Data collection

Stoe IPDS 2 diffractometer	R_{int} = 0.093
φ scans	θ_{max} = 26.0°
Absorption correction: none	$h = -19 \rightarrow 17$
12 432 measured reflections	$k = -12 \rightarrow 12$
3265 independent reflections	$l = -13 \rightarrow 12$
1246 reflections with $I > 2\sigma(I)$	

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F_o^2) + (0.0603P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$R[F^2 > 2\sigma(F^2)]$ = 0.050	$(\Delta/\sigma)_{max}$ = 0.001
$wR(F^2)$ = 0.121	$\Delta\rho_{max}$ = 0.25 e $Å^{-3}$
S = 0.70	$\Delta\rho_{min}$ = −0.18 e $Å^{-3}$
3265 reflections	Extinction correction: *SHELXL*97 (Sheldrick, 1997)
256 parameters	Extinction coefficient: 0.0144 (13)
H-atom parameters constrained	

Table 1
Selected geometric parameters (Å, °).

O2—C6	1.341 (3)	N1—C10	1.470 (3)
O3—C5	1.241 (3)	N2—C12	1.387 (4)
N1—C8	1.463 (3)	N2—C11	1.460 (4)
N1—C7	1.469 (3)	N2—C9	1.470 (3)
C8—N1—C7	111.2 (2)	C12—N2—C11	117.7 (3)
C8—N1—C10	107.3 (2)	C12—N2—C9	117.3 (3)
C7—N1—C10	109.9 (2)	C11—N2—C9	113.3 (3)
C7—N1—C8—C9	−177.0 (2)	C7—N1—C10—C11	176.6 (2)

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

D—H···A	D—H	H···A	D···A	D—H···A
C9—H9A···O2^{i}	0.97	2.59	3.270 (4)	127
O2—H2···N1^{ii}	0.82	2.01	2.748 (3)	150
O2—H2···O3	0.82	2.33	2.752 (3)	113
C7—H7A···O2	0.97	2.51	2.885 (3)	103

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

The high values of the displacement parameters of the F atoms in the CF_3 group indicated, as in flurtamone (Pèpe *et al.*, 1996), possible disorder of these atoms. Following a sequence of refinements and difference Fourier syntheses, disordered atoms F1 and F3 were recognized in a 52 (2):48 (2) ratio in the trifluoromethyl group. Their atomic displacement parameters are only slightly larger than those of the other atoms. H atoms attached to C atoms were included in calculated positions and treated as riding atoms, with C—H = 0.93–0.97 Å and U_{iso}(H) = 1.2 or 1.5U_{eq}(parent C atom). For the hydroxyl atom O2, O—H = 0.82 Å and U_{iso}(H) = 1.5U_{eq}(O).

Data collection: *X-AREA* (Stoe & Cie, 2002); cell refinement: *X-AREA*; data reduction: *X-RED*32 (Stoe & Cie, 2002); program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1997); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *ORTEP*III (Burnett & Johnson, 1996); software used to prepare material for publication: *WinGX* (Farrugia, 1999) and *PARST* (Nardelli, 1995).

References

Aoyagi, N., Kimura, R. & Murata, T. (1974). *Chem. Pharm. Bull.* **22**, 1008–1013.
Aytemir, M. D., Çalış, Ü. & Özalp, M. (2004). *Arch. Pharm.* In the press.
Burnett, M. N. & Johnson, C. K. (1996). *ORTEP*III. Report ORNL-6895. Oak Ridge National Laboratory, Tennessee, USA.
Ellis, B. L., Duhme, A. K., Hider, R. C., Hossain, M. B., Rizvi, S. & van der Helm, D. (1996). *J. Med. Chem.* **39**, 3659–3670.
Enna, S. J. & Maggi, A. (1979). *Life Sci.* **24**, 1727–1738.
Farrugia, L. J. (1997). *J. Appl. Cryst.* **32**, 837–838.
Kimura, R., Matsui, S., Ito, S., Aimoto, T. & Murata, T. (1980). *Chem. Pharm. Bull.* **28**, 2570–2579.
Kordkovos, A. (1988). *Essentials of Medicinal Chemistry*, 2nd edition. New York: John Wiley & Sons.
Martin, J. B. (2001). *Epilepsy Res.* **45**, 3–6.
Nardelli, M. (1995). *J. Appl. Cryst.* **28**, 659.
Pèpe, G., Pfefer, G., Astier, J. P., Marchal, P. & Bossy, A. (1996). *Acta Cryst.* C**52**, 1514–1516.
Schäfer, H. (1985). *Antiepileptic Drugs. Handbook of Experimental Pharmacology*, pp. 199–210. Berlin: Springer.
Sheldrick, G. M. (1997). *SHELXS*97 and *SHELXL*97. University of Göttingen, Germany.
Stoe & Cie (2002). *X-AREA* (Version 1.18) and *X-RED*32 (Version 1.04). Stoe & Cie, Darmstadt, Germany.
Thirumurugan, R., Shanmuga Sundura Raj, S., Shanmugam, G., Fun, H.-K. Chinnakali, K., Chantrapromma, S., Marappan, M. & Kandaswamy, M. (1998). *Acta Cryst.* C**54**, 780–781.
Wilson, C. O., Gisvold, O. & Doerge, R. F. (1971). *Textbook of Organic, Medicinal and Pharmaceutical Chemistry*, 7th ed. Philadelphia: Lippincott Co.