

# Donepezilium oxalate trihydrate, a therapeutic agent for Alzheimer's disease

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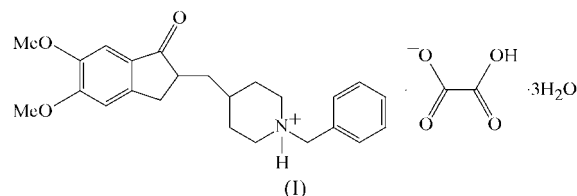
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Donepezil, a cholinesterase inhibitor with good central nervous system penetration, has been crystallized as a tertiary amine salt with a disordered oxalate anion to give the title compound, (*R,S*)-1-benzyl-4-[(5,6-dimethoxy-1-oxoindan-2-yl)methyl]piperidinium hydrogen oxalate trihydrate,  $C_{24}H_{30}NO_3^+ \cdot C_2H_2O_4^- \cdot 3H_2O$ . The indanone and piperidine ring planes are inclined at an angle of  $33.4(1)^\circ$ . A comparison is made with the piperidinium cation bound in acetylcholinesterase in the solid state. The methylene units bridging the indanone–piperidine–benzyl groups determine the molecular shape and conformational features. The structure is stabilized mainly by  $O-H \cdots O$  and  $N-H \cdots O$  hydrogen bonds, with water molecules mediating interactions between oxalate anions and donepezilium cations.

## Comment

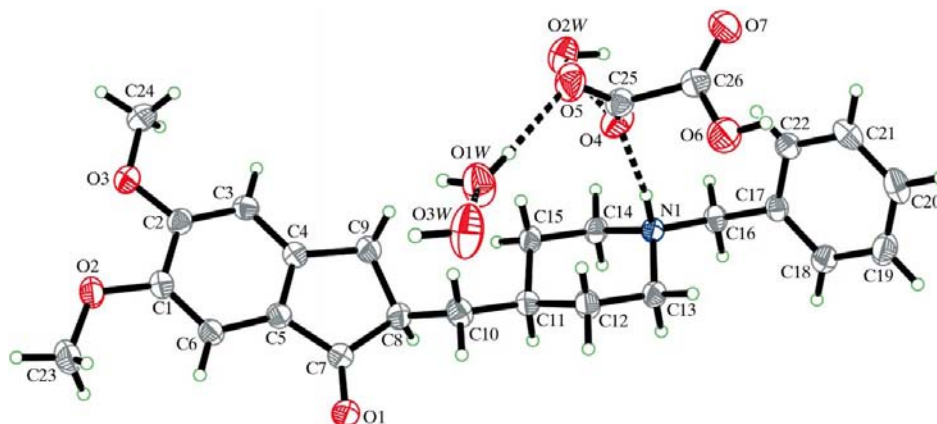
Alzheimer's disease (AD) is a progressive degenerative disorder that ultimately produces the symptoms of senile

dementia. A hallmark of AD is the decrease in number and function of basal forebrain cholinergic neurons (BFCN) (Davies & Maloney, 1976). Studies of AD in animal models also suggest impairment of functional neuronal interactions of BFCN (Villa *et al.*, 2000). This evidence sustains the hypothesis that changes in the cholinergic system are the main cause of AD (Perry, 1986). One promising therapeutic strategy for activating central cholinergic functions has been the use of inhibitors of acetylcholinesterase (AChE).



Donepezil is a potent specific piperidine-based non-competitive and reversible inhibitor of AChE. It acts to inhibit the enzymes which break down unused acetylcholine, thus prolonging the existing acetylcholine and making it more effective. The Eisai Company Limited, Japan, developed the compound as donepezil hydrochloride, and widespread clinical testing began in 1990 for its potential role in AD therapeutics (Kawakami *et al.*, 1996). It is also referred to as E2020 in pharmacological literature. Amongst the class of AChE inhibitors, donepezil has a long half-life, few clinically problematic drug interactions and generally good safety and tolerance. It was approved in 1996 by the US Food and Drug Administration for treatment of mild to moderate AD under the brand name Aricept, with subsequent registrations in Europe and Asia. The enantiomers of donepezil exhibit near identical pharmacological profiles, including inhibitory effects, and consequently it is being developed as a racemic mixture. In continuation of our ongoing programmes on the structure elucidation of drug molecules, and to gain further insight into structure–activity relationships, the crystal structure of donepezilium oxalate trihydrate, (I), has been determined and is reported here (Fig. 1 and Table 1).

From an overall perspective, the bond lengths and angles in (I) are comparable with those in similar closely related



**Figure 1**

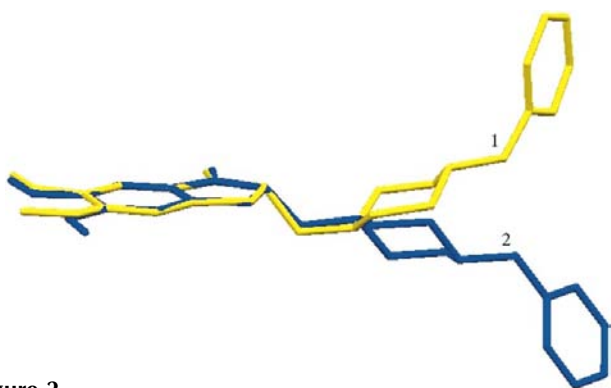
A view of (I), showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 30% probability level and H atoms are shown as small spheres of arbitrary radii. The hydrogen bond is shown as a dashed line. The disordered atoms of the minor component of the oxalate anion (C261, O61 and O71) have been omitted for clarity.

structures. The composite framework of the molecule in terms of structural features may be viewed in four parts, *viz.* an indanone group, a linking group (methylene), a piperidine group and a benzyl group. The donepezil cation is in an extended conformation, with the two benzene rings separated by a centroid-to-centroid distance of 12.018 Å. In the oxalate anion, atoms C26, O6 and O7 are disordered over two interpenetrating sites, with occupancies of 0.604 (4) and 0.396 (4).

The crystal structure of E2020 (Cardozo *et al.*, 1995) has no coordinates available in the Cambridge Structural Database (CSD, Version 5.27, *ConQuest* Version 1.8; Allen, 2002) for comparison. However, the crystal structure of the complex E2020–AChE is available [Kryger *et al.*, 1999; Protein Data Bank (Berman *et al.*, 2000) entry 1EVE] and the extracted ligand structure is used here for comparison. It has been reported that the methoxy groups at the C1 and C2 positions of the indanone group show dramatically increased activity

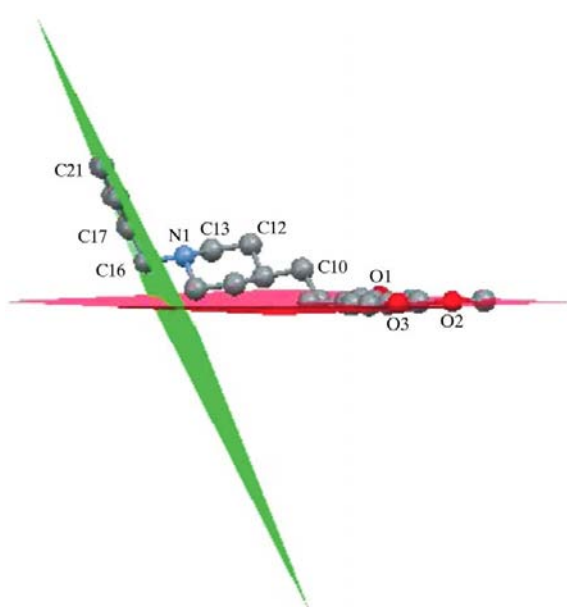
compared with those substituted elsewhere in the indanone group (Sugimoto *et al.*, 1995). Both these methoxy groups in (I) are coplanar with the indanone group, as also seen in the E2020–AChE complex structure, and we believe this contributes to the extension in the planar hydrophobic area at the binding site. Interestingly, both methoxy groups are *cis* oriented in the title compound [ $C6-C1-O2-C23 = -0.3 (3)^\circ$  and  $C3-C2-O3-C24 = -0.0 (2)^\circ$ ], while they are *cis* and *trans* oriented (torsion angles 3.3 and 179.3°, respectively) in E2020–AChE (Fig. 2).

A significant difference between the structures of (I) and E2020–AChE is in the orientation of the benzylpiperidine fragment. The orientation differs principally by a rotation of the benzylpiperidine ring about the C10–C11 bond (Fig. 2), defined by the torsion angles C8–C10–C11–C12 and C8–C10–C11–C15 (Table 1). The corresponding angles observed in E2020–AChE are  $-71.4$  and  $56.8^\circ$ , respectively. The position of the N atom on the benzylpiperidine group and its distance from the carbonyl group are critical for anti-AChE activity (Sugimoto *et al.*, 2002). This N1...O1 distance is 7.211 (2) Å in (I), with the corresponding distance in the E2020–AChE structure being 6.713 Å. Similarly, the distance between the N atom and the centroid of the benzyl ring (C17–C22) is 3.746 Å in (I) and 3.751 Å in E2020–AChE. The displacement of the piperidine ring (the only H-atom-donating site towards binding at the receptor) with respect to the indanone and benzyl groups is illustrated in Fig. 3. The piperidine ring hangs outside these planes; atom N1 is displaced by  $-1.327 (1)$  and  $1.631 (1)$  Å from the benzyl and indanone planes, respectively (1.602 and 0.652 Å, respectively, in E2020–AChE). The dihedral angle between the benzyl and indanone planes is  $67.6 (1)^\circ$  ( $87.2^\circ$  in E2020–AChE).



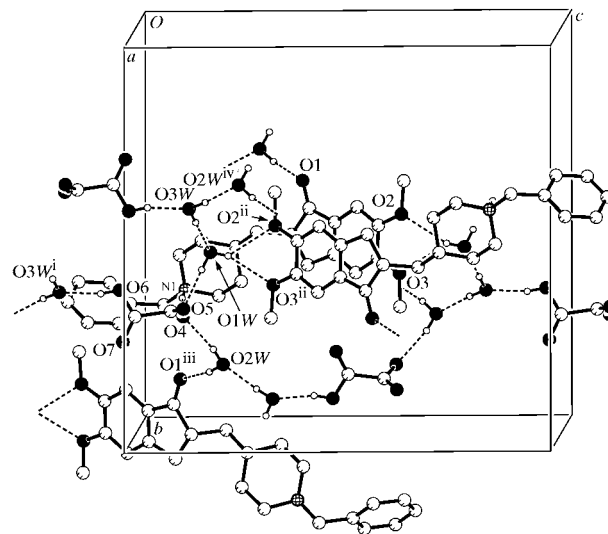
**Figure 2**

An overlay of E2020–AChE (labelled 1) with the title compound (labelled 2) (r.m.s. deviation = 0.053 Å), superimposing the indanone groups. H atoms have been omitted for clarity.



**Figure 3**

Orthogonal orientations of the two aromatic ring planes. H atoms have been omitted for clarity. Selected atoms are labelled for ring identification.



**Figure 4**

Part of the crystal structure of (I), viewed down the *a* axis, showing the networks of hydrogen bonding (dashed lines). A representative set of O atoms are labelled as in Table 2. The minor disordered oxalate component (C261, O61 and O71) and other H atoms attached to C atoms have been omitted for clarity. [Symmetry codes: (i)  $x, y, z - 1$ ; (ii)  $2 - x, 1 - y, 1 - z$ ; (iii)  $1 - x, \frac{1}{2} + y, \frac{1}{2} - z$ ; (iv)  $x, \frac{3}{2} - y, \frac{1}{2} + z$ .]

Different modes of hydrogen-bonding interactions, *viz.* cation–anion, water–anion, water–cation and water–water, stabilize the crystal structure of (I) (Fig. 4). Water molecules play an important role in the cohesion and stability of the crystal structure; two of them (O1W and O2W) are involved in seven hydrogen bonds connecting one oxalate anion and two donepezilium cations as donor, with the third water molecule (O3W) as acceptor (Table 2). In addition, the third molecule (O3W) links the other two water molecules as donor and an oxalate anion as acceptor. The centrosymmetrically related indanone ring systems tend to stack and facilitate a significant C8–H8... $\pi$  interaction (Cg1 is the centroid of the C1–C6 ring in Table 2; interaction not shown in Fig. 4).

In the E2020–AChE structure, donepezil makes no direct hydrogen bonds to the amino acid residues of the binding pocket and only water-bridged hydrogen bonds have been detected. Interestingly, compound (I) also crystallized with three water molecules that similarly mediate the hydrogen bonding.

## Experimental

To obtain crystals suitable for X-ray studies, donepezil oxalate (USV Ltd, Mumbai) was dissolved in a methanol–water solution (60:40 v/v) and the solvents were allowed to evaporate slowly.

### Crystal data

$C_{24}H_{30}NO_3^+ \cdot C_2HO_4^- \cdot 3H_2O$	$Z = 4$
$M_r = 523.57$	$D_x = 1.286 \text{ Mg m}^{-3}$
Monoclinic, $P2_1/c$	Mo $K\alpha$ radiation
$a = 8.5002 (5) \text{ \AA}$	$\mu = 0.10 \text{ mm}^{-1}$
$b = 17.6318 (10) \text{ \AA}$	$T = 294 (2) \text{ K}$
$c = 18.2158 (10) \text{ \AA}$	Block, colourless
$\beta = 97.744 (1)^\circ$	$0.23 \times 0.12 \times 0.09 \text{ mm}$
$V = 2705.2 (3) \text{ \AA}^3$	

### Data collection

Bruker SMART APEX CCD area-detector diffractometer	4754 independent reflections
$\omega$ scans	4003 reflections with $I > 2\sigma(I)$
25718 measured reflections	$R_{\text{int}} = 0.023$
	$\theta_{\text{max}} = 25.0^\circ$

### Refinement

Refinement on $F^2$	$w = 1/[\sigma^2(F_o^2) + (0.0612P)^2 + 0.846P]$
$R[F^2 > 2\sigma(F^2)] = 0.043$	where $P = (F_o^2 + 2F_c^2)/3$
$wR(F^2) = 0.122$	$(\Delta/\sigma)_{\text{max}} < 0.001$
$S = 1.01$	$\Delta\rho_{\text{max}} = 0.40 \text{ e \AA}^{-3}$
4754 reflections	$\Delta\rho_{\text{min}} = -0.20 \text{ e \AA}^{-3}$
394 parameters	
H atoms treated by a mixture of independent and constrained refinement	

**Table 1**

Selected geometric parameters ( $\text{\AA}$ ,  $^\circ$ ).

C1–O2	1.364 (2)	C8–C9	1.537 (2)
C2–O3	1.3548 (19)	C10–C11	1.538 (2)
C7–O1	1.220 (2)	C16–C17	1.500 (2)
C8–C10	1.519 (2)	C16–N1	1.5047 (19)
O2–C1–C6	125.33 (16)	C8–C10–C11	115.29 (14)
O3–C2–C3	124.75 (16)	C17–C16–N1	113.01 (12)
C10–C8–C9	116.24 (15)	C13–N1–C16	112.72 (12)
C8–C10–C11–C12	−176.34 (15)	C8–C10–C11–C15	60.7 (2)

**Table 2**

Hydrogen-bond geometry ( $\text{\AA}$ ,  $^\circ$ ).

Cg1 represents the centroid of the C1–C6 ring.

$D-H \cdots A$	$D-H$	$H \cdots A$	$D \cdots A$	$D-H \cdots A$
N1–H1N...O4	0.91 (2)	1.86 (2)	2.760 (2)	170 (2)
O6–H6A...O3W <sup>i</sup>	0.82	1.78	2.590 (5)	167
O61–H61...O3W <sup>i</sup>	0.82	1.84	2.644 (8)	168
O1W–H1W...O5	0.87 (3)	1.94 (3)	2.809 (3)	178 (3)
O1W–H2W...O2 <sup>ii</sup>	0.77 (3)	2.30 (3)	3.033 (2)	158 (3)
O1W–H2W...O3 <sup>ii</sup>	0.77 (3)	2.40 (3)	2.999 (2)	136 (3)
O2W–H3W...O4	0.84 (3)	1.93 (3)	2.749 (2)	163 (3)
O2W–H4W...O1 <sup>iii</sup>	0.92 (3)	1.95 (3)	2.864 (2)	168 (3)
O3W–H5W...O1W	0.82 (3)	1.95 (3)	2.770 (3)	176 (3)
O3W–H6W...O2W <sup>iv</sup>	0.90 (3)	1.89 (3)	2.783 (3)	174 (3)
C8–H8...Cg1 <sup>v</sup>	0.98	2.81	3.657 (2)	146

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

The site-occupancy factors of the disordered oxalate molecule refined to 0.604 (4) and 0.396 (4). The H atoms of the water molecule and all N- and O-bound H atoms of donepezil were located in a difference density map and refined isotropically. All other H atoms were positioned geometrically and treated as riding on their parent C atoms, with C–H distances of 0.93–0.98  $\text{\AA}$  and an O–H distance of 0.82  $\text{\AA}$ , and with  $U_{\text{iso}}(\text{H}) = 1.2U_{\text{eq}}(\text{C})$  or  $1.5U_{\text{eq}}(\text{methyl C, and O})$ . The methyl groups were allowed to rotate but not to tip.

Data collection: *SMART* (Bruker, 2001); cell refinement: *SAINT* (Bruker, 2001); data reduction: *SAINT*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 1997); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *SHELXTL/PC* (Sheldrick, 1990) and *MERCURY* (Macrae *et al.*, 2006).

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: GA3028). Services for accessing these data are described at the back of the journal.

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